Title

Strategies to Synthesize Template-Constrained Macrocycles with Improved Pharmacological Properties – from Tryptophan Alkylations to cIAP-Selective Antagonists & Glycosylated Peptidomimetics

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Publication Date

2017

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Strategies to Synthesize Template-Constrained Macrocycles with Improved Pharmacological Properties – from Tryptophan Alkylations to cIAP-Selective Antagonists & Glycosylated Peptidomimetics

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Chemistry

by

Brice Harrison Curtin

2017

ABSTRACT OF THE DISSERTATION

Strategies to Synthesize Template-Constrained

Macrocycles with Improved Pharmacological Properties –

from Tryptophan Alkylations to cIAP-Selective Antagonists & Glycosylated Peptidomimetics

by

Brice Harrison Curtin

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2017

Professor Patrick G. Harran, Chair

Peptide-derived macrocycles are a potentially rich source of biologically active lead structures, which are capable of recapitulating a therapeutic protein-protein surface interaction. Their three-dimensional shape influences both the macrocycle's binding to protein surfaces as well as its pharmacological properties. While other cyclization methods have focused on ring formation to yield singular products from a given peptide, small template molecules can also be used as hydrophobic scaffolds to engage and cyclize unprotected peptides in order access regioisomeric variants of each peptide sequence. In this way, we hope to engineer improved pharmacological and therapeutic properties of bioactive or bio-inspired peptides. These designed template molecules incrementally constrain peptide structure through systematic cyclizations to restrict conformation and stabilize against degradation by

metabolic enzymes. These hybrid molecules are intended to retain molecular recognition elements in the biopolymer while displaying that functionality as part of stable polycycles having defined shapes and improved pharmacological properties.

Chapter 2 covers Friedel-Crafts macrocinnamylations of tryptophan-containing peptides, specifically studying the *endo*-pyrroloindoline products produced from such reactions. We found this product to be sensitive to acidic conditions, which lead to regioisomeric rearrangement products. We studied the kinetics of this rearrangement both experimentally and computationally.

In Chapter 3, the synthesis and use of a new, four-armed template molecule, which now bears a terminal alkyne are detailed. We utilized the terminal alkyne as a site for glycosylation through a copper-catalyzed Huisgen cycloaddition as well as a dimerization event. This now third generation template afforded regioisomeric macrocyclic products derived from the second mitochondrial activator of caspases (Smac) N-terminus, which displayed differing affinities for inhibitor of apoptosis proteins (IAPs).

In Chapter 4, methods to engage the terminal alkyne of the third generation template in a unimolecular reaction are investigated. Although a bicyclization reaction eluded us, the data discussed therein may provide insight into further endeavors.

The dissertation of Brice Harrison Curtin is approved.

Jennifer M. Murphy

Neil K. Garg

Patrick G. Harran, Committee Chair

University of California, Los Angeles

2017

This dissertation is dedicated to my family

especially my parents, Mike and Michelle, and my brothers and

to my best friend, Natalie Boehnke.

We made it!

ACKNOWLEDGEMENTS

During my time as a student and especially in the months leading up to the completion of my dissertation, I have continued to reflect upon those that have helped me along the way. I am grateful for all of those that have guided me throughout my academic career. I would not be the scientist I am today without their help.

I was fortunate to work with some great scientists, and their involvement were vital to the success of the projects, which appear in the ensuing chapters:

Rose, T. E.*; Curtin, B. H.*; Lawson, K. V.*; Simon, A.; Houk, K. N.; Harran, P. G. *Chem. Sci.* **2016**, *7*, 4158–4166. (Chapter 2)

Curtin, B. H.; Manoni, F. Park, J.; Lam, Y.-h.; Gravel, M.; Roulston, A.; Harran, P. G. *Submitted.* (Chapter 3)

Adam Simon of Dr. Ken Houk's lab calculated energies of proposed intermediates, which aided in our study of tryptophan alkylations (Ch. 2). Additionally, Dr. Jiyong Park and Dr. Colin (Yu-hong) Lam Dr. Ken Houk's lab performed important computations of structural conformation and binding (Ch. 3). Thank you to Dr. Francesco Manoni for help optimizing the carbometalation (Ch. 3). Dr. Michel Gravel of Dr. Anne Roulston's lab tested compounds for *in vitro* activity against inhibitor of apoptosis proteins (Ch. 3). Dr. Noelle Williams examined Caco-2 cellular permeabilities of both glycone and aglycone compounds (Ch. 3). Dr. Saeed Khan conducted the X-ray crystal analysis of our first crystalline macrocyclic pyrroloindoline (Ch. 2). Lucas Morrill and Dr. Joel Smith of Dr. Neil Garg's lab helped with chiral supercritical fluid chromatography (Ch. 3). Dr. Robert Taylor and Dr. T.C. Ong were helpful with NMR problems and questions. Dr. Greg Khitrov was accommodating with mass spectral analysis (Ch. 3).

Of special note is Dr. Tristin Rose; her mentorship and friendship has indisputably helped me to become both critical and imaginative concerning my own work. She pushed me to think thoroughly and with good scientific principles whenever I encountered a problem in the lab. Her advice and guidance have been an incredible influence, and I will always be grateful.

I would like to thank my advisor, Dr. Patrick Harran, for challenging me with difficult synthetic and scientific problems. His guidance has helped to develop me into a critical and competent scientist.

Thank you to all of my labmates through the years who have been a source of advice: Tristin, Ryan, Hui, Andrew, Ken, Tyler, Emily, and Francesco. You guys helped me through my time at UCLA.

I would also like to thank Thomas Cummings for making my first chemistry class interesting and helping to start me on my current path. Thank you to Dr. Chariklia Sotiriou-Leventis and Dr. Nicholas Leventis for being gracious and allowing me to join their lab as a second-year undergraduate with no laboratory experience. Her mentorship, especially, helped me to realize that getting a doctorate could be an attainable goal and would allow me to continue learning about synthetic chemistry. I also would like to thank Dr. Jeff Winiarz for his guidance – first as an academic advisor then as a research advisor – and for the many discussions of Pink Floyd and the pros and cons of Roger Waters. Jeff's advice helped me to leave my comfort zone and choose UCLA and move across the country.

Lastly but not certainly leastly, I want to thank my family and their continued support. I am extremely lucky to have my best friend, Natalie Boehnke, throughout a majority of our time in grad school. Her support helped me to overcome obstacles that I thought insurmountable, and she has been a source of consistent motivation and encouragement. I want to thank my parents for their support and for helping me through the tough times and for believing in me no matter what. Finally, I would like to thank my brothers for always being encouraging.

I would not have been able to accomplish any of this alone. Thank you so much, truly.

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Curtin, B. H.; Manoni, F. Park, J.; Lam, Y.-h.; Gravel, M.; Roulston, A.; Harran, P. G. "Rapid assembly of complex macrocycles by incrementally amalgamating machine-made oligomers with designed inserts" *Submitted.*

Rose, T. E.*; **Curtin, B. H**.*; Lawson, K. V.*; Simon, A.; Houk, K. N.; Harran, P. G. "On the prevalence of bridged macrocyclic pyrroloindolines formed in regiodivergent alkylations of tryptophan." *Chem. Sci.* **2016**, *7*, 4158–4166. *Equal contributions

Bang, A.; Sadekar, A.; Buback C.; **Curtin, B.**; Acar, S.; Kolasinac, D.; Yin, W.; Rubenstein, D. A.; Lu, H.; Leventis, N.; Sotiriou-Leventis, C. "Evaluation of Dysprosia Aerogels as Drug Delivery Systems: A Comparative Study with Random and Ordered Mesoporous Silicas." *ACS Appl. Mater. Interfaces* **2014**, *6*, 4891–4902.

A. Bang, A. Sadekar, **Curtin, B.**; Buback, C.; Acar, S.; Leventis, N.; Sotiriou-Leventis, C. "Silica and Dysprosia Aerogels as Drug Carriers for Indomethacin and Paracetamol." *PMSE Preprints* **2011**, *105*, 1081–1082.

PRESENTATIONS

Curtin, B. H. "Strategies to Synthesize Template-Constrained Peptidomimetic Macrocycles with Improved Pharmacological Properties." 2017 Organic Graduate Symposium, UCLA, Los Angeles, CA, June 16, 2017.

Curtin, B. H.*; Manoni, F. M.; Park, J.; Lam, Y.-h.; Houk, K. N.; Harran, P. G. "Template-controlled peptide cyclizations to form complex, rigid peptidomimetics." Seaborg Symposium 2016, UCLA, Los Angeles, CA, November 12, 2016. (**poster presentation)**

Curtin, B. H.*; Rose, T. E.; Lawson, K. V.; Manoni, F. M.; Harran, P. G. "Template-controlled peptide cyclizations to form complex, rigid peptidomimetics." University of California Symposium for the Chemical Sciences 2016, Lake Arrowhead, CA, March 31, 2016. (**poster presentation)**

Curtin, B. H.*; Rose, T. E.; Lawson, K. V.; Harran, P. G. "Characterization of a novel class of ansa-bridged macrocyclic pyrroloindolines." Seaborg Symposium 2015, UCLA, Los Angeles, CA, October 19, 2015. (**poster presentation**)

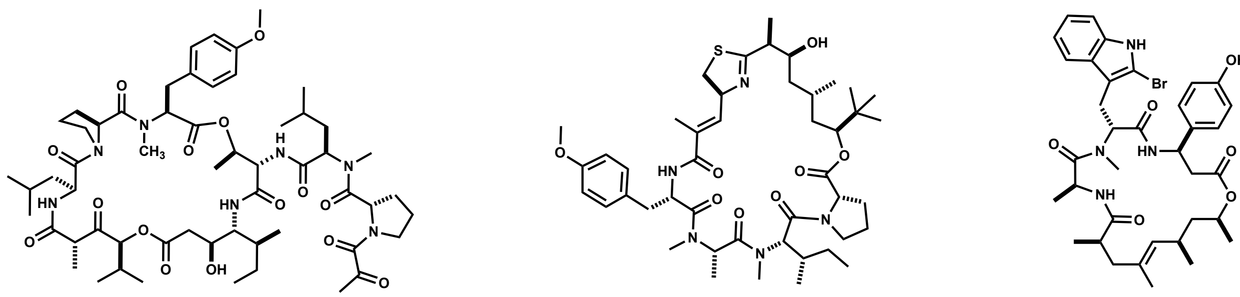
HONORS – AWARDS

2017	Aldrich-UCLA Dissertation Award
2017	American Chemical Society UCLA Research Showcase Travel Award
2012	Profiled on MS&T website (http://discover.mst.edu/2012/01/26/brice_curtin/)
2011	International Genetically Engineered Machine (iGEM) Silver Medal
2010, 2011	Opportunities for Undergraduate Research (OURE) Award Recipient
2010, 2011	William James Scholarship Recipient (MS&T Chemistry Dept.)
2010	International Genetically Engineered Machine (iGEM) Bronze Medal
2009	Grice-Strunk Scholarship Recipient (MS&T Chemical Engineering Dept.)
2008-2012	Trustee's Scholarship Recipient (MS&T)

Chapter 1 – Introduction

1.1. Background and Rationale

Macrocycles are a potentially rich source of unique lead compounds for drug discovery programs owing to their ability to scaffold extended, three-dimensional chemical arrangements.[1–5] This attribute facilitates binding to protein surfaces involved in biological pathways underpinning disease beyond canonical drug targets such as enzymes or receptors. Intracellular signaling events mediated by the association of two proteins – known as protein-protein interactions (PPIs) – provide the largest class of potential drug targets, but PPIs remain recalcitrant to traditional small molecule drug discovery strategies such as high-throughput screening.[6,7] For this reason, alternative tactics have been advocated for targeting PPIs and other protein drug targets with extended and/or solvent-exposed binding sites. Despite the large contact area at PPI interfaces, a majority of the binding energy is often conferred by a few specific interactions between residues – termed hot spots – within the larger protein,[5] and sequences incorporating



plitidepsin
Phase III refractory myeloma

apratoxin A
active against solid tumors

jasplakinolide
F-actin stabilizer

Figure 4.1. Naturally occurring macrocyclic peptides can exhibit promising biological activities and clinical significance. Their structures can range from non-ribosomal peptide macrocycles to peptide-polyketide hybrid macrocycles.

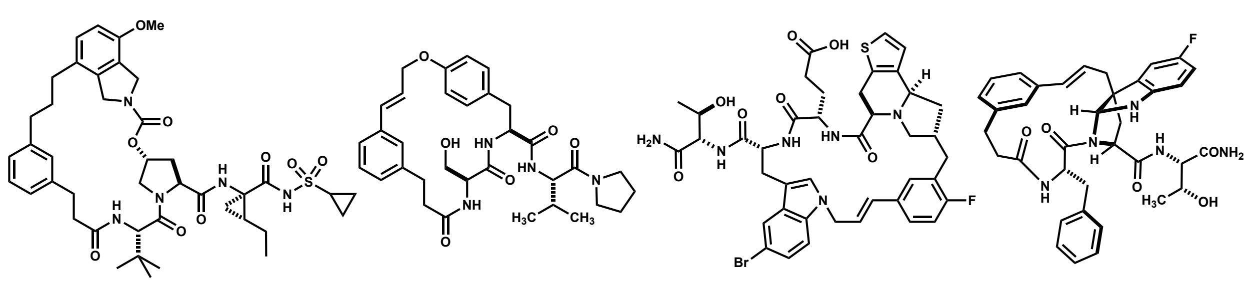
such residues afford a logical starting point for drug discovery.[8,9] However, peptides are typically devoid of activity *in vivo* due to poor transport across biological membranes, poor systemic exposure due to rapid degradation, and limited bioavailability.[5,10] Cyclic peptides often show increased cellular permeability and stability relative to acyclic counterparts, while retaining molecular recognition inherent to the parent biopolymer. Macrocycles are prevalent among naturally occurring bioactive oligopeptides arising from secondary metabolic processing by non-ribosomal peptide synthetases (Fig. 4.1). Such natural products have promising clinical significance and can range in their degree of modification from archetypal non-ribosomal peptides, plitidepside,[11] to more peptide–polyketide hybrid compounds, such as apratoxin a[12,13] and jasplakinolide.[14] Similar modifications have proven useful for improving the pharmacological performance of synthetic peptides.[15,16]

These benefits are thought to result from constraining the peptide to a conformation, which shields polar functional groups, thereby accelerating diffusion across membranes and impedes recognition by proteolytic enzymes that lead to degradation. Additionally, macrocyclization can display the peptide in a conformation, which is pre-organized to bind its target. Numerous synthetic methods are available to form cyclic peptides, including traditional macrolactamization, metathesis,[17,18] copper-catalyzed Huisgen cyclization,[19,20] and cysteine ligation.[21,22] Other unique methods have also utilized aziridine-mediated Ugi multicomponent reactions[23–25] and Pd(0)-catalyzed aminations to build macrocyclic peptides.[26] These cyclization methods have been used to recapitulate β-turns/strands[27–29] and stabilize α-helices,[18,21,30] which have been identified through large-member libraries. Many of these creative methods are both general and high yielding and thus widely adopted by peptide research laboratories. Biochemical methods are also available which can produce pooled libraries of up to 10-trillion cyclic peptides by translating an attached encoding RNA.[31–33] While these methods can be useful for early drug discovery, transforming polypeptides into useful experimental drugs remains a formidable task for the synthetic chemist. Modifying peptides by macrocyclization alone generally does not suffice to overcome the aforementioned challenges; invariably exceptions to this do exist.[34–39] These exceptions include orally bioavailable cyclic peptides – a significant advancement – as well as some PPI inhibitors. Again, such compounds were identified through large, random library screens.

For this reason, we have been pursuing new strategies to more intensively modify the structures of peptides and related macrocycles and polycycles. The central component of our design is a synthetic insert that initiates several successive reactions with linear peptides to form complex macrocyclic composites. This approach molds rather than builds peptide structure and does not require a unique set of monomers and assembly techniques for each sequence. The goal is a straightforward synthetic sequence which transforms logically-derived binding peptides into hybrid products with utility for perturbing target protein-protein interaction, both *in vitro* and *in vivo*.[40–46] This method can be thought of as an abiotic emulation of results achieved by non-ribosomal peptide synthetases, wherein linear peptides are transformed into amphipathic secondary metabolites with significantly altered structures and properties. If successful, our approach could greatly accelerate drug discovery and biochemical research in the area by providing better performing lead molecules thus alleviating the need for time-intensive medicinal chemistry optimization.

The following chapters document prototype designs for small molecule scaffolds that form hybrid peptide macrocycles by reacting with readily-prepared synthetic peptides in a general and predictable manner. These processes are operationally simple and reliably yield peptidomimetic molecules of unprecedented structure. We have carefully studied the reaction pathways involved, and multiple cyclization modes are possible within a given peptide. Collections of regioisomeric macrocycles have been prepared by alkylation of peptide side chains through either palladium-catalyzed or acid-promoted macrocyclizations and polycyclizations.[40,41,43–46] It should be noted that this approach is distinct from other methods, which can only access invariant ring structures. Through collaborative efforts, this synthetic platform has led to the identification of biologically active macrocycles and collections of compounds that chart a course for designing membrane permeable variants (Fig. 1.2). Our studies will contribute to ongoing efforts to codify how macrocyclic structure and properties can be controlled, predicted, and designed.

Our approach to scaffolding macrocyclization reactions is inherently modular. The latest design



Heptatitis C drug-mimetic ***Cell permeable macrocycle*** ***Potential inhibitors of amyloid-β fibril formation***

Figure 1.2. Macrocyclic compounds accessed through our template chemistries have potential as biological probes. Studying pharmacological properties and biological affinities will aid future endeavours.

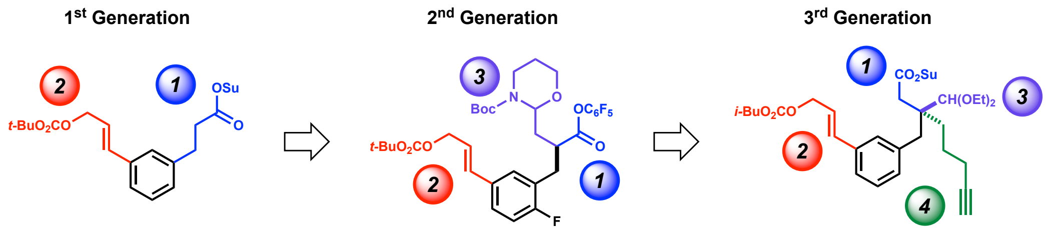


Figure 1.3. Increasingly capable inserts prepared and studied in this thesis work. Reactive nodes: (1) peptide acylation; (2) macrocinnamylation; (3) Pictet-Spengler annulation; (4) transannulation, dimerization, or post-macrocyclization functionalization.

iteration involves a template that bears elements of early prototype designs as well as an alkynyl appendage intended to support reaction discovery and property-altering modification (Fig. 1.3.). This third generation template incorporated the previous reactive groups to incrementally engage peptides through peptide acylation (*i.e.* 1, Fig. 1.3), Pictet-Spengler annulation (*i.e.* 3), and large-ring-forming cinnamylation (*i.e.* 2). A major aim of this template was to engage peptides in four orthogonal reactions including a late-stage functionalization event including transannulation to form conformationally-restricted bicyclic compounds, dimerization, or conjugation of solubilizing groups or other functional handles (*i.e.* 4). Through sequential structural modifications, the active sequence of a bioactive or bio-inspired peptide will be constrained and stabilized to retain biological activity and inhibit proteolysis (Fig. 1.4). The design, synthesis, and implementation of this new template comprise the primary accomplishments documented herein. This dissertation details the steps taken to not only access a small molecule that can engage and cyclize unprotected peptides but also the realization of its use as a scaffold to generally and predictably access polycyclic, natural product-like materials (Chapter 3). In other arenas, we have leveraged our template molecules to prepare collections of macrocycles that are designed to

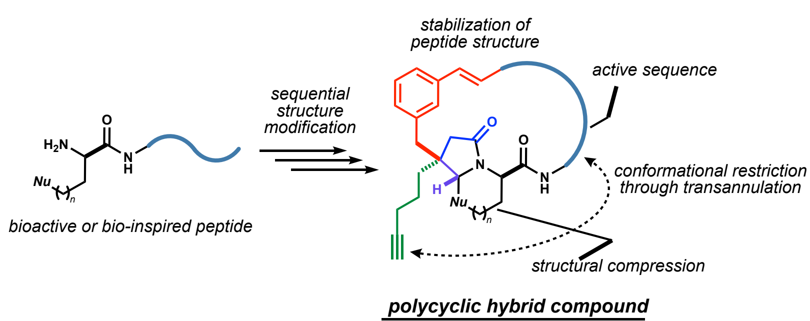


Figure 1.4. The third generation template can incrementally compress and constrain the structure of a bioactive or bio-inspired peptide while retaining molecular recognition of the active sequence. The alkyne was envisioned to engage the peptide through a fourth reaction in order to further restrict conformation.

target a given protein of interest. Along these lines, we have successfully targeted key inhibitor of apoptosis proteins (IAPs) – a family of proteins involved in cancer – and laid groundwork for future studies into the pharmacology and properties of these and related macrocycles. Preliminary studies of alkyne activation in transannulations are also discussed (Chapter 4). Additional studies of earlier template prototypes are described in the next chapter, including an in-depth mechanistic and structural investigation of tryptophan cinnamylations leading to pyrroloindolines and related heterocycles bearing a bridging macrocycle (Chapter 2). Recently, macrocycles identified in the course of these studies have been identified as potential inhibitors of amyloid-beta (Aβ) fibril formation. Future efforts will be able build upon the results herein to prepare and identify molecules with interesting biological activities and pharmacological properties.

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Chapter 2 – On the prevalence of bridged macrocyclic pyrroloindolines formed in regiodivergent alkylations of tryptophan†

2.1 Introduction

The pyrroloindoline (hexahydropyrrolo[2,3-*b*]indole) motif is present in numerous tryptophan- and tryptamine-derived natural products. Methods to synthesize this ring system typically parallel biosynthetic schemes, wherein an indolic precursor is activated by substitution at its C3 position by an external electrophile.[1] The incipient indolenium ion is then captured internally by a proximal nitrogen nucleophile (Fig. 1A). Bimolecular reactions of tryptophan in this manner often proceed without diastereoselectivity.[2] Where achievable, kinetically diastereoselective transformations typically favor an *exo* disposition of the C2-carboxyl group,[3] the extent of which depends strongly on the nature of the electrophile and on N_{α}- and carboxyl substitution.[4] Significant advances in enantioselective synthesis of pyrroloindolines have been recently reported,[5] including catalyst systems that can override the inherent substrate bias of tryptophan.[6] Here, we investigated a different modality wherein the indole activation step is itself

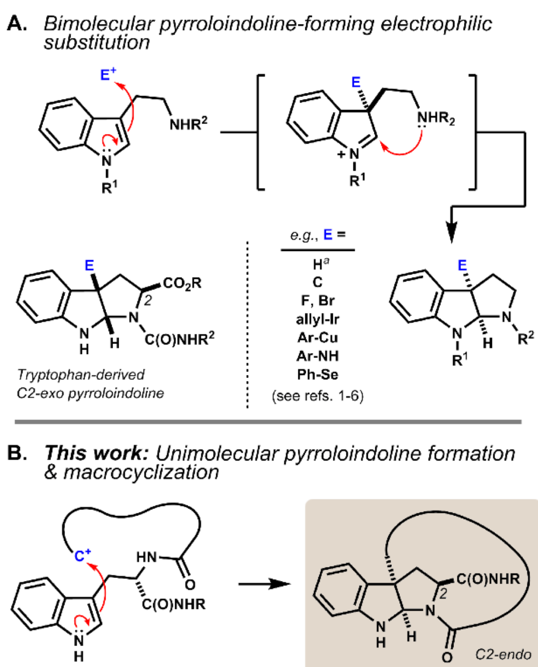


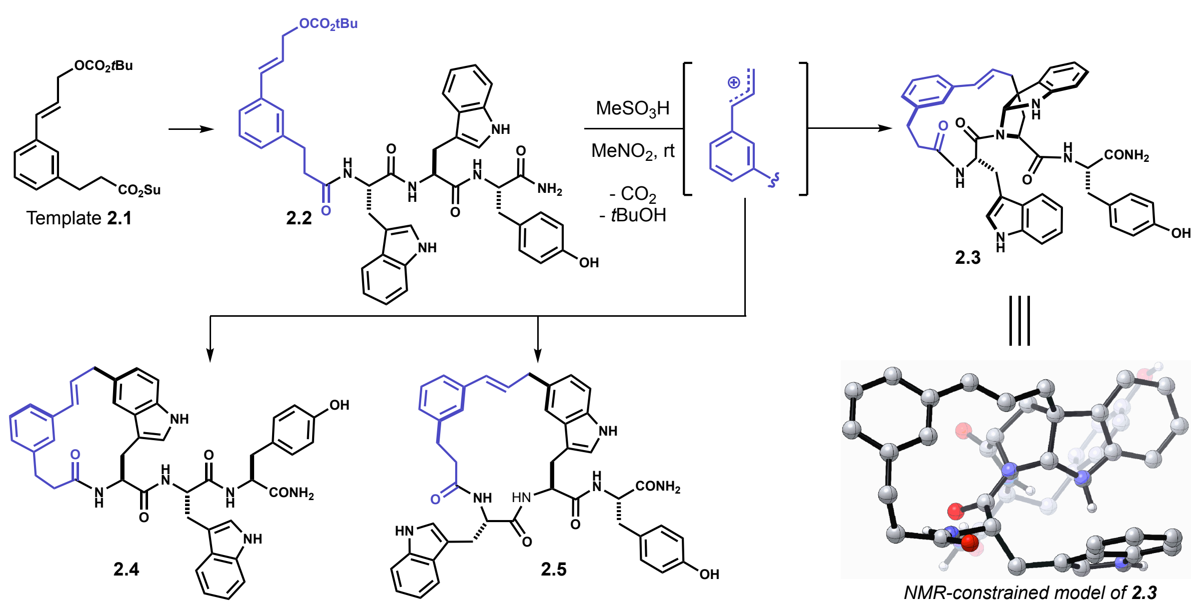
Figure 1. (A) Pyrroloindoline synthesis and biosynthesis typically proceed via bimolecular electrophilic substitution of indole at C3 and capture of the resulting indolenium ion by a proximal nitrogen nucleophile. The reaction of tryptophan is often *exo*-selective. [a]Tautomerization of tryptophan by acid equilibrates to the C2-*endo* pyrroloindoline.[4e,10] (B) Intramolecular *C–C* bond formation at C3 leads to *ansa*-bridged macrocyclic pyrroloindolines.

a ring-forming reaction (Fig. 1B).

Acid-promoted Friedel-Crafts alkylation enables procedurally straightforward, protecting group-free access to densely functionalized macrocycles.[1] The indolic side chain of tryptophan is a powerful partner in this chemistry, because its multident nucleophilicity leads to diverse ring structures. Competing alkylation of indole C3 is particularly interesting as it embeds an *endo*-pyrroloindoline segment directly into an angularly linked, *ansa*-bridged peptidyl macrocycle.[2] Pyrroloindolines bearing a C3a-linked macrocycle are rare, having been identified in only two classes of natural products, the chaetocochins,[7] and nocardioazines.[8] To our knowledge, synthesis of macrocyclic pyrroloindolines by intramolecular indole C3 substitution is limited to one example in an initial communication by us (*vide infra*).[9] The present study accesses six new products bearing these motifs, as well as thirty-nine additional indolic macrocycle isomers, and characterizes their structures and reactivity in detail.

In a recent study of internal alkylations of tryptophan-containing peptides, we characterized the products derived from acidolysis of composite oligomer **2.2** (Scheme 1).[9] When treated with

Scheme 1. Pyrroloindoline-forming macrocyclizations of 5-substituted tryptophans



Oligomer **2.2**, derived from template **2.1** and Trp-Trp-Tyr, forms isomeric macrocycles by direct internal Friedel-Crafts alkylation under acidic conditions (e.g. $MeSO_3H$, $MeNO_2$). Major products **2.4** and **2.5** result from substitution at indole C5. Bridged endo-pyrroloindoline **2.3** was obtained as a minor product.

Brønsted or Lewis acid, degradation of the cinnamyl carbonate in **2.2** led to competing internal Friedel-Crafts alkylations of proximal tryptophan and tyrosine side chains. The distribution of products was sensitive to acid promoter, solvent and temperature. Major products resulted from substitution at indole C5 of both tryptophan residues (**2.4**, **2.5**, Scheme 1). The least polar isomer, a minor product of the reaction, was assigned as *ansa*-bridged polycycle **2.3**, wherein the macrocyclization had formed an angular *C–C* linkage to a newly-formed *endo*-pyrroloindoline. The connectivity and relative stereochemistry of **2.3** was assigned by correlation NMR spectroscopy (HMBC, NOESY). Within limits of preparative isolation and analysis, a single diastereomer of **2.3** was identified in the product mixture.

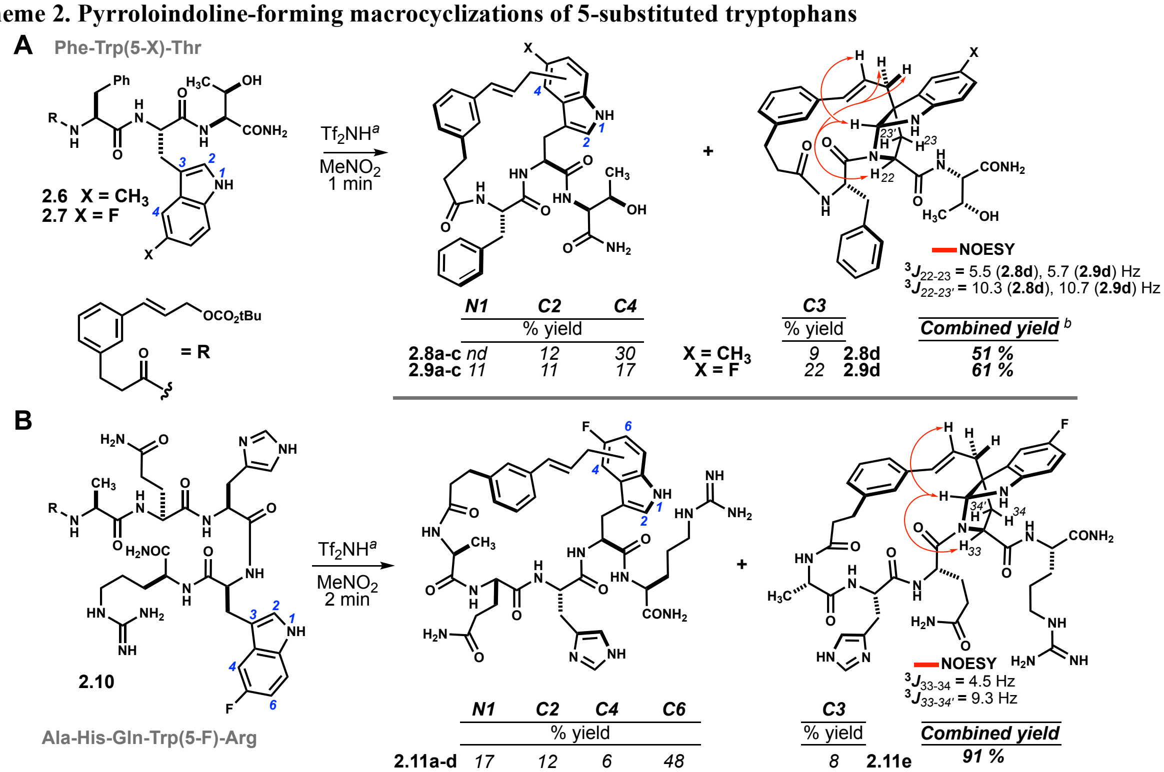
Large ring-forming alkylations of this type were designed to generate topologically varied macrocycles with the intent of studying how ring connectivity and side chain rotational freedom influence pharmacological properties. Macrocyclization alone often improves performance relative to linear counterparts by restricting conformation and masking polar functional groups.[11] Recent efforts have focused on confronting the pharmacokinetic limitations typically faced by macrocycles.[11a,c,12] In particular, stereochemistry and backbone *N*-methylation patterns have been identified in cyclic penta- and hexapeptide lactams,[11d,13] and of related analogs,[11b,14] that enable passive diffusion through membranes and enhance oral bioavailability. More general means to affect these changes would be highly desirable. Along these lines, the increased rigidity and fewer main chain *N–H* bonds in **2.3** made this compound particularly interesting.

Here, we carefully examine the structure and stability of *ansa*-bridged pyrroloindolines related to **2.3**. We survey their prevalence in mixtures of isomeric macrocycles generated by internal Friedel-Crafts alkylations of tryptophan. We evaluate structural features and reaction conditions that influence pyrroloindoline formation, and examined the origin of the observed diastereoselectivity. In addition, we have prepared a member of this new structural class using conventional target-based synthesis, thereby confirming structure and establishing a scalable route to the group in general. Lastly, we show that this new unimolecular pyrroloindoline formation also proceeds in more complex settings.

2.2 Results and Discussion

Analogs of linear oligomer 2.2 were designed to block major pathways of C5 alkylation in an attempt bias macrocyclization towards electrophilic substitution at indole C3. Substrates **2.6** and **2.7** bearing 5-methyl- and 5-fluoro-L-tryptophan, respectively, blocked C5 alkylation and removed competing side chain nucleophiles of Trp1 and Tyr3 (Scheme 2). Treating **2.6** or **2.7** with either methanesulfonic acid or triflimide in nitromethane[‡] led to complete conversion to a mixture of isomeric products within minutes at room temperature. Abundant products were isolated and characterized as *C–C* and *C–N* linked macrocycles **2.8a–d** and **2.9a–d**. Bridged pyrroloindolines **2.8d** and **2.9d** were assigned as *endo-22S,24R,25R* on the basis of sequential NOE correlations about the newly formed pyrrolidine ring (see Scheme 2A). However, these

Scheme 2. Pyrroloindoline-forming macrocyclizations of 5-substituted tryptophans



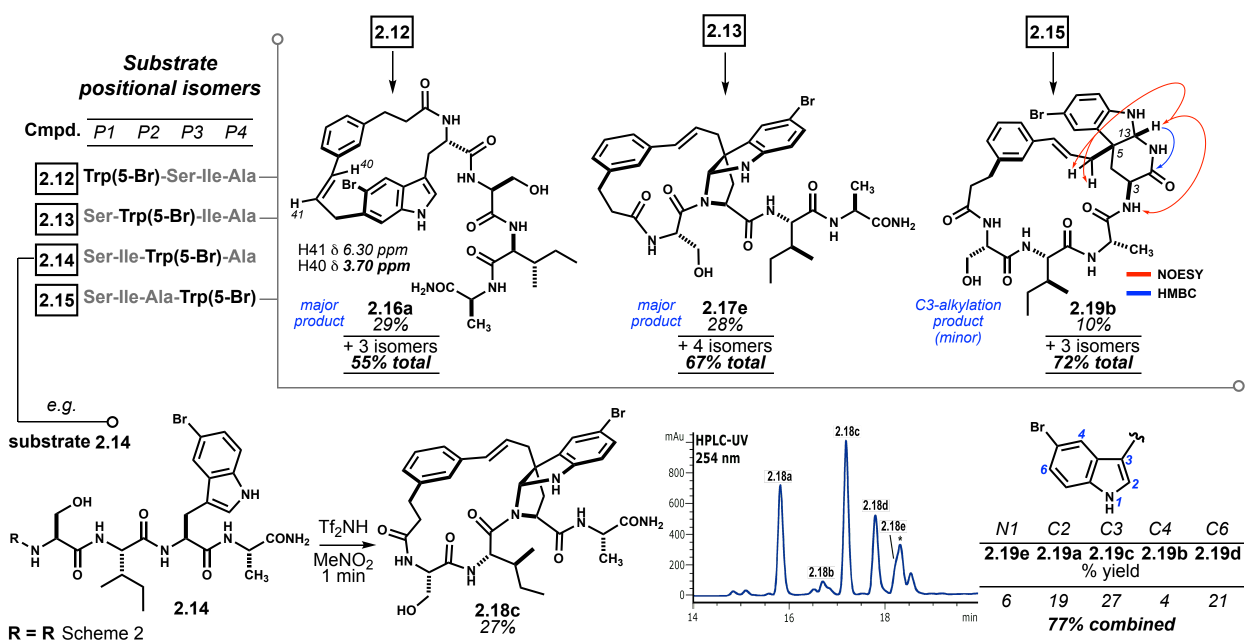
(A), (B) Acidolysis of oligomers **2.6**, **2.7**, or **2.10** promotes internal substitution at indole N1, C2, C3, C4 or C6 (blue). The connectivity and relative stereochemistry of bridged pyrroloindolines **2.8d**, **2.9d**, and **2.11e** was assigned by ^{1}H-^{13}C-HMBC and ^{1}H-^{1}H-NOESY (red arrows), respectively. Reaction Conditions: [a]Tf_2NH 4-6 eq., $MeNO_2$, 5 mM in substrate, rt. [b]Additional products were detected by HPLC; combined yield underestimates actual yield due to characterization of only major products, shown. *nd* = not determined.

materials were again obtained only as minor products. While using triflimide (4–6 eq.) as the acid promoter increased overall yield and remarkably shortened reaction times (1-2 min), it did not appreciably alter product distribution as had been observed for parent substrate **2.2**.[9] Blocking C5 with an electron-donating substituent (i.e. $–CH_3$) had not suppressed reaction at the benzenoid ring or enhanced pyrroloindoline formation as intended, but an electron-withdrawing substituent (i.e. –F) was somewhat more effective in this regard. Both, however, shifted reactivity at the benzenoid ring from C5 to C4. Nonetheless, the formation of 15-membered macrocyclic *endo*-pyrroloindoline products in substrates bearing P2 tryptophan residues appeared to be generally diastereoselective.

Accordingly, we next surveyed substrates varying in the position of tryptophan and in composition of the surrounding peptide. Substrate **2.10**, bearing 5-fluoro-L-tryptophan at P4, underwent rapid cyclization unimpeded by the basic guanidine or imidazole side chains of arginine and histidine, respectively (Scheme 2B). Triflimide improved reaction yield considerably in this case, and afforded 21-membered ring bridged *endo*-pyrroloindoline **2.11e** and isomeric macrocycles **2.11a–d** in 91% combined yield. Notably, the major product resulted from alkylation at indole C6 (i.e. **2.11d**), rather than C4 as had been observed in reactions of **2.6** and **2.7**. Taken together, these data suggest that regioselectivity tracks the inherent indole reactivity, which can be influenced by substitution of the indole nucleus. However, unlike bimolecular variants, the course of these cyclizations also depends on the geometry attainable by a given substrate and therefore the sequence of the embedded peptide. Thus, blocking the highly reactive C5 position of native tryptophan offers a useful means to finely tune the topology of macrocyclic products by shifting ring connectivity to adjacent positions C4 and C6.

To further test the effect of chain length on reaction regioselectivity and pyrroloindoline formation, we examined cyclizations of isomeric substrates **2.12**–**2.15** bearing 5-bromo-L-tryptophan in positions 1 through 4 (Scheme 3). Acidolysis of P1 variant **2.12** resulted primarily in cyclization at indole C6 (i.e. **2.16a**) and, to a lesser extent, at N1 and C7. No pyrroloindoline was observed in this case, presumably due to unfavorable strain associated with formation of a 13-memered ring by C3 substitution. As expected, P2 isomeric sequence **2.13** led to the pyrroloindoline **2.17e** bearing the core 15-membered ring shared by products **2.3**, **2.8d** and **2.9d**. Surprisingly, however, **2.17e** was formed as the major product in 28% yield. It is not yet known whether this improved yield reflects the inherent reactivity of 5-bromoindole. Regioselectivity for C3 alkylation may also benefit from the smaller steric bulk of the serine side chain in **2.17e** relative to tryptophan in **2.3** or to phenylalanine in **8d** and **9d**. Intriguingly, acidolysis of isomeric

Scheme 3. Cyclization scan of oligomers having Trp(5-Br) shifted along the chain (P1→P4).



Pyrroloindoline formation is sensitive to sequence composition and ring size, but favored by 5-bromotryptophan. No pyrroloindoline is formed from P1 isomer **2.12**, whereas P2 and P3 variants **2.13** and **2.14** lead to pyrroloindolines **2.17e** and **2.18c**, respectively, as major products. Internal C3 alkylation of the P4 variant leads instead to cyclization of the terminal carboxamide to *exo*-pyridoindoline **2.19b**. Reaction conditions as in Scheme 2. * Denotes non-isomeric impurity. For detailed product isomer distribution see Appendix Figures A4-A7.

P3 sequence (**2.14**) also led to C3 alkylation and cyclization giving *endo*-pyrroloindoline **2.18c** as the major product in 27% yield. The final P4 variant (**2.15**), however, did not give an analogous pyrroloindoline but instead afforded *exo*-pyridoindoline **2.19b** by cyclization of the terminal carboxamide subsequent to C3 cinnamylation. Interestingly, the observed *exo* configuration had resulted from initial *pro-R* substitution, a facial bias identical to that observed for the pyrroloindoline outcomes. In another case, however, a substrate bearing 5-bromotryptophan at P4 yielded both *exo*- and *endo*-pyridoindolines (1.8:1 dr, see SI Fig. S8†). This suggests that the mechanism for diastereoselection leading to *exo*-**2.19b** is distinct from pyrroloindoline outcomes (*vide infra*). The substrates surveyed here indicate that regioselectivity in tryptophan-based macrocyclizations is sensitive to oligomer composition, but bridged *endo*-pyrroloindoline and pyridoindoline products appear to form frequently.

While facial bias offers one potential rationale for the observed diastereoselectivity, we remained cognizant of the possibility for rearrangement of C3-linked macrocycles to other isomers under the reaction conditions.[15] Indeed, bimolecular electrophilic substitution at indole C2 often proceeds by initial C3 addition and 1,2-migration.[16] When isolated pyrroloindoline **2.18c** was re-subjected to the reaction conditions with Tf_2NH (4 eq.) in $MeNO_2$, partial 1,2-rearrangement to the corresponding C2-linked isomer **2.18a** was observed over a period of several hours. Consistent with previous observations, this slow equilibration of pyrroloindoline products

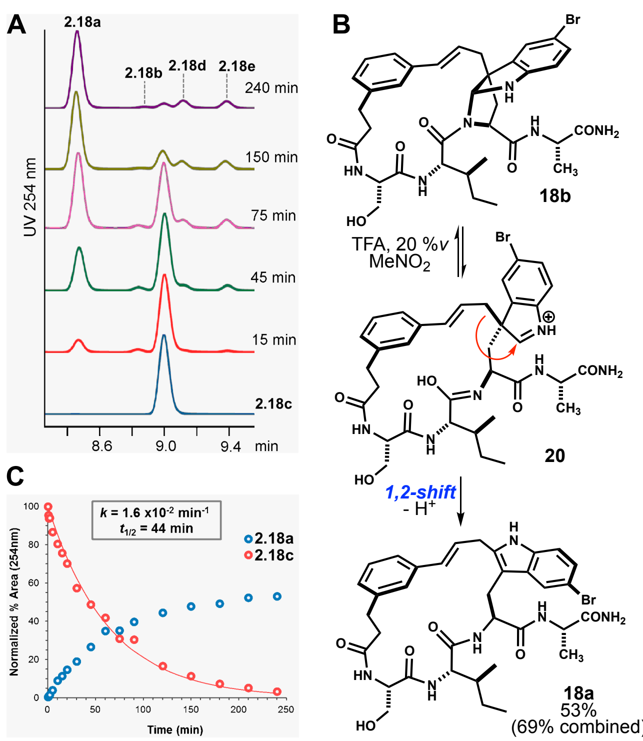


Figure 2. Rearrangement of pyrroloindoline **2.18c**. (A) Time-course HPLC-UV (254 nm) analysis showing rearrangement of isolated **2.18c** to isomer **2.18a** in TFA/$MeNO_2$ solution. Trace regioisomers (labelled) also form in this reaction. (B) Proposed mechanism for 1,2-rearrangement.[18] (C) Kinetic plot showing pseudo-first-order reaction of **2.18c** and accumulation of major product **2.18a**.

suggests that large ring-forming cinnamylations proceed under kinetic control.[17] Under forcing conditions with 20 vol% TFA in $MeNO_2$, complete rearrangement of **2.18c** to **2.18a** was observed within 3 hours ($t_{1/2}$ = 44 min, Fig. 2). Trace formation of other macrocycle isomers indicates that 1,2-rearrangement competes with reversion to a cinnamyl carbocation. The formation of C2-linked **2.18a** in brief acidolysis reactions of linear substrate **2.14** may result from direct substitution at C2.[16b,18] Alternatively, **2.18a** may result from initially unselective C3 alkylation and rapid 1,2-rearrangement of one diastereomer, that corresponding to the *exo*-pyrroloindoline (i.e. *pro*-*S* addition at C3).[19] Though a discrete *exo* diastereomer has not been observed, the latter possibility is supported by the near equal ratio of C3- to C2-linked products in the aforementioned seven examples. In two additional acid-promoted cyclizations, however, indole C2-linked macrocycles were obtained in the absence of pyrroloindoline products (see SI Fig. S8, S9†). Yet, in the case of **2.2→2.3** (Scheme 1), the product of C3 alkylation was obtained without concurrent C2 alkylation.[9]

To further probe the origin of diastereoselectivity in pyrroloindoline-forming macrocyclizations, we examined the 1,2-rearrangement of model *exo*- and *endo*-pyrroloindolines **2.21a** and **2.21b** (Fig. 3A). Under pseudo-first-order conditions using 20 vol% TFA in $MeNO_2$, rearrangement of *exo*-**2.21b** to indole C2-linked product 2.2**2** proceeded at a rate nearly 30-times faster than that of *endo*-**2.21a** (Fig. 3B). An Eyring plot was constructed from rate data at five different temperatures, which revealed activation energies $\Delta G^{\ddagger}_{exo}$ = 20.5 kcal•mol^{-1} and $\Delta G^{\ddagger}_{endo}$ = 22.4 kcal•mol^{-1} for these processes at 22 °C. We next explored this reaction computationally in order to better understand this kinetic difference. Using density functional theory (DFT), *endo*-pyrroloindoline **2.21a** (R = Me) was calculated to be 1.0 kcal•mol^{-1} more stable than the corresponding *exo* diastereomer **2.21b**. This finding is consistent with reported thermodynamic preferences of related pyrroloindolines.[3b,4e,19] Preference for the *endo*-pyrroloindoline in this case is primarily due to 1,3-allylic strain resulting from the tertiary amide (SI Fig. S15†). DFT was also used to calculate the free energy profiles for the reactions of **2.21a** and **2.21b** (SI Fig. S11†). In

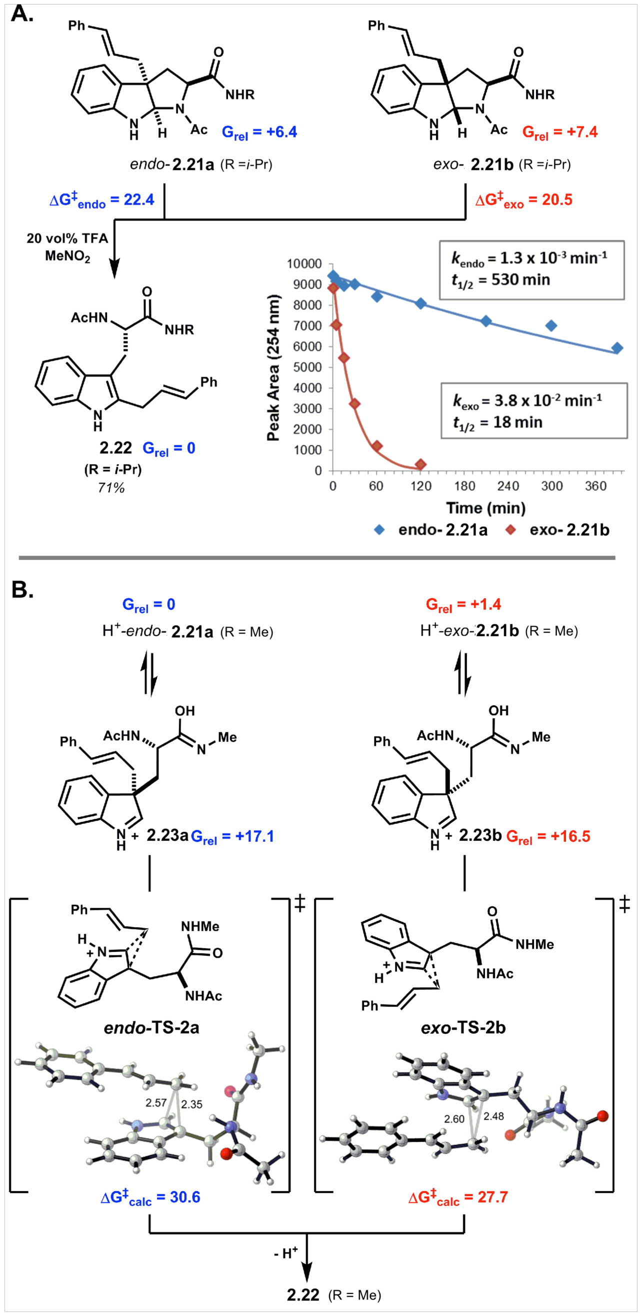
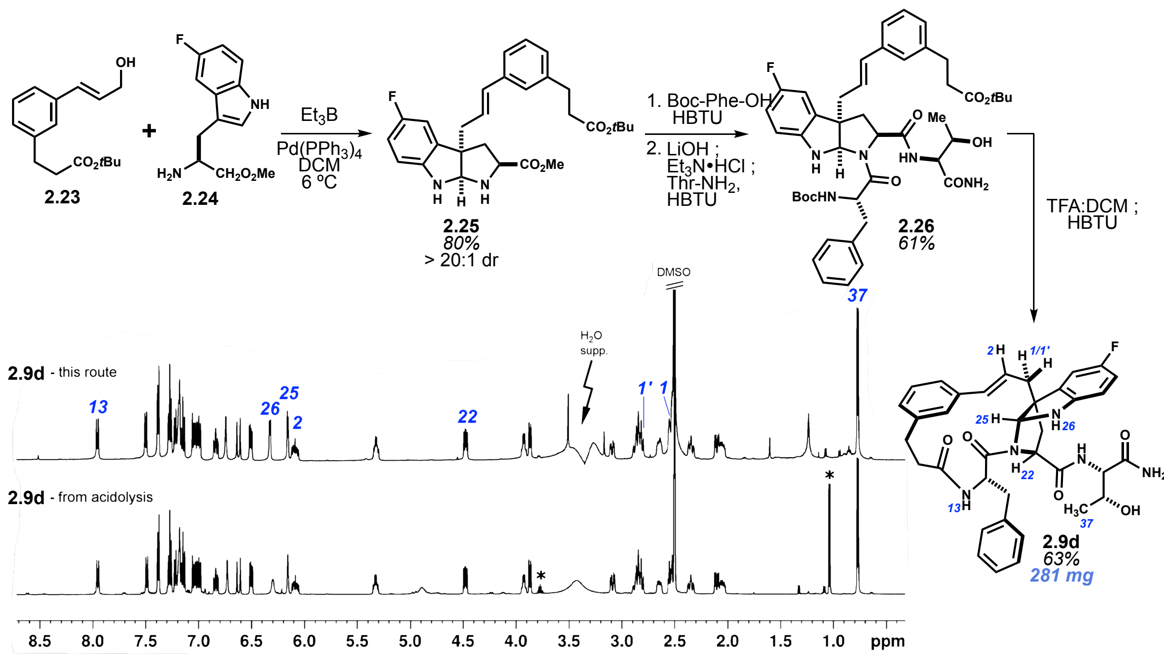


Figure 3. *exo*-Pyrroloindolines rearrange more readily than *endo*-pyrroloindolines. (A) Under acidic conditions, C3α-cinnamyl pyrroloindolines undergo ring-chain tautomerism and 1,2-rearrangement to indole C2-linked isomers. The kinetic plot for rearrangement of **2.21a** and **2.21b** in 20 vol% TFA at 5 °C shows the faster rate of reaction for *exo*-pyrroloindoline **2.21b**. From Eyring analysis, the free energy of activation was 1.9 kcal•mol^{-1} higher for *exo*-**2.21b** relative to *endo*-**2.21a**. (B) DFT calculations indicate that *endo*-pyrroloindoline **2.21a** is the thermodynamically more stable than *exo*-**2.21b**. Cinnamyl 1,2-shift is rate limiting in both cases, and the reaction of *exo*-**2.21b** proceeds via a lower kinetic barrier (see text and further discussion in Appendix†). Note: All free energies are in kcal•mol^{-1}.

each case, 1,2-shift of the cinnamyl group from an intermediate indolium ion (*i.e.* **2.23a**,**b**) was found to be rate-limiting (see SI Figs. S14, S16†). Diastereomeric transition structures **TS-2a** and **TS-2b** bear nearly enantiomeric geometries with respect to the indole ring and migrating cinnamyl group, but differ in orientation of the *S*-alanyl moiety relative to the indolic nucleus. This leads to greater stabilization of transition state **TS-2b** relative to **TS-2a** ($\Delta\Delta G^{\ddagger}_{calc}$ = 2.9 kcal•mol^{-1}), in agreement with the experimentally observed difference in activation energy ($\Delta\Delta G^{\ddagger}_{exp}$ = 1.9 kcal•mol^{-1}). Thus, the more rapid rearrangement of *exo*-pyrroloindoline **2.21b** results both from the higher energy of **2.21b** relative to **2.21a**, and from the lower kinetic barrier for the reaction **2.21b→2.22** relative to **2.21a→2.22**. These findings suggest that the diastereoselectivity observed in pyrroloindoline-forming macrocyclizations arises, at least in part, from the facility of *exo*-pyrroloindolines to rearrange to the corresponding indole C2-linked isomers.

Scheme 2.4. Selective synthesis of pyrroloindoline 2.9d



Bimolecular Pd^0-catalyzed C3-selective cinnamylation of 5-fluoro-L-tryptophan promoted by Et_3B sets up to form the bridging 15-membered ring by lactamization. ^{1}H NMR spectra (500 MHz, DMSO-d_6) of **2.9d** obtained by this route match that of material isolated from the acid-promoted cyclization. Key resonance annotations in blue. * Denotes contaminant signals.

The Friedel-Crafts macrocyclizations under study generate collections of macrocycle isomers that would be time- consuming to prepare individually. Exploring ring diversity in this manner is our approach to refining biological activity. Importantly, isomers of particular interest may also be synthesized by convergent means. This has been demonstrated by a selective synthesis of fluorinated pyrroloindoline **2.9d** (Scheme 4). Starting from 5-fluoro-L-tryptophan methyl ester and cinnamyl alcohol **2.24**, a derivative of template **2.1**, intermolecular Pd^0-catalyzed allylation promoted by Et_3B led to selective C3 cinnamylation and afforded *endo*-pyrroloindoline 2.2**6** in 80% yield as a single diastereomer.[20] The remaining two amino acids were then introduced by first amidation of **2.26** with *N*-Boc-L-phenylalanine, then saponification of the methyl ester and coupling of the resulting carboxylate to L-threonine amide to give **2.27**. Deprotection of the *N*-Boc and *tert*-butyl groups with TFA:DCM (1:1) at 0 °C minimized C3–C2 rearrangement, and lactamization of this *seco*-acid with HBTU completed bridged pyrroloindoline **2.9d**. This material was spectroscopically identical to that obtained by the acidolysis of **2.7** (see annotations Scheme 4). Convergent routes such as this are useful for preparing larger quantities of material, whereas Friedel-Crafts cyclization forms pyrroloindolines and additional macrocycle isomers rapidly and directly. Additionally, we were able to crystalize **2.9d** from a mixture of 20:1 DMF/DMSO (Fig. 4). In the crystal structure, there appears to be a hydrogen bond from amide N4 to aniline N1, which may explain the greater thermodynamic stability of *endo*-pyrroloindolines. Furthermore, we've confirmed the *endo*-stereochemistry of the pyrroloindoline motif and the NMR-constrained structure of a similar pyrroloindoline (Scheme 1 inset).[2] We were unable to determine any crystal-packing interactions in the unit cell, however. This crystal structure is the first instance of such a

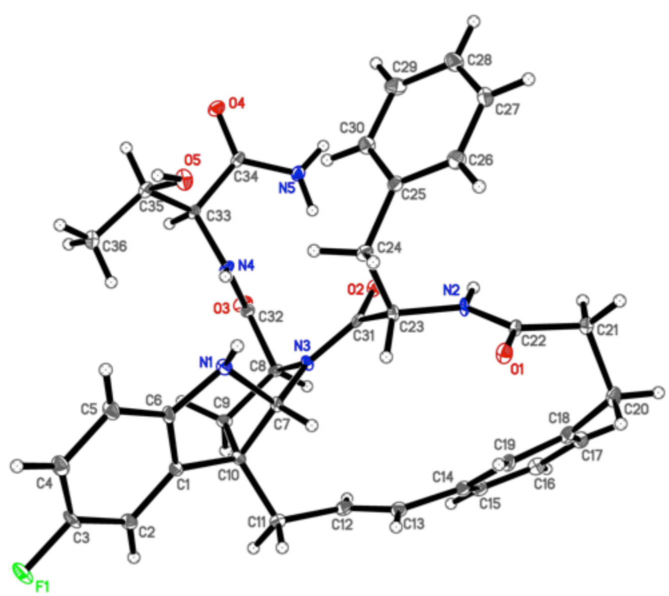
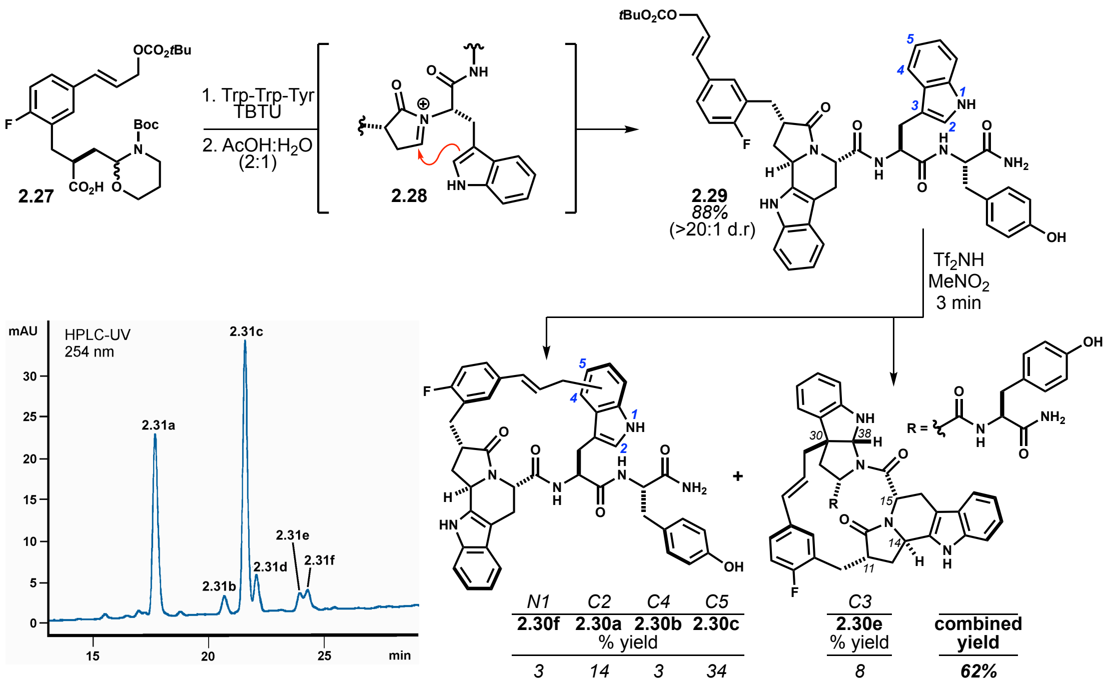


Figure 2.4. Crystal structure of *endo*-pyrroloindoline **2.9d** corroborates prior NOE correlations and NMR-constrained models.

molecule being crystallized and will aid in future endeavors where we need three-dimensional structural information of similar structures.

Internal alkylations using simple template **2.1** form large rings with broad functional group tolerance and procedural ease. Creative opportunity exists to combine macrocyclizations of this type with additional template reactivity to further stabilize the peptide domain by rigidifying product structures. For example, variant **2.28** additionally bears a latent aldehyde designed to

Scheme 2.5. Combining trifunctional template 2.27 with Trp–Trp–Tyr rapidly forms complex polycycles



Initial amidation and Pictet-Spengler cyclization of Trp1 (i.e. **2.29**) followed by acid-promoted cyclization leads to macrocycle isomers **2.31a–f** substituting the periphery of Trp2. Polycycle **2.31e**, results from indole C3 alkylation and cyclization to the *endo*-pyrroloindoline, analogously to related products obtained from template **2.1**. *Note: Peak **2.31d** contained two product isomers that were not identified.

initiate *N*-acyliminium ion cyclizations (e.g. **2.29**, Scheme 5), the results of which depend on the nature of the P1 side chain.[21] Extensive investigations of this reaction by the Meldal laboratory demonstrate flexibility and generally high diastereoselectivity.[22] In direct comparison to template **2.1**, we examined the performance of trifunctional **2.28** using prototypical tryptophan-containing oligomer Trp-Trp-Tyr.[9,22] Acylation of the N-terminus and treatment with aqueous acetic acid promoted diastereoselective Pictet-Spengler cyclization of Trp1 to give intermediate fused tryptoline **2.30** in 88% yield. When treated with Tf_2NH (3 eq.) in $MeNO_2$, this material was cleanly transformed to isomeric products **2.31a–f** resulting exclusively from alkylation of Trp2 with the major product arising from substitution at indole C5, as expected. Alkylation *ortho* to the phenol of tyrosine, anticipated from previous studies of analogous substrate **2.2**, was not oserved.[23] Alkylation of the P1 tryptoline moiety was also not observed, presumably due to strain associated with annulation of this rigid ring system. These results anticipate that templates **2.1** and **2.28** will exhibit subtly different regioselectivity in large ring-forming reactions. That said, we were pleased to find polycyclic pyrroloindoline **2.31e**, despite these differences. This product possesses nine fused rings and a mere five rotatable bonds, whereas Trp-Trp-Tyr itself possesses eleven such bonds. Additionally, **2.31e** bears less polar surface area (161 Å^2) than the starting peptide (181 Å^2), with only non-polar surface area introduced by the template. These alterations tend towards molecular properties advocated for the design of orally bioavailable drugs.[11c,24] Though **2.31e** has not yet been evaluated for biological activity, this outcome exemplifies marked structural alterations that can be quickly achieved. The pharmacological properties of such structures will almost assuredly improve relative to the starting peptide.

2.3 Conclusions

Regiodivergent internal alkylations of tryptophan create macrocycles of varying connectivity in two or three steps from linear peptides. Macrocyclic products bearing embedded *endo*-pyrroloindolines are a valuable facet of this chemistry. The simplicity of the acidolysis method permits even minor constituents to be isolated, screened for function, and characterized with relative ease. In this regard, the general presence of pyrroloindolines and predictability of regiochemical outcomes are more important than the abundance of any one product. For structures of particular interest, convergent target-oriented synthesis is always an option, as we demonstrate. These more step-intensive routes offer scalable access when refined medicinal chemistry is appropriate. Finally, methods combining large ring-formations with additional template-initiated annulation, such as in reactions of **2.28**, hold unique potential to quickly build peptidomimetics of unprecedented structural complexity. Further experiments along these lines are ongoing.

2.4 References

†Chapter 2 has been published in part as: Rose, T. E., Curtin, B. H., Lawson, K. V., Simon, A., Houk, K. N., Harran, P. G., *Chem. Sci.* **2016**, *7*, 4158–4166.

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3 – Using a small molecule template to incrementally remodel biotic peptide structure yields domain-selective, macrocyclic IAP antagonists

3.1 Introduction

The scaffolding in our chemistry has evolved from a core cinnamyl alcohol motif. We have shown how this unit can support large ring forming reactions by exploiting the cinnamyl cation; generated either as a solvated ion pair under acidic conditions or as a metal stabilized complex. The latter allows us to synthesize macrocyclic ethers, amines and lactones while the former permits unique macrocyclizations *via* direct carbon-carbon bonding (*e.g.* **3**, Fig. 3.1A). In neither instance are protecting groups required on the peptide. As our scaffolding has become more functionalized, we are able to sequence additional reactions with macrocyclization. For example, when cinnamyl carbonate containing propionic acid derivative **2** is used to acylate a pyrrolic derivative of Dap-Thr-Tyr, mild acidolysis (aq. AcOH) of the product converts the N-terminus into a pyrrolopiperazine *via* *N*-acyliminium ion cyclization.[1,2] Subsequent exposure to MsOH in $MeNO_2$ initiates internal Friedel-Crafts alkylation to afford a single regioisomeric macrocycle (**4**) in high yield. The secondary alcohol, primary carboxamide, phenol and disubstituted pyrrole are unaffected in the reaction, which occurs within minutes at room temperature.

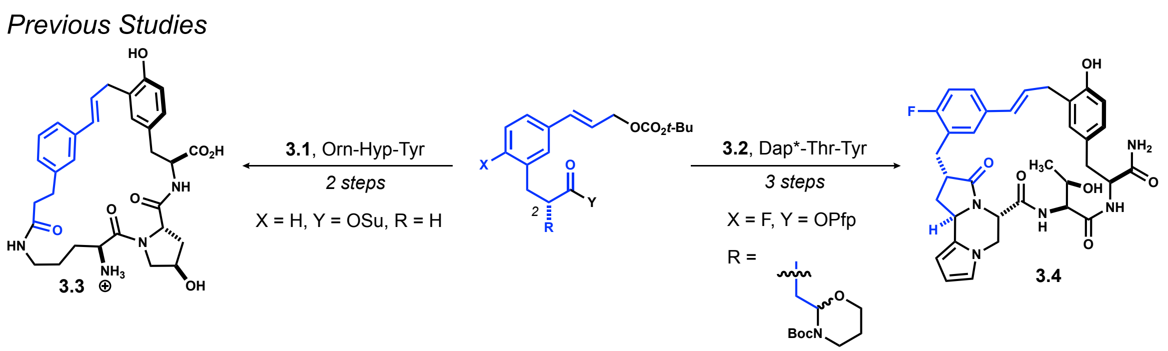


Figure 3.1. Molecular amalgamations made possible by increasingly capable scaffolding reagents. Reagents **3.1** & **3.2** engage unprotected peptides in short processing sequences that generate complex products having defined shapes and altered properties.

Holding **2** constant, myriad variants of this three-step sequence can be executed on a range of functionalized oligomers. The operations are rapid and facile. We are currently generating numerous complex peptidomimetics in this manner. At the same time, our scaffold designs continue to evolve. We felt the methine hydrogen in **2** (namely C2-H) presented another opportunity. By substituting this position, not only would configurational stability at C2 be assured, we could also explore an entirely new series of experiments. If the fourth branch exhibited reactivity orthogonal to the other three, we could ask if initially formed macrocycles could be tagged, transannulated, or multimerized in sequence. The structures generated by such processes would have little precedent and position us to study their

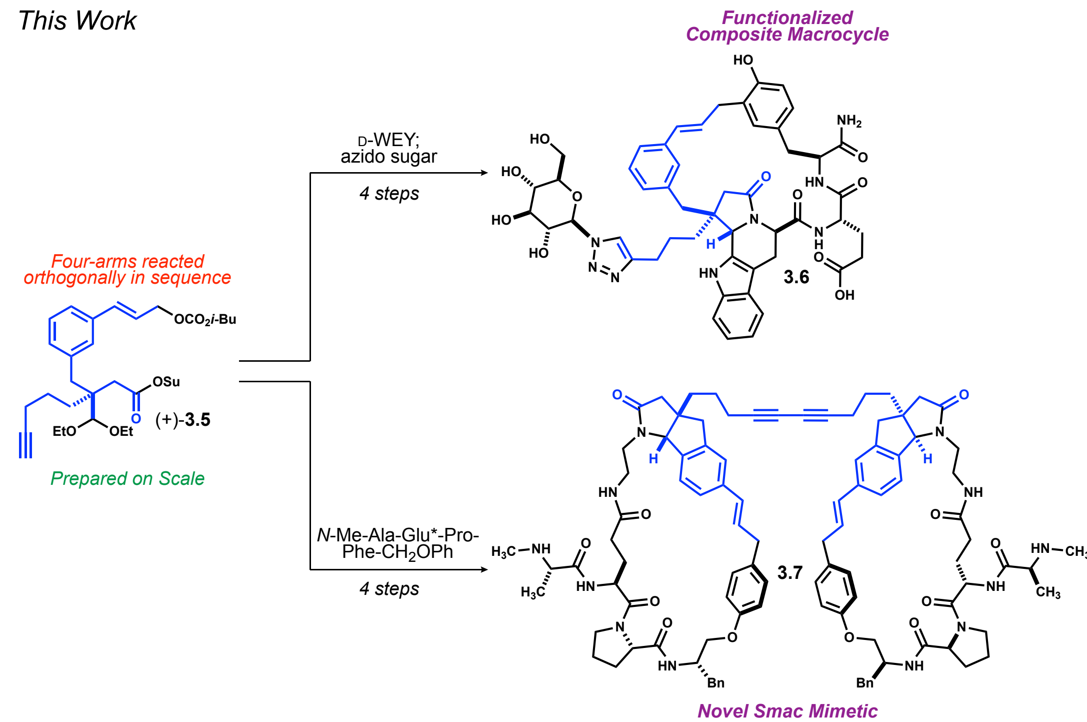


Figure 3.2. New tetra-functional template (+)-**3.5** is capable of remodeling peptide structure to rapidly form composite macrocycles.

properties in detail. Here we describe important steps in this direction.

Based on results from model systems, we chose reagent (+)-**3.5** (Fig. 3.2) as a target. This material retains all capabilities of **2** while adding a normal pentynyl chain at its lone chiral center. The alkyne was anticipated to be inert to macrocyclization and heteroannulation conditions used to react other functional groups in the molecule. It would also provide varied options for manipulating the resultant macrocycles. Before this idea could be tested, however, we faced a difficult synthetic problem. Initially we considered elaborating intermediates used to prepare **3.2**. Because this would have further lengthened a nine-step sequence, it was not attractive. Attention turned instead to *de novo* synthesis of **3.5**. Several tactics to generate this compound seemed plausible; asymmetric conjugate addition of a formyl anion synthon to

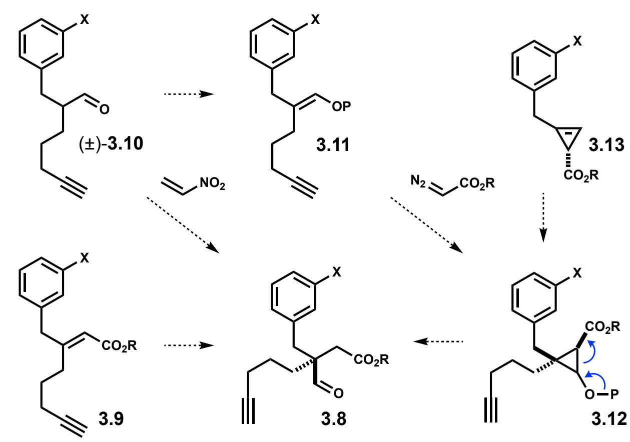


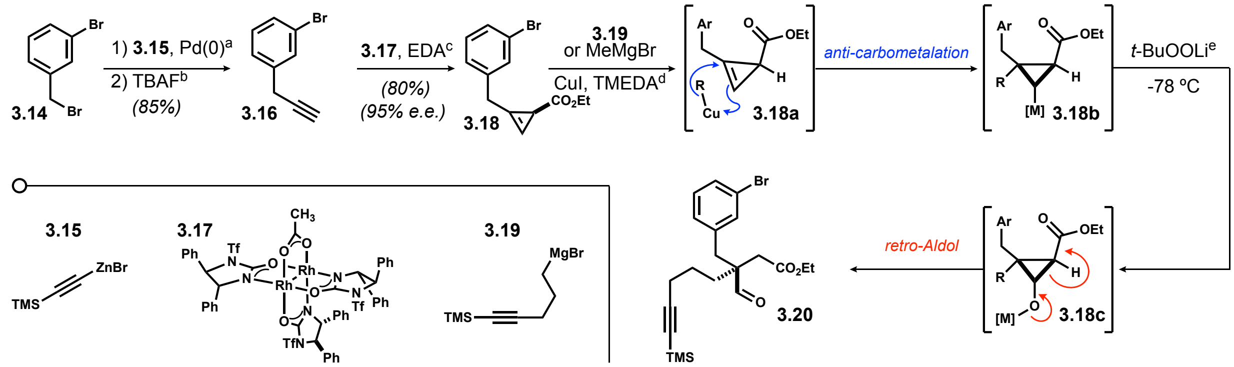
Figure 3.3. Routes contemplated to build a highly functionalized chiral quaternary center.

acrylic esters **3.9** being one of those (Fig. 3.3). Racemic intermediates could be prepared by adding nitromethane to **3.9**, but, in our hands, optically active products were elusive. Fortunately, ideas evolved quickly from **3.9**. Instead of adding a one-carbon nucleophile to **3.9**, we examined reacting a two-carbon electrophile with **3.10**. This involved attempts at catalyzing addition of an enol to nitroethylene.[3] This also proved challenging, but working with aldehyde **3.10** we recognized the enantiotopic faces of its capped enol (**3.11**, P = TBS) might be discriminated *via* asymmetric cyclopropanation.[4] This could generate an intermediate oxygenated cyclopropyl carboxylate (**3.12**), whose fragmentation (as shown) was expected to be facile. At about this same time, Marek *et al.* reported that directed carbometalation of chiral cyclopropenyl carboxylates followed by *in situ* oxidation gave optically active 4-oxobutyrate derivatives directly.[5] These reactions proceeded by way of species analogous to **3.12** and suggested a clear path to enantioenriched (+)-**3.5** beginning with cyclopropene **3.13** and an appropriate organometallic.

3.2 Results and Discussion

m-Bromophenyl propyne was synthesized from commercial 3-bromobenzyl bromide and trimethylsilyl acetylene using a Negishi protocol (Scheme 3.1).[6] We performed a screen of both commercial and synthetic catalysts in the cyclopropenation of **3.16** (Fig. 3.4). Although the commercial paddle-wheel rhodium catalysts screened generally gave high yields, they unfortunately gave low %*e.e.* even at low temperatures. Fortunately, we found that synthetic $Rh_2(OAc)(R,R\text{-DPTI})_3$ (**3.17**) gave good yields and high %*e.e.* at room temperature. We found that cooling the reaction down did not improve %*e.e.* due to

Scheme 3.1. Diastereoselective Carbometalation/Oxidation Sequence Affords Chiral Quaternary Aldehydes

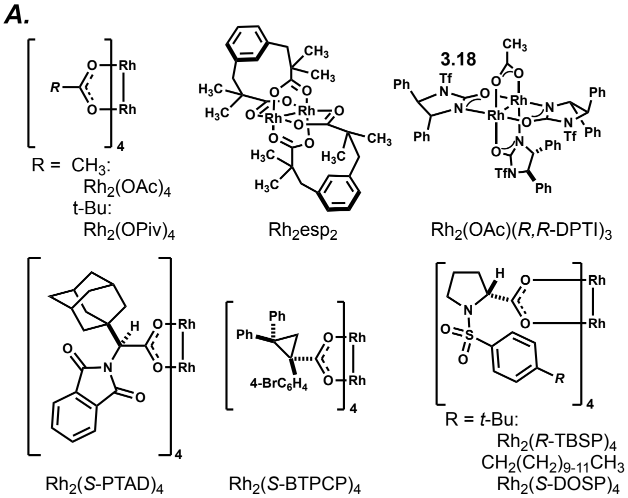


Reaction conditions: a) 0.5 mol% Pd(DPEPhos)Cl_2, 1.4 eq. **3.15**, THF, 22 ºC. b) 2.5 eq. AcOH, 1.5 eq. TBAF, THF, 22 ºC, 85% yield over two steps. c) 3.0 eq. **3.16**, 1 eq. ethyl diazoacetate, 0.25 mol% **3.17**, DCM, 80% yield, 95% *e.e.* d) 2.0 eq. **3.19**, 2.2 eq. TMEDA, 2.2 eq. CuI,; e) then 2.5 eq. *t*BuOOLi; 2:1 NH_4Cl/NH_4OH. EDA = ethyl diazoacetate.

the inability of this particular catalyst to catalyze cyclopropenation at temperatures below 0 ºC. Reaction of propyne **3.16** with ethyl diazoacetate in the presence of Corey's trisimidazolidinone dirhodium complex **3.17** (0.25 mol%, carefully purified according to protocol)[7] afforded cyclopropene carboxylate (+)-**3.18** in 80% yield and 95% *e.e.* as judged by chiral supercritical fluid chromatography. *S* stereochemistry in this material was tentatively assigned by analogy to Corey's precedent, and later corroborated by NMR analyses of diastereomeric derivatives of downstream product (+)-**3.5** (*vide infra*).

With (+)-**3.18** in hand, we next examined copper-mediated carbometalation of its strained alkene. Procedures involving Grignard **3.19** and catalytic amounts of copper salts were not productive in our hands. However, when **3.18** was added slowly to superstoichiometric amounts of **3.19** (freshly prepared,

A.



B.

Catalyst	Loading (mol %)	Temperature (ºC)	Yield[a] (%)	e.e.[b] (%)
$Rh_2(OAc)_4$	0.50	-40 ºC	0	-
$Rh_2(OPiv)_4$	0.50	22 ºC	86	-
Rh_2esp_2	0.50	-40 ºC	85	-
Rh_2esp_2	0.50	22 ºC	85	-
$Rh_2(OAc)DPTI_3$‡	0.50	-40 ºC	30	85
$Rh_2(OAc)DPTI_3$‡	0.50	22 ºC	79	92
$Rh_2(OAc)DPTI_3$†	0.25	22 ºC	80	95
Rh_2(S-PTAD)$_4$	0.50	0 ºC	73	3
Rh_2(S-PTAD)$_4$	0.50	22 ºC	66	0
Rh_2(S-BTPCP)$_4$	0.50	0 ºC	46	0
Rh_2(R-TBSP)$_4$	0.50	0 ºC	80	13
Rh_2(S-DOSP)$_4$	0.50	-78 ºC	0	-
Rh_2(S-DOSP)$_4$	0.50	-40 ºC	30	-10

Figure 3.4. (A) Cyclopropenation catalysts screened. (B) Table of results from cyclopropenation catalyst screen. [a]Isolated yield. [b]Determined by chiral SFC. ‡Purified by column chromatography only. †Purified by column chromatography followed by pTLC.

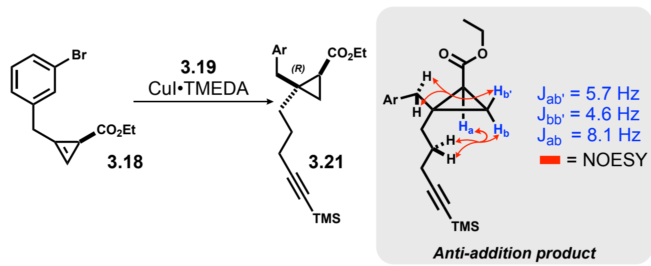


Figure 3.5. NOE correlations in cyclopropane are consistent with carbometalation occurring *anti* to the ester.

1.4 M in THF) and CuI at -40˚C, stirring for 30 min followed by quench with premixed NH_4Cl/NH_4OH cleanly generated cyclopropane **3.21**. Diastereoselectivity appeared high and 2D-NOESY spectra as well as J-couplings of the material were consistent with the major isomer being that drawn (see Fig. 3.5). Sequencing the carbometalation with *in situ* oxidation was more challenging. Among the variety of oxidants examined, only lithium *t*-butyl peroxide proved effective.[5,8]

In optimizing the carbometalation/oxidation sequence, we studied a time-course of the reaction via NMR spectroscopy (Fig. 3.6). By utilizing methylmagnesium bromide in place of **3.19** in the carbometalation, we were able to simplify the ^{1}H-NMR substantively to allow for observation of signal shifts. The time-course was accomplished by removing ~1 mL from the reaction flask and quenching by adding the aliquot to an aqueous 2:1 NH_4OH/NH_4Cl solution. We observed complete carbometalation within 25 min and found that optimal oxidation occurred within 1h. However, we also found that both the carbometalation and oxidation steps were time sensitive: between 30 min and 1h of the carbometalation, we observed baseline decomposition near 2.75 ppm, and between 1h and 1.5 h of the oxidation, we observed a decreased ratio between the aldehyde integration and the aromatic region integration. Furthermore after quenching the system by injecting the above 2:1 solution into the reaction flask at -78 ºC, we observed low amounts of unreacted cyclopropane as well as an unknown by-product that we have tentatively assigned as ethyl maleate, although we are unsure how this is formed. We noted that this by-product was visible in most of both the carbometalation and oxidation time-course NMRs in low amounts; however, its integration was higher after the final quench. We suspected that the difference in quench procedure was the issue. We also rationalized that if we were able to more closely replicate how

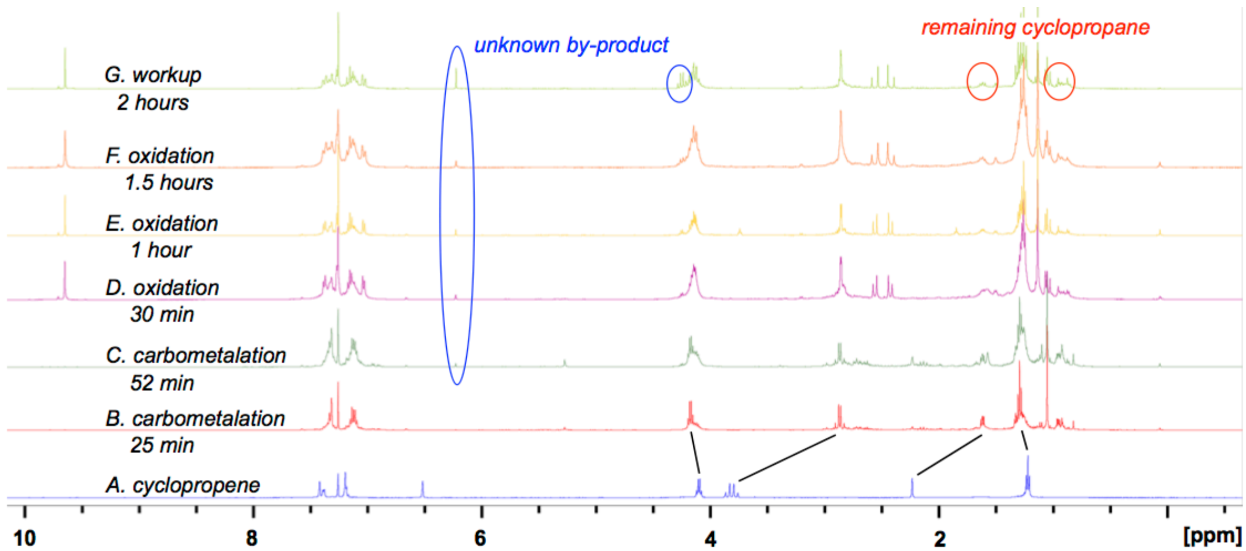


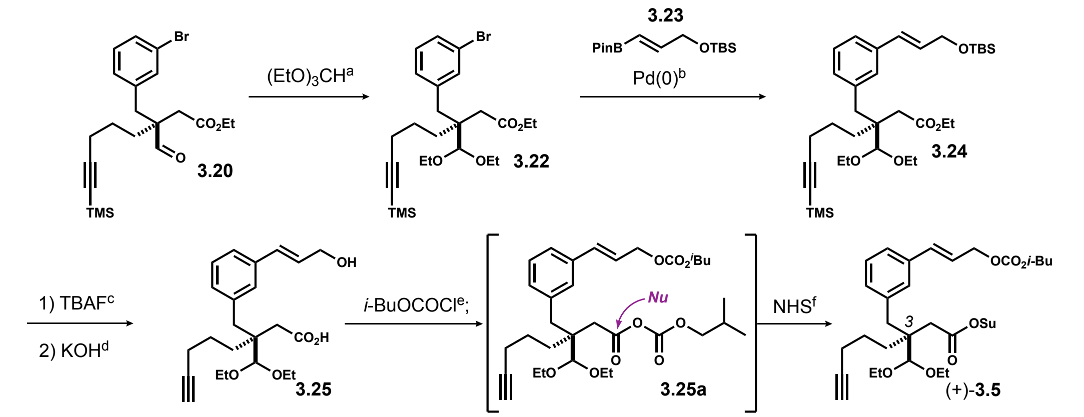
Figure 3.6. NMR time course study of the carbometalation / oxidation of cyclopropene **3.18** using CH_3MgBr. This provided optimized reaction times for both the carbometalation and oxidation steps as well as a suitable quenching protocol to avoid formation of unknown by-products.

we quenched the time-course aliquots then we could mitigate this by-product. Through this study we found both the optimal reaction times and a quenching procedure that alleviates by-product formation.

Using the optimized protocols, we pre-formed an organocopper species prepared from **3.19** and CuI•TMEDA complex and used it to carbometalate (+)-**3.18**. Temperature control while adding **3.19** was important such that organometallic species were largely dissolved at -40 ºC in THF. This was critical for scalability. As observed above, cyclopropene (+)-**3.18** was consumed within 30 min, whereupon the mixture was cooled to -78 ºC and carefully treated with anhydrous *t*-BuOOLi. After 1 hour, the reaction mixture was cannulated out of the reaction flask into a flask containing 2:1 NH_4OH/NH_4Cl, which was initially cooled to 0 ºC. After aqueous workup, aldehyde **3.20** was isolated directly, ostensibly *via in situ* fragmentation of a transient cyclopropanoxide (*i.e.* **3.18c**).

Compound **3.20** was difficult to purify without loss, and therefore crude material was treated with triethylorthoformate in the presence of catalytic TsOH to afford **3.22**. The resultant acetal was cross-coupled with vinyl boronate **3.23** using palladium catalysis to afford stable product **3.24** in 29% overall yield from **3.18**. Desilylation and saponification then afforded hydroxy acid **3.25**. Because of synthetic necessities to access to form both a cinnamyl carbonate and an activated ester, we had to find conditions that would furnish these groups in a facile and scalable fashion. Selective carbonylation of the cinnamyl

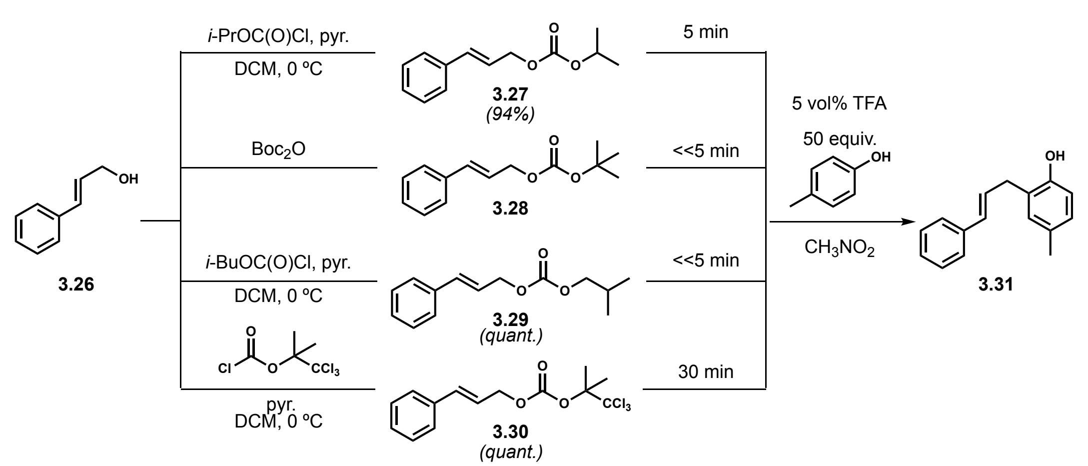
Scheme 3.2. Completion of Template (+)-3.5



Reaction Conditions: a) 10 mol% *p*TSA, 10 eq. $(EtO)_3CH$, EtOH. b) 1 mol% $Pd(PPh_3)_4$, 1.5 eq. **3.23**, 3.0 eq. Na_2CO_3, 5:1 dioxane/H_2O, reflux, 29% yield over three steps. c) 2.5 eq. TBAF, THF, 0 ºC. d) 10 eq. KOH, 2:1 EtOH/H_2O, 50 ºC. e) 2.5 eq. *N*-methylmorpholine, 2.5 eq. *i*BuOCOCl, DCM, -5 ºC; f) 2.5 eq. *N*-hydroxysuccinimide, -5 ºC to 22 ºC, 12h, 52% over three steps, 94% *e.e.* NHS = *N*-hydroxysuccinimide.

alcohol proved to be difficult, but we hypothesized that we could form a bis-carbonylated species to give an activated acyl carbonate, which could then be used for peptide acylation. However, reactions with (*t*-BuOC)$_2$O were capricious and *t*-BuOCOCl is unstable and explosive, therefore we looked at alternative sources of carbonate, which could be prepared with commercial reagents and be competent in macrocyclization reactions. We first examined reactivity of in model systems (Scheme 3.3). After synthesizing carbonates **3.27-3.30** from cinnamyl alcohol (**3.26**), we qualitatively examed at their Friedel-Crafts reaction rates with *p*-cresol in 5 vol% TFA in 5 mM CH_3NO_2. Following each reaction by HPLC-MS revealed that Friedel-Crafts of both **3.28** & **3.29** were complete within 5 minutes, while *i*-propyl carbonate **3.27** was 95% complete in the same timeframe (observed by UV-254 nm). Interestingly,

Scheme 3.3. Relative reaction rates for varied cinnamyl carbonates in an intermolecular Friedel-Crafts reaction



carbonate **3.30** required 30 minutes for complete consumption of starting material. Extended exposure of the above reactions to the acidic reaction conditions did not affect UV-254 nm peak area.

After finding that *i*-butyl carbonate was as competent as *t*-butyl carbonate in the model system, hydroxy acid **3.25** was reacted with excess *iso*-butyl chloroformate. The doubly acylated species formed *in situ* was partially decomposed with *N*-hydroxysuccinimide to afford target (+)-**3.5** in 52% isolated yield. This concise route to (+)-**3.5** gave access to our first four-armed scaffolding reagent on multi-gram scales.

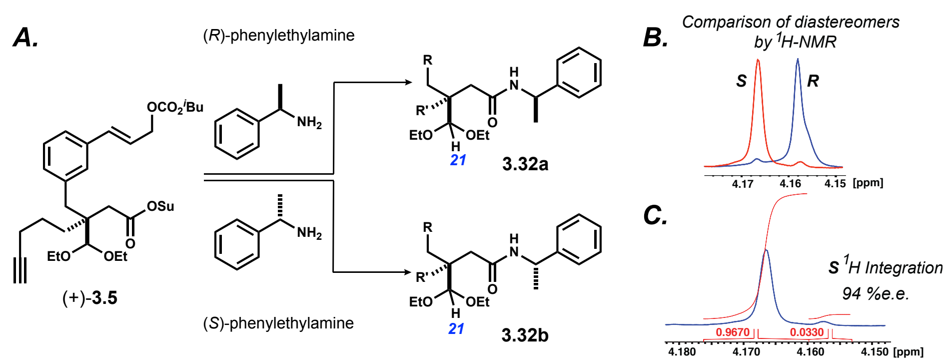
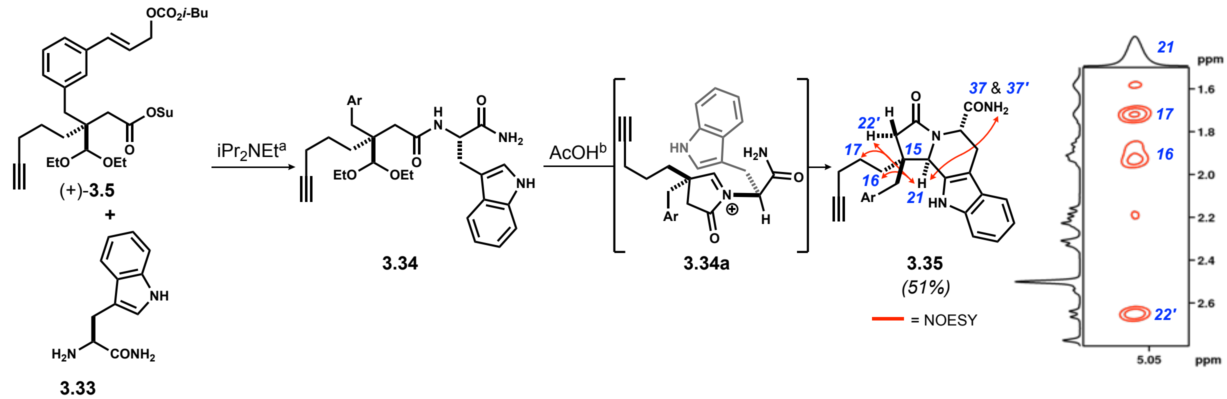


Figure 3.7. Analysis of diastereomeric derivatives of template (+)-**3.5** provided an enantiomeric excess. (A) Template was reacted with either enantiomer of phenylethylamine. (B) Overlay of ^{1}H-NMR spectra of **3.32a** (*R*) and **3.32b** (*S*) zoomed in on methine *H21*. The major diastereomer of **3.32b** corresponds to the minor diastereomer of **3.32a** and vice versa. (C) Integration of *H21* diastereomers in **3.32b** provided an enantiomeric excess of (+)-**3.5**.

Before exploring its utility, we further probed stereochemistry in (+)-**3.5**, whose enantiomeric excess was determined through a diastereomeric derivatization with both enantiomers of phenylethylamine (Fig. 3.7). Each acylation reaction gave two diastereomers, and, by reacting the (+)-**3.5** with both enantiomers, we formed four diastereomers and the minor diastereomer of **3.32a**/**b** should have the same NMR shifts as the major diastereomer in the opposing reaction. We confirmed that the major diastereomeric shifts were indeed distinct from one another while the major/minor enantiomeric shifts matched (Fig. 3.7B). The integration of *H21* in the **3.32b** diastereomeric mixture gave an enantiomeric excess of 94% for template (+)-**3.5** (Fig. 3.7C). We next turned our attention to corroborating the shown absolute stereochemistry of (+)-**3.5** using through-space NOE correlations from a known stereocenter. The template molecule was reacted with L-tryptophan carboxamide to give **3.34** (Scheme 3.4). When that substance was dissolved in 80% aqueous AcOH, its acetal quickly (<1 hr) decomposed to a mixture of diastereomeric hydroxy lactams. These gradually converted to pyrrolo-β-carboline **3.35** (*via* **3.34a**) over the next 12 hours. A

Scheme 3.4. Corroboration of Absolute Stereochemisry of (+)-3.5

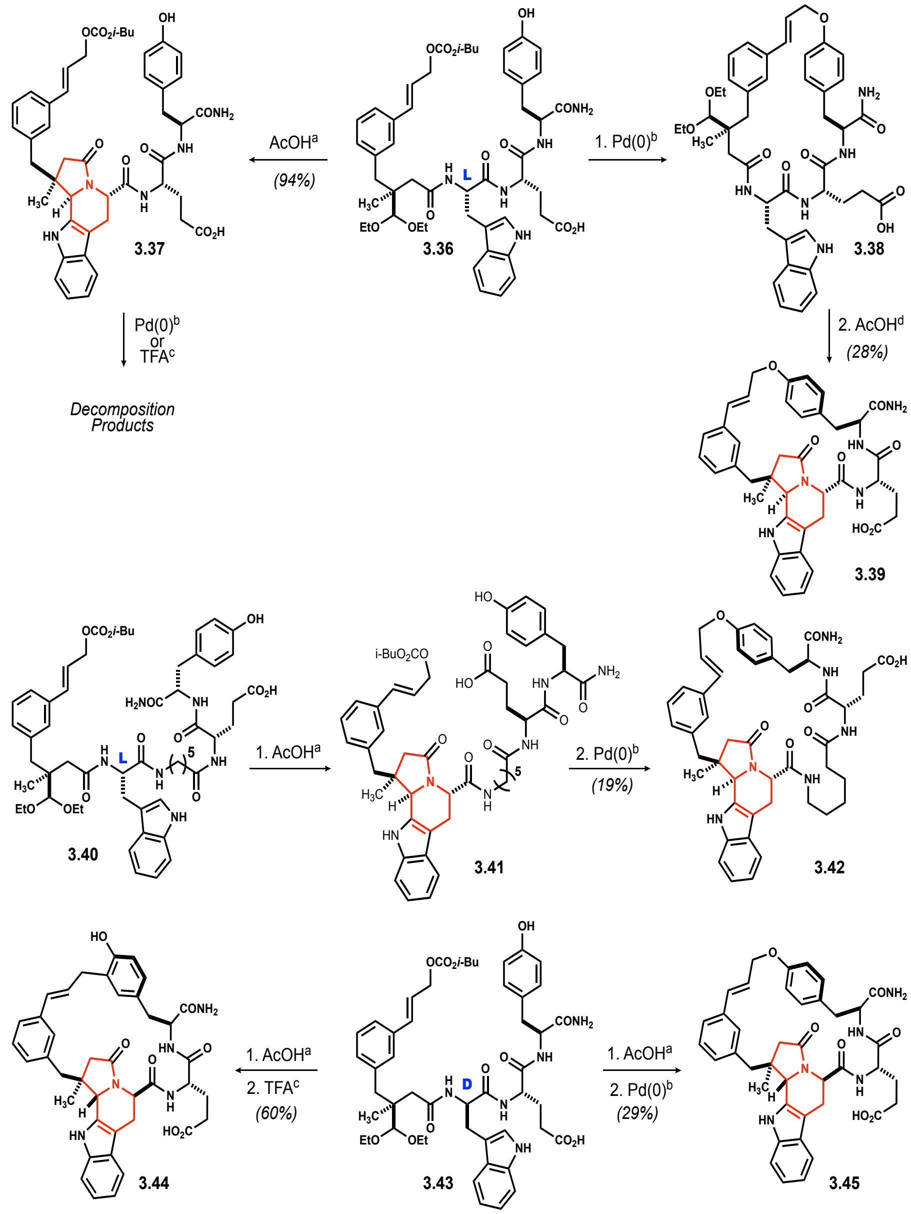


Reaction conditions: a) 1.0 eq. (+)-**3.5**, 1.5 eq. **3.33**, *i*Pr_2NEt, DMF. b) 4:1 $AcOH/H_2O$, 22 ºC, 12 h, 51% yield over two steps. Inset: partial 2-D NOESY spectrum of **3.35** showing key correlations involving *H21*.

single isomer of **3.35** was observed by ^{1}H-NMR and HPLC. Its 2D-NOESY spectrum showed clear correlations between the carboxamide protons *H37*,*37'* and the *C21* methine hydrogen, which in turn correlated with methylene signals *H16* and *H17*. Literature precedent and our own studies indicated the configuration at *C35* would dictate stereochemistry at C21.[1,2,9,10] If true, the relative stereochemical relationships implied from NOE correlations would translate to (+)-**3.5** being *S*-configured, which was further consistent with the earlier assignment of stereochemistry in **3.18** made by analogy to Corey's results.

Initial macrocyclizations with this new scaffold were tested in the absence of the alkyne. An analog of (+)-**3.5** was prepared wherein the C3 pentynyl group was replaced by methyl (by substituting CH_3MgBr for **3.19** in Scheme 1, see Appendix Fig. 3.A1). Acylating Trp-Glu-Tyr with this molecule gave **3.36**. Exposure of **3.36** to aqueous acetic acid gave Pictet-Spengler product **3.37** in high yield (Scheme 3.5). Interestingly, all attempts to macrocyclize this molecule by activating the cinnamyl carbonate under conditions developed previously led to decomposition.[11,12,1] Reversing the order of events solved this problem. Treatment of **3.36** with 5 mol% $Pd(PPh_3)_4$ in DMF at room temperature initiated a high yielding cycloetherification. When that product was dissolved in aqueous acetic acid, it slowly converted to polycycle **3.38** (90% conversion after 4 days at 25 ºC). Following preparative HPLC, analytically pure β-carboline **3.38** was isolated in 28% yield (three steps from (+)-**3.S4**). The 2D-NOESY spectrum showed correlations very similar to those observed in **3.35** (Scheme 3.4) and stereochemistry in **30** was thus

Scheme 3.5. Probing Initial Macrocyclizations with a Three-Armed Model



Reaction conditions: a) 4:1 AcOH/H_2O, 22 ºC, 12 hours. b) 2.0 eq. Cs_2CO_3, 5 mol% $Pd(PPh_3)_4$, DMSO, 10 mM, 4 hours. c) 5 vol% TFA, CH_3NO_2, 5 mM, 2 hours. d) 4:1 AcOH/H_2O, 22 ºC, 4 days. Note: yields quoted throughout reflect analytically pure material isolated (prep-HPLC or SiO_2 chromatography) after full sequence beginning with template.

assigned similarly. A possible explanation for the reluctance of **3.37** to participate in macrocyclization reactions was the conformational restriction imposed by the Pictet-Spengler process. It oriented the *C17* and *C11* β branches *anti* off of a rigid tetrahydroindolizinone core. The effect was marked. Substrate **3.40** was synthesized. It harbored the same residues as **3.36**, but wherein an aminohexanoic acid spacer was inserted in between P1 and P2. Treatment with aqueous acetic acid smoothly initiated a Pictet-Spengler cyclization, but the system remained reluctant to macrocyclize. Only palladium-catalyzed cycloetherification was successful, and in that case product **3.42** was relatively unstable, presumably due to torsional strain present in the macrocycle. Attenuating this strain had a positive impact. Substrate **3.43** was synthesized. This molecule was the same as **3.36** except the tryptophan residue was D-configured. Acetic acid promoted Pictet-Spengler reaction within this molecule occurred cleanly and subsequent macrocyclizations were now facile. Treatment with either TFA in CH_3NO_2 or 5 mol% $Pd(PPh_3)_4$ in DMF gave regioisomeric macrocycles **3.44** and **3.45** in 60% and 29% yield, respectively. Efficient macrocyclization *via* either internal Friedel-Crafts alkylation or Tsuji-Trost cinnamylation was consistent with earlier studies (*e.g.* Fig 3.1A) and reflective of the relative stereochemistry in the Pictet Spengler product now positioning reactive termini *syn*, thereby favoring ring closures. The use of a D-configured P1 residue in conjunction with (+)-**3.5** to permit syntheses of unique structures such as **3.44** and **3.45** was an excellent outcome. It should be noted, however, the same result could in principle be achieved using all L-configured amino acids and the enantiomer of (+)-**3.5**.

Having established the new scaffold frame supported macrocyclizations, we turned to (+)-**3.5** and experiments to test the inertness of its alkyne to both palladium catalysis and acidolysis conditions used for large ring formations (Fig. 3.8). Acylation of D-Trp-Glu-Tyr with (+)-**3.5** and subsequent treatment with aqueous acetic acid followed by TFA in CH_3NO_2 (5 vol %) gave macrocycle **3.46** in 31% isolated yield over three steps. NOE correlations in **3.46** paralleled those observed in **3.35** and **3.44** and were fully consistent with the relative stereochemistry drawn. As we hoped, no products derived from reactions at the alkyne were detected, nor did the carboxylic acid or primary carboxamide interfere. The same three-step sequence beginning with (+)-**3.5** was repeated with D-Trp-Gln-Tyr, Pro-Ala-Lys(D-Trp)-Tyr, and D-Trp-Glu(tyramide) to yield macrocycles **3.47–3.49** in good per step average yields over three steps. We next prepared the *O*-linked regioisomer of **3.49** (namely **3.50**) by changing the third step in the processing sequence. Instead of treating with TFA in $MeNO_2$, the Pictet-Spengler product was exposed to 4 mol% allyl palladium chloride dimer, 10 mol% Xantphos, and superstoichiometric Cs_2CO_3 in DMF.[12] The alkyne was again unaffected. The dipeptide D-Trp-AAP* having its C-terminus condensed with tyramine

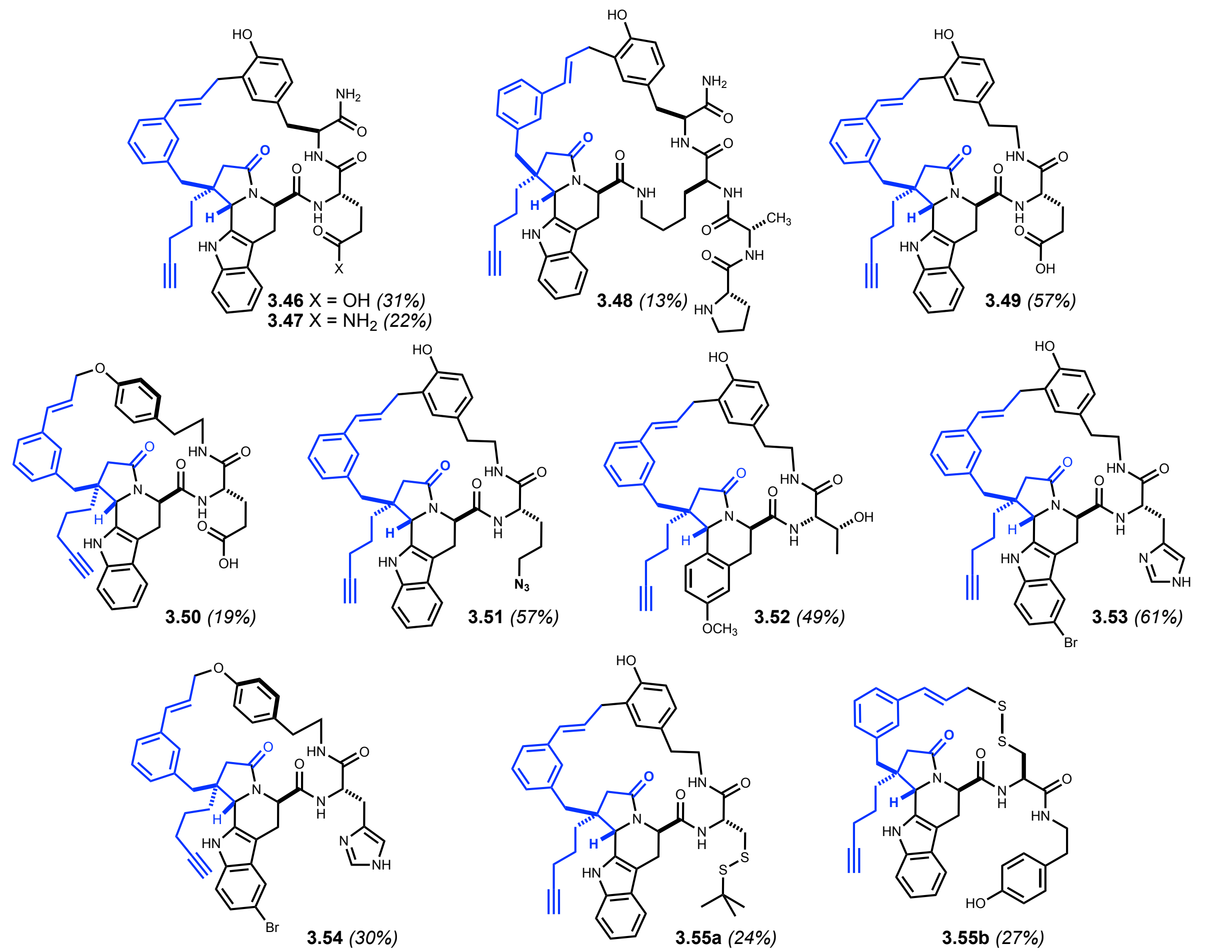


Figure 3.8. Macrocyclic products obtained by acylation of unprotected peptides with (+)-**3.5**, followed by *N*-acyliminium ion cyclization, and either acid-mediated Friedel-Crafts alkylation or palladium-catalyzed macrocycloetherification. Note: for yield calculations see Scheme 3.

was readily processed with (+)-**3.5** to afford polycycle **3.51**. Both the alkyne and the primary azide were unaffected, opening the possibility for transannulations *via* Huisgen cycloadditions should that be desired in future iterations.

Each stage of engagement with (+)-**3.5** was designed to be flexible. Consistent with Meldal's results, the *N*-acyl iminium ion intermediates would react with a range of proximal π-basic aromatics.[1,2,9] For example, when D-3-MeOPhe-Thr(tyramide) was *N*-acylated with (+)-**3.5** and treated with aqueous acetic acid, two isomeric products (1:1) were formed. They were tentatively assigned as epimeric dihydro pyrroloimidazole diones, although alternative structures could not be ruled out.[10] When those materials were treated with 5 vol % TFA in CH_3NO_2, Pictet-Spengler reaction and Friedel-Crafts macrocyclization occurred concomitantly to afford a single macrocyclization product (**3.52**) in good overall yield. Neither the alkyne nor the secondary alcohol were affected. In the case of D-Trp(5Br)-His(tyramide), its reaction with (+)-**3.5** gave a product that resisted Pictet-Spengler reaction in aqueous AcOH. However, addition of 10 vol % H_3PO_4 caused rapid cyclization. Notably, without degrading the cinnamyl carbonate. The product was then converted to macrocycle **3.53** by exposure to TFA in $MeNO_2$. Alternatively, palladium-catalyzed cycloetherifcation afforded macrocyclic cinnamyl ether **3.54**. The alkyne and the unprotected imidazole ring were unaffected by either process.

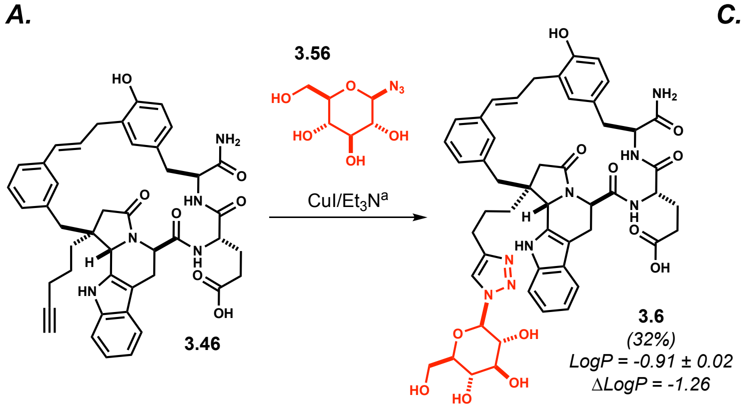
Lastly, in the course of these studies, we discovered what we believe is a unique macrocyclization process. When D-Trp-Cys(S*t*-Bu)(tyramide) was *N*-acylated with (+)-**3.5** and the product was dissolved in aq. AcOH, a Pictet-Spengler reaction occurred uneventfully. However, when that molecule was treated with TFA in $MeNO_2$, two products (~1:1) formed in good yield. One was the internal Friedel-Crafts alkylation product **3.55a**, as expected. The second lacked a *tert*-butyl group and its spectroscopic data were consistent with allylic disulfide containing macrocycle **3.55b**. This outcome was interpreted in terms of a solvated cinnamyl cation being captured by the distal sulfur of the disulfide and the incipient sulfonium ion extruding isobutylene. Macrocyclic allylic disulfides of this type may be manipulated in a host of ways by partial oxygenation reactions and/or sigmatropic rearrangements of derived ylides. Towards this end, experiments to test the generality and efficiency of the macrocyclization reaction, both in the presence and absence of competing internal nucleophiles are ongoing.

In all processing sequences using (+)-**3.5** to date, the alkyne has been inert to chemistries used to synthesize macrocycles having imbedded condensed heterocycles. For the eleven structures depicted in Figure 3, and more, it was possible to integrate (+)-**3.5** into unprotected peptides using simple, telescoped three-step sequences followed by mass-guided preparative HPLC. Pure products were routinely isolated on tens of milligrams scales without incident.

While inert enough to be valuable in our schemes, the alkyne was certainly a handle for further manipulations. Many natural products are glycosylated and this feature can markedly alter solubility and transport properties, relative to the aglycon, in biological systems. Viewing our composite macrocycles as analogous to non-ribosomal peptides, a ready means to add sugars to these compounds was desirable (Fig.

3.9). The alkyne made this trivial. For example, mixing polycycle **3.46** with commercial 1-azido-1-deoxy-β-D-glucopyranoside in the presence of catalytic copper iodide and triethylamine proceeded well to give unique glycoconjugate **3.6** (Fig. 3.9A). Several additional examples of this Huisgen cycloaddition were readily prepared in milligram quantities (**3.57-3.61**, Fig. 3.9B). We found this approach could be generally applied even in the presence of ligating peptide side chains such as carboxylates and imidazole, although the latter did result in lower yield. We have begun to examine passive membrane permeability in

A.



C.

Compound Caco-2 cell permeability Papp value (Unit: 10e-6 cm/s)			
	Caco-2 cell		*Efflux ratio*
	Papp A-->B	Papp B-->A	
Propanolol	32.49	32.49	1.00
Nadolol	0.12	0.58	5.00
Qunidine	13.35	33.38	2.50
Cimetidine	0.34	2.54	7.50
3.46	0.00	0.47	–
3.6	1.09	0.07	0.06
3.47	0.00	0.22	–
3.58	0.00	0.03	–
3.49	0.00	1.44	–
3.59	0.02	0.03	1.43
3.50	0.00	0.70	–
3.60	0.00	0.07	–
3.52	0.57	4.77	8.33
3.62	0.04	0.09	2.50

B.

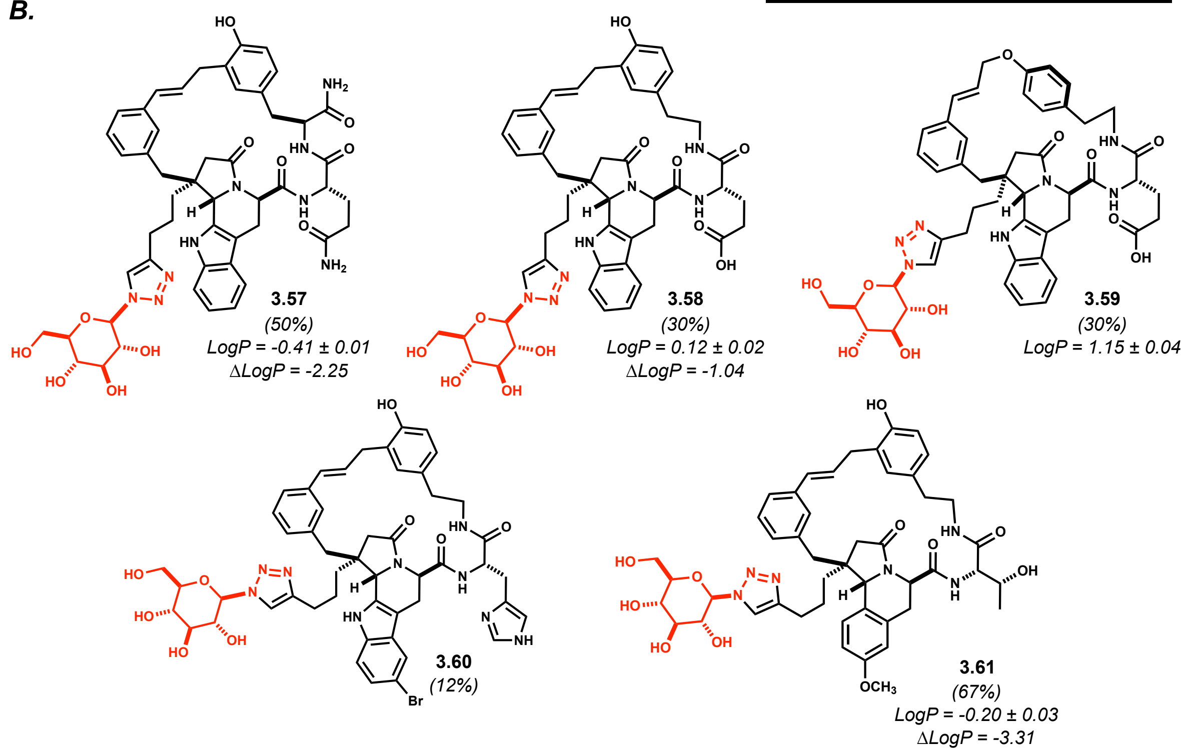


Figure 3.9. (A) Glycosylation of macrocycles affords functionalized, natural product-like compounds in four steps. Reaction conditions: a) 1.5 eq. azido sugar, 2.5 eq. Et_3N, 10 mol% CuI, DMF, 22 ºC. (B) Glycosylated products prepared with both yield, LogP, and change in LogP from aglycone, where applicable. (C) Caco-2 cell permeability screens revealed that highly polar composite macrocycle **3.6** was the most permeable compound tested.

this series. Conventional wisdom suggests molecules of this type will have difficulty entering cells. We are interested in understanding this behavior deeply enough that we might eventually use our templates to facilitate permeability where it would otherwise not exist. In one of our first Caco-2 monolayer screens, compound **3.6** stood out as a substance displaying some passive permeability (Fig. 3.9C). While it is minimal relative to positive controls, the fact we observed any permeability for a molecule having as much exposed polar surface area as **3.6** is striking. The remainder of the set has fairly unremarkable permeability coefficients. However, through collaborations we hope to explore structure / permeability relationships of peptidomimetic macrocycles in detail. Alkyne functionalizations will greatly aid these studies, and we note that the triple bond may also be used for conjugation to cell penetrating peptides and serve as a linker site for assembly of antibody and/or protein drug conjugates.

A major goal for this program is to allow biologically active peptides to be molded directly into potent and stable lead structures for further research. To demonstrate the potential of (+)-**3.5** in this context, we began with a familiar system. The second mitochondria derived activator of caspase (Smac) is a homodimeric protein secreted from mitochondria during programmed cell death.[13] Cytoplasmic Smac relieves inhibitor-of-apoptosis protein (IAP) mediated suppression of caspase activity. It binds avidly to X-chromosome encoded IAP, cellular IAP1 and cellular IAP2, and synergizes with both TRAIL and TNFα to potently induce caspase activation and apoptosis in human cancer cells.[13] Smac exploits a conserved tetrapeptide (AVPI) at its N-terminus to bind BIR domains within IAPs.[14] We had used traditional medicinal chemistry techniques earlier to develop a bivalent small molecule mimic of Smac.[15] That exercise went on to drive much research as well as clinical development programs.[16,17] However, it required several years of experiments. We were interested if the use of (+)-**3.5** might be able to generate Smac mimetic leads more quickly.

In terms of caspase inhibition, it was known from *in vitro* peptide screens that the P2 position of AVPI was tolerant of side chain variations, and that an aromatic residue was preferred at P4.[15,18–20] We therefore prepared peptide **3.62**, wherein the P1 and P3 positions were unaltered. The P2 position was occupied by a glutamic acid derivative that provided both an attachment point for (+)-**3.5** and means to generate an *N*-

acyliminium ion from the composite. Lastly, *O*-phenyl-L-phenylalaninol was placed at P4 such that it could participate in alkylative macrocyclizations while also displaying an aromatic side chain.

Treatment of **3.62** with (+)-**3.5** gave **3.63** in 71% yield and without competitive acylation of the N-terminus. Hydrolysis in aqueous acetic acid then generated hydroxy lactam intermediates. These species

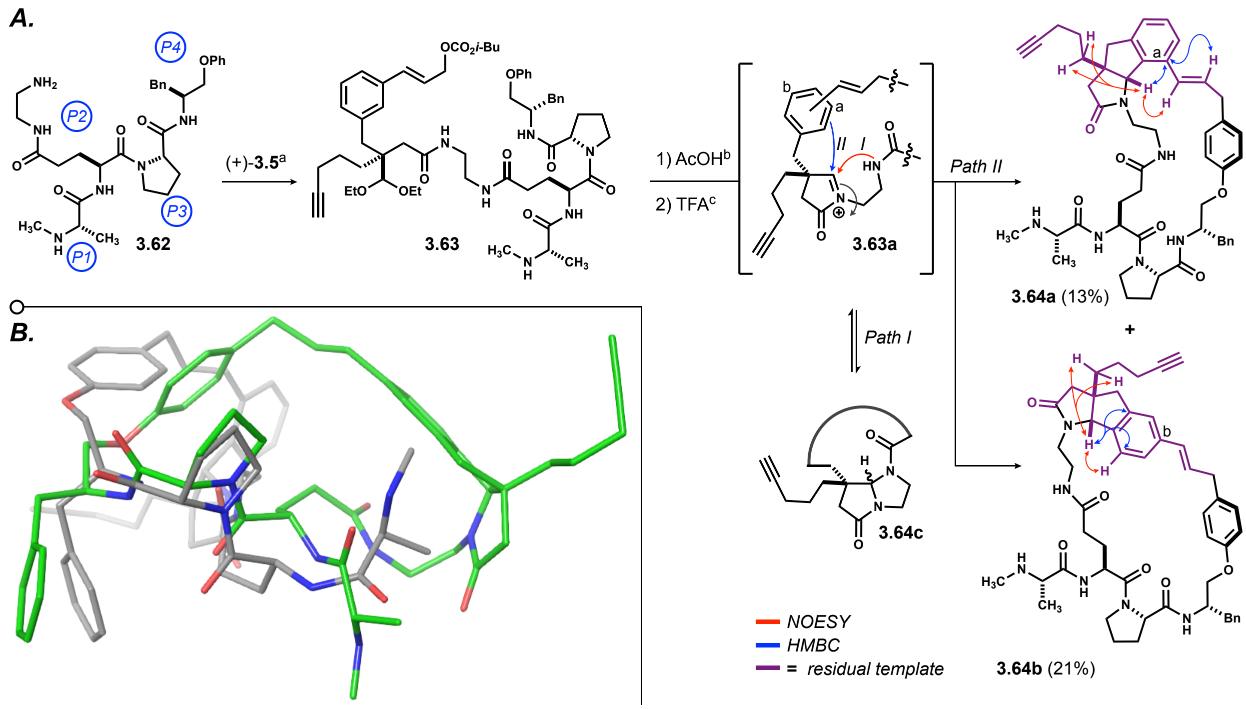


Figure 3.10. (A) Synthesis of macrocyclic Smac mimetic monomers. Reaction conditions: a) 1.0 eq. (+)-**3.5**, 1.5 eq. **3.62**, iPr$_2$NEt, DMF. b) 4:1 AcOH/H$_2$O, 22 ºC, 12 h. c) 1:1 TFA/TFE, 5 mM in substrate, 22 ºC, 7h, 13% yield (**3.64a**) and 21% yield (**3.64b**). (B) Overlay of energy-minimized (*B3LYP-D3*) conformers of **3.64a** (gray) & **3.64b** (green), which orient their peptidyl segments differently within the composite structures.

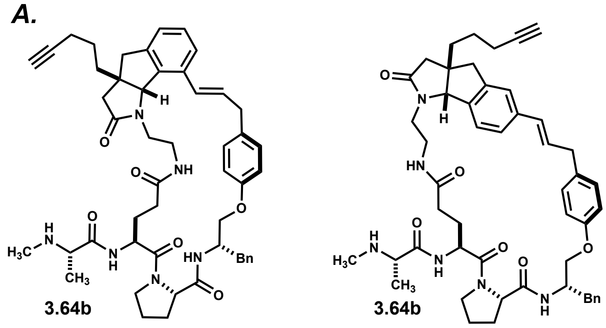
were concentrated to dryness, re-dissolved in trifluoroethanol and treated with TFA (1:1 final, 5 mM in substrate) at 25 ºC. This promoted an *N*-acyliminium ion cyclization and concomitant macrocyclization. The original expectation was that ion **3.64a** (Fig. 3.10) would be trapped by the adjacent amide to form a diacyl imidazolidine (*e.g.* **3.64c**). However, extensive NMR analyses (including HMBC and NOESY spectra) of the two isolated products showed them to be regioisomeric tetrahydroindenopyrrolones **3.64a** and **3.64b**. Similar to logic invoked for **3.52** (*vide supra*), this outcome was rationalized in terms of a transient diacyl imidazolidine (**3.64c**) giving way to more stable C-C bonded products *via* internal Friedel-Crafts alkylation. The closest aromatic ring to ion **3.63a** was that of the scaffold, and therefore

33.64a/b were formed. To our knowledge, these macrocycles are without precedent. Moreover, from (+)-**3.5**, they were prepared and purified in less than 48 hours.

We were now positioned to study how subtle differences in ring connectivity might affect IAP binding and domain selectivity. *In silico* geometry optimization and conformational searches suggested that **3.64a** and **b** would display their peptide regions differently (Fig. 3.10B), although the relevance of this analysis to bound states was as yet unclear. Despite structural homology, slight differences in BIR domain structures within IAPs have been leveraged to design cIAP-selective antagonists.[21,22] Because XIAP, cIAP1, and cIAP2 function independently, and differently, to block apoptosis, selective antagonists have been coveted as research tools.

Smac protein exists as a native dimer and, in the case of XIAP, binds simultaneously to adjacent BIR domains within its structure. We had exploited this previously by dimerizing monomeric BIR3 domain

A.



B.

Compound	XIAP	IC50 (nM) cIAP1	cIAP2	cIAP1/XIAP
Peptide **3.62**	>5000	383 ± 165	2888 ± 393	>13:1
Monomer **3.64a**	>5000	261 ± 51	763 ± 226	>19:1
Dimer **3.65**	>5000	472 ± 217	717 ± 347	>11:1
*Monomer **3.64b***	*>5000*	20 ± 12	60 ± 28	*>250:1*
*Dimer **3.7***	1335 ± 1436	21 ± 5	42 ± 18	*65:1*
Birinapant	289 ± 12	28 ± 4	55 ± 11	10:1

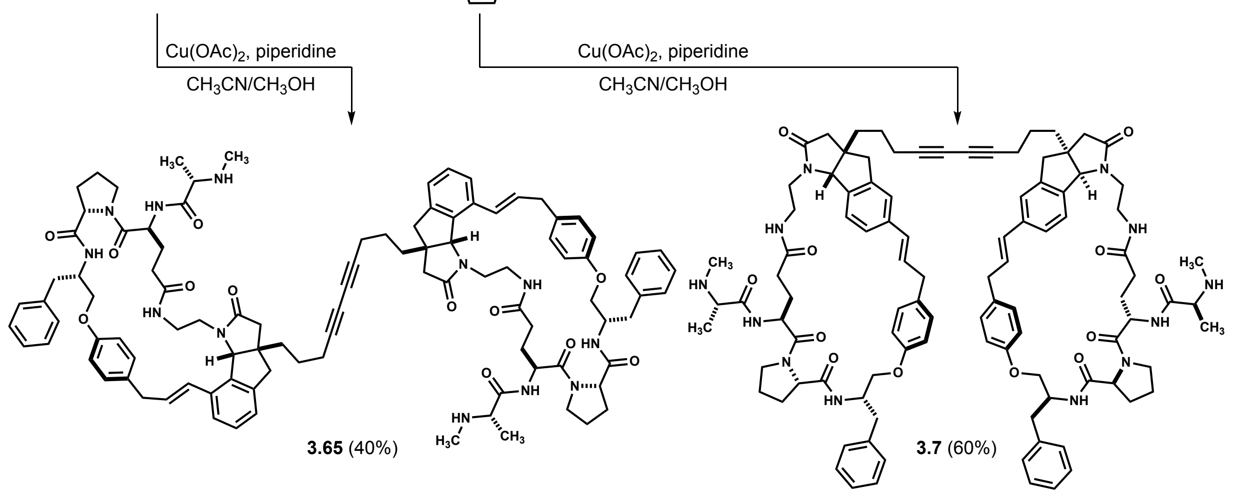


Figure 3.11. (A) Dimerization of macrocyclic monomers. Reaction Conditions: a) 1.0 eq. **3.65a** or **3.65b**, 7.0 eq. $Cu(OAc)_2$, 7.0 eq. piperidine, 1:1 $MeOH/CH_3CN$, 40% yield (**3.66**) or 60% yield (**3.7**). (B) Fluorescence polarization assay for competitive displacement of a labeled bivalent Smac-mimetic peptide from recombinant Bir2-Bir3 constructs of indicated IAP protein. Data is reported as IC_{50} values (average of 2 technical replicates).

ligands, thereby achieving exceptional Smac mimicry.[15] Anticipating similar behavior, we oxidatively dimerized **3.64a** and **3.64b** *via* Glaser coupling. This involved treating their free-base forms with $Cu(OAc)_2$ and piperidine in 1:1 CH_3CN/MeOH at 70 ºC (Fig. 3.11A). Symmetric diynes **3.65** and **3.7** were isolated in 40% and 60% yields, respectively. Avidities for recombinant XIAP, cIAP1, and cIAP2 (BIR2-BIR3 domain constructs) were then evaluated by competitive binding using a fluorescence polarization (FP) assay (Fig. 3.11B). The same fluorescein labeled dimeric Smac peptide FP probe was employed in all experiments (see SI Fig. 3.A3). Tetralogic's clinical compound Birinapant™ was used as a positive control.[23] Linear peptide **3.62** weakly displaced the FP probe from all three IAP constructs, although it did discriminate cIAP1 from cIAP2. Macrocyclic monomer **3.64a** was comparable to its precursor **3.62**, but macrocycle **3.64b** was not. As expected for a monomer,[24] it remained a poor competitor for XIAP, but it displaced the FP probe from cIAPs with low nanomolar efficacy. In fact, it was 13 times more effective than **3.64a** against cIAP1 and nearly 50-fold more efficacious against cIAP2. This highlights a phenomena we did not fully appreciate, yet one that may be general for molecules of this type. Namely, that subtle variations in macrocycle topology and pharmacophore display can markedly alter performance. Macrocyclic monomer **3.64b** also showed excellent cIAP1:XIAP selectivity (>250:1). The ability of dimeric compounds **3.65** & **3.7** to compete for cIAP1/2 binding was similar to their respective monomers, a finding consistent with the 1:2 binding stoichiometry of Smac protein to these particular IAPs. Dimer **3.7**, on the other hand, was the only compound to show competitive binding to XIAP, while remaining able to potently displace the FP probe from cIAPs, especially cIAP1. The data above reflects competition IC_{50} values rather than direct binding constants although, for comparison, Birinipant is reported to bind to full length XIAP and cIAP1 with K_D = 45 nM and <1 nM, respectively.[23]

The apparent discrimination of **3.65** and **3.7** for cIAP1 over XIAP was fascinating and, along lines argued by others, may derive from minor variations in the P4 binding pockets on BIR domains within these proteins.[21,22] To probe this further we employed computational techniques. We studied the molecular dynamics (MD) of **3.64a**/**b** docked into the binding site of cIAP1 as well as XIAP. We found that **3.64b** buried 50 $Å^2$ more surface area compared to **3.64a** when averaged over the last 20 ns of a 100

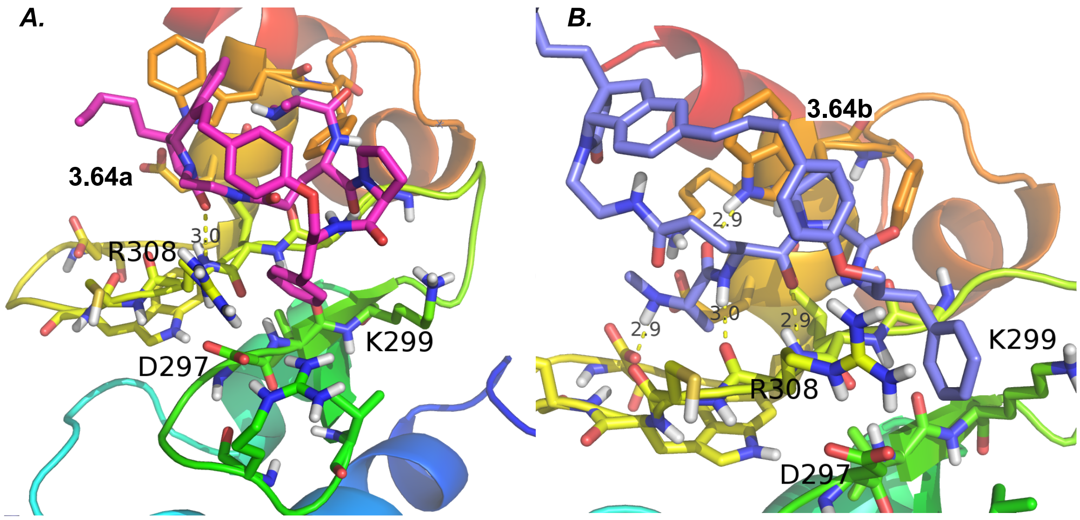


Figure 3.12. (A) & (B) Final snapshots of 100 ns MD simulations of **3.65a** and **3.65b** bound to the BIR3 domain of cIAP1, respectively. Intermolecular hydrogen bonds are indicated in yellow.

ns MD simulation using cIAP1-BIR3 as the protein partner (Fig. 3.12A & B). This observation suggested that **3.64b** interacts with cIAP1 more favorably than **3.64a** and correlated well with competitive binding data. Comparing MD simulations of ligated cIAP1 and XIAP explained the observed selectivity for cIAP1. The hydrophobic binding site in XIAP was unable to accommodate the P4 phenyl substituent, while in cIAP1 it provided a firm anchor for the ligand: after 75 ns of a 100 ns simulation, the phenyl substituent exits the XIAP hydrophobic pocket, which then leads to complex disengagement. Evident from MD data, the hydrophobic pocket of cIAP1 can accommodate a larger substituent relative to the

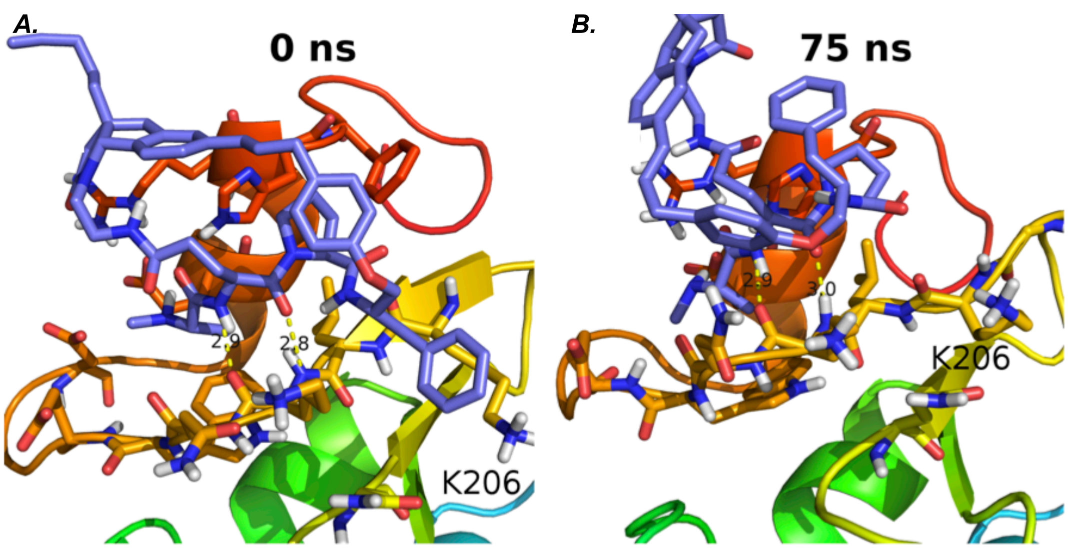


Figure 3.13. Molecular dynamics simulation of **3.64b**, which had been docked into the binding site of BIR2-XIAP leads to complex disengagement after 75 ns of a 100 ns simulation. This is due in part to the expulsion of the P4 phenyl substituent from the hydrophobic pocket, which is smaller due to K206 and corresponds to G306 in BIR3-cIAP1.

constricted site in XIAP, presumably due to the steric demand of K206, which corresponds to G306 in cIAP1 (Fig. 3.13).

The method of lead discovery in the above experiments was highly effective. Using scaffold (+)-**3.5** and an unprotected consensus peptide, we were able to rapidly generate unique macrocyclic ligands for protein surfaces. While this was a proof-of-principle exercise in a well-characterized system, we believe the chemistry has broad potential to create and optimize complex antagonists of protein-protein interactions, especially those mediated by a short-linear-interacting-motif (SLIM) in one partner.[25]

3.3 Conclusion

We have developed a short, scalable and enantioselective synthesis of our first four-armed scaffolding reagent. This molecule can be incrementally integrated into a range of oligomeric substrates, wherein the composite products are stable polycycles having defined conformations. Polar functionality is readily accommodated without the use of protecting groups. By varying the order of events, ring forming modalities and derivatization schemes, countless new complex structures are potentially available. From such collections the search for islands of useful pharmacological properties can proceed in ways not possible previously – which was due, in large part, to limited and/or inconvenient access. Scaffold design and utilization within the project is continually advancing. For example, attempts to utilize the alkyne (and its homologs) in (+)-**3.5** for novel transannulation reactions are ongoing. Bridged macrocycles anticipated from those studies could bring yet another novel compound class into consideration.

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4 – Attempts to form a macrocyclic, transannular linkage by using a terminal alkyne to engage nucleophilic peptide side-chains

4.1 Introduction

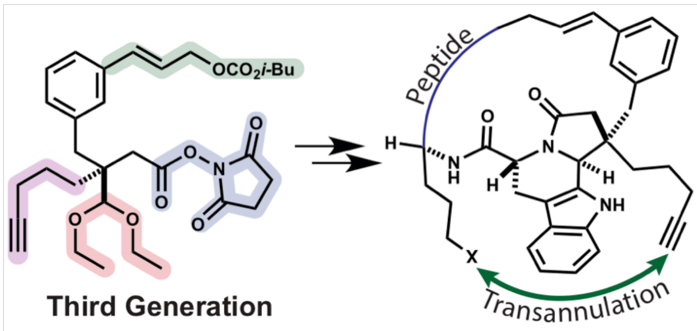


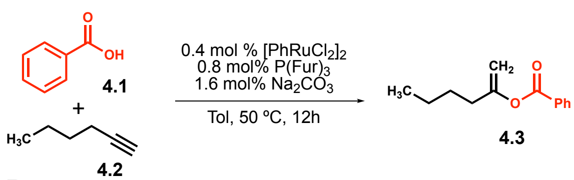
Figure 4.1. The third generation template can engage a peptide in four consecutive reactions using its four arms: peptide acylation (blue), Pictet-Spengler annulation (red), macrocyclization (green), and transannulation (purple). The terminal alkyne is expected to engage some X-group in the peptide backbone to form a transannular linkage in order to access polycyclic hybrid compounds.

Peptides have potential as lead compounds to target protein-protein interactions; however, they are hamstrung by poor cellular transport properties and *in vivo* stability.[1,2] However, cell permeability and proteolytic stability can generally be improved when the linear peptide is cyclized to its macrocyclic counterpart. It is thought that improved pharmacological properties are due to restricted conformational degrees of freedom in addition to the molecule being able to "hide" polar functionalities, thereby limiting the sites of hydration. These sites of hydration must be shed before a molecule can pass through a cellular lipid bilayer. Additionally, others have shown bicyclic peptide systems, which are capable of scaffolding large, extended peptide sequences, can target with high specificity intracellular proteins, such as human prolyl isomerase-1 (hPin-1). [3,4] Our group has focused on cinnamyl ion cyclizations to form macrocyclic peptidomimetics by alkylation of either heteroatom or arene nucleophiles in Tsuji-Trost or Friedel-Crafts reaction manifolds, respectively.[5–10] As the template molecules have become more advanced, we have incorporated functionality to incrementally engage both peptide backbones and side chains.[9,10] The newest template bears a terminal alkyne that we envision could engage peptide side chains in a transannular event. By using the alkyne to form a transannular bond, we hypothesize that bicyclic structures of this type will have restricted conformational flexibility, allowing us to study pharmacological properties upon cyclization. In processing peptides in this way, we take inspiration from non-ribosomal peptide synthetases, which process peptides to generate compounds that often have little remaining peptide character. Previously we have shown that the alkyne could be activated in a late-stage functionalization event for glycosylations and dimerization. To demonstrate the versatility of this system, we aimed to exploit the alkyne as an orthogonal handle form bicyclic peptidomimetics by selectively engaging nucleophilic side-chains (Fig. 4.1).[11–13] After engaging the other three arms sequentially through acylation, Pictet-Spengler annulation, and finally large ring cinnamylation, the terminal alkyne would then act in a fourth engagement with the peptide. We viewed the alkyne as an orthogonal handle to be activated and form large bicyclic rings by engaging amino acid side chains using various chemistries (*e.g.* copper-catalyzed azide alkyne cycloaddition, Glaser coupling, acyloxylations[14–16] and hydroamidations[17–19] as well as thiol-yne reactions[20]). We hypothesized that the alkyne could be also be activated selectively in transition metal catalysis.[12] Although the methodologies to engage alkynes are well studied and robust, the solvents and catalysts used may not be compatible with macrocyclic peptidomimetics and therefore require extensive optimization. The following data are a summary of the attempts to find conditions suitable for engaging a terminal alkyne.

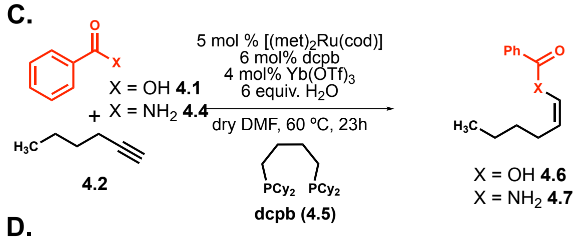
4.2. Results

We began with model systems to engage the alkyne with nucleophilic groups present in natural peptide backbones. It is well established that carboxy side chains do not participate in the other cyclization steps or have adverse effects on solubility or workability. Because of their interness and prevalence in peptides, initial model systems focused on using carboxylate or carboxamides as nucleophiles that can be added across a triple bond in an acyloxylation or hydroamidation reaction, respectively. Reactions of this type are well studied in aliphatic and aryl alkynes and carboxylates/carboxamides.[14–19] However, the solvents used are typically nonpolar (*i.e.* toluene) and, therefore, unable to solubilize our peptide-derived macrocyclic starting materials. Due to solubility concerns, there was a need to find a solvent system to reasonably solubilize our starting materials yet allow for the acyloxylation reaction. The solvent screens made use of a literature model system using

A.



C.



B.

entry	solvent system	additive	% yield (NMR)
1	Toluene	N/A	100
2	Toluene/CH_3CN (1:1)	N/A	2.7
3	Toluene/EtOAc (1:1)	N/A	82
4	Toluene/DMF (1:1)	N/A	0
5	Toluene/MeOH (1:1)	N/A	55
6	Toluene/EtOAc (1:1)	MeOH (10 eq.)	69

D.

entry	X	Additive	% yield (NMR)
1	NH_2	N/A	63
2	OH	N/A	24 (5:1 M/AM)
3	OH	Na_2CO_3 (5 mol%)	0

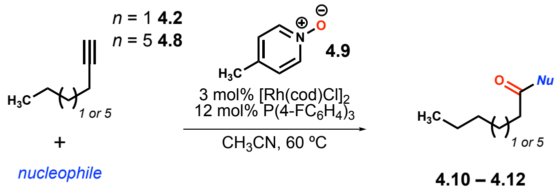
Figure 4.2. (A) acyloxylation reaction conditions to couple benzoic acid and hexyne. (B) Solvent screen table with NMR yields for the acyloxylation reaction. (C) Addition of either benzamide or benzoic acid to hexyne using hydroamidation conditions. (D) NMR yield of the given X-group and additives.

benzoic acid (**4.1**) and hexyne (**4.2**) as the reactive partners with a ruthenium precatalyst and trifuryl phosphine as the ligand; sodium bicarbonate was used as a catalytic additive (Fig. 4.2A).[15] We chose this as a model system because it would allow us to directly compare yields to literature with easily handled material while also screening solvents compatible with peptidomimetics. We found some distinct differences in NMR yields of various solvent systems. Specifically, the NMR yield of the control reaction between **4.1** and **4.2** with toluene as solvent gave a quantitative yield of Markovnikov product **4.3** (entry 1, Fig. 4.2B). Although toluene was a great solvent for this model reaction, it was not a suitable solvent for our purposes. However, when more suitable, polar coordinating solvents such as CH_3CN or DMF were used as co-solvents the reaction was greatly reduced (entries 2 & 4). When polar solvents such as EtOAc or CH_3OH were used as co-solvents the reaction was still viable and gave good or moderate NMR yields, respectively (entries 3 & 5). From these data, we reasoned that using EtOAc as a co-solvent with CH_3OH as an additive could provide a solvent system that would suitably dissolve our macrocyclic starting materials but would still allow the acyloxylation to proceed (entry 6).

Similar to acyloxylations, hydroamidations could also facilitate macrocylizations by adding a carboxamide – present in asparagine and glutamine – across the triple bond to form acyl enamides. This method was attractive for the same reasons as carboxylates but also because it may provide a more stable transannular linkage. We used a similar model system to study and optimize conditions for the abovementioned reasons. We noted that an example of alkyne hydroamidations used DMF as a solvent along with a complex catalyst, ligand, and additive mixture, which gives anti-Markovnikov products such as **4.7** and was an attractive method to pursue because of the solubilizing power of DMF (Fig. 4.2C). Because of the similarities between hydroamidations and acyloxylations, we also wanted to ask the following: could the same solvent and catalyst system used in hydroamidations also be used in acyloxylations to give product **4.6**? In this way, we would have multiple methods to potentially engage peptide side-chains with both carboxy and carboxamide termini. Using benzamide (**4.4**) and **4.2**, we found that the product yield was modest for the control reaction (entry 1, Fig. 4.2D); however, we also found that **4.1** was a competent partner in this reaction, and interestingly gave a 2:1 mixture of Markovnikov (**4.3**) and anti-Markovnikov products (**4.6**, entry 2). While we were able to achieve product formation in good yield, it was interesting to observe that the same additives that aid reaction completion in our acyloxylations actually impaired product formation in our hydroamidations. When sodium carbonate was used, as in 4.2A the reaction with **4.1** shut down completely and we only observed trace amounts of desired product. This could be due to sodium carbonate neutralizing the Lewis acidic $Yb(OTf)_3$ and thus altering the seemingly delicate balance of catalyst/ligand/additives. While we were looking into the reactivity of carboxylate derivatives with alkynes, we were also interested in how the alkyne could be alternatively activated and engaged in order to provide more options for alkyne functionalization.

We next looked at model oxygenations of alkynes, which could subsequently trap a heteroatomic nucleophile such as serine or lysine (Fig. 4.3A).[21] Oxygenation of decyne (**4.8**) and trapping of the putative metaloketene intermediate with methanol made use of picolinic *N*-oxide as an oxidant and a rhodium catalyst/phosphine ligand system to afford methyl ester **4.10** (entry 1, Fig. 3B). This product was recovered in 93% crude recovery after a workup and was spectroscopically pure. Investigating reactions using amino nucleophiles was more difficult. The method required an ammonium salt with a non-coordinating counter ion such as PF_6, which was achieved using a salt metathesis with KPF_6. The

A.



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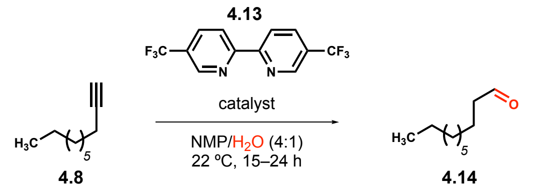
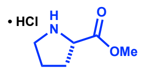
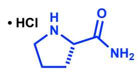


B.

Entry	nucleophile	substrate	Additive	% yield (NMR)
1	MeOH	decyne	N/A	93[a]
2		hexyne	KPF_6 K_2CO_3 (20 mol%)	100
3		hexyne	" "	0

D.

entry	catalyst	ligand	% conv. (NMR)
1	$[(Cp)Ru(ACN)_3]PF_6$ (2 mol%)	(2 mol%)	10
2	$[(Cp)Ru(Naph)]PF_6$ (2 mol%)	(2 mol%)	41

Figure 4.3. (A) oxygenation and nucleophile trapping using a rhodium catalyst affords carboxylate derivatives. (B) table of nucleophiles and the corresponding NMR yield in oxygenation reactions. (C) anti-Markovnikov hydration of alkynes using a ruthenium catalyst and an electron-deficient ligand affords aldehydes. (D) table of catalysts used in hydration reactions and the corresponding percent conversion observed by ^{1}H-NMR.

resultant KCl was less soluble in CH_3CN and could be removed via filtration. Using this method with L-proline methyl ester hydrochloride and hexyne afforded amide **4.11** in 100% yield by NMR (entry 2). We also tested L-proline amide hydrochloride as a nucleophile for the reaction (entry 3); unfortunately, this reaction gave no desired amide **4.12**. It should be noted, however, that reactions using amino nucleophiles appeared to be very capricious and sensitive to the presence of chloride ion. If KCl were not sufficiently removed – noted by an iridescent solution –the reaction would not proceed and gave no desired product (e.g. **4.11**).

Continuing with our exploration of potential reactions to engage the terminal alkyne in our macrocyclic compounds, we turned to research from the Herzon lab in which they have shown that anti-Markovnikov hydration of alkynes can be achieved using a ruthenium catalyst and an electron-deficient bipyridyl ligand (**4.13**, Fig. 4.3C).[22,23] We chose to investigate this reaction area because we saw that both the hydration and acyloxylation chemistries occur through similar reaction mechanisms, only the nucleophile changes in this instance to water and forms an aldehyde after tautomerization. In our hands, we found that this reaction tended to be capricious and highly sensitive to oxygen (Fig. 4.3D). Reaction conversion was low when $[Ru(ACN)_3Cp]PF_6$ was used as the pre-catalyst (entry1). However, we found that pre-catalyst $[(Cp)Ru(Naph)]PF_6$ gave the highest conversion (40% by NMR) after 15 hours (entry 2).

With four potential methods to activate the alkyne using ruthenium and rhodium catalysis, we were also interested in a recent example of using gold catalysis in a multicomponent reaction to form stable butenolides.[24] This method would allow us to engage nucleophilic amino side-chains to give unprecedented bicyclic compounds. Using Au(III) as a catalyst, glyoxylic acid hydrate (**4.15**) and a 2º amine form the corresponding Schiff base, which is then intercepted by a gold acetylide. Subsequent acyloxylation and tautomerization formed products such as **4.16–4.17** (Fig. 4.4A). Using this method even in model systems, however, proved to be low yielding (Fig. 4.4B). Reproducing literature conditions using morpholine as the nucleophile resulted in a lower than expected NMR yield in our hands (entry 1). We chose to switch to morpholine because we wanted to be sure we could reproduce their results. However, this NMR yield is over four times lower than the literature yield after purification (15 vs. 65% yield). Although we found a low NMR yield for the literature control, we were curious to see the performance of an amino acid-derived secondary amine nucleophile in the reaction, specifically the d.r. of such a reaction. We found that the free-base of L-proline amide (entry 2) performed a little better than the control reaction, but, unfortunately, gave a 1:1 d.r. at the γ-position of the butenolide as measured by NMR. Although we found interesting reactivity in the gold-catalyzed reaction, we did not pursue this further in transannulation attempts. Instead, we focused on using the Ru- and Rh-catalyzed alkyne

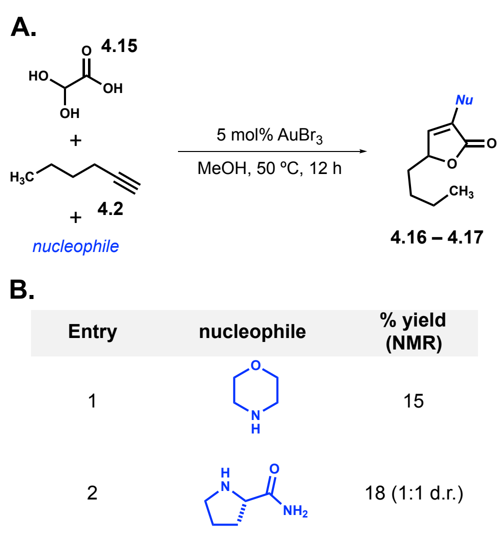


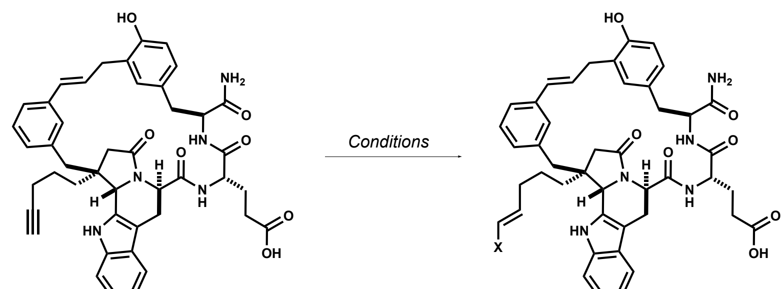
Figure 4.4. (A) Multi-component reaction conditions to form butenolides from hexane, glyoxylic acid hydrate, and a secondary amine nucleophile. (B) Table of nucleophile used and the corresponding NMR yield in each three-component reaction.

activations in our bicyclization attempts because those appeared to give higher yields and a potentially higher chance for success.

After establishing suitable reaction conditions for bicyclization trials, we began looking at ways to engage both the glutamate and terminal alkyne in **3.46** (Fig. 4.5). Beginning with intermolecular alkyne activation to install some X-group, anti-Markovnikov hydration was investigated (entry 1, Fig. 4.5B). For all of the below entries, the percent conversion is obtained by integration of UV-254 nm from HPLC-MS traces. Although we did not use the more active catalyst system, we expected to observe some reactivity; furthermore, this attempt was run concomitantly with the previous models. However, after multiple attempts, we did not observe any hydration by HPLC-MS.

Moving forward, we tested the reactivity of our template using intermolecular reactions before

A.



3.46 4.18

B.

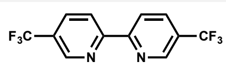
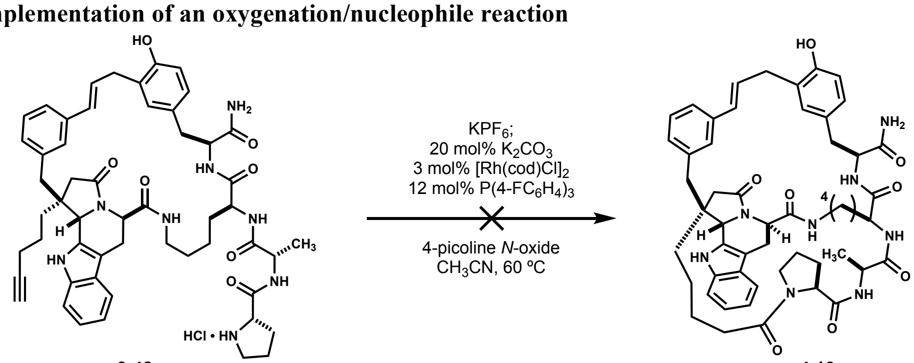
Entry	X	Catalyst	Ligand	Additive	Solvent	% Conv.
1	OH	$[CpRu(ACN)_3]PF_6$ (5%)	 (5%)	N/A	NMP/H_2O (4:1)	0
2	PhCOO	$[PhRuCl_2]_2$ (1.2%)	$P(Fur)_3$ (2.4%)	Na_2CO_3 (4.8%)	Toluene	0
3	PhCOO	$[PhRuCl_2]_2$ (1.2%)	$P(Fur)_3$ (2.4%)	Na_2CO_3 (4.8%) MeOH (10 eq)	Tol/EtOAc	0
4	PhCOO	$[PhRuCl_2]_2$ (0.4%)	$P(Fur)_3$ (0.8%)	Na_2CO_3 (1.6%) MeOH (20 eq.)	Tol/EtOAc	50
5	N/A	$[PhRuCl_2]_2$ (0.4%)	$P(Fur)_3$ (0.8%)	Na_2CO_3 (1.6%) MeOH (20 eq.)	Tol/EtOAc (5 mM)	0
6	N/A	$[(met)_2Ru(cod)]$ (5%)	dcpb (6%)	$Yb(OTf)_3$ (4%) H_2O (6 eq.)	DMF (5 mM)	0

Figure 4.5. (A) Hypothesized alkyne activation in macrocycle 3.46. (B) Table of conditions tried to activate alkyne including the percent conversion by HPLC (UV-254 nm).

moving on to intramolecular cyclizations. We found that intermolecular acyloxylations using benzoic acid proved to be difficult (entries 2–4). Using the literature conditions with toluene as the only solvent, we did not observe any conversion to the corresponding enol ester most likely due to the insolubility of our starting material. We also did not observe conversion using our optimized solvent system of 1:1 toluene/EtOAc and 10 eq. of methanol as an additive. However, when we increased the amount of methanol to 20 equivalents and decreased the catalyst, ligand, and base loading, the reaction resulted in 50% conversion to a mass corresponding to the desired intermolecular product. Additionally we observed a hydration product, which could be derived from decomposition of the product enol ester, under HPLC conditions. Although promising, we were unable to isolate the presumed desired product for further characterization. Attempts to translate these conditions into a bicyclization event, however, were unsuccessful (entry 4). We did not observe any change from starting material to desired bicycle or even dimeric polycycles. Finally, using the conditions from Fig. 4.2C also did not form any desired bicyclic product.

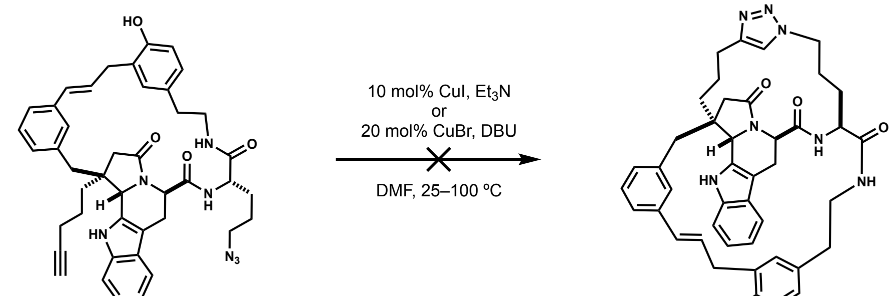
Another transannulation attempt used oxygenation conditions identified in Fig. 4.3 A/B, we attempted alkyne oxygenation and proline amine trapping with the hydrochloride salt of substrate **3.48** (Scheme 4.1). This method proved to be difficult to implement, however. Although removal of KCl from the salt metathesis was facile, no oxygenation was observed in multiple reactions. However, one reaction contained the desired mass of **4.19** as observed by HPLC-MS, but this product was in low abundance and unable to be isolated in purity and scale sufficient for NMR analysis.

Scheme 4.1. Implementation of an oxygenation/nucleophile reaction



3.48 4.19

Scheme 4.2. Transannulation attempts using copper-catalyzed Huisgen cycloadditions

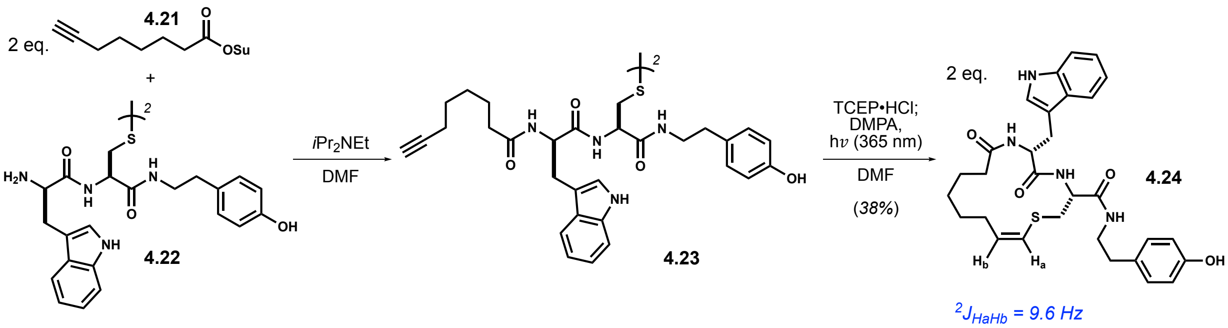


Another effort to use a transition metal to catalyze a bicyclization, utilized chemistry that we had previously shown worked in intermolecular reactions: copper-catalyzed Huisgen cycloaddition (Scheme. 4.2). Treatment of azide-containing polycycle **3.51** with 10 mol% copper(I) iodide and triethyl amine resulted in observation of a dimeric mass by HPLC-MS. Switching to a different copper(I) source, DBU as a base, and higher temperatures, unfortunately did not perform much better to furnish **4.20**. Although the desired mass was observed by HPLC-MS, the product was no longer observed after DMF was removed by either evaporation or workup. The reticence to transannulation is likely due to prohibitive ring strain as the two reactive partners approach the transition state rather than the partners being incompetent reactive centers – due to observation of dimeric product using copper(I) iodide.

Through bicyclization attempts using transition metals as alkyne activators, we began to doubt the viability of such reactions in a transannulation event. Although the reactions were mild, the low-energy transition metal-alkyne coordination complexes were not suitable to macrocyclization reactions. Because of this, we believed that we would need a high-energy intermediate in order to engage the alkyne and overcome entropy as well as ring strain in the bicyclization transition state.

Through conversations with colleagues, we became interested in using the thiol-yne reaction, which formally adds S–H bond across an alkyne, as a potential transannulation reaction.[20] This reaction proceeds through a high-energy sulfur-centered radical, which adds to an alkyne, and the resultant vinyl radical abstracts a hydrogen from another equivalent of thiol, thus propagating the radical pathway. Again, a model system was utilized to probe reaction conditions consisting of two equivalents of octynoic acid derivative **4.19** and dimeric tripeptide **4.20** (Scheme 4.1). The peptide was synthesized solution-phase

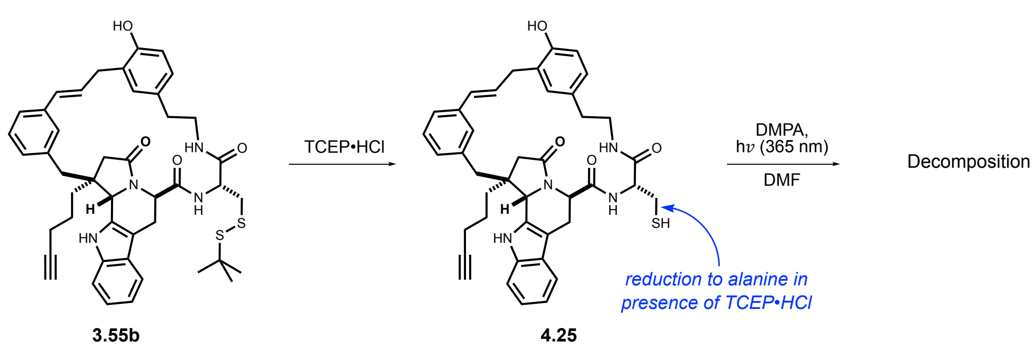
Scheme 4.3. Thiol-yne macrocyclization model system



using cystine to temporarily protect cysteine as its disulfide. The disulfide of seco-precursor **4.21** was reduced in the presence of triscarboxyethylphosphine hydrochloride (TCEP) overnight in DMF. During the overnight reduction, the photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA), was also added under inert conditions. In this way, after the reduction was complete, the solution could be exposed to a UV-365 nm light source in order to initiate the thiol-yne reaction. After 1 hour, the starting material was fully consumed and two products were observed by HPLC-MS (~10:1 ratio). The major product was isolated and determined to be **4.22** using a combination of 1D- and 2D-NMR. The olefin stereochemistry of **4.22** was assigned as the *Z*-isomer based upon the observed $^2J_{HaHb}$ coupling of 9.6 Hz. The other observed product was not isolated but was assumed to be the *E*-olefin diastereomer based on the observed m/z.

After confirmation that thiol-yne could, in our hands, successfully form large rings, we moved on to applying this method in transannulations. With access to previously prepared macrocycle **3.55b**, we were able to reduce the disulfide using TCEP. After accessing thiol **4.23**, we attempted various reaction conditions in order to obtain a transannular thiol-yne cyclization. When TCEP was added to the

Scheme 4.4. Thiol-yne as a potential bicyclization method



photoreaction to reduce possible disulfide side-products, reduction of the C–S bond was observed. Similar reductions have been observed in the literature, however, using other conditions. Most famously, Danishefsky has used native chemical ligations using cysteine followed by reduction to the alanine in order to convergently build protein targets totally synthetically.[25] By removing TCEP, we remedied the C–S bond reduction; however, isolation of bicyclic products still eluded us. Although we were able to

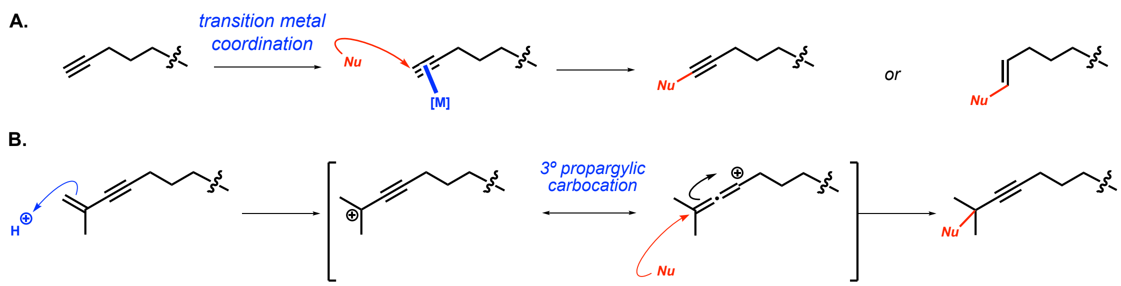
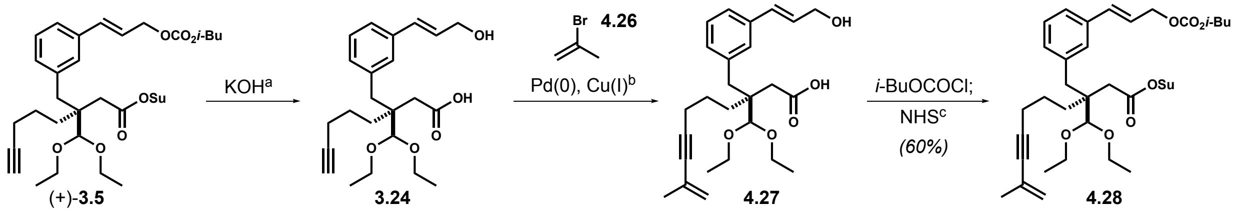


Figure 4.6. (A) Previous methods relied on transition metal-catalyzed alkyne activations to engage nucleophilic peptide side chains. (B) Transforming the terminal alkyne into an ene-yne could access a propargylic carbocation via protonation of the a-olefin. The stabilized carbocation could then intercept an arene nucleophile in a Friedel-Crafts reaction.

detect miniscule amounts of desired mass in crude HPLC-MS spectra, what we observed were mostly unknown decomposition products. We were unable to improve the yield or mitigate decomposition pathways using the given reaction conditions. However, it should be noted that we were only able to obtain ~15 mg of **4.23** and ran few reactions with this material. Access to larger amounts of material would allow us to look at other thiol-yne catalysts and promoters such as triethylborane or indium(III) and aid in method discovery efforts.

At this point, we began thinking about other methods that could increase the alkyne reactivity and considered methods that would transform the alkyne into an overtly reactive functional group rather than using transition metals to access alkyne reactivity (Fig. 6A). Taking inspiration from a previous strategy the lab had used to unselectively form transannular bonds, we transformed the terminal alkyne into an ene-yne moiety, which provides access to an overtly reactive propargylic cation (Fig. 6B). The delocalized cation is expected, in line with previous data, to engage side-chain arene in a Friedel-Crafts alkylation to form stable C–C bonds.[6] The terminal alkyne could either be converted to the ene-yne after macrocyclization, or, more reasonably, the template synthesis could readily be modified to furnish the desired functionality.

Scheme 4.5. Synthesis of a new 'ene-yne template'

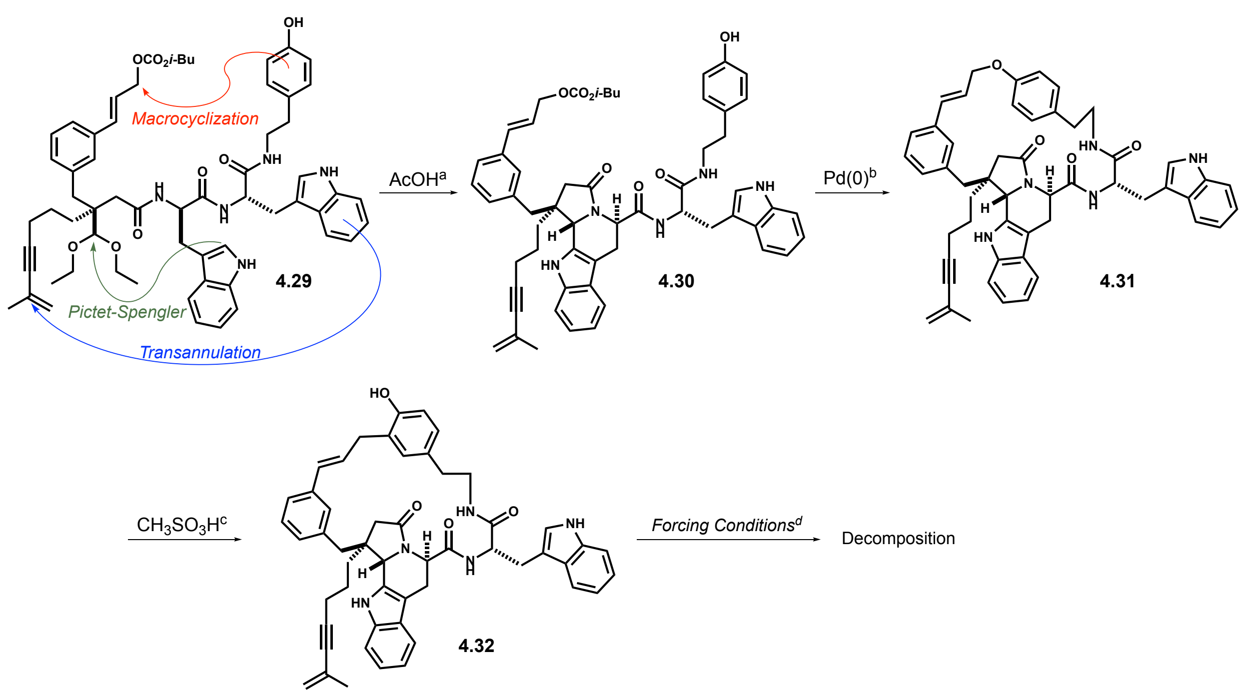


Reaction conditions: a) 5 eq. KOH, 5:1 EtOH/H_2O, 55 ºC, 1 day; b) 8 eq. 2-bromopropene, *i*-Pr_2NH, 4 mol% CuI, 2 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% PPh_3, toluene, 75 ºC, sealed tube, 12 h; c) 2.5 eq. *N*-methylmorpholine, 2.5 eq. *i*BuOCOCl, DCM, -5 ºC; 2.5 eq. *N*-hydroxysuccinimide, -5 ºC to 22 ºC, 12h, 60% over three steps.

Rather than undertake a template synthesis from the beginning, template, (+)-**3.5** was reverted to hydroxy acid **3.24** using super stoichiometric KOH. From here, the terminal alkyne was transformed to vinylacetylide **4.25** under Pd(0)/Cu(I) Sonogashira conditions.[26] These conditions were found to be scalable and could be implemented into our typical quaternary template syntheses with only one extra synthetic step. The final step was accomplished as before: double carbonate formation followed by nucleophilic decomposition of the acylcarbonate to form completed ene-yne template **4.27**. This material was accessed in 60% yield from previous template (+)-**3.5**.

The ene-yne template was then coupled with D-Trp-Trp(tyramide) to form linear precursor **4.27**. The

Scheme 4.6. Attempts to use the ene-yne as a bicyclization method



Reaction Conditions: a) 4:1 AcOH/H_2O, 22 ºC, 12 hours. b) 2.0 eq. Cs_2CO_3, 5 mol% $Pd(PPh_3)_4$, DMSO, 10 mM, 4 hours. c) 5 vol% TFA, CH_3NO_2, 5 mM, 2 hours.

beginning of our synthetic plan was as it had been previously: engage the *P1* D-Trp in a Pictet-Spengler annulation and the *P3* tyramide in a macrocyclization event. The last step of our planned sequence was to engage the *P2* Trp in an acid promoted Friedel-Crafts bicyclization with the ene-yne. Treatment of acylation product **4.29** with aqueous acetic acid (80%) afforded aza-carbazole **4.30**. Because we wanted a single macrocyclic product, we first formed tyrosyl ether **4.31** through a Tsuji-Trost cinnamylation to avoid regioisomeric Friedel-Crafts cyclizations. This material could be treated with low concentrations of TFA to force an *O* to *C* cinnamyl migration to afford product **4.30**. This material, unfortunately, was resistant to cyclization.

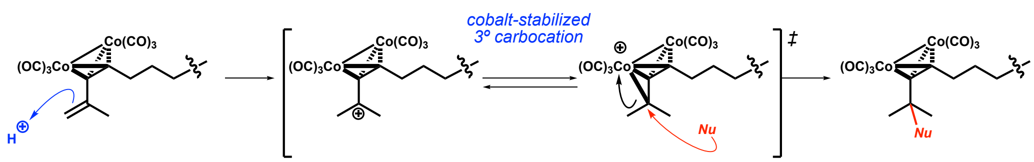
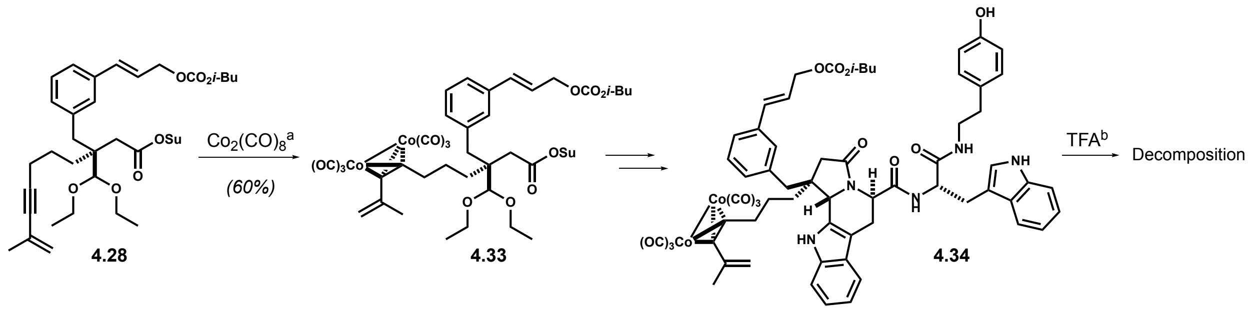


Figure 4.7. Dicobalt acetylenes can form stable cationic species that are capable of trapping arene or alcohol nucleophiles in acid-promoted reactions.

After numerous attempts with different acids (TFA, CH_3SO_3H, and Tf_2NH) and solvents (CH_3NO_2, DCM, and TFE), no desired product was observed by monitoring HPLC-MS traces over time. What we observed were a decrease in percent peak area (UV-254 nm) over time in samples whose concentrations were matched. We hypothesized that the propargylic cation is short-lived and therefore unable to be trapped by the *P2* Trp, and, furthermore, the alkylation transition state is inaccessible due to conformational restrictions and thus leads to by-product formation/oligomerizations.

Without much success engaging aryl peptide side-chains using the ene-yne, we next looked at protecting the internal alkyne as the corresponding acetylenic dicobalt hexacarbonyl. Use of this complex to stabilize propargylic cations and alkylate arene nucleophiles has been known since 1971 when it was first reported by Nicholas et al.[27] The so-called Nicholas reaction proceeds through a cobalt-stabilized carbocation which then can trap a variety of nucleophiles including alcohols and electron-rich aryl species (Fig. 7).[28] The dicobalt can then be decomplexed using an oxidants such as $Fe(NO_3)_3$. Applying this strategy to our system would be facile and completed in a single step. Ene-yne template **4.26** was stirred

Scheme 4.7. A dicobalt-protected ene-yne was unsuccessful in bicyclization reactions



Reaction conditions: a) 1.2 eq. $Co_2(CO)_8$, DCM, 2 h, 60%; b) increasing volumes of TFA (1 to 7.5 vol%), CH_3NO_2, 5 mM.

with dicobalt octacarbonyl in DCM under an argon atmosphere for 1 hour to form dicobalt compound **4.31** in 60% yield after silica chromatography. Formation of this complex was confirmed via ^{13}C-NMR, which showed a shift in the alkynyl carbons and presence of a carbonyl shift at 200 ppm. Additionally, the isolated compound was a dark red oil – a characteristic color for such dicobalt complexes. The cobalt template was then used to process the same tripeptide as above to form Pictet-Spengler product **4.32**. Treating the linear precursor with increasing volumes of TFA resulted in decomposition to multiple near-baseline peaks containing the desired mass in the HPLC-MS. However, isolation of these materials was unsuccessful and the major isomer appeared to match well with ^{1}H-NMR spectrum of **4.31**. Additionally, a Friedel-Crafts bicyclization event would have the same exact mass as a monocyclic isomer, and, because we have two arene nucleophiles, it is possible that the cinnamyl cation engaged both side-chains and led to the observed collection of isomeric peaks in the HPLC-MS spectrum. Throughout acid treatments of the dicobalt materials, we consistently observed loss of color. Although this is only a qualitative observation, the HPLC-MS also appears to show loss of cobalt after treatment with acid. Furthermore, a dicobalt-derivative of **4.31** showed similar behavior: loss of red coloration followed by decomposition to unidentified compounds. Not deterred by the failures, we believe that the ene-yne and its derivatives give us our best opportunity for success, and rather than the chemistry being unusable, we hypothesize that ring size and conformation preferences of the initial macrocycle will be critical to transannulation success. Model systems looking at the feasibility of macrocyclization with this method are ongoing in the lab.

4.3. Conclusions

Methods to engage and cyclize peptides to furnish compounds with a desired arrangement of peptide residues, potent biological activities, and improved pharmacological properties have been an ongoing interest in the lab. The current, described template generation allows us to not only functionalize our macrocyclic peptides products with property-altering groups but also enables a fourth engagement with the peptide backbone in a transannulation event. Multiple attempts have been made toward this end including transition metal-catalyzed and thiol-yne methods as well as acid-promoted reactions of alkyne homologs. Although success has only been found in simple model systems, efforts continue in trying to form a transannular linkage. The ultimate goal is to use this third generation template in conjunction with other template designs and generate multiple library generations in order to refine lead compounds and understand how each template affects the pharmacological properties differently and ultimately target intracellular protein-protein interactions.

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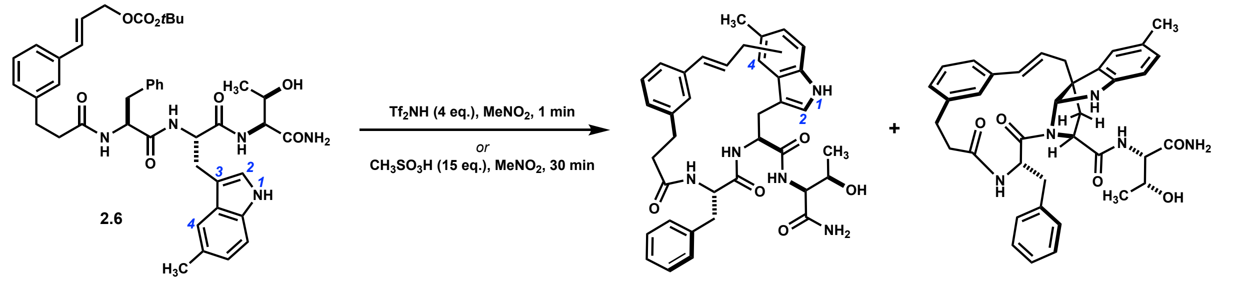
Chapter 2 – Appendix Material

On the prevalence of bridged macrocyclic pyrroloindolines formed in regiodivergent alkylations of tryptophan

Table of Contents

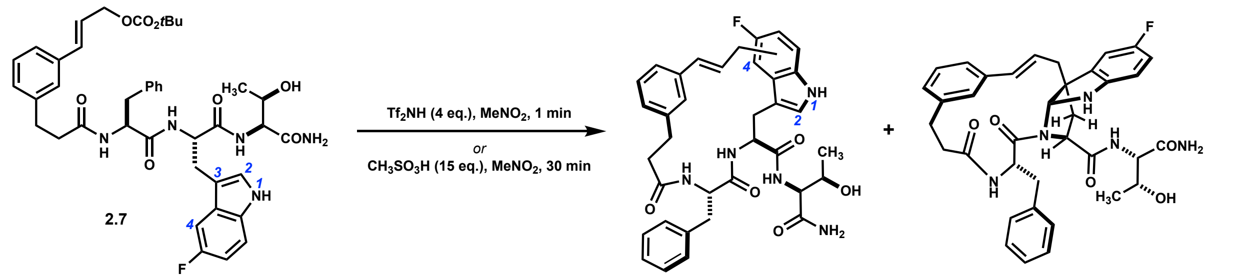
A. Supplementary Figures

Figure A1. **Phe-Trp(5Me)-Thr**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.6**.



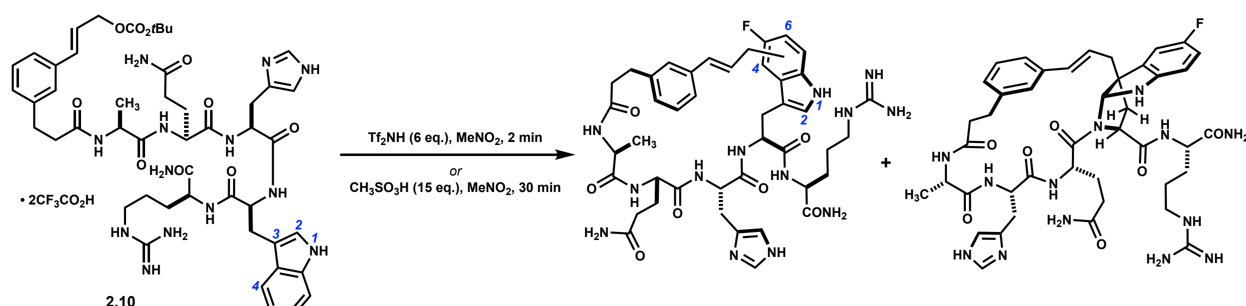
	N1	C2	C4	C3	Combined Yield
	2.8a	**2.8b**	**2.8c**	**2.8d**	
		% yield		% yield	
Tf_2NH	*n.d.*	*11*	*30*	*8*	***50 %***
CH_3SO_3H	*n.d.*	*8*	*27*	*8*	***43 %***

Figure A2. **Phe-Trp(5F)-Thr**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.7**.



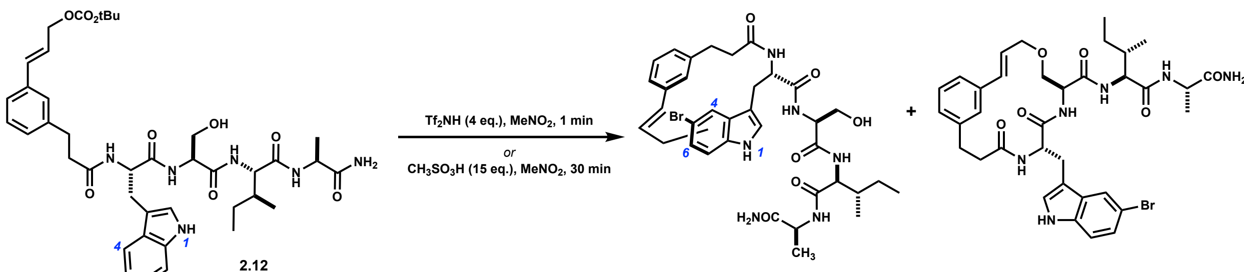
	N1	C2	C4	C3	Combined Yield
	2.9a	**2.9b**	**2.9c**	**2.9e**	
		% yield		% yield	
Tf_2NH	*10*	*17*	*14*	*22*	***62 %***
CH_3SO_3H	*7*	*7*	*16*	*15*	***45 %***

Figure A3. **Ala-Gln-His-Trp(5F)-Arg**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.10**.



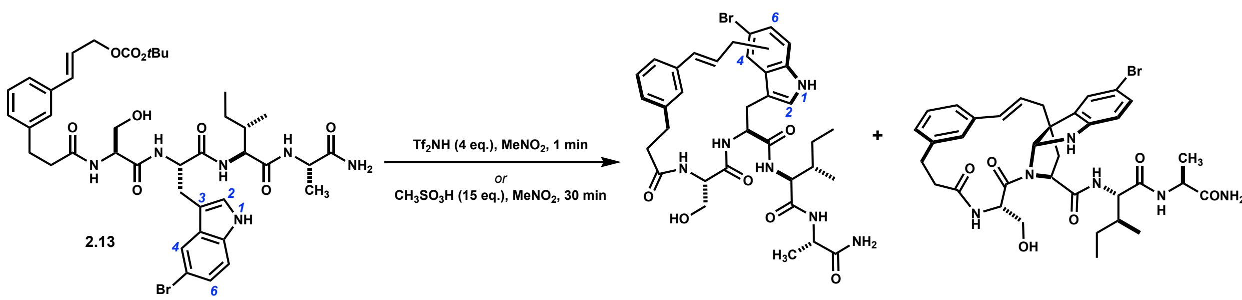
	N1	C2	C4	C6	C3	Combined Yield
	2.11a	**2.11b**	**2.11c**	**2.11d**	**2.11e**	
		% yield			% yield	
Tf_2NH	*17*	*12*	*6*	*48*	*8*	***91 %***
CH_3SO_3H	*6*	*4*	*3*	*19*	*5*	***37 %***

Figure A4. **Trp(5Br)-Ser-Ile-Ala**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.12**.



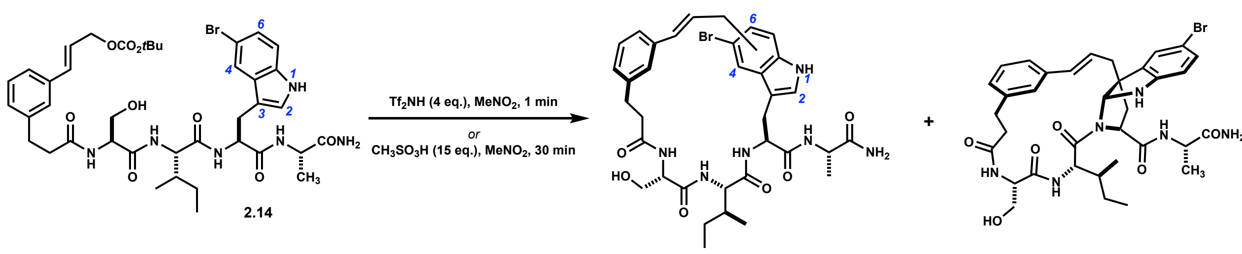
N1	C6	C7		Ser	
2.16d	2.16a % yield	2.16c		2.16b % yield	Combined Yield
11	25	9	Tf_2NH	6	52 %
6	27	14	CH_3SO_3H	0	47 %

Figure A5. **Ser-Trp(5Br)-Ile-Ala**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.13**.



N1	C2	C4	C6		C3	
2.17d	2.17a % yield	2.17b	2.17c		2.17e % yield	Combined Yield
6	14	14	7	Tf_2NH	14	63 %
0	12	13	10	CH_3SO_3H	8	42 %

Figure A6. **Ser-Ile-Trp(5Br)-Ala**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.14**.



N1	C2	C4	C6		C3	
2.18e	2.18a % yield	2.18b	2.18d		2.18c % yield	Combined Yield
6	19	4	21	Tf_2NH	27	77 %
7	5	2	26	CH_3SO_3H	7	48 %

Figure A7. **Ser-Ile-Ala-Trp(5Br)**. Comparative performance of Tf_2NH and $MeSO_3H$ in cyclization of linear precursor **2.15**.

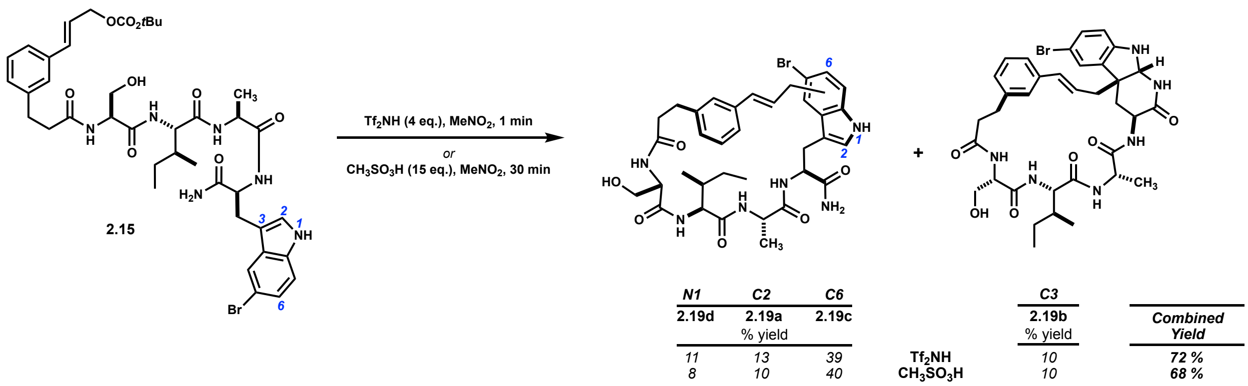


Figure A8**. Nva-Asp-Val-Trp(5Br).** Cyclization of **2.S1** promoted by Tf_2NH forms diastereomeric pyridoindolines **S2a**&**b**.

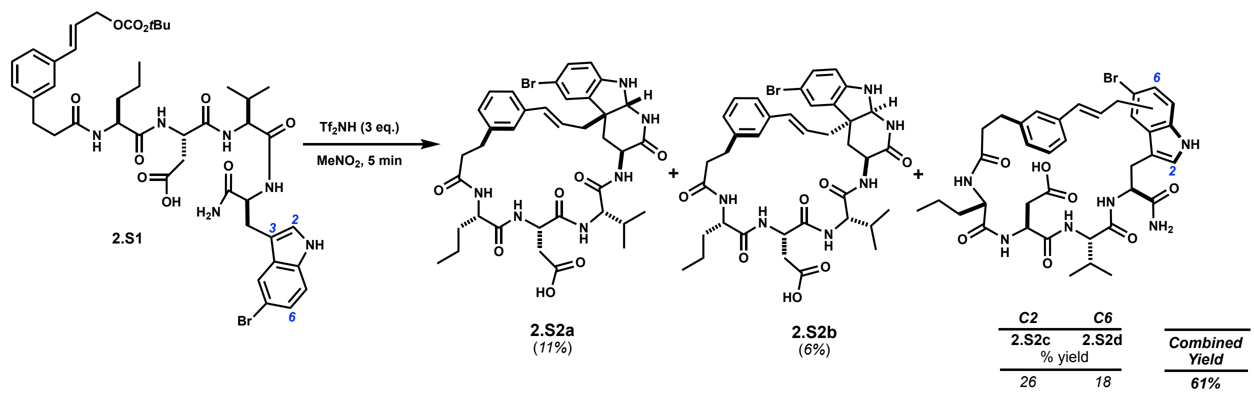
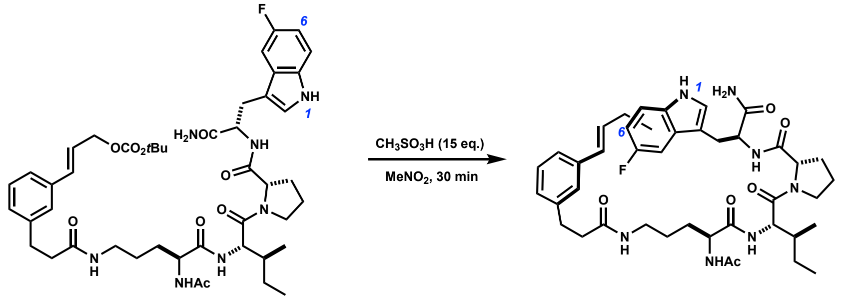


Figure A9. **Ac-Orn(H)-Ile-Pro-Trp(5F)**. Cyclization of **2.S3** promoted by $MeSO_3H$ did not yield an analogous pyrroloindoline.

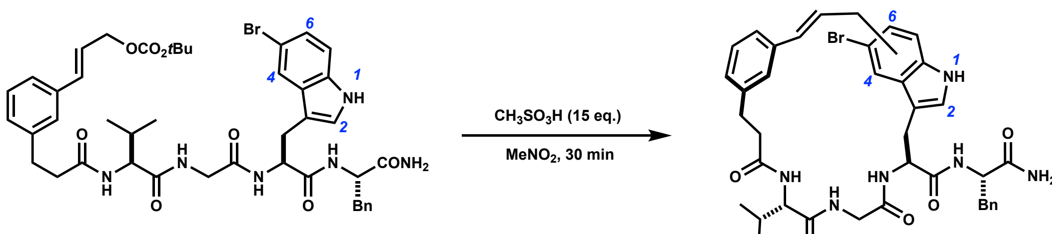


2.S3

N1	*C6*
2.S4b	**2.S4a**
% isolated yield	
19	*34*

Combined Yield
53 %

Figure A10. **Val-Gly-Trp(5Br)-Phe**. Cyclization of **2.S5** promoted by $MeSO_3H$ did not yield an analogous pyrroloindoline.



2.S5

N1	*C2*	*C4*	*C6*
2.S6d	**2.S6a**	**2.S6c**	**2.S6b**
% isolated yield			
14	*6*	*8*	*20*

Combined Yield
48 %

***B*. General Considerations**

Fmoc-5-bromo-L-tryptophan, Fmoc-5-fluoro-L-tryptophan, and Fmoc-5-methyl-L-tryptophan were synthesized by kinetic enzymatic resolution of their racemates according to published procedures.[7] Triflimide was purchased from Oakwood and handled under a dry atmosphere of argon to prepare stock solutions in $MeNO_2$ (1 mg/mL). Methanesulfonic acid ≥99.5% was purchased from Aldrich.

Nitromethane Purification

Pre-treatment of commercial grade nitromethane with either 3Å molecular sieves (7 days) or activated neutral alumina (Aldrich, 58 Å, activated Brockman I, 150 mesh, 12 hrs) is essential for optimal results in Friedel-Crafts cyclizations. Adding H_2O (up to 1000 ppm) to the resultant dry nitromethane has no deleterious effects. For further discussions see: Rose, T. E. Ph.D. Dissertation [Online], University of California, Los Angeles, 2015. pp. 158-160. http://escholarship.org/uc/item/0mx7x1st (Accessed Oct 2, 2015). UMI: 3706064.

HPLC Analysis and Purification

Purification of acidolysis products was performed on an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using an identical system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source. Stationary phase and gradient profile are noted for individual reactions below.

NMR Methods

NMR spectra were recorded on Bruker Advance (500 or 600 MHz) or DRX (500 MHz) spectrometers. 2D NMR data were acquired as previously detailed.[8]

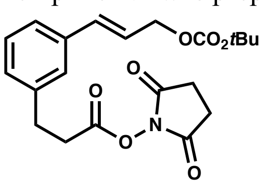
***C*. Experimental Procedures**

Peptide Synthesis

All peptides were synthesized via standard Fmoc solid phase peptide synthesis conditions using Rink Amide MBHA resin (polystyrene, 1% DVB, 0.7 mmol/g).[9]

Linear Precursors Synthesis

Template **2.1** was prepared as described.[10]



2.1

General procedure A – Acylation of peptide by template 1: A round bottom flask was charged with peptide (1.1 equiv.), DMF (10 mL), and *i*Pr_2NEt (4.0 – 6.0 eq.), followed by template **2.1** (1.0 eq.). Reaction progress was monitored by analytical HPLC-UV/MS. Reactions were worked up and purified by column chromatography, trituration, or by preparative HPLC (25%→78% [7 min.] ACN + 0.1% TFA, 18 mL/min, Sunfire C_{18} 19x250 mm) - see details for individual examples below.

General procedure B – Macrocyclization

Using Tf_2NH:

A flask was charged with linear precursor (1 eq.) and nitromethane (5 mM in substrate). The heterogeneous mixture was flushed with argon for 10 mins. A stock solution of Tf_2NH in $MeNO_2$ (4.0 – 6.0 eq., 1 mg/mL stock) was then quickly added. The heterogeneous slurry homogenized and became purple in color. The reaction was stirred for 1 minute (2 minutes for **2.10**). The reaction was quenched with excess *i*Pr_2NEt and concentrated *in vacuo*. The mixture was concentrated, further dried *in vacuo*, diluted with DMSO, and an aliquot was removed and spiked with an equal concentration of internal standard (starting linear precursor). This aliquot was analyzed by HPLC-UV (254 nm) and product peaks were integrated and divided by the internal standard area to provide a yield – uncharacterized products were *not* included towards total yield. Product mixtures were resolved by preparative HPLC purification -— see details per example, below.

Using $MeSO_3H$:
Reactions were carried out in the same manner as for Tf_2NH but using instead $MeSO_3H$ (75 mM in $MeNO_2$, 5 mM in substrate), and were stirred for 30 mins, then neutralized by the addition of *i*Pr_2NEt.

Isomerization of macrocyclic pyrroloindoline ***2.18c:***
Purified **2.18c** was dissolved in a vigorously stirred solution of 1:4 TFA/CH_3NO_2 at room tempertature. Aliquots were removed, quenched with excess *i*Pr_2NEt, taken to dryness, reconstituted in DMSO (75 µL) and analyzed by HPLC-UV (254 nm). Product yield and isomer distribution were determined by peak integration relative to starting **2.18c**. The pseudo-first order rate constant was determined by least-squares fitting of the time-course data to the first-order rate law.

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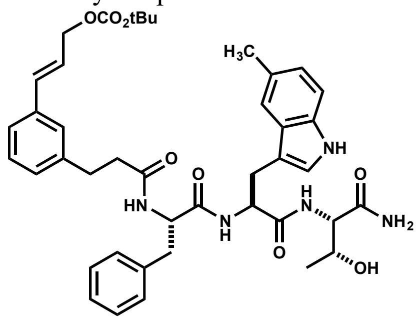
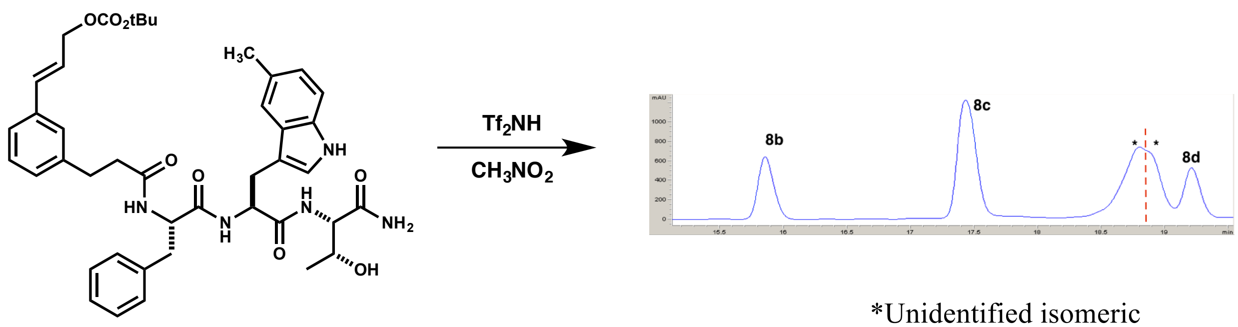
***C*.1.** Acyclic precursors and macrocyclization products

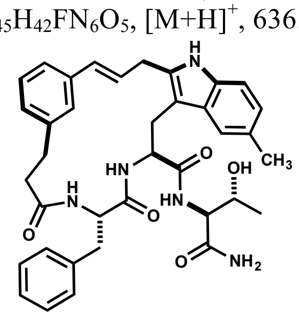


Acyclic Cinnamyl Carbonate 2.6: Synthesized according to Procedure A. After completion of the reaction, the solution was diluted with 100 mL EtOAc and washed 3x50 mL $NaHCO_3$, 3x50 mL NH_4Cl, 1x50 mL brine. Dried with $MgSO_4$ and concentrated *in vacuo*. Chromatographed on SiO_2 with a gradient from 0% to 5% MeOH in $CHCl_3$. White Solid. 81% yield. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.70 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.36 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.21-7.12 (m, 10H), 7.04 (br s, 1H), 6.99 (d, J = 7.5 Hz, 1H), 6.88 (dd, J = 8.2, 1.1 Hz, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.32 (ddd, J = 15.9, 6.3, 6.2 Hz, 1H), 4.90 (d, J = 5.4 Hz, 1H), 4.66 (dd, J = 6.2, 0.8 Hz, 2H), 4.58 (ddd, J = 8.5, 7.5, 4.9 Hz, 1H), 4.52 (ddd, J = 10.0, 8.4, 3.9 Hz, 1H), 4.13 (dd, J = 8.6, 3.2 Hz, 1H), 4.07-4.04 (m, 1H), 3.18-3.14 (m, 1H), 3.03-2.95 (m, 2H), 2.70 (dd, J = 13.9, 10.3 Hz, 1H), 2.62 (apt t, J = 7.9 Hz, 2H), 2.38 (s, 3H), 2.45-2.24 (m, 2H), 1.43 (s, 9H), 1.00 (d, J = 6.3 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 172.0, 171.6, 171.4, 152.8, 141.7, 137.9, 135.8, 134.4, 133.4, 129.1, 128.6, 127.9, 127.6, 126.6, 126.4, 126.1, 124.1, 123.7, 123.2, 122.5, 118.0, 111.0, 109.3, 81.5, 66.9, 66.4, 57.9, 53.8, 53.7, 37.5, 36.7, 30.9, 27.4, 27.1, 21.3, 19.9. MS *m/z* 753.4 (calc'd: $C_{42}H_{51}N_5O_8$, $[M+H]^+$, 753.4).



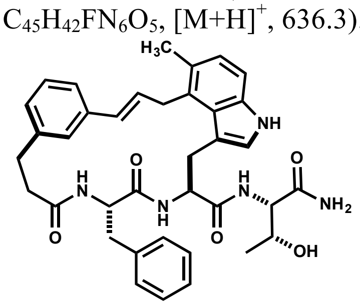
*Unidentified isomeric products

MS *m/z* 636.6 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 636.3).



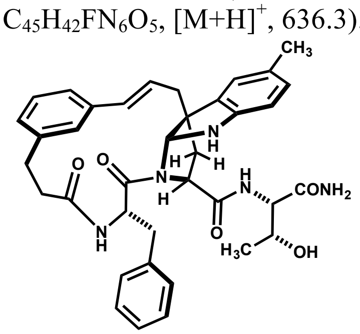
2.8b

MS *m/z* 636.6 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 636.3).



2.8c

MS *m/z* 636.6 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 636.3).



2.8d

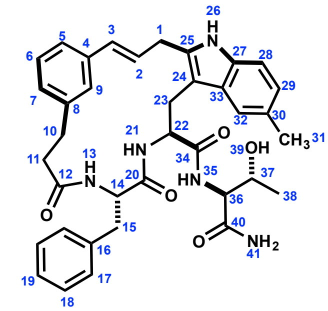
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	40
2.5	30
24	86
29	30

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	40
2	40
30	50

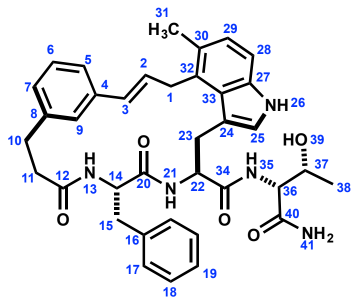
*Macrocyclic Product **2.8b***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	29.8	3.56 (dd, J = 15.6, 6.9 Hz, 1H), 3.78 (dd, J = 15.6, 5.9 Hz, 1H)	HMBC 1->24,25
2	127.8	6.08 (apt dt, J = 15.7, 6.8 Hz, 1H)	COSY 2->1, HMBC 2->4
3	130.3	6.40 (d, J = 15.7 Hz, 1H)	
4	136.6	-	
5	123.9	7.09-7.12 (m, 1H) overlap	
6	127.8	7.14 (dd, J = 7.4, 7.4 Hz, 1H) overlap	
7	127.1	6.95 (br d, J = 7.4 Hz, 1H)	HMBC 7->5
8	141.0	-	
9	124.4	6.98-7.00 (m, 1H) overlap	
10	30.0	2.59-2.65 (m, 1H) overlap, 2.06-2.92 (m, 1H)	HMBC 10->8
11	35.8	2.00 (ddd, J = 14.0, 7.7, 3.1 Hz, 1H), 2.37-2.42 (m, 1H) overlap	
12	171.0	-	
13	-	8.08 (d, J = 8.8 Hz, 1H)	TOCSY 13->14,15, HMBC 13->12
14	52.5	4.79 (ddd, J = 9.4, 9.4, 3.8 Hz, 1H)	
15	38.2	2.61-2.66 (m, 1H) overlap, 2.97-3.02 (m, 1H) overlap	HMBC 15->16
16	137.6	-	
17	129.1	7.17-7.19 (m, 2H) overlap	HMBC 17->19
18	127.4	7.17-7.20 (m, 2H) overlap	HMBC 18->16
19	125.7	7.12-7.15 (m, 1H) overlap	HMBC 19->17
20	172.0	-	
21	-	8.62 (d, J = 7.6 Hz, 1H)	TOCSY 21->22,23, HMBC 21->20
22	54.2	4.67 (ddd, J = 10.6, 7.6, 4.6 Hz, 1H)	
23	26.0	3.02 (dd, J = 14.9, 10.6 Hz, 1H), 3.10 (dd, J = 14.9, 4.6 Hz, 1H) overlap	HMBC 23->24,25
24	105.3	-	
25	133.9	-	
26	-	10.64 (s, 1H)	HMBC 26->24,25,33
27	133.3	-	
28	109.9	7.11 (d, J = 8.3 Hz, 1H) overlap	HMBC 28->30,33
29	121.6	6.83 (dd, J = 8.3, 1.3 Hz, 1H)	HMBC 29->32,31
30	126.3	-	
31	21.1	2.39 (s, 3H)	HMBC 31->29,30,32
32	117.6	7.30 (br s, 1H)	HMBC 32->29,31
33	129.0	-	
34	171.9	-	
35	-	7.66 (d, J = 8.5 Hz, 1H)	HMBC 35->34
36	57.5	4.16 (dd, J = 8.5, 3.1 Hz, 1H)	HMBC 36->40
37	66.0	4.08-4.13 (m, 1H) overlap	
38	19.7	1.08 (d, J = 6.4 Hz, 3H)	HMBC 38->36,37
39	-	not observed	
40	171.8	-	
41	-	6.98-7.00 (m, 1H) overlap, 7.10-7.12 (m, 1H) overlap	HMBC 41->40, TOCSY 41->41'

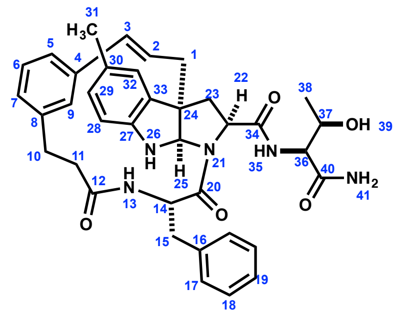
Macrocyclic Product ***2.8c***



(500 MHz, DMSO-d_6, 298K)

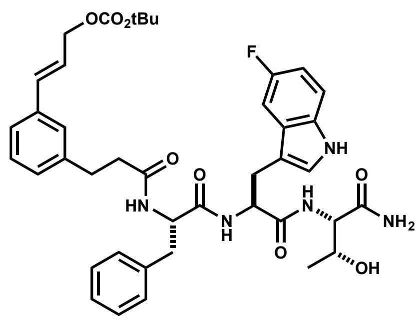
	13C	1H	key correlation
1	32.0	3.82-3.91 (m, 2H)	
2	128.9	6.37 (dt, J = 16.0, 5.4 Hz, 1H)	HMBC 2->4,32, COSY 2->1
3	129.6	6.07 (d, J = 16.0 Hz, 1H)	HMBC 3->5,9
4	136.7	-	
5	123.0	7.02 (d, J = 8.0 Hz, 1H)	
6	127.7	7.09 (dd, J = 8.0, 8.0 Hz, 1H) overlap	HMBC 6->4,8
7	126.8	6.94 (d, J = 8.0 Hz, 1H) overlap	
8	141.1	-	
9	125.3	7.07 (br s, 1H) overlap	
10	29.7	2.54-2.59 (m, 1H) obscured, 2.91-2.97 (m, 1H) overlap	HMBC 10->7,9,12
11	35.9	2.09-2.15 (m, 1H), 2.33-2.39 (m, 1H) overlap	HMBC 11->8,12
12	170.6	-	
13	-	7.94 (d, J = 9.1 Hz, 1H)	HMBC 13->12
14	52.5	4.80-4.88 (m, 1H)	
15	37.9	2.66-2.72 (m, 1H), 2.92-2.97 (m, 1H) overlap	HMBC15->16,17
16	137.7	-	
17	128.8	7.23-7.24 (m, 2H) overlap	HMBC 17->15
18	127.5	7.23-7.25 (m, 2H) overlap	
19	125.6	7.14-7.19 (m, 1H)	
20	171.0	-	
21	-	8.44-8.48 (m, 1H)	HMBC 21->20
22	53.4	4.63-4.70 (m, 1H)	
23	29.5	3.14-3.19 (m, 1H), 3.39 (dd, J = 13.9, 9.9 Hz, 1H)	HMBC 23->24
24	109.5	-	
25	123.3	7.06-7.08 (m, 1H) overlap	HMBC 25->24,27,33
26	-	10.66 (br s, 1H)	COSY 26->25, HMBC 26->24,25,27,33
27	135.4	-	
28	109.2	7.12 (d, J = 8.3 Hz, 1H) overlap	HMBC 28->30,33
29	123.6	6.91 (d, J = 8.3 Hz, 1H)	HMBC 29->27,31,32
30	125.2	-	
31	18.4	2.34 (s, 3H)	HMBC 31->29,30,32
32	128.4	-	
33	126.0	-	
34	170.7	-	
35	-	7.59 (d, J = 8.4 Hz, 1H)	
36	57.6	4.13 (dd, J = 8.4, 3.0 Hz, 1H)	HMBC 36->40
37	65.8	4.04-4.09 (m, 1H)	
38	19.6	1.05 (d, J = 6.2 Hz, 1H)	COSY 38->37, HMBC 38->36,37
39	-	not observed	
40	171.6	-	
41	-	6.87 (br s, 1H), 6.95 (br s, 1H) overlap	

Macrocyclic Product ***2.8d***

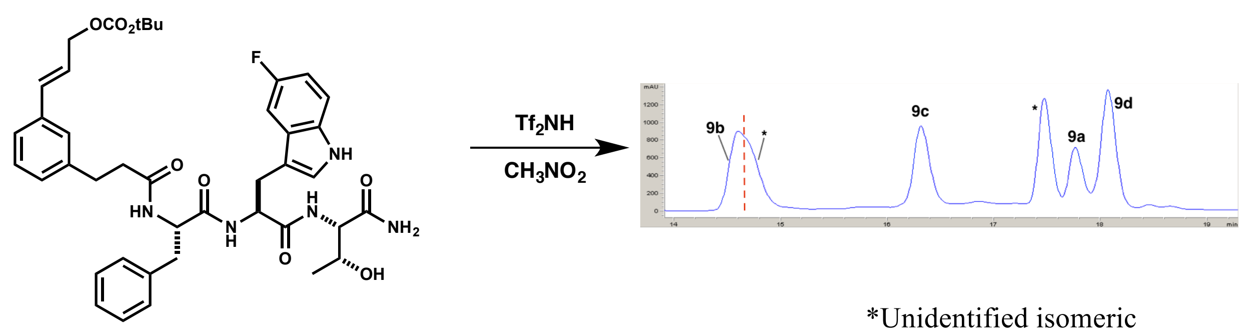


(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	39.3	2.51-2.57 (m, 1H), 2.80 (dd, J = 13.7, 10.0 Hz, 1H)	HMBC 1->24,25
2	126.3	6.05-6.14 (m, 1H)	
3	132.1	6.63 (d, J = 15.8 Hz, 1H)	TOCSY 3->2,1 HMBC 3->4
4	136.9	-	
5	124.3	7.04 (br d, J = 7.6 Hz, 1H)	HMBC 5->3,7
6	128.2	7.15 (dd, J = 7.6, 7.6 Hz, 1H)	HMBC 6->4,8
7	126.8	6.99 (br d, J = 7.6 Hz, 1H)	HMBC 7->5
8	140.5	-	
9	125.0	7.18 (br s, 1H)	
10	30.6	2.62-2.69 (m, 1H), 2.82-2.90 (m, 1H)	
11	37.1	2.01-2.08 (m, 1H), 2.32-3.39 (m, 1H)	HMBC 11->8 TOCSY 11->10,10',11'
12	171.1	-	
13	-	7.96 (d, J = 8.8 Hz, 1H)	HMBC 13->12
14	49.8	5.34 (ddd, J = 8.8, 8.8, 4.8 Hz, 1H)	HMBC 14->20
15	38.3	2.89 (dd, J = 13.9, 8.8 Hz, 1H), 3.09 (dd, J = 13.9, 4.8 Hz, 1H)	HMBC 15->16,17 TOCSY 14->15,13
16	136.5	-	
17	129.8	7.39 (d, J = 7.4 Hz, 2H)	TOCSY 17->18,19
18	127.8	7.28 (dd, J = 7.4, 7.4 Hz, 2H)	HMBC 18->16
19	126.0	7.20-7.24 (m, 1H)	HMBC 19->17
20	171.3	-	
21	-	-	
22	61.6	4.43 (dd, J = 10.4, 5.7 Hz, 1H)	HMBC 22->23,24
23	40.2	2.00-2.07 (m, 1H), 2.50-2.57 (m, 1H)	
24	57.3	-	
25	81.4	6.11 (s, 1H)	HMBC 25->22,24
26	-	not detected	
27	144.9	-	
28	109.9	6.45 (d, J = 7.8 Hz, 1H)	HMBC 28->33
29	128.0	6.84 (dd, J = 7.8, 0.9 Hz, 1H)	HMBC 29->32
30	127.3	-	
31	20.4	2.21 (s, 1H)	HMBC 31->28,30,32
32	122.0	6.91-6.93 (m, 1H)	HMBC 32->27,29
33	135.5	-	
34	170.4	-	
35	-	7.51 (d, J = 7.8 Hz, 1H)	
36	57.2	3.84 (dd, J = 7.8, 2.5 Hz, 1H)	HMBC 36->40
37	65.2	3.91-3.97 (m, 1H)	HMBC 37->40
38	19.3	0.78 (d, J = 6.6 Hz, 3H)	COSY 38->37 TOCSY 38->35,36,37
39	-	not detected	
40	171.5	-	
41	-	6.68 (br s, 1H), 7.20 (br s, 1H)	HMBC 41->40 TOCSY 41->41'

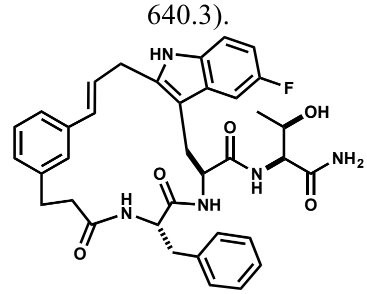
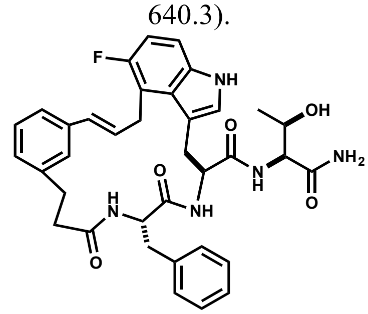


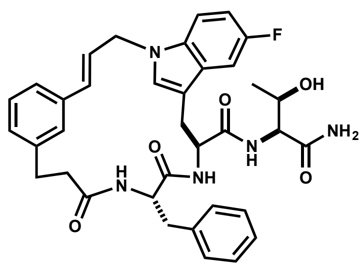
Acyclic Cinnamyl Carbonate 2.7: Synthesized according to Procedure A. Workup and chromatography conditions were the same as for linear precursor **2.6**. White Solid. 62% yield. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.97 (d, J = 2.2 Hz, 1H), 8.29 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 7.8 (d, J = 8.6 Hz, 1H), 7.41 (dd, J = 10.2, 2.4 Hz, 1H), 7.32 (dd, J = 8.8, 4.5 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 7.26 (br. d, J = 7.8 Hz, 1H), 7.23 (br. s, 1H), 7.21 (br. s, 1H), 7.2 (br. s, 1H), 7.14-7.18 (m, 4H), 7.09 (br. s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.9 (ddd, J = 9.0, 9.0, 2.3 Hz, 1H), 6.63 (d, J = 15.7 Hz, 1H), 6.33 (dt, J = 15.9, 6.2 Hz, 1H), 4.67 (dd, J = 6.3, 1.1 Hz, 2H), 4.63 (ddd, J = 8.6, 8.0, 4.9 Hz, 1H), 4.54 (ddd, J = 9.9, 8.4, 4.0 Hz, 1H), 4.16 (dd, J = 8.7, 3.2 Hz, 1H), 4.08 (dddd, J = 6.2, 6.2, 6.2, 3.4 Hz, 1H), 3.17 (dd, J = 15.0, 4.6 Hz, 1H), 3.02 (dd, J = 15.3, 9.3 Hz, 1H), 2.97 (dd, J = 13.7, 4.0 Hz, 1H), 2.71 (dd, J = 13.9, 16.0 Hz, 1H), 2.65 (app t, J = 7.9 Hz, 2H), 2.23-2.38 (m, 2H), 1.4 (s, 9H), 1.02 (d, J = 6.4 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 172.0, 171.5, 171.4, 171.3, 157.6, 155.8, 152.8, 141.7, 137.9, 135.8, 133.4, 132.7, 129.1, 128.6, 127.9, 127.6, 127.5, 126.4, 126.1, 125.9, 124.1, 123.2, 112.14, 112.06, 110.2, 110.2, 109.0, 108.8, 103.3, 103.1, 81.5, 66.9, 66.3, 58.0, 53.7, 53.5, 37.4, 36.7, 30.9, 27.3, 19.9. MS *m/z* 758.8 (calc'd: $C_{41}H_{48}FN_5O_8$, $[M+H]^+$, 758.4).



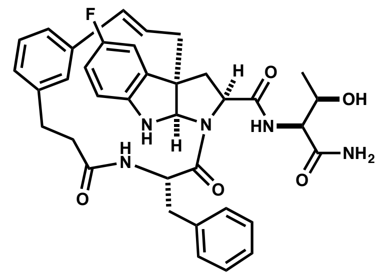
*Unidentified isomeric

products

MS *m/z* 640.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 640.3).	MS *m/z* 640.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 640.3).
 **2.9b**	 **2.9c**
MS *m/z* 640.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 640.3).	MS *m/z* 640.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 640.3).



2.9a



2.9d

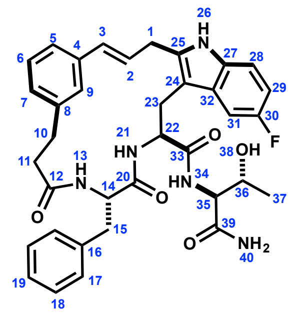
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2.5	30
24	86
29	30

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	40
2	40
30	60

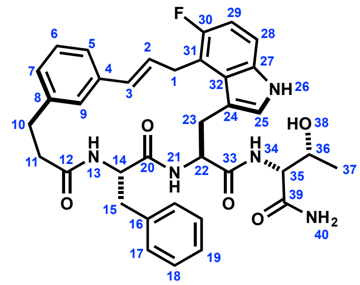
Macrocyclic Product ***2.9b***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	46.6	4.95 (ddd, J = 16.4, 4.7, 1.6 Hz, 1H), 4.83 (dd, J = 16.4,6.9 Hz, 1H)	TOCSY1->2,3 HMBC 1->2,3,25
2	125.5	6.07 (ddd, J = 15.8, 7.1, 4.5 Hz, 1H)	HMBC 2->1,3,4
3	131.0	6.22 (br d, J = 15.9 Hz, 1H)	
4	135.7	-	
5	124.7	7.11 (m, 1H) overlap	HMBC 5->9,7
6	127.8	7.15 (m, 1H) overlap	HMBC 6->4,8
7	128.2	6.96 (m, 1H) overlap	
8	142.0	-	
9	124.5	6.92 (m, 1H) overlap	HMBC 9->7
10	29.1	2.46 (m, 1H) overlap, 2.95 (m, 1H) overlap	HMBC 10->7,8,9,11,12
11	35.5	2.08 (ddd, J = 15.1, 7.2, 2.4 Hz, 1H), 2.40 (ddd, J = 15.2, 11.6, 2.3 Hz, 1H)	TOCSY 11->10
12	170.6	-	
13	-	7.68 (d, J = 8.5 Hz, 1H)	HMBC 13->12 TOCSY 13->14,15
14	52.6	4.71 (m, 1H) overlap	
15	38.9	2.70 (dd, J = 13.6, 8.0 Hz, 1H), 3.02 (dd, J = 13.6, 4.1 Hz, 1H)	HMBC 15->14,16,17,20
16	137.6	-	
17	129.4	7.08 (m, 1H) overlap	HMBC 17->15
18	127.8	7.15 (m, 1H) overlap	HMBC 18->16
19	126.4	7.11 (m, 1H) overlap	HMBC 19->17
20	170.6	-	
21	-	8.60 (d, J = 8.7 Hz, 1H)	TOCSY 21->22,23 HMBC 21->20
22	52.6	4.74 (m, 1H) overlap	HMBC 22->23
23	27.2	3.10 (br. d, J = 14.8 Hz, 1H), 2.90 (m, 1H) overlap	HMBC 23->22,24,25
24	110.8	-	
25	128.1	7.28 (s, 1H)	HMBC 25->1,32,38
26	-	-	
27	132.6	-	
28	110.9	7.45 (dd, J = 7.8, 4.5 Hz, 1H)	HMBC 28->32 TOCSY 28->29,31
29	109.2	6.94 (m, 1H) overlap	HMBC 29->27,30
30	157.0	-	
31	103.8	7.51 (dd J = 9.9, 2.4 Hz, 1H)	HMBC 31->27,30
32	127.8	-	
33	171.9	-	
34	-	7.96 (d, J = 8.8 Hz, 1H)	TOCSY 34->35,36 HMBC 34->33
35	58.0	4.21 (dd, J = 8.8, 3.1 Hz, 1H)	HMBC 35->36
36	66.4	4.10 (m, 1H)	
37	20.0	1.07 (d, J = 6.4 Hz, 3H)	HMBC 37->35,36
38	-	not observed	
39	172.2	-	
40	-	7.2 (br. s, 2H)	HMBC 40->39

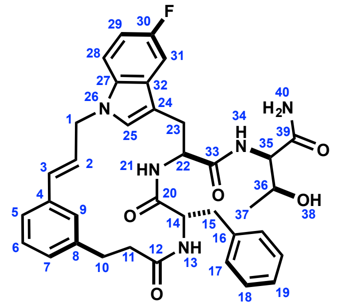
Macrocyclic Product ***2.9c***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	30.0	3.57 (dd, J = 15.3, 7.2 Hz, 1H), 3.80 (dd, J =15.3, 6.3 Hz, 1H)	TOCSY 1->2,3 HMBC 1->2,3,24,25
2	127.6	6.07 (dt, J = 15.6, 6.9 Hz, 1H)	HMBC 2->1,4
3	131.0	6.43 (d, J = 15.9 Hz, 1H)	HMBC 3->1,4,5,9
4	136.8	-	
5	123.6	7.10 (m, 1H) overlap	HMBC 5->9
6	127.9	7.13 (m, 1H) overlap	HMBC 6->4
7	124.0	7.10 (m, 1H) overlap	HMBC 7->5,9
8	141.2	-	
9	125.0	6.98 (br. s, 1)	HMBC 10->8,9 TOCSY 10->11
10	30.4	2.62 (m, 1H) overlap, 2.88 (ddd, J = 13.7, 11.0, 5.6 Hz, 1H)	HMBC 11->8,12
11	35.8	1.98 (ddd, J = 14.0, 7.6, 3.1 Hz, 1H), 2.40 (ddd, J = 13.6, 11.0, 2.6 Hz, 1H)	
12	171.2	-	
13	-	8.07 (d, J - 8.9 Hz, 1H)	COSY 13->14 TOCSY 13->14,15,15' HMBC 13->12
14	52.7	4.75 (ddd, J = 9.3, 9.5, 3.8 Hz, 1H)	HMBC 14->15
15	38.0	2.98 (m, 1H) overlap , 2.65 (m, 1H) overlap	HMBC 15->14,16,17
16	138.1	-	
17	129.5	7.16 (m, 1H) overlap	HMBC 17->18
18	127.7	7.17 (m, 1H) overlap	HMBC 18->16,17
19	128.0	7.14 (m, 1H) overlap	
20	172.1	-	
21	-	8.59 (d, J = 7.8 Hz, 1H)	COSY 21->22 TOCSY 21->22,23 HMBC 21->20
22	54.1	4.66 (ddd, J = 10.2, 7.6, 5.1 Hz, 1H)	HMBC 22->23
23	26.2	3.07 (dd, J - 15.1, 5.2 Hz, 1H), 2.97 (m, 1H) overlap	HMBC 23->22,24,32
24	106.4	-	
25	136.4	-	
26	-	10.91 (s, 1H)	HMBC 26->24,25,27,32
27	131.8	-	
28	111.2	7.18 (m, 1H) overlap	HMBC 28->30 TOCSY 28->29
29	108.4	6.81 (ddd, J = 9.3, 9.3, 2.5 Hz, 1H)	TOCSY 29->28,31 HMBC 29->27,30
30	156.6	-	
31	103.4	7.24 (dd, J = 10.3, 2.7 Hz, 1H)	HMBC 31->27,30
32	129.0	-	
33	172.1	-	
34	-	7.73 (d, J = 8.7 Hz, 1H)	HMBC 34->33 TOCSY 34->35,36,37
35	57.8	4.13 (dd, J = 8.7, 2.9 Hz, 1H)	HMBC 35->36,39
36	66.2	4.07 (m, 1H)	
37	19.5	1.05 (d, J = 6.4 Hz, 3H)	
38	-	4.96 (d, J = 4.9 Hz, 1H)	
39	172.0	-	
40	-	6.93 (m, 1H) overlap	HMBC 40->39

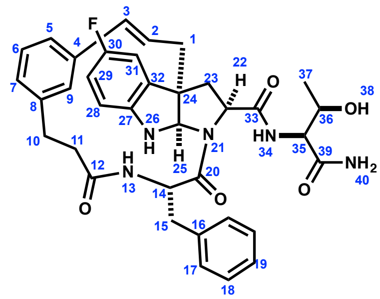
*Macrocyclic Product **2.9a***



(500 MHz, DMSO-d_6, 298K)

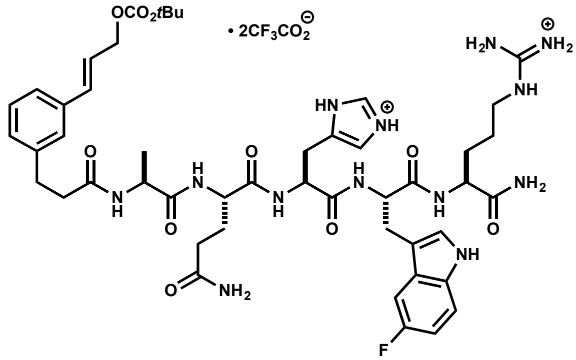
	13C	1H	key correlation
1	27.8	3.76 (dd, J = 16.6, 5.9 Hz, 1H), 3.90 (br. d, J = 16.0 Hz, 1H)	TOCSY1->2,3 HMBC 1->2,3,31
2	130.0	6.07 (d, J = 15.8 Hz, 1H)	HMBC 2->1,31
3	128.8	6.35 (dt, J = 16.0, 5.5 Hz, 1H)	HMBC 3->1,5,9,30,32
4	136.5	-	
5	122.9	7.00 (m, 1H) overlap	HMBC 5->9
6	127.8	7.06 (m, 1H) overlap	HMBC 6->4,8
7	127.1	7.06 (m, 1H) overlap	HMBC 7->9
8	141.3	-	
9	125.8	6.99 (br. s, 1H)	HMBC 9->5,7
10	29.6	2.91 (m, 1H) overlap, 2.52 (m, 1H) overlap	HMBC 10->7,8,9,11,12
11	35.7	2.32 (app t, 13.5 Hz, 1H), 2.08 (m, 1H) overlap	HMBC 11->8,12
12	170.7	-	
13	-	8.1 0 (d, J = 8.9 Hz, 1H)	HMBC 13->12 TOCSY 13->14,15,15'
14	52.6	4.82 (ddd, J = 9.7, 9.7, 4.1 Hz, 1H)	HMBC 14->15
15	38.0	2.89 (m, 1H) overlap, 2.64 (dd, J = 13.3, 10.5 Hz, 1H)	HMBC 15->14,16,17
16	137.7	-	
17	128.8	7.21 (m, 1H) overlap	
18	127.6	7.21 (m, 1H) overlap	
19	127.6	7.15 (m, 1H) overlap	HMBC 19->17
20	171.1	-	
21	-	8.62 (d, J = 6.6 Hz, 1H)	HMBC 21->20 TOCSY 21->22,23
22	53.2	4.66 (m, 1H)	
23	29.1	3.30 (m, 1H) overlap, 3.06 (br. d, J = 13.4 Hz, 1H)	HMBC 23->22,24
24	110.6	-	HMBC 25->27
25	125.8	7.13 (m, 1H) overlap	HMBC 26->24,25,27
26	-	10.96 (br. s, 1H)	
27	133.0	-	
28	110.0	7.18 (m, 1H) overlap	
29	108.8	6.89 (m, 1H) overlap	HMBC 29->27,30,31
30	154.5	-	
31	115.6	-	
32	125.8	-	
33	170.7	-	
34	-	7.74 (d, J = 8.3 Hz, 1H)	HMBC 34->33 TOCSY 34->35,36,37
35	57.8	4.08 (dd, J = 8.7, 3.0 Hz, 1H)	
36	65.8	4.02 (m, 1H)	
37	19.8	0.99 (d, J = 6.4 Hz, 3H)	HMBC 37->35,36
38	-	4.9 (d, J = 5.1 Hz, 1H)	HMBC 38->35,36,37
39	171.7	-	
40	-	7.03 (m, 1H) overlap	HMBC 40->39

Macrocyclic Product ***2.9d***

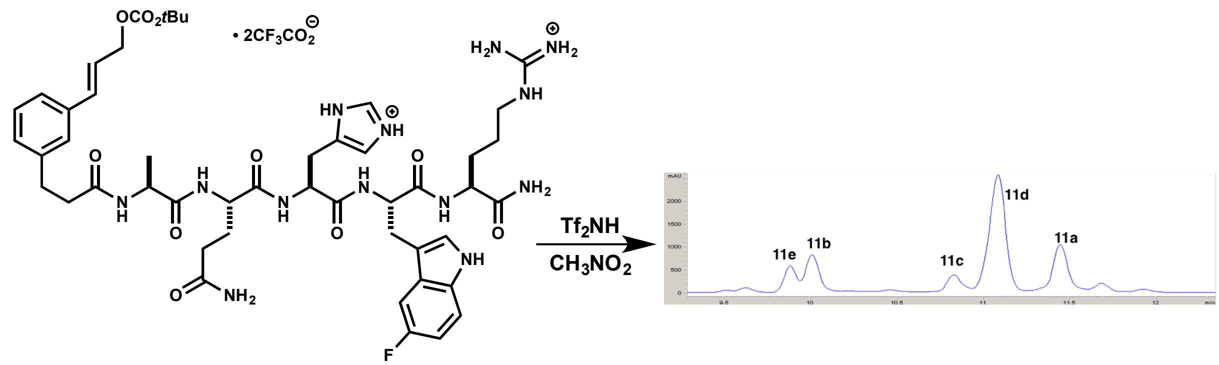


(500 MHz, DMSO-d_6, 298K)

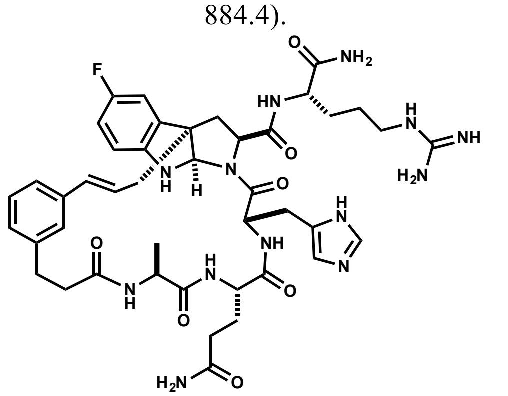
	13C	1H	key correlation
1	39.0	2.51-2.57 (m, 1H), 2.79-2.85 (m, 1H)	HMBC 1->24
2	125.0	6.09 (ddd, J = 15.8, 9.7, 6.2 Hz, 1H)	TOCSY 2->3,1
3	132.6	6.62 (d, J = 15.8 Hz, 1H)	HMBC 3->4
4	136.9	-	
5	124.2	7.05 (br d, J = 8.5 Hz, 1H)	HMBC 5->9,7
6	127.9	7.15 (dd, J = 8.5, 7.4 Hz, 1H)	HMBC 6->4,8
7	127.0	6.99 (br d, J = 7.4 Hz, 1H)	
8	140.5	-	
9	124.9	7.18 (br s, 1H)	HMBC 9->3
10	30.9	2.62-2.67 (m, 1H), 2.85-2.90 (m, 1H)	
11	37.4	2.05 (ddd, J = 13.5, 6.9, 3.8 Hz, 1H), 2.35 (ddd, J = 13.5, 10.8, 3.1 Hz, 1H)	
12	171.4	-	
13	-	7.96 (d, J = 8.8 Hz, 1H)	HMBC 13->12
14	50.1	5.33 (ddd, J = 8.9, 8.8, 4.8 Hz, 1H)	HMBC 14->20
15	38.6	2.82-2.87 (m, 1H), 3.08 (dd, J = 14.0, 4.8 Hz, 1H)	HMBC 15->16,17 TOCSY 15->14,13
16	136.7	-	
17	129.9	7.38 (d, J = 7.4 Hz, 2H)	HMBC 17->19
18	127.8	7.27 (dd, J = 7.4, 7.4 Hz, 2H)	HMBC 18->16
19	126.1	7.20-7.23 (m, 1H)	HMBC 18->17
20	171.2	-	
21	-	-	
22	61.5	4.48 (dd, J =10.3, 5.5 Hz, 1H)	HMBC 22->24 COSY 22->23
23	40.0	2.10 (dd, J = 13.6, 5.5 Hz, 1H), 2.51-2.55 (m, 1H)	HMBC 23->24
24	57.6	-	
25	81.6	6.16 (br s, 1H)	COSY 25->26 HMBC 25->27
26	-	6.32 (br s, 1H)	
27	143.8	-	
28	110.5	6.51 (dd, JHH = 8.6 Hz, JHF = 4.6 Hz, 1H)	HMBC 28->30,32
29	113.7	6.84 (ddd, JHF = 9.0 Hz, JHH = 8.6, 2.7 Hz, 1H)	HMBC 29->27,30
30	156.8 (d, J≈240 Hz)	-	
31	109.3	7.02 (dd, JHF = 8.4 Hz, JHH = 2.7 Hz, 1H)	HMBC 31->27,30
32	136.9	-	
33	170.4	-	
34	-	7.49 (d, J = 8.0 Hz, 1H)	HMBC 34->33
35	57.5	3.86 (ddd, J = 8.0, 2.6 Hz, 1H)	HMBC 35->39
36	65.6	3.90-3.96 (m, 1H)	
37	19.4	0.77 (d, J = 6.6 Hz, 3H)	COSY 37->36 TOCSY 37->36,35,34
38	-	not detected	
39	171.5	-	
40	-	6.73 (br s, 1H), 7.19 (br s, 1H)	TOCSY 40->40'



Acyclic Cinnamyl Carbonate 2.10: Synthesized according to Procedure B. White Powder. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.98 (d, J = 2.3 Hz, 1H), 8.96 (d, J = 1.2 Hz, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.06-8.16 (m, 4H), 7.74 (t, J = 5.7 Hz, 1H), 7.39 (dd, J = 16.0, 2.5 Hz, 1H), 7.36 (br. s, 1H), 7.23-7.34 (m, 7H), 7.09-7.14 (m, 2H), 6.87-6.93 (m, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.35 (dt, J = 16.0, 6.2 Hz, 1H), 4.68 (dd, J = 6.5, 1.0 Hz, 2H), 4.52-4.60 (m, 2H), 4.18-4.28 (m, 2H), 4.16 (ddd, J = 7.9, 5.6 Hz, 1H), 3.03-3.17 (m, 4H), 2.94 (dd, J = 15.9, 15.9, 9 Hz, 2H), 2.75-2.84 (m, 2H), 2.39-4.29 (m, 2H), 2.04-2.17 (m, 2H), 1.80-1.91 (m, 1H), 1.65-1.79 (m, 2H), 1.45-1.55 (m, 2H), 1.43 (s, 9H), 1.15 (d, J = 7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ174.1, 173.1, 172.7, 171.6, 171.4, 171.3, 169.8, 157.6, 156.8, 155.8, 152.8, 141.7, 135.8, 133.7, 133.4, 132.7, 129.3, 129.1, 128.6, 128.0, 127.5, 127.4, 126.4, 125.9, 124.2, 123.3, 117.7, 116.8, 115.3, 115.2, 112.2, 112.1, 109.9, 109.9, 81.5, 66.9, 55.0, 53.4, 52.4, 52.2, 51.5, 48.3, 36.6, 31.3, 30.8, 29.1, 27.3, 25.0, 17.9. MS m/z 1002.7 (calc'd: $C_{48}H_{64}N_{13}O_{10}$, $[M+H]^+$, 1002.5).

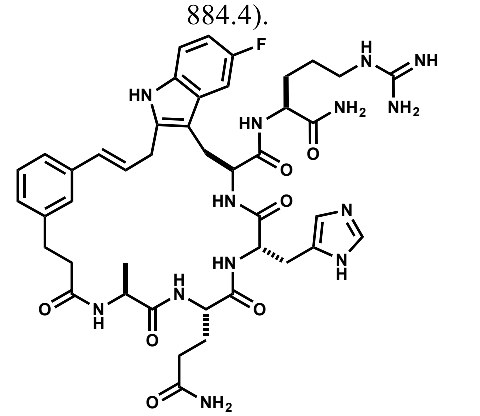


MS m/z 884.4 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 884.4).



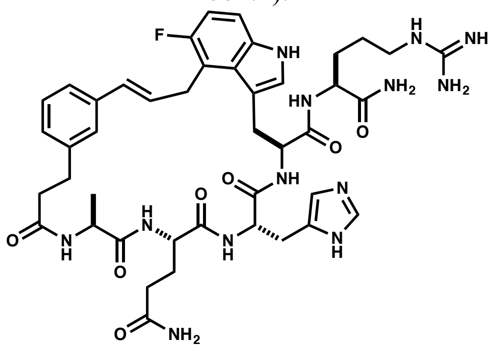
2.11e

MS m/z 884.4 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 884.4).



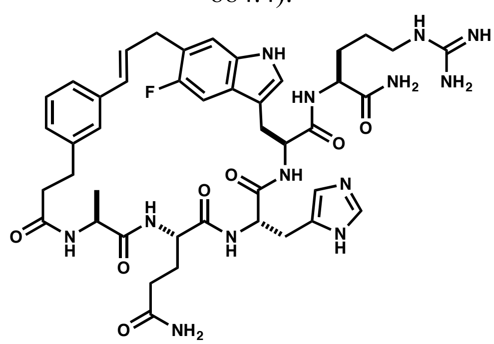
2.11b

MS *m/z* 884.4 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 884.4).



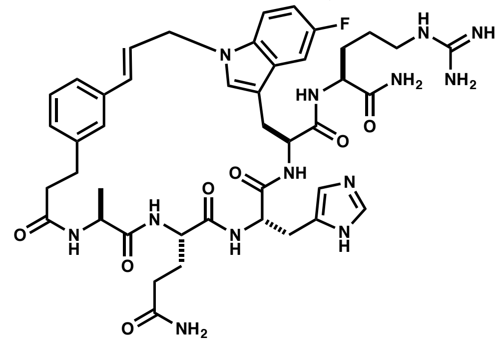
2.11c

MS *m/z* 884.4 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 884.4).



2.11d

MS *m/z* 884.4 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 884.4).



2.11a

Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	10
0.5	10
2	25
17	64

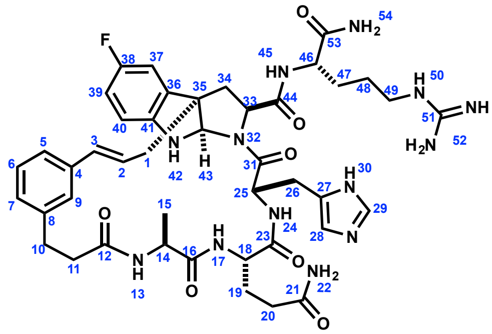
Preparative HPLC method A:
Column: Waters XBridge™ C_{18}, 19x250mm, 5µm.
Solvent A: H_2O + 0.1%v TFA
Solvent B: ACN + 0.1%v TFA
Flow rate: 18.00 ml/min

Time	%B
0	30
2	30
30	100

Preparative HPLC method B:
Same as A
Repurification of **11a, 11c, & 11d**

Time	%B
0	30
2	30
30	55

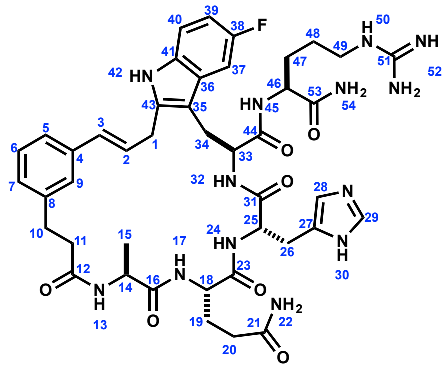
Macrocyclic Product ***2.11e***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlations
1	47.1	4.83 (dd, J 15.5, 6.4 Hz, 1H), 4.99 (dd, J = 15.5, 5.7 Hz, 1H)	HMBC 1->41,43
2	125.4	6.37 (ddd, J = 15.7, 6.4, 5.7 Hz, 1H)	HMBC 2->4
3	131.9	6.65 (br d, J = 15.7 Hz, 1H)	TOCSY 3->2,1
4	135.9	-	
5	125.1	7.15-7.20 (m, 1H) overlap	
6	128.5	7.19-7.24 (m, 1H) overlap	HMBC 6->4,8
7	127.8	7.09 (br d, J = 7.1 Hz, 1H)	
8	141.6	-	
9	125.6	7.25 (br s, 1H) overlap	
10	30.7	2.73-2.86 (m, 2H)	HMBC 10->8,12
11	36.3	2.36-2.51 (m, 2H)	HMBC 11->8,12
12	172.6	-	
13	-	8.24 (d, J = 6.4 Hz, 1H)	HMBC 13->12
14	49.6	7.94-7.98 (m, 1H)	HMBC 14->16
15	17.3	1.14 (d, J = 7.2 Hz, 3H)	TOCSY 15->14,13
16	173.2	-	
17	-	7.81-7.88 (m, 1H)	HMBC 17->16
18	49.6	4.08-4.16 (m, 1H)	
19	27.4	1.65-1.74 (m, 1H), 179-1.87 (m, 1H)	HMBC 19->21
20	31	1.95-2.11 (m, 2H)	HMBC 20->21
21	174.1	-	
22	-	6.81 (br s, 1H), 7.30 (br s, 1H)	HMBC 22->21
23	171.9	-	
24	-	8.12 (d, J = 7.6 Hz, 1H)	HMBC 24->23
25	51.4	4.55-4.62 (m, 1H) overlap	HMBC 25->31
26	26.8	2.92-3.01 (m, 1H) overlap, 3.06-3.12 (m, 1H)	
27	129.6	-	
28	116.9	7.25 (s, 1H) overlap	HMBC 28->29
29	134.1	8.95 (br s, 1H)	HMBC 29->27,28
30	-	Not detected	
31	170.7	-	
32	-	8.02 (d, J = 7.2 Hz, 1H)	HMBC 32->31
33	53.3	4.52-4.59 (m, 1H)	HMBC 33->34
34	27.3	2.92-3.01 (m, 1H) overlap, 3.12-3.22 (m, 1H)	HMBC 34->33,35
35	109.9	-	
36	128	-	
37	103.9	7.45 (dd, JHF = 9.9 Hz, JHH = 2.3 Hz, 1H)	HMBC 37->41
38	157.1 (d, J ≅ 220Hz)	-	
39	109.4	6.98 (ddd, JHF = 9.1 Hz, JHH = 9.1, 2.3 Hz, 1H)	HMBC 39->41
40	111.1	7.48 (dd, JHH = 9.1 Hz, JHF = 4.5 Hz, 1H)	HMBC 40->36
41	132.8	-	
42	-	-	
43	128.5	7.28 (s, 1H)	HMBC 43->1
44	171.9	-	
45	-	8.22 (d, J = 8.1 Hz, 1H)	
46	52.2	4.19-4.28 (m, 1H)	HMBC 46->53
47	29.1	1.54-1.64 m, 1H), 1.69-1.79 (m, 1H)	
48	25	1.43-1.57 (m, 2H)	
49	40.5	3.08-3.15 (m, 2H) overlap	HMBC 49->51
50	-	7.61 (t, J = 5.1 Hz, 1H)	
51	156.9	-	
52	-	14.03-14.44 (m, 3H)	
53	173.4	-	
54	-	7.15 (br s, 1H), 7.31 (br s, 1H)	HMBC 54->53

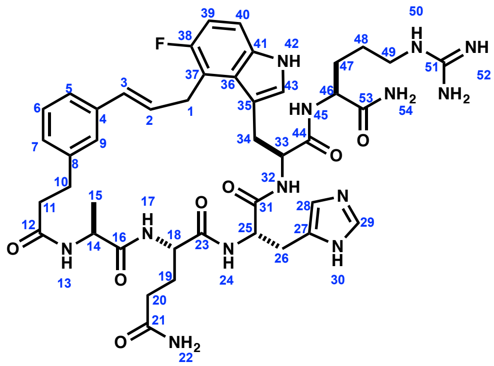
*Macrocyclic Product **2.11b***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlations
1	32.4	3.52 (dd, J = 15.3, 5.6 Hz, 1H), 3.64 (dd, J = 15.3, 6.3 Hz, 1H)	HMBC 1->38,39,40
2	129.3	6.39 (ddd, J = 15.8, 6.3, 5.6 Hz, 1H)	TOCSY 2->1,2 HMBC 2->4
3	129.9	6.30 (br d, J = 15.8 Hz, 1H)	HMBC 3->4
4	137	-	
5	124.1	7.13-7.17 (m, 1H) overlap	HMBC 5->7,9
6	128.3	7.15-7.19 (m, 1H) overlap	HMBC 6->4,8
7	127.3	7.10 (br d, J = 7.2 Hz, 1H)	HMBC 7->9
8	141.1	-	
9	124.5	7.10 (br s, 1H) overlap	HMBC 9->7
10	30.2	2.69-2.76 (m, 1H), 2.77-2.82 (m, 1H) overlap	HMBC 10->7,8,9,12
11	35.4	2.31 (ddd, J = 14.3, 6.5, 6.5 Hz, 1H), 2.44-2.51 (m, 1H) overlap	HMBC 11->8,12
12	171.4	-	
13	-	8.07 (d, J = 7.6 Hz, 1H)	HMBC 13->12
14	47.7	4.12 (qd, J = 7.6, 7.1 Hz, 1H)	HMBC 14->15,16
15	17.6	0.85 (d, J = 7.1 Hz, 3H)	HMBC 15->15,16
16	172.3	-	
17	-	7.86 (d, J = 7.7 Hz, 1H)	HMBC 17->16
18	52.3	3.98 (ddd, J = 8.0, 7.8, 5.4 Hz, 1H)	TOCSY 18->17,18,20 HMBC 18->19,20,23
19	27.3	1.50-1.58 (m, 1H) overlap, 1.70-1.81 (m, 1H) overlap	HMBC 19->20,21
20	30.9	1.91-2.00 (m, 2H)	HMBC 20->21
21	173.9	-	
22	-	6.78 (br s, 1H), 7.22 (br s, 1H) overlap	TOCSY 22->22'
23	171.2	-	
24	-	7.56 (br d, J = 6.8 Hz, 1H)	HMBC 24->23
25	50.7	4.45 (ddd, J = 7.2, 6.8, 5.8 Hz, 1H)	COSY 25->24
26	27.6	2.93 (dd, J = 15.3, 7.6 Hz, 1H), 3.05-3.12 (m, 1H) overlap	HMBC 26->27
27	128.9	-	
28	116.8	7.28 (s, 1H)	HMBC 28->27,30
29	-	not observed	
30	134	8.95 (br s, 1H)	HMBC 30->27,28
31	170	-	
32	-	8.07 (d, J = 7.4 Hz, 1H)	HMBC 32->31
33	53.7	4.60 (ddd, J = 10.9, 7.4, 3.3 Hz, 1H)	TOCSY 33->32,34
34	27.7	2.85 (dd, J = 14.4, 11.1 Hz, 1H), 3.13-3.20 (m, 1H) overlap	HMBC 34->33,35
35	109.8	-	
36	133	-	
37	103.8	7.57 (d, JHF = 11.1 Hz, 1H)	HMBC 37->35,41,38,39
38	155.3 (d, J ≅ 230Hz)	-	
39	120.1	-	
40	112.8	7.21 (d, JHF = 6.4 Hz, 1H)	HMBC 40->38
41	133	-	
42	-	10.83 (d, J = 1.3 Hz, 1H)	HMBC 42->35,36,41
43	125.7	7.17-7.19 (m, 1H) overlap	
44	172.2	-	
45	-	8.70 (br d, J = 7.8 Hz, 1H)	HMBC 45->44
46	52.2	4.25 (ddd, J = 7.8, 7.8, 6.1 Hz, 1H)	TOCSY 46->45,47,48,49
47	28.9	1.55-1.63 (m, 1H) overlap, 1.71-1.78 (m, 1H) overlap	HMBC 47->46
48	25.1	1.47-1.57 (m, 2H) overlap	HMBC 48->49
49	40.3	3.09-3.16 (m, 2H) overlap	HMBC 49->47,48,51
50	-	14.17 (br s) overlap	
51	156.9	-	
52	-	14.17 (br s) overlap	
53	173.3	-	
54	-	7.14 (br s, 1H), 7.39 (br s, 1H)	TOCSY 54'->54

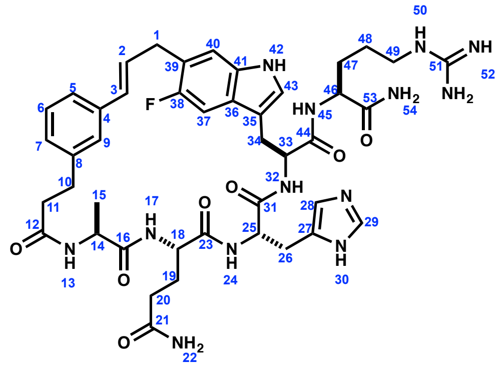
Macrocyclic Product ***2.11c***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlations
1	27.3	3.80-3.91 (m, 2H)	HMBC 1->2,3,37
2	129.2	6.44 (dt, J = 15.8, 6.0 Hz, 1H)	HMBC 2->4,37
3	129.9	6.20 (br d, J = 15.8 Hz, 1H)	HMBC 3->5,9 TOCSY 3->2,1
4	136.9	-	
5	124.4	6.99-7.02 (m, 1H) overlap	
6	128.1	7.13 (dd J = 7.6, 7.6 Hz, 1H)	HMBC 6->4,8
7	127.5	6.99-7.02 (m, 1H) overlap	
8	141.4	-	
9	125.7	7.35 (br s, 1H)	HMBC 9->3,5,7
10	30.4	2.76-2.87 (m, 2H)	HMBC 10->8,12
11	35.9	2.44 (ddd, J = 14.6, 5.7, 5.7 Hz, 1H), 2.56 (ddd, J = 14.6, 9.3, 5.8 Hz, 1H)	HMBC 11->8,12
12	172.6	-	
13	-	8.11 (d, J = 6.0 Hz, 1H)	HMBC 13->12
14	49.3	3.97-4.03 (m, 1H)	HMBC 14->16
15	17.3	1.09 (d, J = 7.2 Hz, 3H)	HMBC 15->14 TOCSY 15->14,13
16	173.2	-	
17	-	8.01 (d, J = 7.5 Hz, 1H)	
18	53	4.00-4.06 (m, 1H) overlap	HMBC 18->23
19	26.8	1.62-1.70 (m, 1H) overlap, 1.73-1.82 (m, 1H) overlap	HMBC 19->21,23
20	30.9	1.95-2.03 (m, 1H), 2.04-2.11 (m, 1H)	HMBC 20->21
21	174.1	-	
22	-	6.87(br s, 1H), 7.30 (br s, 1H) overlap	
23	171.9	-	
24	-	8.27 (d, J = 7.9 Hz, 1H)	HMBC 24->23
25	51.5	4.60 (ddd, J = 9.3, 7.9, 5.1 Hz, 1H)	HMBC 25->31
26	26.2	3.03-3.09 (m, 1H) overlap, 3.22-3.27 (m, 1H)	HMBC 26->27,31
27	129.7	-	
28	116.3	7.30 (s, 1H) overlap	HMBC 28->29 TOCSY 28->29
29	134.1	8.97 (br s, 1H)	
30	-	Not observed	
31	169.7	-	
32	-	7.92 (d, J = 7.9 Hz, 1H)	HMBC 32->31
33	54.3	4.71 (ddd, J = 8.7, 7.9, 5.6 Hz, 1H)	HMBC 33->44
34	29.3	3.02-3.07 (m, 1H), 3.29 (dd, J = 14.8, 5.3 Hz, 1H)	HMBC 34->44
35	110.4	-	
36	125.7	-	
37	116.2	-	
38	154.9	-	
39	109.3	6.92 (dd, JHF = 9.7Hz, JHH = 8.9 Hz, 1H)	HMBC 39->37,41
40	110.7	7.21 (dd, JHH = 8.9 Hz, JHF = 4.4 Hz, 1H)	HMBC 40->36
41	133.4	-	
42	-	10.95 (d, J = 2.4 Hz, 1H)	TOCSY 42->43 HMBC 42->41
43	125.9	7.13 (d, J = 2.4 Hz, 1H)	
44	170.7	-	
45	-	8.01 (d, J = 7.5 Hz, 1H)	TOCSY 45->46,47,48,49,50 HMBC 45->44
46	51.9	4.14 (ddd, J = 8.1, 7.5, 6.0 Hz, 1H)	HMBC 46->53
47	28.3	1.44-1.53 (m, 1H), 1.62-1.70 (m,1 H)	
48	24.4	1.36-1.45 (m, 2H)	
49	40.2	3.03-3.09 (m, 2H) overlap	HMBC 49->47,51
50	-	7.47 (t, J = 5.5 Hz, 1H)	
51	156.6	-	
52	-	13.95-14.37 (m, 3H)	
53	173	-	
54	-	6.92 (br s, 1H) overlap, 6.99 (br s, 1H) overlap	TOCSY 54'->54

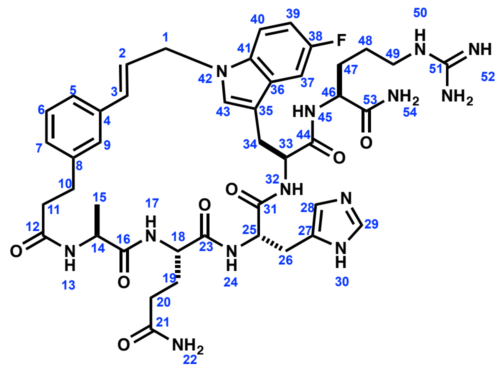
Macrocyclic Product ***2.11d***



(500 MHz, DMSO-d_6, 298K)

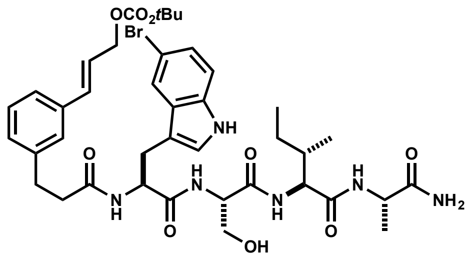
	13C	1H	key correlations
1	32.4	3.52 (dd, J = 15.3, 5.6 Hz, 1H), 3.64 (dd, J = 15.3, 6.3 Hz, 1H)	HMBC 1->38,39,40
2	129.3	6.39 (ddd, J = 15.8, 6.3, 5.6 Hz, 1H)	TOCSY 2->1,2 HMBC 2->4
3	129.9	6.30 (br d, J = 15.8 Hz, 1H)	HMBC 3->4
4	137	-	
5	124.1	7.13-7.17 (m, 1H) overlap	HMBC 5->7,9
6	128.3	7.15-7.19 (m, 1H) overlap	HMBC 6->4,8
7	127.3	7.10 (br d, J = 7.2 Hz, 1H)	HMBC 7->9
8	141.1	-	
9	124.5	7.10 (br s, 1H) overlap	HMBC 9->7
10	30.2	2.69-2.76 (m, 1H), 2.77-2.82 (m, 1H) overlap	HMBC 10->7,8,9,12
11	35.4	2.31 (ddd, J = 14.3, 6.5, 6.5 Hz, 1H), 2.44-2.51 (m, 1H) overlap	HMBC 11->8,12
12	171.4	-	
13	-	8.07 (d, J = 7.6 Hz, 1H)	HMBC 13->12
14	47.7	4.12 (qd, J = 7.6, 7.1 Hz, 1H)	HMBC 14->15,16
15	17.6	0.85 (d, J = 7.1 Hz, 3H)	HMBC 15->15,16
16	172.3	-	
17	-	7.86 (d, J = 7.7 Hz, 1H)	HMBC 17->16
18	52.3	3.98 (ddd, J = 8.0, 7.8, 5.4 Hz, 1H)	TOCSY 18->17,18,20 HMBC 18->19,20,23
19	27.3	1.50-1.58 (m, 1H) overlap, 1.70-1.81 (m, 1H) overlap	HMBC 19->20,21
20	30.9	1.91-2.00 (m, 2H)	HMBC 20->21
21	173.9	-	
22	-	6.78 (br s, 1H), 7.22 (br s, 1H) overlap	TOCSY 22->22'
23	171.2	-	
24	-	7.56 (br d, J = 6.8 Hz, 1H)	HMBC 24->23
25	50.7	4.45 (ddd, J = 7.2, 6.8, 5.8 Hz, 1H)	COSY 25->24
26	27.6	2.93 (dd, J = 15.3, 7.6 Hz, 1H), 3.05-3.12 (m, 1H) overlap	HMBC 26->27
27	128.9	-	
28	116.8	7.28 (s, 1H)	HMBC 28->27,30
29	-	not observed	
30	134	8.95 (br s, 1H)	HMBC 30->27,28
31	170	-	
32	-	8.07 (d, J = 7.4 Hz, 1H)	HMBC 32->31
33	53.7	4.60 (ddd, J = 10.9, 7.4, 3.3 Hz, 1H)	TOCSY 33->32,34
34	27.7	2.85 (dd, J = 14.4, 11.1 Hz, 1H), 3.13-3.20 (m, 1H) overlap	HMBC 34->33,35
35	109.8	-	
36	133	-	
37	103.8	7.57 (d, JHF = 11.1 Hz, 1H)	HMBC 37->35,41,38,39
38	155.3 (d, J ≅ 230Hz)	-	
39	120.1	-	
40	112.8	7.21 (d, JHF = 6.4 Hz, 1H)	HMBC 40->38
41	133	-	
42	-	10.83 (d, J = 1.3 Hz, 1H)	HMBC 42->35,36,41
43	125.7	7.17-7.19 (m, 1H) overlap	
44	172.2	-	
45	-	8.70 (br d, J = 7.8 Hz, 1H)	HMBC 45->44
46	52.2	4.25 (ddd, J = 7.8, 7.8, 6.1 Hz, 1H)	TOCSY 46->45,47,48,49
47	28.9	1.55-1.63 (m, 1H) overlap, 1.71-1.78 (m, 1H) overlap	HMBC 47->46
48	25.1	1.47-1.57 (m, 2H) overlap	HMBC 48->49
49	40.3	3.09-3.16 (m, 2H) overlap	HMBC 49->47,48,51
50	-	14.17 (br s) overlap	
51	156.9	-	
52	-	14.17 (br s) overlap	
53	173.3	-	
54	-	7.14 (br s, 1H), 7.39 (br s, 1H)	TOCSY 54'->54

Macrocyclic Product ***2.11a***

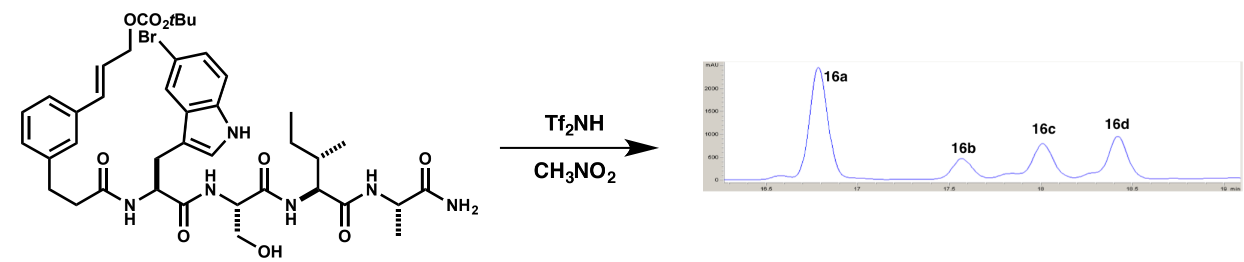


(500 & 600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlations
1	40.7	2.44 (dd, J = 14.3, 8.8 Hz, 1H), 2.68-2.73 (m, 1H)	HMBC 1->35,43
2	124.2	5.91 (ddd, J = 15.7, 8.8, 6.5 Hz, 1H)	COSY 2->1
3	134.2	6.55 (d, J = 15.7 Hz, 1H)	HMBC 3->1,4,5,9
4	136.7	-	
5	122.2	7.04-7.07 (m, 1H) overlap	
6	128.1	7.11-7.16 (m, 1H) overlap	HMBC 6->4,8
7	127.1	7.03-7.07 (m, 1H) overlap	
8	141.3	-	
9	126.2	7.13 (br s, 1H) overlap	HMBC 9->5,7
10	28.7	2.71-2.79 (m, 1H), 2.95-3.01 (m, 1H)	HMBC 10->8,12
11	34.3	2.51-2.57 (m, 1H), 2.59-2.66 (m, 1H)	HMBC 11->8,12
12	171.3	-	
13	-	8.09 (d, J = 8.1 Hz, 1H)	
14	48.3	4.13-4.19 (m, 1H) overlap	HMBC 14->16
15	17.6	1.20 (d, J = 7.3 Hz, 3H)	HMBC 15->14,16 COSY 15->14 TOCSY 15->14,13
16	171.8	-	
17	-	7.00-7.03 (m, 1H) overlap	HMBC 17->16
18	50.6	4.19 (ddd, J = 8.1, 7.8, 5.4 Hz, 1H)	HMBC 18->19,20
19	28.4	1.59-1.70 (m, 1H), 1.70-1.80 (m, 1H)	
20	31	1.99 (ddd, J = 15.5, 9.5, 5.8 Hz, 1H), 2.08 (ddd, J = 15.5, 9.9, 5.7 Hz, 1H)	HMBC 20->21
21	173.5	-	
22	-	6.84 (br s, 1H), 7.31 (br s, 1H)	HMBC 22->21
23	171	-	
24	-	8.77 (d, J = 8.1 Hz, 1H)	TOCSY 24->25,26 HMBC 24->23
25	48.3	5.07 (ddd, J = 9.7, 8.1, 5.2 Hz, 1H)	HMBC 25->31
26	25.6	3.17 (dd, J = 15.9, 5.1 Hz, 1H), 3.00 (dd, J = 15.9, 9.7 Hz, 1H)	HMBC 26->27,28,31
27	128.3	-	
28	117.3	7.50 (s, 1H)	HMBC 28->27,29
29	133.5	8.99 (s, 1H)	HMBC 29->27,28 TOCSY 29->28
30	-	Not detected	
31	170.2	-	
32	-	-	
33	60.1	4.62 (dd, J = 9.3, 4.5 Hz, 1H)	TOCSY 33->34 HMBC 33->1,34,35,44
34	40	2.21 (dd, J = 13.3, 4.5 Hz, 1H), 2.46-2.52 (m, 1H) overlap	HMBC 34->35
35	57.8	-	
36	135	-	
37	109.8	7.10-7.14 (m, 1H)	HMBC 37->38,41
38	156.5 (d, J ≅ 230 Hz)	-	
39	114	6.81-6.88 (m, 1H) overlap	HMBC 39->38,41
40	109.8	6.84 (dd, JHH = 9.1 Hz, JHF = 2.6 Hz, 1H)	HMBC 40->36,38 COSY 40->39
41	144.8	-	
42	-	Not detected	
43	80.3	6.19 (s, 1H)	
44	169.9	-	
45	-	7.56 (d, J = 8.2 Hz, 1H)	HMBC 45->44
46	50.6	4.04 (ddd, J = 8.2, 8.0, 6.0 Hz, 1H)	COSY 46->47 HMBC 46->44,54
47	29.9	0.97-1.06 (m, 1H) overlap, 1.33-1.42 (m, 1H) overlap	HMBC 47->49
48	24.4	1.00-1.11 (m, 1H) overlap, 1.36-1.46 (m, 1H) overlap	
49	39.8	2.89-2.97 (m, 1H) overlap, 3.03-3.11 (m, 1H)	HMBC 49->51
50	-	7.42 (apt t, J = 5.6 Hz, 1H)	
51	156.3	-	
52	-	14.11 (br s, 3H)	
53	172.4	-	
54	-	7.08 (br s, 1H), 7.40 (br s, 1H)	HMBC 55'->54 TOCSY 55'->55

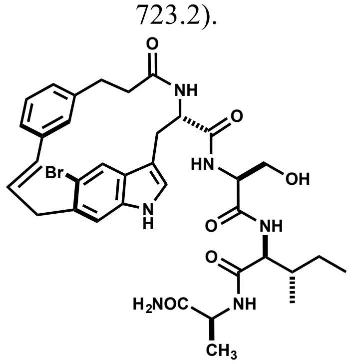


Acyclic Cinnamyl Carbonate 2.12: Synthesized according to Procedure A with 0.41 mmol starting template. Purified via trituration with 3x5 mL methanol. Beige Solid. 170 mg (0.202 mmol) 49% yield. ^{1}H-NMR (500 MHz, DMSO-d$_6$) δ10.99 (d, *J* = 1.9 Hz, 1 H), 8.28 (d, *J* = 7.6 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz. 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.86 (d, *J* = 1.4 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 6.60 (d, *J* = 16.00 Hz, 1 H), 6.32 (dd, *J* = 15.9, 6.3, 6.3 Hz, 1 H), 5.08 (dd, *J* = 5.3, 5.3 Hz, 1 H), 4.66 (d, *J* = 5.95 Hz, 1 H), 4.60 (ddd, *J* = 9.0, 4.3, 4.3 Hz, 1 H), 4.39 (dd, *J* = 13.3, 6.1 Hz, 1 H), 4.22-4.17 (m, 2H), 3.67-3.55 (m, 2H), 3.09 (dd, *J* = 14.5, 3.8 Hz, 1 H), 3.09 (dd, *J* = 14.5, 3.8 Hz, 1 H), 2.85 (dd, *J* = 15.6, 9.9 Hz, 1 H), 2.68-2.57 (m, 2H), 2.32 (dd, *J* = 8.0, 8.0 Hz, 1 H), 1.81-1.76 (m, 1H), 1.43 (s, 9H), 1.20 (d, *J* = 7.2 Hz, 3 H), 1.17-1.12 (m, 1H), 1.10-1.04 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.82 (dd, *J* = 7.4, 7.4 Hz, 3 H). ^{13}C-NMR (126 MHz, d$_6$-DMSO) δ 174.1, 171.9, 171.3, 170.3, 170.2, 152.8, 141.7, 135.8, 134.7, 133.4, 129.3, 128.6, 127.9, 126.4, 126.0, 125.7, 124.2, 123.3, 123.2, 121.0, 113.2, 111.0, 110.1, 81.5, 66.9, 61.5, 57.1, 54.9, 53.2, 48.0, 36.9, 36.7, 31.0, 27.4, 24.1, 18.1, 15.4, 11.4. MS *m/z* [M-OCO$_2$*t*Bu]$^+$, 841.3 (calc'd: $C_{35}H_{44}BrN_6O_6$ [M+H]$^+$, 841.1)

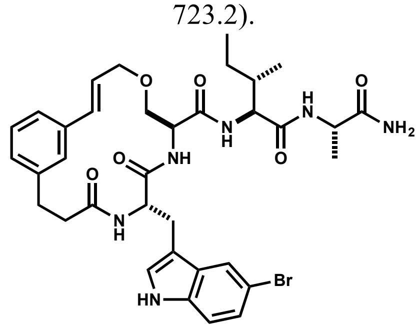


MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).



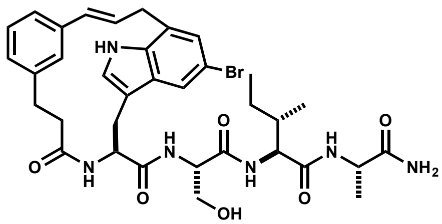
2.16a



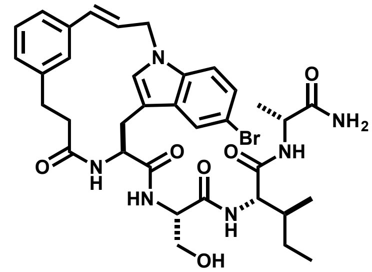
2.16b

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).

MS *m/z* 723.3 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).



2.16d



2.16e

Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2.5	30
24	86
29	30

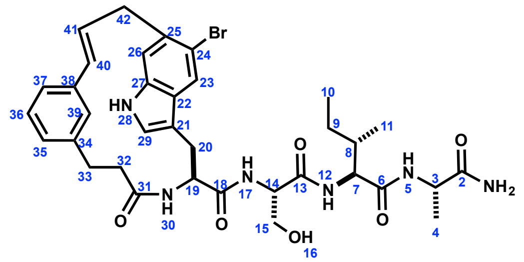
Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	45
2	45
12	50
13	50
15	100

Semi-Prep HPLC Method
Column: Waters XSelect™ C_{18}, 10x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 6.00 mL/min

Time	%B
0	45
1	45
4	50
10	54
12	45

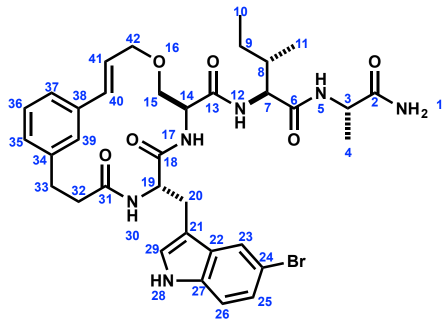
Macrocyclic Product ***2.16a***



(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	-	7.12 ppm (br s) (1H) ; 6.99 ppm (br s) (1H)	HMBC 1 -> 2 / TOCSY 1 -> 1'
2	173.9 ppm	-	HMBC 3 -> 2
3	47.7 ppm	4.21-4.18 ppm (m) (1H)	COSY 5 -> 3
4	17.9 ppm	1.22 ppm (d) J=7.2 Hz (3H)	COSY 3 -> 4
5	-	7.90 ppm (d) J=7.5 Hz (1H)	HMBC 5 -> 6
6	170.1 ppm	-	HMBC 7 -> 6
7	56.9 ppm	4.23-4.21 ppm (m) (1H)	COSY/HMBC 12 -> 7
8	36.4 ppm	1.83-1.78 ppm (m) (1H)	COSY 7 -> 8
9	23.8 ppm	1.46-1.42 ppm (m) (1H) ; 1.18-1.11 ppm (m) (1H)	COSY 8 -> 9
10	11.1 ppm	0.83 ppm (t) J=7.4 Hz (3H)	COSY 9 -> 10
11	15.0 ppm	0.87 ppm (d) J=6.8 Hz (3H)	COSY 8 -> 11
12	-	7.74 ppm (d) J=8.1 Hz (1H)	HMBC 12 -> 13
13	170.5 ppm	-	HMBC 14 -> 13
14	54.6 ppm	4.42 ppm (q) J=6.5 Hz (1H)	COSY 17 -> 14
15	61.3 ppm	3.69 ppm (dd) J=10.3, 5.9 Hz (1H) ; 3.62 ppm (dd) J=10.5, 6.4 Hz (1H)	COSY 14 -> 15
16	-	Not Observed	-
17	-	8.51 ppm (d) J=7.6 Hz (1H)	HMBC 17 -> 18
18	172.7 ppm	-	HMBC 19 -> 18
19	52.6 ppm	4.76 ppm (ddd) J=12.8, 6.2, 4.6 Hz (1H)	COSY 30 -> 19
20	27.7 ppm	3.32 ppm (dd) J=14.3, 3.8 Hz (1H) ; 2.81 ppm (t) J=13.7 Hz (1H)	COSY 19 -> 20
21	109.1 ppm	-	HMBC 20, 28, 29 -> 21
22	126.6 ppm	-	HMBC 26, 29 -> 22
23	122.6 ppm	8.19 ppm (s) (1H)	HMBC 23 -> 21
24	116.2 ppm	-	HMBC 23, 26 -> 24
25	131.6 ppm	-	HMBC 23, 42 -> 25
26	115.4 ppm	7.33 ppm (s) (1H)	TOCSY 23 -> 26
27	136.5 ppm	-	HMBC 23, 28, 29 -> 27
28	-	10.93 ppm (d) J=1.7 Hz (1H)	
29	126.5 ppm	7.23 ppm (d) J= 1.7 Hz (1H)	COSY/TOCSY 28 -> 29
30	-	7.52 ppm (d) J=6.4 Hz (1H)	HMBC 30 -> 31
31	171.7 ppm	-	HMBC 32, 33 -> 31
32	31.3 ppm	2.25 ppm (ddd) J=16.9, 5.6, 1.9 Hz (1H) ; 2.15 ppm (ddd) J=16.9, 12.7, 1.8 Hz (1H)	COSY/TOCSY 33 -> 32
33	25.9 ppm	3.02 ppm (dd) J=16.5, 12.6 Hz (1H) ; 2.45 ppm (dd) J=16.4, 5.6 Hz (1H)	HMBC 33 -> 35, 39
34	141.0 ppm	-	HMBC 32, 33, 36 -> 34
35	126.4 ppm	6.83 ppm (d) J=7.4 Hz (1H)	TOCSY 37 -> 35
36	127.6 ppm	7.05 ppm (t) J=7.7 Hz (1H)	COSY/TOCSY 37 -> 36
37	119.2 ppm	7.17 ppm (d) J=7.7 Hz (1H)	HMBC 37 -> 40, 41 (slight)
38	135.2 ppm	-	HMBC 36 -> 38
39	128.0 ppm	5.52 ppm (s)	TOCSY 37 -> 39
40	132.1 ppm	3.70 ppm (d) J=16.0 Hz (1H)	
41	127.9 ppm	6.30 ppm (dt) J=16.2, 3.9 Hz (1H)	
42	37.7 ppm	3.79 ppm (ddd) J= 17.0, 4.6, 1.5 Hz (1H) ; 3.43 ppm (dt) J=16.7, 2.3 Hz (1H)	COSY 41 -> 42

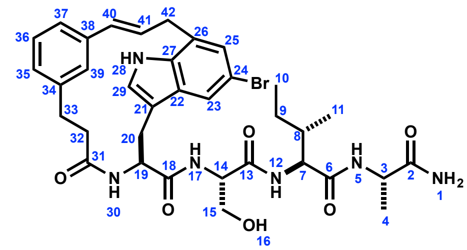
Macrocyclic Product ***2.16b***



(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	-	7.20 ppm (br s) (1H) ; 6.96 ppm (br s) (1H)	TOCSY 1 -> 1'
2	173.9 ppm	-	HMBC 3 -> 2
3	47.8 ppm	4.22 ppm (pentet) J=7.1 Hz (1H)	COSY 3 -> 4
4	18.2 ppm	1.21 ppm (d) J=7.2 Hz (3H)	
5	-	7.90 ppm (d) J=7.5 Hz (1H)	COSY 5 -> 3 ; slight HMBC 5 -> 3
6	170.2 ppm	-	HMBC 5 -> 6
7	56.8 ppm	4.22 ppm (dd) J=8.6, 6.6 Hz (1H)	TOCSY 7 -> 11
8	36.8 ppm	1.77-1.73 ppm (m) (1H)	COSY 7 -> 8
9	23.8 ppm	1.46-1.42 ppm (m) (1H) ; 1.13 -1.08 ppm (m) (1H)	COSY 8 -> 9
10	11.2 ppm	0.82 ppm (dd) J=7.5, 7.5 Hz (3H)	COSY 9 -> 10
11	15.2 ppm	0.85 ppm (d) J=7.0 Hz (3H)	COSY 8 -> 11
12	-	7.70 ppm (d) J=8.7 Hz	COSY 12 -> 7 ; slight HMBC 12 -> 7
13	169.1 ppm	-	HMBC 12 -> 13
14	52.5 ppm	4.60 ppm (ddd) J=7.5, 7.5, 3.6 Hz (1H)	COSY 14 -> 15
15	68.7 ppm	3.75 ppm (dd) J=11.3, 7.1 Hz (1H) ; 3.66 ppm (dd) J=11.1, 3.4 Hz (1H)	HMBC 15 -> 42
16	-	-	-
17	-	8.82 ppm (d) J=7.9 Hz (1H)	COSY 17 -> 14
18	172.0 ppm	-	HMBC 17 -> 18
19	51.8 ppm	5.05 ppm (ddd) J=9.6, 9.6, 9.6 Hz (1H)	COSY 30 -> 19
20	29.1 ppm	2.97 ppm (dd) J=14.6, 4.3 Hz (1H) ; 2.80 ppm (dd) J=14.2, 9.9 Hz (1H)	HMBC 20 -> 21 ; COSY/TOCSY 19 -> 20
21	110.2 ppm	-	HMBC 28, 29 -> 21
22	129.3 ppm	-	HMBC 26, 29 -> 22
23	121.0 ppm	7.85 ppm (d) J=1.9 Hz	HMBC 23 -> 27
24	110.9 ppm	-	HMBC 23, 26 -> 24
25	123.2 ppm	7.14 ppm (dd) J=8.4, 1.7 Hz (1H)	HMBC 25 -> 27 / 23 -> 25
26	113.1 ppm	7.27 ppm (d) J=8.7 Hz (1H)	TOCSY 23 -> 26
27	134.8 ppm	-	HMBC 29 -> 27
28	-	10.91 ppm (d) J=2.1 Hz (1H)	Indole
29	125.3 ppm	7.17 ppm (d) J=2.5 Hz (1H)	COSY/TOCSY 28 -> 29
30	-	8.16 ppm (d) J=9.4 Hz	HMBC 30 -> 31
31	171.2 ppm	-	HMBC 33 -> 31
32	36.6 ppm	2.41-2.36 ppm (m) (1H) ; 2.07 ppm (ddd) J=13.9, 7.1, 3.2 Hz (1H)	COSY/TOCSY 33 -> 32
33	30.2 ppm	3.02-2.97 ppm (m) (1H) ; 2.63-2.60 ppm (m) (1H)	HMBC 35, 39 -> 33
34	141.6 ppm	-	HMBC 33 -> 34
35	127.8 ppm	7.01 ppm (d) J=7.9 Hz (1H)	TOCSY 39 -> 35
36	123.2 ppm	7.16 ppm (dd) J=7.3, 7.3 Hz (1H)	HMBC 36 -> 38
37	125.3 ppm	7.02 ppm (d) J=8.1 Hz (1H)	HMBC 37 -> 40
38	135.9 ppm	-	HMBC 41 -> 38
39	123.9 ppm	7.26 ppm (br s) (1H)	HMBC 40 -> 39
40	131.3 ppm	6.47 ppm (d) J=15.8 (1H)	
41	127.3 ppm	6.04 ppm (ddd) J=15.9, 7.0, 5.6 Hz (1H)	
42	69.6 ppm	4.31 ppm (ddd) J=14.0, 5.1, 1.3 Hz (1H) ; 3.99 ppm (dd) J=14.1, 7.0 Hz (1H)	COSY 41 -> 42 ; HMBC 15 -> 42 / 42 -> 15

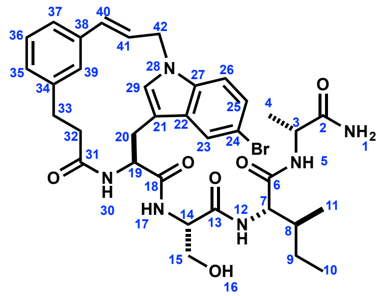
Macrocyclic Product ***2.16c***



(600 MHz, DMSO-d_6, 298K)

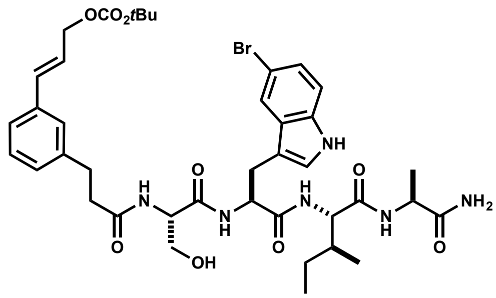
	13C	1H	key correlation
1	-	7.14 ppm (br s) (1H) ; 6.97 ppm (br s) (1H)	TOCSY 1 -> 1'
2	174.1 ppm	-	HMBC 3 -> 2
3	47.6 ppm	4.21 ppm (dd) J=7.3, 7.3 Hz (1H)	COSY 3 -> 4
4	18.0 ppm	1.21 ppm (d) J=7.1 Hz (3H)	
5	-	7.93 ppm (d) J=7.6 Hz (3H)	COSY 5 -> 3
6	170.2 ppm	-	HMBC 5 -> 6
7	56.6 ppm	4.23 ppm (dd) J=8.3, 6.1 Hz (1H)	TOCSY 7 -> 8
8	36.4 ppm	1.83-1.79 ppm (m) (1H)	COSY 8 -> 11 / TOCSY 8 -> 10
9	23.6 ppm	1.48-1.44 ppm (m) (1H)	COSY 9 -> 10
10	11.2 ppm	0.84 ppm (dd) J=7.4, 7.4 Hz (3H)	
11	15.1 ppm	0.88 ppm (d) J=6.8 Hz (3H)	
12	-	7.74 ppm (d) J=8.3 Hz (1H)	COSY/TOCSY 12 -> 7
13	170.3 ppm	-	HMBC 12 -> 13
14	54.7 ppm	4.42 ppm (dd) 13.5, 6.1 Hz (1H)	HMBC 14 -> 13
15	61.1 ppm	3.71-3.64 ppm (m) (2H)	COSY 14 -> 15
16	-	Not Observed	-
17	-	8.51 ppm (d) J=7.5 Hz (1H)	HMBC 17 -> 14
18	172.7 ppm	-	HMBC 17 -> 18
19	53.1 ppm	4.51 ppm (ddd) J=12.4, 8.5, 3.4 Hz	COSY 30 -> 19
20	27.1 ppm	3.23 ppm (dd) J=14.0, 3.0 Hz (1H) ; 2.78 ppm (dd) J=13.4 Hz (1H)	COSY 19 -> 20
21	109.7 ppm	-	HMBC 20, 28, 29 -> 21
22	128.0 ppm	-	HMBC 29 -> 22
23	119.8 ppm	7.95 ppm (d) 1.4 Hz (1H)	COSY/TOCSY 23 -> 25
24	110.0 ppm	-	HMBC 23 -> 24
25	123.9 ppm	7.09 ppm	HMBC 42 -> 25
26	126.9 ppm	-	HMBC 42 -> 26
27	134.6 ppm	-	HMBC 23, 25, 29 -> 27
28	-	10.56 ppm (d) J=1.9 Hz (1H)	
29	126.6 ppm	7.27 ppm (d) J=2.5 Hz (1H)	COSY/TOCSY 28 -> 29
30	-	8.12 ppm (d) J=8.3 Hz	HMBC 30 -> 31
31	172.0 ppm	-	HMBC 32, 33 -> 31
32	34.5 ppm	2.40-2.36 ppm (m) (1H) ; 2.15 ppm (dd) J=14.9, 11.9 Hz (1H)	COSY/TOCSY 33 -> 32
33	27.2 ppm	3.06 ppm (dd) J=13.5, 12.2 Hz (1H) ; 2.36-2.33 (m) (1H)	HMBC 35 -> 33
34	142.6 ppm	-	HMBC 36 -> 34
35	126.5 ppm	6.85 ppm (d) J=7.7 Hz (1H)	TOCSY 35 -> 39
36	128.1 ppm	7.08 ppm (dd) J=7.4, 7.4 Hz (1H)	COSY/TOCSY 35, 37 -> 36
37	120.4 ppm	7.19 ppm (d) J=7.7 Hz (1H)	HMBC 40 -> 37 / TOCSY 37 -> 39
38	137.3 ppm	-	HMBC 36 -> 38
39	127.7 ppm	5.69 ppm (s) (1H)	HMBC 39 -> 40
40	132.3 ppm	4.68 ppm (d) J=16.4 Hz (1H)	
41	126.6 ppm	6.11 ppm (ddd) J=16.3, 5.8, 2.9 Hz (1H)	
42	33.3 ppm	3.89 ppm (dd) J=17.3, 5.9 Hz (1H) ; 3.52-3.49 ppm (m) (1H)	COSY 41 -> 42

Macrocyclic Product **2.16d**

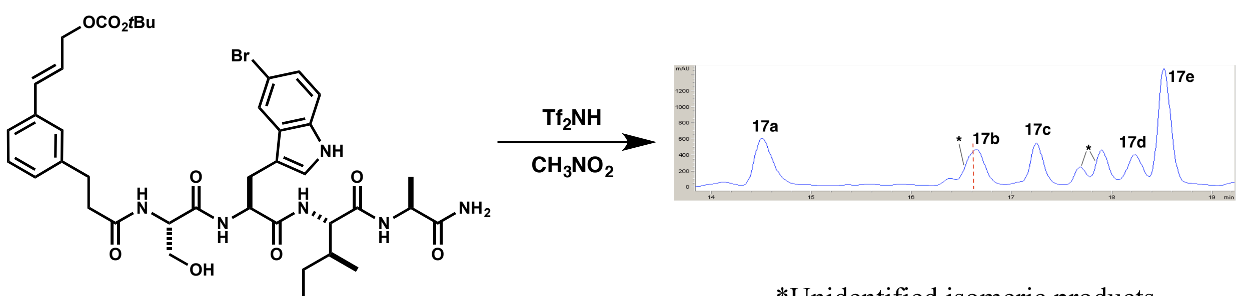


(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	-	7.11 ppm (br s) (1H) ; 6.97 ppm (br s) (1H)	HMBC 1' (slight) -> 3
2	174.1 ppm	-	HMBC 3 -> 2
3	47.9 ppm	4.21-4.18 ppm (m) (1H)	HMBC 5 -> 3
4	18.2 ppm	1.20 ppm (d) 7.1 Hz (3H)	COSY 3 -> 4
5	-	7.89 ppm (d) J=6.2 Hz (1H)	HMBC 5 ->
6	170.3 ppm	-	HMBC 7 -> 6
7	57.2 ppm	4.23-4.20 ppm (m) (1H)	HMBC 12 -> 7
8	36.8 ppm	1.82-1.78 ppm (m) (1H)	COSY 7 -> 8
9	24.0 ppm	1.46-1.42 ppm (m) (1H) ; 1.18-1.13 ppm (m) (1H)	COSY 8 -> 9
10	11.4 ppm	0.83 ppm (dd) J=7.4, 7.4 Hz (3H)	COSY 9 -> 10
11	15.4 ppm	0.87 ppm (d) J=7.2 Hz (3H)	COSY 8 -> 11
12	-	7.73 ppm (d) 8.3 Hz (1H)	HMBC 12 -> 13
13	170.3 ppm	-	HMBC 14 -> 13
14	54.9 ppm	4.39 ppm (ddd) J=6.5, 6.5, 6.5 Hz (1H)	COSY 17 -> 14
15	61.3 ppm	3.69 ppm (dd) J= 10.6, 5.9 Hz (1H) ; 3.62 ppm (dd) J=10.6, 5.9 Hz (1H)	COSY 14 -> 15
16	-	Not Observed	-
17	-	8.34 ppm (d) J=7.5 Hz (1H)	HMBC 17 -> 18
18	172.6 ppm	-	HMBC 19 -> 18
19	53.6 ppm	4.53 ppm (ddd)	COSY 19 -> 20
20	26.9 ppm	3.11 ppm (dd) J=14.9, 1.7 Hz (1H) ; 2.88 ppm (dd) J=14.8, 12.5 Hz (1H)	HMBC 20 -> 29
21	112.1 ppm	-	HMBC 20, 29 -> 21
22	130.3 ppm	-	HMBC 26, 29 -> 22
23	121.3 ppm	7.90 ppm (d) J=1.8 Hz (1H)	COSY/TOCSY 23 -> 25
24	111.9 ppm	-	HMBC 23, 25 (slight), 26 -> 24
25	123.7 ppm	7.25 ppm (d) J=8.7, 1.8 Hz (1H)	
26	112.6 ppm	7.57 ppm (d) J=8.7 Hz (1H)	TOCSY 23 -> 26 ; COSY 25 -> 26
27	136.3 ppm	-	HMBC 23, 25, 29 -> 27
28	-	-	-
29	129.5 ppm	7.37 ppm (s)	HMBV 42 -> 29
30	-	8.38 ppm (d) J=7.6 Hz (1H)	HMBC 30 -> 31 ; COSY 30 -> 19
31	172.5 ppm	-	HMBC 32, 33 -> 31
32	32.8 ppm	2.66 ppm (dd) J=14.0, 14.0 Hz (1H) ; 2.40-2.36 ppm (1H)	HMBC 32 -> 34
33	27.0 ppm	2.66-2.62 ppm (m) (1H) ; 3.09 ppm (dd) J=15.8, 12.9 Hz (1H)	HMBC 33' -> 34,35,39
34	141.7 ppm	-	HMBC 36 -> 34
35	127.4 ppm	6.99 ppm (d) J=8.1 Hz (1H)	COSY 36 -> 35
36	128.0 ppm	7.13 ppm (dd) J=7.6 Hz (1H)	COSY 36 -> 37
37	123.8 ppm	6.98 ppm (d) J=7.1 Hz (1H)	HMBC 37 -> 40
38	137.8 ppm	-	HMBC 41 -> 38
39	125.1 ppm	6.69 ppm (s) (1H)	HMBC 39 -> 40
40	132.2 ppm	6.50 ppm (d) J=15.6 Hz (1H)	
41	128.1 ppm	5.99 ppm (ddd) J=15.5, 7.7, 6.5 Hz (1H)	
42	45.4 ppm	4.80-4.78 ppm (m) (2H)	COSY 41 -> 42

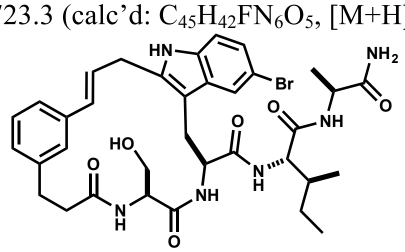


Acyclic Cinnamyl Carbonate 2.13: Synthesized according to Procedure A with 0.350 mmol starting template. Purified via SiO_2 chromatography using a gradient from 1% to 10% methanol in chloroform. Beige Solid. 80% yield. ^{1}H-NMR (500 MHz, DMSO-d$_6$) δ 11.06 (s, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.74 (d, *J* = 1.3 Hz, 1H), 7.29-7.18 (m, 5H), 7.15 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.97 (br s, 2H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.33 (ddd, *J* = 15.9, 6.2, 6.2 Hz, 1H), 5.03 (dd, *J* = 5.5, 5.5 Hz, 1H), 4.66 (d, *J* = 6.1 Hz, 1H), 4.52 (ddd, *J* = 8.0, 8.0, 4.8 Hz, 1H), 4.32 (dd, *J* = 13.6, 6.4 Hz, 1H), 4.19 (pentet, *J* = 7.5 Hz, 1H), 4.15 (dd, *J* = 8.0, 8.0 Hz, 1H), 3.64-3.58 (m, 1H), 3.48 (dd, *J* = 5.8, 5.8 Hz, 1H), 3.14-3.11 (m, 2H), 2.95 (dd, *J* = 14.7, 8.8 Hz, 1H), 2.77-2.74 (m, 2H), 2.46-2.40 (m, 2H), 1.73-1.68 (m, 1H), 1.43 (s, 9H), 1.39-1.35 (m, 1H), 1.20 (d, *J* = 7.1 Hz, 3H), 1.07-1.01 (m, 1H), 0.79 (d, *J* = 7.1 Hz, 3H), 0.79 (dd, *J* = 7.5, 7.5 Hz, 3H). (126 MHz, DMSO-d$_6$) δ174.0, 171.6, 171.2, 170.4, 170.3, 152.8, 141.8, 135.8, 134.7, 133.4, 129.2, 128.6, 128.0, 126.4, 125.5, 124.2, 123.3, 123.3, 120.7, 113.3, 111.0, 109.8, 81.5, 66.9, 61.8, 57.0, 55.0, 53.5, 48.1, 36.6, 30.9, 27.4, 24.2, 18.2, 18.1, 16.7, 15.2, 11.1. MS *m/z* [M-OCO$_2$*t*Bu]$^+$, 841.3 (calc'd: $C_{35}H_{44}BrN_6O_6$ [M+H]$^+$, 841.1)



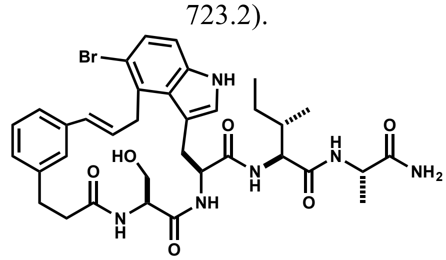
*Unidentified isomeric products

MS *m/z* 723.3 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).



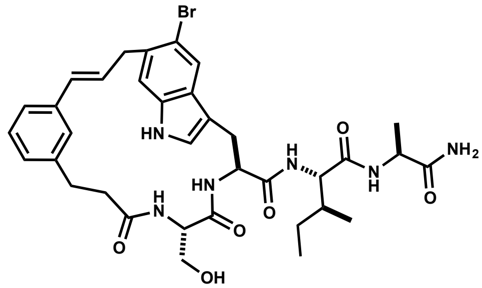
2.17a

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, [M+H]$^+$, 723.2).



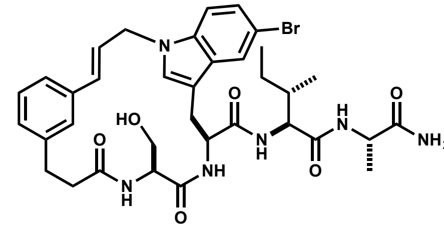
2.17b

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



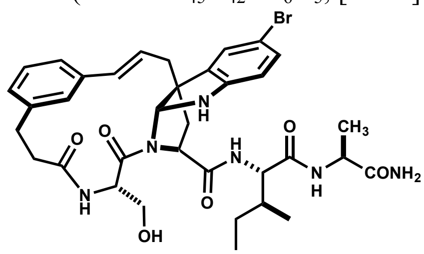
2.17c

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.17d

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.17e

Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2.5	30
24	86
29	30

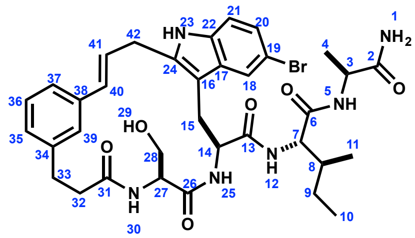
Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent A: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	35
4	45
18	57
18.5	35

Semi-Prep HPLC Method
Column: Waters XSelect™ C_{18}, 10x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 6.00 mL/min

Time	%B
0	45
1	45
9	49

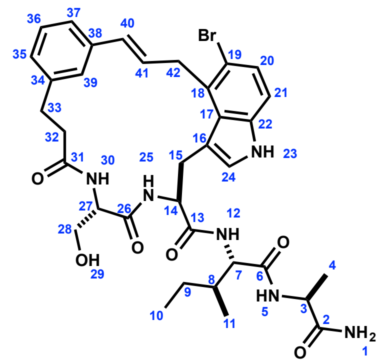
*Macrocyclic Product **17a***



(600 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	-	6.91 ppm (br s) (1H) ; 7.17 ppm (br s) (1H)	HMBC 1 -> 2 / TOCSY 1 -> 1'
2	173.7 ppm	-	HMBC 3 -> 2
3	47.9 ppm	4.19 ppm (p) J=7.1 Hz (1H)	COSY 5 -> 3
4	17.9 ppm	1.22 ppm (d) J=7.1 Hz (3H)	COSY 3 -> 4
5	-	7.97 ppm (d) J=7.1 Hz (3H)	HMBC 5 -> 6
6	170.4 ppm	-	HMBC 7 -> 6
7	56.9 ppm	4.27 ppm (t) J=8.1 Hz (1H)	COSY 12 -> 7
8	36.3 ppm	1.79-1.75 ppm (m) (1H)	COSY 7 -> 8
9	24.1 ppm	1.50-1.46 ppm (m) (1H) ; 1.18-1.11 ppm (m) (1H)	COSY 8 -> 9
10	10.7 ppm	0.86 ppm (t) J=7.4 Hz (3H)	COSY 9 -> 10
11	15.0 ppm	0.88 ppm (d) J=6.8 Hz (3H)	COSY 8 -> 11
12	-	7.81 ppm (d) J=8.9 Hz (1H)	HMBC 12 -> 13
13	171.0 ppm	-	HMBC 14 -> 13
14	25.8 ppm	4.50-4.47 ppm (m) (1H)	COSY 25 -> 14
15	25.9 ppm	3.29 ppm (dd) J=14.7 & 2.4 Hz (1H) ; 2.91 ppm (dd) J=14.7 & 10.3 Hz (1H)	COSY 14 -> 15
16	107.1 ppm	-	HMBC 18 & 23 -> 16
17	129.7 ppm	-	HMBC 21 & 23 -> 17
18	119.7 ppm	7.65 ppm (d) J=1.3 Hz (1H)	COSY 18->20 / TOCSY 18 -> 21
19	110.6 ppm	-	HMBC 18, 20 (slight), 21 -> 19
20	122.8 ppm	7.12 ppm (dd) J=8.5 & 1.4 Hz (1H)	HMBC 18 -> 20
21	112.5 ppm	7.20 ppm (d) J=8.7 Hz (1H)	HMBC 21 -> 17
22	134.2 ppm	-	HMBC 18, 20, 23 -> 22
23	-	10.92 ppm (br s)	
24	136.1 ppm	-	HMBC 15, 22, & 42 -> 24
25	-	8.83 ppm (d) J=8.6 Hz (1H)	HMBC 25 -> 26
26	170.6 ppm	-	HMBC 27 -> 26
27	54.6 ppm	4.56-4.52 ppm (m) (1H)	COSY 30 -> 27
28	62.2 ppm	3.63 ppm (dd) J=9.5 & 5.5 Hz (1H); 3.43 (t) J=9.3 Hz (1H)	COSY/TOCSY 27 -> 28
29	-	Not Observed	-
30	-	8.01 ppm (d) J=7.2 Hz (1H)	HMBC 30 -> 31
31	172.0 ppm	-	HMBC 32 -> 31
32	34.3 ppm	2.59 ppm (ddd) J=14.2, 11.8, & 2.8 Hz (1H) ; 2.21 ppm (ddd) J= 14.4, 6.7, & 2.9 Hz (1H)	COSY/TOCSY 33 -> 32
33	29.3 ppm	3.07 ppm (ddd) J=14.6, 11.7, & 2.0 Hz (1H) ; 2.64 ppm (ddd) J= 14.9, 7.0, & 1.5 Hz (1H)	HMBC 33 -> 34, 35, & 39
34	141.2 ppm	-	HMBC 33 & 32' -> 34
35	127.5 ppm	6.99 ppm (d) J=7.6 Hz (1H)	HMBC 37 & 39 -> 35
36	128.1 ppm	7.18 ppm (t) J=7.2 Hz (1H)	COSY 36 -> 35
37	124.5 ppm	7.06 ppm (d) J=8.0 Hz (1H)	HMBC 40->37
38	136.5 ppm	-	HMBC 41 & 42 -> 38
39	122.5 ppm	7.08 ppm (s) (1H)	HMBC 40 -> 39 ; 39 ->37
40	130.6 ppm	6.57 ppm (d) J=15.7 Hz (1H)	
41	127.9 ppm	5.98 ppm (ddd) J=15.7, 8.4, 5.9 Hz (1H)	
42	29.1 ppm	3.75 (dd) J=14.4 & 5.4 Hz (1H) ; 3.50 (dd) J=14.5 & 8.7 Hz (1H)	COSY/TOCSY 40 & 41 -> 42

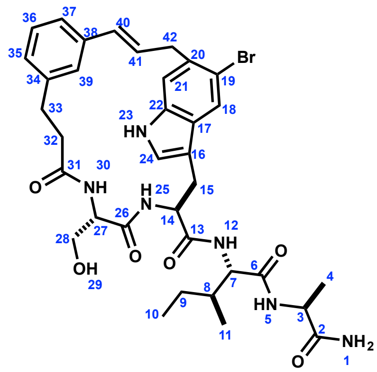
Macrocyclic Product ***2.17b***



(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	-	7.61 ppm (br s) (1H) ; 6.95 ppm (br s) (1H)	TOCSY 1 -> 1'
2	174.1 ppm	-	HMBC 3 -> 2
3	47.9 ppm	4.16 ppm (pentet) J=7.2 Hz (1H)	COSY 3 -> 4 / HMBC 1->3
4	18.1 ppm	1.16 ppm (d) J=7.1 Hz (3H)	
5	-	7.84 ppm (d) J=8.5 Hz (1H)	COSY 5 -> 3
6	170.1 ppm	-	HMBC 7 -> 6
7	56.9 ppm	4.16 ppm (dd) J=8.3, 7.4 Hz (1H)	TOCSY 7 -> 8,11
8	36.3 ppm	1.75-1.71 ppm (m) (1H)	COSY 7 -> 8
9	24.1 ppm	1.41-1.37 ppm (m) (1H) ; 1.09-1.02 ppm (m) (1H)	COSY 8 -> 9
10	11.0 ppm	0.78 ppm (dd) J=7.4, 7.4 Hz (3H)	COSY 9 -> 10
11	15.2 ppm	0.80 ppm (d) J= 6.8 Hz (3H)	COSY 8 -> 11
12	-	7.80 ppm (d) J=7.4 Hz (1H)	COSY 12 -> 7
13	170.4 ppm	-	HMBC 12 -> 13
14	53.0 ppm	4.64-4.58 ppm (m) (1H)	
15	29.4 ppm	3.36-3.34 ppm (m) (1H) ; 3.12 ppm (dd) J=15.0, 2.7 Hz (1H)	COSY 14 -> 15
16	110.8 ppm	-	HMBC 24 -> 16
17	127.4 ppm	-	HMBC 21,24 -> 17
18	129.9 ppm	-	HMBC 20 -> 18
19	115.1 ppm	-	HMBC 21 -> 19
20	124.5 ppm	7.26 ppm (d) J=8.7 Hz (1H)	
21	111.7 ppm	7.19 ppm (d) J=8.6 Hz (1H)	COSY 20 -> 21
22	135.6 ppm	-	HMBC 20,24 -> 22
23	-	11.03 ppm (s) (1H)	Indole
24	124.3 ppm	7.06 ppm (d) J=1.5 Hz (1H)	COSY 23 -> 24
25	-	8.26 ppm (br s) (1H)	COSY 25 -> 14
26	170.7 ppm	-	HMBC 25 -> 26
27	54.0 ppm	4.58 ppm (ddd) J=8.6, 6.5, 6.5 (1H)	COSY 27 -> 28
28	62.1 ppm	3.50-3.41 ppm (m) (2H)	COSY 29 -> 28
29	-	4.80 ppm (dd) J=5.4, 5.4 Hz (1H)	affected by water suppression
30	-	7.84 ppm (d) J=8.5 Hz (1H)	COSY 27 -> 30
31	170.9 ppm	-	HMBC 32, 33 -> 31
32	35.9 ppm	2.48-2.46 ppm (m) (1H) ; 2.32 ppm (ddd) J=14.5, 6.7, 2.5 Hz (1H)	COSY/TOCSY 33 -> 32
33	30.0 ppm	3.03 ppm (dd) J=12.4, 12.4 Hz (1H) ; 2.65-2.61 ppm (m) (1H)	HMBC 33 -> 35,39
34	141.7 ppm	-	HMBC 33,36 -> 34
35	127.5 ppm	6.98 ppm (d) J=7.4 Hz (1H)	HMBC 37 -> 35
36	128.2 ppm	7.11 ppm (dd) J=7.5, 7.5 Hz (1H)	COSY 36 -> 35,37 ; TOCSY 36 -> 37
37	123.0 ppm	7.06 ppm (d) J=7.7 Hz (1H)	HMBC 37 -> 40
38	136.9 ppm	-	HMBC 36 -> 38
39	125.6 ppm	7.03 ppm (br s) (1H)	HMBC 35,37 -> 39
40	130.6 ppm	6.14 ppm (d) J=15.6 Hz (1H)	HMBC 37 -> 40
41	not observed	6.36 ppm (ddd) J=16.0, 5.5, 5.5 Hz (1H)	
42	35.7 ppm	4.05-4.00 ppm (m) (2H)	COSY/TOCSY 40, 41 -> 42

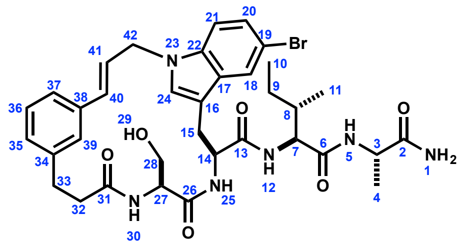
*Macrocyclic Product **2.17c***



(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	-	7.23 ppm (br s) (1H) ; 6.95 ppm (br s) (1H)	TOCSY 1 -> 1'
2	174.0 ppm	-	HMBC 3 -> 2
3	48.0 ppm	4.21 ppm (p) J=7.0 Hz (1H)	COSY 5 -> 3
4	18.2 ppm	1.21 ppm (d) J=7.0 Hz (3H)	
5	-	8.02 ppm (d) J=7.2 Hz (1H)	HMBC 5 -> 6
6	170.6 ppm	-	HMBC 7 -> 6
7	56.7 ppm	4.25 ppm (dd) J=8.6, 8.6 Hz (1H)	TOCSY 7 -> 8
8	36.5 ppm	1.80-1.75 ppm (m) (1H)	COSY/TOCSY 8 -> 11
9	24.2 ppm	1.53-1.49 ppm (m) (1H)	COSY/TOCSY 9 -> 10
10	10.9 ppm	0.86 ppm (dd) J= 7.6, 7.6 Hz	
11	15.1 ppm	0.88 ppm (d) J=6.8 Hz (1H)	
12	-	7.85 ppm (d) J=8.9 Hz (1H)	COSY 12 -> 7
13	170.8 ppm	-	HMBC 12 -> 13
14	57.5 ppm	4.47 ppm (ddd) J=12.0, 9.7, 2.2 Hz (1H)	COSY 25 -> 14
15	26.6 ppm	3.31-3.28 ppm (m) (1H) ; 2.88 ppm (dd) J=14.3, 12.2 Hz (1H)	COSY 14 -> 15
16	111.9 ppm	-	HMBC 15, 24 -> 16
17	128.6 ppm	-	HMBC 21,24 -> 17
18	122.3 ppm	8.23 ppm (s) (1H)	
19	114.6 ppm	-	HMBC 18, 21 -> 19
20	128.7 ppm		HMBC 18,42 -> 20
21	113.3 ppm	7.23 ppm (s) (1H)	
22	135.2 ppm	-	HMBC 18,24 -> 22
23	-	10.93 ppm (d) J=1.7 Hz (1H)	Indole
24	124.2 ppm	7.29 ppm (d) J=1.7 Hz (1H)	COSY 23 -> 24 ; HMBC 15 -> 24
25	-	8.68 ppm (d) J=9.6 Hz (1H)	HMBC 25 -> 26
26	169.4 ppm	-	HMBC 27 -> 26
27	54.8 ppm	4.18 ppm (dd) J=11.9, 6.3 Hz (1H)	COSY/TOCSY 30 -> 27
28	62.1 ppm	3.75-3.72 ppm (m) (1H) ; 3.47-3.44 ppm (m) (1H)	COSY 27 -> 28 ; TOCSY 30 -> 28
29	-	5.36 ppm (dd) J=5.3, 5.3 Hz (1H)	COSY 29 -> 28 ; TOCSY 29 -> 27
30		7.36 ppm (d) J=6.2 Hz (1H)	HMBC 30 -> 31
31	171.2 ppm	-	HMBC 32,33' -> 31
32	33.1 ppm	2.51-2.48 ppm (m) (1H) ; 2.29 ppm (dd) J=15.5, 6.7 Hz (1H)	COSY/TOCSY 33 -> 32
33	27.2 ppm	3.10 ppm (dd) J=15.2, 12.2 Hz (1H) ; 2.50-2.54 ppm (m) (1H)	HMBC 35 -> 33
34	141.8 ppm	-	HMBC 32,33(slight),36 -> 34
35	127.0 ppm	6.91 ppm (d) J=7.6 Hz (1H)	HMBC 32(slight),33 -> 35
36	128.2 ppm	7.13 ppm (dd) J= 7.6, 7.6 Hz (1H)	TOCSY 36 -> 39
37	121.2 ppm	7.28 ppm (d) J=7.2 Hz (1H)	COSY 37 -> 39
38	136.7 ppm	-	HMBC 36,40(slight) -> 38
39	125.8 ppm	6.38 ppm (s) (1H)	HMBC 39 -> 40
40	129.6 ppm	5.43 ppm (d) J=15.9 Hz (1H)	
41	128.6 ppm	6.46 ppm (ddd) J=16.0, 4.8, 4.8 Hz (1H)	
42	38.1 ppm	3.76-3.72 ppm (m) (1H) ; 3.52-3.48 ppm (m) (1H)	COSY/TOCSY 40, 41 -> 42 ; HMBC 21 -> 42

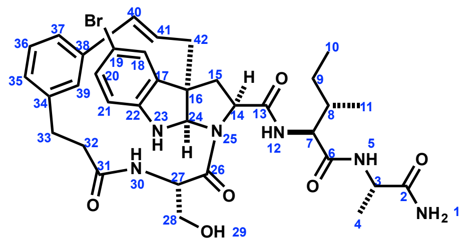
Macrocyclic Product ***2.17d***



(600 MHz, DMSO-d_6, 298K)

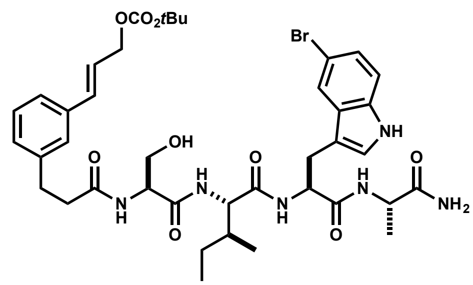
	13C	1H	key correlation
1	-	7.22 ppm (br s) (1H) ; 6.95 ppm (br s) (1H)	TOCSY 1 -> 1'
2	173.3 ppm	-	HMBC 3 -> 2
3	47.7 ppm	4.20 ppm (p) J=7.2 Hz (1H)	COSY 3 -> 4
4	18.0 ppm	1.23 ppm (d) J=7.2 Hz (3H)	
5	-	7.97 ppm (d) J=6.5 Hz (1H)	HMBC 5 -> 6
6	170.1 ppm	-	HMBC 7 -> 6
7	56.7 ppm	4.25 ppm (t) J=8.5 Hz (1H)	COSY 12 -> 7
8	22.2 ppm	1.79-1.76 ppm (m) (1H)	COSY 7 -> 8
9	24.0 ppm	1.48 -1.44 ppm (m) (1H) ; 1.15-1.10 ppm (m) (1H)	COSY 8 -> 9
10	10.7 ppm	0.84 ppm (t) J=7.5 Hz (3H)	COSY 9 -> 10
11	15.0 ppm	0.87 ppm (d) J=6.8 Hz (3H)	COSY 8 -> 11
12	-	7.97 ppm (d) J=9.4 Hz (1H)	HMBC 12 -> 13
13	171.2 ppm	-	HMBC 14 -> 13
14	53.1 ppm	4.62 ppm (ddd) J=12.2, 8.7, & 2.5 Hz (1H)	COSY/TOCSY 14 -> 15
15	26.4 ppm	3.25 ppm (dd) J=14.9, 1.7 Hz (1H) ; 2.86 ppm (dd) J=14.7, 12.5 Hz (1H)	HMBC 15 -> 16
16	110.4 ppm	-	HMBC 15, 24 -> 16
17	128.8 ppm	-	HMBC 21, 24 -> 17
18	120.5 ppm	7.79 ppm (d) J=1.9 Hz (1H)	HMBC 18 -> 20, 22
19	111.3 ppm	-	HMBC 18 -> 19
20	123.2 ppm	7.23 ppm (dd) J=8.5 Hz, 1.9 Hz (1H)	HMBC 18 -> 20
21	111.5 ppm	7.45 ppm (d) J=8.9 Hz (1H)	HMBC 21 -> 17
22	134.4 ppm	-	HMBC 18, 24, 42 -> 22
23	-	-	-
24	127.9 ppm	7.29 ppm (s) (1H)	HMBC 42 -> 24
25	-	8.56 ppm (d) J=8.5 Hz (1H)	COSY 25 -> 14
26	170.0 ppm	-	HMBC 25 -> 26
27	53.5 ppm	4.48 ppm (ddd) J=7.7, 7.7, 5.4 Hz (1H)	HMBC 27 -> 26
28	62.5 ppm	3.54 ppm (dd)	
29	-	Not Observed	-
30	-	7.78 ppm (d) J=7.9 Hz (1H)	COSY 30 -> 27
31	171.0 ppm	-	HMBC 30 -> 31
32	34.7 ppm	2.60-2.54 ppm (m) (1H) ; 2.23 ppm (ddd) J=15.2, 7.5, 2.6 Hz (1H)	HMBC 32 -> 31, 34
33	29.0 ppm	3.04 ppm (ddd) J=14.4, 11.6, 2.2 Hz (1H) ; 2.60-2.54 (m) (1H)	COSY/TOCSY 32 -> 33
34	141.5 ppm	-	HMBC 32 -> 34
35	128.1 ppm	7.18-7.17 ppm (m) (1H)	COSY 35 -> 36 / TOCSY 35 -> 39
36	128.0 ppm	7.01-6.99 ppm (m)	COSY/TOCSY 35, 37 -> 36
37	123.6 ppm	7.18-7.17 ppm (m) (1H)	HMBC 37 -> 40 / TOCSY 37 -> 39
38	135.6 ppm	-	HMBC 41 -> 38
39	123.9 ppm	6.85 ppm (s) (1H)	HMBC 39 -> 35, 37, 40
40	130.4 ppm	6.10 ppm (d) J=16.1 Hz (1H)	
41	125.1 ppm	6.19 ppm (dt) J=15.9, 5.4 Hz (1H)	
42	46.3 ppm	4.92 ppm (d) J=5.1 Hz (2H)	COSY/TOCSY 40, 41 -> 42

Macrocyclic Product ***2.17e***

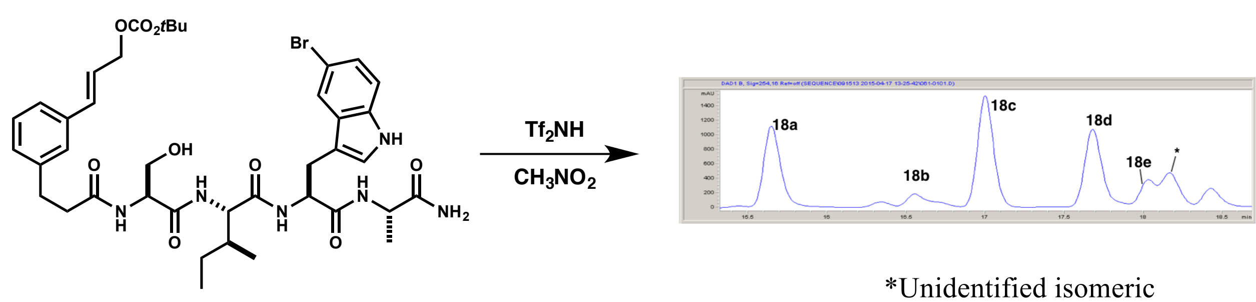


(500 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	-	7.04 ppm (br s) (1H) ; 6.93 ppm (br s) (1H)	HMBC 1 & 1' -> 2
2	173.8 ppm	-	HMBC 3 -> 2
3	48.0 ppm	4.10 ppm (p) J=7.3 Hz (1H)	COSY 5 -> 3
4	17.8 ppm	1.17 ppm (d) J=7.2 Hz (3H)	COSY/TOCSY 3 -> 4
5	-	7.69 ppm (d) J=7.5 Hz (1H)	HMBC 5 -> 6
6	170.3 ppm	-	HMBC 7 -> 6
7	56.5 ppm	4.01 ppm (dd) J=8.8, 5.7 Hz (1H)	COSY 12 -> 7
8	37.0 ppm	1.60-1.54 ppm (m) (1H)	COSY/TOCSY 7->8
9	23.5 ppm	1.18-1.15 ppm (m) (1H) ; 0.87-0.82 ppm (m) (1H)	COSY/TOCSY 8 -> 9
10	11.5 ppm	0.69 ppm (t) J=7.3 Hz (3H)	COSY/TOCSY 9 -> 10
11	15.1 ppm	0.57 ppm (d) J=6.8 Hz (3H)	COSY 7 -> 11
12	-	7.34 ppm (d) J=8.9 Hz (1H)	HMBC 12 -> 13
13	170.8 ppm	-	HMBC 14 -> 13
14	61.2 ppm	4.49 ppm (dd) J=10.4, 5.1 Hz (1H)	COSY/TOCSY 14 -> 15 / HMBC 14 -> 24
15	40.3 ppm	2.60 ppm (dd) J=13.8, 10.5 Hz (1H) ; 2.08 ppm (dd) J=13.8, 5.1 Hz (1H)	HMBC 42 -> 15 / HMBC 15' -> 24
16	57.6 ppm	-	HMBC 14, 15, 18, 42 -> 16
17	137.6 ppm	-	HMBC 21 -> 17
18	124.9 ppm	7.13 ppm (d) J=2.1 Hz (1H)	HMBC 18 -> 16 / TOCSY 18 -> 20, 21
19	109.5 ppm	-	HMBC 18, 20 (slight), 21 -> 19
20	130.3 ppm	7.16 ppm (dd) J= 8.2, 2.2 Hz (1H)	HMBC 18 -> 20
21	111.0 ppm	6.50 ppm (d) J= 8.3 Hz (1H)	COSY TOCSY 20 -> 21
22	146.6 ppm	-	HMBC 18, 20 -> 22
23	-	Not Observed	-
24	81.4 ppm	6.08 ppm (s) (1H)	Aminal (distinctive)
25	-	-	-
26	171.0 ppm	-	HMBC 27 -> 26
27	51.1 ppm	5.08 ppm (dt) 8.4, 5.9 Hz (1H)	COSY 30 -> 27
28	62.9 ppm	3.64-3.61 ppm (m) (1H)	COSY 27 -> 28
29	-	Not Observed	-
30	-	7.63 ppm (d) J= 8.2 Hz (1H)	HMBC 30 -> 31
31	171.8 ppm	-	HMBC 32, 33 -> 31
32	37.6 ppm	2.42 ppm (dt) J=12.4, 3.1 Hz (1H) ; 2.24 ppm (ddd) 12.8, 5.4, 4.0 Hz (1H)	COSY/TOCSY 33 -> 32
33	31.1 ppm	2.95-2.90 ppm (m) (1H) ; 2.69-2.65 ppm (m) (1H)	HMBC 33 -> 34
34	140.6 ppm	-	HMBC 36 -> 34
35	127.3 ppm	7.02 ppm (d) J=6.9 Hz (1H)	COSY/TOCSY 36 -> 35 / HMBC 35 -> 34/37
36	128.6 ppm	7.18 ppm (t) J=7.3 Hz (1H)	HMBC 36 -> 34, 38
37	123.9 ppm	7.11 ppm (d) J=7.7 Hz (1H)	COSY 36->37 / HMBC 37 -> 40
38	137.1 ppm	-	HMBC 41 -> 38
39	125.6 ppm	7.10 ppm (br s) (1H)	HMBC 39 -> 40
40	133.4 ppm	6.60 ppm (d) J=15.7 Hz (1H)	
41	125.4 ppm	6.07 ppm (dt) J=15.7, 7.8 Hz (1H)	
42	39.6 ppm	2.88 ppm (dd) J=12.9, 8.1 Hz (1H) ; 2.51-2.47 ppm (m) (1H)	COSY 41 -> 42 / TOCSY 40 -> 42

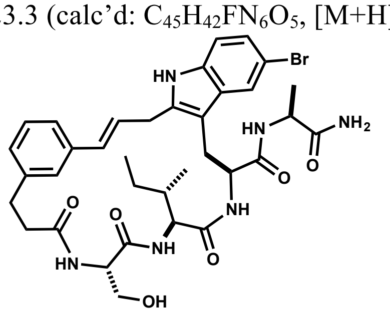


Acyclic Cinnamyl Carbonate 2.14: Synthesized according to Procedure A. Purified via trituration with 3x5 mL methanol. Beige Solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ11.00 (d, J = 2.5 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 1.8 Hz, 1H), 7.26- 7.30 (m, 1H), 7.26 (br. s, 1H), 7.23-7.24 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 2 Hz, 1H), 7.13 (d, J = 2 Hz, 1H), 7.1 (br. d, J = 7.5 Hz, 1H), 7.07 (br. s, 1H), 6.99 (br. s, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.32 (dt, J = 15.6, 6.2 Hz, 1H), 4.65 (dd, J = 6.3, 6.2 Hz, 2H), 4.5 (ddd, J = 9.2, 8.2, 5.0 Hz, 1H), 4.41 (apt q, J = 6.7 Hz, 1H), 4.15 (dddd, J = 7.2, 7.2, 7.2, 7.2 Hz, 1H), 4.07 (dd, J = 7.8, 6.2 Hz, 1H), 3.56 (dd, J = 10.4, 6.0 Hz, 1H), 3.51 (dd, J = 10.4, 6.3 Hz, 1H), 3.11 (dd, J = 14.9, 4.8 Hz, 1H), 2.85 (dd, J = 14.7, 9.4 Hz, 1H), 2.78 (app t, J 543 = 7.9 Hz, 2H), 2.43-2.49 (m, 3H), 1.60-2.49 (m, 1H), 1.41 (s, 9H), 1.19 (d, J = 7 Hz, 3H), 1.08- 1.16 (m, 1H), 0.90-1.00 (m, 1H), 0.65 (d, J = 6.7 Hz, 3H). ^{13}C-NMR (DMSO-d_6, 126 MHz): δ174.4, 172.1, 171.3, 171.3, 171.2, 153.3, 142.2, 136.3, 135.2, 133.9, 129.5, 129.1, 128.5, 126.9, 126.0, 124.7, 123.8, 121.2, 113.7, 111.5, 110.3, 82.0, 67.4, 62.2, 58.0, 55.0, 53.6, 48.7, 37.1, 36.7, 31.4, 27.85, 27.78, 27.6, 24.3, 18.6, 15.7, 11.7. MS m/z 841.4 (calc'd: $C_{40}H_{53}BrN_6O_9$, $[M+H]^+$, 841.1).



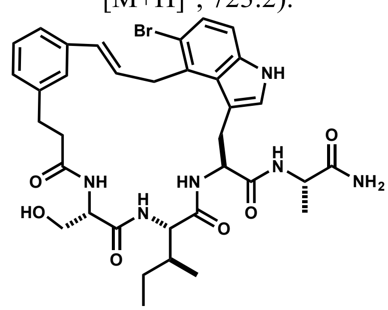
*Unidentified isomeric
product

MS m/z 723.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



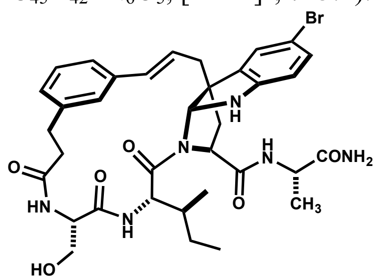
2.18a

MS m/z 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



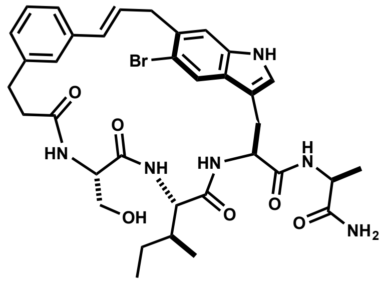
2.18b

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



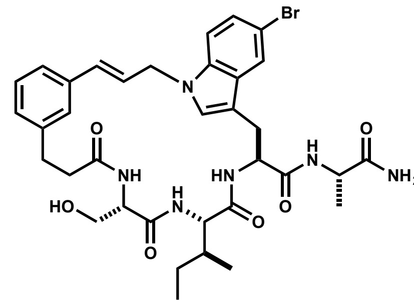
2.18c

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.18d

MS *m/z* 723.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.18e

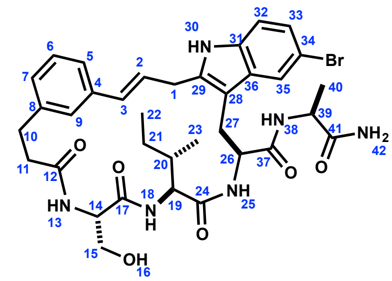
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2.5	30
24	86
29	30

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent A: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	35
4	45
18	57
18.5	35

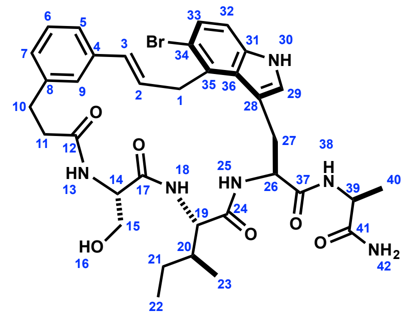
Macrocyclic Product ***2.18a***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	29.6	3.62-3.68 (m, 1H), 3.70-3.76 (m, 1H)	HMBC 1->29, 28
2	126.7	6.53-6.60 (m, 1H) overlap	COSY 2->1
3	131.4	6.53-6.60 (m, 1H) overlap	
4	136.8	-	
5	123.6	7.16-7.20 (m, 1H) overlap	
6	127.9	7.17-7.21 (m, 1H) overlap	
7	127.4	7.02-7.06 (m, 1H)	HMBC 7->5
8	141.4	-	
9	125.3	7.31 (br s, 1H) overlap	HMBC 9->3,5
10	29.9	2.68-2.75 (m, 1H), 3.02-3.10 (m, 1H) overlap	HMBC 10->7,8,9
11	35.1	2.41 (ddd, J = 14.9, 9.2, 2.2 Hz, 1H), 2.58-2.65 (m, 1H)	
12	171.5	-	
13	-	8.11 (d, J = 8.4 Hz, 1H)	
14	55.3	4.25 (ddd, J = 8.4, 5.5, 5.5 Hz, 1H)	
15	61.4	3.46-3.54 (m, 2H)	
16	-	not observed	
17	169.4	-	
18	-	7.29-7.32 (m, 1H) overlap	HMBC 18->17
19	56.6	4.06 (dd, J = 8.0, 6.6 Hz, 1H)	
20	37.3	1.60-1.69 (m, 1H)	
21	23.4	0.88-0.98 (m, 1H), 1.22-1.33 (m, 1H)	
22	10.9	0.71 (t, J = 7.4 Hz, 3H)	
23	15.0	0.68 (d, J = 6.7 Hz, 3H)	
24	170.3	-	
25	-	8.25 (d, J = 8.8 Hz, 1H)	
26	53.6	4.60 (ddd, J = 9.0, 8.8, 5.9 Hz, 1H)	HMBC 26->28
27	26.1	2.91 (dd, J = 14.4, 9.4 Hz, 1H), 3.04-3.10 (m, 1H) overlap	HMBC 27->28,29,36
28	105.9	-	
29	136.6	-	
30	-	10.94 (s, 1H)	
31	133.6	-	
32	112.3	7.17 (d, J = 8.6 Hz, 1H)	HMBC 32->36
33	122.4	7.06 (dd, J = 8.6, 1.9 Hz, 1H)	HMBC 33->31,34, TOCSY 33->32,35
34	110.6	-	
35	120.1	7.70 (d, J = 1.9 Hz, 1H)	HMBC 35->28,31,33,34
36	130.1	-	
37	170.6	-	
38	-	7.84 (d, J = 7.5 Hz, 1H)	
39	18.3	1.20 (d, J = 7.1 Hz, 3H)	
40	47.9	4.17 (dq, J = 7.1, 7.1 Hz, 1H)	
41	173.5	-	
42	-	7.00 (br s, 1H), 7.20 (br s, 1H)	TOCSY 42->42', HMBC 42->41

Macrocyclic Product ***2.18b***

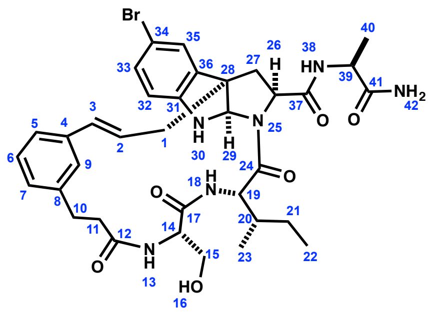


(500 MHz, DMSO-d$_6$, 298K)

*Note: This isolated compound was contaminated O-tert-butoxycarbonyl(cinnamyl alcohol 3-propionic acid)

	13C	1H	key correlation
1	34.9	3.93-3.99 (m, 1H), 4.23-4.28 (m, 1H) overlap	COSY 1→1', HMBC 1→34,35,36
2	128.4	6.45 (ddd, *J* = 16.06, 6.0, 5.5 Hz, 1H)	HMBC 2→4
3	129.8	6.20 (br d, *J* = 16.0 Hz, 1H)	HMBC 3→4
4	137	-	
5	122.9	7.00 (br d, *J* = 7.5 Hz, 1H)	HMBC 5→3
6	127.9	7.10 (dd, *J* = 7.5, 7.5 Hz, 1H)	HMBC 6→4,8, TOCSY 6→5,7,9
7	127.3	6.99 (br d, *J* = 7.5 Hz, 1H) overlap	
8	141.3	-	
9	124.6	7.22 (br s, 1H)	HMBC 9→3
10	28.9	2.68-2.74 (m, 1H) overlap, 3.01-3.05 (m, 1H) overlap	HMBC 10→7,8,9,12
11	34.3	2.48-2.53 (m, 1H) obscured, 2.66-2.72 (m, 1H) overlap	HMBC 11→9,12
12	171.5	-	
13	-	8.10 (d, *J* = 8.3 Hz, 1H)	HMBC 13→12, COSY 13→14
14	56.1	4.23-4.27 (m, 1H) overlap	HMBC 14→15,16
15	62	3.50-3.55 (m, 1H), 3.60 (ddd, *J* = 11.0, 5.7, 5.7 Hz, 1H)	HMBC 15→16
16	169.3	-	
17	-	4.90 (dd, *J* = 5.7, 5.7 Hz, 1H)	HMBC 17→14,15
18	-	7.34 (d, *J* = 8.3 Hz, 1H)	HMBC 18→16, COSY 18→19
19	56.3	4.30 (dd, *J* = 8.3, 7.4 Hz, 1H)	COSY 19→20, HMBC 19→24
20	37.1	1.65-1.72 (m, 1H)	COSY 20→21,23
21	23.9	0.98-1.06 (m, 1H), 1.39-1.48 (m, 1H)	
22	10.9	0.79 (t, *J* = 7.3 Hz, 3H)	COSY 22→21
23	14.8	0.80 (d, *J* = 6.6 Hz, 3H)	
24	170.2	-	
25	-	8.34 (d, *J* = 7.3 Hz, 1H)	HMBC 25→24, COSY 25→26
26	54.3	4.61 (ddd, *J* = 7.8, 7.8, 7.3 Hz, 1H)	HMBC 26→28, COSY 26→27
27	29.1	3.09-3.14 (m, 2H)	HMBC 27→28
28	109.6	-	
29	126.1	7.06 (d, *J* = 2.5 Hz, 1H)	HMBC 29→28,31,36
30	-	11.06 (d, *J* = 2.5 Hz, 1H)	
31	135.6	-	
32	111.8	7.18 (d, *J* = 8.6 Hz, 1H)	HMBC 32→31,34,36
33	124.6	7.26 (d, *J* = 8.6 Hz, 1H)	HMBC 33→31
34	114.9	-	
35	129.7	-	
36	126.6	-	
37	169.5	-	
38	-	7.78 (d, *J* = 7.6 Hz, 1H)	HMBC 38→37
39	18.1	4.16 (dq, *J* = 7.6, 7.0 Hz, 1H)	
40	47.8	1.14 (d, *J* = 7.0 Hz, 1H)	
41	173.3	-	
42	-	6.90 (br s, 1H), 6.91 (br s, 1H)	HMBC 42→41

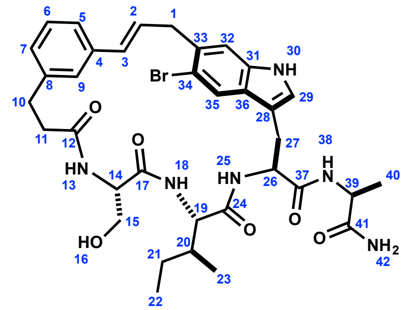
Macrocyclic Product ***2.18c***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	39.5	2.51-2.55 (m, 2H)	HMBC 1->28,29 ; NOESY 1->29
2	124.1	6.18 (ddd, J = 15.7, 8.2, 7.0 Hz, 1H)	COSY 2->1, HMBC 2->4
3	134.3	6.57 (d, J = 15.7 Hz, 1H)	
4	136.8	-	
5	124.4	7.03 (br d, J = 7.6 Hz, 1H)	HMBC 5->3, TOCSY 5->6,7,9
6	128.0	7.16 (dd, J = 7.6, 7.6 Hz, 1H)	HMBC 6->4,8
7	127.5	7.01 (br d, J = 7.6 Hz, 1H)	
8	141.4	-	
9	124.5	7.38 (br s, 1H)	HMBC 9->3
10	29.8	2.75 (apt dd, J = 14.0, 9.8 Hz, 1H), 3.02 (apt dd, J = 14.0, 10.7 Hz, 1H)	HMBC 10->7,9,12
11	35.8	2.31-2.36 (m, 1H) overlap, 2.47-2.54 (m, 1H) overlap	
12	171.3	-	
13	-	7.98 (d, J = 7.9 Hz, 1H)	HMBC 13->12
14	54.7	4.35 (ddd, J = 7.9, 7.0, 5.4 Hz, 1H)	COSY 14->13
15	61.5	3.54 (dd, J = 10.7, 7.0 Hz, 1H), 3.60 (dd, J = 10.7, 5.4 Hz, 1H)	COSY 15->14
16	-	not observed	
17	170.2	-	
18	-	8.03 (d, J = 6.1 Hz, 1H)	HMBC 18->17
19	55.6	4.23 (dd, J = 9.1, 6.1 Hz, 1H)	HMBC 19->24
20	36.4	1.71-1.77 (m, 1H) overlap	COSY 20->19
21	24.1	1.18-1.25 (m, 1H), 1.66-1.73 (m, 1H) overlap	
22	11.0	0.89 (t, J = 7.5 Hz, 3H)	COSY 22->21
23	14.8	0.99 (d, J = 6.8 Hz, 3H)	COSY 23->20
24	172.3	-	
25	-	-	
26	60.3	4.42 (dd, J = 8.7, 6.3 Hz, 1H)	COSY 26->27, HMBC 26->24 NOESY 26->29
27	38.3	2.09 (dd, J = 13.0, 6.3 Hz, 1H), 2.32-2.37 (m, 1H) overlap	HMBC 27->26,28,29,37
28	56.8	-	
29	80.8	6.35 (s, 1H)	HMBC 29->1,24,27,31,36
30	-	not observed	
31	147.8	-	
32	111.1	6.50 (d, J = 8.3 Hz, 1H)	HMBC 32->34,36
33	130.6	7.14 (dd, J = 8.3, 2.1 Hz, 1H)	HMBC 33->31
34	108.8	-	
35	124.9	7.31 (d, J = 2.1 Hz, 1H)	HMBC 35->31
36	136.7	-	
37	169.4	-	
38	-	7.33 (d, J = 7.1 Hz, 1H)	
39	47.4	3.98 (dq, J = 7.1, 6.8 Hz, 1H)	HMBC 39->41
40	17.9	0.83 (d, J = 6.8 Hz, 3H)	COSY 40->39, HMBC 40->41
41	173.3	-	
42	-	6.90 (br s, 1H), 7.38 (br s, 1H)	HMBC 42->41, TOCSY 42->42'

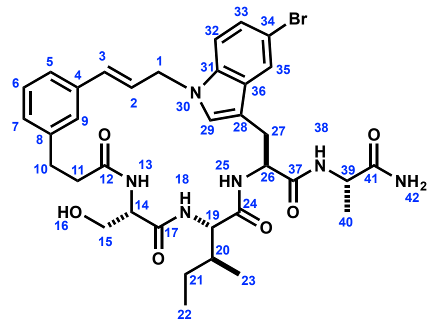
*Macrocyclic Product **2.18d***



(500 MHz, DMSO-d_6, 340K)

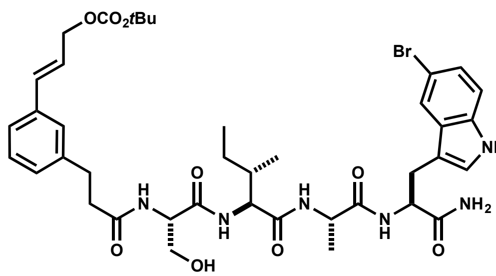
	13C	1H	key correlation
1	38.0	3.68 (apt d, J = 4.1 Hz, 2H)	
2	129.0	6.38 (ddd, J = 16.0, 5.9, 5.9 Hz, 1H)	HMBC 2->4
3	129.4	6.16 (br d, J = 16.0 Hz, 1H)	HMBC 3->5,9
4	136.8	-	
5	123.1	7.18 (d, J = 8.0 Hz, 1H) overlap	
6	127.6	7.16 (dd, J = 8.0, 8.0 Hz, 1H) overlap	HMBC 6->4,9
7	126.8	6.97 (br d, J = 8.0 Hz, 1H)	
8	140.6	-	
9	124.4	7.03 (br s, 1H)	HMBC 9->3,5,7,10
10	29.3	2.78 (ddd, J = 14.8, 7.8, 3.5 Hz, 1H), 2.83-2.89 (m, 1H) overlap	
11	34.7	2.32 (ddd, J = 14.9, 7.8, 3.5 Hz, 1H), 2.50-2.56 (m, 1H)	HMBC 11->12
12	171.4	-	
13	-	7.46 (d, J = 7.4 Hz, 1H)	
14	53.9	4.12 (apt dd, J = 11.9, 6.0 Hz, 1H)	
15	61.6	3.03 (dd, J = 10.8, 6.0 Hz, 1H), 2.84-2.89 (m, 1H) overlap	
16	-	not observed	
17	not observed	-	
18	-	7.38-7.42 (m, 1H) overlap	
19	56.8	4.03 (dd, J = 7.9, 6.4 Hz, 1H)	HMBC 19->24
20	35.8	1.72-1.80 (m, 1H)	
21	23.4	0.99-1.08 (m, 1H), 1.30-1.38 (m, 1H)	
22	10.5	0.80 (t, J = 7.4 Hz, 3H)	
23	14.8	0.84 (d, J = 6.8 Hz, 3H)	
24	170.0	-	
25	-	7.38-7.42 (m, 1H) overlap	
26	52.9	4.62 (apt dd, J = 14.4, 7.5 Hz, 1H)	HMBC 26->37
27	26.5	3.08-3.12 (m, 1H) obscured	HMBC 27->28,37
28	108.8	-	
29	125.0	7.15 (br s, 1H) overlap	HMBC 29->28,31,36
30	-	10.69 (br s, 1H)	HMBC 30->31
31	135.4	-	
32	113.0	7.32 (s, 1H)	HMBC 32->1,36
33	130.0	-	
34	113.6	-	
35	121.7	7.83 (s, 1H)	HMBC 35->28,31,33,34
36	127.4	-	
37	170.3	-	
38	-	7.60 (br s, 1H)	
39	47.6	4.29 (qd, J = 7.1, 7.0 Hz, 1H)	HMBC 39->37,41
40	17.6	1.23 (d, J = 7.1 Hz, 3H)	HMBC 40->41
41	173.4	-	
42	-	6.82 (br s, 1H), 7.06 (br s, 1H)	

*Macrocyclic Product **2.18e***

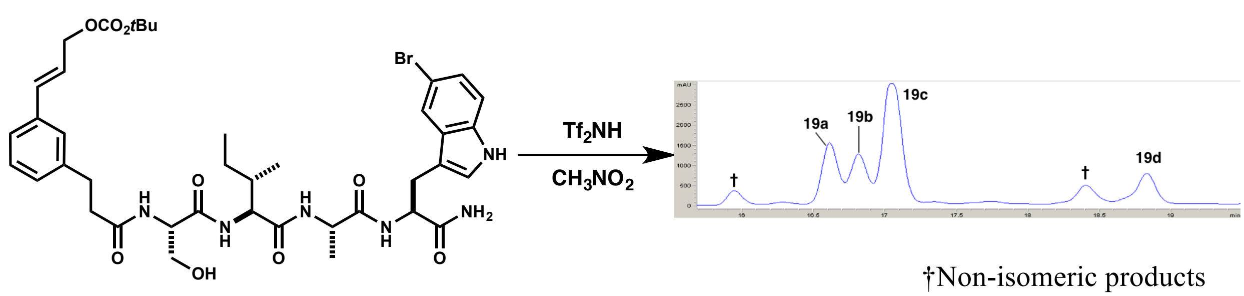


(500 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	47.5	4.83-4.90 (m, 2H)	HMBC 1->2,3,29,31
2	124.7	6.59-6.67 (m, 1H) overlap	HMBC 2->4
3	132.6	6.59-6.67 (m, 1H) overlap	
4	136.2	-	
5	124.5	7.16-7.20 (m, 1H) overlap	HMBC 5->3
6	127.9	7.20 (dd, J = 7.5, 7.3 Hz, 1H) overlap	HMBC 6->4,8
7	128.1	7.04 (ddd, J = 7.3, 1.5, 1.5 Hz, 1H)	
8	141.5	-	
9	124.7	7.41 (br s, 1H)	HMBC 9->3, TOCSY 9->5,6,7
10	29.6	2.70-2.76 (m, 1H), 2.94-3.00 (m, 1H) overlap	HMBC 10->7,8,9
11	34.7	2.42 (ddd, J = 14.5, 8.5, 2.7 Hz, 1H), 2.46-2.51 (m, 1H) obscured	HMBC 11->8
12	171.4	-	
13	-	7.87 (d, J = 7.4 Hz, 1H)	
14	54.5	4.22-4.27 (m, 1H) overlap	HMBC 14->17
15	61.4	3.34-3.40 (m, 2H) obscured	HMBC 15->17
16	-	not observed	
17	170.0	-	HMBC 18->17
18	-	7.70 (d, J = 8.0 Hz, 1H)	HMBC 19->24
19	57.1	4.01 (dd, J = 8.0, 7.1 Hz, 1H)	
20	35.9	1.60-1.68 (m, 1H)	
21	23.6	0.95-1.02 (m, 1H), 1.27-1.34 (m, 1H)	
22	10.7	0.73 (dd, J = 7.6, 7.6 Hz, 3H) overlap	
23	15.0	0.72 (d, J = 7.1 Hz, 3H) overlap	
24	171.2	-	
25	-	7.98 (d, J = 8.2 Hz, 1H)	HMBC 25->24,27
26	52.2	4.56 (ddd, J = 8.6, 8.2, 4.8 Hz, 1H)	HMBC 26->37, COSY 26->25,27
27	26.5	2.99-3.94 (m, 2H) overlap	
28	109.2	-	
29	128.6	7.35 (s, 1H)	HMBC 29->1,27,31,36
30	-	-	
31	134.5	-	
32	111.4	7.44 (d, J = 8.7 Hz, 1H)	HMBC 32->34,36
33	123.1	7.21 (dd, J = 8.7, 1.9 Hz, 1H)	HMBC 33->31,35
34	111.1	-	
35	120.9	7.78 (d, J = 1.9 Hz, 1H)	HMBC 35->31,33
36	129.3	-	
37	170.9	-	
38	-	7.94 (d, J = 7.3 Hz, 1H)	HMBC 38->37
39	47.8	4.21 (dq, J = 7.3, 7.2 Hz, 1H)	HMBC 39->41
40	18.1	1.17 (d, J = 7.2 Hz, 1H)	HMBC 40->39
41	173.8	-	
42	-	7.02 (br s, 1H), 7.32 (br s, 1H)	

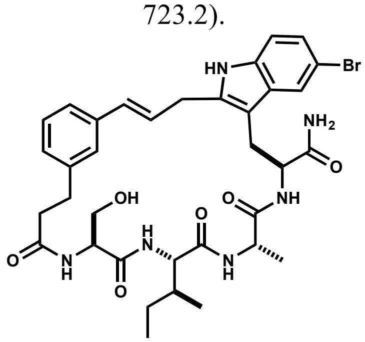


Acyclic Cinnamyl Carbonate 2.15: Synthesized according to Procedure A. Purified via trituration with 3x5 mL methanol. Beige solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ10.99 (d, J = 1.7 Hz, 1H), 7.99 (d, J = 6.7 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.32 (br s, 1H), 7.28 (br s, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.21 (dd, J = 7.5, 7.5 Hz, 1H), 7.17 (d, J = 1.9 Hz, 1H), 7.12 (dd, J = 8.6, 1.7 Hz, 1H), 7.10 (d, J = 7.3 Hz, 1H), 7.03 (br s, 1H), 6.61 (d, J = 16.0 Hz, 1H), 6.31 (ddd, J = 15.9, 6.2, 6.2 Hz, 1H), 5.00 (dd, J = 5.3, 5.3 Hz, 1H), 4.64 (d, J = 6.0 Hz, 1H), 4.39-4.34 (m, 1H), 4.22 (pentet, J = 7.1 Hz, 1H), 4.16 (dd, J = 7.9, 6.7 Hz, 1H), 3.55-3.46 (m, 2H), 3.04 (dd, J = 14.6, 5.7 Hz, 1H), 2.91 (dd, J = 14.7, 7.8 Hz, 1H), 2.78 (dd, J = 7.8, 7.8 Hz, 1H), 2.45 (dd, J = 8.6, 7.3 Hz, 1H), 1.74-1.69 (m, 1H), 1.40 (s, 9H), 1.38-1.33 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 1.07-7.01 (m, 1H), 0.77 (d, J = 6.9 Hz, 3H), 0.76 (dd, J = 7.9, 7.9 Hz, 3H).). ^{13}C-NMR (DMSO-d_6, 126 MHz): δ172.9, 171.8, 171.6, 170.6, 170.4, 152.8, 141.7, 135.9, 134.7, 133.5, 129.2, 128.6, 128.0, 126.4, 125.4, 124.2, 123.3, 123.3, 120.8, 113.3, 111.0, 109.9, 81.5, 66.9, 61.7, 57.0, 54.7, 53.6, 53.2, 48.4, 36.6, 31.0, 27.4, 25.2, 24.1, 18.1, 17.8, 15.3, 11.3. MS m/z, 841.3 (calc'd: $C_{35}H_{44}BrN_6O_6$ $[M+H]^+$, 841.1)



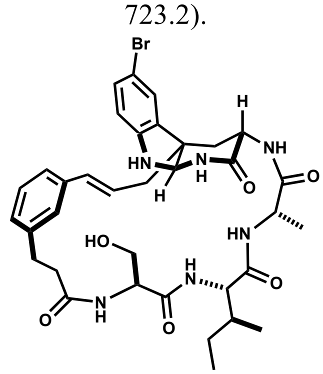
†Non-isomeric products

MS m/z 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



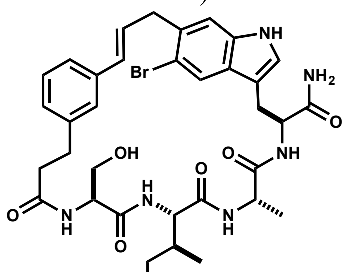
2.19a

MS m/z 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



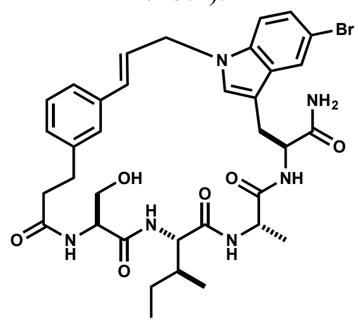
2.19b

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.19c

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.19d

Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2.5	30
24	86
29	30

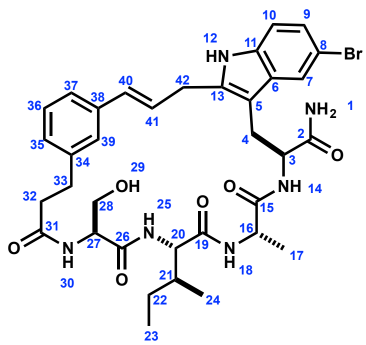
Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent A: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	45
2	45
12	50
13	50

Semi-Prep HPLC Method
Column: Waters XSelect™ C_{18}, 10x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 6.00 mL/min
For re-purification of 2.*19b*

Time	%B
0	38
1	38
20	43
21	38

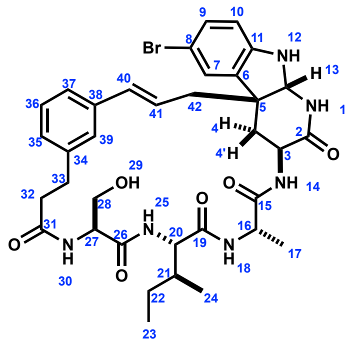
Macrocyclic Isomer ***2.19a***



(600 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	-	7.29 ppm (br s) (1H) ; 6.98 ppm (br s)	TOCSY 1 -> 1'
2	173.0 ppm	-	HMBC 1(slight),3 -> 2
3	53.4 ppm	4.40 ppm (ddd) J=7.5, 7.5, 7.5 Hz (1H)	COSY/TOCSY 14 -> 3
4	26.9 ppm	3.05 ppm (dd) J=14.7, 7.5 Hz (1H) ; 2.92 ppm (dd) J=14.5, 6.8 Hz (1H)	COSY/TOCSY 3 -> 4
5	105.8 ppm	-	HMBC 4,7,12,42(slight) -> 5
6	130.0 ppm	-	HMBC 10,12 -> 6
7	120.0 ppm	7.71 ppm (d) J=1.7 Hz (1H)	HMBC 7 -> 5,11
8	110.8 ppm	-	HMBC 7,10 -> 8
9	122.3 ppm	7.08 ppm (dd) J=8.5, 1.9 Hz (1H)	HMBC 7 -> 9 / 9 -> 7
10	112.3 ppm	7.19 ppm (d) J=8.2 Hz (1H)	COSY 9 -> 10 ; HMBC 10 -> 6,8
11	133.7 ppm	-	HMBC 7,9,12 -> 11
12	-	10.94 ppm (s)	indole
13	136.7 ppm	-	HMBC 4,12,41,42 -> 13
14	-	7.69 ppm (d) J=8.3 Hz	HMBC 14 -> 15
15	171.8 ppm	-	HMBC 16 -> 15
16	47.5 ppm	4.39-4.33 ppm (m) (1H)	COSY/TOCSY 18 -> 16
17	17.4 ppm	1.22 ppm (d) J=7.1 Hz (1H)	COSY/TOCSY 16 -> 17
18	-	8.01 ppm (d) J=7.7 Hz (1H)	HMBC 18 -> 19
19	169.9 ppm	-	HMBC 20 -> 19
20	56.6 ppm	4.14 ppm (d) J=8.0, 5.8 Hz (1H)	COSY/TOCSY 25 -> 20
21	36.8 ppm	1.70-1.66 ppm (m) (1H)	TOCSY 20 -> 21
22	23.7 ppm	1.33-1.28 ppm (m) (1H) ; 1.05-0.98 ppm (m) (1H)	TOCSY 21 -> 22
23	11.1 ppm	0.70 ppm (dd) J=7.4 Hz (3H)	COSY/TOCSY 22 -> 23
24	15.0 ppm	0.76 ppm (d) J=6.8 Hz (3H)	COSY/TOCSY 21 -> 24
25	-	7.49 ppm (d) J=7.9 Hz (1H)	HMBC 25 -> 26
26	170.2 ppm	-	HMBC 27 -> 26
27	55.0 ppm	4.36-4.32 ppm (m) (1H)	COSY/TOCSY 30 -> 27
28	61.3 ppm	3.50-3.45 ppm (m) (2H)	COSY/TOCSY 27 -> 28
29	-	not observed	-
30	-	8.15 ppm (d) J=8.0 Hz (1H)	HMBC 30 -> 31
31	172.0 ppm	-	HMBC 32, 33 -> 31
32	34.6 ppm	2.67 ppm (ddd) J=14.9, 8.4, 6.6 Hz (1H) ; 2.40 ppm (ddd) J=14.5, 6.4, 6.4 Hz (1H)	HMBC 32 -> 34 ; COSY 33 -> 32
33	30.0 ppm	2.89-2.80 ppm (m) (2H)	HMBC 33 -> 34
34	141.4 ppm	-	HMBC 32,33,36 -> 34
35	126.9 ppm	7.03 ppm (d) J=7.4 Hz (1H)	COSY/TOCSY 36 -> 35
36	128.2 ppm	7.20 ppm (dd) J=7.8, 7.8 Hz (1H)	COSY/TOCSY 36 -> 37
37	123.9 ppm	7.16 ppm (d) J=7.6 Hz (1H)	HMBC 37 -> 40 / 40 -> 37
38	136.6 ppm	-	HMBC 36,41 -> 38
39	125.0 ppm	7.37 ppm (s) (1H)	TOCSY 39 -> 35,36,37
40	130.7 ppm	6.54 ppm (d) J=15.7 Hz (1H)	
41	126.6 ppm	6.37 ppm (ddd) J=15.8, 6.8, 6.8 Hz (1H)	
42	29.3 ppm	3.76 ppm (dd) J=16.0, 6.1 Hz (1H) ; 3.62-3.58 ppm (m) (1H)	COSY/HMBC 41 -> 42

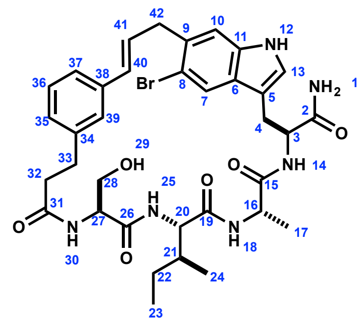
Macrocyclic Product **2.19b**



(600 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	-	7.99 ppm (d) J=3.0 Hz (1H)	COSY 12 -> 13 ; HMBC 13 -> 1; HMBC 1 -> 3,5
2	170.4 ppm	-	HMBC 3,13 -> 2
3	46.0 ppm	4.11 ppm (ddd) J=12.9, 8.2, 4.6 Hz (1H)	COSY/TOCSY 14 -> 3 ; HMBC 3 -> 2
4	35.2 ppm	2.09 ppm (dd) J=13.1, 4.4 Hz (1H) ; 1.99 ppm (dd) J=13.1, 13.1 Hz (1H)	COSY/TOCSY 3 -> 4
5	47.7 ppm	-	HMBC 4,7,12,42 -> 5
6	134.6 ppm	-	HMBC 4,10,42 -> 6
7	125.8 ppm	7.16 ppm (s) (1H)	HMBC 7 -> 5
8	108.3 ppm	-	HMBC 7,10 -> 8
9	130.8 ppm	7.19-7.16 ppm (m) (1H)	COSY 9 -> 10 ; HMBC 9 -> 7
10	110.5 ppm	6.56 ppm (d) J=8.0 Hz (1H)	HMBC 10 -> 6,8
11	148.6 ppm	-	HMBC 7,12,13 -> 11
12	-	not observed	
13	73.2 ppm	4.93 ppm (d) J=3.2 Hz (1H)	HMBC 13 -> 2,4 / 13 -> 4,42 ; NOESY 13 -> 4'
14	-	7.19-7.16 ppm (m) (1H)	HMBC 14 -> 15
15	171.0 ppm	-	HMBC 16 -> 15
16	47.5 ppm	4.29 ppm (pentet) J=7.4 Hz (1H)	COSY/TOCSY 18 -> 16
17	17.5 ppm	1.11 ppm (d) J=7.1 Hz (3H)	COSY/TOCSY 16 -> 17
18	-	7.77 ppm (d) J=8.4 Hz (1H)	HMBC 18 -> 19
19	169.7 ppm	-	HMBC 20 -> 19
20	58.2 ppm	4.05 ppm (dd) J=6.9, 4.6 Hz (1H)	COSY/TOCSY 25 -> 20
21	35.6 ppm	1.88-1.84 (m) (1H)	TOCSY 20 -> 21
22	23.8 ppm	1.32-1.27 ppm (m) (1H) ; 1.23-1.17 ppm (m) (1H)	TOCSY 21 -> 22
23	11.7 ppm	0.81 ppm (dd) J=7.4, 7.4 Hz (3H)	COSY/TOCSY 22 -> 23
24	15.4 ppm	0.84 ppm (d) J=7.0 Hz (3H)	COSY/TOCSY 21 -> 24
25	-	8.19 ppm (d) J=6.7 Hz (1H)	HMBC 25 -> 26
26	171.5 ppm	-	HMBC 27 -> 26
27	53.5 ppm	4.54 ppm (ddd) J=7.8, 7.8, 6.0 Hz (1H)	COSY 27 -> 28
28	61.7 ppm	3.43 ppm (dd) J=9.3, 5.6 Hz (1H) ; 3.14 ppm (dd) J=9.2, 9.2 Hz (1H)	COSY/TOCSY 27 -> 28
29	-	not observed	-
30	-	7.91 ppm (d) J=7.4 Hz (1H)	COSY 30 -> 27
31	171.7 ppm	-	HMBC 30 -> 31
32	34.5 ppm	2.81-2.76 ppm (m) (1H) ; 2.37-2.33 ppm (m) (1H)	COSY 33 -> 32
33	30.1 ppm	2.94-2.89 ppm (m) (1H) ; 2.85-2.81 ppm (m) (1H)	HMBC 35,39 -> 33
34	140.9 ppm	-	HMBC 36 -> 34
35	128.2 ppm	7.04 ppm (d) J=7.4 Hz (1H)	HMBC 35 -> 33
36	128.4 ppm	7.21 ppm (dd) J= 7.6 Hz (1H)	HMBC 36 -> 38
37	124.0 ppm	7.18-7.16 ppm (m) (1H)	TOCSY 35,39 -> 37 ; COSY 36 -> 37
38	136.6 ppm	-	HMBC 41 -> 38
39	125.1 ppm	7.32 ppm (br s) (1H)	TOCSY 39 -> 35
40	134.5 ppm	6.42 ppm (d) J=15.8 Hz	
41	124.1 ppm	6.36 ppm (ddd) J=15.4, 7.2, 7.2 Hz (1H)	
42	43.2 ppm	2.46-2.44 ppm (m) (2H)	COSY 41 -> 42

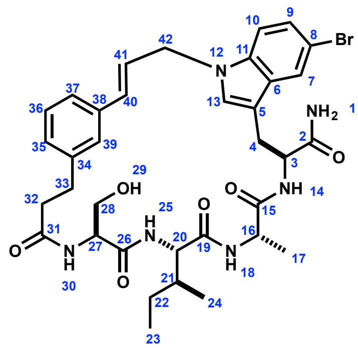
Macrocyclic Product ***2.19c***



(600 MHz, DMSO-d_6, 298K)

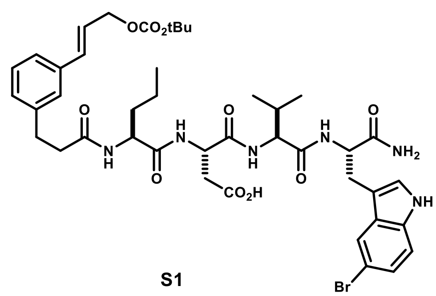
	13C	1H	key correlation
1	-	7.55 ppm (br s) (1H) ; 7.09 ppm (br s) (1H)	TOCSY 1 -> 1'
2	173.6 ppm	-	HMBC 1 -> 2
3	53.2 ppm	4.41 ppm (ddd) J=11.1, 7.9, 3.3 Hz (1H)	COSY 14 -> 3
4	27.2 ppm	3.07 ppm (dd) J=14.6, 3.1 Hz (1H) ; 2.87 ppm (dd) J=14.6, 11.1 Hz (1H)	COSY/TOCSY 3 -> 4
5	109.5 ppm	-	HMBC 4,7,12,13 -> 5
6	127.6 ppm	-	HMBC 10,12,13 -> 6
7	121.7 ppm	7.96 ppm (s) (1H)	HMBC 7 -> 5,8,9,11
8	113.8 ppm	-	HMBC 7,10 -> 8
9	130.5 ppm	-	HMBC 7,42 -> 9
10	113.2	7.35 ppm (s) (1H)	HMBC 42 -> 10 / 10 -> 42
11	135.5 ppm	-	HMBC 7,12,13 -> 11
12	-	10.82 ppm (d) J=1.9 Hz (1H)	indole
13	125.1 ppm	7.17 ppm (d) J=2.2 Hz (1H)	COSY 12 -> 13
14	-	7.72 ppm (d) J= 8.0 Hz (1H)	HMBC 14 -> 15
15	171.6 ppm	-	HMBC 16 -> 15
16	47.5 ppm	4.15 ppm (pentet) J=7.0 Hz (3H)	COSY/TOCSY 18 -> 16
17	17.8 ppm	1.17 ppm (d) J=7.0 Hz (1H)	COSY/TOCSY 16 -> 17
18	-	7.60 ppm (d) J=7.0 Hz (1H)	HMBC 18 -> 19
19	169.4 ppm	-	HMBC 20 -> 19
20	56.3 ppm	4.05 ppm (dd) J=8.4, 5.7 Hz (1H)	COSY/TOCSY 25 -> 20
21	36.6 ppm	1.64-1.59 ppm (m) (1H)	TOCSY 20 -> 21
22	23.5 ppm	1.22-1.17 ppm (m) (1H) ; 0.94-0.89 ppm (m) (1H)	COSY/TOCSY 21 -> 22
23	10.9 ppm	0.67 ppm (dd) J=7.4, 7.4 Hz (3H)	COSY/TOCSY 22 -> 23
24	14.9 ppm	0.67 ppm (d) J=6.8 Hz (3H)	COSY/TOCSY 21 -> 24
25	-	7.41 ppm (d) J=8.5 Hz (1H)	HMBC 25 -> 26
26	169.5 ppm	-	HMBC 27 -> 26
27	54.1 ppm	4.24 ppm (ddd) J=8.3, 6.1, 6.0 Hz (1H)	COSY 27 -> 28
28	61.2 ppm	3.44-3.37 ppm (m) (1H)	COSY/TOCSY 27 -> 28
29	-	4.83 ppm (dd) J=5.3, 5.3 Hz (1H)	COSY/TOCSY 29 -> 27,28
30	-	8.03 ppm (d) J=8.3 Hz (1H)	HMBC 30 -> 31
31	171.2 ppm	-	HMBC 32,33 -> 31
32	35.7 ppm	2.52-2.48 ppm (m) (1H) ; 2.38-2.33 ppm (m) (1H)	COSY 33 -> 32
33	30.0 ppm	2.76-2.72 ppm (m) (2H)	HMBC 39 -> 33
34	141.2 ppm	-	HMBC 32,33,35,36 -> 34
35	128.1 ppm	7.19 ppm (d) J=4.8 Hz (1H)	HMBC 36 -> 35
36	126.7 ppm	7.04-7.01 ppm (m) (1H)	COSY 37 -> 36 ; TOCSY 39 -> 36
37	123.4 ppm	7.19 ppm (d) J=3.7 Hz (1H)	HMBC 39,40 -> 37
38	136.9 ppm	-	HMBC 36,37,40,41 -> 38
39	125.0 ppm	7.09 ppm (s) (1H)	HMBC 40 -> 39
40	129.9 ppm	6.26 ppm (d) J=15.9 Hz (1H)	
41	129.0 ppm	6.37 ppm (ddd) J=15.8, 6.2, 6.2 Hz (1H)	
42	38.3 ppm	3.72 ppm (dd) J=16.1, 6.2 Hz (1H) ; 3.65 ppm (dd) J=16.0, 5.8 Hz (1H)	COSY 41 -> 42

Macrocyclic Product ***2.19d***



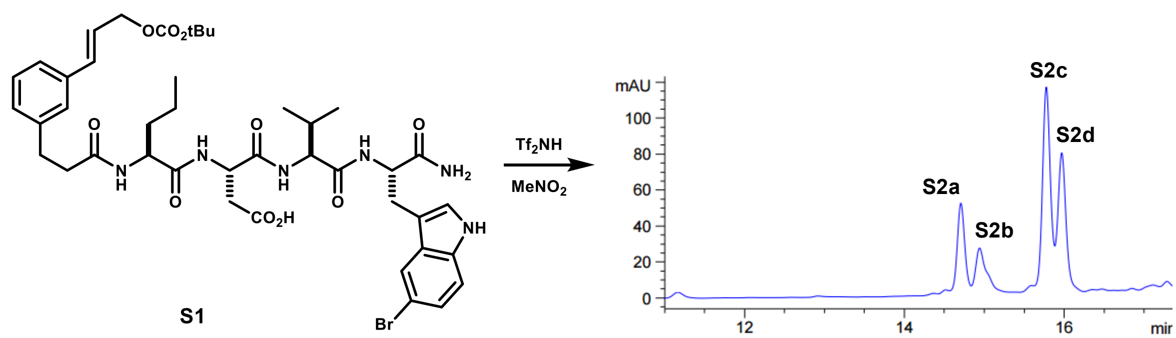
(600 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	-	7.41 ppm (br s) (1H) ; 7.08 ppm (br s) (1H)	TOCSY 1 -> 1'
2	173.2 ppm	-	HMBC 1 -> 2
3	52.7 ppm	4.38 ppm (ddd) J=10.3, 7.5, 2.9 Hz (1H)	COSY 14 -> 3
4	26.8 ppm	3.09 ppm (dd) J=15.0, 2.9 Hz (1H) ; 3.00-2.95 ppm (m) (1H)	COSY/TOCSY 3 -> 4
5	109.7 ppm	-	HMBC 4,7,13 -> 5
6	129.3 ppm	-	HMBC 10,13 -> 6
7	120.7 ppm	7.82 ppm (d) J=1.7 Hz (1H)	
8	111.1 ppm	-	HMBC 7,10 -> 8
9	123.2	7.24-7.21 ppm (m) (1H)	HMBC 7 -> 10 ; COSY 7 -> 9
10	111.5 ppm	7.45 ppm (d) J=8.6 Hz (1H)	COSY 10 -> 9 ; TOCSY 7 -> 10
11	134.4 ppm	-	HMBC 7,13, 42 -> 11
12	-	-	-
13	128.0 ppm	7.28 ppm (s) (1H)	HMBC 42 -> 13
14	-	7.76 ppm (d) J=7.7 Hz (1H)	HMBC 14 -> 15
15	172.0 ppm	-	HMBC 16 -> 15
16	17.3 ppm	1.21 ppm (d) J=7.2 Hz (3H)	COSY/TOCSY 17 -> 16
17	47.6 ppm	4.29 ppm (pentet) J=7.3 Hz (1H)	COSY/TOCSY 18 -> 17
18	-	8.00 ppm (d) J=7.4 Hz (1H)	HMBC 18 -> 19
19	170.3 ppm	-	HMBC 20 -> 19
20	56.7 ppm	4.13 ppm (dd) J=7.5, 6.4 Hz (1H)	COSY/TOCSY 25 -> 20
21	36.5 ppm	1.71-1.67 ppm (m) (1H)	COSY 20 -> 21
22	23.9 ppm	1.38-1.34 ppm (m) (1H) ; 1.09-1.04 ppm (m) (1H)	COSY/TOCSY 21 -> 22
23	10.9 ppm	0.75 ppm (dd) J=7.4 Hz (3H)	COSY/TOCSY 22 -> 23
24	14.9 ppm	0.79 ppm (d) J=6.8 Hz (3H)	COSY/TOCSY 21 -> 24
25	-	7.46 ppm (d) J=7.8 Hz (1H)	HMBC 25 -> 26
26	170.2 ppm	-	HMBC 27 -> 26
27	55.4 ppm	4.23 ppm (ddd) J=7.5, 5.9, 5.9 Hz (1H)	COSY 27 -> 28
28	61.0 ppm	3.57-3.50 ppm (m) (2H)	COSY/TOCSY 27 -> 28
29	-	not observed	-
30	-	8.13 ppm (d) J=7.6 Hz (1H)	HMBC 30 -> 31
31	172.3 ppm	-	HMBC 32,33 -> 31
32	35.5 ppm	2.53-2.50 ppm (m) (1H) ; 2.47-2.44 ppm (m) (1H)	COSY 33 -> 32
33	30.1 ppm	2.87-2.84 ppm (m) (1H) ; 2.82-2.77 ppm (m) (1H)	HMBC 33 -> 35,39
34	141.5 ppm	-	HMBC 32,33,36 -> 34
35	127.5 ppm	7.09 ppm (d) J=7.1 Hz (1H)	HMBC 37 -> 35
36	128.2 ppm	7.24-7.21 ppm (m) (1H)	COSY 37 -> 36, 37
37	124.4 ppm	7.18 ppm (d) J=7.5 Hz (1H)	HMBC 40 -> 37
38	135.9 ppm	-	HMBC 36,41 -> 38
39	124.8 ppm	7.33 ppm (s) (1H)	HMBC 40 -> 39
40	132.3 ppm	6.66 ppm (d) J=15.8 Hz (1H)	
41	124.5 ppm	6.44 ppm (ddd) J=15.8, 6.3, 6.3 Hz (1H)	
42	47.1 ppm	4.93 ppm (dd) J=15.9, 6.0 Hz (1H) ; 4.83 ppm (dd) J=15.9, 6.2 Hz (1H)	COSY 41 -> 42

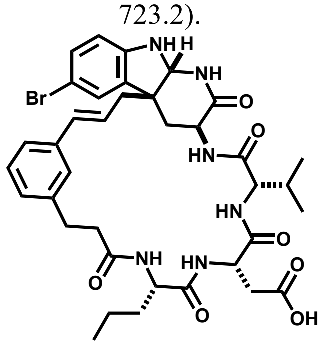


S1

Acyclic Cinnamyl Carbonate 2.S1: Synthesized according to General Procedure A. The reaction was filtered, concentrated, and the residue partitioned between EtOAc and H_2O. The resulting solids were collected by filtration to give **2.S1** (546mg, 62%) as an off-white solid. ^{1}H NMR (DMSO-d_6, 600 MHz): δ 0.69 (d, J = 6.4 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H), 0.77 (t , J = 7.3 Hz, 3H), 1.35-1.47 (m, 2H), 1.43 (s, 9H), 1.47-1.58 (m, 1H), 1.89-1.99 (m, 1H), 2.37-2.46 (m, 1H), 2.46-2.55 (m, 1H), 2.68 (dd, J = 16.4, 5.7 Hz, 1H), 2.75-2.85 (m , 2H), 2.88-2.97 (m, 2H), 3.08 (dd, J = 14.3, 4.6 Hz, 1H), 3.43 (br s, 1H), 4.04-4.10 (m, 1H), 4.22-4.29 (m, 1H), 4.39-4.49 (m, 1H), 4.53-4.59 (m, 1H), 4.67 (d, J = 6.0 Hz, 2H), 6.33 (dt, J = 15.6, 6.0 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 7.04 (s, 1H), 7.11 (d, J = 6.8 Hz, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.21-7.35 (m, 5H), 7.53 (br d, J = 8.3 Hz, 1H), 7.77 (br s, 1H), 7.92-7.98 (m, 1H), 8.01 (d, J = 7.7 Hz, 1H), 8.35 (d, J = 7.2 Hz, 1H), 11.02 (s, 1H), 11.92 (br s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 173.2, 172.3, 172.1,171.5 170.7, 170.4, 162.3, 152.8, 141.7, 135.9, 134.7, 133.5, 129.2, 128.6, 128.1, 126.4, 125.4, 124.2, 123.3, 120.7, 113.3, 111.0, 110.1, 81.5, 66.9, 58.0, 53.3, 52.2, 49.7, 36.6, 35.8, 34.3, 30.9, 30.3, 27.4, 19.0, 18.4, 18.0, 17.5, 13.6. MS m/z 883.2/885.2 (calc'd: $C_{42}H_{56}BrN_6O_{10}$ $[M+H]^+$, 883.3).

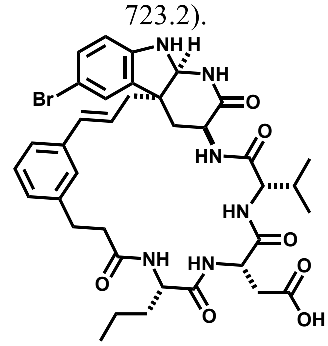


MS m/z 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



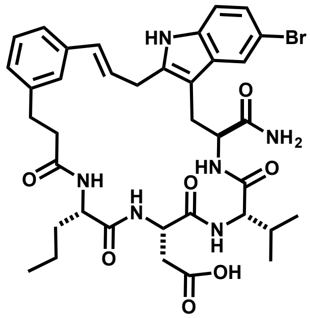
2.S2a

MS m/z 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



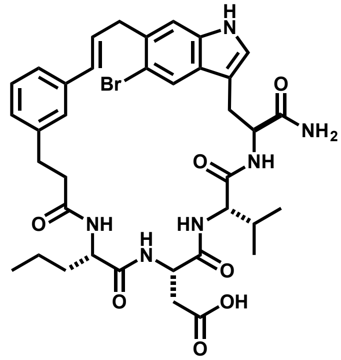
2.S2b

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.S2c

MS *m/z* 723.2 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 723.2).



2.S2d

Analytical HPLC Method
Column: Waters X-Select™ PFP, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	10
3	10
23	70
25	10
30	10

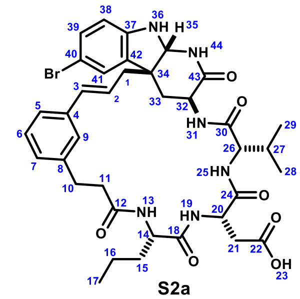
Prep HPLC Method A
Column: Waters X-Select™ PFP, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.00 mL/min

Time	%B
0	40
3	40
23	85

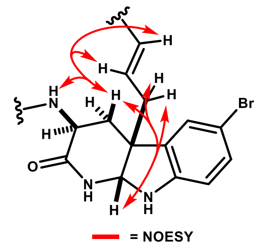
Prep HPLC Method B
Column: Waters X-Select™ PFP, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% HCO_2H
Solvent B: ACN + 0.1% HCO_2H
Flow rate: 18.00 mL/min

Time	%B
0	40
3	40
23	85

Macrocyclic Product ***2.S2a*** (600 MHz, DMSO-d_6, 298K)

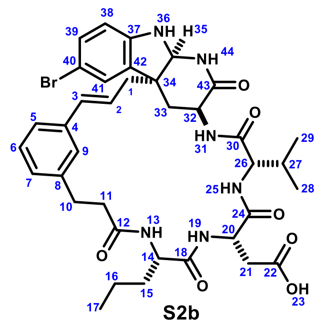


S2a

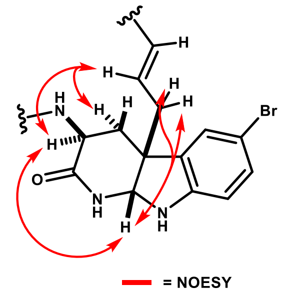


	13C	1H	key correlations
1	41.6	2.38 (dd, *J* = 13.4, 6.6 Hz, 1H), 2.46 (dd, *J* = 13.4, 5.7 Hz, 1H)	HMBC 1→35 NOESY 1→35
2	124.2	6.24-6.28 (m, 1H)	HMBC 2→4 NOESY 2→33
3	134.2	6.24-6.28 (m, 1H)	HMBC 3→1 NOESY 3→33
4	136.7	-	
5	124.1	7.04 (br d, *J* = 7.6 Hz, 1H)	HMBC 5→3
6	127.7	7.15 (dd, *J* = 7.6, 7.6 Hz, 1H)	HMBC 6→4,8
7	128	7.00 (br d, *J* = 7.6 Hz, 1H)	
8	140.1	-	
9	125.5	7.50-7.53 (m, 1H)	HMBC 9→3
10	30.4	2.83-2.88 (m, 2H)	HMBC 10→8,12
11	34.2	2.33-2.38 (m, 1H), 2.90-2.94 (m, 1H)	HMBC 11→8,12
12	170.4	-	
13	-	7.70 (br d, *J* = 8.6 Hz, 1H)	HMBC 13→12
14	50.6	4.26-4.31 (m, 1H)	
15	35.6	1.10-1.17 (m, 1H), 1.50-1.56 (m, 1H)	
16	17.5	0.51-0.57 (m, 1H), 0.63-0.69 (m, 1H)	
17	13.5	0.61-0.65 (m, 3H)	
18	172.1	-	
19	-	8.42 (br d, *J* = 5.7 Hz, 1H)	HMBC 19→18
20	52	4.25 (ddd, *J* = 8.2, 5.7, 5.7 Hz, 1H)	COSY 20→21
21	35.9	2.54-2.59 (m, 2H)	HMBC 21→22
22	171.4	-	
23	-	not detected	
24	170.6	-	
25	-	6.97 (br d, *J* = 8.0 Hz, 1H)	
26	56.9	4.08 (dd, *J* = 8.0, 6.4 Hz, 1H)	TOCSY 26→25,27,28,29 HMBC 26→30
27	30.7	1.89-1.96 (m, 1H)	
28	18.6	0.78 (d, *J* = 6.7 Hz, 3H)	
29	17.9	0.79 (d, *J* = 6.7 Hz, 3H)	
30	169.5	-	
31	-	7.92 (br d, *J* = 7.3 Hz, 1H)	HMBC 31→30 TOCSY 31→32,33 NOESY 31→33
32	46.1	4.00 (ddd, *J* = 12.5, 7.3, 5.0 Hz, 1H)	HMBC 32→30,43
33	33.3	*pro*-S 1.87 (dd, *J* = 13.1, 12.5 Hz, 1H)	
33'		*pro*-R 2.33 (dd, *J* = 13.1, 4.7 Hz, 1H)	
34	47.4	-	
35	74.9	4.82 (d, *J* = 2.3 H, 1H)	HMBC 35→1,34,37,43 COSY 35→36,44
36	-	6.31 (br s, 1H)	HMBC 36→34,37,42
37	148.3	-	
38	110.8	6.62 (d, *J* = 8.3 Hz, 1H)	HMBC 38→40,42
39	130.6	7.18 (dd, *J* = 8.3, 2.0 Hz, 1H)	HMBC 39→37,40,41
40	108	-	
41	126.3	7.05 (d, *J* = 2.0 Hz, 1H)	HMBC 41→34,37,40
42	132.4	-	
43	169.3	-	
44	-	7.96 (d, *J* = 2.3 Hz, 1H)	HMBC 44→32,34

Macrocyclic Product ***2.S2b*** *(600 MHz, DMSO-d_6, 298K)*

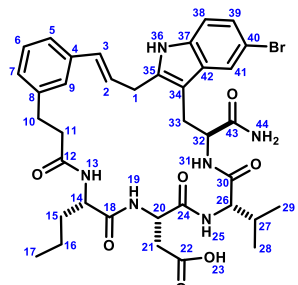


S2b



	13C	1H	key correlations
1	40.7	2.42 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.47-2.52 (m, 1H)	HMBC 1→34 NOESY 1→35,32
2	124.7	6.65 (ddd, *J* = 15.6, 7.6, 7.0 Hz, 1H)	HMBC 2→4 NOESY 2→33'
3	133.2	6.40 (d, *J* = 15.6 Hz, 1H)	HMBC 3→1
4	136.6	-	
5	125.1	6.98 (br d, *J* = 7.6 Hz, 1H)	HMBC 5→3
6	127.9	7.17 (dd, *J* = 7.6, 7.5 Hz, 1H)	HMBC 6→4,8
7	127.5	7.05 (br d, *J* = 7.5 Hz, 1H)	
8	141.3	-	
9	123.9	7.81 (br s, 1H)	HMBC 9→3
10	29.9	2.84-2.91 (m, 1H)	HMBC 10→8,12
11	34.9	2.53-2.60 (m, 1H), 2.64-2.70 (m, 1H)	HMBC 11→8,12
12	171.5	-	
13	-	8.08 (br d, *J* = 7.7, 5.5 Hz, 1H)	TOCSY 13→14,15,16,17
14	52.2	4.16 (ddd, *J* = 8.9, 7.7, 5.5 Hz, 1H)	
15	33.9	1.44-1.52 (m, 1H), 1.62-1.68 (m, 1H)	
16	18.3	1.04-1.13 (m, 2H)	
17	13.4	0.77 (t, *J* = 7.3 Hz, 3H)	
18	171.9	-	
19	-	8.31 (br d, *J* = 6.9 Hz, 1H)	TOCSY 19→20,21
20	51.3	4.27-4.32 (m, 1H)	HMBC 20→22
21	35.3	2.68-2.79 (m, 1H)	HMBC 21→22
22	171.6	-	
23	-	not detected	
24	169.7	-	
25	-	7.12 (d, *J* = 7.1 Hz, 1H)	TOCSY 25→26,27,28,29 HMBC 25→24
26	56.6	4.27-4.32 (m, 1H)	
27	31.5	1.97-2.05 (m, 1H)	HMBC 27→26,30
28	17.6	0.85 (d, *J* = 6.8 Hz, 3H)	
29	18.8	0.87 (d, *J* = 6.8 Hz, 3H)	
30	169.7	-	
31	-	8.23 (br d, *J* = 7.3 Hz, 1H)	TOCSY 31→32,33 HMBC 31→30 NOESY 31→33
32	47.1	4.41 (ddd, *J* = 13.2, 7.3, 4.5 Hz, 1H)	HMBC 32→43 NOESY 32→35
33	35	*pro*-S 1.69 (dd, *J* = 13.2, 13.2 Hz, 1H)	HMBC 33→43
33'		*pro*-R 2.65 (dd, *J* = 13.2, 4.5 Hz, 1H)	
34	48.5	-	
35	72.4	4.83 (br s, 1H)	HMBC 35→1 NOESY 35→1,2,3
36	-	6.21 (br s, 1H)	HMBC 36→34,42
37	147	-	
38	110.7	6.56 (d, *J* = 8.1 Hz, 1H)	HMBC 38→40,42
39	130.3	7.12 (dd, *J* = 8.1, 1.5 Hz, 1H)	
40	108.5	-	
41	126.4	7.25 (d, *J* = 1.5 Hz, 1H)	
42	138.1	-	
43	169.8	-	
44	-	7.60 (s, 1H)	HMBC 44→32,34

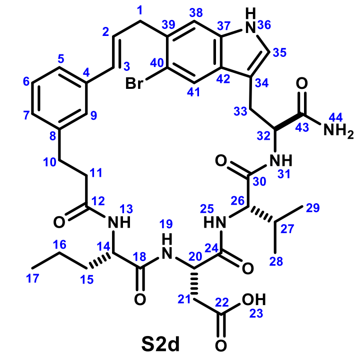
Macrocyclic Product ***2.S2c*** *(600 MHz, DMSO-d$_6$, 298K)*



S2c

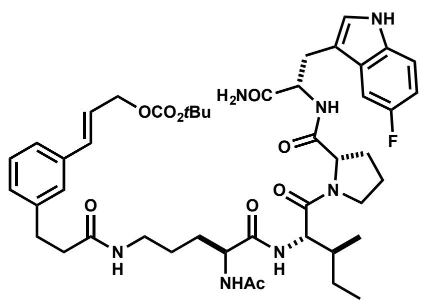
	13C	1H	key correlations
1	29.6	3.69 (dd, J = 16.5, 6.7 Hz, 1H), 3.78 (dd, J = 16.5, 7.0 Hz, 1H)	HMBC 1→2,3,34,35
2	125.5	6.47 (ddd, J = 15.6, 7.0, 6.7 Hz, 1H)	COSY 2→1 HMBC 2→4
3	131.8	6.68 (br d, J = 15.6 Hz, 1H)	HMBC 3→4
4	137	-	
5	123.5	7.25 (br d, J = 7.7 Hz, 1H)	HMBC 5→3 TOCSY 5→6,7,9
6	127.9	7.21 (dd, J = 7.7, 7.5 Hz, 1H)	HMBC 6→4,8
7	127.2	7.04 (br d, J = 7.5 Hz, 1H)	
8	141.3	-	
9	125.8	7.40 (br s, 1H)	HMBC 9→3
10	29.9	2.79 (ddd, J = 14.6, 8.6, 4.4 Hz, 1H), 2.93-2.99 (m, 1H)	HMBC 10→7,9,12
11	35.2	2.45 (ddd, J = 14.6, 8.3, 4.4 Hz, 1H), 2.51-2.56 (m, 1H)	HMBC 11→12
12	171.9	-	
13	-	8.08 (br d, J = 7.7 Hz, 1H)	HMBC 13→12 TOCSY 13→14,15,16,17
14	52.4	4.19 (ddd, J = 8.9, 7.7, 5.3 Hz, 1H)	COSY 14→15 HMBC 14→18
15	33.6	1.44-1.51 (m, 1H), 1.55-1.63 (m, 1H)	COSY 15→16 HMBC 15→18
16	18.5	1.14-1.30 (m, 2H)	
17	13.3	0.79 (dd, J = 7.3, 7.3 Hz, 3H)	
18	172.4	-	
19	-	8.10 (br d, J = 6.5 Hz, 1H)	HMBC 19→18
20	49.6	4.54 (ddd, J = 7.3, 6.5, 6.3 Hz, 1H)	HMBC 20→22,24
21	35.3	2.54 (dd, J = 16.8, 7.3 Hz, 1H), 2.71 (dd, J = 16.8, 6.3 Hz, 1H)	HMBC 21→22
22	171.9	-	
23	-	12.33 (br s, 1H)	
24	170.4	-	
25	-	7.63 (br d, J = 8.3 Hz, 1H)	HMBC 25→24
26	57.5	4.14 (dd, J = 8.3, 5.7 Hz, 1H)	HMBC 26→30
27	29.4	2.00-2.17 (m, 1H)	
28	16.7	0.61 (d, J = 6.8 Hz, 3H)	
29	18.8	0.75 (d, J = 6.8 Hz, 3H)	TOCSY 29→25,26,27,28
30	170	-	
31	-	7.67-7.70 (m, 1H)	HMBC 31→30
32	53.1	4.40 (ddd, J = 8.1, 8.0, 6.0 Hz, 1H)	
33	26.6	2.98 (dd, J = 14.4, 8.0 Hz, 1H), 3.07 (dd, J = 14.4, 6.0 Hz, 1H)	HMBC 33→34
34	105.5	-	
35	136.8	-	
36	-	10.88 (s, 1H)	HMBC 36→34
37	133.8	-	
38	112.2	7.20 (d, J = 8.4 Hz, 1H)	HMBC 38→40,42
39	122.2	7.08 (dd, J = 8.4, 1.8 Hz, 1H)	HMBC 39→37,40
40	110.8	-	
41	120.2	7.69 (d, J = 1.8 Hz, 1H)	HMBC 41→34,37,40
42	129.8	-	
43	172.7	-	
44	-	7.10 (br s, 1H), 7.19 (br s, 1H)	HMBC 44,44'→43

*Macrocyclic Product **2.S2d*** *(500 MHz, DMSO-d_6, 298K)*

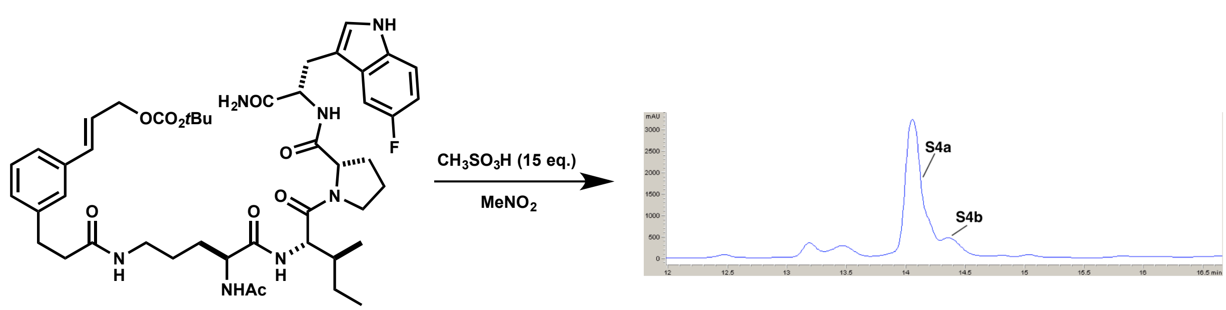


S2d

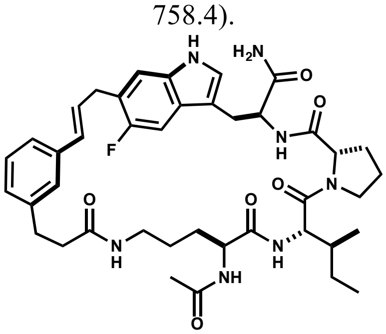
	13C	1H	key correlations
1	39	3.62 (dd, J = 15.5, 5.4 Hz, 1H), 3.72 (dd, J = 15.5, 6.5 Hz, 1H)	HMBC 1→2,3,38,39
2	129.2	6.39 (ddd, J = 15.8, 6.5, 5.4 Hz, 1H)	COSY 1→2 HMBC 2→4
3	130.3	6.24 (br d, J = 15.8 Hz, 1H)	
4	137.3	-	
5	128.3	7.15-7.19 (m, 1H)	HMBC 5→3
6	123.9	7.15-7.19 (m, 1H)	HMBC 6→4,8
7	127.5	6.96-7.01 (m, 1H)	
8	141.3	-	
9	125.1	7.13 (br s, 1H)	HMBC 9→3
10	30.4	2.68-2.75 (m, 1H), 2.77-2.85 (m, 1H)	HMBC 10→8,12
11	35.5	2.34 (ddd, J = 13.9, 5.9, 5.9 Hz, 1H), 2.53-2.61 (m, 1H)	HMBC 11→8,12
12	171.6	-	
13	-	7.90 (br d, J = 7.7 Hz, 1H)	TOCSY 13→14,15,16,17
14	52.1	4.08 (ddd, J = 7.8, 7.7, 5.0 Hz, 1H)	HMBC 14→18
15	34	1.16-1.26 (m, 1H), 1.27-1.36 (m, 1H)	HMBC 15→18
16	17.9	0.77-0.90 (m, 2H)	
17	13.3	0.46 (t, J = 7.3 Hz, 3H)	
18	172	-	
19	-	8.23 (br d, J = 7.4 Hz, 1H)	HMBC 19→18 TOCSY 19→20,21
20	50.5	4.42 (ddd, J = 8.4, 7.4, 5.0 Hz, 1H)	HMBC 20→24
21	35.9	2.55 (dd, J = 16.7, 8.4 Hz, 1H), 2.67 (dd, J = 16.7, 5.0 Hz, 1H)	HMBC 21→22
22	171.9	-	
23	-	12.15 (br s, 1H)	
24	170.5	-	
25	-	6.99-7.04 (m, 1H)	
26	57.6	4.04 (dd, J = 7.6, 5.4 Hz, 1H)	HMBC 26→30
27	30.8	1.89-1.90 (m, 1H)	
28	17.4	0.68 (d, J = 6.8 Hz, 3H)	HMBC 28→25,26,27,29
29	18.9	0.72 (d, J = 6.8 Hz, 3H)	
30	170	-	
31	-	7.84 (br d, J = 8.7 Hz, 1H)	HMBC 31→30 TOCSY 31→32,33
32	53.3	4.46 (ddd, J = 11.8, 8.7, 2.5 Hz, 1H)	
33	27.6	2.83 (dd, J = 14.3, 11.8 Hz, 1H), 3.12 (dd, J = 14.3, 2.5 Hz, 1H)	HMBC 33→34
34	109.9	-	
35	125.4	7.16-7.18 (m, 1H)	HMBC 35→37
36	-	10.76 (d, J = 1.4 Hz, 1H)	
37	135.7	-	
38	130.5	7.36 (s, 1H)	HMBC 38→1,40,42
39	113.5	-	
40	114.1	-	
41	121.9	7.96 (s, 1H)	HMBC 41→1,34,39,40
42	127.8	-	
43	173.6	-	
44	-	7.11 (br s, 1H), 7.51 (br s, 1H)	HMBC 44,44'→43



Acyclic Cinnamyl Carbonate 2.S3: Synthesized according to Procedure A. Purified via SiO_2 chromatography using a gradient from 1% to 10% methanol in chloroform. Beige solid. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.93 (d, J = 2.5 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.83 (t, J = 5.6 Hz, 1H), 7.28-7.37 (m, 5H), 7.22-7.27 (m, 3H), 7.11 (br. d, J = 7.3 Hz, 1H), 7.04 (br. s, 1H), 6.89 (ddd, J = 9.1, 9.1, 2.5 Hz, 1H), 6.64 (d, J = 16 Hz, 1H), 6.34 (dt, J = 16.0, 6.2 Hz, 1H), 4.68 (dd, J = 6.2, 1.1 Hz, 2H), 4.38 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H), 4.26- 4.35 (m, 3H), 3.74 (ddd, J = 9.6, 6.6, 6.6 Hz, 1H), 3.53 (ddd, J = 9.6, 5.7, 6.0 Hz, 1H), 2.96-3.10 (m, 4H), 2.8 (app t, J = 7.8 Hz, 2H), 2.37 (app t, J = 7.8 Hz, 2H), 1.93-2.03 (m, 1H), 1.70-1.91 (m, 6H), 1.47-1.60 (m, 2H), 1.44 (s, 9H), 1.27-2.39 (m, 2H), 1.00-1.08 (m, 1H), 0.84 (d, J = 6.8 Hz, 3H), 0.81 (t, J = 7.4 Hz, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 173.0, 171.7, 171.2, 171.1, 170.2, 169.2, 155.7, 152.8, 141.8, 135.8, 133.4, 132.7, 128.6, 128.0, 127.7, 127.7, 126.4, 125.8, 124.2, 123.3, 112.1, 112.0, 110.32, 110.28, 108.9, 108.7, 103.3, 103.1, 81.5, 67.0, 66.9, 59.5, 54.5, 53.3, 51.9, 47.2, 38.1, 36.9, 36.1, 31.0, 29.6, 28.9, 27.3, 25.8, 24.4, 24.1, 22.5, 14.9, 10.8. MS m/z 876.5 (calc'd: $C_{46}H_{62}N_7O_9$, $[M+H]^+$, 876.5)

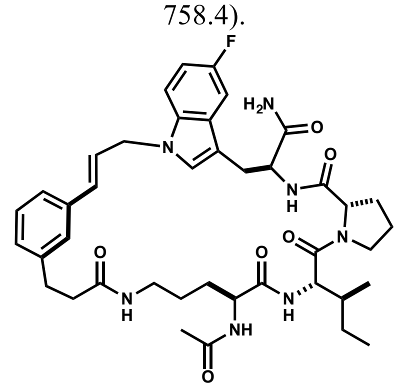


MS m/z 758.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 758.4).



2.S4a

MS m/z 758.1 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 758.4).



2.S4b

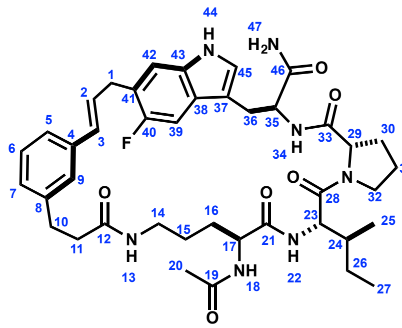
Analytical HPLC Method
Column: Waters XBridge™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2	30
30	60

Preparative HPLC method A:
Column: Waters XBridge™ C_{18}, 19x250mm, 5µm.
Solvent A: H_2O + 0.1%v TFA
Solvent B: ACN + 0.1%v TFA
Flow rate: 18.00 ml/min

Time	%B
0	30
2	30
30	100

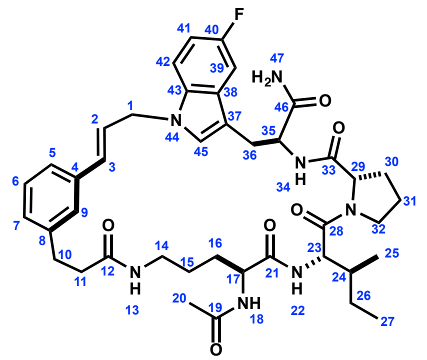
Macrocyclic Product ***2.S4a***



(500 MHz, DMSO-d$_6$, 298K)

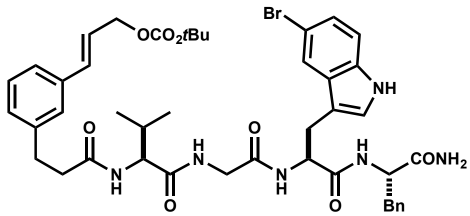
	13C	1H	key correlation
1	31.9	3.58 (br d, J = 5.8 Hz, 2H)	HMBC 1→2,3,41,42
2	129.3	6.38 (dt, J = 15.8, 5.8 Hz, 1H)	TOCSY 2→1 HMBC 2→4,41
3	129.6	6.32 (d, J = 15.8 Hz, 1H)	HMBC 3→5,9
4	136.9	-	
5	123.7	7.15-7.19 (m, 1H) overlap	
6	128.4	7.16-7.21 (m, 1H) overlap	HMBC 6→4,8
7	127.1	6.99-7.04 (m, 1H) overlap	
8	141.5	-	
9	124.8	7.15 (br s, 1H) overlap	
10	30.9	2.71 (t, J = 7.8 Hz, 2H)	HMBC 10→8,12
11	36.9	2.27 (br t, J = 7.8 Hz, 2H)	HMBC 11→8,12
12	171.1	-	
13	-	7.81 (br t, J = 6.0 Hz, 1H)	HMBC 13→12 COSY 13→14,14'
14	37.5	2.77-2.86 (m, 1H), 3.04-3.11 (m, 1H)	COSY 14→15
15	25.6	1.23-1.32 (m, 2H) overlap	COSY 15→16
16	29.6	1.26-1.33 (m, 1H) overlap, 1.48-1.55 (m, 1H) overlap	
17	51.1	4.24-4.30 (m, 1H)	TOCSY 17→14,15,16,18 HMBC 17→21
18	-	7.83 (d, J = 8.4 Hz, 1H)	HMBC 18→19
19	168.8	-	
20	22.1	1.79 (s, 3H)	HMBC 20→19
21	171.5	-	
22	-	7.93 (d, J = 7.7 Hz, 1H)	HMBC 22→21
23	54.7	4.19 (dd, J = 8.8, 7.7 Hz, 1H)	HMBC 23→21,28 TOCSY 23→24,25,26,27
24	35.6	1.63-1.71 (m, 1H) overlap	
25	14.6	0.87 (d, J = 6.8 Hz, 3H)	
26	23.8	0.98-1.09 (m, 1H), 1.45-1.54 (m, 1H) overlap	
27	10.3	0.78 (dd, J = 7.4, 7.4 Hz, 3H)	
28	126.7	-	
29	59.3	4.13 (dd, J = 8.3, 5.0 Hz, 1H)	COSY 29→30,30' TOCSY 29→30,31,32 HMBC 29→33
30	28.8	1.63-1.70 (m, 1H) overlap	
31	24.0	1.66-1.78 (m, 1H) overlap, 1.92-2.01 (m, 1H) overlap	
32	46.8	3.43-3.50 (m, 1H), 3.67-3.74 (m, 1H)	
33	171.2	-	
34	-	7.51 (br d, J = 7.7 Hz, 1H) overlap	HMBC 34→33
35	53.2	4.48 (ddd, J = 9.7, 7.7, 3.8 Hz, 1H)	HMBC 35→37,46
36	27.2	2.93-3.05 (m, 2H) overlap	HMBC 36→37
37	110.2	-	
38	126.1	-	
39	103.5	7.49 (d, JHF = 11.0 Hz, 1H)	HMBC 39→40
40	155.2 (d, J ≈ 240 Hz)	-	
41	119.9	-	
42	112.4	7.22 (d, JHF = 6.4 Hz, 1H)	HMBC 42→40
43	132.6	-	
44	-	10.84 (d, J = 1.9 Hz, 1H)	HBMC 44→37,38,43
45	124.2	7.16-7.18 (m, 1H) overlap	
46	173.6	-	
47	-	7.02 (br s, 1H) overlap, 7.38 (br s, 1H)	HMBC 47→46 TOCSY 47→47'

Macrocyclic Product ***2.S4b***

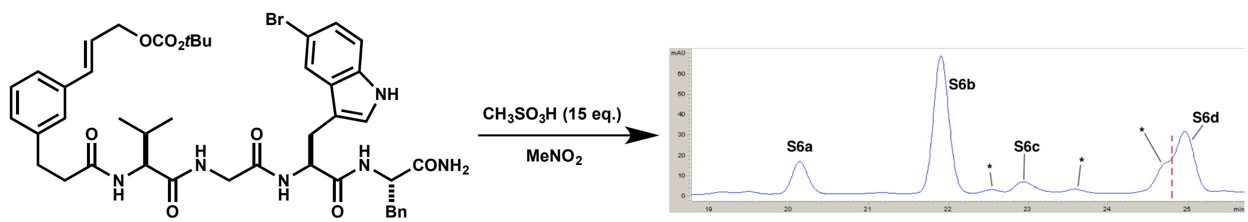


(500 MHz, DMSO-d$_6$, 298K)

	13C	1H	key correlation
1	47	4.49 (dd, *J* = 16.3, 5.6 Hz, 1H), 4.96 (dd, *J* = 16.6, 5.6, Hz, 1H)	HMBC 1→43,45
2	125.6	6.33 (ddd, *J* = 15.8, 5.6, 5.6 Hz, 1H)	TOCSY 2→3,1
3	131.4	6.48 (br d, *J* = 15.8 Hz, 1H)	HMBC 3→4
4	136.1	-	
5	124.3	7.16-7.19 (m, 1H) overlap	
6	128.3	7.14-7.19 (m, 1H) overlap	HMBC 6→4,8
7	127.6	7.03-7.07 (m, 1H)	
8	141.7	-	
9	125.8	7.15 (br s, 1H)	
10	30.6	2.72 (t, *J* = 7.5 Hz, 2H)	HMBC 10→8,12
11	36.7	2.23-2.32 (m, 2H)	HMBC 11→8,12
12	171.2	-	
13	-	7.69 (br t, *J* = 5.7 Hz, 1H)	HMBC 13→12 COSY 13→14
14	37.3	2.82-2.90 (m, 1H), 2.97-3.03 (m, 1H)	COSY 14→15
15	25.4	1.15-1.24 (m, 2H)	COSY 15→16,16' TOCSY 15→16,17
16	29	1.27-1.34 (m, 1H), 1.39-1.46 (m, 1H)	HMBC 16→17 COSY 16→17
17	51.6	4.22-4.28 (m, 1H)	HMBC 17→21
18	-	7.89 (d, *J* = 8.0 Hz, 1H)	
19	169.1	-	
20	22	1.79 (s, 3H)	
21	171.7	-	
22	-	7.99 (d, *J* = 8.6 Hz, 1H)	HMBC 22→21
23	54.4	4.25-4.30 (m, 1H)	
24	35.6	1.67-1.74 (m, 1H)	
25	15.1	0.81 (d, *J* = 6.7 Hz, 3H)	
26	23.5	0.95-1.03 (m, 1H), 1.43-1.51 (m, 1H)	
27	10.6	0.76 (t, *J* = 7.4 Hz, 3H)	
28	170.3	-	
29	59.7	4.16 (dd, *J* = 8.2, 5.0 Hz, 1H)	TOCSY 29→30,31,32 HMBC 29→33
30	28.7	1.57-1.65 (m, 1H), 1.84-1.89 (m, 1H)	
31	23.8	1.59-1.65 (m, 1H), 1.68-1.75 (m, 1H)	
32	46.8	3.45-3.51 (m, 1H), 3.55-3.61 (m, 1H)	
33	171.6	-	
34	-	7.79 (d, *J* = 8.1 Hz, 1H)	HMBC 34→33
35	52.6	4.36-4.42 (m, 1H)	COSY 35→36 HMBC 35→46
36	26.5	2.96-3.03 (m, 1H), 3.08-3.14 (m, 1H)	HMBC 36→35,37
37	110.4	-	
38	128.1	-	
39	103.4	7.37 (dd, *J*HF = 10.1, *J*HH = 2.4 Hz, 1H)	HMBC 39→40,43
40	156.9 (d, *J*≈230 Hz)	-	
41	108.9	6.93 (ddd, *J*HF = 9.4 Hz, *J*HH = 8.9, 2.4 Hz, 1H)	HMBC 41→43
42	110.6	7.44 (dd, *J*HH = 8.9 Hz, *J*HF = 4.5 Hz, 1H)	HMBC 42→38,40
43	132.5	-	
44	-	-	
45	128.7	7.35 (br s, 1H)	HMBC 45→37,38,43
46	173.3	-	
47	-	7.11 (br s, 1H), 7.27 (br s, 1H)	TOCSY 47→47'

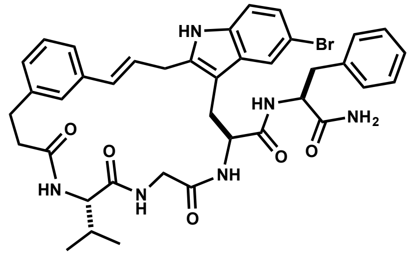


Acyclic Cinnamyl Carbonate 2.S5: Synthesized according to Procedure A. Purified via SiO_2 chromatography using a gradient from 1% to 10% methanol in chloroform. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.77 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 1.86-1.96 (m, 1H), 2.41 (ddd, J = 14.5, 8.7, 5.9 Hz, 1H), 2.55 (dd, J = 14.5, 8.3 Hz, 1H), 2.72-2.88 (m, 4H), 3.03 (apt dt, J = 14.1, 4.9 Hz, 2H), 3.55 (dd, J = 16.6, 5.4 Hz, 1H), 3.74 (dd, J = 16.6, 6.0 Hz, 1H), 4.11 (dd, J = 8.2, 6.9 Hz, 1H), 4.42 (ddd, J = 8.6, 8.6, 5.1 Hz, 1H), 4.47 (ddd, J = 9.0, 8.1, 4.8 Hz, 1H), 4.66 (dd, J = 6.2, 1.1 Hz, 2H), 6.31 (dt, J = 15.9, 6.2 Hz, 1H), 6.61 (br d, J = 15.9 Hz, 1H), 7.05-7.11 (m, 2H), 7.13-7.30 (m, 12H), 7.74 (d, J = 1.9 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 8.16 (t, J = 5.7 Hz, 1H), 11.01 (d, J = 1.9 Hz, 1H). ^{13}C NMR (DMSO-d_6, 126 MHz): δ 173.2, 172.2, 172.1, 171.5, 169.2, 153.3, 142.1, 138.4, 136.3, 135.2, 133.9, 129.7, 129.6, 129.0, 128.5 (2), 126.8, 126.7, 125.9, 124.7, 123.74, 123.70, 121.1, 113.8, 111.5, 110.4, 82.0, 67.4, 58.5, 54.5, 53.9, 42.4, 37.8, 36.9, 31.4, 30.6, 27.8, 19.6,18.6



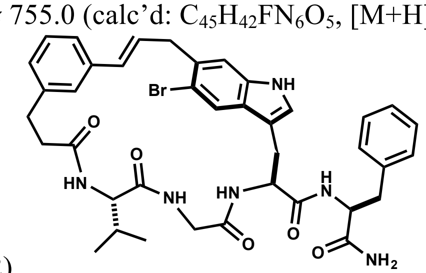
*Unidentified isomeric products

MS m/z 755.0 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 755.2).



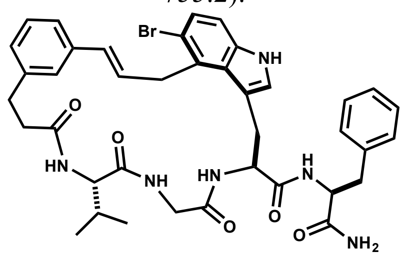
2.S6a

MS m/z 755.0 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 755.2).



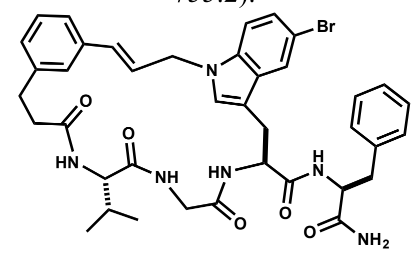
2.S6b

MS *m/z* 755.0 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 755.2).



2.S6c

MS *m/z* 755.0 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 755.2).



2.S6d

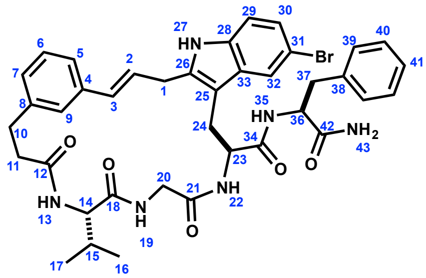
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	30
2	30
30	60

Preparative HPLC method A:
Column: Waters XBridge™ C_{18}, 19x250mm, 5µm.
Solvent A: H_2O + 0.1%v TFA
Solvent B: ACN + 0.1%v TFA
Flow rate: 18.00 ml/min

Time	%B
0	30
2	30
30	100

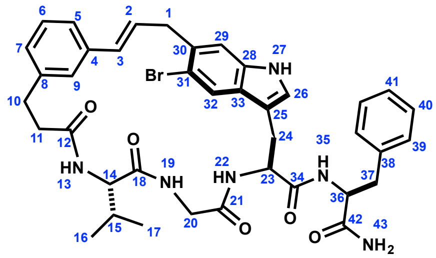
Macrocyclic Product ***2.S6a***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	28.3	3.53 (dd, *J* = 17.2, 5.9 Hz, 1H), 3.81 (dd, *J* = 17.2, 5.9 Hz, 1H)	HMBC 1→25,26
2	127.6	6.56 (ddd, *J* = 16.0, 5.9, 5.9 Hz, 1H)	HMBC 2→4, COSY 2→1
3	130.2	6.37 (br d, *J* = 16.0 Hz, 1H)	
4	136.9	-	
5	123	7.26 (d, *J* = 7.9 Hz, 1H) overlap	HMBC 5→9,3
6	127.97	7.18 (dd, *J* = 7.9, 7.9 Hz, 1H) overlap	HMBC 6→4,8
7	127.95	6.99 (d, *J* = 7.9 Hz, 1H) overlap	
8	140.7	-	
9	124.9	7.20 (s, 1H) overlap	
10	29.8	2.73-2.78 (m, 1H) overlap, 2.89-2.96 (m, 1H) overlap	HMBC 10→9
11	34	2.34-2.40 (m, 1H), 2.72-2.79 (m, 1H) overlap	TOCSY 11→11',10
12	171.3	-	
13	-	7.78 (d, *J* = 9.1 Hz, 1H)	TOCSY 13→14,15,16,17, HMBC 13→12
14	58	3.92 (dd, *J* = 9.1, 6.0 Hz, 1H)	HMBC 14→18
15	29.1	1.92-1.98 (m, 1H)	
16	17.6	0.76 (d, *J* = 3.7 Hz, 3H)	
17	19	0.77 (d, *J* = 3.7 Hz, 3H)	
18	170.8	-	
19	-	6.97 (dd, *J* = 8.0, 2.9 Hz, 1H) overlap	
20	41.1	3.12 (dd, *J* = 16.7, 2.9 Hz, 1H), 3.76 (dd, *J* = 16.7, 8.0 Hz, 1H)	TOCSY 20→19, HMBC 20→18,21
21	167.6	-	
22	-	8.04-8.08 (m, 1H) overlap	HMBC 22→21
23	53.1	4.51-4.56 (m, 1H)	HMBC 23→34
24	26.7	2.72-2.79 (m, 1H) overlap, 2.96-3.00 (m, 1H) obscured	HMBC 24→25,26,33,34
25	106.6	-	
26	136.4	-	
27	-	11.00 (s, 1H)	
28	134.1	-	
29	112.3	7.21 (d, *J* = 8.5 Hz, 1H) overlap	HMBC 29→31
30	122.5	7.12 (dd, *J* = 8.5, 1.6 Hz, 1H)	HMBC 30→28,31
31	110.7	-	
32	120	7.73 (d, *J* = 1.6 Hz, 1H)	HMBC 32→25,28,30,31
33	129.8	-	
34	171.1	-	
35	-	8.04-8.08 (m, 1H) overlap	HMBC 35→34
36	53.5	4.49 (ddd, *J* = 9.0, 8.0, 5.0 Hz, 1H)	HMBC 36→34,38,42
37	37.3	2.86 (dd, *J* = 13.7, 9.0 Hz, 1H), 3.05 (dd, *J* = 13.7, 5.0 Hz, 1H)	HMBC 37→38,39
38	137.5	-	
39	129	7.22 (d, *J* = 7.7 Hz, 2H) overlap	
40	127.9	7.26 (dd, *J* = 7.7, 7.7 Hz, 2H) overlap	HMBC 40→38
41	126	7.15-7.18 (m, 1H) overlap	
42	172.4	-	
43	-	7.15 (br s, 1H), 7.46 (br s, 1H)	HMBC 43→42, TOCSY 43→43'

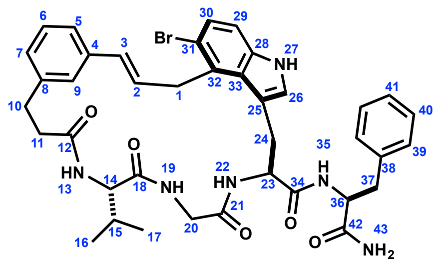
*Macrocyclic Product **2.S6b***



(600 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	38.3	3.61-3.67 (m, 1H) overlap, 3.69-3.75 (m, 1H) overlap	HMBC 1→3
2	129	6.40 (ddd, *J* = 16.0, 5.6, 5.6 Hz, 1H)	HMBC 2→4, COSY 2→1
3	129.1	6.08 (br d, *J* = 16.0 Hz, 1H)	HMBC 3→4,5,9
4	137	-	
5	122.6	7.21 (br d, *J* = 8.0 Hz, 1H)	HMBC 5→3,7,9
6	127.6	7.17 (dd, *J* = 8.0, 8.0 Hz, 1H) overlap	HMBC 6→8,4
7	126.7	6.99 (d, *J* = 8.0 Hz, 1H) overlap	
8	140.9	-	
9	124.5	6.99 (br s, 1H) overlap	HMBC 9→3,5,7
10	29.1	2.68-2.74 (m, 1H), 2.86-2.92 (m, 1H) overlap	HMBC 10→8
11	34.3	2.42-2.48 (m, 1H), 2.53-2.59 (m, 1H)	HMBC 11→8
12	170.9	-	
13	-	7.39 (d, *J* = 8.7 Hz, 1H)	HMBC 13→12
14	57.8	3.92 (dd, *J* = 8.7, 5.9 Hz, 1H)	COSY 14→13, HMBC 14→18
15	29.5	1.83-1.90 (m, 1H)	COSY 15→14
16	17	0.68 (d, *J* = 6.7 Hz, 3H) overlap	COSY 16→15
17	18.6	0.69 (d, *J* = 6.6 Hz, 3H) overlap	
18	170.3	-	
19	-	7.26-7.31 (m, 1H) overlap	
20	40.8	3.09-3.17 (m, 1H) overlap, 3.66-3.72 (m, 1H) overlap	HMBC 20→18,21
21	167.4	-	
22	-	7.75-7.86 (m, 1H) overlap	
23	54.8	4.50-4.56 (m, 1H) overlap	COSY 23→22
24	27.6	2.76-2.82 (m, 1H),3.04-3.10 (m, 1H) overlap	
25	109.9	-	
26	124.4	7.13 (d, *J* = 2.1 Hz, 1H)	HMBC 26→25,28,33, COSY 26→27
27	-	10.71 (br s, 1H)	HMBC 27→25,26,28,33
28	135.1	-	
29	113.1	7.31 (s, 1H)	HMBC 29→1
30	129.6	-	
31	113.8	-	
32	121.9	8.00 (s, 1H)	HMBC 32→25,28,30,31
33	128.1	-	
34	170.5	-	
35	-	7.84 (d, *J* = 8.1 Hz, 1H) overlap	HMBC 35→34
36	53.1	4.56 (ddd, *J* = 8.5, 8.1, 5.4 Hz, 1H) overlap	HMBC 36→38,42
37	37.2	2.91 (dd, *J* = 13.9, 8.5 Hz, 1H) overlap, 3.10 (dd, *J* = 13.9, 5.4 Hz, 1H) overlap	HMBC 37→38,39
38	137.4	-	
39	128.6	7.25-7.28 (m, 2H) overlap	HMBC 39→41
40	127.5	7.25-7.28 (m, 2H) overlap	HMBC 40→38
41	125.5	7.16-7.20 (m, 1H) overlap	
42	172.1	-	
43	-	Not observed	

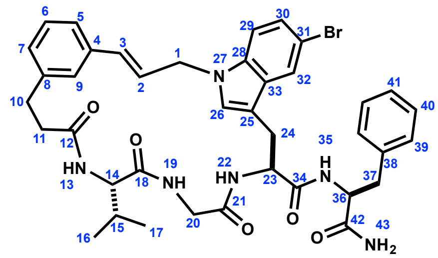
Macrocyclic Product ***2.S6c***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	34.9	3.93 (br dd, *J* = 16.6, 4.1 Hz, 1H), 4.03 (dd, *J* = 16.6, 6.3 Hz, 1H)	HMBC 1→31,33
2	128.2	6.42 (ddd, *J* = 16.0, 6.3, 4.1 Hz, 1H)	COSY 2→1, HMBC 2→4,5
3	129.8	6.13 (br d, *J* = 16.0 Hz, 1H)	
4	136.8	-	
5	123.1	6.99 (dd, *J* = 7.9 Hz, 1H) overlap	
6	127.9	7.14-7.19 (m, 1H) overlap	HMBC 6→8,4
7	127.3	7.09 (d, *J* = 7.9 Hz, 1H) overlap	HMBC 7→10
8	141.3	-	
9	124.62	7.28 (br s, 1H)	HMBC 9→10,5,7
10	29.3	2.68-2.75 (m, 1H) overlap, 2.96-3.03 (m, 1H) overlap	HMBC 10→7,8,9
11	34.3	2.40-2.47 (m, 1H), 2.69-2.77 (m, 1H) overlap	HMBC 11→8
12	171.7	-	
13	-	7.95 (d, *J* = 8.6 Hz, 1H)	TOCSY 13→14,15,16,17, HMBC 13→12
14	57.5	4.24 (dd, *J* = 8.6, 5.6 Hz, 1H)	HMBC 14→18
15	30.1	2.03-2.11 (m, 1H)	HMBC 15→18
16	17.3	0.78 (d, *J* = 6.9 Hz, 3H)	
17	19.1	0.82 (d, *J* = 6.9 Hz, 3H)	
18	171	-	
19	-	7.82-7.86 (m, 1H) overlap	HMBC 19→18
20	42.3	3.58 (dd, *J* = 16.4, 4.8 Hz, 1H), 3.78 (dd, *J* = 16.4, 6.1 Hz, 1H)	COSY 20→19, HMBC 20→18
21	168.2	-	
22	-	8.11 (d, *J* = 8.1 Hz, 1H)	HMBC 22→21
23	54	4.59 (ddd, *J* = 8.4, 8.1, 5.9 Hz, 1H)	HMBC 23→24
24	29.3	2.96-3.03 (m, 1H) overlap, 3.15 (dd, *J* = 14.7, 8.4 Hz, 1H)	HMBC 24→25,34
25	110.1	-	
26	125.5	6.90 (d, *J* = 2.2 Hz, 1H)	HMBC 26→25,33
27	-	11.05 (d, *J* = 2.2 Hz, 1H)	HMBC 27→25,26,28,33
28	135.6	-	
29	111.6	7.17 (d, *J* = 8.5 Hz, 1H) overlap	HMBC 29→31
30	124.55	7.25 (d, *J* = 8.5 Hz, 1H) overlap	
31	114.7	-	
32	129.5	-	
33	126.3	-	
34	170	-	
35	-	7.85 (d, *J* = 8.3 Hz, 1H)	HMBC 35→34
36	53.6	4.39 (ddd, *J* = 8.5, 8.3, 5.3 Hz, 1H)	HMBC 36→34,42
37	37.2	2.74-2.81 (m, 1H) overlap, 2.96-3.02 (m, 1H) overlap	HMBC 37→38,39,42
38	137.4	-	
39	128.9	7.18 (d, *J* = 7.7 Hz, 2H) overlap	HMBC 39→37
40	127.8	7.20-7.25 (m, 2H) overlap	
41	126	7.14-7.19 (m, 1H) overlap	
42	172	-	
43	-	6.99 (br s, 1H) overlap, 7.10 (br s, 1H) overlap	TOCSY 43→43', HMBC 43→42

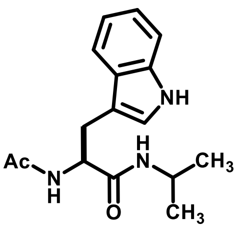
Macrocyclic Product ***2.S6d***



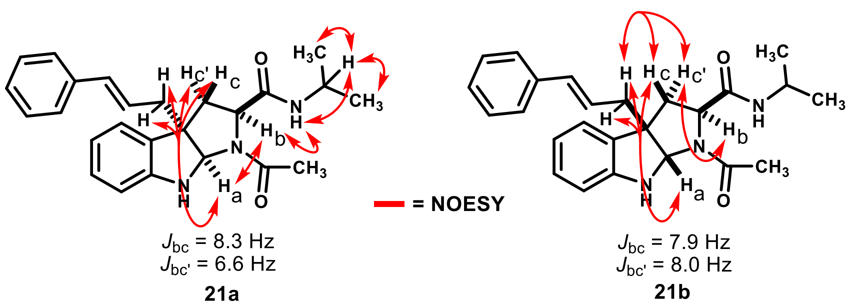
(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	46.8	4.85 (dd, *J* = 16.7, 6.1 Hz, 1H), 4.91 (dd, *J* = 16.7, 5.2 Hz, 1H)	HMBC 1→2,3,28.
2	125.6	6.51 (ddd, *J* = 15.9, 6.1, 5.2 Hz, 1H)	COSY 2→3,1 HMBC 2→4
3	131.5	6.34 (d, *J* = 15.9 Hz, 1H)	
4	135.8	-	
5	123.5	7.20-7.23 (m, 1H)	HMBC 5→3
6	127.7	7.16-7.20 (m, 1H)	HMBC 6→4,8
7	128.1	7.03 (br d, *J* = 7.3 Hz, 1H)	
8	140.6	-	
9	125.8	7.24 (br s, 1H)	HMBC 9→5,7
10	30.1	2.72-2.79 (m, 1H), 2.85-2.93 (m, 1H)	
11	34.7	2.37 (ddd, *J* = 14.4, 7.8, 3.7 Hz, 1H), 2.65-2.72 (m, 1H)	HMBC 11→8,12 TOCSY 11→11',10,1'
12	171.3	-	
13	-	7.77 (d, *J* = 8.6 Hz, 1H)	HMBC 13→12 TOCSY 13→14,15,16,17
14	57.9	3.89 (dd, *J* = 8.6, 6.2 Hz, 1H)	HMBC 14→18
15	29.1	1.90-1.99 (m, 1H)	
16	17.7	0.77 (d, *J* = 6.9 Hz, 3H)	
17	18.7	0.78 (d, *J* = 6.8 Hz, 3H)	
18	170.6	-	
19	-	7.20-7.23 (m, 1H)	HMBC 19→18
20	40.9	3.14 (dd, *J* = 16.8, 4.4 Hz, 1H), 3.63 (dd, *J* = 16.8, 7.0 Hz, 1H)	HMBC 20→18,21 TOCSY 20→19
21	167.6	-	
22	-	8.00 (d, *J* = 9.1 Hz, 1H)	HMBC 22→21 TOCSY 22→23,24
23	51.9	4.56 (ddd, *J* = 11.4, 9.1, 3.1 Hz, 1H)	HMBC 23→25
24	27.2	2.66-2.73 (m, 1H), 3.04-3.10 (m, 1H)	HMBC 24→25,26,33
25	109.8	-	
26	128	7.23 (br s, 1H)	HMBC 26→25
27	-	-	
28	134.3	-	
29	111.7	7.42 (d, *J* = 8.8 Hz, 1H)	HMBC 29→31,33
30	123.1	7.19-7.24 (m, 1H)	HMBC 30→31
31	110.8	-	
32	121.1	7.84 (d, *J* = 1.9 Hz, 1H)	HMBC 32→28,31
33	129.1	-	
34	170.9	-	
35	-	8.21 (d, *J* = 8.1 Hz, 1H)	HMBC 35→34 TOCSY 35→36,37
36	53.4	4.49 (ddd, *J* = 8.9, 8.1, 4.9 Hz, 1H)	HMBC 36→38,42
37	37.1	2.85 (dd, *J* = 13.8, 8.9 Hz, 1H), 3.04 (dd, *J* = 13.8, 4.9 Hz, 1H)	HMBC 37→38
38	137.5	-	
39	128.9	7.22-7.25 (m, 2H)	TOCSY 39→41
40	127.5	7.24-7.28 (m, 2H)	HMBC 40→38
41	126	7.15-7.19 (m, 1H)	HMBC 41→39
42	172.4	-	
43	-	7.11 (br s, 1H), 7.43 (br s, 1H)	TOCSY 43→43' HMBC 43→42

C.2. Synthesis of pyrroloindoline isomerization model system **2.21a&b**

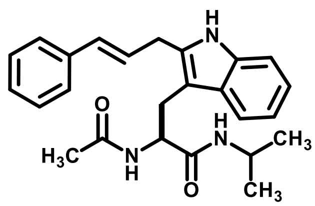


***N*-Acetyl-L-tryptophan isopropyl amide (2.S7):** Boc-L-Tryptophan (1.52 g, 5 mmol) was dissolved in DMF and cooled in an ice bath, then treated with HBTU (2.08 g, 5.5 mmol). The mixture was stirred cold for 10 min, then iPr_2NH (1.05 mL, 6 mmol) was added. The mixture was stirred at rt for 30 min, then concentrated, re-dissolved in EtOAc and washed successively with $NaHCO_3$, 1M HCl, brine, dried over Na_2SO_4 and concentrated. The resulting residue was treated with 4N HCl in dioxane for 30 min, then concentrated and re-dissolved in DMF. The mixture was rendered basic by the addition of iPr_2EtN, cooled to 0 ºC and treated with Ac_2O (708 µL, 7.5 mmol). The mixture was stirred at rt for 30 min, then concentrated, re-dissolved in EtOAc and washed successively with $NaHCO_3$, 1N HCl, brine, dried over Na_2SO_4 and concentrated. The residue was triturated with hexanes:$CHCl_3$ (1:1) and the resulting solid was collected by filtration to give **2.S7** (1.26 g, 73%) as a white solid. ^1H NMR (DMSO-d_6, 400 MHz): δ 0.92 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.78 (s, 3H), 2.88 (dd, J = 14.5, 8.2 Hz, 1H), 3.01 (dd, J = 14.5, 5.8 Hz, 1H), 3.72-3.86 (m, 1H), 4.46 (ddd, J = 8.6, 8.2, 5.9 Hz, 1H), 6.96 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.04 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.30 (ddd, J = 8.0, 1.1,1.0 Hz, 1H), 7.58 (br d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 10.75-10.79 (m, 1H). ^{13}C NMR (DMSO-d_6, 101 MHz): δ 175.7, 174.1, 141.2, 132.6, 128.7, 126.0, 123.8, 123.3, 116.4, 115.4, 58.6, 33.5, 27.8, 27.5, 27.4. MS m/z 288.4 (calc'd: $C_{16}H_{22}N_3O_2$ $[M+H]^+$, 288.4).

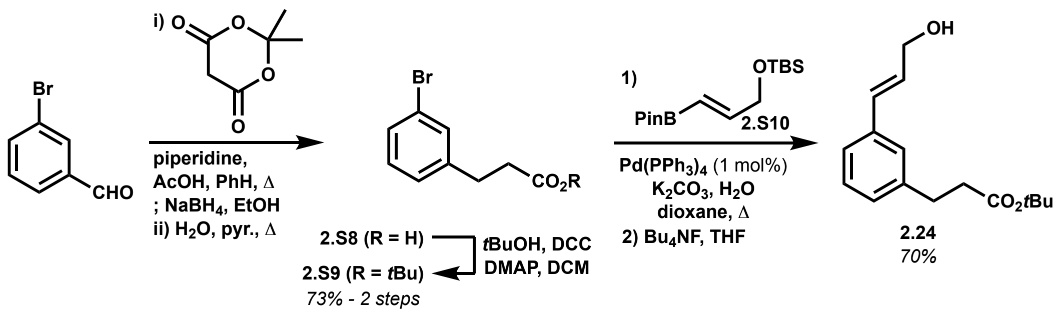


***endo*-Pyrroloindoline (21a) and *exo*-pyrroloindoline (2.21b):** Anhydrous DCM was vigorously sparged with argon for 15 min. To a vial was added *N*-acetyl-L-tryptophan isopropyl amide (**2.S7**, 345 mg, 1 mmol), cinnamyl alcohol (147 mg, 1.1 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol), and the vessel was evacuated and backfilled with argon (x3). DCM (2.5 mL) was added, the mixture was cooled in an ice bath, and Et_3B (1.0 M in hexanes, 1.2 mL) was added in one portion. The resulting suspension was stirred at 0 ºC for 9 hrs, then diluted with EtOAc and washed with sat. $NaHCO_3$ (x2), brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography on SiO_2 eluted with 0→8% MeOH in $CHCl_3$ afforded **2.21a** (150 mg, 37%) and **2.21b** (146 mg, 36%). **2.21a:** R_f = 0.61, 6% MeOH/$CHCl_3$, ^1H NMR ($CDCl_3$, 500 MHz, major rotamer): δ 0.48 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H), 2.01 (s, 3H), 2.49 (dd, J = 13.8, 8.3 Hz, 1H), 2.59 (ddd, J = 13.8, 6.6, 1.0 Hz, 1H), 2.63-2.67 (m, 2H), 3.56-3.70 (m, 1H), 4.36-4.43 (m, 2H), 5.55 (br s, 1H), 5.99 (ddd, J = 15.6, 8.3, 7.0 Hz, 1H), 6.08 (d, J = 7.8 Hz, 1H), 6.40 (d, J = 15.6 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 6.77 (dd, J = 7.4, 7.4 Hz, 1H), 7.04-7.12 (m, 2H), 7.17-7.22 (m, 1H), 7.23-7.29 (m, 4H). ^{13}C NMR ($CDCl_3$, 126 MHz, major rotamer): δ 171.3, 170.2, 147.9, 136.9, 134.0, 132.0, 129.0, 128.5, 127.4, 126.1, 124.4, 123.9, 120.1, 109.6, 80.7, 63.0, 55.6, 42.8, 41.1, 40.5, 22.2, 22.2, 21.3. MS m/z 404.2 (calc'd: $C_{25}H_{30}N_3O_2$ $[M+H]^+$, 404.2). **2.21b:** R_f = 0.50, 6% MeOH/$CHCl_3$, ^1H NMR ($CDCl_3$, 600 MHz, major rotamer): δ 1.17 (d, J = 6.6 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H), 1.92 (s, 3H), 2.37 (dd, J = 13.1, 7.9 Hz, 1H), 2.58 (br dd, J = 13.5, 8.0 Hz, 1H), 2.63 (br dd, J = 13.5, 7.3 Hz,1H), 2.72 (dd, J = 13.1, 8.0 Hz, 1H), 4.04-4.08 (m, 1H), 4.09-4.17 (m, 1H), 5.53 (s, 1H), 6.08 (br d, J = 8.0 Hz, 1H), 6.09 (apt dt, J = 15.5, 7.7 Hz, 1H), 6.38 (d, J = 15.5 Hz, 1H), 6.60 (d, J = 7.7 Hz, 1H), 6.77 (dd, J = 7.3, 7.3 Hz, 1H), 7.08-7.16 (m, 2H), 7.21-7.26 (m, 1H), 7.24-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 150 MHz, major rotamer): δ 172.0, 170.9, 148.5, 137.1, 133.8, 128.8, 128.60, 128.58, 127.4, 126.2, 124.9, 123.3, 118.9, 109.7, 82.7, 62.3, 55.0, 41.8, 41.6, 40.6, 22.8, 22.53, 22.50. MS *m/z* 404.2 (calc'd: $C_{25}H_{30}N_3O_2$ $[M+H]^+$, 404.3).

(*S*)-2-acetamido-3-(2-cinnamyl-1H-indol-3-yl)-N-isopropylpropanamide (2.22): *exo*-Pyrroloindoline **2.21b** (12.7 mg, 31.5 μmol) was dissolved in $MeNO_2$ (5.0 mL) and treated with TFA (1.3 mL). The mixture was stirred at rt for 30 min, then concentrated and dried thoroughly in vacuo. Purification by column chromatography on SiO_2 eluted with 0→2% MeOH in $CHCl_3$ afforded **2.22** (9.0 mg, 71%) as a light yellow film. R_f = 0.48, 6% MeOH/$CHCl_3$. ^{1}H NMR ($CDCl_3$, 500 MHz, major rotamer): δ 0.64 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 1.99 (s, 3H), 3.05 (dd, *J* = 14.1, 10.0 Hz, 1H), 3.28 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.68 (dd, *J* = 16.4, 6.5 Hz, 1H), 3.75 (dd, *J* = 16.4, 6.6 Hz, 1H), 3.76-3.85 (m, 1H), 4.60 (ddd, *J* = 10.0, 7.3, 4.8 Hz, 1H), 5.07 (br d, *J* = 7.3 Hz, 1H), 6.32 (ddd, *J* = 15.7, 6.8, 6.8 Hz, 1H), 6.47 (br d, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 15.7 Hz, 1H), 7.09-7.18 (m, 2H), 7.21-7.34 (m, 4H), 7.34-7.39 (m, 2H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.99 (br s, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 170.3, 170.0, 136.9, 135.5, 134.3, 132.5, 128.8, 128.6, 127.8, 126.3, 126.3, 121.9, 120.0, 118.7, 110.7, 107.3, 54.2, 41.6, 29.9, 28.2, 23.4, 22.6, 21.9. MS *m/z* 404.2 (calc'd: $C_{25}H_{30}N_3O_2$ $[M+H]^+$, 404.2).

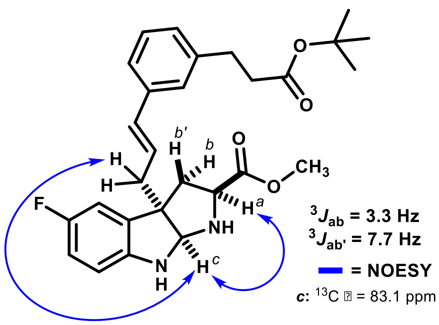


C.**3.** Selective Synthesis of **2.9d**



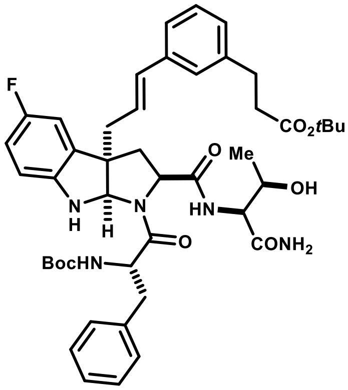
(3-bromophenyl)propanic acid *tert*-butyl ester (2.S8): 3-Bromobenzaldehyde (4.63 g, 25 mmol), Meldrum's acid (3.60 g, 25 mmol), piperidine (198 µL, 2 mmol), AcOH (429 µL, 7.5 mmol) were dissolved in benzene (50 mL) and heated to reflux on a Dean-Stark apparatus. After 30 min, the reaction was cooled in an ice bath and EtOH (5 mL) was added, followed by the addition of $NaBH_4$ (945 mg, 25 mmol) in portions. The mixture was stirred for 90 min, quenched by the addition of H_2O, and concentrated. To the residue was added pyridine (40 mL) and H_2O (4 mL), and the mixture was heated to reflux for 22 hours. The reaction was cooled, concentrated, diluted with 1M NaOH (75 mL), and washed with Et_2O (x2). The aqueous phase was acidified to pH <2 by the addition of conc. HCl, and extracted with DCM (x3). The combined extract was washed with brine, dried over Na_2SO_4 and concentrated to give acid **2.S8** (5.32 g, 93%) as a yellow crystalline solid, which was used without purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (t, *J* = 7.7 Hz, 2H), 2.93 (t, *J* = 7.7 Hz, 2H), 7.10-7.21 (m, 2H), 7.31-7.42 (m, 2H), 9.33 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): 178.8, 142.6, 131.5, 130.2, 129.7, 127.1, 122.7, 35.4, 30.2. MS *m/z* 227.0/229.0 (calc'd: $C_9H_8BrO_2$ $[M-H]^-$, 227.0). This material (5.32 g, 23.2 mmol) was dissolved in anhydrous DCM (75 mL) and treated with *t*-BuOH (6.61 mL, 69.6 mmol), DMAP (3.41 g, 27.9 mmol). The mixture was cooled in an ice bath, DCC (5.75 g, 27.9 mmol) was added. The mixture was refluxed overnight, and the resulting suspension was filtered through a pad of SiO_2, rinsing with DCM. The filtrate was exchanged to THF and treated with a small amount of aqueous AcOH and Norit for 30 min. The volatiles were then removed, and the residue was triturated with 1:1 hexanes:DCM and filtered through a pad of SiO_2, rinsing with the same. The filtrate was evaporated to give ester **2.S9** (5.22 g, 79%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.52 (t, *J* = 7.7 Hz, 2H), 2.87 (t, *J* = 7.7 Hz, 2H), 7.10-7.17 (m, 2H), 7.32 (ddd, *J* = 6.8, 2.1, 2.1 Hz, 1H), 7.34-7.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.0, 143.2, 131.6, 130.1, 129.4, 127.2, 122.5, 80.7, 36.9, 30.8, 28.2.

(*E*)-3-(3-(3-hydroxyprop-1-en-1-yl)phenylpropionic acid *tert*-butyl ester (2.24): Bromide **2.S9** (5.22 g, 18.3 mmol), vinyl boronate **2.S10**[5] (6.55 g, 22.0 mmol), Na_2CO_3 (5.82 g, 54.9 mmol), and dioxane:H_2O (5:1, 48 mL) were sparged vigorously with argon for 10 min. The apparatus was opened briefly to introduce $Pd(PPh_3)_4$ (212 mg, 0.18 mmol), and sparging was continued for 5 min. The mixture was heated to reflux for 2 days, then cooled, and the volatiles were removed by rotary evaporation. The aqueous remainder was diluted, and extracted with EtOAc (x2). The combined extract was washed with brine, dried over Na_2SO_4, concentrated, reconstituted in hexanes:EtOAc (9:1), and filtered through a pad of SiO_2 rinsing with the same. The filtrate was concentrated to give 6.86 g of a red oil. This material was dissolved in THF (55 mL) and treated with Bu_4NF solution (36 mL, 36 mmol), and stirred for 30 min. The mixture was concentrated and partitioned between H_2O and EtOAc. The organic phase was washed with H_2O (x2), brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography on SiO_2 eluted with 15→30% EtOAc in hexanes afforded **2.24** (3.37 g, 71%) as a pale yellow oil. R_f: 0.44 (7:3 hexanes : EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.54 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H), 4.31 (br d, *J* = 5.6 Hz, 2H), 6.35 (dt, *J* = 15.9, 5.6 Hz, 1H), 6.58 (dt, *J* = 15.8, 1.4 Hz, 1H), 7.06-7.11 (m, 1H), 7.20-7.25 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.4, 141.2, 136.9, 131.3, 128.8, 128.6, 127.9, 126.6, 124.5, 80.6, 63.9, 37.2, 31.2, 28.2. MS *m/z* 285.1 (calc'd: $C_{16}H_{22}NaO_3$ $[M+H]^+$, 285.3).



***endo*-pyrroloindoline 2.26:** 5-Fluoro-L-tryptophan methyl ester (59 mg, 0.25 mmol) was freshly freed from its hydrochloride, and was combined with cinnamyl alcohol **2.24** (72 mg, 0.28 mmol) and $Pd(PPh_3)_4$ (14 mg, 0.013 mmol). The vessel was evacuated and backfilled with argon (x3), then DCM (4.2 mL) – previously sparged with argon for 20 min – was added, and the mixture was cooled in an ice bath. Et_3B solution (300 µL, 1.0 M in hexanes) was added, and the reaction was warmed to and held at 6 ºC overnight. The reaction was quenched by addition of 5% aq. K_2CO_3 (50 mL) and extracted with DCM (x3).The combined extract was dried over K_2CO_3 and concentrated. Purification by column chromatography on SiO_2 eluted with 75→85% EtOAc in hexanes afforded **2.26** (96 mg, 80%) as a faintly yellow oil contaminated by ~8 mol% triphenylphosphine oxide. R_f: 0.32 (7:3 hexanes : EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.39 (dd, J = 13.0, 7.9 Hz, 1H), 2.48 (dd, J = 13.0, 3.4 Hz, 1H), 2.51 (t, J = 8.0 Hz, 2H), 2.53 (dd, J = 13.5, 8.0 Hz, 1H), 2.63 (dd, J = 13.5, 6.6 Hz, 1H), 2.86 (t, J = 7.8 Hz, 2H), 3.38 (s, 1H), 3.89 (br dd, J = 7.3, 3.1 Hz, 2H), 4.91 (s, 1H), 6.05 (ddd, J = 15.4, 8.0, 7.3 Hz, 1H), 6.39 (br d, J = 15.7 Hz, 1H), 6.46 (dd, JHH = 8.4 Hz, J_{HF} = 4.2 Hz, 1H), 6.70-6.79 (m, 2H), 7.04 (br d, J = 7.6 Hz, 1H), 7.11 (br s, 1H), 7.12 (br d, J = 7.8 Hz, 1H), 7.18 (dd, J = 7.8, 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 172.3, 157.3 (d, J_{CF} = 236 Hz), 145.6, 141.2, 137.3, 133.7, 132.2 (d, J_{CF} = 9.9 Hz), 128.7, 127.5, 126.4, 125.2, 124.1, 114.7 (d, J_{CF} = 23.3 Hz), 111.0 (d, J_{CF} = 23.8 Hz), 110.2 (d, J_{CF} = 8.1 Hz), 83.2, 80.5, 59.9, 57.9 (d, J_{CF} = 1.6 Hz), 52.1, 41.9, 41.2, 37.1, 31.1, 28.2. MS *m/z* 481.2 (calc'd: $C_{28}H_{34}FN_2O_4$ $[M+H]^+$, 481.6).

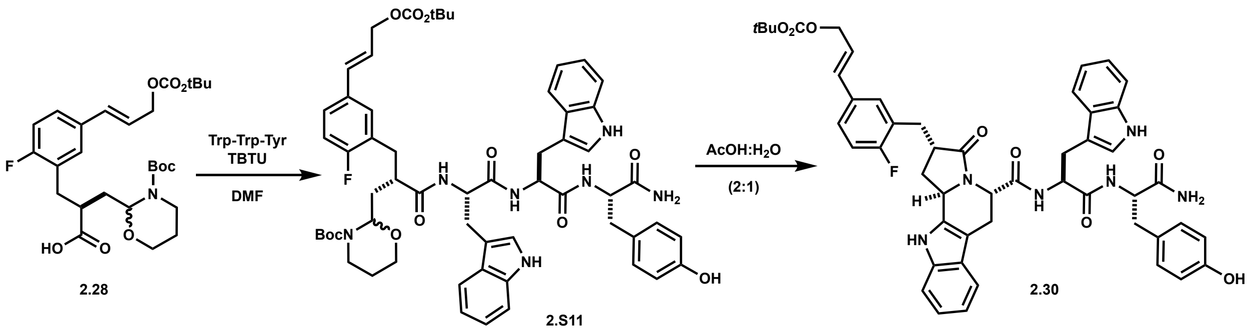
Intermediate 2.27: Pyrroloindoline **2.26** (581 mg, 1.21 mmol) was dissolved in DMF, and Boc-L-phenylalanine and iPr_2EtN (505 µL, 2.9 mmol) were added. The mixture was cooled to 0 ºC, treated with HBTU (550 mg, 1.45 mmol), and allowed to warm to rt. After 40 min, the mixture was diluted with 1:1 brine : 5% aq. K_2CO_3 and extracted with EtOAc (x2). The combined extract was washed with brine, dried over Na_2SO_4 and concentrated. The residue was dissolved in $THF:MeOH:H_2O$ (3:1:1, 12 mL) and treated with LiOH•H2O (102 mg, 2.42 mmol). The mixture was stirred for 3.5 hrs, then additional LiOH (50 mg, 1.21 mmol) was added. After 2 hrs, additional LiOH (50 mg, 1.21 mmol) was again added. The mixture was stirred for 1.5 hrs, then quenched by the addition of Et_3N•HCl (830 mg, 6.0 mmol), concentrated, and further dried in vacuo. The resulting residue was dissolved in DMF (12 mL) and treated with iPr_2EtN (843 µL, 4.84 mmol), L-threonine amide (171 mg, 1.45 mmol), and then by HBTU (550 mg, 1.45 mmol). After stirring for 1 hr, additional L-threonine amide (85 mg, 0.72 mmol) and HBTU (225 mg, 0.72 mmol) were added, and stirring continued for 2.5 hrs. The mixture was concentrated to ~4 mL by rotary evaporation, and partitioned between 5% aq. K_2CO_3 and EtOAc. The aqueous phase was extracted with EtOAc (x1), and the combined organic phase was washed sequentially with H_2O and brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography on SiO_2 eluted with 0→8% MeOH in $CHCl_3$ afforded **2.27** (598 mg, 61%) as a white foam. An analytical sample was obtained by preparative HPLC (19x250mm C18, 40;75-100% ACN + 0.1 *v*% HCO_2H, 18 mL/min). ^1H NMR (500 MHz, DMSO-d_6, ~8:4:1 mixture of rotamers, data is of major): δ 0.66 (d, J = 6.1 Hz, 3H), 1.30 (s, 9H), 1.34 (s, 9H), 2.33 (dd, J = 13.3, 4.2 Hz, 1H), 2.49 (t, J



= 7.8 Hz, 2H), 2.48-2.55 (m, 2H), 2.56 (dd, J = 13.5, 8.8 Hz, 1H), 2.66 (dd, J = 13.8, 6.3 Hz, 1H), 2.77 (t, J = 7.3 Hz, 2H), 2.88 (dd, J = 14.0, 11.8 Hz, 1H), 3.10 (dd, J = 14.0, 1.7 Hz, 1H), 3.79-3.88 (m, 2H), 4.64 (dd, J = 9.5, 4.5 Hz, 1H), 4.74 (ddd, J = 10.9, 8.1, 2.4 Hz, 1H), 4.88 (br s, 1H), 6.17 (ddd, J = 15.7, 7.9, 7.9 Hz, 1H), 6.22 (d, J = 3.8 Hz, 1H), 6.47 (d, J = 15.7 Hz, 1H), 6.60 (dd, J_{HH} = 8.2, J_{HF} = 4.4 Hz, 1H), 6.70-6.74 (m, 1H), 6.76 (br s, 1H), 6.78 (br dd, J = 8.8, 8.8 Hz, 1H), 7.03-7.09 (m, 2H), 7.11-7.27 (m, 5H), 7.26-7.36 (m, 2H), 7.44 (d, J = 7.9 Hz, 1H), 7.48 (apt d, J = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d$_6$, major rotamer): δ 173.5, 171.8, 171.5, 170.5, 156.7 (d, J_{CF} = 233 Hz), 155.8, 144.9, 137.9, 136.9, 135.9, 133.6, 129.9, 128.43, 128.40 (d, J_{CF} = 20.0 Hz), 127.9, 127.2, 126.5, 126.2, 124.9, 123.6, 114.3 (d, J_{CF} = 23.2 Hz), 111.7 (d, J_{CF} = 8.0 Hz), 110.3 (d, J_{CF} = 24.0 Hz), 82.0, 79.7, 78.3, 65.5, 60.6, 57.98, 57.97, 57.5, 52.8, 36.2, 30.4, 28.1, 27.73, 27.70 (2), 19.5. ^{19}F NMR (282 MHz, DMSO-d$_6$, trifluoroacetate salt, mixture of rotamers): δ -73.5, -125.1 (major), -127.0 (minor). MS *m/z* 814.4 (calc'd: $C_{45}H_{57}FN_5O_8$ $[M+H]^+$, 814.4).

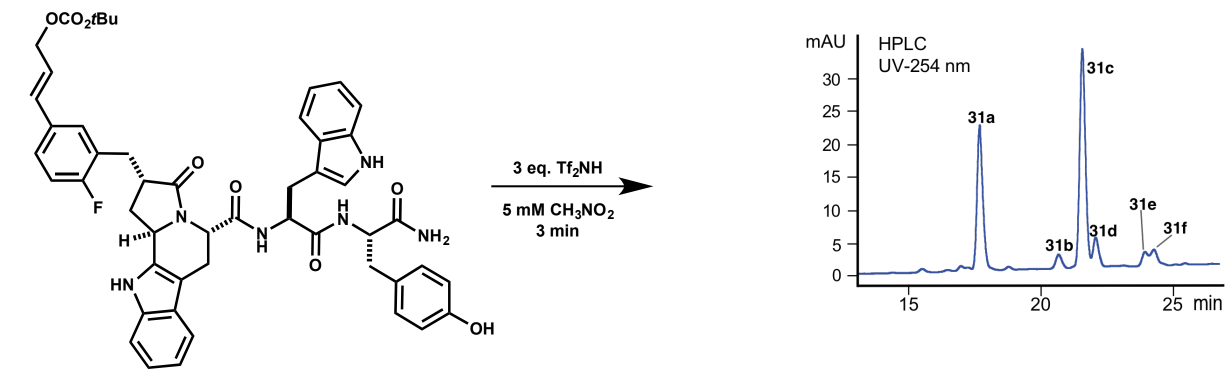
Cyclization of 2.27 to lactam 2.9d: Intermediate **2.27** (570 mg, 0.70 mmol) was dissolved in anhydrous DCM (7 mL) and cooled in an ice bath. Pre-cooled TFA (7 mL) was added, and the initially colorless mixture was stirred for 3.5 hours over which it turned dark pink. The mixture was then concentrated by rotary evaporation (bath 30 ºC) and further dried *in vacuo*. The resulting faintly brown residue was dissolved in DMF (10 mL) and rendered basic by the addition of iPr_2EtN (1.5 mL). This solution was added via syringe pump to a stirred solution of HBTU (1.33 g, 3.5 mmol) in DMF (130 mL) over a period of 1 hr. Stirring was continued for 20 min, and the mixture was then concentrated to ~5 mL by rotary evaporation and partitioned between 5% K_2CO_3 (aq.) and EtOAc. The aqueous phase was extracted with ethyl acetate (x2) and the combined organic phase was washed with H_2O (x1), brine, dried over Na_2SO_4 and concentrated. The resulting residue was triturated with warm MeOH and filtered to give, 169 mg of a white solid. The remaining solution was purified by column chromatography on SiO_2 eluted with 0→10% MeOH in $CHCl_3$ to give additional 112 mg. Macrocycle **2.9d** (combined 281 mg, 63% from **2.27**) obtained in this manner was spectroscopically identical to material isolated previously from acid-promoted cyclization of **2.7**.

C.**4.** Reaction of trifunctional template **2.27** with Trp-Trp-Tyr



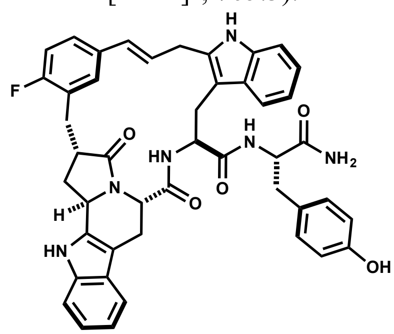
Acyclic cinnamyl carbonate (2.S11). Compound **2.S11** was prepared according to General Procedure A. The reaction was worked up by partitioning between sat. $NaHCO_3$ and EtOAc. The organic phase was then washed with sat. $NaHCO_3$, 1N HCl, H_2O, brine, dried over Na_2SO_4 and concentrated. Purification was accomplished by column chromatography on SiO_2 eluted with 0→10% MeOH in $CHCl_3$ afforded **2.S11** as a colorless film. A yield was not recorded. ^{1}H NMR (CD_3OD, 500 MHz, ~1:1 mixture of diastereomers): δ 1.28 (s, 9H), 1.37 (s, 9H), 1.44 (s, 9H), 1.45 (s, 9H), 1.53-1.69 (m, 2H), 1.92-2.00 (m, 1H), 2.06 (ddd, *J* = 14.0, 8.1, 5.8 Hz, 1H), 2.33-2.45 (m, 2H), 2.46-2.54 (m, 1H), 2.53-2.62 (m, 2H), 2.62-2.74 (m, 3H), 2.74-3.12 (m, 16H), 3.37-3.49 (m, 2H), 3.54-3.66 (m, 2H), 3.73-3.84 (m, 2H), 4.40 (dd, *J* = 7.8, 6.2 Hz, 1H), 4.44-4.52 (m, 3H), 4.52-4.58 (m, 2H), 4.55 (br d, *J* = 6.3 Hz, 2H), 4.60 (br d, *J* = 6.3 Hz, 2H), 5.30-5.39 (m, 1H), 5.45 (dd, *J* = 8.1, 6.4 Hz, 1H), 6.13 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.17 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.44 (br d, *J* = 15.9 Hz, 1H), 6.50 (br d, *J* = 15.9 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.74-6.77 (m, 2H), 6.83 (s, 1H), 6.86-6.93 (m, 4H), 6.93-7.03 (m, 7H), 7.04-7.15 (m, 6H), 7.15-7.22 (m, 2H), 7.29 (apt t, *J* = 7.7 Hz, 1H), 7.32 (apt t, *J* = 7.8 Hz, 1H), 7.40-7.46 (m, 3H), 7.48 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (CD_3OD, 126 MHz, ~1:1 mixture of diastereomers): δ 177.0, 176.9, 176.5, 176.4, 176.0, 175.9, 174.38, 174.36, 174.05, 174.03, 173.4, 173.3, 163.1, 161.2, 157.2, 155.5, 154.93, 154.92, 137.92, 137.91, 137.89, 137.84, 134.03, 134.00, 133.90, 133.87, 133.75, 133.71, 131.34, 131.26, 130.8, 130.73, 130.69, 129.1, 129.0, 128.7, 128.6, 128.5, 128.0, 127.9, 127.84, 127.78, 127.3, 127.2, 124.5, 124.3, 124.1, 122.6, 122.54, 122.52, 120.0, 119.93, 119.90, 119.44, 119.38, 119.31, 119.28, 116.6, 116.5, 116.4, 116.3, 116.2, 112.4, 112.3, 110.7, 110.64, 110.57, 110.51, 83.0, 82.9, 81.7, 81.6, 68.29, 68.27, 61.0, 60.6, 56.2, 56.1, 56.0, 55.9, 55.3, 55.2, 46.0, 44.4, 44.3, 38.6, 38.4, 37.6, 32.8, 32.6, 32.1, 31.8, 30.7, 28.7, 28.61, 28.55, 28.4, 28.3, 28.2, 28.0, 26.2, 26.0. MS *m/z* 958.3 (calc'd: $C_{53}H_{61}FN_7O_9$, [M-Boc+2H]$^+$, 958.8); 940.5 (calc'd: $C_{53}H_{59}FN_7O_8$, [M-OCO$_2$*t*Bu+2H]$^+$, 940.4).

Pyrrolo tetrahydro-β-carboline (2.30). Intermediate **2.S11** (147 mg, 138 μmol) was dissolved in AcOH:H_2O (2:1, 15.7 mL) and stirred at rt for 4 hr. The mixture was concentrated to give **2.30** (106 mg, 88%) as a colorless film. An analytical sample was obtained by preparative HPLC purification. ^{1}H NMR (DMSO-*d$_6$*, 500 MHz): δ 1.43 (s, 9H), 1.90-2.00 (m, 2H), 2.56-2.64 (m, 2H), 2.69 (dd, *J* = 13.9, 7.9 Hz, 1H), 2.79-2.88 (m, 2H), 2.99 (dd, *J* = 14.6, 9.5 Hz, 1H), 3.05-3.13 (m, 2H), 3.20 (d, *J* = 15.6 Hz, 1H), 6.37 (dt, *J* = 15.9, 6.2 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 2H), 6.67 (br d, *J* = 16.0 Hz, 1H), 6.92-6.98 (m, H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.99-7.03 (m, 1H), 7.03-7.06 (m, 2H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, J_{HF} = 9.7, J_{HH} = 8.3 Hz, 1H), 7.21 (br d, *J* = 8.1 Hz, 1H), 7.29 (br s, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.36 (br d, *J* = 7.8 Hz, 1H), 7.40 (ddd, J_{HH} = 8.3, 2.0 Hz, J_{HF} = 5.0 Hz, 1H), 7.47 (dd, J_{HF} = 7.3 Hz, J_{HH} = 2.0 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 9.19 (br s, 1H), 10.78 (s, 1H), 10.81 (d, *J* = 1.6 Hz, 1H). MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, [M-Boc+2H]$^+$, 765.3).



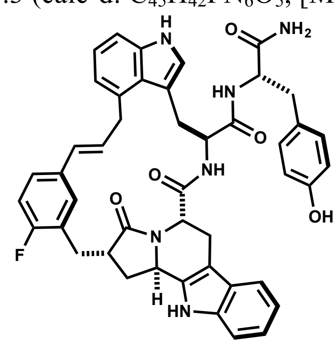
2.31d: This peak contained two isomeric products that were not identified

MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 765.3).



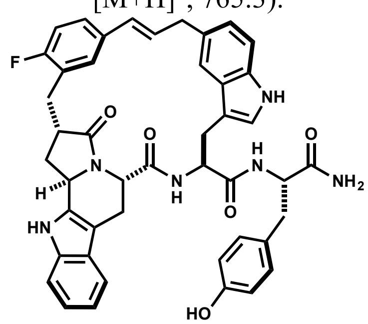
2.31a

MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 765.3).



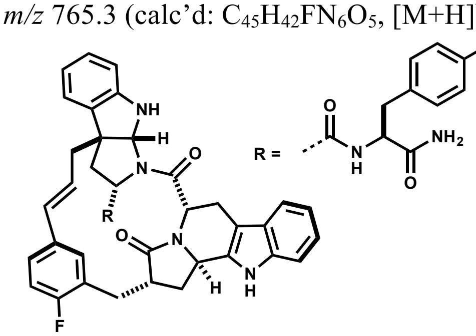
2.31b

MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 765.3).



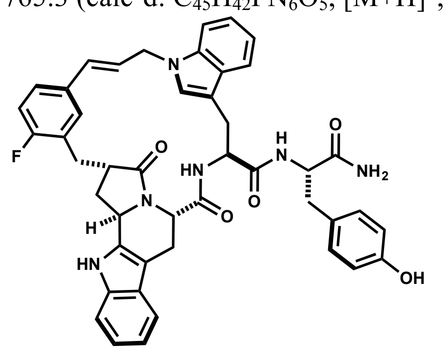
2.31c

MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 765.3).



2.31e

MS *m/z* 765.3 (calc'd: $C_{45}H_{42}FN_6O_5$, $[M+H]^+$, 765.3).



2.31f

Analytical HPLC method:
Column*:* Waters XBridge™ C18, 4.6x250mm, 5µm.
Solvent A*:* H_2O + 0.1%v TFA
Solvent B*:* ACN + 0.1%v TFA
Flow rate: 1.00 ml/min

Time	%B
0	42
2	42
25	60
26	42
31	42

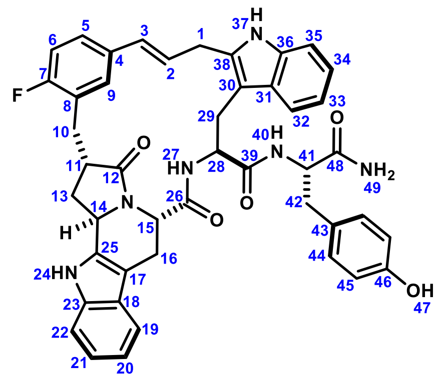
Semi-preparative HPLC method A:
Column*:* Waters XBridge™ C18, 10x250mm, 5µm.
Solvent A*:* H_2O + 0.1%v TFA
Solvent B*:* ACN + 0.1%v TFA
Flow rate: 7.00 ml/min

Time	%B
0	42
2	42
16	50
16.2	100
19	100
19.5	42

Semi-preparative HPLC method B:
Column*:* Waters XSelect™ C18, 10x250mm, 5µm.
Solvent A*:* H_2O + 0.1%v TFA
Solvent B*:* ACN + 0.1%v TFA
Flow rate: 6.00 ml/min
For re-purification of 2.*31e*

Time	%B
0	43
1	43
31	54

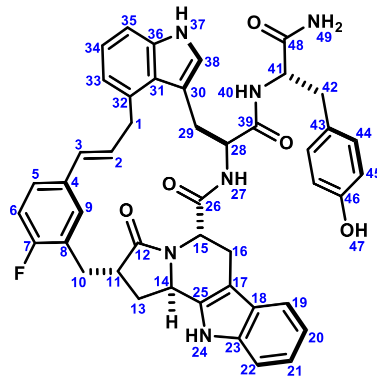
Macrocyclic Product ***2.31a***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	291	3.57 (dd, J = 16.8, 5.6 Hz, 1H), 3.67 (dd, J = 16.8, 5.1 Hz, 1H)	HMBC 1→2,3,30,38
2	126.7	6.24 (ddd, J = 15.8, 5.6, 5.1 Hz, 1H)	TOCSY 2→1,3 HMBC 2→4
3	128.9	5.87 (d, J = 15.8 Hz, 1H)	
4	133.3	-	
5	124.6	7.34-7.37 (m, 1H) overlap	HMBC 5→7 TOCSY 5→7,9
6	114.6	7.09 (dd, J_{HF} = 9.9 Hz, J_{HH} = 1.8 Hz, 1H)	HBMC 6→4,7
7	159.4 (d, J ≈ 240 Hz)	-	
8	123.4	-	
9	129.9	6.69 (dd, J_{HF} = 7.4 Hz, J_{HH} = 1.8 Hz, 1H)	HMBC 9→5,7
10	27.6	2.76-2.82 (m, 1H) overlap, 3.00 (dd, J = 13.5, 5.2 Hz, 1H)	HMBC 10→8,11,12
11	42.2	2.78-2.84 (m, 1H) overlap	
12	173.3	-	
13	29.2	1.95 (ddd, J = 12.7, 9.5, 9.5 Hz, 1H), 2.26 (dd, J = 12.7, 8.0 Hz, 1	HMBC 13→10,11,12 COSY 13→14
14	51.2	4.32 (dd, J = 9.5, 8.0 Hz, 1H)	HMBC 14→25
15	47.3	4.97 (d, J = 8.3 Hz, 1H)	HMBC 15→14,16,26 COSY 15→16
16	23.6	2.78-2.84 (m, 1H) overlap, 2.94 (d, J = 16.8 Hz, 1H) overlap	HMBC 16→15,17,25,26
17	102.9	-	
18	126.2	-	
19	117.8	7.33-7.36 (m, 1H) overlap	
20	118.2	6.88-6.92 (m, 1H) overlap	HMBC 20→18
21	120.2	6.95 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H)	HMBC 21→19
22	110.4	7.17 (br d, J = 7.9 Hz, 1H)	HMBC 22→18
23	135.6	-	
24	-	10.81 (s, 1H)	HMBC 24→17,18,23,25
25	133.7	-	
26	169.9	-	
27	-	8.33 (d, J = 7.8 Hz, 1H)	
28	54.7	4.19 (ddd, J = 7.8, 7.8, 7.8 Hz, 1H)	HMBC 28→29,39 COSY 28→27
29	25.6	2.93-2.97 (m, 2H) overlap	HMBC 29→28,30,31,38
30	106.4	-	
31	128.8	-	
32	117.9	7.51 (d, J = 7.9 Hz, 1H)	HMBC 32→36
33	120.2	6.99 (ddd, J = 7.9, 7.0, 0.9 Hz, 1H)	
34	117.9	7.03 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H)	HMBC 34→36
35	110.2	7.27 (d, J = 8.0 Hz, 1H)	
36	134.8	-	
37	-	10.89 (s, 1H)	HMBC 37→30
38	133.4	-	
39	171.3	-	
40	-	7.33-7.36 (m, 1H) overlap	HMBC 40→39
41	52.7	4.23 (ddd, J = 7.7, 6.2, 6.2 Hz, 1H)	HMBC 41→43 COSY 41→40
42	36.9	2.69 (dd, J = 13.4, 6.2 Hz, 1H), 2.77-2.81 (m, 1H) overlap	HMBC 42→43
43	126.7	-	
44	130.2	6.90 (d, J = 8.3 Hz, 2H)	
45	114.5	6.61 (d, J = 8.3 Hz, 2H)	HMBC 45→43,46
46	155.7	-	
47	-	9.14 (br s, 1H)	
48	171.8	-	
49	-	6.89 (br s, 1H) overlap, 7.29 (br s, 1H)	HMBC 49→48 TOCSY 49'→49

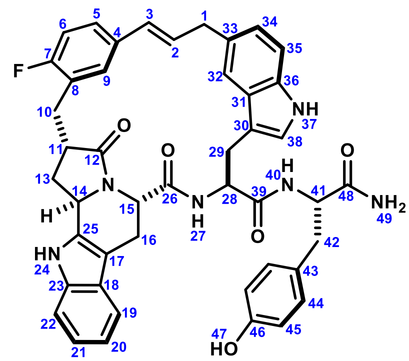
*Macrocyclic Product **2.31b***



(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	37	3.59-3.68 (m, 1H), 3.85-3.95 (m, 1H)	
2	130.5	6.30 (ddd, J = 15.8, 6.2, 4.9 Hz, 1H)	COSY 2→1,1' HMBC 2→4
3	128.5	5.98 (br d, J = 15.8 Hz, 1H)	
4	133.3	-	
5	125.4	7.13-7.18 (m, 1H)	HMBC 5→9
6	114.7	7.02-7.07 (m, 1H)	HMBC 6→4
7	159.7 (d, J ≈ 250 Hz)	-	
8	124.1	-	
9	129.5	6.99-7.03 (m, 1H)	HMBC 10→8,9,12
10	28.3	2.86-2.92 (m, 1H) overlap, 3.01-3.08 (m, 1H)	HMBC 11→12
11	42.2	2.87-2.94 (m, 1H) overlap	
12	173.2	-	
13	29.3	2.00 (ddd, J = 11.6, 10.1, 9.9 Hz, 1H), 2.32-2.40 (m, 1H)	COSY 13→11 TOCSY 13→10,10',11,13' HMBC 13→12
14	51.2	4.57 (apt t, J = 8.3 Hz, 1H)	HMBC 14→17 COSY 14→13
15	48.1	5.22 (d, J = 7.9 Hz, 1H)	HMBC 15→12,17,26
16	24.7	2.80-2.86 (m, 1H) overlap, 2.94 (br dd, J = 16.2, 8.1 Hz, 1H)	
17	103.1	-	
18	126.3	-	
19	110.9	7.21 (d, J = 8.1 Hz, 1H)	HMBC 19→18
20	120.7	-	
21	118.2	6.97-7.01 (m, 1H)	TOCSY 21→19,20,22
22	117.7	7.34 (d, J = 7.8 Hz, 1H)	HMBC 22→17,18,20 COSY 22→21
23	135.6	-	
24	-	10.89 (s, 1H)	HMBC 24→17,18,23,25
25	134.2	-	
26	170.1	-	
27	-	8.56 (br d, J = 5.0 Hz, 1H)	
28	52.7	4.31-4.37 (m, 1H)	HMBC 28→39 TOCSY 28→27,29
29	28.9	3.14 (dd, J = 15.5, 2.4 Hz, 1H), 3.32 (dd, J = 15.5, 10.3 Hz, 1H)	
30	111.1	-	
31	125.8	-	
32	131.2	-	
33	120.5	6.77 (d, J = 7.1 Hz, 1H)	HMBC 33→1 COSY 33→34
34	121	6.93-6.97 (m,1H) overlap	HMBC 34→32,36
35	110	7.19 (d, J = 8.2 Hz, 1H)	COSY 35→34
36	136.6	-	
37	-	10.81 (br d, J = 1.8 Hz, 1H)	HMBC 37→30,31,36,38
38	122	7.00-7.21 (m, 1H)	HMBC 38→30,36
39	170.3	-	
40	-	8.35 (br s, 1H)	
41	53.1	4.42 (ddd, J = 8.7, 7.9, 4.7 Hz, 1H)	HMBC 41→39,43,48
42	36.1	2.74 (dd, J = 14.4, 8.7 Hz, 1H), 2.84 (dd, J = 14.4, 4.7 Hz, 1H)	TOCSY 42→40,41 HMBC 42→39,43,48
43	127.8	-	
44	129.8	7.01 (d, J = 8.3 Hz, 2H)	HMBC 44→46
45	115	6.73 (d, J = 8.3 Hz, 2H)	HMBC 45→43,46
46	155.8	-	
47	-	9.28 (br s, 1H)	HMBC 47→46
48	172.8	-	
49	-	6.88 (br s, 1H), 7.31 (br s, 1H)	HMBC 49→48

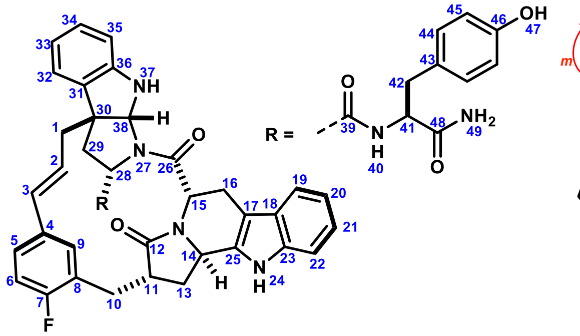
*Macrocyclic Product **2.31c***

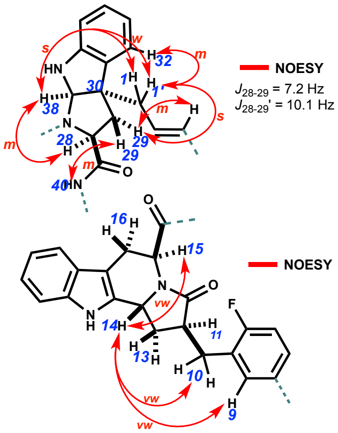


(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	37.5	3.54 (br dd, J = 16.6, 6.7 Hz, 1H), 3.60 (br dd, J = 16.6, 5.4 Hz,	HMBC 1→2,3,33,34
2	129.6	6.36 (ddd, J = 15.8, 6.7, 5.4 Hz, 1H)	HMBC 2→4,33 TOCSY 2→1,3
3	129.3	6.11 (br d, J = 15.8 Hz, 1H)	
4	133.6	-	
5	125.5	7.30 (ddd, JHH = 8.4, 2.0 Hz, JHF = 5.1 Hz, 1H)	TOCSY 5→6,9 HMBC 5→9
6	114.6	7.12 (dd, JHF = 10.0, JHH = 8.4 Hz, 1H)	HMBC 6→4,8
7	159.9 (d, J≈240 Hz)	-	
8	124.5	-	
9	128.8	7.00-7.03 (m, 1H) overlap	HMBC 9→3,5
10	28.4	2.92-3.00 (m, 1H) overlap	HMBC 10→8,11,12,13
11	41.3	2.81-2.87 (m, 1H)	COSY 11→13,13'
12	173.7	-	
13	29.7	2.06 (ddd, J = 12.5, 9.0, 9.0 Hz, 1H), 2.29 (ddd, J = 12.5, 7.5, 2.6 Hz, 1H)	
14	50.7	4.97 (dd, J = 9.0, 7.5 Hz, 1H)	HMBC 14→25
15	48.2	5.00 (d, J = 8.2 Hz, 1H)	HMBC 15→12,14,26
16	24.2	2.93-2.98 (m, 1H) overlap, 3.05 (br d, J = 14.8 Hz, 1H)	HMBC 16→17,25
17	103.1	-	
18	126.2	-	
19	117.4	7.34 (d, J = 7.7 Hz, 1H)	HMBC 19→23
20	118.2	6.91-6.95 (m, 1H) overlap	
21	120.4	6.97-7.00 (m, 1H) overlap	HMBC 21→23 COSY 21→22
22	110.6	7.22 (d, J = 8.0 Hz, 1H)	HMBC 22→20
23	135.8	-	
24	-	10.93 (s, 1H)	HMBC 24→17,18,23,25
25	133.5	-	
26	170.5	-	
27	-	8.28 (d, J = 8.1 Hz, 1H)	HMBC 27→26
28	52.3	4.62 (ddd, J = 8.1, 7.1, 7.1 Hz, 1H)	HMBC 28→26,29,39
29	27.9	2.88 (dd, J = 14.6, 6.8 Hz, 1H), 3.08 (dd, J = 14.6, 7.3 Hz, 1H)	HMBC 29→30
30	109	-	
31	127.2	-	
32	117.4	7.37 (br s, 1H)	TOCSY 32→34,35 HMBC 32→34
33	128.9	-	
34	122.2	6.92-6.95 (m, 1H) overlap	HMBC 34→36
35	111	7.27 (d, J = 8.2 Hz, 1H)	HMBC 35→33
36	134.9	-	
37	-	10.74 (br d, J = 1.6 Hz, 1H)	HMBC 37→30,31,36,38
38	123.9	6.98-7.00 (m, 1H) overlap	HMBC 38→36
39	170.8	-	
40	-	7.50 (br d, J = 7.6 Hz, 1H)	HMBC 40→39
41	53.3	4.17 (ddd, J = 7.6, 6.8, 6.8 Hz, 1H)	COSY 41→42 HMBC 41→39,42,43,48
42	36.3	2.46-2.56 (m, 2H) overlap	HMBC 42→41,43,48
43	127.1	-	
44	129.8	6.77 (d, J = 8.5 Hz, 2H)	HMBC 44→46
45	114.5	6.56 (d, J = 8.5 Hz, 2H)	
46	155.6	-	
47	-	9.12 (br s, 1H)	
48	172.2	-	
49	-	6.83 (br s, 1H), 7.17 (br s, 1H)	HMBC 49→48 TOCSY 49→49'

*Macrocyclic Product **2.31e***

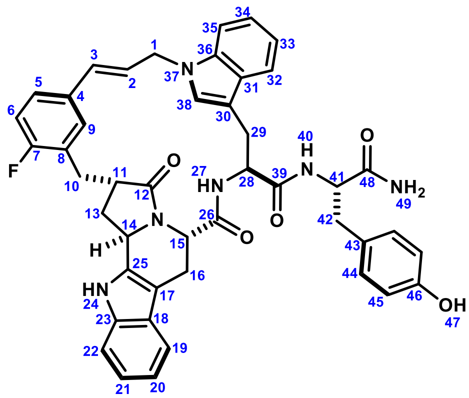




(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	38.8	2.57-2.62 (m, 1H), 2.86 (dd, J = 12.5, 10.4 Hz, 1H)	HMBC 1→30,38 ROESY 1'→29',32,38; 1→38
2	126.9	6.08-6.16 (m, 1H) overlap	HMBC 2→4,5,9
3	130	6.59 (d, J = 15.8 Hz, 1H)	TOCSY 3→1,2 HMBC 3→4 ROESY 3→29'
4	133.6	-	
5	126.6	7.06-7.10 (m, 1H) overlap	HMBC 5→2
6	114.6	7.04-7.10 (m, 1H) overlap	HMBC 6→4,8
7	159.7 (d, J ≈ 250 Hz)	-	
8	130	-	
9	128	7.45 (d, 4JHF = 7.2 Hz, 1H)	HMBC 9→4,8
10	28.7	2.93-2.99 (m, 1H) overlap, 3.02-3.08 (m, 1H) overlap	HMBC 10→11,12 TOCSY 10→11,13,13',14
11	43.2	3.00-3.06 (m, 1H) overlap	
12	173.6	-	
13	29.2	2.13-2.21 (m, 1H), 2.27-2.34 (m, 1H)	HMBC 13'→12
14	51.3	4.42 (dd, J = 8.0, 8.0 Hz, 1H)	HMBC 14→13,17,25 ROESY 14→9,10
15	45	5.66 (d, J = 7.4Hz, 1H)	HMBC 15→12,14,16,26
16	23.6	2.93-3.05 (m, 2H) overlap	HMBC 16→15,26 TOCSY 16→15,16'
17	103.2	-	
18	126.6	-	
19	118.1	7.38 (d, J = 7.6 Hz, 1H)	HMBC 19→23
20	118.5	6.95 (dd, J = 7.6, 7.0 Hz, 1H)	HMBC 20→18,22 COSY 20→19
21	120.6	6.99 (dd, J = 7.7, 7.0 Hz, 1H)	HMBC 21→19,23
22	110.7	7.22 (d, J = 7.7 Hz, 1H)	COSY 22→21 HMBC 22→17,18
23	135.7	-	
24	-	10.88 (s, 1H)	ROESY 24→22,14 HMBC 24→17,23,25
25	134.1	-	
26	169	-	
27	-	-	
28	61.8	4.10 (dd, J = 10.0, 7.1 Hz, 1H)	HMBC 28→30 TOCSY 28→29,29' ROESY 28→38
29	42	1.79 (dd, J = 13.6, 7.2 Hz, 1H), 2.45 (dd, J = 13.6, 10.2 Hz, 1H)	HMBC 29→30
30	57.3	-	
31	135.8	-	
32	122.1	7.14-7.19 (m, 1H) overlap	HMBC 32→34,36
33	119.2	6.83 (dd, J = 7.4, 7.4 Hz, 1H)	
34	128.1	7.14-7.19 (m, 1H) overlap	HMBC 34→32
35	110	6.78 (d, J = 8.1 Hz, 1H)	COSY 35→34 TOCSY 35→32,33,34
36	147.5	-	
37	-	7.33 (d, J = 4.7 Hz, 1H)	HMBC 37→31 ROESY 37→35
38	82.2	6.12 (d, J = 4.7 Hz, 1H)	
39	170	-	
40	-	7.43 (d, J = 9.0 Hz, 1H)	ROESY 40→29
41	52.1	4.10-4.16 (m, 1H)	HMBC 41→43, 48
42	38.4	2.23 (dd, J = 13.4, 8.8 Hz, 1H), 2.59 (dd, J = 13.4, 4.7 Hz, 1H) o	HMBC 42→43,48
43	126.9	-	
44	130.1	6.46 (d, J = 8.3 Hz, 2H)	HMBC 44→46
45	114.5	6.29 (d, J = 8.3 Hz, 2H)	HMBC 45→43,46
46	155.4	-	
47	-	9.01 (s, 1H)	HMBC 47→45,46
48	172.1	-	
49	-	6.68 (br s, 1H), 7.20 (br s,1 H)	HMBC 49→48 TOCSY 49→49'

Macrocyclic Product ***2.31f***

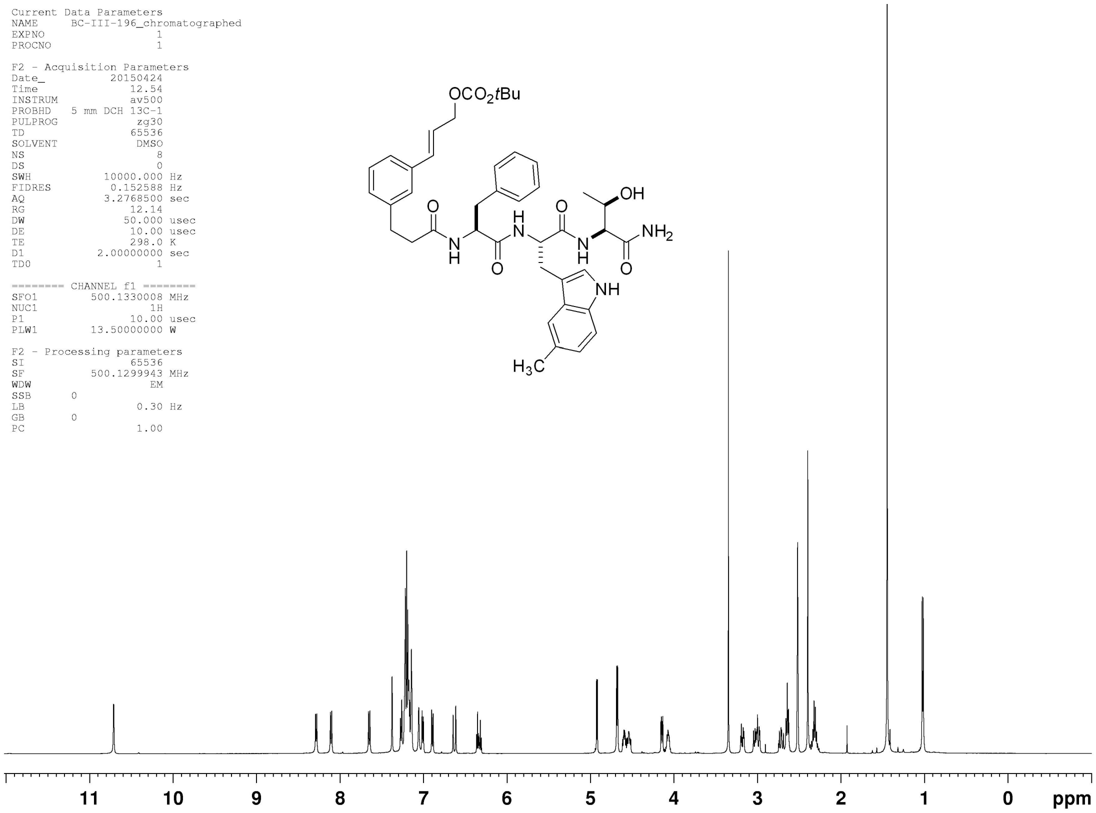


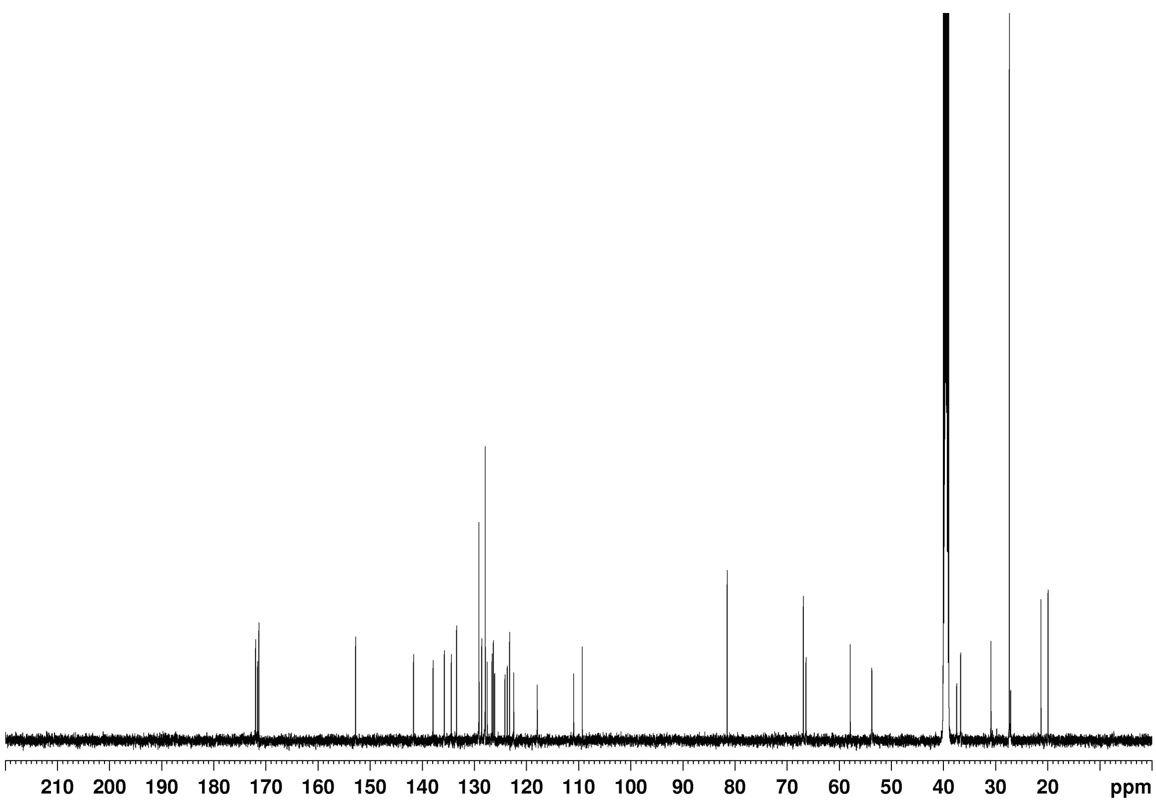
(500 MHz, DMSO-d_6, 298K)

	13C	1H	key correlation
1	46.1	4.72 (dd, J = 15.3, 8.0 Hz, 1H), 5.02 (dd, J = 15.3, 3.5 Hz, 1H)	HMBC 1'→38
2	124.9	6.08 (ddd, J = 15.6, 8.0, 3.5 Hz, 1H)	TOCSY 2→1,3 HMBC 2→4
3	130.8	6.40 (br d, J = 15.6 Hz, 1H)	HMBC 3→5,9
4	132.3	-	
5	127	7.25-7.29 (m, 1H) overlap	HMBC 5→9 TOCSY 5→6,9
6	120.9	7.13-7.19 (m, 1H) overlap	HMBC 6→7,8
7	160.0 (d, J≈230 Hz)	-	
8	124.3	-	
9	127.8	7.10 (br d, JHF = 6.8 Hz, 1H)	HMBC 9→10
10	26.4	2.89-2.95 (m, 1H) overlap, 2.97-3.02 (m, 1H) overlap	
11	41.4	2.76-2.81 (m, 1H) overlap	
12	174.5	-	
13	28.2	2.76-2.81 (m, 1H) overlap	HMBC 13→10,12,14 COSY 13'→11
14	50.7	4.96 (dd, J = 6.9, 6.9 Hz, 1H)	
15	48.6	5.13 (d, J = 7.7 Hz, 1H)	COSY 15→16 HMBC 15→14,26
16	24.5	2.94-3.06 (m, 2H) overlap	HMBC 16→17
17	103	-	
18	126	-	
19	117.5	7.36 (d, J = 7.7 Hz, 1H)	HMBC 19→23 COSY 19→20
20	118.3	6.93 (dd, J = 7.7, 7.0 Hz, 1H)	HMBC 20→22
21	120.4	6.99 (dd, J = 8.0, 7.0 Hz, 1H)	HMBC 21→23
22	110.5	7.22 (d, J = 8.0 Hz, 1H)	
23	135.5	-	
24	-	10.90 (s, 1H)	
25	133.4	-	
26	170.4	-	
27	-	8.53 (d, J = 8.9 Hz, 1H)	HMBC 27→26 COSY 27→28
28	52.3	4.48 (dd J = 12.5, 8.9 Hz, 1H)	COSY 28→29
29	27.5	2.85 (dd, J = 14.9, 12.5 Hz, 1H), 2.95-3.00 (m, 1H) overlap	HMBC 29→28,30,36,38
30	110.7	-	
31	127.3	-	
32	118	7.55 (d, J = 7.7 Hz, 1H)	HMBC 32→36 COSY 32→33
33	118.3	7.04-7.08 (m, 1H)	
34	120.9	7.13-7.19 (m, 1H) overlap	
35	109.5	7.50 (d, J = 8.0 Hz, 1H)	HMBC 35→31 COSY 35→34
36	135.8	-	
37	-	-	
38	124.5	7.13 (s, 1H)	HMBC 38→30,31
39	170.8	-	
40	-	7.59 (d, J = 7.4 Hz, 1H)	HMBC 40→39 COSY 40→41
41	53	4.29 (ddd, J = 7.4, 6.9, 5.9 Hz, 1H)	HMBC 41→48
42	36.6	2.67 (dd, J = 13.6, 6.2 Hz, 1H), 2.74-2.79 (m, 1H)	HMBC 42→43,44,48
43	126.6	-	
44	130	6.87 (d, J = 8.1 Hz, 2H)	HMBC 44→46
45	114.5	6.60 (d, J = 8.1 Hz, 2H)	
46	155.6	-	
47	-	9.14 (s, 1H)	HMBC 47→45,46
48	172.1	-	
49	-	7.07 (br s, 1H), 7.42 (br s, 1H)	TOCSY 49→49'

D. Compiled NMR Spectra

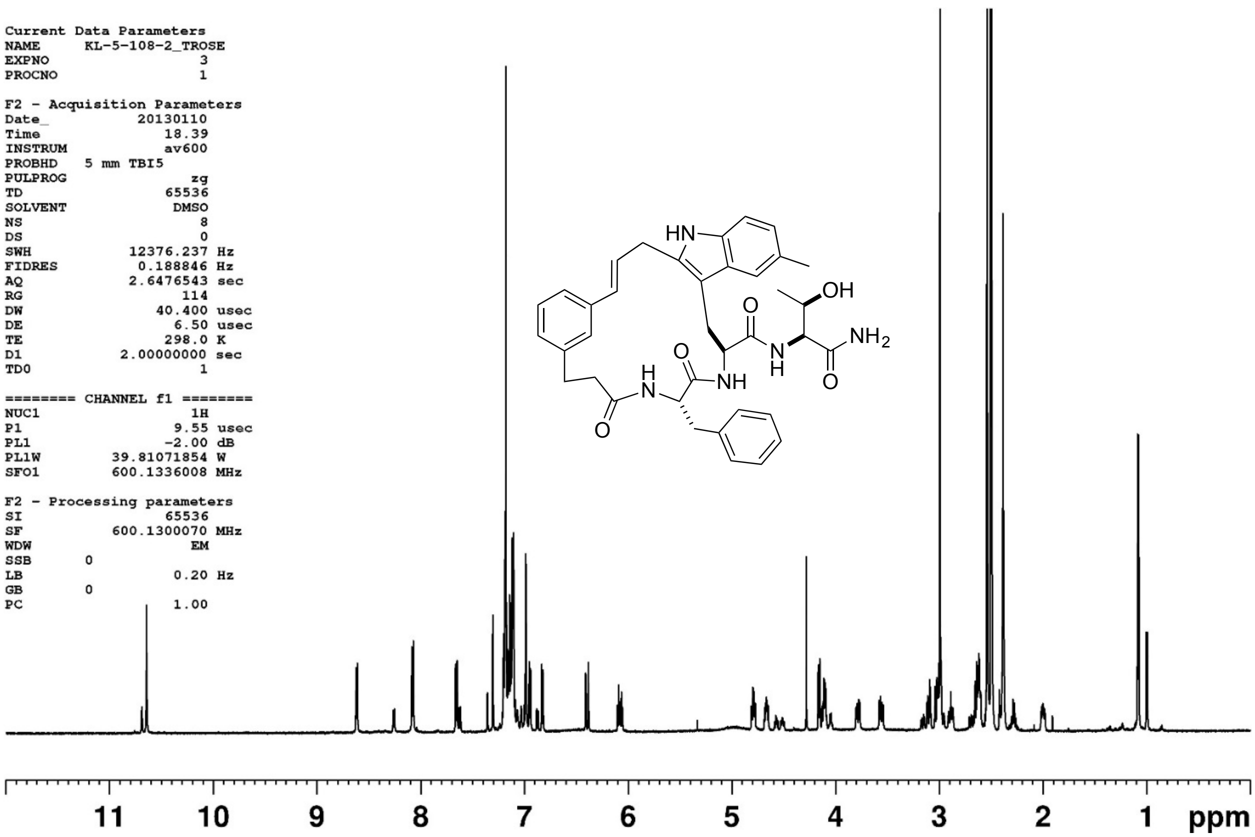
Acyclic Precursor ***2.6***

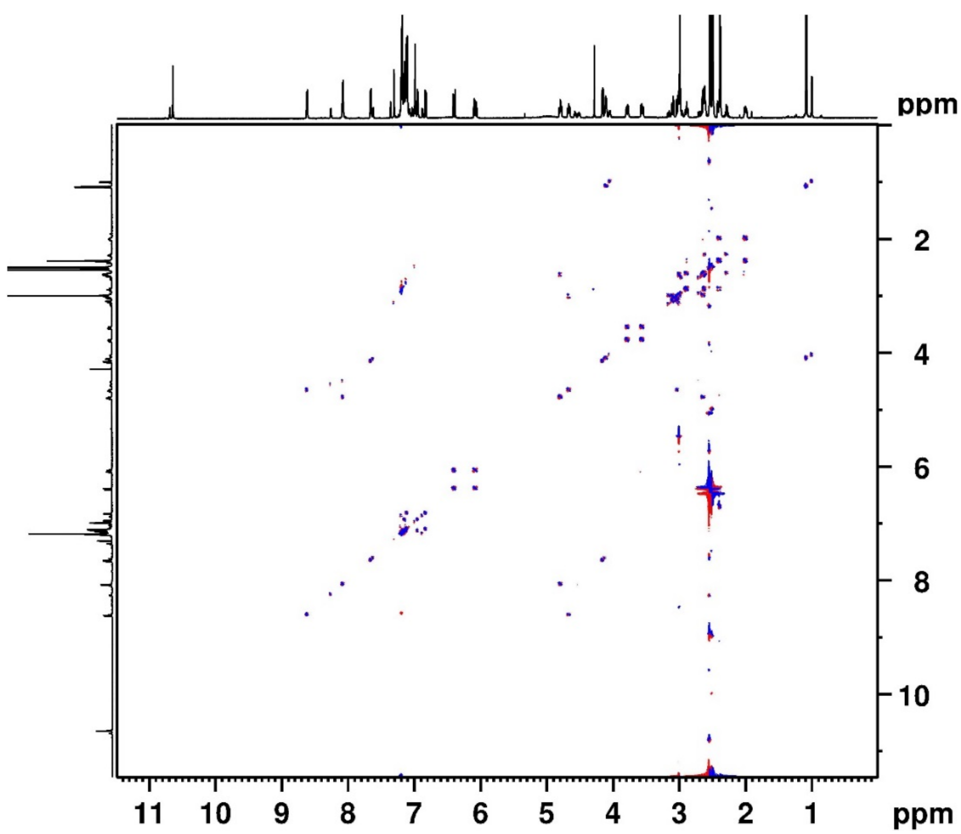




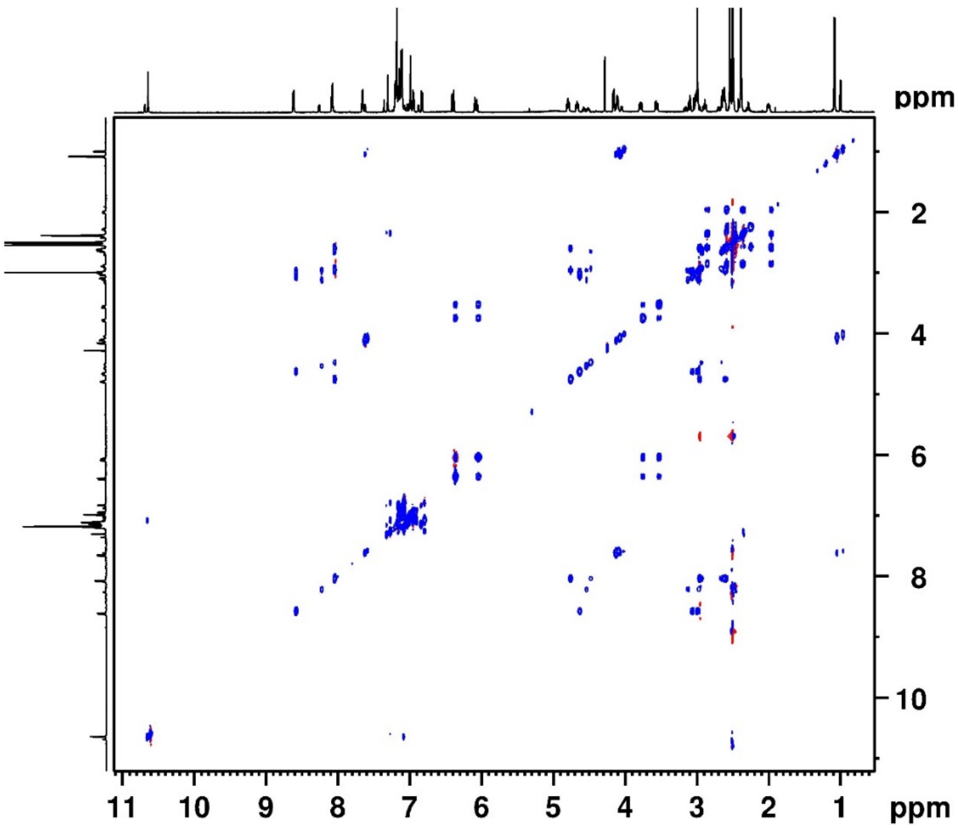
*Macrocyclic Product **2.8b***

```
Current Data Parameters
NAME      KL-5-108-2_TROSE
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130110
Time                 18.39
INSTRUM              av600
PROBHD   5 mm TBI5
PULPROG                 zg
TD                   65536
SOLVENT               DMSO
NS                       8
DS                       0
SWH              12376.237 Hz
FIDRES            0.188846 Hz
AQ               2.6476543 sec
RG                     114
DW                  40.400 usec
DE                    6.50 usec
TE                   298.0 K
D1              2.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.55 usec
PL1                  -2.00 dB
PL1W           39.81071854 W
SFO1           600.1336008 MHz

F2 - Processing parameters
SI                   65536
SF             600.1300070 MHz
WDW                     EM
SSB      0
LB                    0.20 Hz
GB       0
PC                    1.00
```

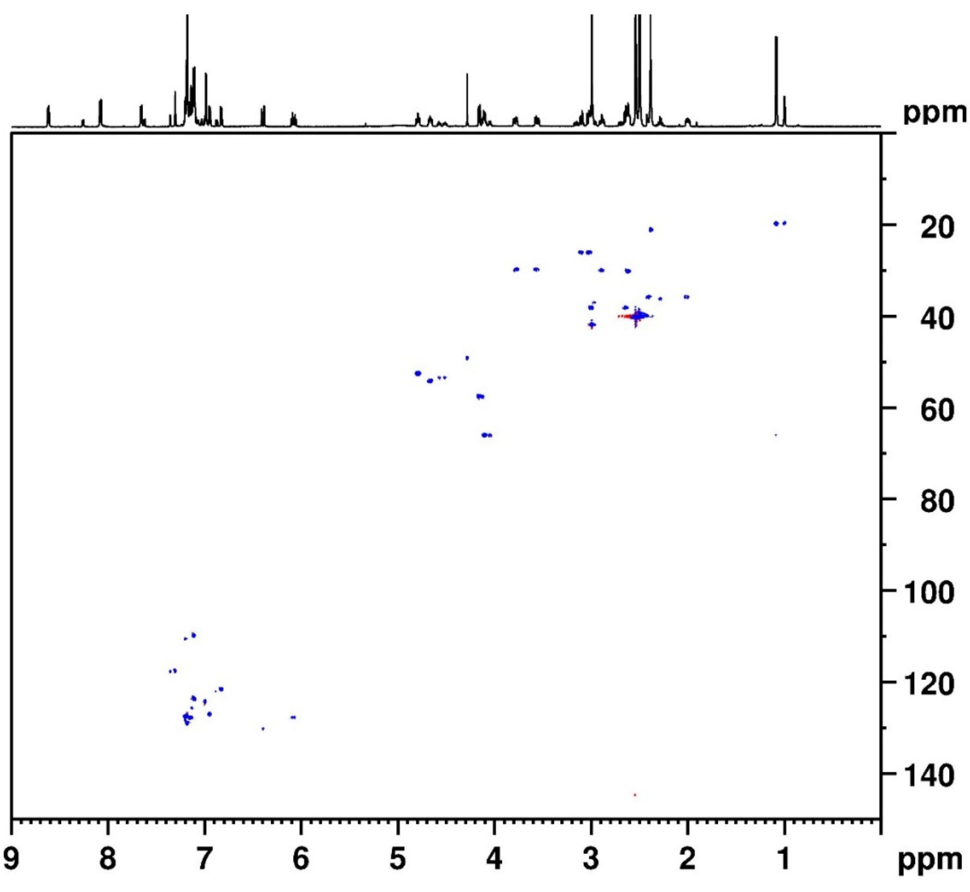




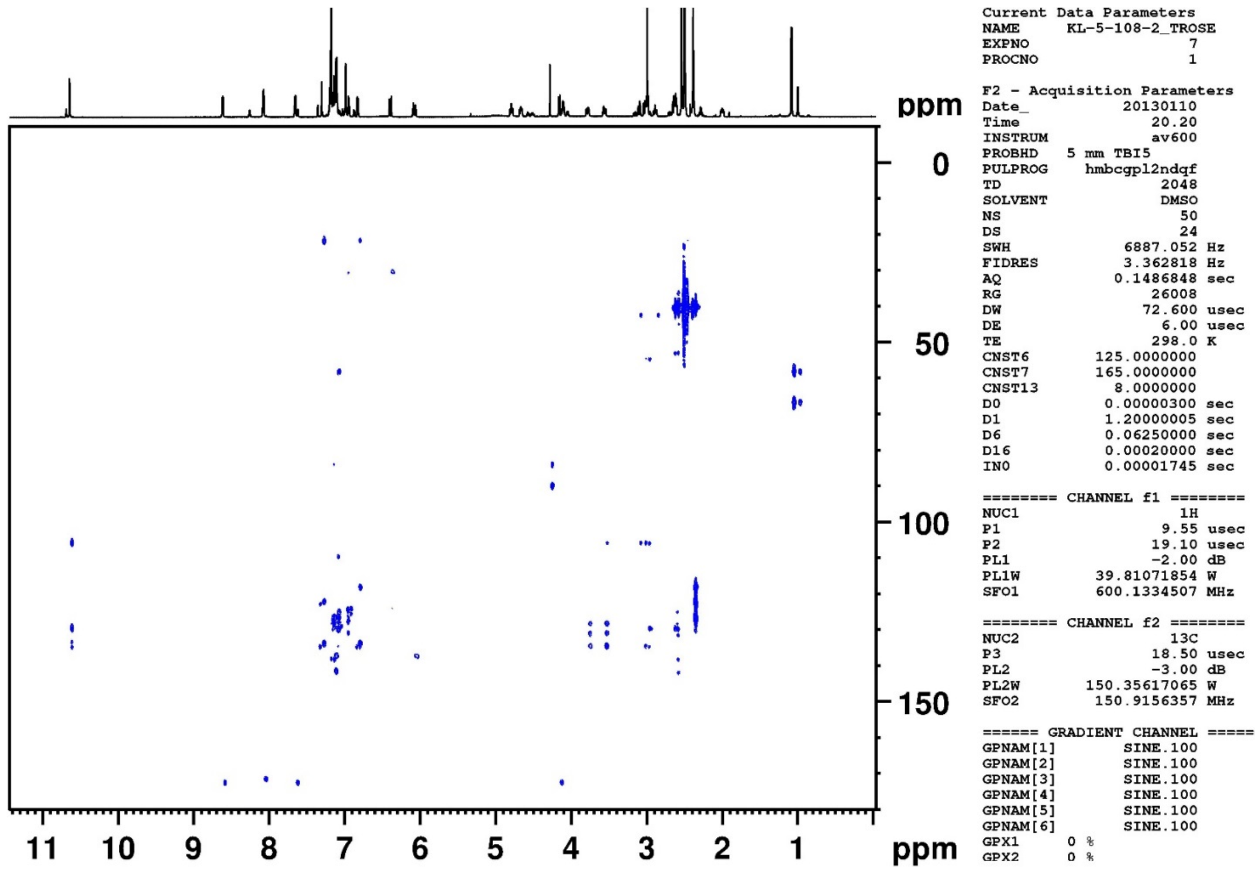

```
Current Data Parameters
NAME      KL-5-108-2_TROSE
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130110
Time                 18.41
INSTRUM              av600
PROBHD   5 mm TBI5
PULPROG         cosygpmfph
TD                    2048
SOLVENT               DMSO
NS                       1
DS                      16
SWH               6887.052 Hz
FIDRES            3.362818 Hz
AQ               0.1486848 sec
RG                     114
DW                  72.600 usec
DE                    6.50 usec
TE                   298.0 K
D0              0.00006044 sec
D1              1.50000000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00014520 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.55 usec
P2                   19.10 usec
PL1                  -2.00 dB
PL1W           39.81071854 W
SFO1           600.1334507 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1       0 %
GPX2       0 %
GPY1       0 %
GPY2       0 %
GPZ1                 10.00 %
GPZ2                 20.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     512
SFO1              600.1335 MHz
FIDRES           13.451290 Hz
SW                  11.476 ppm
FnMODE         States-TPPI
```



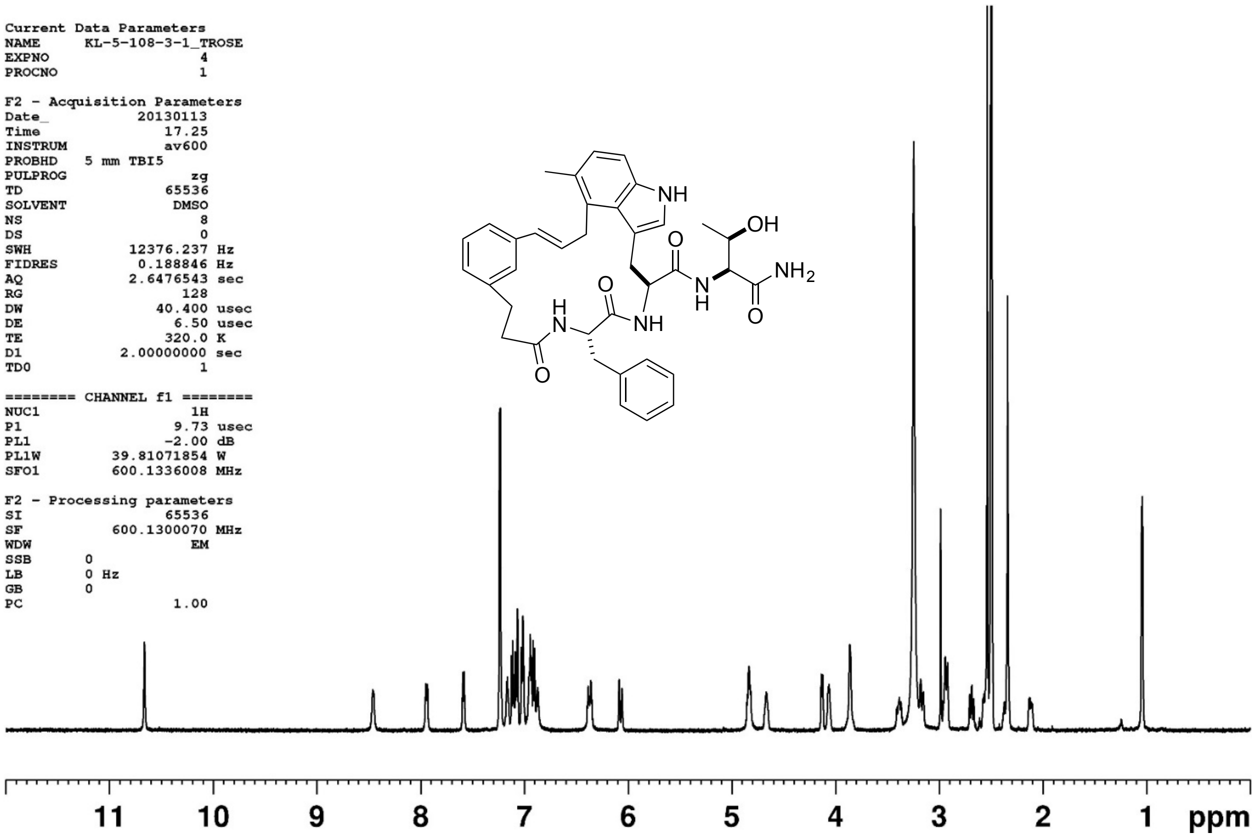
```
Current Data Parameters
NAME      KL-5-108-2_TROSE
EXPNO                    8
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130111
Time                  1.25
INSTRUM              av600
PROBHD   5 mm TBI5
PULPROG      dipsi2etgpsi
TD                    2048
SOLVENT               DMSO
NS                       8
DS                      16
SWH               6887.052 Hz
FIDRES            3.362818 Hz
AQ               0.1486848 sec
RG                     362
DW                  72.600 usec
DE                    6.50 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.50000000 sec
D9              0.06000000 sec
D11             0.03000000 sec
D16             0.00020000 sec
D20             0.00001000 sec
D21             0.00001000 sec
IN0             0.00014520 sec
L1                      14

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.55 usec
P2                   19.10 usec
P6                   40.00 usec
PL1                  -2.00 dB
PL10                 10.44 dB
PL1W           39.81071854 W
PL10W           2.26986504 W
SFO1           600.1334507 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                 30.00 %
GPZ2                 30.00 %
P16                1000.00 usec
```

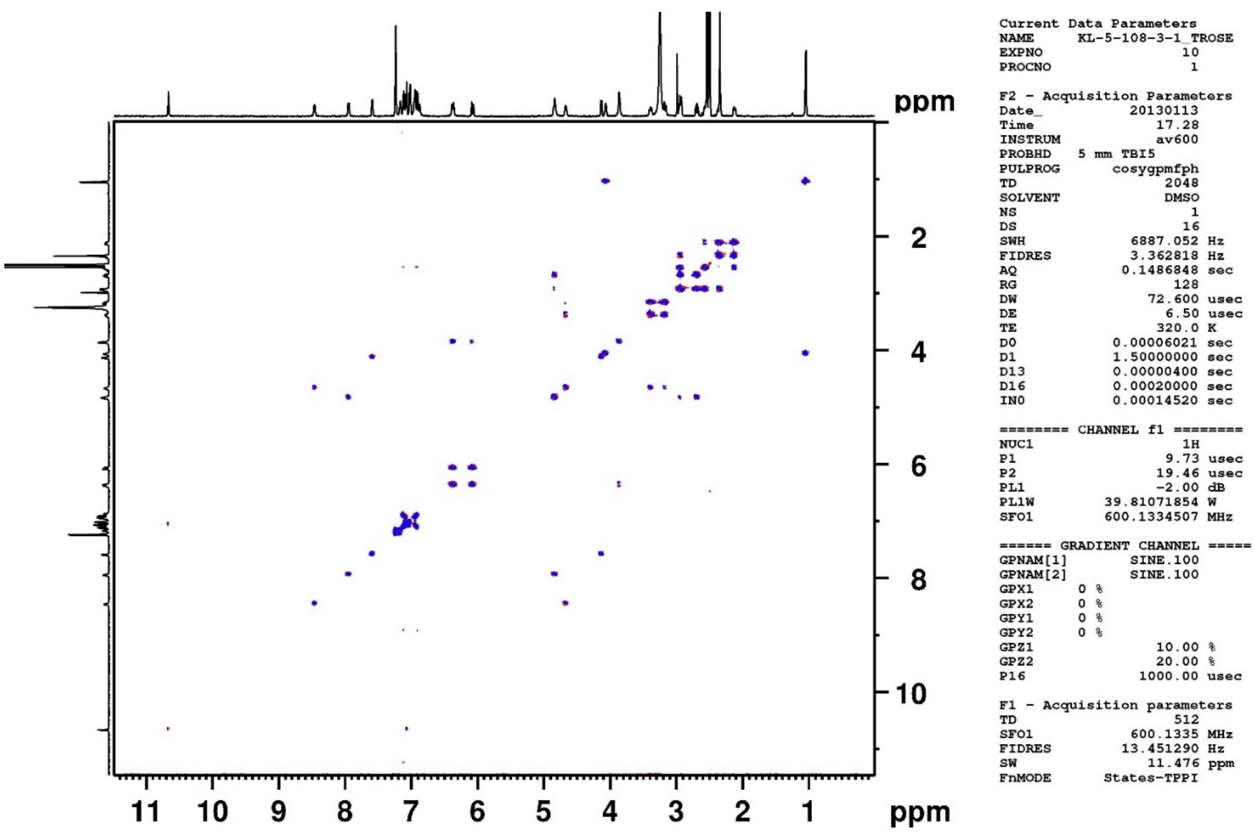


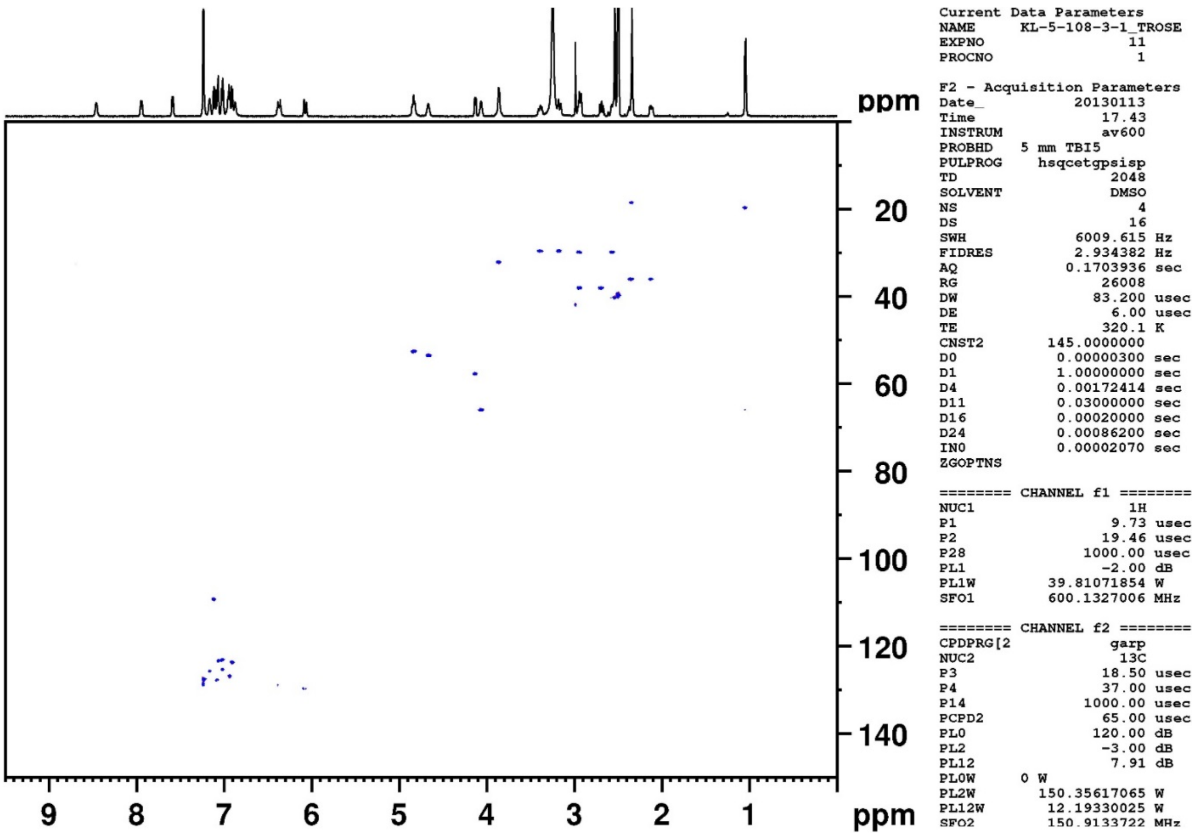
```
Current Data Parameters
NAME      KL-5-108-2_TROSE
EXPNO                    6
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130110
Time                 18.58
INSTRUM              av600
PROBHD   5 mm TBI5
PULPROG       hsqcetgpsisp
TD                    2048
SOLVENT               DMSO
NS                      16
DS                      16
SWH               6009.615 Hz
FIDRES            2.934382 Hz
AQ               0.1703936 sec
RG                   26008
DW                  83.200 usec
DE                    6.00 usec
TE                   298.1 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.00000000 sec
D4              0.00172414 sec
D11             0.03000000 sec
D16             0.00020000 sec
D24             0.00086200 sec
IN0             0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.55 usec
P2                   19.10 usec
P28                1000.00 usec
PL1                  -2.00 dB
PL1W           39.81071854 W
SFO1           600.1327006 MHz

======== CHANNEL f2 ========
CPDPRG[2              garp
NUC2                   13C
P3                   18.50 usec
P4                   37.00 usec
P14                1000.00 usec
PCPD2                65.00 usec
PL0                 120.00 dB
PL2                  -3.00 dB
PL12                  7.91 dB
PL0W        0 W
PL2W          150.35617065 W
PL12W          12.19330025 W
SFO2           150.9133722 MHz
```

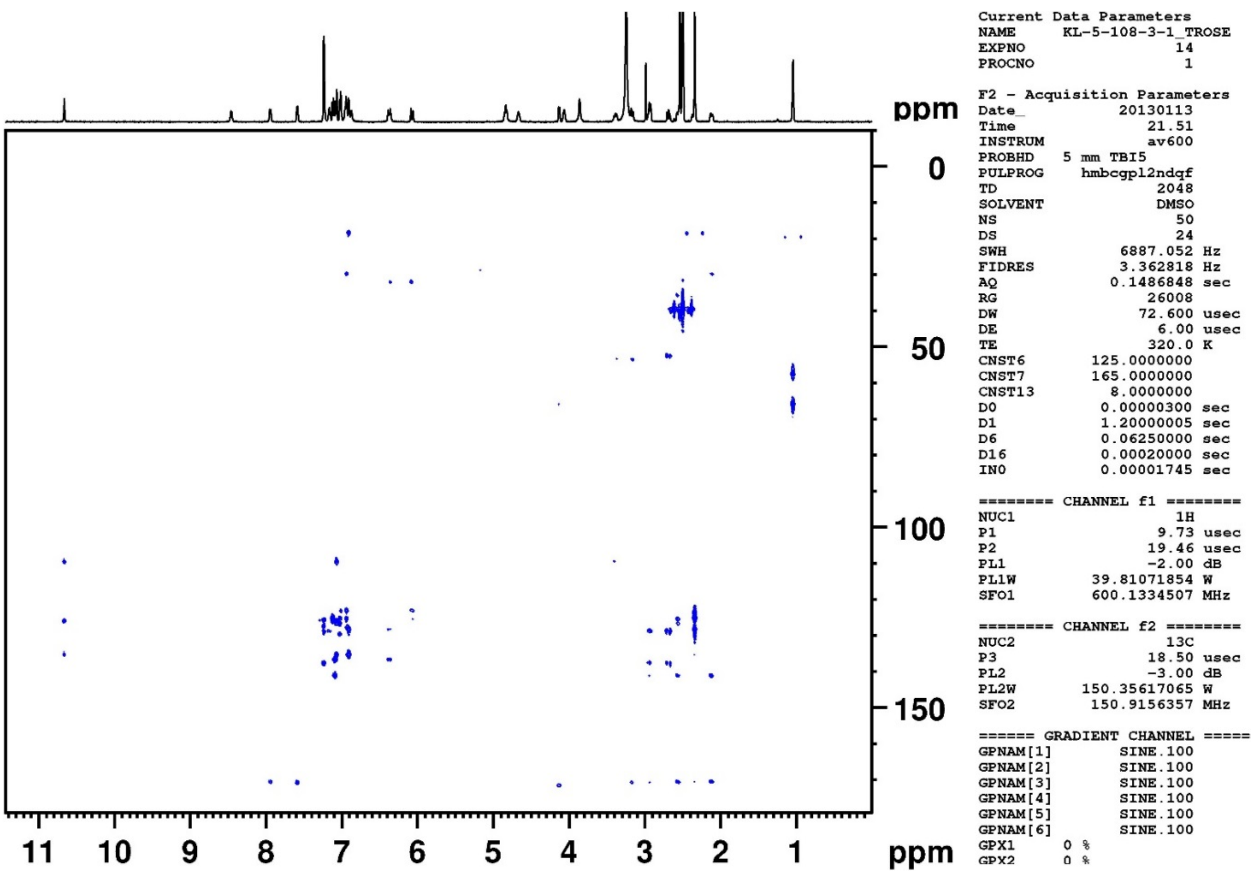

ppm
0
50
100
150
11 10 9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME KL-5-108-2_TROSE
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130110
Time 20.20
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 50
DS 24
SWH 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1486848 sec
RG 26008
DW 72.600 usec
DE 6.00 usec
TE 298.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.55 usec
P2 19.10 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1334507 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPX1 0 %
GPX2 0 %

*Macrocyclic Product **2.8c***

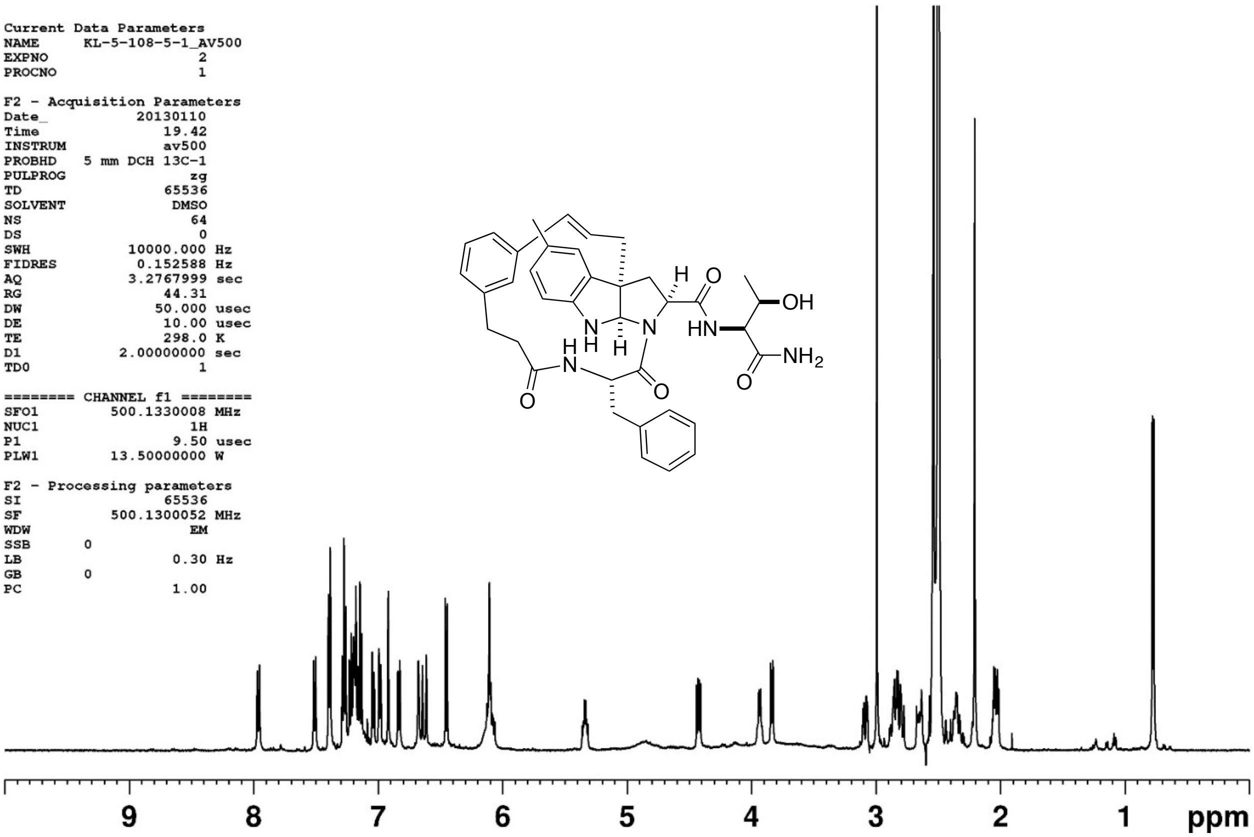




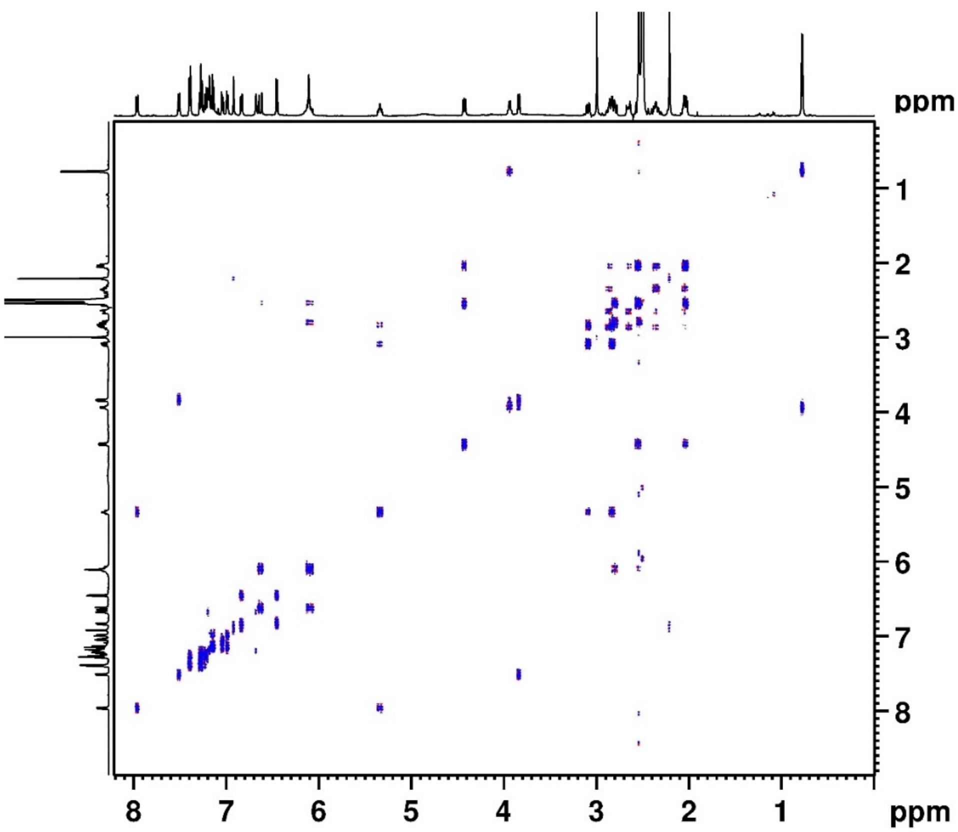

Current Data Parameters
NAME KL-5-108-3-1_TROSE
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130113
Time 17.43
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 320.1 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 9.73 usec
P2 19.46 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 18.50 usec
P4 37.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.91 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 12.19330025 W
SFO2 150.9133722 MHz
ppm
20
40
60
80
100
120
140
9 8 7 6 5 4 3 2 1 ppm


Current Data Parameters
NAME KL-5-108-3-1_TROSE
EXPNO 14
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130113
Time 21.51
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 50
DS 24
SWH 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1486848 sec
RG 26008
DW 72.600 usec
DE 6.00 usec
TE 320.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.73 usec
P2 19.46 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1334507 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPX1 0 %
GPX2 0 %
ppm
0
50
100
150
11 10 9 8 7 6 5 4 3 2 1 ppm

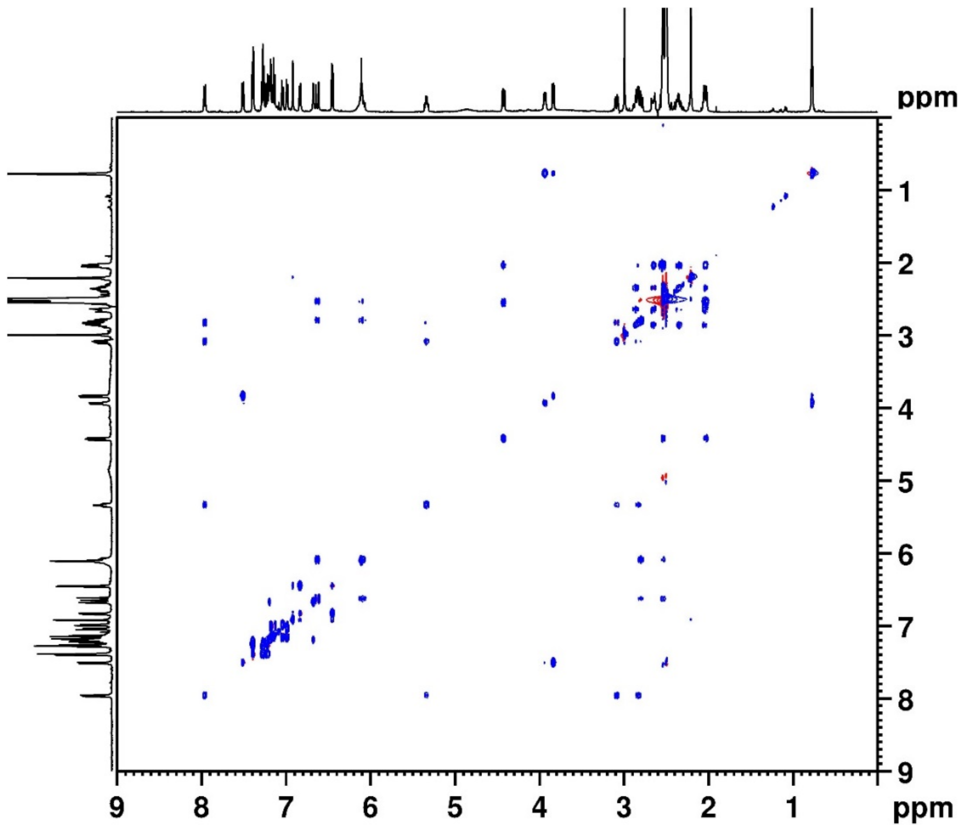
Macrocyclic Product ***2.8d***




```
Current Data Parameters
NAME     KL-5-108-5-1_AV500
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_            20130110
Time                19.42
INSTRUM             av500
PROBHD   5 mm DCH 13C-1
PULPROG                zg
TD                  65536
SOLVENT              DMSO
NS                     64
DS                      0
SWH             10000.000 Hz
FIDRES           0.152588 Hz
AQ              3.2767999 sec
RG                  44.31
DW                 50.000 usec
DE                  10.00 usec
TE                  298.0 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1        500.1330008 MHz
NUC1                   1H
P1                   9.50 usec
PLW1          13.50000000 W

F2 - Processing parameters
SI                  65536
SF          500.1300052 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```



```
Current Data Parameters
NAME     KL-5-108-5-1_AV500
EXPNO                    3
PROCNO                   1

F2 - Acquisition Parameters
Date_            20130110
Time                19.43
INSTRUM             av500
PROBHD   5 mm DCH 13C-1
PULPROG         cosygpmfph
TD                   4096
SOLVENT              DMSO
NS                      4
DS                      8
SWH              5498.534 Hz
FIDRES           1.342415 Hz
AQ              0.3724629 sec
RG                 202.91
DW                 90.933 usec
DE                  10.00 usec
TE                  298.0 K
D0             0.00007880 sec
D1             2.00000000 sec
D13            0.00000400 sec
D16            0.00020000 sec
IN0            0.00018180 sec

======== CHANNEL f1 ========
SFO1        500.1327507 MHz
NUC1                   1H
P1                   9.50 usec
P2                  19.00 usec
PLW1          13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                10.00 %
GPZ2                20.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    256
SFO1          500.1328 MHz
FIDRES          21.486525 Hz
SW                 10.998 ppm
FnMODE        States-TPPI

F2 - Processing parameters
SI                   4096
SF          500.1300046 MHz
WDW                  SINE
SSB                     1
```



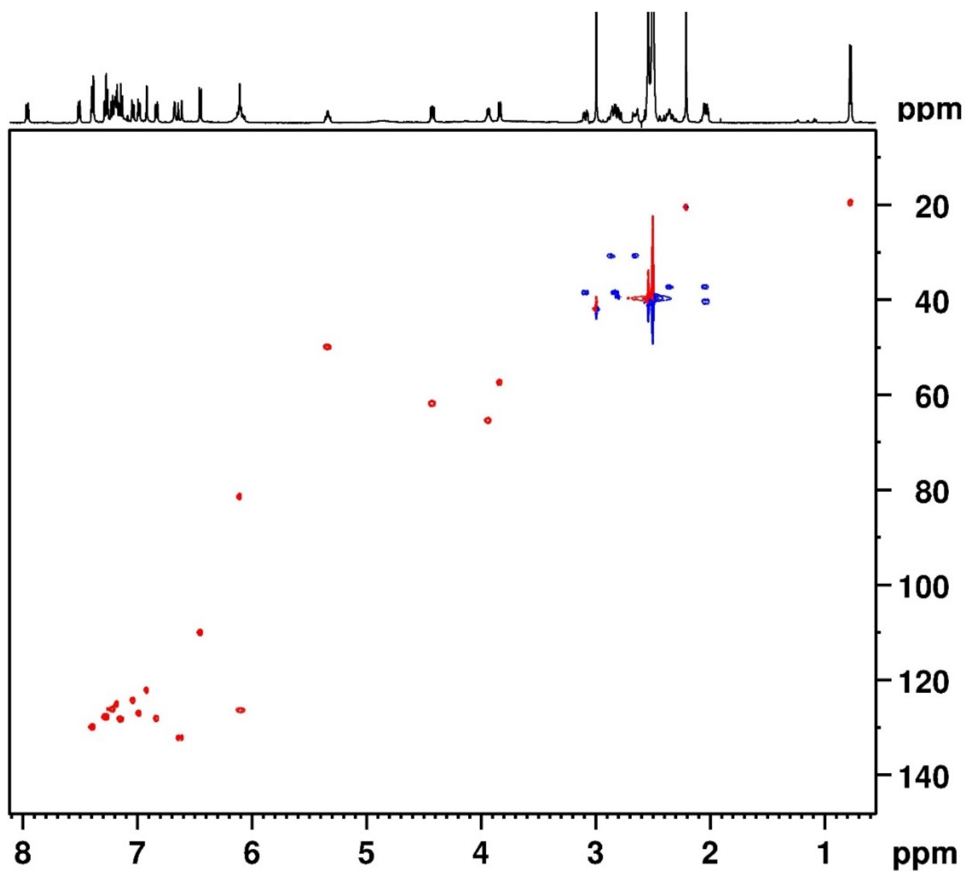
Current Data Parameters
NAME KL-5-108-5-1_AV500
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130110
Time 20.24
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 4
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
L1 24

======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 9.50 usec
P2 19.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz



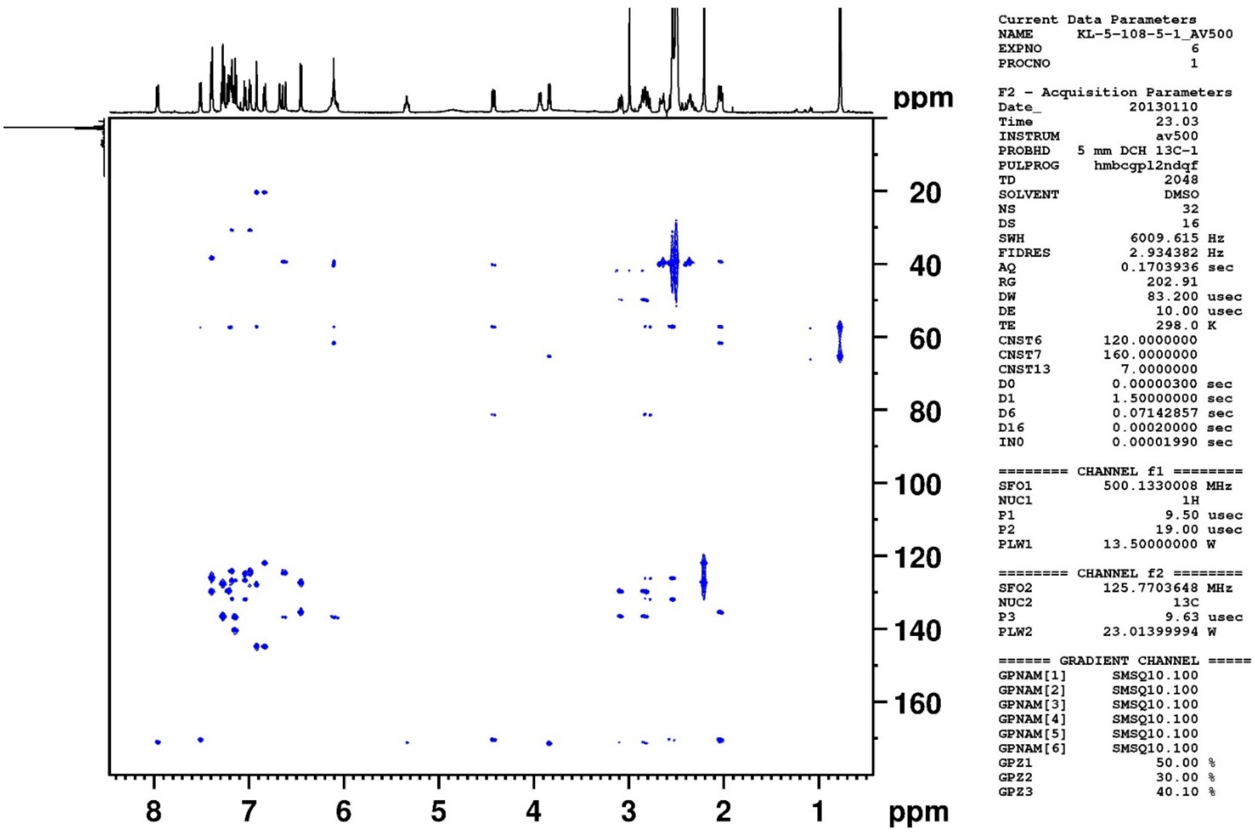
Current Data Parameters
NAME KL-5-108-5-1_AV500
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130110
Time 21.05
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 16
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS

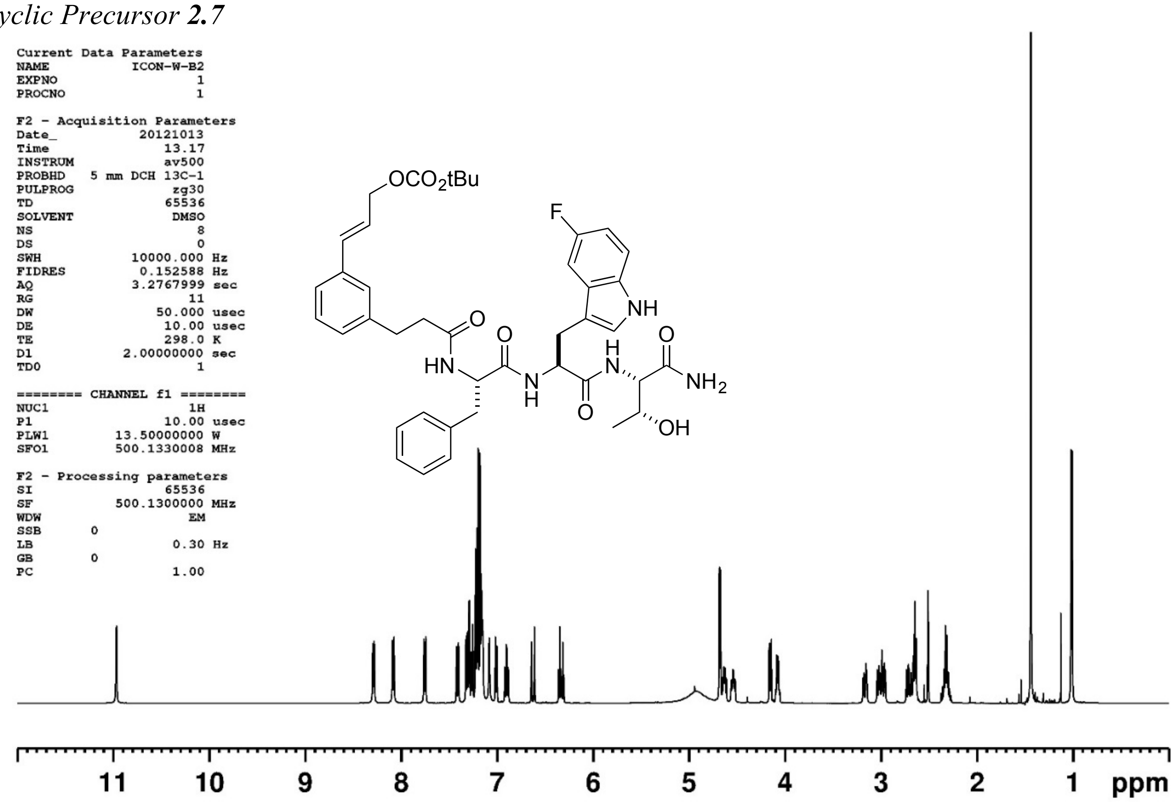
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 9.50 usec
P2 19.00 usec
P28 0 usec
PLW1 13.50000000 W

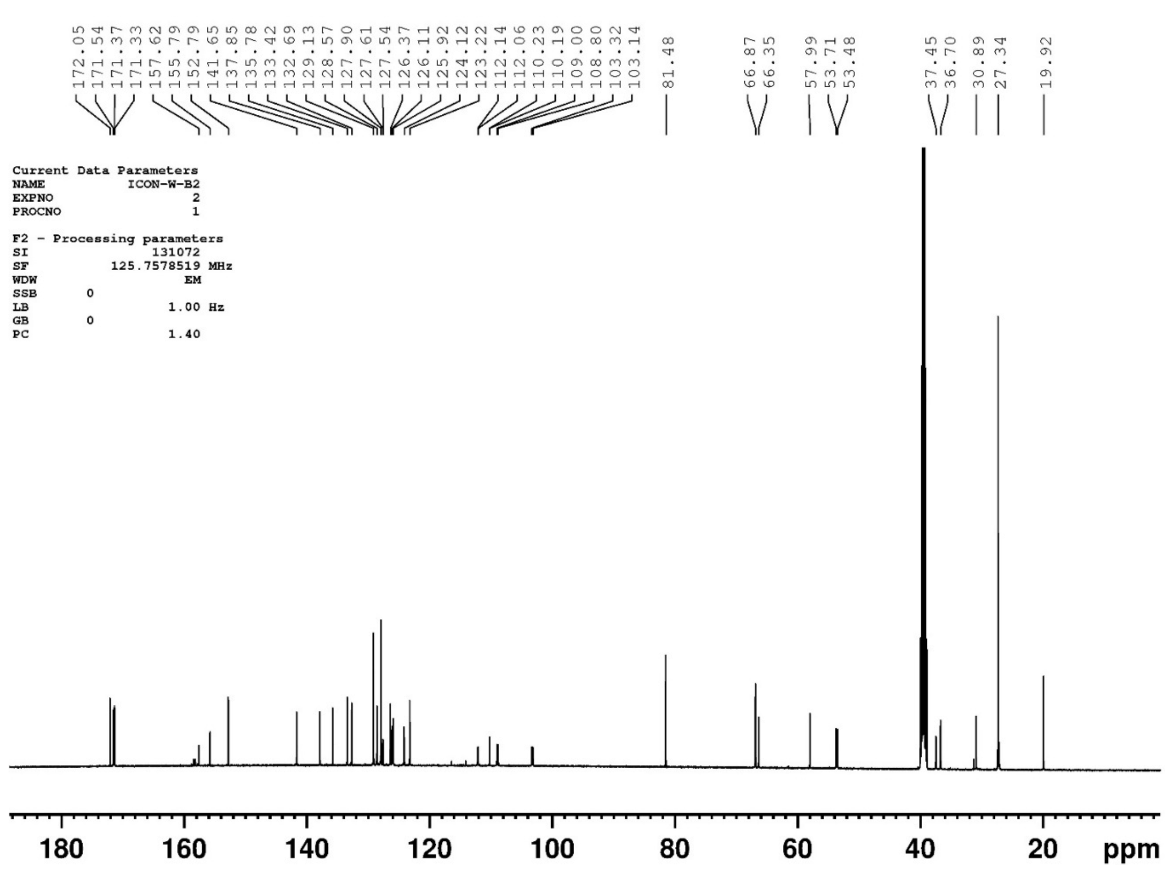
======== CHANNEL f2 ========
SFO2 125.7678496 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W

====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %


ppm
20
40
60
80
100
120
140
160
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME KL-5-108-5-1_AV500
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130110
Time 23.03
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
P1 9.50 usec
P2 19.00 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7703648 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %

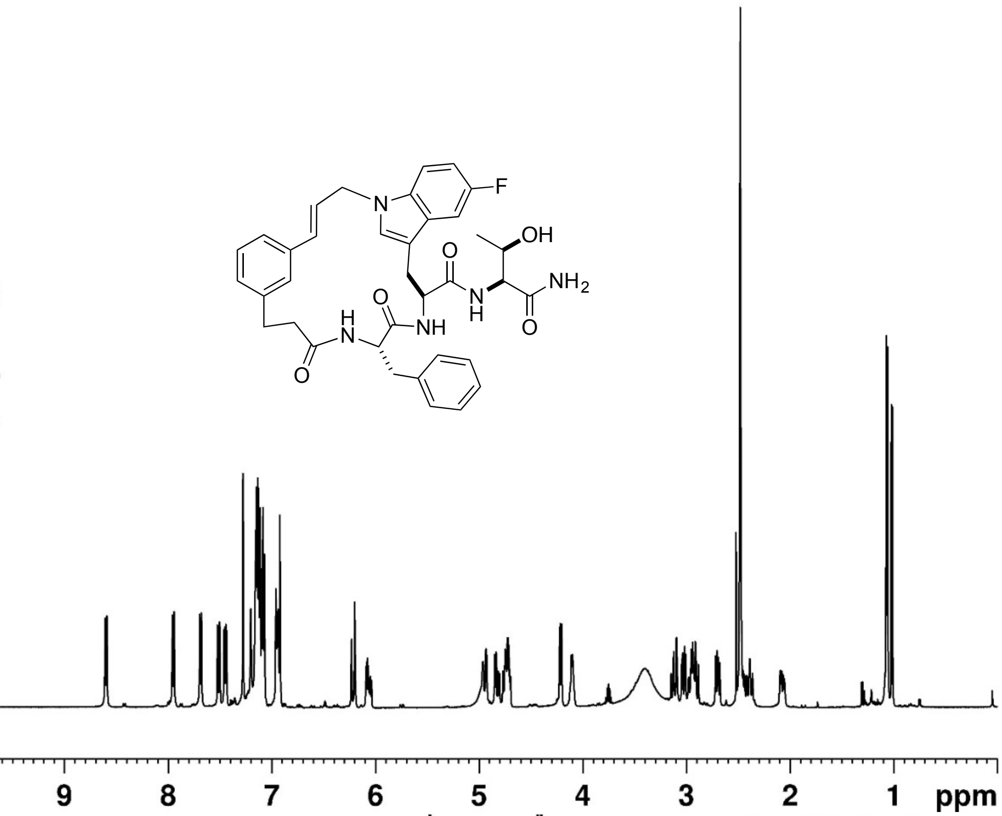
*Acyclic Precursor **2.7***

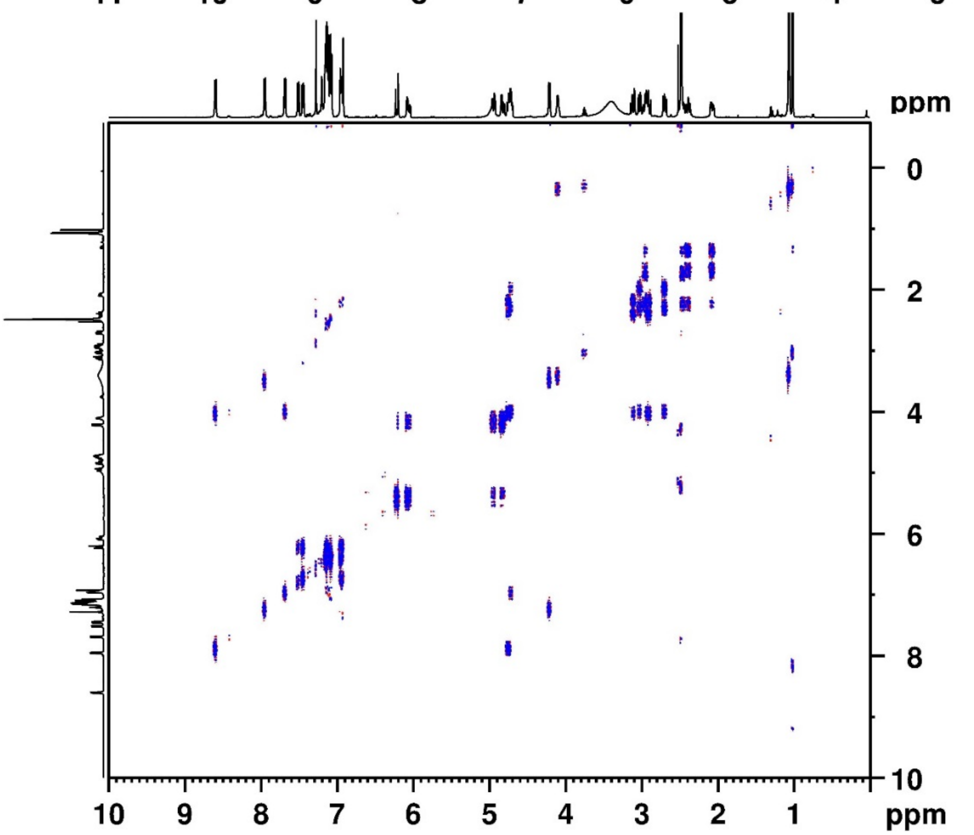




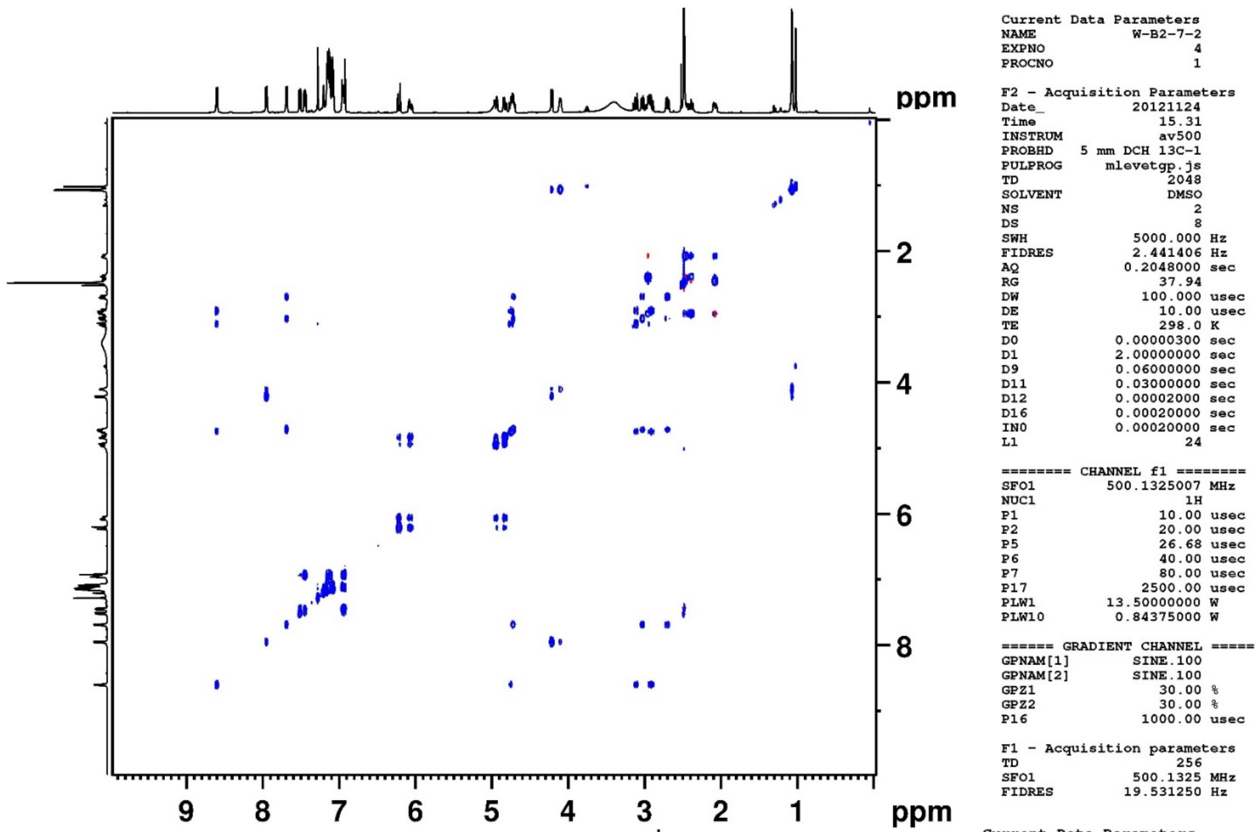
*Macrocyclic Product **2.9a***

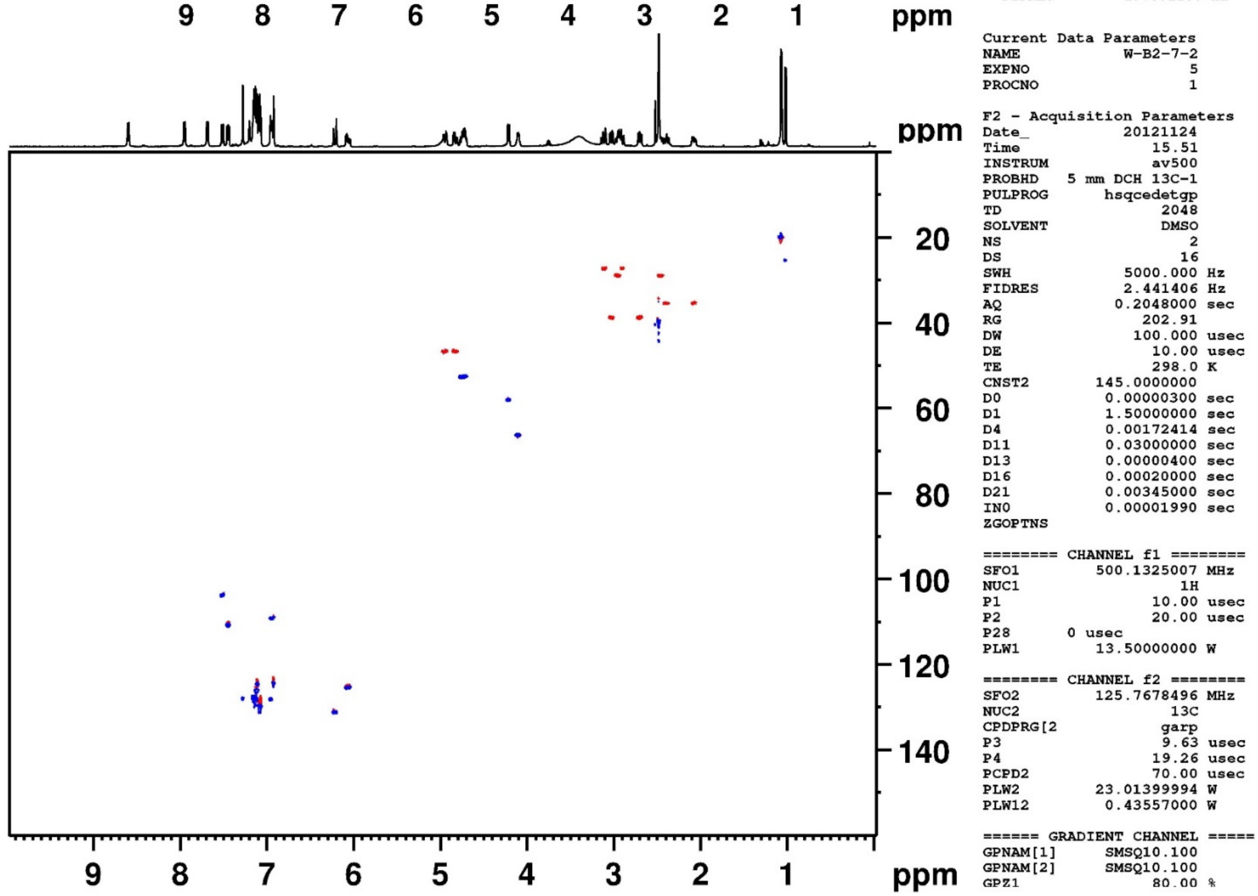
```
Current Data Parameters
NAME            W-B2-7-2
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121124
Time               15.09
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG               zg
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     0
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                     7
DW                50.000 usec
DE                 10.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330008 MHz
NUC1                  1H
P1                 10.00 usec
PLW1         13.50000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300146 MHz
WDW                   EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

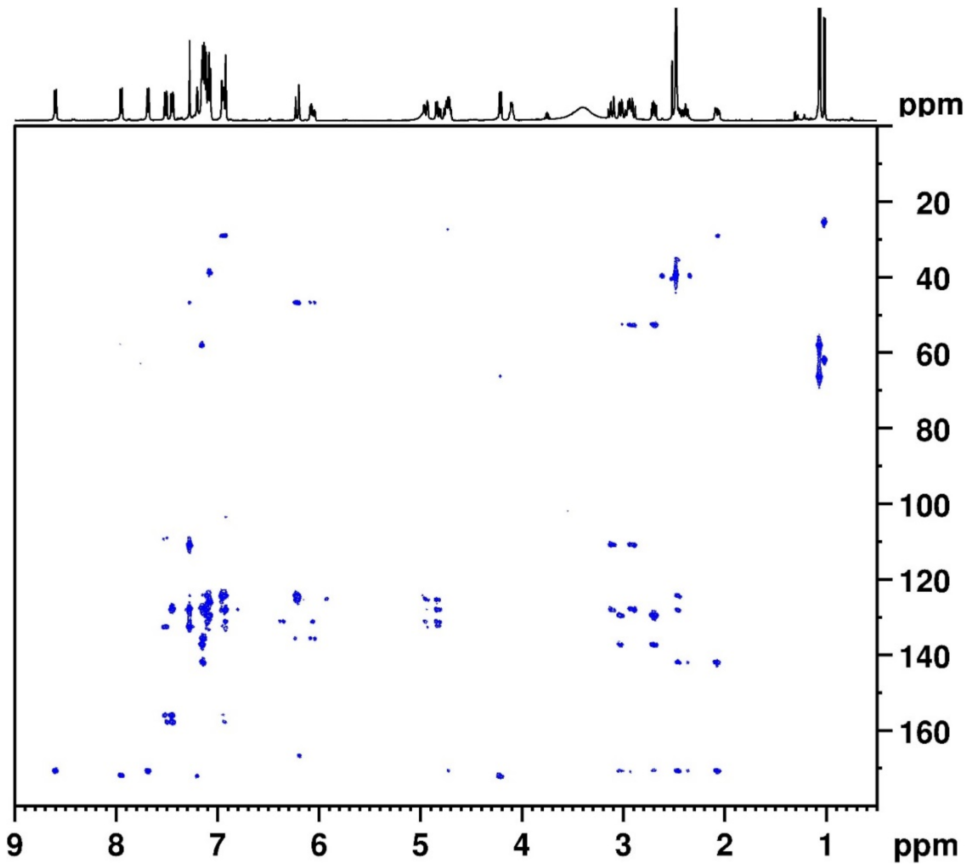





```
Current Data Parameters
NAME            W-B2-7-2
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121124
Time               15.10
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG      cosygpmfph
TD                  4096
SOLVENT             DMSO
NS                     2
DS                     8
SWH             5498.534 Hz
FIDRES          1.342415 Hz
AQ             0.3724629 sec
RG                202.91
DW                90.933 usec
DE                 10.00 usec
TE                 298.0 K
D0            0.00007817 sec
D1            2.00000000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00018180 sec

======== CHANNEL f1 ========
SFO1         500.1327507 MHz
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               10.00 %
GPZ2               20.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   256
SFO1            500.1328 MHz
FIDRES         21.486525 Hz
SW                10.998 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                  2048
SF           500.1300135 MHz
WDW                 SINE
SSB                    1
```


ppm
2
4
6
8
9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME W-B2-7-2
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121124
Time 15.31
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
L1 24
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz

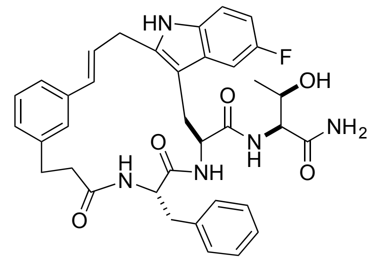

ppm
20
40
60
80
100
120
140
9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME W-B2-7-2
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121124
Time 15.51
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7678496 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %

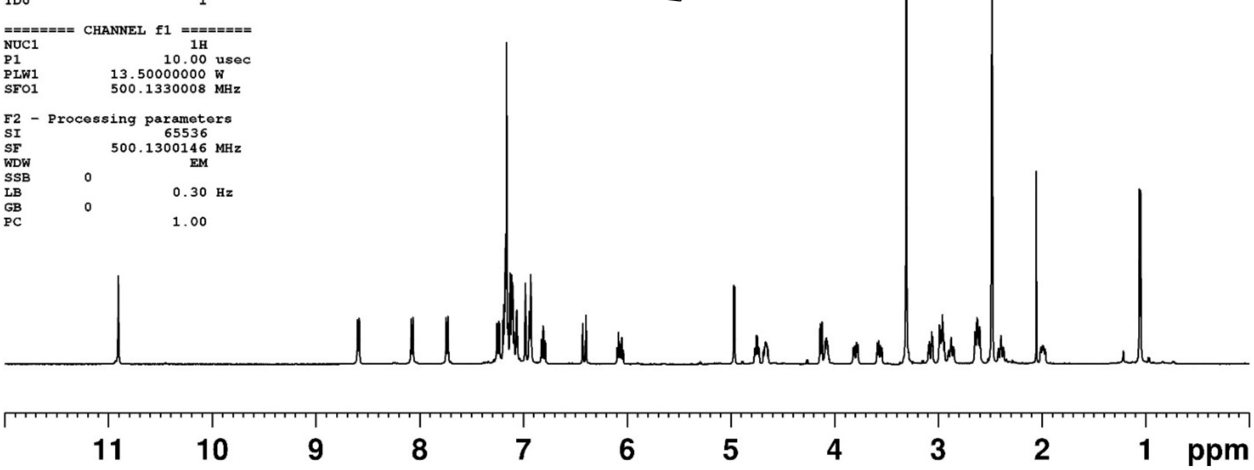


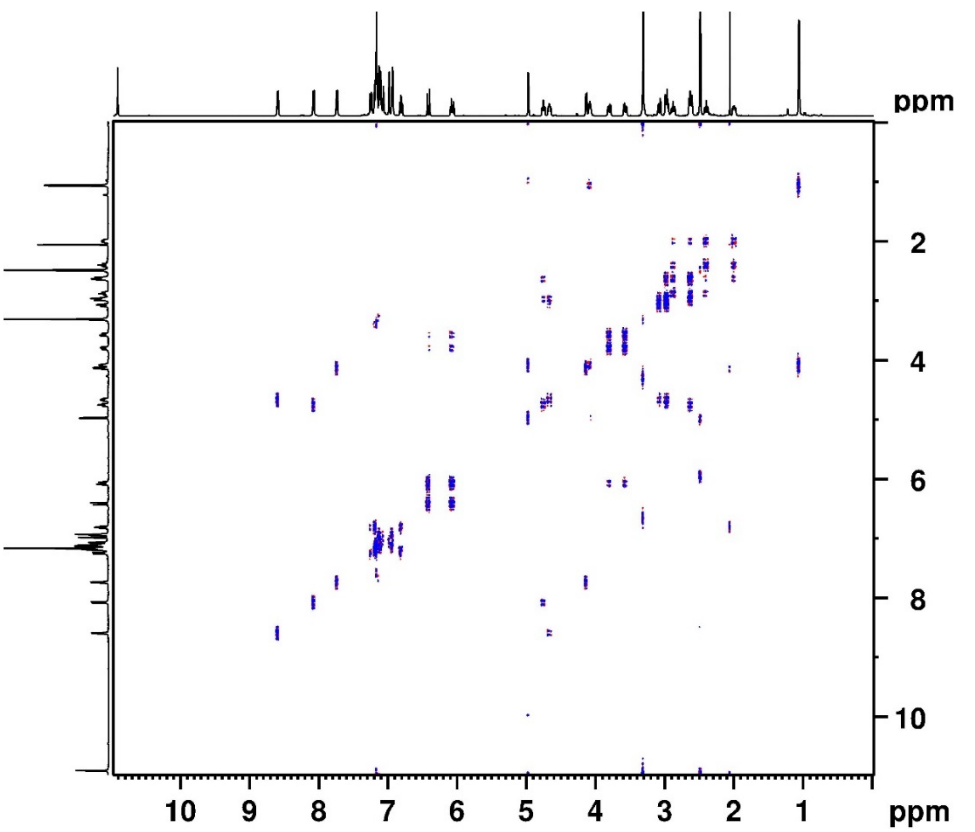

```
Current Data Parameters
NAME            W-B2-7-2
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121124
Time               16.07
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG     hmbcgpl2ndqf
TD                  2048
SOLVENT             DMSO
NS                     4
DS                    16
SWH             6009.615 Hz
FIDRES          2.934382 Hz
AQ             0.1703936 sec
RG                202.91
DW                83.200 usec
DE                 10.00 usec
TE                 298.0 K
CNST6        120.0000000
CNST7        160.0000000
CNST13         7.0000000
D0            0.00000300 sec
D1            1.50000000 sec
D6            0.07142857 sec
D16           0.00020000 sec
IN0           0.00001990 sec

======== CHANNEL f1 ========
SFO1        500.1330008 MHz
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W

======== CHANNEL f2 ========
SFO2        125.7703648 MHz
NUC2                 13C
P3                  9.63 usec
PLW2         23.01399994 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPNAM[4]      SMSQ10.100
GPNAM[5]      SMSQ10.100
GPNAM[6]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
GPZ4               15.00 %
```

*Macrocyclic Product **2.9b***

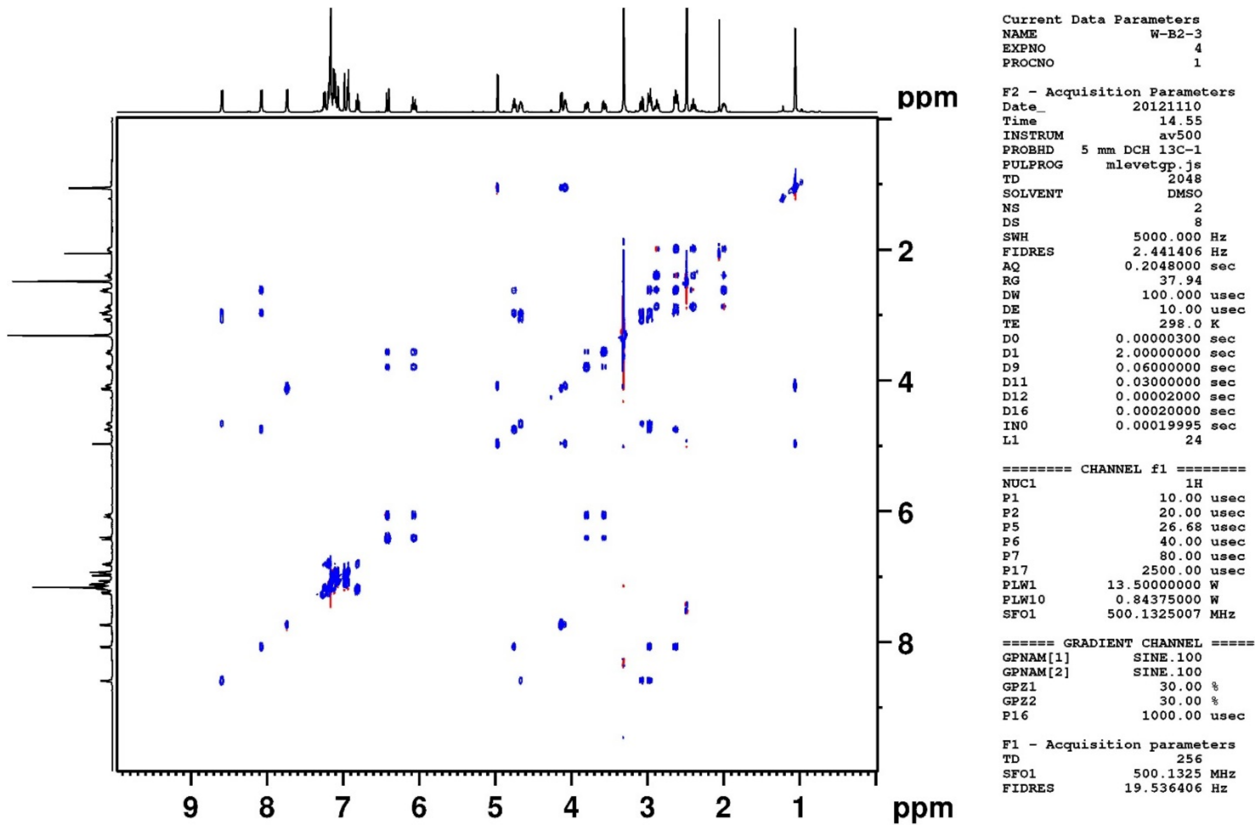
```
Current Data Parameters
NAME              W-B2-3
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121110
Time               14.34
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG               zg
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     0
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                     7
DW                50.000 usec
DE                 10.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PLW1         13.50000000 W
SFO1         500.1330008 MHz

F2 - Processing parameters
SI                 65536
SF           500.1300146 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

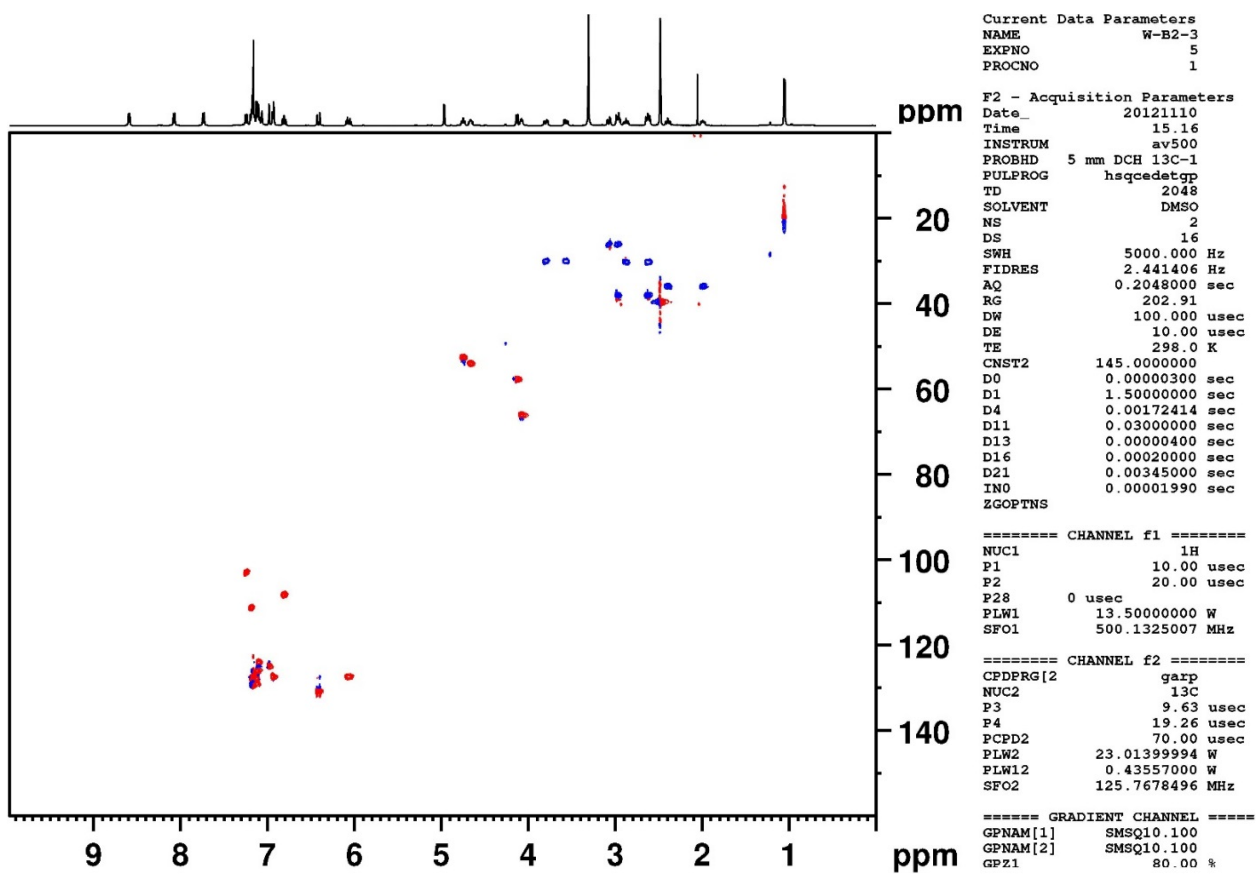


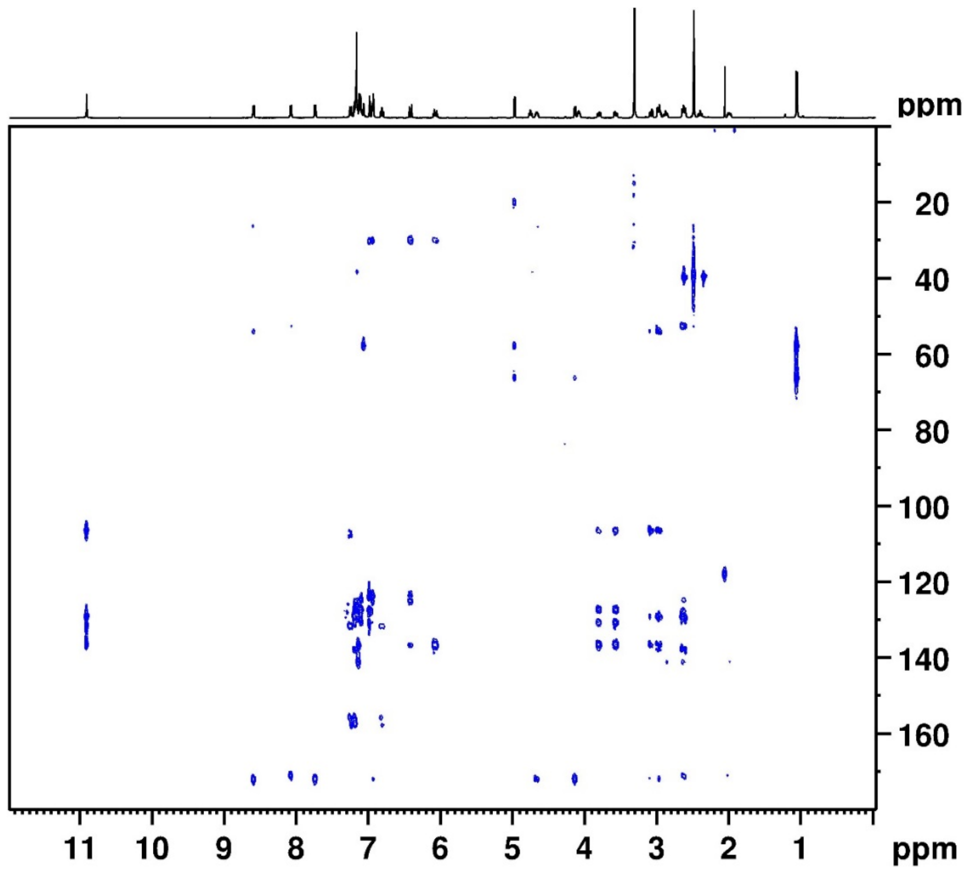





```
Current Data Parameters
NAME              W-B2-3
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121110
Time               14.35
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG      cosygpmfph
TD                  4096
SOLVENT             DMSO
NS                     2
DS                     8
SWH             5498.534 Hz
FIDRES          1.342415 Hz
AQ             0.3724629 sec
RG                202.91
DW                90.933 usec
DE                 10.00 usec
TE                 298.0 K
D0            0.00007815 sec
D1            2.00000000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00018175 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W
SFO1         500.1327507 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               10.00 %
GPZ2               20.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   256
SFO1            500.1328 MHz
FIDRES         21.490080 Hz
SW                11.000 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                  2048
SF           500.1300135 MHz
WDW                 SINE
SSB                    1
```

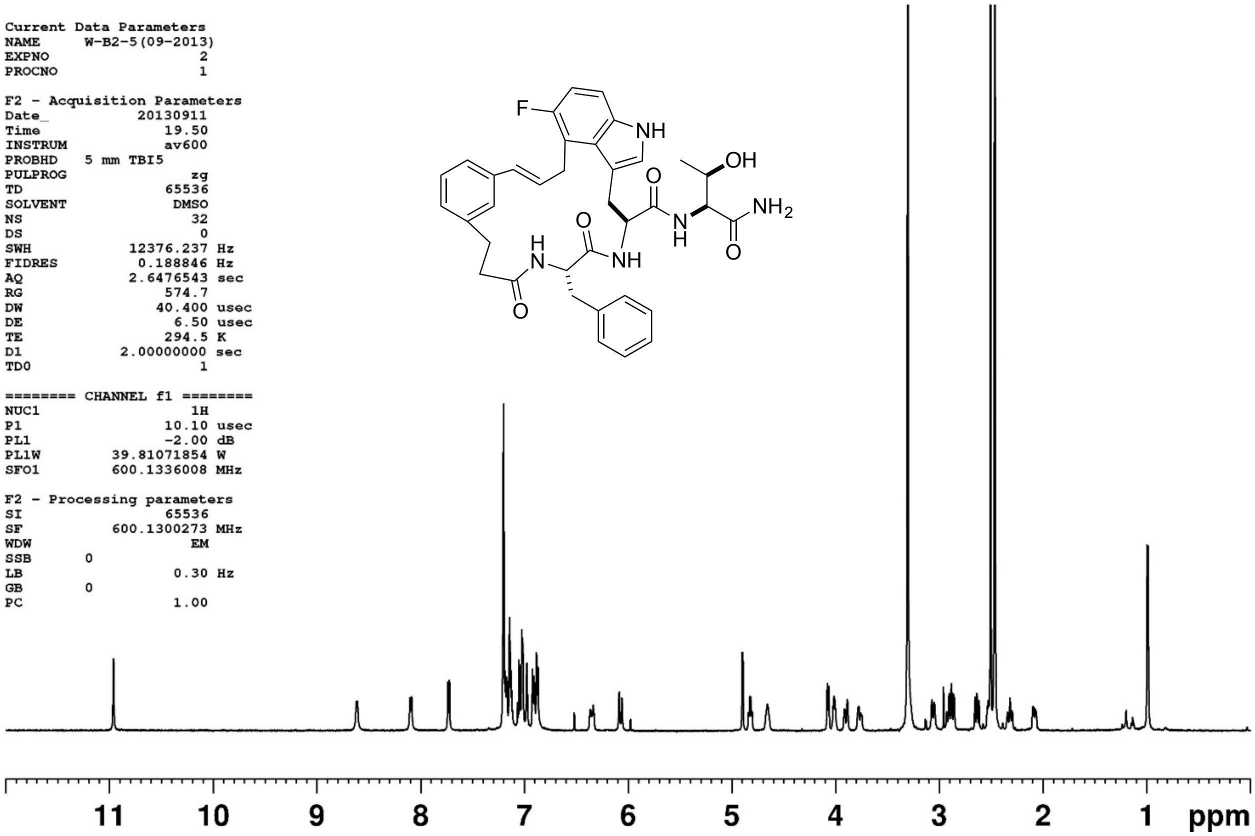

ppm
2
4
6
8
9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-B2-3
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121110
Time 14.55
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019995 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1325007 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz

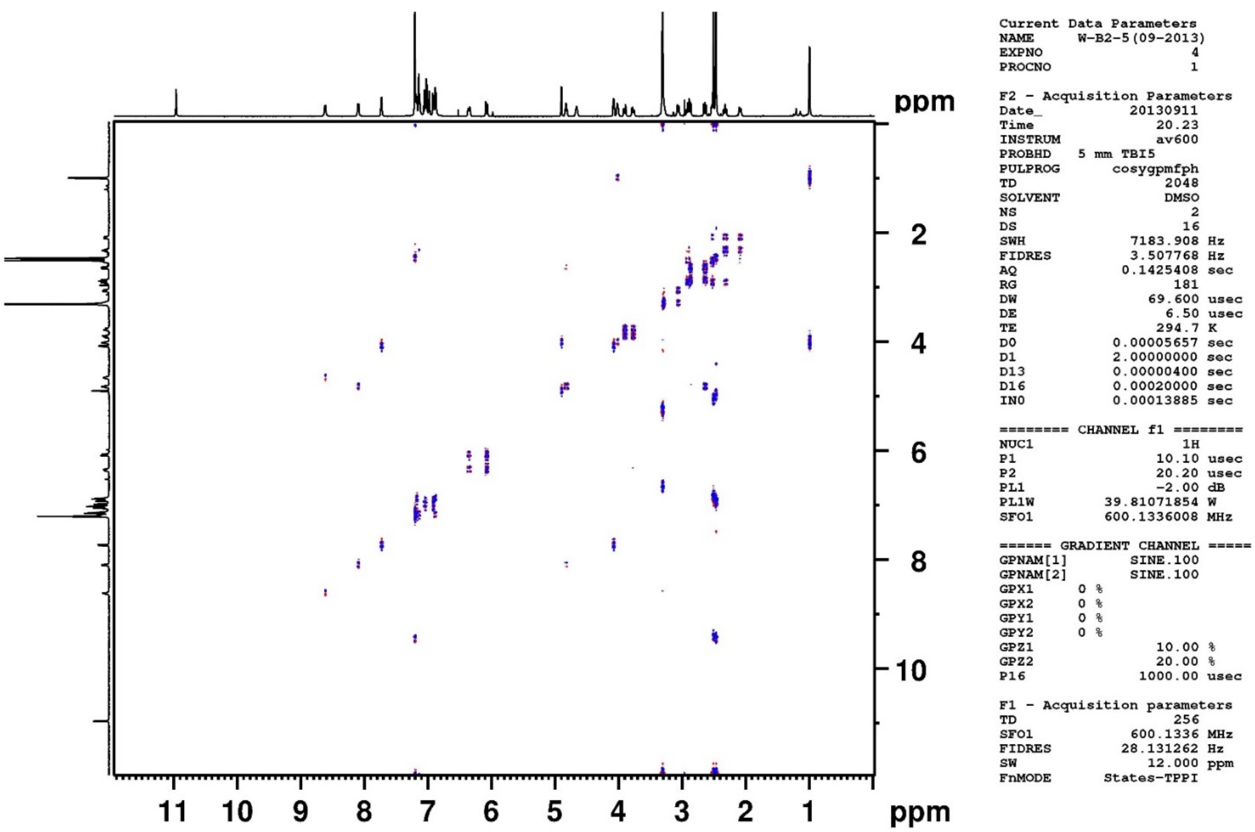

ppm
20
40
60
80
100
120
140
9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-B2-3
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121110
Time 15.16
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W
SFO1 500.1325007 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
SFO2 125.7678496 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %

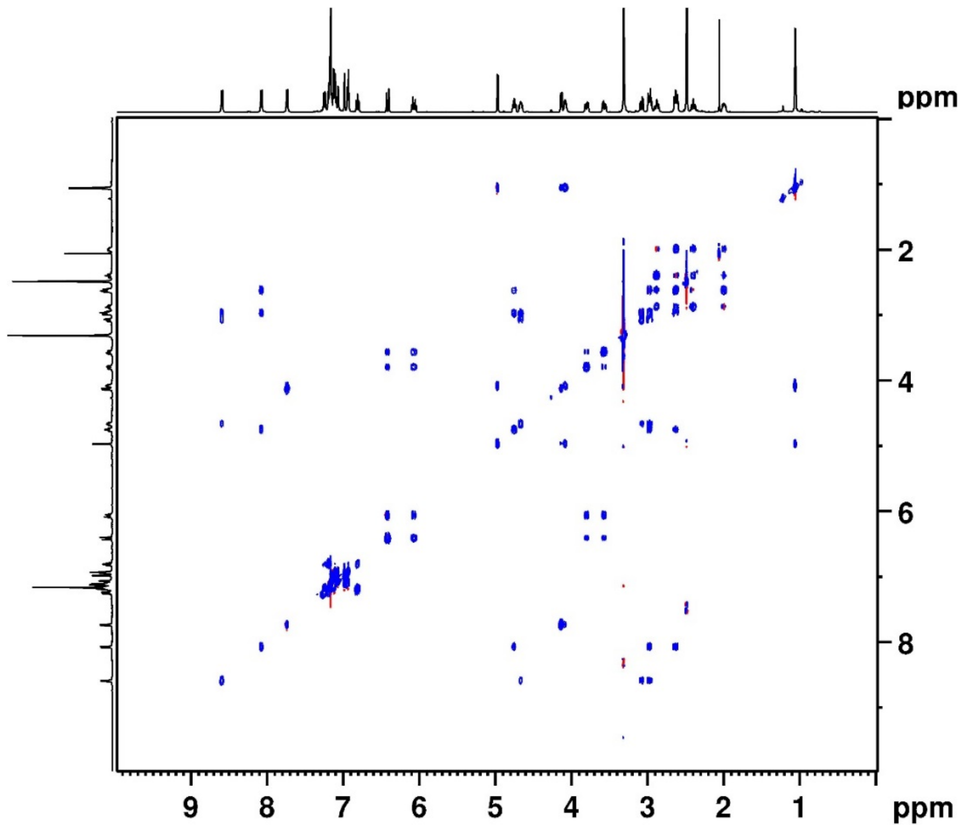



```
Current Data Parameters
NAME              W-B2-3
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121110
Time               15.31
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG     hmbcgpl2ndqf
TD                  2048
SOLVENT             DMSO
NS                     2
DS                    16
SWH             6009.615 Hz
FIDRES          2.934382 Hz
AQ             0.1703936 sec
RG                202.91
DW                83.200 usec
DE                 10.00 usec
TE                 298.0 K
CNST6        120.0000000
CNST7        160.0000000
CNST13         7.0000000
D0            0.00000300 sec
D1            1.50000000 sec
D6            0.07142857 sec
D16           0.00020000 sec
IN0           0.00001990 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W
SFO1         500.1330008 MHz

======== CHANNEL f2 ========
NUC2                 13C
P3                  9.63 usec
PLW2         23.01399994 W
SFO2         125.7703648 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPNAM[4]      SMSQ10.100
GPNAM[5]      SMSQ10.100
GPNAM[6]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
GPZ4               15.00 %
```

*Macrocyclic Product **2.9c***







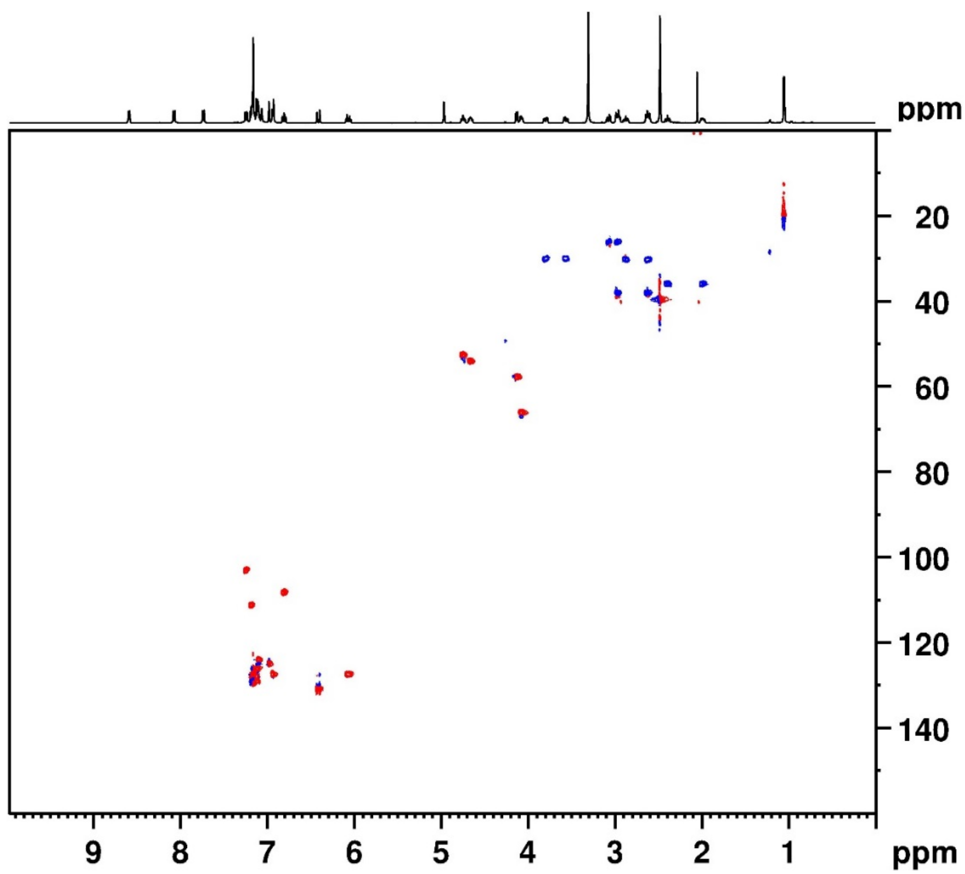
Current Data Parameters
NAME W-B2-3
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121110
Time 14.55
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019995 sec
L1 24

======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1325007 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz



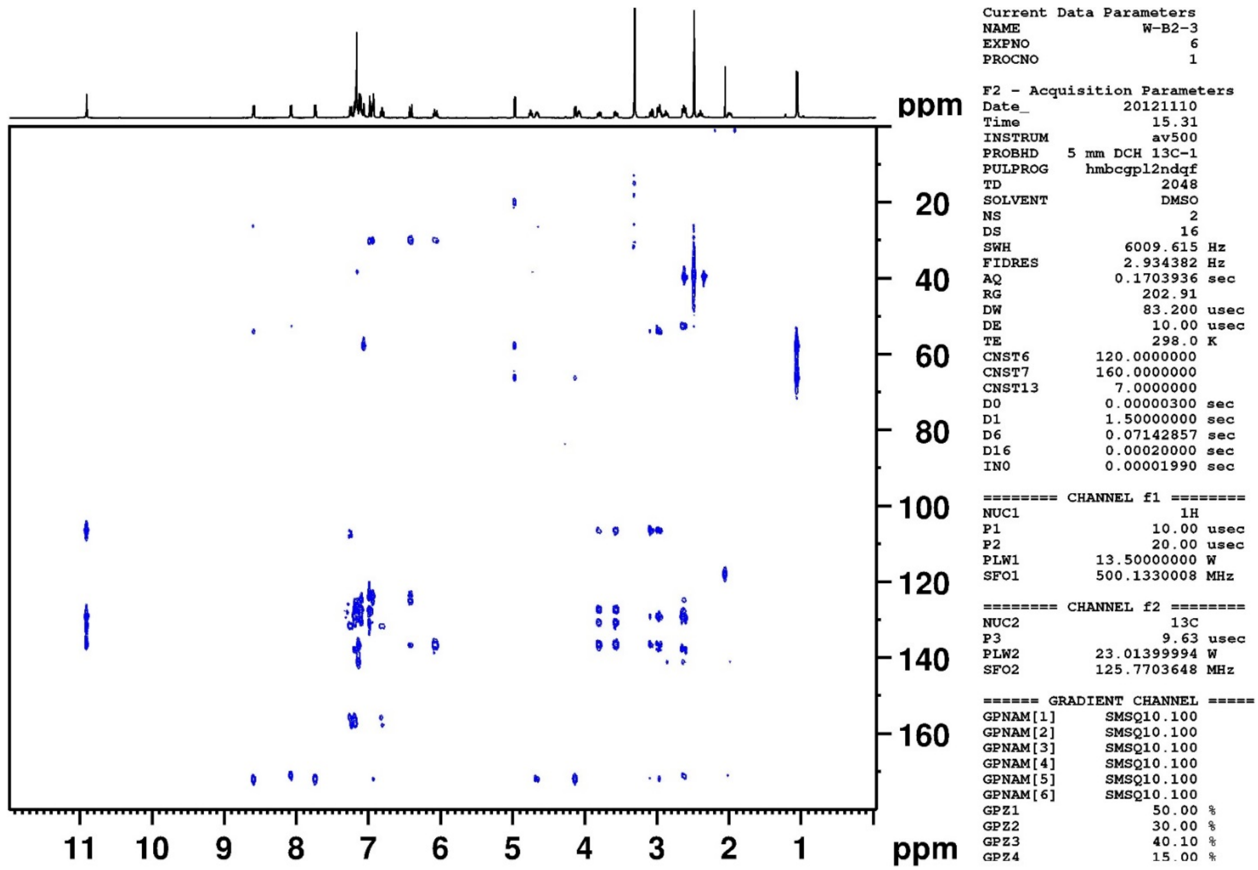
Current Data Parameters
NAME W-B2-3
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121110
Time 15.16
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS

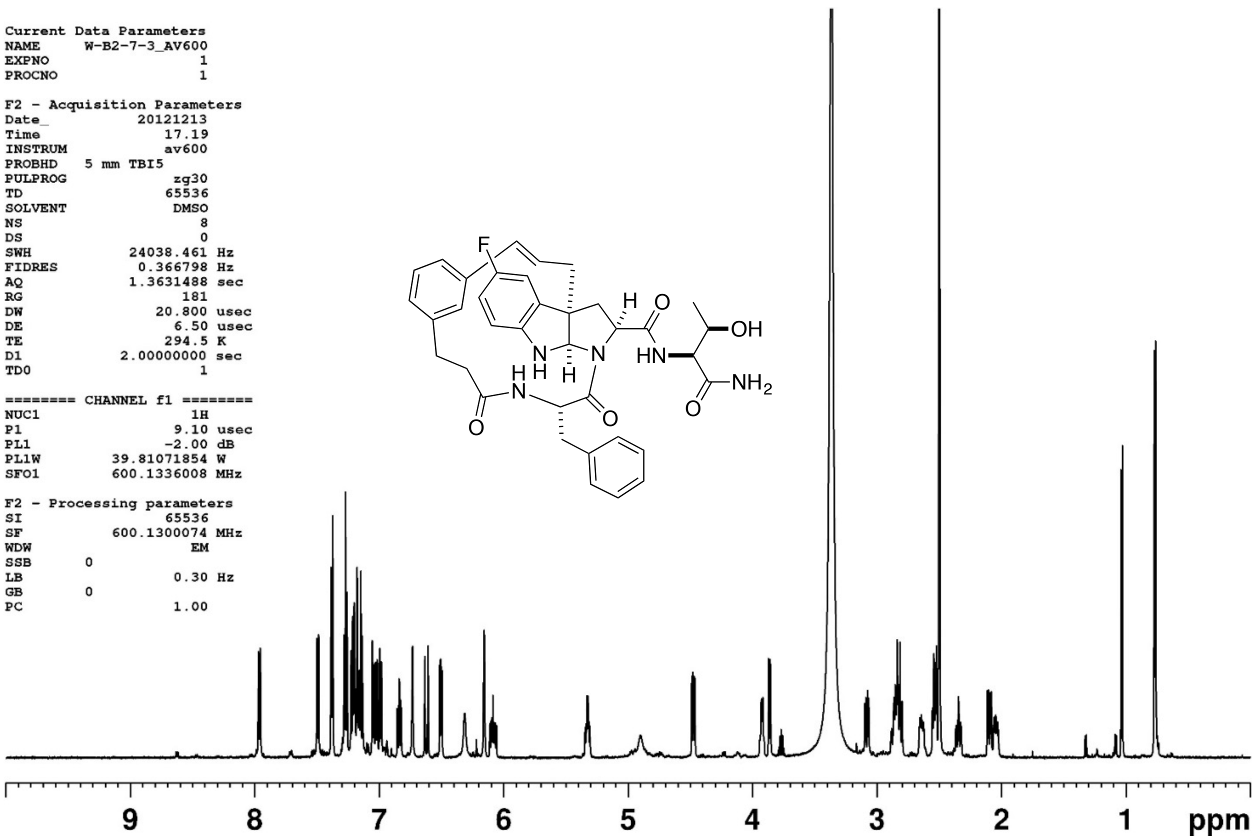
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W
SFO1 500.1325007 MHz

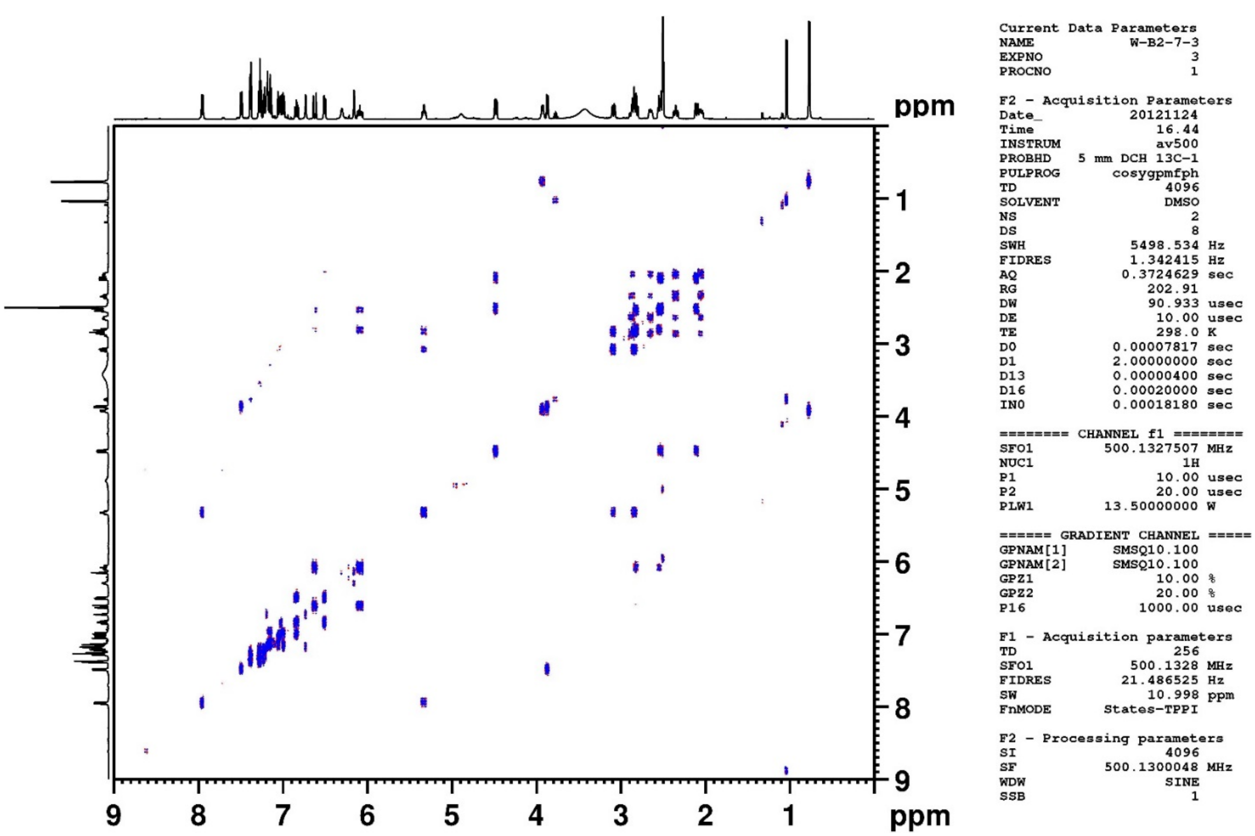
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
SFO2 125.7678496 MHz

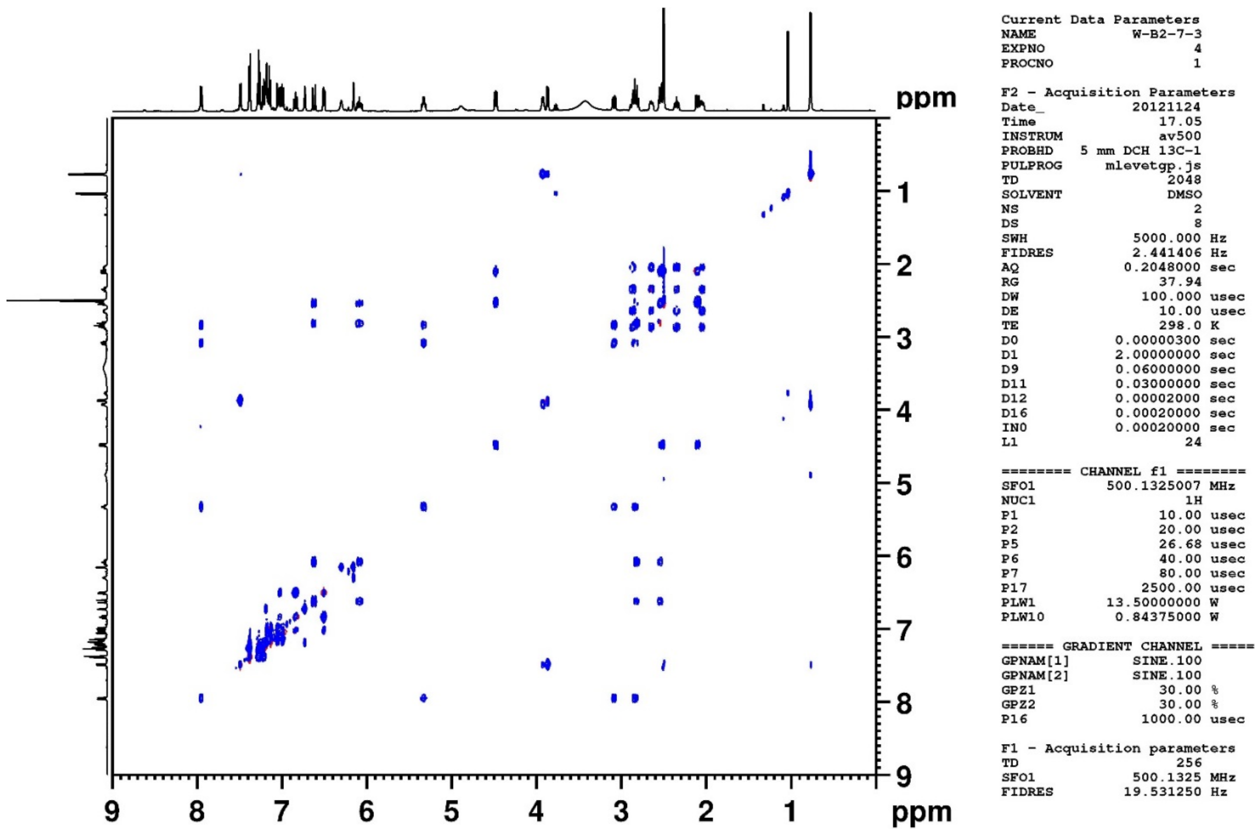
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %

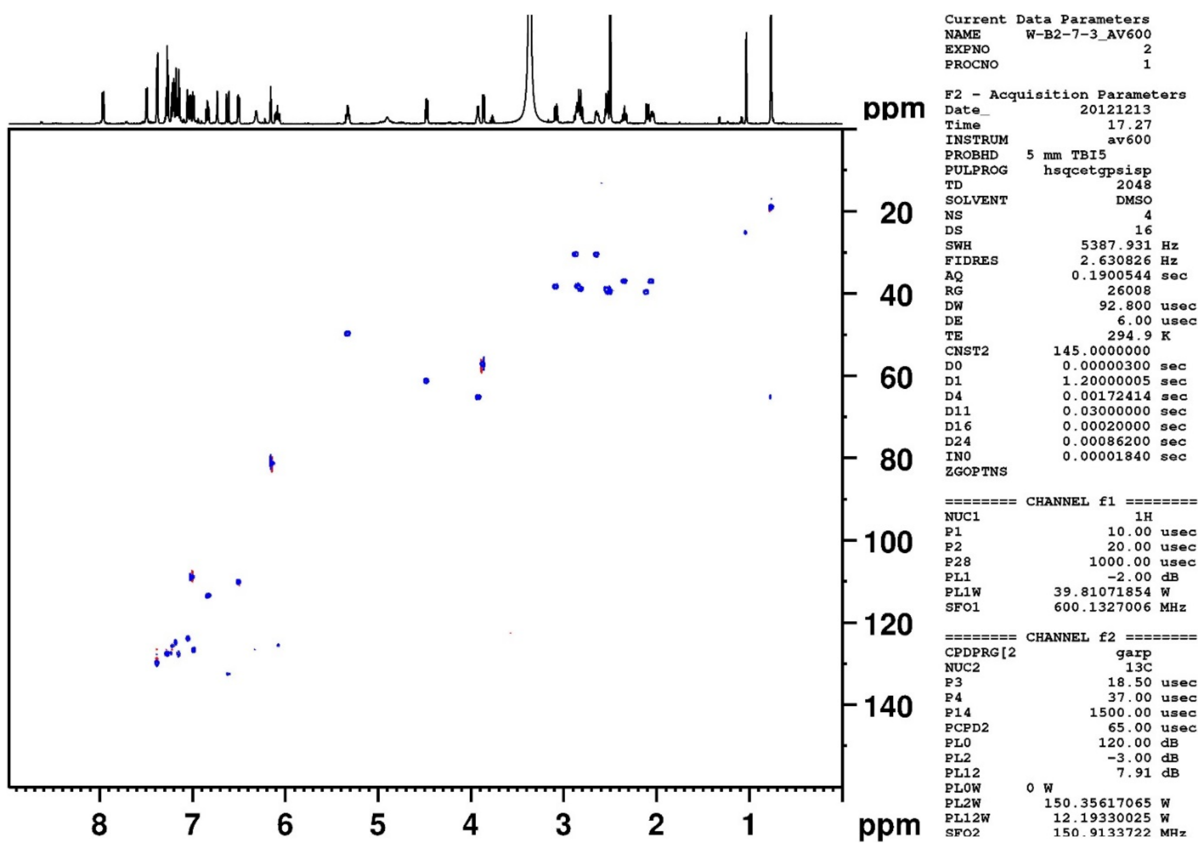

Current Data Parameters
NAME W-B2-3
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121110
Time 15.31
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %
ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1
ppm

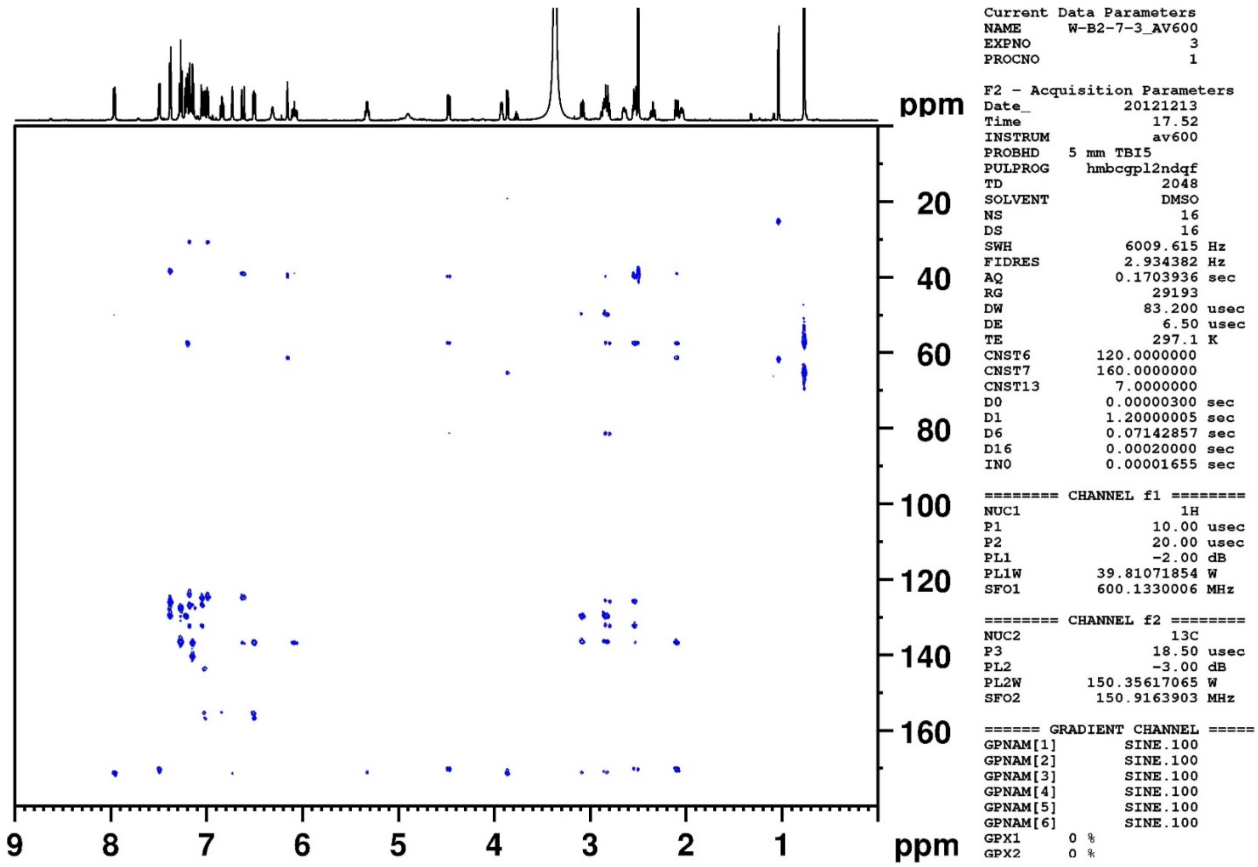
*Macrocyclic Product **2.9d***



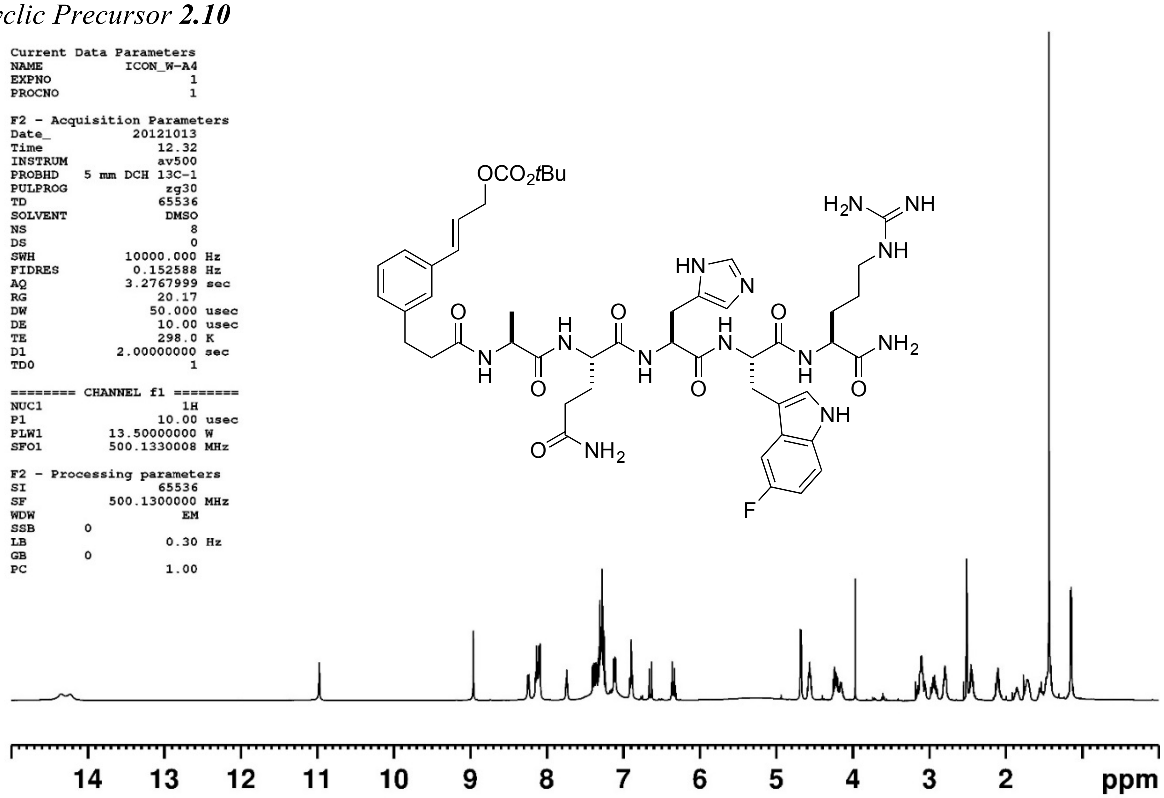


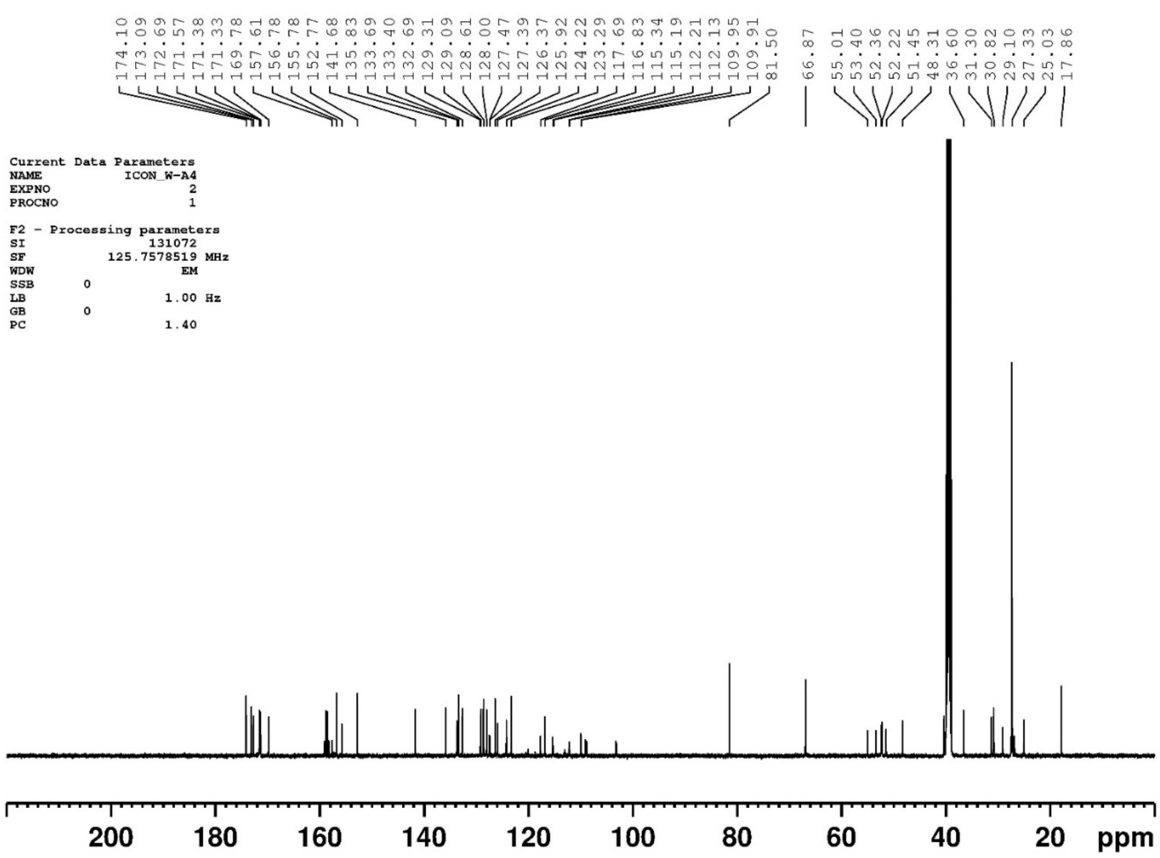

Current Data Parameters
NAME W-B2-7-3
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121124
Time 17.05
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
L1 24
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz
ppm
9 8 7 6 5 4 3 2 1 ppm
1 2 3 4 5 6 7 8 9


Current Data Parameters
NAME W-B2-7-3_AV600
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121213
Time 17.27
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 5387.931 Hz
FIDRES 2.630826 Hz
AQ 0.1900544 sec
RG 26008
DW 92.800 usec
DE 6.00 usec
TE 294.9 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00001840 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 18.50 usec
P4 37.00 usec
P14 1500.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.91 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 12.19330025 W
SFO2 150.9133722 MHz
ppm
8 7 6 5 4 3 2 1 ppm
20 40 60 80 100 120 140

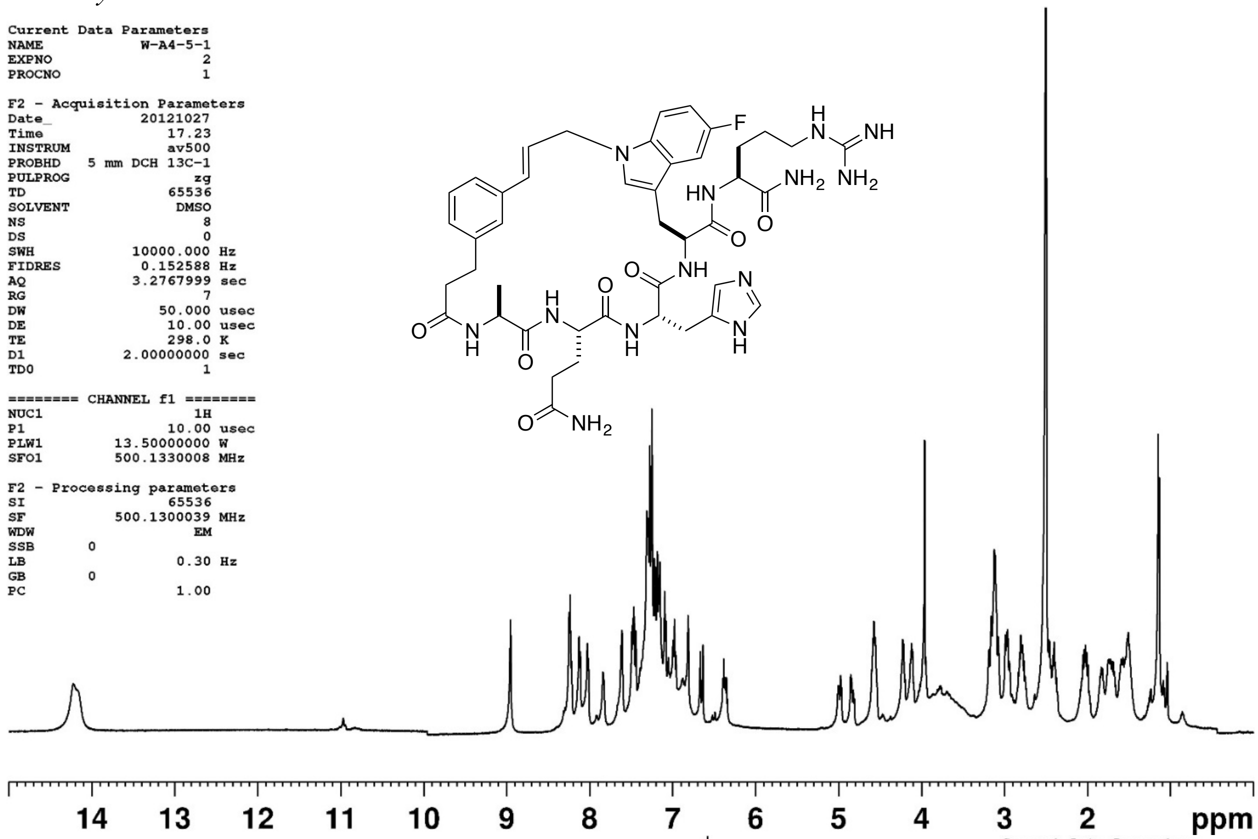

Current Data Parameters
NAME W-B2-7-3_AV600
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121213
Time 17.52
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 16
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 29193
DW 83.200 usec
DE 6.50 usec
TE 297.1 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001655 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1330006 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9163903 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPX1 0 %
GPX2 0 %
ppm
20
40
60
80
100
120
140
160
9
8
7
6
5
4
3
2
1
ppm

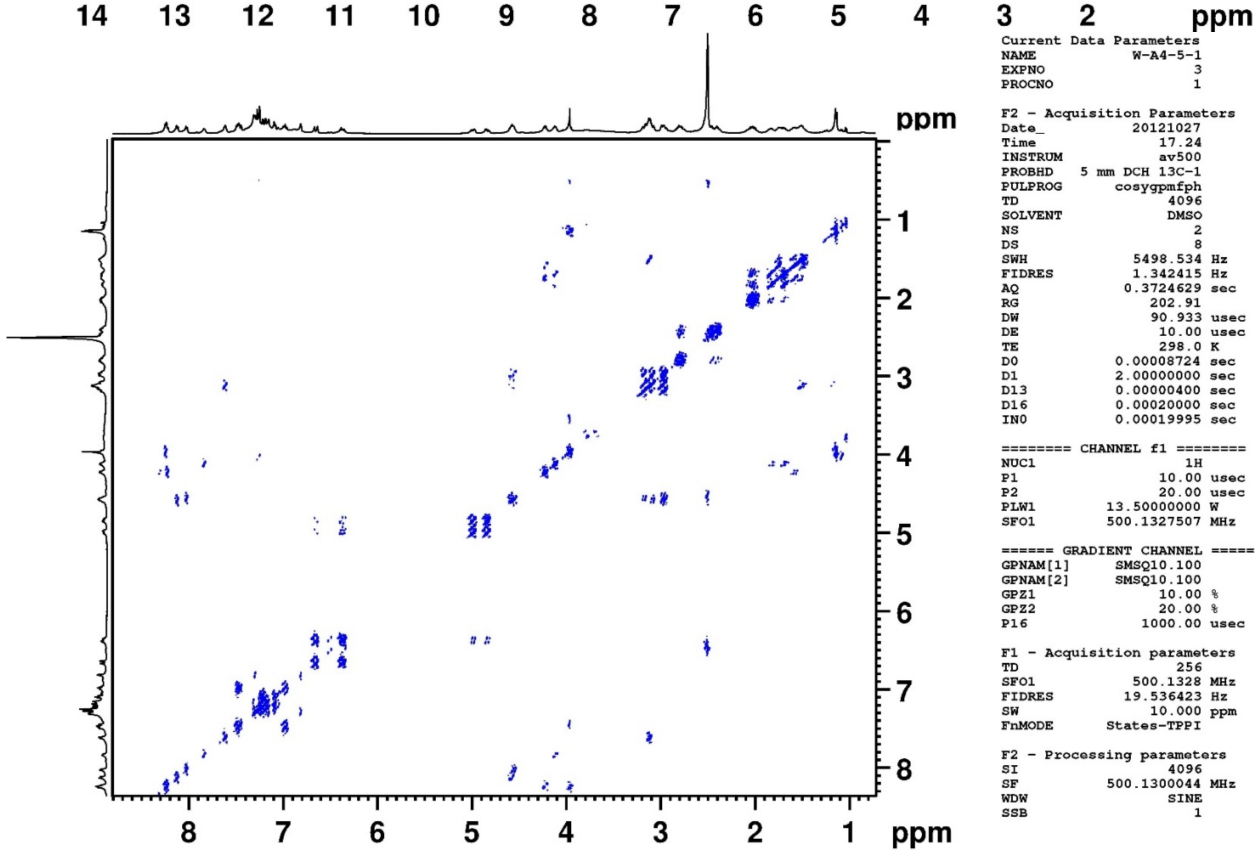
*Acyclic Precursor **2.10***

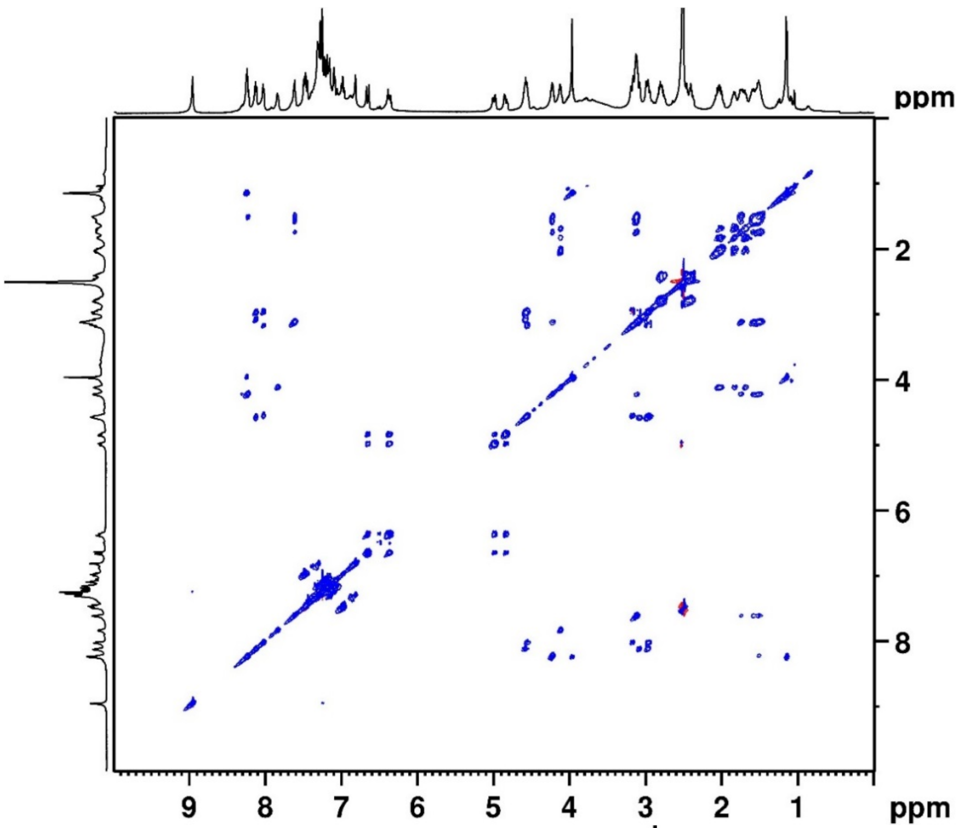




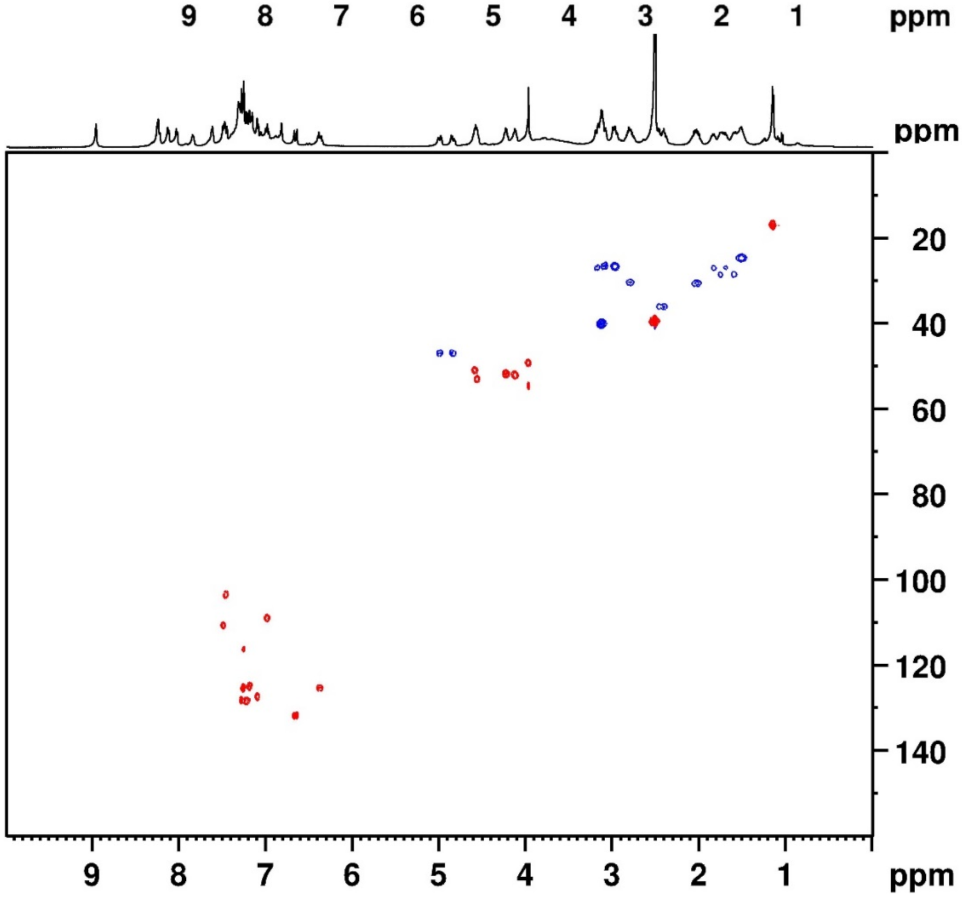
Macrocyclic Product ***2.11a***



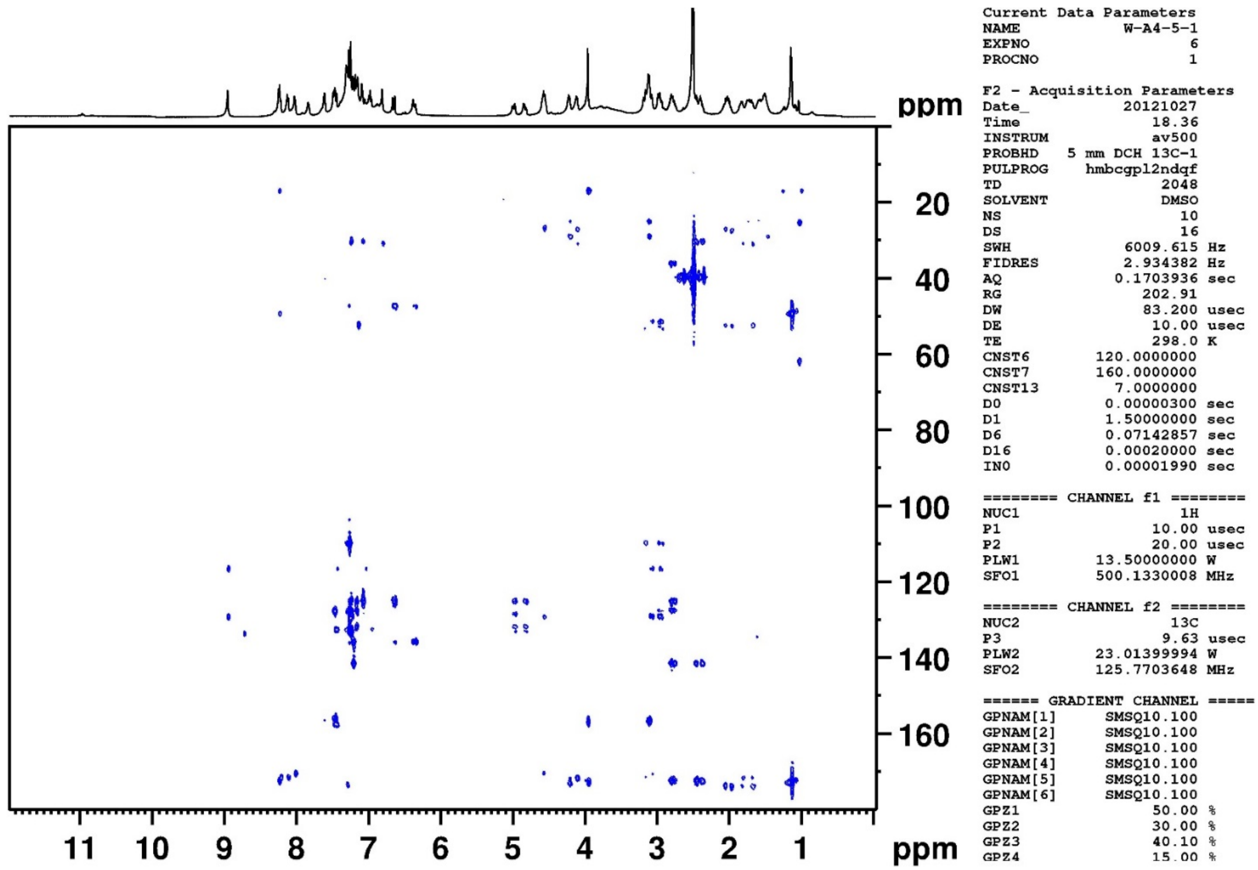




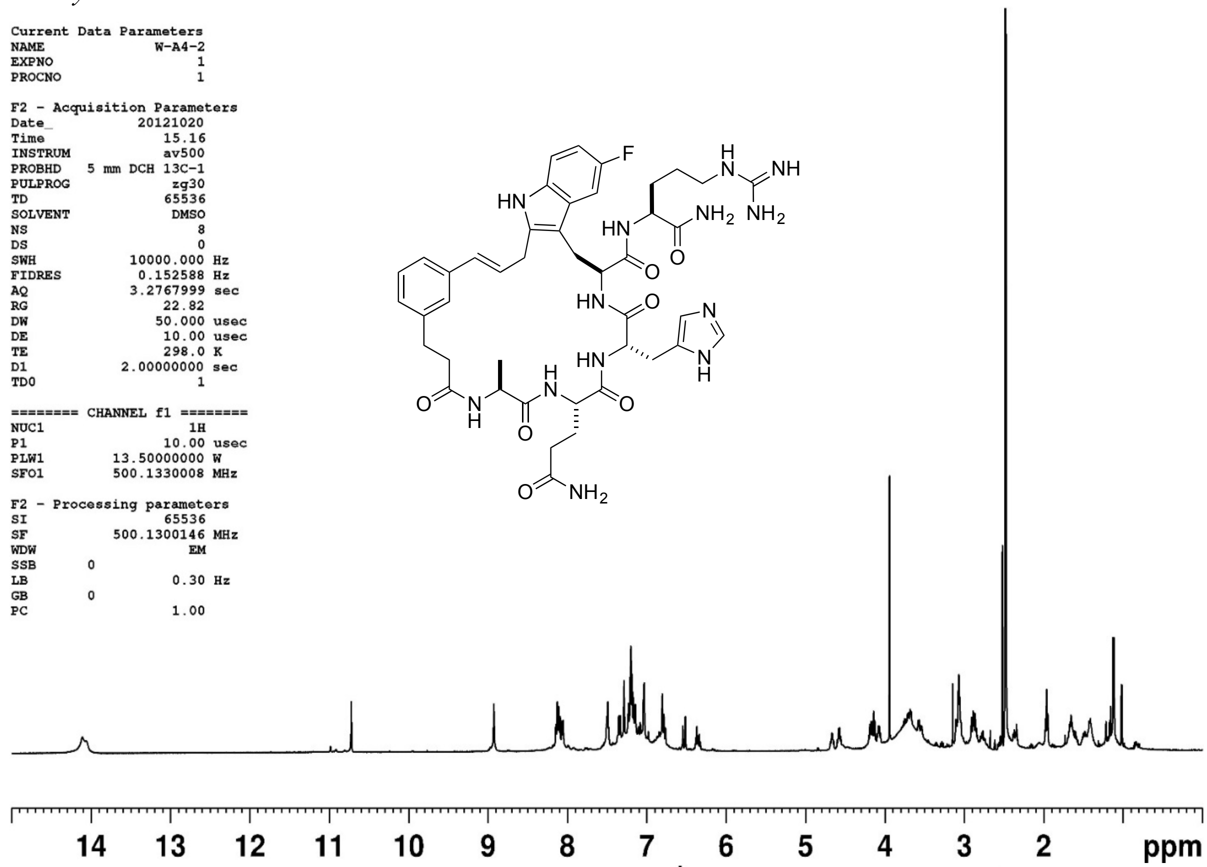

```
Current Data Parameters
NAME              W-A4-5-1
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_             20121027
Time                 17.45
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG       mlevetgp.js
TD                    2048
SOLVENT               DMSO
NS                       2
DS                       8
SWH               5000.000 Hz
FIDRES            2.441406 Hz
AQ               0.2048000 sec
RG                   37.94
DW                 100.000 usec
DE                   10.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              2.00000000 sec
D9              0.06000000 sec
D11             0.03000000 sec
D12             0.00002000 sec
D16             0.00020000 sec
IN0             0.00019995 sec
L1                      24

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.00 usec
P2                   20.00 usec
P5                   26.68 usec
P6                   40.00 usec
P7                   80.00 usec
P17                2500.00 usec
PLW1           13.50000000 W
PLW10           0.84375000 W
SFO1         500.1325007 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPZ1                 30.00 %
GPZ2                 30.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     256
SFO1              500.1325 MHz
FIDRES           19.536406 Hz
```

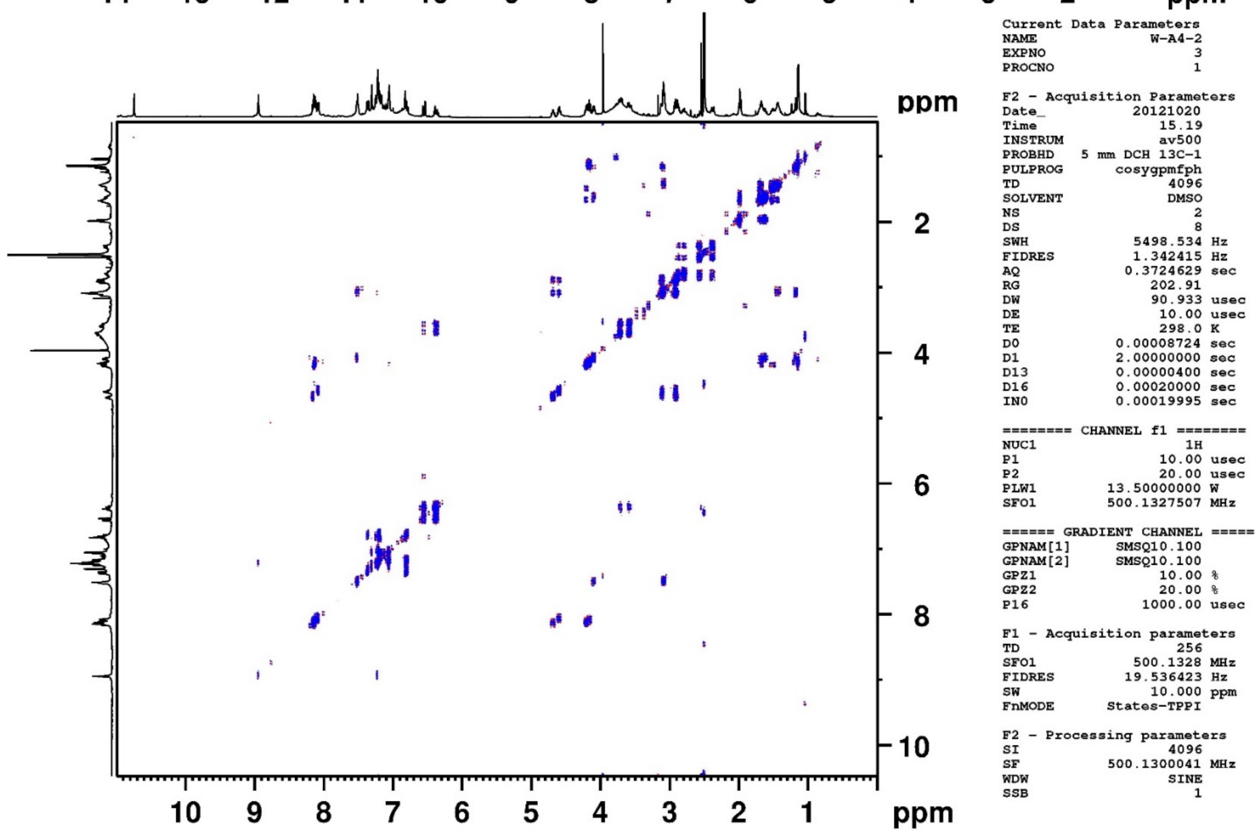


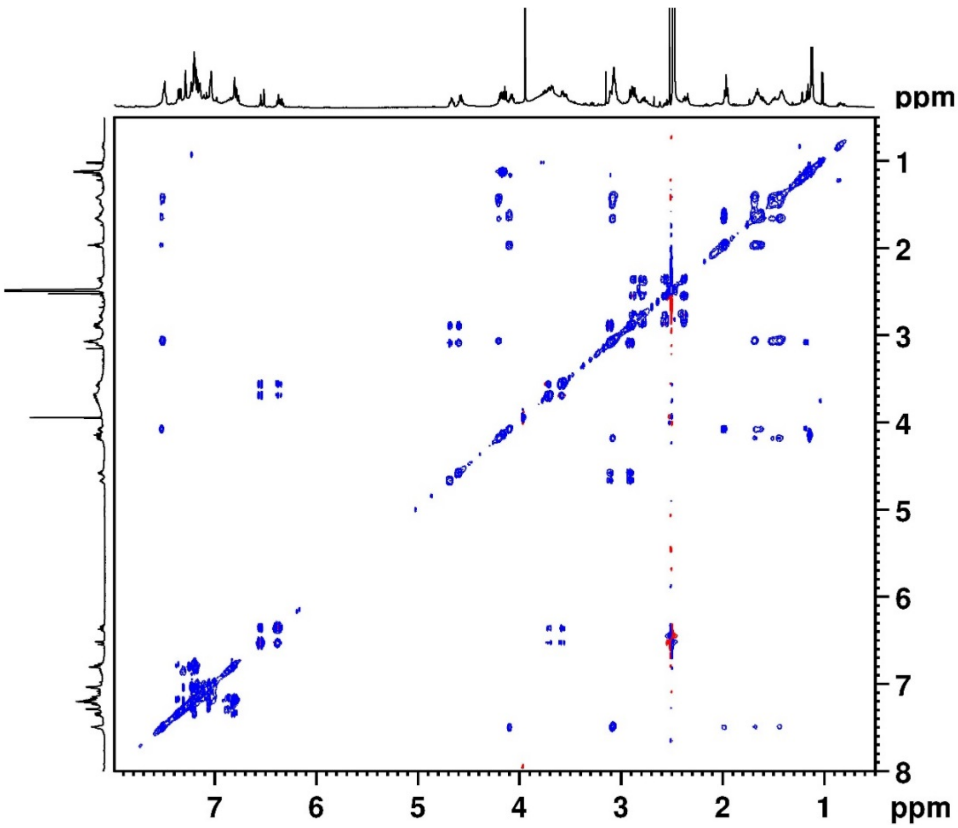

```
Current Data Parameters
NAME              W-A4-5-1
EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
Date_             20121027
Time                 18.06
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG        hsqcedetgp
TD                    2048
SOLVENT               DMSO
NS                       4
DS                      16
SWH               5000.000 Hz
FIDRES            2.441406 Hz
AQ               0.2048000 sec
RG                  202.91
DW                 100.000 usec
DE                   10.00 usec
TE                   298.0 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.50000000 sec
D4              0.00172414 sec
D11             0.03000000 sec
D13             0.00000400 sec
D16             0.00020000 sec
D21             0.00345000 sec
IN0             0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                    1H
P1                   10.00 usec
P2                   20.00 usec
P28       0 usec
PLW1           13.50000000 W
SFO1         500.1325007 MHz

======== CHANNEL f2 ========
CPDPRG[2              garp
NUC2                   13C
P3                    9.63 usec
P4                   19.26 usec
PCPD2                70.00 usec
PLW2           23.01399994 W
PLW12           0.43557000 W
SFO2         125.7678496 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                 80.00 %
```


ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-A4-5-1
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121027
Time 18.36
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 10
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

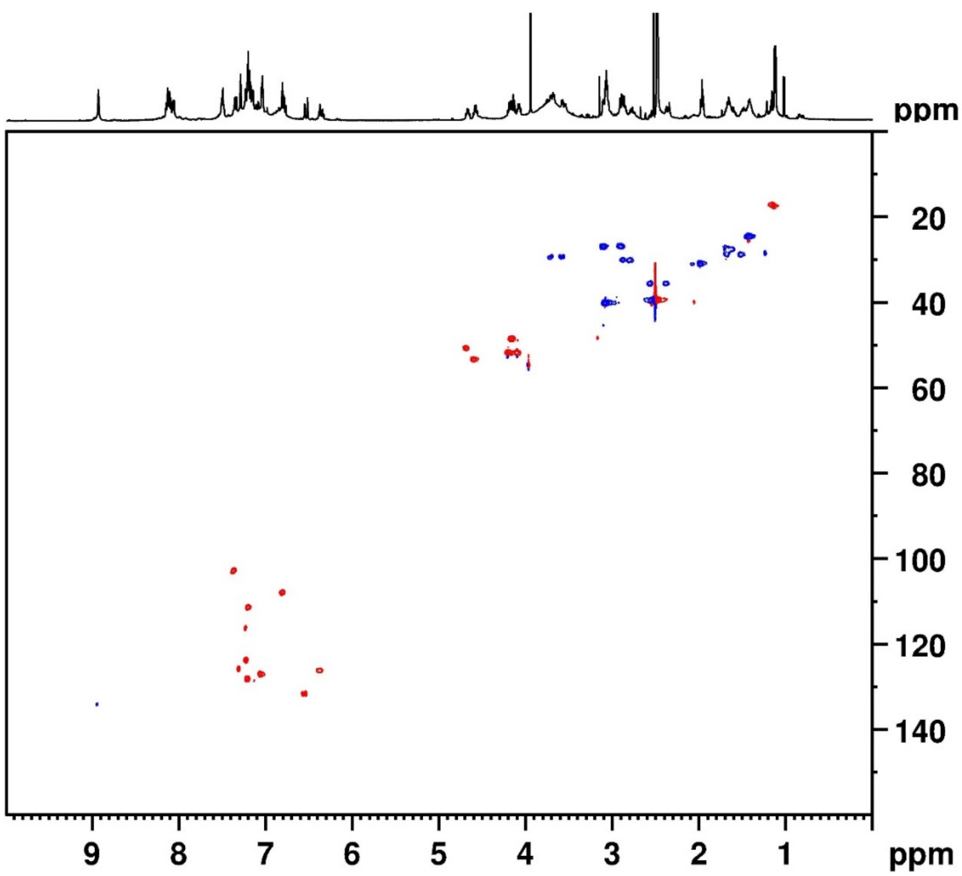
*Macrocyclic Product **2.11b***



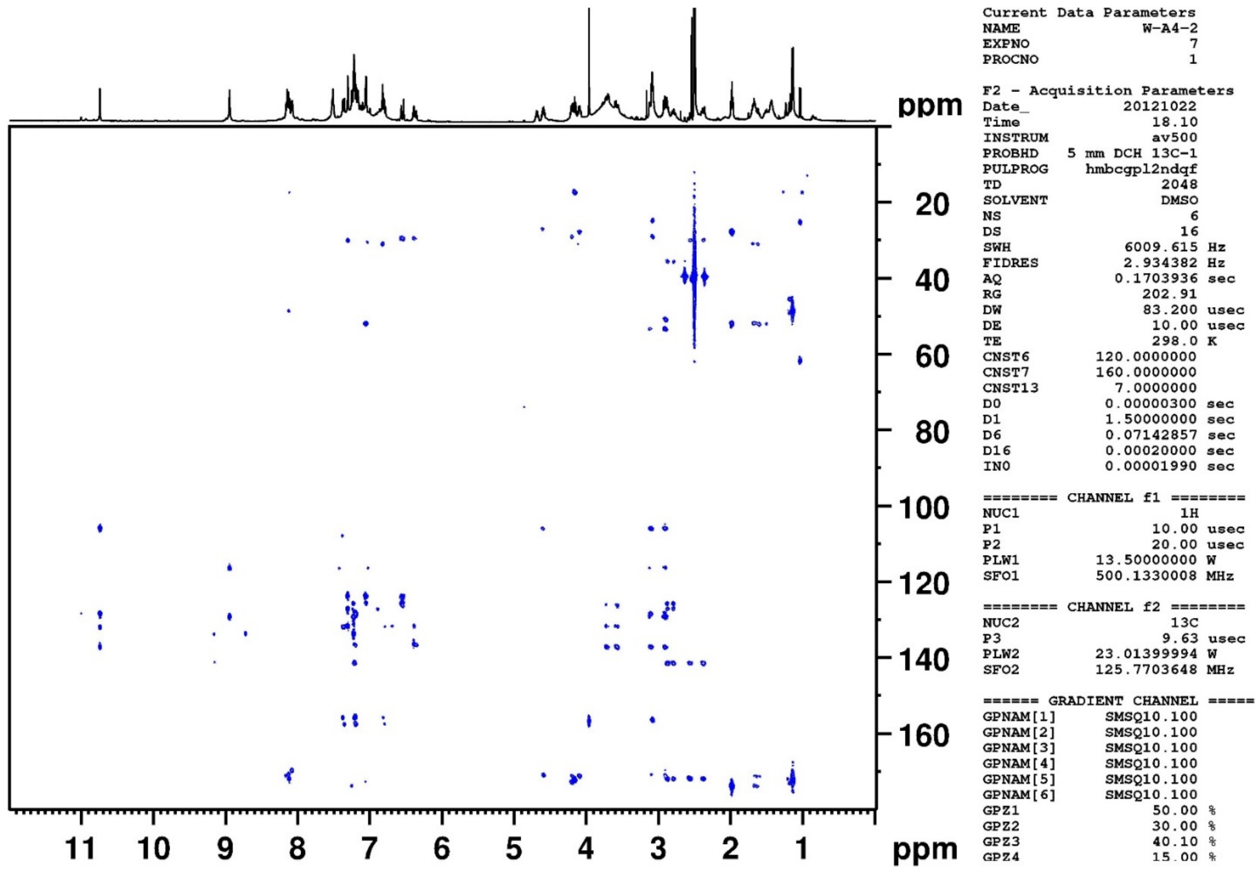




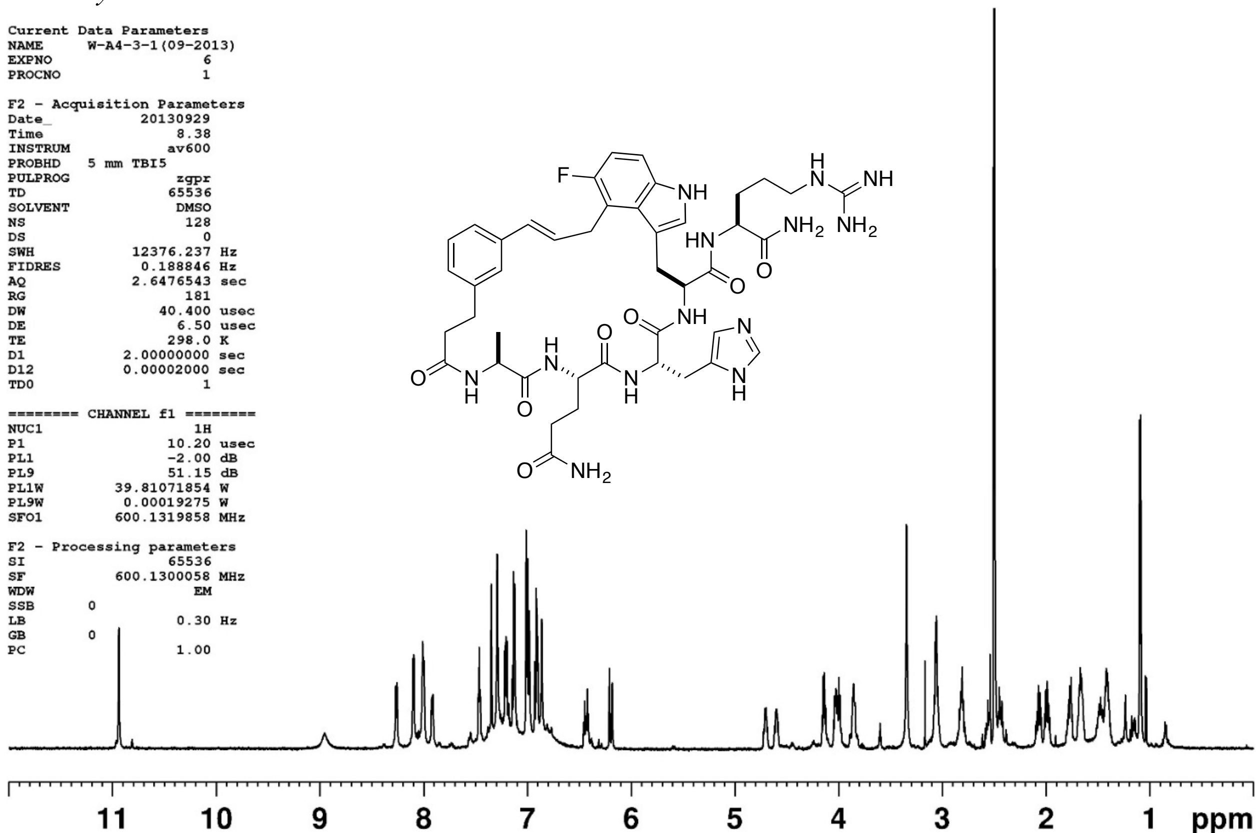
```
Current Data Parameters
NAME            W-A4-2
EXPNO                4
PROCNO               1

F2 - Acquisition Parameters
Date_         20121020
Time             15.40
INSTRUM          av500
PROBHD   5 mm DCH 13C-1
PULPROG    mlevetgp.js
TD                2048
SOLVENT           DMSO
NS                   2
DS                   8
SWH           4000.000 Hz
FIDRES        1.953125 Hz
AQ           0.2560000 sec
RG               37.94
DW             125.000 usec
DE               10.00 usec
TE               298.0 K
D0          0.00000300 sec
D1          2.00000000 sec
D9          0.06000000 sec
D11         0.03000000 sec
D12         0.00002000 sec
D16         0.00020000 sec
IN0         0.00024995 sec
L1                  24

======== CHANNEL f1 ========
NUC1                1H
P1               10.00 usec
P2               20.00 usec
P5               26.68 usec
P6               40.00 usec
P7               80.00 usec
P17            2500.00 usec
PLW1       13.50000000 W
PLW10       0.84375000 W
SFO1       500.1320005 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SINE.100
GPNAM[2]      SINE.100
GPZ1             30.00 %
GPZ2             30.00 %
P16            1000.00 usec

F1 - Acquisition parameters
TD                 256
SFO1           500.132 MHz
FIDRES       15.629138 Hz
```

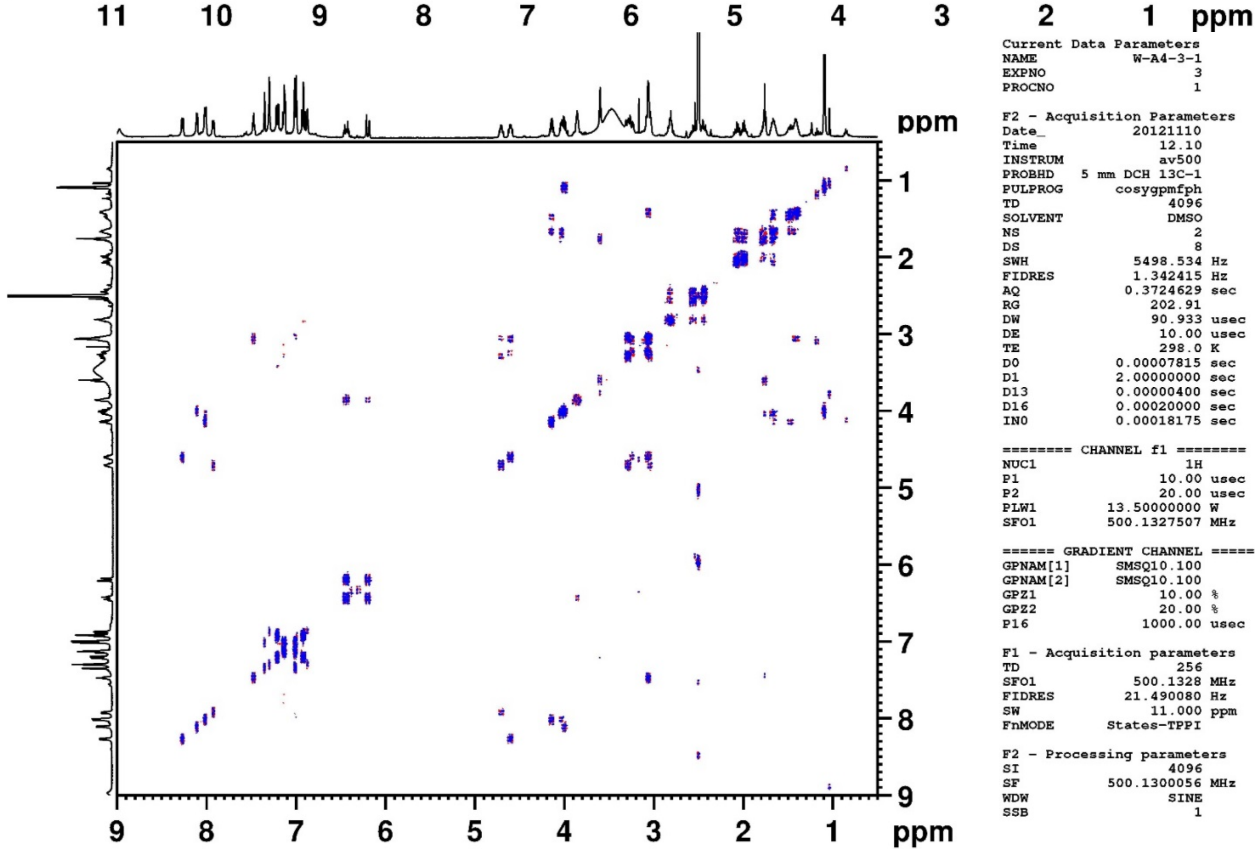


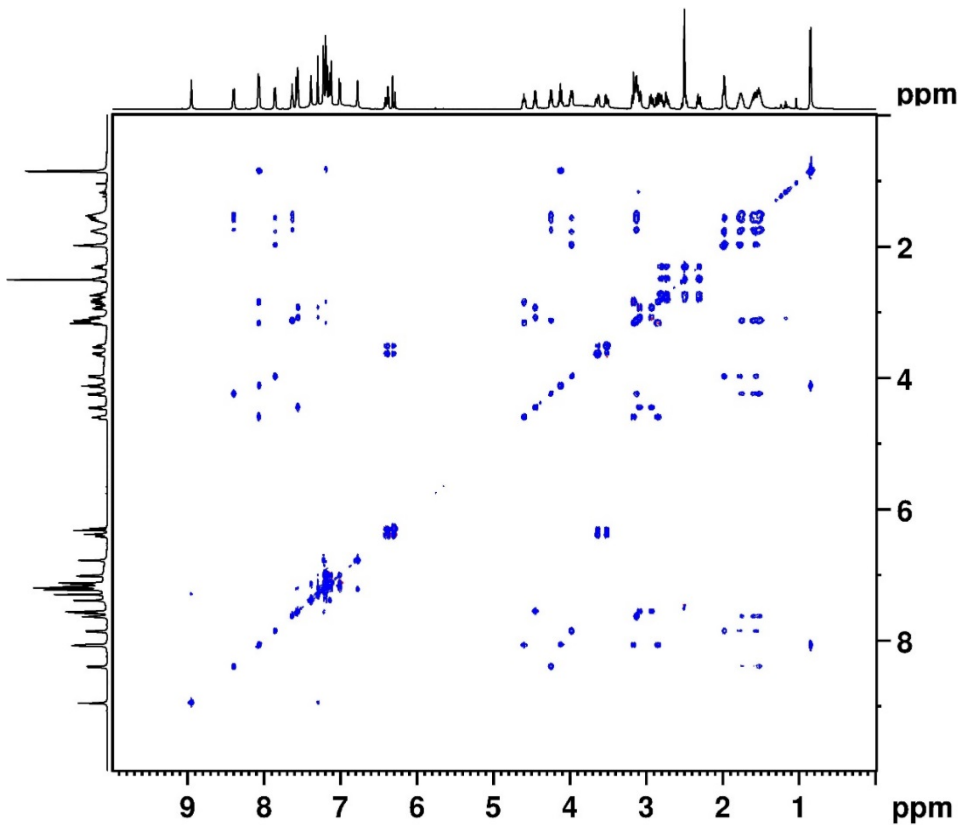
```
Current Data Parameters
NAME            W-A4-2
EXPNO                6
PROCNO               1

F2 - Acquisition Parameters
Date_         20121022
Time             17.40
INSTRUM          av500
PROBHD   5 mm DCH 13C-1
PULPROG     hsqcedetgp
TD                2048
SOLVENT           DMSO
NS                   4
DS                  16
SWH           5000.000 Hz
FIDRES        2.441406 Hz
AQ           0.2048000 sec
RG              202.91
DW             100.000 usec
DE               10.00 usec
TE               298.0 K
CNST2      145.0000000
D0          0.00000300 sec
D1          1.50000000 sec
D4          0.00172414 sec
D11         0.03000000 sec
D13         0.00000400 sec
D16         0.00020000 sec
D21         0.00345000 sec
IN0         0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                1H
P1               10.00 usec
P2               20.00 usec
P28      0 usec
PLW1       13.50000000 W
SFO1       500.1325007 MHz

======== CHANNEL f2 ========
CPDPRG[2          garp
NUC2               13C
P3                9.63 usec
P4               19.26 usec
PCPD2            70.00 usec
PLW2       23.01399994 W
PLW12       0.43557000 W
SFO2       125.7678496 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]     SMSQ10.100
GPNAM[2]     SMSQ10.100
GPZ1             80.00 %
```


ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME W-A4-2
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121022
Time 18.10
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 6
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

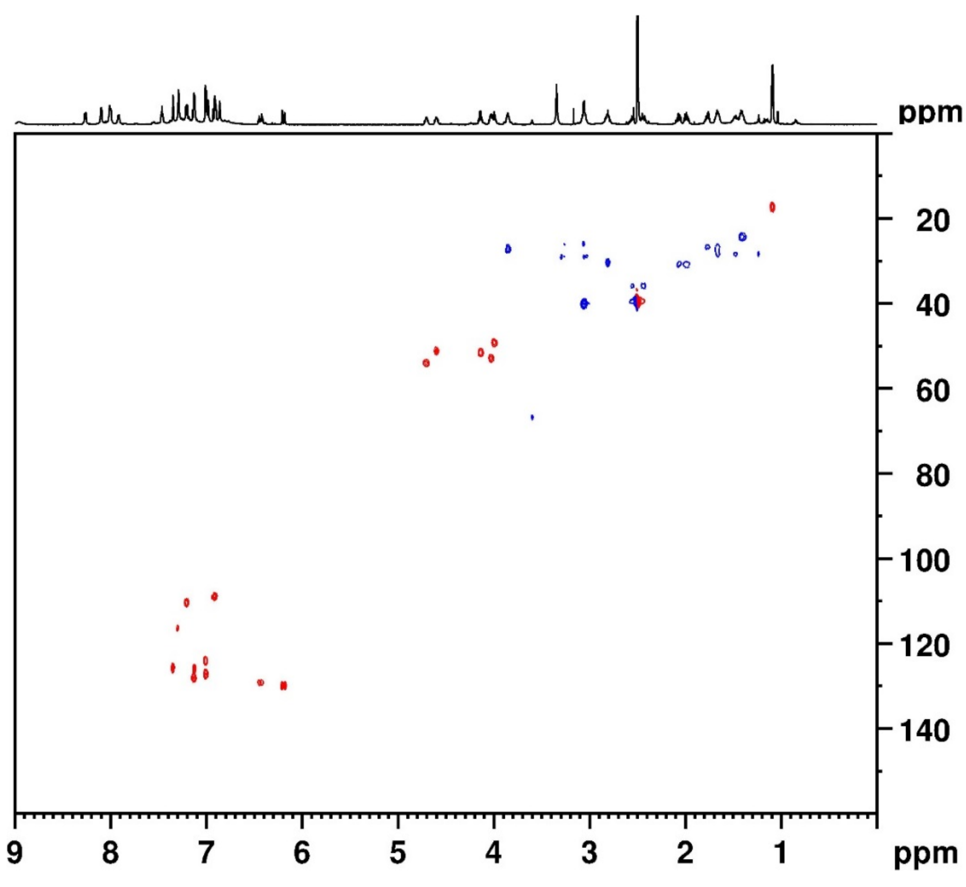
*Macrocyclic Product **2.11c***



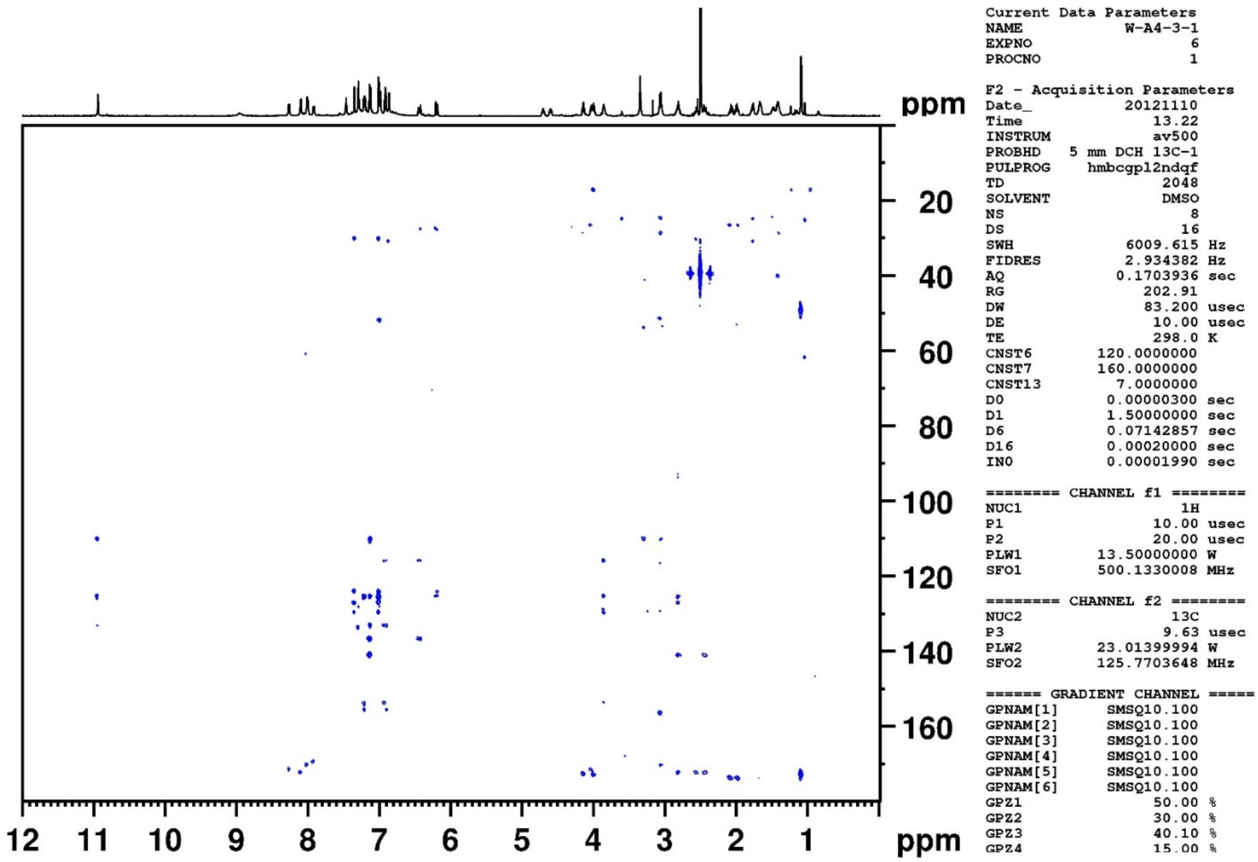





```
Current Data Parameters
NAME        W-A4-4-17(2)
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121023
Time               19.13
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG     mlevetgp.js
TD                  2048
SOLVENT             DMSO
NS                     2
DS                     8
SWH             5000.000 Hz
FIDRES          2.441406 Hz
AQ             0.2048000 sec
RG                 37.94
DW               100.000 usec
DE                 10.00 usec
TE                 298.0 K
D0            0.00000300 sec
D1            2.00000000 sec
D9            0.06000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D16           0.00020000 sec
IN0           0.00019995 sec
L1                    24

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
P5                 26.68 usec
P6                 40.00 usec
P7                 80.00 usec
P17              2500.00 usec
PLW1         13.50000000 W
PLW10         0.84375000 W
SFO1        500.1325007 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPZ1               30.00 %
GPZ2               30.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   256
SFO1            500.1325 MHz
FIDRES         19.536406 Hz
```

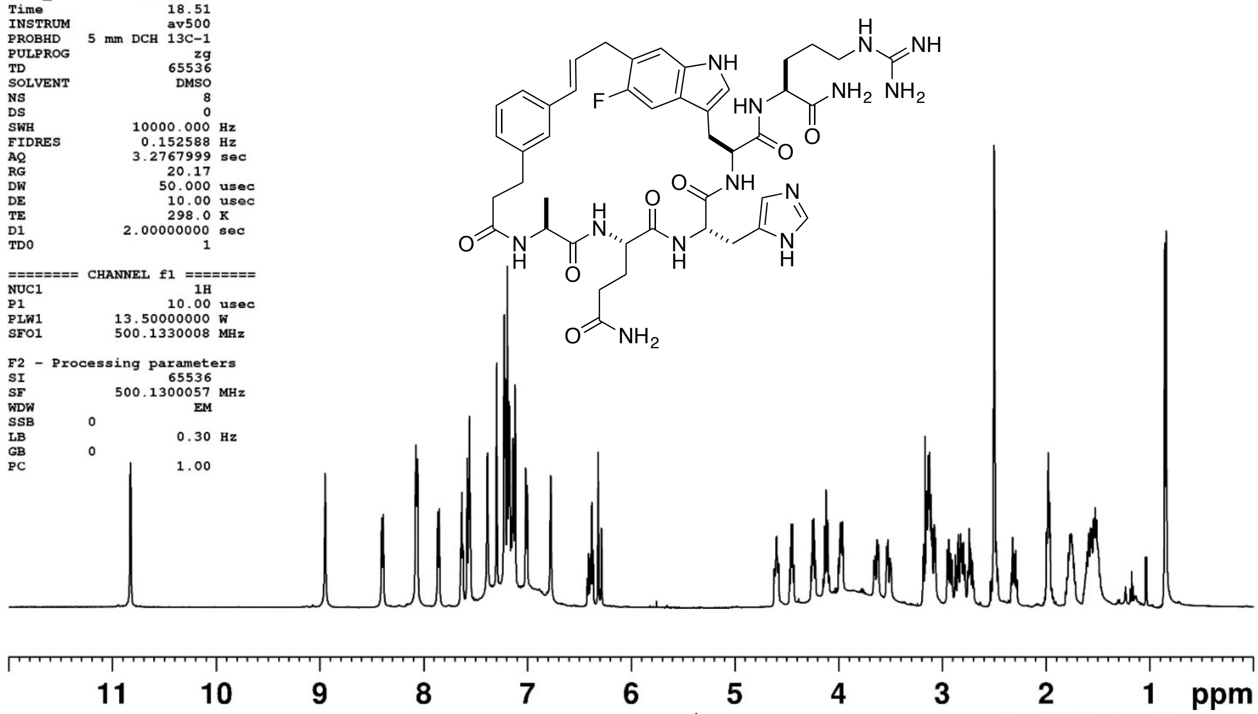


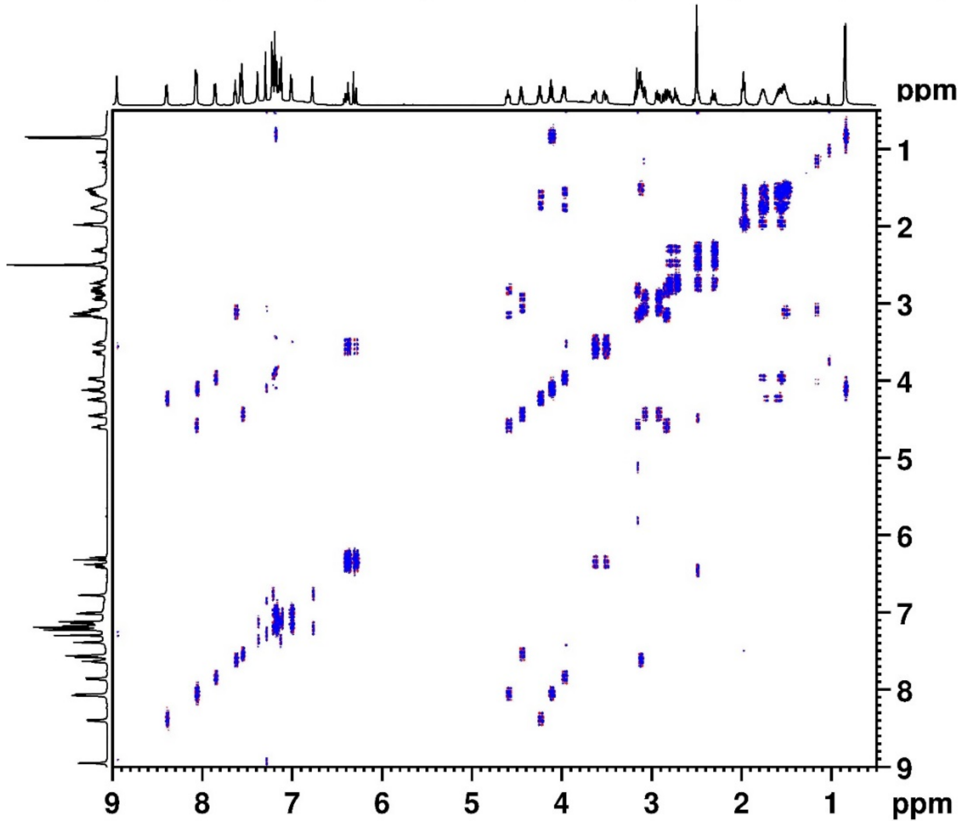

```
Current Data Parameters
NAME            W-A4-3-1
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121110
Time               12.52
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG       hsqcedetgp
TD                  2048
SOLVENT             DMSO
NS                     4
DS                    16
SWH             5000.000 Hz
FIDRES          2.441406 Hz
AQ             0.2048000 sec
RG                202.91
DW               100.000 usec
DE                 10.00 usec
TE                 298.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.50000000 sec
D4            0.00172414 sec
D11           0.03000000 sec
D13           0.00000400 sec
D16           0.00020000 sec
D21           0.00345000 sec
IN0           0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
P28       0 usec
PLW1         13.50000000 W
SFO1        500.1325007 MHz

======== CHANNEL f2 ========
CPDPRG[2            garp
NUC2                 13C
P3                  9.63 usec
P4                 19.26 usec
PCPD2              70.00 usec
PLW2         23.01399994 W
PLW12         0.43557000 W
SFO2        125.7678496 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
```


Current Data Parameters
NAME W-A4-3-1
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121110
Time 13.22
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %
ppm
20
40
60
80
100
120
140
160
12 11 10 9 8 7 6 5 4 3 2 1 ppm

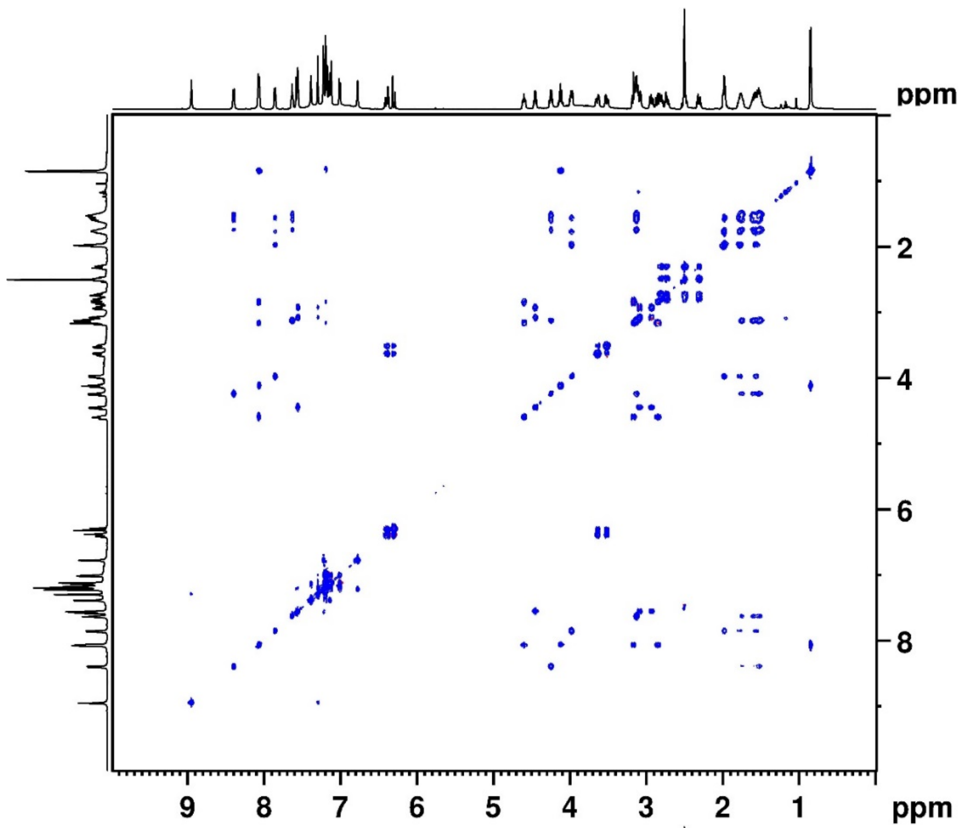
Macrocyclic Product ***2.11d***

```
Current Data Parameters
NAME        W-A4-4-17(2)
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121023
Time               18.51
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG               zg
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     0
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 20.17
DW                50.000 usec
DE                 10.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
PLW1         13.50000000 W
SFO1         500.1330008 MHz

F2 - Processing parameters
SI                 65536
SF           500.1300057 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```






```
Current Data Parameters
NAME        W-A4-4-17(2)
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121023
Time               18.52
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG       cosygpmfph
TD                  4096
SOLVENT             DMSO
NS                     2
DS                     8
SWH             5498.534 Hz
FIDRES          1.342415 Hz
AQ             0.3724629 sec
RG                202.91
DW                90.933 usec
DE                 10.00 usec
TE                 298.0 K
D0            0.00008724 sec
D1            2.00000000 sec
D13           0.00000400 sec
D16           0.00020000 sec
IN0           0.00019995 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W
SFO1         500.1327507 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               10.00 %
GPZ2               20.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   256
SFO1            500.1328 MHz
FIDRES         19.536423 Hz
SW                10.000 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                  4096
SF           500.1300135 MHz
WDW                 SINE
SSB                    1
```



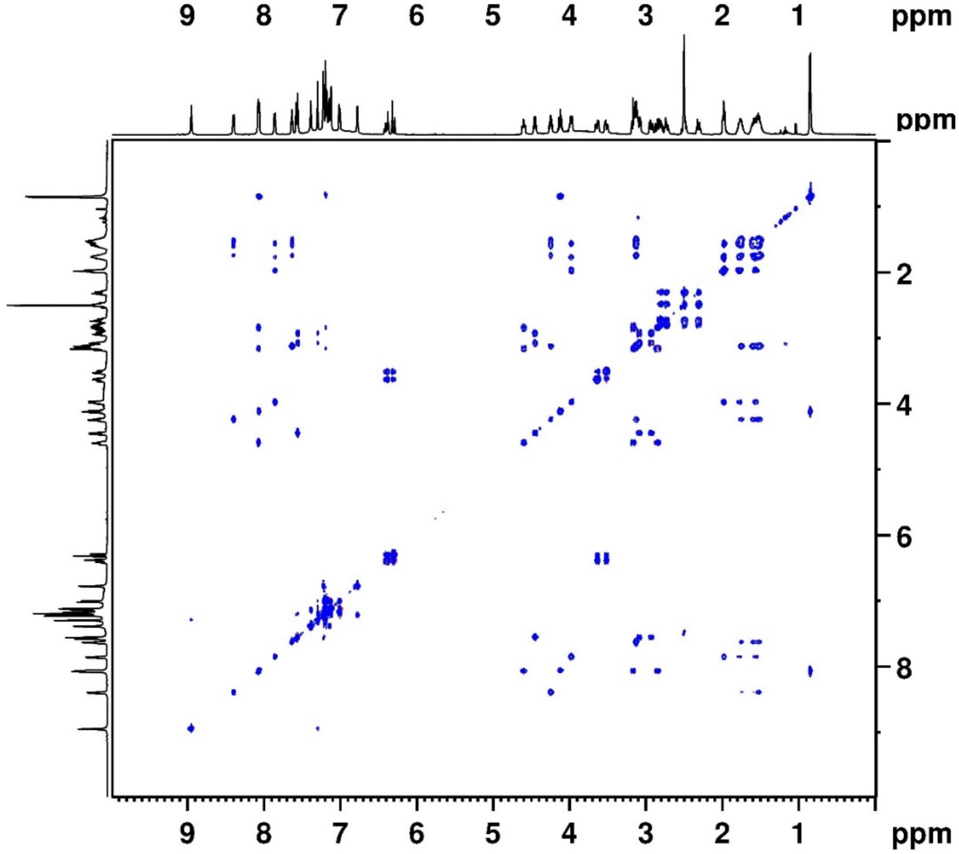
Current Data Parameters
NAME W-A4-4-17(2)
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121023
Time 19.13
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019995 sec
L1 24

======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1325007 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz



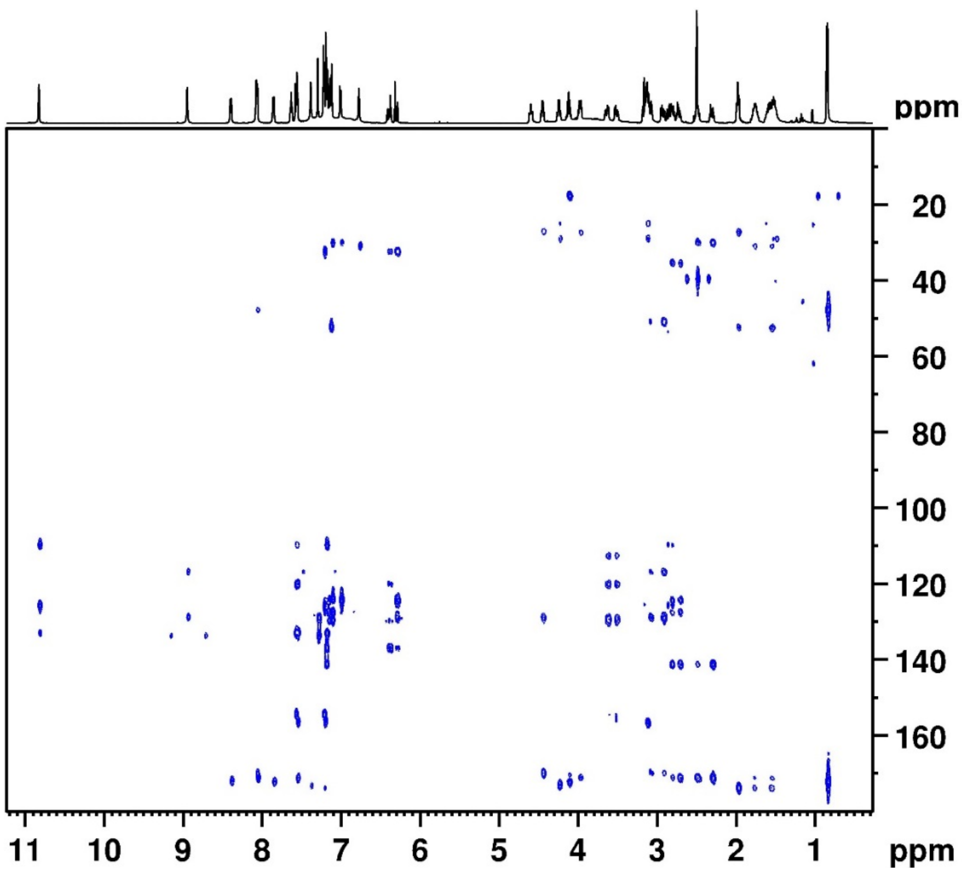
Current Data Parameters
NAME W-A4-4-17(2)
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121023
Time 19.13
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019995 sec
L1 24

======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1325007 MHz

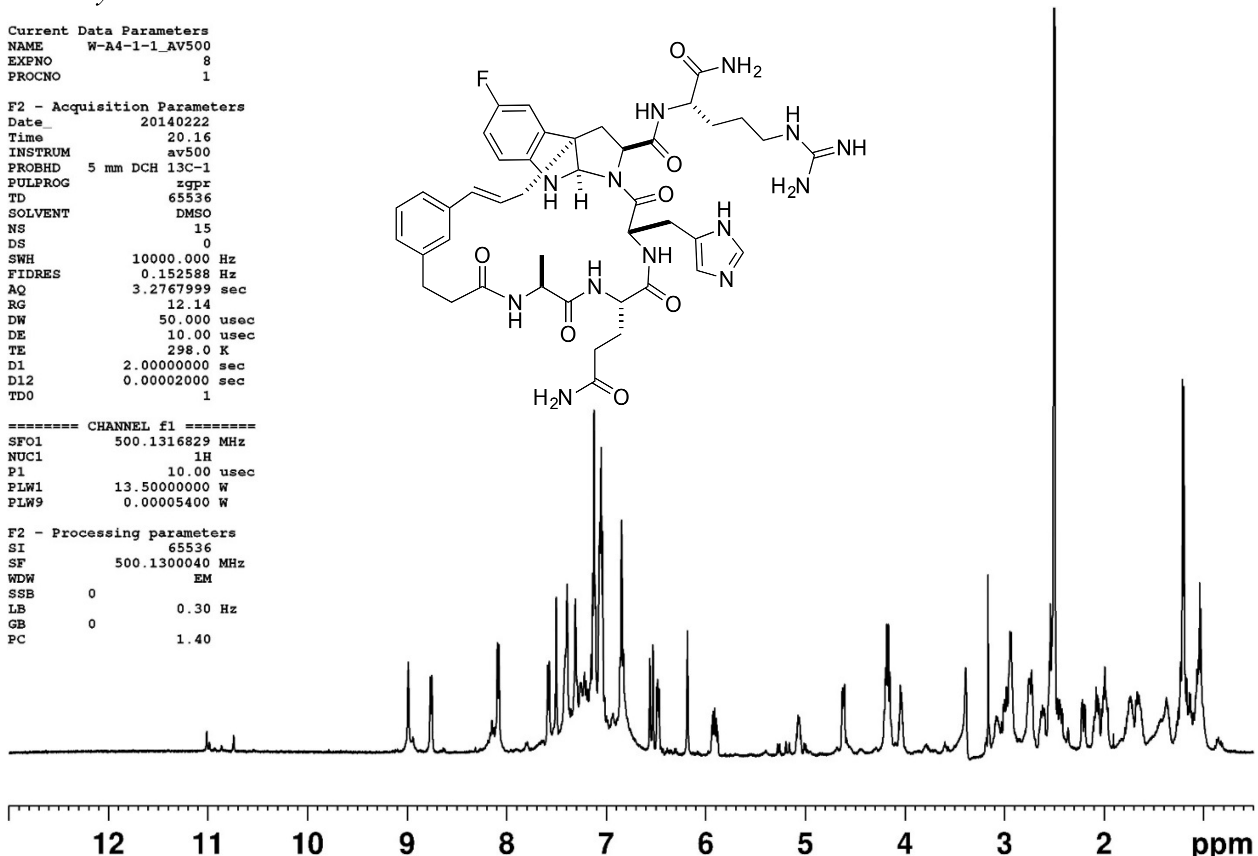
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec

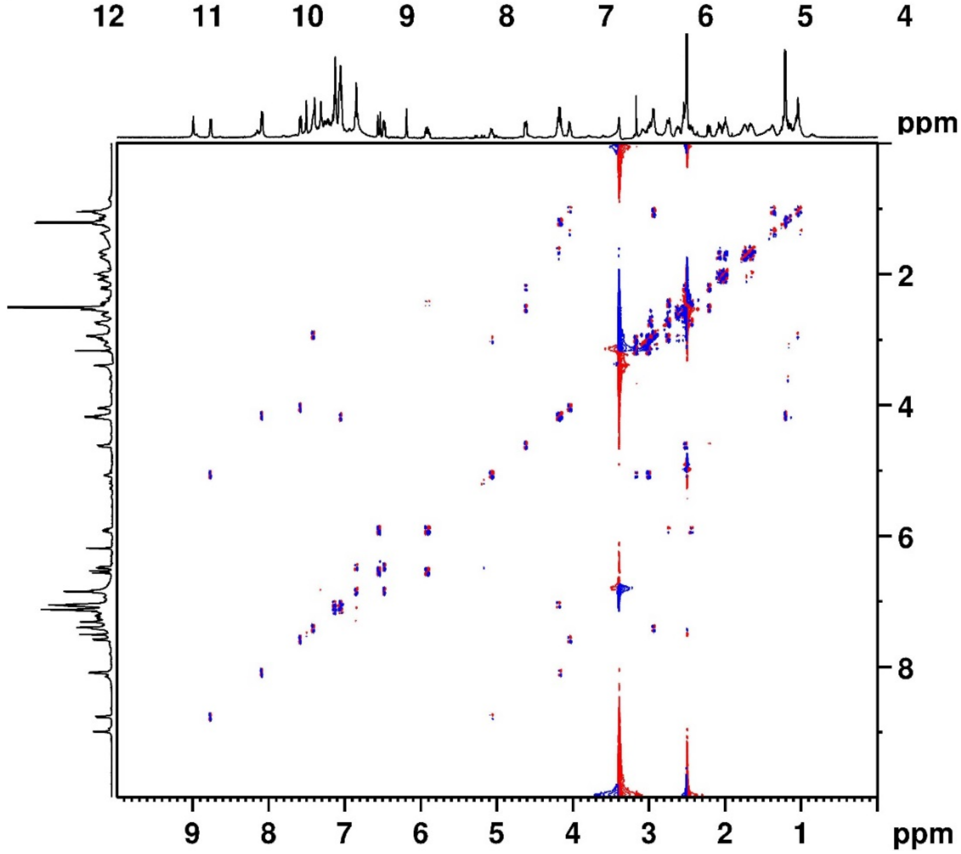
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz

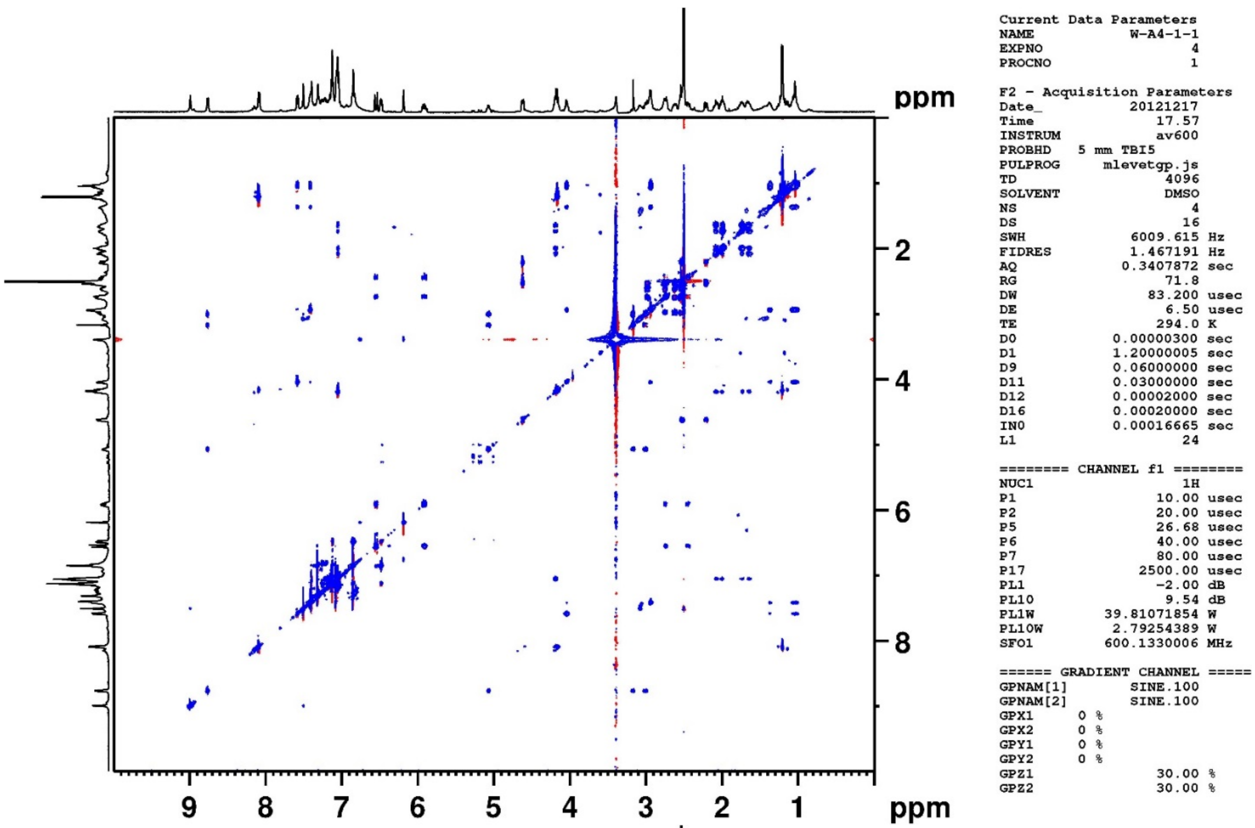


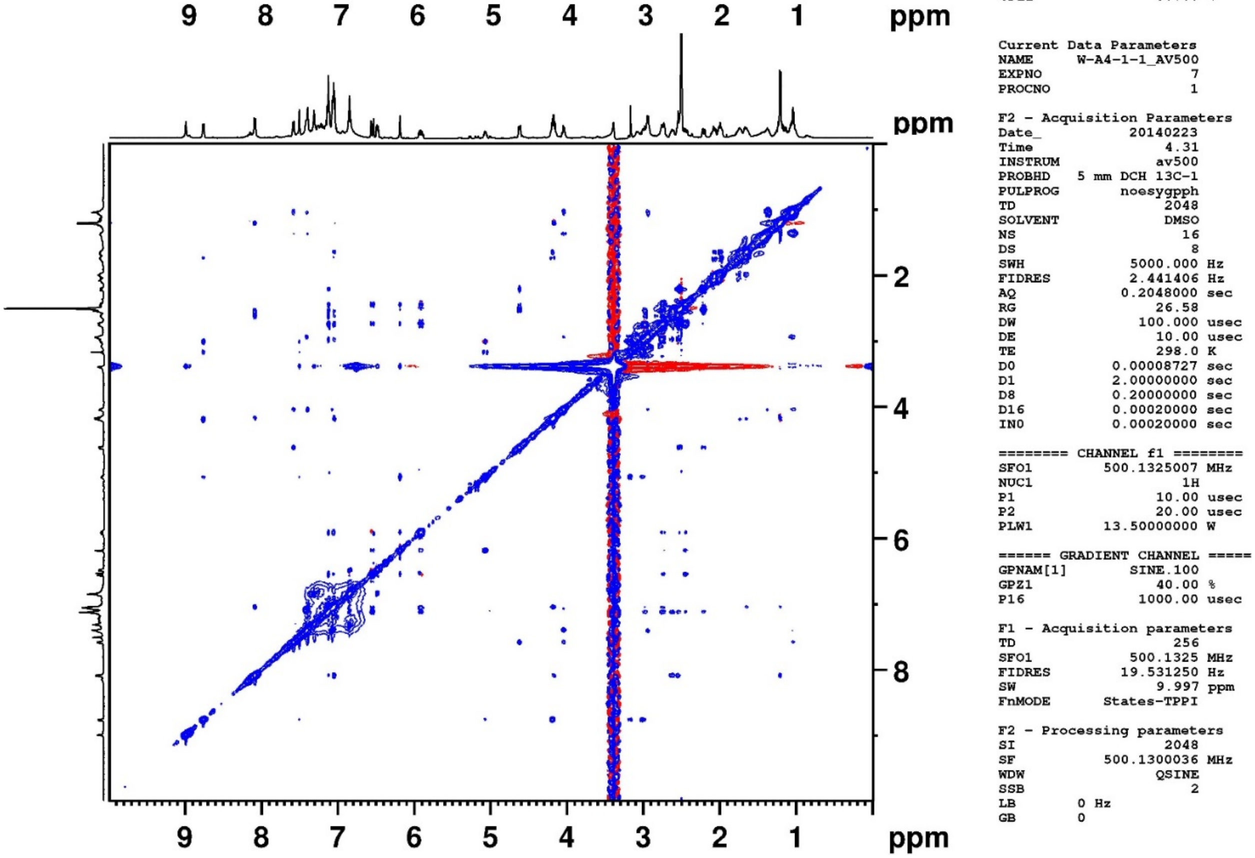

```
Current Data Parameters
NAME        W-A4-4-17(2)
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121023
Time               19.49
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG     hmbcgpl2ndqf
TD                  2048
SOLVENT             DMSO
NS                     6
DS                    16
SWH             6009.615 Hz
FIDRES          2.934382 Hz
AQ             0.1703936 sec
RG                202.91
DW                83.200 usec
DE                 10.00 usec
TE                 298.0 K
CNST6        120.0000000
CNST7        160.0000000
CNST13         7.0000000
D0            0.00000300 sec
D1            1.50000000 sec
D6            0.07142857 sec
D16           0.00020000 sec
IN0           0.00001990 sec

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
PLW1         13.50000000 W
SFO1         500.1330008 MHz

======== CHANNEL f2 ========
NUC2                 13C
P3                  9.63 usec
PLW2         23.01399994 W
SFO2         125.7703648 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPNAM[3]      SMSQ10.100
GPNAM[4]      SMSQ10.100
GPNAM[5]      SMSQ10.100
GPNAM[6]      SMSQ10.100
GPZ1               50.00 %
GPZ2               30.00 %
GPZ3               40.10 %
GPZ4               15.00 %
```

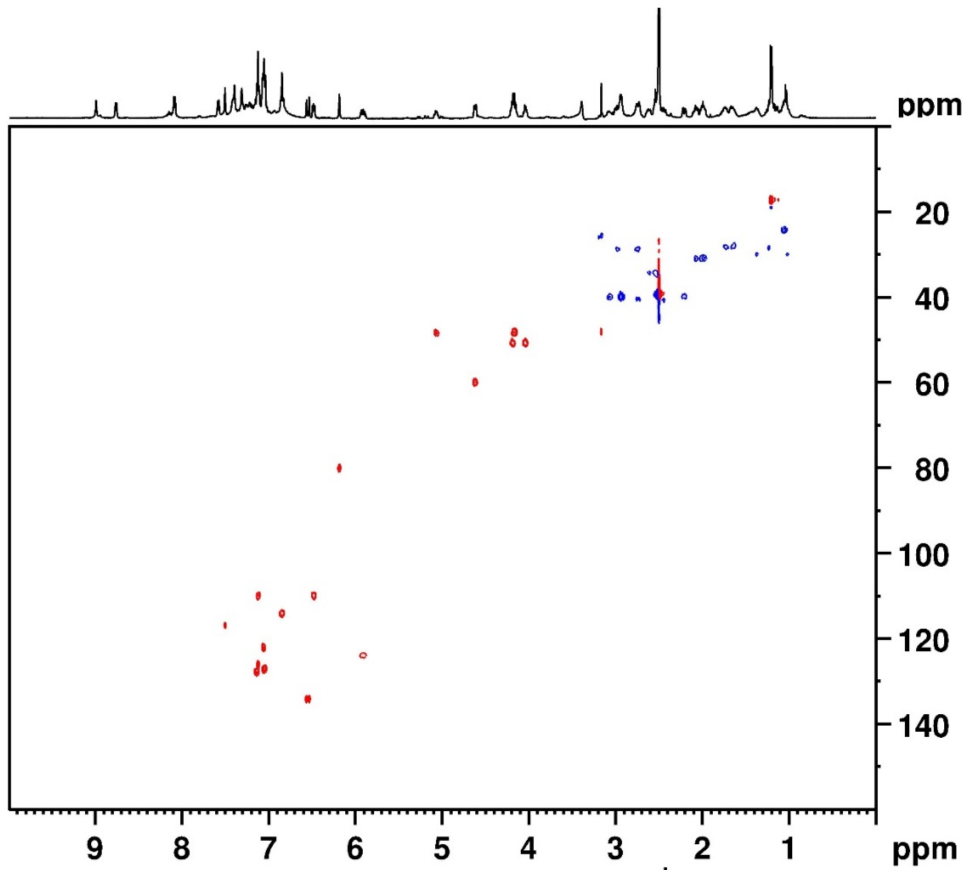
Macrocyclic Product ***2.11e***






ppm
2
4
6
8
9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-A4-1-1
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121217
Time 17.57
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevetgp.js
TD 4096
SOLVENT DMSO
NS 4
DS 16
SWH 6009.615 Hz
FIDRES 1.467191 Hz
AQ 0.3407872 sec
RG 71.8
DW 83.200 usec
DE 6.50 usec
TE 294.0 K
D0 0.00000300 sec
D1 1.20000005 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00016665 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PL1 -2.00 dB
PL10 9.54 dB
PL1W 39.81071854 W
PL10W 2.79254389 W
SFO1 600.1330006 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 30.00 %


ppm
2
4
6
8
9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-A4-1-1_AV500
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140223
Time 4.31
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG noesygpph
TD 2048
SOLVENT DMSO
NS 16
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 26.58
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00008727 sec
D1 2.00000000 sec
D8 0.20000000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz
SW 9.997 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 2048
SF 500.1300036 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0



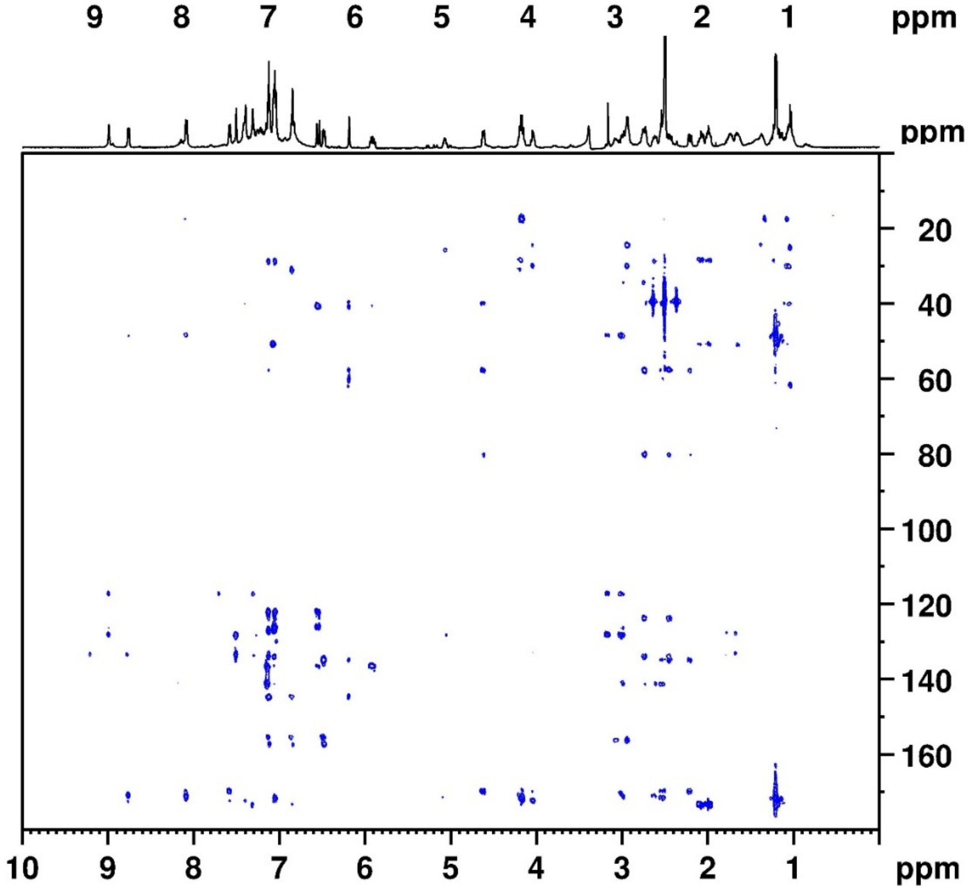
Current Data Parameters
NAME W-A4-1-1_AV500
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121219
Time 17.14
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 6
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W

======== CHANNEL f2 ========
SFO2 125.7678496 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W

====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %



Current Data Parameters
NAME W-A4-1-1_AV500
EXPNO 6
PROCNO 1

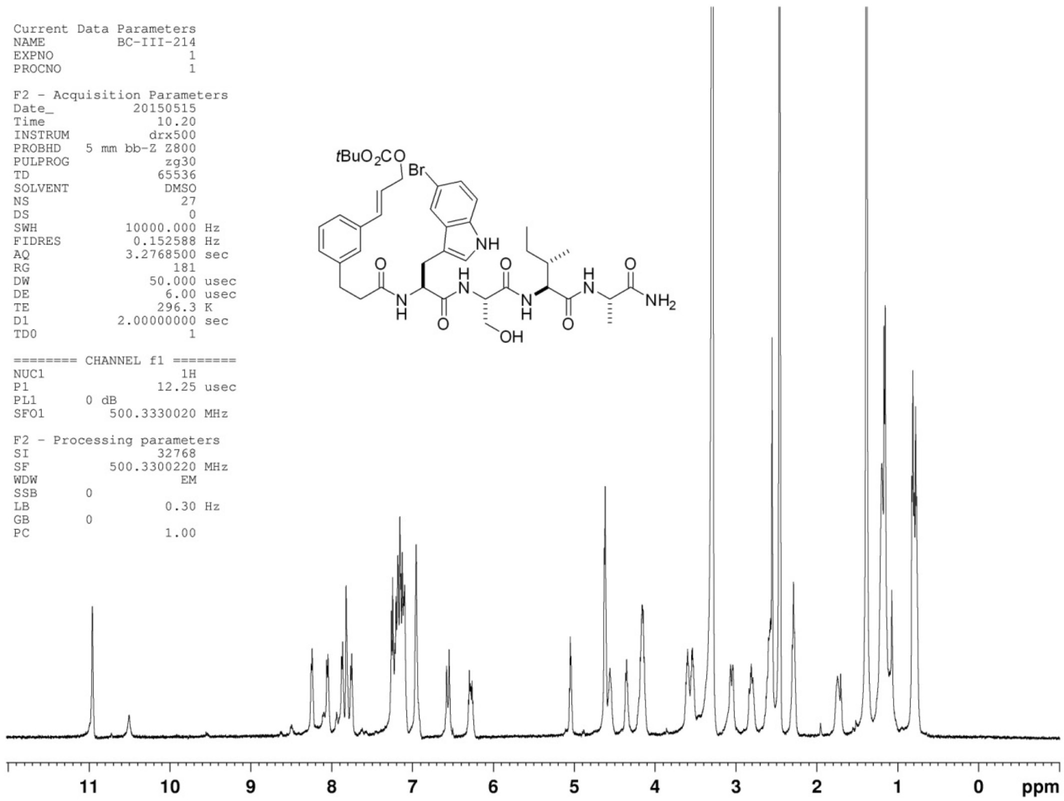
F2 - Acquisition Parameters
Date_ 20140222
Time 20.21
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 64
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 204.86
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec

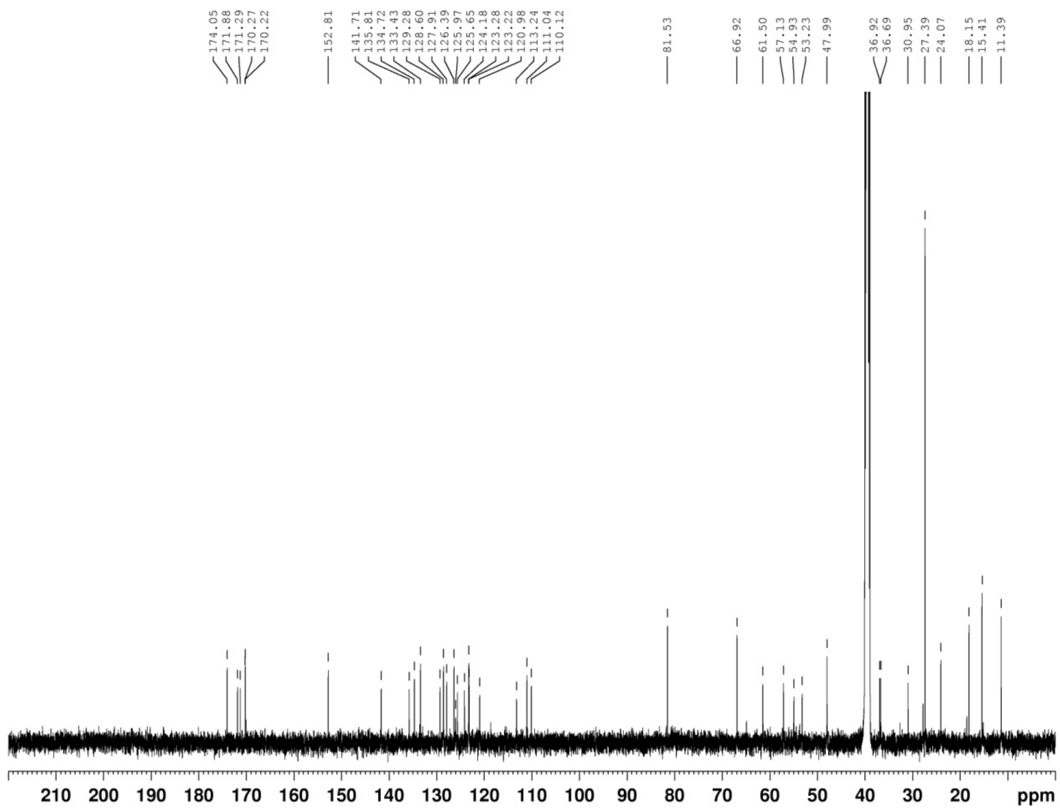
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W

======== CHANNEL f2 ========
SFO2 125.7703648 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W

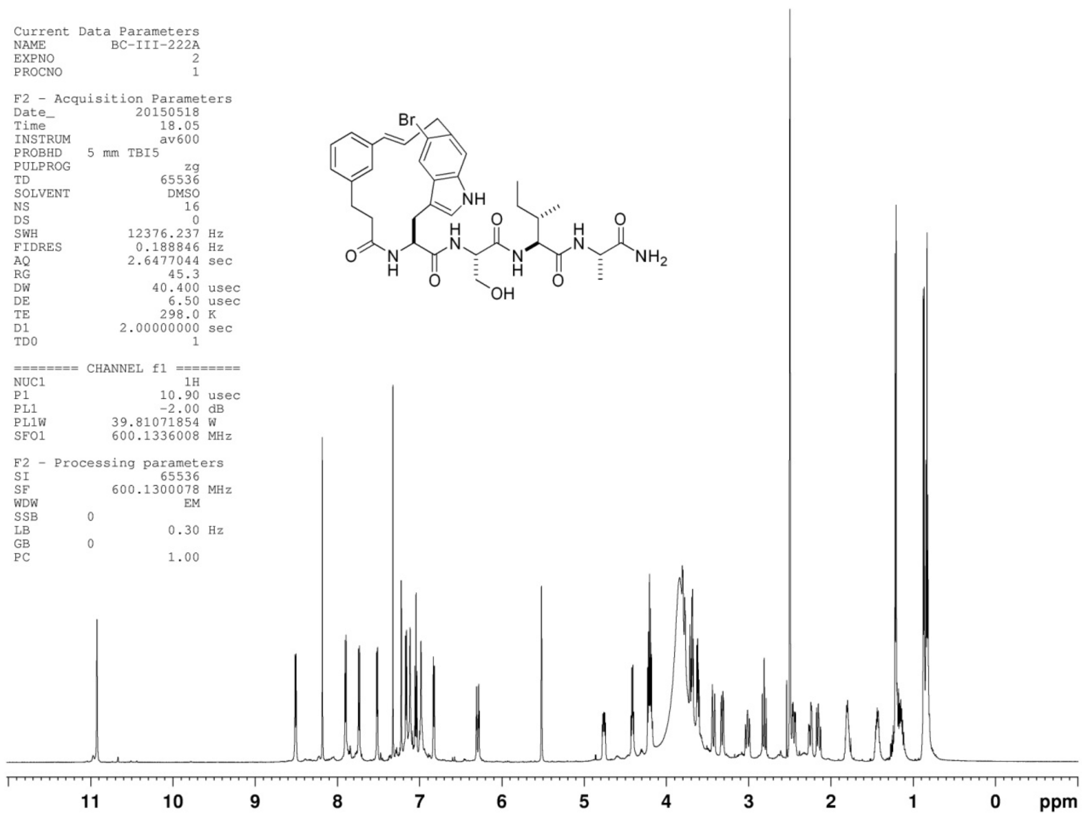
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

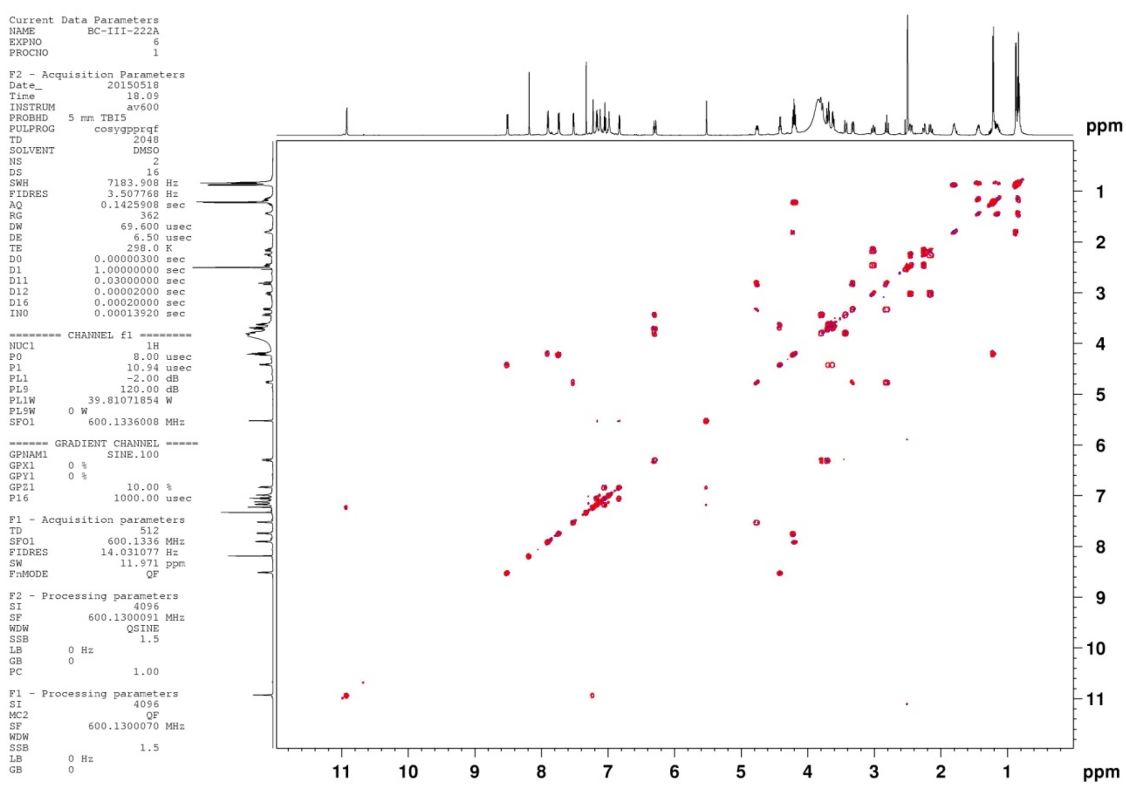
Acyclic Precursor ***2.12***

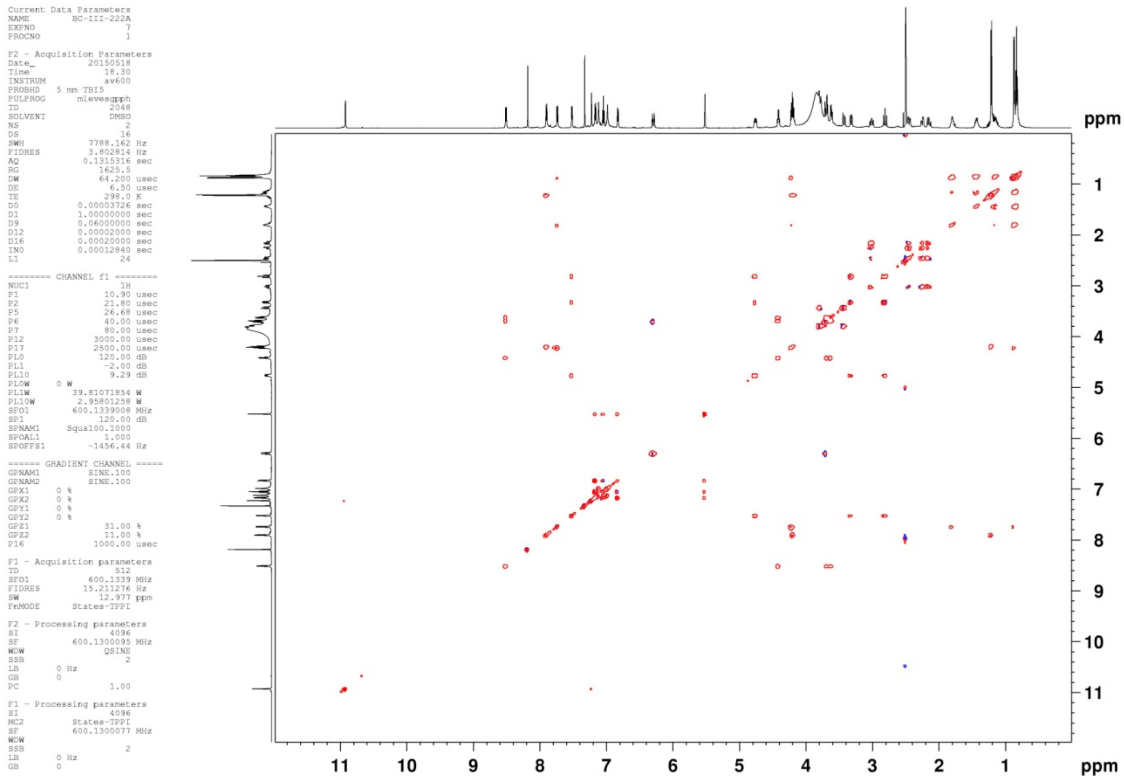




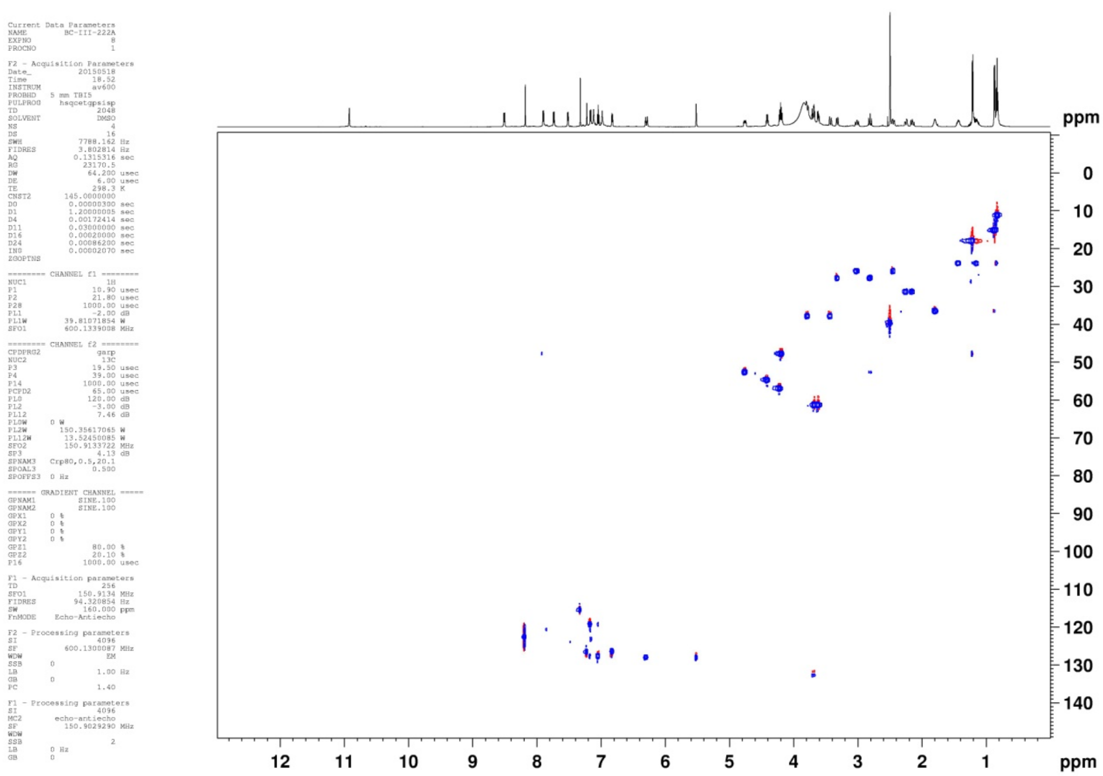
*Macrocyclic Product **2.16a***



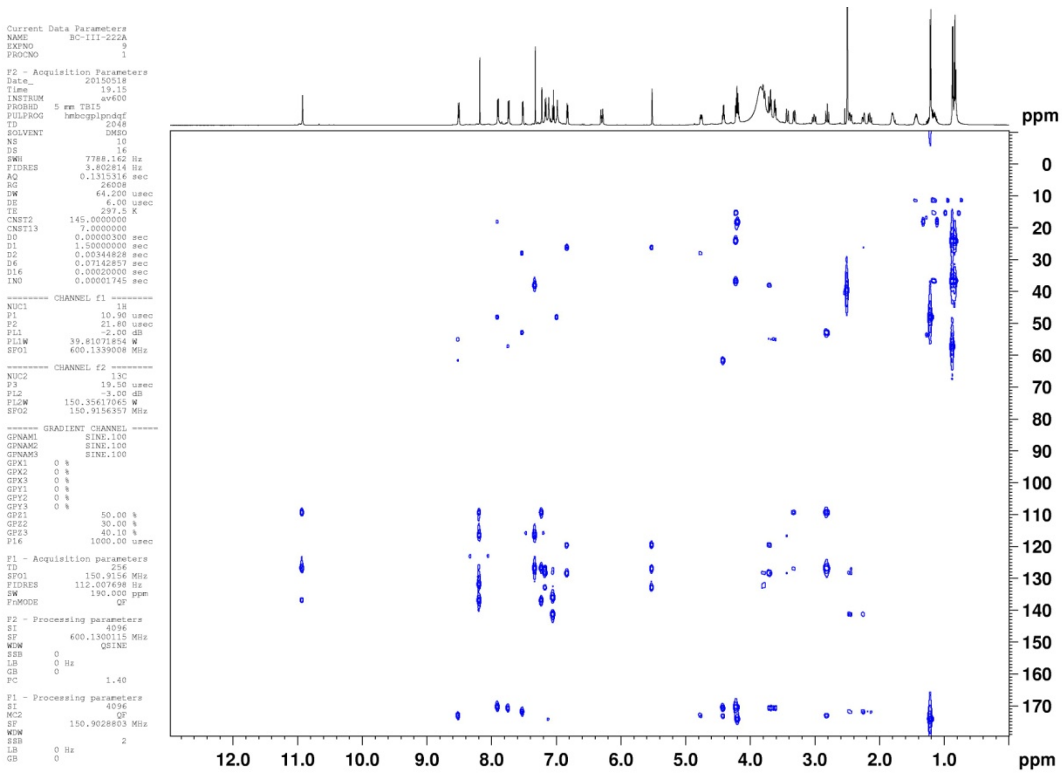




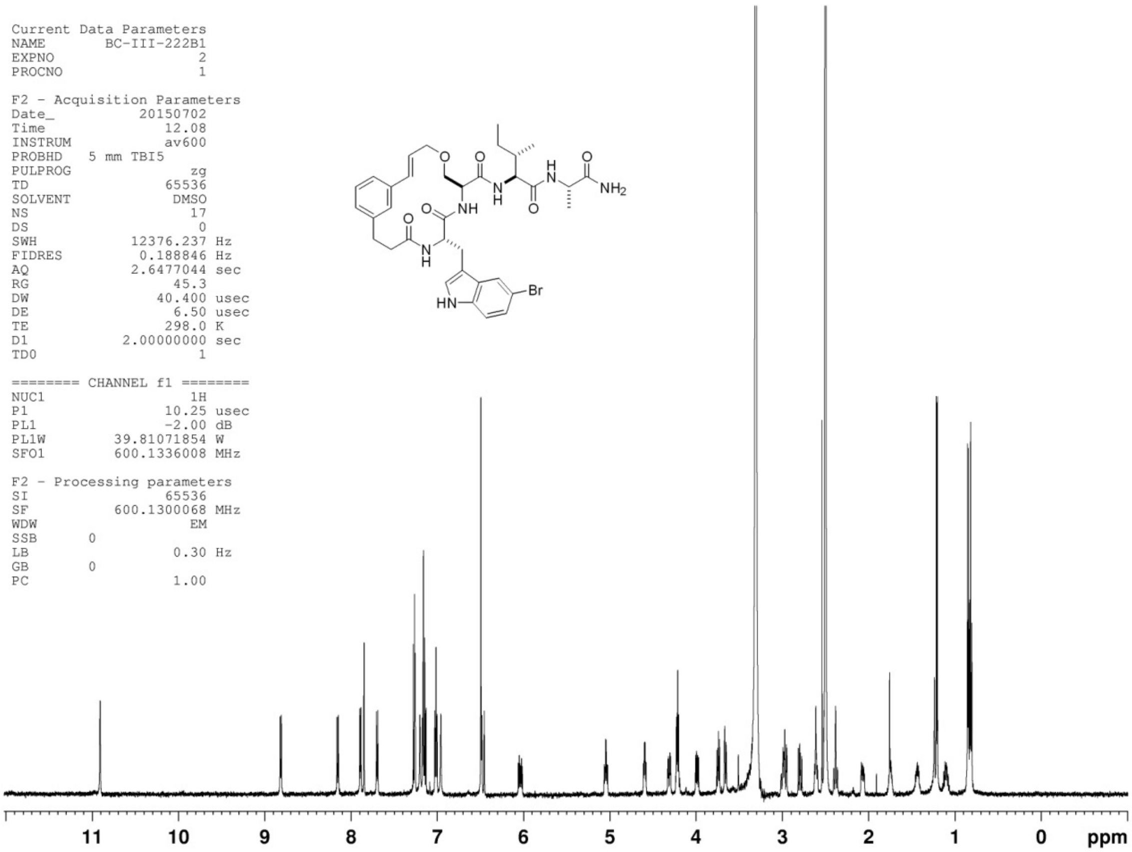
Current Data Parameters
NAME BC-III-222A
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 18.30
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003726 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
P2 21.80 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.29 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.95801258 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300095 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300077 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
1 2 3 4 5 6 7 8 9 10 11
11 10 9 8 7 6 5 4 3 2 1 ppm

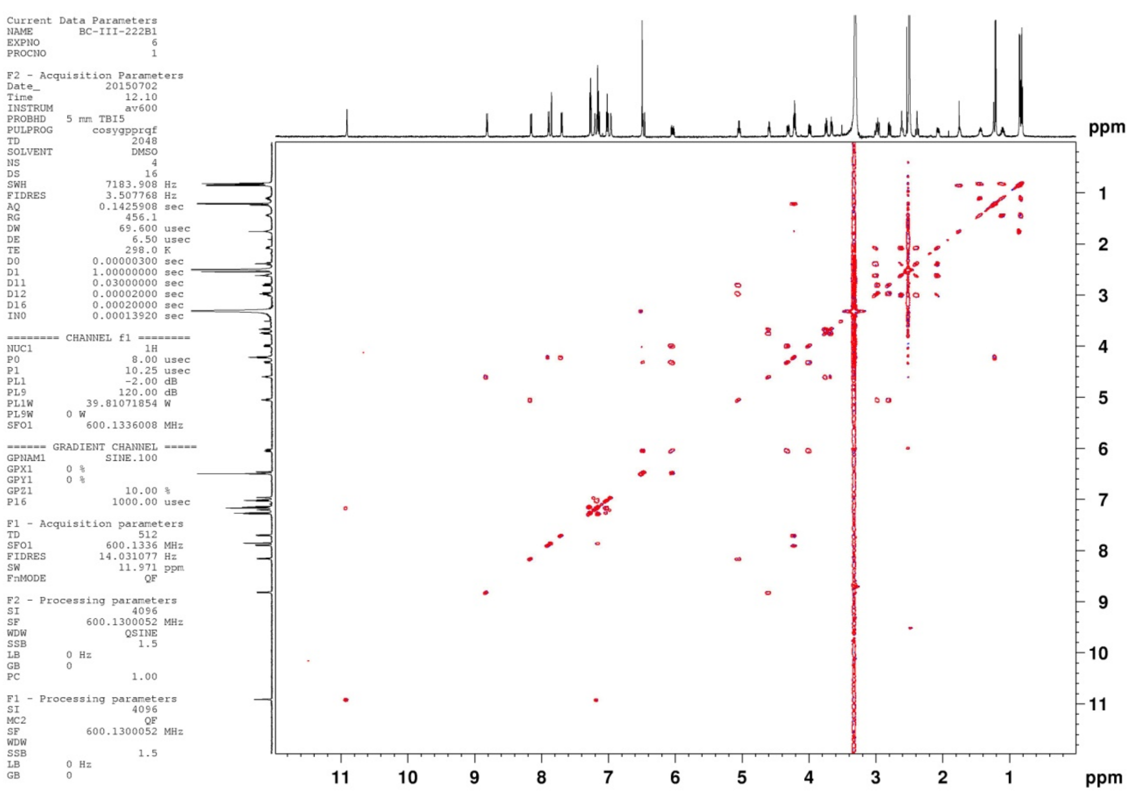


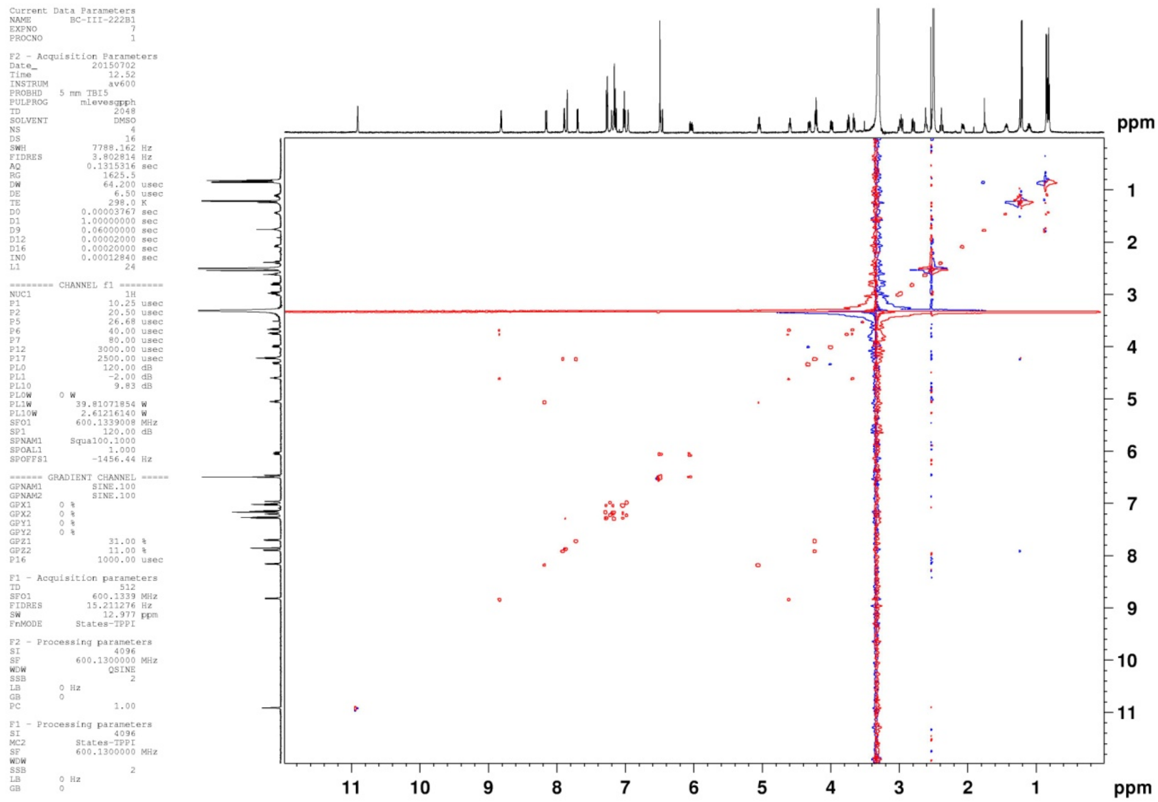
Current Data Parameters
NAME BC-III-222A
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 18.52
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.3 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
P2 21.80 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300087 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029290 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
12 11 10 9 8 7 6 5 4 3 2 1 ppm

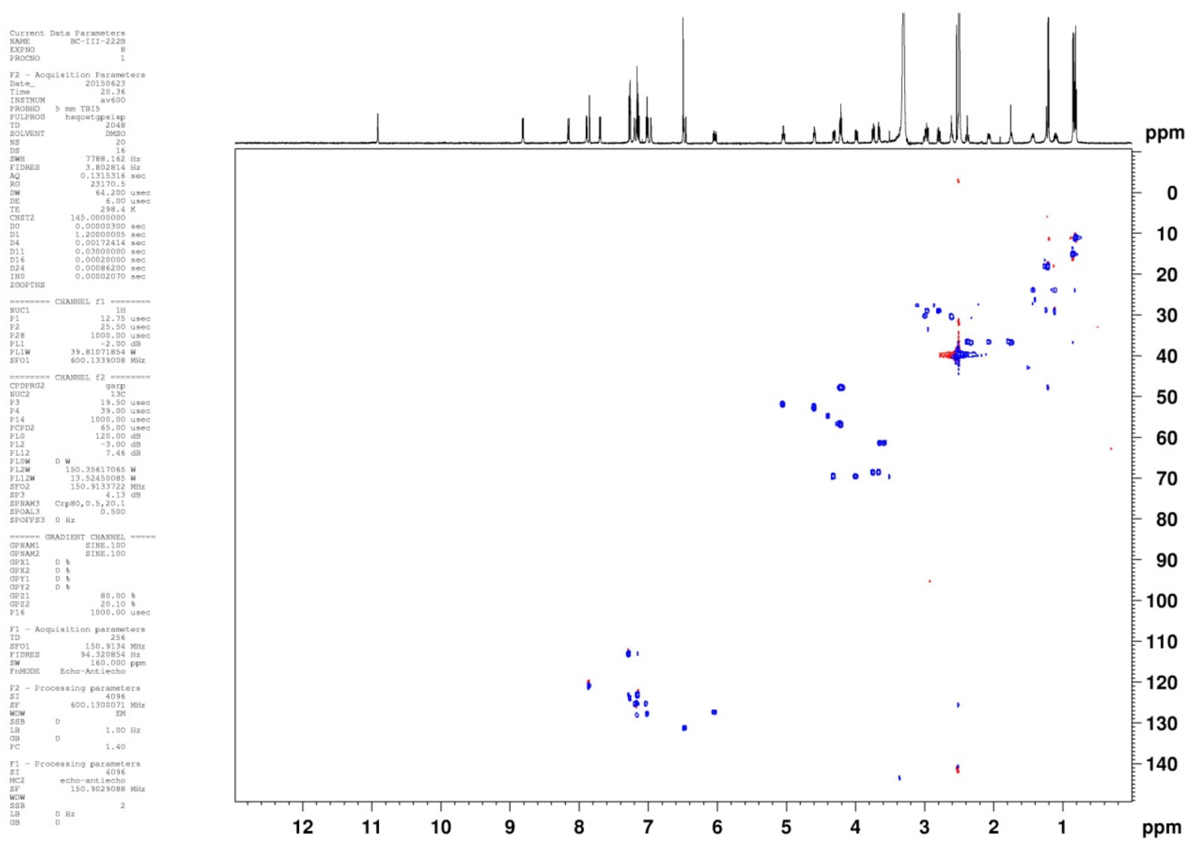

Current Data Parameters
NAME BC-III-222A
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 19.15
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 10
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
P2 21.80 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300115 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028803 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

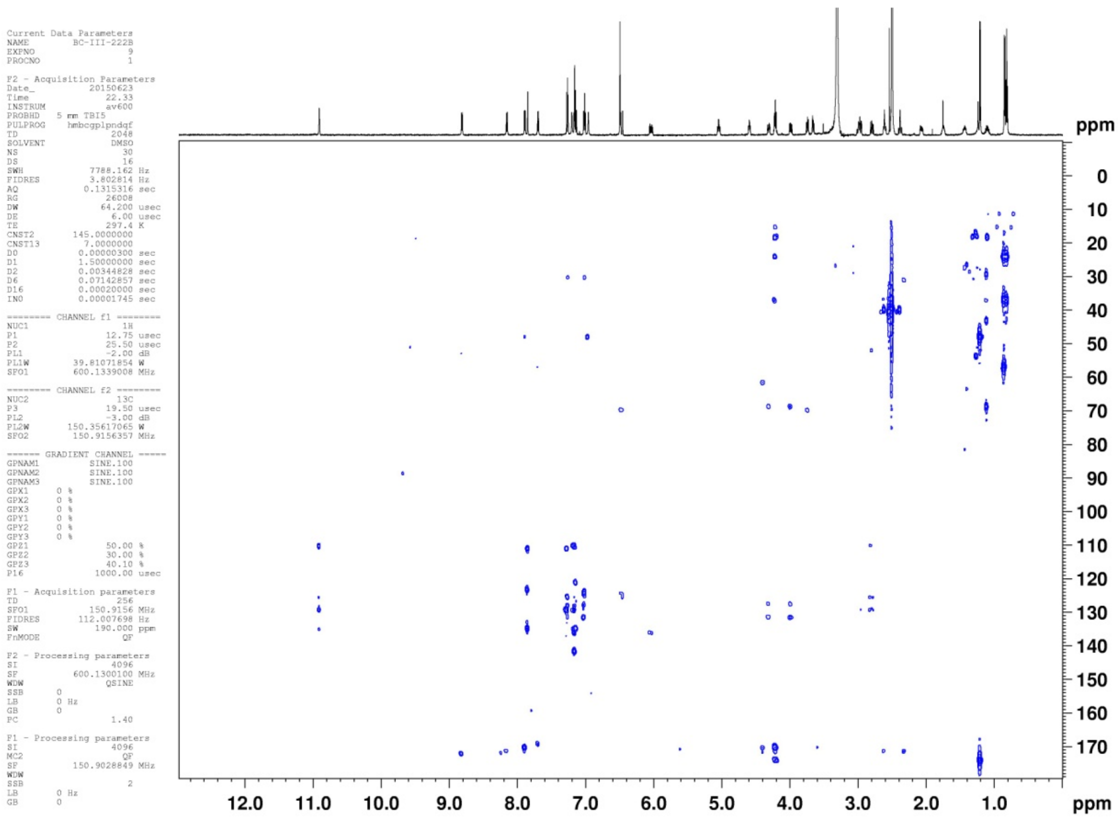
*Macrocyclic Product **2.16b***





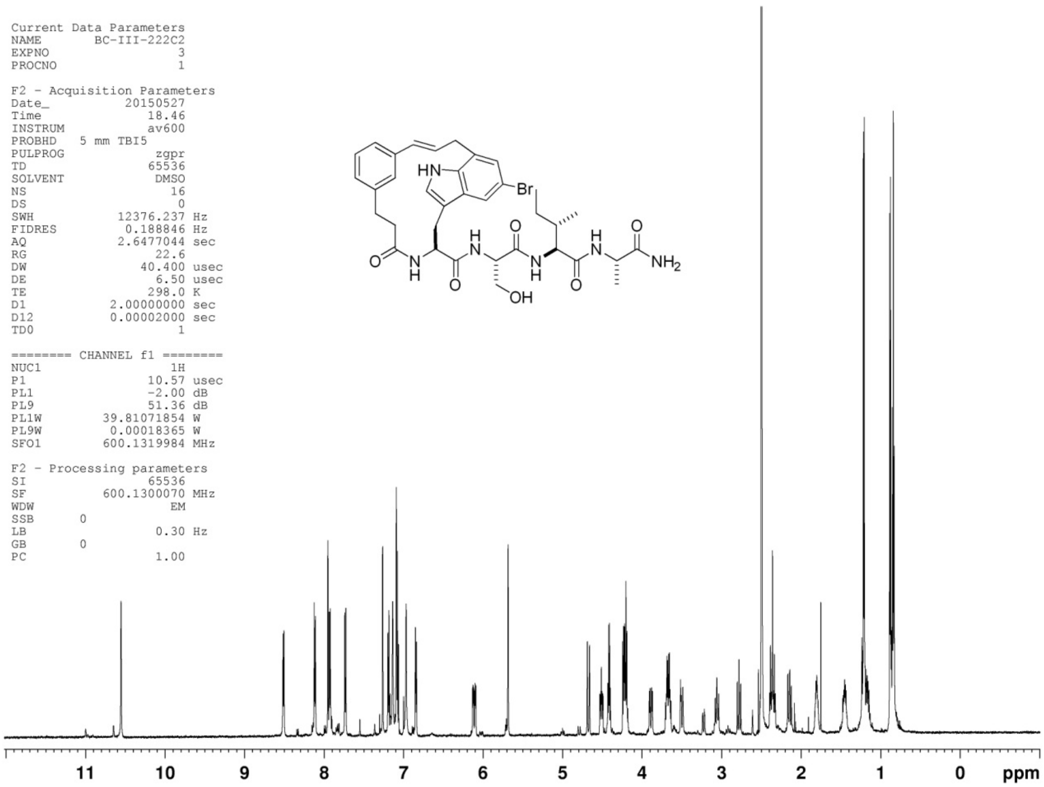

Current Data Parameters
NAME BC-III-222B1
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150702
Time 12.52
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003767 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.25 usec
P2 20.50 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.83 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.61216140 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300000 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300000 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm


Current Data Parameters
NAME BC-III-222B
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150623
Time 20.36
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 20
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 12.75 usec
P2 25.50 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300071 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029088 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

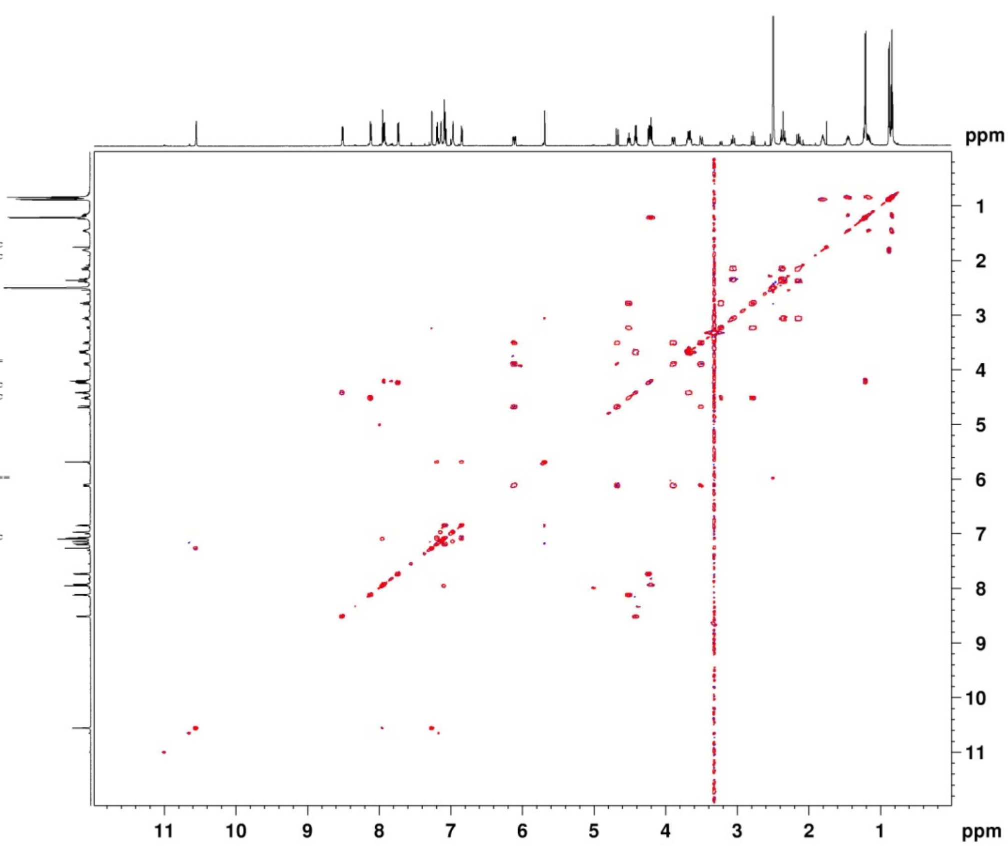

Current Data Parameters
NAME BC-III-222B
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150623
Time 22.33
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 30
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.4 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.75 usec
P2 25.50 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300100 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028849 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

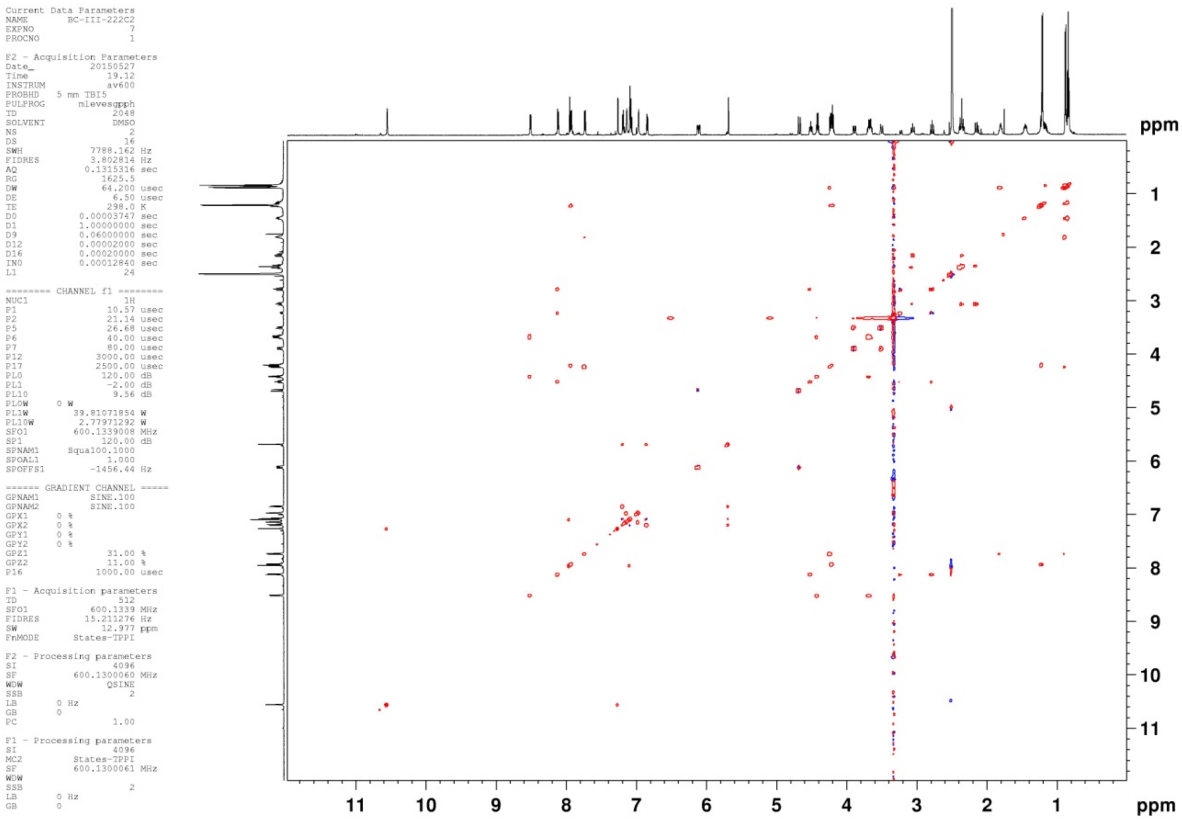
Macrocyclic Product ***2.16c***

```
Current Data Parameters
NAME       BC-III-222C2
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20150527
Time              18.46
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zgpr
TD                65536
SOLVENT            DMSO
NS                   16
DS                    0
SWH          12376.237 Hz
FIDRES        0.188846 Hz
AQ           2.6477044 sec
RG                 22.6
DW               40.400 usec
DE                 6.50 usec
TE                298.0 K
D1           2.00000000 sec
D12          0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.57 usec
PL1               -2.00 dB
PL9               51.36 dB
PL1W        39.81071854 W
PL9W         0.00018365 W
SFO1        600.1319984 MHz

F2 - Processing parameters
SI                65536
SF          600.1300070 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```

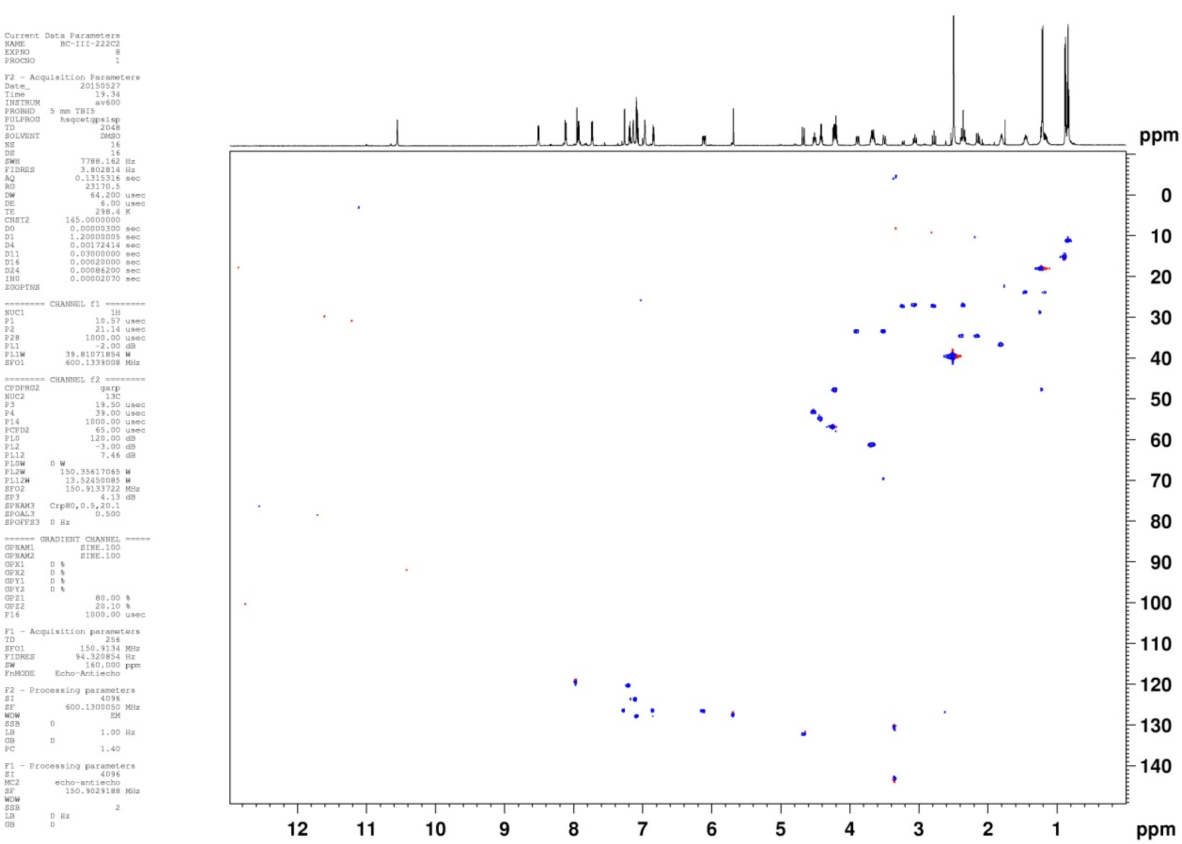


```
Current Data Parameters
NAME       BC-III-222C2
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20150527
Time              18.51
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG      cosygpprqf
TD                 2048
SOLVENT            DMSO
NS                    2
DS                   16
SWH            7183.908 Hz
FIDRES         3.507768 Hz
AQ            0.1425908 sec
RG                456.1
DW               69.600 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00000300 sec
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00013920 sec

======== CHANNEL f1 ========
NUC1                 1H
P0                 8.00 usec
P1                10.57 usec
PL1               -2.00 dB
PL9              120.00 dB
PL1W        39.81071854 W
PL9W     0 W
SFO1        600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM1         SINE.100
GPX1     0 %
GPY1     0 %
GPZ1              10.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  512
SFO1           600.1336 MHz
FIDRES        14.031077 Hz
SW               11.971 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300065 MHz
WDW               QSINE
SSB                 1.5
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 4096
MC2                  QF
SF          600.1300080 MHz
WDW
SSB                 1.5
LB       0 Hz
GB       0
```

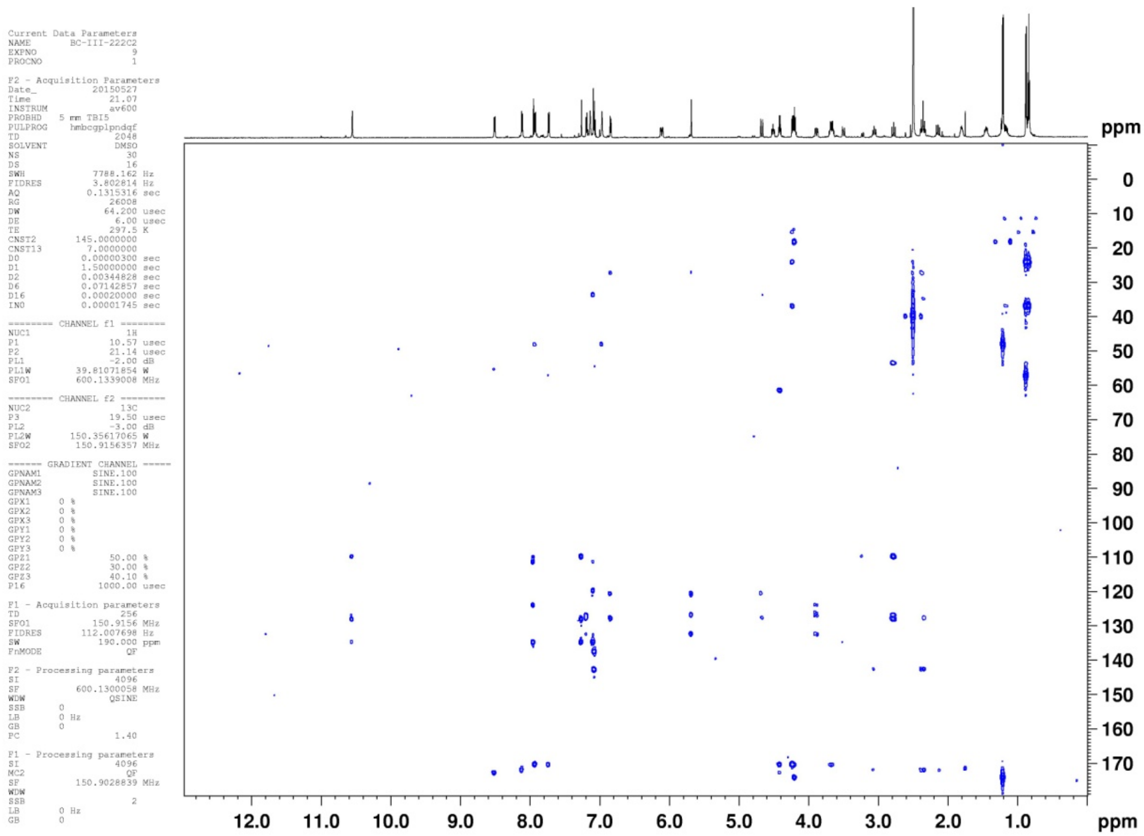




Current Data Parameters
NAME BC-III-222C2
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 19.12
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003747 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.56 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.77971292 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300060 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300061 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
11 10 9 8 7 6 5 4 3 2 1
ppm
1 2 3 4 5 6 7 8 9 10 11

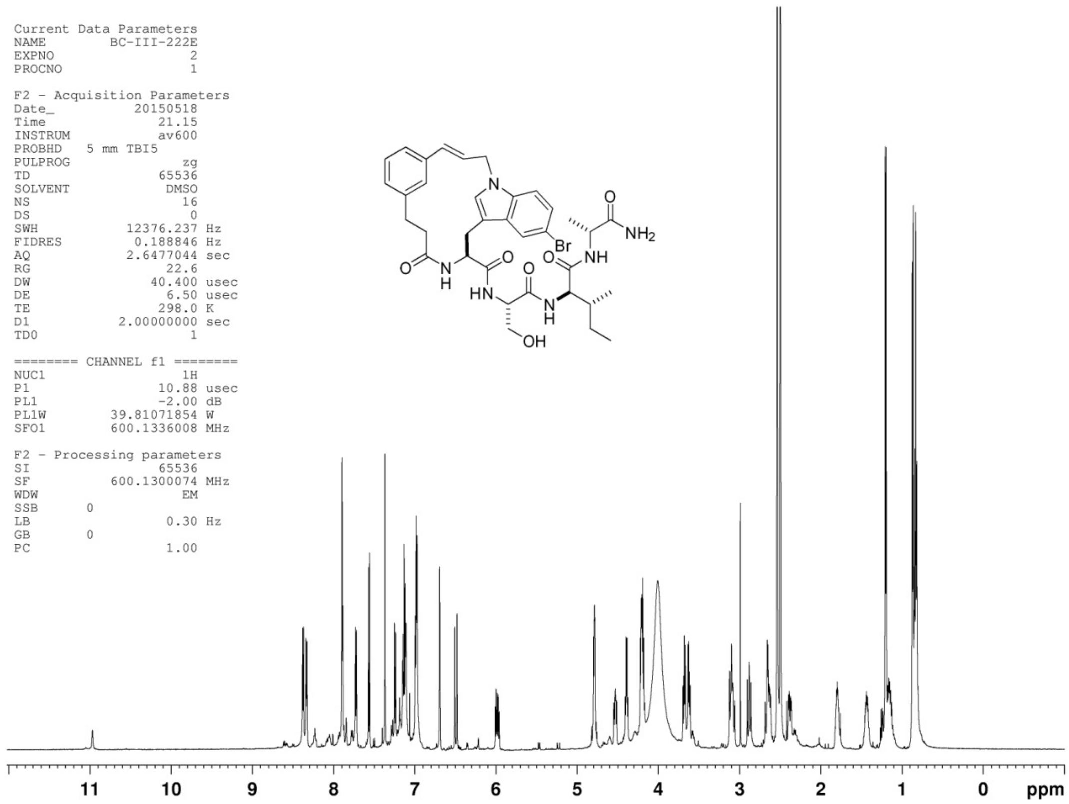


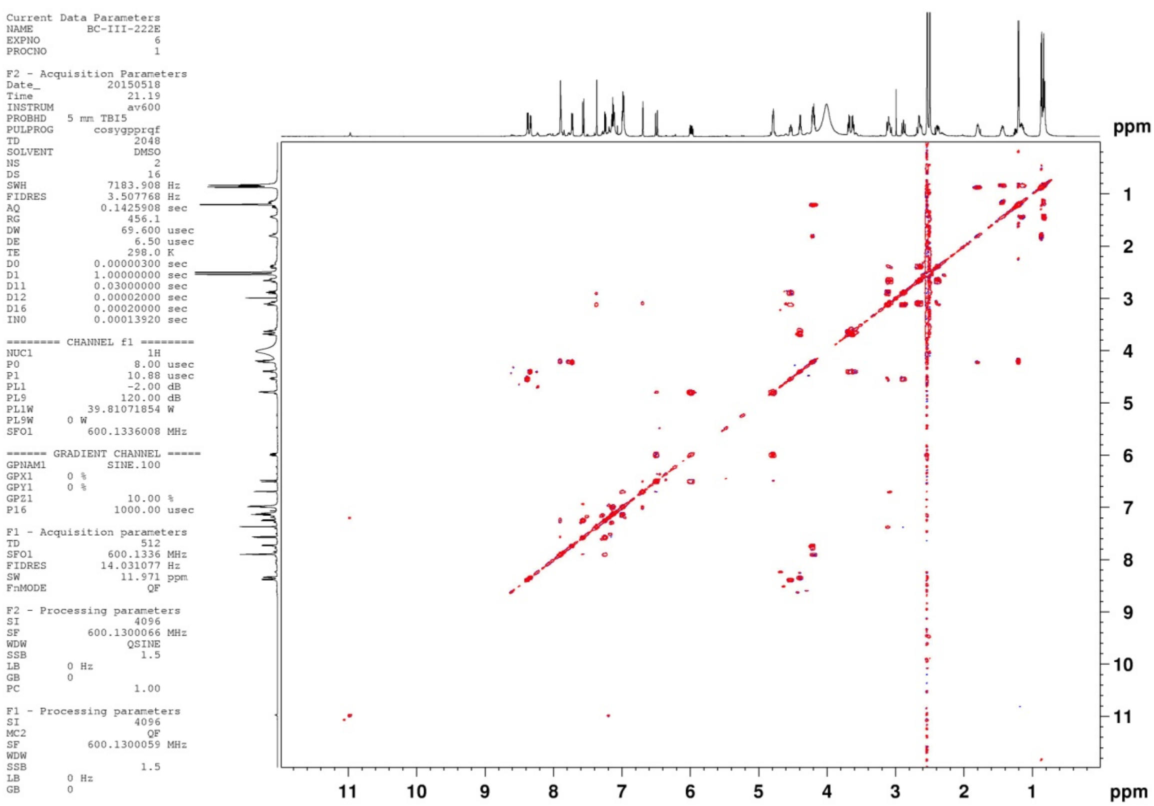
Current Data Parameters
NAME BC-III-222C2
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 19.34
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 16
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029188 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
12 11 10 9 8 7 6 5 4 3 2 1
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140

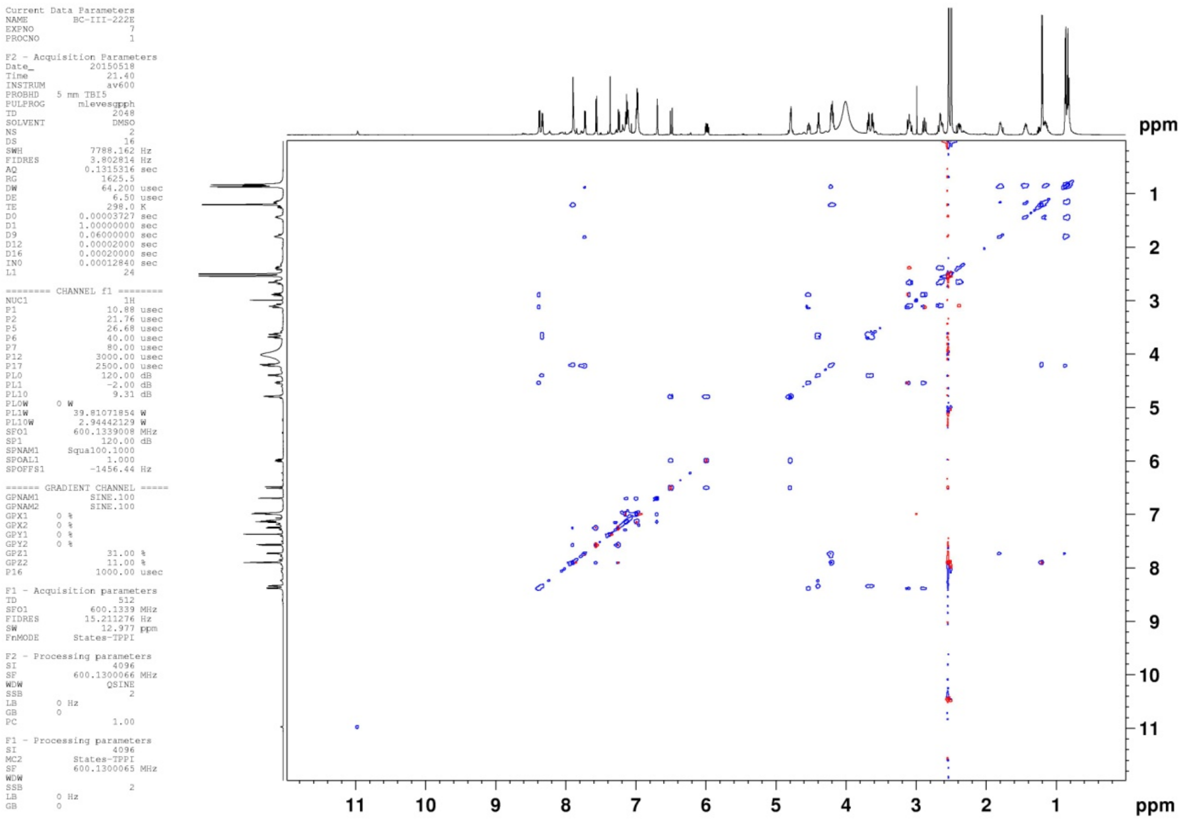


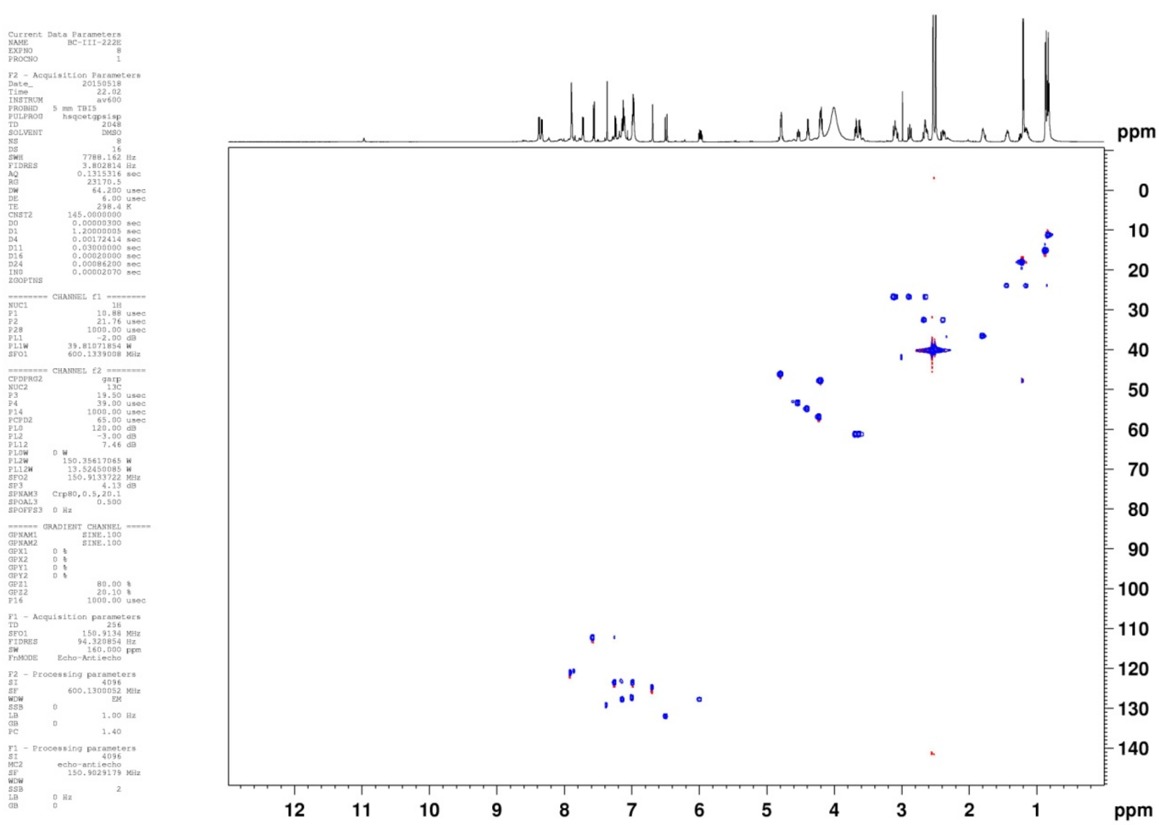
Current Data Parameters
NAME BC-III-222C2
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150527
Time 21.07
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 30
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300058 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028839 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

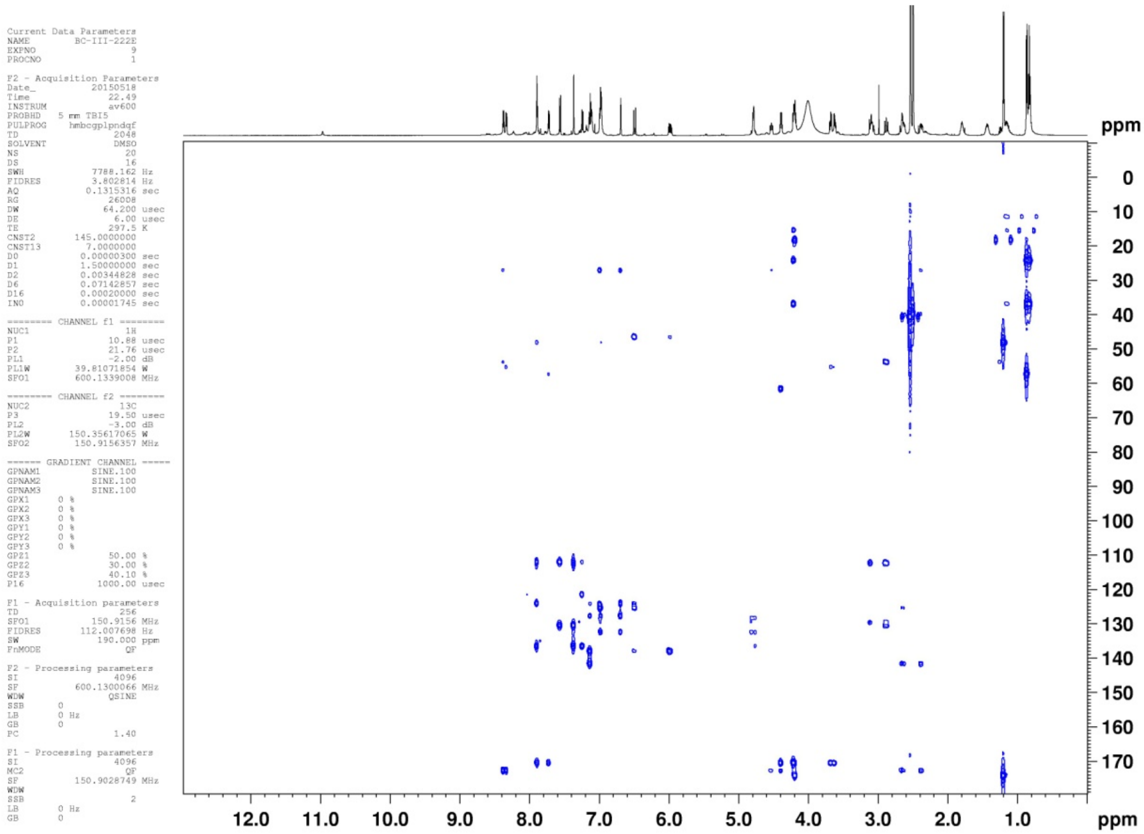
*Macrocyclic Product **2.16d***





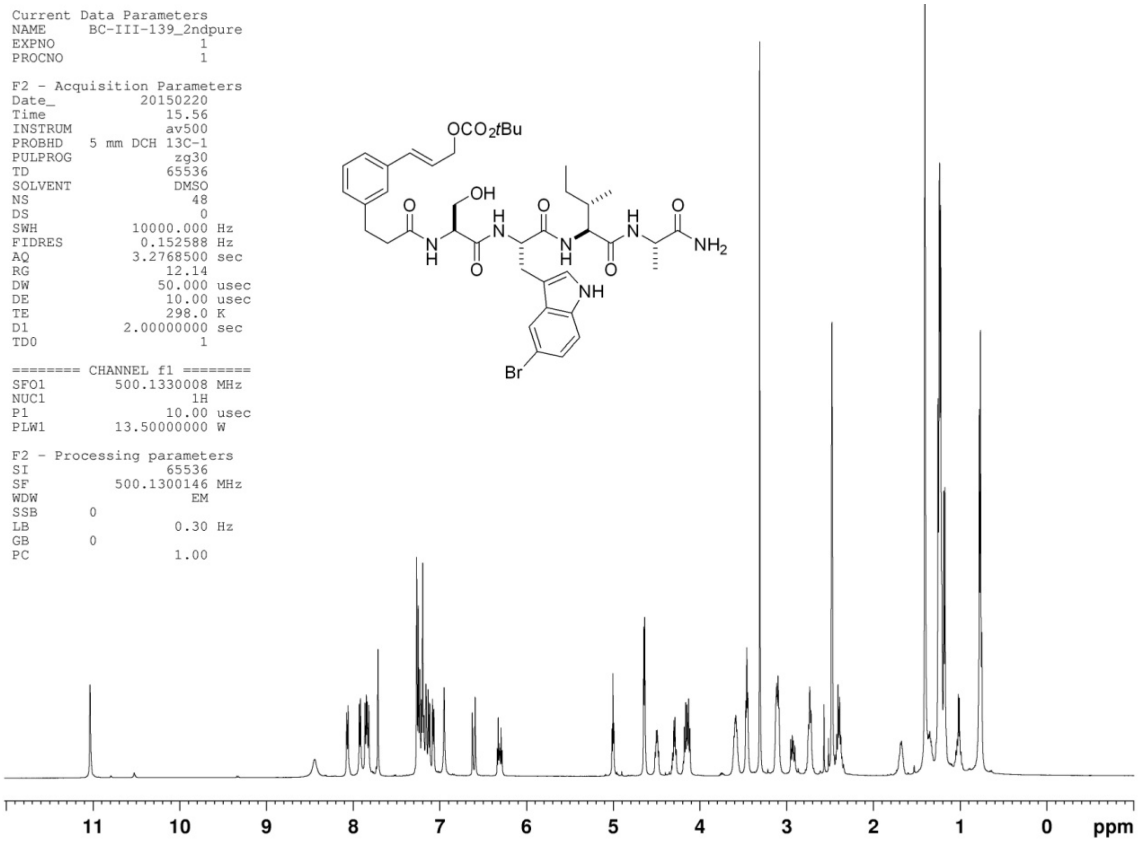

Current Data Parameters
NAME BC-III-222E
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 21.40
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003727 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.88 usec
P2 21.76 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.31 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.94442129 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300066 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300065 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
1 2 3 4 5 6 7 8 9 10 11
11 10 9 8 7 6 5 4 3 2 1 ppm

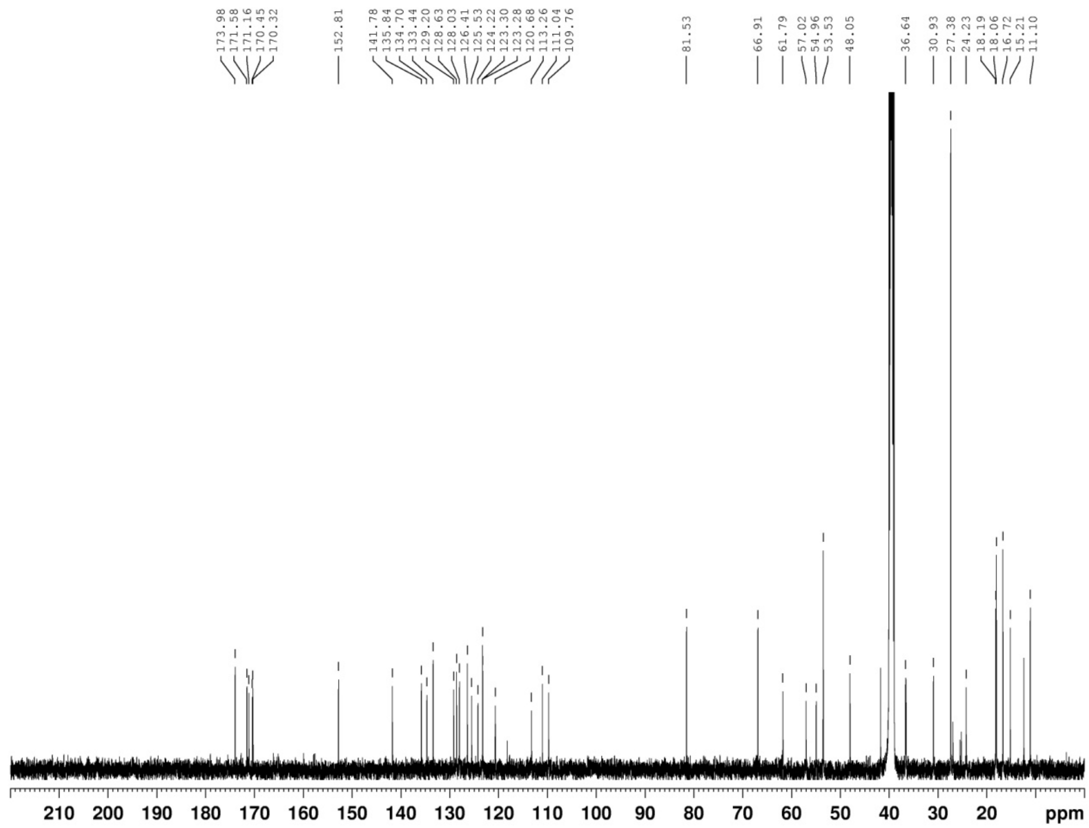

Current Data Parameters
NAME BC-III-222E
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 22.02
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.88 usec
P2 21.76 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300052 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029179 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
12 11 10 9 8 7 6 5 4 3 2 1 ppm



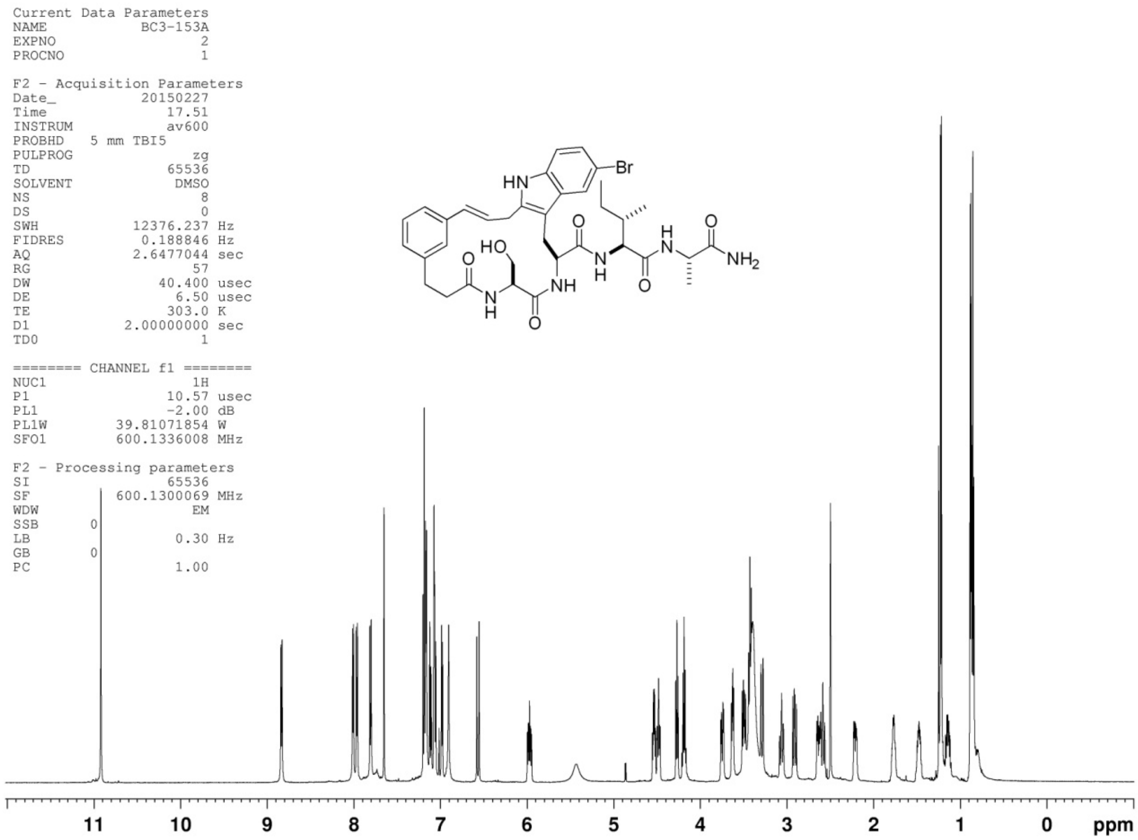
Current Data Parameters
NAME BC-III-222E
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150518
Time 22.49
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 20
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.88 usec
P2 21.76 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300066 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028749 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

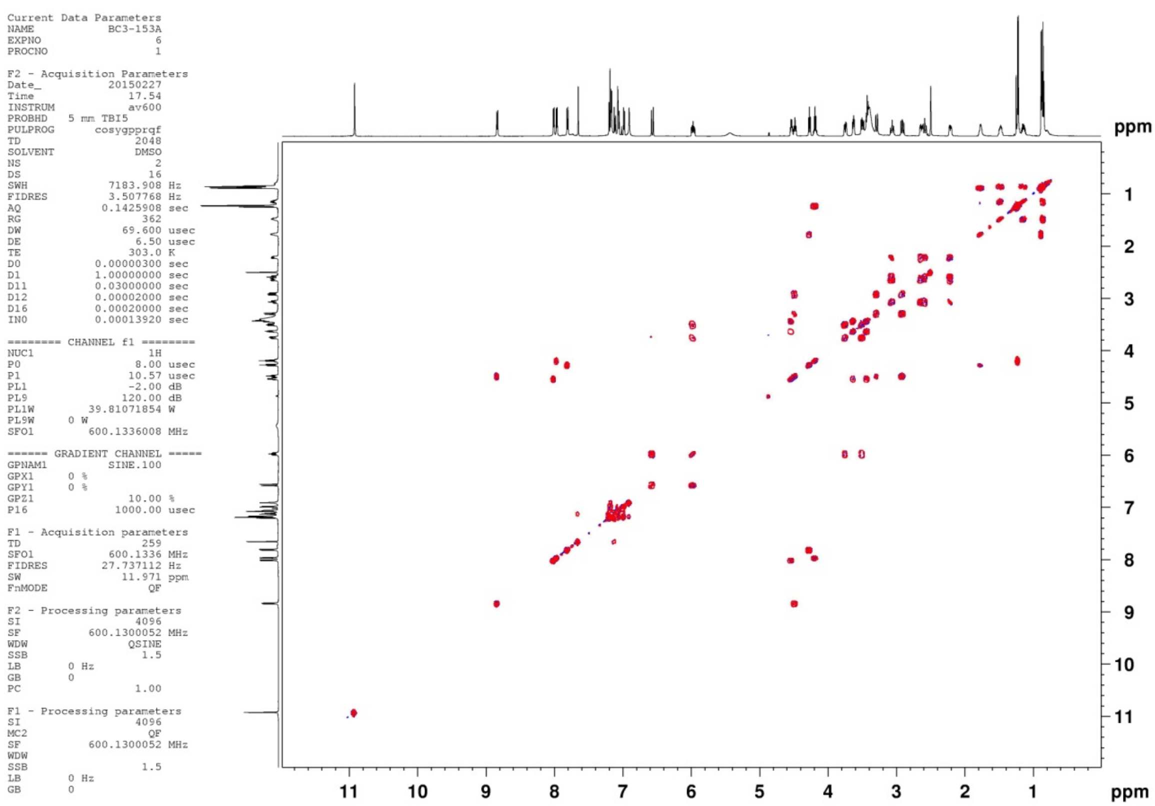
Acyclic Precursor ***2*.13**

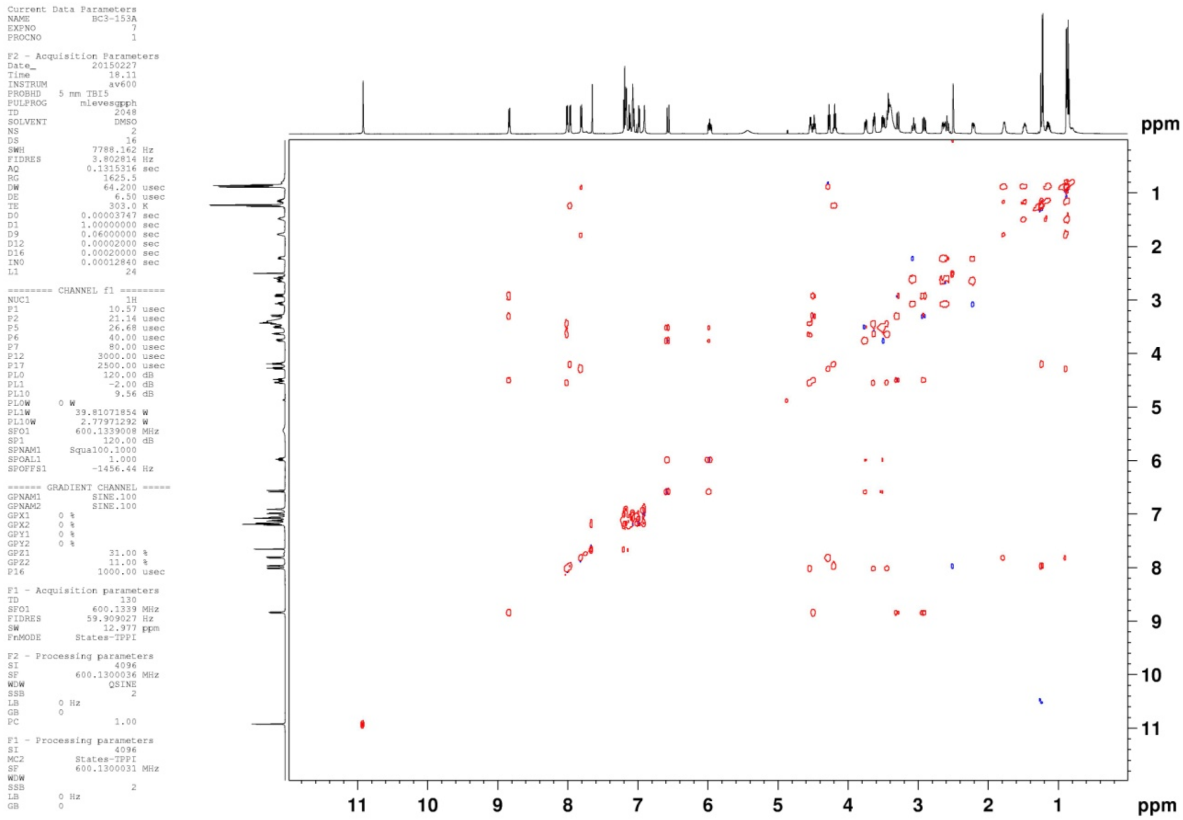


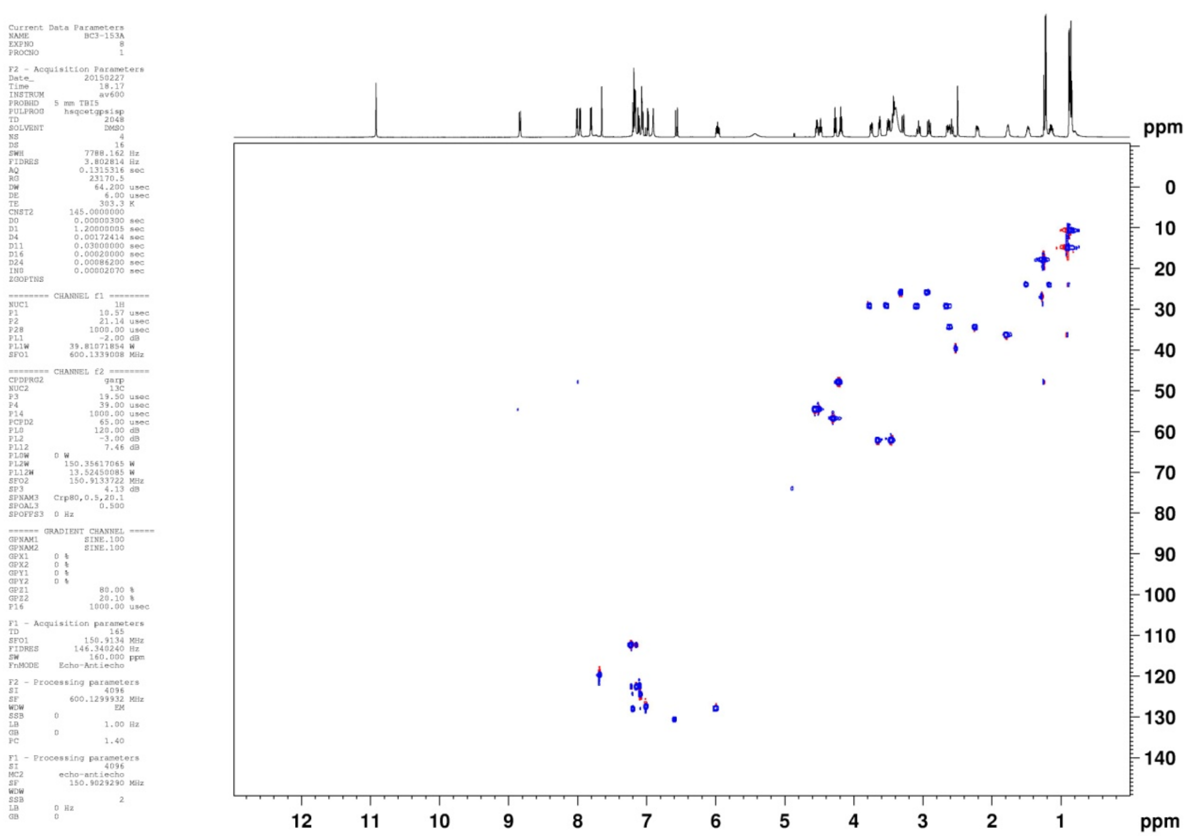


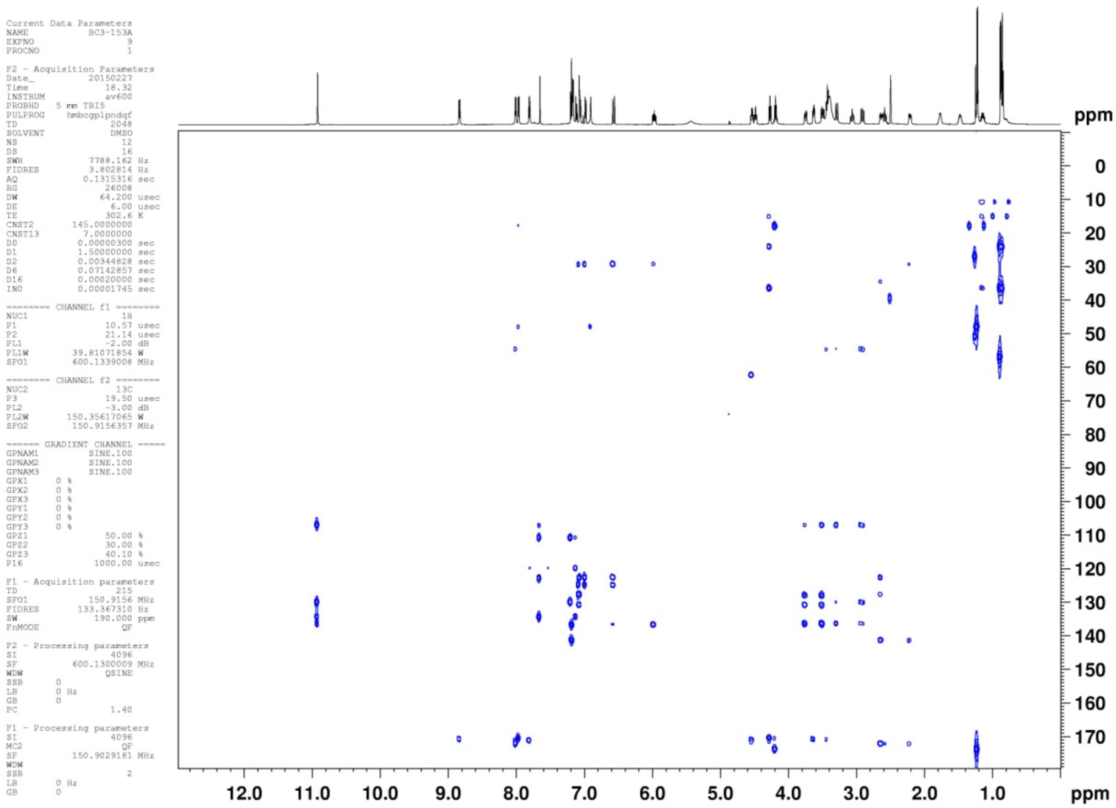
Macrocyclic Product ***2.17a***





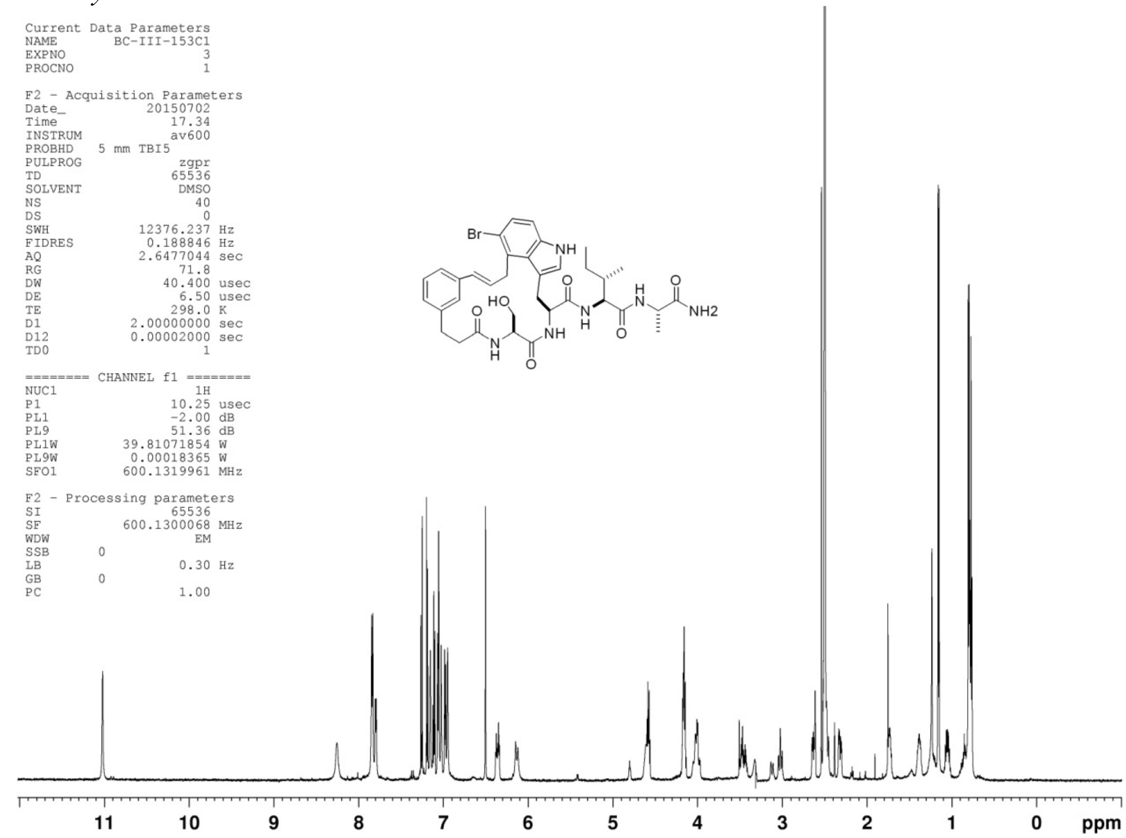

Current Data Parameters
NAME BC3-153A
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150227
Time 18.11
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 303.0 K
D0 0.00003747 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.56 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.77971292 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 130
SFO1 600.1339 MHz
FIDRES 59.909027 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300036 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300031 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

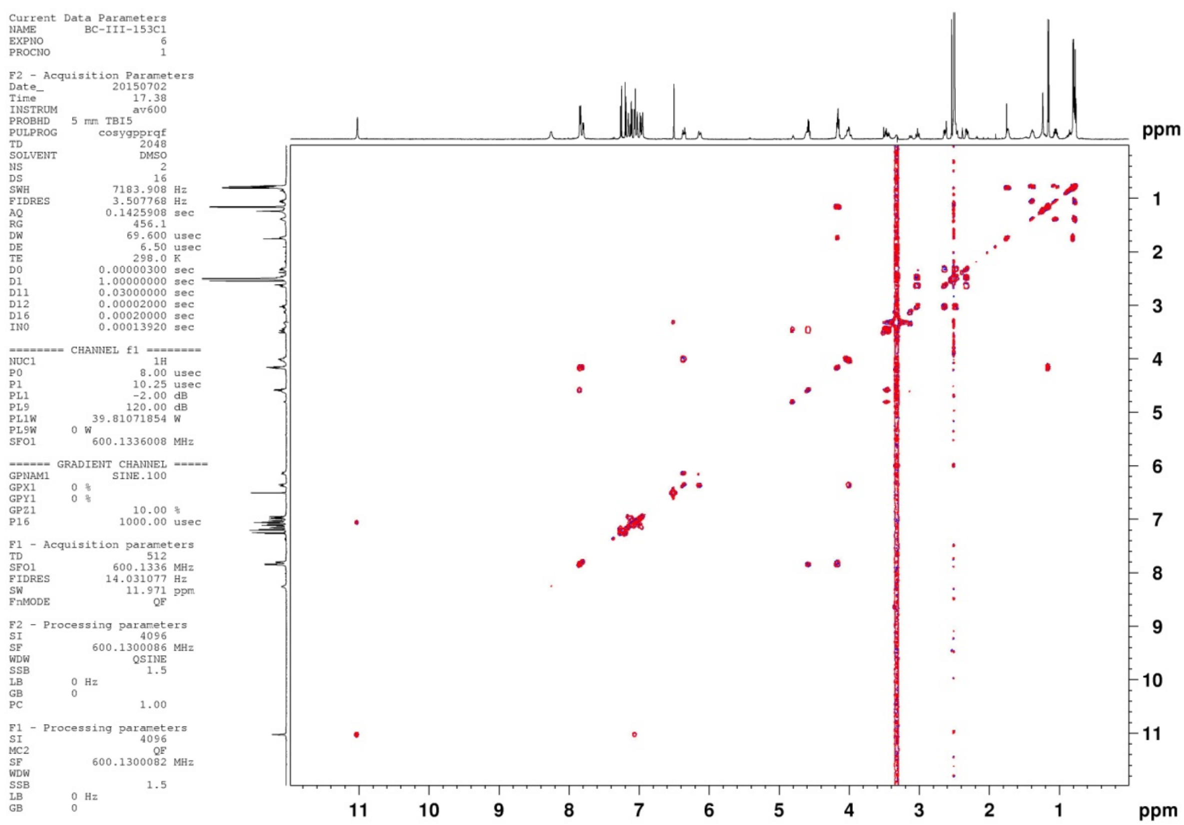

Current Data Parameters
NAME BC3-153A
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150227
Time 18.17
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 303.3 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 165
SFO1 150.9134 MHz
FIDRES 146.340240 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1299932 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029290 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

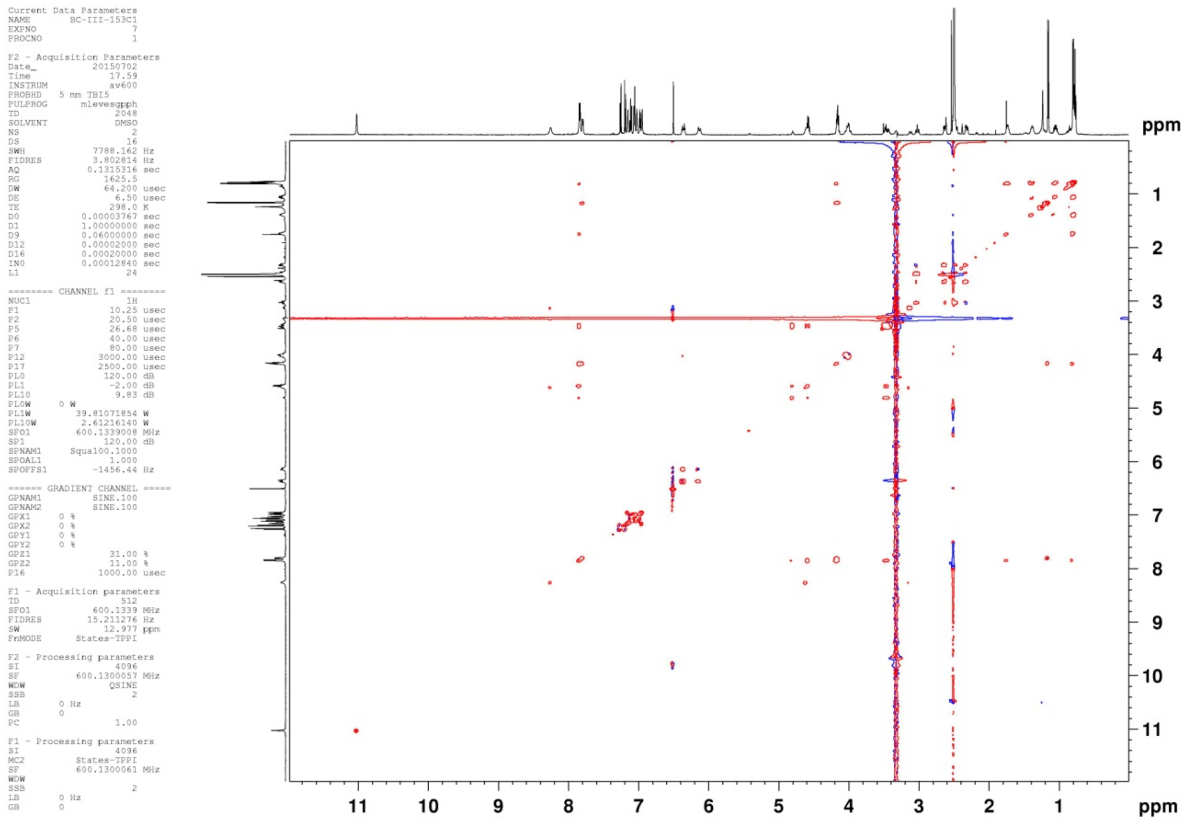


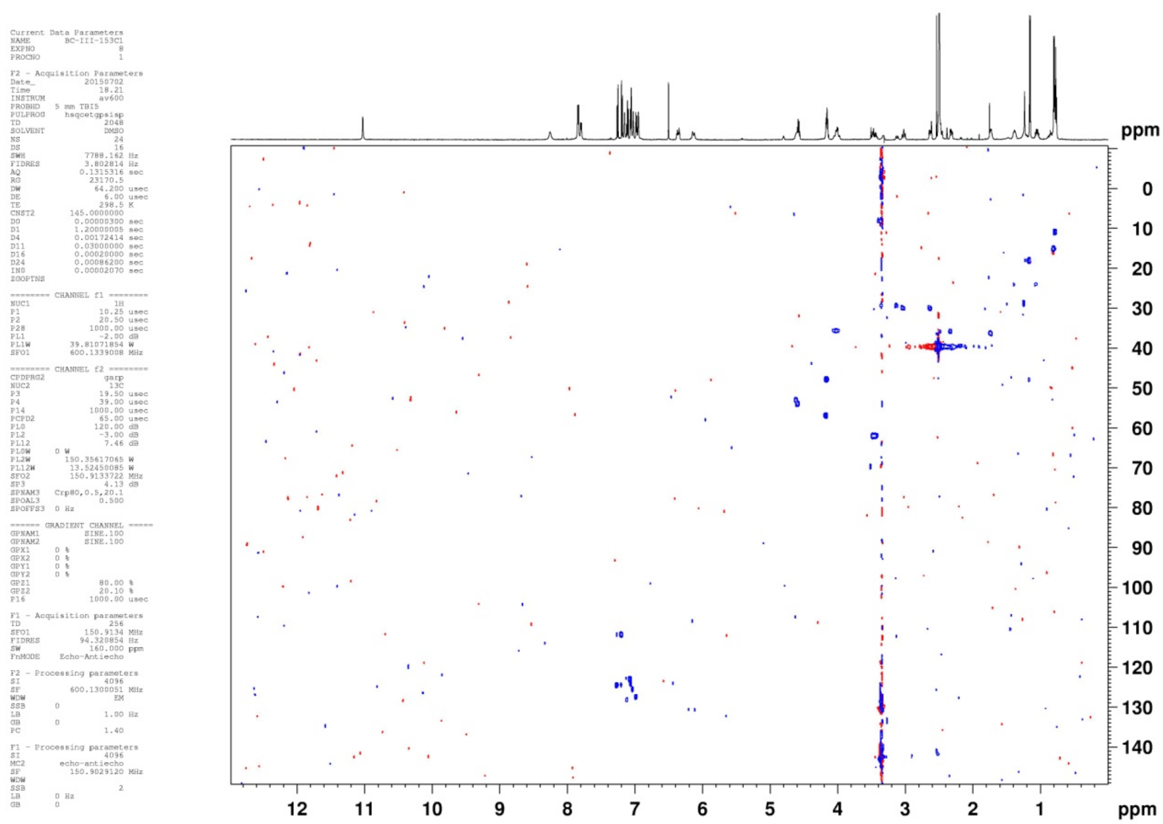
Current Data Parameters
NAME BC3-153A
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150227
Time 18.32
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 12
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 302.6 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 215
SFO1 150.9156 MHz
FIDRES 133.367310 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300009 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9029181 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

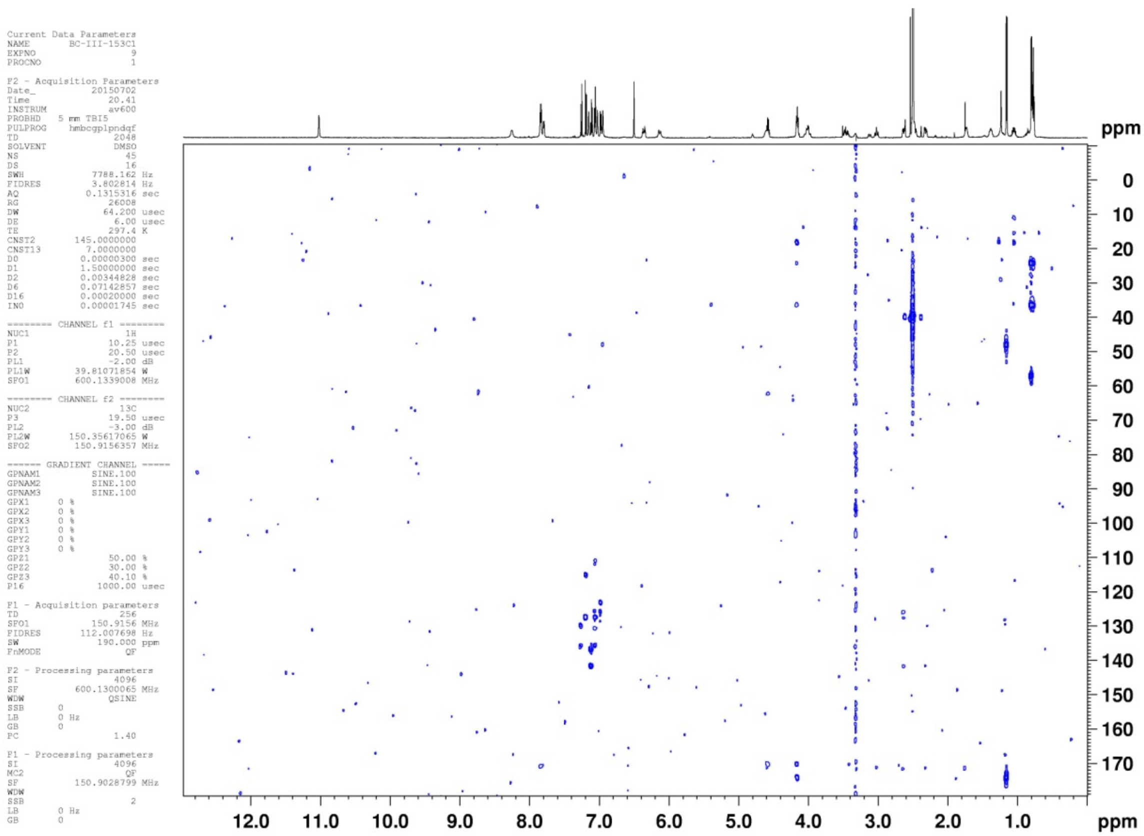
*Macrocyclic Product **2.17b***



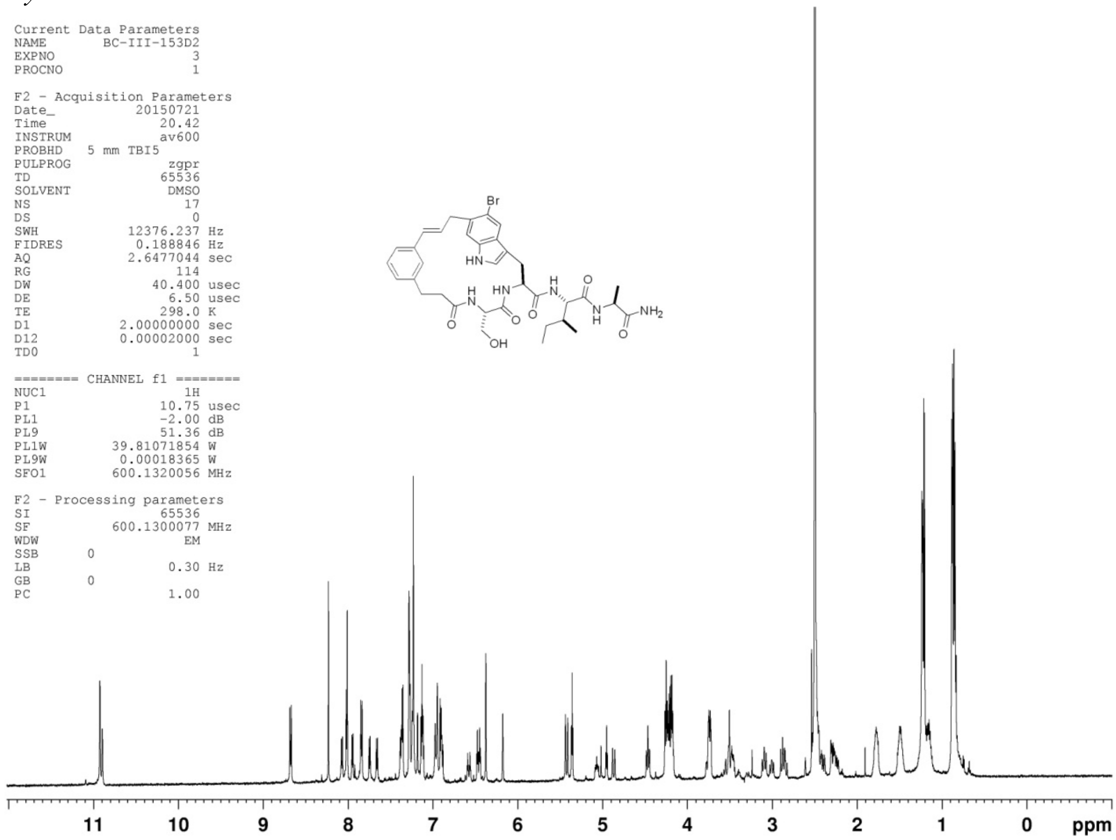


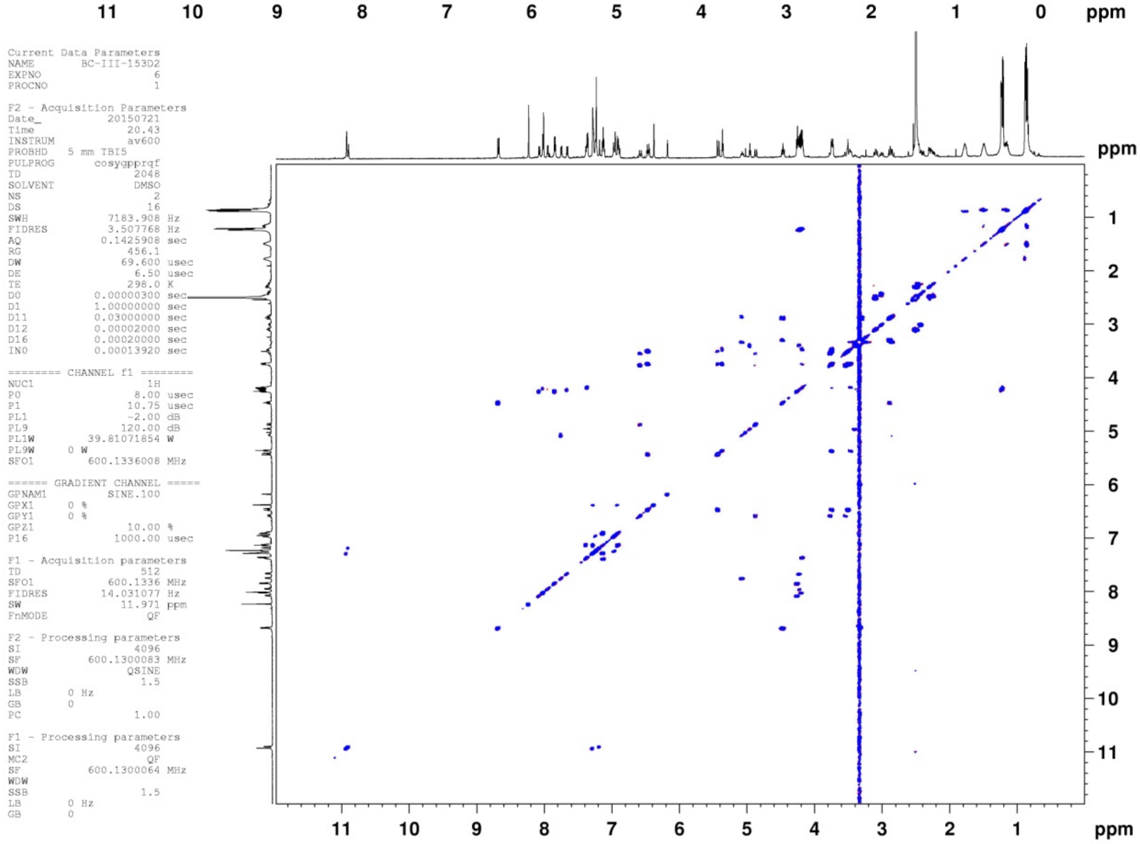

Current Data Parameters
NAME BC-III-153C1
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150702
Time 17.59
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003767 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.25 usec
P2 20.50 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.83 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.61216140 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300057 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300061 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm

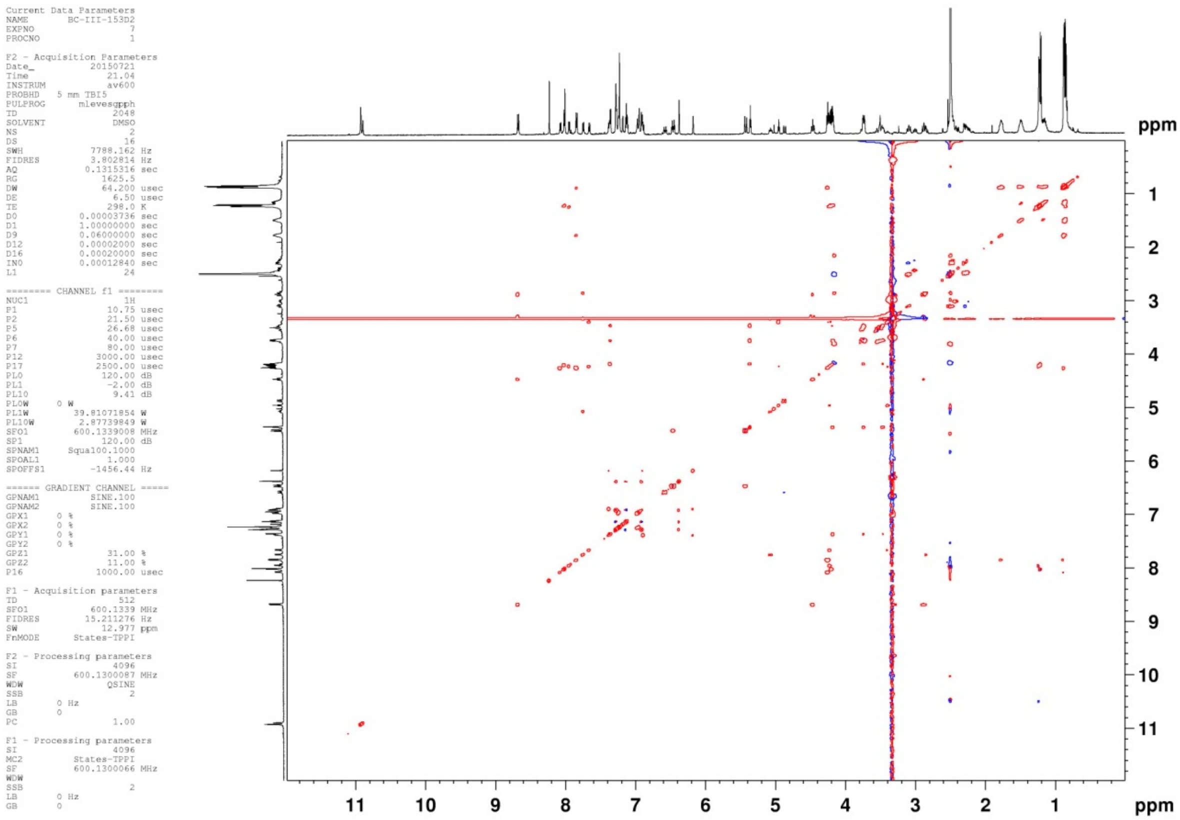

Current Data Parameters
NAME BC-III-153C1
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150702
Time 18.21
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.5 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.25 usec
P2 20.50 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300051 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029120 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
12
11
10
9
8
7
6
5
4
3
2
1
ppm

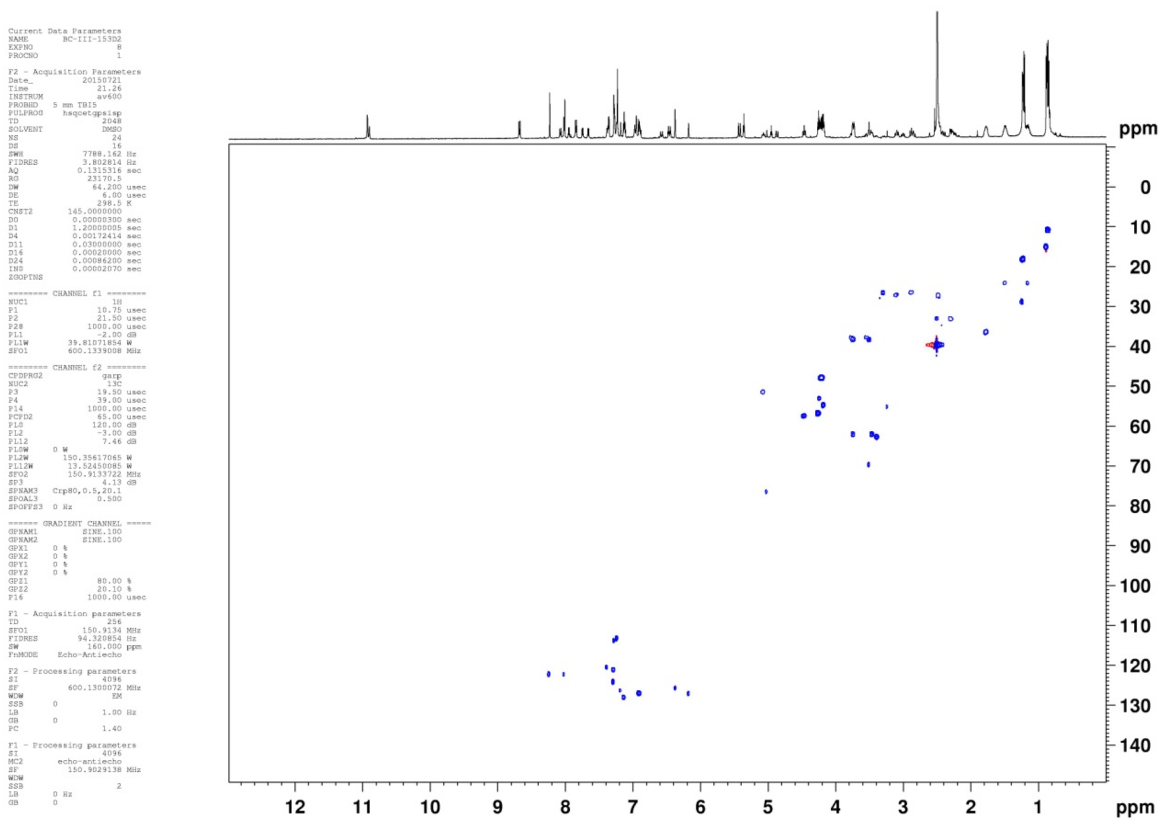

Current Data Parameters
NAME BC-III-153C1
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150702
Time 20.41
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 45
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.4 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.25 usec
P2 20.50 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300065 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028799 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm

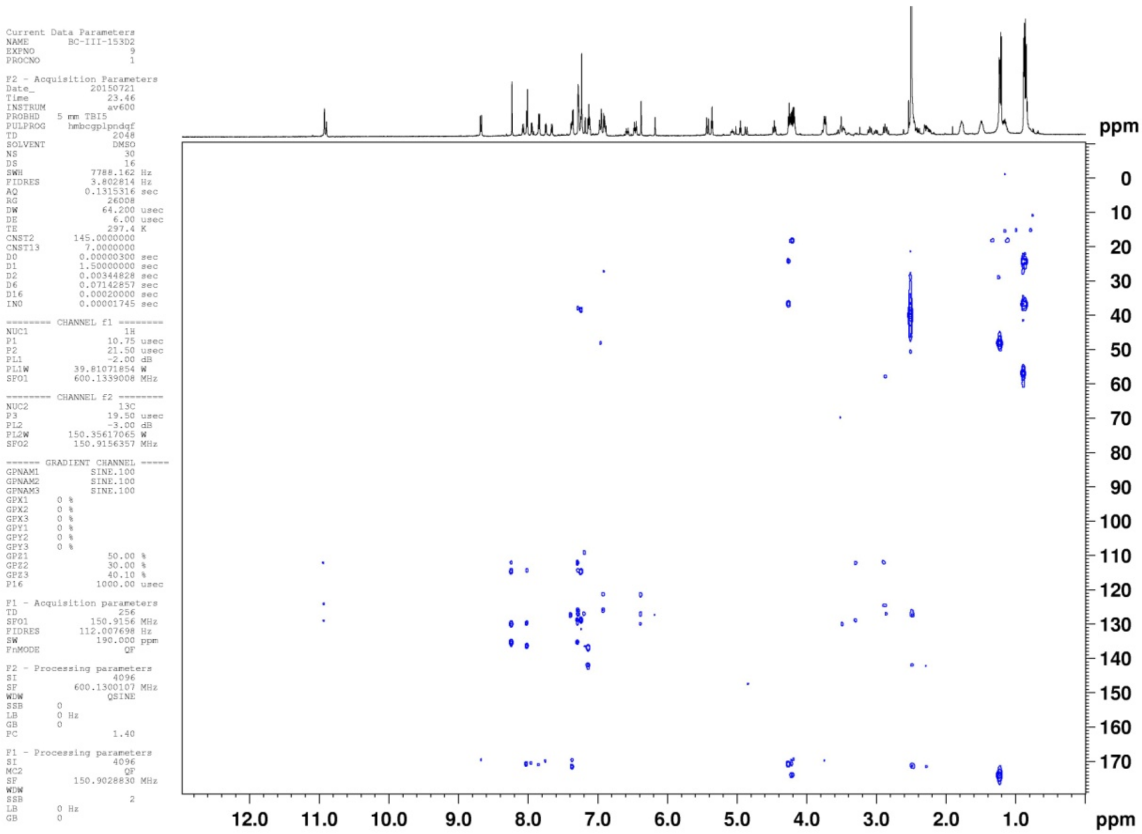
Macrocyclic Product ***2.17c***





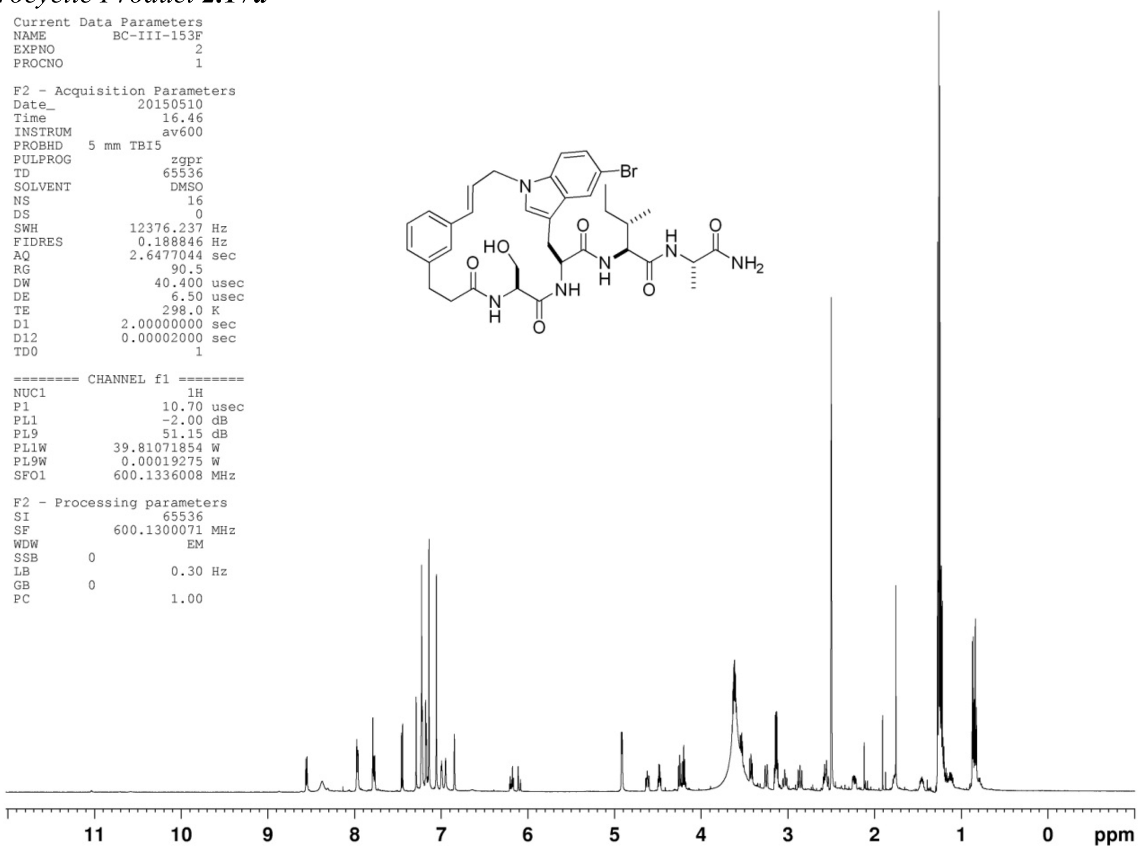

Current Data Parameters
NAME BC-III-153D2
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150721
Time 21.04
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003736 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.75 usec
P2 21.50 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.41 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.87739849 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300087 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300066 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
1
2
3
4
5
6
7
8
9
10
11
11
10
9
8
7
6
5
4
3
2
1
ppm


Current Data Parameters
NAME BC-III-153D2
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150721
Time 21.26
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.5 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.75 usec
P2 21.50 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300072 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029138 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
12
11
10
9
8
7
6
5
4
3
2
1
ppm

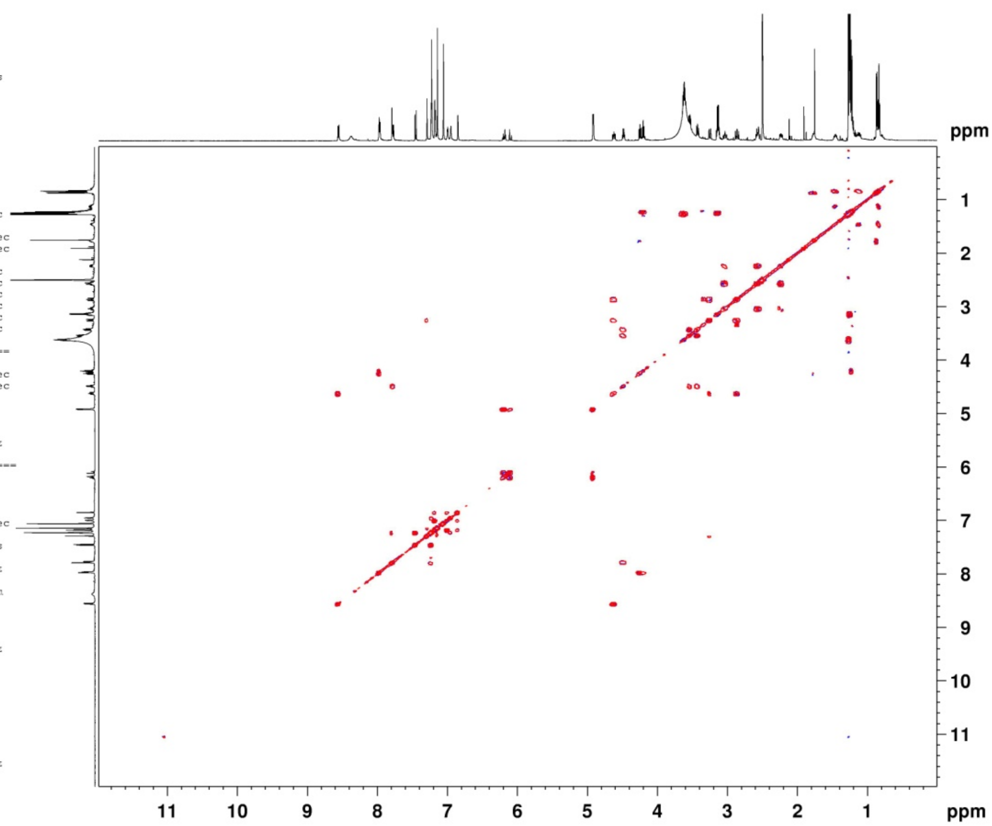

Current Data Parameters
NAME BC-III-153D2
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150721
Time 23.46
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 30
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.4 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.75 usec
P2 21.50 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300107 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028830 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

*Macrocyclic Product **2.17d***

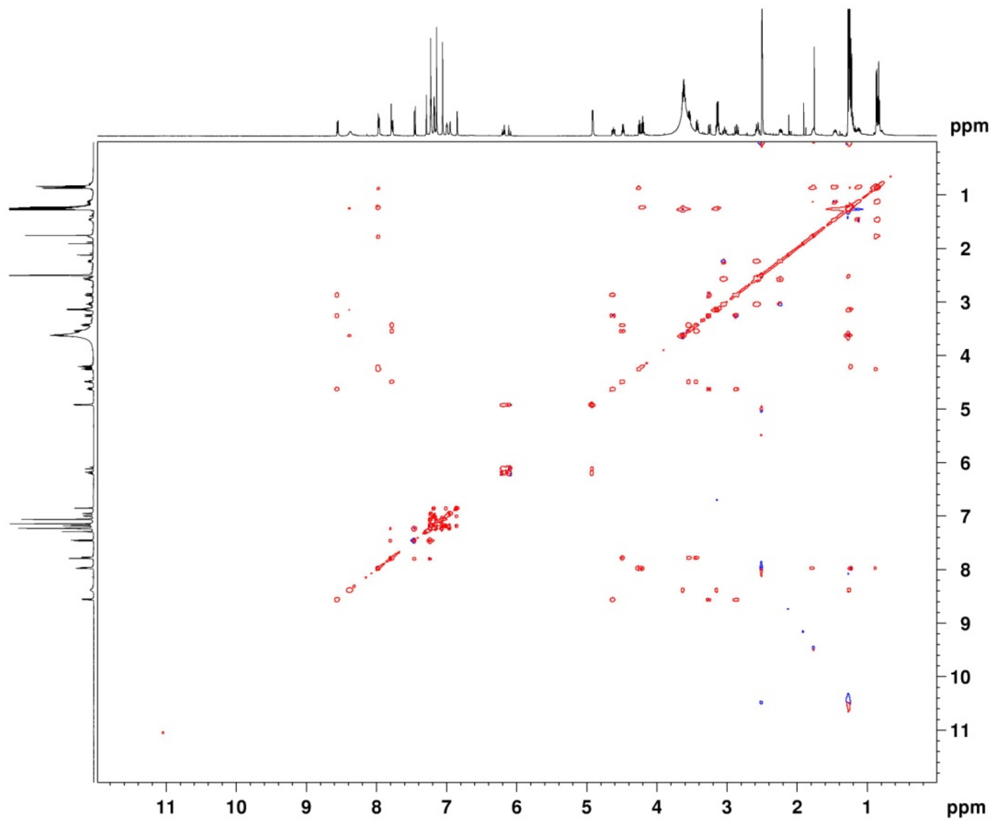
```
Current Data Parameters
NAME          BC-III-153F
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_          20150510
Time              16.46
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zgpr
TD                65536
SOLVENT            DMSO
NS                   16
DS                    0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6477044 sec
RG                 90.5
DW               40.400 usec
DE                 6.50 usec
TE                298.0 K
D1           2.00000000 sec
D12          0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.70 usec
PL1               -2.00 dB
PL9               51.15 dB
PL1W        39.81071854 W
PL9W         0.00019275 W
SFO1        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF          600.1300071 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```



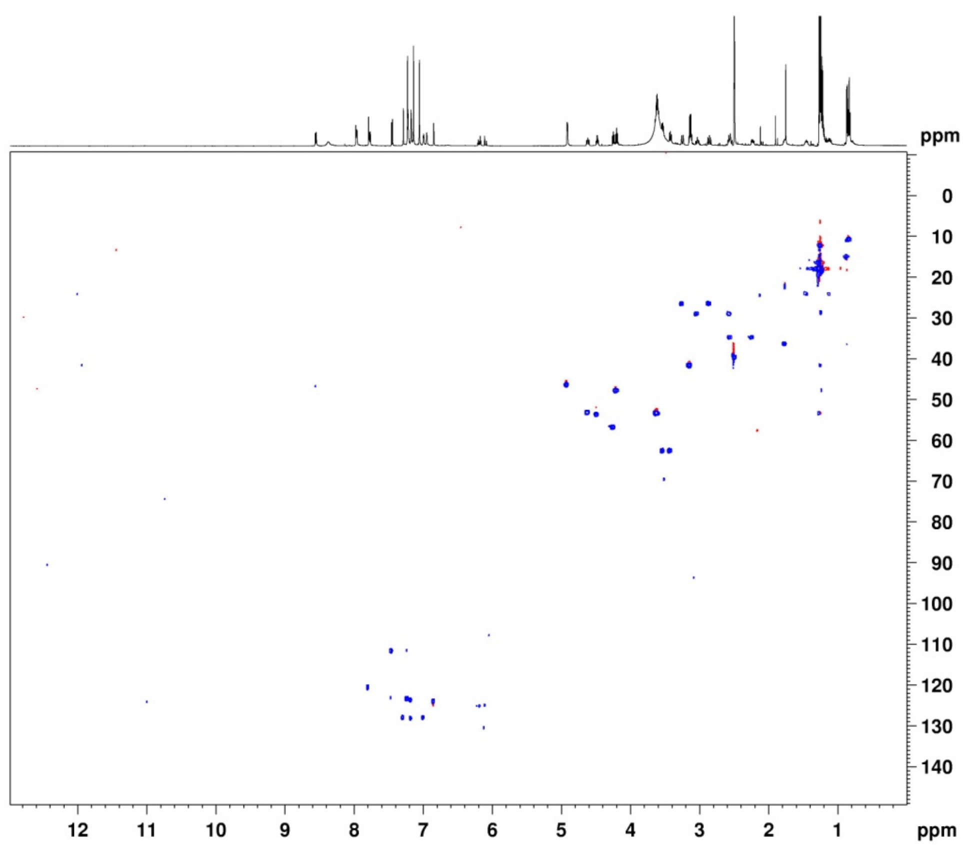

```
Current Data Parameters
NAME          BC-III-153F
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_          20150510
Time              16.52
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG       cosygpprqf
TD                 2048
SOLVENT            DMSO
NS                    2
DS                   16
SWH            7183.908 Hz
FIDRES         3.507768 Hz
AQ            0.1425908 sec
RG                  362
DW               69.600 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00000300 sec
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00013920 sec

======== CHANNEL f1 ========
NUC1                 1H
P0                 8.00 usec
P1                10.70 usec
PL1               -2.00 dB
PL9              120.00 dB
PL1W        39.81071854 W
PL9W     0 W
SFO1        600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM1        SINE.100
GPX1     0 %
GPY1     0 %
GPZ1              10.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  512
SFO1           600.1336 MHz
FIDRES        14.031077 Hz
SW               11.971 ppm
FnMODE               QF

F2 - Processing parameters
SI                 4096
SF          600.1300052 MHz
WDW               QSINE
SSB                 1.5
LB       0 Hz
GB       0
PC                 1.00

F1 - Processing parameters
SI                 4096
MC2                  QF
SF          600.1300052 MHz
WDW
SSB                 1.5
LB       0 Hz
GB       0
```

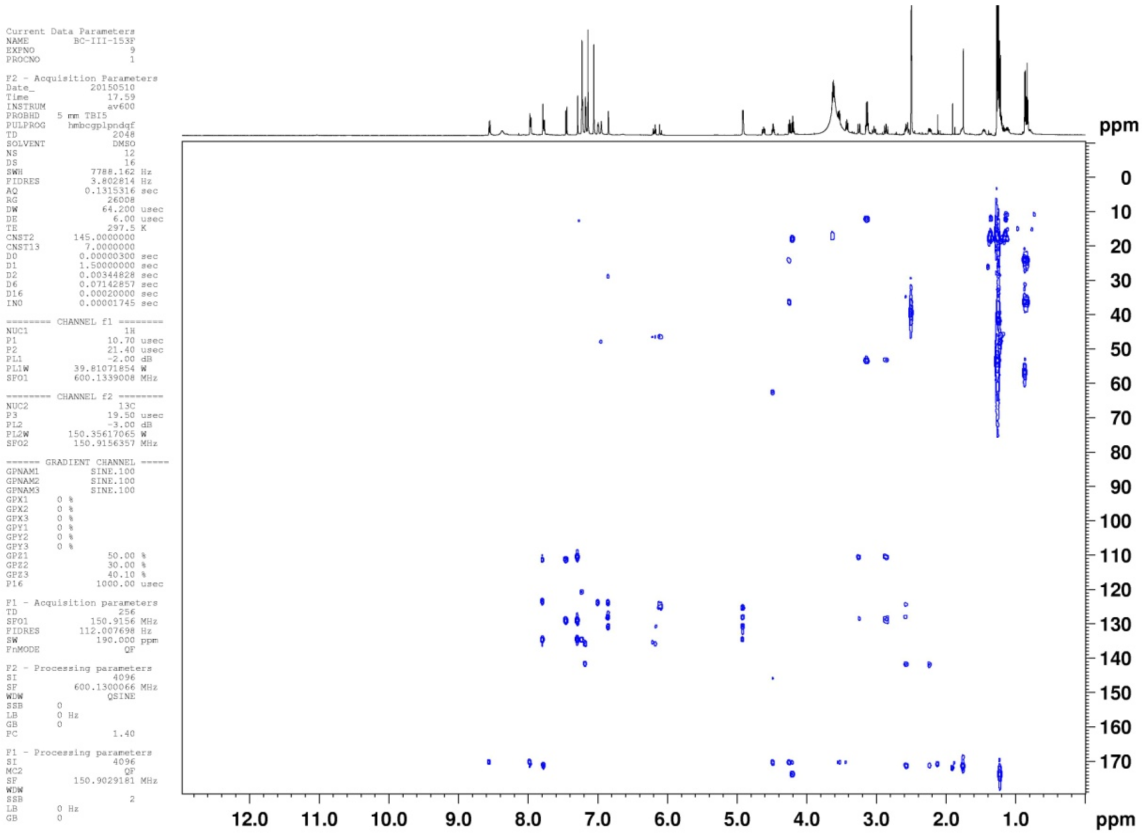


```
Current Data Parameters
NAME          BC-III-153F
EXPNO                   7
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150510
Time                17.13
INSTRUM             av600
PROBHD    5 mm TBI5
PULPROG        mlevesgpph
TD                   2048
SOLVENT              DMSO
NS                      2
DS                     16
SWH              7788.162 Hz
FIDRES           3.802814 Hz
AQ              0.1315316 sec
RG                 1625.5
DW                 64.200 usec
DE                   6.50 usec
TE                  298.0 K
D0             0.00003739 sec
D1             1.00000000 sec
D9             0.06000000 sec
D12            0.00002000 sec
D16            0.00020000 sec
IN0            0.00012840 sec
L1                     24

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.70 usec
P2                  21.40 usec
P5                  26.68 usec
P6                  40.00 usec
P7                  80.00 usec
P12               3000.00 usec
P17               2500.00 usec
PL0                120.00 dB
PL1                 -2.00 dB
PL10                 9.45 dB
PL0W      0 W
PL1W          39.81071854 W
PL10W          2.85101843 W
SFO1          600.1339008 MHz
SP1                120.00 dB
SPNAM1       Squa100.1000
SPOAL1              1.000
SPOFFS1          -1456.44 Hz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                31.00 %
GPZ2                11.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    512
SFO1             600.1339 MHz
FIDRES          15.211276 Hz
SW                 12.977 ppm
FnMODE        States-TPPI

F2 - Processing parameters
SI                   4096
SF            600.1300062 MHz
WDW                 QSINE
SSB                     2
LB        0 Hz
GB        0
PC                   1.00

F1 - Processing parameters
SI                   4096
MC2           States-TPPI
SF            600.1300063 MHz
WDW
SSB                     2
LB        0 Hz
GB        0
```



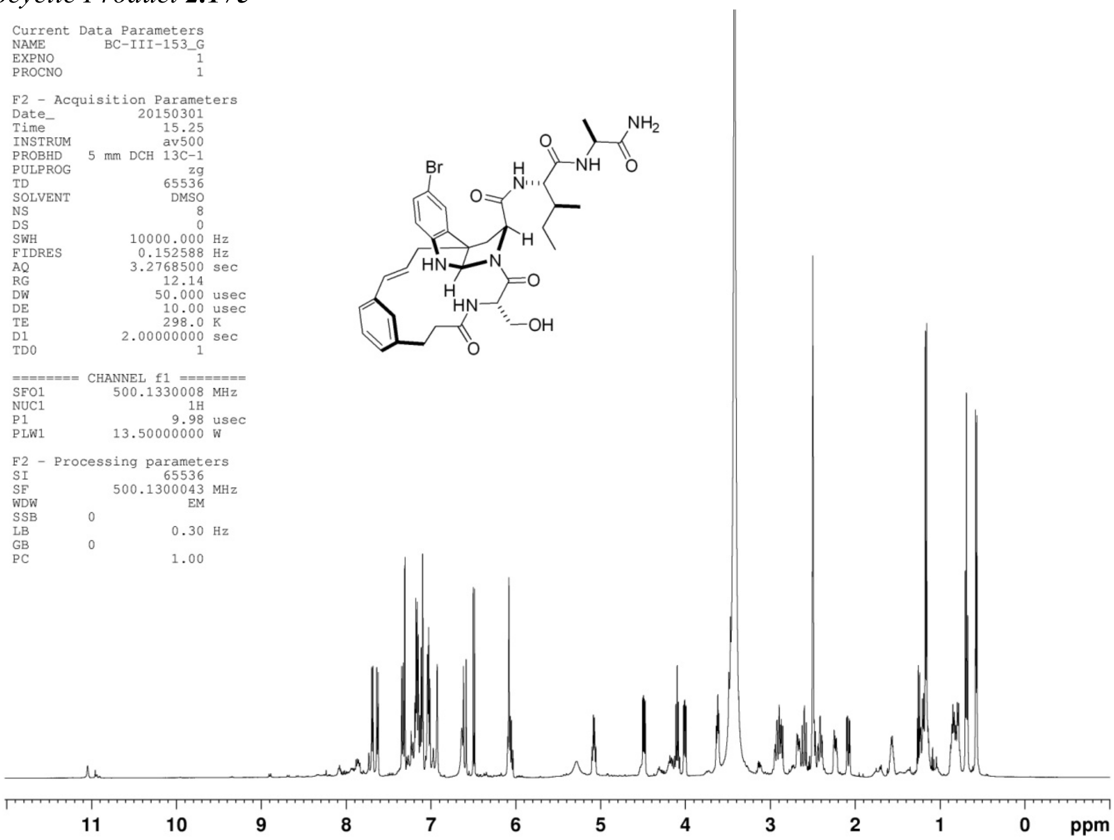

```
Current Data Parameters
NAME          BC-III-153F
EXPNO                   8
PROCNO                  1

F2 - Acquisition Parameters
Date_            20150510
Time                17.35
INSTRUM             av600
PROBHD    5 mm TBI5
PULPROG       hsqcetgpsisp
TD                   2048
SOLVENT              DMSO
NS                      4
DS                     16
SWH              7788.162 Hz
FIDRES           3.802814 Hz
AQ              0.1315316 sec
RG                23170.5
DW                 64.200 usec
DE                   6.00 usec
TE                  298.3 K
CNST2         145.0000000
D0             0.00000300 sec
D1             1.20000005 sec
D4             0.00172414 sec
D11            0.03000000 sec
D16            0.00020000 sec
D24            0.00086200 sec
IN0            0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.70 usec
P2                  21.40 usec
P28               1000.00 usec
PL1                 -2.00 dB
PL1W          39.81071854 W
SFO1          600.1339008 MHz

======== CHANNEL f2 ========
CPDPRG2              garp
NUC2                  13C
P3                  19.50 usec
P4                  39.00 usec
P14               1000.00 usec
PCPD2               65.00 usec
PL0                120.00 dB
PL2                 -3.00 dB
PL12                 7.46 dB
PL0W      0 W
PL2W         150.35617065 W
PL12W         13.52450085 W
SFO2          150.9133722 MHz
SP3                  4.13 dB
SPNAM3    Crp80,0.5,20.1
SPOAL3              0.500
SPOFFS3   0 Hz

====== GRADIENT CHANNEL =====
GPNAM1           SINE.100
GPNAM2           SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                80.00 %
GPZ2                20.10 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    256
SFO1             150.9134 MHz
FIDRES          94.320854 Hz
SW                160.000 ppm
FnMODE      Echo-Antiecho

F2 - Processing parameters
SI                   4096
SF            600.1300051 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   1.40

F1 - Processing parameters
SI                   4096
MC2         echo-antiecho
SF            150.9029290 MHz
WDW
SSB                     2
LB        0 Hz
GB        0
```

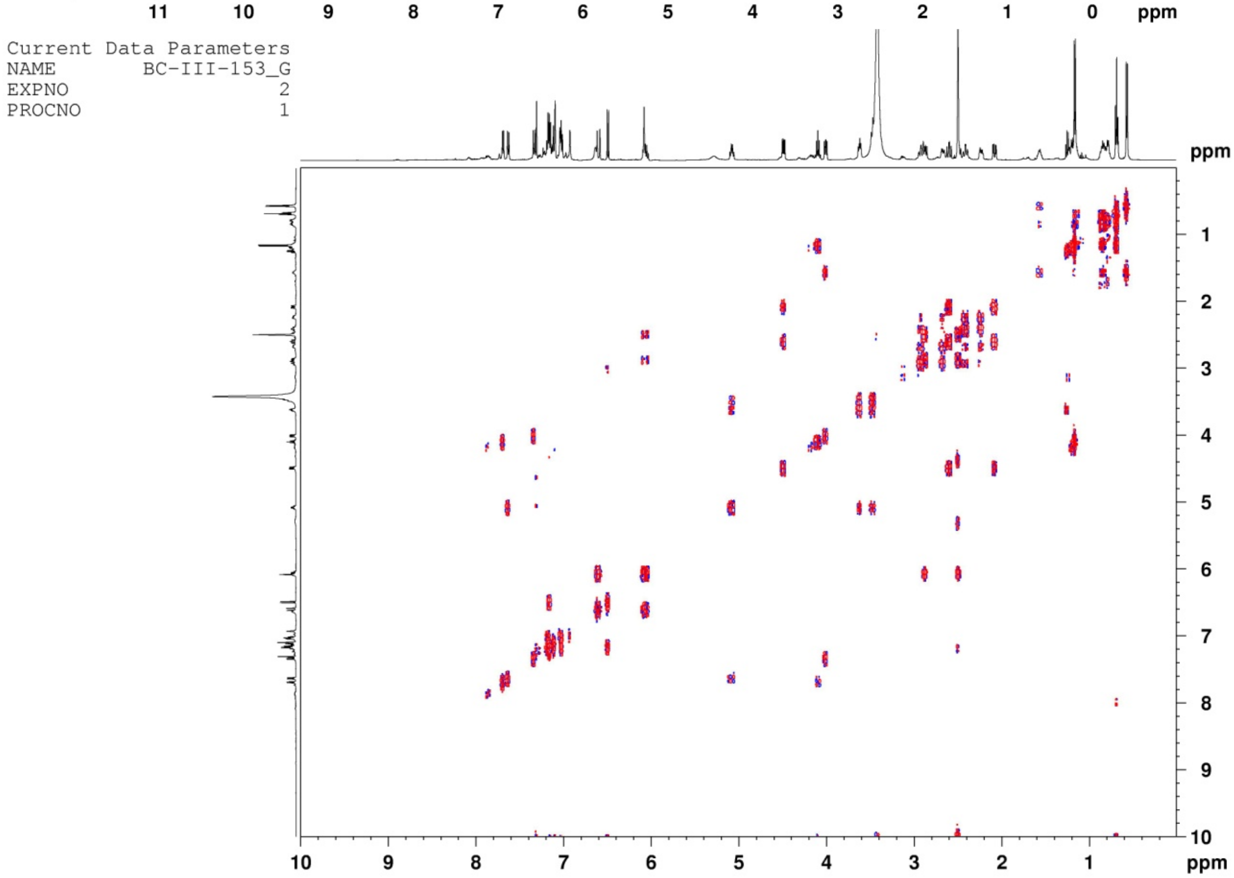


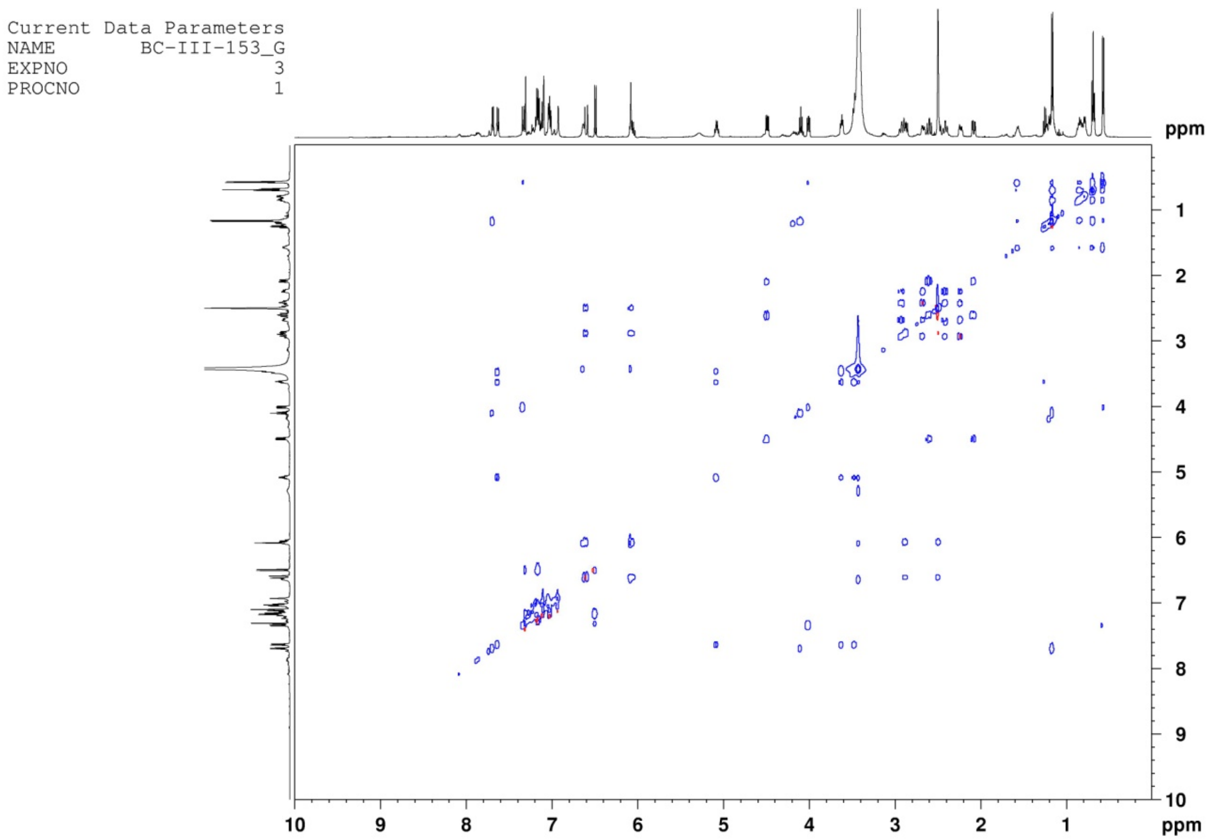


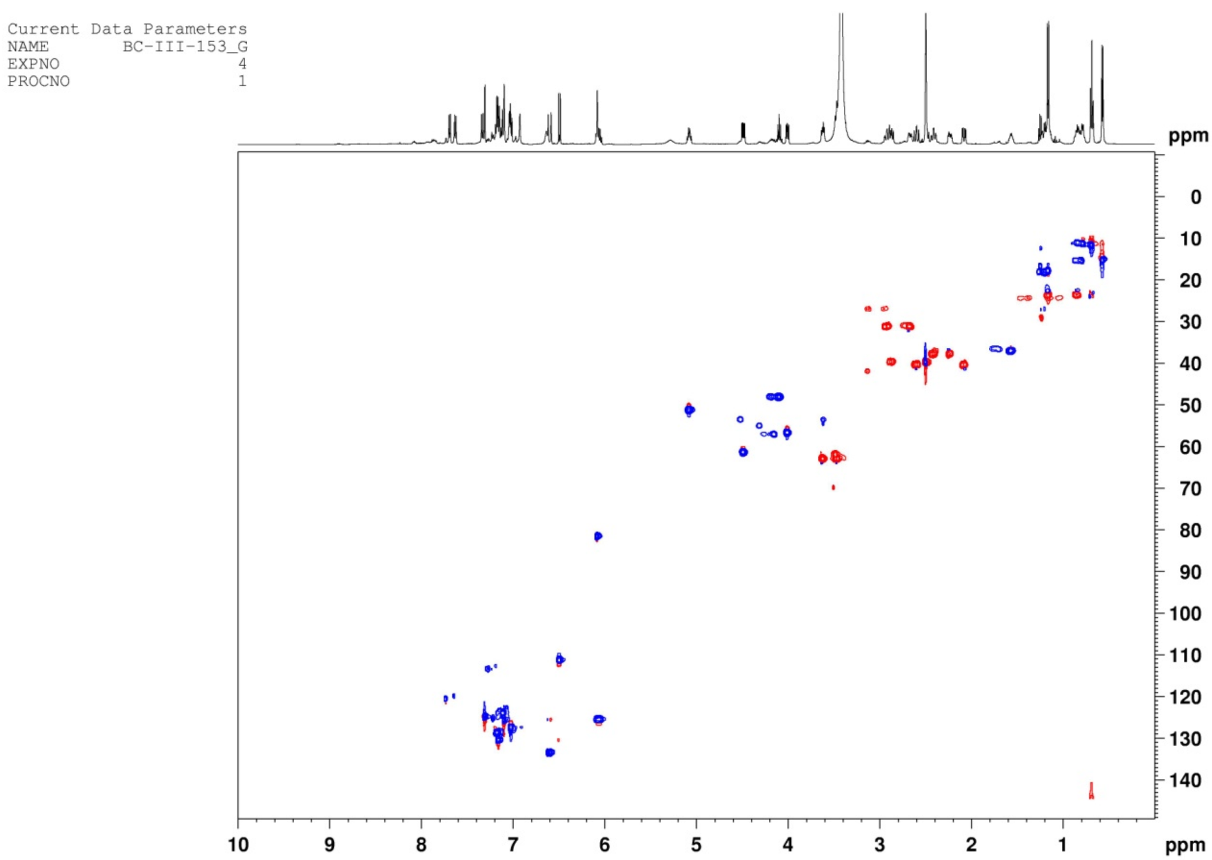
Current Data Parameters
NAME BC-III-153F
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150510
Time 17.59
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 12
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.70 usec
P2 21.40 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300066 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9029181 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

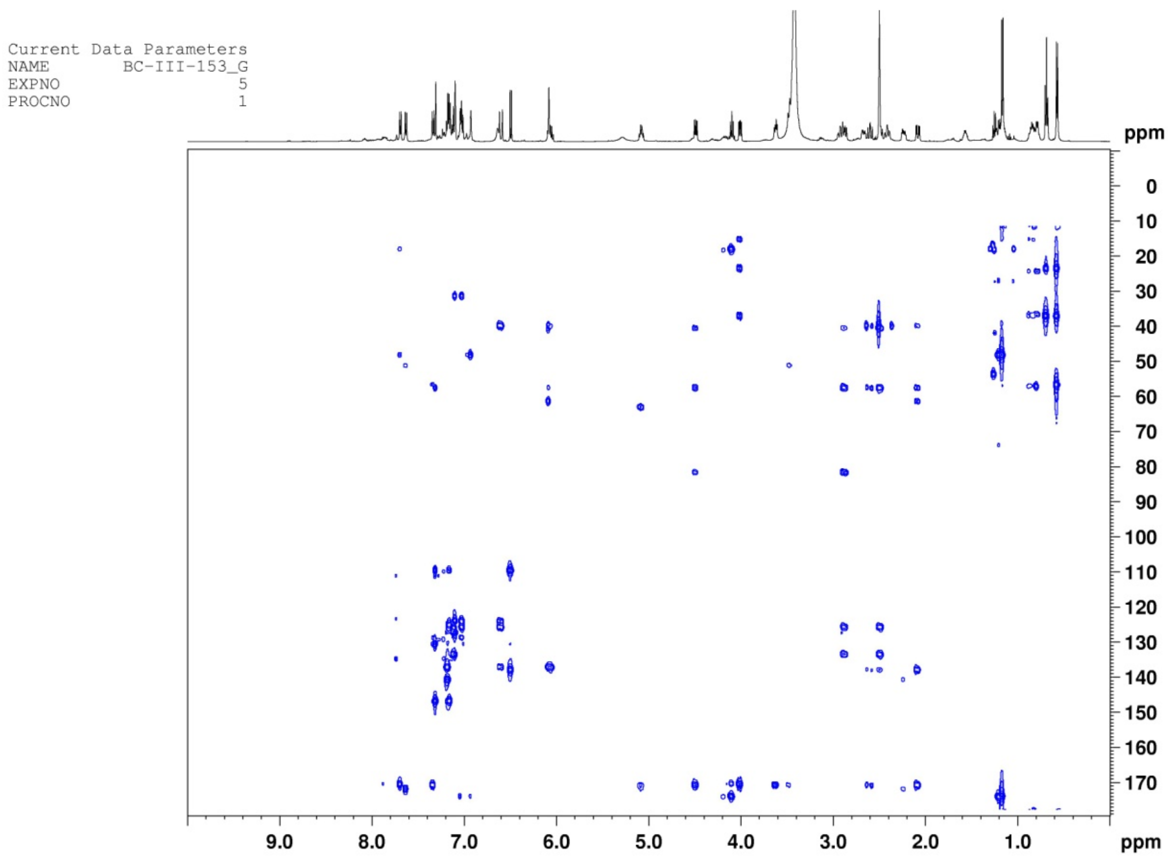
*Macrocyclic Product **2.17e***





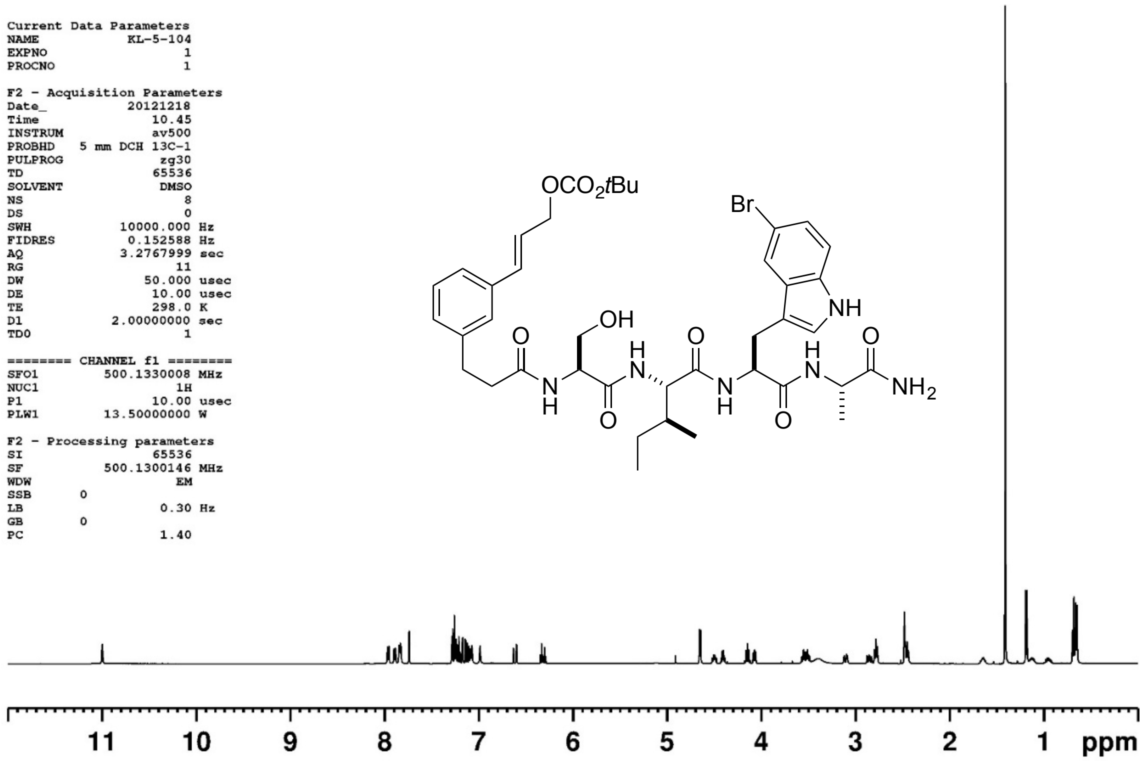

Current Data Parameters
NAME BC-III-153_G
EXPNO 3
PROCNO 1
ppm
1
2
3
4
5
6
7
8
9
10
ppm
10
9
8
7
6
5
4
3
2
1
ppm

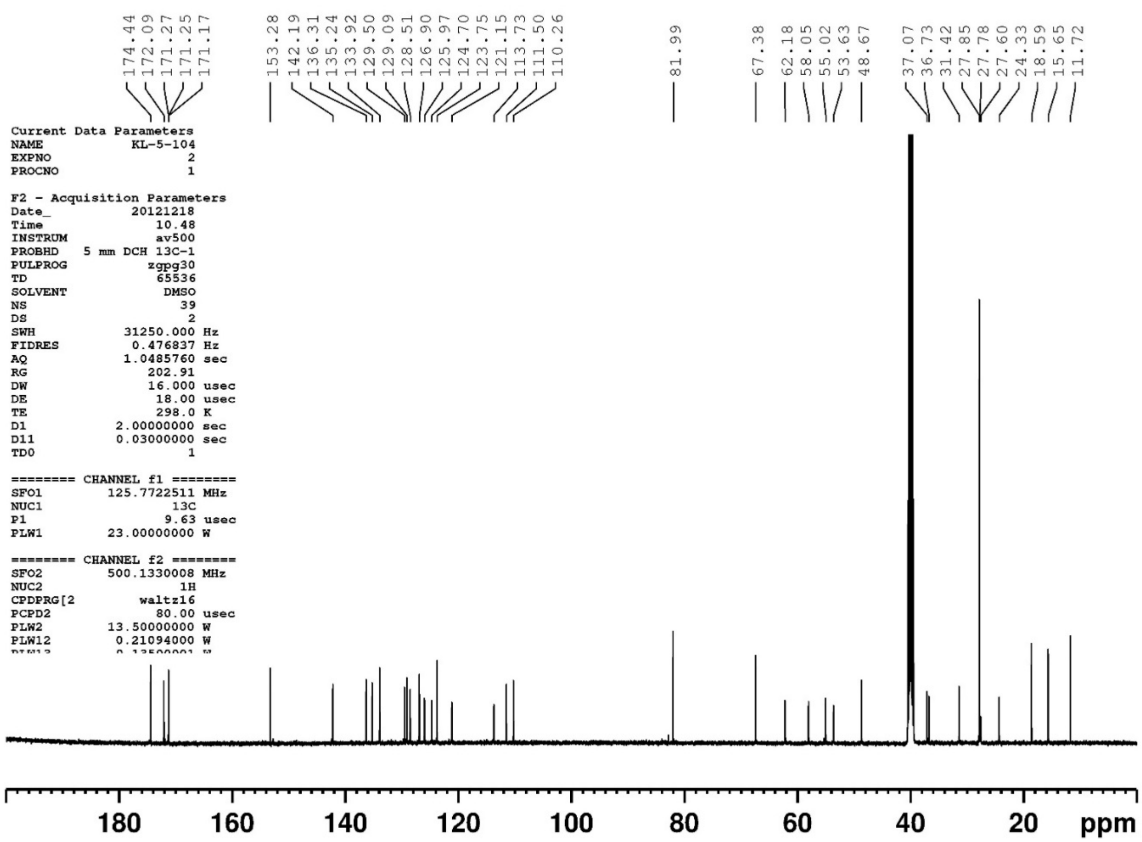

Current Data Parameters
NAME BC-III-153_G
EXPNO 4
PROCNO 1
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
10
9
8
7
6
5
4
3
2
1
ppm



Current Data Parameters
NAME BC-III-153_G
EXPNO 5
PROCNO 1
ppm
ppm

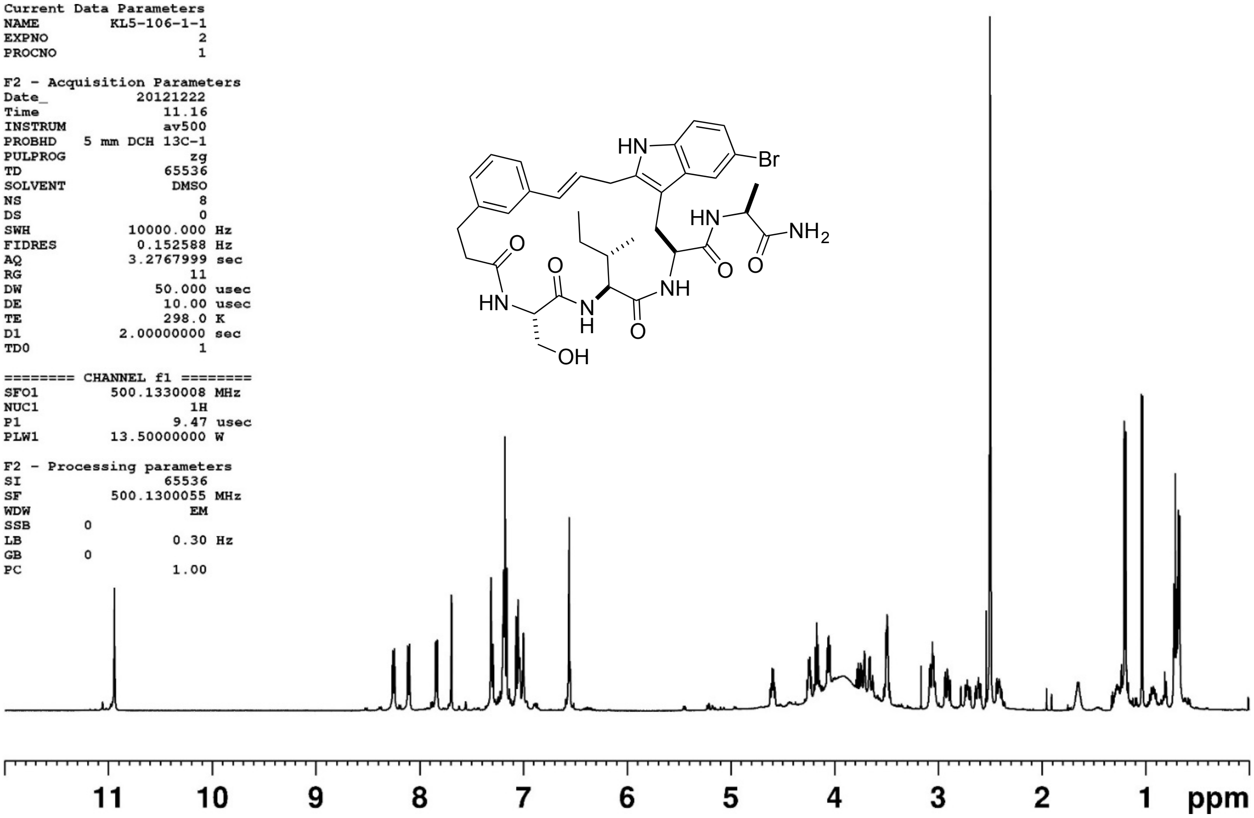
*Acyclic Precursor **2.14***

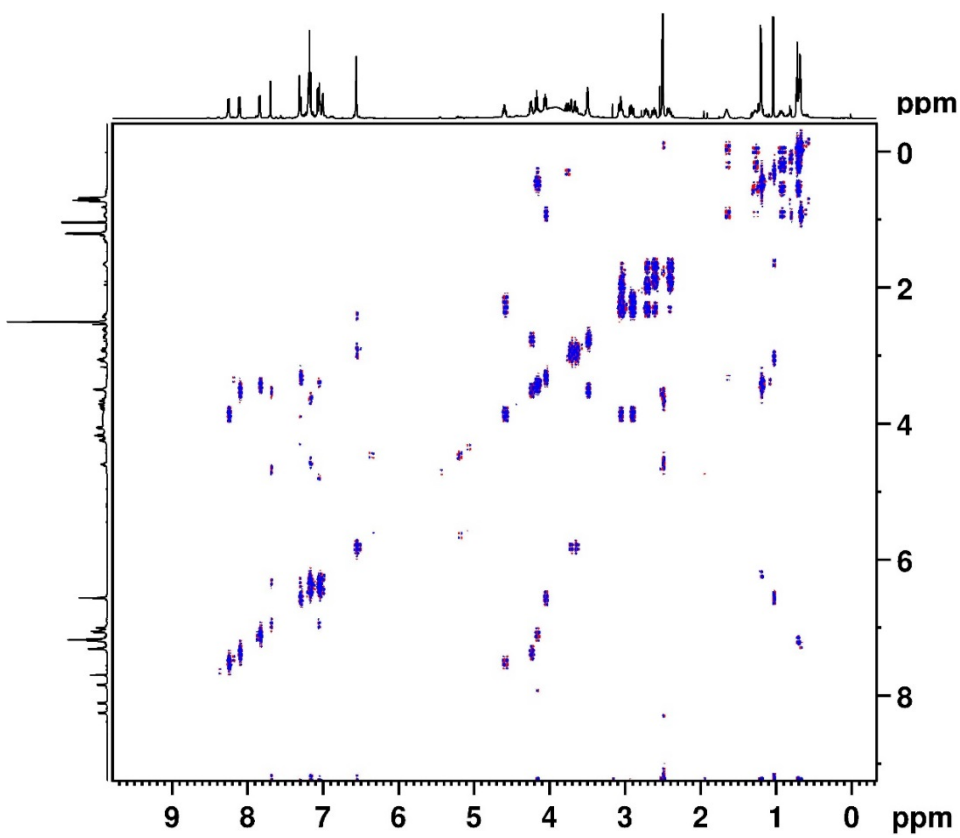




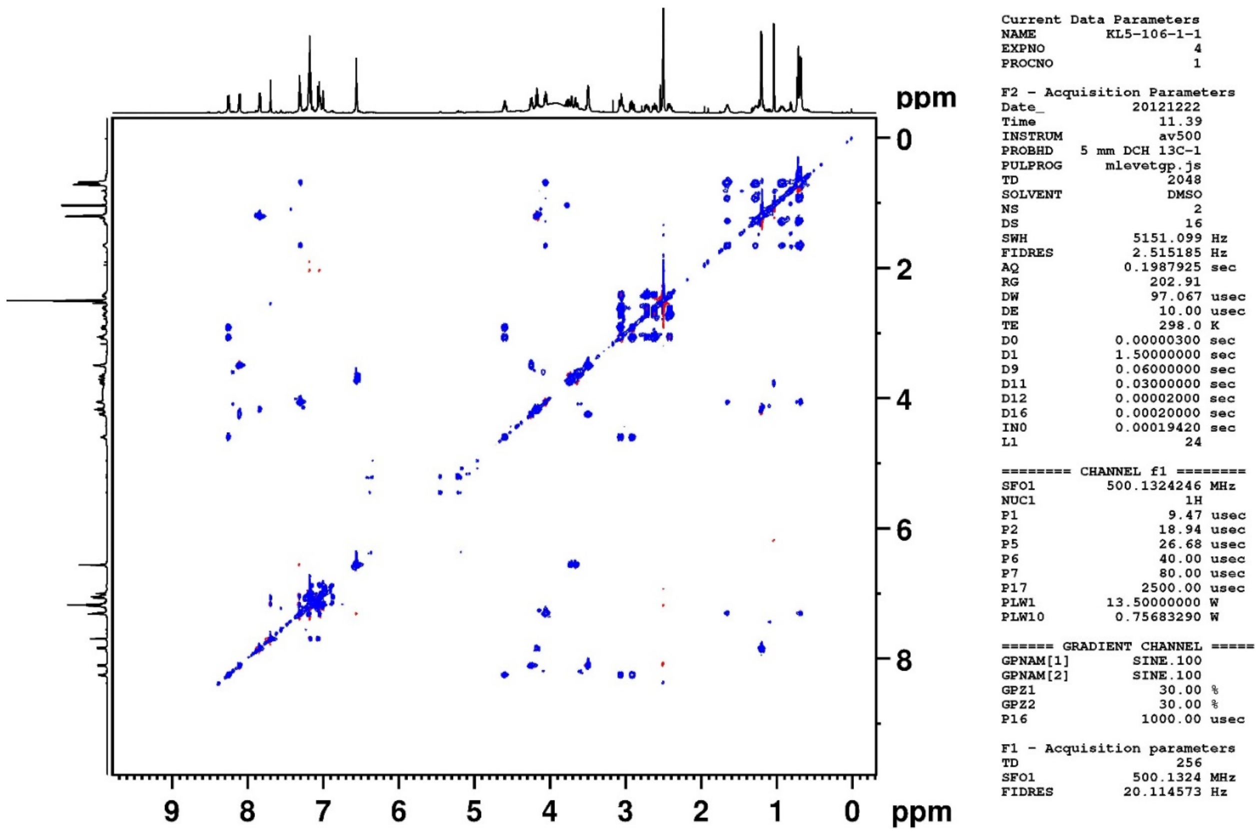
Macrocyclic Product ***2.18a***

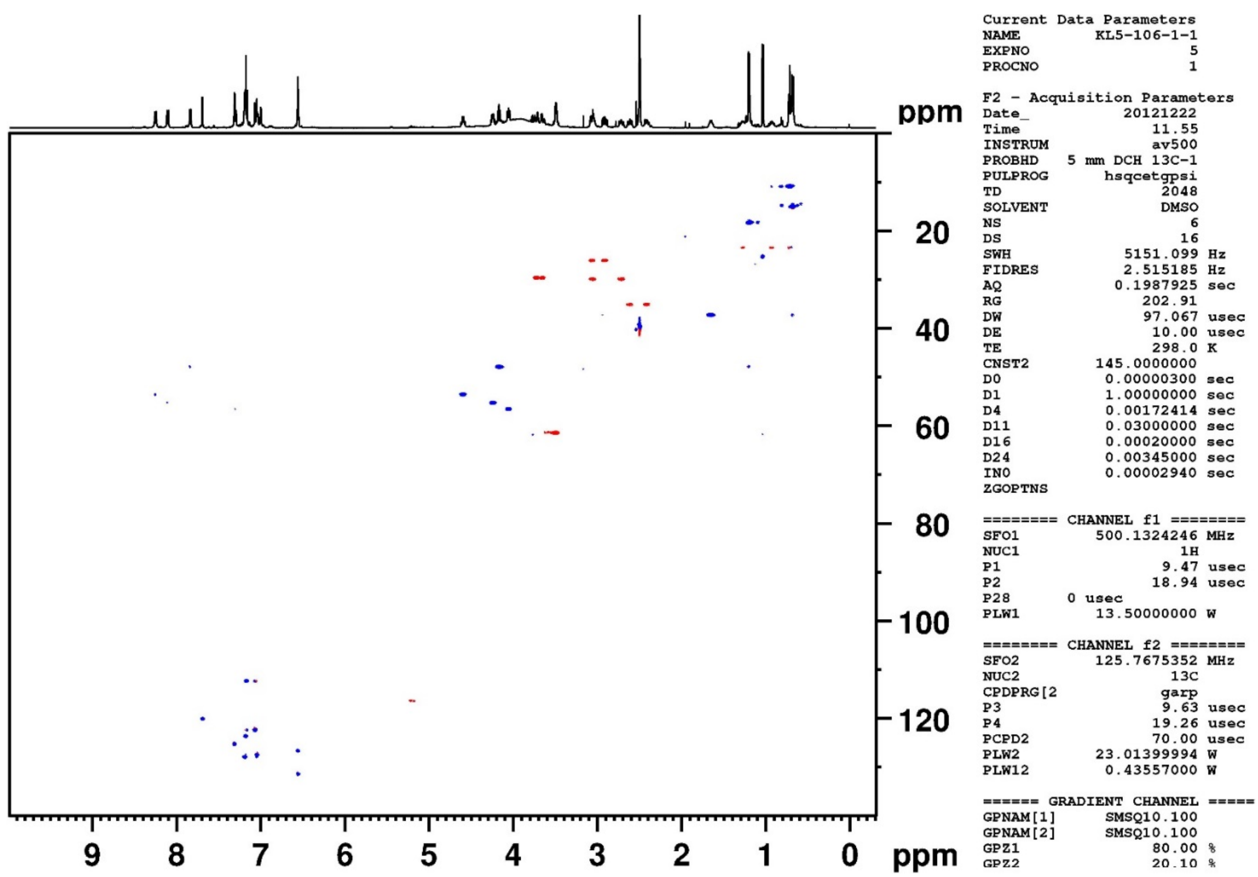
```
Current Data Parameters
NAME          KL5-106-1-1
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20121222
Time                11.16
INSTRUM             av500
PROBHD   5 mm DCH 13C-1
PULPROG                zg
TD                  65536
SOLVENT              DMSO
NS                      8
DS                      0
SWH             10000.000 Hz
FIDRES           0.152588 Hz
AQ              3.2767999 sec
RG                     11
DW                 50.000 usec
DE                  10.00 usec
TE                  298.0 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
SFO1          500.1330008 MHz
NUC1                   1H
P1                   9.47 usec
PLW1          13.50000000 W

F2 - Processing parameters
SI                  65536
SF            500.1300055 MHz
WDW                    EM
SSB       0
LB                   0.30 Hz
GB        0
PC                   1.00
```

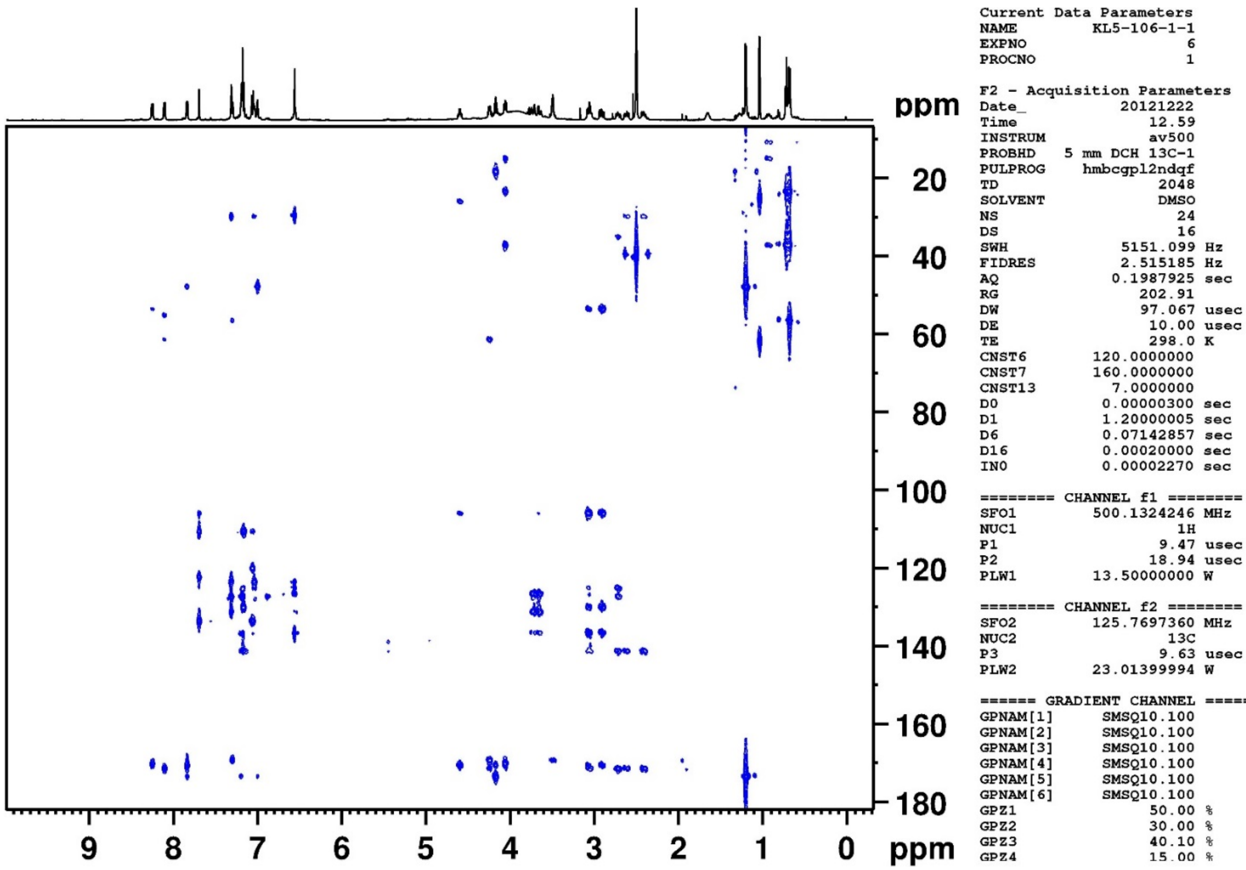





```
Current Data Parameters
NAME          KL5-106-1-1
EXPNO                   3
PROCNO                  1

F2 - Acquisition Parameters
Date_            20121222
Time                11.24
INSTRUM             av500
PROBHD   5 mm DCH 13C-1
PULPROG        cosygpmfph
TD                   2048
SOLVENT              DMSO
NS                      2
DS                      8
SWH              5151.099 Hz
FIDRES           2.515185 Hz
AQ              0.1987925 sec
RG                     11
DW                 97.067 usec
DE                  10.00 usec
TE                  298.0 K
D0             0.00008504 sec
D1             1.50000000 sec
D13            0.00000400 sec
D16            0.00020000 sec
IN0            0.00019420 sec

======== CHANNEL f1 ========
SFO1          500.1324246 MHz
NUC1                   1H
P1                   9.47 usec
P2                  18.94 usec
PLW1          13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPNAM[2]       SMSQ10.100
GPZ1                10.00 %
GPZ2                20.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    256
SFO1             500.1324 MHz
FIDRES          20.114573 Hz
SW                 10.296 ppm
FnMODE        States-TPPI

F2 - Processing parameters
SI                   2048
SF            500.1300135 MHz
WDW                  SINE
SSB                     1
```

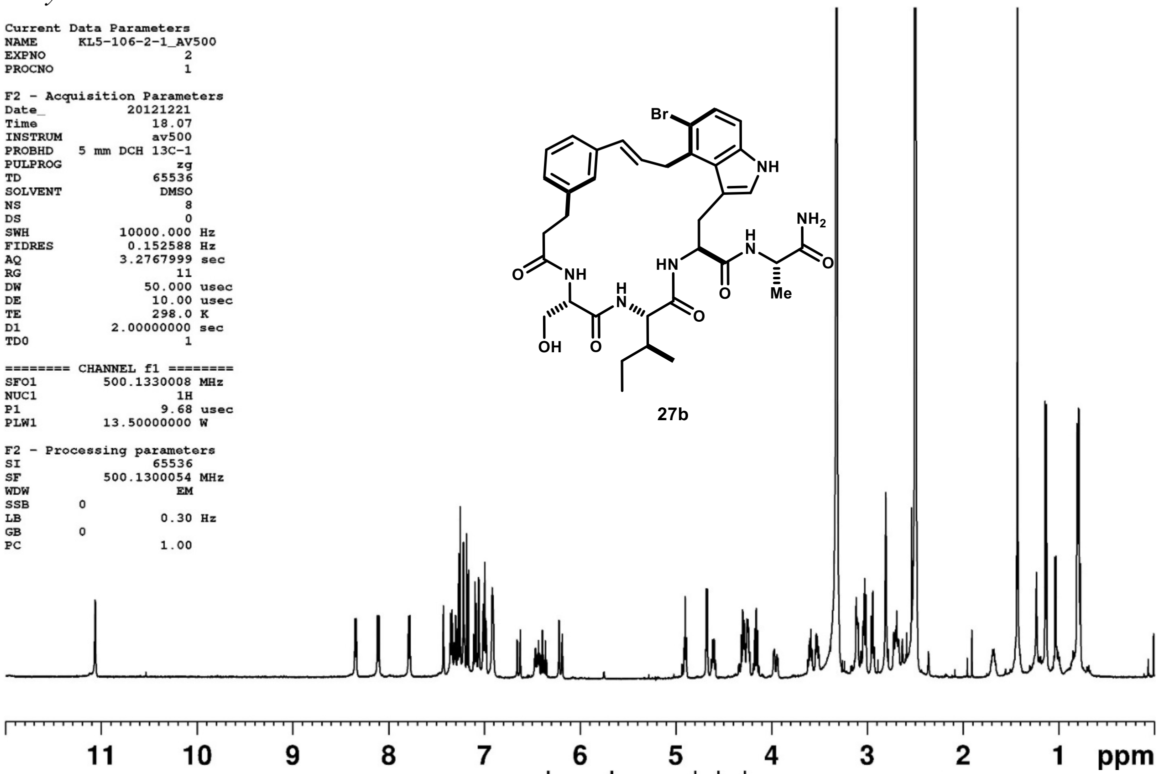

ppm
0
2
4
6
8
9 8 7 6 5 4 3 2 1 0 ppm
Current Data Parameters
NAME KL5-106-1-1
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121222
Time 11.39
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5151.099 Hz
FIDRES 2.515185 Hz
AQ 0.1987925 sec
RG 202.91
DW 97.067 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.50000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019420 sec
L1 24
======== CHANNEL f1 ========
SFO1 500.1324246 MHz
NUC1 1H
P1 9.47 usec
P2 18.94 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.75683290 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1324 MHz
FIDRES 20.114573 Hz

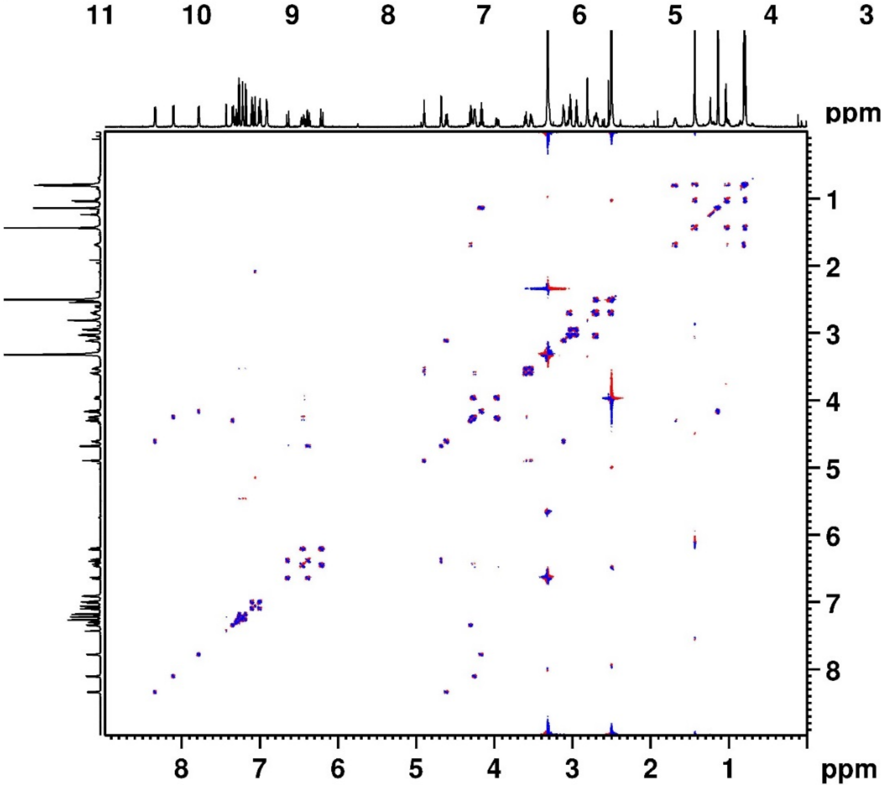

ppm
20
40
60
80
100
120
9 8 7 6 5 4 3 2 1 0 ppm
Current Data Parameters
NAME KL5-106-1-1
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121222
Time 11.55
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcetgpsi
TD 2048
SOLVENT DMSO
NS 6
DS 16
SWH 5151.099 Hz
FIDRES 2.515185 Hz
AQ 0.1987925 sec
RG 202.91
DW 97.067 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00345000 sec
IN0 0.00002940 sec
ZGOPTNS
======== CHANNEL f1 ========
SFO1 500.1324246 MHz
NUC1 1H
P1 9.47 usec
P2 18.94 usec
P28 0 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7675352 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %
GPZ2 20.10 %


ppm
20
40
60
80
100
120
140
160
180
9
8
7
6
5
4
3
2
1
0
ppm
Current Data Parameters
NAME KL5-106-1-1
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121222
Time 12.59
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 5151.099 Hz
FIDRES 2.515185 Hz
AQ 0.1987925 sec
RG 202.91
DW 97.067 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00002270 sec
======== CHANNEL f1 ========
SFO1 500.1324246 MHz
NUC1 1H
P1 9.47 usec
P2 18.94 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7697360 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

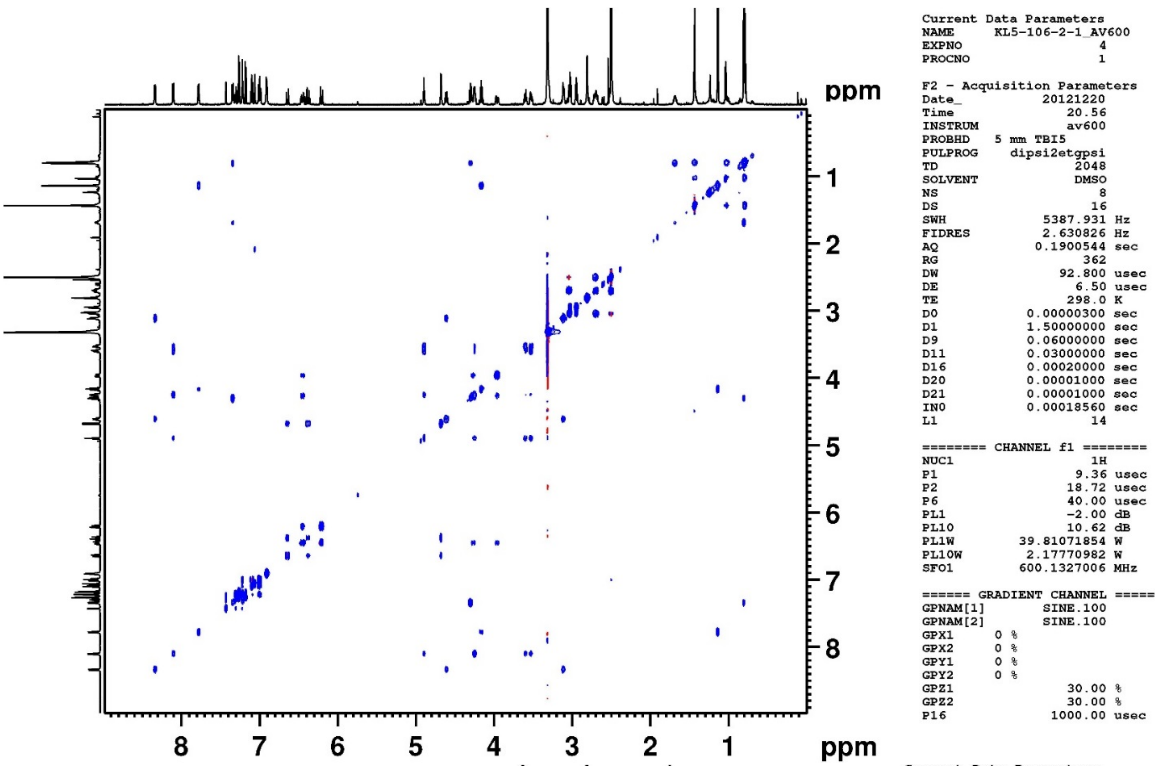
*Macrocyclic Product **2.18b***

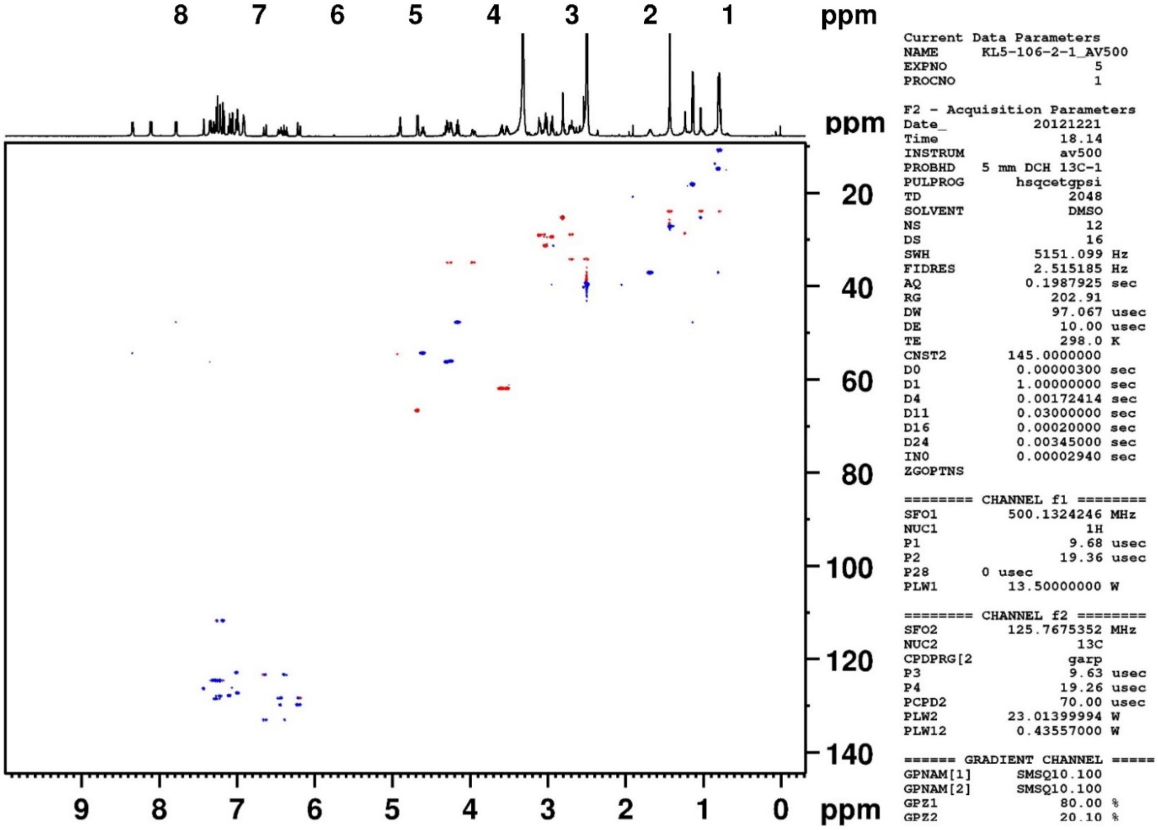
```
Current Data Parameters
NAME      KL5-106-2-1_AV500
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121221
Time              18.07
INSTRUM           av500
PROBHD   5 mm DCH 13C-1
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH          10000.000 Hz
FIDRES        0.152588 Hz
AQ           3.2767999 sec
RG                   11
DW              50.000 usec
DE               10.00 usec
TE               298.0 K
D1          2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1       500.1330008 MHz
NUC1                 1H
P1                 9.68 usec
PLW1        13.50000000 W

F2 - Processing parameters
SI                65536
SF         500.1300054 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```

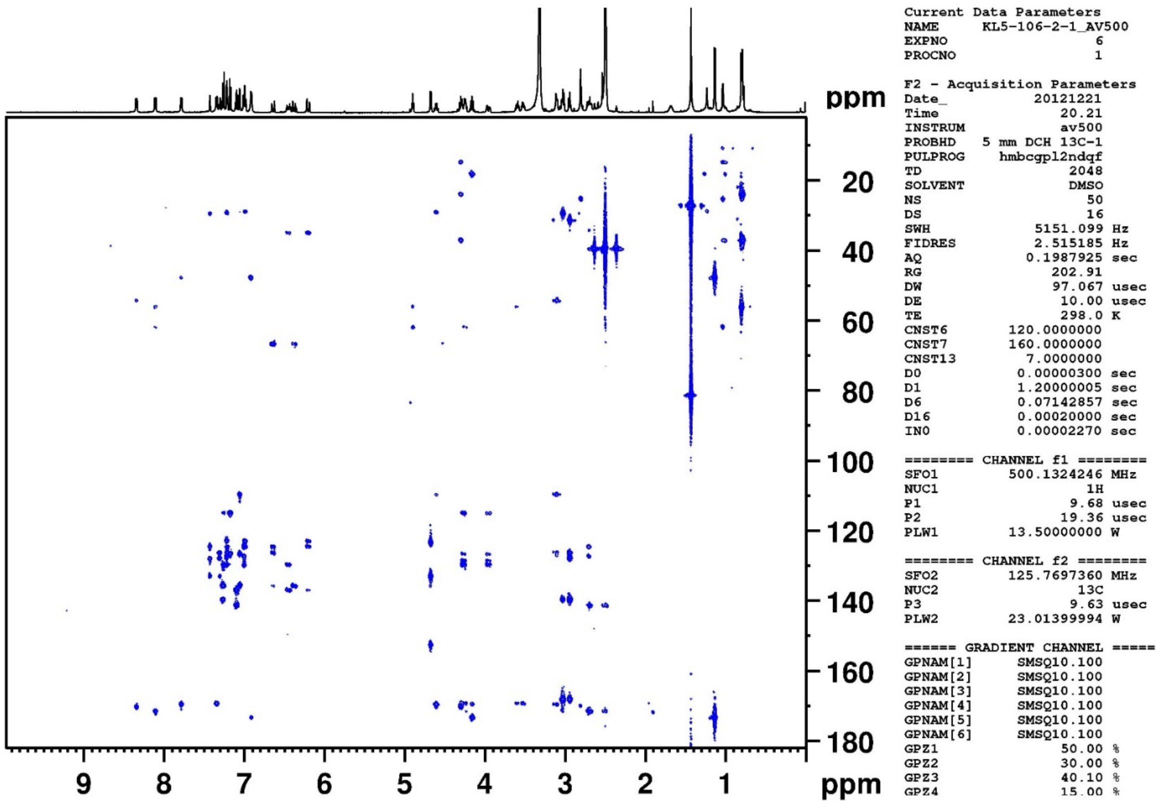





```
Current Data Parameters
NAME      KL5-106-2-1_AV600
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20121220
Time              20.41
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG      cosygpmfph
TD                 2048
SOLVENT            DMSO
NS                    1
DS                   16
SWH            5387.931 Hz
FIDRES         2.630826 Hz
AQ            0.1900544 sec
RG                  114
DW               92.800 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00008088 sec
D1           1.50000000 sec
D13          0.00000400 sec
D16          0.00020000 sec
IN0          0.00018560 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.36 usec
P2                18.72 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1       600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]      SINE.100
GPNAM[2]      SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              10.00 %
GPZ2              20.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI
```

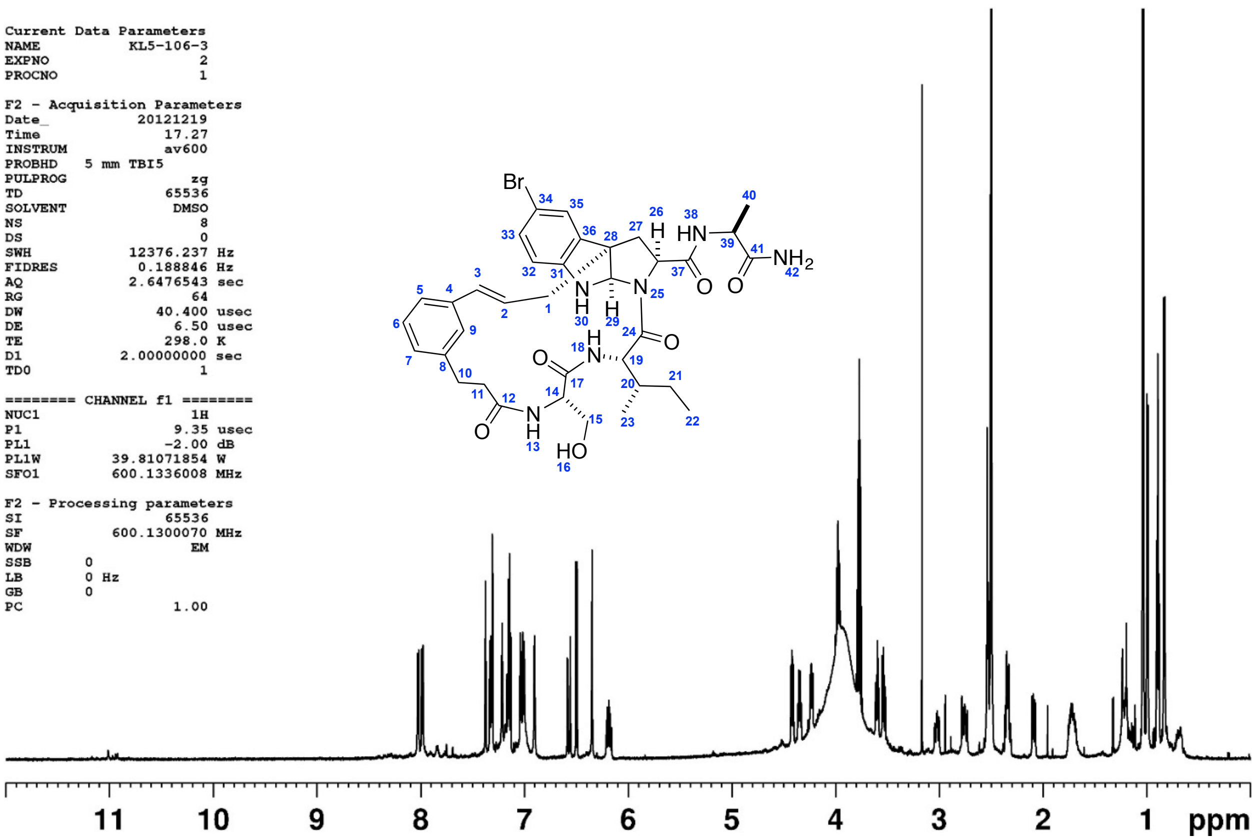

Current Data Parameters
NAME KL5-106-2-1_AV600
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121220
Time 20.56
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG dipsi2etgpsi
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 5387.931 Hz
FIDRES 2.630826 Hz
AQ 0.1900544 sec
RG 362
DW 92.800 usec
DE 6.50 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.50000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D16 0.00020000 sec
D20 0.00001000 sec
D21 0.00001000 sec
IN0 0.00018560 sec
L1 14
======== CHANNEL f1 ========
NUC1 1H
P1 9.36 usec
P2 18.72 usec
P6 40.00 usec
PL1 -2.00 dB
PL10 10.62 dB
PL1W 39.81071854 W
PL10W 2.17770982 W
SFO1 600.1327006 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
ppm
8 7 6 5 4 3 2 1 ppm

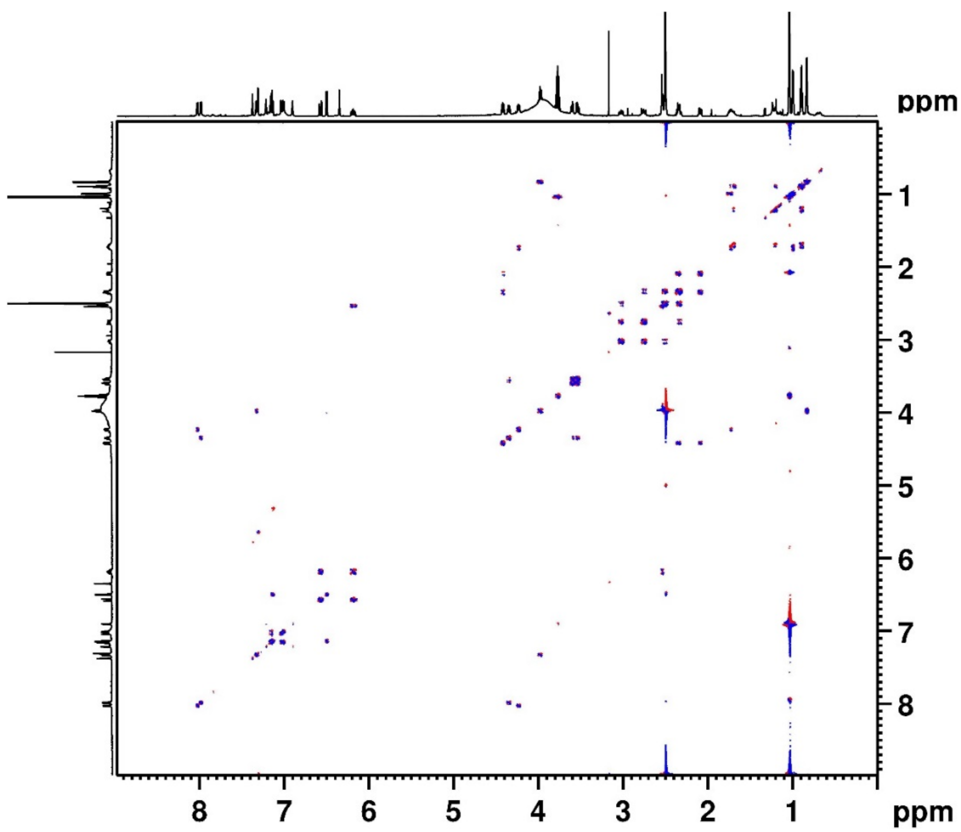

Current Data Parameters
NAME KL5-106-2-1_AV500
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121221
Time 18.14
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcetgpsi
TD 2048
SOLVENT DMSO
NS 12
DS 16
SWH 5151.099 Hz
FIDRES 2.515185 Hz
AQ 0.1987925 sec
RG 202.91
DW 97.067 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00345000 sec
IN0 0.00002940 sec
ZGOPTNS
======== CHANNEL f1 ========
SFO1 500.1324246 MHz
NUC1 1H
P1 9.68 usec
P2 19.36 usec
P28 0 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7675352 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %
GPZ2 20.10 %
ppm
20 40 60 80 100 120 140
9 8 7 6 5 4 3 2 1 0 ppm


Current Data Parameters
NAME KL5-106-2-1_AV500
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121221
Time 20.21
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 50
DS 16
SWH 5151.099 Hz
FIDRES 2.515185 Hz
AQ 0.1987925 sec
RG 202.91
DW 97.067 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00002270 sec
======== CHANNEL f1 ========
SFO1 500.1324246 MHz
NUC1 1H
P1 9.68 usec
P2 19.36 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7697360 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %
ppm
20
40
60
80
100
120
140
160
180
9
8
7
6
5
4
3
2
1
ppm

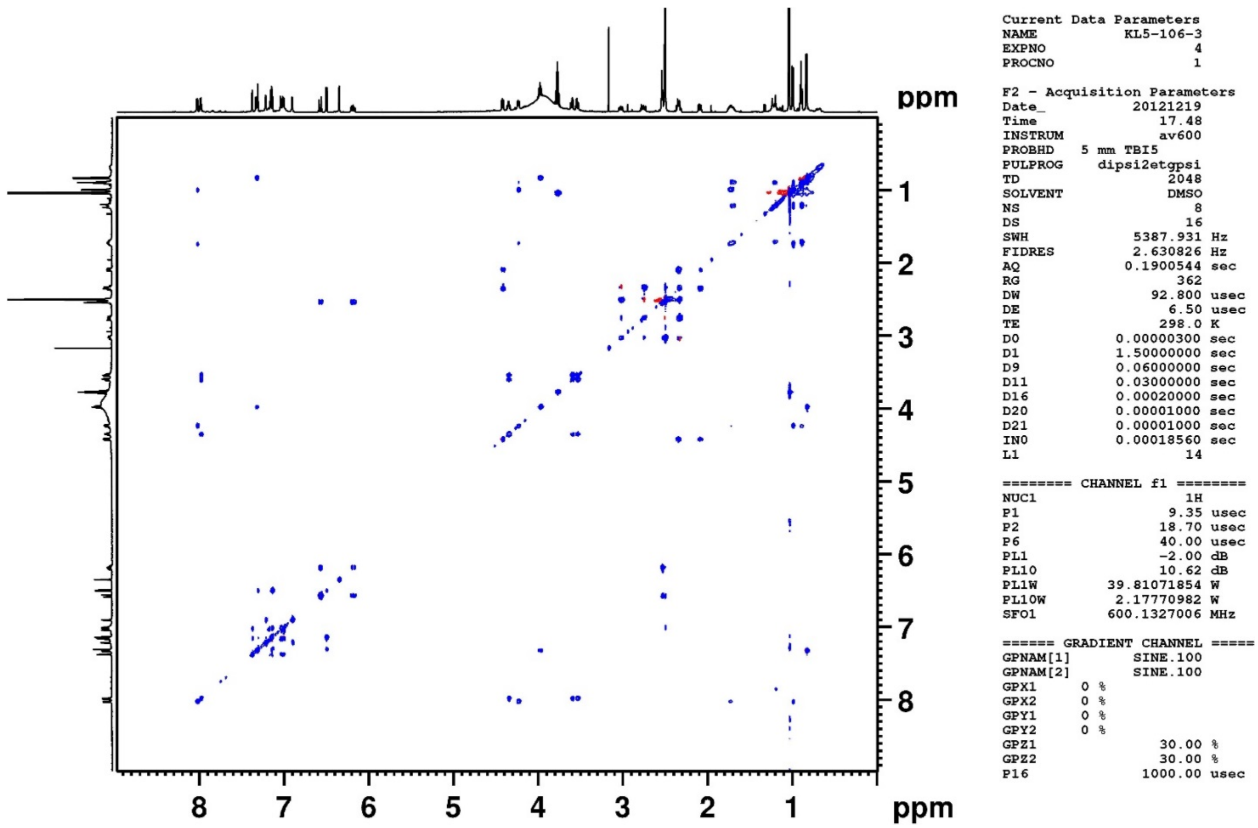
*Macrocyclic Product **2.18c***

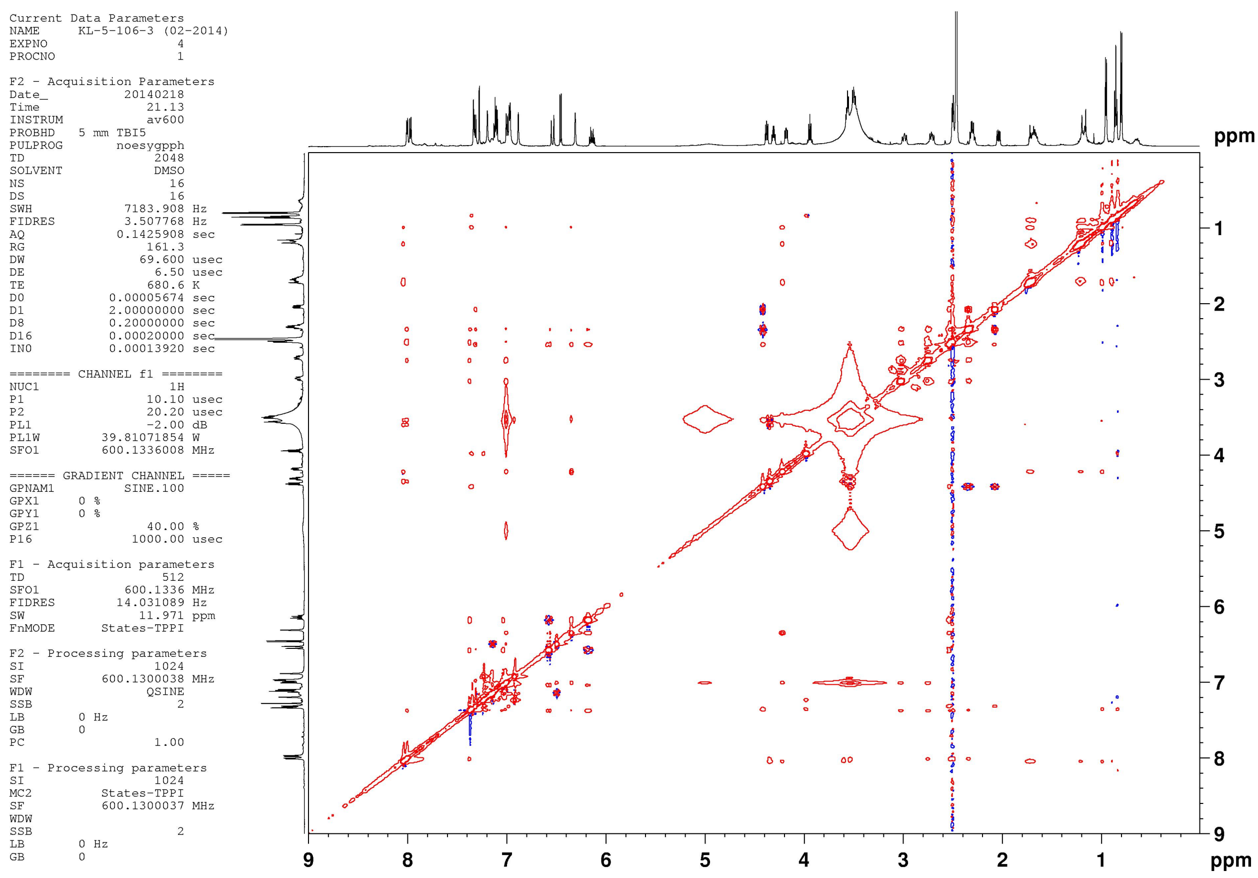
```
Current Data Parameters
NAME          KL5-106-3
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20121219
Time              17.27
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                   64
DW               40.400 usec
DE                 6.50 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.35 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF          600.1300070 MHz
WDW                  EM
SSB      0
LB       0 Hz
GB       0
PC                 1.00
```

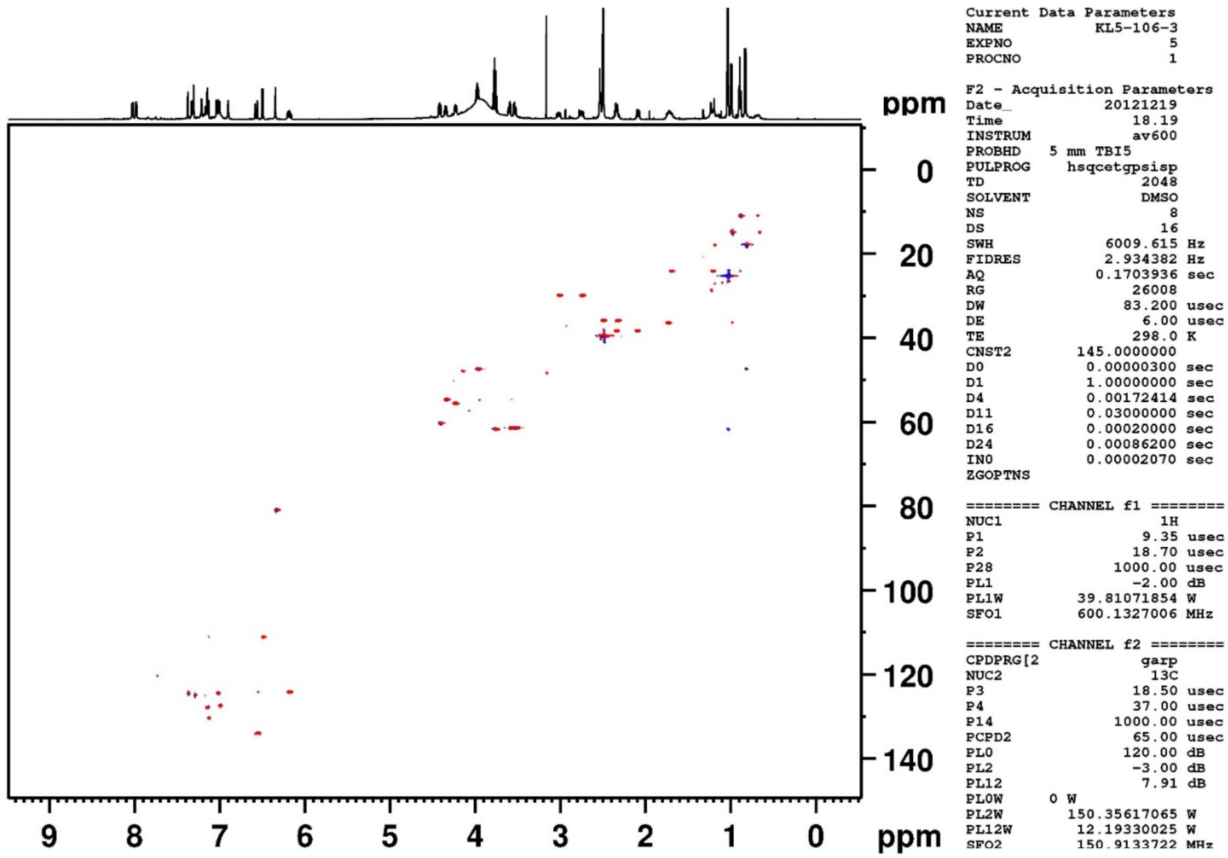
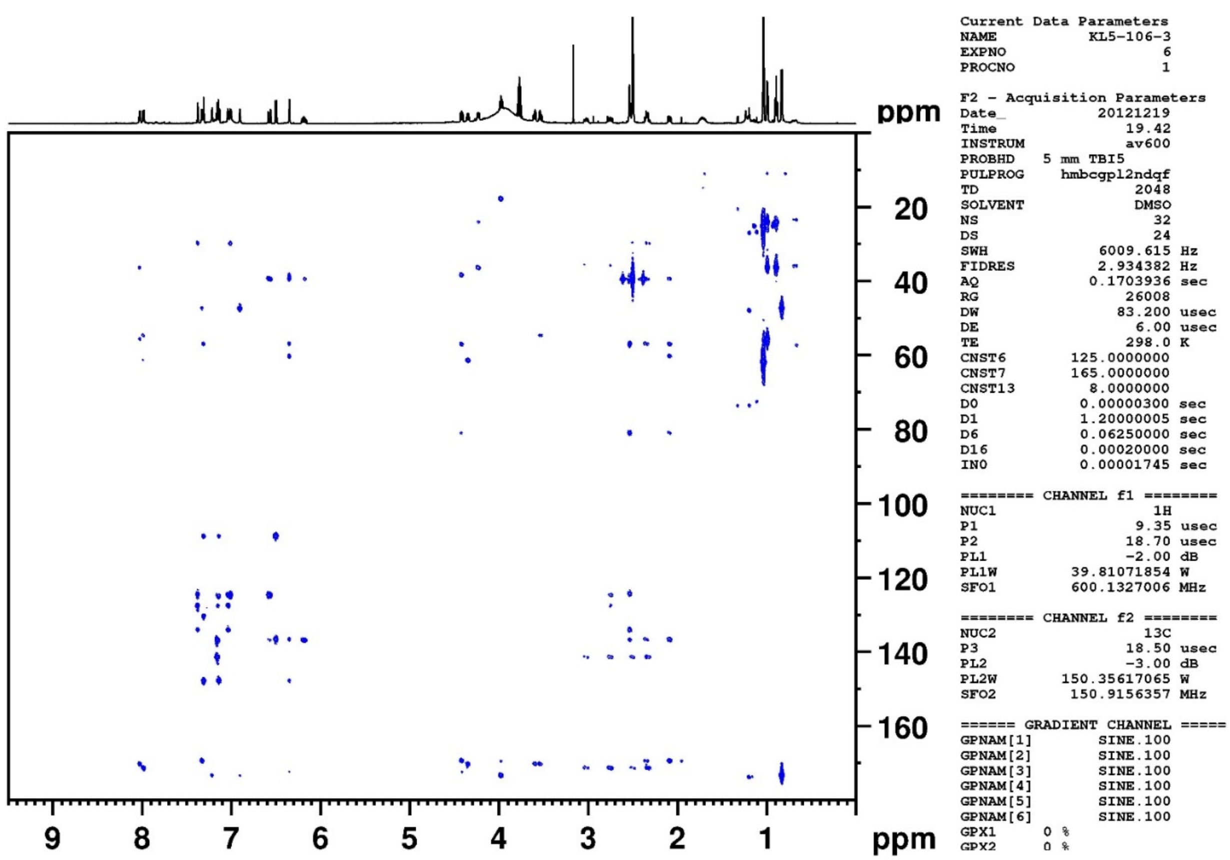




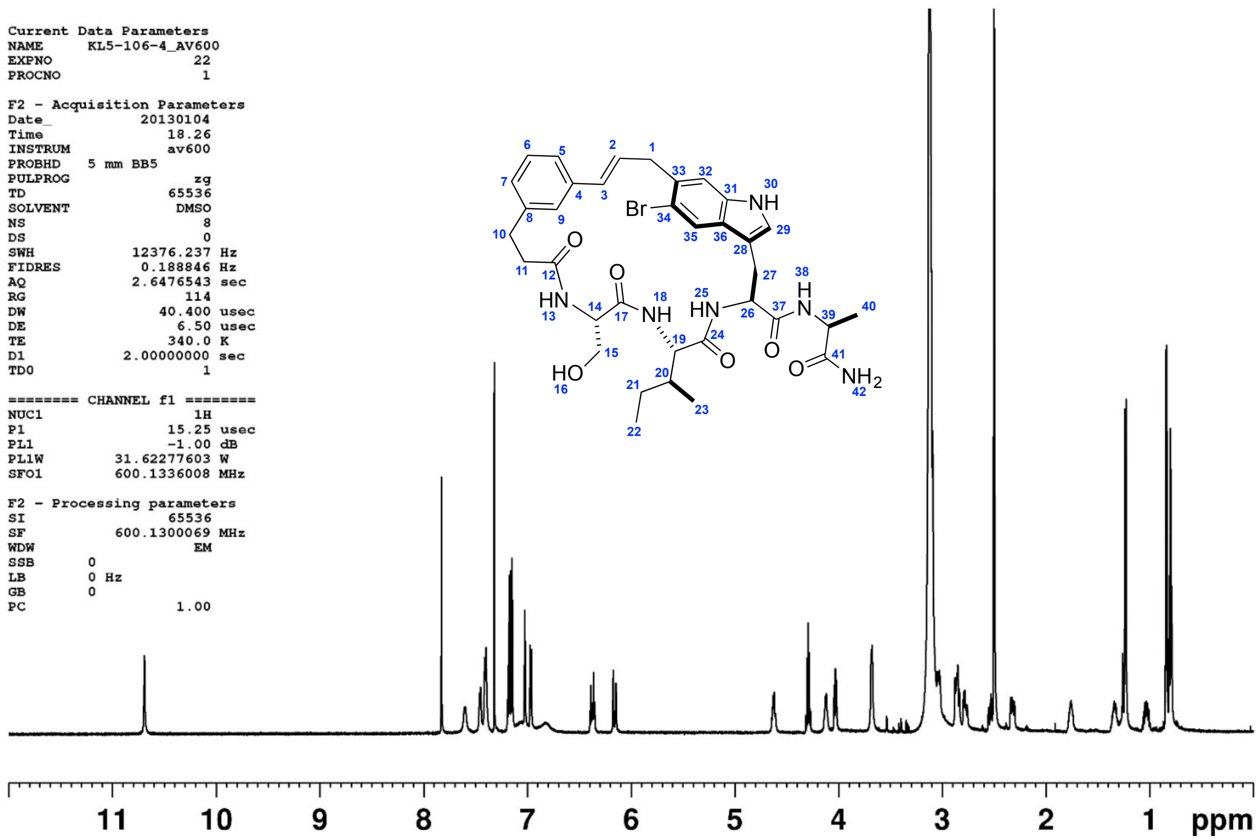

```
Current Data Parameters
NAME          KL5-106-3
EXPNO                 3
PROCNO                1

F2 - Acquisition Parameters
Date_          20121219
Time              17.32
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG      cosygpmfph
TD                 2048
SOLVENT            DMSO
NS                    1
DS                   16
SWH            5387.931 Hz
FIDRES         2.630826 Hz
AQ            0.1900544 sec
RG                   64
DW               92.800 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00008090 sec
D1           1.50000000 sec
D13          0.00000400 sec
D16          0.00020000 sec
IN0          0.00018560 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.35 usec
P2                18.70 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1        600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              10.00 %
GPZ2              20.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  512
SFO1           600.1327 MHz
FIDRES        10.523297 Hz
SW                8.978 ppm
FnMODE      States-TPPI
```

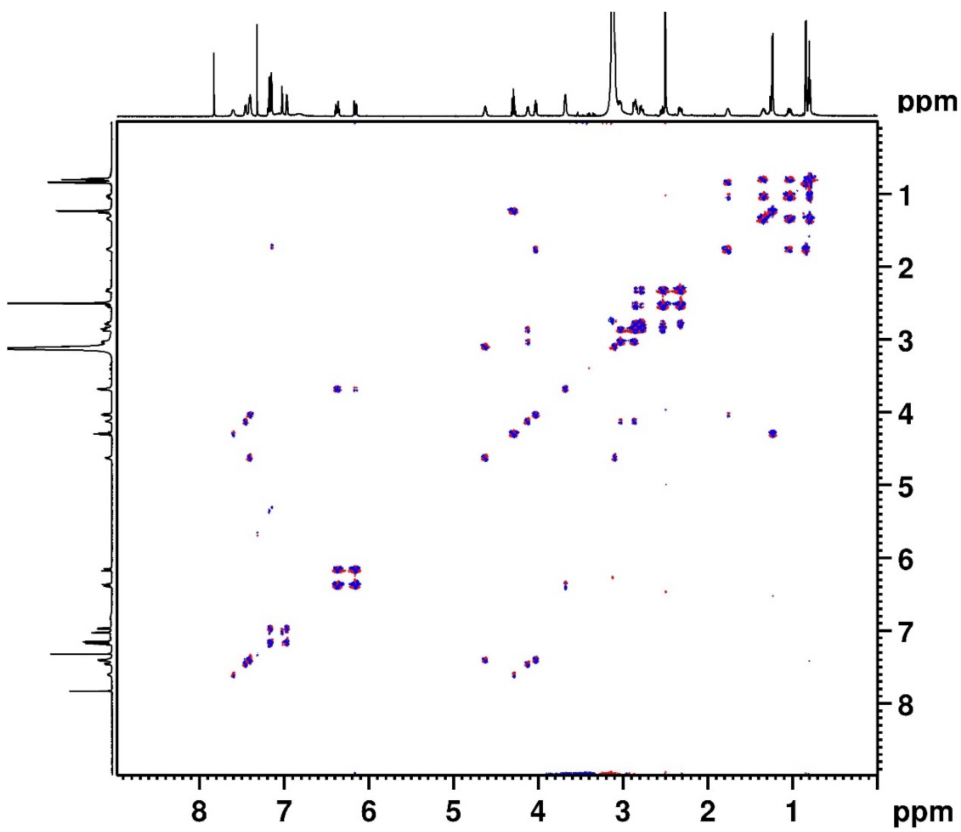

Current Data Parameters
NAME KL5-106-3
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121219
Time 17.48
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG dipsi2etgpsi
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 5387.931 Hz
FIDRES 2.630826 Hz
AQ 0.1900544 sec
RG 362
DW 92.800 usec
DE 6.50 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.50000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D16 0.00020000 sec
D20 0.00001000 sec
D21 0.00001000 sec
IN0 0.00018560 sec
L1 14
======== CHANNEL f1 ========
NUC1 1H
P1 9.35 usec
P2 18.70 usec
P6 40.00 usec
PL1 -2.00 dB
PL10 10.62 dB
PL1W 39.81071854 W
PL10W 2.17770982 W
SFO1 600.1327006 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
ppm
8 7 6 5 4 3 2 1 ppm
1 2 3 4 5 6 7 8


Current Data Parameters
NAME KL-5-106-3 (02-2014)
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140218
Time 21.13
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG noesygpph
TD 2048
SOLVENT DMSO
NS 16
DS 16
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425908 sec
RG 161.3
DW 69.600 usec
DE 6.50 usec
TE 680.6 K
D0 0.00005674 sec
D1 2.00000000 sec
D8 0.20000000 sec
D16 0.00020000 sec
IN0 0.00013920 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
P2 20.20 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPX1 0 %
GPY1 0 %
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1336 MHz
FIDRES 14.031089 Hz
SW 11.971 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 1024
SF 600.1300038 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 States-TPPI
SF 600.1300037 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
9 8 7 6 5 4 3 2 1 ppm
1 2 3 4 5 6 7 8 9


Current Data Parameters
NAME KL5-106-3
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121219
Time 18.19
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 9.35 usec
P2 18.70 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 18.50 usec
P4 37.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.91 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 12.19330025 W
SFO2 150.9133722 MHz
ppm
ppm

Current Data Parameters
NAME KL5-106-3
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121219
Time 19.42
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 24
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 298.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.35 usec
P2 18.70 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPX1 0 %
GPX2 0 %
ppm
ppm

Macrocyclic Product ***2.18d***





Current Data Parameters
NAME KL5-106-4_AV600
EXPNO 25
PROCNO 1

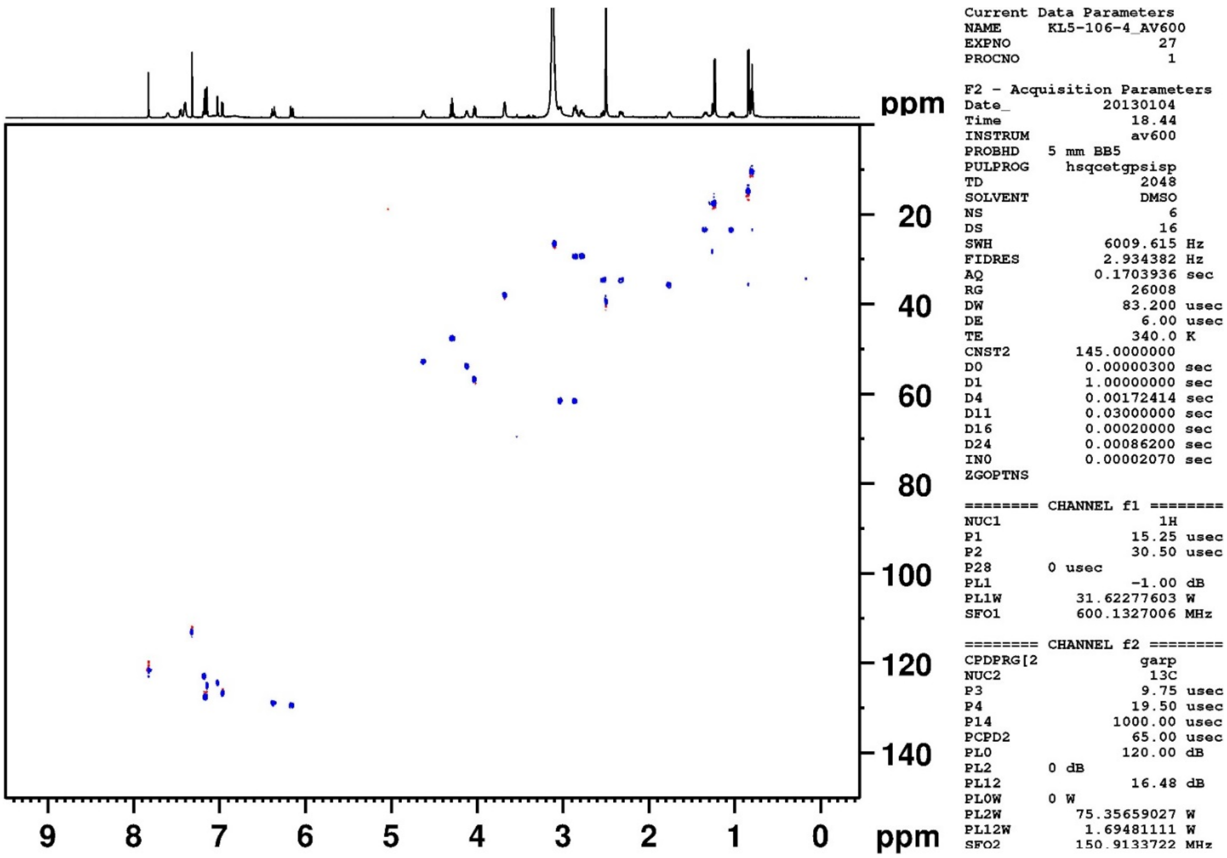
F2 - Acquisition Parameters
Date_ 20130104
Time 18.27
INSTRUM av600
PROBHD 5 mm BB5
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 1
DS 16
SWH 5387.931 Hz
FIDRES 2.630826 Hz
AQ 0.1900544 sec
RG 114
DW 92.800 usec
DE 6.50 usec
TE 340.0 K
D0 0.00007338 sec
D1 1.50000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00018560 sec

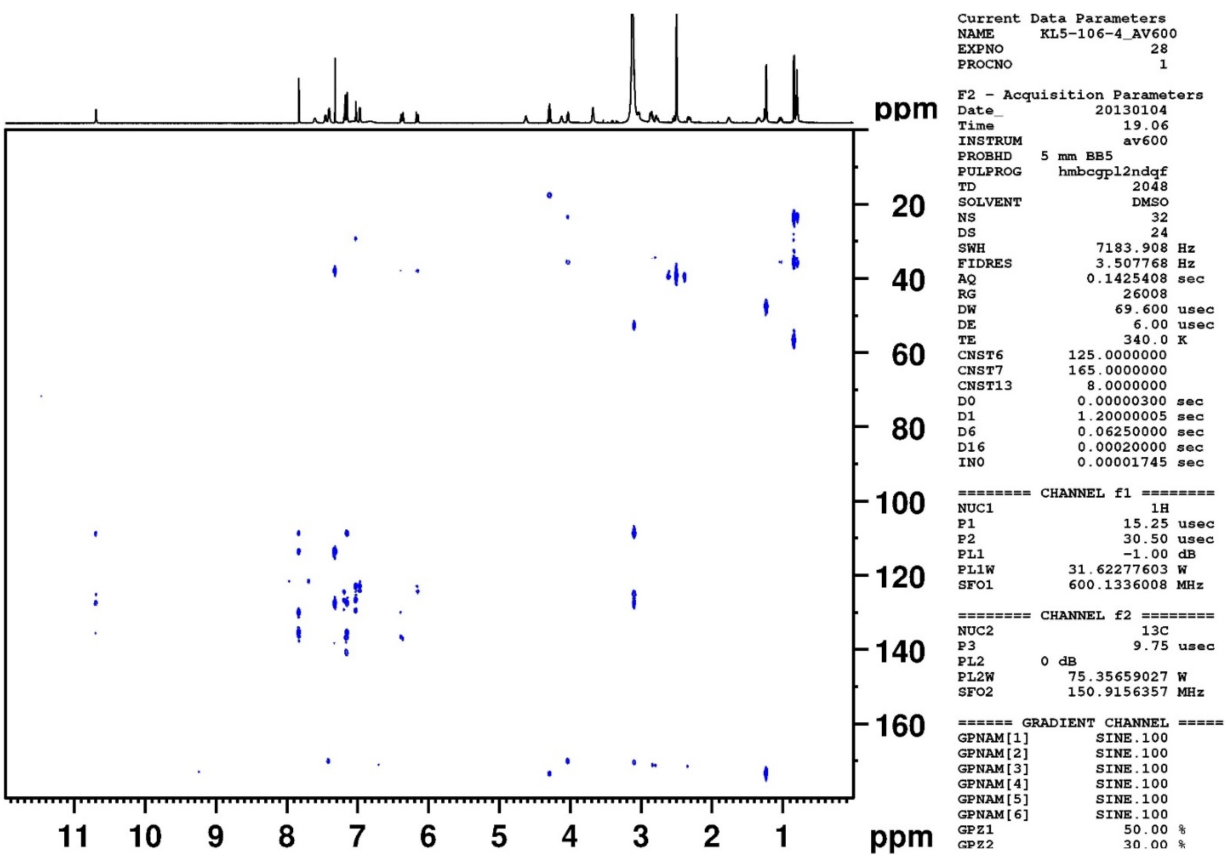
======== CHANNEL f1 ========
NUC1 1H
P1 15.25 usec
P2 30.50 usec
PL1 -1.00 dB
PL1W 31.62277603 W
SFO1 600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 600.1327 MHz
FIDRES 10.523297 Hz
SW 8.978 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI 2048
SF 600.1300095 MHz
WDW QSINE


Current Data Parameters
NAME KL5-106-4_AV600
EXPNO 27
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130104
Time 18.44
INSTRUM av600
PROBHD 5 mm BB5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 6
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 340.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 15.25 usec
P2 30.50 usec
P28 0 usec
PL1 -1.00 dB
PL1W 31.62277603 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.75 usec
P4 19.50 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 0 dB
PL12 16.48 dB
PL0W 0 W
PL2W 75.35659027 W
PL12W 1.69481111 W
SFO2 150.9133722 MHz
ppm
20
40
60
80
100
120
140
9 8 7 6 5 4 3 2 1 0
ppm


Current Data Parameters
NAME KL5-106-4_AV600
EXPNO 28
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130104
Time 19.06
INSTRUM av600
PROBHD 5 mm BB5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 24
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 26008
DW 69.600 usec
DE 6.00 usec
TE 340.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 15.25 usec
P2 30.50 usec
PL1 -1.00 dB
PL1W 31.62277603 W
SFO1 600.1336008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.75 usec
PL2 0 dB
PL2W 75.35659027 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPZ1 50.00 %
GPZ2 30.00 %
ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1
ppm

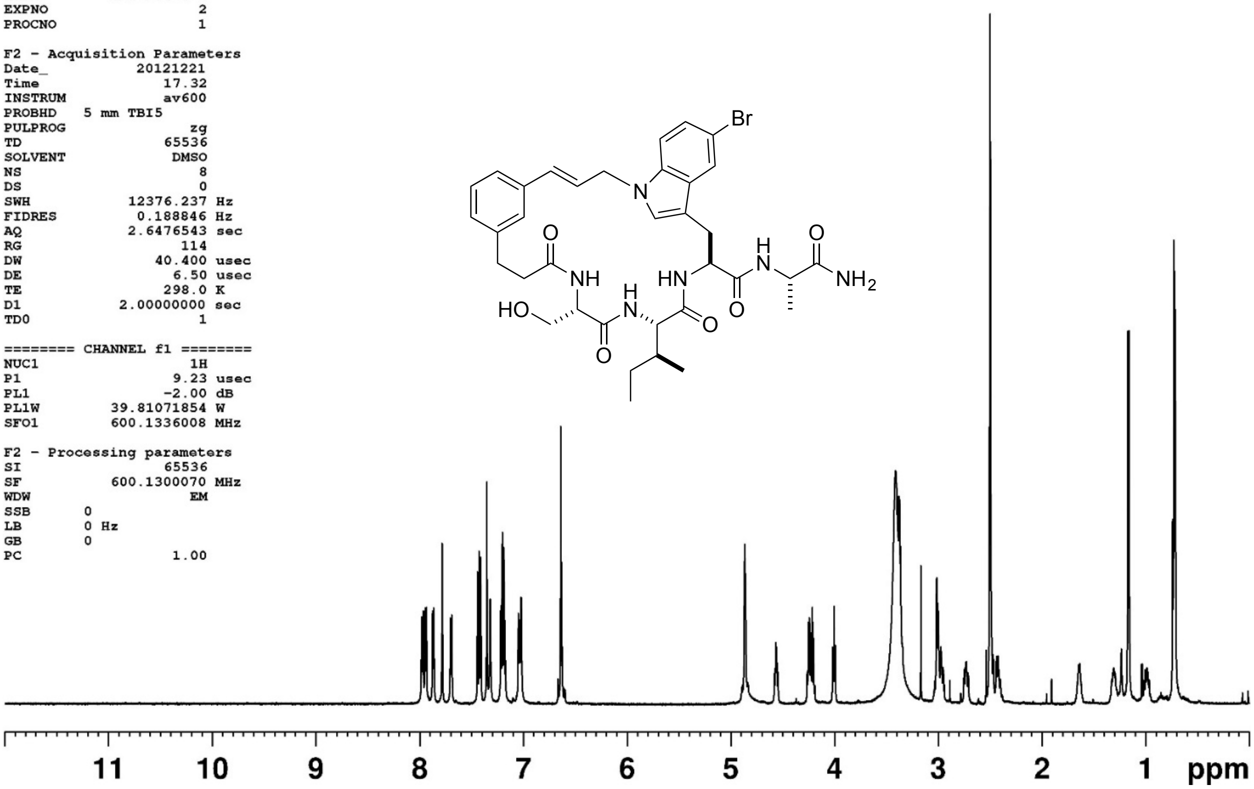
Macrocyclic Product ***2.18e***

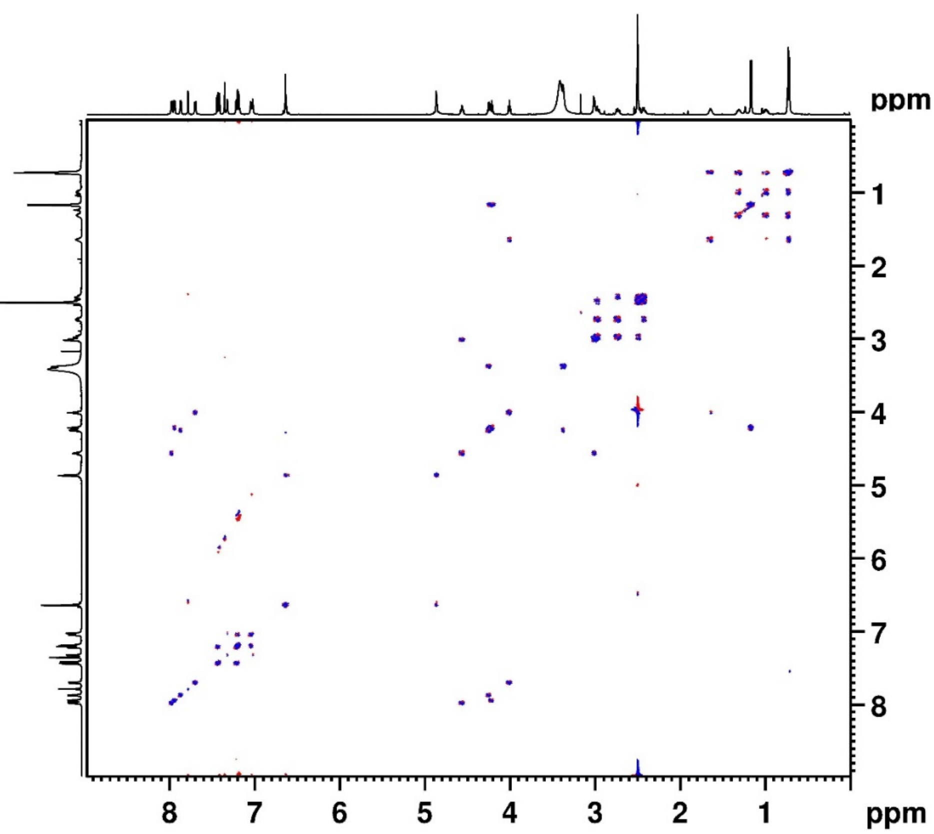
Current Data Parameters
NAME KL5-106-5-1
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121221
Time 17.32
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG zg
TD 65536
SOLVENT DMSO
NS 8
DS 0
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6476543 sec
RG 114
DW 40.400 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.23 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

F2 - Processing parameters
SI 65536
SF 600.1300070 MHz
WDW EM
SSB 0
LB 0 Hz
GB 0
PC 1.00





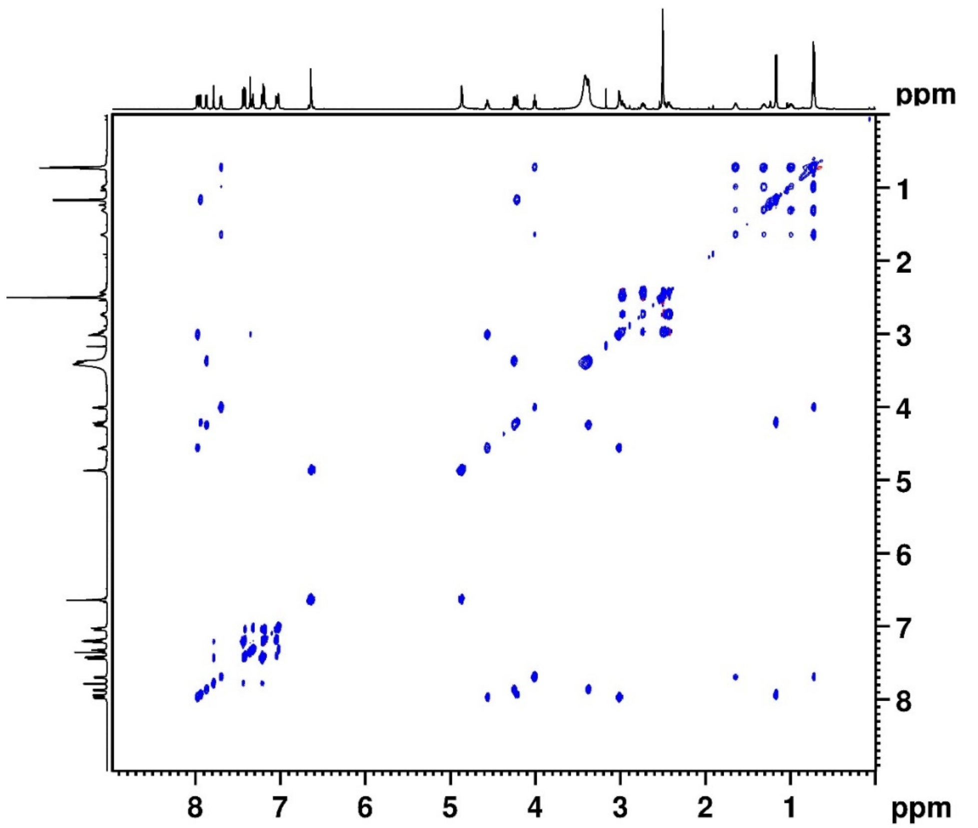
Current Data Parameters
NAME KL5-106-5-1
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121221
Time 17.35
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 1
DS 16
SWH 5387.931 Hz
FIDRES 2.630826 Hz
AQ 0.1900544 sec
RG 114
DW 92.800 usec
DE 6.50 usec
TE 298.0 K
D0 0.00008105 sec
D1 1.50000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00018560 sec

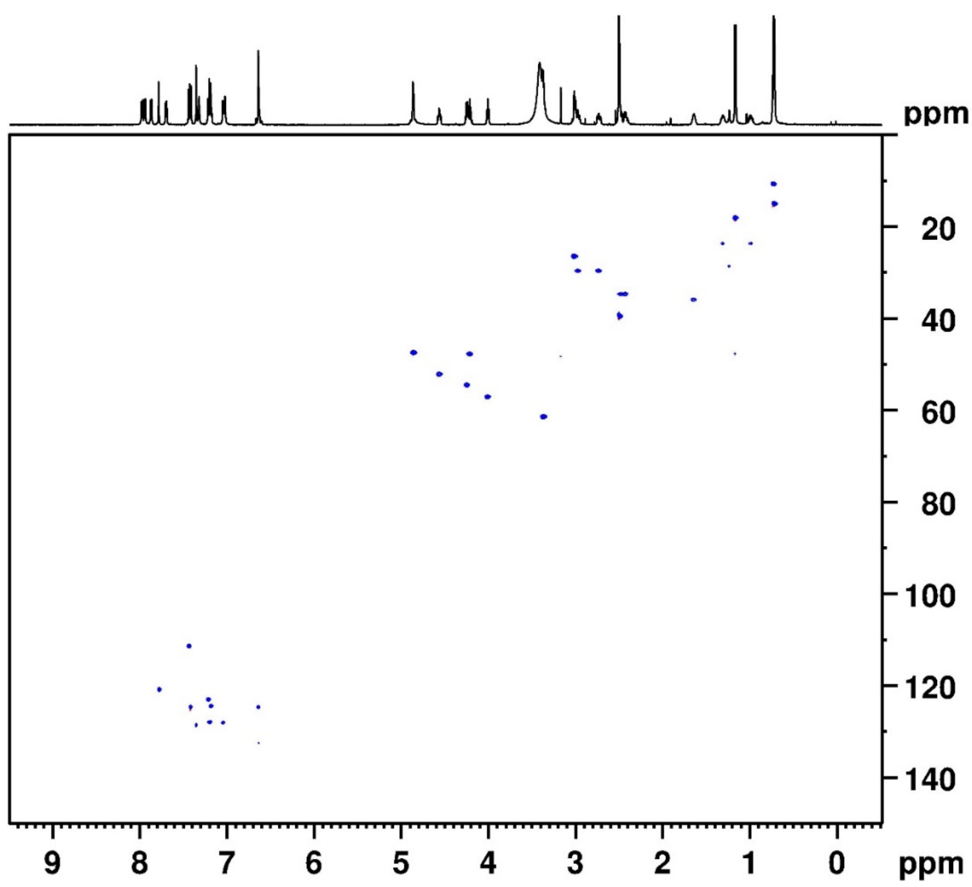
======== CHANNEL f1 ========
NUC1 1H
P1 9.23 usec
P2 18.46 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 600.1327 MHz
FIDRES 10.523297 Hz
SW 8.978 ppm
FnMODE States-TPPI

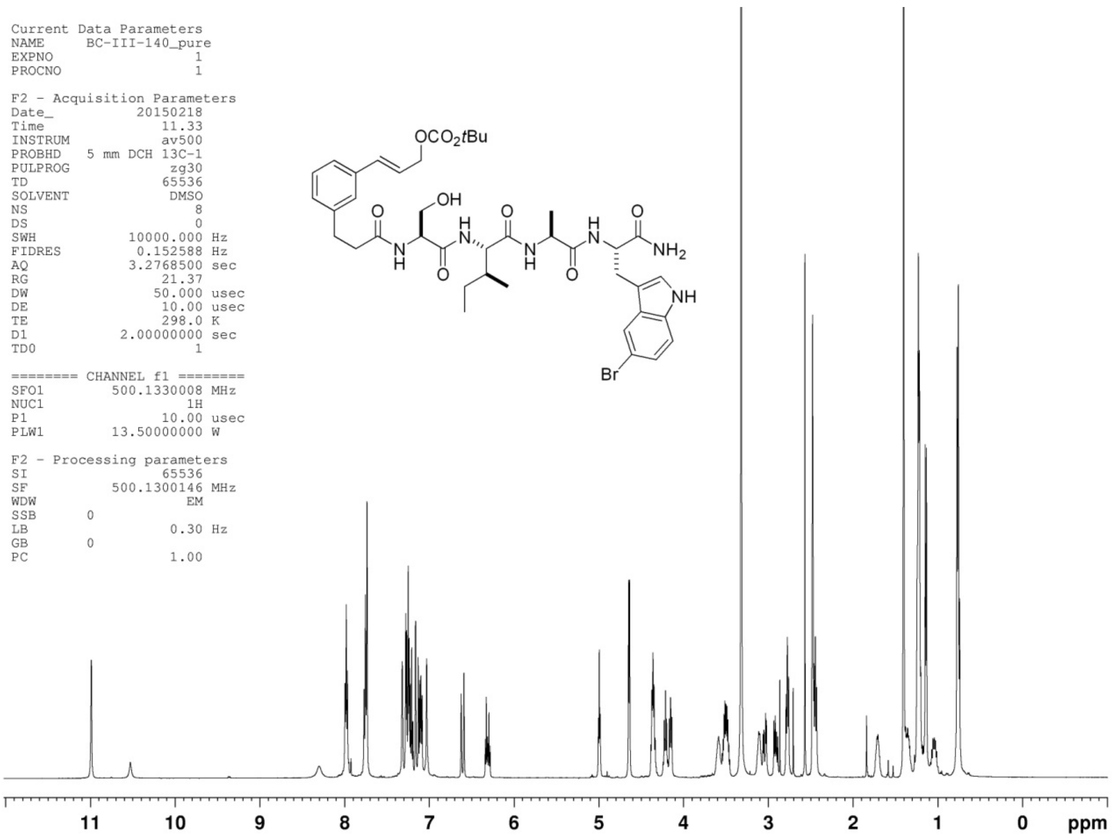


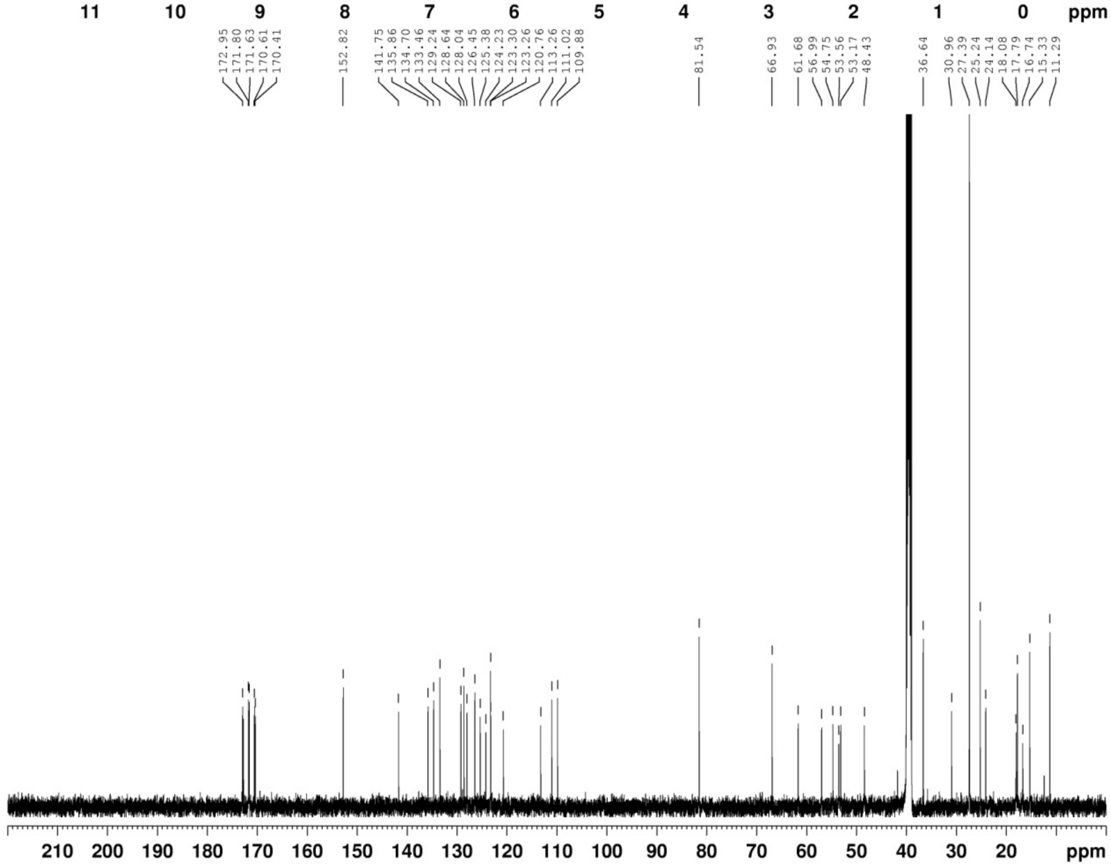

```
Current Data Parameters
NAME          KL5-106-5-1
EXPNO                   4
PROCNO                  1

F2 - Acquisition Parameters
Date_            20121221
Time                17.51
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG     dipsi2etgpsi
TD                   2048
SOLVENT              DMSO
NS                      8
DS                     16
SWH              5387.931 Hz
FIDRES           2.630826 Hz
AQ              0.1900544 sec
RG                    362
DW                 92.800 usec
DE                   6.50 usec
TE                  298.0 K
D0             0.00000300 sec
D1             1.50000000 sec
D9             0.06000000 sec
D11            0.03000000 sec
D16            0.00020000 sec
D20            0.00001000 sec
D21            0.00001000 sec
IN0            0.00018560 sec
L1                     14

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.23 usec
P2                  18.46 usec
P6                  40.00 usec
PL1                 -2.00 dB
PL10                10.74 dB
PL1W          39.81071854 W
PL10W          2.11836123 W
SFO1        600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1       0 %
GPX2       0 %
GPY1       0 %
GPY2       0 %
GPZ1                30.00 %
GPZ2                30.00 %
P16               1000.00 usec
```



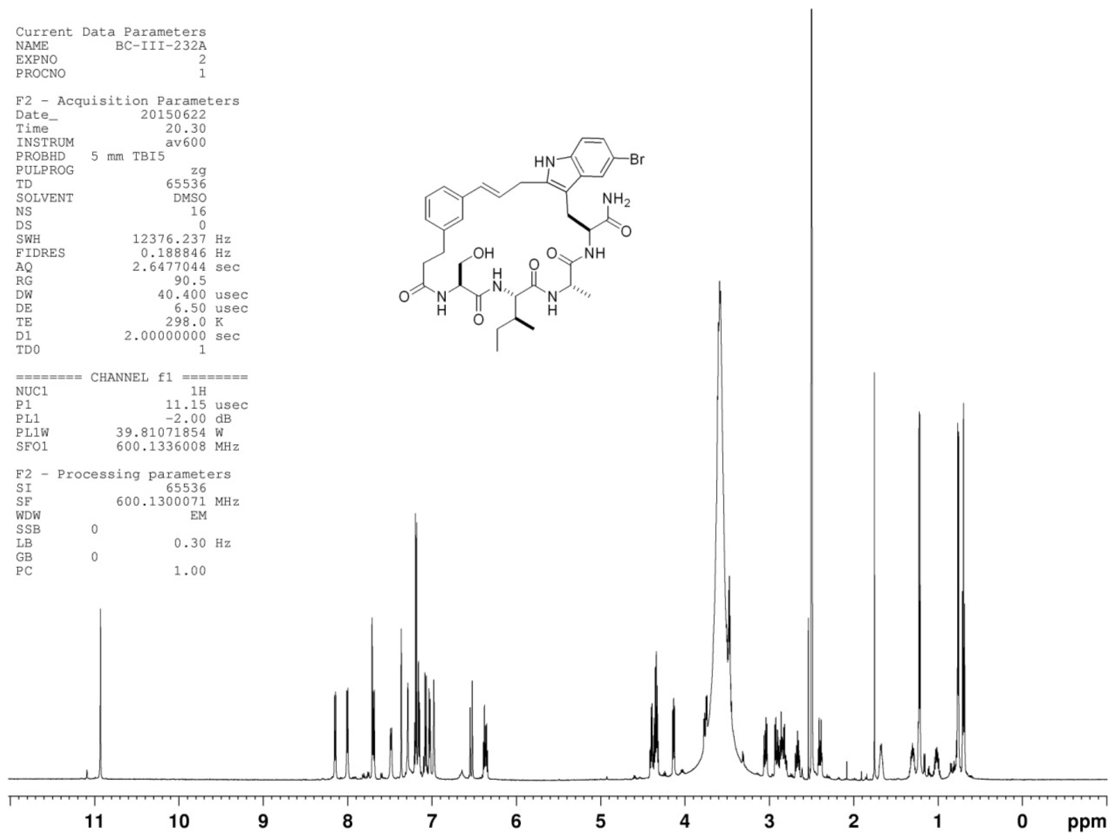

```
Current Data Parameters
NAME          KL5-106-5-1
EXPNO                   5
PROCNO                  1

F2 - Acquisition Parameters
Date_            20121221
Time                18.22
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG     hsqcetgpsisp
TD                   2048
SOLVENT              DMSO
NS                     10
DS                     16
SWH              6009.615 Hz
FIDRES           2.934382 Hz
AQ              0.1703936 sec
RG                  26008
DW                 83.200 usec
DE                   6.00 usec
TE                  298.1 K
CNST2         145.0000000
D0             0.00000300 sec
D1             1.00000000 sec
D4             0.00172414 sec
D11            0.03000000 sec
D16            0.00020000 sec
D24            0.00086200 sec
IN0            0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.23 usec
P2                  18.46 usec
P28               1000.00 usec
PL1                 -2.00 dB
PL1W          39.81071854 W
SFO1        600.1327006 MHz

======== CHANNEL f2 ========
CPDPRG[2             garp
NUC2                  13C
P3                  18.50 usec
P4                  37.00 usec
P14               1000.00 usec
PCPD2               65.00 usec
PL0                120.00 dB
PL2                 -3.00 dB
PL12                 7.91 dB
PL0W       0 W
PL2W         150.35617065 W
PL12W         12.19330025 W
SFO2        150.9133722 MHz
```

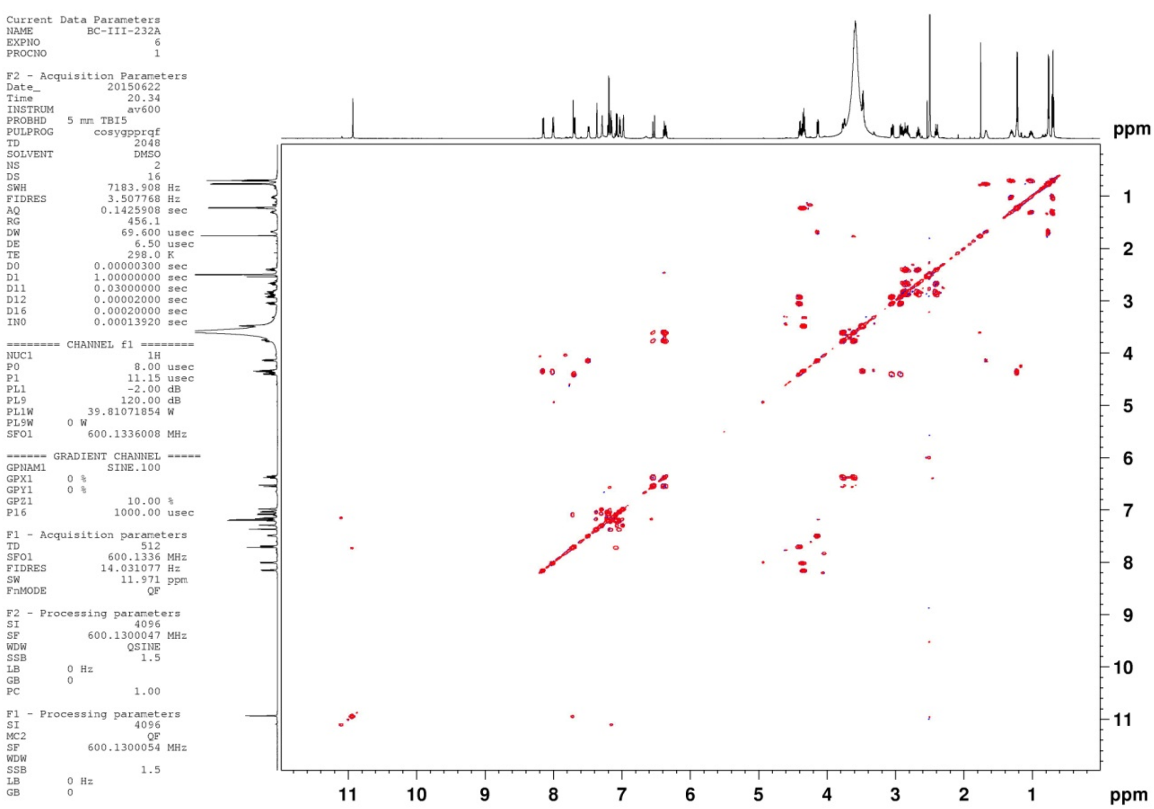
*Acyclic Precursor **2.15***

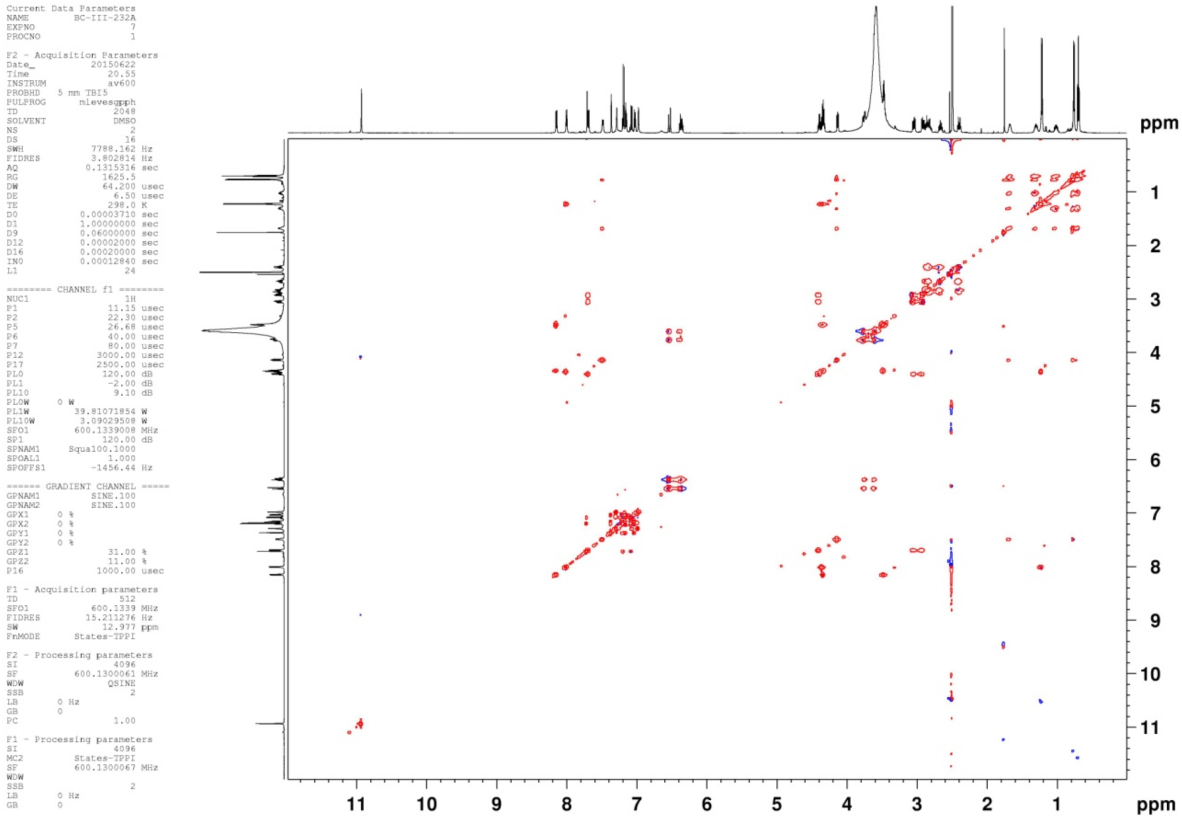


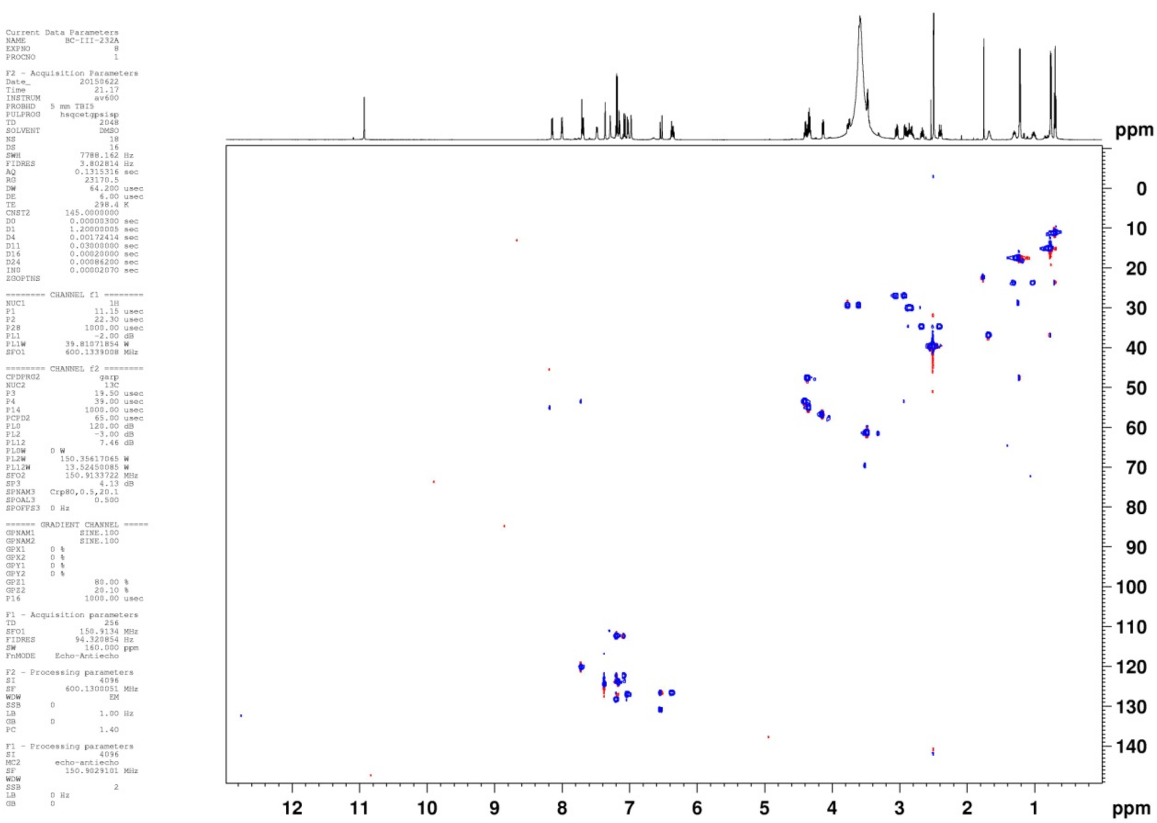


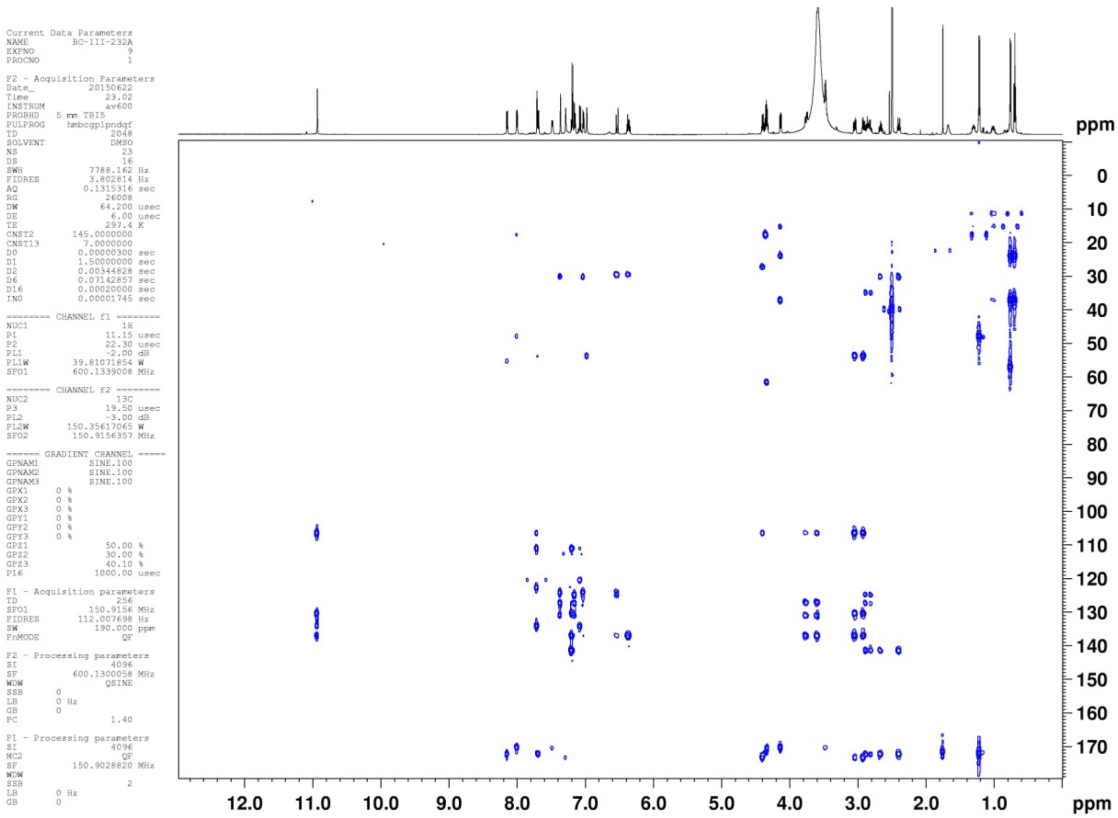
*Macrocyclic Product **2.19a***



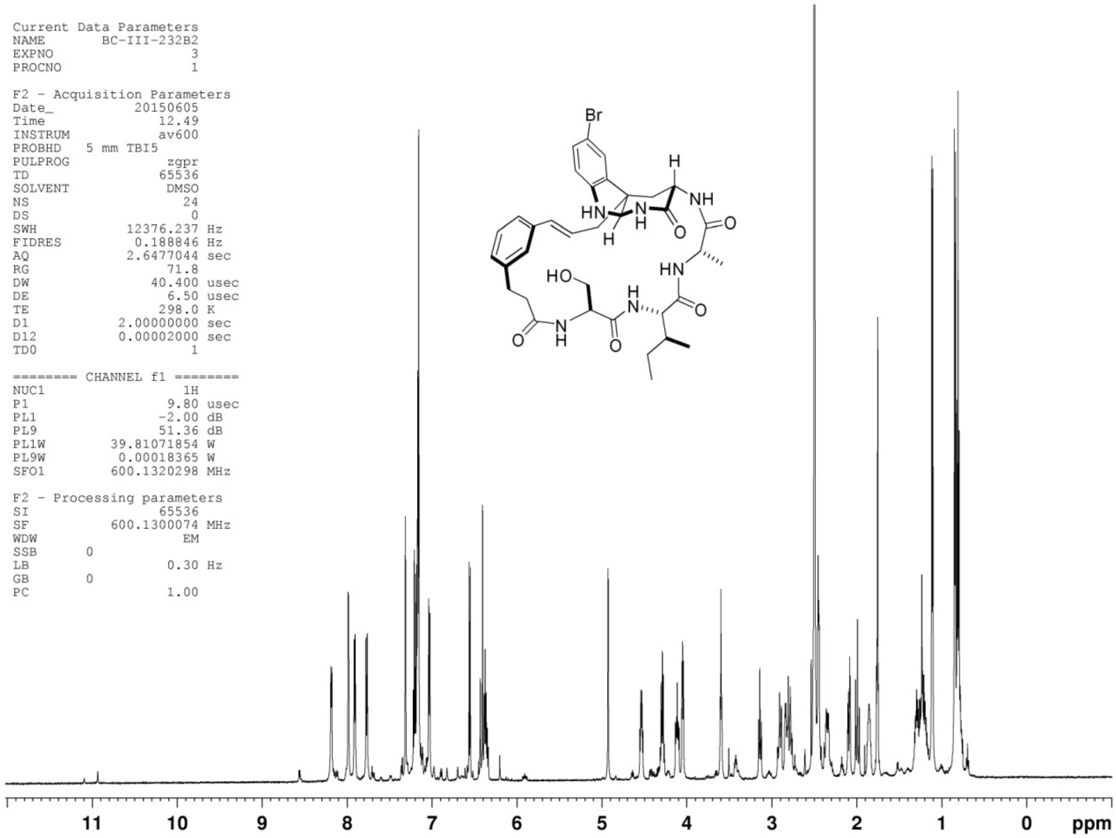


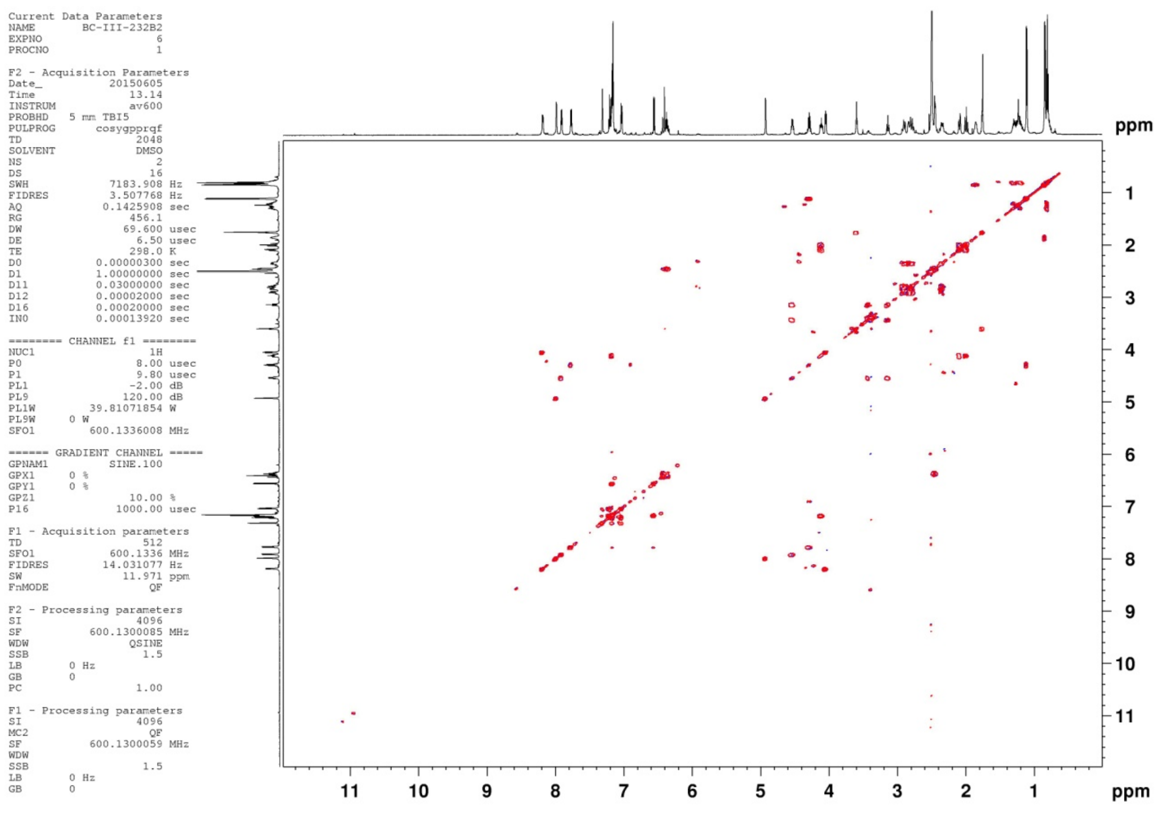

Current Data Parameters
NAME BC-III-232A
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 20.55
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003710 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 11.15 usec
P2 22.30 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.10 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 3.09029508 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300061 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300067 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

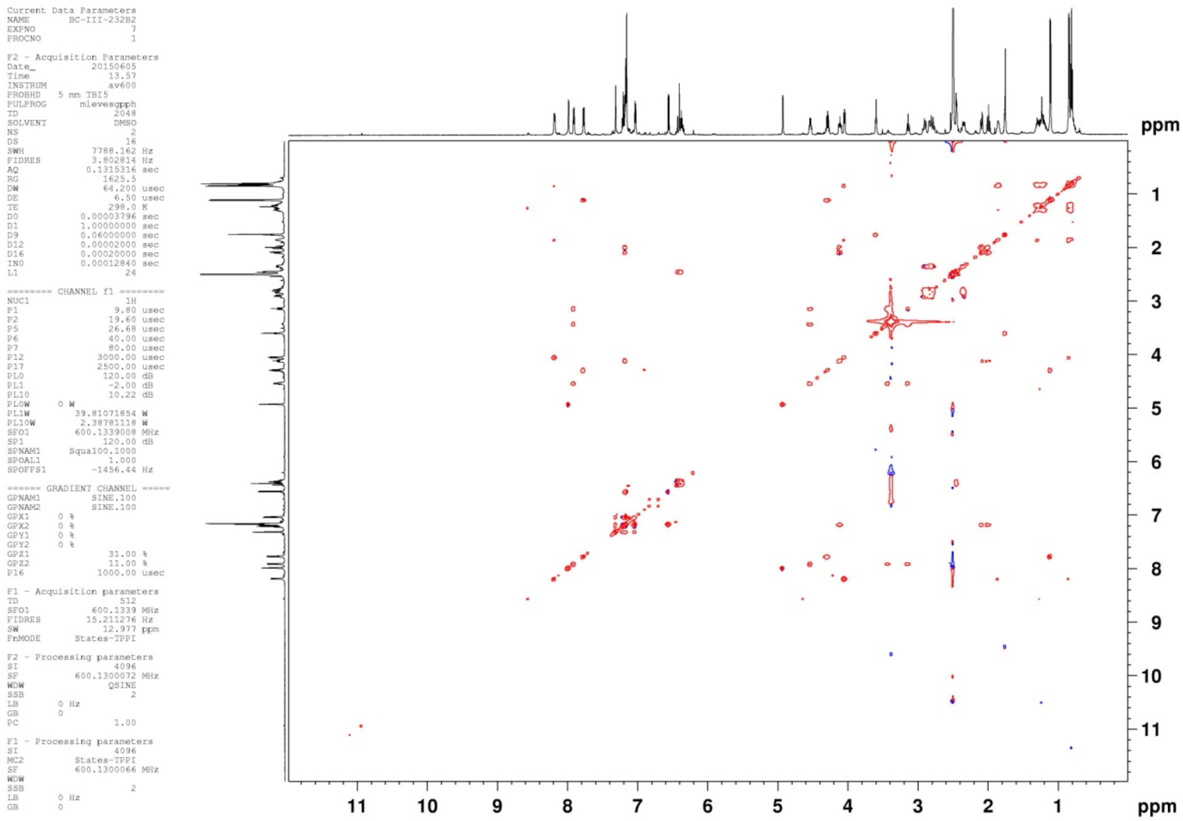

Current Data Parameters
NAME BC-III-232A
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 21.17
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 18
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 11.15 usec
P2 22.30 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300051 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029101 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

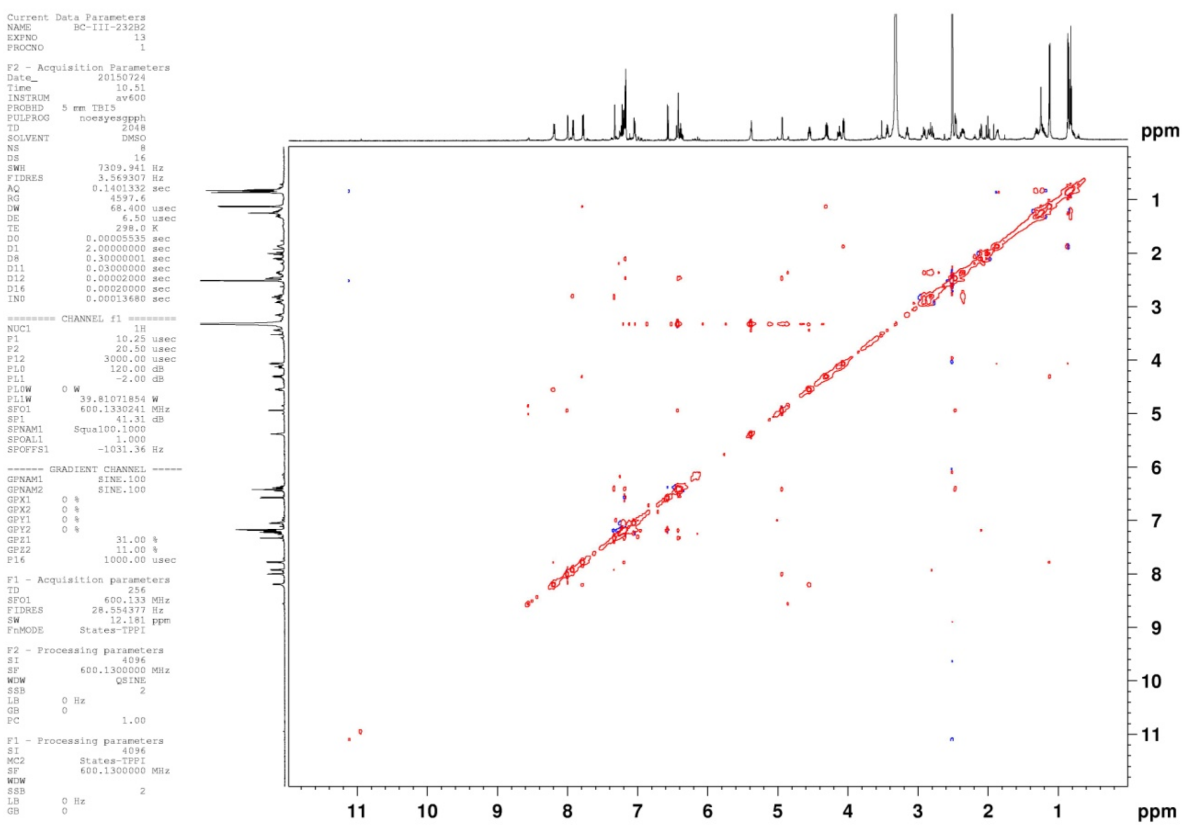

Current Data Parameters
NAME BC-III-232A
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 23.02
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 23
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.4 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 11.15 usec
P2 22.30 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300058 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028820 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

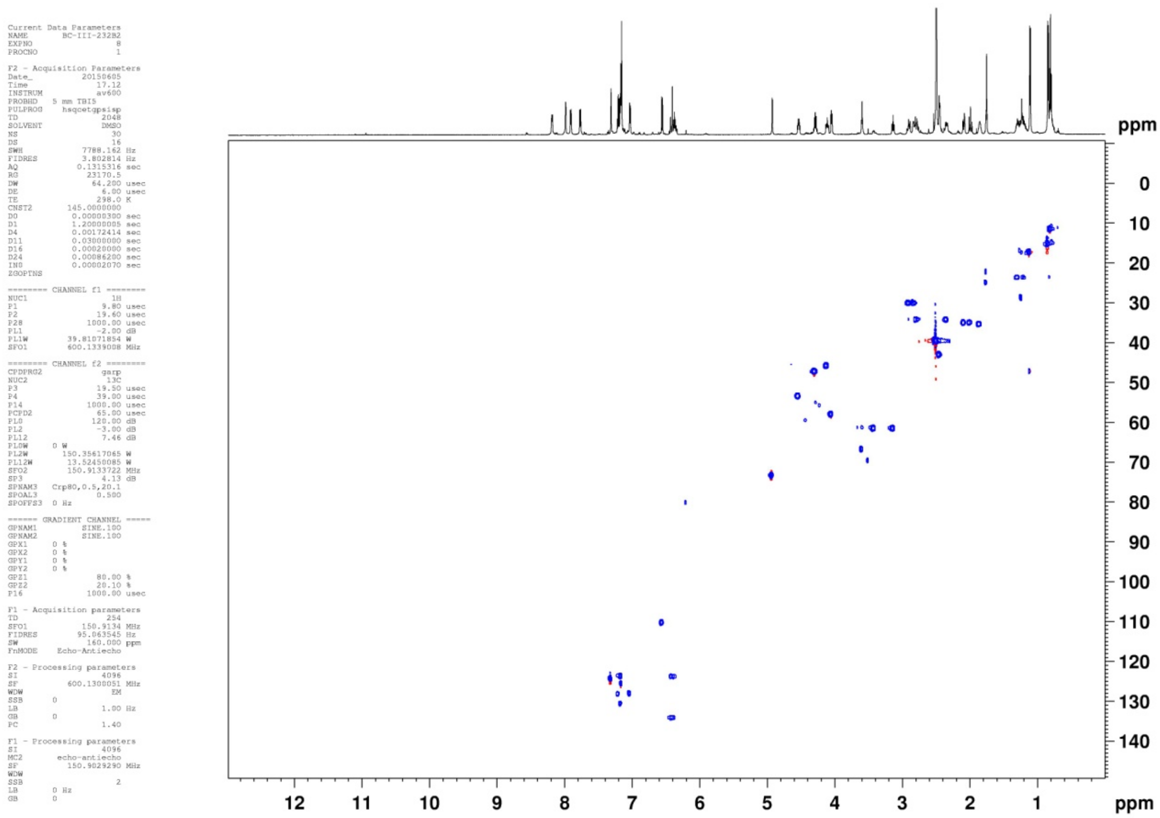
*Macrocyclic Product **2.19b***

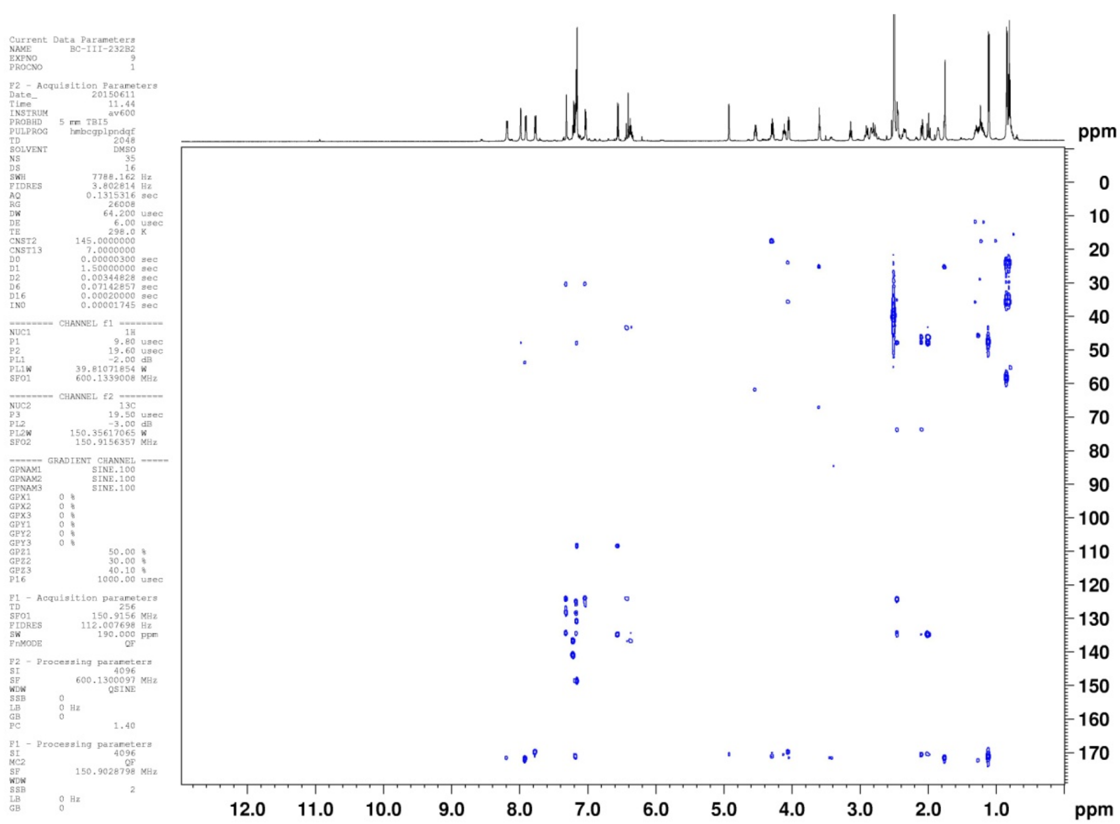




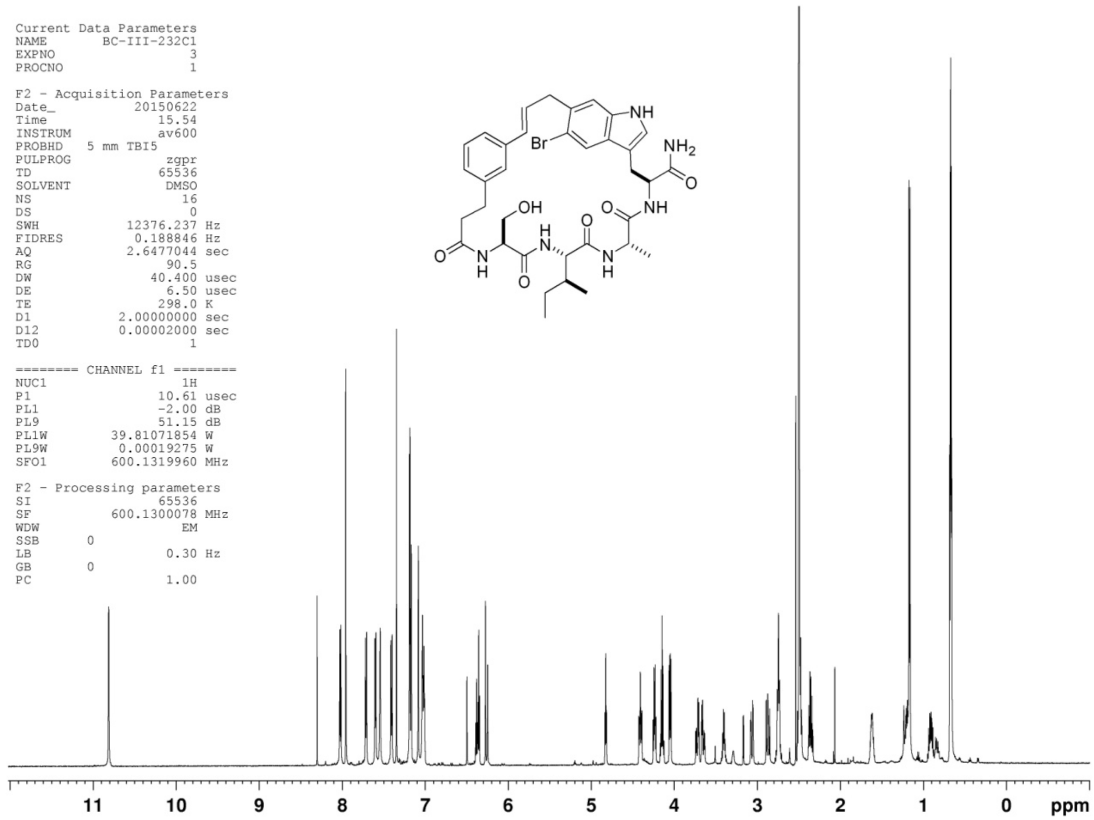

Current Data Parameters
NAME BC-III-232B2
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150605
Time 13.57
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003796 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
P2 19.60 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 10.22 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.38781118 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300072 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300066 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
1 2 3 4 5 6 7 8 9 10 11
11 10 9 8 7 6 5 4 3 2 1 ppm

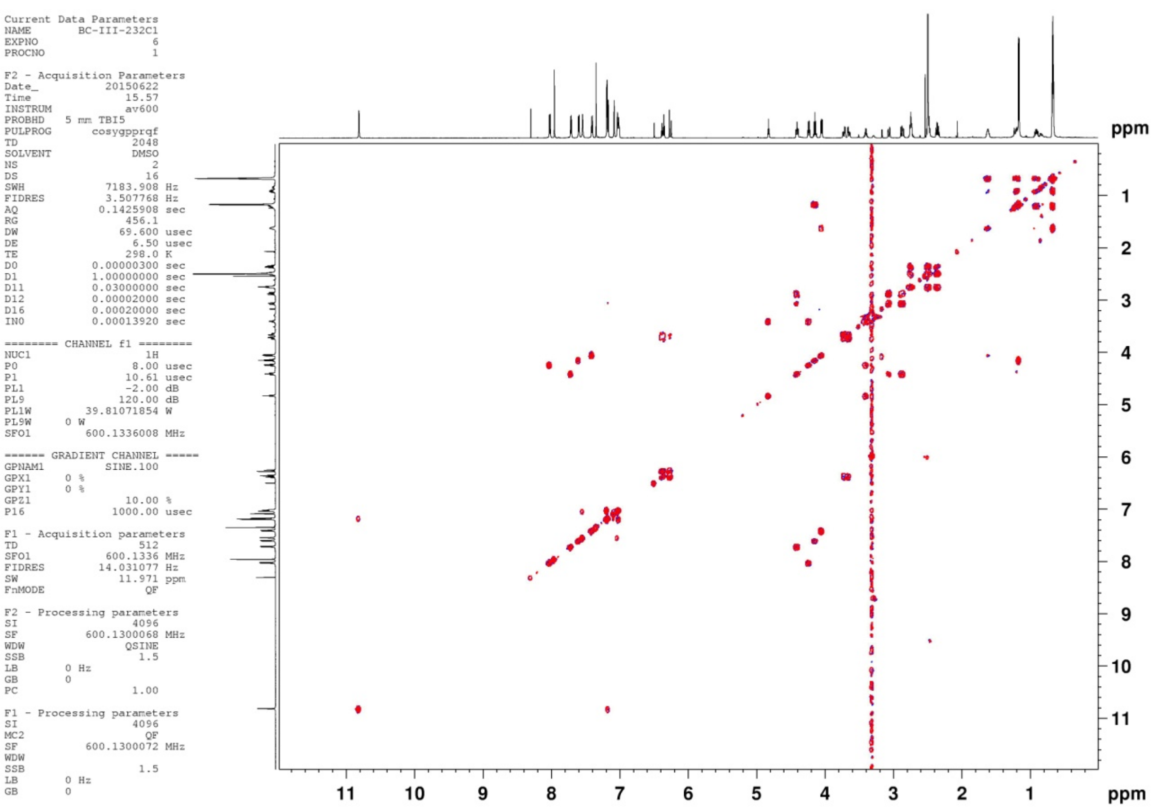

Current Data Parameters
NAME BC-III-232B2
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150724
Time 10.51
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG noesyesgpph
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 7309.941 Hz
FIDRES 3.569307 Hz
AQ 0.1401332 sec
RG 4597.6
DW 68.400 usec
DE 6.50 usec
TE 298.0 K
D0 0.00005535 sec
D1 2.00000000 sec
D8 0.30000001 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00013680 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.25 usec
P2 20.50 usec
P12 3000.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL0W 0 W
PL1W 39.81071854 W
SFO1 600.1330241 MHz
SP1 41.31 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1031.36 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 600.133 MHz
FIDRES 28.554377 Hz
SW 12.181 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300000 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300000 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
1 2 3 4 5 6 7 8 9 10 11
11 10 9 8 7 6 5 4 3 2 1 ppm

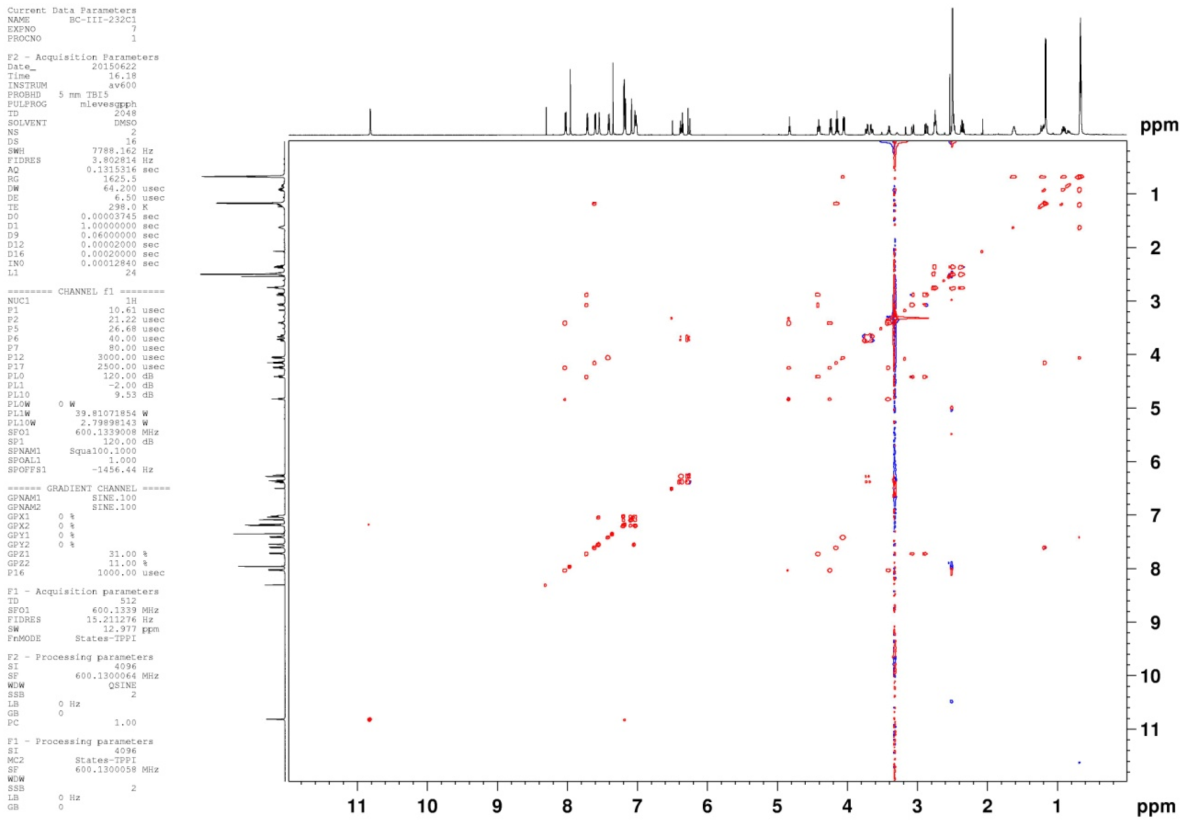

Current Data Parameters
NAME BC-III-232B2
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150605
Time 17.12
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 30
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
P2 19.60 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 254
SFO1 150.9134 MHz
FIDRES 95.063545 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300051 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029290 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

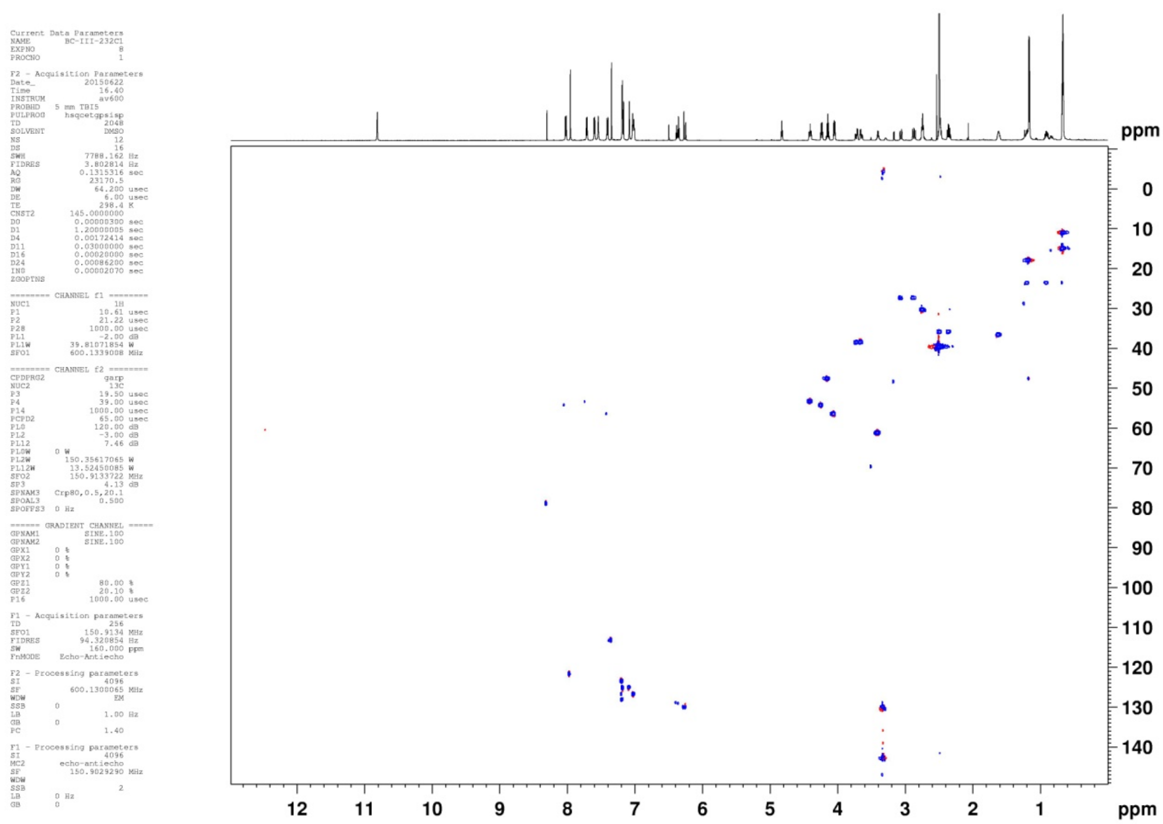

Current Data Parameters
NAME BC-III-232B2
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150611
Time 11.44
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 35
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
P2 19.60 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300097 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9028798 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

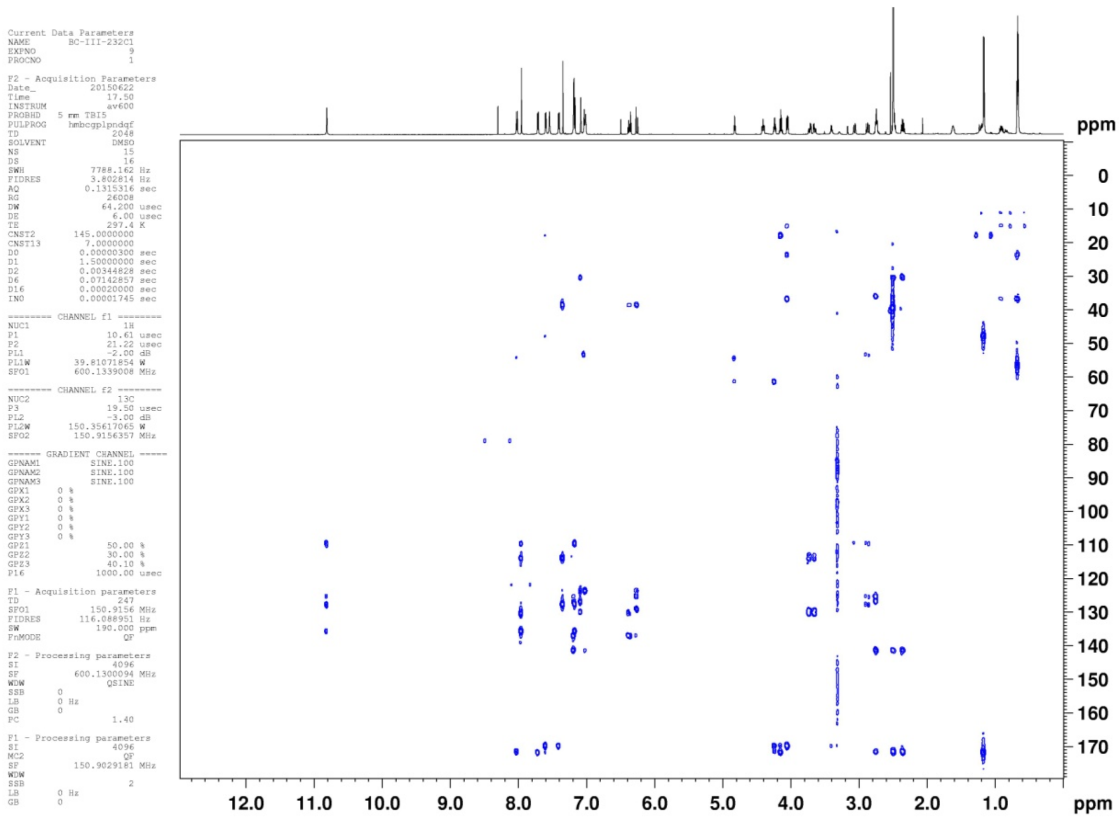
Macrocyclic Product ***2.19c***



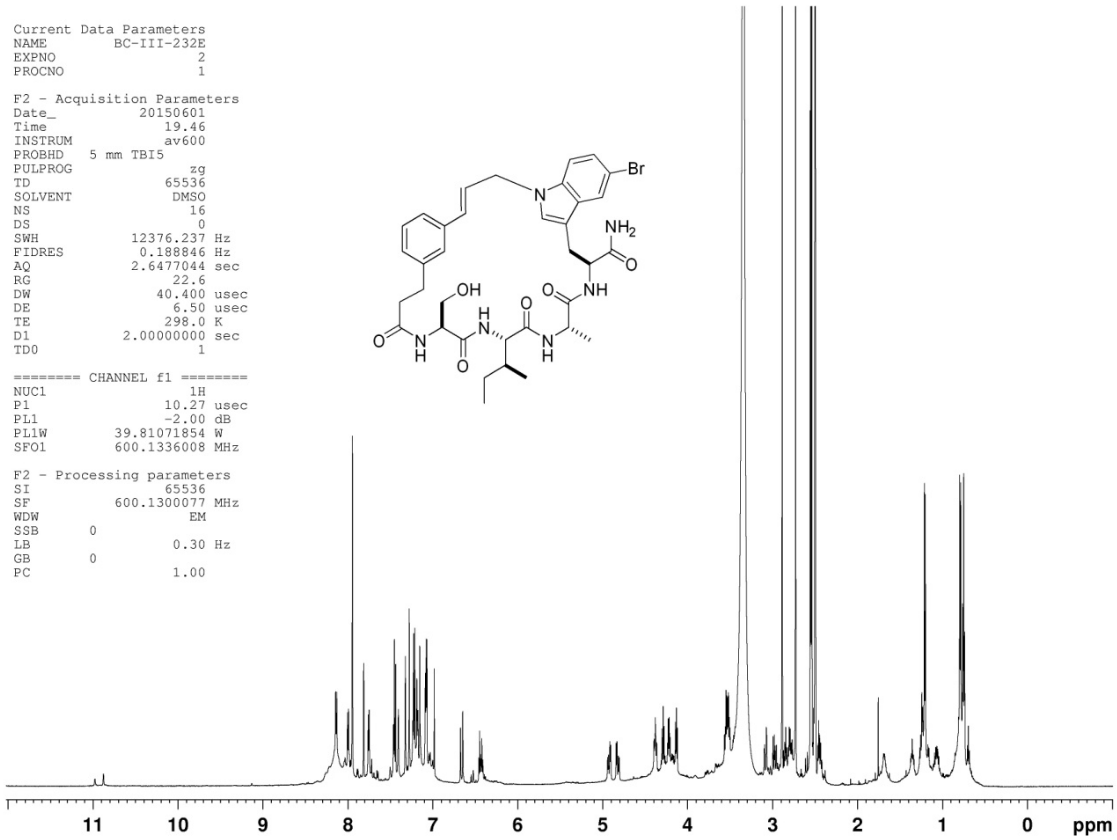


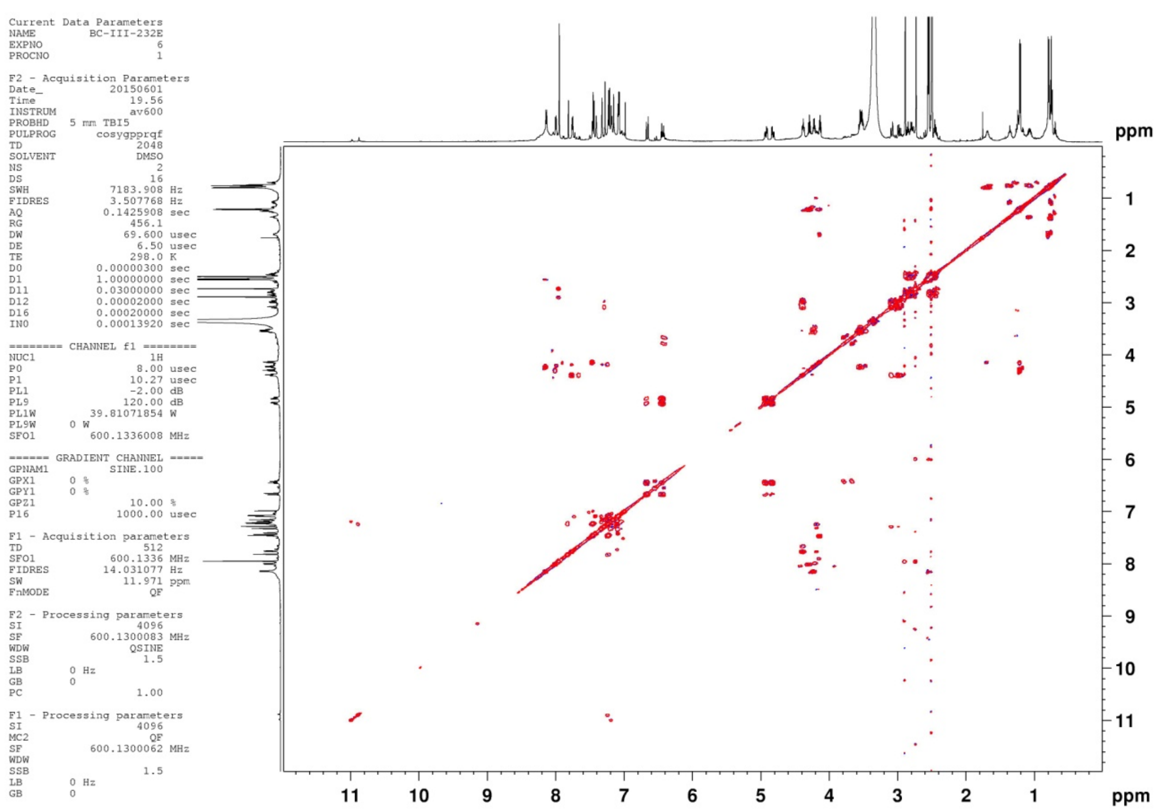

Current Data Parameters
NAME BC-III-232C1
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 16.18
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003745 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.61 usec
P2 21.22 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.53 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.79898143 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300064 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300058 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
11 10 9 8 7 6 5 4 3 2 1 ppm

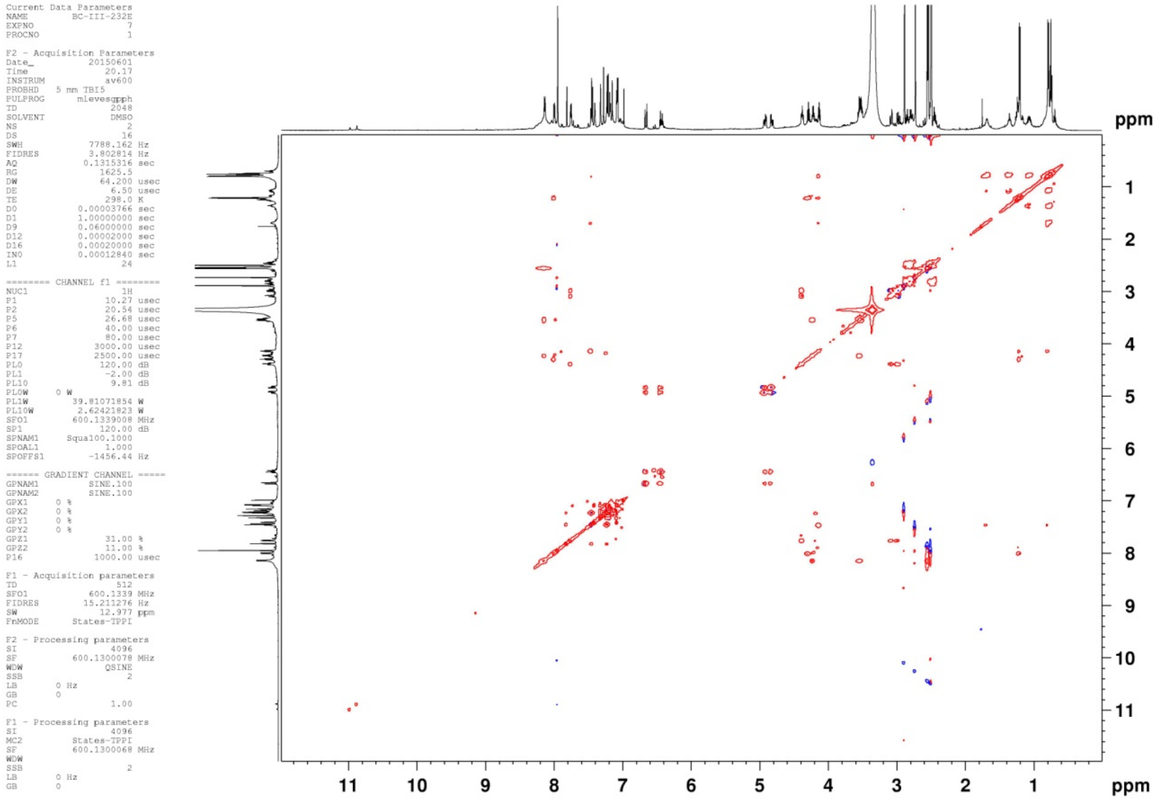

Current Data Parameters
NAME BC-III-232C1
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 16.40
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 12
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.61 usec
P2 21.22 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300065 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029290 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
12 11 10 9 8 7 6 5 4 3 2 1 ppm

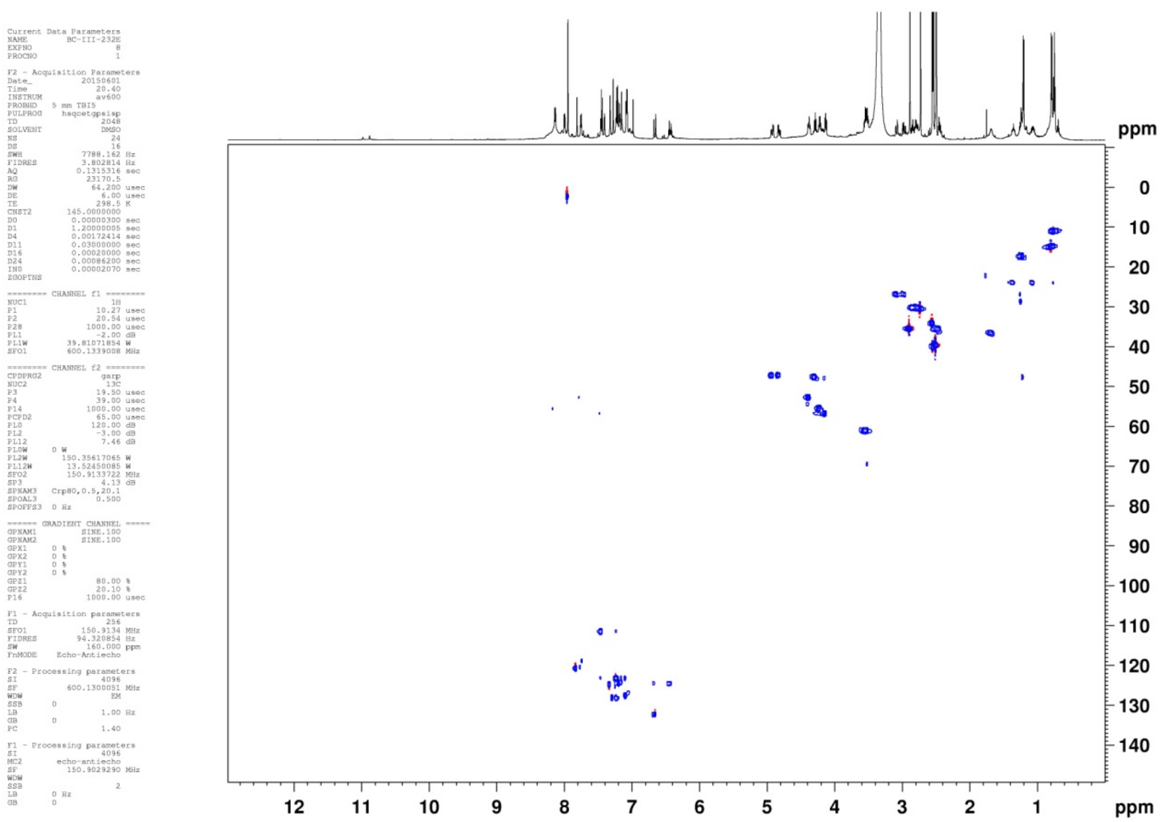

Current Data Parameters
NAME BC-III-232C1
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150622
Time 17.50
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 15
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.4 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.61 usec
P2 21.22 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 247
SFO1 150.9156 MHz
FIDRES 116.088951 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300094 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9029181 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0
ppm

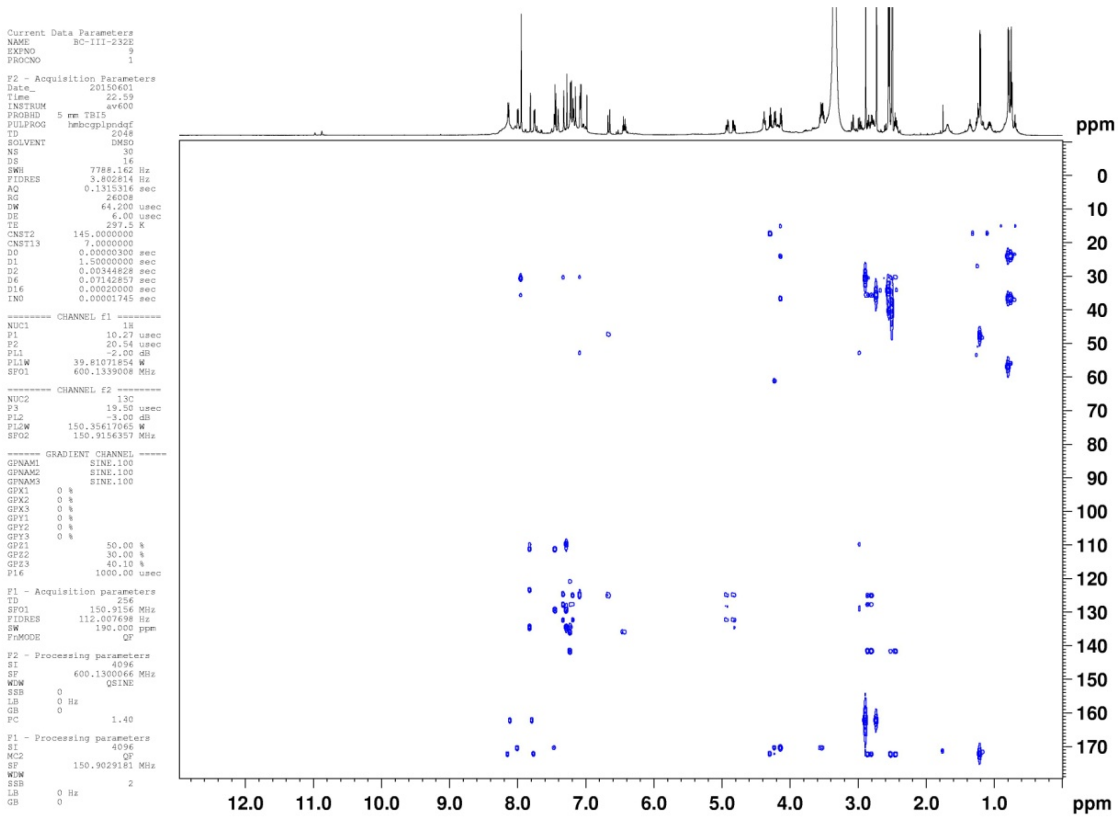
Macrocyclic Product ***2.19d***





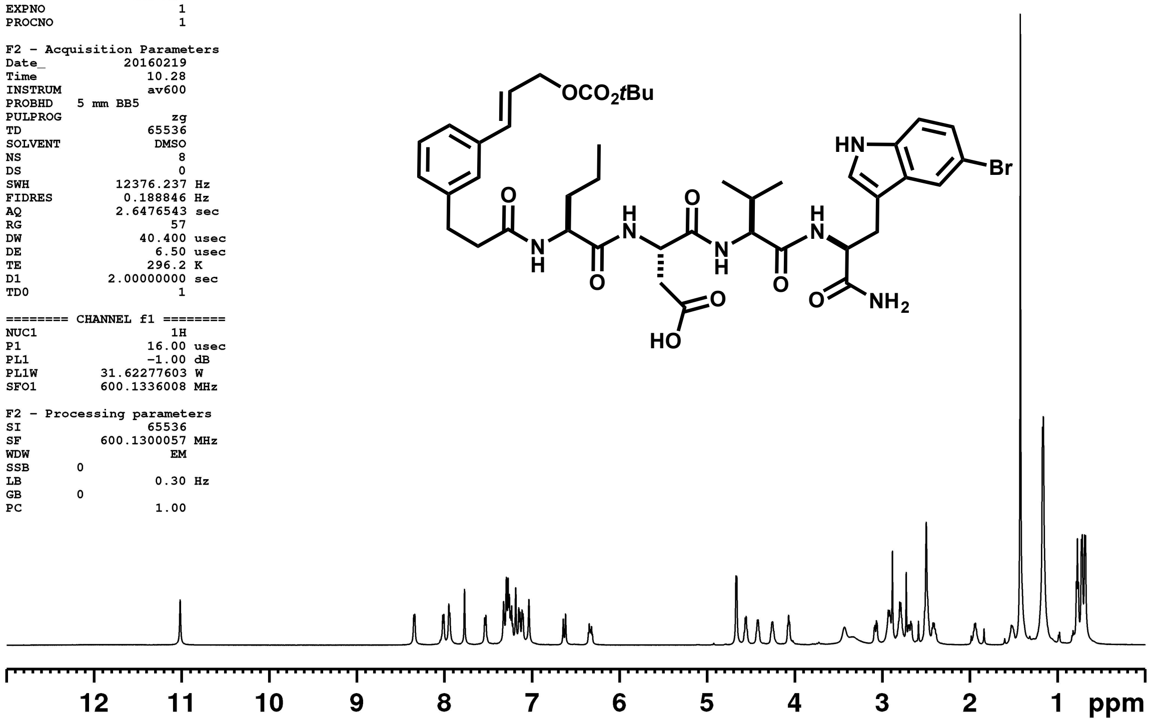

Current Data Parameters
NAME BC-III-232E
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150601
Time 20.17
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 1625.5
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003766 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.27 usec
P2 20.54 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.81 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.62421823 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM1 Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 600.1339 MHz
FIDRES 15.211276 Hz
SW 12.977 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 600.1300078 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 4096
MC2 States-TPPI
SF 600.1300068 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm

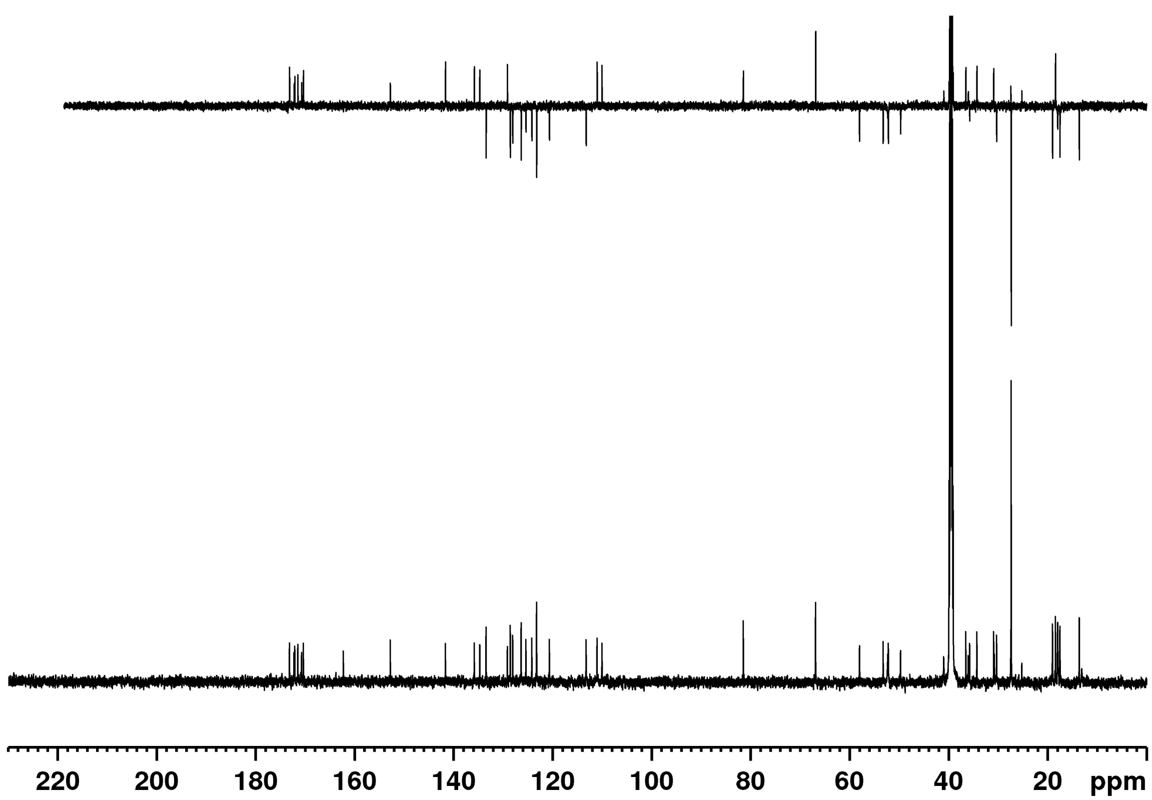

Current Data Parameters
NAME BC-III-232E
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150601
Time 20.40
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.5 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.27 usec
P2 20.54 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz
SP3 4.13 dB
SPNAM3 Crp80,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 80.00 %
GPZ2 20.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9134 MHz
FIDRES 94.320854 Hz
SW 160.000 ppm
FnMODE Echo-Antiecho
F2 - Processing parameters
SI 4096
SF 600.1300051 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 echo-antiecho
SF 150.9029290 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
ppm


Current Data Parameters
NAME BC-III-232E
EXPNO 9
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150601
Time 22.59
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 30
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1315316 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.27 usec
P2 20.54 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
GPY3 0 %
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 150.9156 MHz
FIDRES 112.007698 Hz
SW 190.000 ppm
FnMODE QF
F2 - Processing parameters
SI 4096
SF 600.1300066 MHz
WDW QSINE
SSB 0
LB 0 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 4096
MC2 QF
SF 150.9029181 MHz
WDW
SSB 2
LB 0 Hz
GB 0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm

Acyclic Precursor ***2.S1***

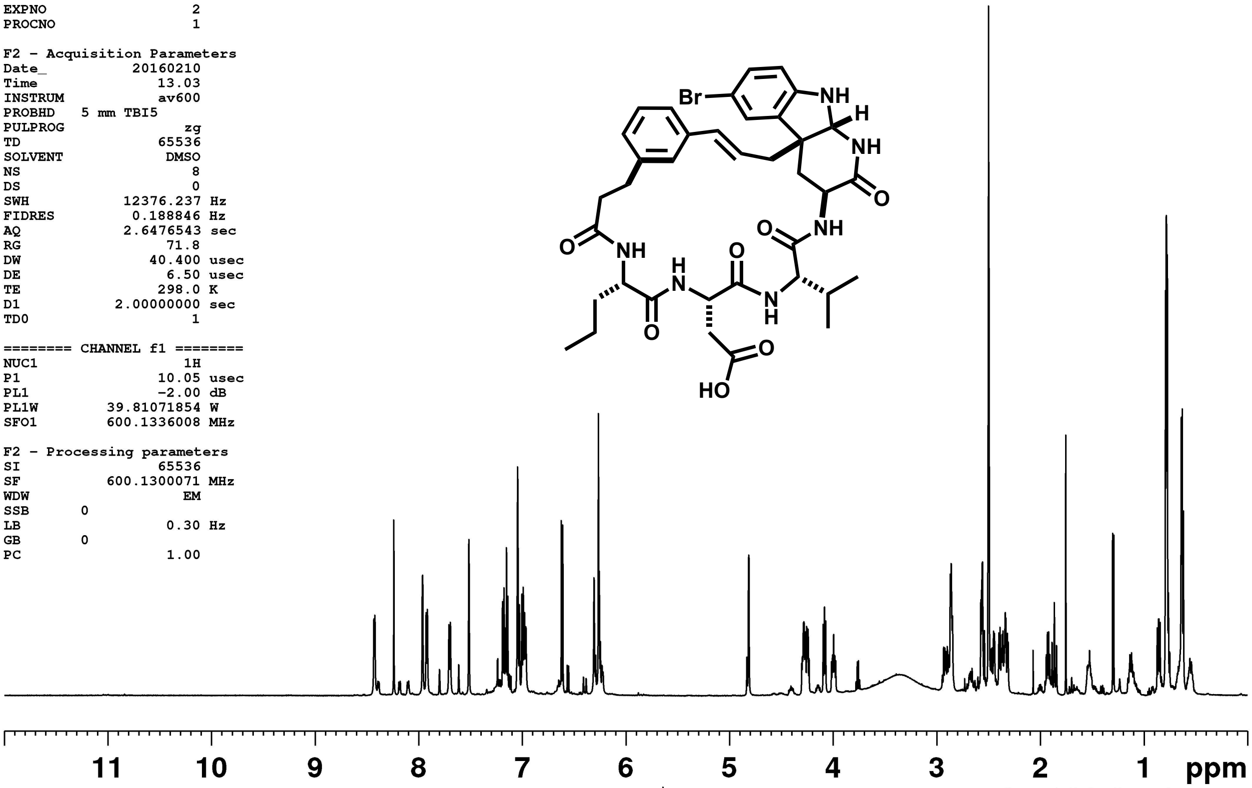
```
Current Data Parameters
NAME              TR6-164
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160219
Time                10.28
INSTRUM             av600
PROBHD   5 mm BB5
PULPROG                zg
TD                  65536
SOLVENT              DMSO
NS                      8
DS                      0
SWH             12376.237 Hz
FIDRES           0.188846 Hz
AQ              2.6476543 sec
RG                     57
DW                 40.400 usec
DE                   6.50 usec
TE                  296.2 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  16.00 usec
PL1                 -1.00 dB
PL1W          31.62277603 W
SFO1          600.1336008 MHz

F2 - Processing parameters
SI                  65536
SF            600.1300057 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```

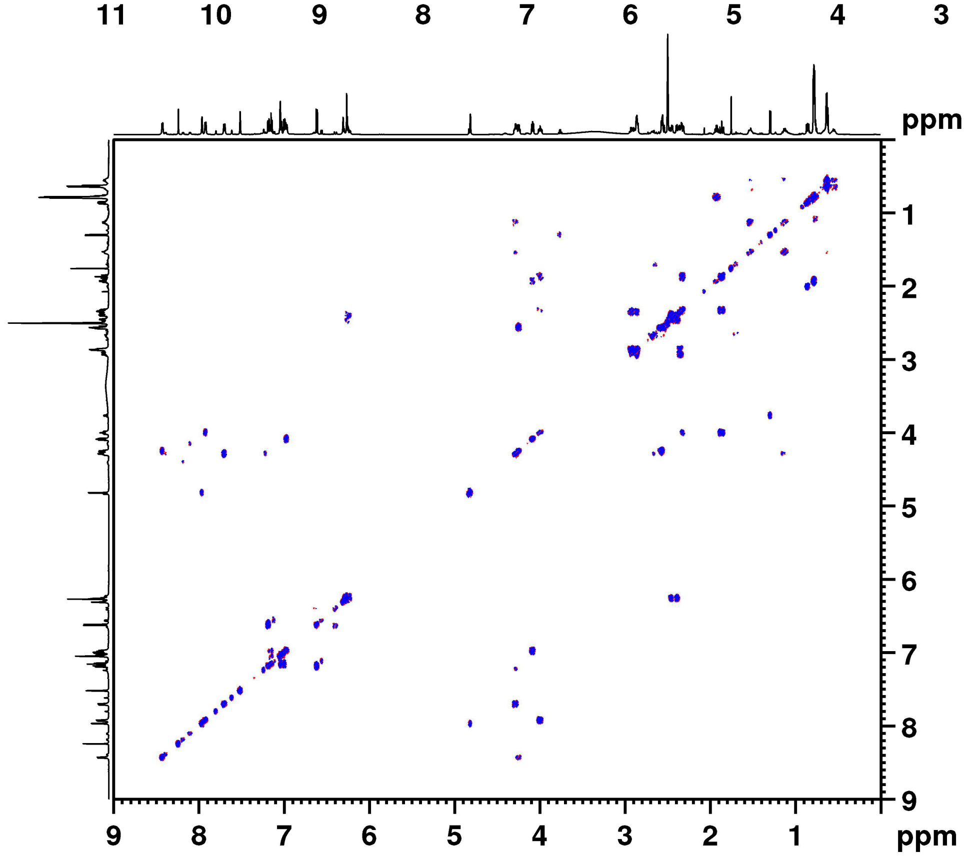




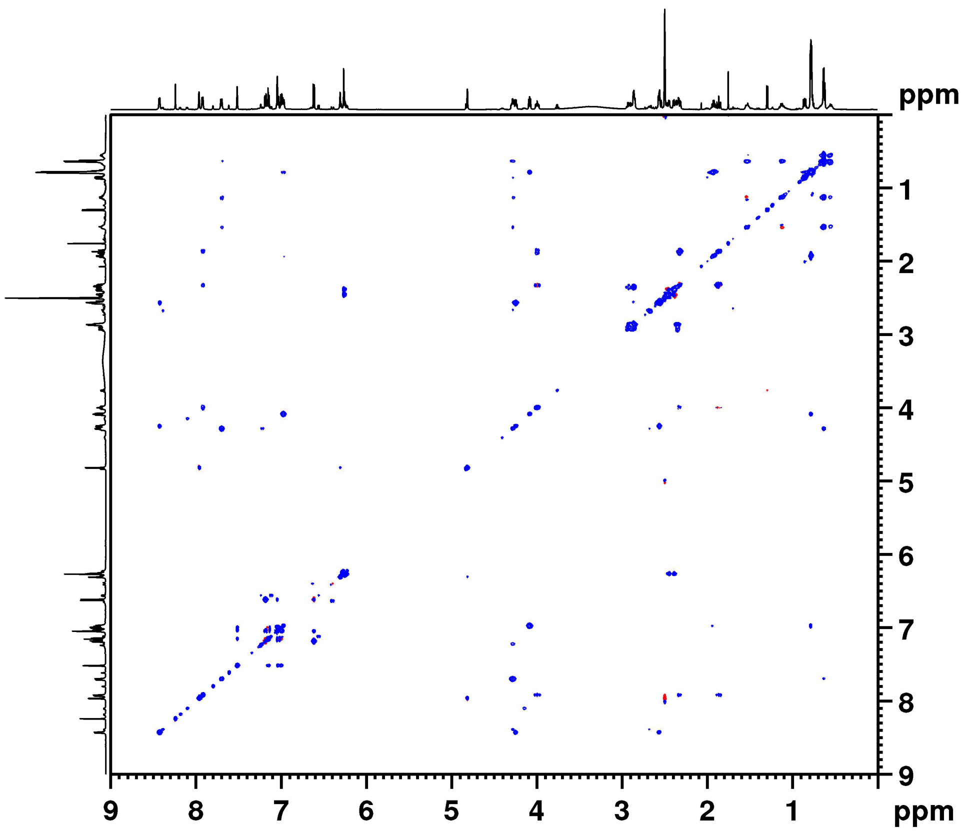
*Macrocyclic Product **2.S2a***

```
Current Data Parameters
NAME            TR6-186B2
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160210
Time                13.03
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG                zg
TD                  65536
SOLVENT              DMSO
NS                      8
DS                      0
SWH             12376.237 Hz
FIDRES           0.188846 Hz
AQ              2.6476543 sec
RG                   71.8
DW                 40.400 usec
DE                   6.50 usec
TE                  298.0 K
D1             2.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.05 usec
PL1                 -2.00 dB
PL1W          39.81071854 W
SFO1          600.1336008 MHz

F2 - Processing parameters
SI                  65536
SF            600.1300071 MHz
WDW                    EM
SSB      0
LB                   0.30 Hz
GB       0
PC                   1.00
```

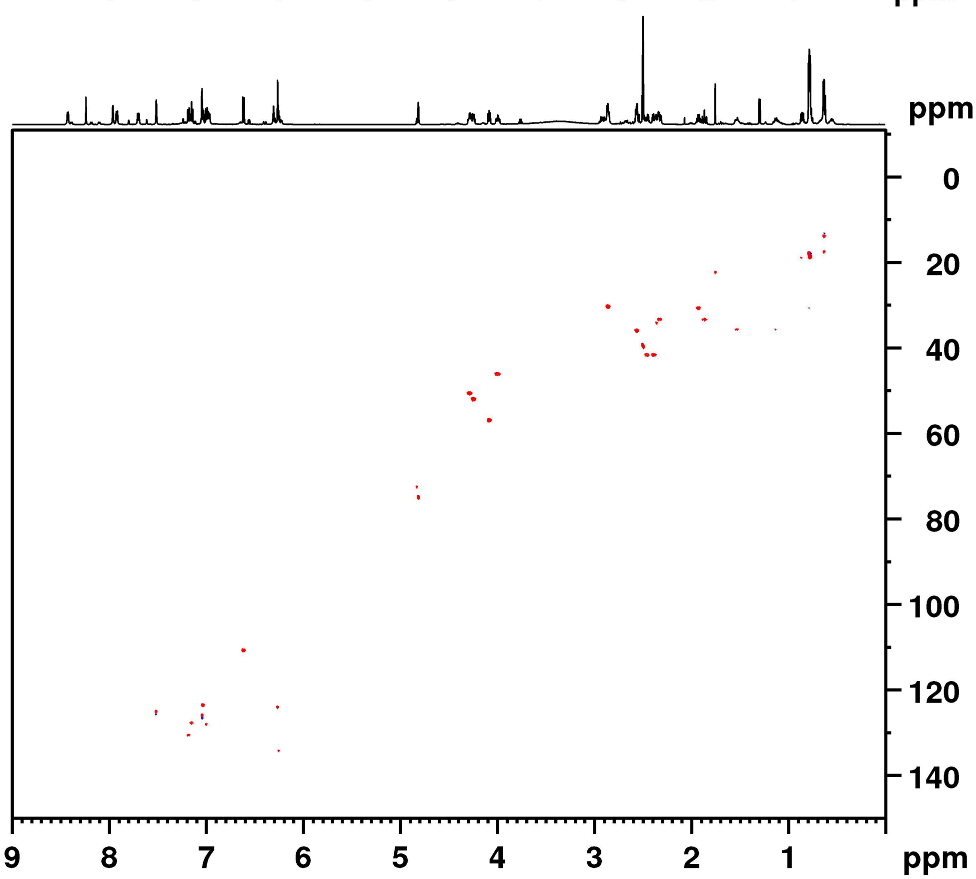




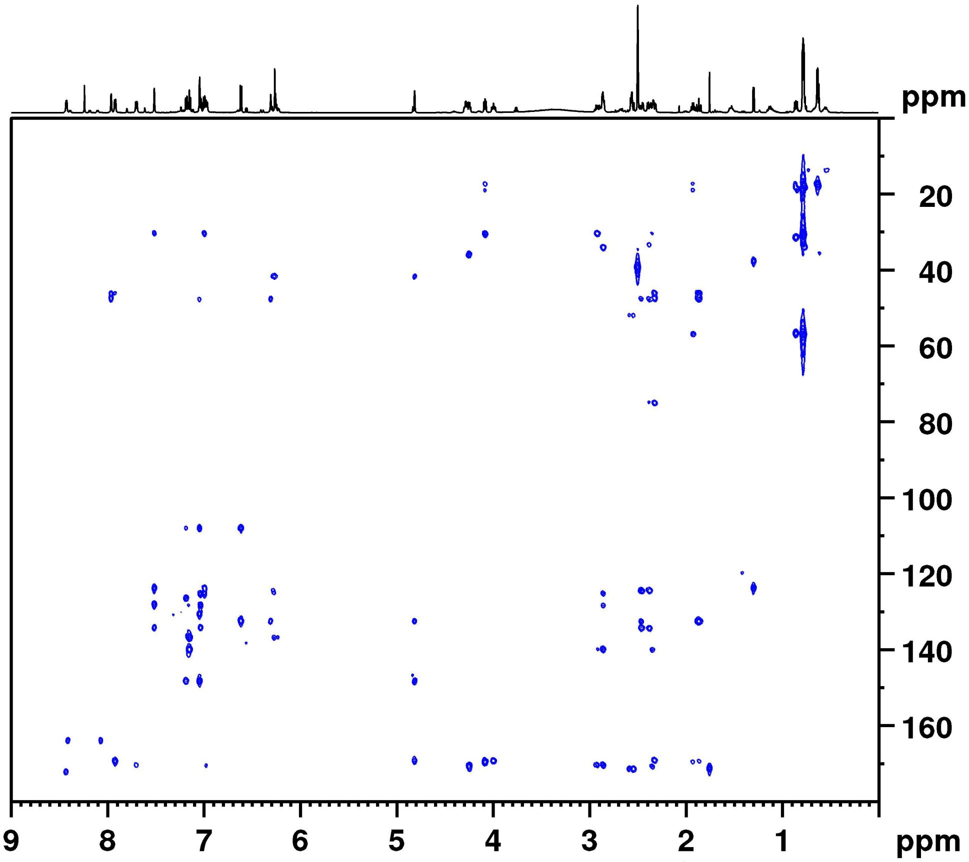

```
Current Data Parameters
NAME            TR6-186B2
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160210
Time                13.05
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG         cosygpprqf
TD                   2048
SOLVENT              DMSO
NS                      2
DS                     16
SWH              7183.908 Hz
FIDRES           3.507768 Hz
AQ              0.1425408 sec
RG                   35.9
DW                 69.600 usec
DE                   6.50 usec
TE                  298.0 K
D0             0.00000300 sec
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
D16            0.00020000 sec
IN0            0.00013920 sec

======== CHANNEL f1 ========
NUC1                   1H
P0                   8.00 usec
P1                  10.05 usec
PL1                 -2.00 dB
PL9                120.00 dB
PL1W          39.81071854 W
PL9W     0 W
SFO1          600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPX1     0 %
GPY1     0 %
GPZ1                10.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    512
SFO1             600.1336 MHz
FIDRES          14.031077 Hz
SW                 11.971 ppm
FnMODE                 QF

F2 - Processing parameters
```




```
Current Data Parameters
NAME            TR6-186B2
EXPNO                   7
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160210
Time                13.26
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG        mlevesgpph
TD                   2048
SOLVENT              DMSO
NS                      2
DS                     16
SWH              7788.162 Hz
FIDRES           3.802814 Hz
AQ              0.1314816 sec
RG                  228.1
DW                 64.200 usec
DE                   6.50 usec
TE                  298.0 K
D0            0.00003780 sec
D1            1.00000000 sec
D9            0.06000000 sec
D12           0.00002000 sec
D16           0.00020000 sec
IN0           0.00012840 sec
L1                     24

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.05 usec
P2                  20.10 usec
P5                  26.68 usec
P6                  40.00 usec
P7                  80.00 usec
P12               3000.00 usec
P17               2500.00 usec
PL0                120.00 dB
PL1                 -2.00 dB
PL10                10.00 dB
PL0W      0 W
PL1W          39.81071854 W
PL10W          2.51188636 W
SFO1          600.1339008 MHz
SP1                120.00 dB
SPNAM[1]    Squa100.1000
SPOAL1              1.000
SPOFFS1          -1456.44 Hz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
```




```
Current Data Parameters
NAME            TR6-186B2
EXPNO                   8
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160210
Time                13.47
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG      hsqcetgpsisp
TD                   2048
SOLVENT              DMSO
NS                      6
DS                     16
SWH              7788.162 Hz
FIDRES           3.802814 Hz
AQ              0.1314816 sec
RG                23170.5
DW                 64.200 usec
DE                   6.00 usec
TE                  298.3 K
CNST2         145.0000000
D0            0.00000300 sec
D1            1.20000005 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
D24           0.00086200 sec
IN0           0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.05 usec
P2                  20.10 usec
P28               1000.00 usec
PL1                 -2.00 dB
PL1W          39.81071854 W
SFO1          600.1339008 MHz

======== CHANNEL f2 ========
CPDPRG[2             garp
NUC2                  13C
P3                  19.50 usec
P4                  39.00 usec
P14               1000.00 usec
PCPD2               65.00 usec
PL0                120.00 dB
PL2                 -3.00 dB
PL12                 7.46 dB
PL0W      0 W
PL2W         150.35617065 W
PL12W         13.52450085 W
SFO2          150.9133722 MHz
```



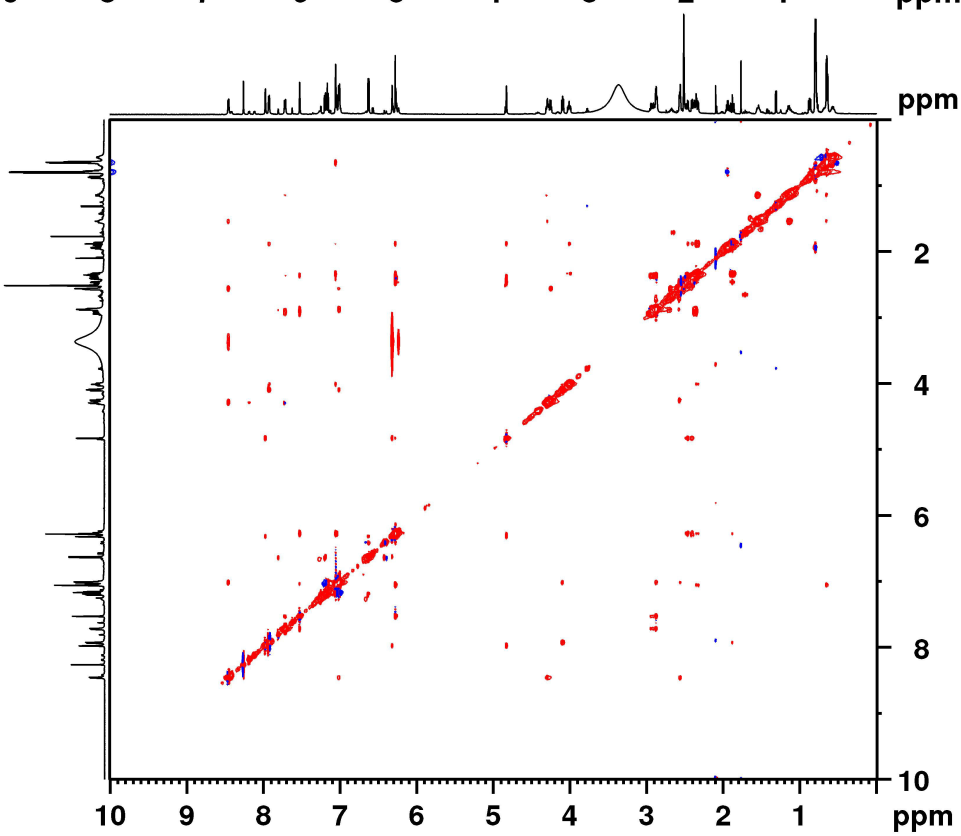
Current Data Parameters
NAME TR6-186B2
EXPNO 9
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160210
Time 14.23
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1314816 sec
RG 26008
DW 64.200 usec
DE 6.00 usec
TE 297.5 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec

======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz

======== CHANNEL f2 ========
NUC2 13C
P3 19.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %



Current Data Parameters
NAME TR6-186B2
EXPNO 13
PROCNO 1

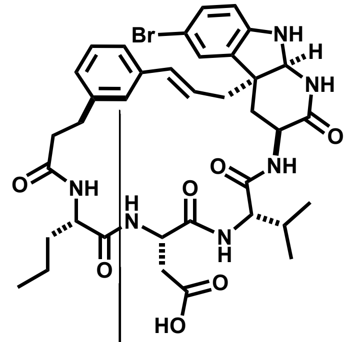
F2 - Acquisition Parameters
Date_ 20160211
Time 8.54
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG noesyesgpph
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 512
DW 83.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00007010 sec
D1 1.50000000 sec
D8 0.30000001 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00016665 sec

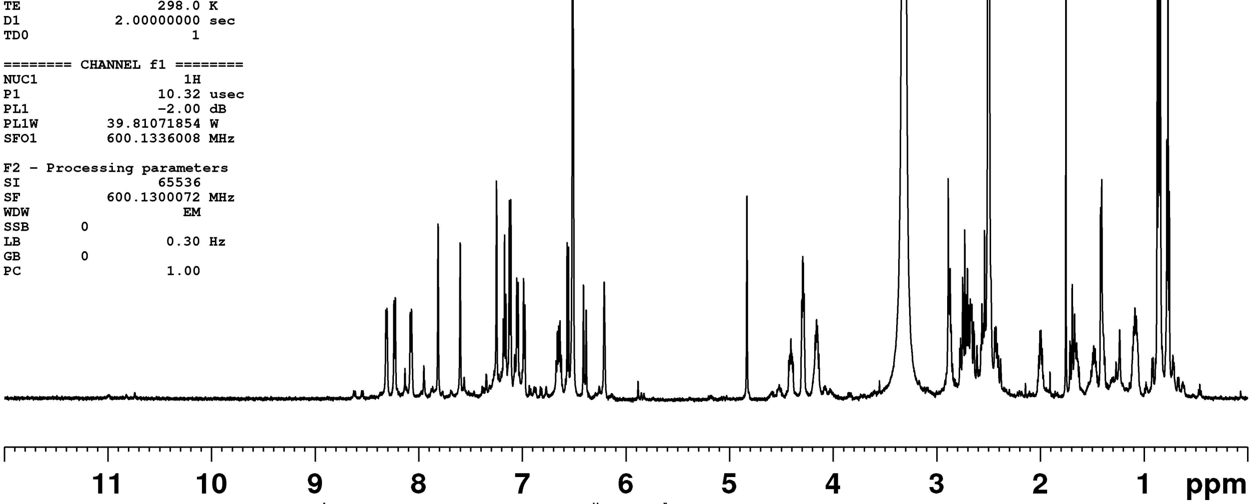
======== CHANNEL f1 ========
NUC1 1H
P1 10.38 usec
P2 20.76 usec
P12 3000.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL0W 0 W
PL1W 39.81071854 W
SFO1 600.1330006 MHz
SP1 41.20 dB
SPNAM[1] Squa100.1000
SPOAL1 1.000
SPOFFS1 -977.55 Hz

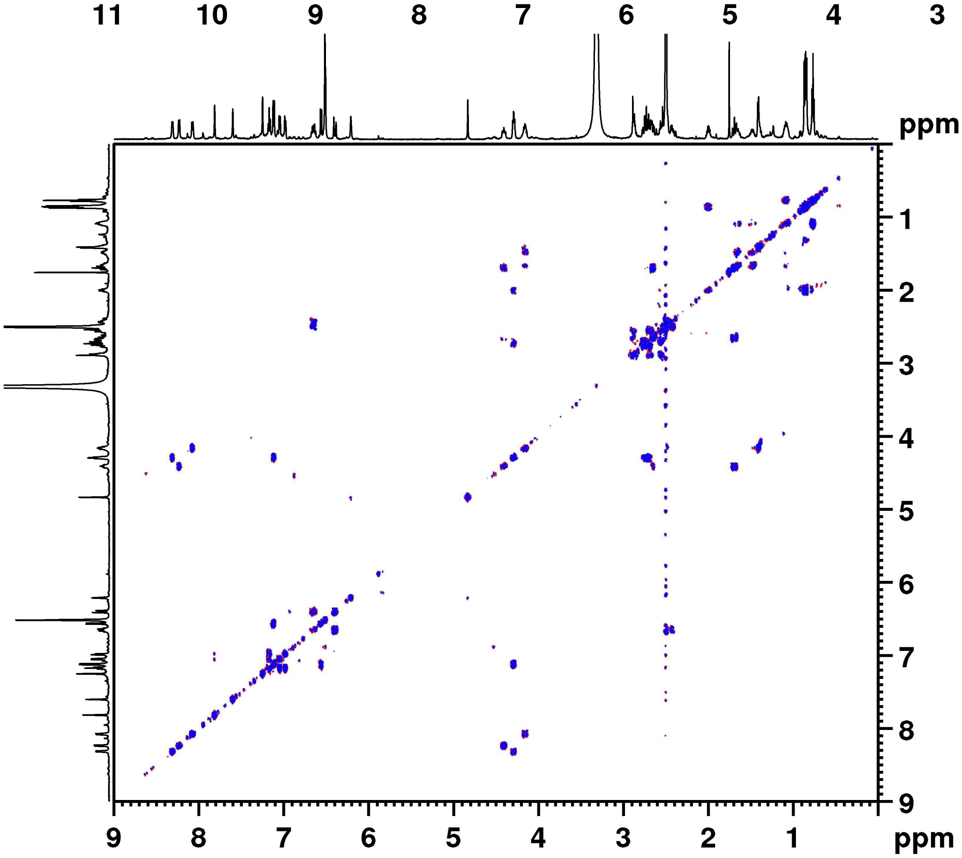
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 31.00 %
GPZ2 11.00 %

Macrocyclic Product ***2.S2b***

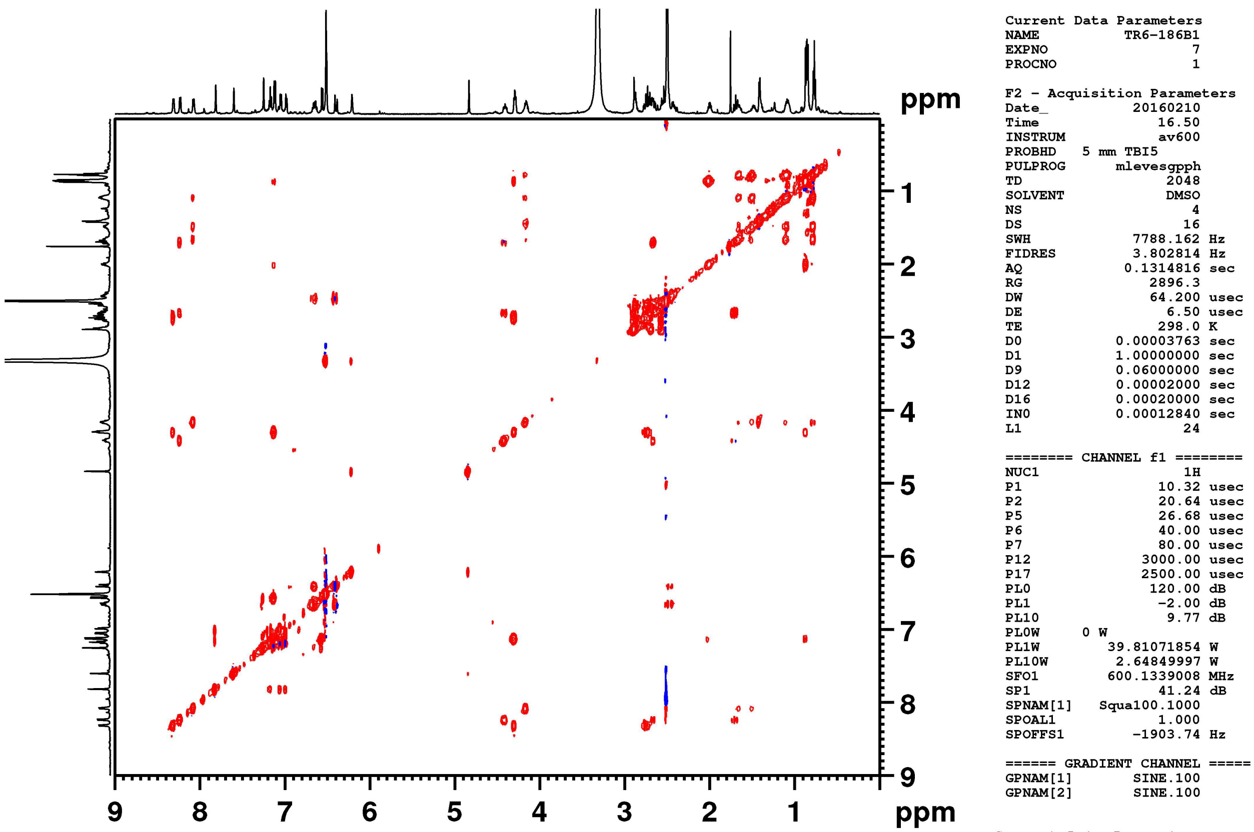
```
Current Data Parameters
NAME          TR6-186B1
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_          20160210
Time              16.32
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG              zg
TD                65536
SOLVENT            DMSO
NS                    8
DS                    0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                 71.8
DW               40.400 usec
DE                 6.50 usec
TE                298.0 K
D1           2.00000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                10.32 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1        600.1336008 MHz

F2 - Processing parameters
SI                65536
SF          600.1300072 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```

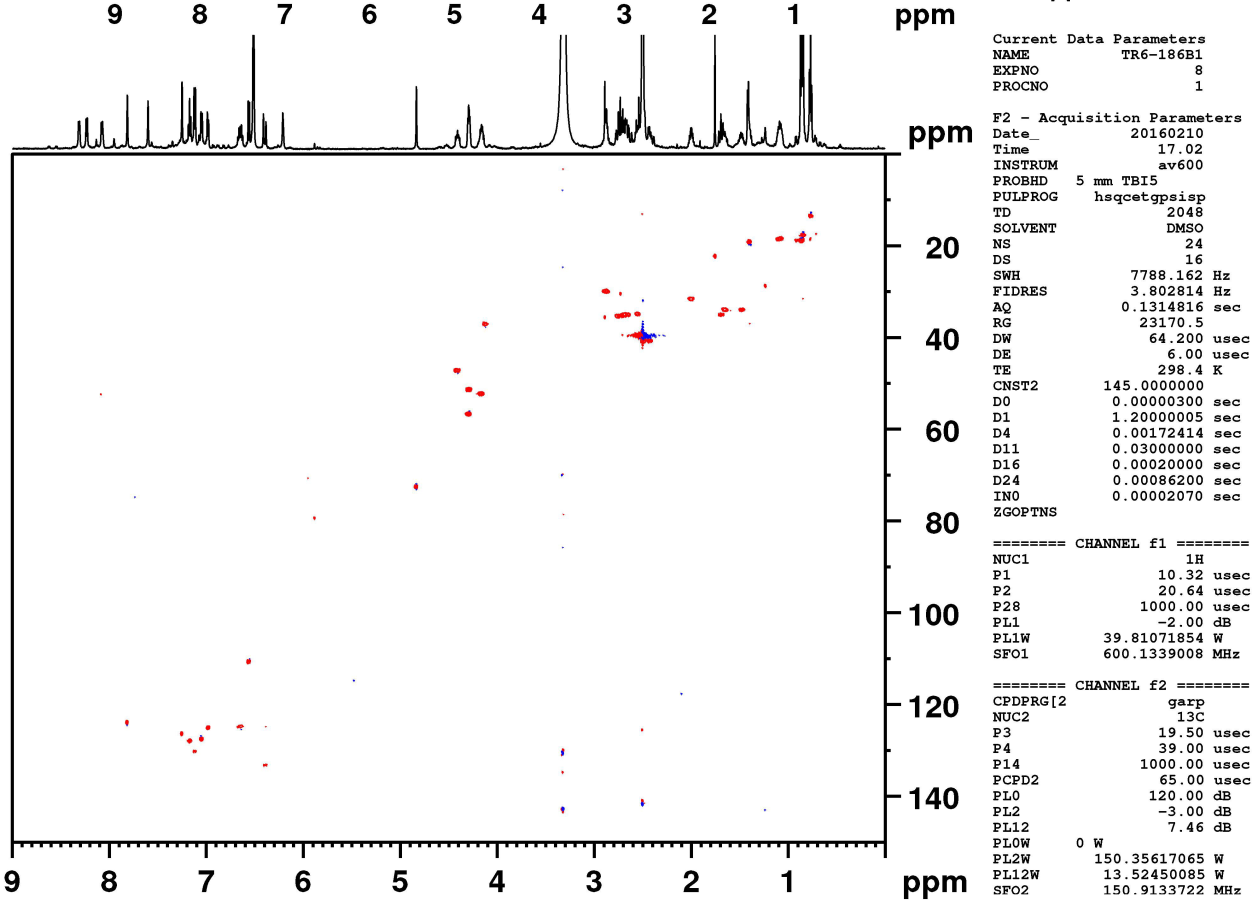


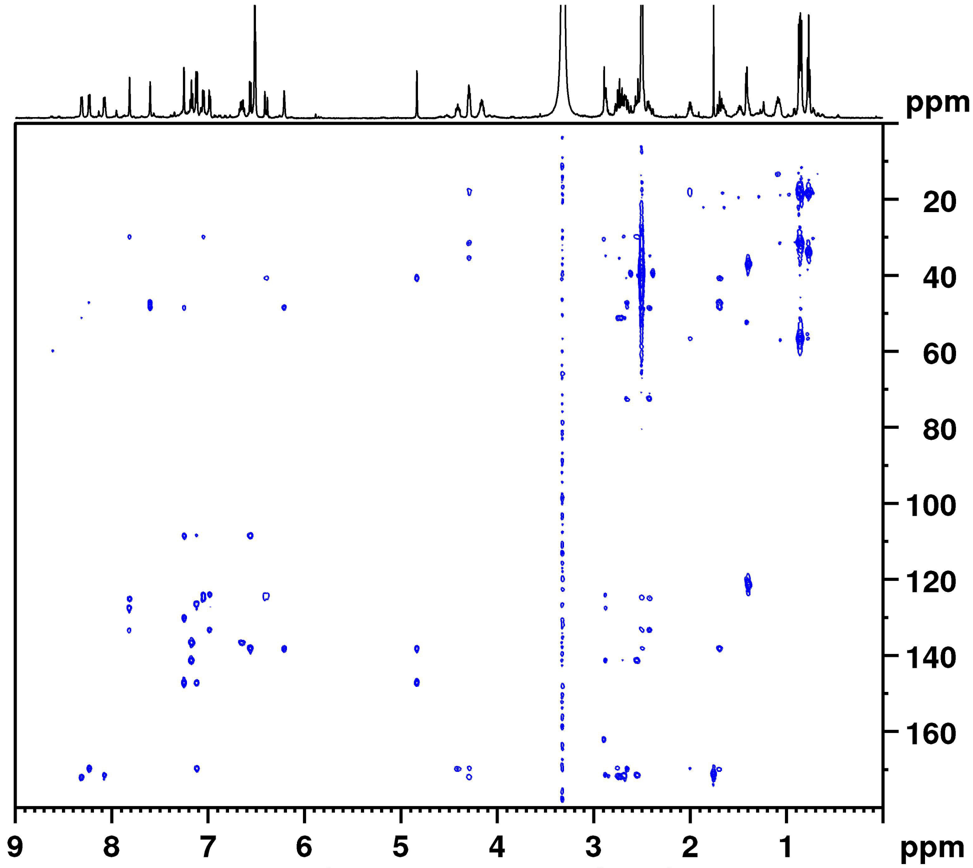




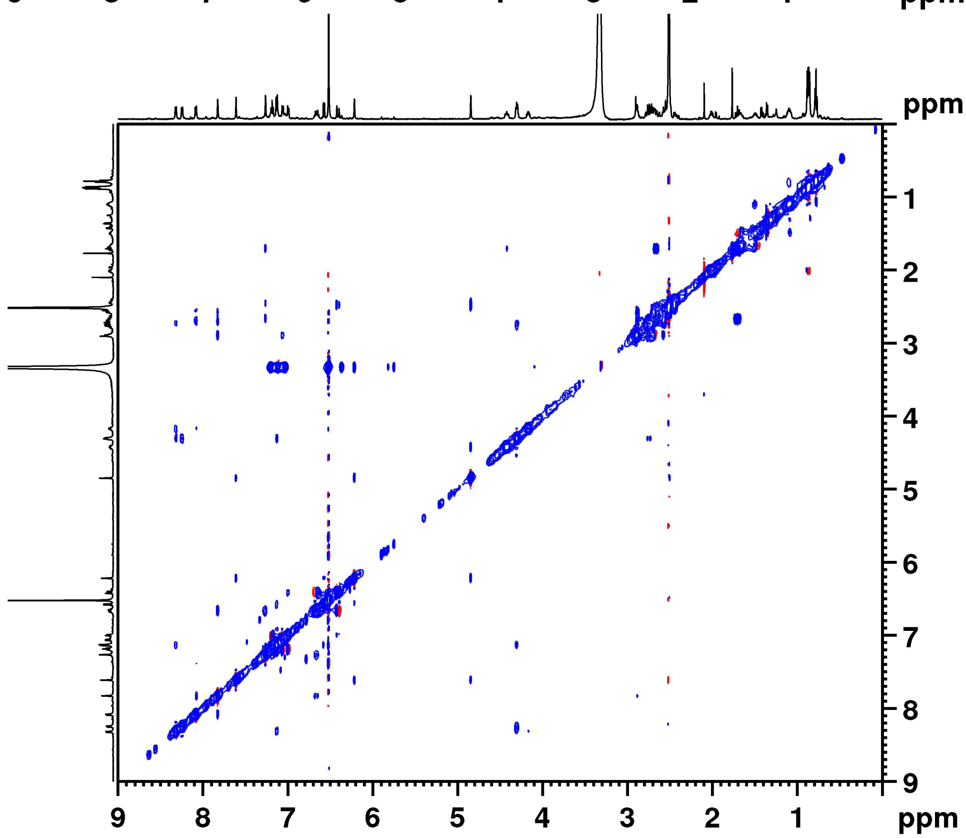

```
Current Data Parameters
NAME          TR6-186B1
EXPNO                 6
PROCNO                1

F2 - Acquisition Parameters
Date_          20160210
Time              16.36
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG      cosygpprqf
TD                 2048
SOLVENT            DMSO
NS                    4
DS                   16
SWH            7183.908 Hz
FIDRES         3.507768 Hz
AQ            0.1425408 sec
RG                 2048
DW               69.600 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00000300 sec
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00013920 sec

======== CHANNEL f1 ========
NUC1                 1H
P0                 8.00 usec
P1                10.32 usec
PL1               -2.00 dB
PL9               51.71 dB
PL1W        39.81071854 W
PL9W         0.00016943 W
SFO1        600.1319971 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPX1      0 %
GPY1      0 %
GPZ1              10.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  161
SFO1            600.132 MHz
FIDRES        44.620449 Hz
SW               11.971 ppm
FnMODE               QF

F2 - Processing parameters
```


ppm
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME TR6-186B1
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160210
Time 16.50
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1314816 sec
RG 2896.3
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003763 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.32 usec
P2 20.64 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.77 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.64849997 W
SFO1 600.1339008 MHz
SP1 41.24 dB
SPNAM[1] Squa100.1000
SPOAL1 1.000
SPOFFS1 -1903.74 Hz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100


ppm
20
40
60
80
100
120
140
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME TR6-186B1
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160210
Time 17.02
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1314816 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.4 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.32 usec
P2 20.64 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz

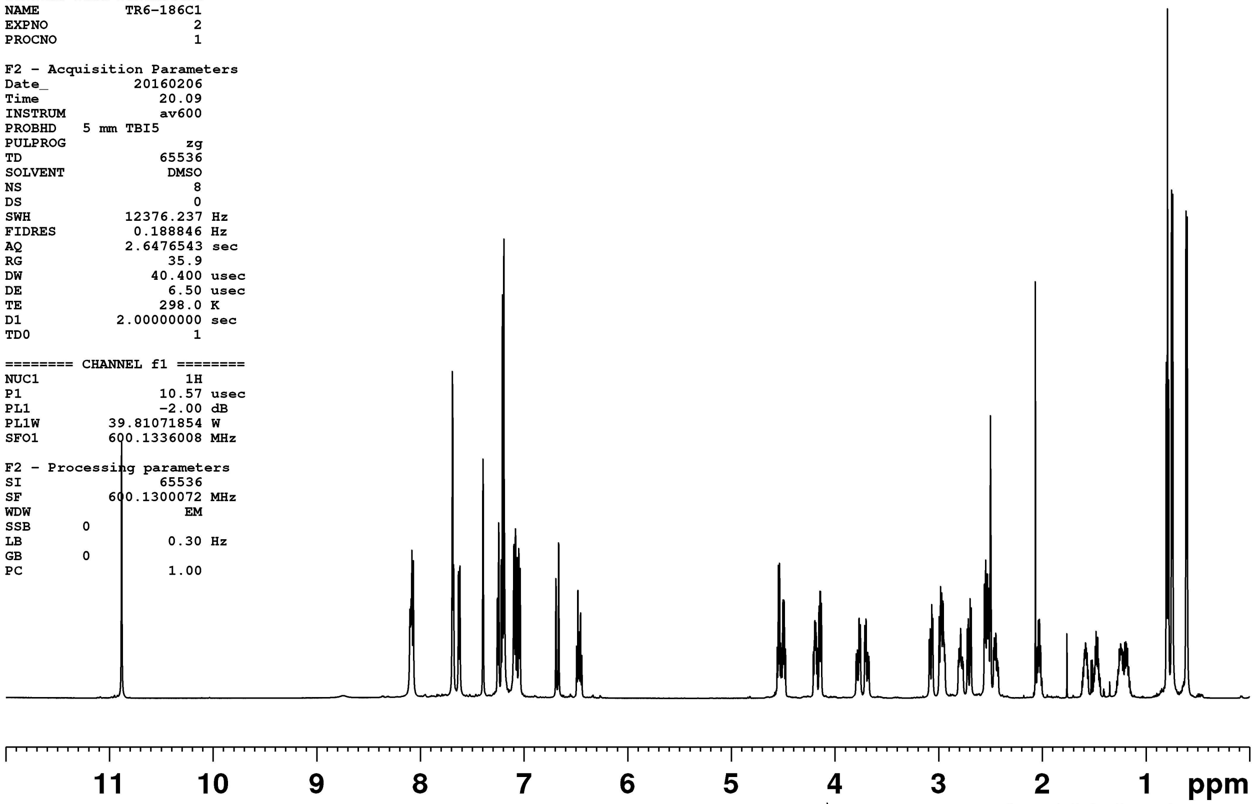


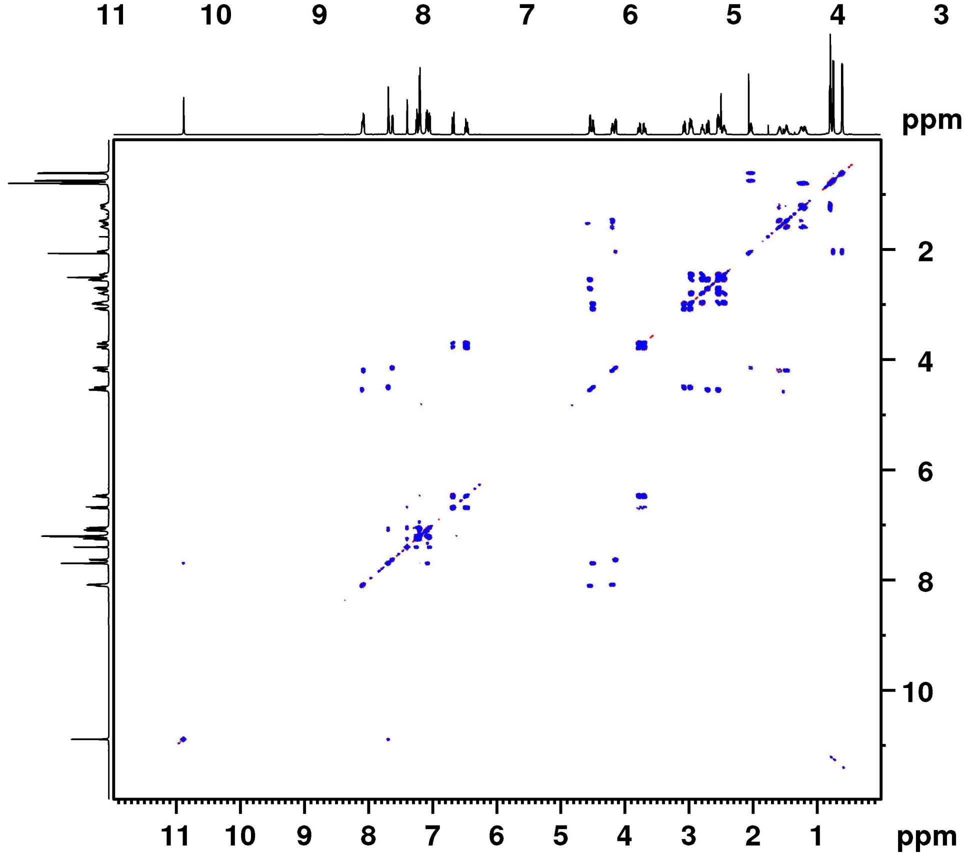
```
Current Data Parameters
NAME            TR6-186B1
EXPNO                   9
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160210
Time                19.22
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG    hmbcgplpndqf
TD                   2048
SOLVENT              DMSO
NS                     60
DS                     16
SWH              7788.162 Hz
FIDRES           3.802814 Hz
AQ              0.1314816 sec
RG                  26008
DW                 64.200 usec
DE                   6.00 usec
TE                  297.6 K
CNST2         145.0000000
CNST13          7.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D2             0.00344828 sec
D6             0.07142857 sec
D16            0.00020000 sec
IN0            0.00001745 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.32 usec
P2                  20.64 usec
PL1                 -2.00 dB
PL1W          39.81071854 W
SFO1          600.1339008 MHz

======== CHANNEL f2 ========
NUC2                  13C
P3                  19.50 usec
PL2                 -3.00 dB
PL2W         150.35617065 W
SFO2          150.9156357 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPNAM[3]         SINE.100
GPX1        0 %
GPX2        0 %
GPX3        0 %
GPY1        0 %
GPY2        0 %
```



```
Current Data Parameters
NAME            TR6-186B1
EXPNO                  14
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160211
Time                10.06
INSTRUM             av600
PROBHD   5 mm TBI5
PULPROG       noesyesgpph
TD                   2048
SOLVENT              DMSO
NS                     16
DS                     16
SWH              6009.615 Hz
FIDRES           2.934382 Hz
AQ              0.1703936 sec
RG                 7298.2
DW                 83.200 usec
DE                   6.50 usec
TE                  298.0 K
D0             0.00007010 sec
D1             1.50000000 sec
D8             0.30000001 sec
D11            0.03000000 sec
D12            0.00002000 sec
D16            0.00020000 sec
IN0            0.00016665 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  10.38 usec
P2                  20.76 usec
P12               3000.00 usec
PL0                120.00 dB
PL1                 -2.00 dB
PL0W        0 W
PL1W          39.81071854 W
SFO1          600.1330006 MHz
SP1                 41.20 dB
SPNAM[1]     Squa100.1000
SPOAL1              1.000
SPOFFS1          -1003.15 Hz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                31.00 %
GPZ2                11.00 %
```

*Macrocyclic product **2.S2c***





Current Data Parameters
NAME TR6-186C1
EXPNO 6
PROCNO 1

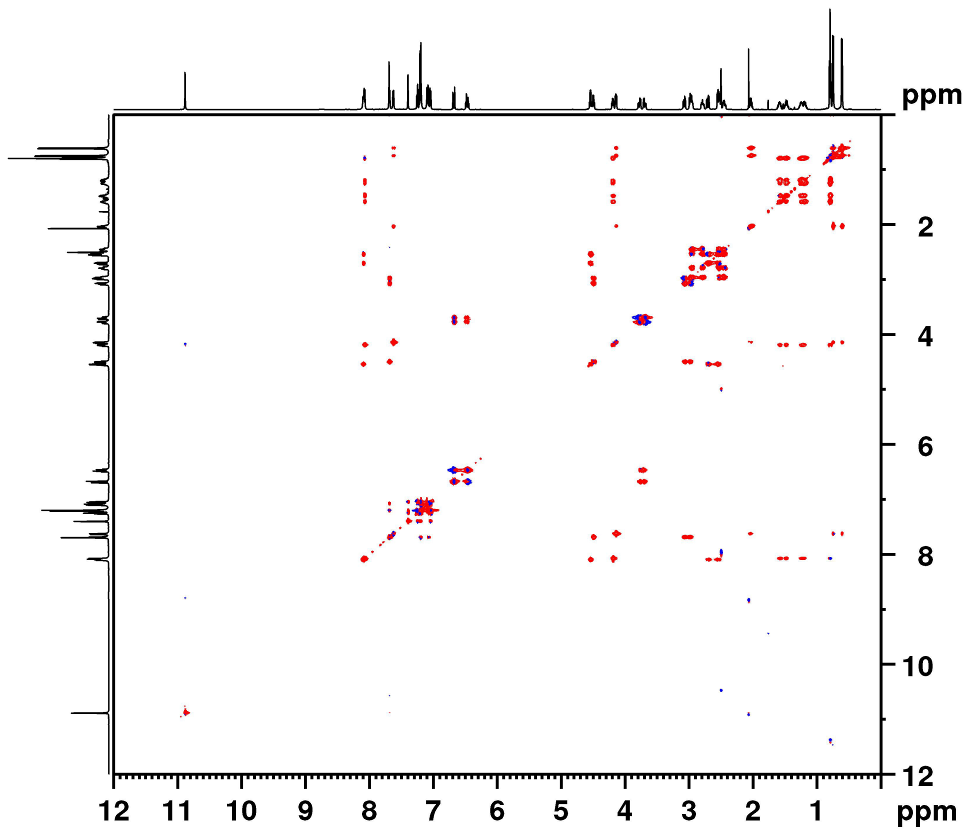
F2 - Acquisition Parameters
Date_ 20160206
Time 20.11
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG cosygpprqf
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 35.9
DW 69.600 usec
DE 6.50 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00013920 sec

======== CHANNEL f1 ========
NUC1 1H
P0 8.00 usec
P1 10.57 usec
PL1 -2.00 dB
PL9 120.00 dB
PL1W 39.81071854 W
PL9W 0 W
SFO1 600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPX1 0 %
GPY1 0 %
GPZ1 10.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 600.1336 MHz
FIDRES 14.031077 Hz
SW 11.971 ppm
FnMODE QF

F2 - Processing parameters

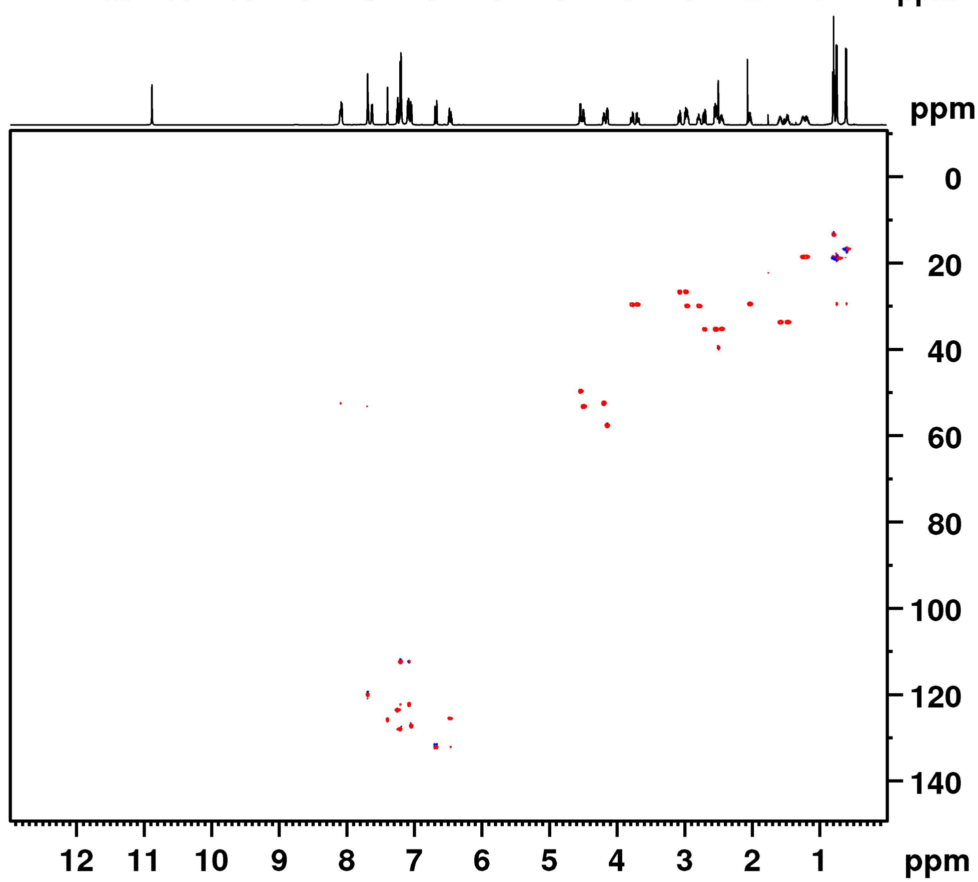


Current Data Parameters
NAME TR6-186C1
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160206
Time 20.32
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevesgpph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1314816 sec
RG 228.1
DW 64.200 usec
DE 6.50 usec
TE 298.0 K
D0 0.00003747 sec
D1 1.00000000 sec
D9 0.06000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00012840 sec
L1 24

======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P12 3000.00 usec
P17 2500.00 usec
PL0 120.00 dB
PL1 -2.00 dB
PL10 9.56 dB
PL0W 0 W
PL1W 39.81071854 W
PL10W 2.77971292 W
SFO1 600.1339008 MHz
SP1 120.00 dB
SPNAM[1] Squa100.1000
SPOAL1 1.000
SPOFFS1 -1456.44 Hz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100

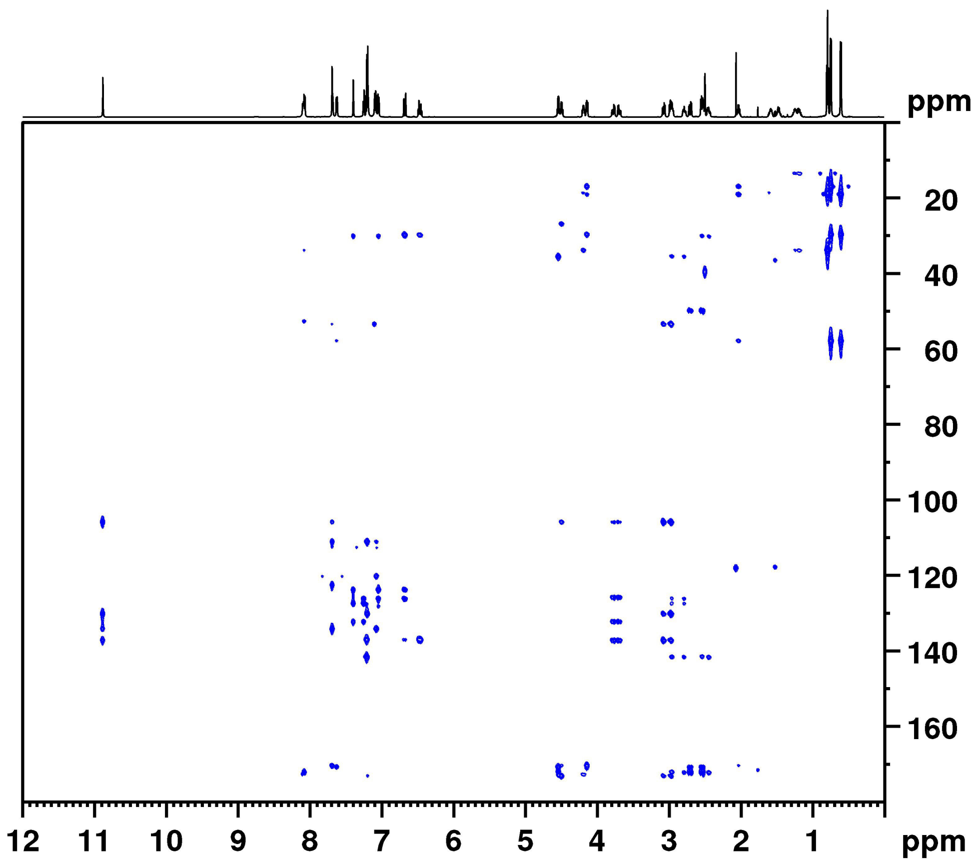


Current Data Parameters
NAME TR6-186C1
EXPNO 8
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160206
Time 20.54
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 7788.162 Hz
FIDRES 3.802814 Hz
AQ 0.1314816 sec
RG 23170.5
DW 64.200 usec
DE 6.00 usec
TE 298.3 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS

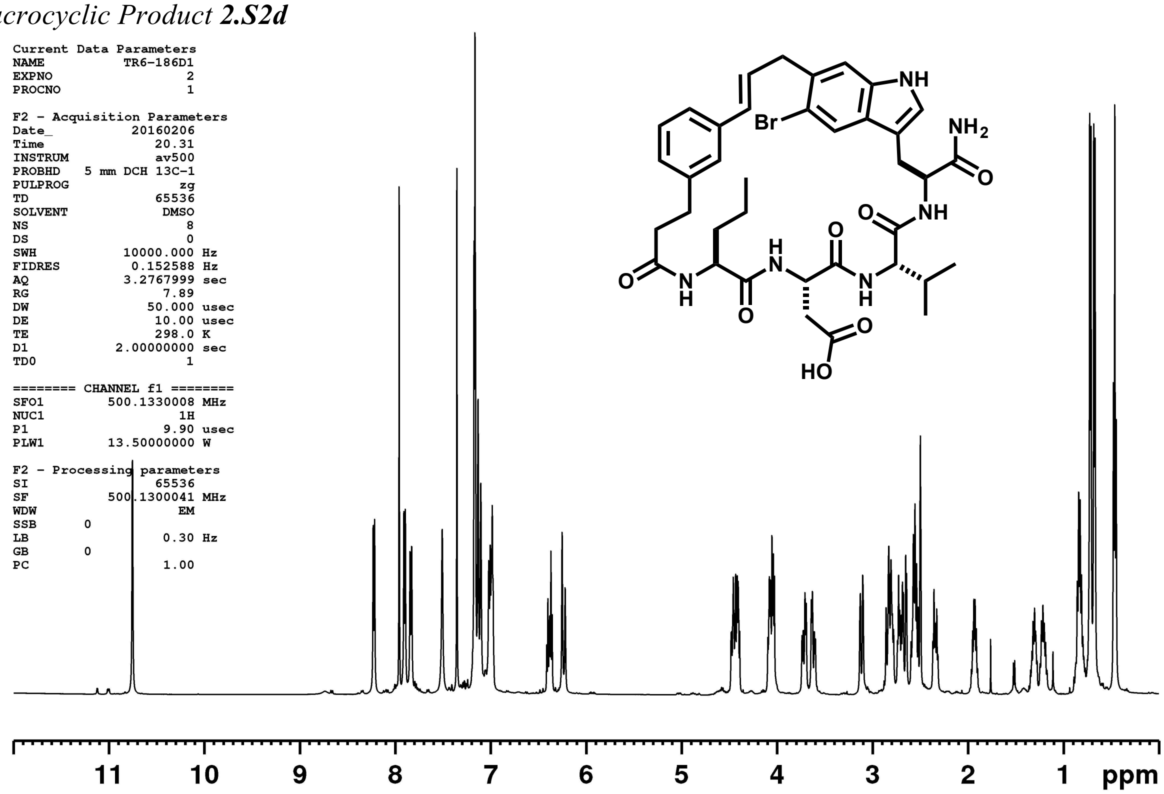
======== CHANNEL f1 ========
NUC1 1H
P1 10.57 usec
P2 21.14 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1339008 MHz

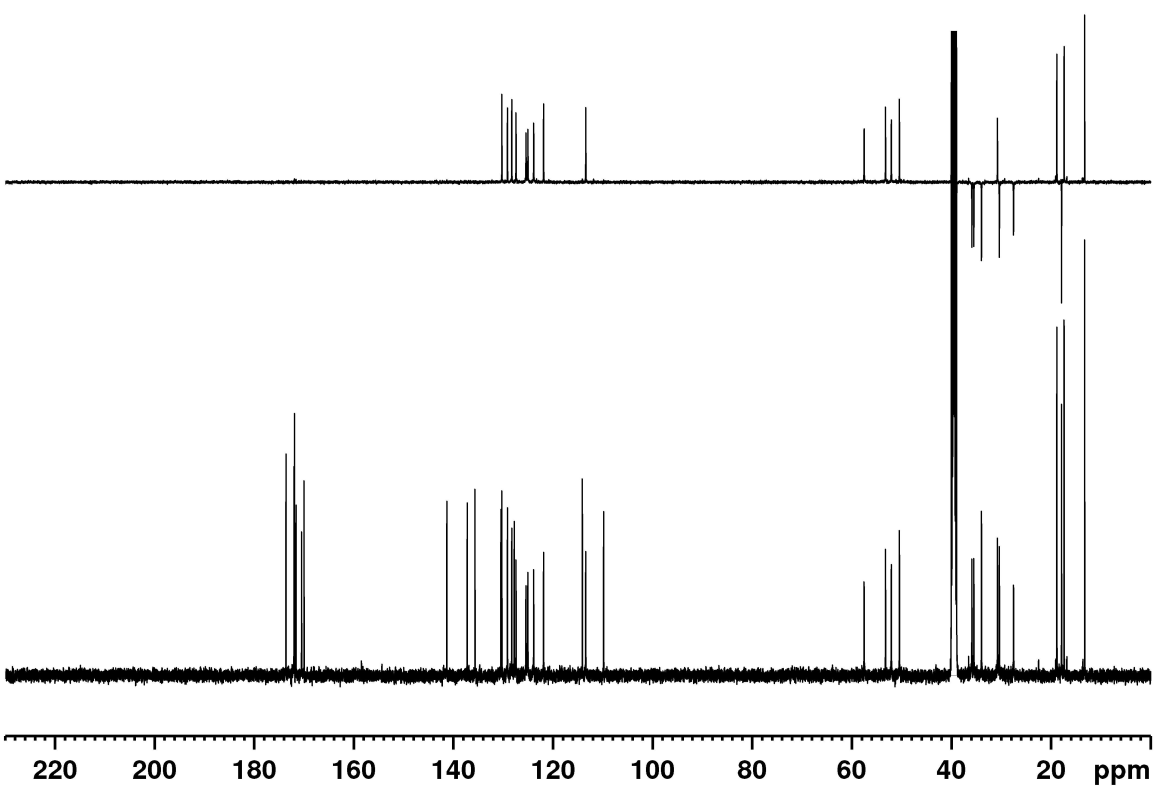
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 19.50 usec
P4 39.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.46 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 13.52450085 W
SFO2 150.9133722 MHz

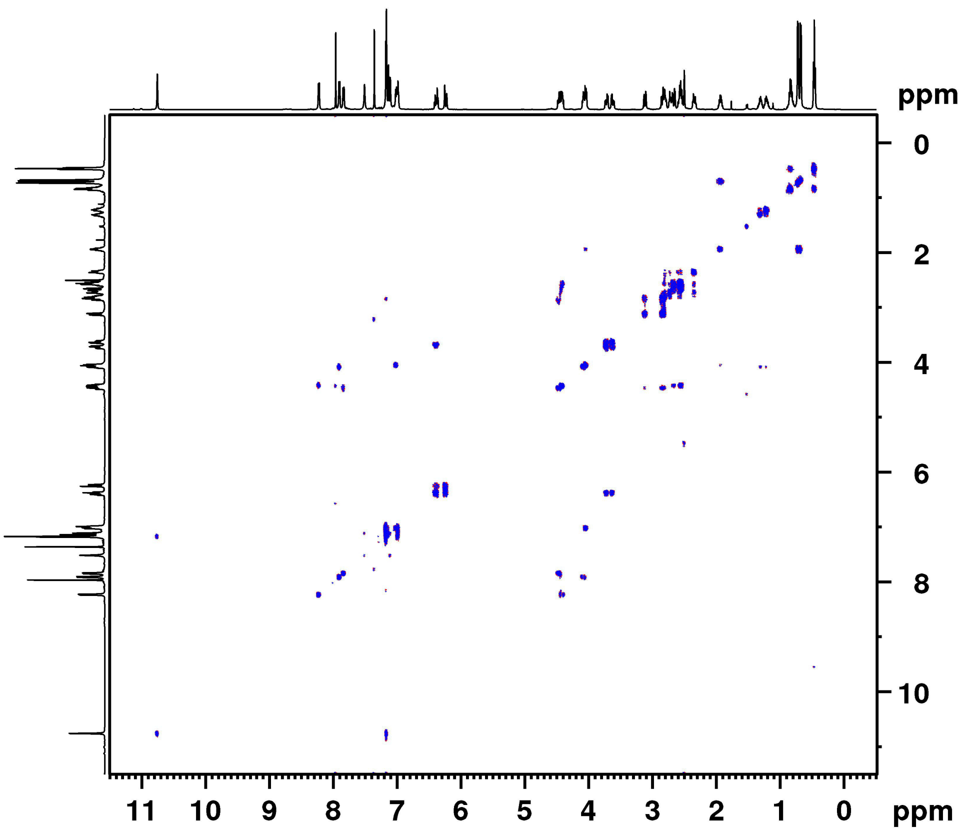



```
Current Data Parameters
NAME          TR6-186C1
EXPNO                 9
PROCNO                1

F2 - Acquisition Parameters
Date_          20160206
Time              21.18
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG    hmbcgplpndqf
TD                 2048
SOLVENT            DMSO
NS                   18
DS                   16
SWH            7788.162 Hz
FIDRES         3.802814 Hz
AQ            0.1314816 sec
RG                26008
DW               64.200 usec
DE                 6.00 usec
TE                297.5 K
CNST2       145.0000000
CNST13        7.0000000
D0           0.00000300 sec
D1           1.50000000 sec
D2           0.00344828 sec
D6           0.07142857 sec
D16          0.00020000 sec
IN0          0.00001745 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                10.57 usec
P2                21.14 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1      600.1339008 MHz

======== CHANNEL f2 ========
NUC2                13C
P3                19.50 usec
PL2               -3.00 dB
PL2W       150.35617065 W
SFO2      150.9156357 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPNAM[3]       SINE.100
GPX1      0 %
GPX2      0 %
GPX3      0 %
GPY1      0 %
GPY2      0 %
```

*Macrocyclic Product **2.S2d***







Current Data Parameters
NAME TR6-186D1
EXPNO 5
PROCNO 1

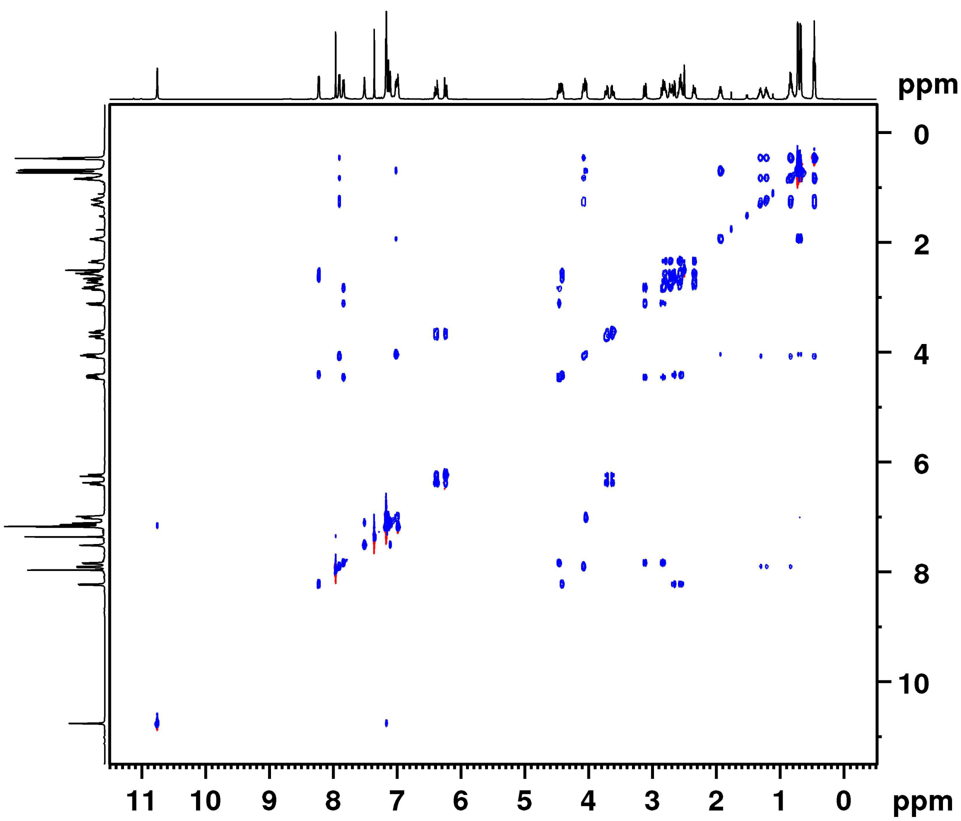
F2 - Acquisition Parameters
Date_ 20160206
Time 20.37
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 7.89
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
D0 0.00007059 sec
D1 1.20000005 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00016640 sec

======== CHANNEL f1 ========
SFO1 500.1327507 MHz
NUC1 1H
P1 9.90 usec
P2 19.80 usec
PLW1 13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 500.1328 MHz
FIDRES 11.737530 Hz
SW 12.016 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI 4096
SF 500.1300028 MHz
WDW QSINE
SSB 1



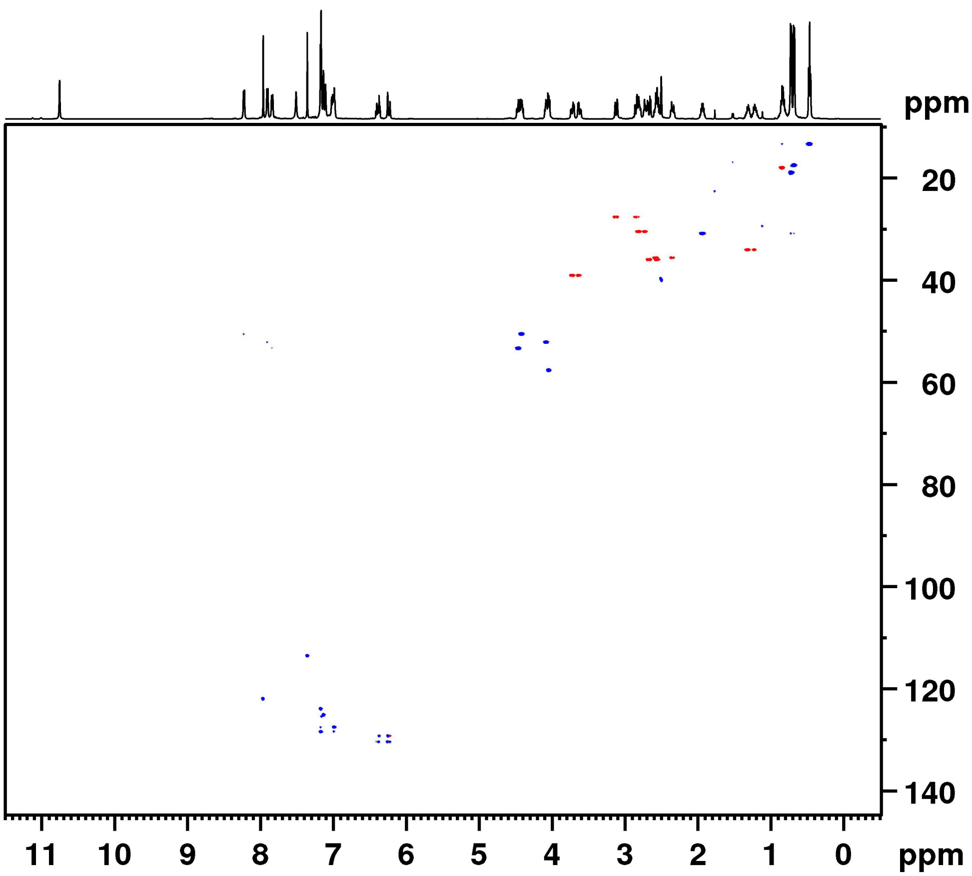
Current Data Parameters
NAME TR6-186D1
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160206
Time 21.01
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 59.34
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.50000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00016640 sec
L1 24

======== CHANNEL f1 ========
SFO1 500.1327507 MHz
NUC1 1H
P1 9.90 usec
P2 19.80 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.92682981 W

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 256
SFO1 500.1328 MHz
FIDRES 23.475060 Hz

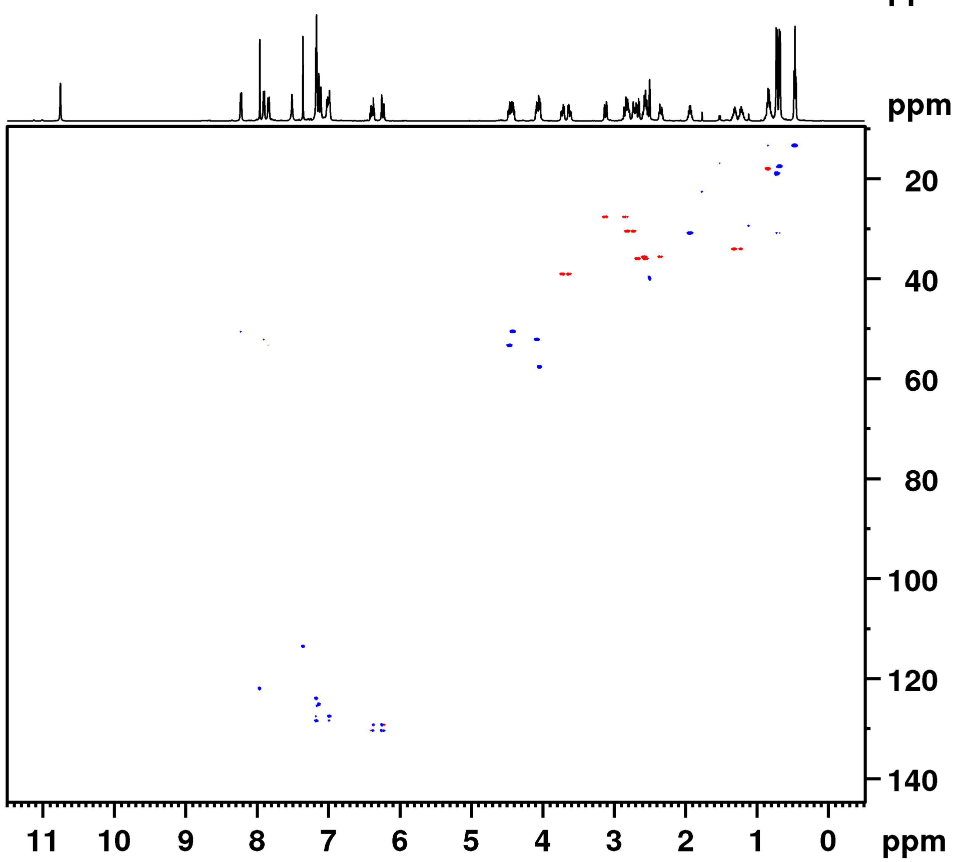


Current Data Parameters
NAME TR6-186D1
EXPNO 7
PROCNO 1

F2 - Acquisition Parameters
Date_ 20160206
Time 21.17
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcetgpsisp.2
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 204.54
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
CNST17 -0.5000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00345000 sec
IN0 0.00002940 sec

======== CHANNEL f1 ========
SFO1 500.1327507 MHz
NUC1 1H
P1 9.90 usec
P2 19.80 usec
P28 1000.00 usec
PLW1 13.50000000 W

======== CHANNEL f2 ========
SFO2 125.7675352 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P14 500.00 usec
P24 2000.00 usec
PCPD2 70.00 usec
PLW0 0 W
PLW2 23.01399994 W
PLW12 0.43557000 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
SPW3 3.26090002 W



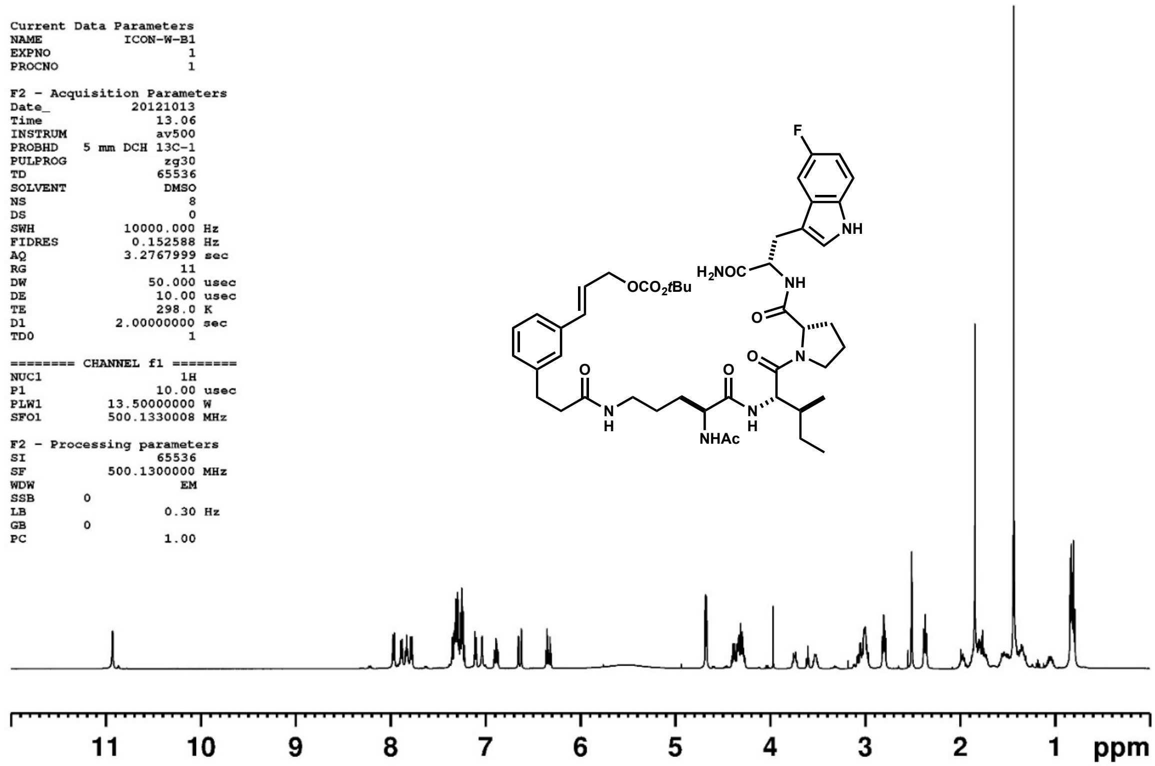
Current Data Parameters
NAME TR6-186D1
EXPNO 7
PROCNO 1

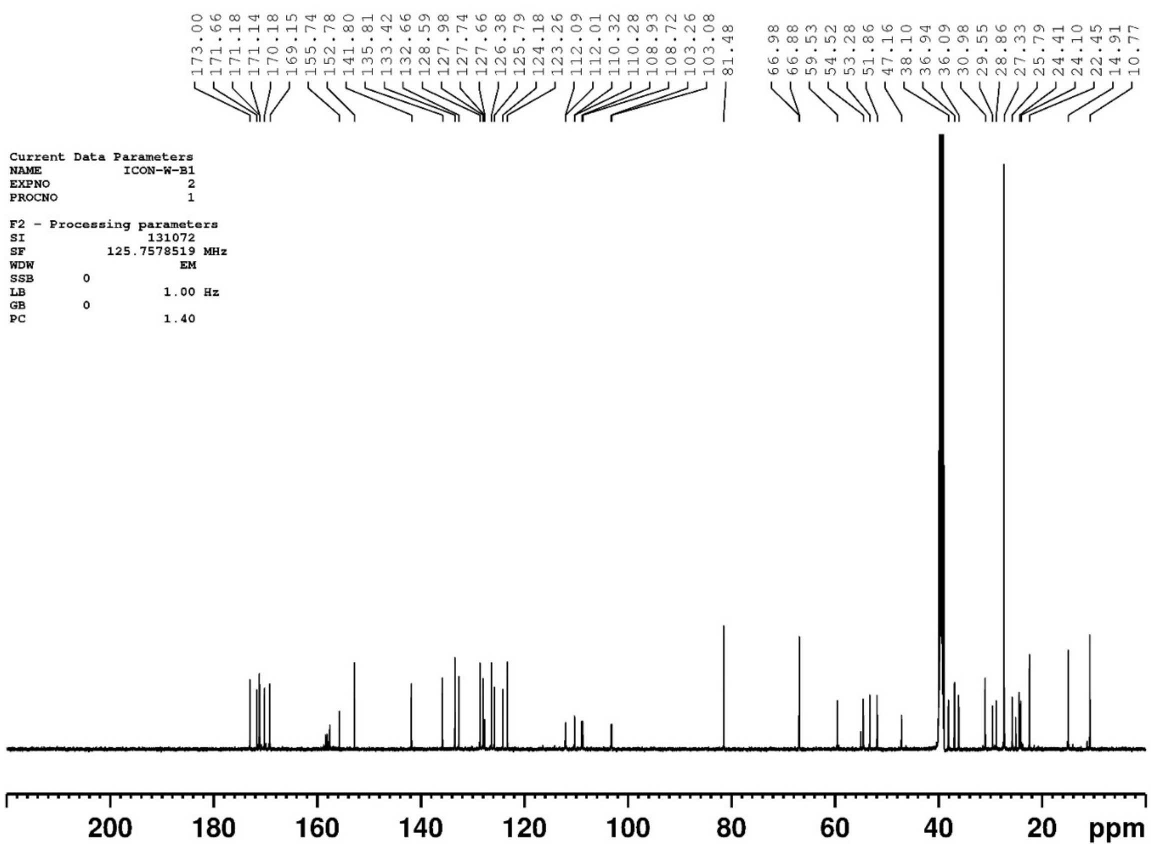
F2 - Acquisition Parameters
Date_ 20160206
Time 21.17
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcetgpsisp.2
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 204.54
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
CNST17 -0.5000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00345000 sec
IN0 0.00002940 sec

======== CHANNEL f1 ========
SFO1 500.1327507 MHz
NUC1 1H
P1 9.90 usec
P2 19.80 usec
P28 1000.00 usec
PLW1 13.50000000 W

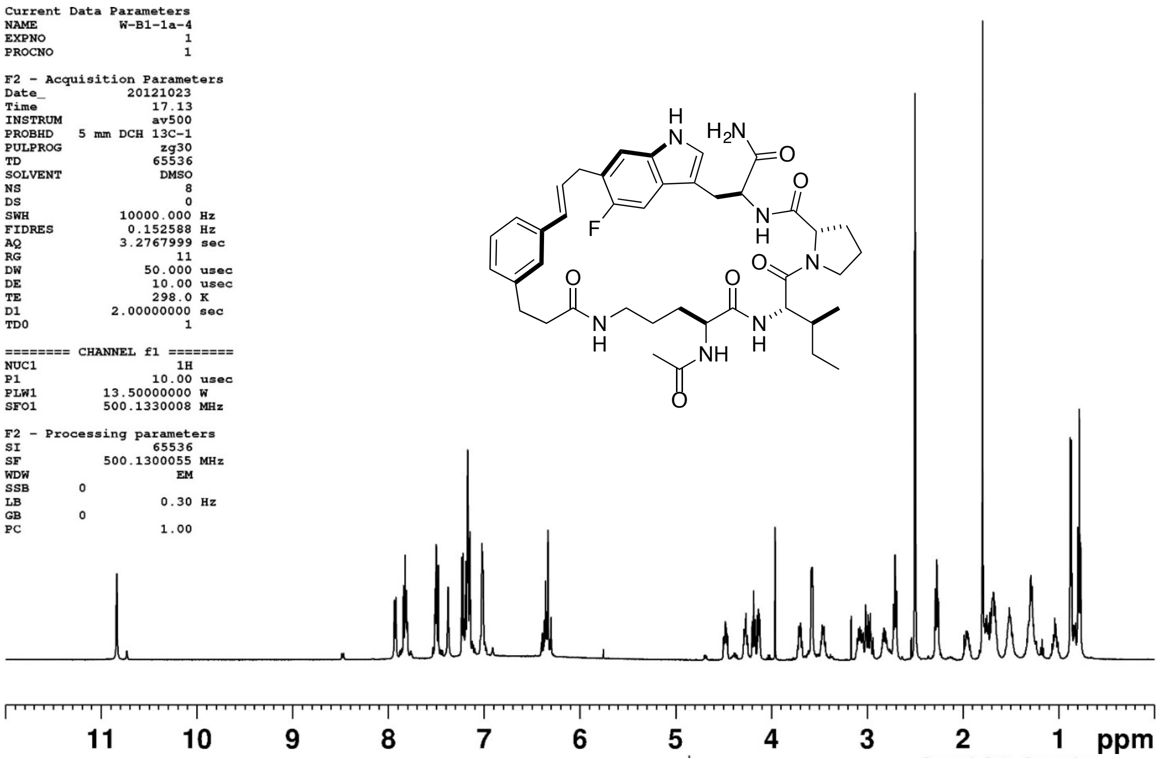
======== CHANNEL f2 ========
SFO2 125.7675352 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P14 500.00 usec
P24 2000.00 usec
PCPD2 70.00 usec
PLW0 0 W
PLW2 23.01399994 W
PLW12 0.43557000 W
SPNAM[3] Crp60,0.5,20.1
SPOAL3 0.500
SPOFFS3 0 Hz
SPW3 3.26090002 W

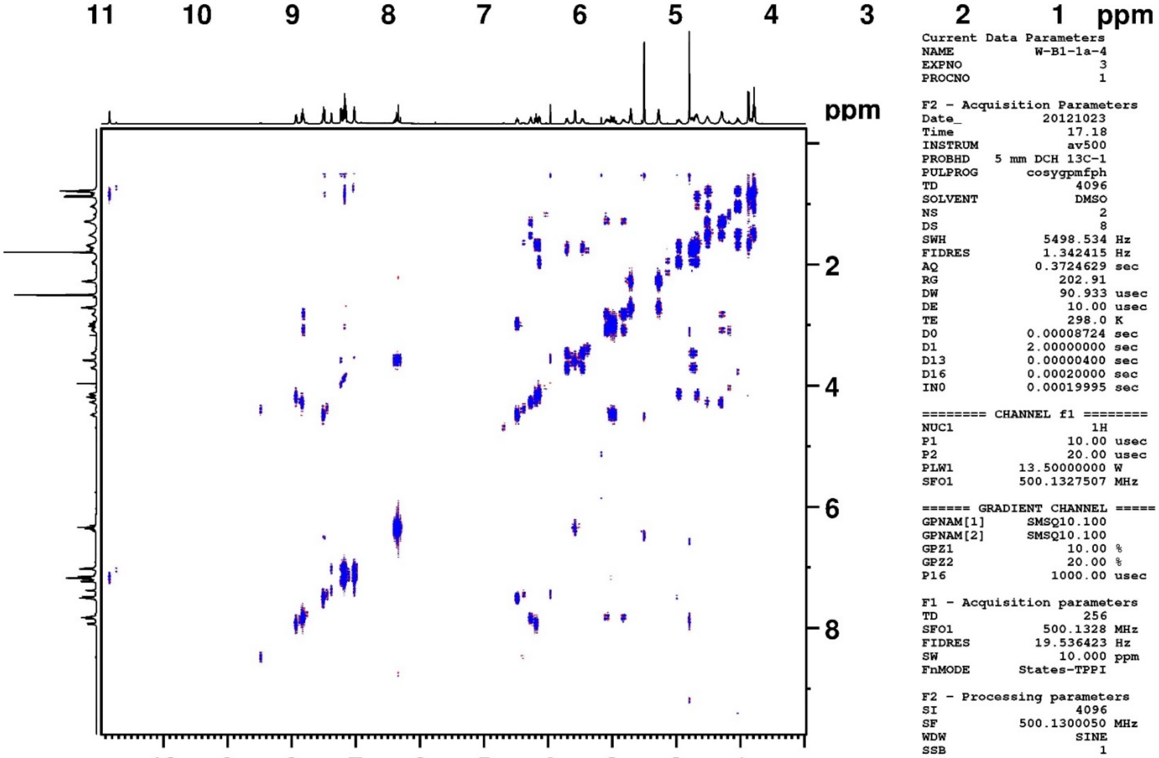
Acyclic Precursor ***2.S1***

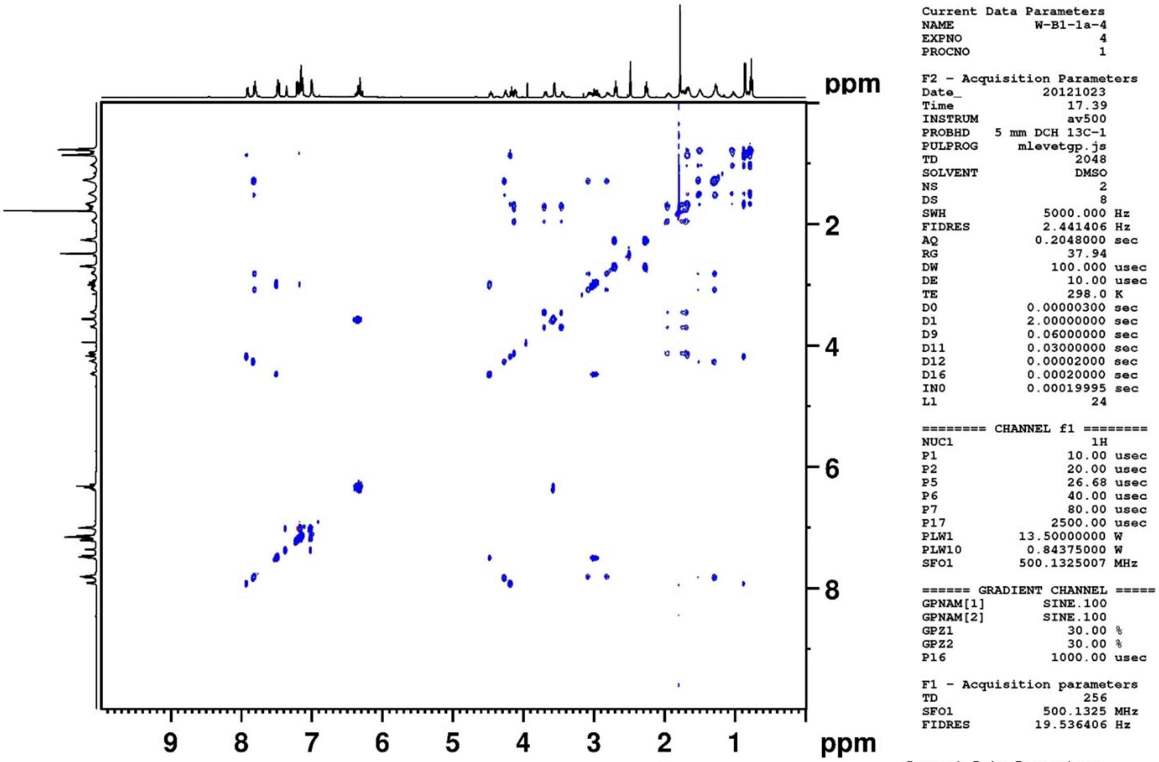


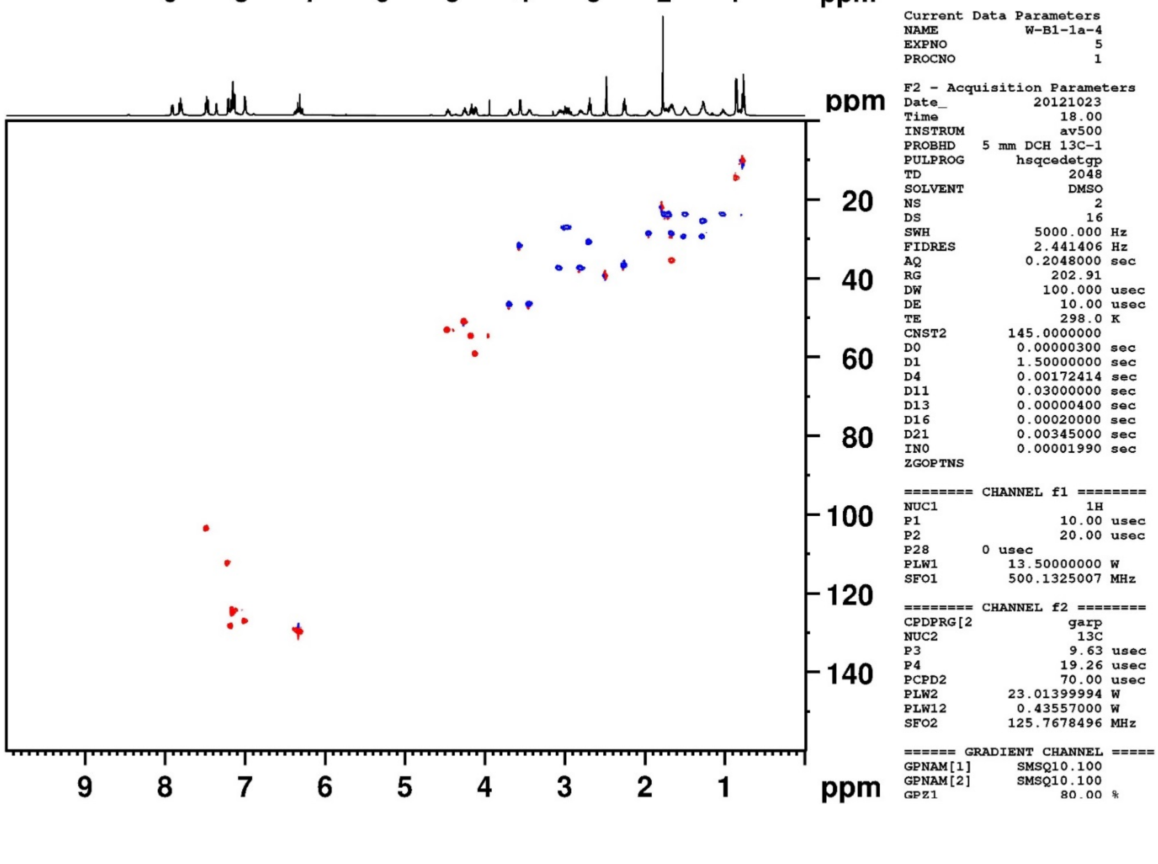


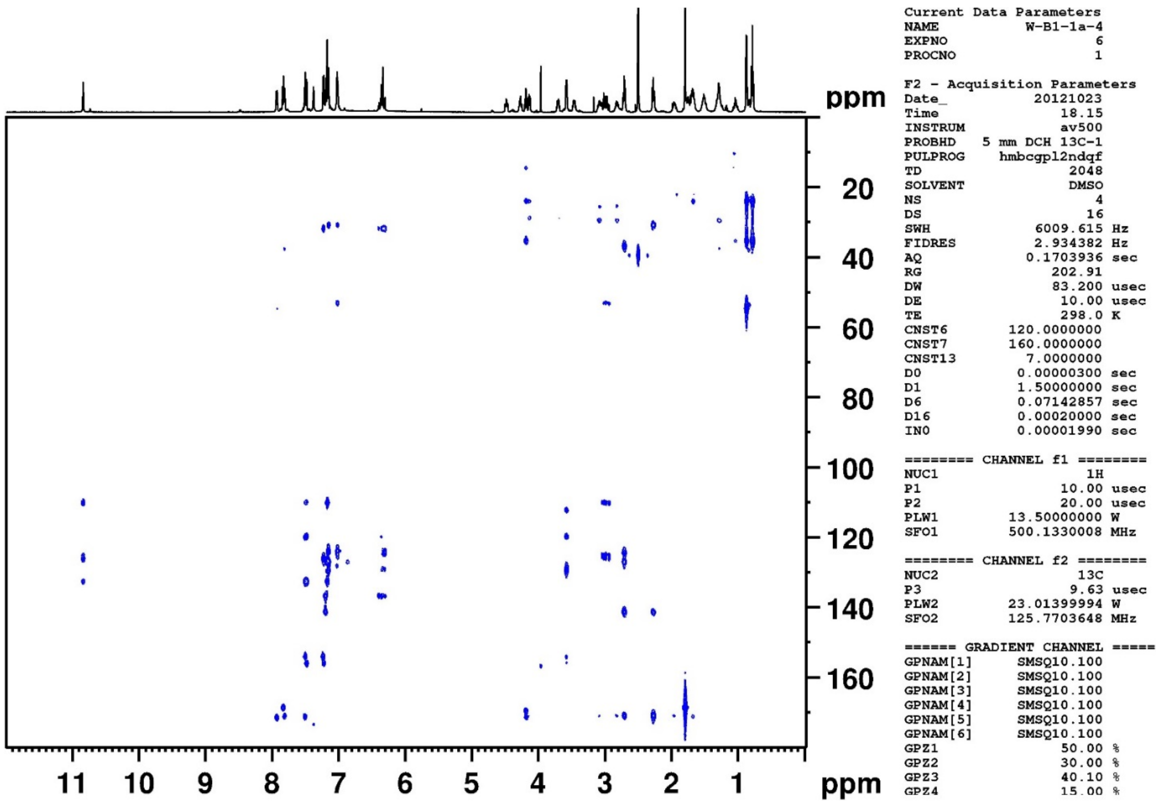
*Macrocyclic Product **2.S2a***



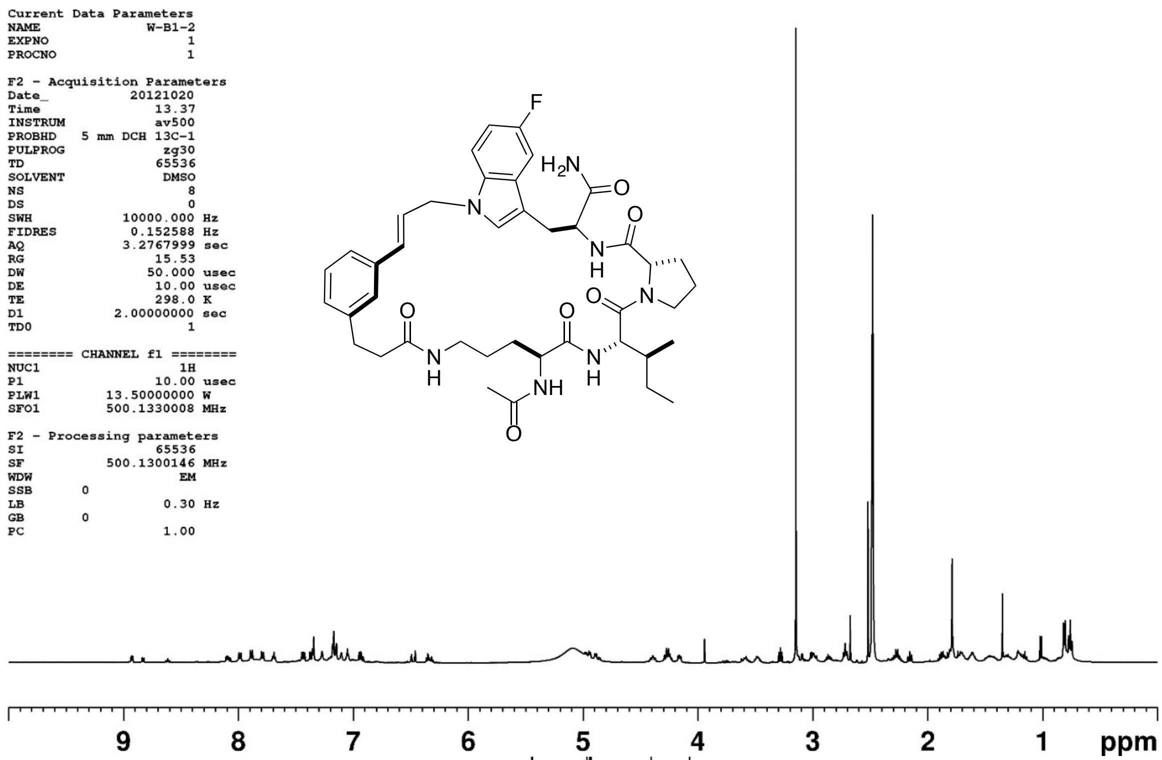


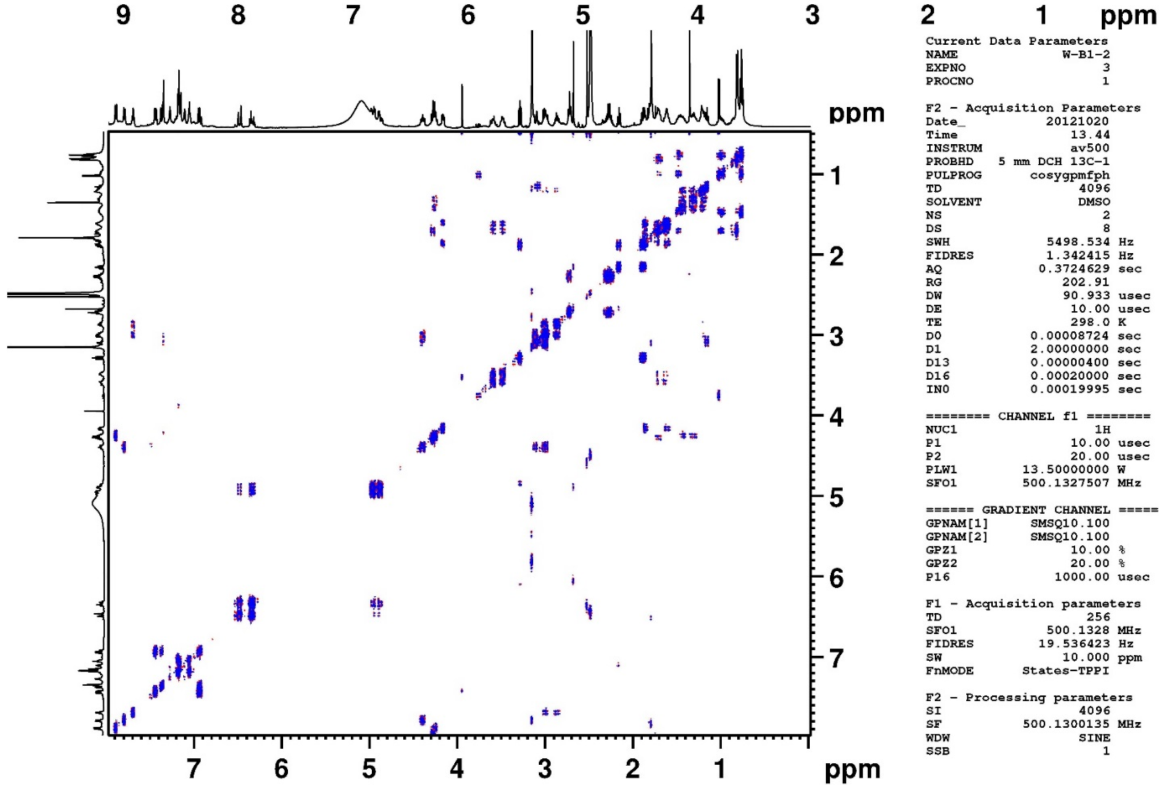

Current Data Parameters
NAME W-B1-1a-4
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121023
Time 17.39
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00019995 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1325007 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.536406 Hz
ppm
ppm

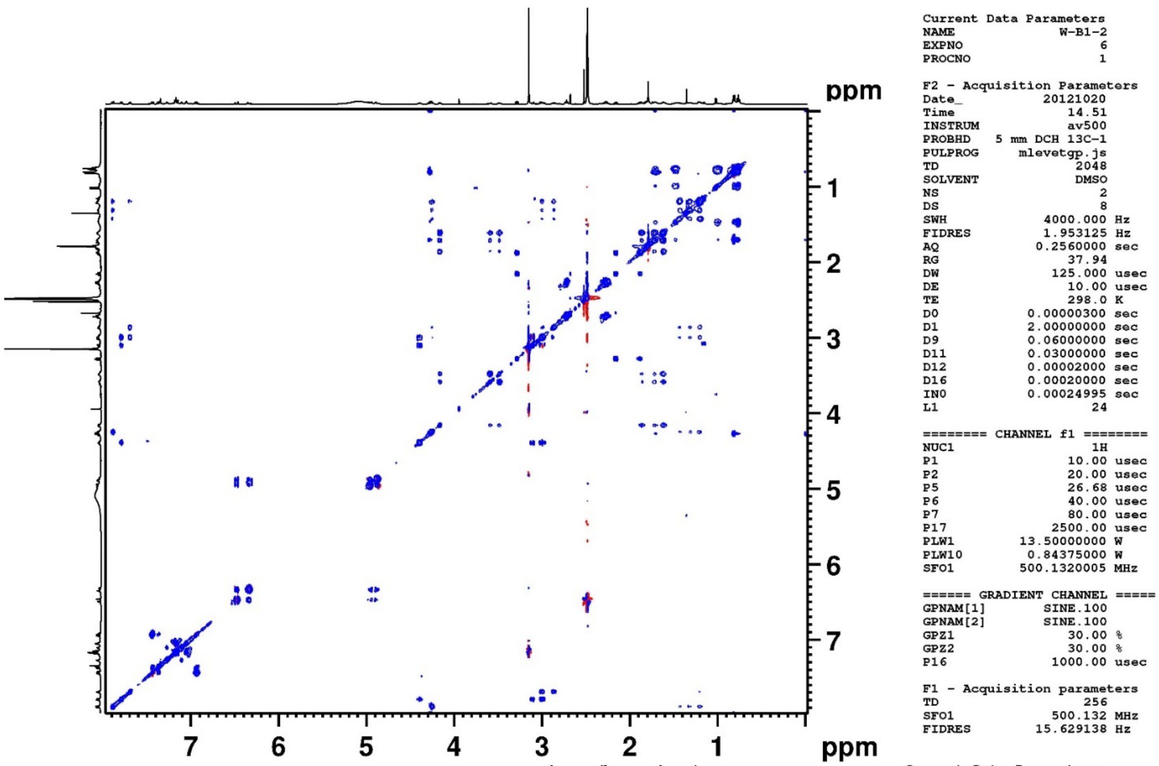

Current Data Parameters
NAME W-B1-1a-4
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121023
Time 18.00
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W
SFO1 500.1325007 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
SFO2 125.7678496 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %
ppm
ppm

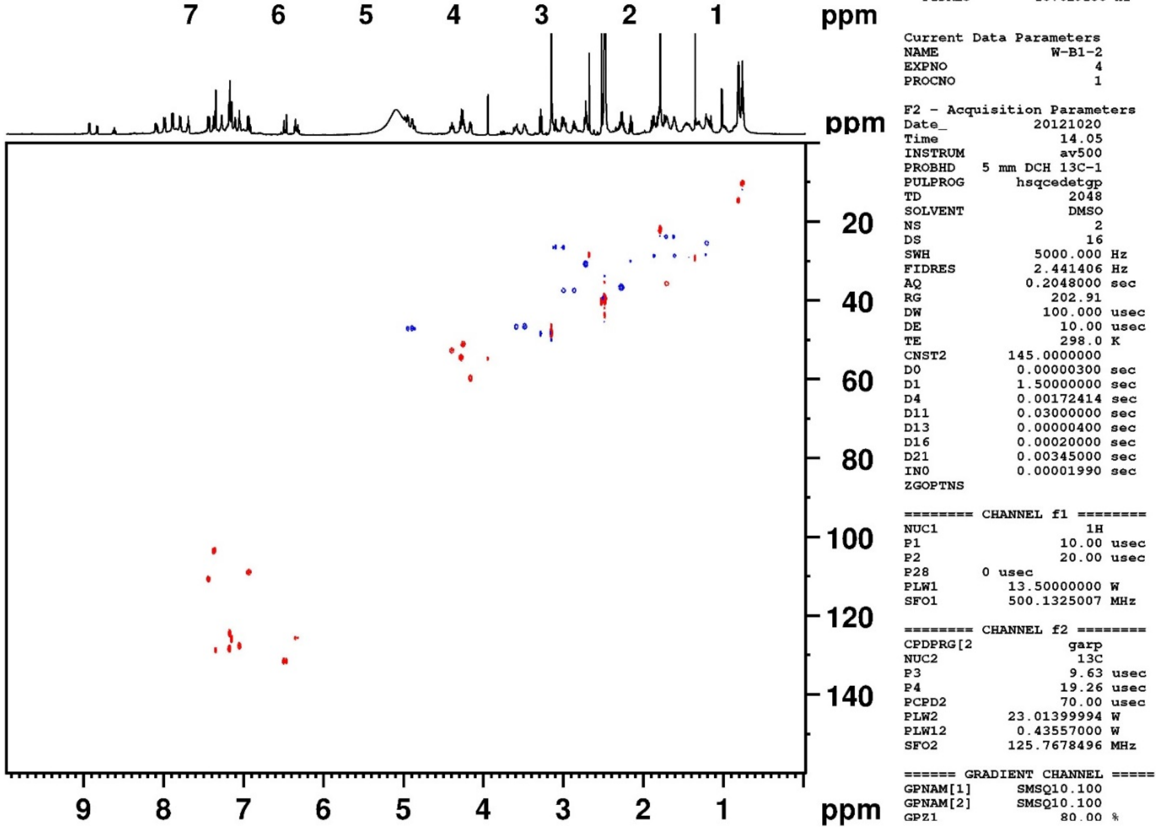

ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-B1-1a-4
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121023
Time 18.15
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

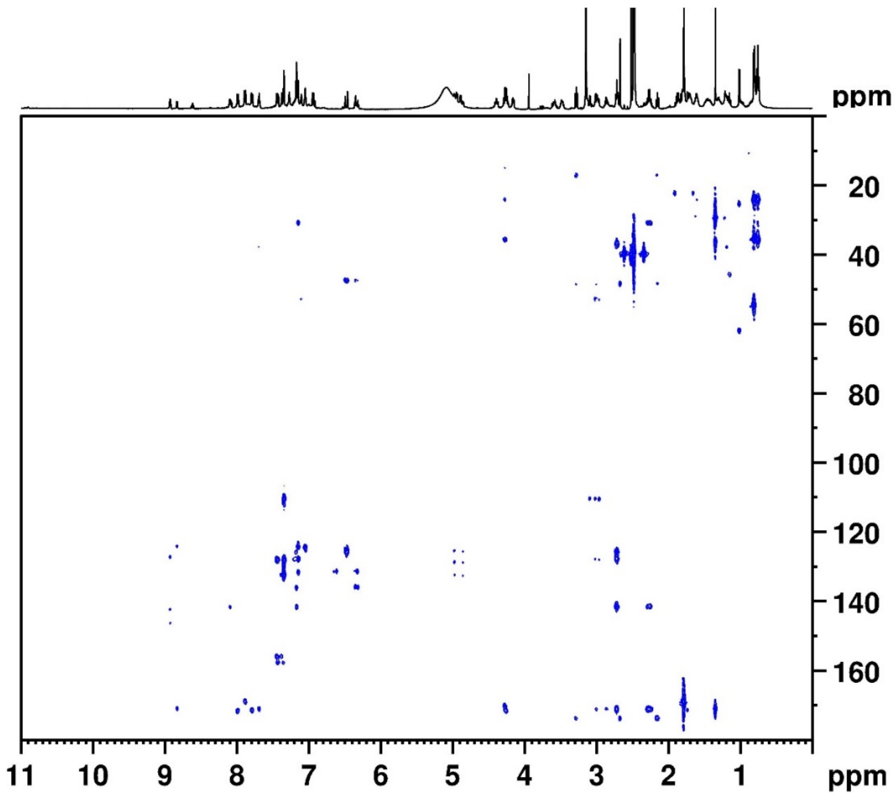
*Macrocyclic Product **2.S2b***






ppm
1
2
3
4
5
6
7
7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-B1-2
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121020
Time 14.51
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 4000.000 Hz
FIDRES 1.953125 Hz
AQ 0.2560000 sec
RG 37.94
DW 125.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00024995 sec
L1 24
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
SFO1 500.1320005 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.132 MHz
FIDRES 15.629138 Hz


ppm
20
40
60
80
100
120
140
9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME W-B1-2
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121020
Time 14.05
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
P28 0 usec
PLW1 13.50000000 W
SFO1 500.1325007 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
SFO2 125.7678496 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %



Current Data Parameters
NAME W-B1-2
EXPNO 5
PROCNO 1

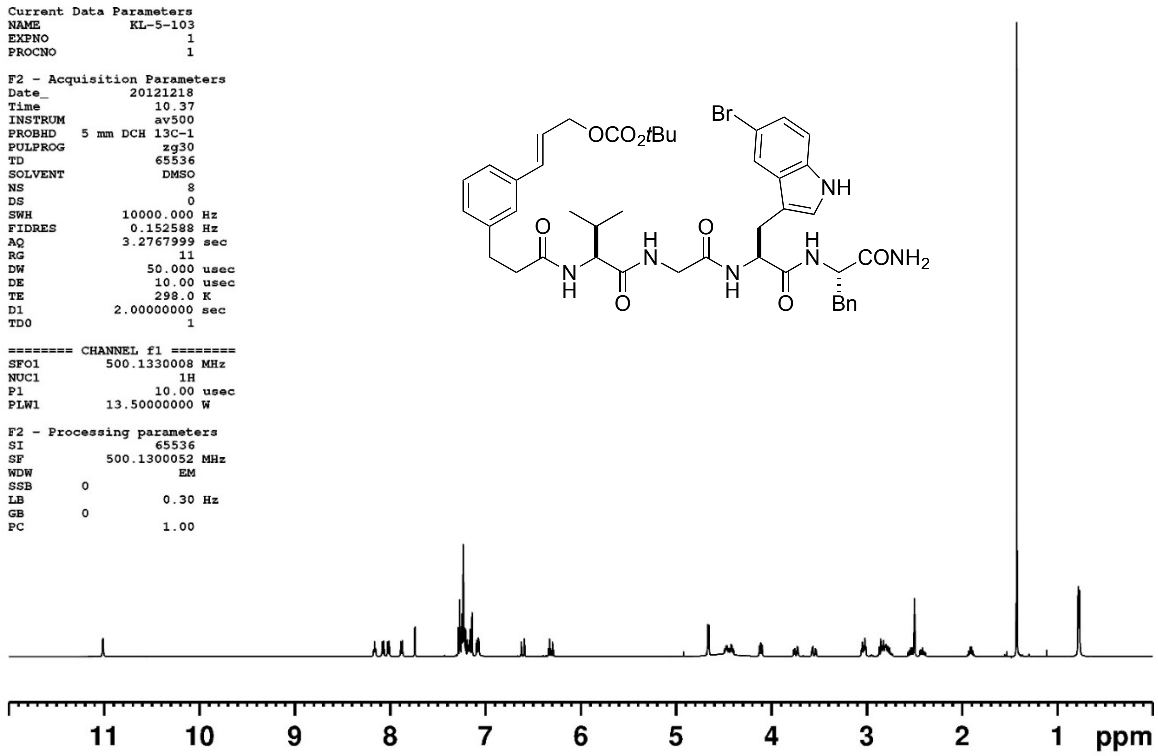
F2 - Acquisition Parameters
Date_ 20121020
Time 14.20
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 4
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec

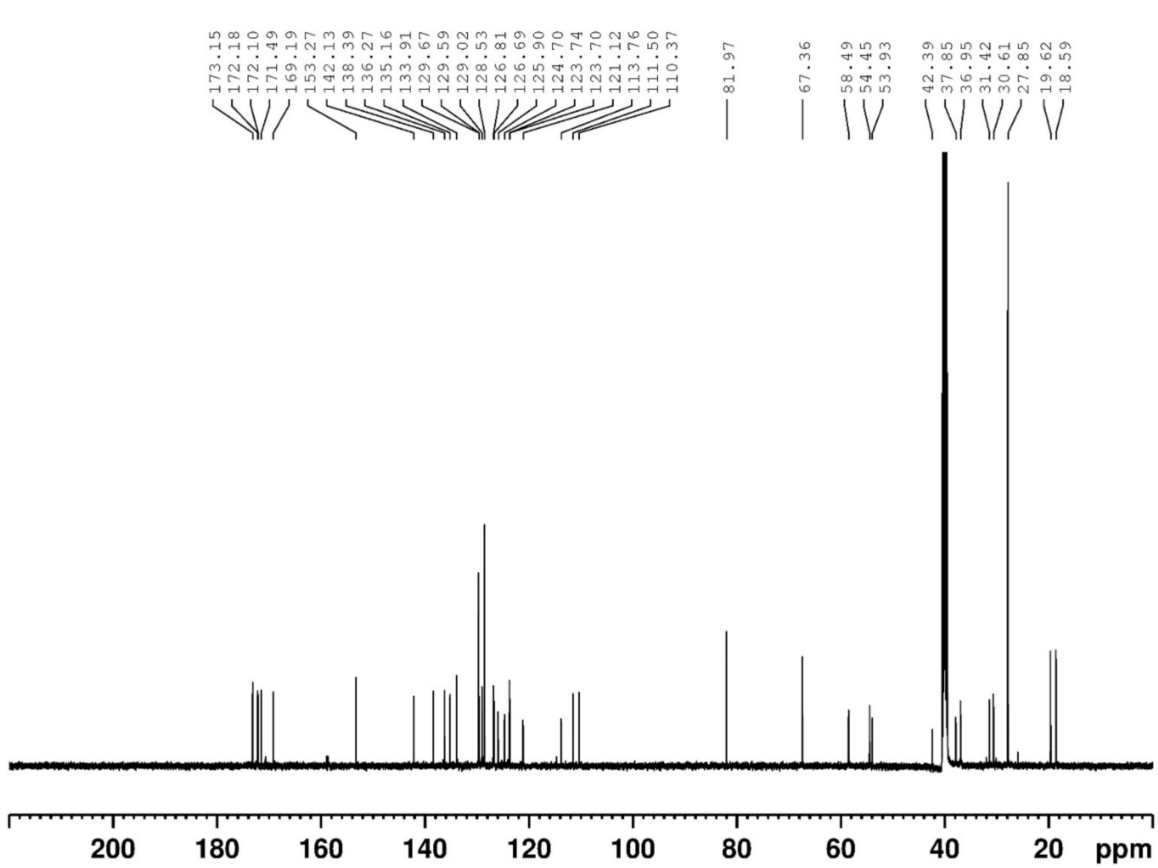
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
SFO1 500.1330008 MHz

======== CHANNEL f2 ========
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
SFO2 125.7703648 MHz

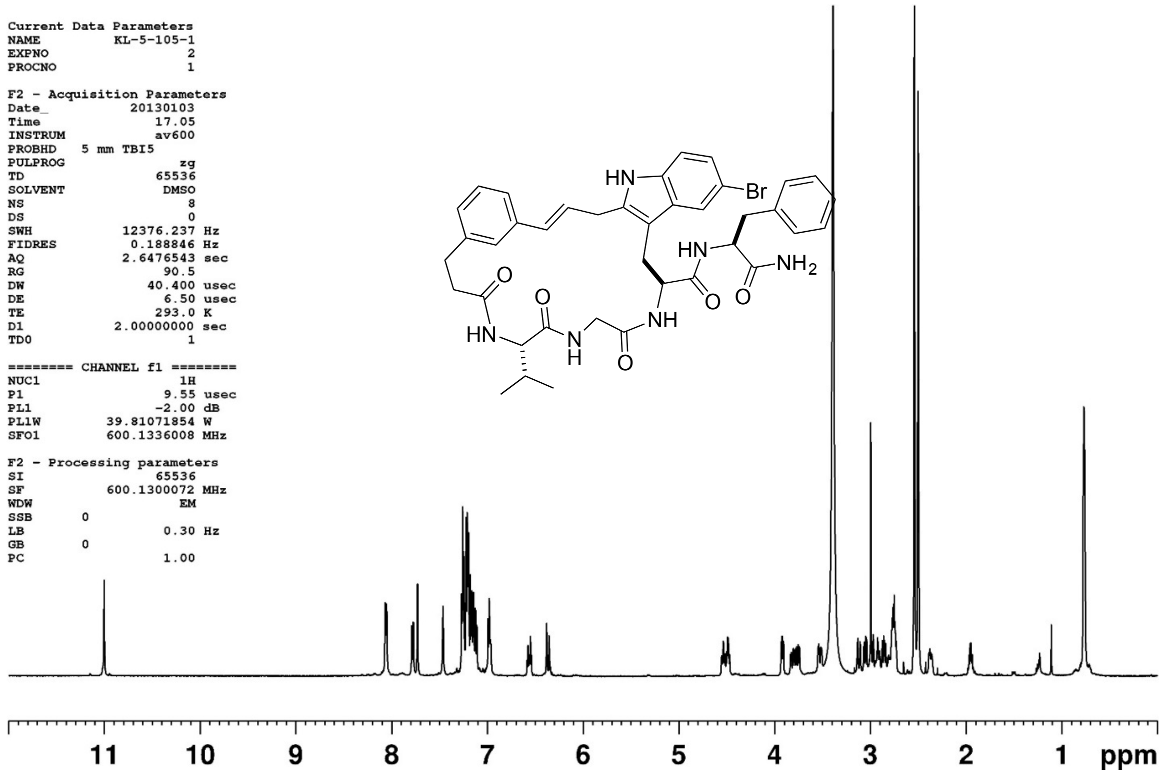
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

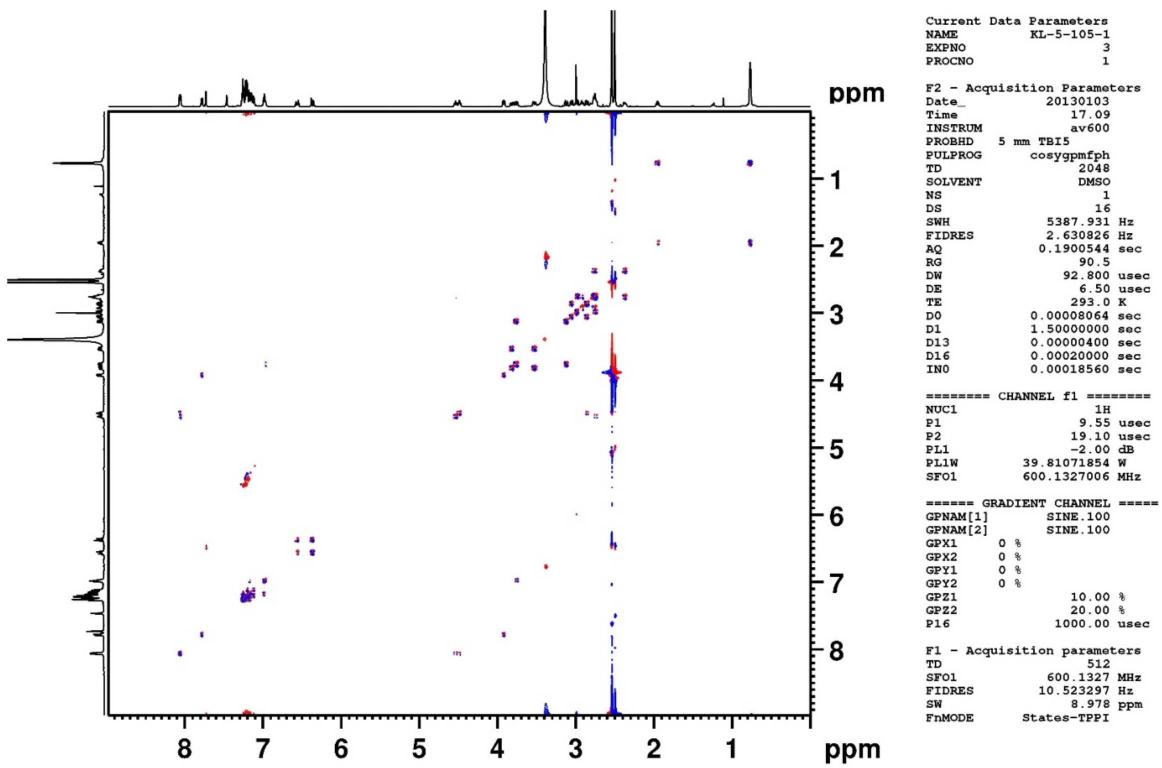
Acyclic Precursor ***2.S3***

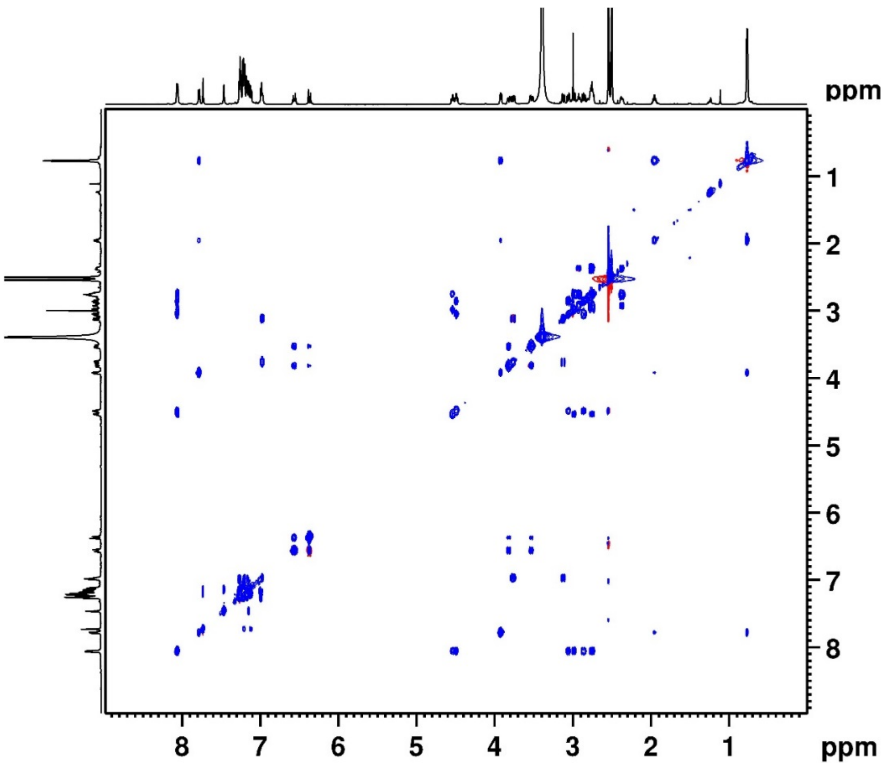




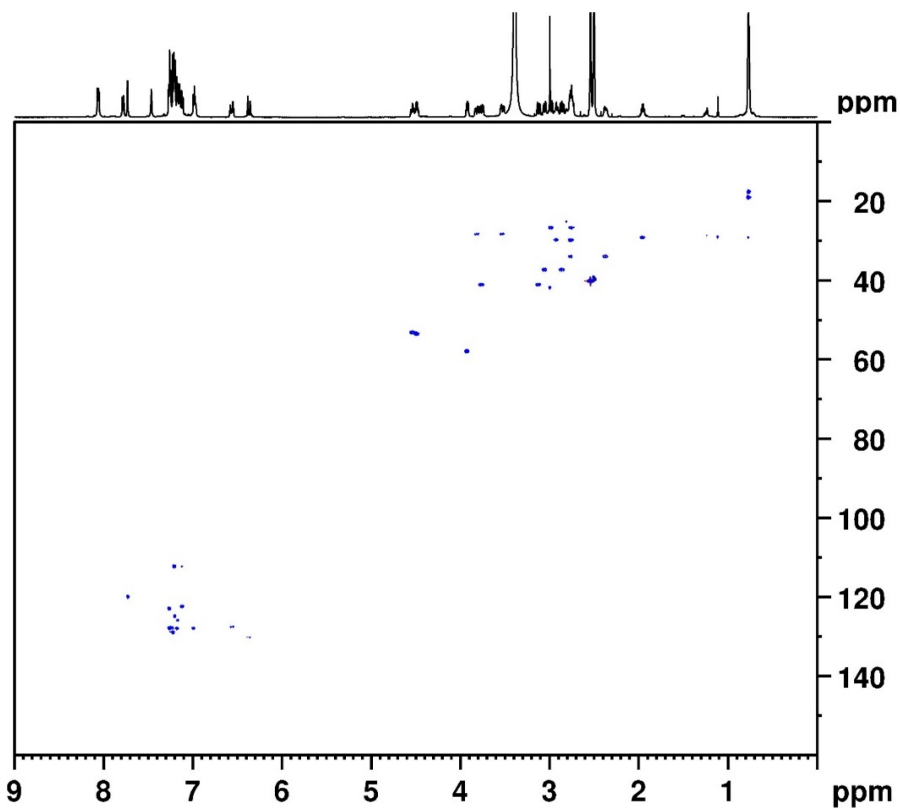
Macrocyclic Product ***2.S4a***



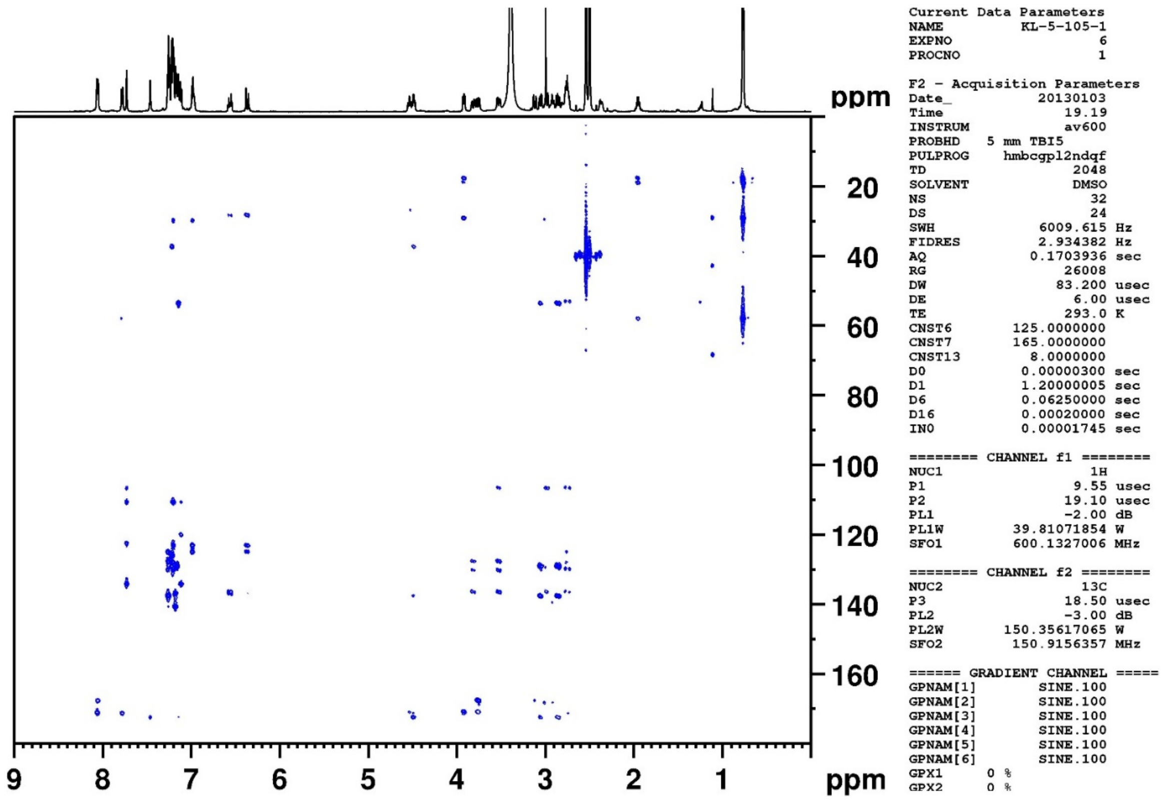




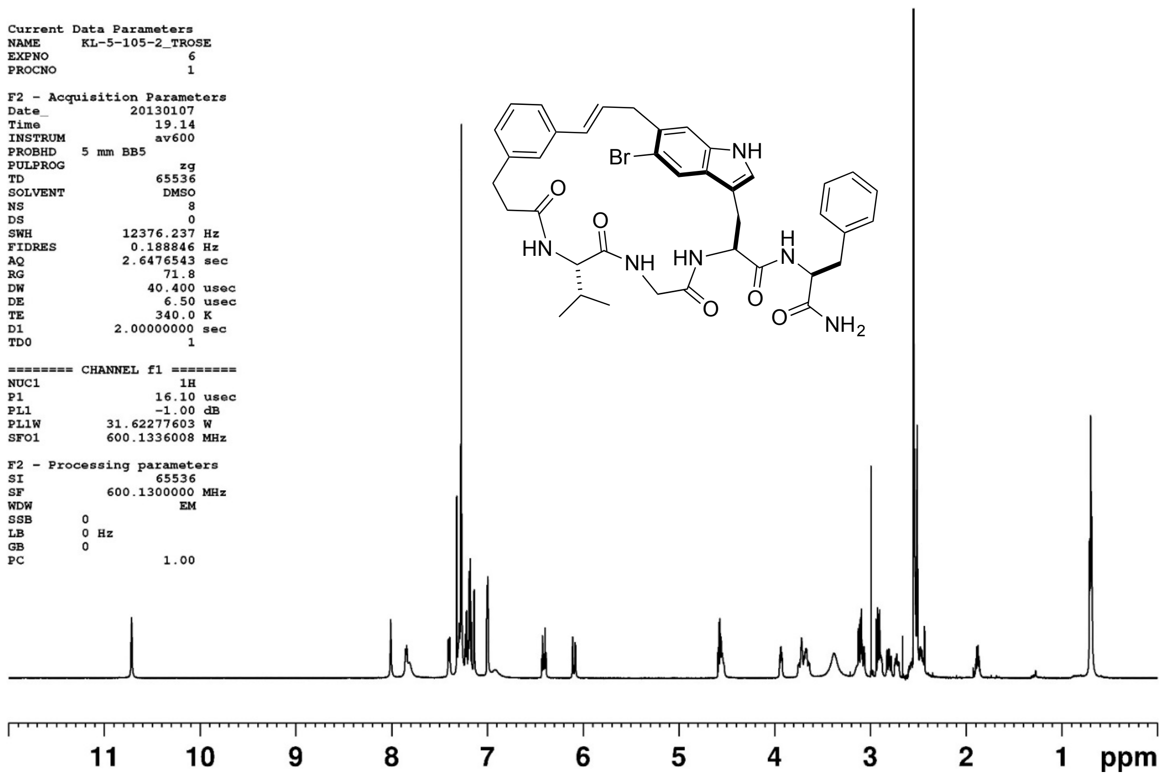

```
Current Data Parameters
NAME          KL-5-105-1
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130103
Time               17.25
INSTRUM            av600
PROBHD   5 mm TBI5
PULPROG    dipsi2etgpsi
TD                  2048
SOLVENT             DMSO
NS                     8
DS                    16
SWH             5387.931 Hz
FIDRES          2.630826 Hz
AQ             0.1900544 sec
RG                   362
DW                92.800 usec
DE                  6.50 usec
TE                 293.0 K
D0            0.00000300 sec
D1            1.50000000 sec
D9            0.06000000 sec
D11           0.03000000 sec
D16           0.00020000 sec
D20           0.00001000 sec
D21           0.00001000 sec
IN0           0.00018560 sec
L1                    14

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.55 usec
P2                 19.10 usec
P6                 40.00 usec
PL1                -2.00 dB
PL10               10.44 dB
PL1W         39.81071854 W
PL10W         2.26986504 W
SFO1         600.1327006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1       0 %
GPX2       0 %
GPY1       0 %
GPY2       0 %
GPZ1               30.00 %
GPZ2               30.00 %
P16              1000.00 usec
```

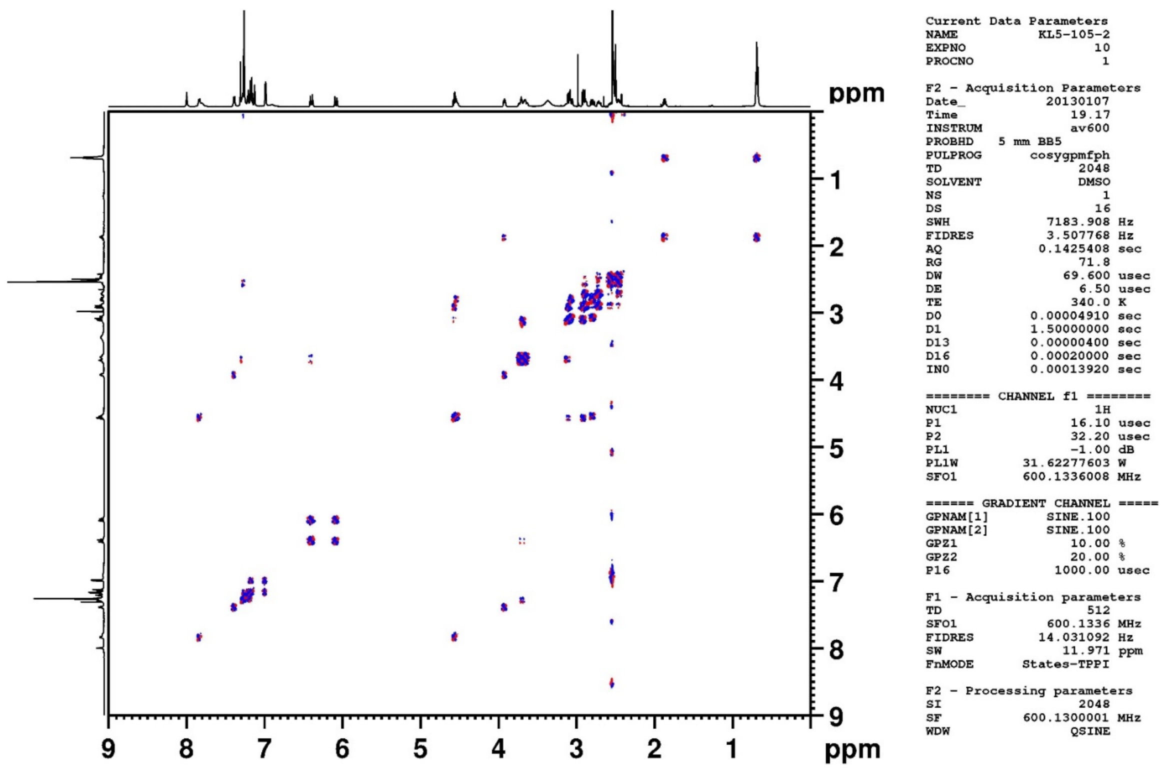


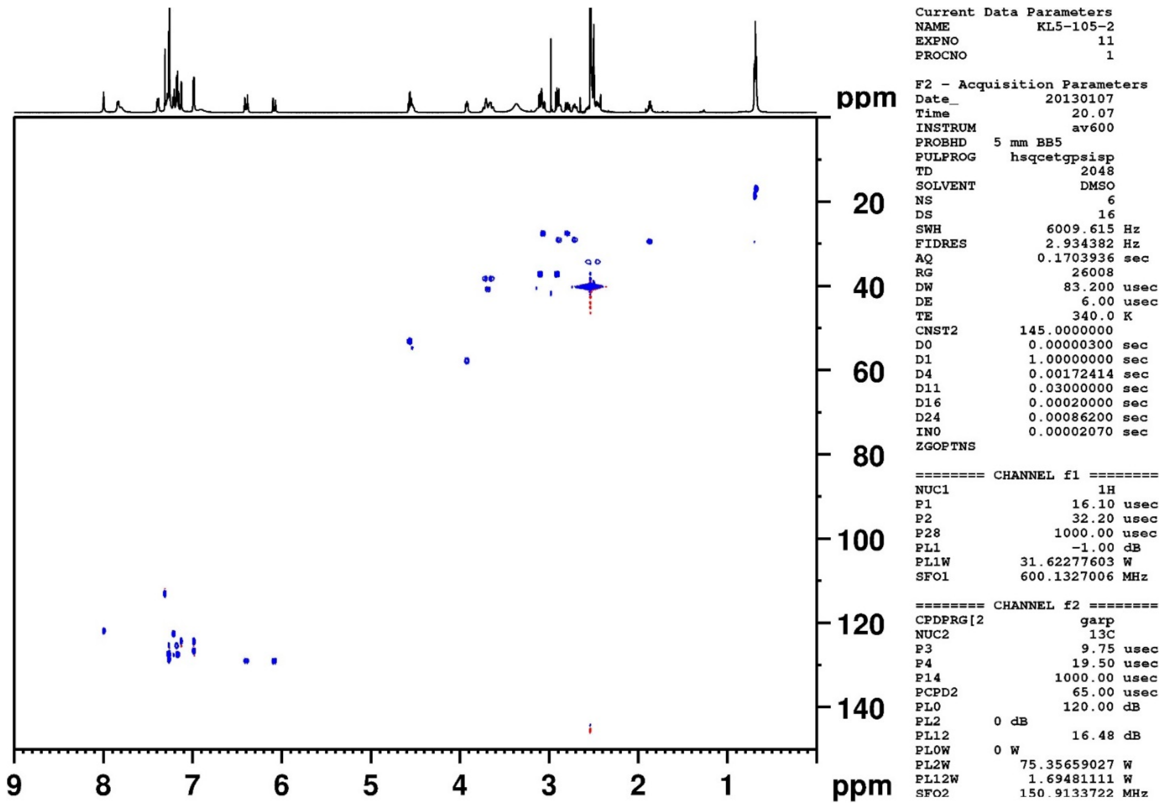

```
Current Data Parameters
NAME          KL-5-105-1
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130103
Time               17.56
INSTRUM            av600
PROBHD   5 mm TBI5
PULPROG     hsqcetgpsisp
TD                  2048
SOLVENT             DMSO
NS                     8
DS                    16
SWH             6009.615 Hz
FIDRES          2.934382 Hz
AQ             0.1703936 sec
RG                 26008
DW                83.200 usec
DE                  6.00 usec
TE                 293.0 K
CNST2        145.0000000
D0            0.00000300 sec
D1            1.00000000 sec
D4            0.00172414 sec
D11           0.03000000 sec
D16           0.00020000 sec
D24           0.00086200 sec
IN0           0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.55 usec
P2                 19.10 usec
P28              1000.00 usec
PL1                -2.00 dB
PL1W         39.81071854 W
SFO1         600.1327006 MHz

======== CHANNEL f2 ========
CPDPRG[2            garp
NUC2                 13C
P3                 18.50 usec
P4                 37.00 usec
P14              1000.00 usec
PCPD2              65.00 usec
PL0               120.00 dB
PL2                -3.00 dB
PL12                7.91 dB
PL0W       0 W
PL2W        150.35617065 W
PL12W        12.19330025 W
SFO2         150.9133722 MHz
```

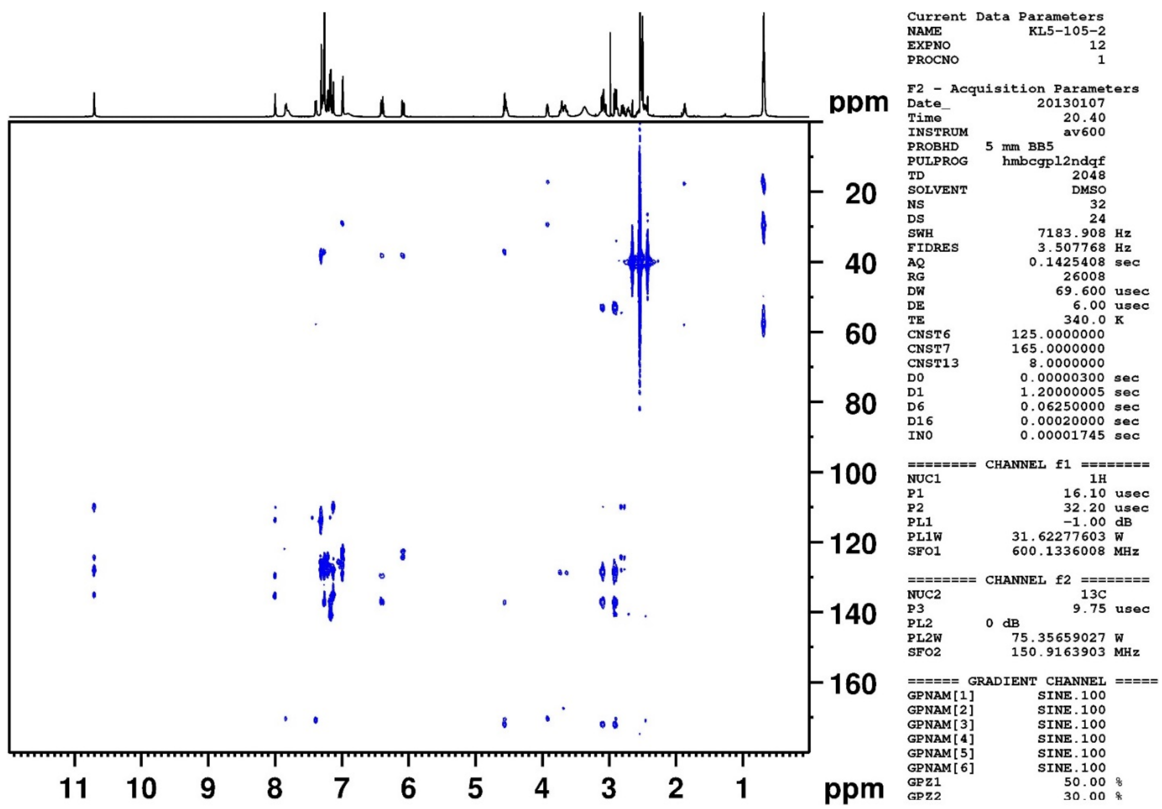

ppm
20
40
60
80
100
120
140
160
9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME KL-5-105-1
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130103
Time 19.19
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 24
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 293.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.55 usec
P2 19.10 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPX1 0 %
GPX2 0 %

*Macrocyclic Product **2.S4b***

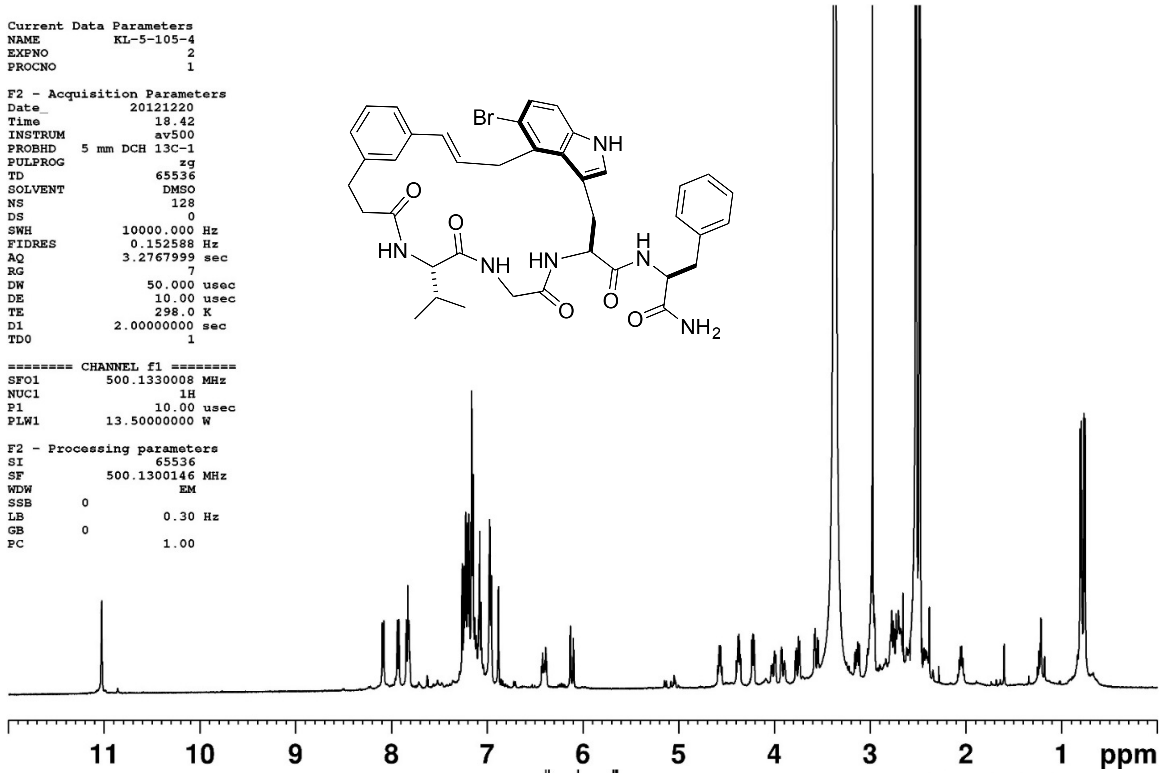


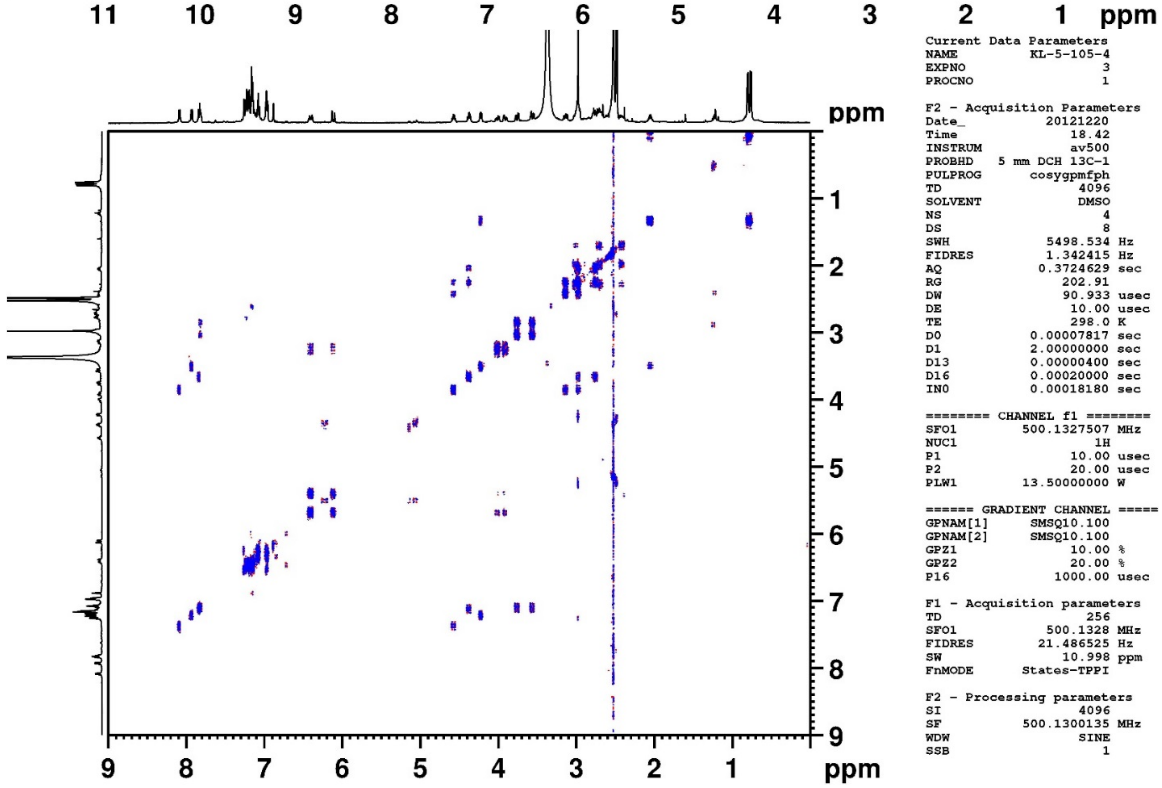


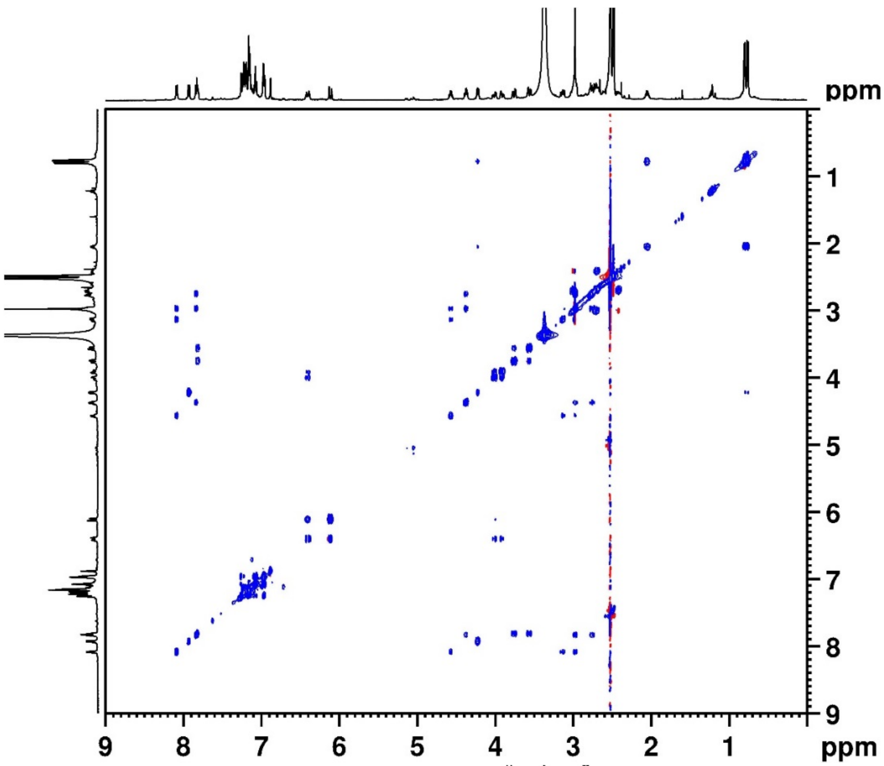

Current Data Parameters
NAME KL5-105-2
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130107
Time 20.07
INSTRUM av600
PROBHD 5 mm BB5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 6
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 26008
DW 83.200 usec
DE 6.00 usec
TE 340.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.00000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 16.10 usec
P2 32.20 usec
P28 1000.00 usec
PL1 -1.00 dB
PL1W 31.62277603 W
SFO1 600.1327006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 9.75 usec
P4 19.50 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 0 dB
PL12 16.48 dB
PL0W 0 W
PL2W 75.35659027 W
PL12W 1.69481111 W
SFO2 150.9133722 MHz
ppm


Current Data Parameters
NAME KL5-105-2
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130107
Time 20.40
INSTRUM av600
PROBHD 5 mm BB5
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 24
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 26008
DW 69.600 usec
DE 6.00 usec
TE 340.0 K
CNST6 125.0000000
CNST7 165.0000000
CNST13 8.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D6 0.06250000 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 16.10 usec
P2 32.20 usec
PL1 -1.00 dB
PL1W 31.62277603 W
SFO1 600.1336008 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 9.75 usec
PL2 0 dB
PL2W 75.35659027 W
SFO2 150.9163903 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPNAM[4] SINE.100
GPNAM[5] SINE.100
GPNAM[6] SINE.100
GPZ1 50.00 %
GPZ2 30.00 %
ppm

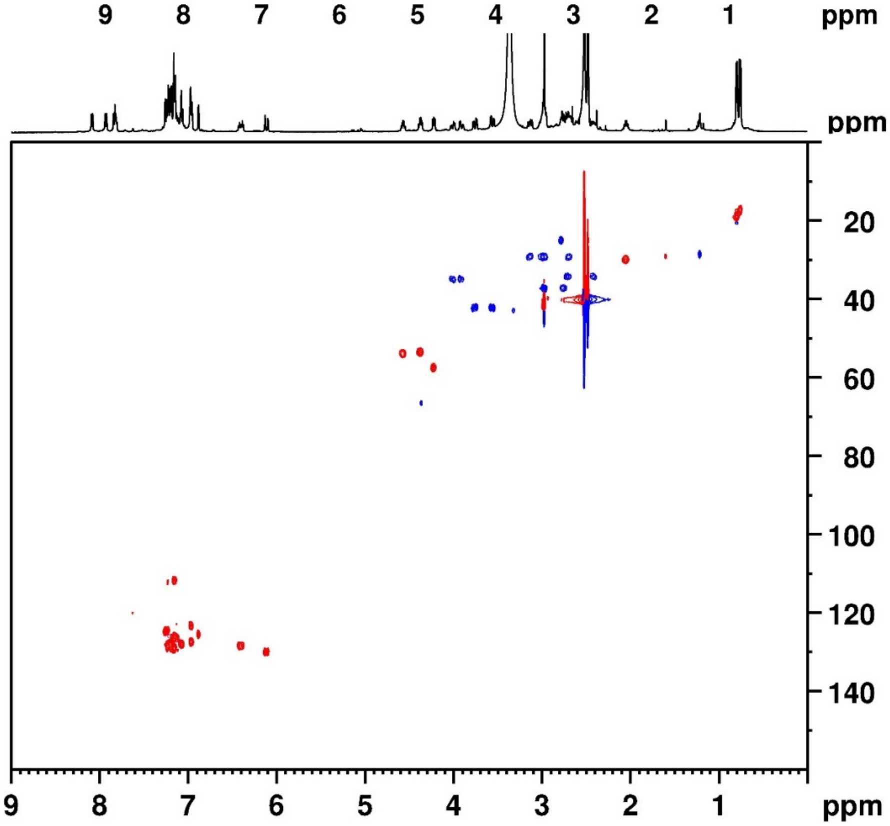
*Macrocyclic Product **2.S4c***



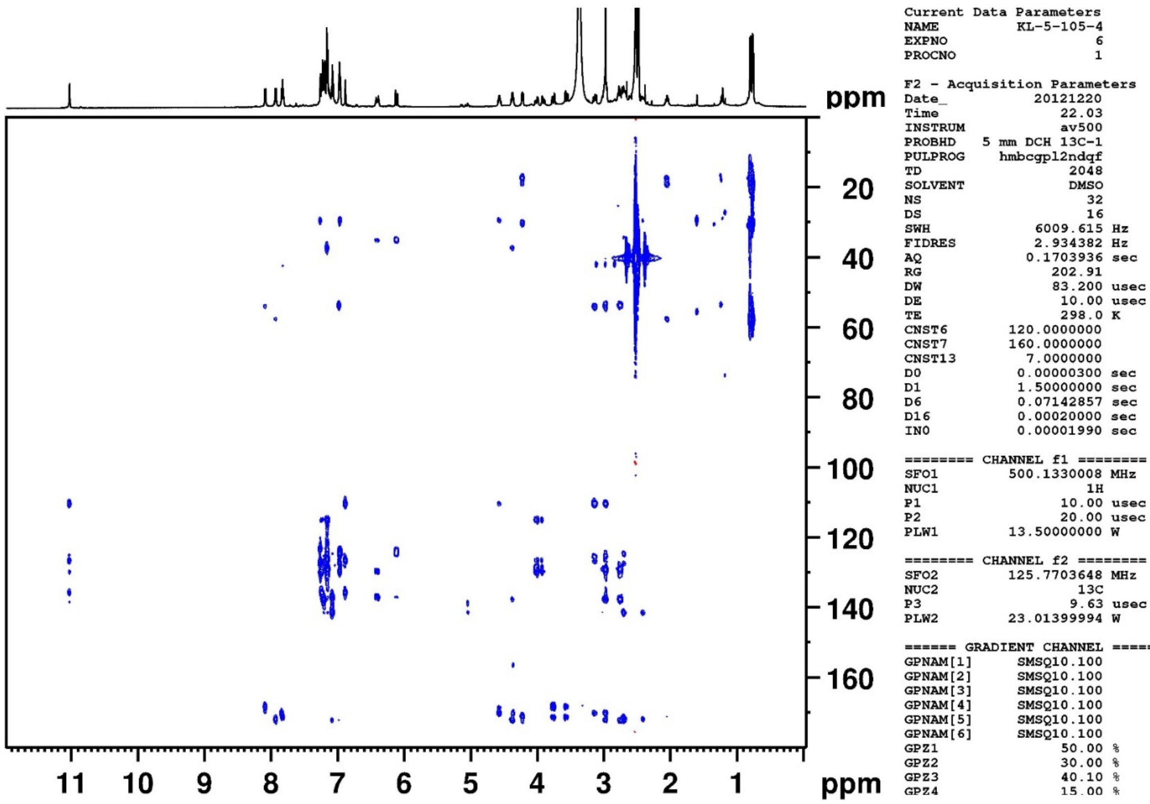




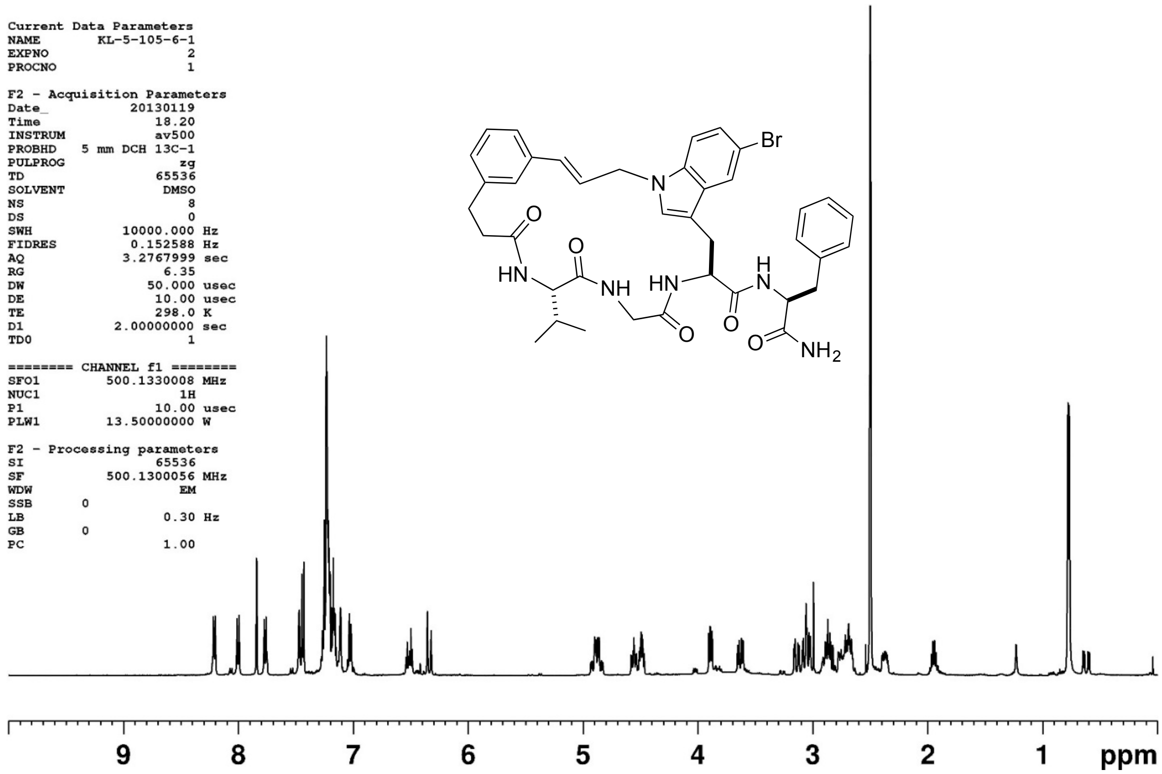

```
Current Data Parameters
NAME          KL-5-105-4
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121220
Time               19.23
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG      mlevetgp.js
TD                  2048
SOLVENT             DMSO
NS                     4
DS                     8
SWH             5000.000 Hz
FIDRES          2.441406 Hz
AQ             0.2048000 sec
RG                 37.94
DW               100.000 usec
DE                 10.00 usec
TE                 298.0 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00020000 sec
L1                    24

======== CHANNEL f1 ========
SFO1         500.1325007 MHz
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
P5                 26.68 usec
P6                 40.00 usec
P7                 80.00 usec
P17              2500.00 usec
PLW1         13.50000000 W
PLW10         0.84375000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPZ1               30.00 %
GPZ2               30.00 %
P16              1000.00 usec

F1 - Acquisition parameters
TD                   256
SFO1            500.1325 MHz
FIDRES         19.531250 Hz
```

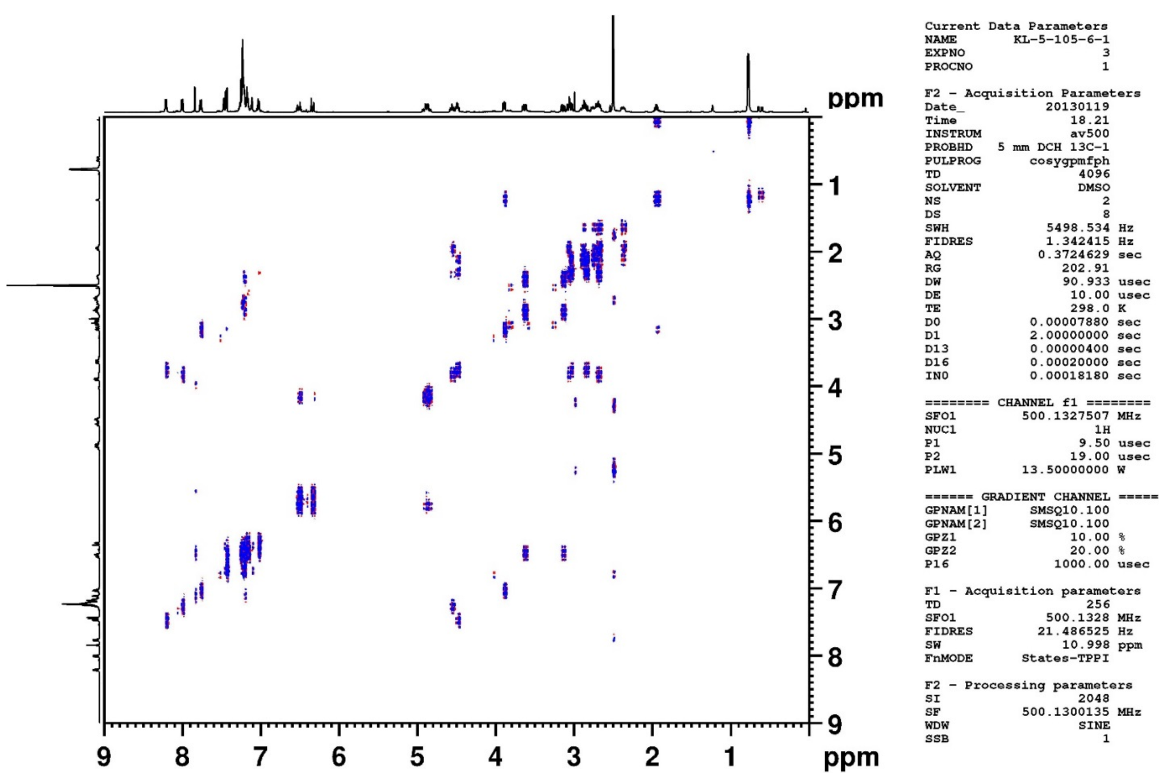


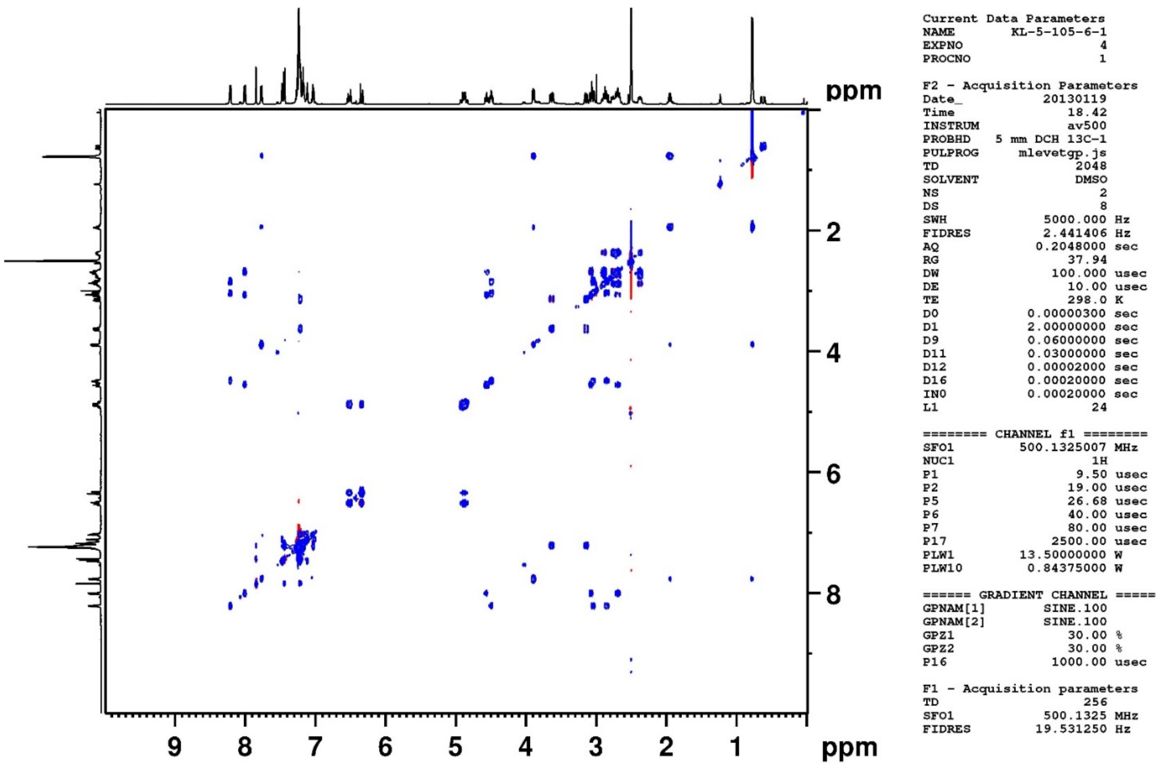

```
Current Data Parameters
NAME          KL-5-105-4
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20121220
Time               20.04
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG      hsqcedetgp
TD                  2048
SOLVENT             DMSO
NS                    16
DS                    16
SWH             5000.000 Hz
FIDRES          2.441406 Hz
AQ             0.2048000 sec
RG                202.91
DW               100.000 usec
DE                 10.00 usec
TE                 298.0 K
CNST2        145.0000000
D0           0.00000300 sec
D1           1.50000000 sec
D4           0.00172414 sec
D11          0.03000000 sec
D13          0.00000400 sec
D16          0.00020000 sec
D21          0.00345000 sec
IN0          0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1325007 MHz
NUC1                  1H
P1                 10.00 usec
P2                 20.00 usec
P28      0 usec
PLW1         13.50000000 W

======== CHANNEL f2 ========
SFO2         125.7678496 MHz
NUC2                 13C
CPDPRG[2            garp
P3                  9.63 usec
P4                 19.26 usec
PCPD2              70.00 usec
PLW2         23.01399994 W
PLW12         0.43557000 W

====== GRADIENT CHANNEL =====
GPNAM[1]      SMSQ10.100
GPNAM[2]      SMSQ10.100
GPZ1               80.00 %
```

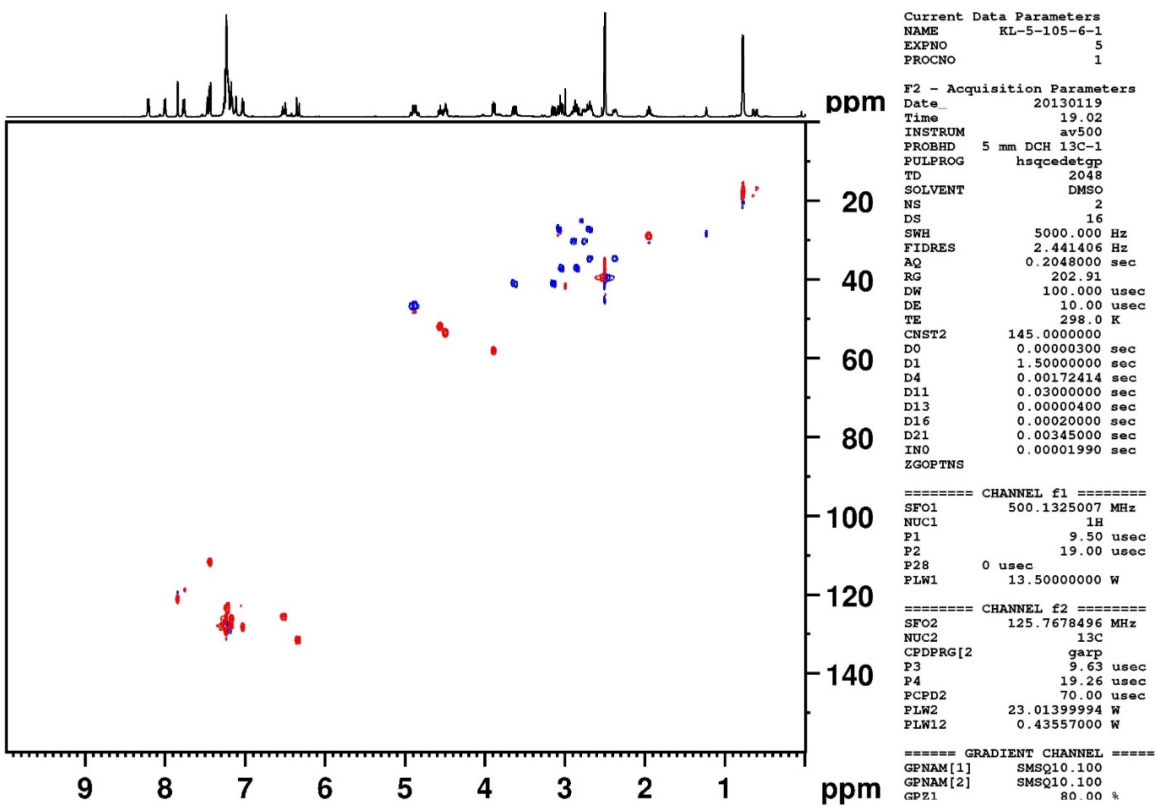

ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME KL-5-105-4
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121220
Time 22.03
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 32
DS 16
SWH 6009.615 Hz
FIDRES 2.934382 Hz
AQ 0.1703936 sec
RG 202.91
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7703648 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

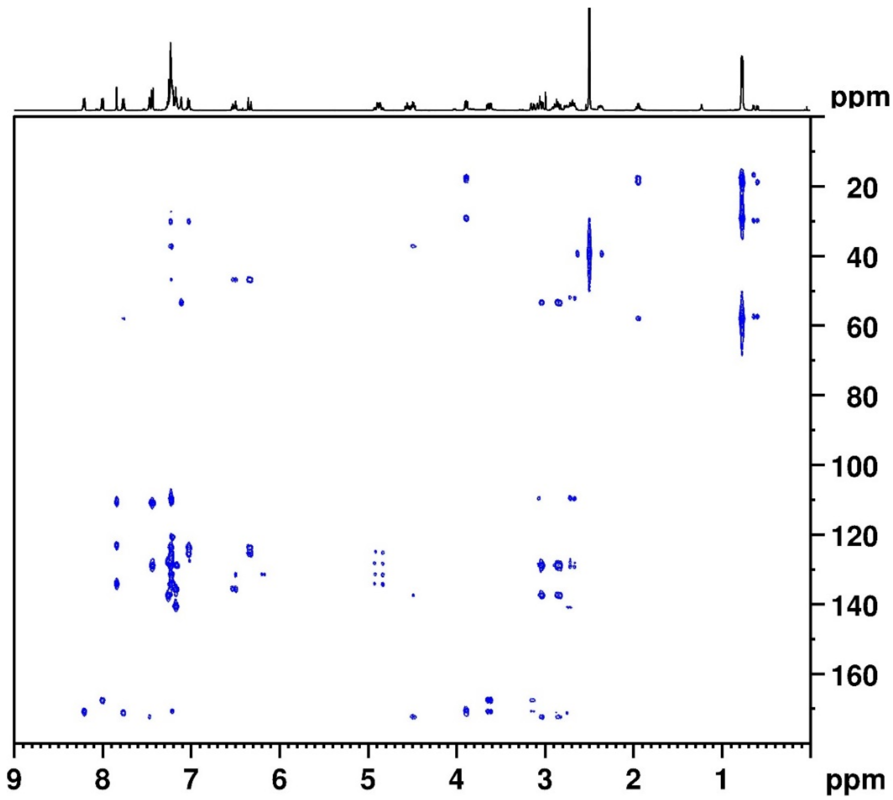
*Macrocyclic Product **2.S4d***





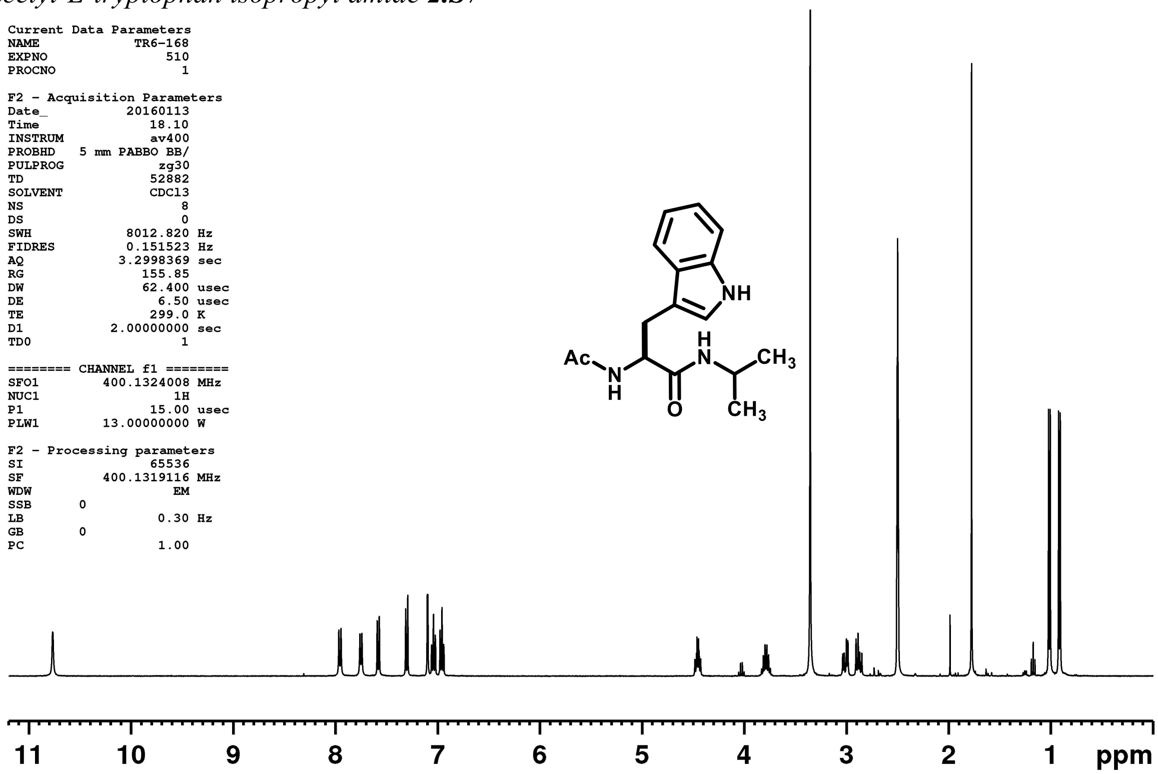

ppm
2
4
6
8
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME KL-5-105-6-1
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130119
Time 18.42
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 37.94
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
L1 24
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 9.50 usec
P2 19.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz

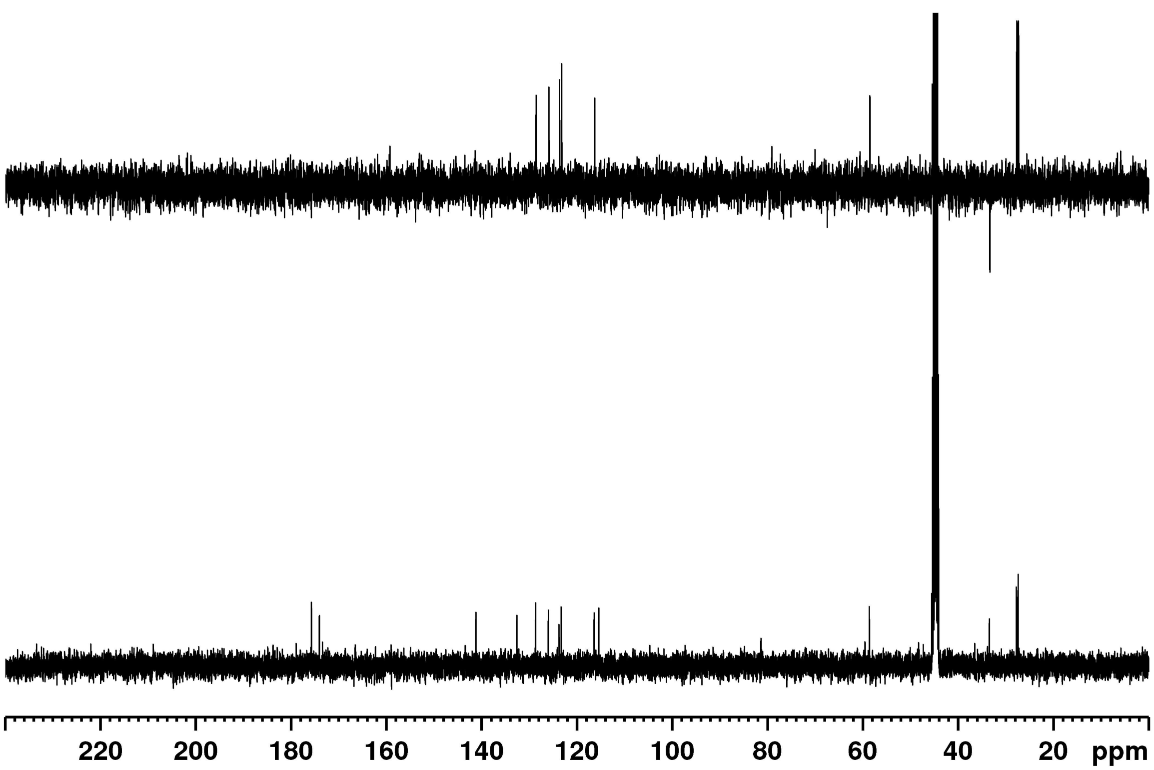

ppm
20
40
60
80
100
120
140
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME KL-5-105-6-1
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130119
Time 19.02
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hsqcedetgp
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 202.91
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D4 0.00172414 sec
D11 0.03000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
D21 0.00345000 sec
IN0 0.00001990 sec
ZGOPTNS
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 9.50 usec
P2 19.00 usec
P28 0 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7678496 MHz
NUC2 13C
CPDPRG[2 garp
P3 9.63 usec
P4 19.26 usec
PCPD2 70.00 usec
PLW2 23.01399994 W
PLW12 0.43557000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 80.00 %



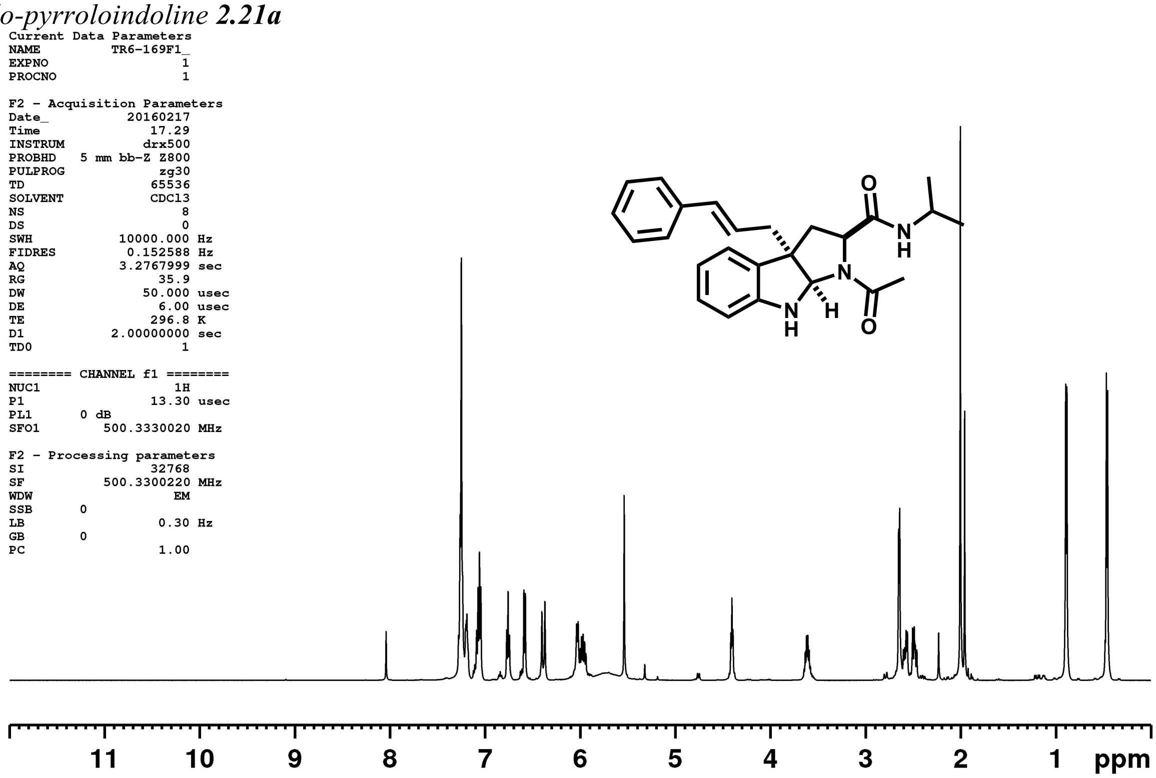

```
Current Data Parameters
NAME          KL-5-105-6-1
EXPNO                    6
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130122
Time                 18.05
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG      hmbcgpl2ndqf
TD                    2048
SOLVENT               DMSO
NS                       6
DS                      16
SWH             6009.615 Hz
FIDRES          2.934382 Hz
AQ             0.1703936 sec
RG                  202.91
DW                  83.200 usec
DE                   10.00 usec
TE                   298.0 K
CNST6          120.0000000
CNST7          160.0000000
CNST13           7.0000000
D0              0.00000300 sec
D1              1.50000000 sec
D6              0.07142857 sec
D16             0.00020000 sec
IN0             0.00001990 sec

======== CHANNEL f1 ========
SFO1         500.1330008 MHz
NUC1                    1H
P1                    9.50 usec
P2                   19.00 usec
PLW1           13.50000000 W

======== CHANNEL f2 ========
SFO2         125.7703648 MHz
NUC2                   13C
P3                    9.63 usec
PLW2           23.01399994 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPNAM[3]        SMSQ10.100
GPNAM[4]        SMSQ10.100
GPNAM[5]        SMSQ10.100
GPNAM[6]        SMSQ10.100
GPZ1                 50.00 %
GPZ2                 30.00 %
GPZ3                 40.10 %
GPZ4                 15.00 %
```

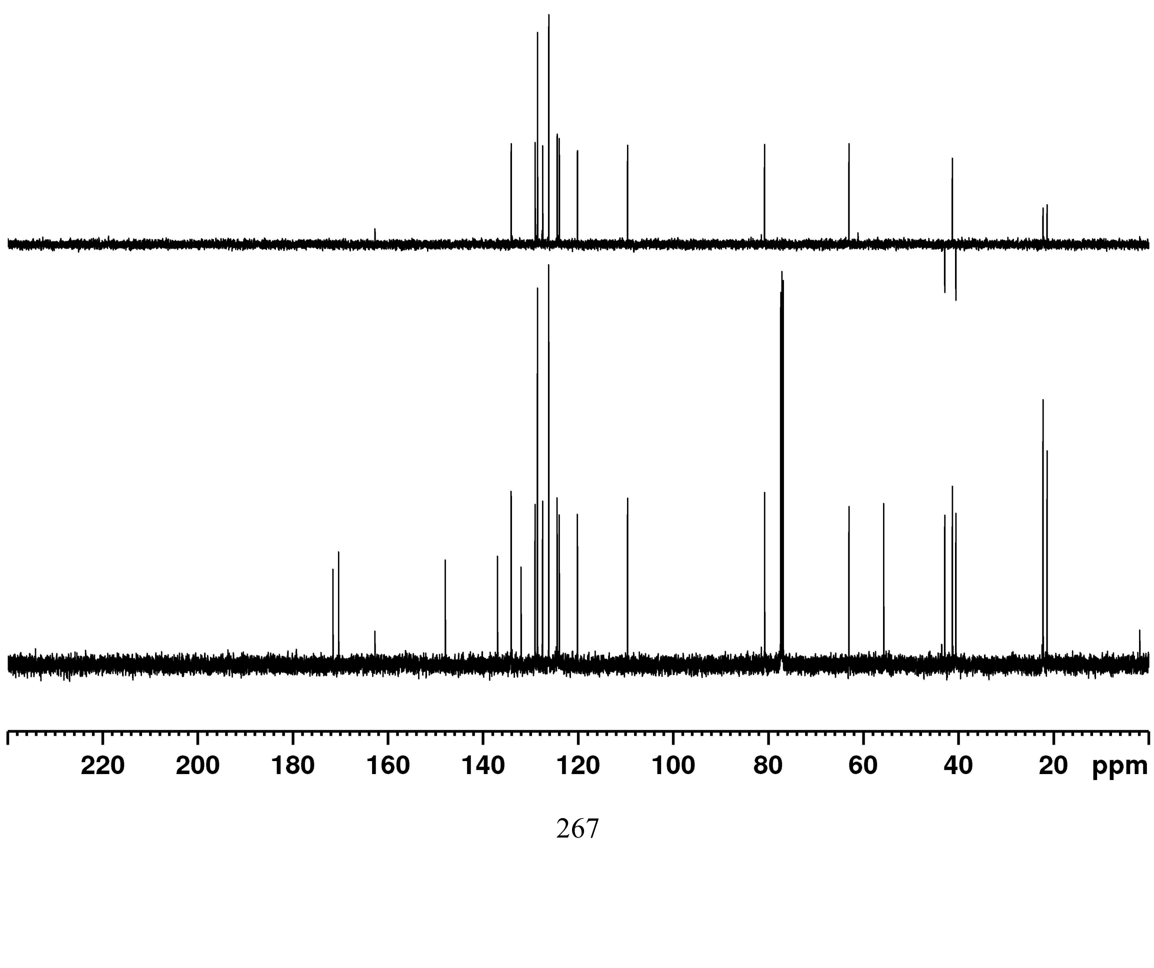
N-acetyl-L-tryptophan isopropyl amide ***2.S7***

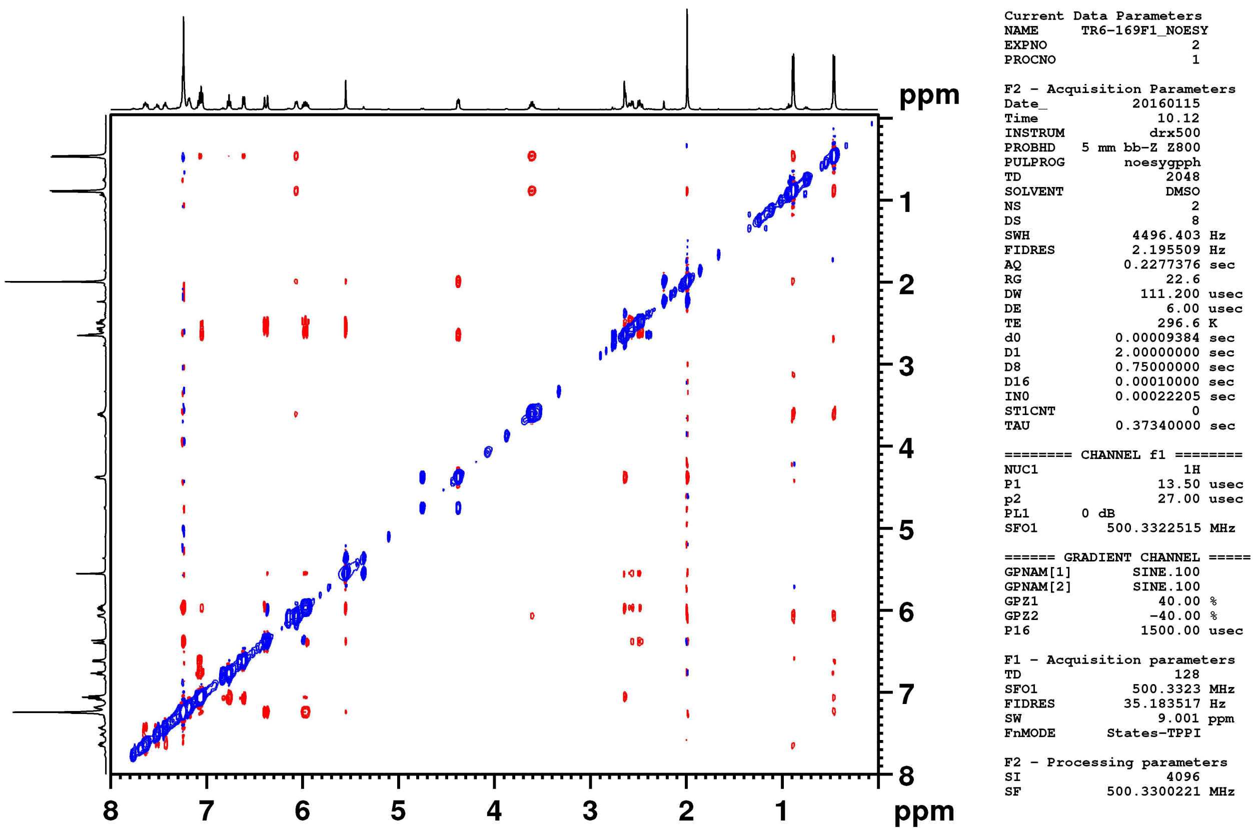




endo-pyrroloindoline ***2.21a***

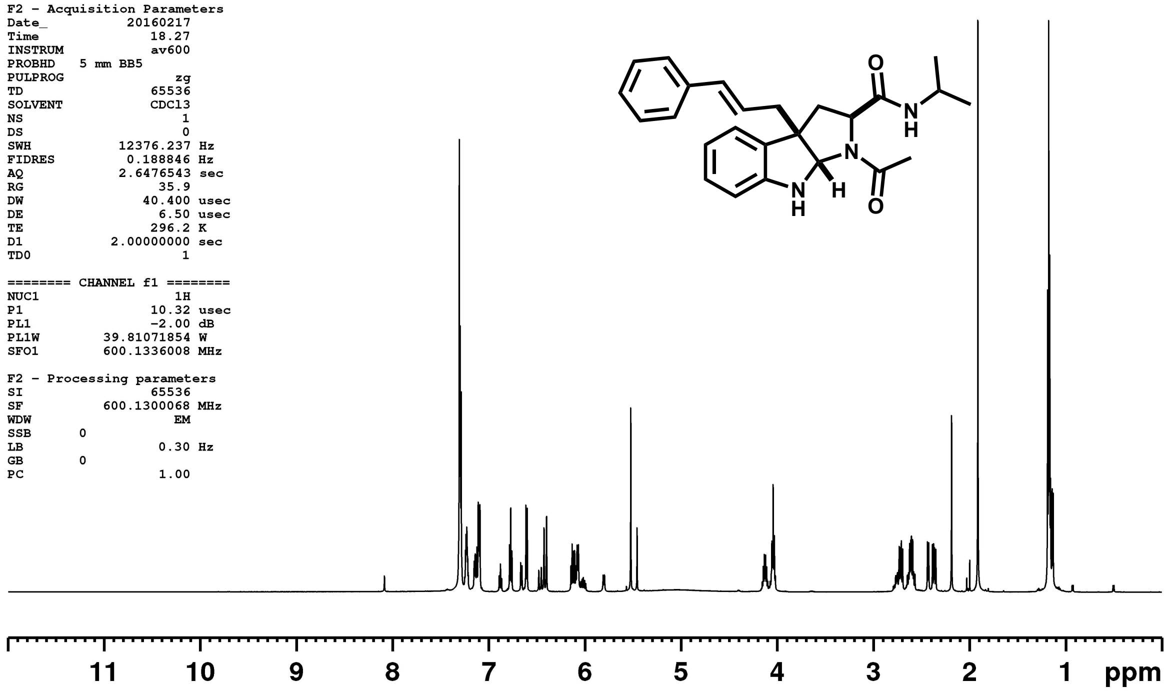


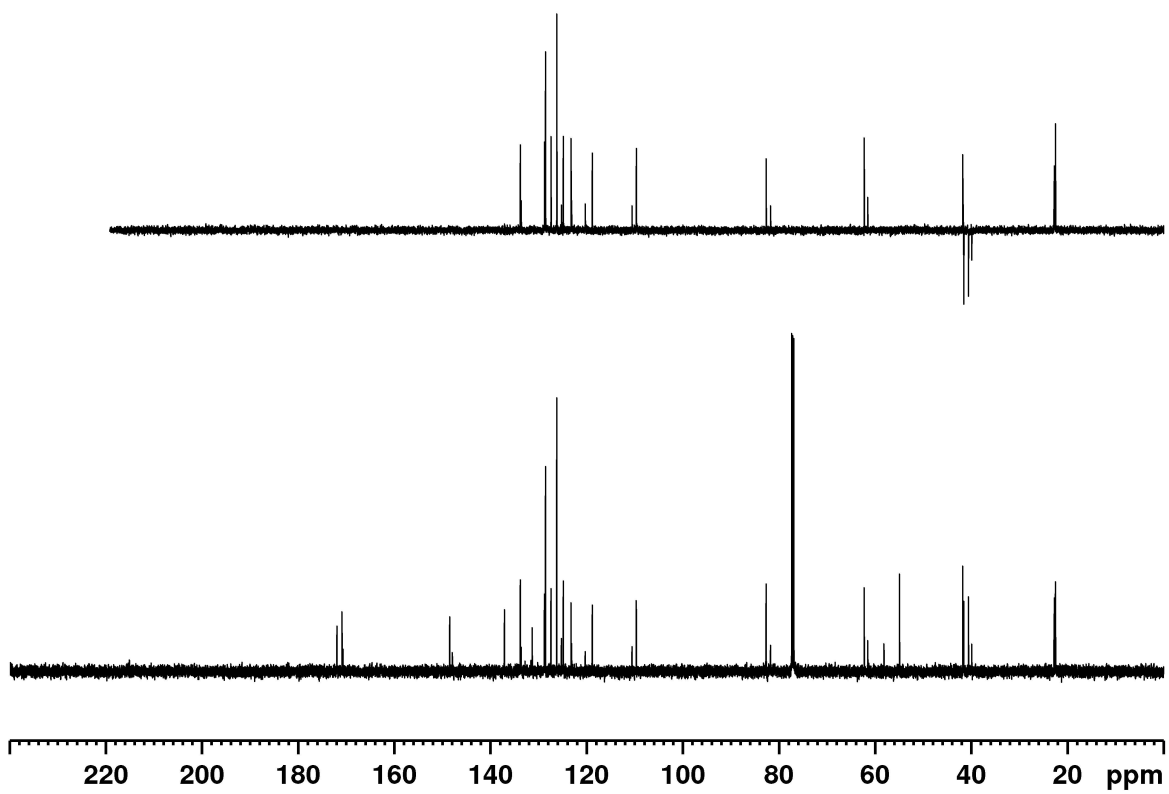


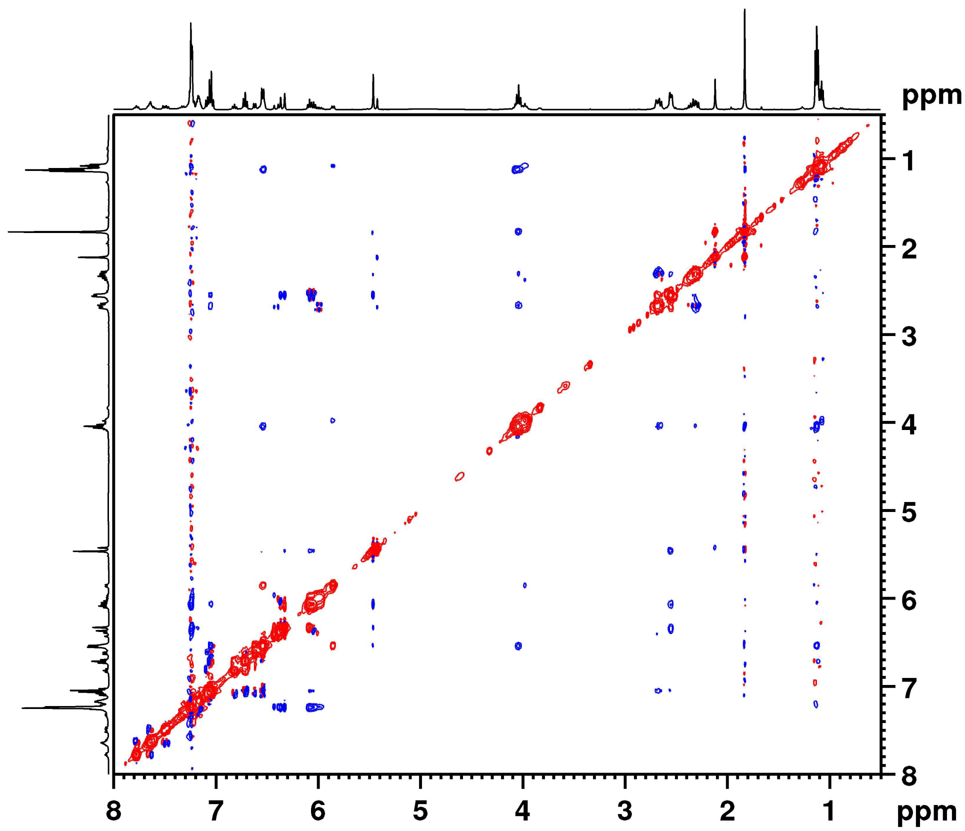

ppm
8
7
6
5
4
3
2
1
ppm
1
2
3
4
5
6
7
8
Current Data Parameters
NAME TR6-169F1_NOESY
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160115
Time 10.12
INSTRUM drx500
PROBHD 5 mm bb-Z Z800
PULPROG noesygpph
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 4496.403 Hz
FIDRES 2.195509 Hz
AQ 0.2277376 sec
RG 22.6
DW 111.200 usec
DE 6.00 usec
TE 296.6 K
d0 0.00009384 sec
D1 2.00000000 sec
D8 0.75000000 sec
D16 0.00010000 sec
IN0 0.00022205 sec
ST1CNT 0
TAU 0.37340000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.50 usec
p2 27.00 usec
PL1 0 dB
SFO1 500.3322515 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 40.00 %
GPZ2 -40.00 %
P16 1500.00 usec
F1 - Acquisition parameters
TD 128
SFO1 500.3323 MHz
FIDRES 35.183517 Hz
SW 9.001 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 4096
SF 500.3300221 MHz

exo-pyrroloindoline ***2.21b***

```
Current Data Parameters
NAME          TR6-169F2_
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20160217
Time               18.27
INSTRUM            av600
PROBHD   5 mm BB5
PULPROG               zg
TD                 65536
SOLVENT            CDCl3
NS                     1
DS                     0
SWH            12376.237 Hz
FIDRES          0.188846 Hz
AQ             2.6476543 sec
RG                  35.9
DW                40.400 usec
DE                  6.50 usec
TE                 296.2 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 10.32 usec
PL1                -2.00 dB
PL1W         39.81071854 W
SFO1         600.1336008 MHz

F2 - Processing parameters
SI                 65536
SF           600.1300068 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```

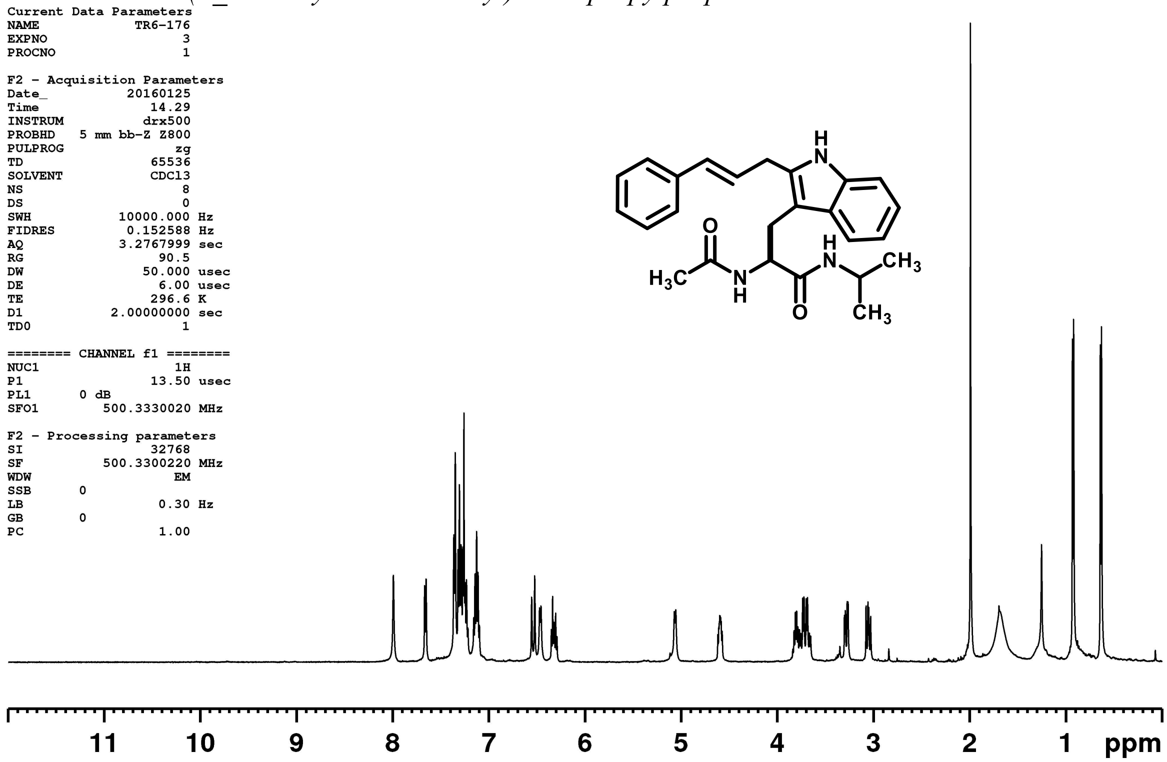


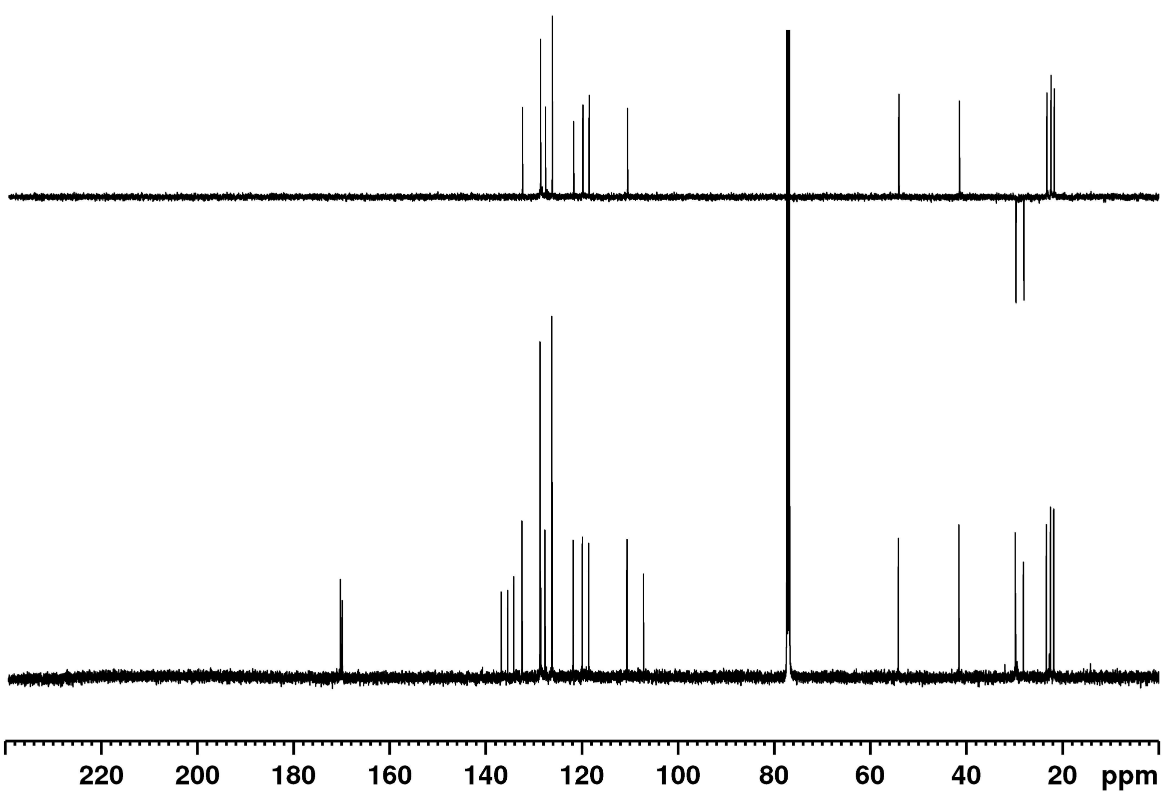




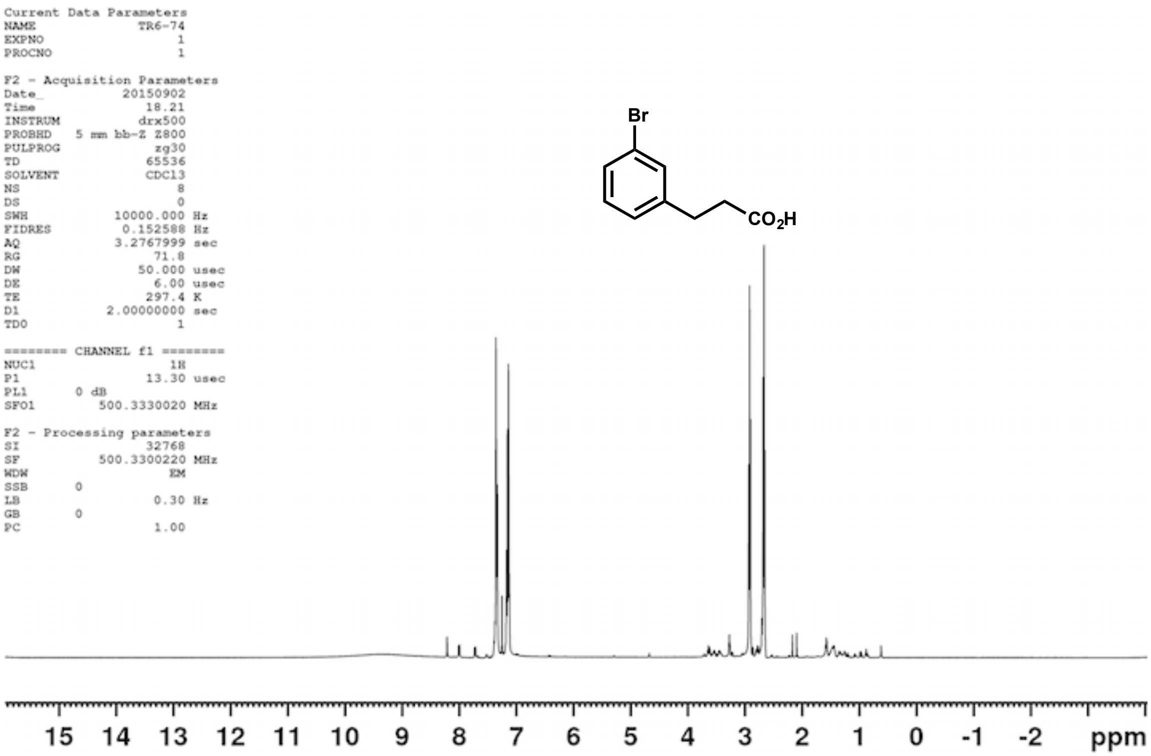

```
Current Data Parameters
NAME            TR6-169F2
EXPNO                  82
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160115
Time                10.00
INSTRUM             av400
PROBHD   5 mm PABBO BB/
PULPROG      noesygpphpp
TD                   2048
SOLVENT             CDCl3
NS                      2
DS                      8
SWH              5154.639 Hz
FIDRES           2.516914 Hz
AQ              0.1986560 sec
RG                    7.7
DW                 97.000 usec
DE                   6.50 usec
TE                  299.0 K
D0             0.00007790 sec
D1             2.00000000 sec
D8             0.75000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
D16            0.00020000 sec
IN0            0.00019400 sec

======== CHANNEL f1 ========
SFO1          400.1319474 MHz
NUC1                   1H
P1                  15.00 usec
P2                  30.00 usec
P17               2500.00 usec
PLW1          13.00000000 W
PLW10          4.32690001 W

====== GRADIENT CHANNEL =====
GPNAM[1]       SMSQ10.100
GPZ1                40.00 %
P16               1000.00 usec

F1 - Acquisition parameters
TD                    256
SFO1             400.1319 MHz
FIDRES          20.135309 Hz
SW                 12.882 ppm
FnMODE        States-TPPI

F2 - Processing parameters
SI                   4096
SF            400.1300184 MHz
```

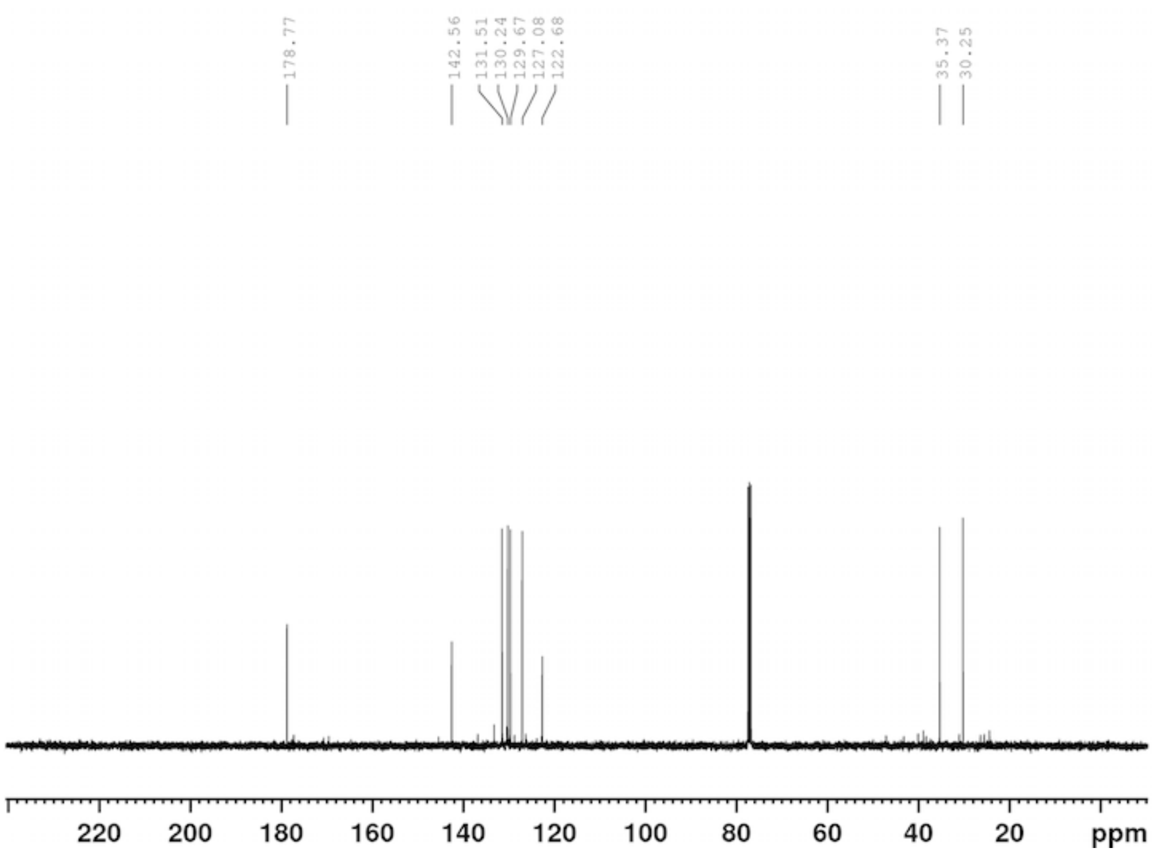
(S)-2-acetamido-3-(2_cinnamyl-1H-indol-3-yl)-N-isopropylpropanamide ***2.22***



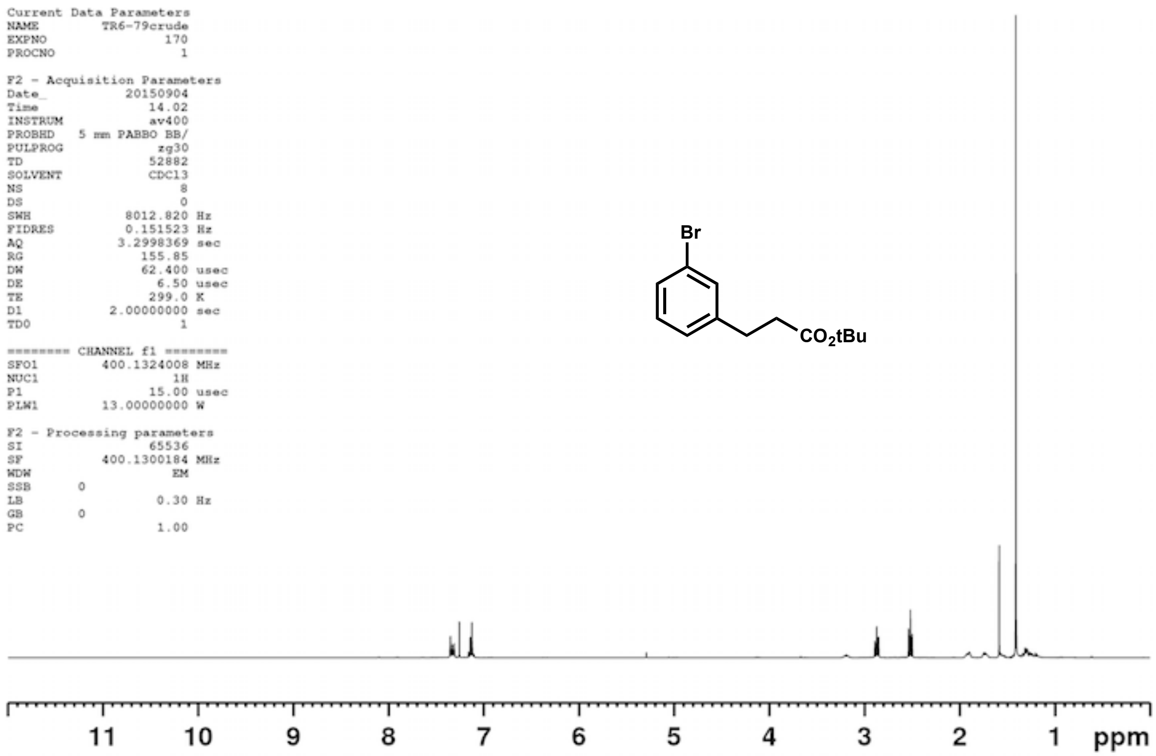


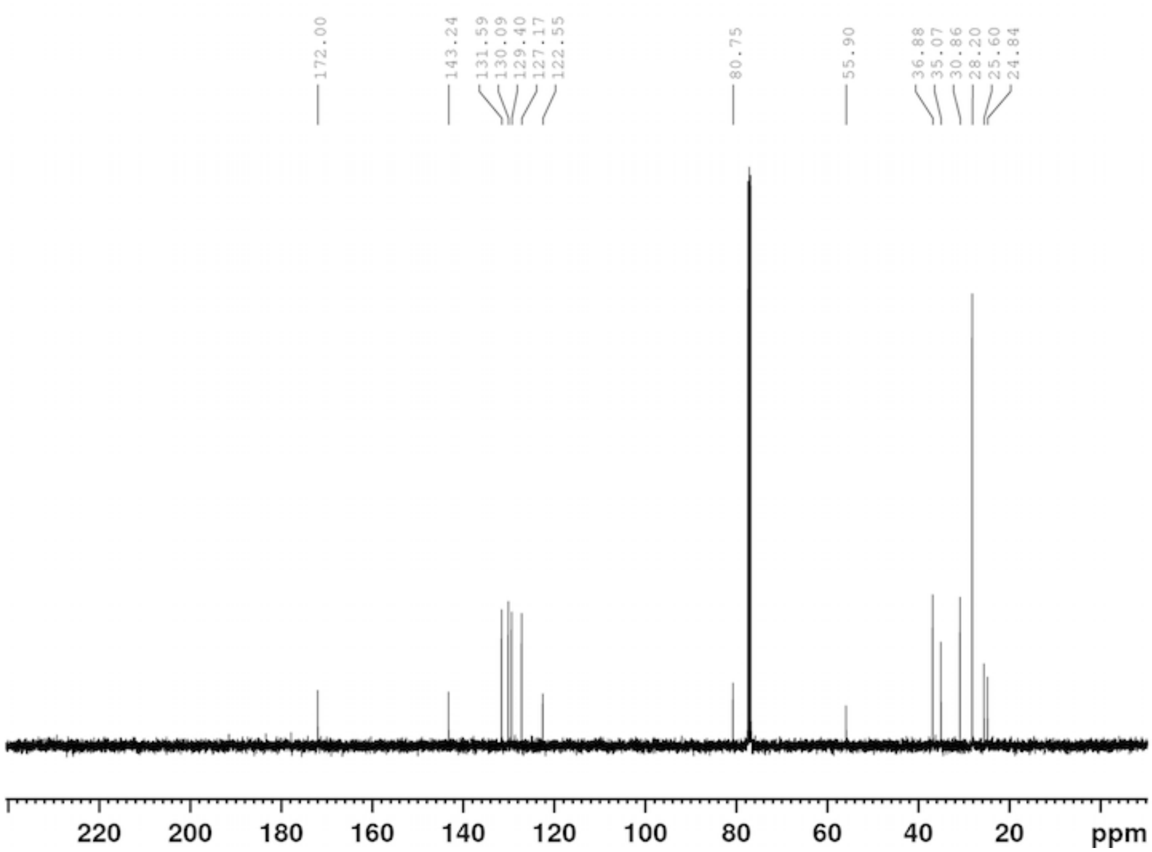
3-(3-Bromophenyl)propionic acid ***2.S5***



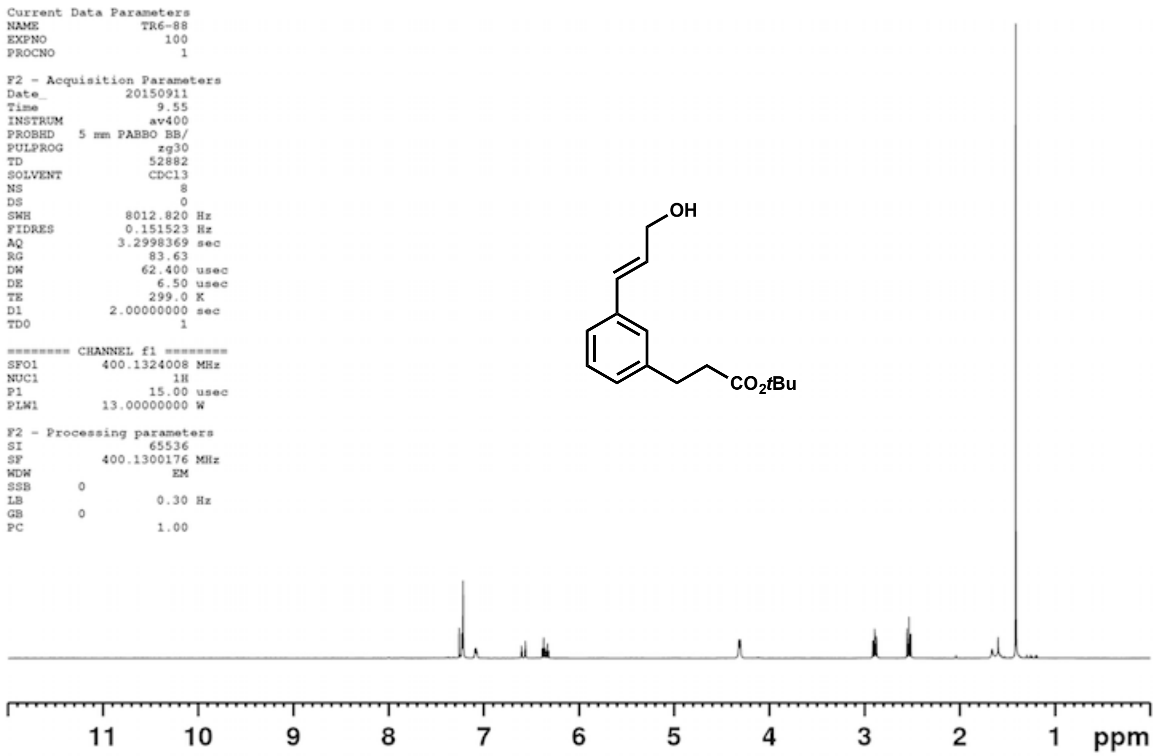


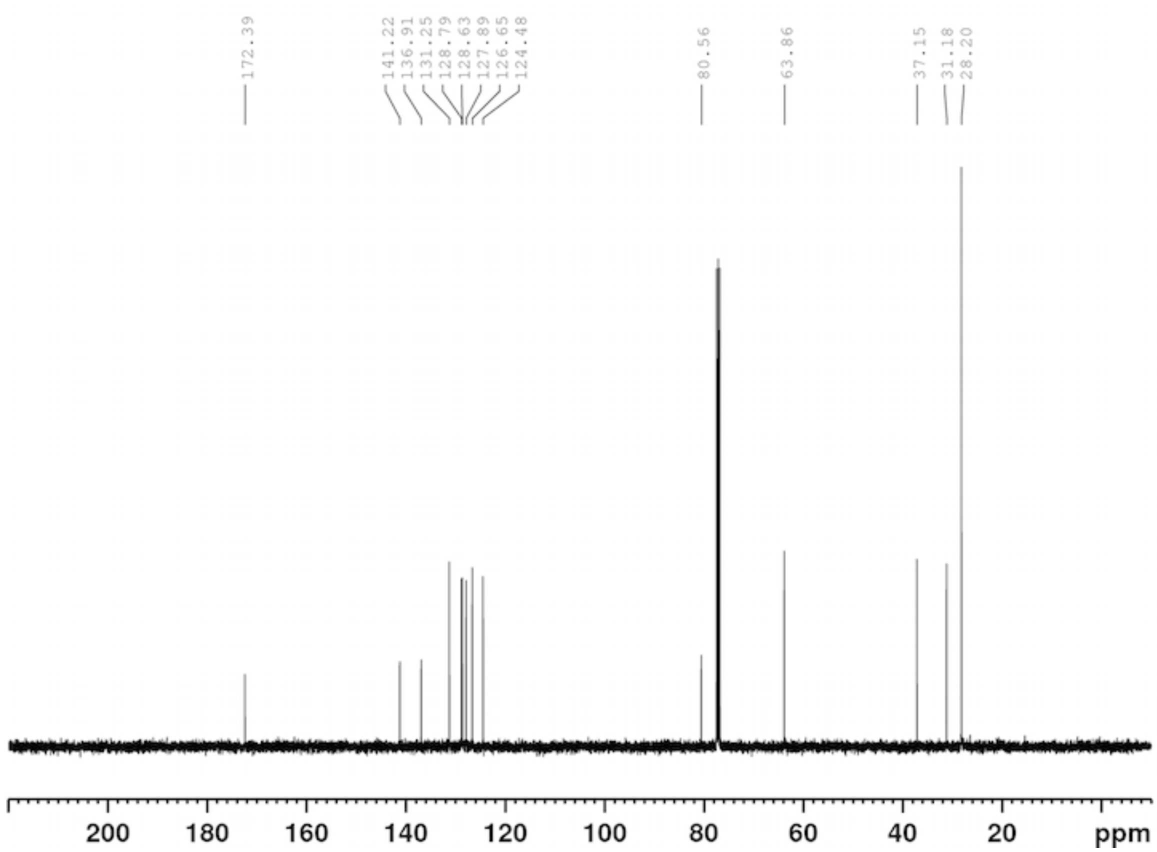
*tert-Butyl 3-(3-bromophenyl)propanoate **2.S6***



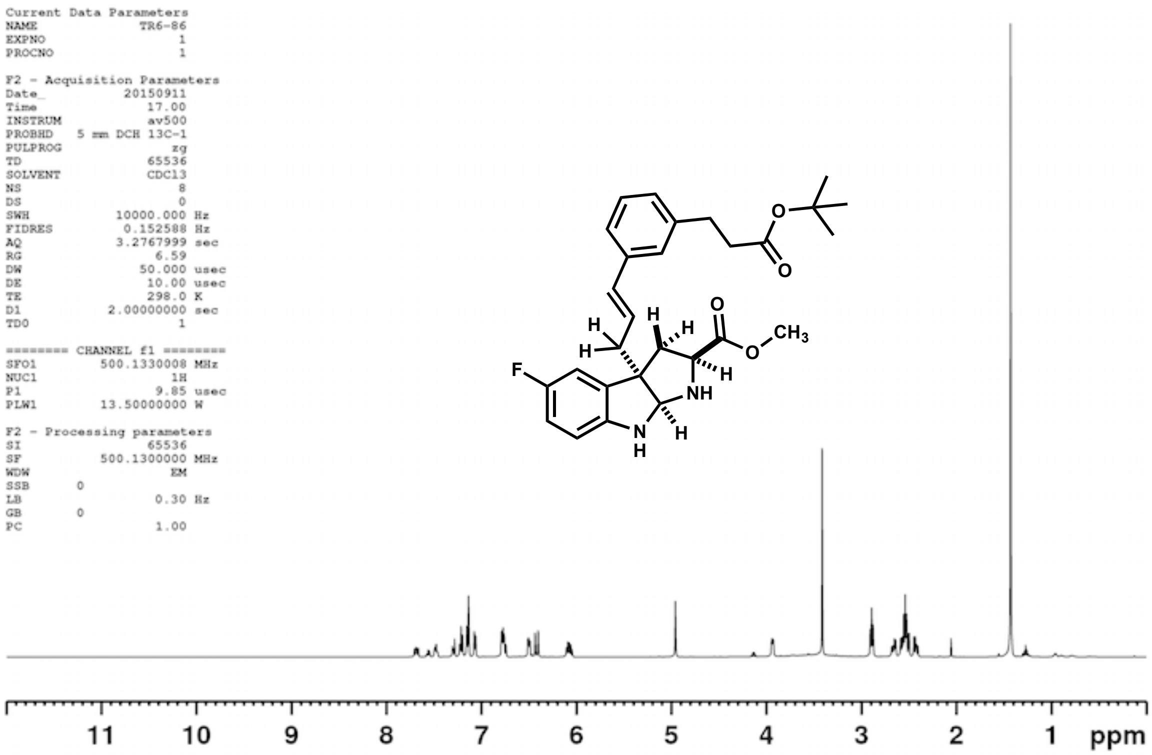


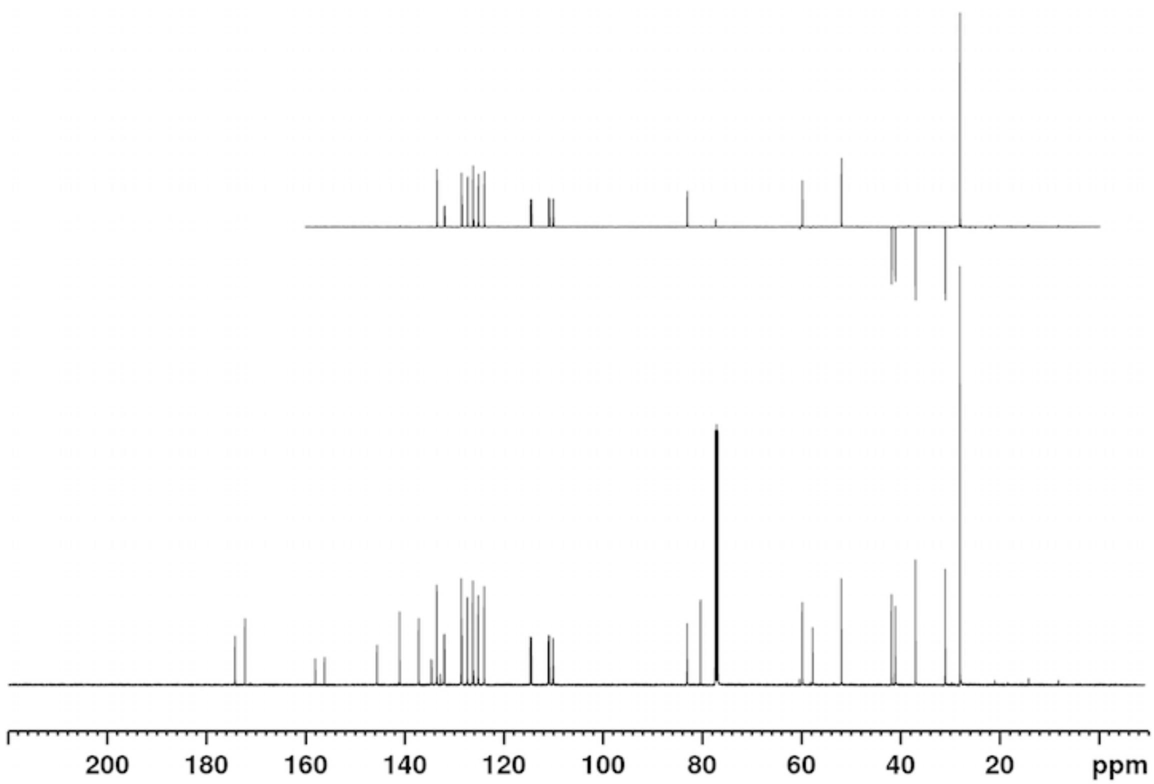
*Cinnamyl Alcohol **2.21***

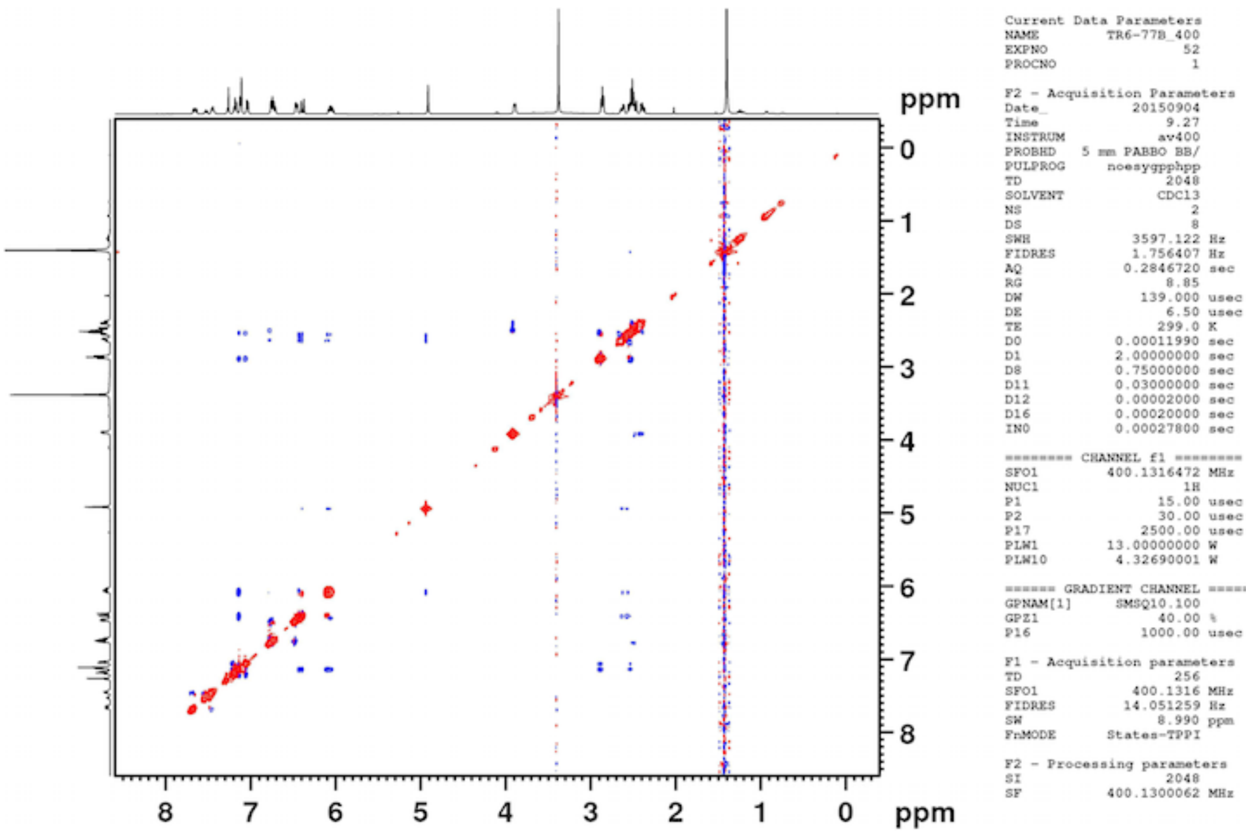




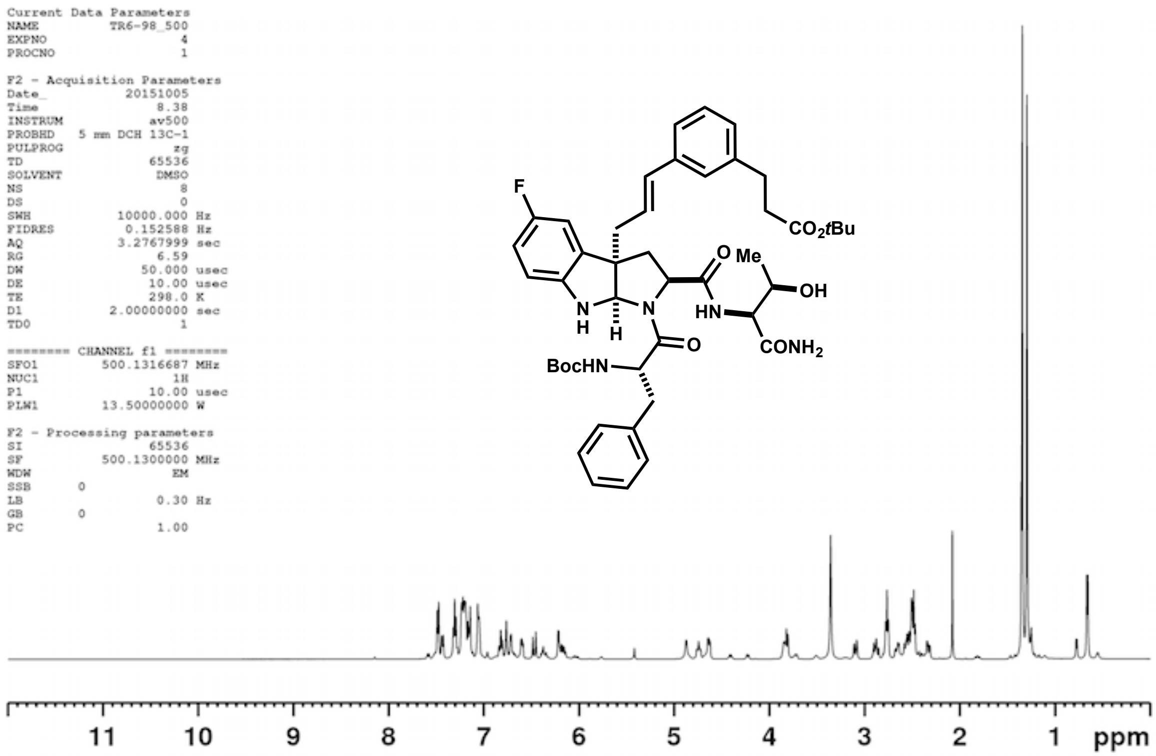
*endo-Pyrroloindoline **2.23***

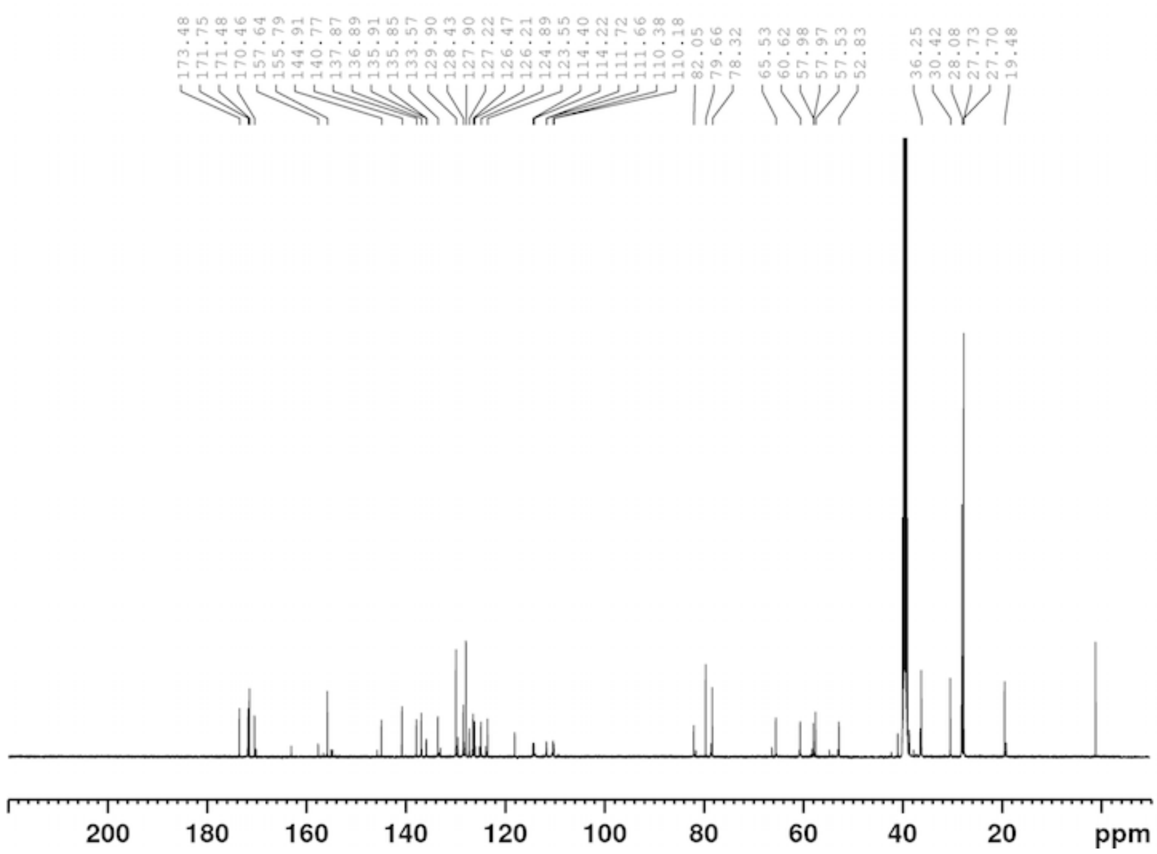




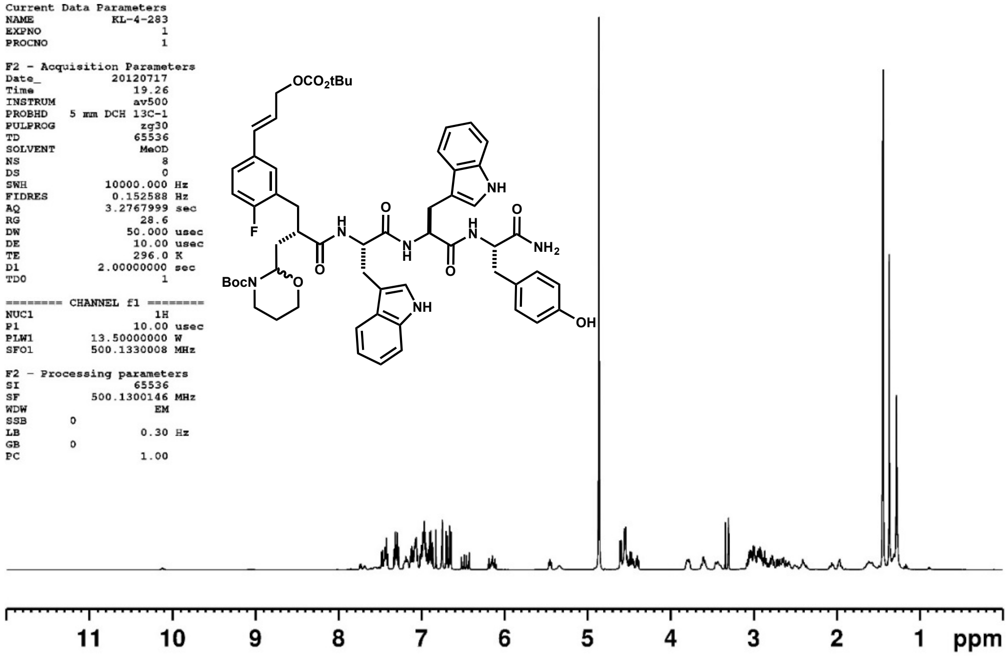

ppm
0
1
2
3
4
5
6
7
8
8 7 6 5 4 3 2 1 0
ppm
Current Data Parameters
NAME TR6-77B_400
EXPNO 52
PROCNO 1
F2 - Acquisition Parameters
Date_ 20150904
Time 9.27
INSTRUM av400
PROBHD 5 mm PABBO BB/
PULPROG noesygpphpp
TD 2048
SOLVENT CDCl3
NS 2
DS 8
SWH 3597.122 Hz
FIDRES 1.756407 Hz
AQ 0.2846720 sec
RG 8.85
DW 139.000 usec
DE 6.50 usec
TE 299.0 K
D0 0.00011990 sec
D1 2.00000000 sec
D8 0.75000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00027800 sec
======== CHANNEL f1 ========
SFO1 400.1316472 MHz
NUC1 1H
P1 15.00 usec
P2 30.00 usec
P17 2500.00 usec
PLW1 13.00000000 W
PLW10 4.32690001 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPZ1 40.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 400.1316 MHz
FIDRES 14.051259 Hz
SW 8.990 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 2048
SF 400.1300062 MHz

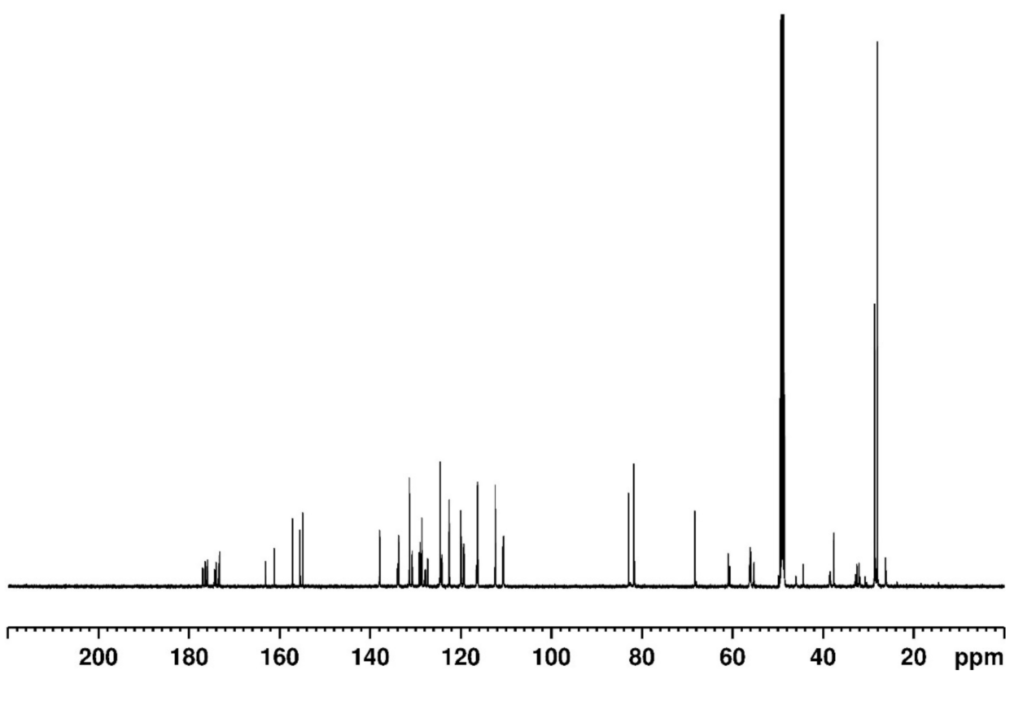
tert-butyl ester ***2.24***





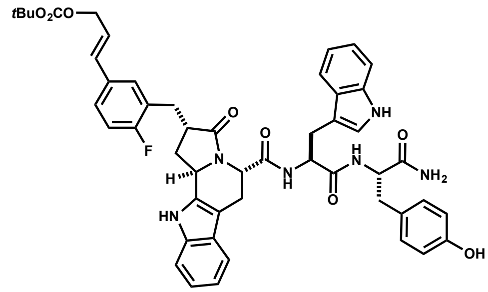
Acyclic Precursor ***2.S8***

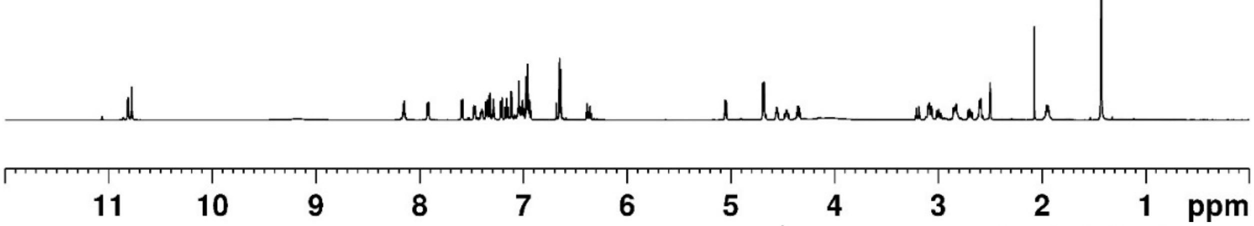


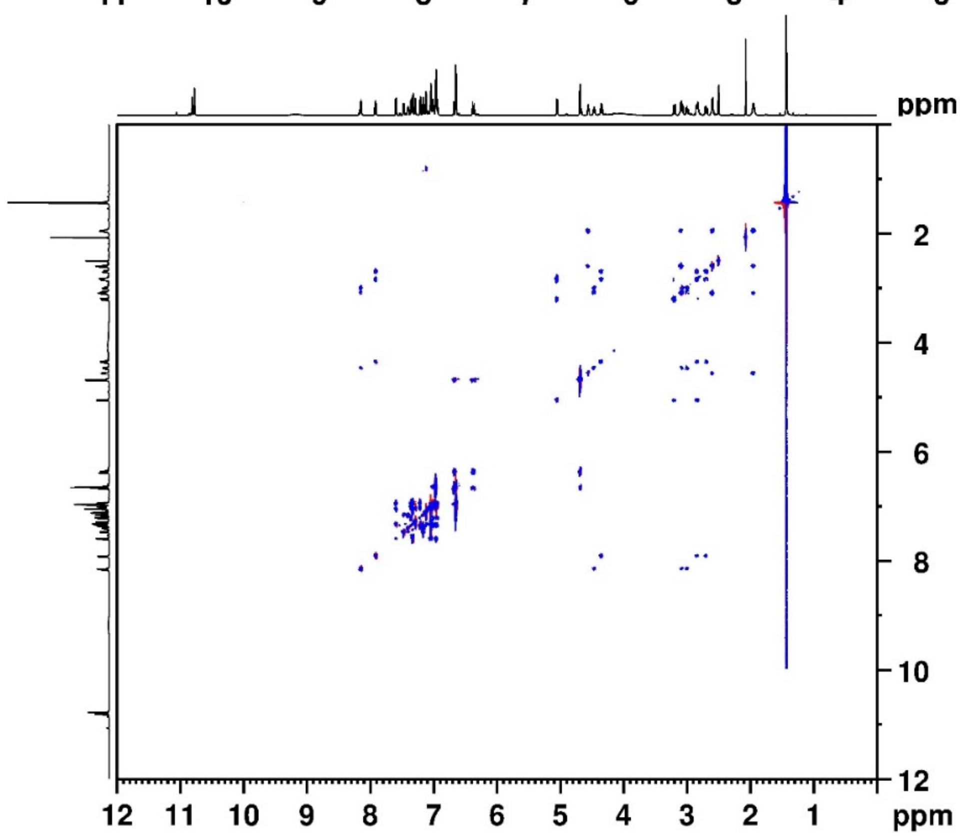


*Tryptoline **2.27***

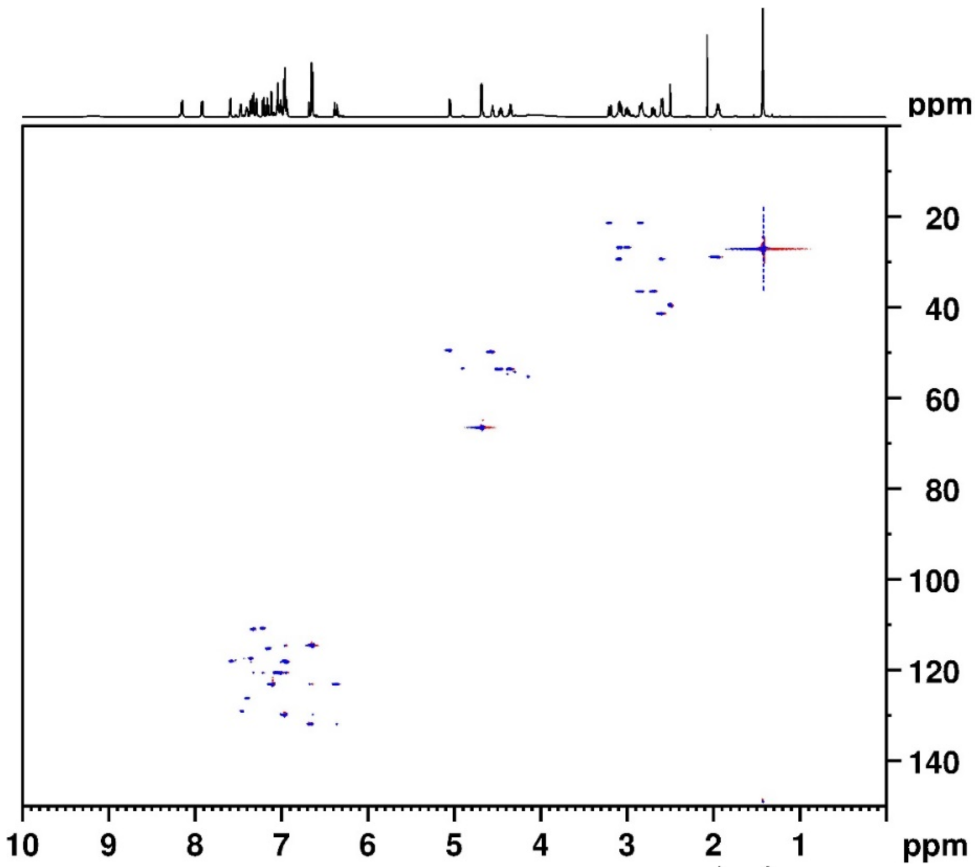
```
Current Data Parameters
NAME        KL-5-2_pHPLC
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130516
Time               19.15
INSTRUM            av600
PROBHD   5 mm TBI5
PULPROG               zg
TD                 65536
SOLVENT             DMSO
NS                     8
DS                     0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                  71.8
DW                40.400 usec
DE                  6.50 usec
TE                 293.5 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.70 usec
PL1                -2.00 dB
PL1W         39.81071854 W
SFO1         600.1336008 MHz

F2 - Processing parameters
SI                 65536
SF           600.1300054 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```



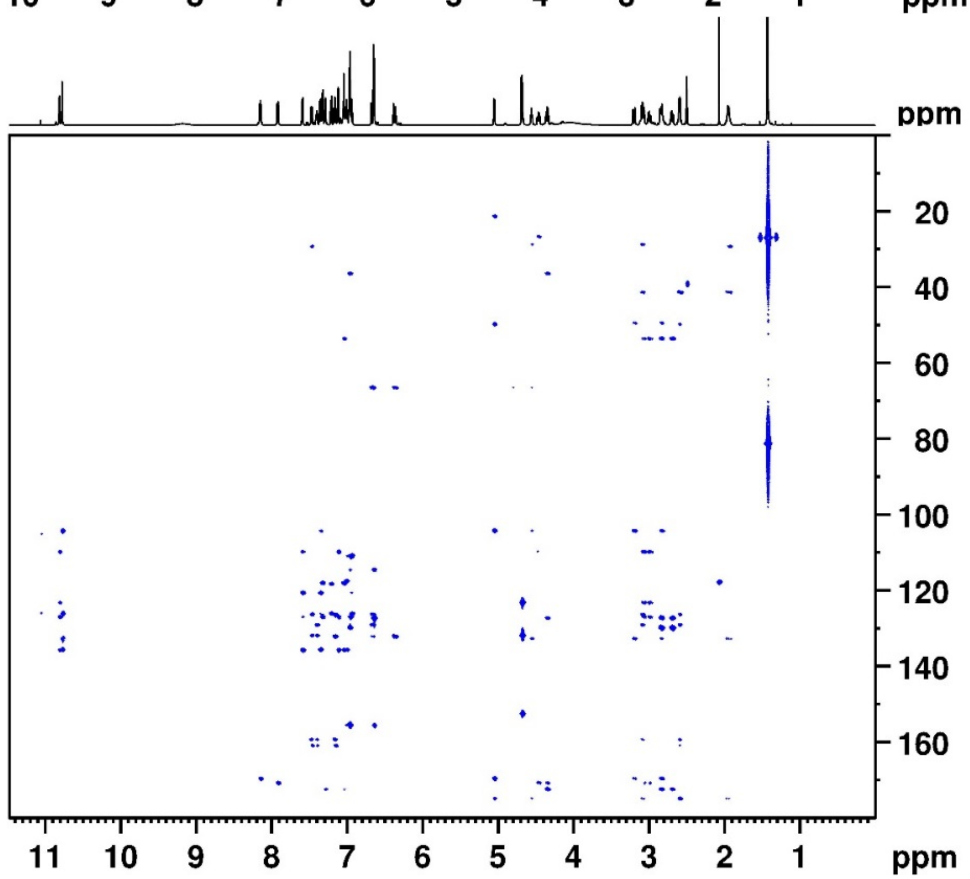





```
Current Data Parameters
NAME        KL-5-2_pHPLC
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20130516
Time               19.17
INSTRUM            av600
PROBHD   5 mm TBI5
PULPROG      mlevetgp.js
TD                  4096
SOLVENT             DMSO
NS                     4
DS                    16
SWH             6009.615 Hz
FIDRES          1.467191 Hz
AQ             0.3407872 sec
RG                   128
DW                83.200 usec
DE                  6.50 usec
TE                 293.6 K
D0            0.00000300 sec
D1            1.20000005 sec
D9            0.06000000 sec
D11           0.03000000 sec
D12           0.00002000 sec
D16           0.00020000 sec
IN0           0.00016665 sec
L1                    24

======== CHANNEL f1 ========
NUC1                  1H
P1                  9.70 usec
P2                 19.40 usec
P5                 26.68 usec
P6                 40.00 usec
P7                 80.00 usec
P17              2500.00 usec
PL1                -2.00 dB
PL10                9.54 dB
PL1W         39.81071854 W
PL10W         2.79254389 W
SFO1         600.1330006 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               30.00 %
```

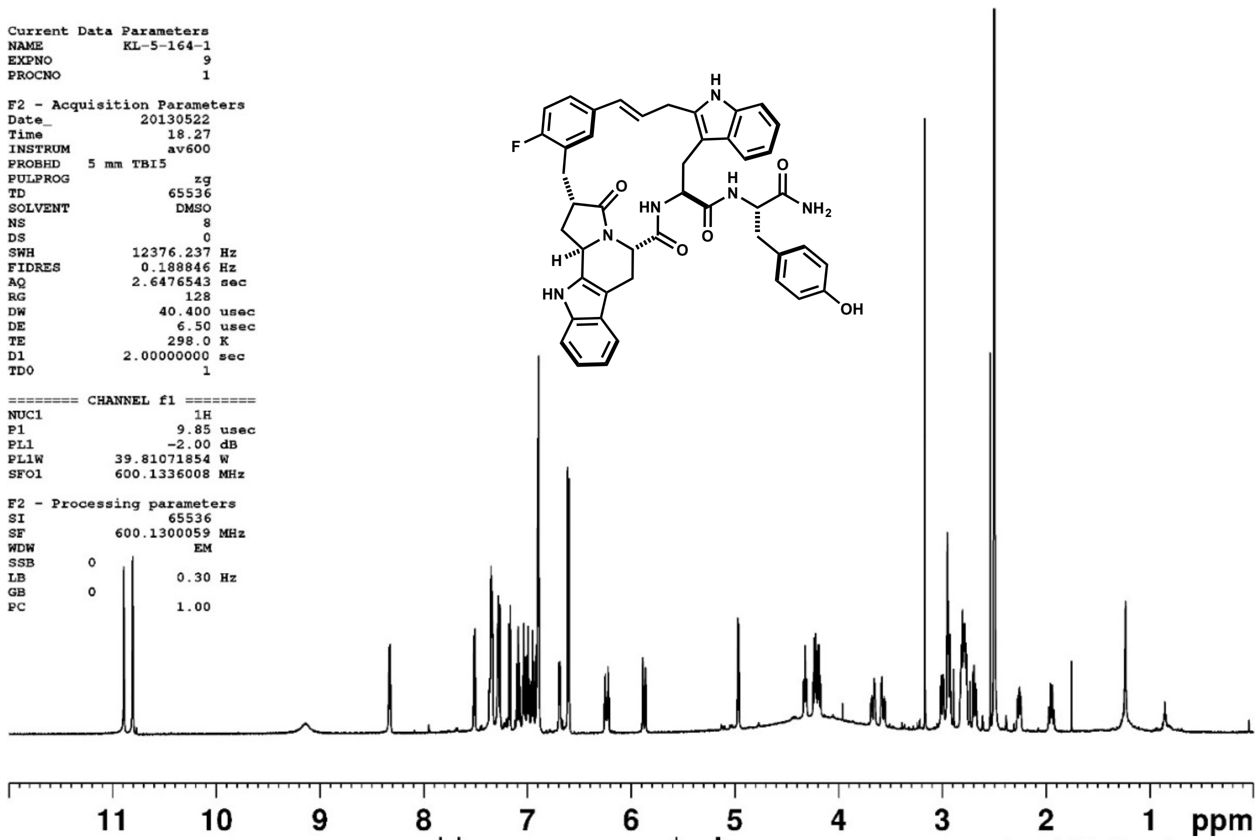


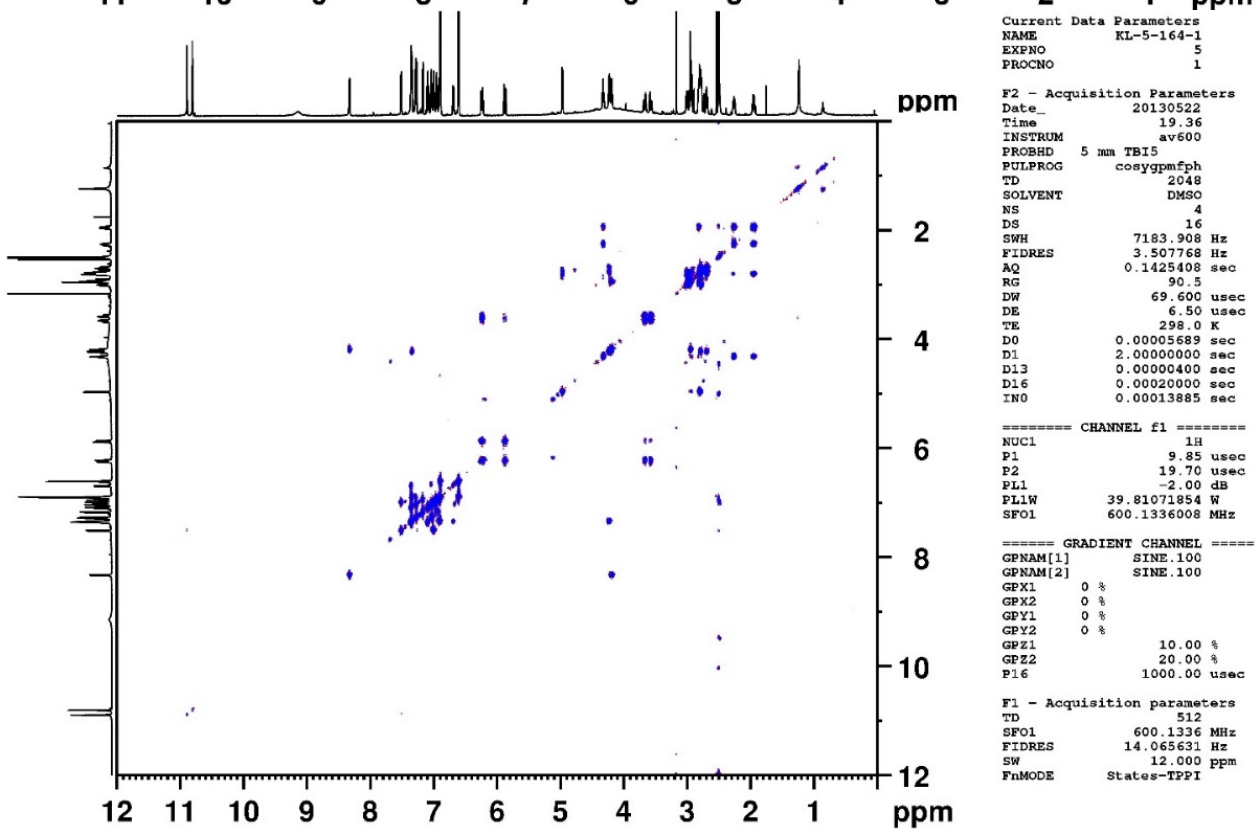

```
Current Data Parameters
NAME          KL-5-2_pHPLC
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130516
Time                 20.25
INSTRUM              av600
PROBHD     5 mm TBI5
PULPROG       hsqcetgpsisp
TD                    2048
SOLVENT               DMSO
NS                       8
DS                      16
SWH               7183.908 Hz
FIDRES            3.507768 Hz
AQ               0.1425408 sec
RG                   16384
DW                  69.600 usec
DE                    6.00 usec
TE                   294.3 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.20000005 sec
D4              0.00172414 sec
D11             0.03000000 sec
D16             0.00020000 sec
D24             0.00086200 sec
IN0             0.00002070 sec
ZGOPTNS

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.70 usec
P2                   19.40 usec
P28                1000.00 usec
PL1                  -2.00 dB
PL1W           39.81071854 W
SFO1         600.1330006 MHz

======== CHANNEL f2 ========
CPDPRG[2              garp
NUC2                   13C
P3                   18.50 usec
P4                   37.00 usec
P14                1000.00 usec
PCPD2                65.00 usec
PL0                 120.00 dB
PL2                  -3.00 dB
PL12                  7.91 dB
PL0W        0 W
PL2W          150.35617065 W
PL12W          12.19330025 W
SFO2         150.9133722 MHz
```

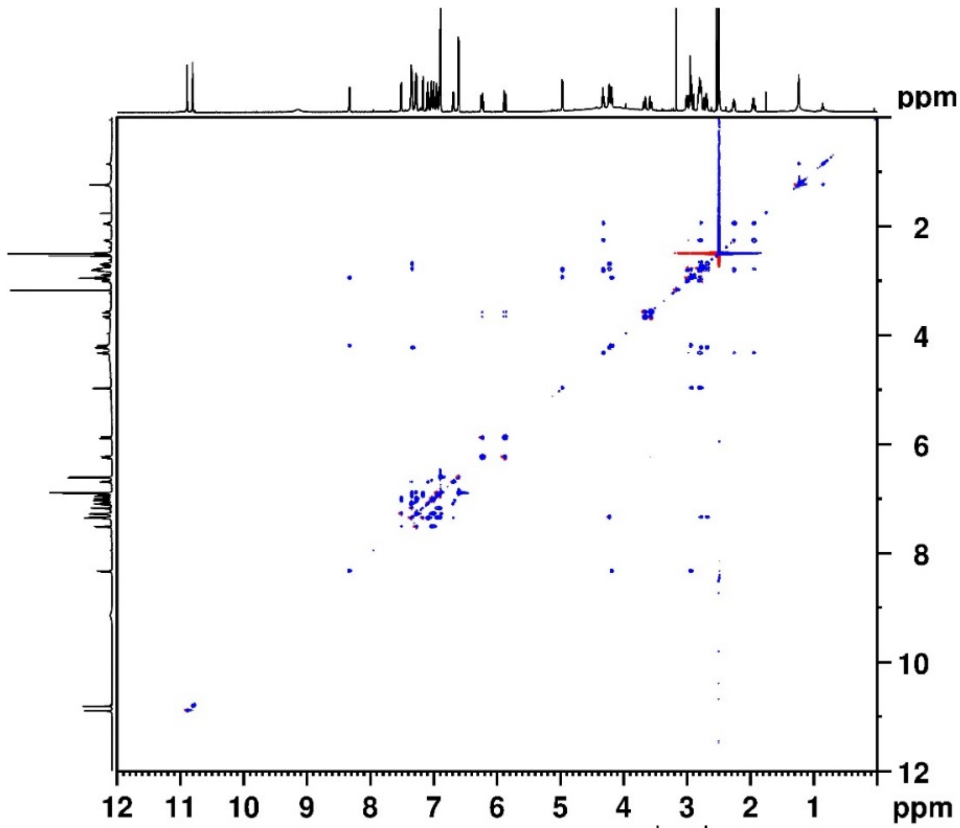



```
Current Data Parameters
NAME          KL-5-2_pHPLC
EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130516
Time                 22.00
INSTRUM              av600
PROBHD     5 mm TBI5
PULPROG      hmbcgplpndqf
TD                    2048
SOLVENT               DMSO
NS                      16
DS                      64
SWH               6887.052 Hz
FIDRES            3.362818 Hz
AQ               0.1486848 sec
RG                   26008
DW                  72.600 usec
DE                    6.00 usec
TE                   296.0 K
CNST2          145.0000000
CNST13           7.0000000
D0              0.00000300 sec
D1              1.20000005 sec
D2              0.00344828 sec
D6              0.07142857 sec
D16             0.00020000 sec
IN0             0.00001745 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.70 usec
P2                   19.40 usec
PL1                  -2.00 dB
PL1W           39.81071854 W
SFO1         600.1334507 MHz

======== CHANNEL f2 ========
NUC2                   13C
P3                   18.50 usec
PL2                  -3.00 dB
PL2W          150.35617065 W
SFO2         150.9156357 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPNAM[3]          SINE.100
GPX1        0 %
GPX2        0 %
GPX3        0 %
GPY1        0 %
GPY2        0 %
```

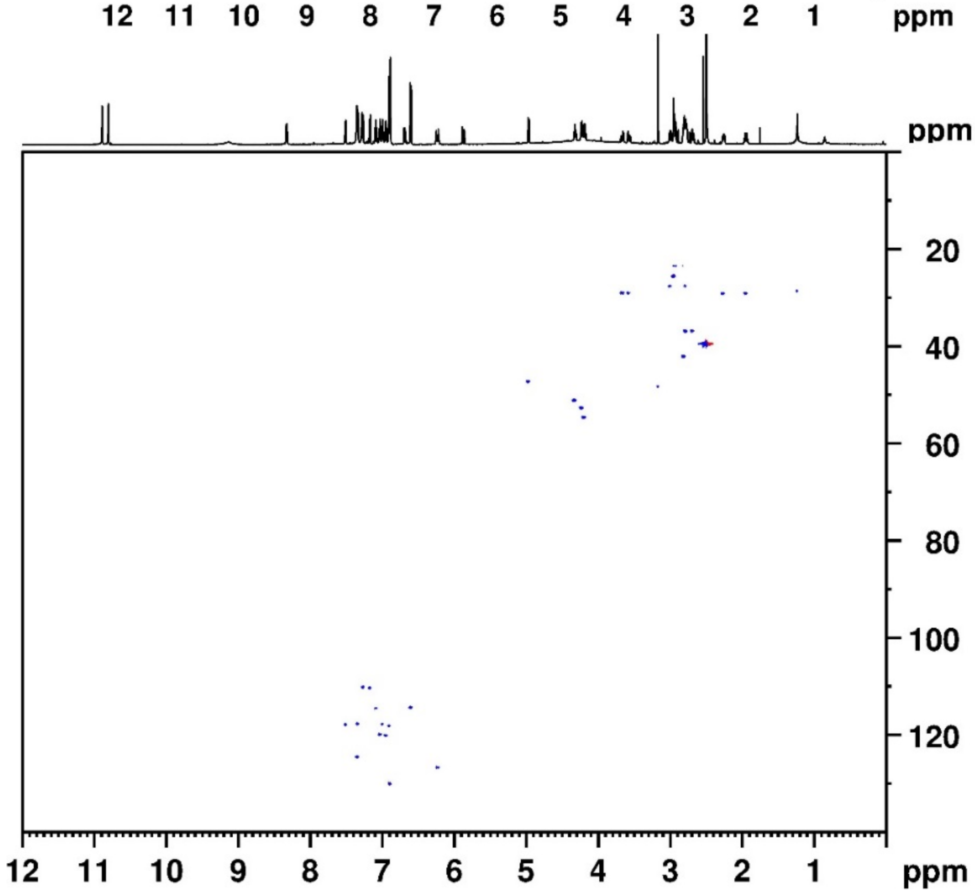
*Macrocyclic Product **2.28a***



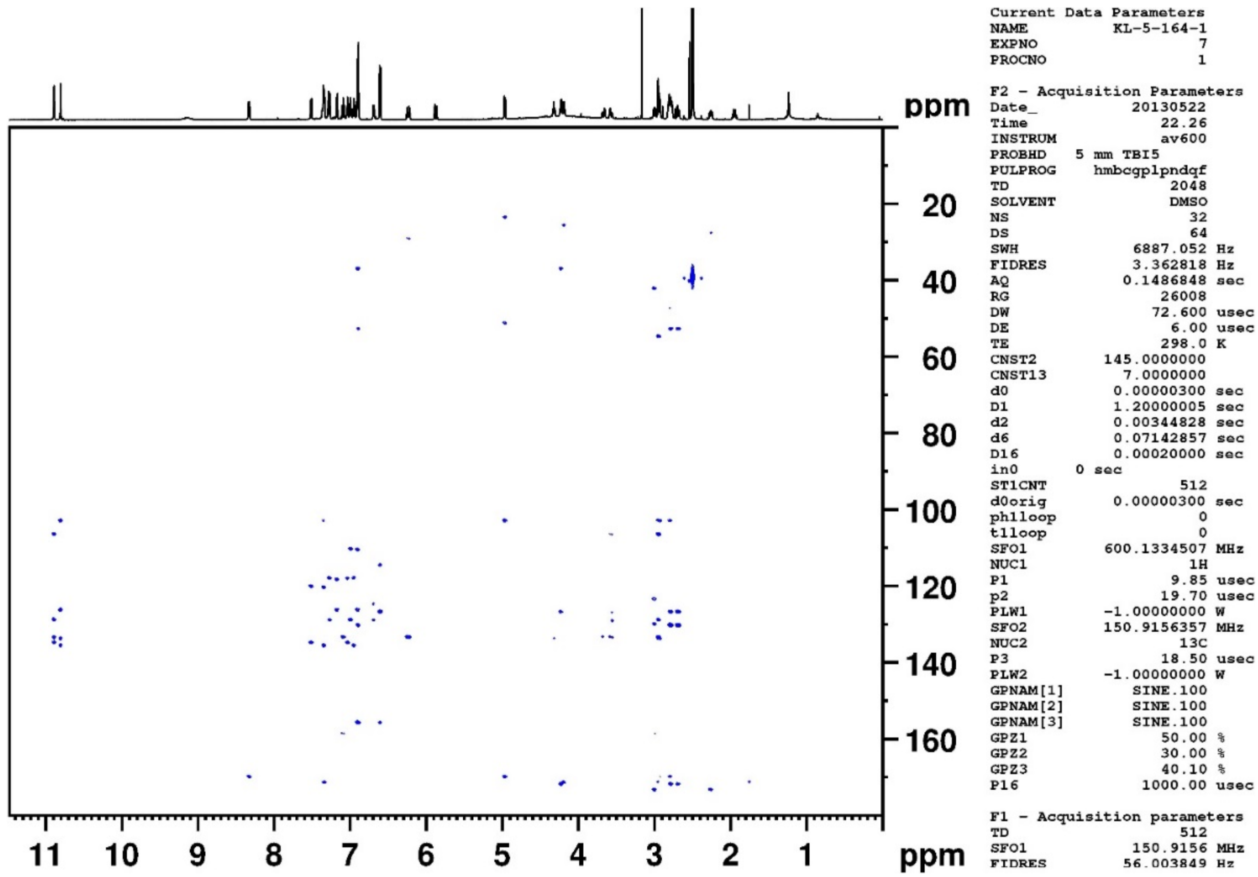





```
Current Data Parameters
NAME            KL-5-164-1
EXPNO                    4
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130522
Time                 18.31
INSTRUM              av600
PROBHD    5 mm TBI5
PULPROG        mlevetgp.js
TD                    4096
SOLVENT               DMSO
NS                       4
DS                      16
SWH              7183.908 Hz
FIDRES           1.753884 Hz
AQ              0.2850816 sec
RG                    90.5
DW                  69.600 usec
DE                    6.50 usec
TE                   298.0 K
D0              0.00000300 sec
D1              1.20000005 sec
D9              0.06000000 sec
D11             0.03000000 sec
D12             0.00002000 sec
D16             0.00020000 sec
IN0             0.00013885 sec
L1                      24

======== CHANNEL f1 ========
NUC1                    1H
P1                    9.85 usec
P2                   19.70 usec
P5                   26.68 usec
P6                   40.00 usec
P7                   80.00 usec
P17                2500.00 usec
PL1                  -2.00 dB
PL10                  9.54 dB
PL1W           39.81071854 W
PL10W           2.79254389 W
SFO1          600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1                 30.00 %
GPZ2                 30.00 %
```




```
Current Data Parameters
NAME            KL-5-164-1
EXPNO                    6
PROCNO                   1

F2 - Acquisition Parameters
Date_             20130522
Time                 20.51
INSTRUM              av600
PROBHD    5 mm TBI5
PULPROG       hsqcetgpsisp
TD                    2048
SOLVENT               DMSO
NS                       8
DS                      16
SWH              7183.908 Hz
FIDRES           3.507768 Hz
AQ              0.1425408 sec
RG                   16384
DW                  69.600 usec
DE                    6.00 usec
TE                   298.1 K
CNST2          145.0000000
d0              0.00000300 sec
D1              1.20000005 sec
d4              0.00172414 sec
d11             0.03000000 sec
D16             0.00020000 sec
D24             0.00086200 sec
DELTA           0.00127570 sec
DELTA1          0.00120632 sec
DELTA2          0.00122414 sec
in0         0 sec
ST1CNT                 256
ZGOPTNS
d0orig          0.00000300 sec
ph1loop                  0
t1loop                   0
SFO1          600.1330006 MHz
NUC1                    1H
P1                    9.85 usec
p2                   19.70 usec
P28                1000.00 usec
PLW1           -1.00000000 W
SFO2          150.9133722 MHz
NUC2                   13C
CPDPRG[2              garp
P3                   18.50 usec
p4                   37.00 usec
P14                1000.00 usec
PCPD2                65.00 usec
PLW0           -1.00000000 W
PLW2           -1.00000000 W
PLW12          -1.00000000 W
SPNAM[3]  Crp80.0.5.20.1
```


ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1
ppm
Current Data Parameters
NAME KL-5-164-1
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130522
Time 22.26
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 32
DS 64
SWH 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1486848 sec
RG 26008
DW 72.600 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
CNST13 7.0000000
d0 0.00000300 sec
D1 1.20000005 sec
d2 0.00344828 sec
d6 0.07142857 sec
D16 0.00020000 sec
in0 0 sec
ST1CNT 512
d0orig 0.00000300 sec
ph1loop 0
t1loop 0
SFO1 600.1334507 MHz
NUC1 1H
P1 9.85 usec
p2 19.70 usec
PLW1 -1.00000000 W
SFO2 150.9156357 MHz
NUC2 13C
P3 18.50 usec
PLW2 -1.00000000 W
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 512
SFO1 150.9156 MHz
FIDRES 56.003849 Hz

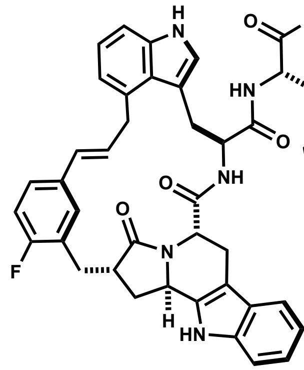
*Macrocyclic Product **2.28b***

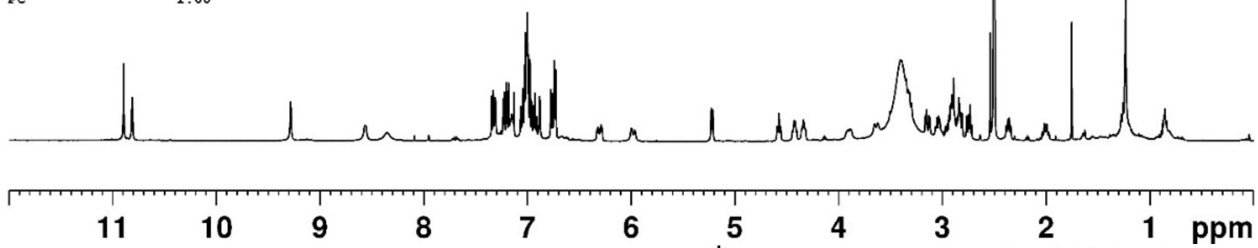
Current Data Parameters
NAME KL-5-255-2 (AV500)
EXPNO 6
PROCNO 1

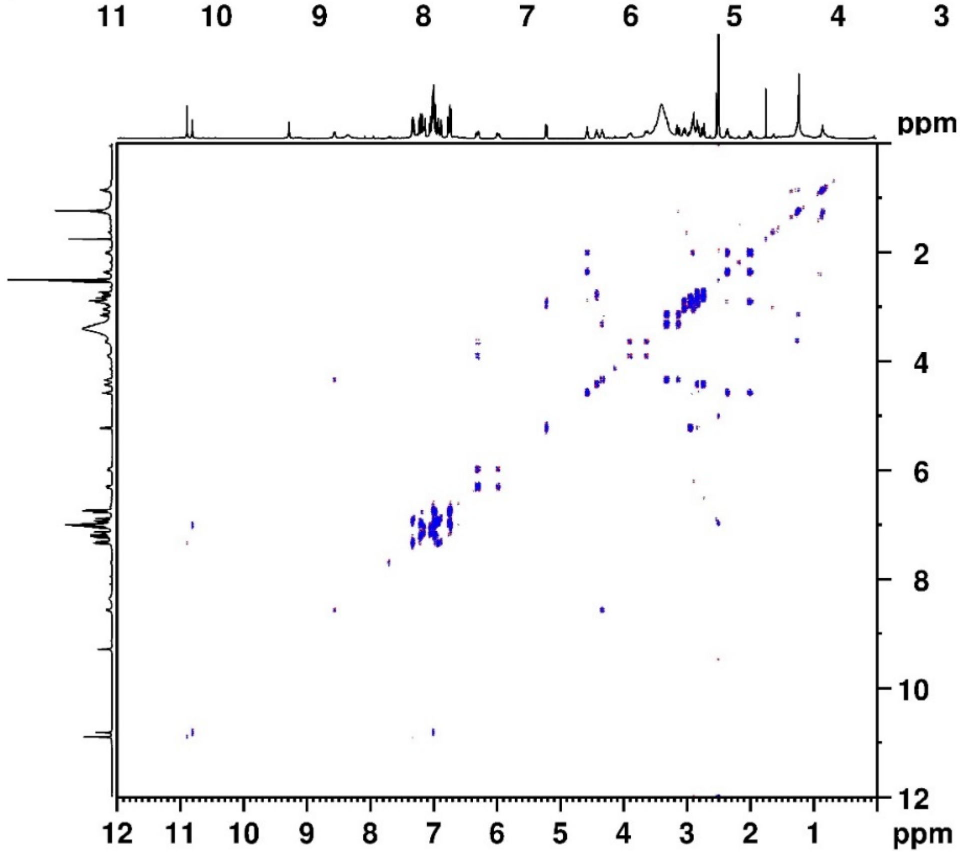
F2 - Acquisition Parameters
Date_ 20140218
Time 20.49
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG zg
TD 65536
SOLVENT DMSO
NS 32
DS 0
SWH 10000.000 Hz
FIDRES 0.152588 Hz
AQ 3.2767999 sec
RG 19.07
DW 50.000 usec
DE 10.00 usec
TE 298.0 K
D1 2.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
P1 9.95 usec
PLW1 13.50000000 W

F2 - Processing parameters
SI 65536
SF 500.1300037 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00







Current Data Parameters
NAME KL-5-255-2 (AV500)
EXPNO 8
PROCNO 1

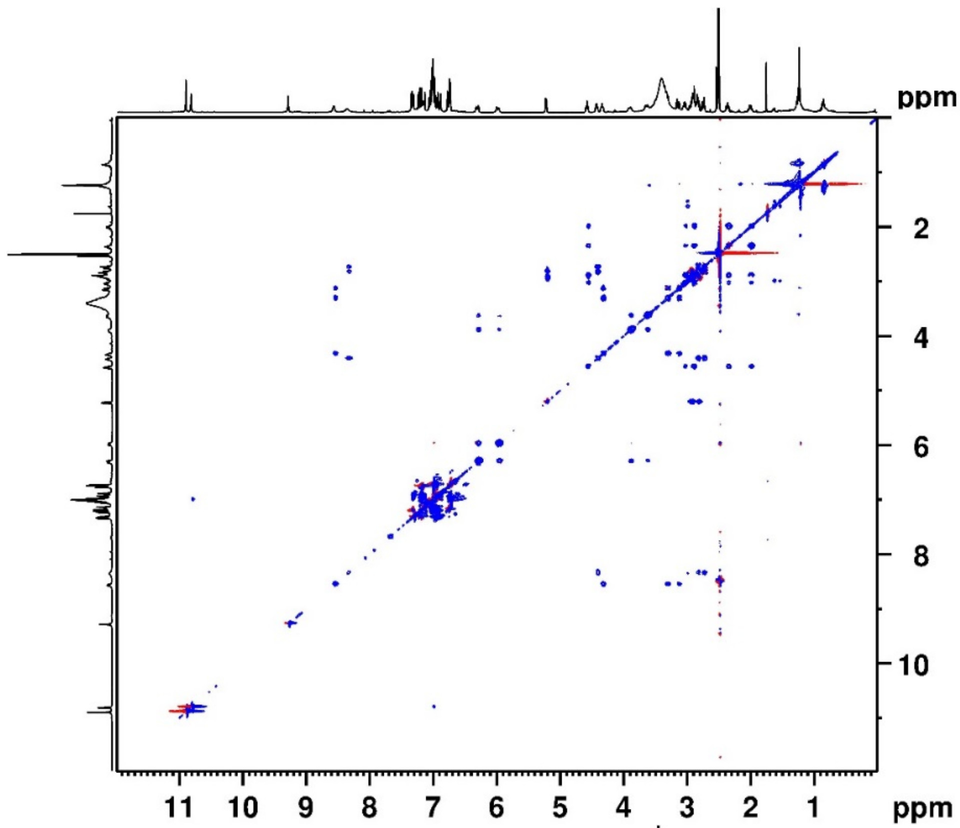
F2 - Acquisition Parameters
Date_ 20140218
Time 21.29
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG cosygpmfph
TD 4096
SOLVENT DMSO
NS 2
DS 8
SWH 6009.615 Hz
FIDRES 1.467191 Hz
AQ 0.3407872 sec
RG 26.58
DW 83.200 usec
DE 10.00 usec
TE 298.0 K
D0 0.00007063 sec
D1 2.00000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00016660 sec

======== CHANNEL f1 ========
SFO1 500.1330008 MHz
NUC1 1H
P1 9.95 usec
P2 19.90 usec
PLW1 13.50000000 W

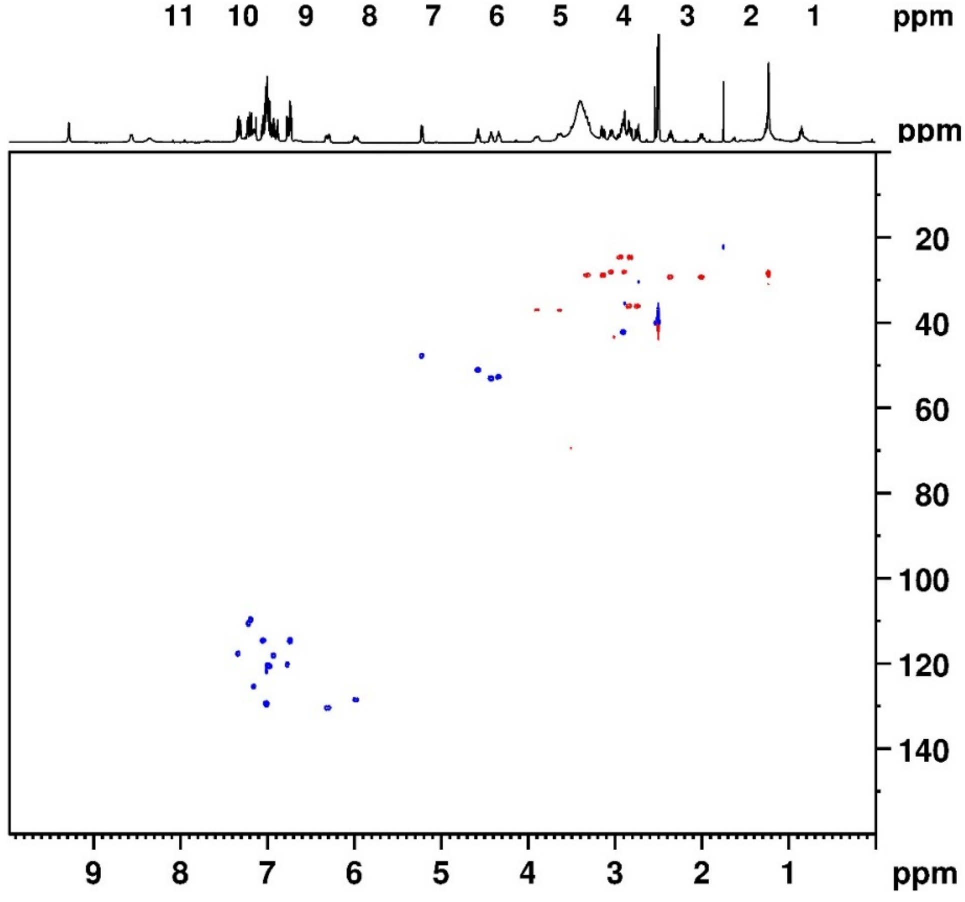
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 500.133 MHz
FIDRES 11.723439 Hz
SW 12.002 ppm
FnMODE States-TPPI

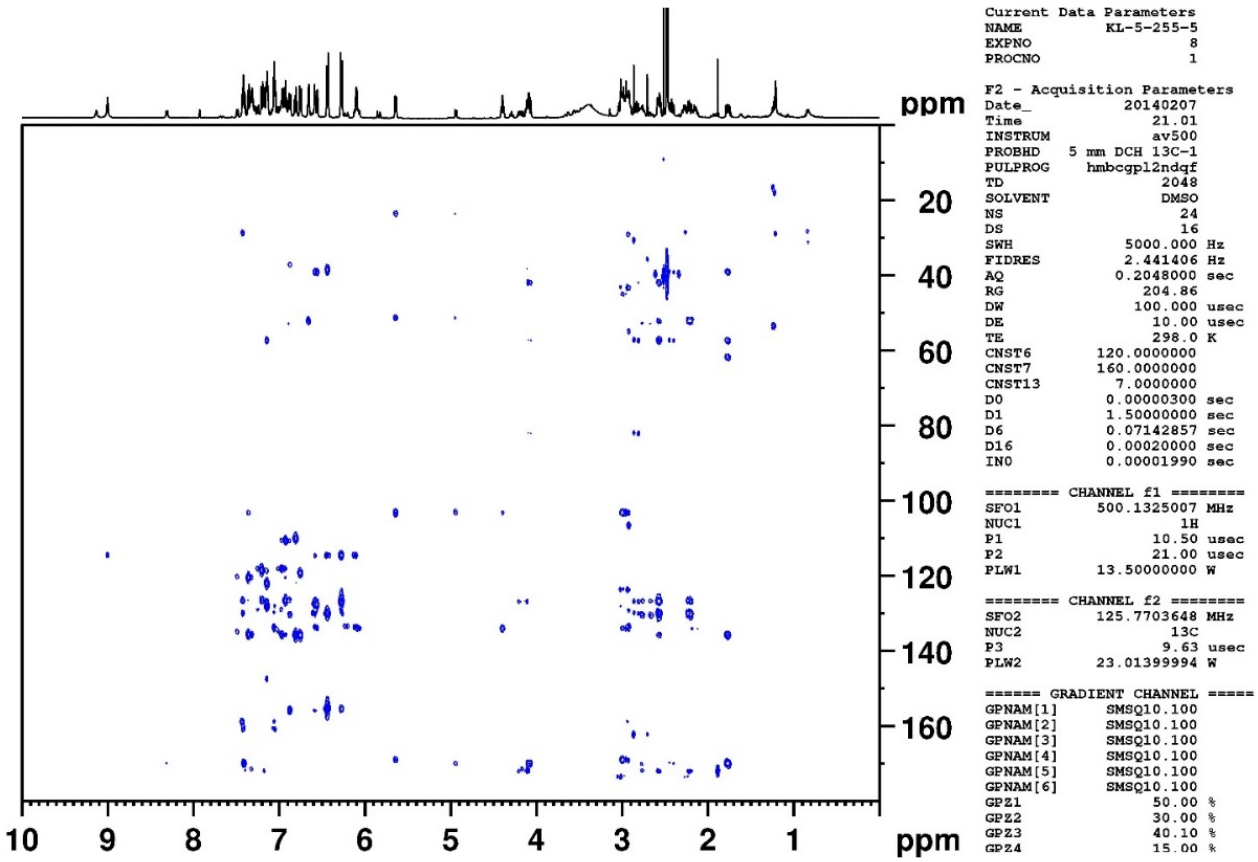
F2 - Processing parameters
SI 2048
SF 500.1300026 MHz
WDW SINE
SSB 1




```
Current Data Parameters
NAME      KL-5-255-2 (AV500)
EXPNO                      7
PROCNO                     1

F2 - Acquisition Parameters
Date_              20140218
Time                  20.49
INSTRUM               av500
PROBHD   5 mm DCH 13C-1
PULPROG         mlevetgp.js
TD                     2048
SOLVENT                DMSO
NS                        2
DS                        8
SWH              6009.615 Hz
FIDRES           2.934382 Hz
AQ              0.1703936 sec
RG                    26.58
DW                 83.200 usec
DE                  10.00 usec
TE                  298.0 K
D0             0.00000300 sec
D1             2.00000000 sec
D9             0.06000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
D16            0.00020000 sec
IN0            0.00016660 sec
L1                       24

======== CHANNEL f1 ========
SFO1         500.1330008 MHz
NUC1                     1H
P1                     9.95 usec
P2                    19.90 usec
P5                    26.68 usec
P6                    40.00 usec
P7                    80.00 usec
P17                 2500.00 usec
PLW1            13.50000000 W
PLW10            0.84375000 W

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPZ1                 30.00 %
GPZ2                 30.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                      512
SFO1                500.133 MHz
FIDRES            11.723439 Hz
```

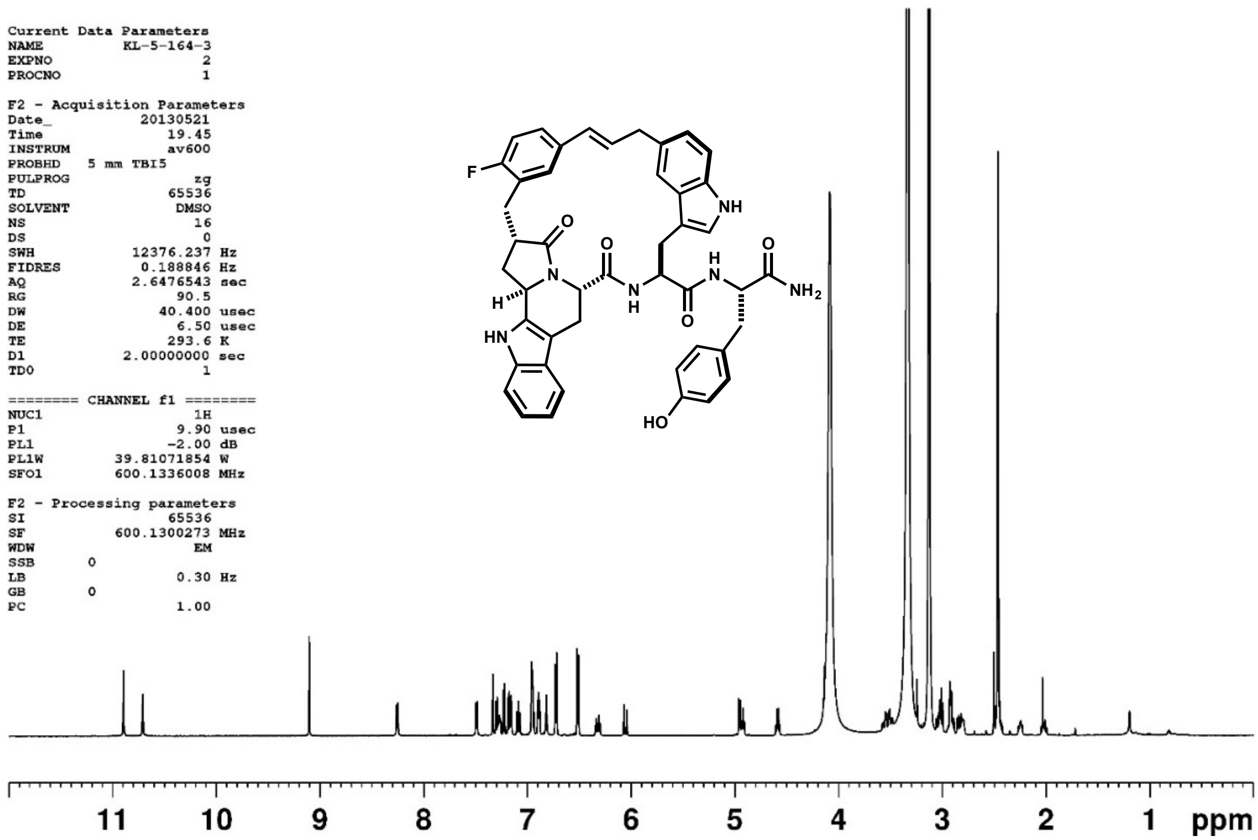


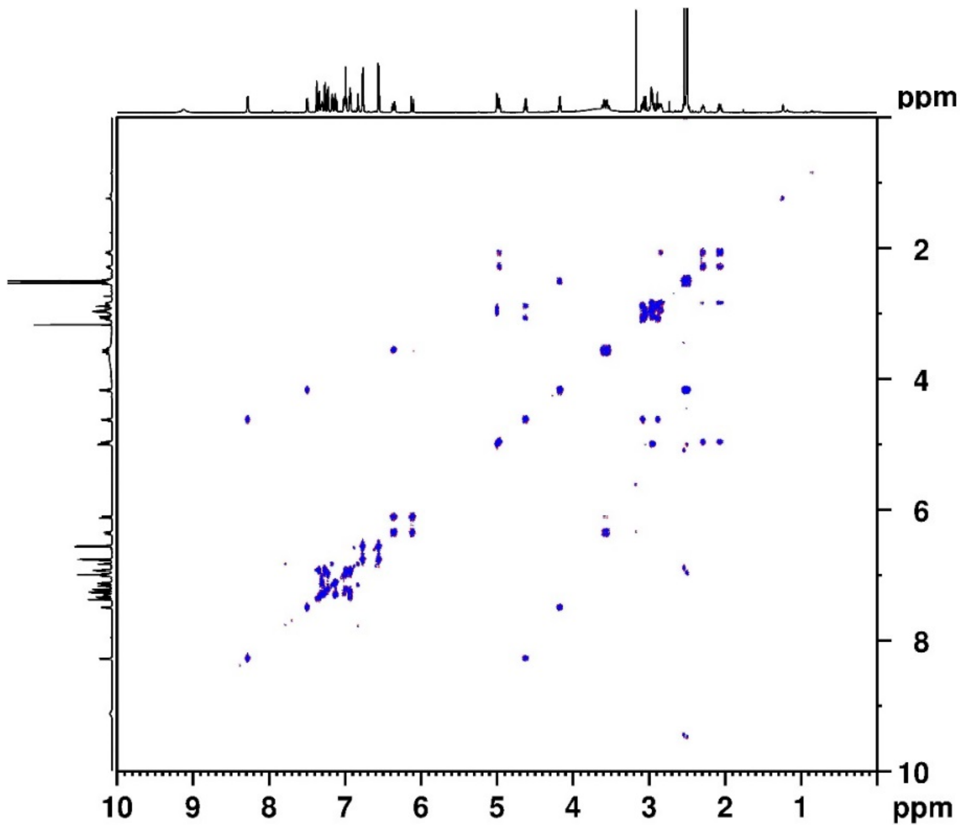

```
Current Data Parameters
NAME      KL-5-255-2 (AV500)
EXPNO                      9
PROCNO                     1

F2 - Acquisition Parameters
Date_              20140218
Time                  22.10
INSTRUM               av500
PROBHD   5 mm DCH 13C-1
PULPROG          hsqcedetgp
TD                     2048
SOLVENT                DMSO
NS                       16
DS                       16
SWH              5000.000 Hz
FIDRES           2.441406 Hz
AQ              0.2048000 sec
RG                   204.86
DW                100.000 usec
DE                  10.00 usec
TE                  298.0 K
CNST2          145.0000000
D0             0.00000300 sec
D1             1.50000000 sec
D4             0.00172414 sec
D11            0.03000000 sec
D13            0.00000400 sec
D16            0.00020000 sec
D21            0.00345000 sec
IN0            0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1         500.1325007 MHz
NUC1                     1H
P1                     9.95 usec
P2                    19.90 usec
P28        0 usec
PLW1            13.50000000 W

======== CHANNEL f2 ========
SFO2         125.7678496 MHz
NUC2                    13C
CPDPRG[2                garp
P3                     9.63 usec
P4                    19.26 usec
PCPD2                 70.00 usec
PLW2            23.01399994 W
PLW12            0.43557000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPZ1                 80.00 %
```



ppm
20
40
60
80
100
120
140
160
10
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME KL-5-255-5
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140207
Time 21.01
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 204.86
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.50 usec
P2 21.00 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7703648 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

*Macrocyclic Product **2.28c***





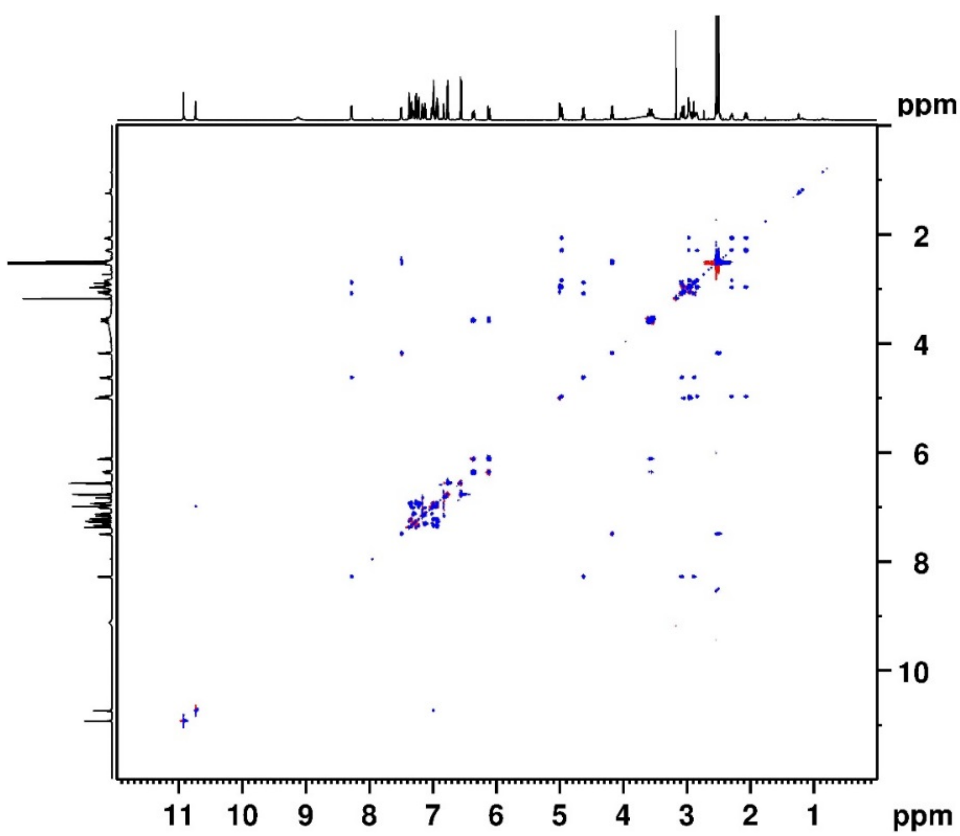
Current Data Parameters
NAME KL-5-164-3
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130523
Time 20.06
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG cosygpmfph
TD 2048
SOLVENT DMSO
NS 2
DS 16
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 90.5
DW 69.600 usec
DE 6.50 usec
TE 298.0 K
D0 0.00005657 sec
D1 2.00000000 sec
D13 0.00000400 sec
D16 0.00020000 sec
IN0 0.00013885 sec

======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
P2 20.20 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 10.00 %
GPZ2 20.00 %
P16 1000.00 usec

F1 - Acquisition parameters
TD 512
SFO1 600.1336 MHz
FIDRES 14.065631 Hz
SW 12.000 ppm
FnMODE States-TPPI

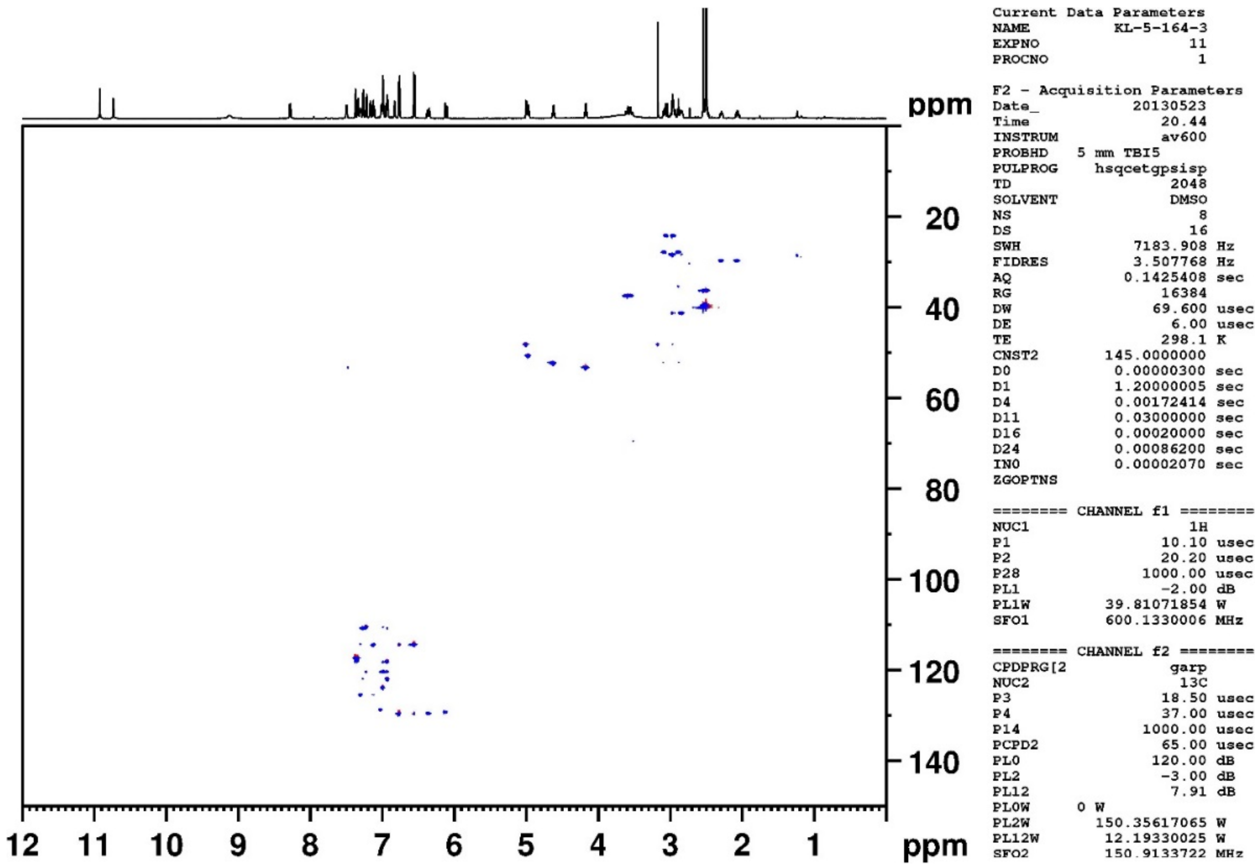


Current Data Parameters
NAME KL-5-164-3
EXPNO 9
PROCNO 1

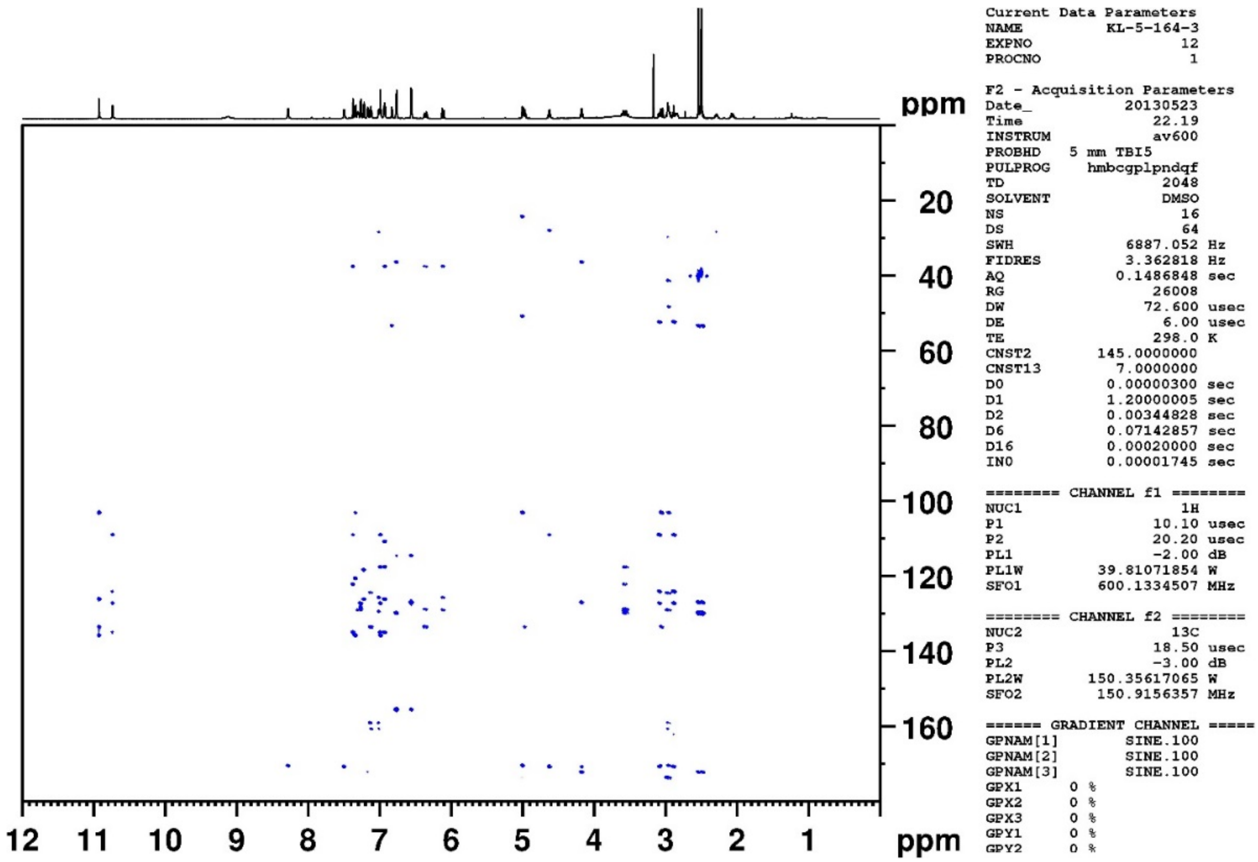
F2 - Acquisition Parameters
Date_ 20130523
Time 19.33
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG mlevetgp.js
TD 4096
SOLVENT DMSO
NS 2
DS 16
SWH 7183.908 Hz
FIDRES 1.753884 Hz
AQ 0.2850816 sec
RG 90.5
DW 69.600 usec
DE 6.50 usec
TE 298.0 K
D0 0.00000300 sec
D1 1.20000005 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00013885 sec
L1 24

======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
P2 20.20 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PL1 -2.00 dB
PL10 9.54 dB
PL1W 39.81071854 W
PL10W 2.79254389 W
SFO1 600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GPZ1 30.00 %
GPZ2 30.00 %



Current Data Parameters
NAME KL-5-164-3
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130523
Time 20.44
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 8
DS 16
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 16384
DW 69.600 usec
DE 6.00 usec
TE 298.1 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
P2 20.20 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1330006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 18.50 usec
P4 37.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.91 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 12.19330025 W
SFO2 150.9133722 MHz
ppm
20
40
60
80
100
120
140
12 11 10 9 8 7 6 5 4 3 2 1 ppm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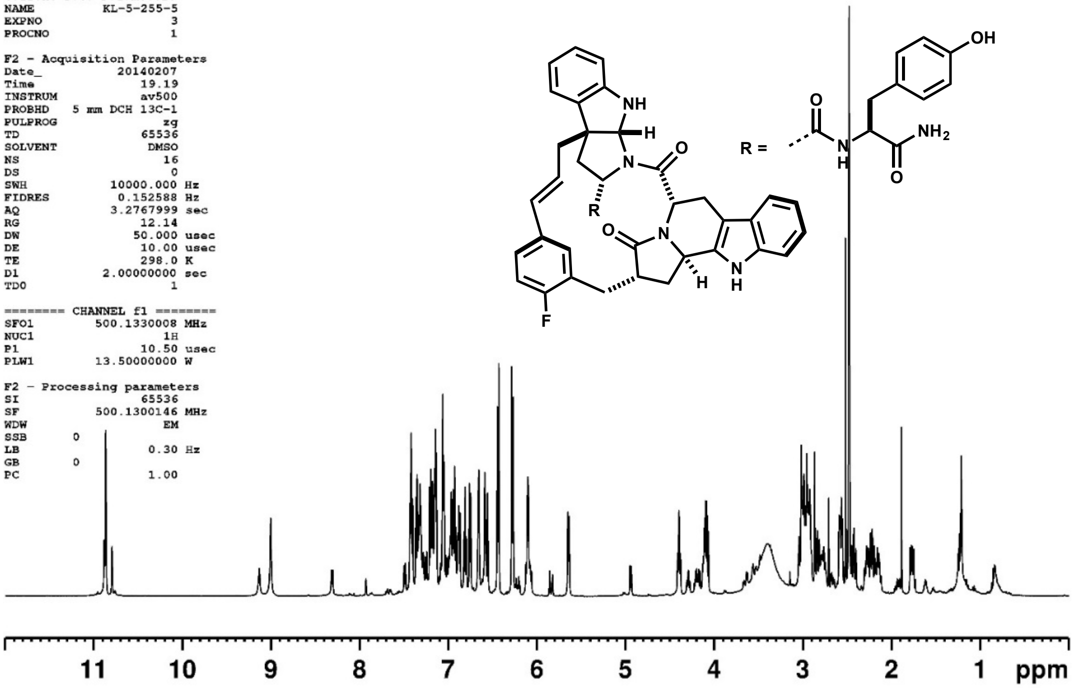
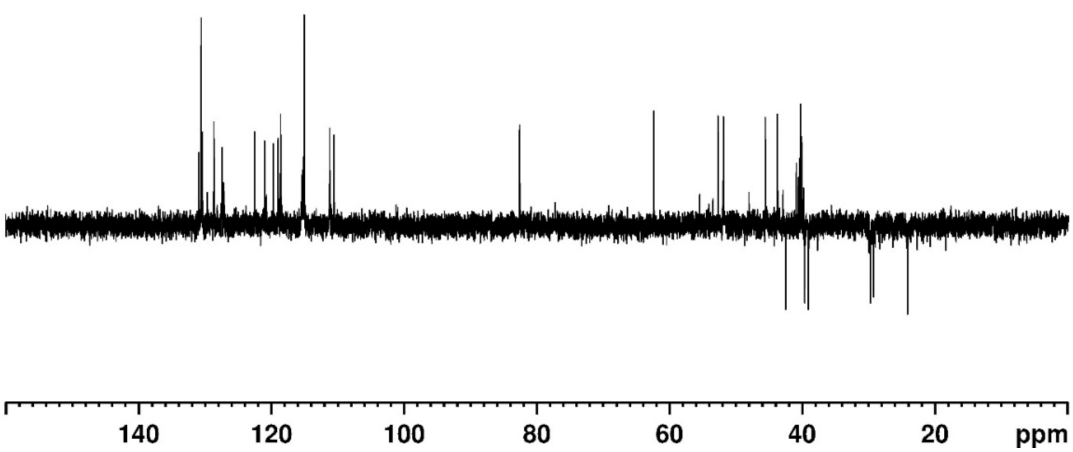
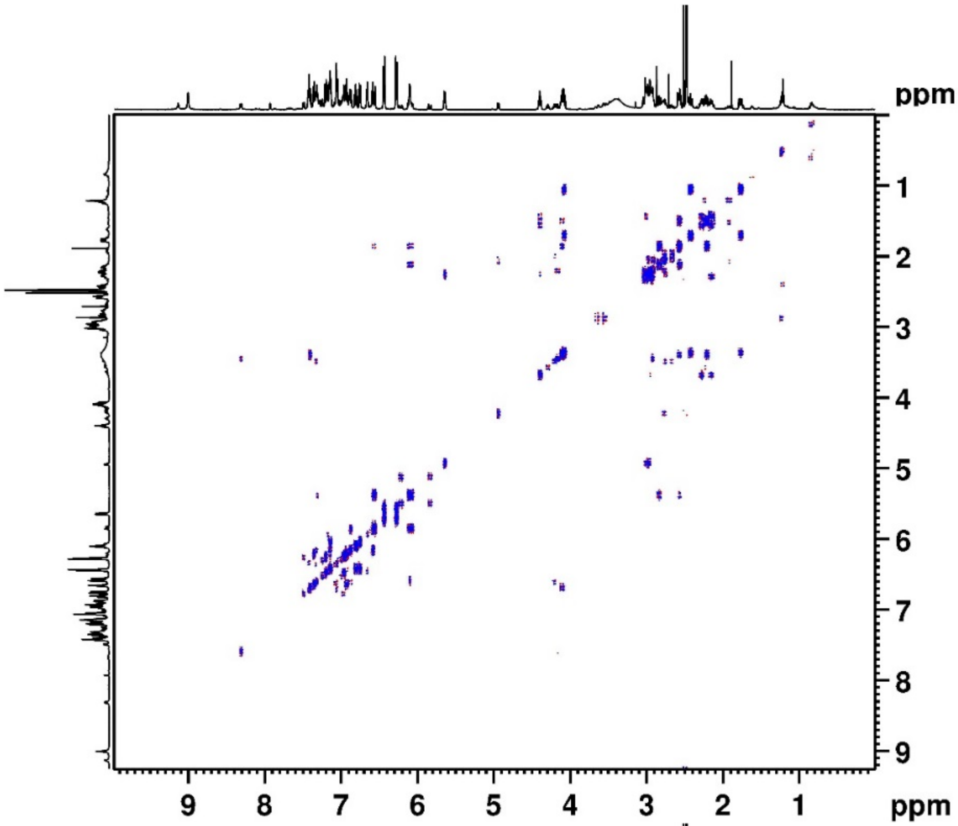
EXPNO 12
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130523
Time 22.19
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 16
DS 64
SWH 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1486848 sec
RG 26008
DW 72.600 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 10.10 usec
P2 20.20 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1334507 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %
ppm
20
40
60
80
100
120
140
160
12 11 10 9 8 7 6 5 4 3 2 1 ppm

Macrocyclic Product ***2.28e***

```
Current Data Parameters
NAME          KL-5-255-5
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20140207
Time               19.19
INSTRUM            av500
PROBHD   5 mm DCH 13C-1
PULPROG               zg
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     0
SWH            10000.000 Hz
FIDRES          0.152588 Hz
AQ             3.2767999 sec
RG                 12.14
DW                50.000 usec
DE                 10.00 usec
TE                 298.0 K
D1            2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         500.1330008 MHz
NUC1                  1H
P1                 10.50 usec
PLW1         13.50000000 W

F2 - Processing parameters
SI                 65536
SF           500.1300146 MHz
WDW                   EM
SSB      0
LB                  0.30 Hz
GB       0
PC                  1.00
```





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Current Data Parameters
NAME            KL-5-255-5
EXPNO                    6
PROCNO                   1

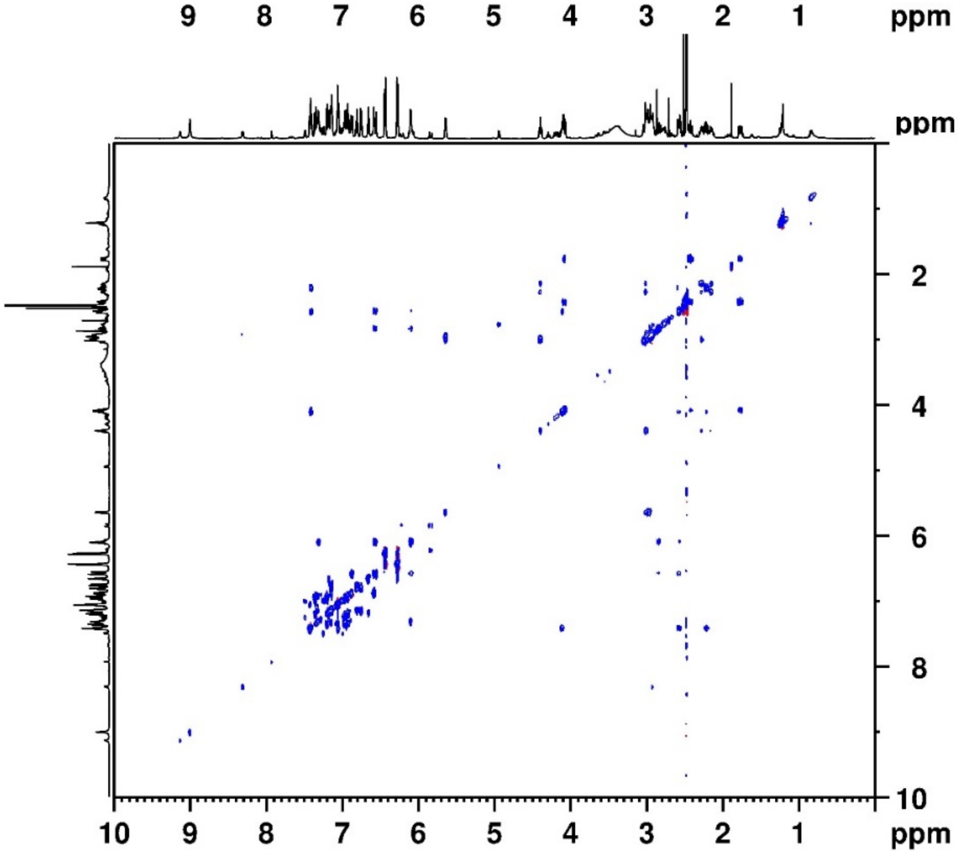
F2 - Acquisition Parameters
Date_             20140207
Time                 19.40
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG        cosygpmfph
TD                    4096
SOLVENT               DMSO
NS                       2
DS                       8
SWH               5000.000 Hz
FIDRES            1.220703 Hz
AQ               0.4096000 sec
RG                  204.86
DW                 100.000 usec
DE                   10.00 usec
TE                   298.0 K
D0              0.00008663 sec
D1              2.00000000 sec
D13             0.00000400 sec
D16             0.00020000 sec
IN0             0.00020000 sec

======== CHANNEL f1 ========
SFO1           500.1325007 MHz
NUC1                    1H
P1                   10.50 usec
P2                   21.00 usec
PLW1           13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPZ1                 10.00 %
GPZ2                 20.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     256
SFO1              500.1325 MHz
FIDRES           19.531250 Hz
SW                   9.997 ppm
FnMODE         States-TPPI

F2 - Processing parameters
SI                    4096
SF             500.1300135 MHz
WDW                   SINE
SSB                      1
```



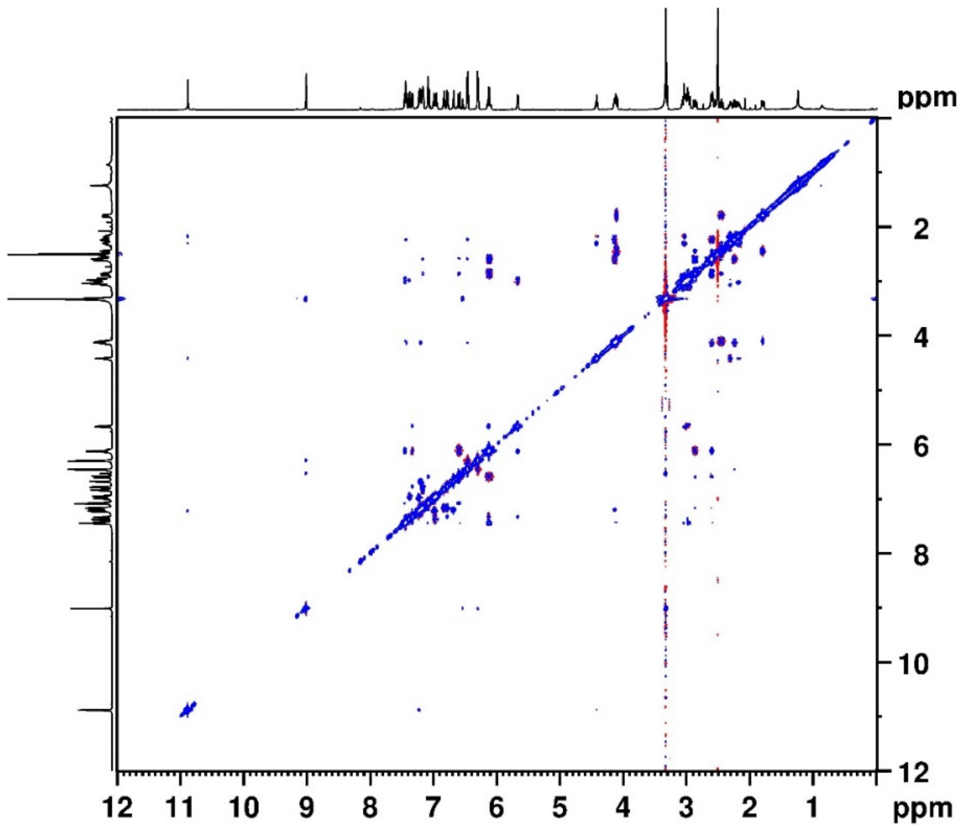

```
Current Data Parameters
NAME            KL-5-255-5
EXPNO                    5
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140207
Time                 19.20
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG        mlevetgp.js
TD                    2048
SOLVENT               DMSO
NS                       2
DS                       8
SWH               5000.000 Hz
FIDRES            2.441406 Hz
AQ               0.2048000 sec
RG                   42.28
DW                 100.000 usec
DE                   10.00 usec
TE                   298.0 K
D0              0.00000300 sec
D1              2.00000000 sec
D9              0.06000000 sec
D11             0.03000000 sec
D12             0.00002000 sec
D16             0.00020000 sec
IN0             0.00020000 sec
L1                      24

======== CHANNEL f1 ========
SFO1           500.1325007 MHz
NUC1                    1H
P1                   10.50 usec
P2                   21.00 usec
P5                   26.68 usec
P6                   40.00 usec
P7                   80.00 usec
P17                2500.00 usec
PLW1           13.50000000 W
PLW10           0.84375000 W

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPNAM[2]          SINE.100
GPZ1                 30.00 %
GPZ2                 30.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     256
SFO1              500.1325 MHz
FIDRES           19.531250 Hz
```

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Current Data Parameters
NAME      KL-5-255-5_HCO2H
EXPNO                    7
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140214
Time                  0.09
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG         noesygpph
TD                    2048
SOLVENT               DMSO
NS                      24
DS                       8
SWH               6009.615 Hz
FIDRES            2.934382 Hz
AQ               0.1703936 sec
RG                   26.58
DW                  83.200 usec
DE                   10.00 usec
TE                   298.0 K
D0              0.00007047 sec
D1              4.00000000 sec
D8              0.10000000 sec
D16             0.00020000 sec
IN0             0.00016640 sec

======== CHANNEL f1 ========
SFO1           500.1330008 MHz
NUC1                    1H
P1                   10.00 usec
P2                   20.00 usec
PLW1           13.50000000 W

====== GRADIENT CHANNEL =====
GPNAM[1]          SINE.100
GPZ1                 40.00 %
P16                1000.00 usec

F1 - Acquisition parameters
TD                     256
SFO1               500.133 MHz
FIDRES           23.475060 Hz
SW                  12.016 ppm
FnMODE         States-TPPI

F2 - Processing parameters
SI                    2048
SF             500.1300028 MHz
WDW                  QSINE
SSB                      2
LB        0 Hz
GB        0
```
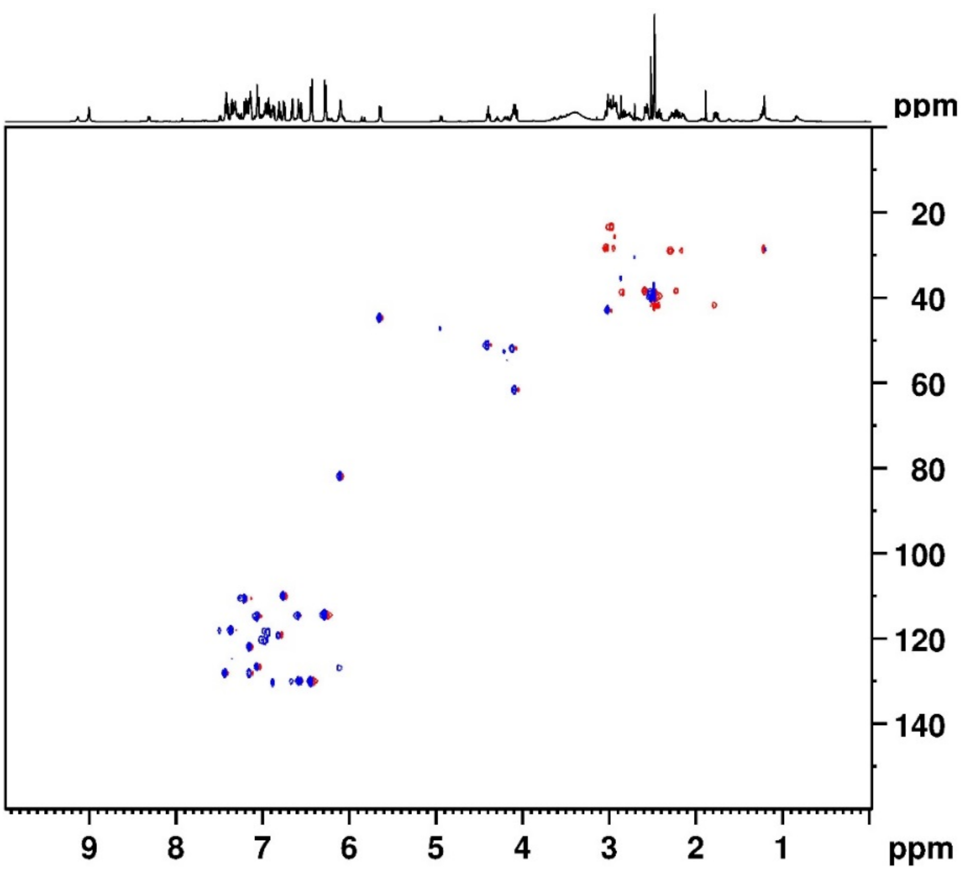
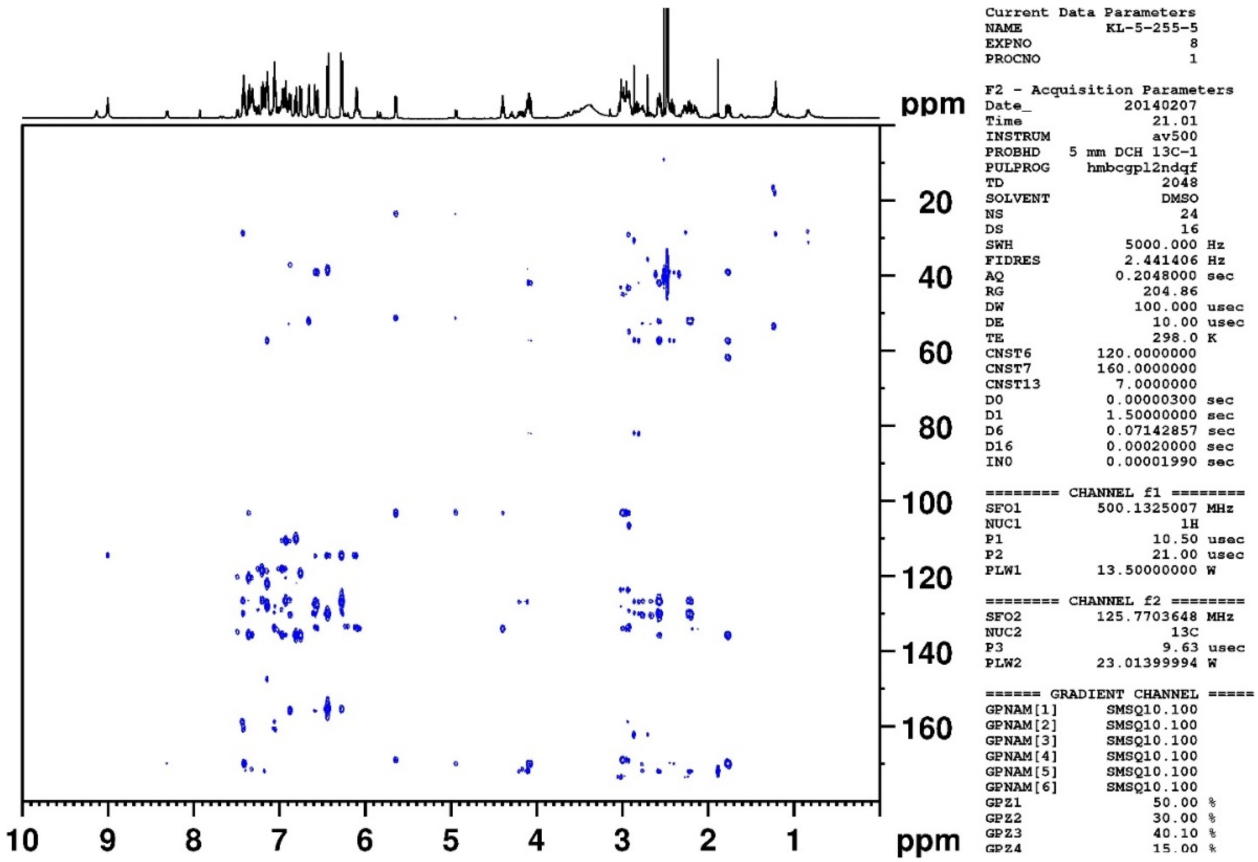
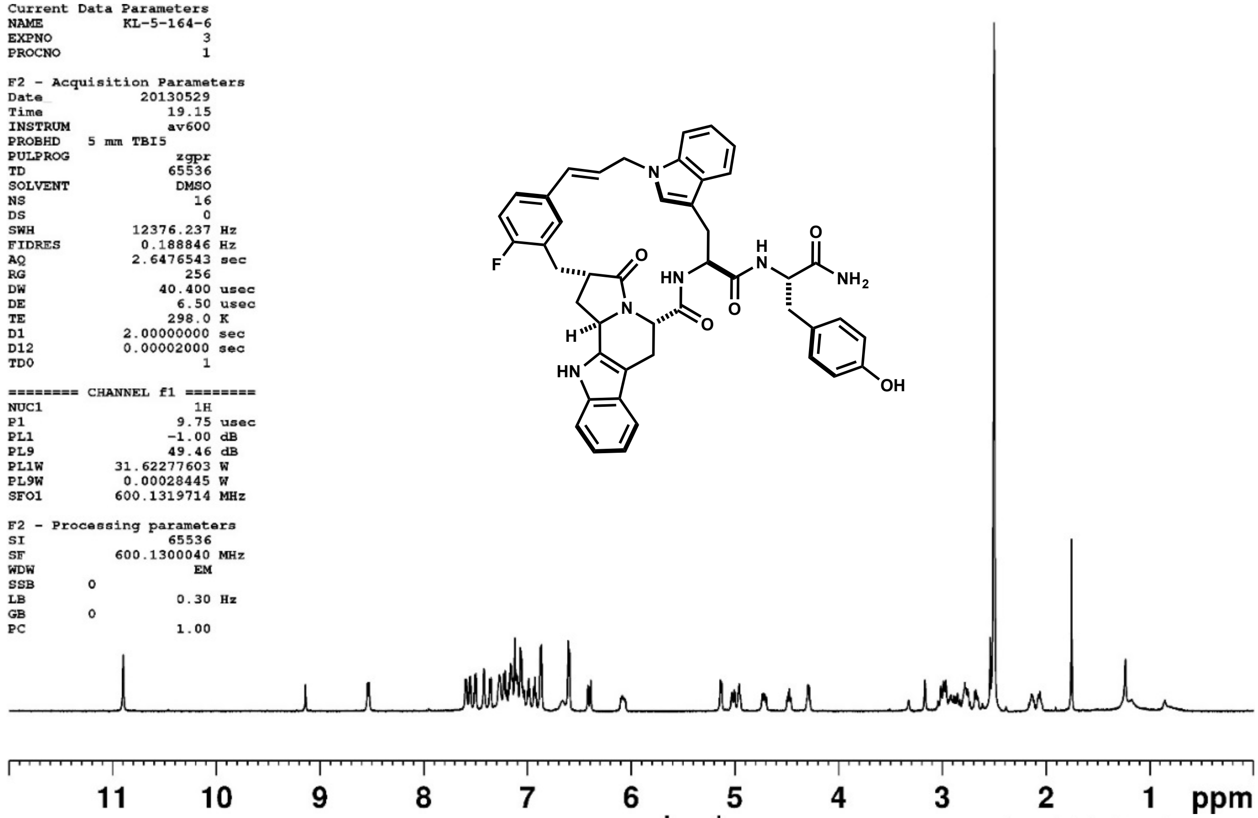



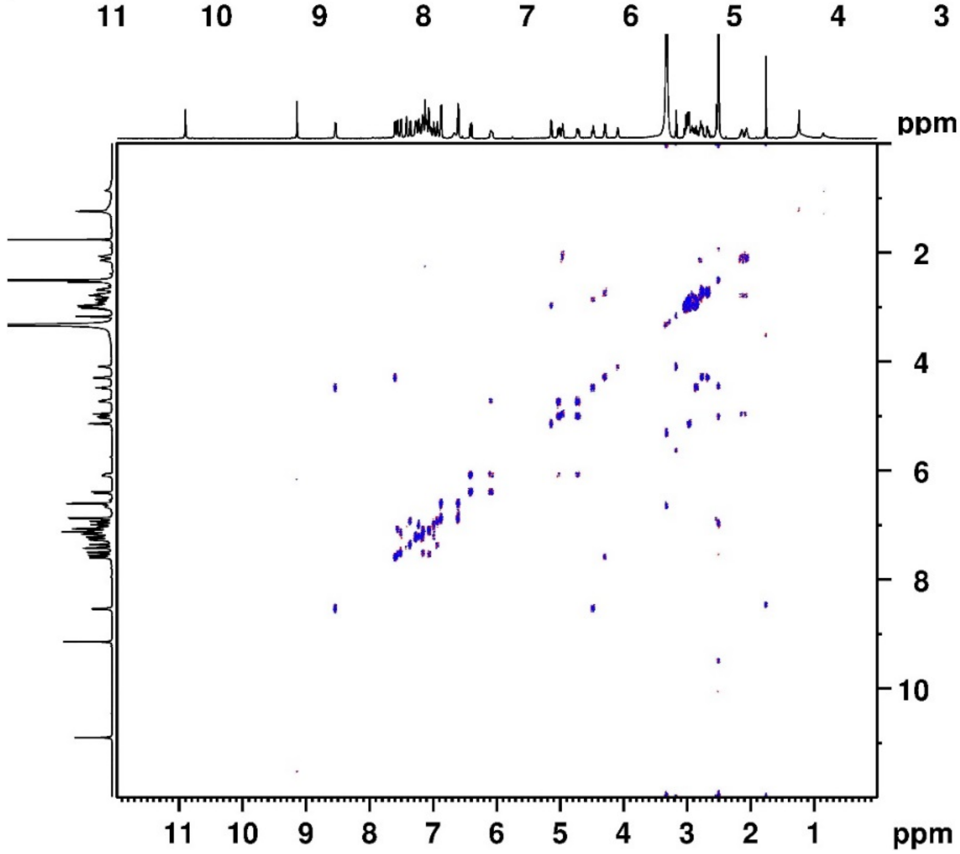

```
Current Data Parameters
NAME           KL-5-255-5
EXPNO                    7
PROCNO                   1

F2 - Acquisition Parameters
Date_             20140207
Time                 20.01
INSTRUM              av500
PROBHD   5 mm DCH 13C-1
PULPROG        hsqcedetgp
TD                    2048
SOLVENT               DMSO
NS                       8
DS                      16
SWH               5000.000 Hz
FIDRES            2.441406 Hz
AQ               0.2048000 sec
RG                  204.86
DW                 100.000 usec
DE                   10.00 usec
TE                   298.0 K
CNST2          145.0000000
D0              0.00000300 sec
D1              1.50000000 sec
D4              0.00172414 sec
D11             0.03000000 sec
D13             0.00000400 sec
D16             0.00020000 sec
D21             0.00345000 sec
IN0             0.00001990 sec
ZGOPTNS

======== CHANNEL f1 ========
SFO1           500.1325007 MHz
NUC1                    1H
P1                   10.50 usec
P2                   21.00 usec
P28       0 usec
PLW1           13.50000000 W

======== CHANNEL f2 ========
SFO2           125.7678496 MHz
NUC2                   13C
CPDPRG[2              garp
P3                    9.63 usec
P4                   19.26 usec
PCPD2                70.00 usec
PLW2           23.01399994 W
PLW12           0.43557000 W

====== GRADIENT CHANNEL =====
GPNAM[1]        SMSQ10.100
GPNAM[2]        SMSQ10.100
GPZ1                 80.00 %
```


ppm
20
40
60
80
100
120
140
160
10
9
8
7
6
5
4
3
2
1
ppm
Current Data Parameters
NAME KL-5-255-5
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20140207
Time 21.01
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG hmbcgpl2ndqf
TD 2048
SOLVENT DMSO
NS 24
DS 16
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 204.86
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
CNST6 120.0000000
CNST7 160.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.50000000 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001990 sec
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.50 usec
P2 21.00 usec
PLW1 13.50000000 W
======== CHANNEL f2 ========
SFO2 125.7703648 MHz
NUC2 13C
P3 9.63 usec
PLW2 23.01399994 W
====== GRADIENT CHANNEL =====
GPNAM[1] SMSQ10.100
GPNAM[2] SMSQ10.100
GPNAM[3] SMSQ10.100
GPNAM[4] SMSQ10.100
GPNAM[5] SMSQ10.100
GPNAM[6] SMSQ10.100
GPZ1 50.00 %
GPZ2 30.00 %
GPZ3 40.10 %
GPZ4 15.00 %

Macrocyclic Product ***2.28f***

```
Current Data Parameters
NAME          KL-5-164-6
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_          20130529
Time              19.15
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG            zgpr
TD                65536
SOLVENT            DMSO
NS                   16
DS                    0
SWH           12376.237 Hz
FIDRES         0.188846 Hz
AQ            2.6476543 sec
RG                  256
DW               40.400 usec
DE                 6.50 usec
TE                298.0 K
D1           2.00000000 sec
D12          0.00002000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.75 usec
PL1               -1.00 dB
PL9               49.46 dB
PL1W        31.62277603 W
PL9W         0.00028445 W
SFO1        600.1319714 MHz

F2 - Processing parameters
SI                65536
SF          600.1300040 MHz
WDW                  EM
SSB      0
LB                 0.30 Hz
GB       0
PC                 1.00
```



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Current Data Parameters
NAME          KL-5-164-6
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_          20130529
Time              20.28
INSTRUM           av600
PROBHD   5 mm TBI5
PULPROG      cosygpmfph
TD                 2048
SOLVENT            DMSO
NS                    4
DS                   16
SWH            7183.908 Hz
FIDRES         3.507768 Hz
AQ            0.1425408 sec
RG                  181
DW               69.600 usec
DE                 6.50 usec
TE                298.0 K
D0           0.00005695 sec
D1           2.00000000 sec
D13          0.00000400 sec
D16          0.00020000 sec
IN0          0.00013885 sec

======== CHANNEL f1 ========
NUC1                 1H
P1                 9.80 usec
P2                19.60 usec
PL1               -2.00 dB
PL1W        39.81071854 W
SFO1        600.1336008 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1        0 %
GPX2        0 %
GPY1        0 %
GPY2        0 %
GPZ1              10.00 %
GPZ2              20.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                  256
SFO1        600.1336 MHz
FIDRES        28.131262 Hz
SW               12.000 ppm
FnMODE      States-TPPI
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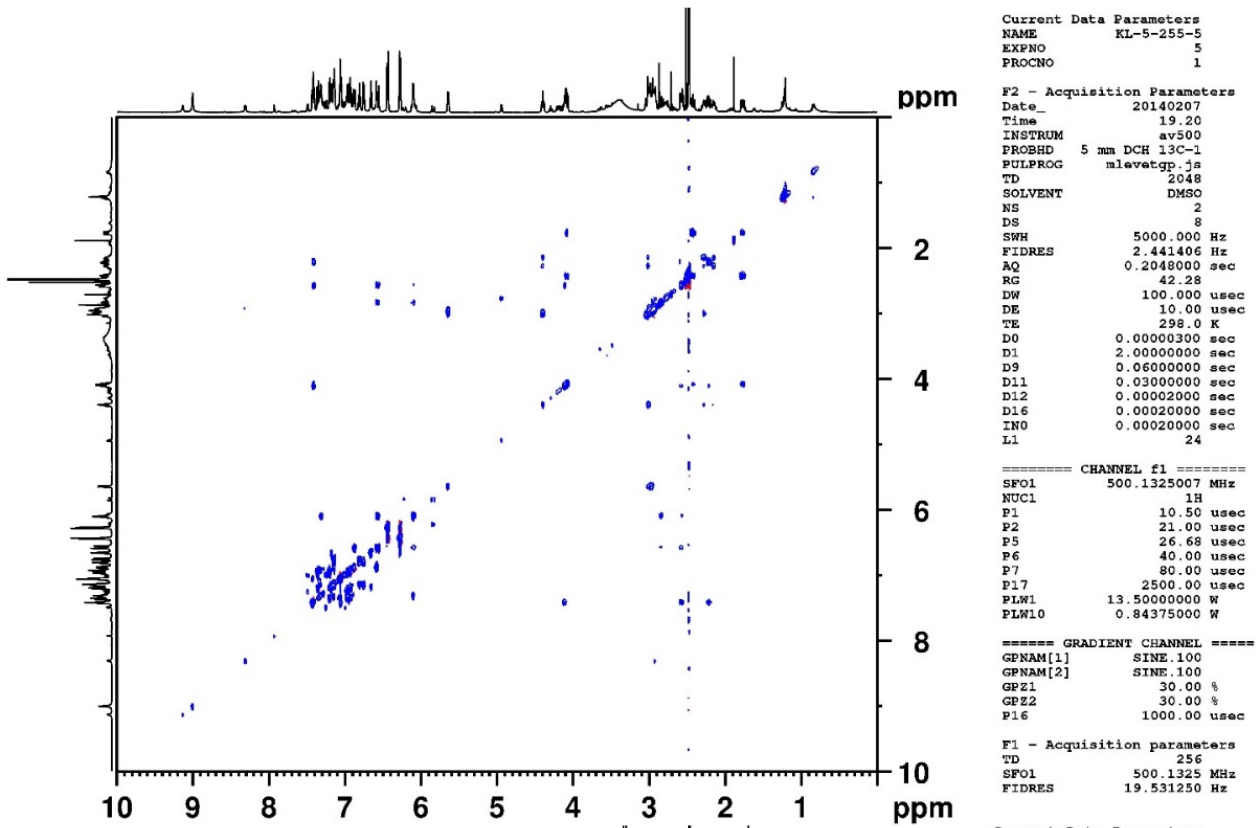
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EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
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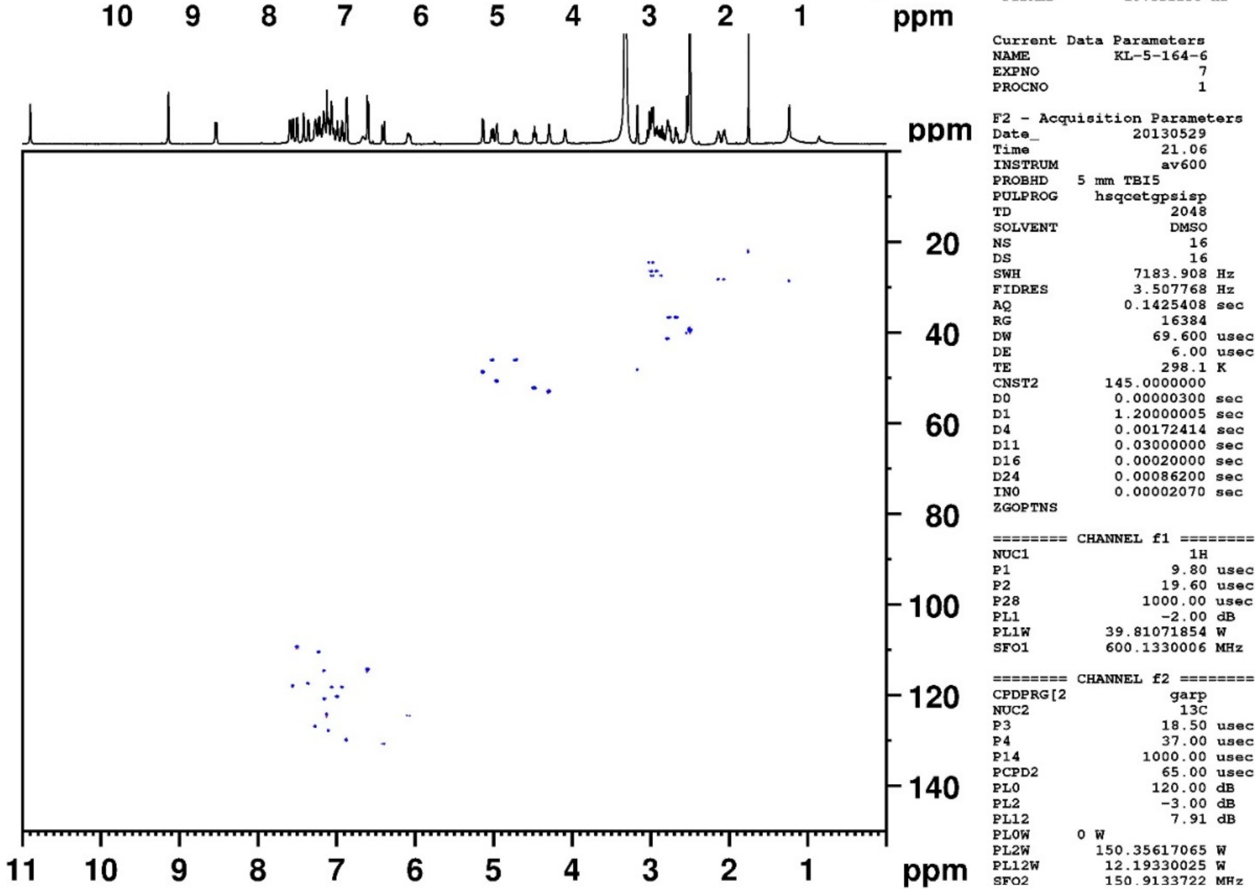
Time 19.20
INSTRUM av500
PROBHD 5 mm DCH 13C-1
PULPROG mlevetgp.js
TD 2048
SOLVENT DMSO
NS 2
DS 8
SWH 5000.000 Hz
FIDRES 2.441406 Hz
AQ 0.2048000 sec
RG 42.28
DW 100.000 usec
DE 10.00 usec
TE 298.0 K
D0 0.00000300 sec
D1 2.00000000 sec
D9 0.06000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
D16 0.00020000 sec
IN0 0.00020000 sec
L1 24
======== CHANNEL f1 ========
SFO1 500.1325007 MHz
NUC1 1H
P1 10.50 usec
P2 21.00 usec
P5 26.68 usec
P6 40.00 usec
P7 80.00 usec
P17 2500.00 usec
PLW1 13.50000000 W
PLW10 0.84375000 W
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPZ1 30.00 %
GPZ2 30.00 %
P16 1000.00 usec
F1 - Acquisition parameters
TD 256
SFO1 500.1325 MHz
FIDRES 19.531250 Hz
ppm
2
4
6
8
10
10 9 8 7 6 5 4 3 2 1 ppm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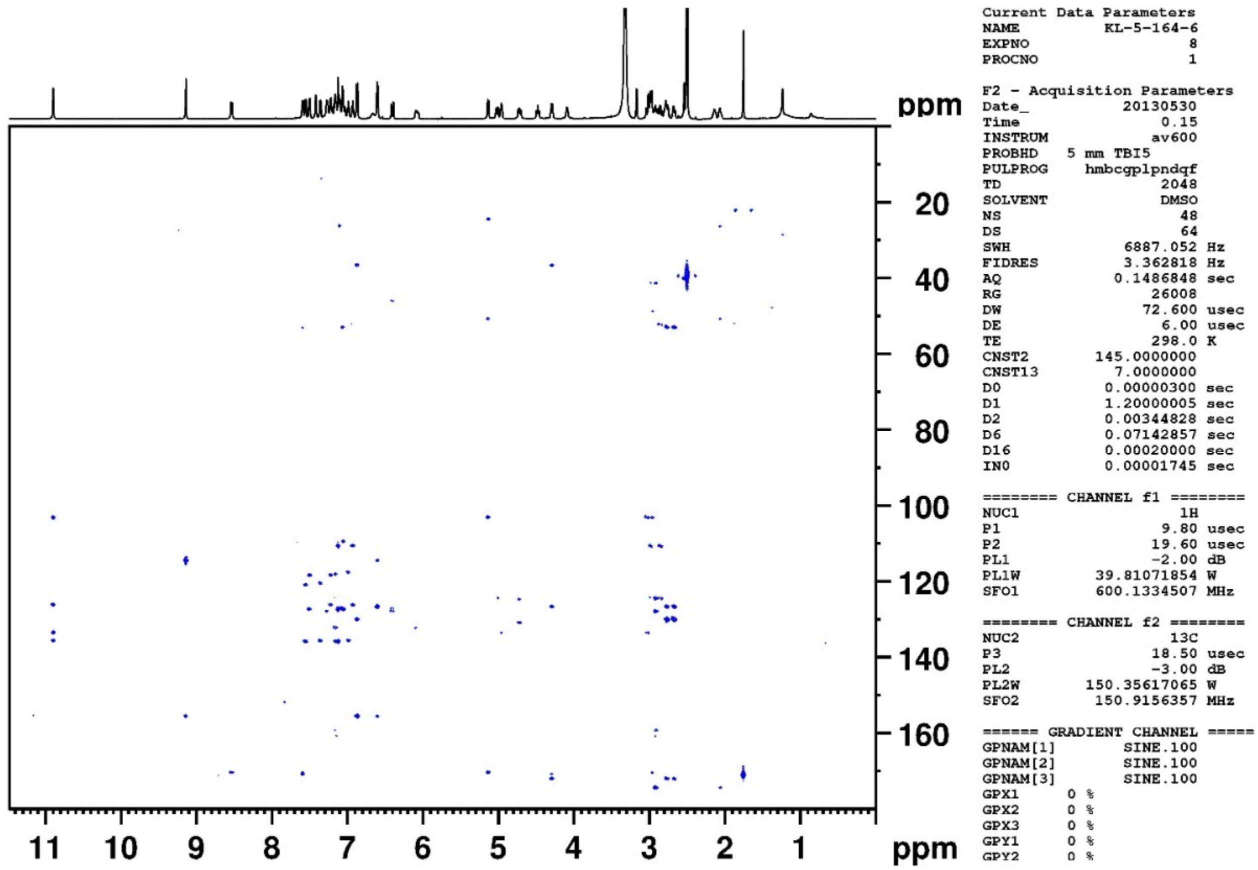
NAME KL-5-164-6
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130529
Time 21.06
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hsqcetgpsisp
TD 2048
SOLVENT DMSO
NS 16
DS 16
SWH 7183.908 Hz
FIDRES 3.507768 Hz
AQ 0.1425408 sec
RG 16384
DW 69.600 usec
DE 6.00 usec
TE 298.1 K
CNST2 145.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00020000 sec
D24 0.00086200 sec
IN0 0.00002070 sec
ZGOPTNS
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
P2 19.60 usec
P28 1000.00 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1330006 MHz
======== CHANNEL f2 ========
CPDPRG[2 garp
NUC2 13C
P3 18.50 usec
P4 37.00 usec
P14 1000.00 usec
PCPD2 65.00 usec
PL0 120.00 dB
PL2 -3.00 dB
PL12 7.91 dB
PL0W 0 W
PL2W 150.35617065 W
PL12W 12.19330025 W
SFO2 150.9133722 MHz
ppm
20
40
60
80
100
120
140
11 10 9 8 7 6 5 4 3 2 1 ppm


ppm
20
40
60
80
100
120
140
160
11 10 9 8 7 6 5 4 3 2 1 ppm
Current Data Parameters
NAME KL-5-164-6
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130530
Time 0.15
INSTRUM av600
PROBHD 5 mm TBI5
PULPROG hmbcgplpndqf
TD 2048
SOLVENT DMSO
NS 48
DS 64
SWH 6887.052 Hz
FIDRES 3.362818 Hz
AQ 0.1486848 sec
RG 26008
DW 72.600 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
CNST13 7.0000000
D0 0.00000300 sec
D1 1.20000005 sec
D2 0.00344828 sec
D6 0.07142857 sec
D16 0.00020000 sec
IN0 0.00001745 sec
======== CHANNEL f1 ========
NUC1 1H
P1 9.80 usec
P2 19.60 usec
PL1 -2.00 dB
PL1W 39.81071854 W
SFO1 600.1334507 MHz
======== CHANNEL f2 ========
NUC2 13C
P3 18.50 usec
PL2 -3.00 dB
PL2W 150.35617065 W
SFO2 150.9156357 MHz
====== GRADIENT CHANNEL =====
GPNAM[1] SINE.100
GPNAM[2] SINE.100
GPNAM[3] SINE.100
GPX1 0 %
GPX2 0 %
GPX3 0 %
GPY1 0 %
GPY2 0 %

Chapter 3 – Appendix Material

Using a new small molecule template to incrementally remodel biotic peptide structure yields domain-selective, macrocyclic IAP antagonists

Table of Contents

A. Supplementary Figures A1–2

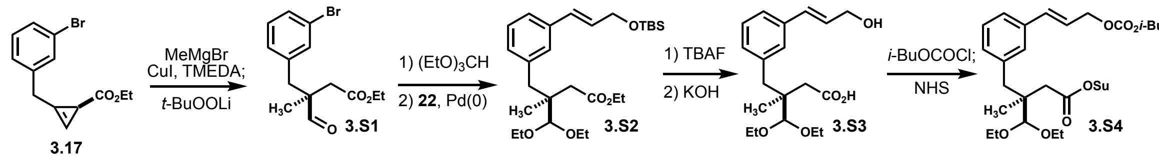


Figure 3.A1. Synthesis of simplified methyl-quaternary template. See main text **Scheme 3.1** for reaction conditions.

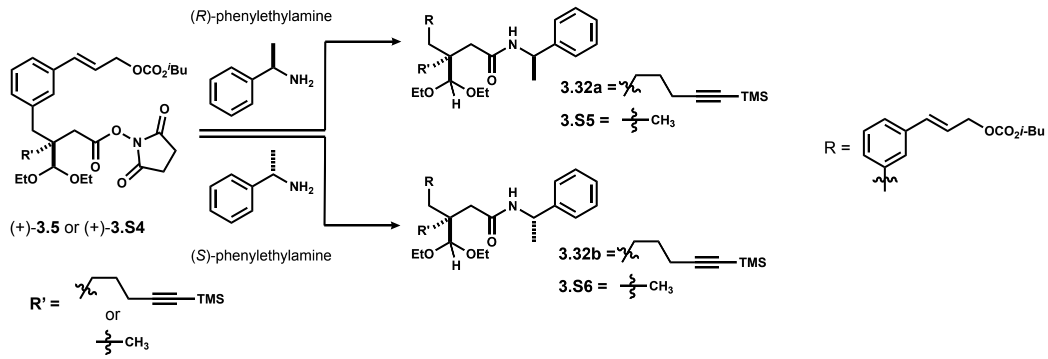


Figure 3.A2. Diastereomeric derivatization of template molecules allowed for indirect enantiomeric analyses.

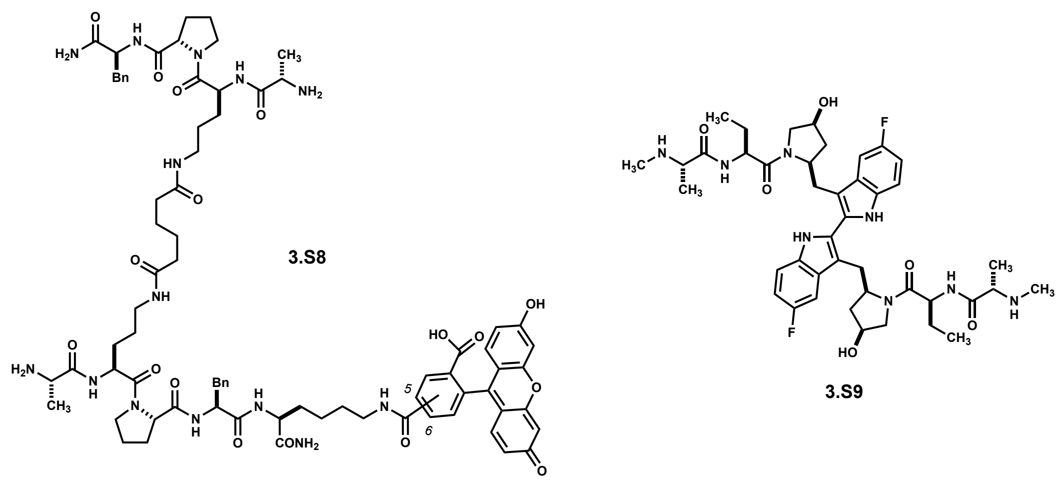


Figure 3.A3. Bivalent FP probe **3.S8** and control compound **3.S9** (Birinapant™) used in *in vitro* FP assays.

B. General Considerations

$Pd(DPEPhos)Cl_2$ was purchased from Strem. Catalyst **3.19** was prepared according to prior literature.[1] (5-bromopent-1-yn-1-yl)trimethylsilane was prepared according to prior literature.[2] *t*-Butylhydroperoxide ~5.5 M solution in decane was purchased from Aldrich and iodometrically titrated (c = 5.4 M).[3] Vinyl boronate **3.23** was prepared using a modified procedure using 1 mol% Schwartz's Reagent.[4] *N*-hydroxysuccinimide was azeotropically dried from benzene. Fmoc-5-bromo-D-tryptophan and Fmoc-3-methoxy-D-phenylalanine were synthesized by kinetic enzymatic resolution of their racemates according to published procedures.[5] L-Phenylalaninol was purchashed from Chem-Impex.

Nitromethane Purification

Pre-treatment of commercial grade nitromethane with either 3Å molecular sieves (7 days) or activated neutral alumina (Aldrich, 58 Å, activated Brockman I, 150 mesh, 12 hrs) is essential for optimal results in Friedel-Crafts cyclizations. Adding H_2O (up to 1000 ppm) to the resultant dry nitromethane has no deleterious effects. For further discussions see: Rose, T. E. Ph.D. Dissertation [Online], University of California, Los Angeles, 2015. pp. 158-160. http://escholarship.org/uc/item/0mx7x1st (Accessed Sept. 12, 2017). UMI: 3706064.

HPLC-MS Analysis and Purification

Purification of acidolysis products was performed on an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using an identical system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source. Stationary phase and gradient profile are noted for individual reactions below.

NMR Methods

NMR spectra were recorded on Brüker Advance (300, 400, 500 or 600 MHz) or DRX (500 MHz) spectrometers and calibrated according to the respective residual solvent peak. 2D NMR data were acquired as previously detailed.[6]

Mass Spectrometry Methods

High-resolution mass spectra (HRMS) of small molecules were obtained on a *Thermo Fisher Scientific Exactive Plus (orbitrap)* with IonSense ID-CUBE DART. HRMS of Dimeric compounds were obtained on a *Waters LCT Premier with ACQUITY UPLC (ESI–TOF)*. Low-resolution mass spectrum of **3.15** was obtained on an Agilent 6890-5975 GC-MS.

Super Critical Fluid Chromatography Method

Enantiomeric excess of cyclopropene (+)-**3.18** was assessed using a Mettler Toledo SFC equipped with a Chiralcel OJ-H column (4.6x250 mm, 5 µm) using 5% *i*-PrOH as co-solvent. Flow rate: 2.0 mL/min.

Experimental Procedures

Peptide Synthesis

All peptides were synthesized via either standard Fmoc solid-phase peptide synthesis using Rink Amide MBHA resin (polystyrene, 1% DVB, 0.7 mmol/g) or Boc/Cbz solution-phase peptide synthesis.[6]

General Procedure A – *Acylation of peptide by template (+)-***3.5** *or (+)-***3.S***4*

A round bottom flask was charged with peptide (1.35 eq.), DMF (1.0 M), and iPr_2NEt (4.0 – 6.0 eq.), followed by template (1.0 eq.). The reaction was heated to 40 ºC. Reaction progress was monitored by analytical HPLC-UV/MS. Reactions were diluted with EtOAc and washed thrice with $NaHCO_3$ followed by brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*.

General Procedure B – *Pictet-Spengler Annulation*

Linear precursor was dissolved in a 4:1 mixture of $AcOH/H_2O$ (0.2 M) and stirred until HPLC analysis confirmed reaction completion – typically 12 hours. The volatiles were removed and the residue was rotovapped from acetonitrile (3x) followed by $CHCl_3$ (3x) to remove residual AcOH.

General Procedure C – *Friedel-Crafts Macrocyclization with CH_3NO_2 as solvent*

A flask was charged with Pictet-Spengler product (1 eq.) and nitromethane (5 mM in substrate). The headspace was flushed with argon for 5 mins. TFA (5 vol%) was then quickly added. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was concentrated *in vacuo* then dissolved in ~1 mL DMSO. Desired product was isolated by preparative HPLC purification – see details per example, below.

General Procedure D – *Friedel-Crafts Macrocyclization with TFE as solvent*

A flask was charged with Pictet-Spengler product (1 eq.) and trifluoroethanol (10 mM in substrate). The headspace was flushed with argon for 5 mins. TFA (10 mM in substrate) was then quickly added. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was concentrated *in vacuo* then dissolved in ~1 mL DMSO. Desired product was isolated by preparative HPLC purification – see details per example, below.

General Procedure E – *Pd(0)-catalyzed Macrocyclization with $Pd(PPh_3)_4$ as catalyst*

A flask was charged with Pictet-Spengler product (1 eq.), Cs_2CO_3 (2 eq.), and DMF (5 mM in substrate) and sparged for 30 minutes. $Pd(PPh_3)_4$ was then added as a solid, and the solution was sparged for another 5 minutes. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was diluted with EtOAc and washed with 3x NH_4Cl and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo.* If purified by preparative HPLC, then the crude was dissolved in ~1 mL DMSO. Otherwise the crude was purified using SiO_2 chromatography – see details per example, below.

General Procedure F –*Macrocyclization with $[PdCl(C_3H_5)]_2$ as catalyst and Xantphos as ligand*

A flask was charged with Pictet-Spengler product (1 eq.), Cs_2CO_3 (2 eq.), and DMF (5 mM in substrate) and sparged for 30 minutes. In a glove bag, a flame-dried Schlenk tube was charged with $[PdCl(C_3H_5)]_2$ (9 mg) and Xantphos (37 mg). Outside of the glovebag, the Schlenk tube was charged with 9 mL of 1:1 THF/DMF, which had been separately sparged for 1 hour. The catalyst solution was stirred for 5 minutes under Ar and 4 mol% Pd was added to the reaction flask via syringe. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was diluted with EtOAc and washed with 3x NH_4Cl and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo.* If purified by preparative HPLC, then the crude was dissolved in ~1 mL DMSO. Otherwise the crude was purified using SiO_2 chromatography – see details per example, below.

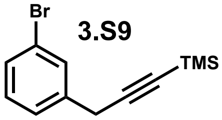
General Procedure G – *Copper(I)-Catalyzed Huisgen Cycloaddition*

A vial was charged with macrocyclic compounds (1 eq.), azidoglucopyranoside (1.5 eq.), and DMF (0.03 M). The solution was sparged for 10 minutes. In a separate vial, a stock solution of copper was prepared. Copper iodide was added to a vial and evacuated and backfilled with argon (3x). DMF (2 mL) was added and the suspension was sparged for 5 minutes. Et_3N (1 mL) was added to the copper suspension and mixed under sparge for 2 minutes until a homogeneous solution was achieved. The copper solution (10 mol% copper) was then added to the reaction flask. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was transferred to an HPLC vial. Desired product was isolated by semi-preparative HPLC purification – see details per example, below.

General Procedure H – *Dimerization of monovalent Smac-mimetics*

The TFA-salt of macrocyclic monomer (1 eq.) was dissolved in 1 mL MeOH and treated with silica-bound carbonate (2 eq.) for 10 minutes. The suspension was filtered and washed 3x with 1 mL MeOH. The combined washes were concentrated *in vacuo* and reconstituted in 1:1 MeOH/CH_3CN (50 mM in substrate). The clear solution was treated with piperidine (7 eq.) and $Cu(OAc)_2$•H_2O (7 eq.); the vial was then capped and heated to 70 ºC. The reaction was monitored by HPLC and complete within 12 hours. The reaction was concentrated and dissolved in ~400 μL DMSO for semi-preparative HPLC purification – see details per example, below.

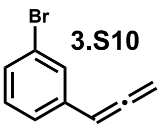
C.1. Synthesis of Template (+)-3.5 & (+)-3.S4



3.S9

(3-(3-Bromophenyl)prop-1-yn-1-yl)trimethylsilane

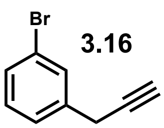
In a flame-dried flask under argon, (Trimethylsilyl)acetylene [15.8 mL, 112 mmol] in 80 mL of dry THF was treated with *n*-BuLi [44.8 mL, 112 mmol] at -78 ºC. While the acetylide solution stirred, zinc(II) bromide [25.2 g, 112 mmol] was fused under vacuum then cooled to room temperature under argon. 80 mL of dry THF was then charged into the flask containing $ZnBr_2$. The $ZnBr_2$ solution was then cannulated into the acetylide solution at -78 ºC. The transmetalation was stirred for 30 min then treated with a solution of 3-bromobenzylbromide [20.0 g, 80 mmol] and Pd(DPEPhos)Cl_2 [115 mg, 0.160 mmol] in 80 mL of dry THF – catalyst loading can be increased to drop reaction time and temperature. The solution warmed to room temperature then eventually heated to 35 ºC. Reaction monitored by crude NMR. After 2 days, reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. Organic layer washed twice with sat. NH_4Cl, $NaHCO_3$, and 1x with brine. Dried with $MgSO_4$ and concentrated *in vacuo*. A portion of crude was purified by silica chromatography using hexanes as eluent. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (t, *J* = 7.9 Hz, 1H), 7.38–7.36 (m, 1H), 7.29–7.26 (m, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 3.63 (s, 2H), 0.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.7, 131.1, 130.1, 129.9, 126.6, 122.7, 103.3, 87.8, 25.9, 0.2.



3.S10

1-bromo-3-(propa-1,2-dien-1-yl)benzene

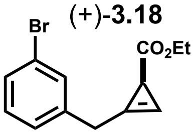
Crude **3.S9** [32 mmol] was dissolved in 30 mL of DCM and 20 mL of MeOH and treated with K_2CO_3 [13.3 g, 96 mmol] under argon. Reaction monitored by TLC. After 5 hours, the reaction was diluted with DCM and washed once with water. The aqueous layer was then extracted twice with DCM. The combined organic layers were dried with Mg_2SO_4. The solvent was removed *in vacuo*. Purified on SiO_2 with hexanes. 1.0 g, 5.2 mmol, 16% yield over two steps (isolated 66% yield of alkyne). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (br s, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.10 (t, *J* = 6.6 Hz, 2H), 5.19 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 210.1, 136.4, 130.2, 129.9, 129.6, 125.4, 122.9, 93.1, 79.5.



3.16

1-Bromo-3-(prop-2-yn-1-yl)benzene

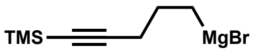
Crude **3.S9** [80 mmol] was dissolved in 400 mL of dry THF and treated with acetic acid [9.2 mL, 160 mmol] followed by slow addition of tetrabutylammonium fluoride [160 mL, 160 mmol] under argon. Reaction monitored by crude NMR. After 15–30 min, THF was removed *in vacuo* and the residue reconstituted in diethyl ether. Organic layer washed twice with water, sat. $NaHCO_3$, and 1x with brine. Ether was completely removed *in vacuo*, the orange oil was dissolved in pentane, and passed through a plug of silica to remove residual tetrabutylammonium salts. Pentane was removed *in vacuo* and the colorless residue was distilled between 67–69 ºC at 4.7 torr. 12.0 g, 85% yield over two steps. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (br s, 1H), 7.40–7.38 (m, 1H), 7.30–7.27 (m, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 3.59 (dd, *J* = 2.7, 0.5 Hz, 2H), 2.25 (t, *J* = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.4, 131.0, 130.1, 1230.0, 126.6, 122.7, 81.1, 71.3, 24.5, MS *m/z* 195.0 (calc'd: $C_9H_8Br^+$, $[M+H]^+$, 195.0).



(+)-**3.18**

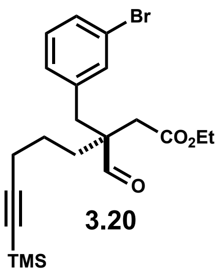
Ethyl (*S*)-2-(3-bromobenzyl)cycloprop-2-ene-1-carboxylate

A flame dried flask was charged with freshly distilled **3.15** [13.0 g, 66.6 mmol], catalyst **3.16** [76 mg, 0.056 mmol), and 320 mL of dry DCM. A solution of ethyl diazoacetate [2.5 g, 22.2 mmol] in 50 mL of dry DCM was added over 12 hours under an argon atmosphere *via* syringe pump. After addition, DCM was completely removed *in vacuo* and residue dissolved in 25 mL hexanes and loaded onto a silica column. Column was eluted with hexanes until removal of starting alkyne. Column then eluted with a gradient from 2% → 6% EtOAc in hexanes. Product was obtained as a yellow oil [5.0 g, 17.5 mmol]. 80% yield, 95% *e.e.* $[\alpha]_D^{25}$ = +22.2º, c = 4.26, $CHCl_3$, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (br s, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.16–7.11 (m, 2H), 6.47 (br s, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.79 & 3.72 (AB quartet, *J* = 17.6 Hz, 2H), 2.19 (br s, 1H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 176.0, 138.6, 131.8, 130.3, 130.1, 127.4, 122.7, 114.1, 96.5, 60.5, 31.1, 20.5, 14.5; MS *m/z* 281.01626 (calc'd: $C_{13}H_{14}O_2Br^+$, $[M+H]^+$, 281.01717).



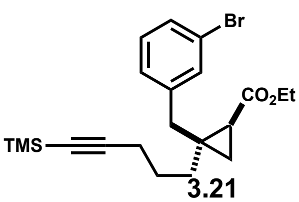
3.19

(5-(Trimethylsilyl)pent-4-yn-1-yl)magnesium bromide
A flask equipped with a condenser was charged with magnesium [2.24 g, 85.4 mmol] then flame-dried under vacuum then flushed with argon. After cooling, the flask was charged with 14 mL of dry THF and treated with an iodine crystal. The flask was then heated with a heatgun until complete dissolution of the orange iodine color. Neat (5-bromopent-1-yn-1-yl)trimethylsilane [9.36 g, 42.7 mmol] was then added at a rate sufficient to maintain a slight reflux. After complete addition, the system was heated to reflux for an additional 30 min. The Grignard reagent was measured to be 1.44 M by titration with menthol/phenanthroline.[7]



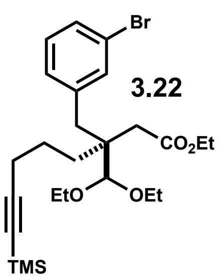
3.20

Ethyl (*S*)-3-(3-bromobenzyl)-3-formyl-8-(trimethylsilyl)oct-7-ynoate
A flame-dried flask was charged with solid copper(I) iodide [6.25 g, 32.8 mmol] then evacuated and backfilled with argon 3x. The flask was charged with 131 mL of dry THF and TMEDA [5.4 mL, 36.1 mmol] and stirred at room temperature for 30 minutes then cooled to -45 ºC. Previously prepared Grignard reagent (**3.18**) [32.8 mmol] was added to the reaction flask and stirred an additional 30 minutes at -45 ºC. Cyclopropene (+)-**3.17** [4.6 g, 16.4 mmol] in 33 mL of dry THF was added to the reaction flask at -45 ºC and stirred for 30 minutes. In a separate flame-dried flask, *t*-butylhydroperoxide [6 mL, 32.8 mmol, c = 5.4 M] was dissolved in 82 mL of dry THF, cooled to -78 ºC, and treated with *n*-BuLi [13.4 mL, 33.6 mmol, c = 2.5 M]. After complete carbometalation as determined by TLC, the reaction flask was cooled to -78 ºC and treated with previously prepared *t*-BuOOLi *via* cannulation. The reaction was stirred at this temperature for one hour – significant decomposition was observed by ^{1}H-NMR at longer time points – then cannulated into a cold solution of 2:1 NH_4Cl / NH_4OH and extracted with EtOAc. The organic layer was washed 3x with water, 1x with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give **21** as a green oil, which was carried forward without purification.



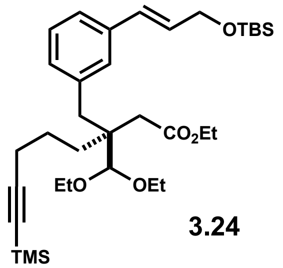
3.21

Ethyl (*S*)-2-(3-bromobenzyl)cycloprop-2-ene-1-carboxylate
A 1 mL aliquot of the above carbometalation was removed and quenched with 2:1 NH_4Cl/NH_4OH and worked up as above. pTLC to remove Grignard byproducts: 4% EtOAc in hexanes. Product was obtained as a colorless residue. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33–7.30 (m, 2H), 7.15–7.11 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.90 & 2.84 (AB quartet, *J* = 15.3 Hz, 2H), 2.16 (t, *J* = 7.3 Hz, 2H), 1.66 (dd, *J* = 8.1, 5.7 Hz, 1H), 1.63–1.57 (m, 2H), 1.36–1.33 (m, 1H), 1.32–1.30 (m, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.28–1.25 (m, 1H), 1.00 (dd, *J* = 8.1, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 176.0, 138.6, 131.8, 130.3, 130.1, 127.4, 122.7, 114.1, 96.5, 60.5, 31.1, 20.5, 14.5.



3.22

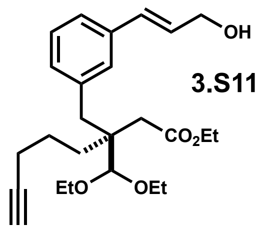
Ethyl (*S*)-3-(3-bromobenzyl)-3-(diethoxymethyl)-8-(trimethylsilyl)oct-7-ynoate
Crude aldehyde **3.21** [10.7 mmol] was dissolved in 50 mL of dry ethanol then treated with ethyl orthoformate [5.3 mL, 32.1 mmol] and *p*-TSA [203 mg, 1.07 mmol]. The reaction was heated to 60 ºC and monitored by ^{1}H-NMR. The reaction was complete within 1 hour. Ethanol was removed *in vacuo* and the residue reconstituted in EtOAc then washed 3x with $NaHCO_3$ and 1x with brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Acetal **3.22** was carried forward without purification.



3.24

Ethyl (*S*,*E*)-3-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzyl)-3-(diethoxymethyl)-8-(trimethylsilyl)oct-7-ynoate

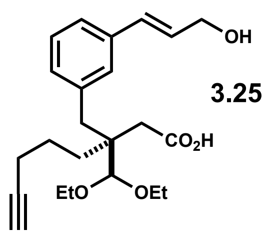
Dioxane and deionized water were sparged with argon for one hour. Crude acetal **3.22** [16.4 mmol], vinyl boronate **3.22** [5.9 g, 19.7 mmol], and Na_2CO_3 [3.4 g, 32.1 mmol] were dissolved in 30 mL of 5:1 dioxane/water. The system was sparged for 15 min, charged with $Pd(PPh_3)_4$ [123 mg, 0.107 mmol], and sparged an additional 15 min. The system was sparged for 15 min, charged with $Pd(PPh_3)_4$ [123 mg, 0.107 mmol], and sparged an additional 15 min. The system was then taken to reflux and monitored by ^{1}H-NMR. After two days, the reaction was complete. Dioxane was removed *in vacuo*, exchanged for EtOAc, and this solution was washed 3x with water and 1x with brine. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The crude product was dissolved in hexanes and chromatographed using a gradient of 0% → 5% EtOAc in hexanes. Collected **23** [2.85 g, 4.73 mmol] as a colorless oil. 29% yield from **17**. $[\alpha]_D^{23}$ = +3.05º, c = 0.46, $CHCl_3$, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22–7.18 (m, 3H), 7.09 (ddd, *J* = 7.2, 1.4, 1.4 Hz, 1H), 6.55 (ddd, *J* = 15.9, 1.5, 1.5 Hz, 1H), 6.25 (ddd, *J* = 15.9, 5.0, 5.0 Hz, 1H), 4.34 (dd, *J* = 5.0, 1.7 Hz, 2H), 4.28 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.82–3.74 (m, 2H), 3.51–3.41 (m, 2H), 2.91 & 2.82 (AB quartet, *J* = 13.4 Hz, 2H), 2.32 (s, 2H), 2.16 (dd, *J* = 6.7, 6.7 Hz, 2H), 1.71–1.48 (m, 6H), 1.28–1.19 (m, 11H), 0.94 (s, 9H), 0.13 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.7, 138.7, 136.7, 130.1, 129.8, 129.3, 128.9, 128.1, 124.2, 108.2, 107.8, 84.4, 66.3, 66.2, 64.0, 60.1, 45.6, 39.6, 37.5, 33.3, 26.2, 26.1, 24.9, 23.7, 20.9, 18.6, 15.7, 15.7, 14.4, 0.3, -5.0.



3.S11

Ethyl (*S*,*E*)-3-(diethoxymethyl)-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)oct-7-ynoate

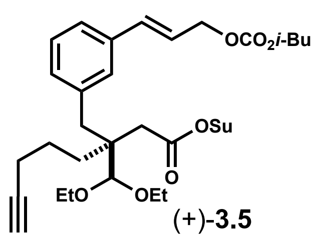
Pure **3.22** [2.29 g, 3.80 mmol] was dissolved in 40 mL of dry THF and cooled to 0 ºC. A solution of TBAF [9.5 mL, 9.50 mmol] was slowly added over 5 minutes. The reaction was monitored by TLC. After 30 minutes, THF was removed *in vacuo* and exchanged for EtOAc and washed 3x with water and 1x with brine. Organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to provide **3.24** as a yellow oil, which was carried forward without purification.



3.25

(*S*,*E*)-3-(Diethoxymethyl)-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)oct-7-ynoic acid

Crude ethyl ester **3.S11** [3.80 mmol] was dissolved in 38 mL of 2:1 $EtOH/H_2O$ and treated with KOH [2.13 g, 38.0 mmol]. The ensuing red solution was then heated to 50 ºC overnight. After stirring for 12 hours, reaction was complete. Solvent was stripped off and the red oil was treated with 200 mL of 0.3 N NaH_2PO_4 and extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The red oil was carried forward without purification.

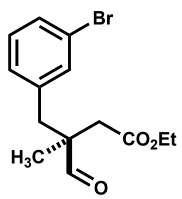


(+)-3.5

2,5-Dioxopyrrolidin-1-yl (*S*,*E*)-3-(diethoxymethyl)-3-(3-(3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)benzyl)oct-7-ynoate

Crude cinnamyl alcohol **3.25** [3.80 mmol] was dissolved in 7.6 mL of dry DCM, treated with *N*-methylmorpholine [1.88 mL, 17.1 mmol], and cooled to -5 ºC under argon. *i*-Butyl chloroformate [1.04 mL, 7.98 mmol] was then added. The reaction was monitored by TLC for full conversion to the di-carbonate species. At this time, solid *N*-hydroxysuccinimide [875 mg, 7.60 mmol] was added to the reaction flask. The ice in the cold bath was replenished and the reaction was allowed to slowly warm overnight. Twelve hours after addition of NHS, solid DMAP [1.39 g, 11.4 mmol] was added to decompose by-product, *i*-butyl succinimidyl carbonate. After stirring with DMAP for

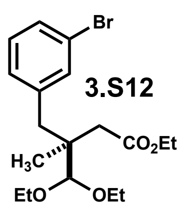
10 min, the reaction was quenched with $NaHCO_3$ and extracted with EtOAc. Organic layer washed 2x with $NaHCO_3$ and 1x with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in a minimum amount of 3:1 hexanes/$CHCl_3$ and loaded onto silica column. Elution with a gradient of 5% → 30% EtOAc/hexanes provided (+)-**3.5** [1.15 g, 1.96 mmol] as a colorless oil. 52% from **23**, 94% e.e. as determined below. $[\alpha]_D^{23}$ = +8.56º, c = 0.58, ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28–7.21 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.30 (ddd, *J* = 15.9, 6.4, 6.4 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 2H), 4.34 (s, 1H), 3.93 (d, *J* = 6.7 Hz, 2H), 3.83–3.78 (m, 2H), 3.54–3.44 (m, 2H), 2.92 & 2.86 (AB quartet, *J* = 14.3 Hz, 2H), 2.84 (br s, 4H), 2.63 (s, 2H), 2.14 (ddd, *J* = 6.5, 6.5, 2.4 Hz, 2H), 2.00–1.95 (m, 1H), 1.76–1.55 (m, 5H), 1.25–1.19 (m, 6H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 167.7, 155.4, 138.1, 136.0, 135.0, 130.9, 129.5, 128.4, 124.8, 122.6, 107.7, 84.6, 74.3, 68.5, 68.5, 66.6, 66.3, 45.6, 39.3, 34.2, 33.1, 27.9, 25.7, 23.54, 19.3, 19.0, 15.6, 15.6; MS *m/z* LRMS: 608.3 (calc'd: $C_{32}H_{43}NO_9 + Na^+$, $[M+Na]^+$, 608.3). HRMS: 584.28709 (calc'd: $C_{32}H_{43}NO_9 - H^-$, $[M-H]^+$, 584.28650).



3.S1

Ethyl (*S*)-3-(3-bromobenzyl)-3-methyl-4-oxobutanoate

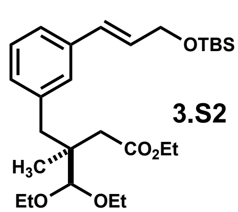
A flame-dried flask was charged with solid copper(I) iodide [6.8 g, 35.7 mmol] then evacuated and backfilled with argon 3x. The flask was charged with 179 mL of dry THF and TMEDA [5.4 mL, 36.1 mmol] and stirred at room temperature for 30 minutes then cooled to -45 ºC. Methylmagnesium bromide [14.9 mL, 35.7 mmol] was added to the reaction flask and stirred an additional 30 minutes at -45 ºC. Cyclopropene (+)-**3.18** [5.0 g, 17.9 mmol] in 36 mL of dry THF was added to the reaction flask at -45 ºC and stirred for 30 minutes. In a separate flame-dried flask, *t*-butylhydroperoxide [7.9 mL, 42.8 M] was dissolved in 107 mL of dry THF, cooled to -78 ºC, and treated with *n*-BuLi [21 mL, 44.6 mmol]. After complete carbometalation as determined by TLC, the reaction flask was cooled to -78 ºC and treated with previously prepared *t*-BuOOLi via cannulation. The reaction was stirred at this temperature a maximum of one hour – significant decomposition was observed at longer reaction times – then cannulated into a cold solution of 2:1 NH_4Cl / NH_4OH and extracted with EtOAc. The organic layer was washed 3x with water, 1x with brine, dried with $MgSO_4$, and concentrated *in vacuo* to give a green oil, which was carried through to the next step.



3.S12

Ethyl (*S*)-3-(3-bromobenzyl)-4,4-diethoxy-3-methylbutanoate

Crude aldehyde **3.S1** [10.7 mmol] was dissolved in 50 mL of dry ethanol then treated with ethyl orthoformate [5.3 mL, 32.1 mmol] and *p*-TSA [203 mg, 1.07 mmol]. The reactionwas heated to 60 ºC and monitored by crude NMR. The reactionwas complete within 1 hour. Ethanol was removed *in vacuo* and the residue reconstituted in EtOAc then washed 3x with $NaHCO_3$ and 1x with brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Acetal **3.S13** [6.4 g, 16.4 mmol, 92% crude recovery] was carried forward without purification.

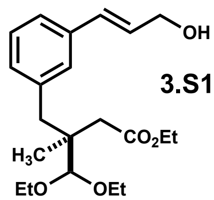


3.S2

Ethyl (*S*,*E*)-3-(3-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzyl)-4,4-diethoxy-3-methylbutanoate

Dioxane and deionized water were sparged with argon for one hour. Crude acetal **3.S13** [16.4 mmol], vinyl boronate **3.22** [5.9 g, 19.7 mmol], and Na_2CO_3 [5.2 g, 49.2 mmol] were dissolved in 41 mL of 5:1 dioxane/water. The system was sparged for 15 min, charged with $Pd(PPh_3)_4$ [123 mg, 0.107 mmol], and sparged an additional 15 min. The system was then taken to reflux and monitored by crude NMR. After two days, reaction was complete. Dioxane was removed *in vacuo*, exchanged for EtOAc, and washed 3x with water and 1x with brine. The organic layer was dried with $MgSO_4$ and concentrated to dryness. The crude product was dissolved in hexanes and chromatographed using a gradient of 0% → 5% EtOAc in hexanes. Collected **3.S2** [2.28 g, 4.76 mmol] as a colorless oil. 29% yield from **3.17**. ^{1}H

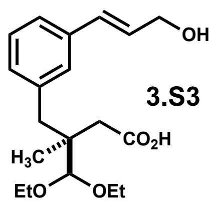
NMR ($CDCl_3$, 500 MHz): δ 7.24–7.18 (m, 3H), 7.05 (ddd, *J* = 7.2, 1.6, 1.6 Hz, 1H), 6.56 (ddd, *J* = 15.7, 1.9, 1.9 Hz, 1H), 6.26 (ddd, *J* = 15.8, 5.1, 5.1 Hz, 1H), 4.35 (dd, *J* = 5.1, 1.8 Hz, 2H), 4.30 (s, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.85–3.78 (m, 2H), 3.55–3.45 (m, 2H), 2.86 & 2.82 (AB quartet, *J* = 13.2 Hz, 2H), 2.35 & 2.28 (AB quartet, *J* = 14.9 Hz, 2H) 1.28–1.22 (m, 9H), 1.00 (s, 3H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.9, 138.6, 136.8, 130.2, 129.8, 129.2, 129.0, 128.1, 124.2, 108.2, 66.7, 66.0, 64.1, 60.1, 42.9, 40.7, 39.4, 26.1, 19.8, 18.6, 15.7, 15.6, 14.4, -5.0.



3.S13

Ethyl (*S*,*E*)-4,4-diethoxy-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)-3-methylbutanoate

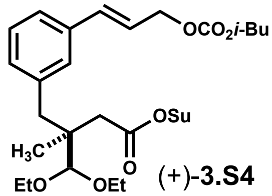
Pure **3.S2** [3.0 g, 6.27 mmol] was dissolved in 21 mL of dry THF and cooled to 0 ºC. A solution of TBAF [14.0 mL, 13.8 mmol] was slowly added over 5 minutes. The reaction was monitored by TLC. After 30 minutes, THF was removed *in vacuo* and exchanged for EtOAc, and the solution was washed 3x with water and 1x with brine. Organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to provide **3.S14** as a yellow oil, which was carried forward without purification.



3.S3

(*S*,*E*)-4,4-Diethoxy-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)-3-methylbutanoic acid

Crude ethyl ester **3.S14** [6.27 mmol] was dissolved in 38 mL of 2:1 EtOH/H_2O and treated with KOH [2.13 g, 38.0 mmol]. The ensuing red solution was then heated to 50 ºC overnight. After stirring for 12 hours, reaction was complete. Solvent was stripped off and the red oil was treated with 200 mL of 0.3 N NaH_2PO_4 and extracted 3x with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated *in vacuo*. The red oil was carried forward without purification.

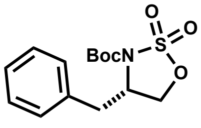


(+)-3.S4

2,5-Dioxopyrrolidin-1-yl (*S*,*E*)-4,4-diethoxy-3-(3-(3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)benzyl)-3-methylbutanoate

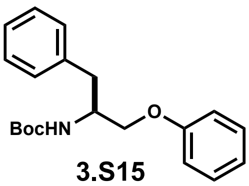
Crude cinnamyl alcohol **3.S3** [1.58 mmol] was dissolved in 3.2 mL of dry DCM, treated with *N*-methylmorpholine [782 μL, 7.11 mmol], and cooled to -5 ºC under argon. *i*-Butyl chloroformate [431 μL, 3.32 mmol] was then added. The reaction was monitored by TLC for full conversion to the di-carbonate species. At this time, solid *N*-hydroxysuccinimide [875 mg, 7.60 mmol] was added to the reaction flask. The ice in the cold bath was replenished and the reaction was allowed to slowly warm overnight. Twelve hours after addition of NHS, solid DMAP [579 mg, 4.74 mmol] was added to decompose by-product, *i*-butyl succinimidyl carbonate. After stirring with DMAP for 10 min, reaction quenched with $NaHCO_3$ and extracted with EtOAc. Organic layer washed 2x with $NaHCO_3$ and 1x with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in a minimum amount of 3:1 hexanes/$CHCl_3$ and loaded onto silica column. Elution with a gradient of 5% → 20% EtOAc/hexanes provided (+)-**3.S4** [615 mg, 1.15 mmol] as a white oil. 65% from **3.S2**, 89% e.e. as determined below. $[\alpha]_D^{23}$ = +15.71º, c = 0.56, ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28–7.21 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.68 (d, *J* = 15.9 Hz, 1H), 6.30 (ddd, *J* = 15.9, 6.4, 6.4 Hz, 1H), 4.77 (d, *J* = 6.4 Hz, 2H), 4.34 (s, 1H), 3.93 (d, *J* = 6.7 Hz, 2H), 3.83–3.78 (m, 2H), 3.54–3.44 (m, 2H), 2.92 & 2.86 (AB quartet, *J* = 14.3 Hz, 2H), 2.84 (br s, 4H), 2.63 (s, 2H), 2.14 (ddd, *J* = 6.5, 6.5, 2.4 Hz, 2H), 2.00–1.95 (m, 1H), 1.76–1.55 (m, 5H), 1.25–1.19 (m, 6H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.2, 167.6, 155.3, 137.9, 135.9, 134.9, 130.8, 129.3, 128.3, 124.7, 122.5, 107.3, 74.2, 68.3, 66.7, 65.9, 43.1, 40.1, 36.2, 27.8, 25.6, 19.4, 18.9, 15.51, 15.48. HRMS: 532.25985 (calc'd: $C_{28}H_{39}NO_9$ - H, $[M-H]^-$, 532.25520).

C.2. Synthesis of *O*-Phenyl-L-phenylalaninol



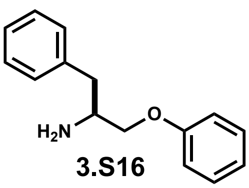
3.S14

***tert*-Butyl (*S*)-4-benzyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide**
The above was prepared using a modified procedure.[8] After reaction completion, **3.S14** was filtered through celite, and the layers separated. The organic layer was washed 3x with 1N HCl, 3x 1N NaOH, and 1x brine. The dark orange organic layer was dried with $MgSO_4$ and treated with activated charcoal for 10 min. The charcoal suspension was filtered through celite, and the colorless solution was concentrated *in vacuo*. The desired product was obtained as a spectroscopically pure off-white solid that matches previous data.



3.S15

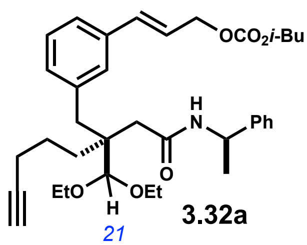
***tert*-Butyl (*S*)-(1-phenoxy-3-phenylpropan-2-yl)carbamate**
Phenol [4.7 g, 50 mmol] in 48 mL of dry DMF was cannulated into a suspension of NaH [2.0 g, 50 mmol] in 48 mL of dry DMF and stirred for 5 min. **3.S14** [40 mmol], dissolved in 96 mL of dry DMF, was cannulated into the reaction flask. The reaction was monitored for completion by NMR. The reactionwas quenched by addition of 0.25 N HCl, and the mixture was then diluted with EtOAc. The layers were separated, and the aqueous layer was extracted 2x with EtOAc. The combined organic layers were washed 2x with 1N HCl, 3x 1N NaOH, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Chromatographed on silica using 10% EtOAc/hexanes to provide **3.S15** as a white solid [6.2 g, 18.9 mmol]. 47% from commercial L-phenylalaninol (4 steps). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–7.26 (m, 5H), 7.21 (d, *J* = 7.2 Hz, 2H), 6.97 (dd, *J* = 7.3, 7.3 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.96 (d, *J* = 8.3 Hz, 1H), 4.19–4.12 (m, 1H), 3.89 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.86 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.02 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.98 (dd, *J* = 13.0, 8.3 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.7, 155.4, 137.9, 129.7, 129.6, 128.7, 126.6, 121.2, 114.6, 79.7, 67.7, 51.4, 37.9, 28.6; MS *m/z* 328.18956 (calc'd: $C_{20}H_{26}NO_3^+$, $[M+H]^+$, 328.19072).



3.S16

(*S*)-1-phenoxy-3-phenylpropan-2-amine
Pure **3.S15** [6.2 g, 18.9 mmol] was dissolved in 160 mL DCM and cooled to 0 ºC. 40 mL of TFA was added to the reaction flask under argon. The reaction was monitored by TLC. After reaction completion, solvents were stripped off and the residue partitioned between ethyl ether and 1N NaOH; the layers were then separated. The ether layer was washed 2x with 1N NaOH and 1x with brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo* to give **3.S16** as a pale yellow, waxy solid [4.2 g, 18.5 mmol]. 98% yield. $[\alpha]_D^{23}$ = +18.5º, c = 1.34. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42–7.29 (m, 7H), 7.05 (ddd, *J* = 7.3, 1.0, 1.0 Hz, 1H), 7.02–6.98 (m, 2H), 3.99 (dd, *J* = 9.0, 4.3 Hz, 1H), 3.87 (dd, *J* = 8.9, 6.6 Hz, 1H), 3.51 (dddd, *J* = 7.7, 6.1, 6.1, 4.4 Hz, 1H), 3.00 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.78 (dd, *J* = 13.3, 8.0 Hz, 1H), 1.55 (br s, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 158.8, 138.5, 129.4, 129.2, 128.5, 126.4, 120.8, 114.5, 72.1, 52.0, 40.6; MS *m/z* 228.13766 (calc'd: $C_{15}H_{18}NO^+$, $[M+H]^+$, 228.13829).

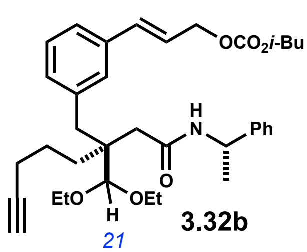
C.3. Enantiomeric Excess Determination of (+)-3.5 and (+)-3.S4



3.32a

(*E*)-3-(3-((*S*)-2-(diethoxymethyl)-2-(2-oxo-2-(((*R*)-1-phenylethyl)amino)ethyl)hept-6-yn-1-yl)phenyl)allyl isobutyl carbonate

Synthesized according to *General Procedure A* and (*R*)-(+)-phenylethylamine using 77 µmol of (+)-**3.5**. Obtained 20 mg [crude, 45%] of **3.32a**. The crude was then dissolved in 500 µL of $CDCl_3$ for ^{1}H-NMR analysis. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.31 (m, 4H), 7.28 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.25–7.23 (m, 2H), 7.20 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.16 (ddd, *J* = 7.4, 1.5, 1.5 Hz, 1H), 6.65 (ddd, *J* = 15.9, 1.2, 1.2 Hz, 1H), 6.34 (d, *J* = 7.3 Hz, 1H), 6.28 (ddd, *J* = 15.9, 6.4, 6.4 Hz, 1H), 5.07 (quint., *J* = 7.0 Hz, 1H), 4.77 (dd, *J* = 6.5, 1.3 Hz, 2H), 4.16 (s, 1H), 3.94 (d, *J* = 6.6 Hz, 2H), 3.73–3.65 (m, 2H), 3.47 (dd, *J* = 9.2, 7.0 Hz, 1H), 3.30 (dd, *J* = 9.0, 7.0 Hz, 1H), 2.85 & 2.72 (AB quartet, *J* = 13.4 Hz, 2H), 2.31 & 2.13 (AB quartet, *J* = 14.0 Hz, 2H), 2.18–2.13 (m, 1H), 2.01–1.95 (m, 1H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.83–1.70 (m, 2H), 1.62–1.49 (m, 2H), 1.48 (d, *J* = 6.9 Hz, 1H), 1.15 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2, 155.3, 143.8, 138.6, 135.7, 135.1, 131.0, 129.6, 128.7, 128.2, 127.3, 126.4, 124.5, 122.4, 108.6, 84.6, 74.3, 68.6, 68.4, 67.2, 65.5, 48.8, 45.9, 40.3, 39.6, 32.7, 27.9, 23.2, 21.9, 19.2, 19.0, 15.7, 15.6; MS *m/z* 608.3 (calc'd: $C_{36}H_{49}NO_6$ + Na^+, $[M+Na]^+$, 614.3).

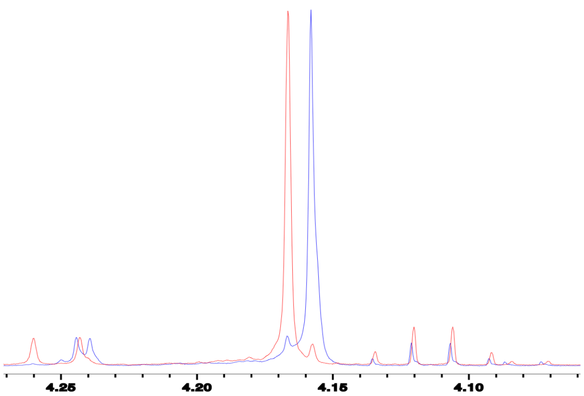


3.32b

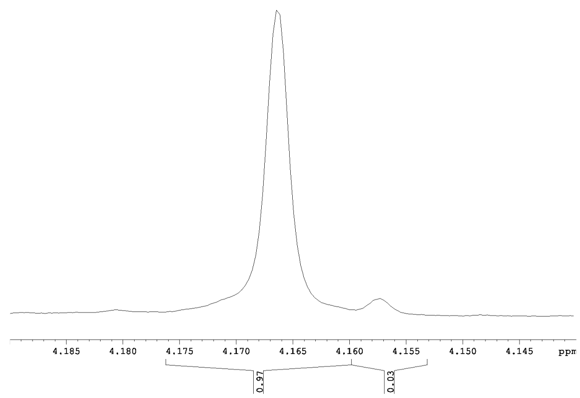
(*E*)-3-(3-((*S*)-2-(diethoxymethyl)-2-(2-oxo-2-(((*S*)-1-phenylethyl)amino)ethyl)hept-6-yn-1-yl)phenyl)allyl isobutyl carbonate

Synthesized according to General Procedure A and (*S*)-(-)-phenylethylamine using 77 µmol of (+)-**3.5**. Obtained 22 mg [crude, 49%] of **3.32b**. The crude was then dissolved in 500 µL of $CDCl_3$ for ^{1}H-NMR analysis. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35–7.32 (m, 4H), 7.28 (dd, *J* = 1.7, 1.7 Hz, 1H), 7.27–7.22 (m, 2H), 7.20–7.17 (m, 2H), 6.64 (ddd, *J* = 15.9, 1.2, 1.2 Hz, 1H), 6.38 (d, *J* = 7.4 Hz, 1H), 6.27 (ddd, *J* = 15.9, 6.5, 6.5 Hz, 1H), 5.07 (quint., *J* = 7.0 Hz, 1H), 4.76 (dd, *J* = 6.5, 1.3 Hz, 2H), 4.17 (s, 1H), 3.93 (d, *J* = 6.7 Hz, 2H), 3.74 (dd, *J* = 8.9, 6.9 Hz, 1H), 3.66 (dd, *J* = 9.2, 6.9 Hz, 1H), 3.42 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.38 (dd, *J* = 9.1, 7.0 Hz, 1H), 2.87 & 2.74 (AB quartet, *J* = 13.4 Hz, 2H), 2.29 & 2.16 (AB quartet, *J* = 14.1 Hz, 2H), 2.10–2.02 (m, 1H), 2.01–1.94 (m, 1H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.78–1.69 (m, 2H), 1.61–1.45 (m, 3H), 1.47 (d, *J* = 6.9 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.2, 155.3, 143.8, 138.6, 135.7, 135.1, 131.1, 129.6, 128.7, 128.2, 127.3, 126.4, 124.5, 122.4, 108.6, 84.6, 74.3, 68.6, 68.4, 66.9, 65.8, 48.9, 45.9, 40.3, 39.5, 33.0, 27.9, 23.2, 21.9, 19.2, 19.0, 15.7, 15.6; MS *m/z* 614.4 (calc'd: $C_{36}H_{49}NO_6$ + Na^+, $[M+Na]^+$, 614.3).

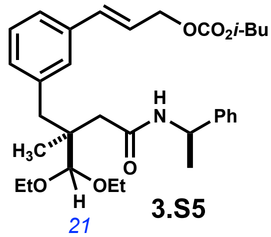
*Overlay of ^{1}H-NMR of **3.32a** and **3.32b** provided evidence of separation of diastereomeric protons. Methine 21 was integrated for the diastereomers in **3.32b** and the integral was normalized to 1.0. The d.r. was found to be 97:3, which gives an approximate enantiomeric excess of 94% e.e. for template (+)-**3.5**.*



Overlay of 1H-NMRs of **3.32a** (blue) & **3.32b** (red) centered at methine *H21*



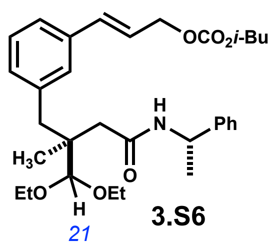
Integration of methine *H21* diastereomers in **3.32b** normalized to 1.00



3.S5

(*E*)-3-(3-((*S*)-2-(diethoxymethyl)-2-methyl-4-oxo-4-(((*R*)-1-phenylethyl)amino)butyl)phenyl)allyl isobutyl carbonate

Synthesized according to General Procedure A and (*R*)-(+)-phenylethylamine using 77 µmol of (+)-**3.S4**. Obtained 22 mg [crude, 49%] of **3.S5**. The crude was then dissolved in 500 µL of $CDCl_3$ for ^{1}H-NMR analysis. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.32 (m, 4H), 7.28–7.20 (m, 4H), 7.14 (ddd, J = 6.9, 1.5, 1.5 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.28 (ddd, J = 15.9, 6.5, 6.5 Hz, 1H), 6.03 (d, J = 7.8 Hz, 1H), 5.12 (quint., J = 7.2 Hz, 1H), 4.77 (dd, J = 6.5, 1.1 Hz, 2H), 4.22 (s, 1H), 3.94 (d, J = 6.2 Hz, 2H), 3.77–3.70 (m, 2H), 3.52–3.49 (m, 1H), 3.32–3.27 (m, 1H), 2.86 & 2.74 (AB quartet, J = 13.0 Hz, 2H), 2.25 & 2.09 (AB quartet, J = 13.9 Hz, 2H), 2.02–1.94 (m, 1H), 1.49 (d, J = 6.9 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.1, 155.4, 143.6, 138.7, 135.7, 135.2, 131.2, 129.7, 128.7, 128.2, 127.4, 126.4, 124.5, 122.4, 108.5, 74.3, 68.5, 67.0, 65.4, 48.7, 43.2, 41.8, 41.2, 27.9, 21.8, 20.4, 19.1, 15.7, 15.6; MS *m/z* 562.4 (calc'd: $C_{32}H_{45}NO_6 + Na^+$, $[M+Na]^+$, 562.3).

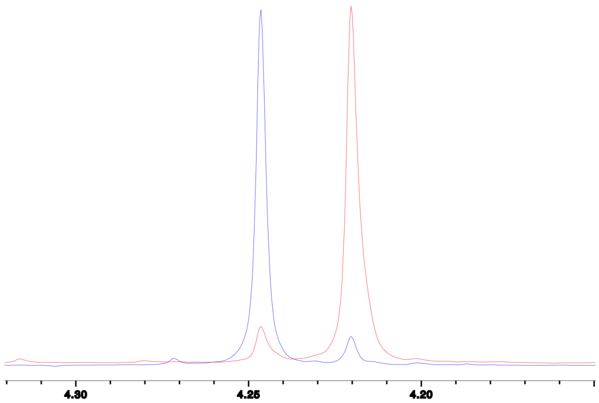


3.S6

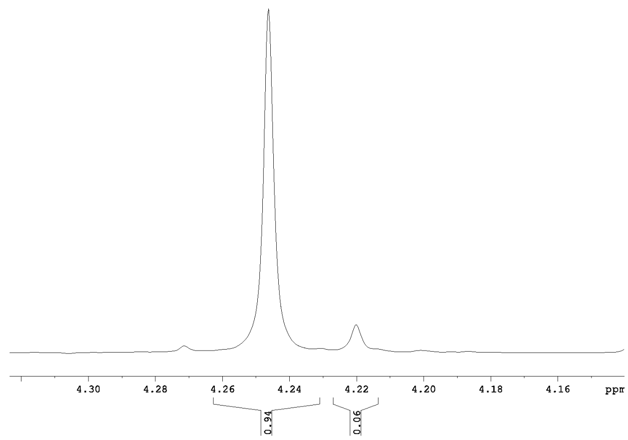
(*E*)-3-(3-((*S*)-2-(diethoxymethyl)-2-methyl-4-oxo-4-(((*S*)-1-phenylethyl)amino)butyl)phenyl)allyl isobutyl carbonate

Synthesized according to General Procedure A and (*S*)-(-)-phenylethylamine using 77 µmol of (+)-**3.S4**. Obtained 22 mg [crude, 49%] of **3.S6**. The crude was then dissolved in 500 µL of $CDCl_3$ for ^{1}H-NMR analysis. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.32 (m, 4H), 7.28–7.23 (m, 3H), 7.19 (dd, J = 7.6, 7.6 Hz, 1H), 7.12 (ddd, J = 7.5, 1.2, 1.2 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 6.27 (ddd, J = 15.8, 6.5, 6.5 Hz, 1H), 6.01 (d, J = 7.8 Hz, 1H), 5.12 (quint., J = 7.1 Hz, 1H), 4.77 (dd, J = 6.5, 1.0 Hz, 2H), 4.25 (s, 1H), 3.94 (d, J = 6.7 Hz, 2H), 3.82–3.69 (m, 2H), 3.51–3.44 (m, 1H), 3.42–3.36 (m, 1H), 2.87 & 2.76 (AB quartet, J = 13.0 Hz, 2H), 2.23 & 2.09 (AB quartet, J = 13.9 Hz, 2H), 2.03–1.94 (m, 1H), 1.48 (d, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.15 (t, J = 7.0 Hz, 3H), 0.96 (d, J = 6.7 Hz, 6H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 171.1, 155.4, 143.6, 138.7, 135.7, 135.1, 131.3, 129.7, 128.8, 128.2, 127.5, 126.4, 124.5, 122.4, 108.6, 74.3, 68.5, 66.7, 65.8, 48.7, 43.1, 41.8, 41.0, 27.9, 21.7, 20.7, 19.0, 15.7, 15.6; MS *m/z* 562.4 (calc'd: $C_{32}H_{45}NO_6 + Na^+$, $[M+Na]^+$, 562.3).

Overlay of [1]*H-NMR of **3.S5** and **3.S6** provided evidence of separation of diastereomeric protons. Methine H21 was integrated for the diastereomers in **3.S6** and the integral was normalized to 1.0. The d.r. was found to be 94:6, which gives an approximate enantiomeric excess of 89% e.e. for template (+)-**3.S4**.*

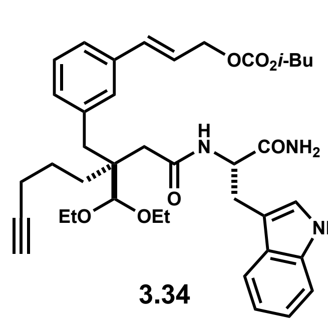


Overlay of 1H-NMRs of **3.S5** (red) & **3.S6** (blue) centered at methine *H21*



Integration of methine *H21* diastereomers in **3.S6** normalized to 1.00

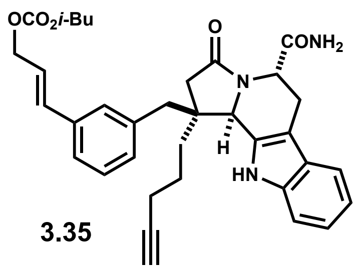
C.4. Absolute stereochemical determination of (+)-3.5



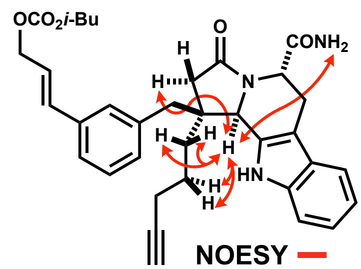
3.34

(*E*)-3-(3-((*S*)-2-(2-(((*S*)-1-amino-3-(1*H*-indol-3-yl)-1-oxopropan-2-yl)amino)-2-oxoethyl)-2-(diethoxymethyl)hept-6-yn-1-yl)phenyl)allyl isobutyl carbonate

Synthesized according to General Procedure A. Obtained 30 mg [45 µmol, 87% crude recovery] of **3.34**.



3.35



(*E*)-3-(3-(((1*S*,5*S*,11b*R*)-5-carbamoyl-3-oxo-1-(pent-4-yn-1-yl)-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indol-1-yl)methyl)phenyl)allyl isobutyl carbonate

Synthesized according to General Procedure B. After reaction completion, solvent was removed, and the crude residue was dissolved in ~500 µL DMSO and purified by semi-preparative HPLC to give 12 mg [21 µmol, 51% yield] of desired **3.35**. The absolute stereochemistry of **3.35** was inferred from the NOE correlations shown relative to the Cα-(*S*) stereocenter retained from L-tryptophan. MS *m/z* 604.3 (calc'd: $C_{35}H_{39}N_3O_5 + Na^+$, $[M+Na]^+$, 604.3).

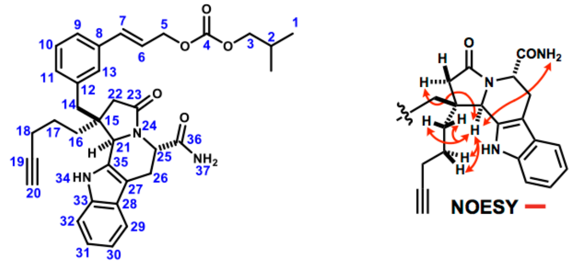
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 1.00 mL/min

Time	%B
0	45
1	45
14	100
15	45

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 18.0 mL/min

Time	%B
0	40
2	40
30	50

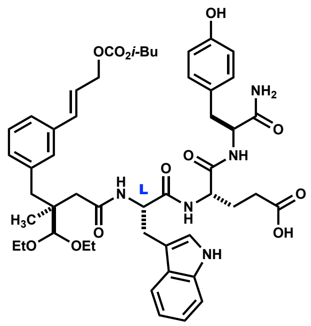
*Pictet-Spengler Product **3.35***



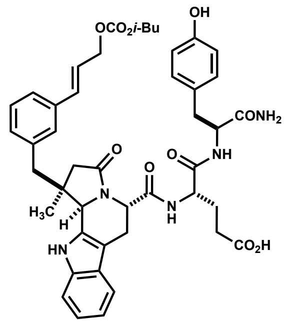
(600MHz, DMSO-d6, 298K)

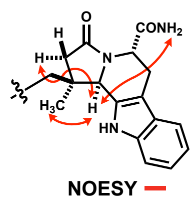
	13C	1H	key correlation
1	18.2 ppm	0.9 ppm (d) J=4.9 Hz (6H)	
2	26.9 ppm	1.92–1.89 ppm (m) (1H)	COSY 2→1
3	73.0 ppm	3.90 ppm (d) 4.5 Hz (2)	TOCSY 3→2
4	154.4 ppm	–	HMBC 3→4
5	67.5 ppm	4.68 ppm (d) J=4.1 Hz (2H)	HMBC 5→4
6	122.8 ppm	6.13–6.10 ppm (m) (1H)	TOCSY 6→5
7	133.4 ppm	6.46 ppm (d) J=15.5 Hz (1H)	COSY 7→6
8	135.0 ppm	–	HMBC 6→8
9	124.2 ppm	7.23 ppm (d) J=6.4 Hz (1H)	HMBC 7→9
10	127.6 ppm	7.14–7.11 ppm (m) (1H)	COSY 9→10
11	130.0 ppm	6.80 ppm (d) J=5.9 Hz (1H)	TOCSY 9→11
12	137.2	–	HMBC 10→12
13	128.5 ppm	6.71 ppm (s) (1H)	HMBC 7→13
14	39.9 ppm	2.33–2.31 ppm (m) ; 2.21–2.19 ppm (m) (2H)	HMBC 14→12
15	45.3 ppm	–	HMBC 14, 16, 21, 22→15
16	34.5 ppm	1.95–1.90 ppm (m) ; 1.88–1.83 ppm (m) (2H)	HMBC 21→16 / TOCSY 16→17
17	23.8 ppm	1.74–1.70 ppm (m) ; 1.60–1.56 ppm (m) 2H)	TOCSY 18→17
18	18.0 ppm	2.33–2.31 ppm (m) ; 2.24–2.20 ppm (m) (2H)	TOCSY 20→18
19	84.2 ppm	–	HMBC 20→19
20	71.1 ppm	2.78 ppm (s) (1H)	
21	59.2 ppm	5.06 pm (s) (1H)	NOESY 21→22, 16, 17, 37, 37'
22	38.6 ppm	2.65 ppm (d) J=15.9 Hz ; 2.17 ppm (d) J=15.9 Hz (2H)	
23	171.9 ppm	–	HMBC 22→23
24	–	–	
25	49.3 ppm	4.82 ppm (d) J=4.5 Hz (1H)	
26	22.9 ppm	3.35 ppm (d) J=15.0 Hz ; 2.55–2.52 Hz (2H)	TOCSY 25→26
27	106.9 ppm	–	HMBC 21, 25, 26→27
28	125.8 ppm	–	HMBC 26→28
29	111.1	7.41 ppm (d) J=6.6 Hz (1H)	HMBC 30→29
30	118.3	7.00 ppm (dd) J=6.3, 6.3 Hz (1H)	HMBC 30→28
31	120.9 ppm	7.12–7.09 ppm (m) (1H)	
32	117.5 ppm	7.41 ppm (d) J=6.6 Hz (1H)	HMBC 31→32
33	136.6 ppm	–	HMBC 31, 34→33
34	–	10.86 ppm (s) (1H)	
35	128.8 ppm	–	HMBC 21, 26→35
36	171.6 ppm	–	HMBC 25, 37→36
37	–	7.48 ppm (s) ; 7.09 ppm (s) (2H)	

C.5. Synthesis of Acyclic Precursors and Macrocyclization Products

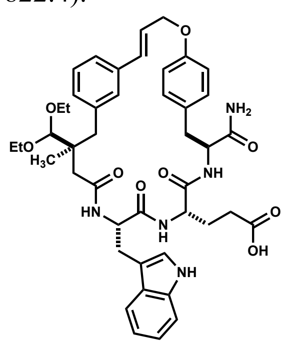


Acyclic Cinnamyl Carbonate 3.36: Synthesized according to Procedure A. Carried forward without purification

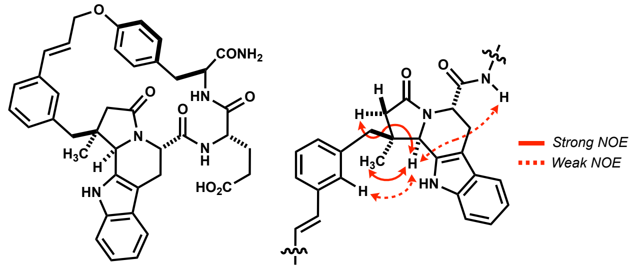




Pictet-Spengler Product 3.37: Synthesized according to Procedure B. Chromatographed on SiO_2 with a gradient from 0% to 5% MeOH in $CHCl_3$ (0.5% AcOH). White Solid. 34 mg, [41 μmol, 94% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.07 (br s, 1H), 10.93 (s, 1H), 9.15 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.30 (br s, 1H), 7.22 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.08 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.01–6.98 (m, 2H), 6.94–6.88 (m, 4 H), 6.63–6.54 (m, 4H), 6.26 (ddd, *J* = 15.9, 6.3, 6.3 Hz, 1H), 5.09 (d, *J* = 6.9 Hz, 1H), 5.01 (s, 1H), 4.72, (d, *J* = 6.1 Hz, 1H), 4.24 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 4.08 (ddd, *J* = 7.9, 7.9, 7.9 Hz, 1H), 3.90 (d, *J* = 6.7 Hz, 2H), 2.82 (dd, *J* = 14.7, 6.5 Hz, 1H), 2.74 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.61 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.41 (d, *J* = 15.8 Hz, 1H), 2.22–2.17 (m, 2H), 2.13–2.00 (m, 3H),1.90 (quint., *J* = 7.0 Hz, 1H), 1.86–1.80 (m, 1H), 1.75–1.65 (m, 1H), 1.42 (s, 3H), 0.89 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ174.1, 172.6, 172.5, 170.6, 170.2, 155.8, 154.5, 137.6, 136.8, 135.4, 133.6, 130.4, 130.1, 129.1, 128.8, 128.2, 127.5, 126.4, 124.5, 123.2, 121.2, 118.7, 117.9, 114.9, 111.4, 107.1, 73.4, 67.7, 62.7, 53.9, 52.2, 49.3, 42.6, 42.1, 36.6, 30.2, 27.3, 26.8, 23.5, 23.2, 18.7; MS *m/z* 822.3 (calc'd: $C_{45}H_{52}N_5O_{10}$+, $[M+H]^+$, 822.4).



Macrocycle 3.38: Synthesized according to Procedure E. Carried forward without purification.



Macrocycle 3.39: Synthesized according to Procedure B. Purified by preparative HPLC – see below for conditions. White Solid. 11.4 mg [16 µmol, 28% yield over three steps]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.04 (br s, 1H), 10.87 (s, 1H), 8.32 (d, J = 9.2 Hz, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.38 (br s, 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.11–7.01 (m, 5H), 7.04 (d, J = 8.9 Hz, 2H), 6.98–6.95 (m, 1H), 6.92 (d, J = 6.8 Hz, 1H), 6.75 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 16.3 Hz, 1H), 6.25 (s, 1H), 5.98 (ddd, J = 16.3, 6.8, 4.0 Hz, 1H), 4.93 (s, 1H), 4.87 (ddd, J = 15.9, 4.0, 1.7 Hz, 1H), 4.80 (dd, J = 15.9, 6.8 Hz, 1H), 4.48–4.44 (m, 1H), 4.32 (d, J = 9.2 Hz, 1H), 4.13 (ddd, J = 9.1, 9.1, 4.8 Hz, 1H), 3.11 (dd, J = 14.5, 5.3 Hz, 1H), 2.76 (dd, J = 14.5, 4.3 Hz, 1H), 2.18 (d, J = 16.8 Hz, 1H), 2.10–2.07 (m, 2H), 2.01–1.94 (m, 1H), 1.82–1.76 (m, 1H), 1.64 (s, 3H), 1.62–1.56 (m, 1H), 1.54–1.48 (m, 1H), 1.41–1.35 (m, 1H); ^{13}C NMR (DMSO-d_6, 126 MHz): δ 174.4, 174.0, 172.2, 171.9, 171.6, 170.1, 157.6, 137.5, 137.0, 134.5, 131.3, 130.7, 130.0, 129.3, 128.1, 127.7, 127.2, 126.5, 126.0, 125.0, 121.2, 118.7, 118.4, 115.0, 111.1, 106.0, 68.4, 52.0, 50.8, 48.6, 47.7, 43.2, 42.4, 36.3, 32.0, 27.1, 26.2, 23.7; MS m/z 704.3 (calc'd: $C_{40}H_{42}N_5O_7^+$, $[M+H]^+$, 704.3).

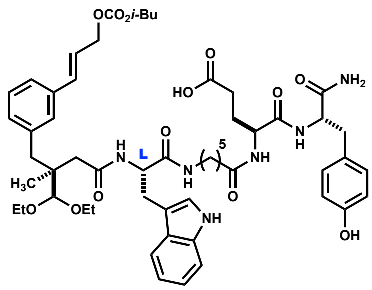
Contaminated with an unknown impurity. ^{13}C-NMR peaks chosen by analogy to Macrocycle ***3.45***

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

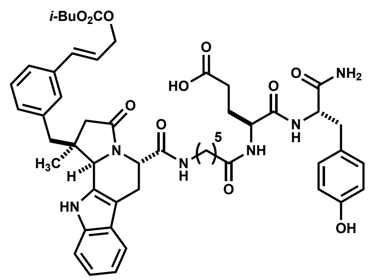
Time	%B
0	25
1	25
14	80
15	25

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

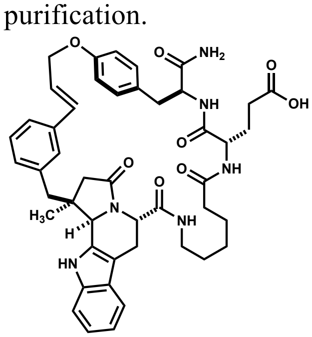
Time	%B
0	45
2	45
10	48



Acyclic Cinnamyl Carbonate 3.40: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.41: Synthesized according to Procedure B. Carried forward without purification.



Acyclic Cinnamyl Carbonate 3.42: Synthesized according to Procedure E. Purified by preparative HPLC – see below for conditions. White Solid. 9 mg [11 µmol, 19% yield over three steps]. MS *m/z* 817.3 (calc'd: $C_{46}H_{53}N_6O_8^+$, $[M+H]^+$, 817.4).

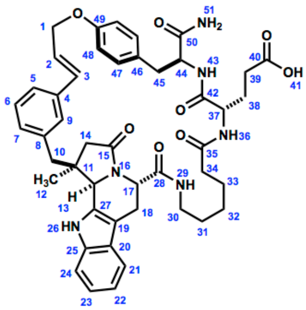
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 1.00 mL/min

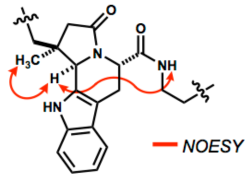
Time	%B
0	25
1	25
14	80
15	25

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 18.0 mL/min

Time	%B
0	42
2	42
10	48

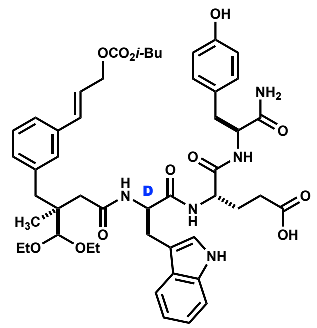
*Macrocycle **3.42***



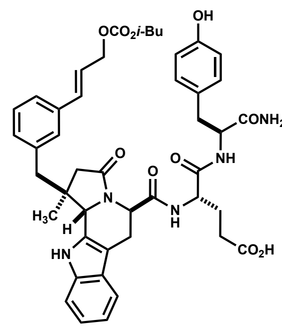


(600 MHz, DMSO-d6, 298K)

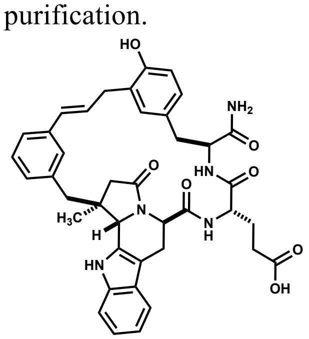
	13C	1H	key correlation
1	67.6 ppm	4.65 ppm (m) (2H)	
2	124.4 ppm	6.10 ppm (ddd) J=16.0, 5.8, 5.8 Hz (1H)	
3	132.1 ppm	6.23 ppm (d) J=16.1 Hz (1H)	
4	135.0 ppm	–	HMBC 2→4
5	124.0 ppm	7.17 ppm (ddd) J=7.7, 1.3, 1.3 Hz (1H)	HMBC 5→3
6	127.7 ppm	7.12 ppm (dd) J=7.5, 7.5 Hz (1H)	HMBC 6→2, 8
7	129.4 ppm	6.95–6.94 ppm (m) (1H)	HMBC 5→7
8	137.3 ppm	–	
9	128.1 ppm	6.31 ppm (dd) J=1.4, 1.4 Hz (1H)	HMBC 5→9
10	40.9 ppm	2.39 ppm (s) (2H)	HMBC 10→8, 7, 9
11	42.3 ppm	–	HMBC 14→11
12	43.7 ppm	2.51 ppm (d) J=15.8Hz; 2.37 ppm (d) J=15.9 Hz (AB quartet) (2H)	
13	172.0 ppm	–	HMBC 12→13 / NOESY 13→12, 29
14	25.3 ppm	1.45 ppm (s) (3H)	COSY 25 -> 14
15	62.1 ppm	5.01 ppm (dd) J=1.4, 1.4 Hz (1H)	
16	–	–	
17	49.1 ppm	4.74 ppm (d) J=7.0 Hz (1H)	
18	23.4 ppm	3.21 ppm (d) J=15.1 Hz; 2.58 ppm (ddd) J=15.3, 6.3, 1.6 Hz (2H)	COSY 17→18
19	106.7 ppm	–	HMBC 15, 17, 18→19
20	126.2 ppm	–	HMBC 22, 24→20
21	117.5 ppm	7.40 ppm (d) J=7.9 Hz (1H)	HMBC 21→19
22	118.4 ppm	6.88 ppm (ddd) J=7.9, 7.0, 0.8 Hz (1H)	COSY 21→22
23	121.0 ppm	6.96 ppm (ddd) J=7.9, 7.0, 0.8 Hz (1H)	COSY 23→22
24	111.1 ppm	7.32 ppm (d) J=7.9 Hz (1H)	TOCSY 21→24
25	136.6 ppm	–	HMBC 21, 23→25
26	–	10.87 ppm (s) (1H)	
27	129.3 ppm	–	HMBC 13, 26→27
28	169.7 ppm	–	HMBC 17→28
29	–	7.74 ppm (dd) J=5.6, 5.6 Hz (1H)	HMBC 29 →28
30	37.7 ppm	2.96–2.93 ppm (m) (2H)	COSY 29→30
31	28.1 ppm	1.29–1.24 ppm (m) ; 1.17–1.13 ppm (m) (2H)	COSY 30→31
32	25.6 ppm	0.93–0.87 ppm (m) (2H)	COSY 31→32
33	24.6 ppm	1.37–1.31 ppm (m) ; 1.22–1.17 ppm (m) (2H)	TOCSY 33→32
34	35.0 ppm	1.98 ppm (ddd) J=14.9, 9.5, 5.7 Hz ; 1.76 ppm (ddd) J=15.0, 9.5, 5.5 Hz (2H)	COSY 34→33
35	171.9 ppm	–	HMBC 34→35
36	–	7.63 ppm (d) J=8.1 Hz (1H)	HMBC 36→35
37	51.2 ppm	4.31 ppm (ddd) J=7.9, 7.9, 5.7 Hz (1H)	TOCSY 36→37
38	27.6 ppm	1.92–1.86 ppm (m) ; 1.74–1.69 ppm (m) (2H)	COSY 37→38
39	29.8 ppm	2.24–2.15 ppm (m) (2H)	COSY 39→38
40	173.9 ppm	–	HMBC 39→40
41	–	not observed	–
42	171.0 ppm	–	HMBC 37→42
43	–	7.95 ppm (d) J=8.2 Hz (1H)	HMBC 43→42
44	54.1 ppm	4.40 ppm (ddd) J=9.9, 8.2, 3.4 Hz (1H)	COSY 43→44
45	36.4 ppm	2.98 ppm (dd) J=14.0, 3.6 Hz ; 2.78 pppm (dd) J=14.0, 10.0 Hz (2H)	COSY 44→45
46	129.9 ppm	–	HMBC 48→46
47	130.2 ppm	7.25 ppm (d) J=8.6, Hz (1H)	HMBC 45→47
48	114.1 ppm	6.93 (d) J=8.7 Hz (1H)	COSY 47→48
49	156.8 ppm	–	HMBC 1→49
50	–	–	–
51	173.0 ppm	–	HMBC 52→51
52	–	7.50 ppm (br s) ; 7.08 ppm (br s) (2H)	



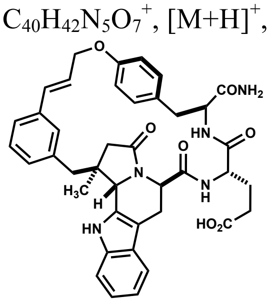
Acyclic Cinnamyl Carbonate 3.43: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S17: Synthesized according to Procedure B. Carried forward without purification.



Macrocycle 3.44: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. White Solid. 3 mg [4.3 µmol, 60% yield over three steps]. MS *m/z* 704.2 (calc'd: $C_{40}H_{42}N_5O_7^+$, $[M+H]^+$, 704.3).



Macrocycle 3.45: Synthesized according to Procedure E. Purified by preparative HPLC using HCOOH instead of TFA – see below for conditions. White Solid. 15 mg [21 µmol, 29% yield over three steps]. MS *m/z* 704.3 (calc'd: $C_{40}H_{42}N_5O_7^+$, $[M+H]^+$, 704.3).

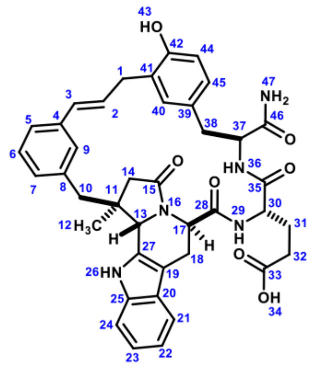
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

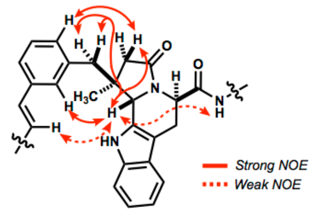
Time	%B
0	45
1	45
14	100
15	45

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA / HCOOH
Solvent B: ACN + 0.1% TFA / HCOOH
Flow rate: 18.0 mL/min

Time	%B
0	40
2	40
14	60

Macrocycle **3.44**

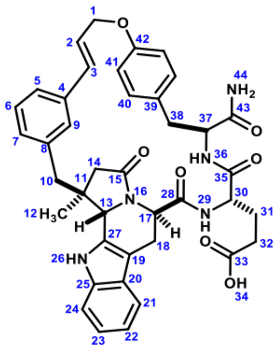


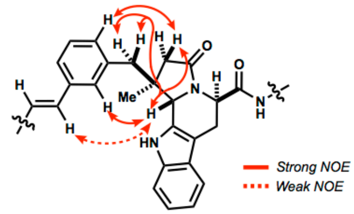


(600 MHz, DMSO-d6, 298K)

	13C	1H	key correlation
1	32.4 ppm	3.40 ppm (dd) J=15.6, 7.8 Hz ; 3.24 ppm (dd) J=15.5, 6.6 Hz (2H)	
2	129.3 ppm	6.32 ppm (ddd) J=15.6, 7.2, 7.2 H (1H)	
3	130.8 ppm	6.52 ppm (d) J-15.7 Hz (1H)	
4	137.7 ppm	–	HMBC 2→4
5	124.2 ppm	7.29 ppm (d) J=7.7 Hz (1H)	HMBC 3→5
6	128.3 ppm	7.35 ppm (dd) J=7.3, 7.3 H (1H)	HMBC 6→4, 8
7	130.0 ppm	7.10 ppm (d) J=7.2 Hz (1H) (1H)	HMBC / COSY 5→7
8	137.7 ppm	–	HMBC 10→8
9	128.1 ppm	7.42 ppm (s) (1H)	HMBC 3, 5→9
10	41.9 ppm	3.39 ppm (d) J=13.8 Hz ; 2.78 ppm (d) J=13.8 Hz (2H)	
11	41.2 ppm	–	HMBC 12, 10→11
12	23.7 ppm	0.81 ppm (s) (3H)	
13	57.0 ppm	5.51 ppm (s) 1H)	NOESY 13→10, 14, 29
14	41.8 ppm	2.29 ppm (d) J=16.1 Hz ; 1.90 ppm (d) J=16.0 Hz	HMBC 14→11, 13
15	171.1 ppm	–	HMBC 14→15
16	–	–	
17	48.8 ppm	5.03 ppm (d) J=66 Hz (1H)	
18	25.3 ppm	3.15 ppm (d) J=15.2 Hz ; 2.88 ppm (dd) J=15.2, 6.5 Hz (2H)	COSY 17→18
19	105.8 ppm	–	HMBC 17, 18→19
20	126.1 ppm	–	HMBC 18→20
21	117.1 ppm	7.36 ppm (d) J=7.4 Hz (2H)	COSY 21→22
22	118.4 ppm	6.98 ppm (dd) J=7.7, 7.7 Hz (1H)	HMBC 22→20
23	120.8 ppm	7.08 ppm (dd) J=7.9, 7.9 Hz (2H)	COSY24→23
24	111.1 ppm	7.35 ppm (d) J=7.6 Hz (1H)	HMBC 24→20 / 22→24
25	136.3 ppm	–	HMBC 21, 23→25
26	–	10.64 (br s) (1H)	
27	130.3 ppm	–	HMBC 13, 18→27
28	170.3 ppm	–	HMBC 17→28
29	–	8.08 ppm (d) J=4.8 Hz (1H)	COSY 29→30
30	52.1 ppm	3.81–3.77 ppm (m) (1H)	COSY 30→31
31	26.7 ppm	1.83–1.77 ppm (m) ; 1.68–1.62 ppm (m) (2H)	COSY 32→31
32	30.2 ppm	2.15 ppm (ddd) J=16.3, 11.1, 5.3 Hz ; 2.06 ppm (ddd) J=16.4, 11.1, 5.2 Hz (2H)	
33	173.9 ppm	–	HMBC 32→33
34	–	12.06 ppm (br s) (1H)	
35	*not observed*	–	
36	–	7.41 ppm (d) J=8.1 Hz (1H)	COSY 36→37
37	53.9 ppm	4.19 ppm (ddd) J=8.1, 8.1, 3.8 Hz (1H)	
38	36.8 ppm	2.66 ppm (dd) J=13.9, 3.5 Hz ; 2.58 ppm (dd) J=13.9, 8.4 Hz (2H)	COSY 37→38
39	127.7	–	HMBC 38, 44→41
40	129.9 ppm	6.86 ppm (d) J=1.7 Hz (1H)	HMBC 38→40
41	125.4 ppm	–	HMBC 44, 1→41
42	153.3 ppm	–	HMBC 1→42
43	–	9.18 ppm (s)	*affected by water suppression*
44	114.3 ppm	6.66 ppm (d) J=8.1 Hz (1H)	COSY 45→44
45	127.8 ppm	6.84 ppm (dd) J=8.2, 1.8 Hz (1H)	HMBC 40→45
46	173.0 ppm	–	HMBC 47→46
47	–	7.37 ppm (br s) ; 6.95 ppm (br s) (2H)	

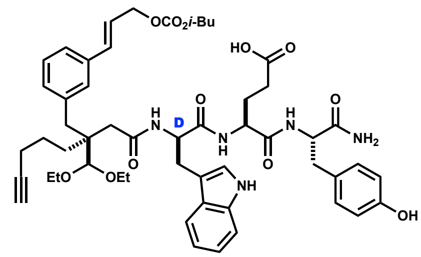
Macrocycle **3.45**



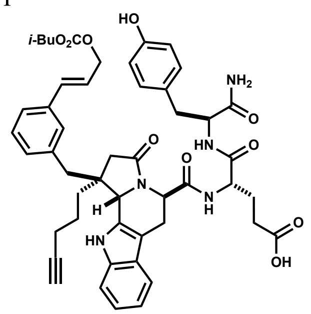


(600MHz, DMSO-d6, 298K)

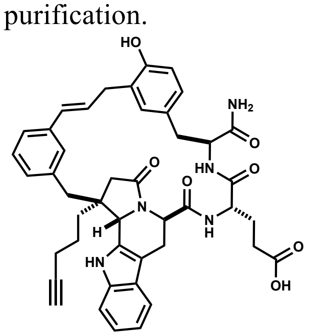
	13C	1H	key correlation
1	66.9 ppm	4.92 ppm (dd) J= 14.6, 5.0 Hz ; 4.81 ppm (d) J=14.5 Hz (2 H)	
2	125.9 ppm	6.38-6.36 ppm (m) (1 H)	
3	132.2 ppm	6.71 ppm (d) J= 15.7 Hz (1 H)	
4	135.7 ppm	–	HMBC 2→4
5	123.0 ppm	7.52 ppm (d) J= 5.6 Hz (1 H)	HMBC 3→5
6	128.4 ppm	7.36-7.34 ppm (m) (1H)	HMBC 6→4
7	131.2 ppm	7.01 ppm (d) J= 5.7 Hz (1 H)	TOCSY 5→7
8	137,5 ppm	–	HMBC 6→8
9	130.0 ppm	7.34 ppm (s) (1 H)	HMBC 3→9 / 5→9
10	40.9 ppm	3.39 ppm (d) J= 13.8 Hz ; 2.73 ppm (d) J=13.7 Hz (2 H)	HMBC 10→8
11	42.0 ppm	–	HMBC 10,13,14→11
12	23.5 ppm	0.74 ppm (s) (3 H)	HMBC 12→14
13	56.8 ppm	5.19 ppm (s) (1 H)	
14	41.2 ppm	2.25 ppm (d) J= 15.3 Hz ; 1.88 ppm (d) J=15.3 Hz (AB quartet) (2 H)	HMBC 13 →14
15	170.9 ppm	–	HMBC 14→15
16	–	–	
17	48.2 ppm	5.08 ppm (d) J= 4.1 Hz (1 H)	
18	26.0 ppm	3.07 ppm (d) J= 15.3 Hz ; 2.90 ppm (dd) J=15.3, 4.2 Hz (2 H)	COSY 17→18
19	105.3 ppm	–	HMBC 13,17,18→19
20	126.1 ppm	–	HMBC 22,24→20
21	117.0 ppm	7.37 ppm (d) J= 6.7 Hz (1 H)	HMBC 21→19
22	118.5 ppm	7.00 ppm (dd) J= 6.7, 6.7 Hz (1 H)	COSY/TOCSY 23→22
23	120.6 ppm	7.11 ppm (dd) J= 6.9, 6.9 Hz (1 H)	HMBC 21 →23
24	111.1 ppm	7.13 ppm (d) J= 6.7 Hz (1 H)	HMBC 22 →24
25	136.3 ppm	–	HMBC 21,23→25
26	–	11.05 ppm (s) (1 H)	
27	130.2 ppm	–	HMBC 13,26→27
28	170.6 ppm	–	HMBC 17→28
29	–	8.12 ppm (d) J= 4.2 Hz (1 H)	HMBC 29→28
30	48.3 ppm	3.70-3.67 ppm (m) (1 H)	COSY 29→30
31	26.4 ppm	1.90-1.85 ppm (m) ; 1.70-1.65 ppm (m) (2 H)	COSY 30→31
32	30.3 ppm	2.28-2.24 ppm (m) ; 2.17-2.13 ppm (m) (2 H)	TOCSY 30→32
33	173.8 ppm	–	HMBC 32→33
34	–	12.11 ppm (br s) (1 H)	
35	171.3 ppm	–	HMBC 30→35
36	–	7.52 ppm (d) J= 5.6 Hz (1 H)	HMBC 36→35
37	54.3 ppm	4.09-4.07 ppm (m) (1 H)	COSY 36→37
38	35.8 ppm	2.83 ppm (d) J= 13.8 Hz ; 2.60 ppm (dd) J=13.9, 9.2 Hz (2 H)	COSY 37→38
39	129.6 ppm	–	HMBC 41→39
40	130.1 ppm	7.16 ppm (d) J= 6.2 Hz (2 H)	HMBC 40→38
41	114.8 ppm	6.83 ppm (d) J= 6.1 Hz (2 H)	COSY 40→38
42	155.7 ppm	–	HMBC 1→42
43	173.1 ppm	–	HMBC 44→43
44	–	7.40 ppm (br s) ; 6.90 ppm (br s) (2 H)	TOCSY 44→44'



Acyclic Cinnamyl Carbonate 3.S18: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S19: Synthesized according to Procedure B. Carried forward without purification.

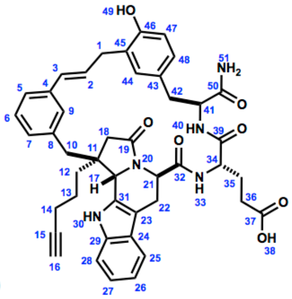


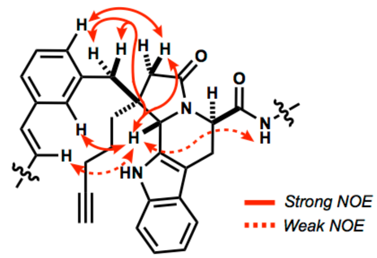
Macrocyclic Product 3.46: Synthesized according to Procedure C. Purified by preparative SiO_2 chromatography 1→10% MeOH/CH_3Cl(0.1% TFA). White Solid. 133 mg [176 µmol, 31% yield over three steps]. MS *m/z* 756.3 (calc'd: $C_{44}H_{46}N_5O_7^+$, $[M+H]^+$, 756.3).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

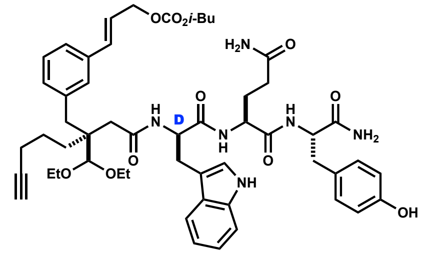
Macrocycle **3.46**



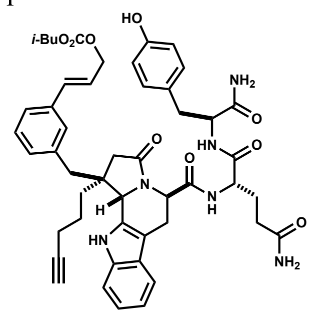


(600MHz, DMSO-d6, 298K)

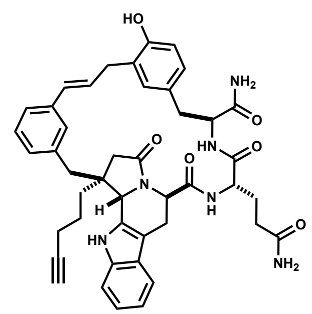
	13C	1H	key correlation
1	32.4 ppm	3.50 ppm (dd) J=15.6, 7.3 Hz ; 3.21 ppm (dd) J=15.6, 6.9Hz (2H)	
2	129.5 ppm	6.33 ppm (ddd) J=15.6, 7.2, 7.2 Hz (1H)	
3	130.5 ppm	6.49 ppm (d) J=15.7 Hz (1H)	
4	137.6 ppm	–	HMBC 2→4
5	123.7 ppm	7.31 pm (d) J=7.7 Hz (1H)	HMBC 3→5
6	128.4 ppm	7.35 ppm (dd) J=7.4, 7.4 H (1H)	HMBC 6→ / TOCSY 6→5, 7
7	130.0 ppm	7.10 ppm (d) J=7.7 Hz (1H)	TOCSY 5→7
8	137.5 ppm	–	HMBC 6→8
9	128.6 ppm	7.37 ppm (s) (1H)	HMBC 3, 5→9
10	39.8 ppm	3.34–3.32 ppm (m) (under water) ; 3.17 ppm J=15.4 Hz (2H)	HMBC 10→8, 7, 9
11	44.1 ppm	–	HMBC 10, 17→11
12	34.7 ppm	1.38–1.33 ppm (m) ; 1.26–1.23 ppm (m)	HMBC 10, 18→12
13	22.6 ppm	1.47–1.40 ppm (m) ; 1.36–1.33 ppm (m) (2H)	COSY 12→13
14	18.1 ppm	1.91 (ddd) J=6.6, 6.6, 2.5 Hz (2H)	
15	83.8 ppm	–	HMBC 13, 14→15
16	70.8 ppm	2.56 ppm (dd) J=2.6, 2.6 Hz (1H)	
17	57.3 ppm	5.60 ppm (s) (1H)	
18	38.1 ppm	2.19 ppm (d) J=16.4 Hz ; 2.09 (d) J=16.4 Hz (2H)	HMBC17, 10→18
19	171.0 ppm	–	HMBC 18→19
20	–	–	
21	48.7 ppm	5.02 (d) J=6.6 Hz (1H)	
22	25.1 ppm	3.17 ppm (d) J=15.5 Hz ; 2.87–2.83 ppm (m) (2H)	COSY 21→22
23	106.0 ppm	–	HMBC 17, 21→23
24	126.1 ppm	–	HMBC 22, 30→24
25	116.9 ppm	7.37 ppm (d) J=7.8 Hz (1H)	HMBC 25→29
26	118.3 ppm	6.98 ppm (dd) J=7.6, 7.6 Hz (1H)	TOCSY/COSY 27→26
27	120.5 ppm	7.08 ppm (ddd) J=7.6, 7.6, 0.8 Hz (1H)	HMBC 27→29
28	110.9 ppm	7.35 ppm (d) J=8.1 Hz (1H)	HMBC 26→28
29	136.4 ppm	–	HMBC 30→29
30	–	10.59 ppm (s) (1H)	
31	130.0 ppm	–	HMBC 17, 30→31
32	170.0 ppm	–	HMBC 21→32
33	–	8.05 ppm (d) J=6.6 Hz (1H)	HMBC 33→32
34	52.0 ppm	3.80 ppm (ddd) J=9.3, 6.7, 4.4 Hz (1H)	TOCSY 33→34
35	26.8 ppm	1.83–1.78 ppm (m) ; 1.68–1.62 ppm (m) (2H)	COSY34→35
36	30.0 ppm	2.15 ppm (ddd) J=16.3, 11.3, 5.1 Hz ; 2.05 ppm (ddd) J=16.4, 11.3, 5.1 Hz (2H)	TOCSY 34→36
37	173.7 ppm	–	HMBC 36→37
38	–	12.06 (1H)	
39	171.1 ppm	–	HMBC 34→39
40	–	7.42 ppm (d) J=7.9 Hz (1H)	HMBC 40→39
41	53.9 ppm	4.20 (ddd) J=8.2, 8.2, 3.8 Hz (1H)	COSY 40→41
42	36.7 ppm	2.66 ppm (dd) J=13.9, 3.4 Hz ; 2.59 ppm (dd) J=14.0, 8.3 Hz (2H)	COSY 41→42
43	127.5 ppm	–	HMBC 42, 47–43
44	129.8 ppm	6.86 ppm (d) J=1.6 Hz (1H)	HMBC 44→46
45	125.4 ppm	–	HMBC 1, 47→45
46	153.2 ppm	–	
47	114.3 ppm	6.66 ppm (d) J=8.1 Hz (1H)	HMBC 47→46
48	127.7 ppm	6.84 ppm (dd) J=8.3, 1.9 Hz (1H)	
49	–	9.17 ppm (s) (1H)	
50	172.7 ppm	–	HMBC 41→50
51	–	7.37 ppm (s) ; 6.95 ppm (br s)	HMBC 51→50



Acyclic Cinnamyl Carbonate 3.S20: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S21: Synthesized according to Procedure B. Carried forward without purification.



Macrocyclic Product 3.47: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. White Solid. 27 mg [36 µmol, 22% yield over three steps]. MS *m/z* 755.3 (calc'd: $C_{44}H_{47}N_6O_6^+$, $[M+H]^+$, 755.4).

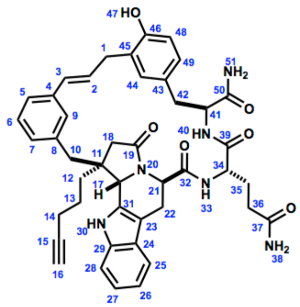
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

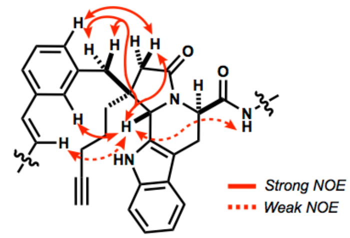
Time	%B
0	25
1	25
14	80
15	25

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	42
2	42
10	48
12	100

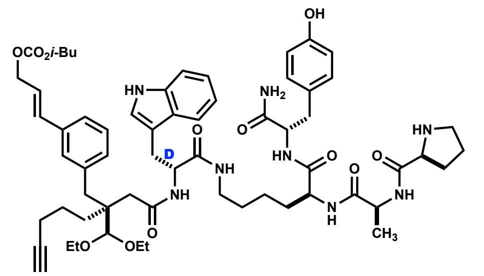
Macrocycle **3.47**



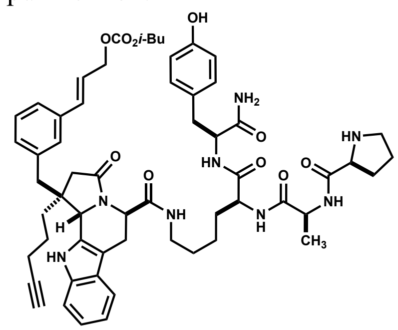


(600MHz, DMSO-d6, 298K)

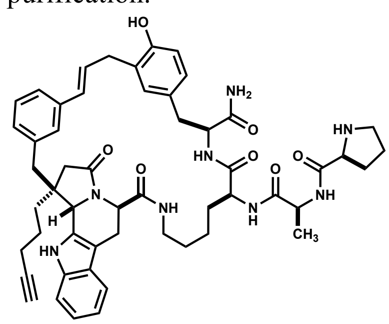
	13C	1H	key correlation
1	32.2 ppm	3.48 ppm (dd) J=15.8, 7.3 Hz ; 3.24 ppm J=15.8, 6.8 Hz (2H)	
2	129.4 ppm	6.35 ppm (ddd) J=15.6, 7.1, 7.1 Hz (1H)	
3	130.7 ppm	6.49 ppm (d) J=15.6 Hz (1H)	
4	137.7 ppm	–	HMBC 2→4
5	124.0 ppm	7.31 ppm (d) J=7.5 Hz (1H)	HMBC 3→5
6	128.4 ppm	7.37–7.34 ppm (m) (1H)	HMBC 6→4, 8
7	130.1 ppm	7.11 ppm (d) J=8.1 Hz (1H)	TOCSY 5→7
8	137.4 ppm	–	HBC 10→8
9	128.6 ppm	7.40 ppm (s) (1H)	HMBC 17→10
10	39.9 ppm	3.33 ppm (d) J=13.9 Hz ; 2.83 ppm (d) J=13.6 Hz (2H) (Ab quartet)	HMBC 17→10
11	44.3 ppm	–	HMBC 10, 17, 18→11
12	34.6 ppm	1.37–1.32 ppm (m) ; 1.25–1.21 ppm (m) (2H)	HMBC 12→10, 11, 17, 18
13	22.5 ppm	1.48–1.41 ppm (m) ; 1.37–1.32 ppm (m) (2H)	HMBC 12→13
14	18.1 ppm	1.92 ppm (ddd) J=6.1, 6.1, 2.3 Hz (2H)	TOCSY 12→14
15	83.9 ppm	–	HMBC 13, 14→15
16	71.0 ppm	2.58 ppm (dd) J=2.5, 2.5 Hz (1H)	
17	57.4 ppm	5.59 ppm (s)	NOESY 17→10, 18, 9, 33
18	38.4 ppm	2.22 ppm (d) J=16.5 Hz ; 2.11 ppm (d) J=16.5 Hz (2H) (AB quartet)	HMBC 10→18
19	171.1 ppm	–	HMBC 18→19
20	–	–	HMBC 22, 24→20
21	48.8 ppm	5.03 ppm (d) J=6.4 Hz	
22	25.0 ppm	3.20 (d) J=15.9 Hz ; 2.85 ppm (dd) J=15.9, 6.4 Hz	COSY/TOCSY 21→22
23	106.1 ppm	–	HMBC 17, 21, 22→23
24	126.0 ppm	–	
25	117.3 ppm	7.41 ppm (d) J=7.8 Hz (1H)	HMBC 25→23
26	118.5 ppm	6.98 ppm (dd) J=7.6, 7.6 Hz (1H)	COSY 25→26
27	120.8 ppm	7.08 ppm (dd) 8.1, 8.1 Hz (1H)	HMBC 25→27
28	111.1 ppm	7.34 ppm (d) J=7.9 Hz (1H)	COSY 28→27
29	136.4 ppm	–	HMBC 25, 27→29
30	–	10.51 (s) (1H)	
31	129.9 ppm	–	HMBC 17, 30→31
32	170.2 ppm	–	HMBC 21→32
33	–	8.18 ppm (d) J=6.3 Hz (1H)	HMBC 33→32
34	52.6 ppm	3.79–3.75 ppm (m) (1H)	COSY 33→32
35	52.6 ppm	1.80–1.74 ppm (m) ; 1.66–1.59 ppm (m) (2H)	COSY 34→35
36	31.4 ppm	2.08–2.01 ppm (m) ; 1.98–1.93 ppm (m) (2H)	COSY 36→35
37	173.9 ppm	–	HMBC 36→37
38	–	7.22 ppm (d) J=6.8 Hz (1H)	HMBC 38→37
39	171.4 ppm	–	HMBC 34→39
40	–	7.33 ppm (d) J=6.4 Hz (1H)	HMBC 40→39
41	54.1 ppm	4.20–4.16 ppm (m) (1H)	COSY 40→41
42	36.8 ppm	2.66 ppm (dd) J=13.8, 2.5 Hz ; 2.54–2.50 ppm (under DMSO) (m) (2H)	COSY 41→42
43	127.6 ppm	–	HMBC 41, 42→43
44	129.9 ppm	6.85 (br s)	HMBC 44→46
45	125.4 ppm	–	HMBC 1, 2→45
46	153.2 ppm	–	
47	–	9.20 ppm (br s) (1H)	
48	114.4 ppm	6.67 ppm (d) J=8.7 Hz (1H)	HMBC 48→43, 45
49	127.8 ppm	6.84 ppm (d) J=8.5 Hz (1H)	HMBC 44→49 / 49→46
50	173.0 ppm	–	HMBC 41→50
51	–	7.38 ppm (br s) ; 7.00 ppm (br s) (2H)	HMBC 51→50



Acyclic Cinnamyl Carbonate 3.S22: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S23: Synthesized according to Procedure B. Carried forward without purification.



Macrocyclic Product 3.48: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. Yellow solid. HCl-salt: 47 mg [49 µmol, 13% yield over three steps]. MS *m/z* 923.4 (calc'd: $C_{53}H_{63}N_8O_7^+$, $[M+H]^+$, 923.5).

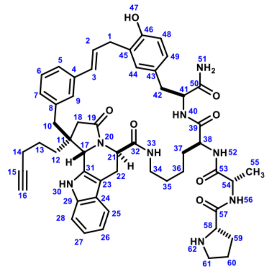
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

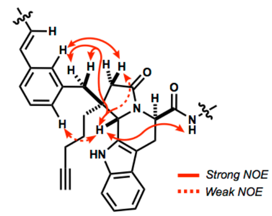
Time	%B
0	25
1	25
14	80
15	25

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	40
2	40
30	50

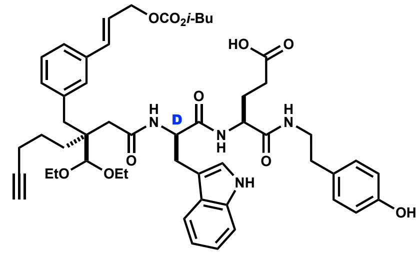
Macrocycle **3.48**



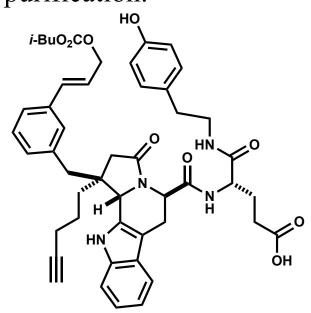


(600MHz, DMSO-d6, 298K)

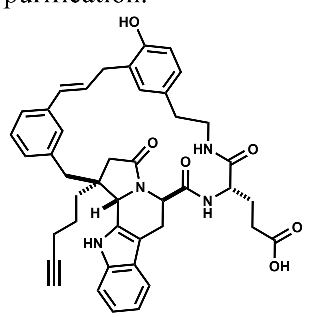
	13C	1H	key correlation
1	32.2 ppm	3.47–3.44 (m) (under water) ; 3.35 (dd) J=16.1, 6.9 Hz (2H)	
2	129.3 ppm	6.46 ppm (ddd) J=15.7, 6.6, 6.6 Hz (1H)	
3	129.5 ppm	6.35 ppm (d) J=15.9 Hz (1H)	
4	137.4 ppm	–	HMBC 2→4
5	124.0 ppm	7.33–7.31 ppm (m) (1H)	HMBC 3→5
6	128.0 ppm	7.31 ppm (dd) J=7.7, 7.7 Hz (1H)	
7	129.5 ppm	7.15–7.13 ppm (m) (1H)	HMBC 5, 9→7
8	137.5 ppm	–	HMBC 10→8
9	128.5 ppm	7.54 ppm (s) (1H)	HMBC 9→5 / TOCSY 9→5
10	40.5 ppm	3.29 ppm (d) J=13.7 Hz ; 2.99 ppm (d) J=13.7 Hz (2H)	HMBC 10→17
11	44.6 ppm	–	HMBC 10, 17→11
12	34.3 ppm	1.32–1.28 ppm (m) ; 1.25–1.21 ppm (m) (2H)	HMBC 10, 17→12
13	22.3 ppm	1.32–1.28 ppm (m) (2H)	HMBC 13→15
14	18.0 ppm	1.88–1.86 ppm (m) (2H)	TOCSY 14→12
15	83.6 ppm	–	HMBC 14→15
16	70.9 ppm	2.52 pm (dd) J=2.4, 2.4 Hz (1H)	
17	57.4 ppm	4.96 ppm (s) (1H)	
18	39.1 ppm	2.91 ppm (d) J=16.1 Hz ; 2.06 ppm (d) J=16.0 Hz (2H)	HMBC 10→18
19	172.2 ppm	–	HMBC 18→19
20	–	–	
21	48.9 ppm	4.88 ppm (d) J=6.6 Hz	
22	21.5 ppm	3.46–3.43 ppm (m) (under water) ; 2.66 ppm (dd) J=15.7, 6.5 Hz (2H)	COSY 21→22
23	106.9 ppm	–	HMBC 21, 17, 22→23
24	126.0 ppm	–	HMBC 26, 28→24
25	117.6 ppm	7.42 ppm (d) J=8.1 Hz (1H)	HMBC 25→23
26	118.4 ppm	7.00 ppm (dd) J=7.9, 7.9 Hz (1H)	COSY 25→26
27	120.9 ppm	7.10 ppm (dd) J=8.1, 8.1 Hz (1H)	HMBC 25→27
28	111.1 ppm	7.40 ppm (d) J=8.2 Hz (1H)	HMBC 26→28
29	136.5 ppm	–	HMBC 25, 27→29
30	–	10.50 ppm (s) (1H)	
31	128.9 ppm	–	HMBC 17→31
32	168.1 ppm	–	HMBC 21→32
33	–	7.56 ppm (dd) J-5.9, 5.9 Hz (1H)	HMBC 33→32
34	38.0 ppm	2.94 ppm (dd) J=13.9, 6.1 Hz ; 2.66 ppm (dd) J=14.1, 5.8 Hz (2H)	COSY 33→34
35	27.8 ppm	1.06–1.01 ppm (m) (2H)	COSY 34→35
36	22.2 ppm	1.06–0.96 ppm (m) (2H)	COSY 35→36
37	30.7 ppm	1.62–1.58 ppm (m) ; 1.42–1.35 ppm (m) (2H)	TOCSY 37→36
38	53.2 ppm	3.97 ppm (ddd) J=8.1, 8.1, 5.3 Hz (1H)	COSY 38→37
39	170.7 ppm	–	HMBC 38→39
40	–	7.60 ppm (d) J=7.2 Hz (1H)	HMBC 40→39
41	53.4 ppm	4.39–4.34 ppm (m) (1H) (overlapped with 54)	COSY 40→41
42	36.3 ppm	2.91 ppm (dd) J=14.0, 4.0 Hz ; 2.78 ppm (dd) J=14.0, 8.9 Hz (2H)	COSY 41→42
43	127.3 ppm	–	HMBC 42→48→43
44	130.4 ppm	6.93 ppm (d) J=1.6 Hz (1H)	HMBC 42→44
45	125.0 ppm	–	HMBC 1, 48→45
46	153.1 ppm	–	HMBC 44, 48, 49→46
47	–	not observed	
48	114.3 ppm	6.68 ppm (d) J=8.2 Hz (1H)	COSY 49→48 / TOCSY 44→48
49	127.4 ppm	6.84 ppm (dd) J=8.3, 1.6 Hz (1H)	TOCSY 44→49
50	172.6 ppm	–	HMBC 41→50
51	–	7.37 ppm (br s) ; 7.20 ppm (br s) (2H)	TOCSY 51→51'
52	–	8.18 ppm (d) J=7.3 Hz (1H)	COSY 52→38
53	171.7 ppm	–	HMBC 52→53
54	48.3 ppm	4.33 ppm (ddd) J=7.0, 7.0, 7.0 Hz (1H) (overlapped with 41)	HMBC 54→53
55	17.5 ppm	1.24 ppm (d) J=7.0 Hz (3H)	COSY 54→55
56	–	8.73 ppm (d) J=7.1 Hz (1H)	COSY 56→54
57	167.5 ppm	–	HMBC 56→57
58	58.3 ppm	4.14 (dddd) J=6.0, 6.0, 6.0, 6.0 Hz (1H)	HMBC 58→57
59	29.3 ppm	2.28–2.22 ppm (m) ; 1.82–1.78 ppm (m) (2H)	COSY 58→59
60	23.3 ppm	1.84–1.78 ppm (m) (2H)	TOCSY 58→60 / COSY 61→60
61	45.3 ppm	3.18–3.12 ppm (m) 2H)	TOCSY 58→61
62	–	9.82 (br s) ; 8.46–8.43 ppm (m) (2H)	COSY 62, 62'→58, 61



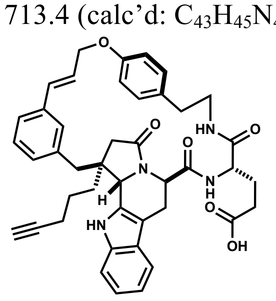
Acyclic Cinnamyl Carbonate 3.S23: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S24: Synthesized according to Procedure B. Carried forward without purification.



Macrocyclic Product 3.49: Synthesized according to Procedure C. Purified by preparative TLC: 3% MeOH / 96.5%CH_3Cl / 0.5%AcOH. White solid. 20 mg [28 µmol, 57% yield over three steps]. MS *m/z* 713.4 (calc'd: $C_{43}H_{45}N_4O_6^+$, $[M+H]^+$, 713.2).

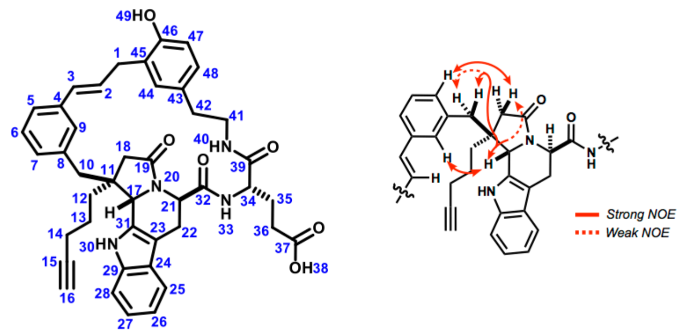


Macrocyclic Product 3.50: Synthesized according to Procedure F. Purified by preparative TLC: 3% MeOH / 96.5%CH_3Cl / 0.5%AcOH. White solid. 8 mg [11 µmol, 19% yield over three steps]. ^{1}H NMR ($CDCl_3$, 500 MHz): δ11.06 (s, 1H), 8.23 (d, *J* = 6.9 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.45–7.42 (m, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.00 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 15.9 Hz, 1H), 6.33 (ddd, *J* = 15.9, 6.6, 4.8 Hz, 1H), 5.25 (s, 1H), 5.06 (d, *J* = 6.6 Hz, 1H), 4.90 (dd, *J* = 15.0, 7.0 Hz, 1H), 4.83 (dd, *J* = 15.0, 4.7 Hz, 1H), 4.11 (dd, *J* = 5.3, 5.3 Hz, 1H), 3.70–3.65 (m, 1H), 3.13 (d, *J* = 15.3 Hz, 1H), 3.01–2.96 (m, 1H), 2.90 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.84 (d, *J* = 13.9 Hz, 1H), 2.74–2.67 (m, 1 H), 2.45–2.36 (m, 2H), 2.23–2.16 (m, 1H), 2.16 (d, *J* = 16.3 Hz, 1H), 2.08 (d, *J* = 16.2 Hz, 1H), 2.02–1.95 (m, 1H), 1.93 (ddd, *J* = 6.9, 6.9, 2.0 Hz, 2H), 1.80–1.73 (m, 1H), 1.70–1.62 (m, 1H), 1.43–1.23 (m, 6H), 1.12–1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ173.8, 171.4, 171.2, 171.0, 155.8, 137.8, 136.7, 135.9, 132.9, 131.7, 131.5, 130.7, 130.04, 129.97, 128.8, 126.3, 126.2, 123.0, 121.1, 118.8, 117.3, 115.5, 111.5, 106.0, 84.2, 71.3, 67.6, 57.7, 52.6, 48.9, 45.2, 40.4, 38.0, 34.4, 34.0, 32.4, 30.5, 26.6, 26.1, 22.6, 18.2; MS *m/z* 713.4 (calc'd: $C_{43}H_{44}N_4O_6 + H^+$, $[M+H]^+$, 713.2).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

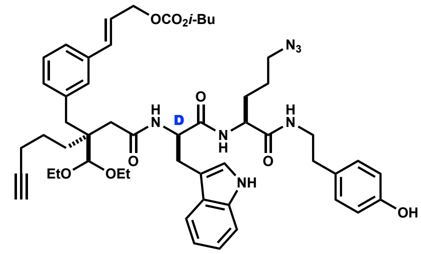
Time	%B
0	45
1	45
14	100
15	45

Macrocycle **3.49**

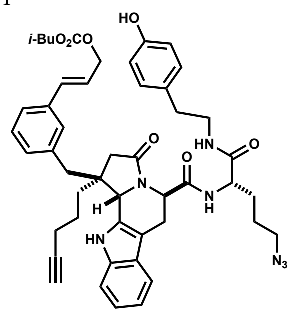


(600MHz, DMSO-d6, 298K)

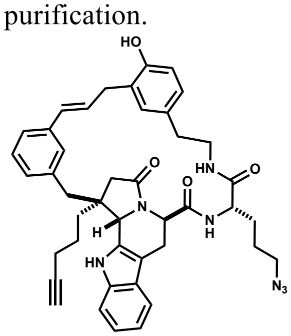
	13C	1H	key correlation
1	31.5 ppm	3.49 ppm (dd) J=16.7, 7.0 Hz ; 3.26 ppm (dd) J=16.7, 6.8Hz (2H)	
2	128.9 ppm	6.38 ppm (ddd) J=15.6, 6.7, 6.7 Hz (1H)	
3	131.0 ppm	6.47 ppm (d) J=15.6 Hz (1H)	
4	137.7 ppm	–	HMBC 2→4
5	123.6 ppm	7.34 pm (d) J=5.8 Hz (1H)	HMBC 3→5
6	128.2 ppm	7.35 ppm (dd) J=5.8, 5.8 Hz (1H)	HMBC 6→4
7	129.9 ppm	7.10 ppm (d) J=5.8 Hz (1H)	HMBC 7→5
8	137.4 ppm	–	HMBC 10→8
9	128.9 ppm	7.45 ppm (s) (1H)	HMBC 9→5
10	39.4 ppm	3.31 & 2.86 ppm (AB quartet) J=14.0 Hz (2H)	
11	44.2 ppm	–	HMBC 10, 12, 17, 18→11
12	34.4 ppm	1.34–1.30 ppm (m) ; 1.17 ppm (ddd) J=13.1, 13.1, 4.1 Hz (2H)	
13	22.5 ppm	1.45–1.41 ppm (m) ; 1.36–1.32 ppm (m) (2H)	COSY 13→12
14	18.1 ppm	1.92 (ddd) J=6.4, 6.4, 2.0 Hz (2H)	HMBC 14→16
15	83.6 ppm	–	HMBC 14→15
16	70.8 ppm	2.58 ppm (dd) J=2.0, 2.0 Hz (1H)	
17	57.3 ppm	5.56 ppm (s) (1H)	
18	38.3 ppm	2.32 & 2.09 ppm (AB quartet) J=16.0 Hz (2H)	
19	171.1 ppm	–	HMBC 18→19
20	–	–	
21	48.8 ppm	5.00 ppm (d) J=5.6 Hz (1H)	
22	24.5 ppm	3.21 ppm (d) J=15.1 Hz ; 2.80 ppm (dd) J=15.1, 5.6 Hz (2H)	COSY 21→22
23	105.7 ppm	–	HMBC 17, 21→23
24	126.0 ppm	–	HMBC 26, 28→24
25	117.1 ppm	7.37 ppm (d) J=7.3 Hz (1H)	HMBC 27→25
26	118.3 ppm	6.97 ppm (dd) J=7.3, 7.3 Hz (1H)	
27	120.5 ppm	7.07 ppm (dd) J=7.3, 7.3 Hz (1H)	
28	110.8 ppm	7.35 ppm (d) J=7.3 Hz (1H)	HMBC 26→28
29	136.1 ppm	–	HMBC 25,27→29
30	–	10.66 ppm (s) (1H)	
31	129.7 ppm	–	HMBC 17→31
32	169.4 ppm	–	HMBC 21, 22'→32
33	–	*not observed*	
34	52.7 ppm	3.62–3.57 ppm (m) (1H)	
35	26.9 ppm	1.61–1.51 ppm (m) (2H)	COSY 34→35
36	31.4 ppm	2.01–1.88 ppm (m) (2H)	TOCSY 34→36
37	173.6 ppm	–	HMBC 36→37
38	–	*not observed*	HMBC 34→39
39	171.6 ppm	–	
40	–	7.37 ppm (dd) J=5.7, 5.7 Hz (1H)	
41	39.6 ppm	3.38–3.32 ppm (m) ; 2.99–2.93 (m) (2H)	COSY 40→41
42	34.2 ppm	2.48–2.45 ppm (m) ; 2.99–2.93 ppm (m) (2H)	TOCSY 40→42
43	129.5 ppm	–	HMBC 47–43
44	129.2 ppm	6.75 ppm (s) (1H)	HMBC 44→46
45	125.2 ppm	–	HMBC 1→45
46	152.6 ppm	–	
47	114.2 ppm	6.69 ppm (d) J=7.8 Hz (1H)	HMBC 47→45
48	126.6 ppm	6.79 ppm (dd) J=7.8 Hz (1H)	HMBC 48→46
49	–	9.21 ppm (br s) (1H)	



Acyclic Cinnamyl Carbonate 3.S26: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S27: Synthesized according to Procedure B. Carried forward without purification.



Macrocyclic Product 3.51: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. Pale yellow solid. 27 mg [37 µmol, 57% yield over three steps]. MS *m/z* 724.4 (calc'd: $C_{43}H_{46}N_7O_4^+$, $[M+H]^+$, 724.4).

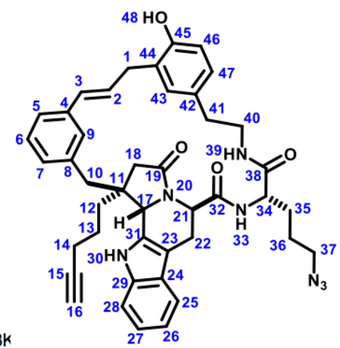
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

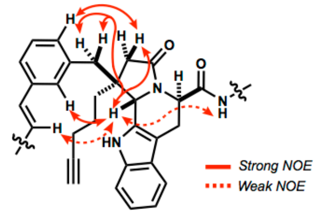
Time	%B
0	45
1	45
14	100
15	45

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	65
2	65
8	75
10	75

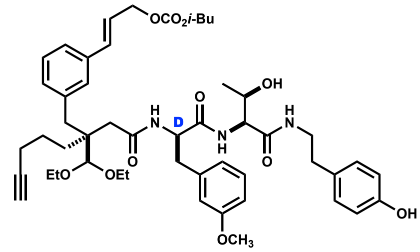
Macrocycle **3.51**



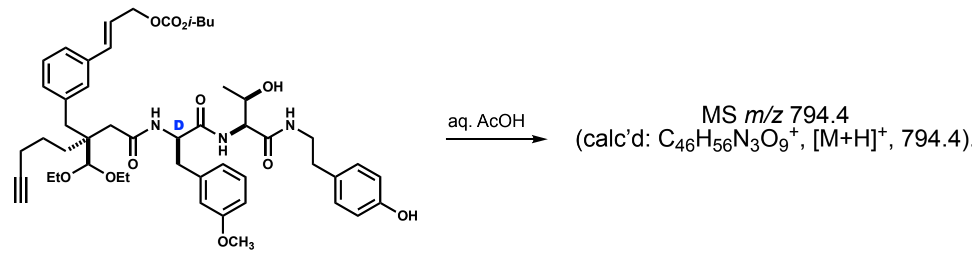


(600MHz, DMSO-d6, 298K

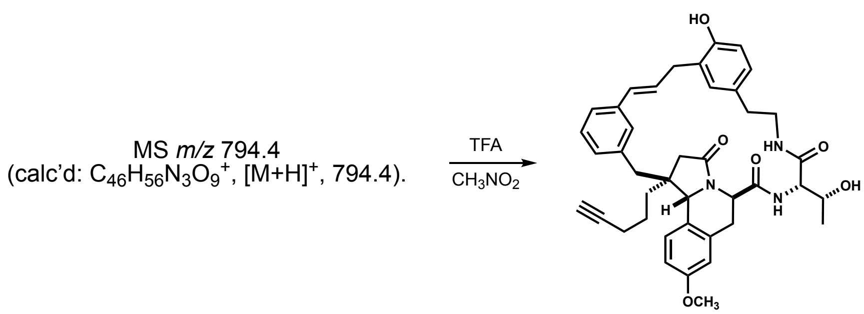
	13C	1H	key correlation
1	31.5 ppm	3.50 ppm (dd) J=16.5, 7.1 Hz ; 3.26 ppm (dd) J=16.4, 6.8Hz (2H)	
2	128.8 ppm	6.39 ppm (ddd) J=15.4, 7.2, 7.2 Hz (1H)	
3	131.1 ppm	6.50 ppm (d) J=15.4 Hz (1H)	
4	137.3 ppm	–	HMBC 2→4
5	123.4 ppm	7.34 pm (d) J=7.2 Hz (1H)	HMBC 3→5
6	128.2 ppm	7.34 ppm (dd) J=7.2, 7.2 Hz (1H)	HMBC 6→4
7	129.9 ppm	7.10 ppm (d) J=7.2 Hz (1H)	HMBC 5, 9→7
8	137.1 ppm	–	HMBC 10→8
9	128.7 ppm	7.44 ppm (s) (1H)	
10	39.4 ppm	3.33 & 2.83 ppm (AB quartet) J=13.6 Hz (2H)	
11	44.5 ppm	–	HMBC 10, 12, 17, 18→11
12	34.7 ppm	1.38–1.31 ppm (m) ; 1.19–1.13 ppm (m) (2H)	HMBC/TOCSY 14→12
13	22.4 ppm	1.45–1.39 ppm (m) ; 1.38–1.31 ppm (m) (2H)	HMBC 13→15 / COSY 14→13
14	17.9 ppm	1.92 (ddd) J=6.8, 6.8, 2.5 Hz (2H)	HMBC 14→16
15	83.5 ppm	–	HMBC 14→15
16	70.7 ppm	2.58 ppm (dd) J=2.5, 2.5 Hz (1H)	
17	57.2 ppm	5.55 ppm (s) (1H)	
18	38.0 ppm	2.25 & 2.09 ppm (AB quartet) J=16.3 Hz (2H)	
19	171.3 ppm	–	HMBC 18→19
20	–	–	
21	48.8 ppm	5.03 ppm (d) J=6.4 Hz (1H)	HMBC 21→19
22	24.8 ppm	3.17 ppm (d) J=15.3 Hz ; 2.83 ppm (dd) J=15.3, 6.3 Hz (2H)	COSY 21→22
23	105.9 ppm	–	HMBC 17, 21, 22→23
24	125.9 ppm	–	HMBC 26, 28→24
25	116.9 ppm	7.36 ppm (d) J=7.9 Hz (1H)	HMBC 25→23
26	118.2 ppm	6.98 ppm (dd) J=7.5, 7.5 Hz (1H)	COSY 27→26
27	120.6 ppm	7.08 ppm (dd) J=7.7, 7.7 Hz (1H)	HMBC 25→27
28	110.8 ppm	7.39 ppm (d) J=7.9 Hz (1H)	HMBC 28→27
29	136.3 ppm	–	HMBC 25,27→29
30	–	11.01 ppm (s) (1H)	
31	129.8 ppm	–	HMBC 17→31
32	169.8 ppm	–	HMBC 21→32
33	–	7.81 (d) J=7.0 Hz (1H)	HMBC 33→32
34	52.0 ppm	3.69–3.66 ppm (m) (1H)	COSY 33→34
35	28.3 ppm	1.45–1.39 ppm (m) ; 1.38–1.31 ppm (m) (2H)	COSY 34→35
36	34.6 ppm	1.38–1.31 ppm (m) ; 1.24–1.18 ppm (m) (2H)	COSY 37→36
37	49.8 ppm	3.13–3.04 ppm (m) (2H)	TOCSY 34→37
38	170.7 ppm	–	HMBC 34→38
39	–	7.45 ppm (dd) J=5.3, 5.3 Hz (1H)	HMBC 39→38
40	39.5 ppm	3.39–3.35 ppm (m) ; 3.02–2.94 (m) (2H)	COSY 39→40
41	34.2 ppm	2.54–2.52 ppm (m) ; 2.34 ppm (ddd) J=13.8, 10.7, 3.1 Hz (2H)	COSY 40→41
42	129.3 ppm	–	HMBC 41, 46–42
43	129.1 ppm	6.76 ppm (s) (1H)	
44	125.3 ppm	–	HMBC 1, 46→44
45	152.5 ppm	–	HMBC 1, 43→45
46	114.1 ppm	6.70 ppm (d) J=8.2 Hz (1H)	COSY 47→46
47	126.5 ppm	6.80 ppm (dd) J=8.2 Hz (1H)	HMBC 47→45
48	–	9.28 ppm (br s) (1H)	



Acyclic Cinnamyl Carbonate 3.S28: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Products 3.S29a & b: Synthesized according to Procedure B. Carried forward without purification.



Macrocyclic Product 3.52: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. White solid. 16 mg [24 μmol, 49% yield over three steps]. MS *m/z* 676.4 (calc'd: $C_{41}H_{46}N_3O_6^+$, $[M+H]^+$, 676.3).

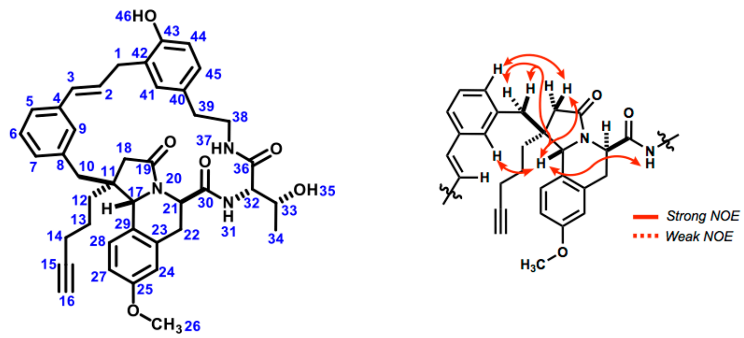
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	45
1	45
14	100
15	45

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

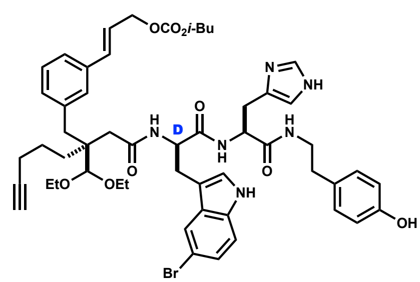
Time	%B
0	50
2	50
8	60
10	85

Macrocycle **3.52**

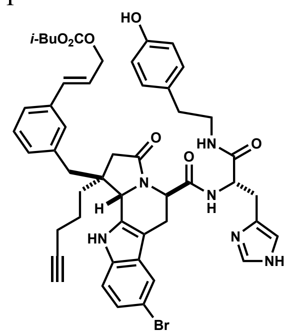


(600MHz, DMSO-d6, 298K)

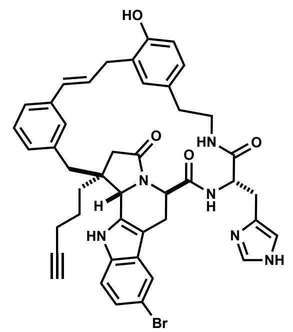
	^{13}C	^{1}H	key correlation
1	31.4 ppm	3.48 ppm (dd) J=16.4, 7.0 Hz ; 3.31 ppm (dd) J=16.5, 6.9 Hz (2 H)	
2	128.8 ppm	6.38 ppm (ddd) J=15.6, 7.2 Hz (1 H)	
3	131.5 ppm	6.51 ppm (d) J=15.7 Hz (1 H)	
4	137.5 ppm	–	HMBC 2→4
5	123.9 ppm	7.36-7.33 ppm (m) (underneath 6 + 28) (1 H)	HMBC 3→5
6	128.2 ppm	7.36-7.33 ppm (m) (underneath 5 + 28) (1 H)	COSY/TOCSY 6→7 HMBC 5,7→6
7	130.1 ppm	7.10 ppm (d) J=4.7 Hz (1 H)	TOCSY 9→7
8	137.5 ppm	–	HMBC 6,10→8
9	128.3 ppm	7.42 ppm (s) (1 H)	HMBC 9→5
10	40.8 ppm	3.16 ppm (d) J=13.9 Hz ; 2.85 ppm (d) J=14.0 (2 H)	
11	45.3 ppm	–	HMBC 10→11
12	34.8 ppm	1.31-1.29 ppm (m) ; 1.19-1.15 ppm (m) (2 H)	HMBC 10,17,18→12
13	22.3 ppm	1.39-1.29 ppm (m) ; 1.19-1.15 ppm (m) (2 H)	
14	18.0 ppm	1.92-1.90 ppm (m) (2 H)	COSY/TOCSY 14→13
15	83.8 ppm	–	HMBC 14,16→15
16	71.0 ppm	2.64 ppm (t) J=2.1 Hz (1 H)	
17	58.7 ppm	5.37 ppm (s) (1 H)	
18	38.8 ppm	2.39 ppm (d) J=16.8 Hz ; 2.09 ppm (d) J=16.6 Hz (2 H)	HMBC 10→18
19	171.1 ppm	–	HMBC 18→19
20	–	–	
21	48.5 ppm	5.04 ppm (d) J=6.4 Hz (1 H)	HMBC 21→19
22	32.3 ppm	3.06 ppm (d) J=15.9 Hz ; 2.90 ppm (dd) J=16.1, 6.1 Hz (2 H)	COSY/TOCSY 21→22
23	133.8 ppm	–	HMBC 17,28,22→23
24	113.9 ppm	6.68 ppm (s) (1 H)	HMBC 22→24
25	157.1 ppm	–	HMBC 28→25
26	55.7 ppm	3.72 ppm (s) (3 H)	HMBC 26→25
27	112.3 ppm	6.80 ppm (d) J=8.2 Hz (1 H)	HMBC 27→24
28	126.7 ppm	7.36-7.33 ppm (m) (underneath 6 + 5) (1 H)	
29	125.0 ppm	–	HMBC 22,24,27→29
30	169.4 ppm	–	HMBC 21→30
31	–	7.51 ppm (d) J=7.6 Hz (1 H)	HMBC 31→30
32	58.2 ppm	3.73-3.71 ppm (m) (1 H) (underneath 24) (1 H)	COSY/TOCSY 31→32
33	66.1 ppm	3.77-3.71 ppm (m) (1 H)	COSY/TOCSY 33→32
34	19.7 ppm	0.86 ppm (d) J=6.1 Hz (3 H)	COSY/TOCSY 33→34
35	–	not observed	
36	169.5 ppm	–	HMBC 32→36
37	–	7.48 ppm (dd) J=5.8, 5.8 Hz (1 H)	HMBC 37→36
38	40.0 ppm	3.36 ppm (dddd) J=6.3, 6.3, 6.3, 6.3 Hz; 3.06-3.02 ppm (m) (2 H)	HMBC 38→36
39	34.3 ppm	2.54-2.48 ppm (m) ; 2.45-2.41 (m) (2 H)	COSY/TOCSY 38→39
40	129.6 ppm	–	HMBC 38,39→40
41	129.2 ppm	6.85 (s) (1 H)	HMBC 41→45 / 45→41
42	125.6 ppm	–	HMBC 1,44→42
43	152.6 ppm	–	HMBC 1,44→43
44	114.3 ppm	6.70 ppm (d) J=8.2 Hz (1 H)	HMBC 44→40
45	126.5 ppm	6.82 ppm (d) J=8.2 Hz (1 H)	COSY/TOCSY 45→44
46	–	not observed	



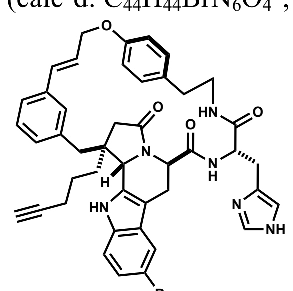
Acyclic Cinnamyl Carbonate 3.S30: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S31: Synthesized according to a modified Procedure B: 10 vol% of conc. H_3O_4P was added to the aqueous acetic acid solution. Carried forward without purification.



Macrocyclic Product 3.53: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions. White solid. TFA salt: 30 mg [33 μmol, 61% yield over three steps]. MS *m/z* 799.3 (calc'd: $C_{44}H_{44}BrN_6O_4^+$, $[M+H]^+$, 799.3).



Macrocyclic Product 3.54: Synthesized according to Procedure F. Purified by preparative HPLC using HCOOH instead of TFA – see below for conditions. White solid. TFA salt: 15 mg [19 μmol, 30% yield over three steps]. MS *m/z* 799.3 (calc'd: $C_{42}H_{51}N_5O_8$, $[M+H]^+$, 799.3).

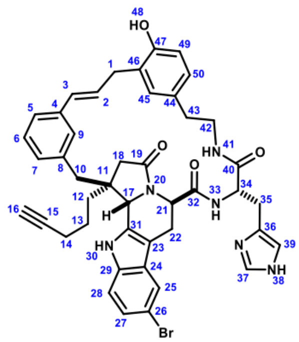
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

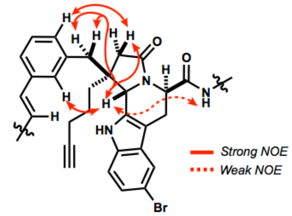
Time	%B
0	45
1	45
14	100
15	45

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA / HCOOH
Solvent B: ACN + 0.1% TFA / HCOOH
Flow rate: 18.0 mL/min

Time	%B
0	55
2	55
8	65

*Macrocycle **3.53***

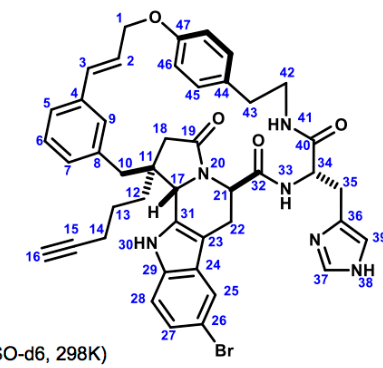


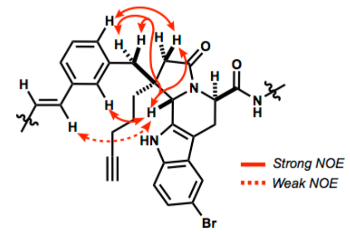


(600MHz, DMSO-d6, 298K)

	13C	1H	key correlation
1	31.4 ppm	3.47 ppm (dd) J=16.1, 5.9 Hz ; 3.32 ppm (dd) j=16.4, 6.1 Hz (2H)	
2	128.9 ppm	6.38 ppm (ddd) J=15.2, 6.5 6.5 Hz (1H)	
3	131.3 ppm	6.49 ppm (d) J=15.7 Hz (1H)	
4	137.5 ppm	–	HMBC 2→4
5	123.8 ppm	7.36–7.35 ppm (m) – underneath 6&28 (1H)	HMBC 3→5
6	128.3 ppm	7.37–7.35 ppm (m) – underneath 5&28 (1H)	HMBC 6→8
7	130.2 ppm	7.10 ppm (d) J=4.7 Hz (1H)	TOCSY 9→7 ; HMBC 9→7 ; HMBC 7→5
8	137.4 ppm	–	HMBC 10→8
9	128.7 ppm	7.44 ppm (s) (1H)	HMBC 9→3
10	39.4 ppm	3.30 ppm (d) J=12.2 Hz ; 2.84 ppm (d) J=12.1 Hz (AB quartet) (2H)	
11	44.5 ppm	–	HMBC 10→11
12	34.6 ppm	1.32–1.29 ppm (m) ; 1.17–1.13 ppm (m) (2H)	HMBC 17→12
13	22.4 ppm	1.40–1.37 pm (m) ; 1.32–1.29 ppm (m) (2H)	TOCSY 13→12
14	18.0 ppm	1.91 (very broad singlet) (2H)	
15	83.8 ppm	–	HMBC 14, 16→15
16	71.0 ppm	2.56 ppm (br s) (1H)	
17	57.3 ppm	5.49 ppm (s) (1H)	NOESY 17→9, 10, 33
18	38.0 ppm	2.26 ppm (d) J=16.4 Hz ; 2.10 ppm (d) J=16.4 Hz (2H)	HMBC 12→18
19	171.4 ppm	–	HMBC 18→19
20	–	–	
21	48.5 ppm	5.01 ppm (d) J=4.5 Hz (1H)	HMBC 21→19
22	24.5 ppm	2.95 ppm (d) J=15.3 Hz ; 2.77 ppm (dd) J=15.3, 4.6 Hz (2H)	TOCSY 21→22 ; COSY 21→22'
23	105.7 ppm	–	HMBC 17, 21, 22→23
24	127.9 ppm	–	HMBC 28, 30→24
25	119.4 ppm	7.46 ppm (s) (1H)	HMBC 25→23
26	111.1 ppm	–`	HMBC 25, 28→26
27	123.3 ppm	7.20 ppm (d) J=8.2 Hz (1H)	TOCSY 25→27
28	113.1 ppm	7.34 ppm (d) J=8.3 Hz (1H)	COSY 28→27
29	135.1 ppm	–	HMBC 25, 27, 30→29
30	–	11.20 ppm (s) (1H)	
31	131.5 ppm	–	HMBC 17, 22, 30→31
32	170.1 ppm	–	HMBC 21→32
33	–	8.11 ppm (d) J+4.9 Hz (1H)	HMBC 33→32
34	51.8 ppm	4.05–4.02 ppm (m) (1H)	COSY 33→34
35	26.4 ppm	2.87–2.83 ppm (m) ; 2.78–2.75 ppm (m) (2H)	COSY/TOCSY 34→35
36	129.2 ppm	–	HMBC 37, 39→36
37	133.4 ppm	8.81 ppm (s) (1H)	
38	–	not observed	
39	116.2 ppm	7.15 ppm (s) (1H)	TOCSY 37→39
40	169.8 ppm	–	HMBC 34→40
41	–	7.42–7.40 ppm (m) (1H)	HMBC 41→40
42	39.8 ppm	3.38–3.34 ppm (m) ; 3.07–3.03 ppm (m) (2H)	COSY 41→42
43	34.1 ppm	2.50 ppm–2.48 ppm (m) (underneath DMSO) ; 2.39–2.36 ppm (m) (2H)	COSY 42→43
44	129.3 ppm	–	HMBC 49→44
45	129.1 ppm	6.77 ppm (s) (1H)	HMBC 45→47
46	125.7 ppm	–	HMBC 1, 49→46
47	152.8 ppm	–	HMBC 1→47
48	–	9.20 ppm (s) – signal lost after water suppression	
49	114.4 ppm	6.71 ppm (d) J=7.3 Hz (1H)	TOCSY/COSY 50→49
50	126.7 ppm	6.81 ppm (d) J=7.2 Hz (1H)	HMBC 45→50

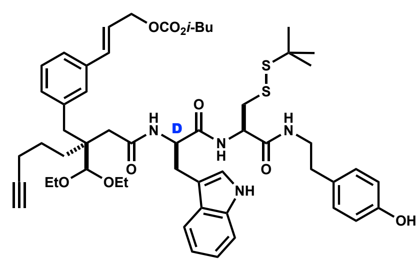
*Macrocycle **3.54***



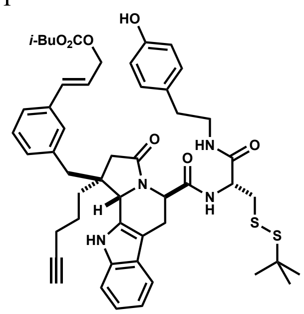


(600MHz, DMSO-d6, 298K)

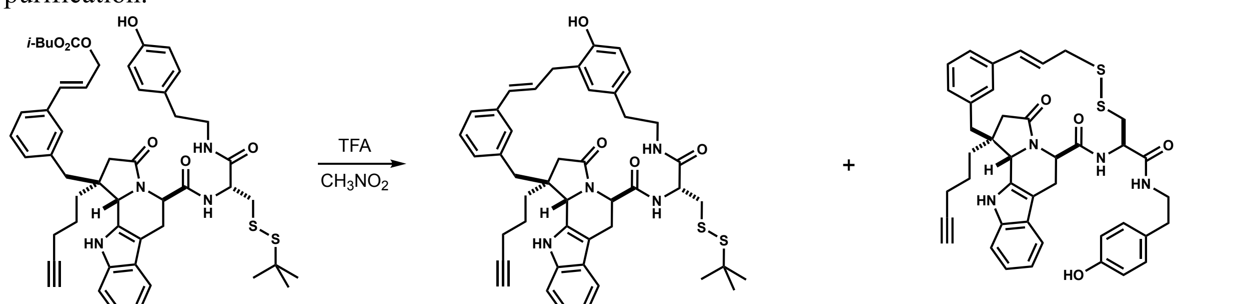
	13C	1H	key correlation
1	67.3 ppm	4.90 ppm (dd) J=15.0, 6.1 Hz; 4.85 ppm (dd) J=15.0, 4.4 Hz (2 H)	
2	125.9 ppm	6.33 ppm (ddd) J=16.1, 5.7, 5.7 Hz (1 H)	
3	132.5 ppm	6.66 ppm (d) J=16.1 Hz (1 H)	
4	135.8 ppm	–	HMBC 2→4
5	123.1 ppm	7.50 ppm (d) J=7.7 Hz (1 H)	HMBC 3→5 HMBC 5→3,7,9
6	128.6 ppm	7.34 ppm (dd) J=7.5, 7.5 Hz (1 H)	HMBC 6→4
7	131.3 ppm	7.15 ppm (d) J=7.4 Hz (1 H)	TOCSY 5→7
8	137.4 ppm	–	HMBC 6→8
9	130.0 ppm	7.31 ppm (s) (1 H)	HMBC 3→9
10	38.5 ppm	3.22 ppm (d) J=13.8, 2.85 Hz; 2.85 (d) J=13.7 Hz (2 H)	HMBC 10→8
11	45.0 ppm	–	HMBC 17,10→11
12	34.1 ppm	1.28-1.25 ppm (m); 1.06 (ddd) J=12.7, 12.7, 3.7 Hz (2 H)	HMBC 18→12
13	22.4 ppm	1.40-1.30 ppm (m) (2 H)	COSY 14→13
14	18.0 ppm	1.92 ppm (ddd) J=6.7, 6.7, 2.0 Hz (2 H)	HMBC 14→14
15	83.9 ppm	–	
16	71.0 ppm	2.58 ppm (dd) J=2.1, 2.1 Hz (1 H)	
17	57.2 ppm	5.15 ppm (s) (1 H)	
18	37.8 ppm	2.18 ppm (d) J=16.4 Hz; 2.10 (d) J=16.4 Hz (2 H)	HMBC 18→11
19	171.0 ppm	–	HMBC 18→19
20	–	–	
21	48.3 ppm	5.06 ppm (dd) J=5.6, 1.4 Hz (1 H)	
22	25.3 ppm	2.84-2.83 ppm (m) (2 H)	HMBC/COSY 21→22
23	105.5 ppm	–	HMBC 22→23
24	127.9 ppm	–	HMBC 28,30→24
25	119.3 ppm	7.43 ppm (d) J=1.5 Hz (1 H)	HMBC 25→23
26	111.3 ppm	–	HMBC 25,27,28→26
27	123.3 ppm	7.23 ppm (dd) J=8.3 Hz (1 H)	HMBC 25→27 / 27→25
28	113.2 ppm	7.38 ppm (d) J=8.5 Hz (1 H)	COSY/TOCSY 28→27
29	135.1 ppm	–	HMBC 25→29
30	–	11.28 ppm (s)	
31	131.5 ppm	–	HMBC 30→31
32	171.1 ppm	–	HMBC 21→32
33	–	8.45 ppm (d) J=7.2 Hz (1 H)	HMBC 33→32
34	51.9 ppm	4.09 ppm (ddd) J=7.4, 7.4, 7.4 Hz (1 H)	COSY/TOCSY 33→34
35	26.1 ppm	2.99 ppm (d) J=14.9, 5.8 Hz; 2.87-2.85 (m) (2 H)	COSY/TOCSY 34→35
36	129.1 ppm	–	HMBC 35,37,39→36
37	117.0 ppm	7.34 ppm (s)	HMBC 35,39→37
38	–	not observed	
39	133.3 ppm	8.85 ppm (s)	
40	170.0 ppm	–	HMBC 34→40
41	–	7.34-7.32 ppm (m) (1 H)	HMBC 41→40
42	40.1 ppm	3.23-3.19 ppm (m); 3.09-3.06 (m) (1 H)	COSY/TOCSY 41→42
43	32.4 ppm	2.70-2.67 ppm (m); 2.41-2.37 (m) (2 H)	COSY/TOCSY 42→43
44	131.2 ppm	–	HMBC 43→44
45	130.0 ppm	7.04 ppm (d) J=8.3 Hz (1 H)	HMBC 43→45
46	115.4 ppm	6.84 ppm (d) J=8.3 Hz (1 H)	HMBC 46→44
47	155.6 ppm	–	HMBC 1,45,46→47



Acyclic Cinnamyl Carbonate 3.S32: Synthesized according to Procedure A. Carried forward without purification.



Pictet-Spengler Product 3.S33: Synthesized according to Procedure B. Carried forward without purification.



3.55a

MS *m/z* 775.4
(calc'd: $C_{45}H_{51}N_4O_4S_2^+$, $[M+H]^+$, 775.3).

3.55b

MS *m/z* 719.3
(calc'd: $C_{41}H_{43}N_4O_4S_2^+$, $[M+H]^+$, 719.3).

Macrocyclic Products 3.55a & 3.55b: Synthesized according to Procedure C. Purified by preparative HPLC – see below for conditions.
3.55a: Yellow solid. 32 mg [41 µmol, 24% yield over three steps]. MS *m/z* 775.4 (calc'd: $C_{45}H_{51}N_4O_4S_2^+$, $[M+H]^+$, 775.3).
3.55b: Pale yellow solid. 33 [46 µmol, 27% yield over three steps]. MS *m/z* 719.3 (calc'd: $C_{41}H_{43}N_4O_4S_2^+$, $[M+H]^+$, 719.3).

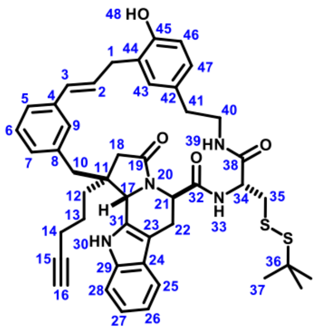
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

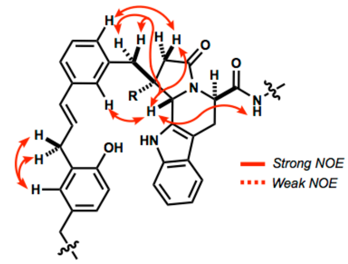
Time	%B
0	45
1	45
14	100
15	45

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	65
2	65
8	75
10	75

*Macrocycle **3.55a***

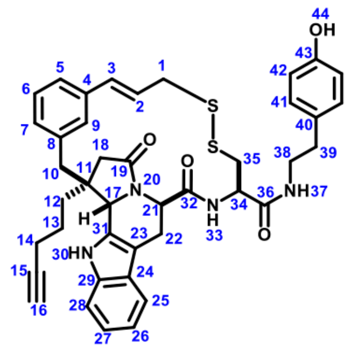


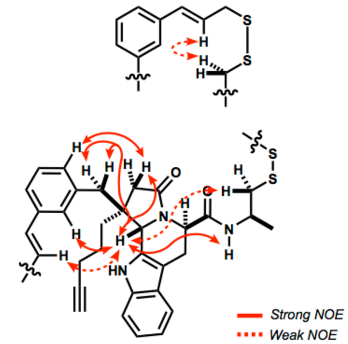


(600MHz, DMSO-d6, 298K)

	^{13}C	^{1}H	key correlation
1	31.7 ppm	3.51 ppm (dd) J=16.2, 6.7 Hz ; 3.24 ppm (dd) J=16.4, 5.8 Hz (2 H)	
2	129.1 ppm	6.40 ppm (ddd) J=15.6, 6.6, 6.6 Hz (1 H)	
3	131.0 ppm	6.46 ppm (d) J=15.7 Hz (1 H)	
4	137.5 ppm	–	HMBC 2→4
5	123.6 ppm	7.35-7.33 ppm (m) (1 H)	HMBC 2→5
6	128.1 ppm	7.35-7.33 ppm (m) (1 H)	HMBC 6→4
7	130.0 ppm	7.08 ppm (d) J=7.0 Hz (1 H)	HMBC 7→5
8	137.4 ppm	–	HMBC 10→8
9	128.9 ppm	7.45 ppm (s) (1 H)	HMBC 9→5
10	39.5 ppm	3.36 ppm (d) J=14.3 Hz ; 2.81 ppm (d) J=145.2 (2 H)	HMBC 10→7,9
11	44.3 ppm	–	HMBC 10,17→11
12	34.8 ppm	1.36-1.31 ppm (m) ; 1.20-1.16 ppm (m) (2 H)	HMBC 17→12
13	22.6 ppm	1.44-1.40 ppm (m) ; 1.35-1.32 ppm (m) (2H)	COSY/TOCSY 13→12
14	18.1 ppm	1.92-1.91 ppm (m) (2 H)	COSY/TOCSY 14→13
15	83.8 ppm	–	HMBC 13,14→15
16	70.9 ppm	2.57 ppm (t) J=2.3 Hz (1 H)	
17	57.3 ppm	5.59 ppm (s) (1 H)	
18	38.1 ppm	2.24 ppm (d) J=16.2 Hz ; 2.08 ppm (d) J=16.3 Hz (2 H)	HMBC 18→11
19	171.2 ppm	–	HMBC 18→19
20	–	–	
21	48.9 ppm	5.04 ppm (d) J=6.4 Hz (1 H)	HMBC 21→19
22	24.2 ppm	3.29 ppm (d) J=15.1 Hz ; 2.81 ppm (dd) J=15.0, 6.2 Hz (2 H)	COSY/TOCSY 21→22
23	106.2 ppm	–	HMBC 17,21,22→23
24	126.2 ppm	–	HMBC 26,28→24
25	117.3 ppm	7.35 ppm (d) J=8.3 Hz (1 H)	HMBC 25→23
26	118.2 ppm	–	HMBC 28→26
27	120.6 ppm	7.08 ppm (dd) J=8.2, 8.2 Hz (1 H)	HMBC 25→27
28	110.9 ppm	7.38 ppm (d) J=8.2 Hz (1 H)	TOCSY 28→25
29	136.5 ppm	–	HMBC 25,27→29
30	–	10.96 ppm (s) (1 H)	
31	129.7 ppm	–	HMBC 17,22→31
32	169.8 ppm	–	HMBC 21→32
33	–	7.87 ppm (d) J=7.3 Hz (1 H)	HMBC 33→32
34	52.6 ppm	3.96 ppm (ddd) J=10.8, 7.3, 3.8 Hz (1 H)	COSY/TOCSY 33→34
35	41.9 ppm	2.73 ppm (dd) J=12.8, 3.6 Hz ; 2.63 ppm (dd) J=12.9, 10.9 Hz (2 H)	COSY/TOCSY 34→35
36	47.2 ppm	–	HMBC 37→36
37	29.1 ppm	1.19 ppm (s) (9 H)	
38	169.2 ppm	–	HMBC 34→38
39	–	7.64 ppm (dd) J=5.7, 5.7 Hz (1 H)	HMBC 39→38
40	39.7 ppm	3.28-3.25 ppm (m) ; 3.12-3.07 (m) (2 H)	COSY/TOCSY 39→40
41	34.2 ppm	2.56-2.52 ppm (m) ; 2.34 (ddd) J=14.0, 11.0, 3.0 Hz (2 H)	COSY/TOCSY 40→41
42	129.4 ppm	–	HMBC 46→42
43	129.3 ppm	6.77 ppm (s) (1 H)	HMBC 43→45
44	125.6 ppm	–	HMBC 1,46→44
45	152.8 ppm	–	HMBC 1→45
46	114.1 ppm	6.68 ppm (d) J=8.0 Hz (1 H)	HMBC 48→46
47	126.9 ppm	6.78 ppm (d) J=8.3 Hz (1 H)	HMBC 43→47
48	–	9.10 ppm (s) (1 H)	

*Macrocycle **3.55b***

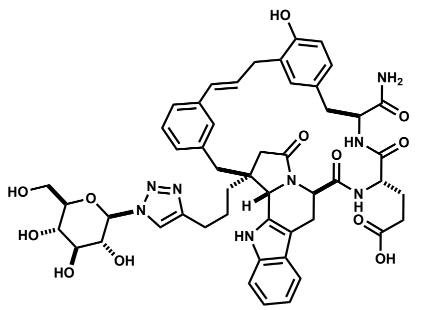




(600MHz, DMSO-d6, 298K)

	^{13}C	^{1}H	key correlation
1	43.2 ppm	3.62 ppm (dd) J=13.9, 9.2 Hz ; 3.46 ppm (dd) J=14.0, 6.2 Hz (2 H)	
2	127.1 ppm	6.24 ppm (ddd) J=15.5, 9.1, 6.2 Hz (1 H)	
3	131.5 ppm	6.58 ppm (d) J=15.4 Hz (1 H)	
4	136.6 ppm	–	HMBC 2→4
5	124.1 ppm	7.21 ppm (d) J=7.5 Hz (1 H)	HMBC 5→3
6	128.3 ppm	7.38 ppm (dd) J=7.6 Hz, 7.6 Hz (1 H)	HMBC 6→4
7	130.5 ppm	7.16 ppm (d) J=7.6 Hz (1 H)	TOCSY 5→7
8	137.3 ppm	–	HMBC 6→8
9	127.0 ppm	7.65 ppm (s) (1 H)	HMBC 3→9
10	39.9 ppm	3.34 ppm (d) J=13.8 Hz ; 2.86 ppm (d) J=13.8 Hz (2 H)	HMBC 10→8
11	43.4 ppm	–	HMBC 10,17→11
12	35.1 ppm	1.43-1.39 ppm (m) ; 1.35-1.32 ppm (m) (2 H)	HMBC 12→11
13	22.8 ppm	1.51-1.45 ppm (m) ; 1.35-1.32 ppm (m) (2 H)	COSY/TOCSY 13→12
14	18.1 ppm	1.94-1.92 ppm (m) (2 H)	COSY/TOCSY 14→13
15	83.8 ppm	–	HMBC 13,14→15
16	70.9 ppm	2.57 ppm (t) J=2.3 Hz (1 H)	
17	55.9 ppm	5.25 ppm (s) (1 H)	
18	38.2 ppm	2.31 ppm (d) J=16.4 Hz ; 2.12 ppm (d) J=16.3 Hz (2 H)	HMBC 18→11
19	171.4 ppm	–	HMBC 18→19
20	–	–	
21	49.8 ppm	4.93 ppm (d) J=5.8 Hz (1 H)	HMBC 21→19,17
22	22.3 ppm	3.39 ppm (d) J=15.5 Hz ; 2.76-2.74 ppm (m) (2 H)	COSY/TOCSY 21→22
23	106.8 ppm	–	HMBC 17,21,22→23
24	124.0 ppm	–	HMBC 26,28→24
25	117.6 ppm	7.45 ppm (d) J=7.7 Hz (1 H)	HMBC 25→23
26	118.3 ppm	7.10 ppm (dd) J=7.5, 7.5 Hz (1 H)	HMBC 28→26
27	120.8 ppm	7.01 ppm (dd) J=7.5, 7.5 Hz (1 H)	HMBC 25→27
28	111.0 ppm	7.42 ppm (d) J=8.0 Hz (1 H)	TOCSY 25→28
29	136.6 ppm	–	HMBC 25,27→29
30	–	10.88 ppm (s) (1 H)	
31	129.5 ppm	–	HMBC 17,30→31
32	168.1 ppm	–	HMBC 21→32
33	–	7.69 ppm (d) J=7.0 Hz (1 H)	HMBC 33→32
34	52.8 ppm	4.02 ppm (ddd) J=10.7, 6.8, 3.9 Hz (1 H)	COSY/TOCSY 33→34
35	40.7 ppm	2.73 ppm (dd) J=11.8, 11.8 Hz ; 2.37 ppm (dd) J=12.3, 3.6 Hz (2 H)	COSY/TOCSY 34→35
36	168.0 ppm	–	HMBC 34→36
37	–	7.93 ppm (t) J=5.6 Hz (1 H)	HMBC 37→36
38	40.5 ppm	3.14-3.03 ppm (m) (2 H)	COSY 37→38
39	33.8 ppm	2.47 ppm (t) J=7.4 Hz (2 H)	COSY/TOCSY 38→39
40	129.1 ppm	–	HMBC 38,42→40
41	129.2 ppm	6.91 ppm (d) J=8.2 Hz (2 H)	HMBC 41→39
42	114.7 ppm	6.65 ppm (d) J=8.2 Hz (2 H)	COSY/TOCSY 41→42
43	155.4 ppm	–	HMBC 41,42→43
44		9.14 ppm (br s) (1H)	

C.5. Synthesis of Glycosylated Macrocycles



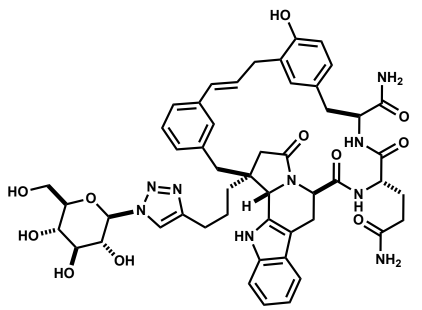
Glycosylated product 3.6: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. 4 mg [4.2 µmol, 32% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.73 (s, 1H), 7.48 (br s, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.37–7.31 (m, 2H), 7.09 (d, *J* = 6.9 Hz, 1H), 7.08 (d, 7.4 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 4.9 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.77 (br s, 1H), 6.66 (*J* = 8.1 Hz, 1H), 6.52 (d, *J* = 15.4 Hz, 1H), 6.37 (ddd, *J* = 15.3, 7.2, 7.2 Hz, 1H), 5.67 (s, 1H), 5.34 (d, *J* = 9.4 Hz, 1H), 5.00 (d, *J* = 6.6 Hz, 1H), 4.14 (ddd, *J* = 7.9, 7.9, 2.7 Hz, 1H), 3.76–3.73 (m, 1H), 3.70–3.66 (m, 2H), 3.53–3.38 (m, 3H) 3.23–3.18 (m, 1H), 2.95–2.86 (m, 1H), 2.63–2.60 (m, 1H), 2.36 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.22 (d, *J* = 16.4 Hz, 1H), 2.15 (d, *J* = 16.0 Hz, 1H), 2.08–2.03 (m, 1H), 1.99–1.94 (m, 1H), 1.78–1.73 (m, 1H), 1.64–1.59 (m, 2H), 1.55–1.50 (m, 1H), 1.38–1.31 (m, 1H), 1.27–1.21 (m, 1H); HRMS *m/z* 961.4422 (calc'd: $C_{50}H_{56}N_8O_{12}$ + H^+, $[M+H]^+$, 961.4090); LRMS *m/z* 961.4 (calc'd: $C_{50}H_{57}N_8O_{12}^+$, $[M+H]^+$, 961.4).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 8.0 mL/min

Time	%B
0	10
0.5	10
9	55



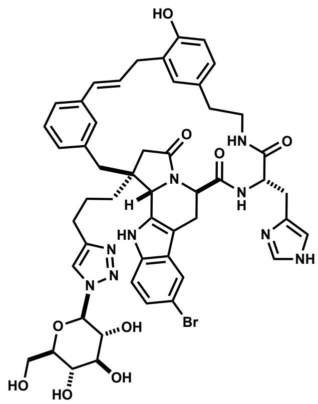
Glycosylated product 3.57: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. 5 mg [5.2 µmol, 40% yield]. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.85 (s, 1H), 7.47 (s, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.10 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.04 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.60–6.55 (m, 1H), 6.53 (d, *J* = 16.0 Hz, 1H), 5.77 (s, 1H), 5.32 (d, *J* = 9.2 Hz, 1H), 5.19 (d, *J* = 6.0 Hz, 1H), 4.17 (d, *J* = 10.7 Hz, 1H), 3.89 (d, *J* = 12.1 Hz, 1H), 3.86–3.83 (m, 1H), 3.83 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.72 (d, *J* = 12.2, 5.2 Hz, 1H), 3.56–3.47 (m, 6H), 3.13 (d, 13.8 Hz, 1H), 2.95 (d, *J* = 16.4, 1H), 2.89 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.75 (d, *J* = 13.3 Hz, 1H), 2.60–2.50 (m, 2H), 2.47 (d, *J* = 16.4 Hz, 1H), 2.17–2.08 (m, 2H), 1.81–1.74 (m, 1H), 1.72–1.63 (m, 3H), 1.42–1.32 (m, 3 H), 1.32–1.27 (m, 3H), 1.13–1.09 (m, 1H); ^{13}C NMR (CD_3OD, 126 MHz): δ 177.8, 176.7, 175.4, 174.2, 173.2, 154.6, 148.5, 140.0, 139.5, 137.9, 132.5, 131.0, 130.8, 130.5, 130.0, 129.9, 129.8, 128.9, 128.3, 127.5, 127.1, 127.0, 123.5, 122.4, 121.0, 119.5, 115.9, 112.1, 108.4, 89.4, 81.1, 78.5, 73.8, 70.9, 62.5, 60.9, 57.4, 56.6, 52.8, 43.4, 42.7, 37.2, 34.8, 32.7, 32.4, 27.6, 26.6, 24.7, 24.5; HRMS *m/z* 960.43384 (calc'd: $C_{50}H_{57}N_9O_{11} + H^+$, $[M+H]^+$, 960.4250); LRMS *m/z* 960.5 (calc'd: $C_{50}H_{57}N_9O_{11} + H^+$, $[M+H]^+$, 960.4).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 7.0 mL/min

Time	%B
0	10
0.5	10
9	55



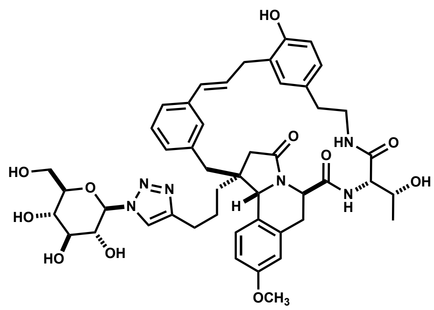
Glycosylated product 3.58: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. TFA salt: 1.5 mg [1.3 μmol,10% yield]. ^{1}H NMR (CD_3OD, 500 MHz): δ 8.63 (s, 1H), 7.56 (s, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.08 (d, *J* = 7.4 Hz, 1H), 6.97 (s, 1H), 6.92 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.1 Hz, 1H), 6.52 (br s), 5.50 (s, 1H), 5.36 (d, *J* = 9.1 Hz, 1H), 5.05 (d, *J* = 6.2, 1H), 4.28 (dd, *J* = 9.0, 5.2 Hz, 1H), 3.88 (d, *J* = 11.9 Hz, 1H), 3.83 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.72 (dd, *J* = 12.1, 5.5 Hz, 1H), 3.57–3.47 (m, 4H), 3.42–3.83 (m, 1H), 3.22 (d, *J* = 15.7 Hz, 1H), 2.99–2.95 (m, 1H), 2.96 (d, *J* = 14.7 Hz, 1H), 2.84–2.77 (m, 1H), 2.56–2.43 (m, 5H), 2.28 (d, *J* = 16.8 Hz, 1H), 1.70–1.64 (m, 1H), 1.61–1.54 (m, 1H), 1.38–1.26 (m, 6H); ^{13}C NMR (CD_3OD, 126 MHz): δ 175.9, 171.9, 171.4, 154.4, 148.4, 140.4, 139.2, 136.9, 135.0, 132.4, 131.7, 131.3, 131.2, 131.2, 131.1, 131.0, 130.1, 130.0, 129.4, 128.6, 127.9, 125.8, 125.8, 122.4, 121.4, 118.1, 115.5, 114.1, 113.4, 108.1, 89.4, 81.1, 78.5, 73.9, 70.9, 62.4, 60.5, 53.2, 51.8, 47.5, 42.1, 41.8, 41.0, 36.0, 35.6, 33.1, 28.1, 26.6, 24.7, 24.4; HRMS *m/z* 1004.2298, 1006.2300 (calc'd: $C_{50}H_{54}BrN_9O_9$ + H^+, $[M+H]^+$, 1004.3301, 1006.3280); LRMS *m/z* 1004.4, 1006.4 (calc'd: $C_{50}H_{54}BrN_9O_9$ + H^+, $[M+H]^+$, 1004.3, 1006.3).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 7.0 mL/min

Time	%B
0	20
0.5	20
7	54



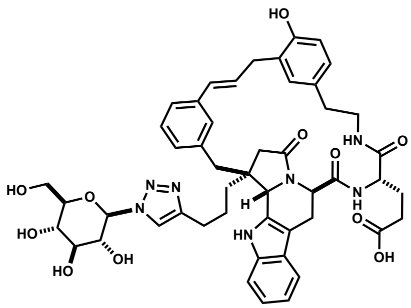
Glycosylated product 3.59: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. 9 mg [10 μmol, 67% yield]. ^{1}H NMR (CD_3OD, 500 MHz): δ 7.63 (s, 1H), 7.50 (s, 1H), 7.34 (ddd, *J* = 8.1, 1.5, 1.5 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.04 (ddd, *J* = 7.0, 1.5, 1.5 Hz, 1H), 7.01 (d, *J* = 2.2 Hz, 1H), 6.84 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.80, (dd, *J* = 8.1, 2.1 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.46 (ddd, *J* = 15.7, 6.2, 6.2 Hz, 1H), 5.51 (d, *J* = 9.3 Hz, 1H), 5.36 (s, 1H), 5.05 (dd, *J* = 6.3, 1.3 Hz, 1H), 3.89 (dd, *J* = 12.3, 2.0 Hz, 1H), 3.86 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.78–3.71 (m, 3H), 3.65–3.59 (m, 1H), 3.57 (ddd, *J* = 4.8, 4.8, 1.7 Hz, 1H), 3.56–3.50 (m, 2H), 3.47–3.44 (m, 1H), 3.34 (dd, *J* = 15.6, 6.0 Hz, 1H), 3.28 (dd, *J* = 5.3, 5.3 Hz, 1H), 3.27–3.21 (m, 2H), 2.95 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.92 (d, *J* = 14.2 Hz, 1H), 2.68 (d, *J* = 16.7 Hz, 1H), 2.62 (ddd, *J* = 14.0, 5.2, 5.2 Hz, 1H), 2.58–2.50 (m, 2H), 2.48–2.42 (m, 1H), 2.21 (d, *J* = 16.6 Hz, 1H), 1.63–1.54 (m, 1H), 1.49–1.40 (m, 1H), 1.36, (ddd, *J* = 13.0, 13.0, 3.8 Hz, 1H), 1.24 (ddd, *J* = 13.3, 13.3 4.5 Hz, 1H), 0.82 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (CD_3OD, 126 MHz): δ 176.0, 171.6, 171.6, 159.9, 154.4, 148.5, 140.1, 138.9, 135.3, 132.6, 131.3, 131.2, 131.0, 130.6, 130.1, 129.8, 128.8, 128.6, 128.1, 125.6, 125.4, 122.3, 115.5, 115.4, 114.6, 89.5, 81.1, 78.5, 73.9, 70.9, 68.2, 62.5, 61.3, 60.4, 55.8, 51.4, 48.2, 42.7, 41.3, 40.6, 36.7, 35.8, 33.4, 32.4, 26.7, 24.4, 19.7; HRMS *m/z* 881.3173 (calc'd: $C_{47}H_{56}N_6O_{11} + H^+$, $[M+H]^+$, 881.4080); LRMS *m/z* 881.4 (calc'd: $C_{47}H_{56}N_6O_{11} + H^+$, $[M+H]^+$, 881.4).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 7.0 mL/min

Time	%B
0	20
0.5	20
9	55



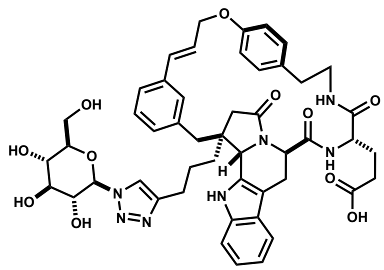
Glycosylated product 3.60: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. 4 mg [4.4 µmol, 29% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.19 (d, *J* = 5.3 Hz, 1H), 7.47 (s, 1H), 7.46 (d, *J* = 5.6 Hz, 1H), 7.36 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 7.34 (ddd, *J* = 8.1, 0.8, 0.8 Hz, 1H), 7.32 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.31 (s, 1H), 7.15 (ddd, *J* = 8.1, 7.2, 0.9 Hz, 1H), 7.05 (ddd, *J* = 7.8, 7.0, 0.8 Hz, 1H), 7.03 (ddd, *J* = 7. 1, 1.2, 1.2 Hz, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.73 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.51 (ddd, 15.8, 6.1, 6.1 Hz, 1H), 6.46 (d, *J* = 15.9 Hz, 1H), 5.45 (s, 1H), 5.24 (d, *J* = 9.0 Hz, 1H), 5.04 (d, *J* = 6.1 Hz, 1H), 3.87 (dd, *J* = 12.2, 1.9 Hz, 1H), 3.82 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.73 (dd, *J* = 8.7, 4.4 Hz, 1H), 3.70 (dd, *J* = 12.0, 5.4 Hz, 1H), 3.60 (dd, *J* = 15.1, 5.7 Hz, 1H), 3.56–3.51 (m, 1H), 3.54 (dd, *J* = 8.9, 8.9 Hz, 1H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.42 (ddd, *J* = 13.5, 11.3, 4.1 Hz, 1H), 3.28 (d, *J* = 14.2 Hz, 1H), 3.21 (dd, *J* = 14.6, 7.0 Hz, 1H), 3.05 (ddd, *J* = 13.4, 4.4, 4.4 Hz, 1H), 2.94 (d, *J* = 14.1 Hz, 1H), 2.89 (d, *J* = 16.5 Hz, 1H), 2.81 (ddd, *J* = 13.4, 6.4, 1.8 Hz, 1H), 2.55–2.38 (m, 3H), 2.24 (d, *J* = 16.5 Hz), 1.94 (ddd, *J* = 17.6, 7.9, 4.3 Hz, 1H), 1.86 (ddd, *J* = 17.5, 8.3, 4.3 Hz, 1H), 1.69–1.55 (m, 2H), 1.45–1.38 (m, 2H), 1.32–1.25 (m, 3H); ^{13}C NMR (CD_3OD, 126 MHz): δ 177.9, 176.7, 172.7, 171.7, 154.5, 140.2, 138.8, 138.4, 131.9, 131.1, 130.9, 130.8, 130.7, 130.1, 129.9, 129.3, 128.1, 127.8, 125.1, 123.0, 122.5, 120.4, 119.0, 115.3, 112.5, 108.7, 89.3, 81.0, 78.5, 73.8, 70.9, 62.4, 59.5, 55.8, 51.8, 49.8, 49.6, 47.5, 42.3, 41.0, 40.2, 36.7, 35.7, 34.4, 30.9, 27.4, 26.7, 24.4, 23.6; MS *m/z* 918.4 (calc'd: $C_{49}H_{57}N_8O_{10}^+$, $[M+H]^+$, 918.4).

Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 7.0 mL/min

Time	%B
0	20
0.5	20
9	56



Glycosylated product 3.61: Synthesized according to Procedure G. Purified by preparative HPLC – see below for conditions. White solid. 3 mg [3.3 μmol, 30% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.74 (d, J = 8.5 Hz, 1H), 7.77 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 7.6, 7.6 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.27 (s, 1H), 7.26 (d, J = 6.8 Hz, 1H), 7.19–7.16 (m, 1H), 7.08 (dd, J = 7.5, 7.5, 0.8 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 15.9, 1H), 5.98 (ddd, 15.8, 7.3, 5.9 Hz, 1H), 5.47 (s, 1H), 5.15 (d, J = 9.2 Hz, 1H), 5.12 (d, J = 5.7 Hz, 1H), 4.97 (dd, J = 12.4, 7.2 Hz, 1H), 4.46 (ddd, J = 7.8, 7.8, 7.8 Hz, 1H), 4.31 (dd, J = 12.3, 5.5 Hz, 1H), 4.86 (dd, J = 12.1 Hz, 1H), 3.84 (dd, J = 9.1, 9.1 Hz, 1H), 3.69 (dd, J = 12.1, 5.4 Hz, 1H), 3.54 (dd, J = 8.9, 8.9 Hz, 1H), 3.51 (ddd, J = 9.6, 5.4, 2.2 Hz, 1H), 3.47 (d, J = 8.9 Hz, 1H), 3.44–3.40 (m, 1H), 3.03 (ddd, J = 16.2, 5.9, 2.2 Hz, 1H), 2.98 (d, J = 12.3 Hz, 1H), 2.64 (dd, J = 7.1, 7.1 Hz, 2H), 2.57–2.52 (m, 1H), 2.55 (d, J = 16.8 Hz, 1H), 2.50–2.44 (m, 1H), 2.36 (d, J = 16.8 Hz, 1H), 1.91 (ddd, J = 16.5, 7.9, 3.3 Hz, 1H), 1.87–1.80 (m, 1H), 1.78–1.70 (m, 1H), 1.64–1.55 (m, 3H), 1.45 (ddd, J = 13.5, 13.5, 3.8 Hz, 1H), 1.34–1.23 (m, 3H); ^{13}C NMR (CD_3OD, 126 MHz): δ 173.7, 172.2, 171.6, 169.7, 155.5, 137.4, 137.1, 137.0, 132.8, 130.2, 129.7, 129.4, 129.3, 128.9, 127.6, 126.4, 126.2, 125.6, 121.7, 121.0, 119.2, 117.4, 114.8, 111.1, 106.7, 87.8, 79.6, 77.1, 72.3, 69.5, 63.9, 61.0, 57.8, 51.6, 50.8, 48.4, 44.2, 42.1, 40.8, 40.0, 36.0, 34.1, 28.7, 27.0, 25.3, 23.2, 22.8; MS m/z 918.5 (calc'd: $C_{49}H_{57}N_8O_{10}^+$, $[M+H]^+$, 918.4).

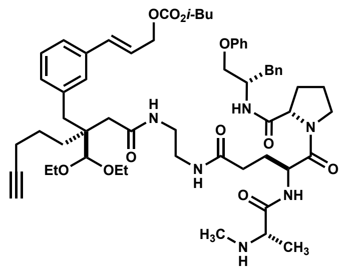
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x150 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	25
1	25
14	80
15	25

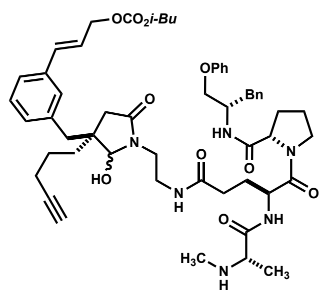
Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 18.0 mL/min

Time	%B
0	20
0.5	20
9	56

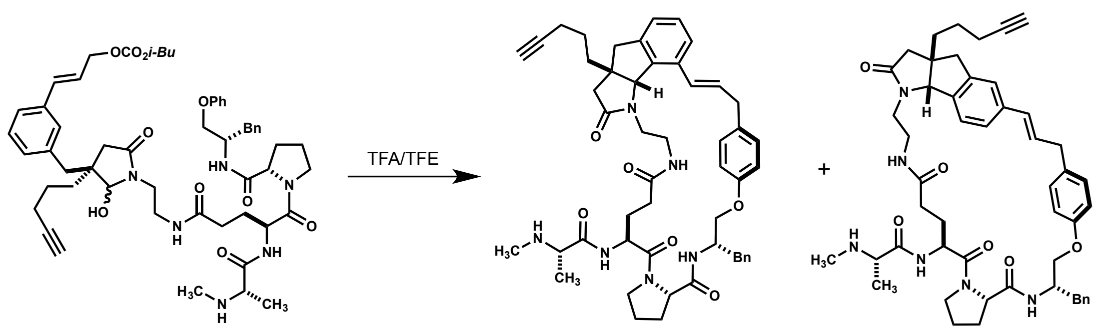
C.6. Synthesis of Smac Mimetic Monomers and Dimers



Acyclic Cinnamyl Carbonate 3.63: Synthesized according to Procedure A with xx mmol of **5**. After completion of the reaction, the solution was diluted with 100 mL EtOAc and washed 3x50 mL $NaHCO_3$, 3x50 mL NH_4Cl, 1x50 mL brine. Dried with $MgSO_4$ and concentrated *in vacuo*. Carried forward without purification.



Hydroxy lactam 3.34: Synthesized according to Procedure B. Diastereomeric mixture was carried forward without purification.



Macrocyclic Product 3.64a and 3.64b: Synthesized according to Procedure D. Purified by preparative HPLC – see below for conditions.
3.64a•TFA: 22 mg [23 umol, 13% yield over three steps]. MS *m/z* 841.4 (calc'd: $C_{50}H_{61}N_6O_6^+$, $[M+H]^+$, 841.5).
3.64b•TFA: 38 mg [40 umol, 21% yield over three steps]. MS *m/z* 841.4 (calc'd: $C_{50}H_{61}N_6O_6^+$, $[M+H]^+$, 841.5).

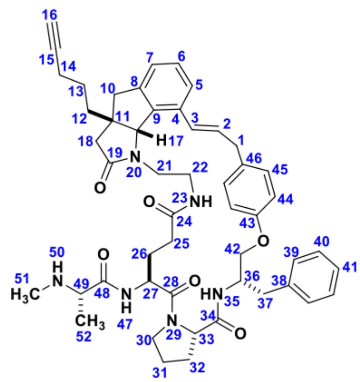
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

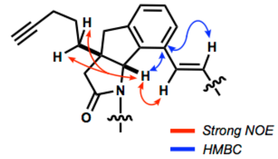
Time	%B
0	40
2.5	30
24	86
29	30

Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 19x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	42
2	42
14	48

Macrocycle **3.64*a***

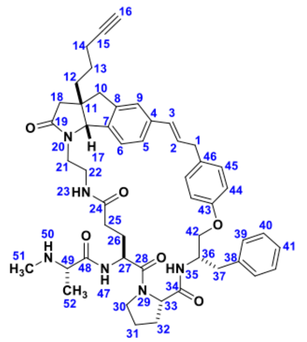


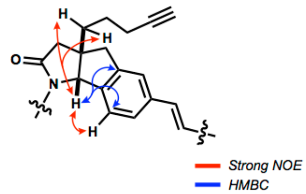


(600MHz, DMSO-d6, 298K)

	13C	1H	key correlation
1	37.5 ppm	3.55–3.49 ppm (m) (2H)	
2	131.7 ppm	6.56–6.51 ppm (m) (1H)	
3	126.6 ppm	6.70 ppm (d) J=15.7 Hz (1H)	
4	134.6 ppm	–	HMBC 2→4
5	122.1 ppm	7.48 ppm (d) J=7.7 Hz (1H)	HMBC 3→5
6	128.8 ppm	7.26–7.24 ppm (m) (1H)	
7	123.5 ppm	7.13 ppm (d) J=7.6 Hz (1H)	HMBC 5→7
8	144.5 ppm	–	HMBC 6, 17→8
9	137.0 ppm	–	HMBC 5, 7→9
10	41.8 ppm	2.92 ppm (d) J=16.8 Hz ; 2.78 ppm (d) J=16.8 Hz (AB quartet) (2H)	HMBC 10→8 ; HMBC 17→10
11	47.9 ppm	–	HMBC 10, 12, 18, 17→11
12	35.2 ppm	1.57–1.52 ppm (m) ; 1.49–1.44 ppm (m) (2H)	HMBC 10, 17, 18→12
13	23.8 ppm	1.39–1.30 ppm (m) (2H)	HMBC 13→15
14	18.1 ppm	2.11 ppm (br s) (2H)	HMBC 14→15
15	84.2 ppm	–	
16	71.3 ppm	2.72 ppm (dd) J=2.3, 2.3 Hz (1H)	
17	68.4 ppm	48.3 ppm (s) (1H)	NOESY 17→3, 12 ; HMBC 17→4
18	41.2 ppm	2.37 ppm (d) J=16.3 Hz ; 2.32 ppm (d) J=16.3 Hz (AB quartet) (2H)	
19	172.7 ppm	–	HMBC 18→19
20	–	–	
21	39.1 ppm	3.34–3.29 ppm (m) ; 2.77–2.74 ppm (m) (2H)	COSY 21→22 ; TOCSY 23→21
22	36.9 ppm	3.00–2.97 ppm (m) ; 2.62–2.57 ppm (m) (2H)	COSY 23→22
23	–	7.56 ppm (dd) J=4.4, 4.4 Hz (1 H)	HMBC 23→24
24	171.7 ppm	–	HMBC 25→24
25	31.0 ppm	2.13–2.08 ppm (m) ; 2.01–1.97 ppm (m) (2H)	HMBC 27→25
26	26.9 ppm	1.91–1.87 ppm (m) ; 1.74–1.70 ppm (m) (2H)	HMBC 27→26
27	50.3 ppm	4.62 ppm (ddd) J=6.7, 6.7, 6.7 Hz (1H)	COSY/TOCSY 47→27
28	169.1 ppm	–	HMBC 27→28
29	–	–	
30	46.6 ppm	3.75–3.73 ppm (m) ; 3.37–3.34 ppm (m) (2H)	TOCSY 33→30
31	24.1 ppm	1.78–1.76 ppm (m) (2H)	TOCSY 33→31
32	28.9 ppm	1.98–1.94 ppm (m) ; 1.54–1.51 ppm (m) (1H)	COSY 33→32
33	60.6 ppm	4.11 ppm (dd) J=8.9, 2.9 Hz (1H)	
34	171.2 ppm	–	HMBC 35→34
35	–	7.36 ppm (d) J=8.5 Hz (1H)	
36	49.1 ppm	4.30–4.26 ppm (m) (1H)	COSY 35→36
37	36.2 ppm	2.97–2.94 ppm (m) ; 2.85–2.81 ppm (m) (2H)	TOCSY 35→37
38	138.4 ppm	–	HMBC 37→38
39	129.2 ppm	7.20 ppm (d) J=7.1 Hz (2H)	COSY 40→39
40	127.8 ppm	7.26 ppm (dd) J=7.2, 7.2 Hz (2H)	HMBC 40→38
41	125.9 ppm	7.19 ppm (dd) J=7.1, 7.1 Hz (1H)	COSY 40→41
42	69.3 ppm	3.90–3.89 ppm (m) ; 3.79–3.76 ppm (m) (2H)	TOCSY 35→42
43	157.1 ppm	–	HMBC 45→43
44	114.9 ppm	6.87 ppm (d) J=8.3 Hz (2H)	TOCSY 45→44
45	129.6 ppm	7.13 ppm (d) j=8.2 Hz (2H)	HMBC 1→45
46	131.6 ppm	–	HMBC 44→46
47	–	8.88 ppm (d) J=7.7 Hz	HMBC 47→48
48	168.6 ppm	–	HMBC 49→48
49	55.8 ppm	3.79–3.77 ppm (m) (1H)	COSY 49→52 ; HMBC 50, 51→49
50	–	8.84 ppm (br s) ; 8.77 ppm (br s) (2H)	
51	30.7 ppm	2.49 ppm (s) (3H)	TOCSY/COSY 50→51
52	15.6 ppm	1.33 ppm (d) J=6.6 Hz (3H)	

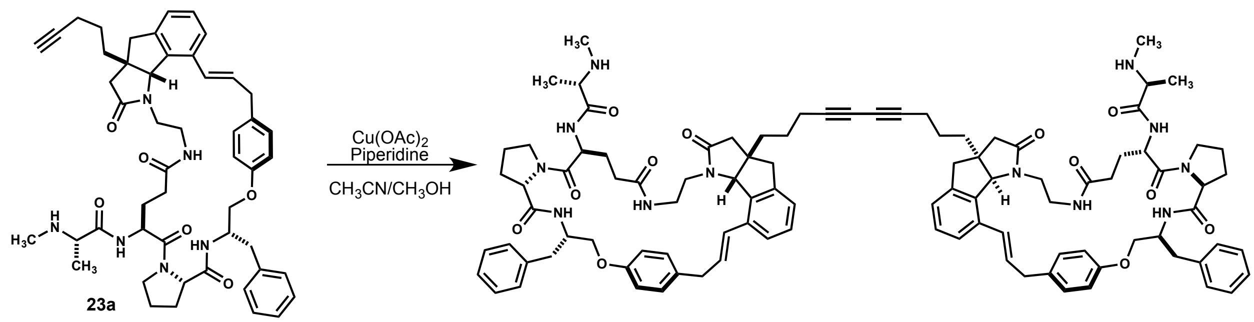
Macrocycle ***3.64b***





(600MHz, DMSO-d6, 298K)

	13C	1H	key correlation
1	37.4 ppm	3.45 ppm (dd) J=14.8, 3.4 Hz ; 3.38–3.35 ppm (m) (2H)	
2	131.0 ppm	6.40–6.35 ppm (m) (1H)	
3	128.8 ppm	6.27 ppm (d) J=15.7 Hz (1H)	
4	137.9 ppm	–	HMBC 2→4
5	123.8 ppm	7.25–7.24 ppm (m) – overlaps with 39, 40, 41 (1H)	COSY 6→5
6	126.1 ppm	7.64 ppm (d) J=7.9 Hz (1H)	HMBC 17→6
7	137.6 ppm	–	HMBC 5, 9→7
8	143.9 ppm	–	HMBC 6, 17→8
9	122.8 ppm	7.21 ppm (s) (1H)	HMBC 2,5→9
10	42.4 ppm	2.95 ppm (d) J=16.4 Hz ; 2.82 ppm (d) J=16.9 Hz (2H)	HMBC 17→10 ; HMBC 10→9
11	47.3 ppm	–	HMBC 10, 17, 18→11
12	36.6 ppm	1.60–1.53 ppm (m) (2H)	HMBC 17→12
13	23.6 ppm	1.42–1.32 ppm (m) (2H)	
14	18.0 ppm	2.11 ppm (ddd) J=5.4, 5.4, 1.8 Hz (2H)	
15	84.0 ppm	–	HMBC 13, 14→15
16	71.1 ppm	2.72 ppm (dd) J=2.0, 2.0 Hz (1H)	
17	70.5 ppm	4.55 ppm (s) (1H)	NOESY 17→6, 12; HMBC 17→6, 7
18	41.6 ppm	2.38 ppm (s) DOUBLE CHECK	HMBC 18→17, 19
19	172.0 ppm	–	HMBC 17→19
20	–	–	
21	38.9 ppm	3.29–3.26 ppm (m) ; 2.97–2.93 ppm (m) (2H)	HMBC 22→21
22	36.2 ppm	3.29–3.26 ppm (m) ; 2.54–2.51 ppm (m) (2H)	HMBC 23→22 ; COSY 23→22
23	–	7.86 ppm (dd) J=4.4, 4.4 Hz (1H)	TOCSY 23→21, 22 ; HMBC 23→24
24	171.4 ppm	–	HMBC 25→24
25	31.1 ppm	2.16–2.13 ppm (m) ; 2.07–2.04 ppm (2H)	
26	26.9 ppm	1.91–1.87 ppm (m) ; 1.62–1.58 ppm (m) (2H)	TOCSY 25→26
27	49.6 ppm	4.34 ppm (ddd) J=9.2, 9.2, 2.1 Hz (1H)	TOCSY 27→26
28	not observed	–	
29	–	–	
30	45.9 ppm	3.34–3.32 ppm (m) ; 3.14 ppm (ddd) J=8.2, 8.2, 8.2 Hz (2H)	TOCSY 31, 32, 33→30
31	23.6 ppm	1.42–1.38 ppm (m) ; 1.36–1.32 ppm (m) (2H)	TOCSY 32, 33→31
32	29.3 ppm	1.81–1.75 ppm (m) ; 1.49–1.45 ppm (m) (2H)	COSY 3332
33	58.4 ppm	4.22 ppm (dd) J=8.2, 2.0 Hz (1H)	HMBC 33→34
34	170.7 ppm	–	HMBC 35→34
35	–	7.90 ppm (d) J=6.8 Hz (1H)	TOCSY 35→36
36	48.8 ppm	4.09–4.08 ppm (m) (1H)	HMBC 42→36
37	36.3 ppm	2.92–2.89 ppm (m) ; 2.80–2.77 ppm (m) (2H)	TOCSY 42→37 ; COSY 36→37
38	138.2 ppm	–	HMBC 36, 37→38
39	129.0 ppm	7.27–7.25 ppm (m) (1H)	HMBC 37→39
40	128.0 ppm	7.31–7.28 ppm (m) (1H)	HMBC 40→38
41	125.9 ppm	7.22–7.21 ppm (m) (1H)	HMBC 41→39
42	68.2 ppm	4.09–4.08 ppm (m) ; 3.97 ppm (dd) J=12.9, 7.1 Hz (2H)	HMBC 42→43
43	156.6 ppm	–	HMBC 45, 44→43
44	132.2 ppm	–	TOCSY 44→45
45	129.4 ppm	7.11 ppm (d) J=8.3 Hz (2H)	HMBC 1→45
46	132.2 ppm	–	HMBC 1→46
47	–	8.65 ppm (d) J=7.7 Hz (1H)	TOCSY 27→47
48	168.4 ppm	–	HMBC 47→48
49	55.6 ppm	3.80–3.77 ppm (m) (1H)	HMBC 49→48
50	–	8.85 ppm (br s) ; 8.75 ppm (br s) (2H)	TOCSY 50→49
51	30.7 ppm	2.53 ppm (dd) J=4.7, 4.7 Hz (3H)	TOCSY 50→51
52	15.4 ppm	1.30 ppm (d) J=6.8 Hz (3H)	TOCSY 49→52



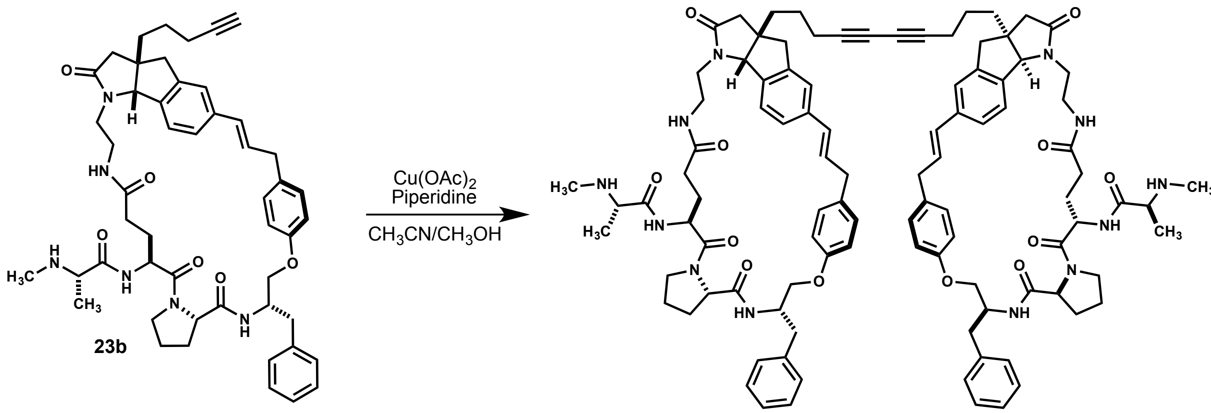
Dimer Product 3.65: Synthesized according to Procedure H. Purified by preparative HPLC – see below for conditions. White solid. Bis-TFA salt: 4.5 mg [2.4 µmol, 40% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.90 (d, J = 7.7 Hz, 1H), 8.81 (br s, 2H), 7.61 (dd, J = 4.7, 4.7 Hz, 1H), 7.49 (d, 7.8 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 7.28–7.23 (m, 3H), 7.23–7.17 (m, 3H), 7.14–7.12 (m, 4H), 6.87 (d, J = 8.2 Hz, 2H), 6.72 (d, J = 15.5 Hz, 1H), 6.53 (ddd, J = 15.5, 8.5, 5.2 Hz, 1H), 4.84 (s, 1H), 4.62 (dd, J = 14.0, 6.8 Hz, 1H), 4.31–4.24 (m, 1H), 4.10 (dd, J = 9.0, 3.2 Hz, 1H), 3.88 (dd, J = 9.5, 4.6 Hz, 1H), 3.78–3.72 (m, 2H), 3.55–3.45 (m, 2H), 3.02–2.93 (m, 1H), 2.95 (dd, J = 18.7, 4.6 Hz, 1H), 2.90–2.80 (m, 1H), 2.83 (dd, J = 13.8, 9.3 Hz, 1H), 2.79–2.76 (m, 2H), 2.37 (d, J = 16.2 Hz, 1H), 2.32 (d, J = 16.2 Hz, 1H), 2.23 (dd, 6.2, 6.2 Hz, 1H), 2.16–2.07 (m, 1H), 2.02–1.93 (m, 1H), 1.92–1.85 (m, 1H), 1.79–1.75 (m, 2H), 1.73–1.67 (m, 1H), 1.53–1.46 (m, 3H), 1.43–1.28 (m, 4H), 1.33 (d, J = 6.87 Hz, 1H) ^{13}C NMR (DMSO-d_6, 126 MHz): δ 172.6, 171.8, 171.2, 168.8, 168.3, 157.2, 144.8, 138.5, 137.2, 134.9, 131.8, 131.7, 129.6, 129.2, 128.2, 128.1, 126.9, 126.1, 124.0, 122.4, 115.0, 77.9, 69.6, 68.6, 65.5, 60.7, 56.0, 50.3, 49.3, 48.4, 46.8, 42.2, 41.3, 40.4, 37.9, 37.2, 36.4, 35.8, 31.2, 30.8, 29.1, 27.2, 24.2, 23.8, 18.8, 15.6 MS m/z 1680.9104 (calc'd: $C_{32}H_{44}NO_9^+$, $[M+H]^+$, 1680.90985).

Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

Time	%B
0	40
2.5	30
24	86
29	30

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 10x250 mm, 5 µm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

Time	%B
0	44
0.5	44
2.5	46
12.0	54



Dimer Product 3.7: Synthesized according to Procedure H. Purified by preparative HPLC – see below for conditions. White solid. Bis-TFA salt: 6.8 mg [3.6 μmol, 60% yield]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.81 (br s, 1H), 8.76 (br s, 1H), 8.65 (d, J = 7.7 Hz, 1H), 7.91 (d, J = 6.6 Hz, 1H), 7.88 (dd, J = 4.1, 4.1 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.37–7.34 (m, 1H), 7.36 (s, 1H), 7.29–7.22 (5H), 7.20 (s, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 6.40–6.35 (m, 1H), 6.27 (d, J = 15.7 Hz, 1H), 4.54 (s, 1H), 4.33 (dd, J = 8.5, 8.5 Hz, 1H), 4.22 (dd, J = 8.1, 2.3 Hz, 1H), 4.09 (d, J = 7.9 Hz, 1H), 3.96 (dd, J = 12.7 Hz, 1H), 3.79–3.75 (m, 1H), 3.64–3.60 (m, 1H), 3.15–3.11 (m, 1H), 2.96–2.89 (m, 2H), 2.83–2.76 (m, 2H), 2.37 (br s, 2H), 2.24 (dd, J = 6.5, 6.5 Hz, 2H), 2.19–2.12 (m, 1H), 2.08–2.03 (m, 1H), 1.91–1.86 (m, 1H), 1.80–1.74 (m, 1H), 1.65–1.47 (m, 5 H) 1.41–1.30 (m, 4H), 1.30 (d, J = 7.0 Hz, 3H) MS m/z 1680.9235 (calc'd: $C_{32}H_{44}NO_9^+$, $[M+H]^+$, 1680.90985).

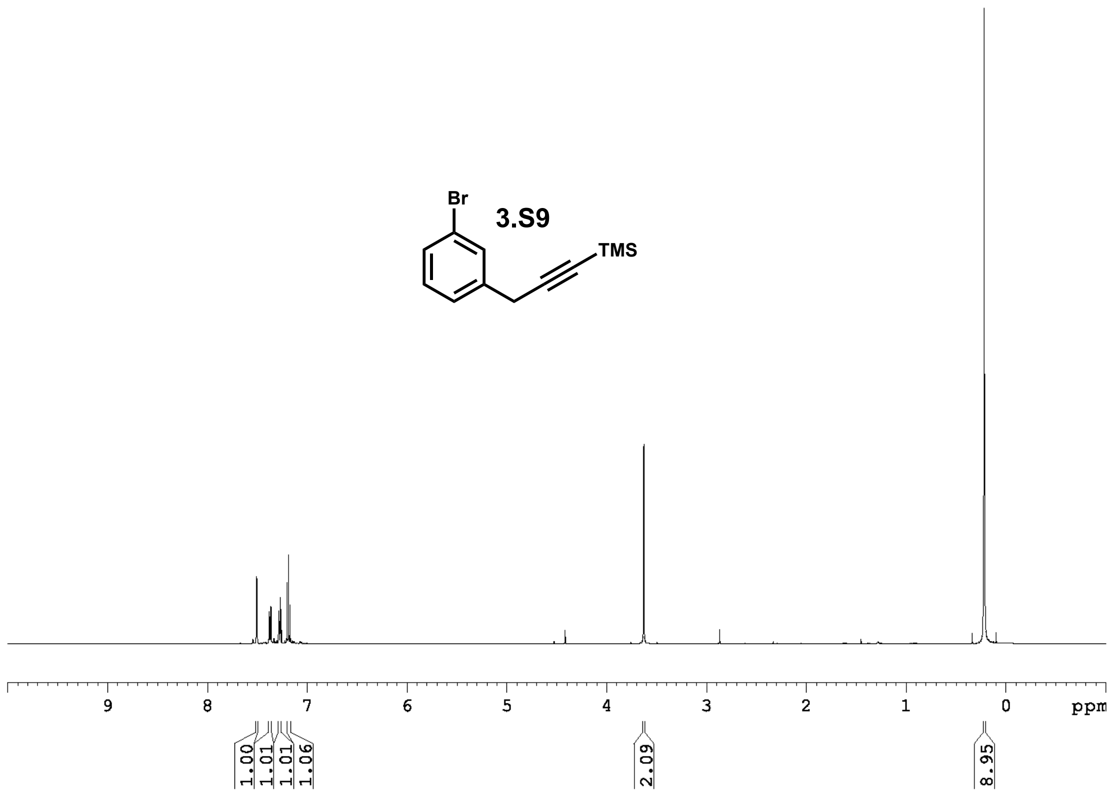
Analytical HPLC Method
Column: Waters Sunfire™ C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 1.00 mL/min

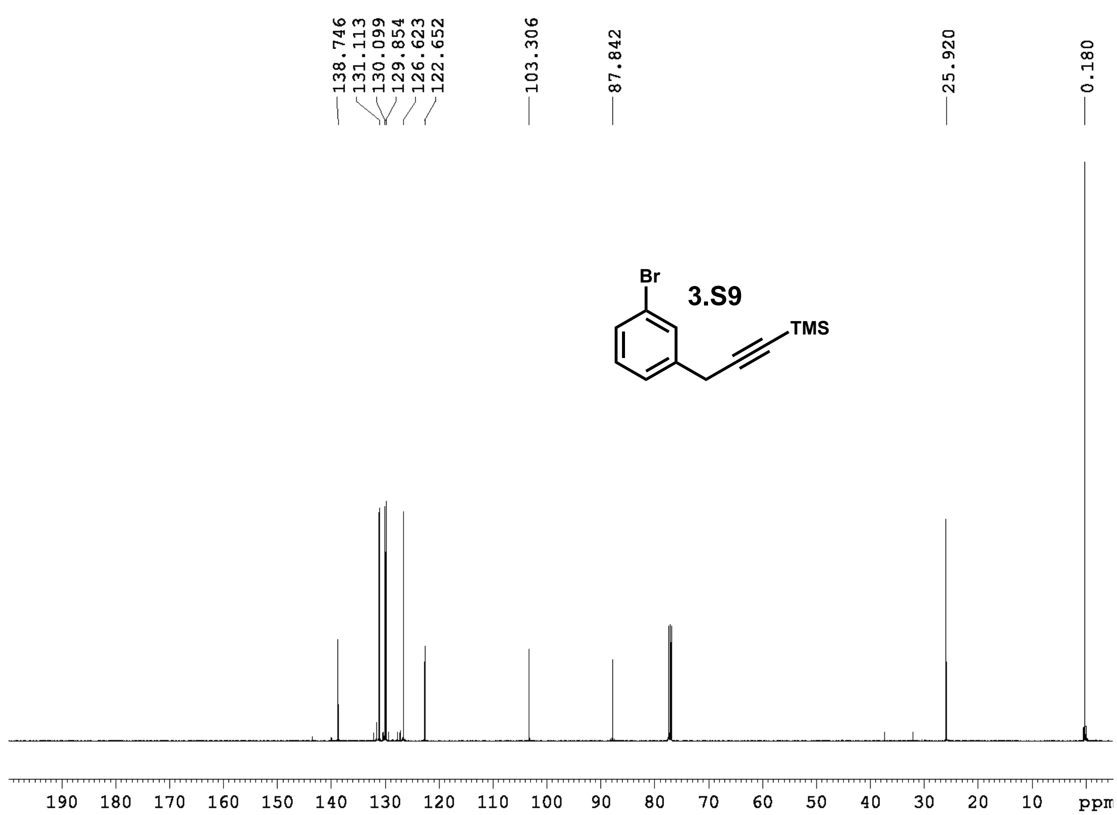
Time	%B
0	40
2.5	30
24	86
29	30

Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 10x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 18.0 mL/min

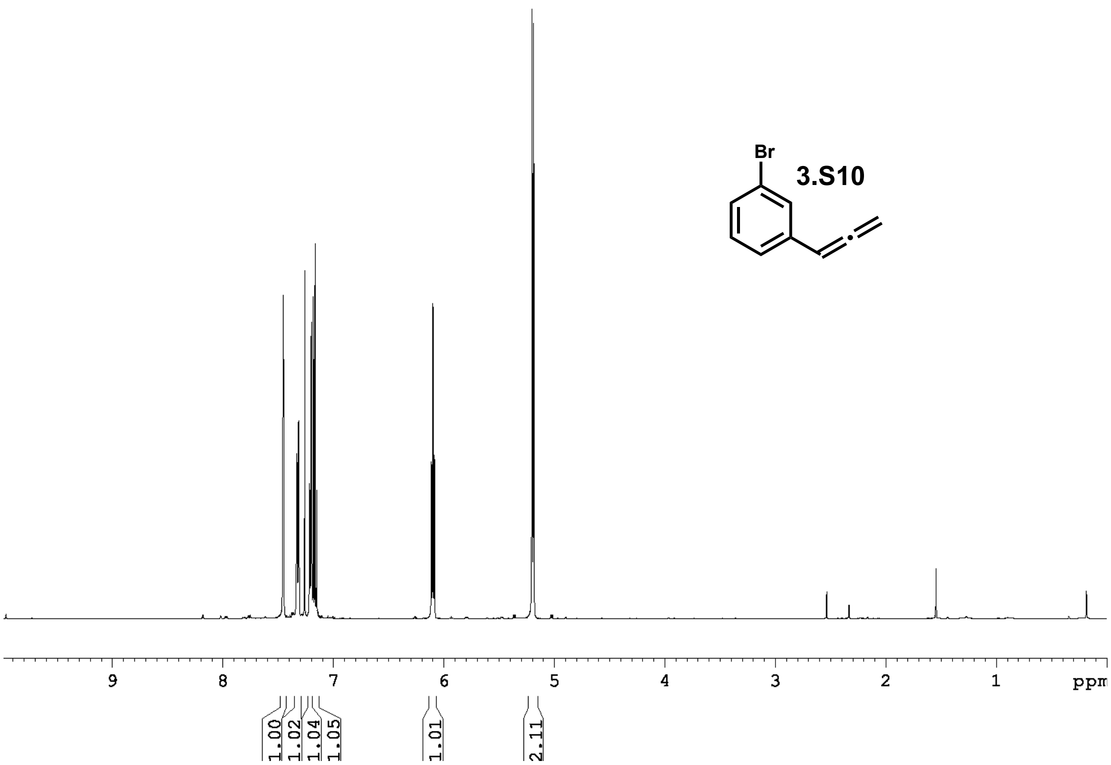
Time	%B
0	44
0.5	44
2.5	46
12.0	54

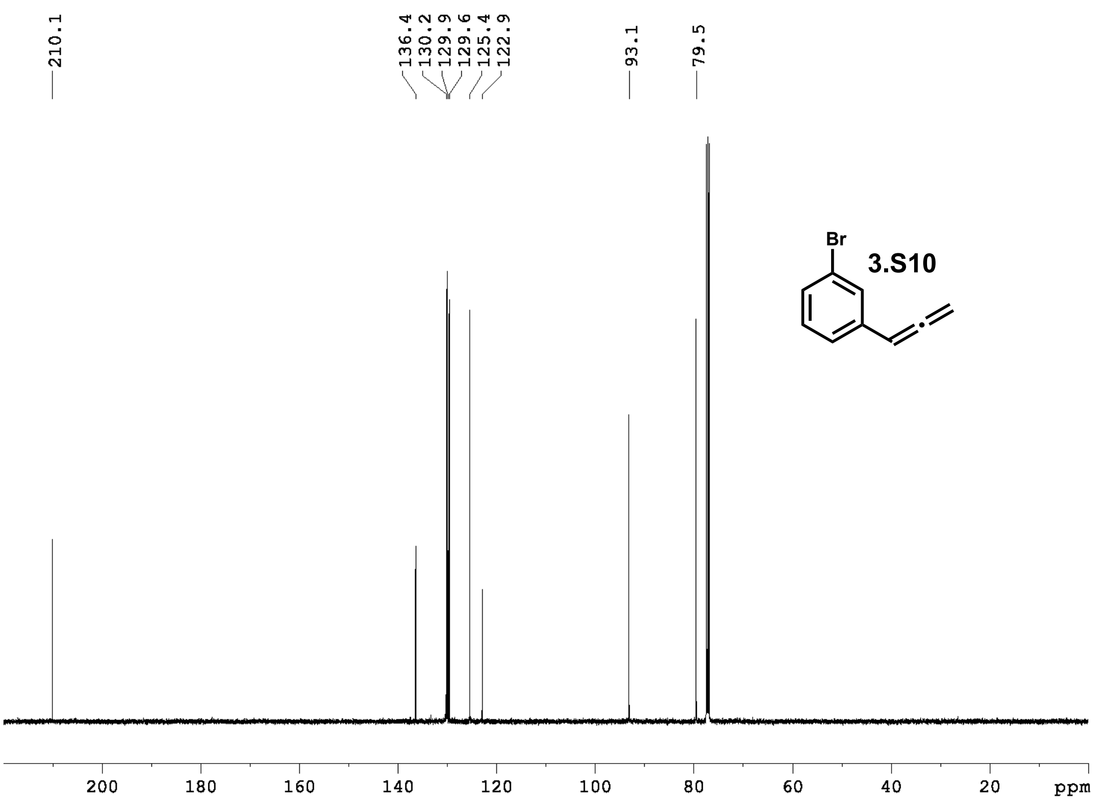
D.1. NMR Spectra – Templates (+)-5 & (+)-S4 and associated intermediates



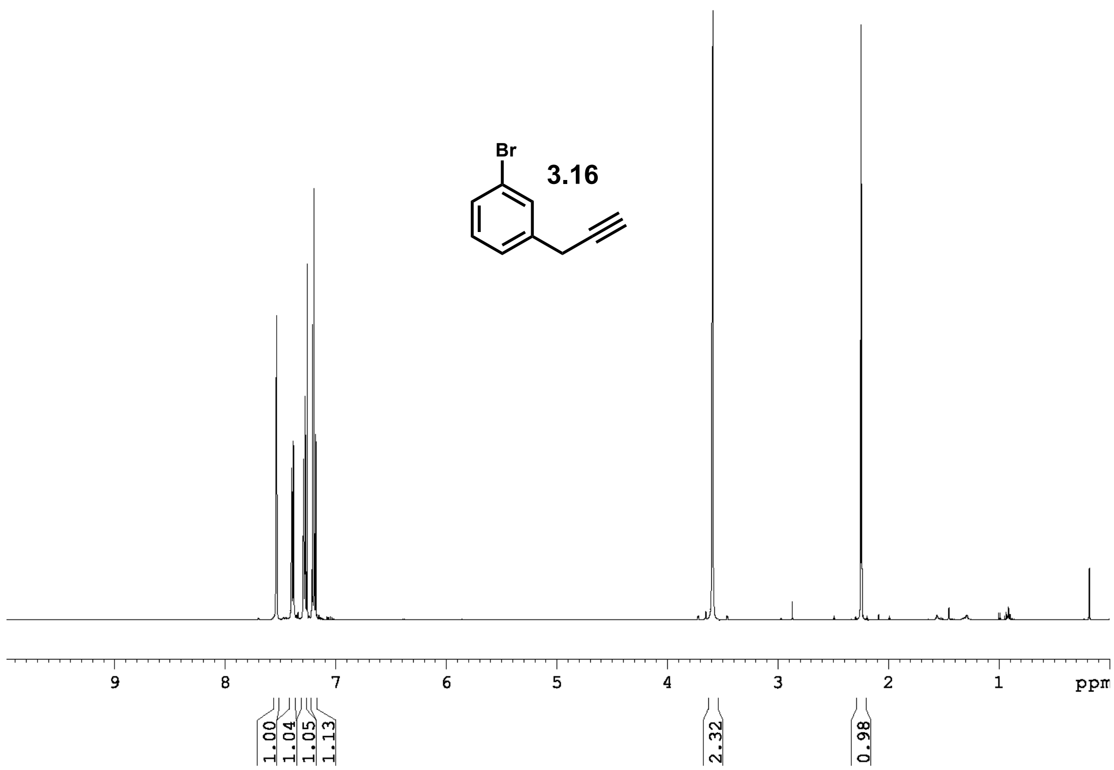


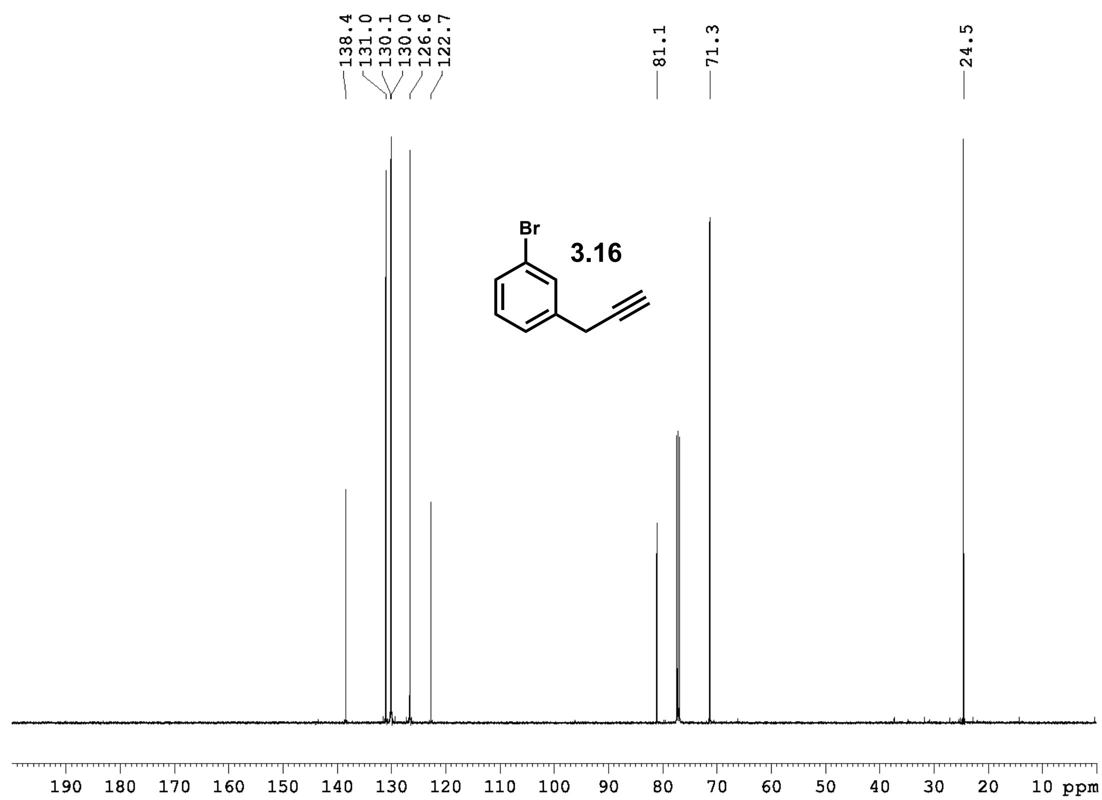
Phenyl allene **3.S10**



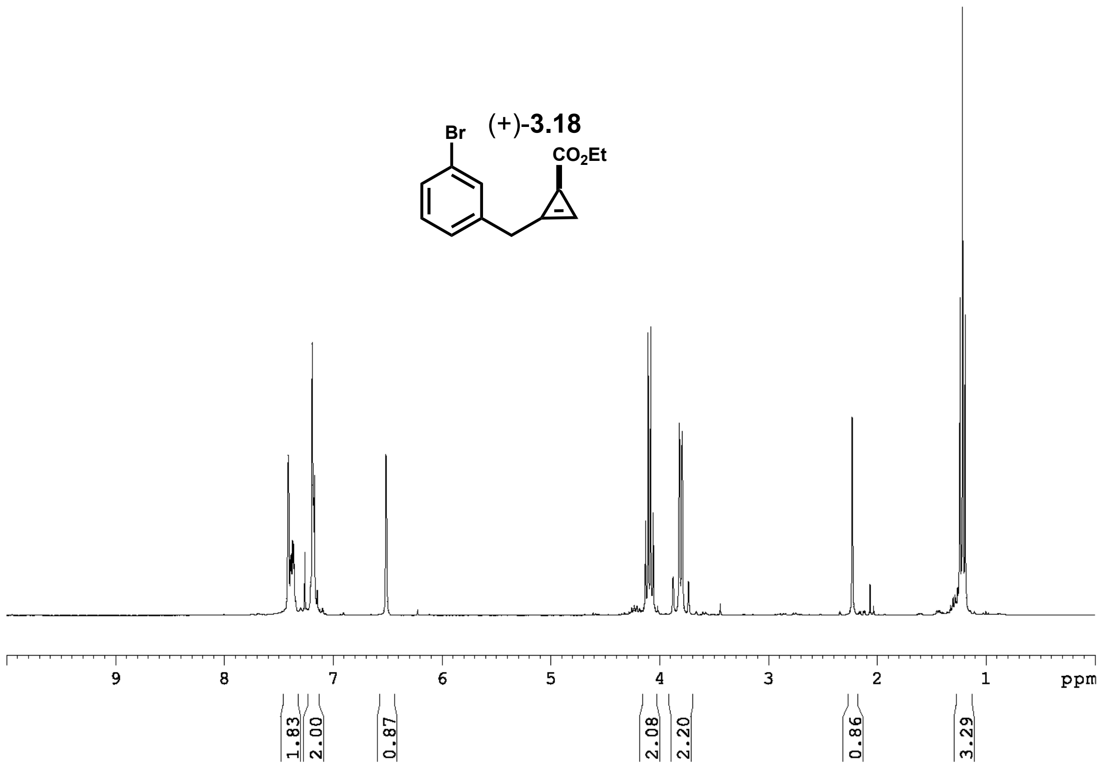


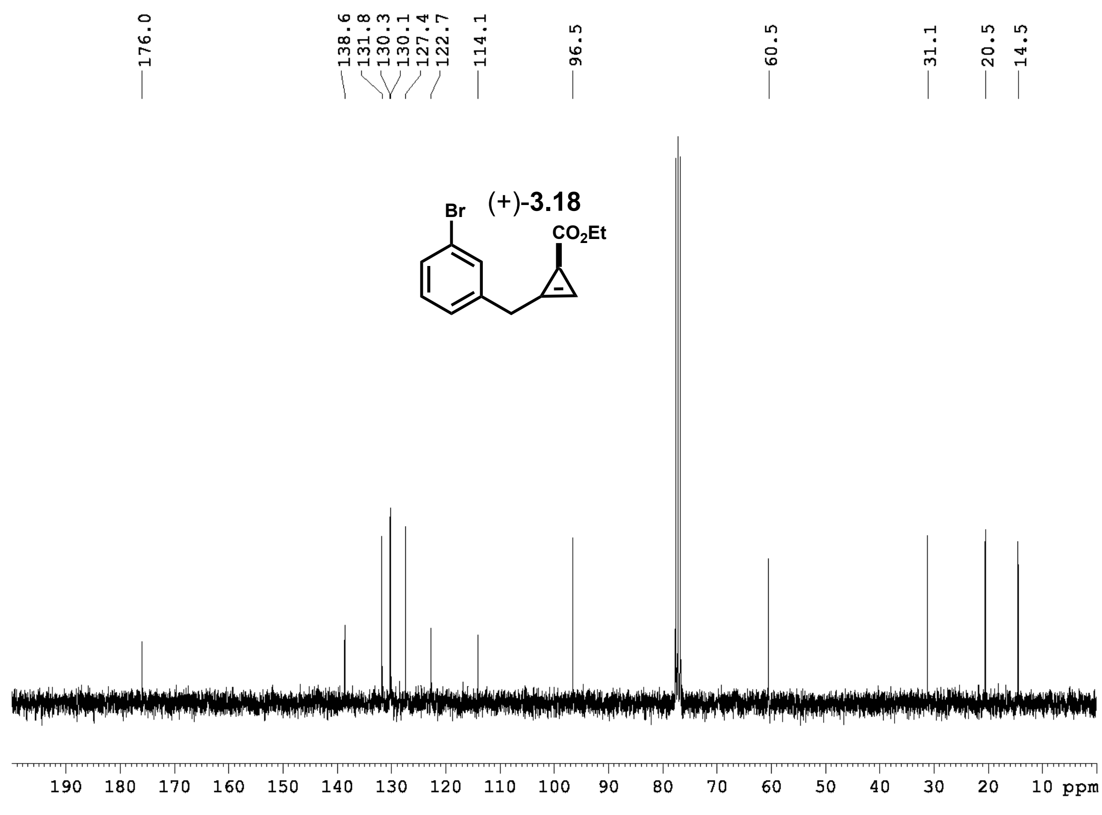
Bromophenyl propyne **3.16**



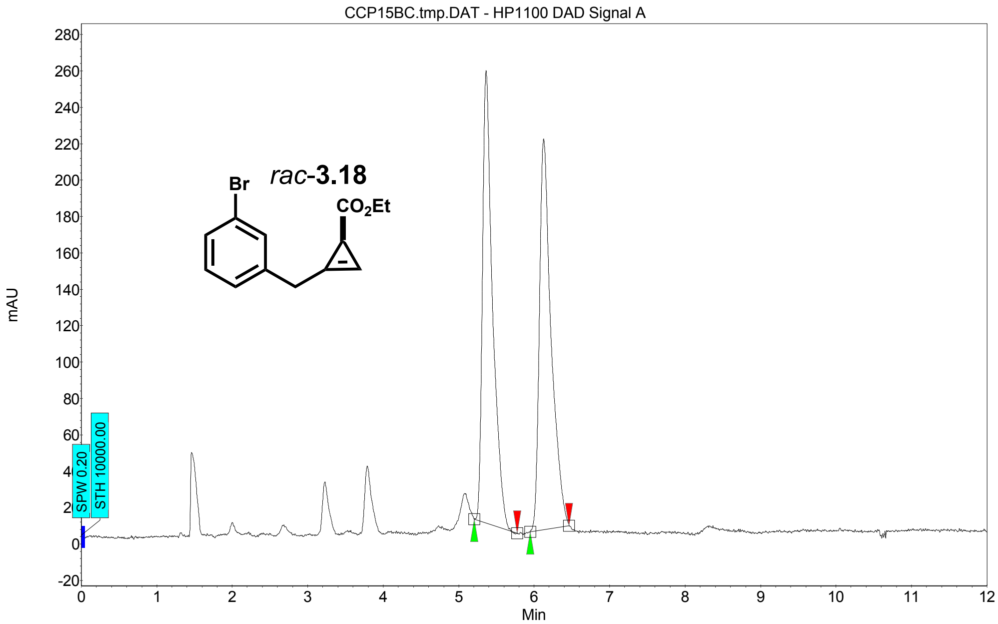


Cyclopropene (+)-**3.18**

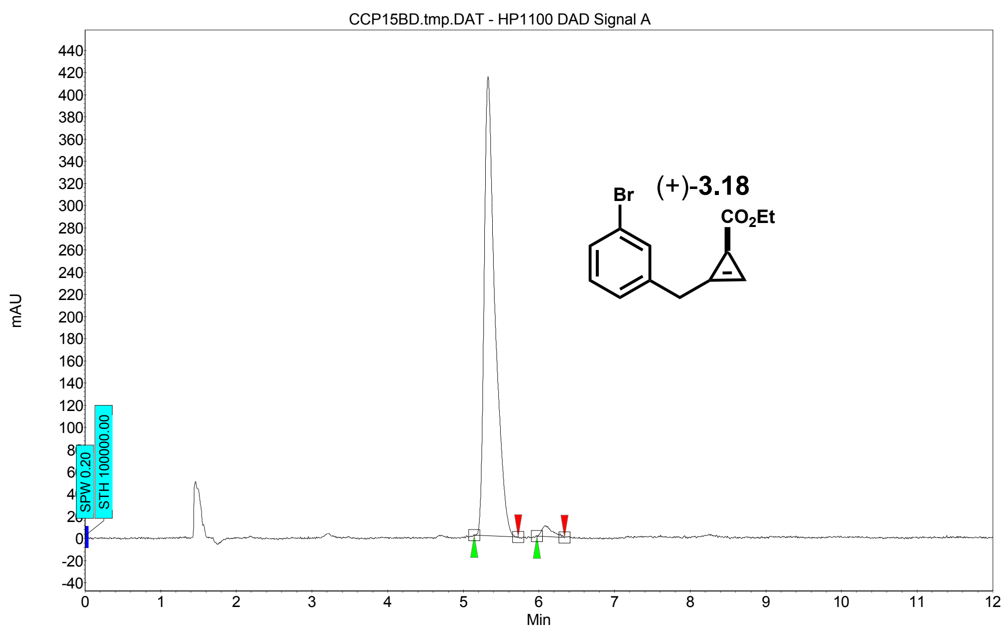




D.1.a. SFC of Cyclopropene carboxylate (+)-3.18

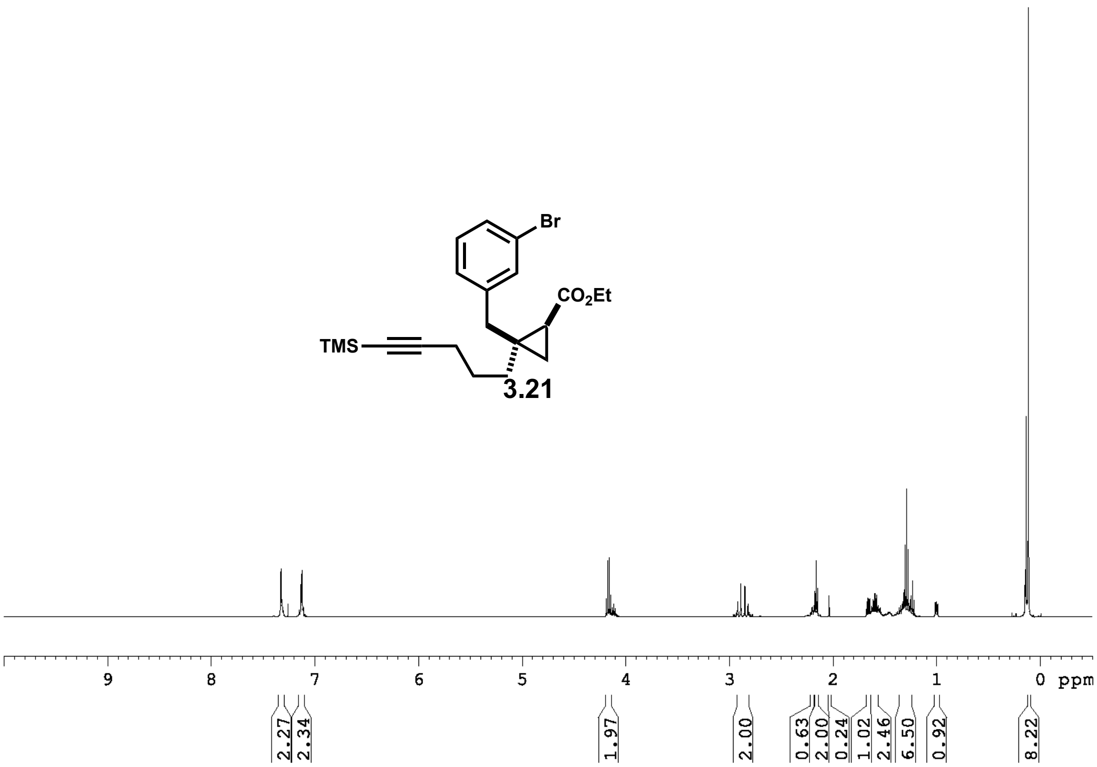


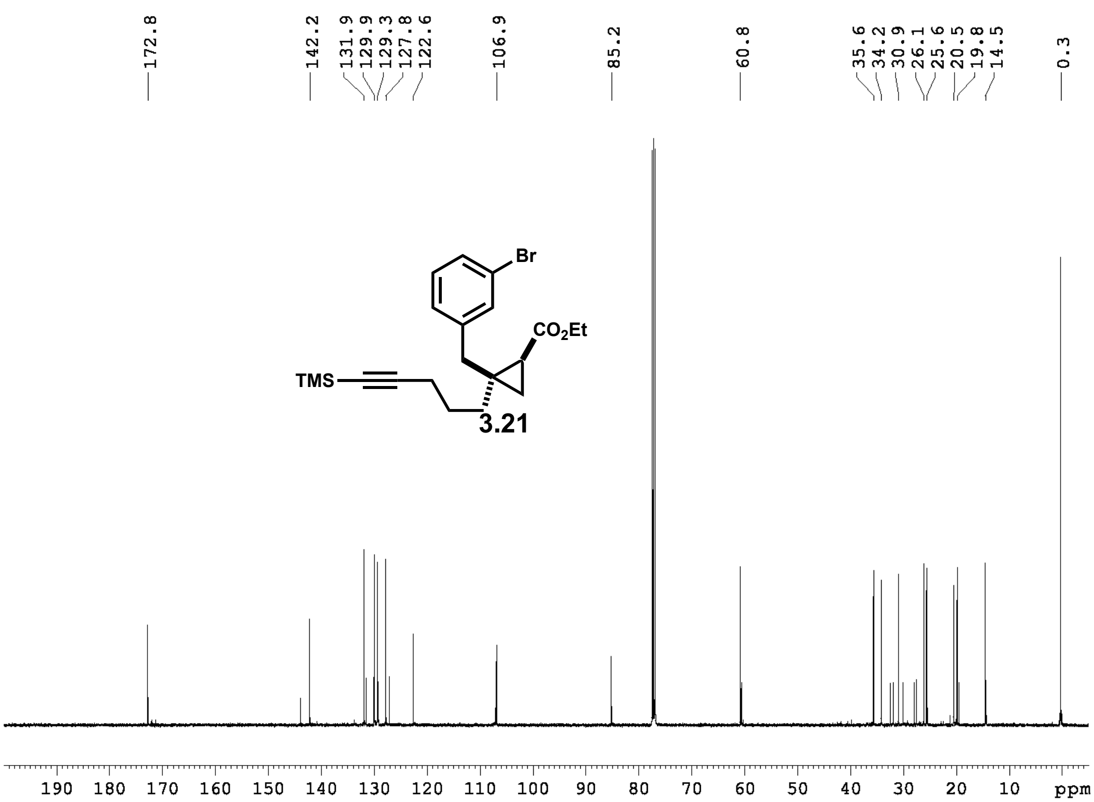
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.20	5.36	5.77	0.00	49.92	248.7	38.6	49.923
2	UNKNOWN	5.95	6.13	6.46	0.00	50.08	214.8	38.7	50.077
Total						100.00	463.5	77.3	100.000

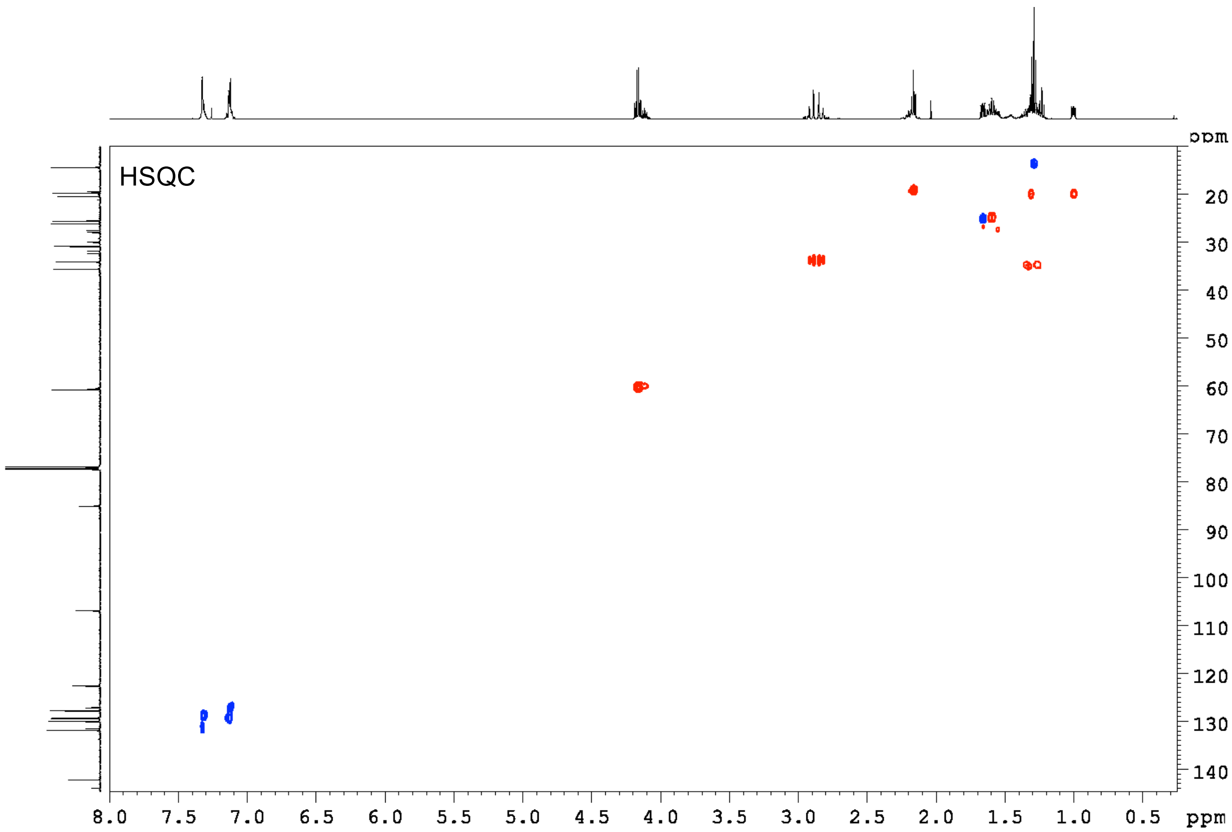


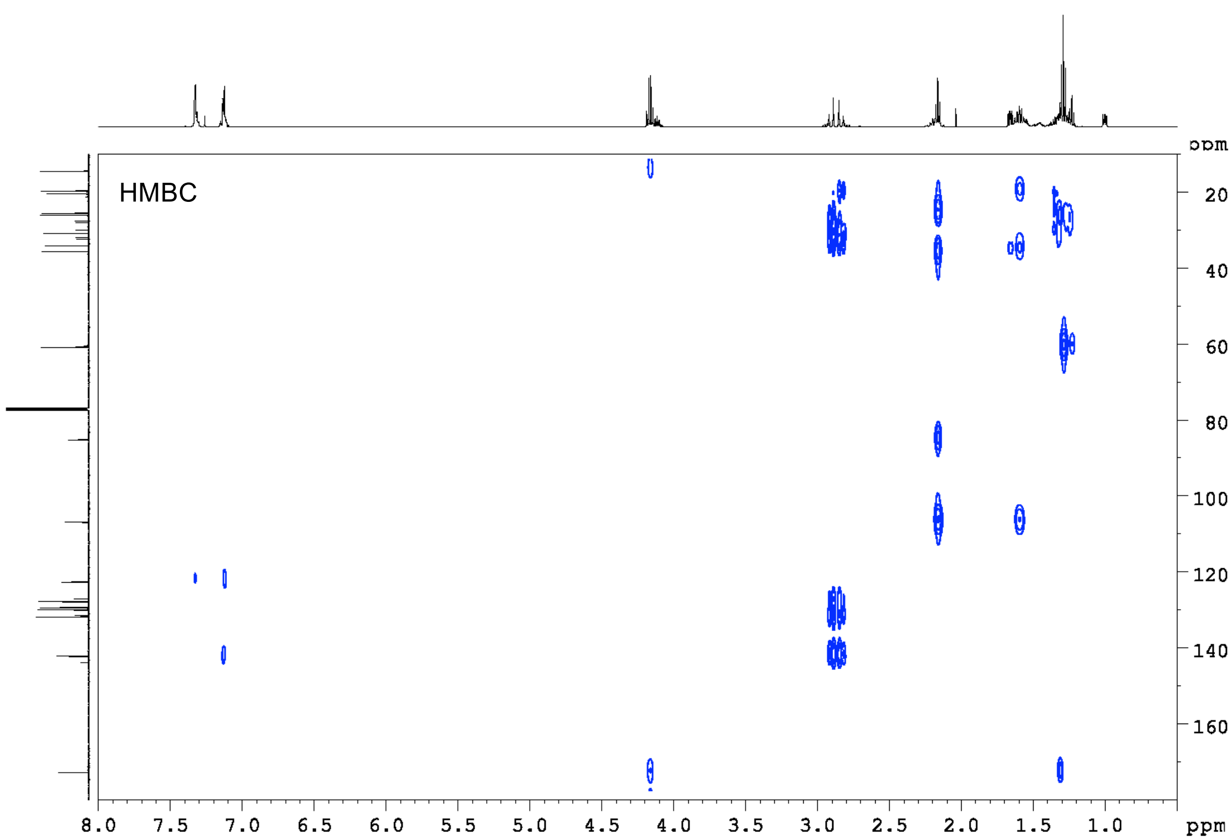
Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	5.14	5.33	5.72	0.00	97.71	413.7	68.5	97.709
2	UNKNOWN	5.97	6.08	6.34	0.00	2.29	9.8	1.6	2.291
Total						100.00	423.5	70.1	100.000

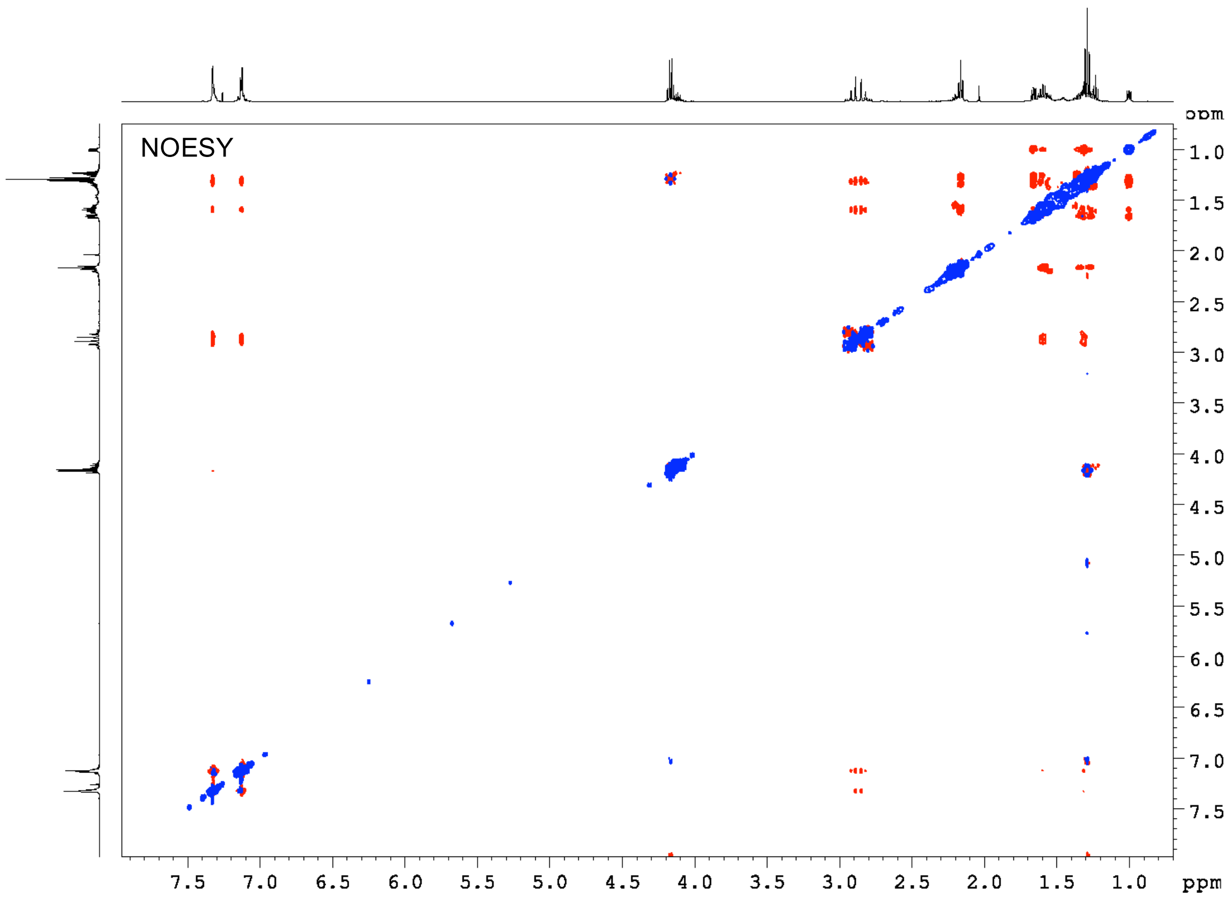
Cyclopropane **3.21**



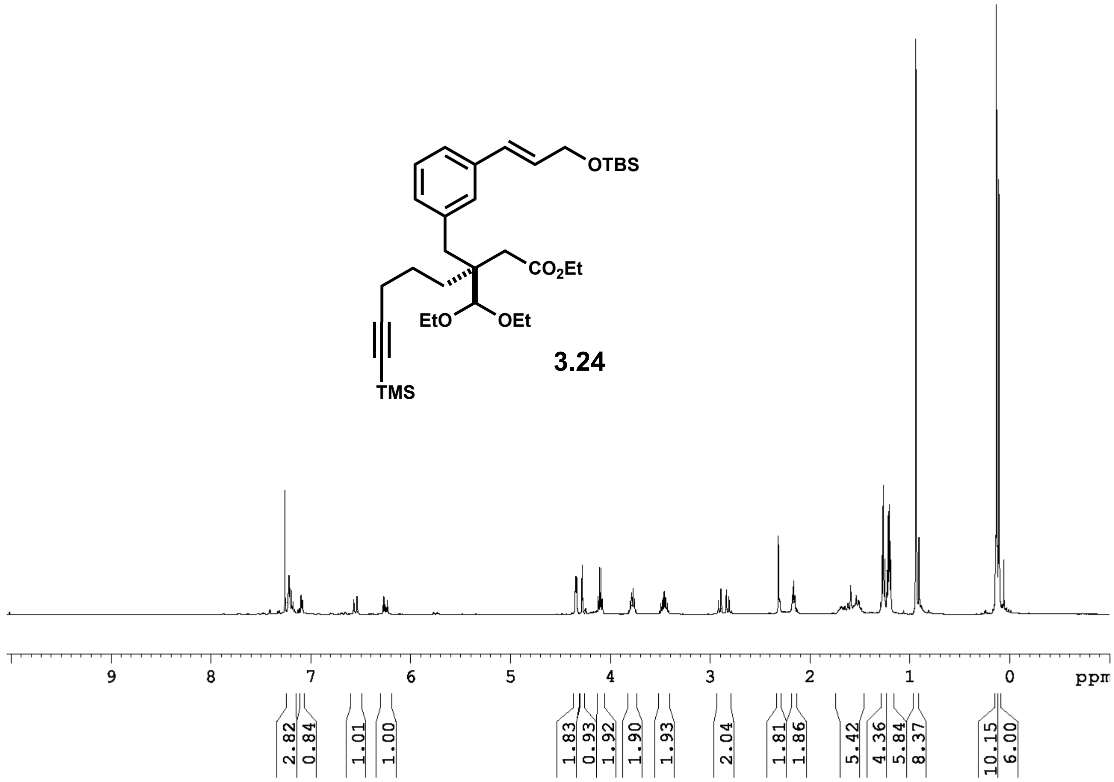


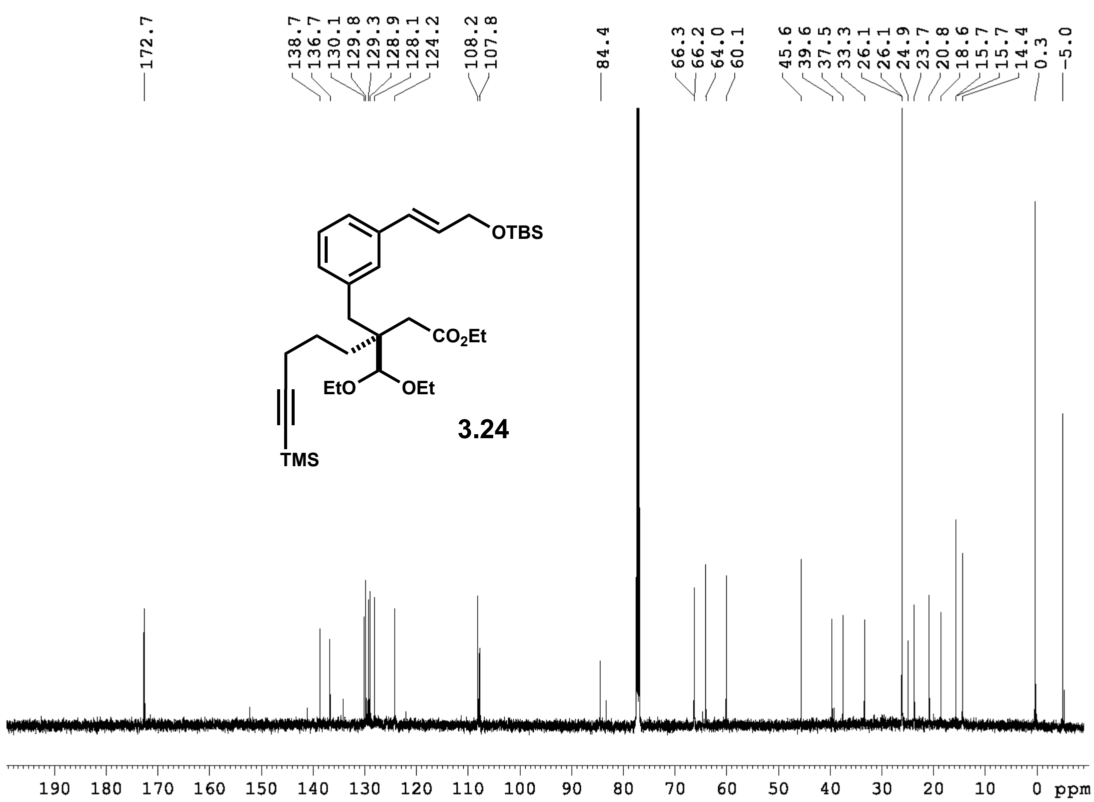

HSQC
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


HMBC
ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

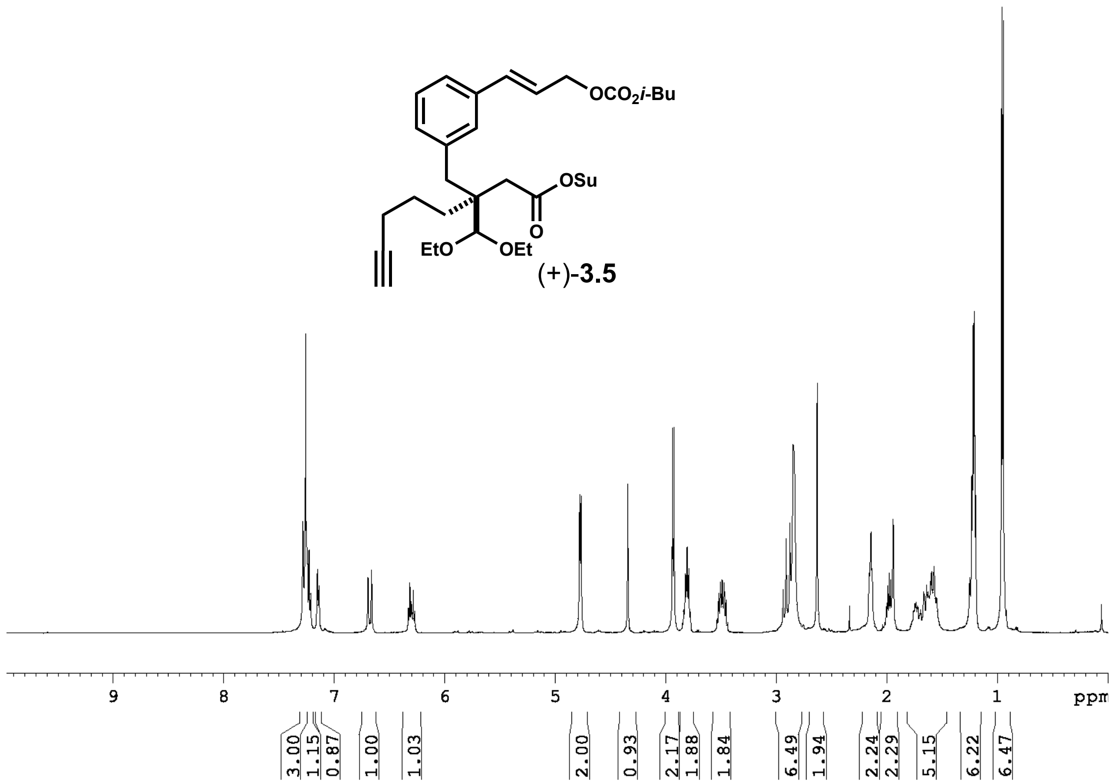

NOESY
ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

Suzuki product **3.24**

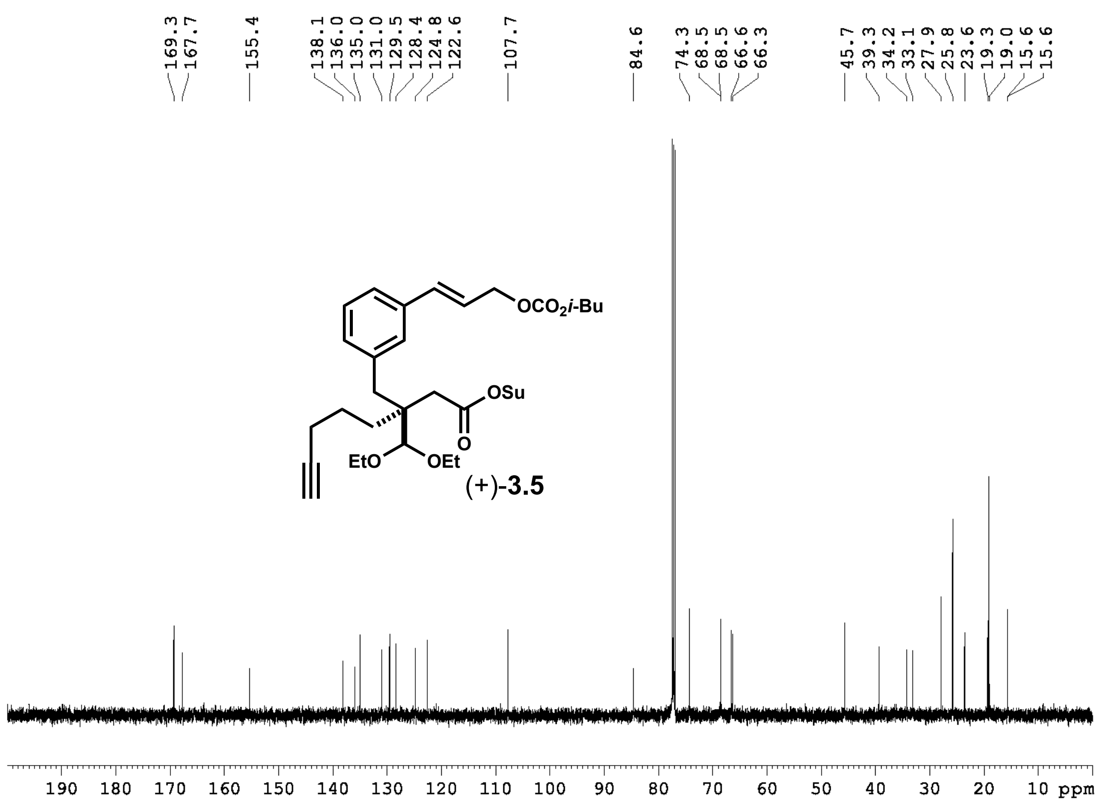




Template (+)-**3.5**

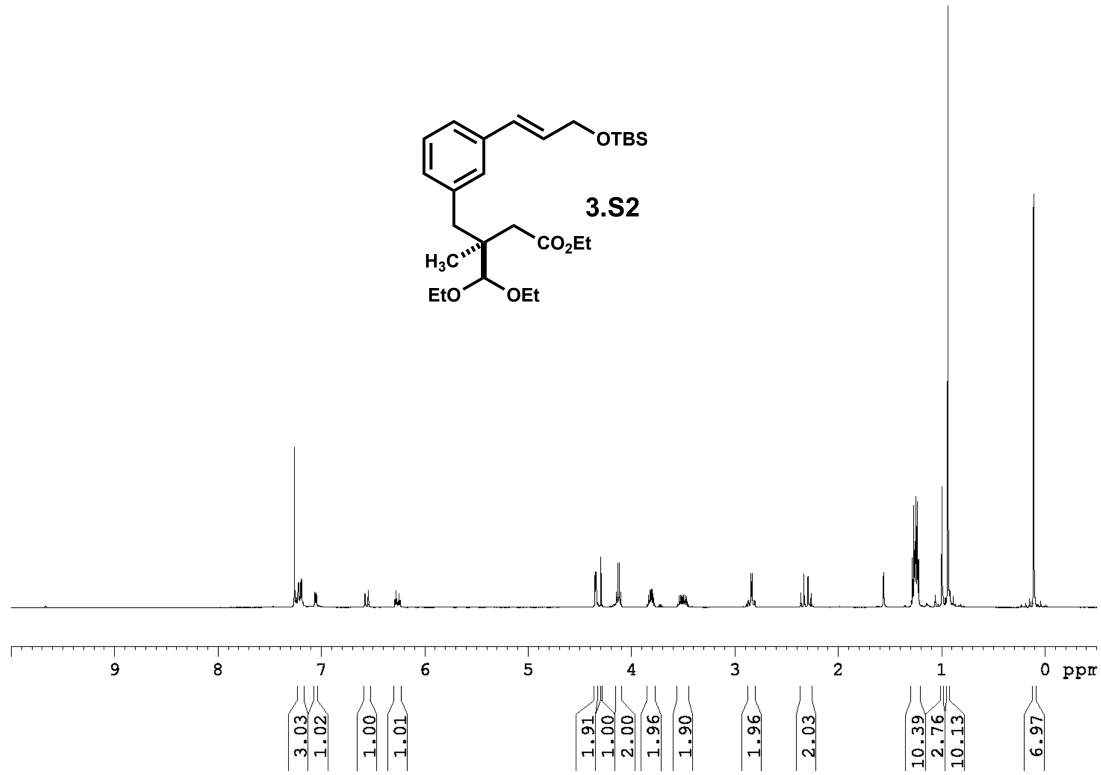


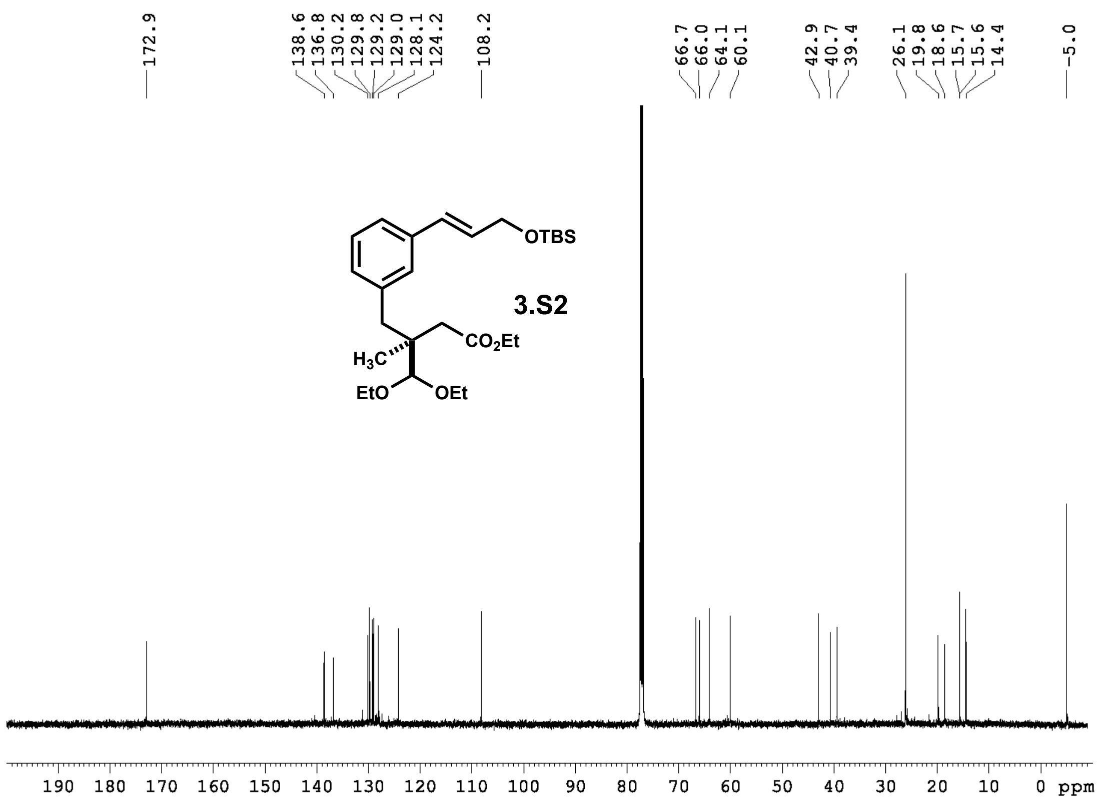
OCO2i-Bu
OSu
O
EtO
OEt
(+)-3.5
9 8 7 6 5 4 3 2 1 ppm
3.00 1.15 0.87 1.00 1.03 2.00 0.93 2.17 1.88 1.84 6.49 1.94 2.24 2.29 5.15 6.22 6.47



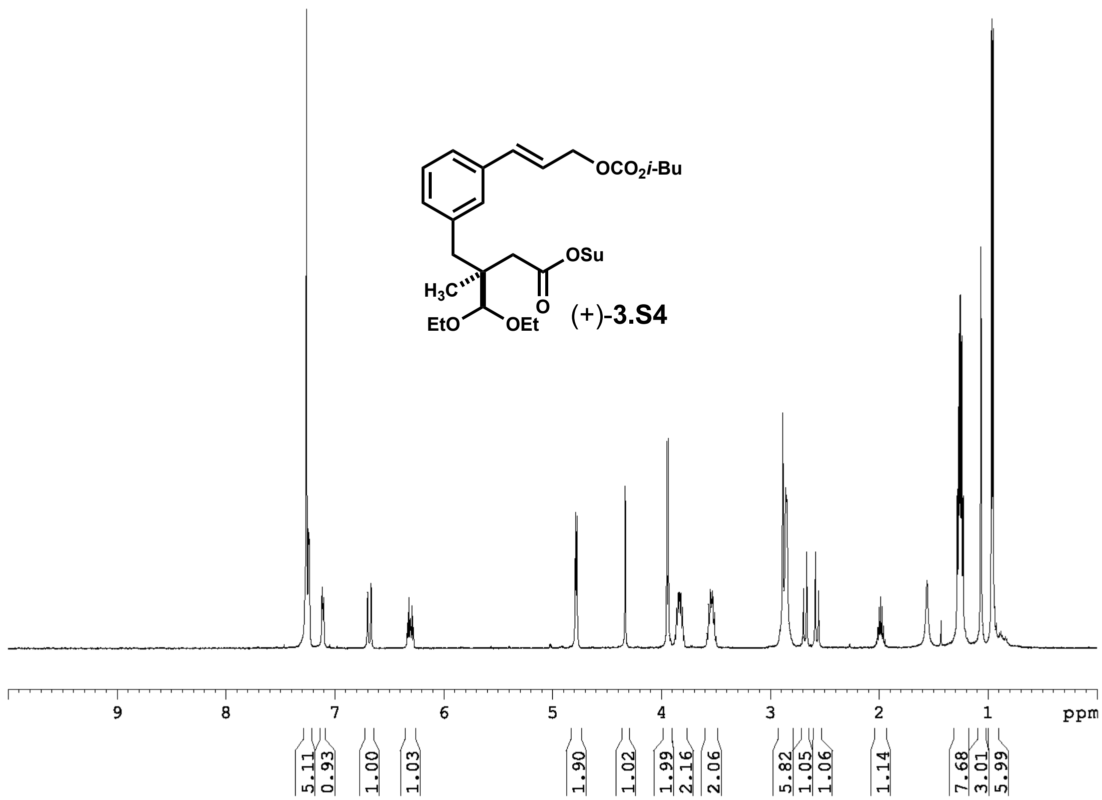
169.3 167.7 155.4 138.1 136.0 135.0 131.0 129.5 128.4 124.8 122.6 107.7 84.6 74.3 68.5 68.5 66.6 66.3 45.7 39.3 34.2 33.1 27.9 25.8 23.6 19.3 19.0 15.6 15.6
OCO2i-Bu
OSu
O
EtO
OEt
(+)-3.5
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

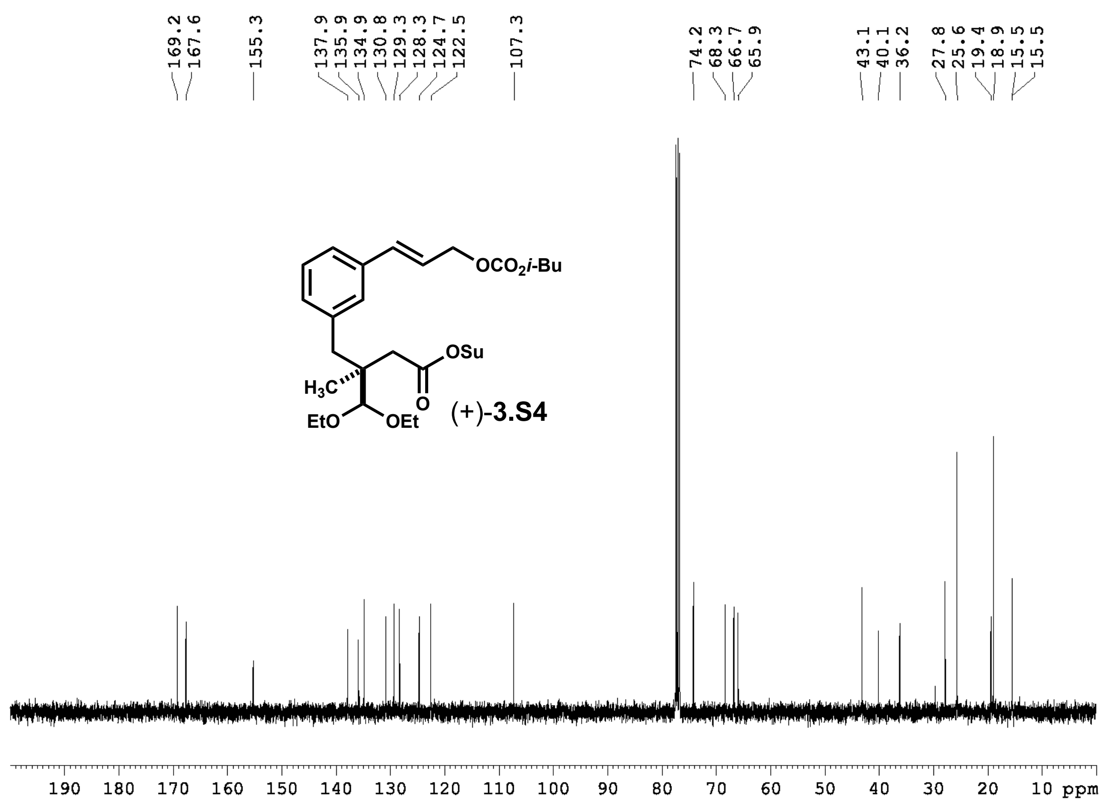
Suzuki product **3.S2**





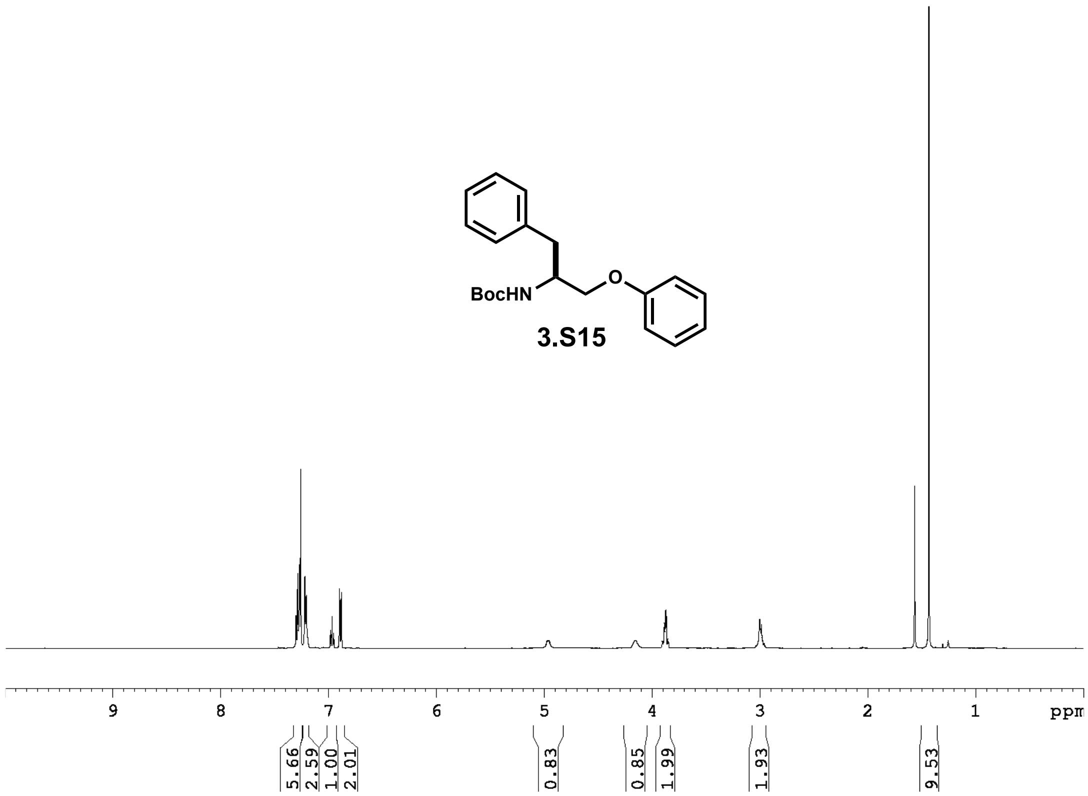
Template **3.S4**

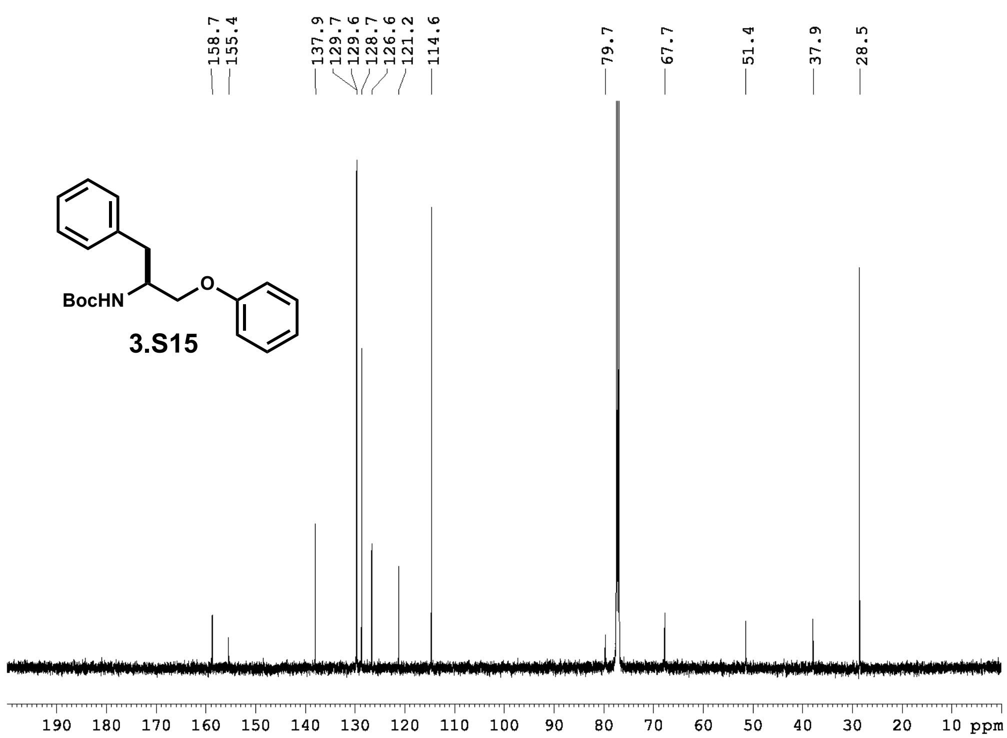




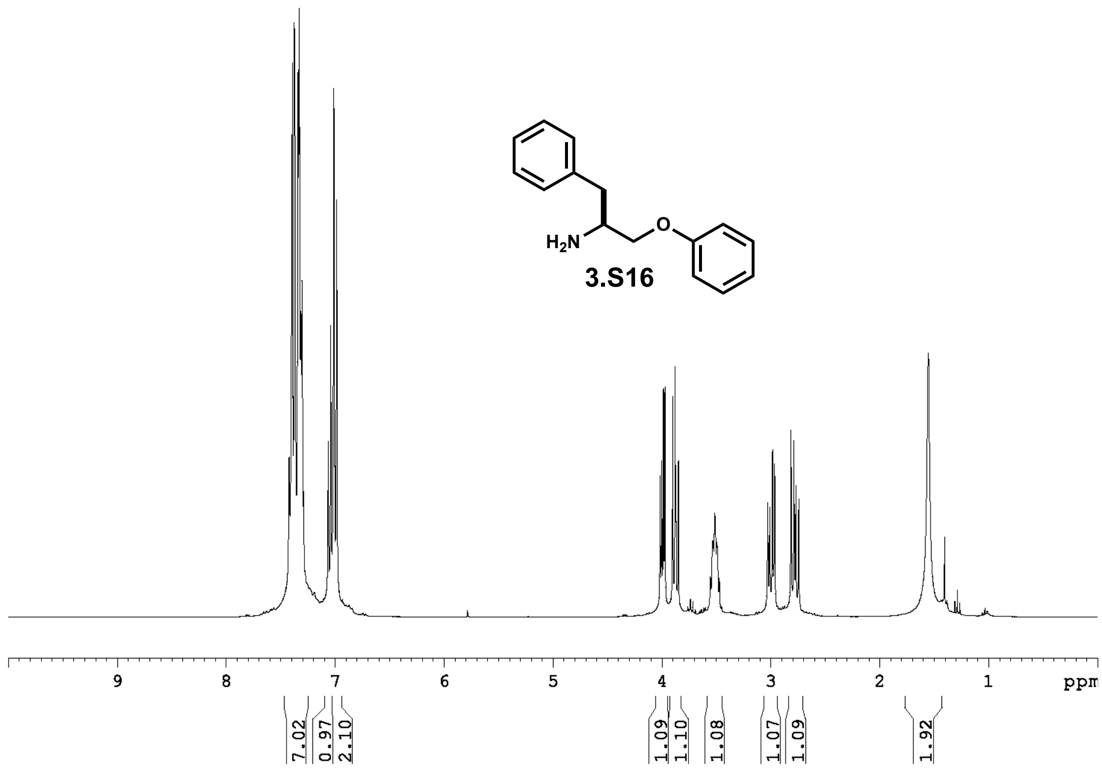
D.2. NMR Spectra – Synthesis of *O*-Phenyl-L-Phenylalaninol

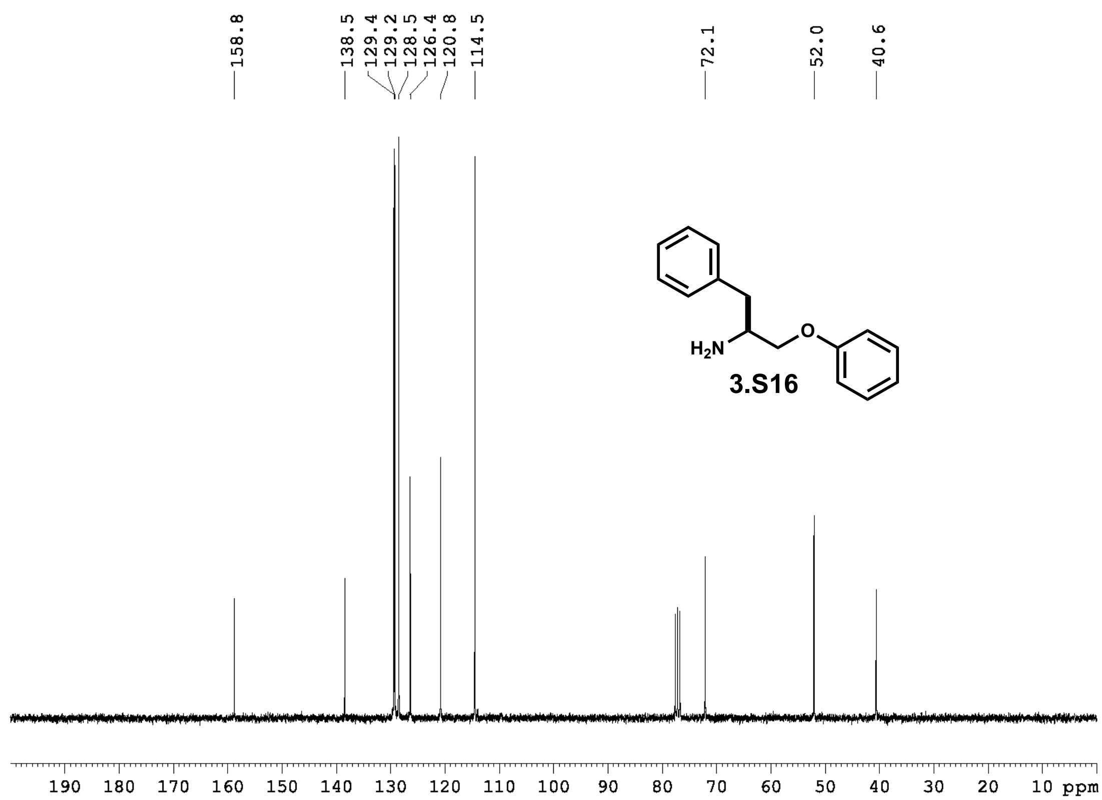
Boc-phenyl phenylalaninol **3.S15**





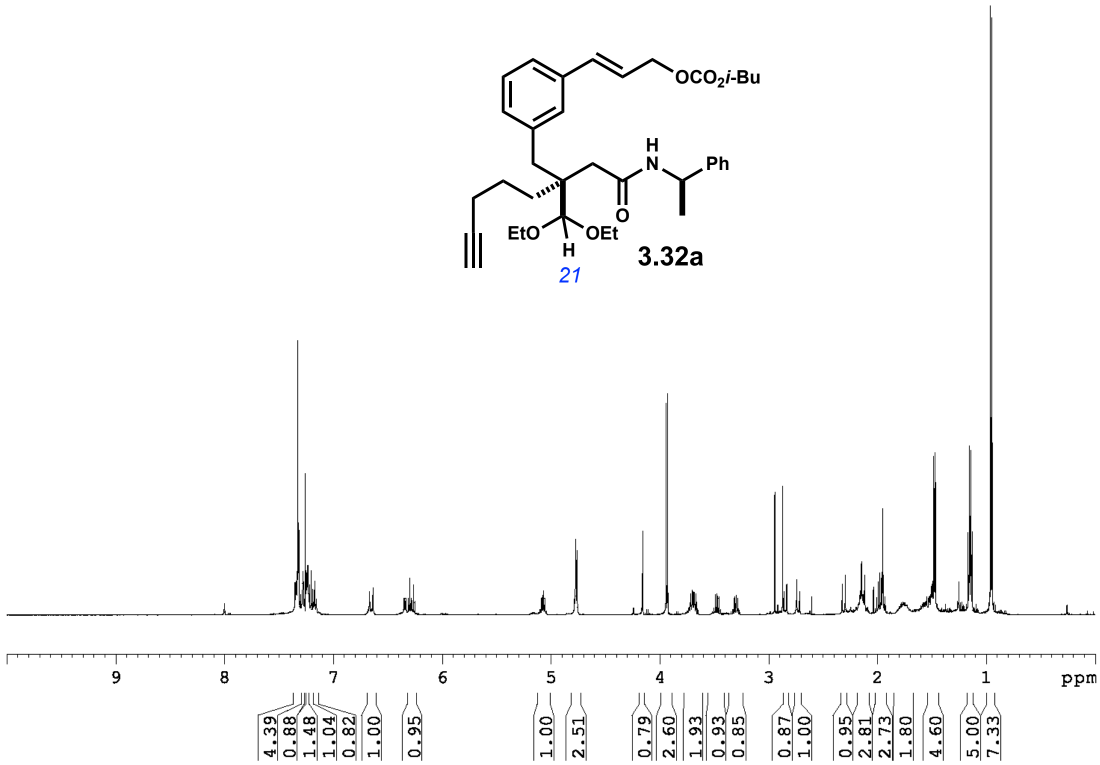
Phenyl phenylalaninol **3.S16**

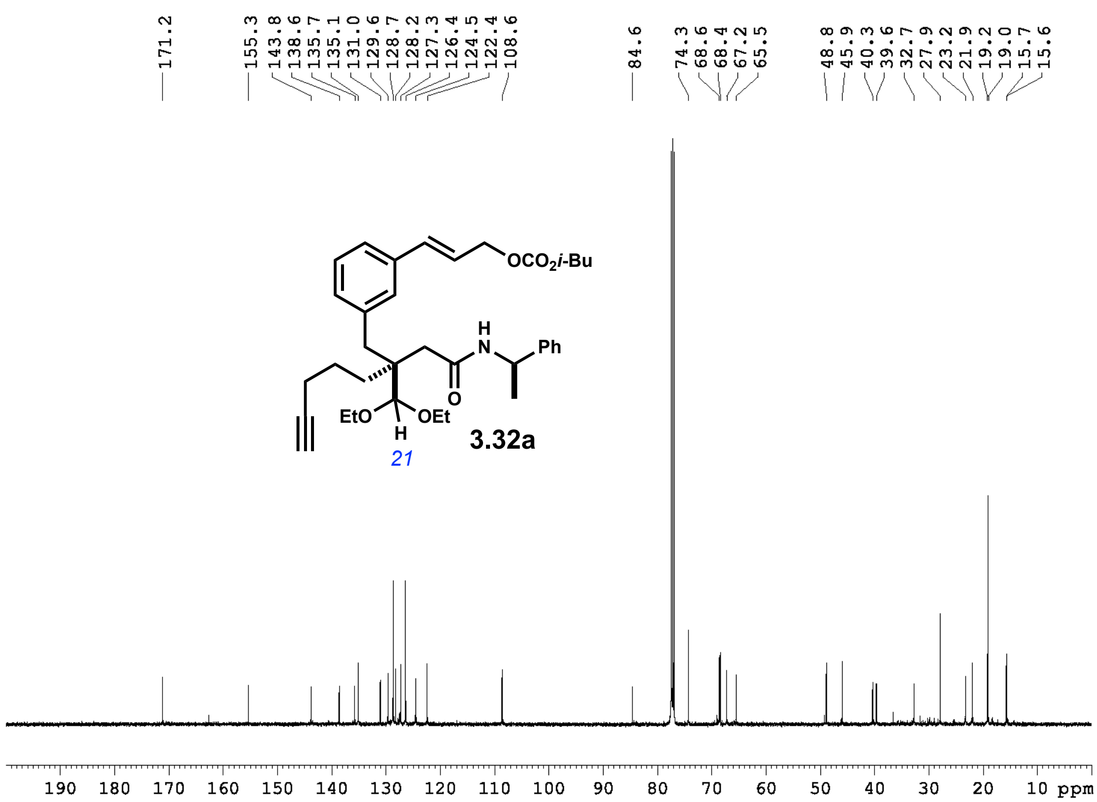




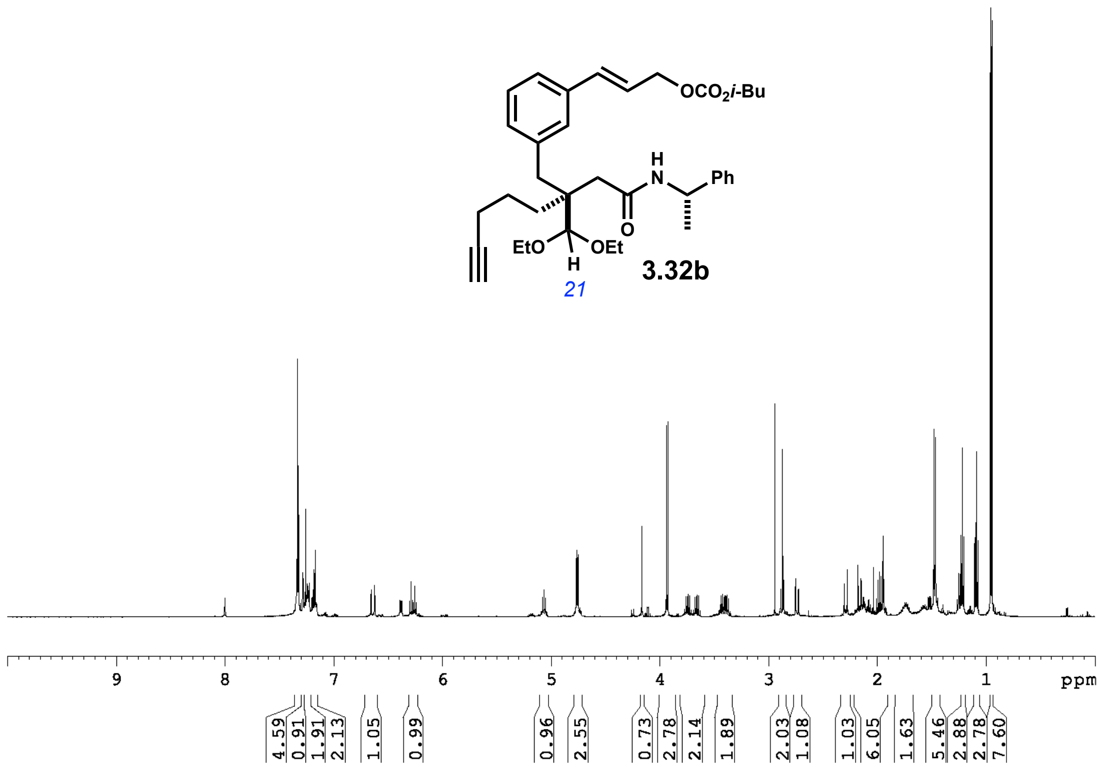
D.3. NMR Spectra – Enantiomeric Excess Determination of (+)-3.5 & (+)-3.S4

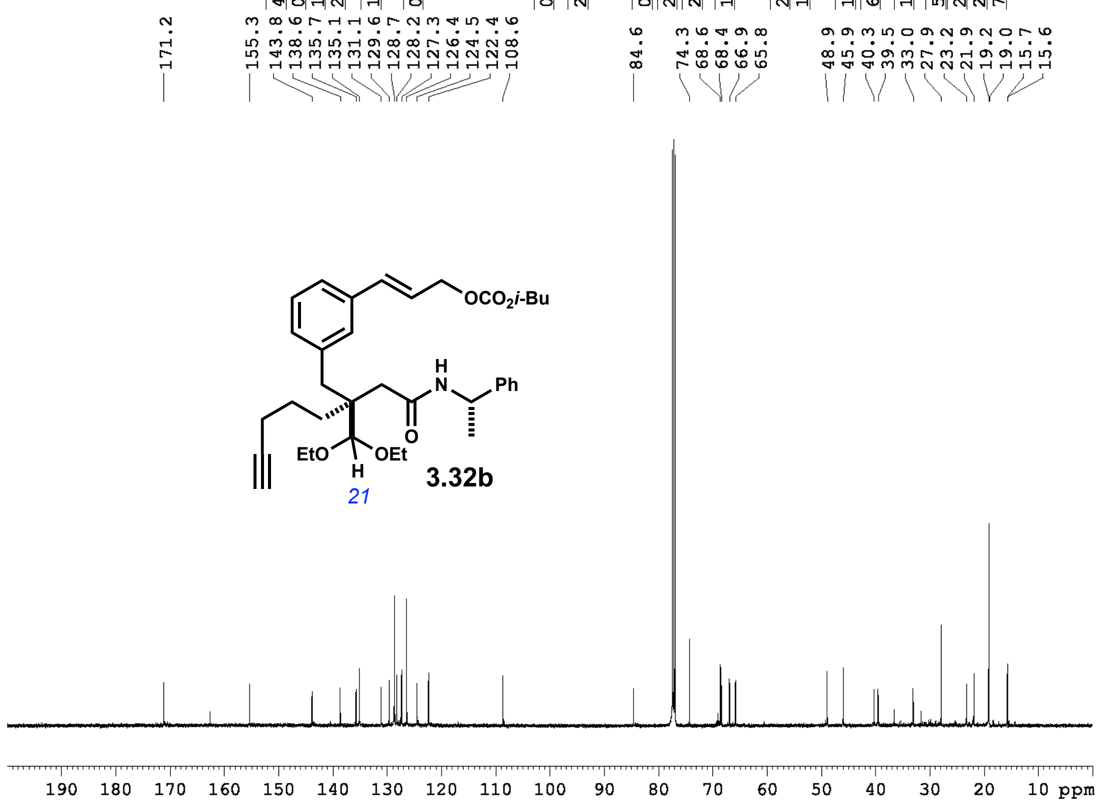
Acylation product **3.32a**



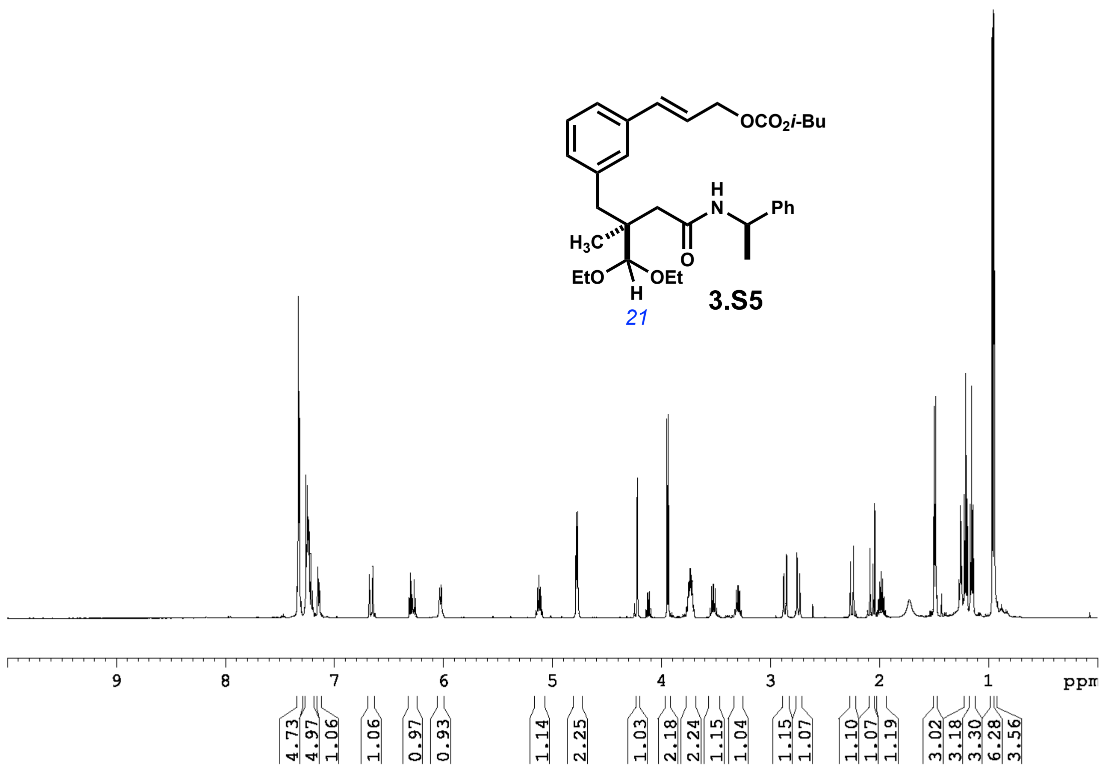


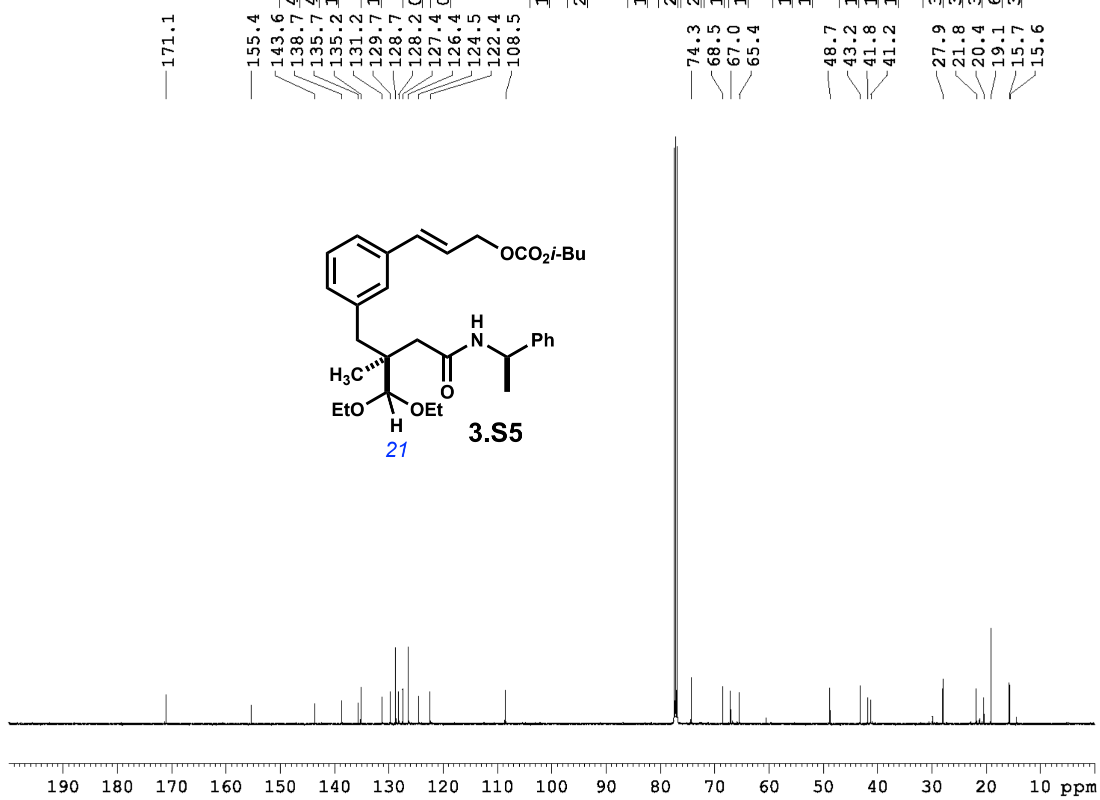
Acylation product **3.32b**



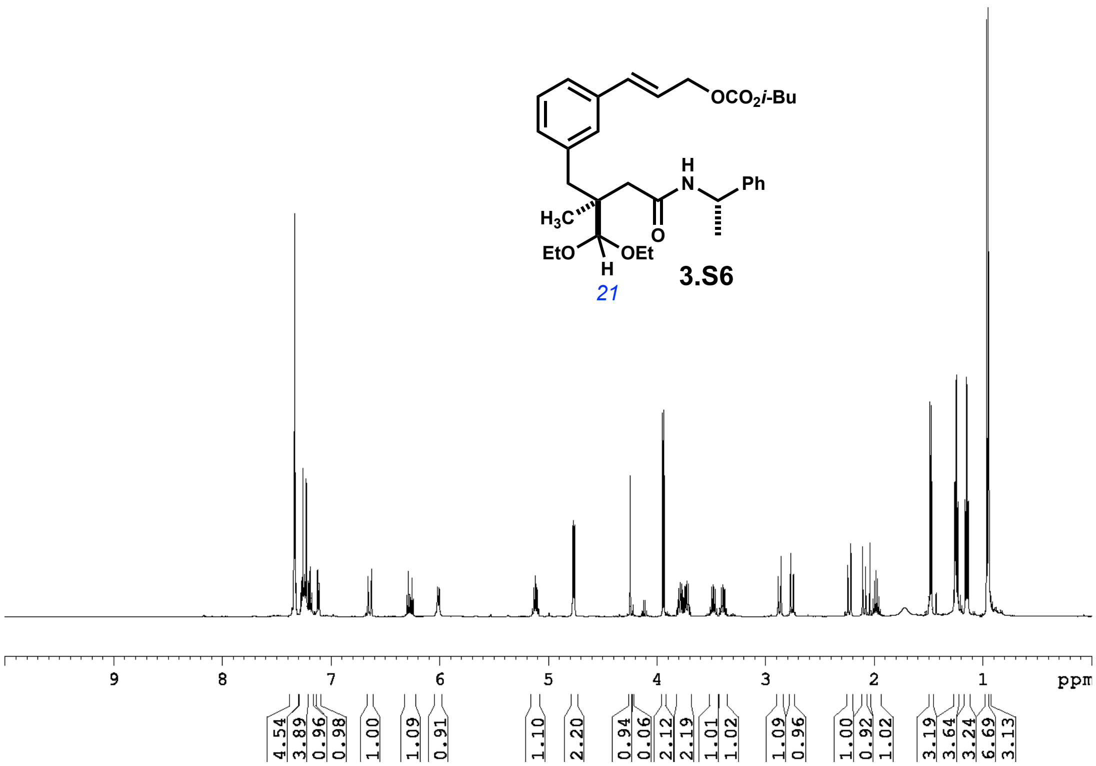


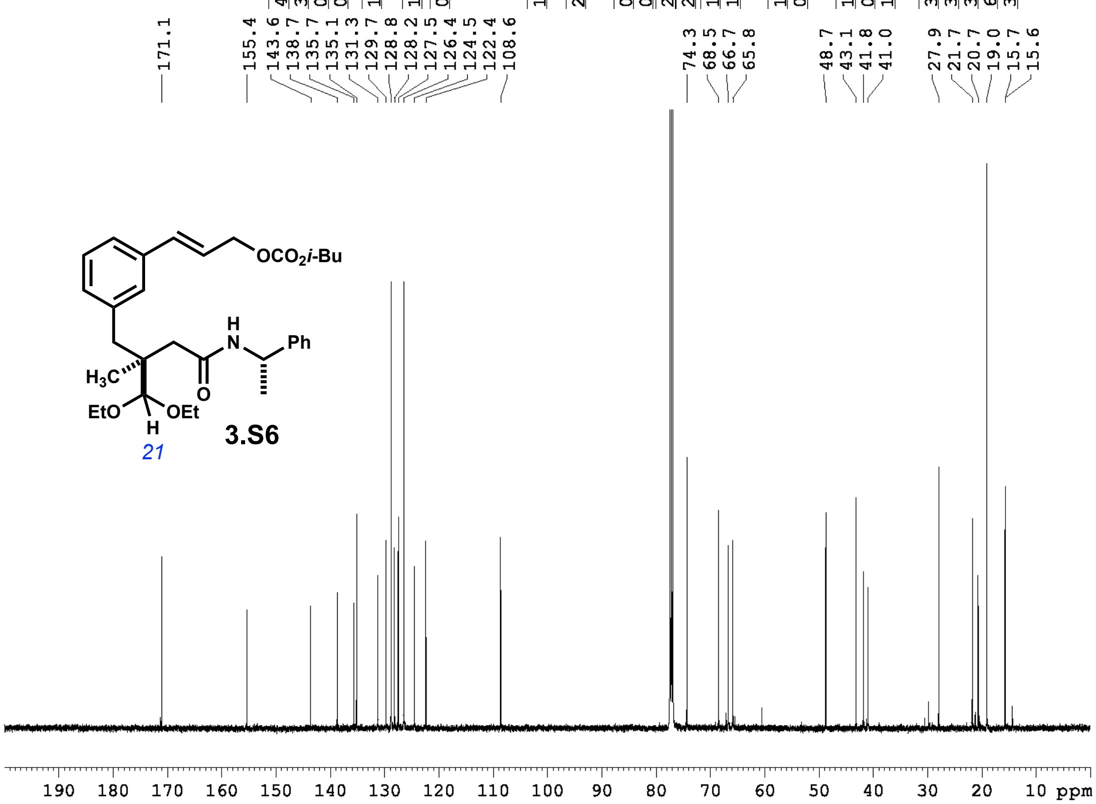
Acylation product **3.S5**





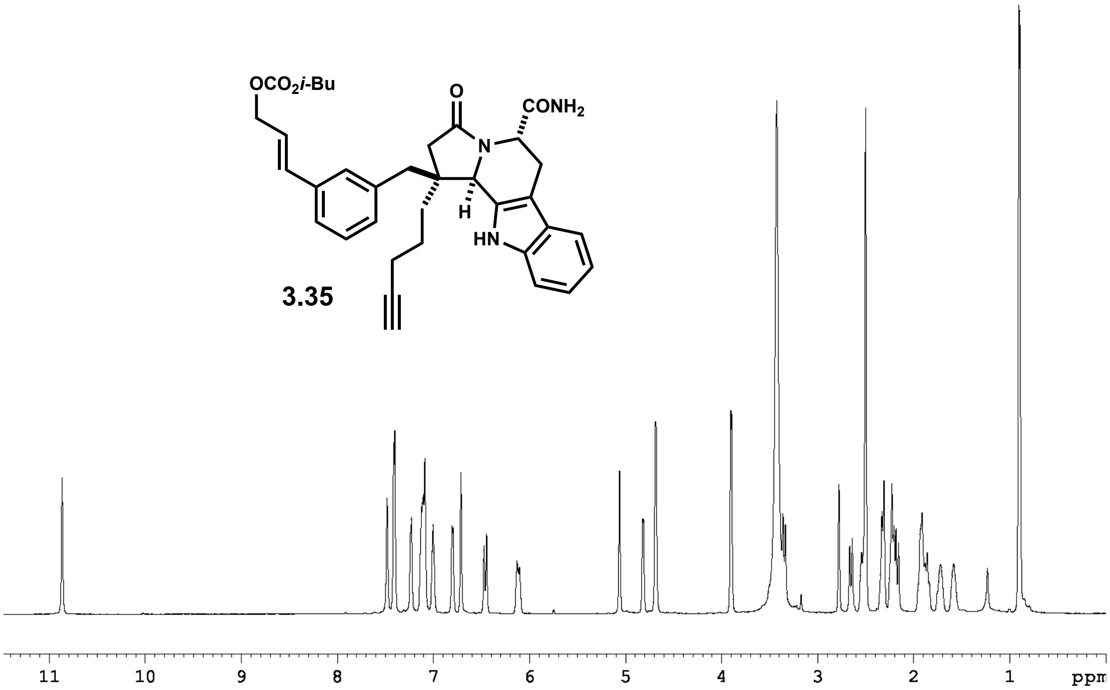
Acylation product **3.S6**

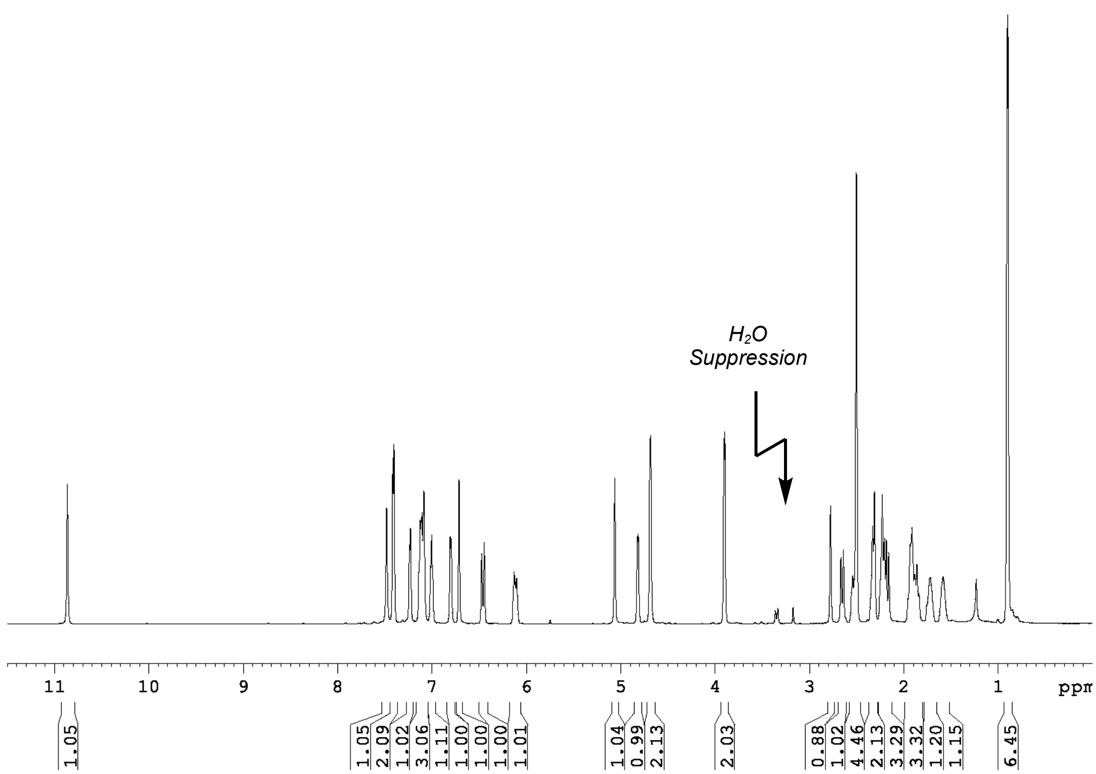


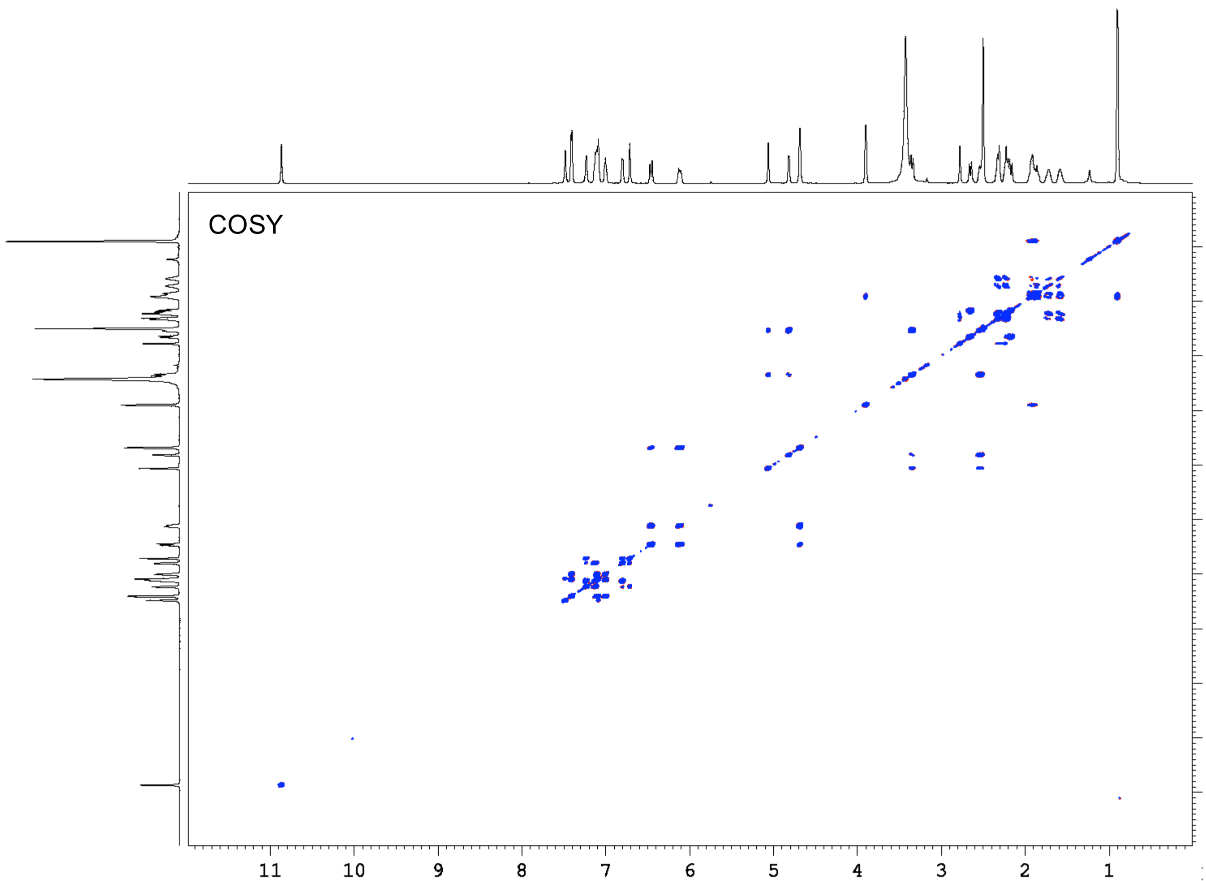


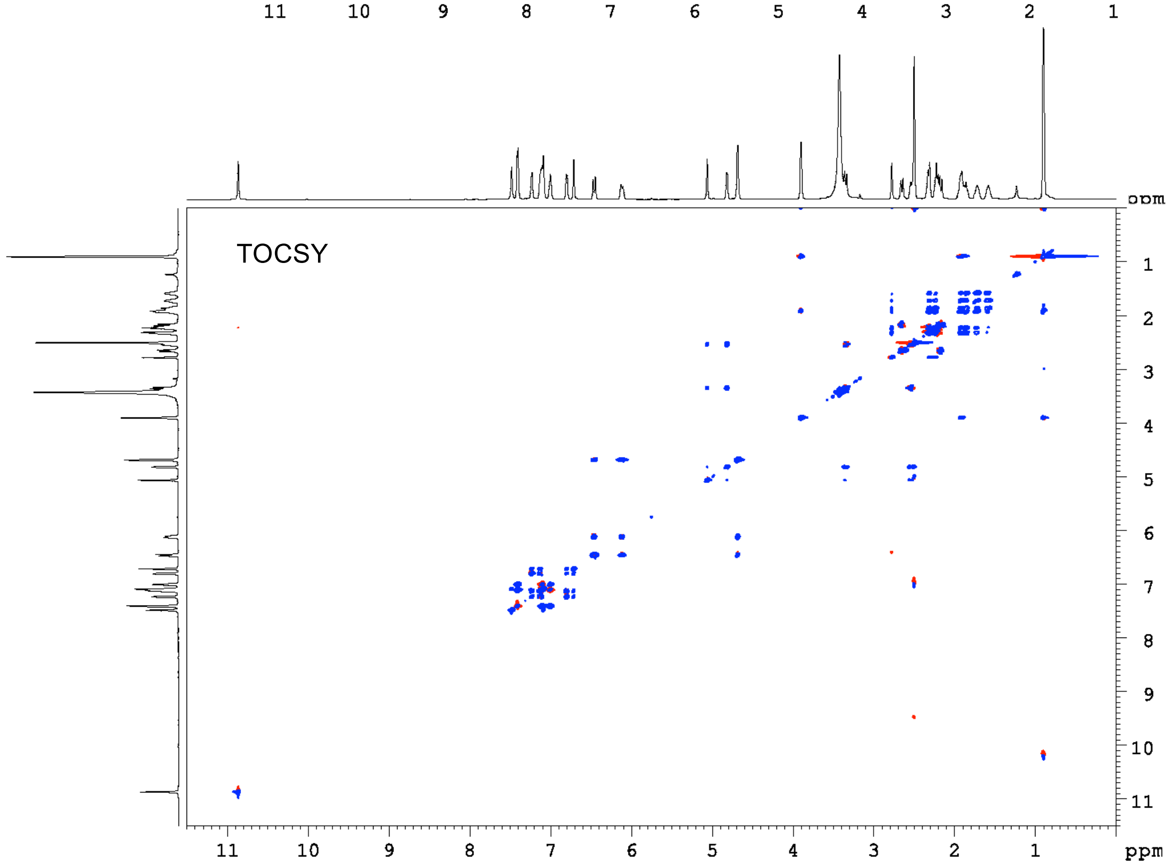
D.4. NMR Spectra – Absolute Stereochemical determination of (+)-3.5

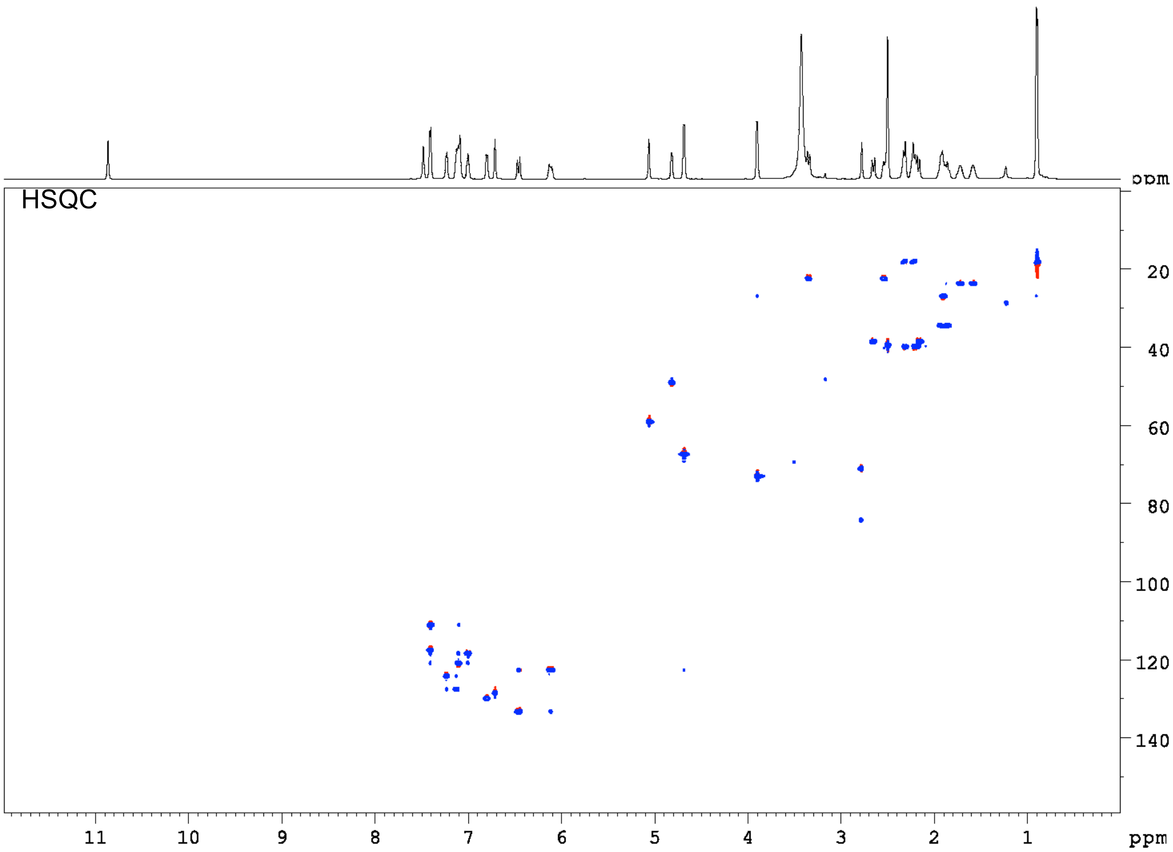
Pictet-Spengler product **3.35**

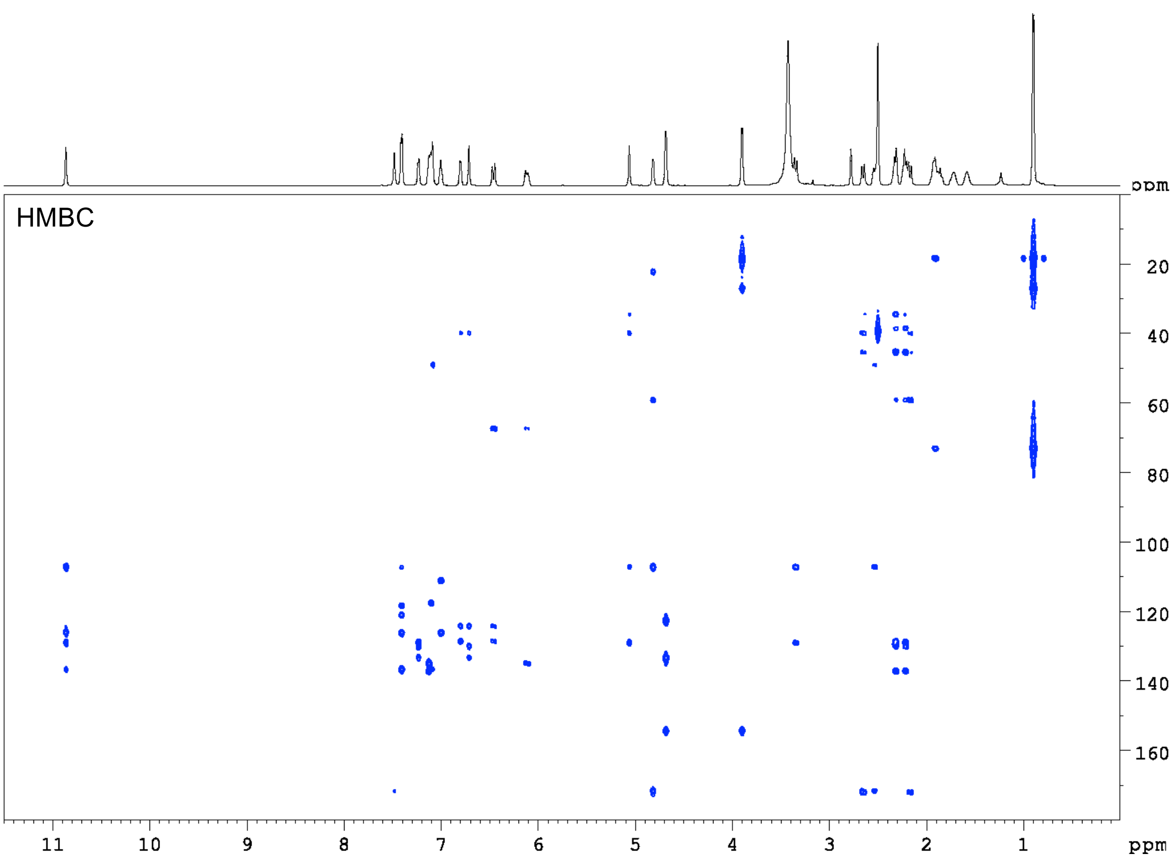





COSY
11
10
9
8
7
6
5
4
3
2
1


TOCSY
11
10
9
8
7
6
5
4
3
2
1
ppm


ppm
HSQC
20
40
60
80
100
120
140
11
10
9
8
7
6
5
4
3
2
1
ppm


ppm
HMBC
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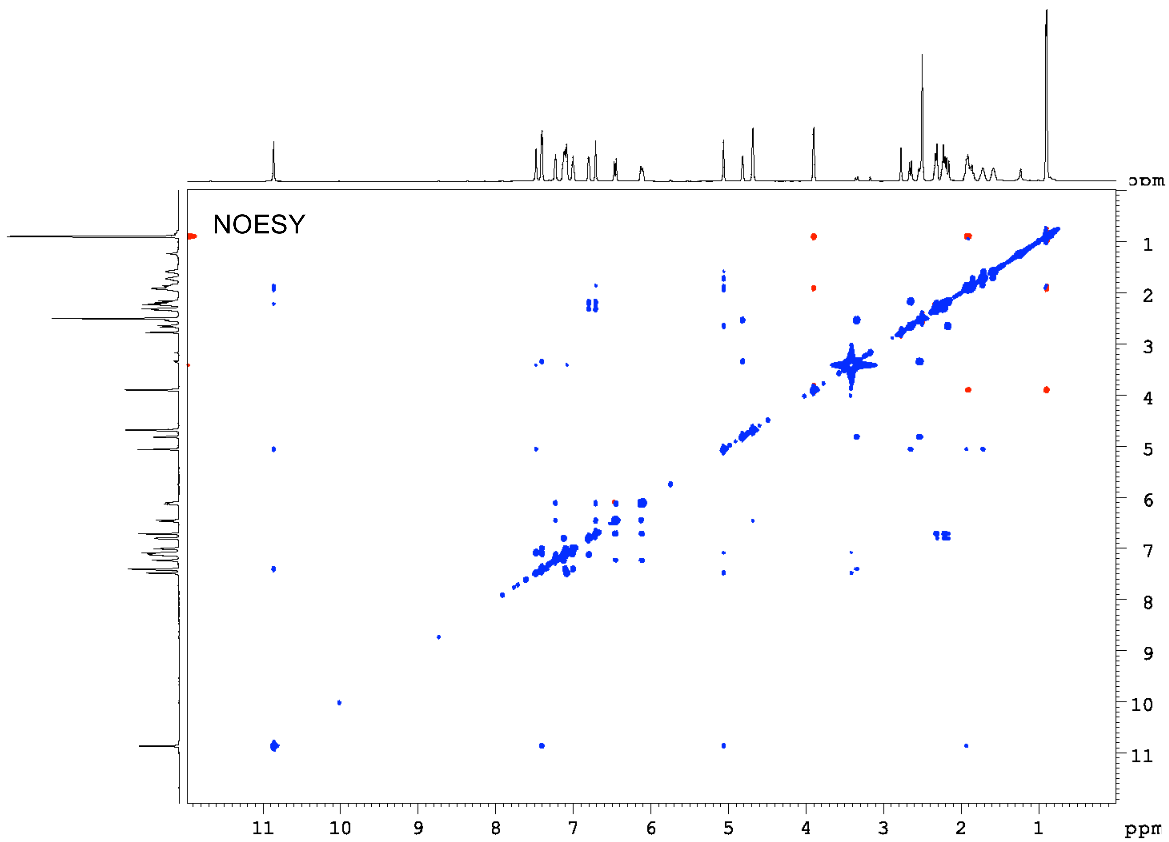
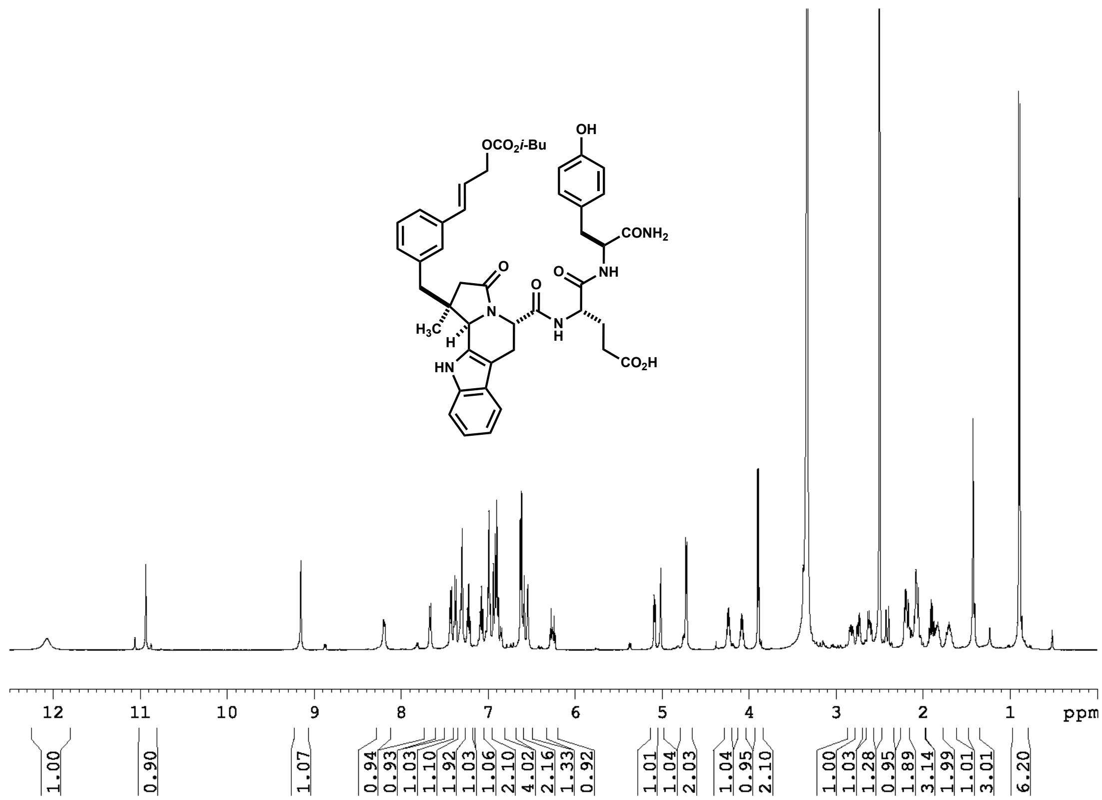
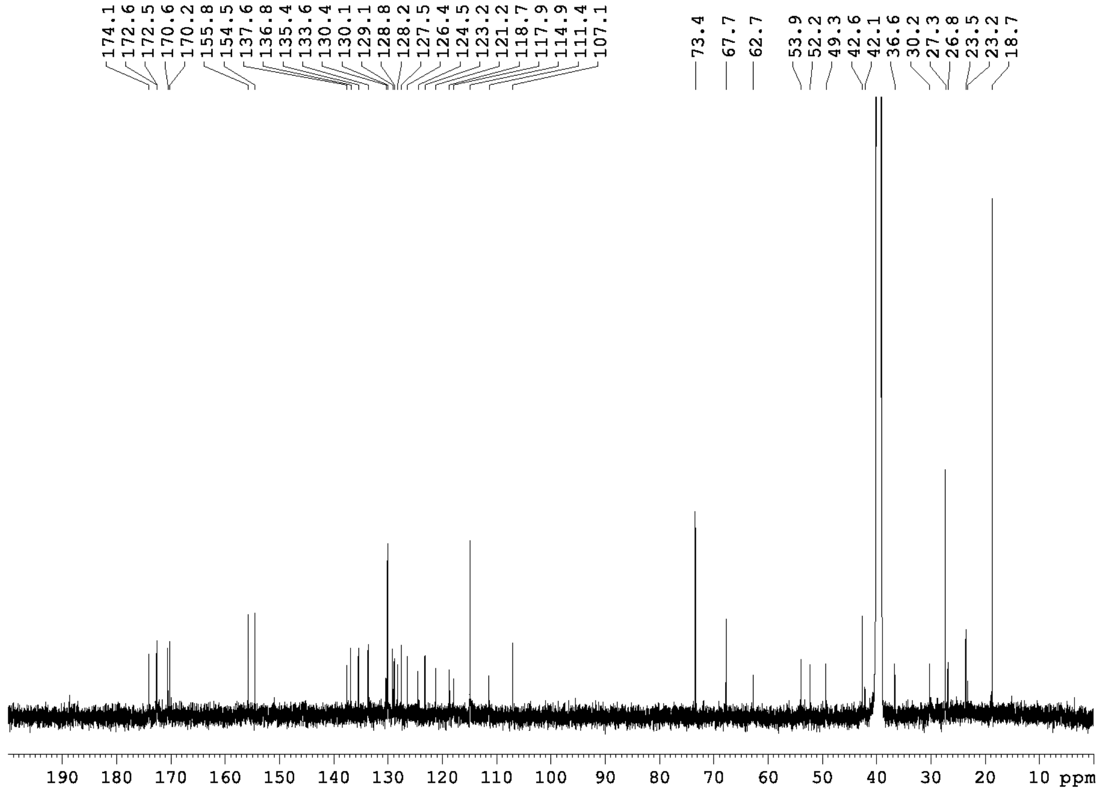
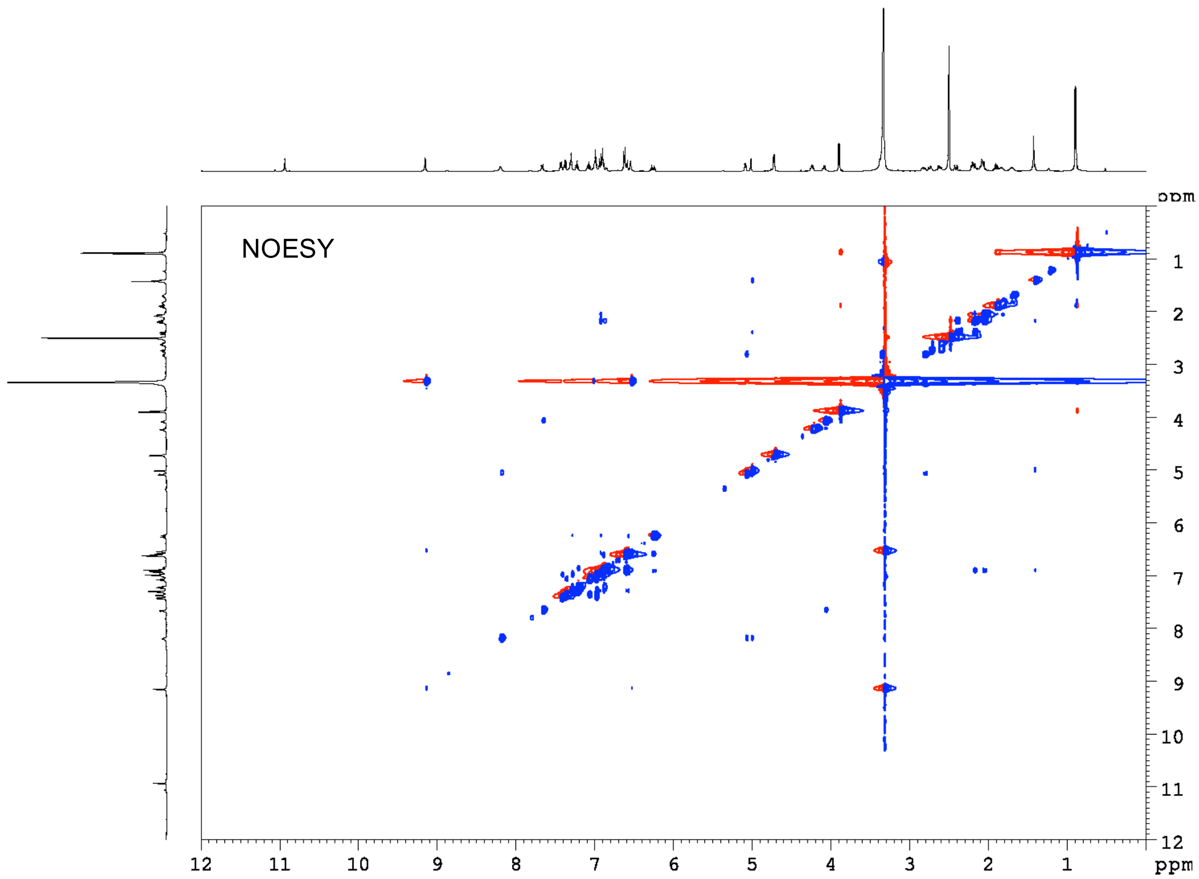
60
80
100
120
140
160
11
10
9
8
7
6
5
4
3
2
1
ppm


NOESY
ppm
1
2
3
4
5
6
7
8
9
10
11
11
10
9
8
7
6
5
4
3
2
1
ppm

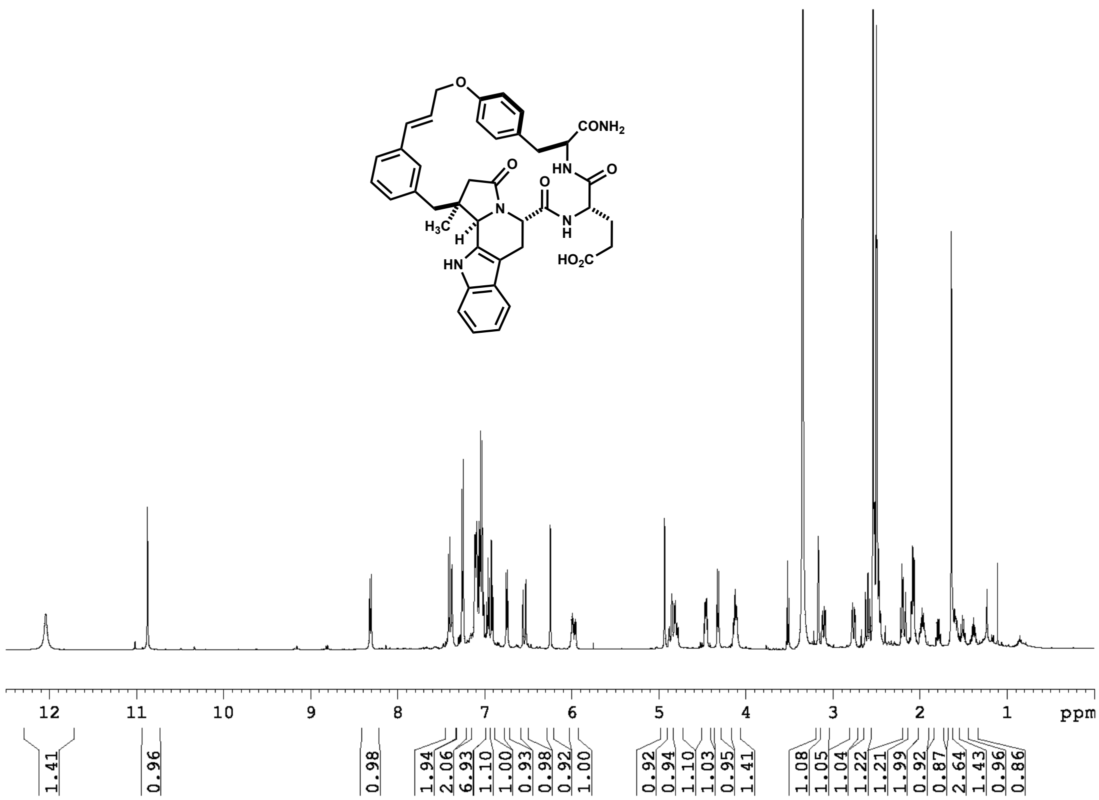
Pictet-Spengler Product **3.37**

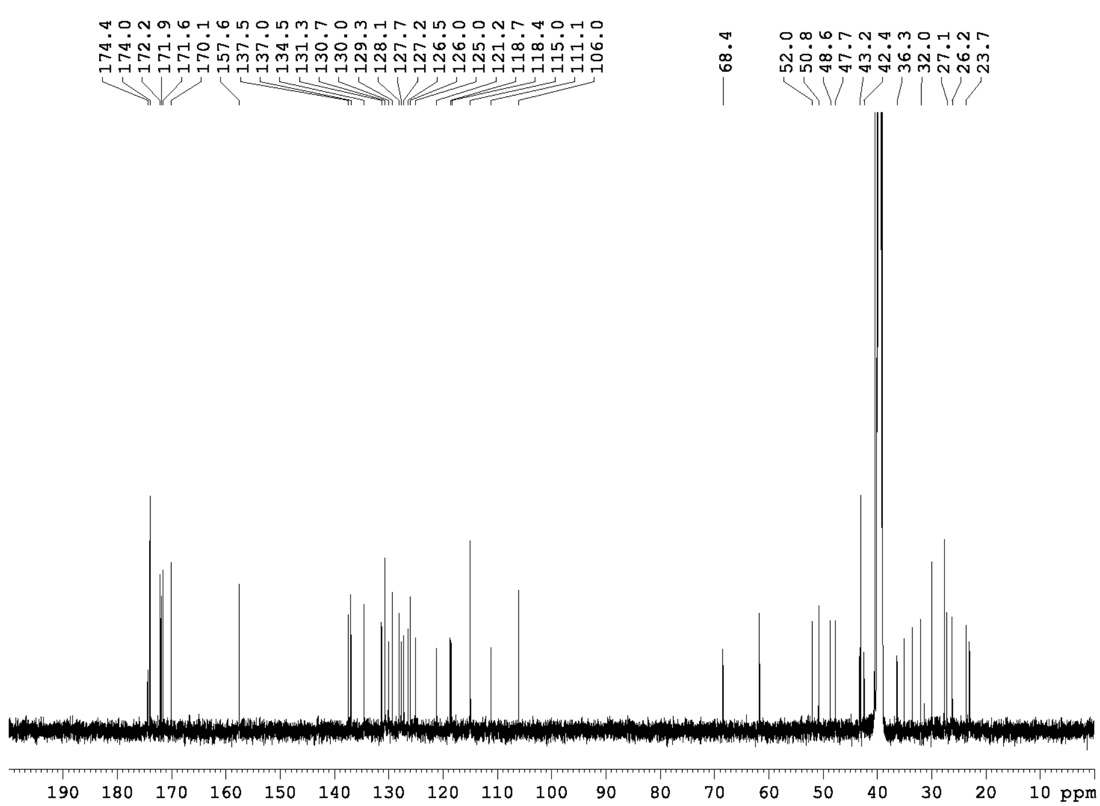


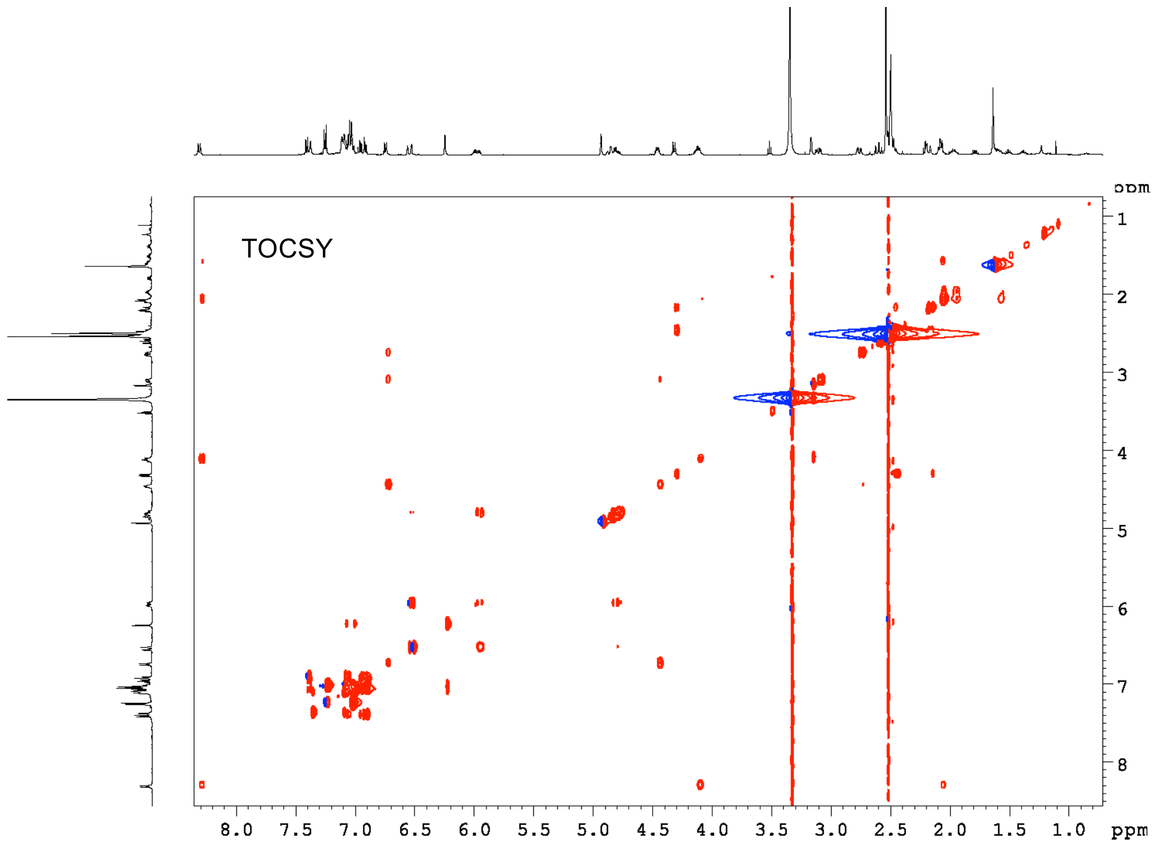



NOESY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Macrocycle **3.39**







TOCSY
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
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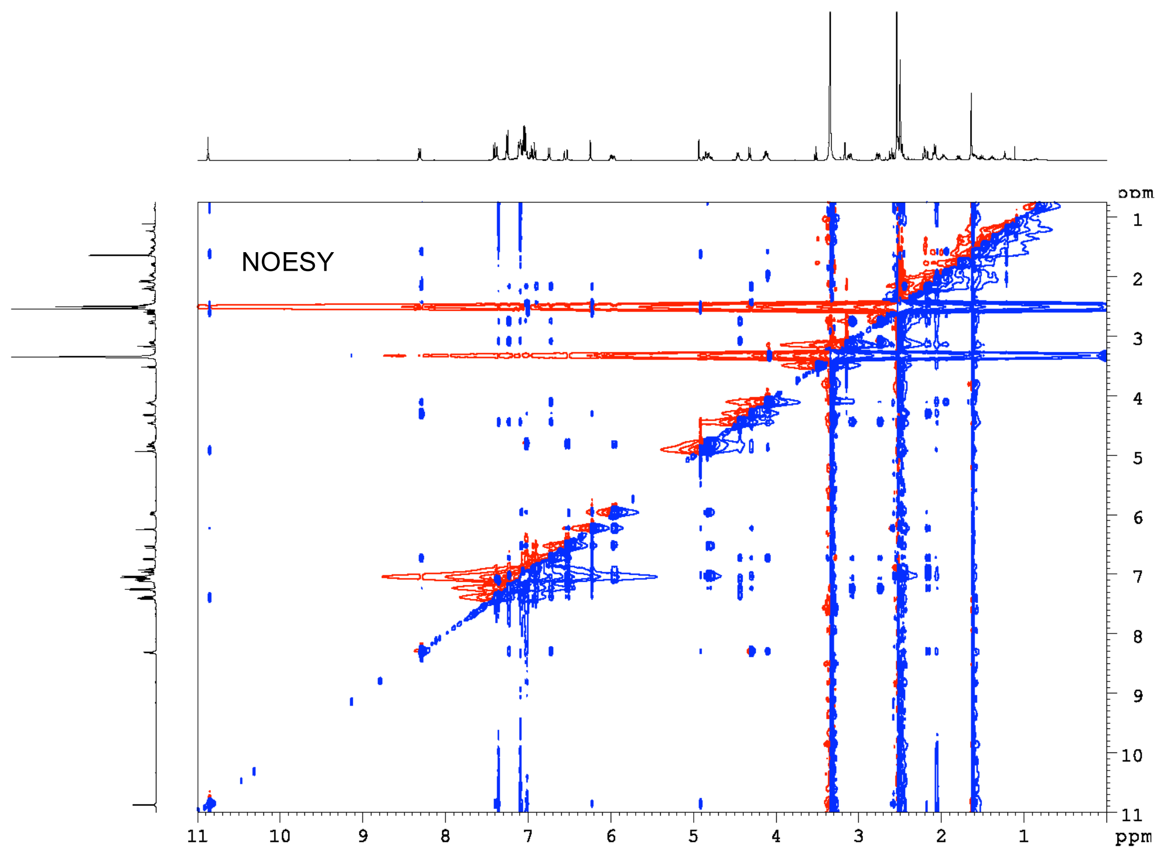
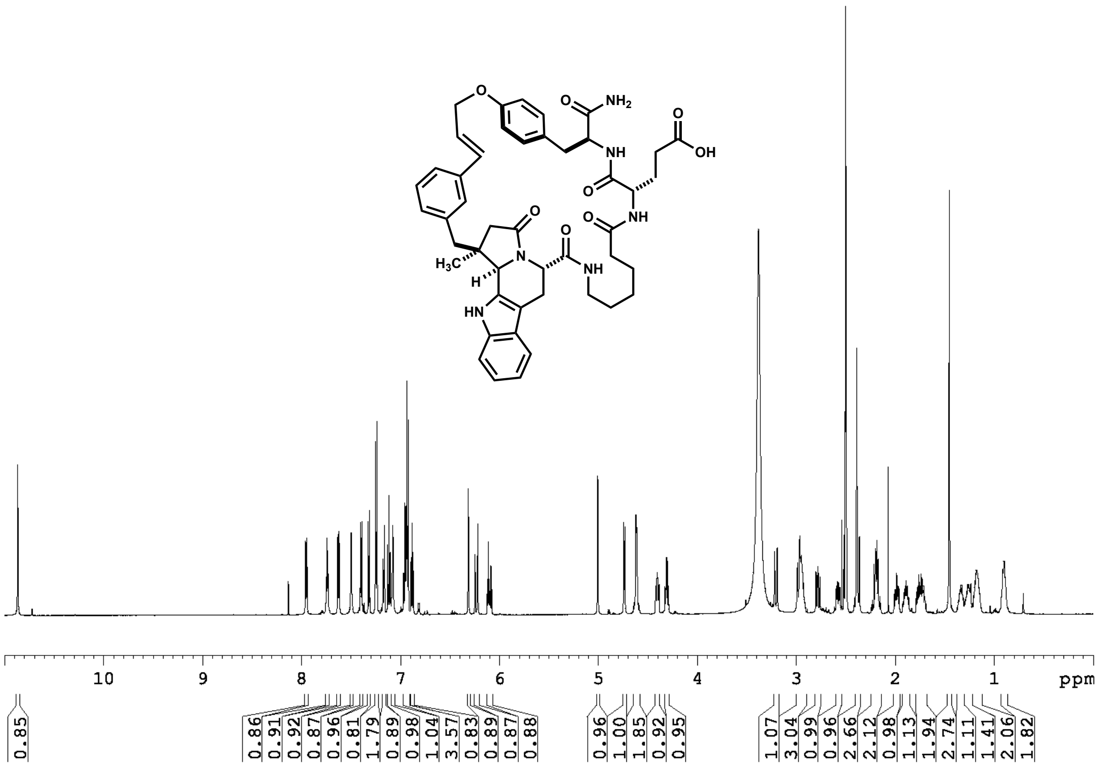
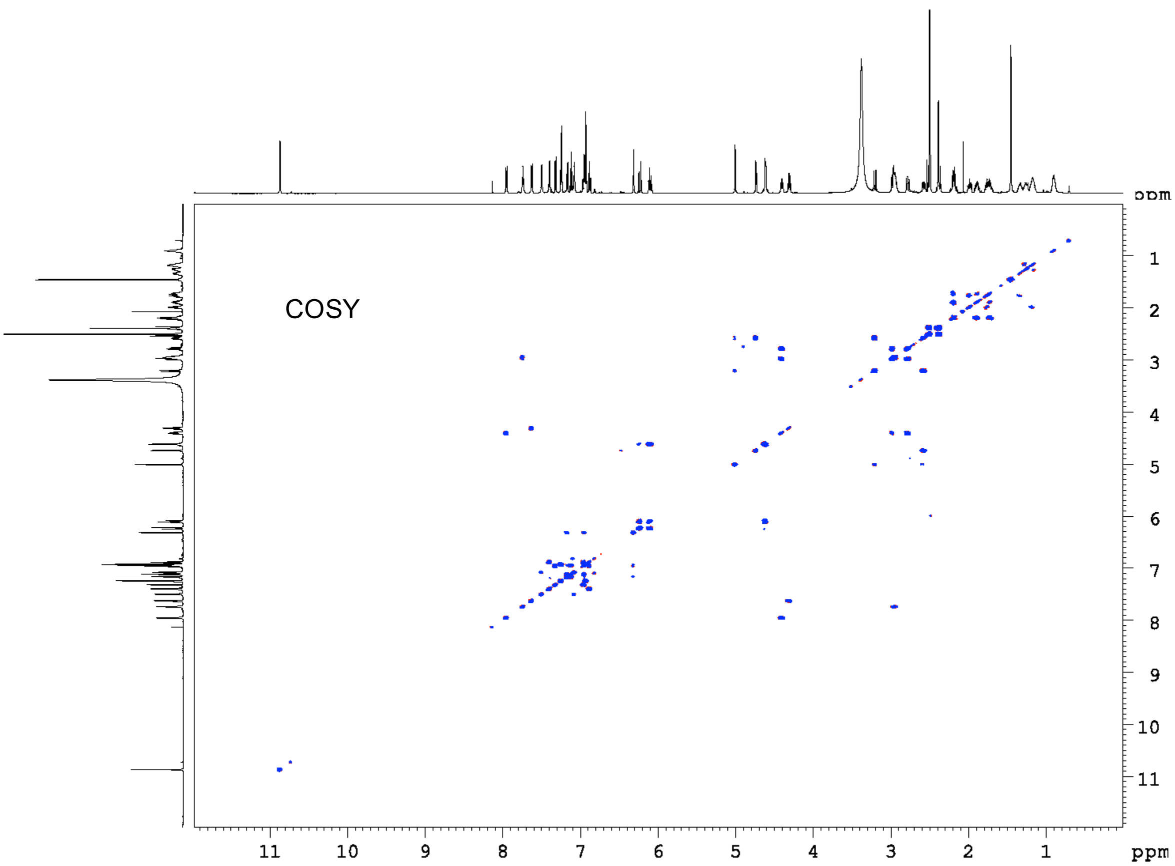
2.0
1.5
1.0

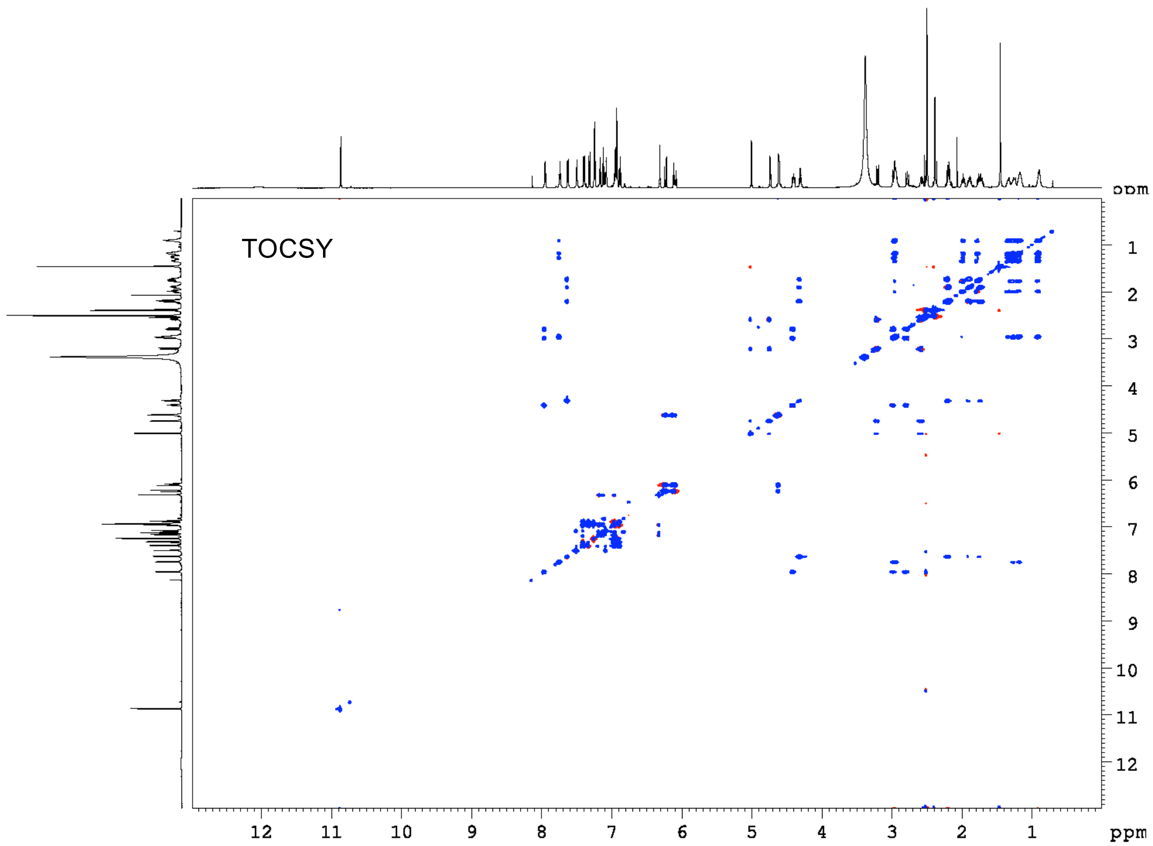


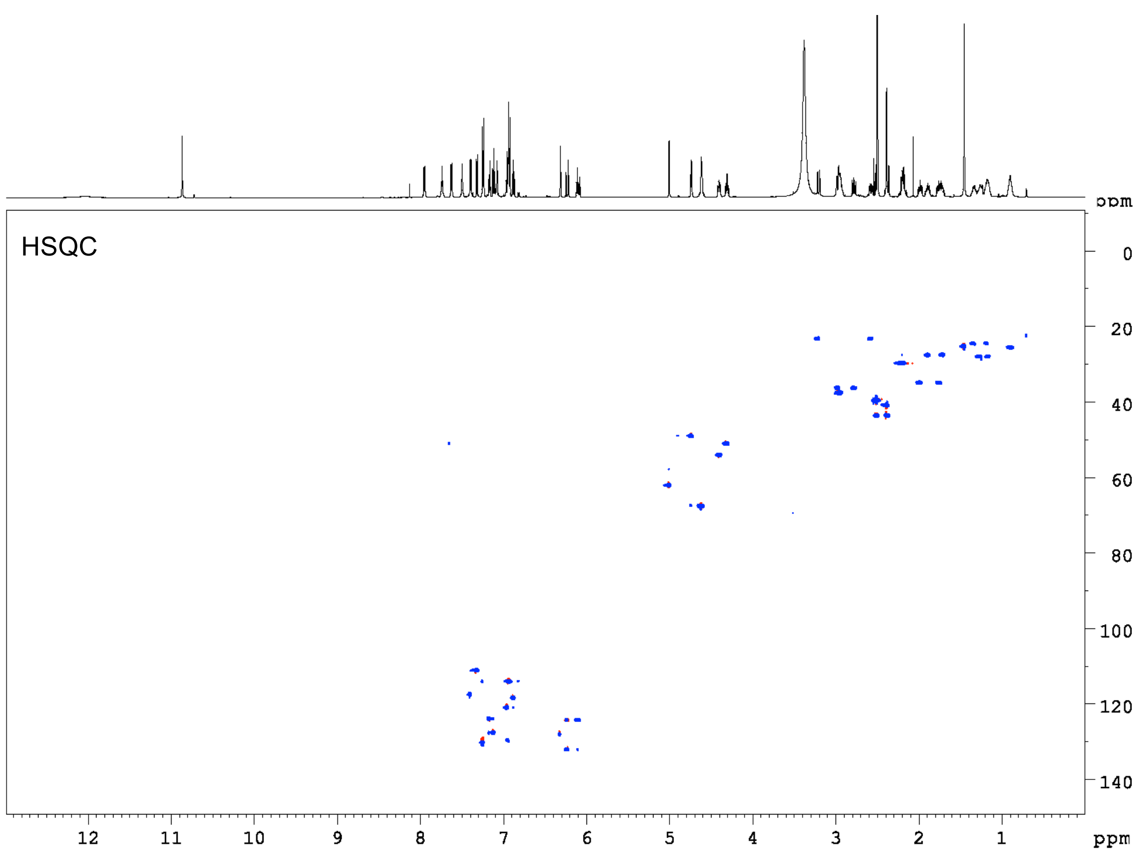
NOESY
ppm
11
10
9
8
7
6
5
4
3
2
1

Macrocycle **3.42**






TOCSY
ppm
12
11
10
9
8
7
6
5
4
3
2
1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100
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4
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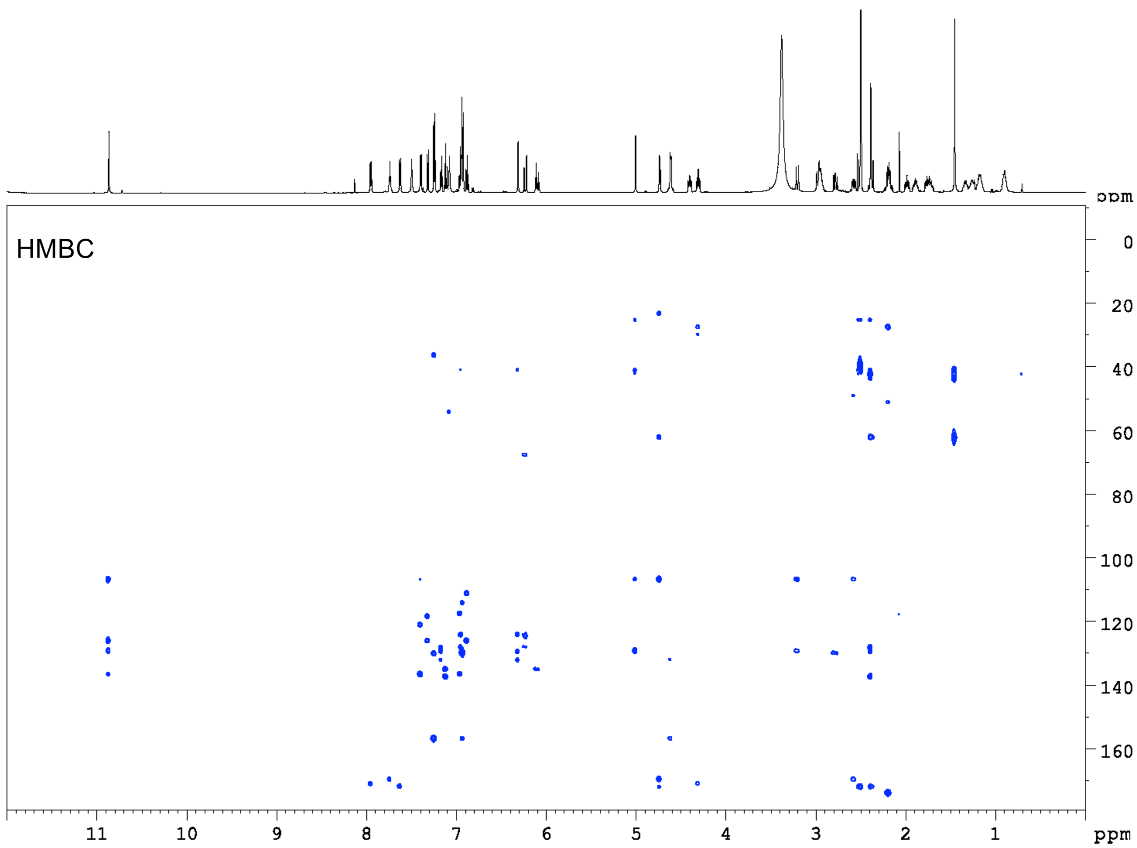
2
1


HMBC
ppm
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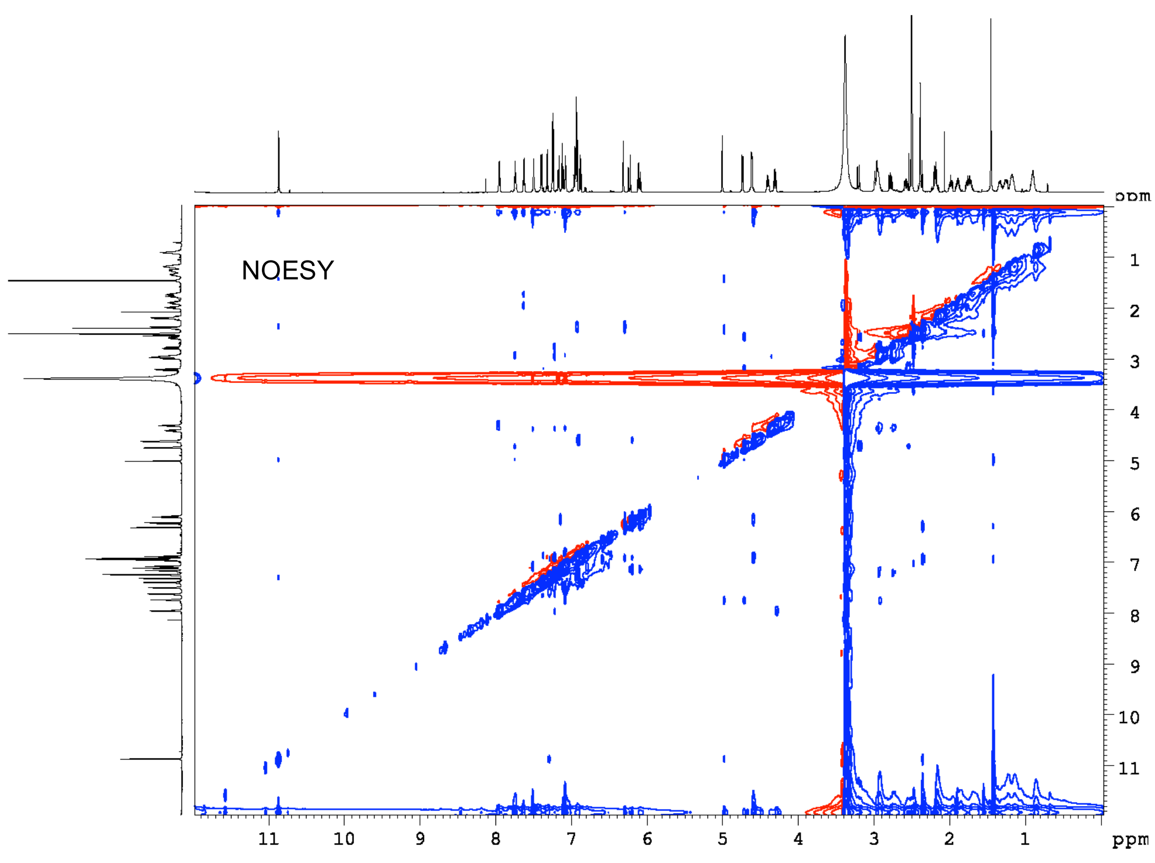
3
2
1
ppm


NOESY
ppm
1
2
3
4
5
6
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9
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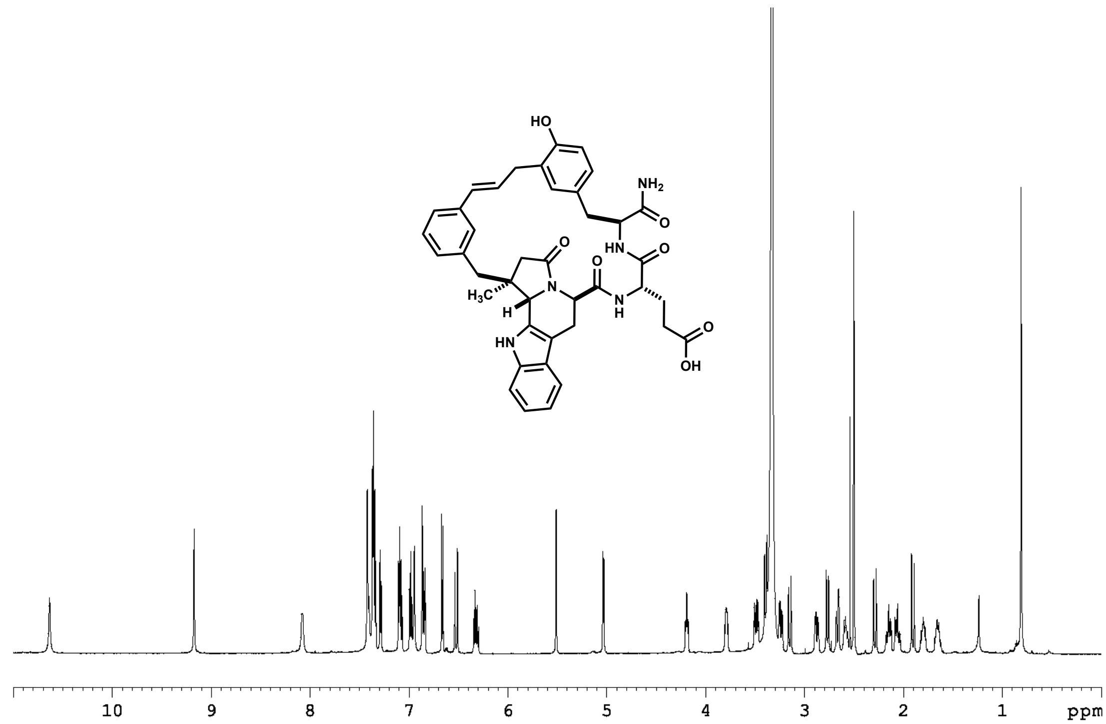
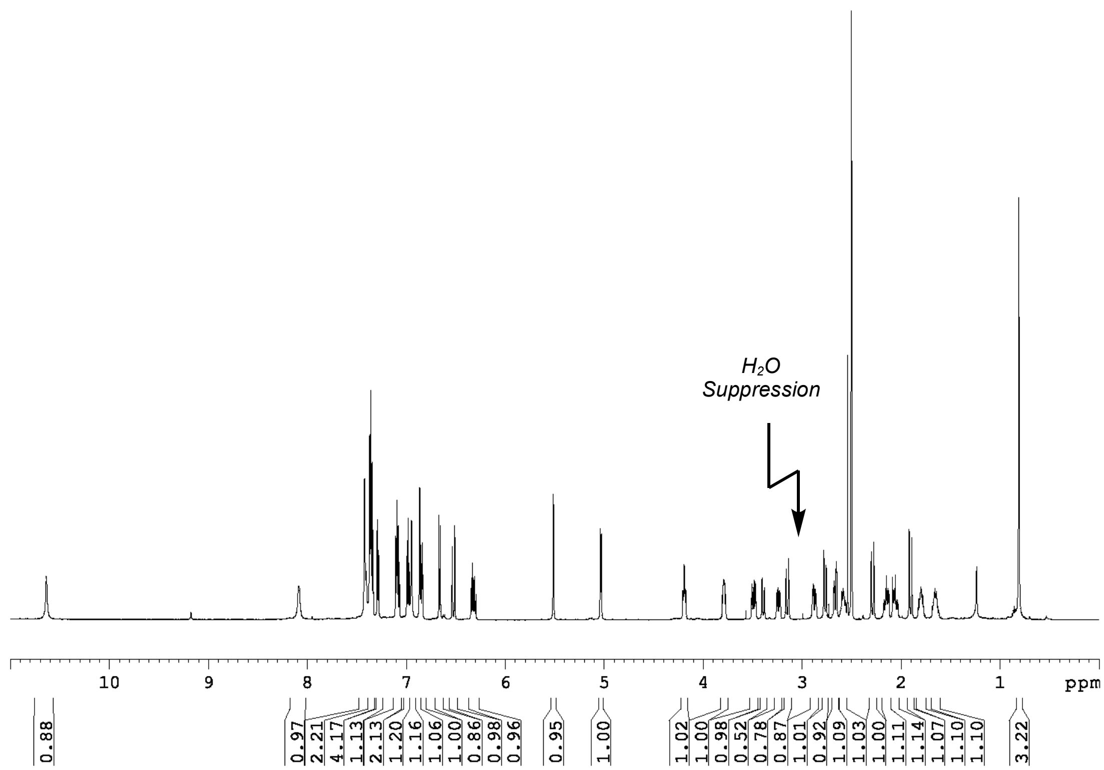
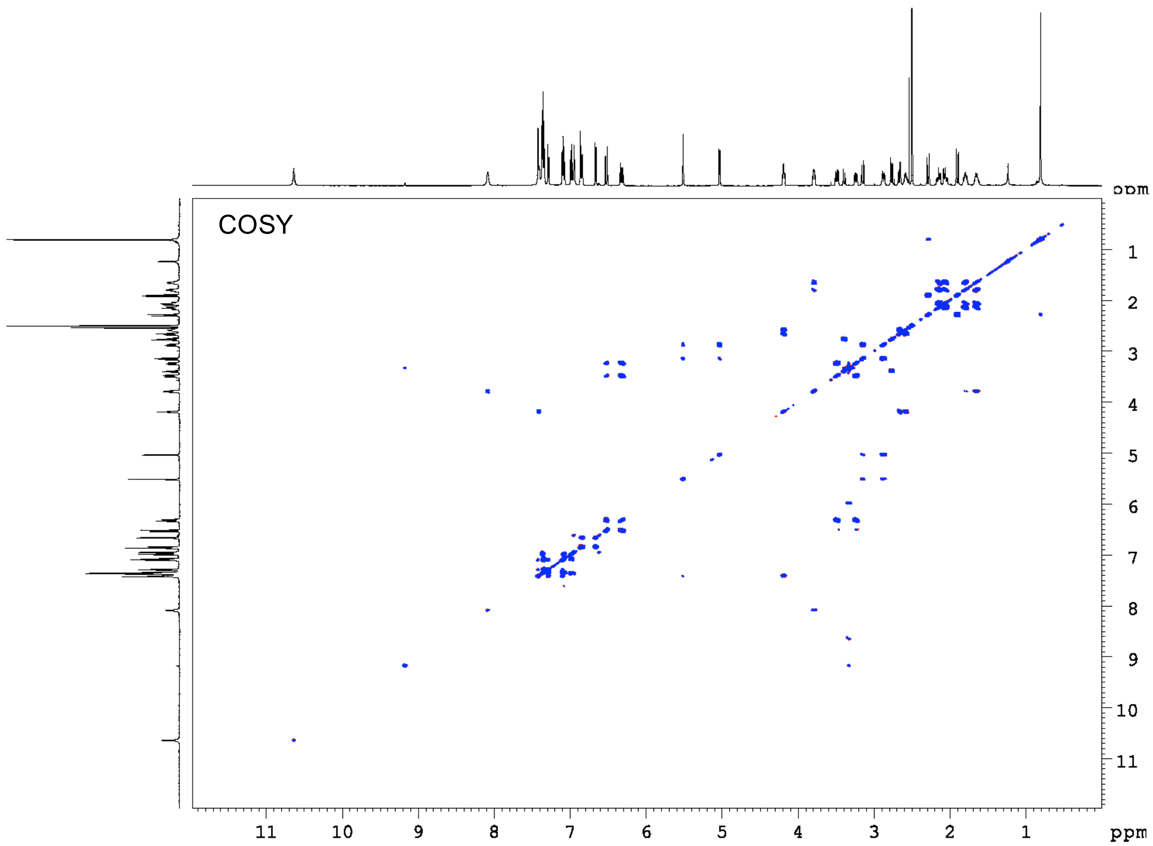
10
9
8
7
6
5
4
3
2
1
ppm

Macrocycle **3.44**






COSY
ppm
11
10
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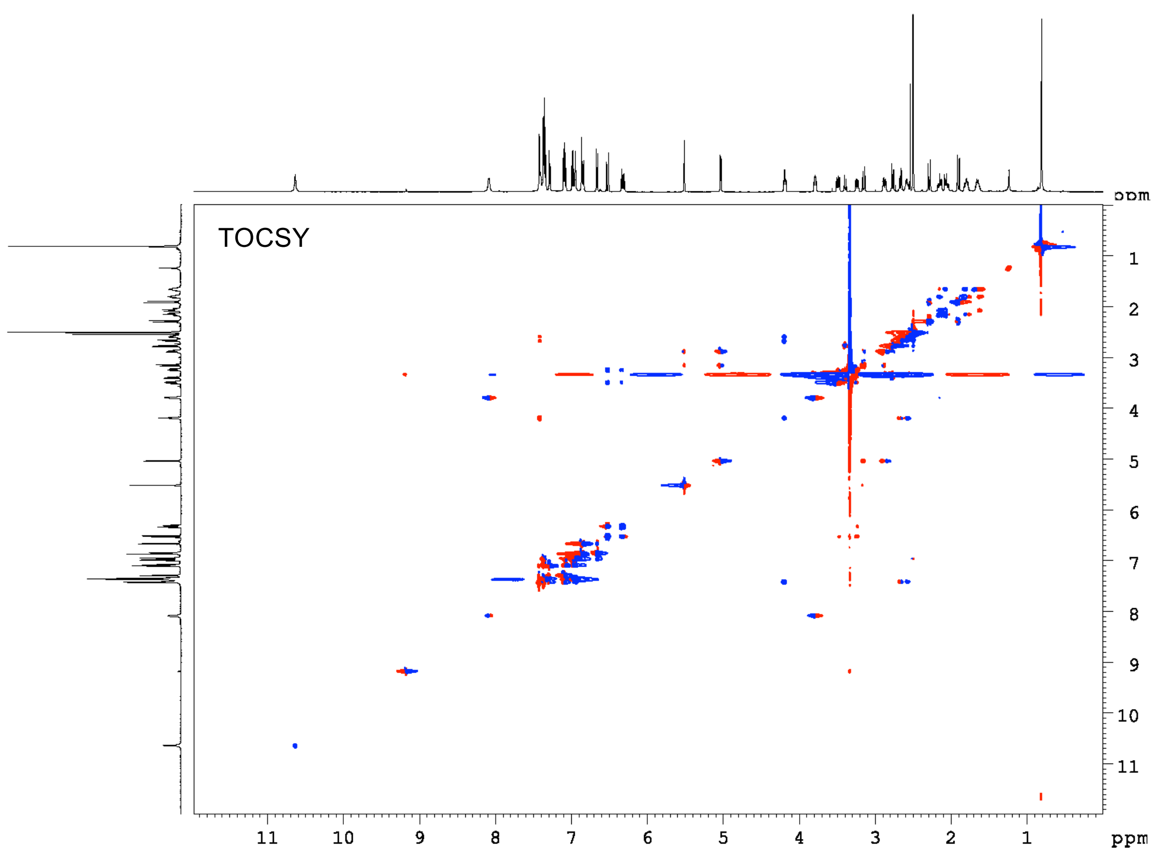
8
7
6
5
4
3
2
1


TOCSY
ppm
11
10
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8
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6
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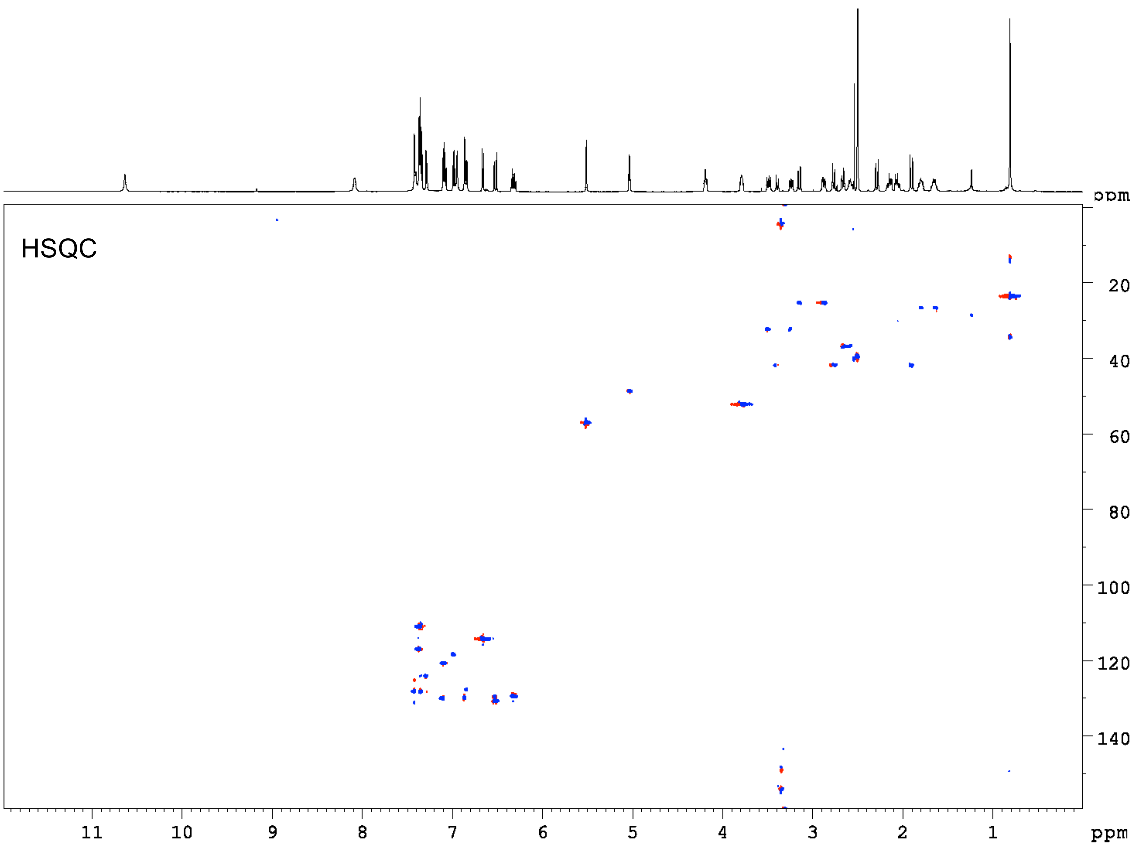
4
3
2
1


HSQC
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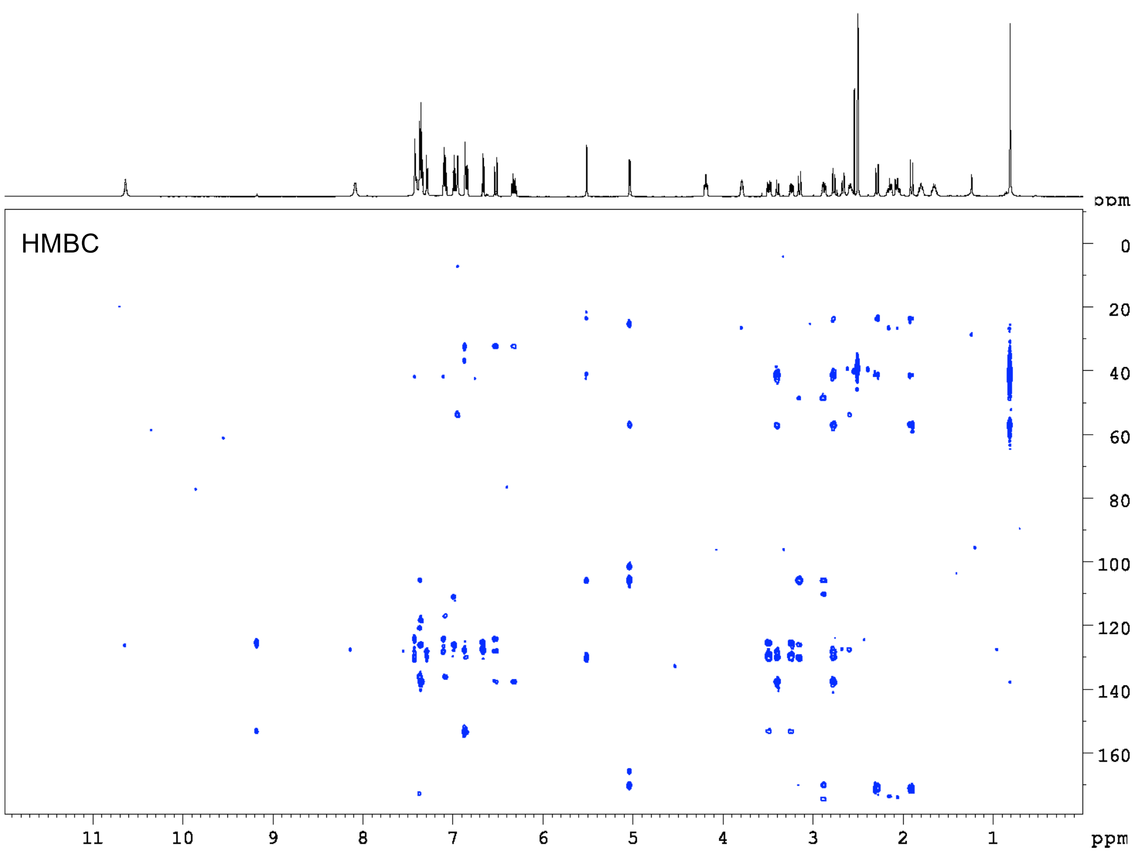
ppm


HMBC
ppm
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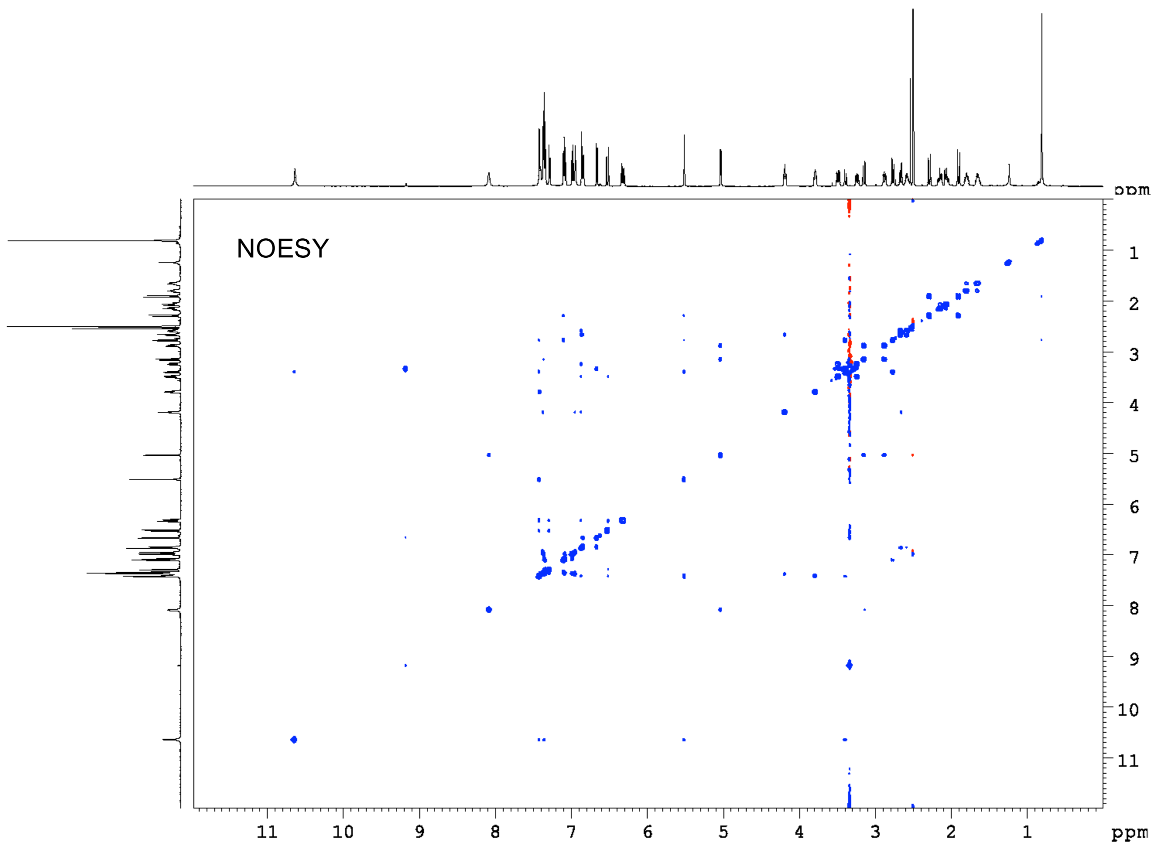
3
2
1
ppm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ppm
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6
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10
9
8
7
6
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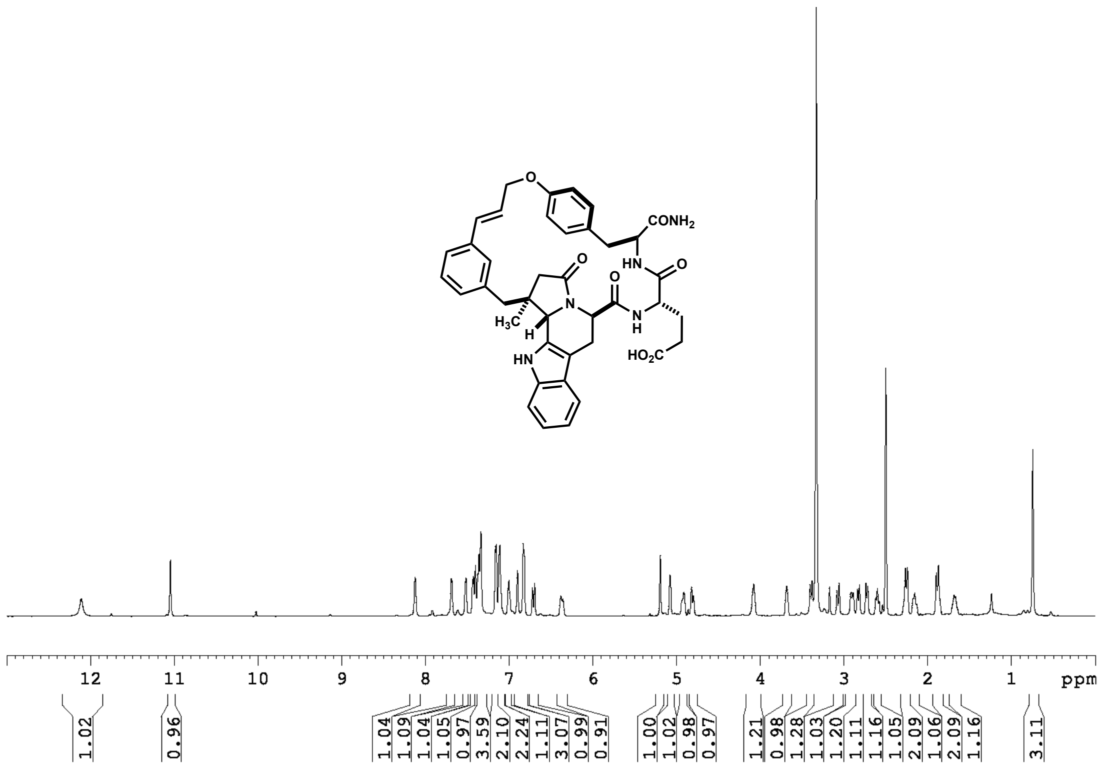
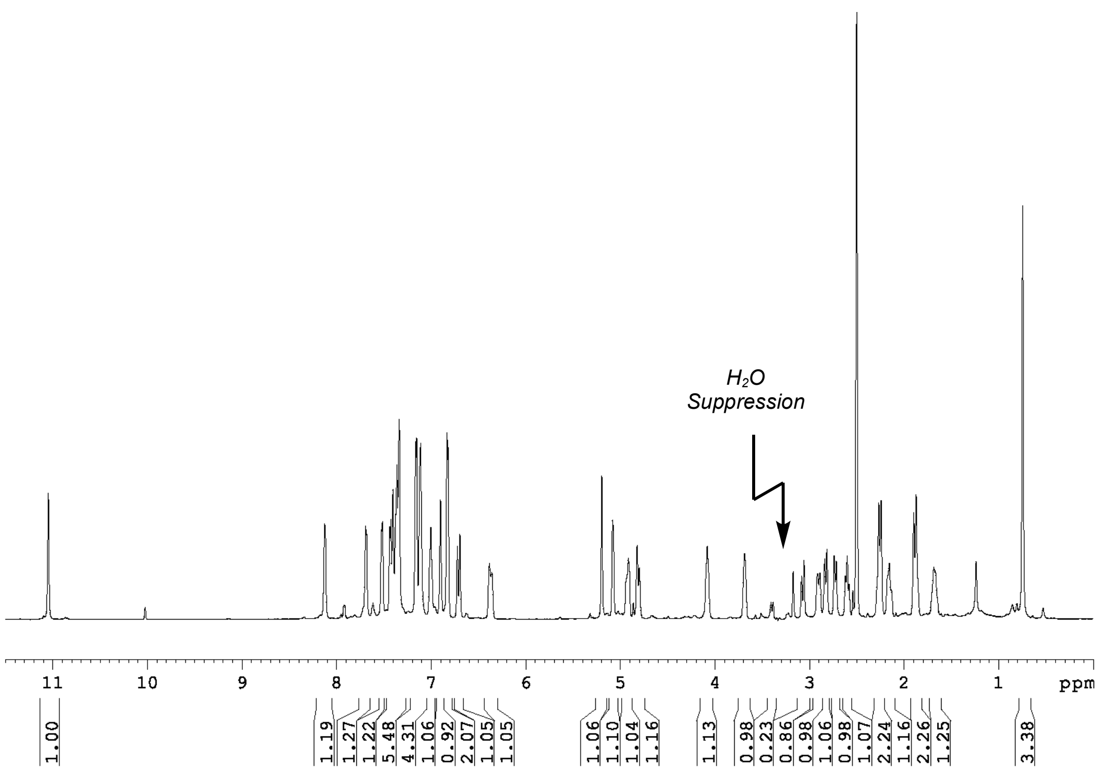
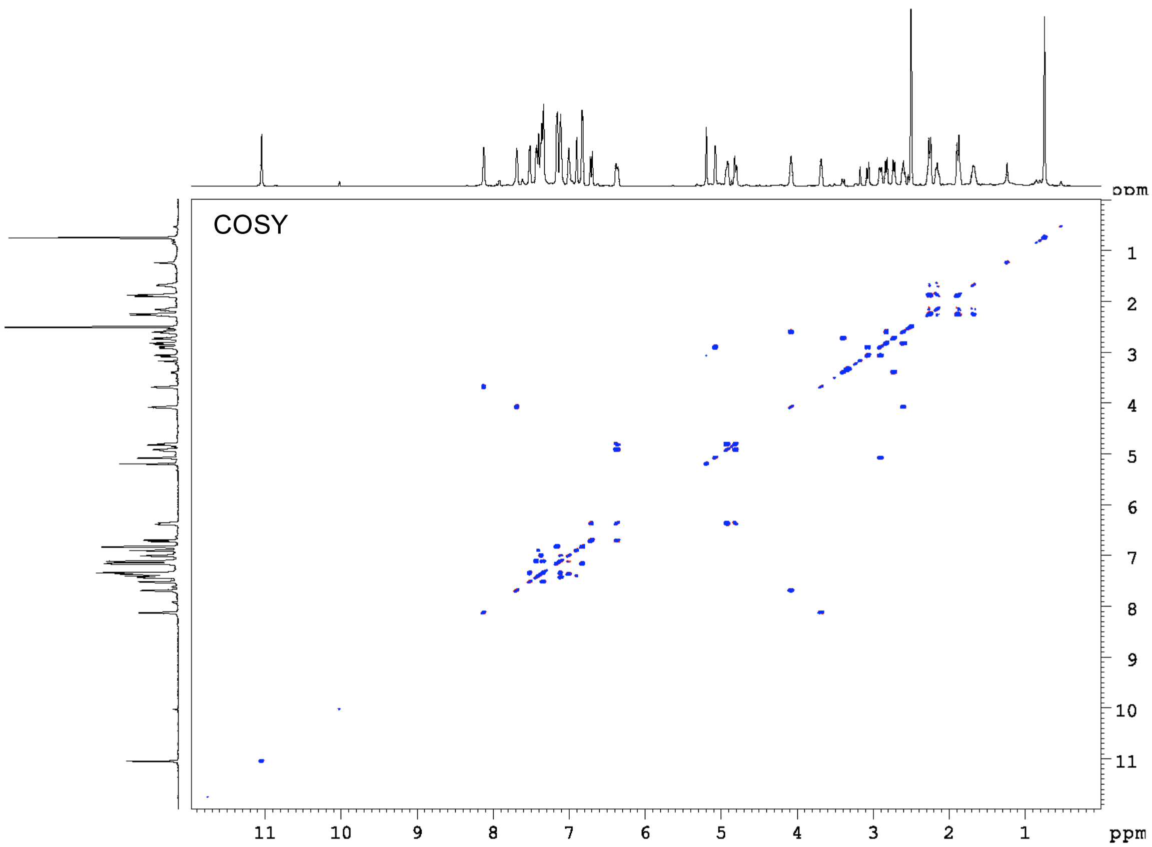
4
3
2
1
ppm

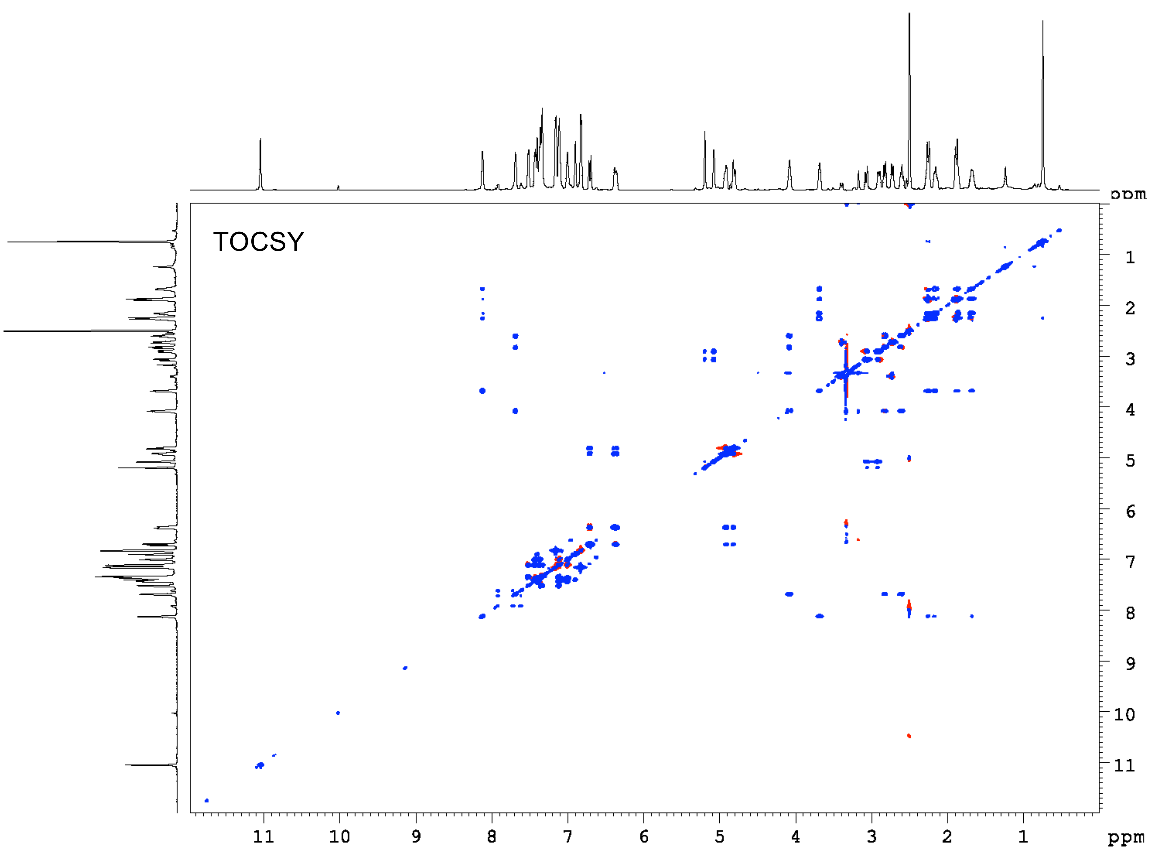
Macrocycle **3.45**



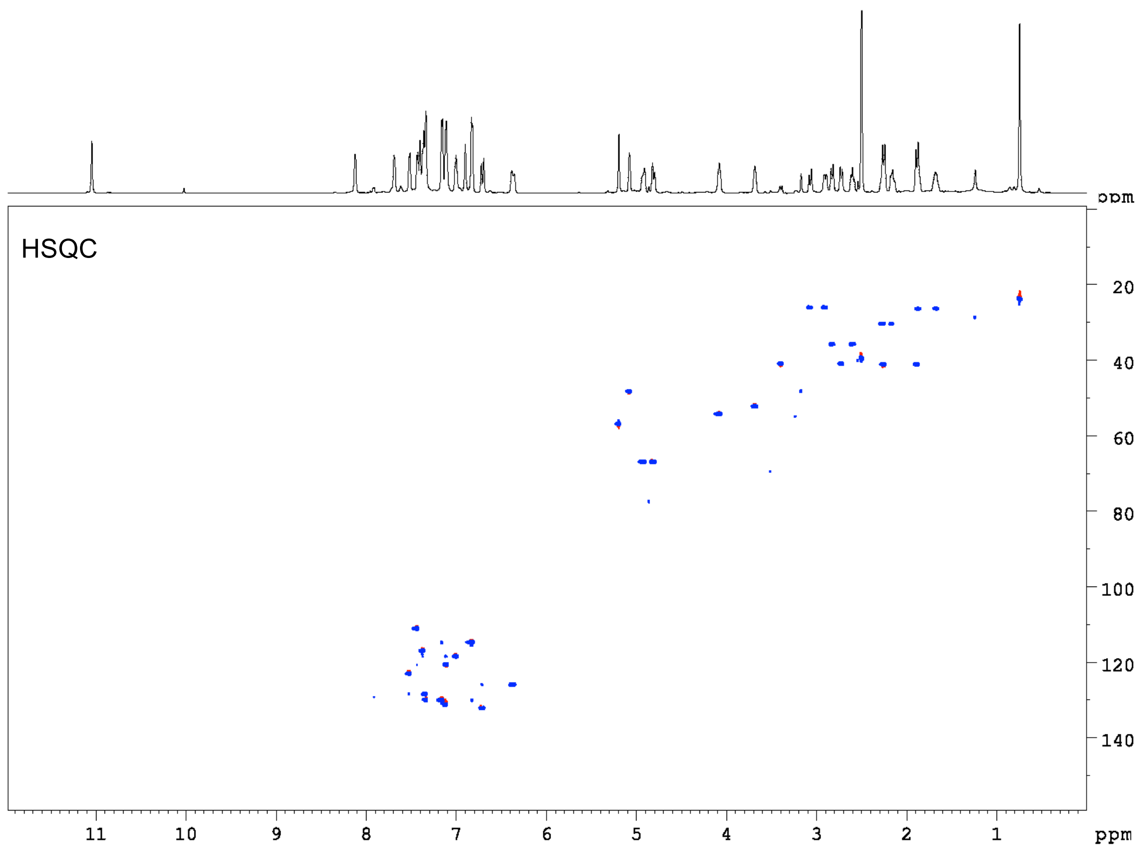




COSY
ppm



TOCSY
ppm



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140
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9
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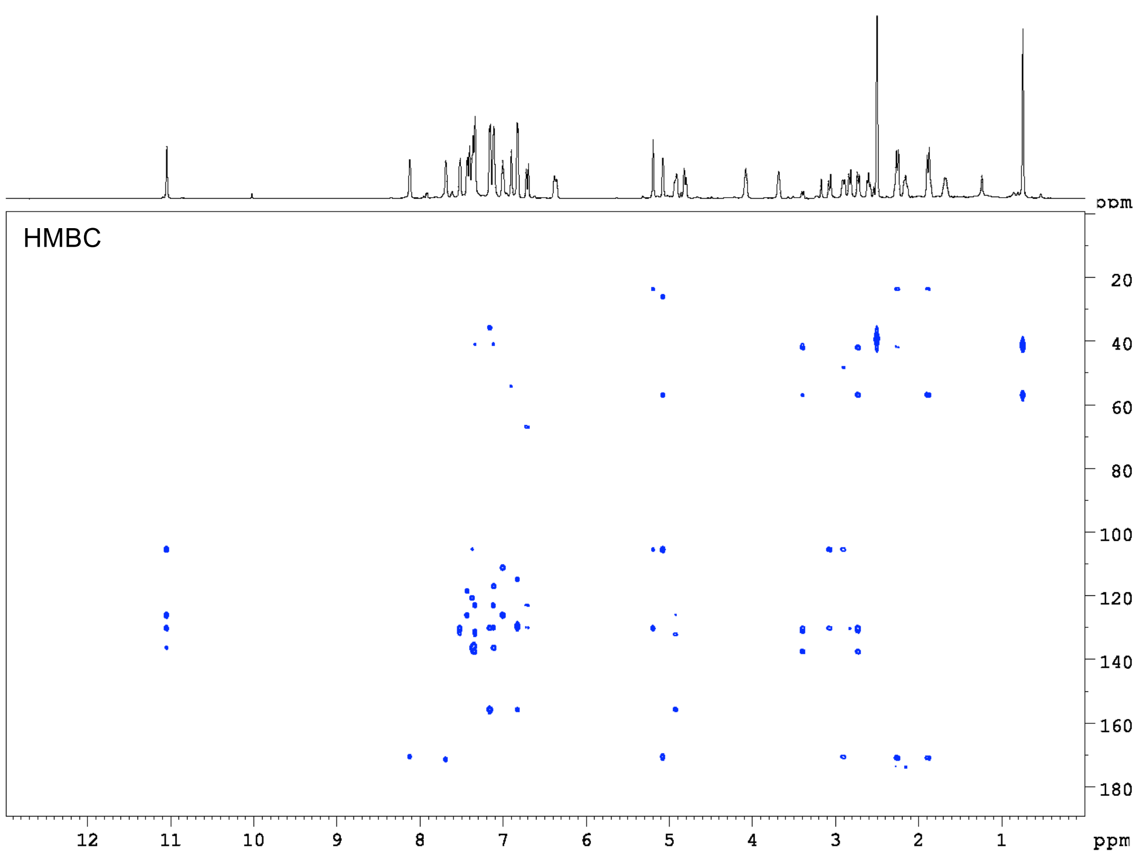
6
5
4
3
2
1
ppm



HMBC
ppm
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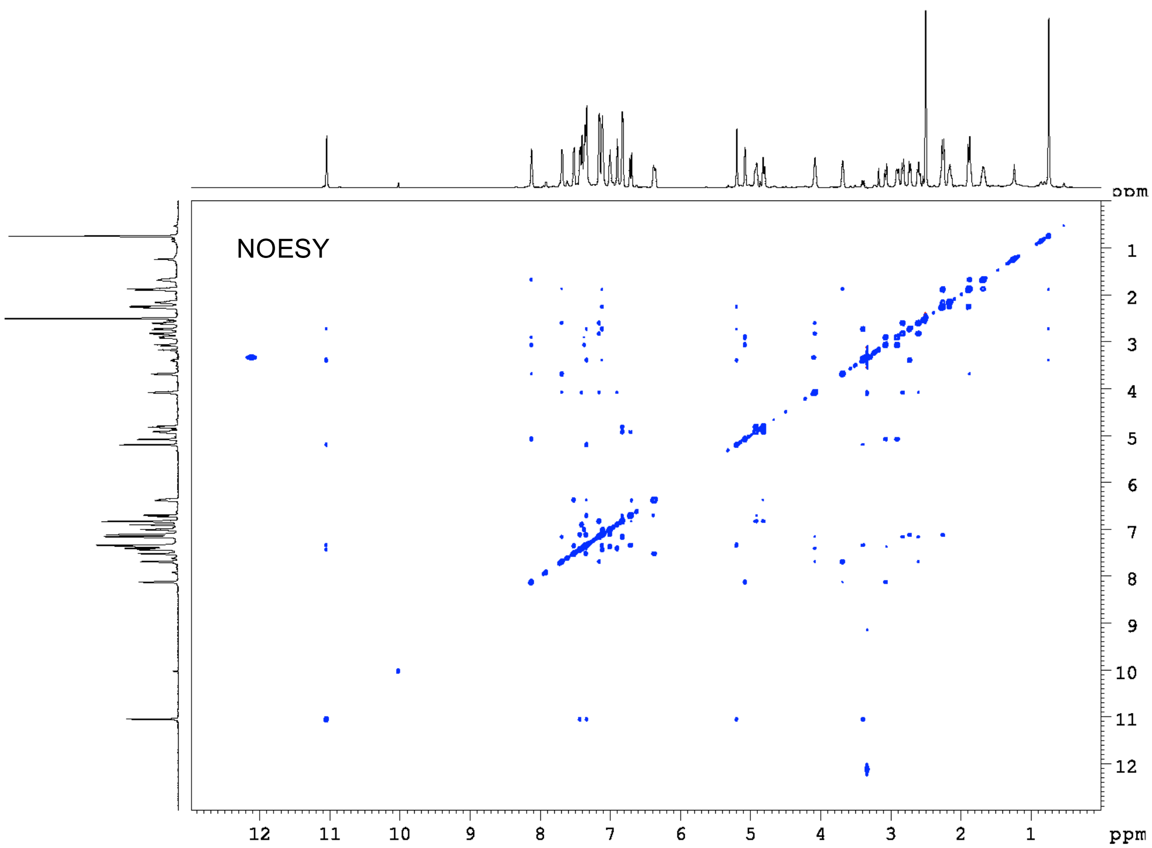
3
2
1
ppm



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ppm
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9
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7
6
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4
3
2
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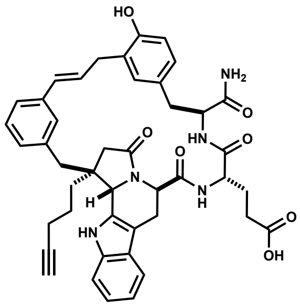
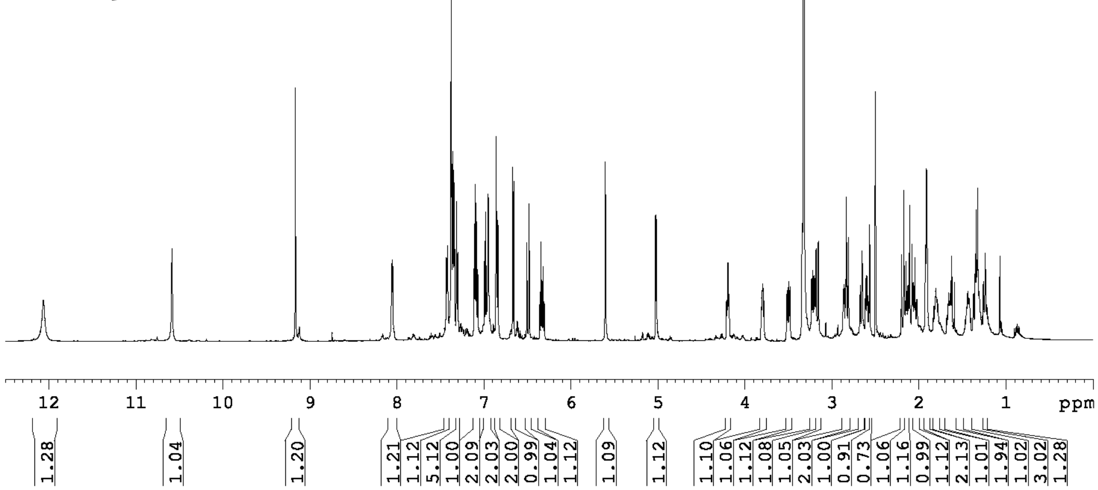
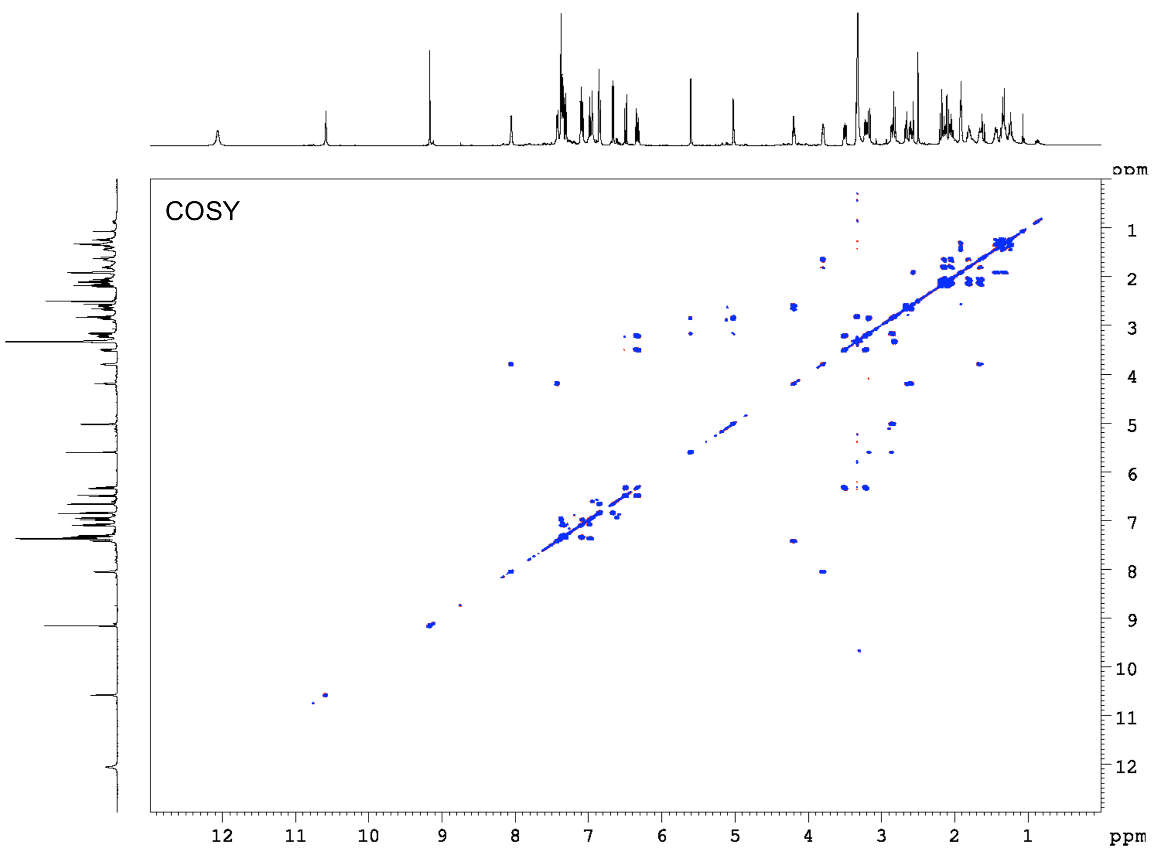
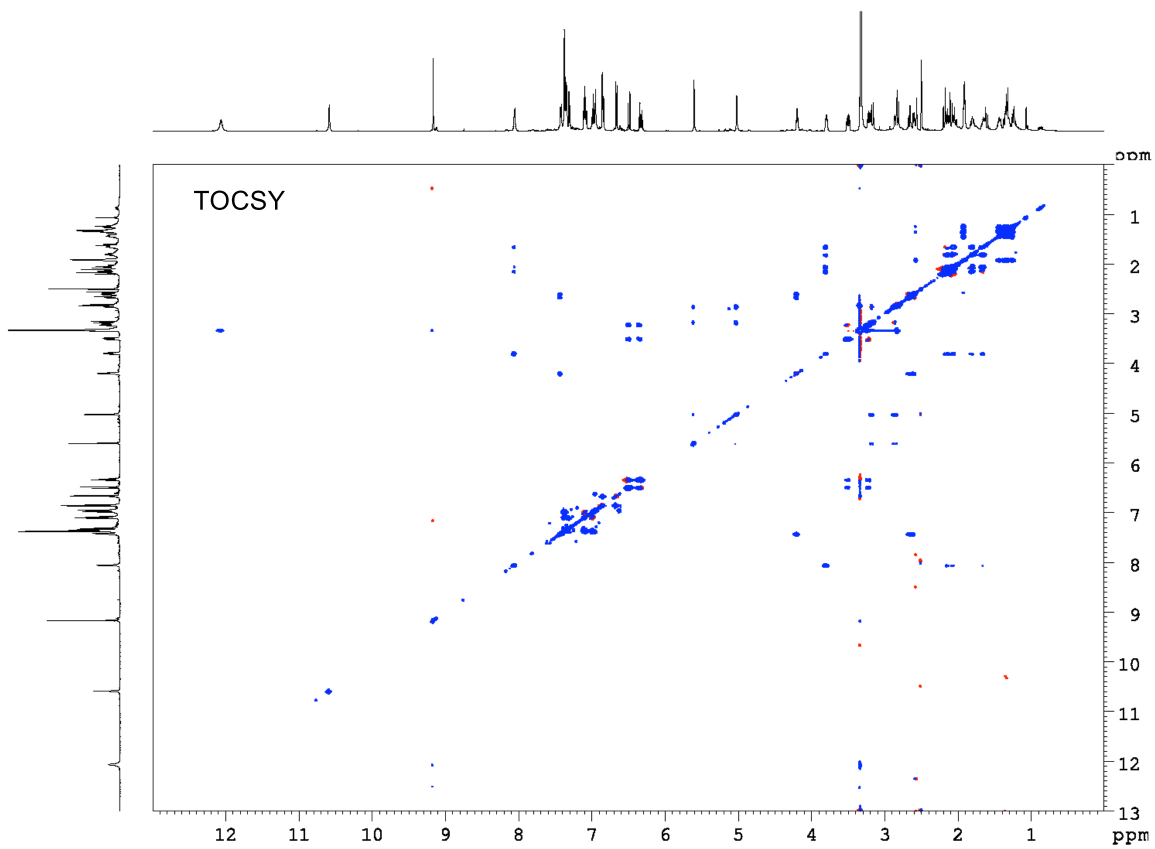
ppm

Macrocycle **3.46**








TOCSY
ppm
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3
4
5
6
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11
10
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7
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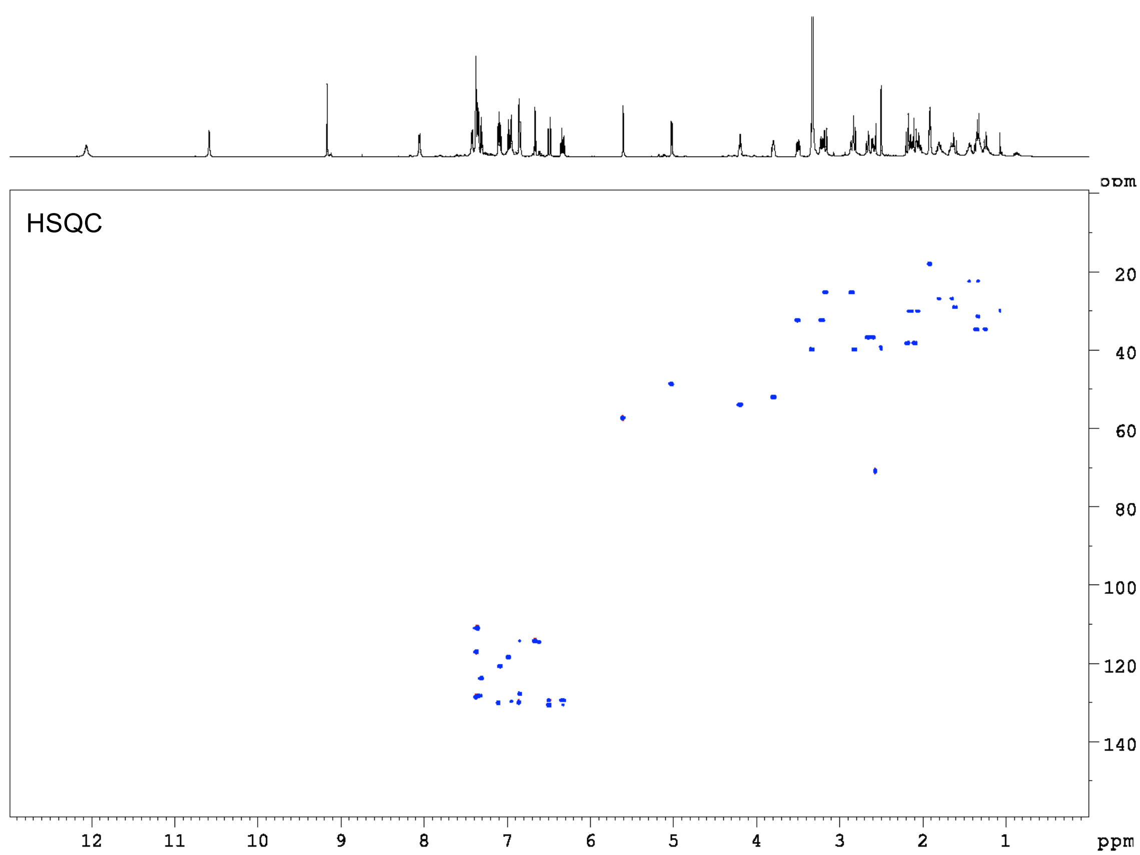
4
3
2
1
ppm


HSQC
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100
120
140
12
11
10
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8
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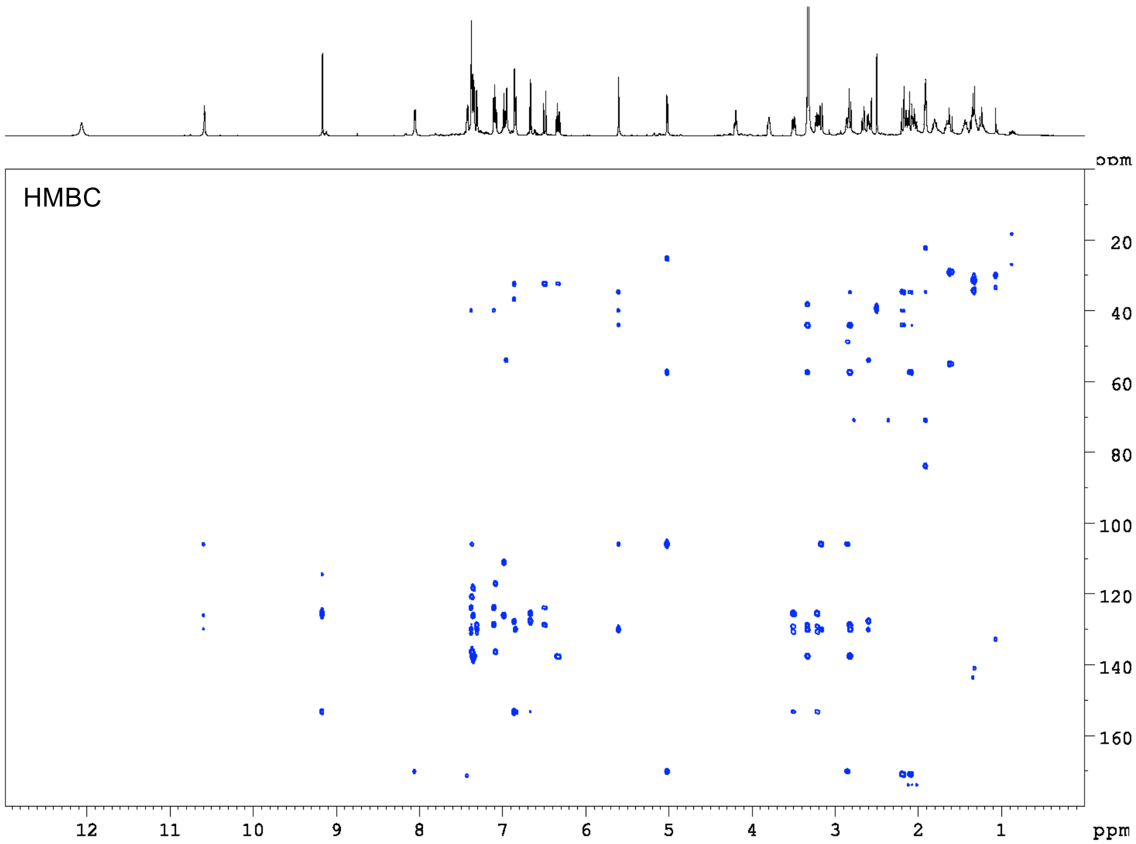
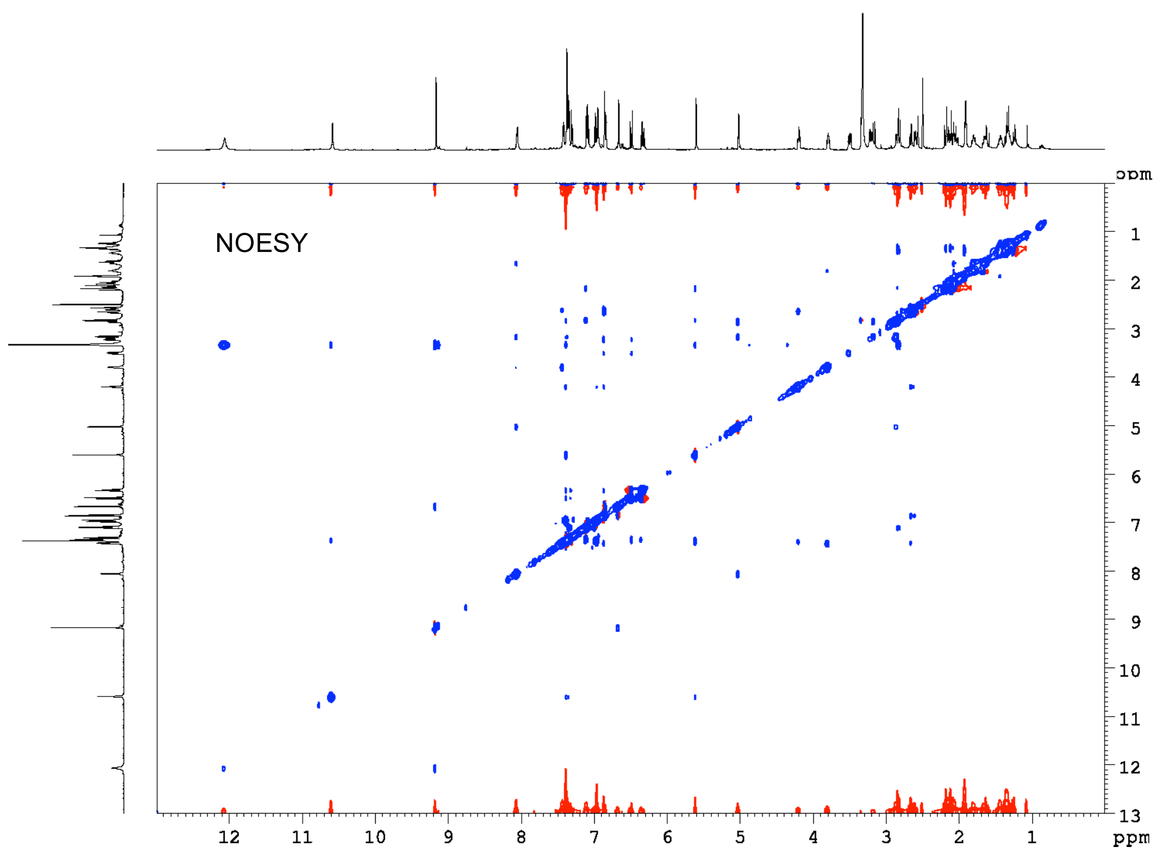
4
3
2
1
ppm


HMBC
ppm
ppm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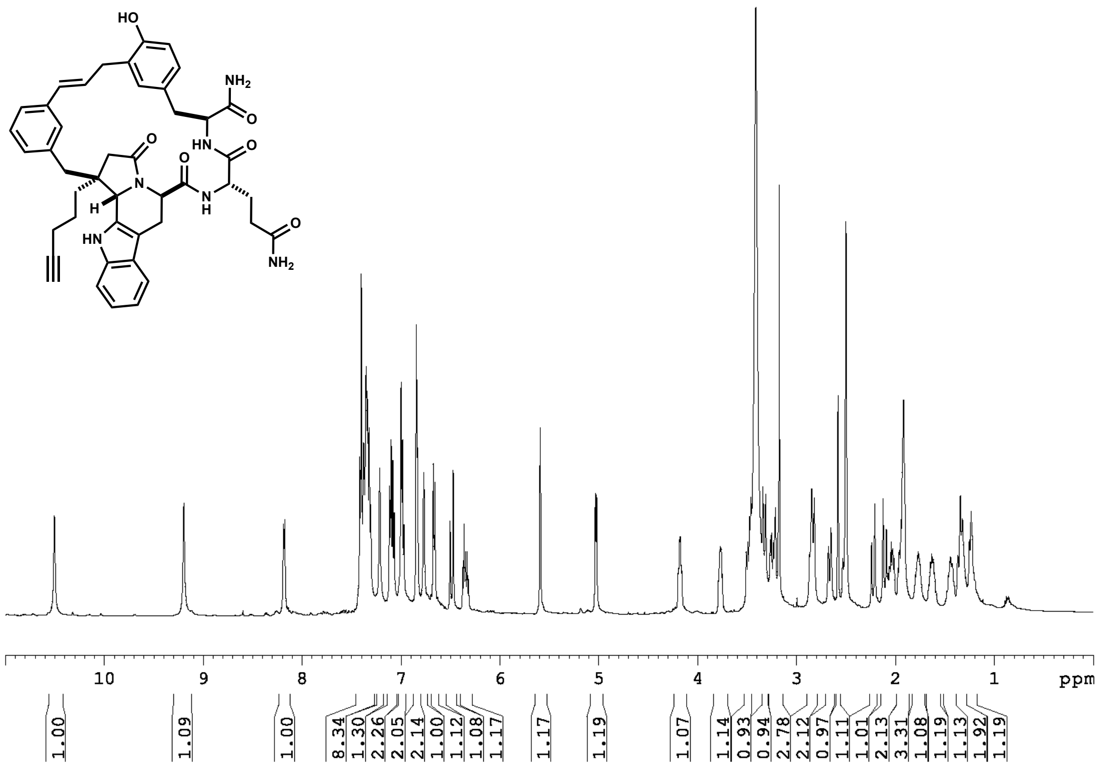
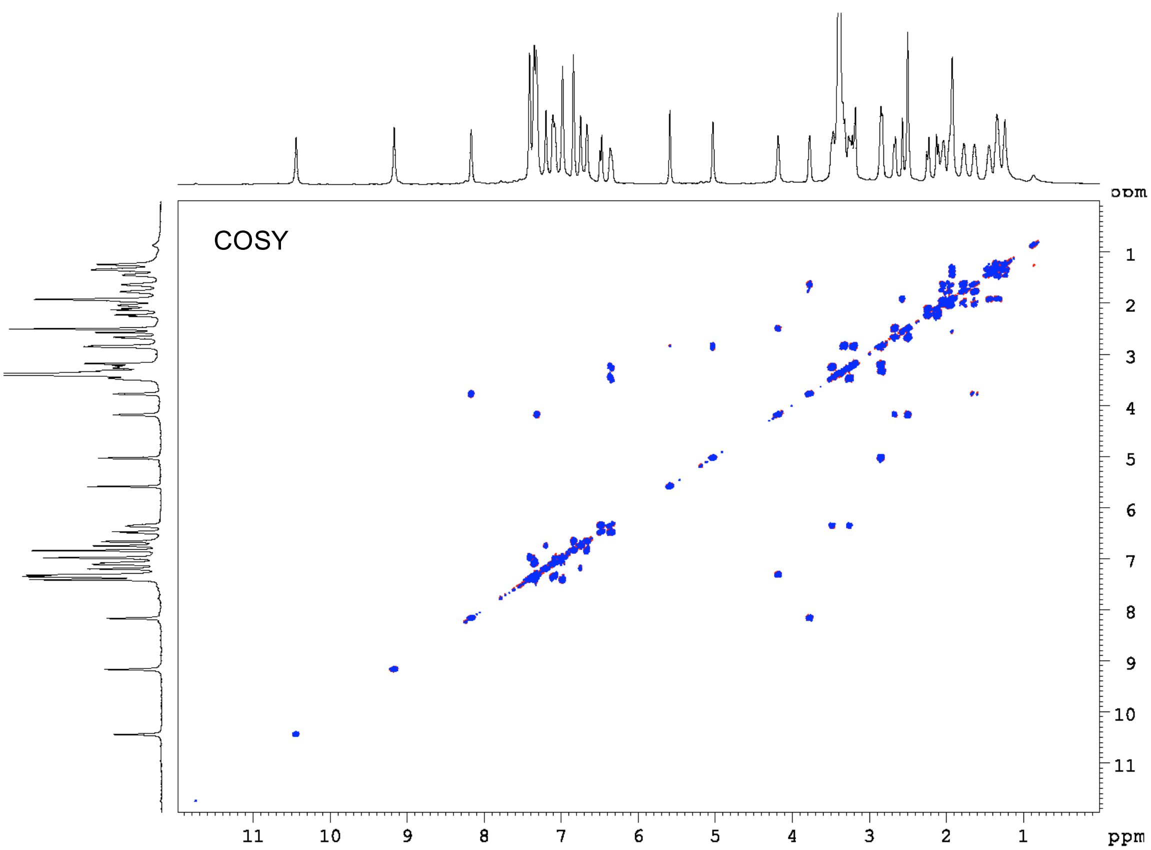
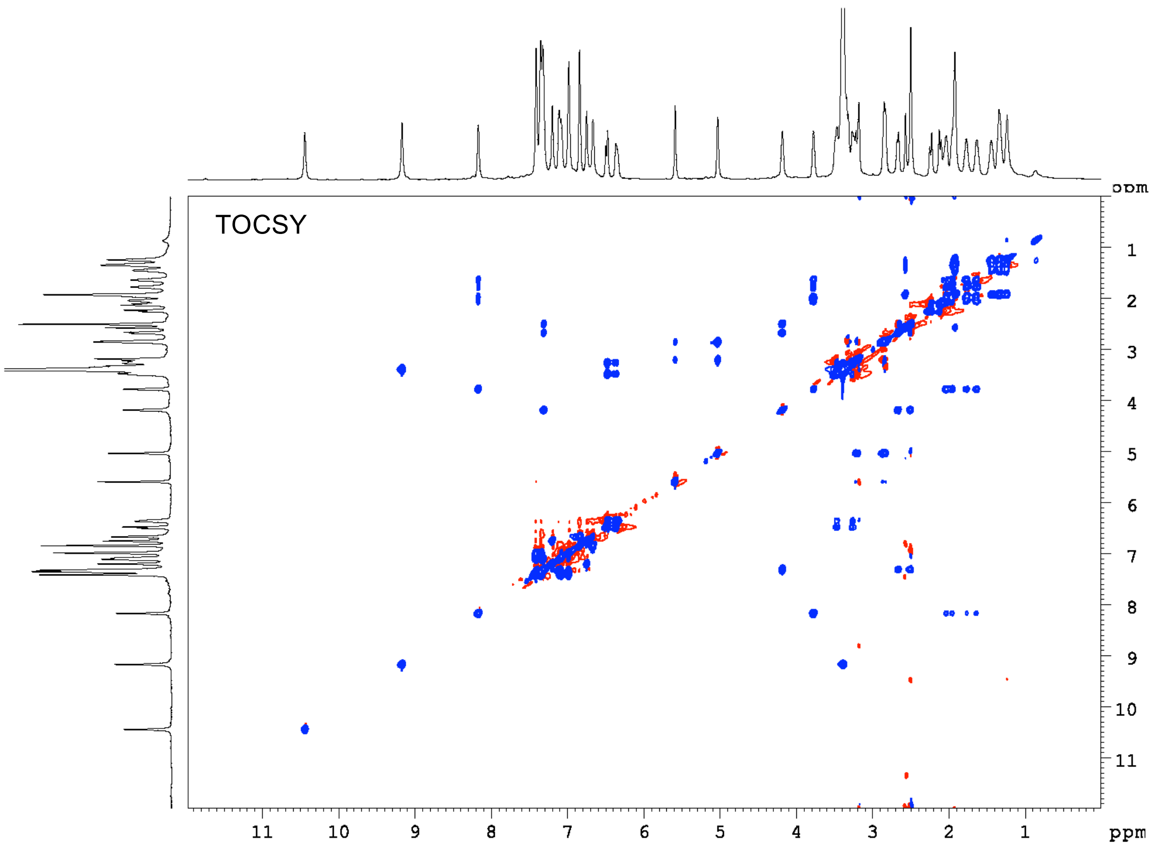
ppm
ppm

Macrocycle **3.47**






TOCSY
ppm
11
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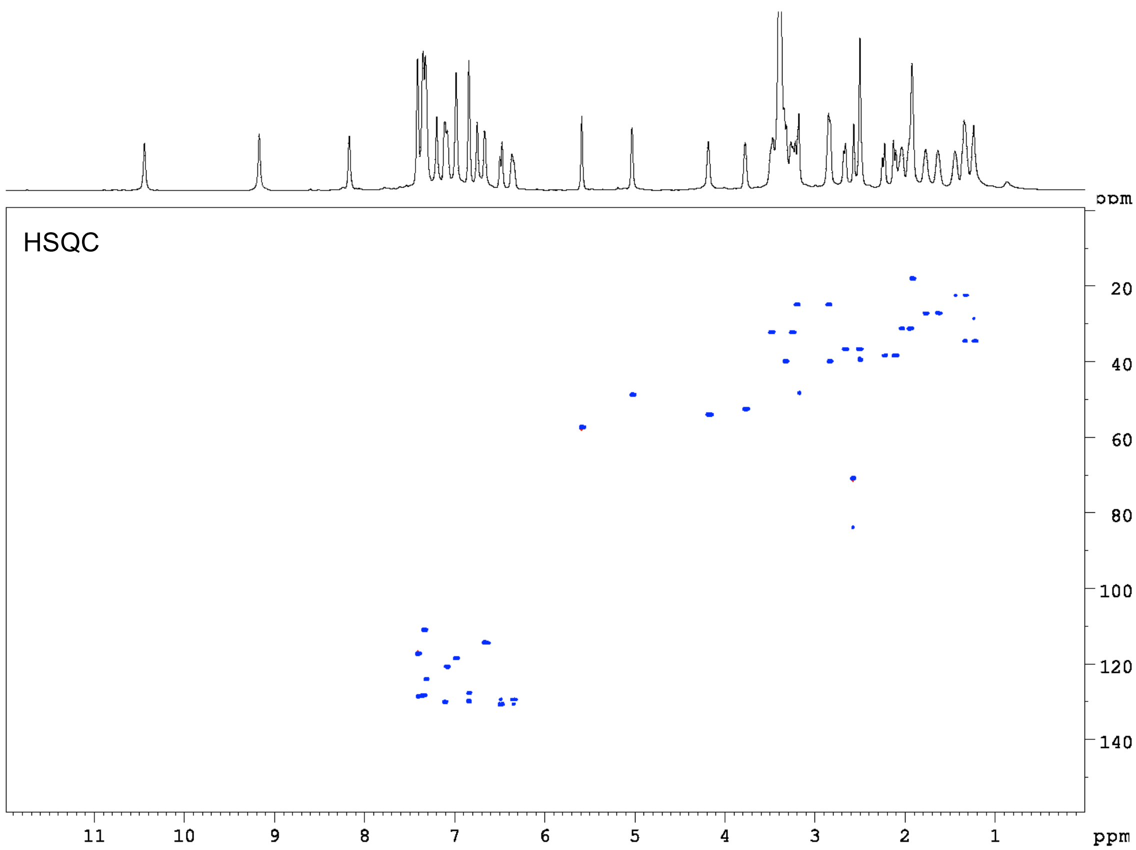
8
7
6
5
4
3
2
1


HSQC
ppm
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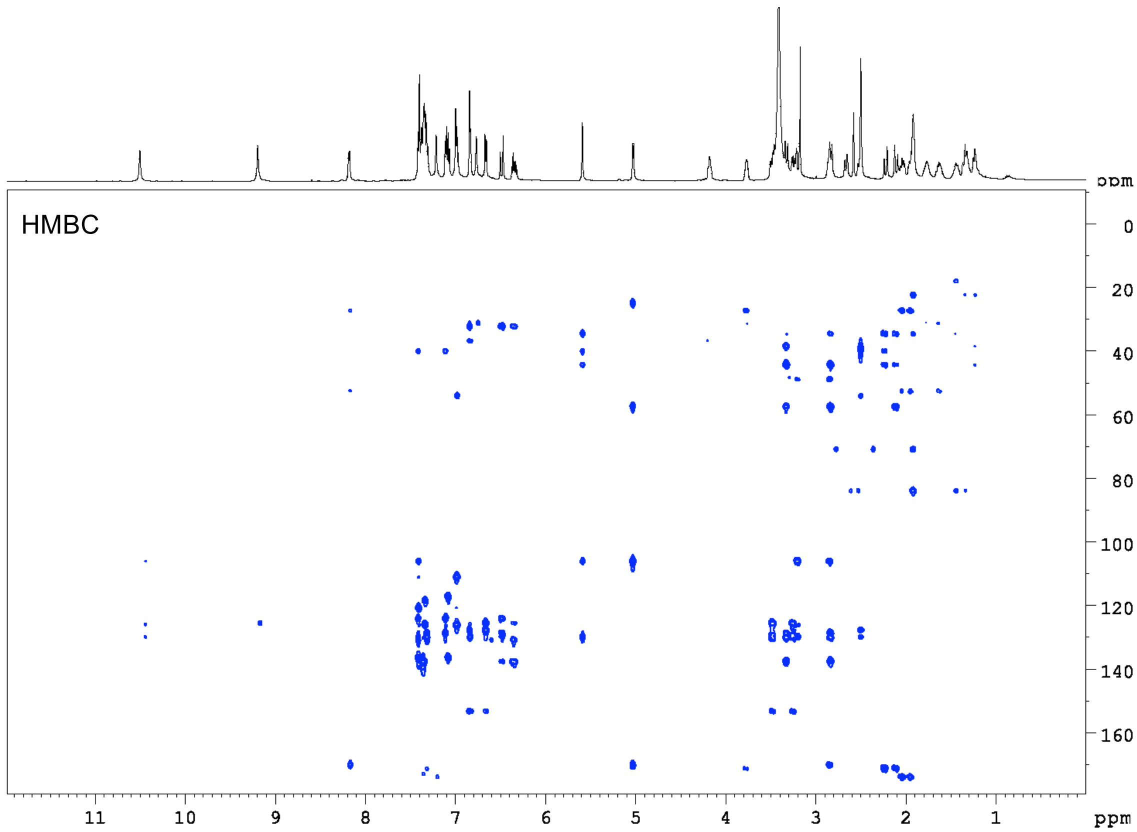
4
3
2
1


HMBC
ppm
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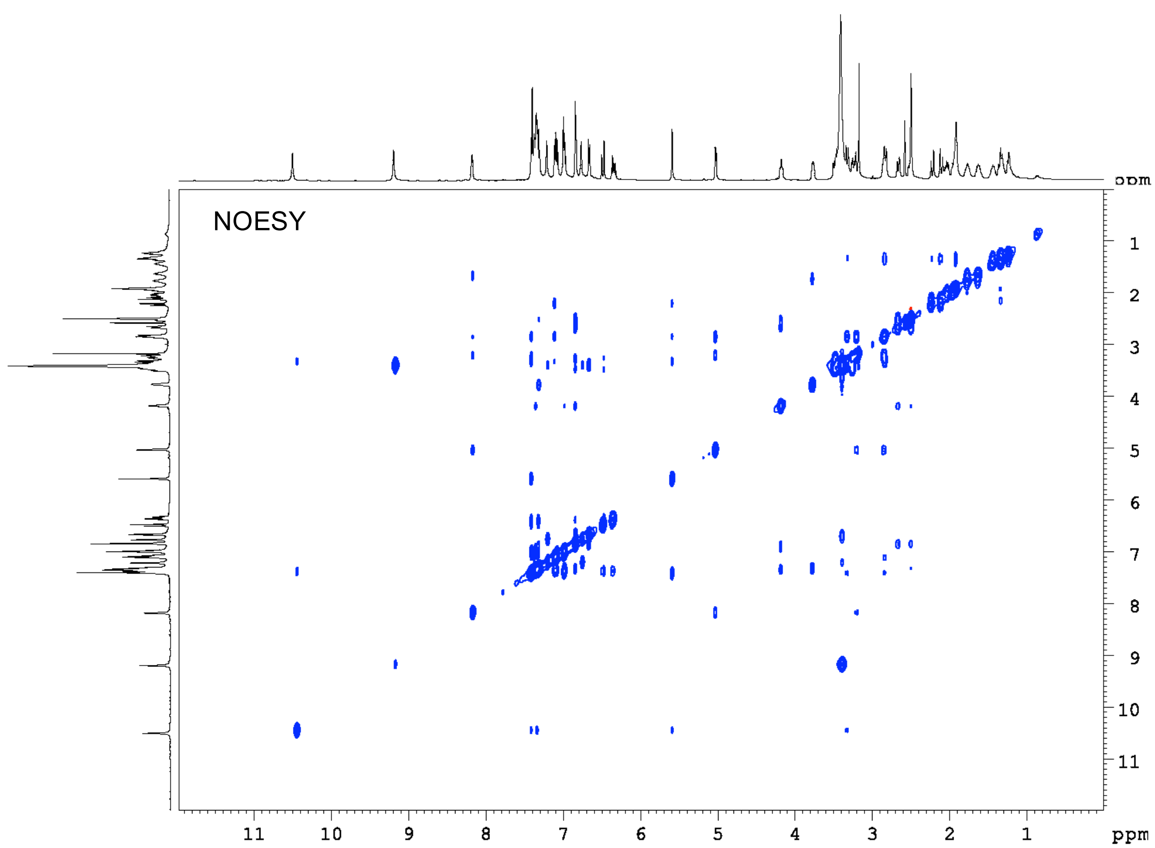
4
3
2
1
ppm


NOESY
ppm
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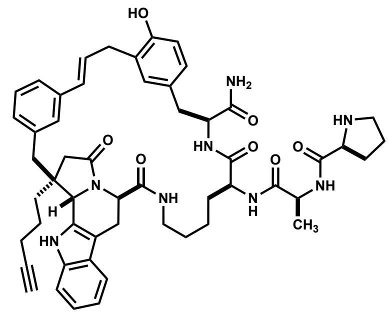
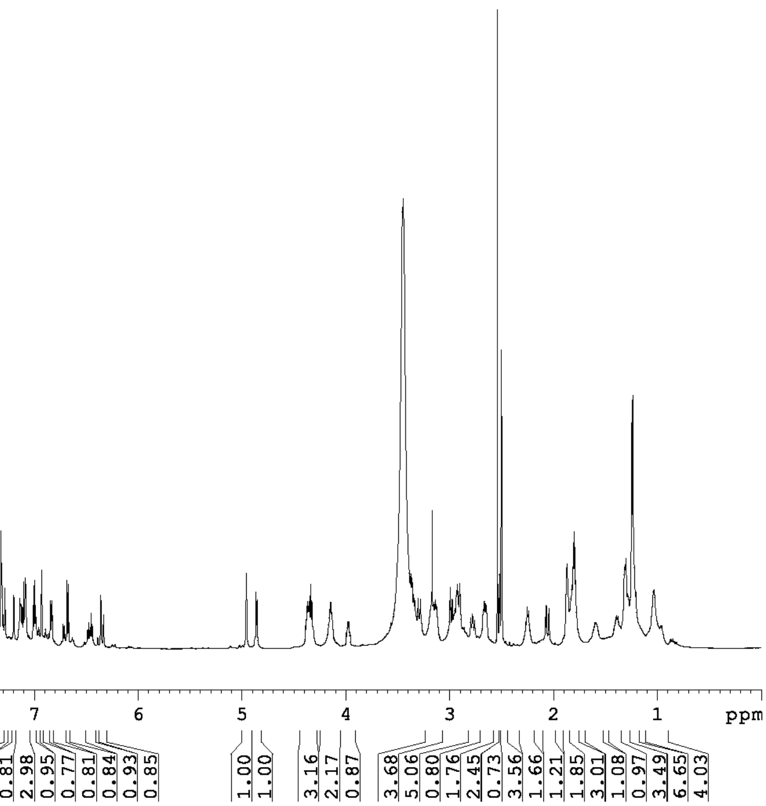
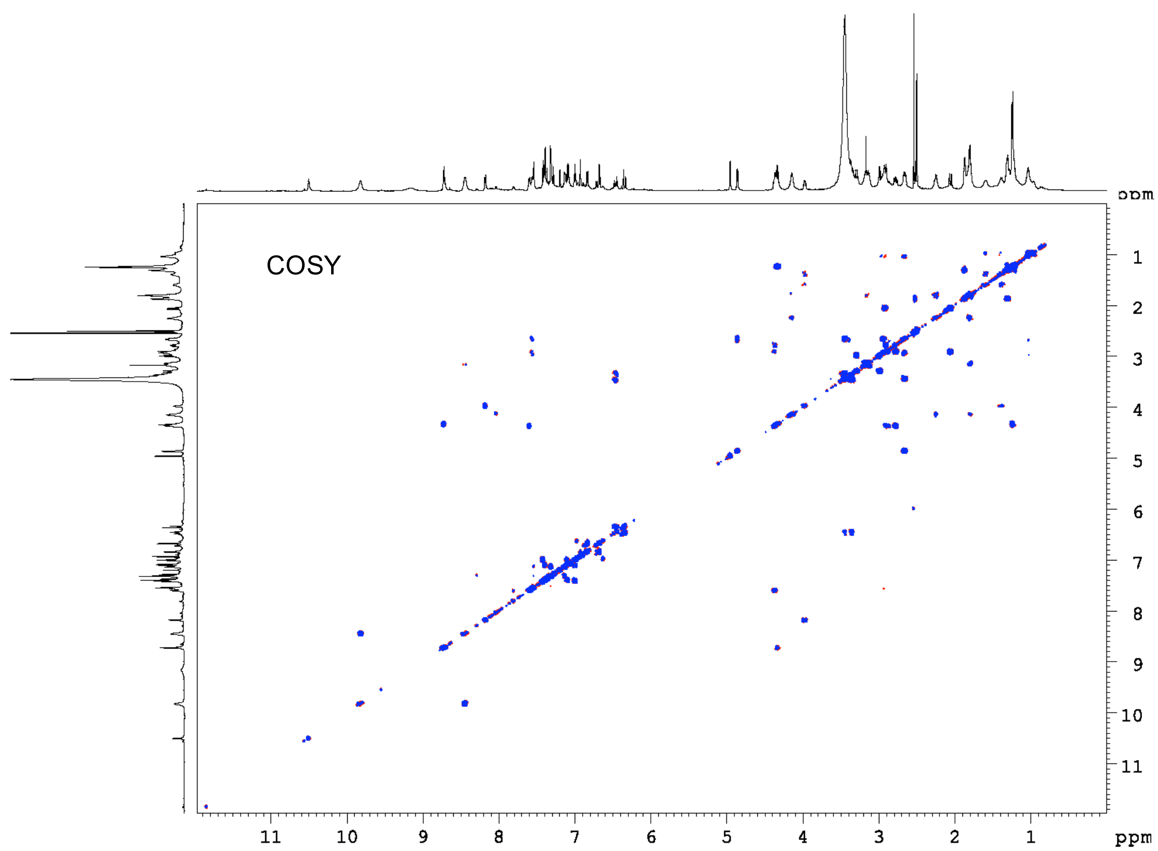
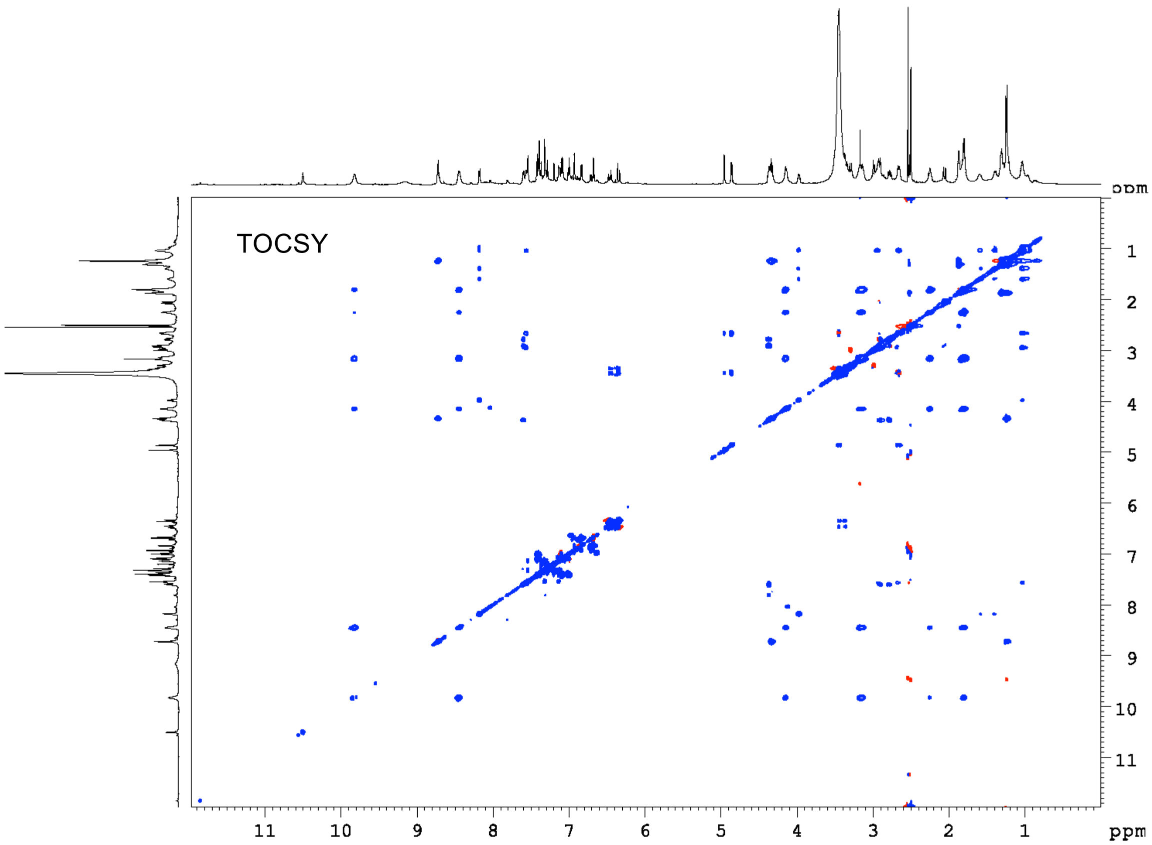
10
9
8
7
6
5
4
3
2
1
ppm

Macrocycle **3.48**








TOCSY
ppm
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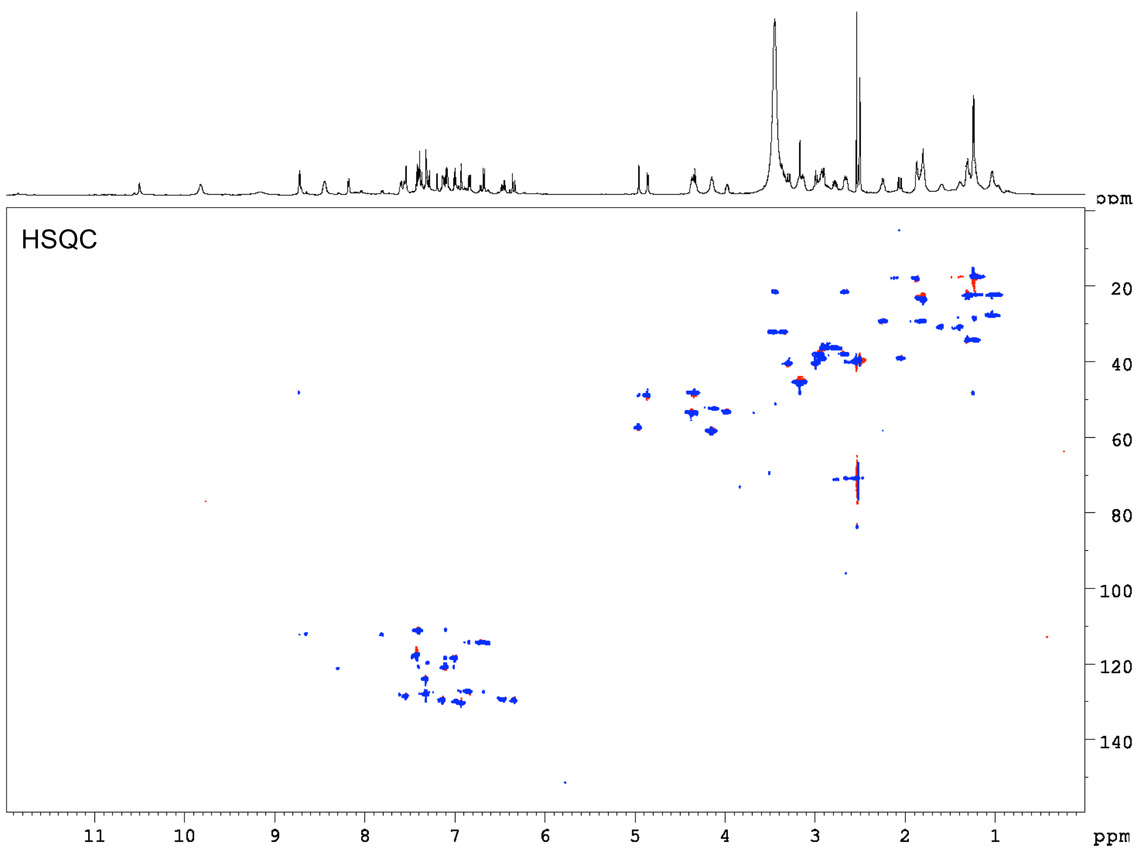
9
8
7
6
5
4
3
2
1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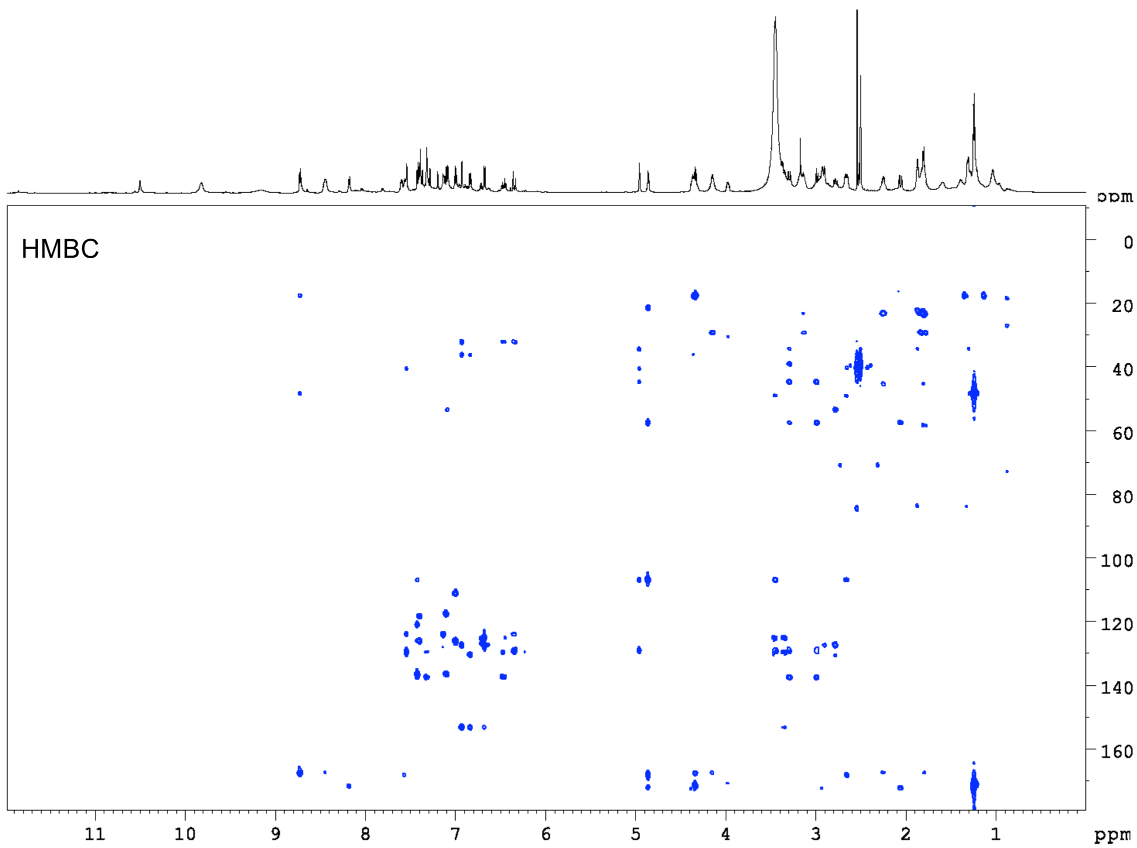
HMBC
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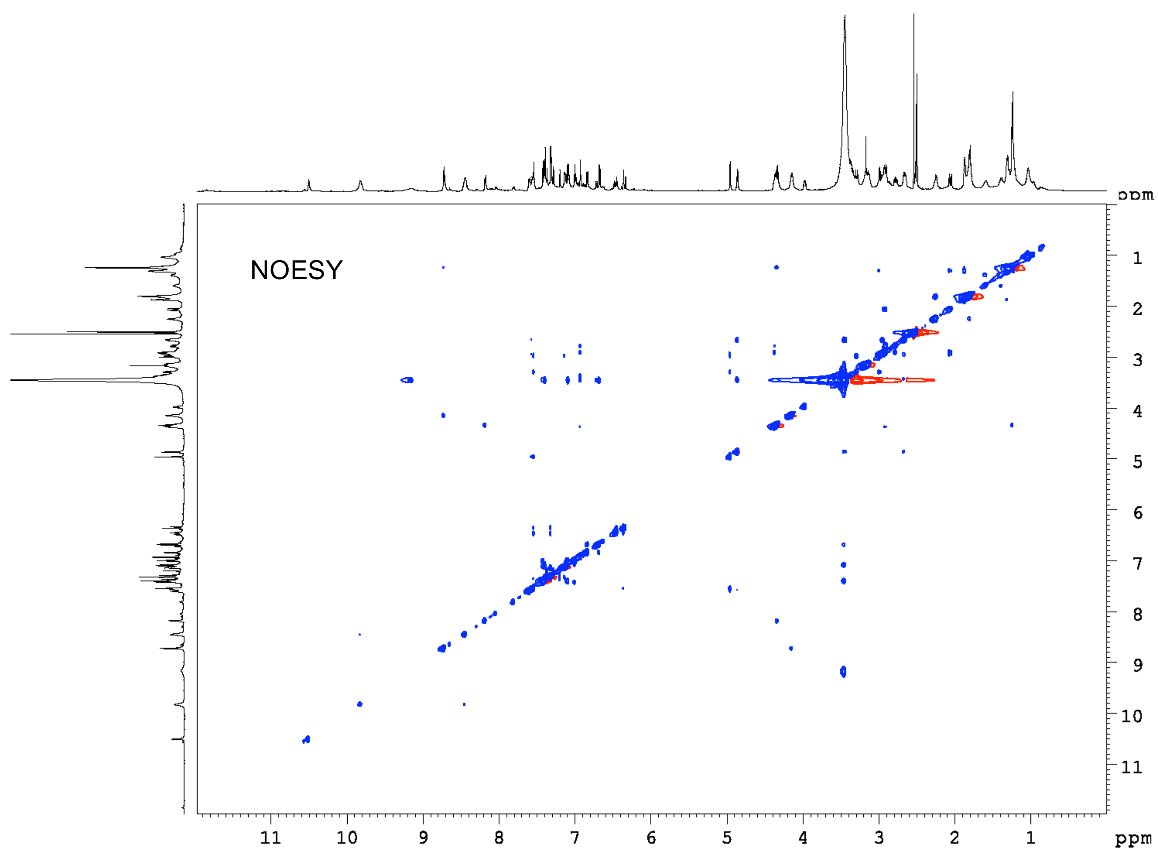
ppm


NOESY
ppm
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9
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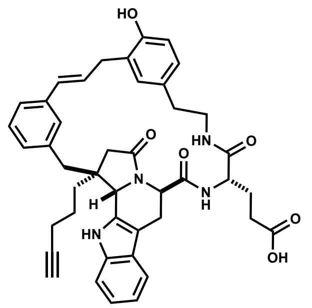
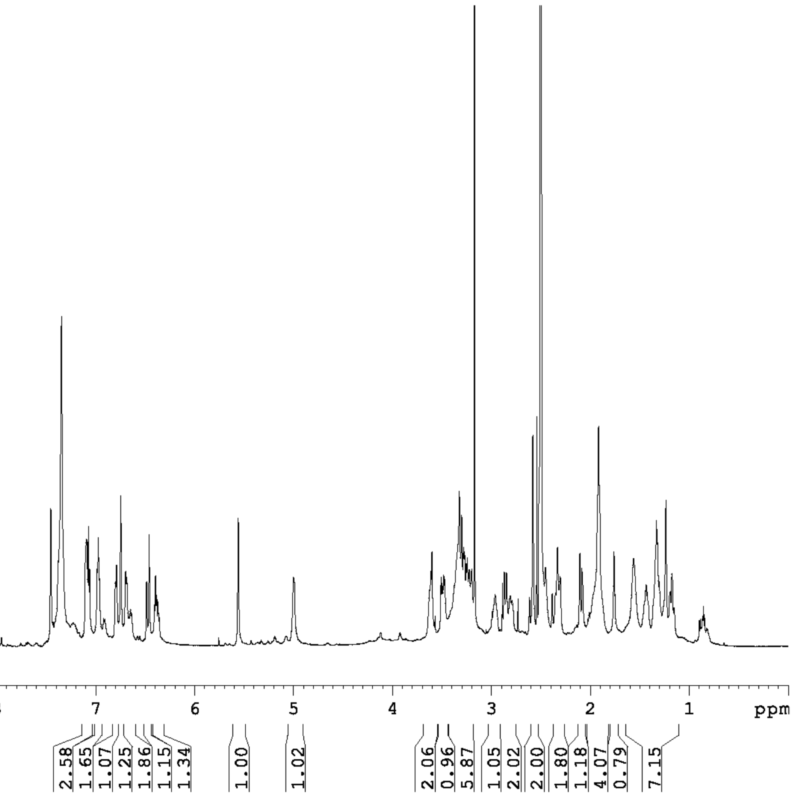
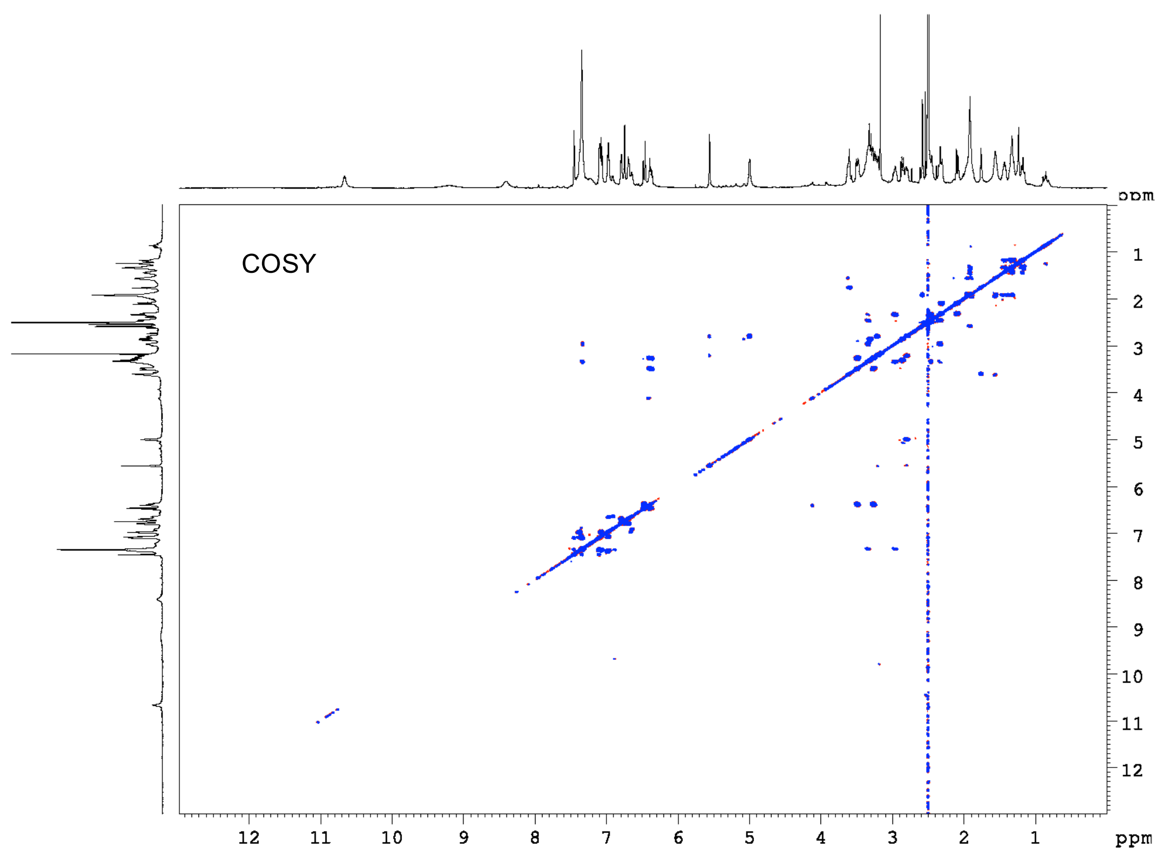
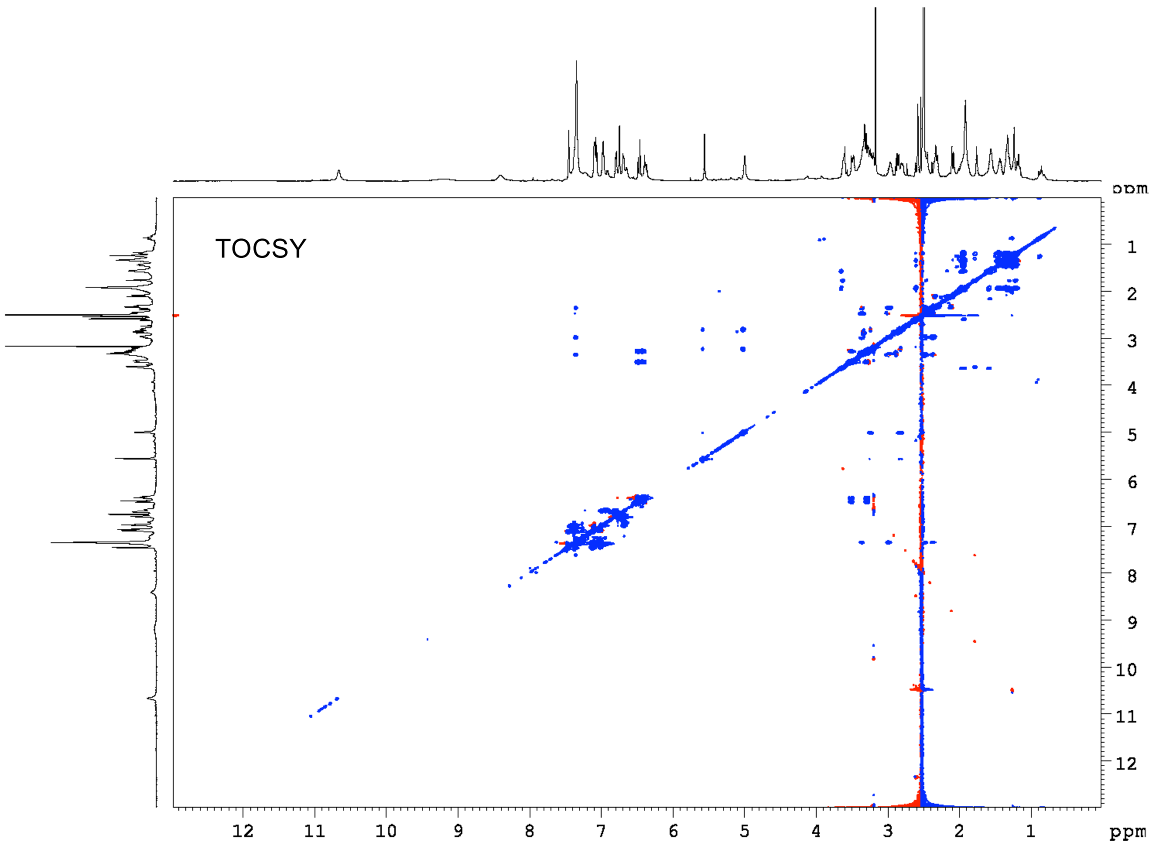
5
4
3
2
1
ppm

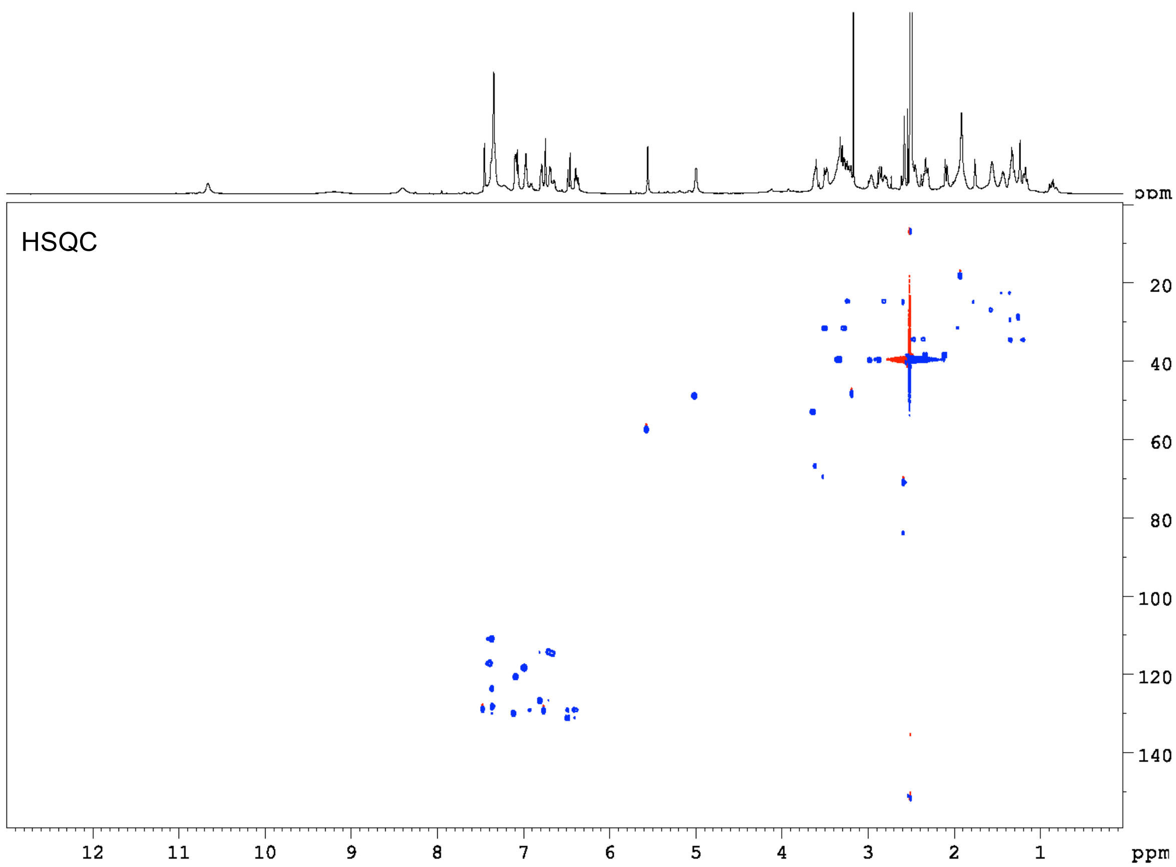
Macrocycle **3.49**

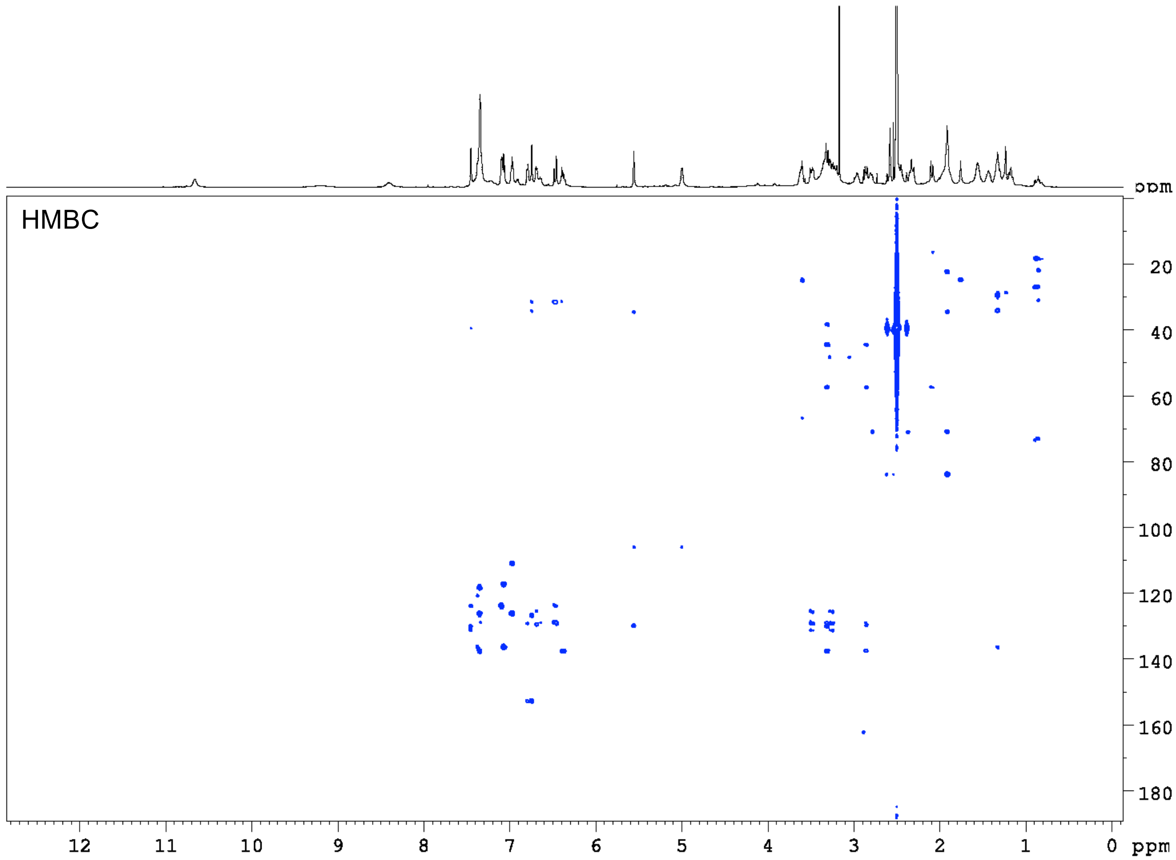







TOCSY
ppm


HSQC
ppm



HMBC
ppm
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100
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10
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6
5
4
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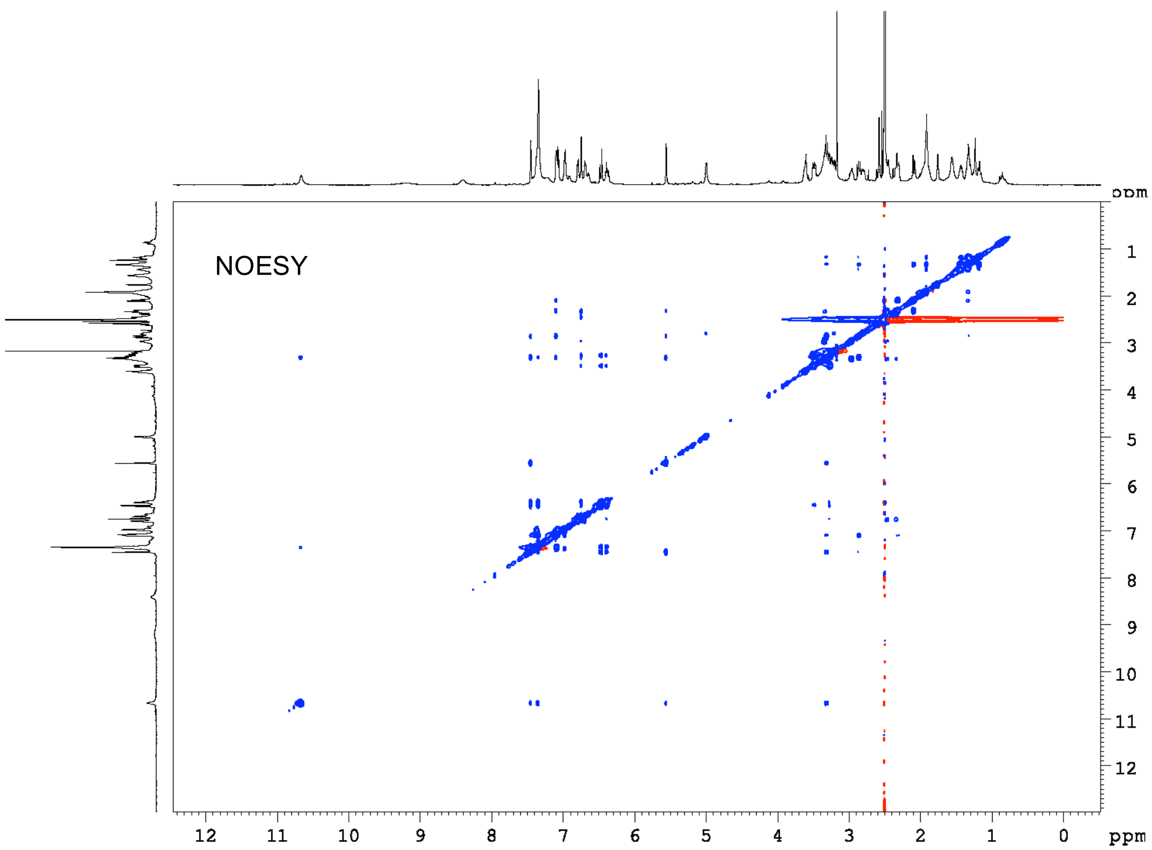
2
1
0
ppm



NOESY
ppm
1
2
3
4
5
6
7
8
9
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12
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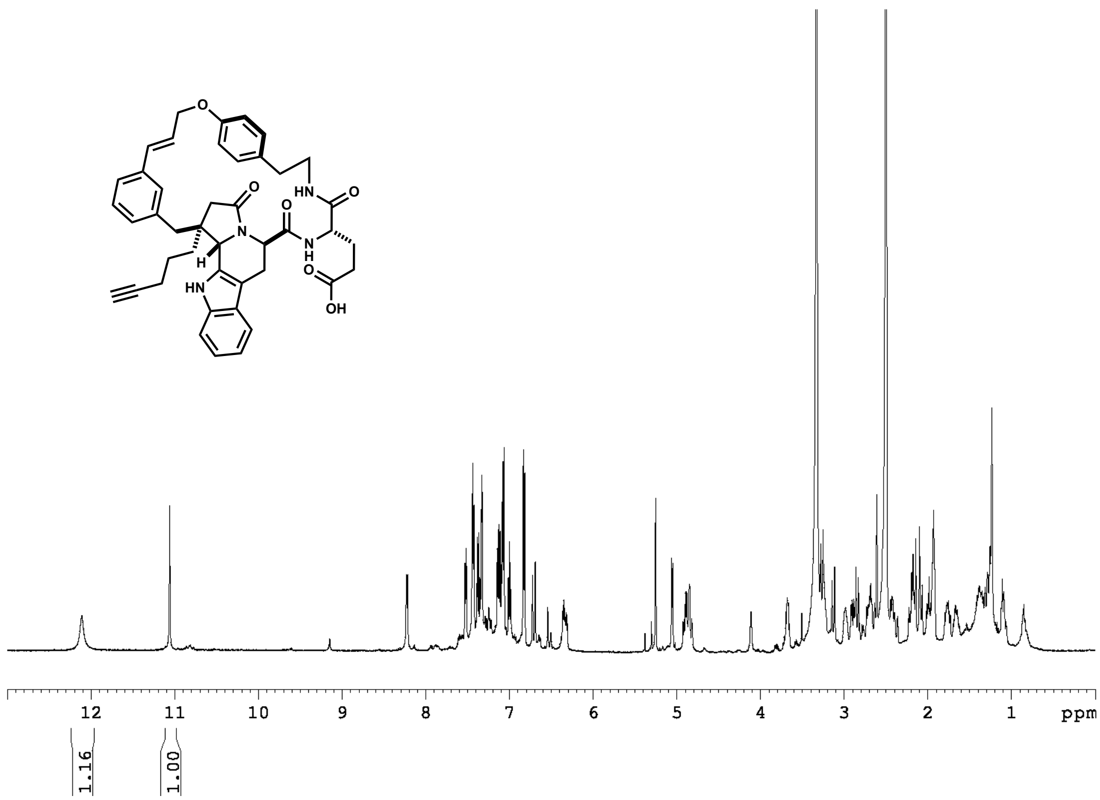
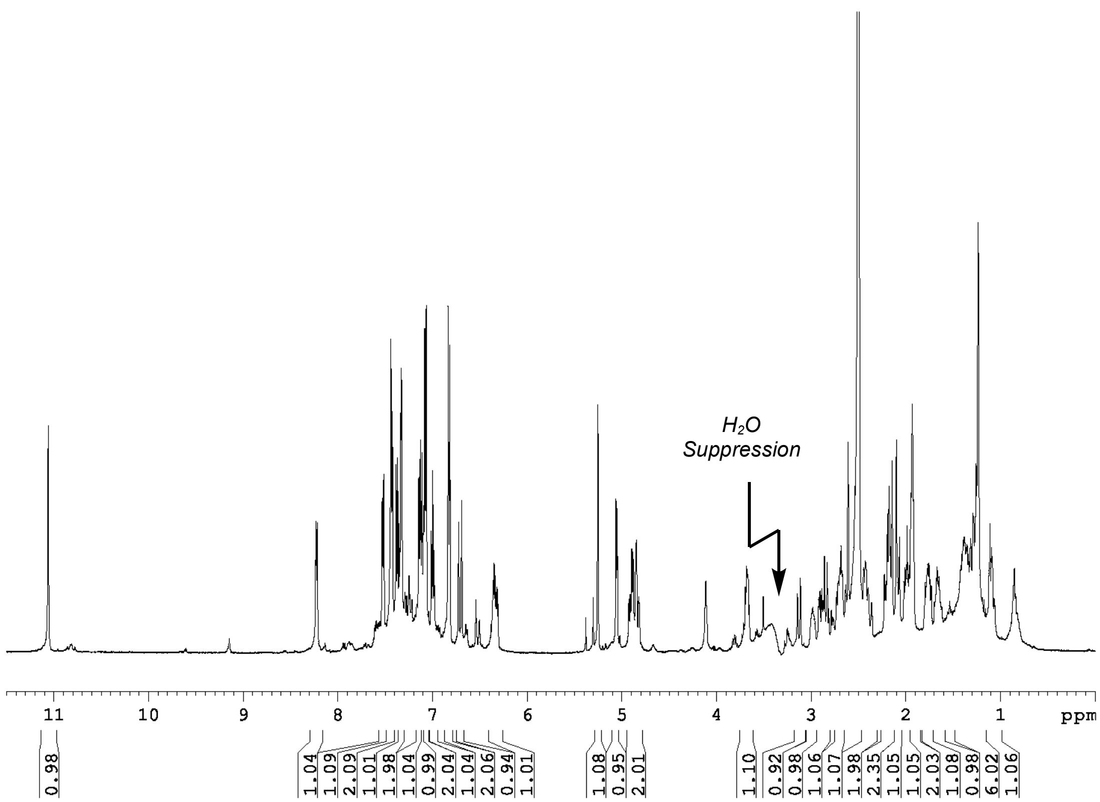
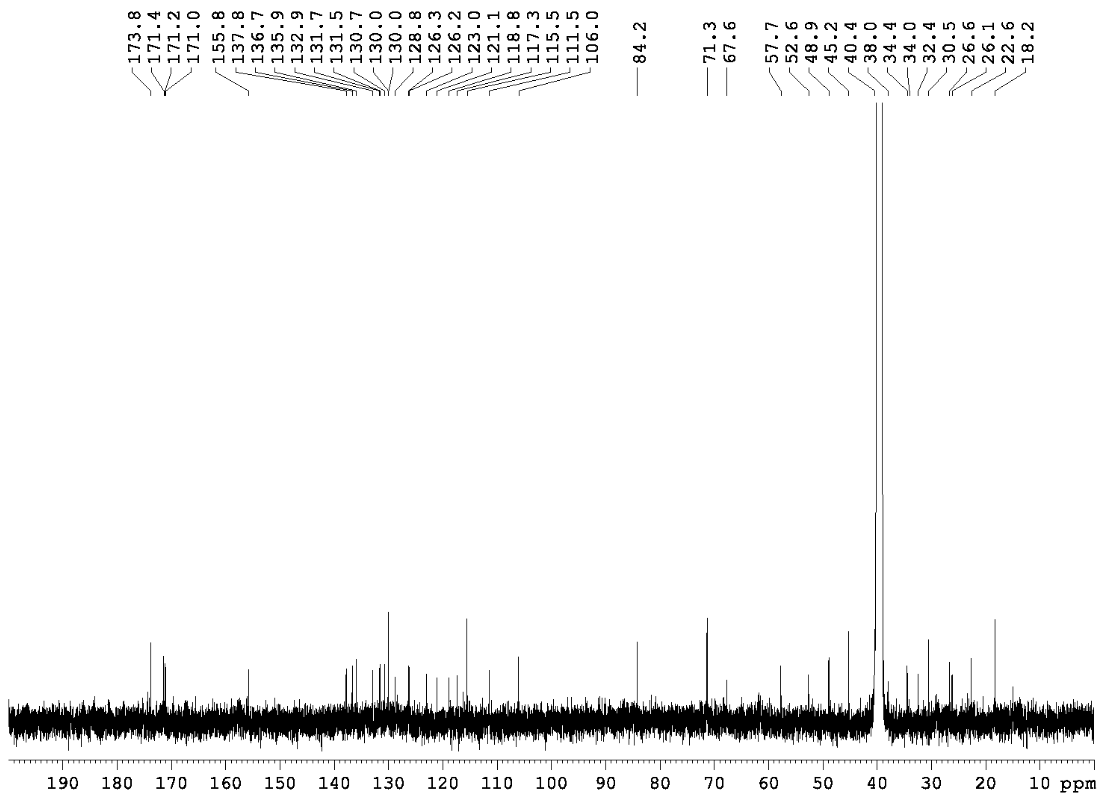
11
10
9
8
7
6
5
4
3
2
1
0
ppm

Macrocycle **3.50**






173.8
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171.2
171.0
155.8
137.8
136.7
135.9
132.9
131.7
131.5
130.7
130.0
130.0
128.8
126.3
126.2
123.0
121.1
118.8
117.3
115.5
111.5
106.0
84.2
71.3
67.6
57.7
52.6
48.9
45.2
40.4
38.0
34.4
34.0
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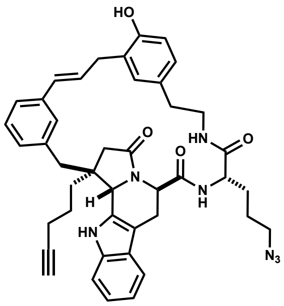
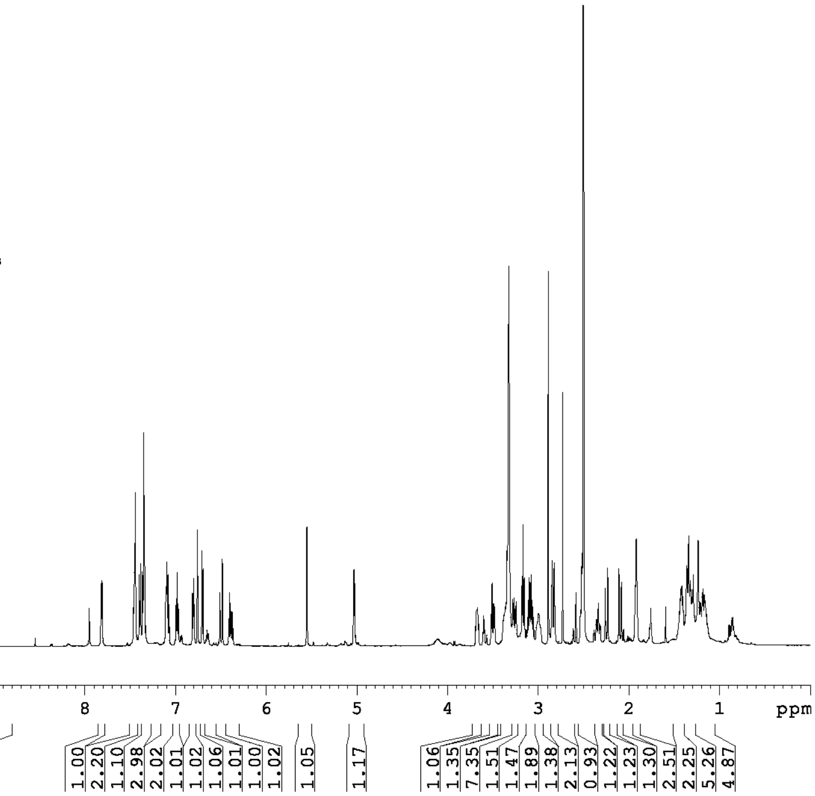
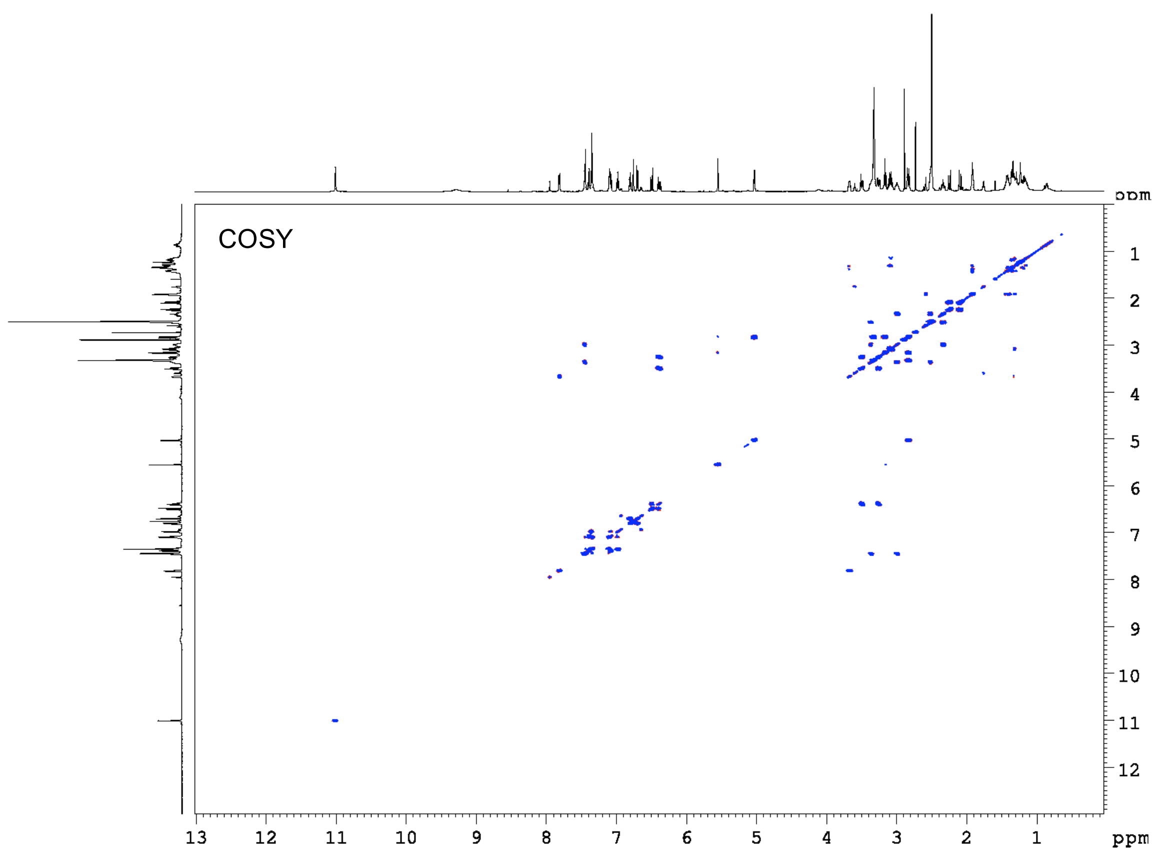
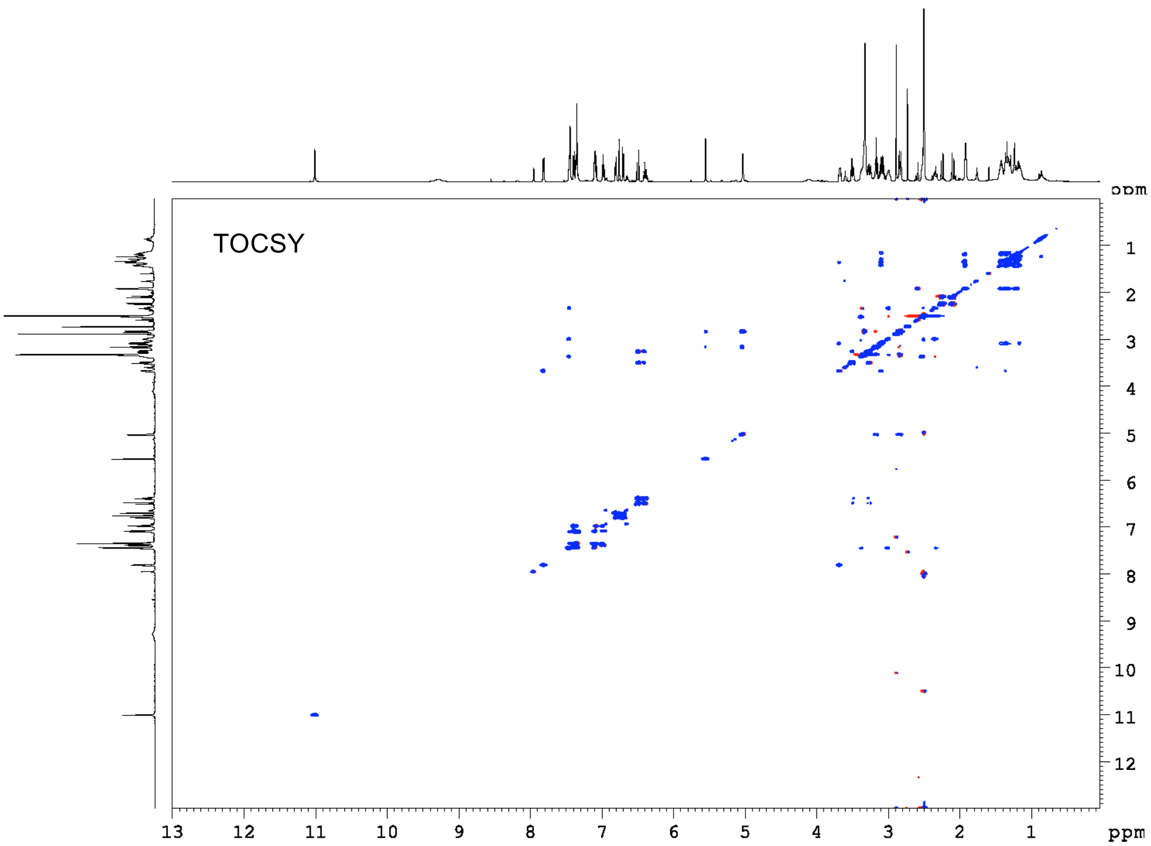
26.1
22.6
18.2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Macrocycle **3.51**








TOCSY
ppm
1
2
3
4
5
6
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11
12
13
12
11
10
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7
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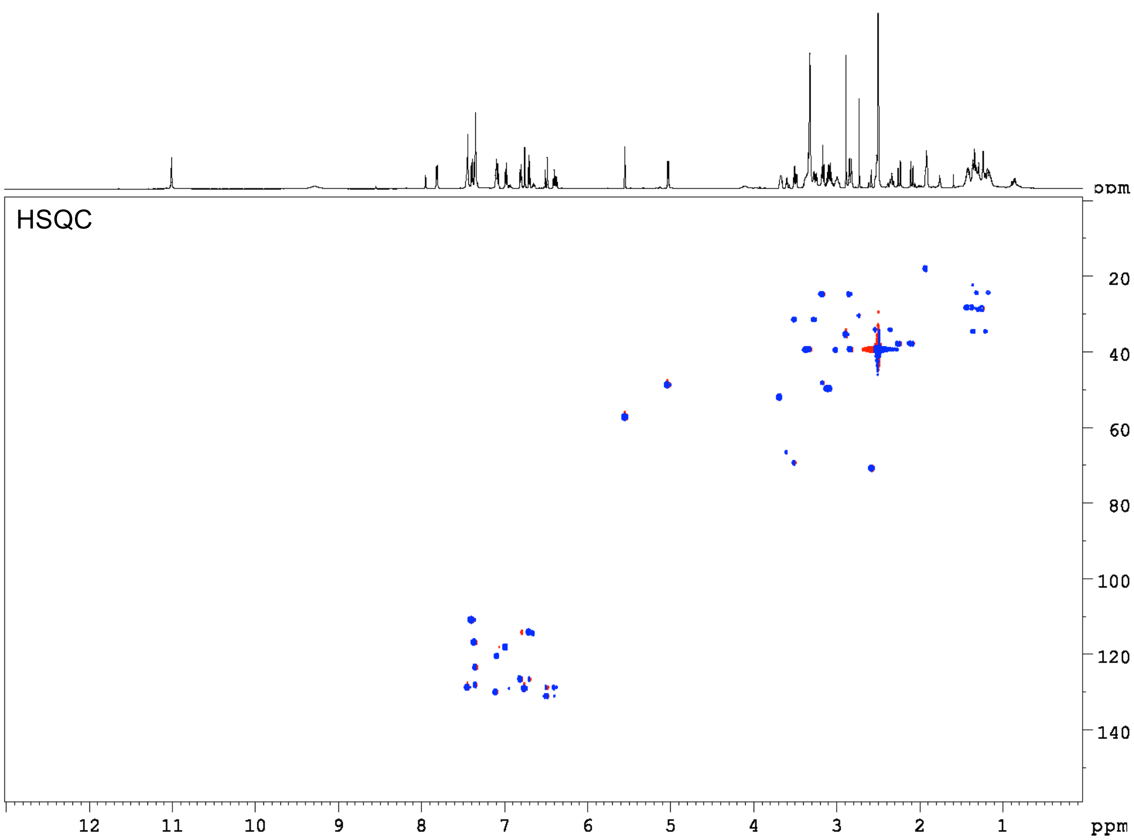
4
3
2
1
ppm


HSQC
ppm
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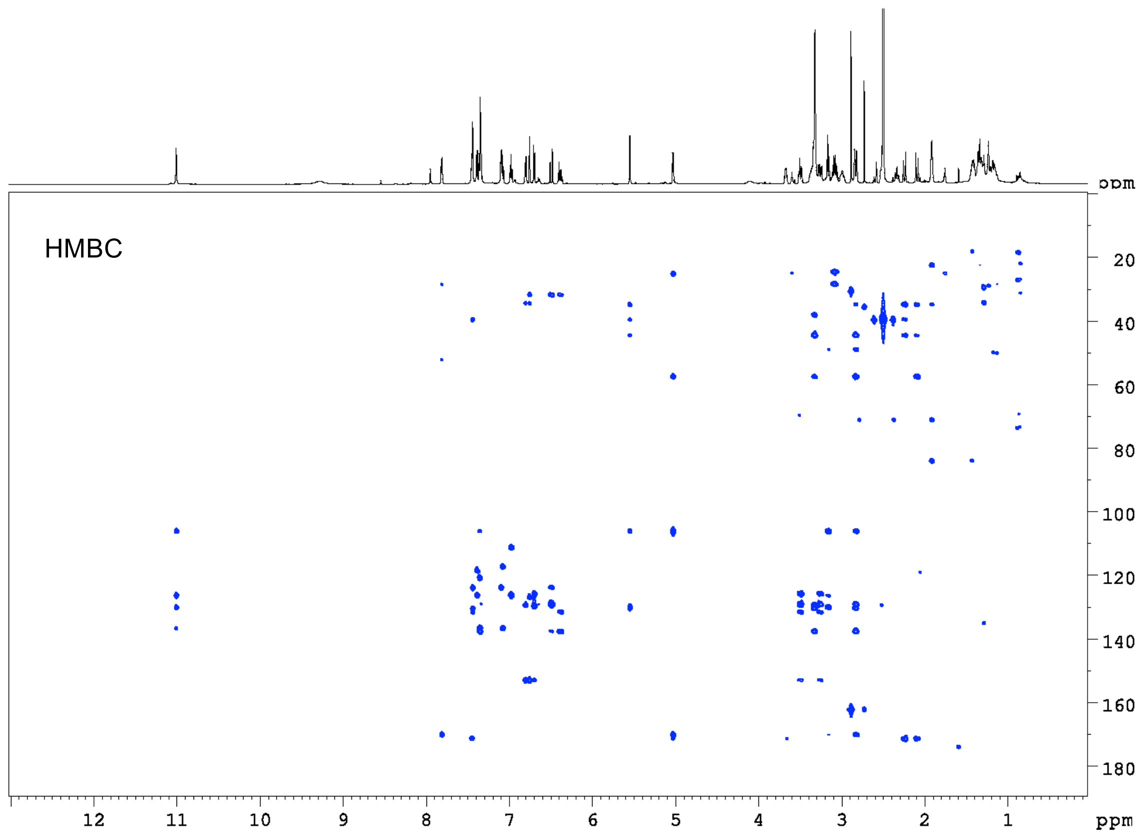
ppm


HMBC
ppm
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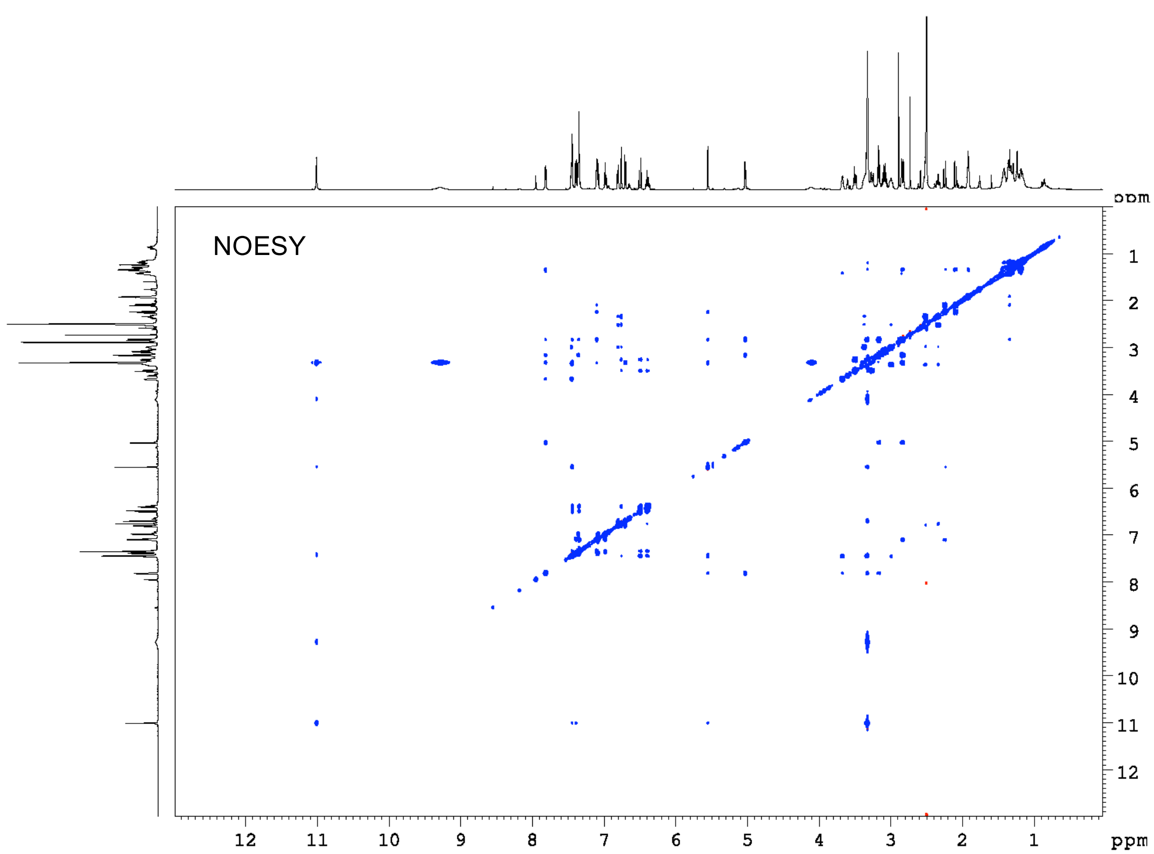
ppm


NOESY
ppm
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6
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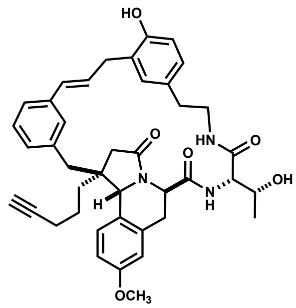
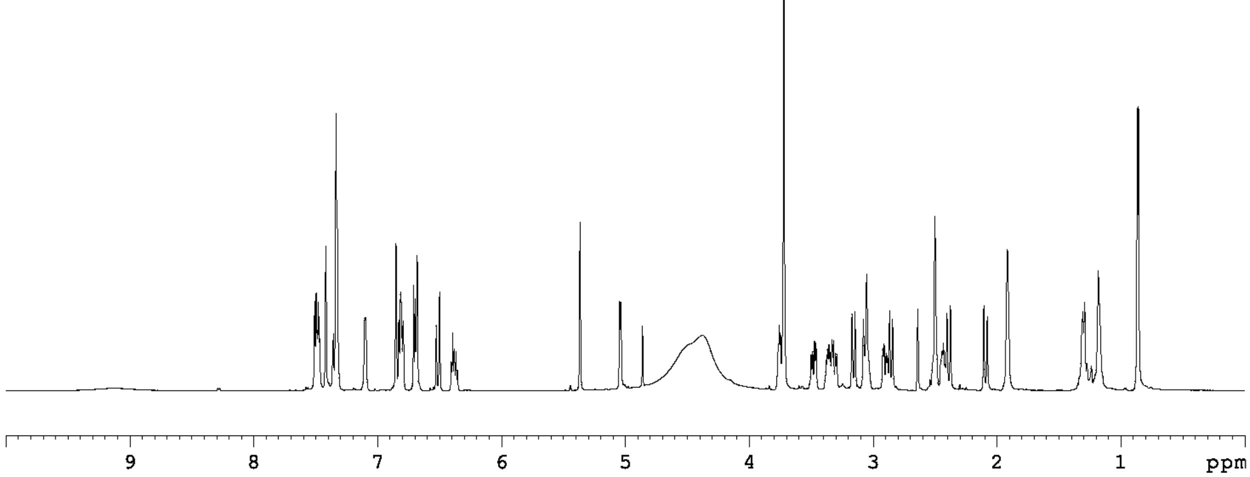
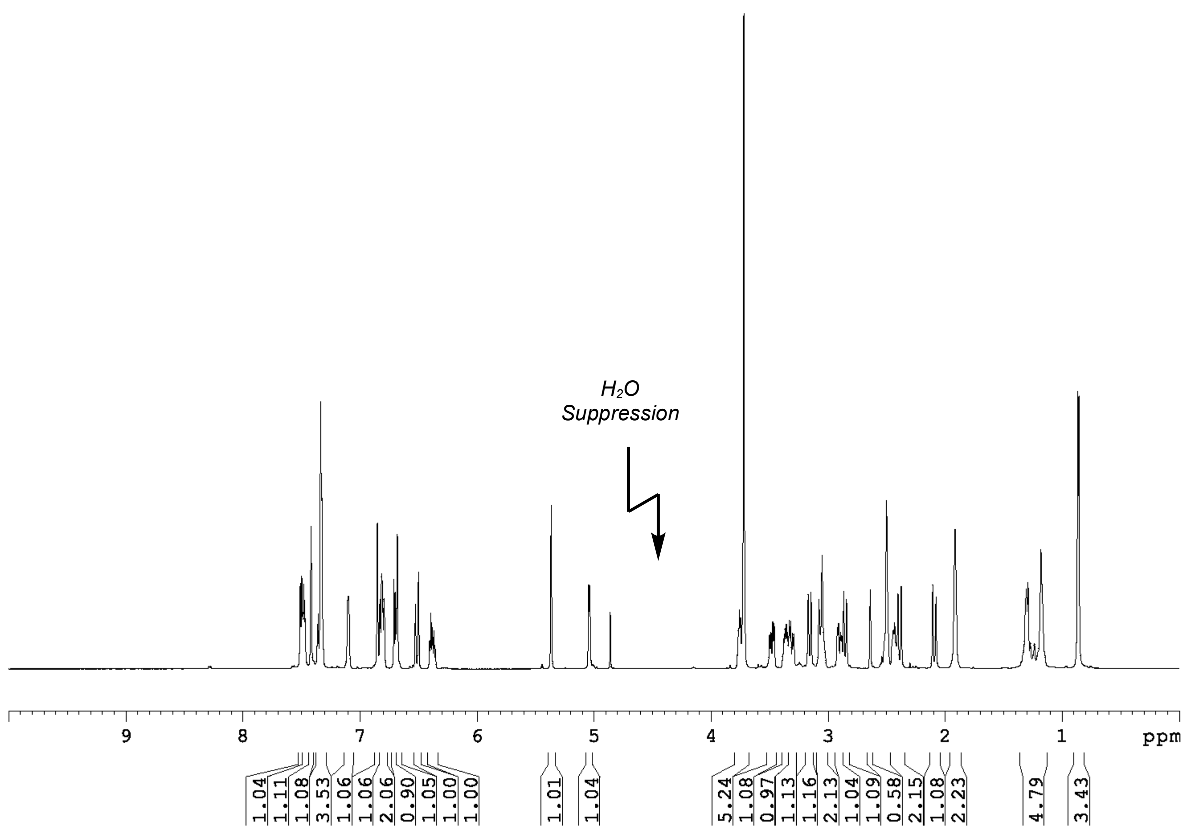
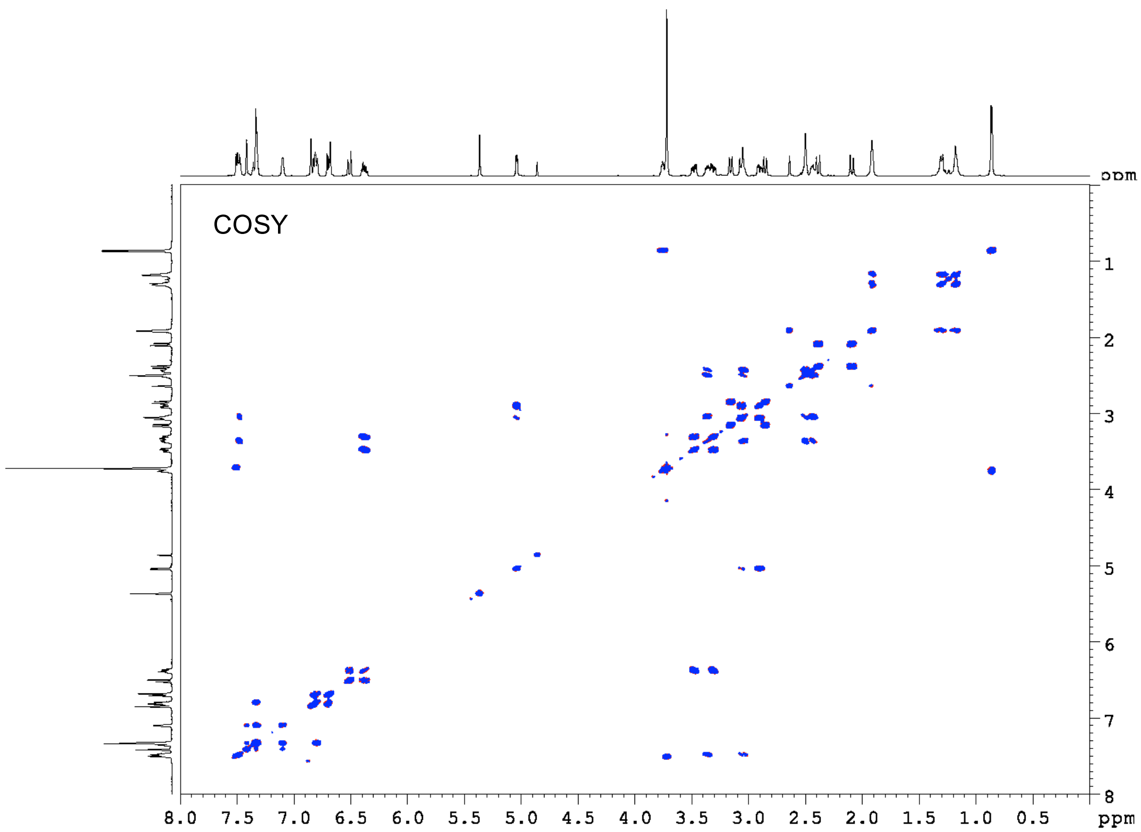
4
3
2
1
ppm

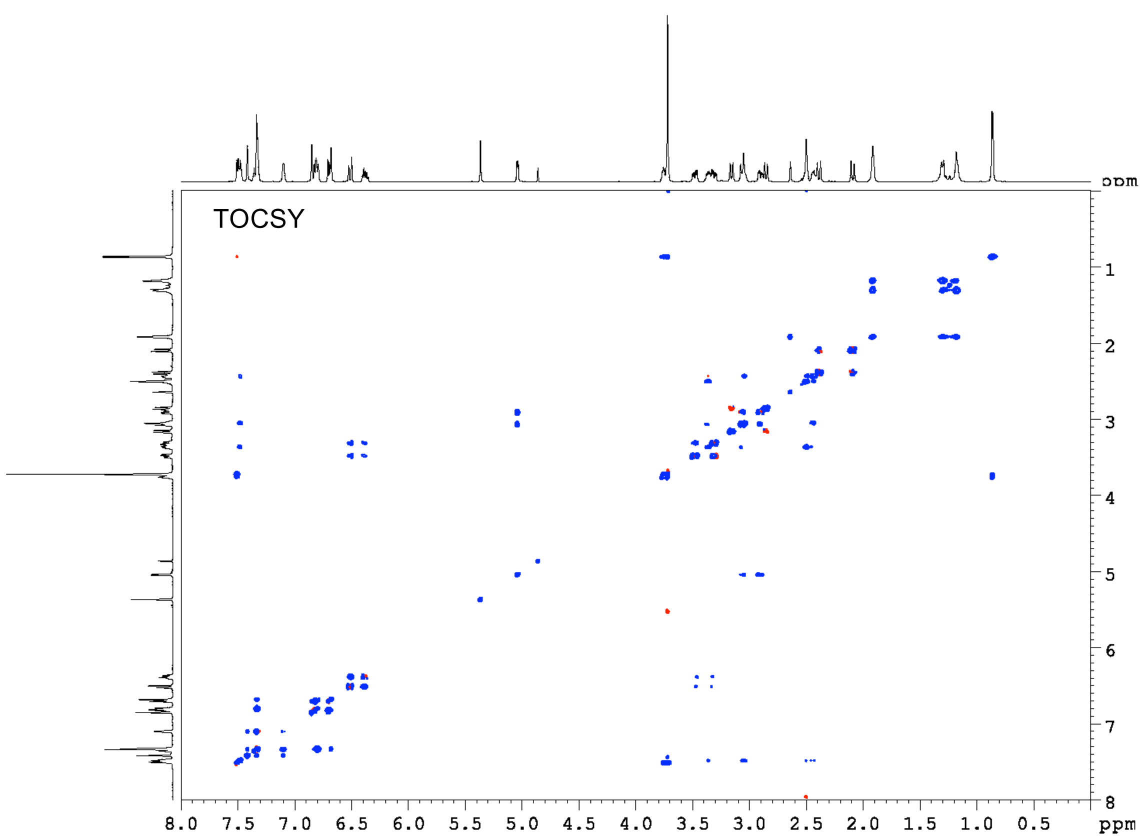
Macrocycle **42**

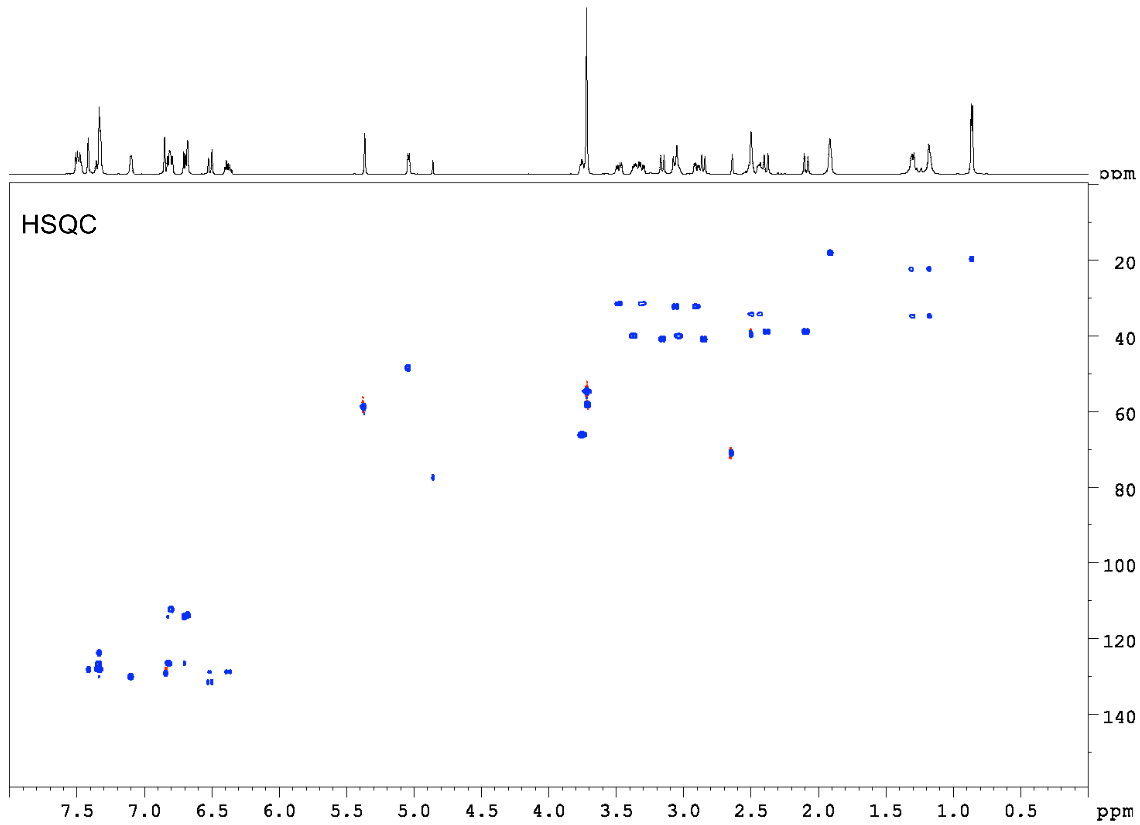


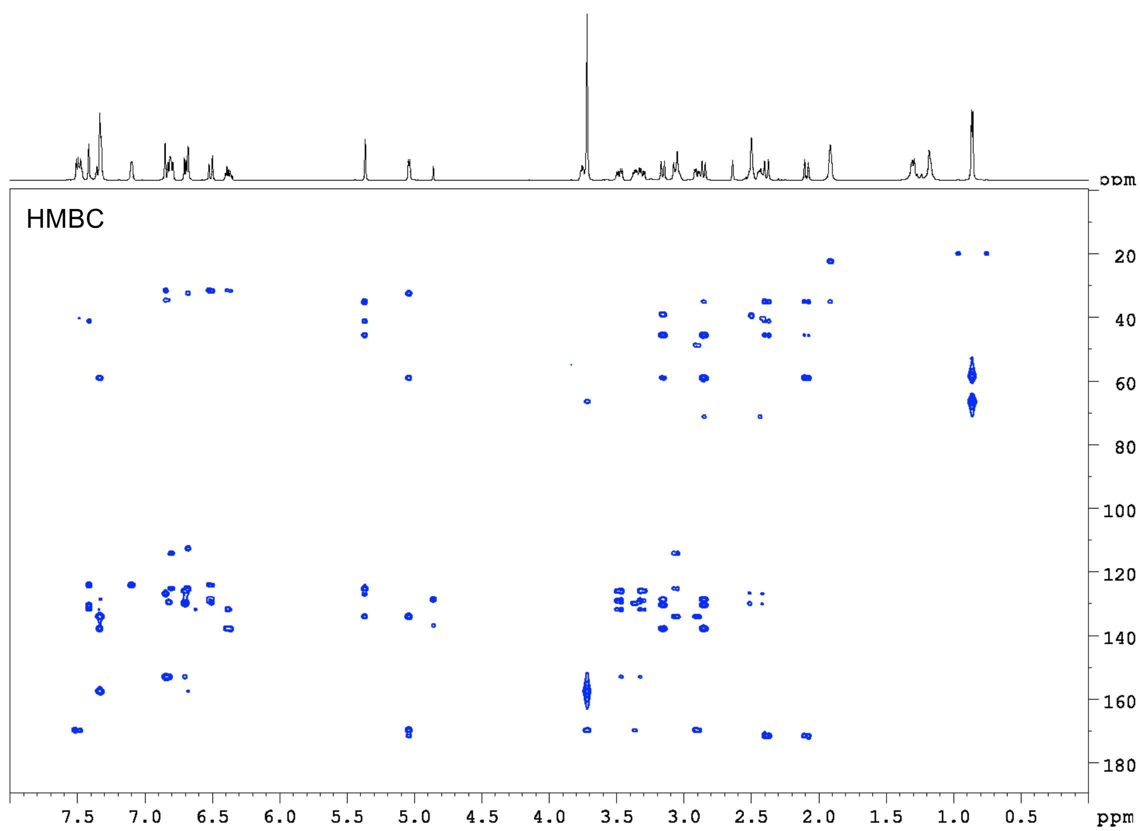


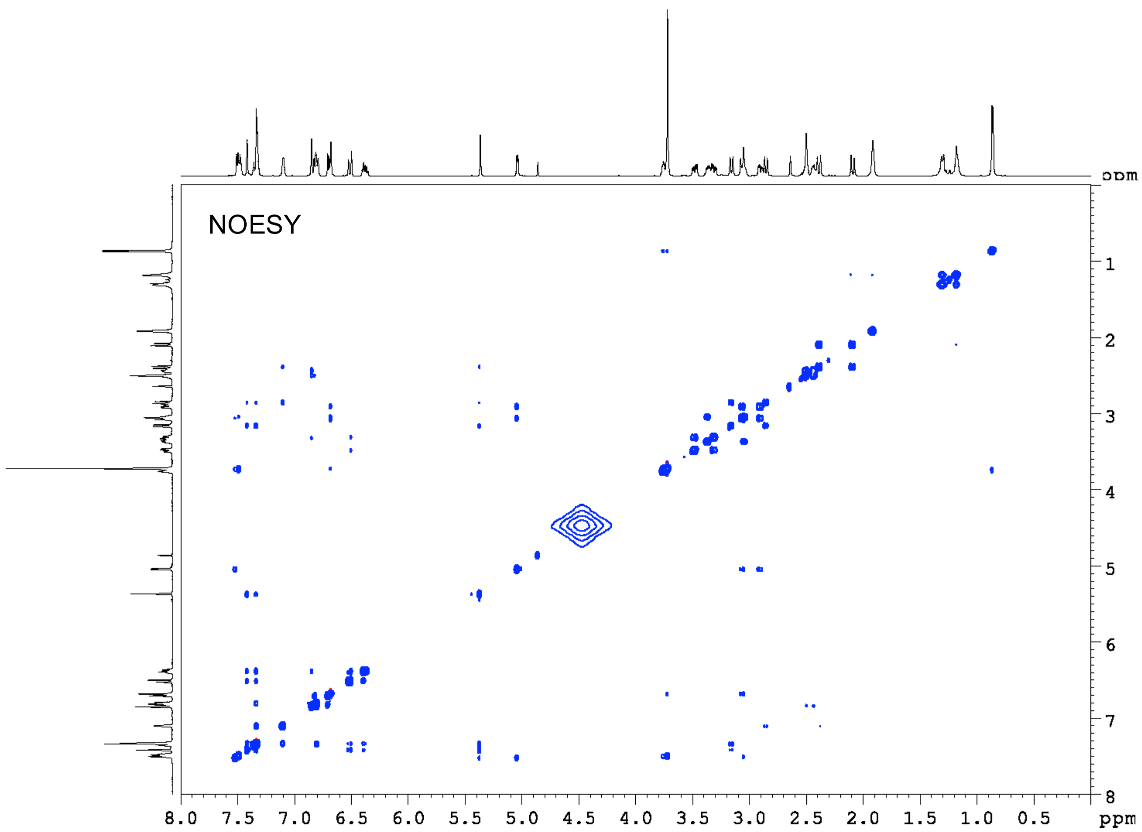



COSY
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8

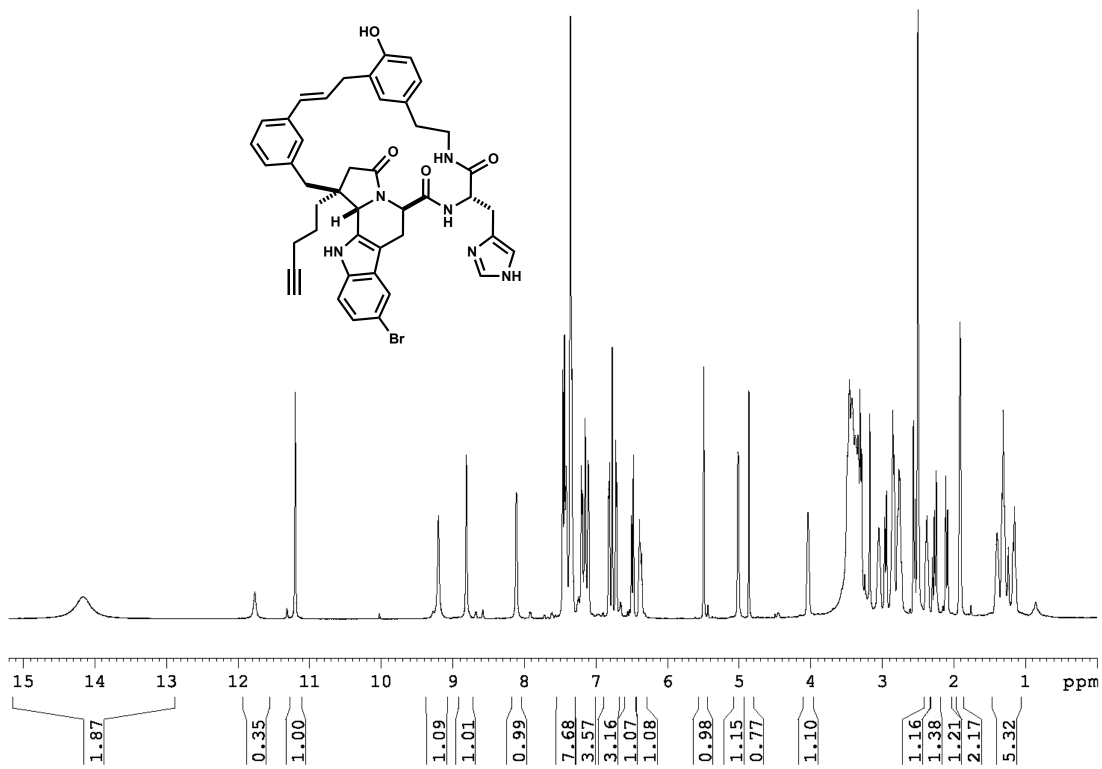

TOCSY
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8

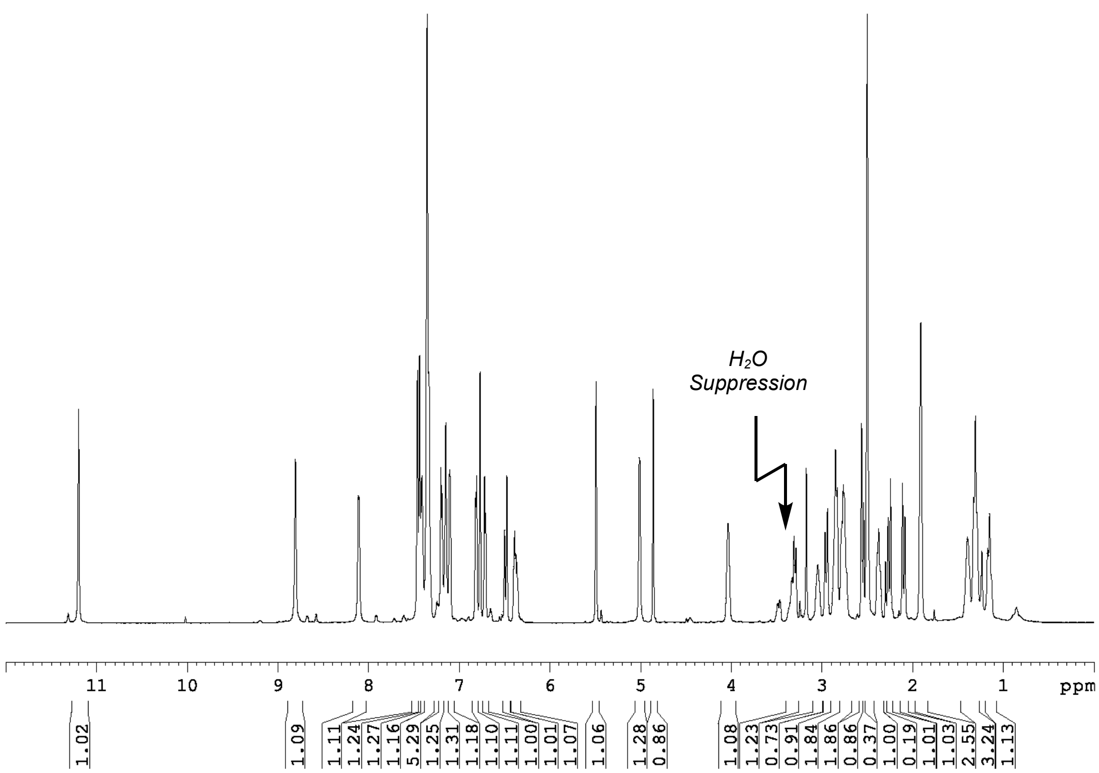

HSQC
ppm
20
40
60
80
100
120
140
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

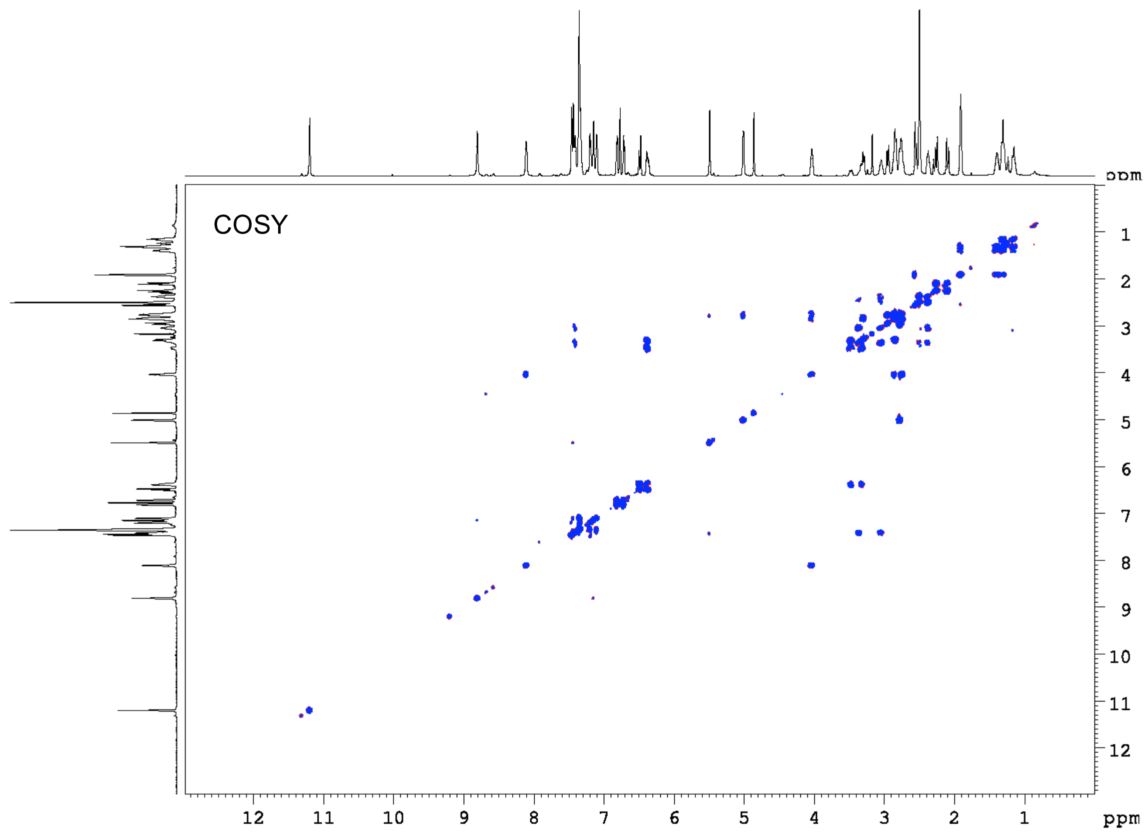

HMBC
ppm
20
40
60
80
100
120
140
160
180
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

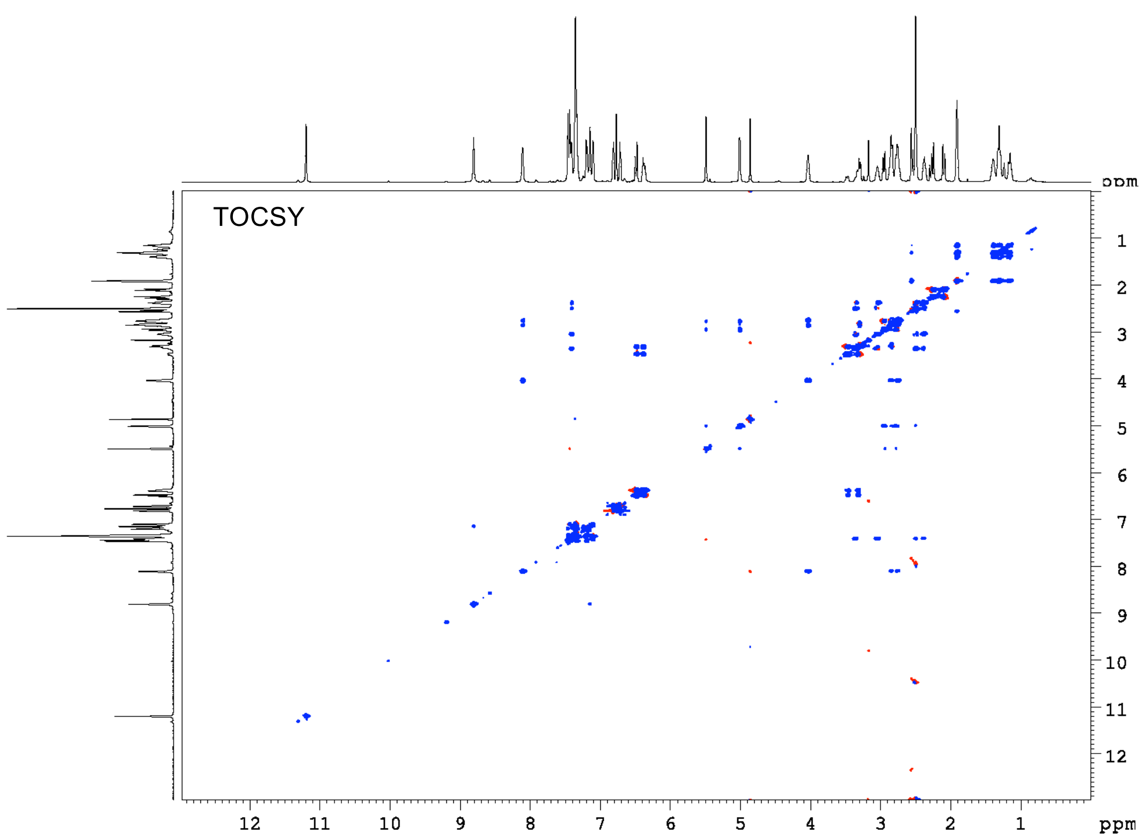

NOESY
ppm
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1 2 3 4 5 6 7 8

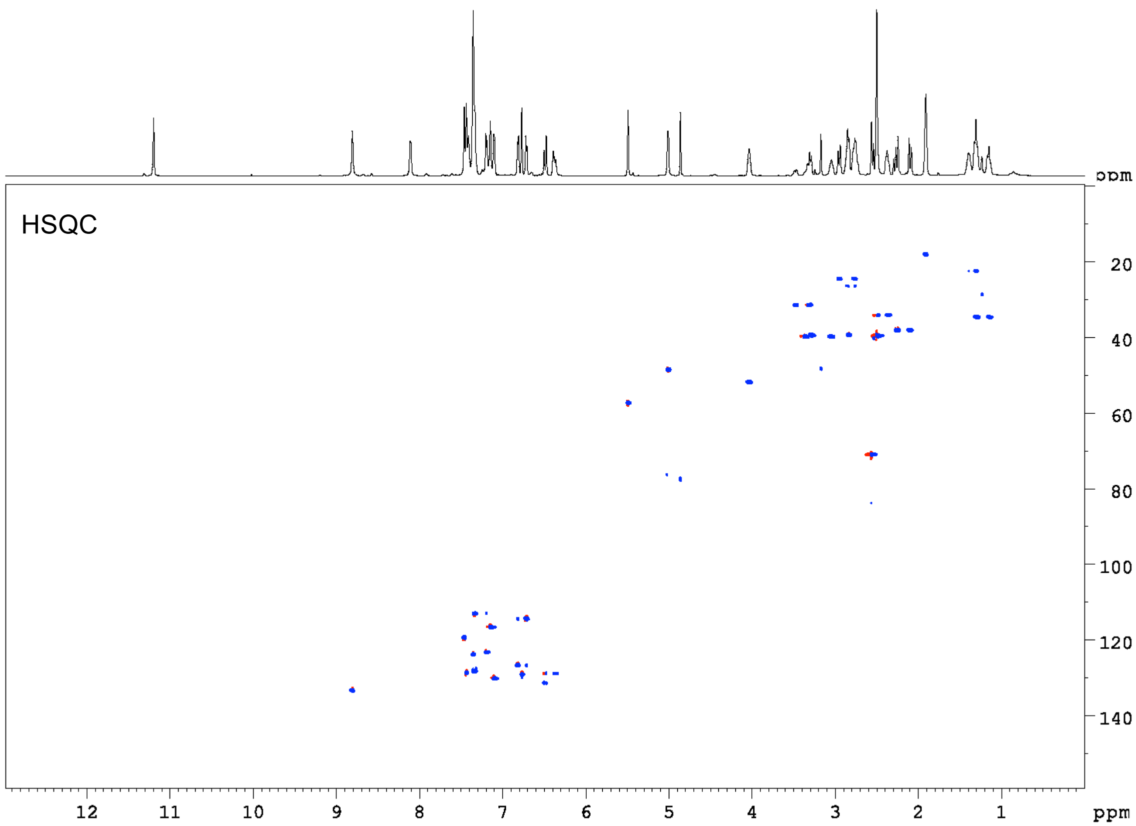
Macrocycle **3.53**

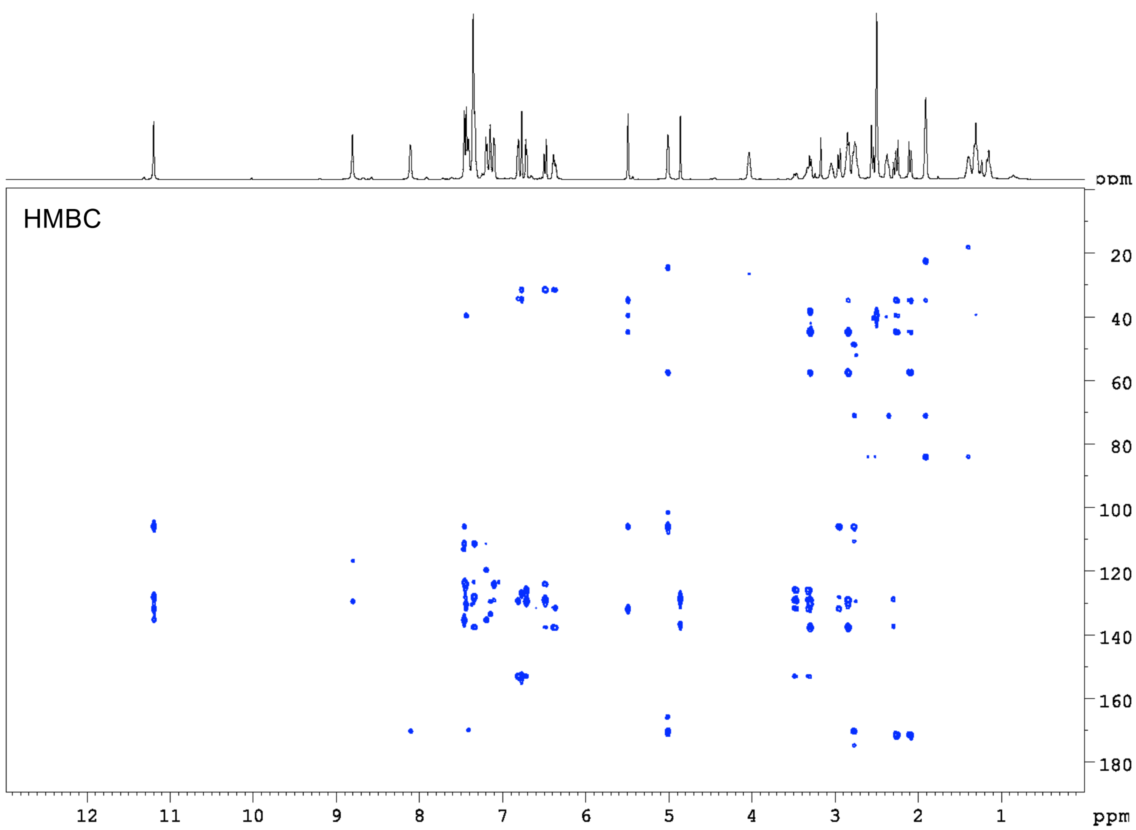


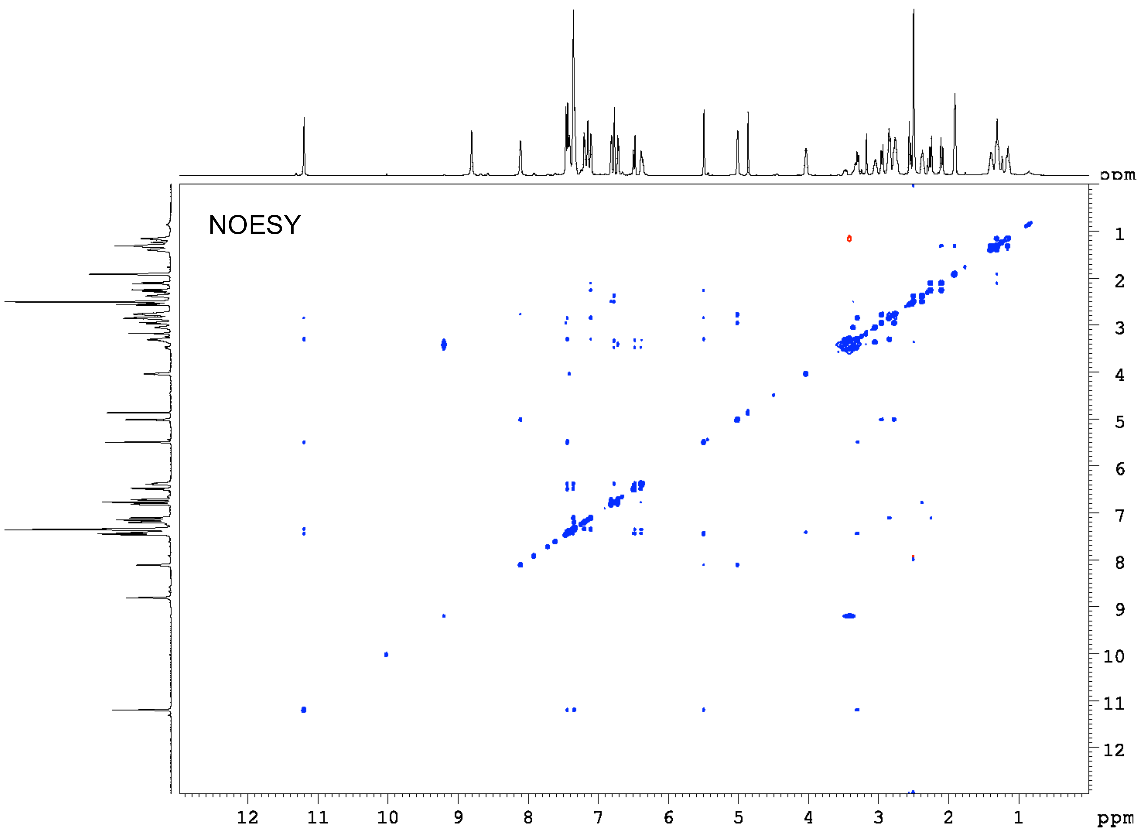



COSY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

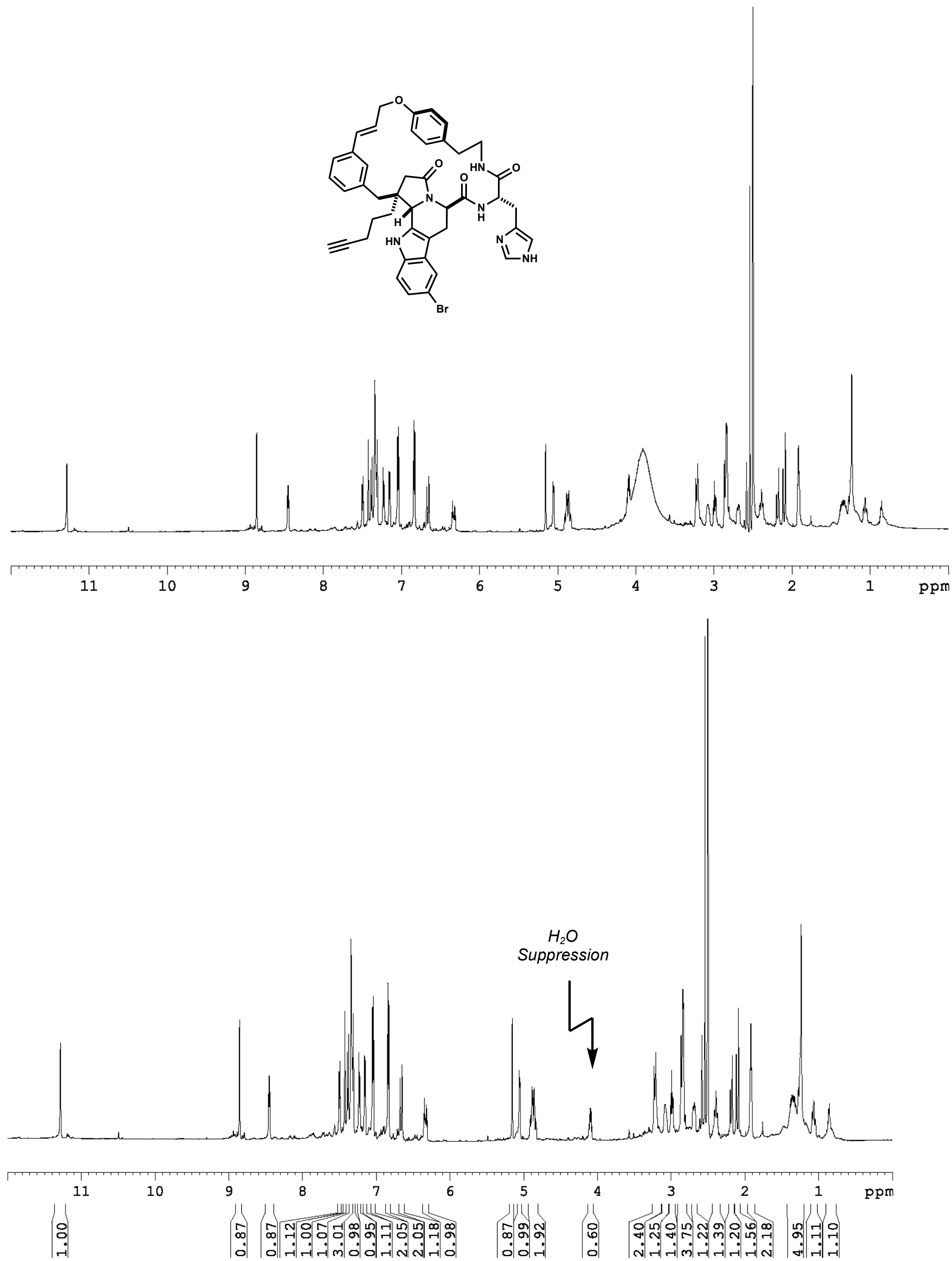

TOCSY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

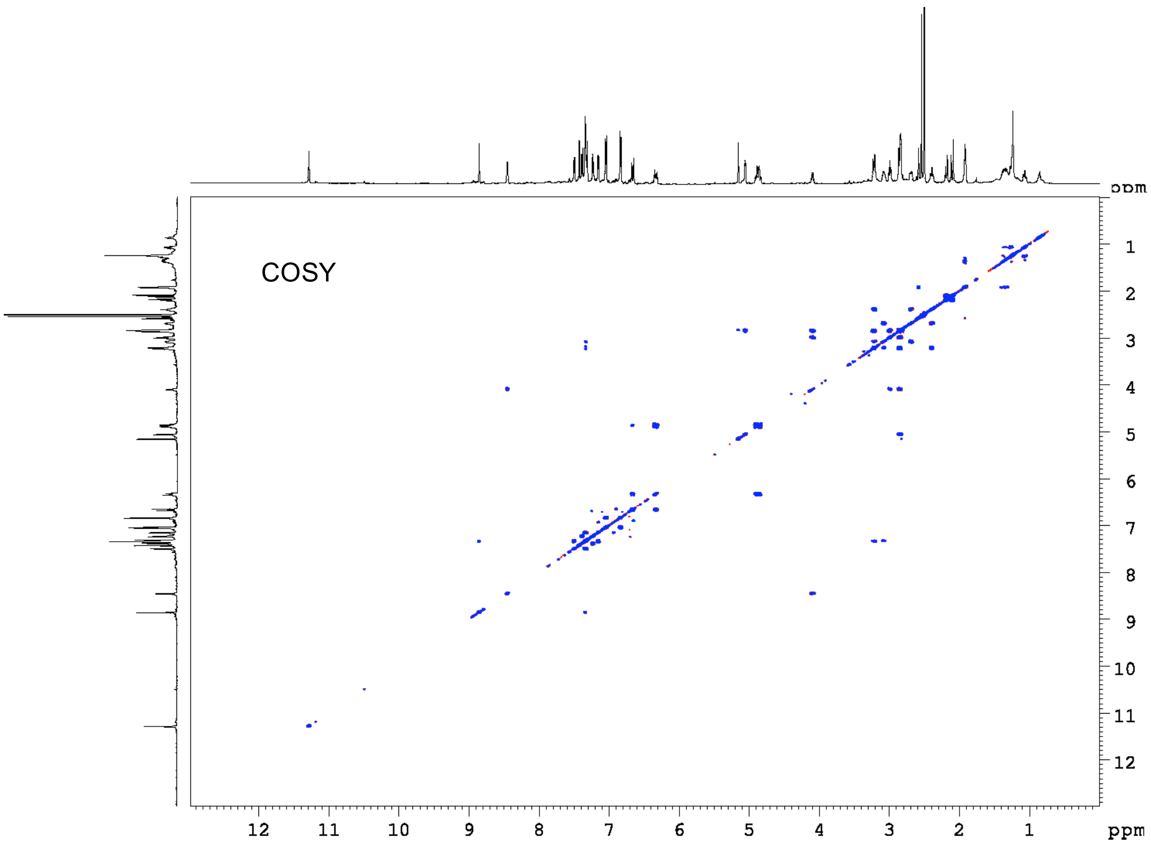

HSQC
ppm
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1
ppm

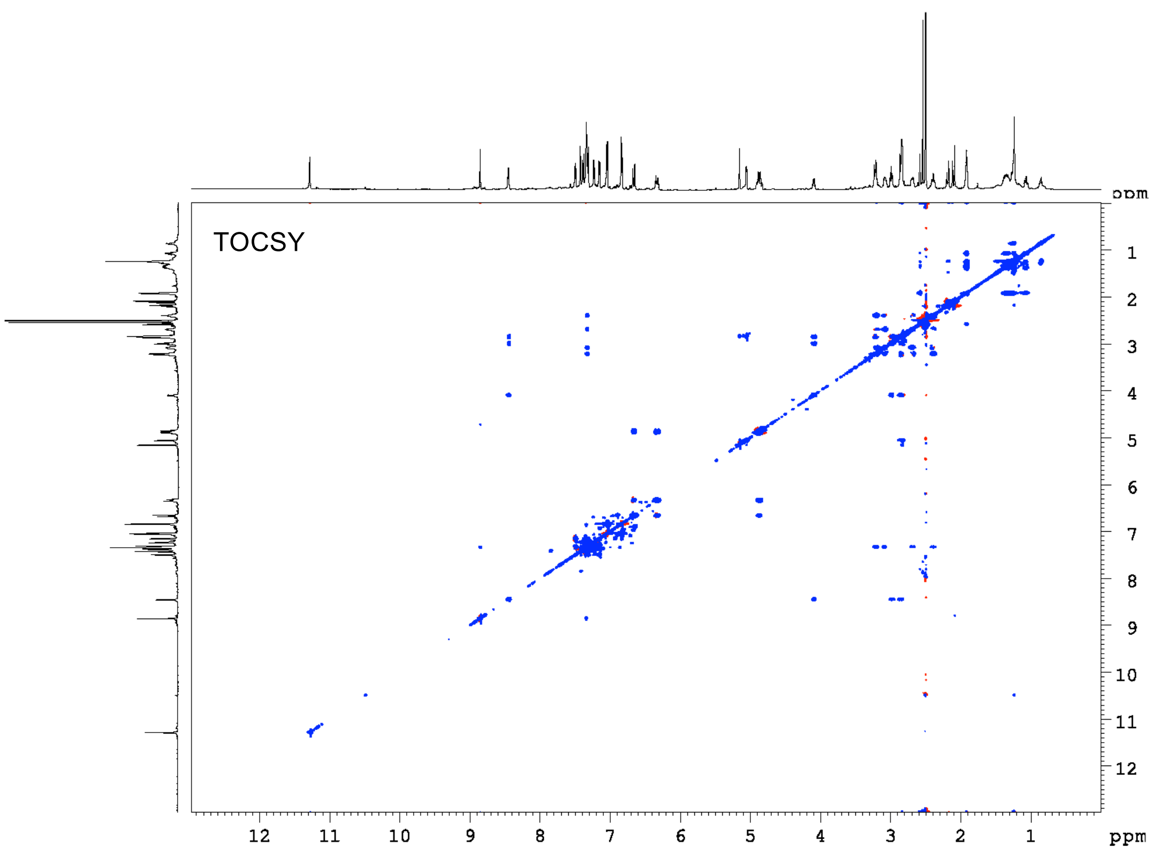

HMBC
ppm
20
40
60
80
100
120
140
160
180
12
11
10
9
8
7
6
5
4
3
2
1
ppm

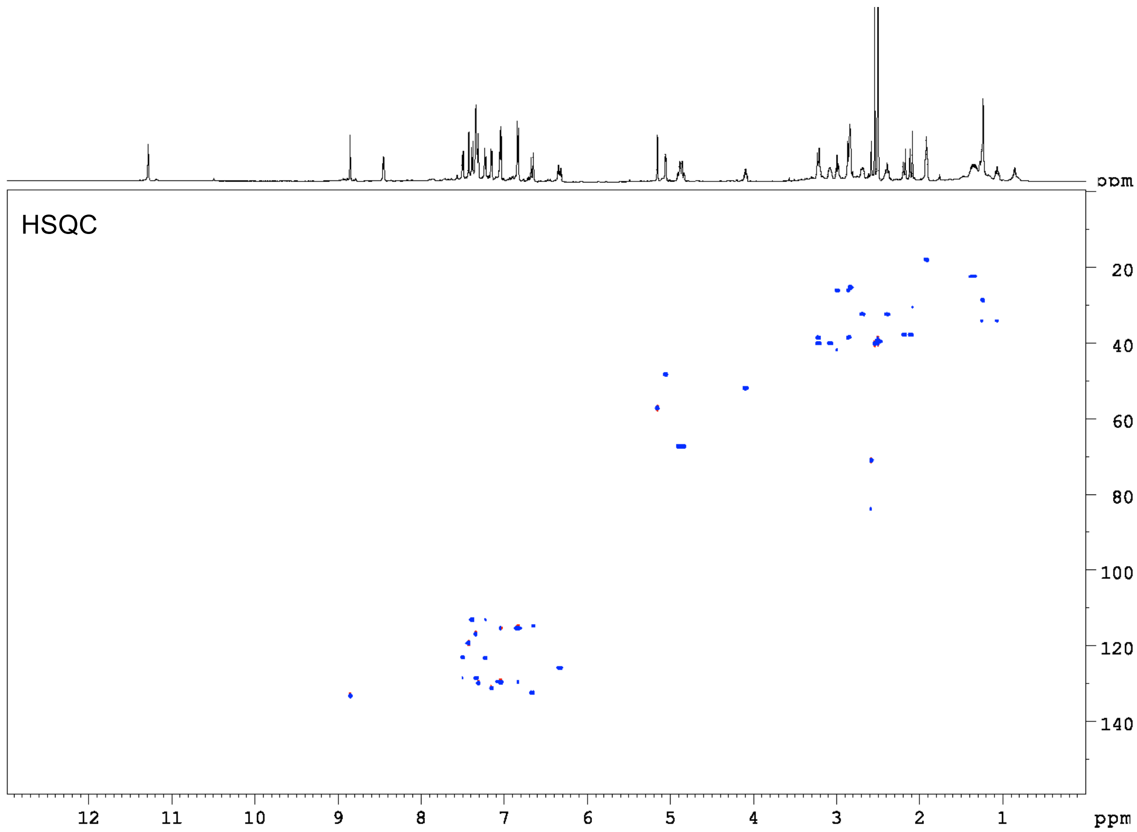

NOESY
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm

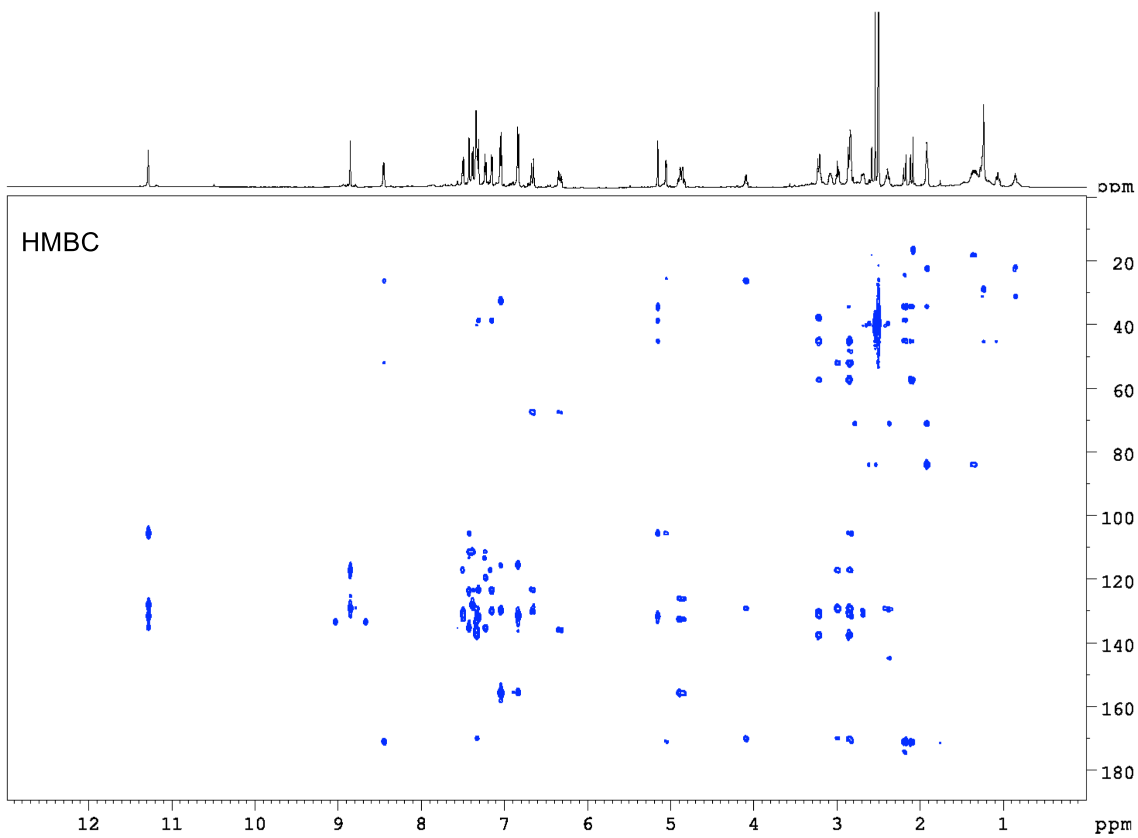
Macrocycle **3.54**

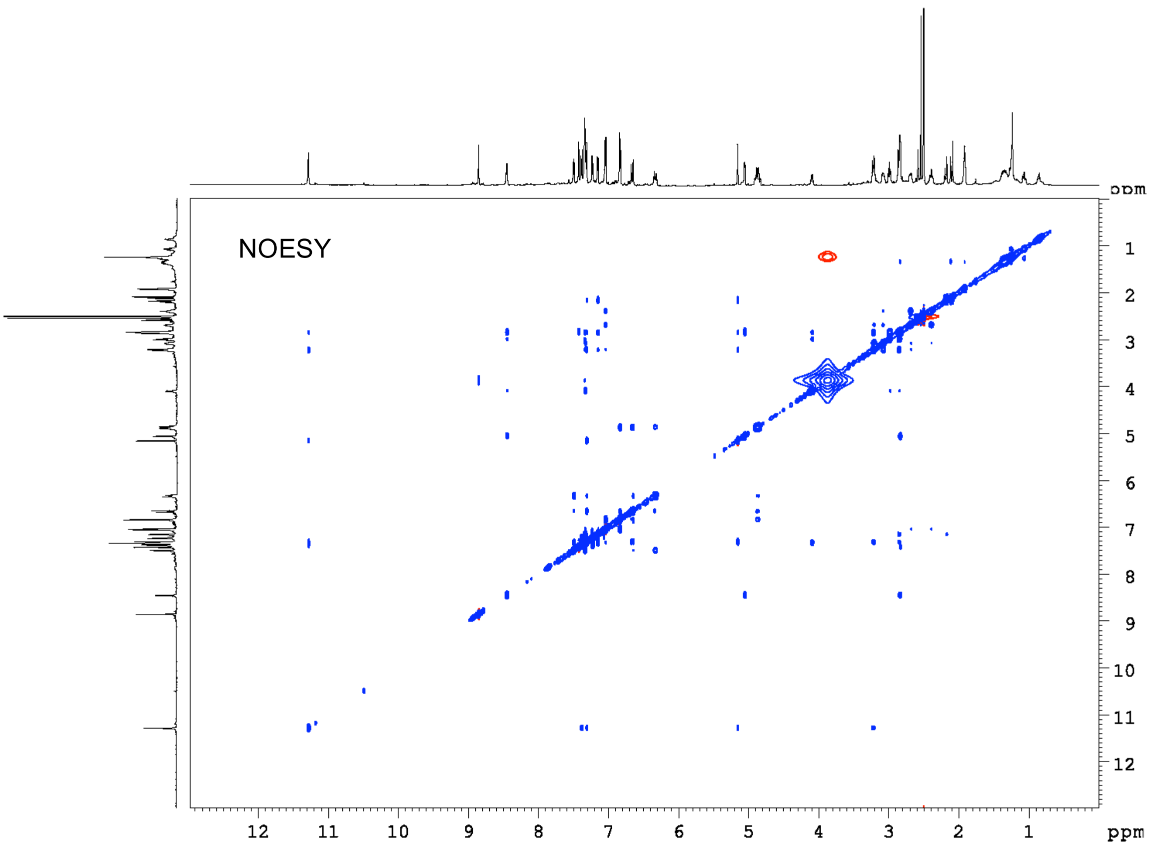



COSY
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm

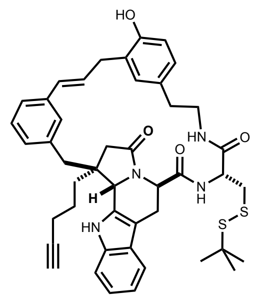

TOCSY
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm

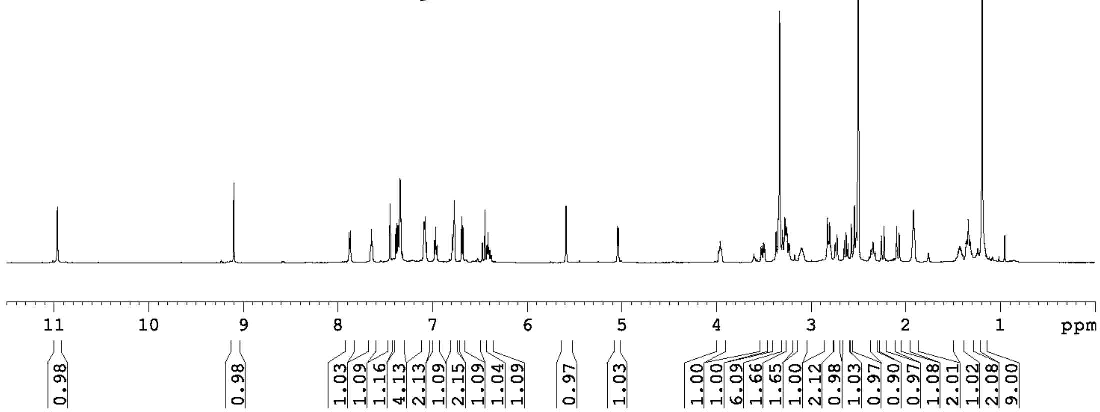

HSQC
ppm
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1
ppm

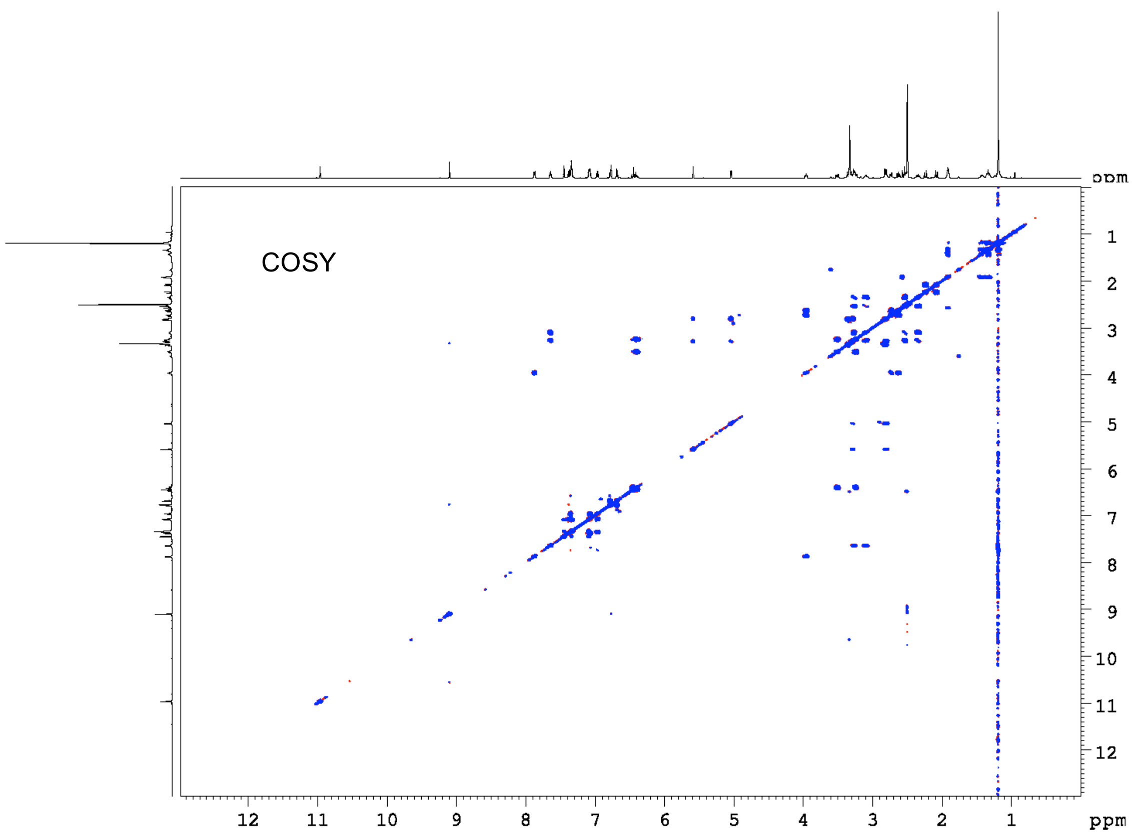

HMBC
ppm
20
40
60
80
100
120
140
160
180
12
11
10
9
8
7
6
5
4
3
2
1
ppm

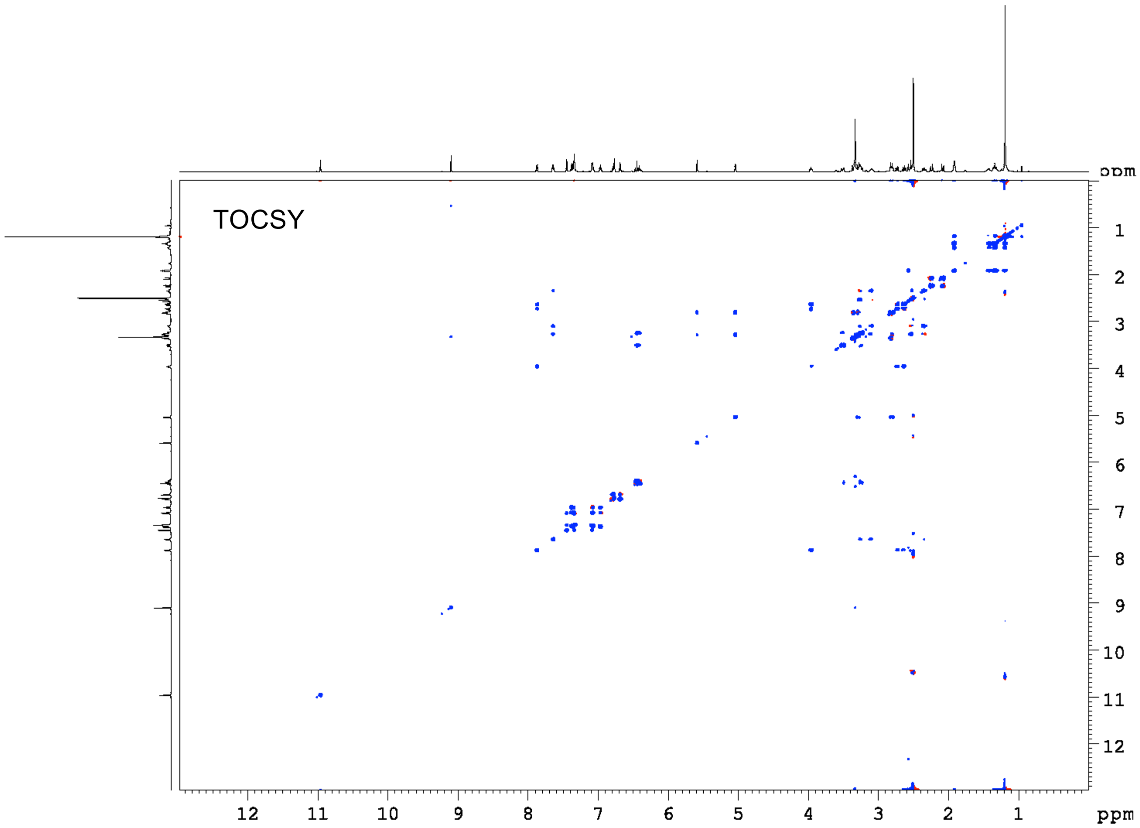

NOESY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

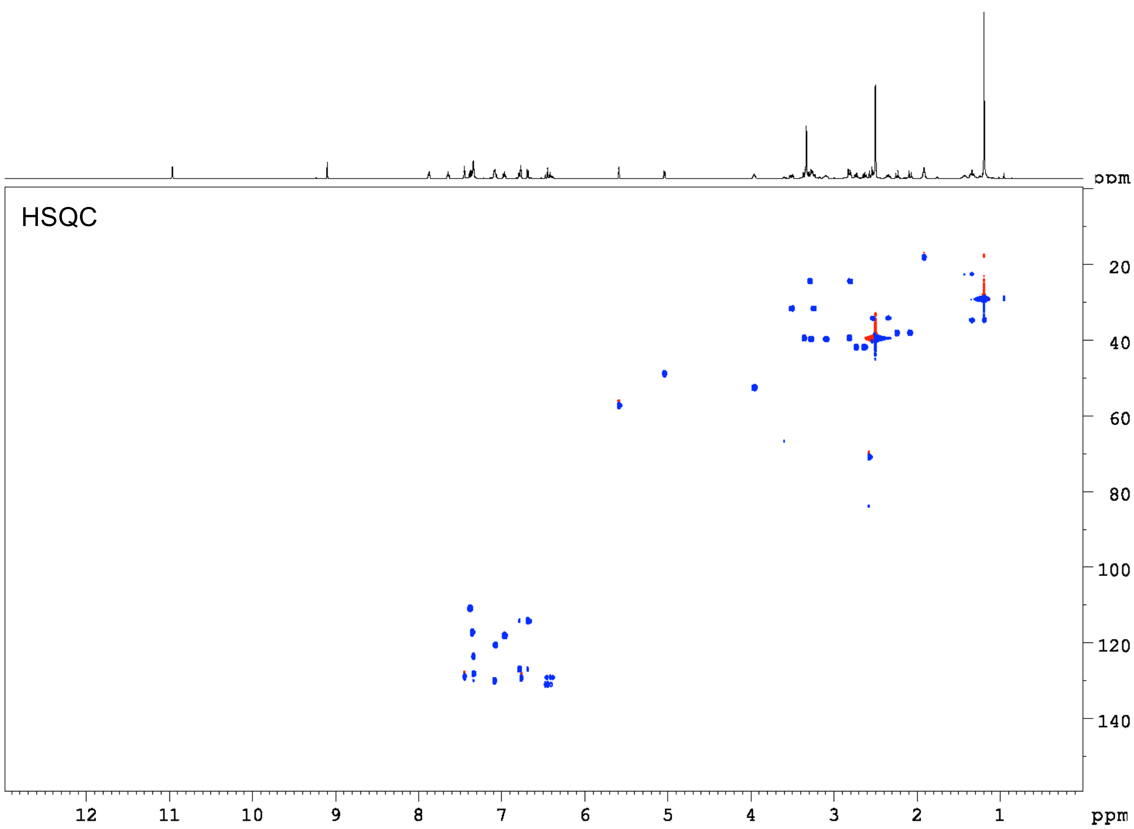
Macrocycle **3.55a**

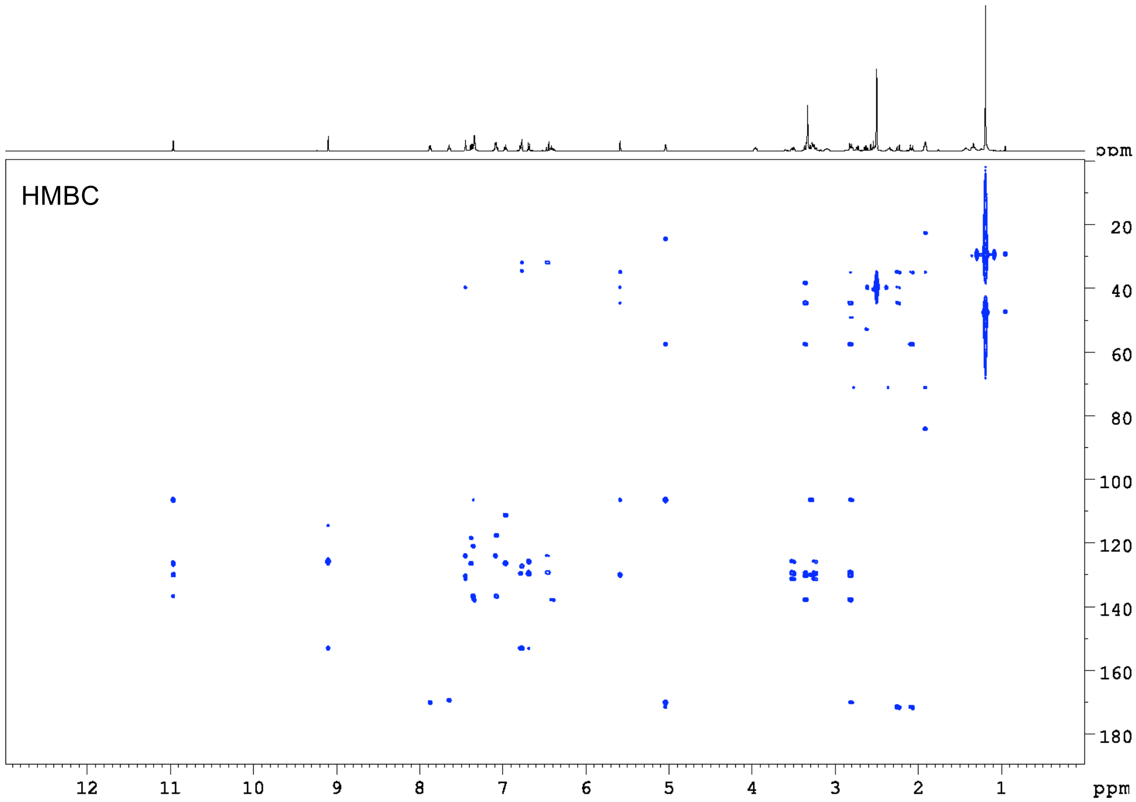


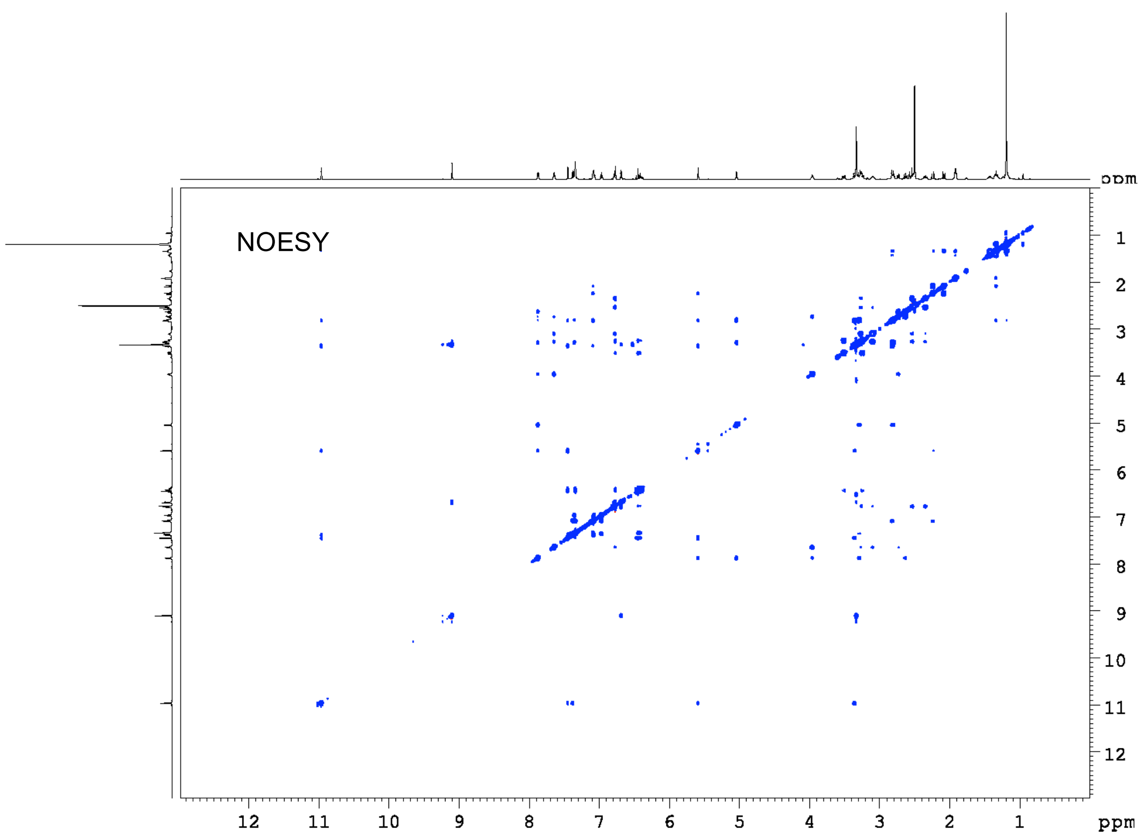




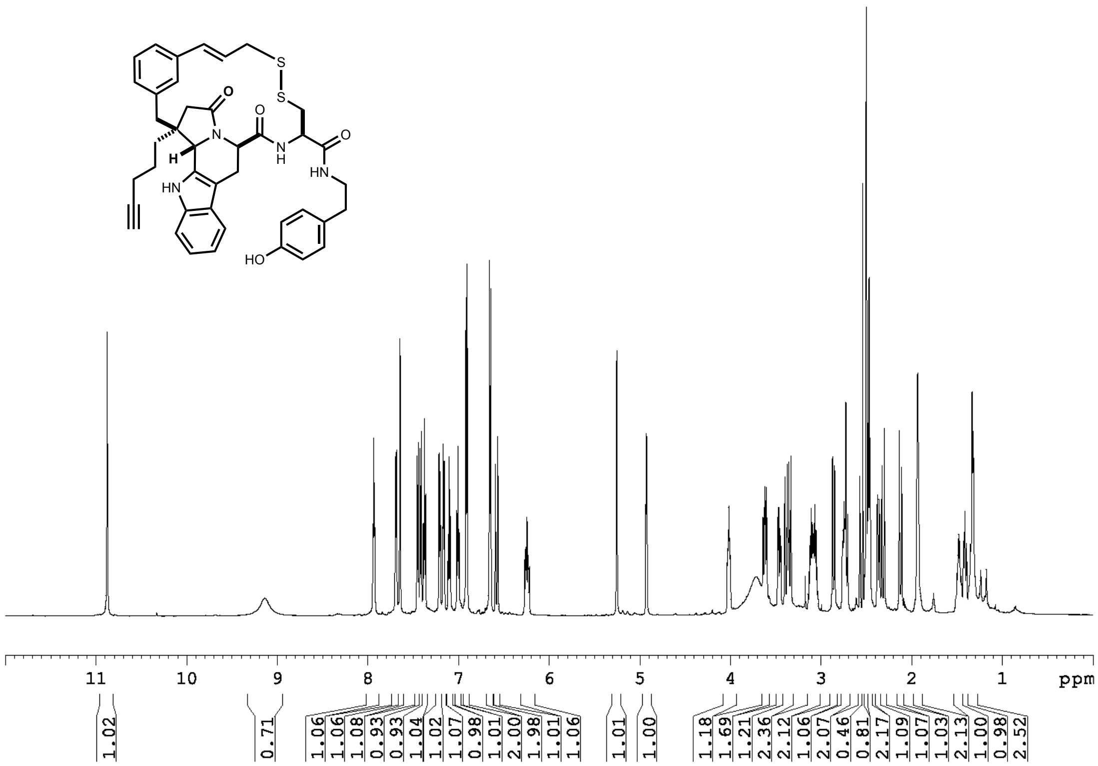

TOCSY
ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm

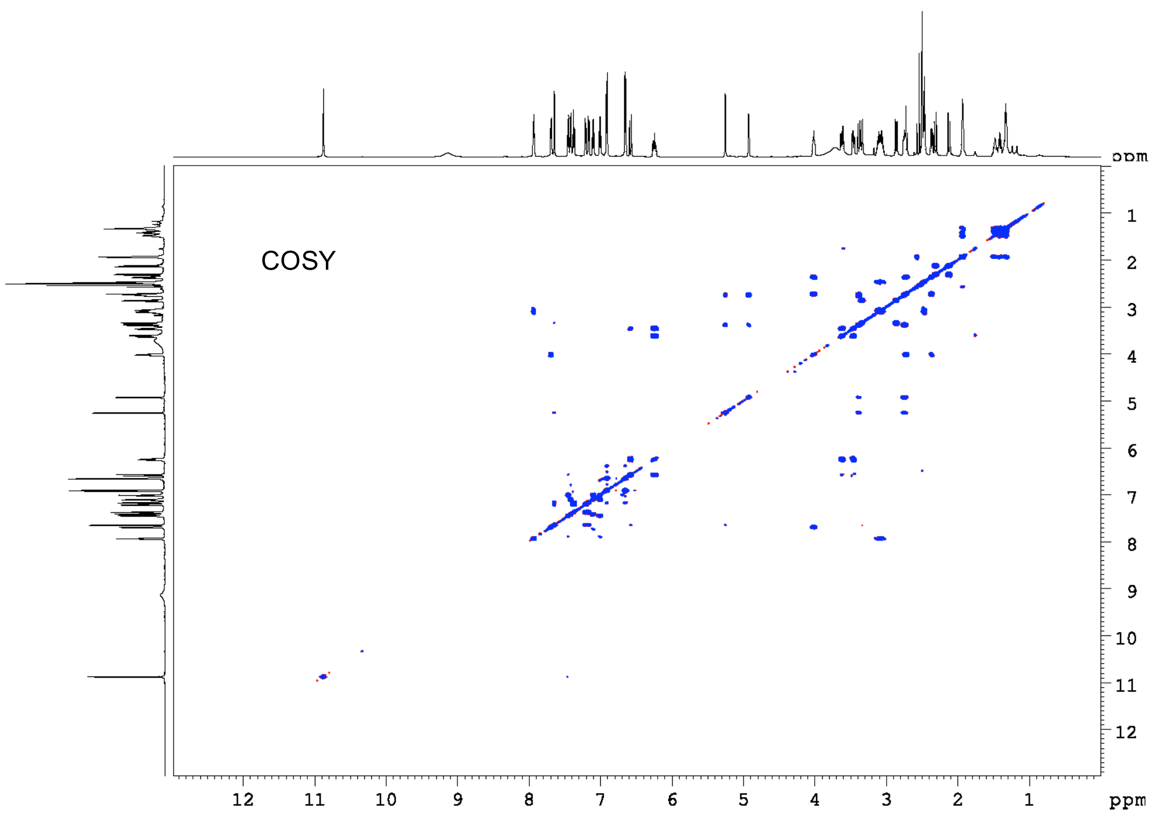

HSQC
ppm
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1
ppm

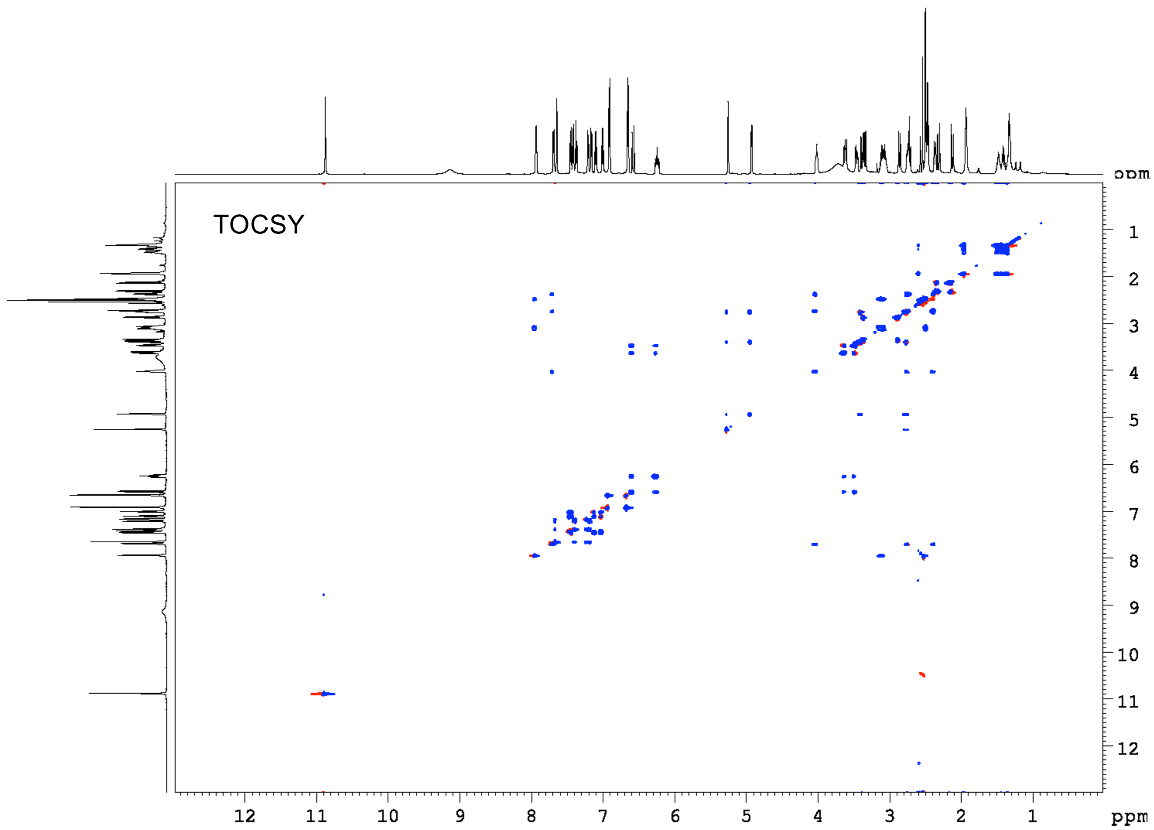

HMBC
ppm
20
40
60
80
100
120
140
160
180
12
11
10
9
8
7
6
5
4
3
2
1
ppm


NOESY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

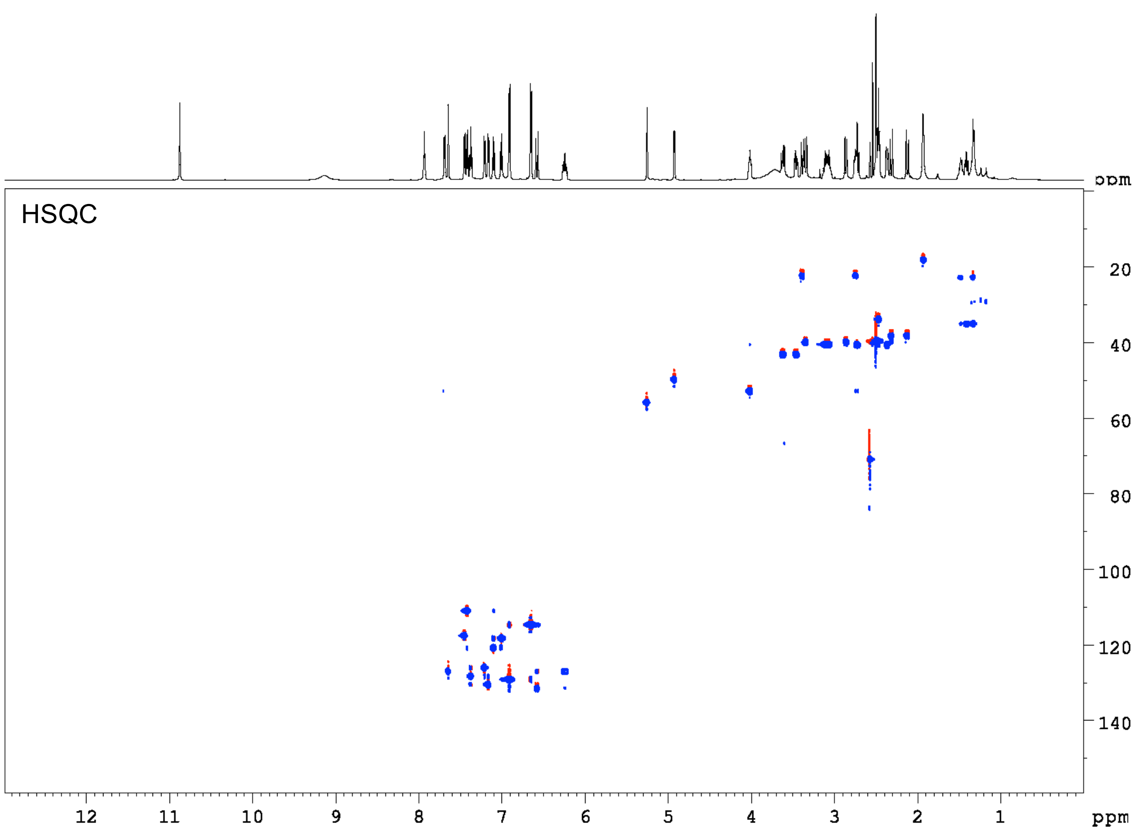
Macrocycle **45b**



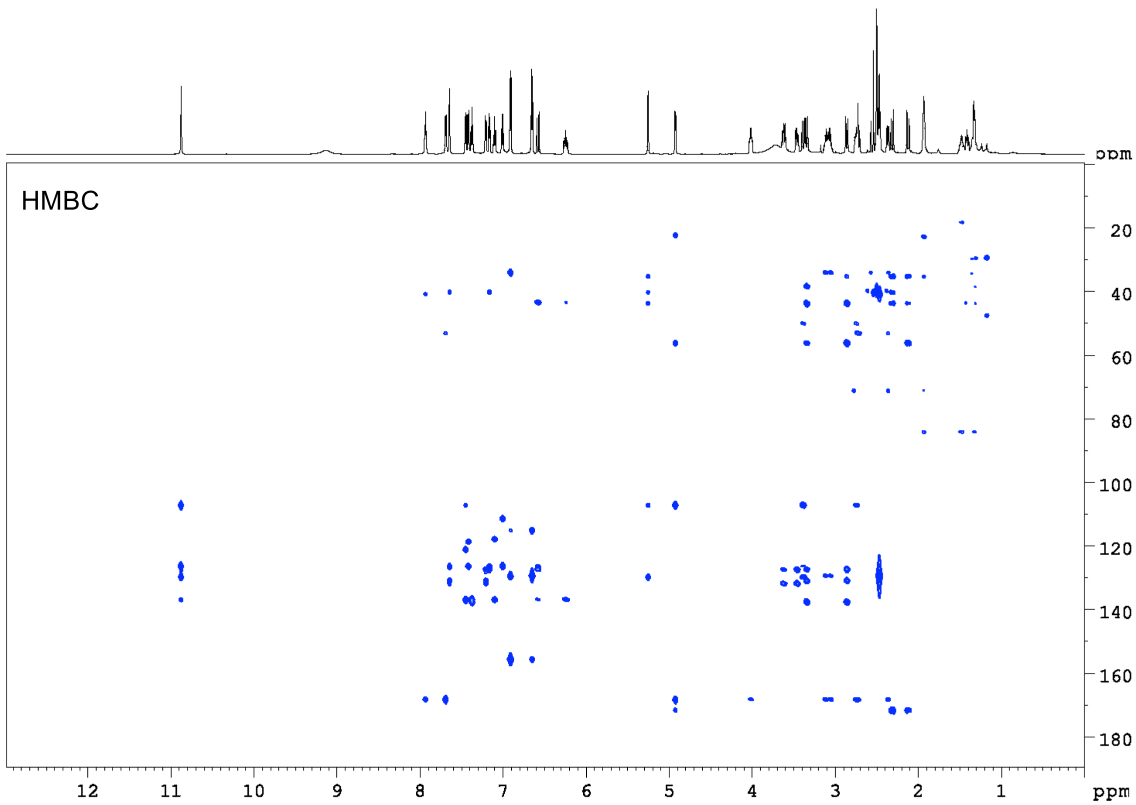


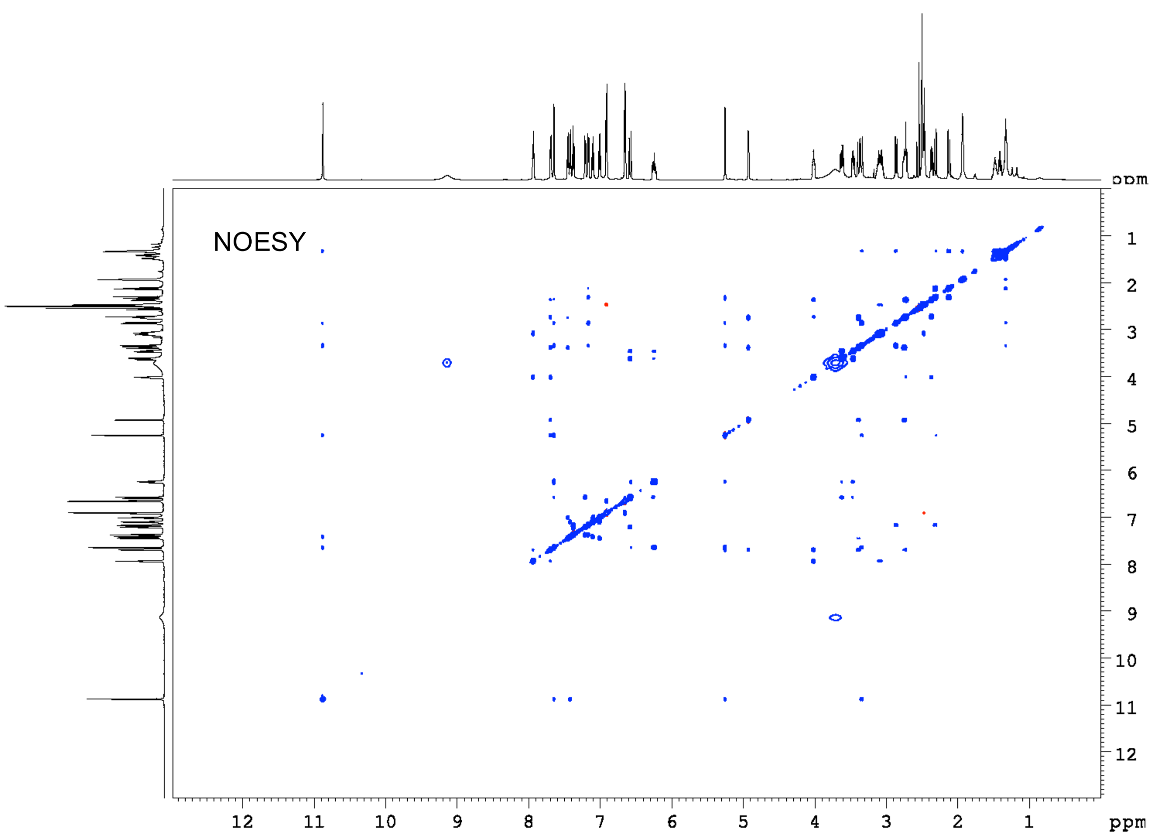


TOCSY
ppm
12
11
10
9
8
7
6
5
4
3
2
1



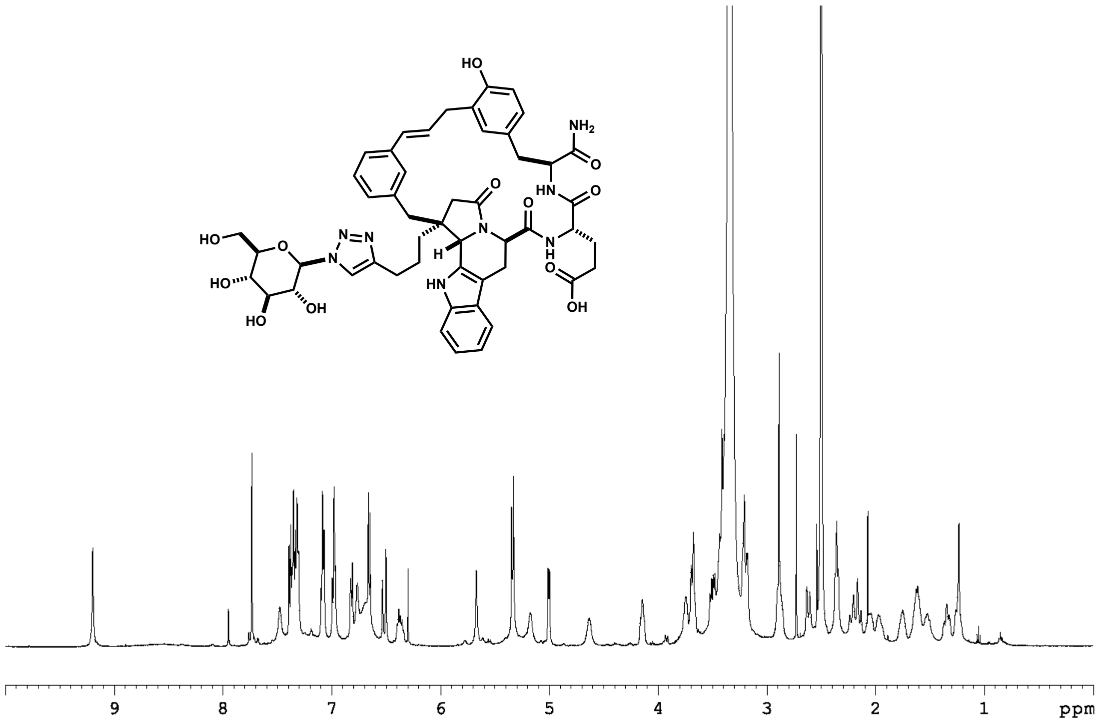
HSQC
ppm
20
40
60
80
100
120
140
12
11
10
9
8
7
6
5
4
3
2
1

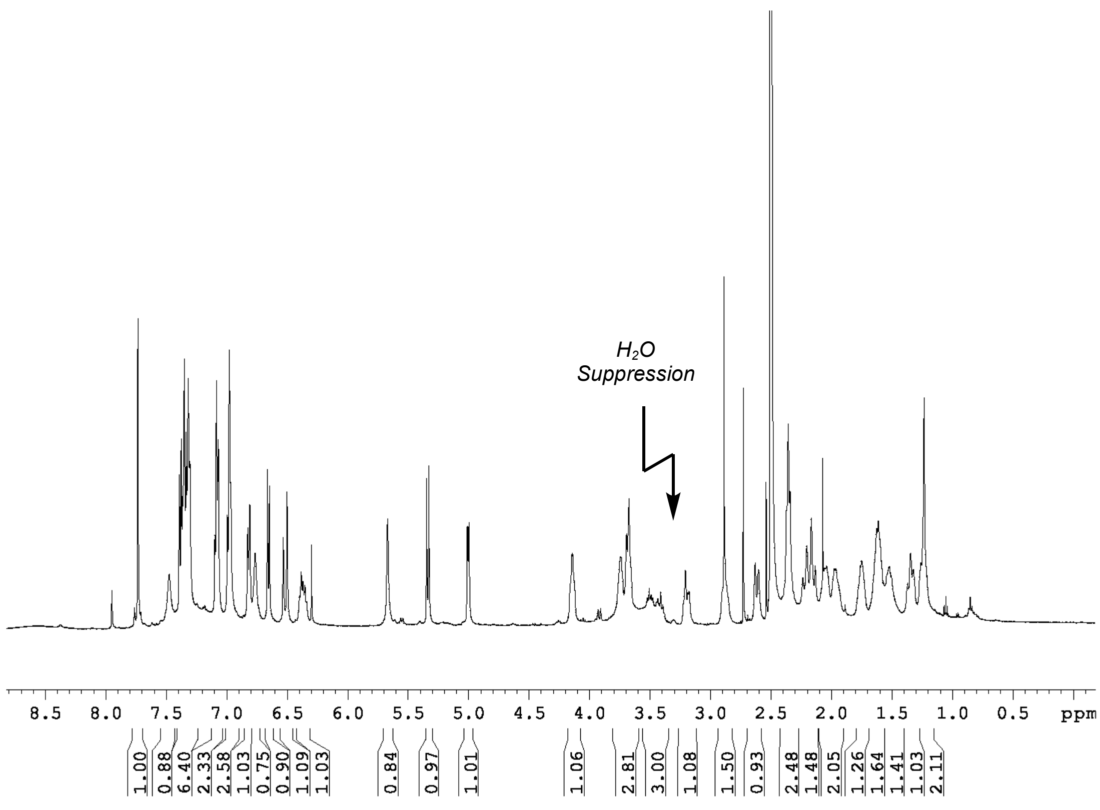

HMBC
20
40
60
80
100
120
140
160
180
12
11
10
9
8
7
6
5
4
3
2
1
ppm


NOESY
1
2
3
4
5
6
7
8
9
10
11
12
12
11
10
9
8
7
6
5
4
3
2
1
ppm

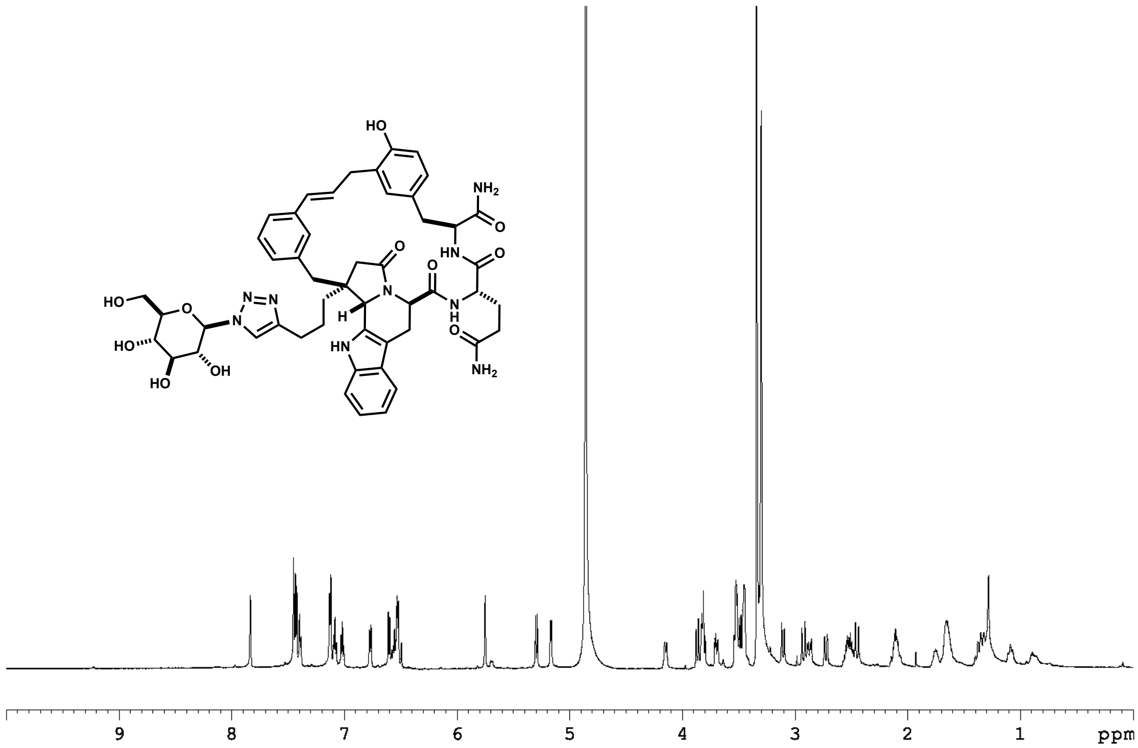
D.5. NMR Spectra – Glycosylated Macrocycles

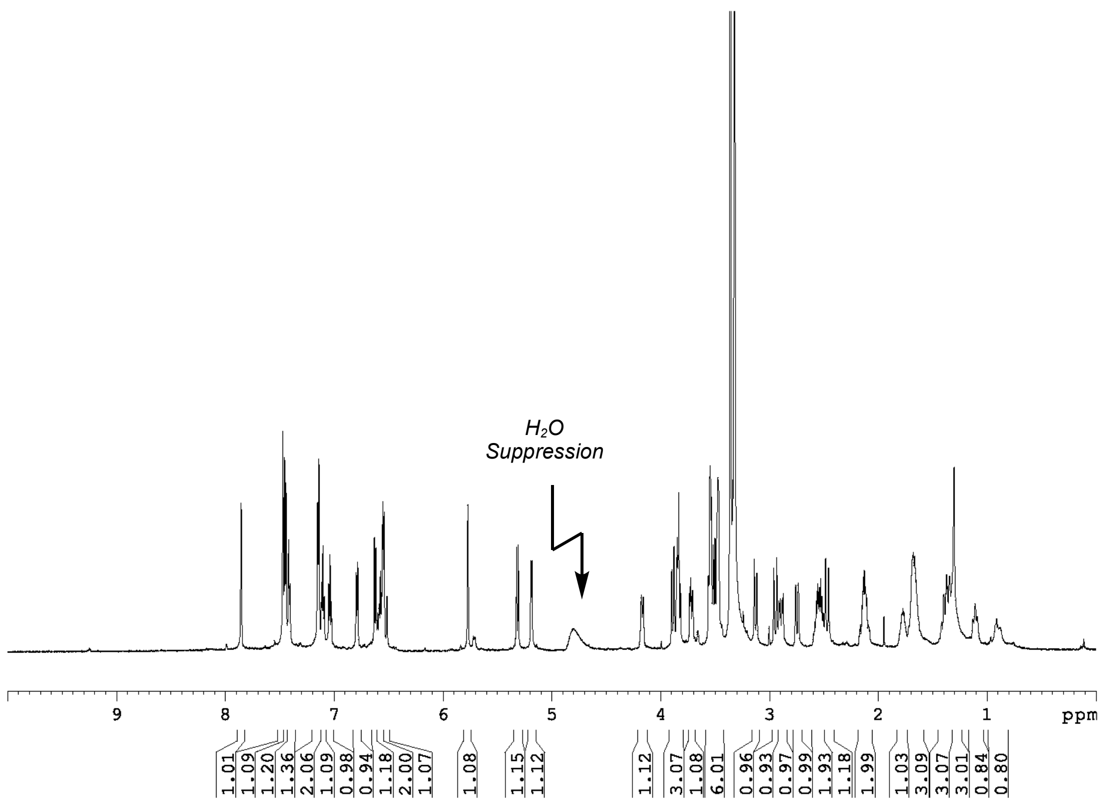
Glycone **3.6**

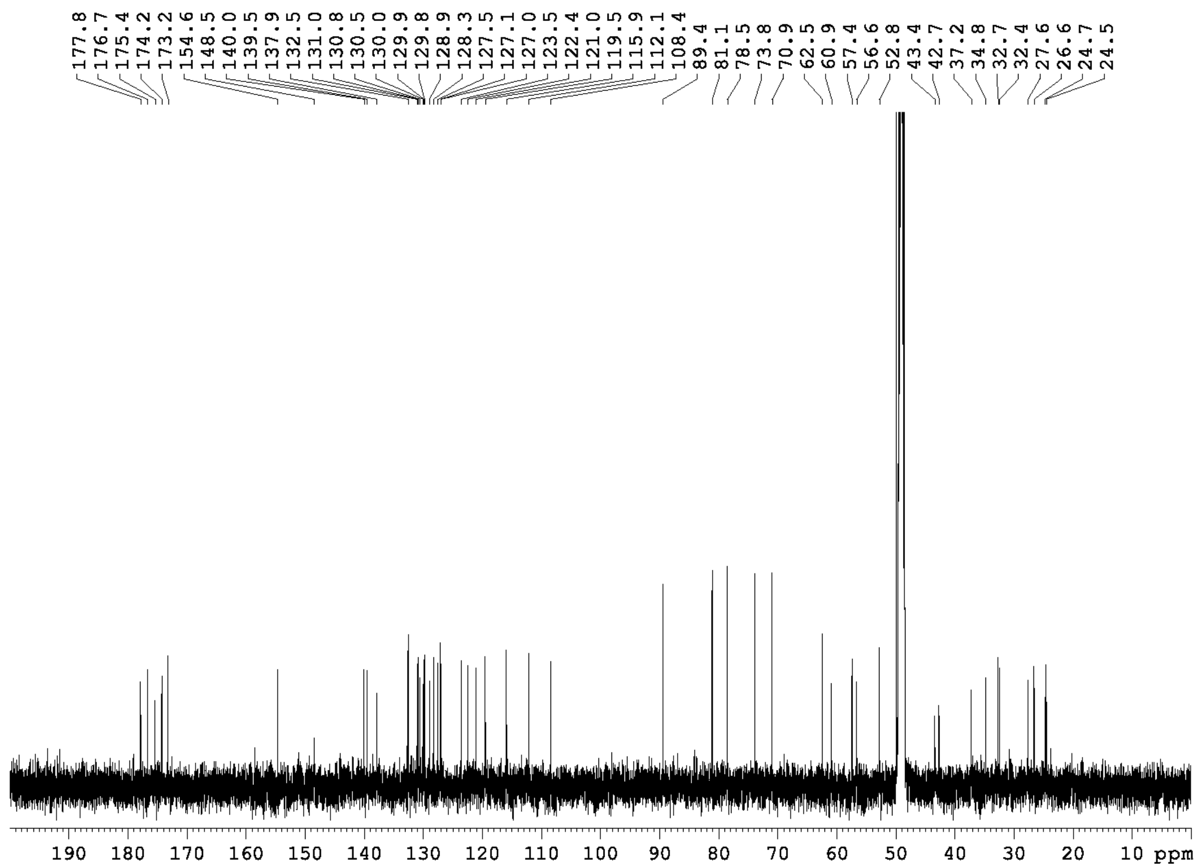




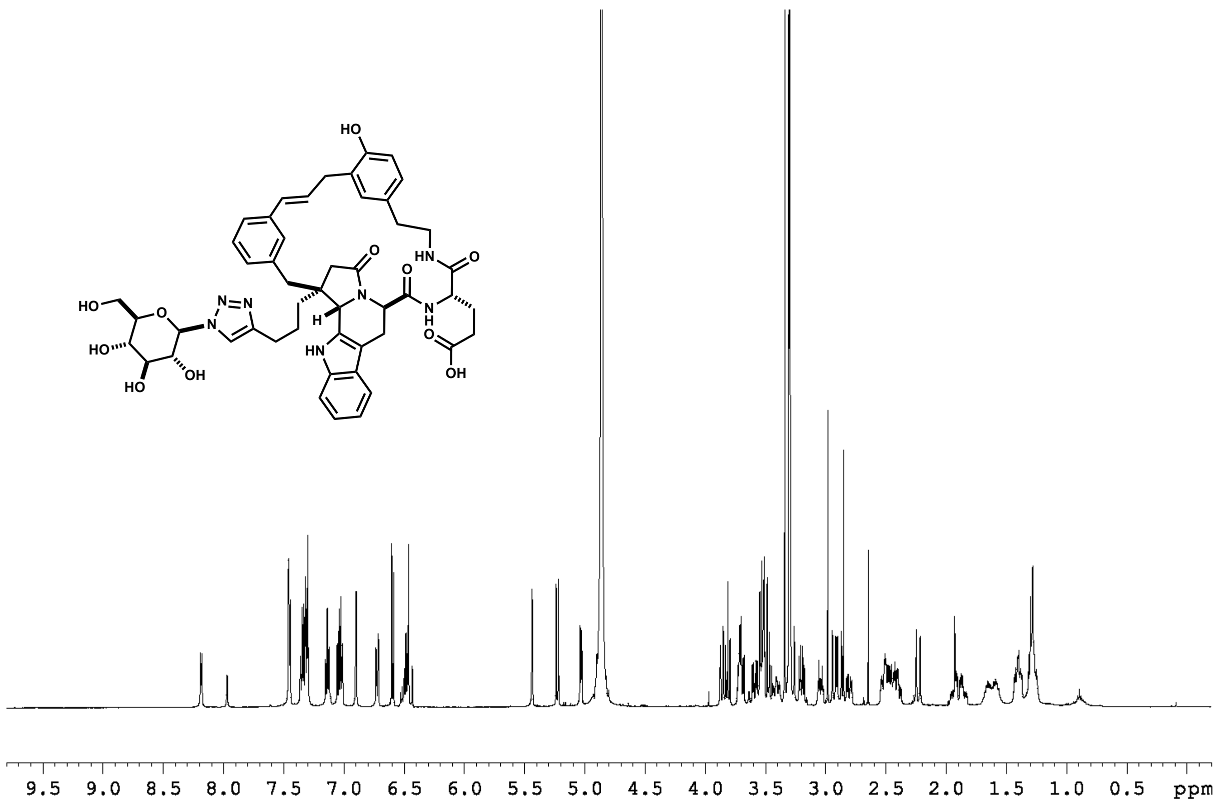
Glycone **3.58**

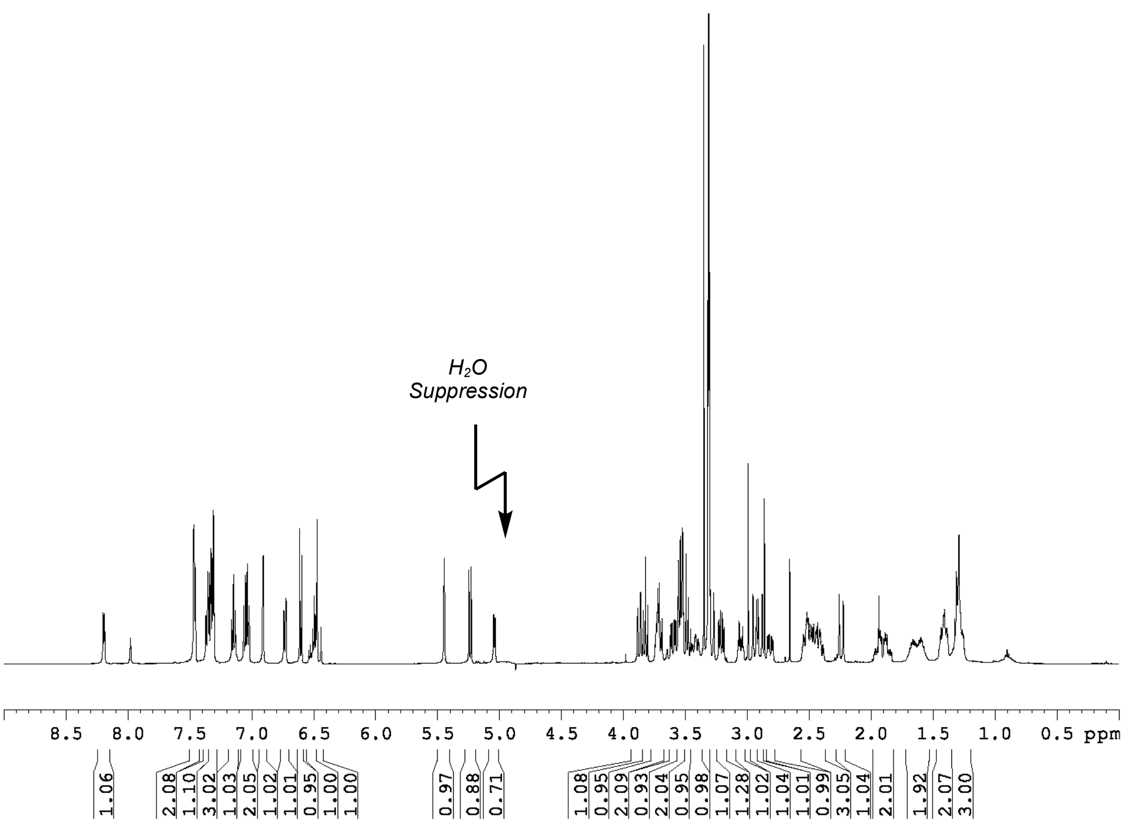

HO
NH2
O
HN
N
H
HO
N=N
HO
OH
HN
NH2
9
8
7
6
5
4
3
2
1
ppm

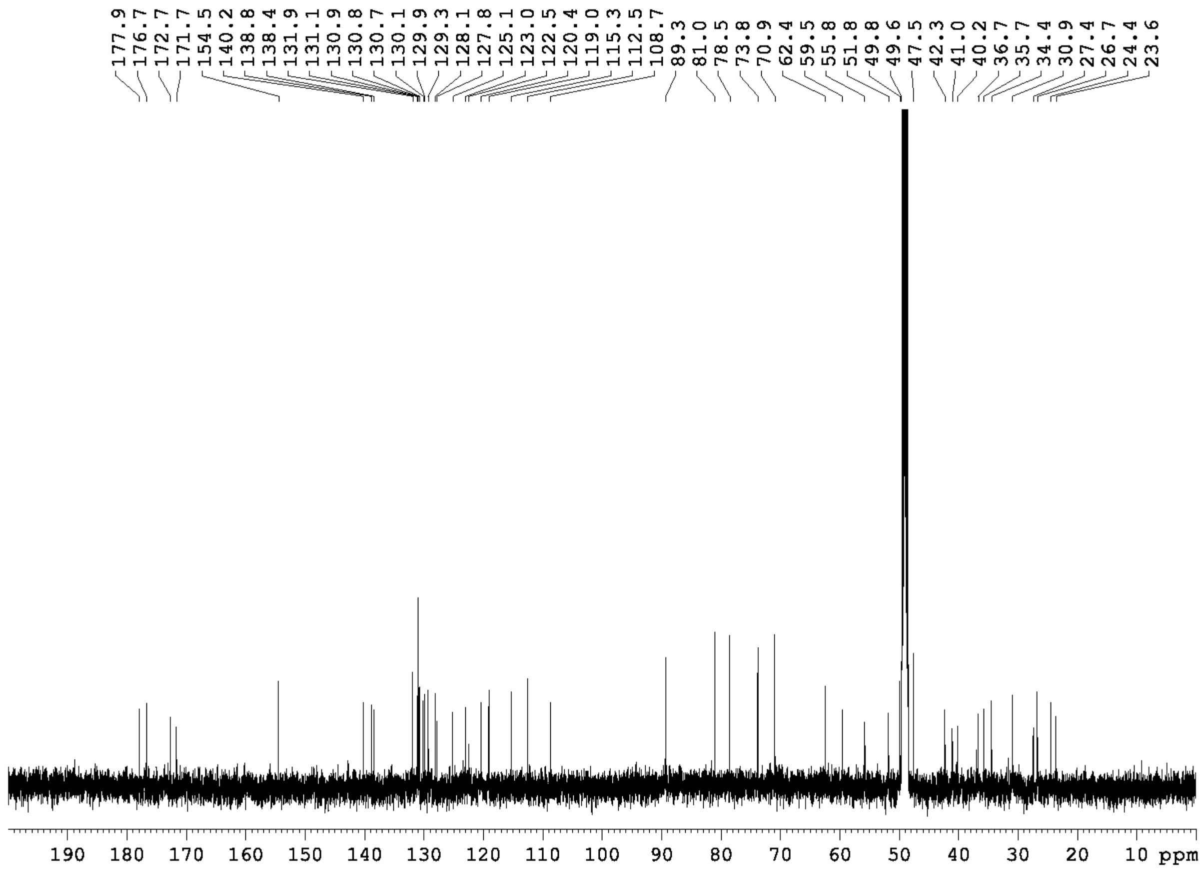

H2O
Suppression
9
8
7
6
5
4
3
2
1
ppm
1.01
1.09
1.20
1.36
2.06
1.09
0.98
0.94
1.18
2.00
1.07
1.08
1.15
1.12
1.12
3.07
1.08
6.01
0.96
0.93
0.97
0.99
1.93
1.18
1.99
1.03
3.09
3.07
3.01
0.84
0.80


177.8
176.7
175.4
174.2
173.2
154.6
148.5
140.0
139.5
137.9
132.5
131.0
130.8
130.5
130.0
129.9
129.8
128.9
128.3
127.5
127.1
127.0
123.5
122.4
121.0
119.5
115.9
112.1
108.4
89.4
81.1
78.5
73.8
70.9
62.5
60.9
57.4
56.6
52.8
43.4
42.7
37.2
34.8
32.7
32.4
27.6
26.6
24.7
24.5
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

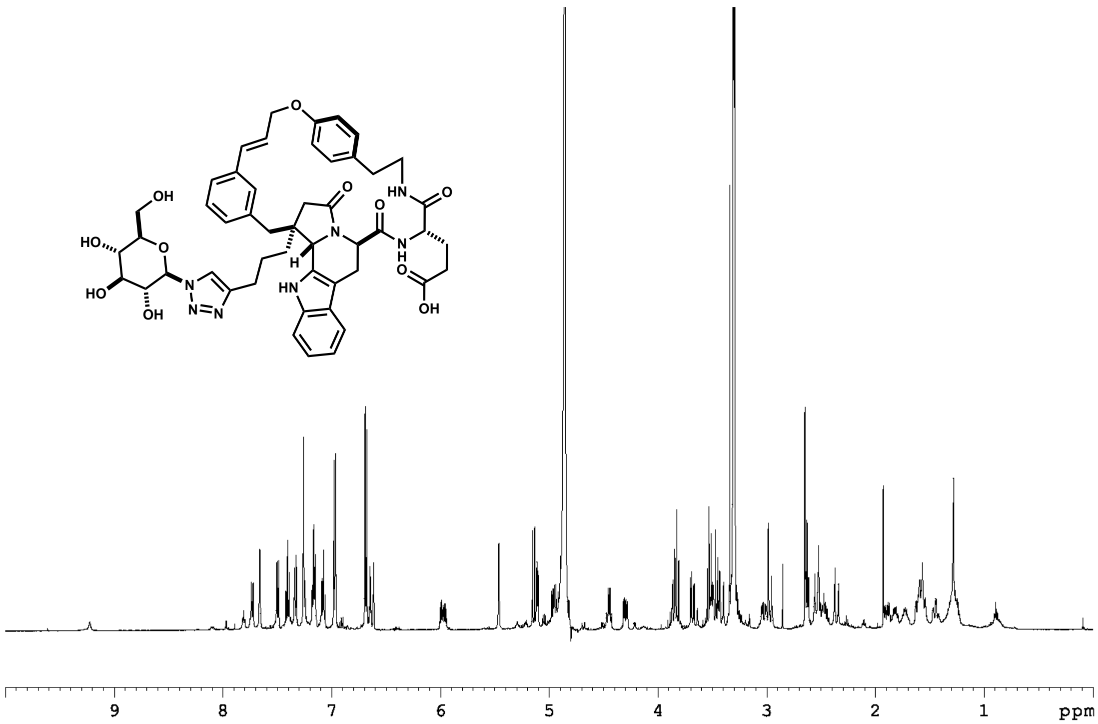
Glycone **3.59**


HO
HN
O
O
N
H
HO
O
N=N
N
HO
HO
OH
HN
O
N
H
O
OH
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

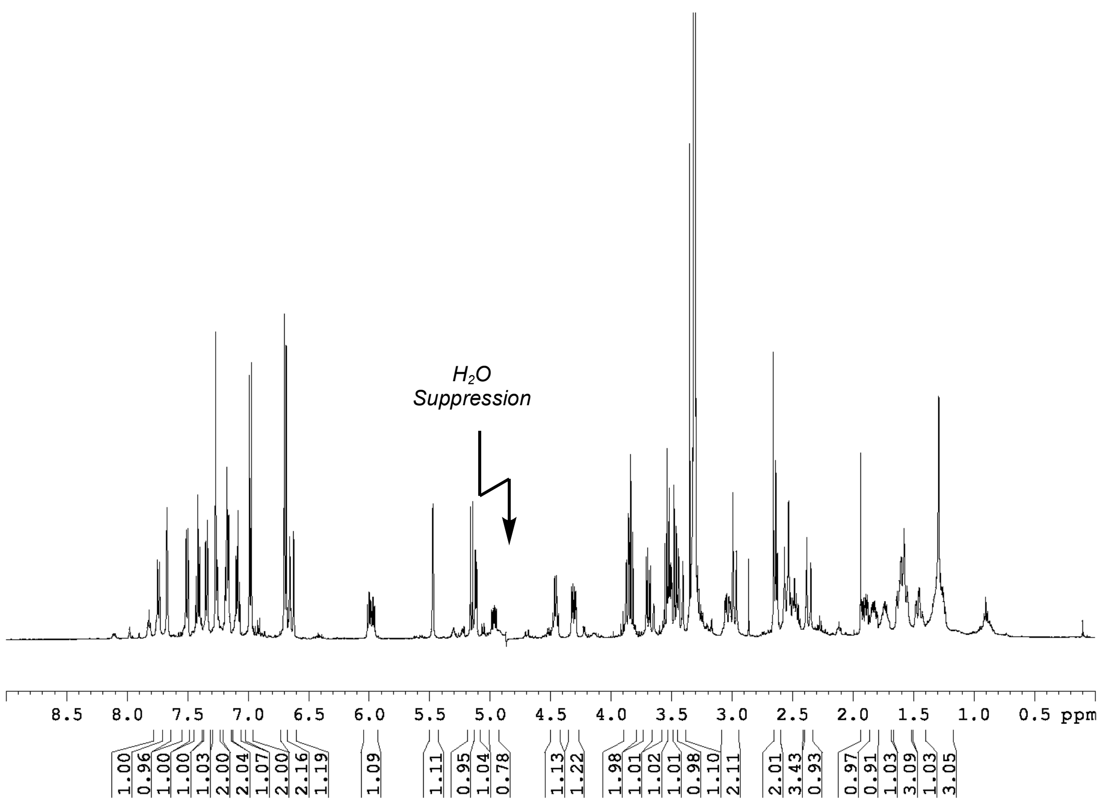

H_2O Suppression
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.06
2.08
1.10
3.02
1.03
2.05
1.02
1.01
0.95
1.00
1.00
0.97
0.88
0.71
1.08
0.95
2.09
0.93
2.04
0.95
0.98
1.07
1.28
1.02
1.04
1.01
0.99
3.05
1.04
2.01
1.92
2.07
3.00


177.9
176.7
172.7
171.7
154.5
140.2
138.8
138.4
131.9
131.1
130.9
130.8
130.7
130.1
129.9
129.3
128.1
127.8
125.1
123.0
122.5
120.4
119.0
115.3
112.5
108.7
89.3
81.0
78.5
73.8
70.9
62.4
59.5
55.8
51.8
49.8
49.6
47.5
42.3
41.0
40.2
36.7
35.7
34.4
30.9
27.4
26.7
24.4
23.6
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

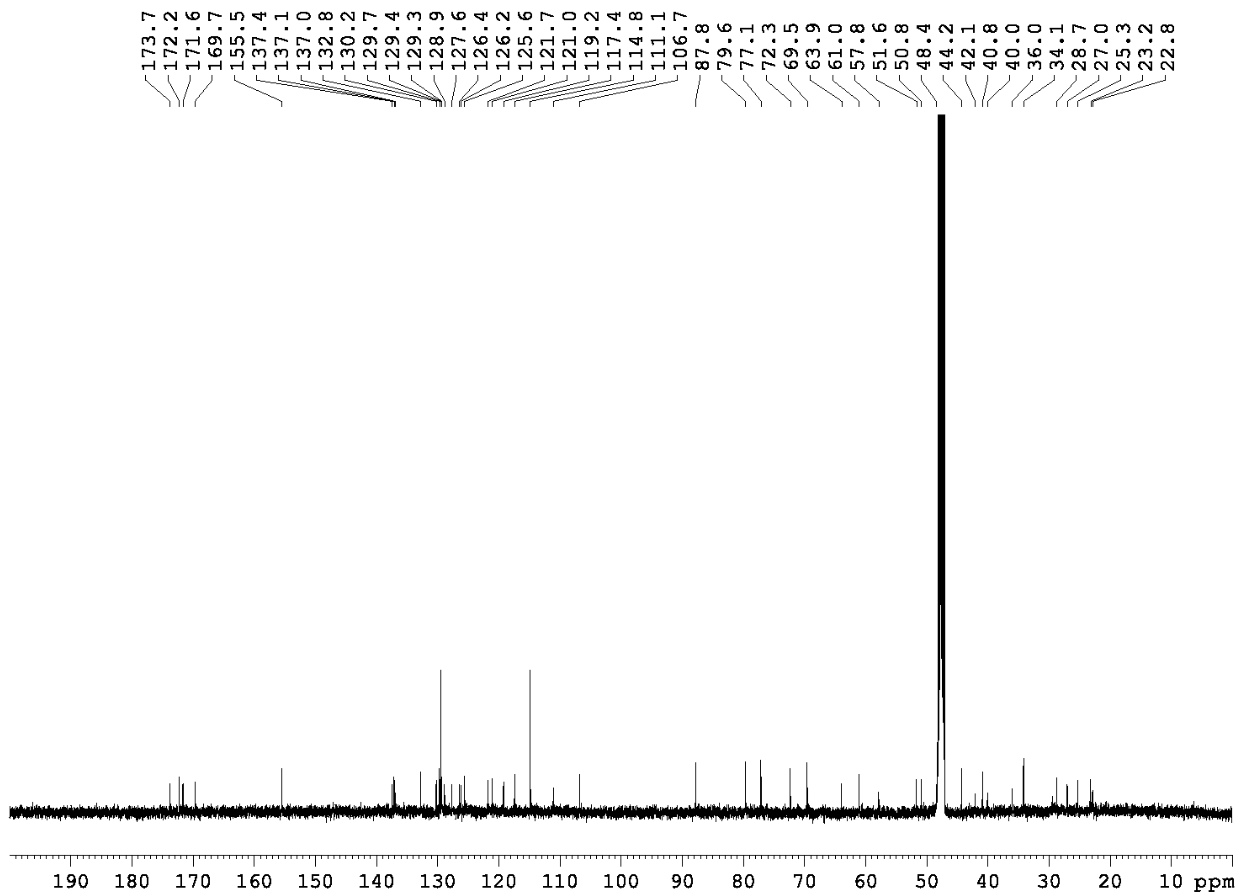
Glycone **3.60**



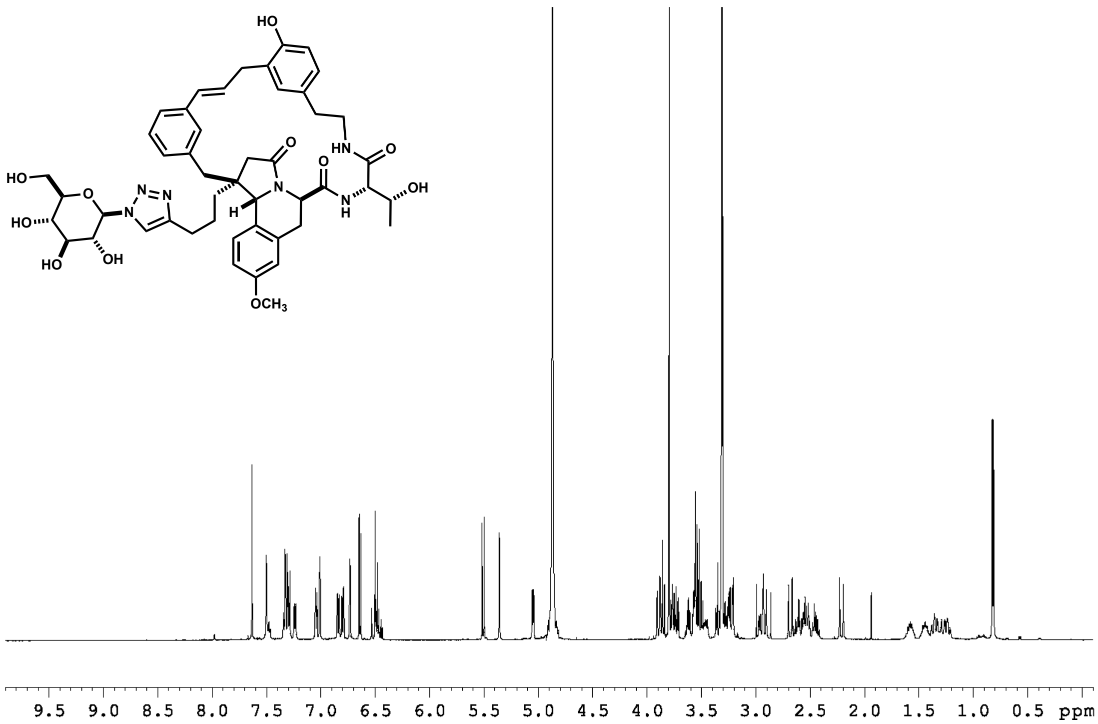
OH
HO
HO
OH
O
N
N
N
O
HN
O
N
H
HN
O
O
NH
O
HN
O
O
OH
9 8 7 6 5 4 3 2 1 ppm

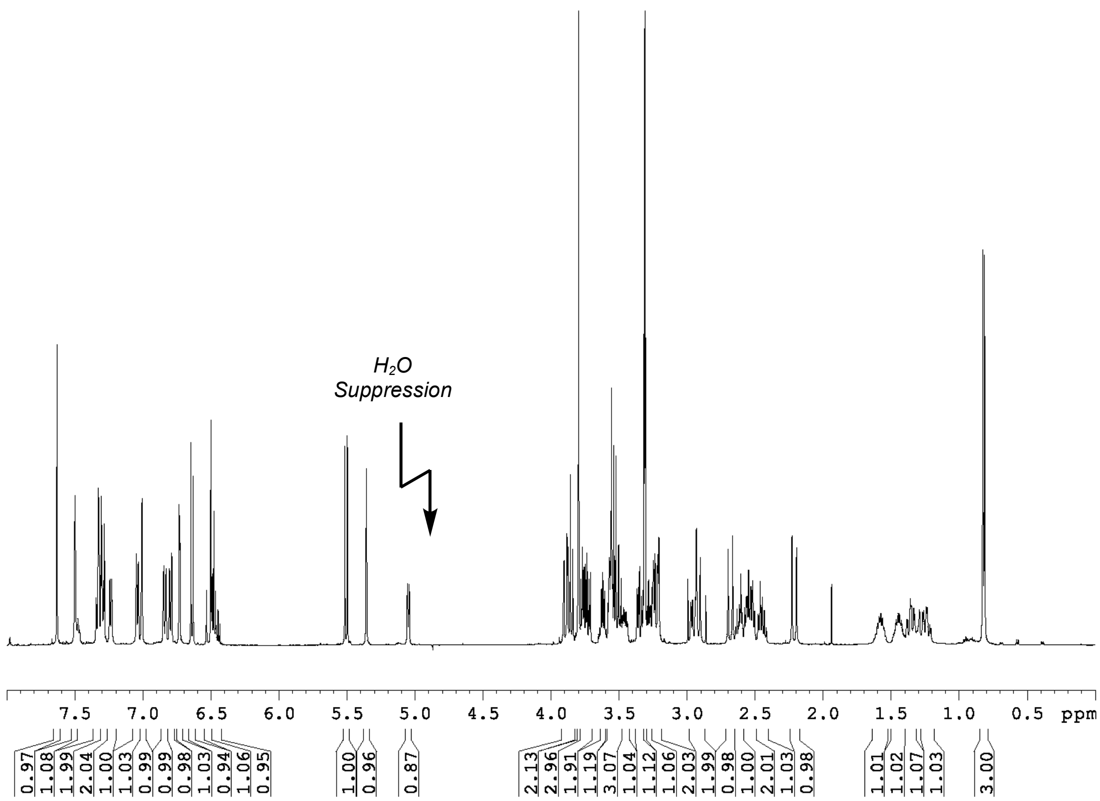


H_2O
Suppression
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 0.96 1.00 1.00 1.03 2.00 2.04 1.07 2.00 2.16 1.19 1.09 1.11 0.95 1.04 0.78 1.13 1.22 1.98 1.01 1.02 1.01 0.98 1.10 2.11 2.01 3.43 0.93 0.97 0.91 1.03 3.09 1.03 3.05


173.7
172.2
171.6
169.7
155.5
137.4
137.1
137.0
132.8
130.2
129.7
129.4
129.3
128.9
127.6
126.4
126.2
125.6
121.7
121.0
119.2
117.4
114.8
111.1
106.7
87.8
79.6
77.1
72.3
69.5
63.9
61.0
57.8
51.6
50.8
48.4
44.2
42.1
40.8
40.0
36.0
34.1
28.7
27.0
25.3
23.2
22.8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Glycone **3.62**


HO
HN
O
O
HO
O
N
N=N
N
O
OH
HO
N
H
HO
OH
H
HO
OH
OCH3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


H_2O Suppression
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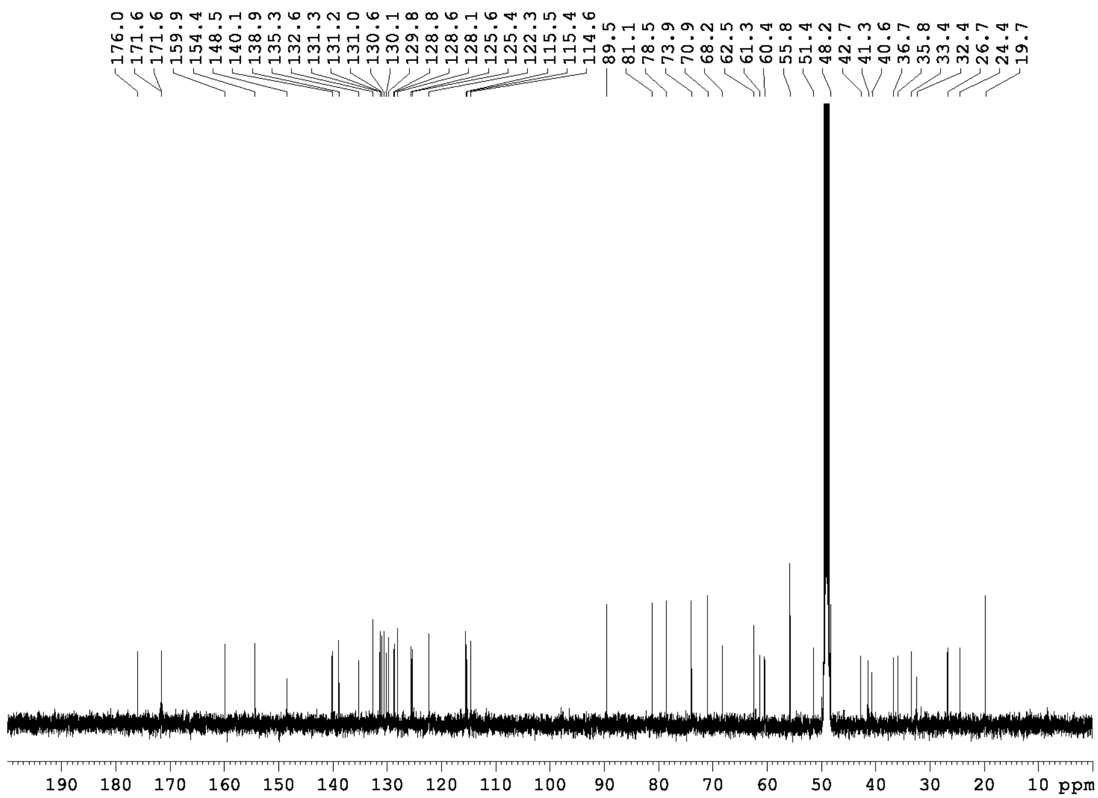
0.97 1.08 1.99 2.04 1.00 1.03 0.99 0.99 0.98 1.03 0.94 1.06 0.95
1.00 0.96 0.87
2.13 2.96 1.91 1.19 3.07 1.04 1.12 1.06 2.03 1.99 0.98 1.00 2.01 1.03 0.98
1.01 1.02 1.07 1.03 3.00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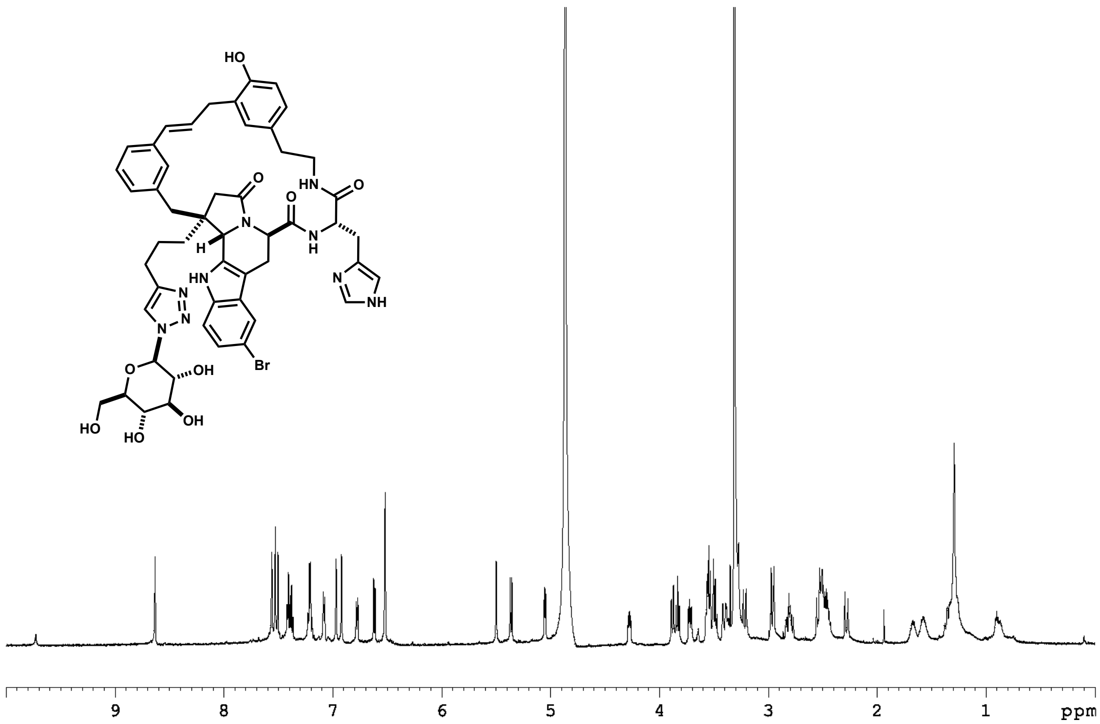
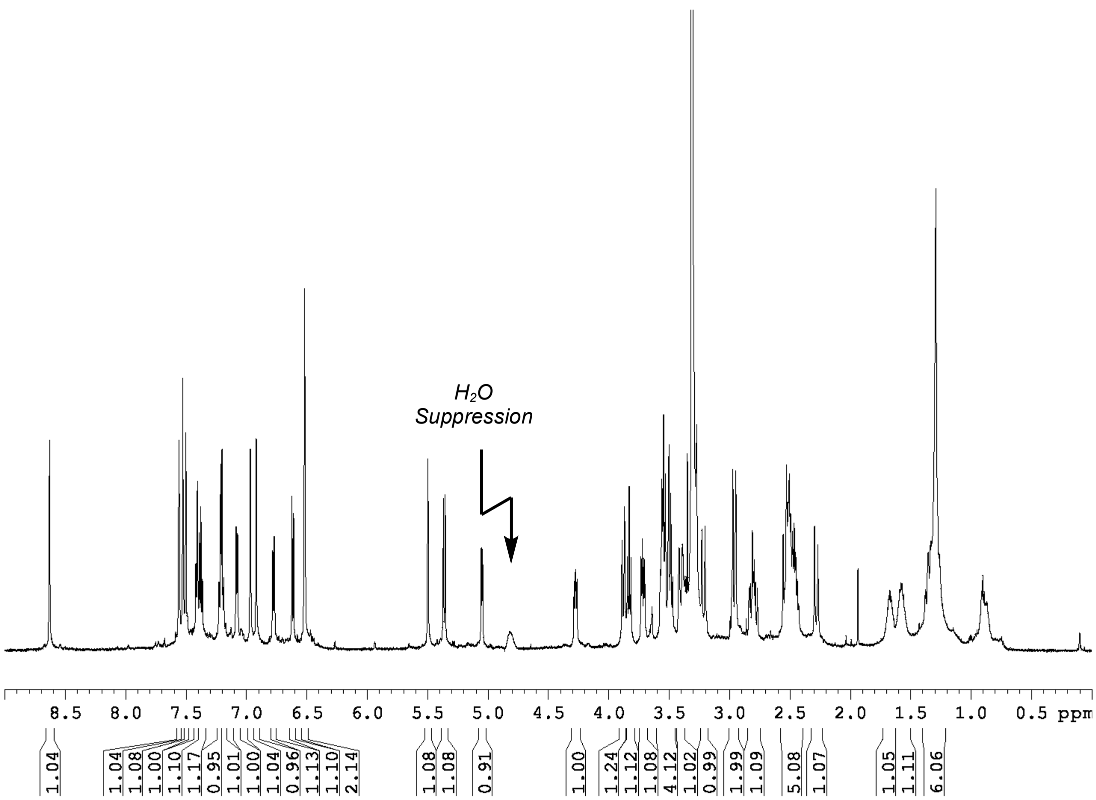
171.6
171.6
159.9
154.4
148.5
140.1
138.9
135.3
132.6
131.3
131.2
131.0
130.6
130.1
129.8
128.8
128.6
128.1
125.6
125.4
122.3
115.5
115.4
114.6
89.5
81.1
78.5
73.9
70.9
68.2
62.5
61.3
60.4
55.8
51.4
48.2
42.7
41.3
40.6
36.7
35.8
33.4
32.4
26.7
24.4
19.7
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Glycone **3.61**


HO
HN
O
O
N
H
O
N
H
HN
N
N
N
N
NH
Br
O
OH
HO
HO
OH
9
8
7
6
5
4
3
2
1
ppm


H_2O
Suppression
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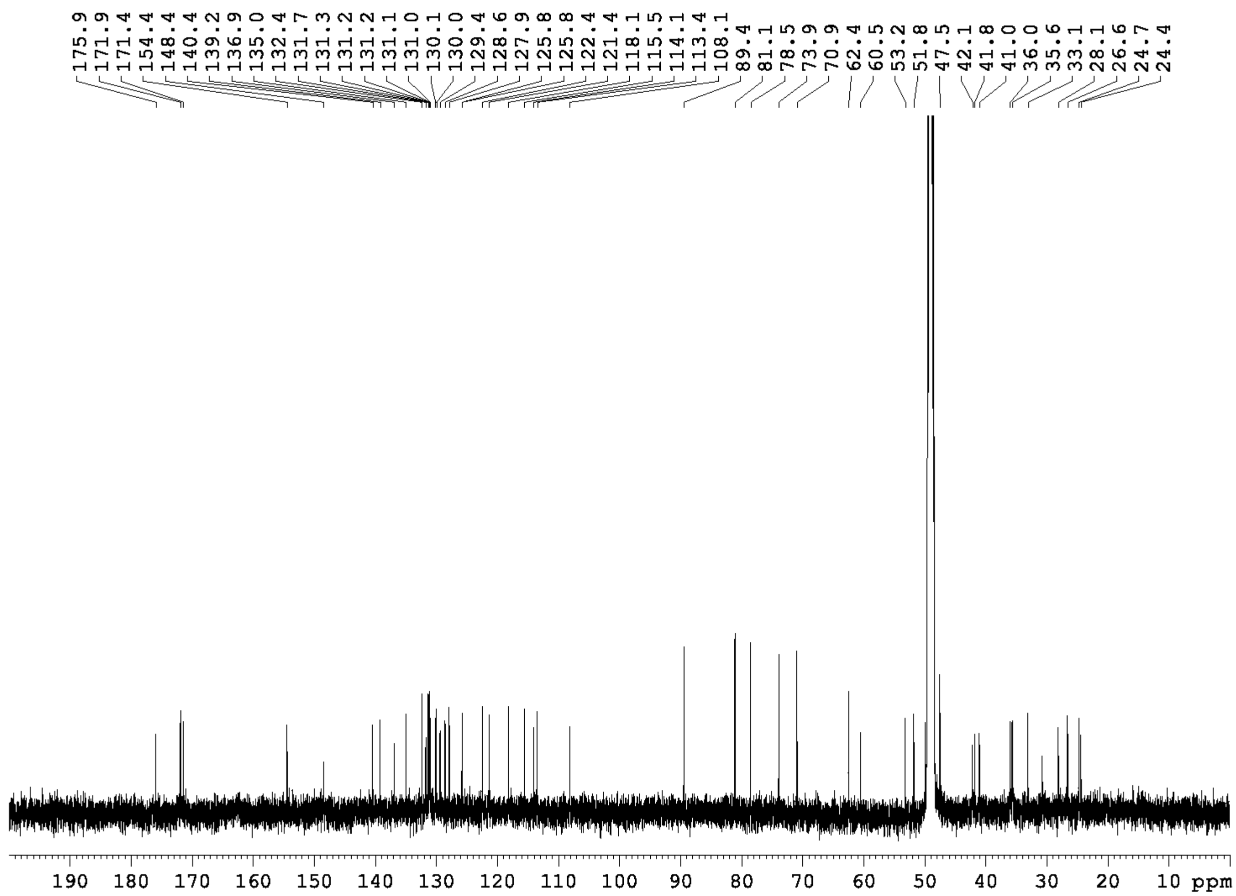
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm
1.04
1.04
1.08
1.00
1.10
1.17
0.95
1.01
1.00
1.04
0.96
1.13
1.10
2.14
1.08
1.08
0.91
1.00
1.24
1.12
1.08
4.12
1.02
0.99
1.99
1.09
5.08
1.07
1.05
1.11
6.06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171.9
171.4
154.4
148.4
140.4
139.2
136.9
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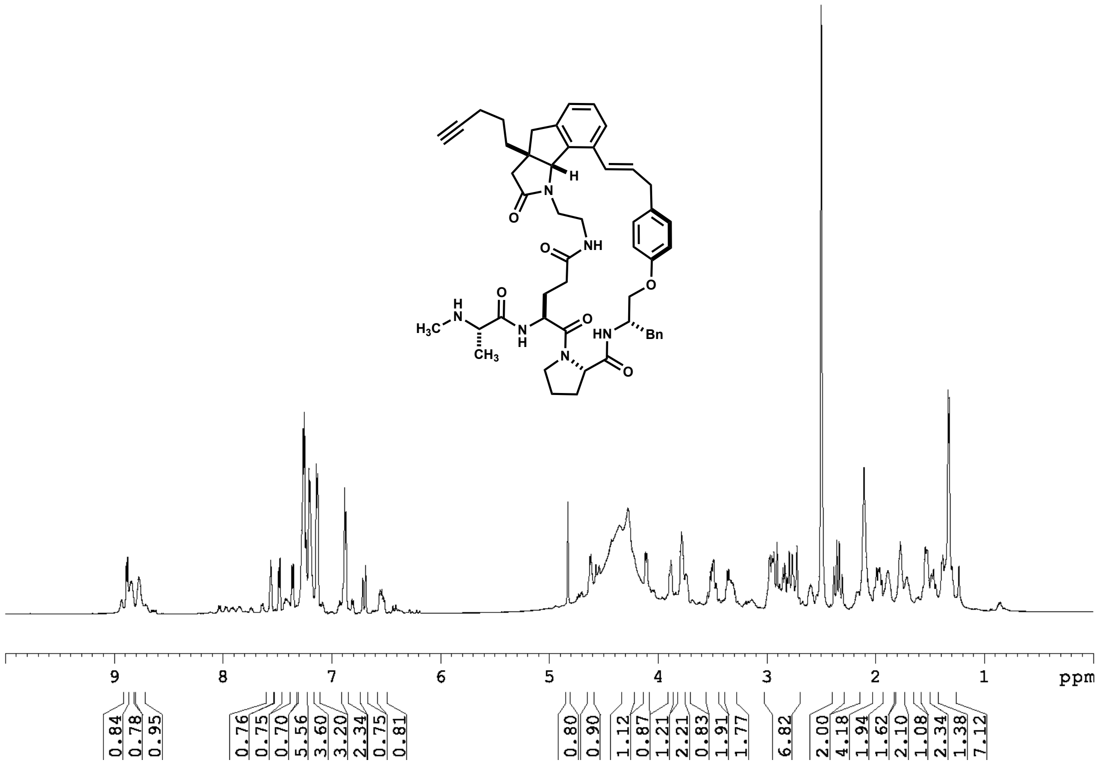
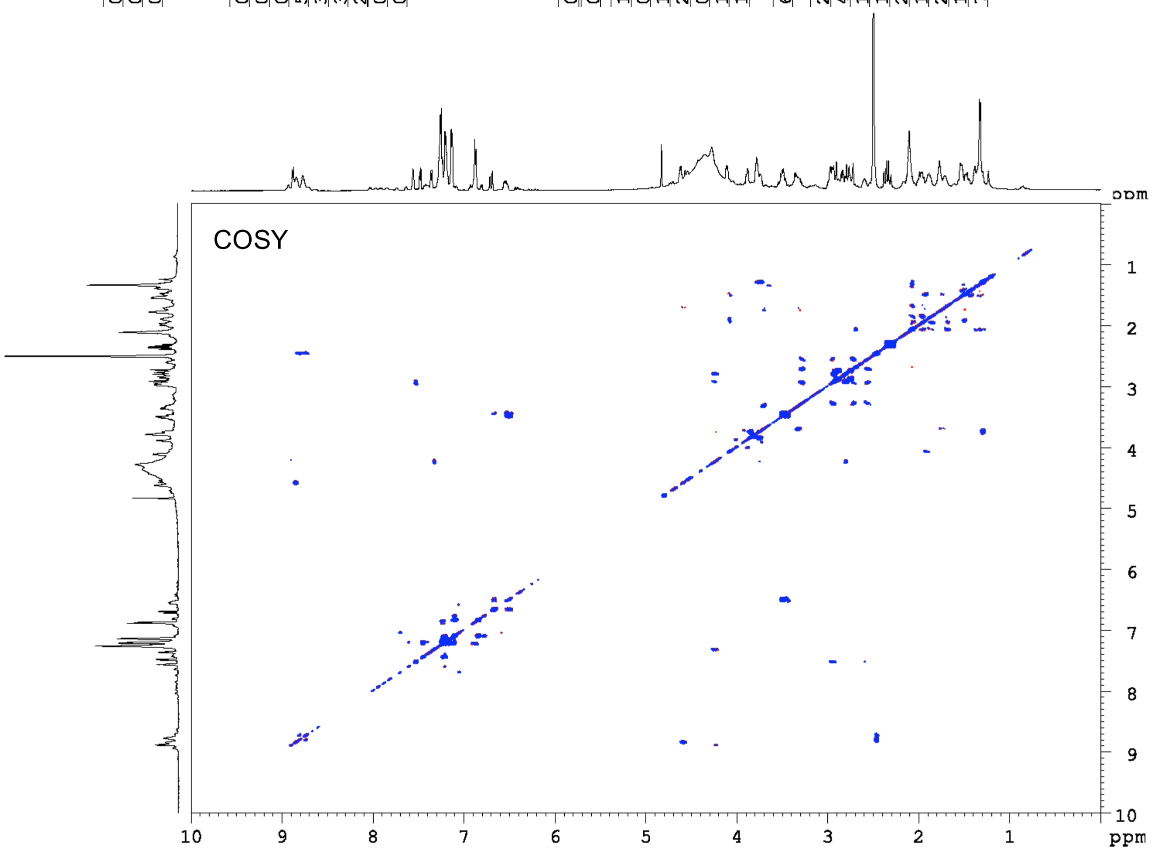
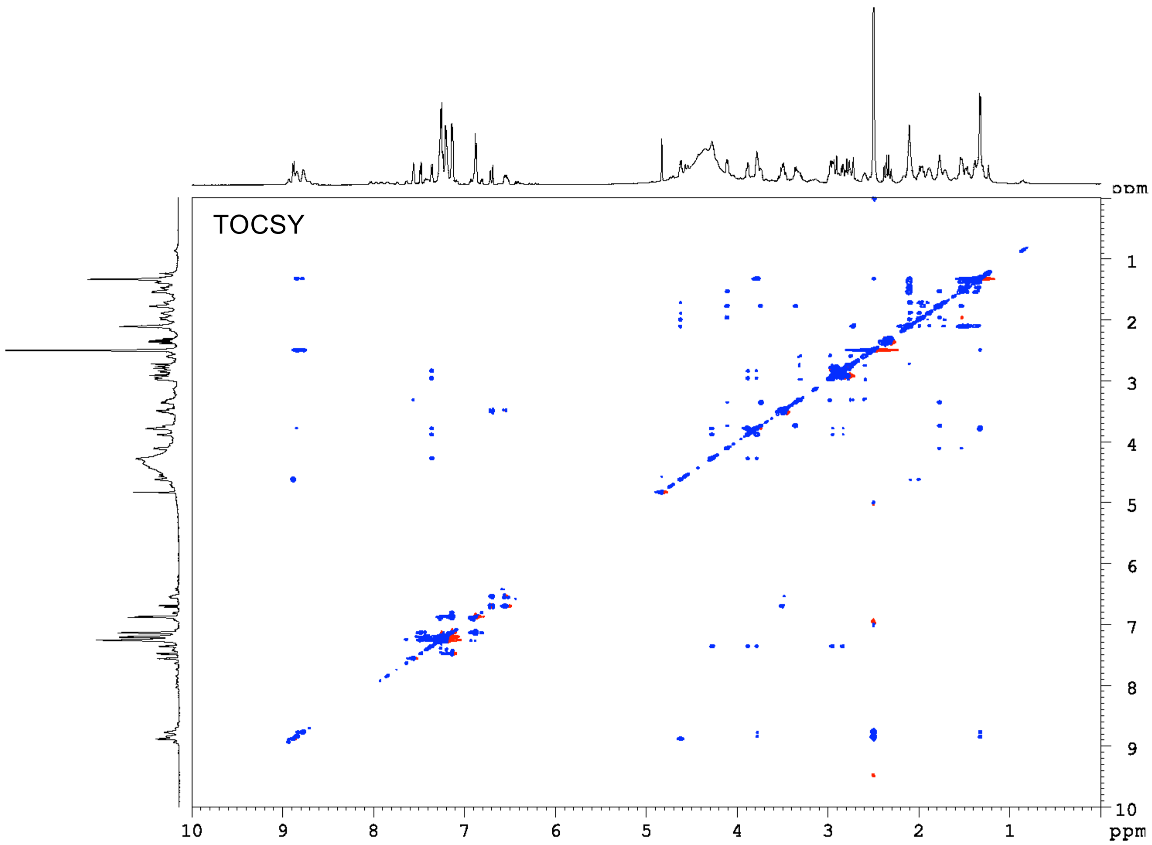
132.4
131.7
131.3
131.2
131.2
131.1
131.0
130.1
130.0
129.4
128.6
127.9
125.8
125.8
122.4
121.4
118.1
115.5
114.1
113.4
108.1
89.4
81.1
78.5
73.9
70.9
62.4
60.5
53.2
51.8
47.5
42.1
41.8
41.0
36.0
35.6
33.1
28.1
26.6
24.7
24.4
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

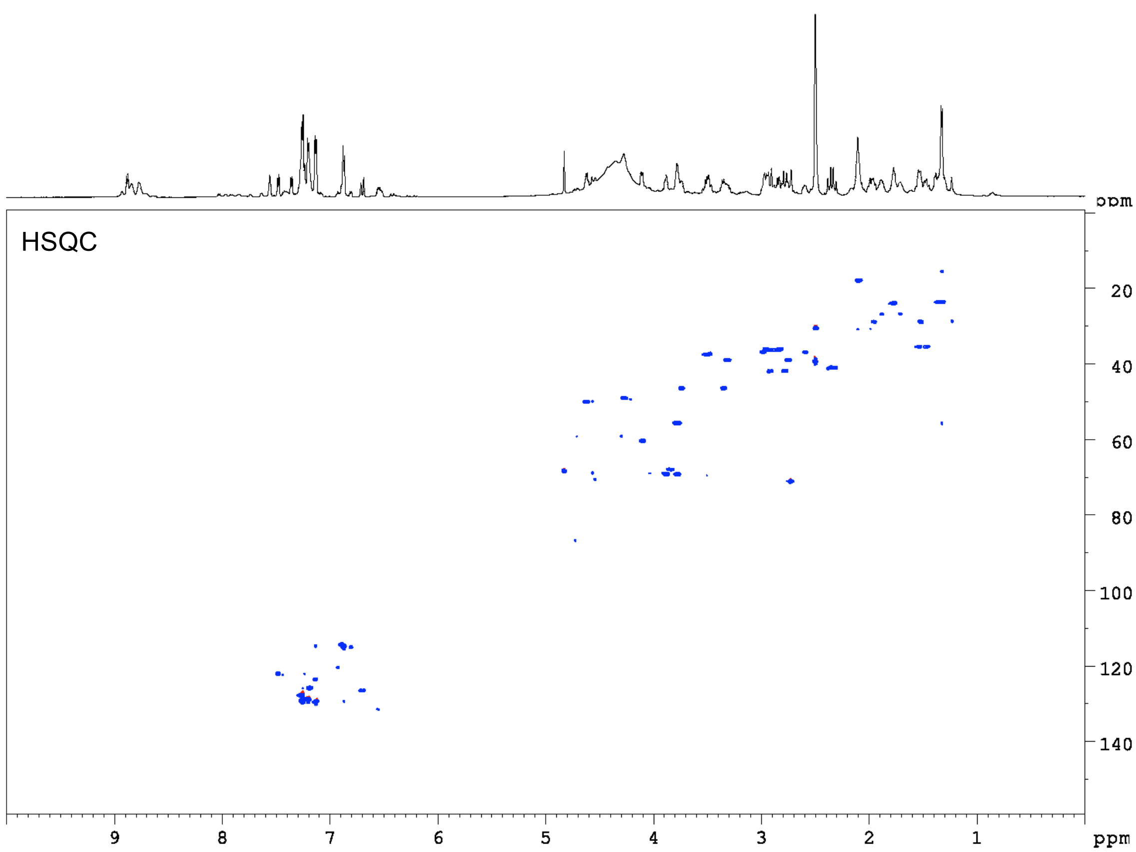
D.6. NMR Spectra – Smac Mimetic Monomers and Dimers

Macrocycle **3.64a**






TOCSY
ppm
1
2
3
4
5
6
7
8
9
10
10
9
8
7
6
5
4
3
2
1
ppm


HSQC
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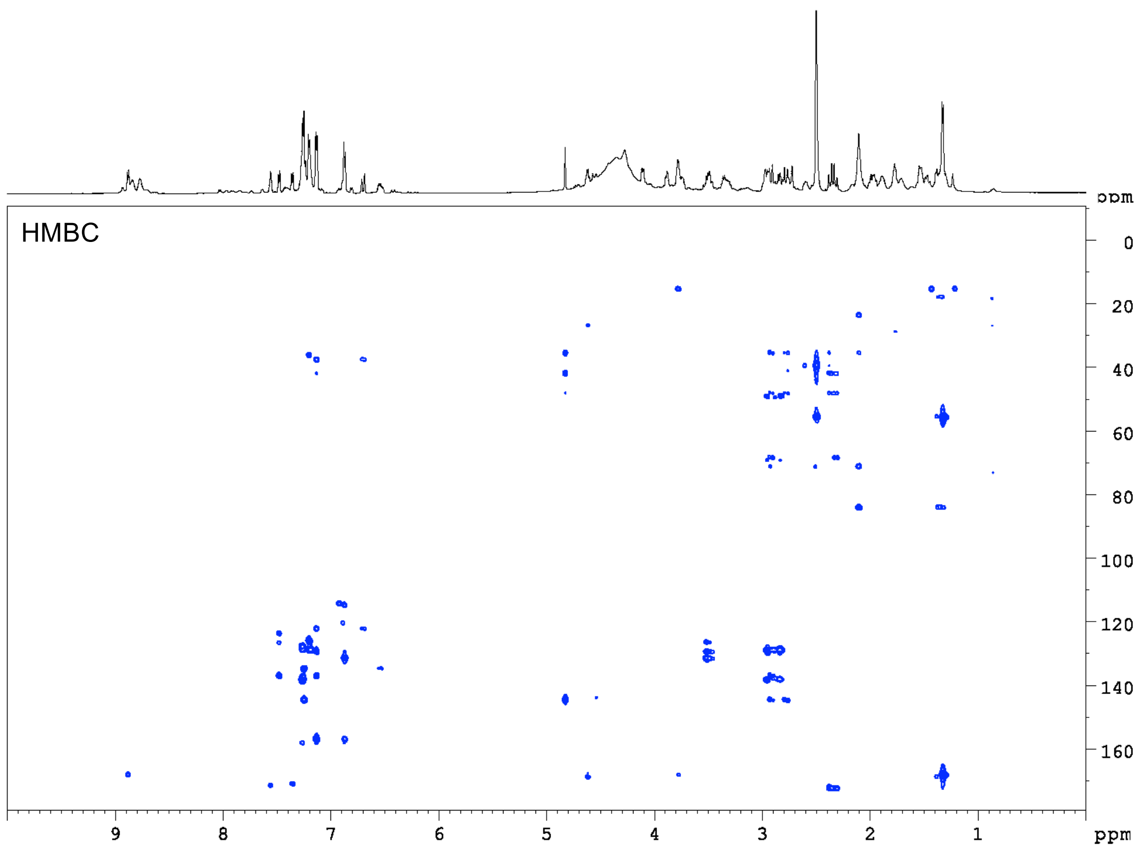
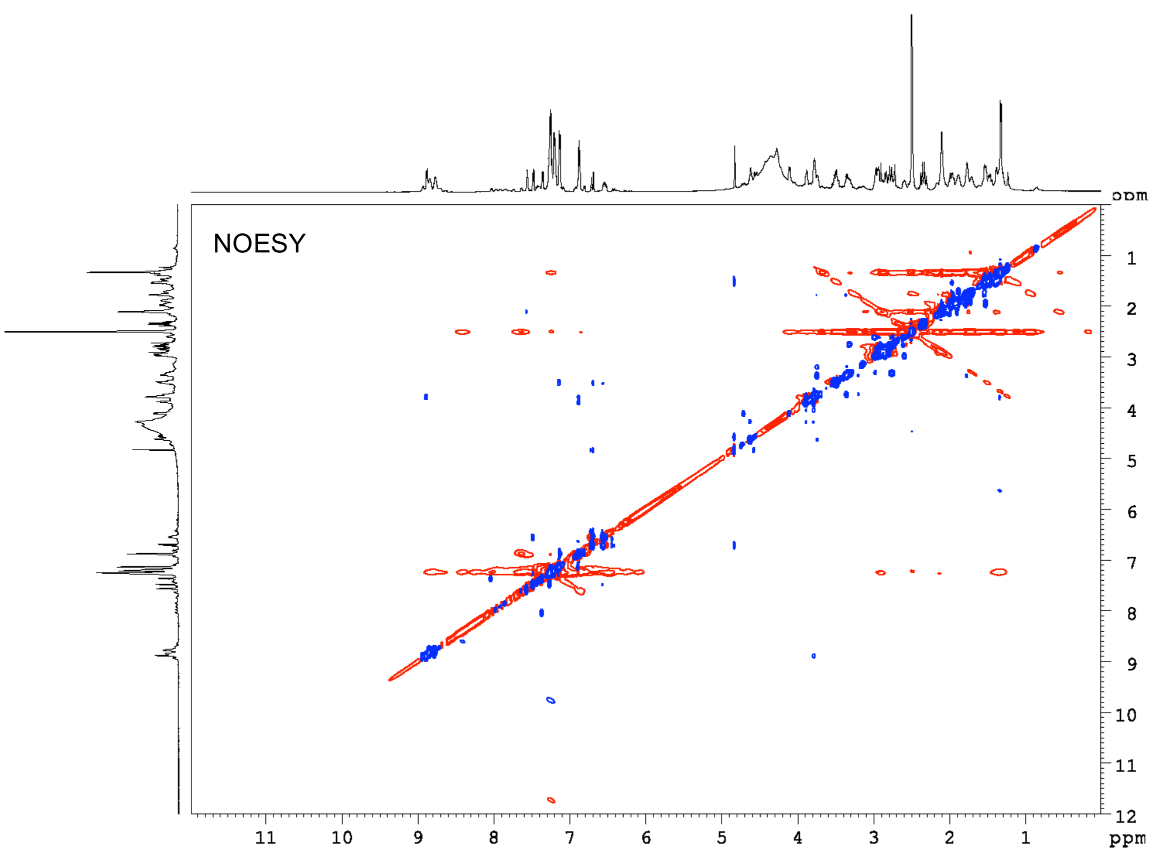
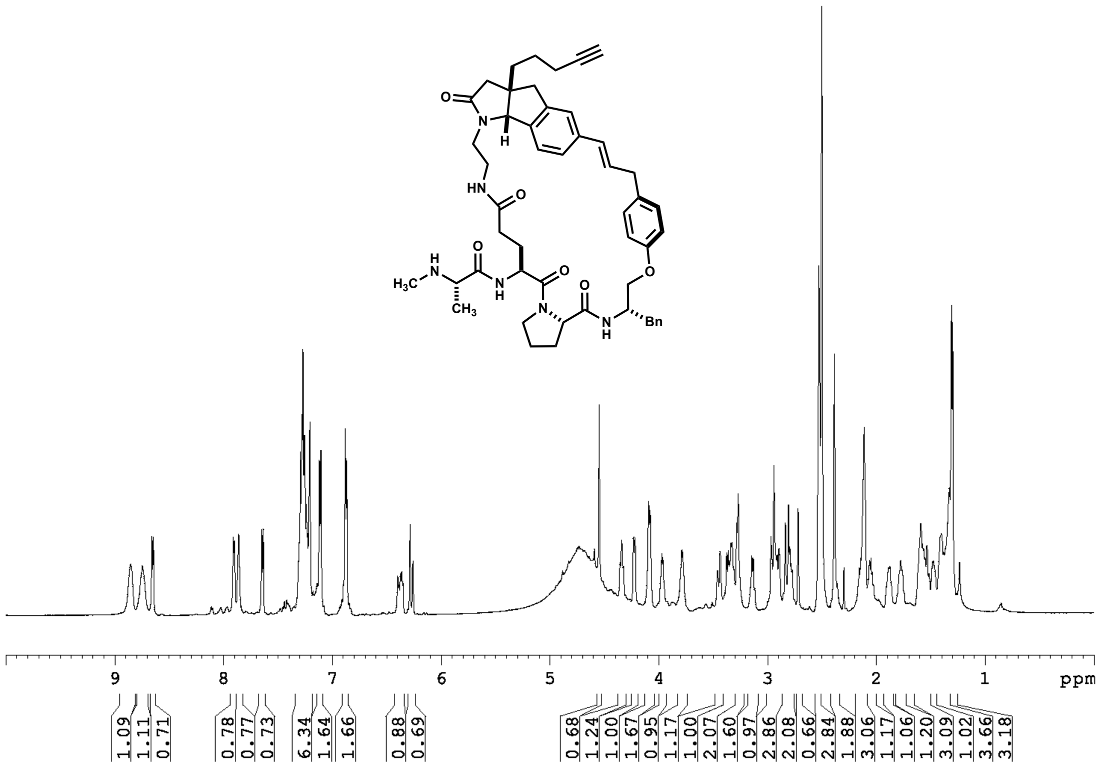
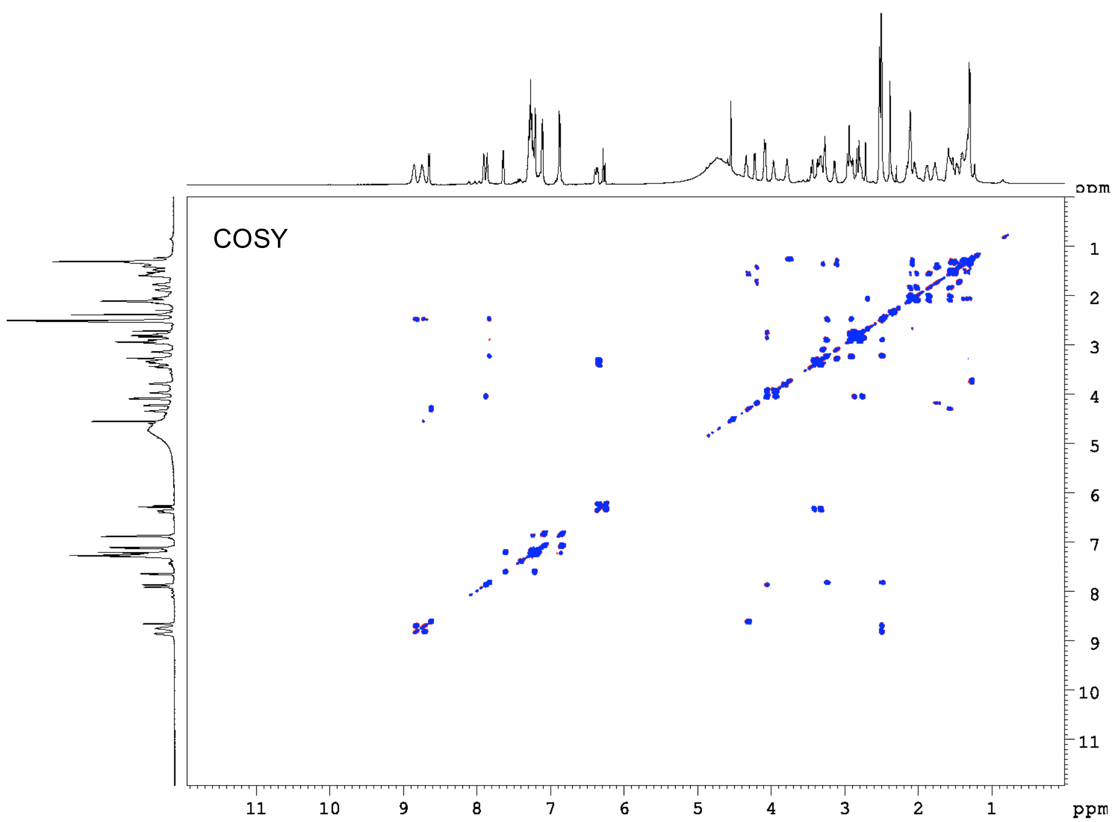
20
40
60
80
100
120
140
9
8
7
6
5
4
3
2
1
ppm

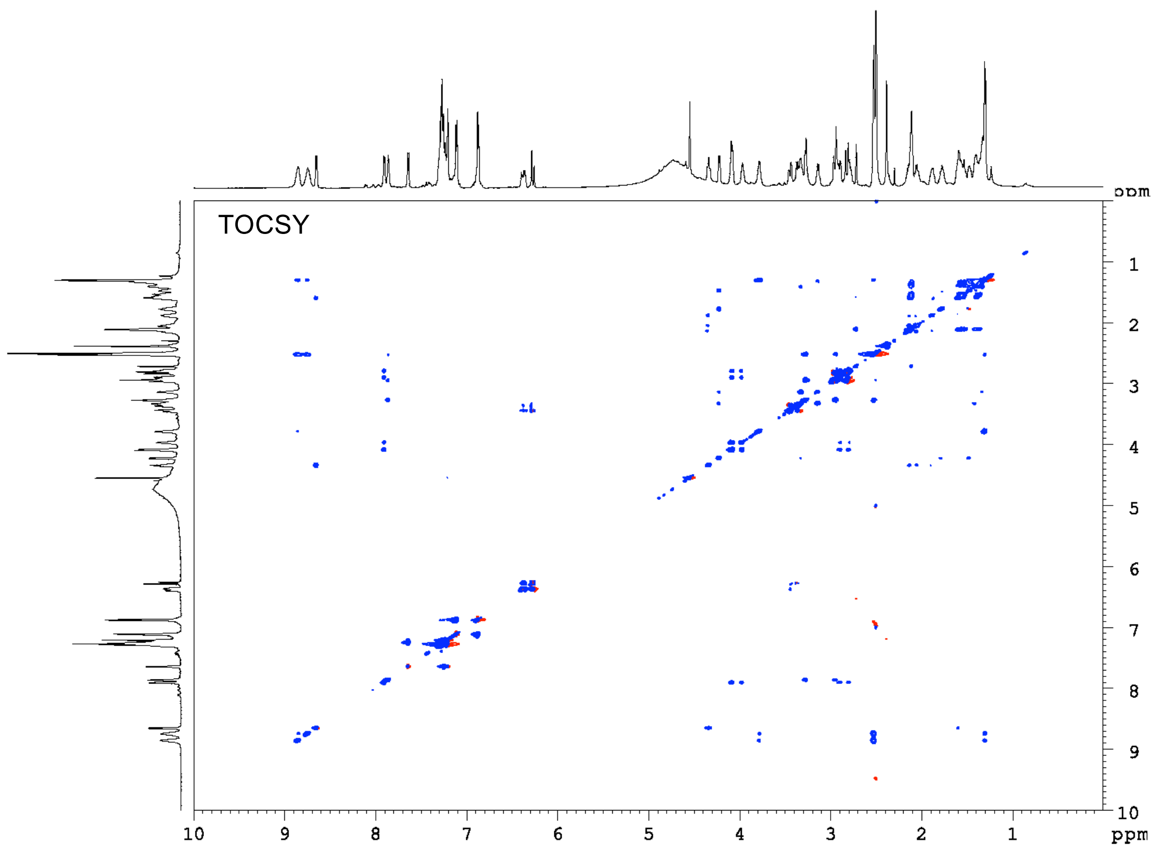

HMBC
ppm
0
20
40
60
80
100
120
140
160
9
8
7
6
5
4
3
2
1
ppm

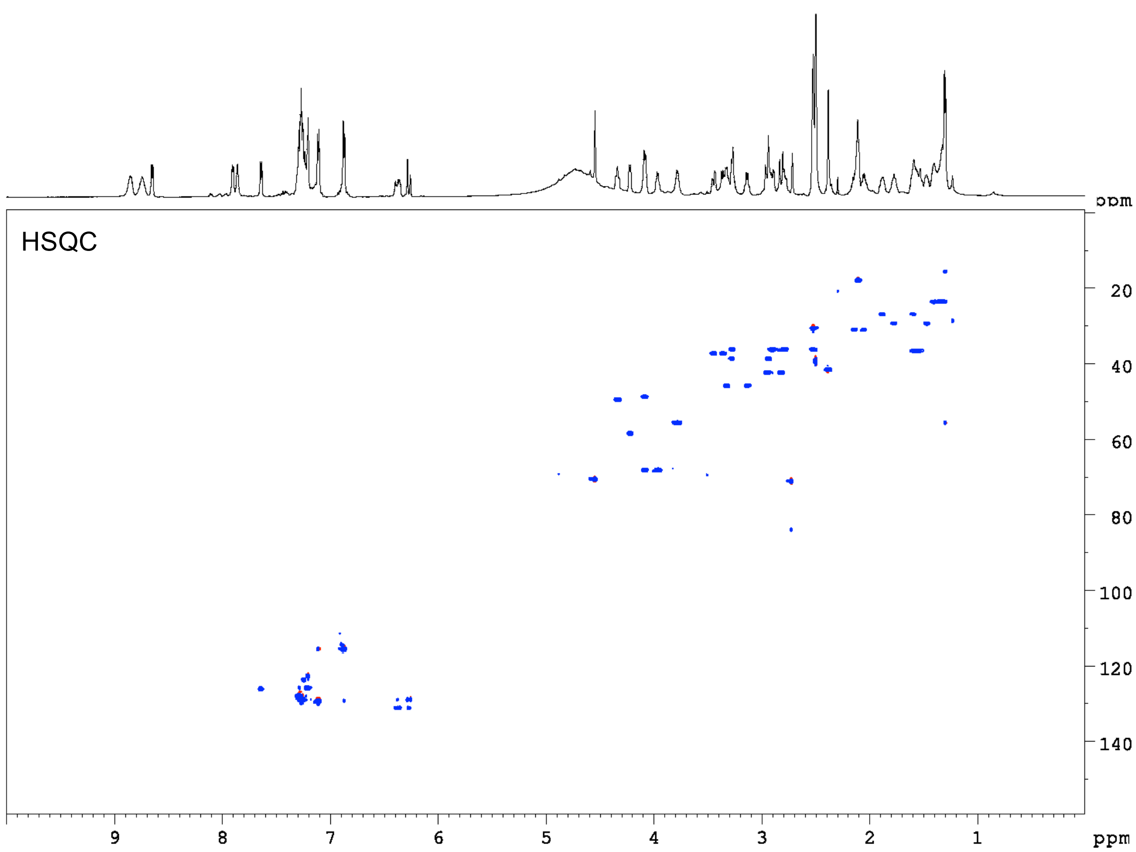

NOESY
ppm
1
2
3
4
5
6
7
8
9
10
11
12
11
10
9
8
7
6
5
4
3
2
1
ppm

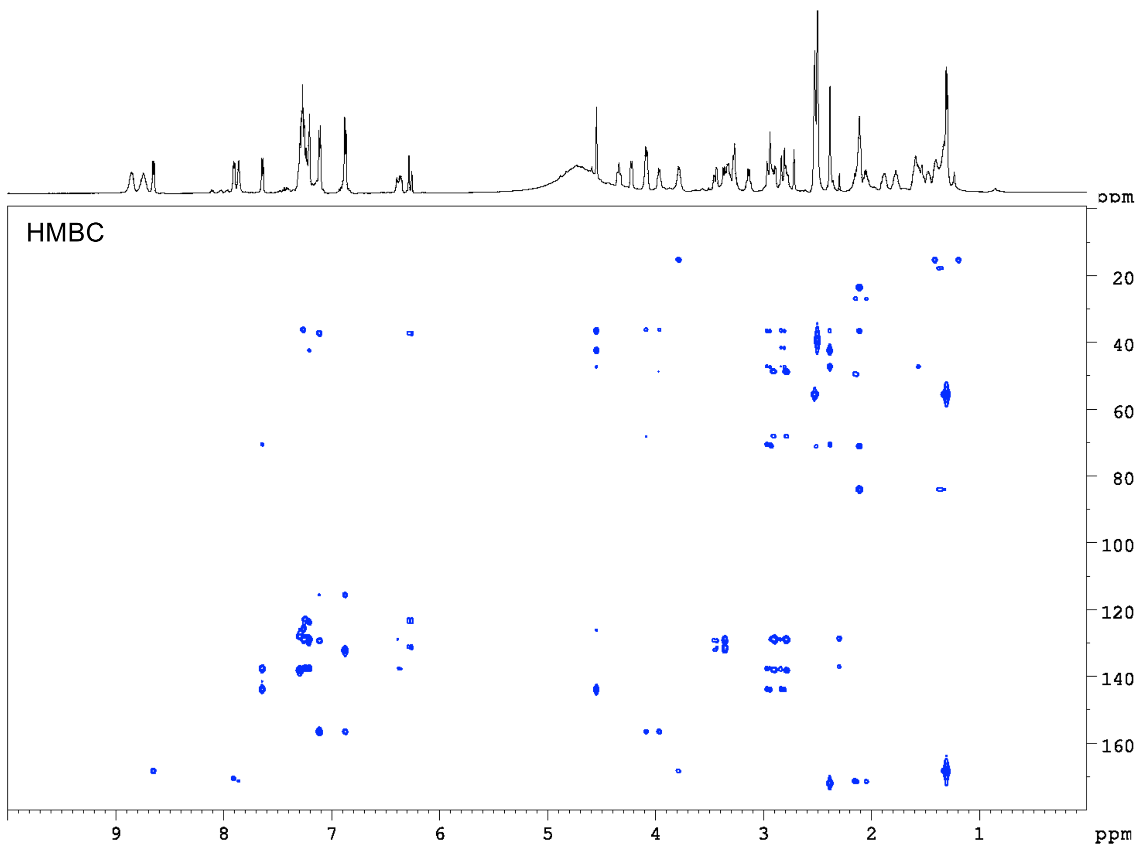
Macrocycle **3.64b**

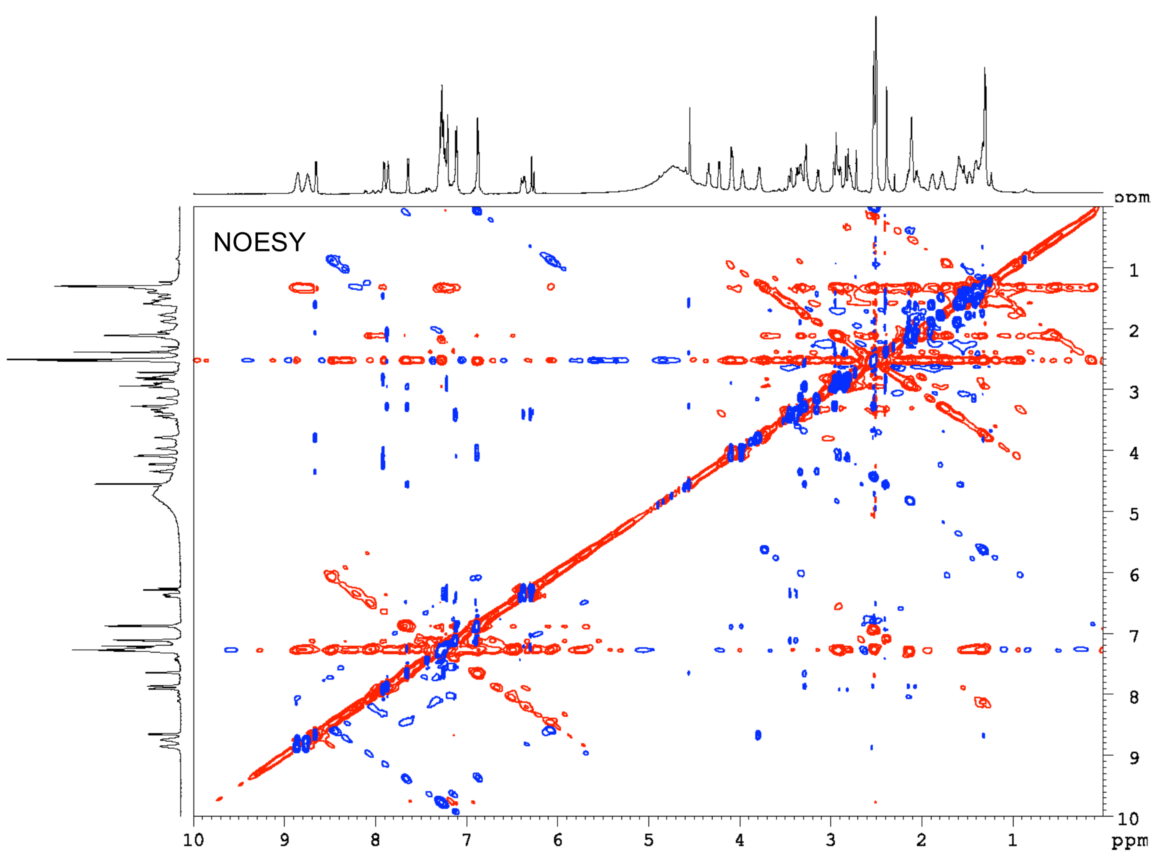




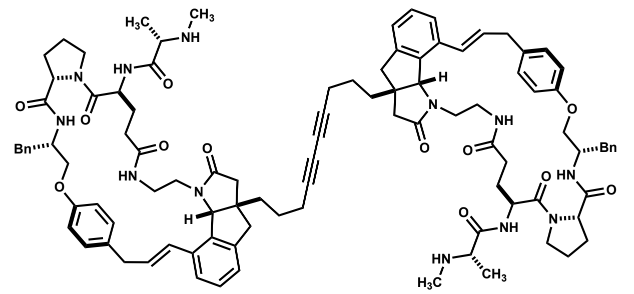

TOCSY
ppm

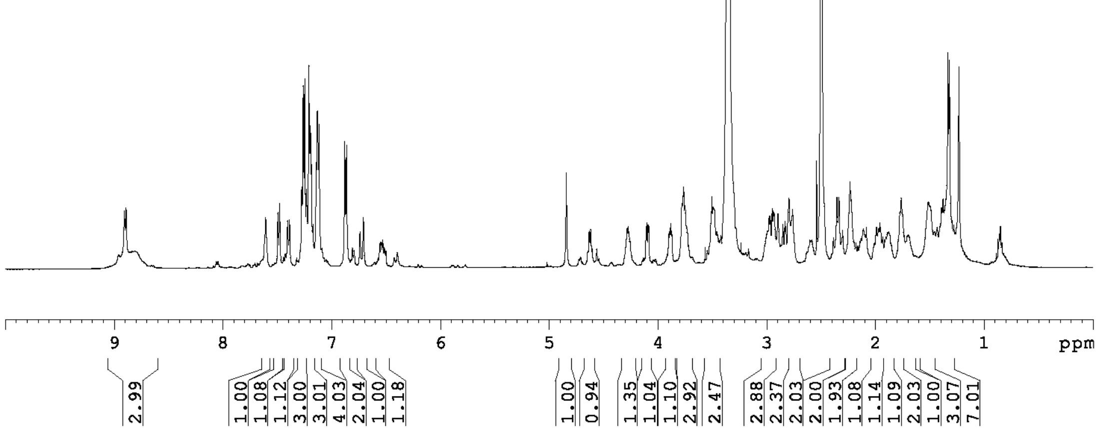

HSQC
ppm

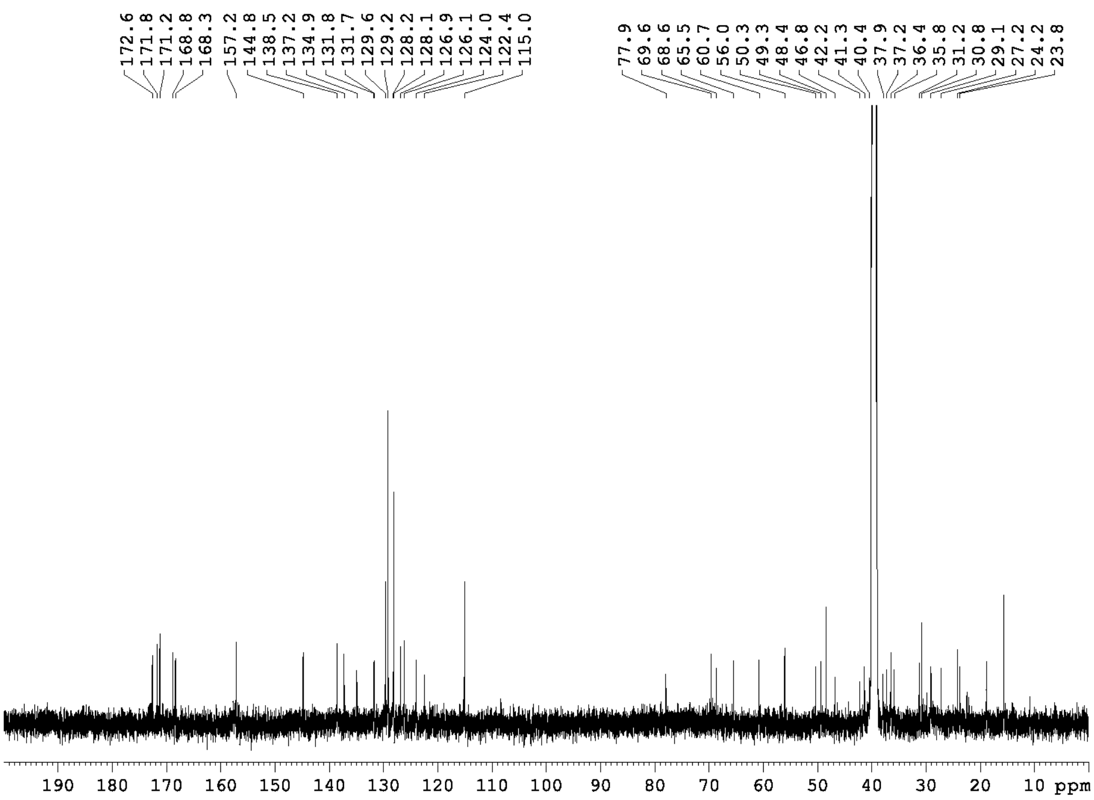

HMBC
ppm
20
40
60
80
100
120
140
160
9
8
7
6
5
4
3
2
1


NOESY
ppm
1
2
3
4
5
6
7
8
9
10

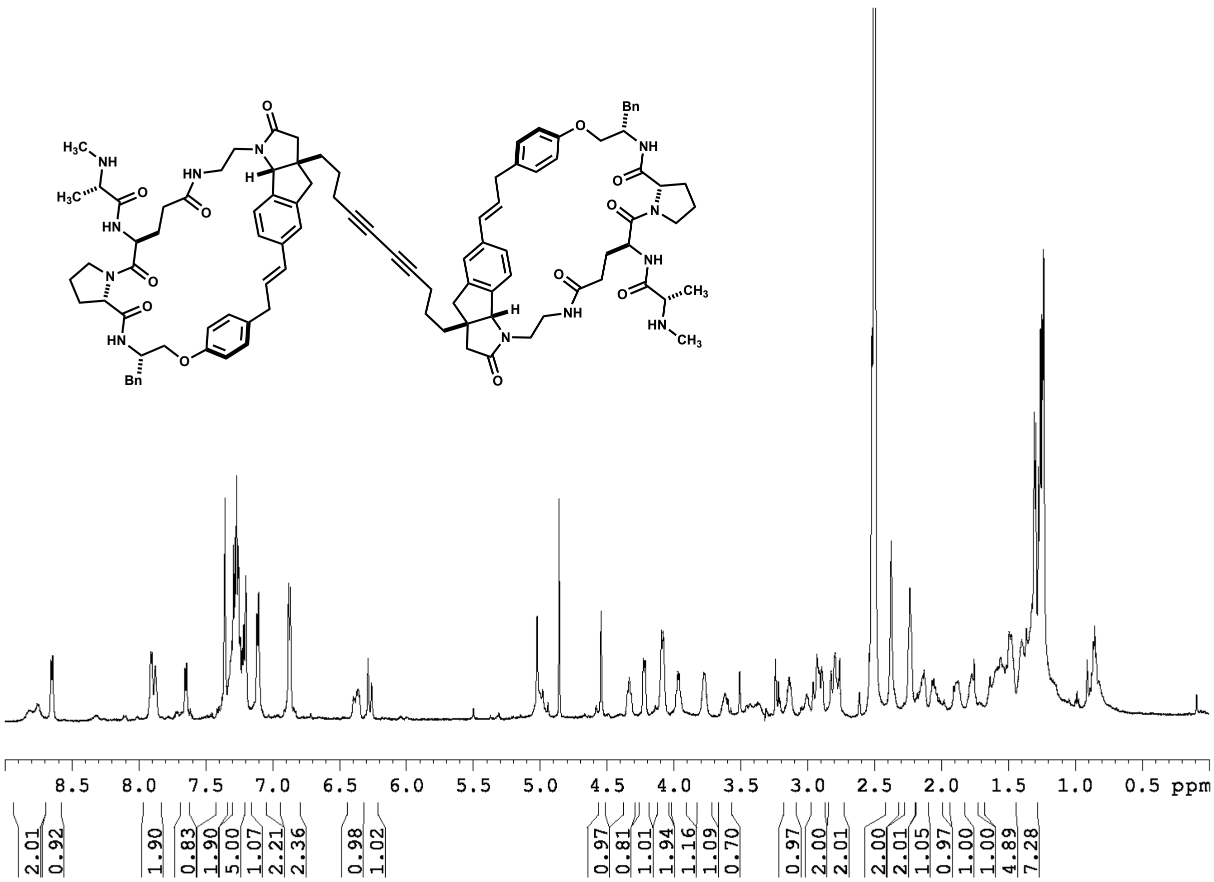
Dimer **3.65**


H3C
CH3
NH
HN
O
N
Bn
H


9 8 7 6 5 4 3 2 1 ppm
2.99
1.00 1.08 1.12 3.00 3.01 4.03 2.04 1.00 1.18
1.00 0.94
1.35 1.04 1.10 2.92 2.47
2.88 2.37 2.03 2.00 1.93 1.08 1.14 1.09 2.03 1.00 3.07 7.01


172.6 171.8 171.2 168.8 168.3 157.2 144.8 138.5 137.2 134.9 131.8 131.7 129.6 129.2 128.2 128.1 126.9 126.1 124.0 122.4 115.0
77.9 69.6 68.6 65.5 60.7 56.0 50.3 49.3 48.4 46.8 42.2 41.3 40.4 37.9 37.2 36.4 35.8 31.2 30.8 29.1 27.2 24.2 23.8
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Dimer **3.7**



8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm
2.01
0.92
1.90
0.83
1.90
5.00
1.07
2.21
2.36
0.98
1.02
0.97
0.81
1.01
1.94
1.16
1.09
0.70
0.97
2.00
2.01
2.00
2.01
1.05
0.97
1.00
1.00
4.89
7.28

E. References

(1) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126* (29), 8916–8918.

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(3) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12* (4), 63–74.

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(7) Lin, H.-S.; Paquette, L. a. *Synth. Commun.* **1994**, *24* (17), 2503–2506.

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Chapter 4 – Appendix Material

Attempts to form a macrocyclic, transannular linkage through terminal alkyne engagement with nucleophilic peptide side-chains

Table of Contents

A. General Considerations

$[PhRuCl_2]_2$, $[Ru(COD)Cl]_2$, $[CpRu(ACN)_3]PF_6$, $[CpRu(Naph)]PF_6$, $(COD)Ru(methallyl)_2$, $AuBr_3$ and $Co_2(CO)_8$ were purchased from Strem. $P(4\text{-}ClC_6H_4)_3$, 1,4-bis(dicyclohexylphosphino)butane, $P(2\text{-furyl})_3$, $Yb(OTf)_3$, 4-picoline *N*-oxide, and tris(2-carboxyethyl)phosphine hydrochloride were purchased from Aldrich. $P(4\text{-}FC_6H_4)$ was prepared according to prior literature.[1] Ligand **4.13** was prepared according to prior literature.[2]

HPLC-MS Analysis and Purification

Purification of acidolysis products was performed on an Agilent 1100/1200 HPLC system equipped with G1361A preparative pumps, a G1314A autosampler, a G1314A VWD, and a G1364B automated fraction collector. Analytical HPLC was performed using an identical system, but with a G1312A binary pump. Mass spectra were recorded using an Agilent 6130 LC/MS system equipped with an ESI source. Stationary phase and gradient profile are noted for individual reactions below.

NMR Methods

NMR spectra were recorded on Brüker Advance (300, 400, 500 or 600 MHz) or DRX (500 MHz) spectrometers and calibrated according to the respective residual solvent peak. 2D NMR data were acquired as previously detailed.[3]

General Experimental Procedures

Peptide Synthesis

All peptides were synthesized via either standard Fmoc solid-phase peptide synthesis using Rink Amide MBHA resin (polystyrene, 1% DVB, 0.7 mmol/g) or Boc/Cbz solution-phase peptide synthesis.[3]

General Procedure A – acyloxylation with $[PhRuCl_2]_2$

A flame-dried flask was charged with benzoic acid [1.25 mmol], $[PhRuCl_2]_2$ [0.4 mol%], tris(2-furyl)phosphine [0.8 mol%], and Na_2CO_3 [1.6 mol%] then flushed with Ar for 30 min. The flask was then charged with appropriate solvent [5 mL] and hexyne [1.63 mmol], and the reaction was heated to 50 ºC. After 24 h, the reaction was concentrated *in vacuo*, and dried on high vacuum. The sample was dissolved in 2 mL $CDCl_3$ spiked with mesitylene [0.543 mmol], and filtered through celite into an NMR tube. Set integration of arene protons to 1.30 – due to incorrect addition of 1.3x excess mesitylene. Following this, the integration of each of the olefin peaks provided the yield. *Fig. 4.1.B. entry 6 contained only 0.27 mmol of mesitylene.*

General Procedure B – hydroamidation with $(COD)Ru(methallyl)_2$

A flame-dried flask was charged with benzamide or benzoic acid [1.0 mmol], $(COD)Ru(methallyl)_2$ [5 mol%], bis(dicyclohexylphosphino)butane [6 mol%], and $Yb(OTf)_3$ [4 mol%] then flushed with Ar for 30 min. The flask was then charged with dry DMF [0.3 M] and H_2O [6.0 mmol], which had been freeze-pump-thawed thrice. Hexyne [2.0 mmol] was added to the flask and the reaction was heated to 60 ºC. After 24 h, the reaction was poured into EtOAc / sat. $NaHCO_3$. The organic layer was washed twice more with $NaHCO_3$ and once with brine. The organic layer was dried with $MgSO_4$, concentrated *in vacuo*, and dried on high vacuum. The sample was dissolved in 2 mL $CDCl_3$ and spiked with mesitylene [0.33 mmol]. Set integration of aryl protons to 1.00. The integration of the vinyl protons were then compared to standard.

General Procedure C – oxygenation with $[Rh(COD)Cl]_2$

If using an ammonium hydrochloride salt, the starting material [0.6 mmol] was dissolved in ACN [2 mL] and treated with KPF_6 [0.6 mmol] for 10 min at 60 ºC. The milky suspension was cooled and then filtered through a 0.2 µm PTFE filter into the following reaction. In the meantime, $[Rh(COD)Cl]_2$ [3 mol%] was weighed out in a glovebag into an oven-dried flask containing a stirbar. Outside the glovebag, picoline *N*-

oxide [1.2 eq.], $P(4\text{-}C_6F_5)_3$ [12 mol%], and K_2CO_3 [20 mol%] were added to the reaction flask. After adding the nucleophile solution, hexyne [0.5 mmol] was added and the headspace was flushed with Ar for 20 min. The reaction was then heated to 60 ºC. After 16 h, the volatiles were removed *in vacuo*. The residue was reconstituted in 2 mL $CDCl_3$ and spiked with mesitylene [0.167 mmol] and filtered through cotton into an NMR tube.

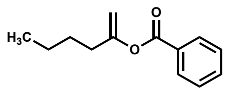
General Procedure D – ruthenium-catalyzed hydrations

In a glovebag, either $[(naph)Ru(Cp)]PF_6$ or $[Ru(ACN)_3Cp]PF_6$ [2 mol%] and bipyridine ligand **4.19** [2 mol%] were added to a vial, which was capped with a septum. The vial was flushed with Ar for 30 min and then charged with 4:1 NMP/H_2O – previously sparged for 1 hour. This solution was heated to 50 ºC for 3 h, cooled, and then treated with decyne [0.5 mmol]. The reaction was stirred for either 15 or 48 h, respectively. After this time, the solution was diluted with EtOAc and washed 2x $NaHCO_3$, 2x NH_4Cl, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The residue was reconstituted in 2 mL $CDCl_3$ and the percent conversion was measured by comparing the alkynyl and the aldehyde proton integrations.

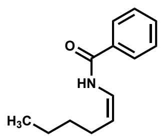
General Procedure E – multicomponent reaction with $AuBr_3$

In a glovebag, a flame-dried flask was charged with glyoxylic acid hydrate [1.0 mmol] and $AuBr_3$ [5 mol%]. The flask was then charged with MeOH [0.5 M], hexyne [2.0 mmol], and morpholine [1.2 mmol]. The reaction was heated to 50 ºC. After 12 h, the volatiles were removed *in vacuo*. The dark residue was reconstituted in 1 mL $CDCl_3$ and spiked with mesitylene [0.33 mmol] and filtered through cotton into an NMR tube. The aryl proton integration was compared to the enamide proton integration.

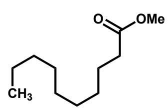
B. Experimental Data
B.1. Transition metal-catalyzed model systems



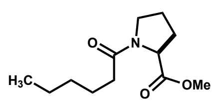
hex-1-en-2-yl benzoate
Synthesized according to general procedure A. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.12–8.08 (m, 2H), 7.59 (tt, *J* = 7.4, 1.4 Hz, 1H), 7.49–7.43 (m, 2H), 4.87 (d, *J*=1.2 Hz, 1H), 4.84 (dd, *J* = 2.4, 1.2 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 1H), 1.58–1.48 (m, 2H), 1.45–1.33 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 9H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 164.8, 156.9, 133.3, 130.0, 128.5, 101.4, 33.2, 28.8, 22.2, 13.9



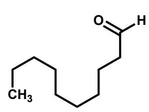
(*Z*)-*N*-(hex-1-en-1-yl)benzamide
Synthesized according to general procedure B.



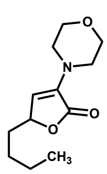
methyl decanoate
Synthesized according to general procedure C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.66 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.66–1.56 (m, 2H), 1.31–1.26 (m, 12H), 0.87 (t, *J* = 6.6 Hz, 3H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.5, 51.6, 34.3, 32.0, 29.5, 29.4 (2C), 29.3, 25.1, 22.8, 14.2



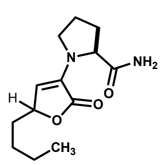
methyl hexanoyl-*L*-prolinate
Synthesized according to general procedure C.



Decanal
Synthesized according to general procedure D.

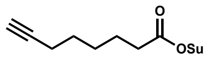


5-butyl-3-morpholinofuran-2(5*H*)-one
Synthesized according to general procedure E.



(2*S*)-1-(5-butyl-2-oxo-2,5-dihydrofuran-3-yl)pyrrolidine-2-carboxamide
Synthesized according to general procedure E.

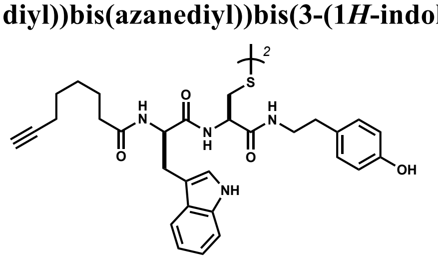
B.2. Thiol-yne model system



2,5-dioxopyrrolidin-1-yl oct-7-ynoate

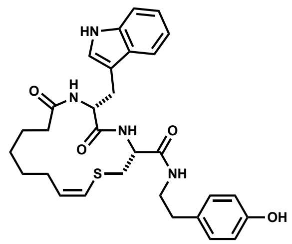
Oct-7-ynoic acid[4] [25.6 mmol] was dissolved in DMF [26 mL] and treated with EDC•HCl [1.6 eq.] and *N*-hydroxysuccinimide [1.5 eq.]. The coupling was stirred for 3 hours until TLC indicated complete reaction. DCM was removed *in vacuo*, and the residue was reconstituted in EtOAc. The solution was then washed 3x NH_4Cl, 3x $NaHCO_3$, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Chromatographed on SiO_2 30 → 80% EtOAc/hexanes. Isolated 5.9 g [25 mmol, 97% over two steps] of a colorless oil. *NMR is of crude reaction and is contaminated with EtOAc. Yield is accurate and reflects purified material.* ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.81 (br s, 4H), 2.59 (t, *J* = 7.4 Hz, 2H), 2.18 (dt, *J* = 6.7, 6.7, 2.6 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.79–1.69 (m, 2H), 1.59–1.45 (m, 4H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 168.6, 84.2, 68.6, 30.9, 27.9, 27.9, 25.7, 24.1, 18.2

***N*,*N*'-((2*R*,2'*R*)-(((2*R*,2'*R*)-disulfanediylbis(3-((4-hydroxyphenethyl)amino)-3-oxopropane-1,2-diyl))bis(azanediyl))bis(3-(1*H*-indol-3-yl)-1-oxopropane-1,2-diyl))bis(oct-7-ynamide)**



Succinimidyl Octynoate [155 mg, 0.65 mmol] was dissolved in DMF [0.5 M] and treated with peptide **4.22** [423 mg, 0.6 eq.], and *i*Pr_2NEt [273 μL, 2.4 eq.]. The coupling reaction was complete within 2 hours as observed by HPLC. The solution was diluted with EtOAc and washed 3x 1N HCl, 3x $NaHCO_3$, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude material was carried forward without purification.

(3*R*,6*R*,*Z*)-6-((1*H*-indol-3-yl)methyl)-*N*-(4-hydroxyphenethyl)-5,8-dioxo-1-thia-4,7-diazacyclopentadec-14-ene-3-carboxamide



In a scintillation vial, linear disulfide **4.23** [55 μmol] was dissolved in DMF [5 mM] and treated with TCEP•HCl [1.0 eq.] and DMPA [50 mol%]. The solution was then sparged for 12 h until disulfide reduction was complete. A compact UV lamp was placed next to the reaction vial and both were covered in aluminum foil. The solution was then irradiated with 365 nm light. After 1 hour, the reaction was complete by HPLC. The reaction was diluted with EtOAc and washed 3x 1N HCl, 3x $NaHCO_3$, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude material was dissolved in 500 μL DMSO and purified half of the material by HPLC. Isolated 12 mg [22 μmol, 40% yield] of a white residue. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.83 (s, 1H), 8.40 (d, *J* = 7.6 Hz, 1H), 7.95 (t, *J* = 5.5 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.36–7.32 (m, 2H), 7.12 (d, *J* = 1.7 Hz, 1H), 7.06 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 7.0, 7.0 Hz, 1H), 6.97 (d, *J* =8.1 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 1H), 6.00 (d, *J* = 9.6 Hz, 1H), 5.42 (ddd, *J* = 9.6, 8.0, 8.0 Hz, 1H), 4.38 (ddd, *J* = 6.7, 6.7, 4.7 Hz, 1H), 4.29 (ddd, *J* = 8.0, 8.0, 3.2 Hz, 1H), 3.24–3.19 (m, 3H), 3.12 (ddd, *J* = 13.8, 13.8, 6.5 Hz, 1H), 3.06–2.98 (m, 1H), 2.61 (dd, *J* = 7.4, 7.4 Hz, 2H), 2.12–1.99 (m, 3H), 1.98–1.94 (m, 2H), 1.51–1.42 (m, 2H), 1.39–1.19 (m, 5H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 172.9, 171.4, 169.5, 155.7, 136.2, 129.6, 129.5, 129.4, 127.3, 125.3, 123.5, 120.9, 118.3, 118.0, 115.1, 111.4, 110.6, 55.0, 51.5, 40.9, 35.7, 34.2, 34.1, 28.3, 28.1, 27.7, 25.3, 17.5

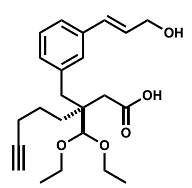
Analytical HPLC Method
Column: Eclipse-XDB C_{18}, 4.6x250 mm, 5 μm
Solvent A: H_2O + 0.1% HCOOH
Solvent B: ACN + 0.1% HCOOH
Flow rate: 1.00 mL/min

Time	%B
0	45
1	45
14	100
15	45

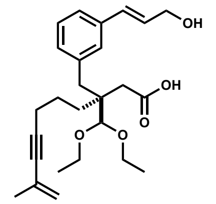
Semi-Preparative HPLC Method
Column: Waters Sunfire™ C_{18}, 10x250 mm, 5 μm
Solvent A: H_2O + 0.1% TFA
Solvent B: ACN + 0.1% TFA
Flow rate: 7.0 mL/min

Time	%B
0	35
0.5	35
14	50

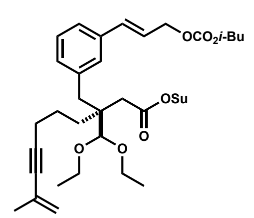
B.3. Ene-yne template synthesis



(*S*,*E*)-3-(diethoxymethyl)-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)oct-7-ynoic acid Template (+)-**3.5** [150 mg, 0.26 mmol] was dissolved in 5:1 EtOH/H_2O [0.2 M] and treated with KOH [5 eq.]. The reaction was then heated to 55 ºC for 24 h until the starting material was fully converted to the cinnamyl alcohol. The reaction was then neutralized with 0.3 M NaH_2PO_4 and extracted 2x with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was then carried forward without purification.

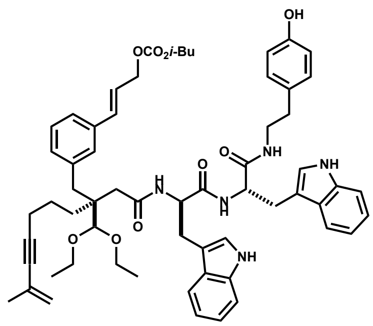


(*S*,*E*)-3-(diethoxymethyl)-3-(3-(3-hydroxyprop-1-en-1-yl)benzyl)-9-methyldec-9-en-7-ynoic acid
Crude cinnamyl alcohol **3.24** [0.85 mmol] was dissolved in toluene [1 mL] and transferred to a conical vial. The original vessel was then washed 3x 0.3 mL toluene. The combined solvents were then freeze-pump-thawed thrice. 2-Bromopropene [8 eq.] and *i*-Pr_2NH [3 eq.] were then added to the vial, and the system was freeze-pump-thawed thrice more. A separate thick-walled tube was charged with $Pd(PPh_3)_2Cl_2$ [2 mol%], PPh_3 [4 mol%], and CuI [4 mol%], sealed with a crimped septa, and then evacuated and backfilled with Ar thrice. The reactant solution was then added to the sealed tube and heated to 70 ºC without an outlet. After 12 h, the reaction was complete by HPLC. The volatiles were removed *in vacuo*, and the residue was diluted with EtOAc and washed 3x 0.3 M NaH_2PO_4 and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was then carried forward without purification.



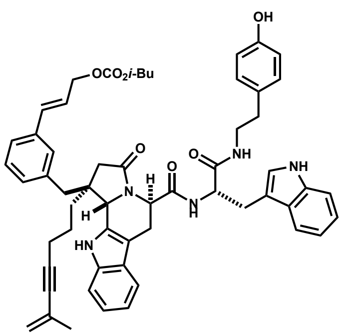
2,5-dioxopyrrolidin-1-yl (*S*,*E*)-3-(diethoxymethyl)-3-(3-(3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)benzyl)-9-methyldec-9-en-7-ynoate
Crude cinnamyl alcohol **4.27** [0.85 mmol] was dissolved in dry DCM [0.05 M], treated with *N*-methylmorpholine [526 µL, 4.8 mmol], and cooled to -5 ºC under argon. *i*-Butyl chloroformate [354 µL, 2.7 mmol] was then added. The reaction was monitored by TLC for full conversion to the di-carbonate species. At this time, solid *N*-hydroxysuccinimide [197 mg, 1.7 mmol] was added to the reaction flask. The ice in the cold bath was replenished and the reaction was allowed to slowly warm overnight. Twelve hours after addition of NHS, solid DMAP [522 mg, 4.3 mmol] was added to decompose by-product, *i*-butyl succinimidyl carbonate. After stirring with DMAP for 10 min, the reaction was quenched with $NaHCO_3$ and extracted with EtOAc. Organic layer washed 2x with $NaHCO_3$ and 1x with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude residue was dissolved in a minimum amount of 3:1 hexanes/$CHCl_3$ and loaded onto silica column. Elution with a gradient of 5% → 30% EtOAc/hexanes provided **4.28** [320 mg, 0.51 mmol] as a colorless oil. 60% from (+)-**3.5**. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26–7.24 (m, 2H), 7.21 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.14 (ddd, *J* = 7.3, 1.7, 1.7 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.28 (ddd, *J* = 15.8, 6.6, 6.6 Hz, 1H), 5.15 (br s, 1H), 5.10 (dd, *J* = 1.5, 1.5 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 2H), 4.34 (s, 1H), 3.92 (d, *J* = 6.7 Hz, 2H), 3.83–3.77 (m, 2H), 3.53–3.43 (m, 2H), 2.92 & 2.85 (AB, *J* = 13.6 Hz, 2H), 2.83 (br s, 4H), 2.64 & 2.61 (AB, *J* = 16.4 Hz, 2H), 2.24 (t, *J* = 6.8 Hz, 2H), 2.01–1.93 (m, 1H), 1.82 (s, 3H), 1.76–1.63 (m, 2H), 1.59–1.53 (m, 2H), 1.21 (dd, *J* = 6.8. 6.8 Hz, 3H), 1.19 (dd, *J* = 6.8, 6.8 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 6H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 169.3, 167.7, 155.3, 138.2, 135.9, 135.0, 130.9, 129.6, 128.4, 127.5, 124.7, 122.5, 120.3, 107.7, 89.4, 82.1, 74.2, 68.5, 66.6, 66.3, 45.6, 39.4, 34.2, 33.2, 27.9, 25.7, 23.9, 23.8, 20.1, 19.0, 15.62, 15.60.

B.4. Ene-yne bicyclization trial precursors



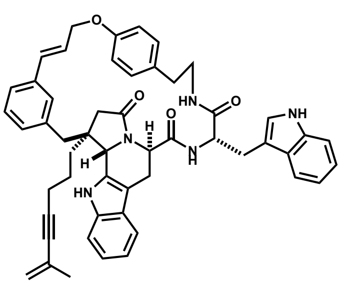
Acylation product 4.29

Template **4.28** [0.37 mmol] was dissolved in DMF [0.5 M] and treated with D-Trp-Trp(tyramide) [1.5 eq.] and *i*Pr_2NEt [5 eq.]. The solution was heated to 35 ºC. The reaction was complete after 12 h. The reaction was diluted with EtOAc and washed 3x 1N HCl, 3x $NaHCO_3$, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude material was carried forward without purification.



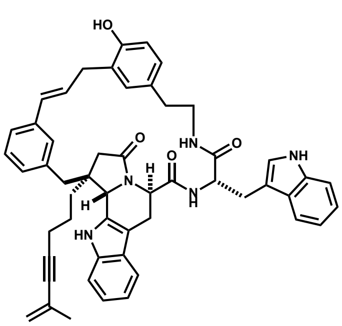
Pictet-Spengler product 4.30

Acyclic product **4.29** [0.37 mmol] was dissolved in a 4:1 mixture of AcOH/H_2O [0.2 M] and stirred for 12 hours until HPLC analysis confirmed reaction completion. The volatiles were removed and the residue was rotovapped from acetonitrile (3x) followed by $CHCl_3$ (3x) to remove residual AcOH. The crude material was carried forward without purification.



Tsuji-Trost product 4.31

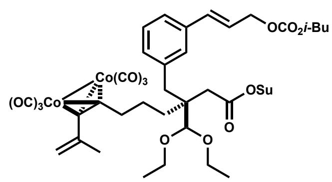
A flask was charged with Pictet-Spengler product **4.30** [0.27 mmol] and DMF [5 mM] and then sparged for 30 minutes. In a glove bag, a flame-dried Schlenk tube was charged with *[PdCl(*C_3H_5*)]*$_2$ [9 mg] and Xantphos [37 mg]. Outside of the glovebag, the Schlenk tube was charged with 9 mL of 1:1 THF/DMF, which had been separately sparged for 1 hour. The catalyst solution was stirred for 5 minutes under Ar and 4 mol% Pd was added to the reaction flask via syringe. Reaction progress was monitored by analytical HPLC-MS. After reaction completion, the reaction was diluted with EtOAc and washed with 3x NH_4Cl and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo.* The crude material was carried forward without purification.



Cinnamyl migration product 4.32

A vial containing crude **4.31** [0.099 mmol] was flushed with Ar then charged with CH_3NO_2 [5 mM] and cooled to 0 ºC. The solution was then treated with CH_3SO_3H [25 eq.]. After 20 min, HPLC indicated reaction completion. The reaction was quenched with *i*Pr_2NEt [1 mL]. The volatiles were removed *in vacuo*. The residue was dissolved in EtOAc and washed 3x $NaHCO_3$, 3x NH_4Cl, 1x brine. The organic layer was concentrated *in vacuo*. Chromatographed on SiO_2 1 → 2% MeOH/$CHCl_3$. Isolated 28 mg [0.035 mmol, 35% over four steps].

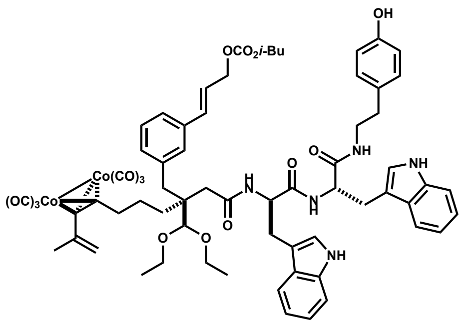
B.5. Dicobalt template synthesis



Dicobalt template 4.33

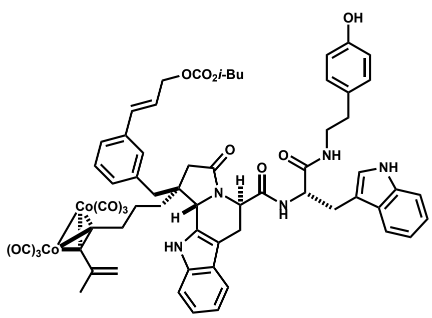
In a glovebag, $Co_2(CO)_8$ [131 mg, 0.38 mmol] was charged into an oven-dried flask. In a separate oven-dried flask, ene-yne template **4.28** [200 mg] was dissolved in dry DCM [0.25 M]. The reactant solution was then added to the flask containing cobalt. The resultant solution was stirred for 1 hour at which time TLC indicated the reaction was complete. The volatiles were then removed *in vacuo* and the residue was chromatographed on SiO_2 directly: 5 → 20 % EtOAc/hexanes. Isolated 175 mg [0.19 mmol, 60%] of dicobalt template **4.33** as a red/black oil. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (s, 1H), 7.27–7.26 (m, 1H), 7.23 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.15 (ddd, *J* = 7.4, 1.4, 1.4 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.30 (ddd, *J* = 15.7, 6.5, 6.5 Hz, 1H), 5.31 (br s, 1H), 5.23 (dd, *J* = 1.4, 1.4 Hz, 1H), 4.77 (dd, *J* = 6.6, 1.0 Hz, 2H), 4.37 (s, 1H), 3.94 (d, *J* = 6.7 Hz, 1H), 3.85–3.76 (m, 2H), 3.54–3.44 (m, 2H), 2.95 & 2.88 (AB, *J* = 13.6 Hz, 2H), 2.85–2.80 (m, 5H), 2.67 (s, 2H), 2.06 (s, 3H), 2.02–1.94 (m, 1H), 1.92–1.84 (m, 1H), 1.76–1.68 (m, 2H), 1.65–1.60 (m, 1H), 1.22 (dd, *J* = 7.0, 7.0 Hz, 3H), 1.19 (dd, *J* = 7.0, 7.0 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 6H), ^{13}C NMR ($CDCl_3$, 126 MHz): δ 200.1, 169.3, 167.7, 155.4, 141.8, 138.2, 136.1, 135.0, 130.8, 129.5, 128.5, 124.8, 122.6, 116.6, 107.7, 101.1, 94.0, 74.3, 68.5, 66.7, 66.4, 45.8, 39.7, 35.1, 34.2, 34.0, 27.9, 27.2, 25.7, 23.6, 19.0, 15.6, 15.5, MS *m/z* 608.3 (calc'd: $C_{32}H_{43}NO_9 + Na^+$, $[M+Na]^+$, 608.3).

B.6. Dicobalt acetylene bicyclization trial precursors



Acylation product 4.S1

Template **4.32** [108 mg, 0.12 mmol] was dissolved in DMF [0.5 M] and treated with D-Trp-Trp(tyramide) [1.15 eq.] and *i*Pr_2NEt [2.2 eq.]. The solution was heated to 35 ºC. The reaction was complete after 12 h. The reaction was diluted with EtOAc and washed 3x 1N HCl, 3x $NaHCO_3$, and 1x brine. The organic layer was dried with $MgSO_4$ and concentrated in vacuo. The crude material was carried forward without purification.

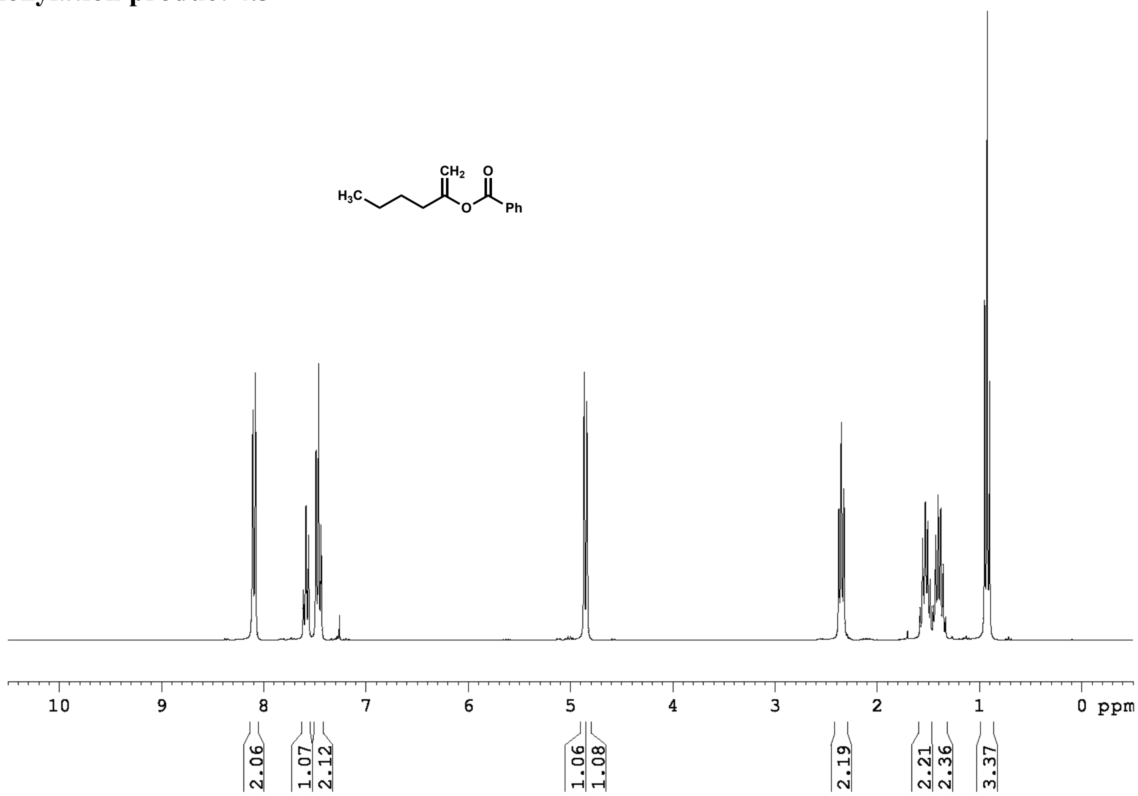


Pictet-Spengler product 4.34

Acyclic product **4.S1** [0.37 mmol] was dissolved in a 4:1 mixture of AcOH/H_2O [0.2 M] and stirred for 12 hours until HPLC analysis confirmed reaction completion. The volatiles were removed and the residue was rotovapped from acetonitrile (3x) followed by $CHCl_3$ (3x) to remove residual AcOH. The crude material was carried forward without purification.

C. NMR Spectra
C.1. Transition metal-catalyzed model systems

Acyloxylation product 4.3



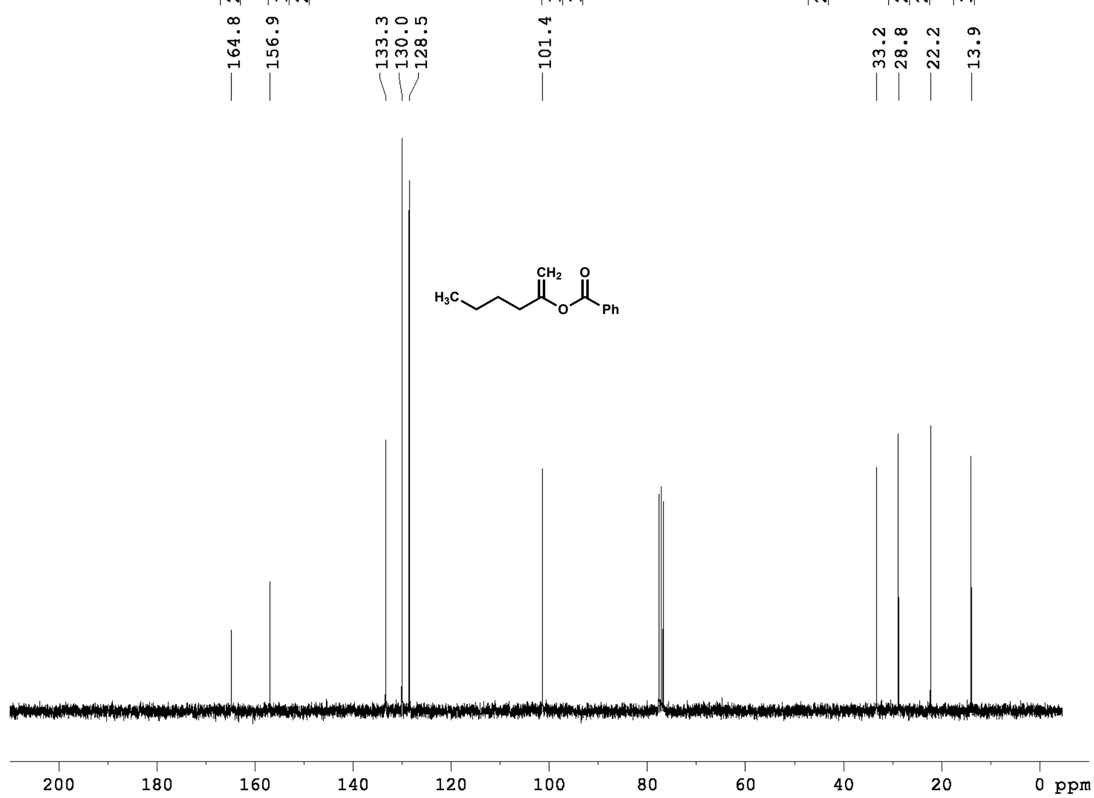


Fig. 4.2.B. Entry 1 yield – *toluene as solvent (control)*

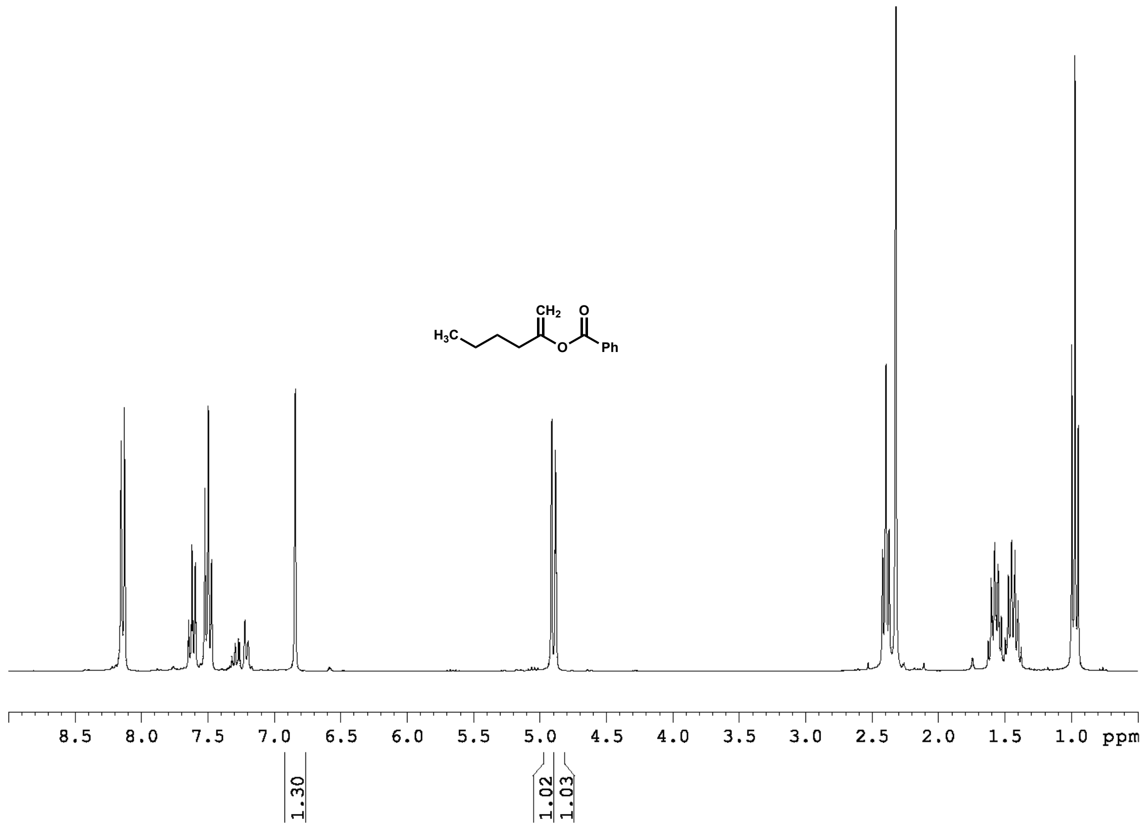


Fig. 4.2.B. Entry 2 yield – *1:1 toluene/CH_3CN as solvents*

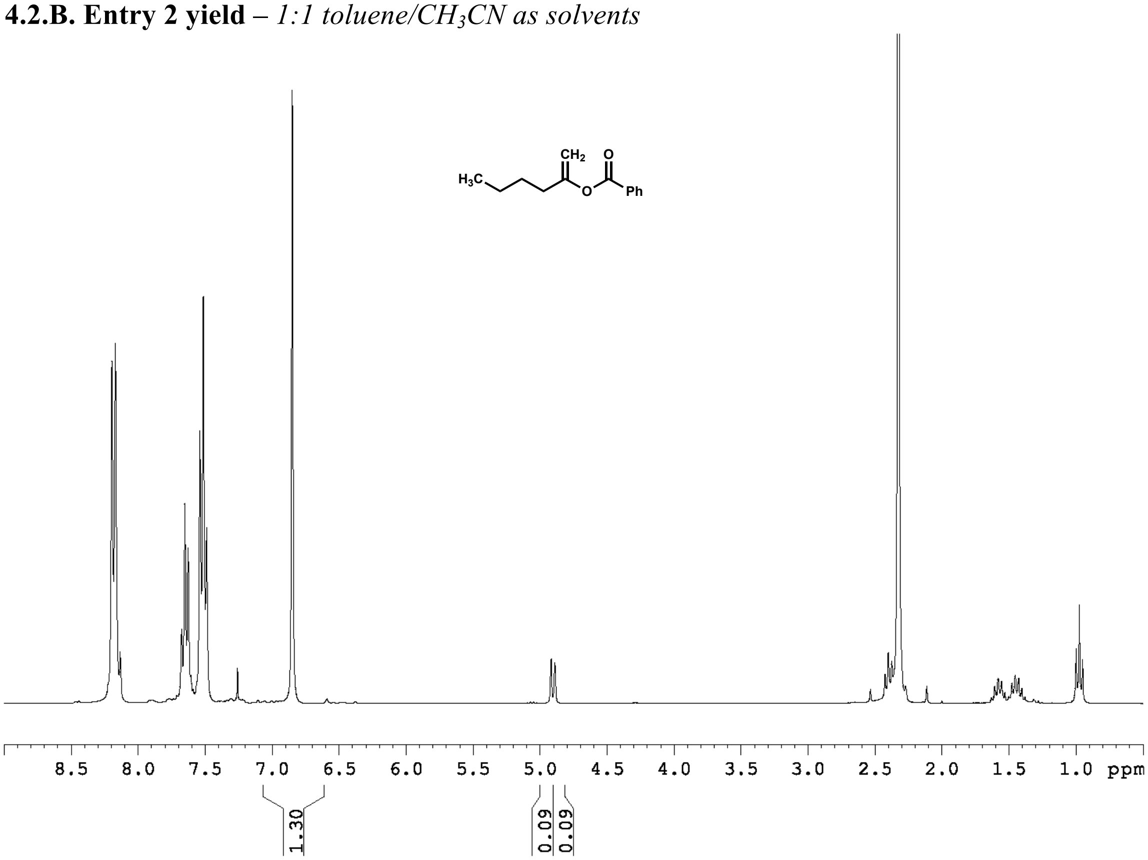


Fig. 4.2.B. Entry 3 yield – *1:1 toluene/EtOAc as solvents*

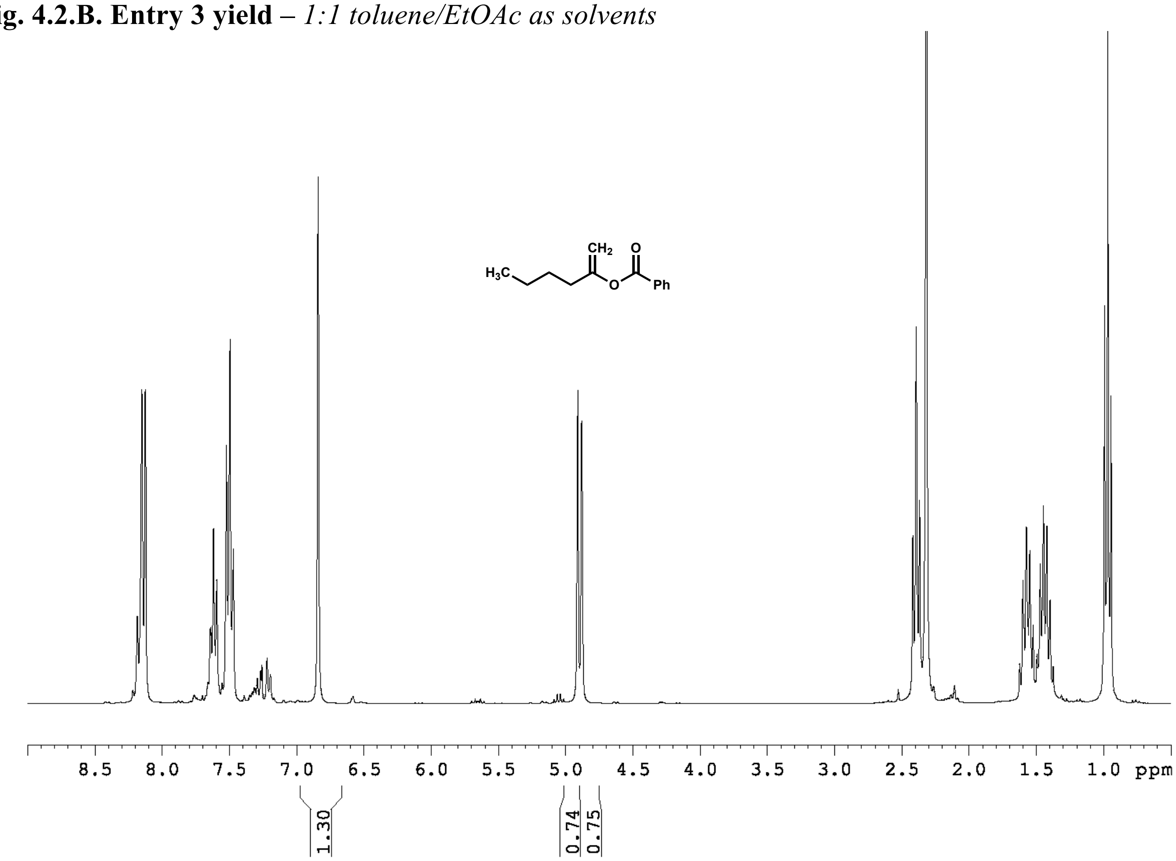


Fig. 4.2.B. Entry 4 yield – *1:1 toluene/DMF as solvents*

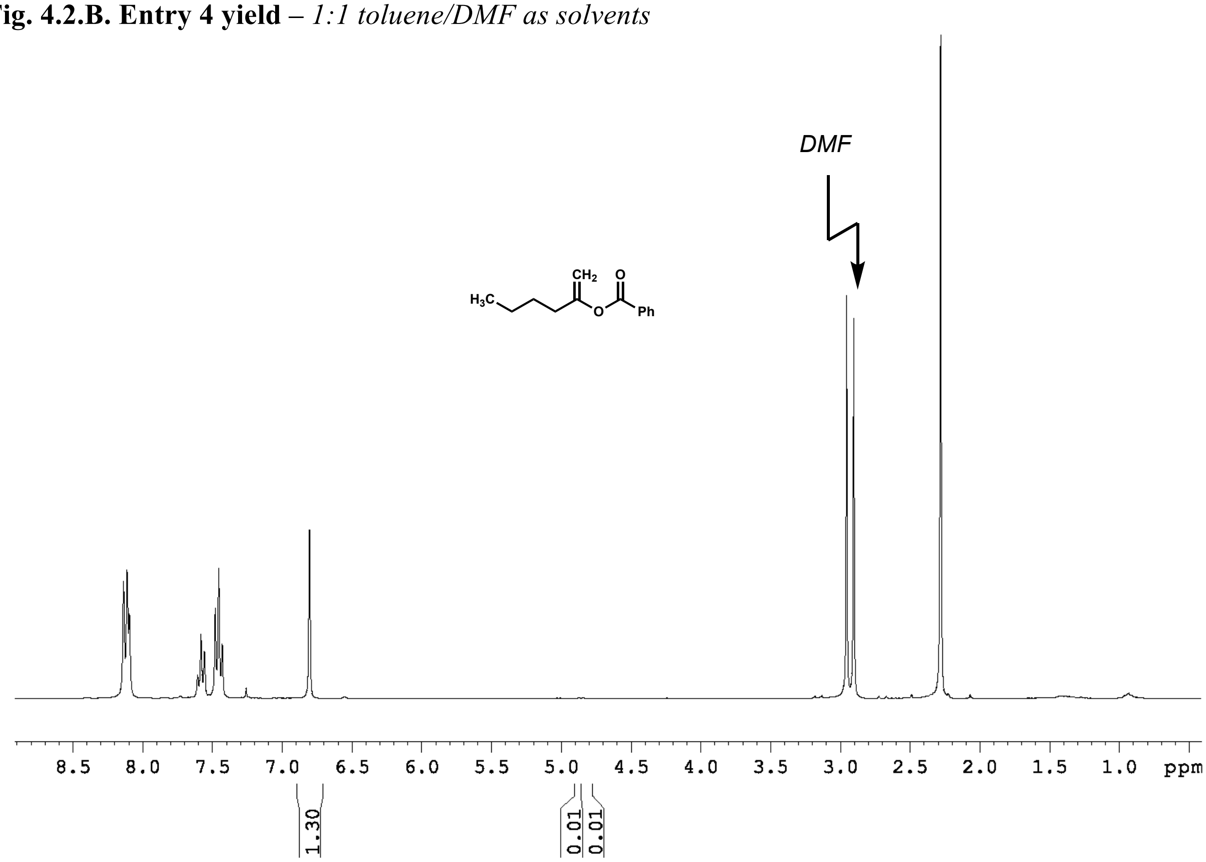


Fig. 4.2.B. Entry 5 yield – *1:1 toluene/MeOH as solvents*

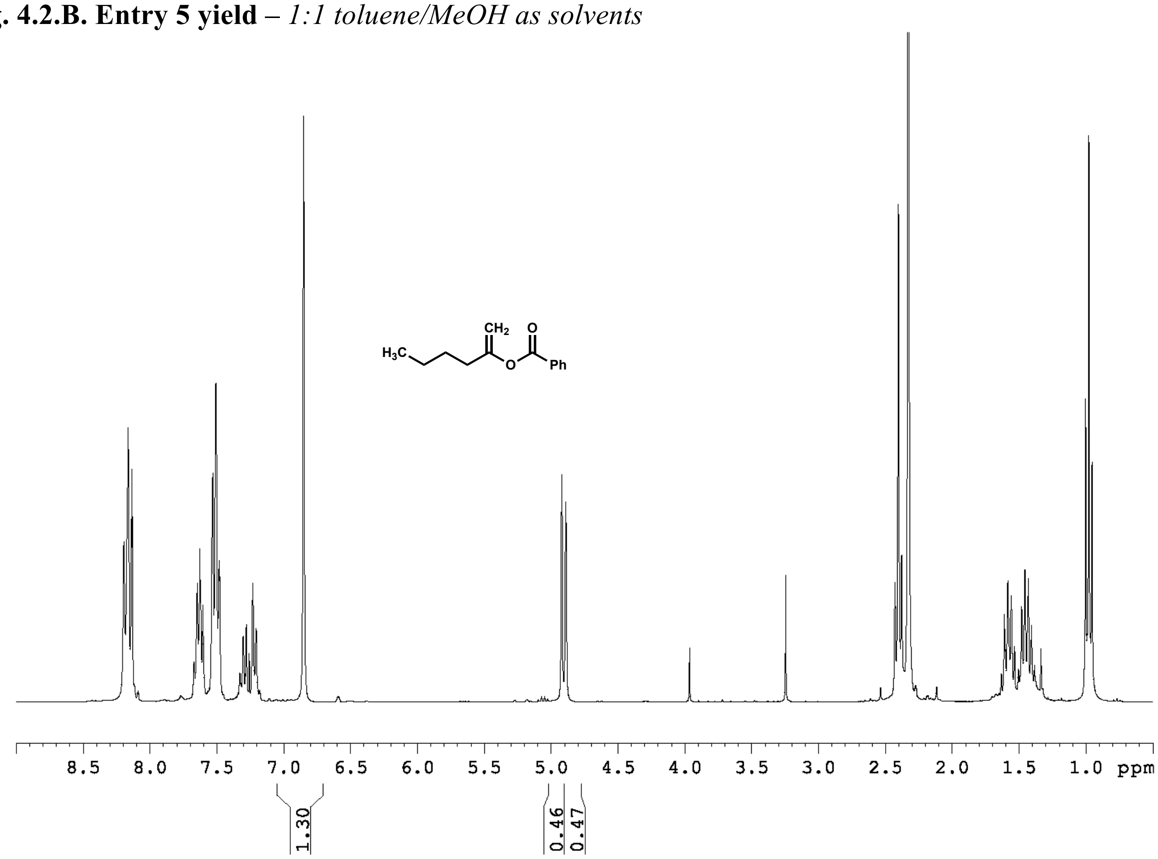


Fig. 4.2.B. Entry 6 yield – *1:1 toluene/EtOAc as solvents with 10 eq. MeOH *used 0.27 mmol mesitylene*

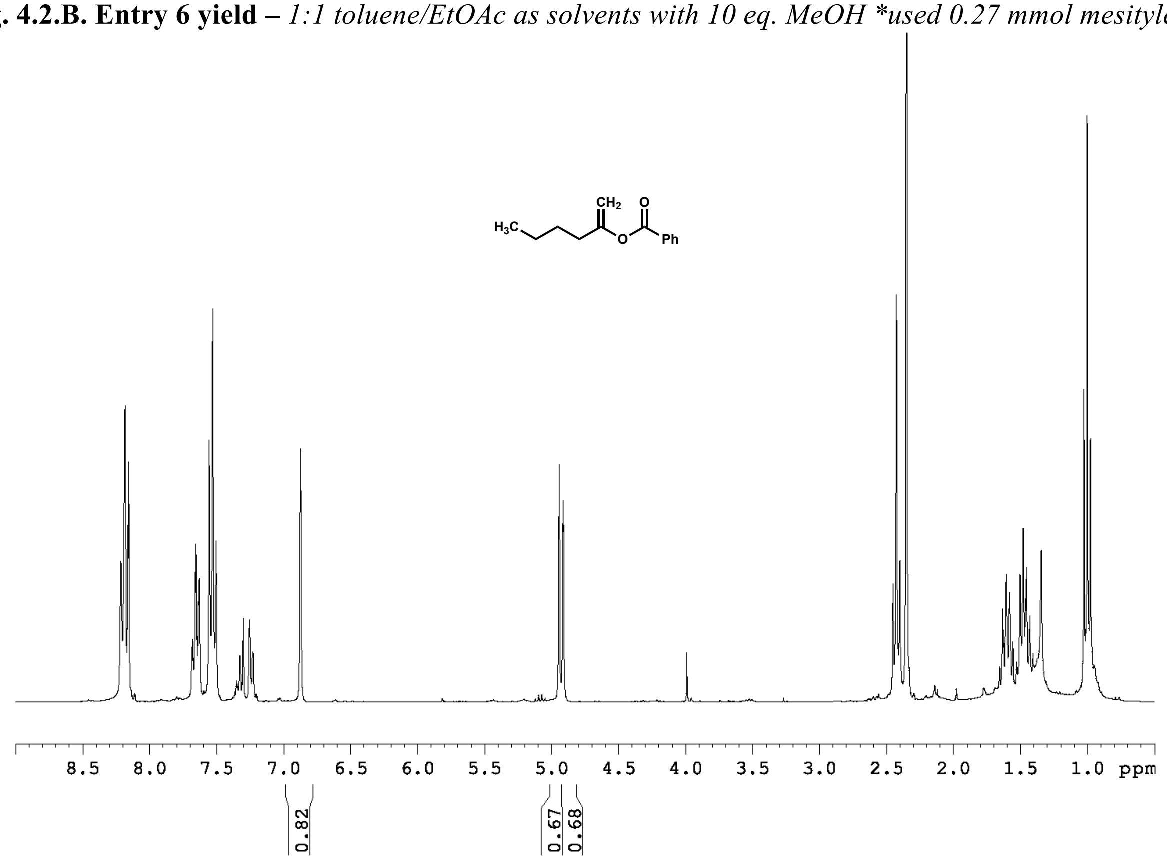


Fig. 4.2.D. Entry 1 yield – *benzamide as nucleophile (control)*

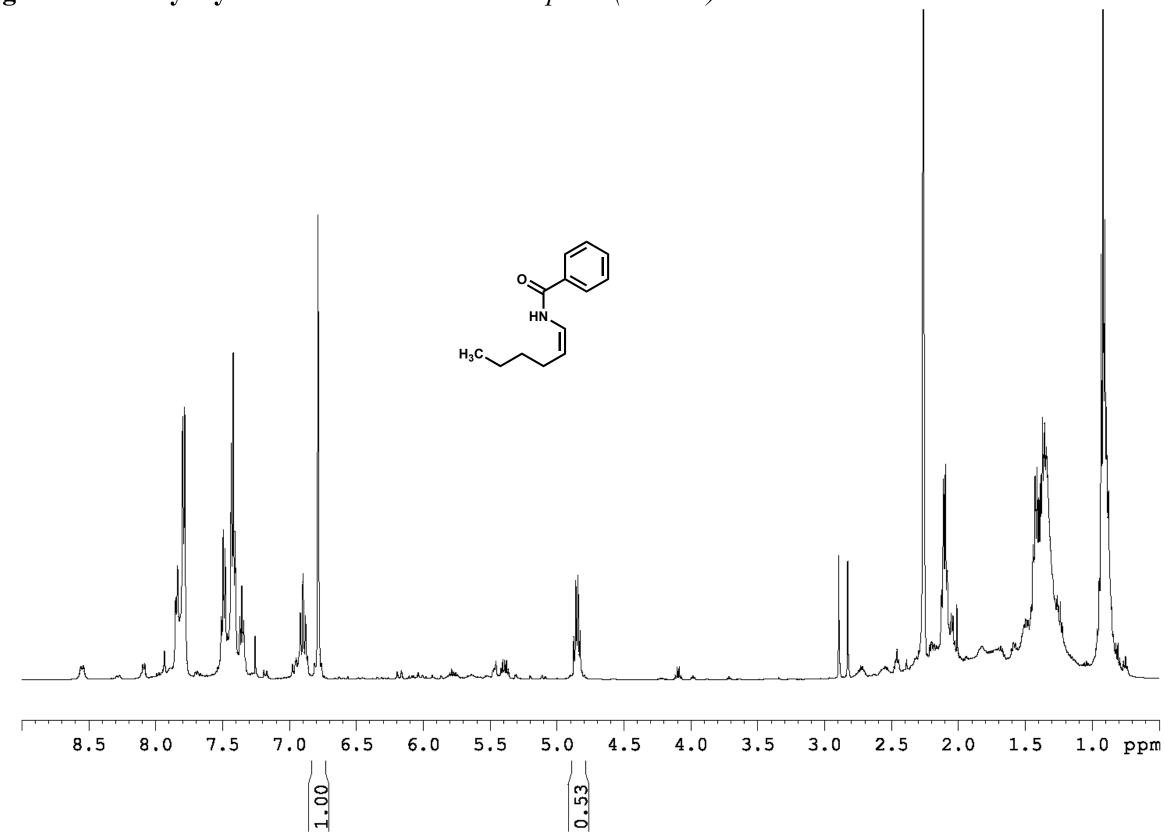


Fig. 4.2.D. Entry 2 yield – *benzoic acid as nucleophile*

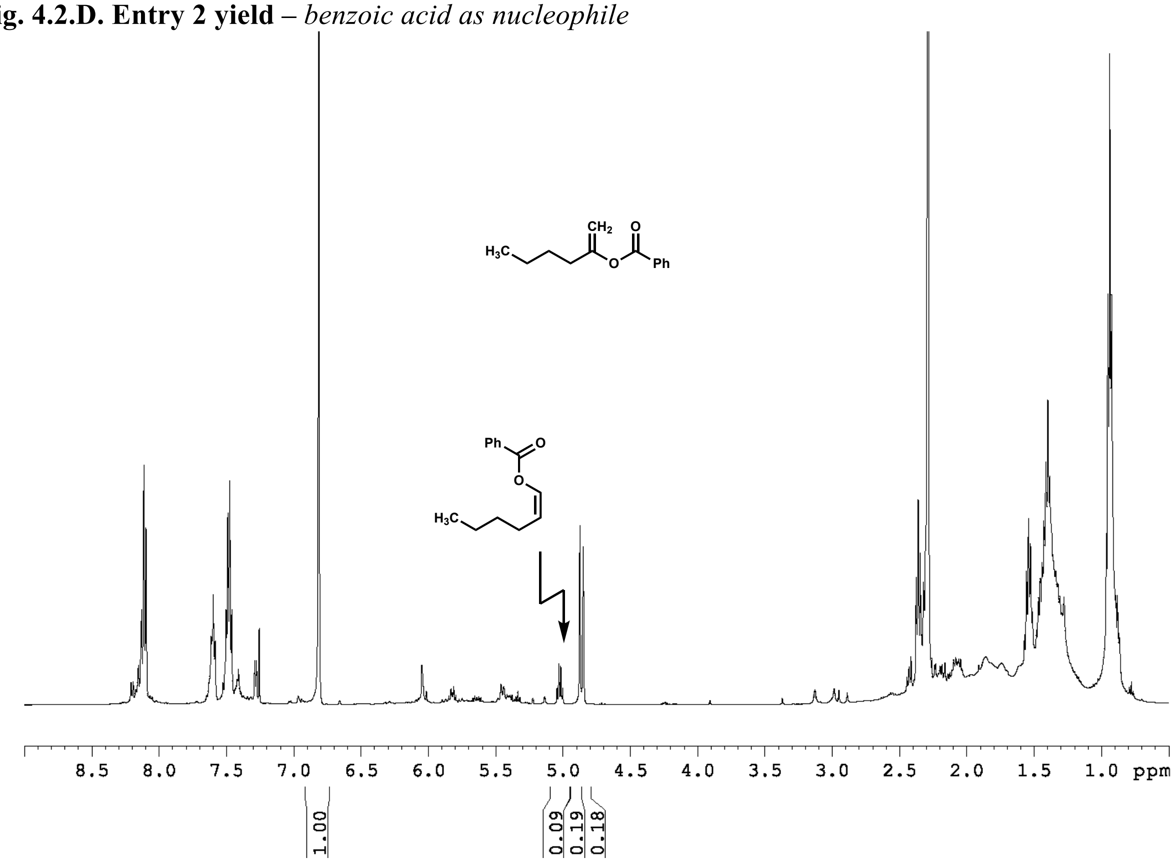
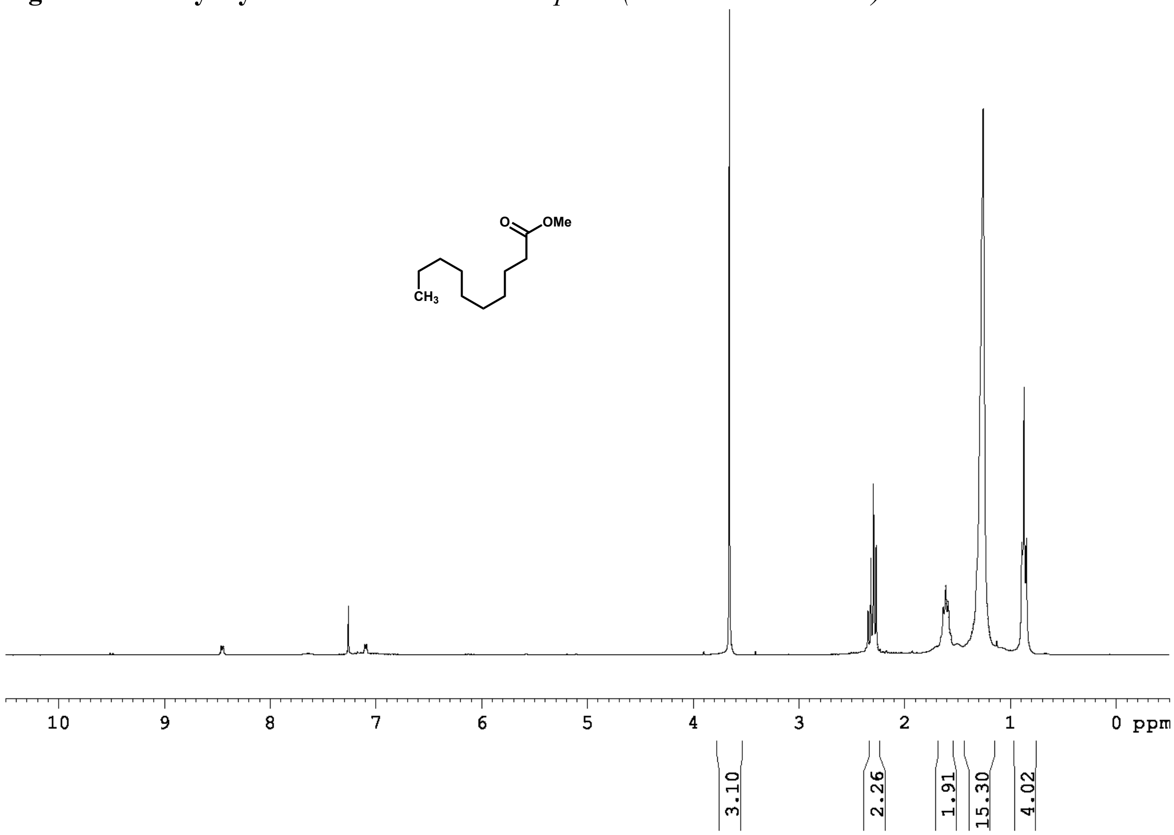


Fig. 4.3.B. Entry 1 yield – *methanol as nucleophile (no internal standard)*



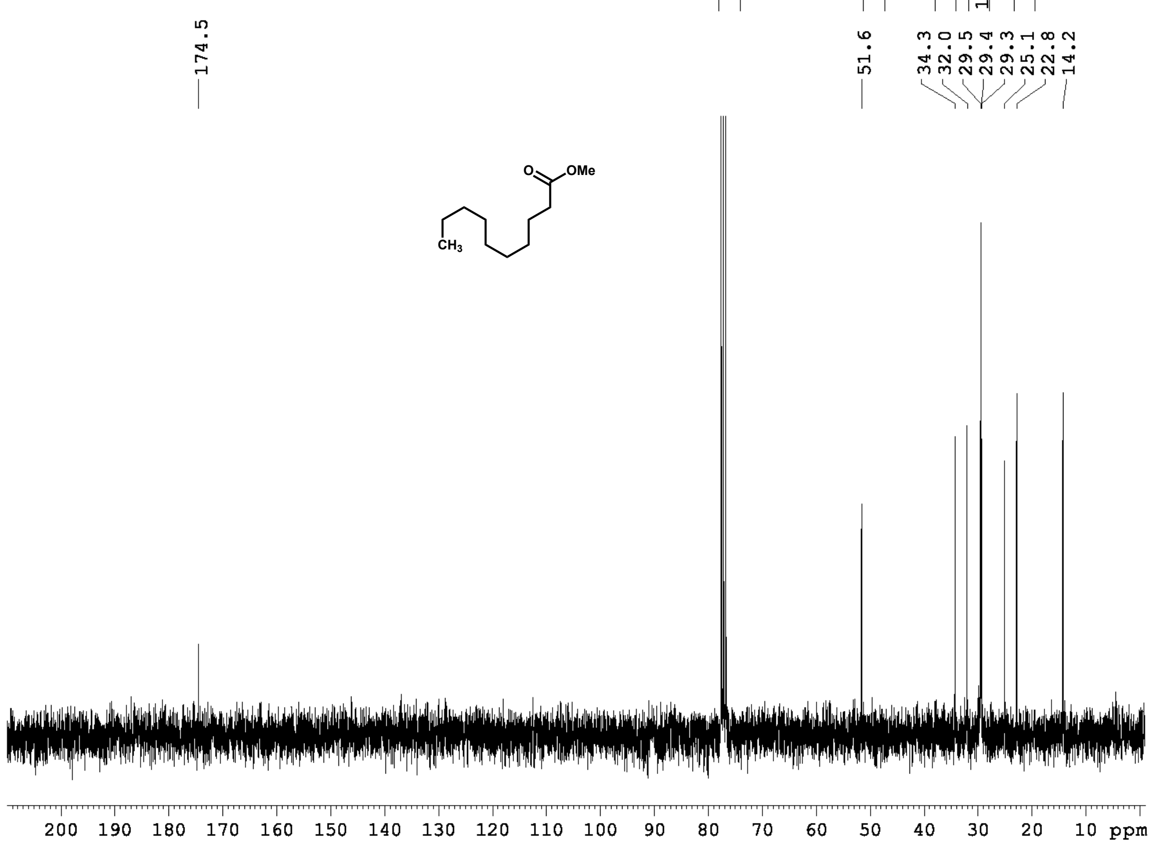


Fig. 4.3.B. Entry 2 yield – *proline methyl ester as nucleophile*

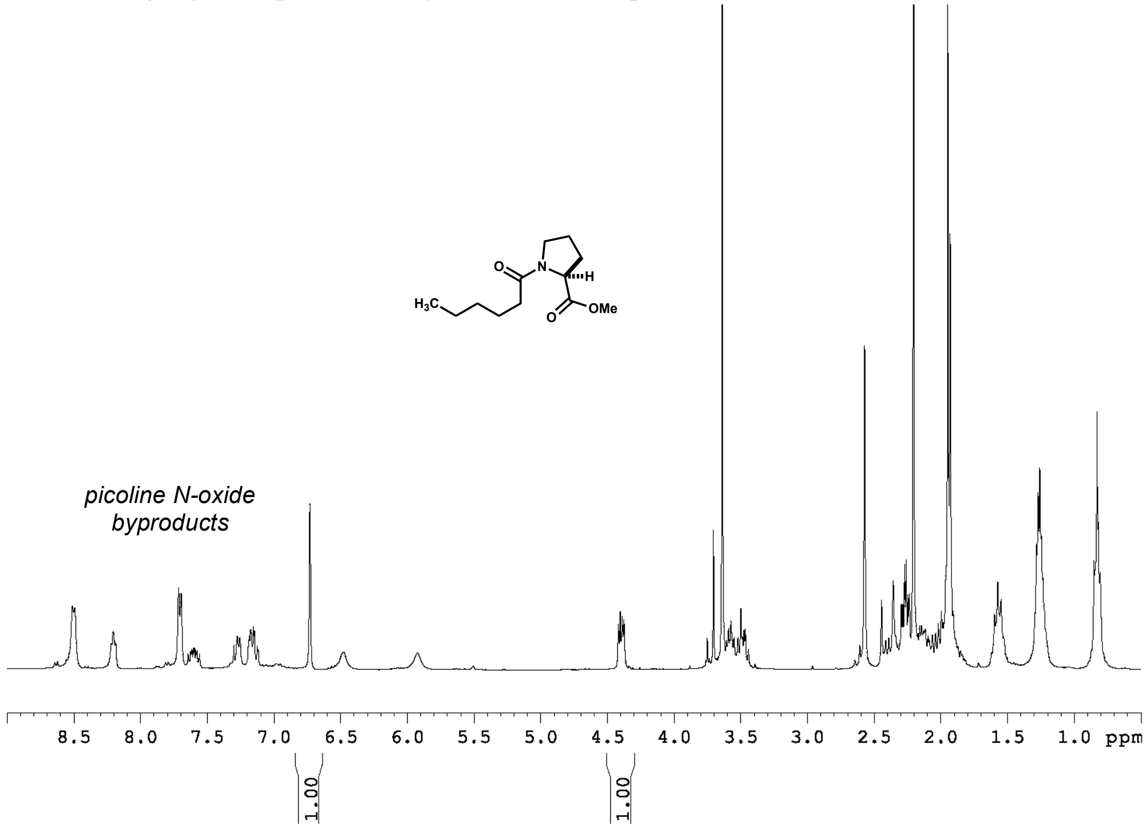


Fig. 4.3.D. Entry 1 yield – *anti-Markovnikov hydration with [Ru(ACN)$_3$Cp]PF$_6$*

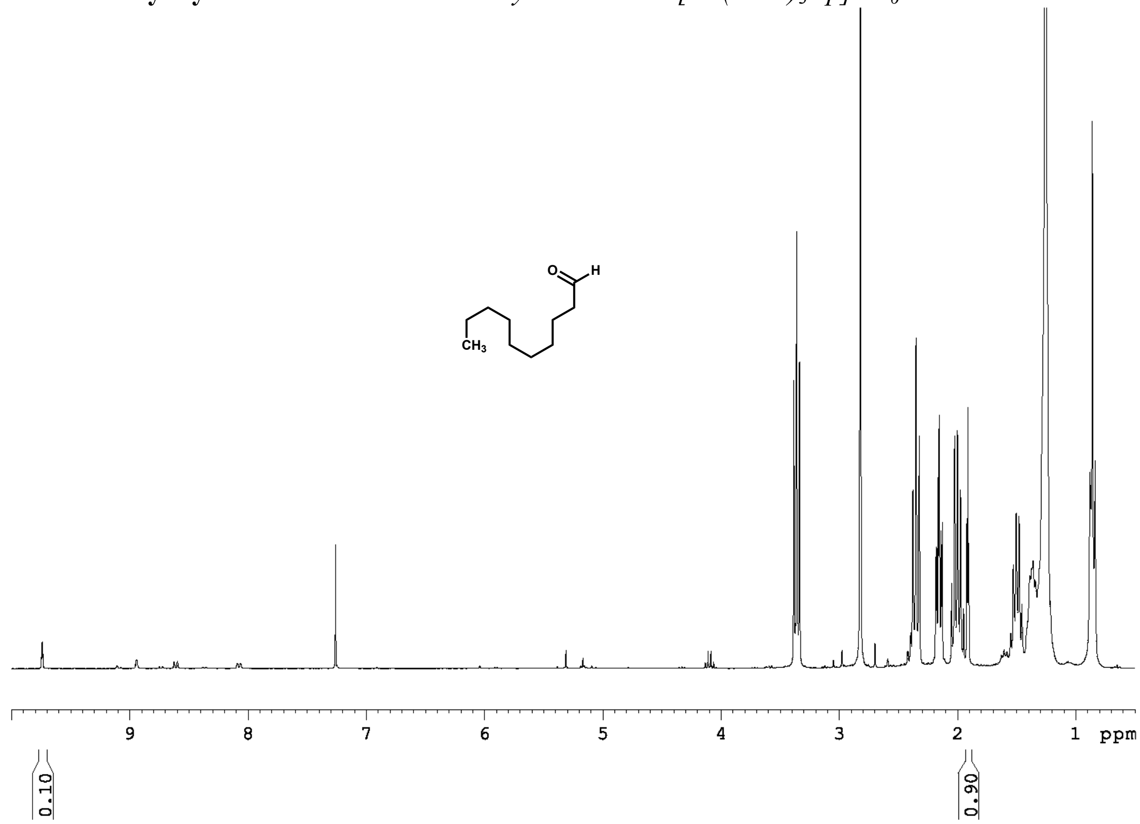


Fig. 4.3.D. Entry 1 yield – *anti-Markovnikov hydration with [(naph)RuCp]PF$_6$*

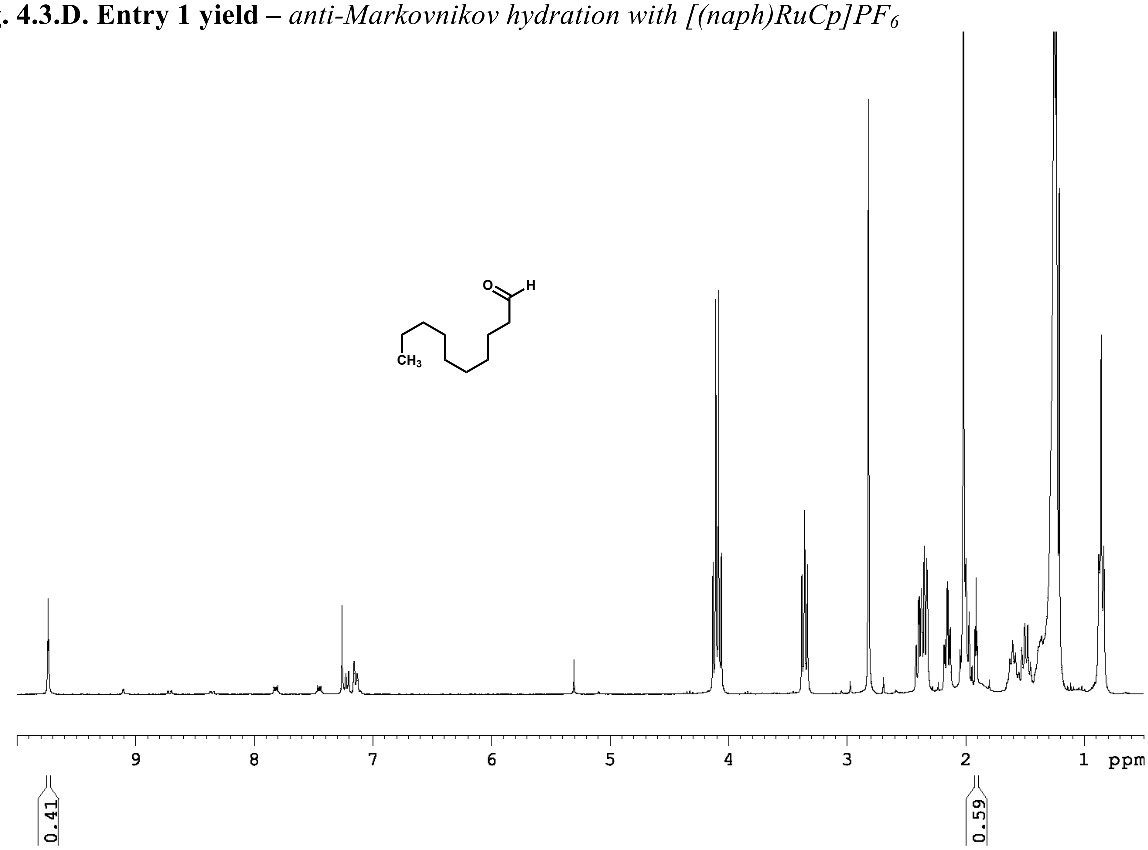


Fig. 4.4.B. Entry 1 yield – *morpholine as nucleophile*

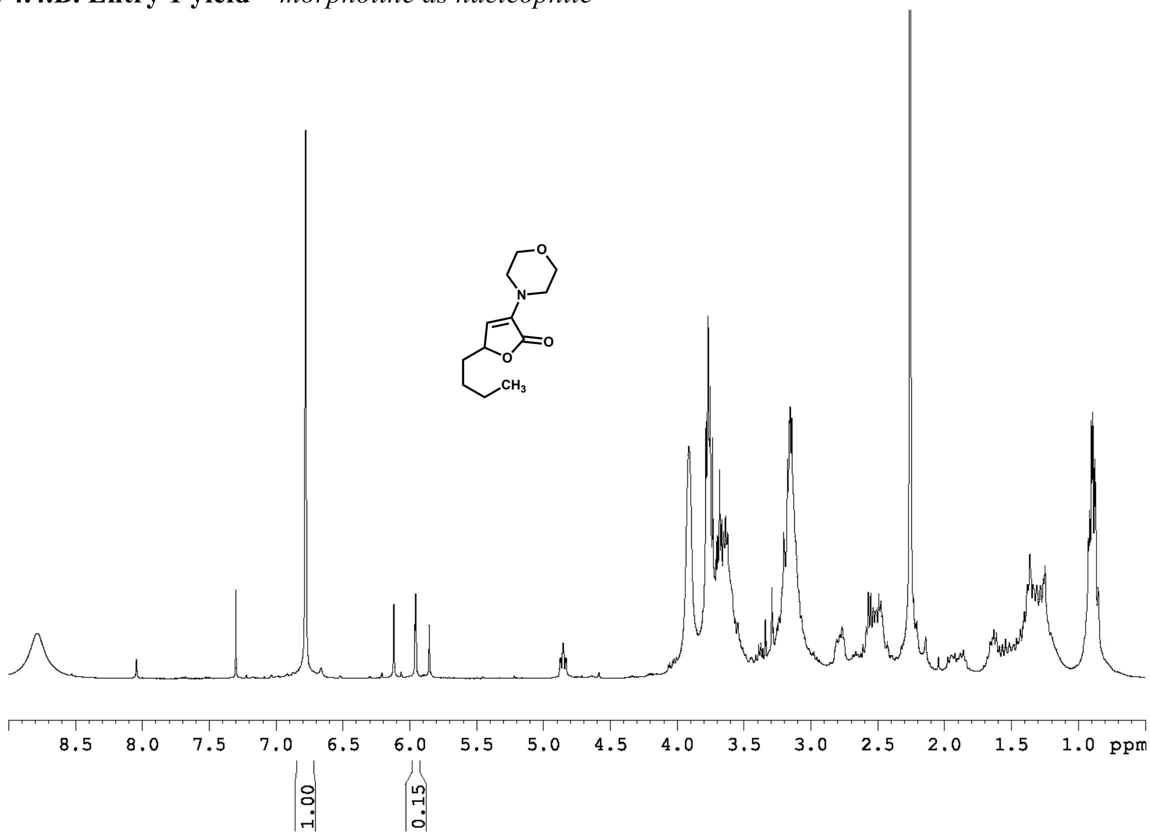
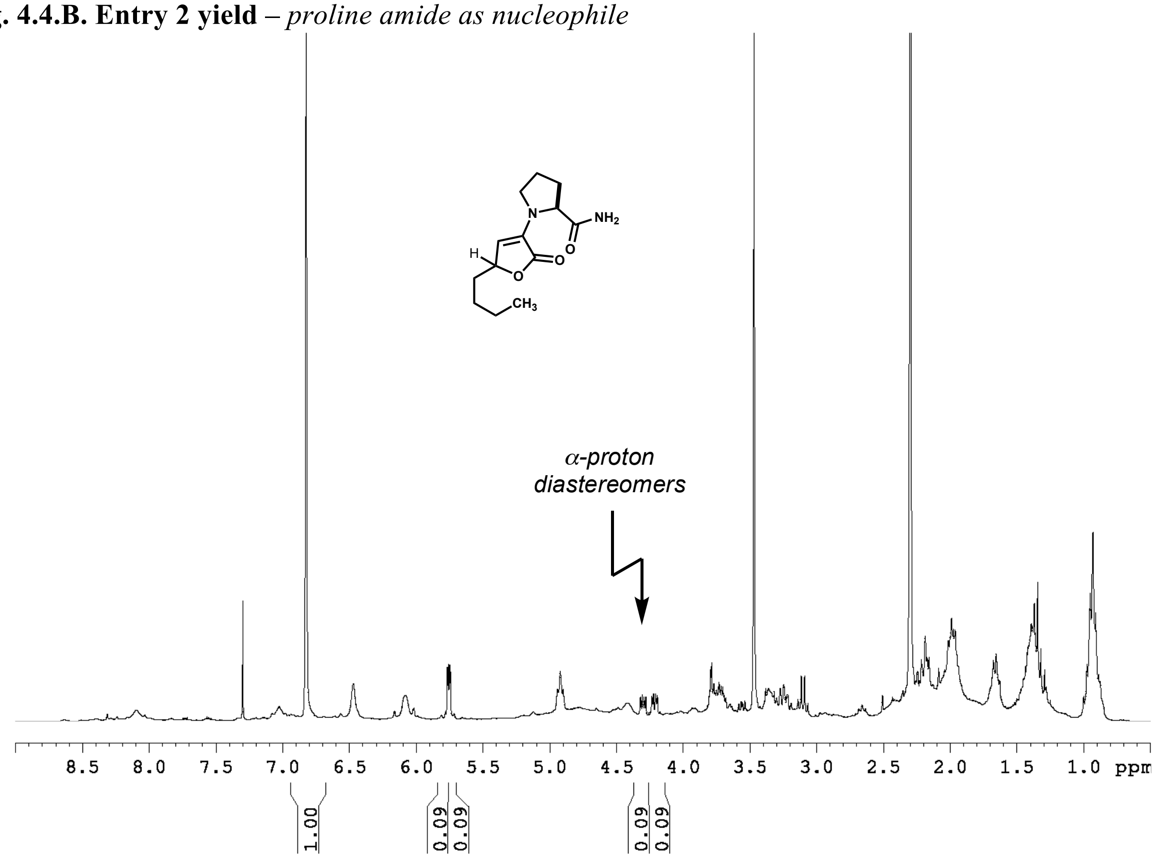
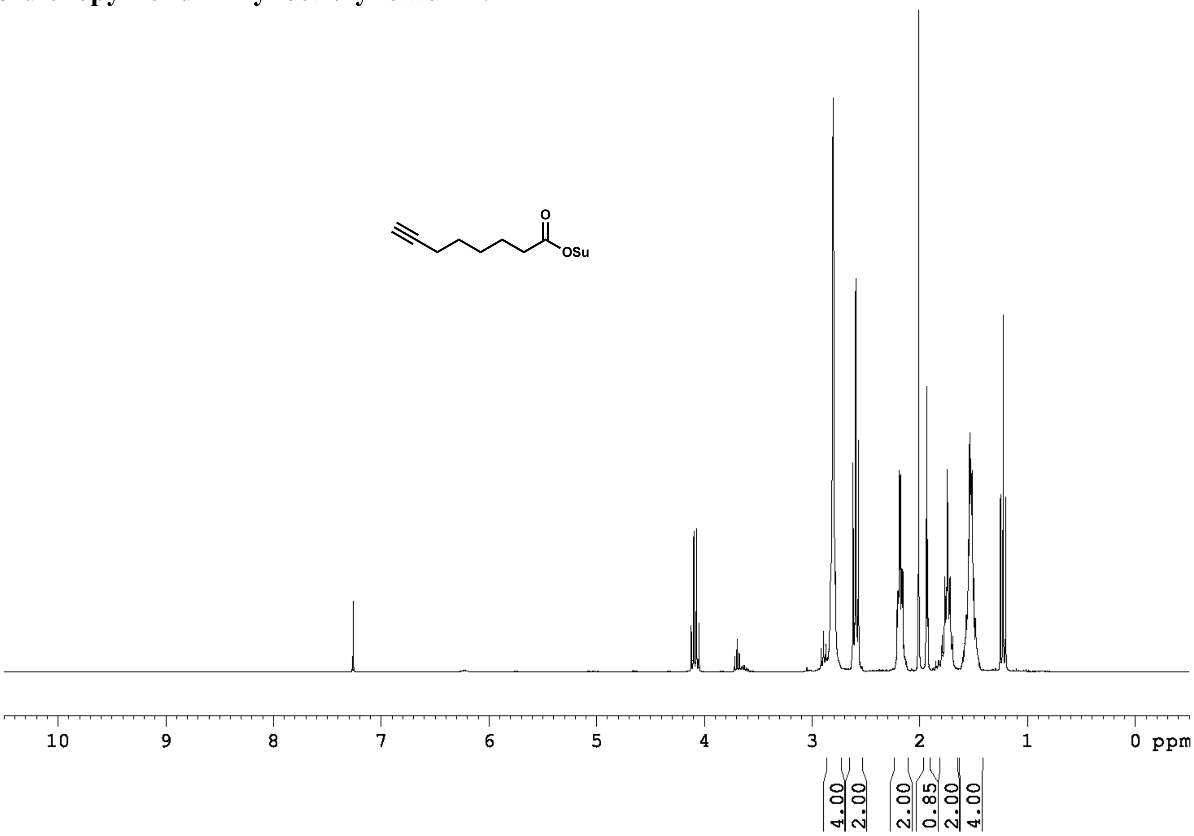
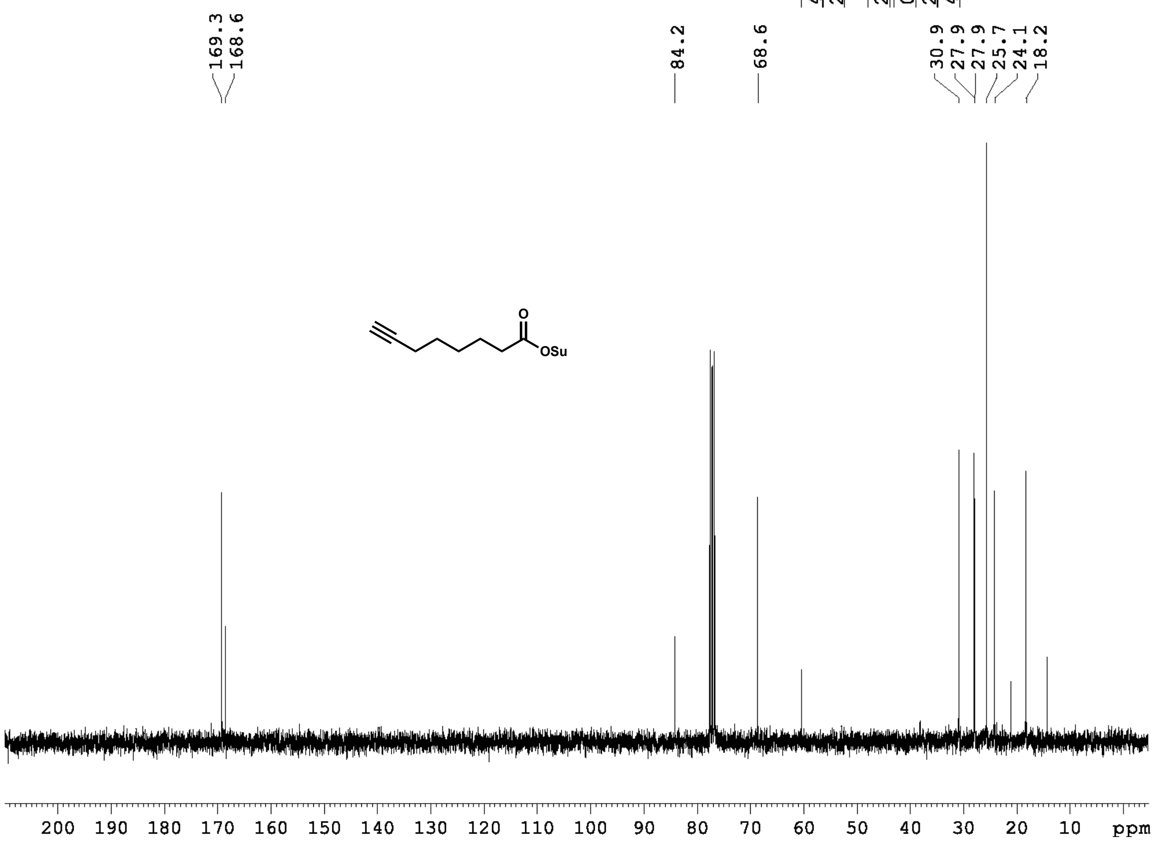


Fig. 4.4.B. Entry 2 yield – *proline amide as nucleophile*

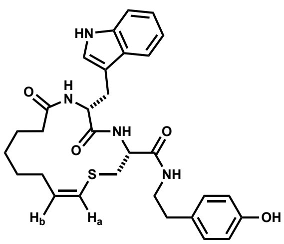


C.2. Thiol-yne model system
2,5-dioxopyrrolidin-1-yl oct-7-ynoate – 4.21

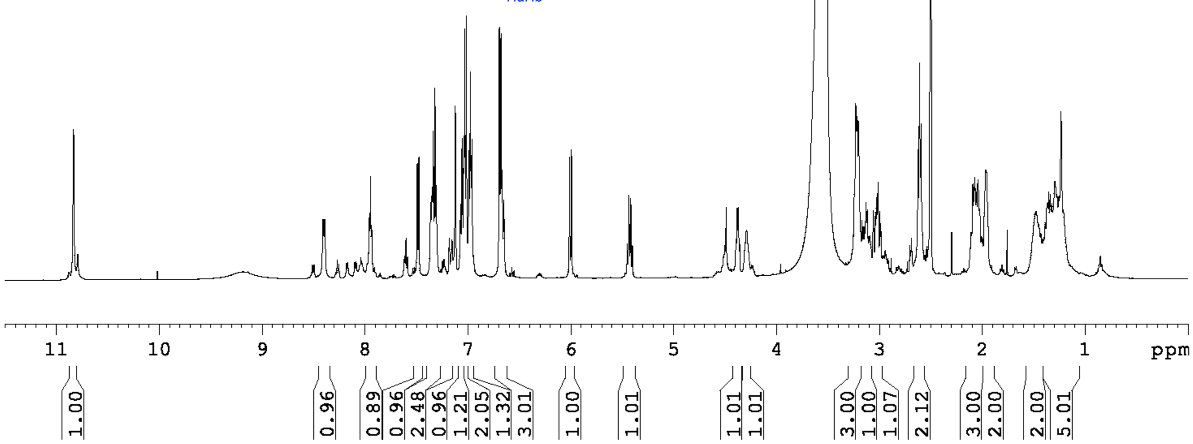


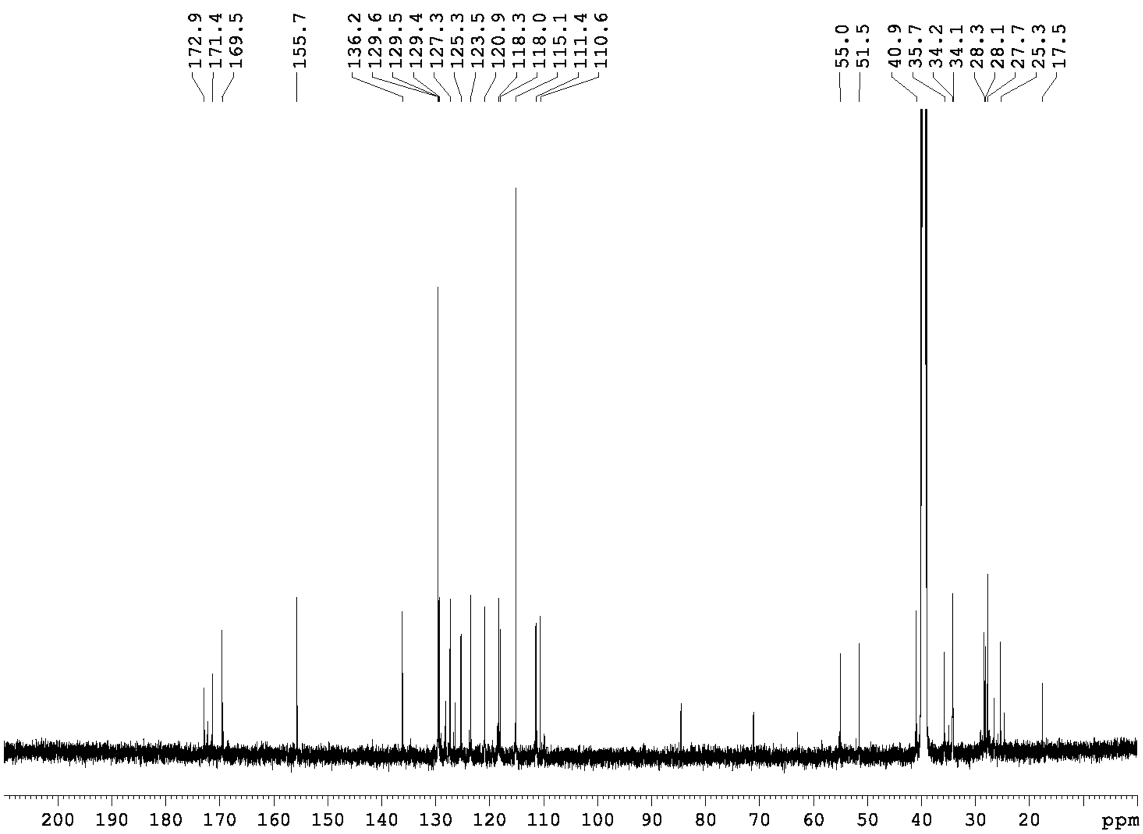


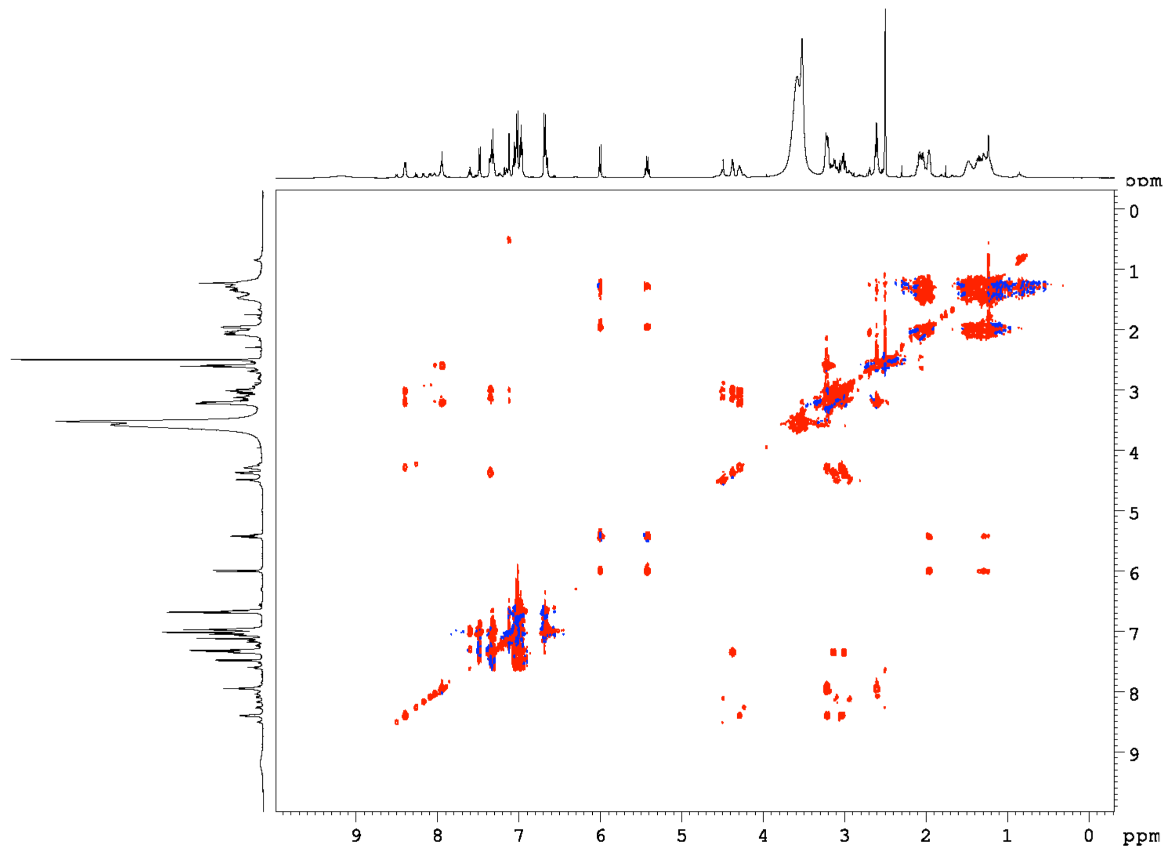
Macrocycle 4.23



$^{2}J_{HaHb}$ = 9.6 Hz



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3
4
5
6
7
8
9
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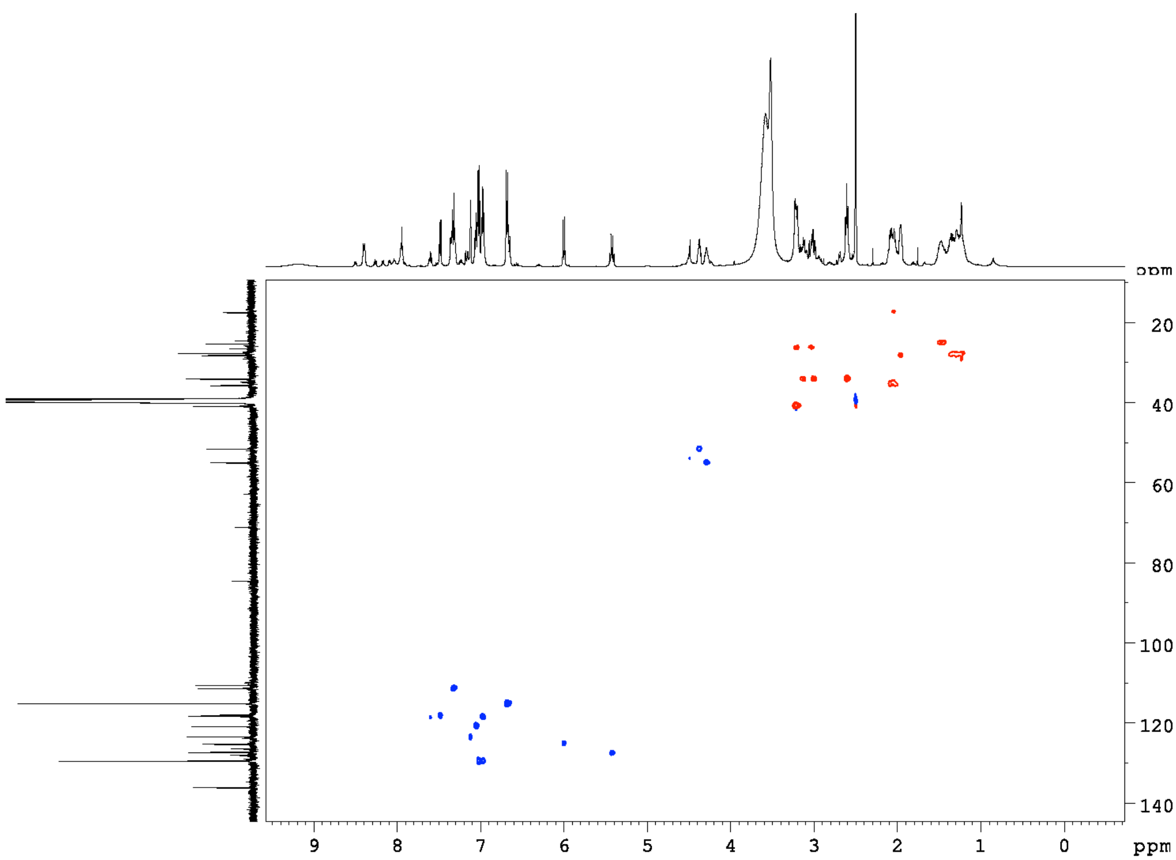
2
1
0
ppm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100
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140
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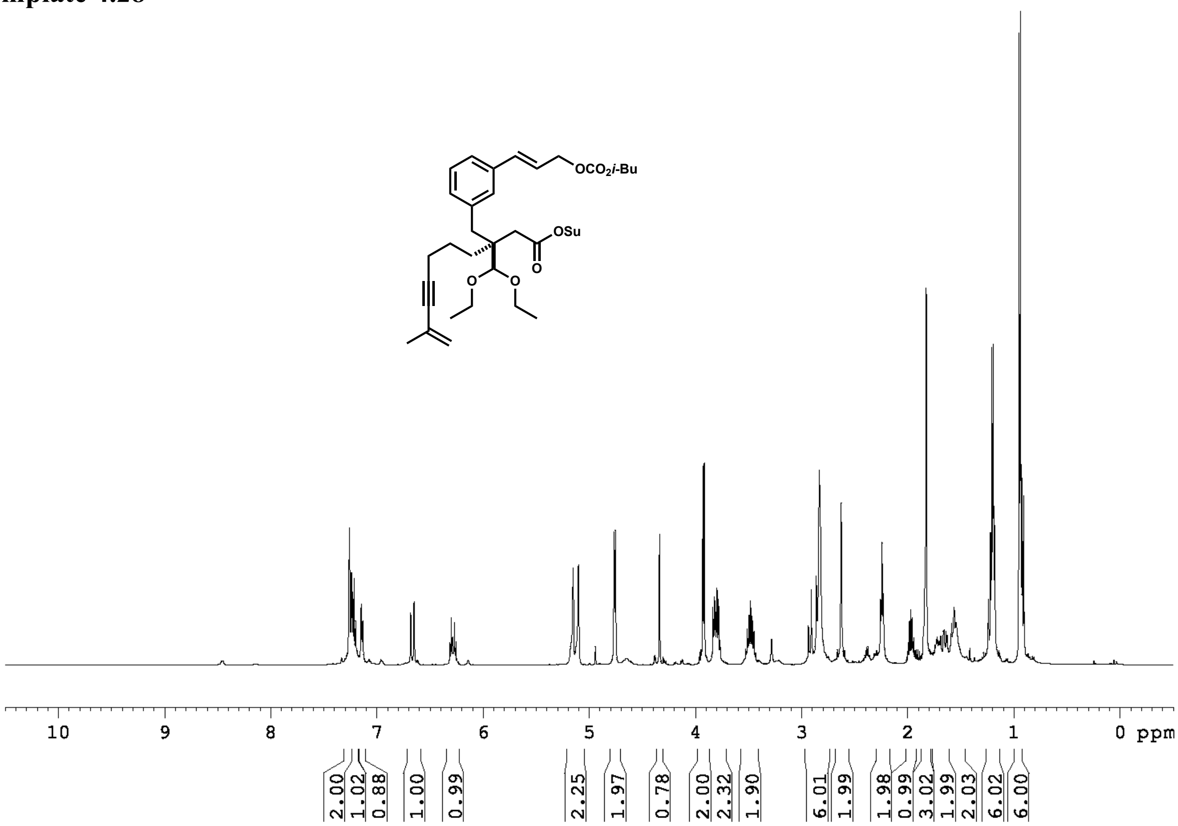
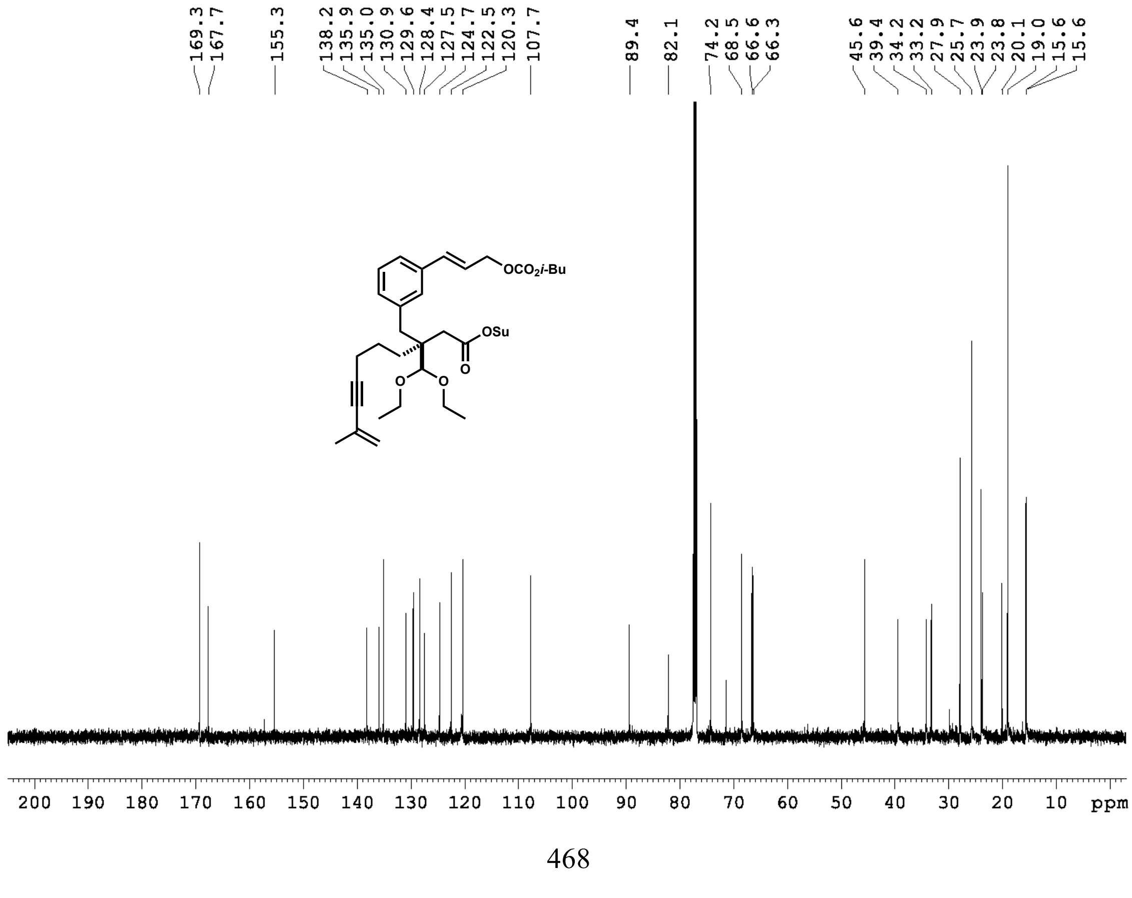
8
7
6
5
4
3
2
1
0
ppm

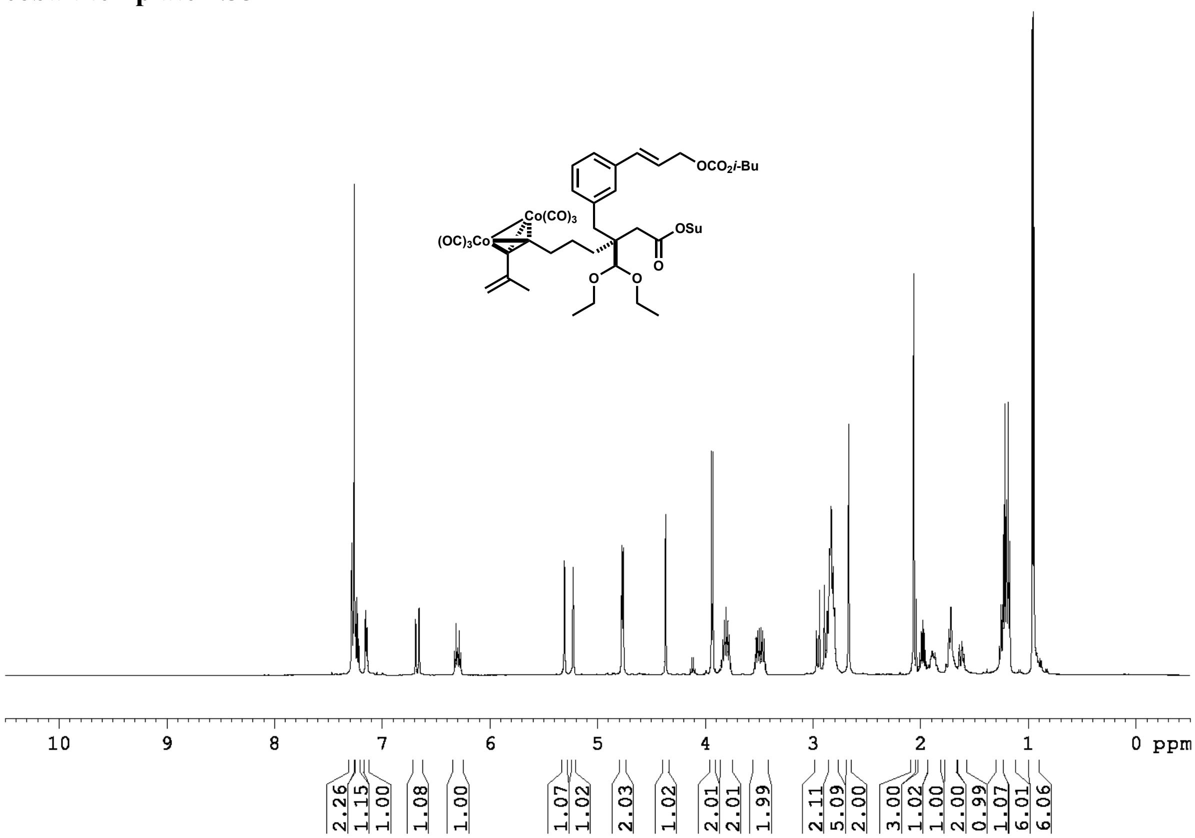
C.3. Ene-yne template synthesis

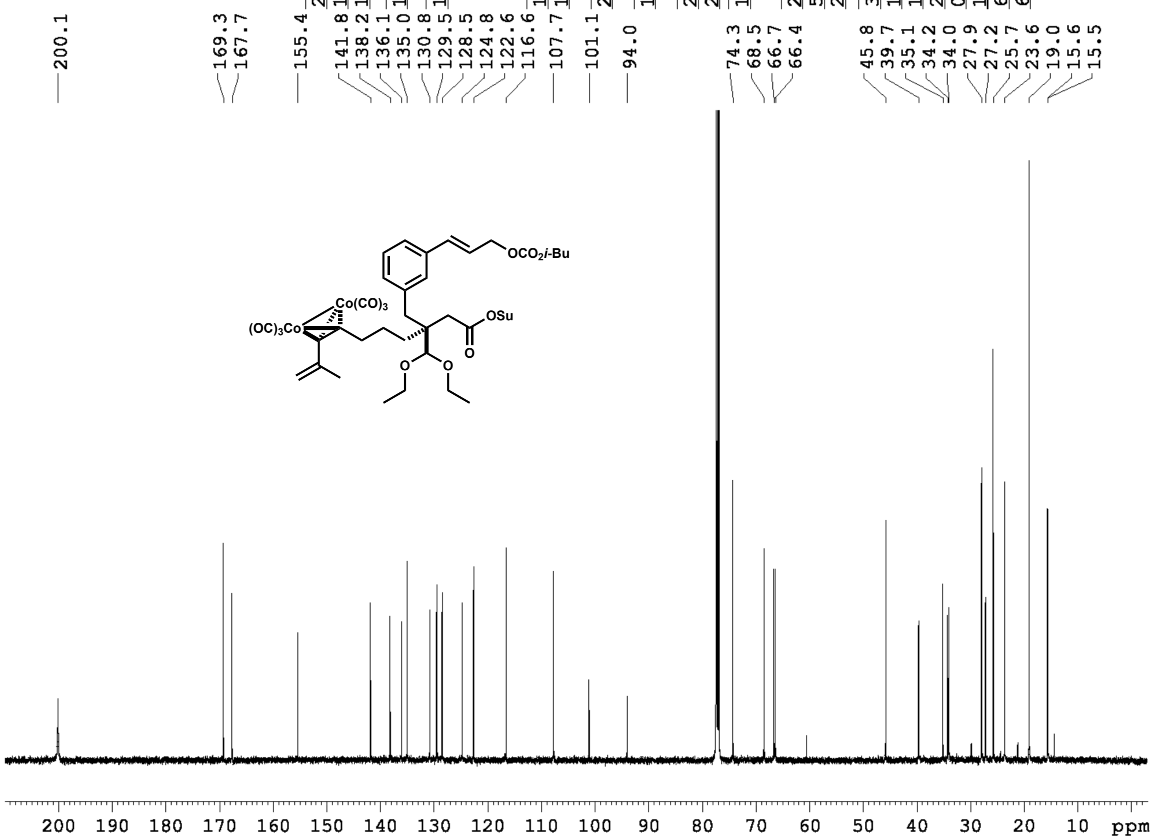
Template 4.28





C.4. Dicobalt template synthesis
Dicobalt template 4.33





D. References

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