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A Method for the Synthesis of Complex Polysulfide Linked Macrocycles Via Sulfur Transalkylation and Applications Thereof

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A Method for the Synthesis of Complex Polysulfide Linked Macrocycles Via Sulfur Transalkylation and Applications Thereof

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Chemistry

by

Luke James Sisto

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ABSTRACT OF THE DISSERTION

A Method for the Synthesis of Complex Polysulfide Linked Macrocycles Via Sulfur Transalkylation and Applications Thereof

by

Luke James Sisto

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2021

Professor Patrick G. Harran, Chair

Peptidyl macrocycles are a compound class with a rich clinical history and great potential for drugging biological targets by mediating protein-protein interactions. Methods to forge S-S disulfide bonds largely rely on the oxidation of dithiol containing substrates. We have developed and implemented a sulfur transalkylative macrocyclization induced by an appended cinnamyl carbonate-based template. This is a mechanistically new method for the construction of peptide macrocycles. The resultant macrocyclic structures contain the functionality of the linear oligomer, while scaffolding this potential pharmacophore in a more conformationally rigid manner. We aim

to improve these macrocyclic structure's biological stability and pharmacology relative to the linear oligomer.

Chapter 2 details the synthesis of mono- and disulfides via sulfur transalkylation induced by a tethered cinnamyl cation. Scope, limitations, and competition with previously reported nucleophilic residues are discussed. Methods to synthetically elaborate these structures are demonstrated and attempted. Synthesis of a potential ghrelin O-acyl transferase inhibitor is disclosed.

Chapter 3 covers the synthesis and development of two new templates designed to forge two macrocyclic bonds in one linear oligomer molecule. The use of these templates in the synthesis of bimacrocycles with sulfur and aryl linkages is divulged.

Chapter 4 centers on the synthesis and chemistry macrocyclic trisulfides. Acidolysis of template capped peptides containing *tert*-butylate trisulfide residues furnishes a mixture of mono-, tri- and pentasulfide linked macrocyclic product. Confirmation of this S_2 exchange event is demonstrated via independent synthesis of the relevant monosulfide congener obtained in these trisulfidation reactions. Additionally, our efforts toward the total synthesis of an antimicrobial trithiocane containing natural product via the trisulfidation reaction are detailed.

The dissertation of Luke James Sisto is approved.

Ellen M. Sletten

Robert T. Clubb

Hosea M. Nelson

Patrick G. Harran, Committee Chair

University of California, Los Angeles

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LIST OF ABBREVIATIONS

PPI	Protein-Protein Interfaces
Trt	Trityl
i-Pr	Iso-propyl
HDAC	Histone deacetylase
i-Bu	*Iso*-butyl
t-Bu	*Tert*-butyl
S t-Bu	*Tert*-butylthio
SS t-Bu	*Tert*-butyldithio
OSu	O-succinimide
TFA, TCA	Trifluoroacetic acid, Trichloroacetic acid
Thr/T	Threonine
Ser/S	Serine
$MeNO_2$, n-$PrNO_2$	Nitromethane, 1-Nitropropane
Leu/L	Leucine
Phe/F	Phenylalanine
Cys/C	Cysteine
Pyrr	Pyrrolidine
mM, μM	Millimolar, micromolar
2D NMR	Two-dimensional Nuclear Magnetic Resonance Spectroscopy
NMR	Nuclear magnetic resonance
Ala/A	Alanine
Glu/E	Glutamate
Lys/K	Lysine
Tyr/Y	Tyrosine
4-Me Pip	4-Methylpiperidine
Asn/N	Asparagine
Trp/W	Tryptamine
Gln/Q	Glutamine
Glu/E	Glutamate
Sar	Sarcosine
Morp	Morpholine
HMBC	Heteronuclear Multiple Bond Correlation
HSQC	Heteronuclear Single Quantum Coherence
DIPEA	Diisopropylethylamine
DMF	Dimethylformamide
NOE (NOSEY)	Nuclear Overhauser Effect Spectroscopy
dr	Diastereomeric ratio
AcOH, AcOOH, AcCl, AcSh	Acetic acid, Peracetic acid, Acetyl chloride, Thioacetic acid
TCEP	Tris(2-carboxyethyl)phosphine hydrochloride
$Sc(OTf)_3$	Scandium triflate
mCPBA	meta-Chloroperoxybenzoic acid
t-BuOOH/ TBHP	*Tert*-butyl hydrogen peroxide
DCM	Dichloromethane

NCS	N-chlorosuccinimide
DPPV	(cis-1,2-Bis(diphenylphosphino)ethene)
Ace.	Acetone
Tol.	Toluene
ACN	Acetonitrile
Boc	*Tert*-butyloxycarbonyl
Quant.	Quantitative
TBSO	*tert*-Butyldimethylsilyl-O
NMM	N-methylmorpholine
HBTU	Hexafluorophosphate Benzotriazole Tetramethyl Uronium
TBAF	Tetrabutylammonium fluoride
HPLC	High Performance Liquid Chromatography
THF	Tetrahydrofuran
SnAr	Nucleophilic aromatic substitution
BPin	Pinacol boranyl
NHS	N-hydroxysuccinimide
EtOAc	Ethyl acetate
Mrp	3-Morpholine carboxylic acid
Tf_2NH	Triflimide
Arg/R	Arginine
Und	11-Aminoundecanoic acid
COSY	Correlation Spectroscopy
TLC/ pTLC	(preparative) Thin Layer Chromatography
OMs	O- methanesulfonyl
Sn2/Sn2’	Nucleophilic substitution/ Nucleophilic substitution prime
TMS	trimethylsilyl
TIPS	triisopropylsilyl
DMP	Dess-Martin Periodinane
MOM	Methoxymethyl acetal
SEM	2-(Trimethylsilyl)ethoxymethyl
Esp	α,α,α',α'-tetramethyl-1,3-benzenediproponoate
Oct	Octanoate
DPTI	diphenyltriflylimidazolidinone
DIBAL	Diisobutylaluminum hydride
LTBA	Lithium aluminum-tri-tert-butoxyhydride
TMEDA	tetramethylethylenediamine
DMPA	2,2-Dimethoxy-2-phenylacetophenone
Phth	Phthalimide
PMB	*para*-Methoxybenzyl
DAST	Diethylaminosulfur trifluoride
Tf_2O	Triflic anhydride
KHMDS	Potassium hexamethyldisilazide
2,6 Lut./ Lut.	2,6- Lutidine
AIBN	Azobisisobutyronitrile
DCE	1,2-dichloroethatne
o-DCB	*orthro*-dichlorobenzene

Hz	Hertz
HRMS	High resolution mass spectrometry
LCMS	Liquid chromatography – mass spectrometry
mol	mole

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Curtin, B. H.; Manoni, F.; Park, J.; **Sisto**, L. J.; Lam, Y.; Gravel, M.; Roulston, A.; Harran, P. G. *J. Org. Chem*. **2018**, 83, 3090-3108. (Chapter 2)

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VITA

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Publications

3) **Sisto**, L. J.; Harran, P. G Sulfane Transalkylations and Metal Catalyzed Allylic Substitutions for the Synthesis of Composite Macrobicyclic Peptides, *Tetrahedron Lett*. **2020**, 61, 151986.

2) **Sisto**, L. J.; Harran, P. G. Syntheses of Hybrid Cyclopeptidyl [n] Sulfanes Via Internal Alkyl-Group. *Tetrahedron Lett.* **2020**, 61, 151985.

1) Curtin, B. H.; Manoni, F.; Park, J.; **Sisto**, L. J.; Lam, Y.; Gravel, M.; Roulston, A.; Harran, P. G. Assembly of Complex Macrocycles by Incrementally Amalgamating Unprotected Peptides with a Designed Four-Armed Insert. *J. Org. Chem*. **2018**, 83, 3090-3108.

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- Brandeis Alumni and Friends Scholarship (2012-2016)

Presentations and Outreach

- CBGSA outreach volunteer, El Marino Elementary Science fair (May 2018)
- Exploring Your Universe (EYU) community outreach volunteer (2017, 2018)
- 2016 Brandeis Scifest

Chapter 1- Introduction

1.1 Background and Rationale

Designing molecules to occupy enzyme active sites has been a well-trod and productive approach in medicinal chemistry. However, many actively researched pharmacological targets lack a conventional binding pocket and are in turn difficult to develop small molecule therapeutics for. Native biochemical interactions with these "undruggable" targets typically involve contact with other proteins via a shallow, solvent exposed interface.[1-2] These protein surfaces often associate with each other by recognition of short linear motifs within the recruiting protein's solvent exposed surface.[3] Engagement of these surfaces (Protein-Protein Interactions, PPIs) requires a conformationally accessible structure, harboring proteomic functionality, and scaffolding it in a suitable three-dimensional arrangement. Macrocycles, in particular small peptide macrocycles, are fitting candidates with these characteristics. A peptide macrocycle can contain functionality reminiscent of a native PPI scaffolding partner while having improve proteolytic stability, pharmacokinetics, ease of synthesis, therapeutic efficacy, and conformational rigidity.[4-6] While macrocycles have always featured prominently in medicinal natural products, only recently has industry pursued *de novo* macrocycle synthesis in earnest (*i.e.* figure 1.1 B, C).[7-11]

Classic tactics for the synthesis of macrocyclic peptides center on methodologies such as reductive amination, amide, and ester bond formation. Recent condensation-based methodologies include ring contractive amide bond formation via O to N-acyl migration[32] and imine forming macrocyclizations with subsequent heterocycle incorporation[30,31]. Advances in copper catalysis have delivered macrocyclizations via Huisgen cycloaddition [23-26], Sonogashira[27], and Glaser

couplings[55-57]. Olefin[17,18] and alkyne[34] metathesis have proven amenable to peptide macrocyclization, relying on ruthenium and molybdenum catalysis respectively. The burgeoning

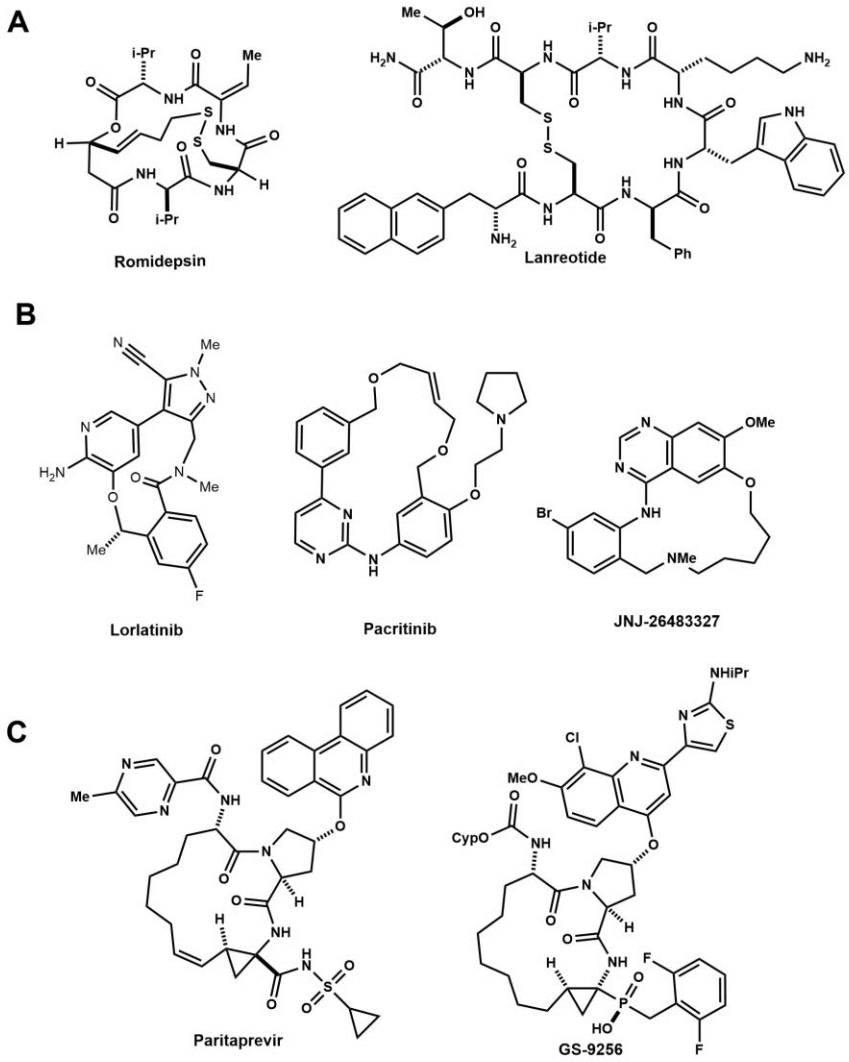

Figure 1.1. A FDA approved disulfide macrocycles. **B** De Novo synthesized peptide macrocycles in recent clinical trials.

field of C-H activation has provided a wealth of new methods to construct peptide macrocyles[20-22]. Palladium catalysis has likewise produced a large body of macrocyclization methods, including examples of Stille[26], Heck[28], and Buchwald-Hartwig[29] couplings. Multicomponent methodologies, mainly Ugi, Yudin, and Passerini reactions, have emerged as an attractive approach for rapid and combinatorial macrocycle library synthesis[16]. More recently, methods to synthesize macrocycles

from genetically encoded peptides have gained prominence, merging biological and chemical synthesis.[54]

With synthetic access to complex peptide macrocycles becoming more feasible, so too has their use as functional therapeutics and biochemical tools. For instance, oncological sciences have seen new macrocyclic kinase inhibitors such as FDA approved Lorlatinib[37], clinical candidates Pacritinib[58], and JNJ-26483327[59] (figure 1.1. B). Additionally, cytostatic agents[36], oncogene specific PPI mediators[35], and apoptosis inducing agents[33] have been reported. Another medical breakthrough enabled by macrocycles is Hepatitis C treatment. Once a chronic and devastating disease, HCV can now be effectively cured in upwards of 90% of patients with macrocyclic compounds (see figure 1.1. C for 2 experimental HCV drugs). This dramatic change in HCV prognosis can be traced to the successful development and adoption of antiviral peptidomimetics, particularly of the macrocyclic and C2 symmetric variety. More general medicinal chemistry targets have also been pursued with these strategies, such as GTPase targeting bimacrocycles[34] and renin inhibtors[38]. As synthetic chemistry and drug discovery programs continued to advance in concert, we expect to see further examples of peptidyl and or *de novo* designed macrocycles in the clinic.

While a litany of new methods has enabled this macrocycle renaissance, very few operate by engaging natural peptidyl functionality beside simple condensation reactions. Turning our attention to the realm of natural products, we frequently see varied C-C and C-heteroatom linkages within macrocycles.[12] Seeking to mirror this outcome, our laboratory has developed a series of chemical templates that can react with unprotected peptidyl functionality under various conditions to afford a diverse host of macrocycles (figure 1.2 B). These templates consist of a cinnamyl carbonate and other electrophiles poised for incremental cyclization reactions, tethered to an

activated ester for ligation to peptidyl amines. Acidolysis furnishes C-C linked macrocycles via Friedel-Crafts alkylation of tyrosine, tryptophan and various unnatural, non-pi basic aromatic side chains.[46-48, 50,51] Alternatively, palladium catalyzed Tsuji-Trost reactions in these systems furnish heteroatom linked macrocycles with tyrosine, histidine, carboxylates, amines and free thiols.[45,49] Emulating the imbedded heterocycles frequently seen in natural products[12], templates have been designed to furnish β-carbolines and other fused heterocycles via Picket-Spengler reactions. [50,52] These hetero- and macrocycle formations decrease the number of amide N-H and freely rotatable bonds present in the products, transforming a peptide into a composite amphipathic structure with increased drug-like character and less peptidyl nature.

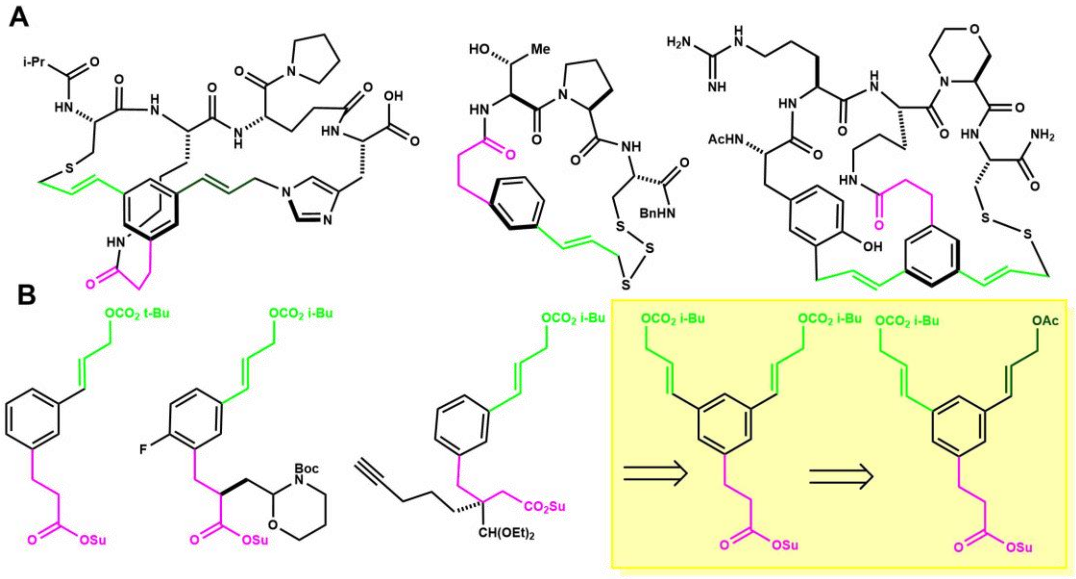

Figure 1.2. A Unique macrocycles derived from the polysulfide transalkylation research program. **B** Evolution of bimacro-cinnamylation templates & previously designed multi-armed templates.

Recent efforts in our research group centered on macrocycles containing disulfides, which are a privileged motif in the chemistry of the proteome[39,40,42]. We have sought unique methods to incorporate this moiety into the template constrained peptide macrocycle project. Disulfides serve as a reductively labile covalent bond, capable of inducing considerable changes in confirmation

and supramolecular association of biomolecules based on their environments.[41,43] Disulfide linked peptide macrocycles have featured prominently in pharmaceutical and natural product chemistry [14], with several somatostatin analogs (*i.e.* lanreotide), the HDAC inhibitor romidepsin, and conotoxins[44] being of note (see figure 1.1. A). Despite this clinical adoption of disulfide linked peptide macrocycles, commonly used methods to forge them thus far rely solely on the oxidation of linear dithiol precursors. We have discovered a new modality for the synthesis of di- and monosulfide linked macrocycles, a redox neutral transalkylation of *tert*-butylated polysulfides to furnish cysteine polysulfide-cinnamyl linked products (chapter 2) .[52]

Additionally, we have developed a series of templates capable of forming multiple macrocyclic linkages (chapter 3.). These templates can participate in one-pot acid induced bimacrocyclizations or engage in sequential metal catalyzed ring forming processes. We demonstrate the use of these templates in forming bimacrocycles from simple peptides in several steps. Such systems hope to emulate the biosynthetic processing of non-ribosomal peptides into poly-macrocyclic products in a synthetic setting.

Despite their presence in the proteomone[42] and obvious analogy to disulfides, trisulfides have received comparatively little attention from the synthetic community. While synthetic programs centered on disulfide bearing peptide macrocycles inspired by natural products are well established and fruitful[13,15], the same cannot be said for trisulfides. Fortunately, our previously discovered sulfur-based transalkylation reaction can be applied to the synthesis of trisulfide linked macrocycles (chapter 4.). In the trisulfidation systems a S_2 exchange event occurred, wherein we isolate mono-, tri-, and pentasulfide linked macrocycles with total yields comparable to the analogous disulfidations. We have applied this unique trisulfidation reaction towards the synthesis

of an antimicrobial trithiocane containing secondary metabolite (chapter 4 & figure 1.3.).[53] Future directions for this technology and applications of the derived structures will be discussed.

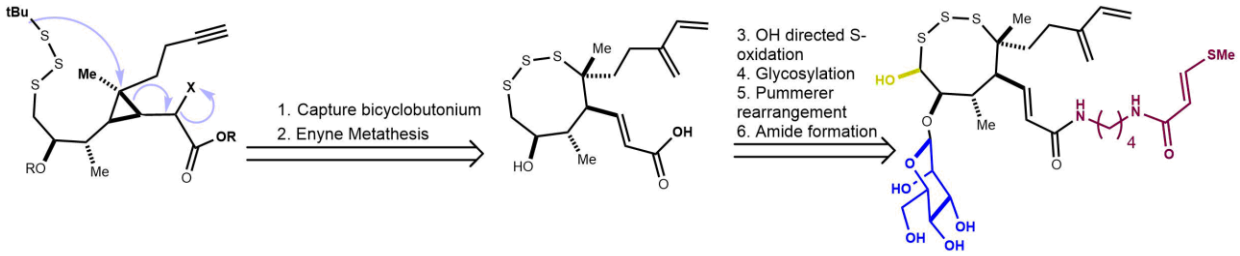

Figure 1.3. Proposed retrosynthesis of a tunicate-derived trithiocane containing antimicrobial natural product.

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2 Synthesis of mono- and disulfide macrocycles via sulfur transalkylation

2.1 Introduction

Disulfides occupy a privileged role in biochemistry and chemical biology[1-3]. Methods to forge disulfides universally require the oxidative formation of a sulfur-sulfur bond[4,5] (figure 2.1 A). This is the case in biosynthesis and synthetic chemistry, with many reported disulfide containing natural products being well-studied.[6] Thioethers are likewise ubiquitous in the proteome and as secondary metabolites. SAM (S-adenosyl methionine), a sulfonium, is central to biomolecule methylation. This impacts mediation of protein translation[7] (*i.e.* Kozak sequences), genomic regulation[8] (*i.e.* DNA methylation), and natural product biosysnthesis[9]. All implicate a net sulfur transalkylation via sulfonium intermediates. Synthetic strategies to form thioethers typically rely on the alkylation or Michael addition of a free thiol (figure 2.1. B). Biosynthetic manifolds also feature the Michael addition of thiols[10,11] (*i.e.* lanthipeptide biosynthesis), as well as the net sulfur transalkylation widely seen in SAM mediated processes.

Sulfur transalkylation is known in total synthesis[14,15] and methodology[16]. Its general utility and study to date has centered on acyclic and small ring containing systems. Oxidative net transalkylation to form macrocycles is known, though the role of oxidant mechanistically distinguishes it from redox neutral variants (scheme 2.1. B).[13] Herein we report the discovery, development, and utilization of a templated based system for the macrocyclization of peptides via sulfur transalkylation. These reactions are hypothesized to proceed through a macrocyclic sulfonium intermediate and at no point is thiol invoked in the proposed mechanism (figure 2.1. C). This stands in contrast with the current paradigm of dithiol oxidation for the formation of disulfide bonds in the context of macrocycles, peptidomimetics, and small molecules.

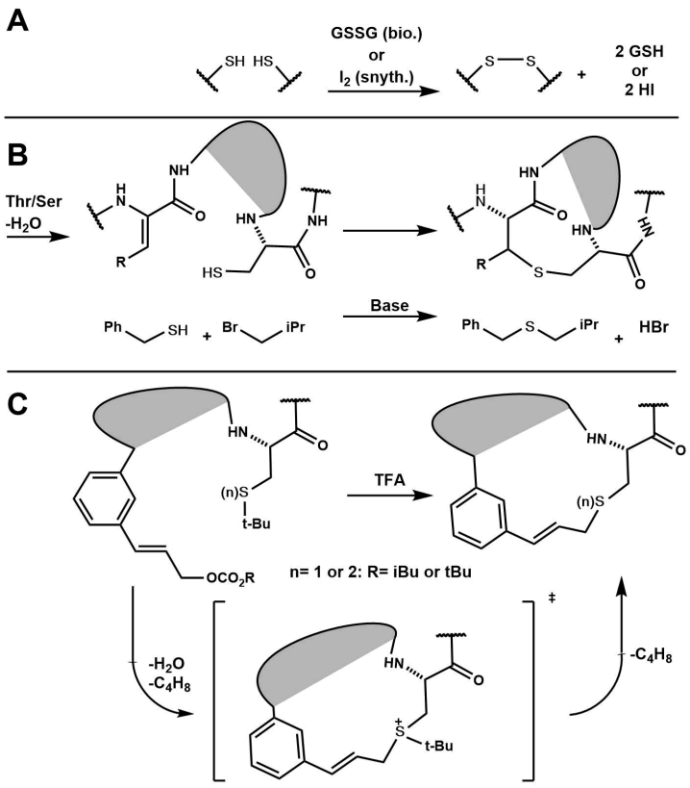
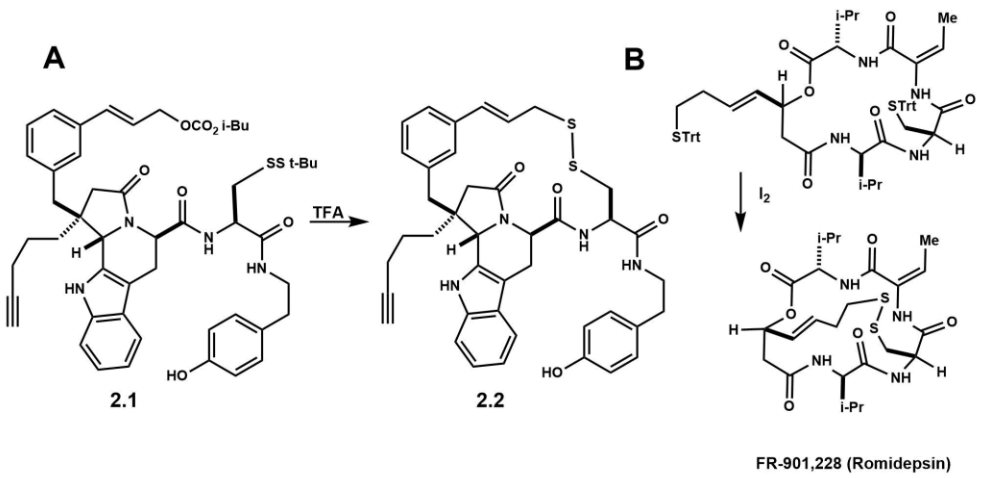


Figure 2.1. A Disulfide biosynthesis proceeds via dithiol oxidation to forge an S-S bond. Synthetic methods mostly employ this manifold, though persulfidations and transalkyation are known. **B** Biosynthesis and synthesis of thioethers center on Michael additions and nucleophilic displacements with thiol respectively. **C** The unified synthetic approach disclosed for synthesis of macrocyclic thioethers and disulfides.

The scope of these sulfidations are presented and competitions with known nucleophilic residues are explored. Use of a previously reported multi-armed template with the transalkylation methodology is demonstrated, as is S-S reduction and subsequent arylation to furnish macrocycles with embedded fluorocarbo- and heterocycles. Efforts towards the selective oxidation and rearrangement of these scaffolds will be discussed. Synthesis of a potential ghrelin-O-acyl transferase inhibitor utilizing the method shall be divulged.



Scheme 2.1. A Discovery of a transalkylative macrocyclization. **B** Examples of sulfur (oxidative) transalkyation in total synthesis

2.2 Results and discussion

2.2.1 Effect of ring size and polar functionality

In the seminal report[17] compound **2.1** was intended to undergo a Friedel-Crafts macrocyclization to furnish a tyrosinyl C-C linked product. An equimolar amount of disulfide **2.2** was isolated and characterized, indicating an apparent sulfur transalkylation (scheme 2.1. A). It should be noted that *tert*-butylated sulfides are inert to acidic conditions, routinely being carried through solution phase peptide synthesis with multiple Boc deprotections (TFA). Seizing upon this intriguingly selective reaction, we first sought to probe the effect of incipient ring size on reaction efficiency. Synthesis commenced with the solution phase coupling of pyrrolidine to (L)-N-Boc-*tert*-butylthiocysteine. The resultant pyrroloamide was deprotected and incrementally extended with one, two or three leucine residues. This set of peptides was in turn N-Boc deprotected and acylated with our previously described template **2.3**. Upon acidolysis we observed slightly higher yields for the four residue macrocyclic disulfide **2.7** (table 2.1. entry 2) compared to the five residue variant **2.9** (table 2.1. entry 3). The three-residue system (**2.4** to **2.5**) afforded the lowest, albeit a synthetically useful yield (table 2.1. entry 1). Given our interest in small (2 to 5 residue)

peptides, we considered an investigation of the upper limit of macrocycle size (6+ residues) to be unnecessary.

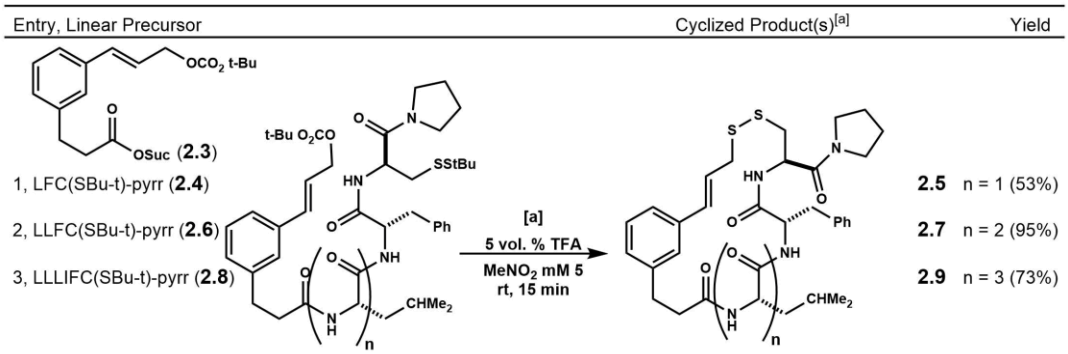


Table 2.1. Impact of ring size on disulfidation.

While we were confident in the identity of our products, it should be noted that conventional through-carbon bond methods of 2D NMR structural validation could not be used to unequivocally prove a disulfide linkage. This was achieved by crystallization of **2.5** via slow diffusion of pentane into a chloroform solution containing this product. The resultant crystal (Figure 2.2) was of space group 19 and featured a cuboid unit cell measuring **a** 5.31100(10)X **b**

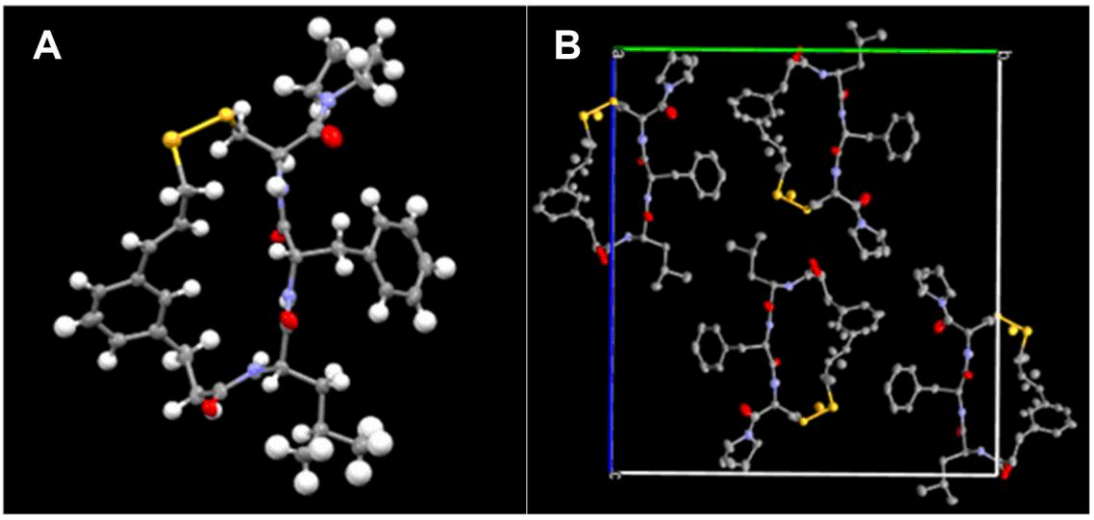
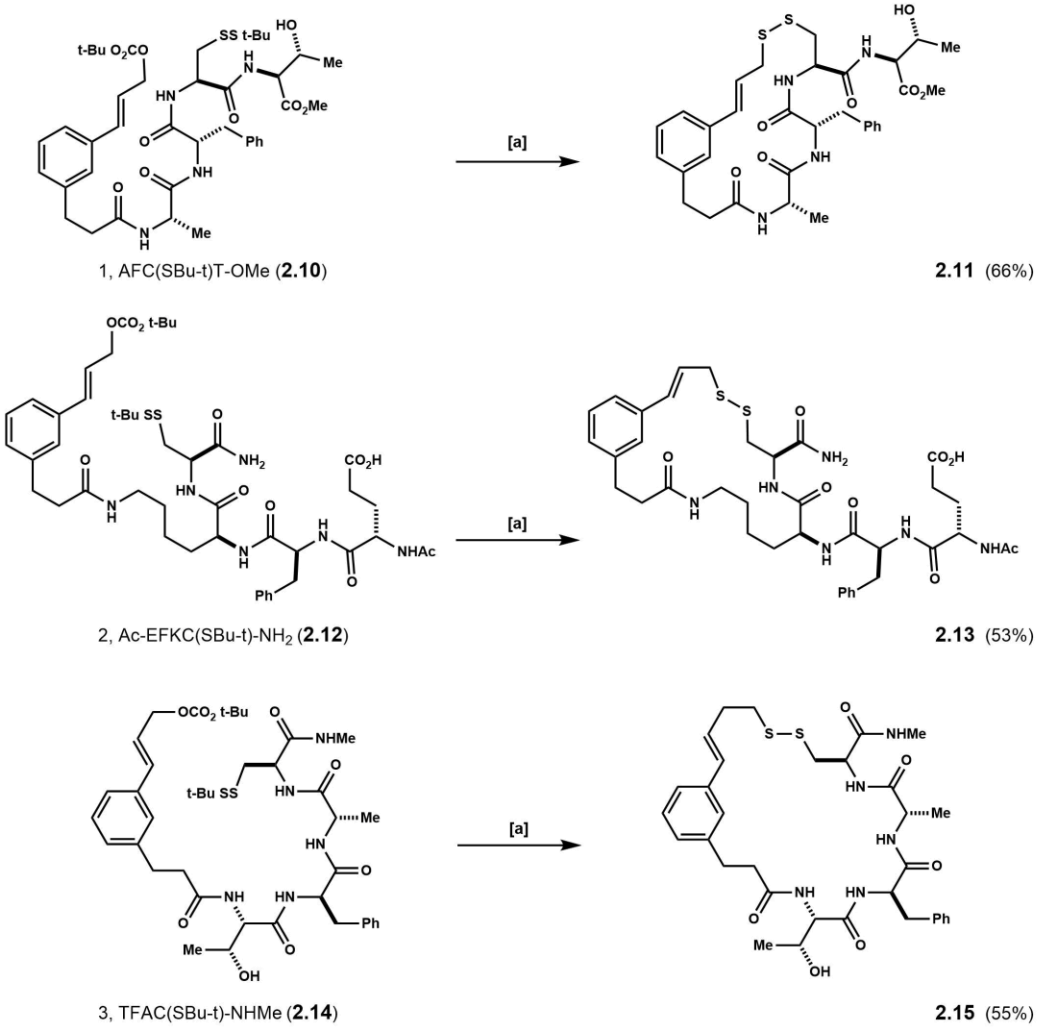


Figure 2.2. A Cyrstal struture of **2.5** as visualized in Mercury 4.2.0 , 50% probability thermal ellipsoids.**B** Unit cell thereof.

23.6454(5)X **c** 26.0025(6) **Å.** This unit cell contained three molecules of **2.5** and showed disorder in the disulfide and olefinic regions. [41]

With the effect of incipient ring size explored and the veracity of the reaction proven by crystallography, we set about testing the system's tolerance of polar functionality. Past reports of cinnamyl carbonate-based macrocyclization methodologies demonstrated a wide array of tolerated functionality[17-19,42]. Investigation started with the incorporation of alcohols, namely threonine, into



[a] 10 vol. % TFA,, 5 mM $MeNO_2$, rt, 15 min.

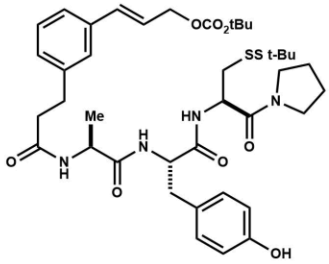
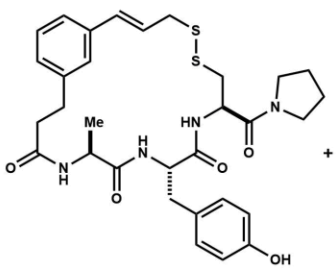
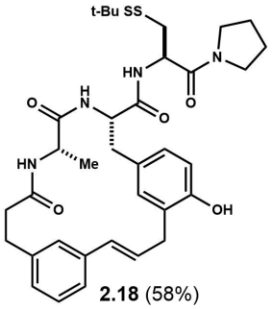
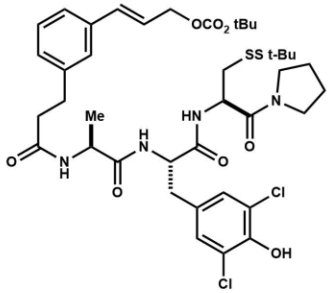
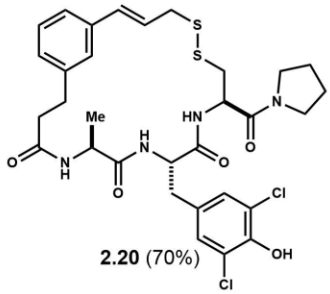
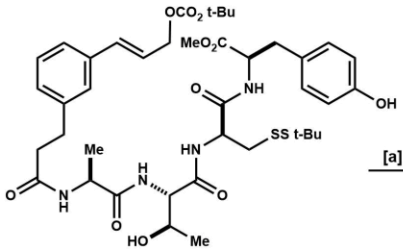
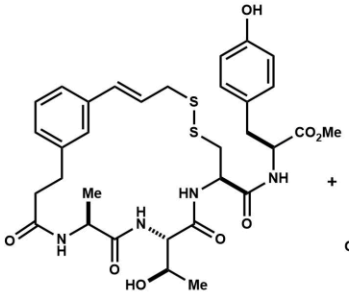
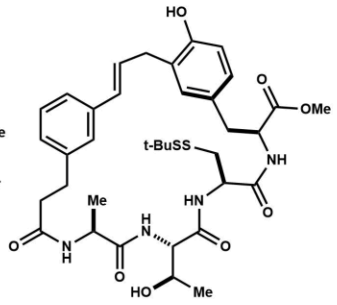
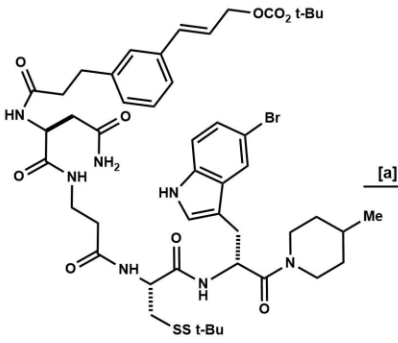
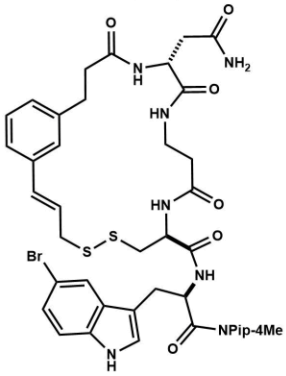
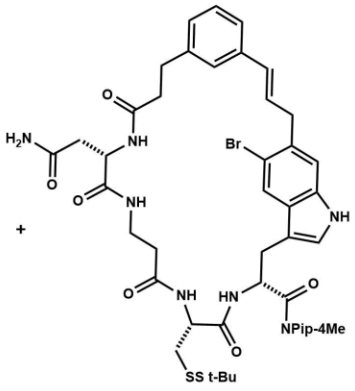
Table 2.2. Impact of polar functionality on transalkylative macrocyclization.

linear precursors. Acidololysis of substates **2.10** and **2.14** smoothly afforded macrocycles **2.11** and **2.15** respectively (table 2.2. entries 1, 3). It should be noted that no ester hydrolysis products of **2.10** or **2.11** were detected in the timespan of experiments. Free carboxylic acid **2.12** readily provided macrocycle **2.13**, a lower yield likely resulting from the poor solubility of product that necessitated HPLC purification opposed to SiO_2 gel column chromatography (table 2.2. entry 2). These experiments by no means capture the full scope of tolerated amino acid functionality. Further examples will demonstrate the compatibility of amines (chapter 2, *vide infra*), imidazoles, guanidines (chapter 3), and polysulfides (chapter 4) with this reaction.

2.2.2 Competitions with aromatic residues and thioetherfication

Competition experiments between sulfide formation and aromatics residues were explored starting with compound **2.16** (table 2.3. entry 1). Upon acidolysis the Friedel-Crafts and disulfide products were readily separable via column chromatography, furnishing disulfide **2.17** and C-C linked macrocycle **2.18** in 35 and 55 % yield respectively. Expectedly, dichloro-tyrosine variant **2.19** provided only the disulfide linked product **2.20** (table 2.3. entry 2). When reacting a substrate containing tyrosine distal from the template, as is the case in compound **2.21**, the ratios of disulfide and Friedel-Crafts product are reversed. Acidolysis of **2.21** provided disulfide **2.22** and carbon-linked product **2.23** in 55 and 28% yield respectively (table 2.3. entry 3).

This suggests that the cinnamyl cation generated under these conditions has approximately equal affinity for *tert*-butyl thiocysteine and tyrosine. Product distribution is dictated by the proximal or distal nature of these residues. A long-standing feature of our template system is the regiodivergent alkylation of tryptophan to form topologically distinct C-C linked macrocycles. We sought to assess the competition and compatibility between tryptophan and *tert*-butyl thiocysteine

Entry, Linear Precursor	Cyclized Product(s)[a]
 1, AYC(SBu-t)-pyrr (**2.16**)	 **2.17** (35%) +  **2.18** (58%)
 2, AY(dichloro)C(SBu-t)-pyrr (**2.19**)	 **2.20** (70%)
 3, ATC(SBu-t)Y-OMe (**2.21**)	 **2.22** (55%) +  **2.23** (28%)
 4, NbAC(SBu-t)5-Br(d)T-NPip-4 Me (**2.24**)	 (**2.25**) (34%) +  (**2.26**) (58%)

[a] 10 vol. % TFA,, 5 mM $MeNO_2$, rt, 15 min.

Table 2.3. Nucleophilic residue competition experiments.

residues. Product **2.24** was cyclized to furnish two readily separable spots corresponding to a mixture of Friedel-Craft products, mass yield 58%, and disulfide **2.26** in 34% yield (table 2.3.

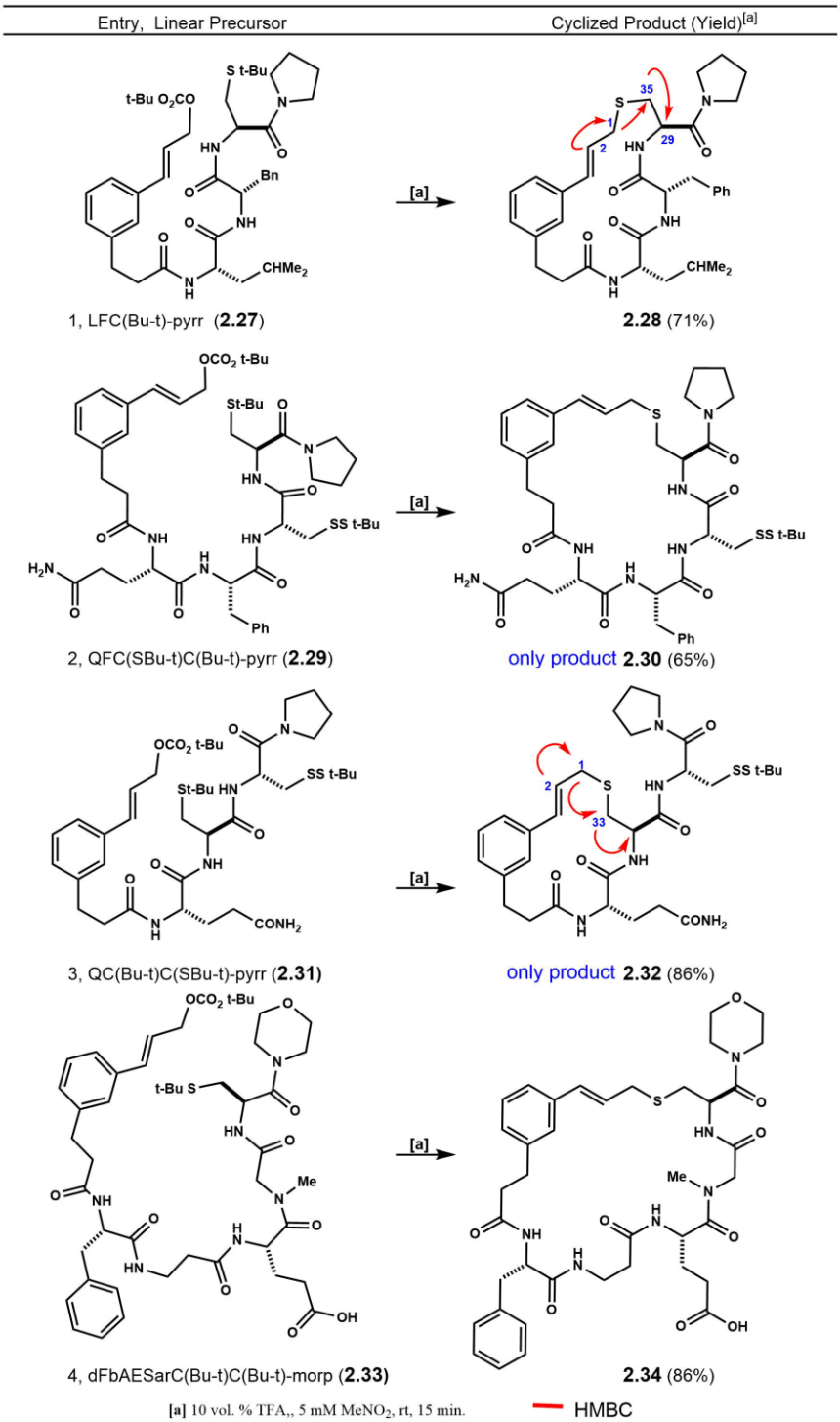


Table 2.4. Macrocyclic monosulfides and residue competitions.

entry 4). HPLC purification and structural elucidation revealed the major tryptophan regioisomer to be **2.25**. These results indicate that tryptophan residues, even halogenated derivates, can readily out compete *tert*-butyl thiocysteine regardless of their proximal or distal nature. Exceptions to this are found when considering substrates with template-fused β-carbolines (*i.e.* **2.1** and **2.39**).

We next sought to extend this methodology to macrocyclic thioethers. Upon cyclization of compound **2.27** we were pleased to find that transalkylation occurred, furnishing macrocyclic thioether **2.28**. This product is analogous to disulfide **2.5**, but isolated in improved yield (table 2.4. entry 1). We next sought to test the competition of *tert*-butyl disulfides verses *tert*-butyl thioethers. Stunningly, we observed complete selectivity for macrocyclic thioether products, regardless of the distal (**2.29**) or proximal (**2.31**) nature of the sulfides (table 2.4. entries 2, 3 respectively). Compound **2.32** is example of a two-residue containing macrocycle obtained in excellent yield. Given the tendency for glutathione mediated reduction of disulfides *in vivo*, these macrocyclic thioethers are likely more structurally stable molecules in potential therapeutic applications. This enables the acyclic disulfide in these structures to undergo synthetic elaboration or *in vivo* reduction and interactions with protein-based targets. These macrocyclic thioetherifications likewise proved tolerant of free carboxylic acids, D-amino acids, and N-methyl amides (table 2.4, entry 4, **2.34**).

Reactivity of the thioethers was confirmed via rigorous 2D H-NMR characterization of **2.27**, namely the HMBC correlations across the thioether bridge as seen in figure **2.3**. Exclusive

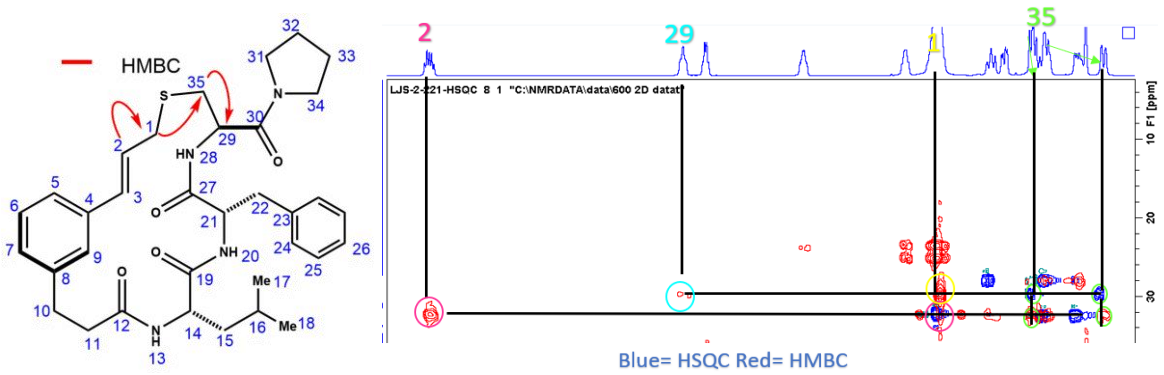


Figure 2.3. Key HMBC correlations of **2.28.**

reactivity of the thioethers in competition with disulfides was established in a similar fashion in compound **2.31** (figure 2.4). Additionally, TCEP reduction of **2.31** and HPLC characterization of the resultant thiol bearing thioether was used to corroborate this outcome.

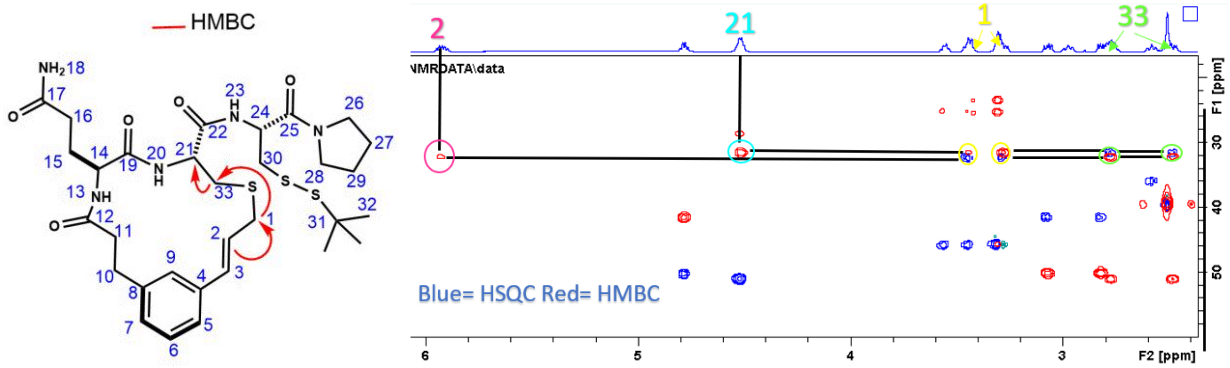
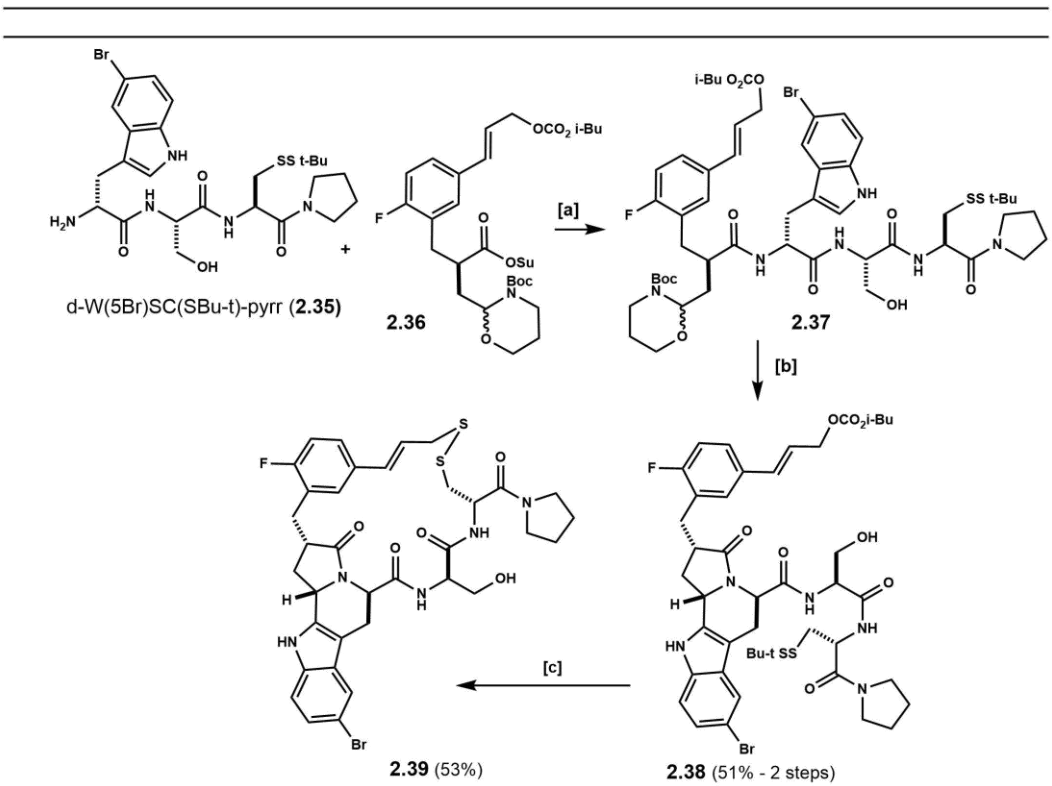


Figure 2.4. Key HMBC correlations of **2.32.**

2.2.3 Embedding hetero- and fluorocycles in disulfide macrocycles.

During our efforts to develop reagents that incrementally react with and alter the properties of peptides, we have reported a series of increasingly functional templates. Template **2.36** was developed to react with N-terminal, non-pi basic heteroaromatics via Pictet-Spengler reactions before subsequent macrocyclizations by various means. Engagement of indoles to furnish β-carbolines is most prominent in our system given tryptophan's place as a canonical amino acid.

While compound **2.3** demonstrated this reaction's compatibility with one template[17], we then sought to employ template **2.36** in a similar fashion[18]. Peptide **2.35** was acylated with template **2.36**, furnishing compound **2.37**. **2.37** was subsequently subjected to mild acidolysis (AcOH) providing Picket-Spengler product **2.38** in 51% yield. Treatment of **2.38** with 10 vol% TFA in 5 mM $MeNO_2$ furnished macrocyclic disulfide **2.39** in 53% yield with a *dr* of 10:1. Lack of NOE correlation between the pyrrolo-β-carboline and tryptophan-derived methines of **2.39** supports a trans relationship, as does literature precedent of relative stereochemistry[18]. The *tert*-butylthiolated cysteine residue performed as intended, allowing three simple operations to convert a linear peptide into a stable polycyclic product having only two freely rotatable bonds. (scheme 2.2.).

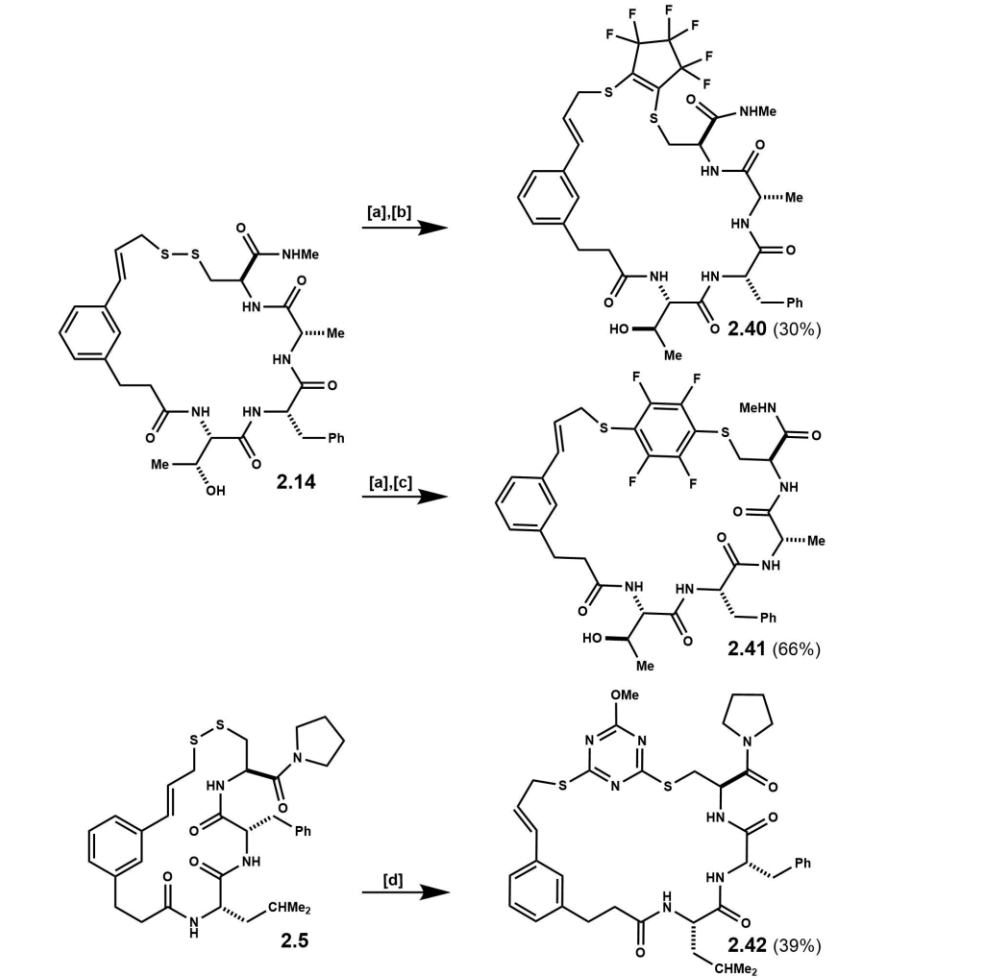


[a] 1.0 equiv **2.36**, 1.1 equiv. **2.35**, 4.0 equiv. iPr_2NEt , DMF, rt ,2 h **[b]** 4:1 AcOH: H_2O, 48 h, rt. **[c]** 10 vol.% TFA, $MeNO_2$, 5 mM, rt, 15 min.

Scheme 2.2. Use of pyrroloindoline forming template **2.36**.

As previously stated, disulfide bonds are reactive *in vivo* and a liability in terms of macrocycle structural integrity. To circumvent this, we sought methods to insert stable

functionality in between reduced dithiols in a macrocyclic fashion. To this end, **2.14** was treated with the selective S-S bond reductant TCEP before reacting with a bis-electrophilic fluorocycle. Firstly, we sought to employ our previously disclosed method to insert octafluorocyclopentene into disulfides.[19] This led to the isolation of macrocycle **2.40** in 33% yield over two steps. Additionally, we exploited the selective thiophilic reactivity of hexafluorobenzene [20-22] to provide.



[a] 2.2 equiv. TCEP HCl, 8.8 equiv. iPr_2NEt, DMF, 25°C, 1 h **[b]** 1.5 equiv. perfluorocyclopentene, 1.5 equiv. Cs_2CO_3, 0.01 M DMF, rt, 1 h **[c]** 5.5 equiv. perfluorobenzene, 5.5 equiv. iPr_2NEt. 0.01 M DMF,45°C, 12 h. **[d]** 4.5 equiv. 2,4-Dichloro-6-methoxy-1,3,5-triazine, 1.1 equiv. TCEP HCl, 15.0 equiv. iPr_2NEt, rt, 12 h.

Scheme 2.3. Elaboration of disulfides via S-S reduction and insertion.

compound **2.41** over two steps. Fluorine is prized in medicinal chemistry for its potential to improve metabolic stability, potency[23,24], and inform structural biochemistry due to its NMR

activity [25,26]. Furthermore, we desired the incorporation of H-bond acceptors amongst other polar functionality into the macrocyclic disulfide bond. A one-pot method was developed to reduce disulfides and engage the resultant dithiol in successive S_NAr reactions to form a macrocycle. Use of 2,4,-dichloro-6-methoxy-1,3,5- triazine in this fashion provided triazine linked macrocycle **2.42** in 39% isolated yield from product **2.5**. It is envisioned that any of the previously depicted macrocyclic disulfides could be elaborated in an analogous fashion as seen in compounds **2.40**-**2.42** (scheme 2.3.), potentially increasing the size of any disulfide derived compound set four-fold.

2.2.4 Oxidations and rearrangements of macrocyclic sulfanes

Cyclic thiosulfinates are known to selectively cross-link cysteine pairs in proteins[27], in addition to serving as starting material for Pummerer type rearrangements[28]. Agar and coworkers reported that cyclic thiosulfinates selectively crosslink dithiol networks in proteins and supported this finding with *in vitro*, *in vivo* and *in silico* demonstrations (figure 2.5, A).[27] Furthermore, highly functionalized macrocyclic thiosulfinates could provide greater selectivity when crosslinking

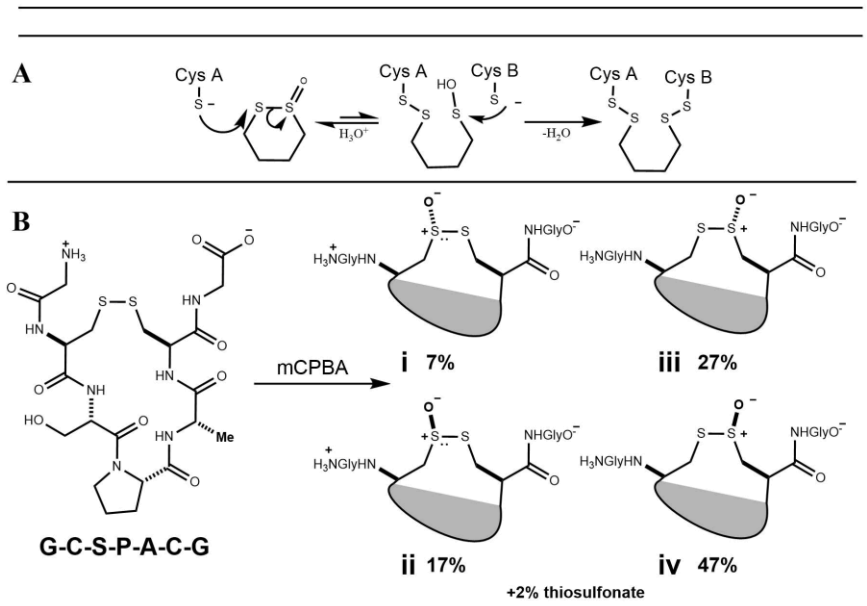


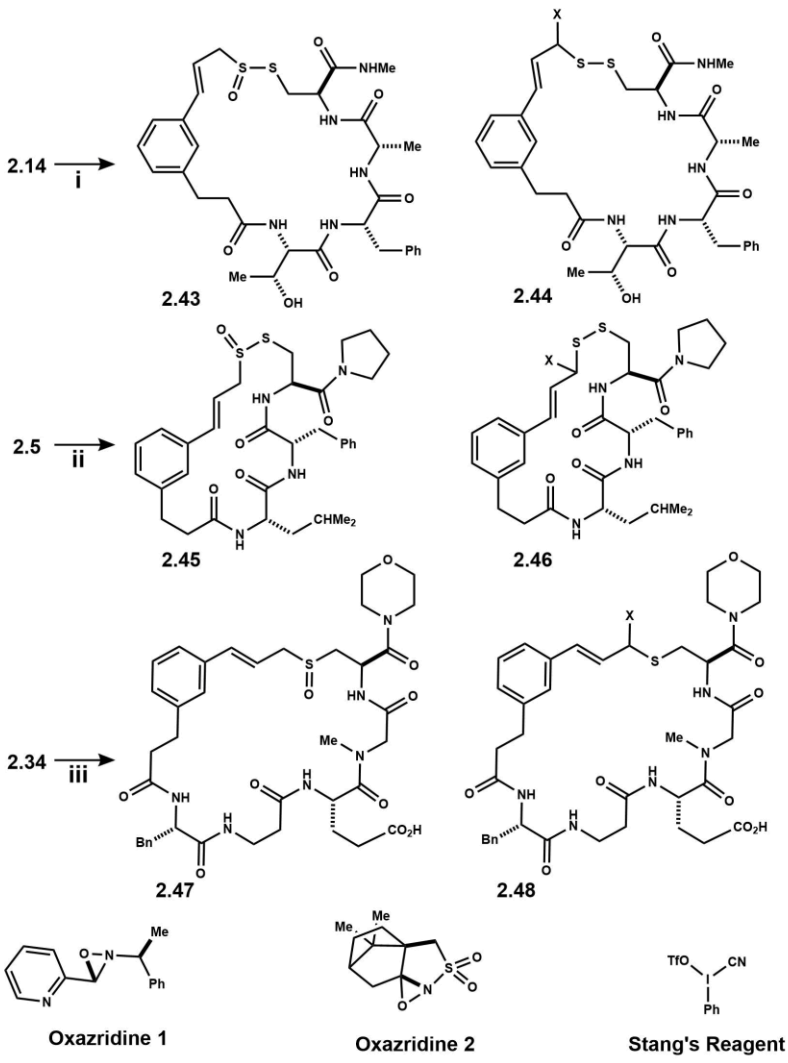
Figure 2.5. A Application of thiosulfinates in protein dithiol cross linking. **B** Oxidation of a macrocyclic disulfide for furnish thiosulfinates.

protein dithiol networks, finding potential use as tool compounds or therapeutics. Additionally, our quest for increasingly rigidified and functionalized peptide macrocycles drove us to investigate the feasibility of Pummerer rearrangements in our systems.

We first synthesized thiosulfinate **2.43** by adapting a sulfoxidation procedure utilizing catalytic $Sc(OTf)_3$ with hydrogen peroxide oxidant.[29] This provided **2.43** in quantitative yield on small scale, with crude NMR indicating a *dr* of 1:1. (table 2.5. entry 1; scheme 2.4). Work by Lucke *et al* informed our thoughts on regio- verses diastereoselectivity in the oxidation of macrocyclic disulfides to macrocyclic thiosulfinate.[43] Upon treating GCSPACG peptide with mCPBA, Lucke and coworkers isolated four major thiosulfinate peaks (**I**-**IV** figure 2.5. B). Regioselectivity for the reaction was 3:1 (**I**, **II** vs **III**, **IV**), whereas the *dr* was 2.7:1 and 1.7:1 for regiochemical pairs **I/II** and **III/IV** respectively. Regiochemical assignments were supported by 2D NMR spectroscopy.

In our systems, compound **2.43** was characterized with the following data. Firstly, monooxygenation was the only compound observed by mass, no spectra indicative of thiosulfonate formation was detected. COSY ^{1}H-NMR resonances of the cinnamyl olefins in compound **2.43** coupled to methylene protons at 4.25 and 4.10 ppm, far (1 ppm) above the usual chemical shift associated with disulfides. The depicted regiochemistry was assigned accordingly. Both diastereomer cinnamyl peaks couple to these signals, supporting their identity as diastereomeric peaks and not regioisomers. Secondly, oxidation of thiosulfinates to thiosulfonate is unlikely, given the stoichiometry of the oxidant and the fact Lucke isolated only 2% of thiosulfonate (figure 2.5. B). Literature supports the difficulty of this oxidation. Furthermore, the branching of the peptidyl fragment of **2.14** leads to much greater steric hindrance relative to the planar cinnamyl

group that flanks the oxidized sulfur of **2.43**. Please note that the entries of table 2.5 correspond to the schemes



Scheme 2.4. Oxidation of sulfide macorcycles.

Entry/Substrate/Scheme	Conditions	Outcome
(1) **2.14 (i)**	$Sc(OTf)_3$/ H_2O_2 in DCM/EtOH	Quant **2.43,** *dr* 1:1
(2) **2.13 (i)**	$Sc(OTf)_3$/ H_2O_2 in DCM/EtOH; 5 vol% TFA in $MeNO_2$	Decomp.
(3) **2.14(i)**	1.1 eq. mCPBA in DCM/DMF	Full con. **2.43,** *dr* 1:1
(4) **2.14 (i)**	1.5 eq. AcOOH in DCM/MeOH	66%. **2.43,** *dr* 3:1
(5) **2.14 (i)**	1.5 eq. t-BuOOH in DCM/MeOH	N.R.
(6) **2.14 (i)**	anhy. $ZnCl_2$ **Oxazridine 1,** various conditions	N.R.
(7) **2.5 (ii)**	1.0 eq. **Oxazridine 2** In CHCl3	N.R.
(8) **2.5 (ii)**	2.0 eq. **Oxazridine 2** $Sc(OTf)_3$ In CHCl3	N.R.
(9) **2.34 (iii)**	2.0 eq. NCS in DCM/DMF	Full con. **2.47**
(10) **2.14 (i)**	2.0 eq. NCS in DCM/MeOH	N.R.
(11) **2.34 (iii)**	Stang's reagent, Various conditions	N.R.
(12) **2.14 (i)**	Stang's reagent, Various conditions	N.R.

Table 2.5. Oxidation of sulfide macorcycles.

depicted above in scheme 2.4, as denoted by roman numerals. While S-oxidized products (**2.43**, **2.45**, **2.47**) were expected and **2.43** was obtained, we consider Pummerer products (**2.44**, **2.46**, **2.48**) a possibility as well. Unfortunately, Pummerer rearrangement derived structures proved elusive. Seeking to exploit the steric bulk of the *t*-butyl disulfide to obtain a thiosulfinate with opposite regiochemistry, linear compound **2.13** was treated with $Sc(OTf)_3$/ H_2O_2. The crude linear thiosulfinate was subjected to cyclization conditions. No desired product was detected, and evidence of decomposition was apparent (table 2.5. entry 2). Seeking an oxidant that could improve the *dr* of the resultant thiosulfinate and inspired by Lucke's work, we first turned to mCPBA. Treatment of **2.14** with 1.1 eq. of mCPBA furnish complete conversion to **2.43** as determined by HPLC, though NMR analysis revealed the *dr* to be 1:1 (table 2.5. entry 3; scheme 2.4 **I**). Peracetic acid provided an improved, albeit modest *dr* of 3:1 (table 2.5 entry 4; scheme 2.4 **I**). Investigation of t-BuOOH as an oxidant proved to be unreactive given tested conditions (table 2.5. entry 5).

Chiral oxaziridines reported to asymmetrically oxidized sulfides to sulfoxides were employed, though no product was obtained (table 2.5. entries 6-8).[30] We explored the common oxidant NCS for the formation of macrocyclic thiosulfinates and sulfoxides. Interestingly, complete conversion to sulfoxide **2.47** (table 2.5. entry 9; scheme 2.4. **III**) was observed by HPLC, while analogous reaction conditions failed to oxidize disulfides (table 2.5. entry 10; scheme 2.4. **III**). The stark reactivity difference between di- and monosulfide oxidation was quite interesting, echoing the observed selectivity found in mono- verses disulfide transalkyative macrocycliczations. However, we soon turned our attention to other applications and modifications of these structures. Stang's reagent has been reported to induce Pummerer-type rearrangements in heterocyclic thioethers[31-33] (figure 2.6, A), although premature hydrolysis in these systems (figure

2.6. A, brackets) could be envisioned to furnish sulfoxides and thiosulfinates. Despite our best efforts, fruitful use of this methodology was elusive (table 2.5. entries 11, 12).

Allylic sulfoxides are well known to undergo [2,3] sigmatropic rearrangements under mild conditions.[34] An analogy from this facile Mislow-Evans rearrangement to allylic disulfides was evident in the research of Crich and coworkers. This group recently reported desulfurative [3,3] sigmatropic rearrangements in allylic disulfides derived from peptidyl substrates (figure 2.5. B).[36,37] Taking place at ambient temperature and induced by PPh_3 or silica gel, we envisioned these reactions could transform our non-branched allylic disulfide macrocycles (*i.e.* **2.14** or **2.7**) to branched products as depicted in scheme **2.4 II** and **III**.

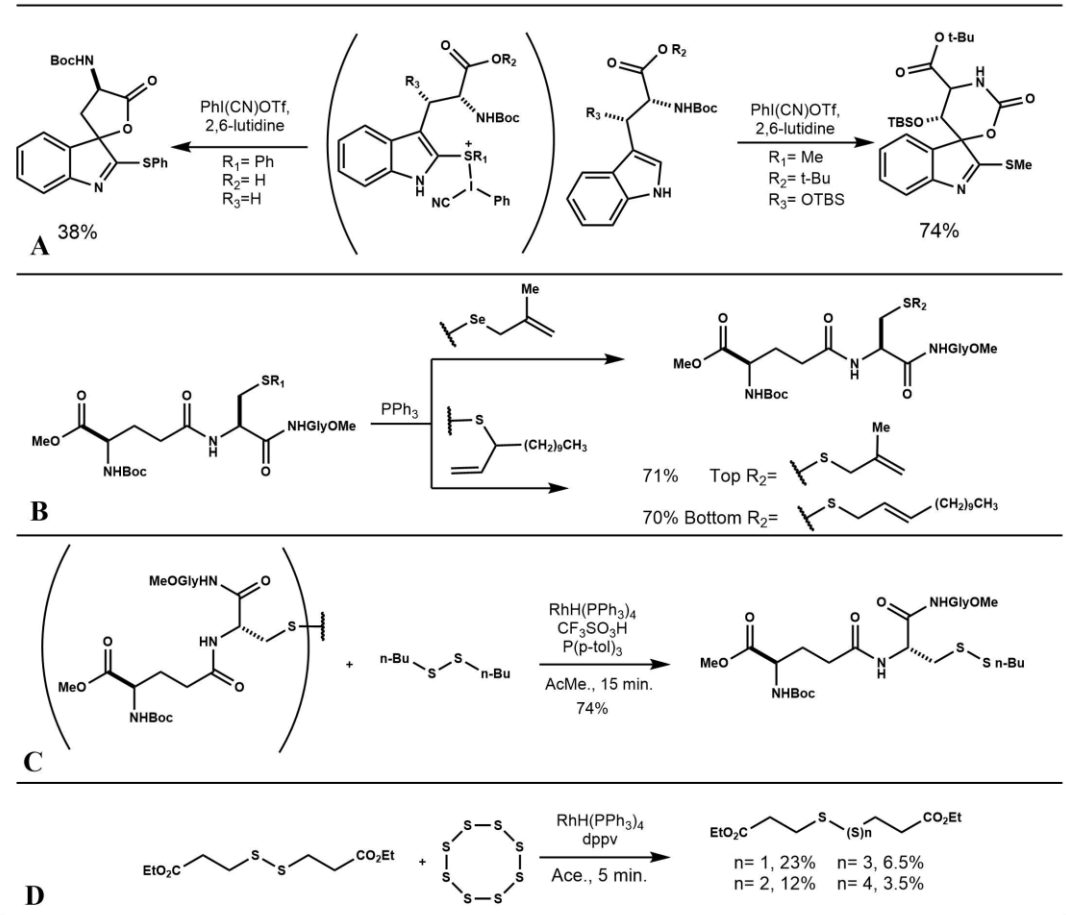
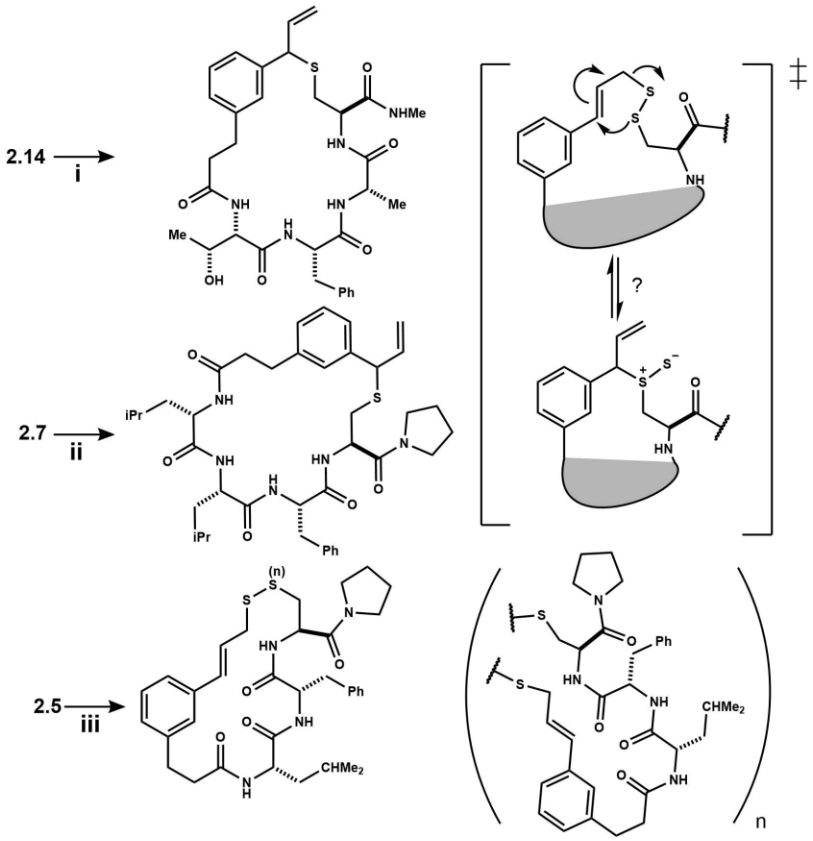


Figure 2.6. Rearrangements and sulfur insertion in disulfides and monosulfides.

Efforts began with Crich's conditions (table 2.6. entry 1; scheme 2.5. **II**), but no product was detected by HPLC or ^{1}H-NMR. Elevated temperatures similarly failed to rearrange the product (table 2.6. entries 2, 3; scheme 2.5. **II**). Considering that aryl phosphines were not sufficient, we elected to use tributyl phosphine as a thiophile. Despite this, no reaction was observed. A rationale for this utter lack of reactivity may come from macrocyclic systems' innately rigid character. The necessary orbital overlap may be kinetically inaccessible in macrocyclic systems, or the resulting ring contracted product too enthalpically costly to contribute to the depicted equilibrium (scheme 2.4. square brackets). Crich and coworkers reported the rate constants for tertiary to primary allylic disulfide rearrangement to be 1.4-1.9 x 10^{-2} s^{-1} verses 0.7-8.6 x 10^{-4} s^{-1} for primary to tertiary, a rate decrease of almost two orders of magnitude.[35] It should be noted that the group's only reported reactions in the latter category involve deselenative rearrangement of allyl selenosulfides to furnish branched and primary allylic sulfides (figure 2.6. B).[36] Regardless of the mechanistic underpinnings, the fact remains desulfurative rearrangement of primary allylic disulfides to branched allylic thioethers remains an unmet challenge in macrocyclic and linear systems.

We then looked away from ring contraction and towards ring expansion via sulfur addition. Work by Yamaguchi initially inspired us to utilize rhodium catalysis to introduce additional sulfur atoms into our systems (figure 2.6. D, scheme 2.5 **III**).[37] Upon treating macrocycle **2.5** with 10 mol% $HRh(PPh_3)_4$, DPPV (cis-1,2-Bis(diphenylphosphino)ethene) ligand, and elemental sulfur no reaction was observed at room temperature (see scheme 2.5, **III**). The reaction was then heated to reflux (acetone, 60°C) for several hours. HPLC monitoring showed only starting material, with no polysulfides detected (table 2.5. entry 5.). Attempts using more sulfur (table 2.5. entry 6) and higher boiling, nonpolar solvent (table 2.5. entry 7) proved fruitless. Our subsequent discovery of



Scheme 2.5. Attempts at rearrangement and S exchange in sulfide macorcycles.

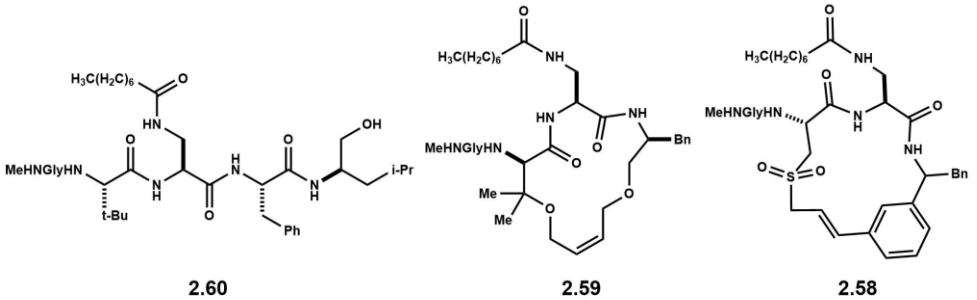
Entry/Substrate/Scheme	Conditions	Results
1, **2.7 (ii)**	2,0 eq. PPh_3 MeCN: MeOH, rt,	**2.7** recovered
2, **2.14 (i)**	3,0 eq. PPh_3 MeCN: MeOH, 65°C, 12 h,	**2.14** recovered
3, **2.14 (i)**	10,0 eq. PPh_3 Polymer Bound MeCN: MeOH, 65°C, 12 h,	**2.14** recovered
4, **2.14 (ii)**	2,0 eq. $P(n\text{-}Bu)_3$ MeCN: MeOH, 65°C, 12 h,	**2.14** recovered
5, **2.5 (iii)**	5 mol% $HRh(PPh_3)_4$, 10 mol% DPPV, 2.0 eq. S_8 Ace. 0.1M, 60°C, 4 h	**2.5** recovered
6, **2.5 (iii)**	5 mol% $HRh(PPh_3)_4$, 10 mol% DPPV, 10.0 eq. S_8 Ace. 0.1M, 60°C, 4 h	**2.5** recovered
7, **2.5 (iii)**	5 mol% $HRh(PPh_3)_4$, 10 mol% DPPV, 10.0 eq. S_8 Tol. 0.1M, 85°C, 4 h	**2.5** recovered
8, **2.5 (iii)**	5 mol% $HRh(PPh_3)_4$, 6 mol% $P(p\text{-}Tol)_3$, 6 mol% F_3CSO_3H MeCN. 0.2M, 85°C,15 m	**2.5** recovered

Table 2.6. Attempted reargangement and S exchange conditions.

a polysulfidation (chapter 4) diverted our attention from these catalytic methods and towards the direct synthesis of polysulfide-linked macrocycles. Further attempts at rhodium catalysis induced disulfide exchange (*i.e*. figure 2.6. C) failed to provide the desired dimeric macrocycles (table 2.5. entry 8, scheme 2.5, **III**).[38]

2.2.5 Sulfur transalkylation to furnish a potential GOAT inhibitor

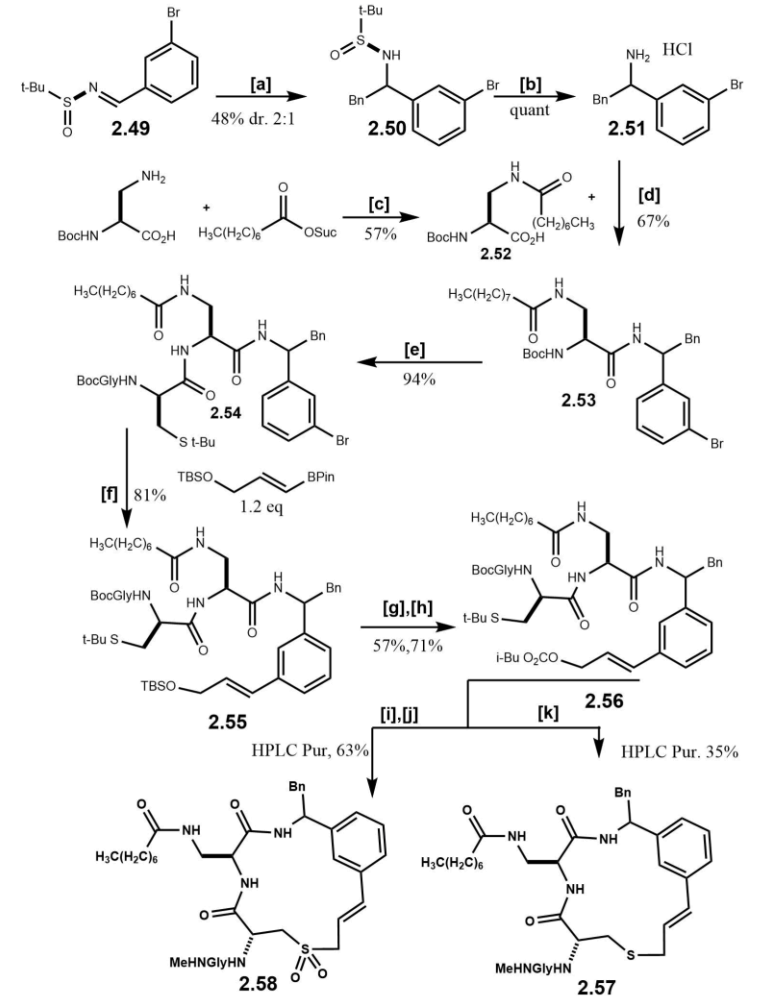
We continually apply our template constrained peptides towards therapeutic ends. Ghrelin O-acyltransferase (GOAT) is a membrane bound protein responsible for activating the hormone ghrelin via serine octanoylation of a non-acylated pro-peptide.[39,40] Ghrelin is implicated in feeding response and analogs induce weight gain in mice. In this vein, we sought to exploit GOAT inhibitors as potential therapeutics for diabetes, Prader-Willi syndrome, and other metabolic aliments. No crystal structure of GOAT has been reported, therefor an SAR of inhibitors must be deduced through iterative rounds of compound synthesis and assay evaluation. Pentapeptide **2.60** and macrocycle **2.59** are representative structures of our efforts to develop peptidomimetic GOAT inhibitors. Macrocyclic inhibitors soon came to the forefront during our *in vitro* evaluation of compounds. We then sought to adapt our template system to the targeted synthesis of a macrocyclic GOAT inhibitor and designed compounds **2.58** and **2.57** to this end.



2.60 **2.59** **2.58**

Figure 2.7.. Peptidomimetic ghrelin O-acyl transferase inhibitors.

Elman's auxiliary-3-bromobenzaldhyde adduct ((S,E)-N-(3-bromobenzylidene)-2-methylpropane-2-sulfinamide) **2.49** was treated with benzylmagnesium chloride to furnish **2.50** in modest yield and *dr*. The auxiliary was then cleaved to provide **2.51**, which was in turn coupled to octanoylated diaminopropionic acid derivative **2.52**, yielding peptide **2.53**. Deprotection and iterative coupling of N-Boc S-t-butyl-L-cysteine and Boc glycine to **2.53** provided product **2.54** in



[a] 2.0 eq. BnMgCl, THF, -50°C, 4 h-> 23°C; 8 h **[b]** 4.0 eq. HCl, MeOH, 0°C, 2 h **[c]** DIPEA, DMF, rt, 2 h **[d]** 1.2 eq. HBTU, 5.0 eq DIEPA, DMF, rt, 1.5 h**[e]**1:1 TFA: DCM; 1.2 eq. HNBoc-StBu-Cys 1.2 eq. DIPEA, DMF; 1:1 TFA: DCM; 1.2 eq. BocGly, 1.2 eq. DIPEA, DMF. **[f]** 10 mol% $Pd(PPh_3)_4$, K_2CO_3, 5:1 THF: H_2O 65°C, 12 h, **[g]** 6.0 eq. TBAF, THF, rt, 1.5 h **[h]** 1.5 eq. iBuOCOCl, 2,0 eq. NMM, THF, rt, 15 min. **[i]** 15 vol. % TFA 5 mM $MeNO_2$, rt, 1 h; **[j]** 2.4 eq. mCPBA, DMF, 0°C, 45 min. **[k]** 10 vol % TFA, 5 mM $MeNO_2$, rt, 1.5 h.

Scheme 2.6. Synthesis of a potenial GOAT inhibitor via S-transalkyation.

good yield. A Suzuki reaction was performed on compound **2.54** with (E)-tert-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane to yield TBSO-protected cinnamyl alcohol **2.55**, which was then deprotected and treated with isobutyl-chloroformate yielding linear substrate **2.56**. Subjecting **2.56** to 10 vol% TFA in nitromethane led to instantaneous removal of the Boc group followed by sluggish cyclization to compound **2.57**. The slower kinetics of this cyclization likely stem from the doubly cationic nature of the macrocyclic sulfonium intermediate bearing an ammonium. This hypothesis is supported by further experiments disclosed in this dissertation (chapter 3), featuring cationic non-participating residues. Compound **2.57** was isolated in subpar yield after HPLC purification. Subjecting **2.56** to 15 vol% TFA followed by oxidation of the crude mixture provided sulfone **2.58** in fair yield after HPLC purification. Unfortunately, neither **2.57** nor **2.58** proved effective inhibitors when tested with our in-house developed assay.

Conclusion 2.3

A novel sulfur-based transalkylation has been developed to synthesize a diverse set of di- and monosulfide linked peptide macrocycles. The reaction proceeds via the acid induced generation of a cinnamyl cation, followed by formation of a macrocyclic sulfonium, and subsequent dealkylation to afford a net transalkylated product. Polar functionalities, such as alcohols, amides, amines, guanidines (chapter 3), and imidazoles (chapter3), are well tolerated. The system has proven capable of forming peptide macrocycles ranging from two to five residues (15 to 26 atoms). This reaction is compatible with previously reported multi-armed, heterocycle forming templates. [17,18] Disulfide linked macrocyclic products can be readily reduced and the resultant dithiol inserted into various fluorocarbo- and heterocycles via successive S_NAr reactions, providing new macrocyclic structures. Selective oxidation of disulfides to thiosulfinates was reported, as well as attempts at desulfurative rearrangements and sulfur exchanges. The

methodology reported here was employed in the syntheses of potential macrocyclic inhibitors of ghrelin O-acyl transferase. Future use of sulfur transalkylations to furnish combinatorial libraries of macrocyclic peptidomimetics can be envisioned. Discovery of novel PPI mediating structures of therapeutic value is a persistent interest of our laboratory. The methods disclosed here add a new modality and several structure classes to the cinnamyl carbonate template system with the potential to be employed to this end.

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3 Synthesis of bimacrocyclic peptidomimetics and enabling templates

3.1 Introduction

Natural products featuring multiple peptide macrocycles are of medical and academic interest.[1] Bioactive bimacrocycles, such as the antibiotics vancomycin, its numerous congeners, and semi-synthetic derivates, have attracted immense synthetic and therapeutic attention. Thioether and disulfide linked polymacrocycles have likewise drawn considerable efforts towards their medicinal use and synthesis. The potent RNA polymerase inhibitor α-amanitin has been used in several antibody-drug conjugates for anticancer purposes.[2,3] HDAC inhibitor romidepsin has been approved for treatment of lymphoma and studied for other oncological maladies.[4,5,10] Ulithiacyclamides, a series of disulfide-bridged thiazole bimacrocyclic peptides, are reported to be cytotoxic against several cell lines.[6] Conotoxins[7] and lanthipeptides[8] have garnered considerable

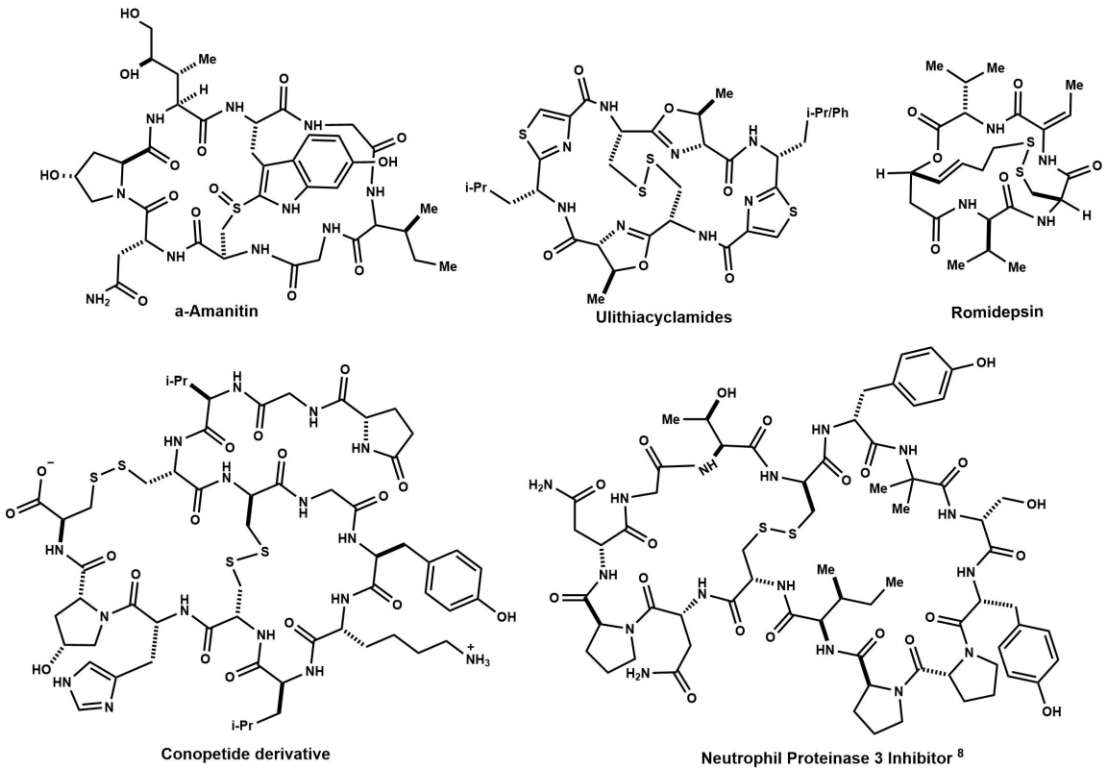


Figure 3.1. Bioactive sulfide linked bimacrocycles.

use and scholarship as analgesics and antibiotics respectively. With such a wide range of potent bioactivities found in the broad structure class of mono- and disulfide linked polymacrocycles, we desired a method to synthesize similar compounds.

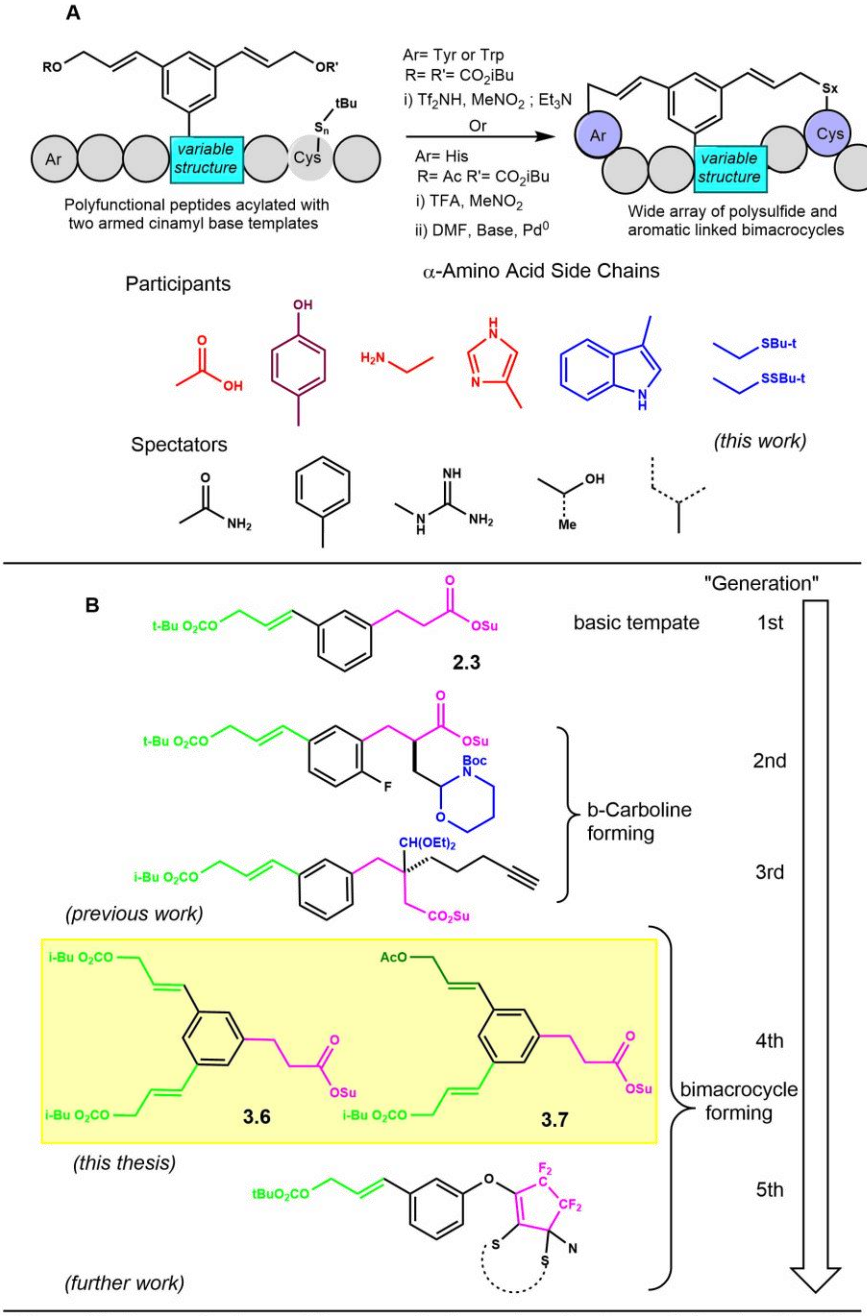


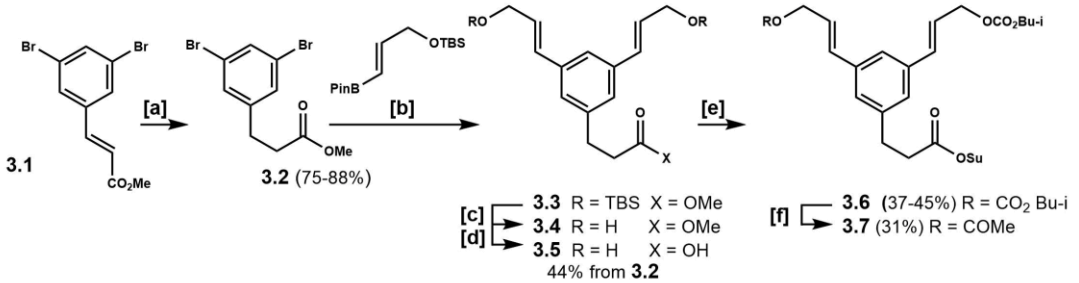
Figure 3.2. **A** general scheme of bimacrocyclization and previously reported nucleophiles. **B** Previously reported monocyclization templates and new bimacrocycle forming templates.

The synthesis of bimacrocyclic peptides is a long-standing goal of our template constrained peptide project, and several templates have been reported towards this end (figure 3.2. B). Given the number of peptidyl nucleophiles the cinnamyl carbonate-based templates can engage (figure 3.2.A), we reasoned that a C2 symmetric template would offer direct access to diverse bimacrocyclic products. While efforts to this end have been reported[11,12], we sought the structural diversity and synthetic flexibility inherent in our cinnamyl carbonate template system.

3.1 Results and discussion

3.2.1 Synthesis of templates 3.6, 3.7, and initial exploration of their use

Synthesis commenced with treatment of carbomethoxymethyltriphenylphosphonium bromide with NaOH to furnish stabilized ylided methyl(triphenylphosphaneylidene)acetate. A Wittig reaction between 3,5 dibromobenzaldehyde and methyl (triphenylphosphaneylidene)acetate furnished trans-methyl-3,5-dibromocinnamate (**3.1**) in excellent yield (scheme 3.1.). Acrylic ester **3.1** was then reduced conjugately reduced with nickel borohydride to afford **3.2**. Exposure of **3.2** to (E)-tert-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-

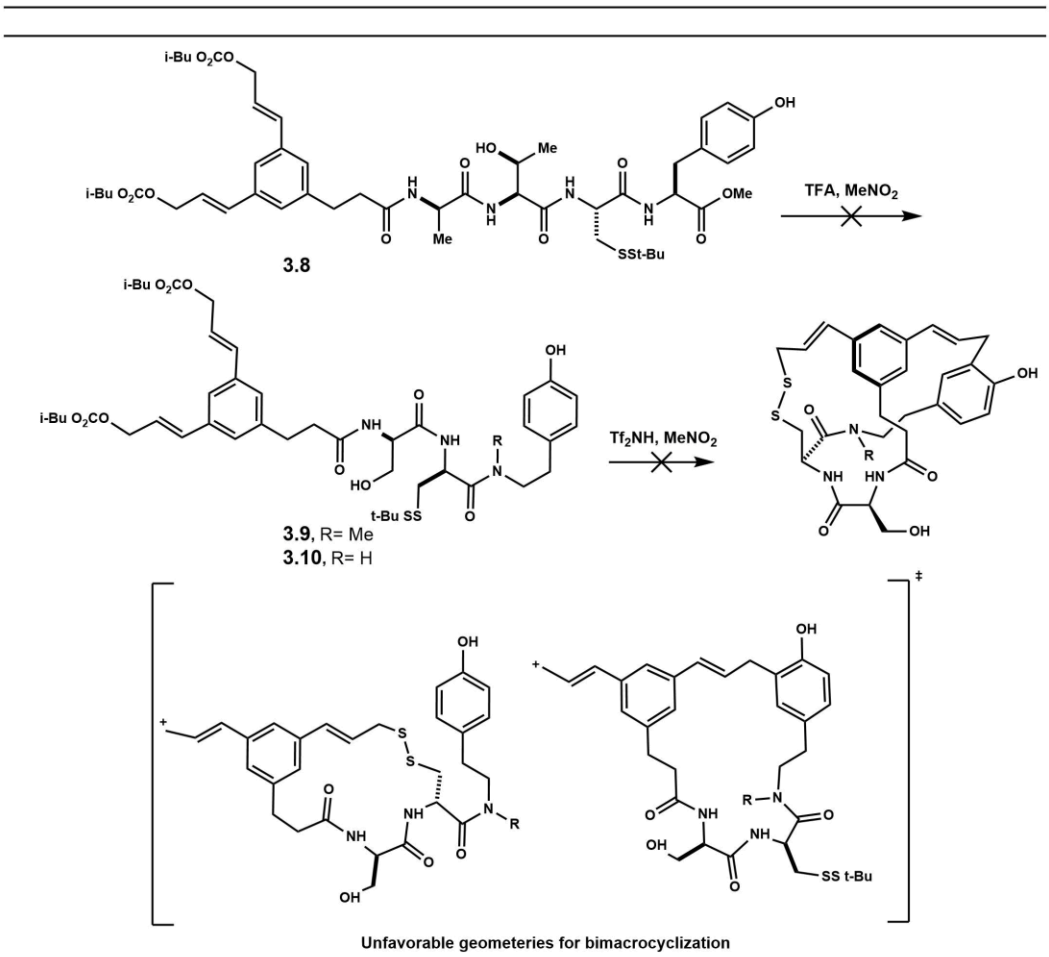


[a] 3.0 equiv. $NaBH_4$,$Ni(OAc)_2$ $4H_2O$ in 2:1 EtOAc:MeOH, 0°C, 15 min. **[b]** 3.0 equiv. boronate, 6.0 equiv. K_2CO_3,10 mol% $Pd(PPh_3)_4$, THF, reflux, 48 h (80%). **[c]**13 mol% 1N HCl, MeOH, 25:1 MeOH:H_2O, rt, 1 h. **[d]** 3.0 equiv. LiOH, 5:1 THF:H_2O, 65°C, 1.5 h **[e]** 3.3 equiv. i-BuOCOCl, 3.3 equiv. NMM, THF, 0°C; 1.25 equiv. N-hydroxy succinimide, 1 h (37-45%).**[f]** 10.0 equiv. AcOH, 1.5 mol% $Pd(PPh_3)_4$, THF, rt, 10-20 min (31%).

Scheme 3.1. Synthesis of dual-armed templates **3.6** and **3.7**.

dioxaborolan-2-yl)allyl)oxy)silane in the presence of catalytic amounts of $Pd(PPh_3)_4$ yielded double Suzuki product **3.3**. Compound **3.3** was desilylated in acidic methanol and the product was saponified to afford carboxylic acid **3.5** in 44% yield over three steps. Activation of **3.5** as its NHS ester was then achieved via a derived mixed anhydride (Scheme 3.1.).

Our initial efforts focused on optimizing **3.6** to form bimacrocycles. Template **3.6** was ligated to the N-terminus of peptide Ala-Thr-(S-tBu)Cys-Tyr-OMe to obtain template-peptide conjugate **3.8**. Use of standard conditions (5 vol% TFA in $MeNO_2$, 5 mM) on **3.8** lead to a



Scheme 3.2. Failed attempts at N-terminal template bimacrocyclization.

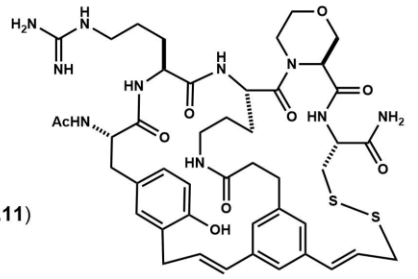
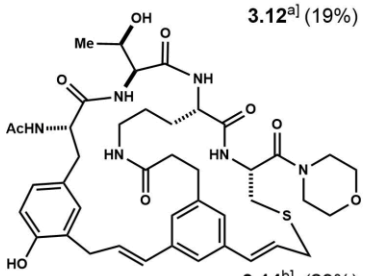
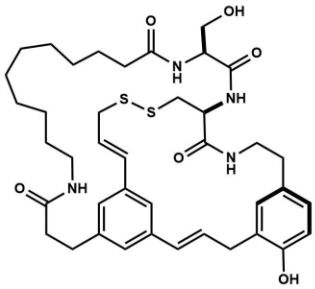
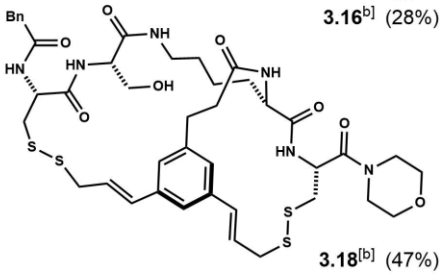
promising initial HPLC trace followed by intractables upon evaporation (scheme 3.2.). We reasoned that a base quenchable acidolysis would circumvent this issue. Triflimide (Tf_2NH) was found to be suitable to this end. However, attempts to use template **3.6** off the N-terminus of peptides lead to the isolation of HPLC peaks with the apparent correct mass, but with ^{13}C- and ^{1}H-NMR indicative of a complex set of oligomers, in addition to poor mass recovery. Such was the case with substrates **3.9** and **3.10**. We reasoned that when linked at the N-terminus, macrocyclization at one cinnamyl unit of **3.6**-derived structures created products with the second cinnamyl motif oriented unfavorably for subsequent intramolecular bimacrocycle forming reactions (scheme 3.2. square brackets). We reasoned that placing template **3.6** on a side chain would place the cinnamyl arms in a suitable position to form a bimacrocycle via successive reactions with flanking nucleophilic residues.

3.2.2 Bimacrocyclic peptidomimetics via one-pot acidolysis of 3.6 derived structures

To our delight this proved feasible. Acylating the distal amine of ornithine central within peptide AcYROMrpC(SBu-t)-NH_2 with template **3.6** and treating the product (**3.11**) with Tf_2NH in $MeNO_2$ rapidly formed complex bimacrocycle **3.12** (table 3.1 entry 1). Internal cinnamylation of tyrosine and alkyl group exchange with the *tert*-butylthiolated cysteine residue occurred concomitantly without interference from the free guanidine of arginine in the case of compound **3.12** (table 3.1. entry 1). Peptide-template adduct **3.13** was likewise cyclized and thioether containing bimacrocycle **3.14** was isolated (table 3.1. entry 2). Both reactions were complete within minutes and bimacrocyclic product was readily isolable following neutralization with Et_3N.

Adding an N-terminal 11-amino undecanoyl spacer to SC(SBu-t)tyramine, followed by deprotection and acylation with **3.6** gave **3.15**. Subsequent acidolysis of this product afforded

bimacrocyclic structure **3.16** (table 3.1. entry 3). Products containing two macrocyclic disulfides were accessible by acylating the α-amine of ornithine within PhAcC(SBu-t)SOC(SBu-t)-morp with **3.6**, followed by treatment with Tf_2NH ($MeNO_2$, rt). This furnished bimacrocyclic structure

Entry	Linear Precursor	Doubly Cyclized Product (Yield)
1	Ac-YROMrpC(SBu-t)-NH_2 (**3.11**)	 **3.12**[a] (19%)
2	Ac-YTOC(Bu-t)-morph (**3.13**)	 **3.14**[b] (29%)
3	UndSC(SBu-t)-tyramine (**3.15**)	 **3.16**[b] (28%)
4	L(ω-PhAc-C(SBu-t)S)-C(SBu-t)-morph (**3.17**)	 **3.18**[b] (47%)

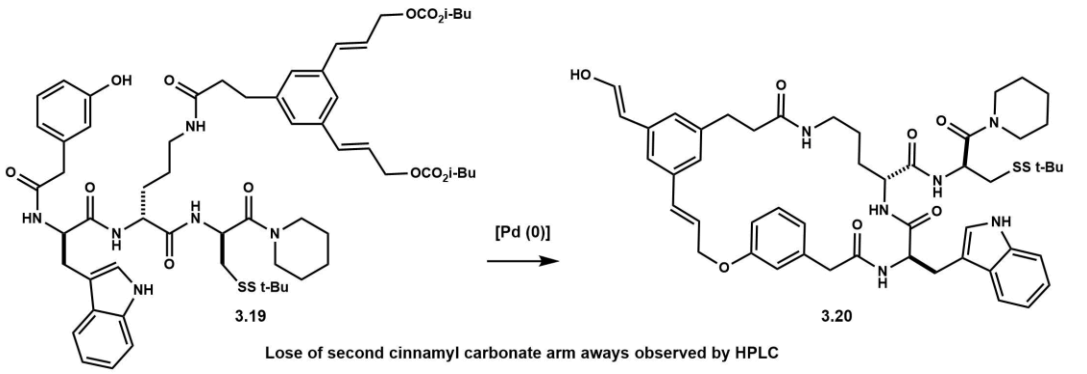
[a] 5 mM $MeNO_2$ solution of template acylated peptide was treated with 6.0 eq. Tf_2NH dissolved in an equal volume of $MeNO_2$, rt, 15 min, Et_3N neutralization **[b]** 5 mM $MeNO_2$ solution of template acylated peptide was treated with 3.0 equiv. $HNTf_2$ dissolved in an equal volume of $MeNO_2$, rt, 15 min, Et_3N neutralization. Yields refer to analytical pure material isolated by preparative HPLC. **3.14** Isolated as a TFA salt.

Table 3.1. Bimacrocyclic sulfanes derived from **3.6**.

3.18, harboring two allylic disulfide units (table 3.1. entry 4). Connectivity in doubly macrocyclized products were assigned using HMBC and HSQC correlations spanning thioether and tyrosyl linkages. In cases where HMBC and HSQC correlations were not observed, NOESY and COSY spectra were used to support assignments. In general, NOESY spectra of bicyclization products were rich with detail, consistent with rigid cage-like structures having well defined conformations (see SI). It should be noted that 6.0 eq. of triflimide (table 3.1. [a]) was necessary for macrocycle **3.12** to cyclize in the same timeframe as the other examples (table 3.1. [b]), likely due to the doubly cationic intermediate implicated in the cyclization (a guanidinium and sulfonium bearing structure).

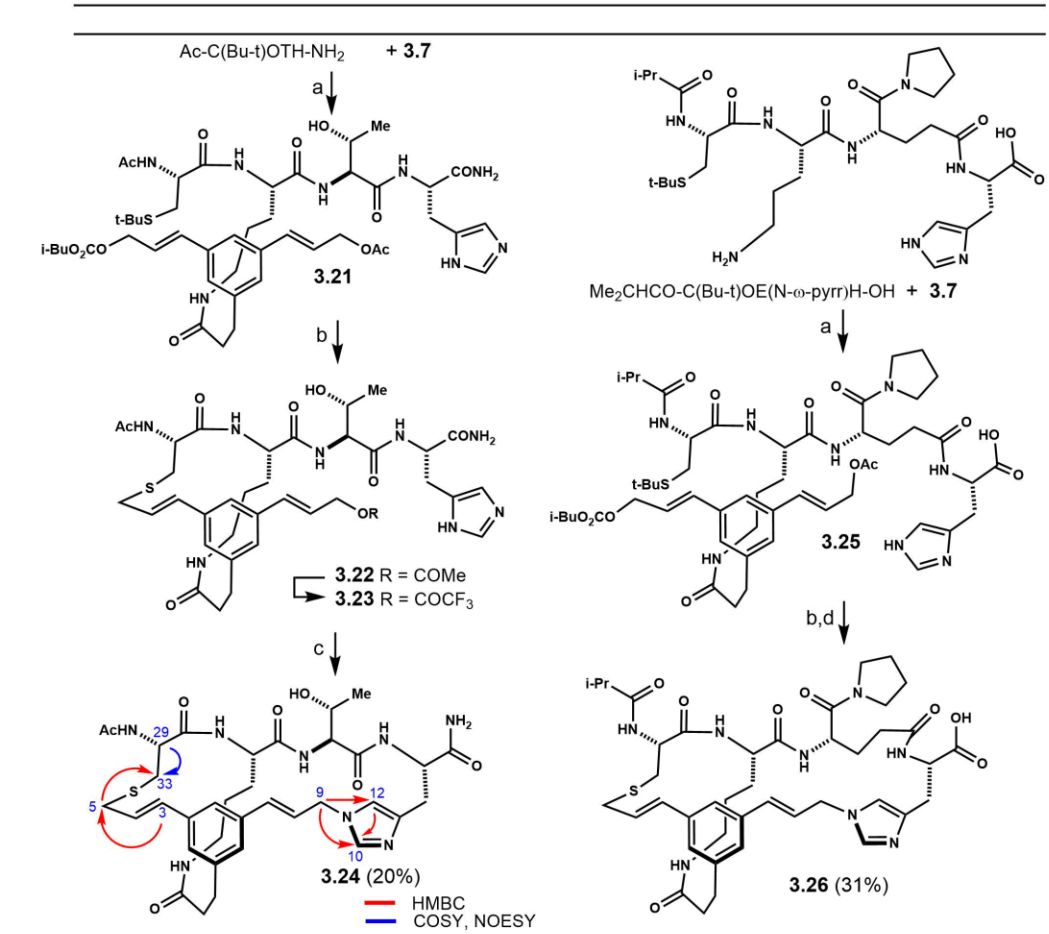
3.2.3 Bimacrocyclic peptidomimetics via palladium catalysis on 3.7 derived structures

Using template **3.6**, the synthesis of complex bimacrocyclic structures was facile and numerous permutations could be envisioned. We had previously shown the cinnamyl carbonate motif could support metal catalyzed ring formations with polar functional groups. However, integrating that methodology with internal sulfidation using template **3.7** required orchestration of steps. For oligomers having a single sulfide nucleophile, acylation with **3.6** and subsequent acidolysis gave macrocyclic sulfides, but the cinnamyl carbonate remaining in products became susceptible to hydrolysis. This complicated handling and isolation. Changing the order of events was similarly unproductive. Peptide conjugates of **3.6** reacted readily with Pd(0) complexes but maintaining the second carbonate intact after initial macrocyclization was difficult (scheme 3.3).



Scheme 3.3. Failed attempts at catalytic bimacrocyclization.

A solution was to convert **3.6** to monoacetyl derivative **3.7** (scheme 3.1. [f]). Compound **3.7** was used to acylate AcC(Bu-t)OTH-NH_2 to afford **3.21**. When this product was treated with 10 vol% TFA in $MeNO_2$, the allylic carbonate reacted selectively to afford macrocyclic monosulfide **3.22**. The remaining cinnamyl acetate was more slowly converted to the corresponding trifluoroacetate **3.23**. The reaction was concentrated to dryness and the crude material dissolved in DMF, treated with *i*Pr_2NEt and catalytic amounts of Pd(0)/Xantphos complex to afford histidine linked bimacrocycle **3.24** (scheme 3.4.). C-terminal carboxylic acid containing substrate **3.25** was treated with acid and the crude cyclic thioether was subjected to the aforementioned catalysis conditions over 12 hours. Compound **3.26** was then isolated, featuring exclusive selectivity for the imidazole over carboxylate residue (scheme 3.4.).



[a] DMF, 5.0 eq. iPr_2NEt, rt,1-2 h **[b]** $MeNO_2$, 5.0 mM, 10 vol% TFA, rt, 3 h **[c]** DMF, 5.0 mM, 7.5 mol% $[Pd(C_3H_5)Cl]_2$, 9.5 mol% Xantphos, 10.0 eq. iPr_2NEt, 45°C, 3 h **[d]** DMF, 5.0 mM, 7.5 mol% $[Pd(C_3H_5)Cl]_2$, 9.5 mol% Xantphos, 10.0 eq. iPr_2NEt, 45°C 12 h. Yields refer to analytical pure material isolated by prep. HPLC. Final products isolated as TFA salts.

Scheme 3.4. Synthesis of Bimacrocyclic sulfides derived from **3.7.**

Connectivities in bimacrocycle **3.24** were established as shown in figure 3.3. Clear HMBC correlations are seen between the cinnamyl protons of carbon 3 to carbon 5. Furthermore, HMBC correlation is seen between carbon 5 and the protons on carbon 33, confirming the macrocyclic sulfur linkage. The identity of carbon 33 is further corroborated by HSQC correlation of its protons. These protons readily couple to methine proton of atom 29 as seen on COSY. The characteristic ^{1}H-NMR peak of the cinnamyl-imidazolyl linkage (on carbon 9) correlates by HMBC to the signals of imidazole carbons 10 and 12.

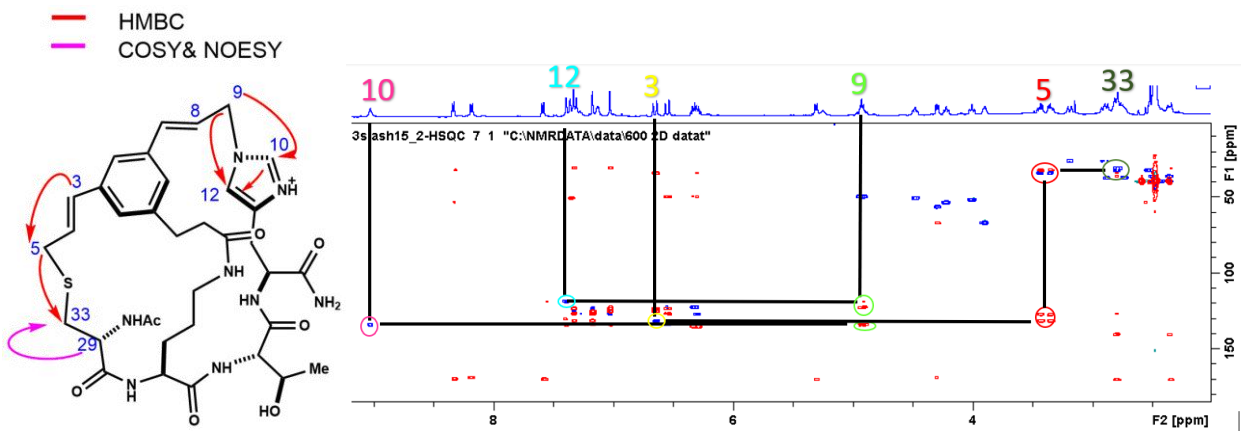


Figure 3.3. Key NMR correlations of **3.24** confirming bimacrocyclization.

It should be noted that the acidolysis step in these reactions are inordinately long compared to earlier examples of sulfur transalkyative macrocyclization. This can be rationalized considering the intramolecular electrostatic repulsion of the sulfonium and imidazolium groups in the key intermediate. Acetyl to trifluoroacetyl ester exchange also extends the required reaction times. Lastly, this method is limited to imidazole and thioether bearing products. No Friedel-Crafts competent residues are tolerated, given the outcome of earlier experiments with non-quenched bimacrocycle forming acidolysis.

3.3 Conclusion

In summation we have designed and described a pair of peptide macrocyclization templates featuring two cinnamyl electrophile arms (**3.6**, **3.7**). When appended to an internal amine residue or suitably long linker, template **3.6** is capable of engaging in Friedel-Crafts and sulfur transalkyative cyclizations to furnish bimacrocyclic molecules containing C-C aryl, mono-, and disulfide linkages via acidolysis (table 3.1.). Combinations of peptidyl nucleophiles for this bimacrocyclization were not exhaustively explored. Thousands of short sequences containing pairs of *t*-butyl sulfide and or non-pi basic residues flanking template-capped amines could be envisioned, synthesized and bimacrocyclized. Acidolysis of similar systems capped with template

3.7 can be subsequently treated with catalytic palladium to afford sulfide-heteroatom linked bimacrocycles (scheme 3.4.). Despite the narrower scope compared to solely acidolysis derived examples, these systems furnish novel bimacrocycles featuring a bridged cinnamyl unit linked to thioethers and imidazoles. While immense insight into the synthesis and efficient use of these templates has been gained, much work remains toward library generation and applied use of these bimacrocyclic molecules.

3.4 References

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4 Polysulfide macrocycles and synthetic progress towards a trithiocane natural product

4.1 Introduction

A vast array of bioactive natural products have been isolated and characterized from diverse sources[1,2]. These structures often serve as logical starting points for the development of potent and selective drugs.[3,4] We attempt to mimic the structure and function of these molecules as chemists, steering their qualities towards potential therapeutic applications with synthesis. Broadly, this aim leads to the pursuit of natural product total syntheses and development of analogs. Our laboratory is engaged in these feats, in addition we pursue the syntheses of potentially bioactive, natural product-like compounds via our unique template constrained peptide macrocyclization system. Our discoveries to date have provided routes to common macrocyclic linkages found in natural product chemistry, including but not limited to macrocyclic esters[5], aryl[6] and thioethers[9], aryl C-C and C-N bond linked products[5], β-carbolines[7,8], sulfides[9], and bimacrocyclic systems[10]. These structural features are accessible through ligation of our templates to poly-nucleophilic oligomers amenable to automated synthesis, followed by successive cyclizations via acidolysis or catalysis. Consequently, this enables the transformation of common peptides and related oligomers into increasingly complex amphipathic peptidomimetics using several simple reaction conditions.

Heterocycles[11] and macrocycles[12] have always occupied a prominent place in the annals of bioactive molecules. Polysulfides represent a fascinating class of natural products, rich in bioactivity, and challenging in constrution.[13] Depicted in figure 4.1. is a sampling of the many unique, biologically active polysulfides isolated from ascidians. These compounds highlight the immense structural and functional diversity found in one clade of marine animal secondary

metabolites. Much interest in the biology[15,16] and total synthesis[17,18] of the pentasulfide varacin (**4.3**) was generated upon its isolation[14]. This molecule's reactivity with DNA lent itself to exploration of antitumor and antimicrobial properties. Decades of subsequent research revealed

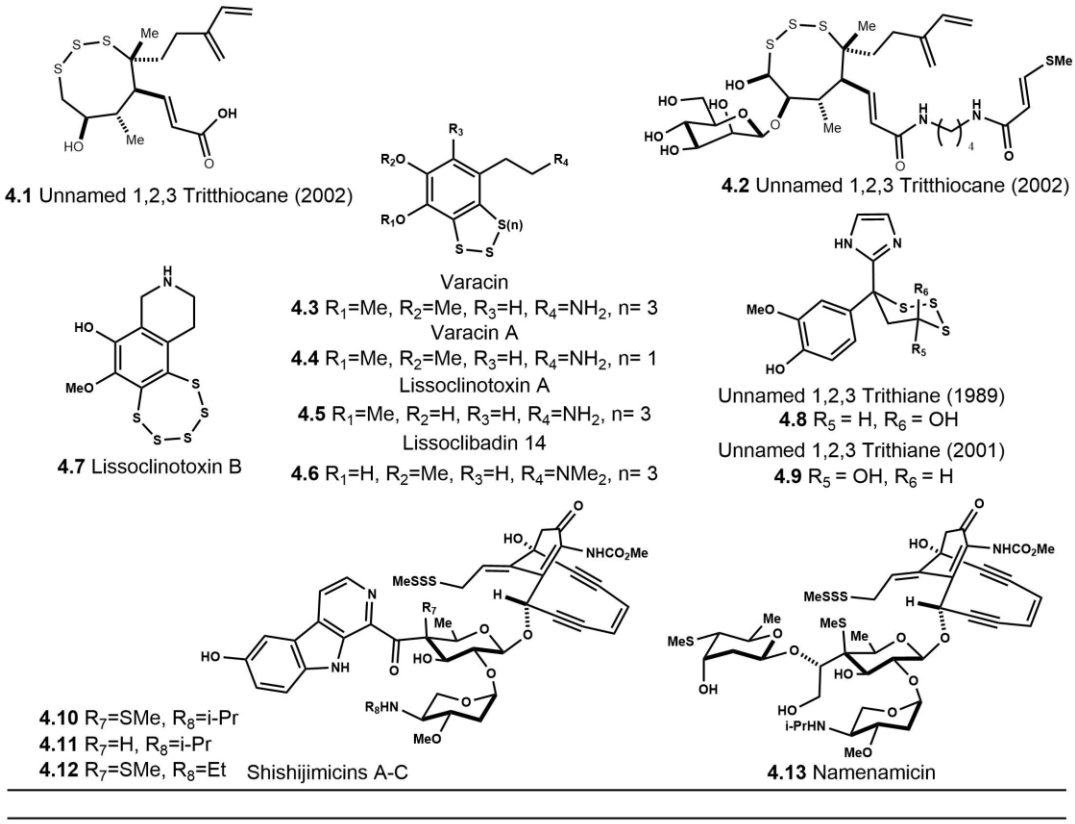


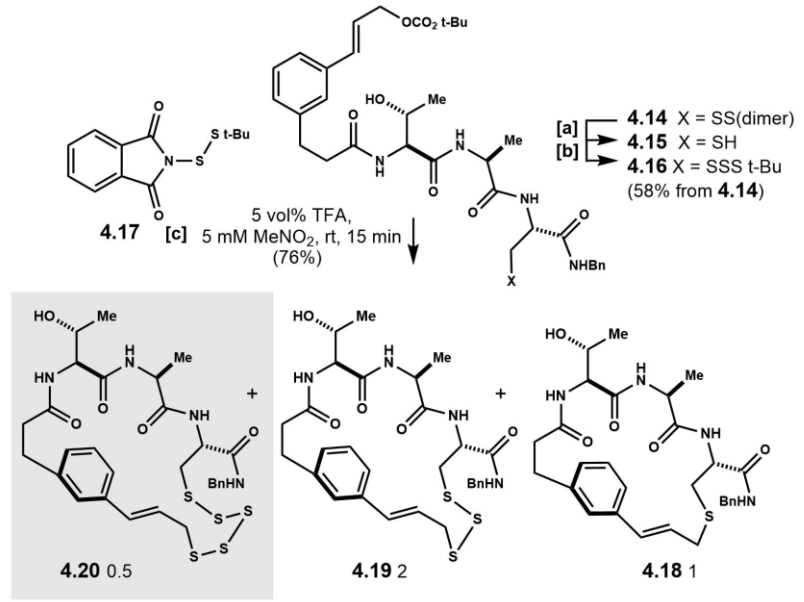
Figure 4.1 Acadian derived polysulfide natural products.

many related bioactive congeners, including the antibacterial lissoclinotoxins (**4.5, 4.7**)[19], antileukemia lissoclibadin 14 (**4.6**)[20], and various varacin-related polysulfides (*i.e.* **4.4**). Trithiane products **4.8**[21] and **4.9**[22] exhibited modest cytotoxicity and bactericidal activity. Trisulfides form the functional trigger in many ascidian-derived enediyne natural products (**4.10**-**4.12**) of immense synthetic[23] and biological interest.[54] Given the potential bioactivity and unquestionable novelty of these structures, incorporation of polysulfide motifs into the template constrained peptide macrocyclization system was pursued.

4.2 Results and discussion

4.2.1 Synthesis of Macrocyclic Polysulfides

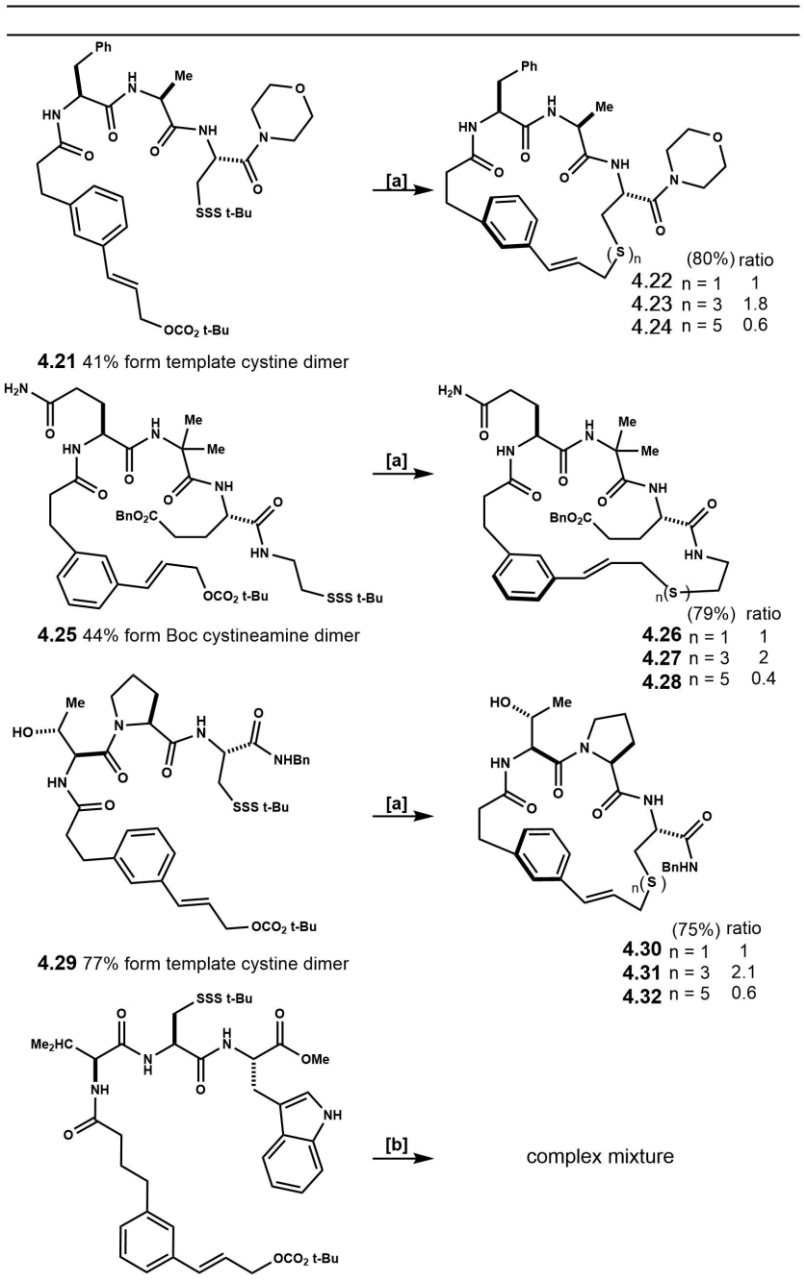
To emulate these novel polysulfide natural products, we investigated the sulfur transalkylation reactions first demonstrated with *tert*-butyl disulfides in our template system. A natural starting point for this endeavor was the synthesis of linear, template-capped *tert*-butyl trisulfides. Employing methods first used by Harpp, Nicolaou[23], and others[24], we elaborated cystine dimer **4.14** into **4.16** via reduction to thiol **4.15** and subsequent treatment with reagent **4.17**. We sought to cyclize this trisulfide in an analogous fashion to previously demonstrated disulfides and thioethers (chapter 2). Subjecting compound **4.16** to acidolysis conditions furnished one spot as visible by TLC and SiO_2 gel column chromatography in good mass yield (76%). It was only upon HPLC purification that the presence of thioether **4.18**, trisulfide **4.19**, and pentasulfide **4.20** were evident in a 1:2:0.5 ratio (scheme 4.1.).



[a] 1.0 equiv. SS dimer, 2.2 equiv. TCEP, 8.8 equiv. iPr_2NEt, DMF, 25°C, 1 h **[b]** 1.5 equiv. **4.17**, DMF, 55°C, 2-3 h **[c]** 5.0 vol. %TFA 5 mM $MeNO_2$, rt 15 min. Yields given for step **[c]** Product ratios detemined from HPLC peak integrals (monitoring @ 254 nm).

Scheme 4.1. Intial synthesis, trisulfidation, and S_2 exchange events.

Further exploration of this trisulfidation and apparent S_2 exchange event began with the synthesis of compound **4.21**(scheme 4.2). Subjecting this material to 5 vol% TFA in 5 mM $MeNO_2$



[a] 5.0 vol. %TFA, 5 mM $MeNO_2$, rt, 15 min., **[b]** 5.0 eq.Tf_2NH 5 mM $MeNO_2$, rt, quench, 5 min.

Scheme 4.2. Scope of trisulfidation and S_2 exchange.

afforded one spot as seen on TLC, in 80% mass yield in respect to the trisulfide after column chromatography. As in the previous example, HPLC purification enabled the facile separation of mono-, tri- and tentative pentasulfides **4.22**, **4.23**, and **4.24.** The ratio was determined by 254 nm HPLC trace integration to be 1:1.8:0.6, close to the ratio found in the first example.

A time trace experiment was performed on **4.21**, in which aliquots were quenched with base and subjected to a standard analytical HPLC method. At one minute the conversion to product seemed quantitative, with a prominent trisulfide peak being seen alongside a smaller thioether peak (figure 4.2, upper panel). It should be noted that this product distribution does not mirror those observed in the preparative samples. At ten minutes the pentasulfide is visible. When short (1 minute) reaction times were employed for substrate **4.29** mostly starting material was isolated, casting doubt on the veracity of the 1-minute time trace of **4.21** as seen in figure 4.3. The relative amount of tri- to monosulfide appears slowly decrease over the next 14 hours. However, trisulfide was not observed to disappear after 48 hours.

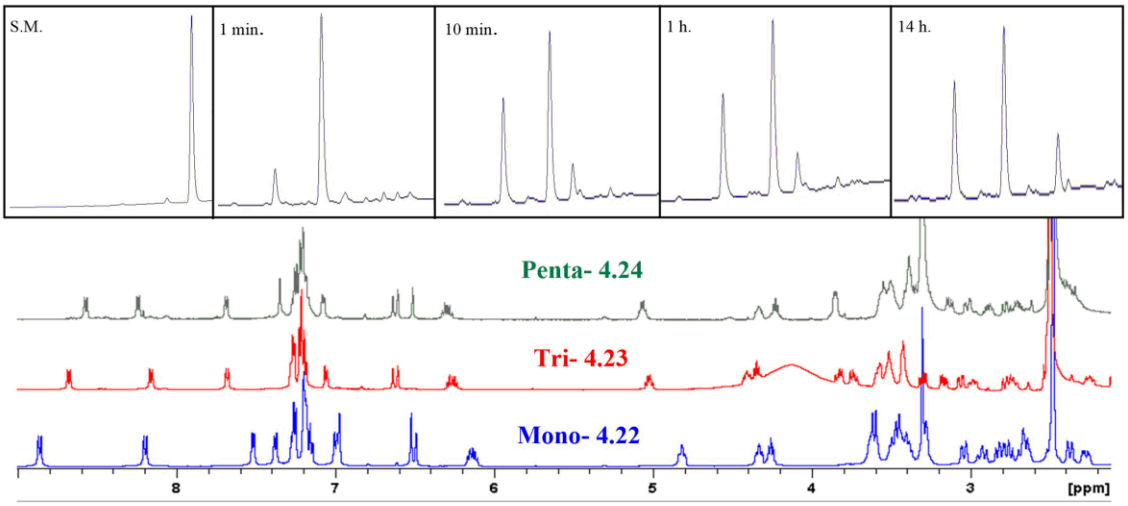


Figure 4.2. Time lapse trisulfidation of **4.21** (5-10 min retention time, 254 nm, top panel) and overlaid ^{1}H-NMR Spectra of **4.22-4.24** (bottom panel).

Cyclization of substrate **4.25**, featuring a primary carboxamide and cysteamine derived trisulfide, furnished a mono-, tri-, and pentasulfide ratio of 1:2:0.4. Acidolysis of the proline containing **4.16** analog, **4.29**, lead to the isolation of compounds **4.30**-**4.32** as proline rotamers with a ratio of 1:2.1:0.6. Attempts to use triflimide, a reaction condition developed for tryptophan containing substrates and bimacrocyclizations (chapter 3), provided a complex mixture (scheme 4.2. **4.33**).

Our method to synthesize thioethers via sulfur transalkylation provided an opportunity to confirm the products of this S_2 exchange by independent synthesis of **4.22**. To this end, linear thioether **4.34** was synthesized and subjected to cyclization conditions. Upon isolation and characterization, the **4.34** derived product was found to spectroscopically match the thioether product isolated from the analogous trifulfidation example (**4.22**). This is evident when the ^{1}H-NMR spectra of the two are overlaid, as seen in figure 4.3. Furthermore, the homologous

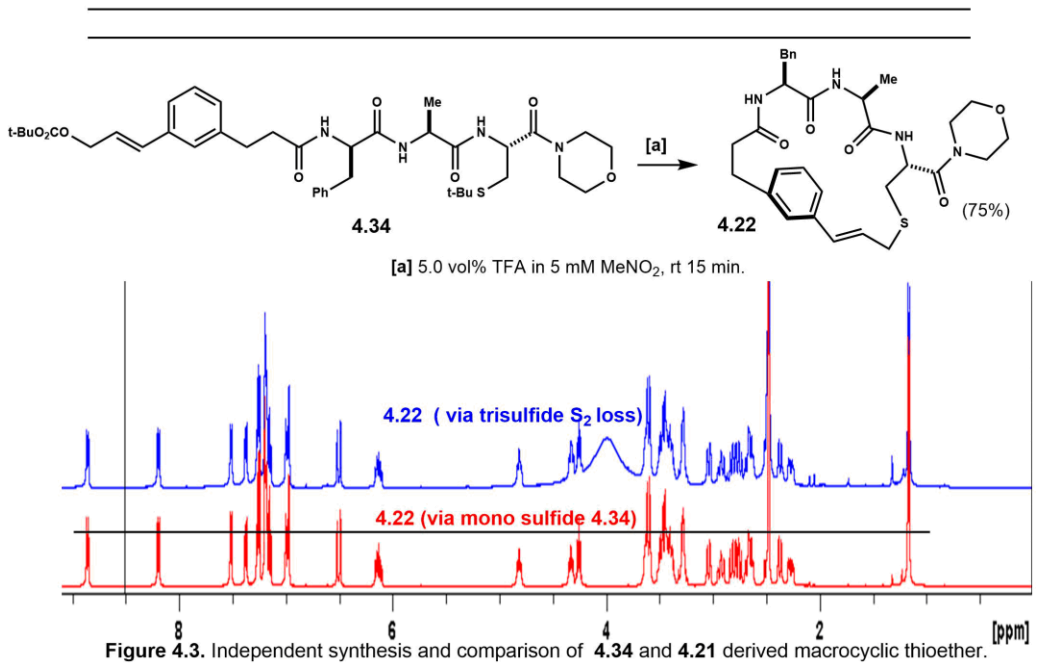


Figure 4.3. Independent synthesis and comparison of **4.34** and **4.21** derived macrocyclic thioether.

relationship between mono-, tri- and pentasulfides can be established in a similar fashion, as seen in figure 4.2. Minor pentasulfide products were chromatographically homogeneous and assigned by mass spectra. However, their ^{1}H-NMR spectra were uniformly complex. Resonances could not be assigned unambiguously, likely due to dynamic sigmatropy in these flexible allylic systems.

The S_2 exchange event was an intriguing occurrence and we sought a mechanistic rationale for this observation. A proposed mechanism is found in figure 4.4. Proton induce fragmentation of the template carbonate furnishes a cinnamyl cation, which forms macrocyclic sulfonium trisulfides **I** and **II**. Products **I** and **II** shed *tert*-butonium or **IV**, yielding macrocycles **V** and **III** respectively. **IV** is envisioned to react with **V** or **II**, leading to cyclic pentasulfide **VI**.

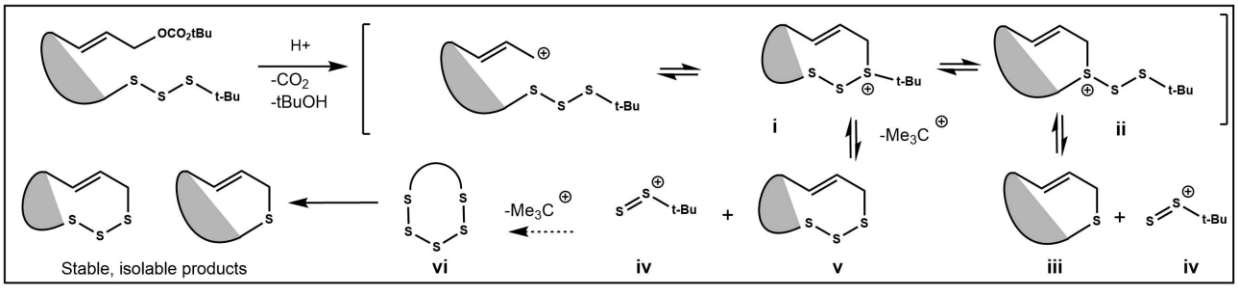


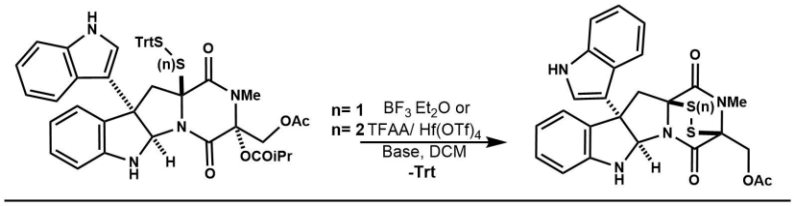
Figure 4.4. Proposed mechanism for S2 exchange observed in trisulfidations.

4.3 Sulfur transalkyation meets non-classical carbocations in synthesis

4.3.1 Conceptual background, discovery, and retrosynthetic plan for the total synthesis of trithiocane natural products 4.1 & 4.2

Intrigued by facile access to novel polysulfide macrocycles we began to apply this discovery towards the total synthesis of bioactive natural products. Examples of transalkylative trisulfidations in total synthesis are known. Movassaghi *et al* reported the apparent polysulfur transalkylation in the total synthesis of (+) Luteoalbusin B (scheme 4.3).[25] No system forming rings larger than seven members has been reported for redox neutral sulfur transalkylation. Given

this precedent, extending the cation induced sulfur transalkylations to an 8-membered trithiocane seemed achievable.



Scheme 4.3. Polysulfide transalkyation in total synthesis.

In 2002 Rezanka and Dembitsky reported the isolation and structural elucidation of trithiocane natural products **4.1** and **4.2** (figure 4.1).[31] These structures harbor a unique 1,2,3 trithiocane ring system. Compound **4.2** features further oxidation, namely a hemipolythioacetal and O-glycosylation. Additionally, an amide bearing a putrescine and likely cysteine derived peptide fragment are found. These compounds display modest bioactivity against *s*. aureus, *b*. subtilis, brine shrimp, and exceptional potency against the sea urchin *p*. lividus as determined by disc diffusion assay and IC50s.

Our retrosynthetic plan centered on the generation of a non-classical, highly stabilized bicyclobutonium via the ionization of a cyclopropyl-carbinol.[32,33] This ion was envisioned to capture the pendant alkyltrisulfide, forming a sulfonium that in turn dealkylates to furnish trithiocane product (figure 4.5.). Nonclassical carbocations are of immense theoretical and

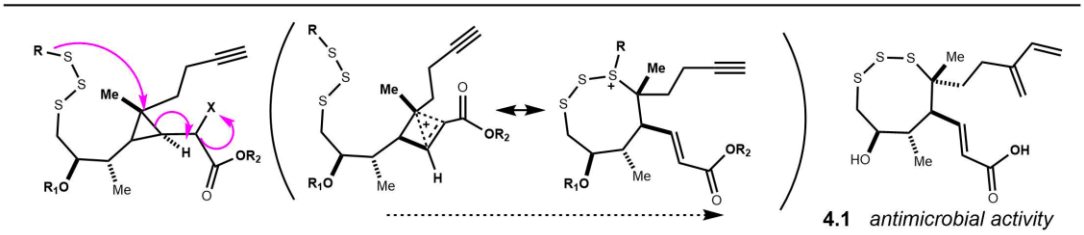
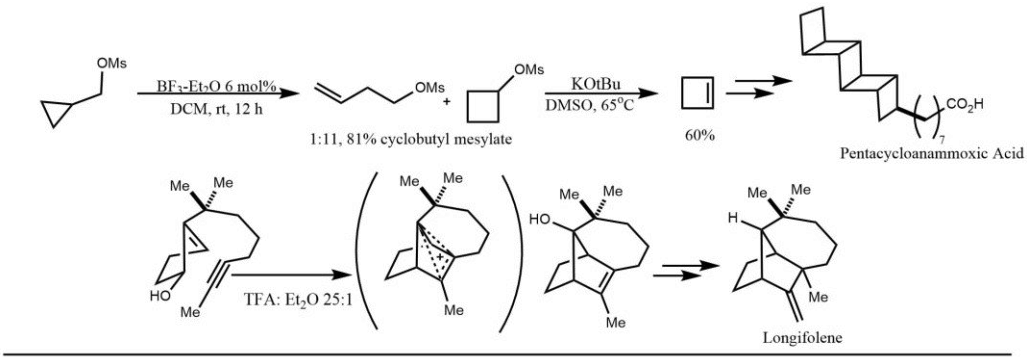


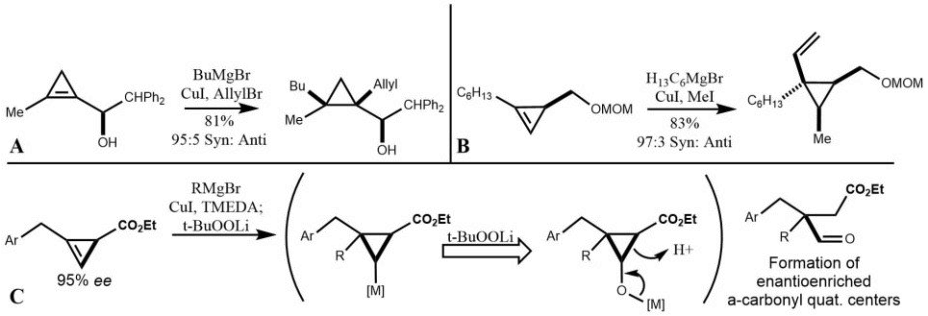
Figure 4.5. Transition state and disconnections for the bicyclobutonium induced sulfur transalkylation as a key step in the proposed total synthesis of trithiocane compounds **4.1** and **4.2.**

historical importance in the development of chemistry.[26] Seminal works in this field inform our understanding of bonding, structure, and underpin modern molecular orbital theory.[27,28] Many examples of nonclassical ion use in total synthesis have been reported. For instance, Johnson employed a Z-norborneyl cation rearrangement in his 1975 synthesis of Longifolene.[29] Corey *et al* reported the use of a bicyclobutonium rearrangement that enabled the synthesis of cyclobutene on scale, facilitating the total synthesis of pentacycloanammoxic acid (scheme 4.4).[30] Bicyclobutonium formation and cation-induced sulfur transalkylation serve as the conceptual inspiration for our route towards trithiocane products **4.1** and **4.2** .



Scheme 4.4. Nonclassical ions in total synthesis.

Several strategies towards the synthesis of these trithiocane natural products have been disclosed by our lab and others. Conceptually, our interest in functionalized cyclopropyl-carbinols stems from work reported by Marek, Fox, and our own group (scheme 4.5). Upon treatment with



Scheme 4.5. Select examples of cyclopropene organometalation and *syn* selective electrophile capture. **A** Marek's exemplar work on alcohol directed *syn* selective cyclopropene metalation. **B** Fox's work on alcohol and protecting group directed *syn* selective cyclopropene metalation. **C** Our lab's work on cyclopropene metalation and oxidative fragmentation to furnish quaternary centers bearing alpha and beta carbonyls.

an organocopper species, cyclopropenes can undergo substituent directed alkylation and concomitant metalation. The resulting cyclopropyl anion can capture a halocarbon electrophile to afford a *syn* functionalize cyclopropane. Marek demonstrated this as depicted in A. Upon treatment of a cyclopropenyl alcohol with cuprate, alkylation is observed at the most substituted carbon and the resultant cyclopropyl anion traps introduced allyl bromide leading to a *syn* functionalized cyclopropane bearing a quaternary center .[61] Fox and coworkers reported MOM-protected cyclopropenyl alcohols can likewise be organo-metalated, capture electrophiles, and furnish *syn* functionalized cyclopropanes also containing quaternary centers (scheme 4.5 B).[40] Recently, our laboratory reported the metalation of an enantioenriched cyclopropenyl-ester, followed by oxidation, and fragmentation of the resultant oxygenated cyclopropane to yield an enantioenriched quaternary center bearing α and β carbonyl functionality (scheme 4.5. C). [8]

Our interest in cyclopropyl-carbinols as synthons in the route to **4.1** is multifaceted. The methods depicted in scheme 4.5 enable the rapid, stereocontrolled construction of two sp^3 centers in a single operation. Considering **4.1** and **4.2** contain three contiguous stereocenters, one of which is quaternary, a highly functionalize cyclopropane would be an excellent synthon provided the

cyclopropane could fragment as desired. Fortunately, the literature is rife with examples of cyclopropane fragmentation. Of particular note is cyclopropyl-carbinol fragmentation via bicyclobutonium formation. As seen in figure 4.5, fragmentation of a functionalized cyclopropane with appended trisulfide is envisioned to concomitantly furnish a tertiary trithiocane, an α,β-unstaturated ester, and a tertiary branched carbon bearing a vinyl group. All of these structural motifs are present in the natural products, we considered this disconnection to be ideal.

To arrive at trithiocane **4.1** from compound **I** as seen in figure 4.6, one can envision the following. Cyclization of **I** as depicted in figure 4.6, followed by silyl deprotection, enyne metathesis, and saponification/deprotection to arrive at natural product **4.1**. Working backward from compound **I** to compound **II**, activation of the cyclopropyl-carbinol, trisulfidation, and deprotection must be performed to obtain **II** (figure 4.6). Compound **II** can be conceivably

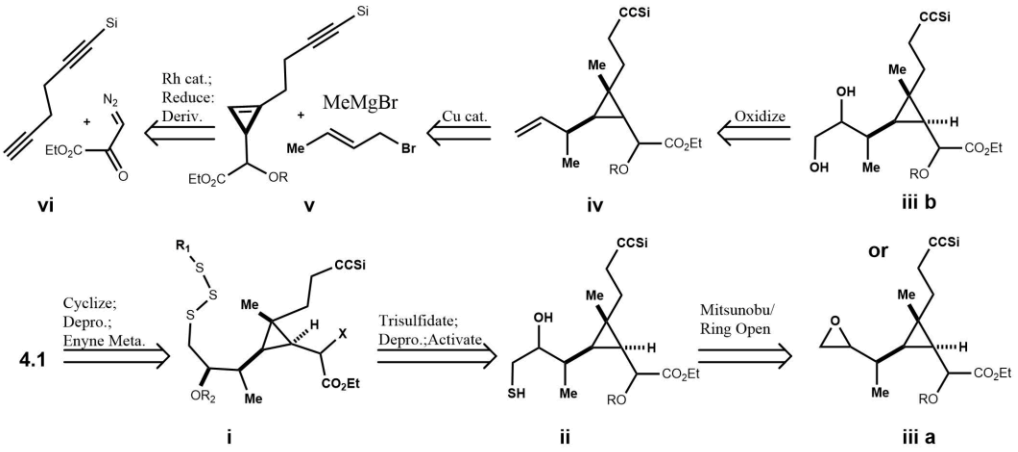


Figure 4.6. General retrosynthesis proposed for total synthesis of **4.1** and **4.2**.

synthesized in two way. Firstly, an epoxide opening using a thiol nucleophile could be performed on epoxide **III a**. Alternatively, a Mitsunobu reaction using thioactetic acid and diol compound **III b** could selectively provide the required terminal thiol of **II**. Both **III a** and **III b** could be readily obtained by oxidation of olefin **IV**. Compound **IV** could be synthesized by treatment of

cyclopropene **V** with methylcuprate, followed by *syn* selective crotylation of the resulting anion with crotyl bromide. Obtaining the correct methyl regiochemistry during crotylation is necessary for obtaining the desired terminal olefin with methyl branching. This requires the cyclopropyl cuprate generated (**I**, figure 4.7.) to engage crotyl bromide in a S_n2' fashion (**III**, figure 4.7.), opposed to a S_n2 manner. Alternatively, allyl bromide could be used to expediently generate a desmethyl model system for testing the key cyclization step. The final retrosynthetic step (**V** to **VI**, figure 4.6) would be the cyclopropenation of an alkyne with ethyl diazopyruvate, reduction, and any alcohol derivatization required for subsequent metalation steps.

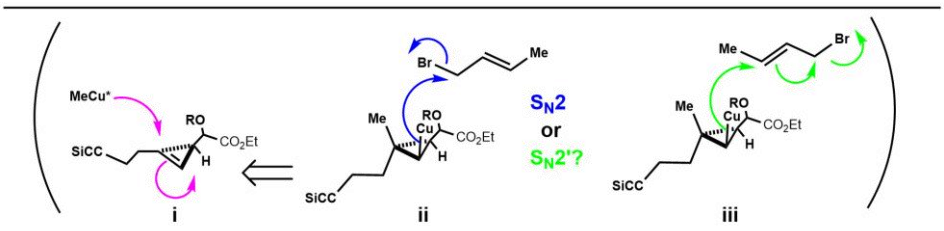
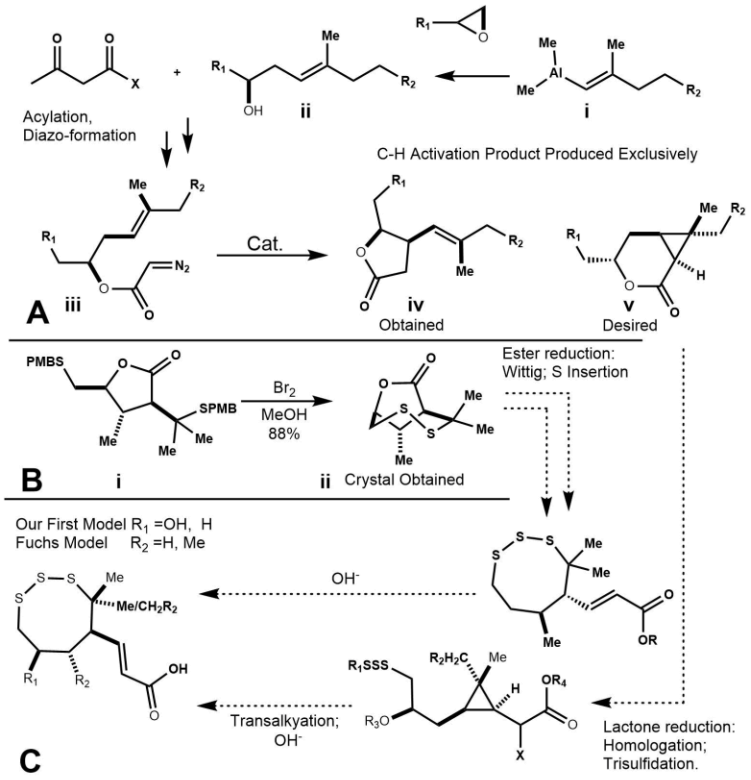


Figure 4.7. Regiochemical considerations for crotylation of a metalated cyclopropene.

Others have worked towards the synthesis of trithiocanes **4.1** and **4.2**, as depicted in Scheme 4.6. Work by Murzinski and Mustafa in our laboratory towards a model system employing a similar transalkylation based approach went as follows (scheme 4.6. A). An organo-aluminum species (**I**) is generated by treating a simple alkyne with $AlMe_3$, which opens an epoxide furnishing alcohol **II**. Compound **II** is then elaborated to diazoacetate ester **III**. Generation of a carbenoid in compound **III** lead to the isolation of C-H insertion product **IV**, a γ-butyrolactone. The desire compound, cyclopropanation product **V**, was not detected (scheme 4.6. A). Fuchs and Weaver of Loughborough U. obtained PMB protected dithiol **I** via Michael addition of thiol an α,β-unstaturated lactone (scheme 4.6. B). Oxidative deprotection of compound **I** afforded bicyclic dithiepane **II** in good yield. Scaling issues prevented the team from pursuing this approach further.

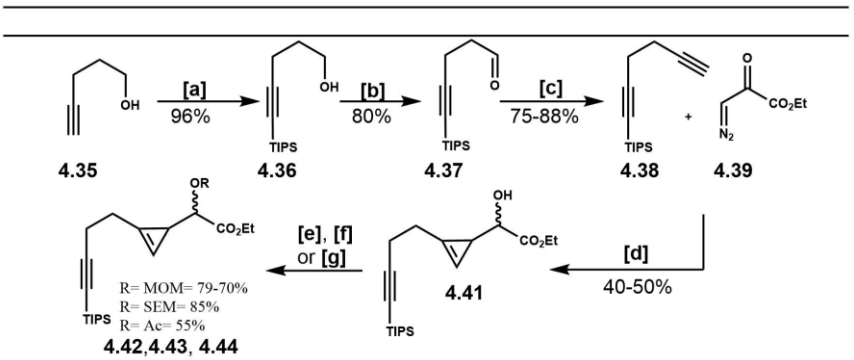
In our model system (scheme 4.6. B), compound **V** would need to be reduced, homologated, and trisulfidated to arrive at the cyclopropane depicted in scheme 4.6. C. Compound **II** in Fuchs' system would need to be reduced, extended via Wittig reaction, and undergo sulfur insertion to arrive at the depicted trithiocane models (scheme 4.6. C). With these previous routes in mind we began our synthesis in earnest.



Scheme 4.6 A Intial route towards a model system developed in our lab **B** Attempted route towards a model system developed by Fuchs and Weaver **C** Potenal end games.

4.3.2 Synthesis of model systems of a transalkyative sulfur cyclization.

After several abortive routes to make a TMS analog of **4.38** via metalation induced homopropargyl heterodimerization, we elected to do the following (scheme 4.7). 4-Pentyn-l-ol

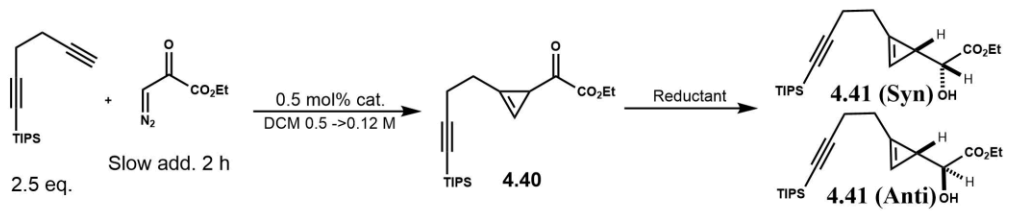


[a] 2.2 eq. EtMgBr reflux, 12 h; 1.1 eq TIPSCl, THF reflux, 6 h,**[b]** 1.05 eq. DMP, 1.1 eq. H_2O, DCM, 0°C, 30 min. **[c]** 1.5 eq. Ohira-Bestmann reagent, 2.2 eq. K_2CO_3, MeOH, 0°C -> rt, 12 h. **[d]** 0.5 mol% $Rh_2(OAc)_4$, DCM, rt, 8 h; 1.0 eq $NaBH_4$, EtOH, -78°C, 20 min.**[e]** 1.5 eq. MOMBr, 3.0 eq. $(i\text{-}Pr)_2NEt$, DCM, 45°C, 12 h. **[f]**1.5 eq. SEMCl, 3.0 eq. $(i\text{-}Pr)_2NEt$, DCM, 45°C, 12 h **[g]** 2.0 eq. AcCl, 0.2 eq DMAP, 5.0 eq. $(i\text{-}Pr)_2NEt$, DCM, rt, 40 min.

Scheme 4.7. Synthesis of common intermediate **4.41.**

(**4.35**) was treated with two equivalents of freshly made ethyl Grignard reagent and to the resulting dianion was added one equivalent of TIPSCl to furnish protected pentynol **4.36** in 96% yield.[34] Dess Martin Periodane oxidation and sequent Ohira-Bestmann homologation yielded TIPS 1,5-hexadiyne **4.38** in 60-70% isolated yield over two steps. The yield of the homologation varied with scale and commercial nature of Ohira-Bestmann reagent starting materials. A sole example of ethyl diazopyruvate reacting with an alkyne is known in literature. The reported product is a furan, likely derived from a (3+2) dipolar cycloaddition pathway.[35]Additional examples could be found, wherein ethyl diazopyruvate reacts with olefins to furnish cyclopropyl-ketoesters in poor to modest yields.[36-38] Initial test reactions using a simple alkyne showed ketone to furan ratios varying from 4 to 7:1. These products were separable by column chromatography and we deemed this route feasible for further pursuit.

To improve the lackluster yields common to ethyl diazopyruvate as a reagent, we explored the effect of dimeric rhodium catalyst ligands on isolated ketone yield. Rhodium acetate furnished cyclopropenyl-ketoester **4.40** in 32% yield (table 4.1. entry 1). Use of the divalent Esp ligand



Entry	Catalyst	Isolated Yield
1	$Rh_2(OAc)_4$	32%
2	$Rh_2(Esp)_2$	21%
3	$Rh_2(TFA)_4$	N.R.
4	$Rh_2(Oct)_4$	16%
5	$Rh_2(OAc)(DPTI)_3$	N.R.

Table 4.1. Catalyst screen for keto-cyclopropeneation.

Conditions	(Syn:Anti)	Isolated Yield
$NaBH_4$, EtOH, -78°C	1:1.2	45% (two steps from **4.38**)
L-Selectride, THF, -78°C	1.5:1	39 % (from **4.40**)
DIBAL, THF, -78°C	2:1	42% (from **4.40**)
$NaBH(OAc)_3$, EtOH, rt		N.R.
LTBA, THF, -78°C to rt		N.R.

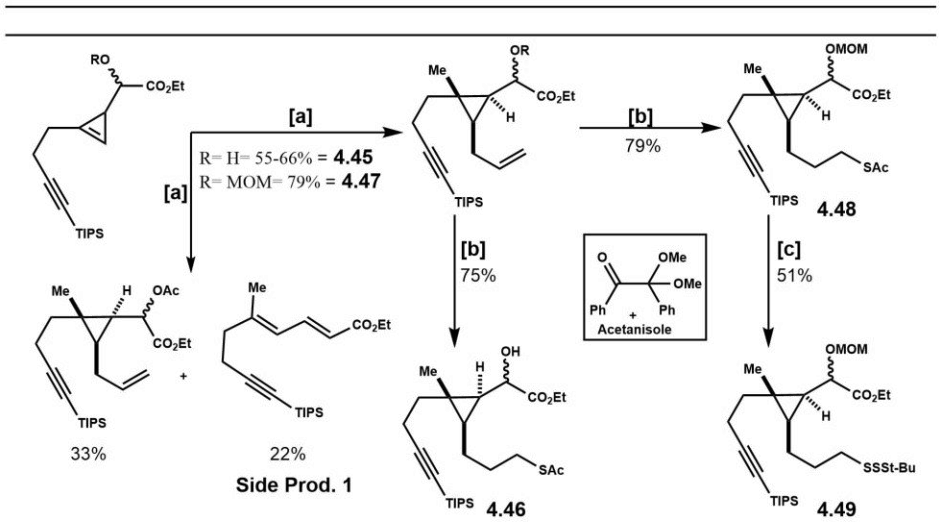
Table 4.2. Diastereoselective reductant screen.

afforded a diminished yield of **4.40** (21%), as did the use of rhodium octanoate (16%) (table 4.1. entries 2, 4 respectively). While the desired reactivity proved diminished for more sterically crowded carboxylate ligands, use of ligands with varying electronics proved more disadvantageous. Rhodium trifluoroacetate provided starting material, as did the chiral diphenyltriflylimidazolidinone complex developed by Corey *et al* (table 4.1. entries 3, 5 respectively).[39] With the most convenient and effective achiral catalyst selected we turned our attention to optimization of other reaction parameters. We hope to leverage the diastereoselective construction of a substituted cyclopropane toward a racemic synthesis.

Slow addition (8 hours) of ethyl diazopyruvate to a solution of 2.5 eq. of **4.38** (0.16 M final molarity) routinely afforded 40-45% yield of ketone **4.40**. Subsequent reduction of **4.40** with $NaBH_4$ provided **4.41** in upwards 70% yield. To minimize handling of the air-sensitive cyclopropenes we developed a telescoped variant of our previously refined cyclopropenation procedure, wherein a solvent swap and $NaBH_4$ reduction at cryogenic temperature were performed (scheme 4.7. [d]). Exploration of various hydride reductants failed to reveal highly

diastereoselective conditions (table 4.2). Relative stereochemistry was deduced considering the Felkin-Ahn model and literature precedent.[55,56] Given the stereoablative nature of the bicyclobutonium forming key step and the development of chromatographic conditions to separate diastereomers (*vide infra*), we elected to carry the mixture forward. With **4.41** in hand, several O-protected analogs were synthesized. Synthesis of MOM protected analog **4.42** was motivated by work of Fox and coworkers[40], featuring diastereoselective functionalization of a MOM protected cyclopropenyl-carbinol. SEM protective derivative **4.43** was envisioned to be reactive under these conditions as well. Acetyl ester **4.44** was synthesized given the precedent of Marek *et al*.[41]

With a host of cyclopropenyl derivatives in hand we turned to conditions developed in our laboratory for the organo-metalation and electrophile capture of cyclopropenes. The reaction began with preformation of 2.0 eq. of methyl Gilman reagent by treating TMEDA solubilized CuI



[a] 2.0 eq. MeMgBr, 2.0 eq. CuI, 2.2 eq. TMEDA, 2.0 eq. Allyl Br, THF, -40->-25°C, 30 min. **[b]** 4.0 eq. AcOH, 0.1 eq. Acetanisole, 0.1 eq. DMPA, 350 nm *hv*, EtOAc, rt, 1 h **[c]** 3.0 eq. LiOH, EtOH,°C, 40min.: 3.0 eq. AcOH; 3.0 eq. PhthSSt-Bu, MeOH, rt , 0.5 h.

Scheme 4.8. Middle game of model system synthesis.

with methylmagnesium bromide. To this cuprate was added cyclopropenyl alcohol derivatives before treatment with allyl bromide furnished the methyl-allyl cyclopropane products (scheme 4.8.

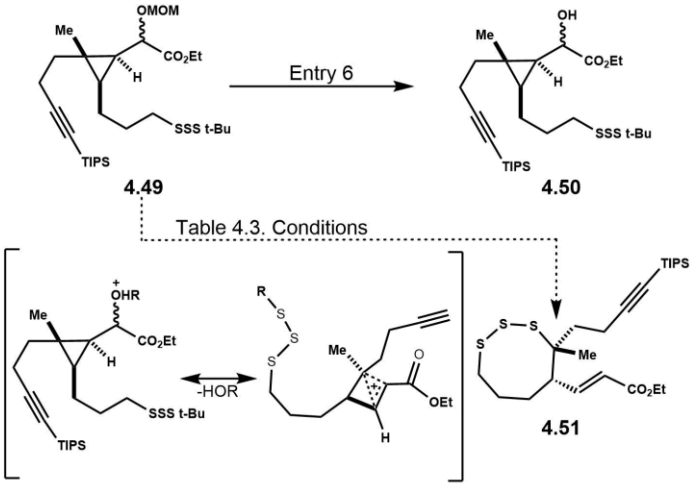
[a]). MOM derivative **4.42** was elaborated into product **4.47**. SEM analog **4.43** could be transformed in an analogous fashion, thought deprotection considerations led to MOM being the sole protecting group of focus. Acetyl ester **4.44** furnished a poor yield of the desired allyl cyclopropane, alongside the ring opened diene side product (**Side Product 1**).

Given our interest in testing trisulfides bearing acid sensitive groups in the trithiocane forming transalkylation, we investigated direct use of alcohol **4.41**. Fortunately, **4.41** proved amenable to the desired transformation. Cyclpropyl-carbinol **4.45** was isolated in 55 to 65% yield and no O-allylation was detected. Subjecting compounds **4.45** and **4.47** to a dual photocatalyst system under UV radiation lead to the isolation of thioesters **4.46** and **4.48** (scheme 4.8. [b]).[42] The reaction was carried out in a rayonet with 350 nm bulbs, reacted at ambient temperature for an hour and was isolated in good yields. Saponification of thioester **4.48** with LiOH, acidic quenching, and treatment with 3.0 eq. of *tert*-butyl phthalimidodisulfide afforded trisulfide **4.49** in 51% yield (scheme 4.8. [c]).

4.3.3 Attempted cyclization of a trithiocane model system via transalkylation.

Initial efforts toward bicyclobutonium formation and cyclization focused on the direct use of MOM protected analog **4.49**. Inspire by our reported reaction conditions for sulfur transalkyative macrocyclizations, TFA in $MeNO_2$ was employed. Given the less stabilized nature of bicyclobutonium relative to cinnamyl cations, we started with 20 vol% of TFA followed by direct evaporation (table 4.3. entry 1). These conditions lead to degradation despite promising TLC results during the reaction. According, we use a sodium bicarbonate quench in all further reactions in this series (as denote by *). Triflimide in $MeNO_2$ at 0°C was used but furnished only decomposition products upon purification, as did similar reactions in n-$PrNO_2$ at -78 °C (table 4.3.

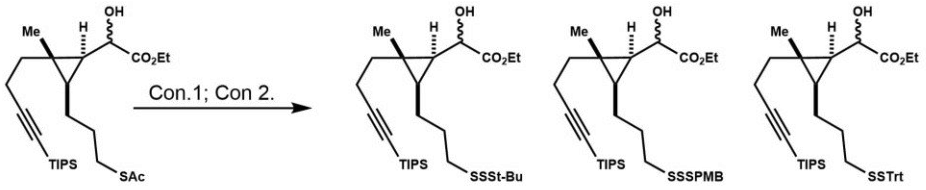
entries 2, 3 respectively). Use of 10 vol% TFA enabled the full conversion of **4.49** to **4.50**, provided a quench was performed (table 4.3. entry 4). Addition of 5 vol% methanesulfonic acid to a solution of n-$PrNO_2$ at -78°C failed to provide the desired trithiocane model system **4.51** (table 4.3. entry 5). Treatment of **4.49** with 1.33 M of hydrochloric acid at ambient temperature furnished alcohol **4.50** in 1.5 hours, comparatively mild conditions for the removal of a MOM group (table 4.3. entry 6). With an adequate supply of **4.50** in hand we ceased our experiments on the direct cyclization of **4.49**. It was at this point that separation of alcohol diastereomers was successfully undertaken.



Entry	Conditions	Result
1	20 vol% TFA, $MeNO_2$, 0°C, 5 min	Decomp.
2	3.0 eq. Tf_2NH, $MeNO_2$, 0°C, 5 min*	Decomp.
3	3.0 eq. Tf_2NH, n-$PrNO_2$, -78°C, 15 min*	Decomp.
4	10 vol% TFA, $MeNO_2$, 0°C, 5 min*	Full Con. **4.50**
5	5 vol% $MeSO_3H$, n-$PrNO_2$, -78°C, 5 min*	Decomp.
6	1.33 M HCl, EtOH, 0°C-> rt, 1.5 h*	66-76% **4.50**

Table. 4.3 Attempts at direct cyclization of **4.49** and synthesis of **4.50.**

Our desire to incorporate acid labile groups into the trisulfides necessitated the use of free alcohol containing thioester **4.46** directly in trisulfidation procedures. The mild base sodium methanethiolate (MeSNa) was employed in further trisulfidation experiments, owing to its extreme selectivity for thioester cleavage an inability to generate alkoxide. While elaborating **4.46** directly to trisulfides **4.50** and **4.52** was facile, chromatographic separation of these compounds form Harpp reagents (PhthSSR) proved challenging. Use of toluene: acetone-based eluent systems and oversized columns was necessary to obtain pure material in this case. Inspired by the voluminous work of Movassaghi[25,57-59] and others[53] we looked to install a trityl trisulfide. Synthesis of the trityl Harpp reagent (PhthSSTrt) was straightforward, however it proved inert under various reaction conditions (table 4.4. entries 2, 3).



4.46 **4.50** **4.52** **4.53**

Entry	Con.1	Con.2	Isolated Yield(s), Product	R, S#
1	3.0 eq. MeSNa, EtOH, 0°C, 10 min	2.0 eq. t-BuSSPhth, MeOH, 0°C-> rt, 1 h	60%, **4.50**	t-Bu, 3
2	3.0 eq. MeSNa, EtOH, 0°C, 10 min	2.0 eq.TrtSSPhth, MeOH, 0°C-> rt, 1 h	N.R.	
3	3.0 eq. MeSNa, EtOH, 0°C, 10 min	2.0 eq. TrtSSPhth, DMF 55,°C 1 h	N.R.	
4	3.0 eq. MeSNa, EtOH, 0°C, 10 min	2.0 eq.PMBSSPhth, MeOH, 0°C-> rt, 1 h	59%, **4.52**	PMB, 3
5	3.0 eq. MeSNa, EtOH, 0°C, 10 min	1.5 eq. TrtSCl, 2.0 eq. Et_3N DCM, 0°C, 15 min.	64%; 93%, **4.53**	Trt, 2

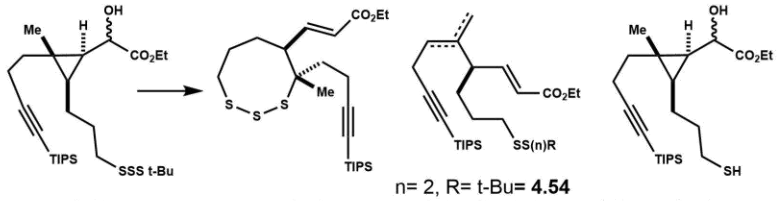
Table 4.4. Thioester cleavage and polysulfidation procedures.

Synthesis of paramethoxybenzy Harpp reagent was likewise facile and provided trisulfide **4.52** in comparable yields to the *tert*-butyl example (table 4.4. entry 4). Trityl trisulfides are known,

however the reagent to synthesize them from thiols is TrtSSCl. The synthesis of this compound required chlorine gas, which we were unable to acquire in a reasonable timeframe. To circumvent this triphenylmethanesulfenyl chloride (TrtSCl) was synthesized and proved to be a competent electrophile in formation trityl disulfides from thiols. In this vein, **4.46** was subjected to standard MeSNa induced thioester cleavage conditions and the resultant thiol was purified. This thiol was immediately dissolved in DCM and treated with TrtSCl to provide trityl disulfide **4.53** in excellent yield. With a diverse set of polysulfides in hand we set about systemically testing conditions for transalkyative cyclizations to furnish model trithiocanes.

We first investigated cyclopropyl-carbinol ionization using BF_3 etherate, adapting a highly dilute variation from literature precedent.[43,44] We recovered starting material **4.50** along with a highly nonpolar decomposition product (table 4.5. entry 1). Inspired by our template system conditions and relevant literature[45,46], we elected to use triflic acid to ionize **4.50** (table 4.4. entry 2). Intractables were recovered. Use of Metal triflates, namely Cu^{2+} and In^{3+},[47] failed to furnish product besides des-*t*-butyl cyclopropane **4.55** and minor impurities lacking acrylate ^{1}H-NMR resonances (table 4.5. entries 3, 4). Synthesis of mesylated derivatives proved similarly challenging to isolate, leading to diene **4.54** in addition to thiol congener **Side Product 2** (table 4.5. entry 7). Treatment of free alcohol **4.50** with $TiCl_4$ at -78°C led to decomposition, with no product **4.51** detectable (table 4.5. entry 10). Treatment with DAST at -30°C and deoxo-fluor® at -78°C furnished trace amounts and 15% yield of **4.54** respectively (table 4.5. entries 8, 13). Use of Martin's Sulfurane at ambient temperature lead to formation of **4.54** in 12% yield, albeit in a chaotic reaction mixture (table 4.5. entry 12).

Taking this into account we elected to form the triflated cyclopropyl-carbinol *in situ* and react it with various reagents in a one-pot fashion. Treatment of a 2,6-lutidine and **4.50** solution



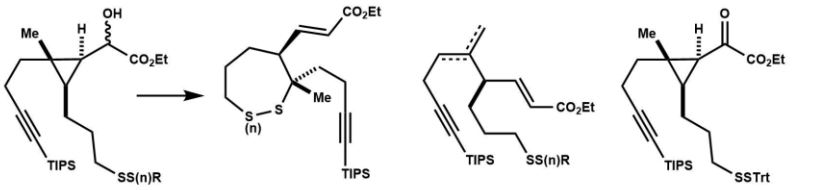
4.50 **4.51** n= 2, R= t-Bu= **4.54** n= 0, R= H= **Side Prod. 2** **4.55**

Entry	Conditions	Results
1	16 eq. BF_3 o Et_2O, DCM, 0°C to rt, 12 h	**4.50** isolated + decomp.
2	5.0 eq. TfOH, DCM, -78°C,10 min	Decomp.
3	1.0 eq. $In(OTf)_3$, DCM, rt	N.R.
4	1.0 eq $Cu(OTf)_2$, DCM, rt	**4.50**+ **4.55**
5	1.4 eq. Tf_2O, 1.5 eq. 2,6-lut., 0.04M DCM, -78°C, 1 h; 32 eq. BF_3 o Et_2O, 5mM DCM, -78°C-> rt, 1 h	57% **4.54** 1:0.6 Internal: Geminal
6	1.4 eq. Tf_2O, 1.5 eq. DTBMP, 0.04M DCM, -78°C, 15 min; 1.4 eq. TFA, 10 mM $MeNO_2$, 0°C->rt, 15 min	**4.54** + decomp
7	1.4 eq.$MeSO_3Cl$, 1.5 eq.Et_3N, 0.1 M DCM, 0°C, 45 min	37% **4.54** 13% Thiol **Side Prod. 2**
8	3.0 eq. Et_2NSF_3, 10 mM DCM, -30°C-> rt various workups	Minor amounts of **4.54**
9	1.5 eq. Tf_2O, 10 mM, DCM, -78°C-> rt, 1 h	Decomp.
10	1.5 eq. $TiCl_4$ 10 mM, DCM, -78°C-> rt, 1 h	Decomp.
11	1.5 eq. Tf_2O, KHMDS 1.4 eq., 10 mM Tol:THF, -78°C, 20 min	35% **4.54**
12	1.5 eq. Martin's Sulfurane, 10 mM DCM, 0°C, 30 min	12% **4.54**
13	1.5 eq. deoxo-fluor ®, 10 mM DCM,-78°C, 30 min	15% **4.54**

Table 4.5. Macrocyclization attempts on *t*-Bu substrate **4.50.**

at standard molarity (0.05M) with triflic anhydride led to the near instantaneous consumption of starting material at -78°C. Dilution of this reaction to 10 mM with a solution containing 16 eq. of BF_3 etherate afforded diene **4.54** in 57% yield after one hour (table 4.5. entry 5). In an attempt to suppress the elimination, we elected to neutralize the reaction with 1.4 eq. of TFA before diluting with $MeNO_2$. Additionally, the solid base 2,6-Di-*tert*-butyl-4-methylpyridine (DTBMP) was used in an attempt to more rigorously control stoichiometry (table 4.5. entry 6). Unfortunately, this led to the isolation of **4.54**. Use of KHMDS as a base furnished **4.54** in diminished yield (table 4.5. entry 12). Use of no base lead to decomposition (table 4.5. entry 9).

Seeking greater acid lability and precedent relative to *tert*-butyl trisulfide **4.50**, we began testing reactions of trityl disulfide **4.53**. Treatment of a solution of **4.53** and 2,6-lutidine with Tf_2O lead to the isolation of diene **4.58** in good yield (table 4.6. entry 2). Formation of triflate was followed by dilution to 10 mM with a 2.5 vol% solution of TFA in n-$PrNO_2$. This reaction furnished diene **4.58** in 47% yield (table 4.6. entry 3). Use of KHMDS as a base led to the isolation of diene **4.58** (53%) in addition to oxidized ketone product **4.59** (21%), the latter product conceivably arising from a Corey-Kim type oxidation mechanism (table 4.6. entry 4). Use of no base with substrate **4.53** lead to decomposition (table 4.6. entry 1), as did MgO and NaH used as such with substrate **4.52** (table 4.6. entries 7, 8 respectively). Treatment of **4.53** and **4.52** with Martin's sulfurane provided the dienes **4.58** and **4.57** in 15% yield and trace amounts respectively (table 4.6. entries 5, 9). As in the case with compound **4.50**, no trace of trithiocane **4.51** or trithiane **4.56** could be found using reported conditions.



n= 2, R= PMB= **4.52**
n= 1, R= Trt= **4.53**

n= 2= **4.51**
n= 1= **4.56**

n= 2, R= PM**B= 4.57**
n= 1, R= Trt= **4.58**

4.59

Entry (S.M.)	Conditions	Results
1 (**4.53**)	1.5 eq. Tf_2O, 10 mM, DCM, -78°C to rt, 20 min to 1 h.	Decomp.
2 (**4.53**)	1.4 eq. Tf_2O, 1.5 eq. 2,6-lut. 10 mM DCM, -78°C, 15 min.	72% **4.58** 1:0.4 Internal: Geminal
3 (**4.53**)	1.4 eq. Tf_2O, 1.5 eq. 2,6-lut. 0.1 M DCM, -78°C, 15 min; 2.5 vol% TFA, n-$PrNO_2$, 10 mM, 15 min.	47% **4.58** 1:0.6 Internal: Geminal
4 (**4.53**)	1.5 eq. Tf_2O, KHMDS 1.4 eq. 10mM Tol:THF, -78°C, 20 min.	53% **4.58** + 21% **4.59** 1:0.8 Internal: Geminal
5 (**4.53**)	1.5 eq. Martin's Sulfurane, 10 mM DCM, 0°C, 30 min.	15% **4.58** 1:1.4 Internal: Geminal
6 (**4.52**)	1.5 eq. Tf_2O, 1.5 eq. 2,6-lut. 10 mM DCM, -78°C, 30 min.	**4.57** 1:0.5 Internal: Geminal
7 (**4.52**)	1.5 eq. Tf_2O, 1.5 eq. MgO, 10 mM DCM, -78°C, 30 min.	Decomp.
8 (**4.52**)	1.5 eq. NaH, 0.1 M Tol, rt, 15 min; 1.5 eq Tf_2O 10 mM DCM, -78°C, 30 min.	Decomp.
9 (**4.52**)	1.5 eq Martin's Sulfurane, 10 mM DCM, 0°C, 30 min.	**4.57** 1:0.5 Internal: Geminal

Table 4.6. Macrocyclization attempts on Trt and PMB substrates **4.53** and **4.52.**

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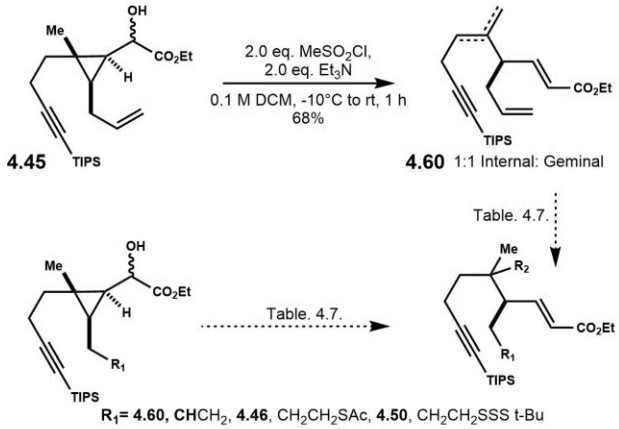
4.3.4 Tertiary thiol forming attempts

Despite the controllable fragmentation of the cyclopropyl-carbinol triflates we ceased our pursuit of cation induced translative trithiocane forming cyclizations. Efforts shifted to the

formation of a tertiary sulfide of desired regiochemistry, through either cyclopropyl-carbinol or pre-fragmented polyene products. To this end cyclopropanes **4.45**, **4.46** and **4.50** (table 4.7 entries 1, 2, 3 respectively) were treated with standard triflation conditions before the introduction of a 1:4 thioactetic acid: DCM solution. Unfortunately, a complex mixture was isolated in the case of all three substrates, with no desired product being apparent by ^{1}H-NMR. Marek and Lanke recently reported the controlled generation and nucleophilic trapping of bicyclobutonium ions via copper



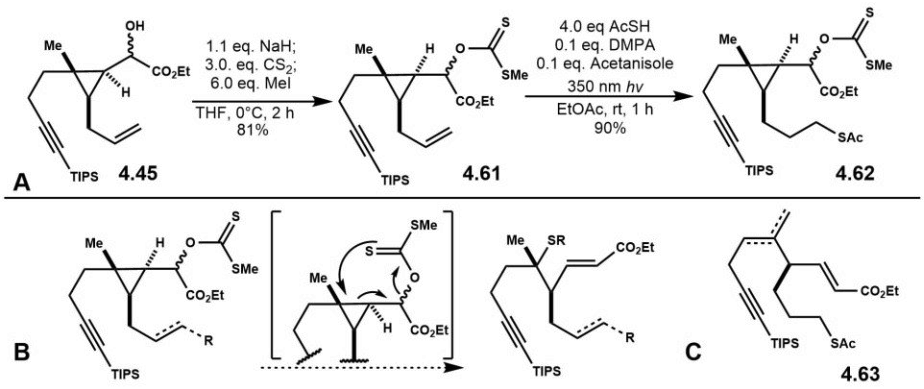
Scheme 4.9. Synthesis of triene **4.60** on scale and attempts at quaternary sulfide formation.

Entry. R_1	Conditions	Results
1. **4.45** 2. **4.46** 3. **4.50**	1.4 eq. Tf_2O, 1.5 eq. 2,6 -lut. 0.04 M DCM, -78°C, 3 min.; 1:4 AcSH DCM, -20°C, 27 min.	Complex mixtures
4. **4.60**	2.8 eq. AcSH, 10 mol% $InCl_3$, 0.1 M DCE, 85 °C, 2 h.	**4.60** recovered
5. **4.58**	$MeSO_2OH$, 0.5 M, 10 mM $MeNO_2$, 0°C, 20 min	Decomp.
6. **4.45**	1.5 eq. TCA, 20 mol% CuBr, 0.05 M DCM, rt, 2 h.	**4.45** recovered

Table 4.7. Attempts at quatenary sulfide formation.

catalysis.[47] Subjecting **4.45** to the reported conditions provided no rearrangement, even with extended reaction times and stoichiometric copper (table 4.7. entry 6). Reactions to elaborate the polyenes derived from cyclopropyl-carbinol fragmentation were undertaken. Geminal olefins are reported to undergo hydrosulfidation with thioacetic acid in the presence of catalytic $InCl_3$.[48] Subjecting triene **4.45** to these conditions lead to the recovery of starting material (table 4.7. entry 4). An attempt was made to elaborate trityl disulfide containing diene **4.58** product to dithiepane via acidolysis and cyclization. These conditions failed to furnish the desired product, leading to intractables (table 4.7. entry 5).

Allylic rearrangements featuring O to S connectivity are known.[49-51] Based on these precedents we synthesized xanthate **4.61**, planning to use the cyclopropane moiety in analogy to a vinyl group. Thioester **4.62** was synthesized via photocatalysis, the xanthate surviving the transformation intact despite the thiyl radicals invoked in this reaction mechanism (scheme 4.10). Our initial investigations centered on a thermal rearrangement of cyclopropyl-xanthates to afford the desired S-migrated product (scheme 4.10, square brackets). Neat thermolysis at 200°C led to instantaneous conversions of starting material, with an acrylate derivative visible on crude ^{1}H-NMR (table 4.8. entry 1). pTLC purification of this reaction afforded triene **5.60** in 19% yield, along with decomposition products. Thermolysis at 180°C in o-DCB achieved similar results for both olefin and thioester derivatives (table 4.8, entries 2, 3 respectively), furnishing 40% isolated yield of **4.60** and trace amounts of **4.63**. Seeking the mildest thermolysis conditions, compound **4.61** was dissolved in d4 o-DCB, heated incrementally, and observed by ^{1}H-NMR (table 4.8. entry 4, figure 4.8).



Scheme 4.10. A Synthesis of cyclopropyl xanthates **4.61** and **4.62**.. **B** Desired cyclopropyl-xanthate rearrangement. **C** Depiction of product **4.63**.

Entry, Substrate	Conditions	Results	Entry, Substrate	Conditions	Results
1, **4.61**	Neat, 200°C, 5 min	19 % **4.60** + decomp.	5, **4.61** 6, **4.62**	S_8, AIBN, DCE 0.07 M, 85°C, 1 h	Complex mixture
2, **4.61**	o-DCB 0.1 M 180°C, 5 min	40% **4.60** + **4.61** recovered	7, **4.62**	AIBN 0.2 M Tol, 80°C, 6 h	**4.62** recovered
3, **4.62**	o-DCB 0.1 M 180°C, 5 min	**4.63** + decomp.	8, **4.62**	Lauroyl Perox. 0.2 M Tol, 80°C, 6 h	**4.62** +**4.63** (trace)
4, **4.61**	d4-o-DCB 0.1 M 125-170°C	17% **4.60** + decomp.	9, **4.61** 10, **4.62**	AIBN, Sn_2Me_6 0.2 M Tol, 80°C, 2 h	**S.M.** recovered

Table 4.8. Attempted radical and thermal reargangements of cyclopropyl xanthates.

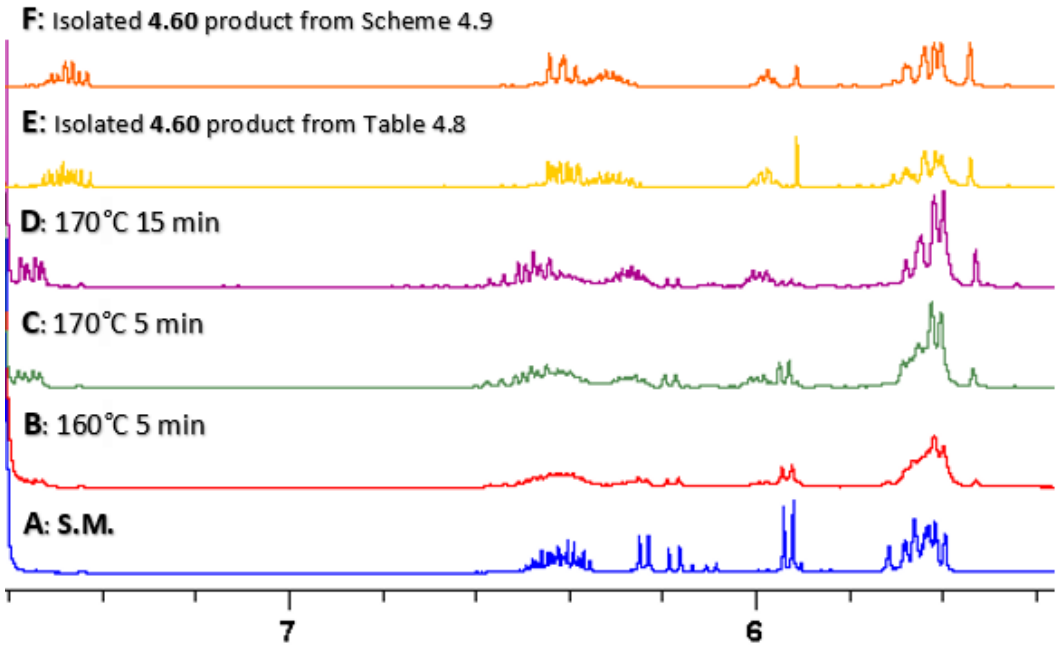


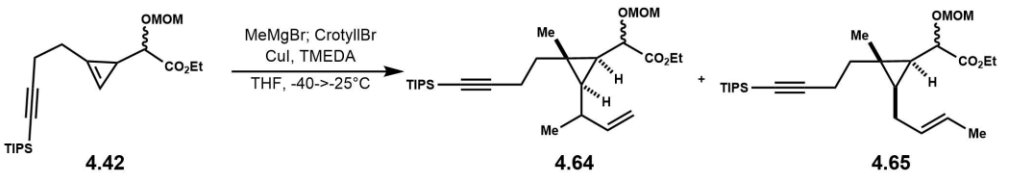
Figure 4.8. NMR time/ temperature trace of thermolysis of **4.61**

Triene **4.60** was observed and confirmed as the resultant unsaturated ester product seen in previous thermolysis attempts. Furthermore, no intermediate acrylate-bearing tertiary thiol could be observed in the timeframe of ^{1}H-NMR monitoring (Figure 4.8).

We next attempted to induce radical initiated rearrangements of xanthates **4.61** and **4.62**. Care was taken to select conditions without a mechanistically available source of hydrogen, ruling out common tin hydride mediated Barton-McCombie conditions. Use of elemental sulfur as a radical chain propagator with AIBN as an initiation yielded intractable mixtures (table 4.8. entries 5, 6). Use of a stoichiometric amount of AIBN failed to furnish product, leading to isolation of starting material **4.62** (table 4.8. entry 7). This result indicates the radicals formed in AIBN thermolysis are not persistent enough to induce the desired reaction, hence the ubiquitous use of $HSnBu_3$ for chain propagation. Seeking a hydrogen free variant of classic Barton- McCombie conditions, we elected to use hexamethylditin in lieu of $HSnBu_3$. The ensuing reaction led to recovered starting material (table 4.8, 9, 10). Lauroyl peroxide has been used to furnish a Barton-McCombie deoxygenation or Schonberg rearrangement depending on solvent.[52] We elected to use toluene in hopes of inducing a sulfide transposition concomitant with cyclopropyl fragmentation and acrylate double bond formation. While these conditions (table 4.8. entry 8) led to product, the isolated material proved to be triene **4.60**.

While the allylated cyclopropane **4.45** proved useful in model systems to test cyclizations, a method to introduce the α-branched methallyl group needed for natural products **4.1** and **4.2** was sought. Initial attempts with crotyl tosylates and phospinocarboxylates proved unfruitful. Cuprate intermediate derived from cyclopropene **4.42** was found to readily react with crotyl bromide to furnish a mixture of regio- and diastereomers in 65% mass yield (scheme 4.11). Compounds **4.64** and **4.65** proved inseparable by preparative scale chromatography. Considering thiol-ene reactions

are largely selective for terminal olefins, subsequent reaction and chromatography could likely separate **4.64** and **4.65** derived structures. While the results of this experiment were encouraging, we shifted focus to model systems of trithiocane ring formation by various means.



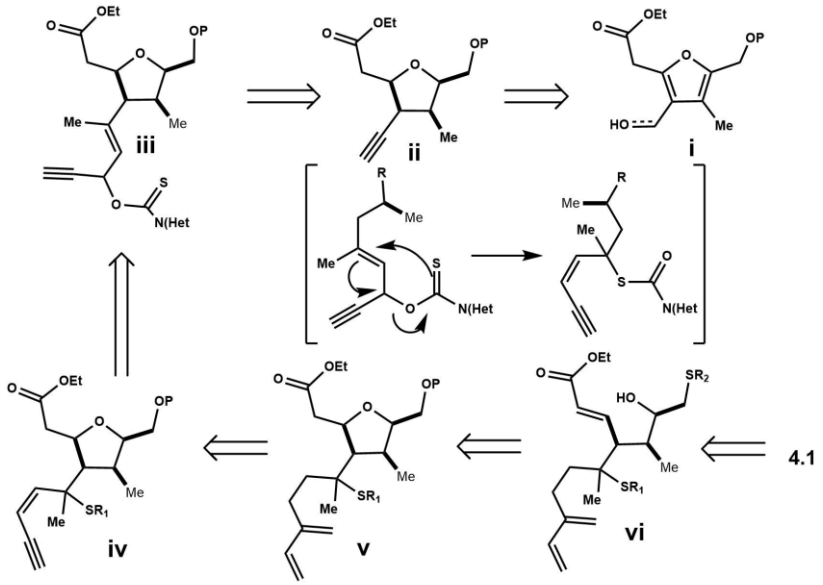
Scheme 4.11. Crotylation of cuprate to furnish complete carbon skeleton of **4.1**.

4.4 Conclusion

4.4.1 Chapter four conclusion

In summary we have reported a template-based system to elaborate *tert*-butyl trisulfide containing peptides into trisulfide linked macrocycles. Upon cyclization an apparent S_2 exchange event occurred, after which mono-, tri- and pentasulfide linked compounds could be isolated by preparative HPLC purification. This is the first reported preparative method for the synthesis of trisulfide linked peptide macrocycles to date. The veracity of this S_2 exchange was proven by the independent synthesis of a thioether product first isolated from the cyclization of a trisulfide. This cation-induced transalkylation of a polysulfide informed the design and implantation of an attempted synthetic route to trithiocane containing natural products (**4.1** & **4.2**, figure 4.1). A number of complex model systems were synthesized and numerous cyclization attempts via cation induced sulfur transalkylation, xanthate rearrangements, and tertiary sulfide formation were made. While the cyclization to form the key ring system proved elusive, great strides were made in the rapid synthesis of a highly functionalize cyclopropane core containing all the requisite carbons of compound **4.1**.

While bicyclobutonium induced sulfur transalkylation proved to be unsuccessful in a bimolecular reaction, the extremely selective fragmentation of said ion suggests the route may have a future. Surely some sulfur-based nucleophile could be introduced to the bicyclobutonium and, given the right conditions form the long sought tertiary sulfide required for the trithiocane core. This product could then be synthetically elaborated into a dithiepane and sulfur insertion may furnish the final trithiocane product. Nucleophiles of interest for intercepting the bicyclobutonium in a bimolecular fashion are thioacetates, thiobenzoates, benzylthiols, hydrogen sulfide, and salts thereof. Other modalities of sulfur-carbon bond formation could be explored, such as Michael additions or [3,3] sigmatropic rearrangement. For instance, **4.1** could be synthesized by doing the following. Furan compound **I** (scheme 4.12.), could be exhaustively hydrogenated and



Scheme 4.12 Proposed 3,3 sigmatropic rearrangement obtain tertiary thiol.

homologated to furnish compound **II**. Tetrahydrofuran **II** could be treated with $AlMe_3$ and propargyl aldehyde to furnish thiocarbamate **III** after thiocarbamylation. Compound **III** could undergo [3,3] sigmatropic rearrangement to furnish compound **IV** bearing a tertiary thiol center (scheme 4.12. square brackets). This compound could be selectively reduced and undergo enyne

metathesis to provide **V.** Treatment of **V** with base would generate an enolate, which may ring open the THF. Conversion of OP to a suitable sulfur group (**VI**, scheme 4.12) may enable the oxidative dithiepane formation as seen in the work of Fuchs (scheme 2.6 B).[62] Only sulfur insertion would remain to synthesize trithiocane **4.1**. Synthesis of the trithiocanes (**4.1** and **4.2**) remains an unachieved goal, it is hoped that the work in this dissertation may enable that goal.

4.4.2 Dissertation conclusion

Taken as a whole, the research disclosed in this dissertation enables the synthesis of libraries of sulfur linked peptidomimetic macrocycles. Di-, mono- and exotic trisulfides rich in functionality can be rapidly synthesized. Several reliable methods to elaborate disulfides have been reported, including oxidation, fluorocarbo- and heterocycle insertion. New templates capable of forming multiple macrocyclic linkages have been invented, enabling the synthesis of cage-like, natural product inspired molecules from simple peptides in several steps. Synthetic efforts have advanced the synthesis of novel trithiocane natural products further than previously achieved in our group. Continued refinement and applied use of the basic methods reported here are ongoing. We hope to augment the methods pioneered here with *in silico* generation and screening of massive virtual libraries.[60]

4.5 References

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A *Chapter Two- Appendix material*

Synthesis of mono- and disulfide macrocycles via sulfur transalkylation

Table of contense

Chapter 2 Experimental Procedures

General Methods.
Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon at room temperature. Solvents were dried on activated alumina solvent drying system. Nitromethane was dried by storing for 24 hours over neutral Brockmann I Alumina before being filtered onto to activated 3 angstrom molecular sieves for extended storage. DMF was distilled over CaH_2 onto activated 3 angstrom molecular sieves for extended storage. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF254 (0.25 mm). TLC was visualized with UV light (254 nm) and stained using $KMnO_4$. Flash chromatography was performed on silica gel 60 (240-400 mesh). 1D NMR spectra for peptidal substrates were recorded on a Bruker Avance (500 MHz) spectrometer using MeOH-*d*4 or DMSO-*d*6 as solvent and referenced relative to residual MeOH (δ= 3.31 ppm), $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. ^{13}C NMR spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual MeOH-*d*4 (δ = 49.00 ppm) or DMSO (δ = 39.52 ppm). HSQC, HMBC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. 2D NMR experiments were recorded on a Bruker Avance (600 MHz). High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART IDCUBE, Waters GST Premier, and Waters LCT Premier. All HPLC traces are shown at 254 nm and depict preparative purifcation of macrocycles on a SunFire® C18 OBD 5 um 19 x 250 mm column using an Agilent 1100/1200 Series HPLC.

General Procedure A - Peptide Synthesis:
All peptides were synthesized by 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.[1]

General Procedure B - Acylation of Organic-Soluble Peptides with Templates:
Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **3** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the reaction was diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The organic phase was then dried over $MgSO_4$, concentrated under reduced pressure. The resulting compound was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent gradient.

General Procedure C - Acylation of Water-Soluble Peptides with Templates:
Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **X** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the solvent was removed via roto evaporator and the residue dissolved in 2 ml of DMSO, passed through a 0.5 micron filter and purified via preparative HPLC (procedure used to prepare sequences containing His and Glu residues).

General Procedure D - Peptide Macrocyclization with Template 2.3:
A scintillation vial was charged with a stir bar and template capped peptide (1.0 equiv.) before being capped with a septum and backfilled thrice with argon. Nitromethane (as described in the materials section) was added to the substrate to afford a concentration of 5.26 mM before 5 volume % TFA was added, bringing the final molarity to 5.00 mM. After the addition of TFA the reaction was stirred for 15 minutes before the solvent was removed under reduced pressure. Crude product was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent or preparative HPLC depending on the polarity of the resultant macrocycle.

General Procedure E - Template 2.46 Pictet Spengler:
Peptide-template **2.46** adduct (as described above in the general peptide-template acylation procedure) was dissolved in 4:1 H_2O: AcOH to afford a 0.1 M solution. The reaction was stirred for 48h at room temperature before evaporation of solvent and evaporation thrice with MeCN and Thrice with $CHCl_3$. resulting compound was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent.

Template 2.3:
Template **2**.**3** was synthesized according to our published procedure.[2]

Template 2.46:
Template **2.46** was synthesized according to our published procedure.[3]

Linear Precursor 2.4:
Synthesized according to general procedure **B**, obtained in 75% isolated yield.

^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.26 (s, 1H), 7.21 (dt, *J* = 7.3, 6.3 Hz, 4H), 7.16 (dt, *J* = 3.9, 3.1 Hz, 3H), 7.11–7.08 (m, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.9, 6.2 Hz, 1H), 4.89 (dd, *J* = 7.5, 6.9 Hz, 1H), 4.65 (dd, *J* = 6.3, 1.3 Hz, 2H), 4.56 (dd, *J* = 7.7, 6.6 Hz, 1H), 4.26 (t, *J* = 7.4 Hz, 1H) 3.55–3.48 (m, 2H), 3.37 (t, *J* = 6.9 Hz, 2H), 3.00 (d, *J* = 7.7 Hz), 2.92 (d, *J* = 7.5 Hz), 2.89 (dd, *J* = 4.3, 3.7 Hz), 2.86 (dd, *J* = 7.1, 2.1 Hz, 2H), 2.82 (dd, *J* = 6.7 , 8.9 Hz, 1H) 2.49 (t, *J* = 7.5 Hz, 2H), 1.93–1.89 (m, 2H), 1.85 (dd, *J* = 12.7, 6.4 Hz, 2H), 1.45 (s, 9H),1.40–1.33 (m, 3H), 1.29 (s, 9H),0.79 (dd, *J* = 24.8, 6.2 Hz, 6H); ^{13}C NMR (MeOH-d_4,126 MHz) δ = 173.7, 173.1, 171.1, 168.6, 141.1, 136.7, 136.5, 133.8, 129.1, 128.4, 12800, 126.4, 124.3, 122.8, 81.5, 67.0, 54.1, 51.7, 50.6, 46.6, 45.9, 41.0, 40.2, 37.2, 37.0, 36.7, 31.2, 28.8, 26.6, 25.5, 24.2, 23.7, 22.08, 20.56.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{43}H_{62}N_4O_7S_2H$ 811.41; found 811.3.

Macrocycle 2.5:
Synthesized according to general procedure **D**, obtained in 53% isolated yield.
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.64 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.28 (s, 2H), 7.18 (dd, *J* = 16.8, 9.8 Hz, 5H), 7.12–7.04 (m, 3H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.25 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.80 (dd, *J* = 14.7, 7.8 Hz, 1H), 4.53 (dd, *J* = 13.1, 6.9 Hz, 1H), 4.12 (td, *J* = 9.4, 5.5 Hz, 1H), 3.63 (dd, *J* = 13.5, 7.3 Hz, 1H), 3.54 (dd, *J* = 13.5, 7.8 Hz, 1H), 3.02 (ddd, *J* = 13.8, 9.7, 6.9 Hz, 2H), 2.96–2.89 (m, 1H), 2.82 (dt, *J* = 13.7, 6.8 Hz, 2H), 2.76–2.69 (m, 1H), 2.55 (ddd, *J* = 13.1, 8.9, 4.2 Hz, 1H), 2.48 (dd, *J* = 15.5, 12.4 Hz, 2H), 1.89–1.81 (m, 1H), 1.81–1.70 (m, 3H), 1.49 (tt, *J* = 13.0, 6.6 Hz, 1H), 1.38–1.29 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (DMSO-d_6, 126 MHz,) δ 171.8, 171.4, 169.9, 167.2, 141.6, 136.9, 136.4, 133.3, 129. 4, 128.2, 128.1, 127.9, 126.3, 125.4, 125.0, 124.1, 53.0, 52.1, 50.4, 45.9, 45.6, 42.0, 41.5, 37.7, 35.2, 29.9, 29.6, 25.6, 24.2, 23.7, 22.9 21.3.; HRMS-ESI (m/z): [M+H] calcd. for $C_{34}H_{44}N_4O_4S_2H$ 637.28768; found 637.28638.

Linear Precursor 2.6:
Synthesized according to general procedure **B**, obtained in 87% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ = 7.31 (s, 1H), 7.25 (m, 4H), 7.21 (t, *J* = 6.4, 3H), 7.14 (d, *J* = 7.2, 1H), 6.67 (d, *J* = 15.9, 1H), 6.34 (dt, *J* = 15.5, 6.2, 1H), 4.94 (dd, *J* = 7.4, 6.8, 1H), 4.70 (d, *J* = 6.1, 2H), 4.62 (t, *J* = 7.1, 1H), 4.41–4.28 (m, 2H), 3.56 (td, *J* = 6.8, 2.1, 2H), 3.41 (t, *J* = 6.8, 2H), 3.14 (dd, *J* = 13.8, 6.7, 1H), 3.07 (dd, *J* = 13.5, 7.7, 1H), 3.03–2.83 (m, 4H), 2.58 (m, 2H), 2.00-1.85 (m, 4H), 1.66–1.57 (m, 3H), 1.50 (s, 9H),1.44 (m, 3H) 1.35 (s, 9H), 0.92 (dd, *J* = 15.2, 5.0, 6H), 0.86 (dd, *J* = 18.6, 5.0, 6H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 173.8, 173.6, 172.9, 171.1, 168.5, 153.6, 141.1, 136.7 136.5, 133.8, 129.0, 128.4, 128.0, 126.4, 124.3, 122.9, 81.5, 67.0, 54.2, 51.9, 51.7, 50.6, 46.6, 45.9, 41.02, 40.4, 40.3, 37.2, 37.0, 31.2, 28.9, 26.6, 25.5, 24.4, 24.3, 23.7, 22.3, 22.0, 20.7, 20.5.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{43}H_{62}N_4O_7S_2H$ 924.50; found 924.4.

Macrocycle 2.7:
Synthesized according to general procedure **D**, obtained in 95% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.03 (dd, *J* = 15.6, 6.9 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 6.4 Hz, 1H), 7.36 (s, 1H), 7.28–7.19 (m, 6H), 7.13 (t, *J* = 7.8 Hz, 2H), 6.54 (d, *J* = 15.5 Hz, 1H), 6.12 (dt, *J* = 15.3, 7.6 Hz, 1H), 4.91 (dd, *J* = 14.3, 8.3 Hz, 1H), 4.44 (t, *J* = 9.0 Hz, 1H), 4.01 (dt, *J* = 8.8, 6.7 Hz, 1H), 3.78 (d, *J* = 5.7 Hz, 1H), 3.62–3.53 (m, 2H), 3.53–3.40 (m, 2H), 3.28 (t, *J* = 6.6 Hz, 2H), 3.15 (dd, *J* = 17.7, 8.2 Hz, 2H), 2.96–2.89 (m, 1H), 2.89–2.80 (m, 2H), 2.67–2.58 (m, 2H), 2.54–2.45 (m, 2H), 1.92–1.80 (m, 2H), 1.76 (dd, *J* = 13.2, 6.5 Hz, 2H),1.44 (dd, *J* = 12.7, 6.4 Hz, 1H), 1.38–1.30 (m, 4H), 1.25 (dd, *J* = 14.0, 6.2 Hz, 1H), 0.79 (s, 6H), 0.74 (d, *J* = 6.3 Hz, 3H), 0.67 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126 MHz) δ 173.6, 173.5, 171.0, 167.7, 142.0, 138.4, 136.8, 133.7, 129.5, 128.9, 128.5, 126.7, 126.1, 125.6, 125.2, 54.0, 53.2, 52.2, 50.0, 46.3, 46.1, 42.1, 41.3, 37.4, 37.2, 31.4, 30.0, 26.0, 24.5, 24.2, 23.4, 23.3, 21.9, 21.7.; HRMS-ESI (m/z): [M+H] calcd. for $C_{40}H_{55}N_5O_5S_2H$ 750.37174; found 750.3711.

Linear Precursor 2.8:
Synthesized according to general procedure **B**, obtained in 52% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz δ = 7.29 (s, 1H), 7.27-7.15 (m, 7H) 7.13 (d, J = 7.0 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.3 Hz, 1H) 4.92 (m, 1H), 4.67 (dd, J = 6.3, 1.1 Hz, 2H), 4.59 (dd, J = 8.3, 6.2 Hz, 1H), 4.33 (dd, J = 9.8, 5.2Hz, 1H), 4.31-4.25 (m, 2H), 3.54 (t, J = 6.6 Hz, 1H), 3.40 (t, J = 6.3 Hz, 2H), 3.14 (dd, J = 13.9, 6.1 Hz, 1H), 3.06 (dd, J = 13.4, 7.7 Hz, 1H), 2.99-2.90 (m, 3H), 2.88 (dd, J = 13.4, 6.6 Hz, 1H), 2.64-2.53 (m, 2H), 1.99-1.91 (m, 2H), 1.90-1.84 (m, 2H), 1.71-1.50 (m, 9H), 1.48 (s, 9H), 1.33 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.4 Hz, 6H), 0.89 (d, J = 6.1 Hz, 3H), 0.85 (d, J = 6.4, 3H), 0.83 (d, J = 6.0 Hz, 3H) ^{13}C NMR (126 MHz, MeOH-d_4) δ 174.0, 173.9, 173.3, 173.0, 171.2, 168.4, 153.6, 141.1, 136.8, 136.5, 133.7, 129.0, 128.4, 128.0, 126.3, 124.3, 122.9, 81.5, 67.0, 54.4, 52.3, 52.1, 52.0, 50.6, 46.6, 45.9, 41.1, 40.4, 40.2, 39.9, 37.3, 37.0, 31.2, 28.9, 26.6, 25.5, 24.5, 24.4, 24.3, 23.7, 22.2, 22.1 22.1, 20.7, 20.7, 20.5.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{55}H_{84}N_6O_9S_2H$ 1037.58; found 1037.4.

Macrocycle 2.9:
Synthesized according to general procedure **D**, obtained in 73% isolated yield.

^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.42 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 8.4 Hz, 2H), 7.30 (s, 1H), 7.25-7.03 (m, 7H), 6.50 (d, *J* = 15.6 Hz, 1H), 6.20 (dt, *J* = 15.5, 7.5 Hz, 1H), 4.82 (dd, *J* = 14.7, 7.5 Hz, 1H), 4.55 (dd, *J* = 13.6, 7.6 Hz, 1H), 4.19 – 4.09 (m, 3H), 3.56 (d, *J* = 7.4 Hz, 2H), 3.27 (d, *J* = 6.2 Hz, 3H), 3.04 (ddd, *J* = 19.6, 13.5, 6.6 Hz, 2H), 2.93 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.85–2.74 (m, 3H), 2.56-2.42 (m, 5H), 1.83–1.68 (m, 4H), 1.49 (dd, *J* = 15.0, 7.1 Hz, 5H), 1.43 (dd, *J* = 14.7, 7.1 Hz, 2H), 1.39 – 1.28 (m, 2H), 1.25 (d, *J* = 29.5 Hz, 2H), 0.87 – 0.71 (m, 19H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.8, 172.2, 171.8, 170.6, 167.8, 142.1, 137.7, 136.8, 134.0, 129.7, 128.4, 128.2, 126.8, 126.5, 124.8, 124.7, 53.8, 52.5, 52.1, 51.6, 50.4, 46.3, 46.1, 41.6, 40.9, 37.9, 37.0, 31.1, 30.0, 26.0, 24.7, 24.4, 24.2, 23.6, 23.4, 23.4, 22.0, 22.0, 21.7.; HRMS-ESI (m/z): [M+H] calcd. for $C_{46}H_{66}N_6O_6S_2H$ 863.45580; found 863.46053.

Linear Precursor 2.10:
Synthesized according to general procedure **B**, obtained in 83% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.37-7.06 (m, 9H), 6.63 (d, J = 15.9 Hz, 1H), 6.30 (dt, J = 15.9, 6.3 Hz, 1H), 4.74 (dd, J = 8.9, 4.8 Hz, 1H), 4.66 (d, J = 5.7 Hz, 1H), 4.63 (dd, J = 8.6, 5.4 Hz, 1H), 4.47 (d, J = 3.0 Hz, 1H), 4.28 (dd, J = 6.4 , 3.1 Hz, 1H), 4.45 (d, J = 7.2 Hz, 1H), 3.71 (s, 3H), 3.24 (dd, J = 13.6, 5.0 Hz, 1H), 3.17 (dd, J = 14.1, 5.0 Hz, 1H), 3.07 (dd, J = 13.5, 9.0 Hz, 1H), 2.99 (dd, J = 14.1, 8.8 Hz, 1H), 2.85 (t, J = 7.7 Hz, 2H), 2.48 (t, J = 8.4 Hz, 2H), 1.46 (s, 9H), 1.32 (s, 9H), 1.19 (d, J = 7.6 Hz, 3H), 1.17 (d, J = 6.8 Hz, 3H) ^{13}C NMR (MeOH-d_4,126 MHz) δ174.0, 173.9, 171.9, 171.2, 170.8, 153.6, 141.3, 136.8, 136.5, 133.5, 129.1, 128.5, 128.2, 127.9, 126.5, 126.3, 124.3, 122.9, 81.5, 67.2, 67.1, 58.6, 54.6, 53.0, 51.5, 49.4, 41.4, 37.0, 36.8, 31.1, 29.0, 26.7, 19.0 16.4.; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{41}H_{58}N_4O_{10}S_2Na$ 853.35; found 853.3.

Macrocycle 2.11:
Synthesized according to general procedure **D**, obtained in 66% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.54 (d, J = 8.5 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 7.3 Hz, 1H), 7.49 (d, J = 7.1 Hz, 1H), 7.27 (s, 1H), 7.24- 7.13 (m, 6H), 7.03 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 6.25 (dt, J = 15.8, 7.6 Hz, 1H), 5.05 (d, J = 5.3 Hz, 1H), 4.74-4.66 (m, 1H), 4.55-4.45 (m, 1H), 4.33 (dd, J = 8.6, 3.1 Hz, 1H), 4.19-4.11 (m, 1H), 4.09-4.01 (m, 1H), 3.62 (s, 3H), 3.57 (dd, J = 15.9, 7.4 HZ, 1H), 3.18 (dd, J = 13.5, 4.6 Hz, 1H), 3.09 (dd, J = 14.1, 4.0 Hz, 1H), 2.96 (dd, J = 13.3, 9.5 Hz, 1H), 2.94-2.89 (m, 1H), 2.80 (dd, J = 14.1, 8.6 Hz, 1H), 2.74-2.66 (m, 1H), 2.43-2.35 (m, 1H), 1.10 (d, J = 7.3 Hz, 3H), 1.06 (d, J = 6.4 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.1, 171.2, 170.9, 170.8, 170.4, 141.4, 137.3, 136.5, 133.3, 129.5,128.1, 127.9, 127.8, 126.8, 126.3, 124.8, 123.1, 66.2, 57.8, 53.5, 52.8, 51.9, 48.9, 43.5, 43.5, 40.9, 37.2, 35.2, 30.0, 20.1, 18.1.; HRMS-ESI (m/z): [M+H] calcd. for $C_{32}H_{40}N_4O_7S_2H$ 657.24112; found 657.24121.

Linear Precursor 2.12:
Synthesized according to general procedure **C**, obtained in 29% isolated yield.
H NMR (MeOH-d_4, 500 MHz) δ 8.08 (d, *J* = 7.4 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 7.8, 2.5 Hz, 1H), 7.76 (t, *J* = 5.4 Hz, 1H), 7.27 (m, 4H), 7.20 (m, 5H), 7.15 (d, *J* = 3.8 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.67 – 6.58 (m, 1H), 6.31 (dt, *J* = 15.7, 6.1 Hz, 1H), 4.65 (d, *J* = 6.1 Hz, 2H), 4.53 – 4.46 (m, 1H), 4.38 (dd, *J* = 12.0, 6.5 Hz, 1H), 4.15 (d, *J* = 5.5 Hz, 2H),3.54 (s, 1H), 3.11 – 3.01 (m, 2H), 3.00 – 2.92 (m, 3H), 2.77 (t, *J* = 7.8 Hz, 3H), 2.34 (t, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 8.0 Hz, 1H), 1.78 (s, 3H), 1.77 – 1.73 (m, 1H), 1.70 – 1.58 (m, 2H), 1.57-1.49 (m, 1H) 1.41 (s, 9H),1.36-1.30 (m, 5H) 1.26 (s, 9H).;^{13}C NMR (MeOH-d_4,126 MHz) δ 174.9, 173.8, 173.7, 173.5, 172.8, 172.6, 172.3, 153.6, 141.2, 136.8, 136.5, 133.7, 128.9, 128.4, 128.2, 127.9, 126.5, 126.4, 124.3, 122.9, 81.5, 67.1, 54.8, 54.2, 53.3, 52.6, 41.2, 38.6, 37.5, 36.6, 31.5, 30.7, 29.7, 28.9, 28.5, 26.6, 26.6, 26.4, 22.8, 21.1.; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{46}H_{66}N_6O_{11}S_sNa$ 965.41; found 965.9.

Macrocycle 2.13:
Synthesized according to general procedure **D**, obtained in 54% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.21 (d, *J* = 6.5 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 5.4 Hz, 1H), 7.30 (s, 1H), 7.21 (m, 5H), 7.16 (td, *J* = 8.6, 4.2 Hz, 2H), 7.11 (s, 1H), 7.09 7.01 (m, 1H), 6.47 (d, *J* = 15.6 Hz, 1H), 6.21-6.11 (m, 1H), 4.50 (td, *J* = 10.3, 4.0 Hz, 1H), 4.37 (td, *J* = 8.2, 4.1 Hz, 1H), 4.13 (dd, *J* = 13.7, 7.6 Hz, 1H), 3.98 (dd, *J* = 13.8, 6.8 Hz, 1H), 3.54 (d, *J* = 7.1 Hz, 2H), 3.21 (dd, *J* = 13.5, 3.7 Hz, 1H), 3.14 (d, *J* = 8.8 Hz, 1H), 3.09 (dd, *J* = 14.2, 3.6 Hz, 1H), 2.92 (s, 2H), 2.81 (dd, *J* = 11.3, 5.6 Hz, 2H), 2.76 (m, 1h) 2.30 (t, *J* = 6.1 Hz, 2H), 2.11 (t, *J* = 7.8 Hz, 2H), 1.80 (s, 3H), 1.74 (dd, *J* = 14.1, 6.4 Hz, 1H), 1.68-1.53 (m, 3H), 1.32-1.09 (m, 6H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 174.40, 172.2, 172.14, 171.9, 171.8, 171.6, 170.1, 141.9, 138.3, 136.7, 133.1, 129.6, 129.0, 128.6, 128.5, 126.7, 126.6, 125.7, 124.6, 54.7, 54.2 52.8, 52.5, 41.9, 41.6, 38.6, 37.5, 37.3, 31.8, 31.6, 30.54 29.3, 27.7, 23.0, 22.9.; HRMS-ESI (m/z): [M+H] calcd. For $C_{37}H_{48}N_6O_8S_2H$ 769.3054; found 769.3021.

Linear Precursor 2.14:
Synthesized according to general procedure **B**, obtained in 75% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz δ = 7.33-7.15 (m, 8H), 6.64 (d, J = 15.8 Hz, 1H), 6.31 (dt, J = 15.8, 6.3 Hz, 1H) 4.70-4.64 (m, 2H), 4.60-4.55 (m, 1H), 4.48 (t, J =7.5 Hz, 1H), 4.25 (d, J = 4.59 Hz, 1H), 4.20 (q, J= 7.2Hz, 1H), 4.03-3.95 (m,

1H), 3.25 (dd, J= 13.5, 5.0 Hz, 1H), 3.12 (dd, J= 13.5, 7.1 Hz, 1H), 3.00-2.96 (m, 1H), 3.96-3.93 (m, 1H), 3.93-3.87 (m, 3H), 2.75-2.68 (m. 3H), 2.83-2.57 (m, 2H), 1.47 (s, 9H), 1.31 (s, 9H), 1.22 (d, J= 7.3, 3H), 0.99 (d, J= 6.3, 3H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 174.1, 173.7, 172.1, 171.4, 171.1, 153.6, 141.2, 136.8, 136.5, 133.7, 129.0, 128.4, 128.1, 127.9, 126.5, 126.4, 124.3, 122.9, 81.5, 67.1, 66.9, 58.7, 55.2, 53.0, 49.3, 41.1, 37.1,36.8, 31.2, 28.8, 26.6, 25.2, 18.3, 15.9; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{41}H_{59}N_5O_9S_2$ 852.36; found 852.3

Macrocycle 2.15:
Synthesized according to general procedure **D**, obtained in 49% yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.26 (d, J= 7.8 Hz, 1H), 7.98 (m, 1H), 7.91 (d, J= 8.1 Hz, 1H), 7.85 (d, J= 5.8 Hz, 1H), 7.71 (d, J= 7.2 Hz, 1H), 7.44 (s, 1H), 7.25-7.11 (m, 7H), 7.06 (d, J= 7.4, 1H), 6.50 (d, J= 15.6 Hz, 1H), 6.26 (m, 1H), 4.51 (q, J= 7.3 Hz, 1H), 4.43 (m, 1H), 4.26 (p, J= 7.2 Hz, 1H), 3.76 (t, J= 6.6 Hz, 1H), 3.58 (q, J= 6.8 Hz, 2H), 3.51-3.45 (m, 1H), 3.07 (dd, J= 13.7, 5.3 Hz, 1H), 2.96-2.86 (m. 3H), 2.81 (dd, J= 13.6, 9.6 Hz, 1H), 2.76-2.65 (m, 2H), 2.65-2.54 (m, 2H overlap) 2.59 (d, J= 4.5 Hz, 3H), 2.48 (m, 2H), 1.18 (d, J= 7.1 Hz, 3H), 0.68 (d, J= 6.2 Hz, 3H)
^{13}C NMR (DMSO-d_6, 126MHz) δ 173.1, 172.6, 171.0, 170.7, 169.8, 142.0, 138.1, 137.0, 133.3, 129.6, 129.0, 128.5, 128.0, 126.7, 125.8, 125.6, 125.1, 66.5, 61.9, 54.6, 53.4, 48.8, 41.5, 41.4, 37.1, 36.5, 31.4, 26.2, 20.2,18.4.; HRMS-ESI (m/z): [M+H] calcd. For $C_{32}H_{41}N_5O_6S_2H$ 656.257654 ; found 656.25606.

Linear Precursor 2.16:
Synthesized according to general procedure **B**, obtained in 72% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.26 (t, *J* = 17.5 Hz, 3H), 7.13 (d, *J* = 6.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 13.5 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.93 (dd, *J* = 7.8, 6.5 Hz, 2H), 4.68 (dd, *J* = 6.3, 1.1 Hz, 2H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 1H), 3.58–3.44 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 1H), 3.34-3.30 (m, 1H), 3.05 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.97 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.94–2.84 (m, 4H), 2.58-2.49 (m, 2H), 1.94 (dt, *J* = 12.9, 6.6 Hz, 2H), 1.86 (dt, *J* = 13.1, 6.4 Hz, 2H), 1.49 (s, 9H), 1.32 (s, 9H), 1.24 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 175.0, 174.6, 172.6, 169.8, 157.3, 155.0, 142.6, 137.8, 135.1, 131.5, 131.2, 129.8, 129.22, 128.44, 127.71, 125.6, 124.2, 116.1, 82.9, 68.4, 55.8, 51.8, 50.3, 48.0, 47.3, 42.5, 38.4, 37.9, 32.6, 30.2, 28.1, 26.9, 25.1, 18.0.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{56}N_4O_8S_2$ 785.36; found 784.9.

Macrocycle 2.17:
Synthesized according to general procedure **D**, obtained in 35% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.52 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 6.9 Hz, 2H), 7.23-7.12 (m, 2H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.60 (t, *J* = 10.3 Hz, 2H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.26 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.77 (dd, *J* = 14.8, 7.8 Hz, 1H), 4.37 (dd, *J* = 13.1, 6.6 Hz, 1H), 4.08 (p, *J* = 7.2 Hz, 1H), 3.57 (ddd, *J* = 38.0, 13.5, 7.6 Hz, 2H), 3.39 (dt, *J* = 10.1, 6.7 Hz, 1H), 3.25 (dt, *J* = 10.2, 7.0 Hz, 3H), 3.02 (dd, *J* = 13.3, 7.8 Hz, 1H), 2.96-2.84 (m, 2H), 2.80 (dd, *J* = 13.3, 6.4 Hz, 1H), 2.71 (dt, *J* = 13.9, 6.6 Hz, 2H), 1.891.69 (m, 4H), 1.14 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.4, 171.8, 170.6, 167.7, 156.3, 142.0, 136.9, 133.7, 130.7, 128.7, 128.6, 127.4, 125.9, 125. 5, 124.7, 115.2, 54.0, 50.8, 49.6, 46.3, 46.1, 42.4, 42.1, 37.0, 35.6, 30.4, 26.0, 24.2, 18.6.; HRMS-ESI (m/z): [M+H] calcd. for $C_{31}H_{38}N_4O_5S_2H$ 611.23564; found 611.23333.

Macrocycle 2.18:
Synthesized according to general procedure **D**, obtained in 58% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.11 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 7.00 (s, *1*H) 6.94 (d, J = 7.5, 1H), 6.91 (s, 1H) 6.83 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 6.22-6.08 (m, 2H), 4.75 (q, *J* = 7.2 Hz, 1H), 4.54-4.47 (m, 2H), 3.54 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.45 (dt, *J* = 9.9, 6.9 Hz, 2H), 3.38 (d, *J* = 4.9 Hz, 1H), 3.35 (d, *J* = 4.2 Hz, 1H), 3.32 (d, *J* = 6.9 Hz, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 3.04 (dt, *J* = 13.0, 9.8 Hz, 2H), 2.83 (ddd, *J* = 17.0, 12.3, 4.6 Hz, 2H), 2.64 (dd, *J* = 14.3, 10.7 Hz, 2H), 2.29-2.21 (m, 1H), 1.94-1.81 (m, 2H), 1.80-1.72 (m, 2H), 1.27 (s, 9H), 1.11 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.4, 172.4, 171.6, 171.4, 171.3, 168.1, 153.7, 153.7, 142.3, 137.4, 137.4, 130.6, 130.2, 129.4, 128.8, 128.4, 128.2, 128.0, 125.9, 124.7, 124.2, 115.2, 53.9, 50.6, 48.3, 48.1, 46. 5, 46.2, 42.1, 36.9, 36.0, 32.4, 30.0, 29.9, 26.1, 24.2, 20.6.; HRMS-ESI (m/z): [M+H] calcd. for $C_{35}H_{46}N_4O_5S_2H$ 667.29824; found 667.29924.

Linear Precursor 2.19:
Synthesized according to general procedure **B**, obtained in 31% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.30-7.20 (m, 4H), 7.14-7.09 (m, 1H) 7.09 (s, 1H) 6.63 (d, J = 16.0 Hz, 1H) 6.30 (dt, J = 16.0, 6.3 Hz, 1H) 4.90 (t, J = 7.1 Hz, 1H) 4.67 (dd, J = 6.5, 1.0 Hz, 2H) 4.57 (t, J = 7.0 Hz, 1H) 4.28 (q, J = 7.15, 1H) 3.65-3.49 (m, 2H) 3.03 (dd J = 13.5, 7.5 Hz, 1H) 2.96 (dd, J = 13.9, 6.7, 1H) 2.92-2.80 (m, 4H), 2.52 (m, 2H) 1.98-1.90 (m, 2H) 1.88-1.80 (m, 2H) 1.46 (s, 9H), 1.45 (s, 3H), 1.29 (s, 9H) ^{13}C NMR (MeOH-d_4,126 MHz) δ 173.7, 173.3, 170.7, 168.6, 153.6, 148.1, 141.3, 136.4, 133.7, 129.3, 129.1, 128.4, 127.9, 126.3, 124.3, 122.9, 121.6, 81.5, 67.1, 53.9, 50.6, 49.1, 46.6, 46.0, 41.2, 37.0, 36.0, 31.2, 28.9, 26.7, 25.5, 23.7, 16.6.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{54}N_4O_8S_2Cl_2H$ 853.28; found 853.2.

Macrocycle 2.20:
Synthesized according to general procedure **D**, obtained in 70% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.93 (s br, 1H) 8.64 (d, J = 8.1 Hz, 1H) 8.09 (d, J = 7.5 Hz, 1H), 7.42 (d, J = 7.1 Hz), 7.31 (s, 1H), 7.18 (d, J = 4.4 Hz, 2H), 7.11 (s, 1H), 7.08-7.04 (m, 1H), 6.53 (d, J = 15.6 Hz, 1H), 6.26 (dt, J = 15.6, 7.1 Hz, 1H) 4.77 (q, J = 7.3 Hz, 1H) 4.42 (dd, 12.6, 7.1 Hz, 1H), 4.13-4.05 (m, 1H) 3.63-3.52 (m, 2H) 3.50-3.44 (m, 1H), 3.49-3.26 (m, 3H) 3.06 (q, 6.8 Hz, 1H) 2.99-2.91 (m, 2H) 2.82 (q, J = 6.7 Hz, 1H) 2.76-2.68 (m, 1H) 1.90-1.72 (m, 4H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.1, 171.3, 170.0, 167.4, 147.5, 141.5, 136.4, 133.4, 130.0, 129.5, 128.2, 128.1, 125.7, 124.9, 123.9, 121.7, 53.1, 50.8, 49.1, 45.9, 45.7, 41.8, 41.8, 36.1, 35.0, 29.9, 25.6, 23.7, 18.3.; HRMS-ESI (m/z): [M+H] calcd. for $C_{31}H_{36}Cl_2N_4O_5S_2H$ 679.1582; found 679.1577.

Linear Precursor 2.21:
Synthesized according to general procedure **B**, obtained in 56% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.26 (m, 3H), 7.13 (d, *J* = 6.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 13.5 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.93 (dd, *J* = 7.8, 6.5 Hz, 2H), 4.68 (dd, *J* = 6.3, 1.1 Hz, 2H), 4.59 (t, *J* = 7.1 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 1H), 3.58-3.44 (m, 2H), 3.38 (t, *J* = 6.8 Hz, 1H), 3.34-3.30 (m, 1H), 3.05 (dd, *J* = 13.4, 8.0 Hz, 1H), 2.97 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.94-2.84 (m, 4H), 2.58 – 2.49 (m, 2H), 1.94 (dt, *J* = 12.9, 6.6 Hz, 2H), 1.86 (dt, *J* = 13.1, 6.4 Hz, 2H), 1.49 (s, 9H), 1.32 (s, 9H), 1.24 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (MeOH-d_4,126 MHz δ) 175.5, 173.1, 172.1, 172.0, 157.3, 155.0, 142.6, 137.8, 135.1, 131.3, 129.8, 129.2, 128.5, 127.7, 125.6, 124.2, 116.3, 82.9, 68.4, 68.1, 59.9, 55.7, 55.7, 54.3, 52.7, 51.1, 42.9, 38.5, 37.6, 32.7, 30.2, 30.2, 28.0, 28.0, 19.0, 19.9, 17.8.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{41}H_{58}N_4O_{11}S_2H$ 847.36; found 847.2.

Macrocycle 2.22:
Synthesized according to general procedure **D**, obtained in 55% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.22 (s, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 2H), 8.22 (d, *J* = 8.2 Hz, 1H), 7.40 (d, *J* = 7.1 Hz, 1H), 7.29 (s, 1H), 7.24-7.11 (m, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.25 (dt, *J* = 15.5, 7.6 Hz, 1H), 5.31 (s, 1H), 4.57 (td, *J* = 8.3, 4.7 Hz, 1H), 4.33 (dd, *J* = 14.2, 8.0 Hz, 1H), 4.25 (dd, *J* = 7.1, 4.3 Hz, 1H), 4.23-4.13 (m, 1H), 3.99 (dd, *J* = 5.7, 5.0 Hz, 1H), 3.55 (s, 1H), 3.54 (s, 3H), 3.07 (dd, *J* = 13.6, 4.6 Hz, 1H), 3.04-2.98 (m, 1H), 2.93-2.85 (m, 2H), 2.82 2.72 (m, 2H), 2.59 (dd, *J* = 15.1, 2.6 Hz, 1H), 2.44-2.40 (m, 1H), 1.22 (d, *J* = 7.3 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.8, 172.1, 171.9, 170.0, 169.6, 169.2, 156.5, 142.0, 137.0, 133.7, 130.5, 128.6, 128.3, 127.4, 126.9, 125.5, 123.7, 115.5, 66.8, 58.0, 54.7, 53.5, 52.3, 49.4, 43.1, 41.8, 36.3, 35.6, 34.8, 30.4, 30.0, 19.2, 18.8.; HRMS-ESI (m/z): [M+H] calcd. for $C_{36}H_{48}N_4O_8S_2H$ 729.29864; found 729.30100.

Macrocycle 2.23:
Synthesized according to general procedure **D**, obtained in 28% isolated yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.24 (s, 1H), 8.25 (d, *J* = 7.3 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.25 (s, 1H), 7.20-7.10 (m, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.92 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.7, 6.8 Hz, 1H), 5.00 (s, 1H), 4.53 (td, *J* = 8.6, 4.9 Hz, 1H), 4.30 (dd, *J* = 13.5, 7.6 Hz, 1H), 4.27-4.14 (m, 1H), 4.05 (dd, *J* = 7.3, 4.6 Hz, 1H), 3.95-3.86 (m, 1H), 3.56 (s, 2H), 3.44 (dd, *J* = 15.4, 6.9 Hz, 2H), 3.33 (dd, *J* = 15.4, 6.5 Hz, 1H), 3.33 (dd, *J* = 15.4, 6.5 Hz, 1H), 3.12 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.94 (dd, *J* = 12.9, 8.9 Hz, 1H), 2.87 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.81 (t, *J* = 7.1 Hz, 1H), 2.73 (dd, *J* = 14.7, 8.8 Hz, 1H), 2.37-2.29 (m, 1H), 1.25 (s, 9H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 173.0, 172.0, 170.4, 170.3, 154. 1, 141.8, 137.6, 131.0, 130.9, 129.1, 128.9, 127.7, 127.6, 126.5, 125.7, 124.7, 115.4, 66.6, 59.1, 54.9, 52.3, 49.2, 48.2, 43.0, 36.7, 36.36, 33.0, 31.3, 30.0, 19.8, 18.2.; HRMS-ESI (m/z): [M+H] calcd. for $C_{32}H_{40}N_4O_8S_2H$ 751.3563; found 751.3531.

Linear Precursor 2.24:
Synthesized according to general procedure **B**, obtained in 66% isolated yield.
^{1}H NMR two rotamers present (MeOH-d_4, 500 MHz δ = 7.76-7.58 (m, 1H), 7.40-7.01 (m, 7H), 6.70-6.55 (m, 1H), 6.36-6.30 (m, 1H), 5.49 (s, 2H), 5.16-5.06 (m, 1H), 4.71-4.60 (m, 3H), 4.40-4.26 (m, 1H), 3.74-3.64 (m ,1H), 3.54-3.43 (m, 1H), 3.41-3.32 (m, 1H), 3.23-3.01(m, 3H), 3.00-2.85 (m, 3H), 2.82-2.52 (m, 5H), 2.50-2.39 (m, 3H) 1.56-1.41. (m, 9H), 1.40-1.30 (m, 2H), 1.30-1.25 (m ,9H) 0.95-0.60(m, 3H), 0.47—0.43 (m, 1H^{13}C NMR (126 MHz, MeOH-d_4) δ 173.7, 173.4, 172.9, 170.5, 170.3, 169.8, 153.6, 141.2, 136.5, 135.2, 133.7, 129.4, 128.5, 127.9, 126.3, 125.1, 124.3, 123.9, 122.9, 120.6, 112.8, 111.9, 109.1, 81.5, 67.1, 53.4, 50.0, 46.0, 42.4, 41.5, 37.2, 36.5, 35.8, 35.2, 34.0, 33.0, 32.9, 31.1, 30.2, 28.9, 26.7, 20.4 . LC-MS-ESI (m/z): [M+H] calcd. for $C_{48}H_{66}BrN_7O_9S_2$ 1028.36; found 1028.4.

Macorcycle 2.25:
Synthesized according to general procedure **D**, obtained in 34% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 11.22-11.02 (m, 1H), 8.55-8.40 (m, 1H), 8.37-8.27 (m, 1H), 8.09-7.98 (m, 1H), 7.74-7.62 (m ,1H), 7.61-7.53 (m, 1H) 7.34-6.94 (m, 7H), 6.84 (s, 1H), 6.41-6.29 (m, 1H), 6.18-6.6.02 (m, 1H), 4.96-4.86 (m 1H), 4.61-4.53 (m ,1H), 4.43-4.35 (m, 1H), 4.34-4.19 (m, 1H), 3.87-3.75 (m, 1H), 3.72-3.61 (m, 1H), 3.55-3.47 (m, 1H)

3.12-2.86 (m, 4H), 2.86-2.58 (m ,4H), 2.45-2.24 (m, 5H), 1.60-1.17 (m, 4H), 1.00-0.88 (m, 1H), 0.88-0.58 (m, 3H), 0.49—0.10 ^{13}C NMR (DMSO-d_6, 126MHz) 172.2, 171.7, 171.6, 171.2, 169.7, 169.6, 142.3, 137.0, 135.2, 133.2, 129.8, 128.8, 128.4, 128.0, 126.2, 126.0, 123.8, 123.3, 121.1, 113.8, 111.7, 110.2, 51.7, 50.7, 49.4, 45.7, 42.4, 37.0, 36.6, 35.9, 35.7, 33.7, 33.3, 30.8, 30.4, 28.6, 21.9, MS-ESI (m/z): [M+H] calcd. for $C_{39}H_{48}BrN_7O_6S_2$ 854.24; found 854.5.

Macrocycle 2.26:
Synthesized according to general procedure **D**, obtained in 59% isolated yield.
^{1}H NMR two rotomers present (DMSO-d_6, 600 MHz) δ 11.15-10.85 (m, 1H), 8.22-8.12 (m, 1H), 7.97-7.82 (m, 1H), 7.77-7.57 (m, 2H), 7.52-7.41 (m ,1H), 7.36-7.28 (m, 1H), 7.24-7.14 (m, 4H), 7.11-7.00 (m, 2H), 6.86-6.72 (m, 1H), 6.46-6.25 (m, 2H), 5.02-4.91 (m, 1H), 4.50-4.37 (m, 2H), 4.36-4.25 (m, 1H), 4.11-3.98 (m ,1H), 3.75-3.59 (m, 2H), 3.25-2.91 (m, 5H), 2.90- 2.55 (m, 1H), 2.34-2.03 (m, 4H), 1.80-1.58 (m, 3H), 1.30-1.28 (m, 1H), 1.25-1.20 (m, 9H), 1.00-0.85 (m, 3H). ^{13}C NMR (DMSO-d_6, 126MHz) δ;171.9, 171.7, 171.2, 170.3, 169.3, 169.2, 142.1, 137.6, 136.0, 130.9, 129.5, 129.0, 128.7, 127.8, 126.2, 125.7, 124.5, 122.4, 114.4, 113.7, 108.7, 107.6, 58.4, 52.7, 52.0, 50.3, 48.0, 42.9, 42.6, 42.1, 37.7, 36.9, 35.6, 35.4, 30.9, 30.3, 30.0, 22.2, 22.0 MS-ESI (m/z): [M+H] calcd. For $C_{43}H_{56}BrN_7O_6S_2$ 910.30; found 910.8

Linear Precursor 2.27:
Synthesized according to general procedure **B**, obtained in 70% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.32-7.23 (m, 5H), 7.22-7.18 (m, 3H), 7.14 (d, *J* = 7.0 Hz, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.74-4.71 (m, 1H), 4.70 (d, *J* = 5.3 Hz, 2H), 4.64 (t, *J* = 7.2 Hz, 1H), 4.35 (t, *J* = 7.4 Hz, 1H), 3.60-3.54 (m, 1H), 3.52-3.47 (m, 1H), 3.40 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 2H), 3.10 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.98-2.89 (m, 4H), 2.73 (dd, *J* = 12.8, 5.7 Hz, 1H), 2.55 (td, *J* = 7.6, 3.4 Hz, 2H), 1.96 (ddd, *J* = 19.5, 12.7, 6.5 Hz, 1H), 1.91-1.86 (m, 2H), 1.50 (s, 9H), 1.45-1.41 (m, 2H), 1.40-1.34 (m, 1H), 1.32 (s, 9H), 0.84 (dd, *J* = 29.0, 6.3 Hz, 6H); ^{13}C NMR (MeOH-d_4,126 MHz δ) δ 175.1,174.5, 172.5, 170.3, 155.0, 142.5, 138.9, 137.9, 135.2, 130.5, 129.8, 129.5, 129.3, 127.8, 127.8, 125.7, 125.7, 124.3, 82.9, 68.4, 55.5, 53.0, 52.9, 48.1, 47.2, 43.5, 38.7, 38.4, 32.6, 31.3, 30.8, 28.0, 26.9, 26.9, 25.6, 25.2, 23.5, 22.0.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{43}H_{62}N_4O_7S_2$ 779.44; found 779.7.

Macrocycle 2.28:
Synthesized according to general procedure **D**, obtained in 71% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.80 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.24-7.13 (m, 4H), 7.05 (d, *J* = 7.1 Hz, 3H), 6.94 (s, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.5, 7.6 Hz, 1H), 4.73 (t, *J* = 7.3 Hz, 1H), 4.61 (dd, *J* = 12.7, 6.4 Hz, 1H), 4.07 (dd, *J* = 13.3, 9.4 Hz, 1H), 3.50 (dd, *J* = 12.4, 9.1 Hz, 1H), 3.02 (t, *J* = 13.1 Hz, 1H), 2.95 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.76 (ddd, *J* = 27.2, 13.5, 9.8 Hz, 4H), 2.40 (dd, *J* = 13.3, 2.5 Hz, 1H), 1.90 (d, *J* = 5.6 Hz, 1H), 1.81 (s, 3H), 1.48 (dd, *J* = 12.6, 6.2 Hz, 1H), 1.41 – 1.23 (m, 2H), 0.81 (dd, *J* = 51.5, 6.4 Hz, 6H); ^{13}C NMR (DMSO-d_6, 126MHz) 171.2, 171.1, 167.7, 167.4, 141.0, 136.4, 136.0, 132.8, 129.2, 129.2, 127.6, 126.9, 126.0, 125.8, 123.9, 121.0, 52.0, 52.0, 48.9, 45.8, 45.4, 41.2, 38.2, 32.6, 32.4, 29.9, 28.0, 25.3, 24.2, 23.7, 22.9, 21.0.; HRMS-ESI (m/z): [M+H] calcd. for $C_{34}H_{44}N_4O_4SH$ 605.31561; found 605.31404.

Linear Precursor 2.29:
Synthesized according to general procedure **B**, obtained in 67% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.29 (s, 1H), 7.26-7.18 (m, 2H), 7.13 (d, *J* = 5.8 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.97 (t, *J* = 7.1 Hz, 1H), 4.67 (d, *J* = 6.1 Hz, 2H), 4.47 (t, *J* = 6.9 Hz, 1H), 4.34 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.77 (dt, *J* = 10.2, 6.7 Hz, 1H), 3.60 (dd, *J* = 17.1, 6.9 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 3.09 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.94 (m, , 4H), 2.84 (dd, *J* = 12.8, 7.4 Hz, 1H), 2.60-2.54 (m, 2H), 2.27-2.16 (m, 2H), 1.99 (ddd, *J* = 19.3, 13.6, 7.0 Hz, 3H), 1.87 (dt, *J* = 13.9, 6.9 Hz, 3H), 1.47 (s, 7H), 1.31 (s, 7H), 1.29 (s, 9H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 177.7, 175.2, 173.5, 172.0, 170.0, 155.0, 142.6, 137.9, 135.1, 135.0, 129.9, 129.2, 127.7, 125.7, 125.7, 124.3, 82.9, 79.5, 68.4, 54.9, 54.2, 52.1, 48.1, 47.4, 43.3, 42.45, 38.6, 32.6, 32.6, 31.3, 31.0, 30.3, 28.8, 28.1, 26.9, 25.1.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{49}H_{72}N_6O_9S_2H$ 985.46; found 985.9.

Macrocycle 2.30:
Synthesized according to general procedure **D**, obtained in 65% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.80 (d, *J* = 8.3 Hz, 1H), 9.76 (d, *J* = 7.6 Hz, 1H), 9.53 (d, *J* = 7.2 Hz, 1H), 9.23 (d, *J* = 7.6 Hz, 1H), 8.82 (s, 1H), 8.68 (t, *J* = 6.2 Hz, 5H), 8.60 (dd, *J* = 20.3, 7.4 Hz, 4H), 8.25 (s, 1H), 7.93 (d, *J* = 15.7 Hz, 1H), 7.71-7.61 (m, 1H), 6.17 (dd, *J* = 14.3, 8.2 Hz, 1H), 5.95 (dd, *J* = 13.4, 7.8 Hz, 1H), 5.92-5.84 (m, 1H), 5.50 (dd, *J* = 13.7, 7.6 Hz, 1H), 4.64 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.53-4.45 (m, 2H), 4.45-4.23 (m, 4H), 4.20 (dd, *J* = 13.9, 9.4 Hz, 1H), 4.14-4.05 (m, 2H), 3.45-3.17 (m, 8H), 3.10-3.00 (m, 1H), 2.78 (s, 9H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 173.7, 172.2, 171.3, 170.9, 169.1, 167.8, 141.6, 137.4, 136. 5, 132.4, 129.1, 128.3, 128.0, 127.6, 126.9, 126.2, 125.6, 123.4, 54.2, 52.8, 52.4, 50.6, 47.8, 46.1, 45.7, 42.1, 37.4, 33.9, 31.5, 31.3, 29.6, 26.9, 25.6, 23.8.; HRMS-ESI (m/z): [M+Na] calcd. For $C_{40}H_{54}N_6O_6S_3Na$ 833.31647 found 833.3139.

Linear Precursor 2.31:
Synthesized according to general procedure **B**, obtained in 80% isolated yield.

^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.29 (s, 1H), 7.26-7.18 (m, 2H), 7.13 (d, *J* = 5.8 Hz, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.97 (t, *J* = 7.1 Hz, 1H), 4.67 (d, *J* = 6.1 Hz, 2H), 4.47 (t, *J* = 6.9 Hz, 1H), 4.34 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.77 (dt, *J* = 10.2, 6.7 Hz, 1H), 3.60 (dd, *J* = 17.1, 6.9 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 3.09 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.94 (m, , 4H), 2.84 (dd, *J* = 12.8, 7.4 Hz, 1H), 2.60-2.54 (m, 2H), 2.27-2.16 (m, 2H), 1.99 (ddd, *J* = 19.3, 13.6, 7.0 Hz, 3H), 1.87 (dt, *J* = 13.9, 6.9 Hz, 3H), 1.47 (s, 7H), 1.31 (s, 7H), 1.29 (s, 9H); ^{13}C NMR (MeOH-d_4,126 MHz δ) δ 177.7, 175.2, 173.5, 172.0, 170.0, 155.0, 142.6, 137.9, 135.1, 135.0, 129.9, 129.2, 127.7, 125.7, 125.7, 124.3, 82.9, 79.5, 68.4, 54.9, 54.2, 52.1, 48.1, 47.4, 43.3, 42.5, 38.6, 32.6, 32.6, 31.3, 31.0, 30.3, 28.8, 28.1, 26.9, 25.1.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{63}N_5O_8S_3H$ 838.39; found 838.4.

Macrocycle 2.32:
Synthesized according to general procedure **D**, obtained in 86% isolated yield.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.53 (d, *J* = 8.1 Hz, 1H), 8.48 (d, *J* = 8.3 Hz, 1H), 8.06 (d, *J* = 9.1 Hz, 1H), 7.28-7.13 (m, 3H), 7.10 (s, 1H), 7.03 (d, *J* = 6.4 Hz, 1H), 6.74 (s, 1H), 6.44 (d, *J* = 15.7 Hz, 1H), 5.92 (dt, *J* = 15.3, 7.5 Hz, 1H), 4.78 (dd, *J* = 14.4, 7.3 Hz, 1H), 4.56-4.49 (m, 2H), 3.56 (dt, *J* = 13.5, 6.8 Hz, 1H), 3.48-3.40 (m, 2H), 3.30 (dd, *J* = 13.6, 6.5 Hz, 2H), 3.27 (d, *J* = 6.4 Hz, 1H), 3.07 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.98 (t, *J* = 11.1 Hz, 1H), 2.82 (dd, *J* = 13.0, 6.2 Hz, 1H), 2.78 (dd, *J* = 13.3, 7.9 Hz, 2H), 2.58 (t, *J* = 11.2 Hz, 1H), 2.28-2.19 (m, 1H), 2.12-1.99 (m, 2H), 1.93-1.82 (m, 2H), 1.79 (dd, *J* = 13.5, 6.8 Hz, 3H), 1.70-1.59 (m, 1H), 1.29 (s, 9H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 174.12, 171.80, 171.58, 170.19, 167.55, 141.53, 136.84, 133.23, 128.76, 128.17, 126.60, 125.88, 123.72, 51.73, 51.58, 50.87, 48.16, 46.42, 46.26, 42.25, 36.66, 32.93, 32.28, 32.09, 30.87, 30.03, 29.46, 26.03, 24.16. HRMS-ESI (m/z): [M+H] calcd. for $C_{31}H_{45}N_5O_5S_3H$ 664.26556; found 664.26818.

Linear Precursor 2.33:
Synthesized according to general procedure **B**, obtained in 53 % isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz δ = 7.32-7.09 (m, 8H), 7.07-6.96 (m, 1H), 6.67-6.57 (m, 1H), 6.34-6.24 (m, 1H), 4.71-4.61(m, 2H), 4.13-4.02 (m, 2H) 3.72-3.48 (m, 8H), 3.43-3.35 (m, 2H), 3.23-3.16 (m, 2H), 3.10-3.00 (m, 1H), 2.98-2.90 (m, 2H), 2.87-2.69 (m, 4H), 2.51-2.28 (m, 6H), 2.16-2.01 (m, 1H), 2.00-1.97 (m, 1H), 1.89-174 (m, 1H), 1.54-1.38 (m, 9H), 1.34-1.24 (m, 9H): ^{13}C NMR (126 MHz, MeOH-d_4) δ 175.0, 173.5, 172.9, 172.3, 171.6, 169.3, 168.6, 153.6, 141.2, 137.1, 137.1, 136.4, 133.7 129, 128.5, 128.0, 127.8, 126.4, 124.3,122.9, 81.5, 67.1, 66.4, 60.2, 54.7, 50.9, 49.2, 46.3, 42,6, 42.1, 37.8, 37.2, 36.0, 35.5, 34.7, 31.2, 30.0, 29.7, 29.2, 26.7, 13.0, ; LC-MS-ESI (m/z): [M+H] calcd. For $C_{48}H_{69}N_6O_{12}S$+ 953.47; found 953.5.

Macrocycle 2.34:
Synthesized according to general procedure **D**, obtained in 75% isolated yield.
^{1}H NMR two amide rotamers present (DMSO-d_6, 600 MHz) δ 8.72-8.28 (m, 1H), 8.24-7.97 (m, 2H), 7.70-7.53 (m, 1H), 7.38-6.92 (m, 9H), 6.54-6.28 (d, J= 15.6, 1H), 6.25-6.07 (m, 1H), 4.94-4.82 (m, 1H), 4.76-4.55 (m, 1H), 4.49-4.32 (m, 1H), 4.27; 3.84 (m, 1H), 4.16-4.04 (m, 1H), 3.58- 3.38 (m, 8H), 3.34-3.24 (m, 2H), 3.10-2.98 (m, 3H), 2.89-2.78 (m, 1H), 2.77-2.55 (m, 5H), 2.47-216 (m, 5H), 2.04-1.84 (m, 1H), 1.76-1.60 (m, 1H) 1.32-1.20 (m, 2H) ^{13}C NMR (DMSO-d_6, 126MHz) δ174.5, 172.4, 171.9, 171.6, 171.3, 168.6, 167.7, 142.0, 138.7, 136.9, 132.7, 129.5, 128.5, 128.0, 127.1, 126.7, 126.1, 123.6 66.6, 54.9, 50.7, 49.1, 48.9, 48.4, 46.1, 42.6, 37.7, 37.1, 36.2, 35.9, 35.3, 34.3, 33.9, 31.1, 26.6, 21.1 HRMS-ESI (m/z): [M+] calcd. for $C_{39}H_{50}N_6O_9S$ 778.34; found 778.4

Linear Precursor 2.38:
Synthesized according to general procedures **B** and **E**, obtained in 51% yield over two steps from peptide.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.52 (m, 1H), 7.29 (dd, J = 7.1, 1.9 Hz, 1H), 7.16- 7.11 (m, 3H), 6.89 (t, J = 9.3 Hz, 1H), 6.55 (d, J = 16.0 Hz, 1H), 6.19 (dt, J = 16.0, 6.2 Hz, 1H), 5.70 (d, J = 7.0 Hz, 1H) , 5.11 (t, J = 7.5 Hz, 1H), 4.64 (dd, J = 6.2, 0.7 Hz, 2H), 4.41 (t, J = 5.5 Hz, 2H), 3.72 (d, J = 5.5 Hz, 2H) , 3.68- 3.60 (m, 1H), 3.57-3.49 (m, 1H) , 3.41-3.35 (m, 2H), 3.35-3.30 (m, 2H), 3.30-3.28 (m, 2H), 3.26-3.17 (m, 1H), 2.96 (dd, J = 13.5, 7.1 Hz, 1H), 2.93-2.85 (m, 2H), 2.79 (dd, J = 13.5, 6.9 Hz, 1H), 2.71- 2.58 (m, 2H), 1.96-1.86 (m, 2H), 1.86-1.76 (m, 2H), 1.74-1.65 (m, 1H), 1.46 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 176.1, 170.7, 170.4, 168.7, 160.8 (d, J = 43.7), 153.6, 135.4, 134.0, 132.7, 132.5, 129.2, 128.4, 126.4, 126.0, 123.8, 122.9, 120.3, 115.0, 112.3, 111.7, 103.9, 66.9, 61.5, 55.2, 50.9, 50.85, 50.3, 46.6, 46.0, 43.1, 40.9, 32.0, 26.7, 25.5, 23.7, 22.07.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{44}H_{55}BrFN_5O_8S_2H$ 944.27; found 943.8.

Macrocycle 2.39:
Synthesized according to general procedure **D**, obtained in 53% yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.09 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 7.0 Hz, 1H), 7.74 (d, J = 8.8Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.14 (dd, J = 8.6, 1.8 Hz, 1H), 7.12-7.07 (m, 2H) , 6.54 (d, J = 15.7 Hz, 1H), 6.36 (dt, J = 15.7, 9.4 Hz, 1H), 5.09 (d, 7.2 Hz, 1H), 4.88 (t, J = 5.8 Hz, 1H), 4.81-4.76 (m, 1H), 4.74- 4.67 (m, 1H), 4.28-4.21 (m, 1H), 3.66-3.41 (m, 6H) , 3.40-3.27 (m, 2H), 3.26-3.17 (m, 2H), 3.10 (dd, J = 16.4, 5.3 Hz, 1H), 2.97-2.92 (m, 2H), 2.90 (dd, J = 12.8, 4.2 Hz, 1H) , 2.82-2.74 (m, 1H), 2.69 (dd, J = 16.1, 7.7 Hz, 1H) , 1.88-170 (m, 4H), 1.56-147 (m, 1H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 174.3, 169.5, 169.4, 168.2, 159.5, 135.3, 135.1, 133.5, 131.5, 128.7, 127.9,

126.7, 125.3, 123.9, 120.8, 115.4, 115.3, 113.6, 111.6, 105.1, 61.6, 56.1, 51.1, 50.0, 49.3, 46.7, 46.4, 43.5, 42.5, 41.9, 33.8, 26.2, 26.0, 25.1, 24.2, 21.2.; HRMS-ESI (m/z): [M+H] calcd. For $C_{35}H_{37}BrFN_5O_5S_2H$ 770.1484; found 770.1491.

Macrocycle 2.40:
To a 0.02 M solution of **48** in DMF was added TCEP HCl (2.2 equiv.) and $EtN(iPr)_2$ (8.8 equiv.) at room temperature. After 1 hour the reaction was diluted with EtOAc, extracted thrice with saturated $NaHCO_3$, once with brine and dried over $MgSO_4$. The solvent was removed, and the crude product was taken up in 0.01 M DMF. 1.5 equiv. of Cs_2CO_3 was added followed by 1.5 equiv. of perfluorocyclopentene as a 1 M solution in MeCN. The reaction was stirred at room temperature for 1 hour. After this time the reaction was diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The solvent was removed under reduced pressure and the resultant residue was taken up in DMSO an purified via HPLC for a 30% yield of **49** over two steps.
^{1}H NMR (500 MHz, DMSO) δ 8.36 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 4.7 Hz, 1H), 7.97 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 10.8 Hz, 1H), 7.84 (d, *J* = 9.7 Hz, 1H), 7.34 (s, 1H), 7.22 (dd, *J* = 12.9, 5.8 Hz, 2H), 7.18 (t, *J* = 5.6 Hz, 3H), 7.07 (dd, *J* = 13.0, 7.7 Hz, 2H), 6.46 (d, *J* = 15.7 Hz, 1H), 6.21 – 6.13 (m, 1H), 4.41 (dt, *J* = 13.1, 8.4 Hz, 2H), 4.22 – 4.14 (m, 1H), 3.89 (d, *J* = 6.9 Hz, 2H), 3.72 – 3.65 (m, 1H), 3.50 (dd, *J* = 12.7, 6.4 Hz, 1H), 3.17 (dd, *J* = 12.4, 7.7 Hz, 1H), 3.03 (dd, *J* = 13.8, 5.5 Hz, 2H), 2.89 – 2.80 (m, 1H), 2.76 (m, 1H), 2.63 – 2.60 (m, 2H), 2.58 (d, *J* = 4.6 Hz, 2H), 2.55 – 2.50 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.71 (d, *J* = 6.3 Hz, 3H).
^{13}C NMR (126 MHz, DMSO) δ 172.84, 172.76, 171.46, 170.70, 169.35, 142.12, 137.96, 136.28, 134.15, 129.55, 128.95, 128.61, 126.81, 125.76, 125.34, 123.75, 66.51, 60.41, 54.82, 52.67, 49.17, 40.58, 40.49, 40.41, 40.32, 40.24, 40.15, 40.07, 39.99, 39.91, 39.82, 39.65, 39.48, 37.10, 36.95, 35.35, 32.55, 31.46, 30.24, 26.28, 19.61, 17.90. .; HRMS-ESI (m/z): [M+H] calcd. For $C_{37}H_{41}F_6N_5O_6S_2H$ 830.24807; found 830.24618.

Macrocycle 2.41:
To a 0.02 M solution of **48** in DMF was added TCEP HCl (2.2 equiv.) and $EtN(iPr)_2$ (8.8 equiv.) at room temperature. After 1 hour the reaction was diluted with EtOAc, extracted thrice with saturated $NaHCO_3$, once with brine and dried over $MgSO_4$. The solvent was removed and the crude product was taken up In 0.01 M DMF. 5.5 equiv. of $EtN(iPr)_2$ was added followed by 5.5 equiv. of perfluorobenzene. The reaction was stirred at 45°C for 12 hours. After this time the reaction was diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The solvent was removed under reduced pressure and the resultant residue was taken up in DMSO an purified via HPLC for a 66% yield of **50** over two steps.
^{1}H NMR (500 MHz, DMSO) δ 8.04 (d, *J* = 6.9 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.0 Hz, 1H), 7.81 (d, *J* = 4.6 Hz, 1H), 7.78 (d, *J* = 6.8 Hz, 1H), 7.23 (m, 2H), 7.17 (m, 5H), 7.04 (d, *J* = 6.7 Hz, 1H), 6.94 (s, 1H), 6.14 (d, *J* = 15.7 Hz, 1H), 6.11 – 6.03 (m, 1H), 4.39 (dd, *J* = 14.1, 7.1 Hz, 1H), 4.21 (dd, *J* = 13.8, 7.2 Hz, 1H), 4.11 (p, *J* = 7.0 Hz, 1H), 3.92 (t, *J* = 5.8 Hz, 1H), 3.81 – 3.75 (m, 1H), 3.74 – 3.64 (m, 2H), 3.39 (dd, *J* = 13.8, 5.7 Hz, 1H), 3.17 (dd, *J* = 13.7, 7.4 Hz, 1H), 3.03 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.90 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.69 (t, *J* = 8.1 Hz, 2H), 2.46 – 2.42 (m, 2H), 2.37 (d, *J* = 4.4 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.78 (d, *J* = 6.2 Hz, 3H).
^{13}C NMR (126 MHz, DMSO) δ 172.91, 172.55, 171.16, 171.03, 169.58, 148.50-147.50(m, 2C), 146.5-145.5 (m, 2C) 142.06, 137.92, 136.62, 133.55, 129.61, 128.94, 128.59, 128.03, 127.26, 126.81, 124.78, 123.77, 115.01-114.83 (m, 1C), 113.09-112.93 (m, 1C), 66.60, 60.30, 54.83, 53.33, 49.24, 40.57, 40.48, 40.40, 40.32, 40.24, 40.15, 40.07, 39.98, 39.81, 39.65, 39.48, 37.31, 37.27, 37.16, 35.52, 31.19, 25.87, 20.12, 17.43.; HRMS-ESI (m/z): [M+H] calcd. For $C_{38}H_{41}F_4N_5O_6S_2H$ 804.251266; found 804.24919.

Macrocycle 2.42:
To a 0.02 M solution of **48** in DMF was added TCEP HCl (1.1 equiv.) and $EtN(iPr)_2$ (15.0 equiv.) at room temperature. After stirring for 1 h, 4.5 equiv. 2,4-Dichloro-6-methoxy-1,3,5-triazine was added and the reaction was stirred another 11 hours. After this time the reaction was diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The solvent was removed under reduced pressure and the resultant residue was taken up in DMSO an purified via HPLC for 39% yield of **51** over a one pot, two reaction sequence.
^{1}H NMR (500 MHz, DMSO ^{1}H NMR (500 MHz, DMSO) δ 8.35 (d, J= 8.0 Hz, 1H), 7.93 (d, J= 7.6 Hz, 1H), 7.51 (d, J= 7.8 Hz, 1H), 7.33 (s, 1H), 7.21-6.99 (m, 8H), 6.60 (d, J= 15.7 Hz, 1H), 6.39 (dt, J= 15.7, 6.8 Hz, 1H), 4.89 (dd, J= 13.5, 7.7 Hz, 1H), 4.49-4.40 (m, 1H), 4.01-3.91 (m, 2H), 3.88 (s, 3H), 3.47-3.39(m, 2H), 3.38-3.33 (m, 1H), 3.32-3.22 (m,. 2H), 3.02 (dd, J= 13.9, 4.8 Hz, 1H), 2.92-2.83 (m, 1H), 2.73 (dd, J= 14.0, 8.8 Hz, 1H), 2.68 (q, J= 7.2), 2.52-2.50 (m, 1H), 2.37-2.29 (m, 1H), 1.82-1.67 (m, 4H), 1.29 (q, J= 6.6 Hz, 1H), 1.25-1.16 (m, 2H), 0.73 (d, J= 6.5 Hz, 3H), 0.69 (d, J= 6.4 Hz, 3H) ^{13}C NMR (126 MHz, DMSO) δ 182.2, 181.8, 172.14, 172.09, 170.9, 168.0, 167.9, 142.1, 137.7, 136.8, 132.9, 129.7, 128.8, 128.4, 126.7, 125.8, 125.5, 125.0, 55.7, 53.9, 52.2, 50.2, 46.4, 46.2, 41.2, 37.3, 36.2, 32.4, 32.1, 30.5, 26.0, 24.4, 24.2, 23.2, 22.1; HRMS-ESI (m/z): [M+H] calcd. For $C_{38}H_{47}N_7O_5S_2H$ 746.315837; found 746.31540.

Table 2.5: Experimental procedures.

Table 2.5: Entry 1
$Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.2 eq.) was suspended in 0.5 ml of DCM:EtOH (9:1) and stirred in a dram vial. 50% H_2O_2 solution (14.4 µL, 25 µmol, 5.0 eq) was added to the stirring suspention. After 5 minutes, macrocycle **2.14** (33 mg, 50 µmol, 1.0 eq) was added. The reaciton was monitored byTLC and HPLC. After 55 minutes the reaction was diluted with 15:1 MeCN:MeOH, passed through a plug of silica and evaporated to afford 35 mg of macrocycle **2.43** in quantitative yield. This product was shown to be two diastereomers upon ^{1}H NMR analysis in DMSO-d6, *dr* 1:1.

Table 2.5: Entry 2
$Sc(OTf)_3$ (4.9 mg, 10 µmol, 0.2 eq.) was suspended in 0.5 ml of DCM:EtOH (9:1) and stirred in a dram vial. 50% H_2O_2 solution (14.4 µL, 25 µmol, 5.0 eq) was added to the stirring suspention. After 5 minutes compound **2.13** (42 mg, 50 µmol, 1.0 eq) was added. The reaciton was monitored byTLC and HPLC. After 55 minutes the reaction was diluted with 15:1 MeCN:MeOH, passed through a plug of silica and evaporated. The crude product obtained was suspended in 9.5 ml of nitromethane and 0.5 ml of THF was added. After 10 minutes the solvent was evaporated, TLC and crude ^{1}H-NMR indicated decomposition had occured.

Table 2.5: Entry 3
2.14 (11.5 mg, 17.5 µmol, 1.0 eq.) was dissolved in 0.2 ml of DCM:DMF and stirred in a dram vial (4:1), mCBPA (4.8 mg, 21. µmol, 1.2 eq.) of was added. The reaction was stirred at room temperature for 30 minutes before the solvent was removed. A crude NMR determined the *dr*. to be 1.4:1 in MeOD-d4.

Table 2.5: Entry 4
2.14 (112 mg, 0.171 mmol, 1.0 eq.) was dissolved in DCM:MeOH (9:1) and cooled to -78°*C* in a dram vial equipped with stir bar. 32% w/v Peracetic acid in AcOH (40 µL, 19. µmol, 1.1 eq.) was added and the reaction was warmed to room temperature over 40 minutes. At 25 minutes ~(-30°*C*) an extra 25 µL of AcOOH was added. After onedeoxygenated a drop of DMS was added and the solvent was removed. Column chromatagraphy furnished 75 mg of **2.43** in 66% yield with a *dr* of 3:1.
(95:1 ->90:1 $CHCl_3$:MeOH), *Rf* = 0.46 (9:1 $CHCl_3$:MeOH ^{1}H NMR two diastereomers present
2.43 ^{1}H-NMR(MeOH-d_4, 500 MHz) δ 7.28-7.16 (m, 9H), 6.80 (d, J= 15.8, 1H), 6.20-6.05 (m, 1H), 4.62-4.57 (m, 1H), 4.51 (dd, J= 10.7, 4.3 Hz, 1H), 4.21-4.14 (m, 2H), 4.10-4.4 (m, 1H), 3.87 (d, J= 6.0 Hz, 1), 3.77 (dd, J= 14.4, 4.3 Hz, 1H), 3.61-3.55 (m, 1H), 3.24 (q, J= 6.7 Hz, 1H), 3.05-2.94 (m, 2H), 2.88-2.80 (m, 2H), 2.78-2.74 (m, 3H), 2.72-2.65 *m, 2H), 1.36 (d, J= 7.2 Hz, 3H), 0.77 (d, J= 6.4 Hz, 3H) ^{13}C NMR (DMSO-d_6, 126MHz) δ 173.5, 173.1, 171.7, 170.5, 170.0, 142.4, 138.4, 138.1, 136.5, 129.6, 129.1, 128.8, 128.5, 126.6, 126.4, 125.0, 117.2, 66.3, 62.6, 59.7, 54.2, 49.1, 37.4, 36.6, 34.7, 31.7, 30.0, 26.3, 20.2, 18.1. HRMS-ESI (m/z): [M+] calcd. for $C_{32}H_{41}N_5O_7S_2$+ 671.24; found 671.9.

Table 2.5: Entry 5
2.14 (11.5 mg, 17.5 µmol, 1.0 eq) was dissolved in 0.4 ml of DCM:MeOH (9:1) and cooled to -78°*C* in a dram vial equipped with stir bar. 90% TBHP (2µ , 20 µmol, 1.1 eq) was added to teh solution and the reaction was warmed to room temperature. After 1deoxygenated with no reaction 6 µL of TBHP was added. No reaction was observed.

Table 2.5: Entry 6.1
Oxaziridine 1 (11.3 mg, 50 µmol, 1.2 eq) of was dissolved in 4.1 ml of $CHCl_3$: MeCN (4:1) in a dram vial equipped with stir bar. **2.14 (**27 mg, 41.5 µmol, 1.0 eq.) was added followed by of $ZnCl_2$ (6.8 mg 50 µmol, 1.2 eq.) After 30 minutes one extra eq. of **Oxaziridine 1** and $ZnCl_2$ was added. No reaction was observed.

Table 2.5: Entry 6.2
2.14 (11.5 mg , 17.5 µmol, 1.0 eq) dissolved in 0.2 ml of $CHCl_3$: MeCN (9:1) in a dram vial equipped with stir bar. **Oxaziridine 1** (8 mg, 35 µmol, 2.0 eq.) was added followed by $ZnCl_2$ (3.8 mg, 28 µmol, 1.6 eq.). No reaction was observed byTLC or HPLC.

Table 2.5: Entry 7
2.5 (127 mg, 0.2 mmol, 1.0 eq.) was dissolved in 12.5 ml of $CHCl_3$ in a scintillation vial equipped with stir bar. **Oxaziridine 2** (46 mg, 0.2 mmol, 1.0 eq.) of was then added. After 1 hour, no conversion was detected byTLC or HPLC.

Table 2.5: Entry 8
2.5 (32 mg, 50 µmol, 1.0 eq.) was dissolved in 0.5 ml of $CHCl_3$ in a dram vial equipped with stir bar. **Oxaziridine 2** (23 mg, 0.1 mmol, 2.0 eq.) was then added, followed $Sc(OTf)_3$ (by 2.5 mg, 5 µmol, 10 mol%). After 1deoxygenated no conversion was detected byTLC or HPLC.

Table 2.5: Entry 9
2.34 16 mg, 20 µmol, 1.0 eq.) was dissolved in 2.0 ml of DCM:DMF (9:1) and cooled to 0°*C* in a dram vial equipped with stir bar. NCS (5.3 mg, 40 µmol, 2.0 eq.) was dissolved in 1 ml DCM and added dropwise over 5 minutes. HPLC monitoring revealed full converion to a peak mass consistent with sulfoxide **2.47**.

Table 2.5: Entry 10
2.14 (12.5 mg, 19 µmol, 1.0 eq.) was dissolved in 1 ml of DCM:MeOH (9:1) and cooled to 0°*C* in a dram vial equipped with stir bar. (3.3 mg, 25 µmol, 1.3 eq.) of NCS was added and the reaction was warmed to room temperature. After 1deoxygenated no conversion was detected byTLC or HPLC.

Table 2.5: Entry 11
2.34 (13 mg, 17 µmol, 1.0 eq) was dissolved in 3.3 ml of dry MeCN and cooled to 0°*C* in a dram vial equipped with stir bar. To this solution was added of 2,6 lutidine (8.1 µl, 70 µmol, 4.0 eq.). Stang's reagent (2.1 mg, 0.333 eq. every 10 min; 38 mg, 6.0 eq. total) was added every ten minutes over 3 hours. No product was detected, 4 and 3 extra equivlents of base and Stang's reagent were added respectively.

Table 2.5: Entry 12
11.5 mg (11.5 mg 17.5 µmol, 1.0 eq) of macrocycle **2.14** was dissolved in 3.5 ml of dry MeCN and cooled to 0°*C* in a dram vial equipped with stir bar. To this solution was added 2,6 lutidine (8.1 µl, 70 µmol, 4.0 eq.) followed by freshly prepared Stang's reagent (19.9 mg, 0.052.5 mmol, 3.0 eq.). No product was detected by HPLC.

Table 2.6: Experimental procedures.
Table 2.6: Entry 1
2.7 (18.4 mg, 24 µmol, 1.0 eq.) was dissolved in 0.5 ml of MeCN:MeOH(1:1) in a dram vial equipped with stir bar. PPh_3 (12.5 mg, 48 µmol, 2.0 eq.) was added and the solution was stirred at ambient temperature overnight. No rearrangement product was observed after 16 hours.

Table 2.6: Enrty 2
2.14 (11.5 mg, 17.5 µmol, 1.0 eq.) was dissolved in 0.35 ml of MeCN: MeOH (3:1)) in a dram vial equipped with stir bar. PPh_3 (13.7 mg, 5.25 µmol, 3.0 eq.) of was added and the reaction was heated to 65°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Enrty 3
2.14 (11.5 mg, 17.5 µmol, 1.0 eq.) was dissolved in 0.35 ml of MeCN: MeOH (3:1)) in a dram vial equipped with stir bar. Polymer-bound PPh_3 (60.0 mg, 0.175 mmol, 10.0 eq) of was added and the reaction was heated to 65°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Enrty 4
2.14 (33 mg, 50 µmol, 1.0 eq.) was dissolved in 1 ml of MeCN: MeOH (3:1) in a dram vial equipped with stir bar. The solution was freezed-pumped-thawed thrice and cooled to 0°*C*. PBu_3 (20 µL, ~55 µmol, 1.1 eq, with ~25% oxide impurity) was added to the solution and the reaction was stirred. After 30 minutes 0.5 ml of DMF was added, along with 40 µL of PBu_3. The reaction was heated to 65°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Entry 5
2.5 (32 mg, 50 µmol, 1.0 eq.) was dissolved in 1.0 ml of acetone in a dram vial equipped with stir bar. DPPV (2.0 mg, 5 µmol, 10 mol%) and $HRh(PPh_3)_4$ (2.9 mg, 2.5 µmol, 5 mol%) of was added. Elemental sulfur (3.2 mg, 0.1 mmol, 2.0 eq.) of was then added. After stirring at room temperature for 1.5 h, 0.5 ml of DMF was added and the reaction was heated to 60°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Entry 6
2.5 (32 mg, 50 µmol, 1.0 eq.) was dissolved in 0.5 ml of acetone in a dram vial equipped with stir bar. 2 DPPV (2.0 mg, 5 µmol, 10 mol%) and $HRh(PPh_3)_4$ (2.9 mg, 2.5 µmol, 5 mol%) of was added. 16 mg (0.5 mmol, 10.0 eq) of Elemental sulfur was added. After stirring at room temperature for 1.5 h, 0.5 ml of DMF was added and the reaction was heated to 60°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Entry 7
2.5 (32 mg, 50 µmol, 1.0 eq.) was dissolved in 0.5 ml of toluene in a dram vial equipped with stir bar. DPPV (2.0 mg, 5 µmol, 10 mol%) and $HRh(PPh_3)_4$ (2.9 mg, 2.5 µmol, 5 mol%) was added. Elemental sulfur (16 mg, 0.5 mmol, 10.0

eq) of was then added. After stirring at room temperature for 1.5 h, 0.5 ml of DMF was added and the reaction was heated to 85°*C* overnight. No rearrangement product was observed by HPLC after 12 hours.

Table 2.6: Entry 8
To a two neck flask equipped with a reflux condenser was placed **2.5** (64 mg, 0.1 mmol, 1.0 eq.), $HRh(PPh_3)_4$ (5.8 mg, 5 µmol, 5 mol%) and $P(p\text{-}Tol)_3$ (6 mg, 20 µmol, 20 mol%). These solids were dissolved in 0.5 ml of dry degassed acetone and 0.1 ml of CF_3SO_3H stock solution (0.45 ml of 50 ml of MeCN). The reaction was heated to 60°*C* for 30 minutes. No rearrangement product was observed by HPLC.

Scheme 2.6: Experimental procedures.

2.49
Was Prepared as descibed in literature.[5]
2.49 : Two imine isomers present ^{1}H NMR ($CDCl_3$, 400 MHz,) δ 8.50 (s, 0.9H), 8.23-8.20 (m, 0.3H) 8.02-7.99 (m, 1H), 7.75-7.60 (m, 2H), 7.33 (t, J= 7.7 Hz, 1H), 1.26 (s, 9H) . LC-MS-ESI (m/z): [M+H] calcd. for $C_{11}H_{14}BrNOS$, 288.00; found 287.7.

2.50:
2.49 (1.35 g ,4.67 mmol, 1.0 eq.) was dissolved in 47 ml of dry THF in a round bottom flask equipped with a stir bar. The reaction was cooled to -50°*C* and benzylmagnesium chloride (9.5 ml ,1.0 M in THF, 9.5 mmol, 2.0 eq.) was added over 20 minutes.The reaction was kept at -50°*C* for 4 hours before warming to room temperature overnight. The reaction was poured into cold saturated NH_4Cl (100 ml), extracted thrice with EtOAc (100 ml) washed once with brine (150 ml) and dried over $MgSO_4$. The solvent was removed in vacuo to furnish 853 mg (48%) of an off-white crystalline powder. Crude NMR revealed a *dr* of 2:1. This tan solid was used directly in the next step without purifcation. Two rotamers+ diastereomers present ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.48-6.93 (m, 9H), 4.66-4.49 (m, 1H), 4.00-3.73 (br, 1H), 3.34-2.97 (m, 2H), 1.50-1.28 (m, 2H), 1.24-1.08 (m, 9H). LC-MS-ESI (m/z): [M+H] calcd. for $C_{18}H_{22}BrNOS$, 380.06; found 379.9.

2.51
2.50 product (853 mg 2.24 mmol, 1.0 eq.) was dissolved in 22 ml of MeOH in a round bottom flask equipped with a stir bar and the reaction was cooled to 0°*C*. HCl (2.24 ml, 4 M in 1,4-dioxane, 8.96 mmol, 4.0 eq.) was added, the reaction was warmed to room temperatue, and stirred for 2 hours. The solvent was removed and this product (611 mg, 99% yield) was used directly in the next step without purifcation.

2.52
N-hydroxysuccinimidyl-octanoate (1.6 g, 6.6 mmol, 1.0 eq.) and Boc-DAP-OH (1.35 g, 6.6 mmol, 1.0 eq.) were dissolved in 12 ml of DMF and 4 ml of iPr_2NEt in a round bottom flask equipped with a stir bar. The reaction was stirred at room temperature for 2 hours before the reaction was diluted with 25 ml of water and the reaction was acidified with 2 N HCl until precipitation of product. The reaction was then extracted with 200 ml of EtOAc and the organic layer was washed with NH_4Cl twice and brine twice. The organic layer was dried over $MgSO_4$, filtered and a crude NMR was taken. This product appeared as a gummy solid and was used directly in the next step without purifcation (57% yield).
2.52 ^{1}H NMR ($CDCl_3$, 400 MHz,) δ6.60-6.42 (br, 1H), 6.14-5.96 (br, 1H), 4.26-4.18 (m, 1H), 3.90-3.70 (m, 1H), 2.23 (m, J= 7.7 Hz, 2H), 1.71-1.55 (m, 2H), 1.45 (s, 9H), 1.33-1.23 (m, 8H) 087. (t, J= 6.8 Hz, 3H)). LC-MS-ESI (m/z): [M+H] calcd. $C_{31}H_{44}BrN_3O_4$, 602.25; found 602.5.

2.53:
HBTU (291.1, 1.53mmol, 1.2 eq.), **2.51** (400 mg, 1.28 mmol, 1.0 eq.), and **2.52** (508 mg, 1.53 mmol, 1.2eq.) were dissolved in 3 ml of DMF in a round bottom flask equipped with a stir bar. iPr_2NEt (1.40 ml, 6.4 mmol, 5.0 eq) was added the reaction was stirred at room temperature for 1.5 hours. After this time the reaction was diluted with EtOAc (30 ml), washed thrice with NH_4Cl, thrice with $NaHCO_3$, and thrice with brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. This product appeared as a tan foam, was used directly in the next step without purification (67% yield). LC-MS-ESI (m/z): [M+, -Boc] calcd. for $C_{30}H_{42}BrN_3O_4$ 488.19; Found 488.2.

2.46:
2.45 product (182 mg, 0.31 mmol, 1.0 eq.) was dissolved in 6 ml of 1:1 DCM:TFA in a scintillation vial equipped with a stir bar. After 25 minutes the solvent was removed in vacuo. The residue was dissolved in 2 ml of DMF, (L) N Boc S-tertbutylthio cysteine (103 mg, 0.37 mmol, 1.2 eq.) and HTBU (141 mg, 0.37 mmol, 1.2 eq.) were then added. iPr_2NEt (0.30 ml, 1.7 mmol, 5.5 eq.) was added and reaction was stirred for 1.5 hours. After this time the reaction was diluted with EtOAc (10 ml), washed thrice with NH_4Cl, thrice with $NaHCO_3$, and thrice with brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. This product was directly dissolved in in 6 ml of 1:1 DCM:TFA. After 25 minutes the solvent was removed. The residue was dissolved in 2 ml of DMF, Boc Gly OH (65 mg,

0.37 mmol, 1.2 eq.) and HTBU (141 mg, 0.37 mmol, 1.2 eq.) were added. iPr_2NEt (0.30 ml, 1.7 mmol, 5.5 eq.) was added and reaction was stirred for 1.5 hours. After this time the reaction was diluted wiht EtOAc (10 ml), washed thrice with NH4Cl, thrice with $NaHCO_3$, and thrice with brine. The organic layer was dried over $MgSO_4$, the solvent removed in vacuo, and the product charaterized by HPLC. 241 mg of product as a tan foam was obtained (94%). LC-MS-ESI (m/z): [M+H] calcd. for $C_{39}H_{58}BrN_5O6_S$ 804.33; found 804.2.

2.55:
To a flask equipped with stir bar and reflux condenser was added **2.52** product (240 mg, 0.30 mmol, 1.0 eq), anhydrous K_2CO_3 (124 mg, 0.9 mmol, 3.0 eq.), and E)-tert-butyldimethyl((3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)oxy)silane (107 mg, 035 mmol, 1.2 eq.). These compounds were dissolved in 2.4 ml of 4:1 THF: H_2O and the reaction was sparged with argon for 30 minutes. After this time $Pd(PPh_3)_4$ (36 mg, 0.030 mmol, 10 mol%) was added and the reaciton was heated to 65°*C* overnight. After 12 hours the reaction was cooled, the THF was removed in vacuo, and the residue was partitioned between EtOAc and water. The aqueous layer was back extracted once with EtOAc and the combined organic layers were washed thrice with brine. The solution was dried over $MgSO_4$, the solvent was removed in vacuo, the product charaterized by HPLC (216 mg, 81%) and appeared as an off-white foam. LC-MS-ESI (m/z): [M+H] calcd. for $C_{48}H_{77}N_5O_7SSi$ 896.53; found 896.9.

Linear Precursor 2.56:
2.55(216 mg, 0.24 mmol, 1.0 eq.) was dissolved in 1ml of THF in a scintillation vial equipped with a stir bar and cooled to 0°*C*. 1 M TBAF in THF (1 ml, 1 mmol, 4.2 eq.) was added. The reaction was stirred for 1 hour, after that time additional 1 M TBAF (0.5 ml, 0.5 mmol, 2.1 eq.) was added. After 1.5 hours total time the reaction was diluted with EtOAc, washed thrice with NH_4Cl, twice with $NaHCO_3$, and twice with brine. The organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude reaction was purified by silica gel column chromatagraphy (99:1 ->93: $CHCl_3$:MeOH), *Rf* = 0.70 (15:1 $CHCl_3$:MeOH. 108 mg of a clear oil was obtained (57%) and HPLC analysis reavealed the target mass. LC-MS-ESI (m/z): [M+H] calcd. for $C_{42}H_{63}N_5O7_S$, 782.44; found 782.3.

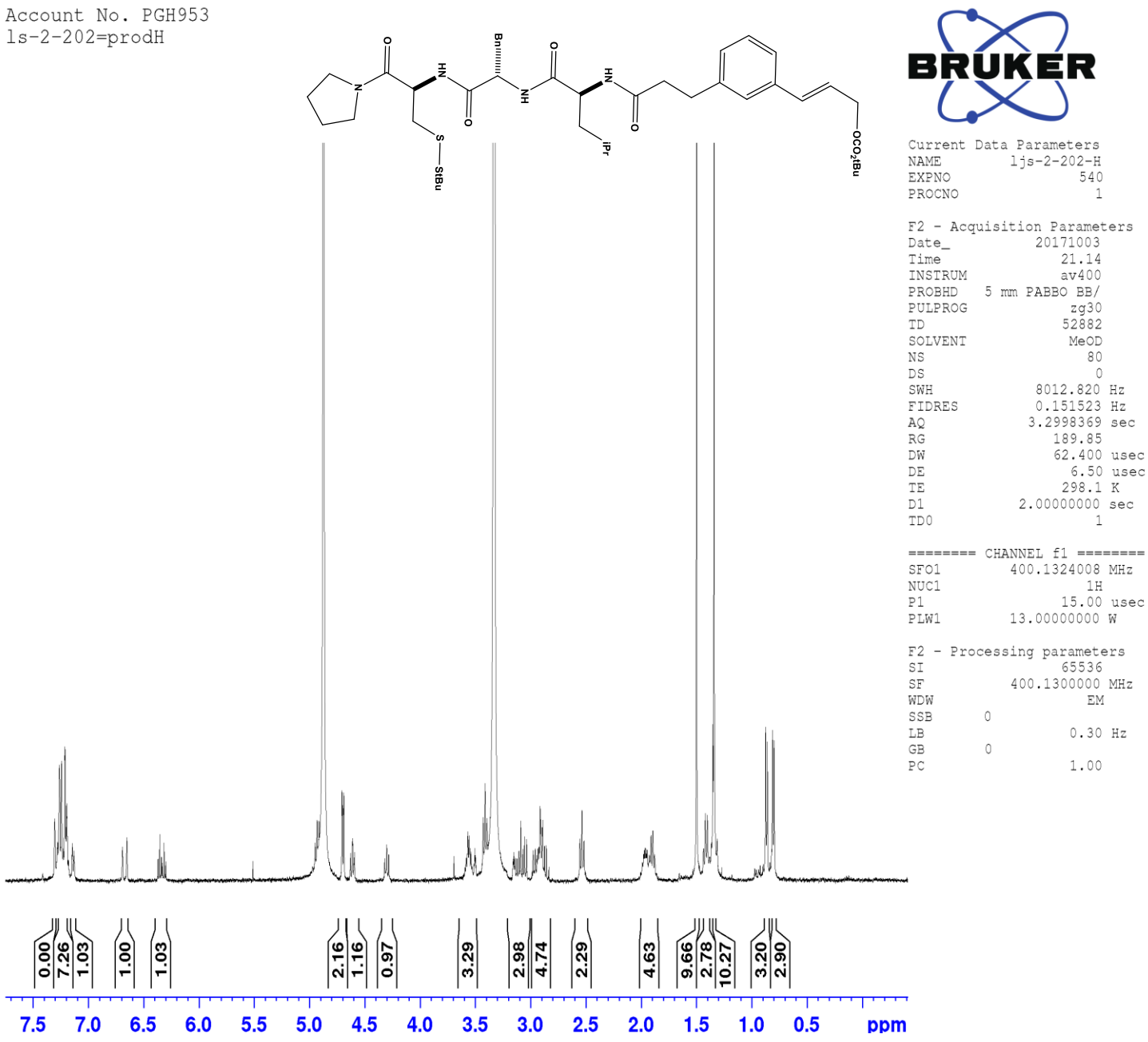
All the material from the reaction above (108 mg, 0.138 mmol, 1.0 eq.) was dissolved in 1.4 ml of dry THF in a scintillation vial equipped with a stir bar. The solution was cooled to 0°*C* and of N-methylmorpholine (30 µL, 0.276 mmol, 2.0 eq.) was added, followed by isobutyl chloroformate (20 µL, 0.276 mmol, 2.0 eq.). After 15 minutes the reaction was quenched with saturated NH_4Cl and diluted with EtOAc. The organics layers were washed twice with $NaHCO_3$, twice with brine, and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by silica gel column chromatagraphy (200:1 ->95:1 $CHCl_3$:MeOH), *Rf* = 0.65 (25:1 $CHCl_3$:MeOH.) 87 mg of a gummy solid was obtained for 71% isolated yield.
2.56 ^{1}H NMR (MeOH-d_4, 500 MHz δ 7.37-7.07 (m, 9H), 6.69 (d, J= 15.9 Hz, 1H), 6.41-6.33 (m, 1H), 5.17-5.09 (m, 1H), 4.81-4.70 (m, 2H), 4.42-4,4.32 (m, 2H), 3.93 (d, J= 6.6 Hz, 1H), 3.88 (d, J= 16.8 Hz, 1H), 3.81-3.74 (m, 1H), 3.46-3.40 (m, 1H), 3.28-3.3.22 (m, 1H), 3.15-3.3.05 (m, 2H), 3.00, (dd, J= 13.0, 5.5 Hz, 1H), 2.96-2.88 (m, 1H), 2.00-1.90 (m, 2H), 1.44 (s, 9H), 1.35-1.20 (m, 12H), 0.96 (d, J= 6.7 Hz, 6H), 0.89 (t, J= 7.0 Hz, 3H), (^{13}C NMR (126 MHz, MeOH-d_4) δ.171.9, 171.1, 169.2, 157.0, 155.4, 142.5, 138.0, 136.5, 134.0, 129.1, 128.5, 127.9, 126.5, 126.1, 125.3, 124.9, 123.0, 79.5, 73.7, 67.8, 55.1, 54.4, 43.6, 42.3, 40.7, 35.4, 31.5, 29.9, 29.1, 28.9, 28.7, 27.7, 27.4, 25.3, 25.3, 17.8, 13.0 LC-MS-ESI (m/z): [M+H] calcd. for $C_{47}H_{71}N_5O9_S$, 882.50; found 882.3.

Macrocycle 2.57:
In a vial equipped with stir bar, **2.56** (32 mg, 36 µmol, 1.0 eq.) was dissolved in 6.9 ml of nitromethane at room temperature. 0.72 ml of TFA (10 vol%) was added and the reaction was stirred at room temperature for 1.5 hours. After this time the solvent was removed in vacuo and the residue was purified by preperative HPLC, affording 9.1 mg of **2.49** product (35% yield) as a white film.
2.57 ^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.96-8.80 (m, 1H), 8.63-8.8.50 (m, 1H), 8.34-8.15 (m, 1H), 8.02-7.66 (br, 3H), 7.65-7.50 (m, 1H), 7.40-7.00 (m, 9H), 6.55 (d, J= 15. 5 Hz, 1H), 6.09-5.91 (m, 1H), 5.10-4.94 (m, 1H), 4.82-4.47 (m, 2H), 3.29-2.80 (m, 7H), 2.65-2.51 (m, 1H), 1.97-1.67 (m, 2H), 1.49-1.01 (m, 12H), 0.90-0.72 (m, 3H). ^{13}C NMR 173.0, 169.9, 169.8, 166.6, 144.0, 139.4, 138.0, 133.1, 129.5, 128.7, 128.6, 128.5, 126.5, 125.1, 123.2, 54.4, 53.3, 52.6, 35.5, 32.9, 32.5, 31.7, 29.2, 29.0, 25.5, 22.6, 14.4. HRMS-ESI (m/z): [M+H] calcd. for $C_{33}H_{45}N_5O_4S$, 608.32; found 608.3

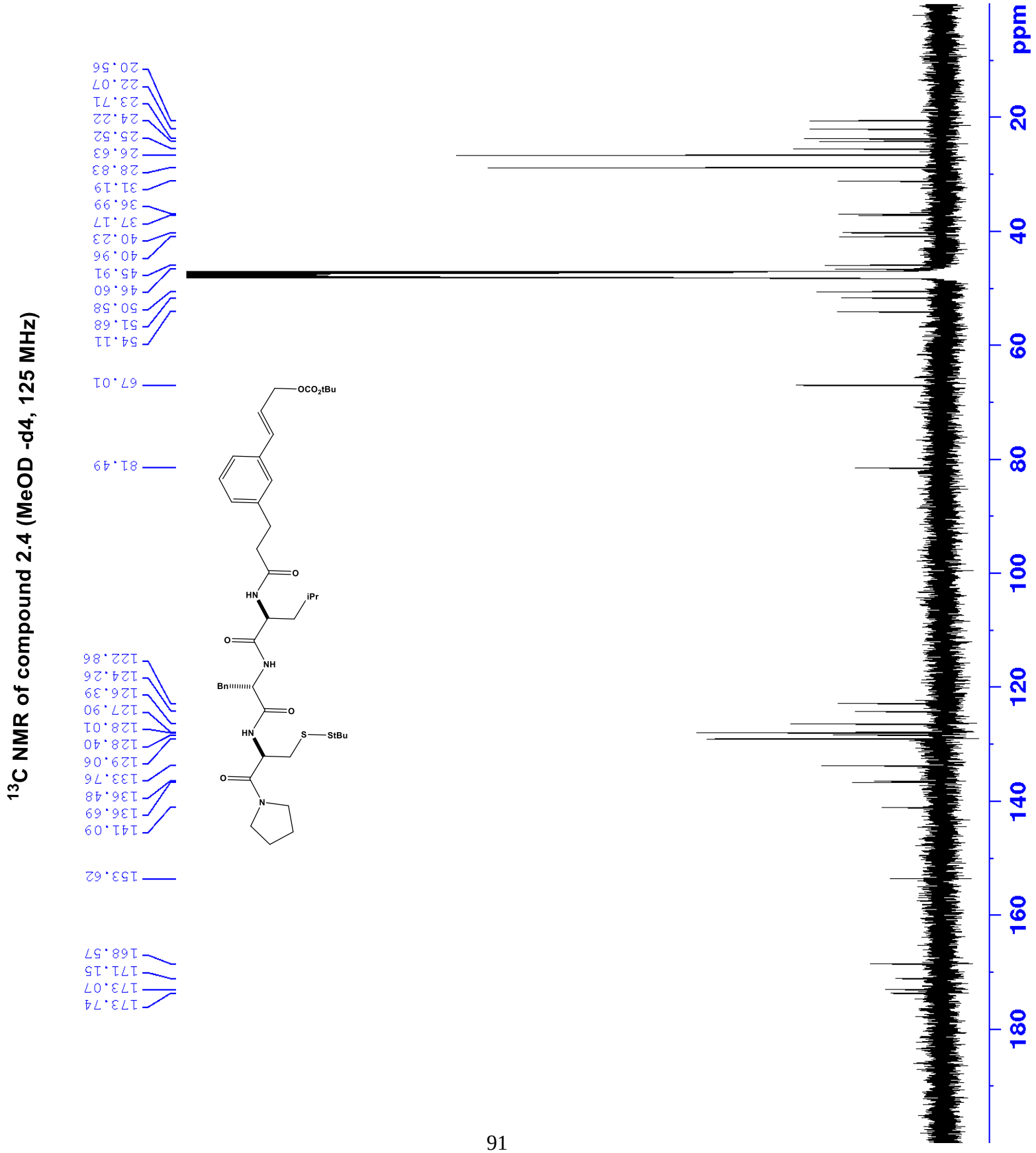
Macrocycle 2.58:
In a vial equipped with stir bar, **2.56** (57 mg, 64 µmol, 1.0 eq.) was dissolved in 10.9 ml of nitromethane at room temperature. 1.8 ml of TFA (10 vol%) was added and the reaction was stirred at room temperature for 1.5 hours. After this time the solvent was removed in vacuo, the residue was redissolved in 0.5 ml of DMF, and cooled 0°*C*. mCPBA (35 mg, 0.15 mmol, 2.4 eq.) was added and the reaction was stirred for 45 minutes. After this time the reaction quenched with DMS, the solvent was removed in vacuo and the residue was purified by preperative HPLC, affording 30.1 mg of **2.50** product (63% yield) as a white film.^{1}H NMR (DMSO-d_6, 500 MHz) 8.82 (d, J= 8.0 Hz, 1H), 8.03 (d, J= 8.4 Hz, 1H), 7.90-7.84 (m, 5H), 7.72 (t, J= 5.9 Hz, 1H), 7.70- 7.66 (m, 3H), 7.55-7.50 (m, 3H), 7.41-7.37 (m, 1H), 7.34-7.23 (m, 4H),

7.22-7.15 (m, 2H), 7.11, J= 7.2 Hz, 1H), 6.79 (d, J= 15.9 Hz, 1H), 6.40-6.31 (m, 1H), 5.03-4.93 (m, 1H), 4.53 (q, J= 7.8 Hz, 1H), 4.45-4.30 (m, 2H), 3.99-3.90 (m, 1H), 3.09 (dd, J= 15.7, 6.6 Hz, 1H), 3.02-2.93 (m, 2H), 1.91 (t, J= 7.4 Hz, 2H), 1.37-1.14 (m, 12H), 0.84 (t, J= 6.5 Hz, 3H), ^{13}C NMR (DMSO-d_6, 126MHz) δ 173.7, 169.7, 168.5, 166.6, 144.4, 139.4, 138.6, 136.7, 133.8, 133.1, 131.1, 129.5, 129.3, 128.5, 128.4, 59.3, 54.7, 53.3, 50.3, 42.0, 35.6, 31.7, 29.1, 29.0, 25.5, 22.6, 14.4 HRMS-ESI (m/z); [M+H] calcd. for $C_{33}H_{45}N_5O_6S$, 640.31; found 640.3.

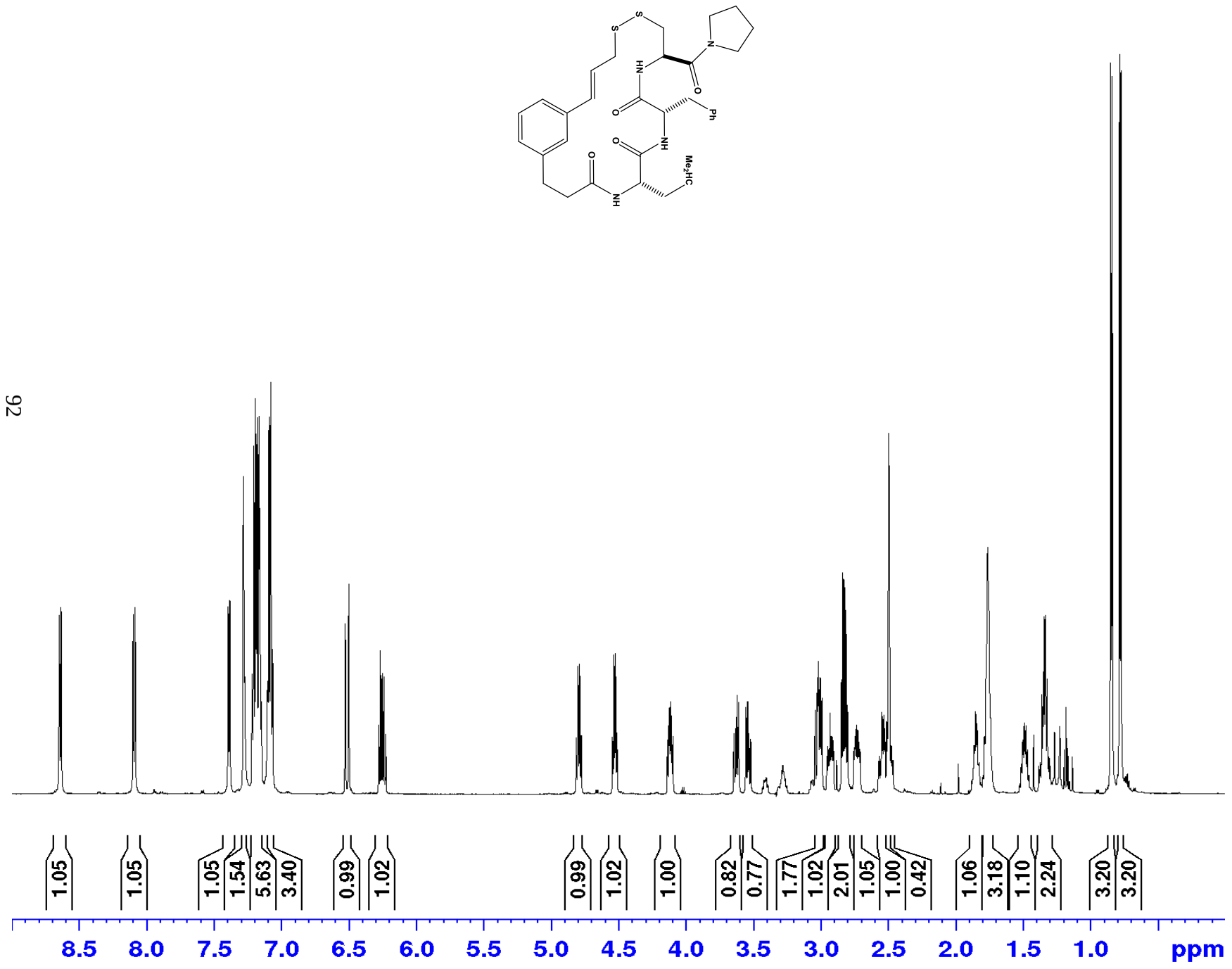
^{1}H NMR of compound 2.4 (MeOD -d4, 400 MHz)



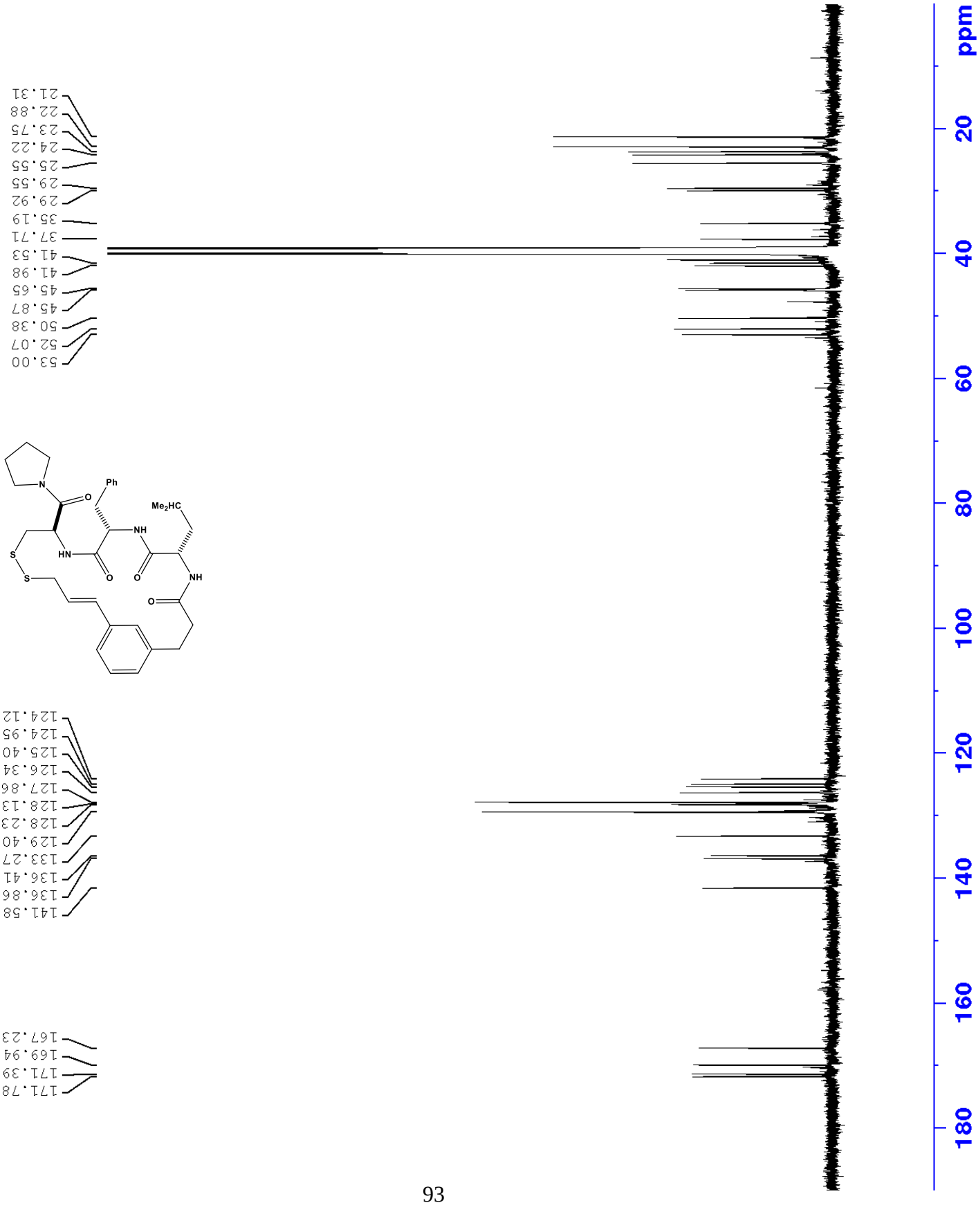
^{13}C NMR of compound 2.4 (MeOD -d4, 125 MHz)



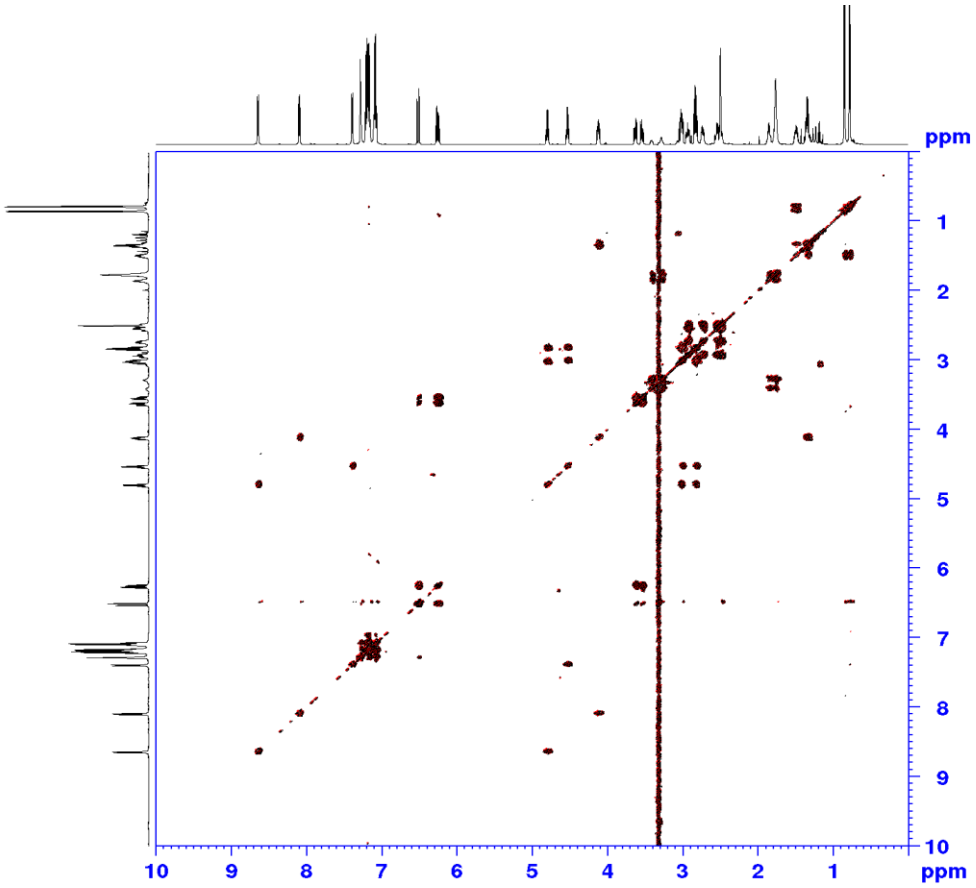
^{1}H NMR of macrcocycle 2.5 (DMSO-d6, 500 MHz)



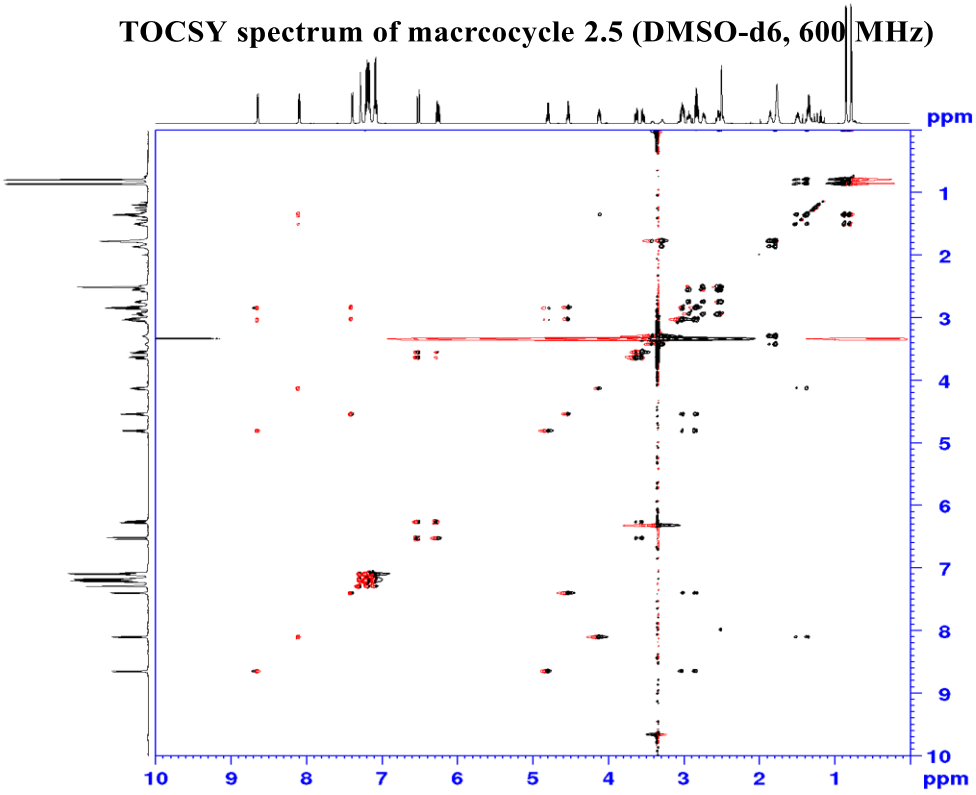
^{13}C NMR of macrocycle 2.5 (DMSO-d6, 125 MHz)



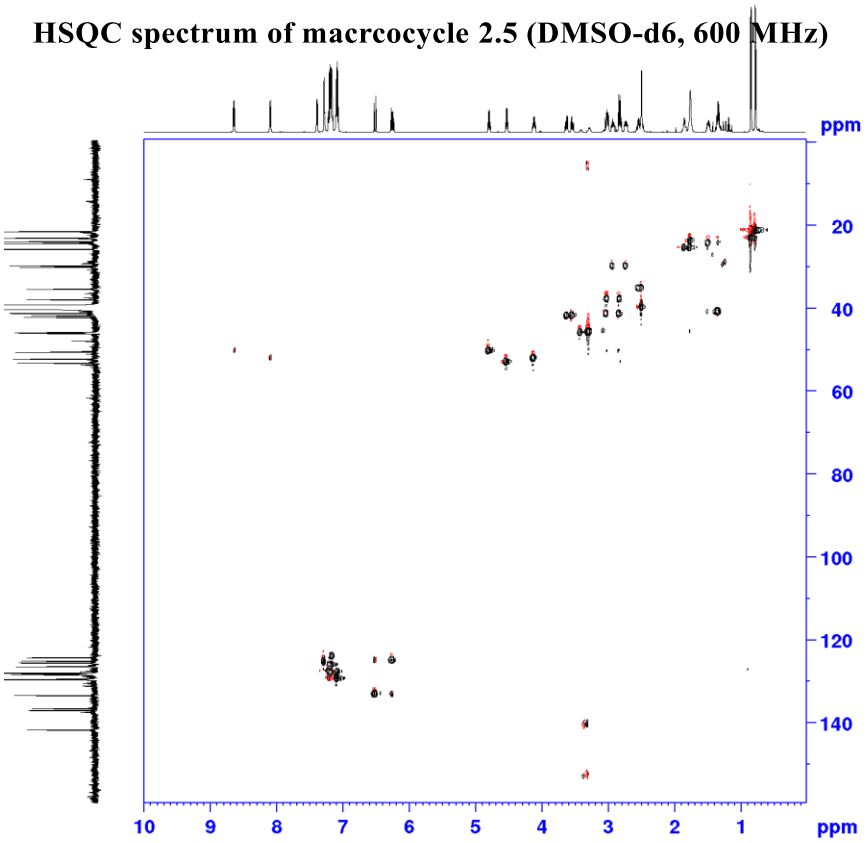
COSY spectrum of macrcocycle 2.5 (DMSO-d6, 600 MHz)



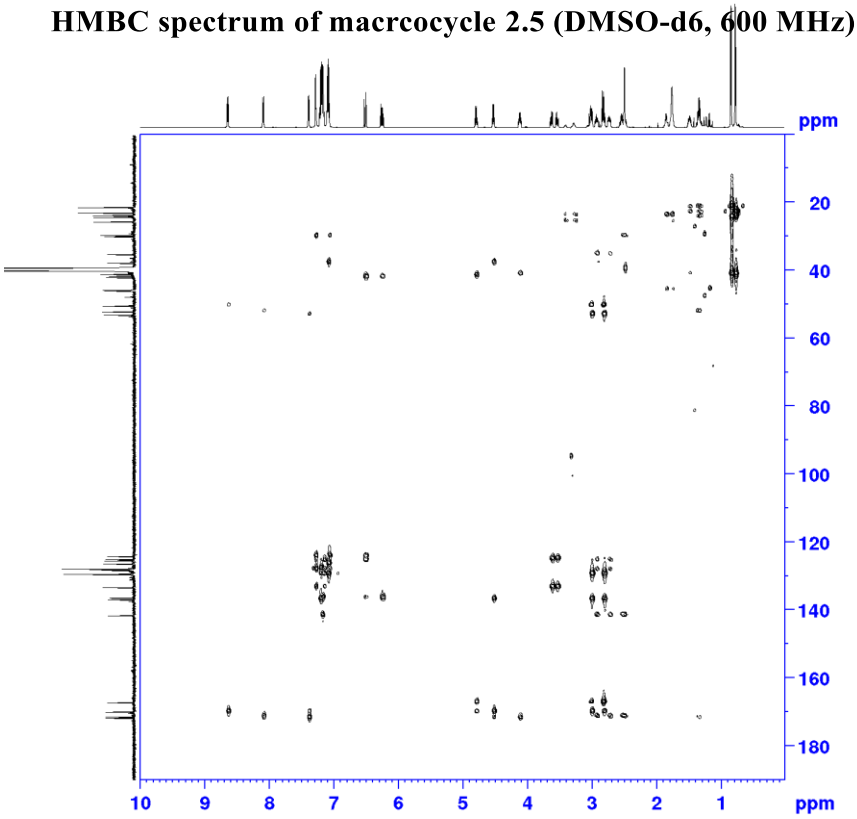
TOCSY spectrum of macrcocycle 2.5 (DMSO-d6, 600 MHz)



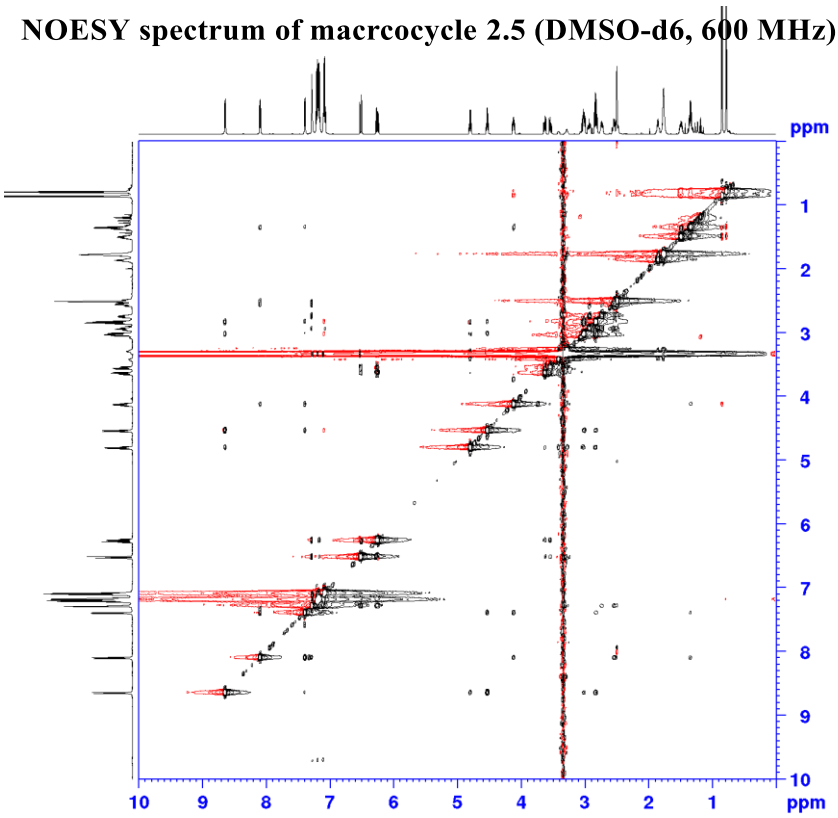
HSQC spectrum of macrcocycle 2.5 (DMSO-d6, 600 MHz)



HMBC spectrum of macrcocycle 2.5 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 2.5 (DMSO-d6, 600 MHz)



Chemical details

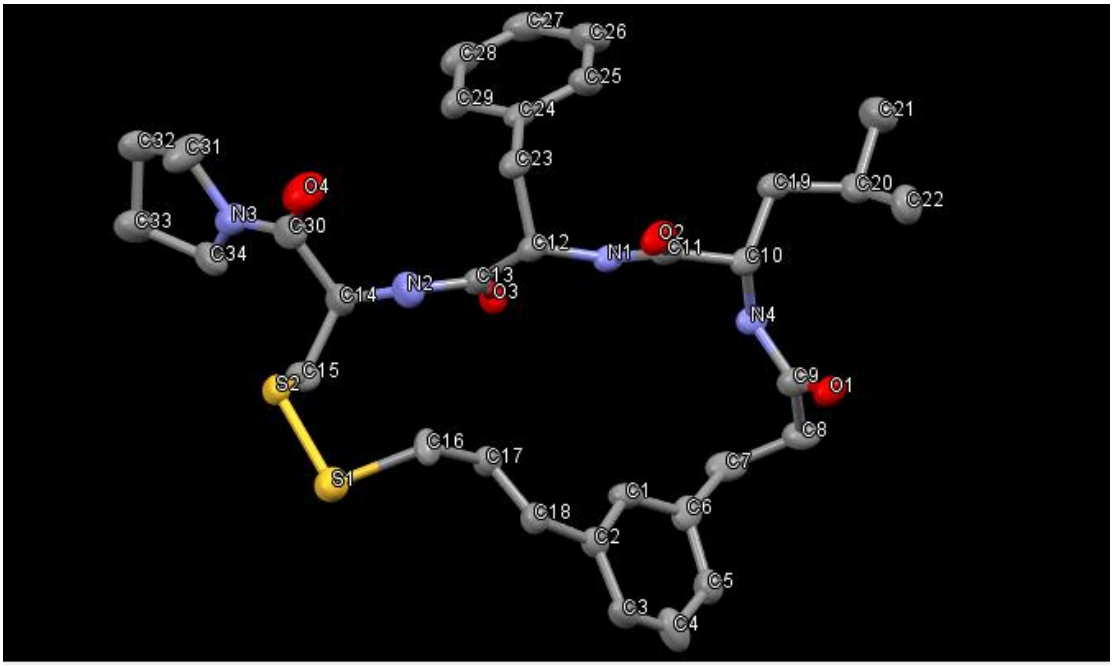
Formula	C_{34} H_{44} N_4 O_4 S_2

Crystal details

Space group	P 2_1 2_1 2_1 (19)
Unit cell	***a*** 5.31100(10)Å ***b*** 23.6454(5)Å ***c*** 26.0025(6)Å ***α*** 90° ***β*** 90° ***γ*** 90°
Cell volume	3265.41
Reduced cell	***a*** 5.311Å ***b*** 23.645Å ***c*** 26.003Å ***α*** 90.000° ***β*** 90.000° ***γ*** 90.000°
Z, Z'	4, 1
Habit	block
Disorder	C1,C16,C17,C18,C2,C3 and C16A,C17A,C18A,C1A,C2A,C3A disordered ov occupancies 0.511:0.489; C15,C32,O1,S2 and C15A,C32A,O1A,S2A disorder with occupancies 0.806:0.194.
Colour	colorless

Experimental details

R-factor (%)	3.34
Temperature (K)	100
Density (CCDC)	1.29544



Labeled Heavy Atoms 2.5 Crystal Structure

Atoms List of 2.5 Crystal Structure

Number	Label	Charge	SybylType	Xfrac + ESD	Yfrac + ESD	Zfrac + ESD	Symm. op.
1	S1	0	S.3	0.28625(16)	0.57473(3)	0.84069(3)	x,y,z
2	S2	0	S.3	0.34267(16)	0.49802(3)	0.87610(3)	x,y,z
3	O1	0	O.2	0.6941(9)	0.52085(19)	0.50154(13)	x,y,z
4	O2	0	O.2	0.2956(4)	0.40596(8)	0.60457(7)	x,y,z
5	O3	0	O.2	0.9304(4)	0.42421(8)	0.73606(7)	x,y,z
6	O4	0	O.2	0.4050(4)	0.34800(10)	0.84994(10)	x,y,z
7	N1	0	N.am	0.6597(4)	0.40843(8)	0.64832(8)	x,y,z
8	H1N	0	H	0.8245	0.4123	0.6476	x,y,z
9	N2	0	N.am	0.5795(5)	0.42301(10)	0.78617(9)	x,y,z
10	H2	0	H	0.4148	0.4269	0.7851	x,y,z
11	N3	0	N.am	0.7153(5)	0.35577(9)	0.90792(9)	x,y,z
12	N4	0	N.am	0.8766(4)	0.45781(9)	0.55668(8)	x,y,z
13	H4N	0	H	1.0070	0.4498	0.5762	x,y,z
14	C1	0	C.2	0.809(2)	0.5857(4)	0.6498(5)	x,y,z
15	H1	0	H	0.7997	0.5482	0.6627	x,y,z
16	C2	0	C.2	0.6315(16)	0.6242(5)	0.6689(3)	x,y,z
17	C3	0	C.2	0.648(2)	0.6794(4)	0.6525(4)	x,y,z
18	H3	0	H	0.5327	0.7077	0.6635	x,y,z
19	C4	0	C.2	0.8211(7)	0.68978(15)	0.62258(12)	x,y,z
20	H4	0	H	0.8353	0.7284	0.6128	x,y,z
21	C5	0	C.2	0.9992(6)	0.65414(12)	0.60079(11)	x,y,z
22	H5	0	H	1.1195	0.6691	0.5774	x,y,z
23	C6	0	C.2	1.0038(5)	0.59704(12)	0.61274(11)	x,y,z
24	C7	0	C.3	1.1919(6)	0.55857(12)	0.58757(12)	x,y,z
25	H7A	0	H	1.2118	0.5241	0.6088	x,y,z
26	H7B	0	H	1.3570	0.5779	0.5861	x,y,z
27	C8	0	C.3	1.1140(5)	0.54118(12)	0.53267(12)	x,y,z
28	H8A	0	H	1.0926	0.5758	0.5117	x,y,z
29	H8B	0	H	1.2523	0.5189	0.5172	x,y,z
30	C9	0	C.2	0.8747(5)	0.50700(11)	0.52980(11)	x,y,z
31	C10	0	C.3	0.6693(5)	0.41835(10)	0.55391(10)	x,y,z
32	H10	0	H	0.5464	0.4338	0.5284	x,y,z
33	C11	0	C.2	0.5285(5)	0.41093(10)	0.60447(10)	x,y,z
34	C12	0	C.3	0.5324(5)	0.39933(11)	0.69710(10)	x,y,z
35	H12	0	H	0.3803	0.4242	0.6979	x,y,z
36	C13	0	C.2	0.7035(5)	0.41701(10)	0.74114(10)	x,y,z
37	C14	0	C.3	0.7013(6)	0.42350(11)	0.83640(10)	x,y,z
38	H14	0	H	0.8849	0.4165	0.8308	x,y,z
39	C15	0	C.3	0.6758(7)	0.48032(14)	0.86461(14)	x,y,z
40	H15A	0	H	0.7549	0.5105	0.8438	x,y,z
41	H15B	0	H	0.7656	0.4783	0.8979	x,y,z
42	C16	0	C.3	0.206(4)	0.5540(10)	0.7711(6)	x,y,z
43	H16A	0	H	0.1530	0.5138	0.7703	x,y,z
44	H16B	0	H	0.0621	0.5772	0.7590	x,y,z
45	C17	0	C.2	0.4249(13)	0.5621(3)	0.7352(3)	x,y,z
46	H17	0	H	0.5558	0.5348	0.7339	x,y,z
47	C18	0	C.2	0.4352(12)	0.6079(3)	0.7051(2)	x,y,z
48	H18	0	H	0.2963	0.6331	0.7077	x,y,z
49	C19	0	C.3	0.7582(6)	0.36058(11)	0.53336(10)	x,y,z
50	H19A	0	H	0.8906	0.3456	0.5564	x,y,z
51	H19B	0	H	0.6150	0.3338	0.5341	x,y,z
52	C20	0	C.3	0.8620(6)	0.36353(12)	0.47862(11)	x,y,z
53	H20	0	H	1.0046	0.3911	0.4786	x,y,z
54	C21	0	C.3	0.9662(8)	0.30638(14)	0.46244(14)	x,y,z
55	H21A	0	H	0.8285	0.2789	0.4605	x,y,z
56	H21B	0	H	1.0906	0.2936	0.4877	x,y,z
57	H21C	0	H	1.0466	0.3098	0.4287	x,y,z

58	C22	0	C.3	0.6663(7)	0.38435(14)	0.44009(11)	x,y,z
59	H22A	0	H	0.7364	0.3825	0.4053	x,y,z
60	H22B	0	H	0.6207	0.4235	0.4481	x,y,z
61	H22C	0	H	0.5160	0.3604	0.4421	x,y,z
62	C23	0	C.3	0.4425(5)	0.33724(11)	0.70354(11)	x,y,z
63	H23A	0	H	0.3489	0.3339	0.7363	x,y,z
64	H23B	0	H	0.3243	0.3281	0.6753	x,y,z
65	C24	0	C.2	0.6530(5)	0.29448(10)	0.70339(10)	x,y,z
66	C25	0	C.2	0.7379(6)	0.27059(11)	0.65822(12)	x,y,z
67	H25	0	H	0.6601	0.2808	0.6266	x,y,z
68	C26	0	C.2	0.9335(7)	0.23224(12)	0.65799(15)	x,y,z
69	H26	0	H	0.9893	0.2164	0.6264	x,y,z
70	C27	0	C.2	1.0485(7)	0.21672(13)	0.70349(16)	x,y,z
71	H27	0	H	1.1830	0.1902	0.7035	x,y,z
72	C28	0	C.2	0.9661(7)	0.24001(13)	0.74861(14)	x,y,z
73	H28	0	H	1.0445	0.2296	0.7801	x,y,z
74	C29	0	C.2	0.7702(6)	0.27841(12)	0.74900(11)	x,y,z
75	H29	0	H	0.7149	0.2940	0.7807	x,y,z
76	C30	0	C.2	0.5946(6)	0.37199(13)	0.86552(12)	x,y,z
77	C31	0	C.3	0.6299(6)	0.30514(15)	0.93542(15)	x,y,z
78	H31A	0	H	0.5994	0.2735	0.9112	x,y,z
79	H31B	0	H	0.4731	0.3129	0.9548	x,y,z
80	C32	0	C.3	0.8505(9)	0.29107(17)	0.97264(19)	x,y,z
81	H32A	0	H	0.7873	0.2754	1.0055	x,y,z
82	H32B	0	H	0.9690	0.2637	0.9569	x,y,z
83	C33	0	C.3	0.9743(7)	0.34800(13)	0.98062(15)	x,y,z
84	H33A	0	H	0.8871	0.3695	1.0080	x,y,z
85	H33B	0	H	1.1533	0.3433	0.9904	x,y,z
86	C34	0	C.3	0.9519(7)	0.37792(13)	0.92974(12)	x,y,z
87	H34A	0	H	0.9426	0.4194	0.9346	x,y,z
88	H34B	0	H	1.0967	0.3690	0.9072	x,y,z
89	S2A	0	S.3	0.5891(8)	0.53888(17)	0.84246(17)	x,y,z
90	O1A	0	O.3	0.687(4)	0.5300(8)	0.5211(6)	x,y,z
91	C1A	0	C.3	0.847(2)	0.5685(4)	0.6463(4)	x,y,z
92	H1A	0	H	0.8598	0.5288	0.6513	x,y,z
93	C2A	0	C.3	0.6682(18)	0.6012(4)	0.6725(4)	x,y,z
94	C3A	0	C.3	0.6476(16)	0.6573(5)	0.6609(3)	x,y,z
95	H3A	0	H	0.5177	0.6781	0.6774	x,y,z
96	C15A	0	C.3	0.508(4)	0.4699(7)	0.8636(6)	x,y,z
97	H15C	0	H	0.5223	0.4676	0.9015	x,y,z
98	H15D	0	H	0.3317	0.4613	0.8540	x,y,z
99	C16A	0	C.3	0.179(5)	0.5643(11)	0.7776(8)	x,y,z
100	H16C	0	H	0.1819	0.5234	0.7694	x,y,z
101	H16D	0	H	0.0022	0.5775	0.7748	x,y,z
102	C17A	0	C.3	0.3399(15)	0.5959(4)	0.7396(3)	x,y,z
103	H17A	0	H	0.3225	0.6359	0.7379	x,y,z
104	C18A	0	C.3	0.4987(14)	0.5725(4)	0.7095(3)	x,y,z
105	H18A	0	H	0.5092	0.5324	0.7109	x,y,z
106	H31C	0	H	0.4471	0.3064	0.9428	x,y,z
107	H31D	0	H	0.6704	0.2701	0.9163	x,y,z
108	C32A	0	C.3	0.756(4)	0.3097(9)	0.9747(9)	x,y,z
109	H32C	0	H	0.8183	0.2713	0.9827	x,y,z
110	H32D	0	H	0.6366	0.3199	1.0024	x,y,z
111	H33C	0	H	1.1349	0.3271	0.9839	x,y,z
112	H33D	0	H	0.9541	0.3741	1.0101	x,y,z

Bond List for 2.5 Cysrtal Structure

Number	Atom1	Atom2	Type	Polymeric	Cyclicity	Length	SybylType
1	S1	S2	Unknown	no	cyclic	2.056(1)	1

2	S1	C16	Unknown	no	cyclic	1.92(2)	1
3	S2	C15	Unknown	no	cyclic	1.842(4)	1
4	O1	C9	Unknown	no	acyclic	1.252(5)	2
5	O2	C11	Unknown	no	acyclic	1.243(3)	2
6	O3	C13	Unknown	no	acyclic	1.224(3)	2
7	O4	C30	Unknown	no	acyclic	1.225(4)	2
8	N1	H1N	Unknown	no	acyclic	0.880 1	
9	N1	C11	Unknown	no	cyclic	1.338(3)	un
10	N1	C12	Unknown	no	cyclic	1.453(3)	1
11	N2	H2	Unknown	no	acyclic	0.880	1
12	N2	C13	Unknown	no	cyclic	1.351(4)	un
13	N2	C14	Unknown	no	cyclic	1.458(4)	1
14	N3	C30	Unknown	no	acyclic	1.332(4)	un
15	N3	C31	Unknown	no	cyclic	1.466(4)	1
16	N3	C34	Unknown	no	cyclic	1.475(4)	1
17	N4	H4N	Unknown	no	acyclic	0.879	1
18	N4	C9	Unknown	no	cyclic	1.357(3)	un
19	N4	C10	Unknown	no	cyclic	1.445(3)	1
20	C1	H1	Unknown	no	acyclic	0.95	1
21	C1	C2	Unknown	no	cyclic	1.40(1)	un
22	C1	C6	Unknown	no	cyclic	1.44(1)	un
23	C2	C3	Unknown	no	cyclic	1.38(1)	un
24	C2	C18	Unknown	no	cyclic	1.46(1)	un
25	C3	H3	Unknown	no	acyclic	0.95	1
26	C3	C4	Unknown	no	cyclic	1.23(1)	un
27	C4	H4	Unknown	no	acyclic	0.951	1
28	C4	C5	Unknown	no	cyclic	1.388(5)	un
29	C5	H5	Unknown	no	acyclic	0.950	1
30	C5	C6	Unknown	no	cyclic	1.386(4)	un
31	C6	C7	Unknown	no	cyclic	1.501(4)	1
32	C7	H7A	Unknown	no	acyclic	0.990	1
33	C7	H7B	Unknown	no	acyclic	0.990	1
34	C7	C8	Unknown	no	cyclic	1.542(4)	1
35	C8	H8A	Unknown	no	acyclic	0.990	1
36	C8	H8B	Unknown	no	acyclic	0.989	1
37	C8	C9	Unknown	no	cyclic	1.508(4)	1
38	C10	H10	Unknown	no	acyclic	1.000	1
39	C10	C11	Unknown	no	cyclic	1.523(4)	1
40	C10	C19	Unknown	no	acyclic	1.541(4)	1
41	C12	H12	Unknown	no	acyclic	0.999	1
42	C12	C13	Unknown	no	cyclic	1.520(4)	1
43	C12	C23	Unknown	no	acyclic	1.553(4)	1
44	C14	H14	Unknown	no	acyclic	1.000	1
45	C14	C15	Unknown	no	cyclic	1.537(4)	1
46	C14	C30	Unknown	no	acyclic	1.542(4)	1
47	C15	H15A	Unknown	no	acyclic	0.989	1
48	C15	H15B	Unknown	no	acyclic	0.989	1
49	C16	H16A	Unknown	no	acyclic	0.99	1
50	C16	H16B	Unknown	no	acyclic	0.99	1
51	C16	C17	Unknown	no	cyclic	1.50(2)	1
52	C17	H17	Unknown	no	acyclic	0.949	1
53	C17	C18	Unknown	no	cyclic	1.34(1)	un
54	C18	H18	Unknown	no	acyclic	0.951	1
55	C19	H19A	Unknown	no	acyclic	0.989	1
56	C19	H19B	Unknown	no	acyclic	0.990	1
57	C19	C20	Unknown	no	acyclic	1.528(4)	1
58	C20	H20	Unknown	no	acyclic	0.999	1
59	C20	C21	Unknown	no	acyclic	1.520(5)	1
60	C20	C22	Unknown	no	acyclic	1.525(4)	1
61	C21	H21A	Unknown	no	acyclic	0.980	1
62	C21	H21B	Unknown	no	acyclic	0.979	1
63	C21	H21C	Unknown	no	acyclic	0.979	1

64	C22	H22A	Unknown	no	acyclic	0.979	1
65	C22	H22B	Unknown	no	acyclic	0.979	1
66	C22	H22C	Unknown	no	acyclic	0.980	1
67	C23	H23A	Unknown	no	acyclic	0.989	1
68	C23	H23B	Unknown	no	acyclic	0.990	1
69	C23	C24	Unknown	no	acyclic	1.507(4)	1
70	C24	C25	Unknown	no	cyclic	1.379(4)	un
71	C24	C29	Unknown	no	cyclic	1.392(4)	un
72	C25	H25	Unknown	no	acyclic	0.951	1
73	C25	C26	Unknown	no	cyclic	1.379(4)	un
74	C26	H26	Unknown	no	acyclic	0.950 1	
75	C26	C27	Unknown	no	cyclic	1.381(6)	un
76	C27	H27	Unknown	no	acyclic	0.951	1
77	C27	C28	Unknown	no	cyclic	1.368(5)	un
78	C28	H28	Unknown	no	acyclic	0.951	1
79	C28	C29	Unknown	no	cyclic	1.381(5)	un
80	C29	H29	Unknown	no	acyclic	0.950	1
81	C31	H31A	Unknown	no	acyclic	0.991	1
82	C31	H31B	Unknown	no	acyclic	0.991	1
83	C31	C32	Unknown	no	cyclic	1.556(6)	1
84	C32	H32A	Unknown	no	acyclic	0.990	1
85	C32	H32B	Unknown	no	acyclic	0.991	1
86	C32	C33	Unknown	no	cyclic	1.512(5)	1
87	C33	H33A	Unknown	no	acyclic	0.990	1
88	C33	H33B	Unknown	no	acyclic	0.990	1
89	C33	C34	Unknown	no	cyclic	1.505(5)	1
90	C34	H34A	Unknown	no	acyclic	0.990	1
91	C34	H34B	Unknown	no	acyclic	0.990	1

Angle List for 2.5 crystal structure

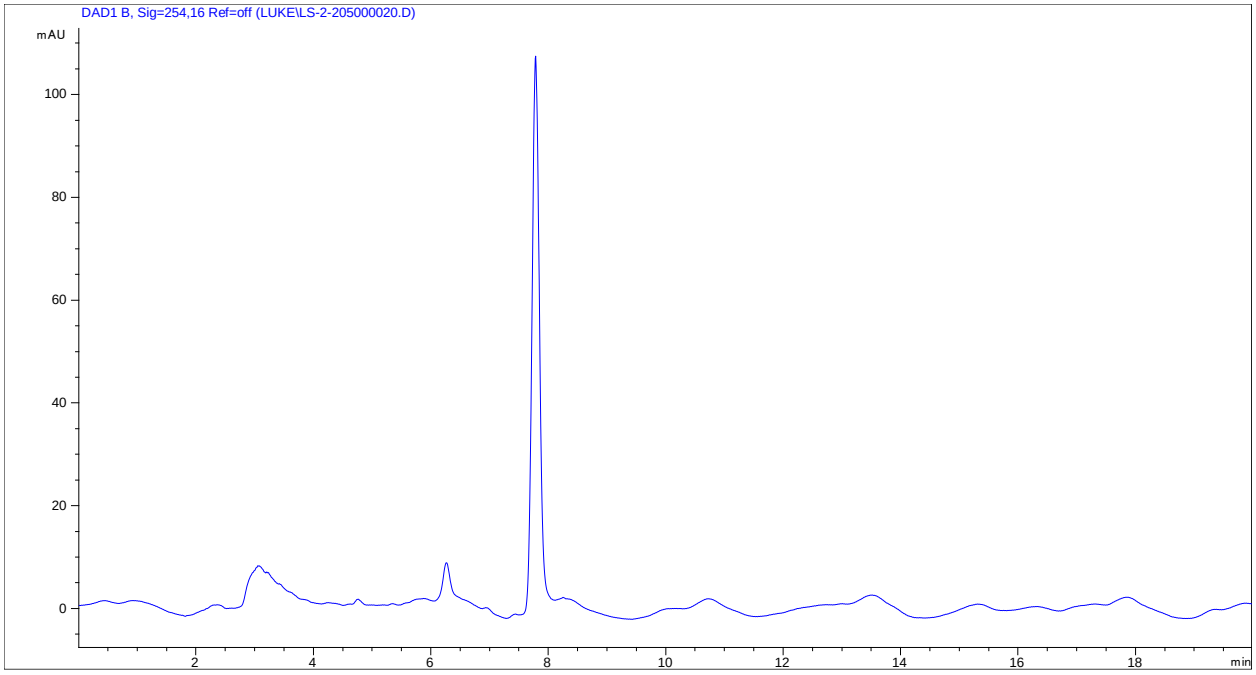
Number	Atom1	Atom2	Atom3	Angle
1	S2	S1	C16	103.2(6)
2	S1	S2	C15	105.5(1)
3	H1N	N1	C11	119.7
4	H1N	N1	C12	119.8
5	C11	N1	C12	120.5(2)
6	H2	N2	C13	117.9
7	H2	N2	C14	117.9
8	C13	N2	C14	124.1(2)
9	C30	N3	C31	119.3(3)
10	C30	N3	C34	128.8(3)
11	C31	N3	C34	111.5(2)
12	H4N	N4	C9	119.2
13	H4N	N4	C10	119.3
14	C9	N4	C10	121.5(2)
15	H1	C1	C2	117
16	H1	C1	C6	117
17	C2	C1	C6	126.9(9)
18	C1	C2	C3	117.6(9)
19	C1	C2	C18	122.6(8)
20	C3	C2	C18	119.8(8)
21	C2	C3	H3	122
22	C2	C3	C4	115.7(9)
23	H3	C3	C4	122
24	C3	C4	H4	114.9
25	C3	C4	C5	130.3(6)
26	H4	C4	C5	114.8
27	C4	C5	H5	119.6
28	C4	C5	C6	120.8(3)
29	H5	C5	C6	119.6
30	C1	C6	C5	108.6(5)

31	C1	C6	C7	131.1(5)
32	C5	C6	C7	120.3(3)
33	C6	C7	H7A	109.1
34	C6	C7	H7B	109.1
35	C6	C7	C8	112.7(2)
36	H7A	C7	H7B	107.9
37	H7A	C7	C8	109.0
38	H7B	C7	C8	109.0
39	C7	C8	H8A	108.7
40	C7	C8	H8B	108.6
41	C7	C8	C9	114.5(2)
42	H8A	C8	H8B	107.6
43	H8A	C8	C9	108.6
44	H8B	C8	C9	108.7
45	O1	C9	N4	122.2(3)
46	O1	C9	C8	122.3(3)
47	N4	C9	C8	115.3(2)
48	N4	C10	H10	107.1
49	N4	C10	C11	113.9(2)
50	N4	C10	C19	110.9(2)
51	H10	C10	C11	107.1
52	H10	C10	C19	107.1
53	C11	C10	C19	110.4(2)
54	O2	C11	N1	120.8(2)
55	O2	C11	C10	120.1(2)
56	N1	C11	C10	119.0(2)
57	N1	C12	H12	107.9
58	N1	C12	C13	109.8(2)
59	N1	C12	C23	112.2(2)
60	H12	C12	C13	107.8
61	H12	C12	C23	107.8
62	C13	C12	C23	111.3(2)
63	O3	C13	N2	124.0(2)
64	O3	C13	C12	123.0(2)
65	N2	C13	C12	113.0(2)
66	N2	C14	H14	107.5
67	N2	C14	C15	113.3(2)
68	N2	C14	C30	105.7(2)
69	H14	C14	C15	107.5
70	H14	C14	C30	107.4
71	C15	C14	C30	115.1(2)
72	S2	C15	C14	111.1(2)
73	S2	C15	H15A	109.4
74	S2	C15	H15B	109.4
75	C14	C15	H15A	109.4
76	C14	C15	H15B	109.4
77	H15A	C15	H15B	108.0
78	S1	C16	H16A	109
79	S1	C16	H16B	109
80	S1	C16	C17	112(1)
81	H16A	C16	H16B	108
82	H16A	C16	C17	109
83	H16B	C16	C17	109
84	C16	C17	H17	120
85	C16	C17	C18	120(1)
86	H17	C17	C18	120.0
87	C2	C18	C17	128.4(7)
88	C2	C18	H18	115.8
89	C17	C18	H18	115.7
90	C10	C19	H19A	109.0
91	C10	C19	H19B	109.0
92	C10	C19	C20	113.1(2)

93	H19A	C19	H19B	107.8
94	H19A	C19	C20	108.9
95	H19B	C19	C20	108.9
96	C19	C20	H20	107.7
97	C19	C20	C21	110.4(3)
98	C19	C20	C22	112.4(2)
99	H20	C20	C21	107.7
100	H20	C20	C22	107.8
101	C21	C20	C22	110.7(3)
102	C20	C21	H21A	109.4
103	C20	C21	H21B	109.5
104	C20	C21	H21C	109.5
105	H21A	C21	H21B	109.5
106	H21A	C21	H21C	109.5
107	H21B	C21	H21C	109.4
108	C20	C22	H22A	109.5
109	C20	C22	H22B	109.5
110	C20	C22	H22C	109.5
111	H22A	C22	H22B	109.4
112	H22A	C22	H22C	109.5
113	H22B	C22	H22C	109.5
114	C12	C23	H23A	108.8
115	C12	C23	H23B	108.7
116	C12	C23	C24	113.9(2)
117	H23A	C23	H23B	107.6
118	H23A	C23	C24	108.7
119	H23B	C23	C24	108.8
120	C23	C24	C25	121.3(2)
121	C23	C24	C29	120.8(2)
122	C25	C24	C29	117.9(2)
123	C24	C25	H25	119.3
124	C24	C25	C26	121.3(3)
125	H25	C25	C26	119.4
126	C25	C26	H26	119.9
127	C25	C26	C27	120.3(3)
128	H26	C26	C27	119.9
129	C26	C27	H27	120.5
130	C26	C27	C28	119.1(3)
131	H27	C27	C28	120.4
132	C27	C28	H28	119.6
133	C27	C28	C29	120.8(3)
134	H28	C28	C29	119.6
135	C24	C29	C28	120.7(3)
136	C24	C29	H29	119.7
137	C28	C29	H29	119.6
138	O4	C30	N3	122.4(3)
139	O4	C30	C14	120.4(3)
140	N3	C30	C14	117.2(3)
141	N3	C31	H31A	110.9
142	N3	C31	H31B	110.9
143	N3	C31	C32	104.2(3)
144	H31A	C31	H31B	109.0
145	H31A	C31	C32	110.9
146	H31B	C31	C32	110.9
147	C31	C32	H32A	111.2
148	C31	C32	H32B	111.2
149	C31	C32	C33	102.9(3)
150	H32A	C32	H32B	109.1
151	H32A	C32	C33	111.2
152	H32B	C32	C33	111.2
153	C32	C33	H33A	110.6
154	C32	C33	H33B	110.7

155	C32	C33	C34	105.3(3)
156	H33A	C33	H33B	108.8
157	H33A	C33	C34	110.7
158	H33B	C33	C34	110.8
159	N3	C34	C33	103.8(3)
160	N3	C34	H34A	111.0
161	N3	C34	H34B	111.0
162	C33	C34	H34A	110.9
163	C33	C34	H34B	111.0
164	H34A	C34	H34B	109.0

2.5 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control
    Column Flow : 15.000 ml/min
    Stoptime : 20.00 min
    Posttime : Off

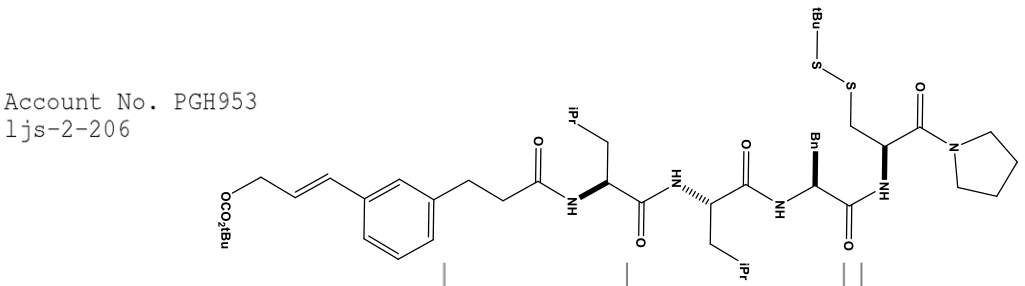
PressureLimits
    Minimum Pressure : 0 bar
    Maximum Pressure : 400 bar

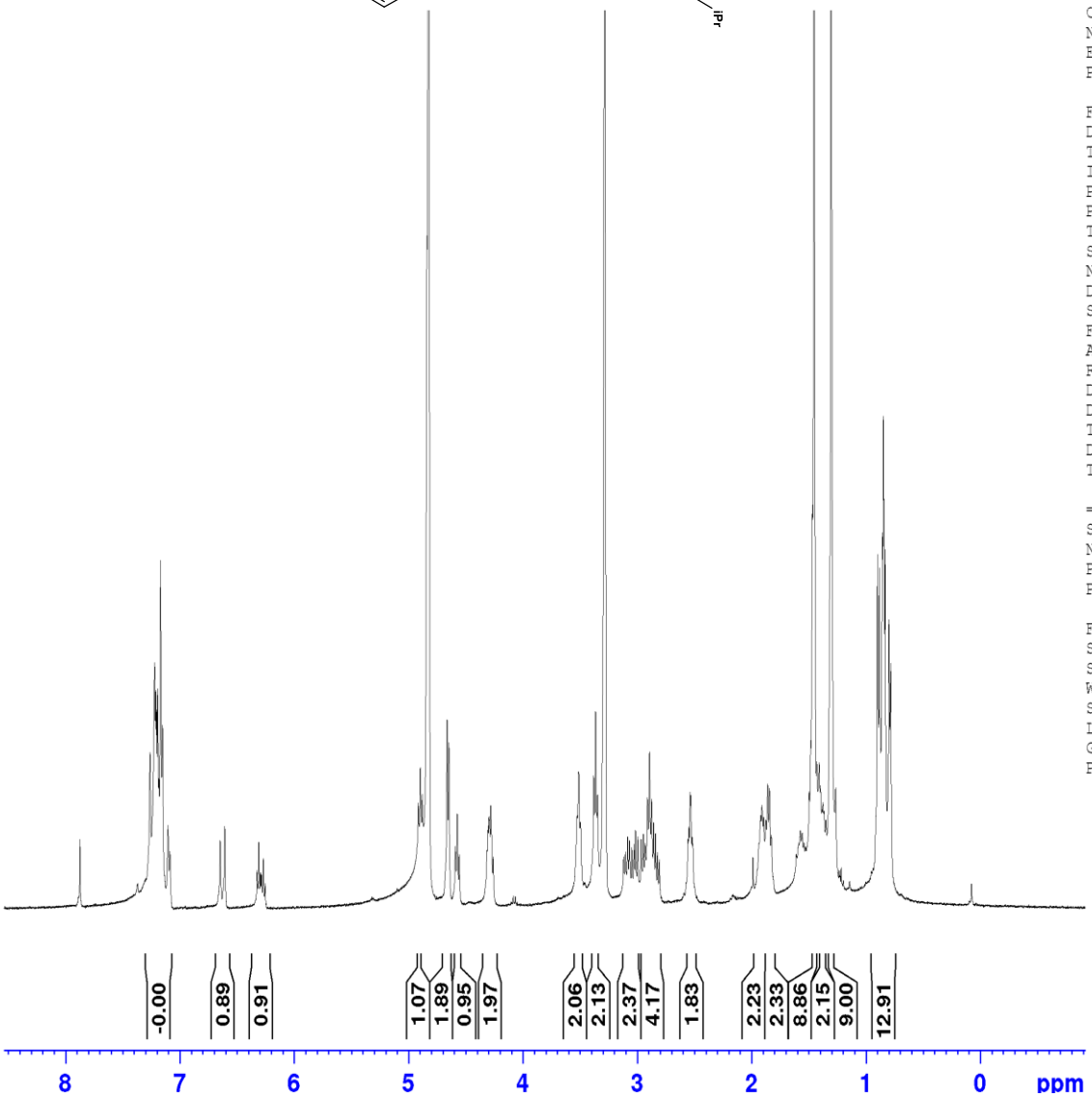
Auxiliary
    Flow Ramp : 800.000 ml/min^2
    Compressibility : 75*10^-6/bar

Timetable

Time	Solv.B	Flow	Pressure
0.00	65.0	10.000	
2.00	65.0	18.000	
14.00	95.0	18.000	
16.00	100.0	18.000	
20.00	35.0	18.000	

^{1}H NMR of compound 2.6 (MeOD -d4, 500 MHz)





Account No. PGH953
ljs-2-206

BRUKER

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Current Data Parameters
NAME          ljs-2-206H
EXPNO                480
PROCNO                 1

F2 - Acquisition Parameters
Date_           20171005
Time               20.47
INSTRUM            av400
PROBHD   5 mm PABBO BB/
PULPROG             zg30
TD                 52882
SOLVENT             MeOD
NS                    40
DS                     0
SWH             8012.820 Hz
FIDRES          0.151523 Hz
AQ              3.2998369 sec
RG                155.85
DW                62.400 usec
DE                 6.50 usec
TE                298.2 K
D1           2.00000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         400.1324008 MHz
NUC1                   1H
P1                 15.00 usec
PLW1         13.00000000 W

F2 - Processing parameters
SI                 65536
SF           400.1300184 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
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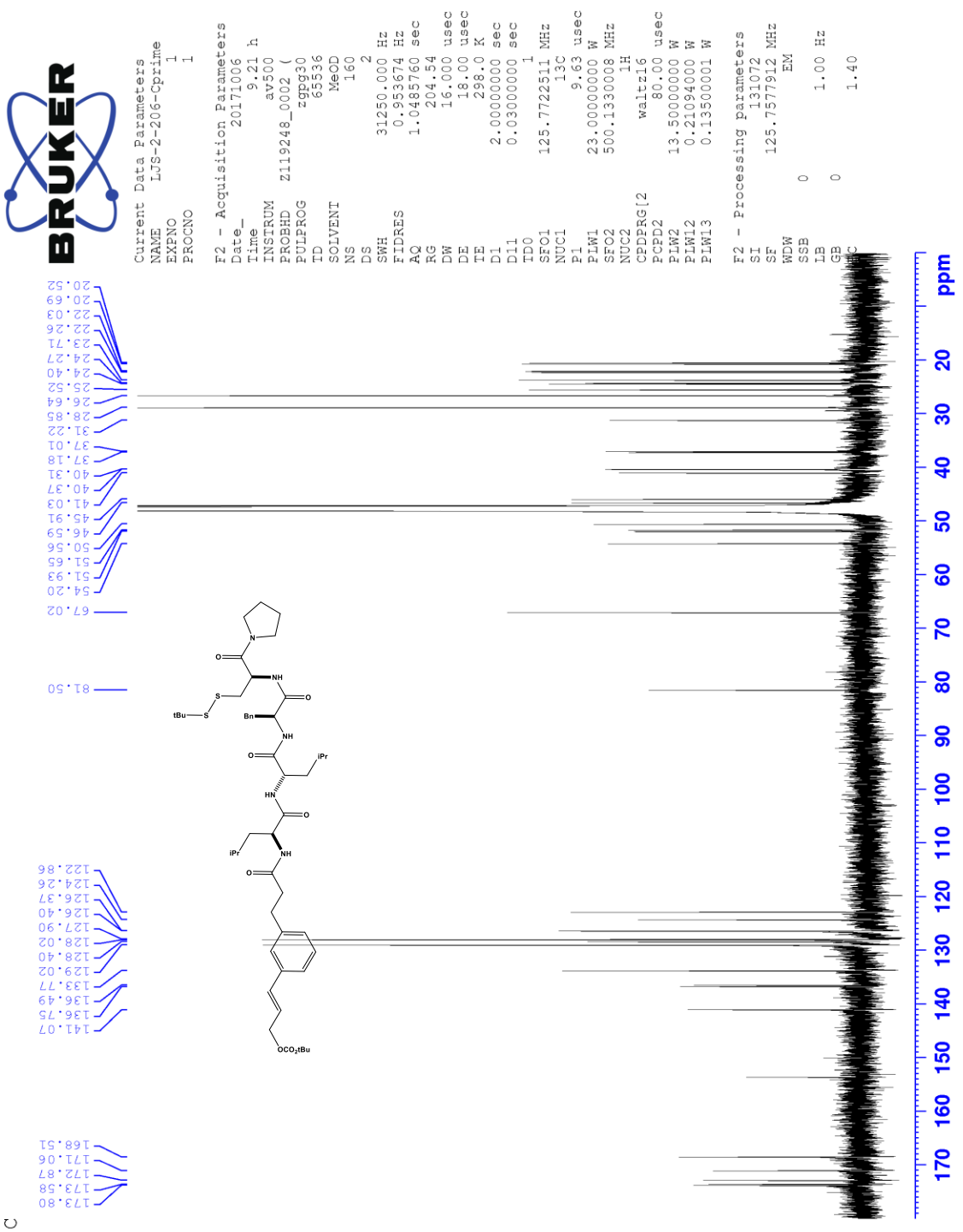
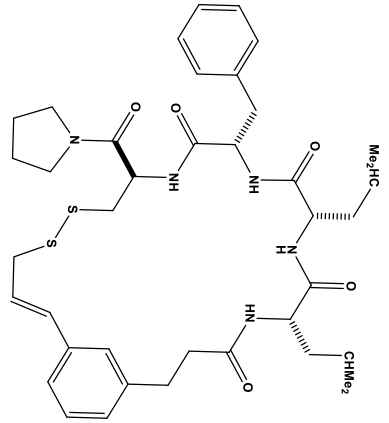
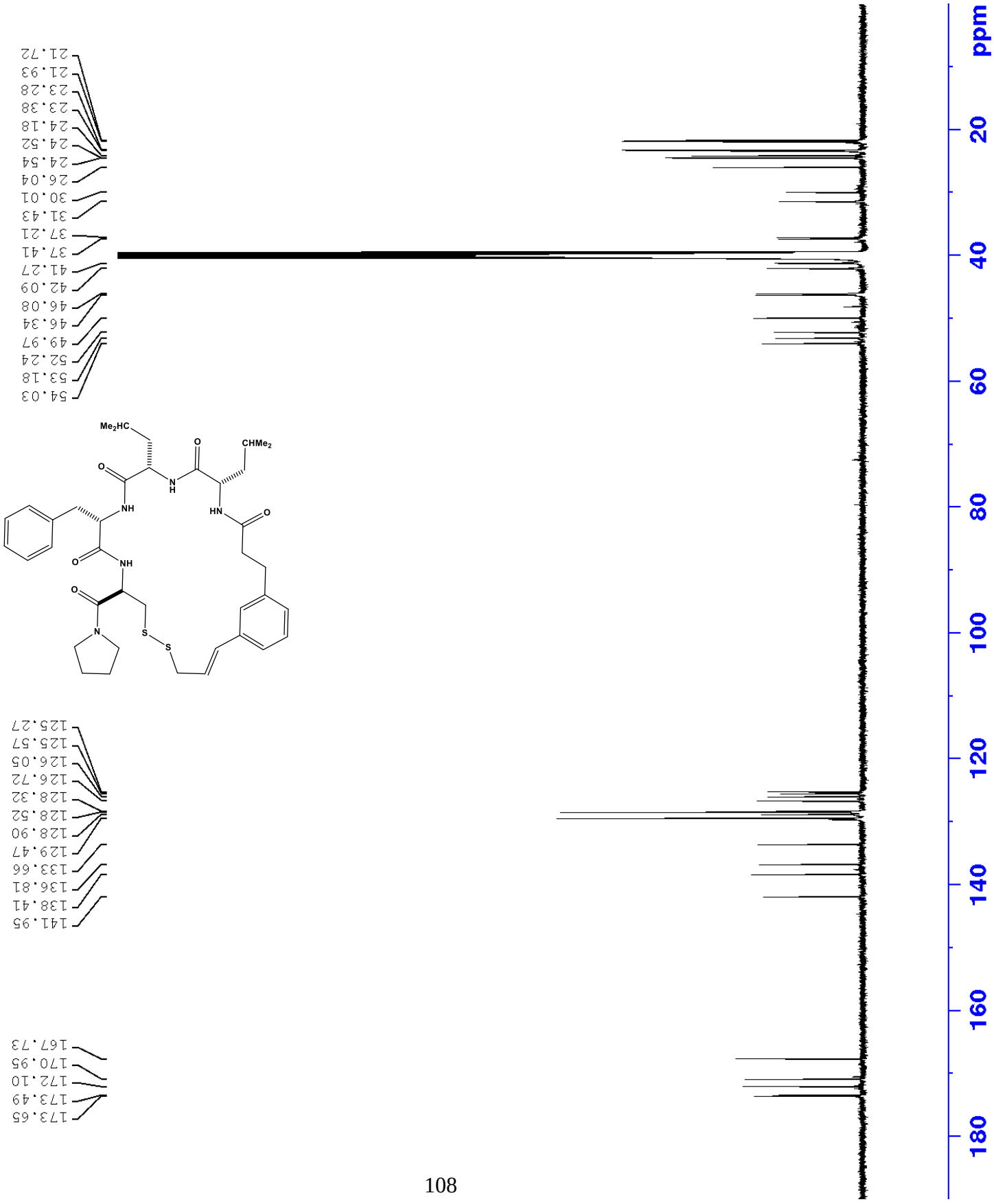
^{13}C NMR of compound 2.6 (MeOD -d4, 125 MHz)



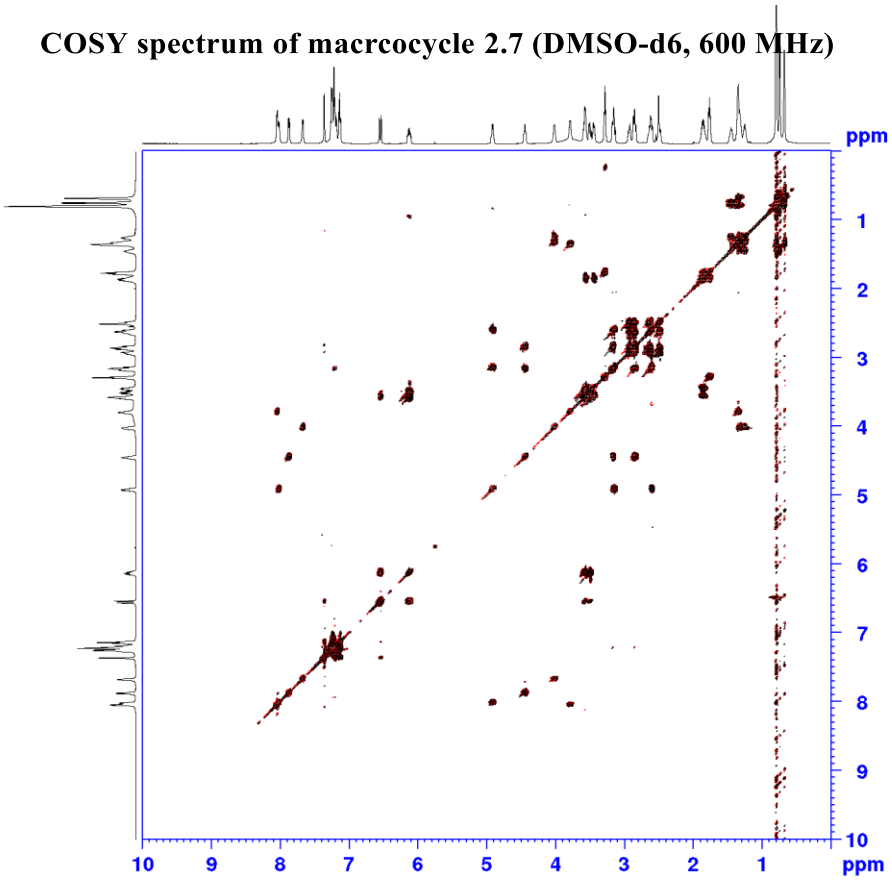
^{1}H NMR of macrcocycle 2.7 (DMSO-d6, 500 MHz)



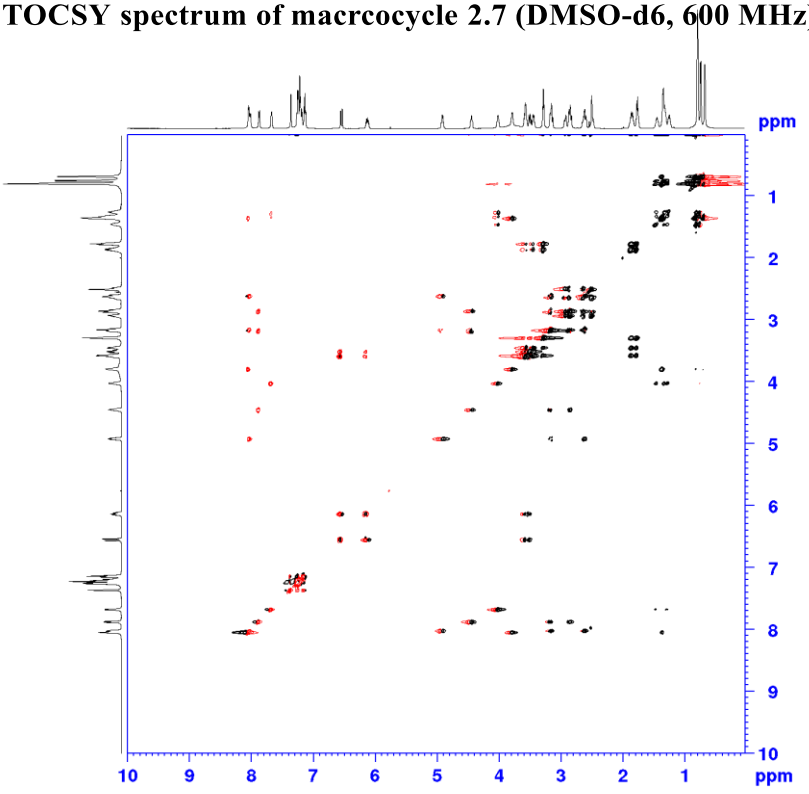
^{13}C NMR of macrcocycle 2.7 (DMSO-d6, 125 MHz)



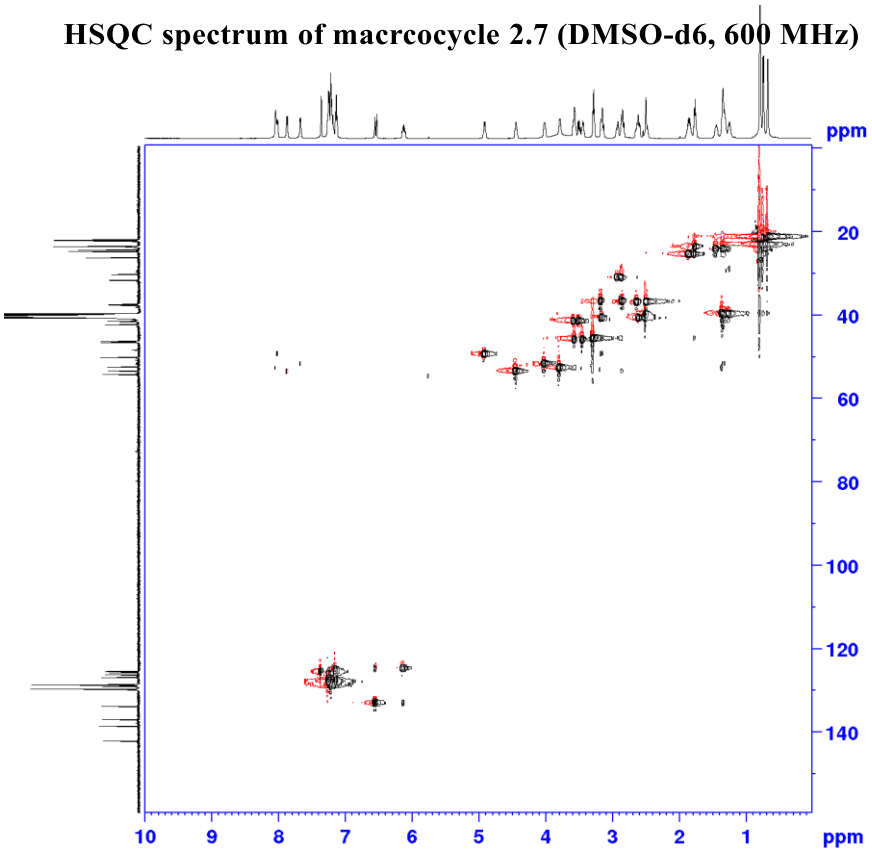
COSY spectrum of macrcocycle 2.7 (DMSO-d6, 600 MHz)



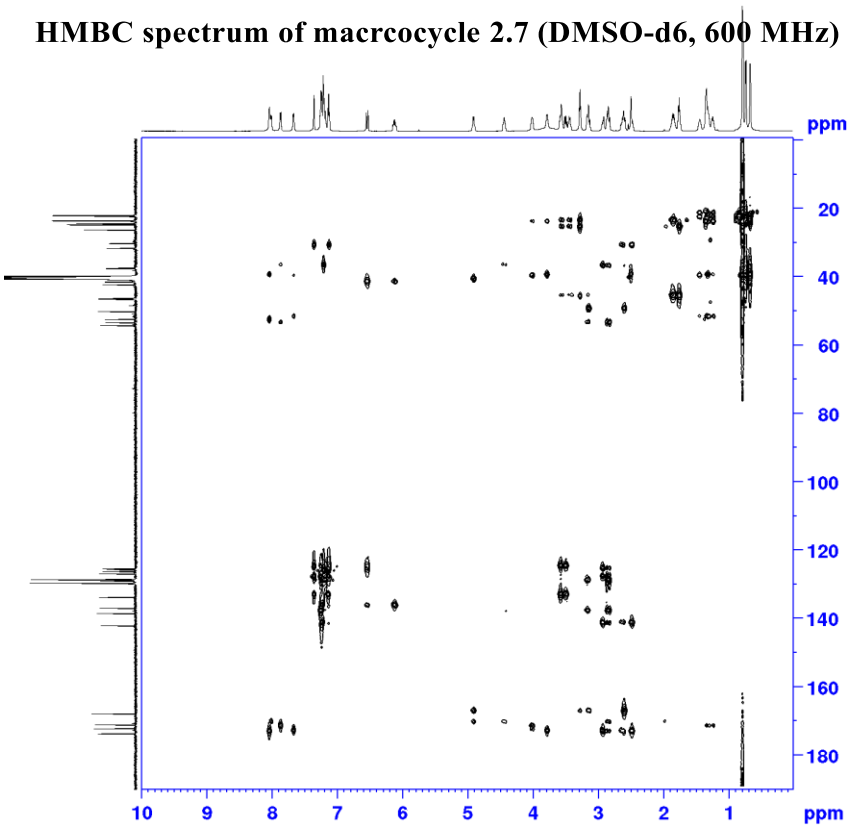
TOCSY spectrum of macrcocycle 2.7 (DMSO-d6, 600 MHz)



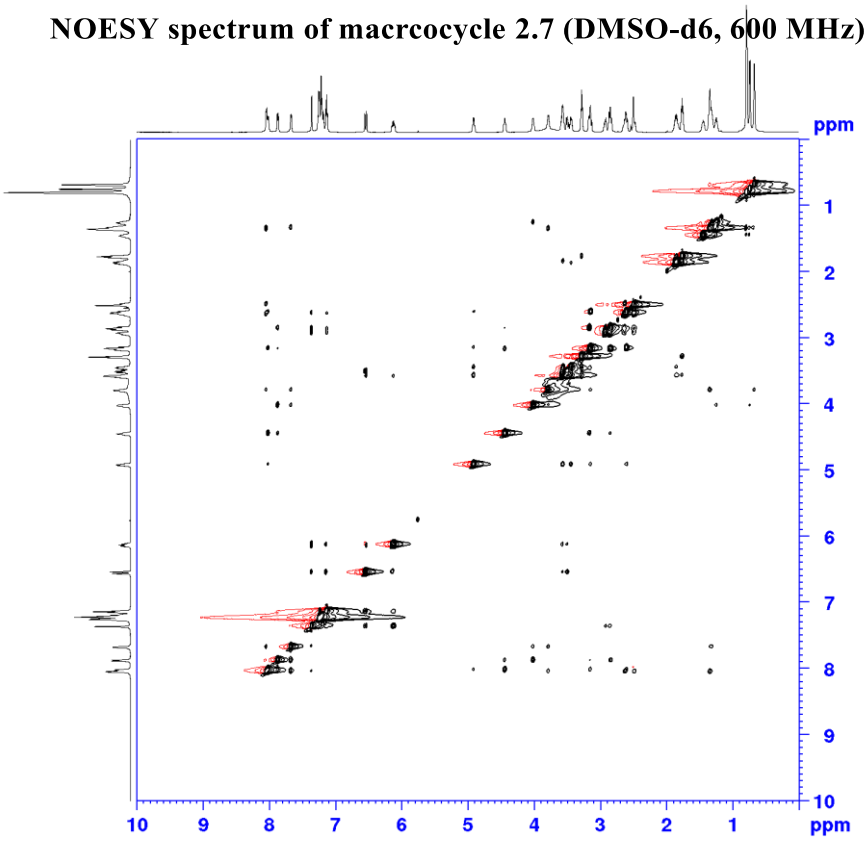
HSQC spectrum of macrcocycle 2.7 (DMSO-d6, 600 MHz)



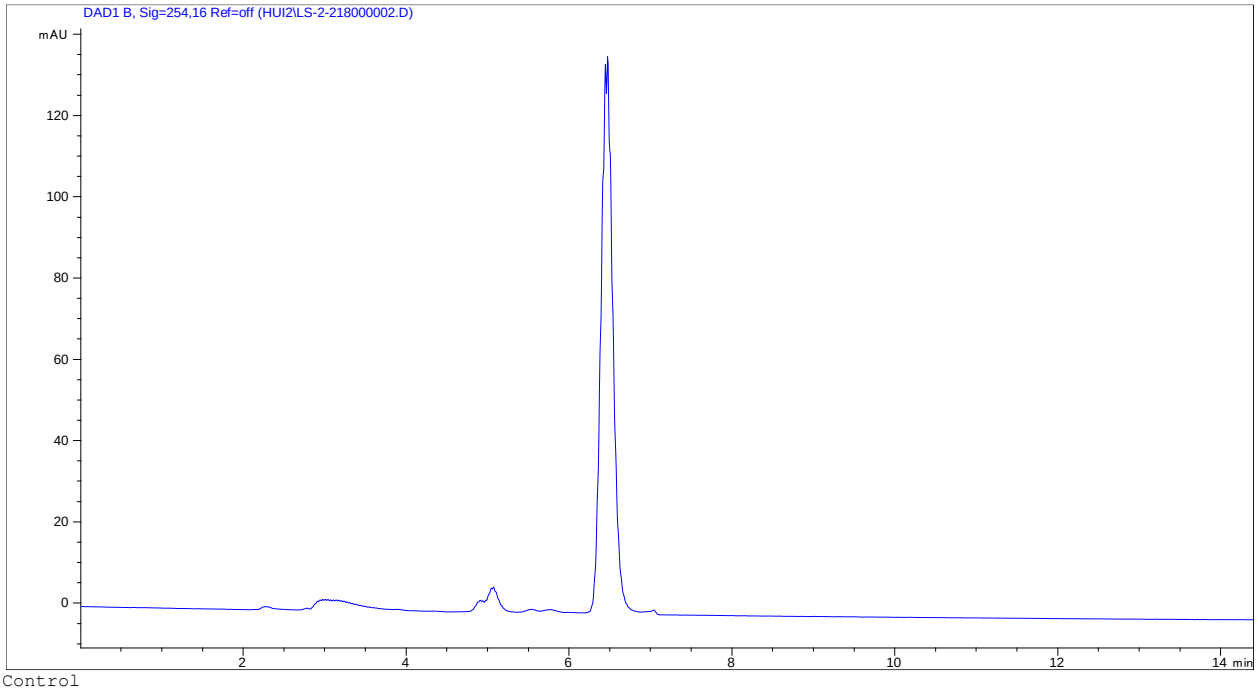
HMBC spectrum of macrcocycle 2.7 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 2.7 (DMSO-d6, 600 MHz)

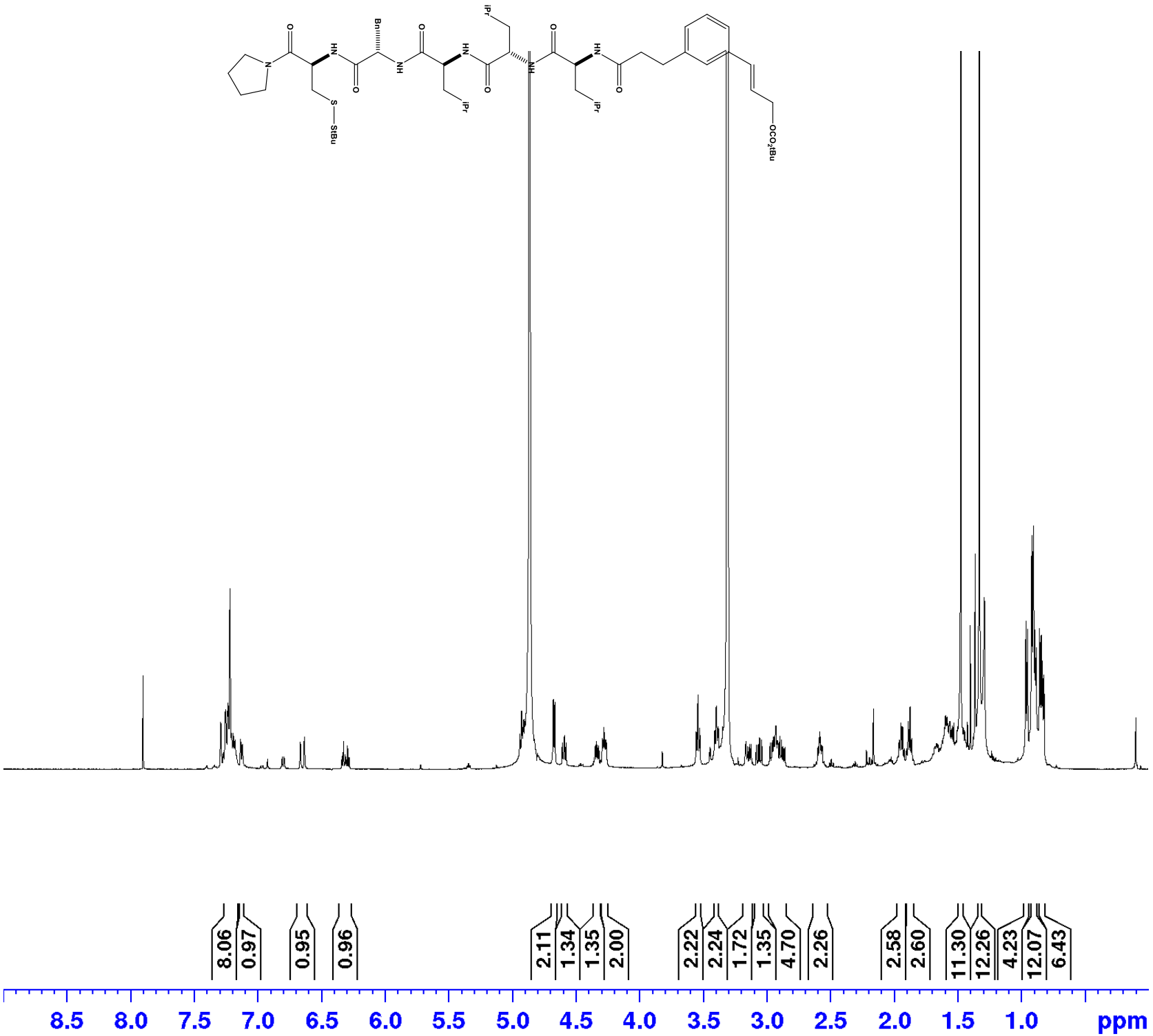


2.7 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

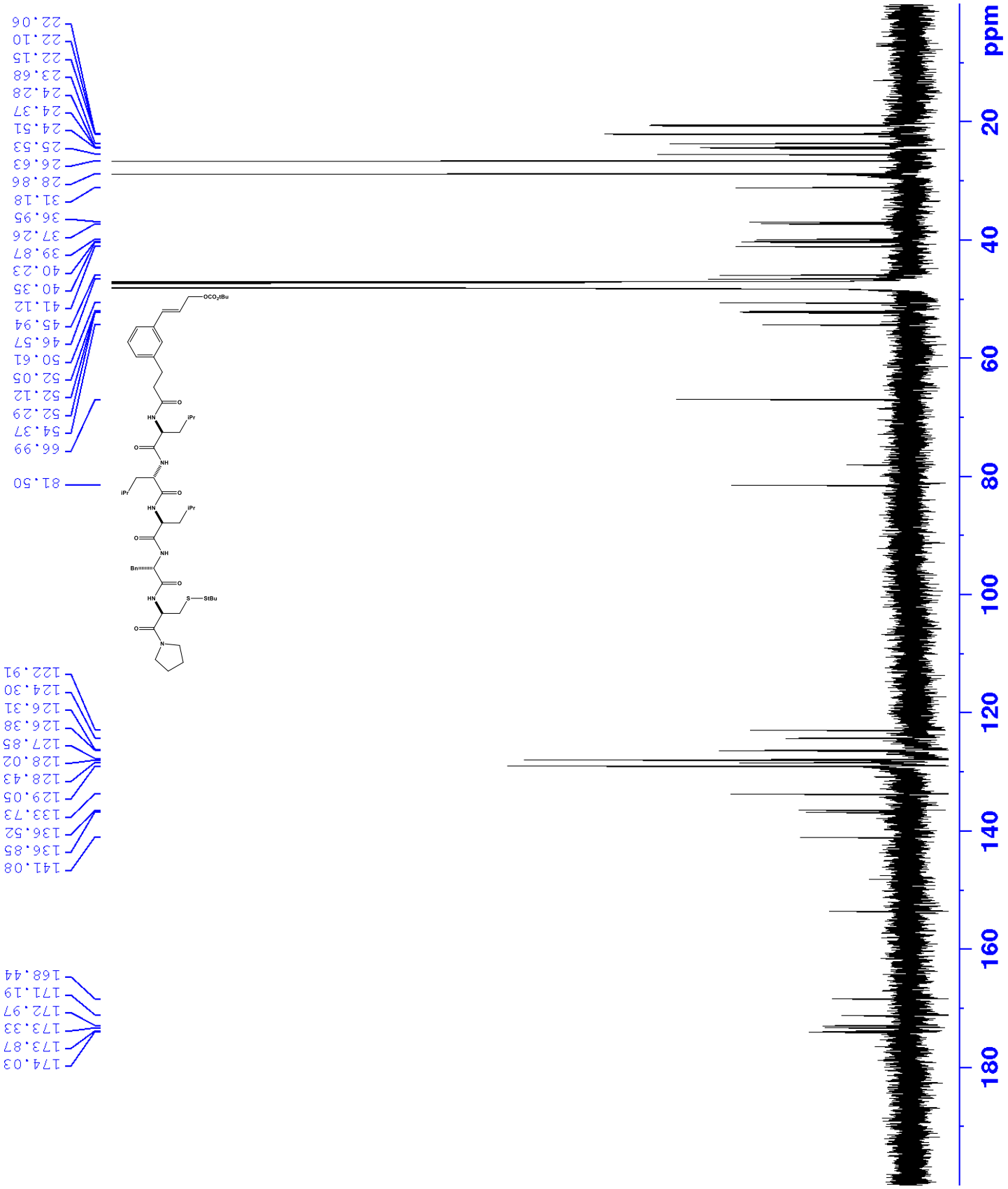



```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         14.00 min
    Posttime               :      Off


PressureLimits
    Minimum Pressure       :        0 bar
    Maximum Pressure       :      400 bar

Purge

Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar


Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00   80.0    10.000
         2.00   80.0    18.000
        10.00  100.0    18.000
        12.00  100.0    18.000
        14.00   35.0    18.000
\
```

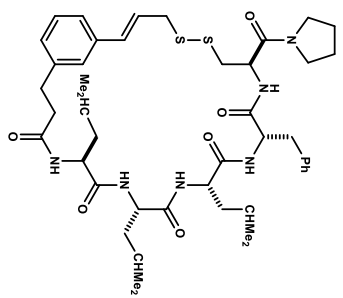
^{1}H NMR of compound 2.8 (MeOD -d4, 500 MHz)



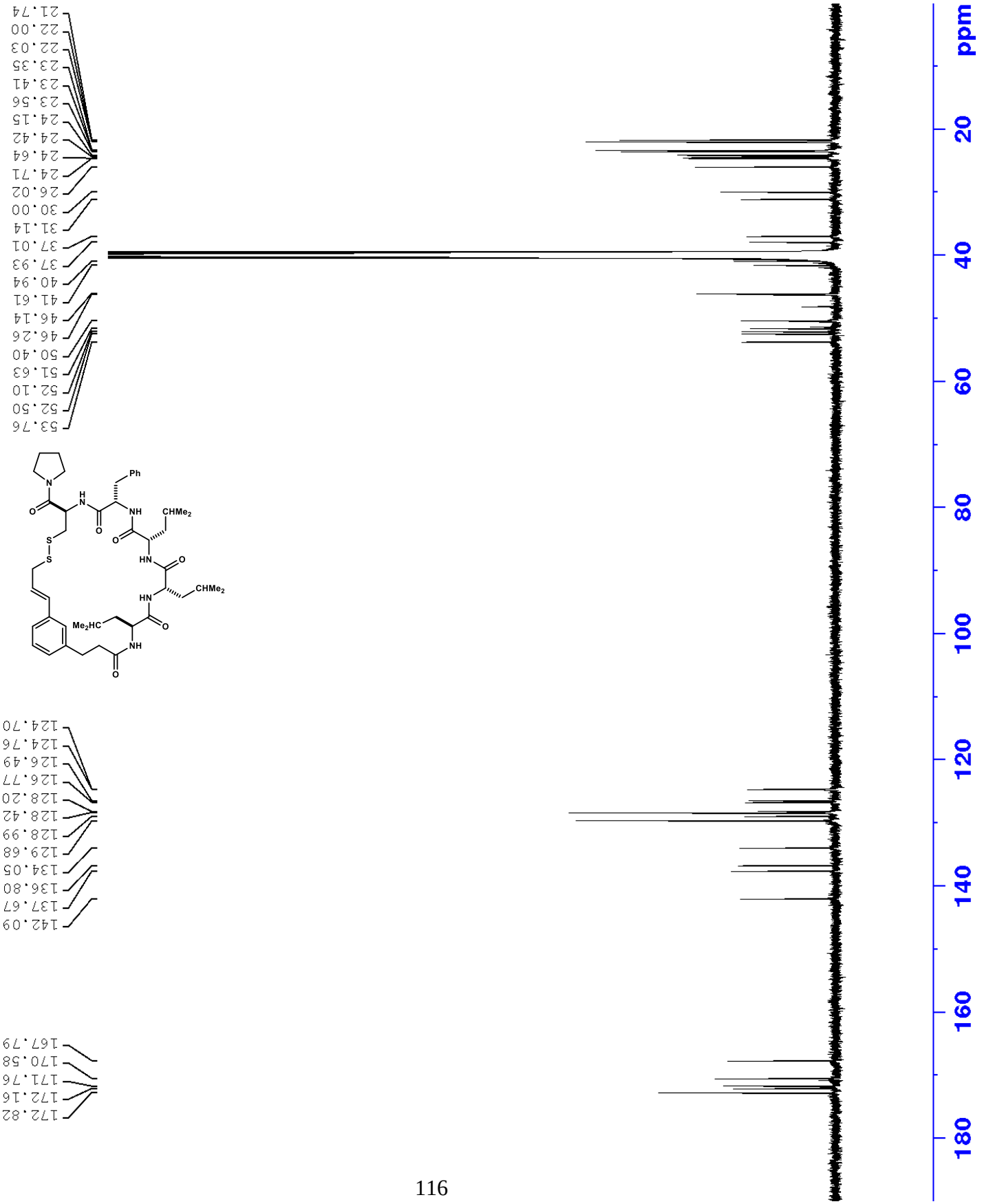
^{13}C NMR of compound 2.8 (MeOD -d4, 125 MHz)



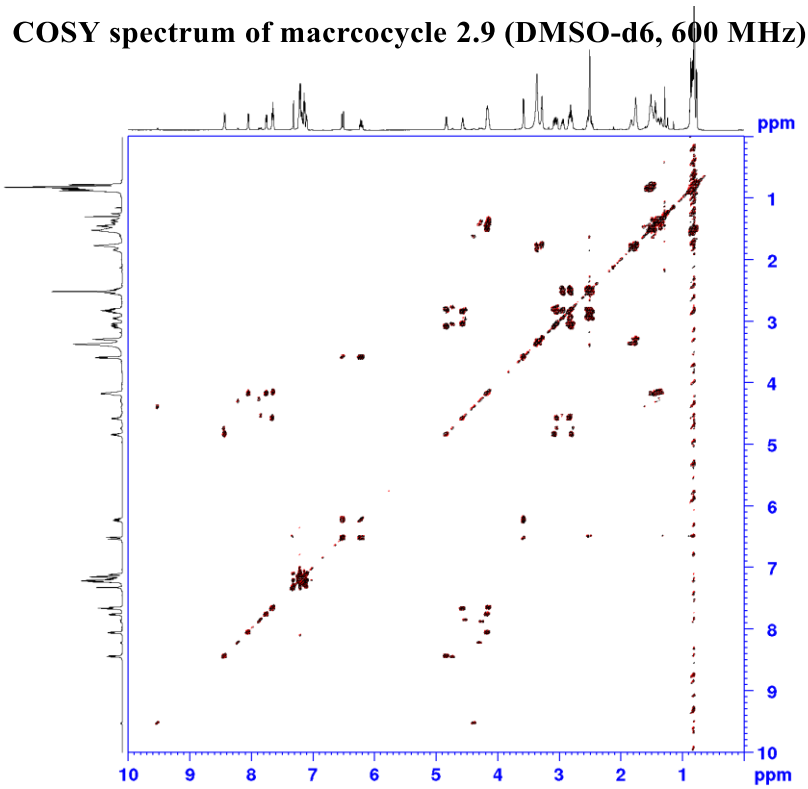
^{1}H NMR of macrcocycle 2.9 (DMSO-d6, 500 MHz)



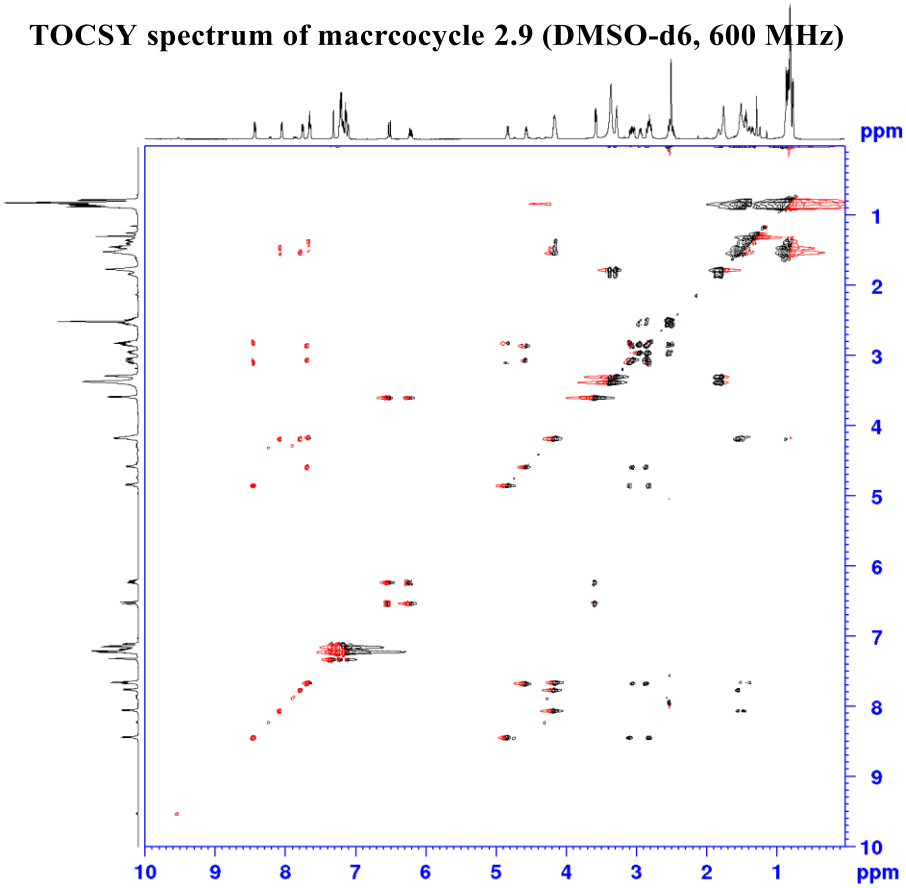
^{13}C NMR of macrocycle 2.9 (DMSO-d6, 126 MHz)



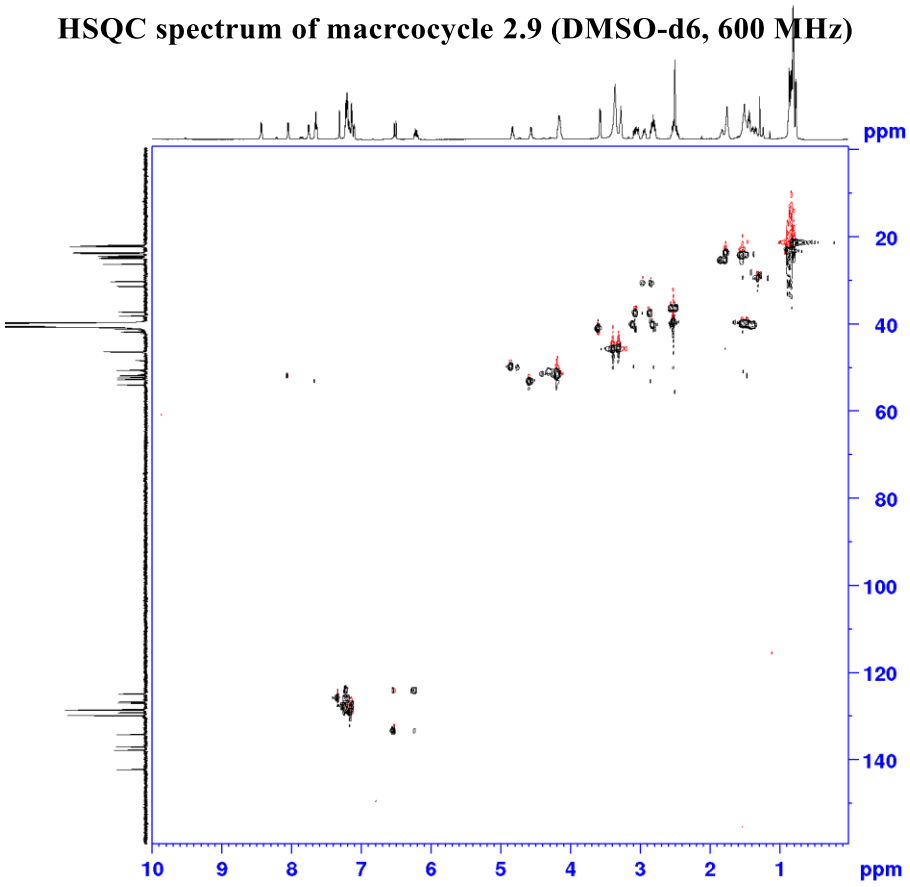
COSY spectrum of macrcocycle 2.9 (DMSO-d6, 600 MHz)



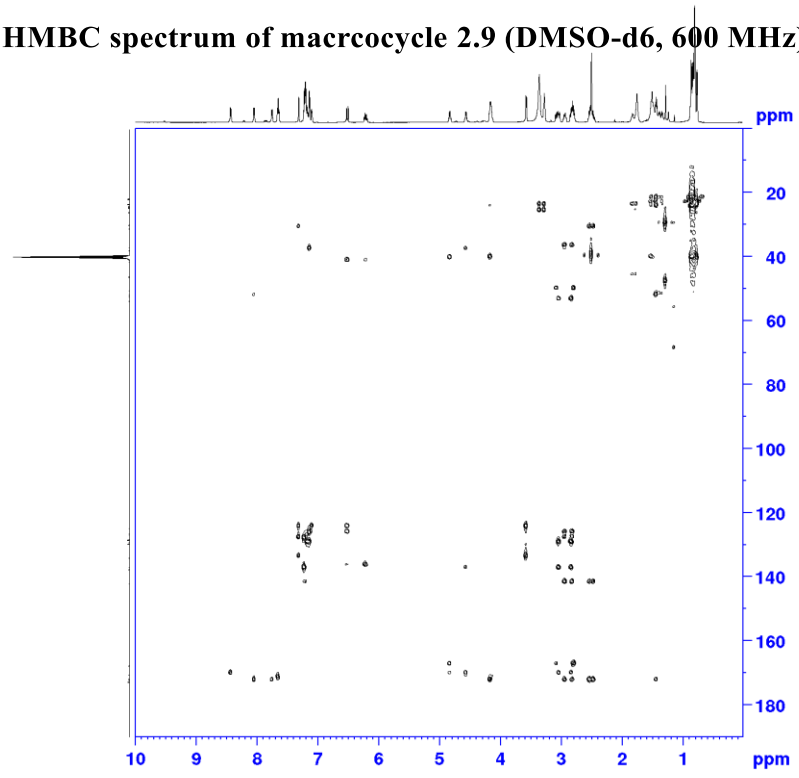
TOCSY spectrum of macrcocycle 2.9 (DMSO-d6, 600 MHz)



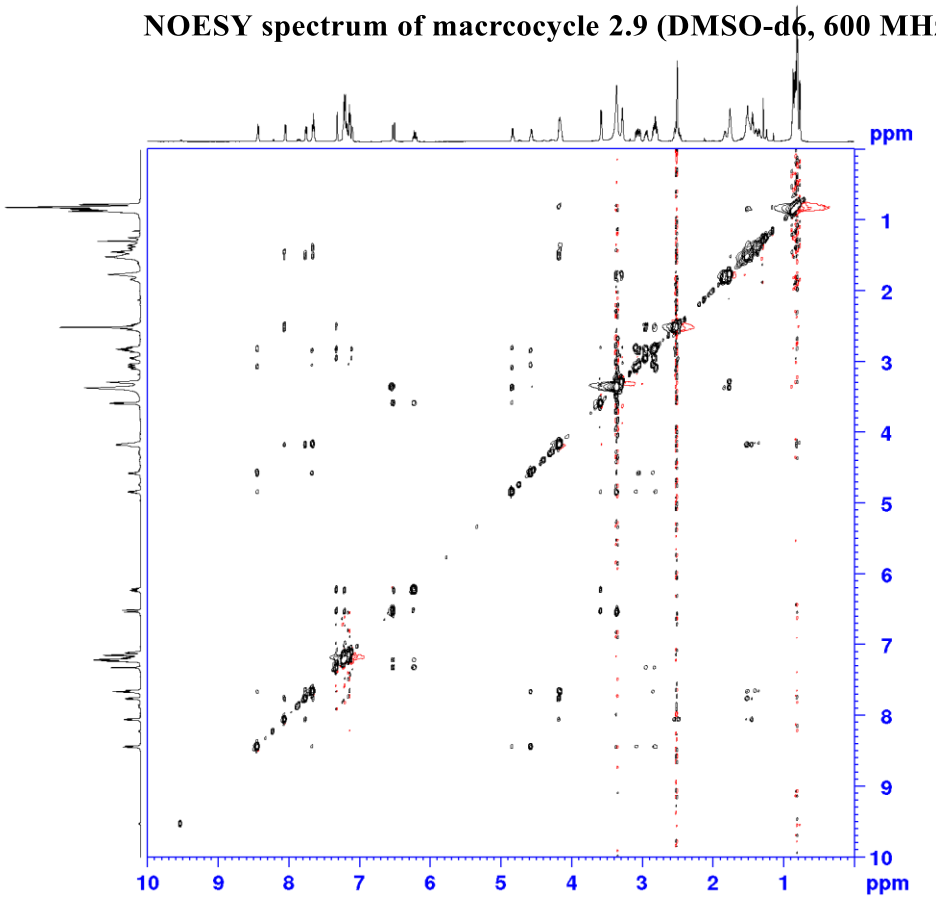
HSQC spectrum of macrcocycle 2.9 (DMSO-d6, 600 MHz)



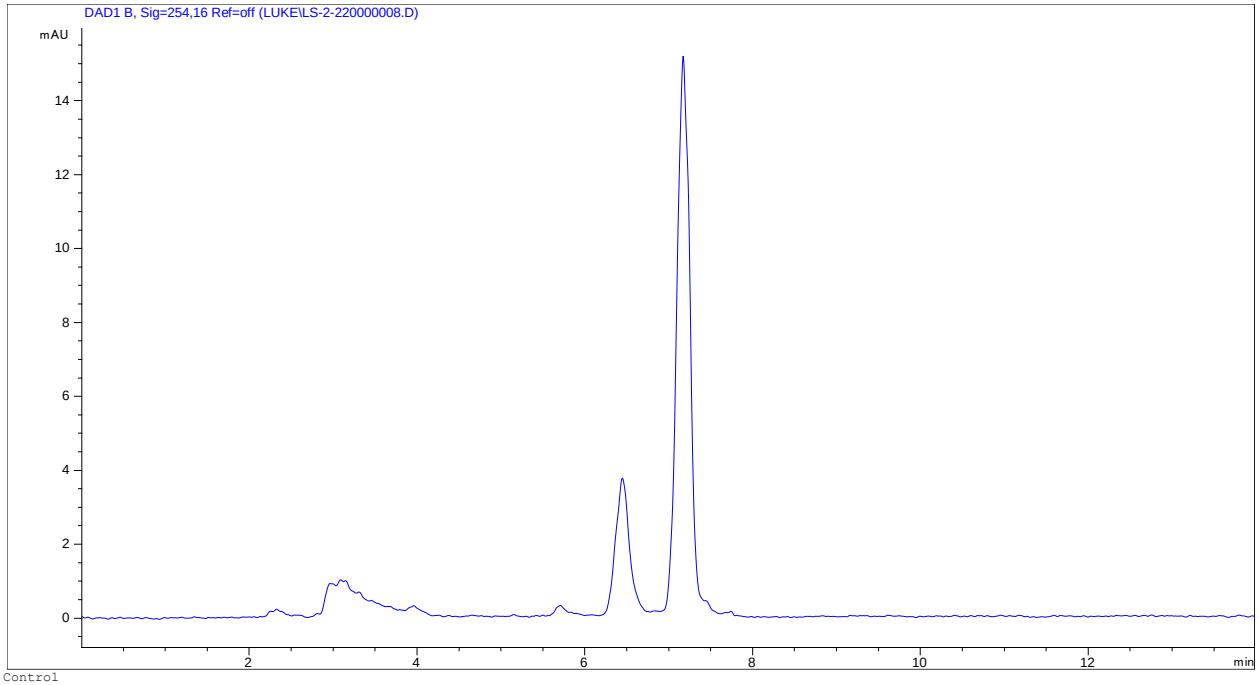
HMBC spectrum of macrcocycle 2.9 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 2.9 (DMSO-d6, 600 MHz)



2.9 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	15.000 ml/min
Stoptime	:	14.00 min
Posttime	:	Off

Solvents

Solvent A	:	20.0 % (Water)
Solvent B	:	80.0 % (Organic)

PressureLimits

Minimum Pressure	:	0 bar
Maximum Pressure	:	400 bar

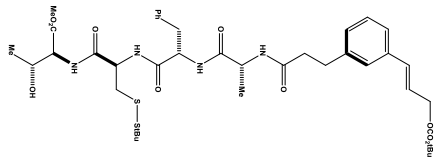
Auxiliary

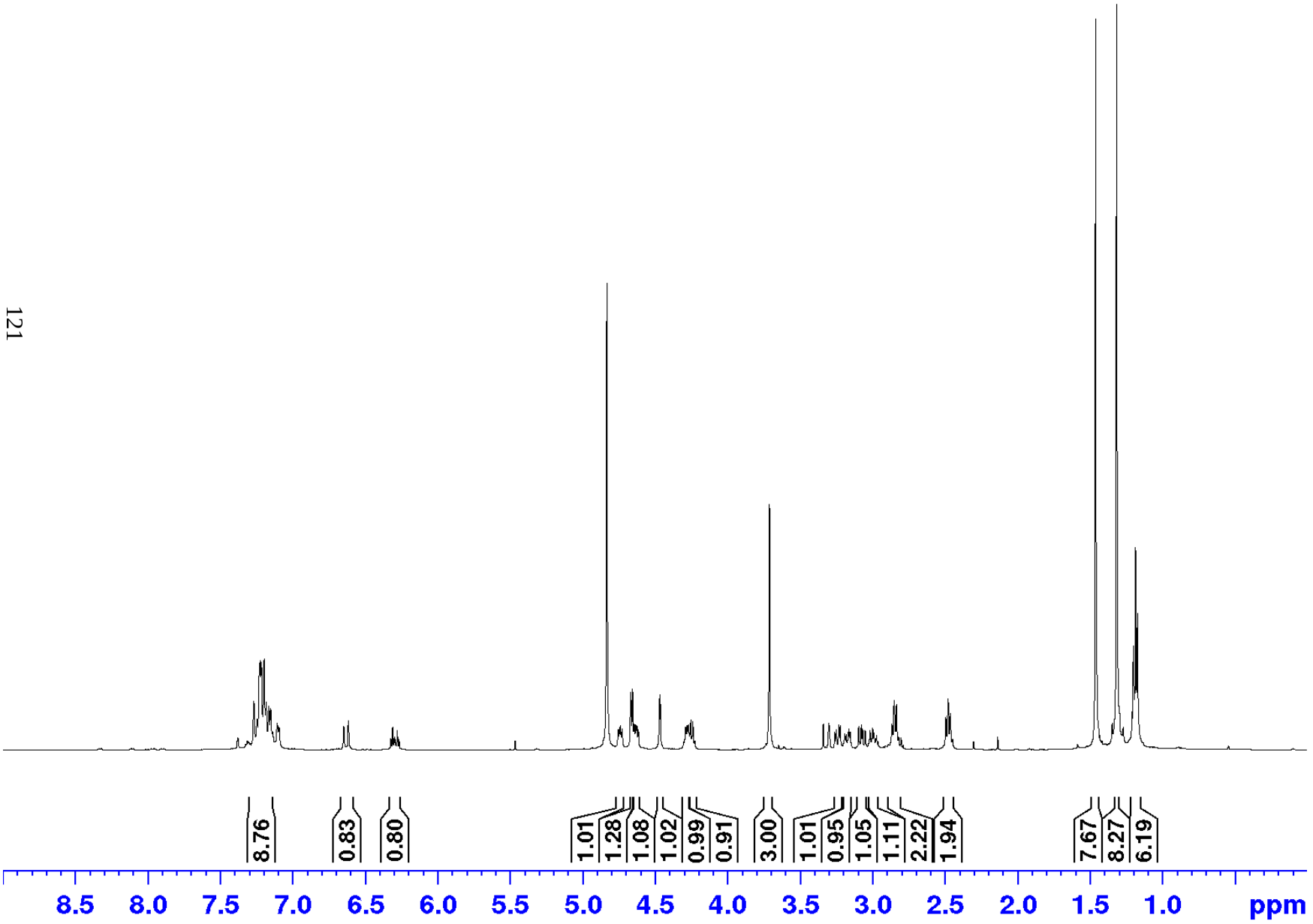
Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

Timetable

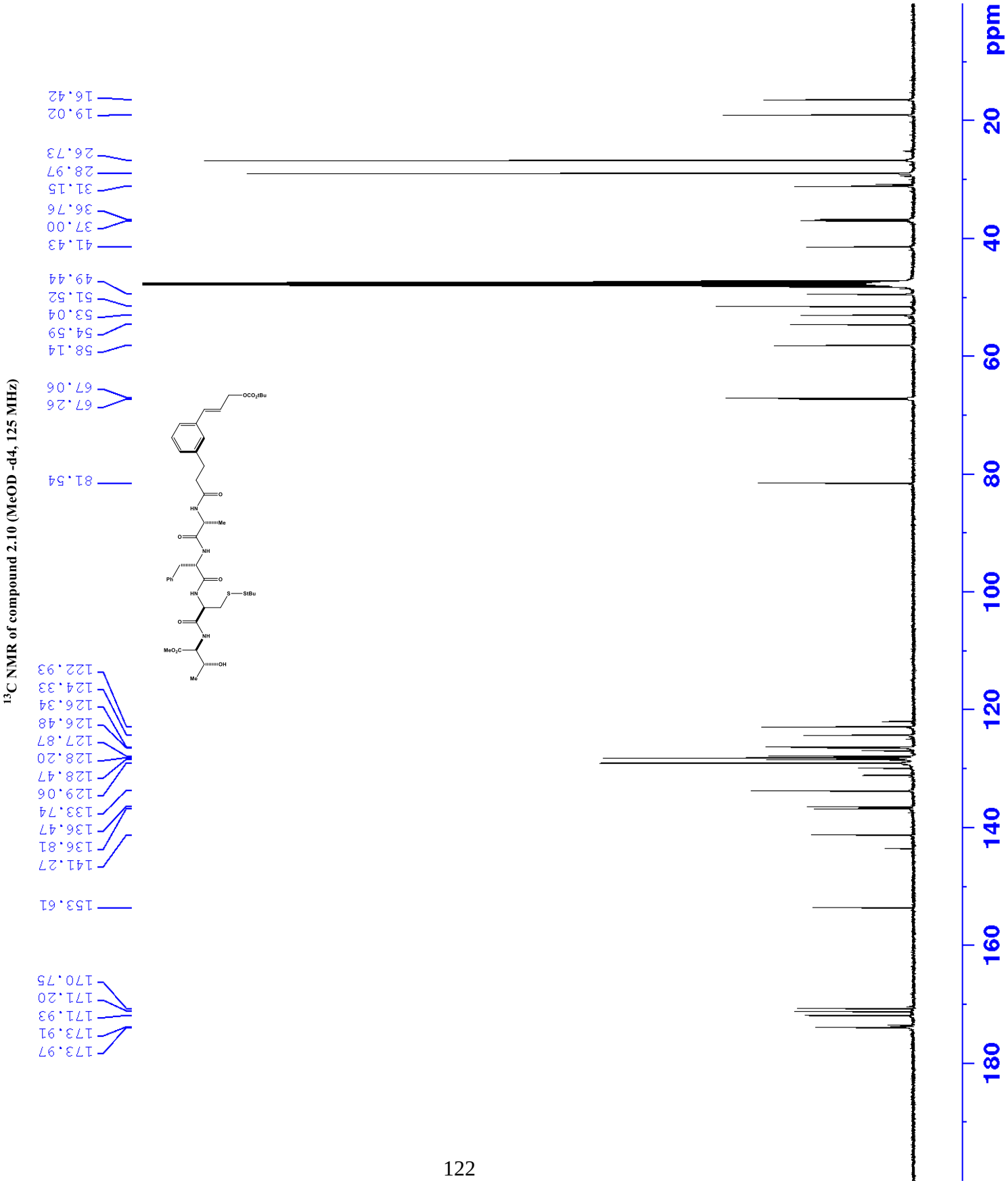
Time	Solv.B	Flow	Pressure
0.00	80.0	10.000	
2.00	80.0	18.000	
10.00	100.0	18.000	
12.00	100.0	18.000	
14.00	35.0	18.000	

^{1}H NMR of compound 2.10 (MeOD -d4, 500 MHz)

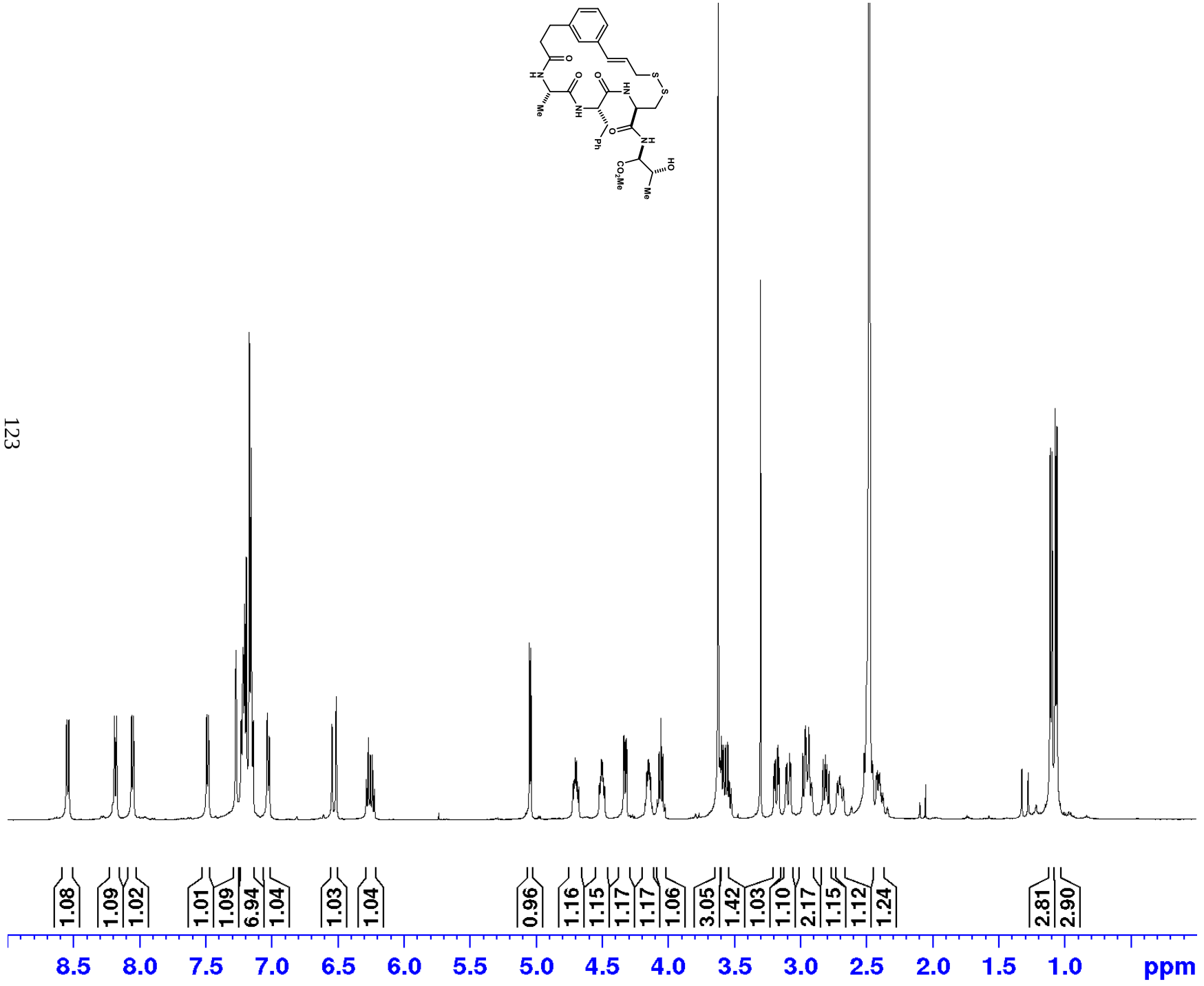




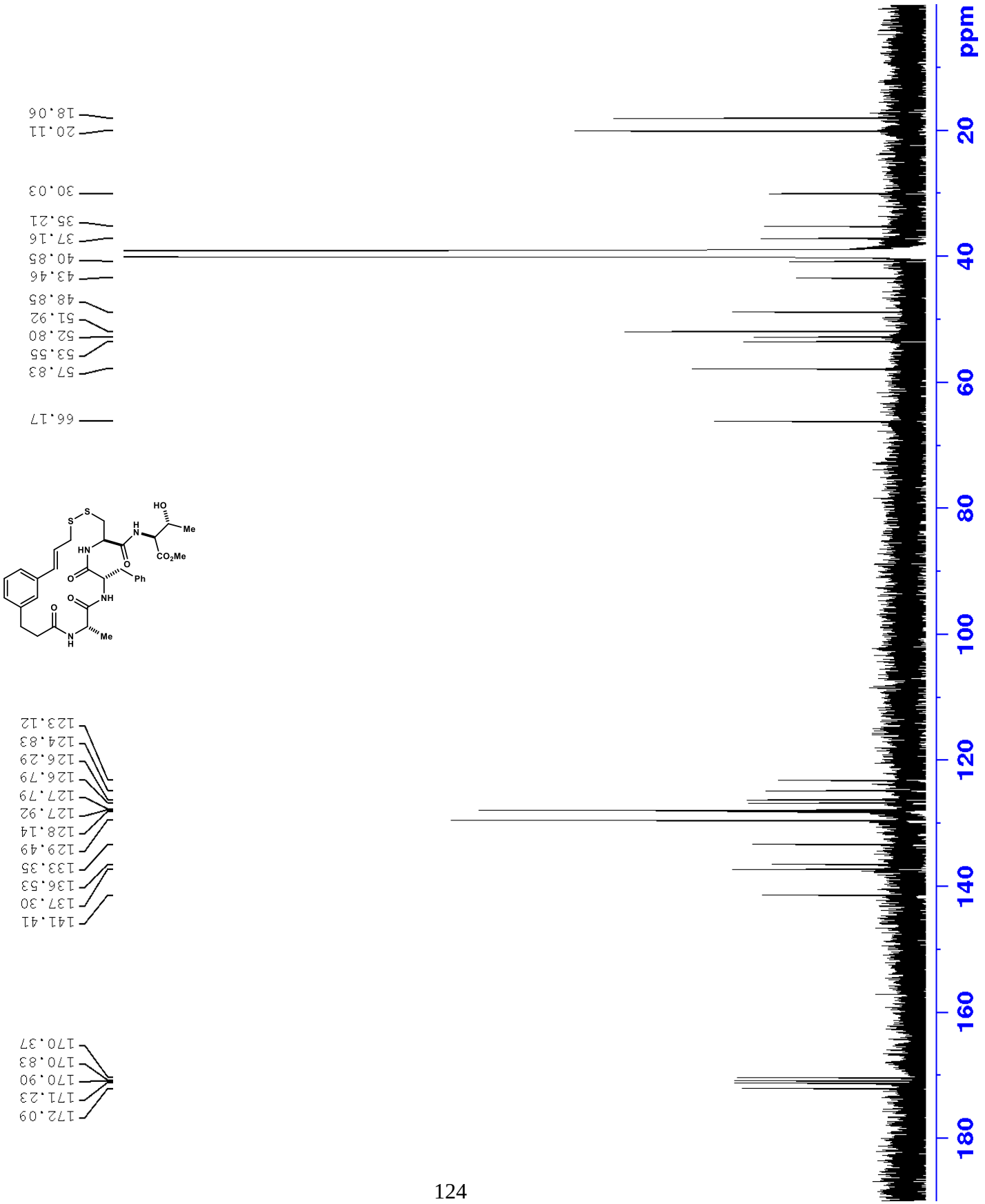
^{13}C NMR of compound 2.10 (MeOD -d4, 125 MHz)



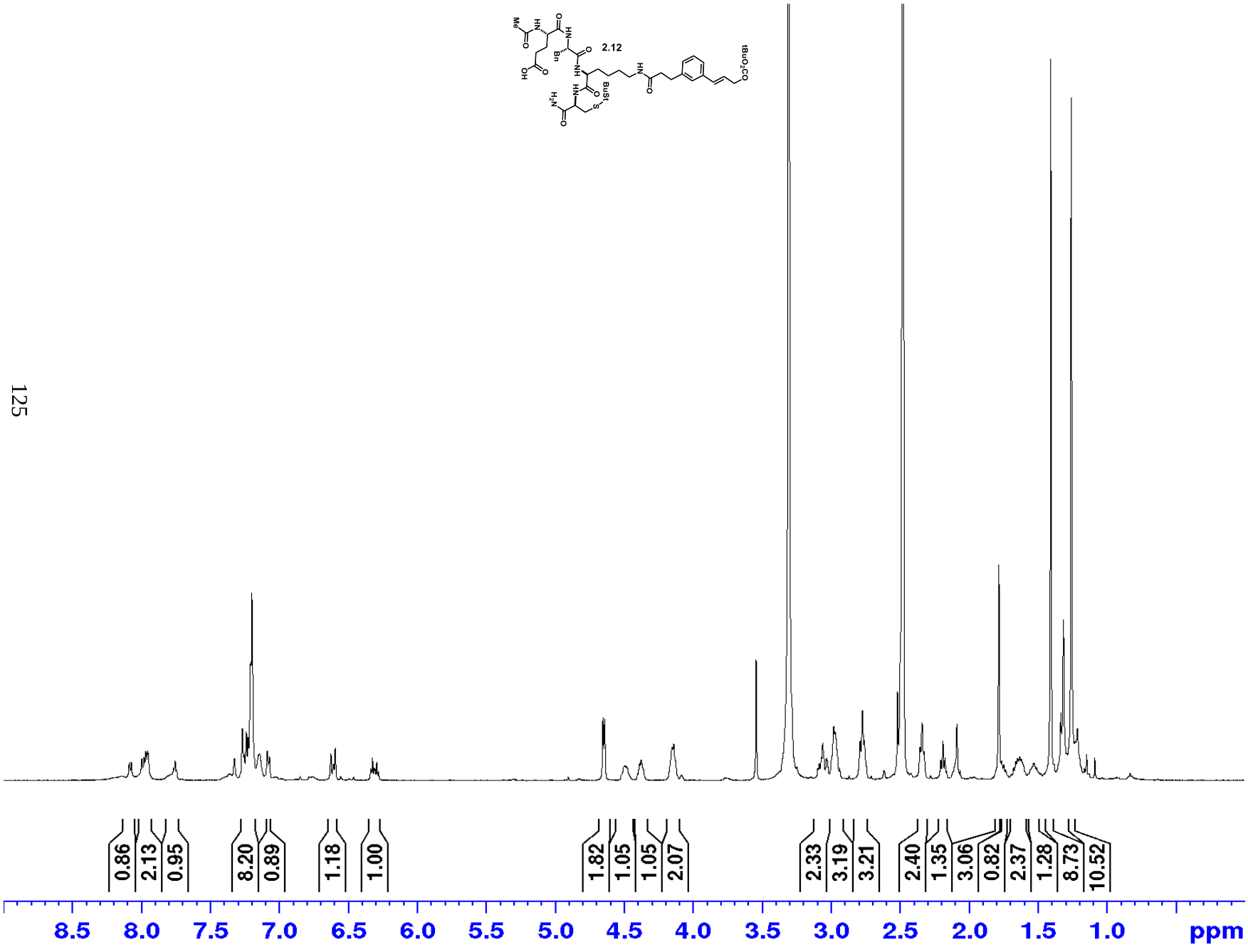
^{1}H NMR of macrcocycle 2.11 (DMSO-d6, 500 MHz)



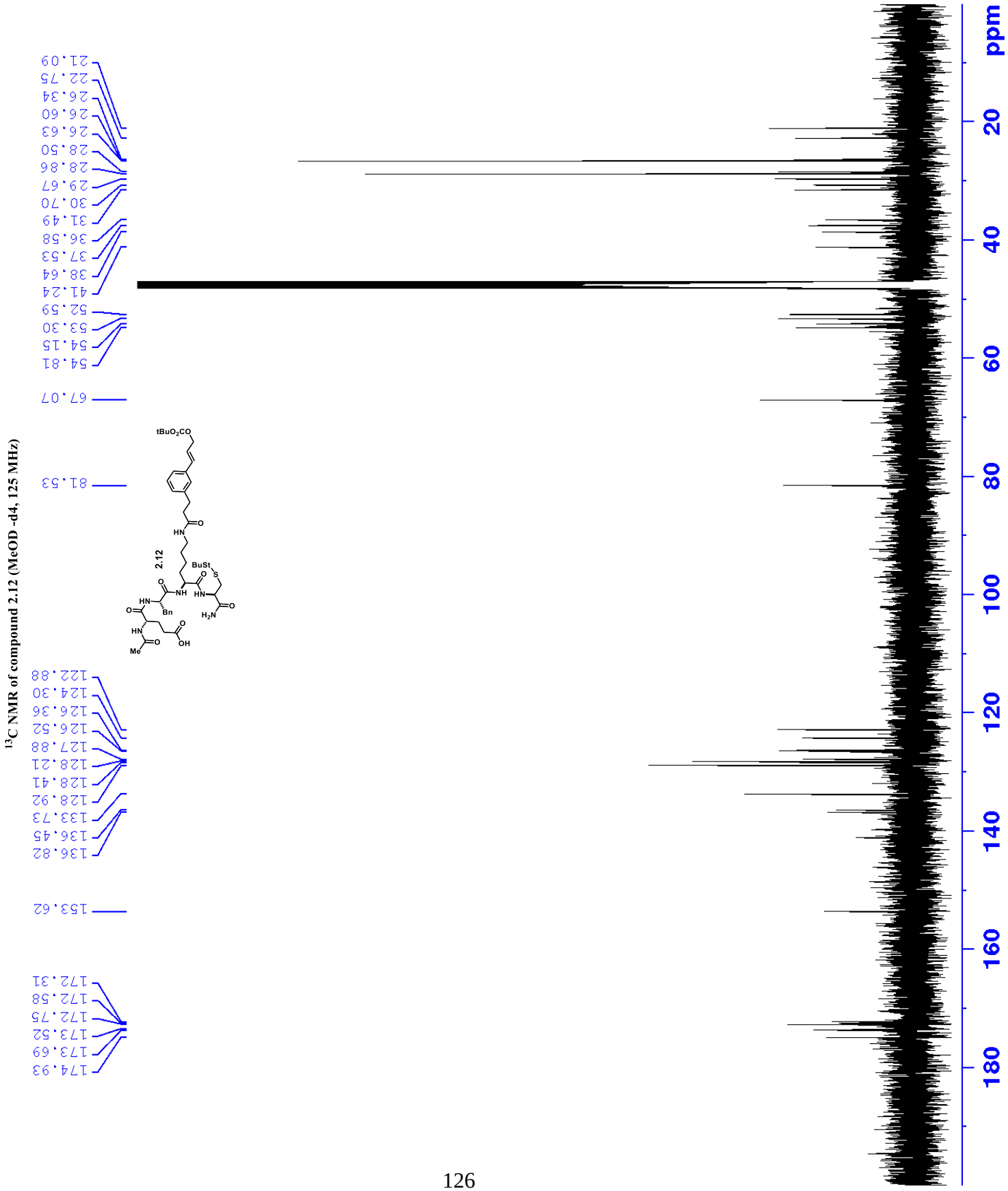
^{13}C NMR of macrocycle 2.11 (DMSO-d6, 126 MHz)



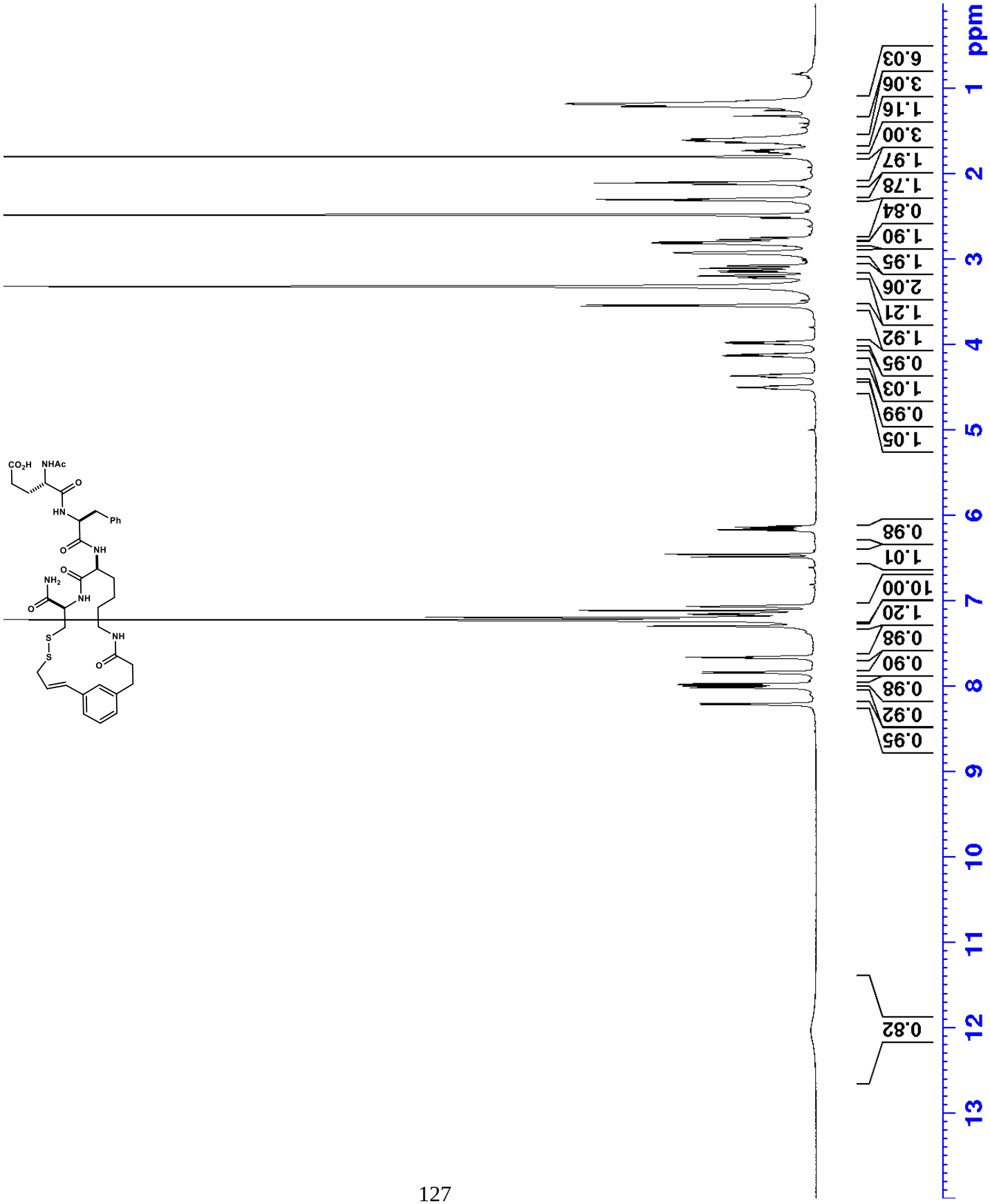
^{1}H NMR of compound 2.12 (DMSO -d6, 500 MHz)



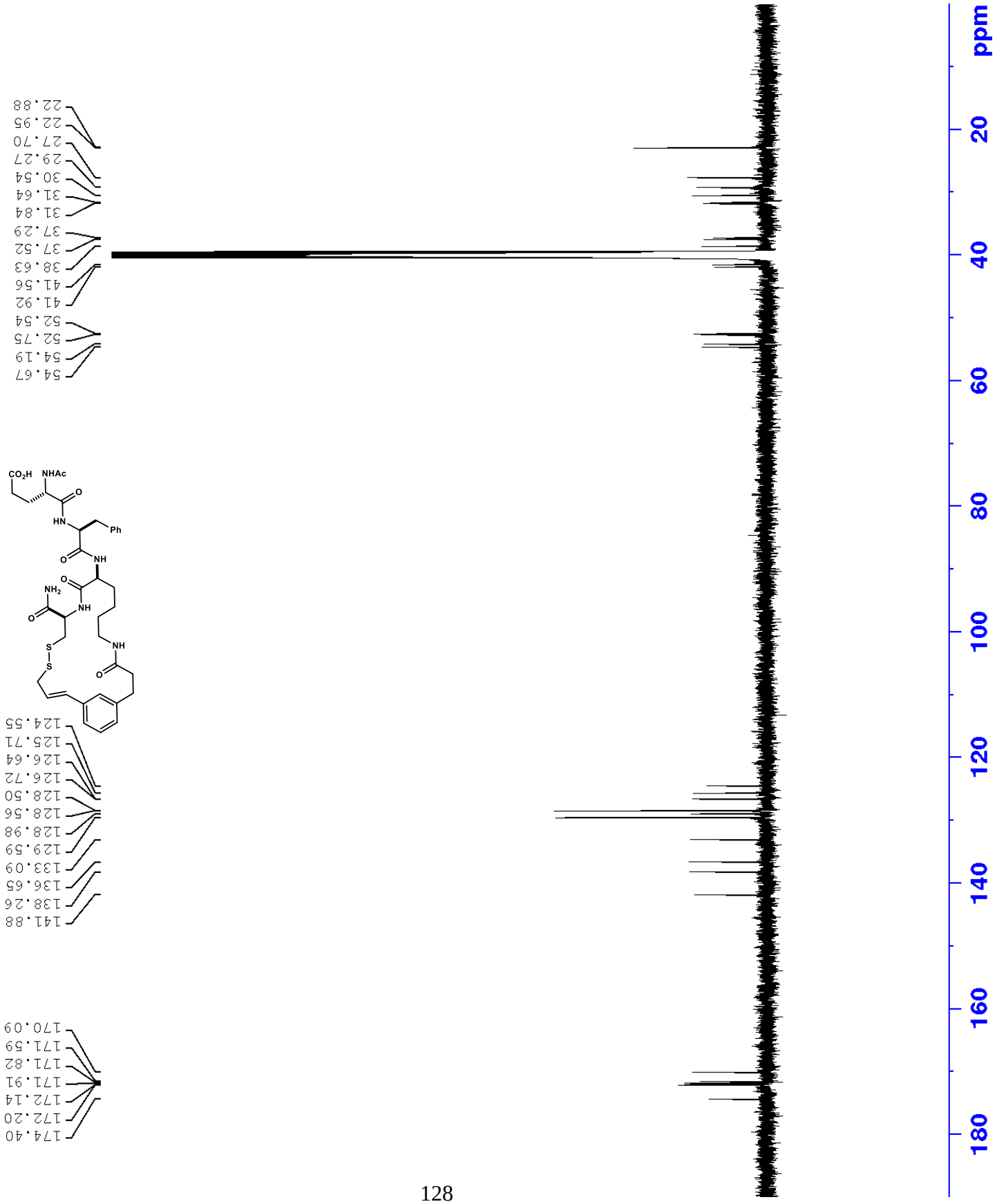
^{13}C NMR of compound 2.12 (MeOD -d4, 125 MHz)



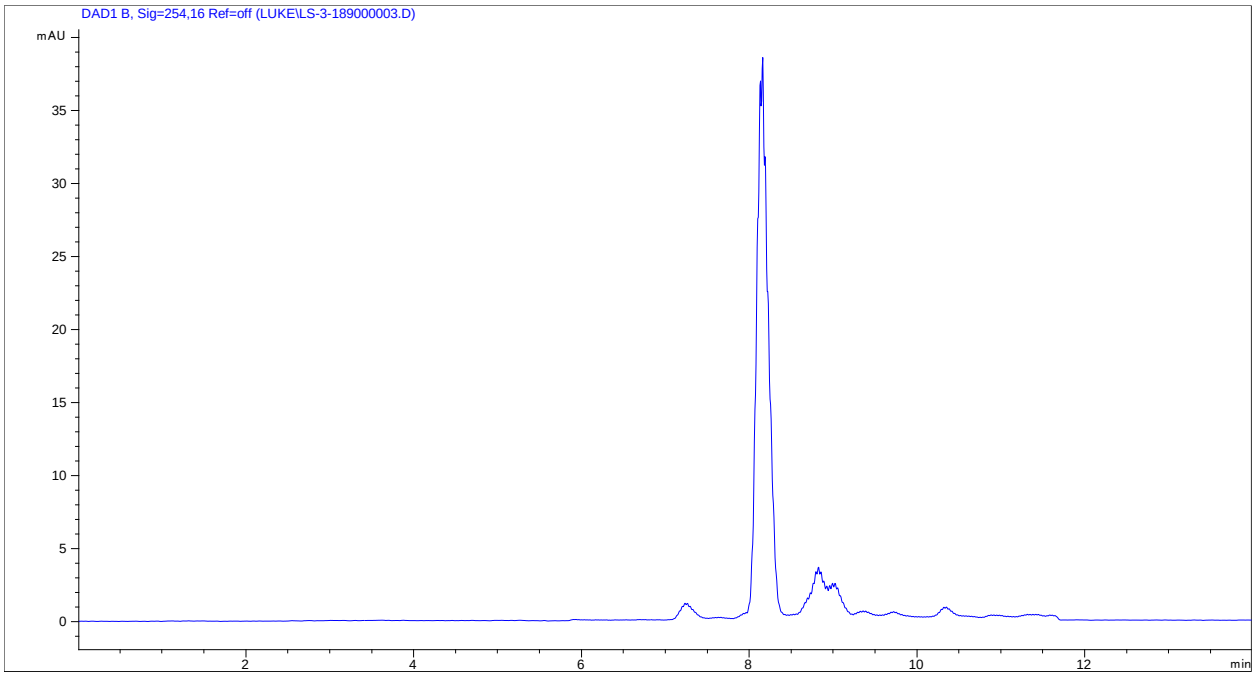
^{1}H NMR of macrocycle 2.13 (DMSO-d6, 500 MHz)



^{13}C NMR of macrcocycle 2.13 (DMSO-d6, 126 MHz)



2.13 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	12.000 ml/min
Stoptime	:	14.00 min
Posttime	:	Off

Solvents

Solvent A	:	60.0 % (Water)
Solvent B	:	40.0 % (Organic)

Purge

Purge State	:	off

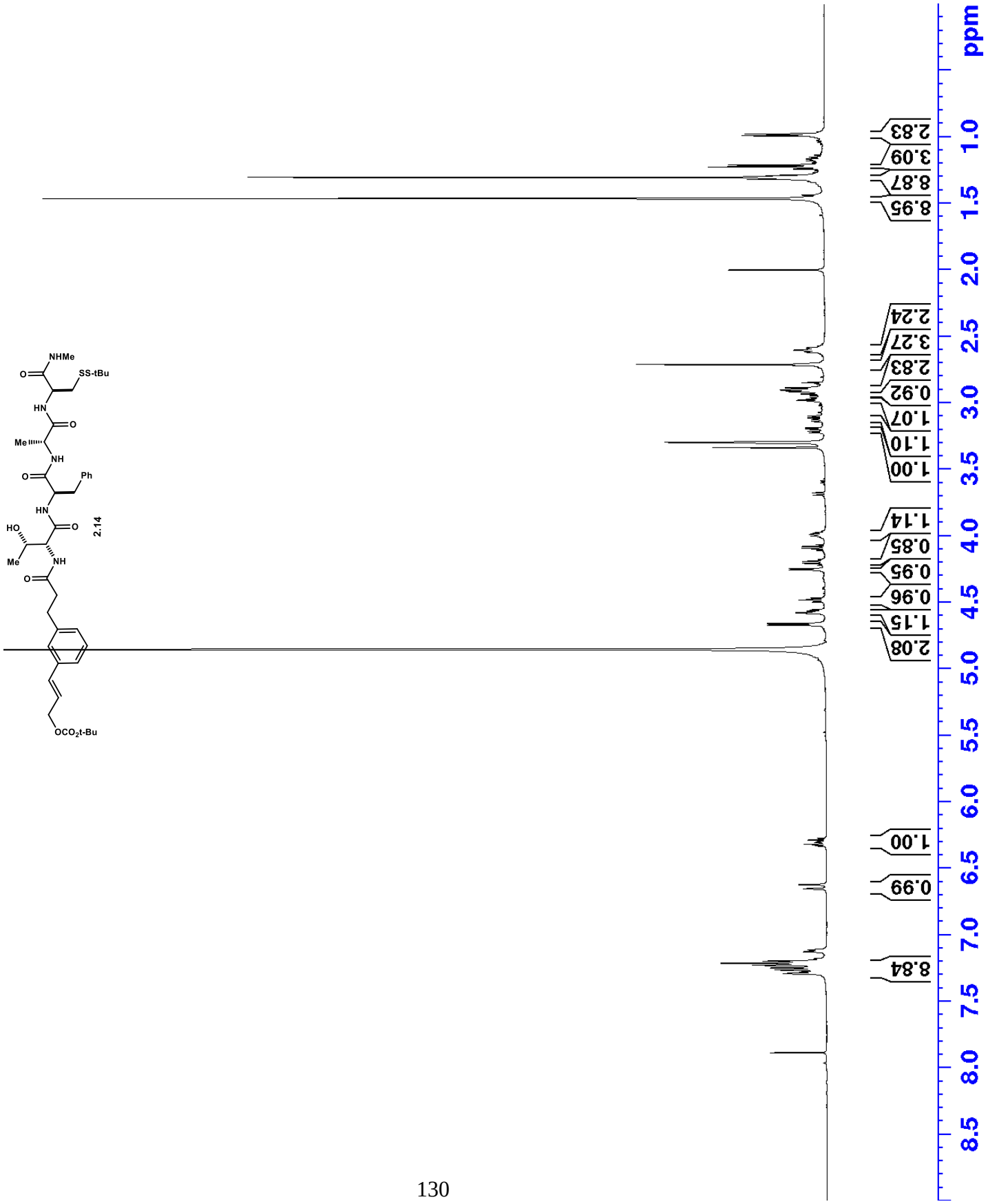
Auxiliary

Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

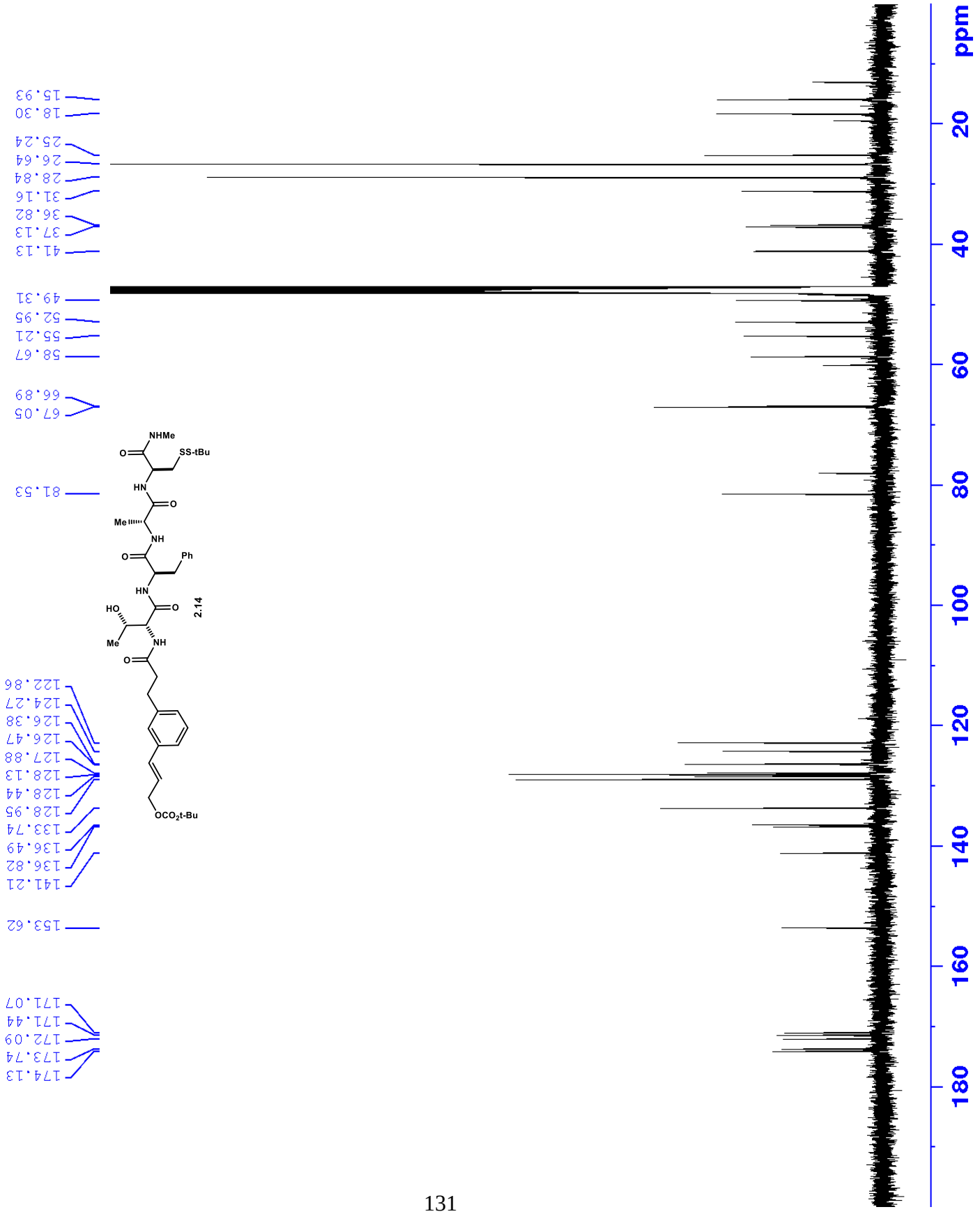
Timetable

Time	Solv.B	Flow	Pressure
0.00	40.0	12.000	400
2.00	40.0	12.000	400
8.00	65.0	15.000	400
13.00	100.0	15.000	400
14.00	40.0	15.000	400

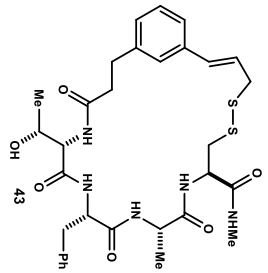
^{1}H NMR of compound 2.14 (MeOD -d4, 500 MHz)

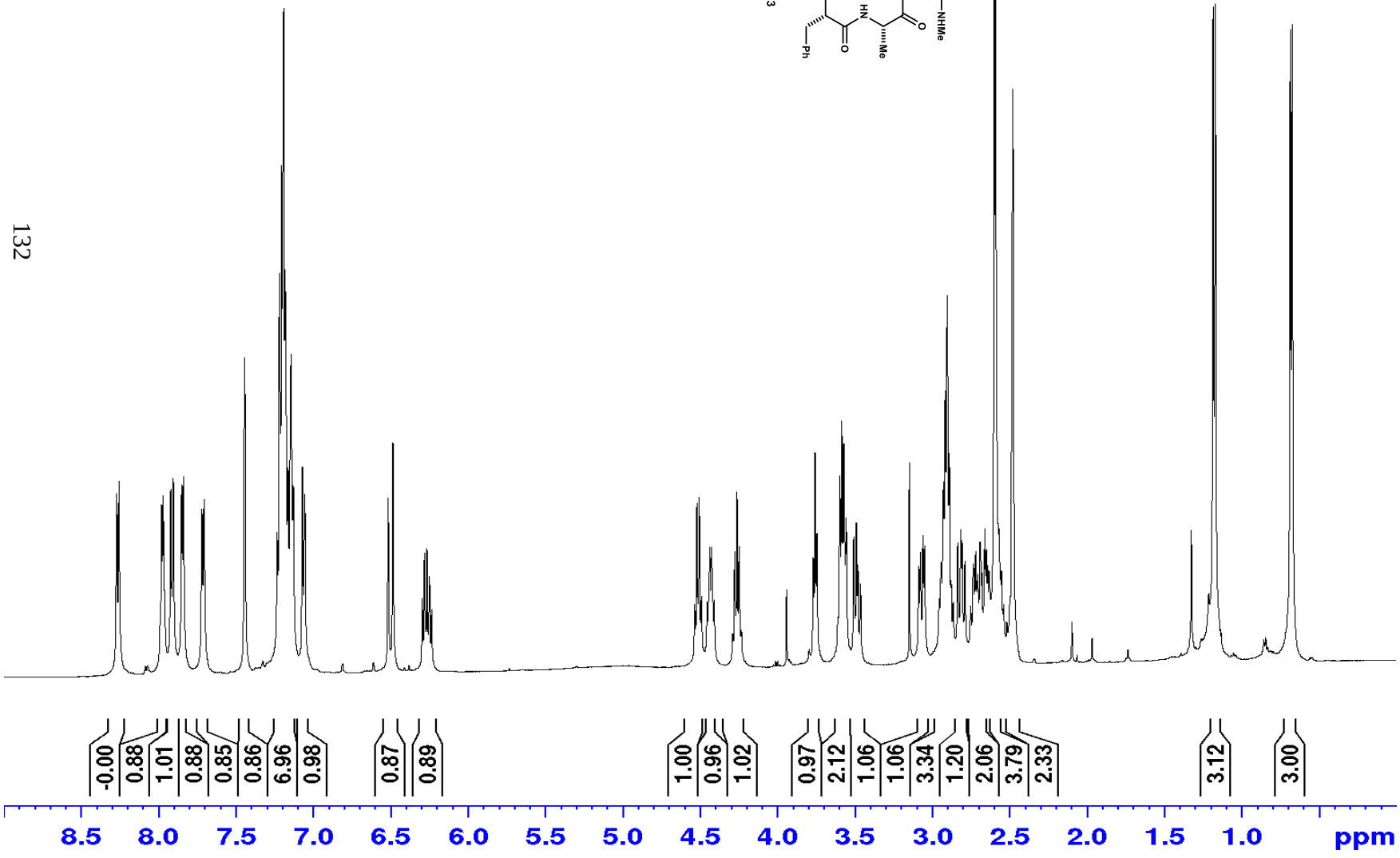


^{13}C NMR of compound 2.14 (MeOD -d4, 125 MHz)

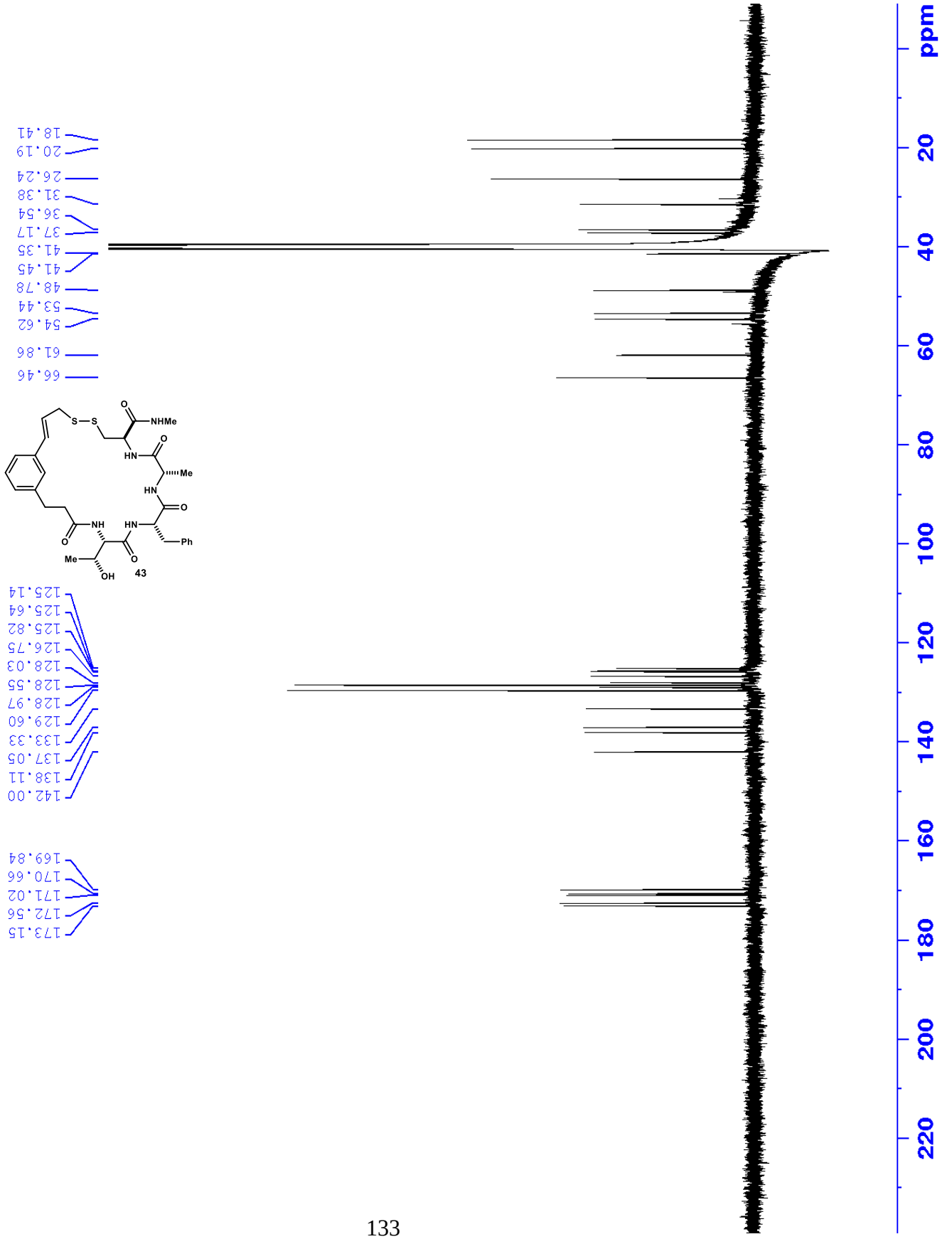


^{1}H NMR of macrcocycle 2.15 (DMSO-d6, 500 MHz)

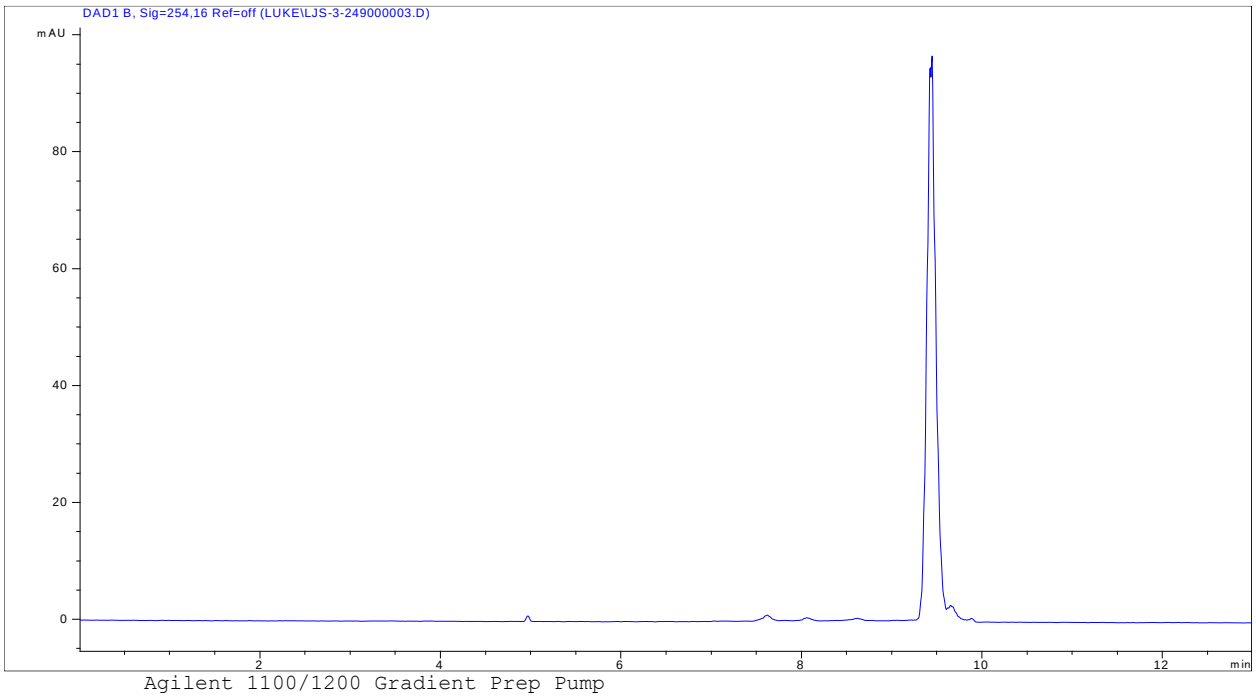




^{13}C NMR of macrocycle 2.15 (DMSO-d6, 126 MHz)



2.15 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

==========

Control

Column Flow	:	18.000 ml/min
Stoptime	:	13.00 min
Posttime	:	0.50 min

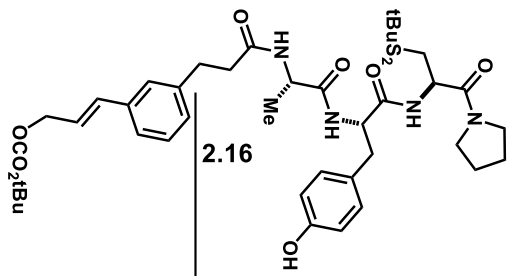
Solvents

Solvent A	:	70.0 % (Water)
Solvent B	:	30.0 % (Organic)

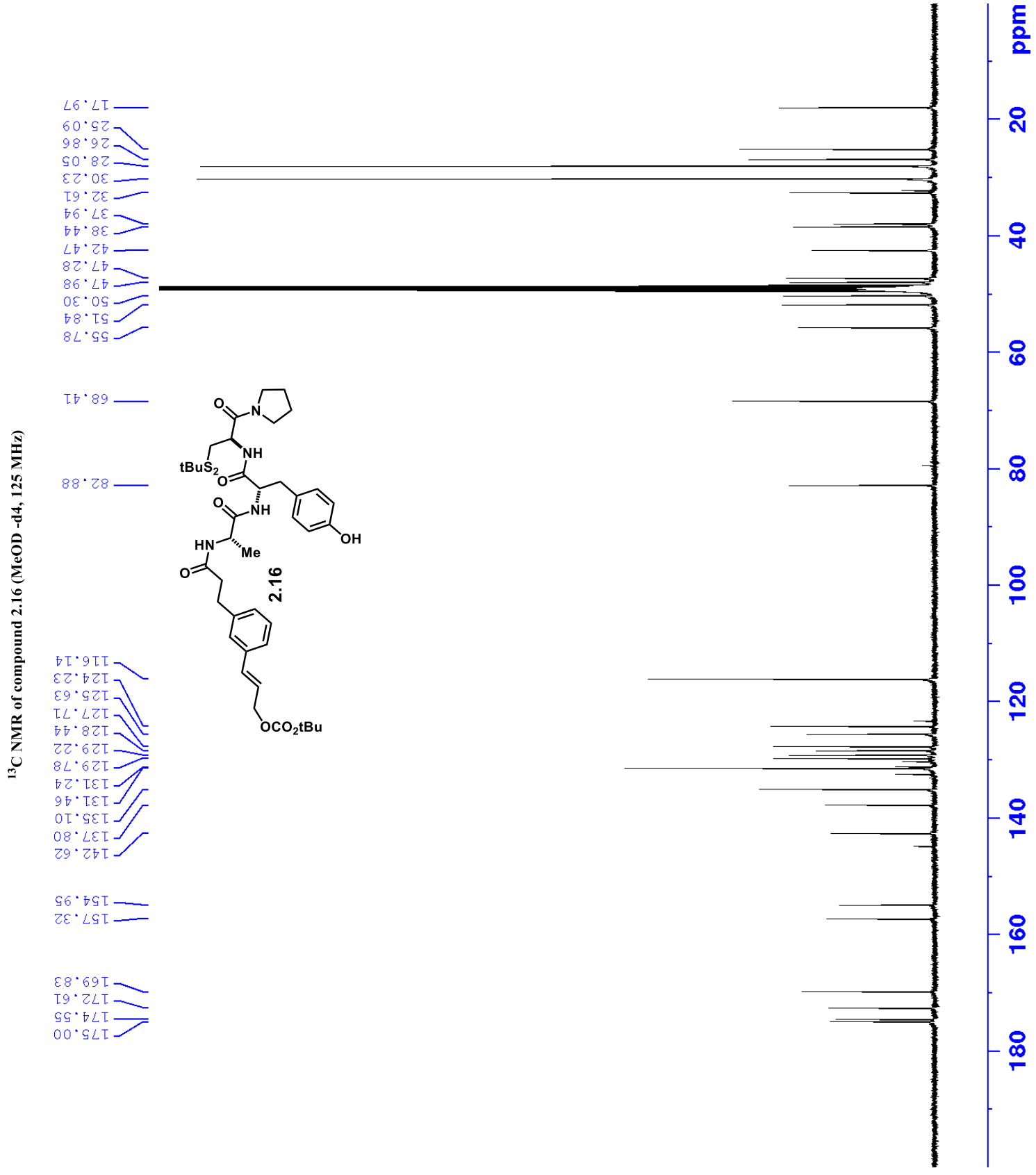
Timetable

Time	Solv.B	Flow	Pressure
0.00	30.0	12.000	
0.50	30.0	12.000	
11.00	80.0	18.000	
11.50	100.0	18.000	
12.50	100.0	18.000	
13.00	30.0	18.000	

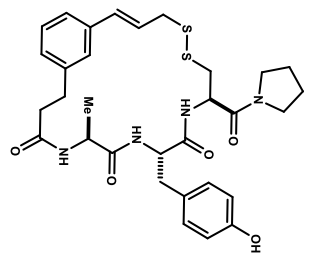
^{1}H NMR of compound 2.16 (MeOD -d4, 500 MHz)



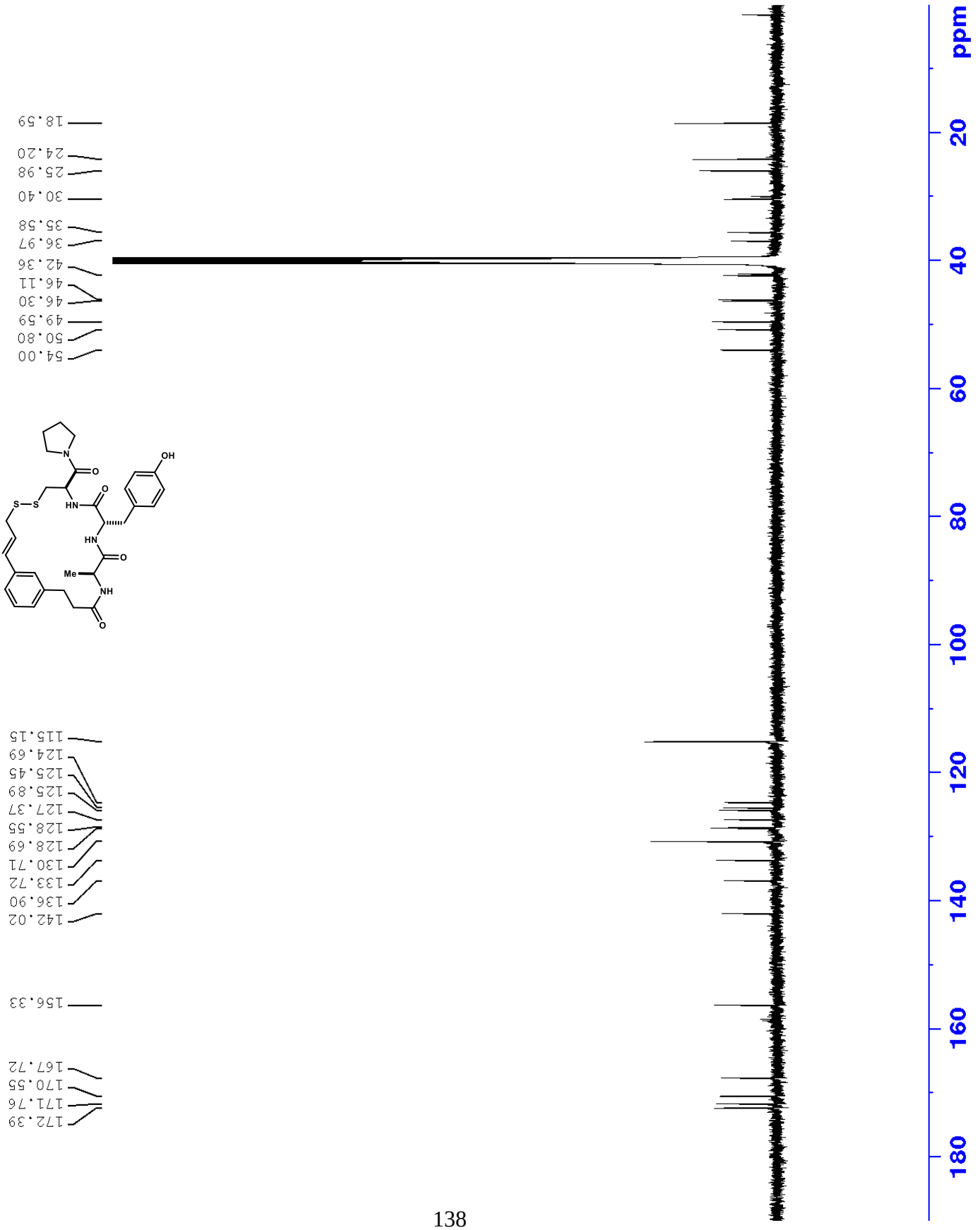
^{13}C NMR of compound 2.16 (MeOD -d4, 125 MHz)



^{1}H NMR of macrcocycle 2.17 (DMSO-d6, 500 MHz)

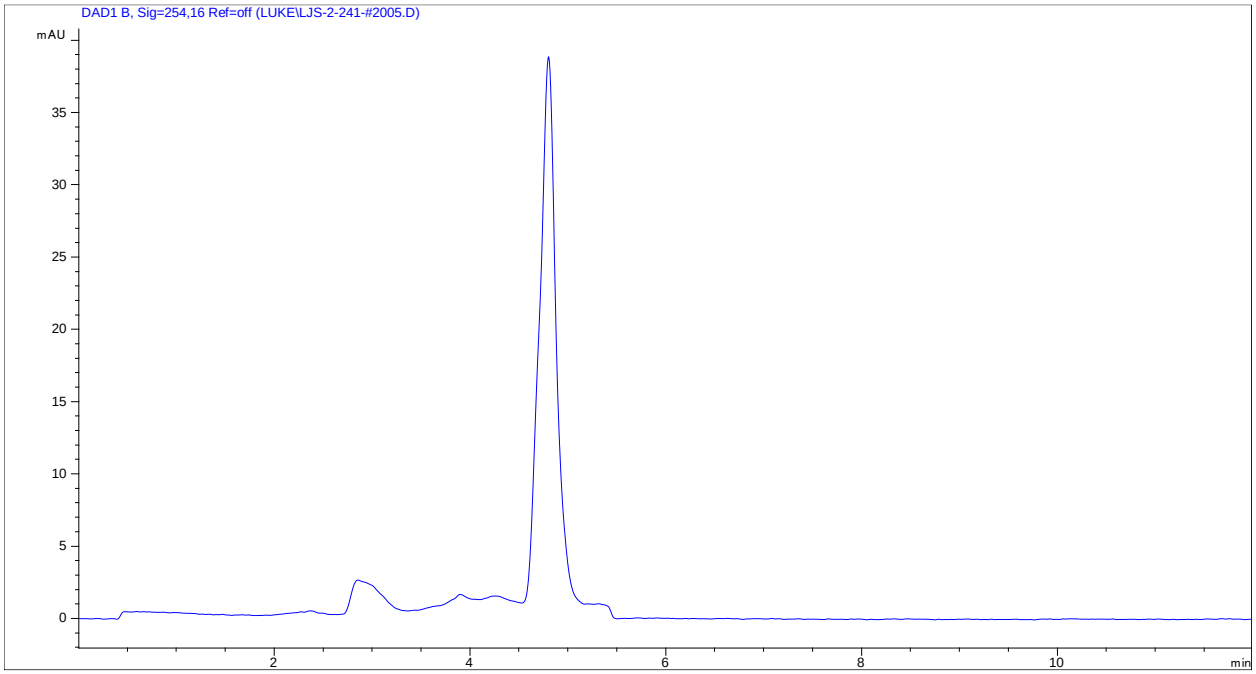


^{13}C NMR of macrocycle 2.17 (DMSO-d6, 125 MHz)



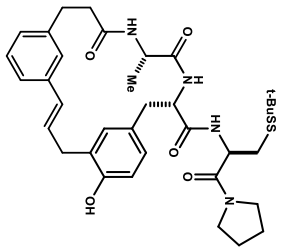
2.17 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

254nmhplc trace

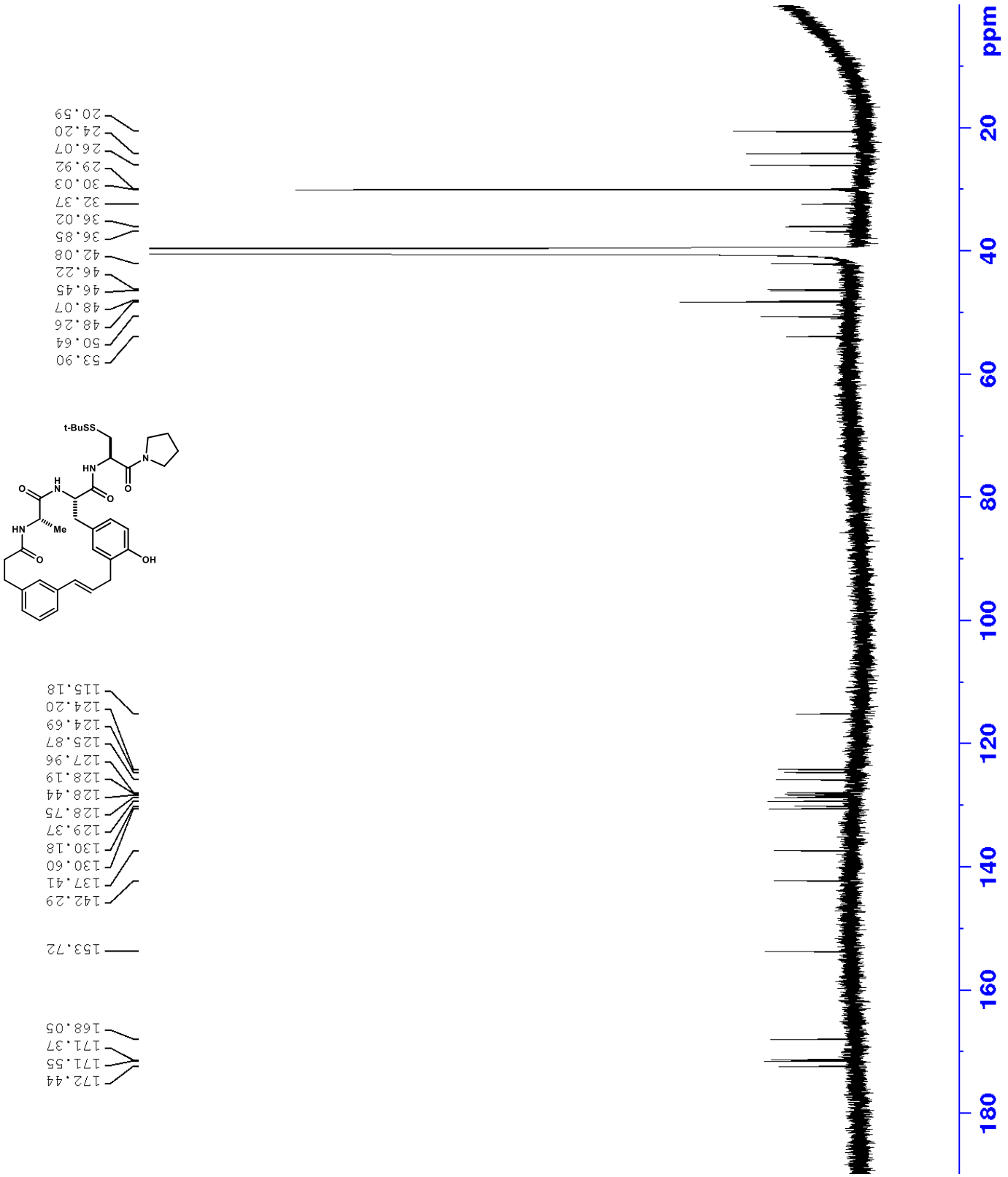



```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         12.00 min
    Posttime               :      Off

Solvents
    Solvent A              :       40.0 % (Water)
    Solvent B              :       60.0 % (Organic)

Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar


Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00    60.0    10.000
         2.00    60.0    18.000
        10.00    80.0    18.000
        11.00   100.0    18.000
        12.00    35.0    18.000
```

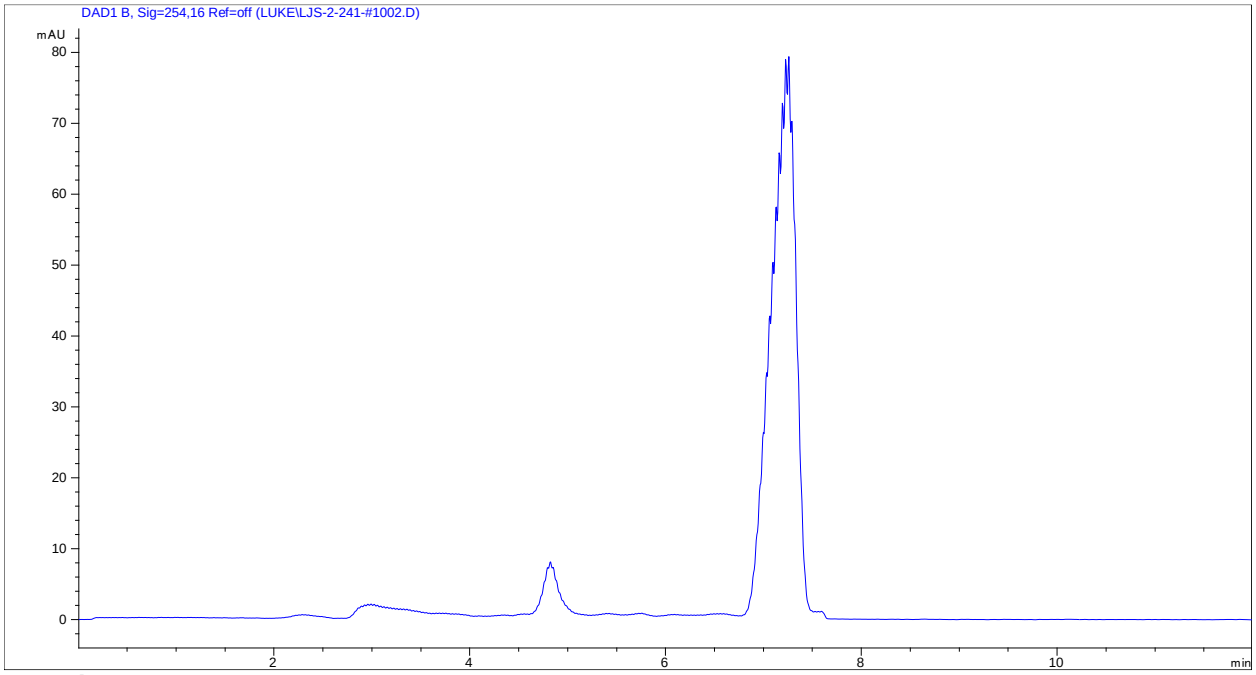
^{1}H NMR of macrcocycle 2.18 (DMSO-d6, 500 MHz)



^{13}C NMR of macrcocycle 2.18 (DMSO-d6, 125 MHz)



2.8 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	15.000 ml/min
Stoptime	:	12.00 min
Posttime	:	Off

Solvents

Solvent A	:	40.0 % (Water)
Solvent B	:	60.0 % (Organic)

Purge

Purge State	:	off

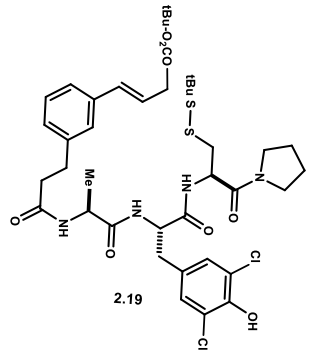
Auxiliary

Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

Timetable

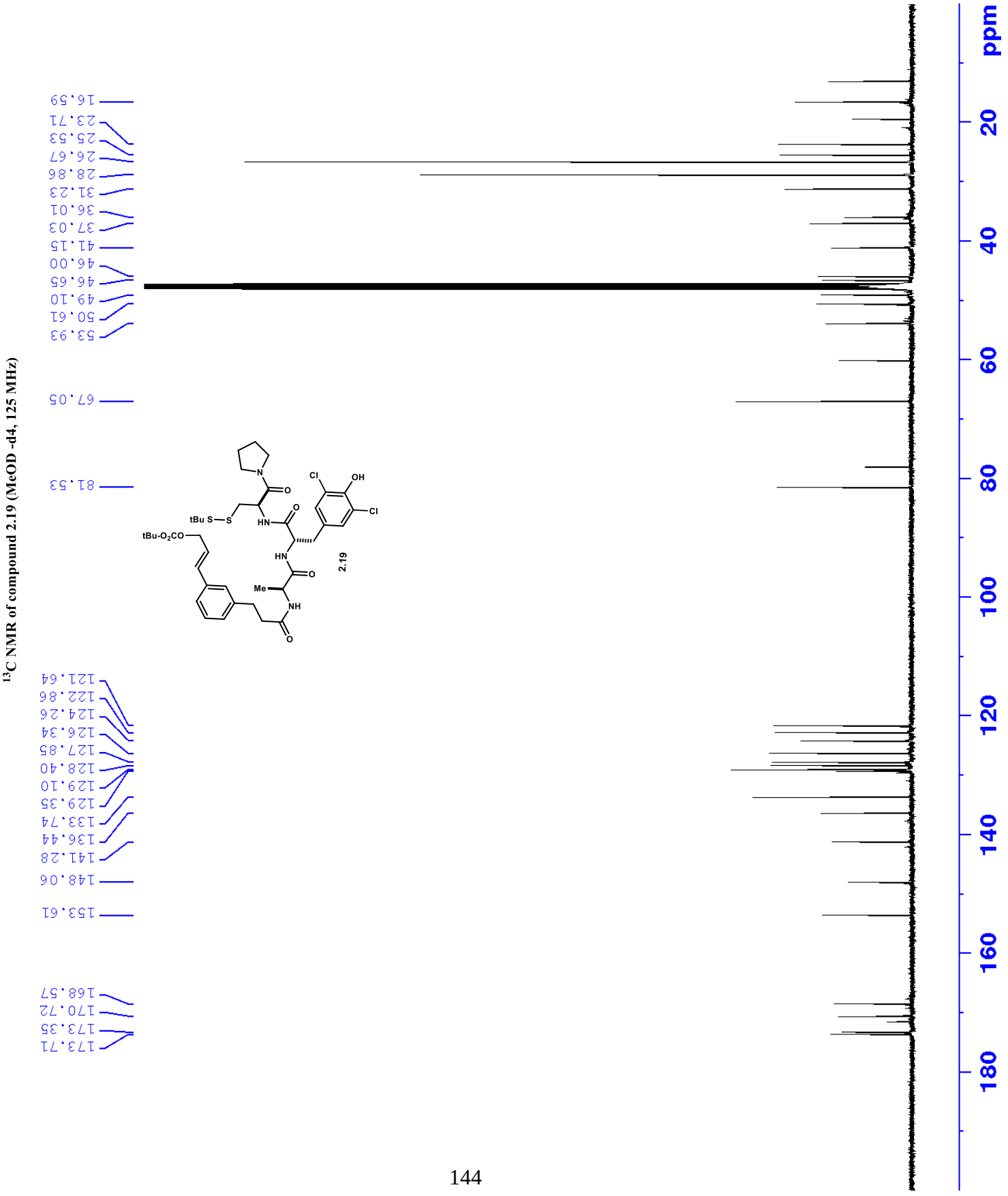
Time	Solv.B	Flow	Pressure
0.00	60.0	10.000	
2.00	60.0	18.000	
10.00	80.0	18.000	
11.00	100.0	18.000	
12.00	35.0	18.000	

^{1}H NMR of compound 2.19 (MeOD -d4, 500 MHz)

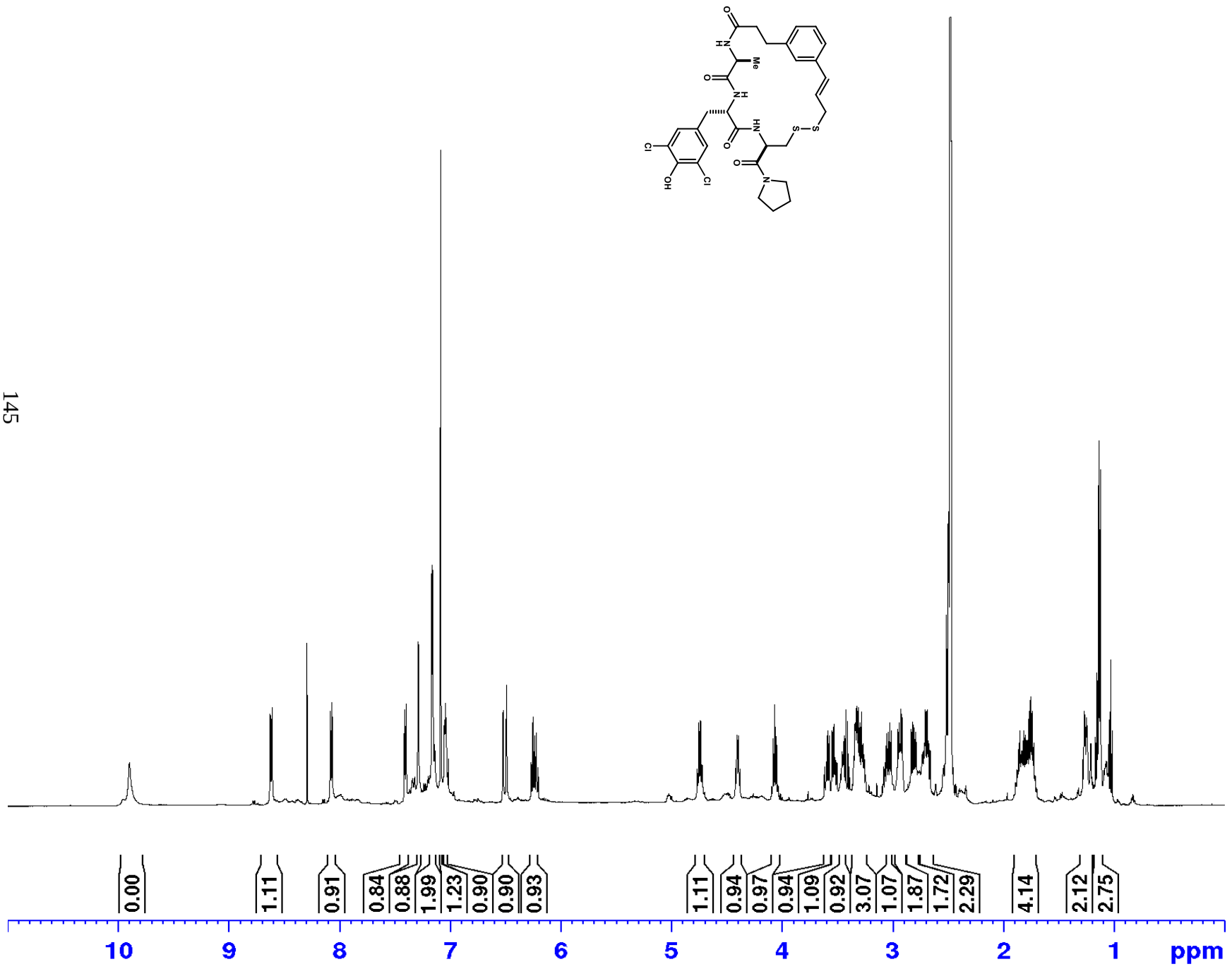


2.19

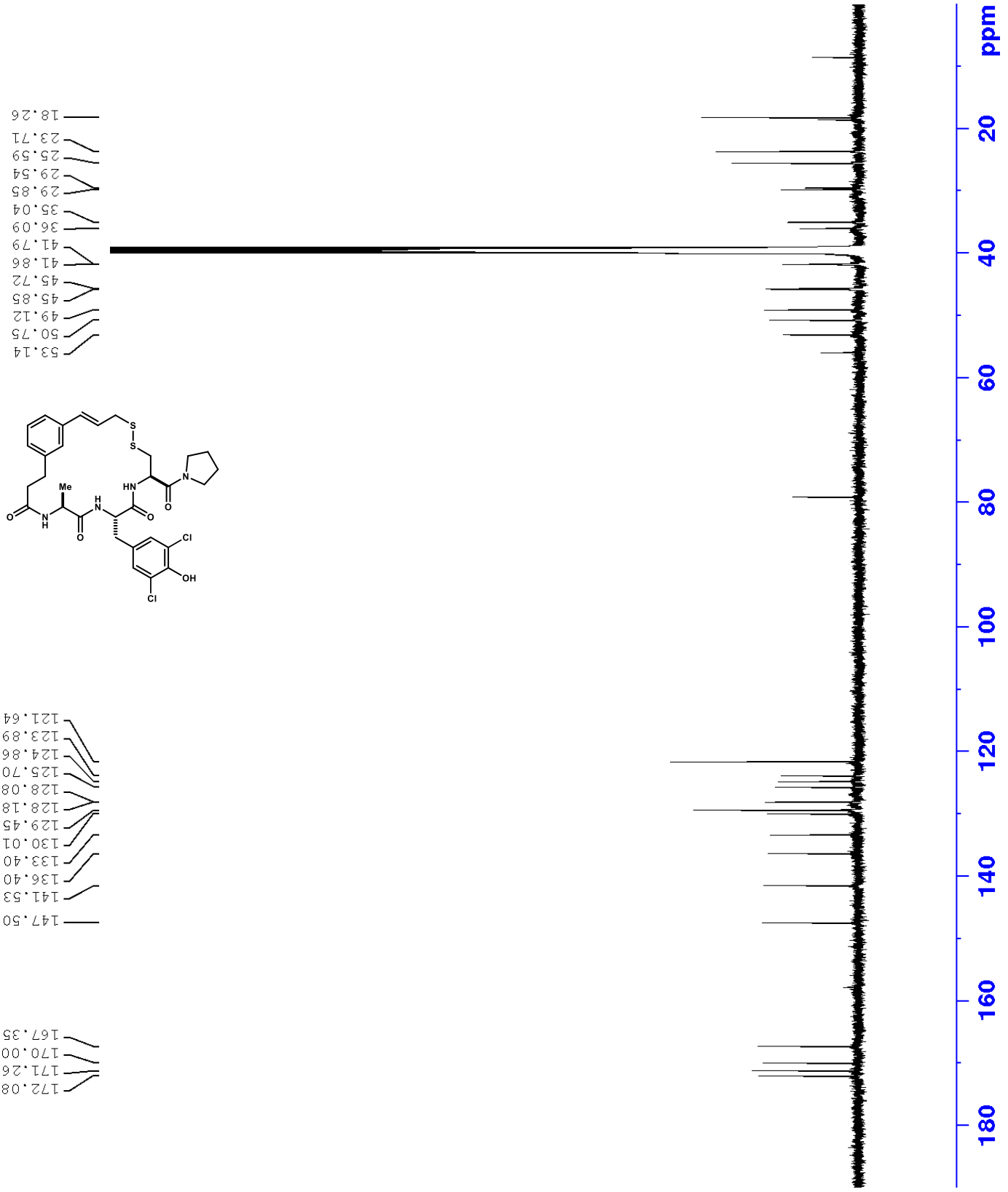
^{13}C NMR of compound 2.19 (MeOD -d4, 125 MHz)



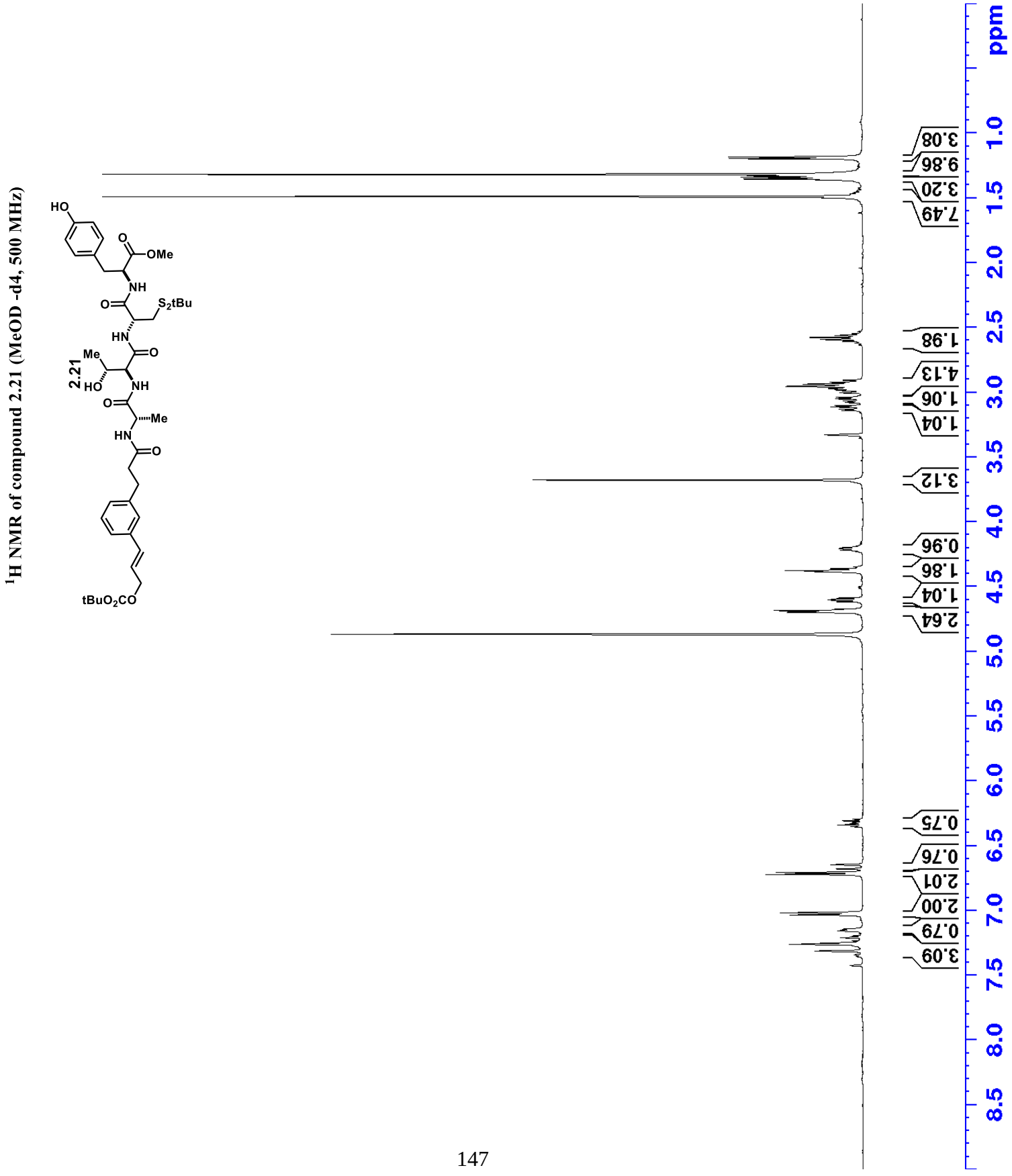
^{1}H NMR of macrcocycle 2.20 (DMSO-d6, 500 MHz)



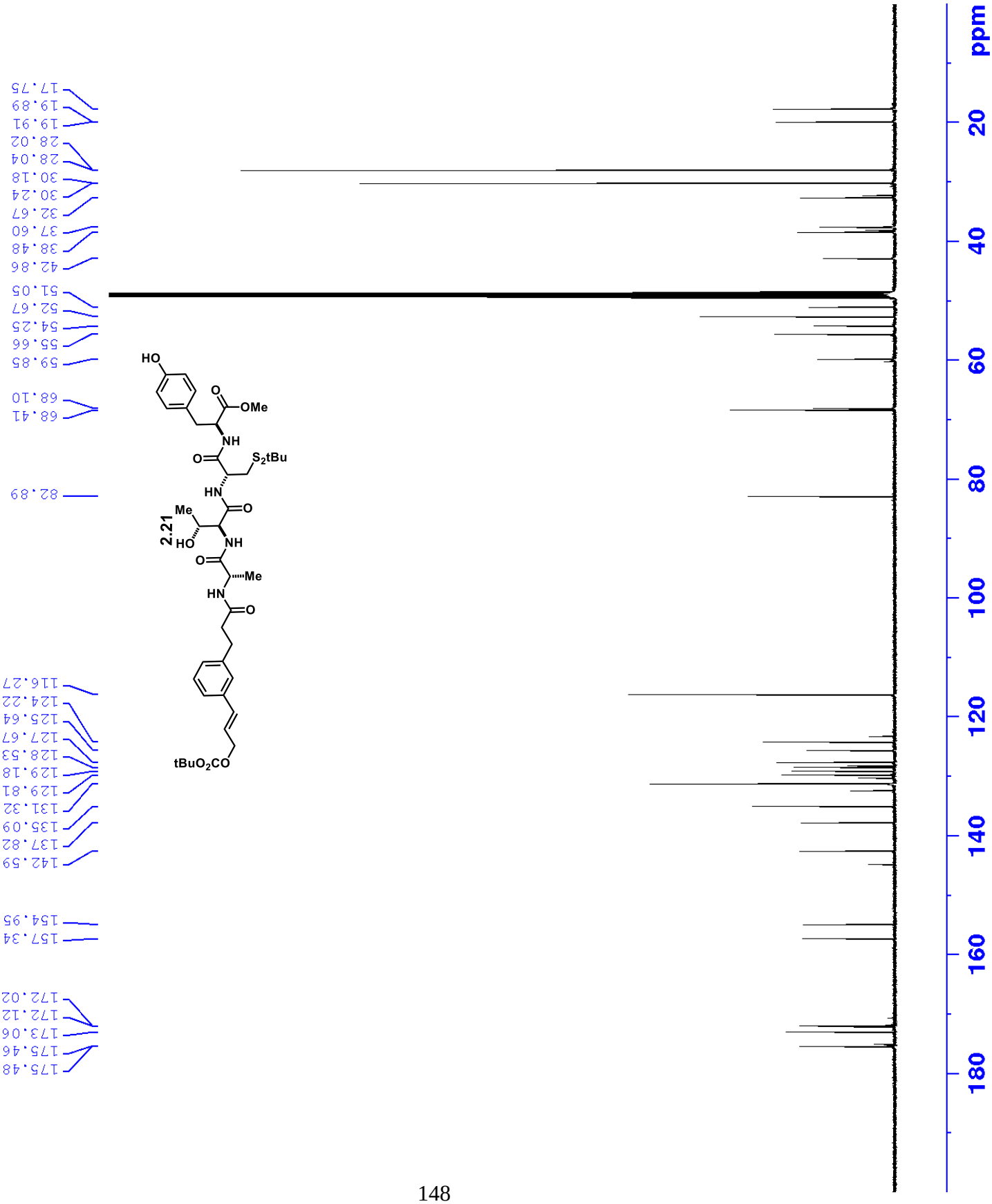
^{13}C NMR of macrocycle 2.20 (DMSO-d6, 126 MHz)



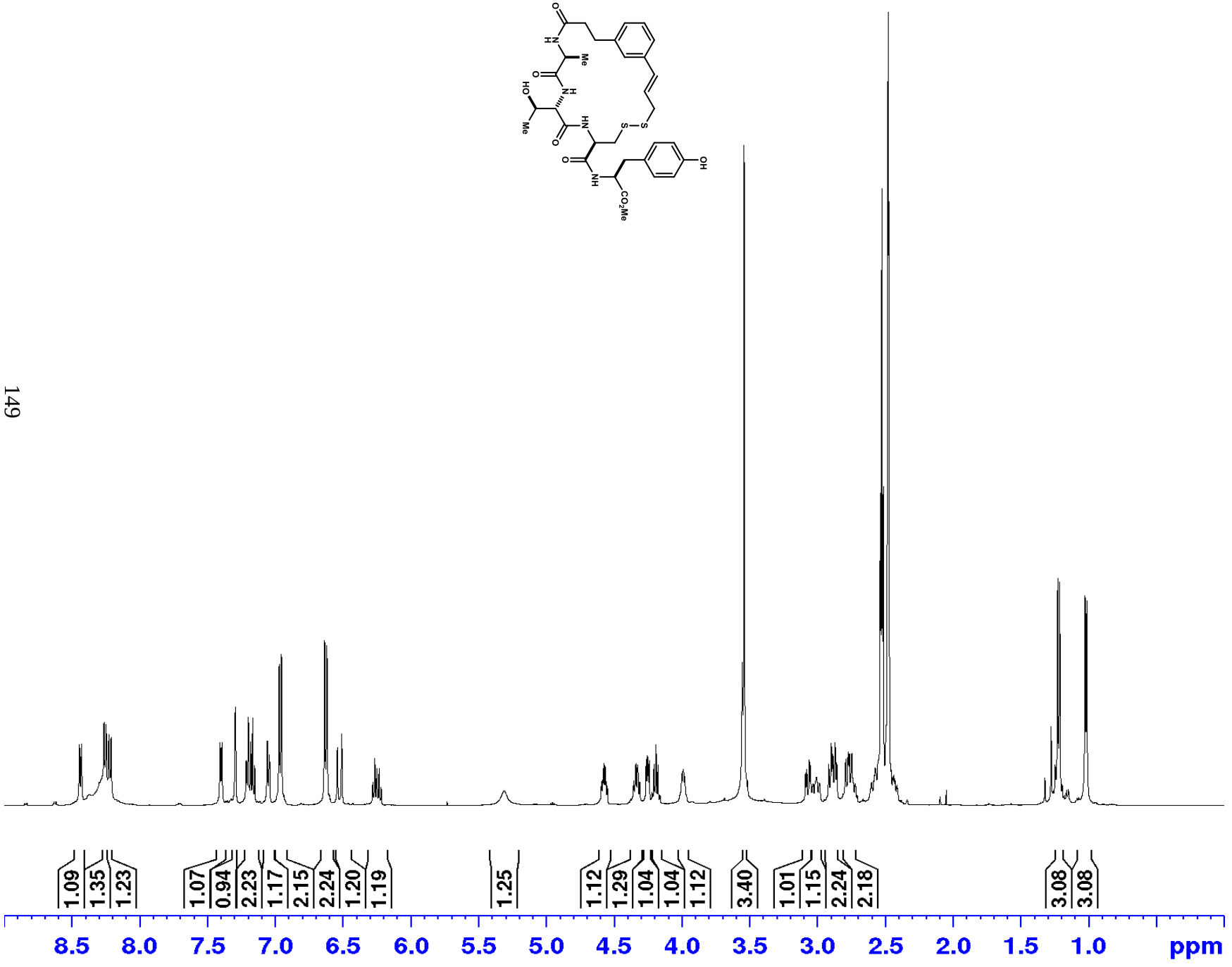
^{1}H NMR of compound 2.21 (MeOD -d4, 500 MHz)



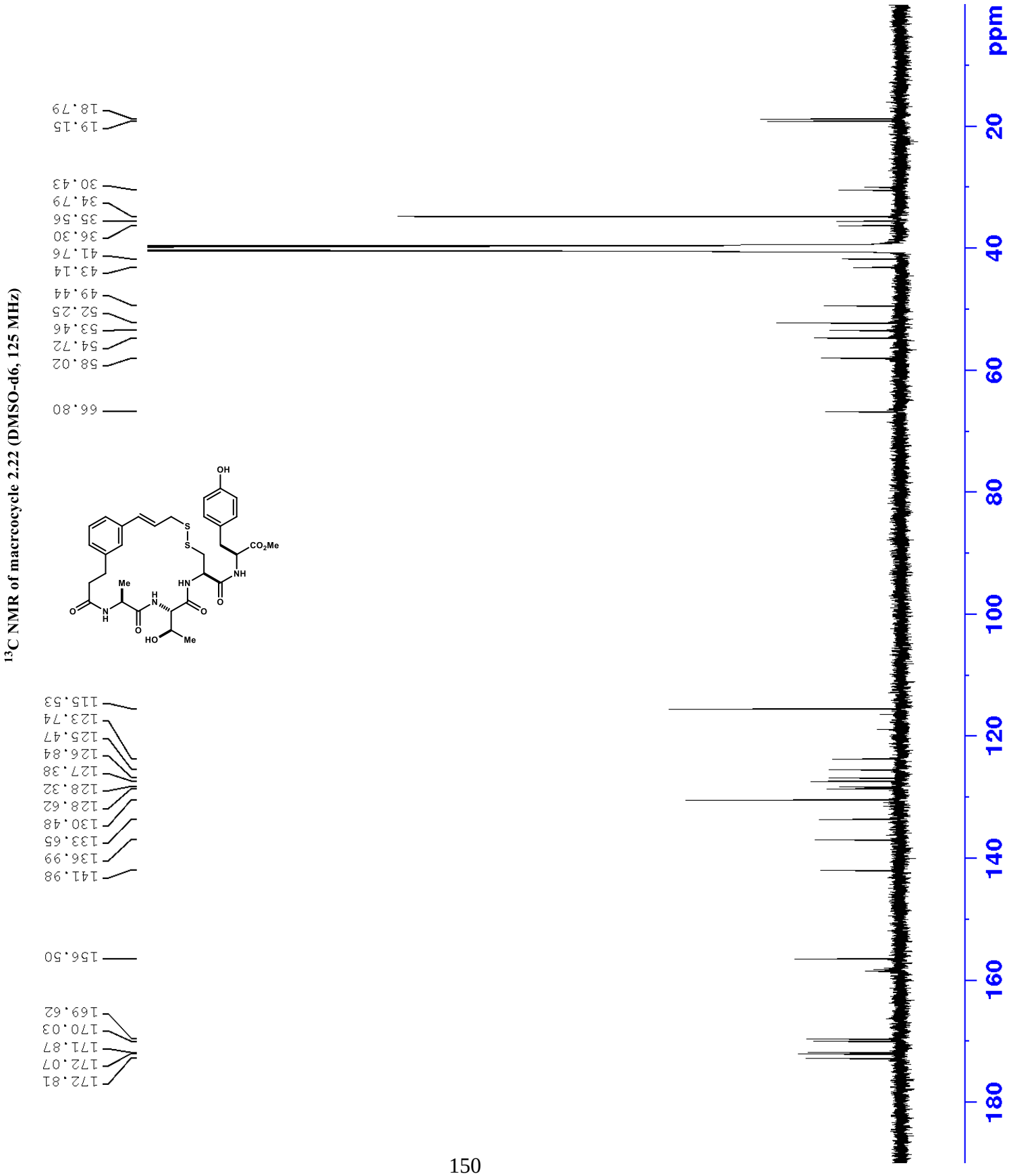
^{13}C NMR of compound 2.21 (MeOD -d4, 125 MHz)



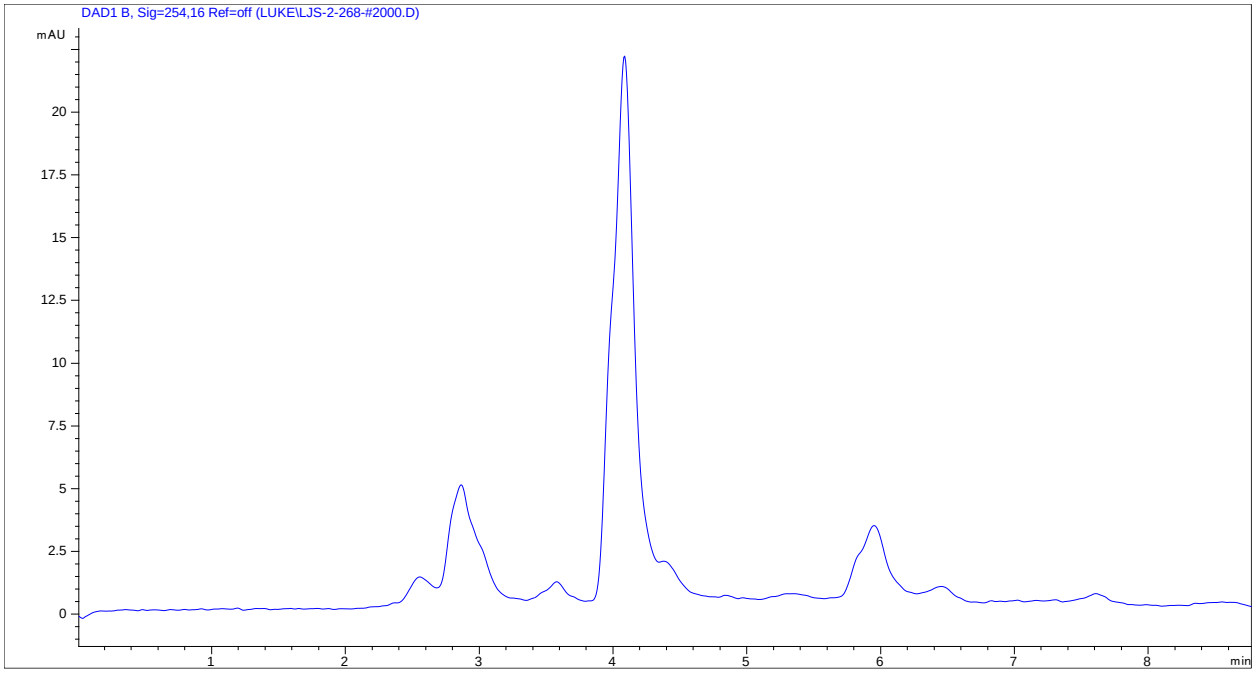
^{1}H NMR of macrcocycle 2.22 (DMSO-d6, 500 MHz)



^{13}C NMR of macrcocycle 2.22 (DMSO-d6, 125 MHz)

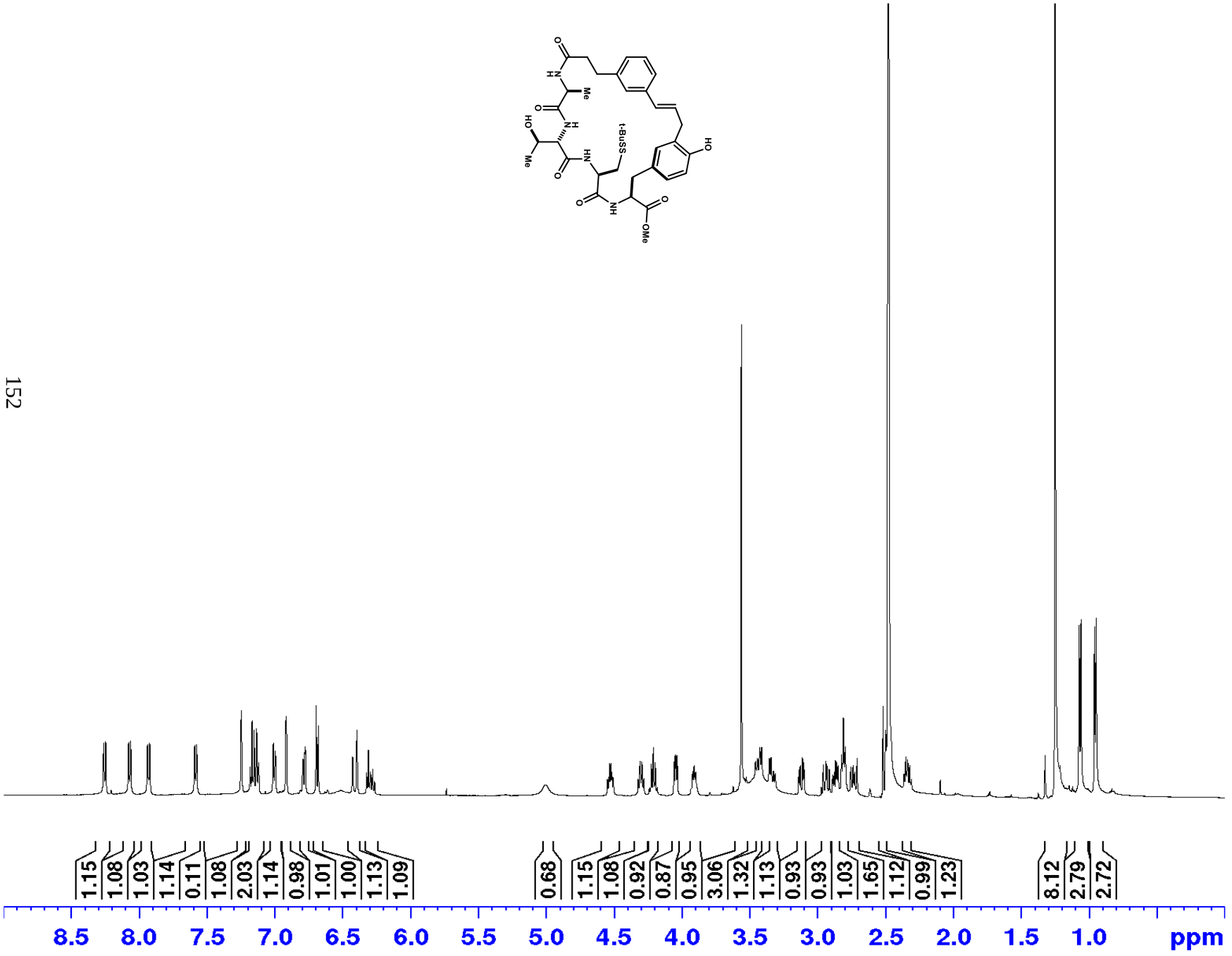


2.22 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

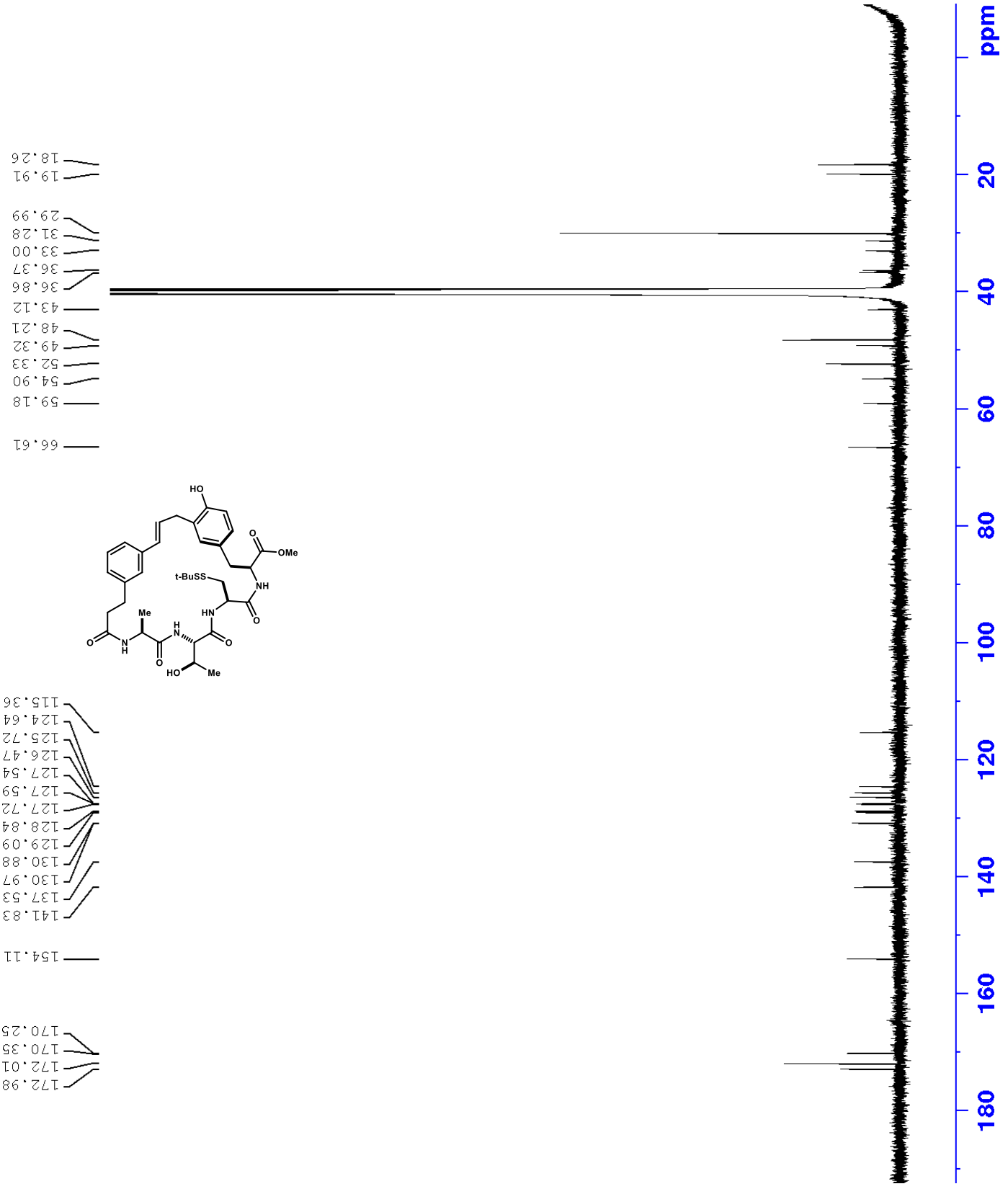



```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         12.00 min
    Posttime               :      Off

Solvents
    Solvent A              :        0.0 % (Water)
    Solvent B              :      100.0 % (Organic)

Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar


      Time    Solv.B   Flow  Pressure
    |-------|-------|--------|-------|
         0.00  100.0    10.000
         2.00  100.0    18.000
        10.00  100.0    18.000
        11.00  100.0    18.000
        12.00   35.0    18.000
```

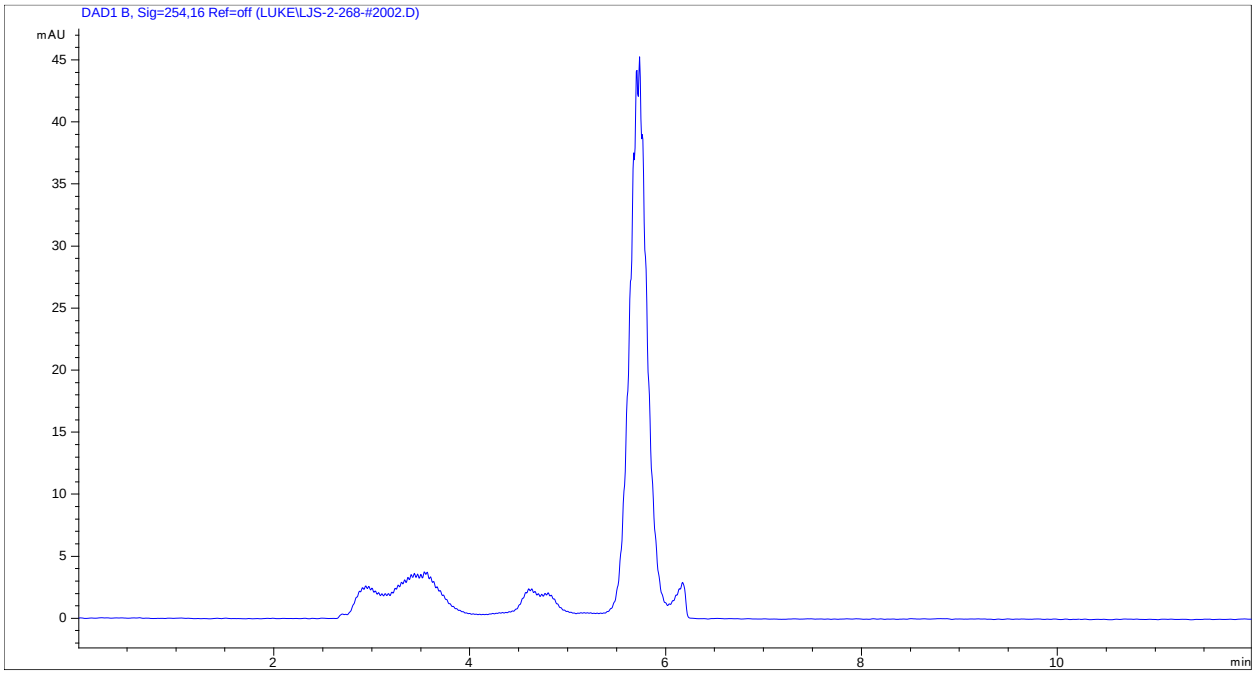
^{1}H NMR of macrcocycle 2.23 (DMSO-d6, 500 MHz)



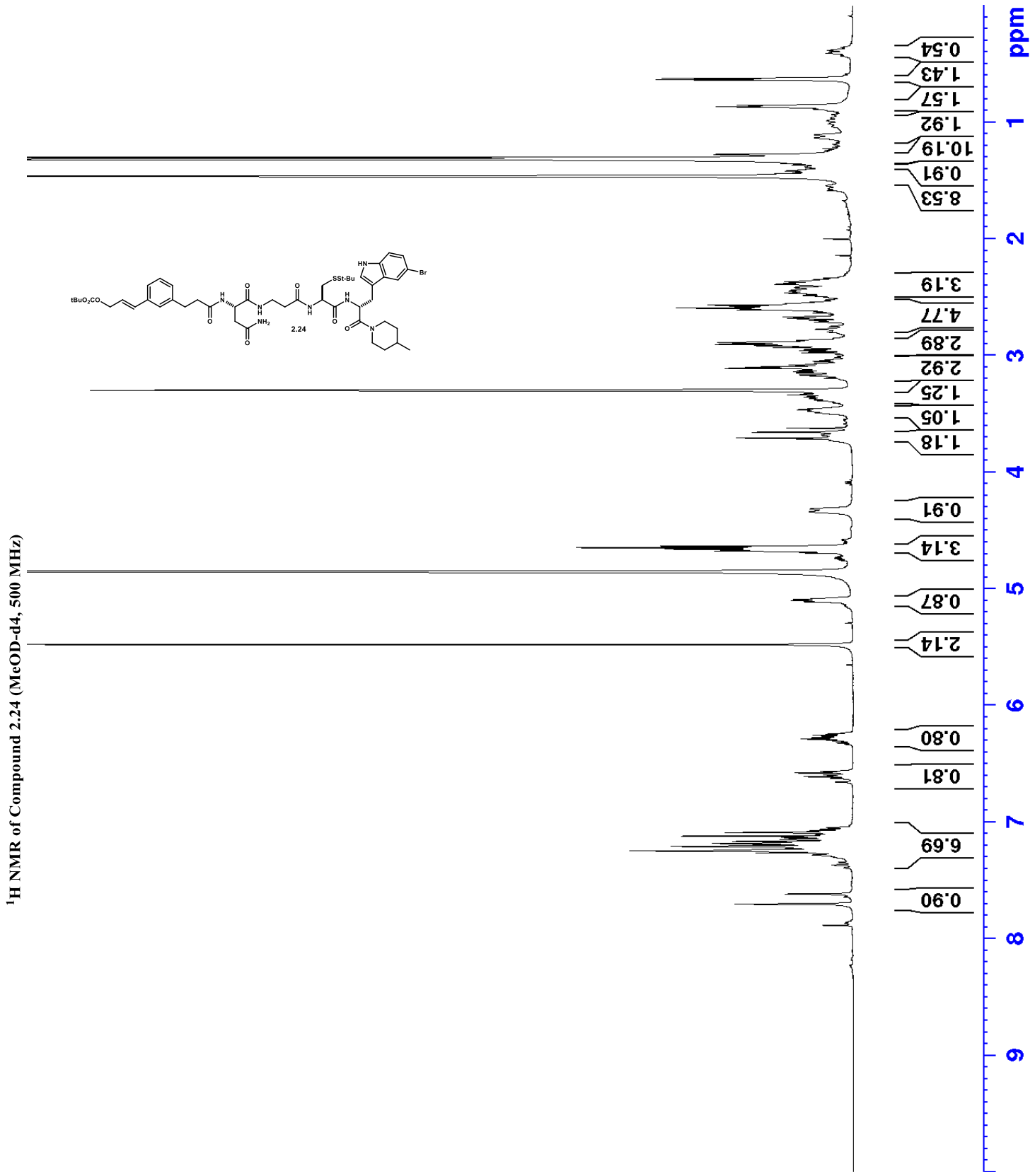
^{13}C NMR of macrocycle 2.23 (DMSO-d6, 125 MHz)

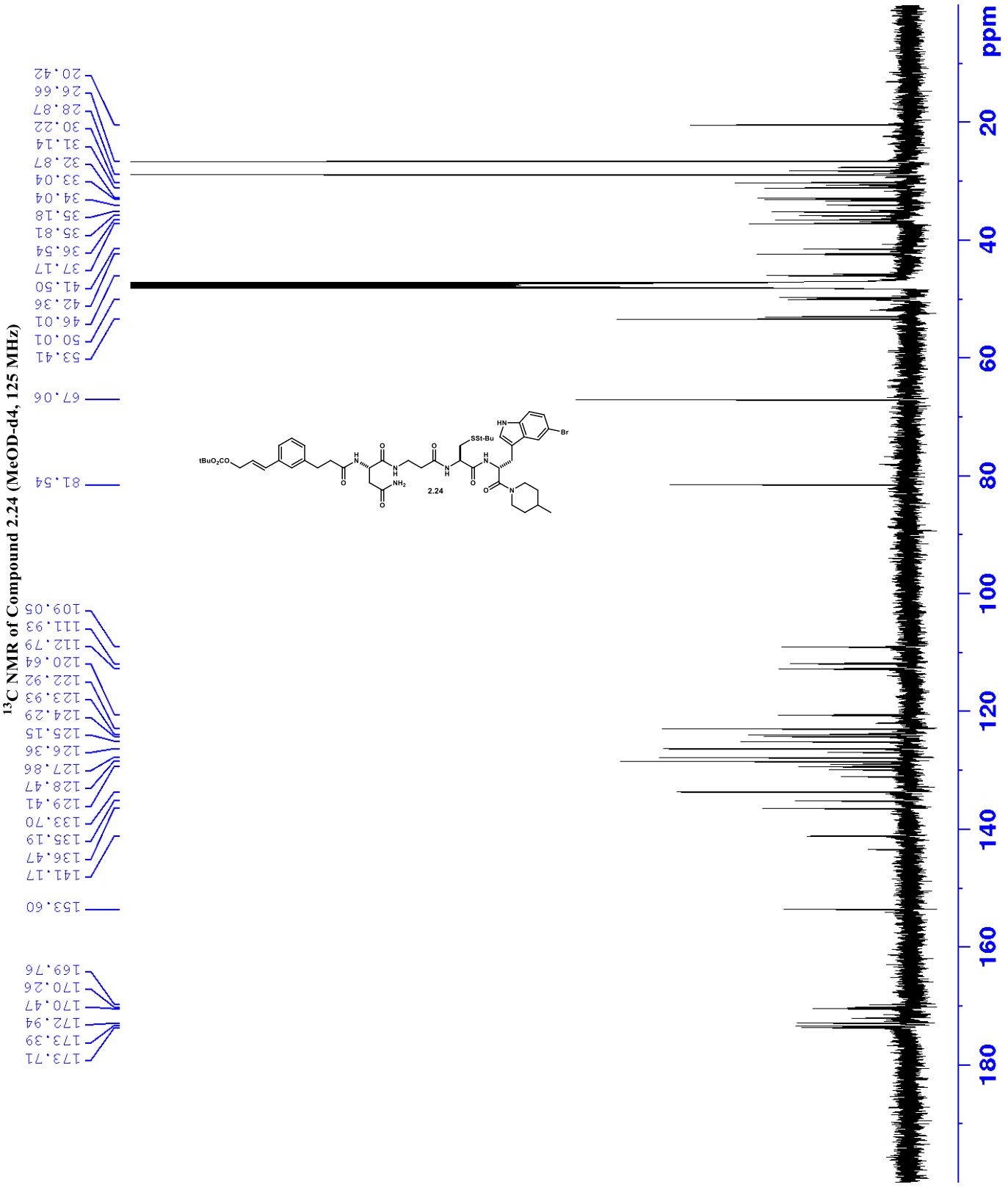


2.23 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

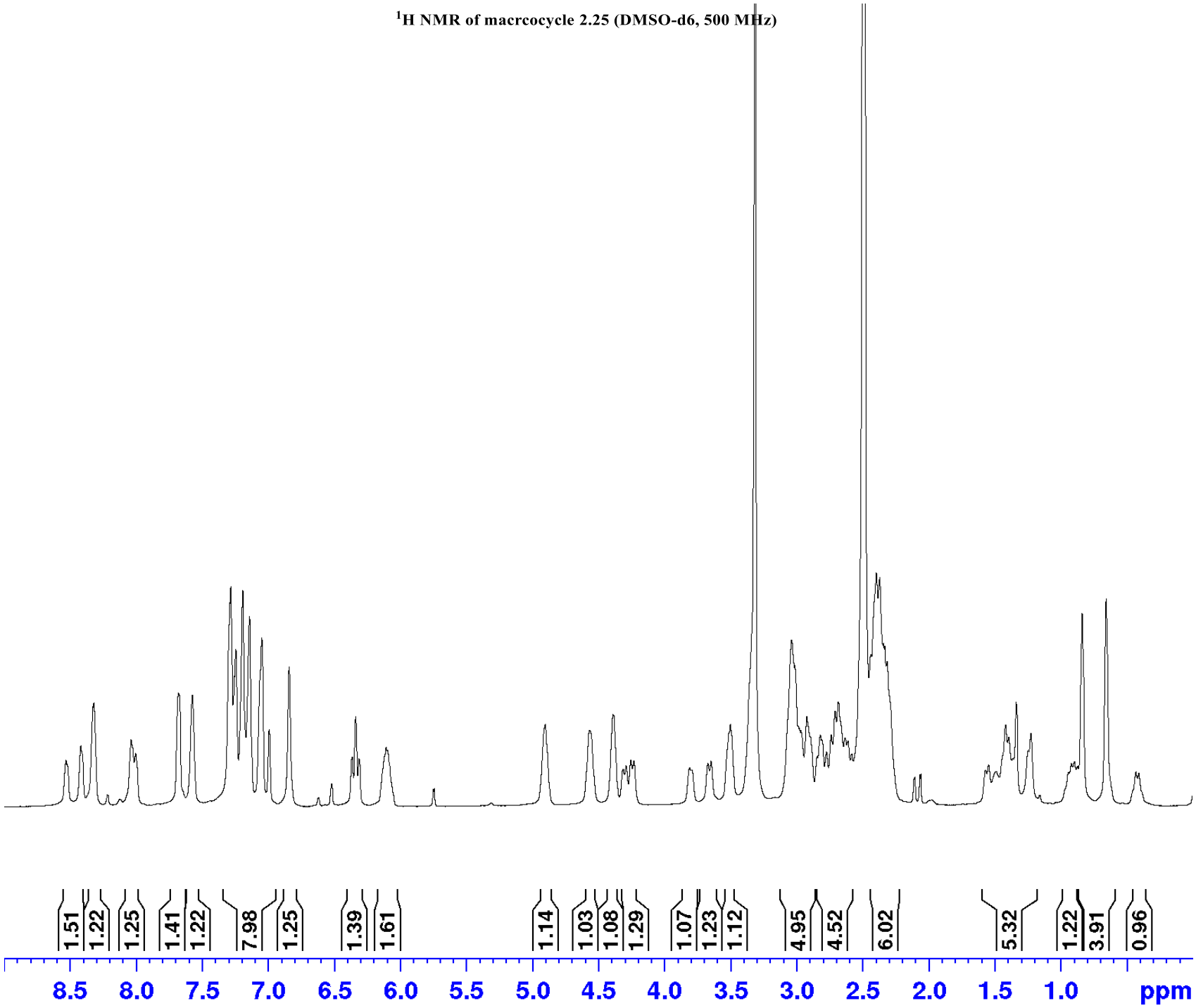



```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         12.00 min
    Posttime               :      Off

Solvents
    Solvent A              :        0.0 % (Water)
    Solvent B              :      100.0 % (Organic)

Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar

Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00  100.0    10.000
         2.00  100.0    18.000
        10.00  100.0    18.000
        11.00  100.0    18.000
        12.00   35.0    18.000
```

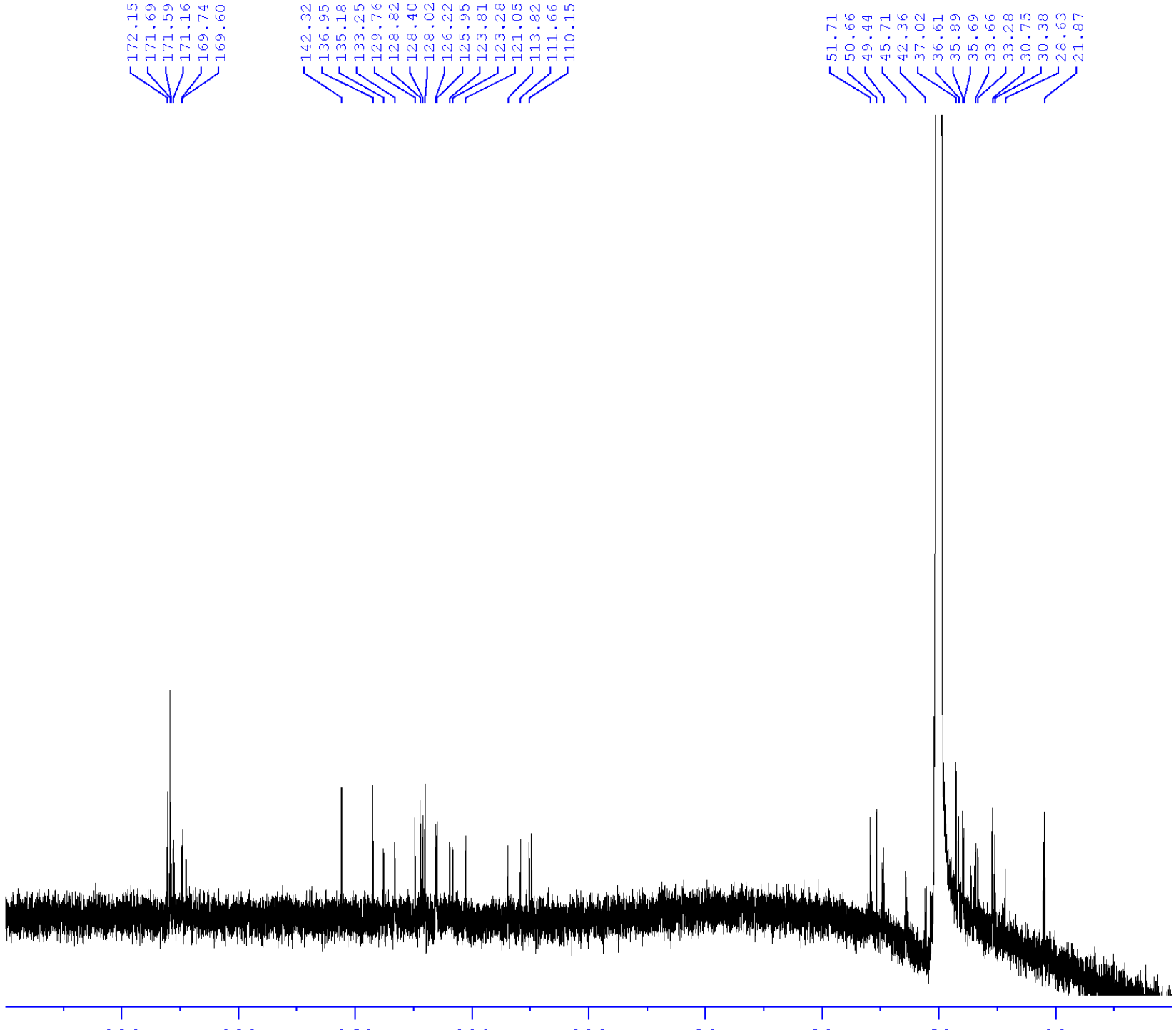

^{1}H NMR of Compound 2.24 (MeOD-d4, 500 MHz)
2.24
tBuO2CO
SSt-Bu
HN
Br
NH2
ppm
0.54
1.43
1.57
1.92
10.19
0.91
8.53
3.19
4.77
2.89
2.92
1.25
1.05
1.18
0.91
3.14
0.87
2.14
0.80
0.81
6.69
0.90


^{13}C NMR of Compound 2.24 (MeOD-d4, 125 MHz)
20.42
26.66
28.87
30.22
31.14
32.87
33.04
34.04
35.18
35.81
36.54
37.17
41.50
42.36
46.01
50.01
53.41
67.06
81.54
109.05
111.93
112.79
120.64
122.92
123.93
124.29
125.15
126.36
127.86
128.47
129.41
133.70
135.19
136.47
141.17
153.60
169.76
170.26
170.47
172.94
173.39
173.71
ppm
20
40
60
80
100
120
140
160
180
2.24

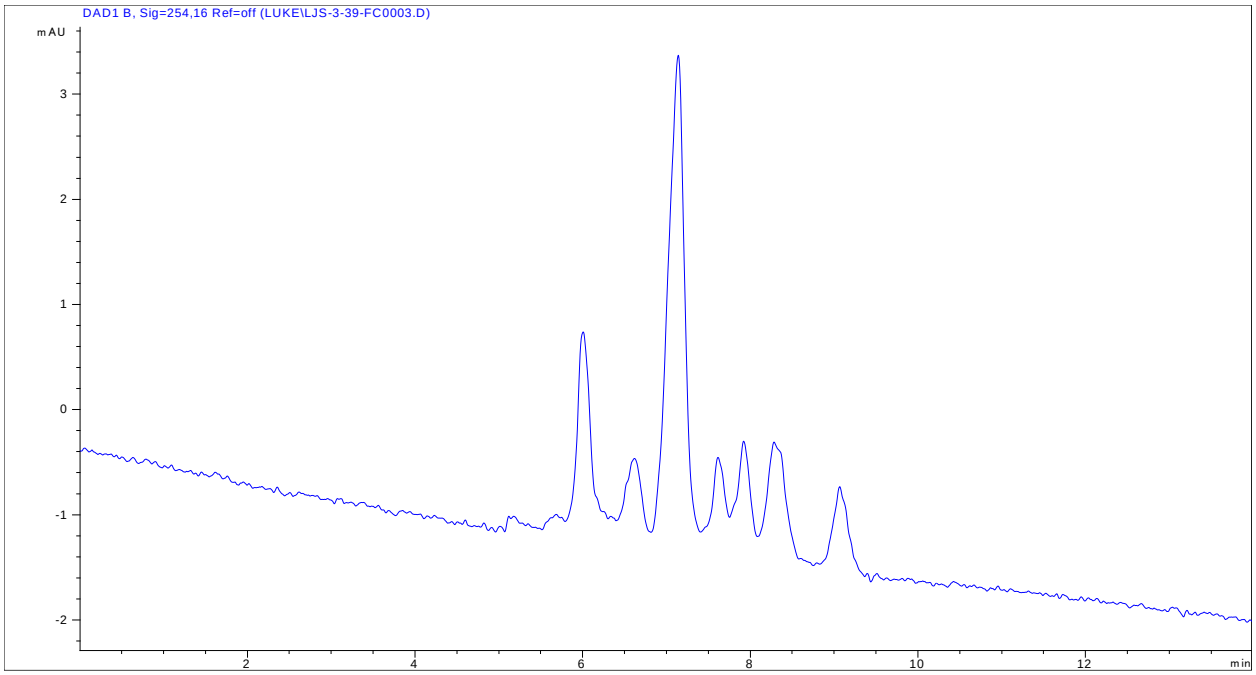
^{1}H NMR of macrcocycle 2.25 (DMSO-d6, 500 MHz)



^{13}C NMR of macrcocycle 2.25 (DMSO-d6, 125 MHz)



2.25 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



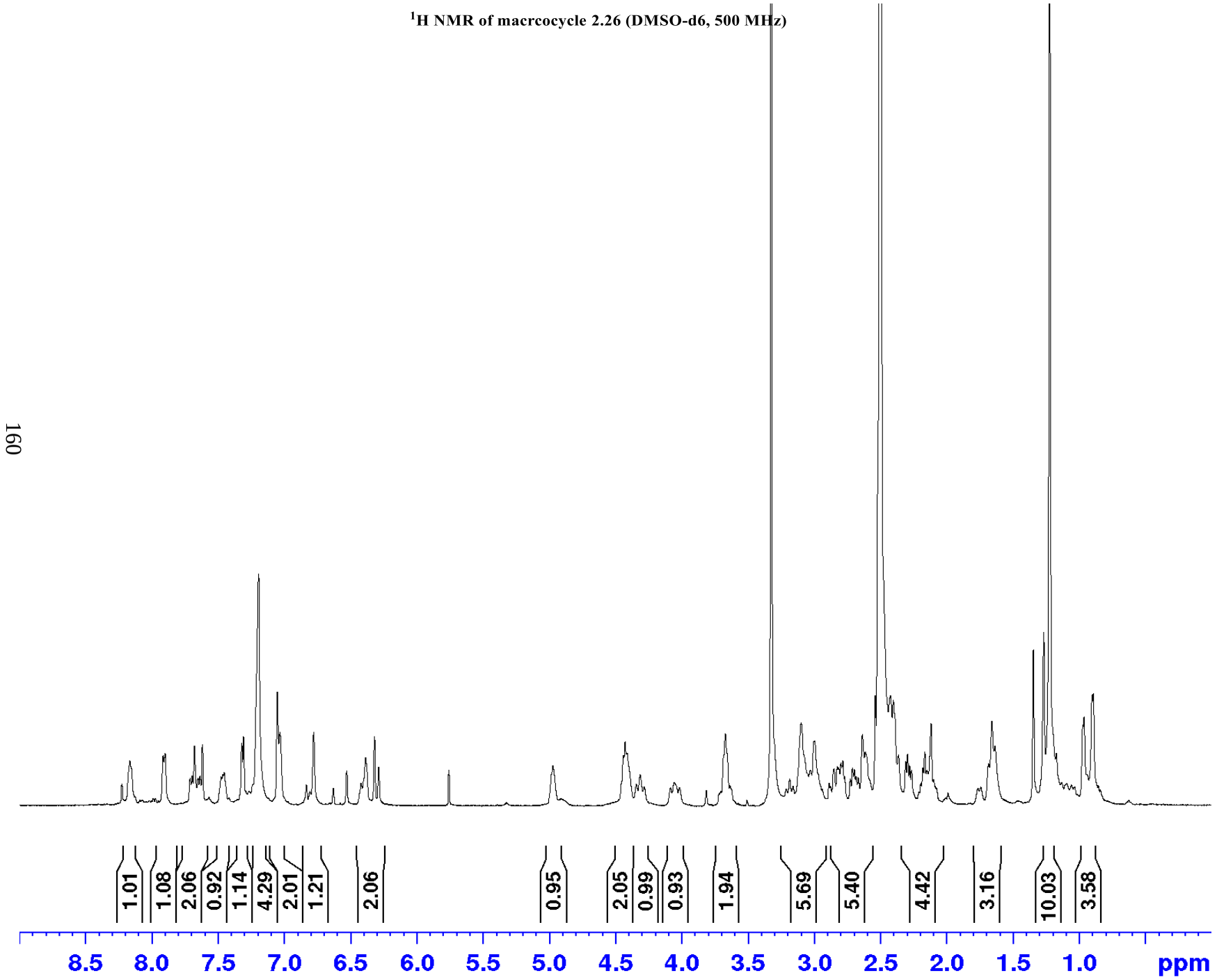
Agilent 1100/1200 Gradient Prep Pump

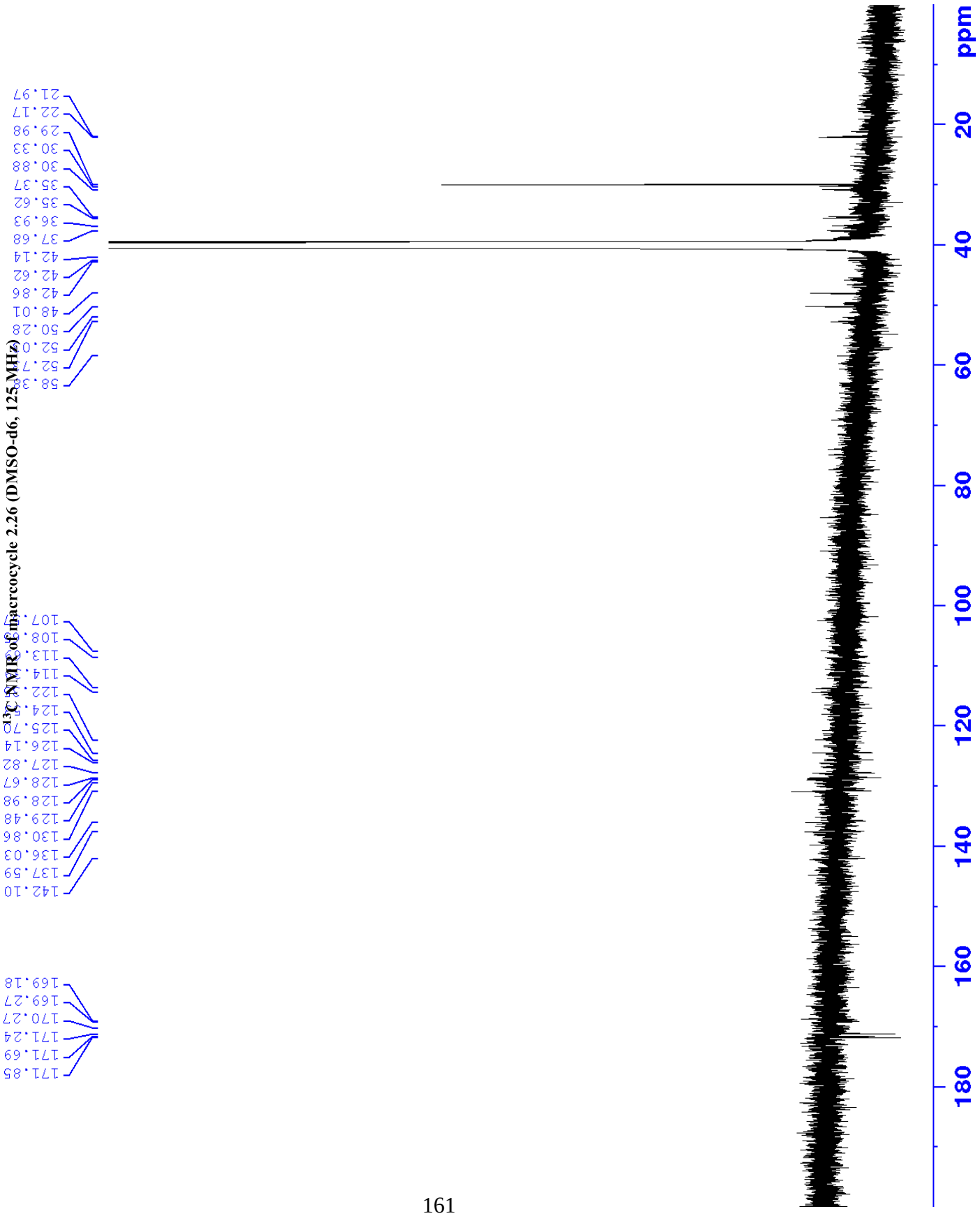
Control
- Column Flow : 15.000 ml/min
- Stoptime : 14.00 min
- Posttime : Off

Solvents
- Solvent A : 28.0 % (Water)
- Solvent B : 72.0 % (Organic)

Timetable

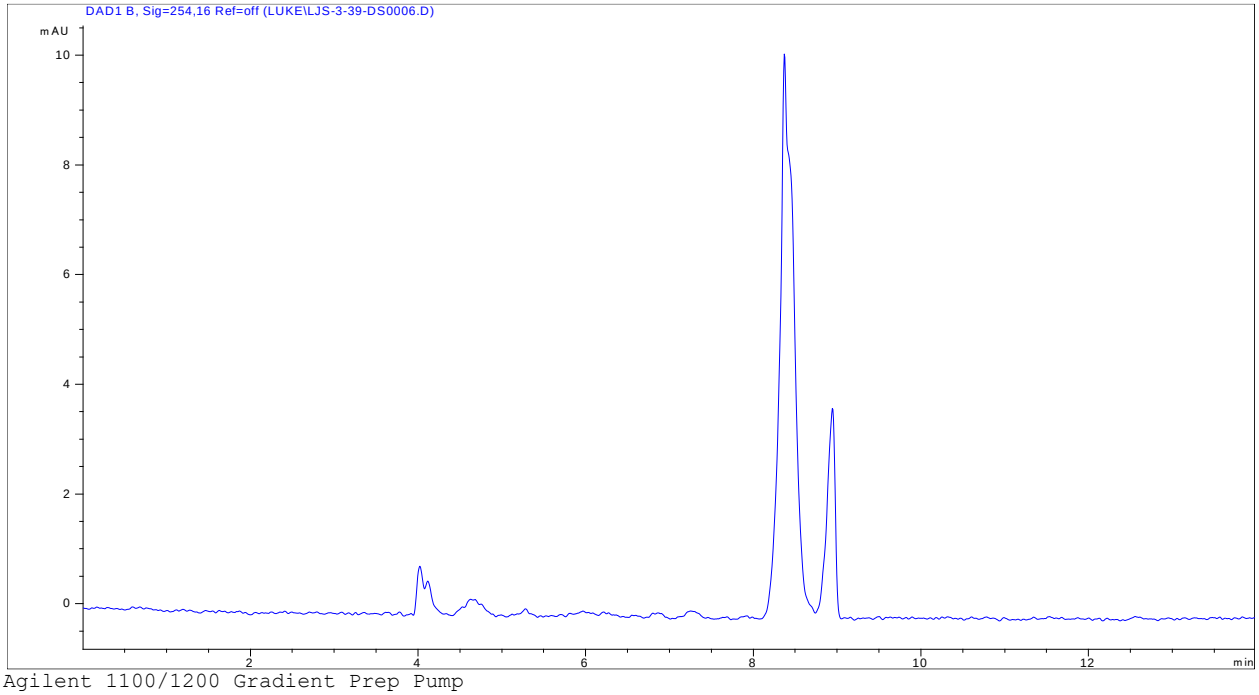
Time	Solv.B	Flow	Pressure
0.00	72.0	10.000	
2.00	72.0	18.000	
12.00	90.0	18.000	
13.00	100.0	18.000	
14.00	35.0	18.000	


^{1}H NMR of macrcocycle 2.26 (DMSO-d6, 500 MHz)
160
1.01
1.08
2.06
0.92
1.14
4.29
2.01
1.21
2.06
0.95
2.05
0.99
0.93
1.94
5.69
5.40
4.42
3.16
10.03
3.58
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
ppm



^{13}C NMR of macrcocycle 2.26 (DMSO-d6, 125 MHz)

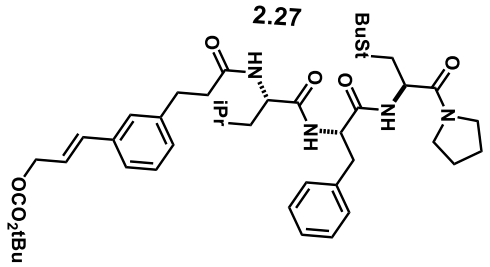
2.26 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



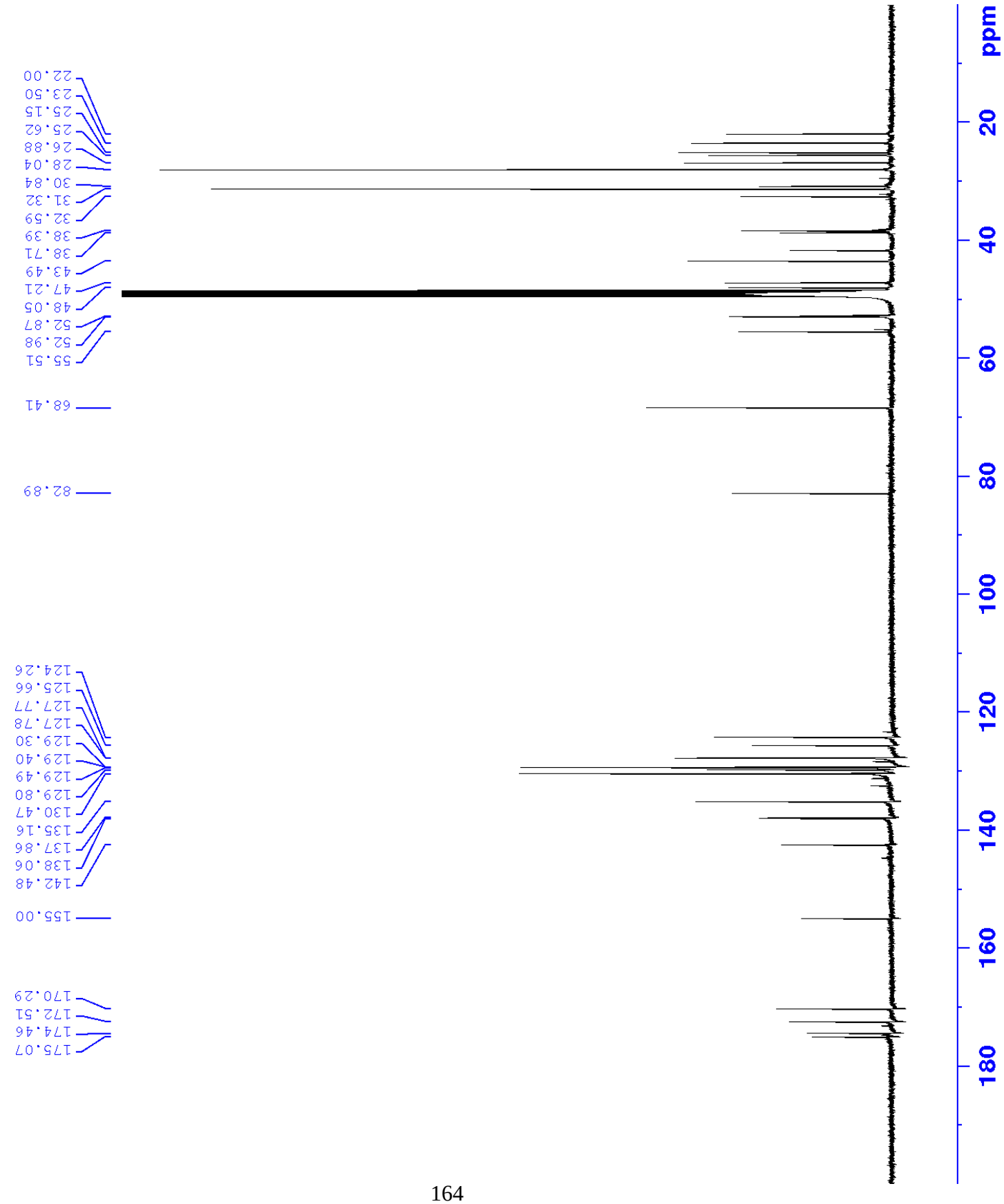
Agilent 1100/1200 Gradient Prep Pump

```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         14.00 min
    Posttime               :      Off

Solvents
    Solvent A              :       50.0 % (Water)
    Solvent B              :       50.0 % (Organic)

Timetable

       Time     Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00    50.0    10.000
         2.00    50.0    18.000
        12.00    85.0    18.000
        13.00   100.0    18.000
        14.00    35.0    18.000
```

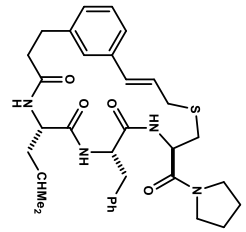
^{1}H NMR of compound 2.27 (MeOD -d4, 500 MHz)

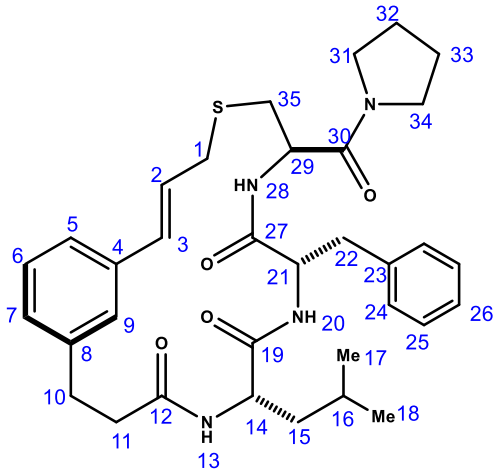


^{13}C NMR of compound 2.27 (MeOD -d4, 125 MHz)



^{1}H NMR of macrcocycle 2.28 (DMSO-d6, 500 MHz)

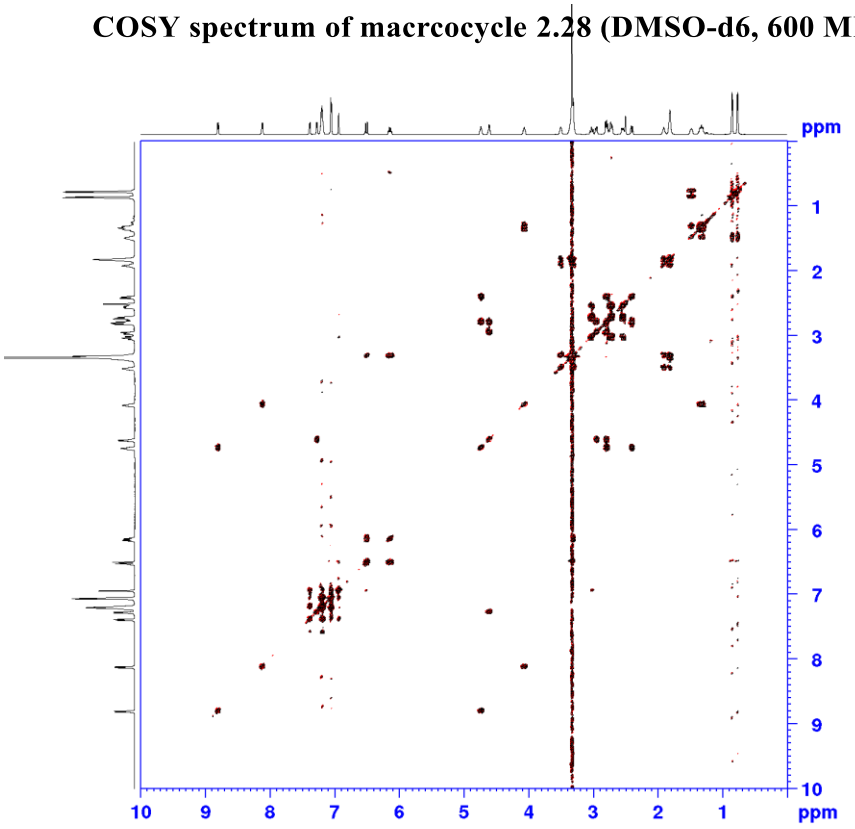




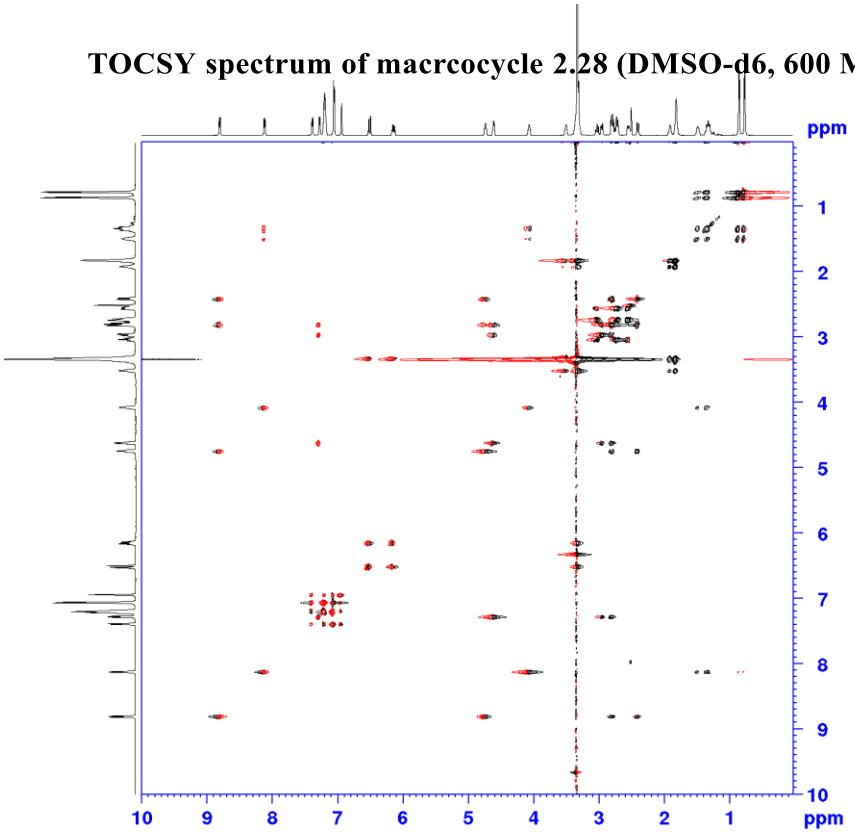
atom	*13C*	*1H*	Corr.
1	32.4	3.33 (m, 2H, overlap/ water)	2->1 COSY 2->HMBC
2	132.8	6.50, (d, J = 15.7 Hz, 1H)	key
3	123.9	6.14 (dt, *J* = 15.5, 7.6 Hz, 1H),	2->3 HMBC 2->3 COSY
4	136.0		3->4 HMBC 2->4 HMBC
5	121.0	7.38 (d, *J* = 7.6 Hz, 1H),	
6	127.6	7.05 (m, 1H)	5->6 HMBC
7	129.2	7.05 (m, 1H)	5->7 HMBC
8	141.0		11->8 HMBC
9	125.8	6.94 (s, 1H)	
10	28.0	3.02 (t, *J* = 13.1 Hz, 1H), 2.79 (m, 1H)	9->10 HMBC 7->10 HMBC
11	32.6	2.72 (m, 1H), 2.54 (m, 1H)	10->11 HMBC 10->11 COSY
12	171.2		11->12 HMBC 14->12 HMBC
13		8.12 (d, *J* = 8.2 Hz, 1H)	14->13 COSY
14	52.0	4.07 (dd, *J* = 13.3, 9.4 Hz, 1H)	key
15	41.2	1.41 – 1.23 (m, 2H)	14->15 COSY 14->15 HMBC
16	24.2	1.53-1.42 (m, 1H)	15->16 HMBC 15->16 COSY
17	22.9	0.85 (d, J = 6.4, 3H)	16->17 COSY

			16->17 HMBC
18	21.0	0.76 (d, J = 6.4, 3H)	16->18 COSY 16->18 HMBC
19	171.1		14->19 HMBC 21->19 HMBC
20		7.28 (d, *J* = 7.6 Hz, 1H)	21->20 COSY
21	52.0	4.61 (dd, *J* = 12.7, 6.4 Hz, 1H)	key
22	38.2	2.95 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.79 (m, overlap, 1H)	21->22 HMBC 21->22 COSY
23	136.4		21->23 HMBC
24	126.9	7.20 (m, overlap, 2H)	21->24 HMBC
25	126.0	7.20 (m, overlap, 2H)	21->25 HMBC
26	129.2	7.06 (m, 1H overlap, 1H)	23->26 HMBC
27	167.4		21->27 HMBC 29->27 HMBC
28		8.80 (d, *J* = 8.4 Hz, 1H)	COSY 29->28
29	48.9	4.73 (t, *J* = 7.3 Hz, 1H)	
30	167.7		35->30 HMBC
31	45.4	3.50 (m, 1H), 3.33 (m, 1H, overlap w/ water)	
32	23.7	1.81 (m, 2H, overlap)	
33	25.3	1.91 (m, 1H), 1.81 (m, 1H)	
34	45.8	3.33 (m, 2H, overlap w/ water)	
35	29.9	2.79 (m, overlap 1H) 2.40 (dd, *J* = 13.3, 2.5 Hz, 1H)	1->35 HMBC

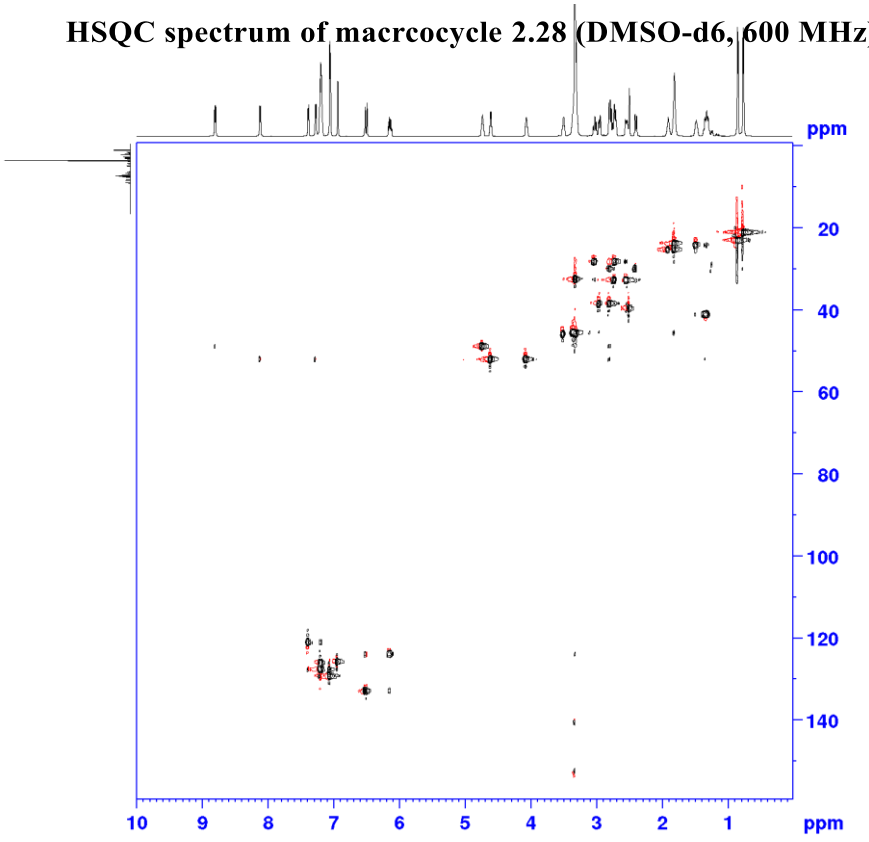
COSY spectrum of macrcocycle 2.28 (DMSO-d6, 600 MHz)



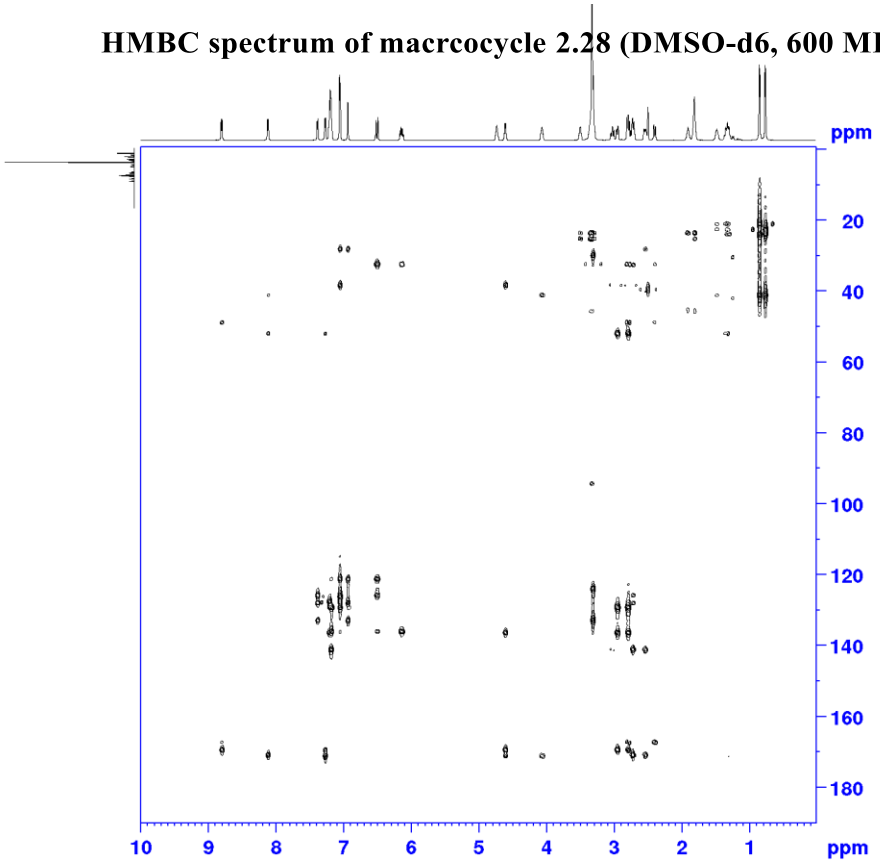
TOCSY spectrum of macrcocycle 2.28 (DMSO-d6, 600 MHz)



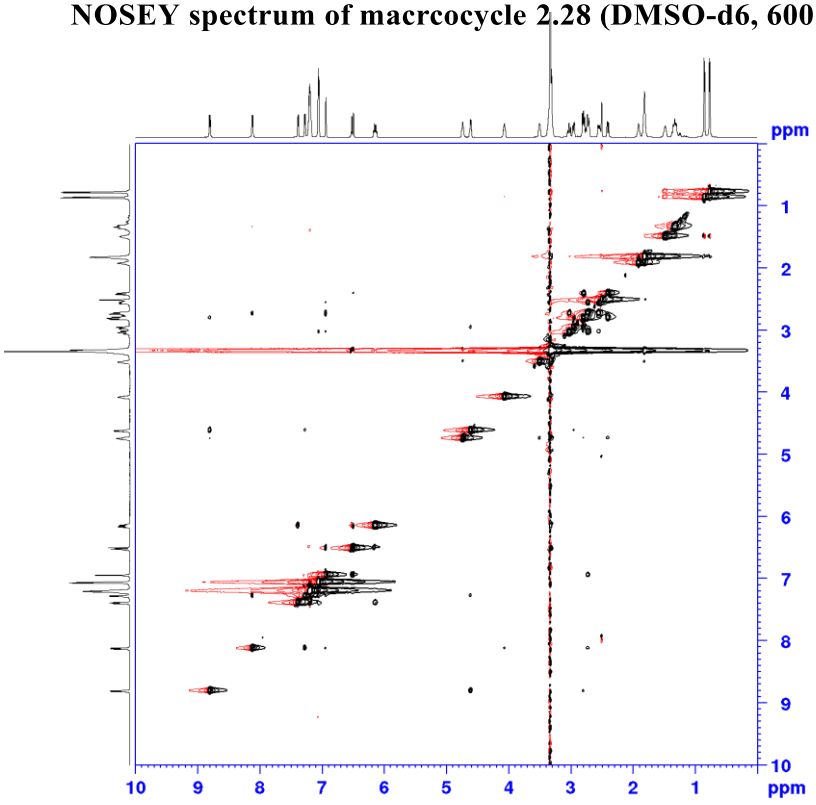
HSQC spectrum of macrcocycle 2.28 (DMSO-d6, 600 MHz)



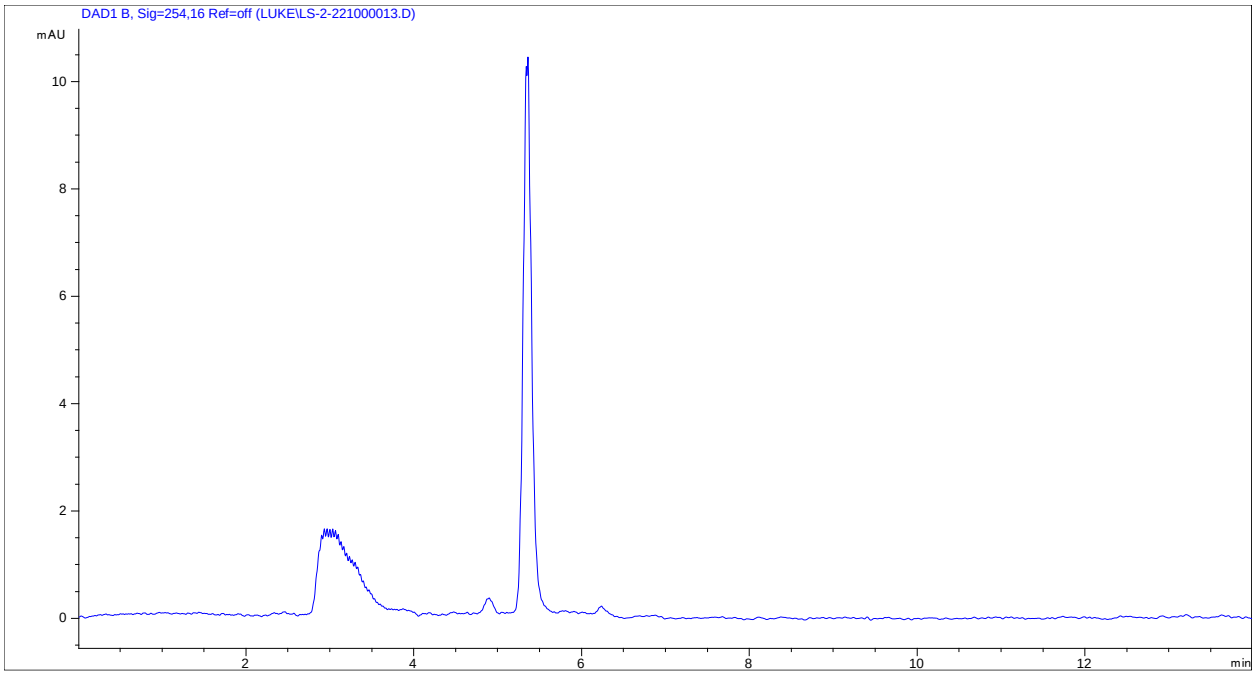
HMBC spectrum of macrcocycle 2.28 (DMSO-d6, 600 MHz)



NOSEY spectrum of macrcocycle 2.28 (DMSO-d6, 600 MHz)

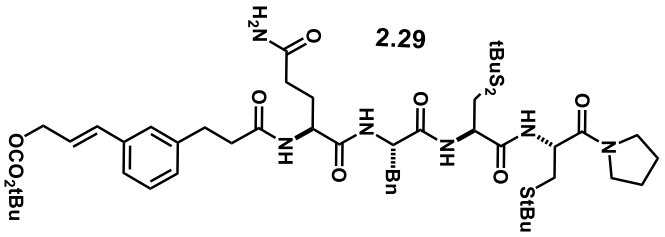


2.28 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

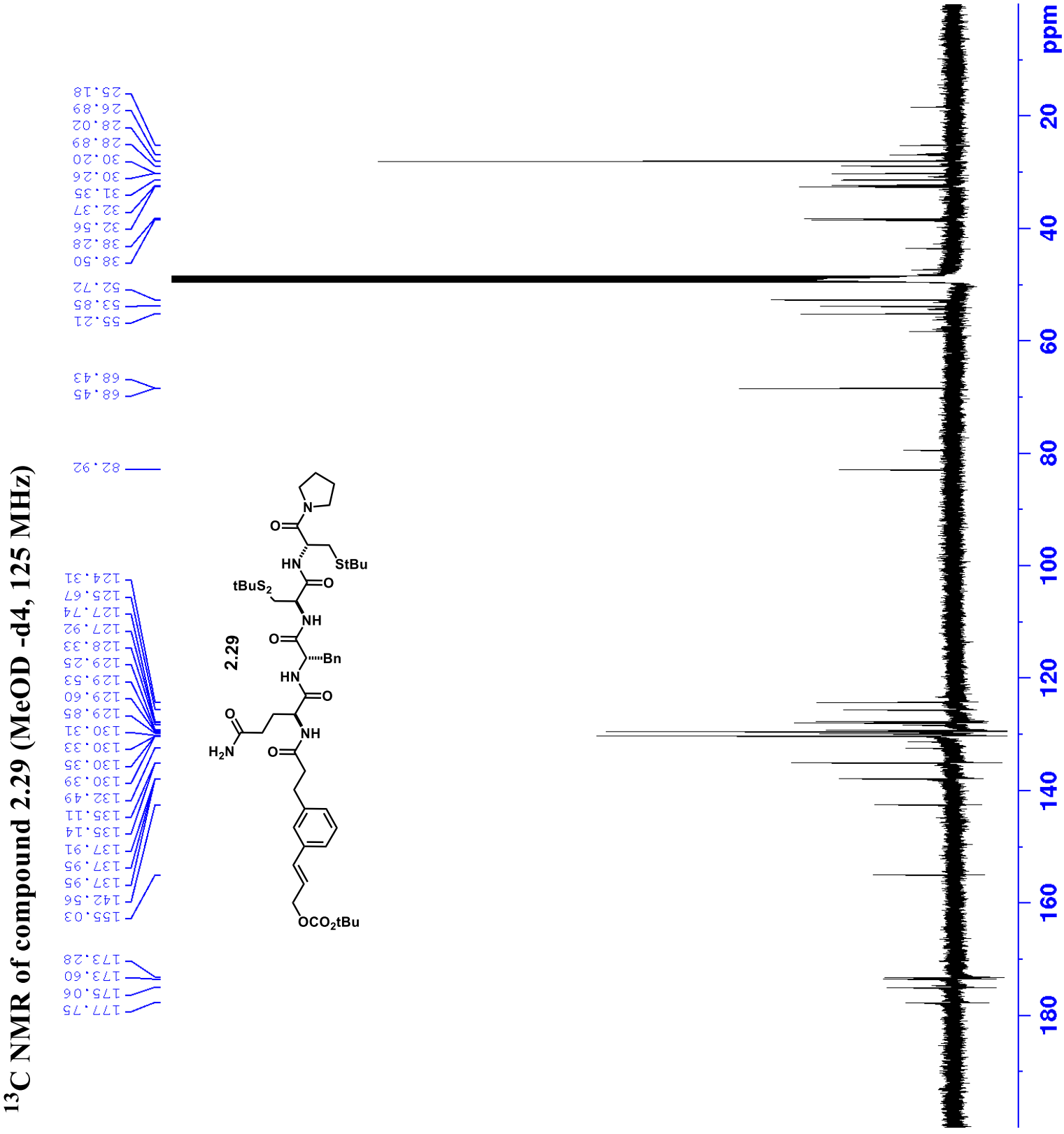



```
Control
    Column Flow            :      15.000 ml/min
    Stoptime               :         14.00 min
    Posttime               :      Off

Solvents
    Solvent A              :       30.0 % (Water)
    Solvent B              :       70.0 % (Organic)

PressureLimits
    Minimum Pressure       :        0 bar
    Maximum Pressure       :      400 bar


Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar

Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00   70.0    10.000
         2.00   70.0    18.000
        10.00   95.0    18.000
        12.00  100.0    18.000
        14.00   35.0    18.000
```

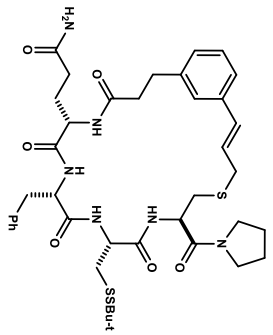
^{1}H NMR of compound 2.29 (MeOD -d4, 500 MHz)



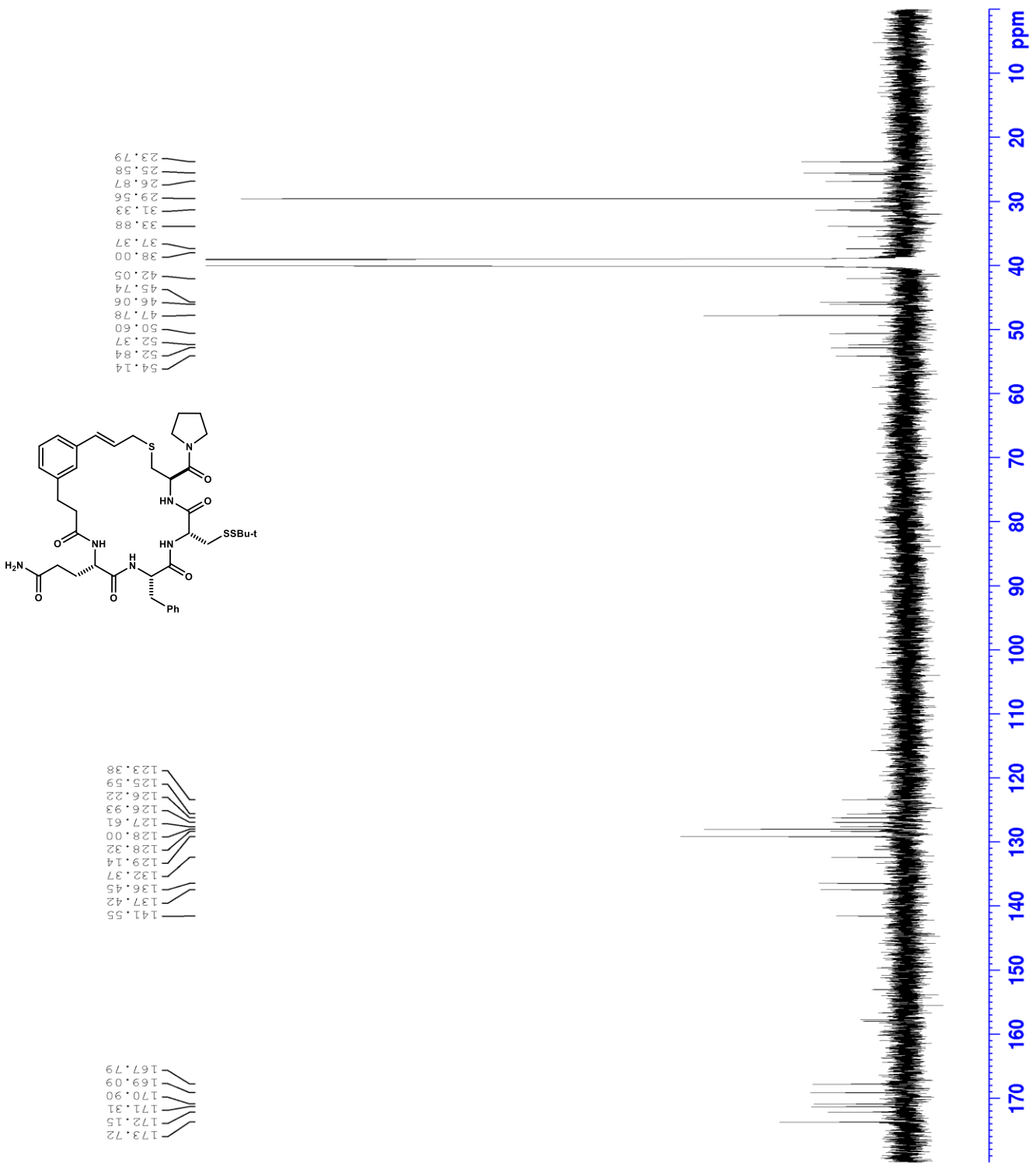
^{13}C NMR of compound 2.29 (MeOD -d4, 125 MHz)



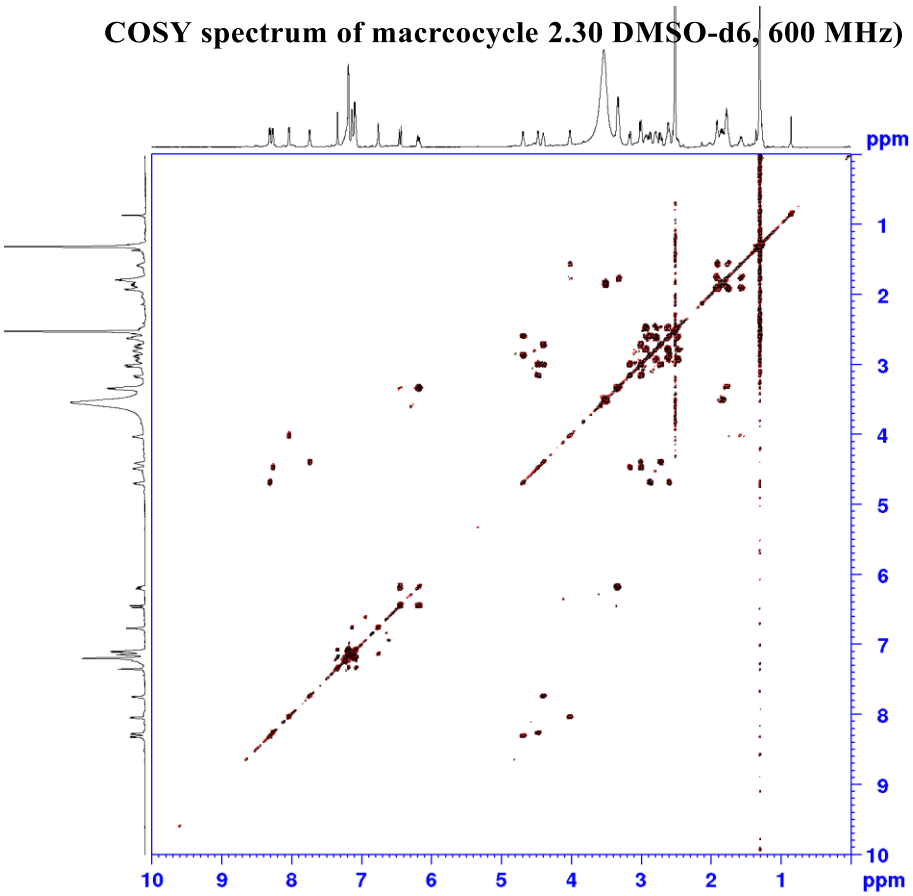
^{1}H NMR of macrcocycle 2.30 (DMSO-d6, 500 MHz)



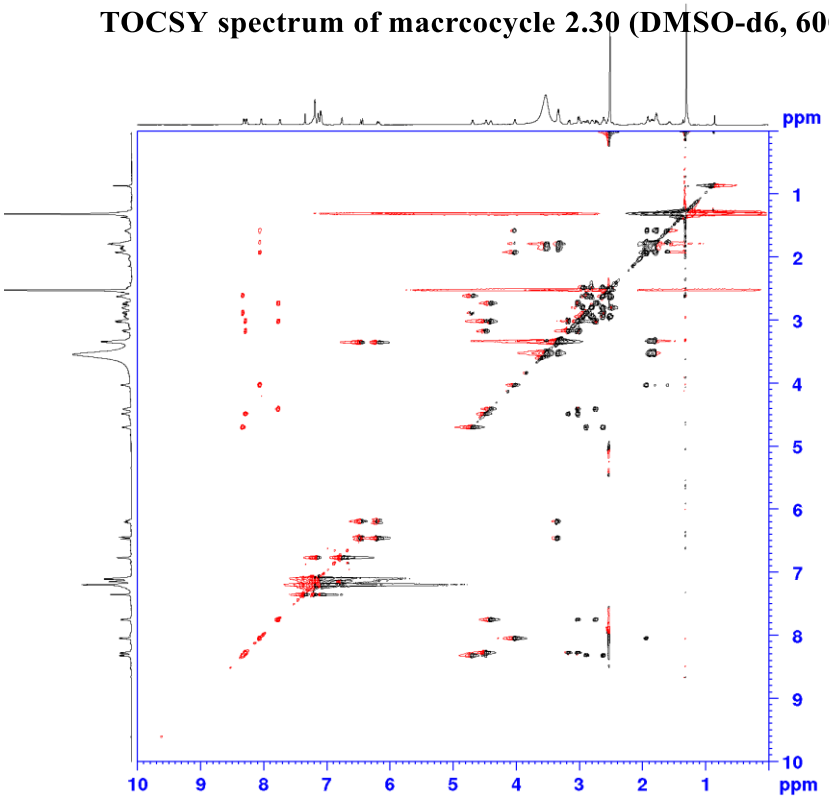
^{13}C NMR of macrocycle 2.30 (DMSO-d6, 126 MHz)



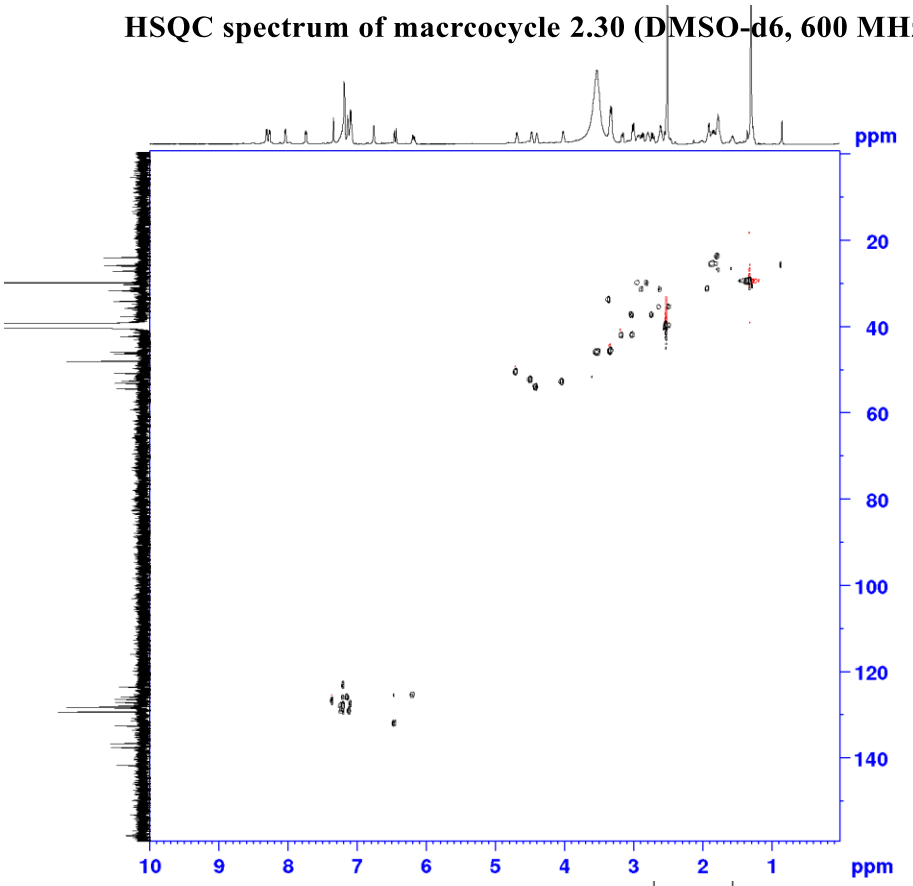
COSY spectrum of macrcocycle 2.30 DMSO-d6, 600 MHz)



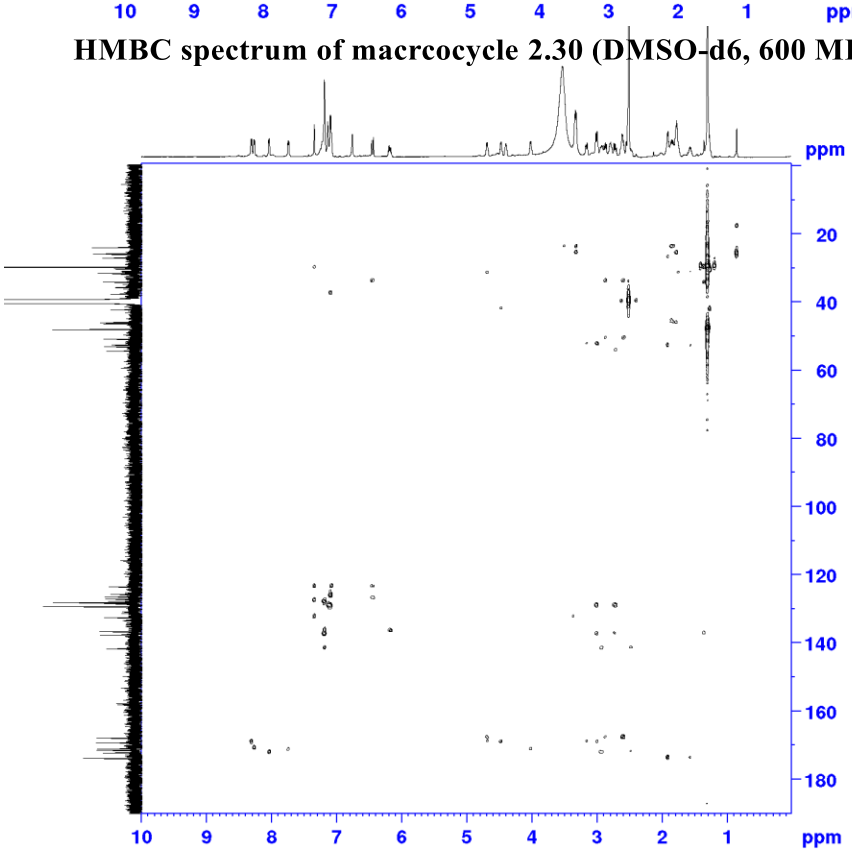
TOCSY spectrum of macrcocycle 2.30 (DMSO-d6, 600 MHz)



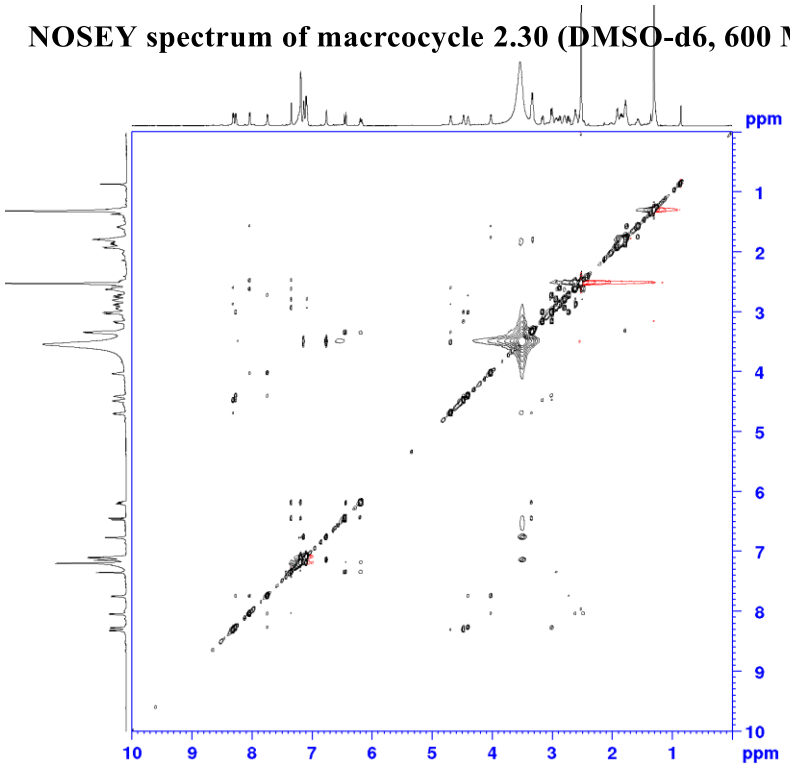
HSQC spectrum of macrcocycle 2.30 (DMSO-d6, 600 MHz)



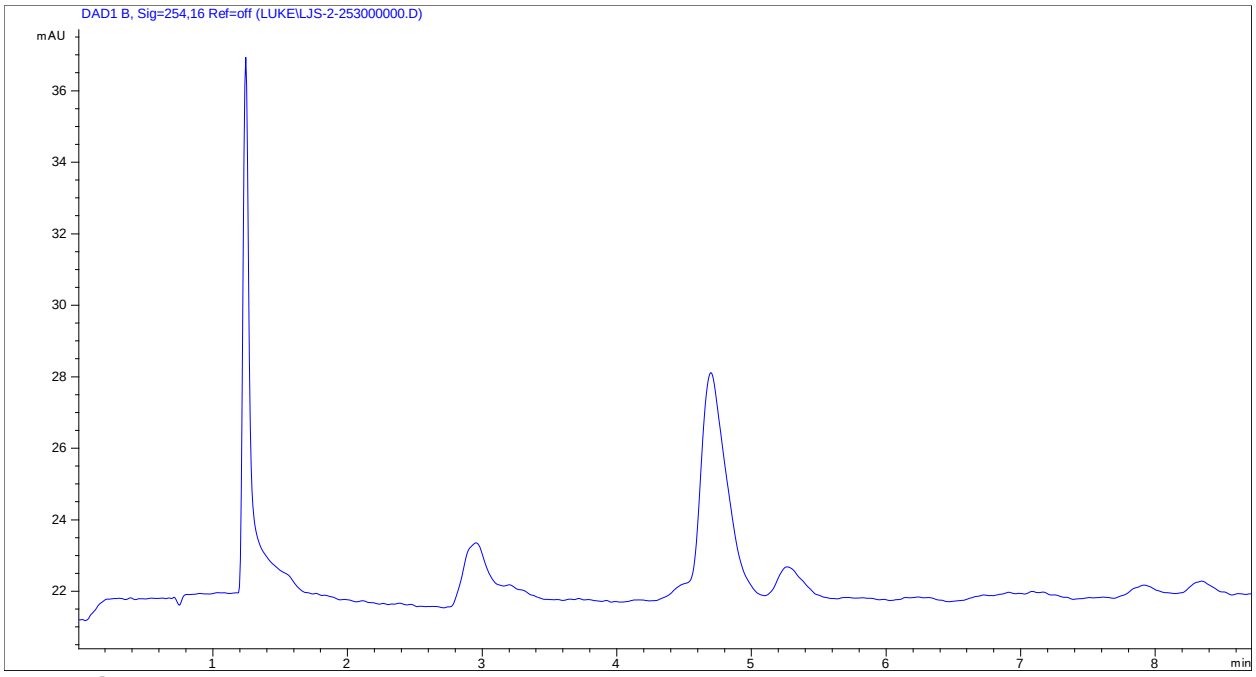
HMBC spectrum of macrcocycle 2.30 (DMSO-d6, 600 MHz)



NOSEY spectrum of macrcocycle 2.30 (DMSO-d6, 600 MHz)



2.30 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	15.000 ml/min
Stoptime	:	20.00 min
Posttime	:	Off

Solvents

Solvent A	:	65.0 % (Water)
Solvent B	:	35.0 % (Organic)

PressureLimits

Minimum Pressure	:	0 bar
Maximum Pressure	:	400 bar

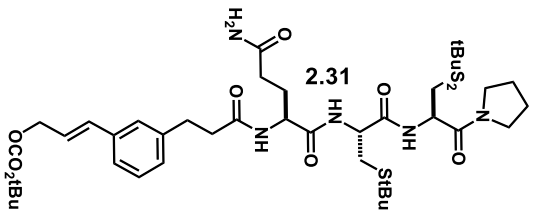
Auxiliary

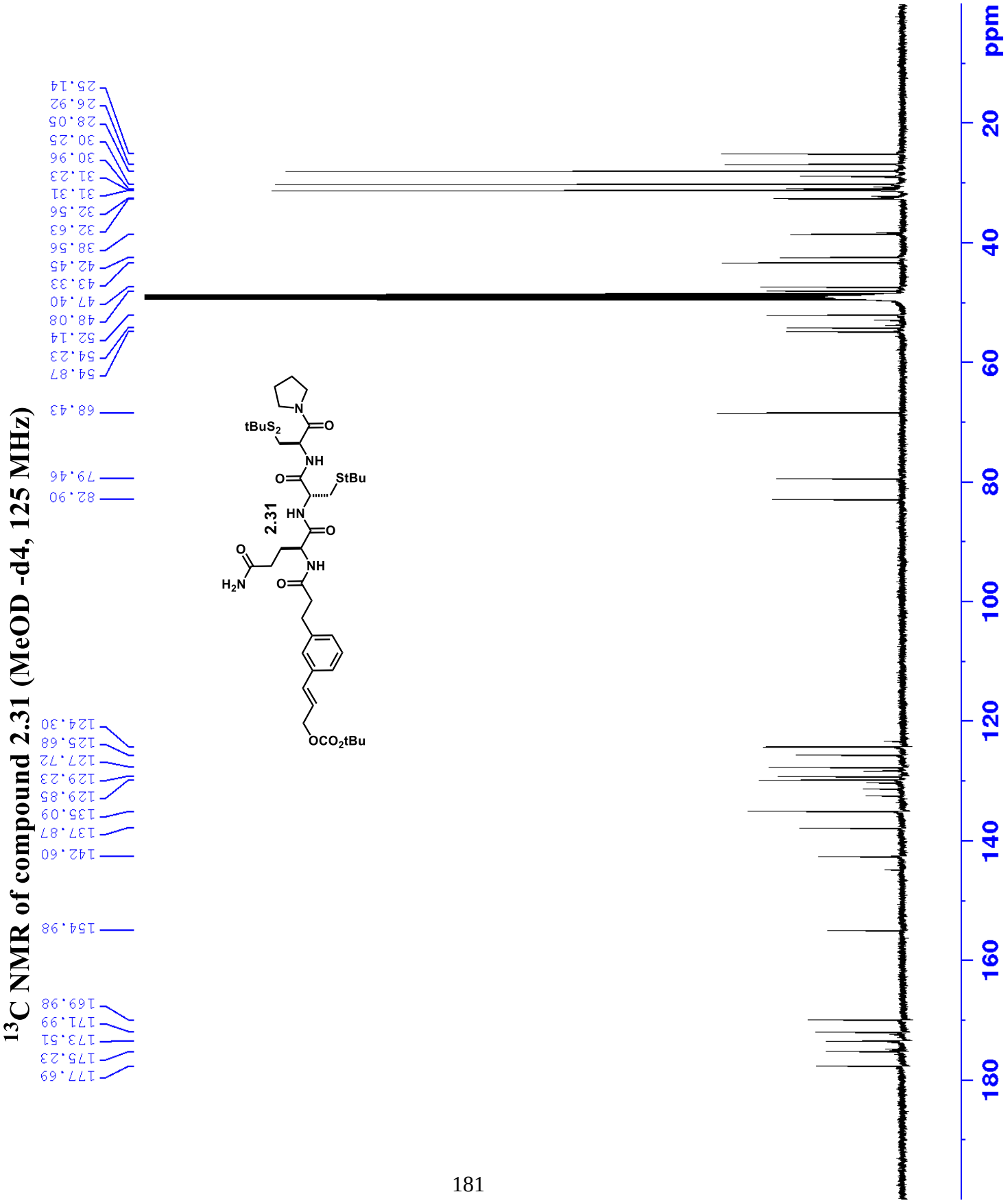
Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

Timetable

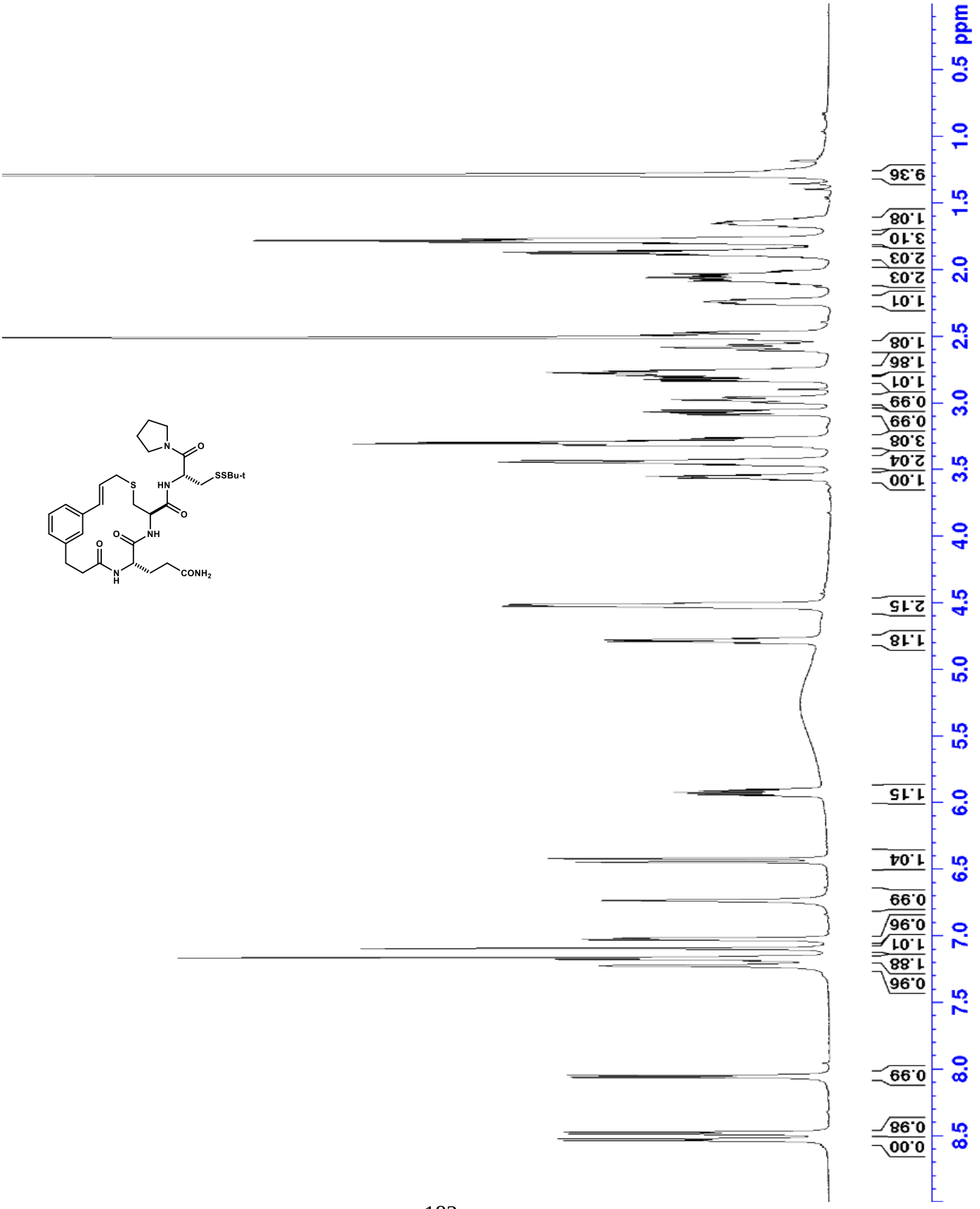
Time	Solv.B	Flow	Pressure
0.00	45.0	10.000	
2.00	45.0	18.000	
14.00	80.0	18.000	
16.00	100.0	18.000	
20.00	35.0	18.000	

^{1}H NMR of compound 2.31 (MeOD -d4, 500 MHz)

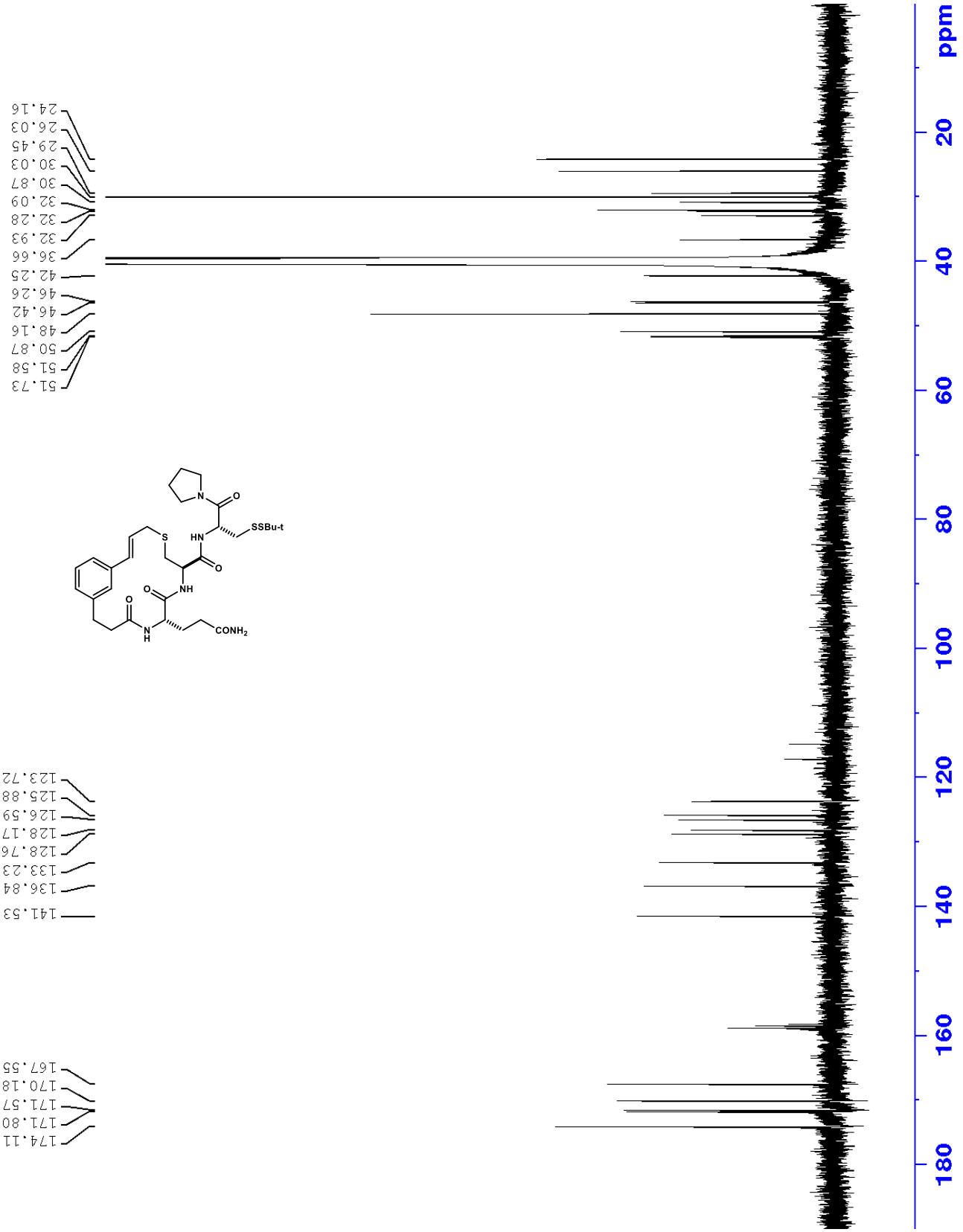


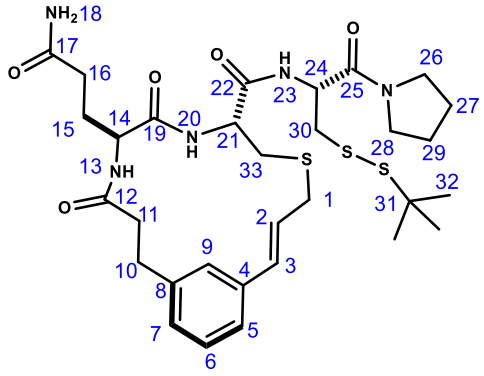

13C NMR of compound 2.31 (MeOD -d4, 125 MHz)
25.14
26.92
28.05
30.25
30.96
31.23
31.31
32.56
32.63
38.56
42.45
43.33
47.40
48.08
52.14
54.23
54.87
68.43
79.46
82.90
124.30
125.68
127.72
129.23
129.85
135.09
137.87
142.60
154.98
169.98
171.99
173.51
175.23
177.69
2.31
tBuS2
StBu
OCO2tBu
H2N
NH
HN
O
N
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of macrocycle 2.32 (DMSO-d6, 500 MHz)



^{13}C NMR of macrocycle 2.32 (DMSO-d6, 125 MHz)

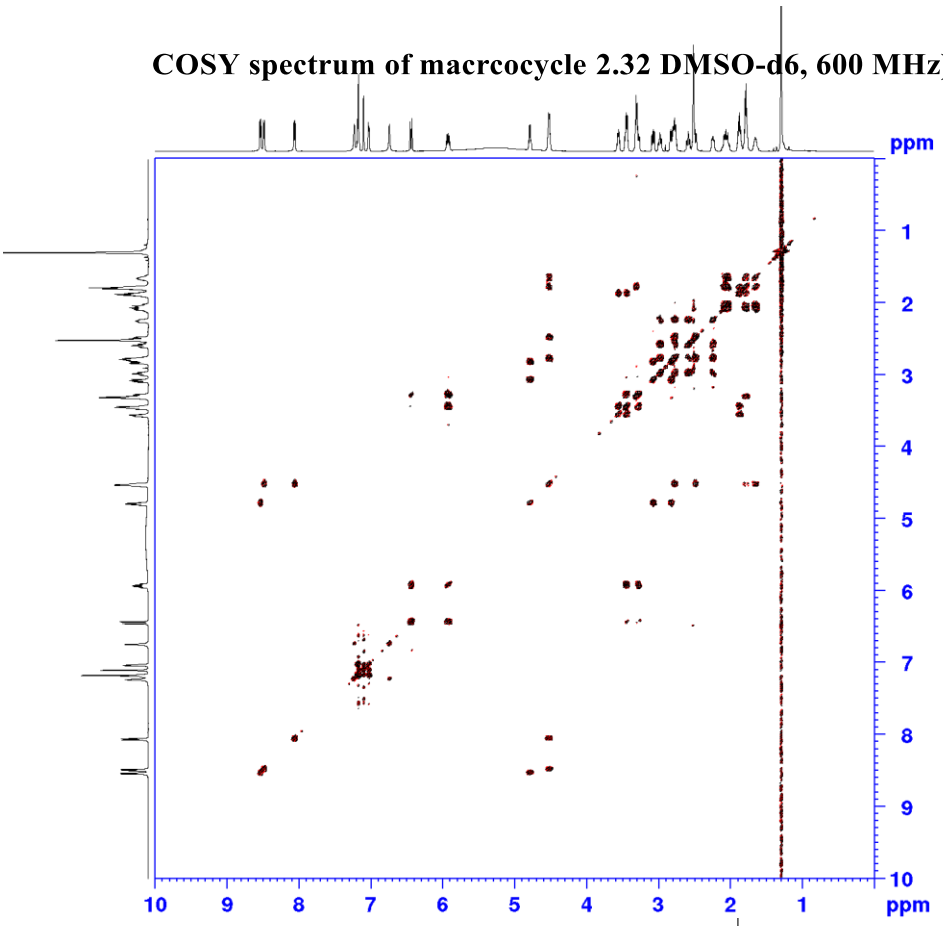




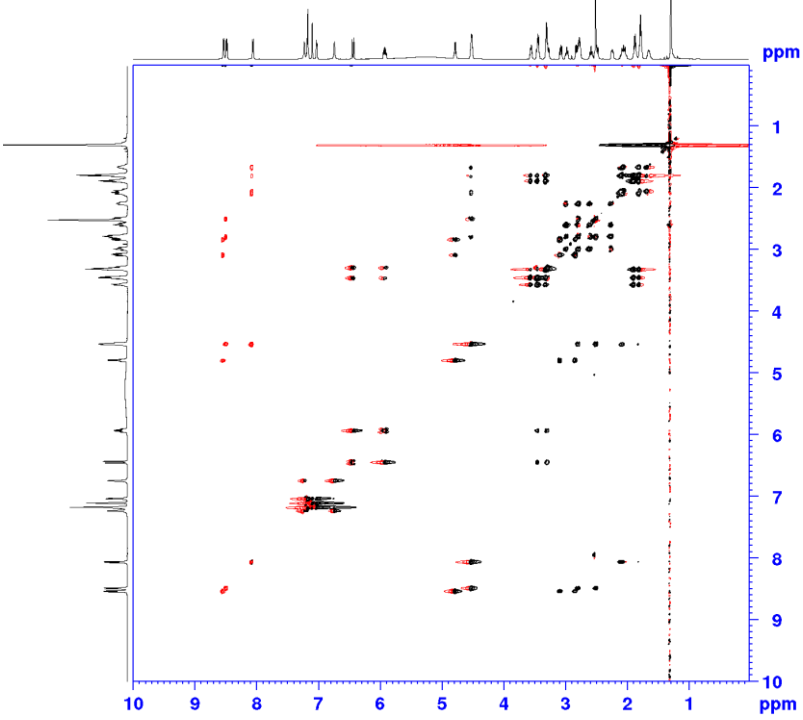
	13C	1H	
1	32.3	3.44 (m, 1H), 3.28 (m, 1H)	2->1 HMBC 3->1 HMBC 2->1 cosy
2	125.2	5.92 (dt, J = 15.7, 7.7 Hz, 1H)	3->2 HMBC 3->2 COSY
3	132.5	6.44 (d, J = 15.7 Hz, 1H)	Key
4	136.2		2->4 HMBC 3->4 HMBC
5	123.0	7.17 (m, 1H)	6->5 COSY
6	127.8	7.18 (m, 1H)	7->6 COSY
7	127.4	7.03 (d, J = 6.4 Hz, 1)	9->7 HMBC
8	140.9		9->8 HMBC 7->8 HMBC
9	125.8	7.10 (s, 1H)	key
10	30.3	2.98 (m, 1H), 2.77 (m, 1H)	9->10 HMBC 7->10 HMBC
11	36.0	2.58 (m, 1H), 2.24 (m, 1H)	10->11 COSY
12	171.1		
13		8.06 (d, J = 9.0 Hz, 1)	
14	51.0	4.51 (m, 1H, overlap)	
15	29.0	1.78 (m, 1H), 1.65 (m, 1H)	COSY 14->15
16	31.4	2.12-1.98 (m, 2H)	
17	173.5		16->17 hmbc
18		7.22 (s, 1H) 6.74 (s, 1H)	
19	171.2		14->19 HMBC 21->19 HMBC
20		8.48 (d, J = 8.4, 1H)	21->20 HMBC
21	51.0	4.51 (m, 1H, overlap)	
22	169.6		21->22 HMBC

			24->22 HMBC
23		8.53 (d, J = 8.0 Hz, 1H)	24->23 COSY
24	50.2	4.78 (dd, J = 14.3, 7.3Hz, 1H)	
25	166.9		HMBC 24->25
26	45.7	3.59-3.51 (m, 1H), 3.48-3.41 (m, 1H)	
27	25.2	1.91-1.83 (m, 2H)	
28	45.7	3.33-3.28 (m, 2H)	
29	23.4	1.81-1.74 (m, 2H)	
30	41.5	3.08 (dd, J = 12.3, 7.6 Hz, 1H) 2.82 (dd, J = 13.0, 6.2 Hz, 1)	COSY 24->30
31	47.5 (48.2)		
32	30.0	1.29 (s, 9H)	
33	31.6	2.77 (m, 1H), 2.48 (m, 1H)	21->33 HMBC 1->33 HMBC

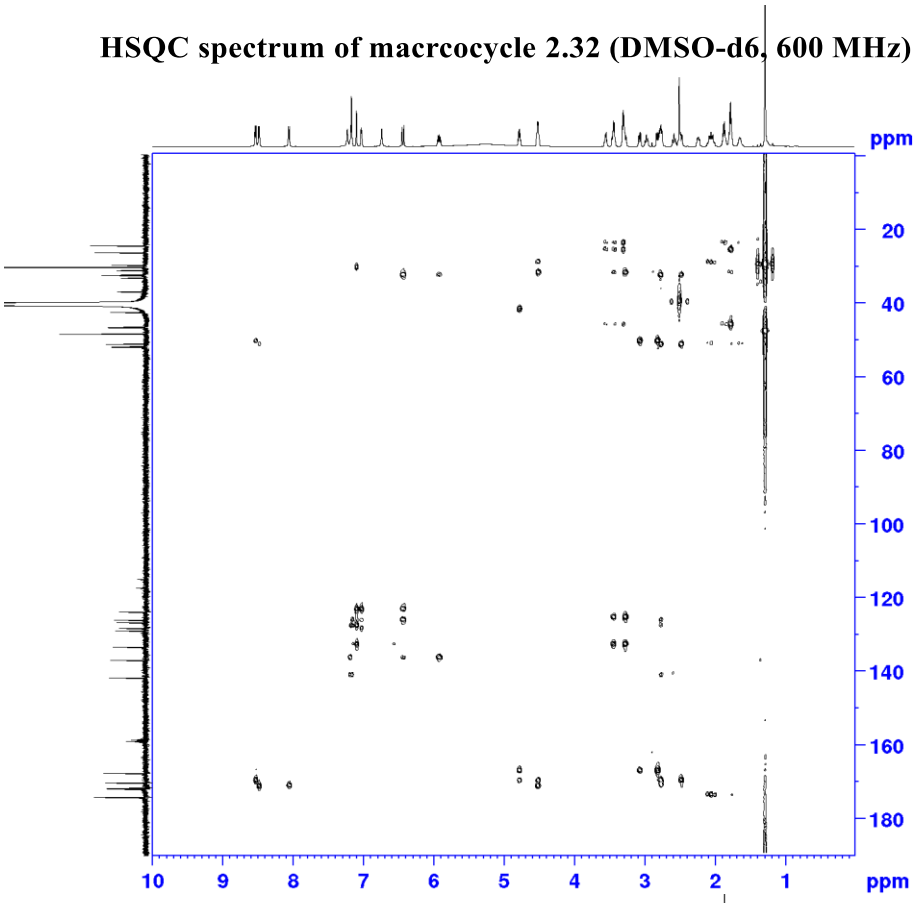
COSY spectrum of macrcocycle 2.32 DMSO-d6, 600 MHz)



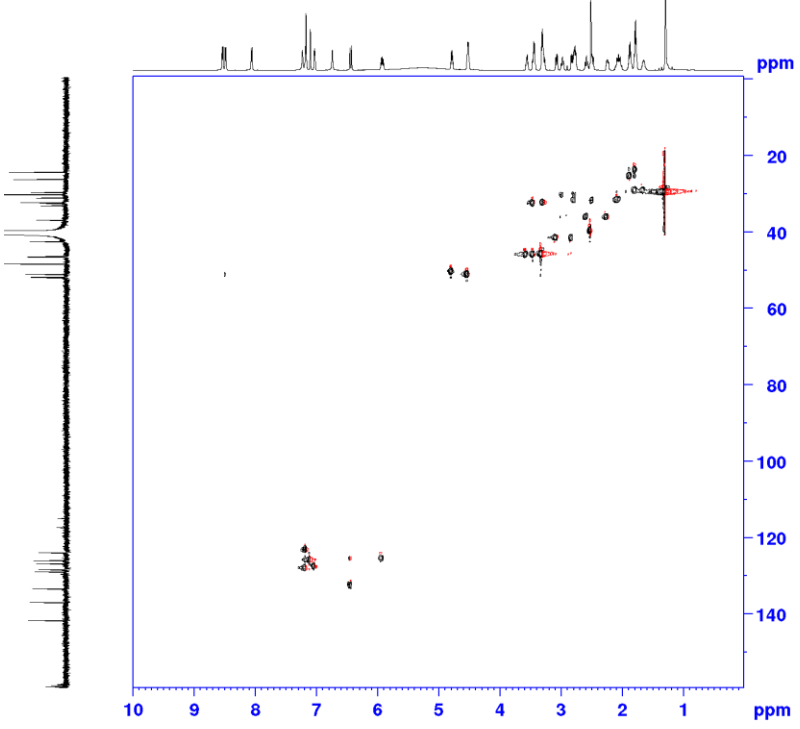
TOXSY spectrum of macrcocycle 2.32 DMSO-d6, 600 MHz)



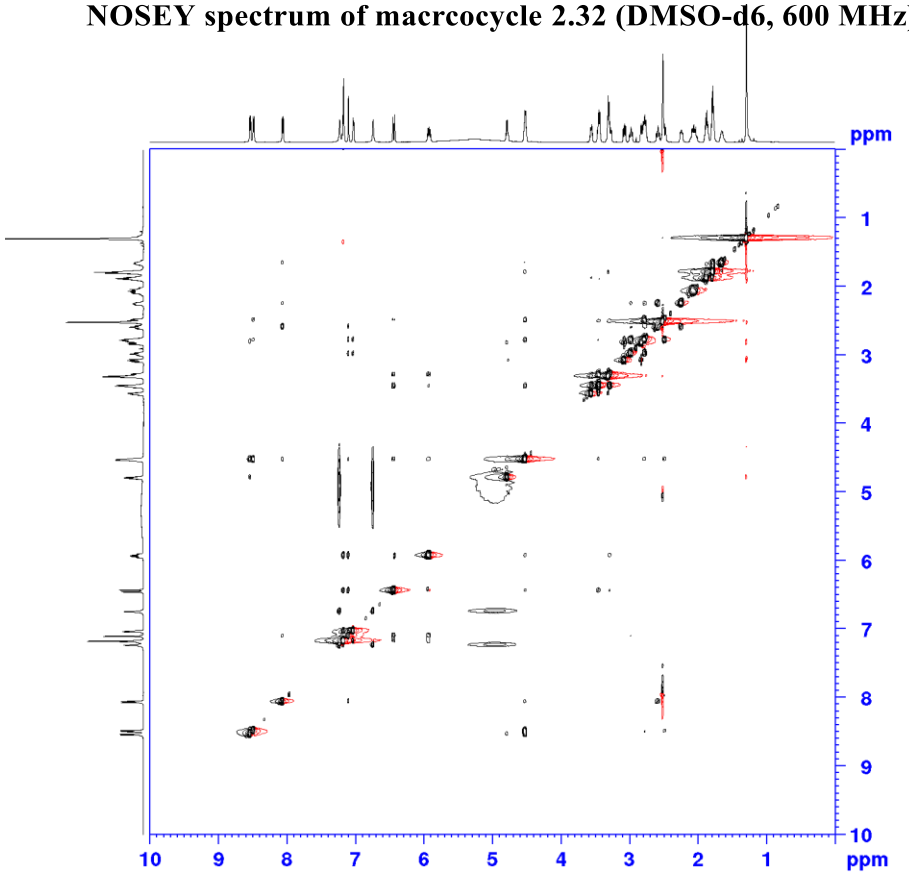
HSQC spectrum of macrcocycle 2.32 (DMSO-d6, 600 MHz)



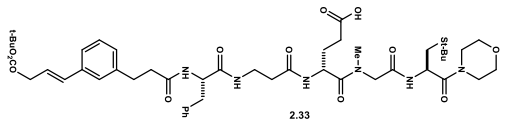
HMBC spectrum of macrcocycle 2.32 (DMSO-d6, 600 MHz)



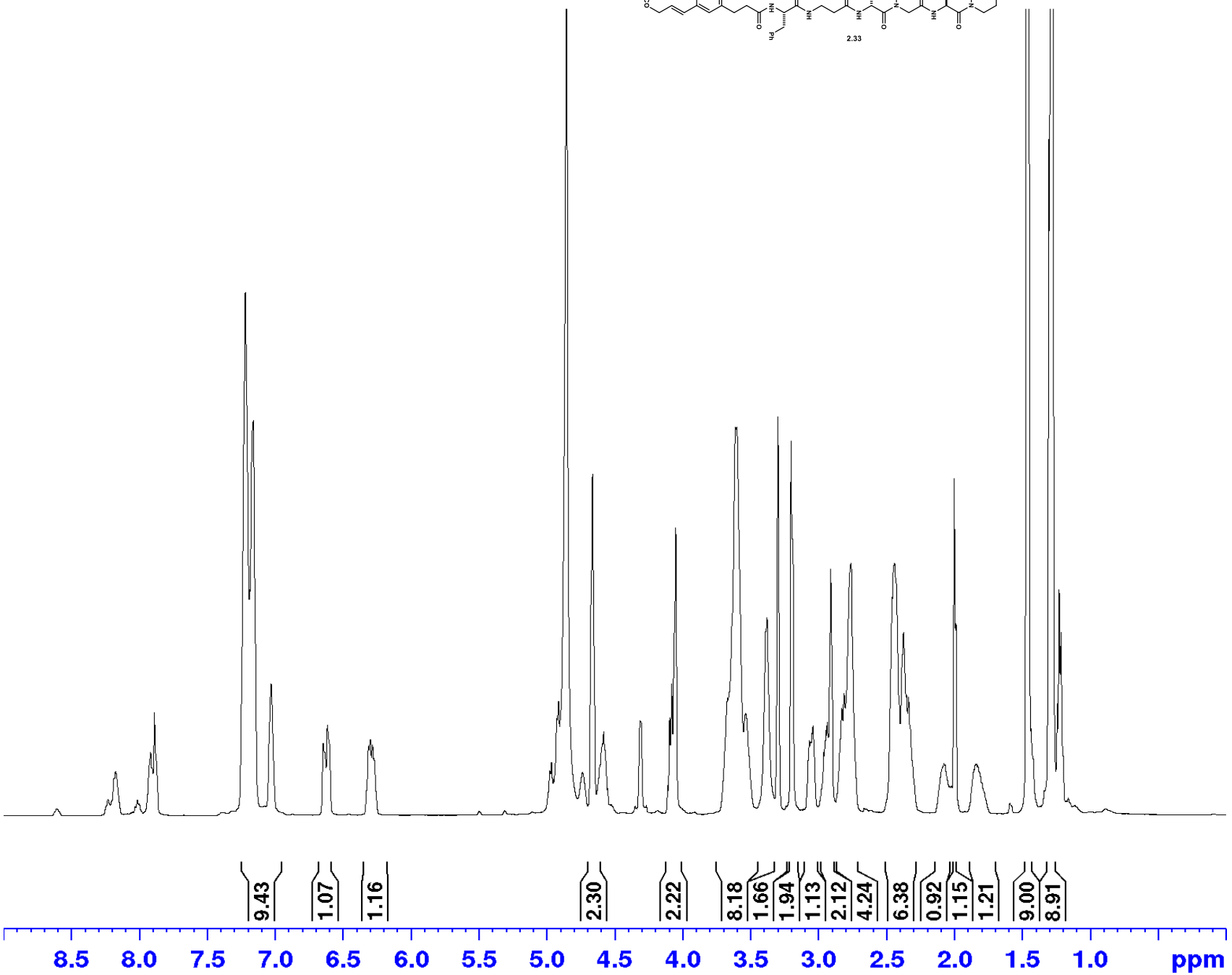
NOSEY spectrum of macrcocycle 2.32 (DMSO-d6, 600 MHz)



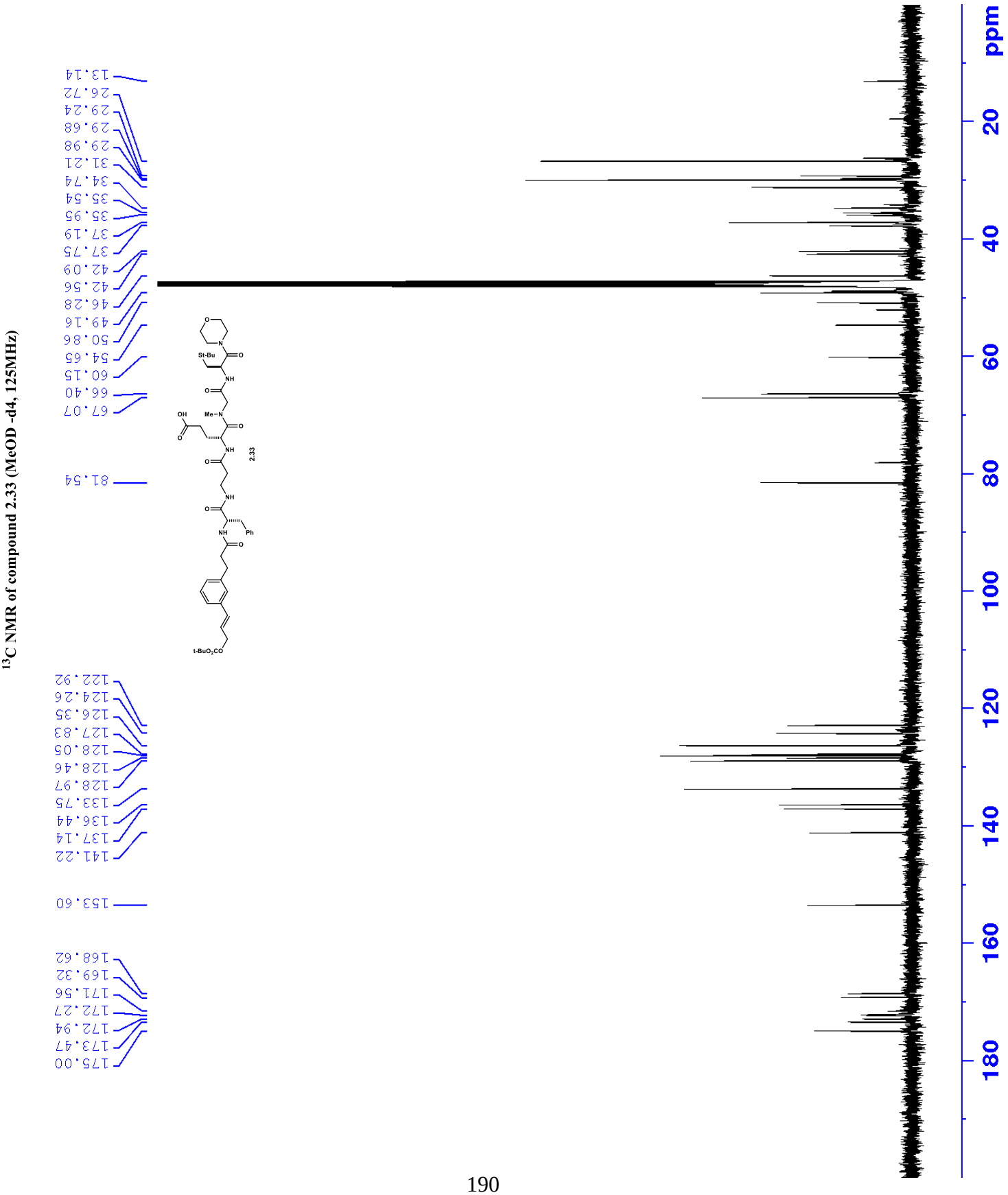
^{1}H NMR of compound 2.33 (MeOD -d4, 500 MHz)



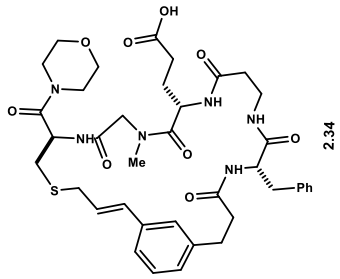
2.33



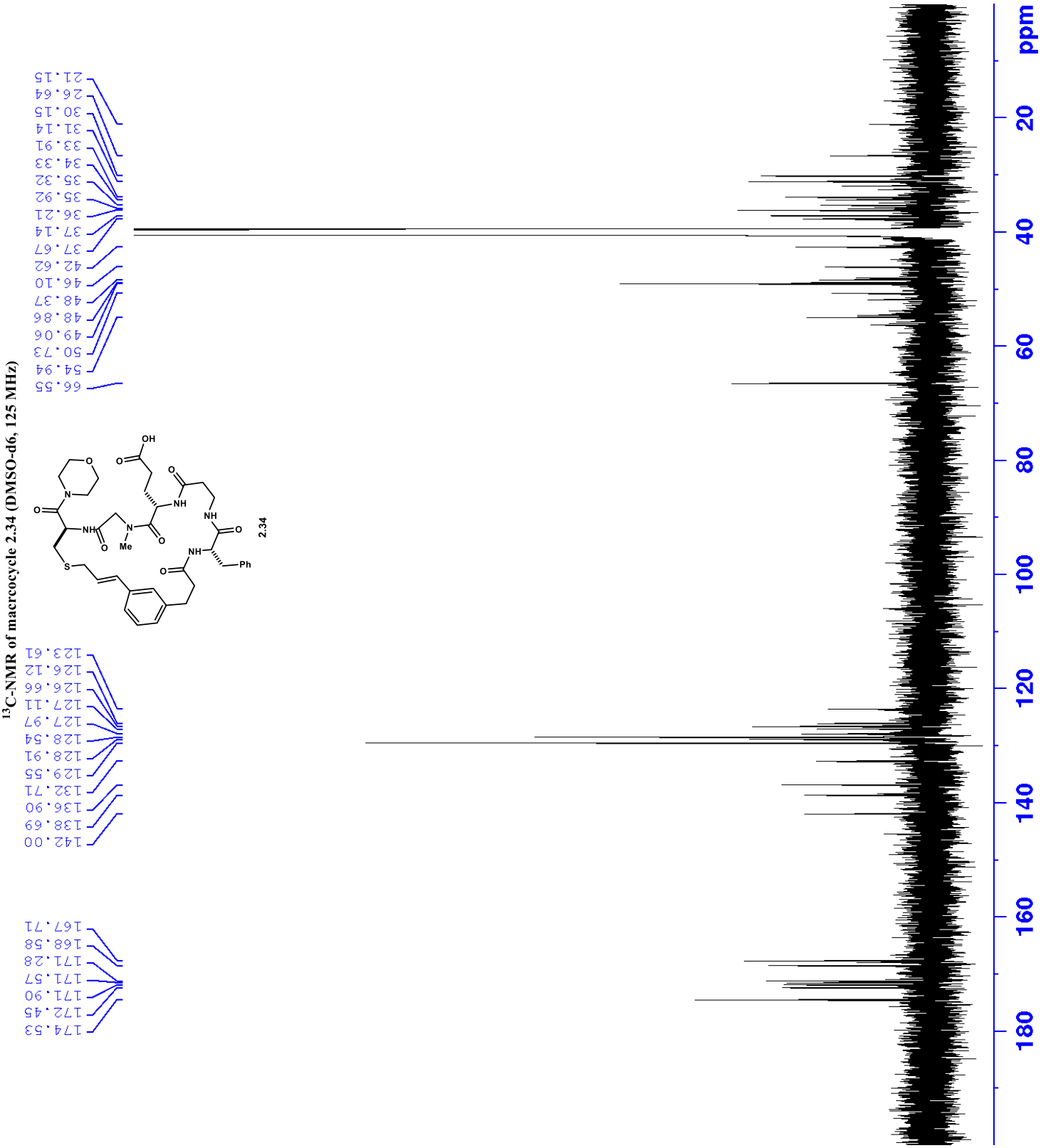
^{13}C NMR of compound 2.33 (MeOD -d4, 125MHz)



^{1}H NMR of macrcocycle 2.34 (DMSO-d6, 500 MHz)

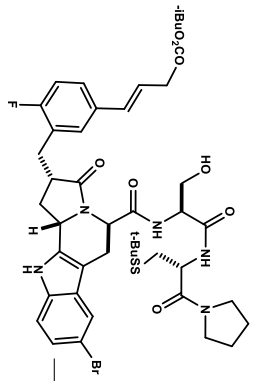


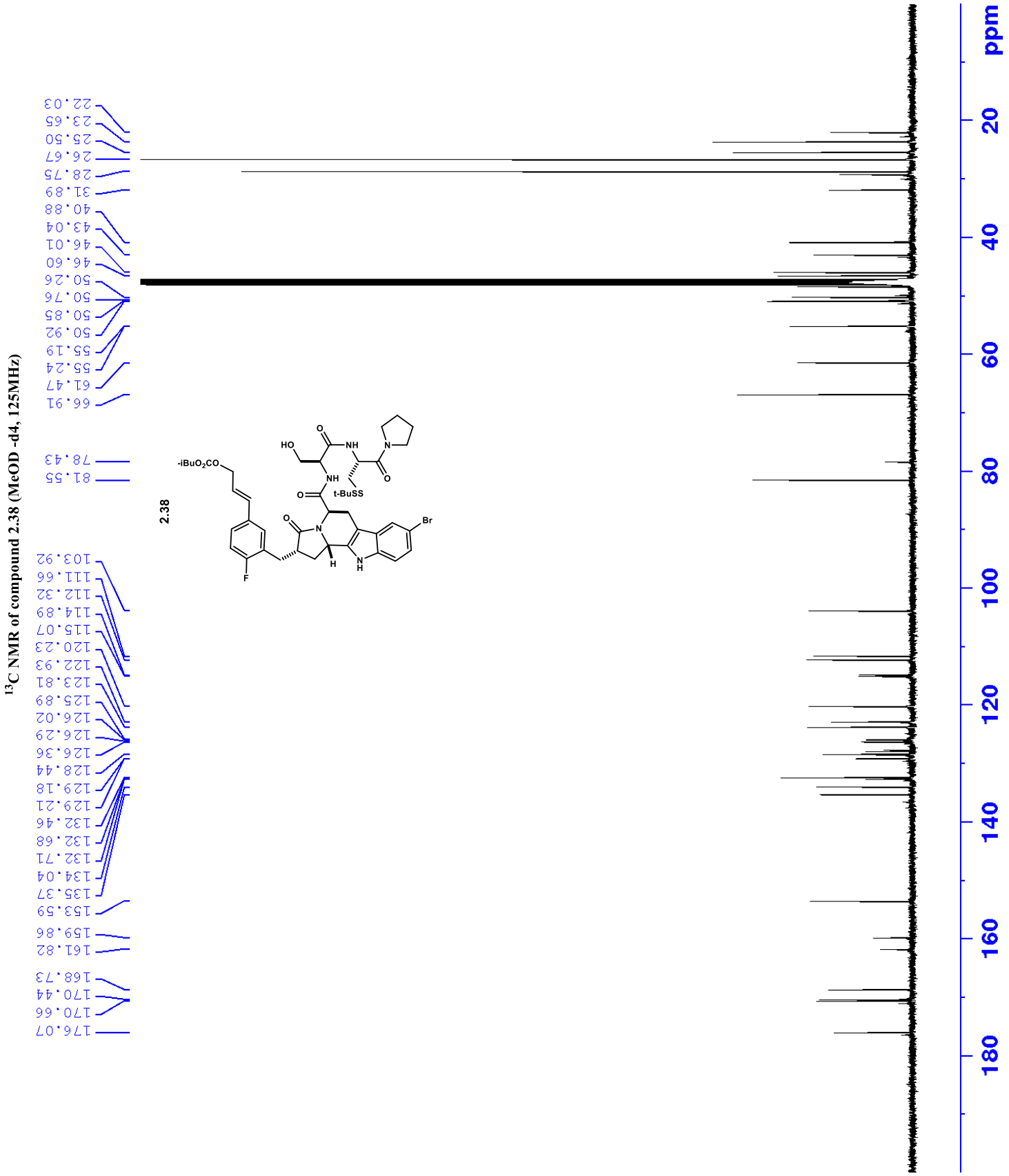
2.34


^{13}C-NMR of macrcocycle 2.34 (DMSO-d6, 125 MHz)
21.15
26.64
30.15
31.14
33.91
34.33
35.32
35.92
36.21
37.14
37.67
42.62
46.10
48.37
48.86
49.06
50.73
54.94
66.55
123.61
126.12
126.66
127.11
127.97
128.54
128.91
129.55
132.71
136.90
138.69
142.00
167.71
168.58
171.28
171.57
171.90
172.45
174.53
2.34
ppm
20
40
60
80
100
120
140
160
180

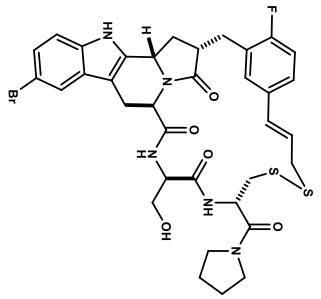
^{13}C NMR of compound 2.38 (MeOD -d4, 125MHz)

2.38

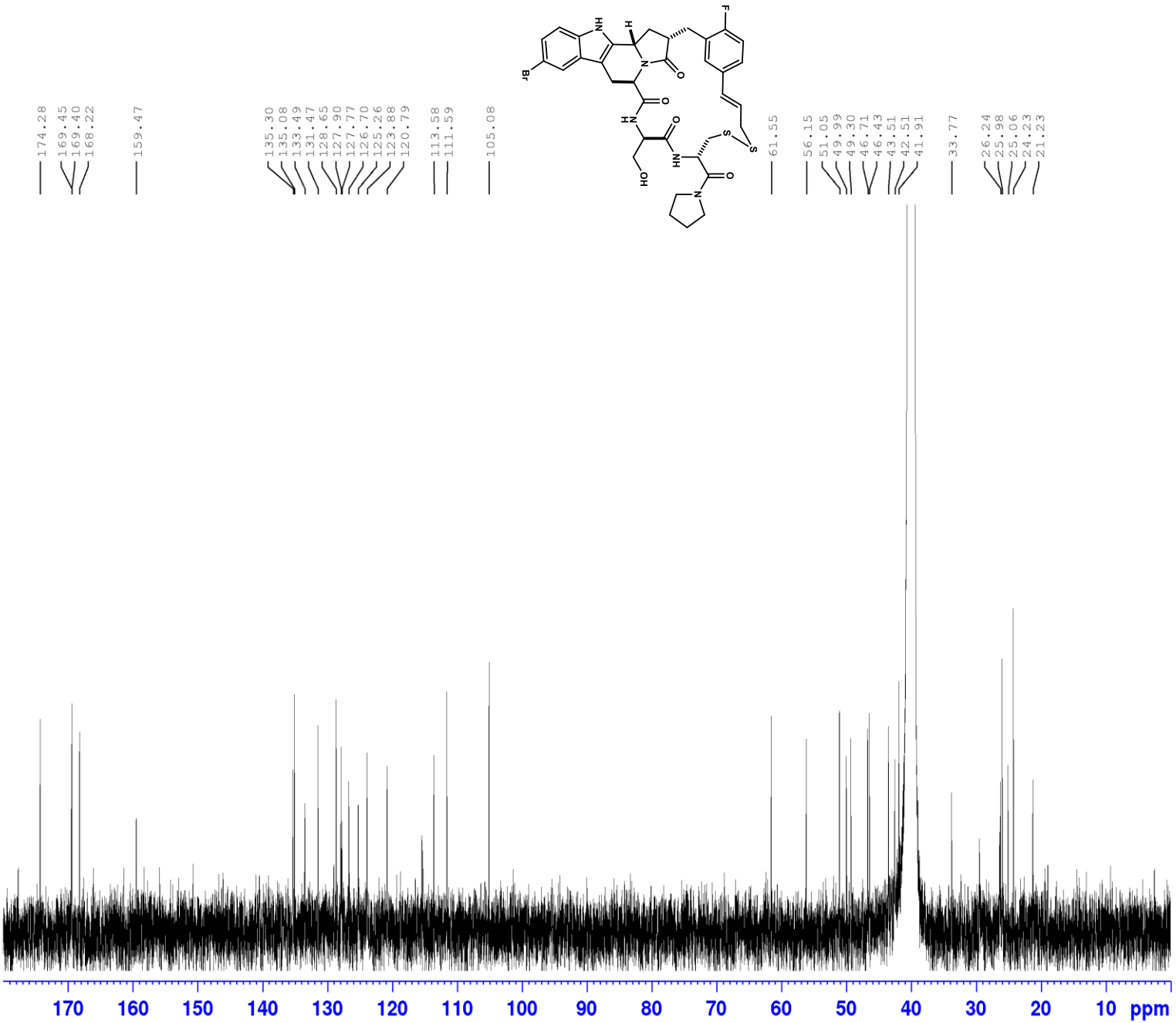



^{13}C NMR of compound 2.38 (MeOD -d4, 125MHz)
2.38
22.03
23.65
25.50
26.67
28.75
31.89
40.88
43.04
46.01
46.60
50.26
50.76
50.85
50.92
55.19
55.24
61.47
66.91
78.43
81.55
103.92
111.66
112.32
114.89
115.07
120.23
122.93
123.81
125.89
126.02
126.29
126.36
128.44
129.18
129.21
132.46
132.68
132.71
134.04
135.37
153.59
159.86
161.82
168.73
170.44
170.66
176.07
ppm
20
40
60
80
100
120
140
160
180

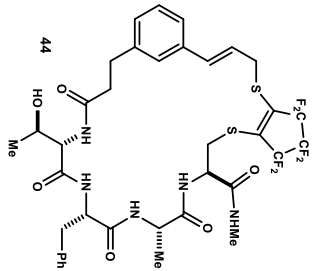
^{1}H NMR of macrcocycle 2.39 (DMSO-d6, 500 MHz)



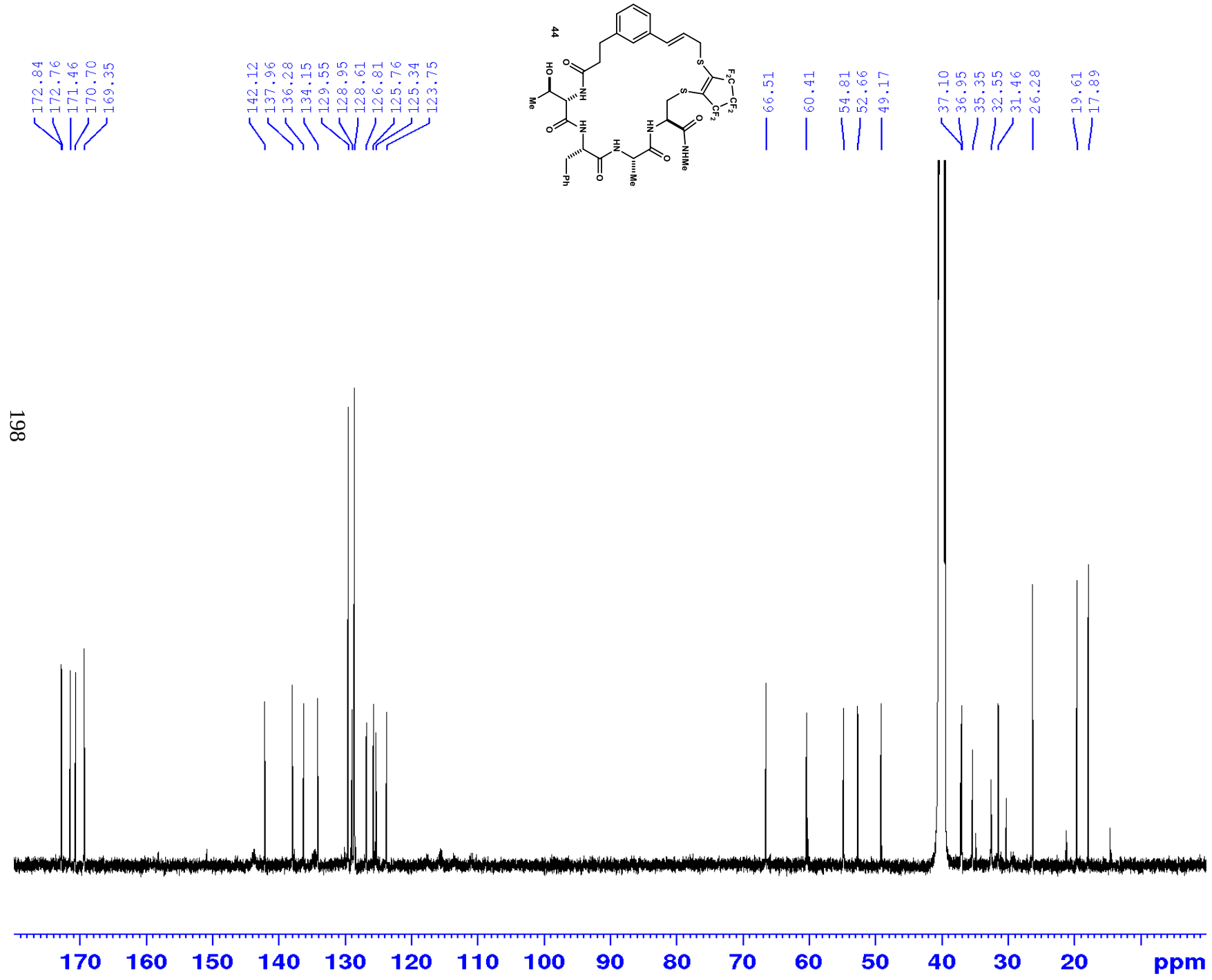
^{13}C NMR of macrcocycle 2.39 (DMSO-d6, 126 MHz)



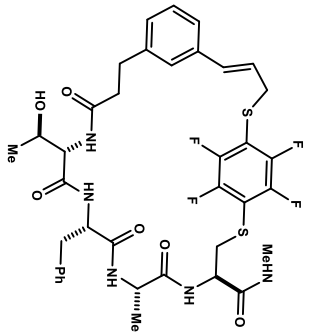
^{1}H NMR of macrcocycle 2.40 (DMSO-d6, 500 MHz)

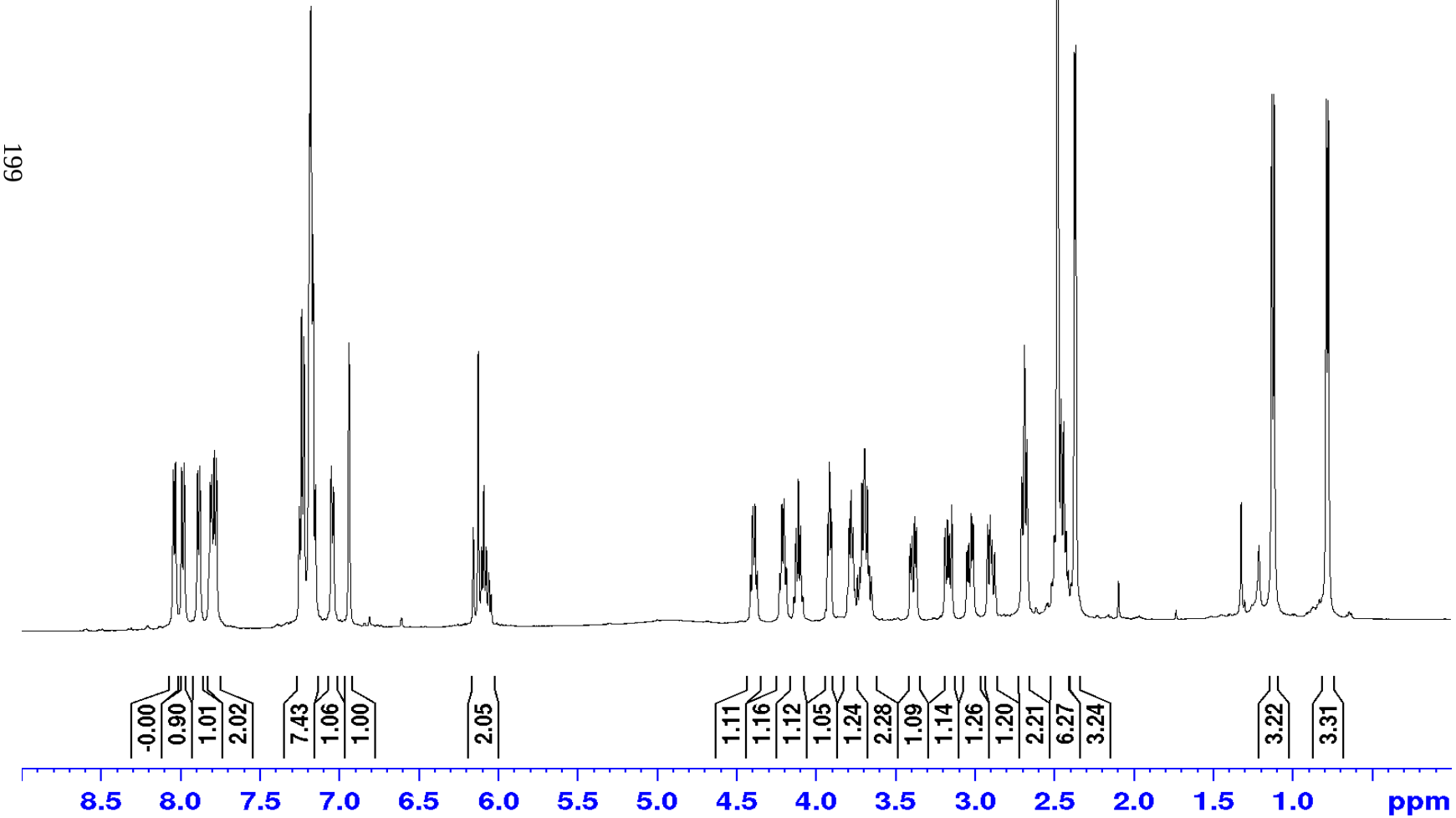


^{13}C NMR of macrcocycle 2.40 (DMSO-d6, 126 MHz)

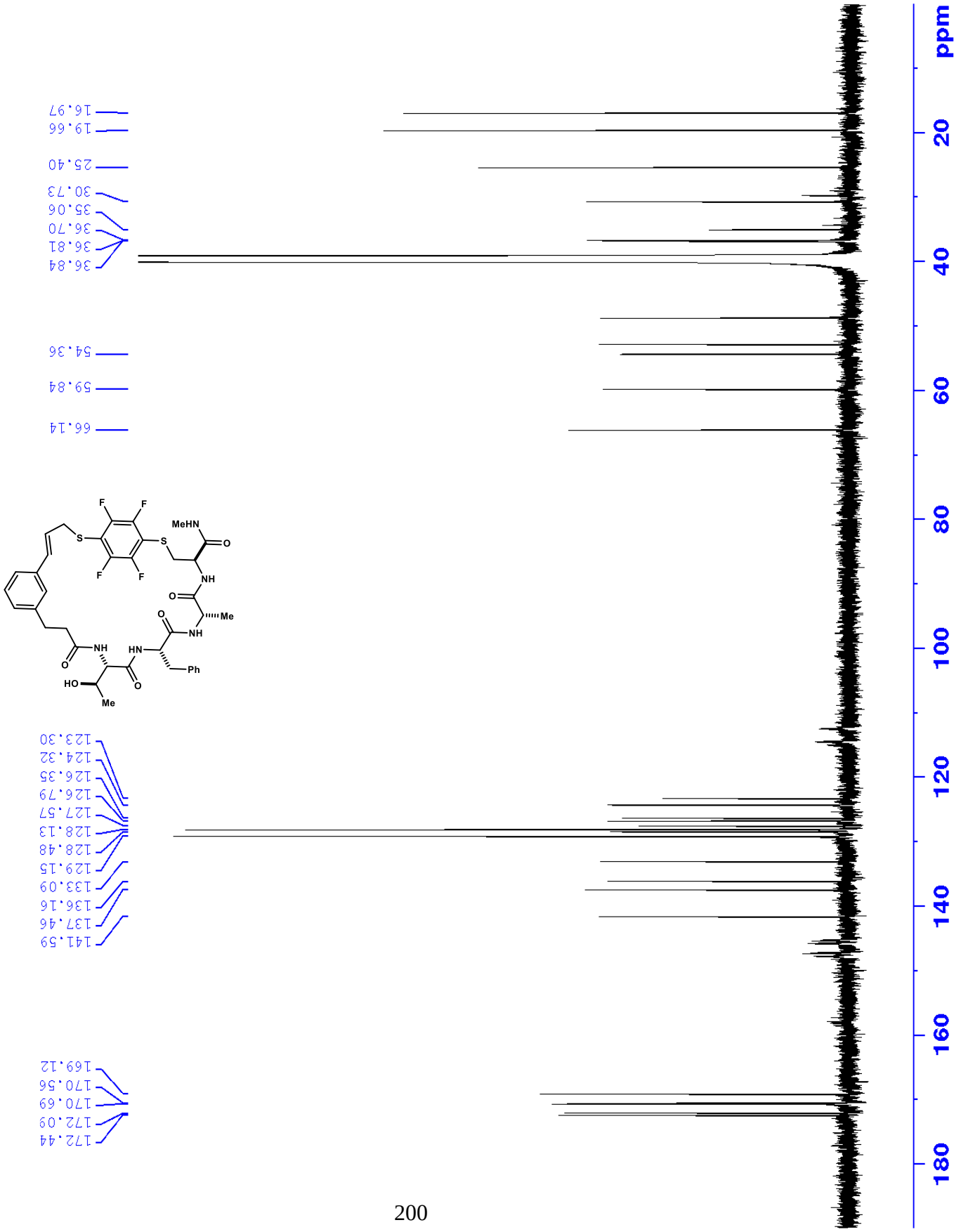


^{1}H NMR of macrcocycle 2.41 (DMSO-d6, 500 MHz)

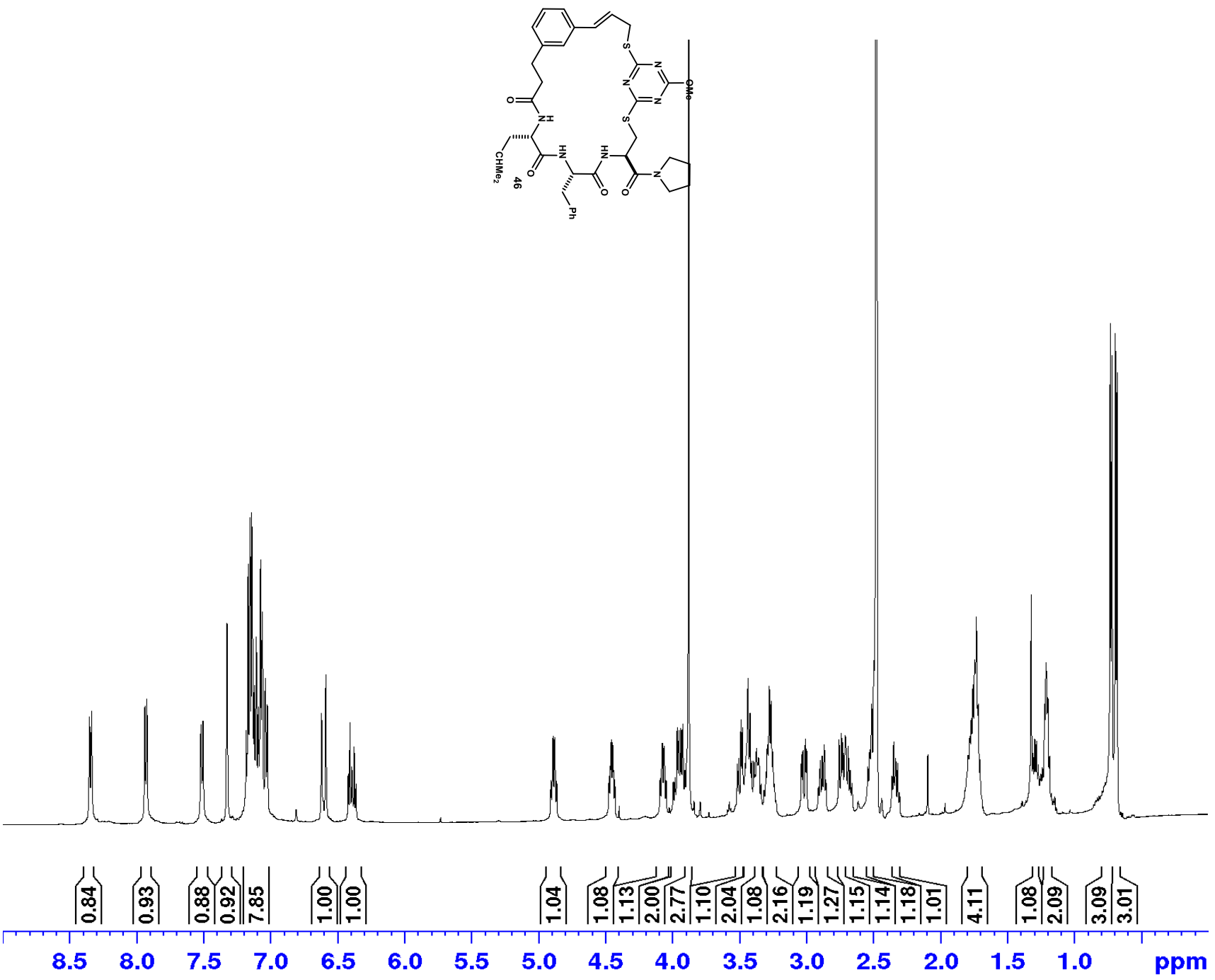




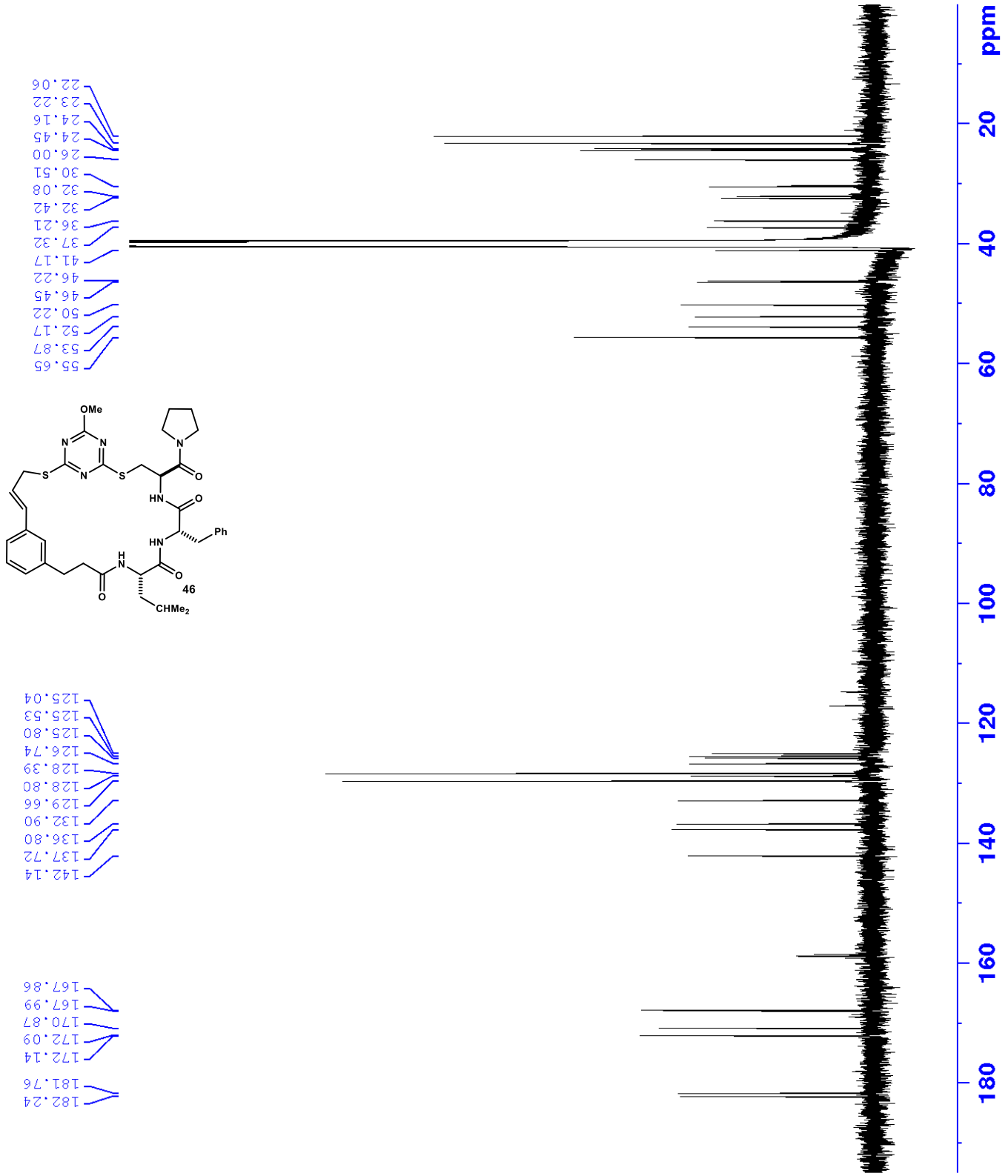
^{13}C NMR of macrcocycle 2.41 (DMSO-d6, 126 MHz)



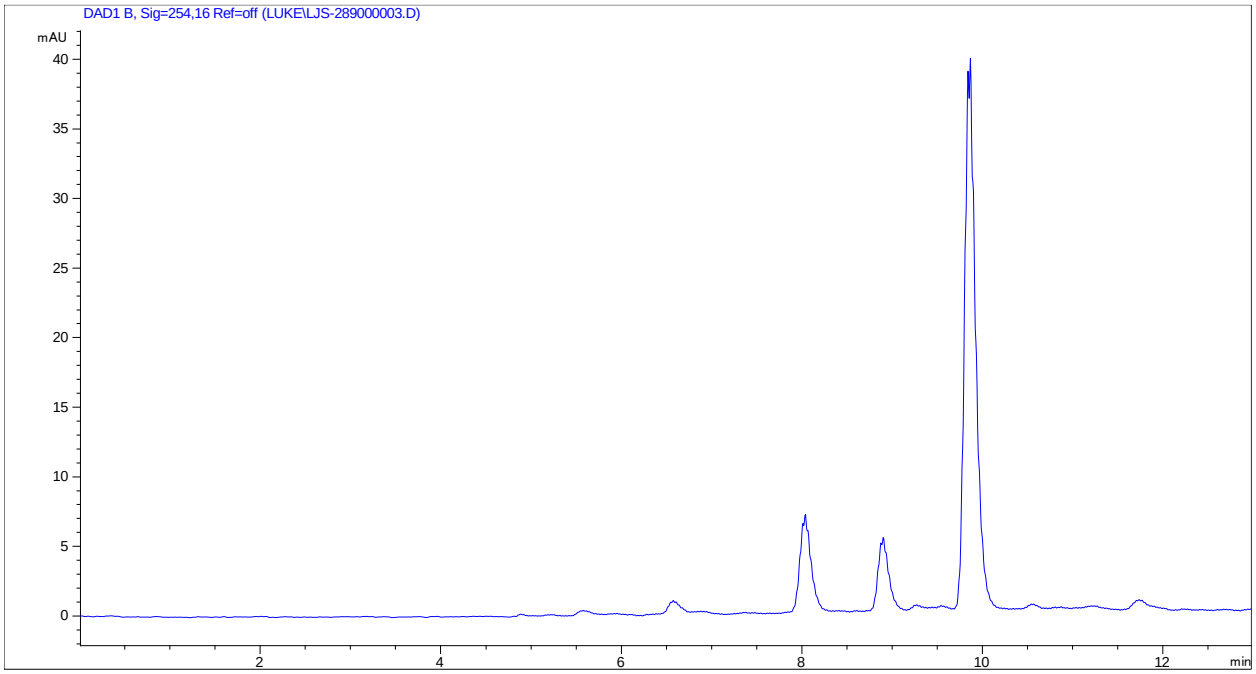
^{1}H NMR of macrcocycle 2.42 (DMSO-d6, 500 MHz)



^{13}C NMR of macrocycle 2.42 (DMSO-d6, 126 MHz)



2.42 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	18.000 ml/min
Stoptime	:	13.00 min
Posttime	:	0.50 min

Solvents

Solvent A	:	40.0 % (Water)
Solvent B	:	60.0 % (Organic)

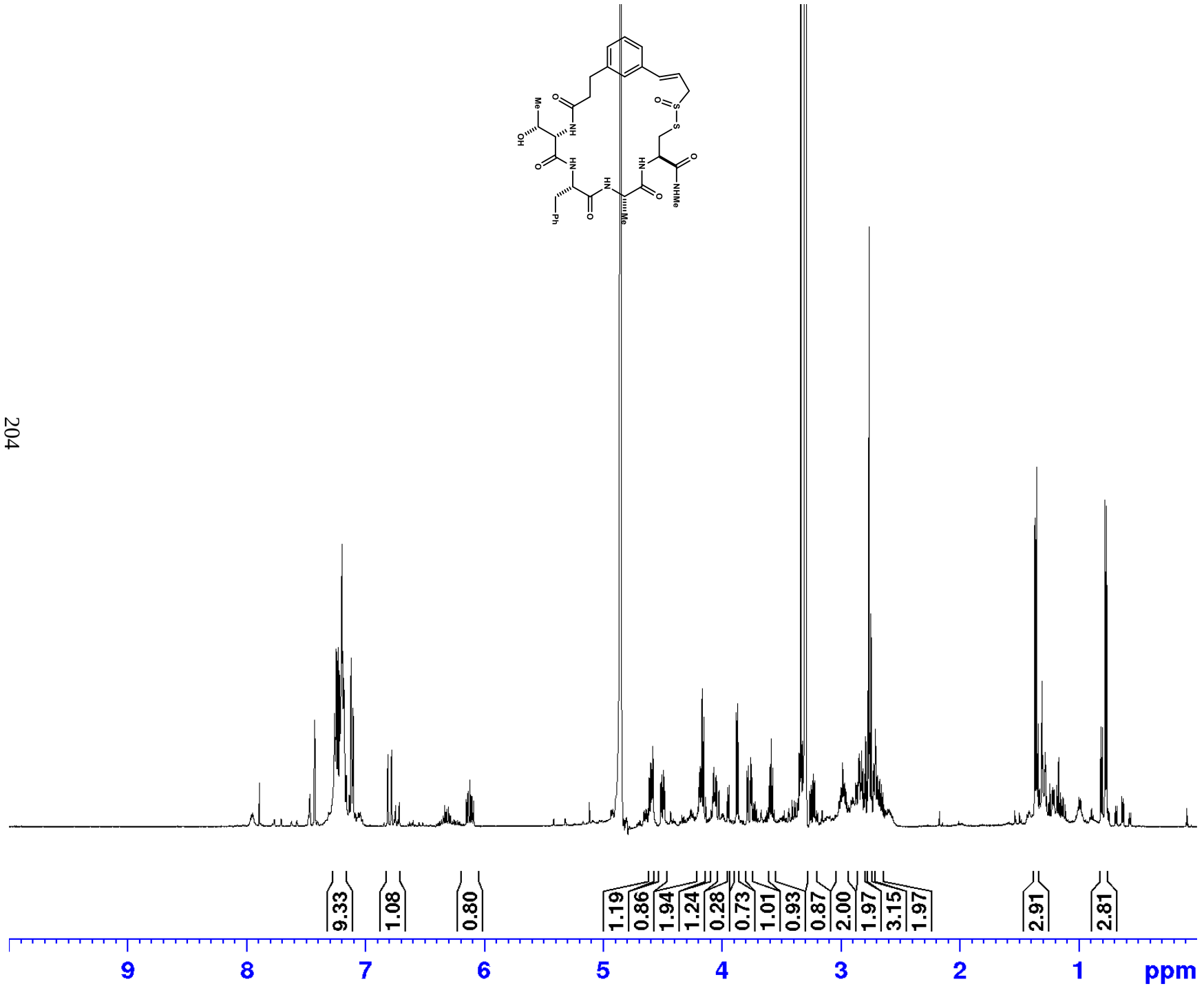
Auxiliary

Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

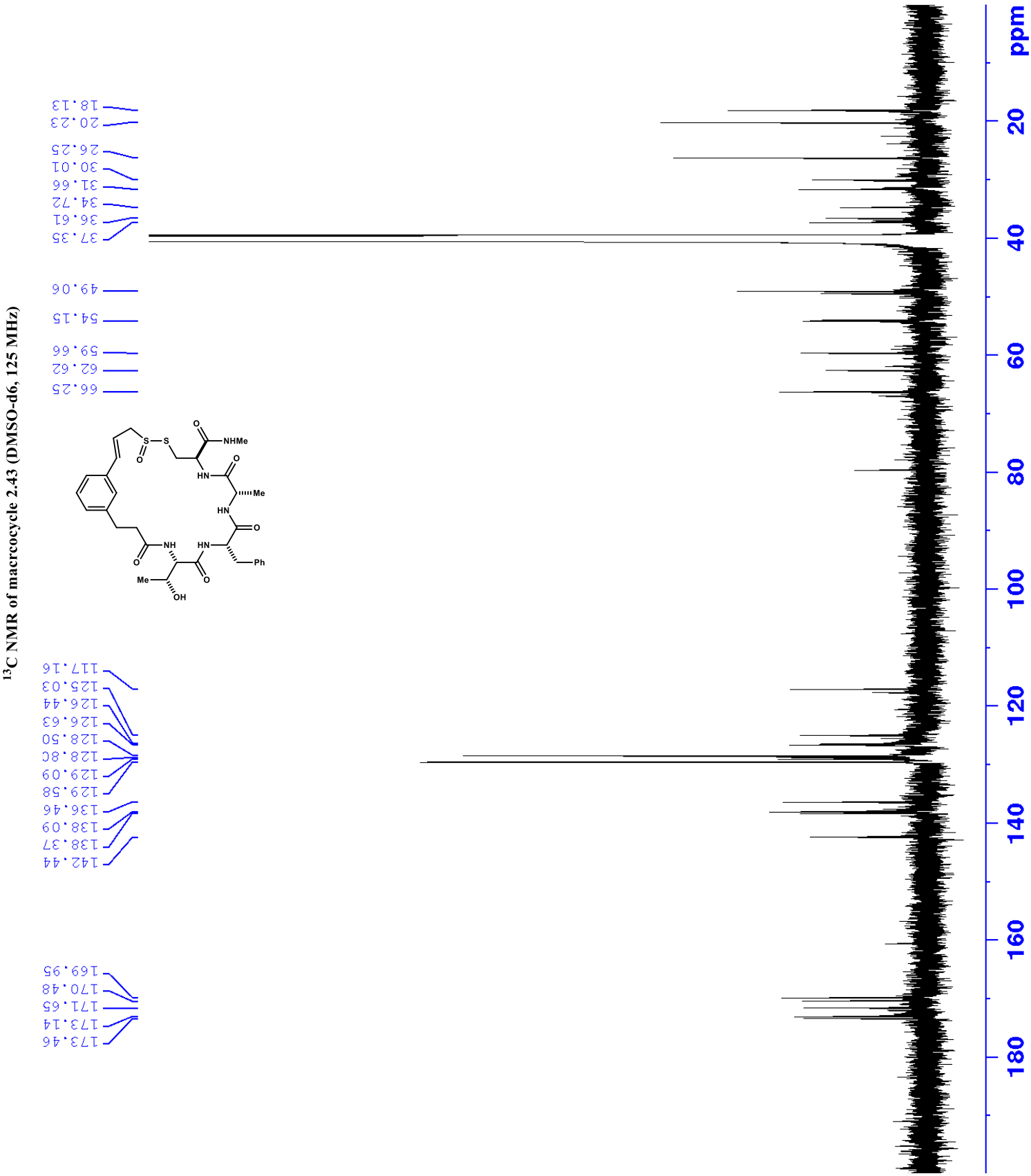
Timetable

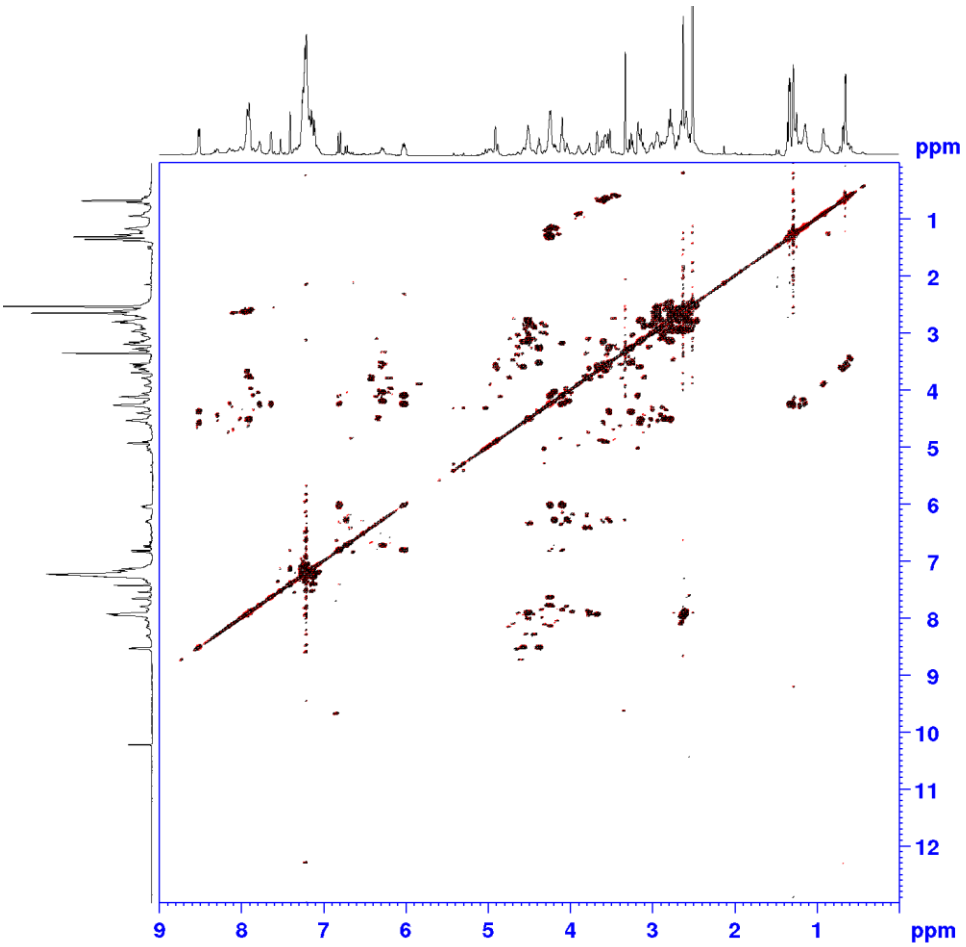
Time	Solv.B	Flow	Pressure
0.00	60.0	12.000	
0.50	60.0	12.000	
11.00	95.0	18.000	
11.50	100.0	18.000	
12.50	100.0	18.000	
13.00	60.0	18.000	

^{1}H NMR of macrcocycle 2.43 (MeOD-d4, 600 MHz)



^{13}C NMR of macrocycle 2.43 (DMSO-d6, 125 MHz)



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EXPNO                         6
PROCNO                        1

F2 - Acquisition Parameters
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Time                    19.41
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PROBHD    5 mm TBI5
PULPROG          cosygpprqf
TD                      2048
SOLVENT                 DMSO
NS                         2
DS                        16
SWH                7788.162 Hz
FIDRES             3.802814 Hz
AQ                 0.1314816 sec
RG                     456.1
DW                    64.200 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                0.00012820 sec

======== CHANNEL f1 ========
NUC1                       1H
P0                       8.00 usec
P1                      11.49 usec
PL1                     -2.00 dB
PL9                    120.00 dB
PL1W            39.81071854 W
PL9W          0 W
SFO1             600.1339008 MHz

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

F1 - Acquisition parameters
TD                       512
SFO1                600.1339 MHz
FIDRES             30.475550 Hz
SW                    13.000 ppm
FnMODE                    QF

F2 - Processing parameters
SI                       4096
SF                600.1300061 MHz
WDW                    QSINE
SSB                       1.5
LB            0 Hz
GB            0
PC                        1.00

F1 - Processing parameters
SI                       4096
MC2                       QF
SF                600.1300087 MHz
WDW                    QSINE
SSB                       1.5
LB            0 Hz
GB            0
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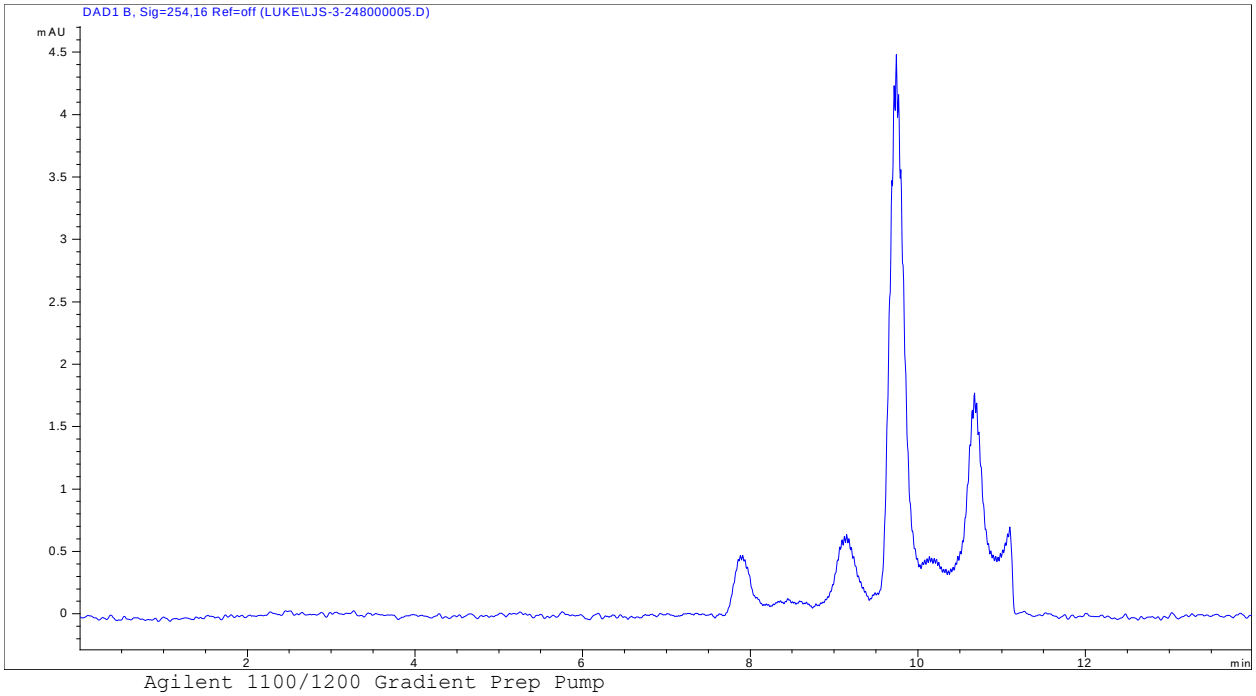
2.43, Table 2.5, entry 1 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

==========

Control

Column Flow	:	15.000 ml/min
Stoptime	:	14.00 min
Posttime	:	Off

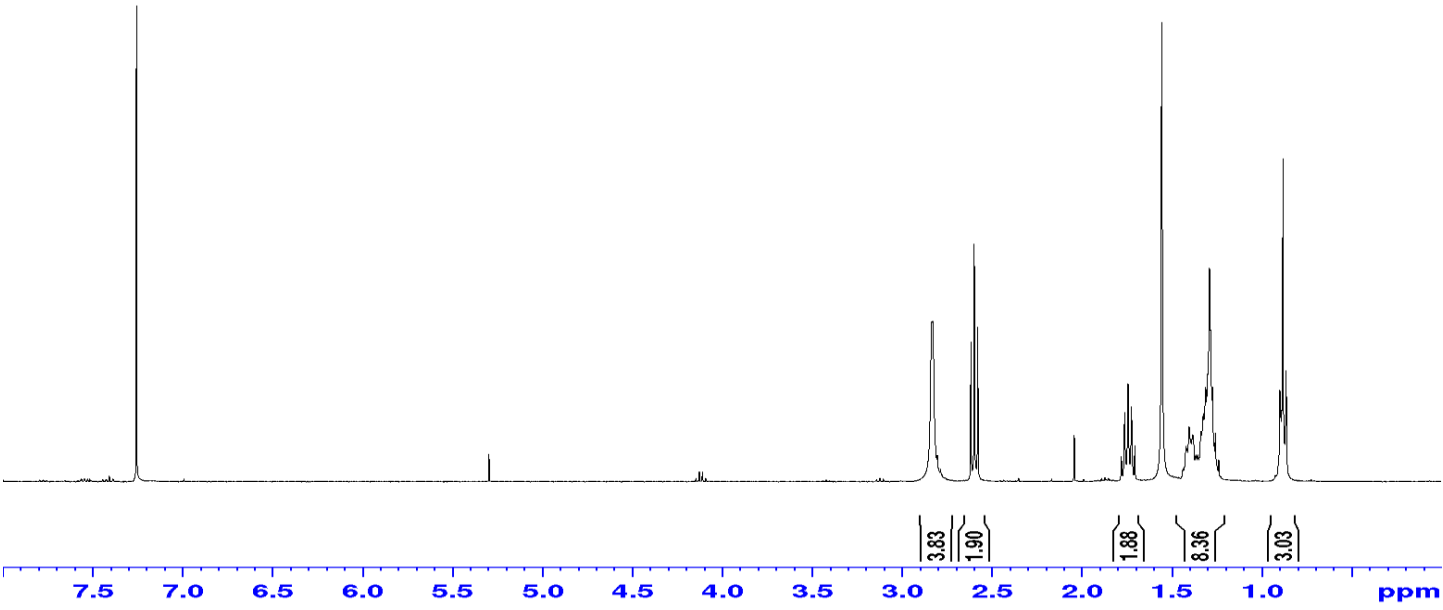
Solvents

Solvent A	:	60.0 % (Water)
Solvent B	:	40.0 % (Organic)

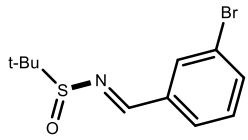
Timetable

Time	Solv.B	Flow	Pressure
0.00	40.0	12.000	400
2.00	40.0	15.000	400
8.00	70.0	15.000	400
13.00	90.0	15.000	400
14.00	40.0	15.000	400

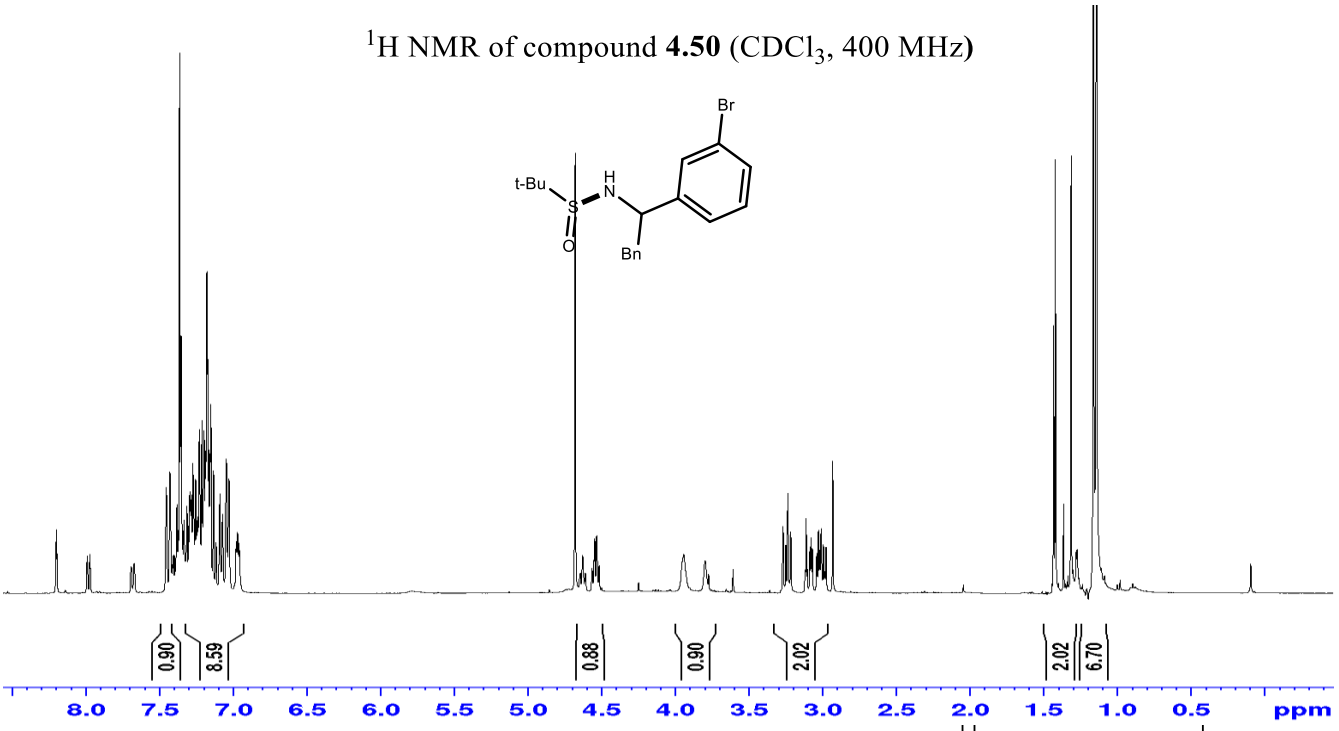
crude ^{1}H NMR of compound **N-hydroxysuccinimidyl-octanoate** ($CDCl_3$, 400 MHz**)**



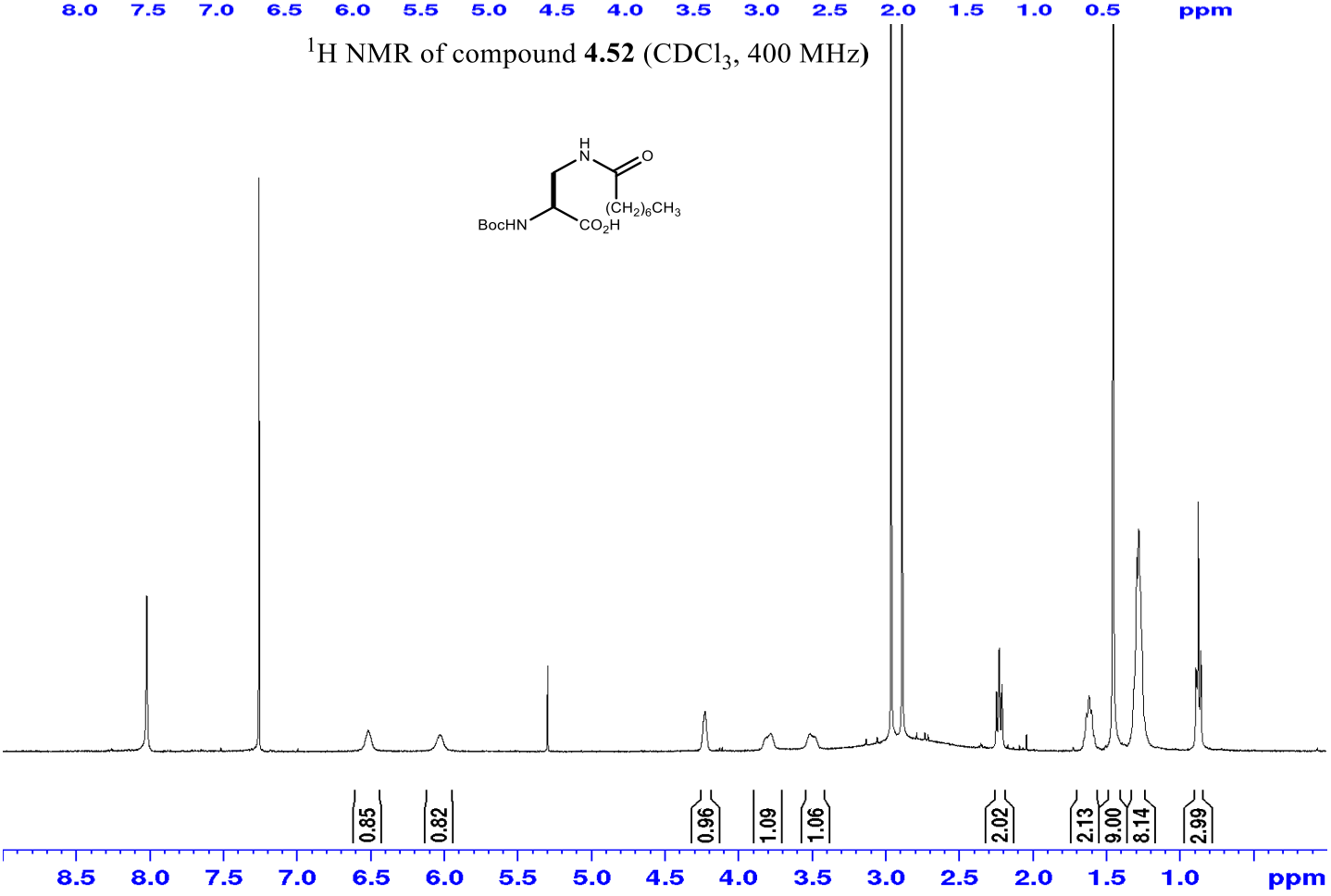
^{1}H NMR of compound **4.49** ($CDCl_3$, 400 MHz**)**

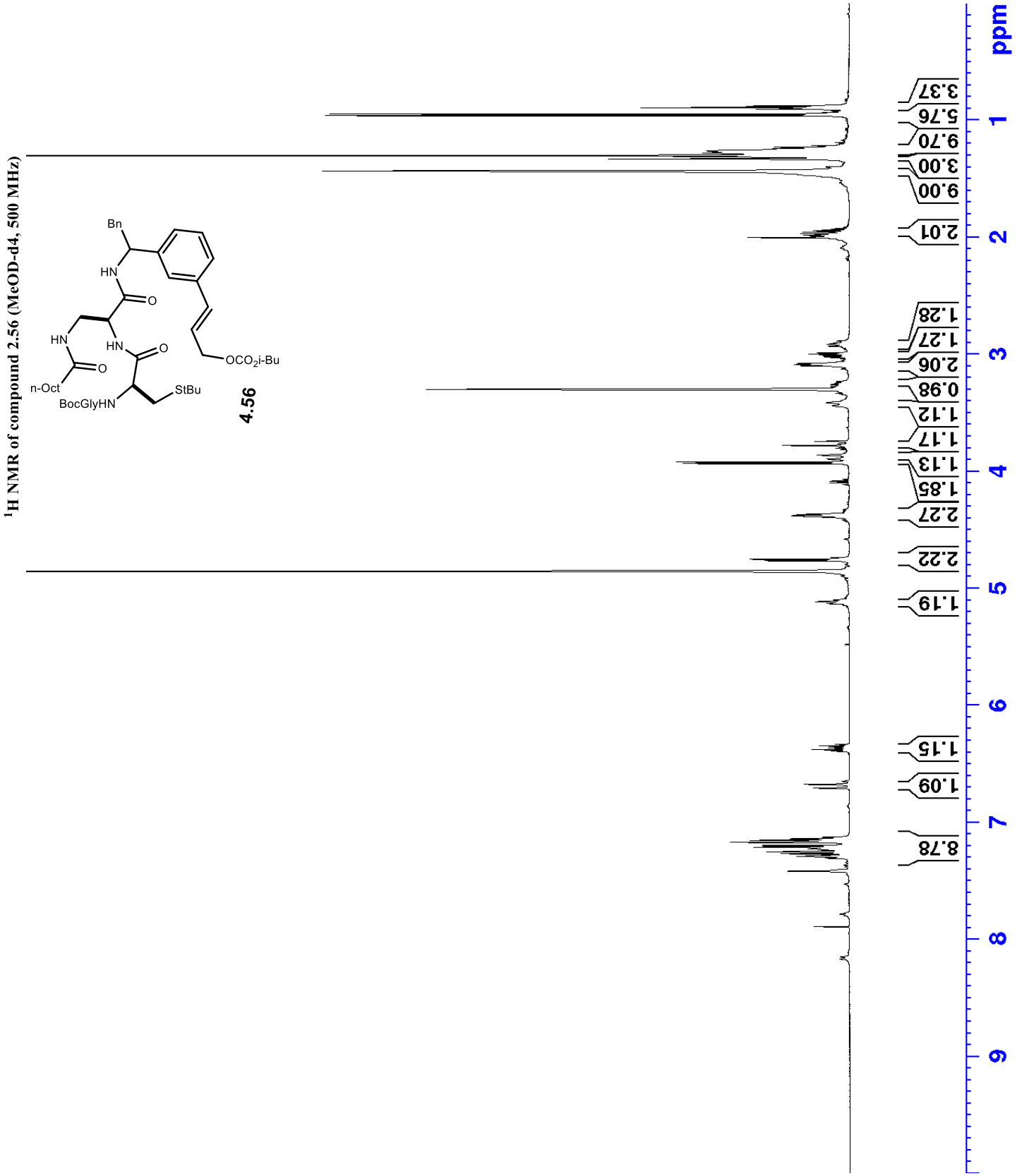


^{1}H NMR of compound **4.50** ($CDCl_3$, 400 MHz)

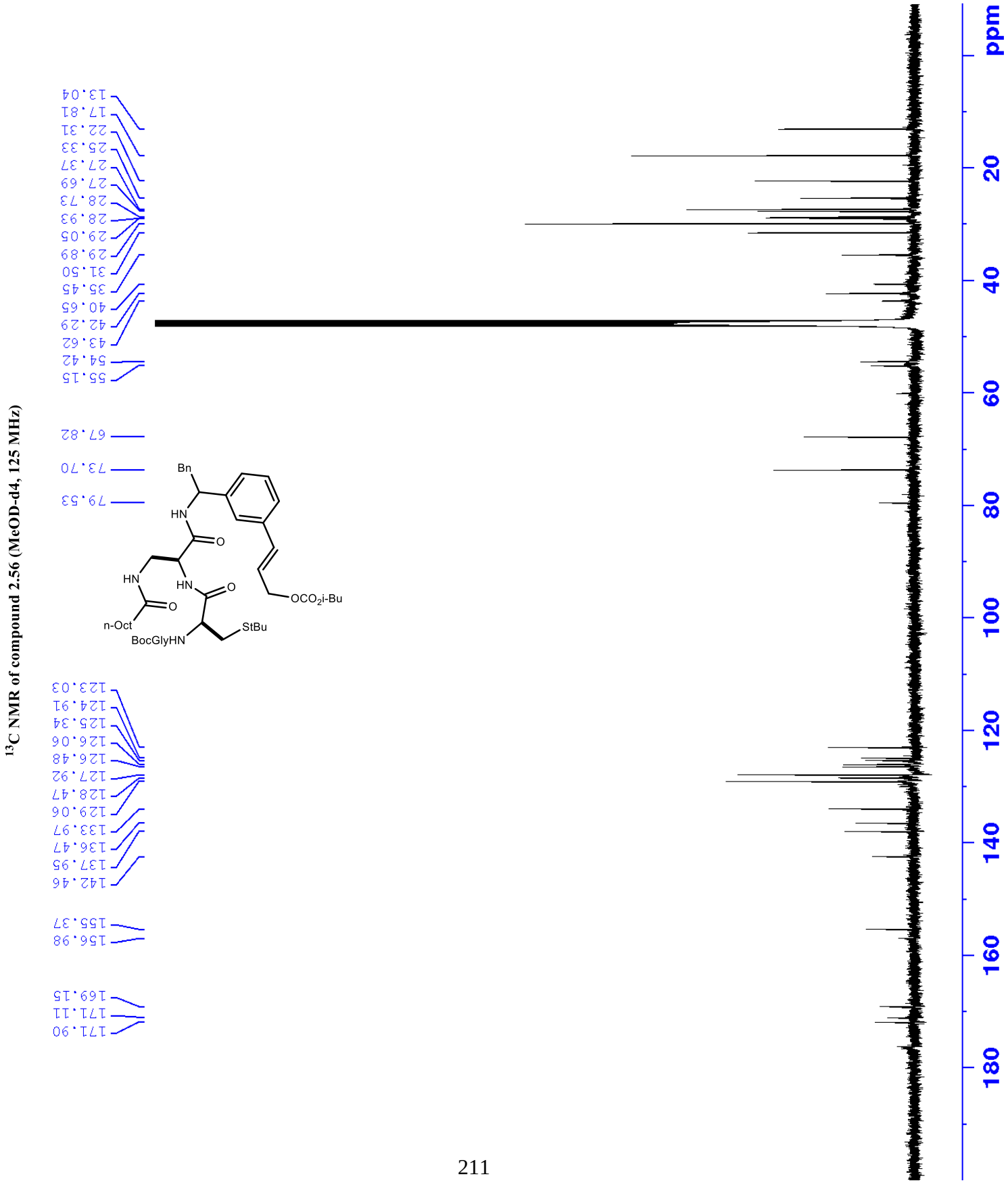


^{1}H NMR of compound **4.52** ($CDCl_3$, 400 MHz)

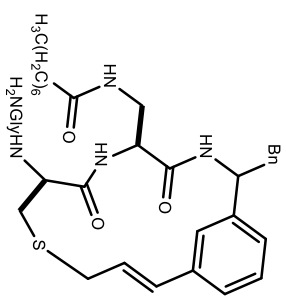


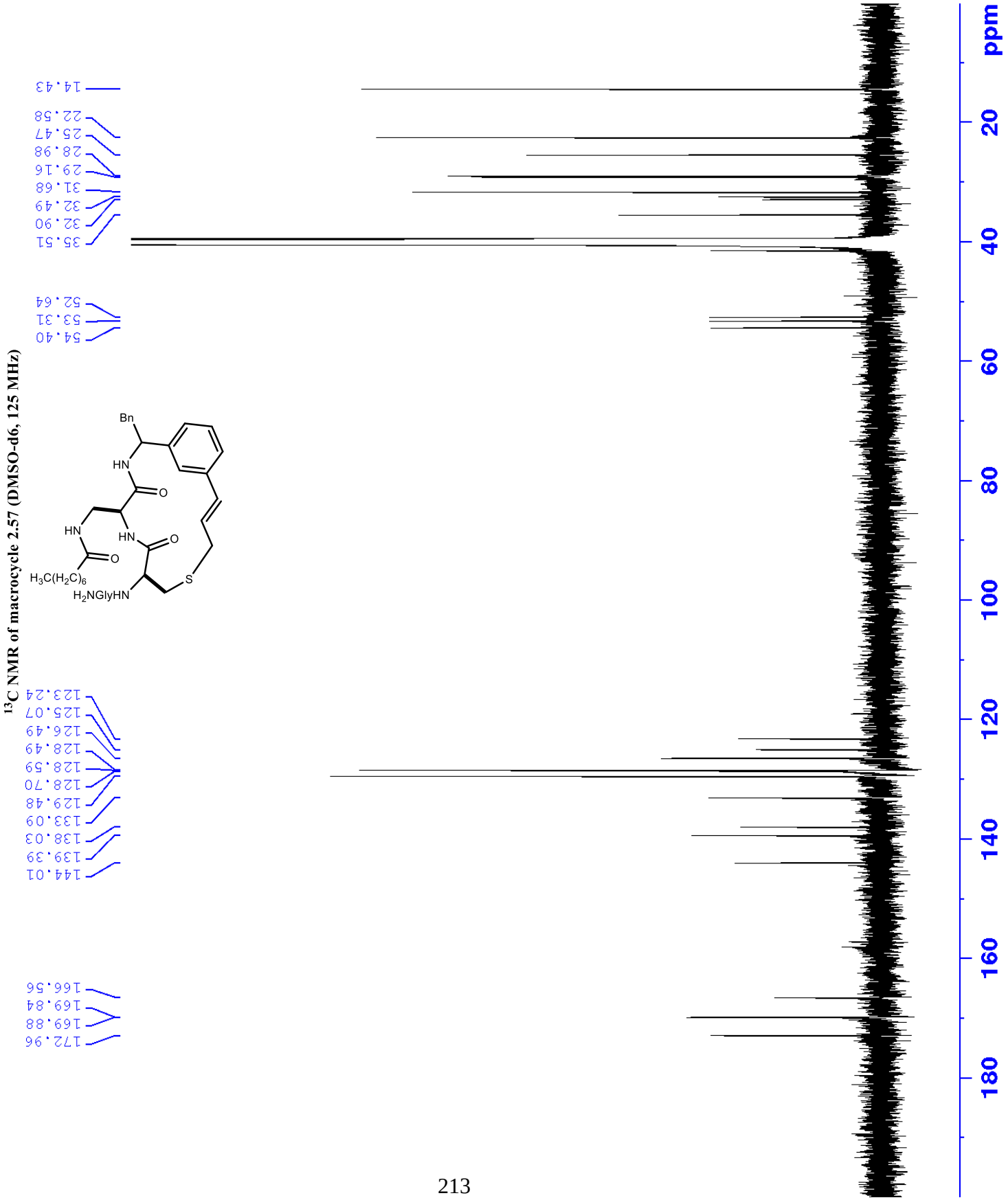

^{1}H NMR of compound 2.56 (MeOD-d4, 500 MHz)
Bn
HN
O
HN
HN
O
O
n-Oct
BocGlyHN
StBu
OCO$_2$i-Bu
4.56
3.37
5.76
9.70
3.00
9.00
2.01
1.28
1.27
2.06
0.98
1.12
1.17
1.13
1.85
2.27
2.22
1.19
1.15
1.09
8.78
ppm
1
2
3
4
5
6
7
8
9

^{13}C NMR of compound 2.56 (MeOD-d4, 125 MHz)

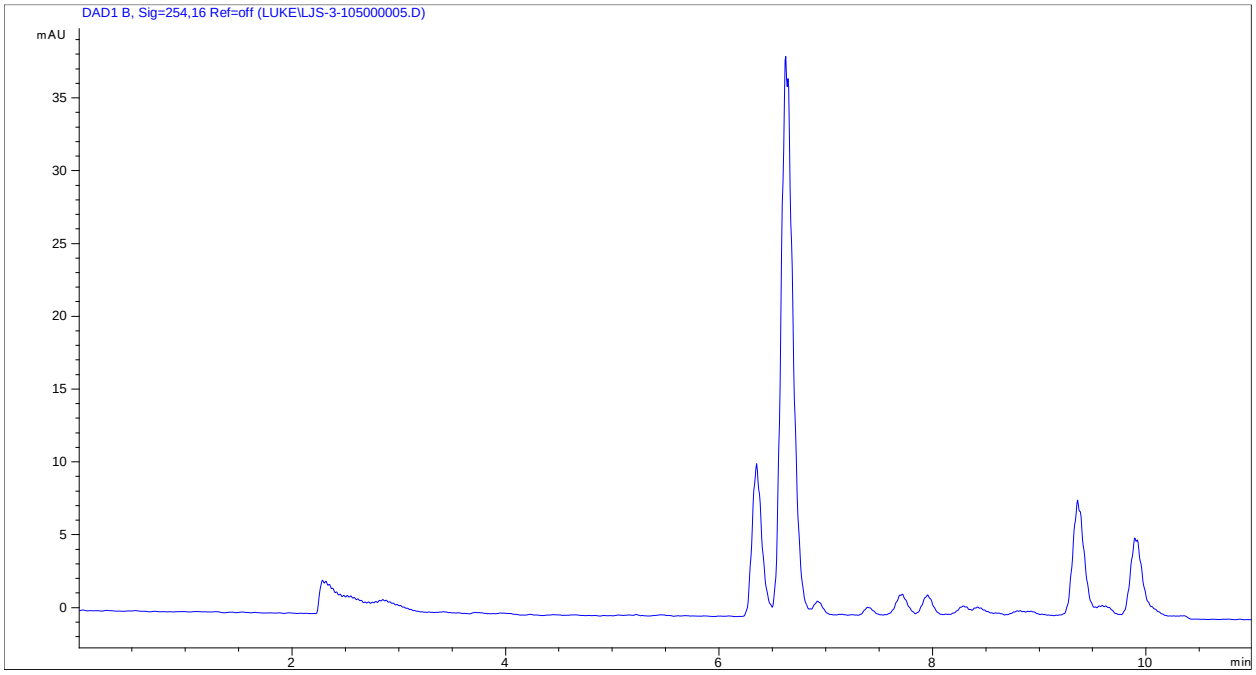


^{1}H NMR of macrocycle 2.57 (DMSO-d6, 500 MHz)




^{13}C NMR of macrocycle 2.57 (DMSO-d6, 125 MHz)
14.43
22.58
25.47
28.98
29.16
31.68
32.49
32.90
35.51
52.64
53.31
54.40
123.24
125.07
126.49
128.49
128.59
128.70
129.48
133.09
138.03
139.39
144.01
166.56
169.84
169.88
172.96
Bn
HN
O
HN
HN
O
O
$H_3C(H_2C)_6$
$H_2NGlyHN$
S
ppm
20
40
60
80
100
120
140
160
180

2.49 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

Control
- Column Flow : 20.000 ml/min
- Stoptime : 11.00 min
- Posttime : Off

Solvents
- Solvent A : 55.0 % (Water)
- Solvent B : 45.0 % (Organic)

PressureLimits
- Minimum Pressure : 0 bar
- Maximum Pressure : 400 bar

Timetable

Time	Solv.B	Flow	Pressure
0.00	45.0	20.000	
2.00	45.0	20.000	
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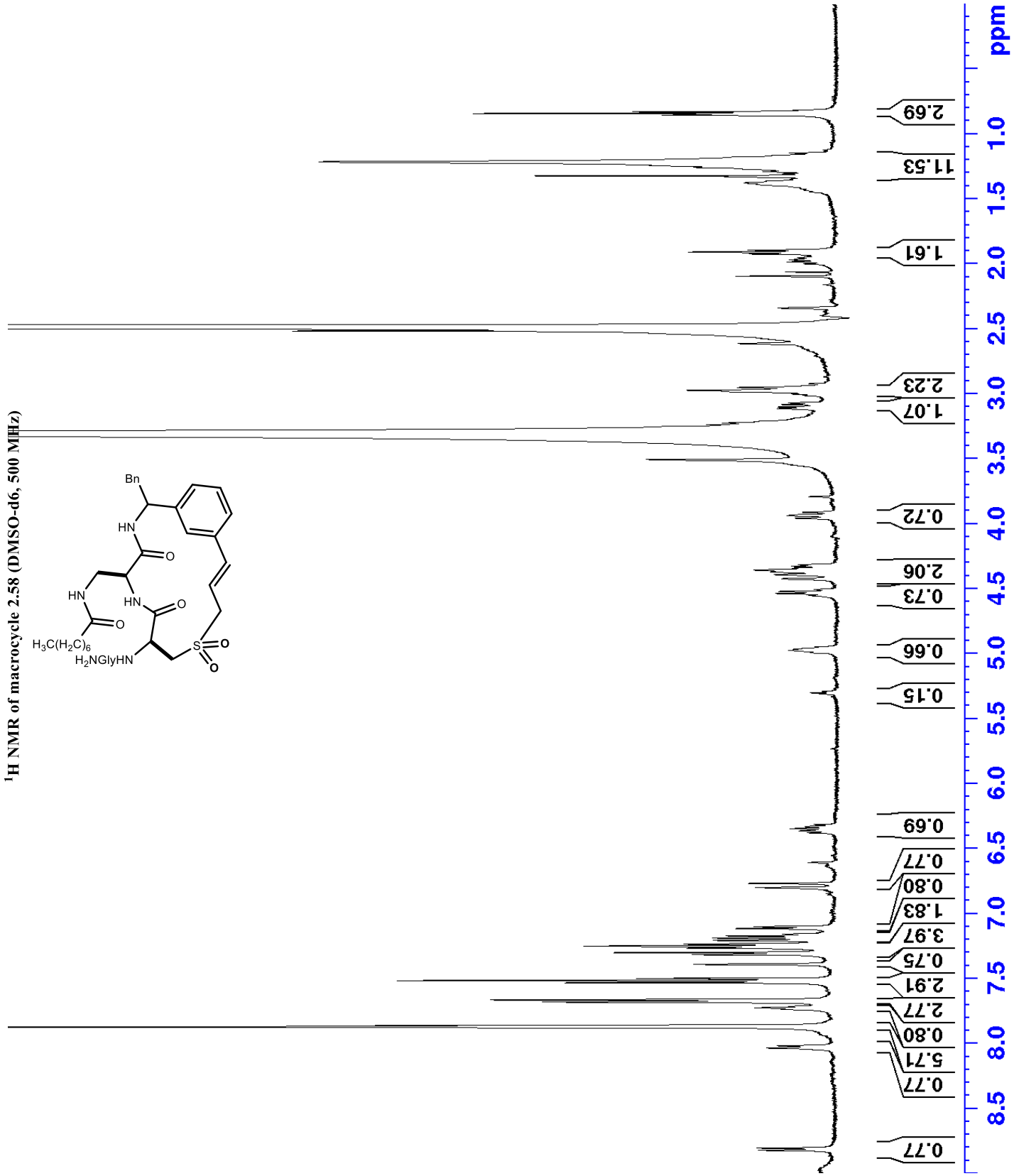
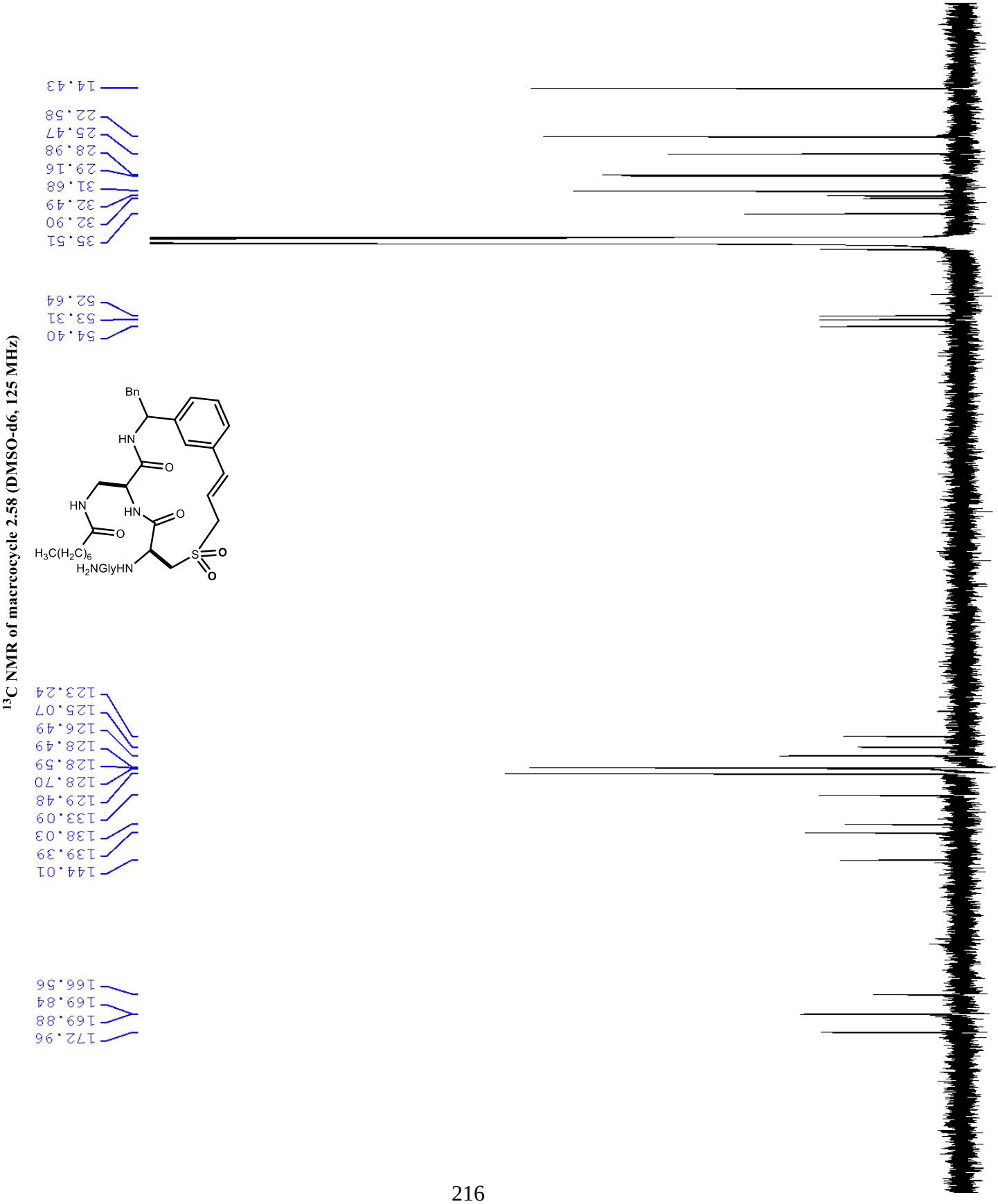
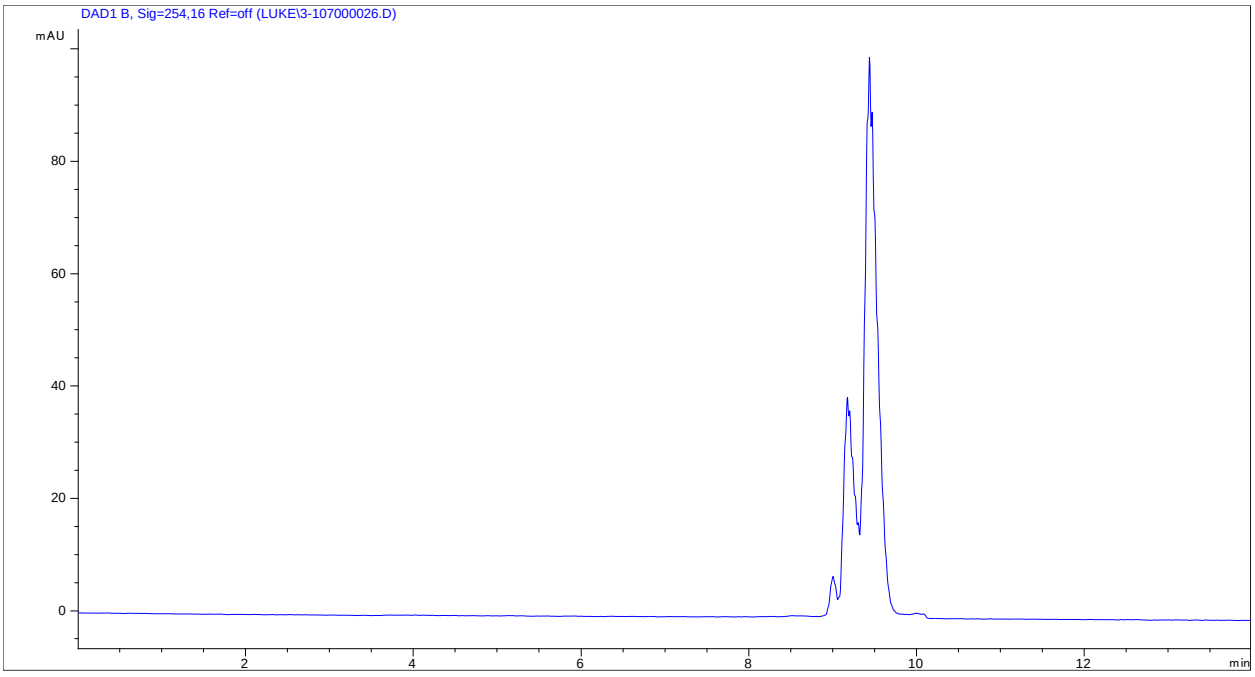
10.50	100.0	20.000	
11.00	40.0	20.000	


^{1}H NMR of macrocycle 2.58 (DMSO-d6, 500 MHz)
Bn
HN
O
HN
HN
O
HN
O
$H_3C(H_2C)_6$
$H_2NGlyHN$
S
O
O
2.69
11.53
1.61
2.23
1.07
0.72
2.06
0.73
0.66
0.15
0.69
0.77
0.80
1.83
3.97
0.75
2.91
2.77
0.80
5.71
0.77
0.77
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
ppm

^{13}C NMR of macrcocycle 2.58 (DMSO-d6, 125 MHz)



2.50 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

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======================================================================

Control
    Column Flow            :      20.000 ml/min
    Stoptime               :         14.00 min
    Posttime               :      Off

Solvents
    Solvent A              :       65.0 % (Water)
    Solvent B              :       35.0 % (Organic)

PressureLimits
    Minimum Pressure       :        0 bar
    Maximum Pressure       :      400 bar


Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00   35.0    20.000
         2.00   35.0    20.000
         7.00   50.0    20.000
        12.00   75.0    20.000
        13.00  100.0    20.000
        14.00   40.0    20.000
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Relevant ^{1}H-NMR for table 2.5

Table 2.5 Entry 1

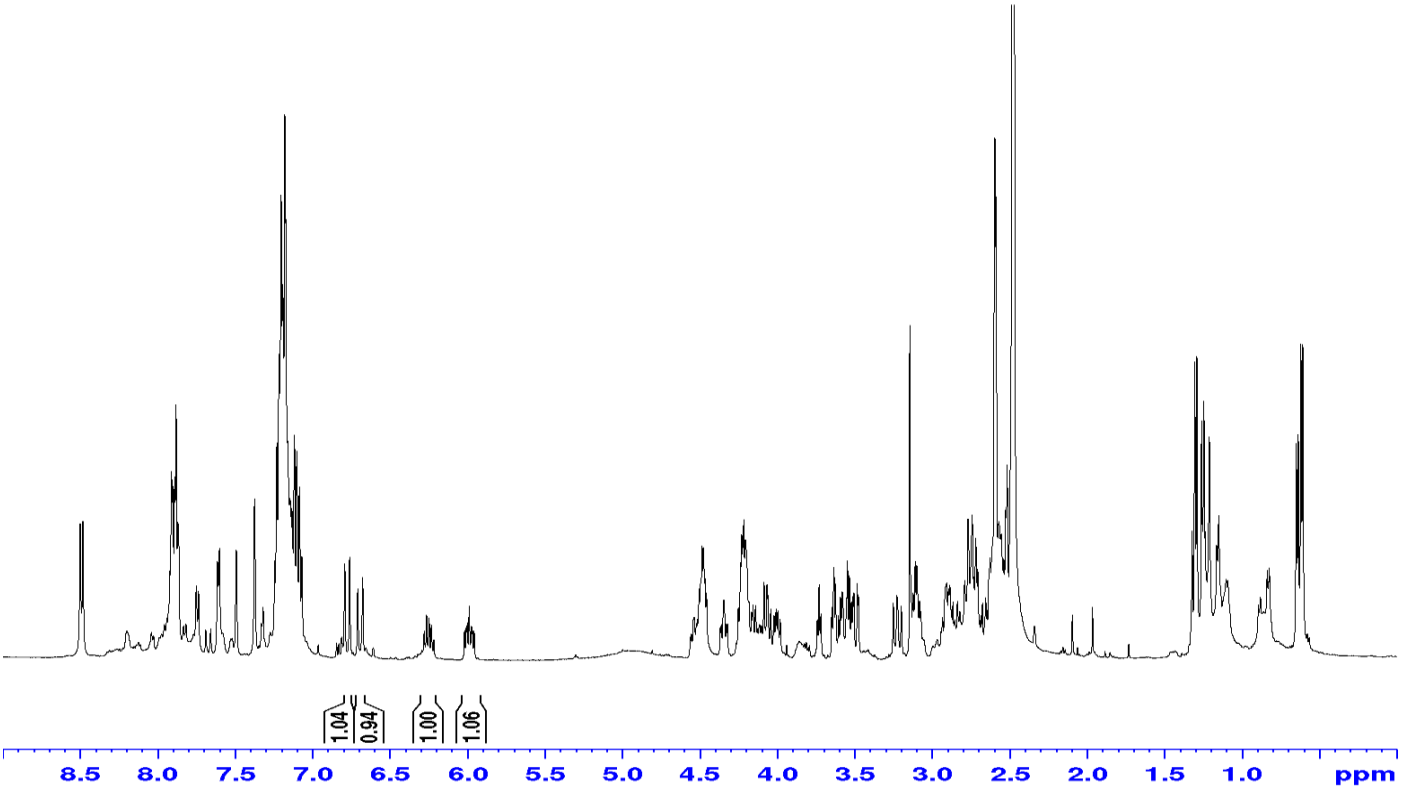


Table 2.5 Entry 3

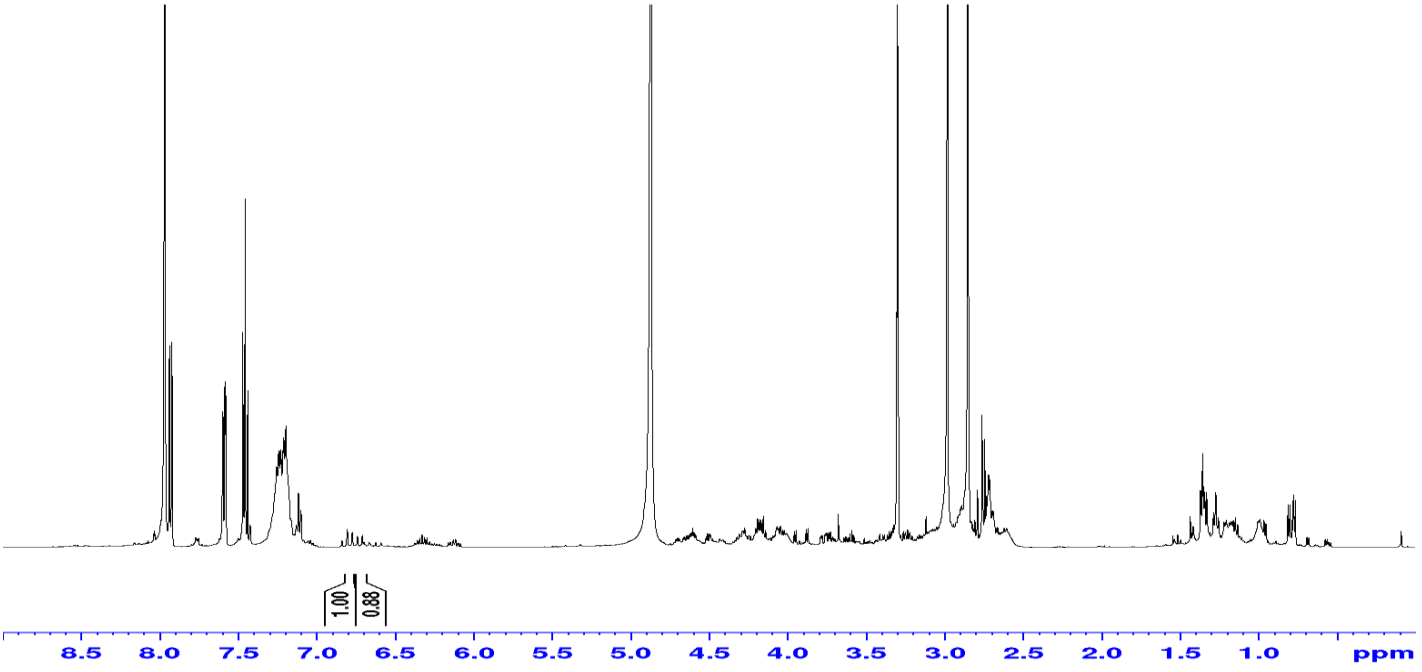


Table 2.5 Entry 4 See **2.43** spectra.

B *Chapter Three- Appendix material*

Synthesis of bimacrocyclic peptidomimetics and enabling templates

Table of contense

Chapter 3 Experimental Procedures

General Methods.
Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon at room temperature. Solvents were dried on activated alumina solvent drying system. Nitromethane was dried by storing for 24 hours over neutral Brockmann I Alumina before being filtered onto to activated 3 angstrom molecular sieves for extended storage. DMF was distilled over CaH_2 onto activated 3 angstrom molecular sieves for extended storage. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF254 (0.25 mm). TLC was visualized with UV light (254 nm) and stained using $KMnO_4$. Flash chromatography was performed on silica gel 60 (240-400 mesh). 1D NMR spectra for peptidal substrates were recorded on a Bruker Avance (500 MHz) spectrometer using MeOH-*d*4 or DMSO-*d*6 as solvent and referenced relative to residual MeOH (δ= 3.31 ppm), $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. ^{13}C NMR spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual MeOH-*d*4 (δ = 49.00 ppm) or DMSO (δ = 39.52 ppm). HSQC, HMBC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. 2D NMR experiments were recorded on a Bruker Avance (600 MHz). High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART IDCUBE, Waters GST Premier, and Waters LCT Premier. All HPLC traces are shown at 254 nm and depict preparative purifcation of macrocycles on a SunFire® C18 OBD 5 um 19 x 250 mm column using an Agilent 1100/1200 Series HPLC.

General Procedure A - Peptide Synthesis:
All peptides were synthesized by 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.[1]

General Procedure B - Acylation of Organic-Soluble Peptides with Templates:
Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **X** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the reaction was either diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The organic phase was then dried over $MgSO_4$, concentrated under reduced pressure. The resulting compound was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent gradient.

General Procedure C - Acylation of Water-Soluble Peptides with Templates:
Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **X** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the solvent was removed via roto evaporator and the residue dissolved in 2 ml of DMSO, passed through a 0.5 micron filter and purified via preparative HPLC. (procedure used to prepare sequences containing His and Glu residues)

General Procedure D - ***Template 10 Derived Peptide Macrocycle Syntheses:***
A scintillation vial was charged with a stir bar and template capped peptide (1.0 equiv.) before being capped with a septum and backfilled thrice with argon. Nitromethane (as described in the materials section) was added to the substrate to afford a concentration of 5.00 mM. In a separate vial, Tf_2NH (3.0 equiv. for neutral substrates, 6.0 equiv. for cationic residues) was dissolved in an equal volume of $MeNO_2$ as the substrate. The acid solution was rapidly added to the substrate solution via syringe and the resulting solution was stirred for 15 minutes. After said time 10 volume % triethylamine was added, and the solvent as removed under reduced pressure. The obtained residue dissolved in ~2 mL of DMSO, passed through a 0.5 micron filter and purified via preparative HPLC.

General Procedure E- ***Template 11 Derived Peptide Macrocycle Syntheses:***
A scintillation vial was charged with a stir bar and template capped peptide (1.0 equiv.) before being capped with a septum and backfilled thrice with argon. Nitromethane (as described in the materials section) was added to the substrate to afford a concentration of 4.50 mM. 10 volume % TFA was added to bring the total concertation to 5.0 mM. The reaction was stirred at ambient temperature for 2-3 hours before the solvent was removed via vacuum. The residue was placed on a high vacuum for over an hour.

A scintillation vial was charged with $PdCl(C_3H_5)]_2$ (7 mg, 0.019 mmol dimer), xanthphos (27.5 mg, 0.048 mmol), a stir bar and capped with a septum. Backfill thrice with Argon. A quantity of DMF (10 ml for catalyst solution, and the required volume for the substrate in the next step) was frozen, pumped, backfilled with Argon, and thawed in three cycles. 10 ml THF from a solvent system was added to the ligand and catalyst, followed by 10 ml of degassed DMF. The resultant yellow solution was stirred under argon at room temperature for 30 minutes.

The crude product from the acidolysis was taken up in a volume of dry degassed DMF (as described in the materials section) as to make a 5 mM solution. To this solution was added a volume of catalysis stock solution equivalent to 7.5 mol% of Pd monomer. 10.0 equiv. of iPr_2NEt was rapidly added and the reaction was placed in an 45ºC oil bath for 3-12 hours. After said time the solvent was removed. The residue was dissolved in ~2 ml of DMSO, passed through a 0.5 micron filter and purified via preparative HPLC.

Figure S1: Synthesis of C2 symmetric templates 3.6 and 3.7

3.1: Dibromocinnamic Acid Methyl Ester

A 500 ml round bottom flask was charged with a stir bar and 3,5-Dibromobenzaldhyde (12.5 g, 47.4 mmol, 1.0 equiv.). In an Erlenmeyer flask, (Methoxycarbonylmethyl)triphenylphosphonium Bromide (21.6 g, 52.0 mmol, 1.1 equiv.) was dissolved in 100 ml of DCM and stirred vigorously with 300 ml of 1 N NaOH for 10 minutes. The aqueous layer was then extracted twice with DCM (100 ml) and the combined organic phase was washed with brine followed by drying with Na_2SO_4. The dry, ylide containing solution was filtered into the flask containing 3,5-Dibromobenzaldhyde. 76 ml of DCM was added to bring the total volume to 376 ml and a reflux condenser was affixed before heating to reflux for 2 hours. After this time the solvent was reduced ~95% and an equal volume of hexanes was added. The residue was loaded onto a silica gel column, using 1:1 DCM: Hexanes and purified using the same eluent to afford 3,5-Dibromocinnamic Acid Methyl Ester as a white crystalline solid (15.15 g, 42.6mmol, 90% isolated yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (t, J = 1.7 Hz, 1H) 7.56 (dd J = 1.7, 0.4 Hz, 2H), 7.52 (d, J = 16.0 Hz, 1H), 6.41 (d, J = 16.0 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 141.6, 137.9, 135.3, 129.5, 123.5, 120.7, 52.0.; LC-MS-ESI (m/z): [M-H] calcd. for $C_{10}H_8Br_2O_2$-H 316.88; found 316.91.

3.2: 3,5 Dibromohydrocinnamic Acid Methyl Ester

A 500 ml round bottom flask was charged with a stir bar, 3,5-Dibromocinnamic Acid Methyl Ester (13.64 g, 42.6 mmol, 1.0 equiv.), $Ni(OAc)_2$ $4H_2O$ (16.0 g, 64.3 mmol, 1.5 equiv.) and of 315 ml of 2:1 EtOAc: MeOH before being cooled to 0℃. $NaBH_4$ (4.9 g, 129.5 mmol, 3.0 equiv.) was added portion wise over 15 minutes. The resulting black suspension was stirred at 0℃ 5 minutes before being passed through a pad of celite. This filtered solution was washed once with H_20 and once with brine. The aqueous phase was washed twice with 150 ml of DCM before the combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. Removal of solvent and purification via silica gel chromatography afforded Dibromohydrocinnamic Acid Methyl Ester (12.06 g, 37.45mmol, 70% isolated yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (s, 1H), 7.26 (d, J = 1.1 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.60 (t, J = 7.6, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.6, 144.4, 132.2, 130.3, 122.9, 51.8, 35.0, 30.2.; LC-MS-ESI (m/z) [M-H] calcd. for $C_{10}H_{10}Br_2O_2$-H 318.9; found 318.9.

3.3: Methyl 3-(3,5-bis((E)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)propanoate (3.3):

A 250 ml round bottom flask was charged with a stir bar, Dibromohydrocinnamic Acid Methyl Ester(11.0 g, 34.1 mmol, 1.0 equiv.) , K_2CO_3 (28.2 g, 204.6 mmol, 6.0 equiv.) and (E)-3-(*tert*-Butyldimethylsilyloxy)propene-1-yl-boronic acid pinacol ester[2] (32.9 g, 102.3 mmol, 3.0 equiv.). The solids were dissolved in 68 ml of 5:1 THF: H_2O and sparged with argon for 30 minutes. $Pd(PPh_3)_4$ (3.9 g, 3.4 mmol, 10 mol%) was added, a reflux condenser was fitted and the reaction was heated to 65˚C. After 48 hours the THF was removed and the aqueous layer was washed thrice with EtOAc. The combined organic was washed thrice with saturated $NaHCO_3$ and twice with brine before being dried over $MgSO_4$. Said solution wash evaporated and either purified via silica gel chromatography to afford Methyl 3-(3,5-bis((E)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)propanoate as a colorless oil (80% isolated yield on 4.08 mmol scale) or carried crude for further reactions (assumed 34.1 mmol) ^{1}H NMR ($CDCl_3$,500 MHz) 7.22 (s, 1H), 7.07 (s, 2H), 6.55 (d, J = 15.9, 2H), 6.28 (dt, J = 3.6 Hz, 2H), 4.34 (dd, J = 5.0, 1.7 Hz, 4H), 3.67 (s, 3H), 2.97-2.87 (m, 2H), 2.66-2.59 (m, 2H), 0.94 (s, 18H), 0.11 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0 141.0 137.6,130.0,127.7, 125.4, 122.6, 63.9, 51.7 35.7, 30.9, 30.5, 26.0, -5.3.; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{28}H_{48}O_4Si_2Na$ 327.3; found 327.3.

3:4. Methyl 3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoate

Crude Methyl 3-(3,5-bis((E)-3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)phenyl)propanoate from the previous reaction (~34.1 mmol assumed) was dissolved in 133 ml of MeOH and 2.24 ml of H_2O was added. A 1 N HCl solution in methanol (4.4 ml, 4.4 mmol, 13 mol%) was added and the reaction was stirred at room temperature for an hour before TLC indicated the consumption of starting material. The solvent was evaporated and the resultant compound, Methyl 3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoate was used without any purification. ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.25 (s, 1H), 7.12 (s, 2H), 6.57 (d, J = 16.0 Hz, 2H), 6.36 (dt, J = 16.0, 5.7 Hz, 2H), 4.32 (d, J = 5.6 Hz, 4H), 3.67 (s, 3H), 2.93 (t, J = 7.8 Hz, 2H), 2.63 (t, J = 9 Hz, 2H); ^{13}C NMR (CDCl3,125 MHz,) δ 172.4, 141.2, 137.3, 130.8, 129.0, 125.8, 122.8, 63.7, 51.7, 35.6, 30.8; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{16}H_{20}O_4Na$ 299.12; found 299.3.

3.5: 3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoic acid

The crude diol product from the reaction above (Methyl 3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoate ~34.1 mmol) was dissolved in 133 ml of 5:1 THF:H_2O.Anhydrous LiOH (2.4 g, 100 mmol, 2.9 eq) was dissolved in 3ml

of H_2O and added to the reaction. The reaction was heated to 65˚C for 1.5 hours. After said time TLC indicated full saponification of the methyl ester. The solvent was removed, and the reaction was acidified to ~2.0 pH with 4.5M Phosphoric acid. The acidified aqueous layer was extracted five times with EtOAc. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified via silica gel chromatography (1:1 Hexane:EtOAc-> pure EtOAc) to afford 3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoic acid (3.9 g, 14.9 mmol, 44% yield over 3 steps from dibromide) as a viscous light yellow gel. ^{1}H NMR (MeOH-d_4, 500 MHz,): δ 7.29 (s, 1H), 7.18 (s, 2H), 6.58 (d, J = 15.9 Hz, 2H), 6.38 (dt, J = 15.9, 5.6 Hz, 2H), 4.23 (dd J = 5.5, 1.2 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), ^{13}C NMR (MeOH-d_4, 125 MHz): δ 175.3, 141.4, 137.5, 130.0, 128.9, 125.2, 122.3, 62.3, 35.3, 30.5.;LC-MS-ESI [M+Na] calcd. for $C_{15}H_{18}O_4Na$ 285.11; found 285.3.

3.6: Template 8 (2,5-dioxopyrrolidin-1-yl3-(3,5-bis((E)-3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate)

3-(3,5-bis((E)-3-hydroxyprop-1-en-1-yl)phenyl)propanoic acid (3.9 g, 14.9 mmol, 1.0 equiv.) was dissolved in in 150 ml of dry THF and N-Methylmorpholine (5.4 ml, 49.2 mmol, 3.3 equiv.) was added. The reaction was cooled to 0˚C and isobutylchloroformate (6.4 ml, 49.2 mmol, 3.3 equiv.) was added dropwise over 5 minutes. After stirring a further 25 minutes at 0˚C, a solution of N-hydroxysuccinimide (2.2 g, 18.7 mmol, 1.25 equiv.) in 8 ml of dry THF was added via syringe. The reaction was stirred a further 30 minutes before it was poured into 200 ml of saturated $NaHCO_3$ and partitioned between 200 ml of EtOAc. The phases were separated and the aqueous was extracted twice with 100 ml of EtOAc. The combined organic phases were washed twice with brine and dried over $MgSO_4$. The solvent was removed via reduced pressure and the residue was purified by silica gel chromatography (50:1 DCM:Diethyl Ether->16:1) to afford **Template 3.6 (2,5-dioxopyrrolidin-1-yl3-(3,5-bis((E)-3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate** (3.07 g, 5.49 mmol, 37% isolated yield).

^{1}H NMR ($CDCl_3$, 500 MHz,): δ 7.28 (s, 1H), 7.16 (d, J = 1.3, 2H), 6.65 (d, J = 16.0, 2H), 6.31 (t, J = 16.0, 6.4 Hz, 2H), 4.78 (dd, J = 6.2, 1.2 Hz, 4H), 3.94 (d, J = 6.7 Hz, 4H), 3.04 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.86-2.81 (br s, 4H), 2.03-1.94 (m, 2H) 0.96 (d, J = 6.7 Hz, 12H). ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 169.0, 167.8, 155.2, 139.8, 136.9, 134.0, 126.4, 123.4, 74.2, 68.1, 32.6, 30.3, 27.8, 25.6, 18.9.; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{28}H_{48}O_4Si_2Na$ 327.3; found 327.3.

3.7: Template 9: 2,5-dioxopyrrolidin-1-yl 3-(3-((E)-3-acetoxyprop-1-en-1-yl)-5-((E)-3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate

4.25 grams of **2** (2,5-dioxopyrrolidin-1-yl3-(3,5-bis((E)-3-((isobutoxycarbonyl)oxy)prop-1-en-1-yl)phenyl)propanoate (7.59 mmol) was dissolved in 152 ml of dry, degassed THF (0.05 M resultant solution) 4.2 ml of AcOH (~10 equiv.) was added and the solution was sparged with argon for 15 minutes. The septum was quickly removed and 132 mg of $Pd(PPh_3)_4$ (1.5 mol%) was added. After 10 minutes the reaction was diluted 5-fold with 1:1 EtOAc: Hexanes and passed through a silica plug. The diluted reaction mixture was washed with saturated $NaHCO_3$ once, dried over $MgSO_4$ and filtered. The solvent was removed via reduced pressure and the residue was purified via silica gel column chromatography. An eluent gradient as follows was used 2.5:1 Hex:EtOAc->2:1->1.75:1->1.5:1->1:1 Hexane:EtOAc. Said reaction afforded 1.17 g of **Template 9** (31% isolated yield), 1.15 g of **S5** (33% isolated yield) and 368 mg of starting material (9% isolated yield).

Template 3.7:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (s, 1H), 7.16 (s, 2H), 6.65 (d, J = 16.1 Hz, 1H), 6.62 (d, J = 16.1 Hz, 1H), 6.36-6.26 (m, 2H), 4.78 (dd, J = 6.5, 0.8 Hz, 2H) 4.78 (dd, J = 6.3, 0.7 Hz, 2H), 3.94 (d, J = 6.8, 2H), 3.04 (t, J = 7.4 Hz, 2H), 2.91 (t, J = 7.8 Hz, 2H), 2.84 (s, 4H), 2.11 (s, 3H), 1.99 (m, 1H), 0.96 (d, J = 6.8, 6H) ^{13}C NMR ($CDCl_3$,125 MHz,): δ 170.8, 169.0, 167.8, 155.2, 139.8, 137.0, 136.9, 134.1, 133.5, 126.3, 124.0, 123.5, 123.4, 74.2, 68.1, 64.9, 32.6, 30.3, 29.7, 27.8, 25.6, 21.0, 18.9.; HRMS-ESI (m/z): [M+Na] calcd. for $C_{28}H_{48}O_4Si_2Na$ 524.189654; found 524.18912.

Template S5: (2E,2'E)-(5-(3-((2,5-dioxopyrrolidin-1-yl)oxy)-3-oxopropyl)-1,3-phenylene)bis(prop-2-ene-3,1-diyl) diacetate:

^{1}H NMR ($CDCl_3$, 500 MHz,): δ 7.28 (s, 1H), 7.15 (d, J = 1.1 Hz, 2H), 6.61 (d, J = 16.0 Hz, 2H), 6.30 (dt, J = 16.0, 6.4 Hz, 2H), 4.72 (dd, J = 6.4, 1.2 Hz), 3.03 (t, J = 7.5 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 2.84 (s, 4H), 2.10 (s, 6H);^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.9, 169.0, 167.8, 139.8, 137.0, 133.5, 126.3, 123.4, 64.9, 32.6, 30.3, 25.6, 21.0.

Linear Precursor 3.8:

Synthesized according to general procedure **B**, obtained in 82% isolated yield.

^{1}H NMR (MeOH-d_4, 500 MHz δ = 7.34 (s, 1H), 7.29-2.21 (s, 1H), 7.05-6.99 (m, 2H), 6.74-6.66 (m, 4H), 6.43-6.34 (m, 2H), 4.78 (d, J= 6.2 Hz, 4H), 4.64 (dd, J= 9.0, 4.8 Hz, 1H), 4.58 (dd, J= 8.3, 5.9 Hz, 1H), 4.36-4.26 (m, 2H), 4.23-4.17 (m, 1H), 3.94 (d, J= 6.6 Hz, 4H) 3.78 (s, 3H), 3.15-3.02 (m, 2H), 3.01-2.89 (m ,4H), 2.65-2.50 (m, 2H), 2.00-1.90 (m ,2H), 1.35-1.25 (m, 12 H), 1.18 (d, J= 6.4 Hz, 3H), 0.96 (d, J= 6.7 Hz, 12H) (^{13}C NMR (126 MHz, MeOH-d_4) δ 174.2, 171.7, 170.8, 170.7, 156.0, 155.4, 141.7, 136.8, 133.7, 130.0, 127.2, 126.1, 123.1, 114.9, 73.7, 67.8, 66.6, 58.3, 52.3,

51.3, 49.8, 41.4, 37.0, 36.2, 31.2, 28.8, 28.8, 27.7, 18.6, 17.8, 16.2 .; LC-MS-ESI (m/z): [M+Na] calcd. For $C_{49}H_{70}N_4O_{14}S_2$ 1025.42, found 1025.6.

Linear Precursor 3.9:
Synthesized according to general procedure **B**, obtained in 52% isolated yield.
^{1}H NMR two amide isomers present (MeOH-d_4, 500 MHz δ = 7.34-7.27 (m, 1H), 7.24-7.19 (m, 2H) , 7.13-6.96 (m, 2H), 6.76-6.59 (m, 4H), 6.41-6.28 (m, 2H), 5.20-5.05 (m, 2H), 4.77-4.69 (m, 4H), 4.50-4.41 (m ,1H), 3.98-3.88 (m, 4H), 3.72-3.67 (m, 2H), 3.65-3.56 (m ,1H), 3.02-2.86 (m, 7H), 2.81-2.75 (m, 1H), 2.75-2.69 (m, 1H), 2.64-2.54 (m, 2H), 1.99-1.89 (m, 2H), 1.34-1.24 (m, 9 H), 0.97-0.91 (m, 12H) ^{13}C NMR (126 MHz, MeOH-d_4) δ 173.8, 170.6, 170.2, 155.8, 155.4, 141.7, 141.7, 136.8, 133.8, 129.7, 129.5, 126.1, 123.1, 122.9, 114.9, 73.7, 67.9, 61.7, 55.1, 51.8, 49.1, 41.6, 41.4, 37.1, 37.0, 35.4, 33.8, 33.5, 32.1, 31.0, 28.9, 27.7, 17.8 .; LC-MS-ESI (m/z): [M+] calcd. $C_{44}H_{63}N_3O_{11}S_2$ 873.39; found 873.2.

Linear Precursor 3.10:
Synthesized according to general procedure **B**, obtained in 62% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz δ = 8.03 (t, J= 5.4 , 1H), 7.32(s, 1H), 7.23 (s, 2H), 7.00 (d, J= 8.4 Hz, 1H), 6.68 (d, J= 8.3, 2H), 6.60 (d, J=15.6, Hz, 2H) 6.40-6.32 (m ,2H), 4.75 (d, J= 6.2 Hz, 4H), 4.58 (q, J= 4.5 Hz, 1H), 4.40 (t, J= 6.0 Hz, 1H), 3.92 (d, J= 6.6 Hz, 4H), 3.74 (dd, J= 10.7, 5.8 Hz, 2H), 3.65 (dd, J= 10.7, 6.4 Hz, 2H), 3.14 (dd, J= 13.6, 4.9 Hz, 1H), 2.92 (t, J= 7.5 Hz, 2H), 2.91-2.92 (m, 1H), 2.68 (t, J= 7.4 Hz, 2H), 2.62-2.56 (m, 2H), 1.99-1.89 (m, 2H), 1.32 (S, 9H), 0.95 (d, J= 6.8 Hz, 12H). ^{13}C NMR (126 MHz, MeOH-d_4)171.6, 171.2, 170.7, 155.5, 155.4, 141.7, 136.7, 133.7, 129.7, 129.7, 129.4, 126.1, 123.1, 122.9, 114.9, 73.7, 61.6, 60.1, 55.3, 53.2, 53.2, 41.4, 41.3, 36.9, 34.1, 31.0, 28.9, 28.9, 27.7, 21.3, 19.5, 17.8 .; LC-MS-ESI (m/z): [M+H] calcd. for. $C_{43}H_{61}N_3O_{11}S_2$ 860.38; found 860.5.
Exact Mass: 860.38

Linear Precursor 3.11:
Synthesized according to general procedure **C**, obtained in 30% isolated yield.
^{1}H (MeOH-d_4, 500) MHz 7.30 (s, 1H) 7.20 (s, 2H), 7.03 (t, J = 8.7 Hz, 2H), 6.73-6.62 (m, 4H) , 6.40-6.31 (m, 2H), 4.78-4.72 (m, 4H), 4.72-4.53 (m, 3H), 4.51-4.43 (m, 1H), 4.42-4.26 (m, 2H), 6.91 (d, J = 6.6 Hz, 4H), 3.88-3.77 (m, 2H), 3.66-3.58 (m, 1H) 3.56-3.43 (m, 1H), 3.42-3.32 (m, 1H), 3.28-3.07 (m, 6H), 3.06-2.95 (m, 2H), 2.94- 2.87 (m, 2H), 2.83-2.74 (m, 1H), 2.53-2.44 (m, 2H), 1.99-1.90 (m, 2H), 1.91 (s, 3H), 1.87-1.74 (m, 2H), 1.72-1.64 (m, 2H), 1.64-1.49 (m, 4H), 1.31 (rotamer split t-Bu group, 4H and 5H), 0.94 (d, J = 6.7 Hz, 12H).; ^{13}C NMR (MeOH-d_4,126 MHz) δ 173.9, 173.8, 173.0, 172.7 172.5, 172.3 172.2, 172.0, 171.9, 171.7, 169.8, 169.2, 168.7 (amide carbons from both rotomers listed, all other peaks are for major rotomer) 157.2, 155.9, 155.4, 141.7, 136.8, 133.7, 136.8, 133.7, 129.8, 127.5, 126.2, 124.7, 123.2, 114.9, 73.7, 67.9, 67.2, 66.1, 56.7, 55.4, 53.2, 52.9, 52.6, 52.3, 51.9, 49.2, 43.5, 42.1, 40.8, 40.7, 40.5, 40.0, 38.5, 38.1, 37.6, 37.3, 36.5, 31.4, 28.9, 27.7, 24.6, 21.0 17.8.; LC-MS-ESI (m/z): [M+H] calcd. For $C_{56}H_{88}N_{10}O_{15}S_2H$ 1241.61; found 1242.0.

Macrocycle 3.12
Synthesized according to general procedure **D**, 19% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) (resonances form major conformer listed) δ 9.14 (br, 1H), 8.12 (d, J = 5.3 Hz, 1H), 8.05, (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1), 7.87 (d, J= 7.8 Hz, 1H), 7.82 (br, 1H), 7.64 (br, 1H), 7.53 (t, J = 5.4 Hz, 1H), 7.33 (s, 2H), 7.25 (s, 3H), 7.17 (s, 1H), 6.94 (s, 1H), 6.69 (s, 2H), 6.67 (d, J = 15.8 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 6.25-6.19 (m, 2H), 4.88 (s, 1H), 4.80-4.74 (m, 1H), 4.67-4.59 (m, 1H), 4.52-4.44 (m, 2H), 4.17 (d, J = 11.5 Hz, 1H), 4.02-3.98 (m, 2H), 3.72-3.61 (m, 1H), 3.45-3.38 (m, 4H), 3.14-3.08 (m, 4H), 3.00 (q, J = 7.6 Hz, 1H), 2.93-2.88 (m, 1H), 2.87-2.76 (m, 4H), 2.56-2.45 (m,2H), 2.18-2.09 (m, 2H), 1.89 (s, 3H), 1.49-1.43 (m, 1H), 1.20-1.13 (m, 2H), 0.77-0.56 (m, 2H).; ^{13}C NMR (prominent peaks of major conformer listed) (DMSO-d_6, 126MHz) δ 171.9, 171.4, 171.3, 171.1, 169.5, 169.4, 157.1, 154.4, 141.1, 137.5, 137.2, 134.4, 133.3, 130.5, 130.4, 129.6, 128.7, 127.2, 126.2, 124.2, 123.8, 123.6, 114.7, 68.8, 67.1, 53.5, 53.3, 53.0, 51.9, 49.1, 47.9, 46.5, 43.4, 40.9, 38.5, 38.1, 34.8, 30.2, 28.7, 26.2, 25.7, 24.9, 22.9, 21.1,; HRMS-ESI (m/z): [M+H] calcd. For $C_{45}H_{60}N_{10}O_9S_2H$ 949.4064; found 949.4082.

Linear Precursor 3.13
Synthesized according to general procedure **B**, obtained in 45% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.31 (s, 1H), 7.21 (s, 2H), 7.07 (dd, J = 8.4, 3.7 Hz, 2H), 6.72-6.64 (m, 4H), 6.36 (dt, J = 15.9, 6.3 Hz, 2H), 4.89 (dd, J = 8.2, 6.0 Hz, 1H), 4.75 (d, J = 6.3), 4.60 (dd, J = 9.3, 5.3 Hz, 1H), 4.37 (dd, J = 8.9, 4.8 HZ, 1H), 4.33 (d, J = 4.2 Hz, 1H), 4.19-4.13 (m, 1H) , 3.92 (d, J = 6.6 Hz, 4H), 3.72-3.48 (m, 8H), 3.21-3.09 (m, 2H), 3.06 (dd, J = 14.1, 5.2 Hz, 1H), 2.98-2.91 (m, 2H), 2.89 (t, J = 7.1 Hz, 2H), 2.80 (dd, J = 14.2, 9.3 Hz, 1H), 2.75 (dd, J = 12.9, 6.0 Hz, 1H), 2.46 (dd, J = 14.9, 7.0 Hz, 2H) 1.99-1.93 (m, 2H), 1.91 (s, 3H), 1.84-1.74 (m, 1H), 1.65-1.55 (m, 2H), 1.54-1.44 (m, 2H), 1.30 (d, J = 2.9 Hz, 9H), 1.16 (d, J = 6.4 Hz, 3H), 0.96 (d, J = 6.7 Hz, 12H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 173.8, 172.9, 171.9, 170.7, 169.2, 155.9, 155.4, 141.7, 136.8, 133.7, 129.9, 127.6, 126.1, 123.1, 123.0, 114.8, 73.7, 70.2, 67.8, 66.9, 66.2, 60.1, 58.5, 55.3, 52.3, 49.2, 38.3, 37.5, 36.3, 29.9, 29.7, 28.7, 27.9, 27.7, 25.4, 21.0, 21.0, 18.5, 18.0, 17.8 LC-MS-ESI (m/z): [M+H] calcd. For $C_{56}H_{82}N_6O_{15}SH$ 1111.6; found 1111.4.

Macrocycle 3.14:
Synthesized according to general procedure **D**, 29% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.03 (d, J = 7.5 Hz, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.36 (s, 1H), 7.28 (t, J = 6.0, 1H), 7.05 (s, 1H), 7.00 (s, 1H), 6.90 (s, 1H), 6.82 (dd, J = 8.3,1.5 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 15.8 Hz, 1H), 6.39 (m, 1H), 6.33 (m, 1H), 6.34 (m, 1H), 6.26 (d, J = 7.5, 1H), 4.61 (m, 1H), 4.55 (m, 1H), 4.17 (dd, J = 7.8, 4.3 Hz), 3.89 (m, 1H), 3.82 (m, 1H), 3.12 (d, J = 13.5, 3.0 Hz,1H), 3.57-3.48 (m, 4) 3.50-3.40 (m, 4H), 3.37-3.30 (m, 2H) 3.32-3.35 (m, 2H) 3.12 (d, J = 1 3.5, 3.0 Hz, 1H), 2.90-2.76 (m, 2H) 2.88-2.75 (m, 2H), 2.81-2.75 (m, 2H) 2.58 (d,J = 13.5, 5.1 Hz,1H), 2.35 (m, 2H) 1.87 (s, 1H) 0.97 (d, J = 6.1 Hz, 3H) 1H 0.76 (m, 2H) 0.88-0.77 (m, 2H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 171.4, 171.0, 170.7, 169.4, 169.3, 168.9, 154.0, 141.2, 138.2, 136.1, 132.2, 130.6, 130.3, 129.5, 128.7, 128.5, 127.9, 126.1, 121.7, 114.6 , 67.4, 66.6, 57.6, 53.9, 52.5, 50.2, 45.9, 42.7, 37.9, 37.5, 37.1, 36.6, 34.0, 32.2. 28.6, 25.0, 22.9, 19.0.; HRMS-ESI (m/z): [M+H] calcd. For $C_{42}H_{54}N_6O_9SH$ 841.3571; found 841.3561.

Linear Precursor 3.15
Synthesized according to general procedure **B**, obtained in 27% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.32 (s, 1H) 7.22 (s, 2H) 7.03 (d, J = 8.4, 2H), 6.71 (d, J = 8.4, 2H) 6.68 (d, J = 16.0 Hz, 2H), 6.42-6.33 (m, 2H) 4.77 (d, J = 6.0 Hz, 4H) 4.65-4.59 (m, 1H) 4.48-4.42 (m, 1H) 3.94 (d, J = 6.6 Hz, 4H) 3.84-3.70 (m, 2H) 3.16 (dd, J = 13.6, 5.0, 1H) 3.09 (t, J = 6.9 Hz, 2H) 3.02-2.85 (m, 4H) 2.70 (t, J = 7.5 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.32-2.26 (m, 2H), 2.01-1.91 (m, 2H) 1.68-1.59 (m, 2H) 1.34 (s, 9H) 1.32-1.11 (m, 14H), 0.96 (d, J = 6.8 Hz, 12H) 0.93 (m, 2H).; ^{13}C NMR (MeOH-d_4,126 MHz) δ175.3, 173.5, 171.3, 170.6, 155.5, 155.4, 141.5, 136.7, 133.8, 129.7, 129.4, 126.2, 123.1, 123.0, 114.9, 73.7, 67.8, 61.6, 55.4, 53.2, 47.1, 41.4, 41.2, 39.0, 37.0, 35.4, 34.1, 31.4, 29.17, 29.14, 29.03, 28.97, 28.89, 28.87, 27.7, 26.5, 25.4, 17.9, 17.8.; LC-MS-ESI (m/z): [M+H] calcd. For $C_{54}H_{82}N_4O_{12}S_2H$ 1043.53; found 1043.0.

Macrocycle 3.16:
Synthesized according to general procedure **D**, 28% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 9.08 (s, 1H), 8.10 (d, J = 8.0 Hz), 7.93 (d, J = 7.0Hz, 1H), 7.80 (s, 1H), 7.77 (s, 1H), 7.65 (t, 5.7 Hz 1H), 6.98 (s, 1H) 6.95 (S, 1H), 6.85 (s,1 H) 6.84 (d, J = 12.4 Hz, 1H, 1H) 6.67 (d, J = 8.0Hz, 1H), 6.50-6.42 (m, 1H) 6.39 (m, J = 15.5Hz, 1H), 6.35 (d, J = 15.5Hz, 1H), 5.18 (s, 1H), 4.60 (m, 1H), 4.23 (m, 1H), 3.59, 3.52 (m, 2H), 3.54 (m,1H) 3.39 (m, 1H), 3.37 (m 2H) 3.36 (m, 1H) 3.25 (m, 1H), 3.13 (m, 1H) 2.98 (m, 1H) , 2. 98-2.88 (m, 2H) 2.86-2.76 (m, 2H), 2.65-2.57 (m, 2H), 2.41-2.25 (m, 2H), 2.22-2.14 (m, 1H) 2.02-1.97 (m, 1H) 1.54 (m, 1H 1.38 (m, 1H) 1.20-1.00 (m, 14H), 0.95 (m, 2H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 171173.4,.4, 171.3 170.0, 153.4, 141.1, 138.1, 136.3, 133.0, 130.7, 130.5 130.3, 127.1, 127.0, 126.2, 126.2, 119.3, 115.2, 61.8, 55.8, 52.7, 42.6, 41.7, 41.3, 36.5, 35.3, 34.3, 32.0, 30.8, 29.7, 29.2, 29.2, 29.0, 28.5, 26.6, 25.7.; HRMS-ESI (m/z): [M+H] calcd. For $C_{40}H_{54}N_4O_6S_2H$ 751.3563; found 751.3531.

Linear Precursor 3.17:
Synthesized according to general procedure **B**, obtained in 68% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.32 (s,1H) 7.31-7.26 (m, 4H) 7.24-7.19 (m, 3H) 6.67 (d J = 15.9 Hz, 2H) 6.37 (dt J = 15.9, 6.4 Hz, 2H) 5.10 (m, 1H) 4.75 (dd, J = 6.4, 1.0 Hz, 1H), 4.65 (dd, J = 8.5, 5.2 Hz, 1H), 4.31 (t, J = 5.1 Hz, 1H) 4.25 (dd, J = 8.9, 5.2 Hz, 1H), 3.92 (d, J = 6.7 Hz, 4H), 3.80 (dd, J = 11.0, 5.2 Hz, 1H) 3.72 (dd, J = 11.0, 5.2 Hz, 1H) 3.69-3.61 (m, 6H) 3.59 (d, J = 1.8 Hz, 2H) 3.58-3.55 (m, 2H) 3.17 (dd, J = 13.6, 5.3 Hz, 1H) 3.15-3.10 (m, 1H) 3.07 (dd, J = 13.4, 7.1 Hz, 2H) 3.01(dd, J = 13.6, 8.6 Hz, 1H) 2.91 (t, J = 7.5 Hz,2H) 2.87 (dd, J = 13.5, 6.6 Hz, 1H) 2.62-2.50 (m, 2H) , 1.99-1.88 (m, 2H) 1.70-1.61 (m, 1H) 1.56-1.47 (m, 1H) 1.45-1.36 (m, 2H) 1.31 (s, 9H) 1.30 (s, 9H) 0.95 (d, J = 6.7 Hz, 12H); ^{13}C NMR (MeOH-d_4,126 MHz) 173.7, 173.2, 172.4, 171.1, 170.4, 169.0, 155.4, 141.6, 136.8, 135.1, 133.8, 128.9, 128.3, 126.6, 126.2, 123.1, 123.0, 73.7, 67.9, 66.4, 66.3, 61.3, 55.7, 53.5, 53.2, 46.2, 42.6, 42.1, 41.5, 41.3, 38.6, 36.9, 31.2, 31.1, 28.9, 28.2, 27.7, 22.5, 17.8.; LC-MS-ESI (m/z): [M+Na] calcd. For $C_{60}H_{90}N_6O_{14}S_4Na$1269.53; found 1269.2.

Macrocycle 3.18:
Synthesized according to general procedure **D**, 47% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 8.40-8.08 (m, 2H), 7.89-7.78 (m, 1H), 7.42 (s, 1H), 7.40-7.30 (m, 1H) 7.30-7.16 (m, 5H), 7.12 (s, 1H), 6.99 (s, 1H),6.49 (d, J = 15.2 Hz, 1H), 6.48 (d, J = 15.2 Hz, 1H), 6.32-6.22 (m, 2H), 4.87-4.76 (m, 1H), 4.40-4.30 (m, 1H), 4.15-4.08 (m, 1H), 4.08-4.00 (m, 1H), 3.70-3.27 (m, 16H), 3.20 (d, J = 12.7 Hz , 1H), 3.14-3.06 (m, 1H), 3.05-2.96 (m, 2H), 2.85-2.76 (m, 2H), 2.71-2.60 (m, 2H) 1.40-1.20 (m, 6H); ^{13}C NMR (DMSO-d_6, 126MHz) δ172.2, 171.8, 170.9, 170.8, 169.6, 167.3, 141.8, 137.1, 136.9, 136.3, 133.4, 132.3, 129.6, 128.6, 127.1, 126.8, 126.4, 125.6, 124.9, 124.2, 66.6, 66.5, 61.5, 56.3, 54.0, 51.9, 48.0, 45.9, 43.9, 42.6, 42.4, 42.3, 41.7, 37.6, 37.3, 31.9, 27.8, 18.5, 17.2, HRMS-ESI (m/z): [M+H] calcd. For $C_{42}H_{54}N_8O_8S_4H$ 899.2964; found 899.2996.

Linear Precursor 3.19:
Synthesized according to general procedure **B**, obtained in 38% isolated yield.

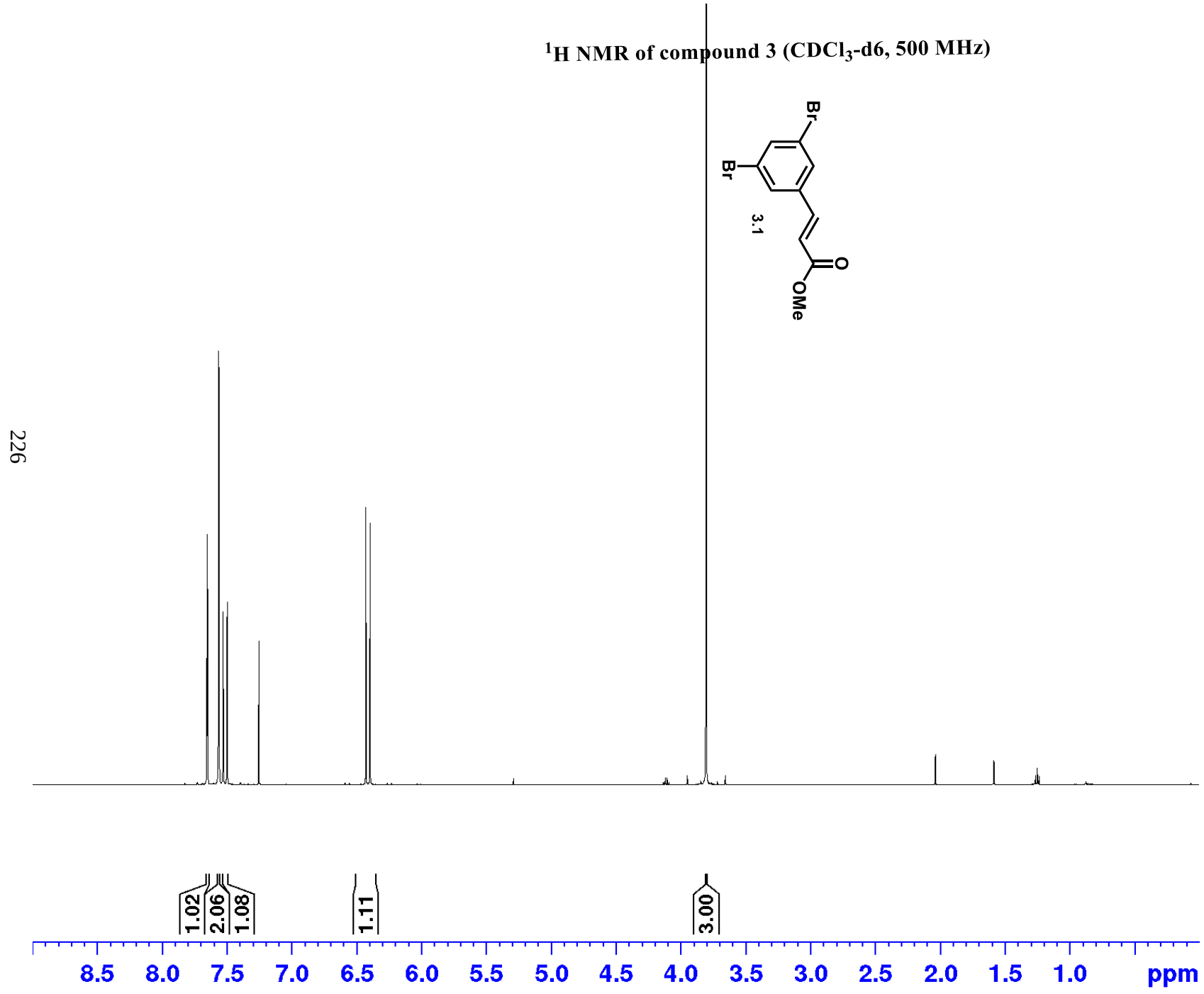
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.56 (d, J= 7.9 Hz, 1H), 7.31 (d, J= 8.1 Hz, 1H), 7.30-7.25 (m, 1H), 7.21-7.14 (m, 2H), 7.10-6.96 (m, 4H), 6.69-6.61 (m, 4H), 6.58-6.51 (m, 1H), 6.33 (dt, J= 15.9, 6.3 Hz, 2H), 5.13 (t, J= 6.9 Hz, 1H), 4.73 (dd, J= 6.3, 1.1 Hz, 4H), 4.68 (dd, J= 8.2, 5.5 Hz, 1H), 4.33 (dd, J= 8.7, 5.0 Hz, 1H), 3.91 (d, J= 6.6 Hz, 1H), 3.61-3.43 (m, 4H), 3.30 (q, J= 1.6 Hz, 2H), 3.25 (dd, J= 14.7, 5.4 Hz, 1H),3.16-2.95 (m, 5H), 2.93-2.87 (m, 2H), 2.81 (dd, J= 13.5, 7.1 Hz, 1H), 2.44 (t, J= 7.7 Hz, 2H), 1.91 (sept, J= 6.7 Hz, 2H), 1.68-1.59 (m, 5H), 1.54-1.46 (m, 3H), 1.30 (s, 9H), 0.94 (d, J= 6.7 Hz, 12H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 173.7, 172.6, 172.6, 172.6, 171.8, 168.4, 157.3, 155.4, 141.7, 136.8, 136.6, 136.4, 133.7, 129.3, 129.2, 127.4, 126.1, 123.2, 123.1, 123.0, 121.1, 119.9, 118.5, 118.1, 115.7, 113.6, 110. 9, 109.4, 73.7, 67.8, 60.1, 54.1, 52.7, 43.3, 42.2, 41.6, 38.2, 37.5, 31.4, 28.9, 27.7, 27.3, 25.3, 25.0, 24.0, 19.5, 17.8, 13.0 HRMS-ESI (m/z): [M+Na] calcd $C_{61}H_{80}N_6O_{12}S_2$ 1175.52; found 1175.7.

Linear Precursor 3.21:
Synthesized according to general procedure **C**, obtained in 59% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 8.22 (s, 1H), 7.30 (s, 1H), 7.20 (s, 2H), 7.13 (s, 1H), 6.67 (d, J = 16.1 Hz, 1H), 6.63 (d, J = 16.1 Hz, 1H), 6.36 (dt, J = 16.1, 6.4 Hz, 1H), 6.33 (dt, J = 16.1, 6.3 Hz, 1H), 4.75 (dd, J = 6.4 , 1.2 Hz, 2H), 4.71 (dd, J = 6.3, 1.2 Hz, 2H), 4.64 (dd, J = 8.8, 4.6 Hz, 1H), 4.43 (dd, J = 8.1, 6.2 Hz, 1H), 4.35 (dd, J = 9.1, 4.9 Hz, 1H), 4.24 (d, J = 3.9 Hz, 1H), 4.21-4.15 (m, 1H), 3.92 (d, J = 6.6 Hz, 1H), 3.33 (s, 1H), 3.27 (dd, J = 15.4, 4.6 Hz, 1H), 3.22-3.09 (m, 2H), 3.05 (dd, J = 15.4, 8.9 Hz, 1H), 2.96 (dd, J = 12.9, 6.0 Hz, 1H), 2.90 (t, J = 7.5 Hz, 2H), 2.81 (dd, J = 12.9, 8.2 Hz, 1H), 2.48 (t, J = 7.8 Hz, 2H), 2.07 (s, 3H), 2.00 (s, 3H), 1.98-1.88 (m, 2H), 1.84-1.75 (m, 1H), 1.68-1.60 (m, 1H), 1.58-1.44 (m, 2H), 1.31 (s, 9H), 1.17 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H); ^{13}C NMR (MeOH-d_4,126 MHz) 173.8, 173.5, 173.0, 172.3, 172.1, 171.3, 170.8, 155.4, 141.7, 137.0, 136.8, 134.1, 133.8, 133.2, 131.4, 126.01, 125.97, 123.6, 123.1, 122.8, 117.0, 73.7, 67.8, 66.8, 64.7, 59.1, 54.3, 53.5, 52.5, 42.1, 38.3, 37.5, 31.3, 29.9, 29.4, 28.2, 27.7, 27.5, 25.5, 21.1, 19.5, 18.7, 17.8.; LC-MS-ESI (m/z): [M+H] calcd. For $C_{46}H_{68}N_8O_{12}SH$ 957.48 found 957.4.

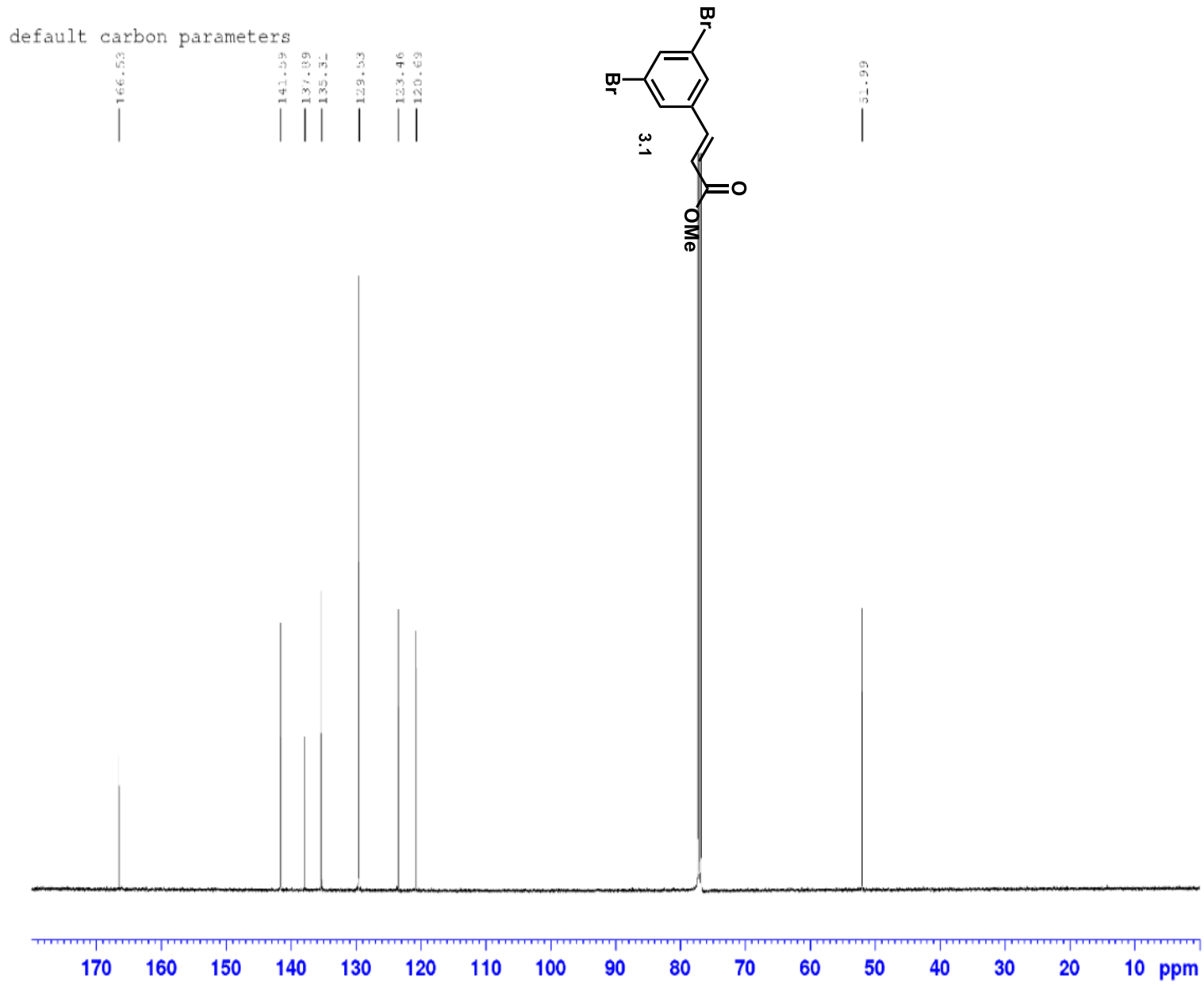
Macrocycle 3.24:
Synthesized according to general procedure **E**, 20% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 14.5 (br, 1H), 9.06 (s, 1H), 8.36 (d, J = 6.5 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.41 (s, 1H), 7.40-7.25 (m, 4H), 7.20 (s, 1H), 7.16 (m, 1H), 7.05 (s, 1H), 6.68 (d, 15.7 Hz, 1H), 6.58 (d, 15.7 Hz, 1H), 6.40-6.26 (m, 2H), 5.33 (d,J = 8.0 Hz, 1H), 4.55-4.45 (m, 1H), 4.35-4.29 (m, 1H) , 4.28-4.21 (m, 1H) 4.07-3.98 (m, 1H), 3.44-3.35 (m, J, 2H) 3.19 (m, 1H),2.95 (m,1H) 2.89 (m, 1H) 2.88-2.72 (m, 4H), 2.53-2.40 (m, 2H) 2.49-2.36 (m, 2H), 1.89 (s, 3H), 1.30- 1.13 (m, 4H), 1.02 (d, J = 4.9 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 172.6, 171.1, 171.0, 170.9, 170.6, 169.9, 141.3, 136.1, 135.2, 134.7, 132.4, 128.0, 127.6, 126.0, 124.1, 123.5, 119.6, 67.7, 57.2, 54.2, 52.5, 51.4, 50.4, 37.9, 37.0,34.9, 33.0, 31.5, 29.2, 27.1, 25.7, 22.8, 19.4.; HRMS-ESI (m/z): [M+H] calcd. For $C_{35}H_{46}N_8O_7SH$ 723.32884; found 723.32796.

Linear Precursor 3.25:
Synthesized according to general procedure **C**, obtained in 39% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 8.65 (d, J = 1.1 Hz, 1H), 7.31 (s, 1H), 7.21 (s, 2H), 6.67 (d, J = 16 Hz, 1H) 6.64 (d, J = 16 Hz, 1H) 6.37 (dt, J = 16, 6.5 Hz, 1H) 6.34 (dt, J = 16, 6.3 Hz, 1H) 4.76 (dd, J = 6.3, 1.2 Hz, 2H) 4.72 (dd, J = 6.3, 1.1 Hz 2H) , 4.64 (dd, J = 8.1, 4.7 Hz, 1H) 4.49 (dd, J = 8.6, 5.8 Hz, 1H) 4.48 (dd, J = 10.2, 4.0 Hz, 1H) 4.33 (dd, 8.6, 4.9 Hz, 1H) 3.93 (d, J = 6.6, 1H) 3.62-3.49 (m, 2H), 3.46- 3.32 (m, 2H) 3.27 (dd, J = 15.2, 4.7, 1H) 3.24-3.10 (m, 2H) 3.06 (dd, J = 15.1, 8.1, 2H), 3.01 (dd, J = 12.9, 5.7 Hz, 2H) 2.91 (t, J = 7.65, 2H) 2.82 (dd, J = 12.9, 8.6 Hz, 1H) 2.54 (sp, J = 6.9 Hz, 1H) 2.50 (t, J = 7.4 Hz, 1H) 2.45-2.29 (m, 2H) 2.08 (s, 3H) 2.02-1.91 (m, 3H) 1.91-1.82 (m, 2H) 1.82-1.74 (p, J = 7.2 Hz, 2H) 1.31 (s, 9H) 1.12 (dd, J = 17.0, 6.9 Hz, 6H), 0.96 (d, J = 6.7 Hz, 6H); ^{13}C NMR (MeOH-d_4,126 MHz) δ 178.82, 173.83, 173.35, 172.83, 172.44, 171.74, 171.24, 170.20, 155.36, 141.7, 136.9, 136.8, 133.8, 133.5, 133.2, 130.7 126.00, 125.94, 123.6 , 123.1, 122.9, 117.1, 73.7, 67.8, 64.7, 53.5, 53.0, 52.7, 50.4, 46.3, 45.9, 42.0, 38.2, 37.5, 34.6, 31.3, 30.8, 29.9, 29.7 , 28.6, 27.7, 26.6 25.6, 25.4, 23.7, 19.5, 18.7, 18.3, 17.8.; LC- MS-ESI (m/z): [M+H] calcd. For $C_{53}H_{78}N_8O_{13}SH$ 1067.55; found 1067.50.

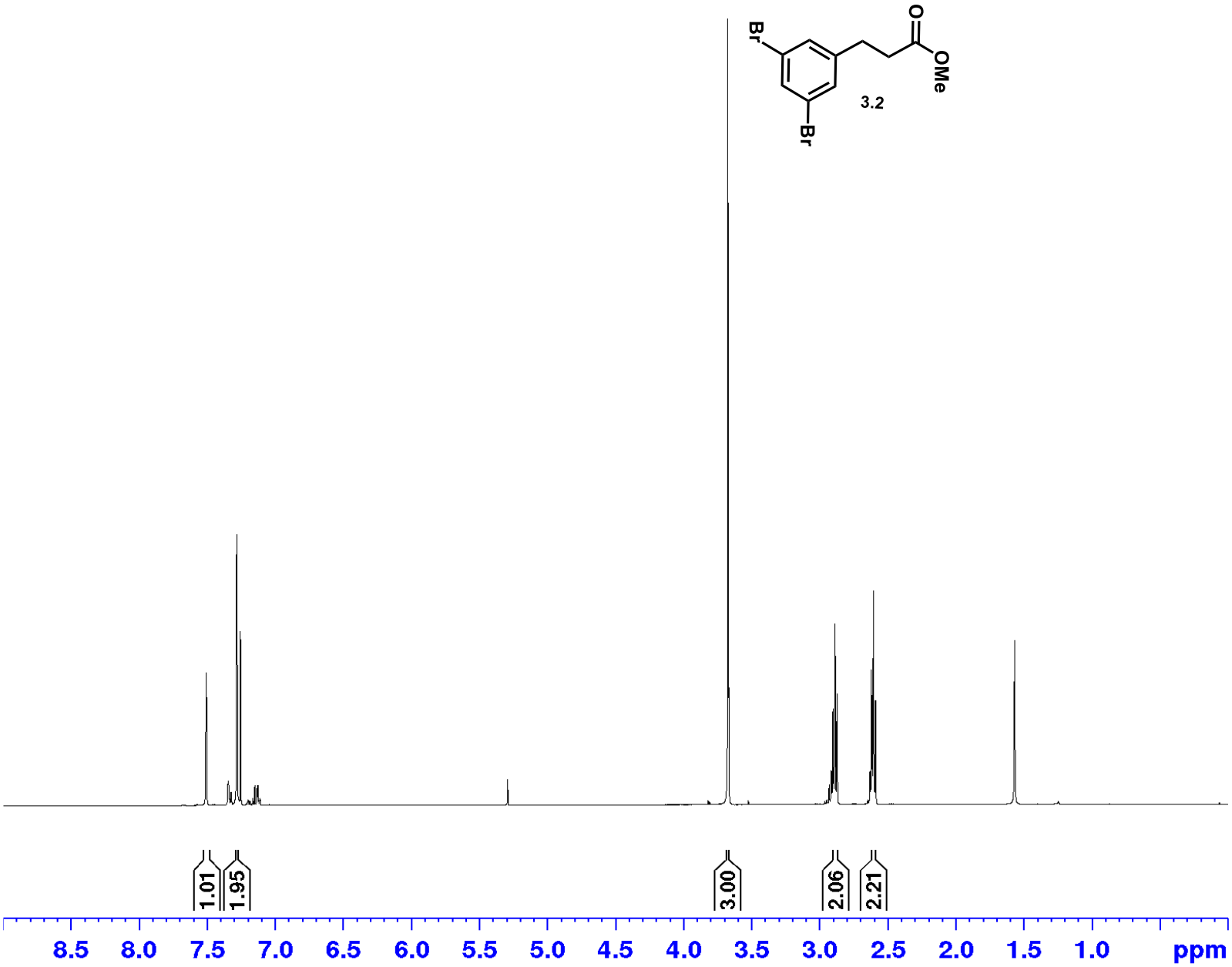
Macrocycle 3.26:
Synthesized according to general procedure **E**, 31% yield after preparative HPLC.
^{1}H NMR (DMSO-d_6, 600 MHz) δ 13.2 (br, 2H), 8.91 (br, 1H), 8.26 (d, J = 7.4, 1H) 8.25 (d, J = 12.5 Hz ,1H) 7.99 (d, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.22 (s, 1H), 7.09 (s, 1H), 7.03 (s, 1H), 6.96 (d, 15.6 Hz, 1H), 6.81 (d, J = 8.3 Hz), 6.60 (d, J = 15.7 Hz, 1H) 6.37 (dt, J = 15.7 , 6.6 Hz, 1H) 6.20 (dt, J = 15.6, 5.6 Hz, 1H) 4.94-4.81 (m, 2H) , 4.72 (q, J = 7.6 Hz, 1H) 4.58 (m,1H) 4.31 q, J = 7.8 Hz, 1H) 3.85 (q, J = 4.5 Hz, 1H), 3.52-3.36 (m, 4H), 3.28-3.19 (m, 3H) 3.13 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H) 2.68 (m, 2H), 2.47 (m, 1H) 2.41 (m, 1H), 2.21 (m, 1H), 2.09 (m, 1H) 1.86 (m, 1H), 1.82-1.67 (m, 4H) , 1.56-1.15 (m, 5H), 1.00 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H) 0.89-0.78 (m, 1H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 176.7, 172.7, 172.1, 171.7, 170.8, 170.3, 168.5, 142.0, 137.2, 136.2, 135.5, 135.2, 134.0, 129.2, 127.4, 126.0, 123.7, 120.6, 119.0, 54.7, 50.8, 50.4, 50.2, 49.6, 49.0, 46.0, 45.9, 38.7, 33.9, 33.5, 32.5, 31.3, 28.5, 27.3, 26.0, 25.6, 24.2, 20.2, 19.9.; HRMS-ESI (m/z): [M+H] calcd. For $C_{42}H_{56}N_8O_8SH$ 833.4020; found 833.4010.


^{1}H NMR of compound 3 ($CDCl_3$-d6, 500 MHz)
Br
Br
3.1
O
OMe
226
1.02
2.06
1.08
1.11
3.00
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
ppm

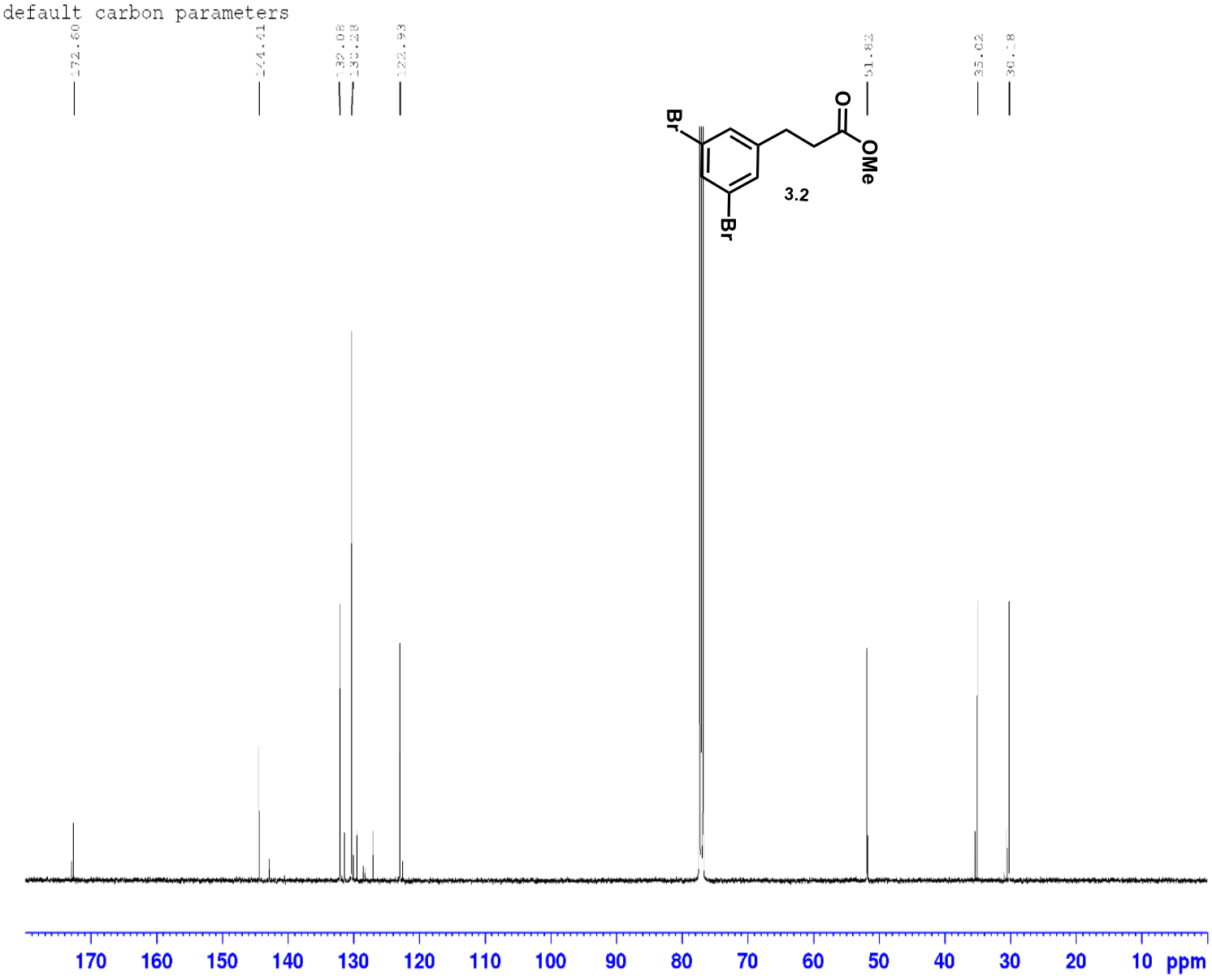
^{13}C NMR of compound 3.1 ($CDCl_3$, 126 MHz)



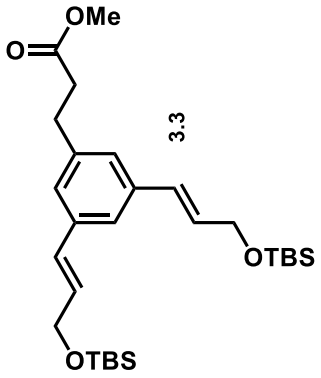
^{1}H NMR of compound 3.2 ($CDCl_3$, 500 MHz)



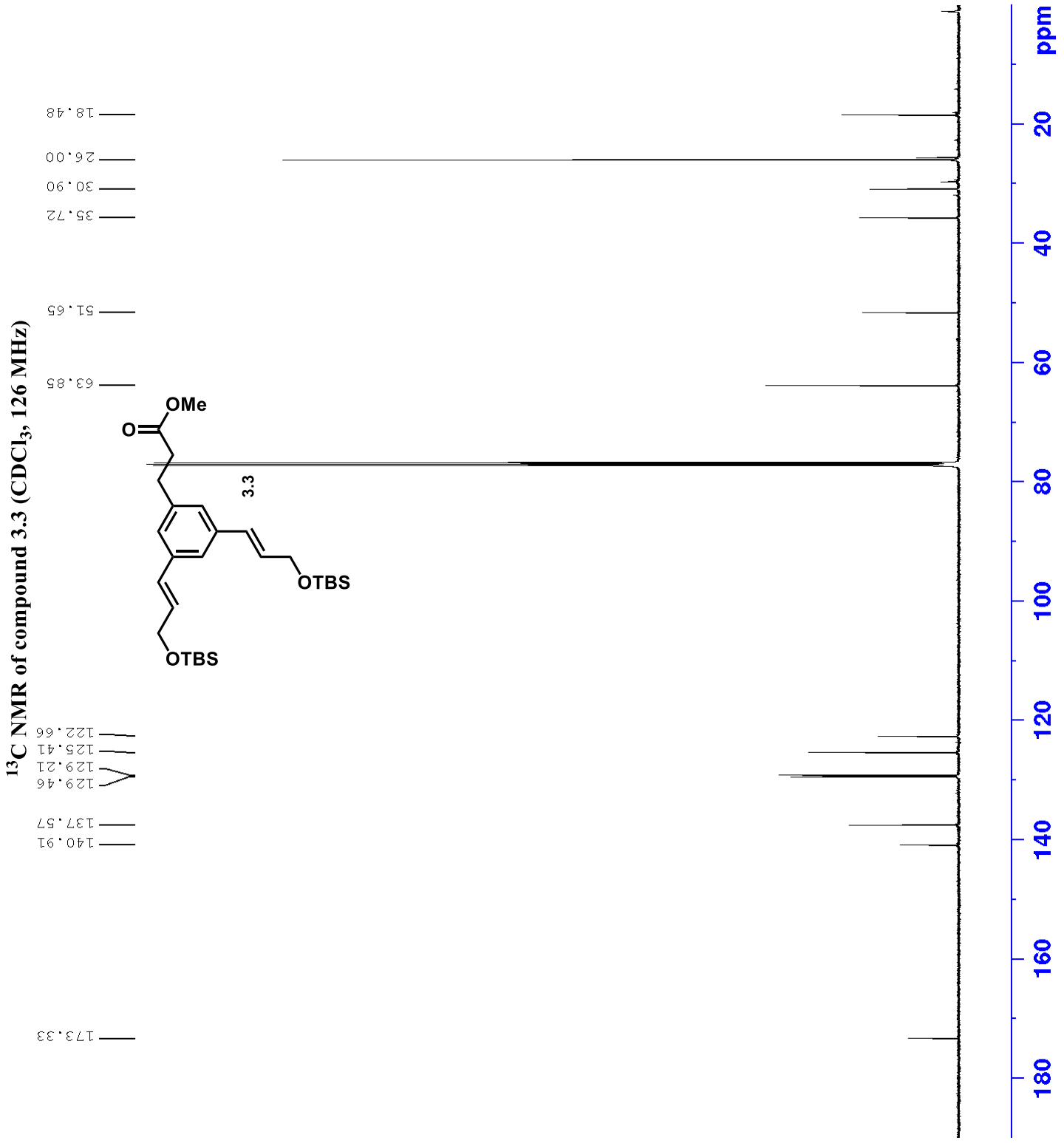
^{13}C NMR of compound 3.2 ($CDCl_3$, 126 MHz)



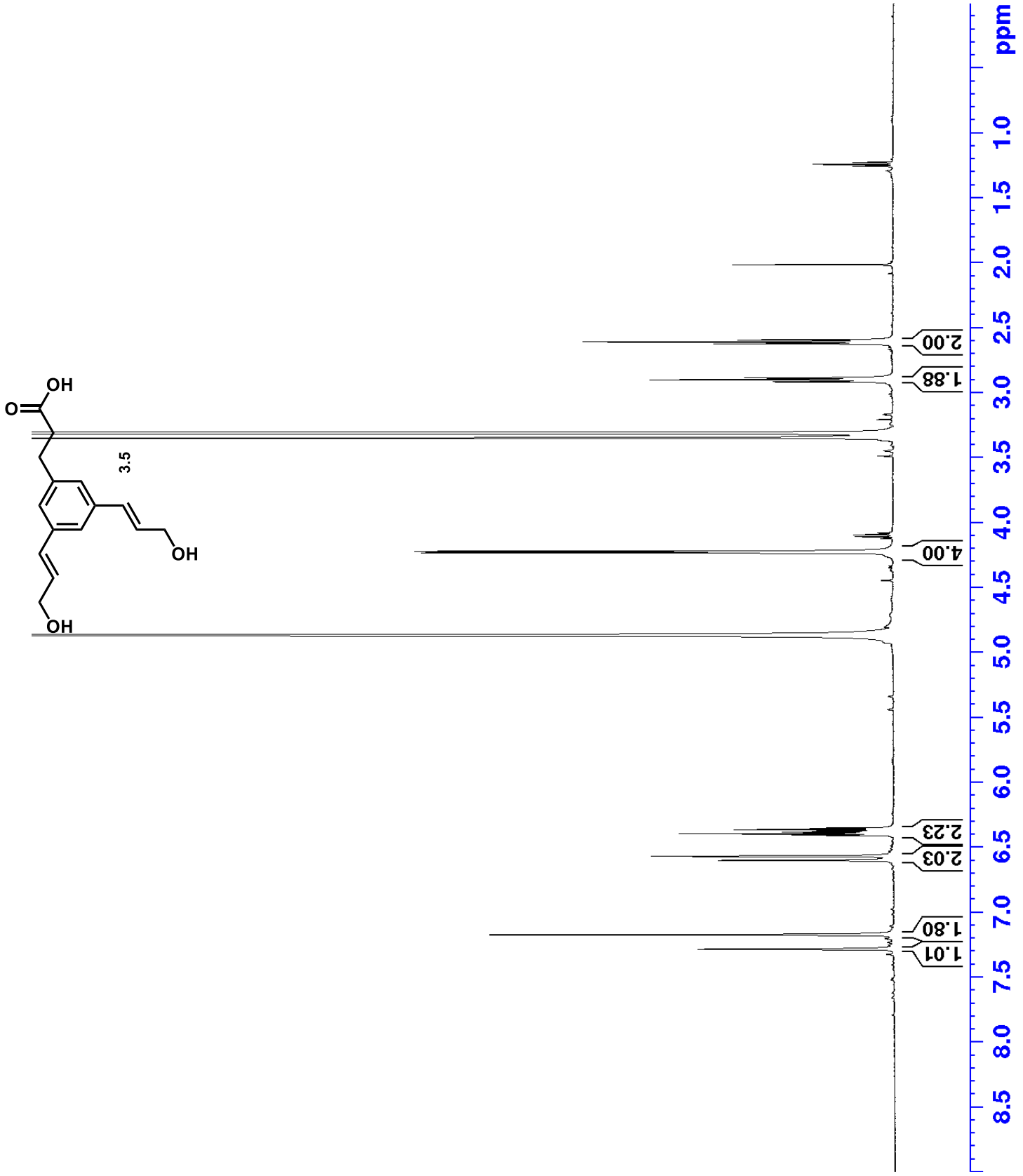
^{1}H NMR of compound 3.3 ($CDCl_3$, 400 MHz)



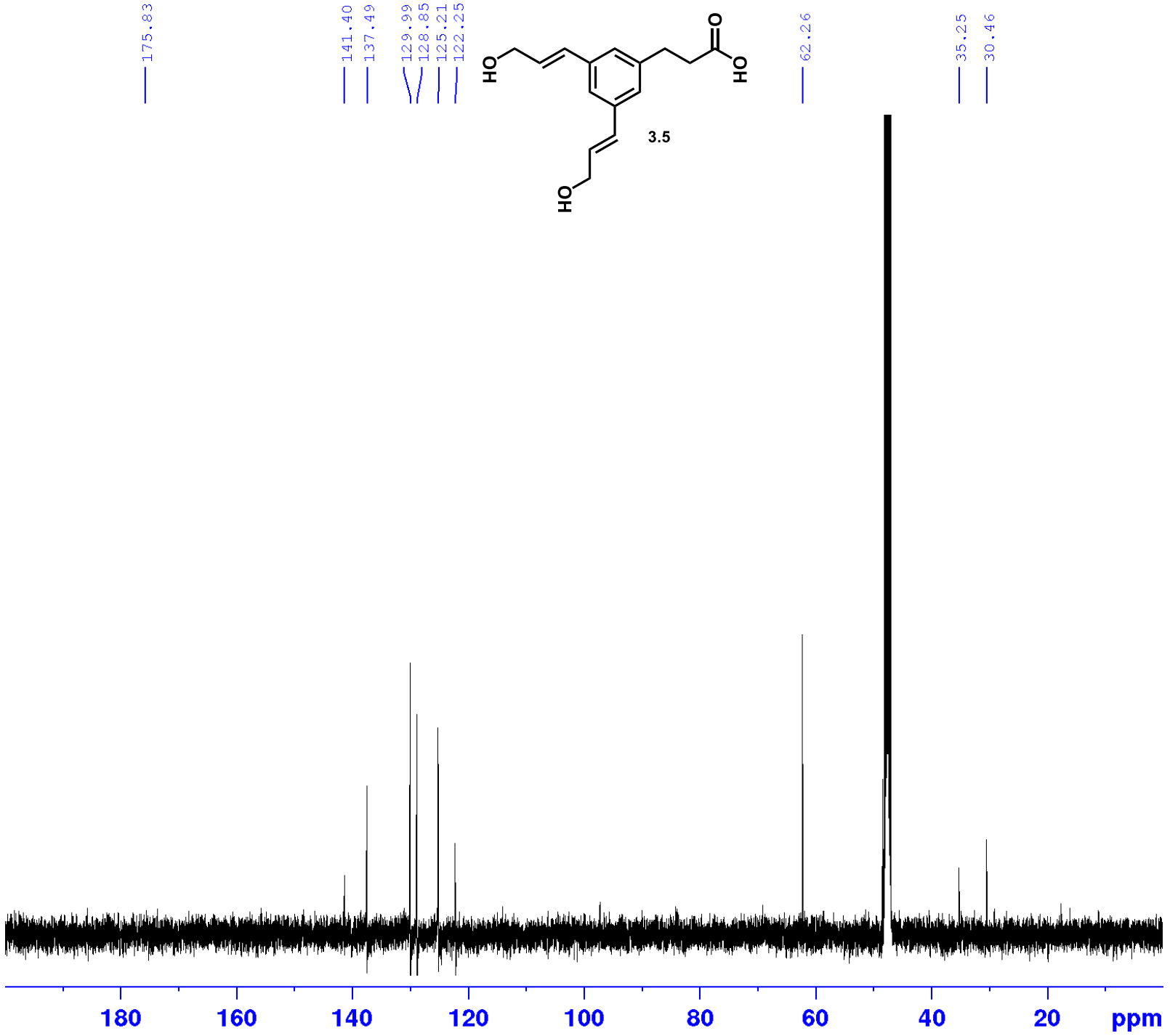
3.3


^{13}C NMR of compound 3.3 (CDCl$_3$, 126 MHz)
18.48
26.00
30.90
35.72
51.65
63.85
122.66
125.41
129.21
129.46
137.57
140.91
173.33
OMe
O
3.3
OTBS
OTBS
ppm
20
40
60
80
100
120
140
160
180

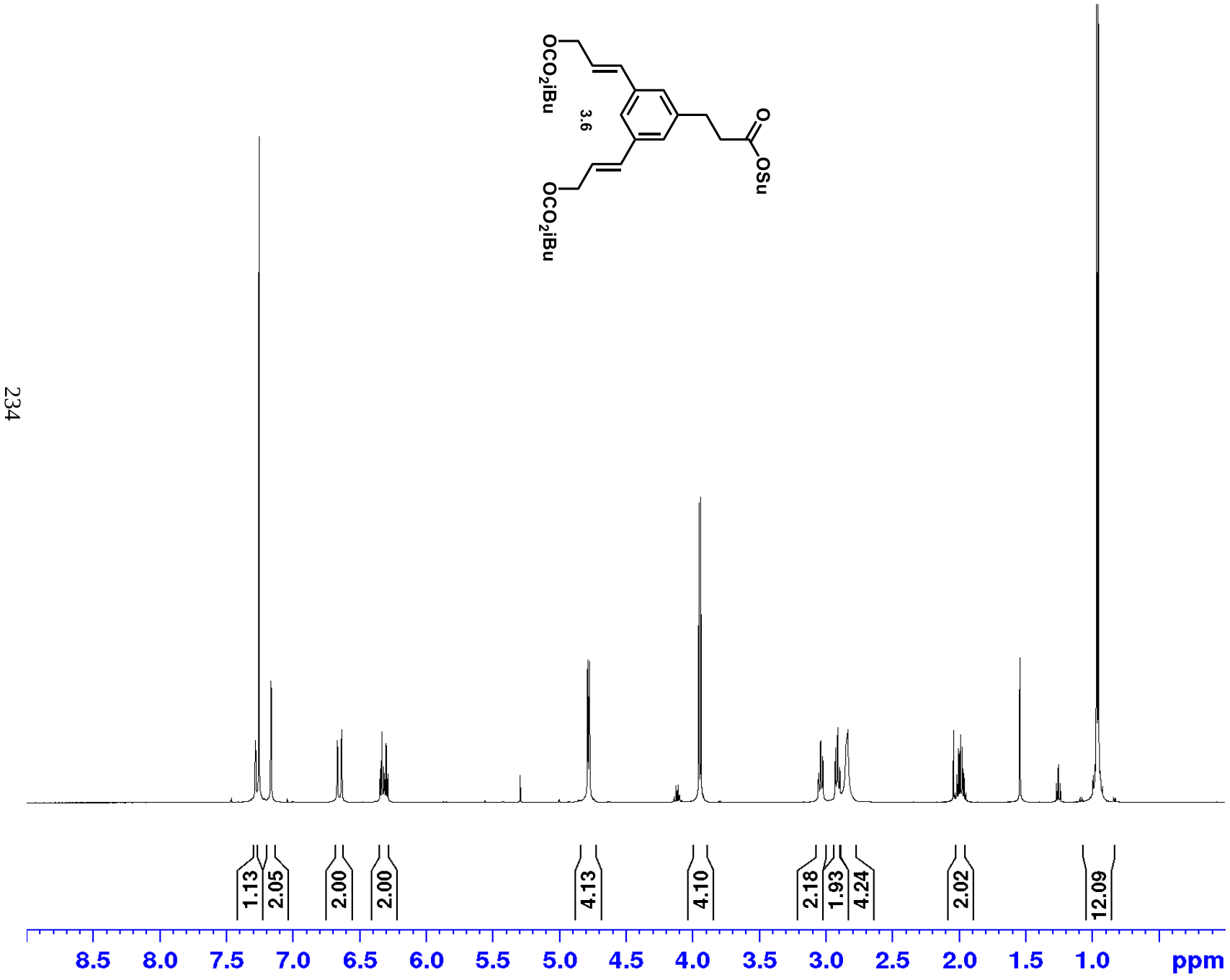
^{1}H NMR of compound 3.5 ($CDCl_3$, 400 MHz)



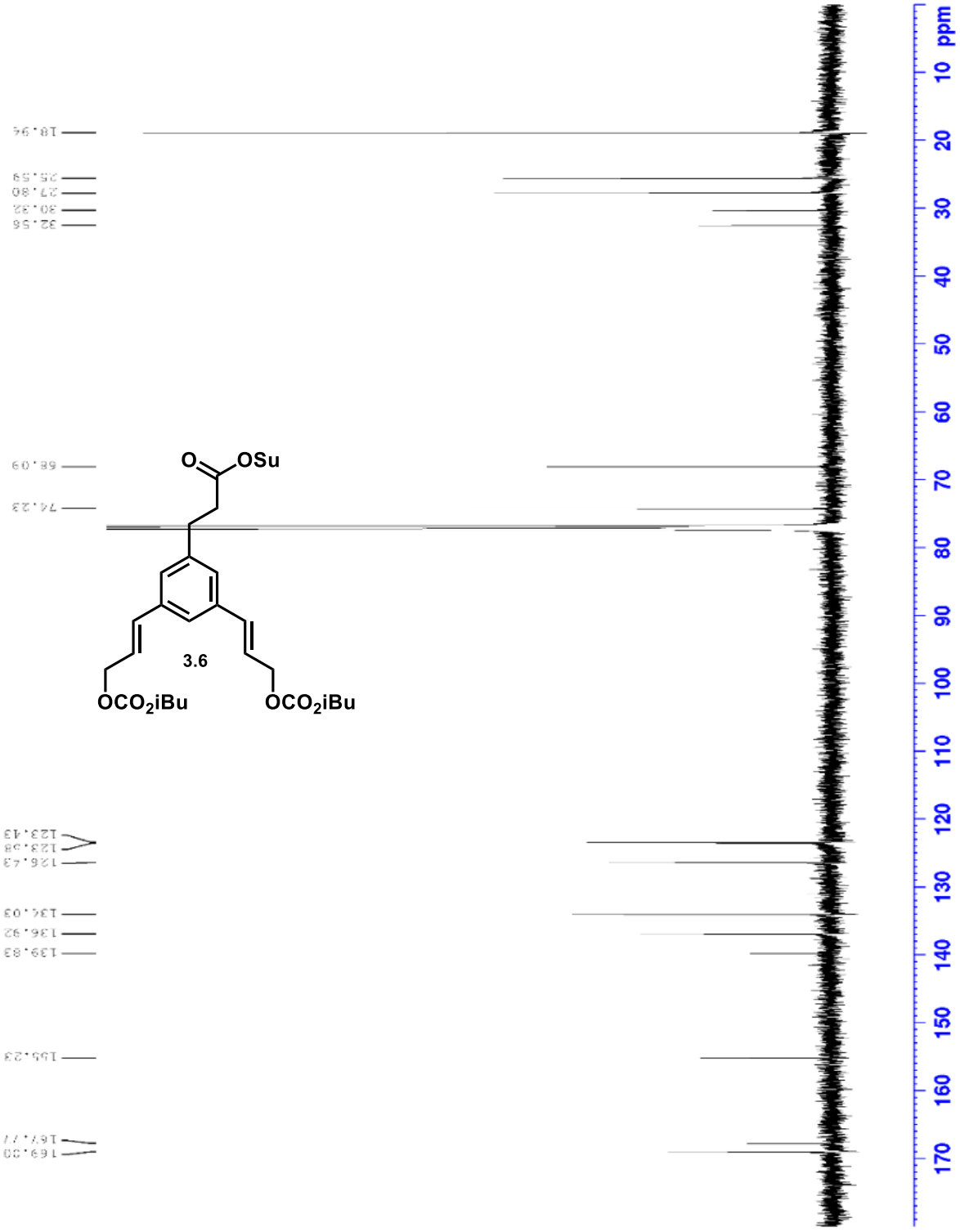
^{13}C NMR of compound 3.5 ($CDCl_3$, 125 MHz)

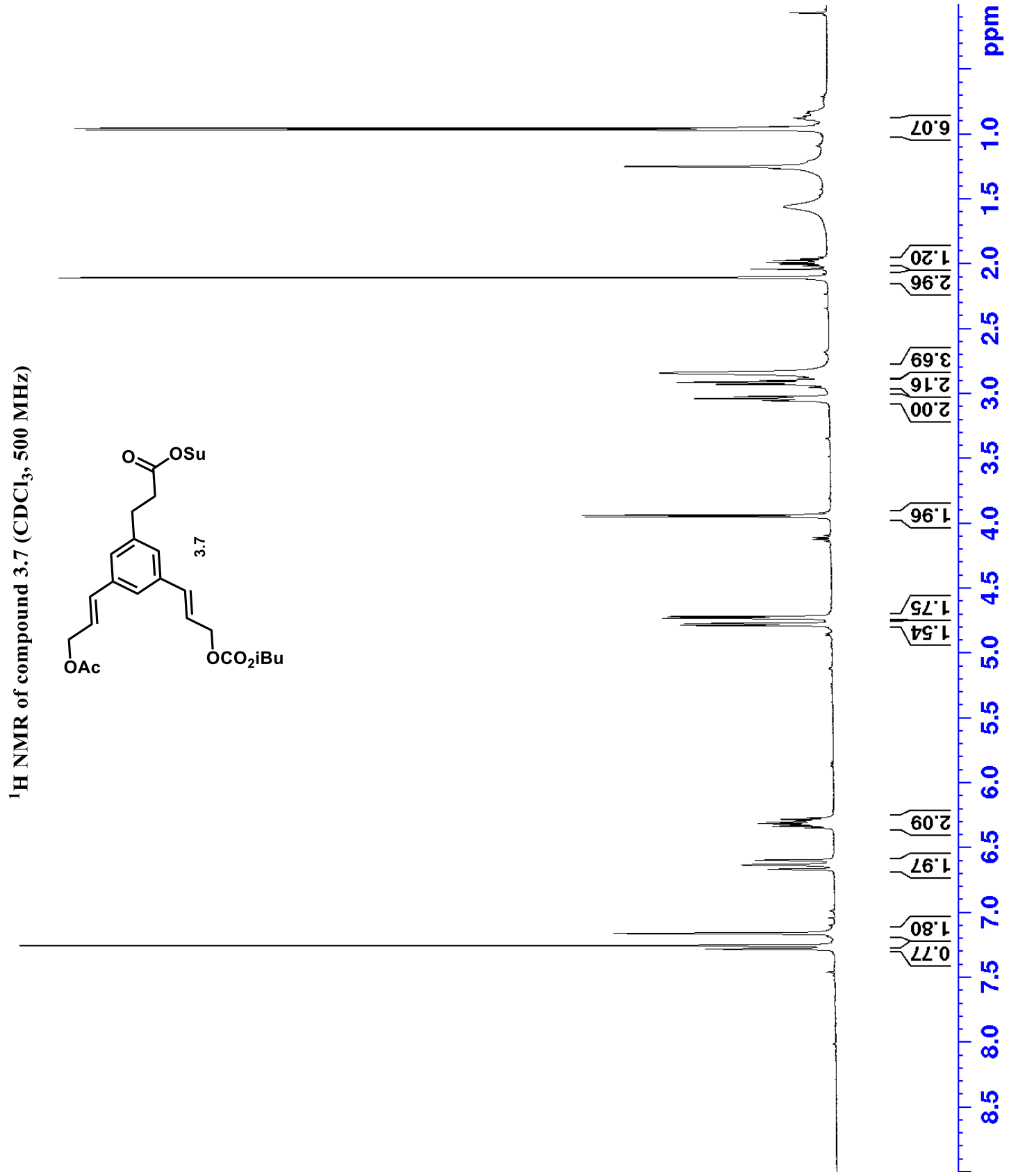


^{1}H NMR of compound 3.6 ($CDCl_3$, 500 MHz)

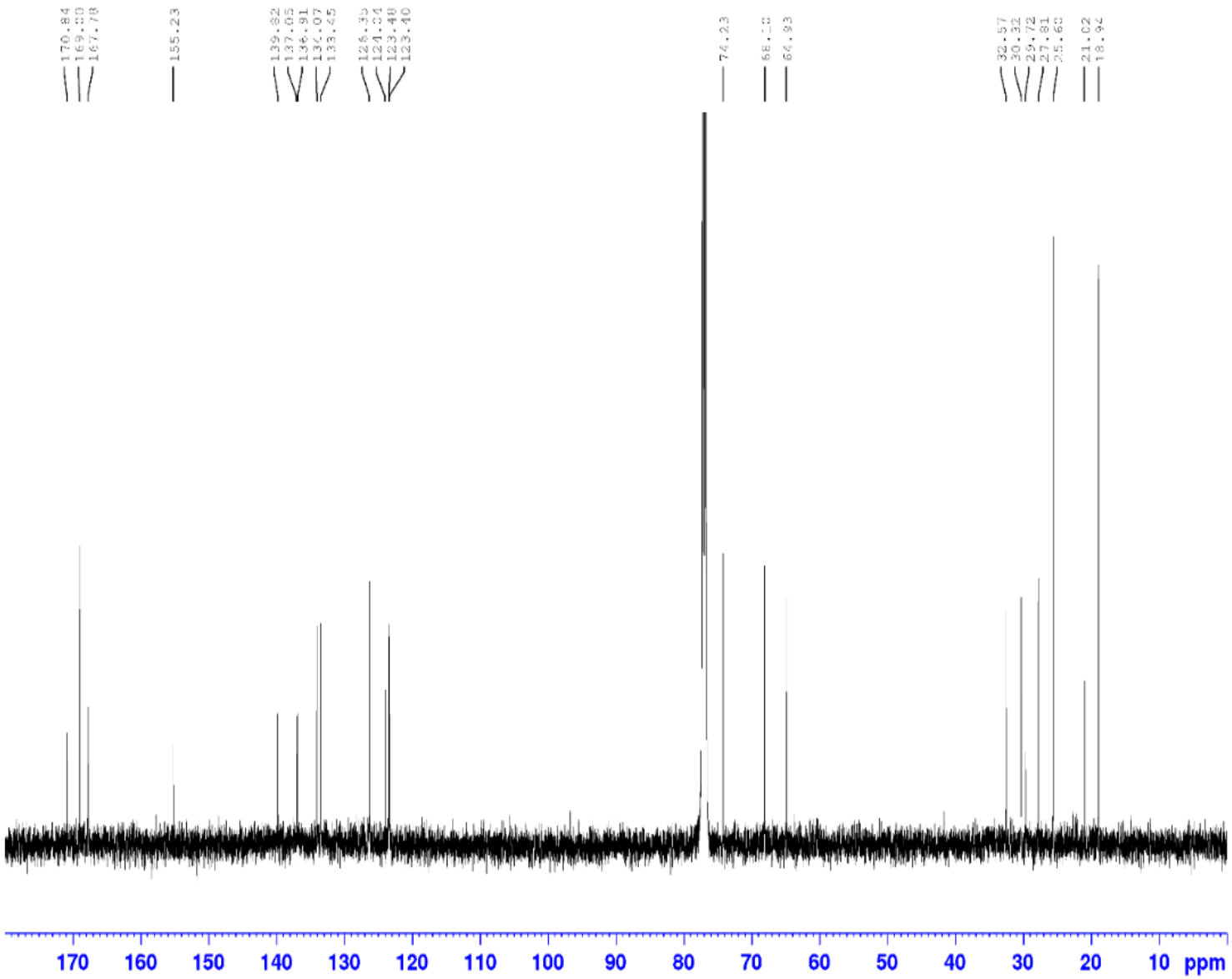


^{13}C NMR of compound 3.6 ($CDCl_3$, 126 MHz)

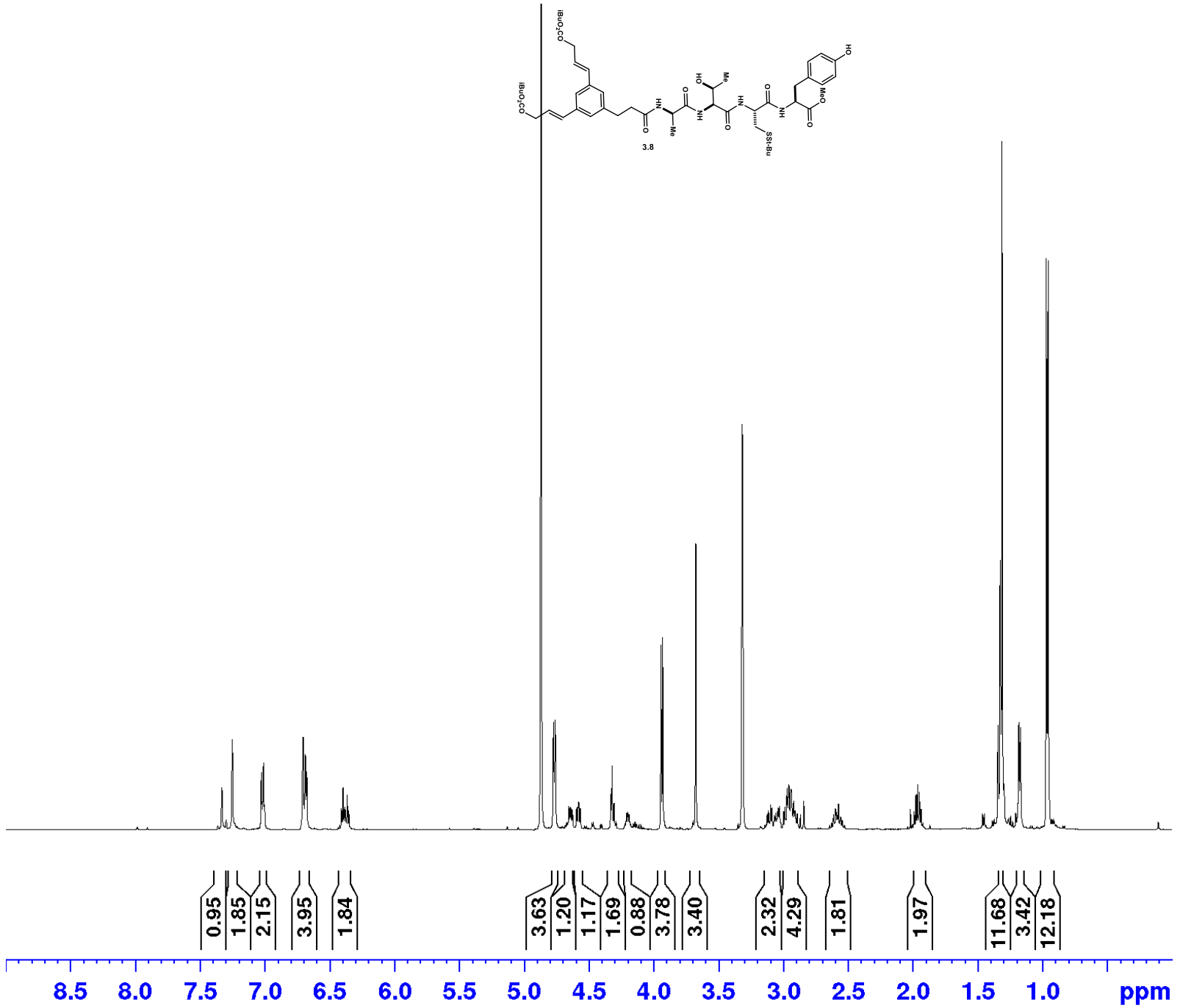


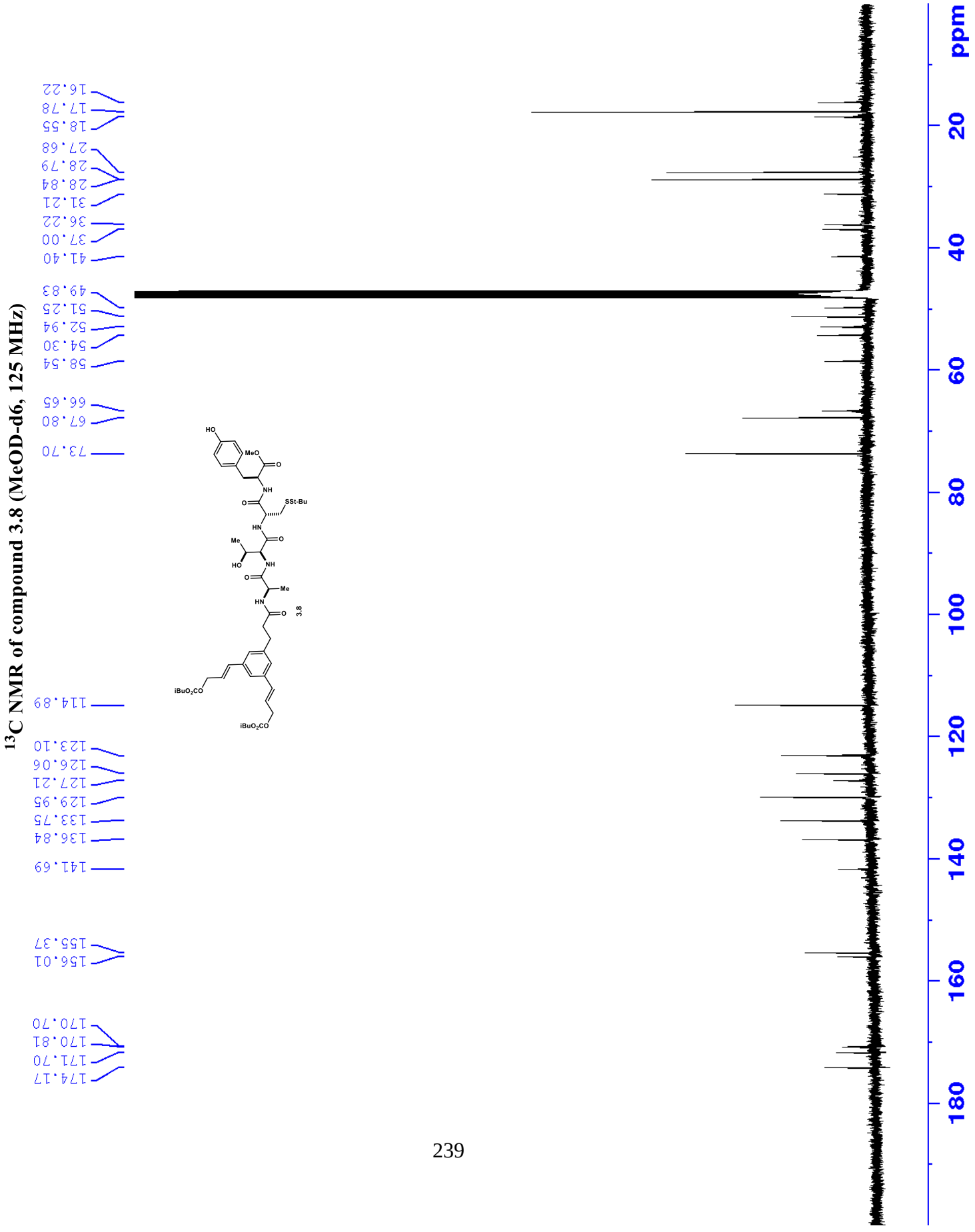

¹H NMR of compound 3.7 (CDCl3, 500 MHz)
O
OSu
3.7
OAc
OCO2iBu
6.07
1.20
2.96
3.69
2.16
2.00
1.96
1.75
1.54
2.09
1.97
1.80
0.77
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

^{13}C NMR of compound 3.7 ($CDCl_3$, 126 MHz)

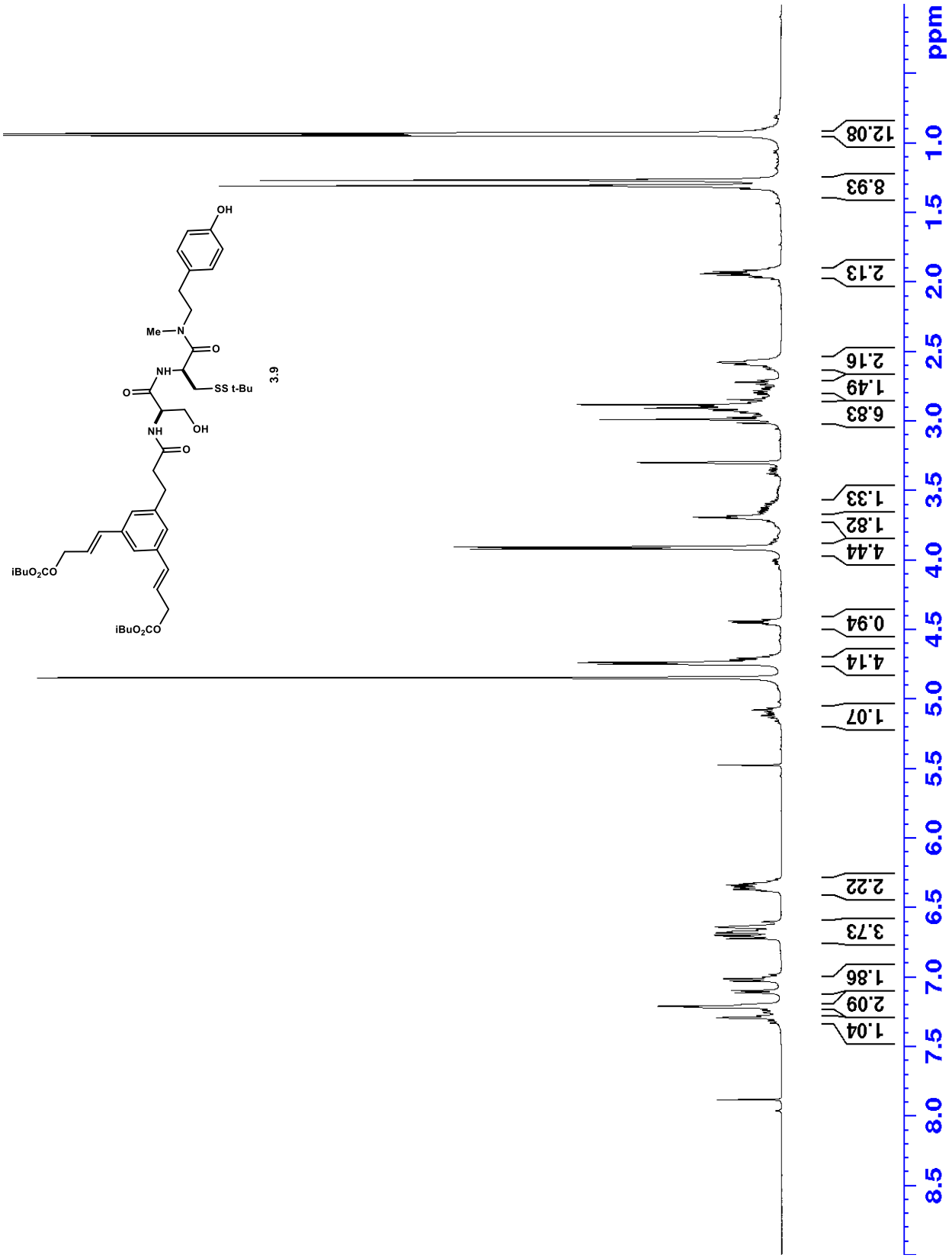


^{1}H NMR of compound 3.8 (MeOD-d6, 500 MHz)

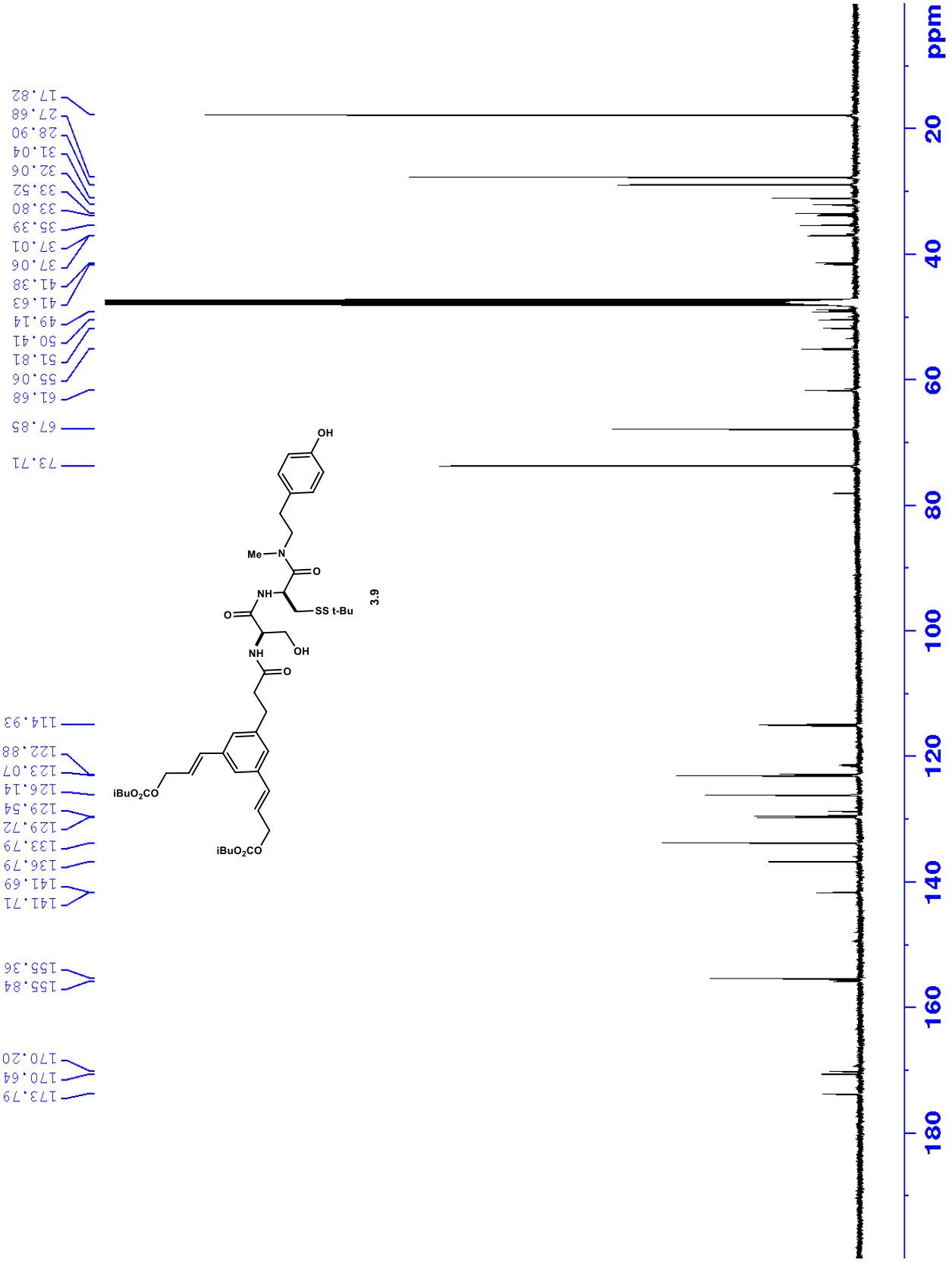



^{13}C NMR of compound 3.8 (MeOD-d6, 125 MHz)
16.22
17.78
18.55
27.68
28.79
28.84
31.21
36.22
37.00
41.40
49.83
51.25
52.94
54.30
58.54
66.65
67.80
73.70
114.89
123.10
126.06
127.21
129.95
133.75
136.84
141.69
155.37
156.01
170.70
170.81
171.70
174.17
ppm
20
40
60
80
100
120
140
160
180
HO
MeO
O
NH
O
SSt-Bu
HN
O
Me
HO
NH
O
Me
HN
O
3.8
iBuO2CO
iBuO2CO

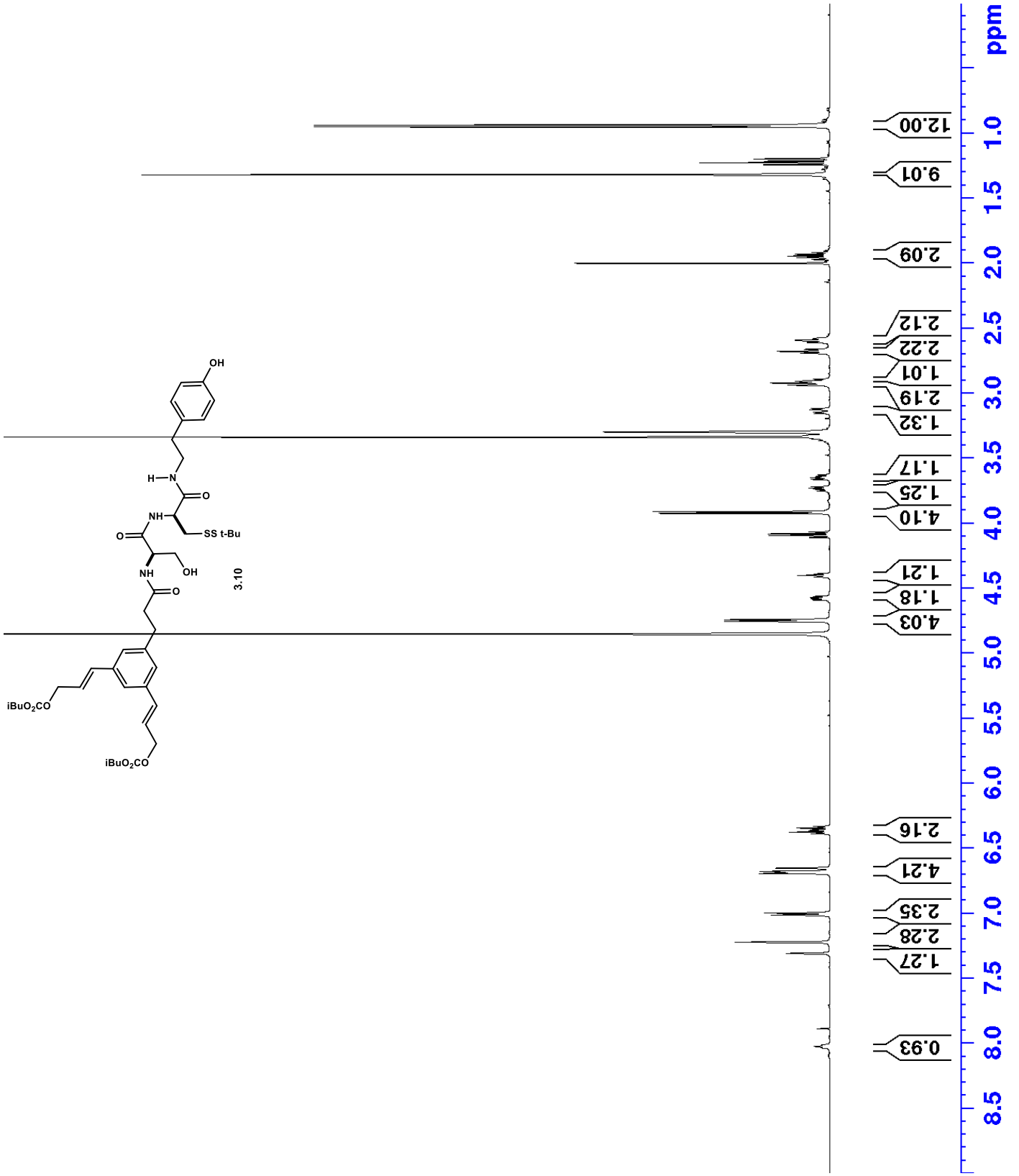
^{1}H NMR of compound 3.9 (MeOD-d6, 500 MHz)

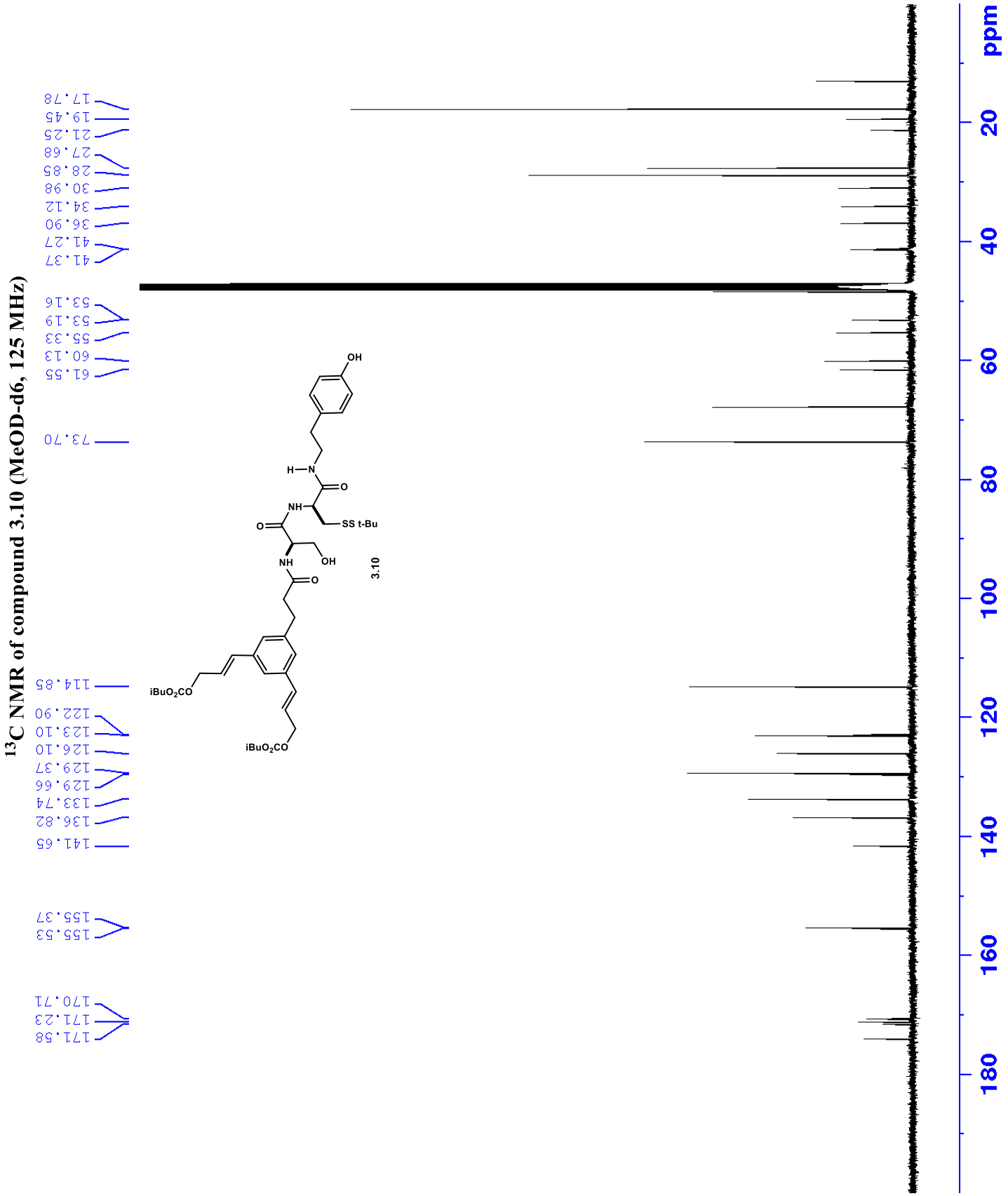


^{13}C NMR of compound 3.9 (MeOD-d6, 125 MHz)

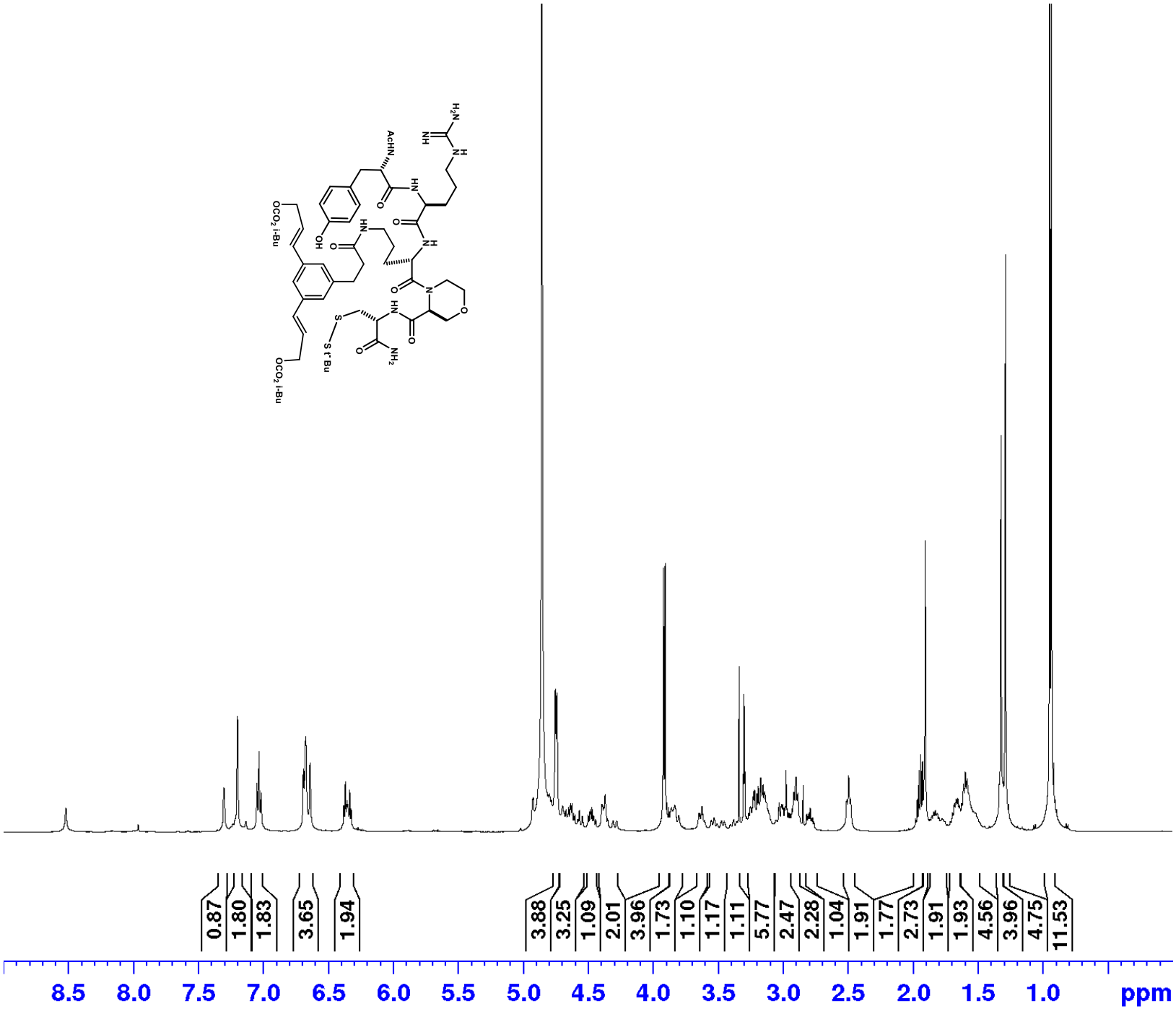


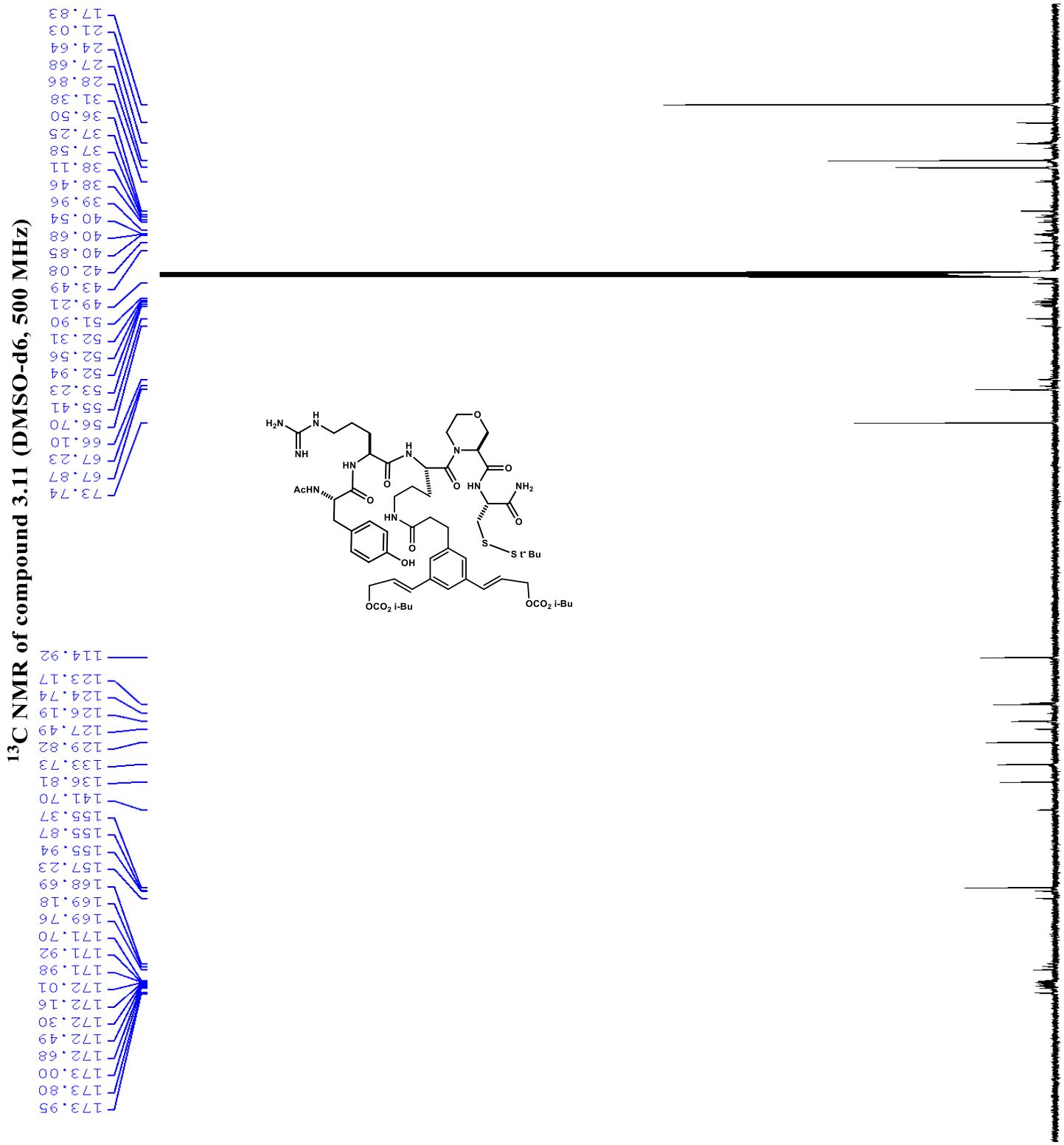
^{1}H NMR of compound 3.10 (MeOD-d6, 500 MHz)



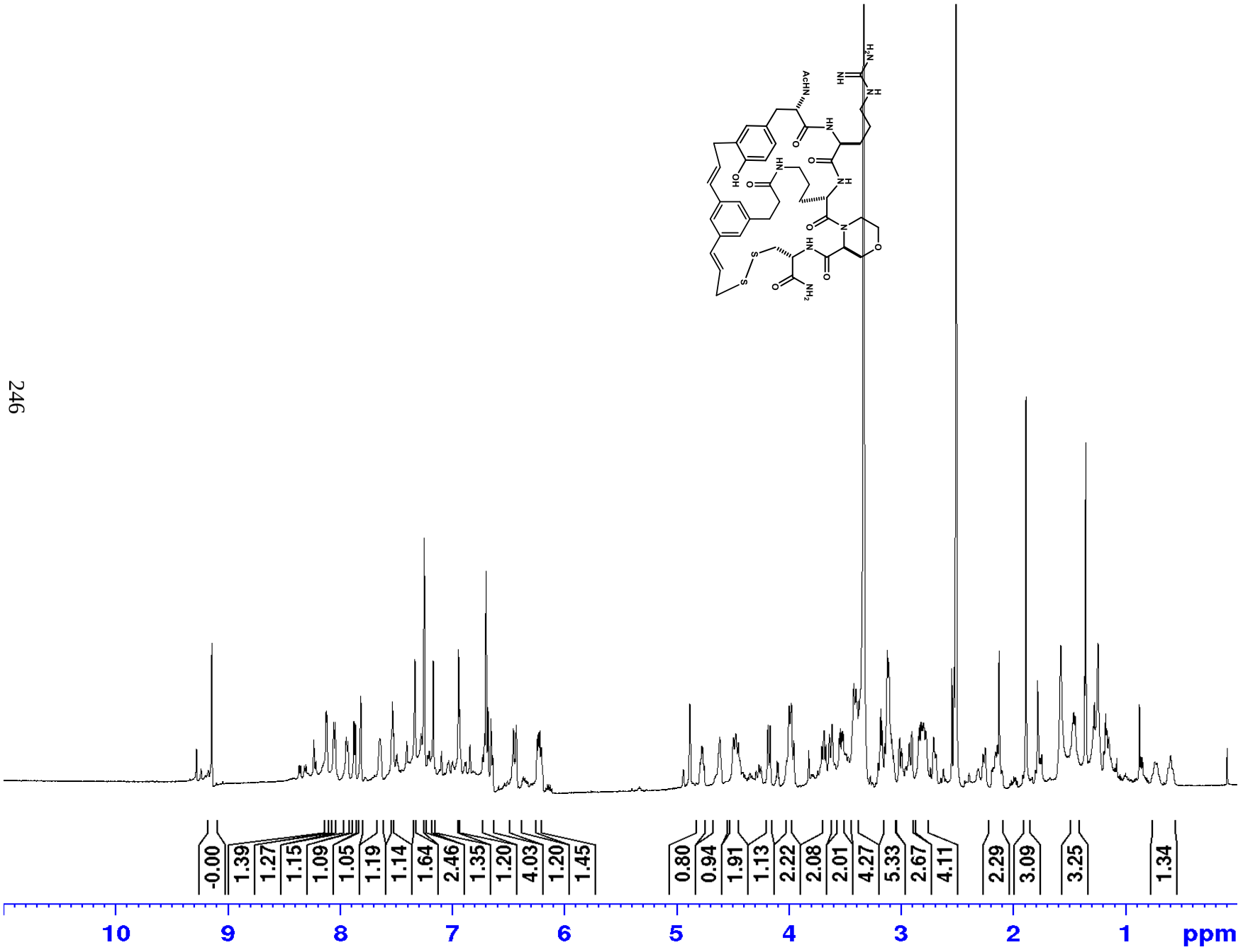

13C NMR of compound 3.10 (MeOD-d6, 125 MHz)
17.78
19.45
21.25
27.68
28.85
30.98
34.12
36.90
41.27
41.37
53.16
53.19
55.33
60.13
61.55
73.70
114.85
122.90
123.10
126.10
129.37
129.66
133.74
136.82
141.65
155.37
155.53
170.71
171.23
171.58
OH
H—N
O
NH
O
SS t-Bu
NH
OH
O
iBuO2CO
iBuO2CO
3.10
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 3.11 (DMSO-d6, 500 MHz)

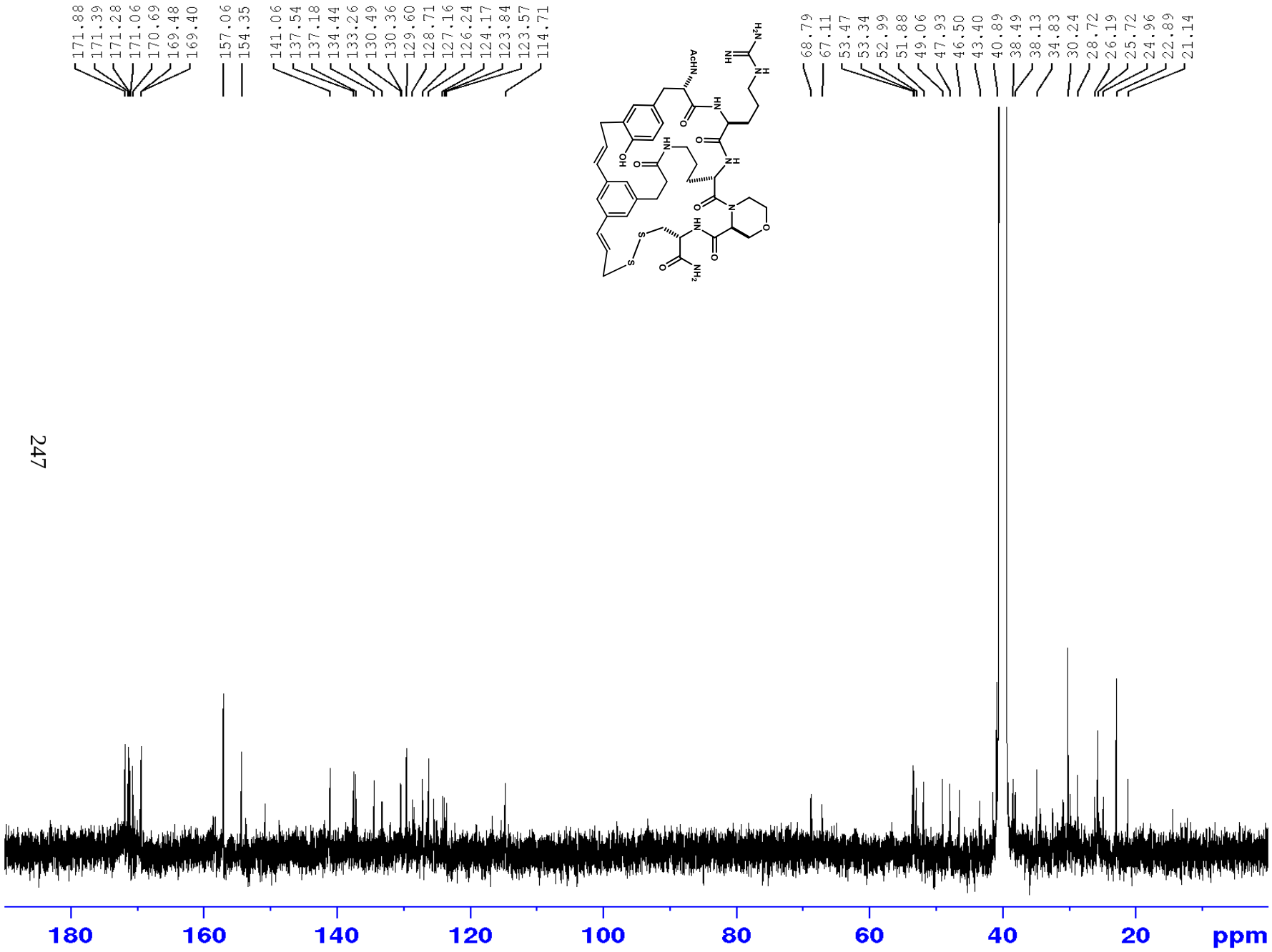



^{13}C NMR of compound 3.11 (DMSO-d6, 500 MHz)
17.83
21.03
24.64
27.68
28.86
31.38
36.50
37.25
37.58
38.11
38.46
39.96
40.54
40.68
40.85
42.08
43.49
49.21
51.90
52.31
52.56
52.94
53.23
55.41
56.70
66.10
67.23
67.87
73.74
114.92
123.17
124.74
126.19
127.49
129.82
133.73
136.81
141.70
155.37
155.87
155.94
157.23
168.69
169.18
169.76
171.70
171.92
171.98
172.01
172.16
172.30
172.49
172.68
173.00
173.80
173.95

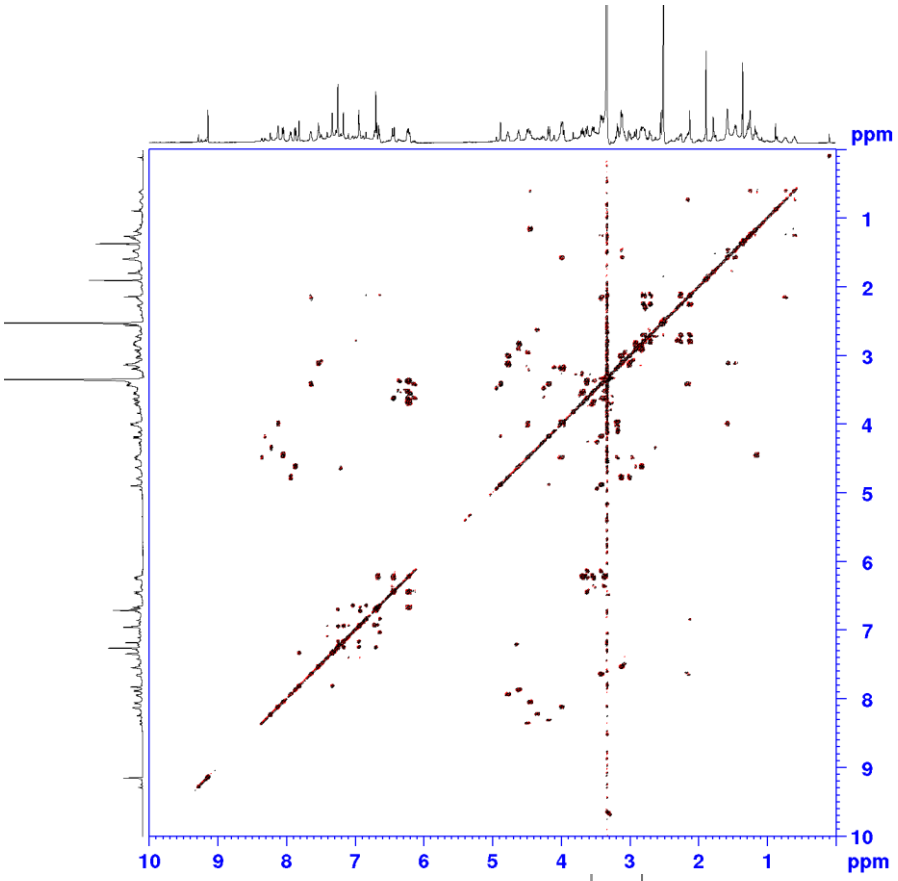
^{1}H NMR of macrcocycle 3.12 (DMSO-d6, 600 MHz)



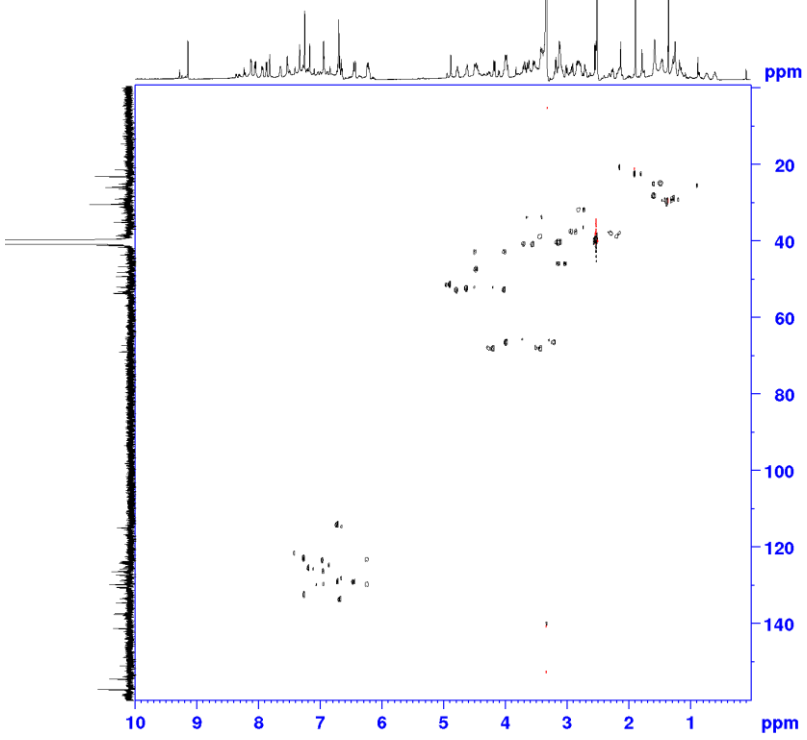
^{13}C NMR of macrcocycle 3.12 (DMSO-d6, 150 MHz)



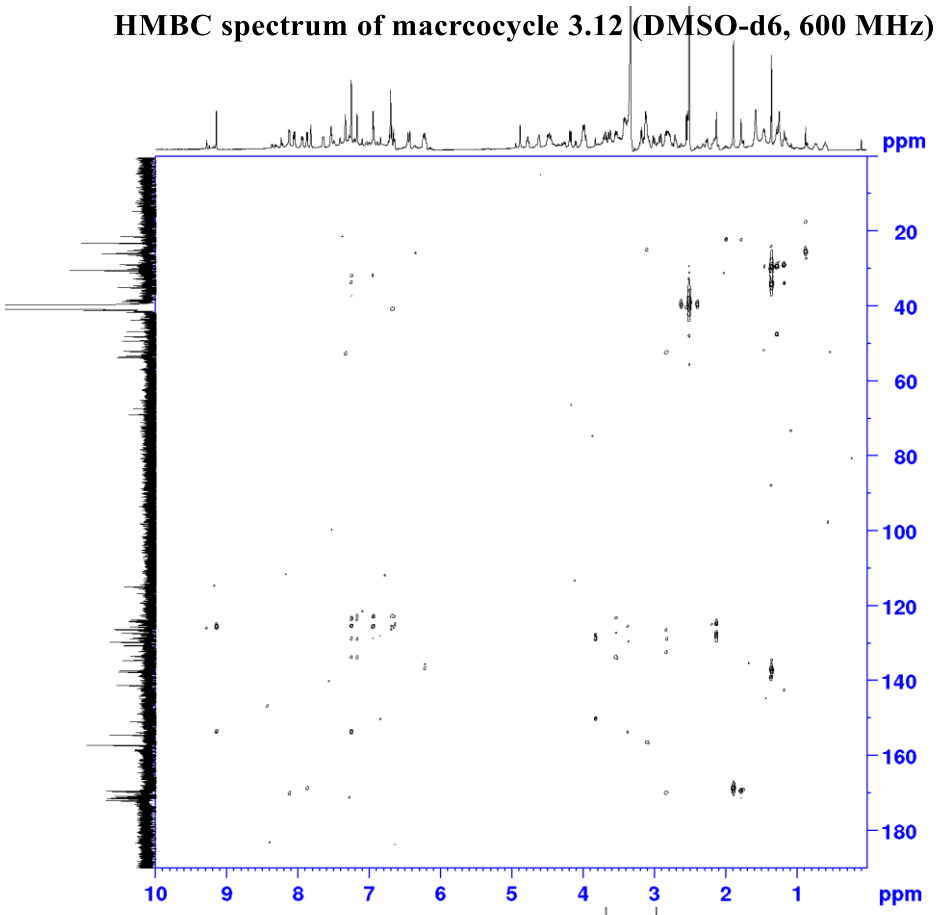
COSY spectrum of macrcocycle 3.12 (DMSO-d6, 600 MHz)



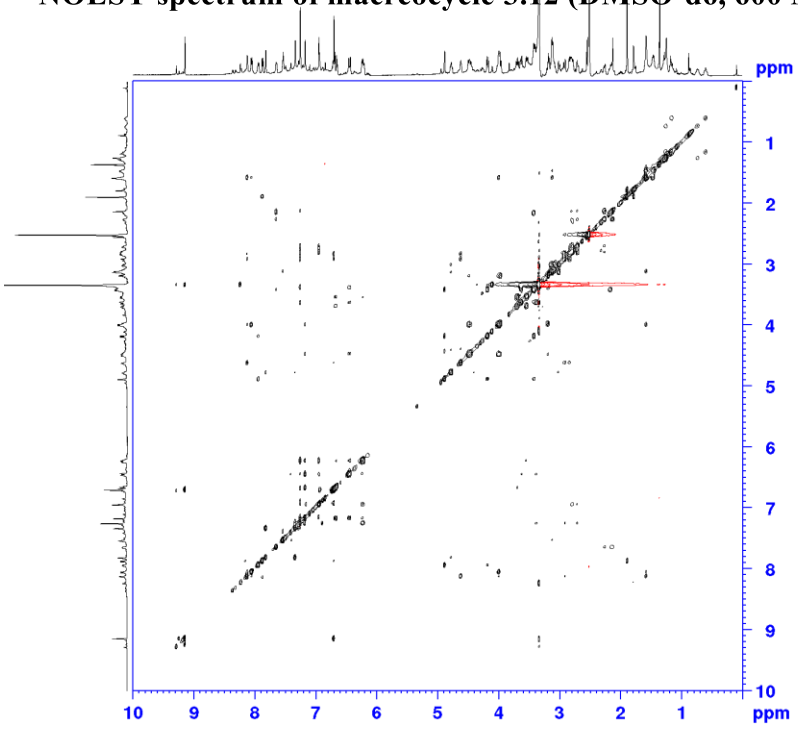
HSQC spectrum of macrcocycle 3.12 (DMSO-d6, 600 MHz)



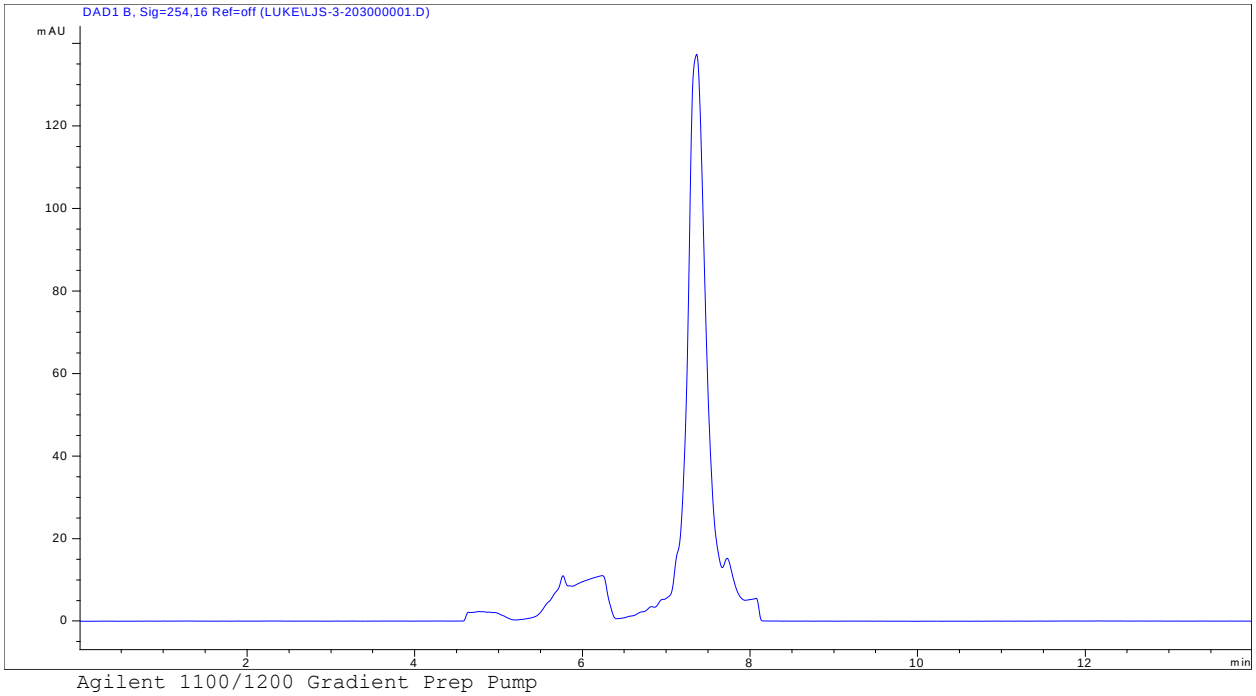
HMBC spectrum of macrcocycle 3.12 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 3.12 (DMSO-d6, 600 MHz)



3.12 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

==========

Control

Column Flow	:	12.000 ml/min
Stoptime	:	14.00 min
Posttime	:	Off

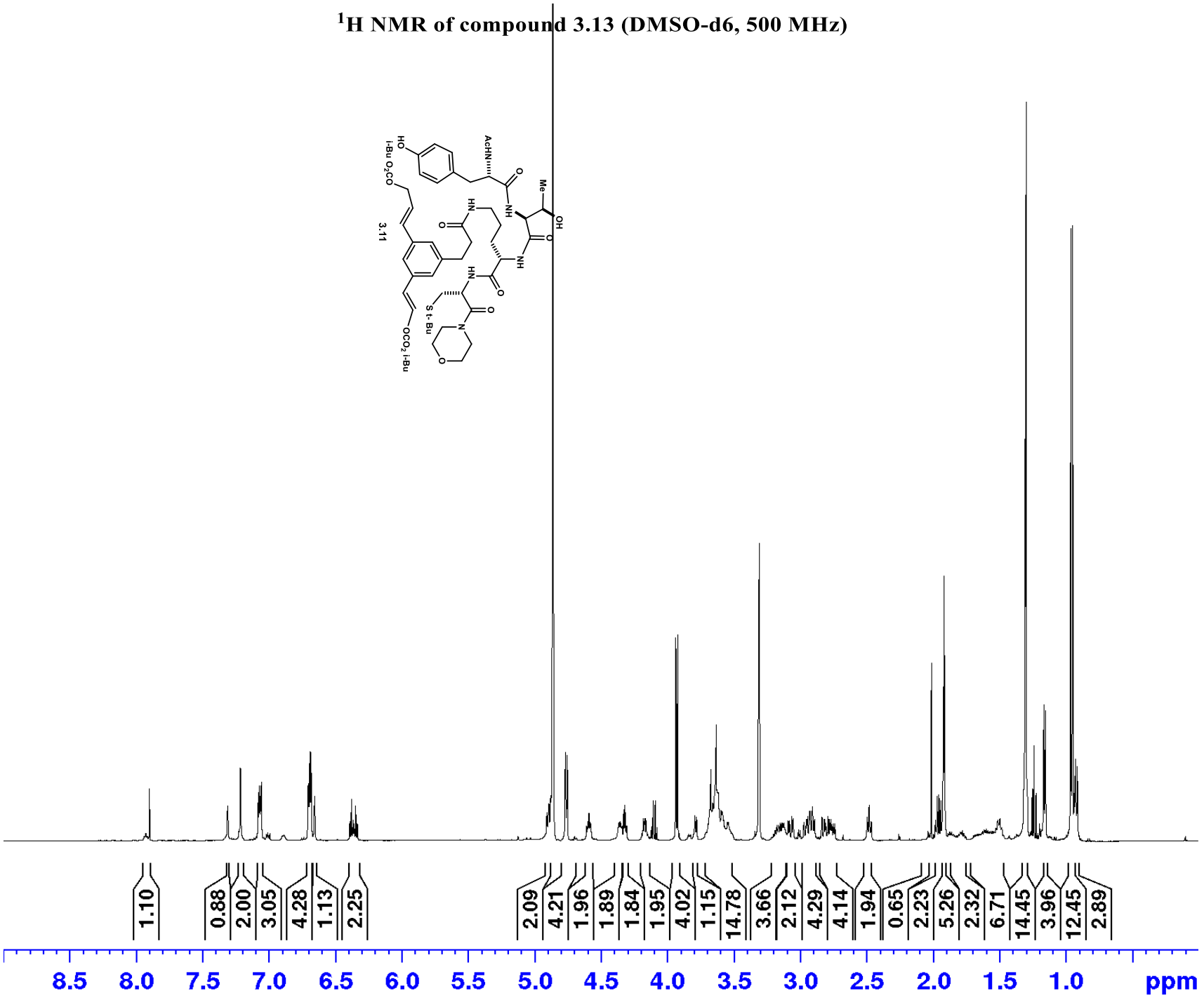
Solvents

Solvent A	:	75.0 % (Water)
Solvent B	:	25.0 % (Organic)

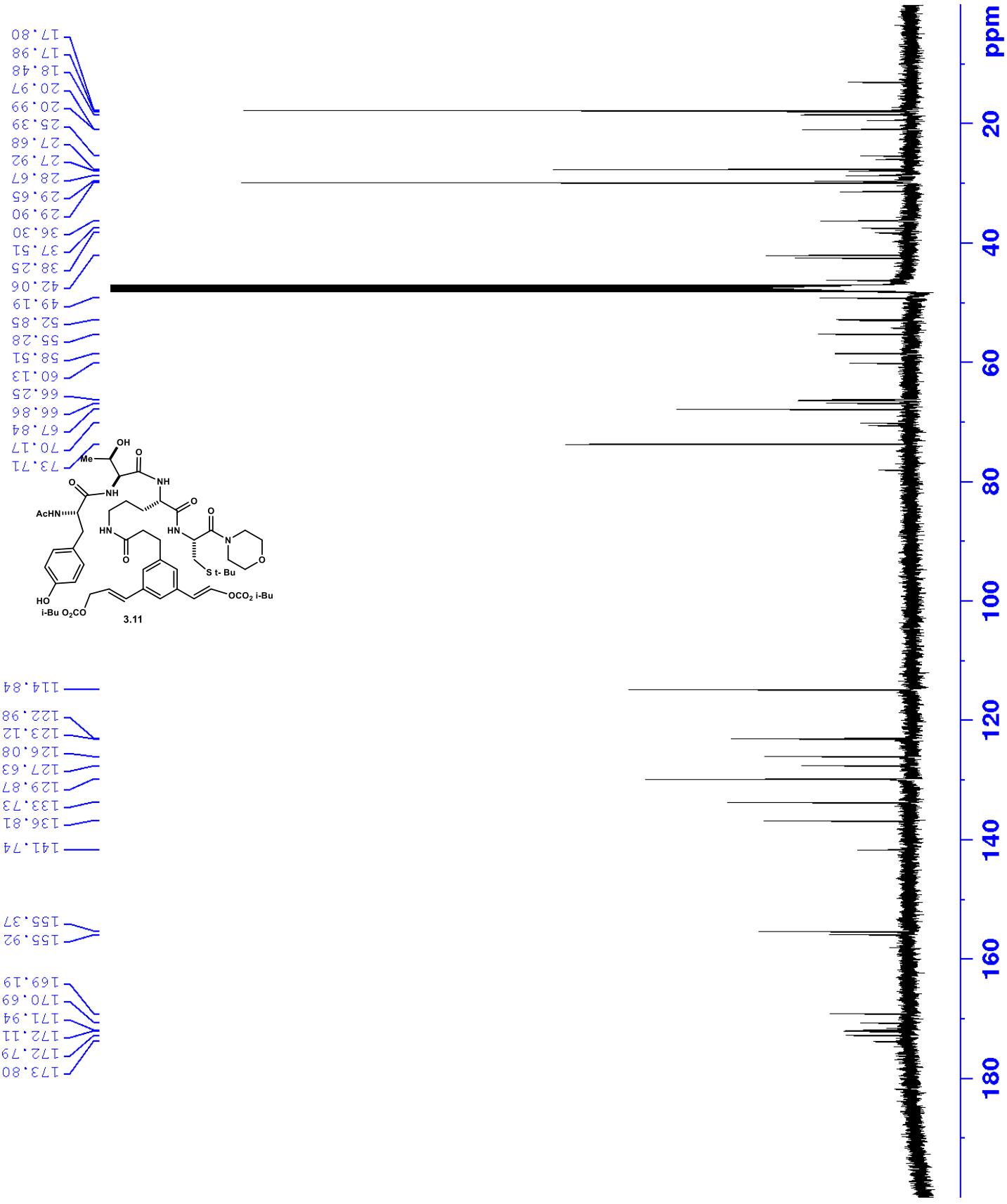
Timetable

Time	Solv.B	Flow	Pressure
0.00	25.0	12.000	400
2.00	25.0	15.000	400
8.00	65.0	15.000	400
13.00	85.0	15.000	400
14.00	25.0	15.000	400

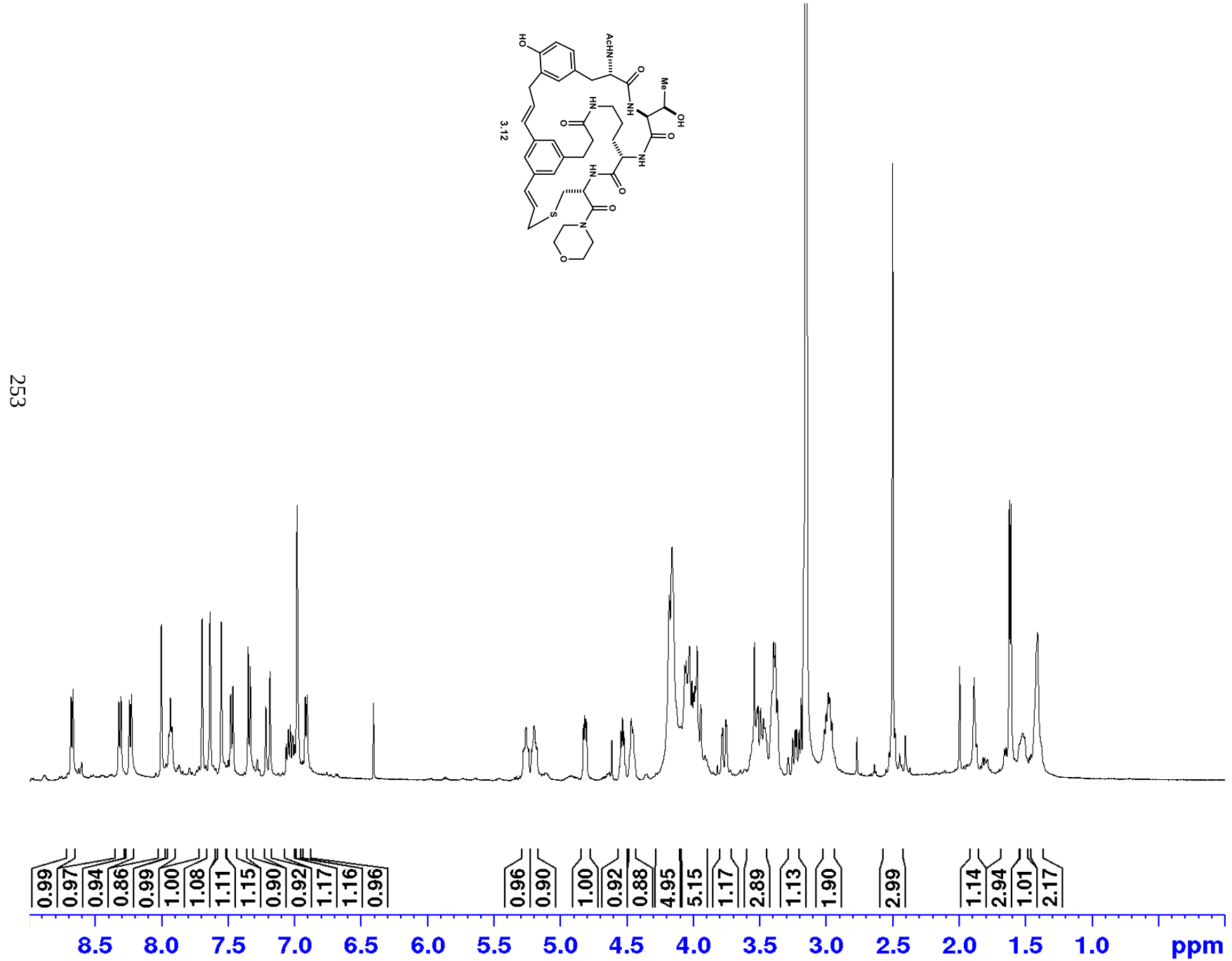
^{1}H NMR of compound 3.13 (DMSO-d6, 500 MHz)



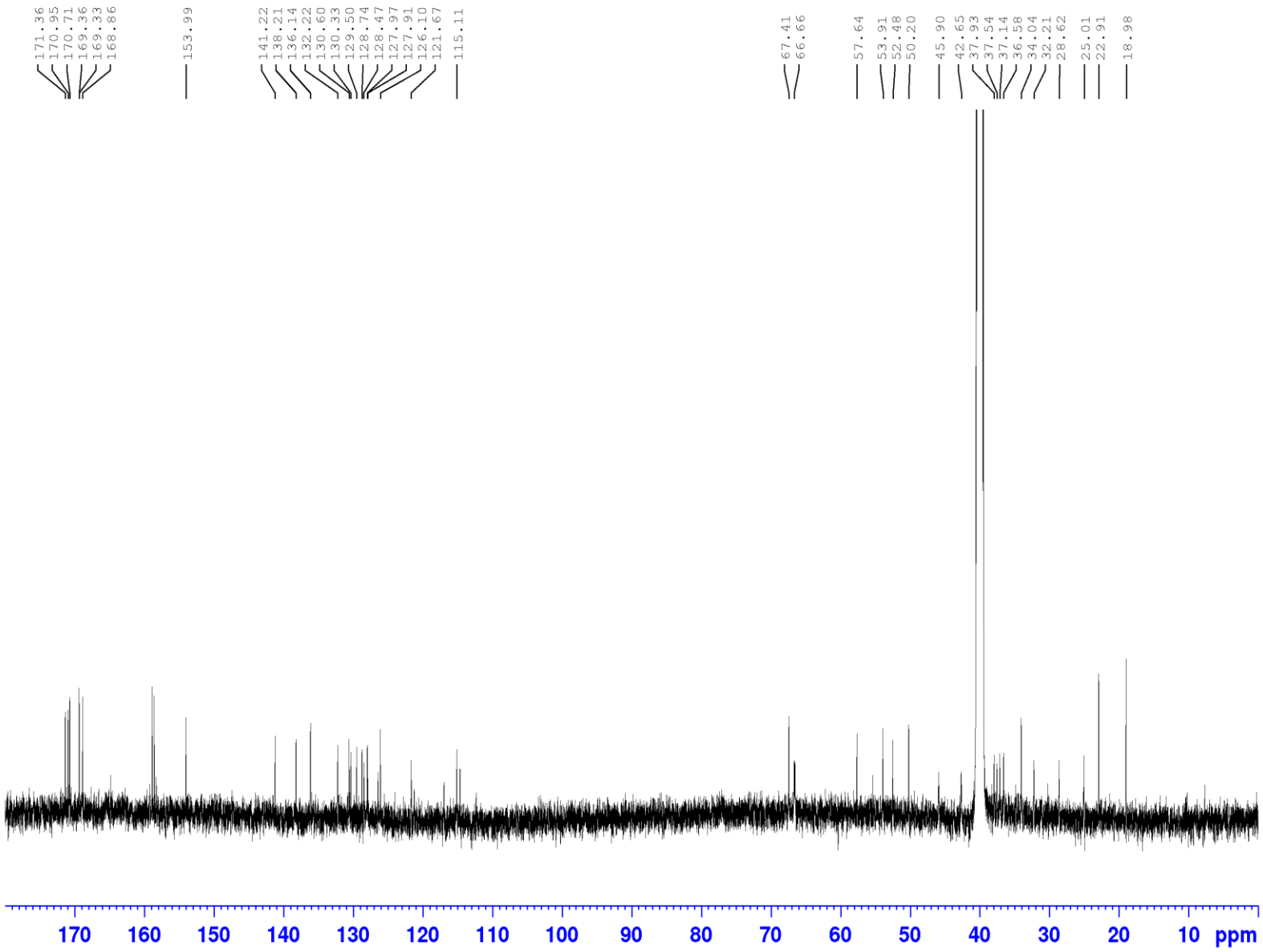
^{13}C NMR of compound 3.13 (DMSO-d6, 125 MHz)

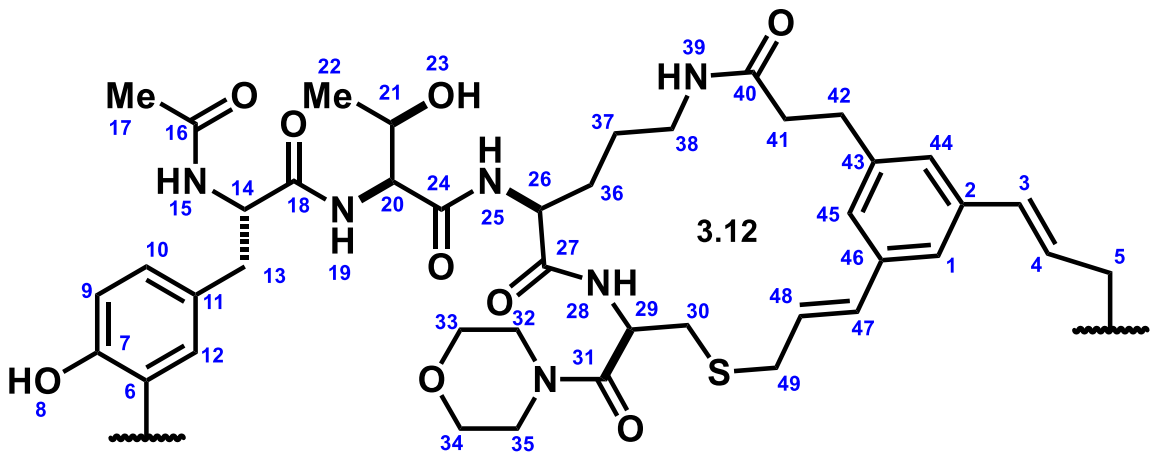


^{1}H NMR of macrcocycle 3.14 (DMSO-d6, 600 MHz)



^{13}C NMR of macrcocycle 3.14 (DMSO-d6, 126 MHz)

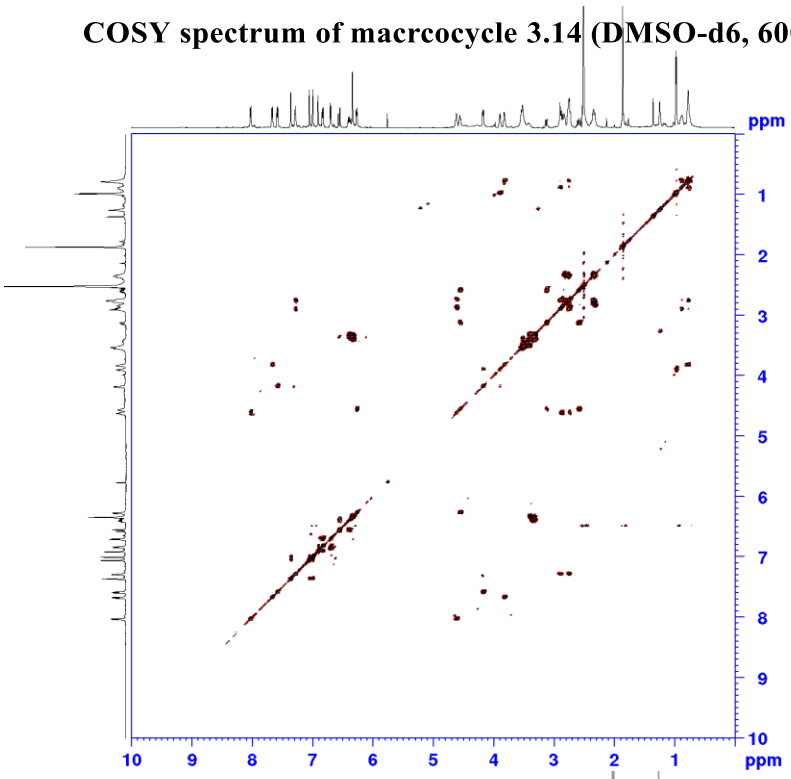




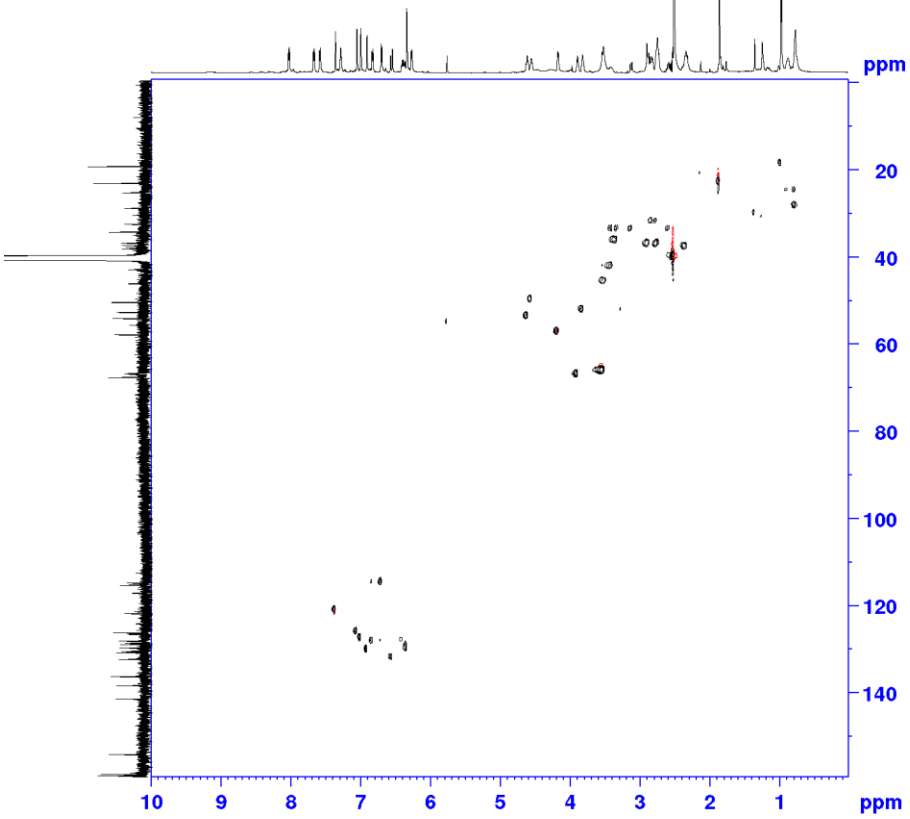
	13C	*1H*	*Corr.*
1	121.7	7.36 (s, 1H)	key
2	138.2	X	HMBC 1->2
3	130.3	6.33 (m, 1H) overlap	HMBC 1->3
4	129.4	6.34 (m, 1H) overlap	COSY 3->4
5	34.0	3.37-3.30 (m, 2H)	HMBC 3->5 COSY 3-> 5
6	128.5		HMBC 9->6
7	154.0		key
8			
9	114.6	6.69 (d, J = 8.0, 1H)	key
10	128.7	6.82 (d, J = 8.0, 1H)	COSY 9->10 HMBC 9->10
11	130.6		HMBC 9->11
12	126.1	6.90 (s, 1H)	HMBC 10->12
13	37.1	2.88-2.75 (m, 2H)	HMBC 10->13 COSY 14->13
14	53.9	4.61 (m, 1H)	COSY 15->14
15		8.03 (d, J = 7.5 Hz, 1H)	HMBC 17->15
16	169.4		HMBC 17->16
17	22.9	1.87 (s, 1H)	key
18	170.7		
19		7.67 (d, J = 8.2 Hz, 1H)	COSY 20->19
20	57.6	4.17 (dd, J = 7.8, 4.3 Hz)	COSY 21->20
21	67.4	3.89 (m, 1H)	COSY 22->21
22	19.0-cor	0.97 (d, J = 6.1 Hz, 3H)	key

23	x	x	
24	171.0	x	HMBC 21->24 HMBC 20->24
25	x	7.66 (d, J = 8.8 Hz, 1H)	COSY 26->25
26	52.5	3.80 (m, 1H)	key
27	169.3		
28		6.26 (d, J = 7.5, 1H)	COSY 29->28
29	50.2	4.55 (m, 1H)	
30	36.6	3.12 (d, J = 13.5, 3.0 Hz) 1H 2.58 (d, J = 13.5, 5.1 Hz)	COSY 29->30 HMBC 49->30
31	168.9		
32	45.9	3.50 (m, 2H) overlap	NOSY 33->32 COSY 33->32
33	67.4	3.48-3.57 (m, 2H) overlap	
34	66.6	3.48-3.57 (m, 2H) overlap	
35	42.7	3.40 (m, 2H) overlap	NOSY 34->35 COSY 34->35
36	28.6	0.76 (m, 2H) overlap	HMBC 26->36 COSY 26->36
37	25.0	0.88-0.77 (m, 2H) overlap	HMBC 26->37 COSY 26->37
38	37.1	2.76-2.90 (m, 2H)	COSY 37&36->38 NOSY 37&36->38
39		7.28 (t, J = 6.0, 1H)	COSY 38->39
40	171.4		HMBC 41->40
41	37.9	2.35 (m, 2H)	HMBC 42->41 COSY 42->41
42	32.2	2.81-2.75 (m, 2H)	HMBC 44&45->42
43	141.2		HMBC 41->43
44	127.9	7.00 (s, 1H)	HMBC 1->44
45	126.1	7.05 (s, 1H)	HMBC 1->43
46	136.1		HMBC 1->46
47	132.2	6.55 (d, J = 15.8 Hz, 1H)	HMBC 1->47
48	128.0	6.39 (m, 1H) overlap	COSY 47->48
49	37.5	3.32-3.35 (m, 2H) overlap	HMBC 47->49 COSY 47->49 HMBC 30->49

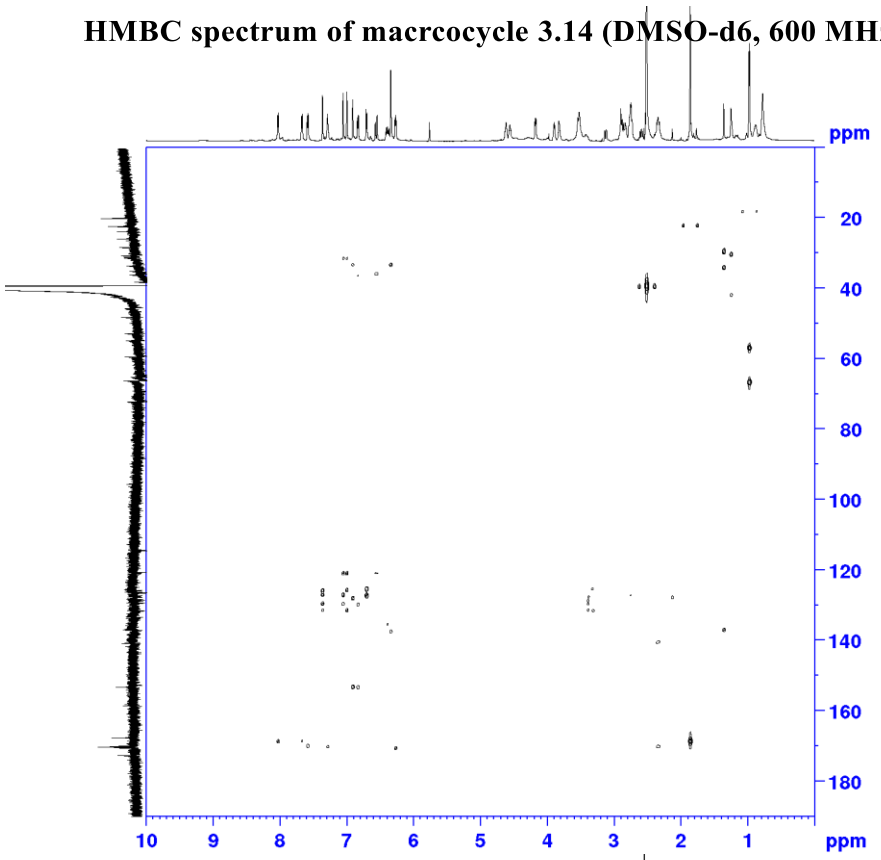
COSY spectrum of macrcocycle 3.14 (DMSO-d6, 600 MHz)



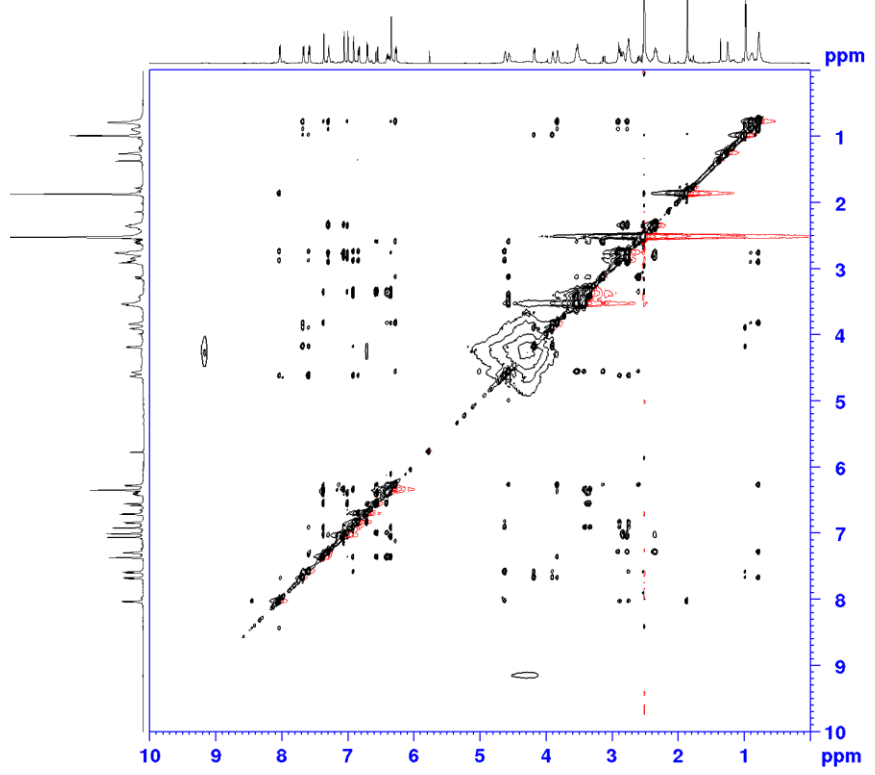
HSQC spectrum of macrcocycle 3.14 (DMSO-d6, 600 MHz)



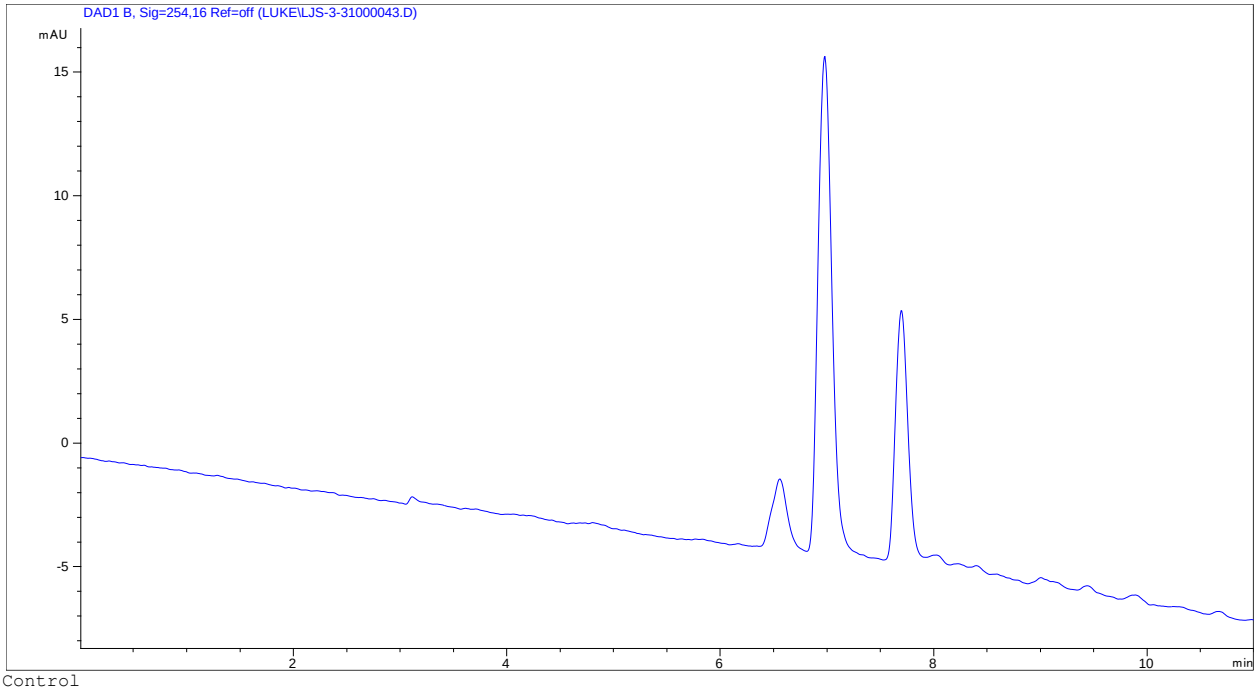
HMBC spectrum of macrcocycle 3.14 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 3.14 (DMSO-d6, 600 MHz)



3.14 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control
Column Flow : 15.000 ml/min
Stoptime : 14.00 min
Posttime : Off

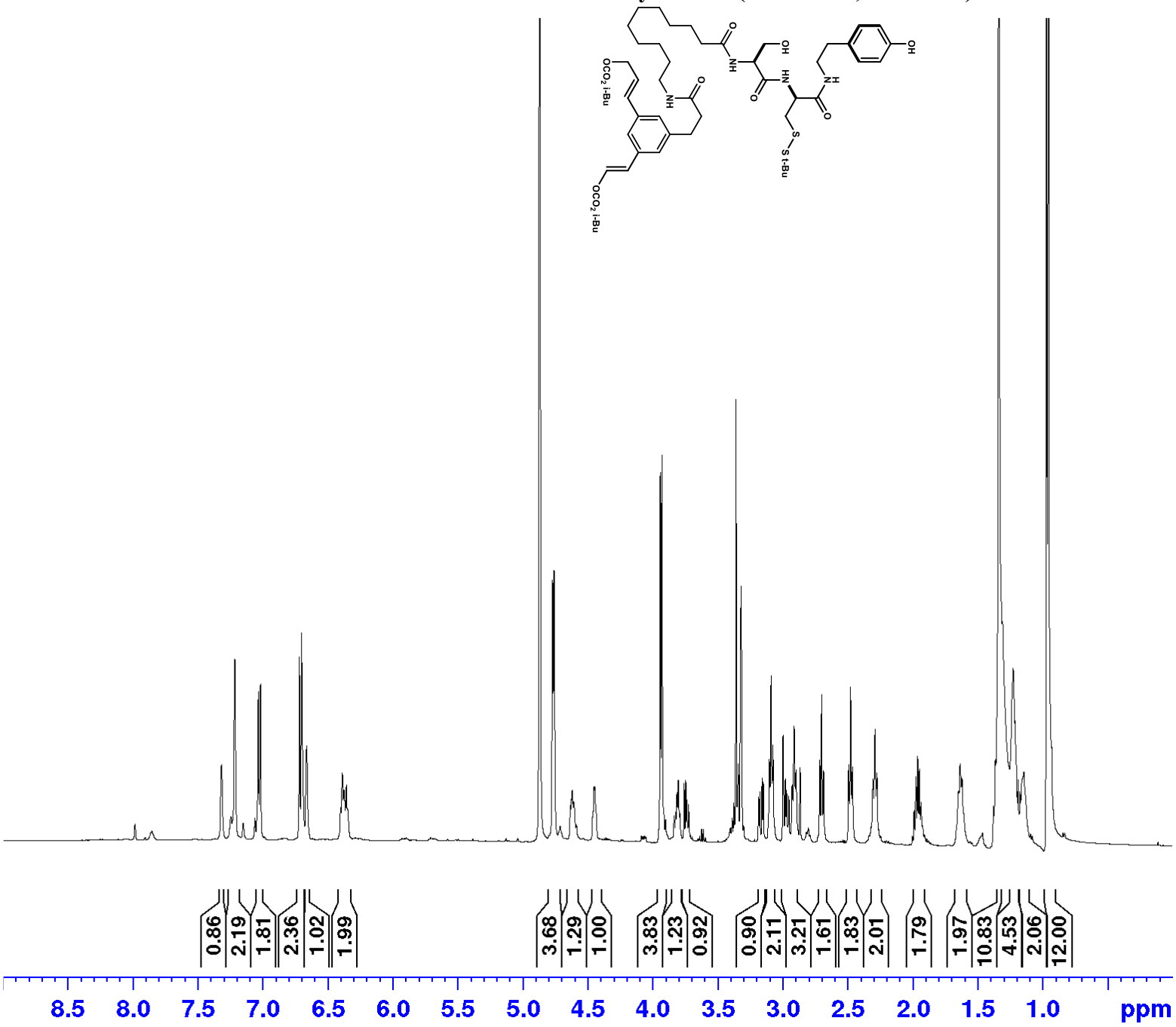
Solvents
Solvent A : 70.0 % (Water)
Solvent B : 30.0 % (Organic)

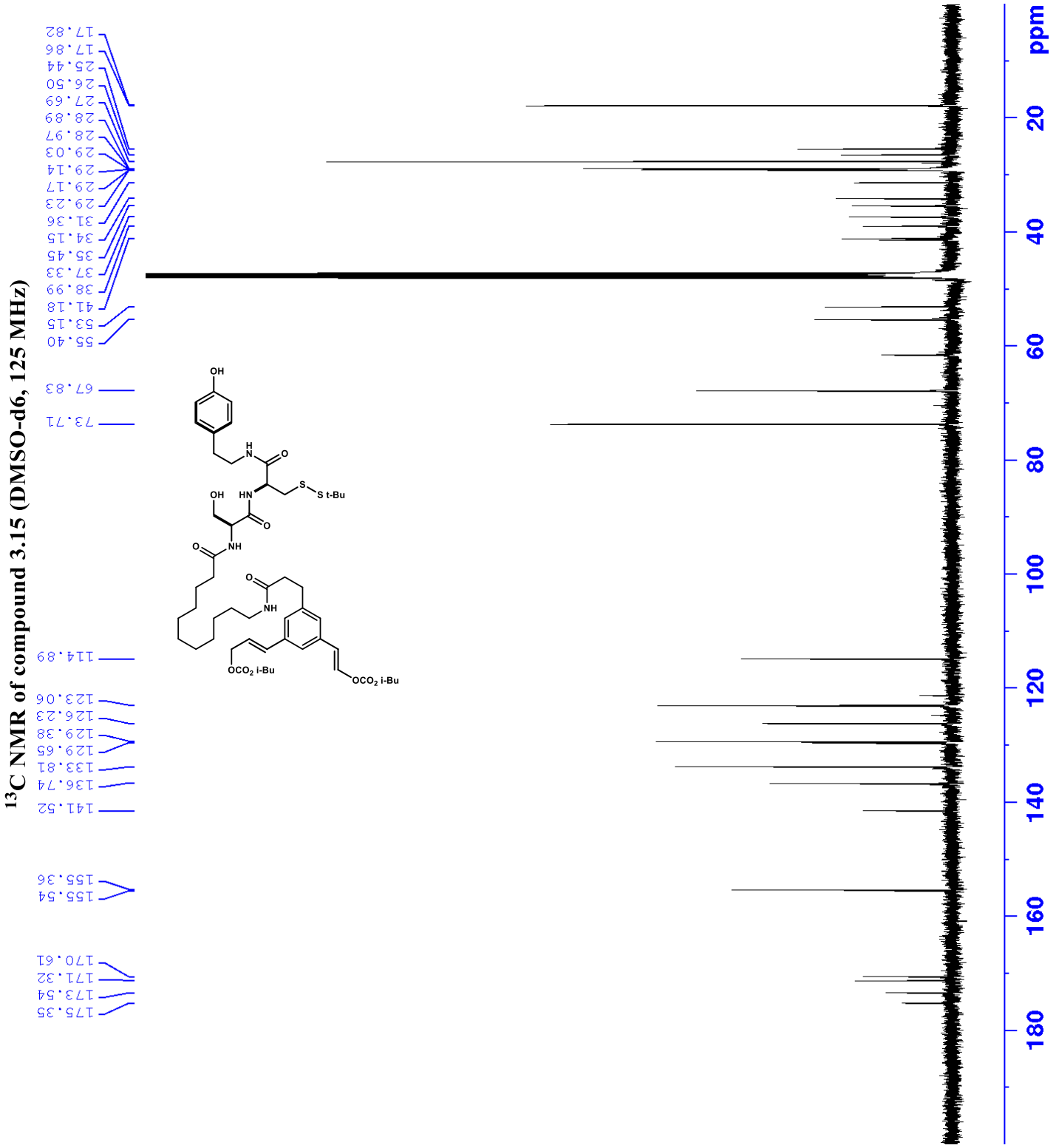
Auxiliary
Flow Ramp : 800.000 ml/min^2
Compressibility : 75*10^-6/bar

Timetable

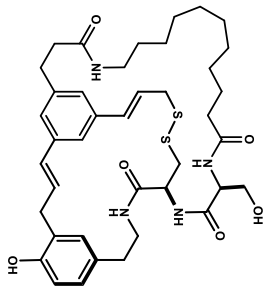
Time	Solv.B	Flow	Pressure
0.00	30.0	10.000	
2.00	30.0	18.000	
12.00	75.0	18.000	
13.00	100.0	18.000	
14.00	35.0	18.000	

^{1}H NMR of macrcocycle 3.15 (DMSO-d6, 500 MHz)

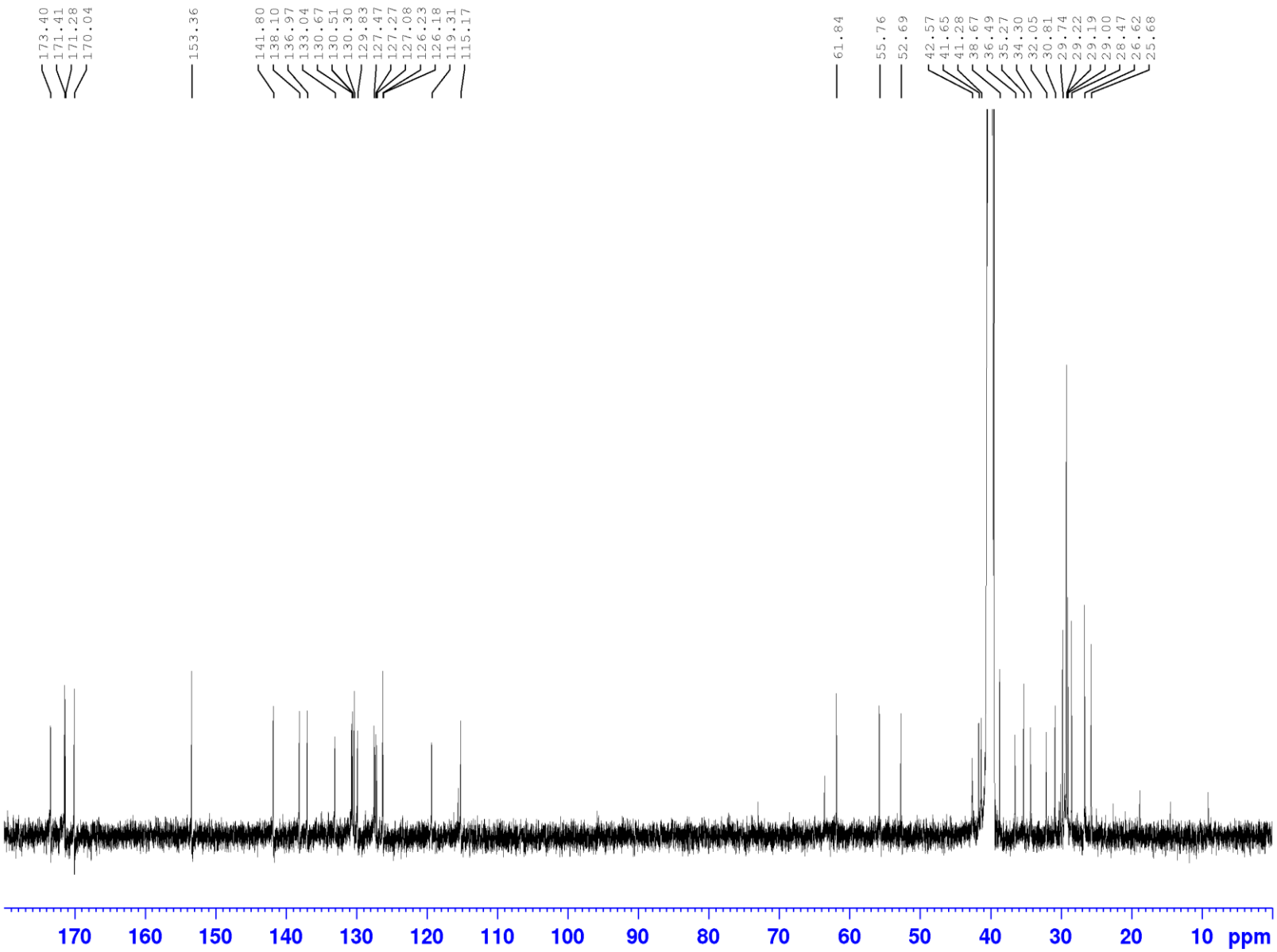


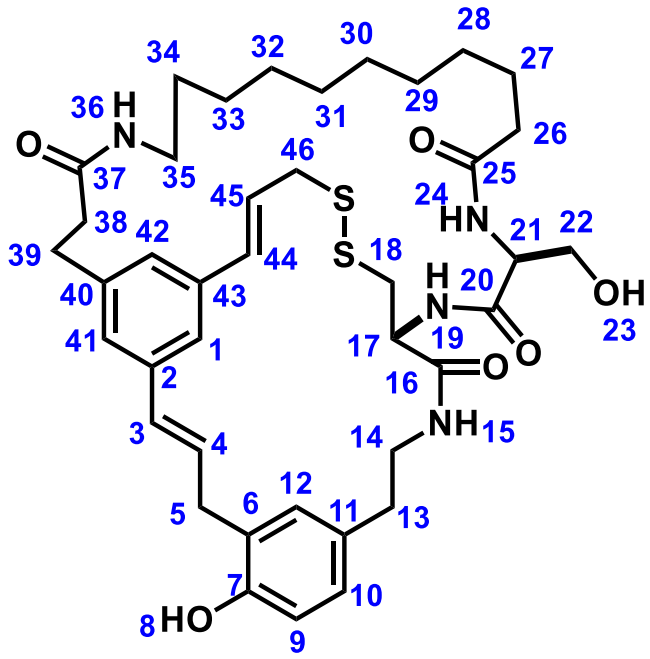

^{13}C NMR of compound 3.15 (DMSO-d6, 125 MHz)
17.82
17.86
25.44
26.50
27.69
28.89
28.97
29.03
29.14
29.17
29.23
31.36
34.15
35.45
37.33
38.99
41.18
53.15
55.40
67.83
73.71
114.89
123.06
126.23
129.38
129.65
133.81
136.74
141.52
155.36
155.54
170.61
171.32
173.54
175.35
OH
HN
S
S t-Bu
NH
OCO2 i-Bu
OCO2 i-Bu
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of macrcocycle 3.16 (DMSO-d6, 600 MHz)



^{13}C NMR of macrcocycle 3.16 (DMSO-d6, 126 MHz)

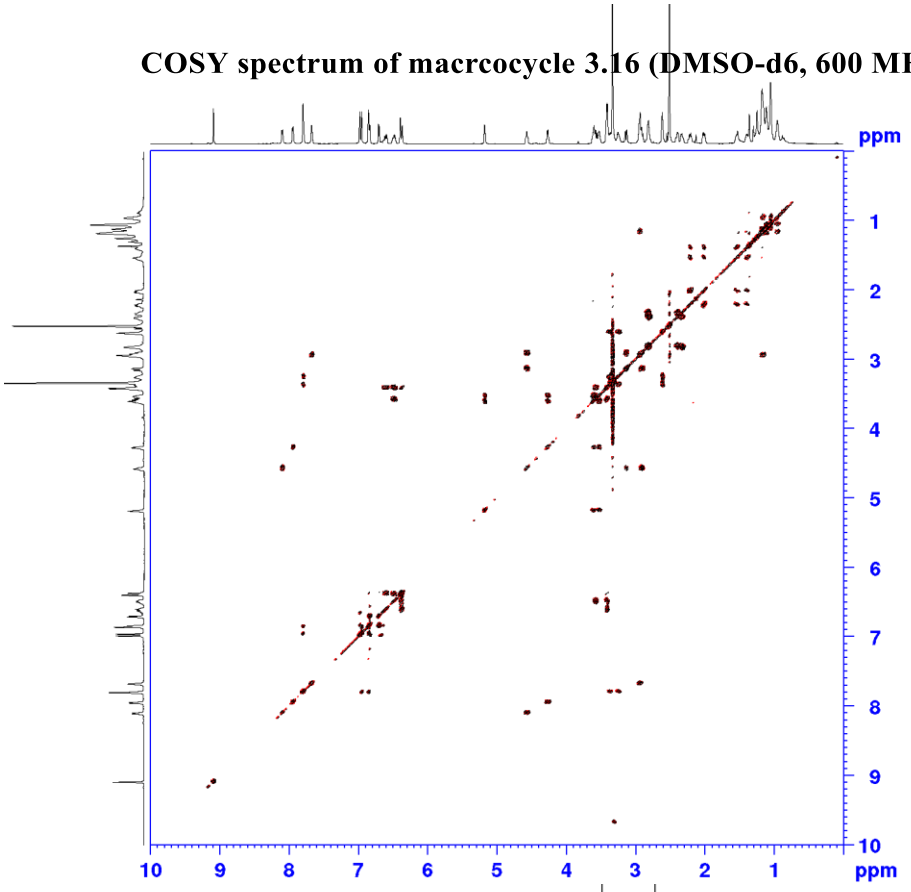




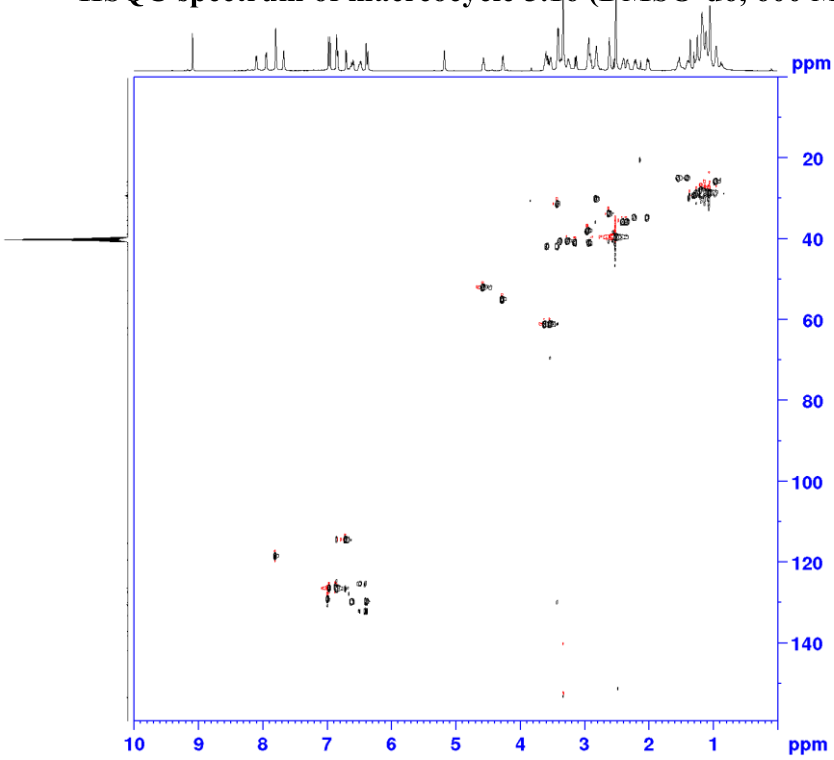
	13C	*1H*	*Corr.*
1	119.3	7.77 (s, 1H)	
2	138.1		HMBC 4-> 2
3	133.0	6.35 (d, J = 15.5Hz, 1H)	
4	130.7	6.39 (m, J = 15.5Hz, 1H)	
5	32.0	3.37 (m 2H)	
6	126.2		HMBC 4-> 6
7	153.4		
8		9.08 (s, 1H)	
9	115.2	6.67 (d, J = 8.0Hz, 1H)	
10	127.1	6.84 (d, J = 12.4 Hz, 1H, overlap)	Cosy 9->10 HMBC 9-> 10
11	130.3		HMBC 13->11 HMBC 14-> 11
12	119.3	7.80 (s, 1H)	
13	34.3	2.58 (m, 2H)	COSY 14->13
14	41.6	3.25, 3.36 (m, 2H)	COSY 15->14
15		7.76 (s, 1H)	
16	170.0		
17	52.7	4.60 (ddd J = 3.5,7.1, 10.4 Hz, 1H)	
18	41.7	3.13, 2.89 (m, 2H)	
19		8.10 (d, J = 8.0 Hz)	
20	173.4		HMBC 22-> 20
21	55.8	4.23 (m, 1H)	
22	61.8	3.59, 3.52 (m, 2H)	COSY 21->22
23	x	5.18 (s, 1H)	
24	x	7.93 (d, J = 7.0Hz, 1H)	
25	171.3		
26	35.3	2.22-2.14, 2.02-1.97 (ddd, J = 6.4, 6.6, 14 Hz, 2H)	

27	26.6	1.54, 1.38 (m, 2H)	HMBC 26->27
28	25.7	0.95 (m, 2H overlap)	HMBC 26->27
29	28.5	1.30-120 (overlap, m, 2H))	
30	29.0	1.20-1.10 (overlap m, 2H)	
31	29.2	1.10-1.00 (overlap m, 2H)	
32	29.2	1.10-1.00 (overlap m, 2H)	
33	29.7	1.10-1.00 (overlap m, 2H)	
34	30.8		COSY 34->35&37 HMBC 34->32
35	32.0	2.84-2.72 (m, 2H)	
36	x	7.65 (t, 5.7Hz 1H)	HMBC 36->34
37	171.4	x	HMBC 39&38-> 37
38	36.5	2.41-2.25 (m, 2H)	
39	30.1	2.81-273 (m, 2H)	
40	136.3	X	HMBC 39&38-> 37
41	126.2	6.85 (s, 1H)	
42	127.0	6.95 (S, 1H)	
43	141.1	X	HMBC 45-> 43
44	130.5	6.34 (d, J = 16.0Hz, 1H)	
45	126.2	6.50-6.42 (m, 1H)	
46	42.6	3.54, 3.39 (m, 2H)	

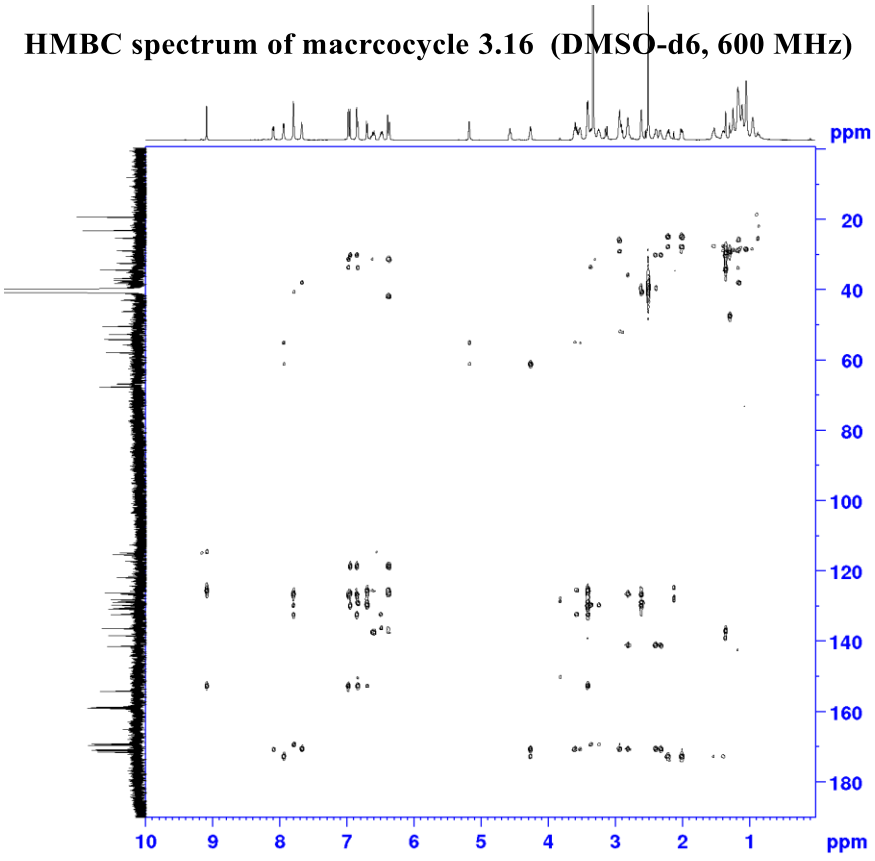
COSY spectrum of macrcocycle 3.16 (DMSO-d6, 600 MHz)



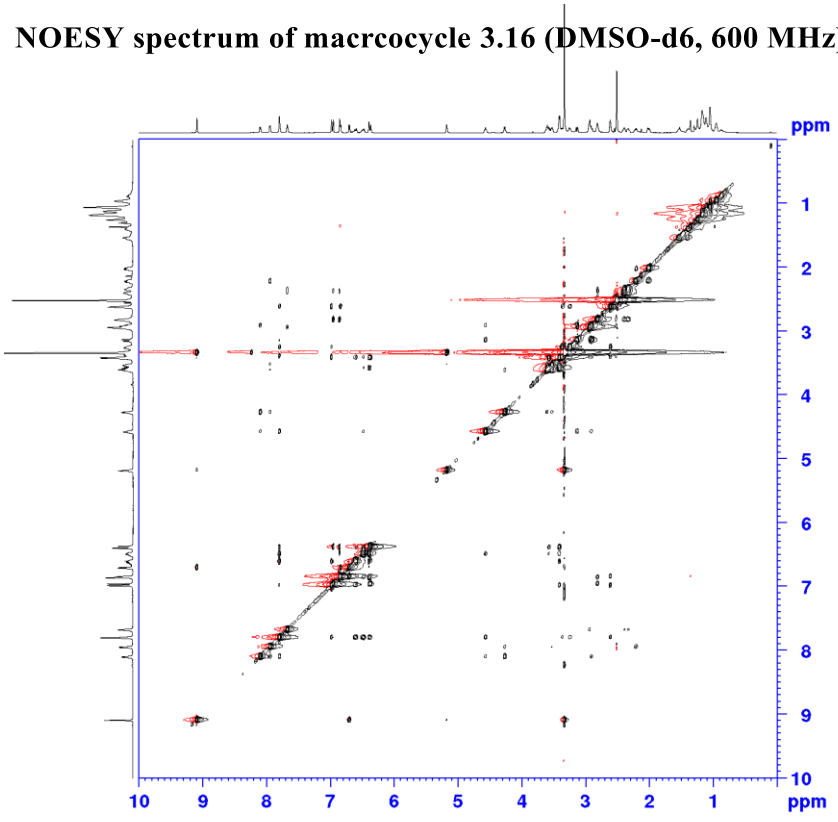
HSQC spectrum of macrcocycle 3.16 (DMSO-d6, 600 MHz)



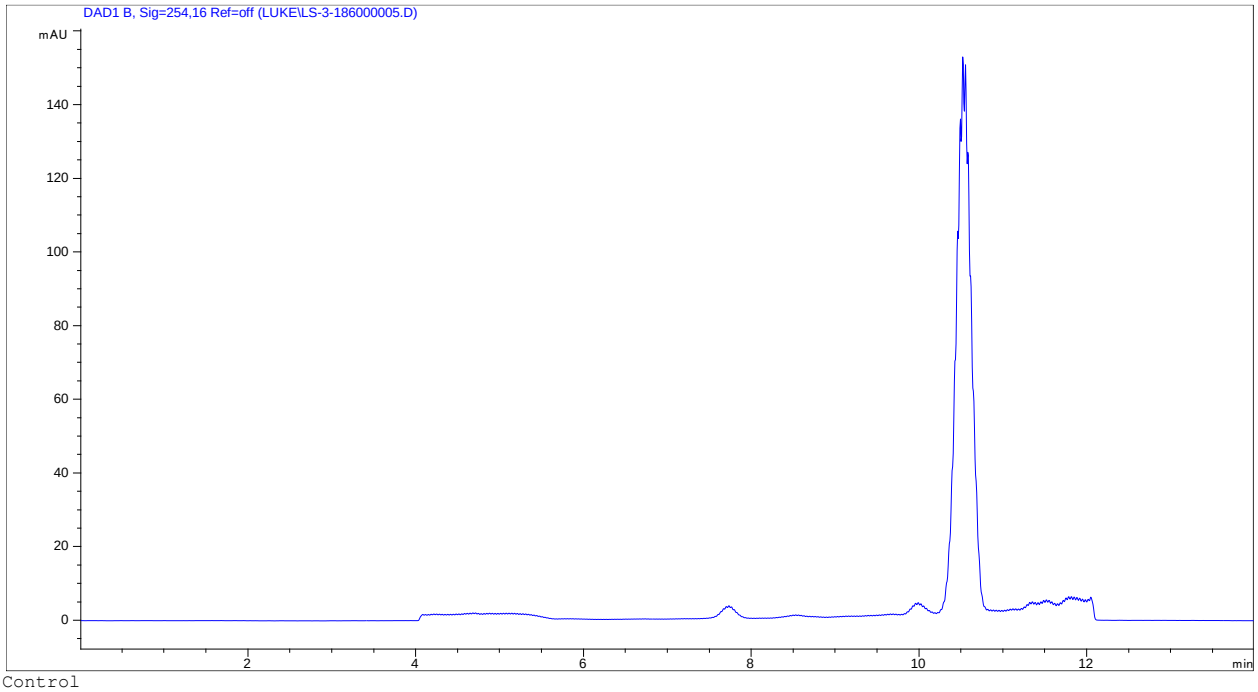
HMBC spectrum of macrcocycle 3.16 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 3.16 (DMSO-d6, 600 MHz)



3.16 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control
    Column Flow   :   12.000 ml/min
    Stoptime   :   14.00 min
    Posttime   :   Off

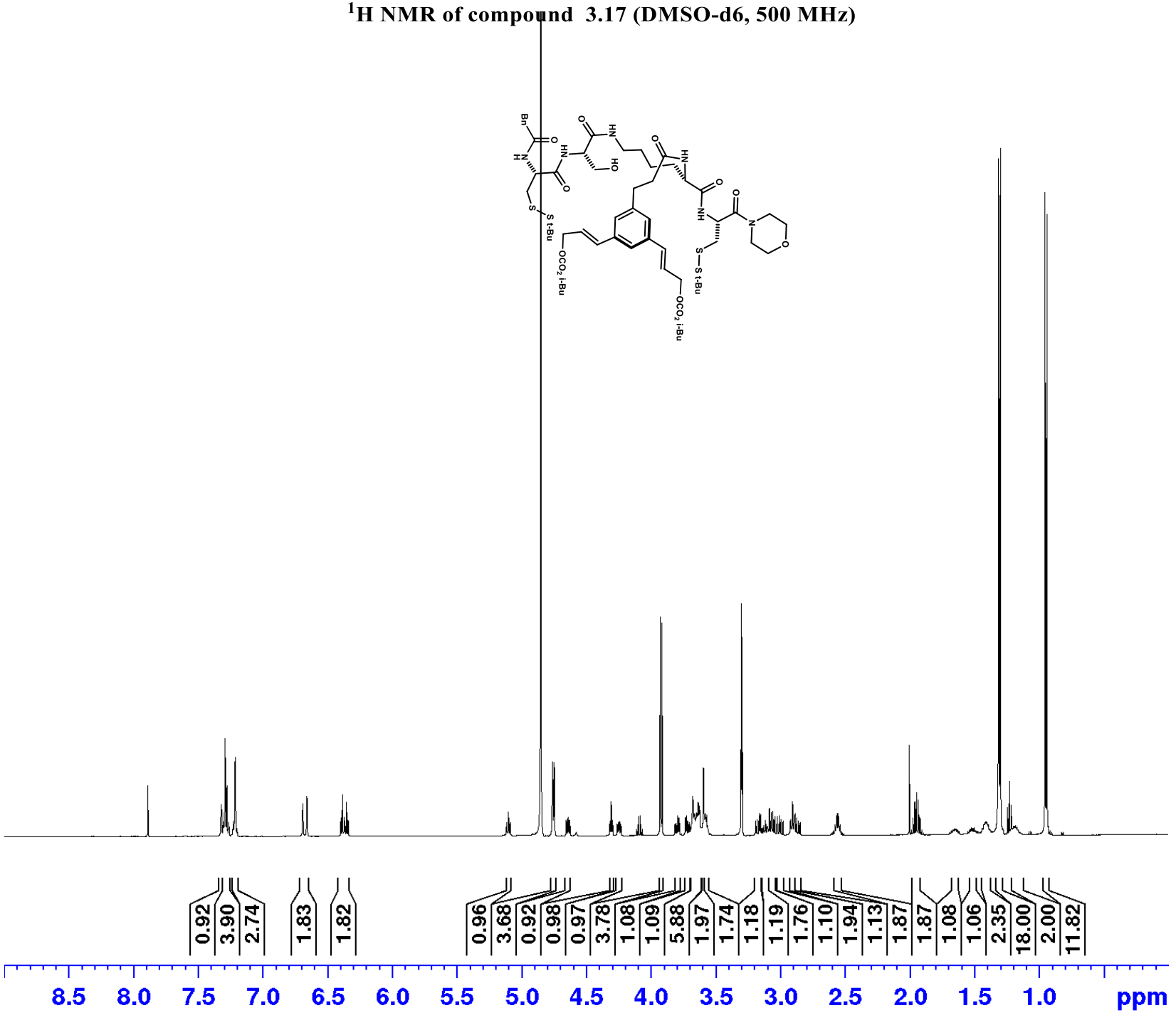
Solvents
    Solvent A   :   60.0 % (Water)
    Solvent B   :   40.0 % (Organic)

Auxiliary
    Flow Ramp   :   800.000 ml/min^2
    Compressibility   :   75*10^-6/bar

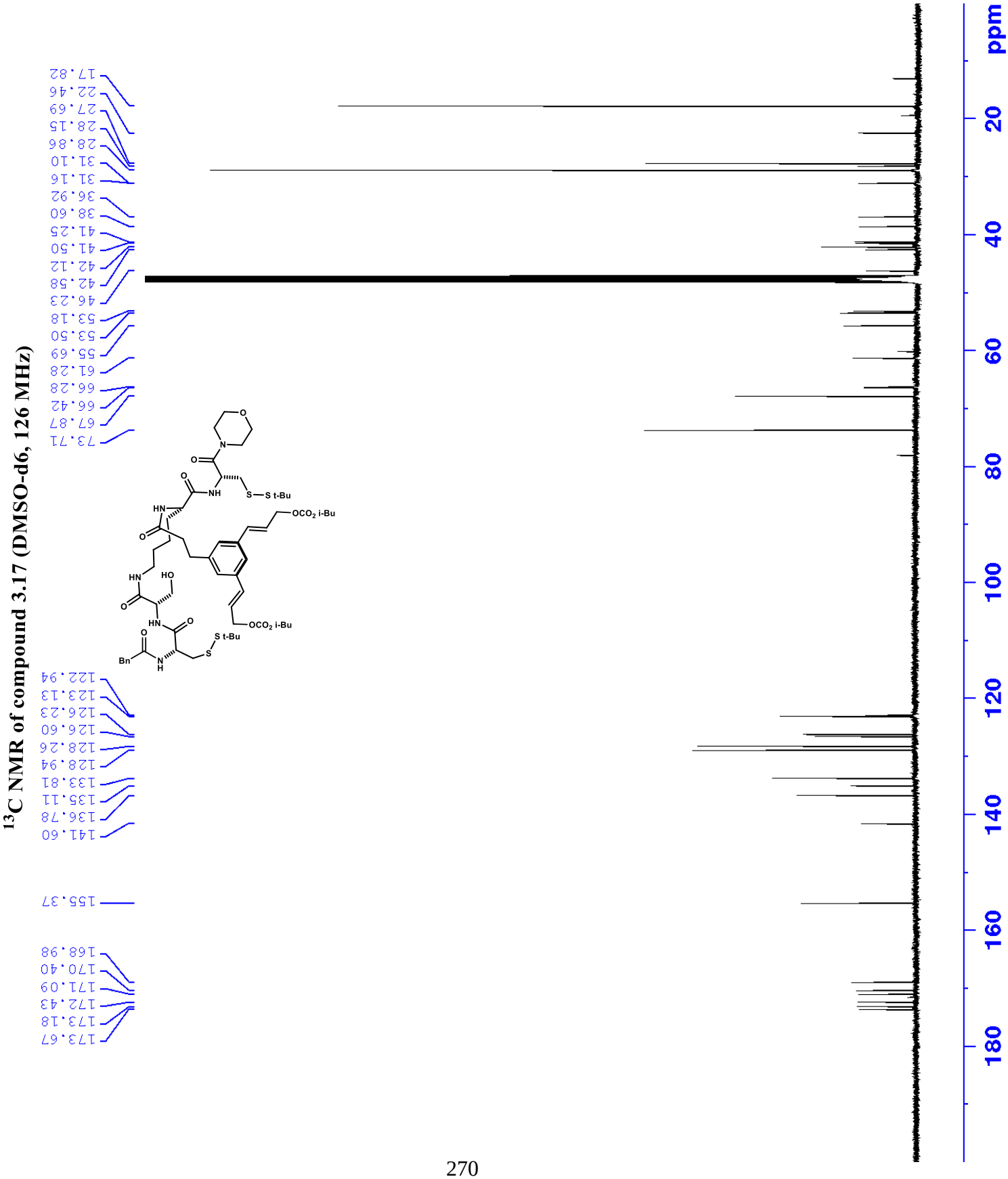
Timetable

Time	Solv.B	Flow	Pressure
0.00	40.0	12.000	400
2.00	40.0	12.000	400
8.00	65.0	15.000	400
13.00	100.0	15.000	400
14.00	40.0	15.000	400

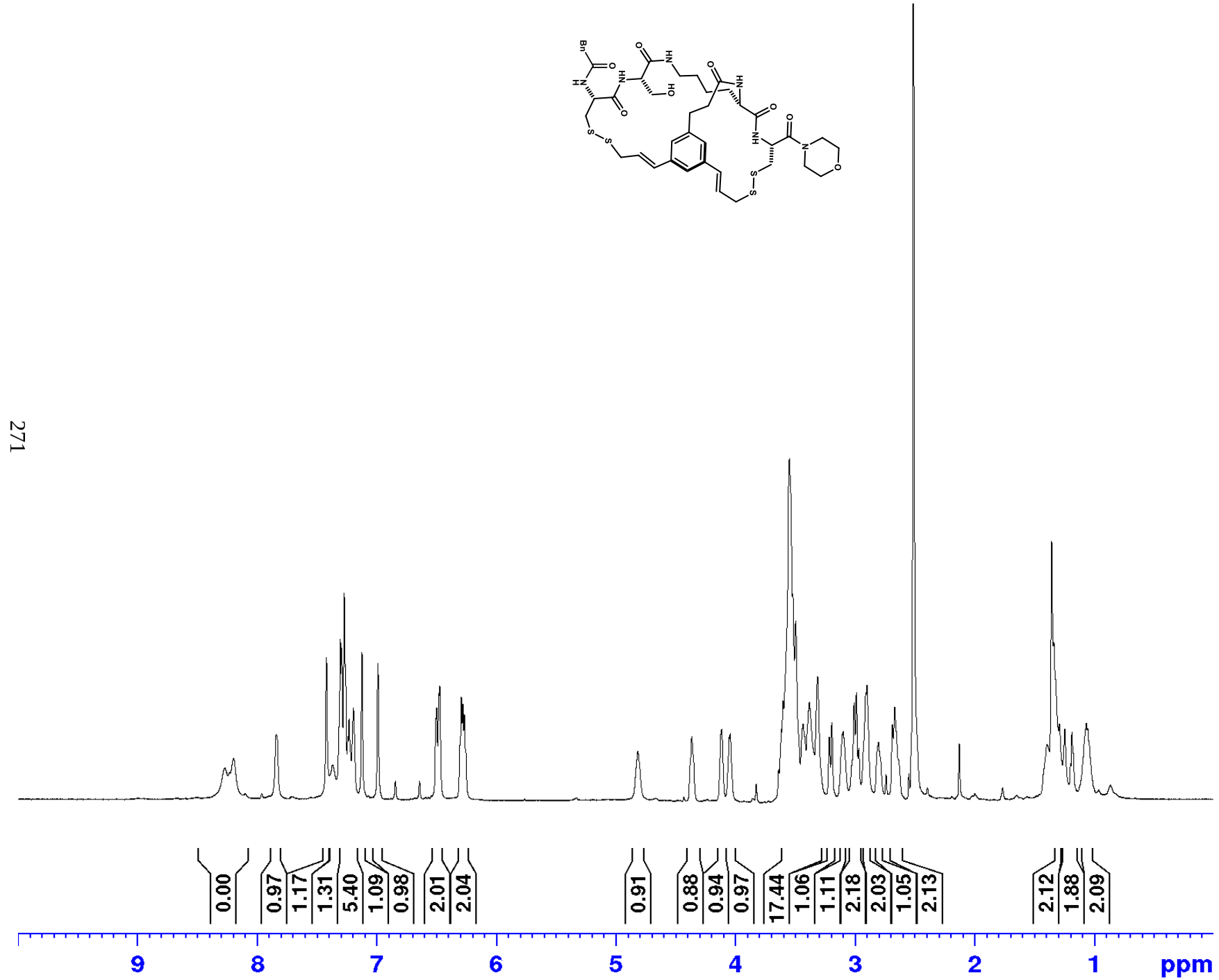
^{1}H NMR of compound 3.17 (DMSO-d6, 500 MHz)



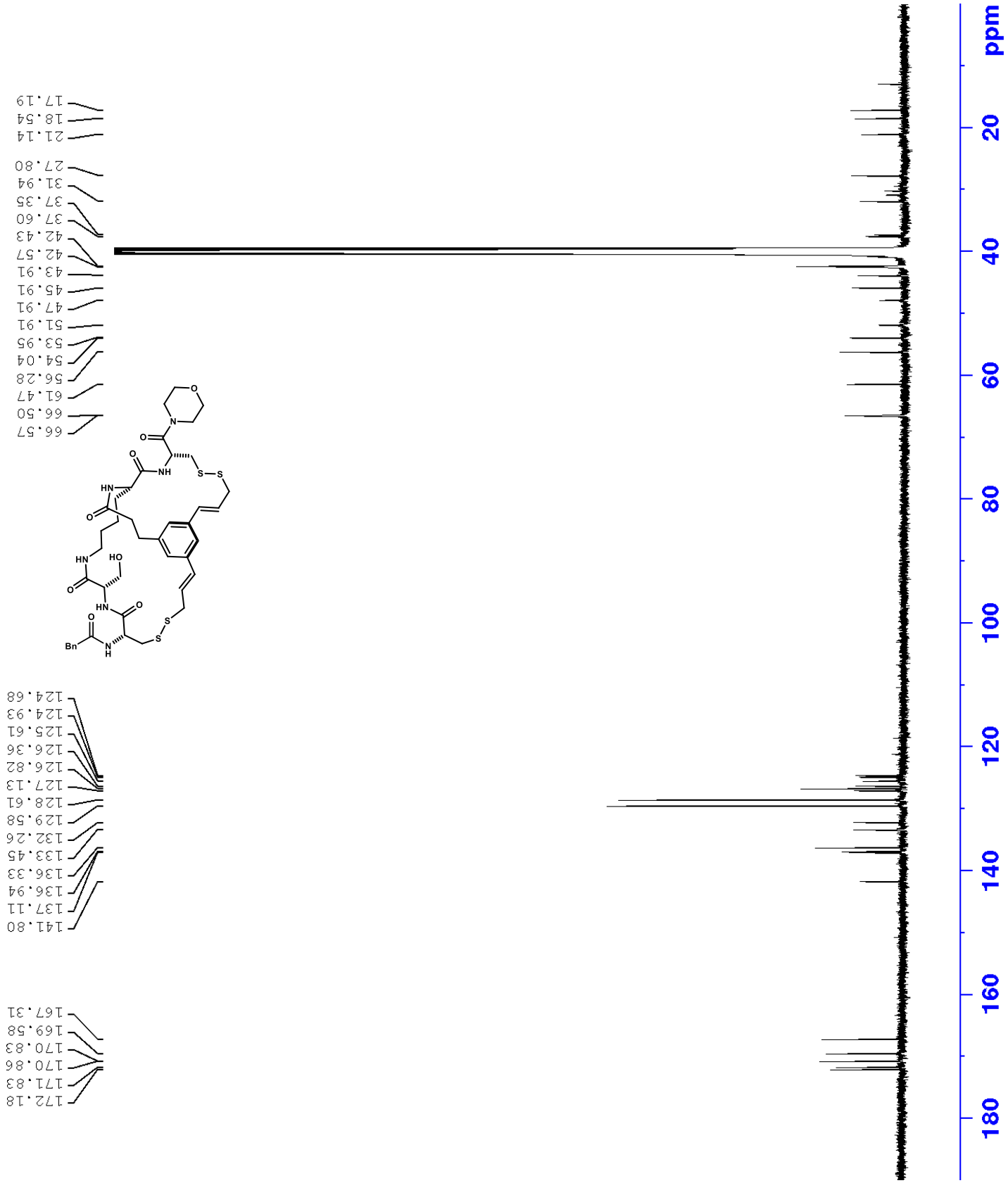
^{13}C NMR of compound 3.17 (DMSO-d6, 126 MHz)

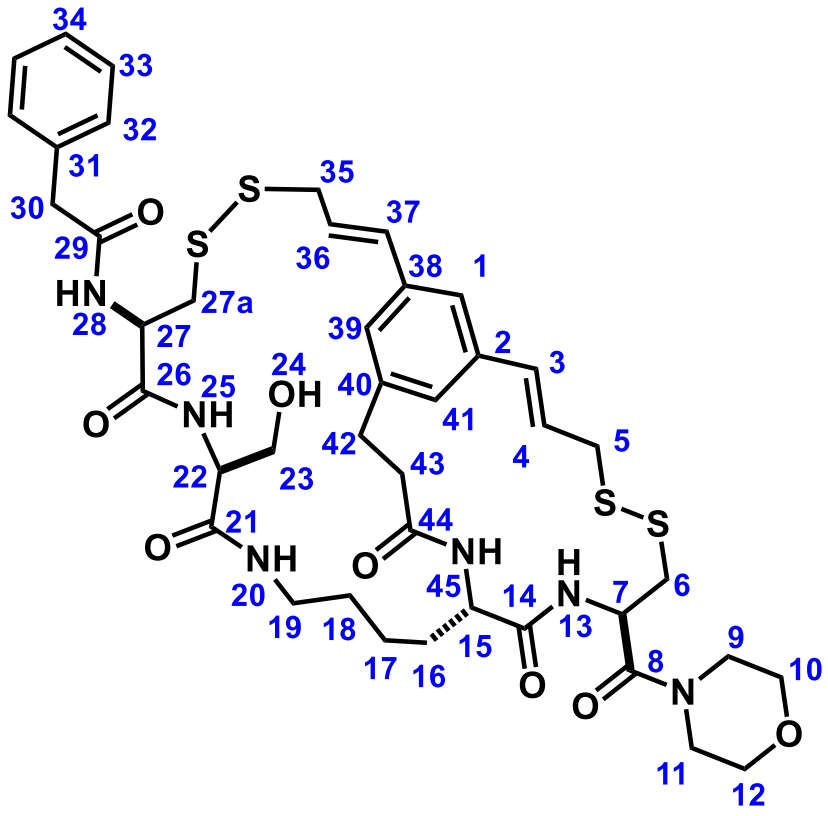


^{1}H NMR of macrcocycle 3.18 (DMSO-d6, 600 MHz)



^{13}C NMR of macrocycle 3.18 (DMSO-d6, 126 MHz)

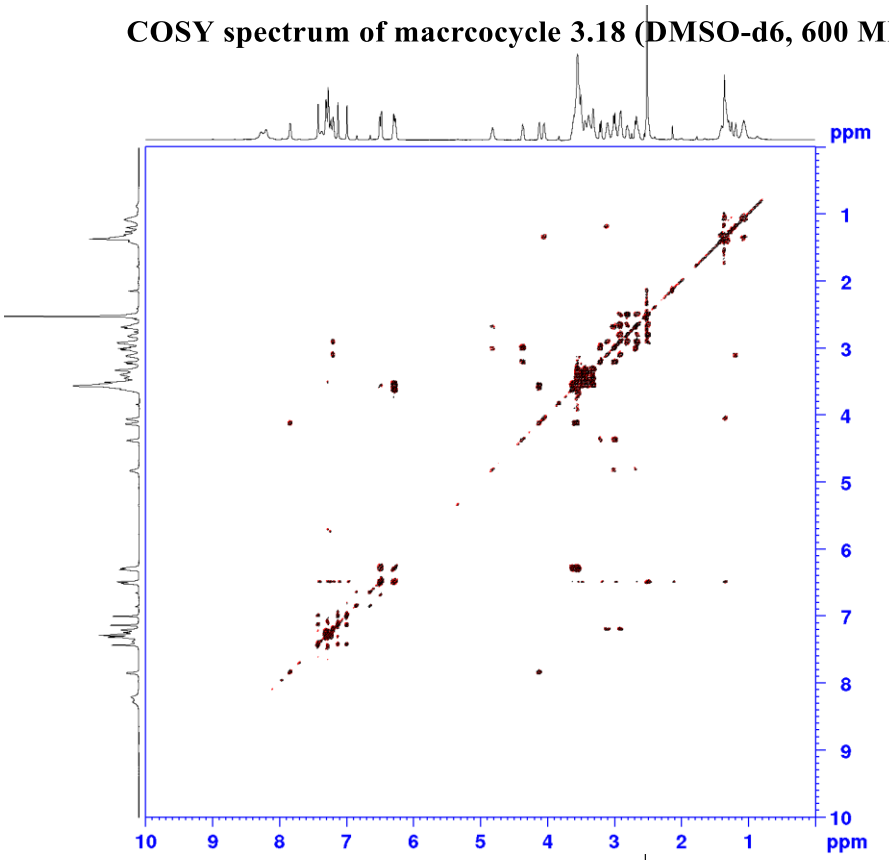




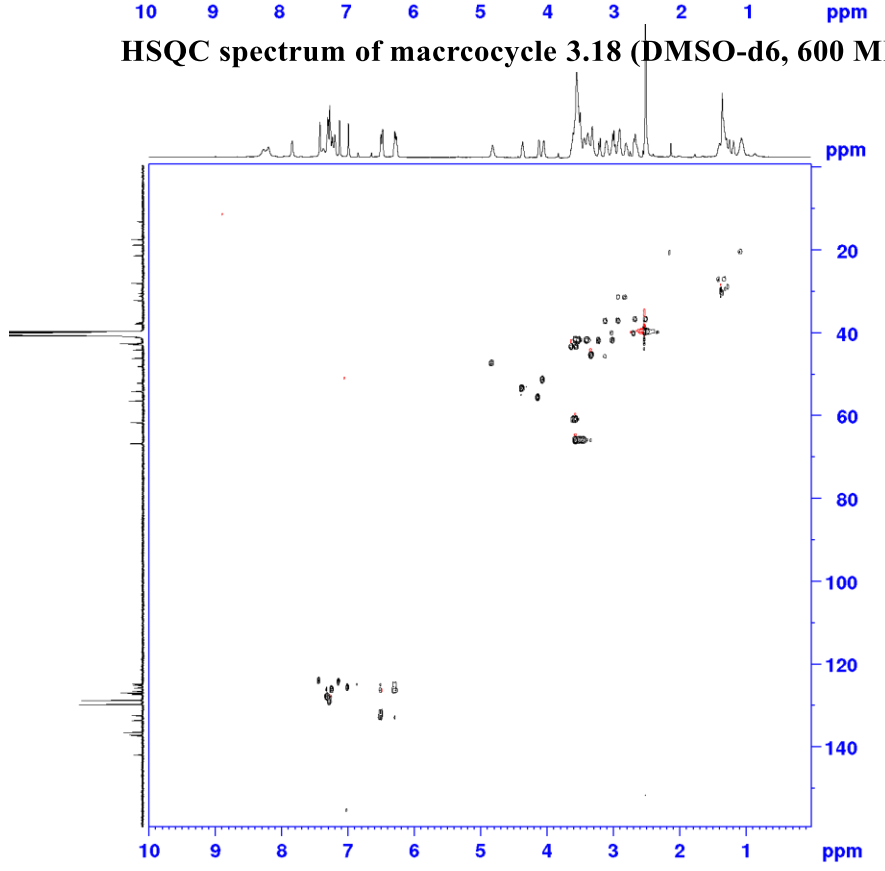
	13C	*1H*	*Corr.*
1	124.6	7.42 (s, 1H)	Key
2	137.1		
3 overlap w/37	132.3	6.54-6.45 (d, 15.5 Hz, 1H)	HMBC 39->37 HMBC 41->37 HMBC 1->37
4 overlap w/36	125.6	6.22-6.32 (m, 1H)	HMBC 3-> 4 COSY 3->4
5 overlap w/35	42.3	3.53 (m, 2H)	HMBC 4->5 HMBC 3->5 COSY 4->5
6	37.6	3.01, 2.68 (m ,2H)	COSY/NOESY 7->6
7	48.0	4.85 (m, 2H)	NOESY 11->7
8	167.3		
9	66.5	3.57 (m, 2H)	
10	42.4	3.48 (m, 2H)	
11	66.6	3.52 (m,2H)	
12	42.6	3.50 (m, 2H)	
13	na	8.19 (m, 1H)	NOESY/COSY 7->13
14	171.8		
15	51.9	4.04 (m, 1H)	Key
16	18.5	1.33 (m, 2H)	15->16 COSY 15->16 HMBC
17	17.2	1.14-1.00 (m, 2H)	HMBC 15->17 COSY 16->17
18	27.8	1.20-1.30 (m, 2H)	
19	45.9	3.10, 2.91 (m, 2H)	
20		7.20 (m, 1H)	NOESY 19->20
21	170.9		
22	54.0	4.10 (m, 1H)	

23	61.5	3.56 (m, 2H obscured)	COSY 22->23 HMBC 22->23
24			
25	na	7.83 (m, 1H)	COSY/NOSY 22->25
26	169.6		
27	56.3	4.35 (m, 1H)	NOESY 22->27
27alpha	37.6	3.20, 2.98 (m, 2H)	COSY/NOESY 27->27a
28	na	8.26 (m, 1H)	NOESY/COSY 27-28
29	172.2	x	
30	41.7	3.53 (m, 2H)	HMBC 32->30
31	136.3	na	HMBC 32/33->31
32	127.1	7.29 (m, 2H)	
33	129.6	7.25 (m, 2H)	
34	128.6	7.22 (m, 1H)	
35 overlap w/5	43.9	3.63 (m, 2H)	HMBC 36->35 HMBC 37->35
36 overlap w/4	126.8	6.22-6.32 (m, 1H)	HMBC 37->36 COSY 37-> 36
37 overlap w/3	133.5	6.54-6.45 (d, J= 15.5 Hz, 1H)	HMBC 39->37 HMBC 41->37 HMBC 1->37
38	136.9		
39	124.7	7.13 (s, 1H)	HMBC 1->39
40	141.8		
41	126.4	6.99 (s, 1H)	HMBC 1->41
42	31.9	2.93-2.85, 2.82-2.76 (m, 2H)	HMBC 39/41->42
43	37.3	2.63, 2.48 (m, 2H obscured)	NOESY/COSY 43->44
44	170.8		
45		7.37 (m, 1H)	NOESY 14->45

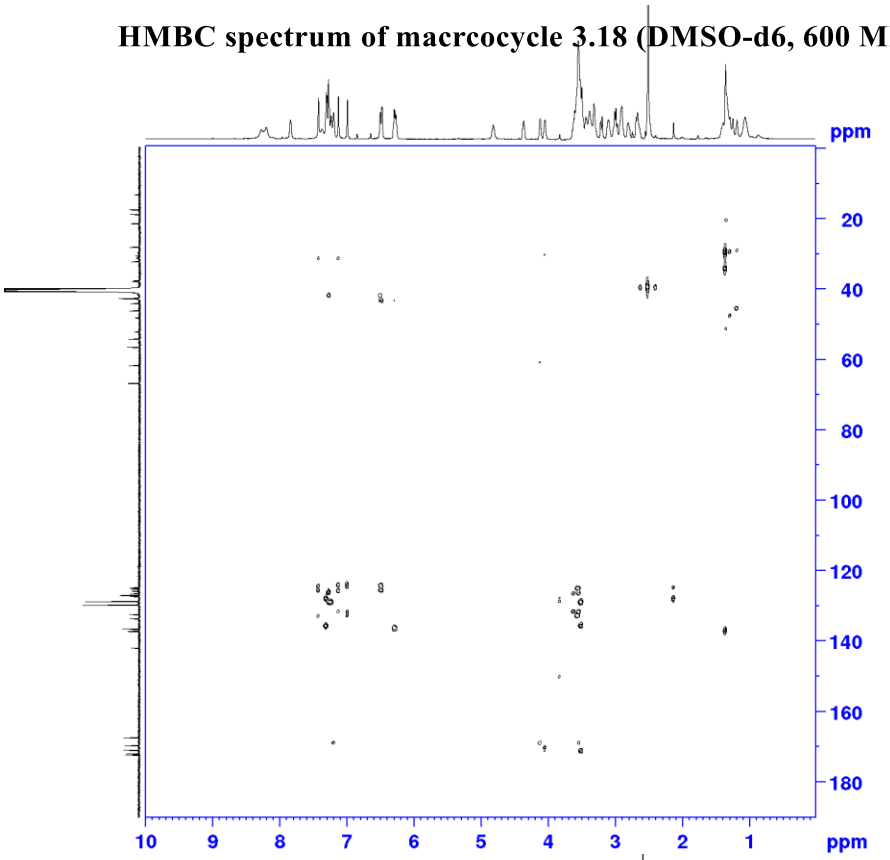
COSY spectrum of macrcocycle 3.18 (DMSO-d6, 600 MHz)



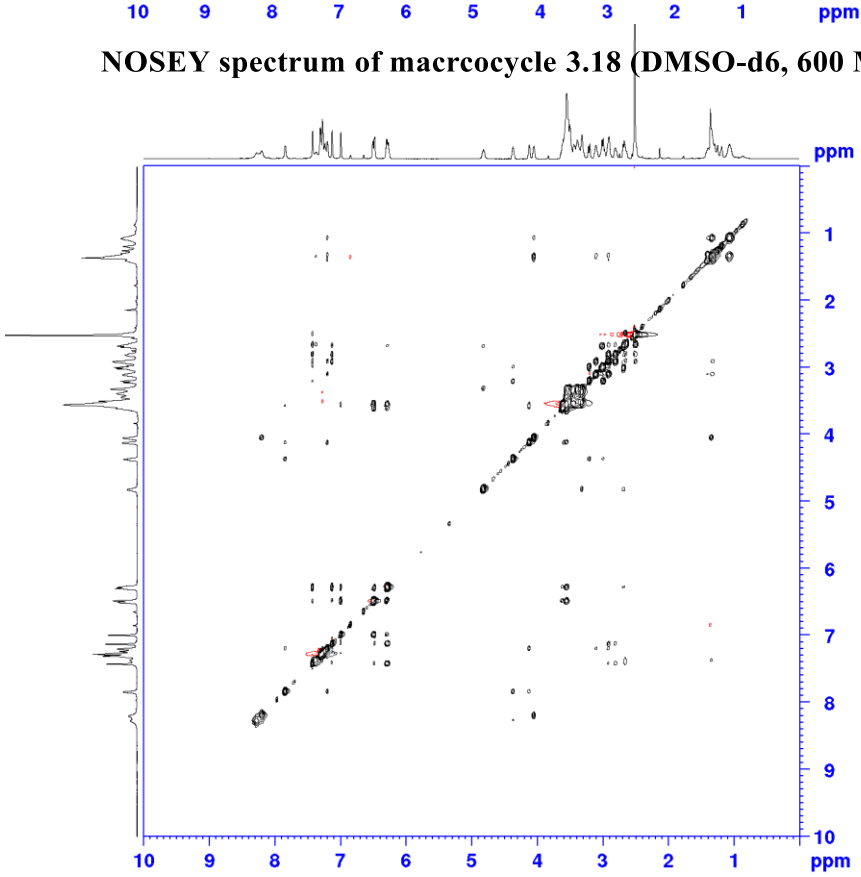
HSQC spectrum of macrcocycle 3.18 (DMSO-d6, 600 MHz)



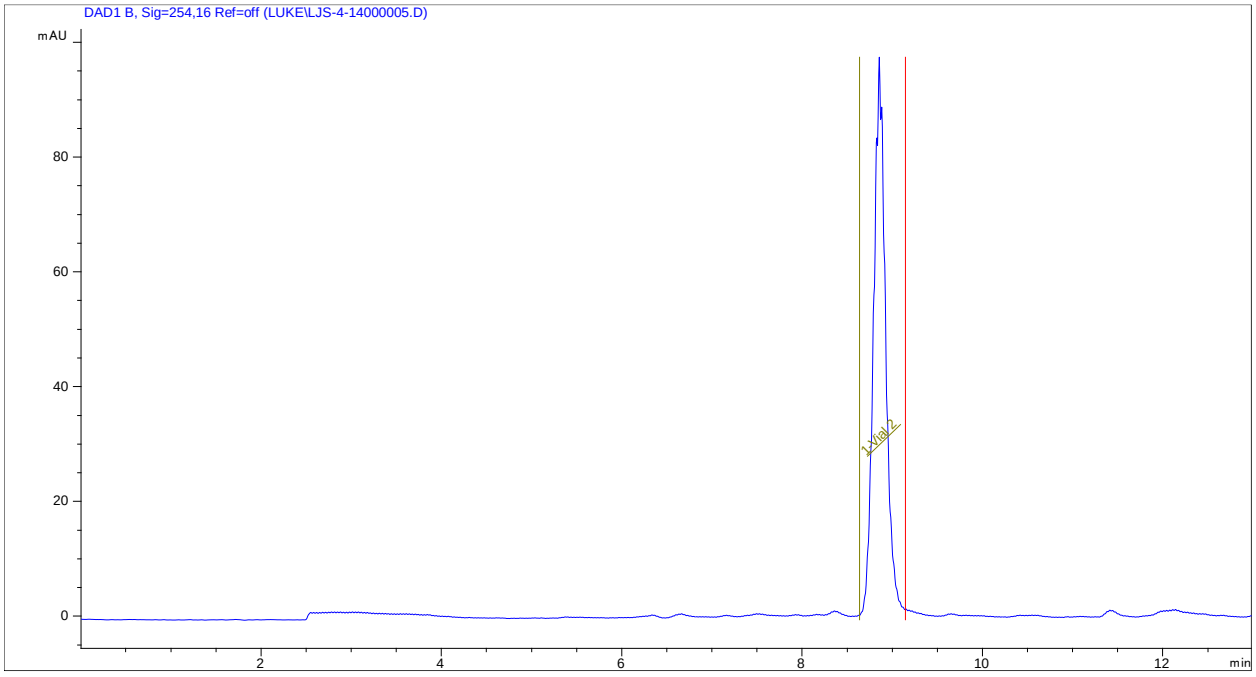
HMBC spectrum of macrcocycle 3.18 (DMSO-d6, 600 MHz)



NOSEY spectrum of macrcocycle 3.18 (DMSO-d6, 600 MHz)

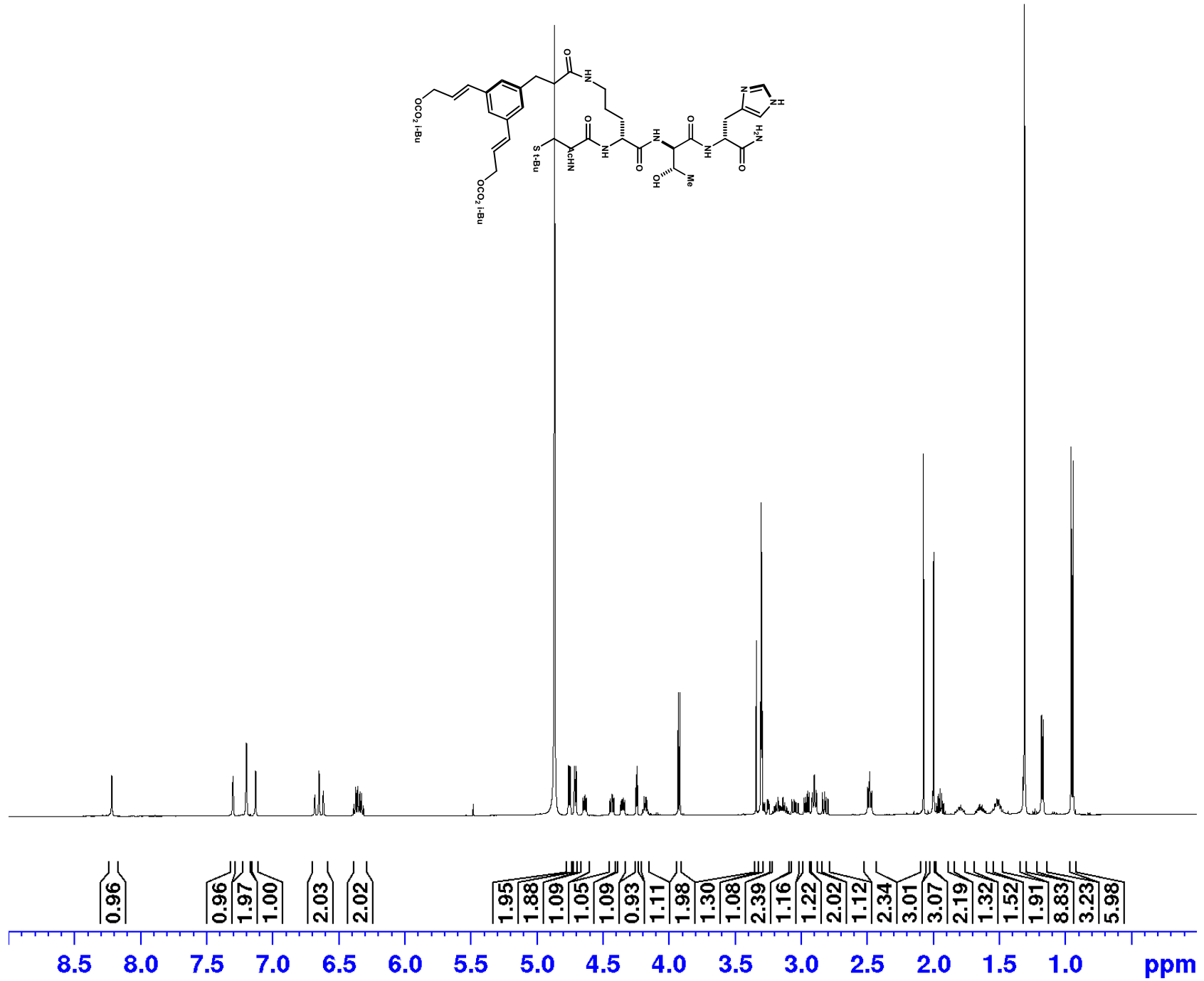


3.18 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column

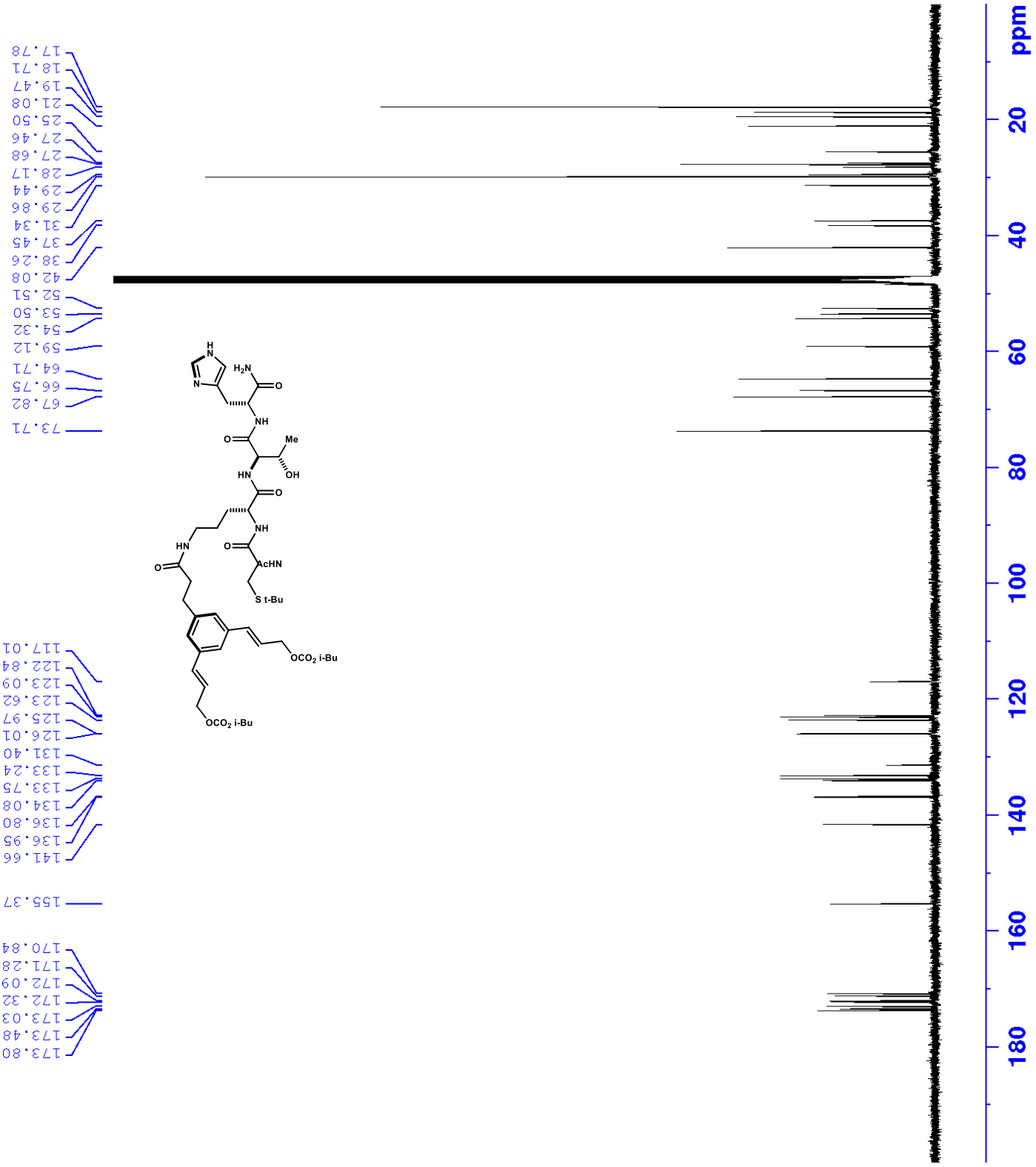



```
Control
    Column Flow            :      12.000 ml/min
    Stoptime               :         13.00 min
    Posttime               :          0.50 min

Solvents
    Solvent A              :       50.0 % (Water)
    Solvent B              :       50.0 % (Organic)

Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar

Timetable

       Time    Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00   50.0    12.000
         0.50   50.0    12.000
        11.00   90.0    15.000
        11.50  100.0    15.000
        12.50  100.0    15.000
        13.00   30.0    15.000
```

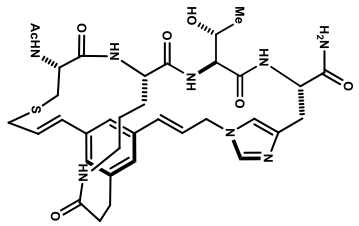
^{1}H NMR of compound 3.21 (MeOD-d4, 500MHz)



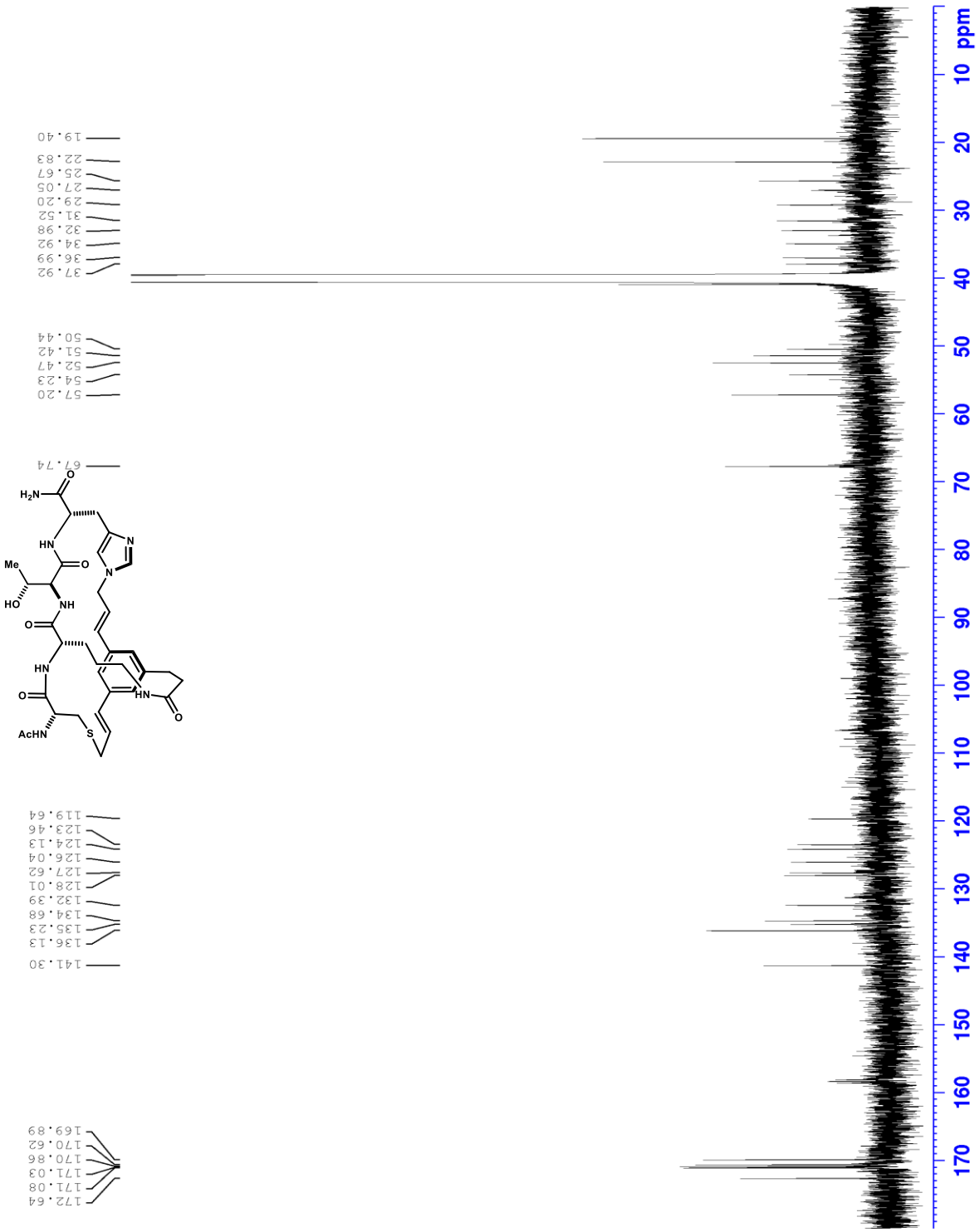
^{13}C NMR of compound 3.21 (MeOD-d4, 125MHz)

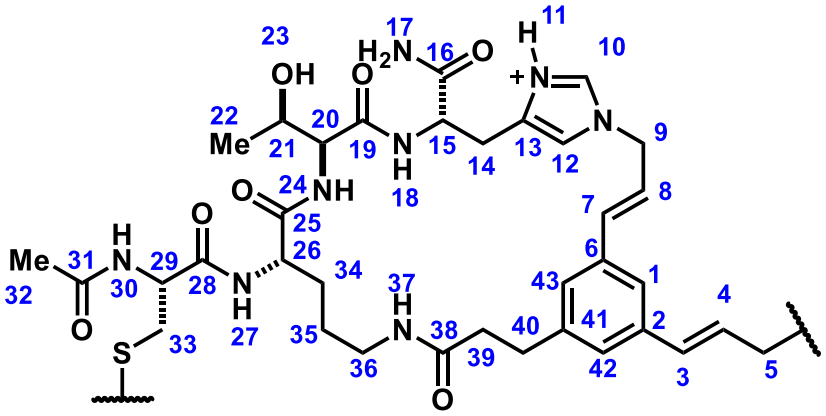


^{1}H NMR of macrcocycle 3.24 (DMSO-d6, 600 MHz)



^{13}C NMR of macrocycle 3.24 (DMSO-d6, 126 MHz)

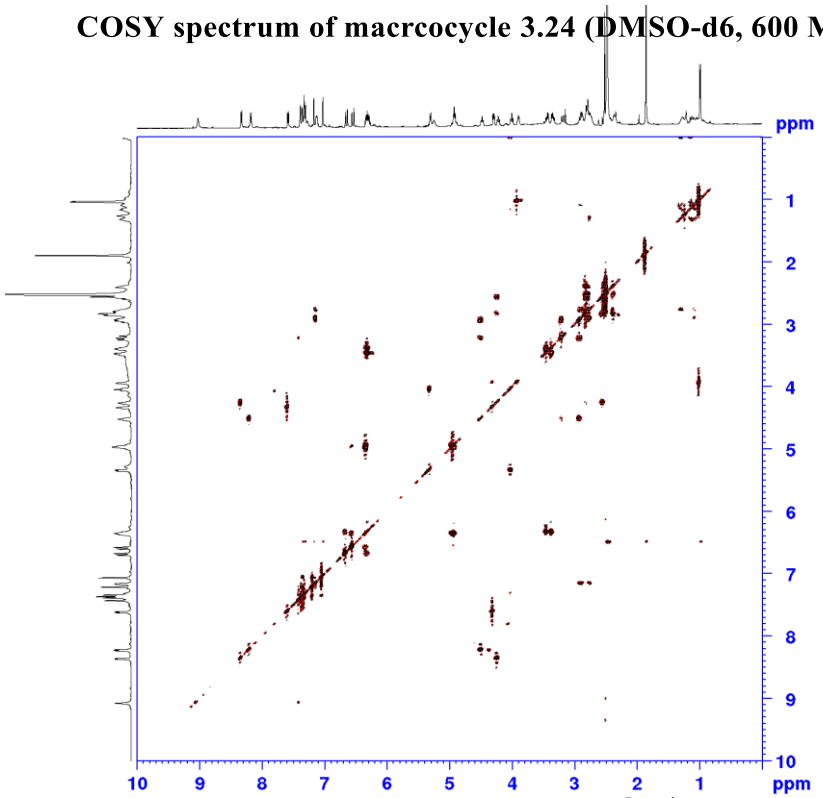




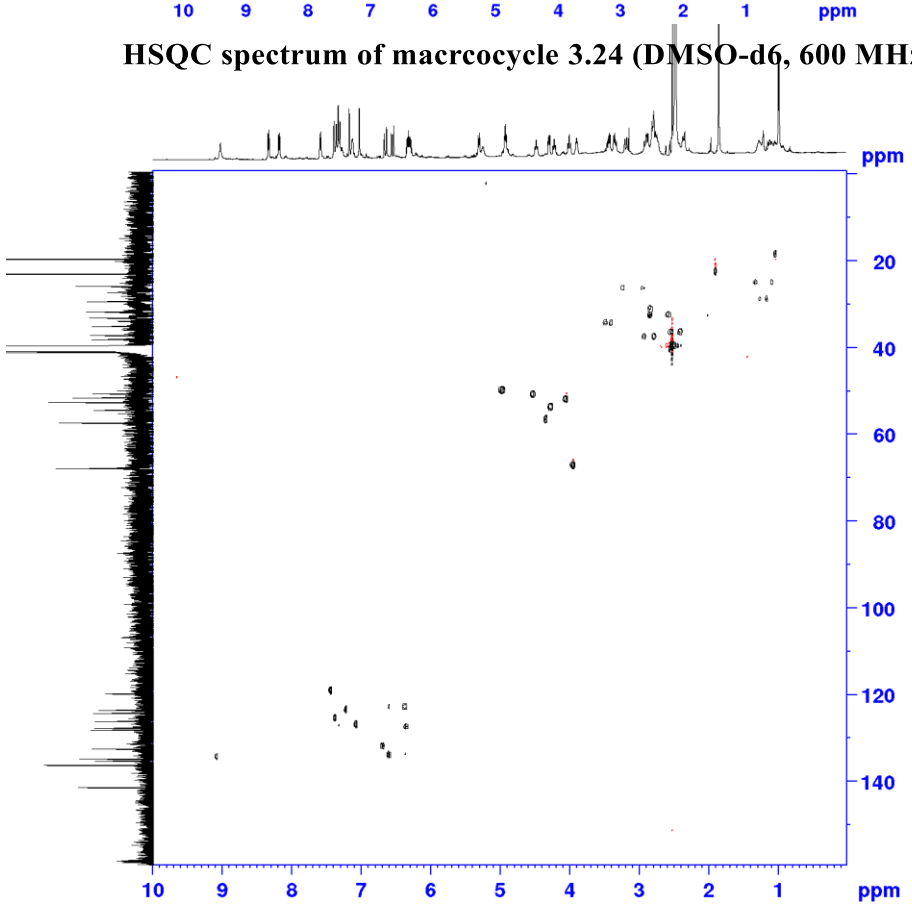
	C13	*H1*	*Corr.*
1	124.1	7.20 (s, 1H)	key
2	135.2		HMBC/HSQC 4->2
3	132.4	6.68 (d, J = 15.7 Hz, 1H)	key
4	123.5	6.36-6.29 (m, 1H overlap)	COSY 3->4 HMBC->HSQC 3->4
5	34.9	3.44-3.35 (m, J, 2H)	COSY 4->5 HMBC->HSQC 4->5
6	136.1		HMBC/HSQC 8->6
7	135.2	6.58 (d, J = 15.7 Hz, 1H)	
8	127.6	6.29-6.24 (m, 1H overlap)	COSY 7->8 HMBC->HSQC 7->8
9	50.4	4.98-4.85 (m, 2H)	Key
10	134.7	9.03 (br, 1H)	NOESY 9->10
11		14.5 (br, 1H)	
12	119.6	7.41 (s, 1H)	HMBC/HSQC 10->12
13	128.0	na	HMBC/HSQC 12->13
14	27.0	3.19 (m, 1H), 2.89 (m, 1H)	
15	51.4	4.55-4.45 (m, 1H)	Key
16	170.9		
17		7.36, 7.30 (s, 2H)	HMBC 17->15
18	na	8.18 (d, J = 8.4 Hz, 1H)	COSY 15->18
19	169.9		
20	57.2	4.29 (dd, J = 8.4, 4.4 Hz, 1H)	HMBC/HSQC 21->20 COSY 21->20
21	67.7	3.93-3.86 (m, 1H)	HMBC/HSQC 22->21

			COSY 22->21
22	19.4	1.03 (d, J = 4.9 Hz, 3H)	key
23		5.33 (d, J = 8.0 Hz, 1H)	
24	na	7.60 (d, J = 8.0 Hz, 1H)	COSY 20->24
25	171.0		
26	52.4	4.04-3.97 (m, 1H)	key
27		8.22 (d, J = 8.1 Hz, 1H)	
28	170.6		
29	54.2	4.22 (m, 1H)	NOESY 5->29
30		8.33 (d, J = 6.5, 1H)	COSY 29->30
31	171.1		HMBC 32->31
32	22.8	1.85 (s, 3H)	Key
33	32.9	2.84,2.55 (m, 2H)	HMBC/HSQC 5->33 COSY 29->33 NOESY 5->33
34	29.2	1.27, 1.17 (m, 2H),	NOESY 26->34 COSY 26->34
35	25.7	1.30, 1.13 (m, 2H)	NOESY 34->35 COSY 34->35
36	37.9	2.92, 2.77 (m, 2H)	NOESY 34/35->36 COEST 34/35->36
37		7.16 (m, 1H)	COSY 36->37
38	172.6		HMBC 39->38
39	37.0	2.53-2.40 (m, 2H)	
40	31.5	2.85-2.75 (m, 2H)	HMBC/HSQC 42/3->40
41	36.9	2.49-2.36 (m, 2H)	COSY/NOESY 40->41
42	125.3	7.33 (s, 1H)	HMBC/HSQC 1->42
43	126.9	7.03 (s, 1H)	HMBC/HSQC 1->43

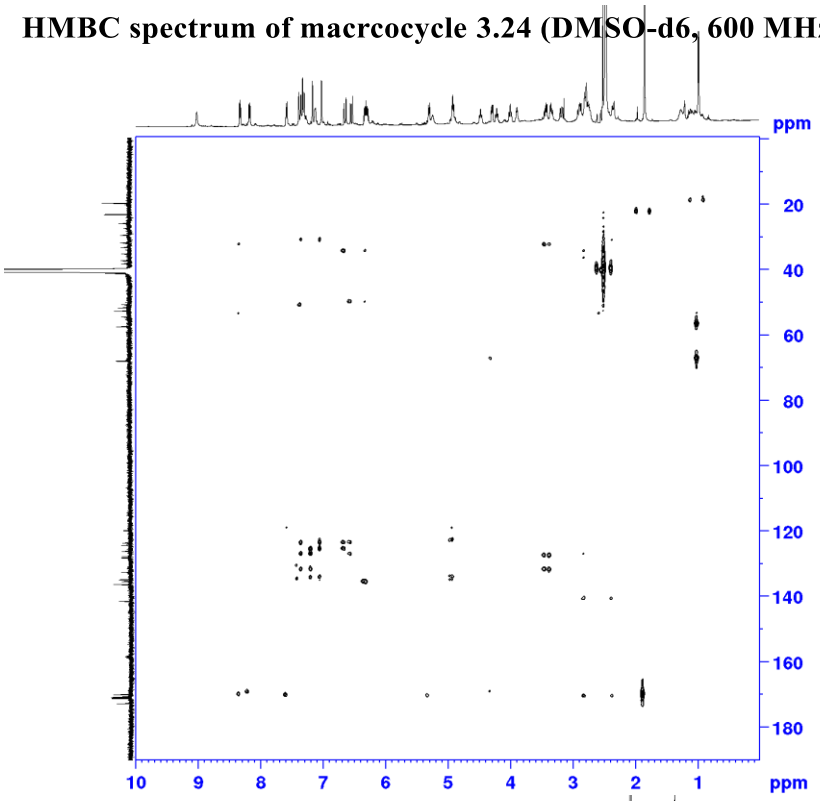
COSY spectrum of macrcocycle 3.24 (DMSO-d6, 600 MHz)



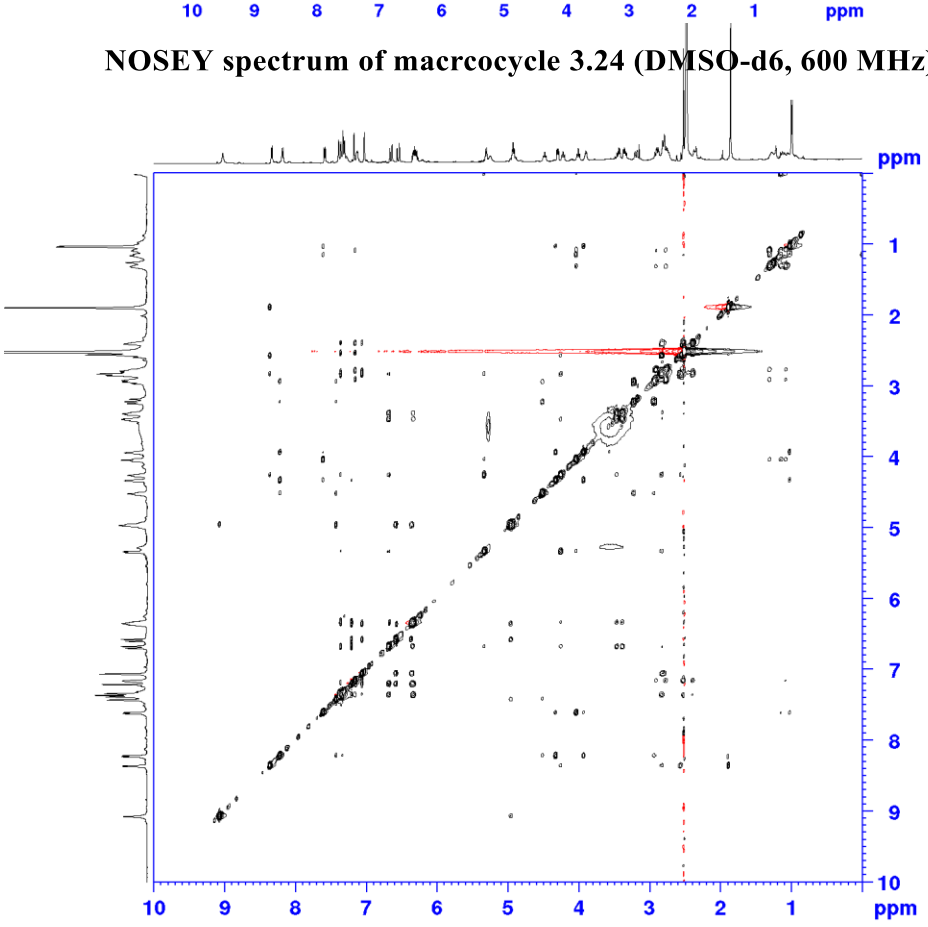
HSQC spectrum of macrcocycle 3.24 (DMSO-d6, 600 MHz)



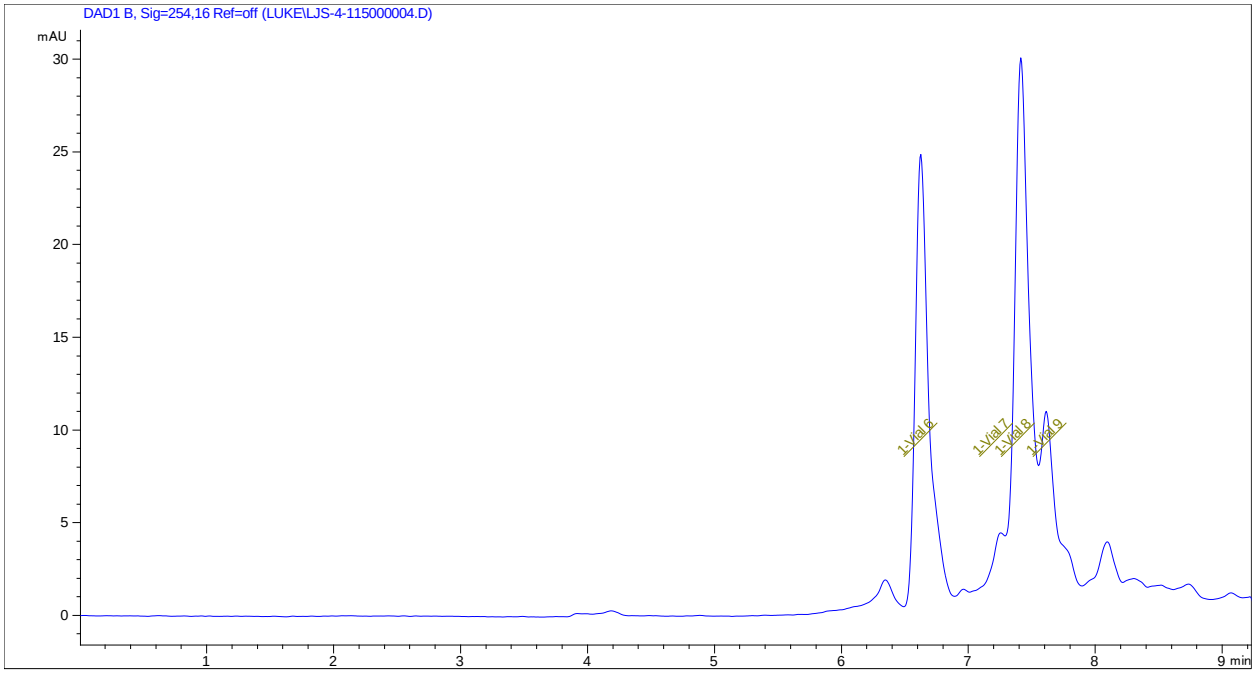
HMBC spectrum of macrcocycle 3.24 (DMSO-d6, 600 MHz)



NOSEY spectrum of macrcocycle 3.24 (DMSO-d6, 600 MHz)

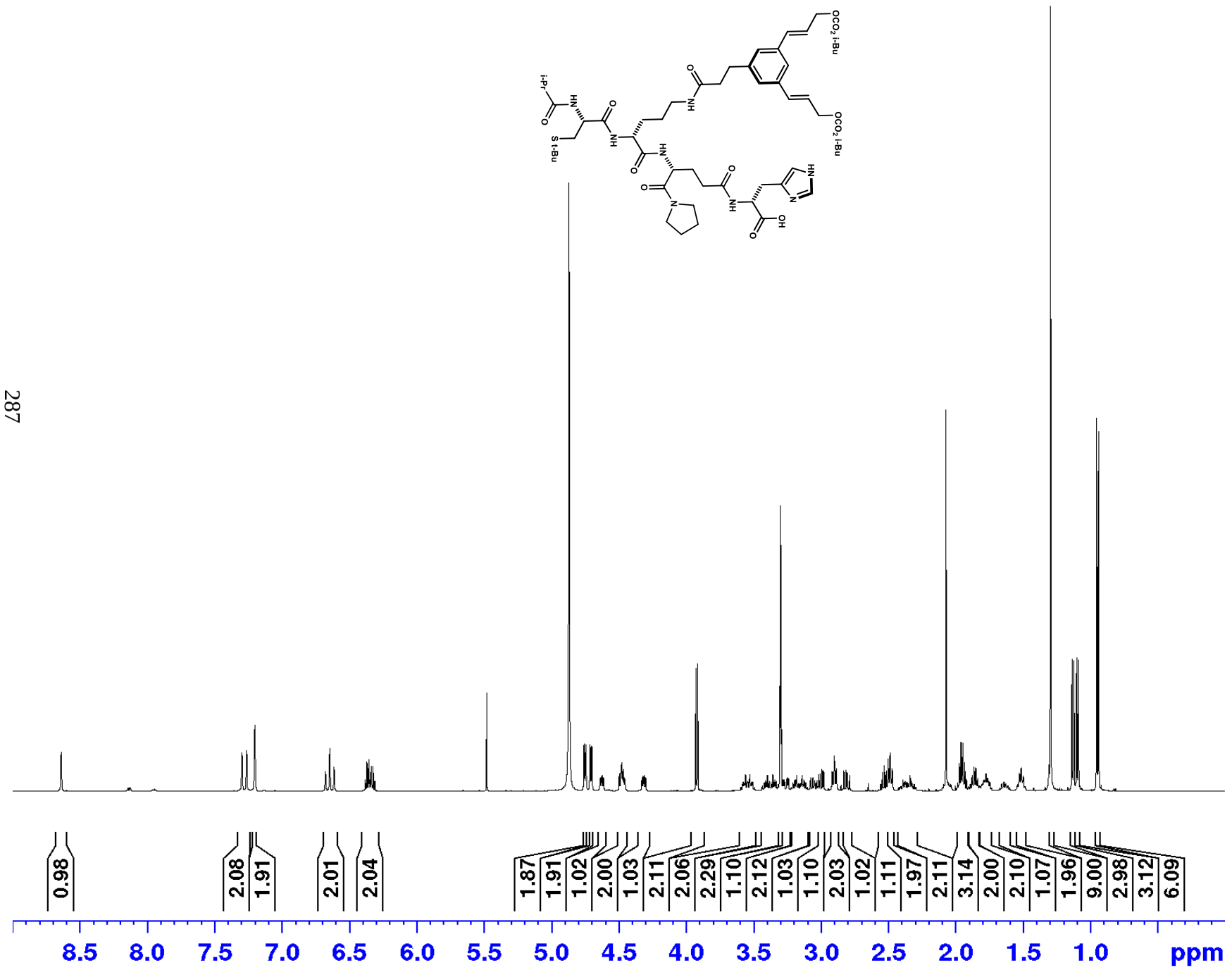


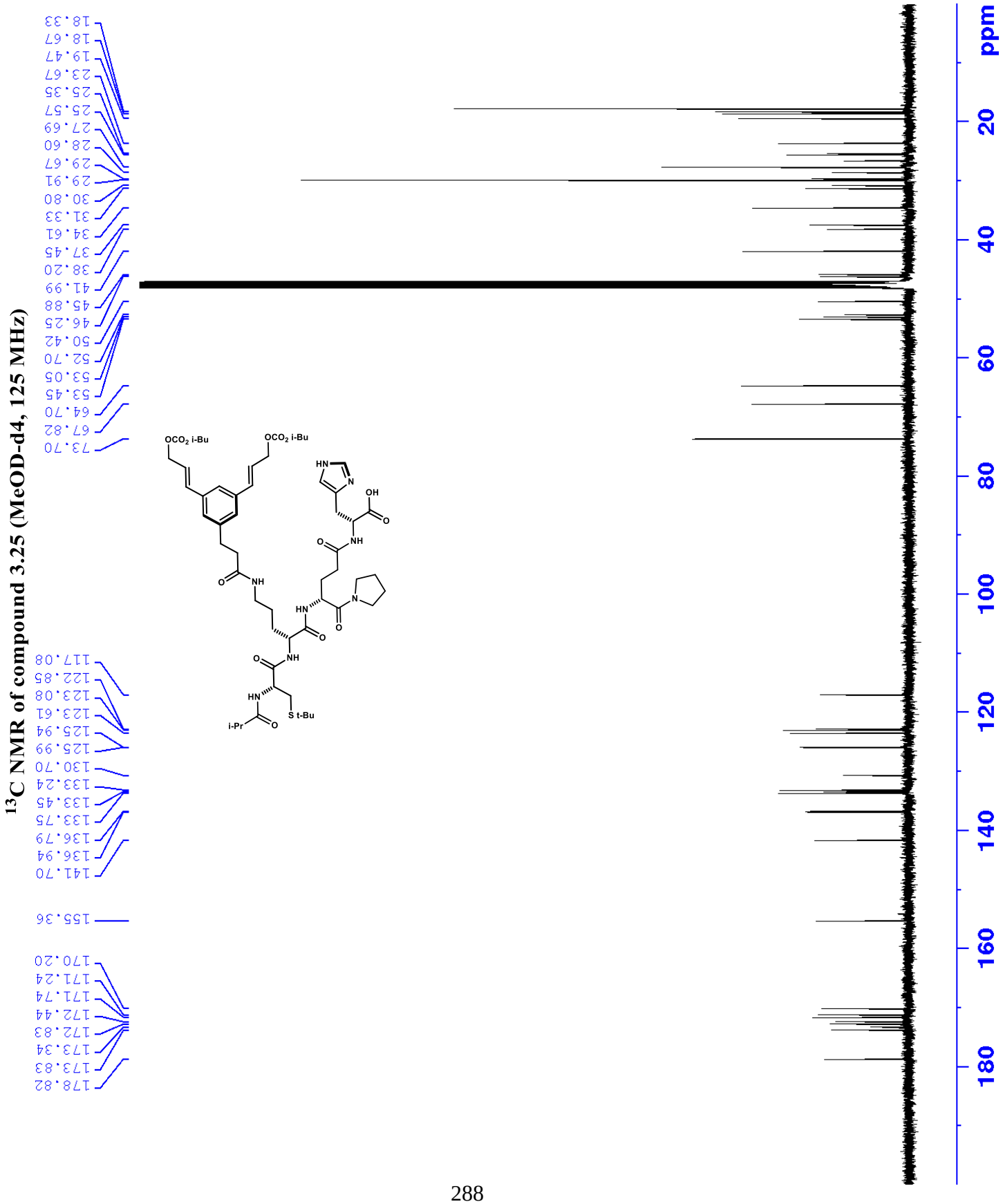
3.24 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



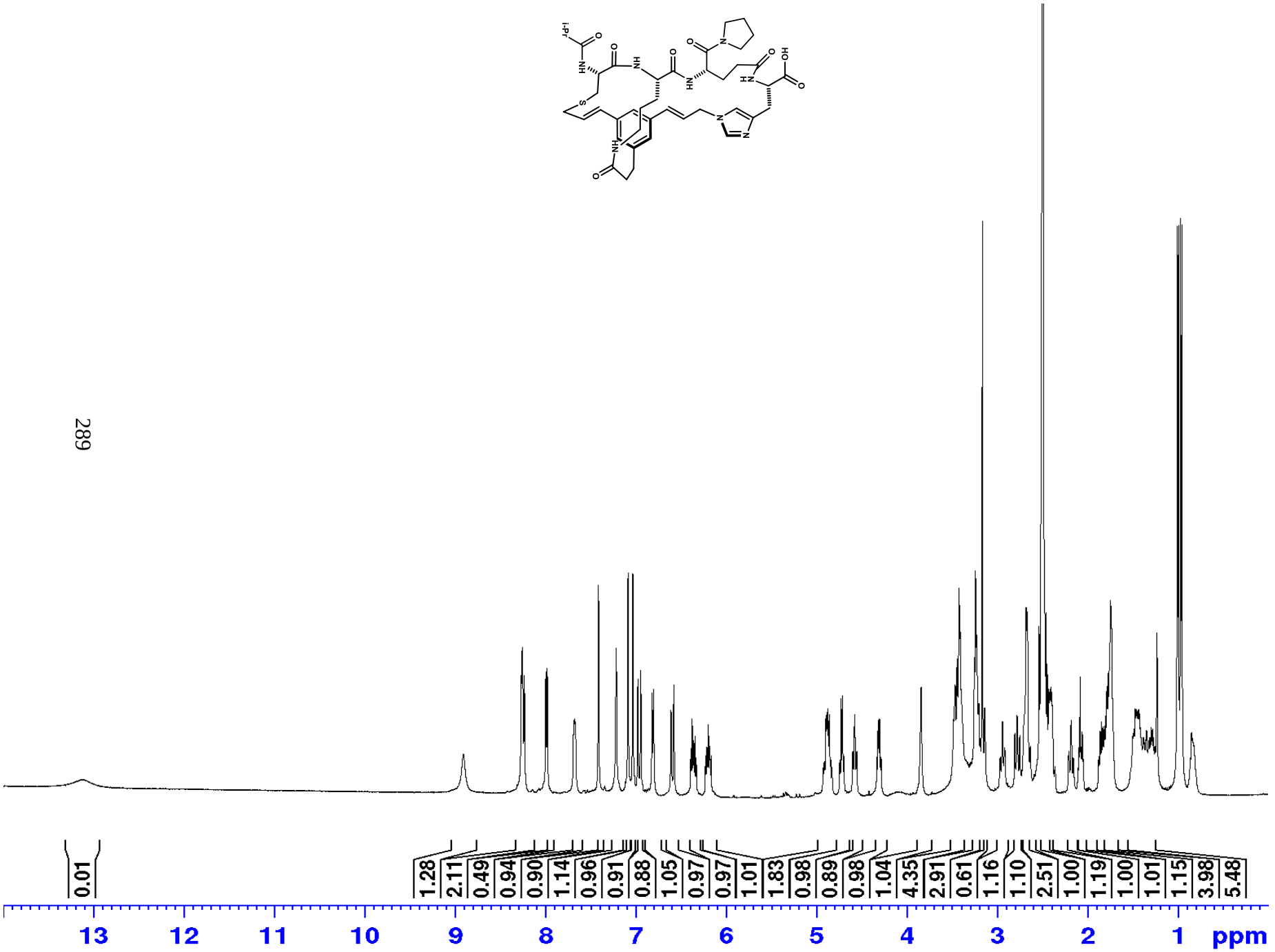

```
Control
    Column Flow            :      12.000 ml/min
    Stoptime               :         13.00 min
    Posttime               :          0.50 min

Solvents
    Solvent A              :       82.0 % (Water)
    Solvent B              :       18.0 % (Organic)


Auxiliary
    Flow Ramp              :      800.000 ml/min^2
    Compressibility        :      75*10^-6/bar


Timetable

       Time     Solv.B   Flow  Pressure
    |--------|-------|--------|-------|
         0.00    18.0    12.000
         0.50    18.0    12.000
        11.00    40.0    18.000
        11.50   100.0    18.000
        12.50   100.0    18.000
        13.00    18.0    18.000
```

^{1}H NMR of compound 3.25 (MeOD-d4, 500 MHz)

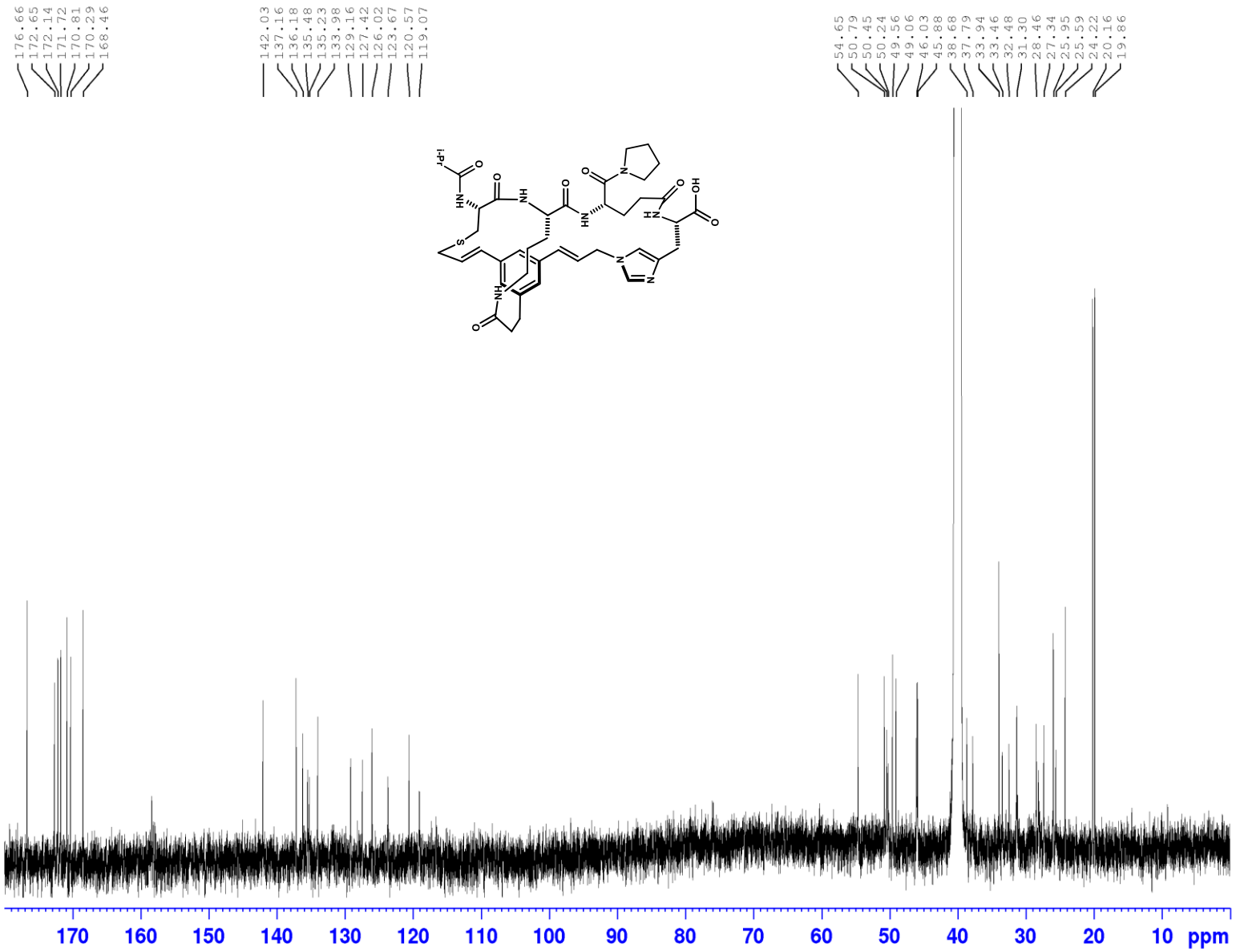


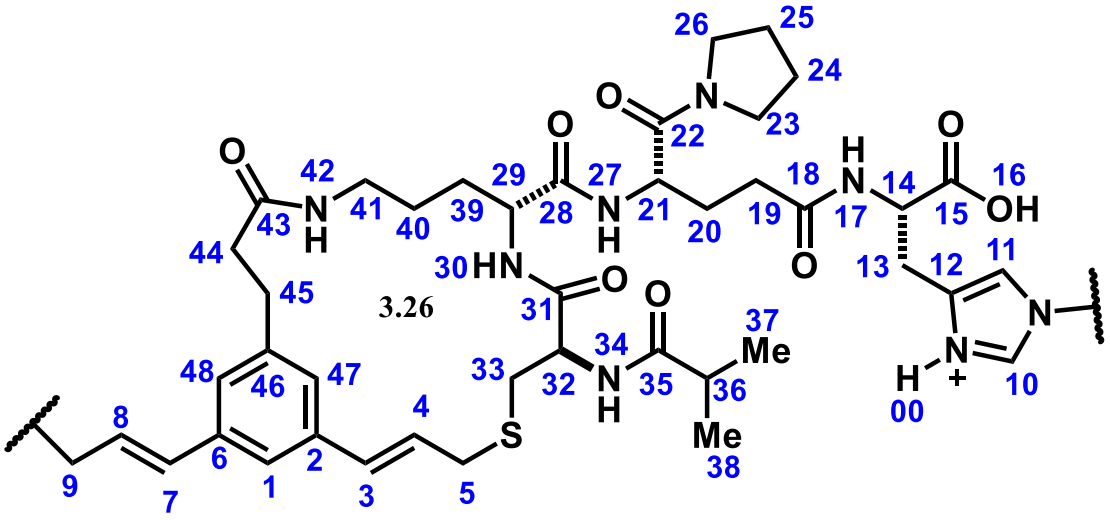

^{13}C NMR of compound 3.25 (MeOD-d4, 125 MHz)
18.33
18.67
19.47
23.67
25.35
25.57
27.69
28.60
29.67
29.91
30.80
31.33
34.61
37.45
38.20
41.99
45.88
46.25
50.42
52.70
53.05
53.45
64.70
67.82
73.70
117.08
122.85
123.08
123.61
125.94
125.99
130.70
133.24
133.45
133.75
136.79
136.94
141.70
155.36
170.20
171.24
171.74
172.44
172.83
173.34
173.83
178.82
ppm
20
40
60
80
100
120
140
160
180
OCO2 i-Bu
OCO2 i-Bu
HN
N
OH
O
NH
O
NH
O
HN
N
O
O
NH
O
HN
i-Pr
O
S t-Bu

^{1}H NMR of macrcocycle 3.26 (DMSO-d6, 600 MHz)



^{13}C NMR of macrcocycle 3.26 (DMSO-d6, 150 MHz)



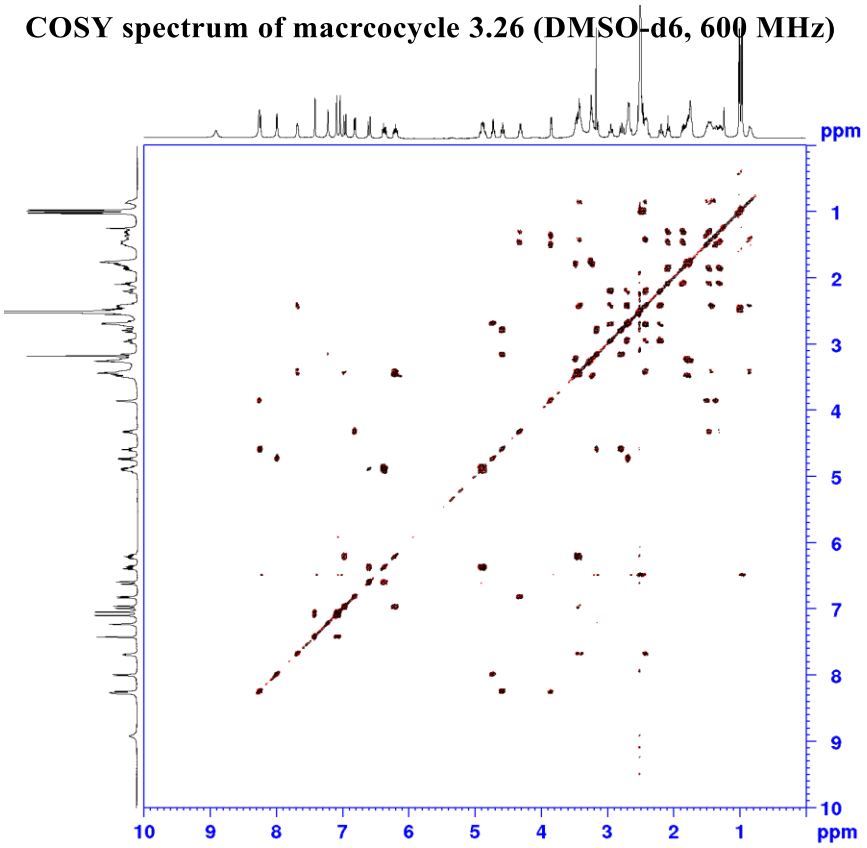


	13C	*1H*	*Corr.*
00		13.2 (br, 1H) (overlap w/16)	
1	120.6	7.41 (s, 1H)	key
2	136.4	na	4->2 HMBC/HSQC
3	133.9	6.96 (d, J = 15.6 Hz, 1H)	1->3 HMBC/HSQC
4	125.4	6.20 (dt, J = 15.6, 5.6 Hz, 1H)	Cosy 3->4
5	31.7	3.44 (m, 2H overlap with 23)	Cosy 4->5 3->5 HMBC/HSQC
6	136.2	na	8->6 HMBC/HSQC
7	135.5	6.60 (d, J = 15.7 Hz 1H	1->7 HMBC/HSQC 48->7 HMBC/HSQC
8	123.7	6.37 (dt, J = 15.7 , 6.6 Hz, 1H)	Cosy 7->8
9	49.1	4.94-4.81 (m, 2H)	Cosy 8->9 7->9 HMBC/HSQC
10	135.3	8.91 (br, 1H)	9->10 HMBC/HSQC 9->10 Noesy
11	119.1	7.22 (s, 1H)	9->11 HMBC/HSQC
12	142.0		
13	27.4	3.16, 2.76 (m, 2H)	11->13 NOESY 14->13 HMBC/HSQC 14->13 COSY
14	49.6	4.58 (m,1H)	15->14 HMBC/HSQC
15	176.6	na	Key

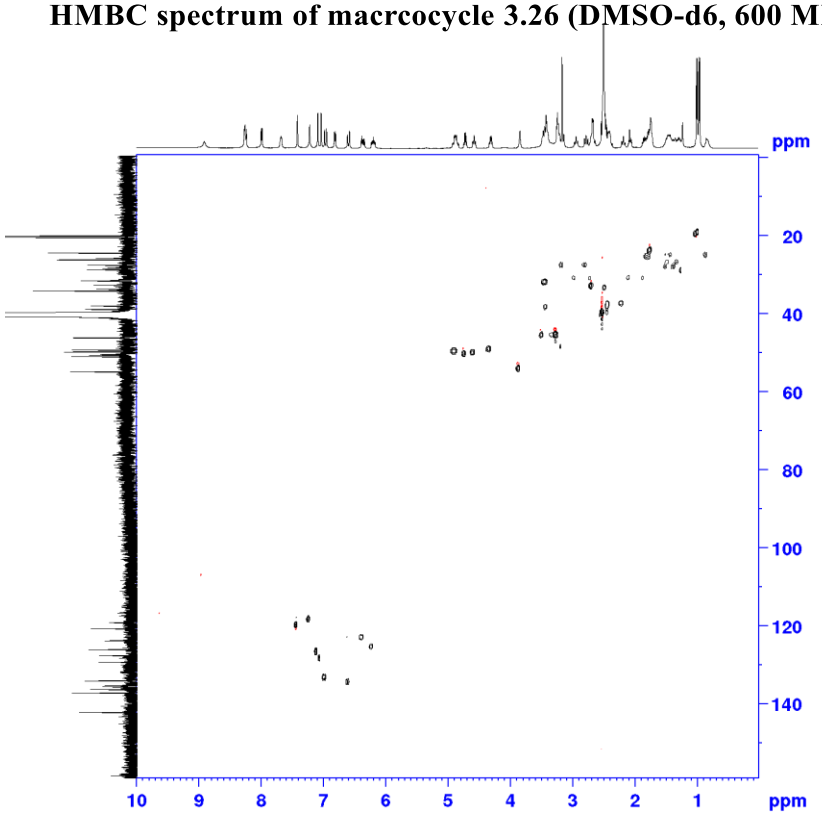
16		13.2 (br, 1H)	
17	na	7.99 (d, J = 7.8, 1H)	Cosy 14->17
18	171.7	na	20->18 HMBC/HSQC
19	31.3	2.09,1.86 (m, 2H)	COSY 20->19 NOSEY 21->19
20	26.0	1.45, 1.30 (m, 2H)	COSY 21->20 NOSEY 21->20
21	50.4	4.31 (q, J = 7.8 Hz, 1H)	NOSey 23/26->21
22	172.6		
23	46.0	3.48 (m, 2H)	COSY 24->23 24->23 HMBC/HSQC
24	23.6	1.74 (m, 2H)	key
25	25.6	1.79 (m, 2H)	key
26	45.9	3.22 (m, 2H)	COSY 25->26 25->26 HMBC/HSQC
27	na	6.81 (d, J = 8.3 Hz)	COSY 21->27
28	168.5		
29	54.6	3.85 (q, J = 4.5 Hz, 1H)	
30	na	8.25 (d, J = 12.5 Hz ,1H)	COSY 29->30
31	170.8		
32	50.8	4.72 (q, J = 7.6, 1H)	
33	32.5	2.68 (m, 2H)	Cosy 32->33 NOESY 5->33
34	na	8.26 (d, J = 7.4, 1H)	COSY32->34
35	170.3		
36	33.5	2.47 (m, 1H)	
37	19.9	0.96 (d, J = 6. 8 Hz, 3H)	key
38	20.2	1.00 (d, J = 6.8 Hz, 3H)	Key
39	27.3	1.49, 1.36 (m, 2H, overlap w/ 20)	COSY 29->39 NOSEY 29->39
40	24.2	0.83,1.41 (m ,2H)	COSY 39->40
41	38.3	3.43-3.38 (m, 2H	COSY 40->41 MHBC.HSQC 39->41
42	na	7.70 (m, 1H)	COSY 41->43

43	172.1		
44	37.2	2.41, 2.21 (m, 2H)	
45	31.4	2.95, 2.78 (m, 2H)	HMBC/HSQC 48/47->45
46	142.0		
47	127.4	7.03 (s, 1H)	Cosy 1->47 HMBC/HSQC 3->47
48	126.0	7.09 (s, 1H	Cosy 1->48 HMBC/HSQC 47->28

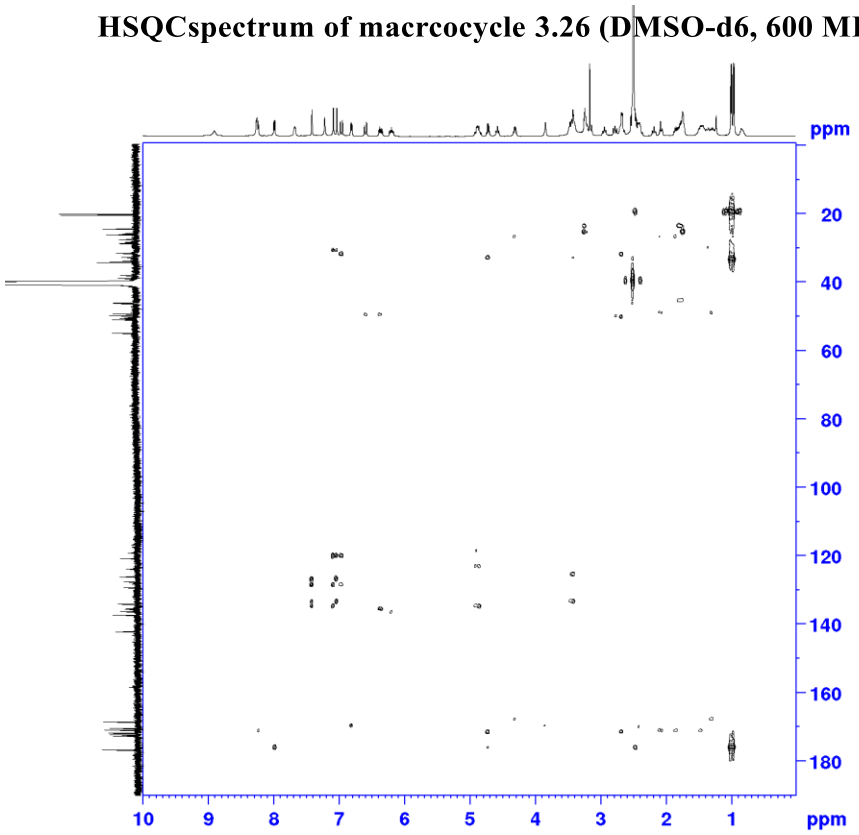
COSY spectrum of macrcocycle 3.26 (DMSO-d6, 600 MHz)



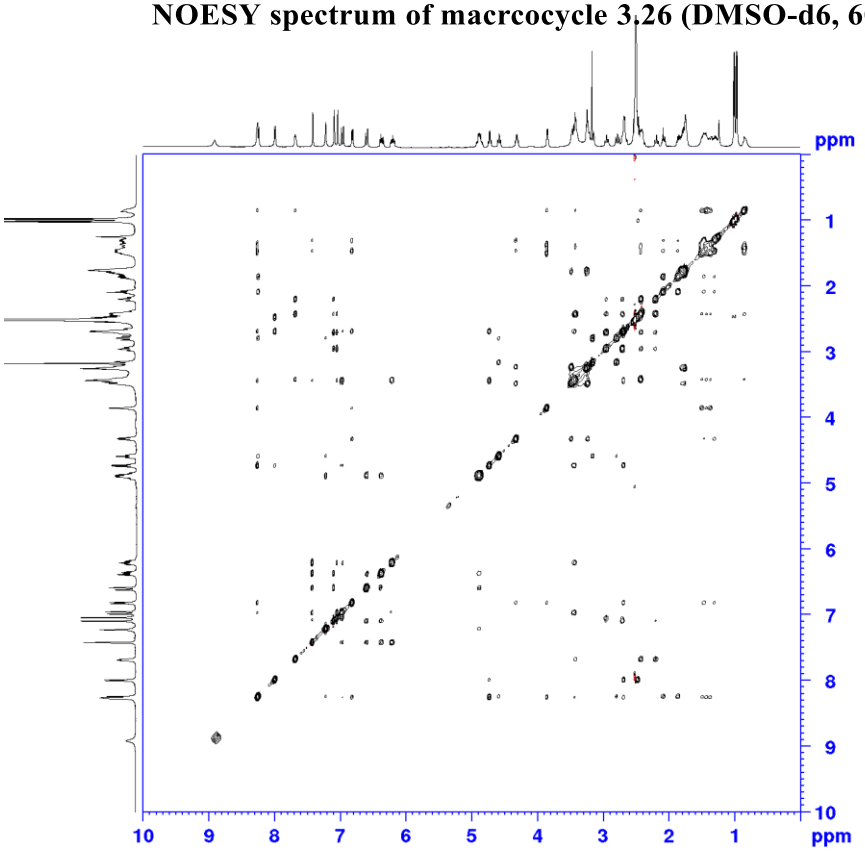
HMBC spectrum of macrcocycle 3.26 (DMSO-d6, 600 MHz)



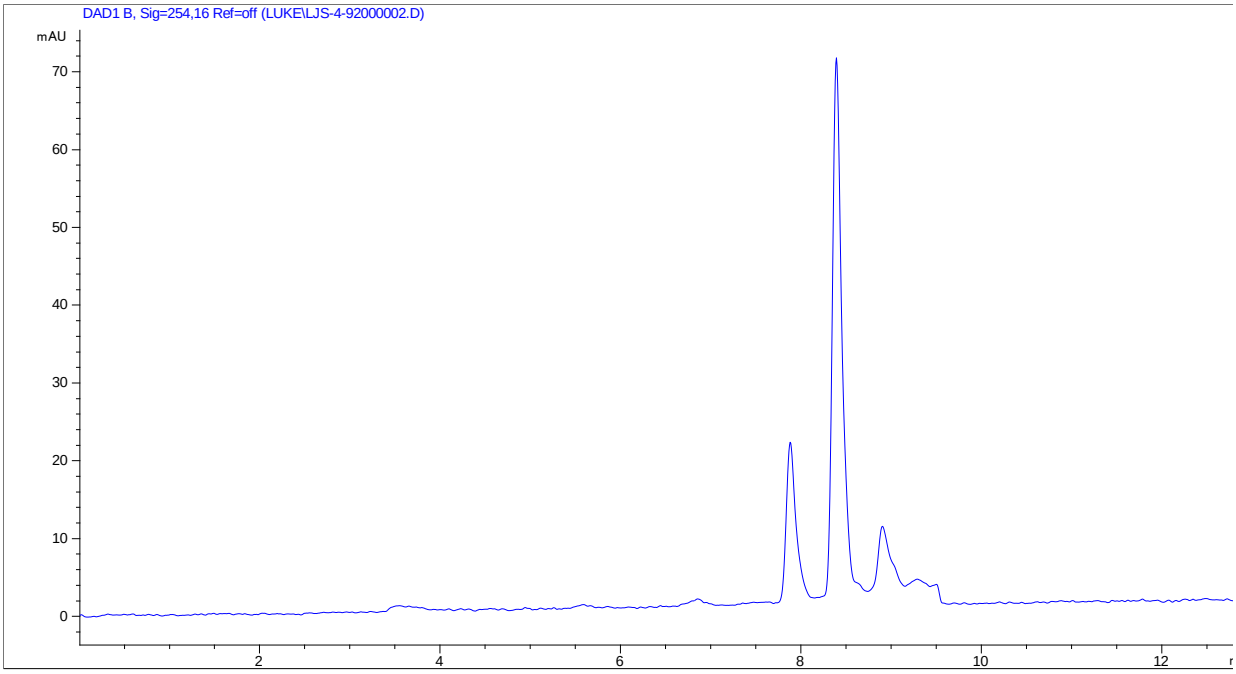
HSQCspectrum of macrcocycle 3.26 (DMSO-d6, 600 MHz)



NOESY spectrum of macrcocycle 3.26 (DMSO-d6, 600 MHz)



3.26 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Control

Column Flow	:	12.000 ml/min
Stoptime	:	13.00 min
Posttime	:	0.50 min

Solvents

Solvent A	:	80.0 % (Water)
Solvent B	:	20.0 % (Organic)

Auxiliary

Flow Ramp	:	800.000 ml/min^2
Compressibility	:	75*10^-6/bar

Timetable

Time	Solv.B	Flow	Pressure
0.00	20.0	12.000	
0.50	20.0	12.000	
11.00	45.0	18.000	
11.50	100.0	18.000	
12.50	100.0	18.000	
13.00	30.0	18.000	

C *Chapter Four- Appendix material*

Polysulfide macrocycles and synthetic progress towards a trithiocane natural product

Table of contense

Chapter 4 Experimental Procedures

General Methods.

Unless stated otherwise, reactions were performed in flame-dried glassware under positive pressure of argon at room temperature. Solvents were dried on activated alumina solvent drying system. Nitromethane was dried by storing for 24 hours over neutral Brockmann I Alumina before being filtered onto to activated 3 angstrom molecular sieves for extended storage. DMF was distilled over CaH_2 onto activated 3 angstrom molecular sieves for extended storage. Thin layer chromatography (TLC) was performed on pre-coated plates Sorbent Technologies, silica gel 60 PF254 (0.25 mm). TLC was visualized with UV light (254 nm) and stained using $KMnO_4$. Flash chromatography was performed on silica gel 60 (240-400 mesh). 1D NMR spectra for peptidal substrates were recorded on a Bruker Avance (500 MHz) spectrometer using MeOH-*d*4 or DMSO-*d*6 as solvent and referenced relative to residual MeOH (δ= 3.31 ppm), $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants (*J*) in Hertz. ^{13}C NMR spectra were recorded on the same instruments (125 MHz) with total proton decoupling referenced relative to residual MeOH-*d*4 (δ = 49.00 ppm) or DMSO (δ = 39.52 ppm). HSQC, HMBC, COSY and NOESY NMR experiments were used to aid assignment of NMR peaks when required. 2D NMR experiments were recorded on a Bruker Avance (600 MHz). High-resolution mass spectra were recorded on Thermo Scientific Exactive® Mass Spectrometer with DART IDCUBE, Waters GST Premier, and Waters LCT Premier. All HPLC traces are shown at 254 nm and depict preparative purifcation of macrocycles on a SunFire® C18 OBD 5 um 19 x 250 mm column using an Agilent 1100/1200 Series HPLC.

General Procedure A - Peptide Synthesis:

All peptides were synthesized by 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.[1]

General Procedure B - Acylation of Organic-Soluble Peptides with Templates:

Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **3** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the reaction was diluted with EtOAc, washed thrice with saturated NH_4Cl and once with brine. The organic phase was then dried over $MgSO_4$, concentrated under reduced pressure. The resulting compound was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent gradient.

General Procedure C - Acylation of Water-Soluble Peptides with Templates:

Peptide TFA salts (1.0 equiv.) were dissolved in DMF to afford a 0.2 M solution before addition of a stir bar and Template **X** as NHS ester (1.1 equiv.). Addition of iPr_2NEt (5.0 equiv.) was followed by stirring at room temperature for 2 hours. After this time the solvent was removed via roto evaporator and the residue dissolved in 2 ml of DMSO, passed through a 0.5 micron filter and purified via preparative HPLC. (procedure used to prepare sequences containing His and Glu residues)

General Procedure D - Synthesis Trisulfide Linear Precursor:

A dimeric cystine containing peptide was synthesized and capped with template **3** as described above. This dimeric disulfide was dissolved in DMF to afford a 0.1 M solution before the addition of TCEP (2.2 equiv.) and iPr_2NEt (8.8 equiv.). After 1 hour the reaction was diluted with EtOAc, washed thrice with saturated $NaHCO_3$ and once with brine before drying over $MgSO_4$. Solvent was removed under reduced pressure. The resultant thiol was directly dissolved in DMF to afford a 0.05 M solution and tertbutyl-phthalimido disulfide (**31**,1.5 equiv.) was added. The reaction was capped with a septum and backfilled thrice with argon. The reaction was heated to 55˚C and stirred under argon for 2 hours before dilution with EtOAc. The organic phase was washed thrice with saturated NH_4Cl and once with brine. The organic phase was then dried over $MgSO_4$, concentrated under reduced pressure. The resulting compound was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent.

General Procedure E - Peptide Macrocyclization with Template 3:

A scintillation vial was charged with a stir bar and template capped peptide (1.0 equiv.) before being capped with a septum and backfilled thrice with argon. Nitromethane (as described in the materials section) was added to the substrate to afford a concentration of 5.26 mM before 5 volume % TFA was added, bringing the final molarity to 5.00 mM. After the addition of TFA the reaction was stirred for 15 minutes before the solvent was removed under reduced pressure. Crude product was purified via standard phase silica gel chromatography using a $CHCl_3$: MeOH based eluent or preparative HPLC depending on the polarity of the resultant macrocycle.

Linear Precursor 4.16:
Synthesized according to general procedure **D**, obtained in 57% isolated yield over four steps from Boc protected dimer.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.30-7.26 (m, 5H), 7.25-7.19 (m, 3H), 7.13 (dt, J = 6.7, 1.6 Hz, 1H), 6.64 (d, J = 16.0 Hz, 1H), 6.31 (dt, J = 16.0, 6.3 Hz, 1H), 4.70 (dd, J = 9.3, 5.3 Hz, 1H), 4.67 (dd, J = 6.3, 1.4 Hz, 2H), 4.39 (m, 2H), 4.28 (q, J = 7.3 Hz, 2H), 4.21 (d, J = 4.2 Hz, 1H), 4.12-4.05 (m, 1H), 3.42 (dd, J = 13.9, 5.3 Hz, 1H), 3.18 (dd, J = 14.0, 9.3 Hz, 1H), 2.92 (t, J = 7.8 Hz, 2H), 2.61 (t, J = 8.3 Hz, 2H), 1.47 (s, 9H), 1.38 (d, J = 7.3 Hz, 3H), 1.35 (s, 9H), 1.04 (d, J = 6.4 Hz, 1H);
^{13}C NMR (MeOH-d_4,126) MHz δ 174.4, 173.6, 171.8, 170.6, 153.6, 141.1, 138.1, 136.5, 133.7, 128.4, 128.1, 127.9, 127.1, 126.8, 126.3, 124.3, 122.9, 81.5, 67.0, 66.9, 59.0, 52.8, 49.9, 42.7, 39.4, 37.0, 31.1, 28.8, 26.6, 18.5, 16.1.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{38}H_{54}N_4O_8S_3H$ 791.32; found 791.2

Macrocycle 4.18:
Synthesized according to general procedure **E,** obtained in 29% yield from **4.16**.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.81 (t, J = 5.6 Hz, 8.65 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 7.0 Hz, 1H), 7.36 (d, J = 8.2 Hz, 1H), 7.33-7.25 (m, 4H), 7.35-7.12 (m, 2H), 7.07-7.00 (m, 2H), 6.57 (d, J = 15.7 Hz, 1H), 6.13 (dt, J = 15.7 Hz, 6.0 Hz, 1H), 4.86 (d, J = 4.9 Hz, 1H), 4.66-4.57 (m, 1H), 4.43-4.35 (m, 1H), 4.35-4.28 (m, 2H), 4.17-4.10 (m, 1H), 4.02 (dd, J = 9.1, 2.2 Hz, 1H), 3.48 (dd, J = 13.5, 9.6 Hz, 1H), 3.27 (dd, J = 13.5, 5.8 Hz, 1H), 3.08-2.93 (m, 2H), 2.75 (dd, J = 14.9, 8.4 Hz, 1H), 2.62 (dd, J = 13.7, 10.0 Hz, 1H), 1.17 (d, J = 6.6, 3H), 0.99 (d, J = 6.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) 172.3, 172.0, 170.2, 169.9, 141.8, 139.5, 136.9, 133.8, 128.6, 127.6, 127.3, 126.2, 124.4, 121.9, 66.6, 59.2, 52.1, 42.5, 32.7, 32.2, 30.4, 29.0, 20.9, 20.3 HRMS-ESI (m/z): [M+H] calcd. For $C_{29}H_{36}N_4O_5SH$ 553.24847; found 553.24782.

Macrocycle 4.19:
Synthesized according to general procedure **E,** obtained in 57% yield from **4.16**.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.58 (t, J = 6.9 Hz, 1H), 8.39 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.4 Hz, 1H), 7.30-7.16 (m, 7H), 7.08 (d, J = 7.5 Hz, 1H), 6.57 (d, J = 15.6 Hz, 1H), 6.24 (dt, J = 15.6, 7.6 Hz, 1H), 4.64 (dd, J = 15.2, 7.4 Hz, 1H), 4.38 (p, J = 7.0 Hz, 1H), 4.30 (dd, J = 15.3, 6.1 Hz, 1H), 4.23 (dd, J = 15.3, 6.1 Hz, 1H), 4.11-4.01 (m, 2H), 3.75 (dd, J = 8.0, 2.4 Hz, 2H), 3.29 (dd, J = 13.5, 7.0 Hz, 1H), 3.15 (dd, J = 13.8, 7.3 Hz, 1H), 3.05-2.96 (m, 1H), 2.84-2.75 (m, 1H), 2.75-2.67 (m, 1H), 2.44 (m, obscured, 1H) 1.20 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.2 Hz, 3H) ^{13}C NMR (126 MHz, DMSO) 172.6, 172.4, 170.5, 169.6, 142.1, 139.5, 136.8, 134.6, 128.71, 128.65, 128.4, 127.7, 127.5, 127.2, 124.6, 123.6, 66.5, 59.2, 59.2, 52.9, 48.5, 42.6, 41.6, 41.4, 36.25, 36.3, 30.9, 20.5, 19.1.; HRMS-ESI (m/z): [M+H] calcd. For $C_{29}H_{36}N_4O_5S_3H$ 617.1926; found 617.19192.

Macrocycle 4.20:
Synthesized according to general procedure **E.**
HRMS-ESI (m/z): [M+H] calcd. For $C_{29}H_{36}N_4O_5S_3H$ 681.1366756; found 681.1355.

Linear Precursor 4.21:
Synthesized according to general procedure **D**, obtained in 58% isolated yield over three steps from template capped dimer (3 steps). ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.35-7.05 (m, 8H), 7.02 (d, J = 6.5 Hz, 1H), 6.61 (d, J = 15.8 Hz, 1H), 6.28 (dt, J = 15.8, 5.7 Hz, 1H), 5.30-5.22 (m, 1H), 4.71-4.62 (m, 2H), 4.43-4.31 (m, 1H), 3.73-3.47 (m, 8H), 3.28 (dd, J = 12.6, 5.8 Hz, 1H), 3.11 (d, J = 14.0 Hz, 1H), 3.05 (dd, J = 14.0, 6.0 Hz, 1H), 2.90-2.82 (m, 1H), 2.81-2.72 (m, 2H), 2.50-2.40 (m, 2H), 1.46 (s, 9H), 1.35 (m, 9H), 1.31 (d, J = 7.0 Hz, 3H); ^{13}C NMR (MeOH-d_4,126 MHz δ) δ 175.0 (d), 174.0, 173.3, 170.0, 155.0. 138.4, 137.8, 135.1, 130.3, 129.8, 129.5, 129.1 128.2, 127.8, 127.7, 125.6, 124.2, 82.9, 68.4, 67.8, 67.7, 61.5, 55.7, 50.3, 50.1, 47.5, 43.9, 41.3, 39.0, 38.5, 38.1, 32.6, 30.3, 28.1, 18.4.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{66}N_4O_8S_3H$ 817.33; found 817.2.

Linear Precursor 4.34:
Synthesized according to general procedure **B**, obtained in 74% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.26-7.13 (m, 9H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.3 Hz, 1H), 4.91 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 2H), 4.62 (dd, *J* = 9.4, 5.0 Hz, 1H), 4.33 (d, *J* = 7.1 Hz, 1H), 3.74-3.49 (m, 8H), 3.11 (dd, *J* = 14.0, 5.1 Hz, 1H), 2.95 (dd, *J* = 12.7, 8.4 Hz, 1H), 2.84 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.76 (dt, *J* = 8.8, 6.1 Hz, 3H), 2.44 (td, *J* = 7.5, 3.5 Hz, 2H), 1.47 (s, 9H), 1.30 (m, 12H); ^{13}C NMR (MeOH-d_4,126 MHz δ) δ175.1, 174.0, 173.5, 170.6, 142.6, 138.4, 137.8, 135.1, 130.3, 129.8, 129.4, 129.1, 127.7, 127.7, 125.6, 124.2, 82.9, 68.4, 67.8, 67.7, 55.8, 50.5, 50.3, 47.6, 43.9, 43.4, 38.8, 38.5, 32.6, 31.3, 31.1, 28.0, 18.1.; LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{56}N_4O_8SH$ 753.39; found 753.4

Macrocycle S4.22:
Synthesized according to general procedure **E**, obtained in 75% isolated yield from **4 .34**.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.86 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.30-7.23 (m, 2H), 7.22-7.13 (m, 4H), 7.02-6.93 (m, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.82 (td, *J* = 9.8, 3.7 Hz, 1H), 4.33 (td, *J* = 10.1, 3.9 Hz, 1H), 4.26 (p, *J* = 6.7 Hz, 1H), 3.61 (dd, *J* = 16.2, 6.6 Hz, 3H), 3.45 (m, 5H), 3.33 – 3.26 (m, 2H), 3.04 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.93 (t, *J* = 12.8 Hz, 1H), 2.79 (m, 2H), 2.71-2.61 (m, 2H), 2.37 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.31-2.22 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 171.2 , 171.1, 170.3, 167.5, 141.3, 137.8, 136.4, 133.3, 129.1, 128.2, 126.4, 126.2, 124.2, 121.4, 66.3, 66.1, 54.8, 47.8, 47.4, 45.5, 42.22, 37.8, 33.0, 32.7, 29.8, 28.25, 19.6.; HRMS-ESI (m/z): HRMS-ESI (m/z): [M+H] calcd. for $C_{31}H_{38}N_4O_5SH$ 579.26357; found 579.26441.

Macrocycle 4.22:
Synthesized according to general procedure **E**, obtained in 22% yield from **4.16**.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.86 (d, *J* = 8.7 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.30-7.23 (m, 2H), 7.22 – 7.13 (m, 4H), 7.02-6.93 (m, 2H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.13 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.82 (td, *J* = 9.8, 3.7 Hz, 1H), 4.33 (td, *J* = 10.1, 3.9 Hz, 1H), 4.26 (p, *J* = 6.7 Hz, 1H), 3.61 (dd, *J* = 16.2, 6.6 Hz, 3H), 3.45 (m, 5H), 3.33-3.26 (m, 2H), 3.04 (dd, *J* = 13.8, 3.8 Hz, 1H), 2.93 (t, *J* = 12.8 Hz, 1H), 2.79 (m, 2H), 2.71- 2.61 (m, 2H), 2.37 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.31-2.22 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ 171.2 , 171.1, 170.3, 167.5, 141.3, 137.8, 136.4, 133.3, 129.1, 128.2, 126.4, 126.2, 124.2, 121.4, 66.3, 66.1, 54.8, 47.8, 47.4, 45.5, 42.22, 37.8, 33.0, 32.7, 29.8, 28.25, 19.6.; HRMS-ESI (m/z): [M+H] calcd. For $C_{31}H_{38}N_4O_5SH$ 579.2642; found 579.2655.

Macrocycle 4.23:
Synthesized according to general procedure **E**, obtained in 43% yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.68 (d, J = 8.6 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.1 Hz, 1H), 7.30-7.15 (m, 6H), 7.06 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 15.6 Hz, 1H), 6.26 (dt, J = 15.6, 7.7 Hz, 1H), 5.02 (dd, J = 15.1, 7.1 Hz, 1H), 4.44-4.38 (m, 1H), 4.37-4.31 (m, 1), 3.82 (dd, J = 12.8, 7.2, 1H), 3.73 (dd, J = 13.0, 7.7 Hz, 1H), 3.62-3.47 (m, 4H), 3.46-3.38 (m, 2H), 3.30 (dd, J = 13.4, 7.3 Hz, 1H), 3.17 (dd, J = 13.4, 6.1 Hz, 1H), 3.07 (dd, J = 13.9, 3.9 Hz, 1H), 3.02-2.93 (m, 1H), 2.77 (dd, J = 13.8, 10.3 Hz, 1H), 2.74-2.67 (m, 1H), 2.30-2.20 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 126MHz) δ172.1, 172.0, 171.0, 167.9, 142.1, 138.4, 136.8, 134.7, 129.6, 128.7, 128.6, 128.4, 127.3, 126.7, 124.7, 123.6, 66.5, 55.1, 48.9, 48.5 45.9, 42.7, 42.6, 41.1, 38.0, 36.2, 31.2, 30.5, 19.3.; HRMS-ESI (m/z): [M+Na] calcd. For $C_{31}H_{38}N_4O_5S_3Na$ 665.19020; found 665.18756.

Macrocycle 4.24:
Synthesized according to general procedure **E.**
HRMS-ESI (m/z): [M+] calcd. For $C_{31}H_{38}N_4O_5S_5$ 706.144581; found 706.14144

Linear Precursor 4.25:
Synthesized according to general procedure **D**, obtained in 37% isolated yield over four steps from Boc protected dimer.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.37-7.18 (m , 8H), 7.12-7.08 (m, 1H), 6.63 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.3 Hz, 1H), 5.13-5.03 (m, 2H), 4.66 (dd, J = 6.3, 1.3 Hz, 2H), 4.29-4.22 (m, 1H), 4.15-4.06 (m, 1H), 3.56 (t, J = 6.9 Hz, 2H), 3.03-2.98 (m ,2H), 2.93-2.80 (m, 3H), 2.60-2.49 (m, 2H), 2.46 (t, J = 8.3 Hz, 2H), 2.30-2.18 (m, 3H), 2.09- 1.95 (m, 2H), 1.94-1.84 (m, 1H), 1.46 (s, 9H), 1.41 (s, 3H), 1.39 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (MeOH-d_4,126 MHz) δ176.1, 175.6, 174.2, 173.0, 172.8, 172.5, 153.6, 141.2, 136.5, 136.1, 133.7, 131.1, 129.9, 129.0, 128.5, 128.1, 127.82, 127.77, 126.9, 126.4, 124.3, 123.0, 81.5, 67.0, 66.0, 56.6, 54.2, 53.3, 38.1, 37.0, 36.8, 31.0, 30.3, 28.9, 26.7, 26.6, 26.1, 24.3, 24.1.; LC-MS-ESI (m/z): [M+Na] calcd. for $C_{44}H_{63}N_5O_{10}S_3Na$ 940.36; found 939.9.

Macrocycle 4.26:
Synthesized according to general procedure **E**, obtained in 24% yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.26 (s, 1H), 8.01 (d, J = 6.3 Hz, 1H), 7.70 (t, J = 5.6 Hz, 1H) 7.61 (d, J = 8.1 Hz, 1H), 7.36-7.25 (m, 6H), 7.20 (d, J = 7.7 Hz, 1H), 7.17 (s, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.74 (s, 1H), 6.51 (d, J = 15.7 Hz, 1H), 6.11 (dt, J = 15.7, 7.2 Hz, 1H), 5.03 (s, 2H), 4.23-4.15 (m, 1H), 4.04 (dd, J = 13.3, 6.3 Hz, 1H), 3.24 (dd, J = 13.8, 6.8 Hz, 1H), 3.18-3.10 (m, 1H), 2.90-2.81 (m, 1H), 2.77-2.66 (m, 1H), 2.45-2.27 (m, 4H), 2.15-2.08 (m, 1H), 2.01-1.87 (m, 2H), 1.85-1.75 (m, 2H), 1.61-1.51 (m, 1H), 1.32 (s, 1H), 1.29 (s, 3H), 1.27-1.24 (m, 1H), 1.22 (s, 3H), 1.21-1.18 (m,1H) ^{13}C NMR (DMSO-d_6, 126MHz) δ 174.3, 174.2, 172.9, 172.6, 172.4, 171.4, 141.7, 137.0, 136.7, 133.0, 128.9, 128.4, 128.4, 127.3, 125.8, 123.3, 65.8, 56.5, 53.8, 52.3, 35.0, 33.3, 31.9, 30.6, 30.3, 28.3, 27.6, 25.8, 25.4.; HRMS-ESI (m/z): [M+H] calcd. For $C_{35}H_{45}N_5O_7SH$ 680.3118; found 680.3097.

Macrocycle 4.27:
Synthesized according to general procedure **E**, obtained in 42% yield.
^{1}H NMR (DMSO-d_6, 500 MHz) δ 8.35 (s, 1H) 8.09 (d, J = 5.0 Hz , 1H) 7.69 (t, J = 4.9 Hz, 1H) 7.64 (d, J = 8.2, 1H) 7.34 (s, 1H) 7.32-7.25 (m, 5H) 7.22 (s, 1H) 7.20-7.11 (m, 2H) 7.03 (d, J = 7.2 Hz, 1H) 6.75 (s, 1H) 6.53 (d, J = 15.7 Hz, 1H)n 6.23-6.14 (m, 1H) 5.01 (s, 2H) 4.16-4.08 (m, 1H) 3.86-3.79 (m, 1H) 3.66 (d, J = 7.6 Hz, 2H) 3.53-3.43 (m, 1H) 3.06-

2.94 (m, 2H) 2.82-2.69 (m, 2H) 2.42 (t, J = 7.7 Hz, 2H) 2.15-2.06 (m, 1H) 1.99 (t, J = 7.6 Hz, 2H) 1.97-1.91 (m, 1H) 1.79-1.63 (m, 2H) 1.35-1.29 (m, 1H)1.28 (d, J = 13.8 Hz, 6H) 1.21-1.18 (m, 1H) ^{13}C NMR (DMSO-d_6, 126MHz) δ 174.5, 174.1, 172.9, 172.7, 171.6, 142.0, 136.8, 136.6, 134.1, 128.83, 128.78, 128.39,128.31, 128.26, 127.0, 125.2, 124.9, 65.9, 56.6, 54.7, 52.8, 41.0, 38.4, 36.4, 31.7, 30.6, 30.5, 27.2, 27.0, 25.7, 25.5.; HRMS-ESI (m/z): [M+H] calcd. For $C_{35}H_{45}N_5O_7S_3H$ 744.2559; found 744.2584.

Macrocycle 4.28:
Synthesized according to general procedure **E.** [M+H] calcd. For $C_{35}H_{45}N_5O_7S_5H$ 808.2057; found 808.2029.

Linear Precursor 4.29:
Synthesized according to general procedure **D**, obtained in 77% isolated yield.
^{1}H NMR at least two rotamers present (MeOH-d_4, 500 MHz δ = 7.36-7.07 (m, 9H), 6.63 (d, J= 15.9, 1H), 6.30 (dt, J= 15.9, 6.3 Hz, 1H), 4.70-4.65 (m, 2H), 4.61-4.56 (m, 1H), 4.43-4.36 (m, 3H), 4.06-3.98 (m, 1H), 3.75-3.59 (m, 2H) 3.43 (dd, J= 13.9, 5.3 Hz, 1H), 3.32-3.26 (m, 2H), 3.17 (dd, J= 13.9, 9.3 Hz, 1H), 2.90 (t, J= 7.6 Hz, 1H), 2.58 (t, J= 7.6 Hz, 1H), 2.25-2.08 (m, 1H), 1.97-1.86 (m, 2H), 1.46 (s, 9H), 1.36 (s, 9H) (^{13}C NMR (126 MHz, MeOH-d_4) δ.173.7, 172.9, 170.6, 170.6, 153.6, 141.1, 138.1, 136.5, 134.0, 128.4, 128.1, 128.0, 127.1, 127.1, 126.8, 124.3, 122.9, 122.7, 81.5, 67.0, 66.9, 60.8, 56.4, 52.8, 52.8, 48.4, 42.8, 39.2, 36.7,31.0, 29.0, 28.8, 26.7, 24.7, 18.2 LC-MS-ESI (m/z): [M+H] calcd. for $C_{40}H_{56}N_4O_8S_3$ 817.33; found 817.5.

Macrocycle 4.30:
Synthesized according to general procedure **E**, obtained in 44% isolated yield.
^{1}H NMR two rotamers present (DMSO-d_6, 500 MHz) δ 8.53-8.34 (m, 1H), 8.32-8.17 (m, 1H), 7.32-7.07 (m, 7H) 7.06-6.96 (m, 1H), 6.63-6.41 (m, 1H), 6.40-5.94 (m, 1H), 4.68-4.53 (m, 1H), 4.49-4.35 (m, 1H) 4.34-4.14 (m, 3H), 3.98-3.63 (m, 2H), 3.61-3.15 (m, 3H), 2.85-2.72 (m, 1H), 2.69-2.50 (m, 2H), 2.41-2.15 (m, 2H), 2.13-1.91 (m, 2H), 1.87-1.70 *m, 2H), 1.70-1.55 (m, 1H), 1.42-0.60 (m, 6H) ^{13}C NMR (DMSO-d_6, 126MHz) δ172.5, 171.8, 170.7, 168.7, 142.3, 139.7, 137.5, 133.7, 128.7, 127.5, 127.4, 127.2, 126.0, 125.2, 123.6, 123.2, 67.0 60.8, 59.0, 55.8, 53.2,47.7, 42.5, 35.7, 34.8, 34.1, 30.5, 29.4, 25.7, 24.1, 19.8 HRMS-ESI (m/z): [M+] calcd. for $C_{31}H_{38}N_4O_5S$, 578.26: found 578.8

Macrocycle 4.31:
Synthesized according to general procedure **D**, obtained in 27% isolated yield.
^{1}H NMR two rotamers present (DMSO-d_6, 500 MHz) δ 8.66-8.43 (m ,1H), 8.36-8.20 (m, 1H), 8.02-7.89 (m, 1H), 7.40-7.14 (m, 8H), 7.09-7.00 (m, 1H), 6.67 (d, J= 15.7 Hz, 1H), 6.54-6.38 (m, 1H), 4.77-4.55 (m, 1H), 4.52-4.45 (m, 1H), 4.39-4.4.32 (m, 1H), 4.29-4.23 (m, 2H), 4.13-4.03 (m, 1H), 3.91-3.78 (m, 2H), 3.76-3.64 (m, 2H), 3.49-3.28 (m, 2H), 3.18-3.11 (m, 1H), 3.05-2.96 (m, 1H), 2.81-2.66 (m, 2H), 2.65-2.57 (m, 1H), 2.06-1.99 (m, 1H), 1.76-1.59 (m, 3 H), 1.13-0.68 (m, 3H) ^{13}C NMR (DMSO-d_6, 126MHz) 172.0, 170.3, 169.5, 169.0, 142.1, 139.4, 139.4, 137.1, 128.7, 128.7, 127.7, 127.5, 127.4, 126.3, 125.7, 125.3, 124.8, 117.3, 60.2, 55.8, 52.9, 47.5, 42.6, 42.0, 35.1, 31.9, 31.2, 30.0, 25.3, 22.2, 21.2, 19.8, 14.6 HRMS-ESI (m/z): [M+H] calcd. for calcd. for for $C_{31}H_{38}N_4O_5S_3$, 643.21; found 643.6

Macrocycle 4.31:
HRMS-ESI (m/z): [M+H] calcd. For $C_{31}H_{38}N_4O_5S_5$ 707.152406; found 707.1528

Linear Precursor 4.33:
Synthesized according to general procedure **E**, obtained in 34% isolated yield.
^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.92-7.85 (m, 1H), 7.48 (d, J= 7.9 Hz, 1H), 7.31 (d, J =8.2 Hz, 1H), 7.26-7.03 (m, 6H), 7.02-6.92 (m, 1H), 6.60 (d, J= 15.9 Hz, 1H), 6.26 (dt, J= 15.9, 6.3 Hz, 1H), 4.81-4.70 (m, 2H), 4.65 (dd, J= 6.3, 1.1 Hz, 2H), 4.17-4.13 (m, 1H), 3.61 (s, 3H), 3.36-3.18 (m, 4H), 3.12-3.03 (m, 1H), 2.95-2.81 (m, 2H), 2.63-2.47 (m, 2H), 1.91 (sept, J= 6.9 Hz, 1H), 1.46 (s, 9H), 1.33 (s, 9H), 0.77 (d, J= 6.8 Hz, 6H). ^{13}C NMR (126 MHz, MeOH-d_4) δ 173.9, 172.3, 172.1, 170.4, 153.6, 141.1, 136.6, 136.5, 133.8, 131.1, 128.4, 127.9, 127.3, 126.4, 124.3, 123.2, 122.8, 121.1, 118.5, 111.0, 109.0, 81.5, 67.1, 53.5, 52.1, 51.4, 39.8, 37.1, 31.3, 30.5, 30.5, 28.9, 27.1, 26.7, 18.4, 17.3 MS-ESI (m/z): [M+H] calcd. For $C_{42}H_{58}N_4O_8S_3$ 844.13; found 844.5

Scheme 4.7: Experimental procedures

4.38:
To a round bottom flask equipped with stir bar was added**, 4.37** (6.56 g , 27.5 mmol, 1.0 eq), K_2CO_3 (7.60 g, 55 mmol, 2.0 eq.), and 410 ml of dry MeOH, cooled to 0°*C*. Ohira-Bestman reagent (6.34, 33 mmol, 1.2 eq.) was added dropwise and the reaction was warmed to room temperature overnight. After 16deoxygenated the reaction was diluted with water (500ml) and the mixture was washed with hexanes thrice (300 ml). The organic layes were combined, washed with brine and dried over $MgSO_4$. Product was purified bycolumn chromatography (100% Hex->90% Hex: 10% Et_2O) to furnish 5.65 g of 4.38 diyne product as a clear oil in 88% yield. The reaction could be scaled to 73 mmol scale with a slightly diminished yield (~75%). Product on this scale could be adequately purified by a short silica plug and pure

hexane eluent. *Rf* = 0.65, Hexane **4.38** ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 2.50-2.45 (m, 2H), 2.44-2.38 (m, 2H), 1.98 (t, J= 2.5 Hz, 1H), 1.09-1.01 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 106.6, 82.7, 81.6, 69.2, 20.0, 19.1, 18.6, 11.2, ; HRMS (m/z): [M+] calcd. for $C_{15}H_{26}Si$ 234.18038; found 234.17983

4.38
4.38 was synthesized according to our published procedure.[6]

4.39
4.39 was synthesized according to our published procedure.[7]

4.40:
In a dram vial equipped with stir bar **4.38** (117 mg, 0.5 mmol, 3.0 eq.) and $Rh_2(OAc)_4$ (0.7 mg, 10 μmol, 2 mol%) were dissolved 0.4 ml of DCM. A Solution of ethyl diazopyruvate (23 mg, 0.16 mmol, 1.0 eq.) in DCM was added over of 30 minutes. After that time the reaction was filtered through a pad of celite and the pad washed with DCM. The collected solvent was removed *in vacuo* and the residue was purified bycolumn chromatography (95:5 ->70:10 Hex:EtOAc). 16 mg of **4.40** was isolated pure as a light yellow oil, for a 29% yield **4.40** *Rf* = 0.24, Hexane:EtOAc 9:1 ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.39 (q, J= 1.4 Hz, 1H), 4.27 (q, J= 7.1, 2H), 2.84 (d, J= 1.4, 1H), 2.83-2.70 (m, 2H), 2.60-2.51 (m, 2H), 1.34 (t, J= 7.1 Hz, 3H), 1.11-0.95 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 198.5, 163.4, 113.7, 106.3, 94.2, 81.8, 61.8, 26.7, 25.3, 18.6, 17.8, 14.1, 11.2; HRMS (m/z): [M+H] calcd. For $C_{20}H_{32}O_3Si$, 349.21935; found 349.22900

4:41:
A Flame dried 100ml flask equipped with stir bar was charged with **4.38** product (4.66 g, 19.9 mmol, 2.5 eq.) and $Rh_2(OAc)_4$ (8.2 mg, 0.5 mol%), followed by 19.2 ml of DCM. Ethyl diazoacetate (1.09 g, 7.69 mmol, 1.0 eq.) was dissolved in 29.5 ml of DCM and this solution was added bysyringe pump to **4.38** over 8 hours. After this time the reaction passed through a pad of celite and the collected solvent was removed *in vacuo*. This residue was resolved in 153 ml of EtOH and cooled to -78°*C*. $NaBH_4$ (290 mg, 7.69 mmol, 1.0 eq) was added portion-wise over 10 minutes followed by additional stirring for 10 minutes. After completion by TLC, the reaction was poured into 500 ml of cold EtOAc and washed with cold NH_4Cl (150ml) thrice, $NaHCO_3$ once (150ml). Aqueous layer was back extracted twice with 100 ml of EtOAc and the combined organic layers were washed with brine (300 ml). The organic layers were then dried over $MgSO_4$ and the solvent removed in vacuo . This residue was purified by column chromatography (9:1->7:1->5:1->4:1) to furnish 1.2 g of **4.41** as a light yellow oil in 45% yield. **4.41** *Rf* = 0.32, Hexane:EtOAc 4:1 ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.69-6.59 (m, 1H), 4.30-4.20 (m, 2H), 3.98-3.89 (m, 1H) 2.84 (d, J= 1.4, 1H), 2.85-2.65 (m, 2H), 2.56-2.51 (m, 2H), 2.51-2.48 (m, 1H) 1.81-1.80 (m, 1H), 1.34-1.26 (m, 3H) 1.08-0.96 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 175.1, 175.0, 122.4, 121.9, 107.5, 107.4, 102. 1, 101.6, 81.2, 81.1, 74.4, 74.1, 61.3, 61.3, 26.1, 25.9, 22.7, 22.6, 18.6, 18.1, 18.0, 14.3, 14.3, 11.2.; HRMS (m/z): [M+] calcd. for $C_{20}H_{34}O_3Si$, 351.23500 found 351.23501.

4.42:
To a flame dried flask with activated 3A molecular sieves, stir bar, and reflux condenser was added 10 ml of dry DCM, followed by **4.41** (701 mg, 2.0 mmol, 1.0 eq). The reaction was cooled to 0°*C*, and iPr_2NEt (1.08 ml, 6.0 mmol, 3.0 eq.) was added dropwise, followed by MOMBr (0.325 ml, 4.0 mmol, 2.0 eq.). The reaction was warmed to 42°C for 3 h or until complete by TLC. 0.5 ml of cold saturated $NaHCO_3$ was added and the reaction was stirred a further 20 minutes. After this time the reaction was poured into a separatory funnel with 50 ml of EtOAc and extract thrice with saturated $NHCl_4$, once with $NaHCO_3$, and twice with brine. The organic layers were then dried over $MgSO_4$ and solvent was removed in vacuo. This residue was purified by silica gel column chromatography (15:1->6:1 Hexane:EtOAc) to afford 562 mg of **4.42** as an light yellow oil for 71% yield. *Rf* = 0.50, Hexane:EtOAc 7:1 **4.42** ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.71;6.64(s, 1H), 4.75-4.63 (m, 2H) 4.23-4.15 (m, 2H), 3.89:3.82 (d, J= 4.7, 1H), 3.40-3.35 (m, 3H), 2.84 (d, J= 1.4, 1H), 2.83-2.65 (m, 2H), 2.56-2.51 (m, 2H), 2.57-2.49 (m, 1H) 1.88-1.84 (m, 1H), 1.34-1.26 (m, 3H) 1.10-0.95 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 172.1, 172.1, 122.3, 121.9, 107.4, 107.4, 102. 3, 101.7, 95.7, 95.7, 81.1, 80.2, 60.6, 60.6, 55.8, 55.7, 26.1, 25.9, 20.8,18.6, 18.0, 18.0, 14.3, 14.3, 11.2.; HRMS (m/z): [M+] calcd. For $C_{22}H_{38}O_4Si$, 347.27647; found 347.25452.

4.43
4.41 product (317 mg, 0.9 mmol, 1.0 eq.) was dissolved in 15 ml of dry DCM. This volume was added to a two-neck flask with stir bar, reflux condenser and activated 3A molecular sieve powder. The flask was cooled to 0°*C* and dry iPr_2NEt (0.234 ml, 1.35 mmol, 1.5 eq.) was added by syringe, followed the dropwise addition of SEMCl (0.223 ml, 1.26 mmol, 1.4 eq.). The reaction was warmed to 42°*C* for 12 h or until complete by TLC. 3 ml of cold saturated $NaHCO_3$ was added and the reaction was stirred a further 30 minutes. After this time the reaction was poured into a separatory funnel with 50 ml of EtOAc and extract thrice with saturated $NHCl_4$, once with $NaHCO_3$, and twice with brine. The organic layers were then dried over $MgSO_4$ and solvent was removed in vacuo. This residue was purified by silica gel column chromatography (15:1->8:1 Hexane:EtOAc) to afford 184 mg of **4.43** as an light yellow oil for 85% yield *Rf* =

0.36, Hexane: EtOAc 9:1 **4.43** ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.75 (s, 0.5H) 6.68 (s, 0.5H) 4.84-4.78 (m, 1H), 4.74- 4.70 (m, 1H), 4.27-4.18 (m, 2H), 3.97 (d, J= 4.7, 0.5H), 3.90 (d, J= 5.4, 0.5H), 3.91-3.60 (m, 2H), 2.86-2.74 (m, 2H), 2.60-2.49 (m, 2H), 1.89 (d, J= 5.0 Hz, 1H), 1.35-1.29 (m, 3H), 1.10-1.04 (m, 21H), 0.05 (s, 9H). ^{13}C NMR ($CDCl_3$,125 MHz) δ 172.2, 122.3, 121.8, 107.4, 107.4, 102.9, 101.7, 93.8, 93.8, 81.0, 81.0, 80.7, 79.9, 65.6, 65.5, 60.6, 60.5, 34.7, 31.6, 26.1, 26.0, 26.0, 20.9, 18.6, 18.1, 18.0, 14.3, 14.3, 11.2, -1.4. MS-ESI (m/z): [M+] calcd$C_{26}H_{48}O_4Si_2$, 480.31; found 480.6.

4.44:

4.41 (1.02 g, 2.9 mmol, 1.0 eq.) and DMAP (71 mg, 0.58 mmol, 0.2 eq.) were added to a flame dried flask equipped with stir bar, dissolved in 32.2 ml of DCM and cooled to 0°*C*. Dry iPr_2NEt (2.6 ml, 14.5 mmol, 5.0 eq.) and AcCl(0.413 ml, 5.8, 2.0 eq.) were then added. After 40 minutes the solvent was removed in vacuo and residue was by silica gel column chromatography (10:1->5:1 Hexane:EtOAc) to afford 626 mg of **4.44** as a yellow oil for 55% yield *Rf* = 0.61, Hexane: EtOAc, 6:1^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.68 (s, 0.5H), 6.64 (s, 0.5H), 4.68 (d, J= 4.8 Hz, 0.5H), 5.59 (d, J= 5.6 Hz, 0.5H), 4.27-4.14 (m, 2H), 2.81-2.66 (m, 2H), 2.57-2.50 (m, 2H), 2.18-2.11 (m, 3H), 1.88 (d, J= 5.4 Hz, 1H), 1.30-1.22 (m, 3H), 1.09-0.99 (m, 21H). ^{13}C NMR ($CDCl_3$,125 MHz) δ 170.6, 170.5, 169.9, 121.9, 121.1, 107.2, 107.1, 102.1, 101.3, 81.2, 81.1, 78.6, 77.8, 61.0, 61.0, 25.9, 25.7, 20.8, 19.3, 19.1, 18.6, 18.0, 17.9, 14.2, 11.2 MS-ESI (m/z): [M+H] calcd. $C_{22}H_{36}O_4Si$, 393.24 found 393.4

Scheme 4.8: Experimental procedures

4.45

A flame dried flask with stir bar was charged with solid CuI (1.70 g, 8.9 mmol, 2.0 eq.) and backfilled with argon thrice. The flask was charged with 34 ml of dry THF, followed by freshly distilled TMEDA (1.45 ml, 9.8 mmol, 2.2 eq.) before stirring at room temperature for 30 minutes. After this time the reaction was cooled to -45°*C* and MeMgBr (12.7 ml of 0.7 M in THF, 8.9 mmol, 2.0 eq.) was added. The reaction was stirred at -45°*C* for 30 minutes after Grignard addition, followed by the addition of **4.42** product (1.56 g, 4.45 mmol, 1.0 eq.) in 11.3 ml of dry DCM. After addition of substrate the reaction was stirred at -45°*C* for 30 minutes. Allyl bromide was then added (0.78 ml, 8.9 mmol, 2.0 eq.) and the reaction was warmed to -20°*C* over 30 minutes. The reaction was then quenched with 2:1 NH_4Cl:NH_4OH, diluted with 150 ml of EtOAc, washed thrice with water (120 ml), once with brine (120 ml) and dried over $MgSO_4$. The solvent was then removed in vacuo and the residue purified by silica gel column chromatography (10:1-> 7:1->5:1-.3:1 Hexane: EtOAc) to afford 1.2 g of **4.45** product was a light yellow oil in 66% yield. *Rf* = 0.45, Hexane: EtOAc, 5:1 **4.45** ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 6.00-5.74 (m, 1H), 5.16-4.87 (m, 2H), 4.33-4.16 (m ,2H), 3.90-3.81 (m, 0.6H), 3.71 (dd, J= 10.2, 6.0 Hz, 0.4H), 2.79 (d, J= 6.0 Hz, 0.4H), 2.65 (d, J= 5.2 Hz, 0.3H), 2.61 (d, J= 6.0 Hz, 0.3H), 2.53-2.24 (m, 3H), 2.16-2.00 (m, 2H), 1.90-1.75 (m, 1H), 1.35-1.28 (m, 3H), 1.20-0.91 (m, 24H), 0.90-0.81 (m, 1H), 0.60- 0.52 (m, 1H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 175.3, 174.9, 137.8, 137.8, 144.9, 114.7, 109.2,109.1, 80.1, 80.0, 71.4, 70.4, 61.6, 36.3, 35.5, 35.5, 33.1, 33.0, 29.3, 28.8, 27.7, 27.6, 24.9, 24.2, 18.6, 18.5, 17.5, 17.3, 14.2,14.2, 11.3 MS-ESI (m/z): [M+H] calcd. $C_{24}H_{42}O_3Si$ 407.29760 found 407.29744.

4.46

4.45 product (407 mg, 1.0 mmol, 1.0 eq.), acetanisole (14.9 mg, 0.01 mmol, 0.1 eq.) and 2,2-dimethoxy-2-phemylacetophenone (25.2 mg, 0.1 mmol, 0.1 eq.) were placed in a vial equipped with a stir bar, These products were dissolved in 5 ml of EtOAc and the resulting solution was freezed-pumped-thawed thrice. Thioacetic acid (0.22 ml, 3.24 mmol, 4.0 eq.) was added and the reaction was placed in a Rayonet photoreactor and irradiated with 350 nm UV light over 1 hour. After this time the solvent was removed in vacuo and the product was purified by silica gel column chromatography (8:1->7:1->6:1-> 4.1-> 3:1, Hexane: EtOAc) to furnish 362 mg of **4.45** as a foul smelling yellow gel in 75% yield. . *Rf* = 0.63, Hexane: EtOAc, 4:1 **4.46** ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 4.33-4.17 (m, 2H),3.83 (d, J= 9.1 Hz, 0.6H), 3.72 (m, J= 10.2 Hz, 0.4 H), 2.91 (t, J= 7.4 Hz, 1H), 2.88-2.75 (m, 1H), 2.50-2.38 (m, 1H), 2.31 (s, 3H), 2.34-2.25 (m, 1H), 1.89-1.74 (m, 1H), 1.72-1.63 (m, 1H), 1.63- 1.53 (m, 2H), 1.53-1.46 (m, 1H), 1.46-1.37 (m, 1H), 1.34-1.26 (m, 4H), 1.19-0.96 (m, 24H), 0.84-.0.72 (m, 1H), 0.57- 0.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz),: δ 196.1, 195.8, 175.3, 174.9, 109.2, 109.1, 80.2,80.0, 71.5, 70.5, 61.7, 61.6, 36.2, 36.2, 35.8, 35.4, 30.7, 30.6, 29.8, 29.7, 29.0, 28.8, 28.1, 28.0, 28.0, 27.9,24.7, 24.1, 18.7, 18.5, 18.5, 17.5, 17.4, 14.3, 14.2, 11.3, 11.3 MS-ESI (m/z): [M+H] calcd. for $C_{26}H_{46}O_4SSi$ 483.29; found 483.6.

4.47

A flame dried flask with stir bar was charged with solid CuI (299 mg, 1.57 mmol, 2.0 eq.) and backfilled with argon thrice. The flask was charged with 6 ml of dry THF, followed by freshly distilled TMEDA (0.26 ml, 1.72 mmol, 2.2 eq.) before stirring at room temperature for 30 minutes. After this time the reaction was cooled to -45°*C* and MeMgBr (2.24

ml of 0.7 M in THF, 1.57 mmol, 2.0 eq.) was added. The reaction was stirred at -45°*C* for 30 minutes after Grignard addition, followed by the addition of **4.42** product (310 mg, 0.78 mmol, 1.0 eq.) in 2ml of dry DCM. After addition of substrate the reaction was stirred at -45°*C* for 30 minutes. Allyl bromide was then added (0.24 ml, 2.73 mmol, 3.5 eq.) and the reaction was warmed to -20°*C* over 30 minutes. The reaction was then quenched with 2:1 NH_4Cl:NH_4OH, diluted with 40 ml of EtOAc, washed thrice with water (20 ml), once with brine (20 ml) and dried over $MgSO_4$. The solvent was then removed in vacuo and the residue purified by silica gel column chromatography (15:1-> 10:1->7:1-.5:1 Hexane: EtOAc) to afford 278 mg of **4.47** product was a clear oil in 79% yield. *Rf* = 0.66, Hexane: EtOAc, 5:1
4.47 ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 5.94;-5.68(m, 1H), 5.27-4.90 (m, 2H), 4.80-4.57 (m, 2H) 4.30-4.09 (m, 2H), 3.81-3.65(m, 1H), 3.47-3.34 (m, 3H), 2.49-2.36 (m, 1H), 2.35-2.21 (m, 1H), 2.19-1.93 (m, 2H), 1.91-1.72 (m, 1H), 1.54-1.42 (m, 1H), 1.33-1.26 (m, 3H), 1.11-0.96 (m, 24), 0.92-0.69 (m, 2H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ172.4, 137.8, 137.6, 114.9, 114.8, 108.9, 95.9, 95.6, 60.9, 56.3, 55.9, 36.4, 35.5, 33.9, 33.3, 33.0, 28.6, 27.3, 24.7, 24.5, 18.6, 14.2, 14.1, 11.3 . HRMS (m/z): [M+H] C26H46O4Si calcd. for 451.32382; found 451.32352.

4.48
4.47 product (362 mg, 0.81 mmol, 1.0 eq.), acetanisole (12 mg, 0.081 mmol, 0.1 eq.) and 2,2-dimethoxy-2-phemylacetophenone (20.6 mg, 0.081 mmol, 0.1 eq.) were placed in a vial equipped with a stir bar. These products were dissolved in 5 ml of EtOAc and the resulting solution was freezed-pumped-thawed thrice. Thioacetic acid (0.22 ml, 3.24 mmol, 4.0 eq.) was added and the reaction was placed in a Rayonet photoreactor and irradiated with 350 nm UV light over 1hour. After this time the solvent was removed in vacuo and the product was purified by silica gel column chromatography (10->8:1->7:1->6:1-> 5.1-> 4:1, Hexane: EtOAc) to furnish 335 mg of **4.48** as a foul smelling yellow oil in 79% yield. *Rf* = 0.29, Hexane: EtOAc, 5:1
4.48 ^{1}H NMR ($CDCl_3$, 500 MHz,): δ 4.70-4.60 (m, 2H), 4.28-4.13 (m, 2H), 3.73 (d, J= 9.5 Hz, 0.6H), 3.67 (d, J= 9.4 Hz, 0.4H), 3.38 (s, 3H), 2.94-2.86 (m, 1H), 2.83 (t, J= 7.2 Hz, 1H), 2.46-2.38 (m, 1H), 2.31 (s, 3H), 2.29-2.23 (m, 1H), 1.92-1.73 (m, 2H), 1.55-1.32 (m, 2H), 1.31-1.25 (m, 3H), 1.12-0.97 (m, 24H), 0.75-0.62 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz),: δ 195.9, 195.8, 172.4, 172.4, 172.3, 108.9, 108.9, 95.9, 95.7, 80.2, 80. 2, 76.5, 75.8, 60.9, 60.9, 56.3, 56.0, 36.3, 35.4, 33.7, 30.6, 30.6, 29.7, 29.7, 28.9, 28.9, 28.9, 28.1, 27.9, 27.6, 24.5, 24.5, 18.6, 18.6, 18.5, 18.4, 17.6, 17.6, 14.3, 14.1, 11.3, 11.3. MS-ESI (m/z): [M+H] calcd. $C_{28}H_{50}O_5Ssi$, 527.31; found 527.5.

4.49 product (small scale)
4.48 product (38 mg, 0.07 mmol, 1.0 eq.) was dissolved in 1.4 ml of deoxygenated EtOH and cooled to 0°*C*. A 0.25 M stock solution of LiOH is EtOH (0.84 ml, 0.21 mmol, 3.0 eq.) was added. After 25 minutes TLC indicated consumption of starting material and 0.15 M stock solution of AcOH was added (0.14 ml, 0.21 mmol, 3.0 eq.) *Tert*-butyl phthalimido disulfide (47 mg, 0.175 mmol, 2.5 eq.) the reaction allowed to warm to room temperature over 30 minutes before the solvent was removed in vacuo. This mixture was purified by silica gel column chromatography (15->10:1->9:1->7.5:1-> 6.1-> 5:1, Hexane: EtOAc) to furnish 21.6 mg of **4.49** as a yellow oil in 51 % yield.

4.49 product (large scale)
4.48 product (229 mg, 0.435 mmol, 1.0 eq.) was dissolved in 8.8 ml of deoxygenated EtOH and cooled to 0°*C*. Sodium Methanethiolate (91 mg, 1.305 mmol, 3.0 eq.) was added. After 10 minutes TLC indicated consumption of starting material and AcOH was added (75 µl, 1.305 mmol, 3.0 eq.). The solvent was removed in vacuo and the residue was palce on a vacuum pump for an hour. After this time the residue was dissolved in 8.8 ml of MeOH, cooled to 0°*C* and *Tert*-butyl phthalimido disulfide (233 mg, 0.87 mmol, 2.0 eq.) was added. The reaction was warmed to room temperature over 30 minutes before the solvent was removed in vacuo. This mixture was purified by silica gel column chromatography (15->10:1->9:1->7.5:1-> 6.1-> 5:1, Hexane: EtOAc) to furnish 110.5 mg of **4.49** as a yellow oil in 42 % yield. *Rf* = 0.45, Hexane: EtOAc, 6:1
4.49 ^{1}H NMR ($CDCl_3$, 500 MHz,): 4.73-4.63 (m, 2H), 4.27-4.12 (m, 2H), 3.75 (d, J= 9.6 Hz, 0.4H), 3.68 (d, J= 9.6 Hz, 0.6H) , 3.38 (s, 3H), 3.00-2.86 (m, 1H), 2.83 (t, J= 7.2, 1H), 2.48-2.36 (m, 1H), 2.35-2.24 (m ,1H), 1.90-1.71 (m, 3H), 1.55-1.45 (m, 1H), 1.38 (s, 9H), 1.33-1.27 (m, 3H), 1.12-0.97 (m, 24H), 0.79-0.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz),: δ 172.4, 172.3, 109.0, 108.9, 95.9, 95.7, 80.2, 80.2, 76.5, 75.8, 61.0, 60.9, 56.3, 56.0, 48.9, 48.9, 38.8, 38.8, 36.4, 35.5, 34.2, 33.8, 29.9, 29.1, 29.0, 28.9, 27.8, 27.7, 27.6, 24.7, 24.5, 18.7, 18.6, 18.6, 17.6, 17.6, 14.3,14.2, 11.3, 11.3 MS-ESI (m/z): [M+H] calcd. $C_{30}H_{56}O_4S_3Si$, 605.31; found 605.4.

Side Product 1
^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.54 (dd, J= 15.2, 11.6 Hz, 1H), 6.03 (d, J= 11.6 Hz, 1H), 5.77 (d, J= 15.2 Hz, 1H), 4.19 (q, J= 7.13 Hz, 2H), 2.47-2.40 (m, 2H), 2.37-2.31 (m, 2H), 1.89 (d, J= 0.88 Hz, 3H), 1.28 (t, J= 7.1 Hz, 3H), 1.07-0.99 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,) δ 167.6, 147.3, 140.6, 124.4, 119.6, 107.4, 81.3, 60.1, 39.2, 18.6, 18.6, 17.0, 14.3, 11.2. MS-ESI (m/z): [M+H] calcd. $C_{21}H_{36}O_2Si$, 349.25; found 349.5

Table 4.4: Successful experimental procedures.

Table 4.4: Entry 1 (4.50)

4.46 product (0.335 mg, 0.694 mmol, 1.0 eq.) was dissolved in 14 ml of deoxygenated EtOH and cooled to 0°*C*. Sodium methanethiolate (146 mg, 2.08 mmol, 3.0 eq.) was added. After 10 minutes TLC indicated consumption of starting material and AcOH was added (119 µl, 2.08 mmol ,3.0 eq.). The solvent was removed in vacuo and the residue was placed on a vacuum pump for an hour. After this time the residue was dissolved in 14 ml of MeOH, cooled to 0°*C* and *Tert*-butyl phthalimido disulfide (371 mg, 1.39 mmol, 2.0 eq.) was added the reaction allowed to warm to room temperature over 30 minutes before the solvent was removed in vacuo. This mixture was purified by silica gel column chromatography (2%->2.5%->3.3%->%5 acetone in toluene) to furnish 223 mg of **4.50** as a yellow gel in 62 % yield. *Rf* = 0.45, Hexane: EtOAc, 6:1

4.50 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 4.33-4.18 (m, 2H), 3.88-3.80 (m, 0.6H) 3.73 (dd, J= 10.0, 5.9 Hz, 0.4H), 2.93 (t, J= 7.1 Hz, 1H), 2.90-2.82 (m, 1H), 2.80-2.65 (m, 1H), 2.57-2.40 (m, 1H), 2.36- (m, 1H), 1.92-1.75 (m, 3H), 1.38 (s, 9H), 1.34-1.29 (m, 3H), 1.11-1.00 (m, 24H), 0.85-0.74 (m, 1H), 0.61-0.49 (m, 1H), ^{13}C NMR ($CDCl_3$, 125 MHz),: δ175.3, 175.0, 109.2, 109.1, 80.1, 80.0, 71.5, 70.5, 61.8, 61.7, 48.9, 48.9, 38.9, 38.7, 36.3, 35.8, 35.5, 29.9, 28.9, 28.2, 28.1, 27.5, 24.7, 24.2, 18.7, 18.5, 17.5, 17.4, 14.4, 14.2, 11.3, 11.3. MS-ESI (m/z): [M+H] calcd. $C_{28}H_{52}O_3S_3Si$, 560.28; Found 560.5.

Table 4.4: Entry 4 (4.52)

4.46 product (257 mg, 0.548 mmol, 1.0 eq.) was dissolved in 11 ml of deoxygenated EtOH and cooled to 0°*C*. Sodium Methanethiolate (115 mg, 1.64 mmol, 3.0 eq.) was added. After 10 minutes TLC indicated consumption of starting material and AcOH was added (94 µl, 1.64 mmol, 3.0 eq.). The solvent was removed in vacuo and the residue was placed on a vacuum pump for an hour. After this time the residue was dissolved in 11 ml of MeOH, cooled to 0°C and paramethoxybenzylphthalimidodisulfide (271 mg, 0.82 mmol, 1.5 eq.) was added. The reaction allowed to warm to room temperature over 30 minutes before the solvent was removed in vacuo. This mixture was purified by silica gel column chromatography (2%->2.5%->3.3%->%5 acetone in toluene) to furnish 198 mg of **4.52** as a yellow gel in 59 % yield. *Rf* = 0.42, Hexane: EtOAc, 8:1

4.52 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.25-7.20 (m, 2H), 6.90-6.82 (m, 2H), 4.31-4.20 (m, 2H) 4.06-4.02 (m, 1H) 3.80 (s, 3H), 2.88 (t, J= 7.1 Hz, 1H), 2.81 (t, J= 7.3, 1H), 2.54-2.35 (m, 2H), 2.34-2.20 (m, 2H), 1.98-1.70 9m, 4H), 1.50-1.39 (m, 2H), 1.34-1.22 (m, 3H), 1.19-0.94 (m, 24H), 0.82-0.73 (m, 1H), 0.57-0.43 (m, 1H). NMR ($CDCl_3$, 125 MHz),: δ 175.3, 175.0, 130.7, 130.6, 130.6, 130.4, 128.6, 128.6, 114.0, 114.0, 109.1, 109.1, 80.2, 80.1, 61.8, 61.7, 55.3, 42.5, 38.5, 38.3, 36.3, 36.2,35.8, 35.5, 31.6, 28.9, 28.1, 28.0, 27.7, 27.6, 18.7, 18.7, 18.6, 17.5, 17.4, 14.3, 11.3, 11.3. MS-ESI (m/z): [M+H] calcd. $C_{32}H_{52}O_4S_2Si$, 593.3; found 593.4.

Table 4.4: Entry 5A (4.55)

4.46 product (117 mg, 0.24 mmol, 1.0 eq.) was dissolved in 4.8 ml of deoxygenated EtOH (freeze-pump-thaw thrice). The reaction was cooled to 0°*C* and sodium methanethiolate (50.8 mg, 0.72 mmol, 3.0 eq.) was added. After 10 minutes AcOH was added (41.5 µl, 0.72 mmol, 3.0 eq.) and the solvent was removed in vacuo. The residue was quickly purified by silica gel column chromatography (9:1->5:1 Hexane: EtOAc) to furnish 66 mg of **4.55** as light-yellow gel. *Rf* = 0.39, Hexane: EtOAc, 5:1

4.55 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 4.33-4.17 (m, 2H),3.83 (d, J= 9.1 Hz, 0.6H), 3.73 (m, J= 10.2 Hz, 0.4 H) 2.62-2.49 (m, 2H), 2.48-2.2.25 (m, 2H), 1.93-1.73 (m, 2H), 1.73-1.61 (m, 2H), 1.59-1.35 (m, 4H), 1.35-1.26 (m, 3H), 1.18-0.95 (m, 24H), 0.82-.0.72 (m, 1H), 0.55- 0.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz),: δ 175.3, 175.0, 109.1, 109.1, 80.2, 80.1, 71.5, 70.5, 61.7, 36.3, 36.2, 35.8, 35. 5, 34.2, 34.1, 28.0, 28.0, 27.6, 27.5, 24.7, 24.5, 24.3, 24.1, 18.7, 18.6, 18.6, 18.5, 17.5, 17.4, 14.3, 14.2, 11.3, 11.3. HRMS-ESI (m/z): [M+H] calcd. $C_{26}H_{46}O_4SSi$ 482.28806 found 483.29502.

Table 4.4: Entry 5B (4.53)

4.55 product (66.4 mg, 0.15 mmol, 1.0 eq.) was dissolved in 0.75 ml of dry THF and cooled to 0°*C*. Triethylamine (42 µl, 0.30 mmol, 2.0 eq.) was added, followed by trityl sulfenyl chloride (70 mg, 0. 225 mmol, 1.5 eq.)and the reaction was warmed to room temperature over 10 minutes. After that time the reaction was quenched with water (1 ml), diluted with EtOAc (10 ml) and washed once with brine. The organic layer was dried over $MgSO_4$ and the solvent was remove in vacuo. The residue was purified by silica gel column chromatography (9:1->6:1 Hexane: EtOAc) to furnish 100 mg of **4.53** as a light yellow gel. *Rf* = 0.47, Hexane: EtOAc, 7:1 **4.53** ^{1}H NMR ($CDCl_3$, 500 MHz,) δ7.47-7.38 (m, 5H), 7.33-7.19 (m, 10H), 4.30-4.14 (m, 2H),3.77 (d, J= 8.6 Hz, 0.6H), 3.67 (m, J= 10.0 Hz, 0.4 H) 2.82-270(br, 0.6H), 2.62-2.53 (m, 0.4H), 2.51-2.34 (m, 1H), 2.30-2.16 (m, 1H)m 1.89-1.75 (m, 1H), 1.76-1.60 (m, 3H), 1.52-1.33 (m, 3H), 1.31-1.24 (m, 3H), 1.24-0.97 (m, 24H), 0.66-0,56 (m, 1H), 0.46-0.37 (m, 1H) ^{13}C NMR ($CDCl_3$, 125 MHz),: δ 175.3, 174.9, 143.9, 143.9, 130.2, 130.2, 127.8, 128.7, 126.9, 126.9, 109.2, 109.1, 80.1, 80.0, 71.5, 70.9, 70.9, 70,4, 61.7, 61.7, 54.4, 36.5, 36.4, 36.3, 36.1, 35.8, 35.5, 28.9, 28.9, 27.9, 27.5, 27.5, 24.7, 24.1, 18.7, 18.6, 18.5, 18.4, 17.5, 17.4, 11.3, 11.3 MS-ESI (m/z): [M+H] calcd. for $C_{43}H_{58}O_3S_2Si$ 441.28532 found 441.28429.

Scheme 4.9: Experimental procedure.

4.60

4.45 (150 mg, 0.369 mmol, 1.0 eq.) was dissolved in 4 ml of dry DCM and cooled to -10°*C*. NEt_3 was added (100 µl, 0.74 mmol, 2.0 eq.) followed by the dropwise addition of $MeSO_2Cl$ (60 µl, 0.74 mmol, 2.0 eq) . The reaction was stirred for 55 minutes before the solvent was removed in vacuo and the product was purified by silica gel column chromatography (20:1->15:1->10:1 Hexane: EtOAc) to furnish 99 mg of **4.60** as a clear oil in 68% yield. *Rf* = 0.55, Hexane: EtOAc, 20:1

4.60 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.98-6.80 (m, 1H), 5.88-5.62 (m, 2H), 5.40-5.32 (m, 0.4 H), 5.11-4.90 (m, 3H), 4.17 (q, J= 7.1 Hz, 2H), 3.04-2.85 (m ,2H), 2.48-2.19 (m ,4H), 1.65-1.57 (m, 1.3H), 1.28 (t, J= 7.1 Hz, 3H), 1.09-0.97 (m, 21H) ^{13}C NMR ($CDCl_3$, 125 MHz,: δ 166.6, 166.5, 150.2, 150.1, 147.1, 136.6, 135.8, 122.2, 121.4, 121.3, 116.7, 116.4, 112.0, 108.0, 106.8, 80.9, 80.1, 60.3, 60.3, 50.7, 48.2, 37.0, 36.2, 33.9, 18.6, 18.5, 14.3, 11.3. MS-ESI (m/z): [M+H] calcd. for $C_{24}H_{40}O_2Si$, 389.28; found 389.5.

Scheme 4.10: Experimental procedure.

4.61:

4.45 product (300 mg, 0.738 mmol, 1.0 eq.) was dissolved in 0.75 ml of THF and added to a stirring suspension of NaH (32 mg, 0.811 mmol, 1.1 eq.) at 0°C. This mixture was stirred at 0°*C* for 30 minutes before the addition of CS_2 (0.14 ml, 2.2 mmol, 3.0 eq.). This mixture was stirred at 0°*C* for 30 minutes before the addition of MeI (0.274 mmol, 4.4 mmol, 6.0 eq.) and further stirring for 1 hour at this temperature. The reaction was then quenched with ice and NH_4Cl (2 ml). With mixture was extracted with EtOAc (15 ml) and the organic layer was washed with brine (15 ml), dried over Na_2SO_4 before the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (20:1->15:1->10:1, Hexane: EtOAc) to furnish 297 mg of **4.61** as a yellow gel in 81 % yield. *Rf* = 0.41, Hexane: EtOAc, 20:1.

4.61 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 5.92-5.72 (m, 1H), 5.44 (d, J= 9.9 Hz, 0.4H), 5.15 (d, J= 10.7 Hz, 0.6H), 5.12-4.90 (m, 2H), 4.31- 4.13 (m, 2H), 2.58 (d, J= 2.58 Hz, 3H), 2.49-2.29 (m, 2H), 2.24-2.16 (m, 1H), 2.07-1.98 (m, 1H), 1.97-1.62 (m, 1H), 1.54-1.43 (m, 1H), 1.28 (td, J= 7.1, 1.6 Hz, 3H), 1.13-1.01 (m, 24H), 1.00-0.86 (m, 2H) NMR ($CDCl_3$, 125 MHz),: δ 215.8, 215.4, 169.1, 169.0, 137.3, 137.2, 115.1, 108.7, 108.7, 81.6, 81.1, 61.5, 61.5, 36.4, 35.4, 32.9, 32.8, 32. 5, 31.5, 28.8, 28.7, 26.0, 25.0, 19.4, 19.1, 18.6, 18.5, 18.1, 17.4, 17.4, 14.1, 14.1, 11.3, 11.3. MS-ESI (m/z): [M+H] calcd. $C_{26}H_{44}O_3S_2Si$, 497.25; found 497.6.

4.62

4.61 product (120 mg, 0.2415 mmol, 1.0 eq.), acetanisole (3.6 mg, 0.024mmol, 0.1 eq.) and 2,2-dimethoxy-2-phemylacetophenone (6 mg, 0.024 mmol, 0.1 eq.) were placed in a vial equipped with a stir bar, these products were dissolved in 1.5 ml of EtOAc and the resulting solution was freezed-pumped-thawed thrice. Thioacetic acid (0.065 ml, 0.97 mmol, 4.0 eq.) was added and the reaction was placed in a Rayonet photoreactor and irradiated with 350 nm UV light over 1 hour. After this time the solvent was removed and the product was purified by silica gel column chromatography (10->8:1->7:1->6:1-> 5.1-> 4:1, Hexane: EtOAc) to furnish 124 mg of **4.62** as a foul smelling yellow oil in 90% yield. *Rf* = 0.32, Hexane: EtOAc, 15:1.

4.62 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 5.43 (d, J= 10.0 Hz, 0.4 H), 5.14 (d, J= 10.5, Hz, 0.6H), 4.30-4.14 (m, 2H), 2.96-2.83 (m, 2H), 2.59 (s, 1.2 H), 2.58 (s, 1.8 H), 2.36-2.33 (m, 2H), 2.32 (s, 1.2H), 2.32 (m, 1.8H), 2.31-2.27 (m, 2H), 1.73-1.59 (m, 4H), 1.28 (t, J= 7.1 Hz, 3H), 1.11-1.01 (m, 24H), 0.93-0.82 (m, 2H) NMR ($CDCl_3$, 125 MHz),: δ 216.1, 215.4, 195.8, 195.7, 169.1, 168.9, 108.7, 108.6, 81.7, 81.1, 80.5, 61.5, 48.3, 36.4, 32.7, 31.7, 31.7, 30.7, 30.6, 30.4, 30.3, 29.6, 29.5, 29.3, 29.1, 28.9, 28.8, 27.8, 27.8, 24.9, 19.4, 19.3, 18.7, 18.4, 17.4, 17.4, 14.2, 14.0, 11.3, 11.3 MS-ESI (m/z): [M+H] calcd. for $C_{28}H_{48}O_4S_3Si$ 573.25; found 573.4.

Scheme 4.11: Experimental procedure.

4.64 & **4.65**:

A flame dried flask with stir bar was charged with solid CuI (143 mg, 0.75 mmol, 2.0 eq.) and backfilled with argon thrice. The flask was charged with 2.9 ml of dry THF, followed by freshly distilled TMEDA (0.125 ml, 0.83 mmol, 2.2 eq.) before stirring at room temperature for 30 minutes. After this time the reaction was cooled to -45°*C* and MeMgBr (1.0 ml of 0.75 M in THF, 0.75 mmol, 2.0 eq.) was added. The reaction was stirred at -45°*C* for 30 minutes after Grignard addition, followed by the addition of **4.42** product (310 mg, 0.78 mmol, 1.0 eq.) in 1 ml of dry DCM. After addition of substrate the reaction was stirred at -45°*C* for 30 minutes. Crotyl bromide was then added (0.14 ml, 0.376 mmol, 3.5 eq.) and the reaction wa warmed to -20°*C* over 30 minutes. The reaction was then quenched with 2:1 NH_4Cl:NH_4OH, diluted with 20 ml of EtOAc, washed thrice with water (10 ml), once with brine (10 ml) and dried over $MgSO_4$. The solvent was then removed in vacuo and the residue purified by silica gel column chromatography (15:1-> 10:1->7:1-.5:1 Hexane: EtOAc) to afford 278 mg of **4.64** and **4.65** product was a light tan oil in 65% yield. *Rf* = 0.71, Hexane: EtOAc, 5:1.

4.64 & **4.65** ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.00-5.62 (m, 1H), 5.48-5.33 (m, 1H), 5.06-4.81 (m, 1H), 4.73-4.61 (m, 2H), 4.31-4.14 (m, 2H), 3.77 (t, J= 10.0 Hz, 0.6H), 3.66 (dd, J= 10.0, 7.0 Hz, 0.4H), 3.43-3.30 (m, 3H), 2.50-2.16 (m, 3H), 2.08-1.96 (m, 1H), 1.91-1.81 (m, 1H), 1.78-1.69 (m, 1H), 1.67-1.61 (m, 1H), 1.60-1.53 (m, 1H), 1.34-1.26 (m, 3H), 1.16-0.95 (m, 23H), 0.88-0.66 (m, 2H), 0.59-0.47 (m, 1H) . ^{13}C NMR ($CDCl_3$, 125 MHz,) δ 172.4, 172.4, 172.3, 172.3, 143.1,

143.0, 130.3, 130.0, 125.4, 125.3, 112.3, 112.2, 96.0, 95.8, 95.8, 95.7, 95.5, 95.5, 80.3, 80.2, 80.1, 80.0, 76.4, 75.8, 75.5, 75.3, 60.9, 60.9, 60.9, 60.8, 56.3, 56.0, 56.0, 55.8, 37.8, 37.4, 37.2, 36.7, 36.5, 36.4, 35.8, 35.6, 35.5, 35.5, 34.3, 34.0, 33.9, 33.5, 32.0, 31.8, 29.3, 25.4, 25.4, 24.8, 24.7, 24.4, 19.8, 19.7, 19.7, 19.4, 18.6, 18.6, 18.4, 18.0, 17.9, 17.8, 17.7, 17.6, 17.6, 14.2, 14.1, 11.3, 11.3. MS-ESI (m/z): [M+H] calcd. for $C_{27}H_{48}O_4Si$ 465.33; found 465.4.

Table 4.1: Experimental procedure.
General Procedure for table 4.1 Entries 1-5
A solution of ethyl diazopyruvate (28 mg, 0.2 mmol, 1.0 eq.) in 1.25 ml of DCM was added to a stirring solution of **4.38** (117mg, 0.5 mmol, 2.5 eq.) and catalyst (0.001 mmol, 0.5 mol%) in DCM (0.4 ml) over 2 hours by syringe pump. After this time the reactions were diluted with 5 ml of DCM, passed through a plug of celite and the solvent was removed in vacuo. TLC was taken with product and starting material as standard and cospots. If product was detected, the crude residues were purified by small scale silica gel column chromatography as described for **4.40** synthesis procedure above.

Table 4.2: Experimental procedures.
All reaction are carried out in dram or scintillation vials epuipped with stir bars.

Table 4.2: Entry 1 See **4.48** preparative scale procedure above.

Table 4.2: Entry 2
4.40 (289 mg, 0.83 mmol, 1.0 eq.) was dissolved in 8.3 ml of dry THF and cooled to -78°C. 1.7ml of 1 M L-selectride solution (1.7 mmol, 2.05 eq.) was added dropwise and the reaction was stirred 10 minutes before quenching with 1.0 ml of cold acetone. The reaction was diluted with 50 ml of EtOAc. The combined organics were washed once with NH_4Cl , twice with brine followed by drying over $MgSO_4$. This residue was purified by column chromatography (9:1->7:1->5:1->4:1) to furnish 120 mg of **4.41** as a light yellow oil in 44% yield. NMR comparison with $NaBH_4$ derived alcohol revealed a D.R. of 1.5:1 opposed to 1:1.2 obtained by$NaBH_4$.

Table 4.2: Entry 3
4.40 (52 mg, 0.15 mmol, 1.0 eq) was dissolved in 1.5 ml of dry THF and cooled to -78°C. DIBAL solution (0.14 ml, 0.14 mmol, 1 M in THF, 0.93 eq) was added dropwise. After 5 minutes 2 ml of saturated NH_4Cl was added and the mixture was extracted twice with EtOAc (5 ml). The combined organic layers were washed with brine thrice (5 mL) , dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. This residue was purified by column chromatography (9:1->7:1->5:1->4:1) to furnish 25 mg of **4.41** as a light yellow oil in 39% yield. NMR comparison with $NaBH_4$ derived alcohol revealed a D.R. of 2:1 opposed to 1:1.2 obtained by$NaBH_4$.

Table 4.2: Entry 4.
4.40 (52 mg, 0.15 mmol, 1.0 eq.) was dissolved in 1.5 ml of EtOH. $NaBH(OAc)_3$ was added (64 mg, 0.30 mmol, 2.0 eq.). After stirring at room temperature for 3 hours no product was detected by TLC.

Table 4.2: Entry 5
4.40 (52 mg, 0.15 mmol, 1.0 eq.) was dissolved in 1.5 ml of dry THF and cooled to -78°C. $LiAl(Ot\text{-}Bu)_3$ (42 mg, 0.165 mmol, 1.1 eq.) in 0.3 ml of dry THF was added dropwise. The reaction was monitored byTLC and warmed to room temperature. After reacting at ambient temperature for 12 hours not product was detected on TLC.

Table 4.3: Experimental procedures.
All reaction are carried out in dram or scintillation vials epuipped with stir bars.

Table 4.3: Entry 1
4.49 product (4.4 mg, 7.3 µmols, 1.0 eq.) was dissolved in 1.15 ml of $MeNO_2$ and cooled to 0°C. 0.29 ml of TFA (20 vol%) was added and the reaction was monitored for starting material consumption. After 10 minutes the solvent was removed in vacuo. Degradation was apparent.

Table 4.3: Entry 2
4.49 product (4.3 mg, 7.1 µmols, 1.0 eq.) was dissolved in 0.7 ml of $MeNO_2$ and cooled to 0°C. 6 mg of Tf_2NH (21.3 µmols,, 3.0 eq.) was dissolved in 0.7 ml of $MeNO_2$ and added to the substrate. After 5 minutes the reaction was quenched with EtN_3. After the solvent was removed in vacuo degradation was apparent.

Table 4.3: Entry 3
4.49 product (6.1 mg, 10.1 µmols, 1.0 eq.) was dissolved in 1 ml of $PrNO_2$ and cooled to -78°*C*. 6 mg of Tf_2NH (30.2 µmols, 3.0 eq.) was dissolved in 1 ml of $MeNO_2$ and added to the substrate. After 15 minutes the reaction was quenched with $NaHCO_3$ (2 ml). After the solvent was removed in vacuo degradation was apparent.

Table 4.3: Entry 4
4.49 product (5.5 mg, 8.8 µmols, 1.0 eq.) was dissolved in 1.57 ml of $MeNO_2$ and cooled to 0°*C*. 0.175 ml of TFA (10 vol%) was added and the reaction was monitored for starting material consumption. After 10 minutes the reaction was quenched with $NaHCO_3$ (2 ml), TLC showed loss of MOM group.

Table 4.3: Entry 5
4.49 product (4.0 mg, 6.6 µmols, 1.0 eq.) was dissolved in 1 ml of $PrNO_2$ and cooled to -78°*C*. A stock solution of $MeSO_3H$ in $PrNO_2$ (25:75 vol%) was made and 0.25 ml was added to the substrate. After 5 minutes the reaction was quenched with $NaHCO_3$ (2 ml). After the solvent was removed in vacuo degradation was apparent.

Table 4.3: Entry 6
4.49 product (201 mg, 0.346 mmol, 1.0 eq.) was dissolved in 5 ml of EtOH and cooled to 0°*C*. A 3 M solution of HCl in EtOH was made with AcCl, and 4 ml was added to the substrate before warming to room temperature. After 1.5 hours the reaction was poured into a separator funnel containing 50 ml of cold saturated $NaHCO_3$. Extract the aqueous layer twice with 100 ml of EtOAc. Combined organics were extracted with saturated $NaHCO_3$ (50 ml) and twice with brine (100 ml) before drying over $MgSO_4$. This was followed by filtration, removal of solvent in vacuo and purification by silica gel column chromatography to furnish 128 mg of **4.50** in 66% yield. See **4.50** entry for characterization data.

Table 4.4: Experimental procedures.
All reaction are carried out in dram or scintillation vials epuipped with stir bars.

Table 4.4: Entry 1
See **4.50** entry for characterization data and reaction details.

Table 4.4: Entry 2
4.46 product (334 mg, 0.69 mmol, 1.0 eq.) was dissolved in 14 ml of deoxygenated EtOH and cooled to 0°*C*. Sodium Methanethiolate (97 mg, 1.83 mmol, 2.0 eq.) was added. After 10 minutes TLC indicated consumption of starting material and AcOH was added (82 µl, 1.83 mmol, 2.0 eq.). The solvent was removed in vacuo and the residue was placed on a vacuum pump for an hour. The residue was then was dissolved in 14 ml of MeOH, *Trityl* phthalimido disulfide (454 mg, 1 mmol, 1.5 eq.) was added and this solution was stirred at room temperature for 1 h. After this time the solvent was removed in vacuo and the mixture was purified by silica gel column chromatography (2%->2.5%->3.3%->%5 acetone in toluene) to furnish **4.55**, but no detectable trityl trisulfide.

Table 4.4: Entry 3
4.46 product (97 mg, 0.2 mmol, 1.0 eq.) was dissolved in 4 ml of deoxygenated EtOH and cooled to 0°C. Sodium Methanethiolate (42 mg, 0.60 mmol, 3.0 eq.) was added. After 10 minutes TLC indicated consumption of starting material and AcOH was added (34 µl, 0.6 mmol , 3.0 eq.). The solvent was removed in vacuo and the residue was placed on a vacuum pump for an hour. *Trityl* phthalimido disulfide (136 mg, 0.4 mmol, 1.5 eq.) was dissolved in 4 ml of DMF and this solution was used to dissolve the substrate mixture. The reaction was heated to 55°C, after 45 minutes the solvent was removed in vacuo. This mixture was purified by silica gel column chromatography (2%->2.5%->3.3%->%5 acetone in toluene) to furnish 4.55, but no detectable trityl trisulfide.
See **4.52** entry for characterization data and reaction details

Table 4.4: Entry 5
See **4.52** entry for characterization data and reaction details.

Table 4.4: Entry 6
See **4.53** entry for characterization data and reaction details.

Table 4.5: Experimental procedures.
All reaction are carried out in dram or scintillation vials epuipped with stir bars.

Table 4.5: Entry 1
4.50 product (12 mg, 21µmol, 1.0eq.) was dissolved in 2.13 of dry DCM and cooled to 0°C. As stock solution was prepared of 100 µl of BF_3 etherate (47% BF_3 by weight) in 900 µl of DCM. 400 µl of this stock solution (0.336 mmol, ~16 eq.) was added to the substrate and the reaction was warmed to room temperature. No conversion was immediately. After 15 hours. the reaction diluted with saturated NH_4Cl (3 ml) and extracted with EtOAc twice (3 ml). Organic layers with washed once with brine (5 ml), dried over $MgSO_4$, and filtered. Solvent was removed in vacuo, and the residue was loaded onto pTLC. pTLC purification in 5:1 hexane: EtOAC eluent yielded two spots. The lower spot

(*Rf* = 0.46, Hexane: EtOAc, 5:1) was determined to be recovered starting. The top spot (*Rf* = 0.71, Hexane: EtOAc, 5:1) was determined to be olefin product **5.54** among other impurities. Mass recover was poor, less than 2 mg in both spots.

Table 4.5: Entry 2
4.50 product (9.5 mg, 26.9 μmol, 1.0 eq.) was dissolved in 1.7 ml of dry nitropropane and cooled to -78°C. 50 μl of TfOH (0.565 mmol, ~33 eq.) was added to 1 ml of DCM to form a stock solution. 0.15 ml (~5 eq) of stock solution was added. After 10 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over MgSO4, filtered, and the solvent removed in vacuo. TLC of the crude reaction mixture showed apparent decomposition of starting material.

Table 4.5: Entry 3
4.50 product (7.4 mg, 13.2 μmol , 1.0 eq.) was dissolved in 1.3 of dry DCM. $In(OTf)_3$ (7.4 mg, 13.2μmol, 1.0 eq.) was added and the reaction was monitored by TLC. After 3 hours there was no consumption of starting material.

Table 4.5: Entry 4
4.50 product (9.8mg, 17.5 μmol , 1.0 eq.) was dissolved in 1.75 of dry DCM. $Cu(OTf)_2$ (6.3 mg, 13.2μmol, 1.0 eq.) was added and the reaction was monitored by TLC. A more polar (*Rf* = 0.56, Hexane: EtOAc, 3:1) spot appeared relative to starting material (*Rf* = 0.88, Hexane: EtOAc, 3:1). After 45 minutes 3.0 addition equivalents of $Cu(OTf)_2$ were added. After a total of 3 hours, the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was preformed in 4:1 Hexane:EtOAc eluent. ^{1}H-NMR determination of the two major bands indicated a loss of t-butyl trisulfide but no formation of unsaturated ester.

Table 4.5: Entry 5
4.50 product (14.5 mg , 25.8 μmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar and activate 3A molecular sieves powder. A 0.15 M stock solution of 2,6 lutidine in DCM was prepared and the substrate was dissolved in it (0.26 ml 38.7 μmol, 1.5 eq.). The reaction was cooled to -78°C and a 0.10 M stock solution of Tf_2O was prepared. Tf_2O stock solution was added (0.37 ml, 36.2 μmol, 1.40 eq to the substrate dropwise over 5 minutes. After 1 h at -78°C 32eq. of BF_3 etherate was added (50 μl of stock solution prepared as describe in entry 1) and the reaction was warmed to room temperature over 40 minutes before dilution with EtOAc (5 ml), washing once with $NaHCO_3$ (2.5 ml), once with 0.5 M HCl (2.5 ml), and once with brine (2.5 ml) before drying over $MgSO_4$. The reaction was filtered through a chem wipe and a short SiO_2 plug to furnish 8 mg of product. ^{1}H- and ^{13}C-NMR of crude material showed **5.54** product in ~90% purity. See Entry **5.54** for characterization data

Table 4.5: Entry 6
4.50 product (15.0 mg, 26.7 μmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar and activate 3A molecular sieves powder. 2,6-di-*tert*-butyl 4- methylpyridine (7.7 mg, 35.7 μmol, 1.4 eq.) was added, the solids were dissolved in 2.43 ml of DCM, and the reaction was cooled to -78°C. 0.1M Tf_2O stock solution was added dropwise over 5 minutes (0.364, 0.0374 mmol, 1.4 eq.). 2.5 ml of $MeNO_2$ was prepared with 1.4 eq. of TFA. After 15 minutes this solution was added to the substrate and the reaction was warmed to room temperature over 30 minutes. TLC with standards confirmed only decomposition and product **4.54.**

Table 4.5: Entry 7
4.50 product (27.2 mg, 48.4 μmol, 1.0 eq.) was dissolved in 0.5 ml of dry DCM in a flame dried dram vial equipt with stir bar and activated 3A molecular sieves powder. The reaction was cooled to 0°C and NEt3 (10.3 μl, , 72.6 μmol, 1.5 eq.) was added follow by addition of 50 μml of $MeSO_2Cl$ stock solution (100 μml $MeSO_2Cl$: 900 μml, 1.33 eq.) The reaction was monitored byTLC, after 40 minutes the reaction was diluted with EtOAc(5ml), washed once with NH_4Cl (2.5 ml), and once with brine (2.5 ml) before drying over $MgSO_4$. The reaction was filtered and the solvent removed in vacuo. The residue was purified by small-scale SiO_2 column chromatography (15:1->10:1->7:1) Hex;EtOAc in a peptide to afford 9.7 mg of **4.54** for 37% yield and 2.6 mg of related thiol product congener **Side product 2**. **5.54**. (*Rf* = 0.58, Hexane: EtOAc, 8:1). **Side product 2**. (*Rf* = 0.81, Hexane: EtOAc, 8:1)
4.54
^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.91-6.77 (m, 1H), 5.82 (d, J= 14.7, 1H), 5.79 (d, J= 14.7, 1H), 5.37 (3.57, J= 6.4 Hz, 0.6H), 4.96 (d, J= 22.4, 0.7H), 4.18 (q, J= 7.0 Hz, 1H), 2.97 (d, J= 6.7 Hz, 1H), 2.90-2.83 (m, 2H), 2.40 (t, J= 7.1 Hz, 1H), 2.2 (q, J= 6.7 Hz, 1H), 1.78-1.62 (m, 6H), 1.38 (s, 9H), 1.34-1.25 (m, 4H), 1.08-1.01 (m, 21H) NMR ($CDCl_3$, 125 MHz),: δ 166.6, 166.5, 150.5, 150.5, 147.3, 136.7, 122.3, 121.4, 121.1, 111.9, 108.0, 106.7, 80.9, 80.1, 60.3, 60.3, 50.6, 48.9, 48.9, 48.2, 39.0, 33.7, 31.3, 30.3, 29.9, 29.9, 26.5, 26.5, 26.3, 19.0, 18.5, 14.3, 13.5, 11.3. MS-ESI (m/z): [M+H] calcd. $C_{43}H_{56}O_2S_2Si$ 697.35; found 697.6.
Side product 2

^{1}H NMR ($CDCl_3$, 500 MHz,) δ 6.91-6.74 (m, 1H), 5.94-5.75 (m, 1H), 5.37 (t, J= 6.5 Hz, 0.5H), 4.99 (s, 0.25H), 4.93 (s, 0.25H), 4.25-4.14 (m, 2H), 2.97 (d, J= 6.7 Hz, 1H), 2.88-2.80 (m, 2H), 2.45-2.32 (m, 1H), 2.28-2.15 (m, 1H), 1.78-1.61 (m, 5H), 1.32-1.27 (m, 3H), 1.09-0.80 (m, 24H)^{13}C NMR ($CDCl_3$, 125 MHz,) δ 166.6, 166.5, 150.4, 150.4, 147.2, 136.6, 122.4, 121.5, 121.2, 111.9, 107.9, 106.7, 80.9, 80.2, 60.3, 60.3, 50.6, 38.4, 33.7, 29.7, 19.0, 18.6, 14.3, 13.4 MS-ESI (m/z): [M+] calcd. $C_{24}H_{42}O_2SSi$, 422.27; found 422.5.

Table 4.5: Entry 8
4.50 product (17.4 mg, 31.0 µmol, 1.0 eq.) was dissolved in 2.5 ml of dry DCM in a flame dried dram vial equipped with stir bar and cooled to -30°C. 300 µl of 0.325 M Et_2NSF_4 was added (1.33 eq.) and the reaction was warmed to room temperature over 30 minutes. The reaction was then diluted with EtOAc (5 ml), washed once with water (5 ml), brine (5 ml) and dried over $MgSO_4$. The reaction was filtered, the solvent removed in vacuo, and the residue. Crude ^{1}H-NMR revealed formation of **4.54** along with aliphatic decomposition products.

Table 4.5: Entry 9
4.50 product (21.3 mg, 37.0 µmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 3.2 ml of dry DCM, and cooled to -78°C 0.1 M Tf_2O stock solution (580 µml, 1.5 eq.) was added and the reaction was monitored by TLC over 1.5 hours. Consumption of starting material was slow, and upon warming to -40°C a baseline decomposition product was visible.

Table 4.5: Entry 10
4.50 product (21.3 mg, 37.0 µmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 3.2 ml of dry DCM, and cooled to -78°C. 0.1 M $TiCl_4$ stock solution (580 µml, 1.5 eq.) was added and the reaction was monitored by TLC . Consumption of starting material near instantaneous and complete baseline decomposition product was visible.
Table 4.5: Entry 11
4.50 product (17.1 mg, 30.5 µmol, 1.0 eq.) was dissolved in 0.55 ml of toluene and cooled to -0°*C*. 0.47 ml of 0.1 M KHMDS stock solution (1.5 eq) was added to the substrate and the reaction was stirred at -0°*C* for 10 minutes before cooling to -78°C . 0.47 ml of 0.1 M of Tf_2O stock solution (1.5 eq) was added and the reaction was stirred at -78°C for 20 minutes before the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 5.8 mg of **4.54** product was characterized for a 37% yield.

Table 4.5: Entry 12
4.50 product (17.2 mg, 30.7 µmol, 1.0 eq.) was dissolved in 1 ml of DCM at room temperature. 1.4 ml of a 34 mM solution of Martin's Sulfurane (1.55 eq.) in DCM was added. After 10 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over MgSO4, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 2.0 mg of **4.54** product was characterized for a 12 % yield.

Table 4.5: Entry 13
4.50 product (17.1 mg, 30.4 µmol, 1.0 eq.) was dissolved in 1.4 ml of THF and cooled to -78°C. 66.6 µml of 0.7 M deoxo-fluor ® (1.5 eq.) was added to the diluted substrate. Full conversion was observed by TLC after 10 minutes. After 15 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml), and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 2.4 mg of **4.54** product was characterized for a 15 % yield.

Table 4.6: Experimental procedures.

Table 4.6: Entry 1
4.53 product (23.8 mg, 33.3 µmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 2.8 ml of dry DCM, and cooled to -78°C. 0.1 M Tf_2O stock solution (510 µml, 1.5 eq.) was added and the reaction was monitored by TLC over 1.5 hours. Consumption of starting material was slow, and upon warming to -40°*C* a baseline decomposition product was visible.

Table 4.6: Entry 2
4.53 product (23.8 mg, 33.3 µmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 2.5 ml of dry DCM, in addition of 220µl of 0.15 M 2,6 lutidine stock (1.0 eq.) solution and cooled to -78°C. l of 0.1 M Tf_2O (510 µ, 50 µmol, 1.5 eq.) was added and the reaction was stirred for 5 minutes before warming to -40°C over 10 minutes. After 15 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml)

and the combined organics were washed once with brine (3 ml). The organic layers were dried over MgSO4, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 16.8 mg of **4.58** product was obtained as a clear film in 75 % yield. *Rf* = 0.40, Hexane: EtOAc, 8:1.
4.58 ^{1}H NMR ($CDCl_3$, 500 MHz,) δ 7.44-7.41 (m, 5H), 7.31-7.21 (m, 10H), 6.76 (dd, J= 15.7, 7.5 Hz, 0.66H), 6.73 (dd, J= 15.7, 8.3 Hz, 0.33H), 5.73 (dd, J= 15.7, 1.1 Hz, 0.33H), 5.71 (dd, J= 15.7, 1.3 Hz, 0.66H), 5.26 (t, J= 6.4 Hz, 0.7H), 4.91 (m, 0.3H), 4.83 (m, 0.3H), 4.16 (q, J= 7.2 Hz, 2H), 2.92 (d, J= 6.8 Hz, 1H), 2.72-2.59 (m, 1H), 2.44-2.31 (m, 1H), 2.18-2.11 (m, 0.6H), 1.68-1.60 (m, 2H), 1.50 (d, J= 1.0 Hz, 1H), 1.26 (q, J= 7.3 Hz, 3H), 1.06-1.01 (m, 21H). ^{13}C NMR ($CDCl_3$, 125 MHz,) δ 166.6, 166.5, 150.5, 150.5, 143.9, 143.8, 136.6, 130.2, 127.8, 126.9, 122.1, 121.1, 111.7, 106.8, 70.9, 60.4, 60.3, 50.4, 48.0, 36.6, 36.5, 33.6, 31.2, 30.3, 26.5, 26.4, 21.1, 18.9, 18.6, 18.5, 14.3, 14.3, 14.2, 13.4, 11.3 . MS-ESI (m/z): [M+] calcd. $C_{43}H_{56}O_2S_2Si$, 696.35; found 696.2

Table 4.6: Entry 3
4.53 product (23.8 mg, 33.3 μmol, 1.0eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 330 μl of 0.15 M 2,6 lutidine stock (1.0 eq.) solution and cooled to -78°C. of 0.1 M Tf_2O (510 μl , 50 μmol,1.5 eq.) was added and the reaction was stirred for five minutes. After this time 2 ml of 2.5 vol% TFA in n-$PrNO_2$ was added and the reaction was stirred a further 10 minutes. After 15 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 10.9 mg of **4.58** product was characterized for a 49 % yield.

Table 4.6: Entry 4
4.53 product (16.6 mg, 23.2 μmol, 1.0 eq.) was dissolved in 0.42 ml of toluene and cooled to -78°C. 0.1 M KHMDS stock solution (0.36 ml, 35 μmol, 1.5 eq) was added to the substrate and the reaction was stirred at -0°C for 5 minutes before cooling to -78°C. .0.1 M Tf_2O stock solution (0.36 ml, 35 μmol, 1.5 eq) was added and the reaction was stirred at -78°C for 20 minutes before the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent to afford 8.6 mg of **4.58** product in 53% yield and 3.6 mg ketone of **4.59** in 21% yield.

Table 4.6: Entry 5
4.53 product (20.3 mg, 28.4 μmol, 1.0 eq.) was dissolved in 1 ml of DCM at room temperature. A 34 mM solution of Martin's Sulfurane (1.4 ml, 44 μmol, 1.55 eq.) was added. After 10 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was performed in 8:1 Hexane:EtOAc eluent and 3.0 mg of **4.58** product was isolated for a 15 % yield.

Table 4.6: Entry 6
4.52 product (16 mg, 26.2 μmol, 1.0 eq.) was added to a flame dried dram vial equipped with stir bar, dissolved in 2 ml of dry DCM, in addition to 2,6-lutidine (5.4 μl, 39 μmol, 1.5 eq.) solution and cooled to -78°*C*. 0.1 M Tf_2O (510 μL, 39 μmol, 1.5 eq.) was added and the reaction was stirred for 5 minutes before warming to -40°*C* over 10 minutes. After 15 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. Crude ^{1}H-NMR showed **4.57** was present among impurities.

Table 4.6: Entry 7
4.52 product (15.8 mg, 25.3 μmol, 1.0 eq.) and MgO (1.5 mg, 38 μmol , 1.5 eq.) were added to a flame dried dram vial equipped with stir bar. 2.0 ml of dry DCM was added, the solution and cooled to -78°C. of 0.1 M Tf_2O stock solution (400 μL, 40 μmol, 1.58 eq.) was added. Consumption of starting material was slow, and upon warming to -40°C a baseline decomposition product was visible.

Table 4.6: Entry 8
4.52 product (15.3 mg, 25.0 μmol, 1.0 eq.) and NaH (1.5 mg, 38 μmol, 1.5 eq.) was suspended in 0.2 ml of toluene and stirred at room temperature for 30 minutes before being cooled to -78°C. 1.8 ml of DCM was added followed by 0.1 M Tf_2O stock solution (400 μl, 40 μmol, 1.58 eq.). A complex miture was visible on TLC upon addition of Tf_2O.

Table 4.6: Entry 9
4.52 product (17.8 mg, 28.2 μmol , 1.0 eq.) was dissolved in 1 ml of DCM at room temperature. A 34 mM solution of Martin's Sulfurane (1.4 ml, 44 μmol, 1.55 eq.) was added. After 10 minutes the reaction was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. pTLC purification was

performed in 8:1 Hexane:EtOAc eluent. While **4.57** product was detected by ^{1}H-NMR, it was contaminated with Martin's Sulfurane derived side products.

Table 4.7: Experimental procedures.

General procedure for entires 1-3
Cyclopropylcarbinol (**4.45**, **4.46** or **4.50**) was dissolved in 0.15 M 2,6 lutidine stock solution in DCM to make a 0.1 M solution of substrate. This solution was cooled to -78°C and a volume of 0.15 M Tf_2O stock solution in DCM was added (1.4 eq.). After 3 minutes of stirring a volume of 4:1 DCM:AcSH equal to the reaction volume was added. The reaction was warmed to -20°*C.* over 27 minutes. The reaction was quenched by pouring into cold $NaHCO_3$ (4 ml) and dilution with EtOAc (5 ml). The organic was washed with $NaHCO_3$ (10 ml) twice, once with brine, and dried over $MgSO_4$. Decomposition was evident with **4.50** as substrate. pTLC purification **4.46** and **4.45** derived reactions yielded multiple bands of fouling smelling over-mass yellow oil. Initially the extra mass was thought to be residual AcSH, but rigorous co-evaporation with low boiling solvents in high vacuum failed to remove it. ^{1}H-NMR of these bands revealed no detectable unsaturated ester signals.

Table 4.7: Entry 4
4.60 product (19.4 mg, 50 µmol, 1.0 eq.) and $InCl_3$ (1.1 mg, 5 µmol, 10 mol%) was dissolved in 50 µl of DCE: AcSH (5:1) stock solution (~3 eq.). The reaction was heated to 85°C for 3 hours. After this time the reaction was diluted with 3 ml of Et_2O, extracted with 1 M HCl (2 ml), water (2 ml) and brine (2ml). TLC and NMR of isolated product confirmed no reaction occurred, only starting material **4.60** was recovered.

Table 4.7: Entry 5
4.58 product (10.6 mg, 14.9 µmol, 1.eq.) was dissolved in 2 ml of $MeNO_2$ and cooled to 0°C. $MeSO_3H$ (65 µl, 75 µmol, 0.5 M) was added. The reaction was stirred at 0°C for 20 minutes before it was poured into a test tube of $NaHCO_3$ (4 ml), extracted twice with EtOAc (3 ml) and the combined organics were washed once with brine (3 ml). The organic layers were dried over MgSO4, filtered, and the solvent removed in vacuo. TLC of the crude reaction mixture showed apparent decomposition of starting material.

Table 4.7: Entry 6
4.46 product (19.3 mg, 40 µmol, 1.0 eq.) was dissolved in 400 µl of DCM. Trichloroacetic acid (9.8 mg, 60 µmol, 1.5 eq.) was added. The reaction was monitored by TLC, extended reaction times (4 hrs.) did not lead to conversion.

Table 4.8: Experimental procedures.

Table 4.8: Entry 1
4.61 product (19.9 mg, 40 µmol, 1.0 eq.) was placed in a conical pressure vessel with stir bar. The reaction was placed in an oil bath at 200°C for 25 minutes. After this time the residue was purified by pTLC with 20:1 Hexane: EtOAc as eluent and two major spots were found. The least polar spot (. *Rf* = 0.55, Hexane: EtOAc, 20:1) was found to be **4.60** and was isolated in 19 % yield (2.9 mg). The most polar spot (. *Rf* = 0.39, Hexane: EtOAc, 20:1) was found to be intractable material.

Table 4.8: Entry 2
4.61 product (19.9 mg, 40 µmol, 1.0 eq.) was dissolved in 400 µl of o-DCB and placed in a conical pressure vessel with stir bar. The reaction was placed in a 180°C oil bath 5 minutes. After this time the residue was purified by pTLC with 20:1 Hexane: EtOAc as eluent and two major spots were found. The least polar spot (. *Rf* = 0.55, Hexane: EtOAc, 20:1) was found to be **4.60** and was isolated in 40% yield (6.1 mg). The most polar spot (. *Rf* = 0.39, Hexane: EtOAc, 20:1) was found to be intractable material.
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Table 4.8: Entry 3
4.62 product (17.2 mg, 30 µmol, 1.0 eq.) was dissolved in 300 µl of o-DCB and placed in a conical pressure vessel with stir bar. The reaction was placed in a 180°C oil bath 5 minutes. After this time the residue was purified by pTLC with 15:1 Hexane: EtOAc as eluent and two major spots were found. The least polar spot (. *Rf* = 0.36, Hexane: EtOAc, 15:1) was found to be trace amounts of **4.63**, contaminated with EtOAc. The most polar spot (. *Rf* = 0.25, Hexane: EtOAc, 15:1) was found to be intractable material.

Table 4.8: Entry 4
2.61 product (19.9 mg, 40 µmol, 1.0 eq.) was dissolved in 400 µl of o-DCB-d4 and placed in an NMR tube. The tube was heated for 10 minutes at 110 and 125°C, then 7 minutes at 140°C, followed by 5 minutes at 150, 160 and 170°C. 1H-NMR spectra were taken after each time period. The tube was heated at 170°C for 15 minutes before being loaded onto pTLC and purified with 20:1 Hexane: EtOAc as eluent. Two major spots were found. The least polar spot (. *Rf* =

0.55, Hexane: EtOAc, 20:1) was found to be **4.60** and was isolated in 17% yield (2.6 mg). The most polar spot (. *Rf* = 0.39, Hexane: EtOAc, 20:1) was found to be intractable material.

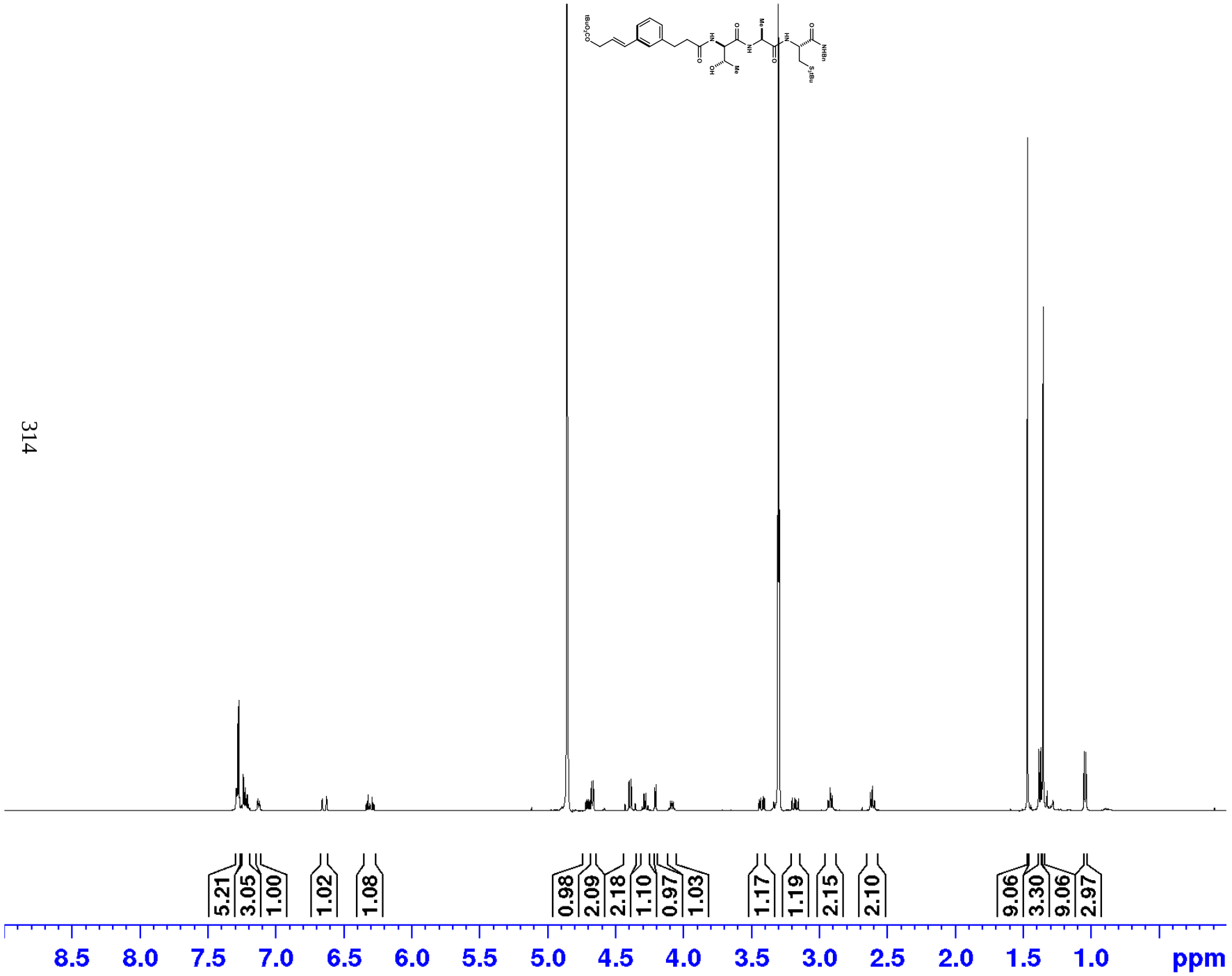
Table 4.8: General procedure for entries 5 & 6
Product (**4.61** or **4.62**, 1.0 eq.), S_8 (40 mol%) and AIBN (1.0 eq) were dissolved in DCE to make a 0.066 M solution in a sealed vessel equipped with stir bar. The reaction was heated to 85°C for 1 hour. After this time the reaction was cooled to room temperature and 10 eq. of NaBH4 in methanol was added. The reaction was stirred for 1 hour at room temperature. The reaction was then poured into 1M H_2SO_4 and extracted with DCM. Signifcate base line decomposition product and numerous spots were visible in both cases.

Table 4.8: Entry 7
4.62 (17.2 mg, 30 µmol, 1.0 eq) and AIBN (1 mg, 20 mol%) was dissolved in 0.15 ml of toluene and heated to 80°C. Every hour 1 mg of AIBN was added. After 6 hours the solvent was removed in vacuo. Crude 1H-NMR and TLC with standard showed only starting material.

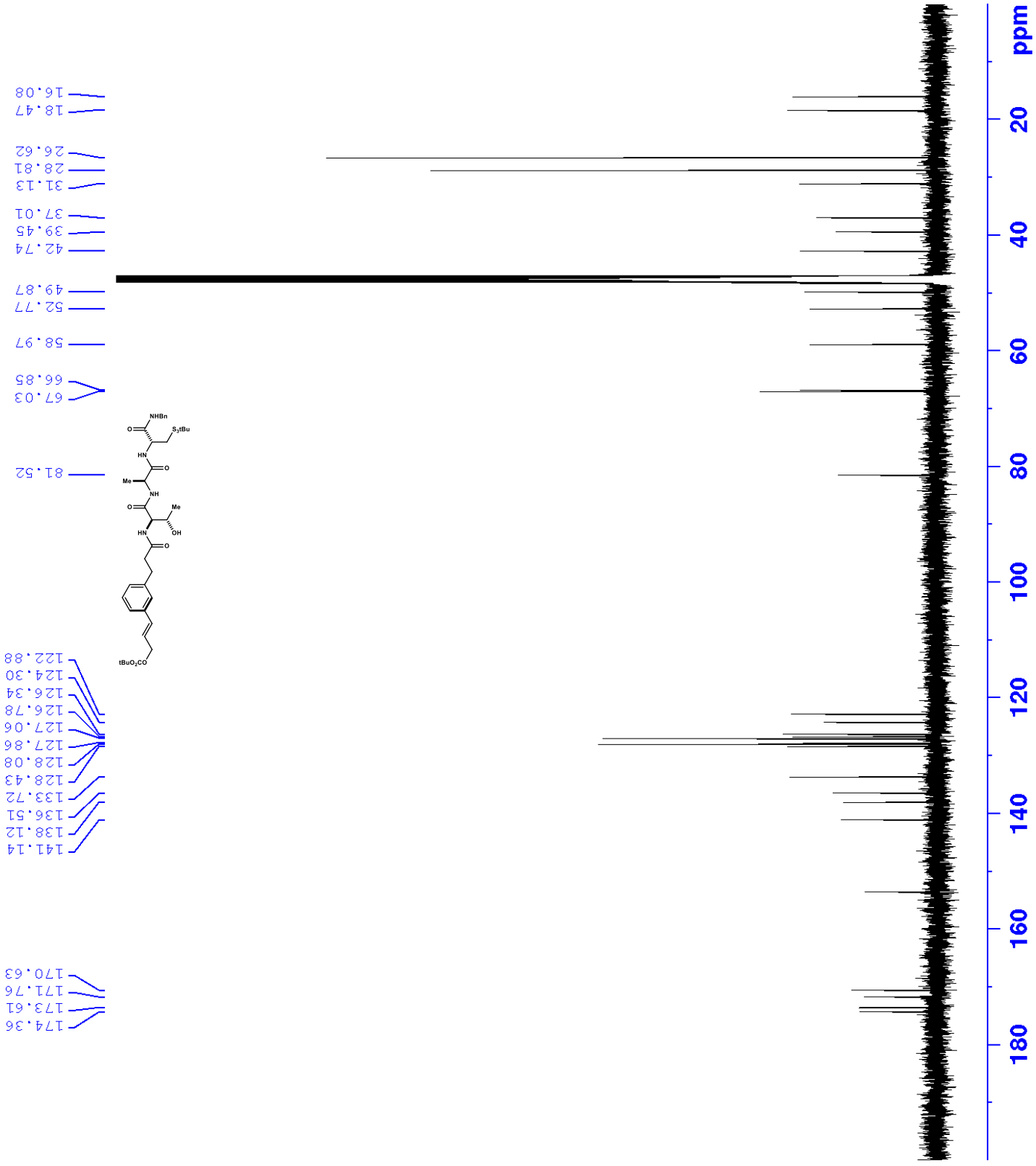
Table 4.8: Entry 8
4.62 (17.2 mg, 30.0 µmol, 1.0 eq.) and lauroyl peroxide (2.4 mg. 6.0 µmol 20 mol%) was dissolved in 0.15 ml of toluene dram vial equipped with stir bar. The reaction was heated to 80°C, every hour 2.4 mg of lauroyl peroxide was added. After 6 hours the solvent was removed in vacuo and residue was purified by pTLC with 15:1 Hexane: EtOAc as eluent. Two major spots were found. The Most polar spot (. *Rf* = 0.36, Hexane: EtOAc, 15:1) was found to be **4.63**, contaminated with Starting material 6.62 (1.9 mg) . The least polar spot (. *Rf* = 0.45, Hexane: EtOAc, 15:1) was found to be intractable material.

Table 4.8: General procedure for entries 9 & 10
Product (**4.61** or **4.62**, 1.0 eq.) and AIBN (1.25 eq.) was dissolved in toluene to make a 0.1M solution in a dram vial equipped with stir bar. Hexamethyltin (1.25 eq) was added and the reaction was heated to 85°C for 2 hours. After this time the solvent was removed, and the residue was loaded onto pTLC for purification. Isolated bands contained starting material, albeit in low mass recovery.

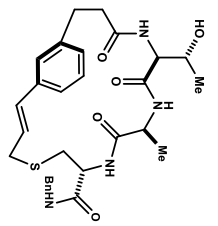
^{1}H NMR of compound 4.16 (MeOD-d4, 500 MHz)



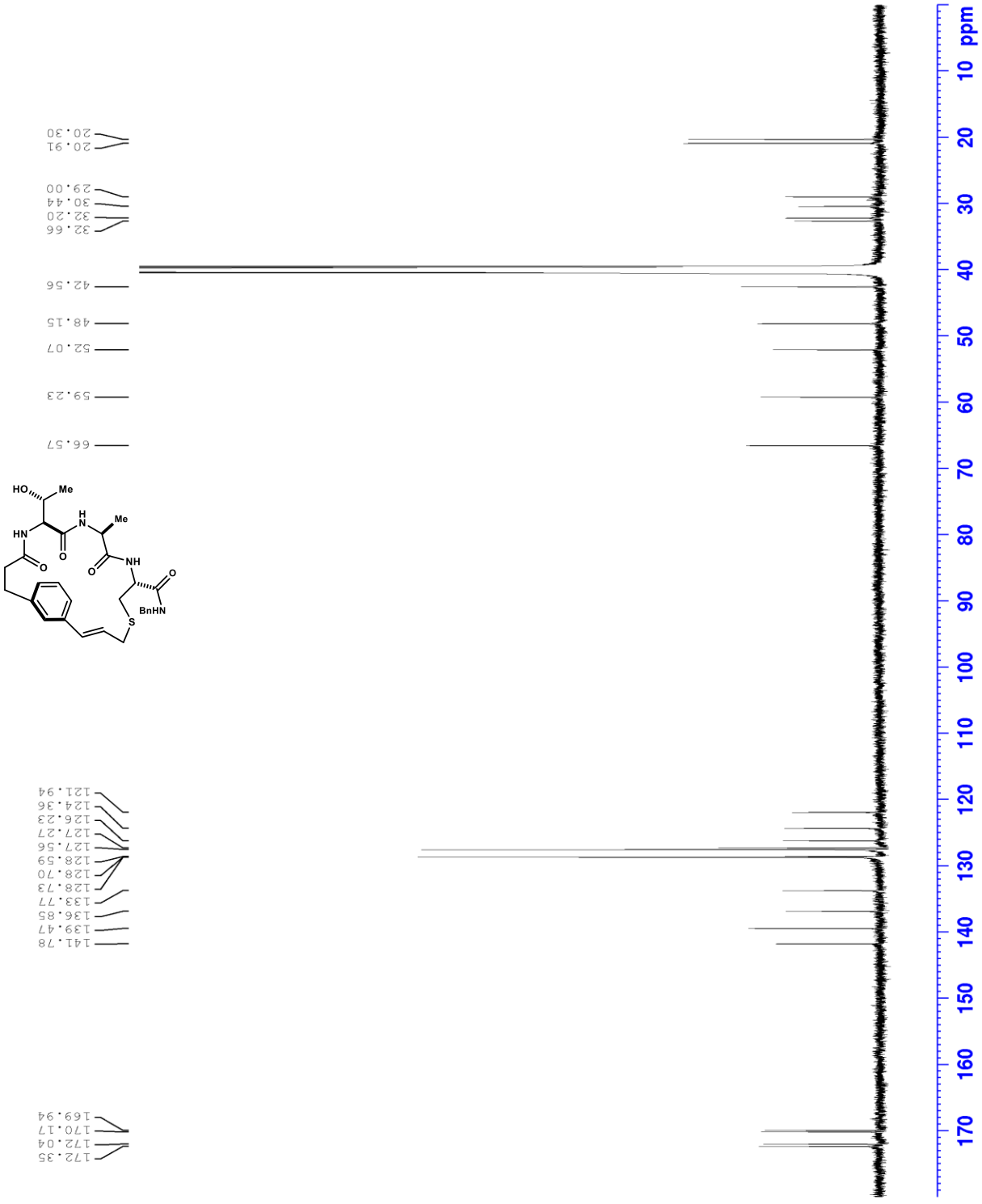
^{13}C NMR of compound 4.16 (MeOD-d4, 125 MHz)



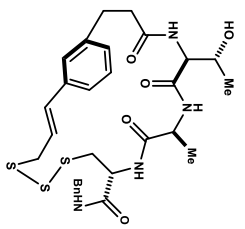
^{1}H NMR of macrcocycle 4.18 (DMSO-d6, 500 MHz)



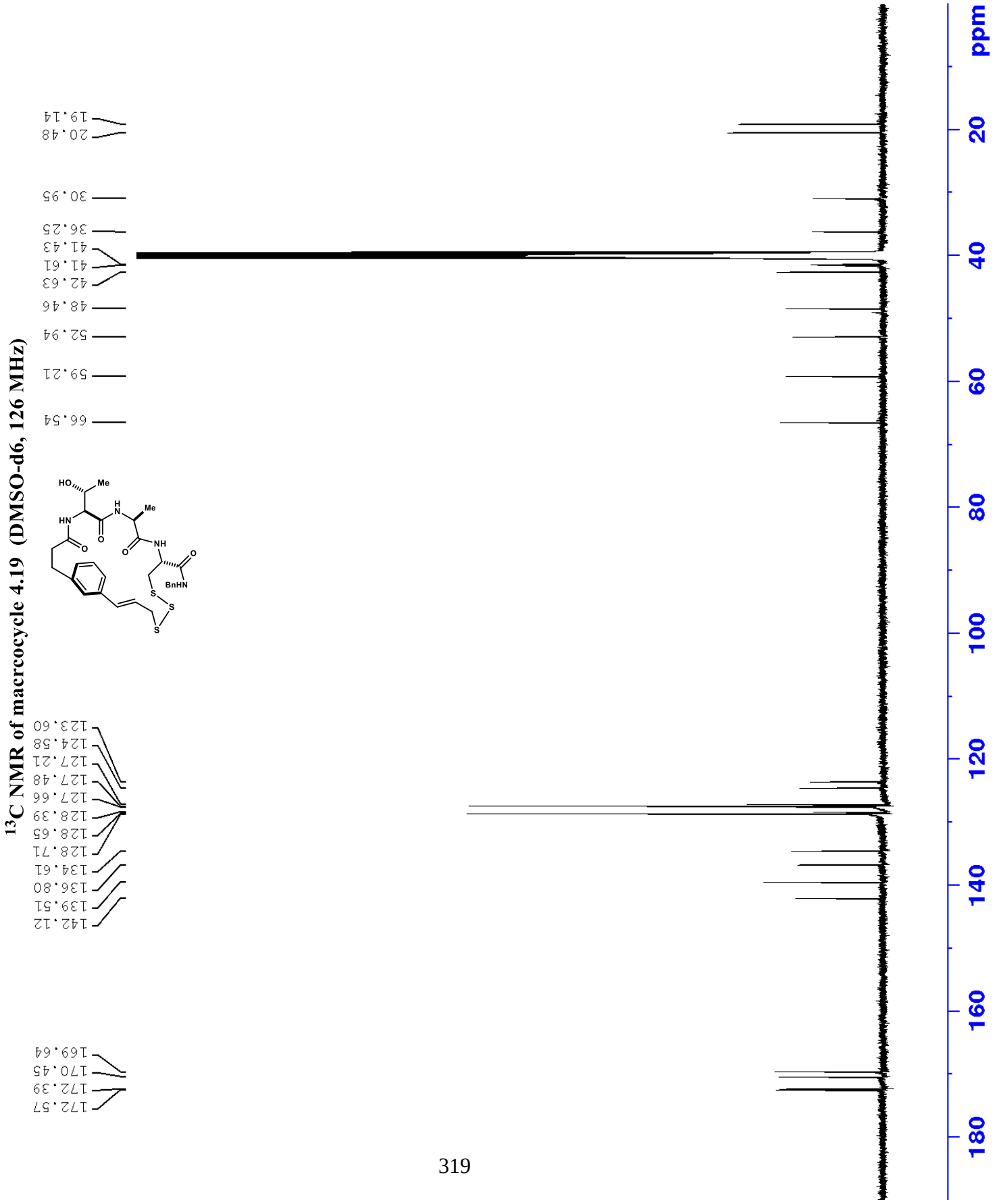
^{13}C NMR of macrocycle 4.18 (DMSO-d6, 126 MHz)



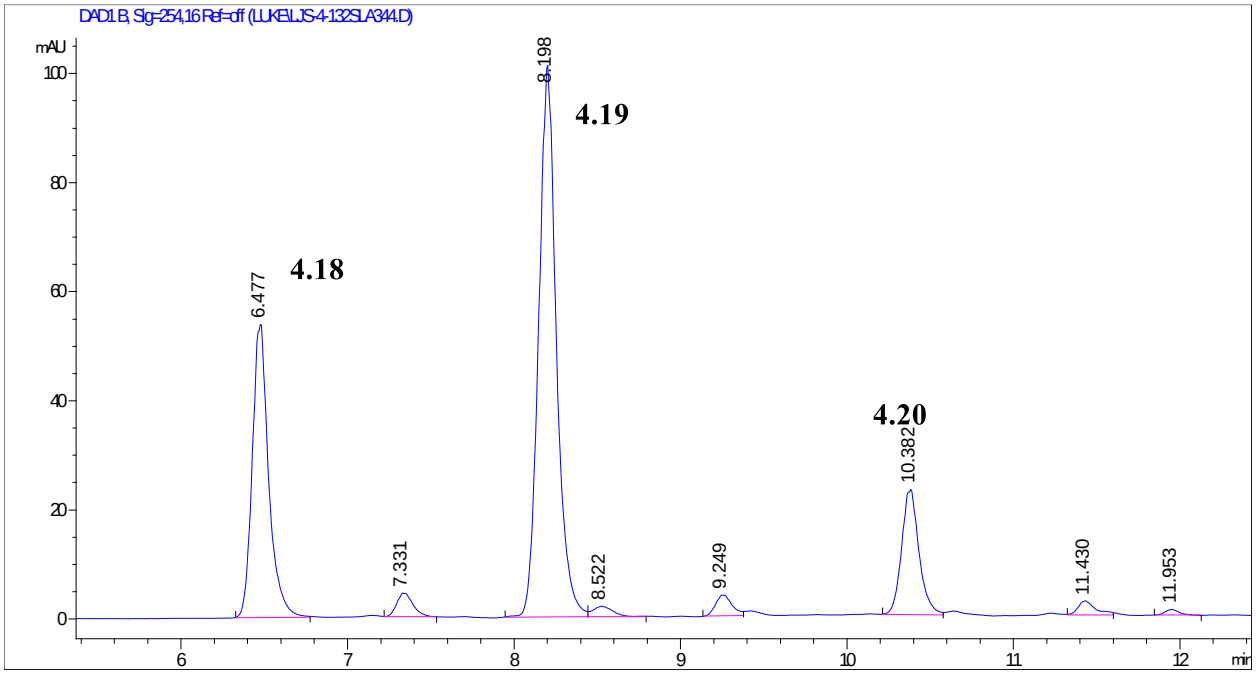
^{1}H NMR of macrcocycle 4.19 (DMSO-d6, 500 MHz)



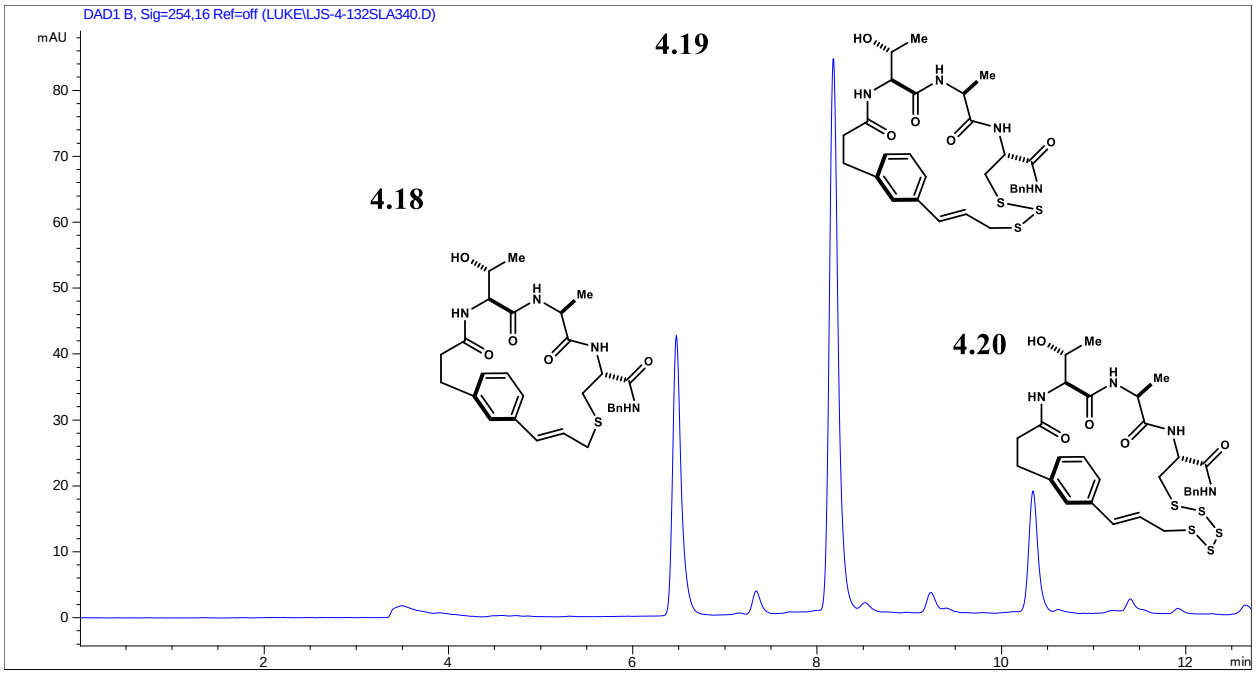
^{13}C NMR of macrocycle 4.19 (DMSO-d6, 126 MHz)



254 nm HPLC Trace & Conditions for Trisulfide 4.19 and S_2 Products



Mono= 26.6% Tri= 54.0% Penta= 12.1% Unidentified= 7.3%



Control

Column Flow	:	12.000 ml/min
Stoptime	:	13.00 min
Posttime	:	0.50 min

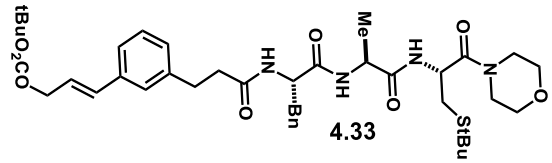
Solvents

Solvent A	:	55.0 % (Water)
Solvent B	:	45.0 % (MeCN)

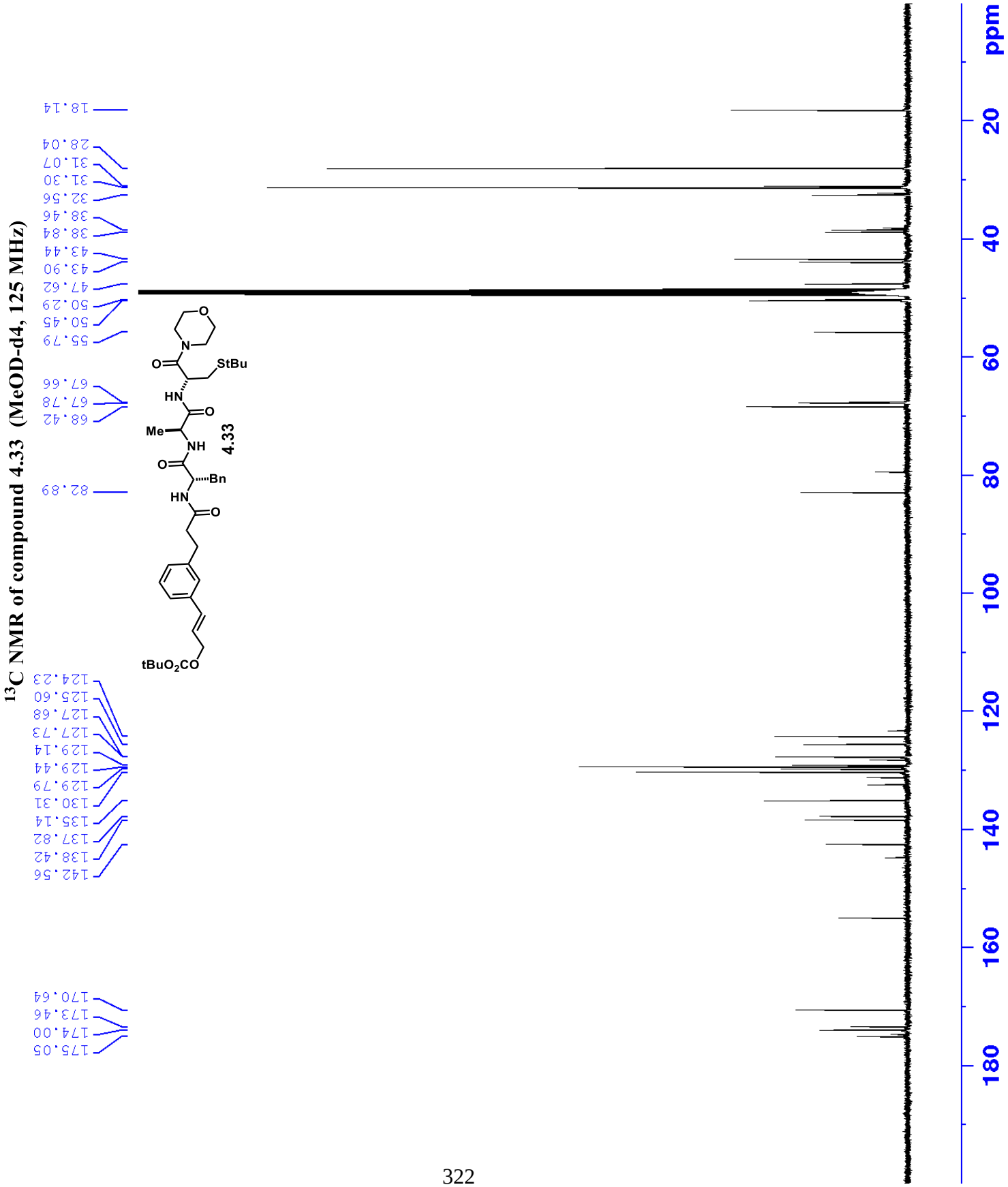
Timetable

Time	Solv.B	Flow	Pressure
0.00	45.0	12.000	
0.50	45.0	12.000	
11.00	95.0	18.000	
11.50	100.0	18.000	
12.50	100.0	18.000	
13.00	45.0	18.000	

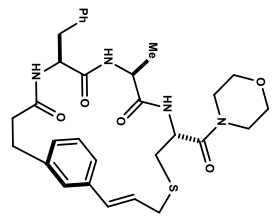
^{1}H NMR of compound 4.34 (MeOD-d4, 500 MHz)



4.33

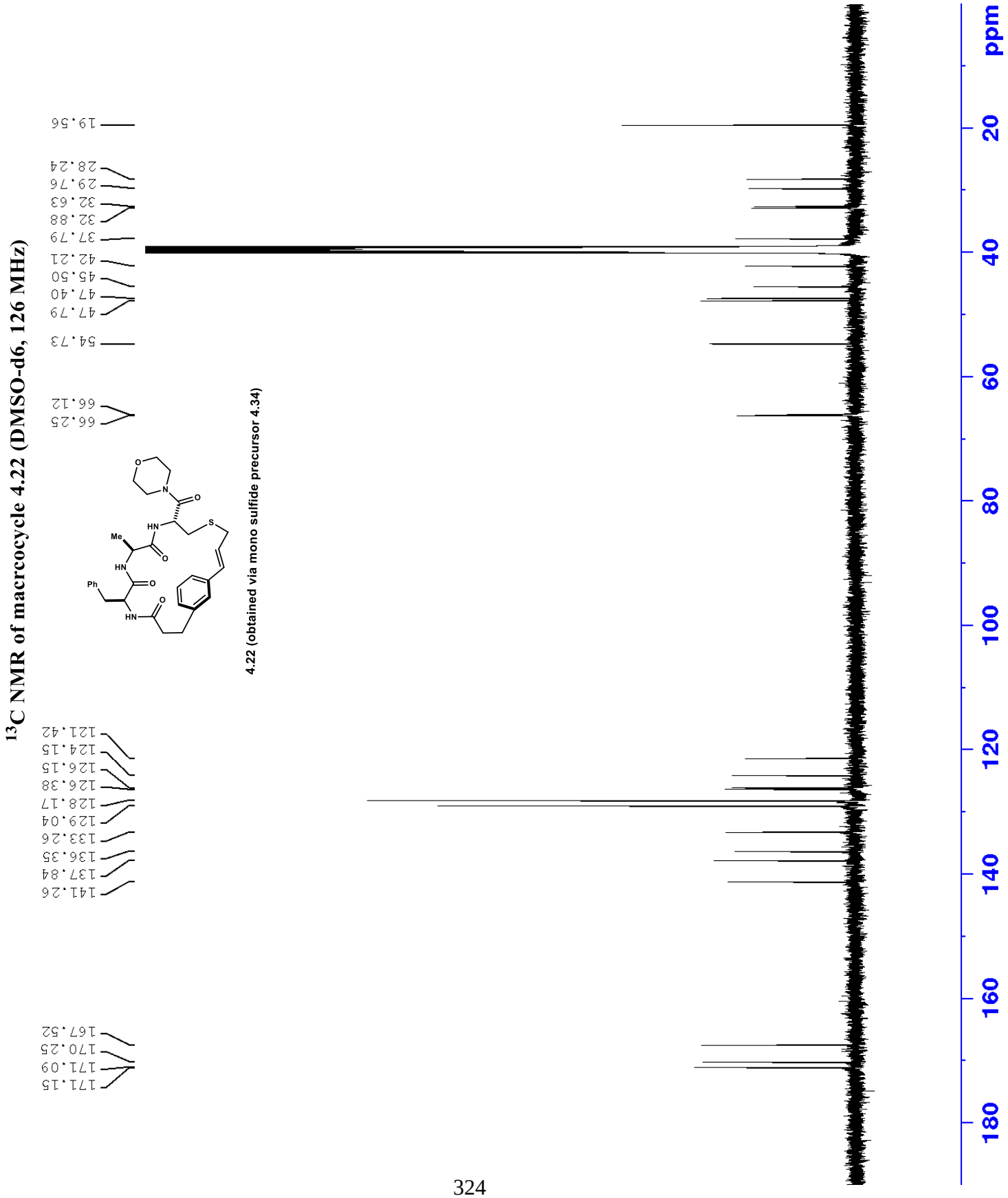

^{13}C NMR of compound 4.33 (MeOD-d4, 125 MHz)
18.14
28.04
31.07
31.30
32.56
38.46
38.84
43.44
43.90
47.62
50.29
50.45
55.79
67.66
67.78
68.42
82.89
124.23
125.60
127.68
127.73
129.14
129.44
129.79
130.31
135.14
137.82
138.42
142.56
170.64
173.46
174.00
175.05
4.33
Me
NH
Bn
HN
StBu
tBuO2CO
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of macrcocycle 4.22 (DMSO-d6, 500 MHz)

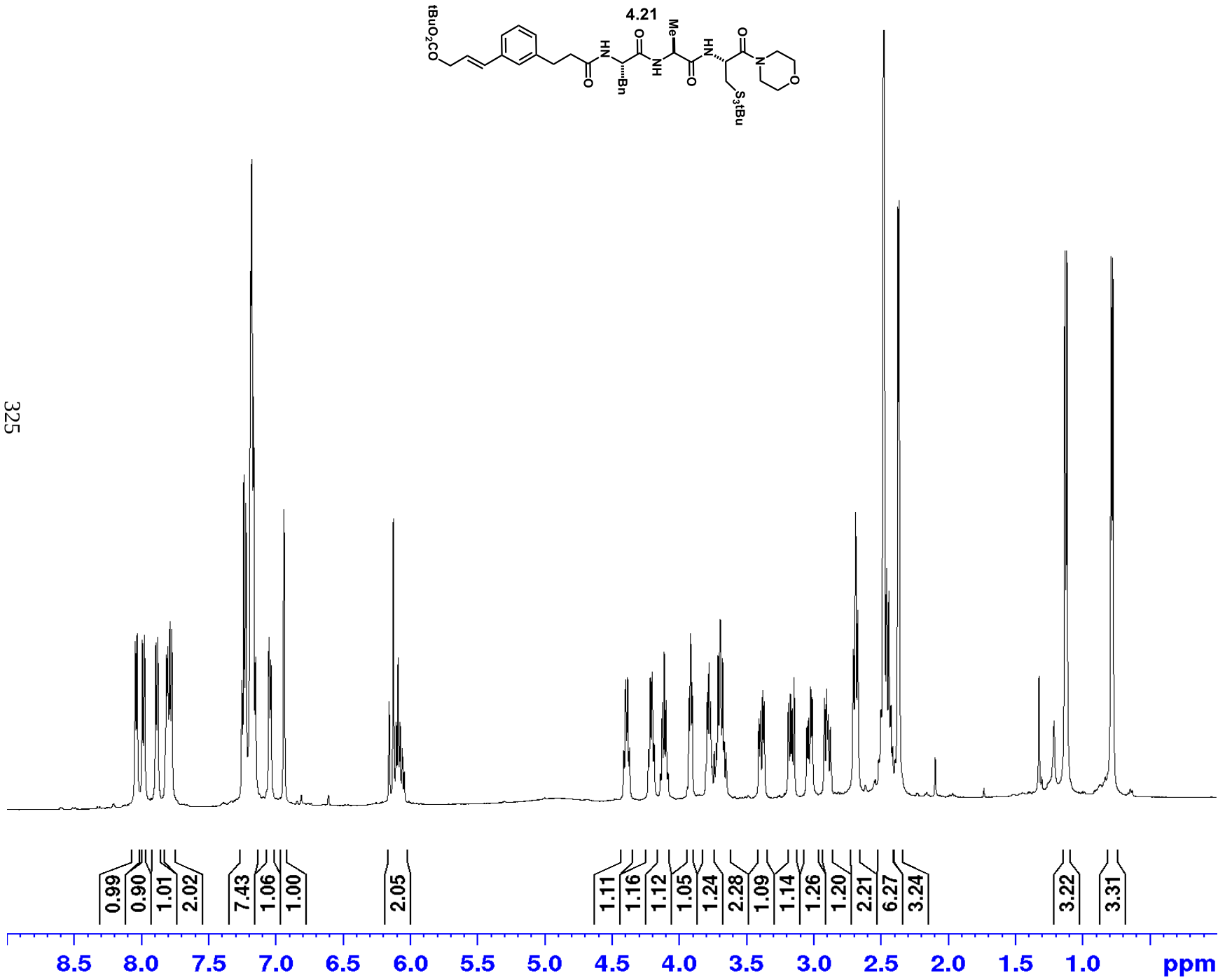


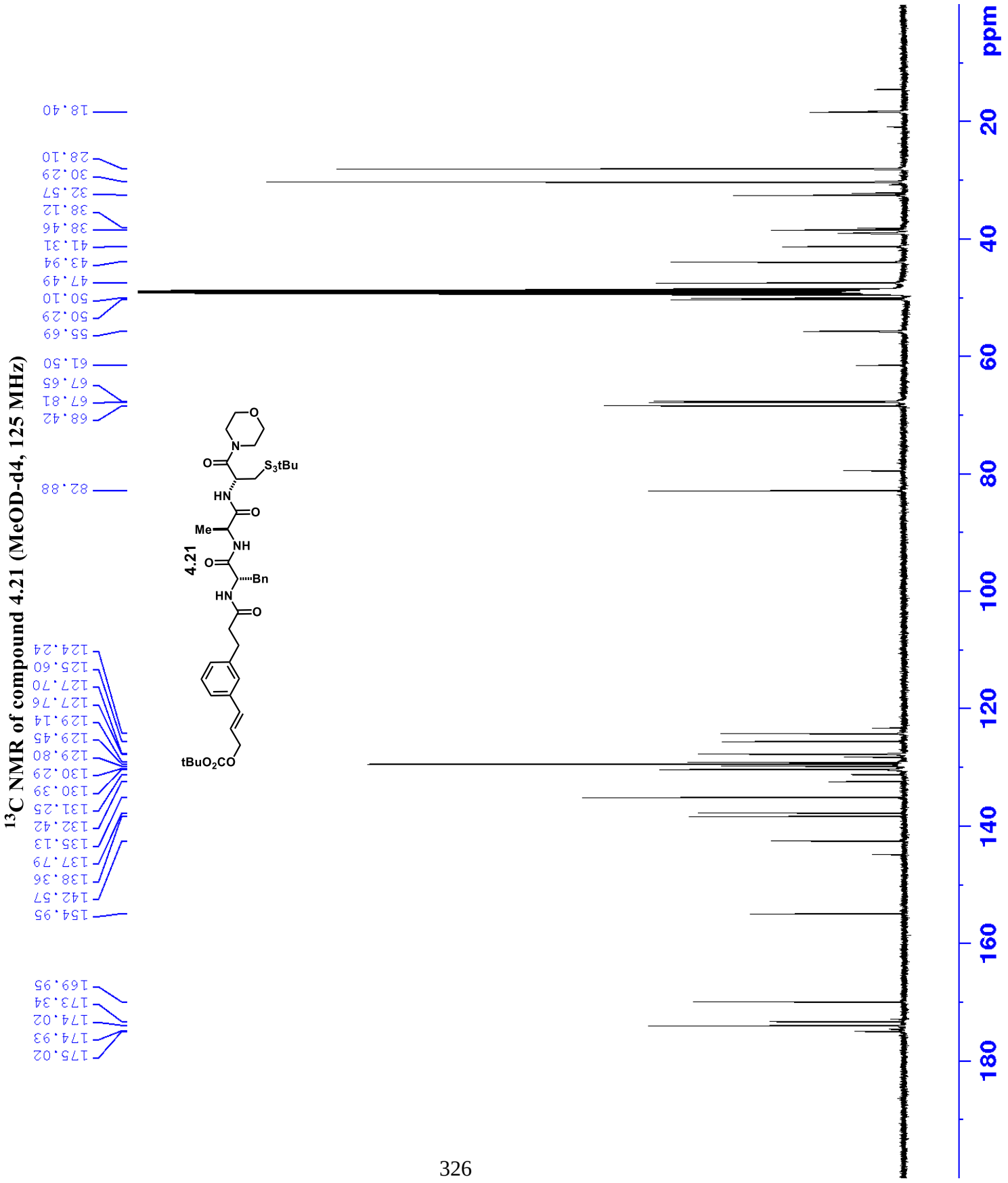
4.22 (obtained via mono sulfide precursor 4.34)

^{13}C NMR of macrocycle 4.22 (DMSO-d6, 126 MHz)

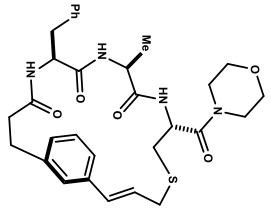


^{1}H NMR of compound 4.21 (MeOD-d4, 500 MHz)

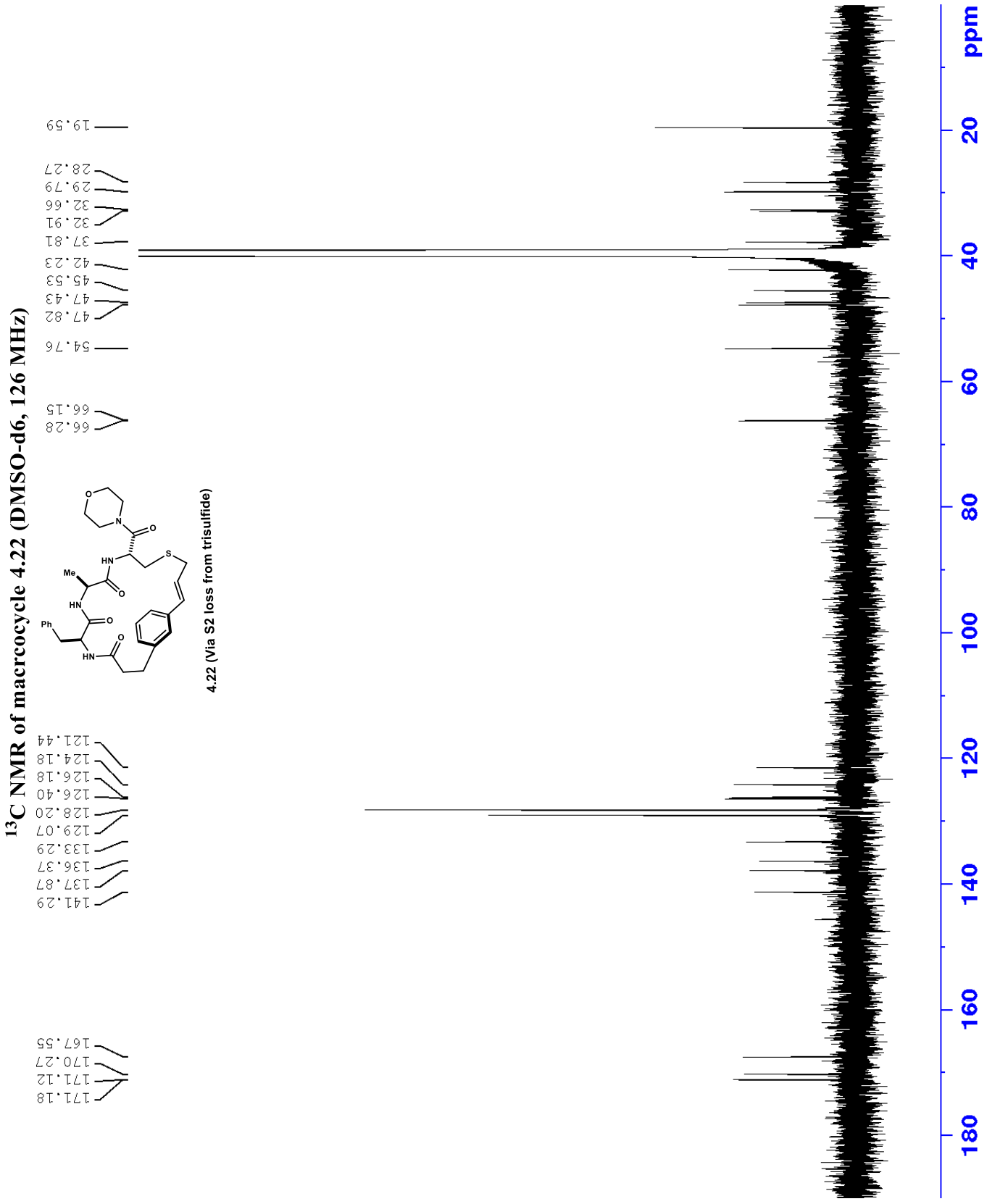



^{13}C NMR of compound 4.21 (MeOD-d4, 125 MHz)
18.40
28.10
30.29
32.57
38.12
38.46
41.31
43.94
47.49
50.10
50.29
55.69
61.50
67.65
67.81
68.42
82.88
124.24
125.60
127.70
127.76
129.14
129.45
129.80
130.29
130.39
131.25
132.42
135.13
137.79
138.36
142.57
154.95
169.95
173.34
174.02
174.93
175.02
4.21
S$_3$tBu
Me
Bn
tBuO$_2$CO
ppm
20
40
60
80
100
120
140
160
180

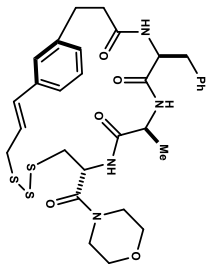
^{1}H NMR of macrcocycle 4.22 (DMSO-d6, 500 MHz)



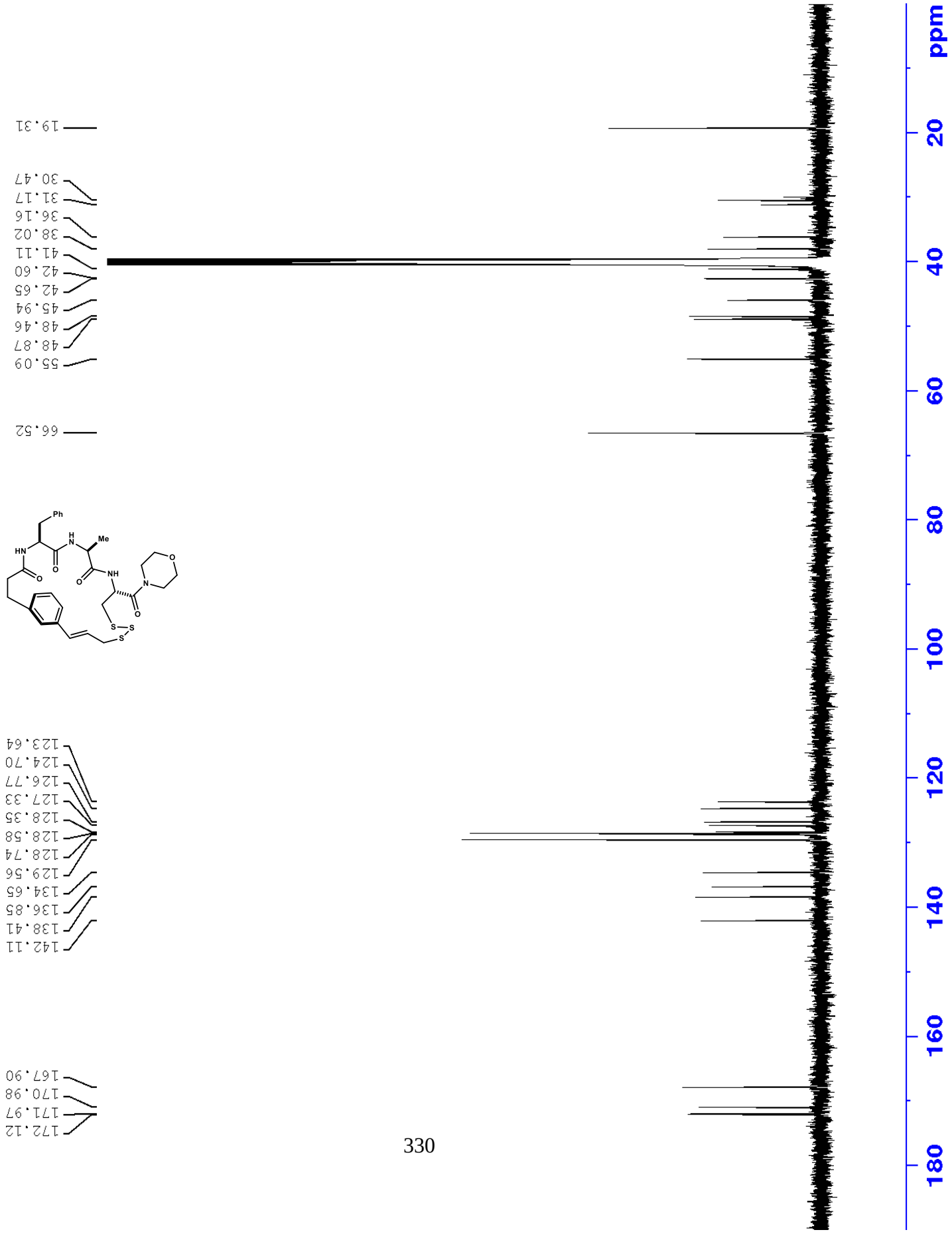
4.22 (Via S2 loss from trisulfide)

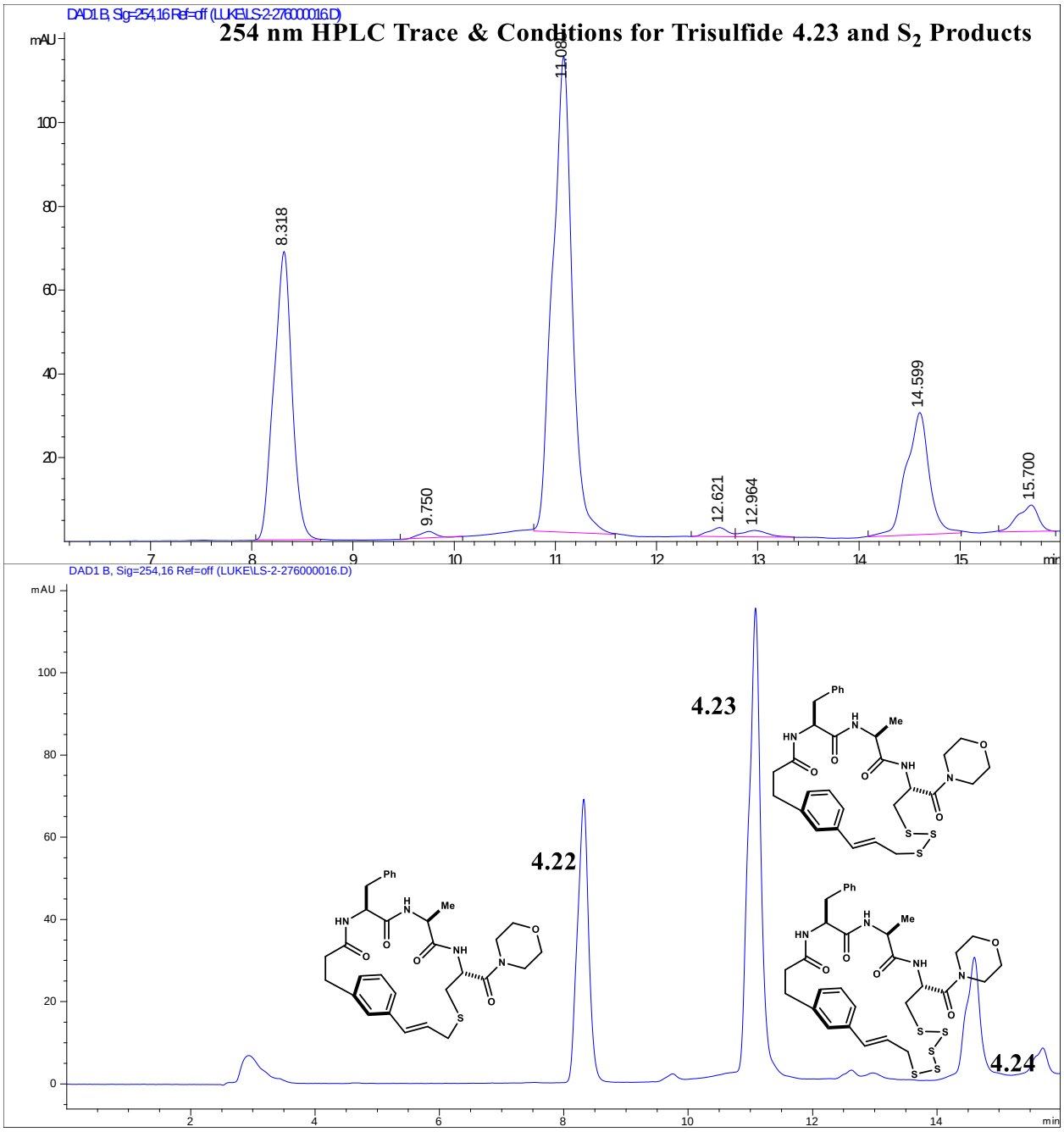

13C NMR of macrocycle 4.22 (DMSO-d6, 126 MHz)
4.22 (Via S2 loss from trisulfide)
19.59
28.27
29.79
32.66
32.91
37.81
42.23
45.53
47.43
47.82
54.76
66.15
66.28
121.44
124.18
126.18
126.40
128.20
129.07
133.29
136.37
137.87
141.29
167.55
170.27
171.12
171.18
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of macrcocycle 4.23 (DMSO-d6, 500 MHz)



^{13}C NMR of macrocycle 4.23 (DMSO-d6, 125 MHz)





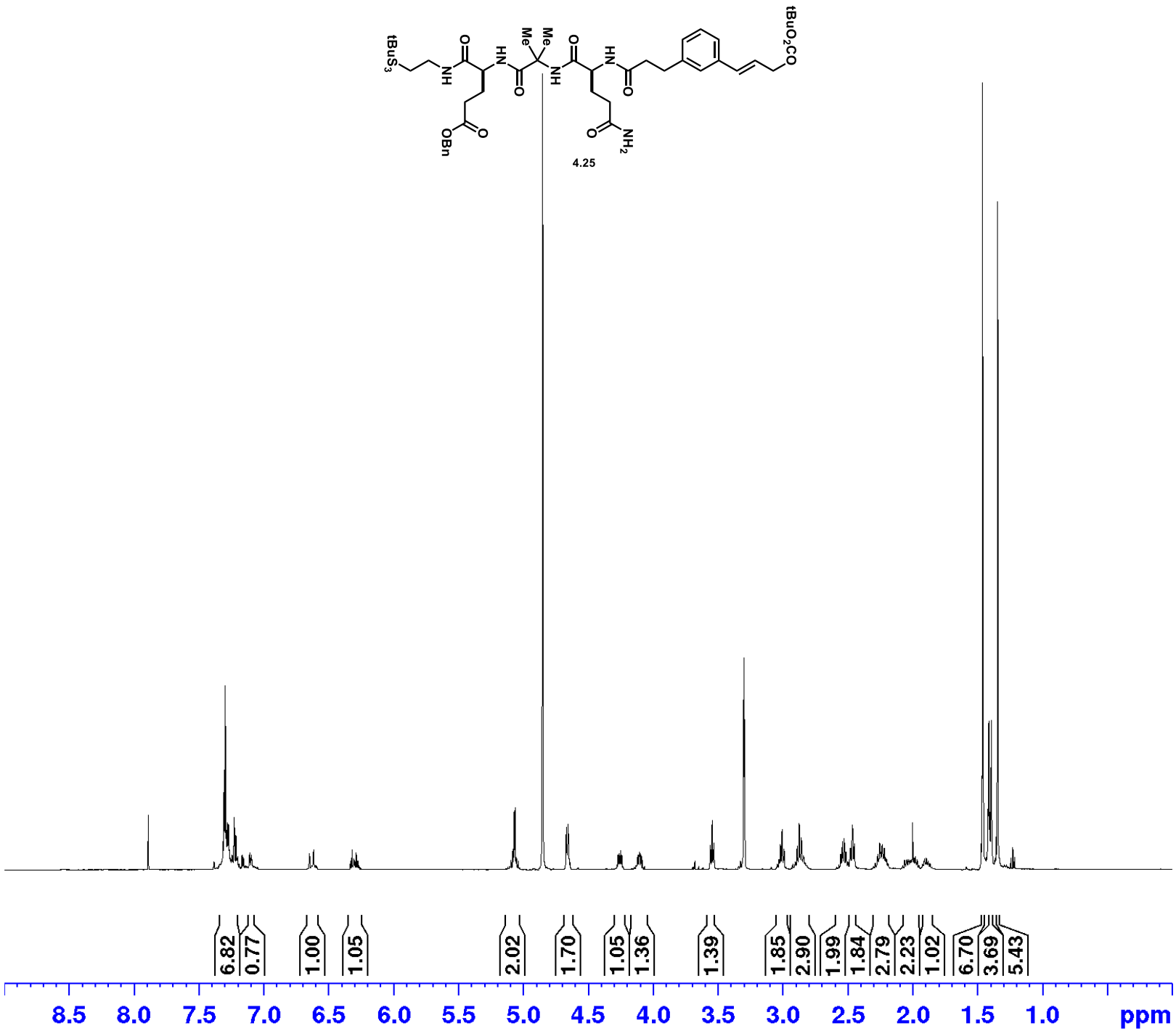

```
Control
    Column Flow          :      15.000 ml/mir
    Stoptime             :         16.00 min
    Posttime             :      Off

Solvents
    Solvent A            :      55.0 % (Water
    Solvent B            :      45.0 % (MeCN)
```

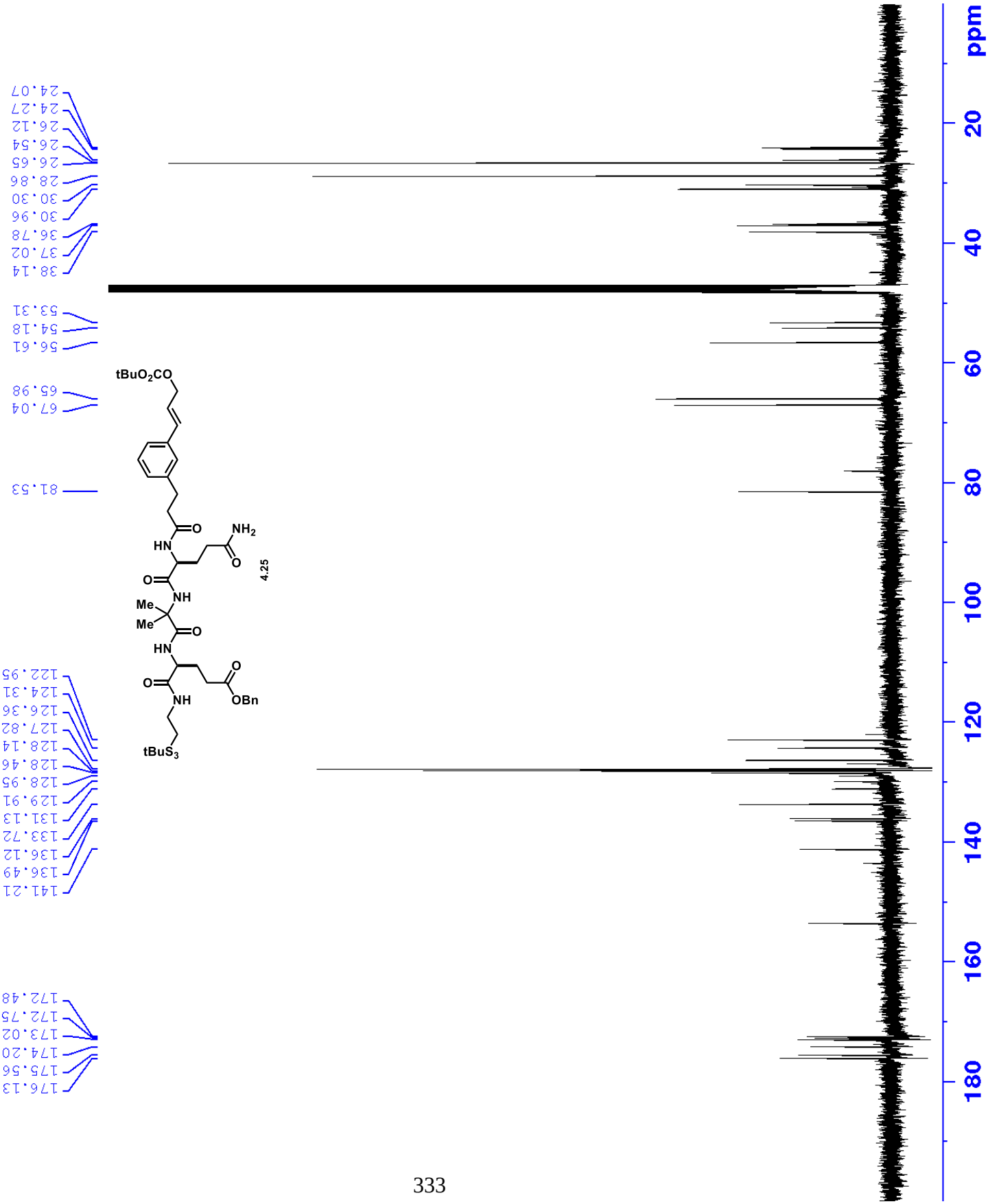
Timetable

Time	Solv.B	Flow	Pressure
0.00	45.0	10.000	
2.00	45.0	18.000	
14.00	80.0	18.000	
15.00	80.0	18.000	
16.00	35.0	18.000	

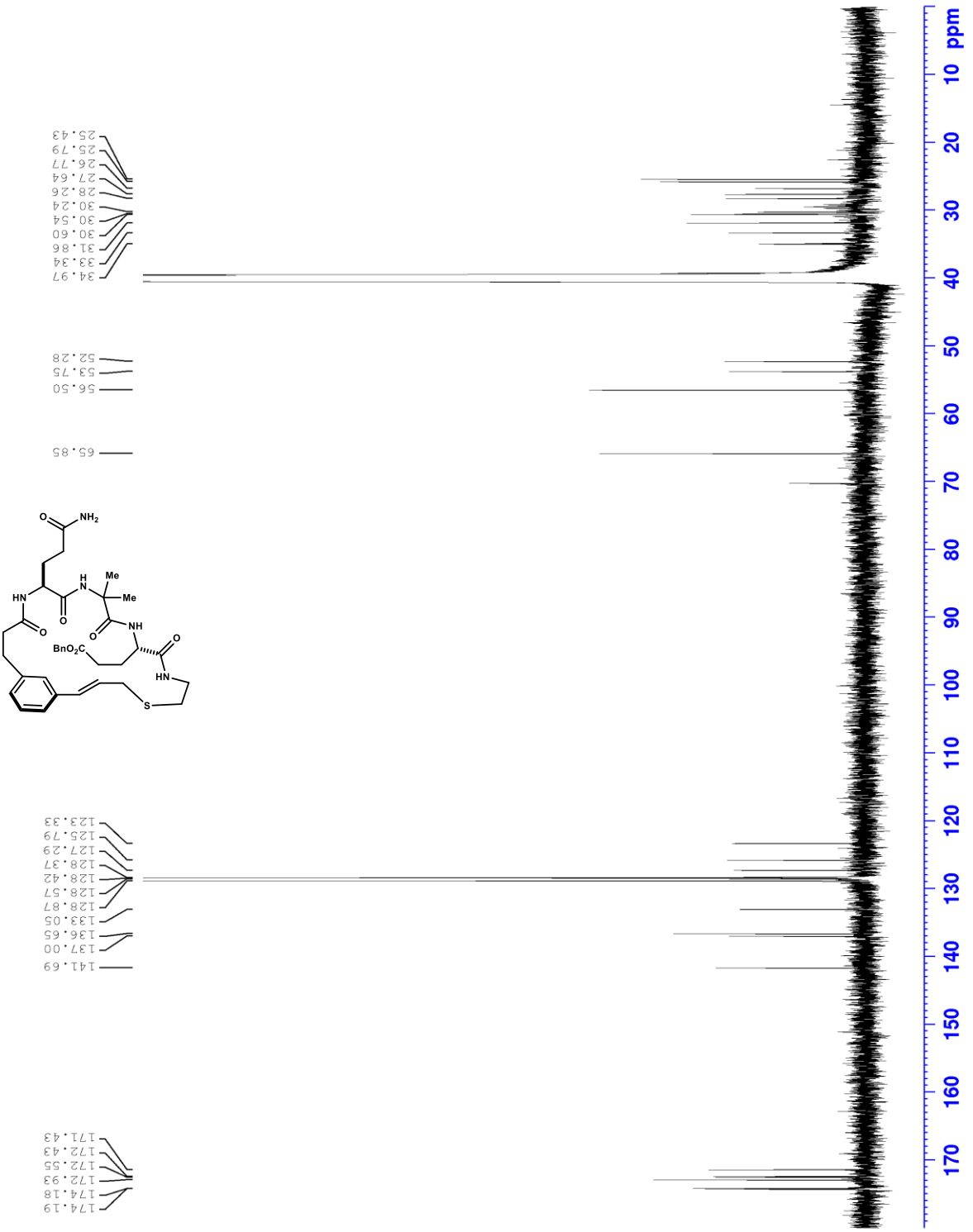
^{1}H NMR of compound 4.25 (MeOD-d4, 500MHz)



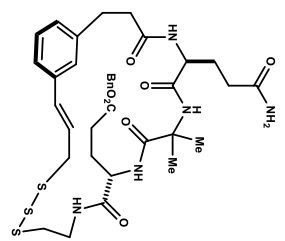
^{13}C NMR of compound 4.25 (MeOD-d4, 125 MHz)



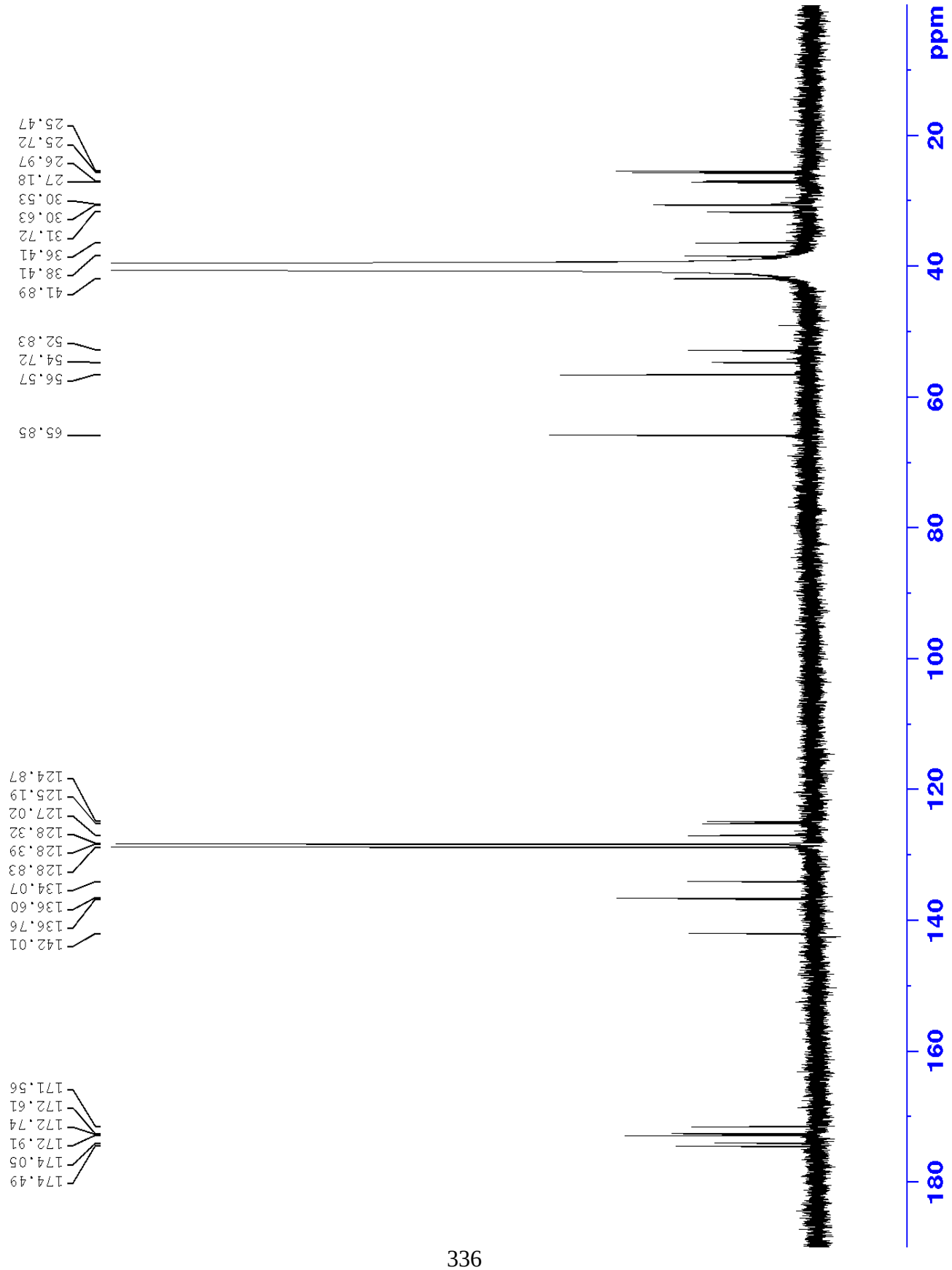
^{1}H NMR of macrcocycle 4.26 (DMSO-d6, 500 MHz)



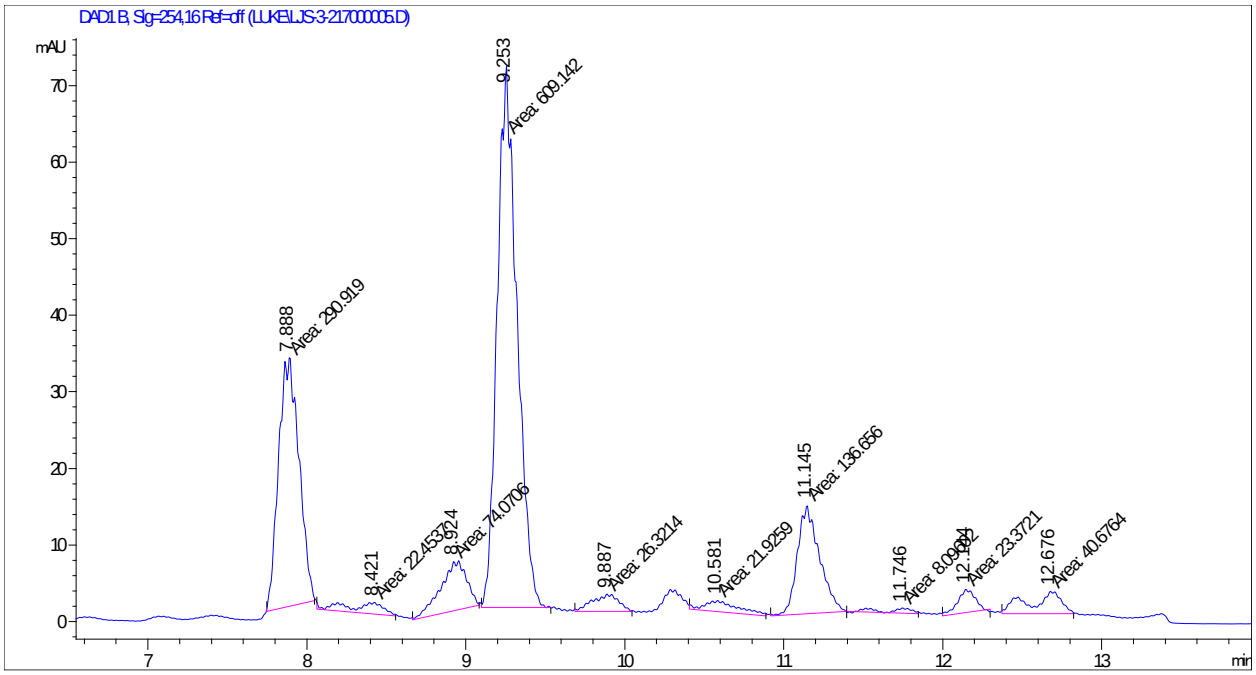
^{1}H NMR of macrcocycle 4.27 (DMSO-d6, 500 MHz)



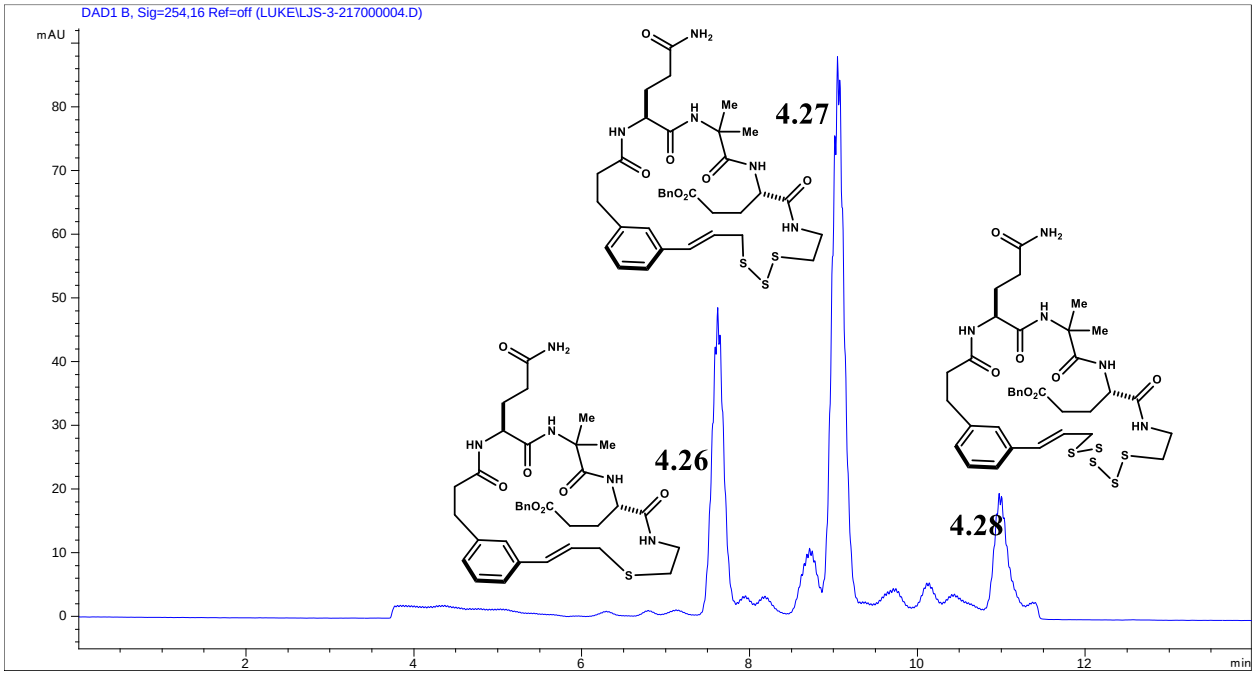
^{13}C NMR of macrcocycle 4.27 (DMSO-d6, 126 MHz)



254 nm HPLC Trace & Conditions for Trisulfide 4.27 and S_2 Products



Mono= 23.2% Tri= 48.6% Penta= 10.9% Unidentified= 17.3 %



Control

Column Flow	:	15.000 ml/
Stoptime	:	14.00 m
Posttime	:	Off

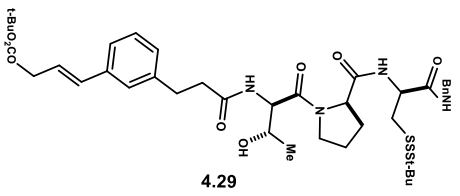
Solvents

Solvent A	:	55.0 % (W
Solvent B	:	45.0 % (M

Timetable

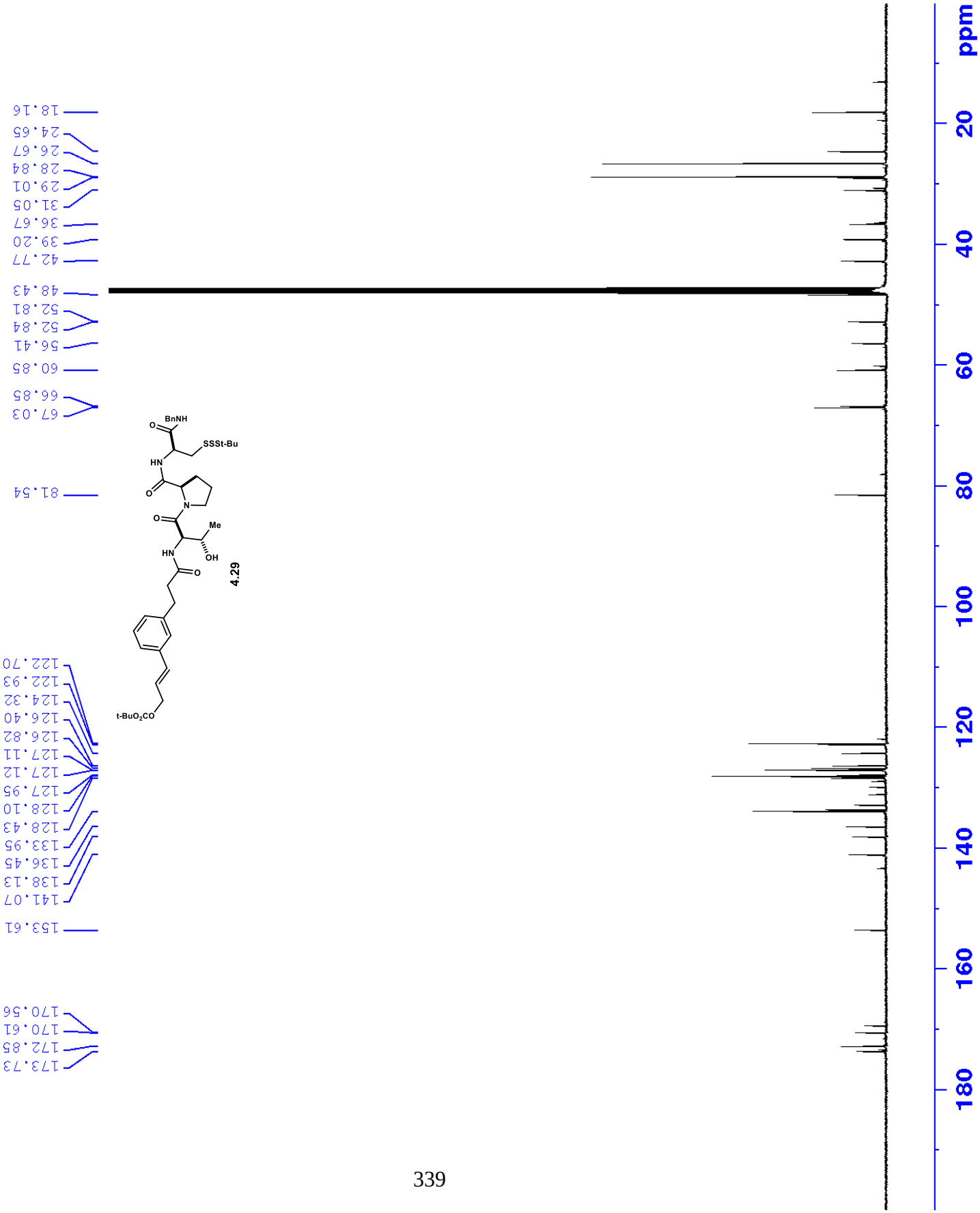
Time	Solv.B	Flow	Pressure
0.00	45.0	12.000	400
2.00	45.0	15.000	400
8.00	80.0	15.000	400
13.00	100.0	15.000	400
14.00	45.0	15.000	400

^{1}H NMR of compound 4.29 (MeOD-d4, 500 MHz)

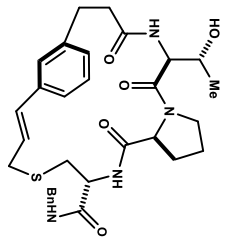


4.29

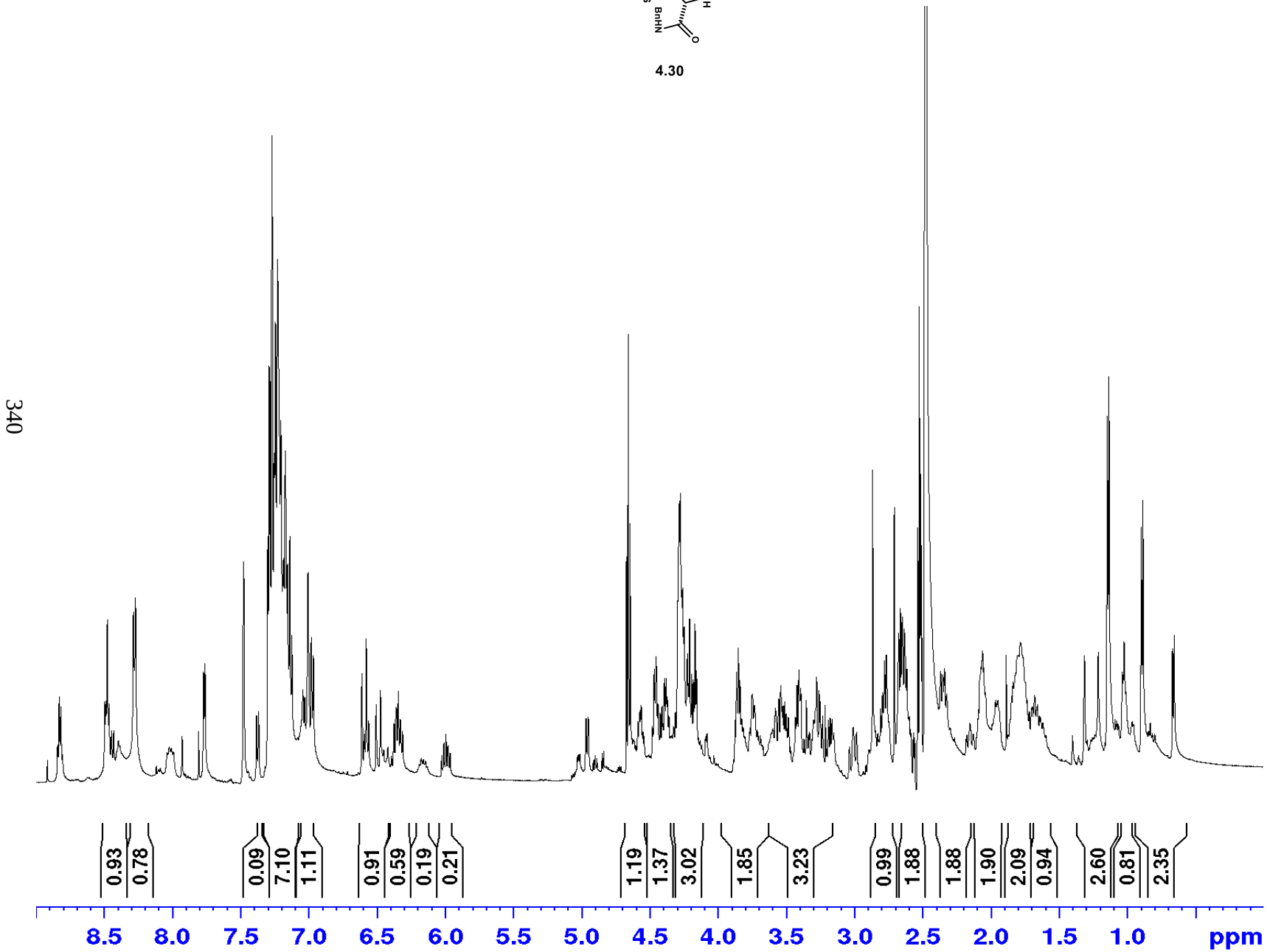
^{13}C NMR of compound 4.29 (MeOD-d4, 125 MHz)

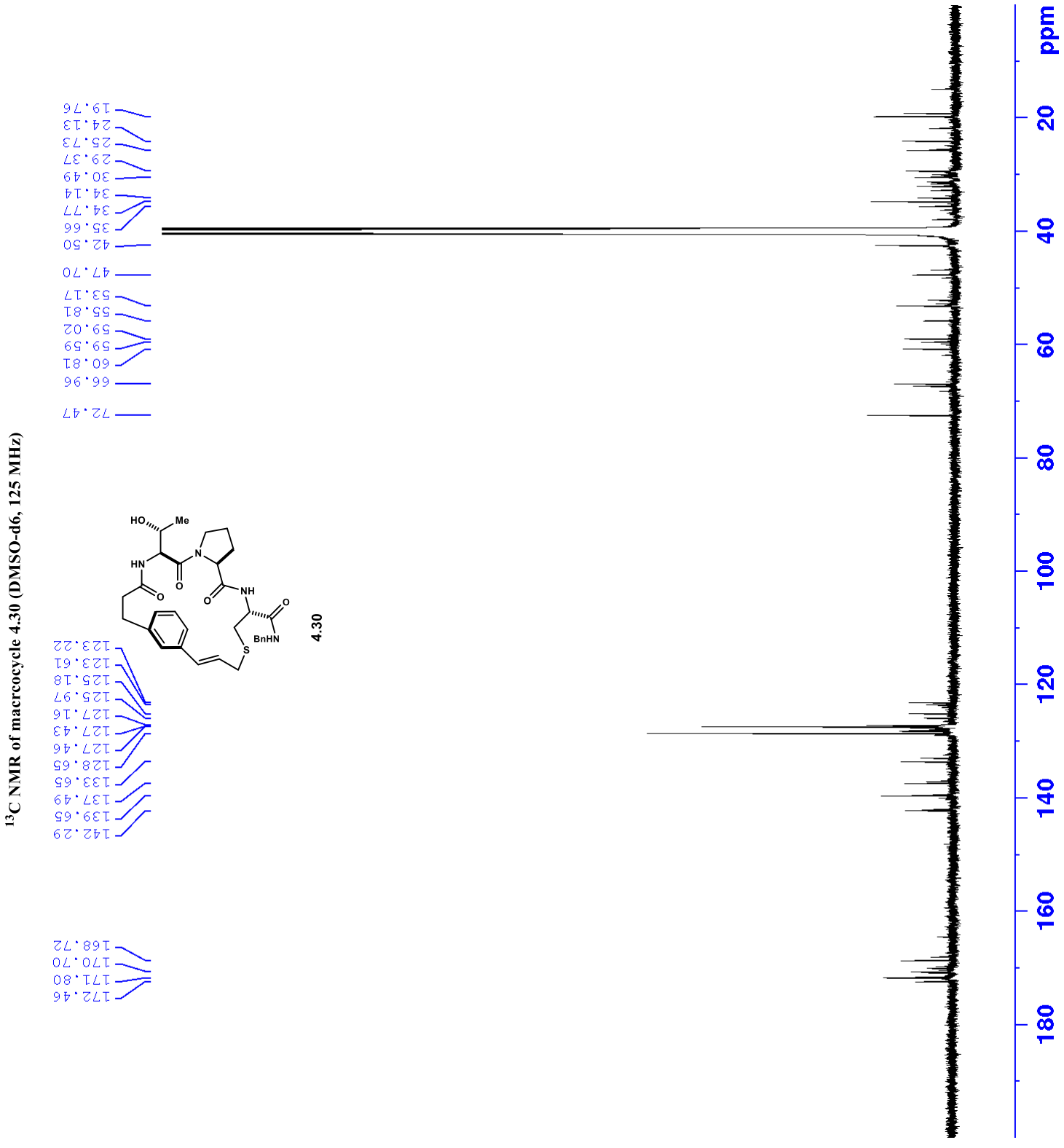


^{1}H NMR of macrcocycle 4.30 (DMSO-d6, 500 MHz)

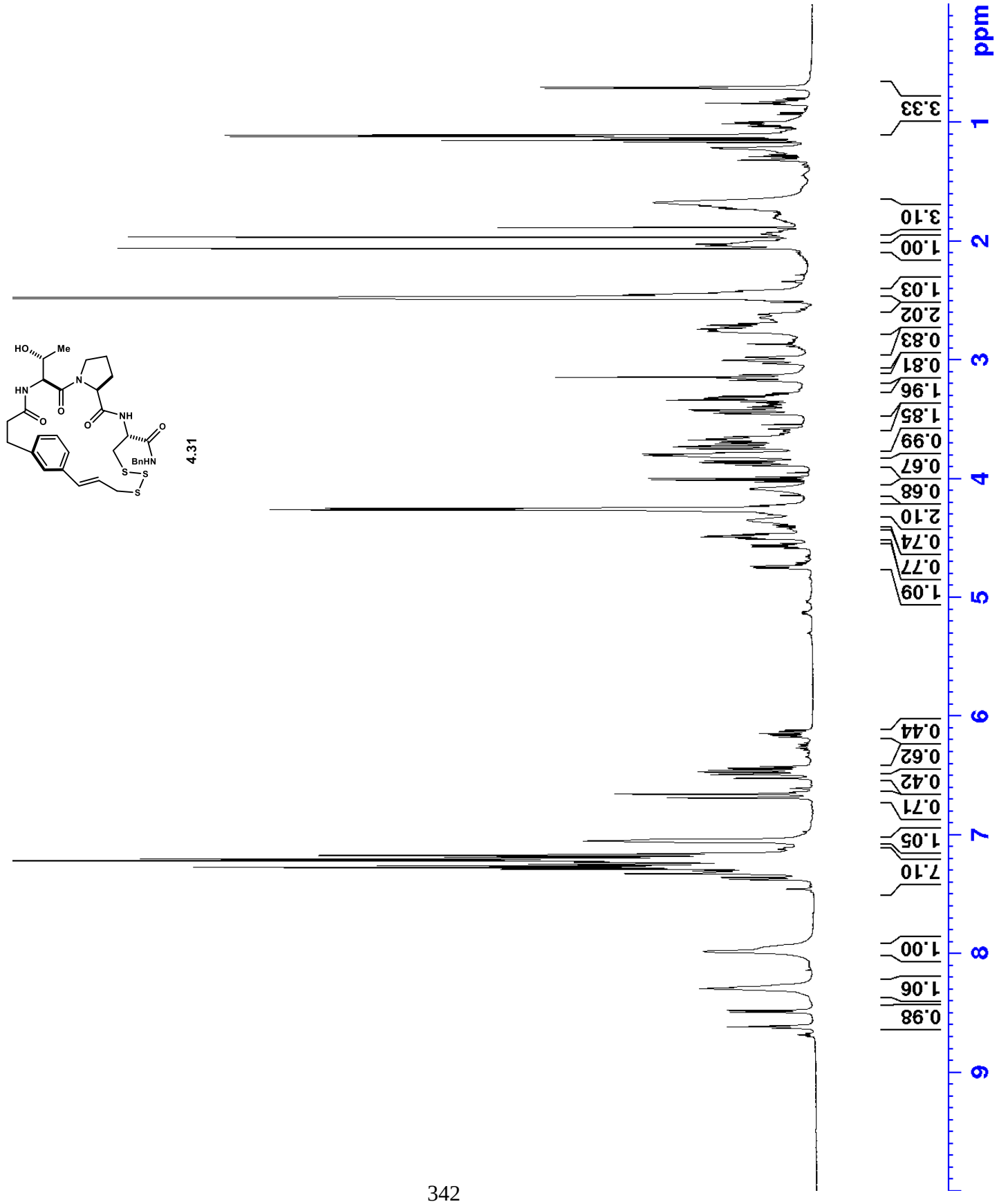


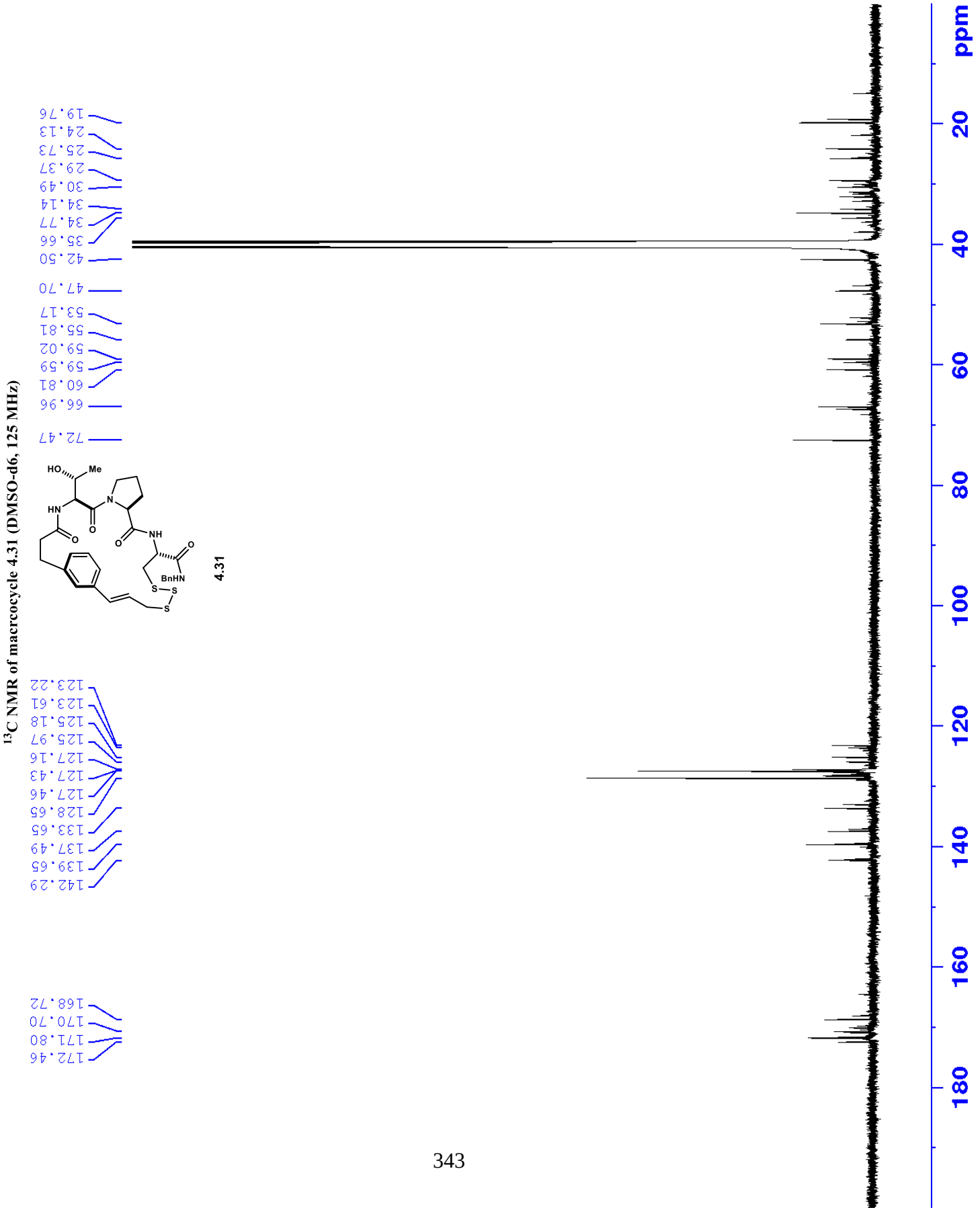
4.30



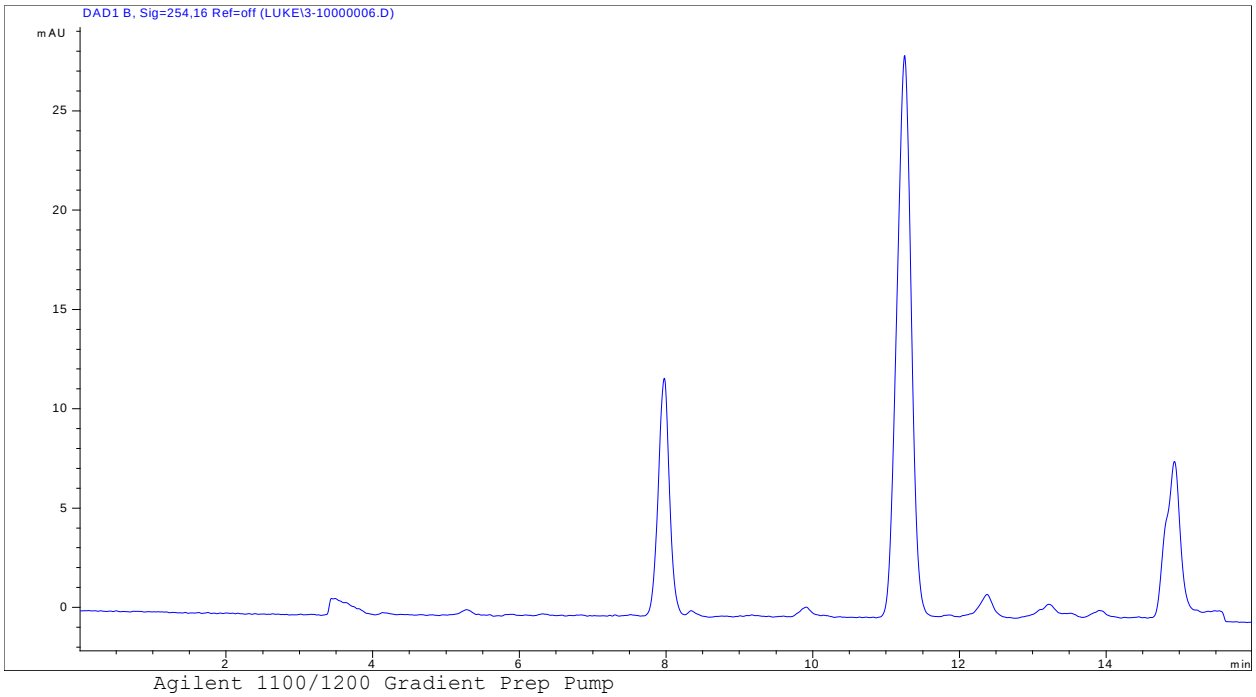

^{13}C NMR of macrocycle 4.30 (DMSO-d6, 125 MHz)
19.76
24.13
25.73
29.37
30.49
34.14
34.77
35.66
42.50
47.70
53.17
55.81
59.02
59.59
60.81
66.96
72.47
123.22
123.61
125.18
125.97
127.16
127.43
127.46
128.65
133.65
137.49
139.65
142.29
168.72
170.70
171.80
172.46
HO
Me
HN
N
O
NH
BnHN
S
4.30
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of macrocycle 4.31 (DMSO-d6, 500 MHz)




^{13}C NMR of macrcocycle 4.31 (DMSO-d6, 125 MHz)
19.76
24.13
25.73
29.37
30.49
34.14
34.77
35.66
42.50
47.70
53.17
55.81
59.02
59.59
60.81
66.96
72.47
123.22
123.61
125.18
125.97
127.16
127.43
127.46
128.65
133.65
137.49
139.65
142.29
168.72
170.70
171.80
172.46
HO
Me
HN
O
N
NH
BnHN
S
4.31
ppm
20
40
60
80
100
120
140
160
180

4.31 254nm hplc trace
SunFire® C18 OBD 5um
19x250mm column



Agilent 1100/1200 Gradient Prep Pump

==========

Control

Column Flow	:	15.000 ml/min
Stoptime	:	16.00 min
Posttime	:	Off

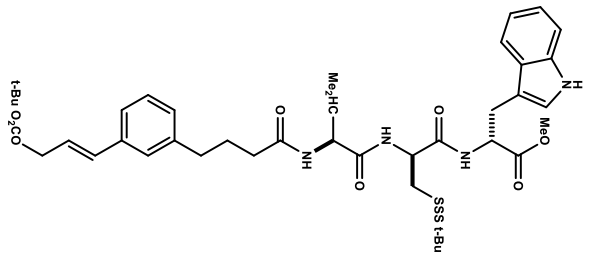
Solvents

Solvent A	:	60.0 % (Water)
Solvent B	:	40.0 % (Organic)

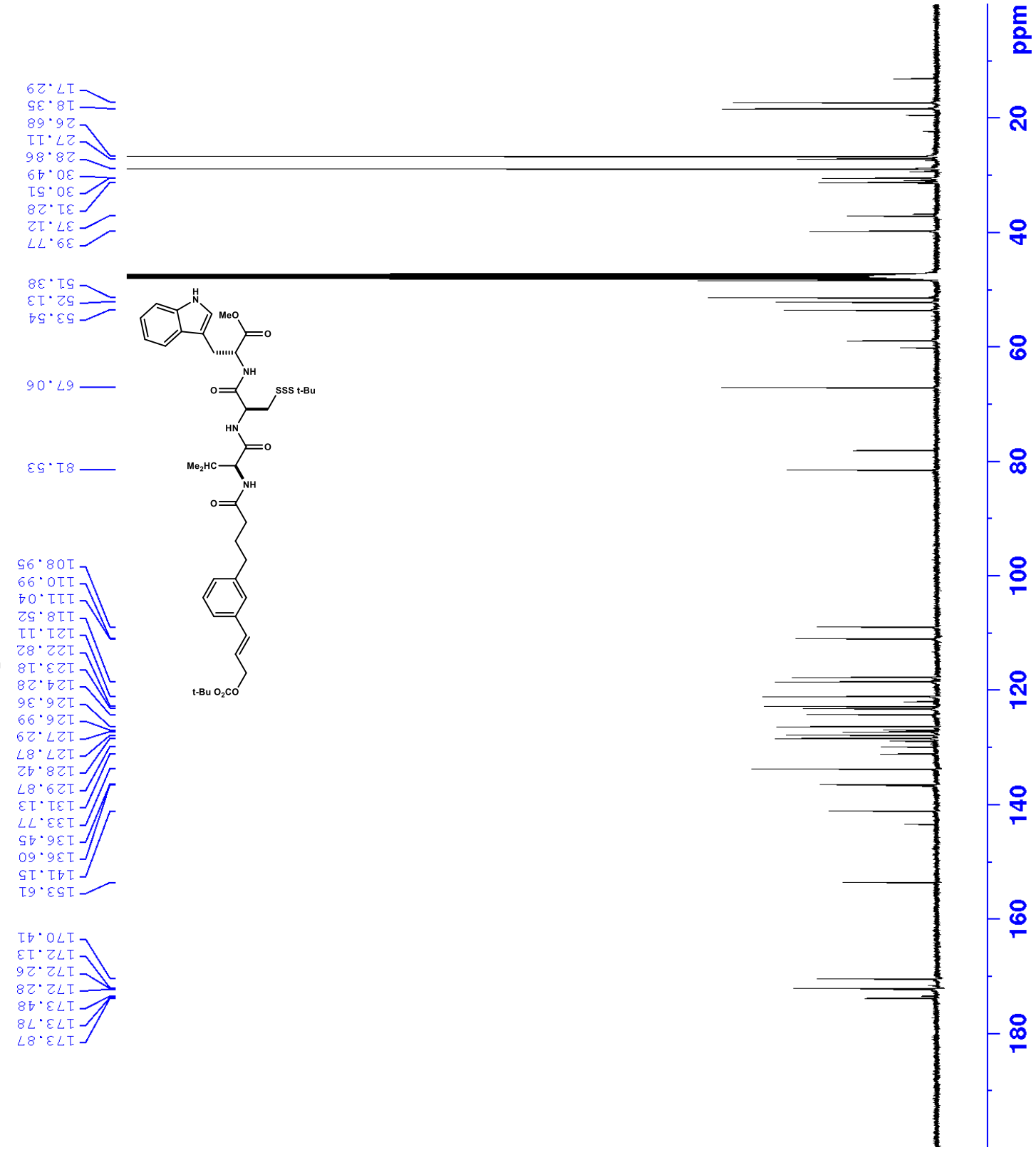
Timetable

Time	Solv.B	Flow	Pressure
0.00	40.0	10.000	
2.00	40.0	18.000	
14.00	80.0	18.000	
15.00	100.0	18.000	
16.00	35.0	18.000	

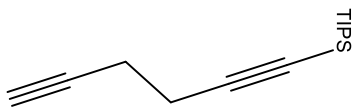
^{1}H NMR of compound 4.33 (MeOD-d4, 500 MHz)

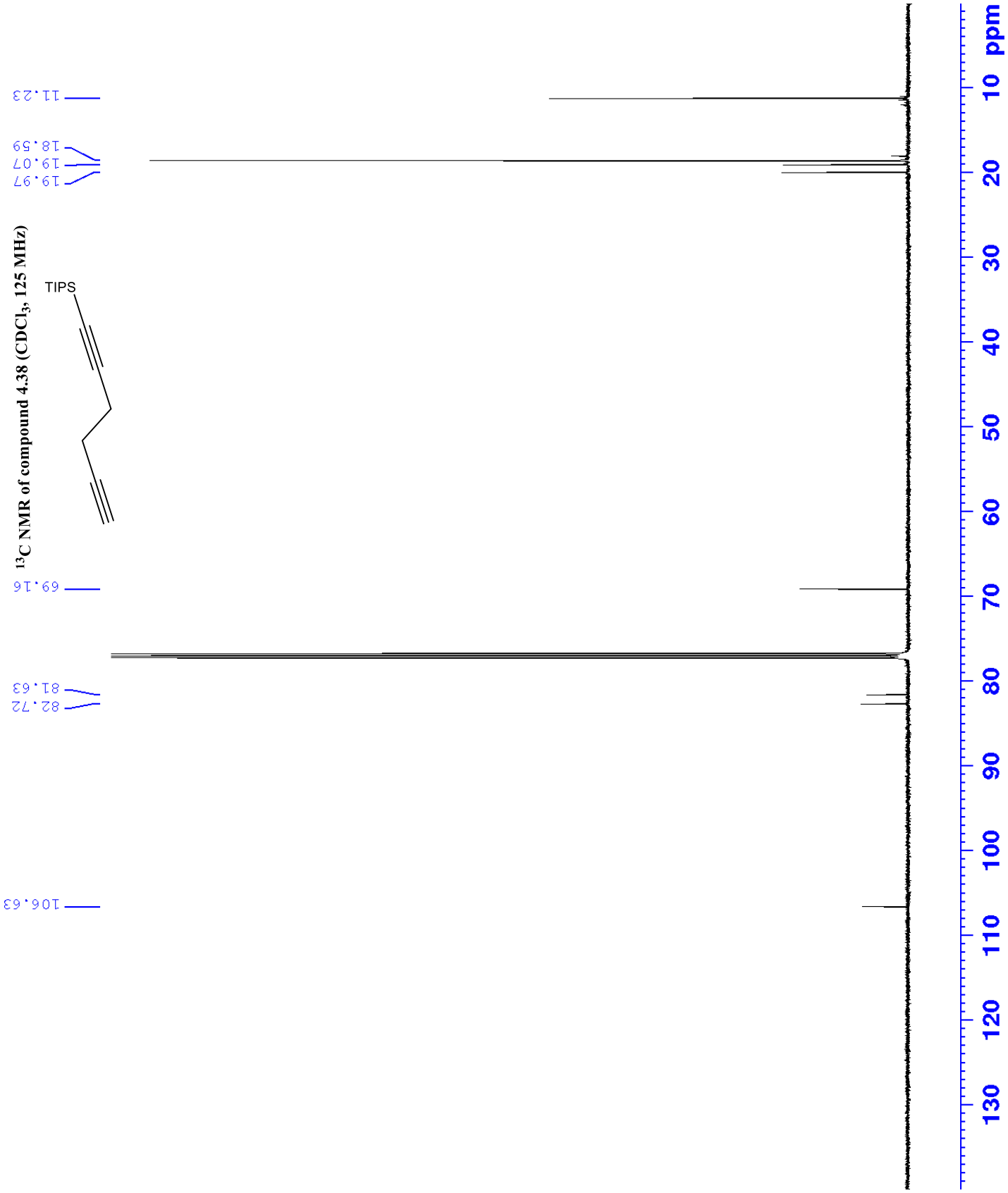


^{13}C NMR of compound 4.33 (MeOD-d4, 125 MHz)

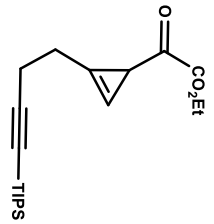


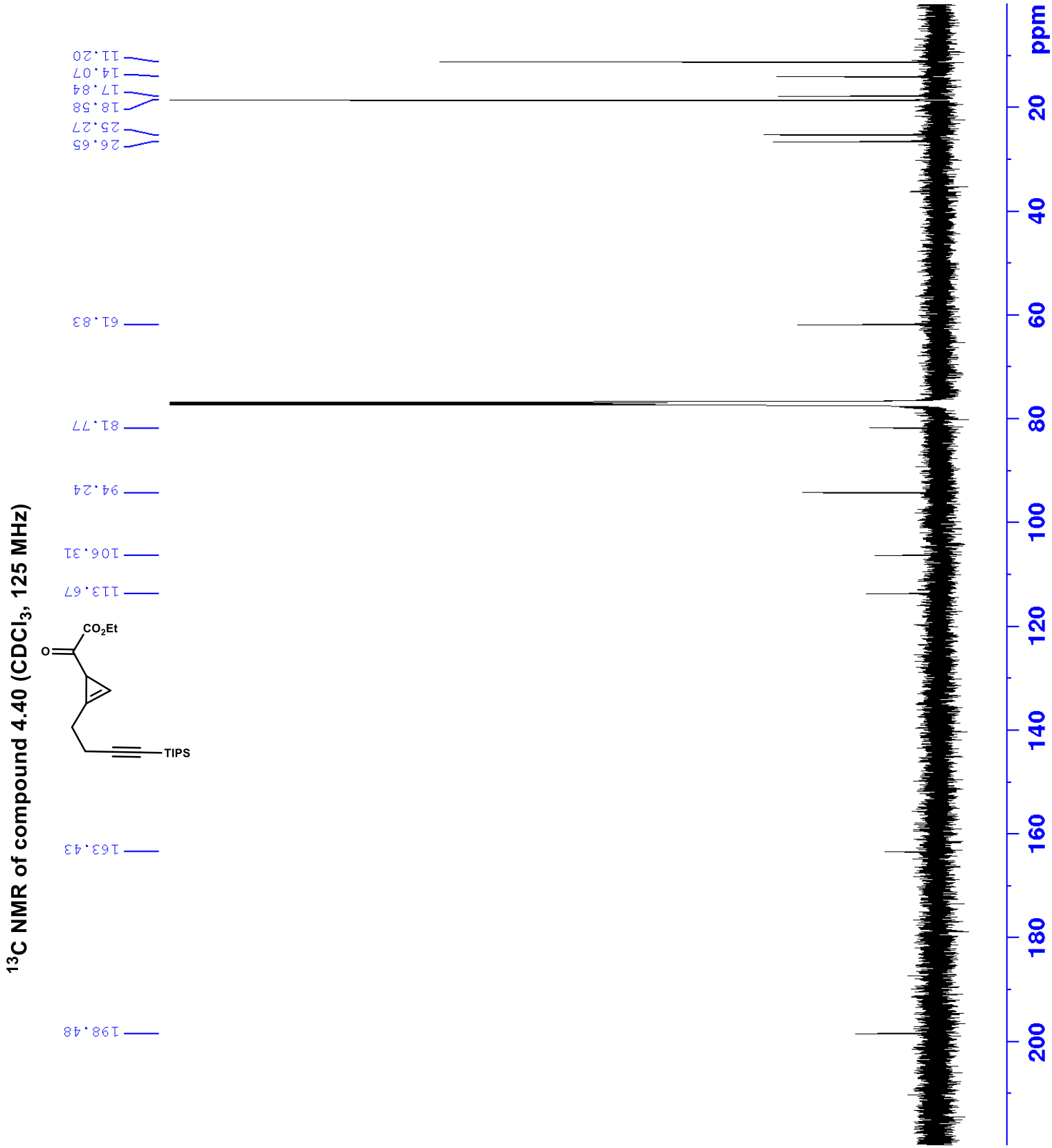
^{1}H NMR of compound 4.38 ($CDCl_3$, 500 MHz)



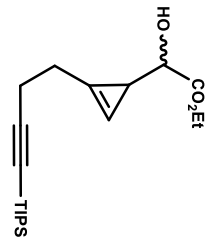

^{13}C NMR of compound 4.38 ($CDCl_3$, 125 MHz)
TIPS
11.23
18.59
19.07
19.97
69.16
81.63
82.72
106.63
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130

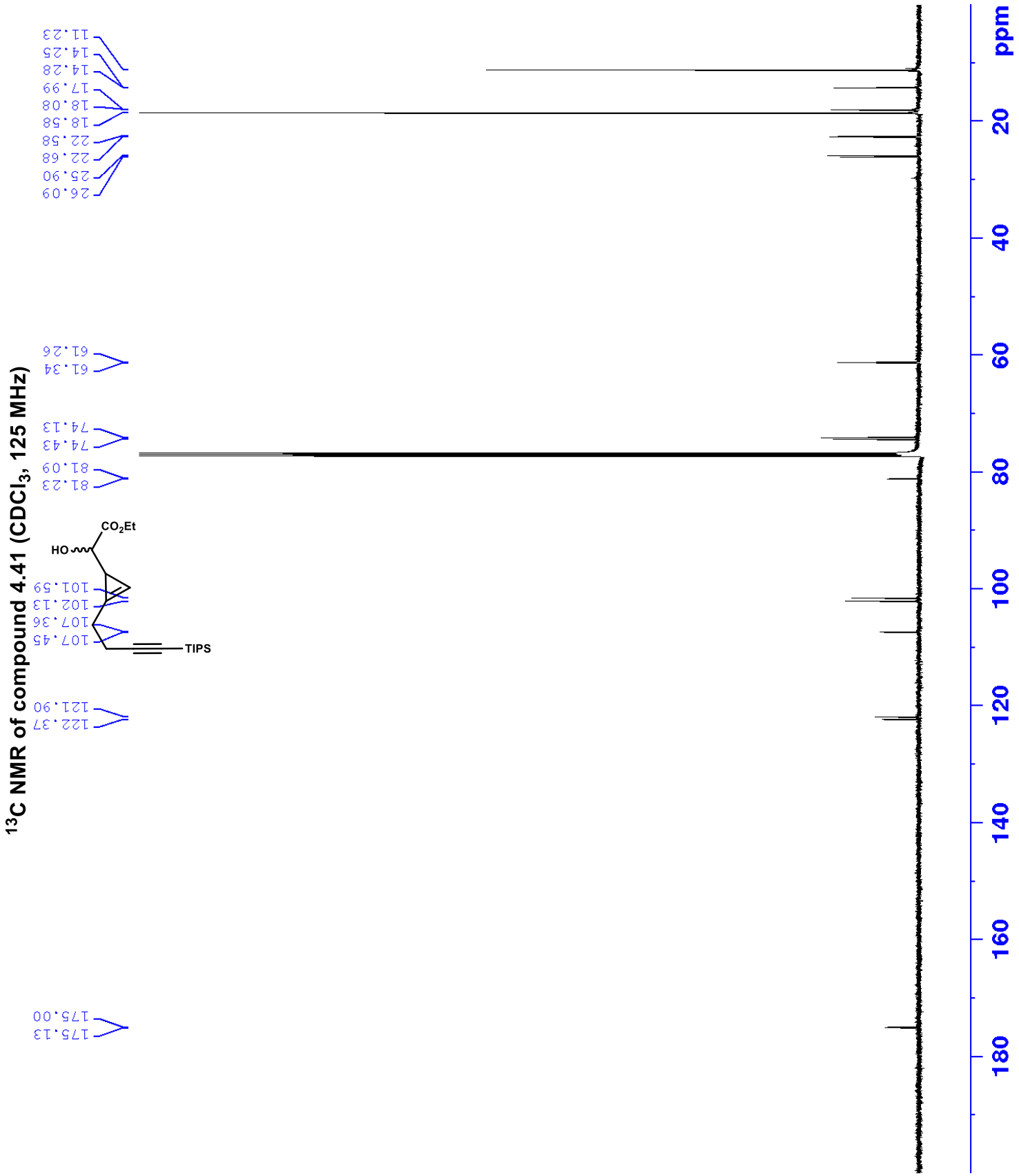
^{1}H NMR of compound 4.40 ($CDCl_3$, 500 MHz)



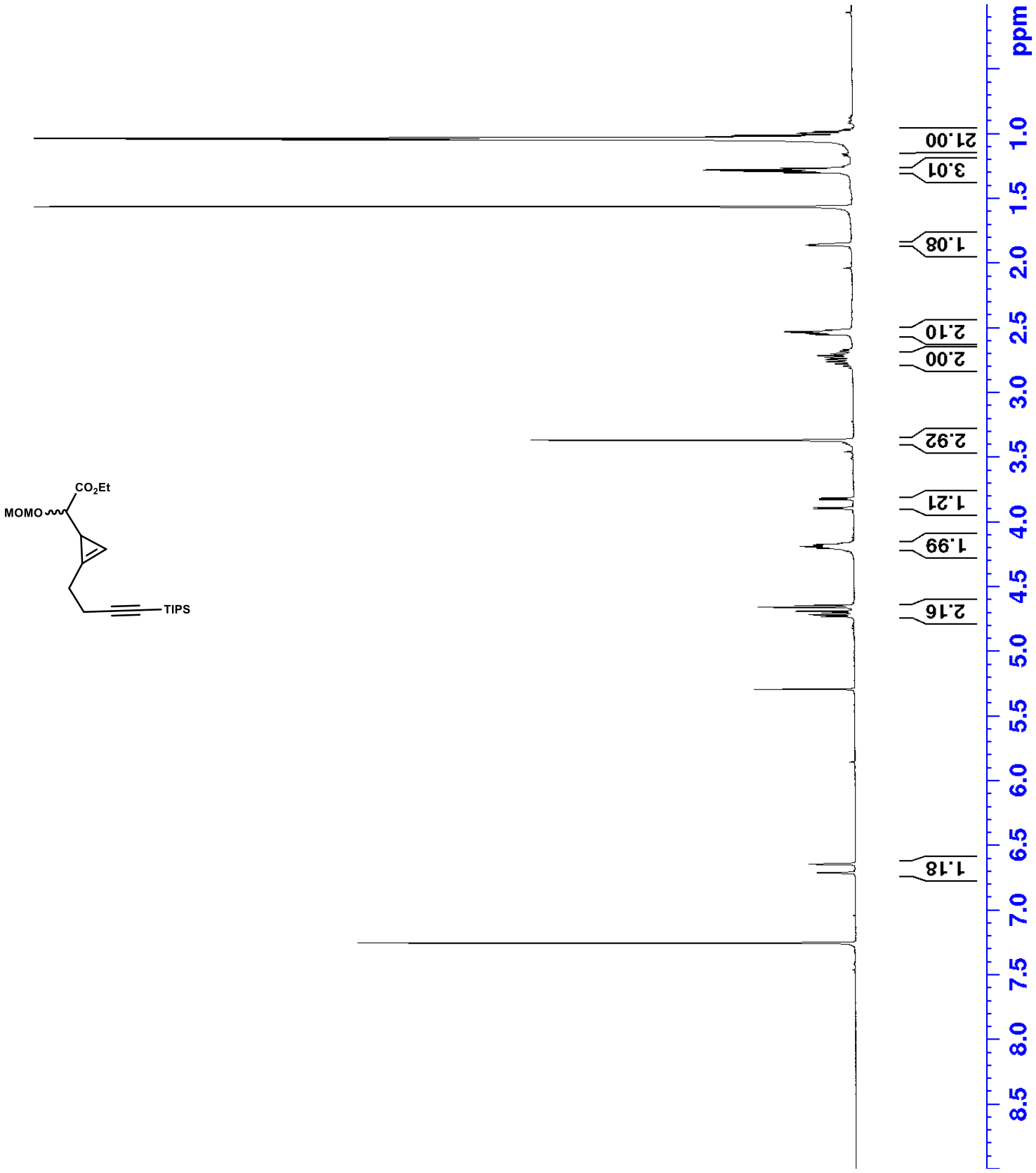

^{13}C NMR of compound 4.40 ($CDCl_3$, 125 MHz)
11.20
14.07
17.84
18.58
25.27
26.65
61.83
81.77
94.24
106.31
113.67
163.43
198.48
CO2Et
O
TIPS
ppm
20
40
60
80
100
120
140
160
180
200

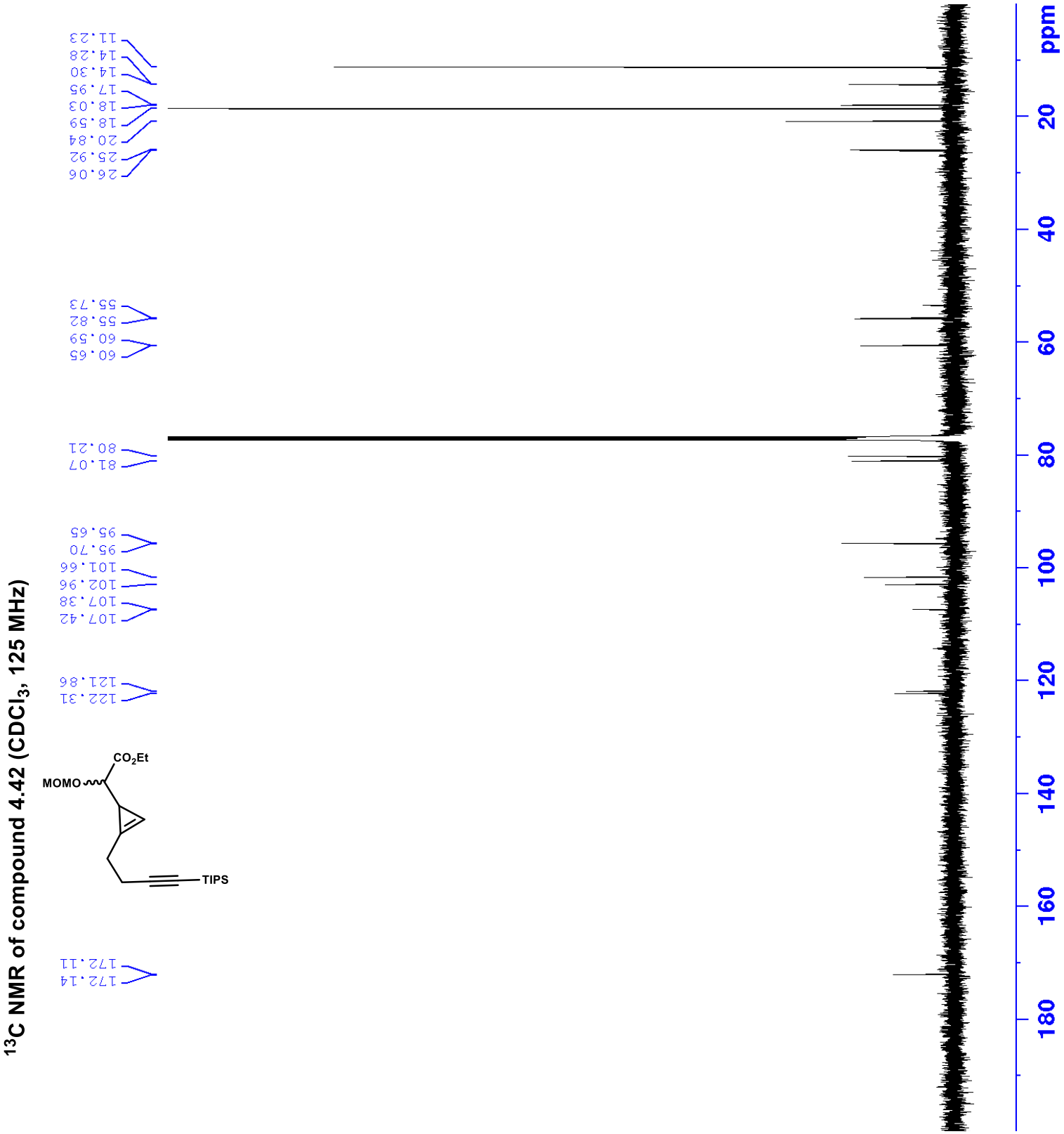
^{1}H NMR of compound 4.41 ($CDCl_3$, 500 MHz)

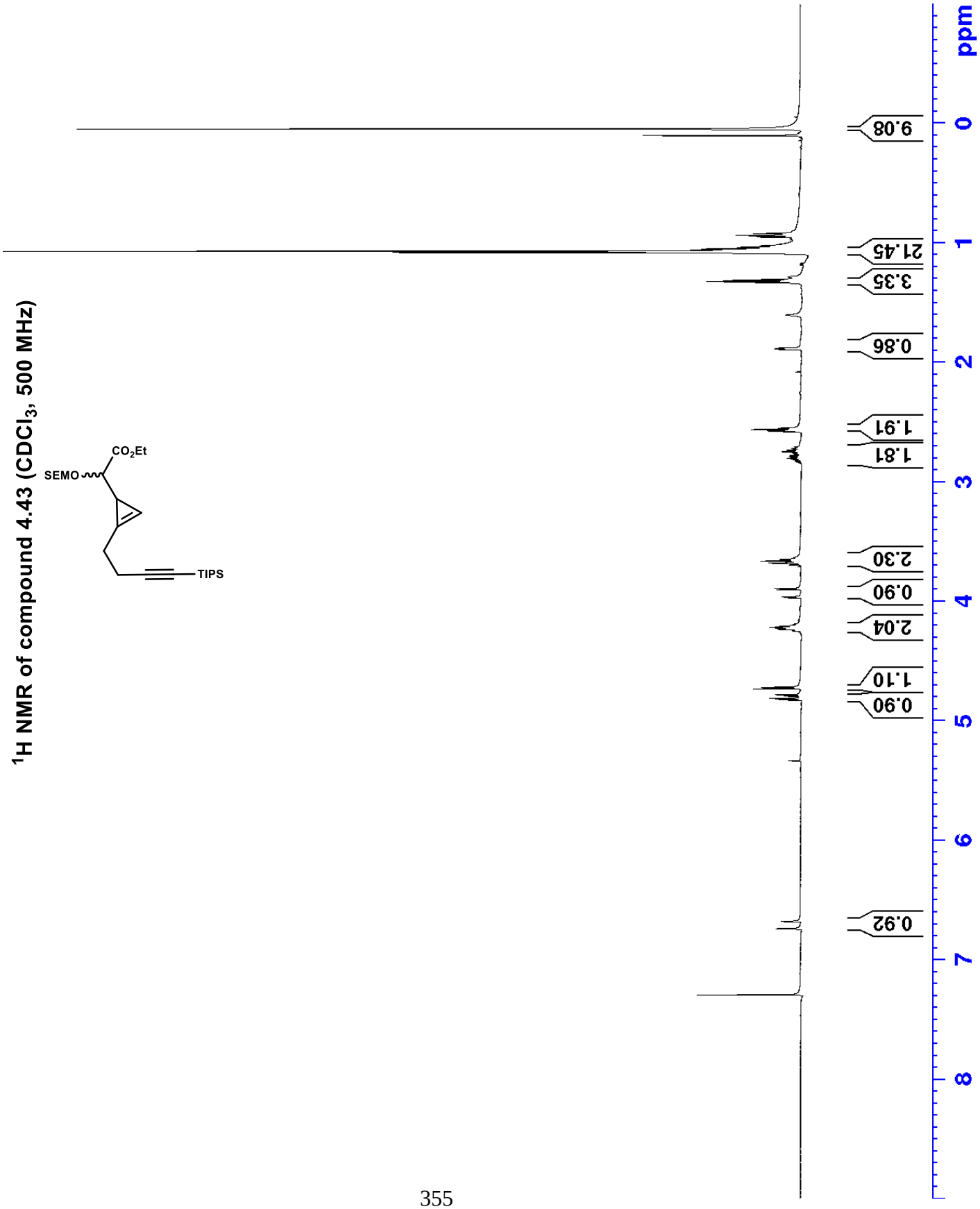


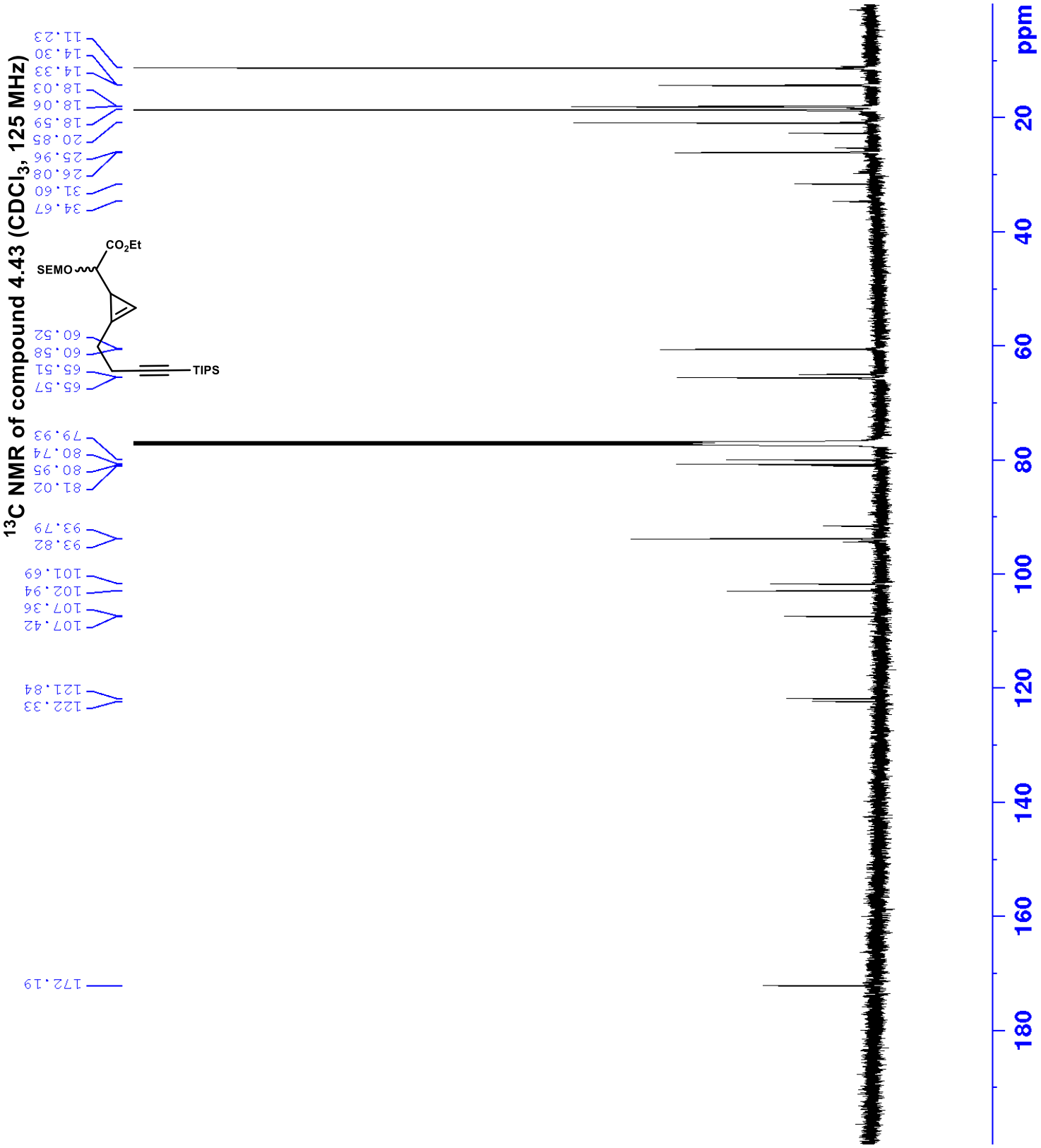

^{13}C NMR of compound 4.41 ($CDCl_3$, 125 MHz)
11.23
14.25
14.28
17.99
18.08
18.58
22.58
22.68
25.90
26.09
61.26
61.34
74.13
74.43
81.09
81.23
101.59
102.13
107.36
107.45
121.90
122.37
175.00
175.13
CO2Et
HO
TIPS
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 4.42 ($CDCl_3$, 500 MHz)

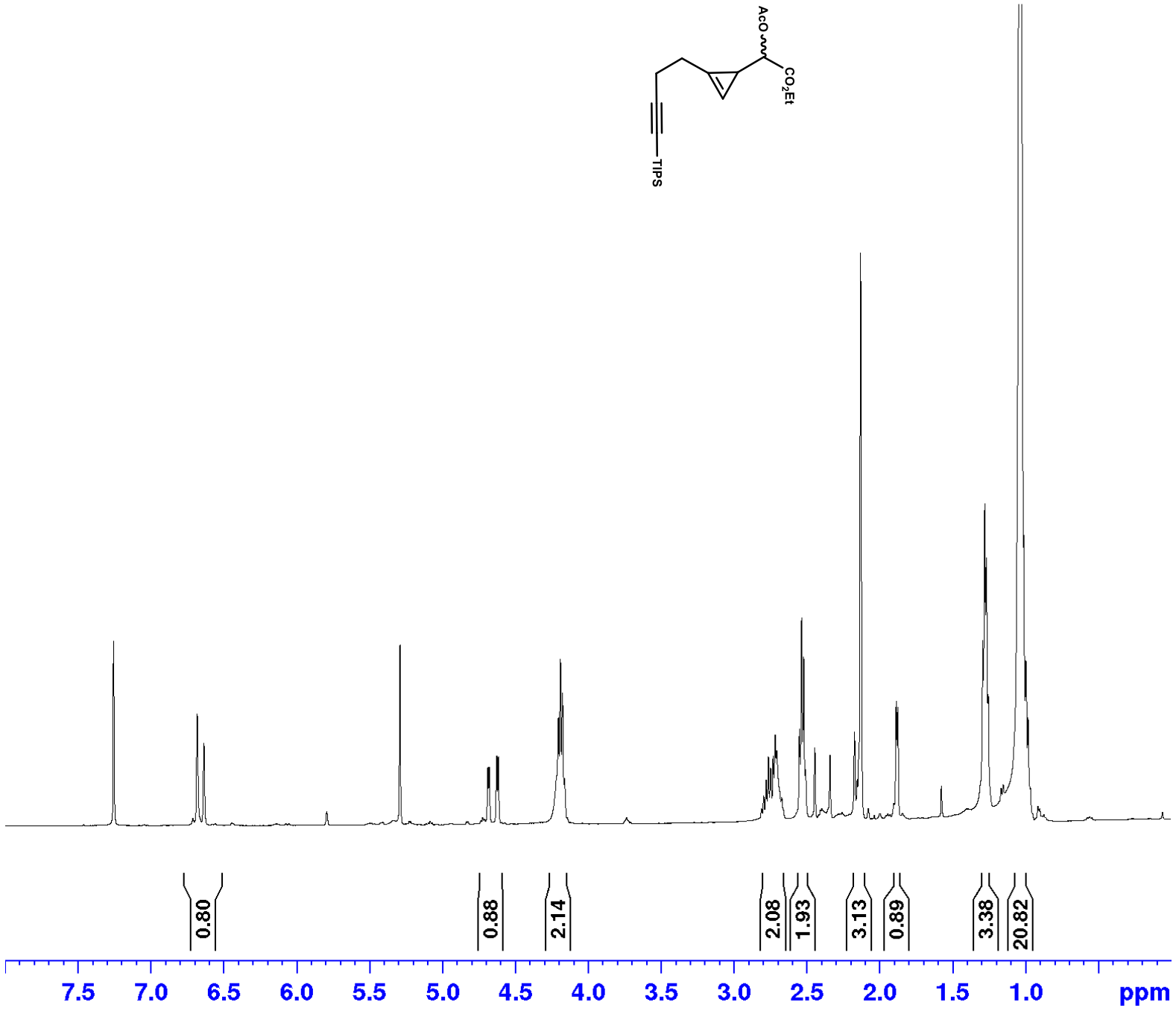


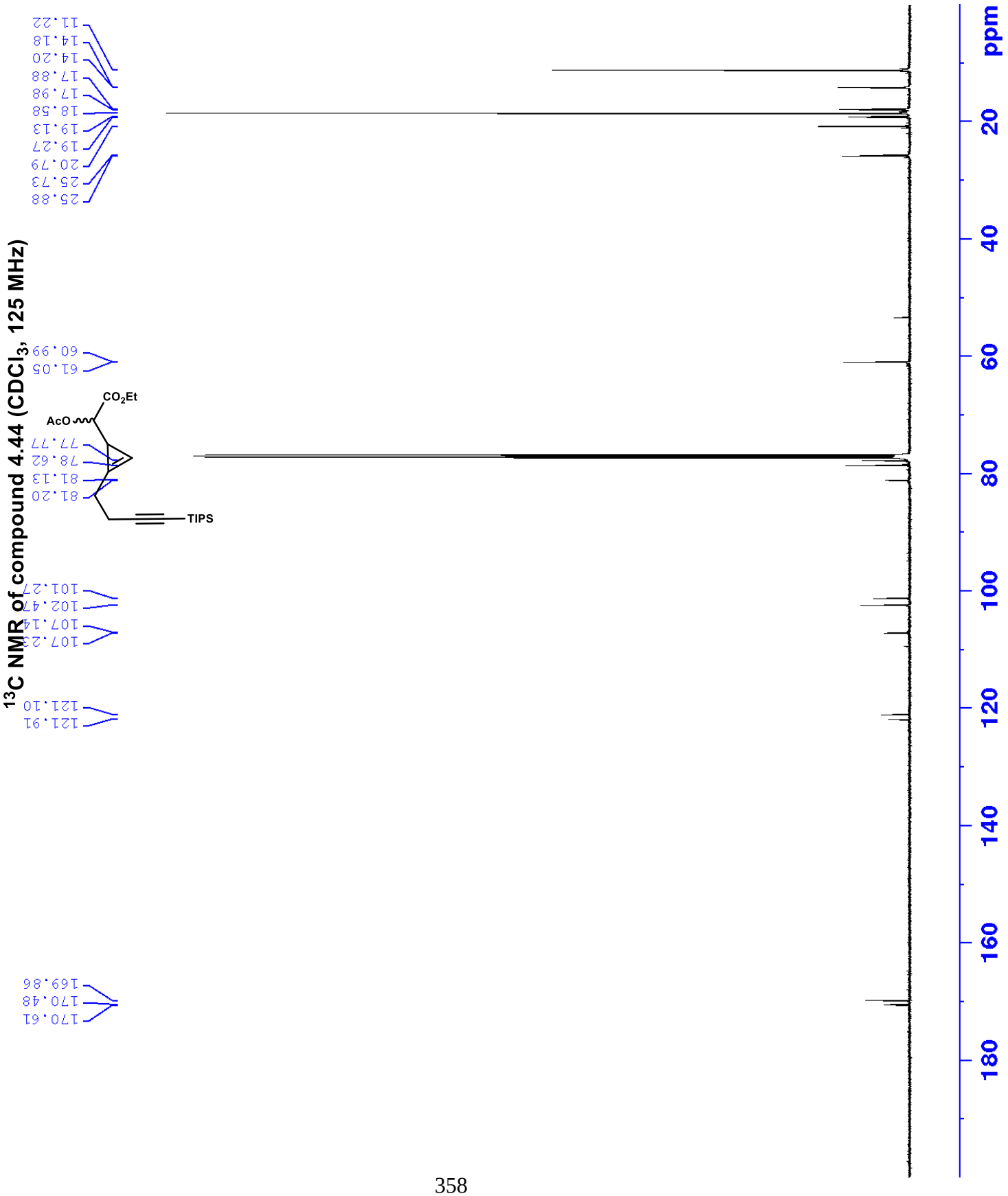

^{13}C NMR of compound 4.42 ($CDCl_3$, 125 MHz)
11.23
14.28
14.30
17.95
18.03
18.59
20.84
25.92
26.06
55.73
55.82
60.59
60.65
80.21
81.07
95.65
95.70
101.66
102.96
107.38
107.42
121.86
122.31
172.11
172.14
CO2Et
MOMO
TIPS
ppm
20
40
60
80
100
120
140
160
180


^{1}H NMR of compound 4.43 ($CDCl_3$, 500 MHz)
CO_2Et
SEMO
TIPS
9.08
21.45
3.35
0.86
1.91
1.81
2.30
0.90
2.04
1.10
0.90
0.92
ppm
0
1
2
3
4
5
6
7
8

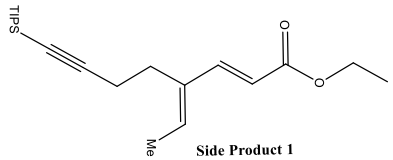

^{13}C NMR of compound 4.43 ($CDCl_3$, 125 MHz)
11.23
14.30
14.33
18.03
18.06
18.59
20.85
25.96
26.08
31.60
34.67
CO2Et
SEMO
60.52
60.58
65.51
65.57
TIPS
79.93
80.74
80.95
81.02
93.79
93.82
101.69
102.94
107.36
107.42
121.84
122.33
172.19
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 4.44 ($CDCl_3$, 500 MHz)



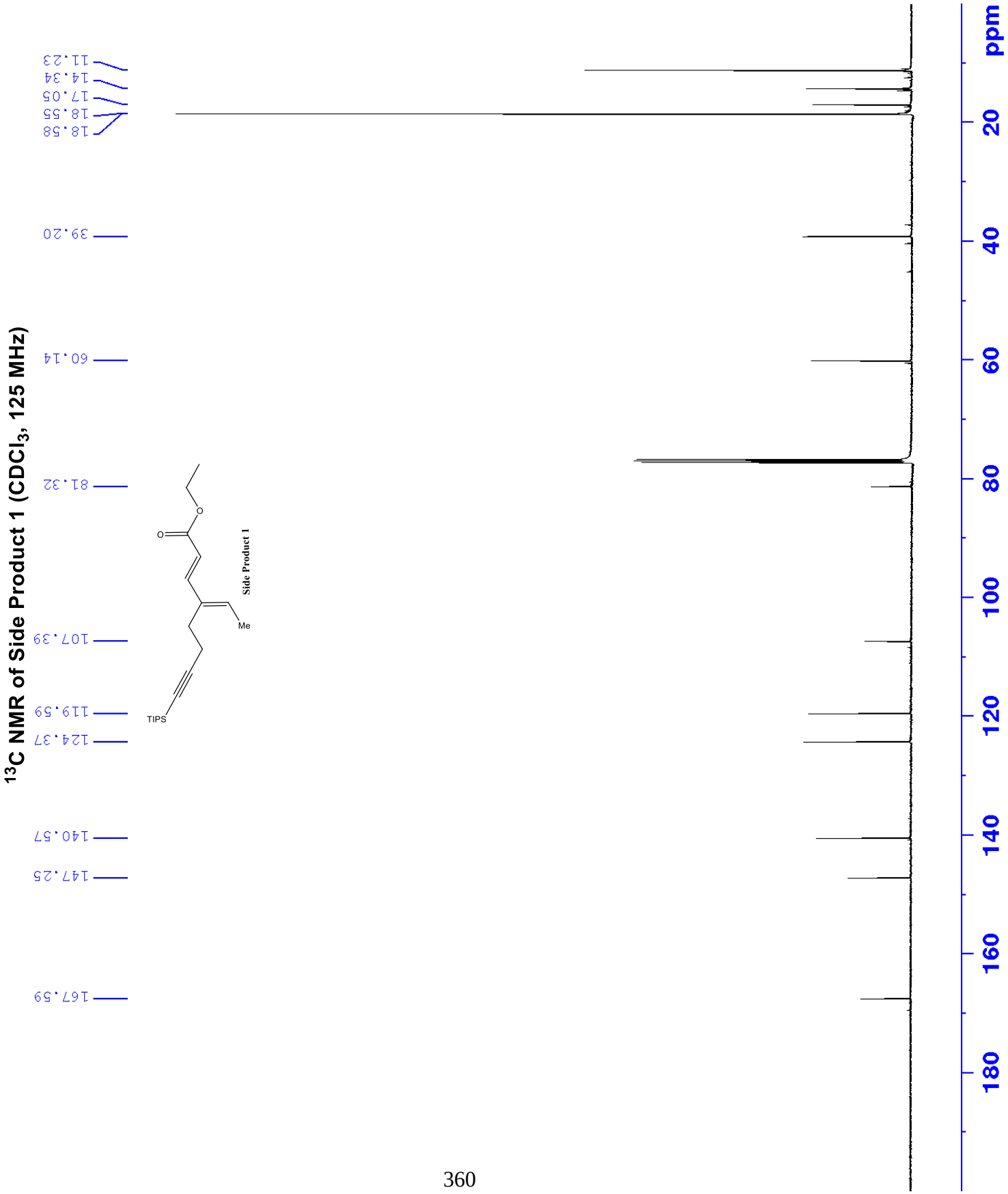

^{13}C NMR of compound 4.44 ($CDCl_3$, 125 MHz)
11.22
14.18
14.20
17.88
17.98
18.58
19.13
19.27
20.79
25.73
25.88
60.99
61.05
CO_2Et
AcO
77.77
78.62
81.13
81.20
TIPS
101.27
102.47
107.14
107.23
121.10
121.91
169.86
170.48
170.61
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of Side Product 1 ($CDCl_3$, 500 MHz)

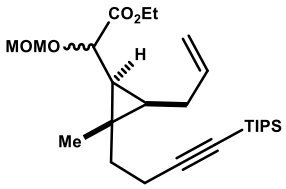


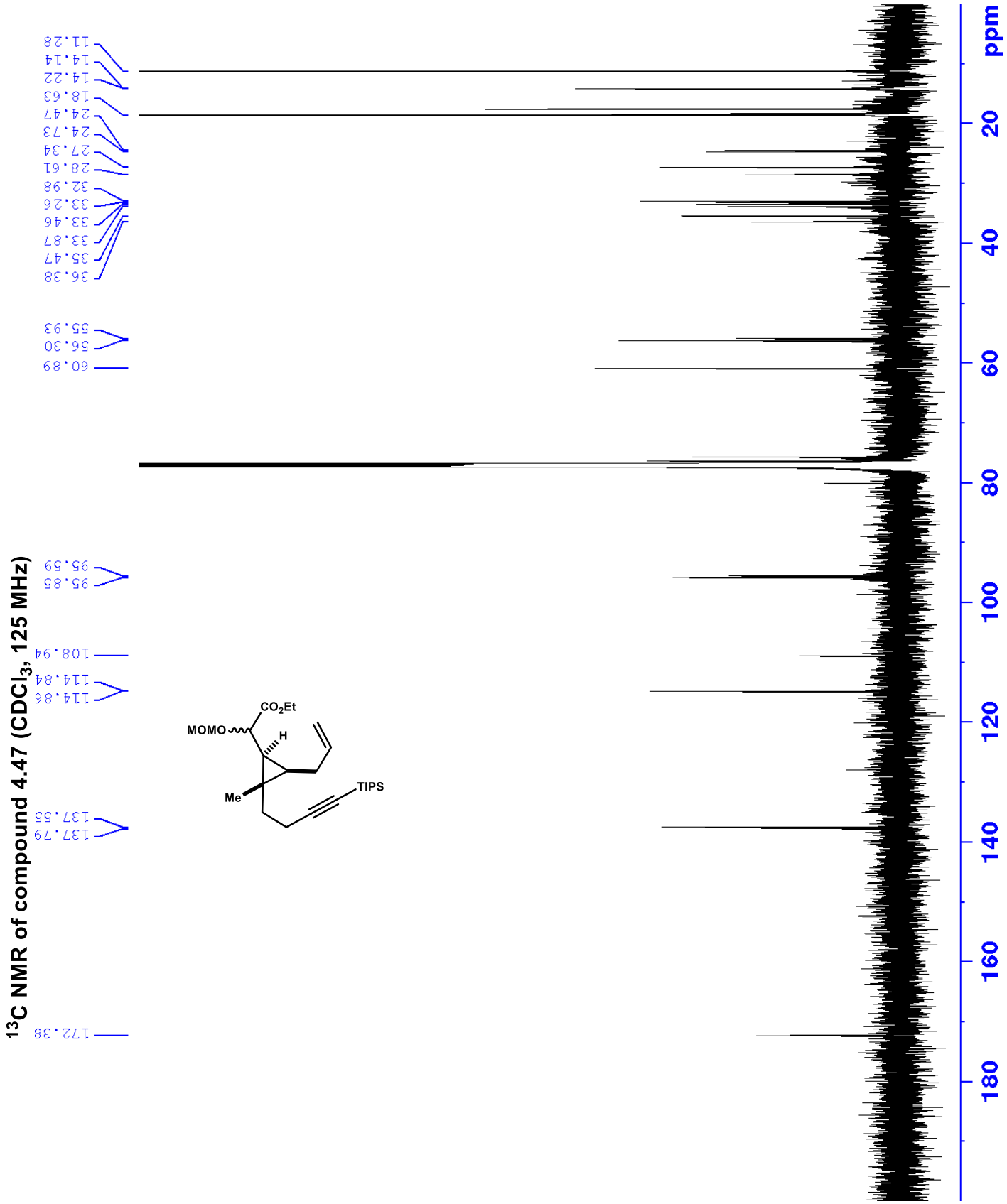
Side Product 1

359

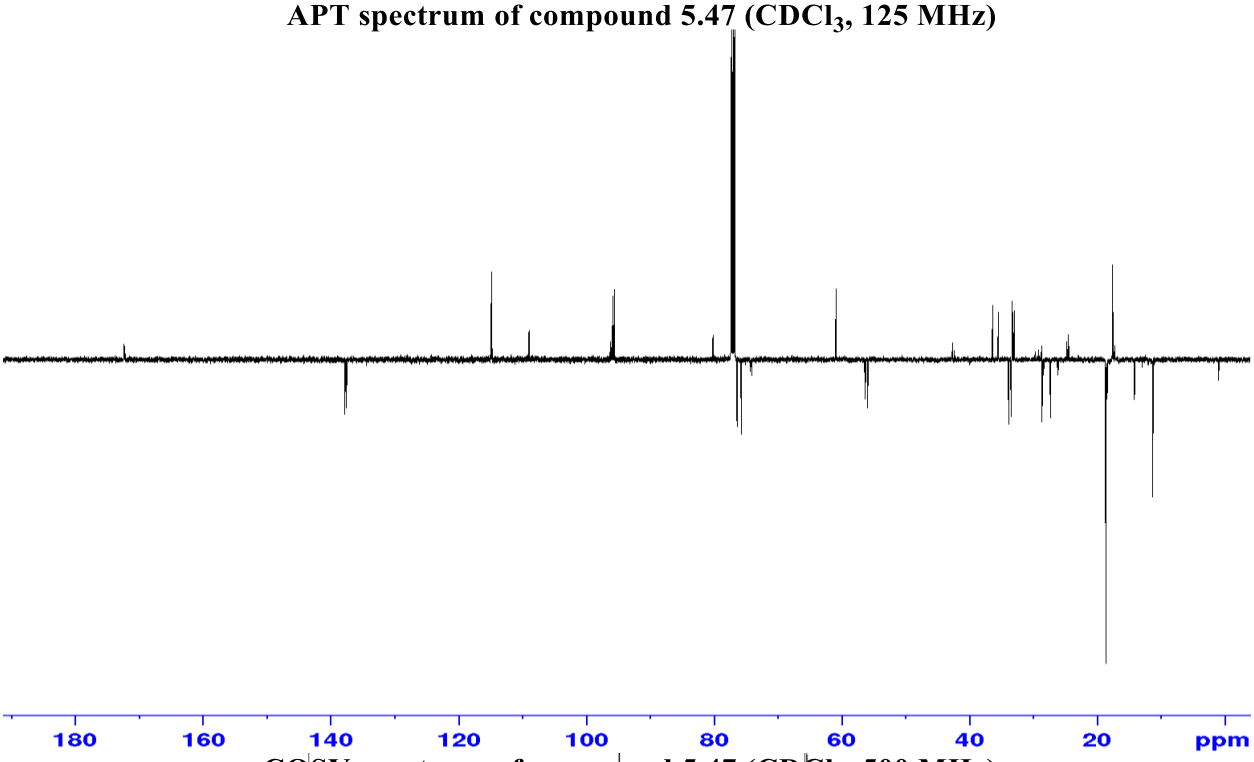

^{13}C NMR of Side Product 1 (CDCl$_3$, 125 MHz)
11.23
14.34
17.05
18.55
18.58
39.20
60.14
81.32
107.39
119.59
124.37
140.57
147.25
167.59
O
O
Me
TIPS
Side Product 1
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 4.47 ($CDCl_3$, 500 MHz)

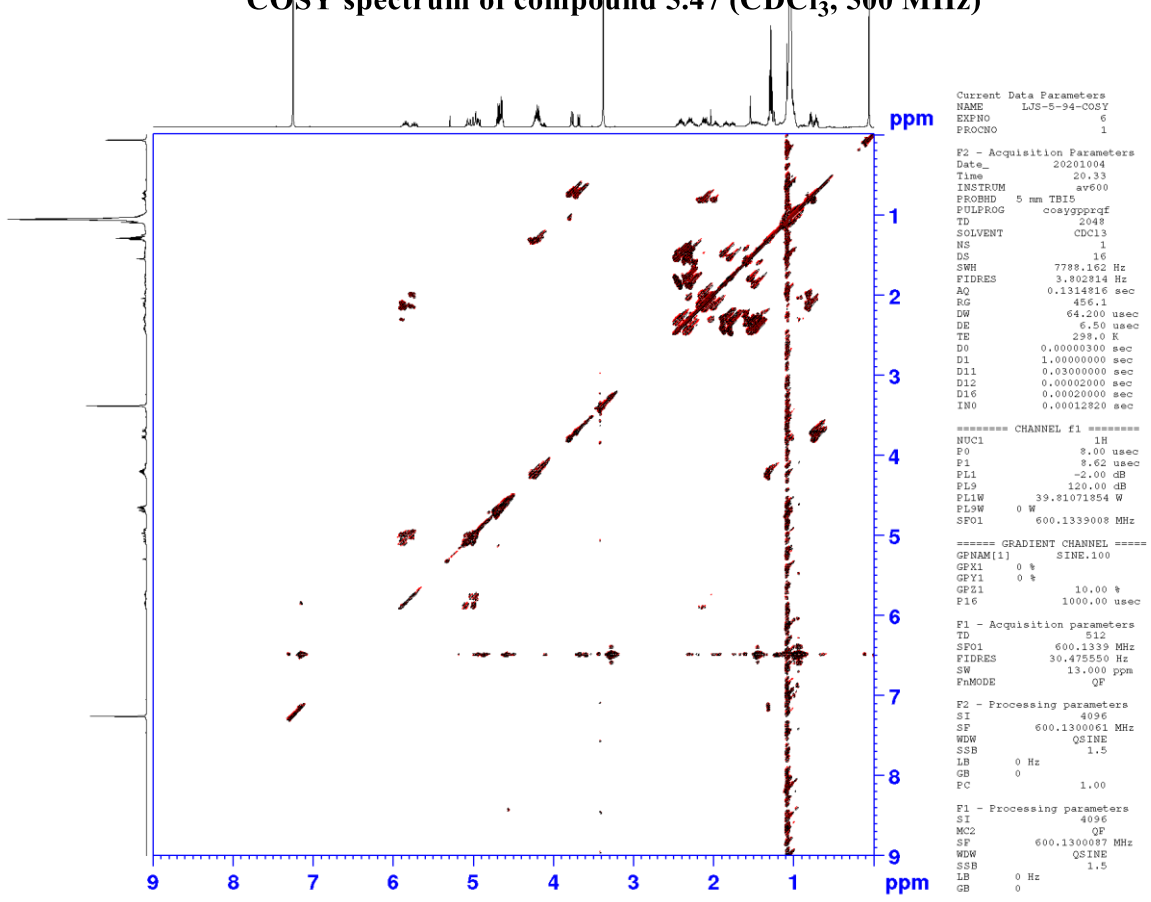



^{13}C NMR of compound 4.47 ($CDCl_3$, 125 MHz)
11.28
14.14
14.22
18.63
24.47
24.73
27.34
28.61
32.98
33.26
33.46
33.87
35.47
36.38
55.93
56.30
60.89
95.59
95.85
108.94
114.84
114.86
137.55
137.79
172.38
CO2Et
MOMO
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180

APT spectrum of compound 5.47 ($CDCl_3$, 125 MHz)



COSY spectrum of compound 5.47 ($CDCl_3$, 500 MHz)

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Current Data Parameters
NAME        LJS-5-94-COSY
EXPNO                   6
PROCNO                  1

F2 - Acquisition Parameters
Date_           20201004
Time              20.33
INSTRUM           av600
PROBHD    5 mm TBI5
PULPROG      cosygpprqf
TD                2048
SOLVENT           CDCl3
NS                   1
DS                  16
SWH            7788.162 Hz
FIDRES         3.802814 Hz
AQ             0.1314816 sec
RG                456.1
DW               64.200 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           0.00012820 sec

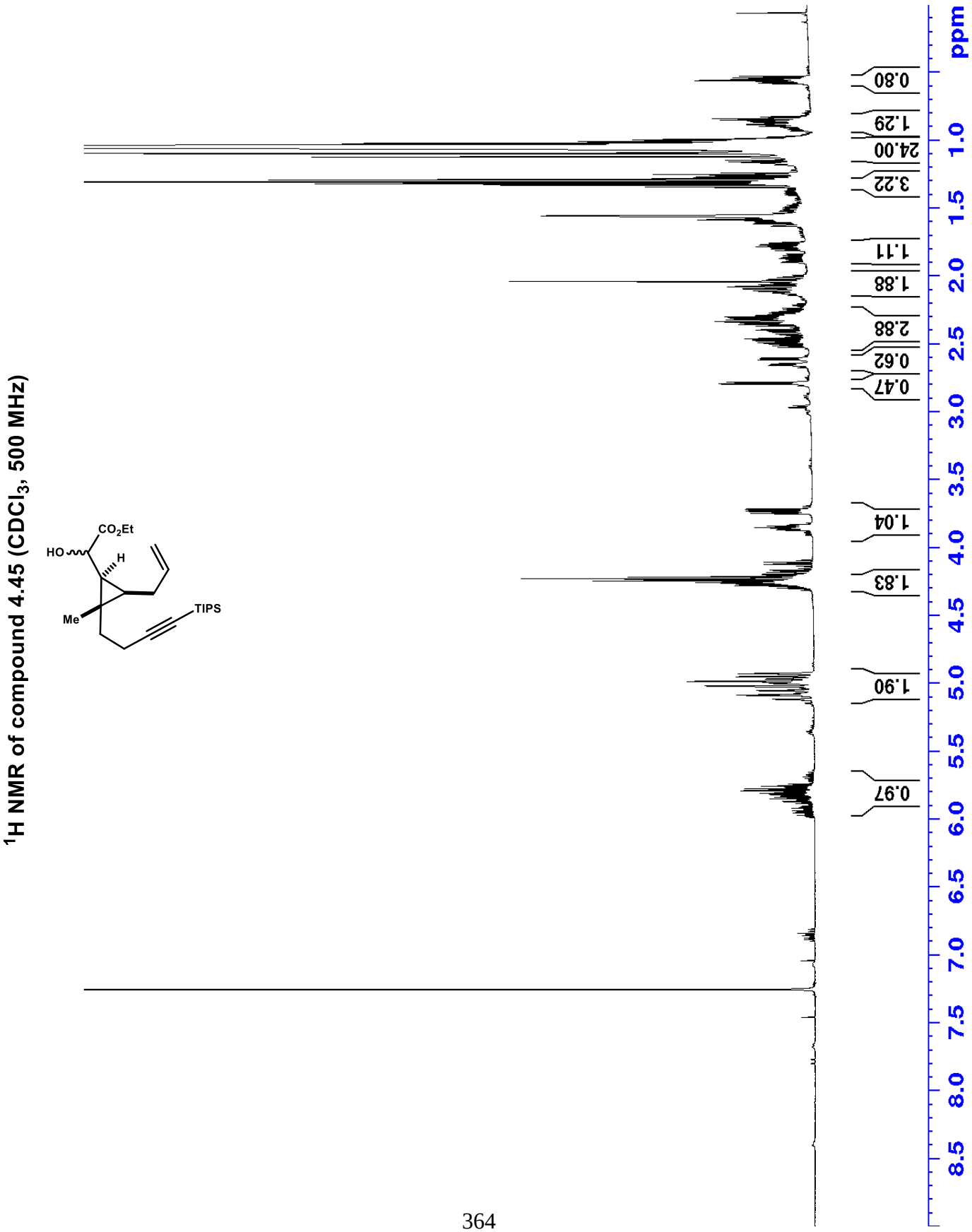
======== CHANNEL f1 ========
NUC1                 1H
P0                 8.00 usec
P1                 8.62 usec
PL1               -2.00 dB
PL9              120.00 dB
PL1W       39.81071854 W
PL9W     0 W
SFO1        600.1339008 MHz

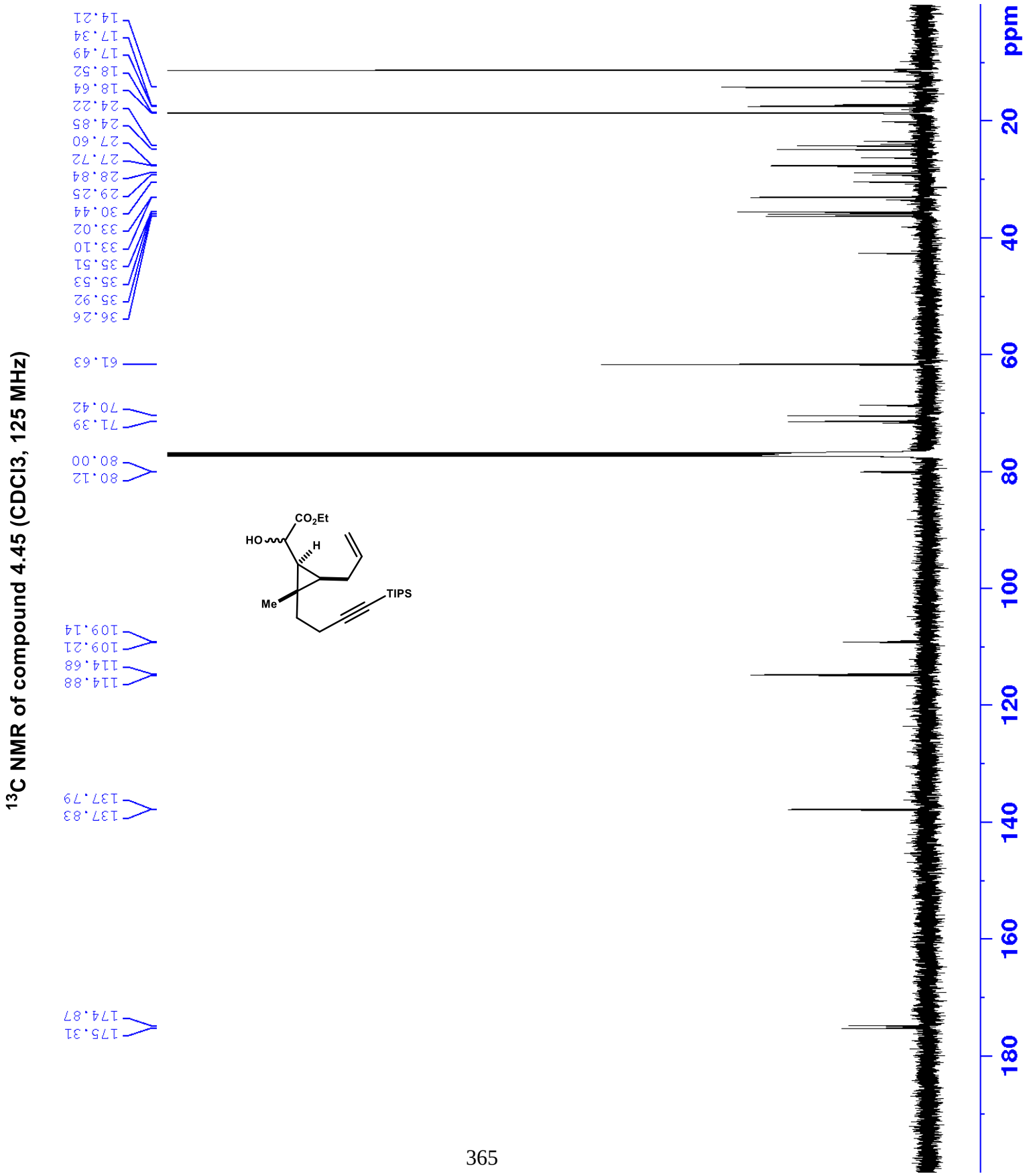
====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPX1     0 %
GPY1     0 %
GPZ1              10.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                 512
SFO1            600.1339 MHz
FIDRES         30.475550 Hz
SW                13.000 ppm
FnMODE              QF

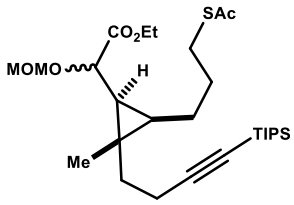
F2 - Processing parameters
SI                 4096
SF            600.1300061 MHz
WDW                QSINE
SSB                  1.5
LB       0 Hz
GB       0
PC                 1.00

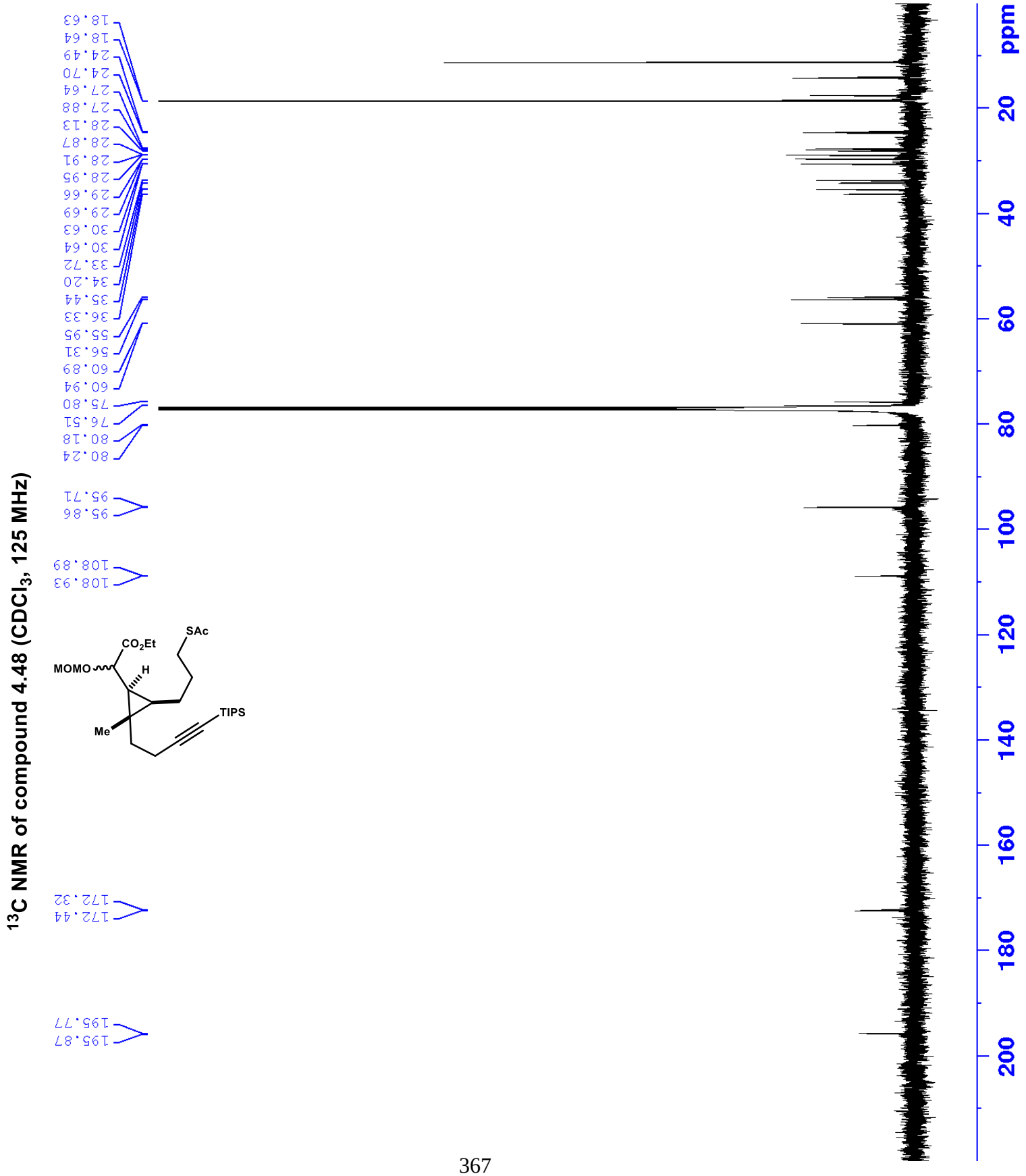
F1 - Processing parameters
SI                 4096
MC2                QF
SF            600.1300087 MHz
WDW                QSINE
SSB                  1.5
LB       0 Hz
GB       0
```


^{1}H NMR of compound 4.45 (CDCl$_3$, 500 MHz)
CO$_2$Et
HO
H
Me
TIPS
0.80
1.29
24.00
3.22
1.11
1.88
2.88
0.62
0.47
1.04
1.83
1.90
0.97
ppm
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

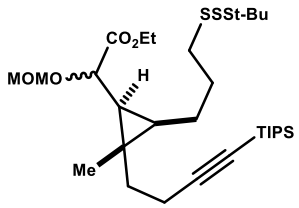

^{13}C NMR of compound 4.45 (CDCl3, 125 MHz)
14.21
17.34
17.49
18.52
18.64
24.22
24.85
27.60
27.72
28.84
29.25
30.44
33.02
33.10
35.51
35.53
35.92
36.26
61.63
70.42
71.39
80.00
80.12
109.14
109.21
114.68
114.88
137.79
137.83
174.87
175.31
CO2Et
HO
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 4.48 ($CDCl_3$, 500 MHz)

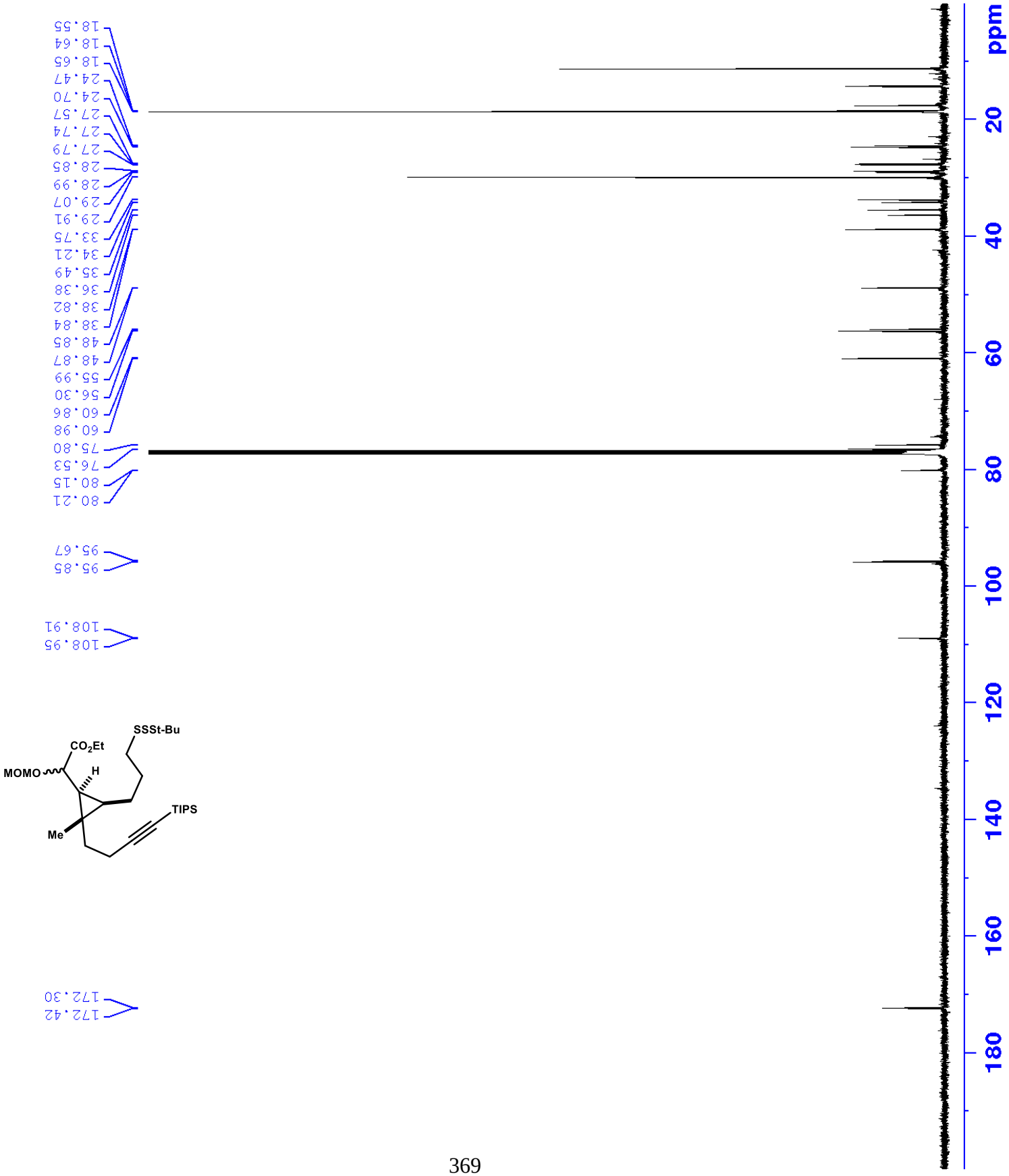



^{13}C NMR of compound 4.48 ($CDCl_3$, 125 MHz)
18.63
18.64
24.49
24.70
27.64
27.88
28.13
28.87
28.91
28.95
29.66
29.69
30.63
30.64
33.72
34.20
35.44
36.33
55.95
56.31
60.89
60.94
75.80
76.51
80.18
80.24
95.71
95.86
108.89
108.93
172.32
172.44
195.77
195.87
CO2Et
SAc
MOMO
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180
200

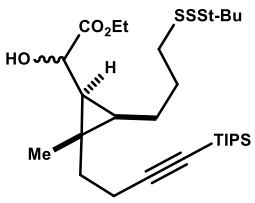
^{1}H NMR of compound 4.49 ($CDCl_3$, 500 MHz)

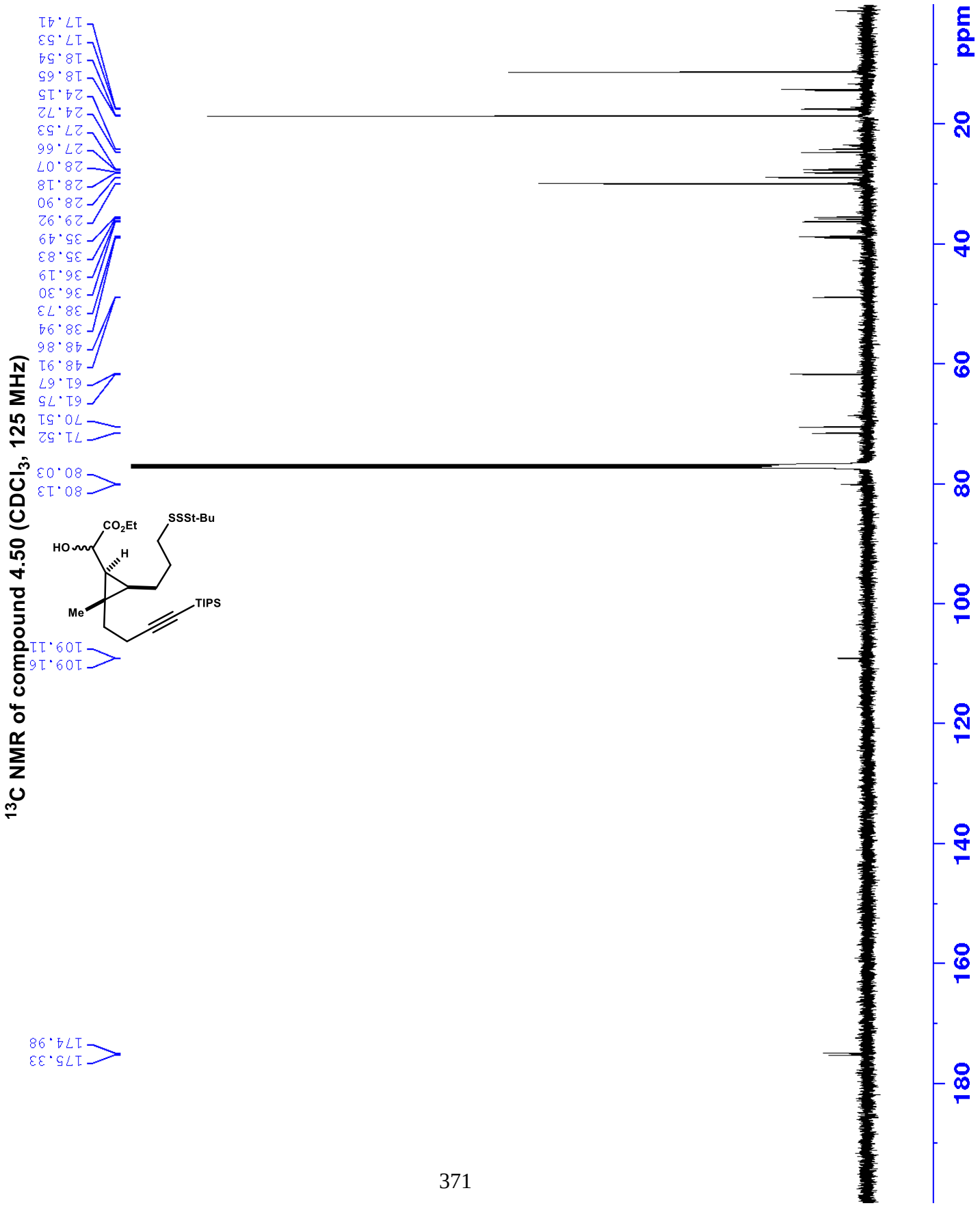


^{13}C NMR of compound 4.49 ($CDCl_3$, 125 MHz)

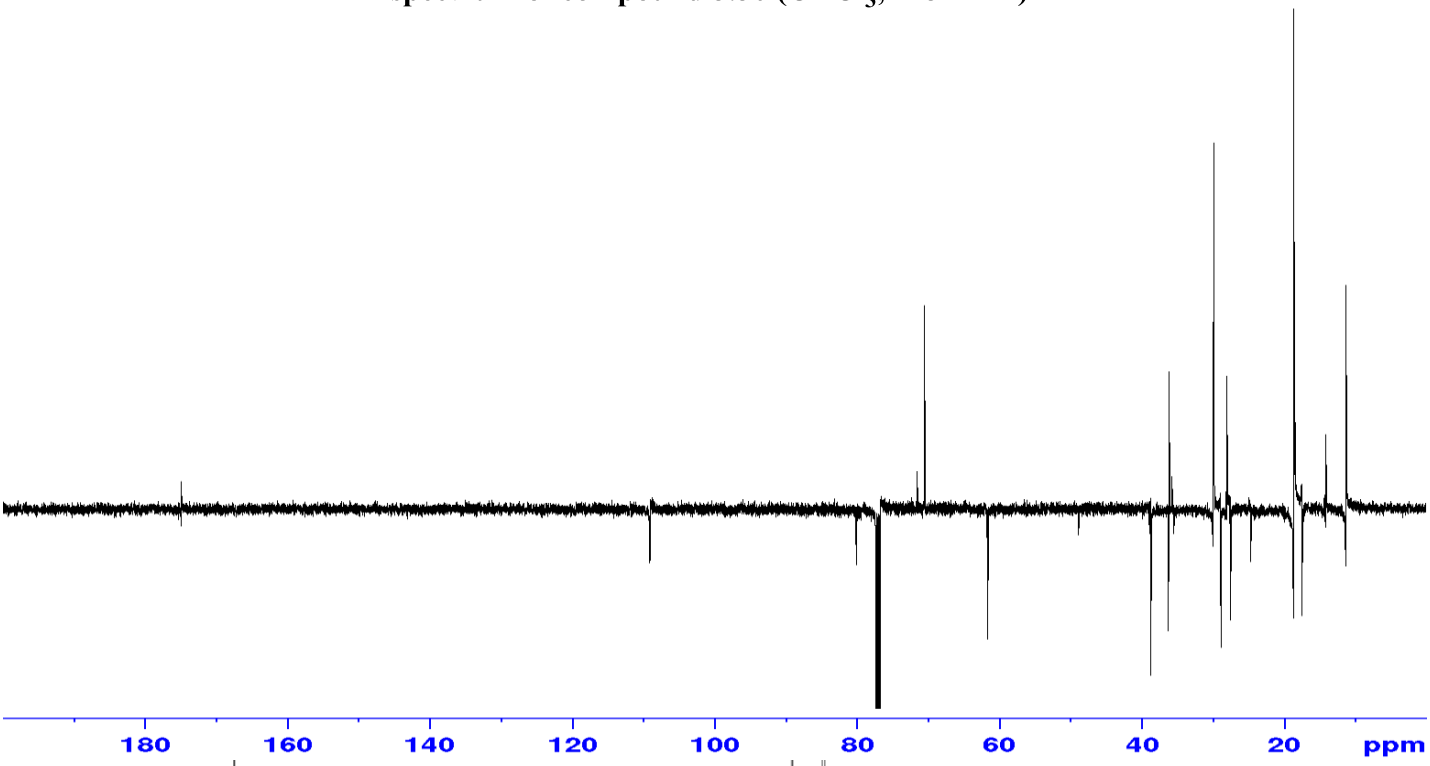


^{1}H NMR of compound 4.50 ($CDCl_3$, 500 MHz)

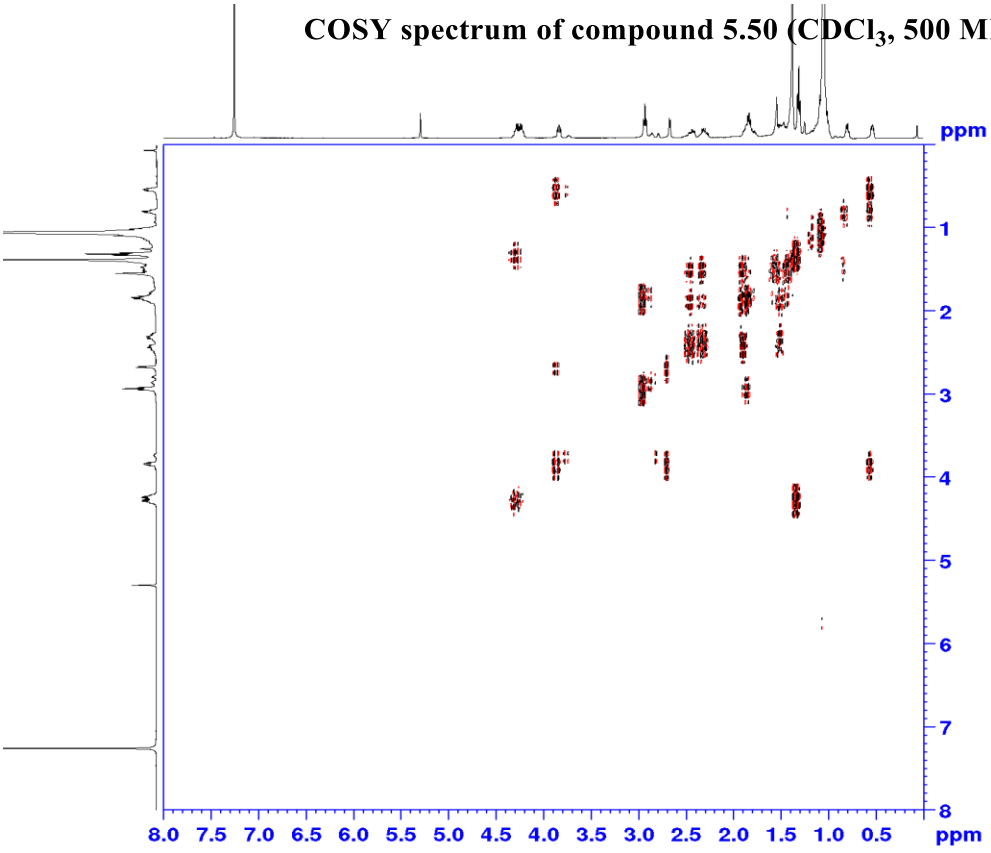



^{13}C NMR of compound 4.50 (CDCl$_3$, 125 MHz)
17.41
17.53
18.54
18.65
24.15
24.72
27.53
27.66
28.07
28.18
28.90
29.92
35.49
35.83
36.19
36.30
38.73
38.94
48.86
48.91
61.67
61.75
70.51
71.52
80.03
80.13
109.11
109.16
174.98
175.33
CO2Et
SSSt-Bu
HO
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180

APT spectrum of compound 5.50 ($CDCl_3$, 125 MHz)



COSY spectrum of compound 5.50 ($CDCl_3$, 500 MHz)

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Current Data Parameters
NAME      ljs-5-103-COSY-ts-REPURE
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_           20201017
Time              14.23 h
INSTRUM           av500
PROBHD    Z119248_0002 (
PULPROG     cosygpmfphpp
TD                2048
SOLVENT           CDCl3
NS                   2
DS                   8
SWH            7500.000 Hz
FIDRES         7.324219 Hz
AQ             0.1365333 sec
RG                204.54
DW                66.667 usec
DE                10.00 usec
TE                298.0 K
D0           0.00005387 sec
D1           2.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00013320 sec
TDav                 1
SFO1         500.1330008 MHz
NUC1                1H
P1                10.00 usec
P2                20.00 usec
P17             2500.00 usec
PLW1         13.50000000 W
PLW10         0.84375000 W
GPNAM[1]      SMSQ10.100
GPZ1              10.00 %
GPNAM[2]      SMSQ10.100
GPZ2              20.00 %
P16             1000.00 usec

F1 - Acquisition parameters
TD                 256
SFO1            500.133 MHz
FIDRES         58.652401 Hz
SW              15.011 ppm
FnMODE       States-TPPI

F2 - Processing parameters
SI                2048
SF           500.1300000 MHz
WDW               QSINE
SSB                  1
LB        0 Hz
GB        0
PC                1.00

F1 - Processing parameters
SI                2048
MC2          States-TPPI
SF           500.1300000 MHz
WDW               QSINE
SSB                  1
LB        0 Hz
GB        0
```
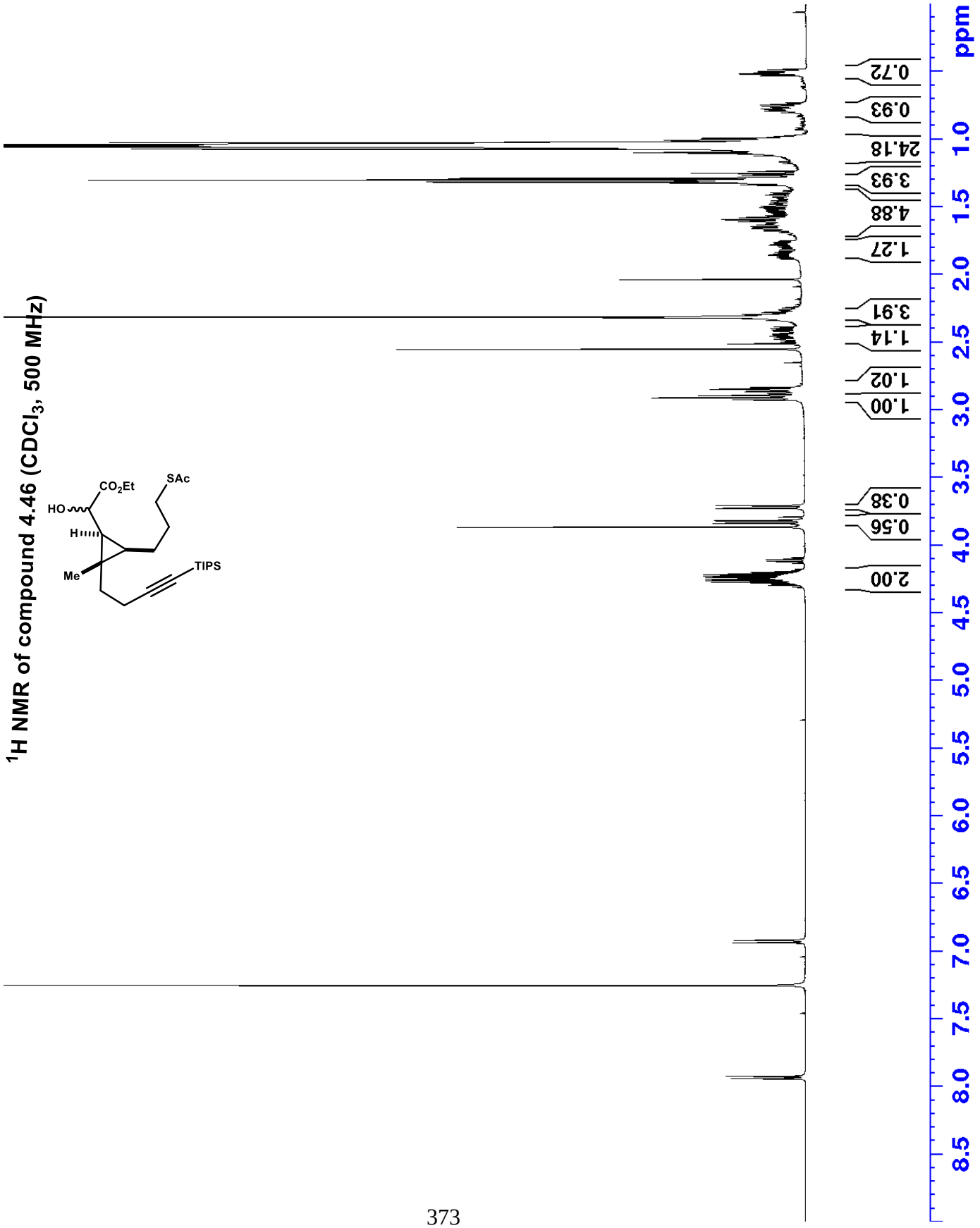
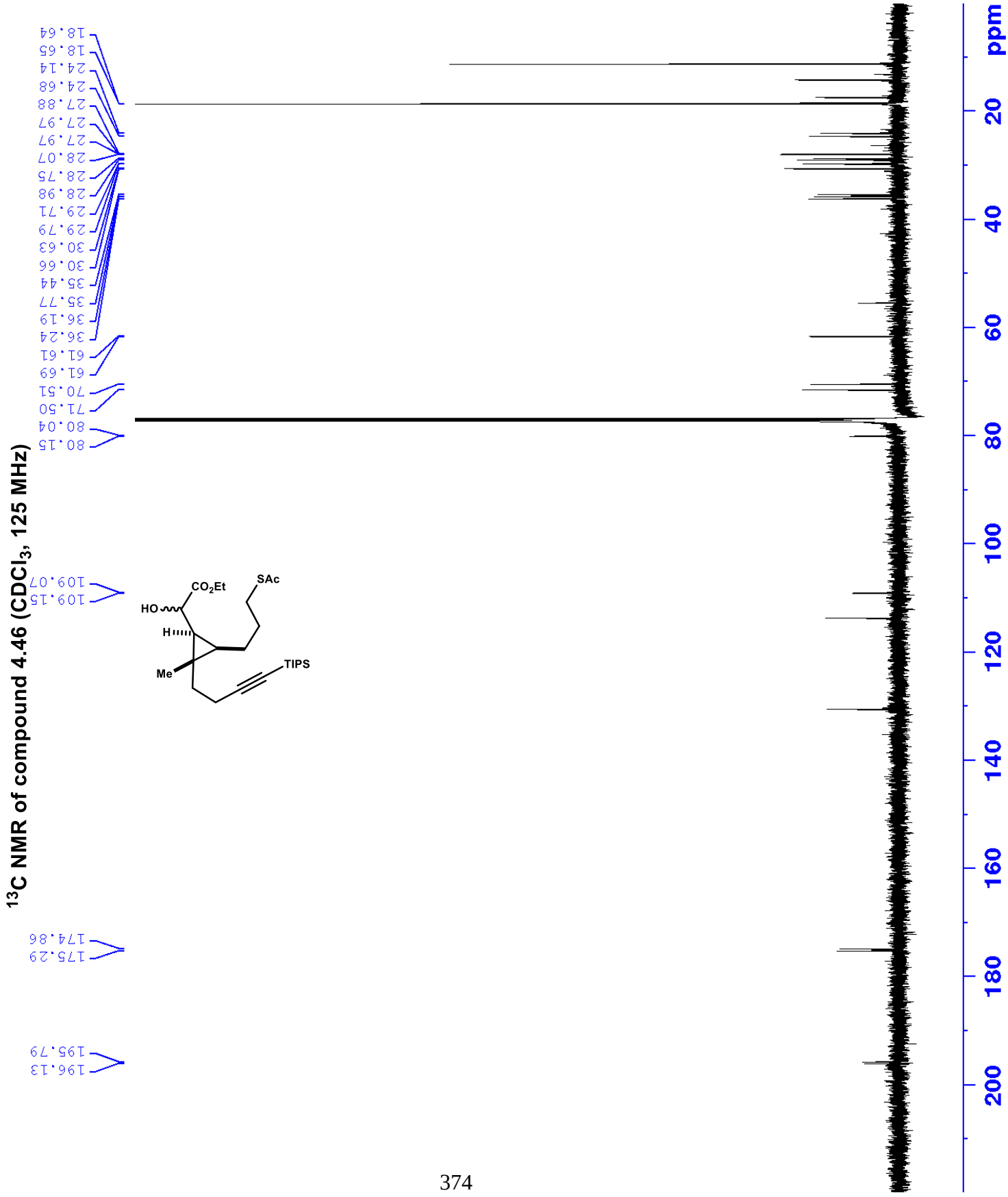
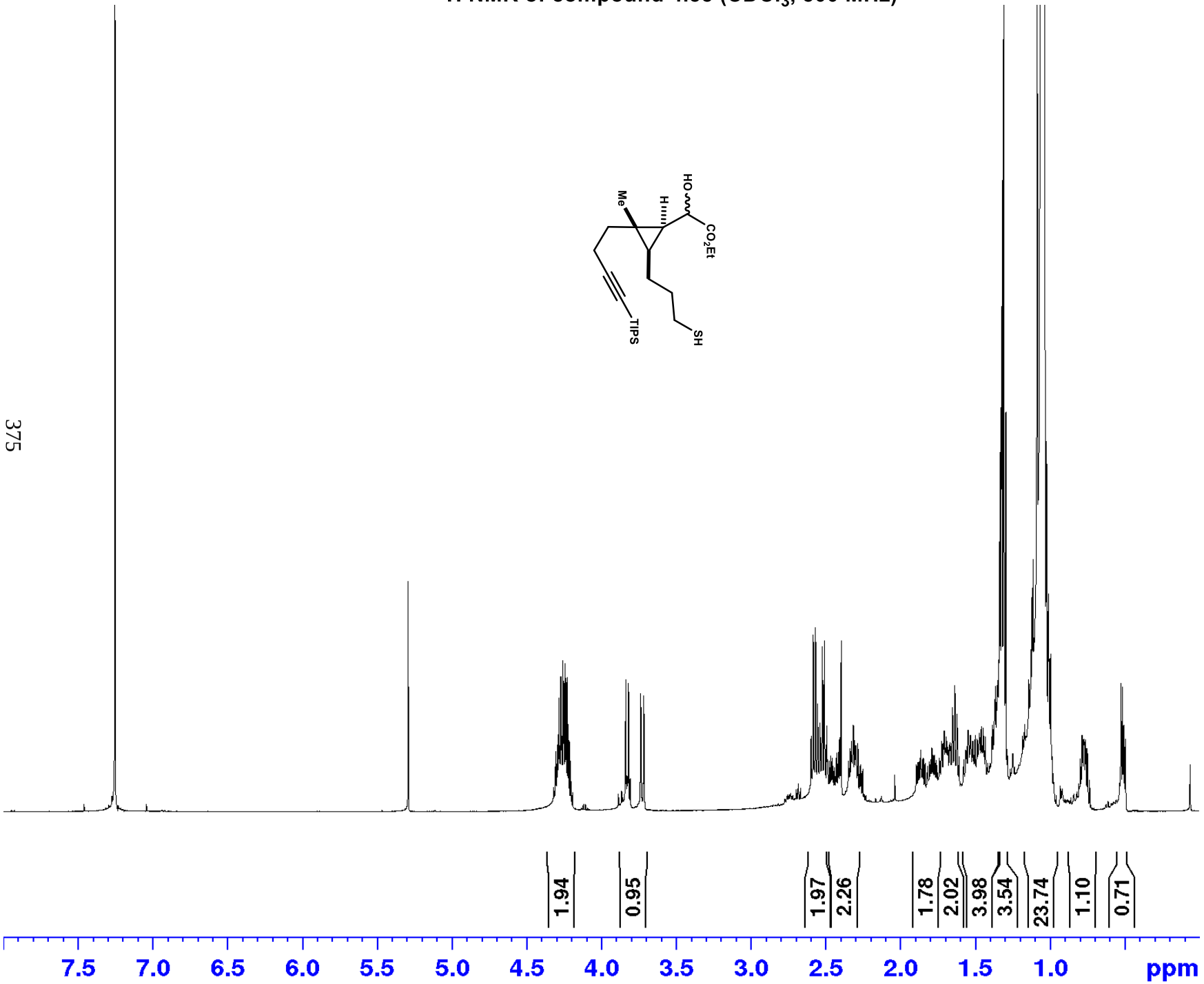
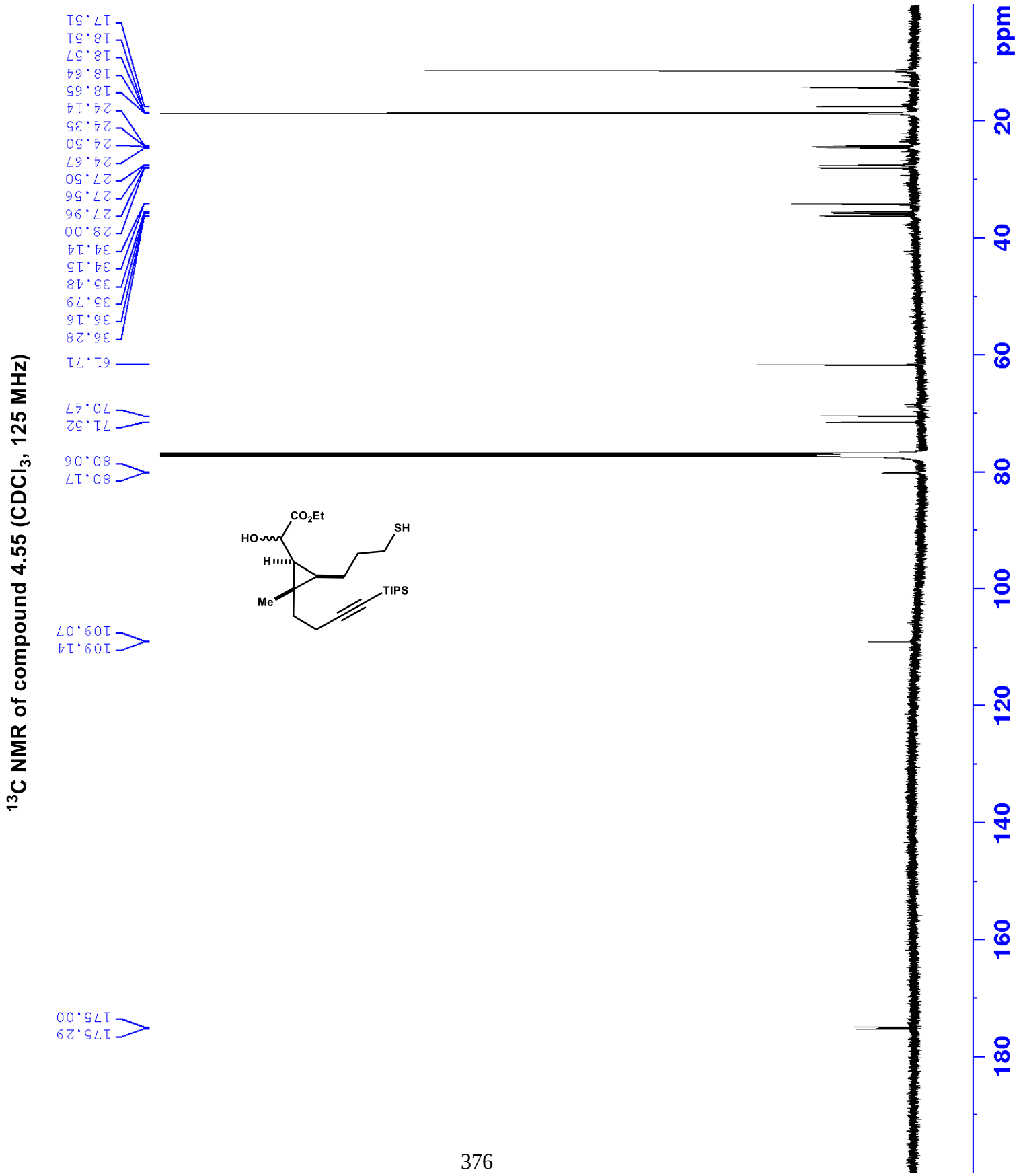
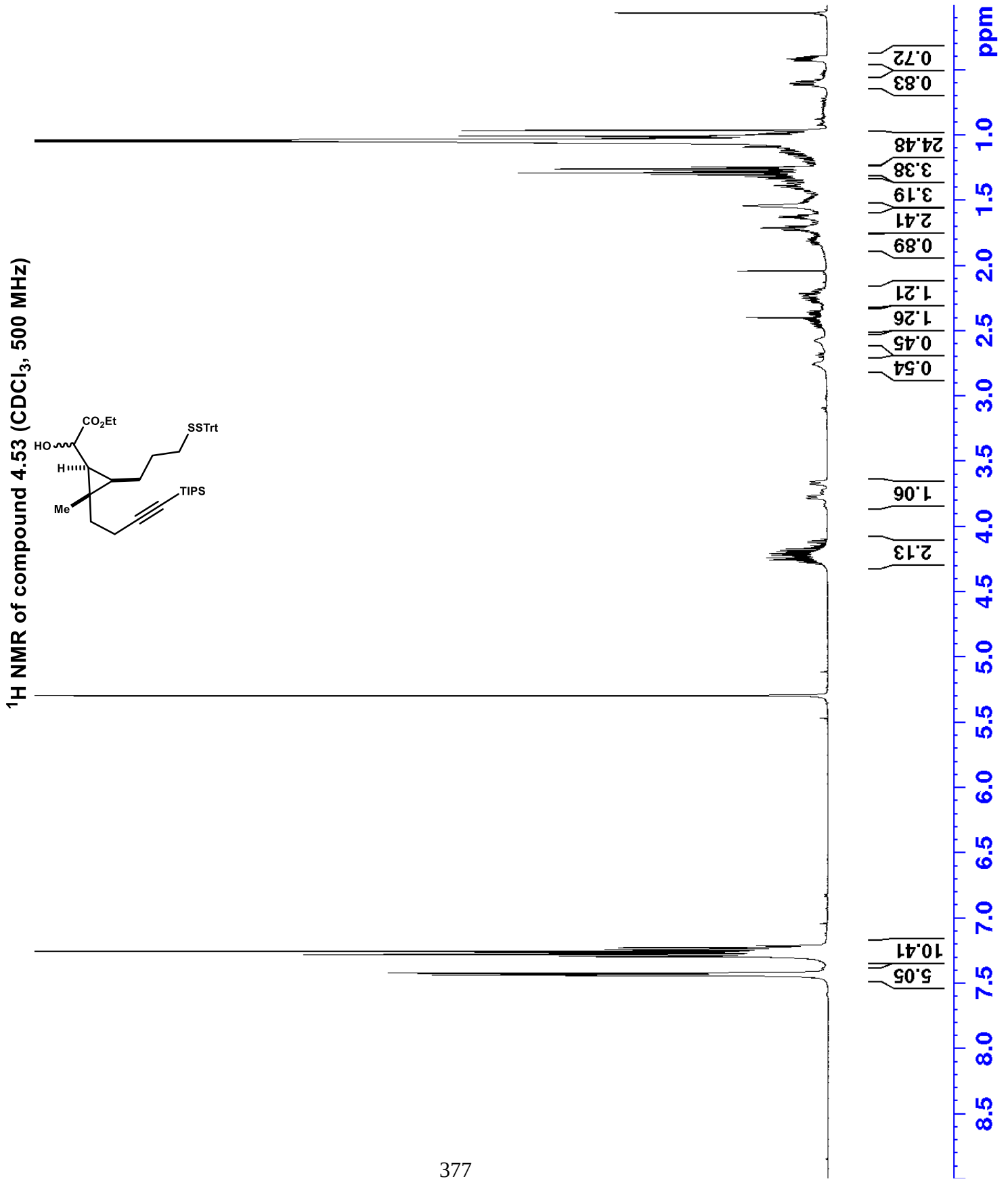


^{1}H NMR of compound 4.46 ($CDCl_3$, 500 MHz)
HO
CO_2Et
SAc
H
Me
TIPS
0.72
0.93
24.18
3.93
4.88
1.27
3.91
1.14
1.02
1.00
0.38
0.56
2.00
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

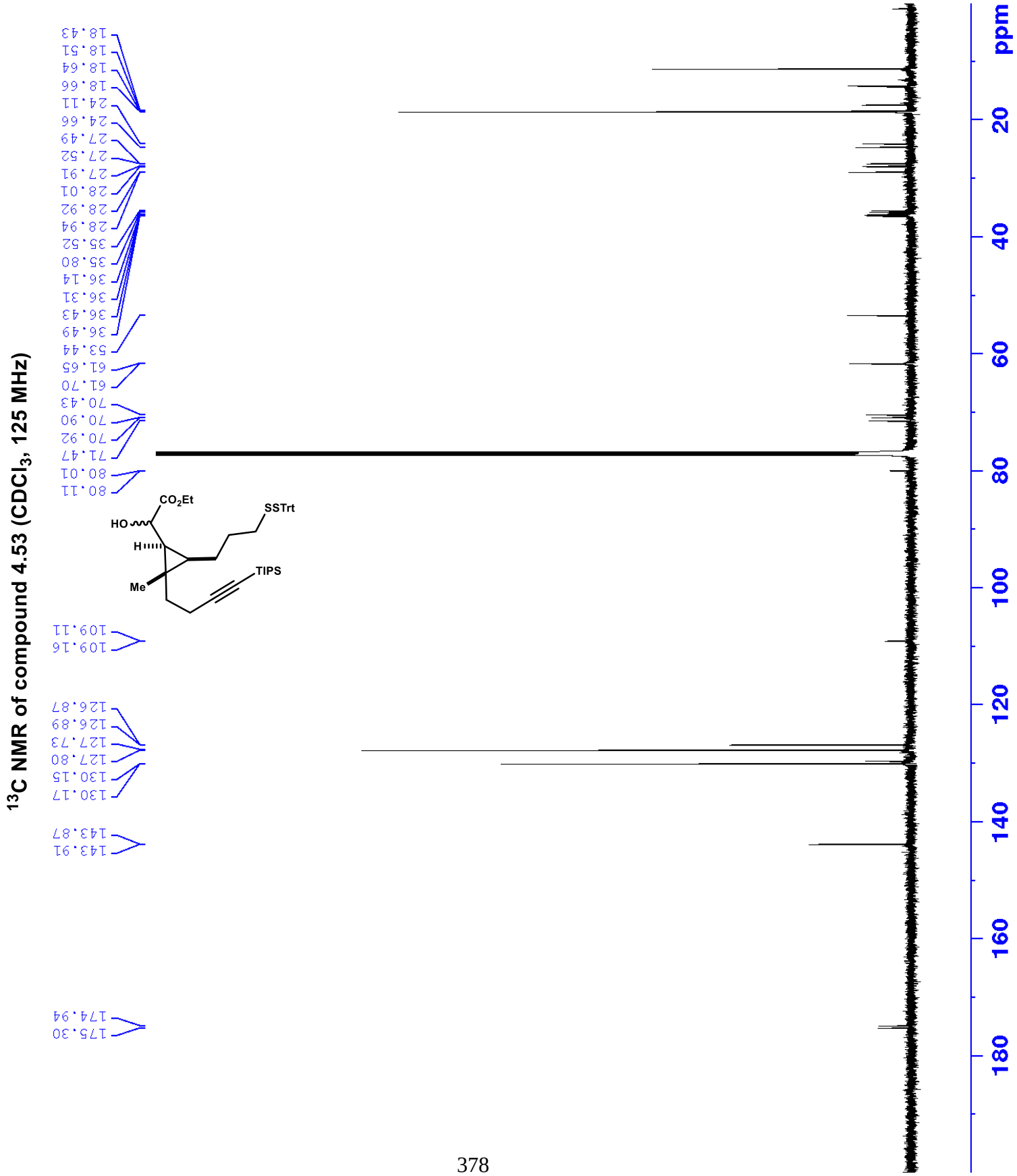

^{13}C NMR of compound 4.46 ($CDCl_3$, 125 MHz)
18.64
18.65
24.14
24.68
27.88
27.97
27.97
28.07
28.75
28.98
29.71
29.79
30.63
30.66
35.44
35.77
36.19
36.24
61.61
61.69
70.51
71.50
80.04
80.15
109.07
109.15
174.86
175.29
195.79
196.13
CO2Et
SAc
HO
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180
200

^{1}H NMR of compound 4.55 ($CDCl_3$, 500 MHz)

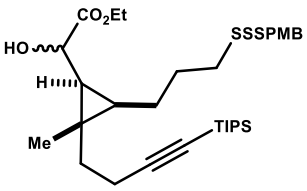


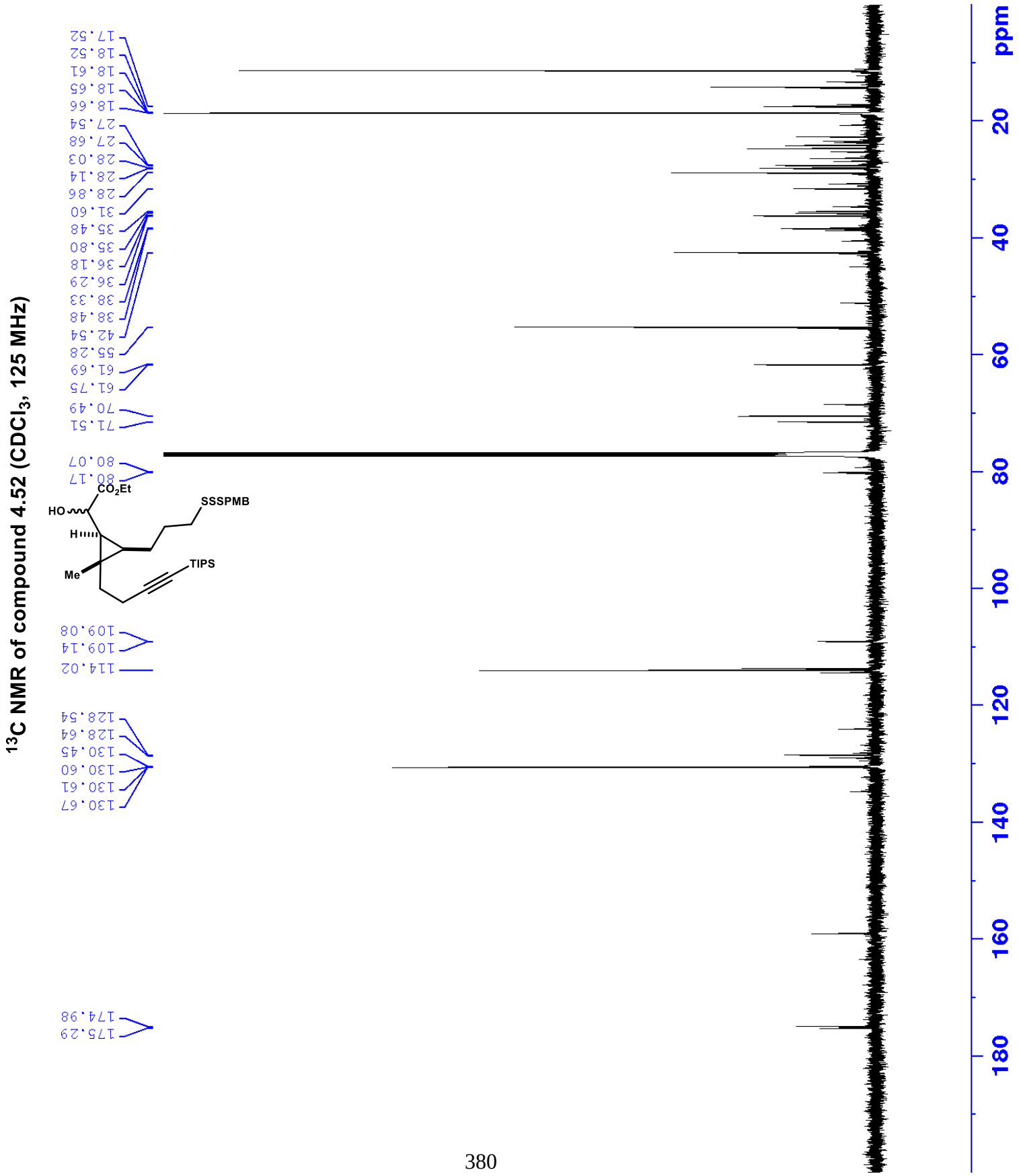

^{13}C NMR of compound 4.55 ($CDCl_3$, 125 MHz)
17.51
18.51
18.57
18.64
18.65
24.14
24.35
24.50
24.67
27.50
27.56
27.96
28.00
34.14
34.15
35.48
35.79
36.16
36.28
61.71
70.47
71.52
80.06
80.17
109.07
109.14
175.00
175.29
CO2Et
HO
H
Me
SH
TIPS
ppm
20
40
60
80
100
120
140
160
180


^{1}H NMR of compound 4.53 ($CDCl_3$, 500 MHz)
CO_2Et
HO
H
Me
SSTrt
TIPS
0.72
0.83
24.48
3.38
3.19
2.41
0.89
1.21
1.26
0.45
0.54
1.06
2.13
10.41
5.05
ppm
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

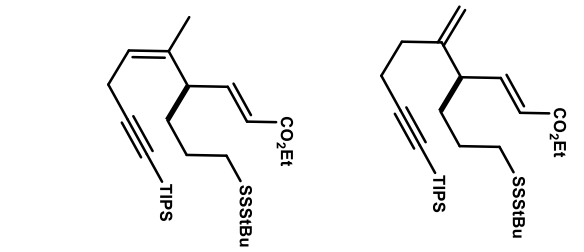

^{13}C NMR of compound 4.53 ($CDCl_3$, 125 MHz)
18.43
18.51
18.64
18.66
24.11
24.66
27.49
27.52
27.91
28.01
28.92
28.94
35.52
35.80
36.14
36.31
36.43
36.49
53.44
61.65
61.70
70.43
70.90
70.92
71.47
80.01
80.11
CO2Et
HO
H
Me
SSTrt
TIPS
109.11
109.16
126.87
126.89
127.73
127.80
130.15
130.17
143.87
143.91
174.94
175.30
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 4.52 ($CDCl_3$, 500 MHz)

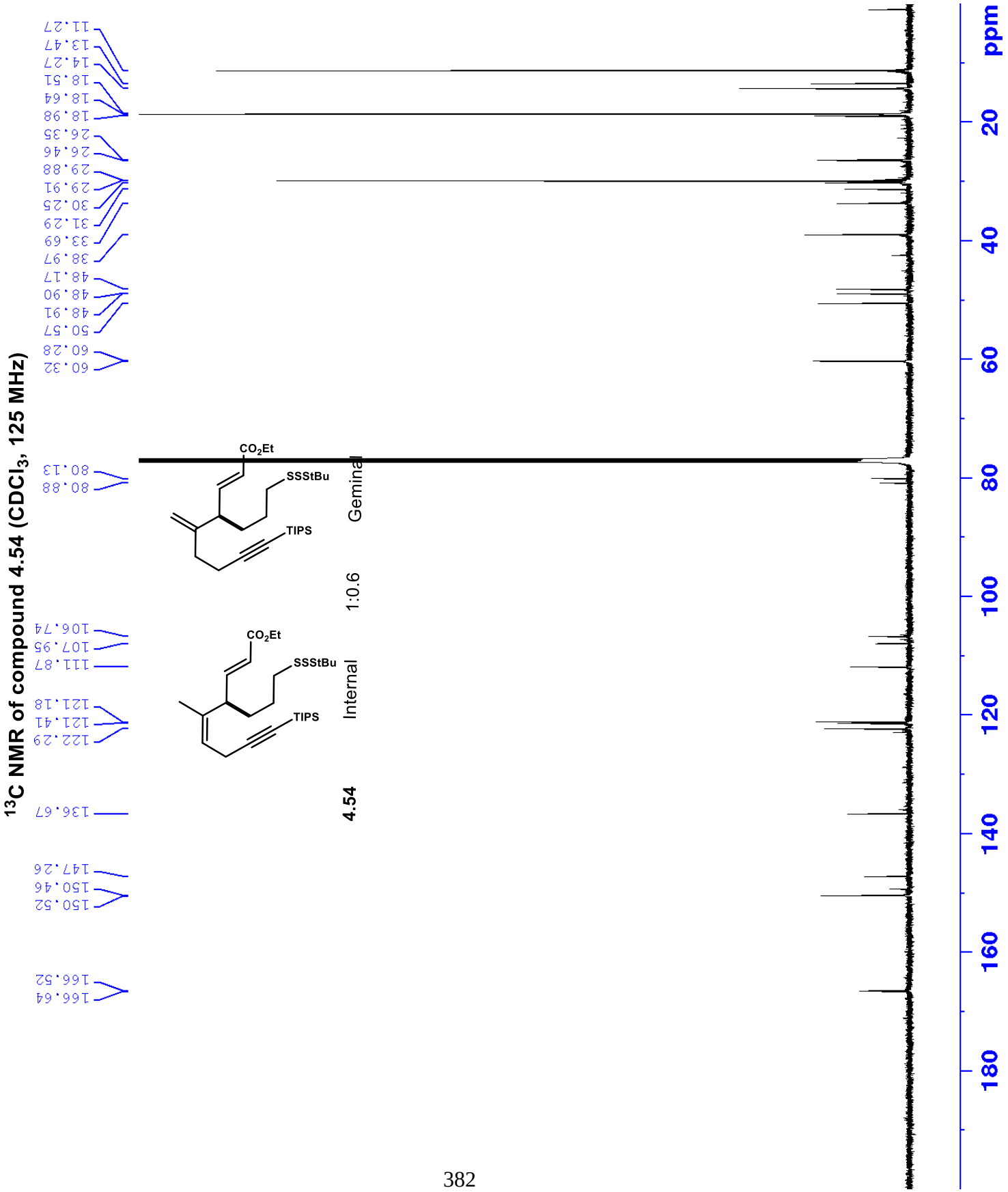



^{13}C NMR of compound 4.52 ($CDCl_3$, 125 MHz)
17.52
18.52
18.61
18.65
18.66
27.54
27.68
28.03
28.14
28.86
31.60
35.48
35.80
36.18
36.29
38.33
38.48
42.54
55.28
61.69
61.75
70.49
71.51
80.07
80.17
109.08
109.14
114.02
128.54
128.64
130.45
130.60
130.61
130.67
174.98
175.29
HO
CO2Et
H
Me
SSSPMB
TIPS
ppm
20
40
60
80
100
120
140
160
180

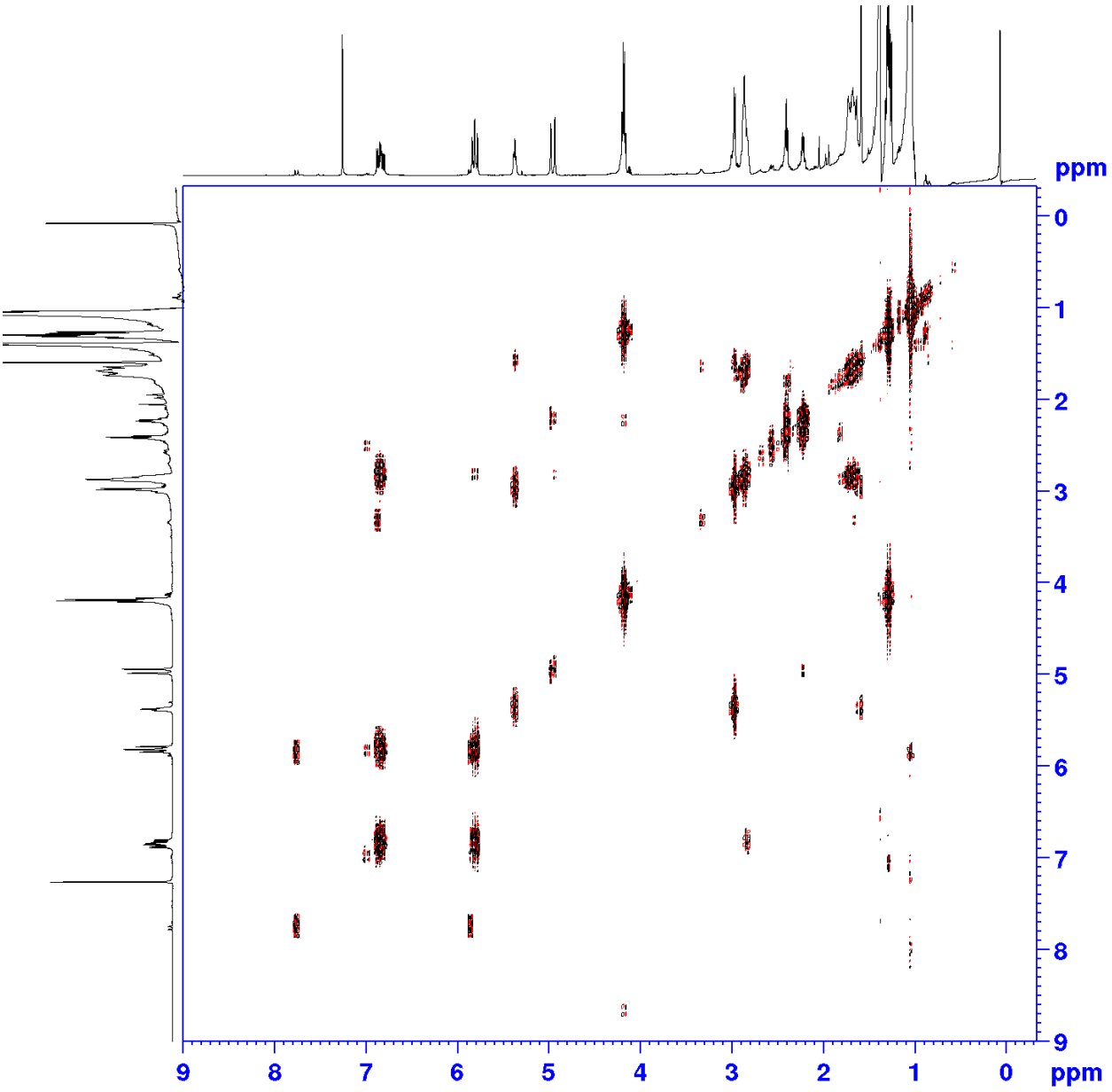
^{1}H NMR of compound 4.54 ($CDCl_3$, 500 MHz)



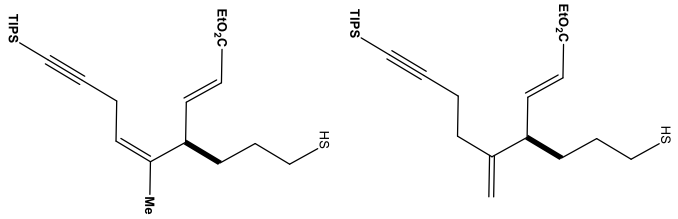
4.54 Internal 1:0.6 Geminal


^{13}C NMR of compound 4.54 (CDCl$_3$, 125 MHz)
11.27
13.47
14.27
18.51
18.64
18.98
26.35
26.46
29.88
29.91
30.25
31.29
33.69
38.97
48.17
48.90
48.91
50.57
60.28
60.32
80.13
80.88
106.74
107.95
111.87
121.18
121.41
122.29
136.67
147.26
150.46
150.52
166.52
166.64
CO2Et
SSStBu
TIPS
Geminal
1:0.6
Internal
4.54
ppm
20
40
60
80
100
120
140
160
180

COSY spectrum of compound 5.54 ($CDCl_3$, 500 MHz)

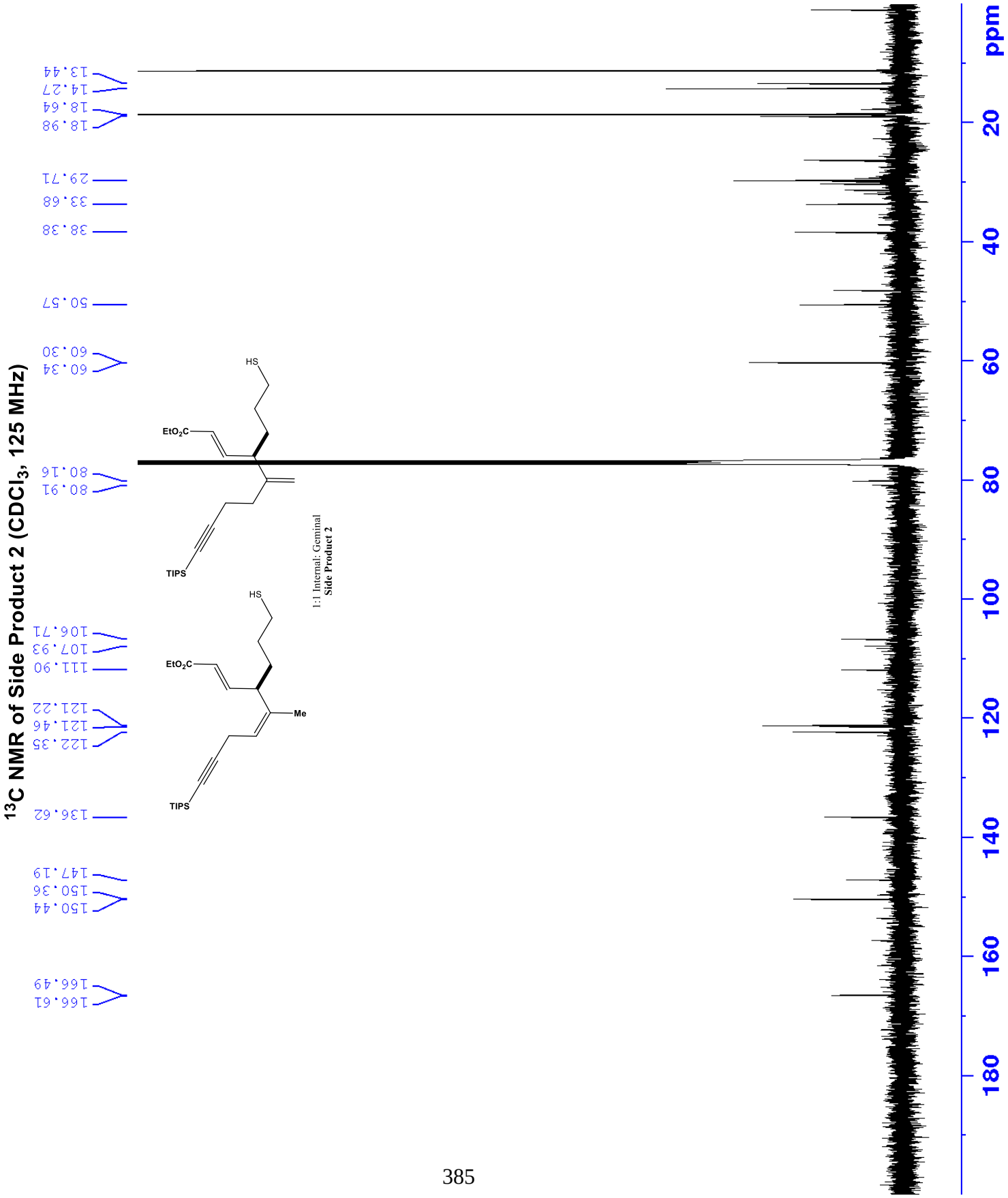


^{1}H NMR of Side Product 2 ($CDCl_3$, 500 MHz)

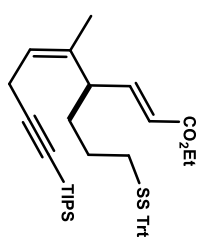


1:1 Internal: Geminal
Side Product 2

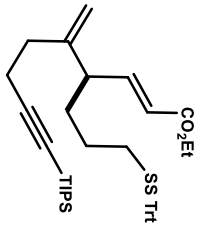
384


^{13}C NMR of Side Product 2 (CDCl$_3$, 125 MHz)
ppm
20
40
60
80
100
120
140
160
180
13.44
14.27
18.64
18.98
29.71
33.68
38.38
50.57
60.30
60.34
80.16
80.91
106.71
107.93
111.90
121.22
121.46
122.35
136.62
147.19
150.36
150.44
166.49
166.61
HS
EtO2C
TIPS
1:1 Internal: Geminal
Side Product 2
HS
EtO2C
Me
TIPS

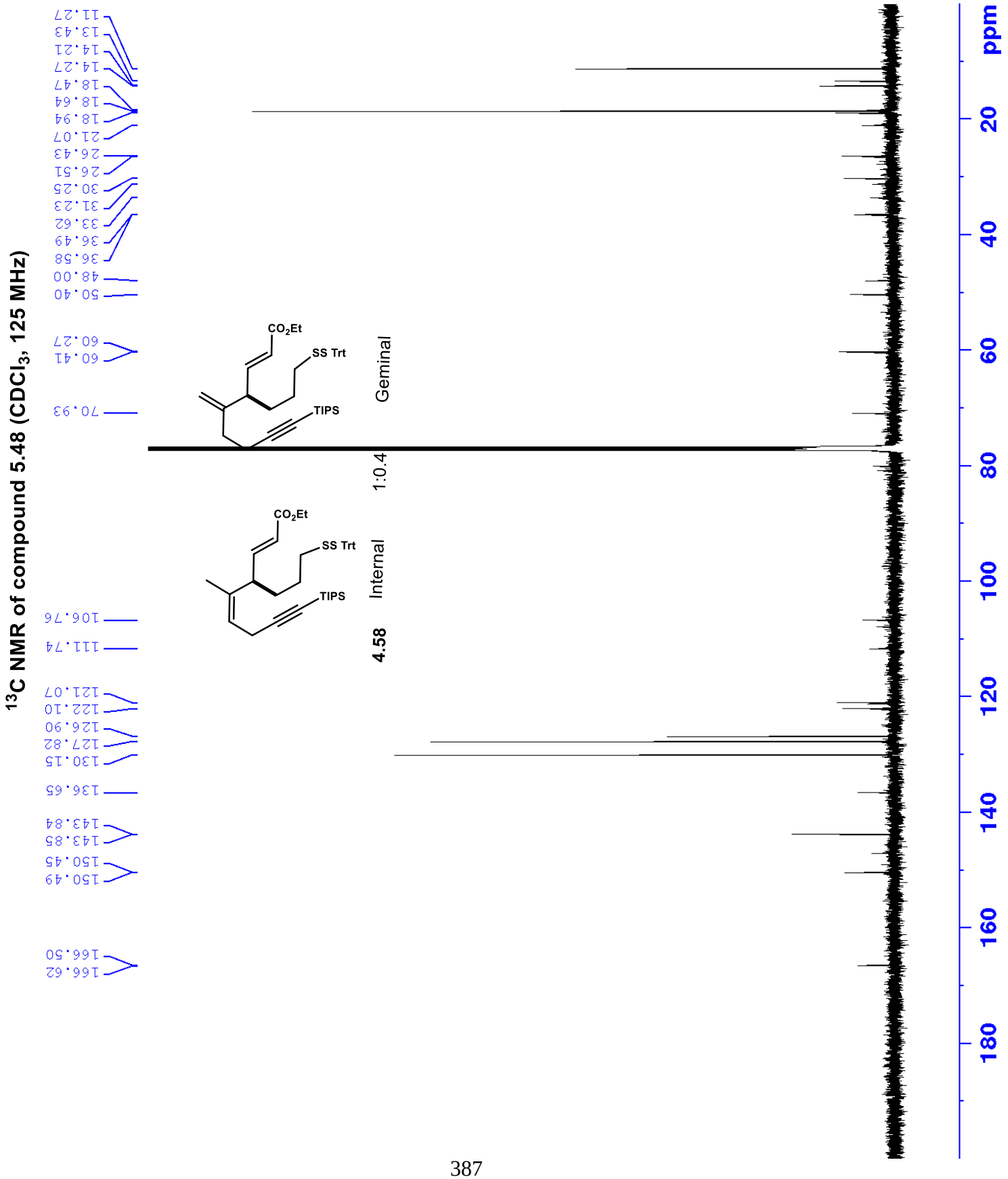
^{1}H NMR of compound 5.48 ($CDCl_3$, 500 MHz)



4.58 Internal 1:0.4 Geminal

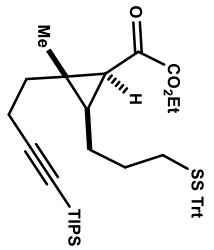


386

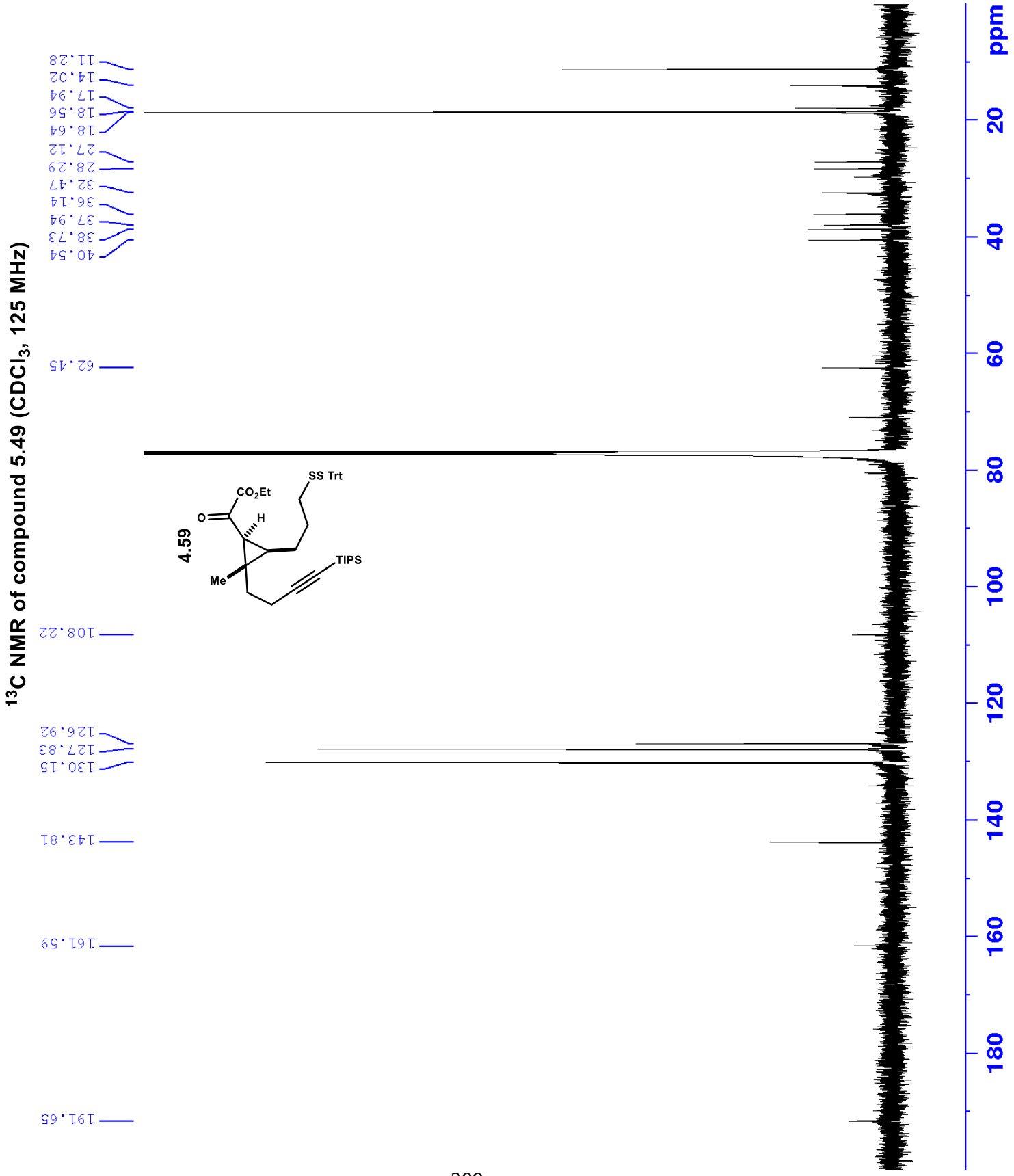

^{13}C NMR of compound 5.48 ($CDCl_3$, 125 MHz)
11.27
13.43
14.21
14.27
18.47
18.64
18.94
21.07
26.43
26.51
30.25
31.23
33.62
36.49
36.58
48.00
50.40
60.27
60.41
70.93
106.76
111.74
121.07
122.10
126.90
127.82
130.15
136.65
143.84
143.85
150.45
150.49
166.50
166.62
CO2Et
SS Trt
TIPS
Geminal
1:0.4
Internal
4.58
ppm
20
40
60
80
100
120
140
160
180

^{1}H NMR of compound 5.49 ($CDCl_3$, 500 MHz)

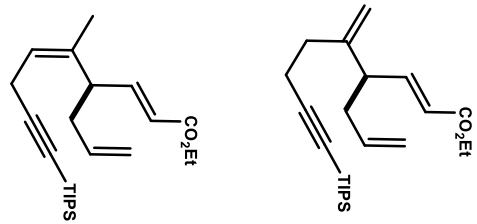
4.59



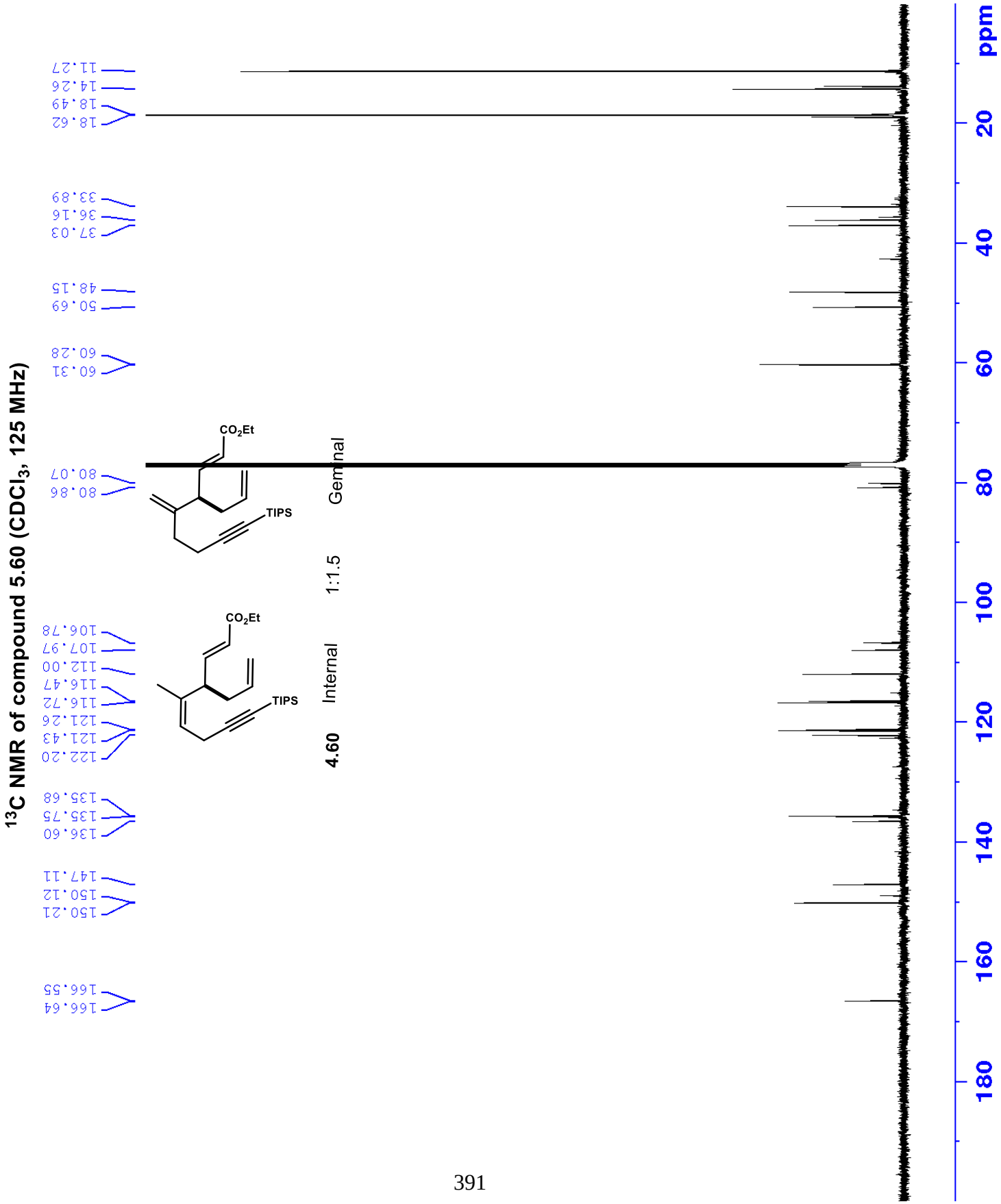
388

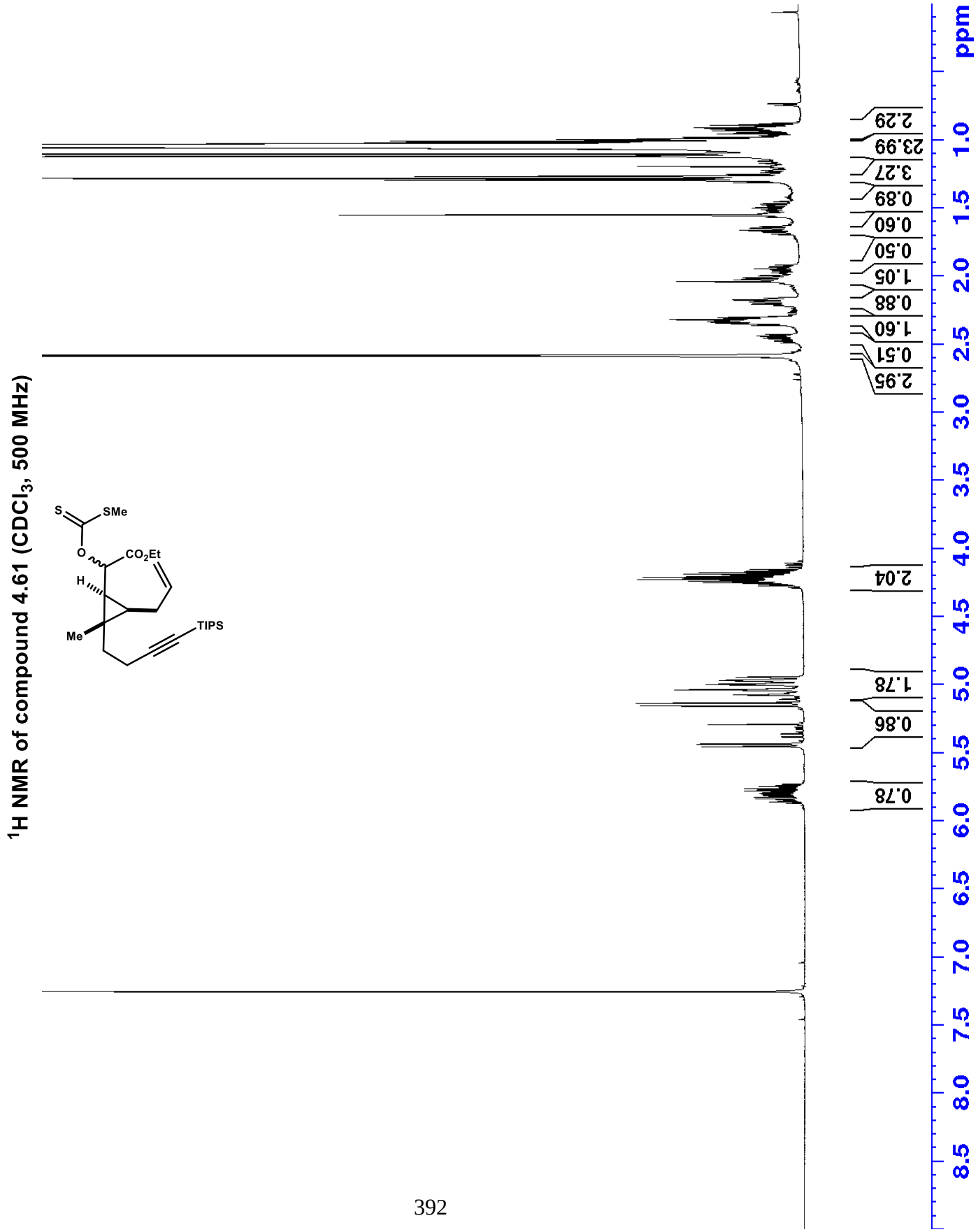

^{13}C NMR of compound 5.49 (CDCl$_3$, 125 MHz)
11.28
14.02
17.94
18.56
18.64
27.12
28.29
32.47
36.14
37.94
38.73
40.54
62.45
108.22
126.92
127.83
130.15
143.81
161.59
191.65
4.59
CO$_2$Et
O
H
SS Trt
TIPS
Me
ppm
20
40
60
80
100
120
140
160
180

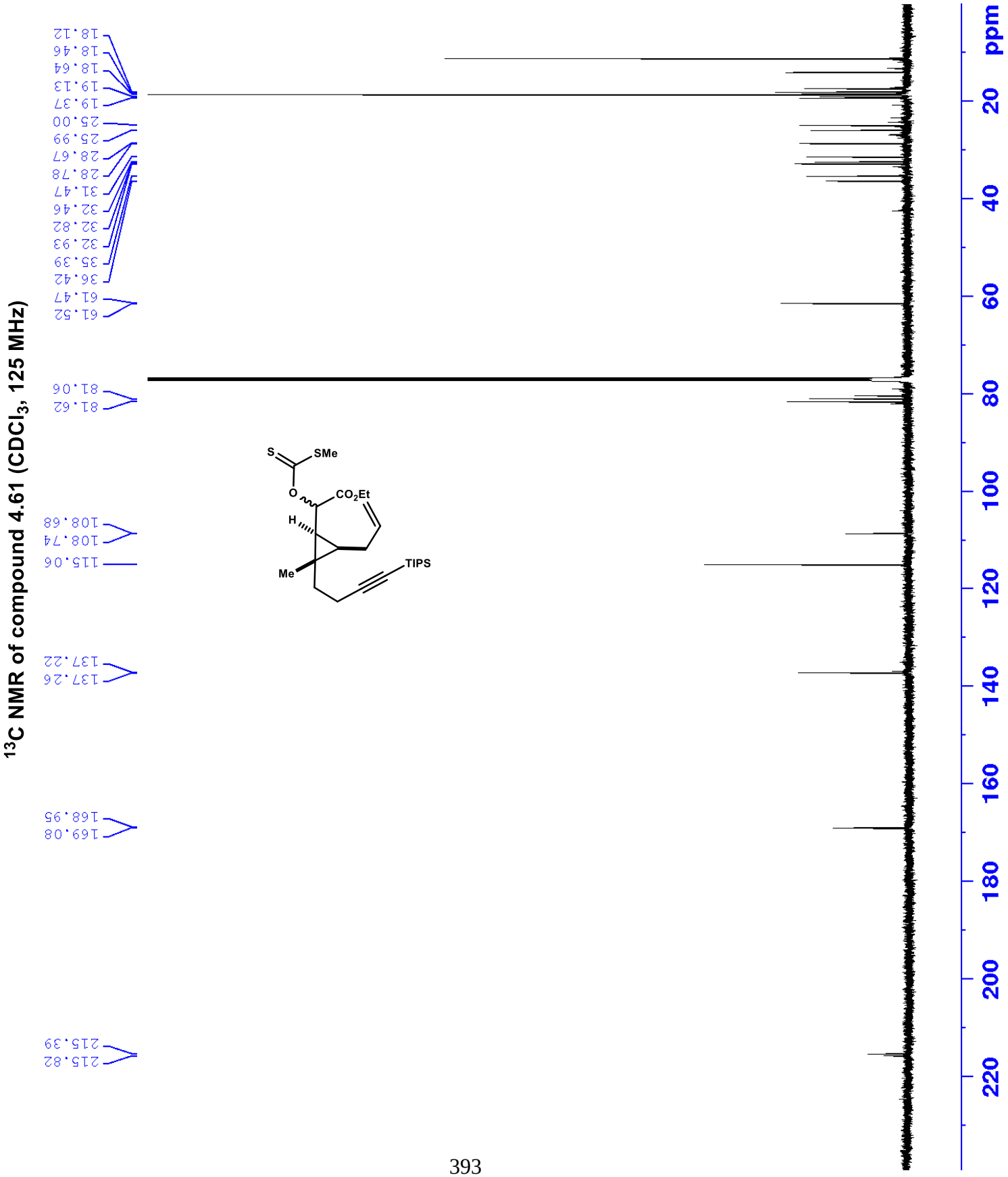
^{1}H NMR of compound 5.60 ($CDCl_3$, 500 MHz)

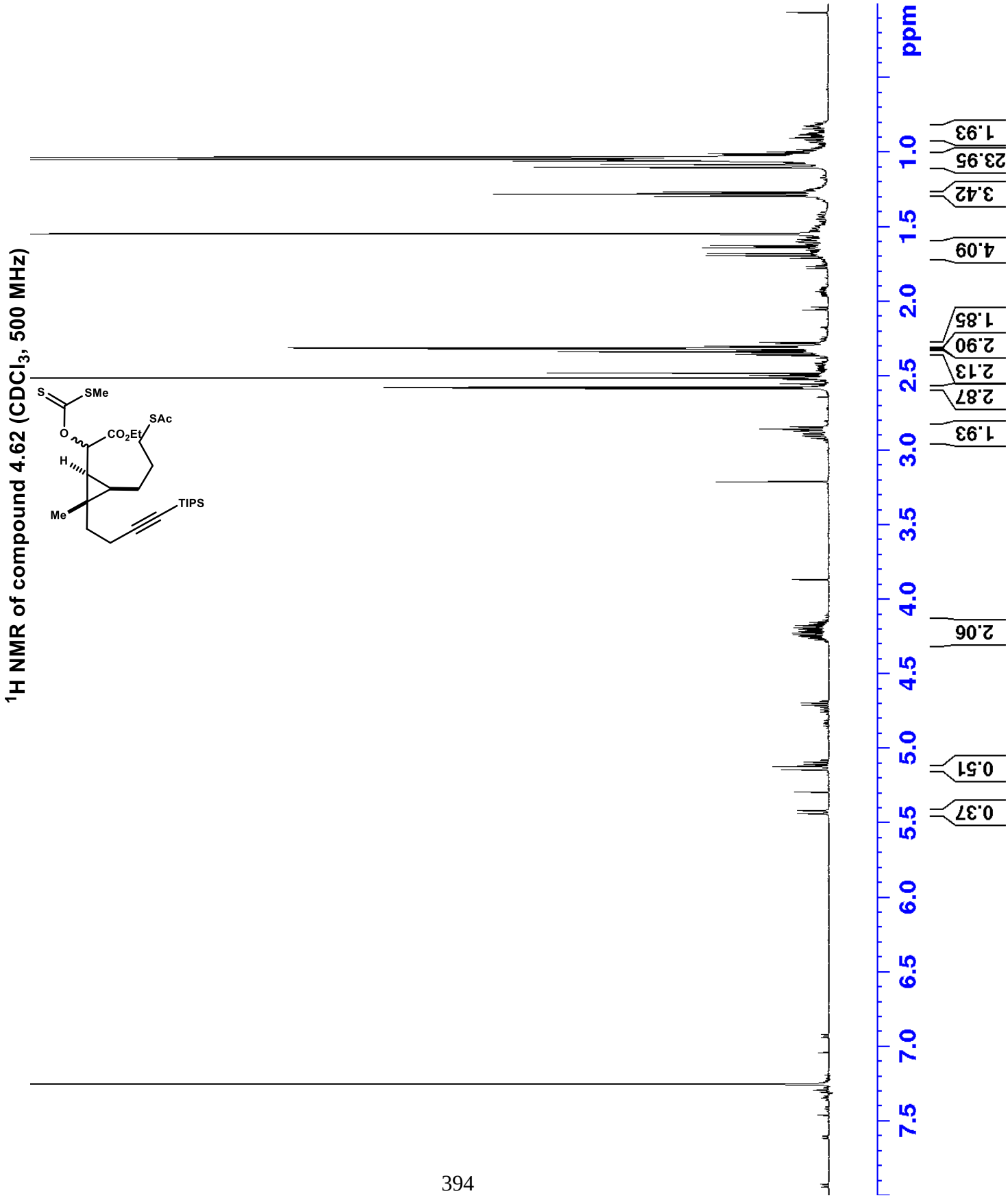


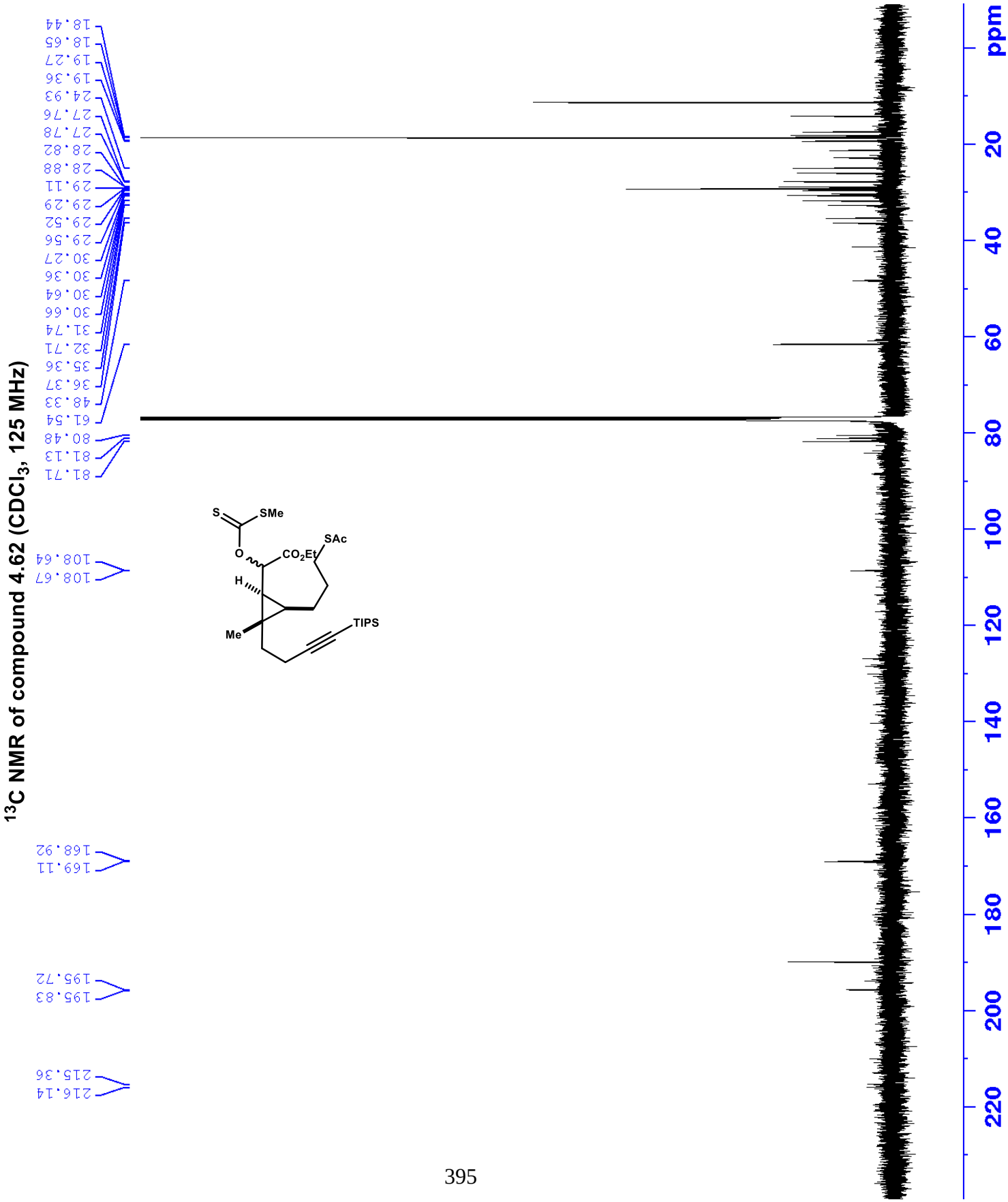
4.60 Internal 1:1.5 Geminal


^{13}C NMR of compound 5.60 (CDCl$_3$, 125 MHz)
11.27
14.26
18.49
18.62
33.89
36.16
37.03
48.15
50.69
60.28
60.31
80.07
80.86
106.78
107.97
112.00
116.47
116.72
121.26
121.43
122.20
135.68
135.75
136.60
147.11
150.12
150.21
166.55
166.64
CO2Et
TIPS
CO2Et
TIPS
4.60
Internal
1:1.5
Geminal
ppm
20
40
60
80
100
120
140
160
180

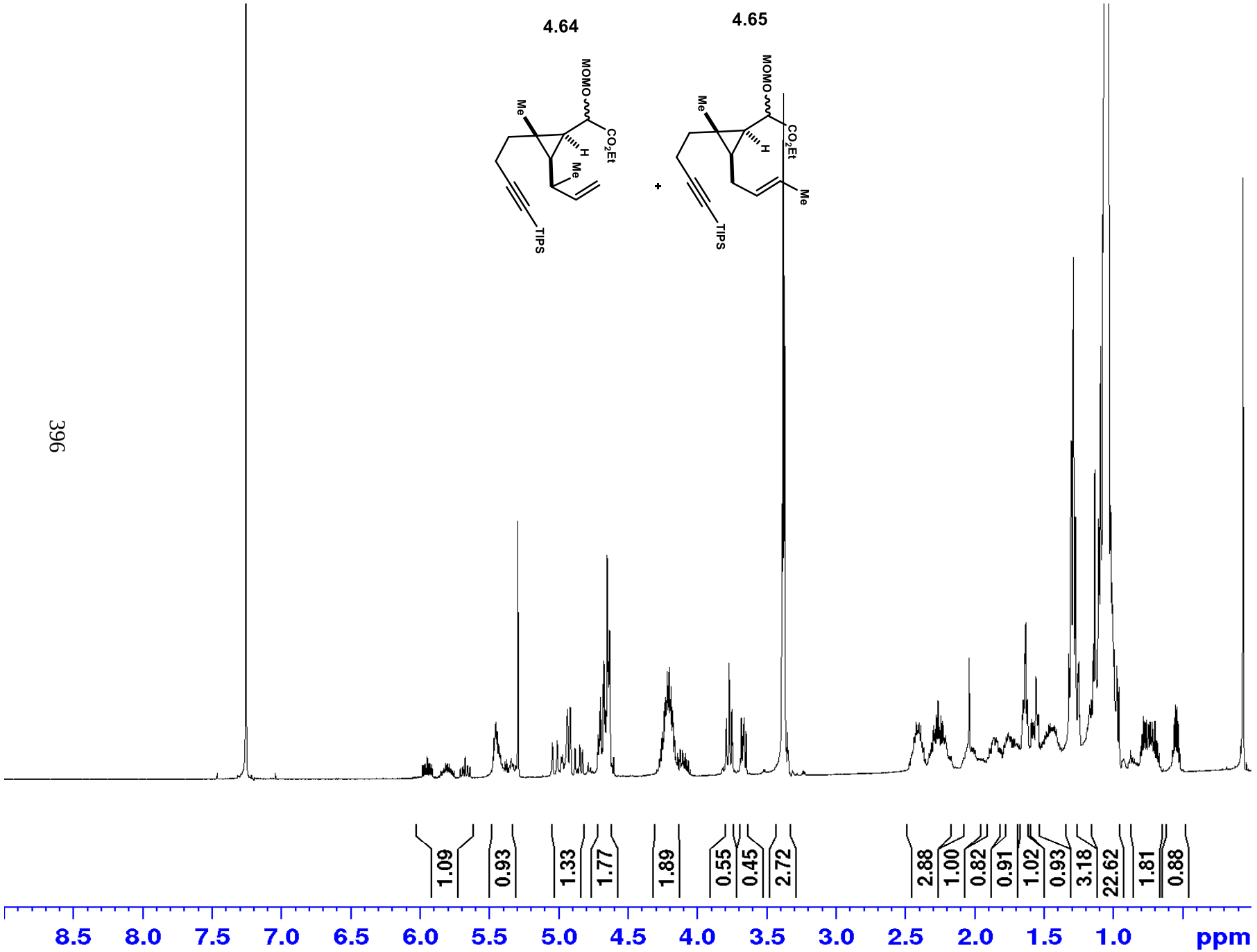

^{1}H NMR of compound 4.61 ($CDCl_3$, 500 MHz)
S
SMe
O
CO_2Et
H
Me
TIPS
2.29
23.99
3.27
0.89
0.60
0.50
1.05
0.88
1.60
0.51
2.95
2.04
1.78
0.86
0.78
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

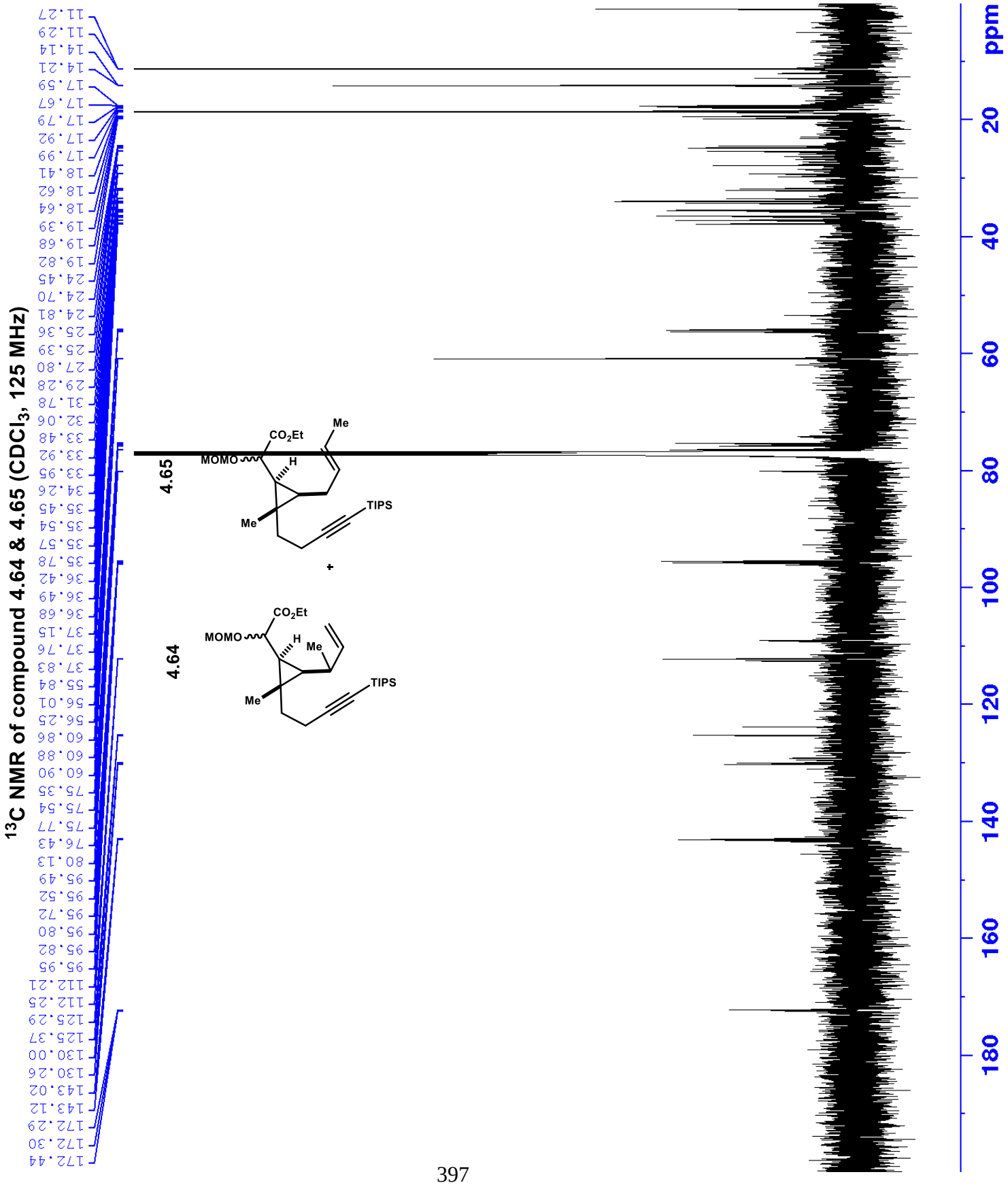

^{13}C NMR of compound 4.61 ($CDCl_3$, 125 MHz)
18.12
18.46
18.64
19.13
19.37
25.00
25.99
28.67
28.78
31.47
32.46
32.82
32.93
35.39
36.42
61.47
61.52
81.06
81.62
108.68
108.74
115.06
137.22
137.26
168.95
169.08
215.39
215.82
S
SMe
O
CO2Et
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180
200
220


^{1}H NMR of compound 4.62 ($CDCl_3$, 500 MHz)
S
SMe
O
CO_2Et
SAc
H
Me
TIPS
ppm
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
1.93
23.95
3.42
4.09
1.85
2.90
2.13
2.87
1.93
2.06
0.51
0.37


^{13}C NMR of compound 4.62 ($CDCl_3$, 125 MHz)
18.44
18.65
19.27
19.36
24.93
27.76
27.78
28.82
28.88
29.11
29.29
29.52
29.56
30.27
30.36
30.64
30.66
31.74
32.71
35.36
36.37
48.33
61.54
80.48
81.13
81.71
108.64
108.67
168.92
169.11
195.72
195.83
215.36
216.14
S
SMe
O
CO2Et
SAc
H
Me
TIPS
ppm
20
40
60
80
100
120
140
160
180
200
220

^{1}H NMR of compound 4.64 & 4.65 ($CDCl_3$, 500 MHz)




^{13}C NMR of compound 4.64 & 4.65 ($CDCl_3$, 125 MHz)
ppm
20
40
60
80
100
120
140
160
180
4.65
4.64
MOMO
CO_2Et
H
Me
TIPS
+

Relavant ^{1}H-NMR for table 4.1 ^{1}H NMR ($CDCl_3$, 400 MHz)
Table 4.1 Entry 1

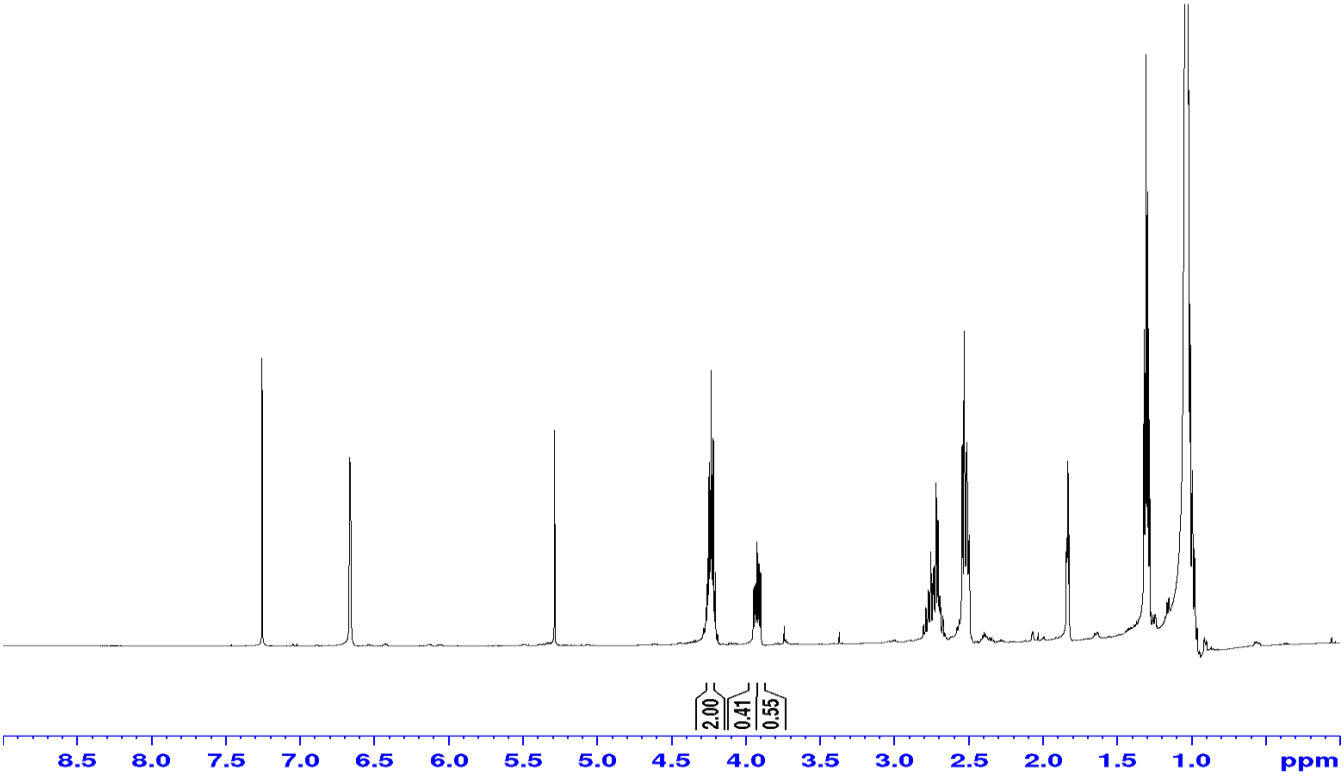


Table 4.1. Entry 2 ^{1}H NMR ($CDCl_3$, 400 MHz)

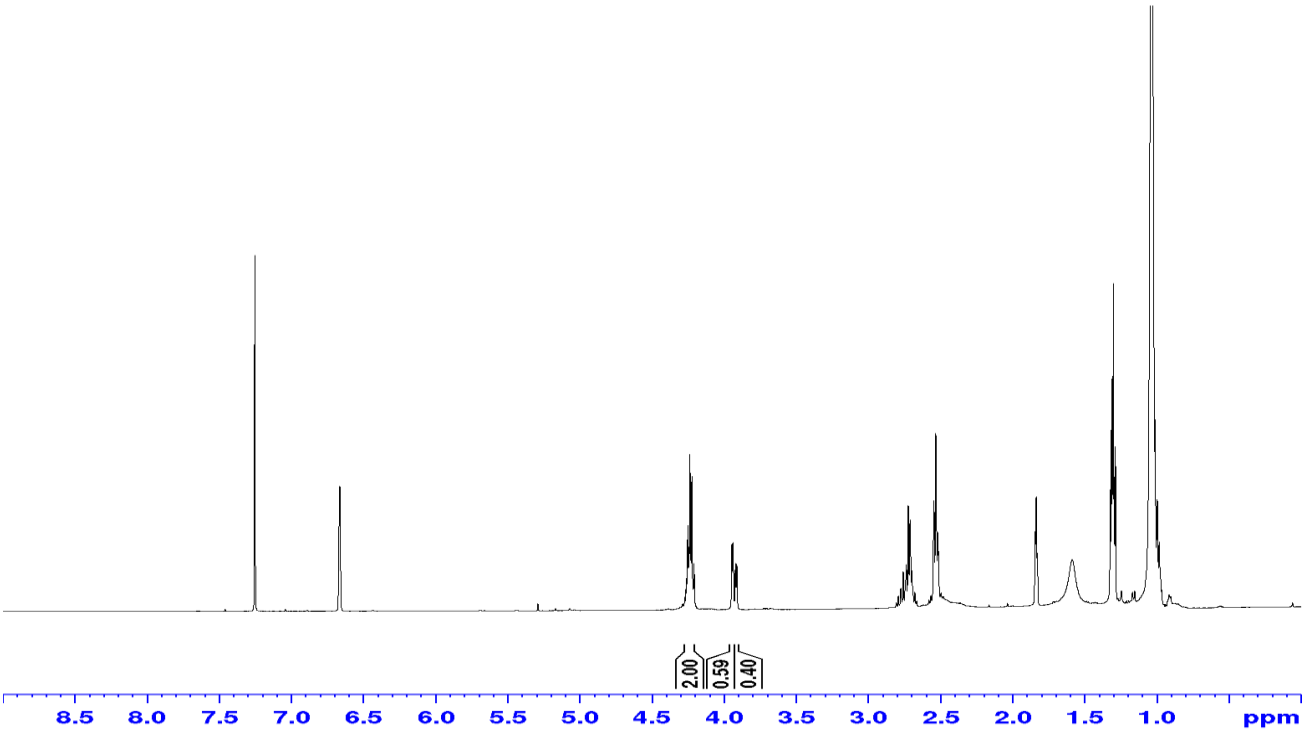
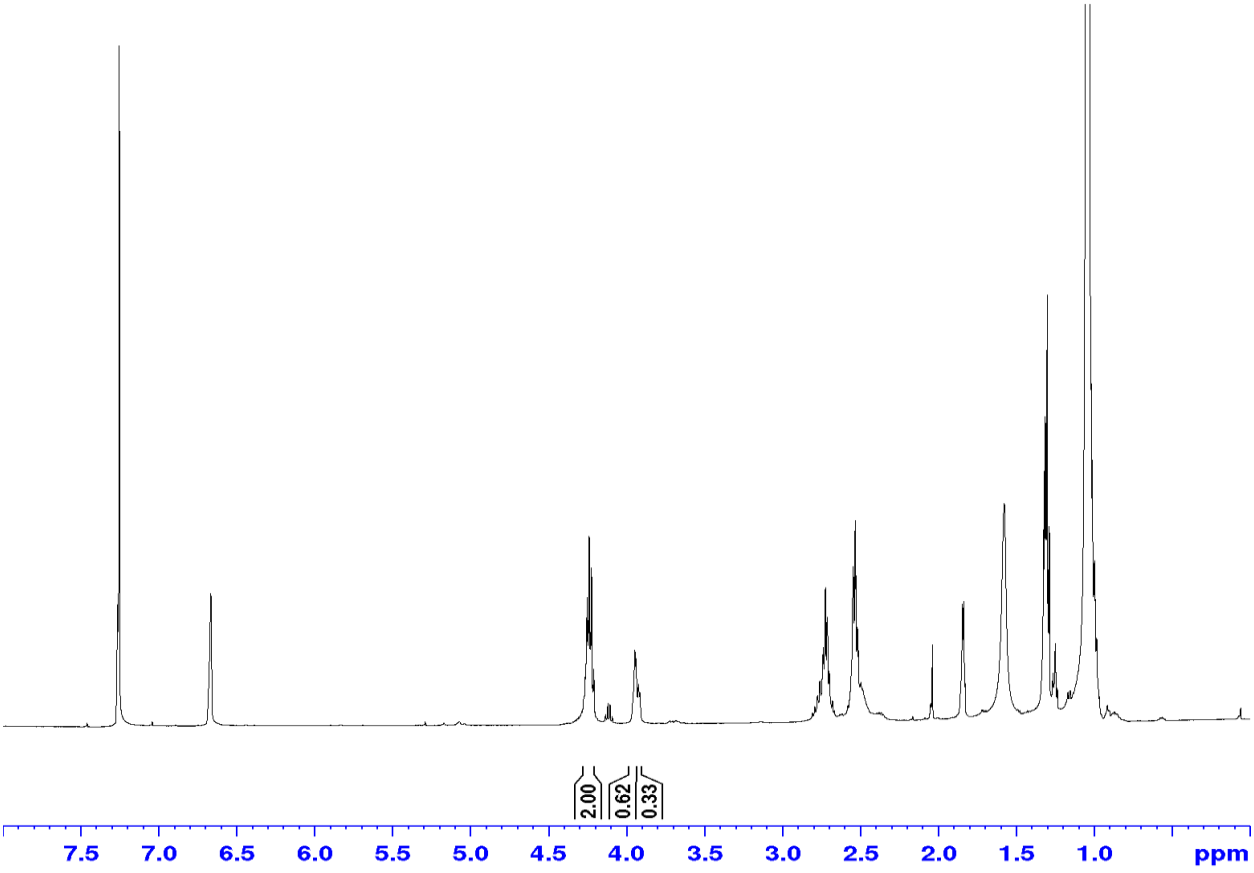


Table 4.1. Entry 3 ^{1}H NMR ($CDCl_3$, 400 MHz)



Relevant ^{1}H-NMR for table 4.5 ^{1}H NMR ($CDCl_3$, 400 MHz)
Table 4.5 Entry 1

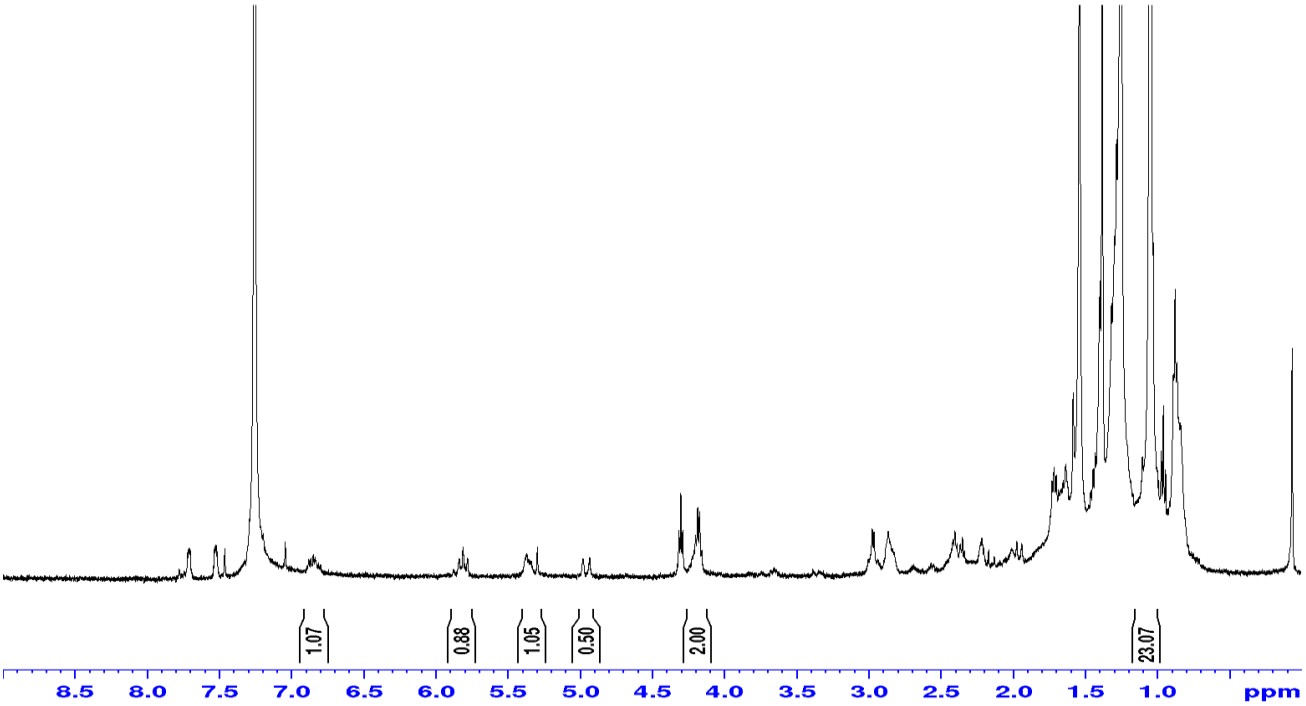


Table 4.5 Entry 4-Recovered S.M. ^{1}H NMR ($CDCl_3$, 400 MHz)

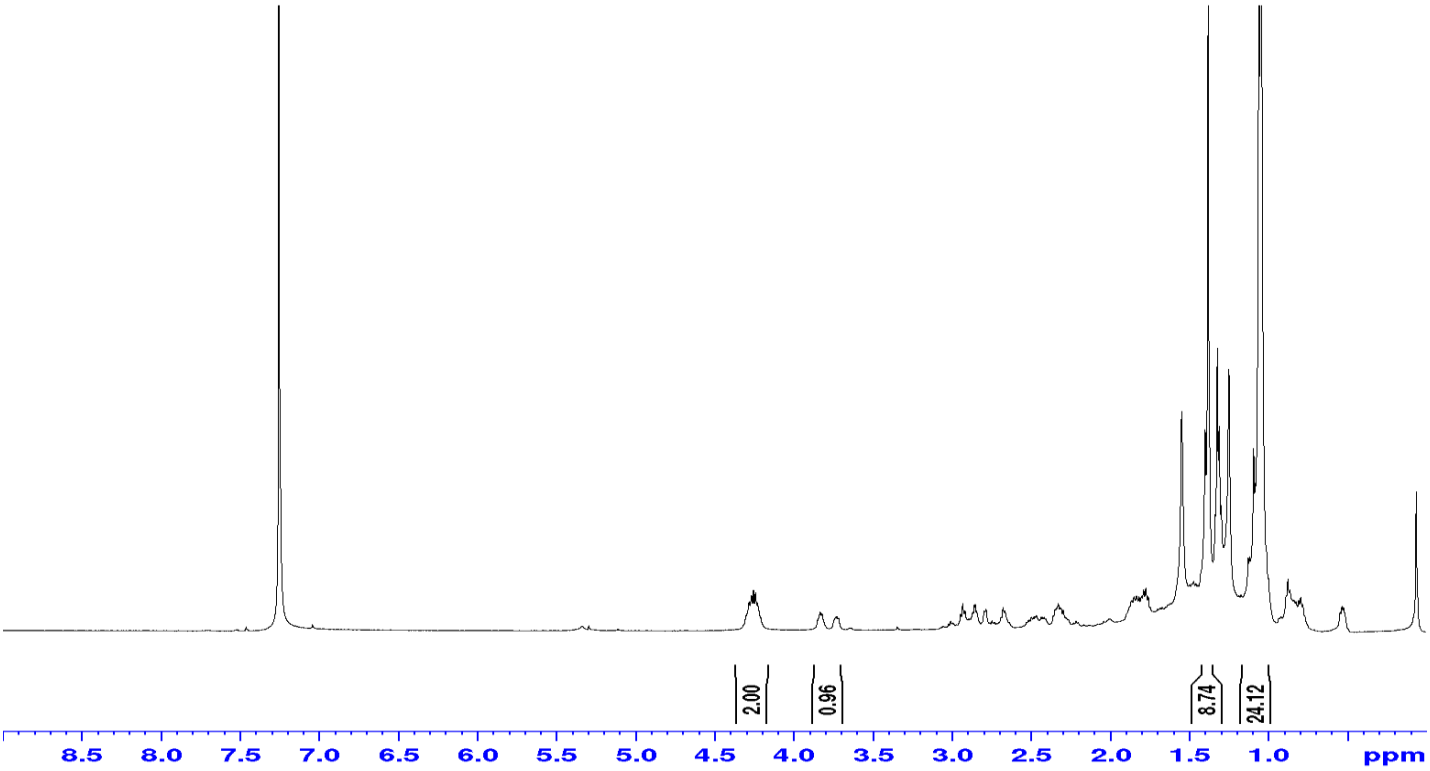


Table 4.5 Entry 4-DestertButyl Side Prod. ^{1}H NMR ($CDCl_3$, 400 MHz)

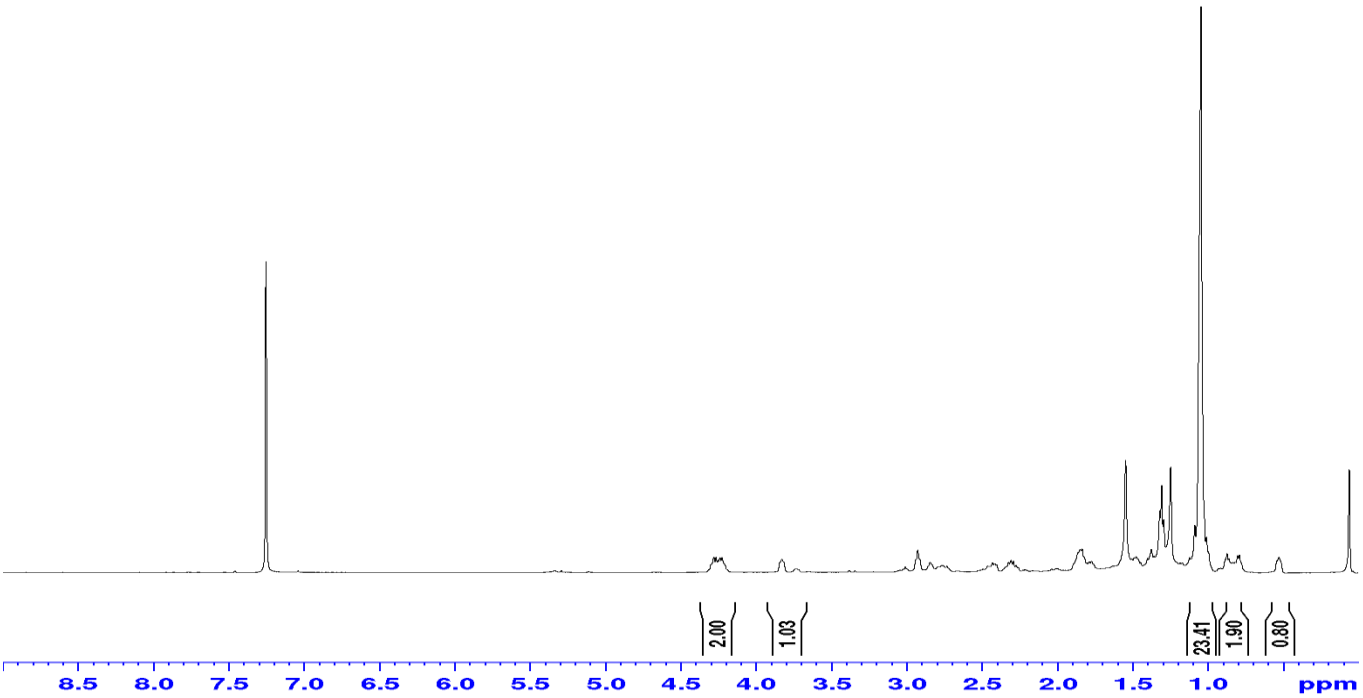


Table 4.5 Entry 5 5.54 product ^{1}H NMR ($CDCl_3$, 400 MHz)

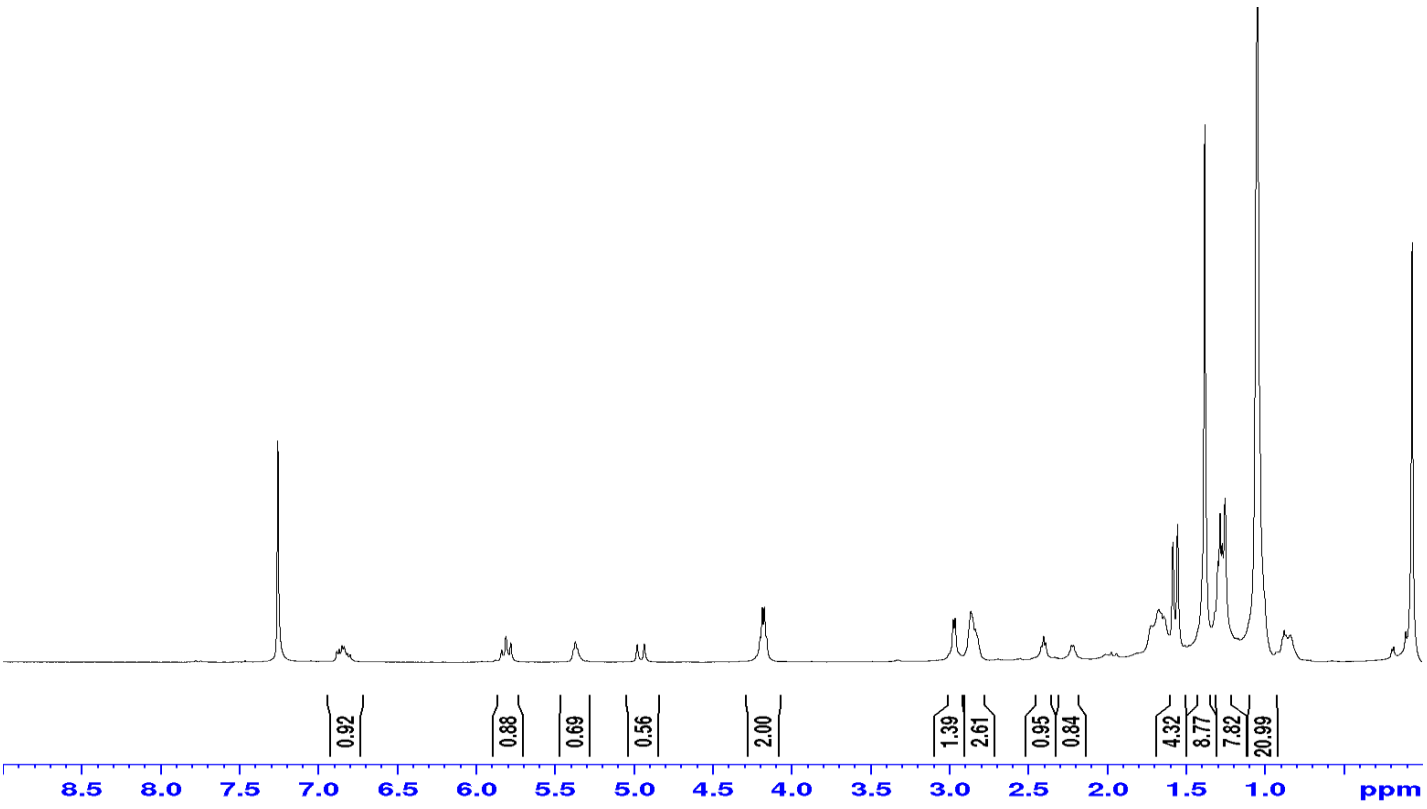


Table 4.5 Entry 7 5.54 product
See 5.54 spectra
Table 4.5 Entry 7 Side Product 2

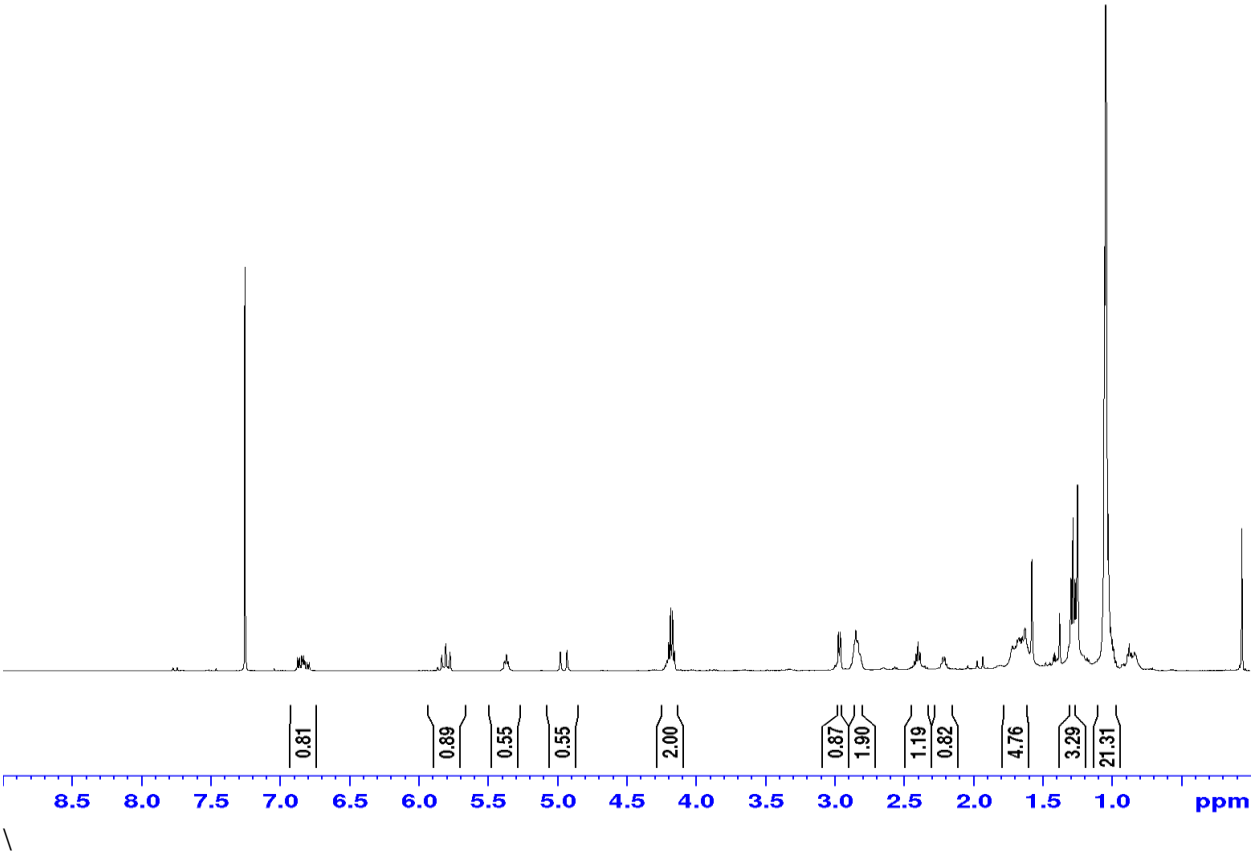


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Table 4.5 Entry 8 Crude NMR

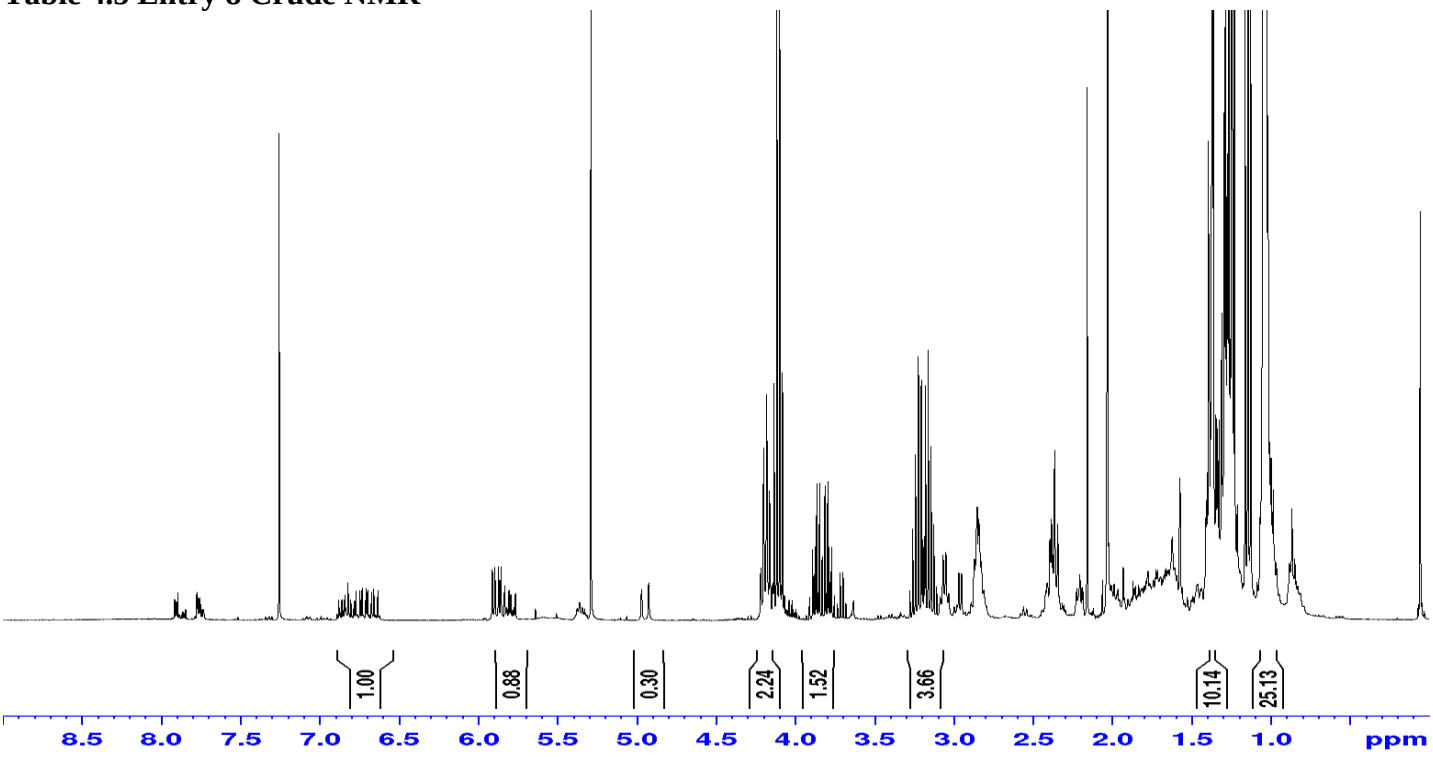


Table 4.5 Entry 11 Crude NMR

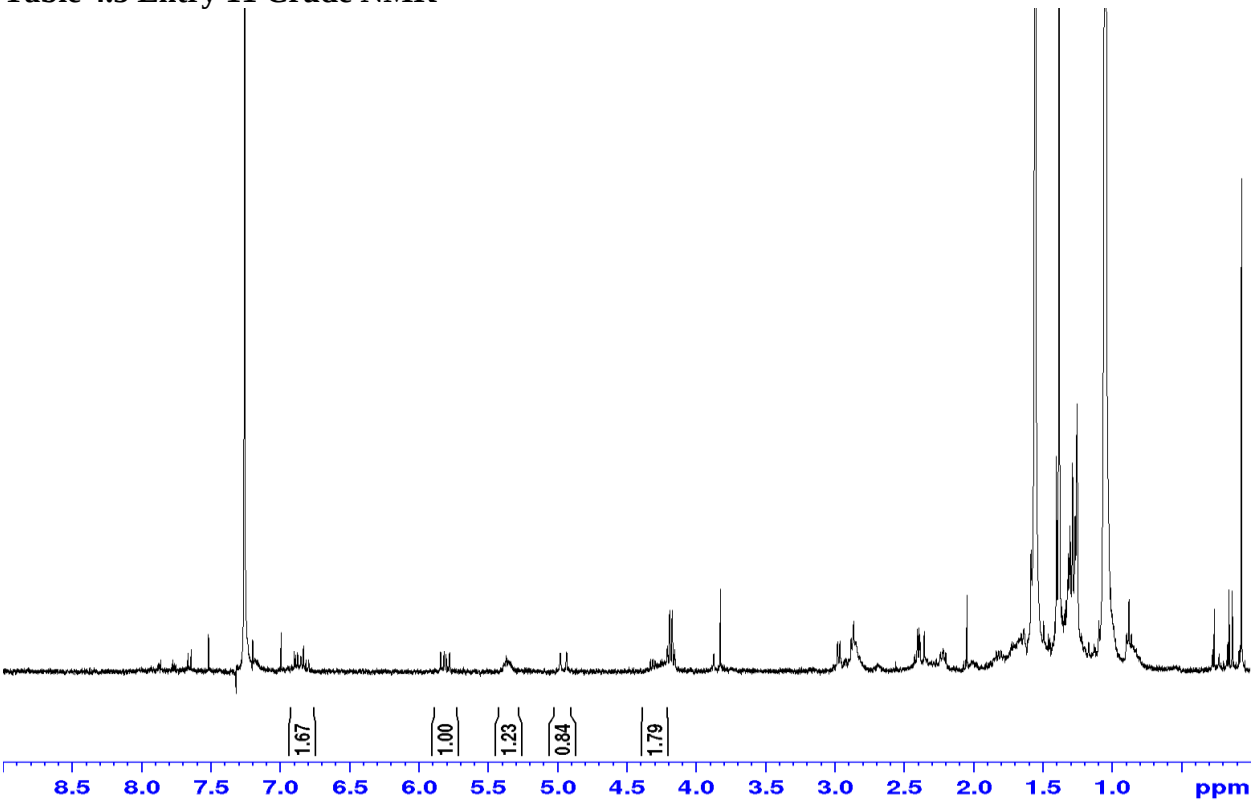


Table 4.5 Entry 12

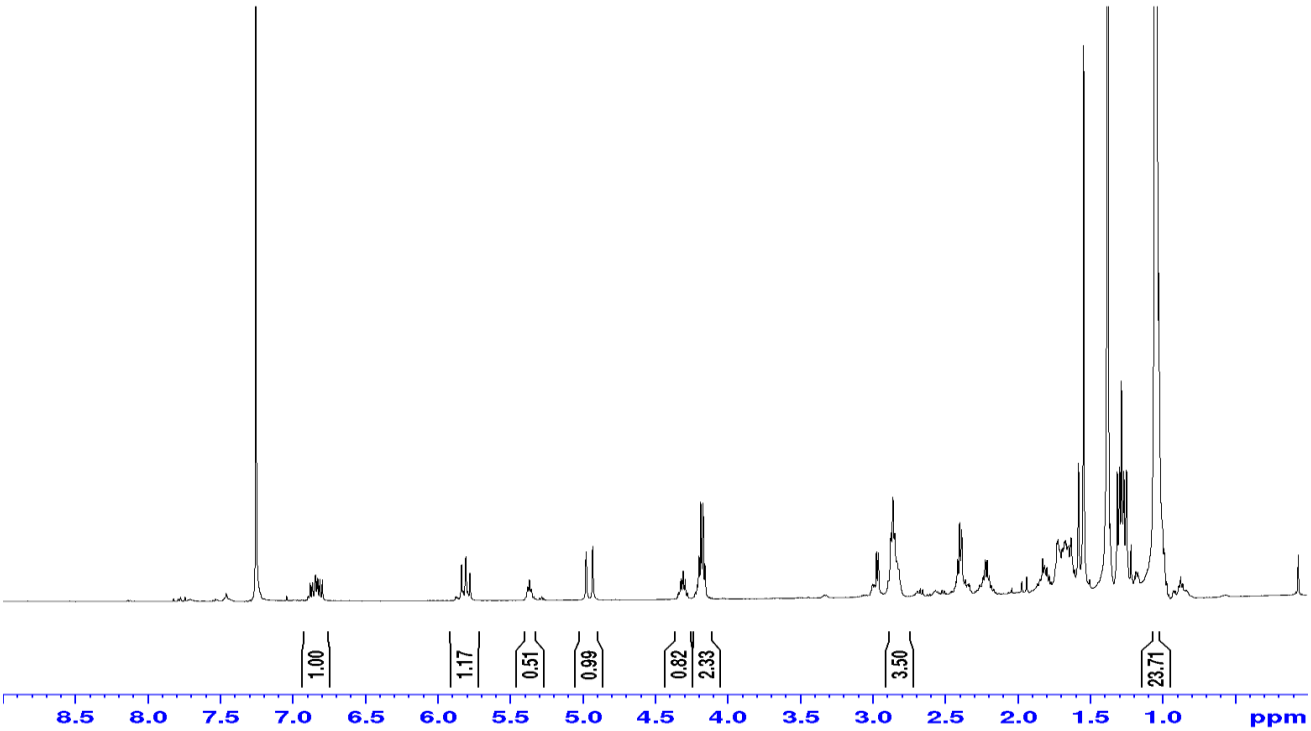
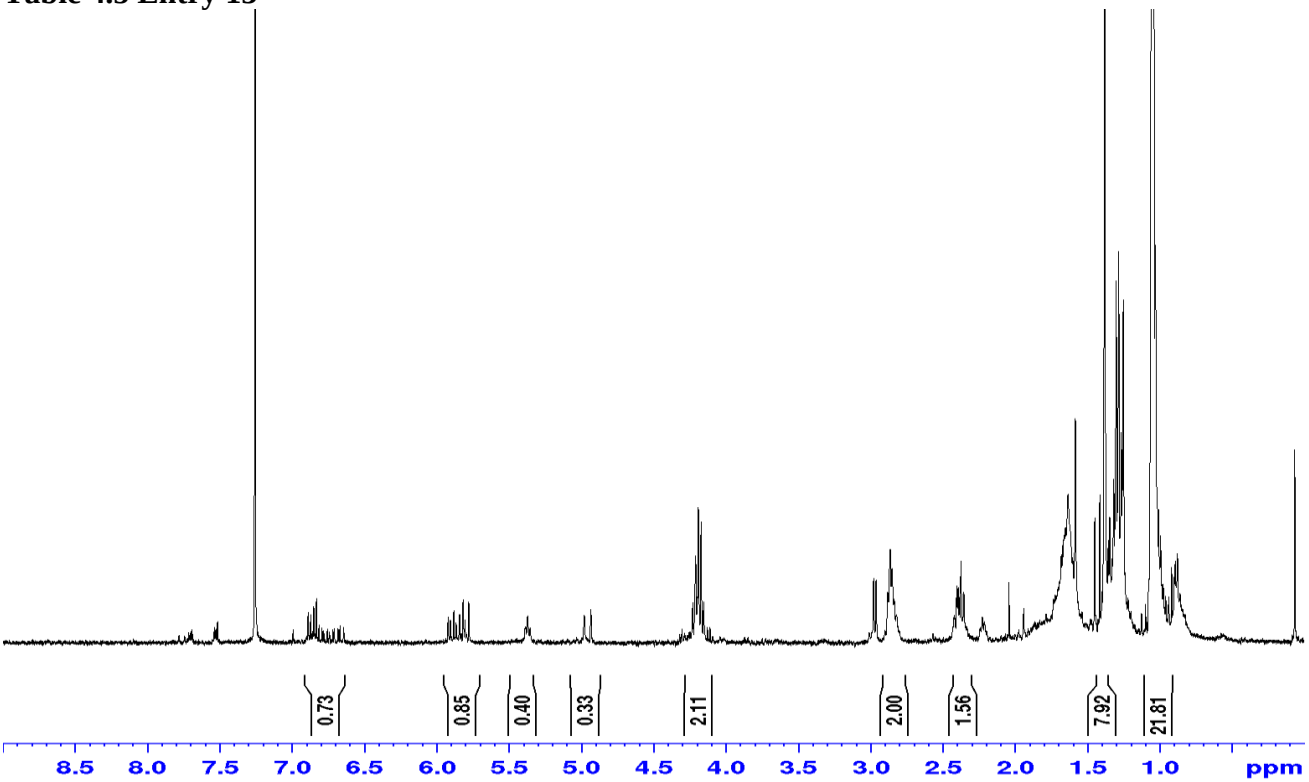


Table 4.5 Entry 13



Relevant ^{1}H-NMR for table 4.6
Table 4.6 Entry 2 See 5.58 spectra.
Table 4.6 Entry 3 Isolated 5.58

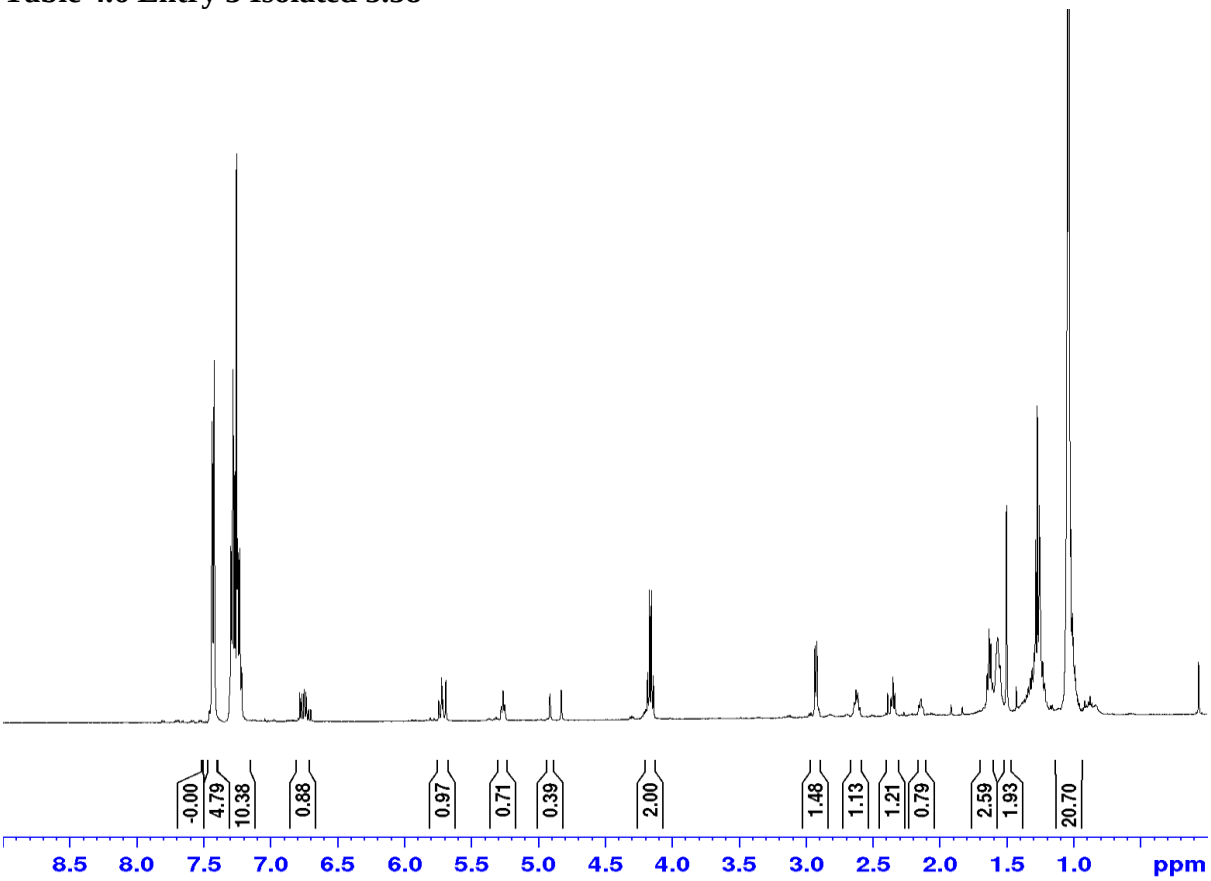


Table 4.6 Entry 4 Isolated 5.58

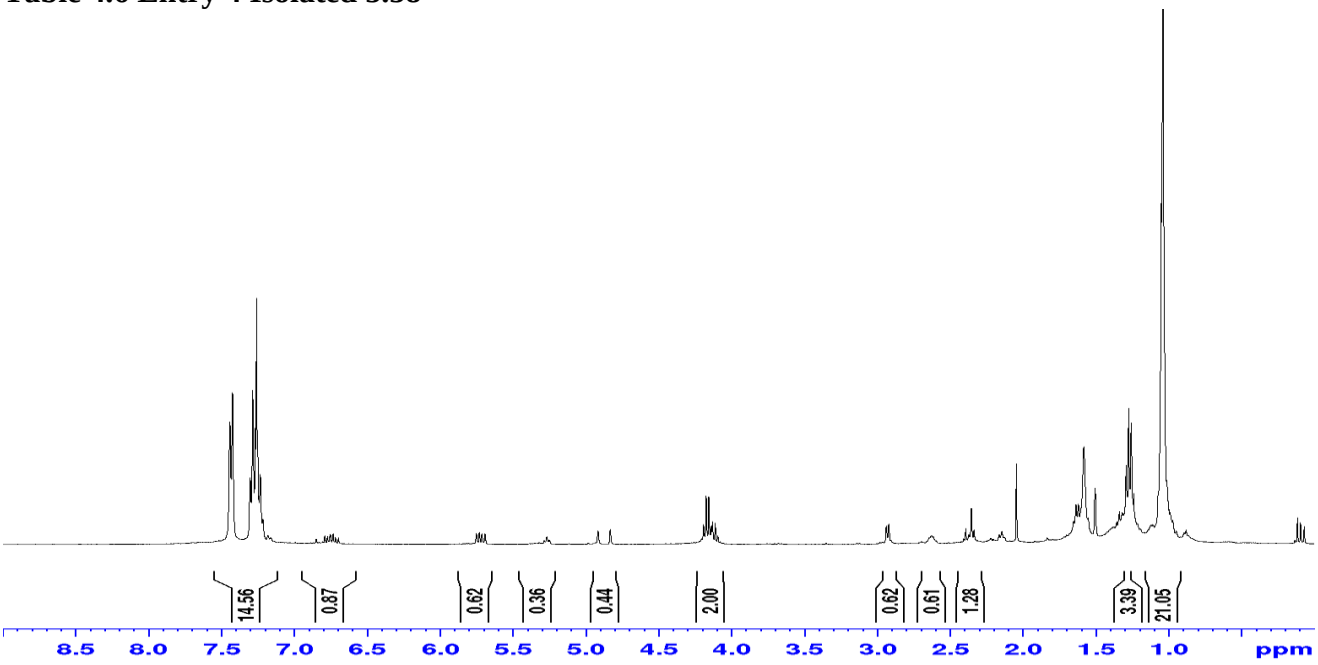


Table 4.6 Entry 5

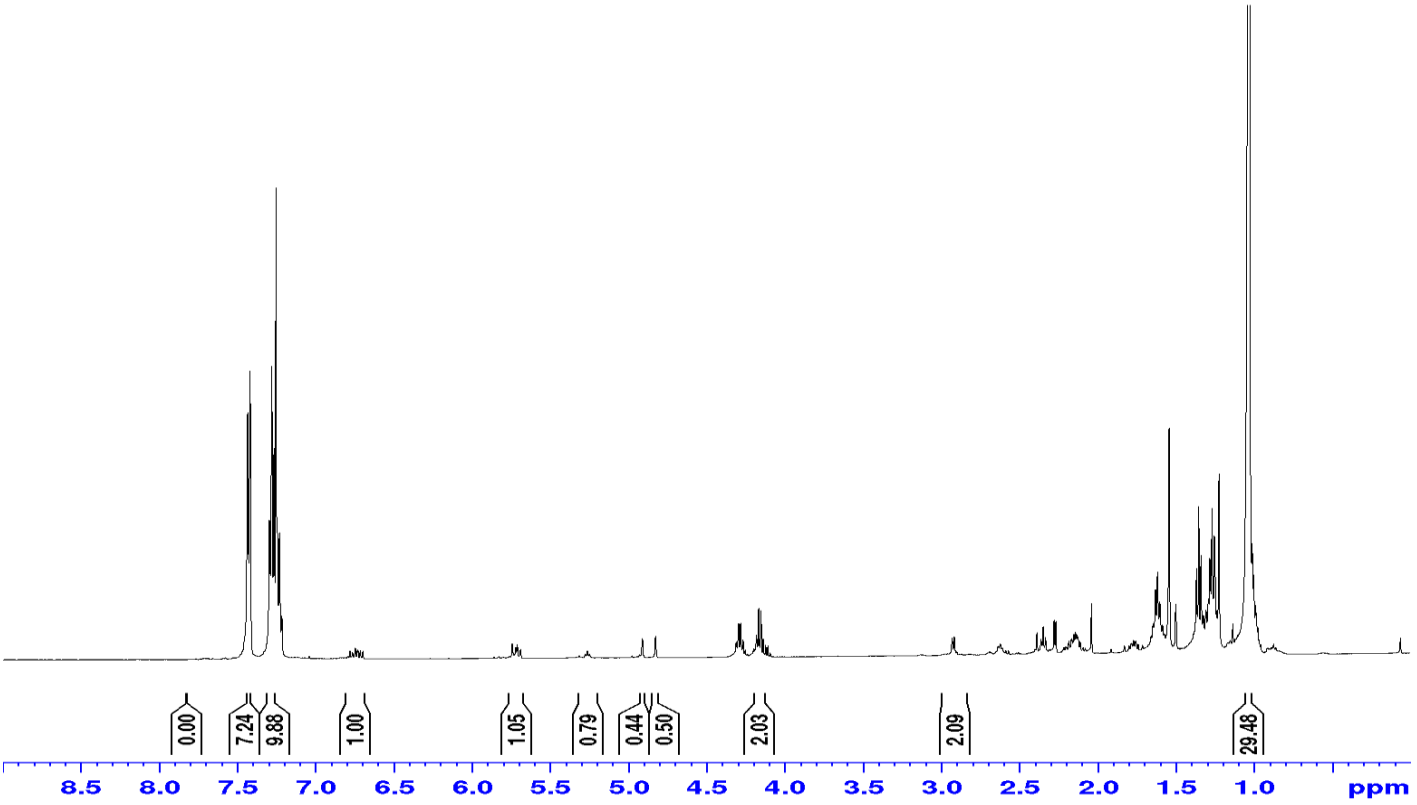


Table 4.6 Entry 6

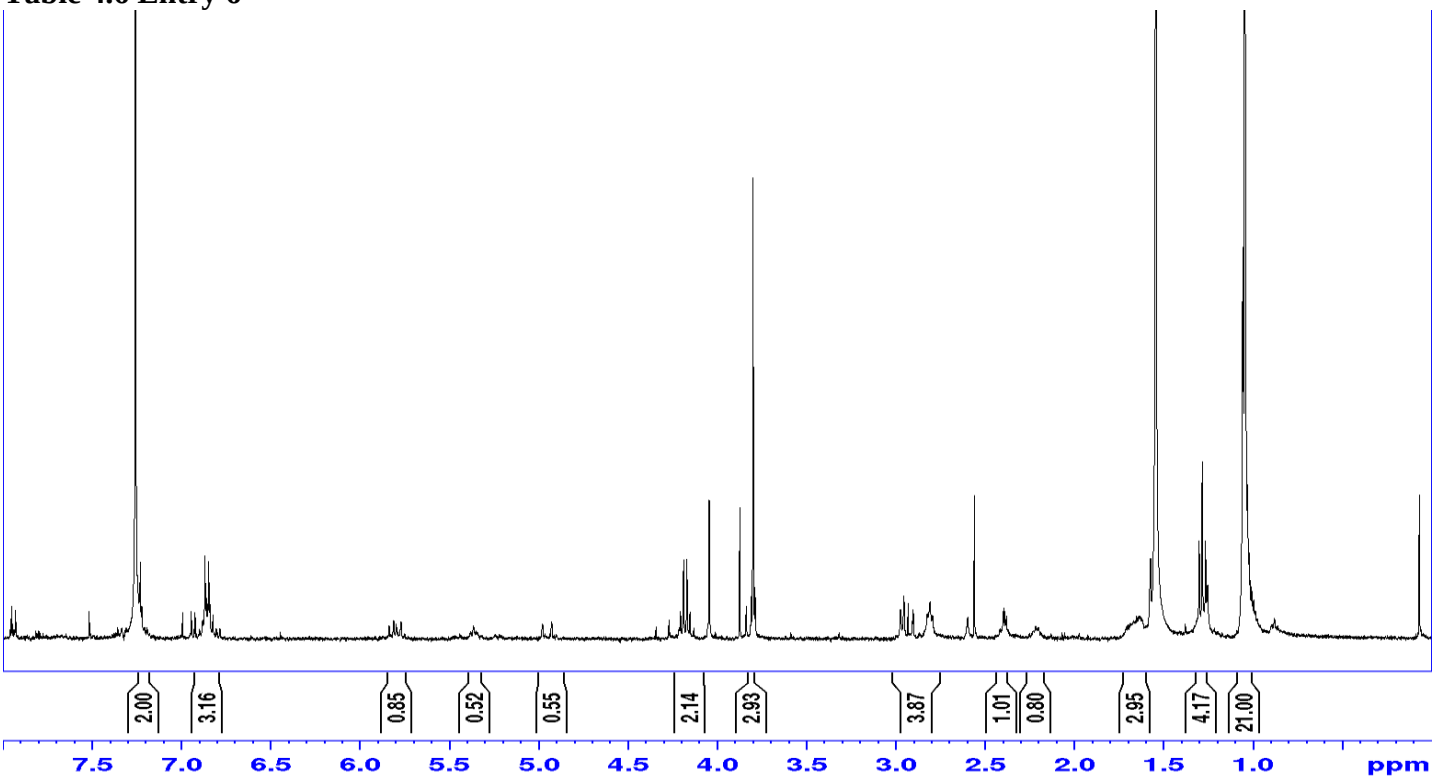
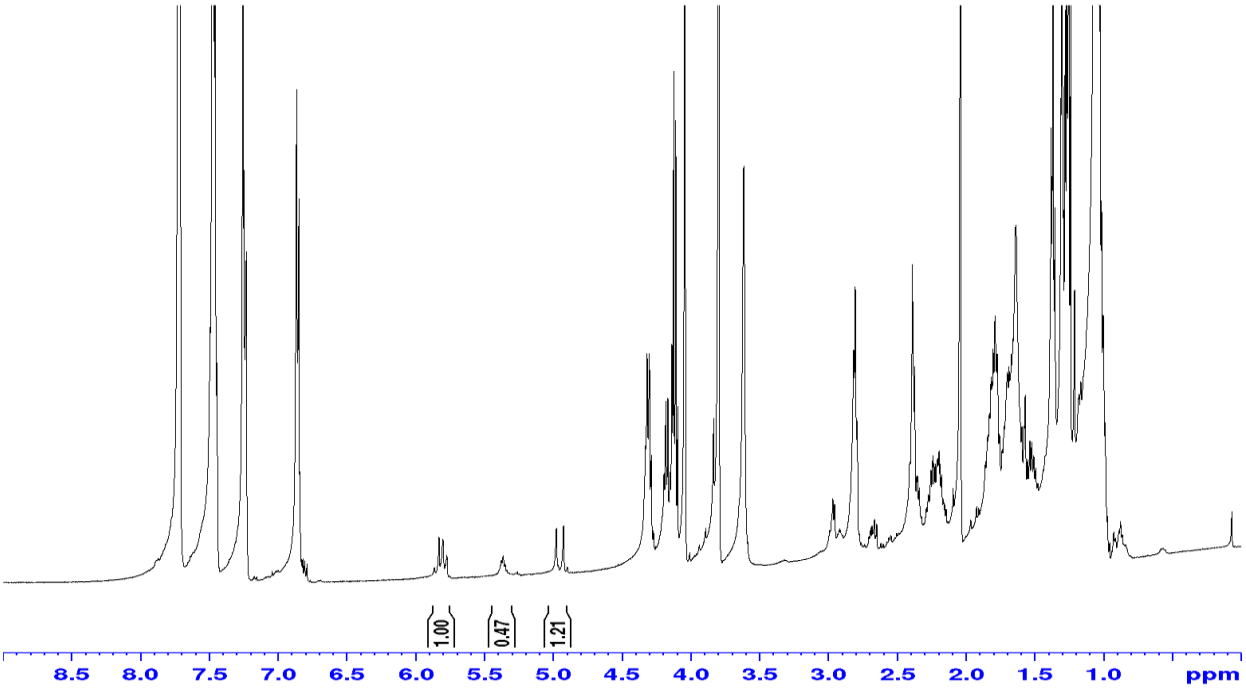
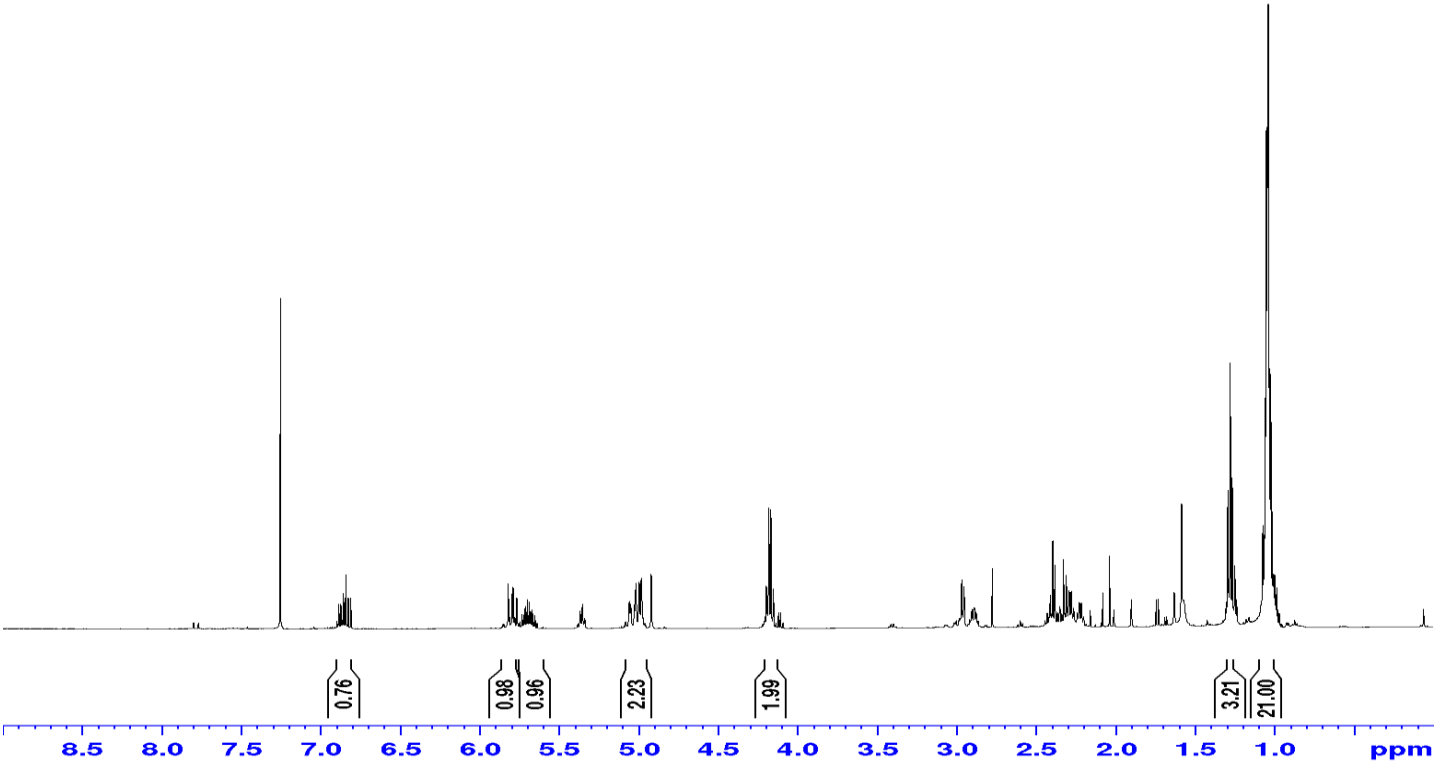


Table 4.6 Entry 9



Relevant ^{1}H-NMR for table 4.7
table 4.7 entry 4



Relevant ^{1}H-NMR for table 4.8
Table 4.8 entry 1

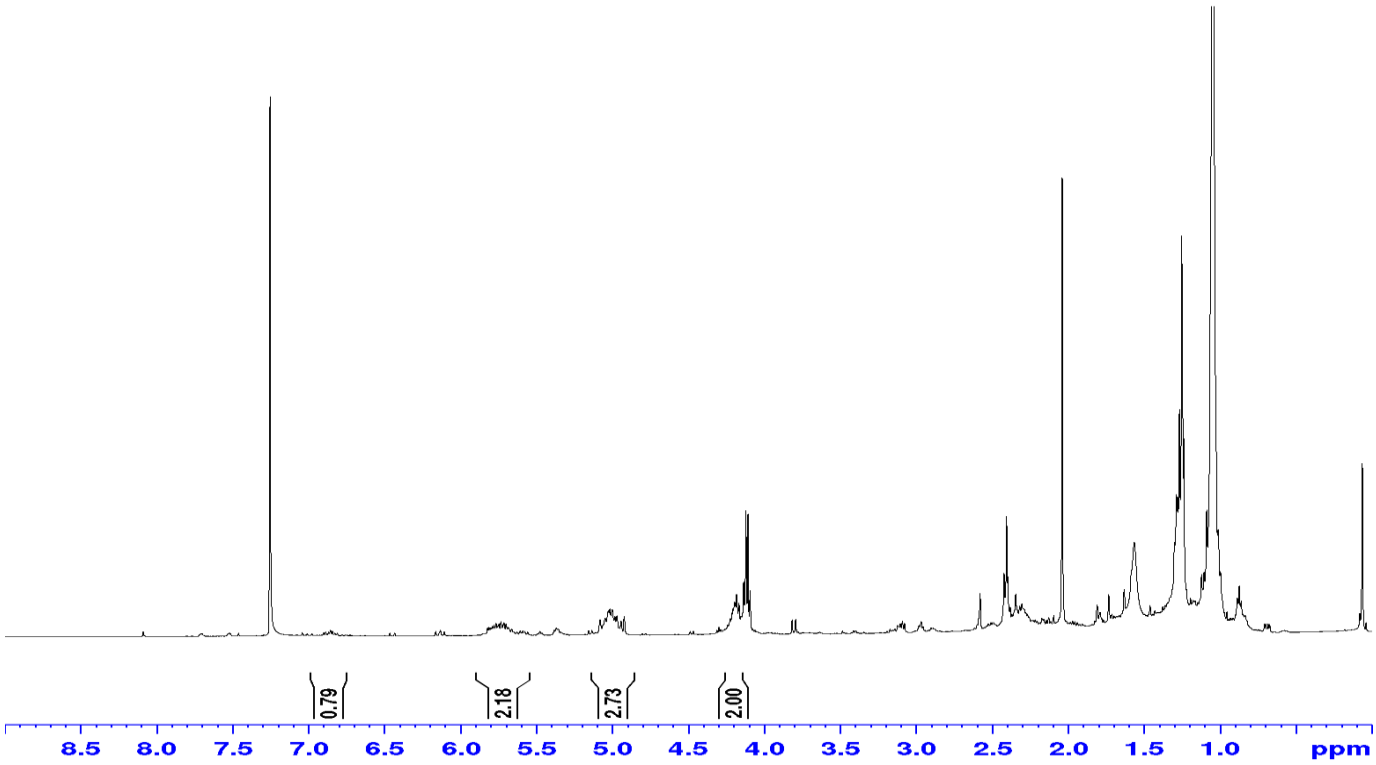


Table 4.8 entry 2

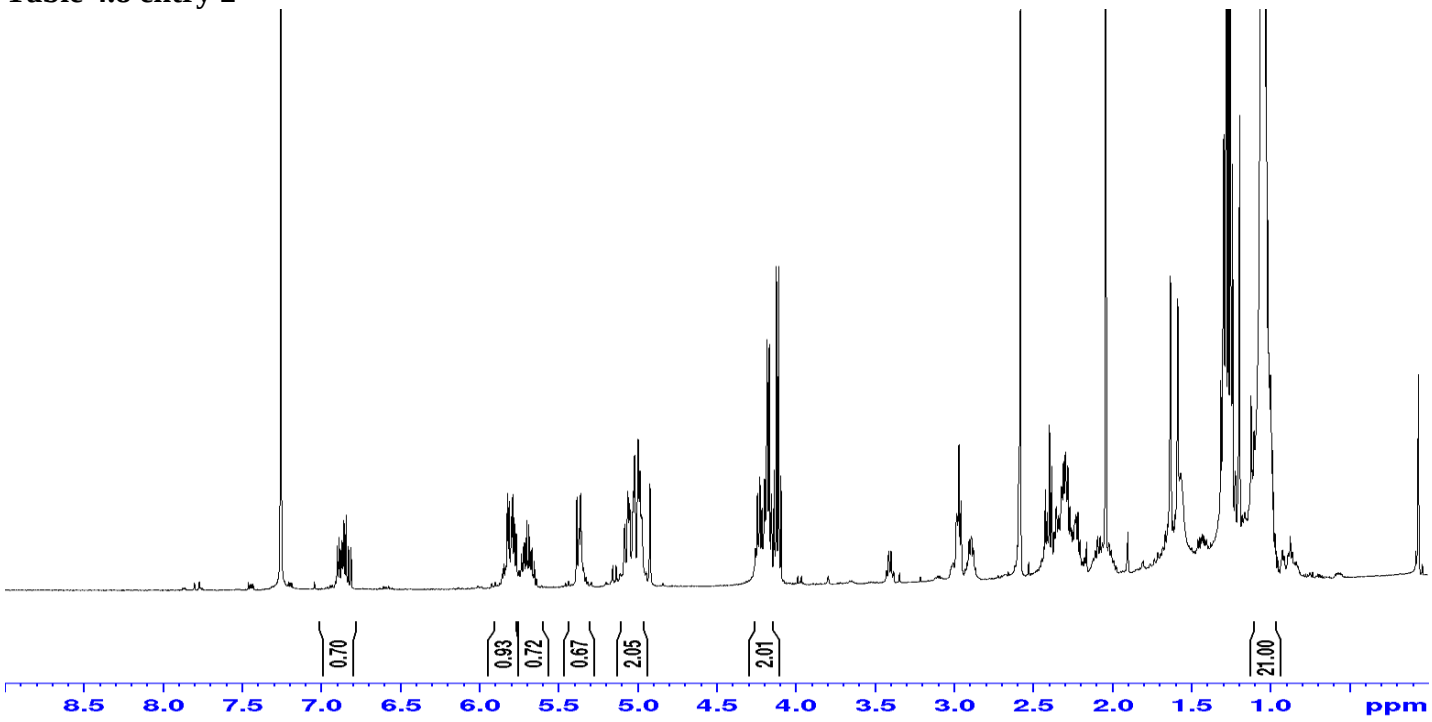


Table 4.8 entry 4- 125°C

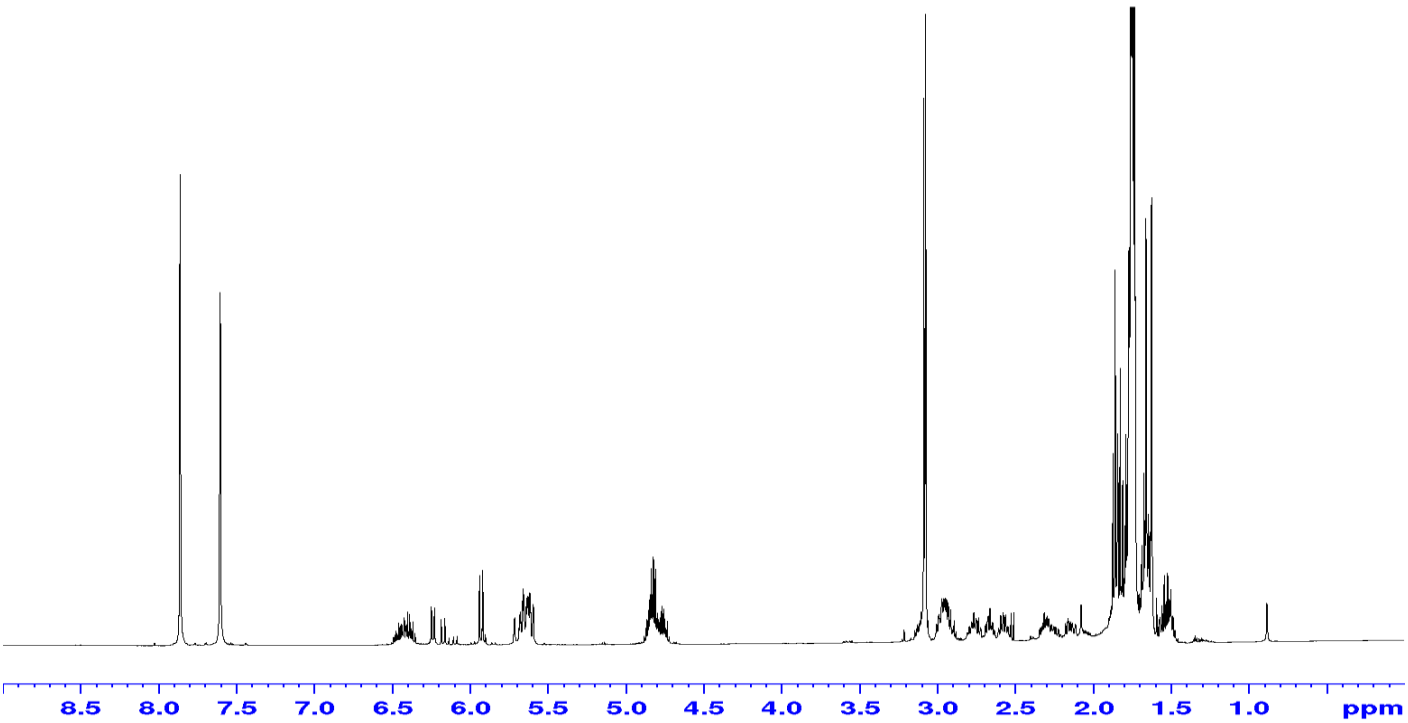


Table 4.8 entry 4- 140°C

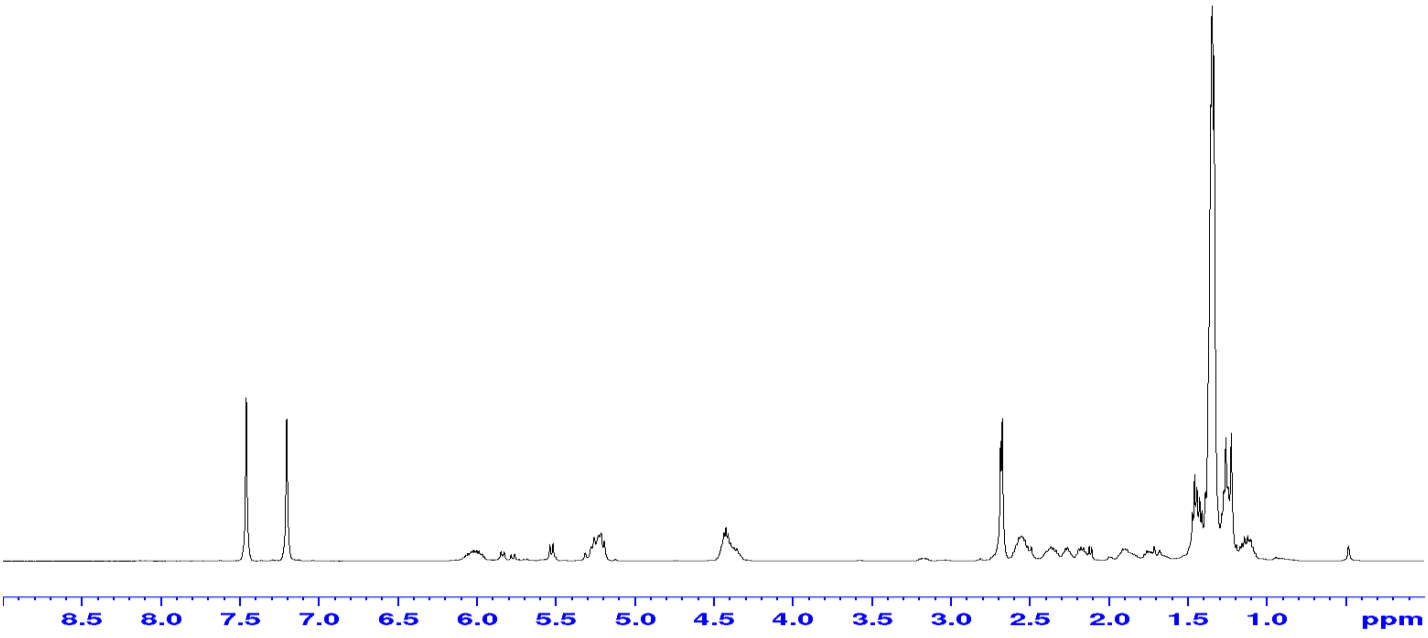


Table 4.8 entry 4- 150°C

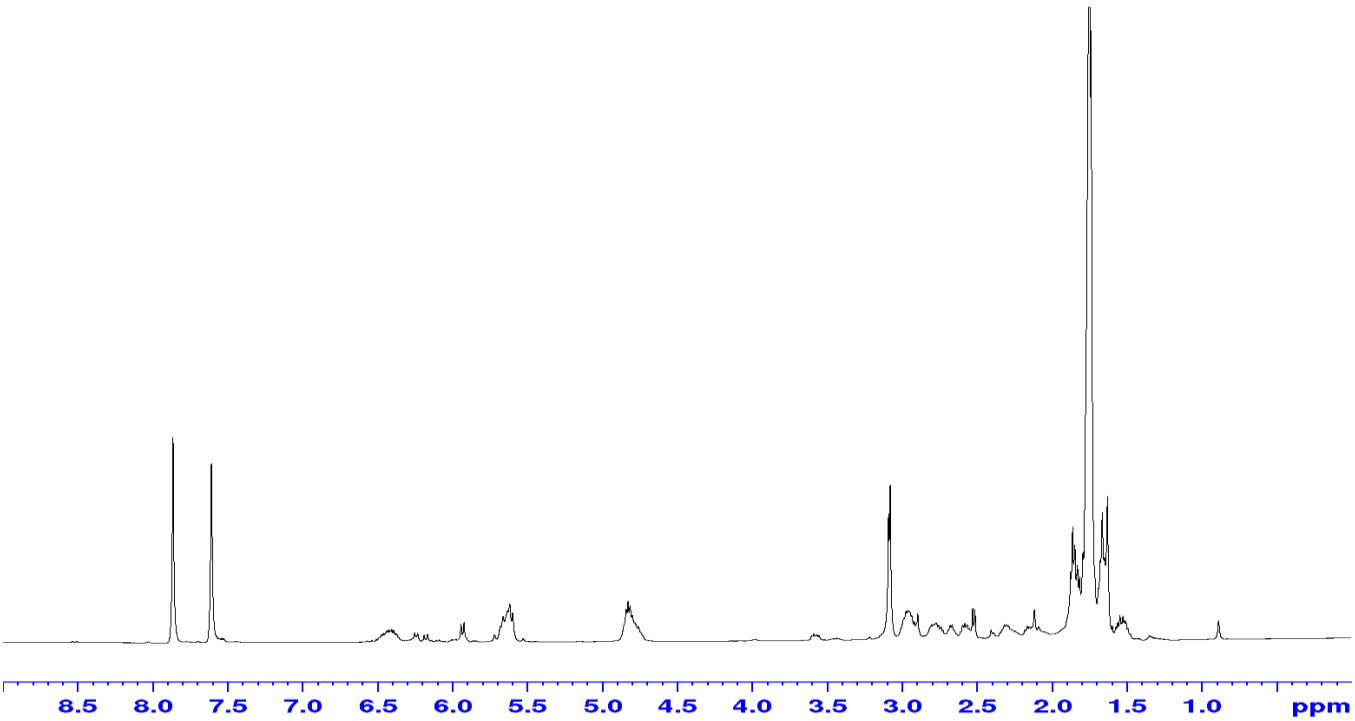


Table 4.8 entry 4- 160°C

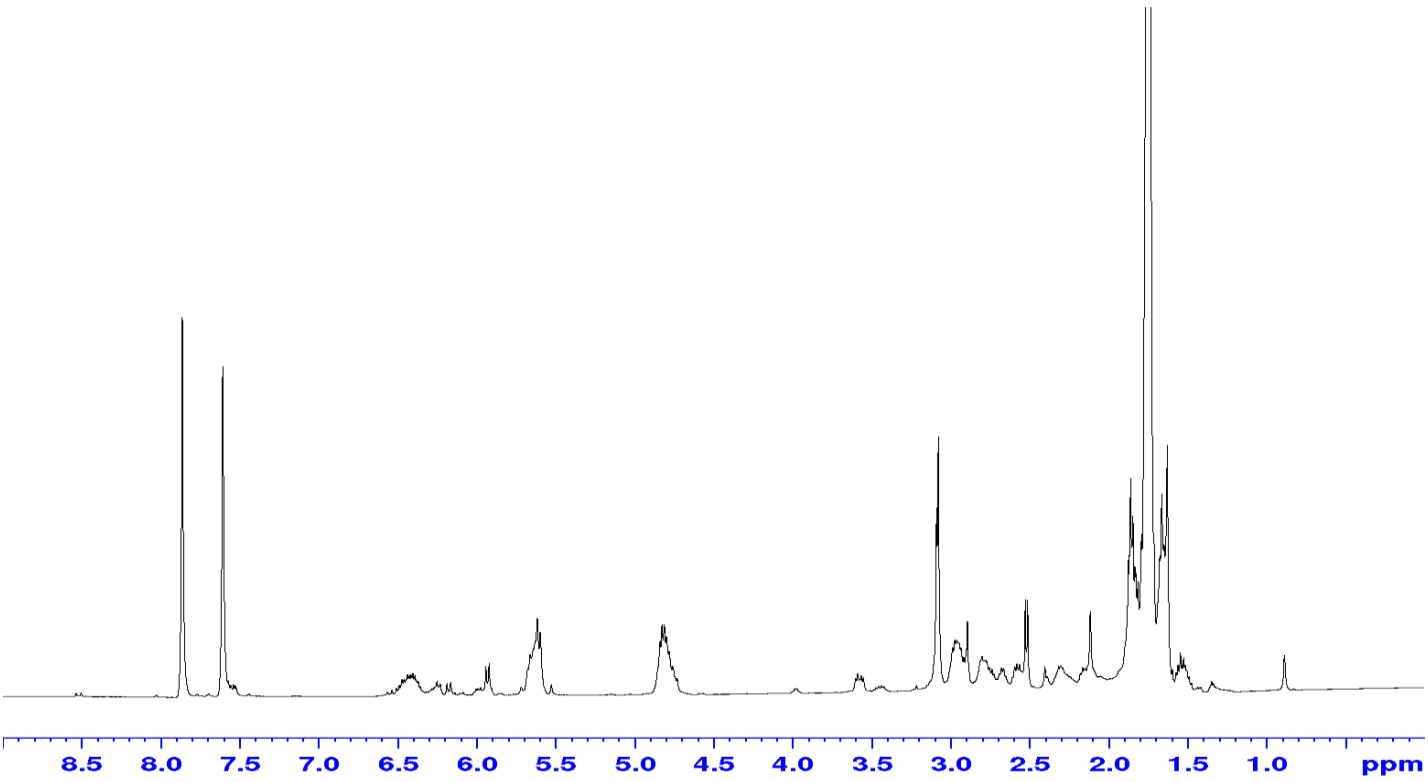


Table 4.8 entry 4- 5 minutes 170°C

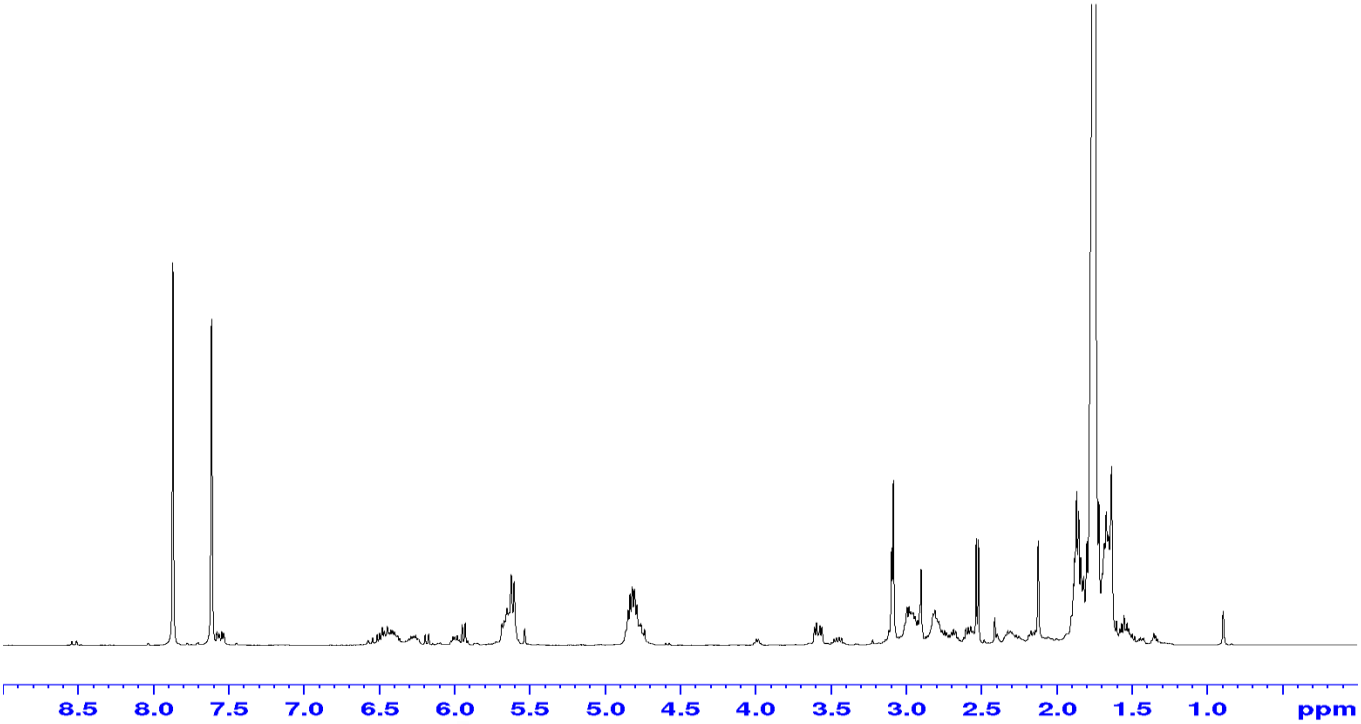


Table 4.8 entry 4- 15 minutes 170°C

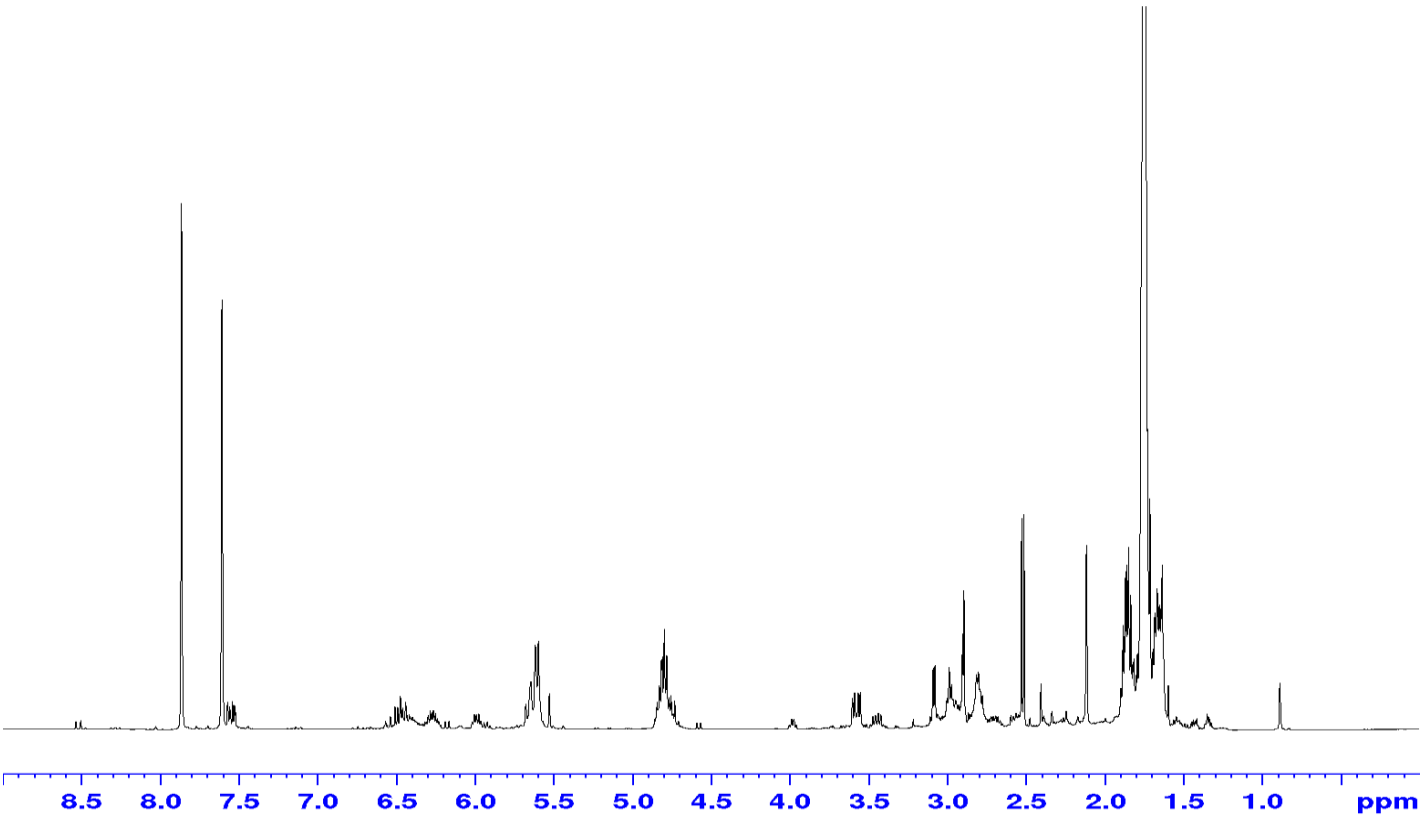


Table 4.8 entry Isolated 4.60 product

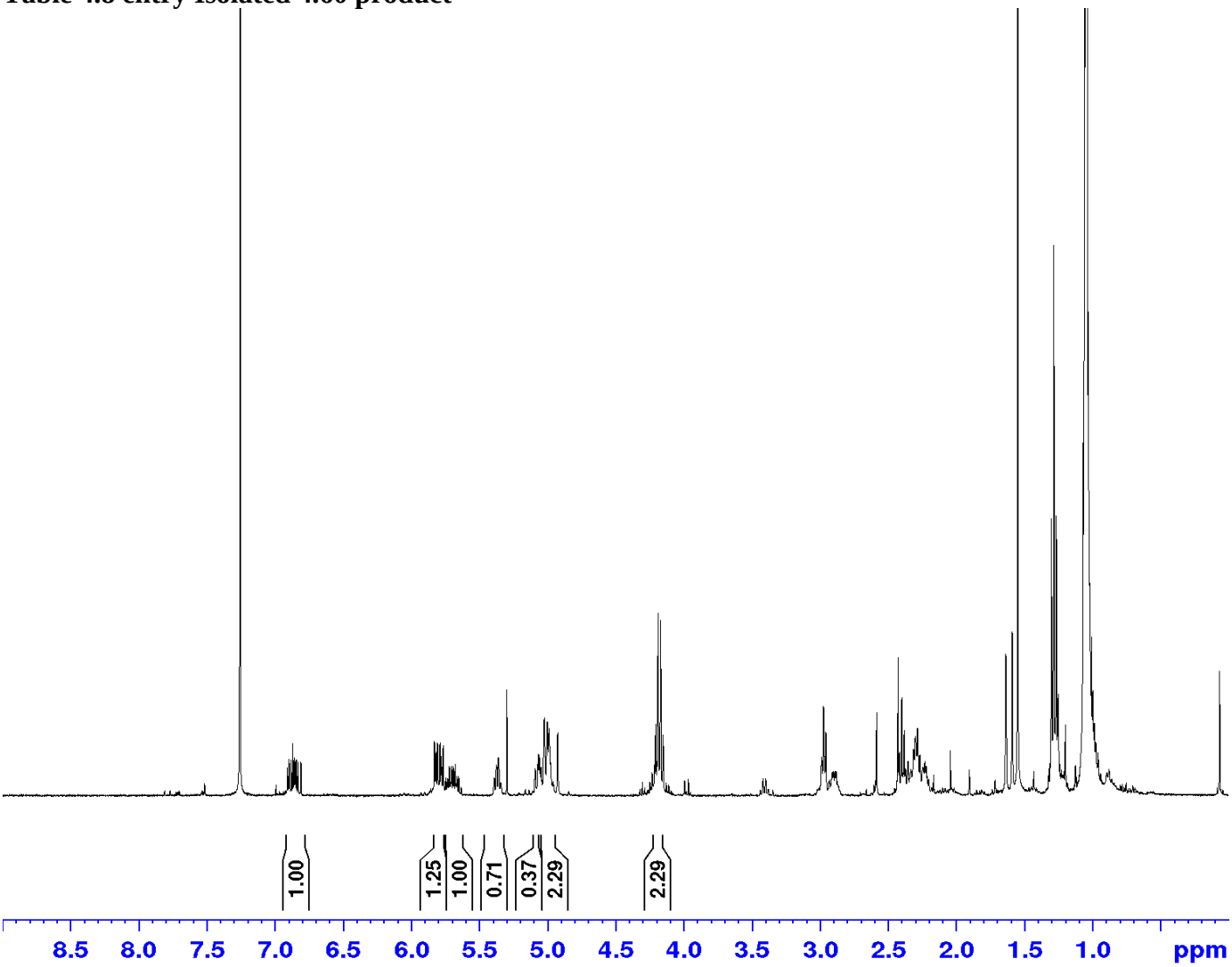
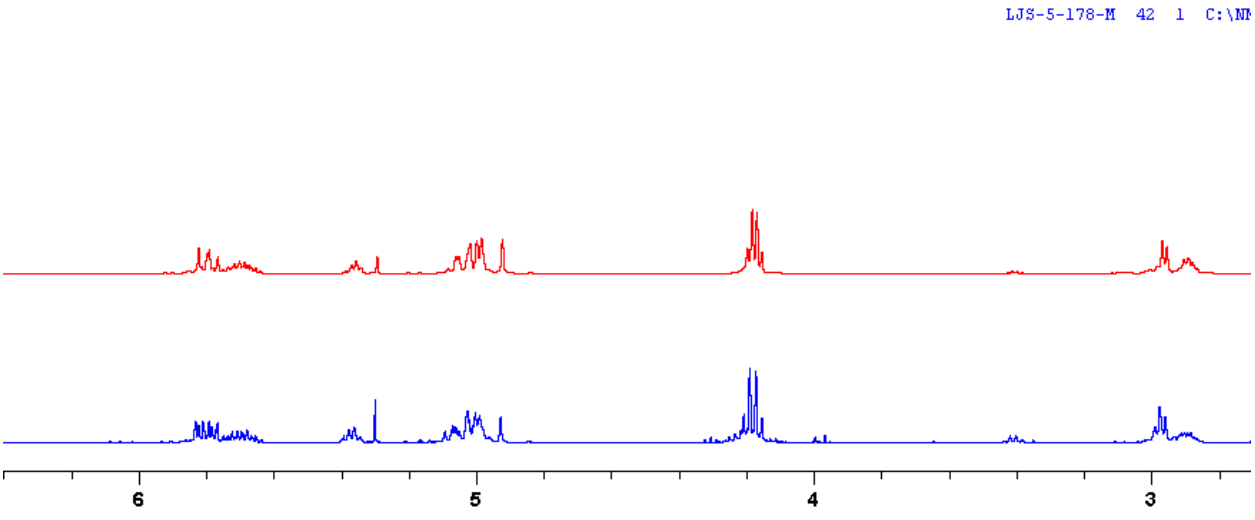


Table 4.8 entry isolated 4.60 product overlaid with scheme 4.9 derived 4.60 product



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