Title

Total Syntheses of Pentacyclic Ambiguine Natural Products and Studies toward the Total Syntheses of Prenylated Indole Alkaloids: Versicamides and Carneamides

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Total Syntheses of Pentacyclic Ambiguine Natural Products and Studies toward the Total Syntheses of Prenylated Indole Alkaloids: Versicamides and Carneamides

by

Hwisoo Ree

A dissertation submitted in partial satisfaction of the

requirements for the degree of

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in

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University of California, Berkeley

Committee in charge:

Professor Richmond Sarpong, Chair
Professor Kurt Vollhardt
Professor Thomas Maimone
Professor Xavier Darzacq

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Total Syntheses of Pentacyclic Ambiguine Natural Products

and
Studies toward the Total Syntheses of Prenylated Indole Alkaloids: Versicamides and Carneamides

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Abstract

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The medicinally relevant indole structure is frequently encountered in drug candidates and naturally occurring molecules. These indole alkaloids exhibit diverse molecular structures and exert exciting biological functions that are useful to human and plant health. Many of these important natural products lack effective means for their chemical synthesis, therefore limiting access. My dissertation focuses on the study of new strategies to synthesize indole alkaloids.

The first chapter describes my efforts at functionalizing the C2 position of brevianamide F, which is proposed to be a common intermediate in the unified synthesis of prenylated indole alkaloids, versicamide and carneamide natural products. Several synthetic routes to directly functionalize the indole C2 position of brevianamide F were investigated, and a C2-borylated brevianamide was prepared. Advancing this intermediate to reverse-prenylated brevianamide F, and optimizing its diborylation will be key to achieving the proposed syntheses.

In Chapter 2, the first synthesis of a pentacyclic ambiguine (ambiguine P) is discussed. As part of a team, we developed a strategy that takes advantage of sequential, robust, alkylative functionalizations of indole, leading to the rapid construction of the ambiguine core structure. Key to the success of the synthesis is the use of a Nicholas reaction to alkylate at C2, crafting a fused seven-membered ring that is characteristic of the pentacyclic ambiguines, as well as the use of an amide-directed functionalization at C12 to set a requisite quaternary center. A versatile late-stage intermediate was prepared that may be applicable to the synthesis of the other pentacyclic ambiguines. The first total synthesis of ambiguine P was completed in 21 steps from carvone via a late-stage C–H oxidation.

Chapter 3 describes the use of the synthesis strategy and knowledge acquired from the studies described in Chapter 2 to synthesize related ambiguines of higher oxygenation levels. From the advanced intermediate prepared in the synthesis of ambiguine P and described in Chapter 2, various synthetic sequences are examined to access ambiguines L, I, N, and J. Various strategies have been explored to install the C10 hydroxy group that is common to most members of the ambiguine family. Late-stage oxidation of the pentacyclic scaffold has proven to be a challenge

due to the presence of the oxidation-sensitive indole moiety. Ultimately, the desired oxidation state at the C10 position was achieved through formation of an alkene, from which the seven-membered E ring of the scaffold is functionalized. The resulting C25 and C26 oxidation products map onto ambiguines N and O, respectively, thereby paving way for their completion.

List of Abbreviations

Ac	acetyl
AIBN	azobis(iso-butyronitrile)
BBN	borabicyclo[3.3.1]nonane
br	broad
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
cod	1,5-cyclooctadiene
CuTC	copper(I)-thiophene-2-carboxylate
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAl-H	diisobutyl aluminum hydride
DMAP	(4-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide

DMP	Dess−Martin periodinane
DMSO	dimethylsulfoxide
dtbpy	4,4'-di-*tert*-buthyl-2,2'-dipyridyl
EDC	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide
EI	electron impact ionization
equiv	equivalent
ESI	electrospray ionization
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
IR	infrared
L-selectride	lithium tri-(*sec*-butyl)borohydride
LAH	lithium aluminum hydride
LCMS	liquid chromatography mass spectrometry
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
mp	melting point
Ms	methanesufonyl
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
n	normal
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PDC	pyridinium dichromate
p	*para*
Ph	phenyl
phen	1,10-phenanthroline
PIDA	phenyl iododiacetate
PIFA	[bis(trifluoroacetoxy)iodo]benzene
pin	pinacol
PPTS	pyridinium *para*-toluenesulfonate
pyr	pyridine
q	quartet
quant.	quantitative
rt	room temperature
s	singlet
sec	secondary
t	triplet
TBAF	tertrabutylammonium fluoride
TBHP	*tert*-butylhydrogenperoxide
TBS	*tert*-butyldimethylsilyl
TCDI	1,1'-thiocarbonyldiimidazole

tert	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFDO	methyl(trifluoromethyl)dioxiarane
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
tol	toluene
Ts	*para*-toluenesulfonyl

Contents

Chapter 1

Studies toward the Total Syntheses of Versicamides and Carneamides

Prenylated indole alkaloids represent a large family of secondary metabolites that possess potent antitumor, antibacterial, insecticidal, and anthelmintic activity among others.[1-4] This family of indole alkaloids includes the brevianamides,[5-8] paraherquamides,[9-11] stephacidins,[12] versicolamides,[13, 14] and notoamides.[15] They are commonly found in terrestrial and marine organisms, especially in the various fungi of the genera *Penicillium* and *Aspergillus.*[1] These natural products make up one of the most structurally diverse classes of secondary metabolites that have been isolated, and tend to share a common diketopiperazine ring, a cyclic amino acid residue, and at least one isoprene unit. The broad array of biological activities and high structural diversity make these natural products attractive synthetic targets.

It was our aim to develop a unified synthesis that would provide access to both the versicamide and carneamide natural products from a common intermediate (Figure 1). This unifying approach would facilitate the synthesis of the proposed natural products as well as related analogs, thus streamlining structure-activity relationship studies.[16]

1.1 Discovery of Carneamides and Versicamides

The versicamides and carneamides represent a subset of the prenylated indole alkaloids where the C2 reverse-prenyl group in some of these molecules either engages the amide nitrogen of the diketopiperazine to form an eight-membered ring or remains unmodified.[1]

Carneamides A–C (**1–3**) were isolated from the marine-derived fungus *Aspergillus carneus* (Trichocomaceae) KMM 4638,[17] and dihydrocarneamide A (**4**) was isolated from the marine-derived endophytic fungus *Paecilomyces variotii* EN-291. While carneamides **1–3** did not display cytotoxic activity against several tested cell lines, dihydrocarneamide A (**4**) exhibits cytotoxic activity against NCI-H460 tumor cells (IC_{50}= 69.3 μmol/L).[18]

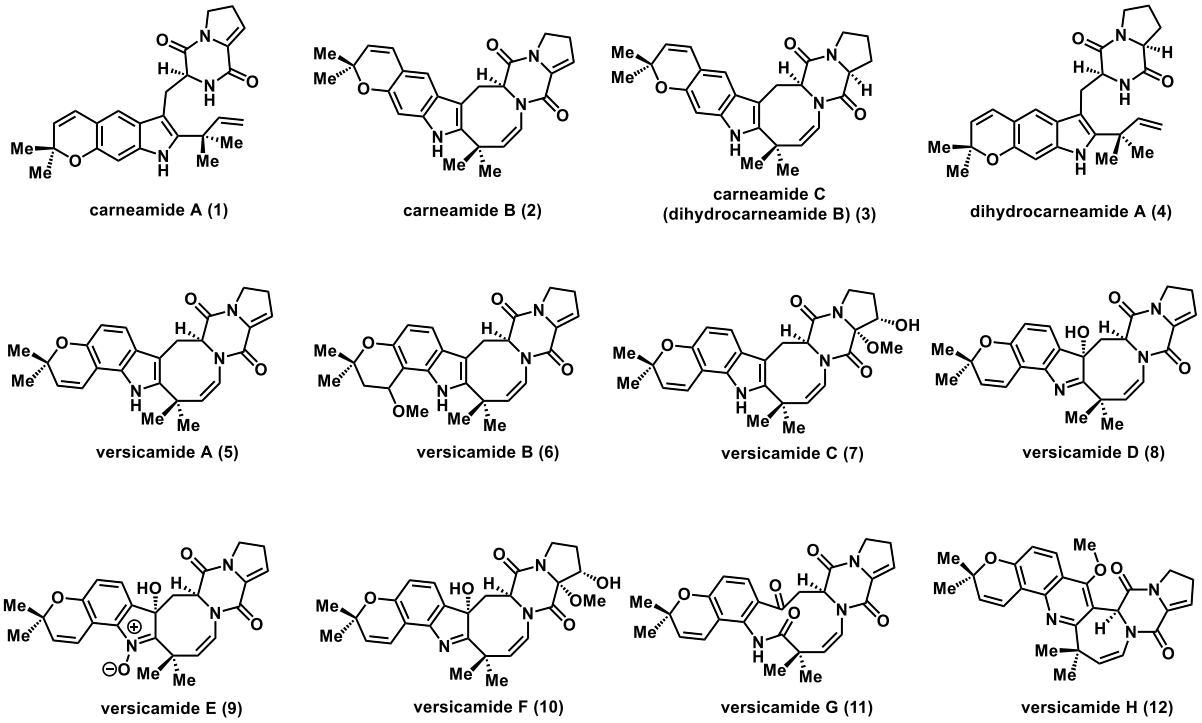
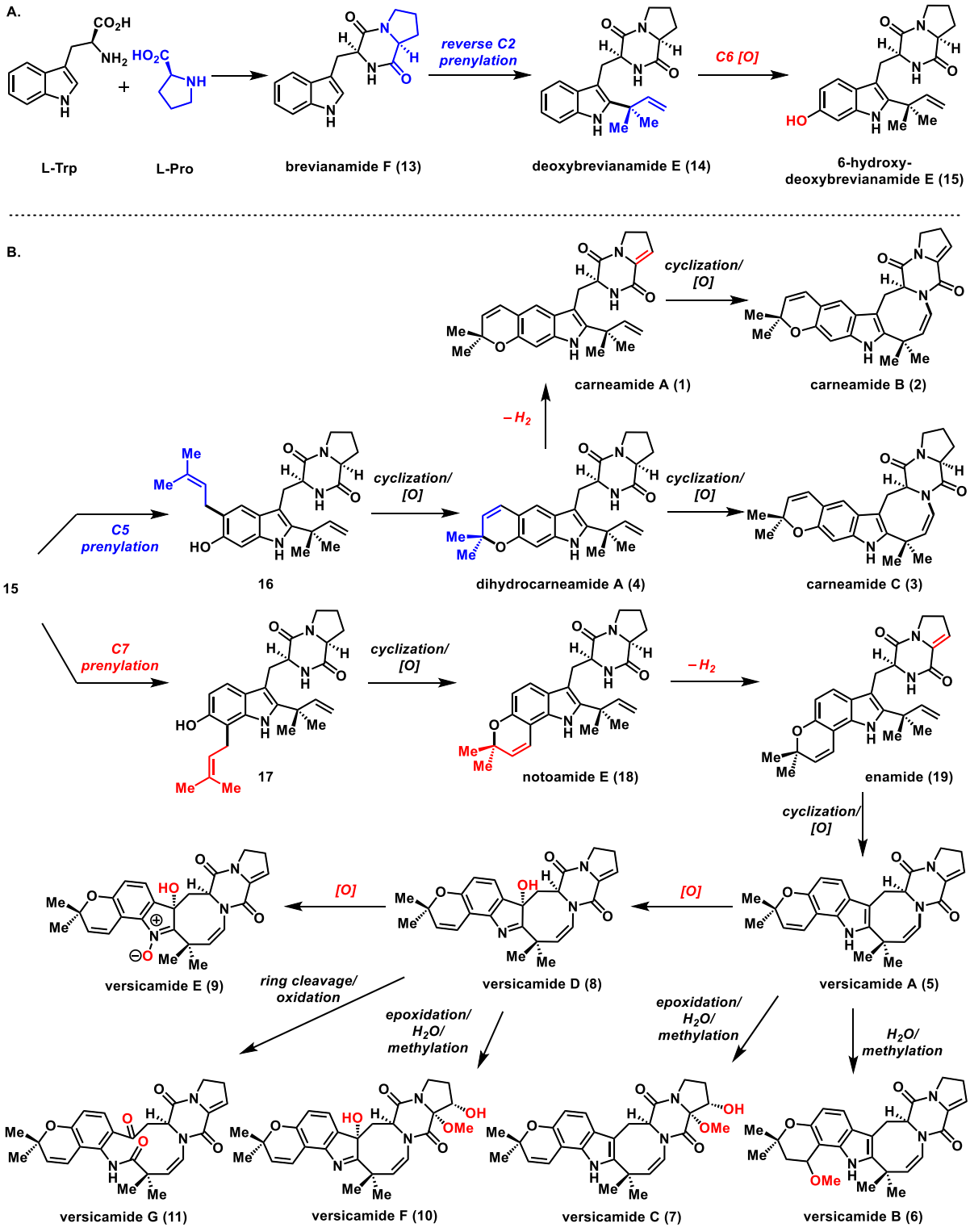


Figure 1. Structures of carneamides and versicamides.

Versicamides A–H (**5**–**12**) were isolated from the marine-derived fungus *Aspergillus versicolor* HDN08-60.[1, 2] Their cytotoxicities have been determined against HeLa, HCT-116, HL-60, and K562 cell lines, and only versicamide H (**12**) exerted cytotoxic activity (IC_{50}= 19.4, 17.7, 8.7 and 22.4 μM, respectively) and protein tyrosine kinase (PTK) inhibitory activity. Access to these natural products in reasonable amounts through chemical synthesis will allow for a more comprehensive exploration of their function beyond the cytotoxicity studies that have been conducted thus far.

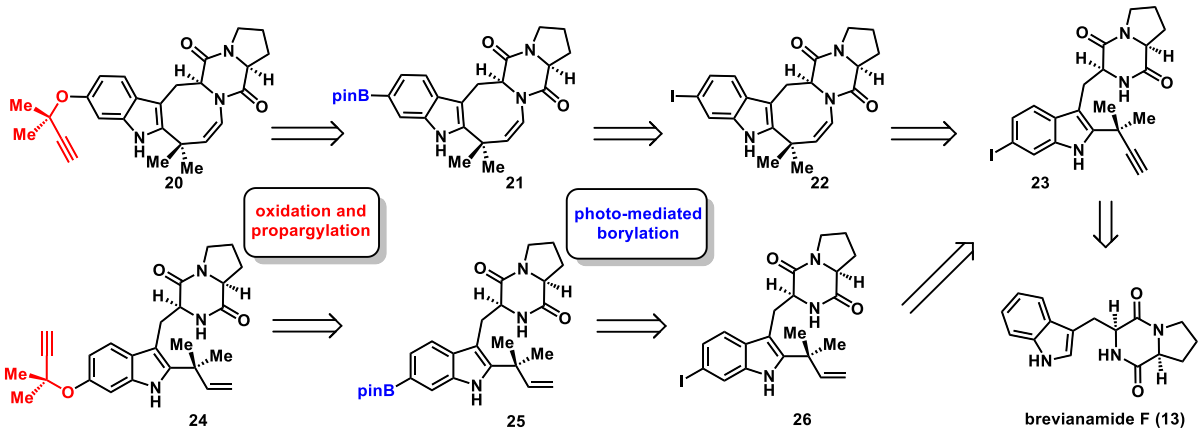
The presumed biogenetic precursor to many members of this family of natural products is believed to be brevianamide F (**13**, Scheme 1A), a cyclic dipeptide derived from L-tryptophan and L-proline. Brevianamide F likely undergoes C2 reverse-prenylation and C6 hydroxylation to give 6-hydroxy-deoxybrevianamide E (**15**), which could serve as a common intermediate to both the carneamides and versicamides. Specifically, C5 prenylation of **15** produces the carneamides, whereas C7 prenylation leads to the versicamides following a series of cyclizations and oxidations (Scheme 1B).



Scheme 1. Proposed biosynthesis of carneamides and versicamides.

To date, there have been no reported total syntheses of this family of natural products. It is important to develop efficient synthetic routes to these molecules to facilitate further investigations into their biological activities. The goal of the work presented in this report is to develop a direct, unified synthetic approach to the core skeletal framework of the versicamides and carneamides. Inspired by the proposed biosynthetic pathway,[1] we envisioned a direct C2 reverse-prenylation of brevianamide F to be key to achieving this goal.

1.2 Retrosynthetic Strategy



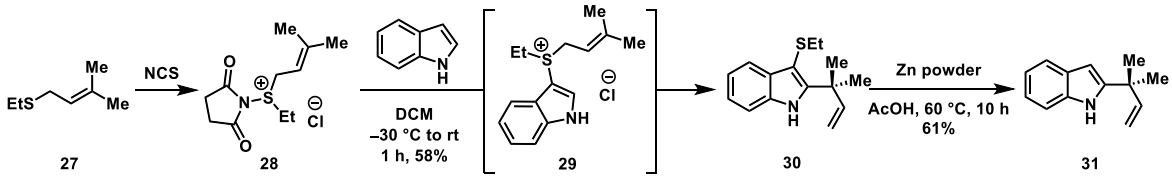
Scheme 2. Retrosynthesis of carneamides and versicamides.

Our retrosynthetic strategy to construct the core skeletal framework of several indole alkaloids bearing a reverse-prenyl group at C2 is shown in Scheme 2. Installation of the chromene unit was planned from **20** or **24** following the Williams group's precedent[19] by oxidation and propargylation of a C6 borylated precursor (**21** or **25**; see **43**→**46** in Scheme 5). In turn, the borylated precursors (**21** and **25**), would be prepared by a site-selective C6 iodination (see **13**→**23**) and photo-mediated borylation that has been developed by the Larionov and Li groups and further optimized by our group during a synthesis of stephacidin A.[20-23]

Our intention was to develop an expedient approach that would enable installation of both the C2 reverse-prenyl group and the eight-membered ring from a common intermediate (i.e., **23**). I envisioned a direct functionalization on the indole moiety of brevianamide F to install a *tert*-propargyl group (see **13**→**23**, Scheme 2) at C2 as the key step in the synthesis.

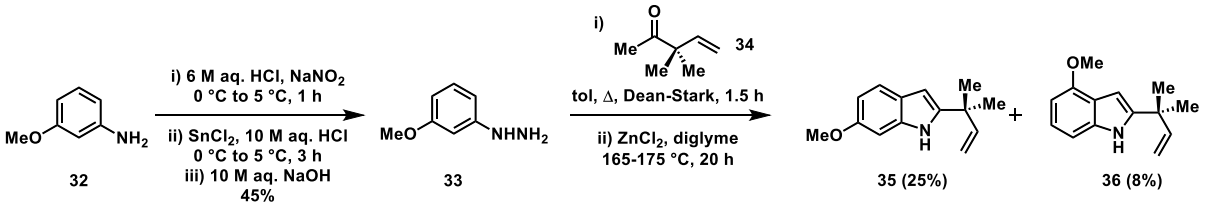
1.3 Previous approaches to reverse C2 prenylation

In 1981, Kametani et al. reported the total syntheses of brevianamide E and deoxybrevianamide E,[24] where C2 reverse-prenylated indole **31** (Scheme 3) was utilized as a key building block. On the basis of the precedent of Tomita,[25] treating indole with succinimide-2-(3,3-dimethylallyl)ethylsulphonium chloride (**28**), sets up a thio-Claisen rearrangement via the intermediacy of **29**, generating C2 reverse-prenylated indole derivative **30**. A subsequent reductive desulphurization using zinc and acetic acid gave reverse-prenylated indole **31**.



Scheme 3. Tomita's C2 reverse prenylation of indole.

As a part of their studies toward the synthesis of paraherquamide F in 2002,[19] the Williams group prepared reverse-prenylated indole **35** (Scheme 4) using a Fisher indolization. However, the indole ring formation step exhibited poor site selectivity, resulting in a mixture of 4-methoxyindole (**36**) and 6-methoxyindole (**35**).



Scheme 4. Williams' C2 reverse-prenylation using a Fisher indole synthesis.

In 2007, Williams et al. reported the total syntheses of notoamides C (**44**, Scheme 5) and D (**45**).[15] In their retrosynthesis, they envisioned reverse-prenylated indole derivative (**43**) as a key building block. C2 reverse-prenylated indole **43** was prepared by modifying Tatsuta's boron-mediated reverse-prenylation.[26] Tatsuta's reverse-prenylation was inspired by Danishefsky's total synthesis of gypsetin,[27] where *N*-phthaloyltryptophan methyl ester was first converted to a 3-chloroindolenine derivative (not shown).

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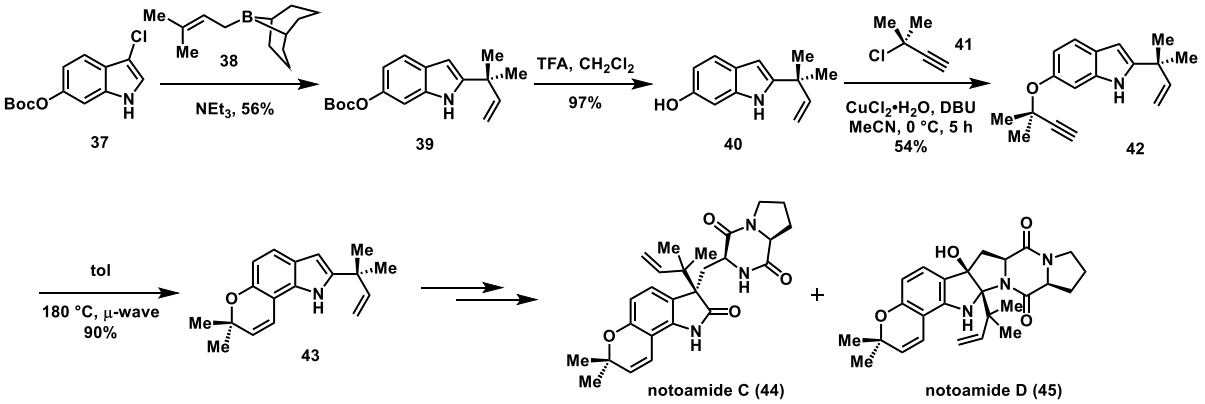
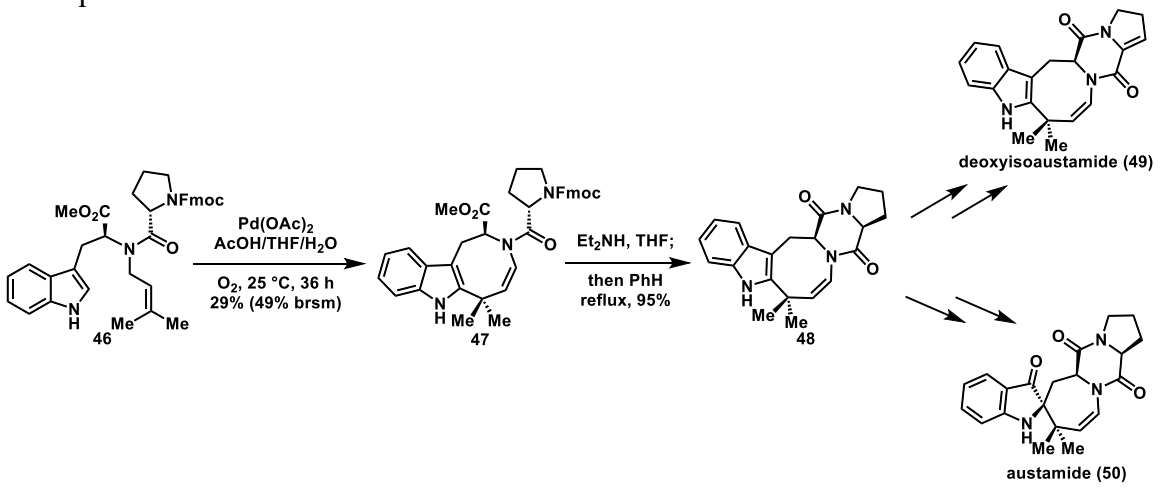


Scheme 5. Williams' total syntheses of notoamides C and D.

In general, the previously reported syntheses of reverse-prenylated indole alkaloids by Kametani and Williams start from an indole moiety lacking a C3 substituent. Because C3 is the most reactive site on the indole moiety, installing a temporary blocking group at C3 prior to reverse-prenylation was necessary. The need to remove the C3 substituent at a later stage renders these syntheses inefficient. Additionally, starting from 6-hydroxyindole in the Williams syntheses required protection of the hydroxy group, and adding steps to the synthesis.

We envisioned that the direct C2 functionalization of brevianamide F would provide a more straightforward and efficient approach for reverse-prenylation, as well as for constructing the eight-membered ring.

Syntheses of indole alkaloids that contain an eight-membered ring, such as deoxyisoaustamide (**49**, Scheme 6)[28] and okaramine N,[29] have been previously achieved by the Corey group. In their total synthesis of **49**, the key step employed was a palladium-mediated conversion of an *N*-prenylated tryptophan derivative (**46**) to the dihydroindoloazocine tricycle (**47**) in one step.



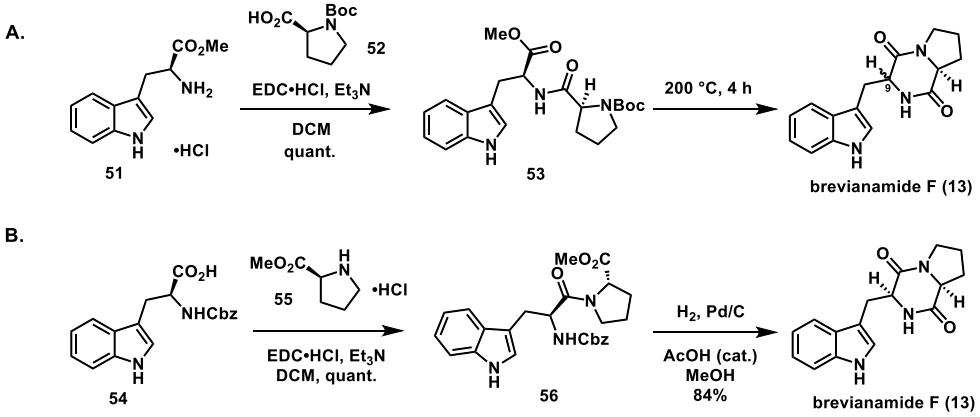
Scheme 6. Corey's syntheses of deoxyisoaustamide and austamide.

Although Corey's synthesis represents a short and unique route, the key step is low

yielding and the range of natural products accessible using this approach is limited. Inspired by the biosynthetic hypothesis for the genesis of the carneamides and versicamides,[2] we proposed to assemble these alkaloids by direct C2 functionalization and subsequent elaboration to furnish the eight-membered ring. This strategy was anticipated to provide a unified approach from readily available brevianamide F.

1.4 Synthesis of brevianamide F

To prepare brevianamide F (Scheme 7), I initially followed Caballero's procedure[30] by coupling tryptophan methyl ester hydrochloride (**51**) and Boc-proline (**52**) followed by thermal cleavage of the Boc group and cyclization (Scheme 7A). Brevianamide F (**13**) was obtained in 63% overall yield, but the thermal conditions required for Boc cleavage and cyclization resulted in the formation of a 2:1 to 1:1 mixture of diastereomers (epimeric at the C9 position), which presented problems during purification of larger scale quantities. Alternatively, starting from Cbz protected tryptophan (**54**, Scheme 7B) and subjecting the resulting dipeptide (**56**) to hydrogenolysis in the presence of a catalytic amount of acetic acid[31] afforded brevianamide F without epimerization. The product was purified by recrystallization on multigram scale.

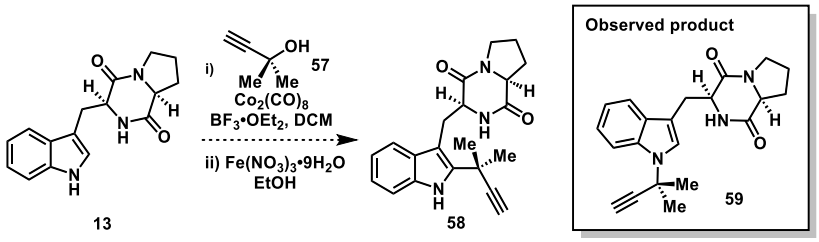


Scheme 7. Preparation of brevianamide F.

1.5 Studies toward C2 functionalization

Our first attempt to functionalize the C2 position sought to make use of Nicholas-type chemistry[32-35] to engage a cobalt-complexed propargylic alcohol with an indole nucleophile. Precedent for the Lewis acid-mediated reactions of indoles[36, 37] and other carbon-based nucleophiles[38, 39] with cobalt-stabilized propargyl cations has been previously demonstrated by various groups.

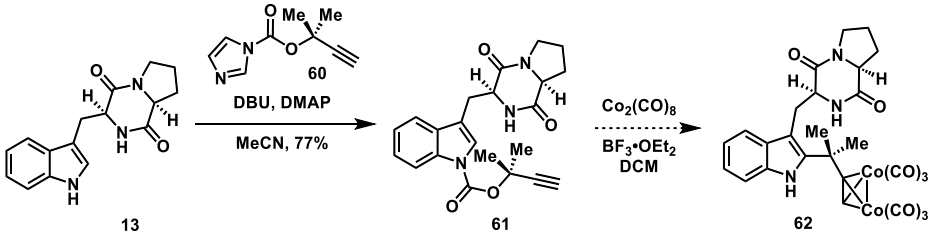
As shown in Scheme 8, treating brevianamide F (**13**) with propargyl alcohol derivative **57** and dicobalt octacarbonyl in the presence of a Lewis acid was expected to promote nucleophilic addition of the in situ generated cobalt-complexed propargylic cation to the C2 position of **13**. Several Lewis acids were tested, however, the major product observed was *N*-alkylated **59**. Various derivatives of **13** where the indole nitrogen is protected were also subjected to the reaction conditions, but only protecting group cleavage (Boc, SEM) or no conversion of the starting material (TIPS) was observed.



Scheme 8. Proposed *tert*-alkylation on brevianamide F via Nicholas reaction.

I also explored tethering the propargylic alcohol to the indole nitrogen in the form of a carbamate to block the indole nitrogen from attacking the propargyl carbocation, while simultaneously directing the propargylation to C2 under Nicholas reaction conditions via a pseudo-intramolecular process (Scheme 9). Carbamate **61** was prepared using a method for selective indole N-acylation reported by the Sarpong group.[40] The desired product (**61**) was obtained in 77% yield. This is the first example of a selective coupling of the *tert*-propargyl group to an indole bearing a diketopiperazine.

Treating carbamate **61** with dicobalt octacarbonyl to generate the corresponding alkyne-dicobalt hexacarbonyl complex appeared to proceed cleanly as judged by TLC analysis. However, upon treating the resulting intermediate with $BF_3 \cdot OEt_2$, only cleavage of the carbamate was observed. Attempts to isolate the alkyne-dicobalt hexacarbonyl complex (**62**) in order to gain insight into the progression of the reaction upon the addition of Lewis acids proved unfruitful since the cobalt complex was unstable on silica gel and only traces of this compound were ever isolated.

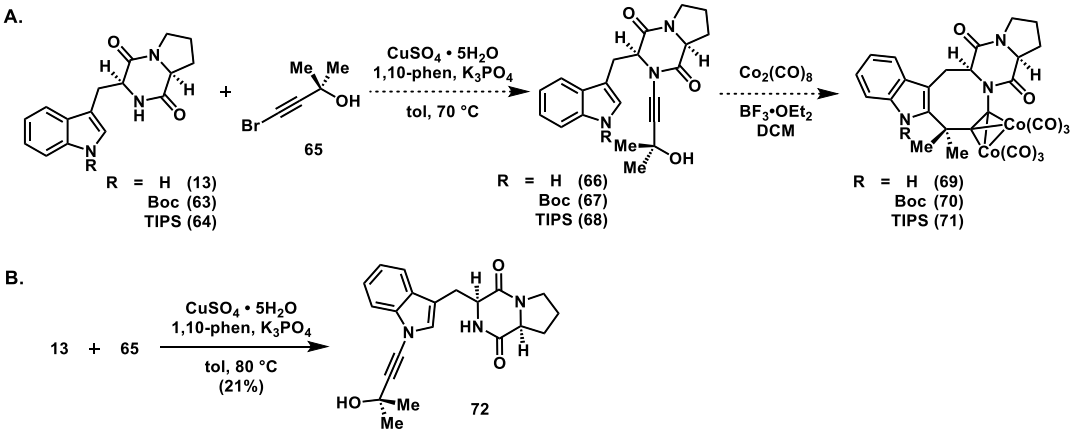


Scheme 9. Proposed pseudo-intramolecular Nicholas reaction.

Since direct C2 propargylation of brevianamide F using a propargylic alcohol turned out to be challenging, I envisioned an alternative intramolecular Nicholas reaction of **66** (Scheme 10A) to form the 8-membered ring. Subjecting brevianamide F to the reaction conditions reported by Rabasso (70 °C, Scheme 10A)[41] in an attempt to form the ynamide led to no conversion. Raising the temperature to 80 °C resulted in alkynylation of the indole nitrogen to give **72** in 21% yield

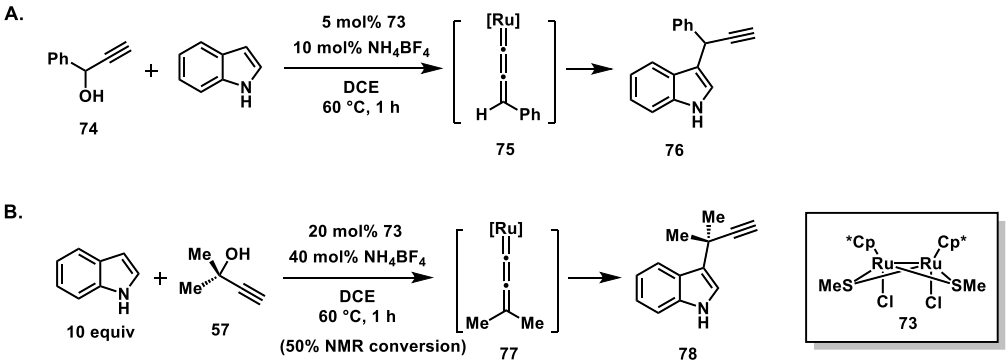
(Scheme 10B).

Alkynylation of brevianamide F bearing protecting groups on the indole nitrogen (*e.g.*, R = Boc, TIPS) was also tested (Scheme 10A); under the reaction conditions, Boc-protected brevianamide F (**63**) partially reverted to brevianamide F (**13**). The TIPS protecting group was more robust, but *N*-alkynylation of the diketopiperazine nitrogen did not proceed. Using an excess of bromoalkyne **65** and raising the reaction temperature to 110 °C resulted in only epimerization of the starting material without ynamide formation.



Scheme 10. Proposed intramolecular Nicholas reaction via ynamide synthesis.

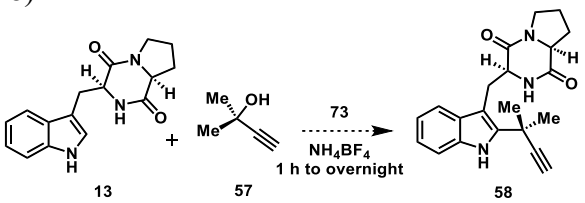
In 2002, the Hidai group reported novel propargylic substitution reactions of propargylic alcohols catalyzed by thiolate-bridged diruthenium complexes (*e.g.*, **73**, Scheme 11) via allenylidene ruthenium intermediates (e.g., **75**).[42] In the same year, the Uemura group expanded the scope of nucleophiles used in the ruthenium-catalyzed propargylic substitution reactions to include alkenes, thiols and aromatic compounds.[43-45] Inspired by the reported propargylation of aromatic compounds (Scheme 11), C2 propargylation of brevianamide F was attempted under the analogous reaction conditions.



Scheme 11. Ruthenium catalyzed substitution of indole.

[Cp*RuCl(SMe)]$_2$ (**73**) was prepared according to Nishibayashi's procedure[42] and was tested successfully by running a control reaction of indole with dimethyl propargyl alcohol (Scheme 11B) to verify the reliability of the reaction setup.

Under the same reaction conditions reported by the Uemura group, no conversion of brevianamide F (**13**; Scheme 12, entry 1) was observed. Increasing the temperature and changing the solvent (entries 2, 3) did not have any effect on the reaction. However, reacting **13** with an excess of the propargylic alcohol (used as a solvent) under microwave heating at elevated temperature (entry 4) gave a low conversion (<5%) to the indole *N*-propargylated product (**59**, Scheme 8).



13 57 58

entry	solvent	cat. loading	13	temp
1	DCE	40 mol%	5 equiv	60 °C
2	CH_2Cl_2	20 mol%	5 equiv	60 °C
3	DCE	10 mol%	0.5 equiv	90 °C
4*	57	20 mol%	-	90 °C

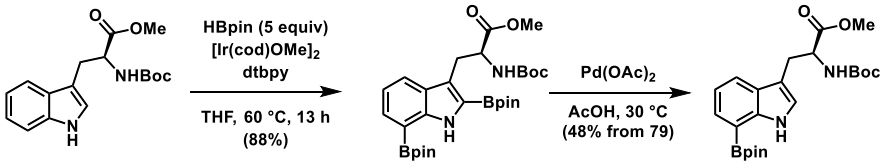
*stirred under microwave for 30 min

Scheme 12. Reaction conditions for ruthenium catalyzed substitution of **13**.

The Zhan group has developed an $FeCl_3$-catalyzed substitution reaction of propargylic alcohols with electron-rich carbon nucleophiles such as pyrrole and furan to directly construct C–C bonds. [46] I wondered whether this approach could be extended to the C2 propargylation of brevianamide F. In practice, subjecting brevianamide F to the conditions reported by Zhan et al. resulted in low reactivity (overnight, 60 °C). Further attempts to improve conversion, by increasing reaction temperature and time, accelerated the consumption of the starting material to produce a complex mixture of products.

Given that direct propargylic substitution at the C2 position of brevianamide F has been problematic, alternative approaches to C2 functionalization were then investigated.

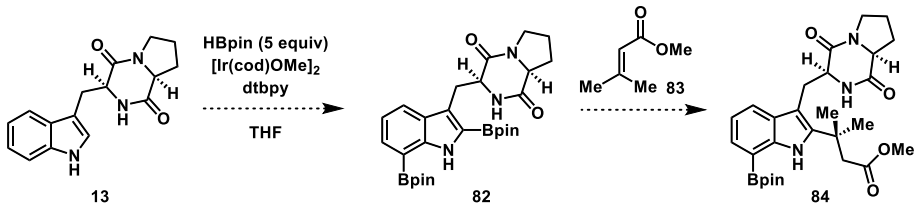
Several halogenation conditions (*e.g.*, NIS, NBS, I_2, pyridinium tribromide, and phenyltrimethyl ammonium tribromide in various solvents) were attempted with brevianamide F to functionalize the C2 position. However, only low conversions to mixtures of different halogenated compounds were observed.



79 80 81

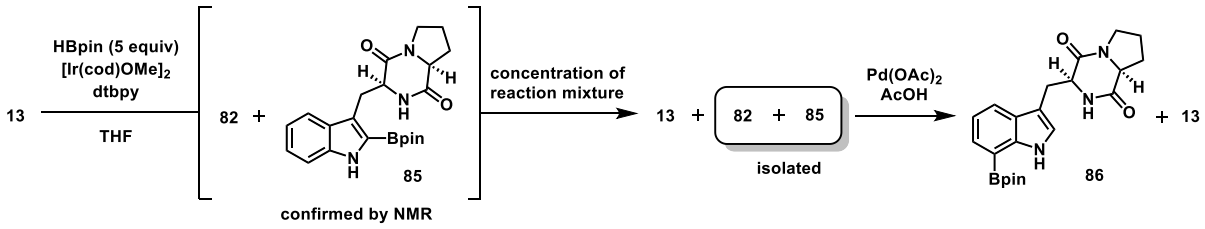
Scheme 13 Movassaghi's borylation/protodeborylation sequence.

In 2005, Movassaghi reported a C2, C7 diborylation/C2 protodeborylation sequence with protected tryptophan derivative **79** (Scheme 13) to obtain C7 borylated tryptophan methyl ester **81**, which built on work by the Hartwig group.[47] Since the indole C2 position (of **80**) is more nucleophilic and thus more susceptible to protodeborylation, I posited that if C2 and C7 diborylated brevianamide F could be prepared, then it should be possible to selectively convert the C2 position to a more useful functional group (Scheme 14). For example, conjugate addition of **82** to methyl 3,3-dimethylacrylate (**83**) would give **84**, which could be elaborated to the eight-membered ring or the reverse prenyl group.

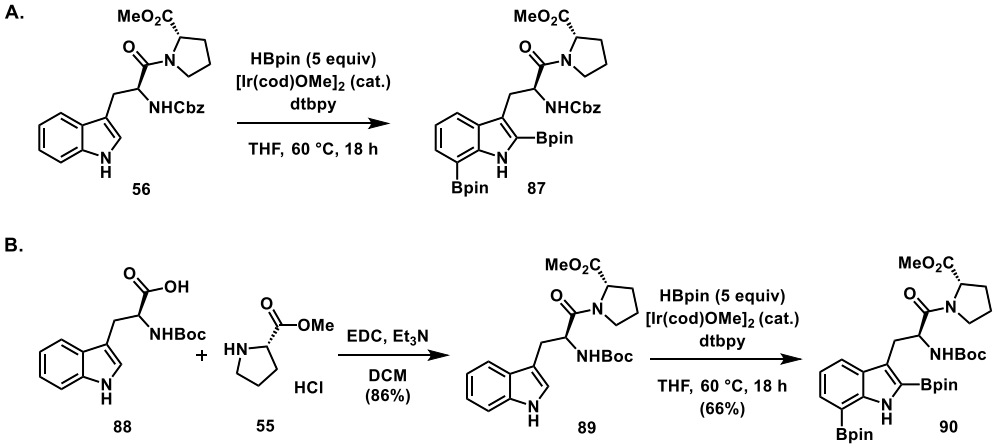


Scheme 14. Proposed borylation/conjugate addition of brevianamide F.

Diborylation on brevianamide F was tested under the conditions reported by Movassaghi; however, the reaction was capricious. By monitoring the reaction in a J-Young tube with deuterated THF (Scheme 15), full conversion of the starting material to a mixture of C2/C7 diborylated (**82**) and C2 monoborylated brevianamide F (**85**) was observed. The ^{1}H NMR spectrum of the crude reaction mixture in $CDCl_3$ after concentration (to remove THF-*d*8) suggested that some of the C2 monoborylated compound had reverted back to brevianamide F (**13**). The C2/C7 diborylated **82** and C2 monoborylated **85** were not separable, and subjecting the mixture to C2 protodeborylation conditions gave C7 monoborylated brevianamide F (**86**) and **13**. The best result for diborylation so far employs 10 mol% $[Ir(cod)OMe]_2$ loading and heating at 60 °C for 18 h. The desired product (**82**) is isolated in 19% yield, but the yields have been inconsistent from run-to-run.



Scheme 2. Borylation of brevianamide F.



Scheme 3. Diborylation of **56** and **88**.

As a control reaction, a precursor of brevianamide F (**56**, Scheme 16A) was subjected to

the same diborylation reaction conditions. ^{1}H NMR analysis of the crude reaction mixture showed clean conversion of **56** to diborylated product **87**. This result suggests that the diketopiperazine ring renders the functionalization of brevianamide F unproductive (compare **56**→**87** to the reaction with **13** in Scheme 15).

An alternative approach involving the diborylation of **89** to **90** followed by C2 deborylative conjugate addition and Boc-cleavage to forge the diketopiperazine ring is currently underway (Scheme 16B).

1.6 Conclusions and Future Plans

In conclusion, several synthetic routes to directly functionalize the C2 position of brevianamide F have been investigated. The next step is to advance **90** to reverse-prenylated brevianamide F, which should pave the way for the total syntheses of various carneamides and versicamides. Optimizing the diborylation of brevianamide F will be key to advancing and streamlining the proposed syntheses.

1.7 References

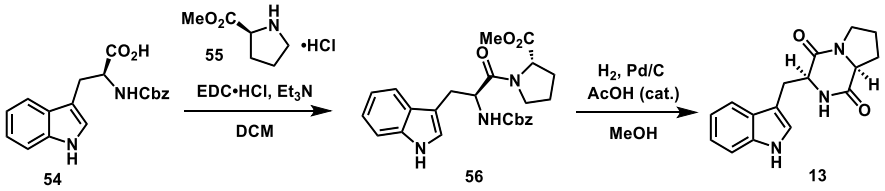
(1) Netz, N.; Opatz, T. *Mar. Drugs* **2015**, *13*, 4814.
(2) Peng, J.; Gao, H.; Li, J.; Ai, J.; Geng, M.; Zhang, G.; Zhu, T.; Gu, Q.; Li, D. *J. Org. Chem.* **2014**, *79*, 7895.
(3) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. *Top. Curr. Chem.* **2000**, *209*, 97.
(4) Chen, M.; Shao, C. L.; Fu, X. M.; Xu, R. F.; Zheng, J. J.; Zhao, D. L.; She, Z. G.; Wang, C. Y. *J. Nat. Prod.* **2013**, *76*, 547.
(5) Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999.
(6) Birch, A. J.; Wright, J. J. *J. Chem. Soc., D: Chem. Comm.* **1969**, 644.
(7) Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329.
(8) Wilson, B. J.; Yang, D. T. C.; Harris, T. M. *Appl. Microbiol.* **1973**, *26*, 633.
(9) Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135.
(10) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiot.* **1990**, *43*, 1375.
(11) Blizzard, T. A.; Mrozik, H.; Fisher, M. H.; Schaeffer, J. M. *J. Org. Chem.* **1990**, *55*, 2256.
(12) Qian-Cutrone, J.; Huang, S.; Shu, Y.Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556.
(13) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem. Int. Ed.* **2008**, *47*, 3573.
(14) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63.
(15) Grubbs, A. W.; Artman, G. D., 3rd; Tsukamoto, S.; Williams, R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2257.
(16) Shimokawa, J. *Tetrahedron Lett.* **2014**, *55*, 6156.

(17) Zhuravleva, O. I.; Afiyatullov, S. S.; Denisenko, V. A.; Ermakova, S. P.; Slinkina, N. N.; Dmitrenok, P. S.; Kim, N. Y. *Phytochemistry* **2012**, *80*, 123.
(18) Zhang, P.; Li, X. M.; Wang, J. N.; Li, X.; Wang, B. G. *Chin. Chem. Lett.* **2015**, *26*, 313.
(19) Cox, R. J.; Williams, R. M. *Tetrahedron Lett.* **2002**, *43*, 2149.
(20) Chen, K.; Zhang, S.; He, P.; Li, P. *Chem. Sci.* **2016**, *7*, 3676.
(21) Mfuh, A. M.; Schneider, B. D.; Cruces, W.; Larionov, O. V. *Nat. Protoc.* **2017**, *12*, 604.
(22) Mfuh, A. M.; Doyle, J. D.; Chhetri, B.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2016**, *138*, 2985.
(23) Mukai, K.; Pereira de Sant'Ana, D.; Hirooka, Y.; Mercado-Marin, E. V.; Stephens, D. E.; Kou, K. G. M.; Richter, S. C.; Kelley, N.; Sarpong, R. *Nat. Chem.* **2018**, *10*, 38.
(24) Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 959.
(25) Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles* **1976**, *4*, 733.
(26) Tatsuta, K.; Mukai, H.; Mitsumoto, K. *J. Antibiot.* **2001**, *54*, 105.
(27) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025.
(28) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.
(29) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.
(30) Caballero, E.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2003**, *68*, 6944.
(31) Wauters, I.; Goossens, H.; Delbeke, E.; Muylaert, K.; Roman, B. I.; Van Hecke, K.; Van Speybroeck, V.; Stevens, C. V. *J. Org. Chem.* **2015**, *80*, 8046.
(32) Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21.
(33) Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, *18*, 4163.
(34) Padmanabhan, S.; Nicholas, K. M. *Tetrahedron Lett.* **1983**, *24*, 2239.
(35) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207.
(36) Nakagawa, M.; Ma, J.; Hino, T. *Heterocycles* **1990**, *30*, 451.
(37) Isaji, H.; Nakazaki, A.; Isobe, M.;Nishikawa, T. *Chem. Lett.* **2011**, *40*, 1079.
(38) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128.
(39) Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.
(40) Heller, S. T.; Schultz, E. E.; Sarpong, R. *Angew. Chem. Int. Ed.* **2012**, *51*, 8304.
(41) Gomes, F.; Fadel, A.; Rabasso, N. *J. Org. Chem.* **2012**, *77*, 5439.
(42) Nishibayashi, Y.; Wakiji, I.; Hidai, M. *J. Am. Chem. Soc.* **2000**, *122*, 11019.
(43) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846.
(44) Inada, Y.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 15172.
(45) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 6060.
(46) Zhan, Z.; Yu, J.; Liu, H.; Cui, Y.; Yang, R.; Yang, W.; Li, J. *J. Org. Chem.* **2006**, *71*, 8298.
(47) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056.

1.8 Experimental Section

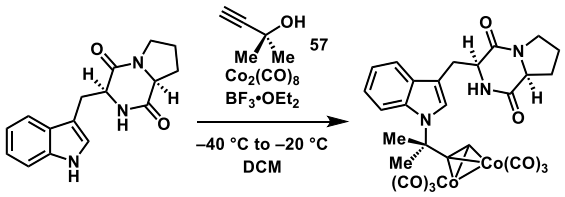
General Procedures. Unless stated otherwise, all reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Tetrahydrofuran (THF), benzene, toluene, acetonitrile (MeCN), methanol (MeOH), and triethylamine (Et_3N), were degassed with argon for 60 min and passed through activated alumina columns. Dichloromethane (DCM) was distilled over calcium hydride

before use. Reaction progress was monitored by thin layer chromatography (TLC) on Silicycle Siliaplate™ glass-backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation and potassium permanganate stain. Volatile solvents were removed under reduced pressure with a rotary evaporator. All flash column chromatography was performed using Silicycle Silia*Flash*® silica gel (60 Å, 230–400 mesh, 40–63 μm). ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker spectrometers operating at 300, 400, 500, or 600 MHz for ^{1}H (75, 100, 125, and 150 MHz for ^{13}C) in $CDCl_3$ or DMSO-*d*6. Chemical shifts are reported relative to the residual solvent signal (∂ 7.26 for ^{1}H NMR, ∂ 77.16 for ^{13}C NMR in $CDCl_3$; ∂ 2.50 for ^{1}H NMR, ∂ 39.52 for ^{13}C NMR in DMSO-*d*6). NMR data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Splitting is reported with the following symbols: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, dtd = doublet of triplet of doublets, hept = heptet, m = multiplet. Low-resolution mass spectra (LC/MS) were acquired using a Shimidazu LCMS-2020. IR spectra were acquired on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory, and data is reported as frequency of absorption in cm^{-1}. Only select IR peaks are reported. High-resolution mass spectra (HRMS) were acquired using a Perkin Elmer AxION 2 TOF-MS at the Lawrence Berkeley National Laboratory Catalysis Center, which is supported by the Director, Office of Science, of the US Department of Energy under contract no. DE-AC02-05CH11231.



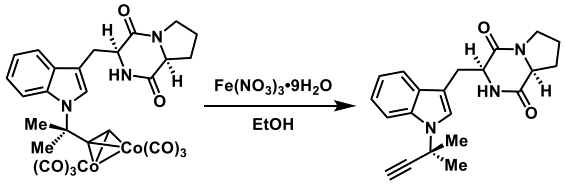
Brevianamide F To a solution of (*S*)-proline methyl ester (2.94 g, 17.7 mmol, 1.2 equiv) and Et_3N (1.79 g, 17.7 mmol, 1.2 equiv) in dry DCM (60 mL) at 0 °C was added *N*-benzyloxycarbonyltryptophan hydrogen chloride (5.00 g, 14.8 mmol, 1.0 equiv) and EDC·HCl (3.39 g, 17.7 mmol, 1.2 equiv). The reaction mixture was stirred at rt for 18 h and was then washed with 2 M HCl (2×20 mL) and a solution of saturated aqueous $NaHCO_3$ (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the crude *N*-benzyloxycarbonyl-L-tryptophyl-L-proline methyl ester as a foam (6.65 g, 14.8 mmol, 100%). This material was used directly without purification. A portion of dipeptide **56** (5.00 g, 11.1 mmol, 1.0 equiv) was dissolved in dry methanol (30 mL), and to the resulting solution was added Pd/C (5% Pd, 0.4 g, 0.188 mmol, 0.017 equiv) and acetic acid (5 drops). The reaction mixture was stirred for 4 h at rt under an atmospheric pressure of hydrogen. The mixture was filtered through a pad of Celite®, and after removal of solvent and trituration with ether, the desired product was obtained (2.57 g, 9.37 mmol, 84%) as a white solid. mp 172−175 °C; lit.[1] 174 °C (acetone). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (bs, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.22 (td, *J* = 8.0 and 1.7 Hz, 1H), 7.13 (td, *J* = 7.9 and 0.9 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 5.76 (bs, 1H), 4.37 (dd, *J* = 10.8, 2.9 Hz, 1H), 4.08 (dd, *J* = 7.6 Hz, 1H), 3.76 (dd, *J* = 15.1, 3.2 Hz, 1H), 3.72 – 3.54 (m, 2H), 2.97 (dd, *J* = 15.1, 10.9 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.07 – 1.84 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 165.7, 136.8, 126.8, 123.5, 122.8, 120.0, 118.6, 111.7, 109.9, 59.3, 54.7,

45.5, 28.4, 26.9, 22.7. The spectroscopic data are consistent with those reported in the literature.[1]



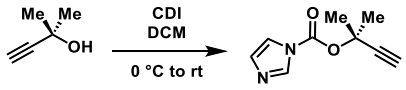
13 S1

To a solution of 2-methyl-3-butyn-2-ol (0.168 g, 2.0 mmol 2.0 equiv) in DCM (20 mL) was added dicobalt octacarbonyl (0.684 g, 2.0 mmol, 2.0 equiv) and the mixture was stirred for 2 h at rt, at which time complete consumption of the propargylic alcohol was achieved as judged by TLC analysis. Brevianamide F (0.283 g, 1.0 mmol, 1.0 equiv) was then added, and the resulting mixture cooled to –40 °C. BF_3·OEt (0.426 g, 3.0 mmol, 3.0 equiv) was subsequently added dropwise and the reaction mixture was stirred at –25 °C for 12 h, then diluted with DCM (20 mL), and washed with saturated aqueous $NaHCO_3$ solution (3×10 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash chromatography (ethyl acetate: hexanes = 3:1) to give the desired cobalt complex as a dark red solid (0.375 g, 0.59 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.23 (s, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.29 (s, 1H), 5.65 (bs, 1H), 4.32 (dd, *J* = 11.0, 3.5 Hz, 1H), 4.06 (t, *J* = 7.6 Hz, 1H), 3.73 – 3.55 (m, 3H), 2.93 (dd, *J* = 15.0, 10.9 Hz, 1H), 2.33 (dt, *J* = 10.3, 6.6 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.08 – 1.86 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.1, 169.4, 165.6, 135.5, 129.6, 124.3, 121.7, 119.9, 119.1, 114.3, 108.8, 101.6, 74.6, 60.1, 59.3, 55.1, 45.5, 32.2, 32.2, 29.8, 28.4, 26.6, 22.7.



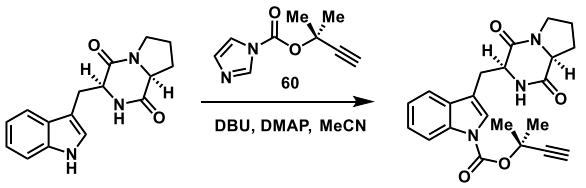
S1 59

To a solution of the cobalt complex **S1** (0.200 g, 0.315 mmol, 1.0 equiv) in ethanol (6 mL) was added $Fe(NO_3)_3$·$9H_2O$ (0.509 g, 1.26 mmol, 4.0 equiv), and the resulting mixture was stirred at rt for 4 h. The mixture was concentrated, and then reconstituted in DCM (10 mL) and brine (10 mL). The aqueous layer was additionally extracted with DCM (3×5 mL), and the combined organic extract was dried over anhydrous Na_2SO_4. The crude residue was purified by flash chromatography (ethyl acetate) to give the desired product as a white solid (0.103 g, 0.294 mmol, 93%). mp 79–85 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 5.76 (bs, 1H), 4.43 – 4.34 (m, 1H), 4.07 (t, *J* = 7.5 Hz, 1H), 3.75 (dd, *J* = 15.1, 3.2 Hz, 1H), 3.70 – 3.55 (m, 2H), 2.92 (dd, *J* = 15.1, 11.0 Hz, 1H), 2.59 (s, 1H), 2.36 – 2.28 (m, 1H), 1.98 (s, 1H), 1.96 (s, 1H), 2.07 – 1.83 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7 165.6, 135.7, 128.9, 123.7, 122.0, 119.8, 118.9, 113.6, 108.4, 85.8, 72.7, 54.9, 52.3, 45.5, 30.0, 28.4, 27.1, 22.7. IR (thin film): 3233, 2964, 1662, 1457, 1312, 1196, 743 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{21}H_{23}N_3O_2$ $[M+H]^+$: m/z 350.1863, found 350.1865.



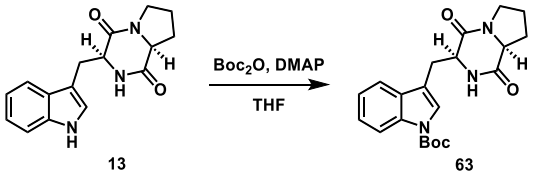
57 60

To a solution of 1,1'-carbonyldiimidazole (1.45 g, 8.92 mmol, 1.5 equiv) in DCM (20 mL) was added 2-methyl-3-butyn-2-ol (0.500 g, 5.94 mmol, 1.0 equiv) dropwise at 0 °C. The reaction mixture was warmed to rt and stirred for 12 h. The mixture was diluted with DCM (20 mL) and the organic layer was washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, then concentrated in vacuo to give the desired imidazole carbamate as a white solid (1.03 g, 5.77 mmol, 97%). This material was pure by ^1H and ^{13}C NMR analysis and used without further purification. mp 59–63 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.39 (s, 1H), 7.05 (s, 1H), 2.67 (s, 1H), 1.84 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.5, 137.1, 130.5, 117.2, 82.8, 76.4, 74.4, 28.8. IR (thin film): 3287, 2119, 1758, 1291, 994, 837 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_9H_{10}N_2O_2$ $[M+H]^+$: m/z 179.0815, found 179.0811.



13 61

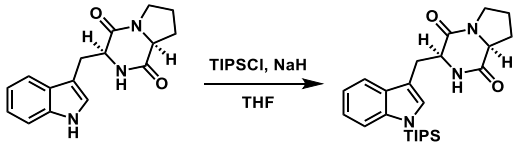
To a solution of brevianamide F (0.142 g, 0.5 mmol, 1.0 equiv) in MeCN (1.5 mL) was added the imidazole carbamate (**60**) (0.0980 g, 0.55 mmol, 1.1 equiv), 1,8-diazabicyclo(5.4.0)undec-7-ene (0.0152 g, 0.1 mmol, 0.2 equiv) and a catalytic amount of 4-dimethylaminopyridine (DMAP; one small crystal). The reaction mixture was stirred at rt for 4 h and was quenched with 1.5 mL of 1 M HCl solution. The mixture was diluted with DCM (5 mL), washed with brine (3×3 mL), dried over anhydrous Na_2SO_4, and then concentrated in vacuo. Flash chromatography with ethyl acetate gave the desired product as a white solid (0.152 g, 0.387 mmol, 77%). mp 84–87 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 8.20 (bs, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.49 (bs, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.28 (t, J = 7.3 Hz, 1H), 5.76 (bs, 1H), 4.44 – 4.33 (m, 1H), 4.10 (t, J = 7.4 Hz, 1H), 3.72 (dd, J = 15.2, 2.5 Hz, 1H), 3.69 – 3.54 (m, 2H), 2.90 (dd, J = 15.2, 11.0 Hz, 1H), 2.68 (s, 1H), 2.45 – 2.21 (m, 1H), 2.19 – 1.99 (m, 2H), 1.92 (s, 3H), 1.91 (s, 3H), 1.98 – 1.86 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 165.1, 148.6, 135.9, 129.6, 125.4, 124.3, 123.2, 118.8, 115.8, 115.7, 83.8, 75.1, 73.8, 59.3, 54.1, 45.6, 29.2, 29.1, 26.6, 22.7. IR (thin film): 3225, 1737, 1667, 1454, 1381, 1255, 1131, 835, 761 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{22}H_{23}N_3O_4Na$ $[M+Na]^+$: m/z 416.1581, found 416.1573.



13 63

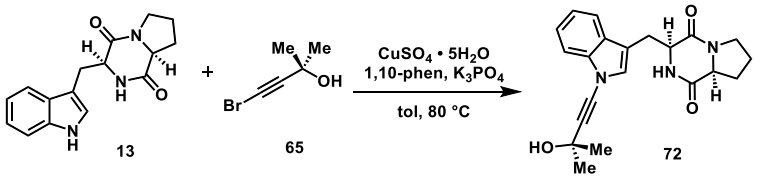
To a solution of brevianamide F (0.189 g, 0.667 mmol, 1.0 equiv) in THF (6 mL) was added di-

tert-butyldicarbonate (0.146 g, 0.667 mmol, 1.0 equiv) and DMAP (8.2 mg, 0.067 mmol, 0.1 equiv) and the resulting mixture was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure, diluted with DCM (10 mL), and washed with brine (3×5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (ethyl acetate) to give the desired product as a yellow solid (0.185 g, 0.481 mmol, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (bs, 1H), 7.59 – 7.41 (m, 2H), 7.34 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.84 (bs, 1H), 4.37 (d, *J* = 10.2 Hz, 1H), 4.12 – 4.00 (m, 1H), 3.80 – 3.47 (m, 3H), 2.89 (dd, *J* = 15.2, 11.0 Hz, 1H), 2.38 – 2.24 (m, 1H), 2.12 – 1.81 (m, 3H), 1.67 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 165.2, 149.4, 135.9, 129.5, 125.1, 124.6, 122.9, 118.8, 115.7, 114.9, 84.1, 59.3, 54.1, 45.6, 28.4, 28.3, 26.6, 22.7. The spectroscopic data are consistent with those reported in the literature.[2]



13 64

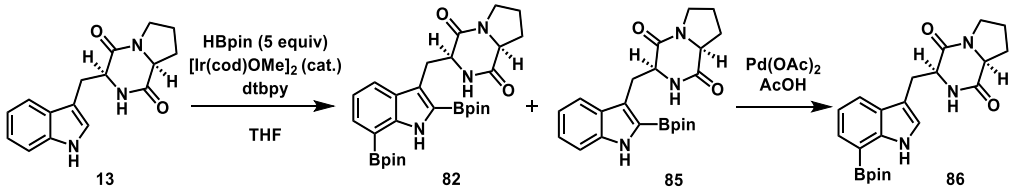
To a cooled (0 °C) solution of brevianamide F (0.100 g, 0.353 mmol, 1.0 equiv) in THF (2 mL) was added sodium hydride (60% in mineral oil, 0.0282 g, 0.706 mmol, 2.0 equiv) and the resulting mixture was stirred at rt for 1 h. The reaction mixture was again cooled to 0 °C, and triisopropyl chloride (0.136 g, 0.706 mmol, 2.0 equiv) was added dropwise to the mixture. After stirring for 16 h at rt, the mixture was diluted with ethyl acetate (5 mL) and water (5 mL). The biphasic mixture was vigorously mixed and the layers separated. The aqueous layer was additionally extracted with ethyl acetate (3×5 mL), and the combined organic extract was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. Purification by flash chromatography (ethyl acetate) gave the desired product as a white solid (0.0601 g, 0.137 mmol, 39%). mp 68–69 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.17 – 7.10 (m, 2H), 5.71 (bs, 1H), 4.37 (dd, *J* = 10.5, 2.5 Hz, 1H), 4.06 (t, *J* = 7.7 Hz, 1H), 3.73 (dd, *J* = 15.0, 3.5 Hz, 1H), 3.69 – 3.53 (m, 2H), 2.99 (dd, *J* = 15.1, 10.6 Hz, 1H), 2.38 – 2.26 (m, 1H), 2.03 – 1.82 (m, 3H), 1.69 (hept, *J* = 7.4 Hz, 3H), 1.14 (dd, *J* = 7.5, 2.7 Hz, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 165.6, 141.7, 130.3, 130.2, 122.2, 120.0, 118.4, 114.4, 112.0, 59.2, 55.0, 45.4, 28.4, 26.9, 22.6, 18.2, 12.9. IR (thin film): 2946, 2867, 1679, 1451, 1304, 1016, 741, 689, 520 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{25}H_{37}N_3O_2Si$ $[M+H]^+$: m/z 440.2728, found 440.2722.



13 65 72

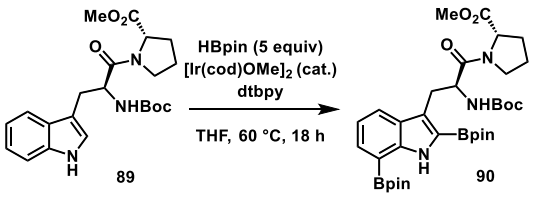
Bromoalkyne (**65**) was prepared following the procedure reported by Marino.[3] To a solution of brevianamide F (50.0 mg, 0.176 mmol, 1.0 equiv), $CuSO_4 \cdot 5H_2O$ (4.4 mg, 0.018 mmol, 0.1 equiv), 1,10-phenanthroline (6.3 mg, 0.035 mmol, 0.2 equiv), potassium phosphate tribasic (75.0 mg, 0.352 mmol, 2.0 equiv) in toluene (0.5 mL) at 80 °C was added a solution of the 4-bromo-2-methylbut-3-yn-2-ol (**65**) (43.0 mg, 0.264 mmol, 1.5 equiv) in toluene (0.5 mL) dropwise. The

reaction mixture was stirred at 80 °C for 18 h. The mixture was then cooled to rt, filtered through a pad of Celite®, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (3% MeOH in DCM) to give the product as a light-yellow solid (13.5 mg, 0.0369 mmol, 21%). mp 81–86 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.07 (s, 1H), 5.97 (bs, 1H), 4.32 (d, *J* = 8.8 Hz, 1H), 4.04 (t, *J* = 7.9 Hz, 1H), 3.70 – 3.60 (m, 2H), 3.57 (t, *J* = 9.4 Hz, 1H), 2.96 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.56 (bs, 1H), 2.33 – 2.24 (m, 1H), 2.01 – 1.83 (m, 3H), 1.68 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 165.3, 138.8, 127.6, 127.0, 124.4, 122.3, 119.1, 113.1, 111.6, 75.7, 73.8, 65.7, 59.4, 54.4, 45.6, 31.91, 31.89, 28.4, 26.5, 22.7. IR (thin film): 3397, 2978, 2250, 1665, 1459, 1168, 959, 745 cm^{-1}. HRMS (ESI+) m/z calc'd for $C_{21}H_{23}N_3O_3Na$ $[M+Na]^+$: m/z 388.1632, found 388.1620.



To a solution of brevianamide F (0.0142 g, 0.05 mmol, 1.0 equiv), 4,4'-di-*tert*-butyl-2,2'-bipyridine (2.7 mg, 0.01 mmol, 0.2 equiv) and $[Ir(cod)OMe]_2$ (3.1 mg, 0.005 mmol, 0.1 equiv) in THF (0.5 mL) was added pinacolborane (0.0320 g, 0.25 mmol, 5.0 equiv). The reaction mixture was heated at 60 °C for 18 h and then concentrated in vacuo. The crude material was purified by flash chromatography (20% acetone in DCM) to give a mixture of **82** and **85**. For reference, data for **82** is as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (bs, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.71 (dd, *J* = 6.9, 1.1 Hz, 1H), 7.12 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.83 (bs, 1H), 4.23 (d, *J* = 8.0 Hz, 1H), 3.94 (t, *J* = 7.5 Hz, 1H), 3.87 (dd, *J* = 14.7, 3.2 Hz, 1H), 3.65 – 3.56 (m, 1H), 3.51 (dt, *J* = 11.6, 5.4 Hz, 1H), 3.39 (dd, *J* = 14.7, 9.0 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.90 – 1.76 (m, 3H), 1.43 – 1.38 (m, 24H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 166.1, 143.2, 132.0, 126.8, 124. 5, 123.5, 122.7, 119.9, 119.5, 84.8, 84.1, 83.3, 59.2, 56.8, 45.5, 26.0, 25.14, 25.08, 25.06, 24.98, 24.95, 24.7, 22.7.

To a mixture of **82** and **85** (0.0261 g, 0.0487 mmol, 1.0 equiv) dissolved in acetic acid (0.2 mL) was added palladium diacetate (1.1 mg, 0.0049 mmol, 0.1 equiv). The mixture was stirred at rt for 12 h and then concentrated in vacuo. The crude mixture was purified by flash chromatography (10%→20% acetone in DCM) to give the desired product as a brown solid (0.0109 g, 0.0266 mmol, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (bs, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.20 – 7.11 (m, 2H), 5.72 (bs, 1H), 4.35 (dd, *J* = 10.6, 1.9 Hz, 1H), 4.06 (t, *J* = 7.6 Hz, 1H), 3.77 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.70 – 3.52 (m, 2H), 2.97 (dd, *J* = 15.1, 10.9 Hz, 1H), 2.37 – 2.26 (m, 1H), 2.06 – 1.84 (m, 3H), 1.40 (s, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 165. 7, 142.0, 130.1, 128.9, 125.7, 123.4, 122.1, 119.6, 109.5, 84.1, 59.3, 54.7, 45.5, 30.0, 27.0, 25.14, 25.07, 24.96, 22.7.



To a solution of Boc-Trp-Pro-OMe (0.208 g, 0.5 mmol, 1.0 equiv), 4,4'-di-*tert*-butyl-2,2'-bipyridine (0.0134 g, 0.05 mmol, 0.1 equiv) and $[Ir(cod)OMe]_2$ (0.0166 g, 0.025 mmol, 0.05 equiv) in THF (5 mL) was added pinacolborane (0.320 g, 2.5 mmol, 5.0 equiv). The reaction mixture was heated at 60 °C for 18 h and then concentrated in vacuo. The crude material was purified by flash chromatography (10% acetone in DCM) to give the desired product as a light brown solid (0.220 g, 0.329 mmol, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.24 (bs, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 6.5 Hz, 1H), 7.13 (t, J = 7.4 Hz, 1H), 6.03 (d, J = 7.5 Hz, 1H), 4.63 (dd, J = 8.5, 4.3 Hz, 1H), 4.49 – 4.43 (m, 1H), 4.02 – 3.90 (m, 3H), 3.75 (s, 3H), 3.32 – 3.28 (m, 1H), 2.30 – 1.97 (m, 4H), 1.57 (s, 9H), 1.46 – 1.33 (m, 24H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 172.1, 155. 8, 142.9, 131.5, 127.1, 123.3, 122. 7, 119.6, 119.2, 111.6, 84.4, 84.3, 84.1, 83.9, 83.8, 78.9, 58.9, 54.1, 52.3, 47.0, 29.0, 28.3, 28.2, 27.8, 27.0, 25.1, 25.04, 24.98, 24.9, 24.6.

References

(1) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107.
(2) Caballero, E.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **2003**, *68*, 6944.
(3) El-Gendy, B. E. D. M.; Rateb, M. E. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3125.
(4) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841.

1.9 Appendix to Chapter 1: Spectra

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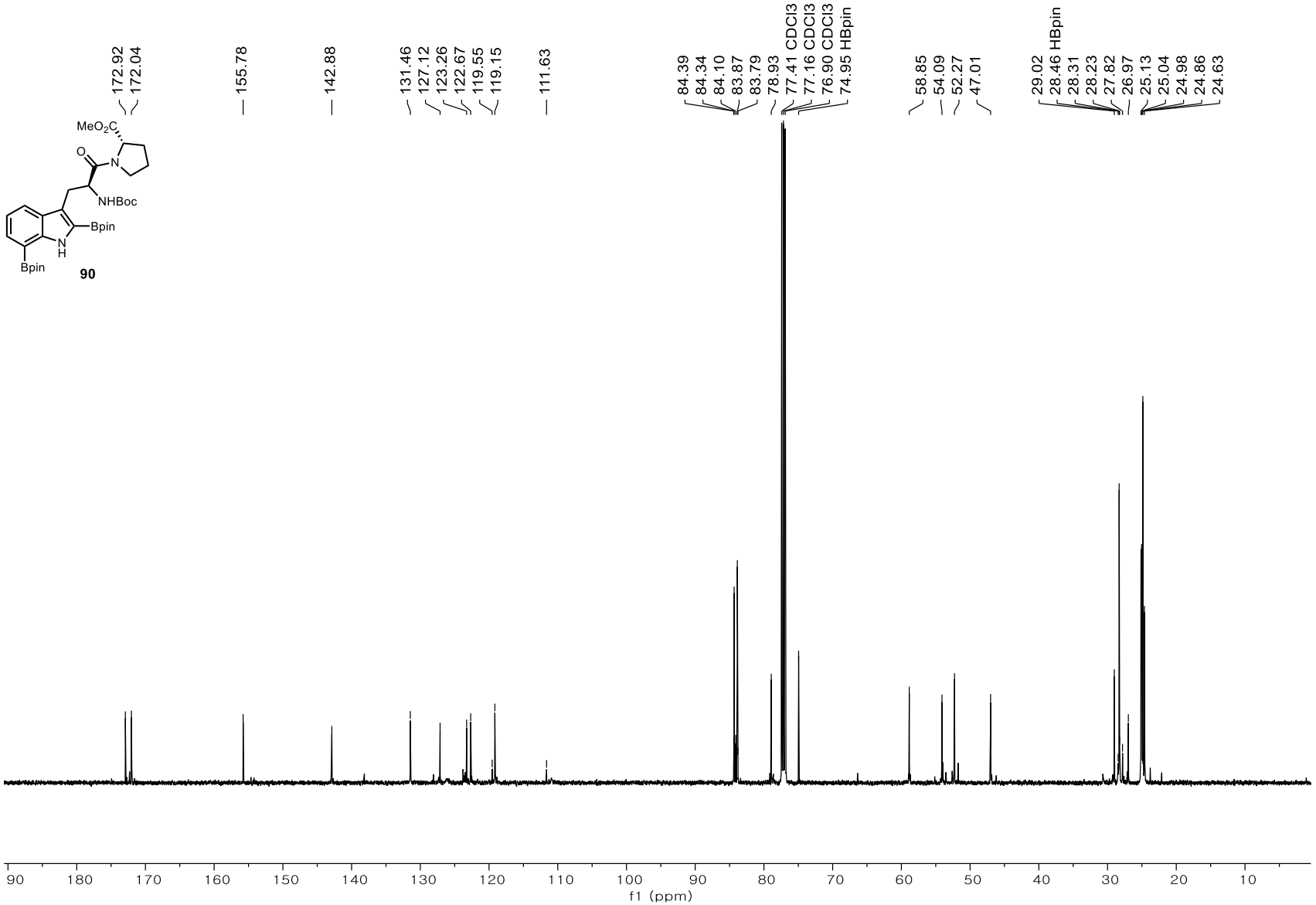
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84.39
84.34
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77.41 CDCl3
77.16 CDCl3
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27.82
26.97
25.13
25.04
24.98
24.86
24.63
MeO2C
O
N
NHBoc
Bpin
N
H
Bpin
90
90
180
170
160
150
140
130
120
110
100
90
80
70
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30
20
10
f1 (ppm)

Chapter 2

Total Synthesis of (−)-Ambiguine P

2.1 Isolation, Biosynthesis and Background

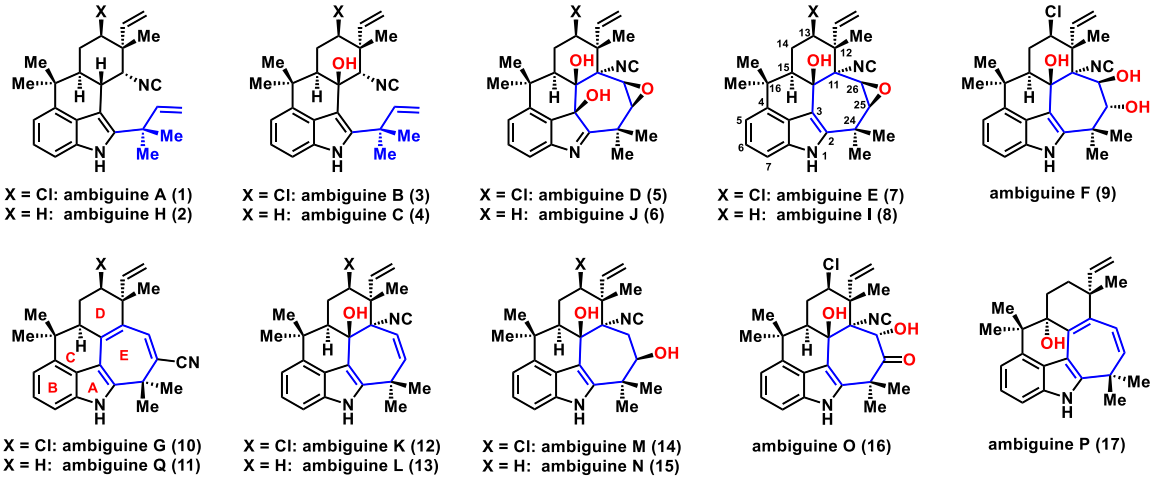
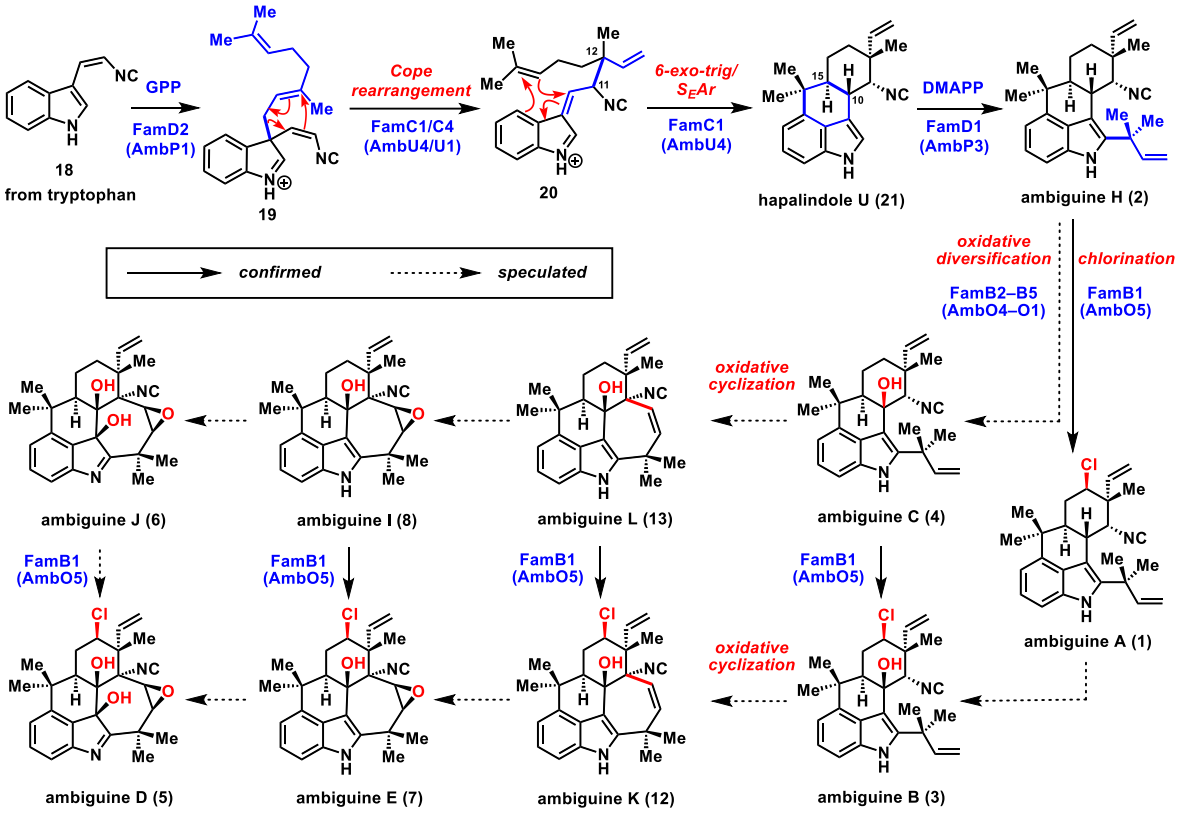


Figure 1. Isolated ambiguine natural products.

The ambiguine natural products,[1] illustrated in Figure 1, are a subset of a larger family of indole secondary metabolites termed the hapalindoles.[2] With the exception of ambiguines A, B, C, and H (**1–4**), which are tetracyclic, the ambiguine class of molecules possess a fused pentacyclic scaffold, featuring a characteristic seven-membered ring moiety. Since their first reported isolation from *Fischerella ambigua* in 1992 and given their intriguing chemical structures,[1a] there have been continuous efforts aimed at their total syntheses.[3-6] Biosynthetically related members of the hapalindole family such as the fischerindoles[7] and welwitindolinones,[7b, 8] exert a broad spectrum of biological activities, including antimicrobial, antifungal, insecticidal, anticancer, and phytotoxicity.[1a, 1c, 2a, 2c-d, 7b, 9] Therefore, there is interest in exploring the function of the ambiguines

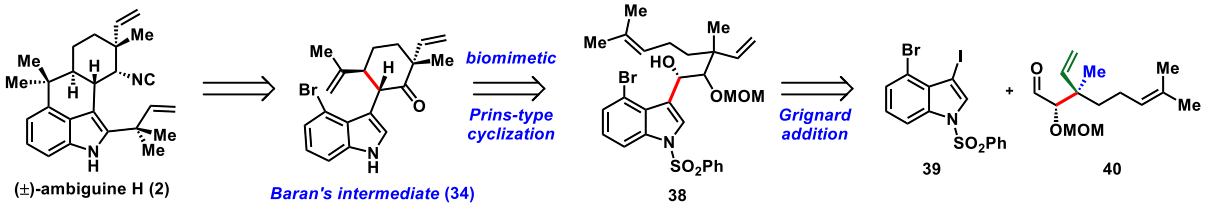
in a biological context. While rudimentary bioactivity studies on the ambiguines have been conducted,[1c-f] they are far from comprehensive. It is our anticipation that structurally related derivatives of the ambiguines, which may be accessed *en route* to their chemical preparation, may also possess interesting activity. As such, a total synthesis of the pentacyclic ambiguines could provide opportunities to unveil their biological potential as well as set the stage for a comprehensive understanding of their biosynthesis, especially with respect to the poorly understood latter stages that lead to the fused seven-membered ring.



Scheme 1. Proposed biosynthetic pathway for ambiguines.

Many studies on ambiguine biosynthesis[10] indicate that they are biosynthetically related to the hapalindole-type natural products (Scheme 1). However, the characterization of the gene cluster from *Fischerella ambigua* UTEX 1903 by the Liu and Sherman groups provided critical insights that were necessary in proposing a complete biosynthetic pathway.[10d-e] Thus, biosynthesis of the hapalindole family starts from indole vinyl isonitrile (**18**), which is derived from tryptophan. The alkylation of indole vinyl isonitrile (**18**) with geranyl pyrophosphate is mediated by FamD2 to give indolenine intermediate **19**.[10d-e, 10g] This is followed by an enzymatic Cope rearrangement catalyzed by a heterodimer of Stig cyclases FamC1/C4 that sets the C11 and C12 stereocenters within **20**.[10l] The FamC1 subunit of the FamC1/C4 heterodimer effects a 6-*exo*-trig cyclization where the C10 and C15 stereocenters are generated, and subsequent electrophilic aromatic substitution (SEAr) furnishes hapalindole U (**21**). FamD1-mediated reverse-prenylation with dimethylallyl pyrophosphate[10d-e, 10j] gives ambiguine H (**2**), which is hypothesized by Liu and

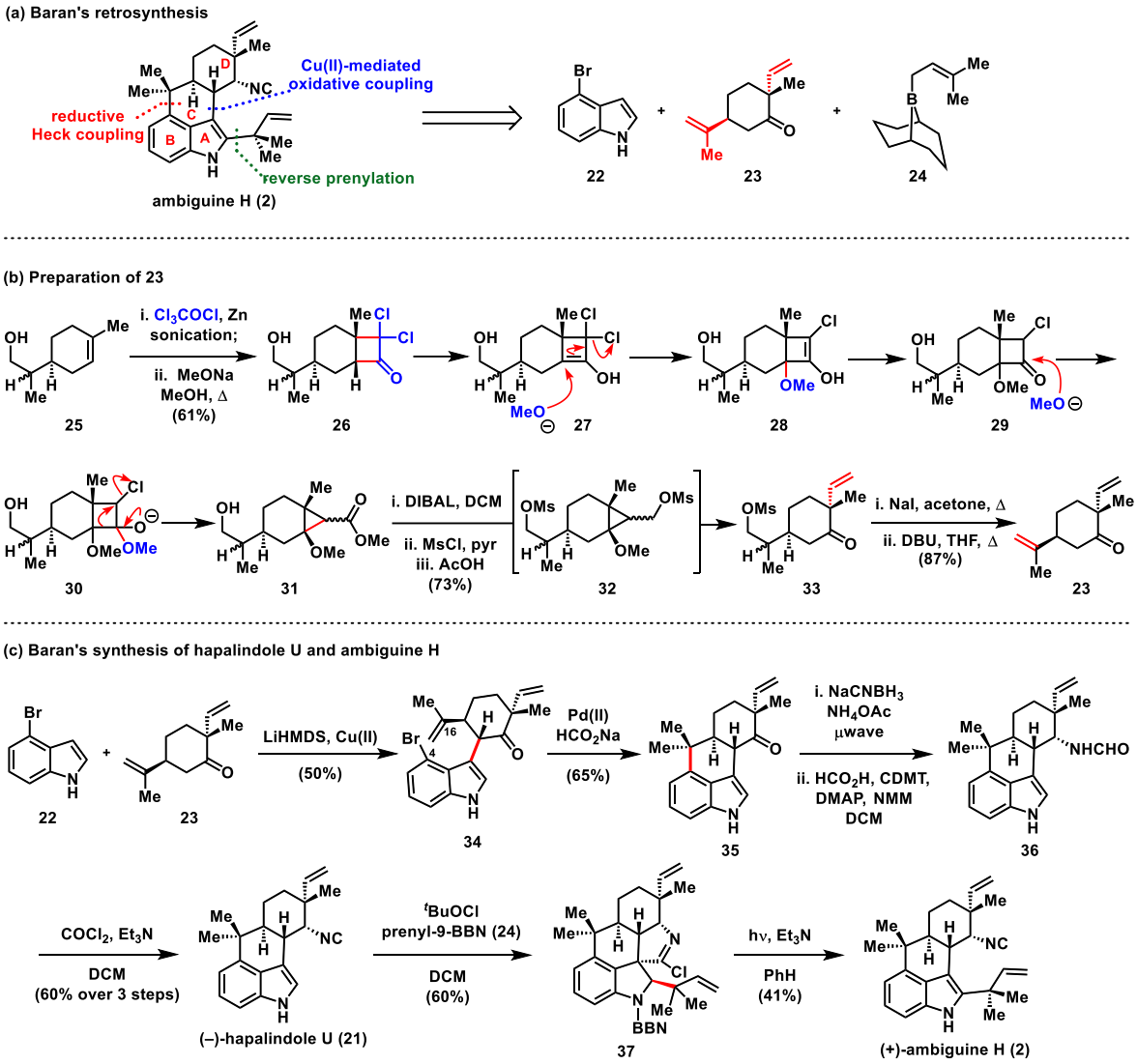
Sherman to be further elaborated to the pentacyclic ambiguines by at least five non-heme iron-dependent oxygenases, one of which is shown to be a halogenase that is responsible for late-stage chlorinations of hapaindoles and ambiguines, while the other four are Rieske oxygenases.



Scheme 2 Maji's racemic formal synthesis of (±)-ambiguine H (**2**).

At the onset of our studies, no syntheses had been disclosed for the pentacyclic ambiguines (**5**–**17**) despite numerous reported approaches.[3] Without sound knowledge of the biosynthesis, bioinspired and chemoenzymatic strategies toward the pentacyclic congeners have not been developed. On the other hand, successful syntheses of the less complex tetracyclic ambiguine H (**2**) were disclosed by the Baran[4] and Maji[5] groups in 2007 and 2018, respectively, with Maji executing a biomimetic 6-*exo*-trig Prins-type cyclization to intercept an intermediate reported by Baran *en route* to (±)-ambiguine H (**2**, Scheme 2).

In Baran group's retrosynthetic analysis of ambiguine H,[4] they sought to bring together indole moiety **22** and ketone **23** by a Cu(II)-mediated indole−enolate coupling previously developed in their group[11] (Scheme 3a). Fragment **23** was prepared in 7 steps from *p*-menth-1-en-9-ol (**25**, Scheme 3b), where a [2+2] cycloaddition followed by a ring contraction induced by sodium methoxide gave cyclopropane **31**. DIBAL reduction, mesylation and cyclopropane ring-opening set the C12 quaternary stereocenter that is common to the ambiguine natural products. Ketone **23** was then coupled to 4-bromoindole (**22**) using stoichiometric Cu(II) 2-ethylhexanoate and a reductive Heck coupling formed the C4−C16 bond to give **34** (Scheme 3c). Subsequent reductive amination, formylation, and dehydration furnished the isonitrile functionality to afford (–)-hapalindole U (**21**). Subjecting (–)-hapalindole U to Danishefsky's procedure[12] in using prenyl-9-BBN (**24**) for direct C2 reverse-prenylation on indole moieties gave chloroimidate **37**, which then underwent photoinduced fragmentation to regenerate the isonitrile and indole motifs to complete the first total synthesis of (+)-ambiguine H (**2**). Efficient construction of the ABD tricyclic core through their oxidative coupling methodology set the stage for a divergent synthetic strategy to access (–)-hapalindole U (**21**), (+)-ambiguine H (**2**), (–)-fischerindole l, and (+)-welwitindolinone A.

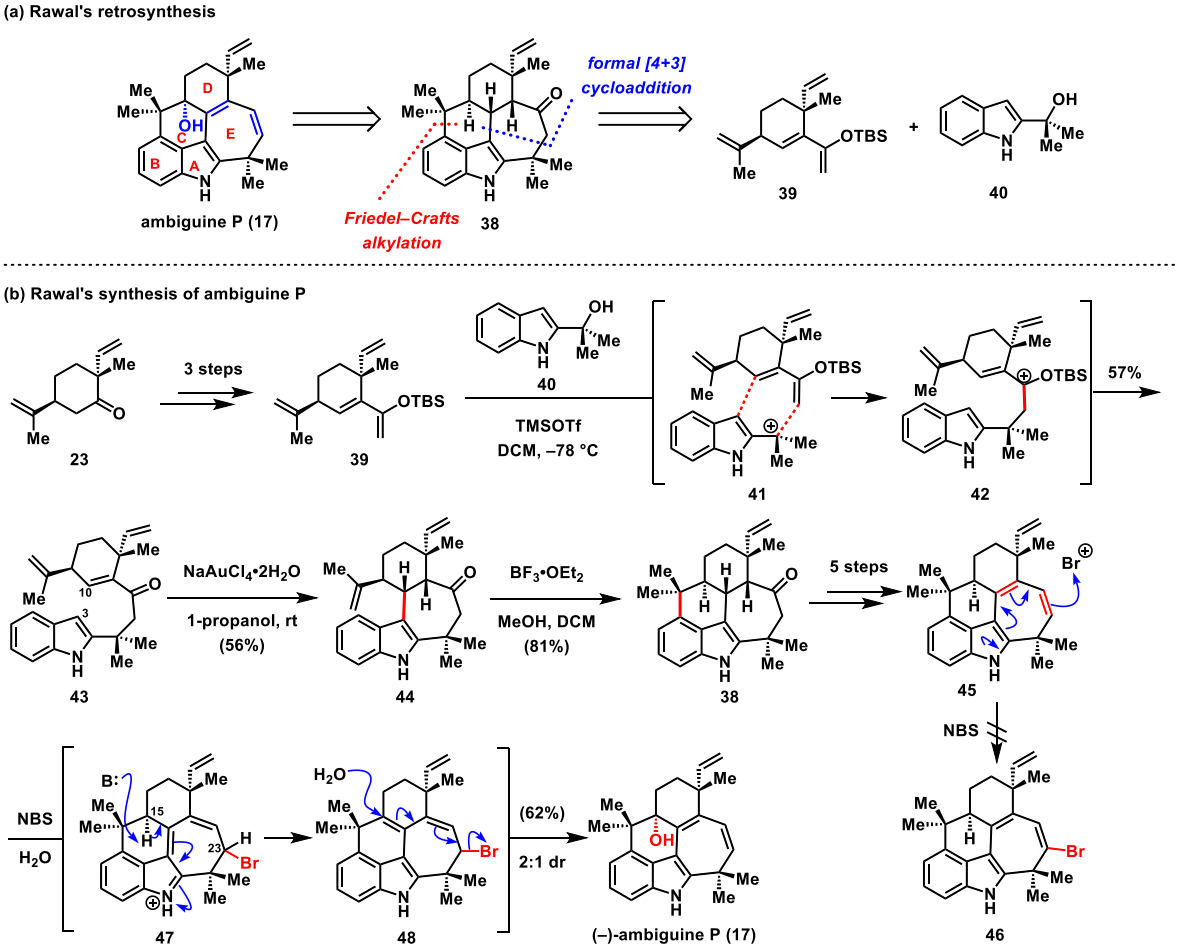


Scheme 3. Baran's total synthesis of (–)-hapalindole U (**21**) and (+)-ambiguine H (**2**).

The installation of the seven-membered E ring resident in the pentacyclic ambiguines is believed to pose a significant synthetic challenge that has left the synthesis of these natural products unconquered. Herein, we report a divergent synthesis strategy for the preparation of the pentacyclic ambiguines that has culminated in the first total synthesis of (–)-ambiguine P (**17**). The synthesis takes advantage of sequential alkylations of an unfunctionalized indole core to rapidly construct the pentacyclic framework of the natural product.

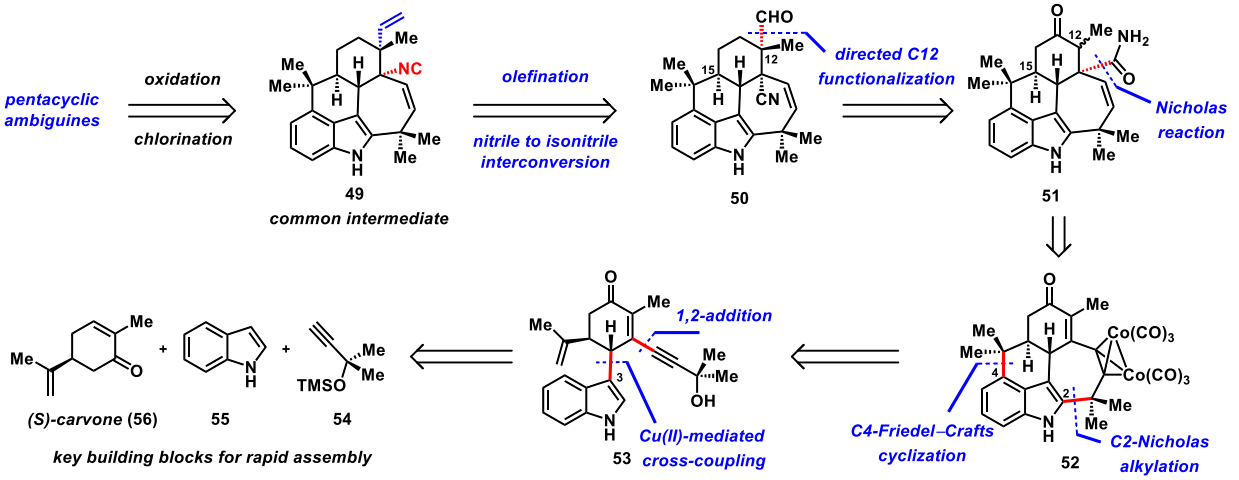
Shortly after we completed and published this synthesis plan, the Rawal group disclosed a second route to the same natural product (Scheme 4).[6] To build the seven-membered ring, they envisioned a formal [4+3] cycloaddition between indole fragment **40** and enol silane **39**, which is prepared in three steps from the same intermediate (**23**) that the Baran group had used in their synthesis of ambiguine H. When combined with TMSOTf, they observed the formation of enone **43,** which was then treated with a gold salt to effect the desired C3−C10 bond formation through

conjugate addition. This two-step α-alkylation/conjugate addition sequence afforded the cycloheptanone and formally resembles a [4+3] cycloaddition. BF_3-mediated Friedel–Crafts cyclization at C4 formed the C ring to complete the pentacyclic core structure. Conjugated diene **45** was obtained after several functional group manipulations, and is proposed to be the common precursor to ambiguines P (**17**) and Q (**11**, Figure 1). When **45** was treated with NBS in an attempt to obtain bromide **46** *en route* to ambiguine Q, they instead isolated (–)-ambiguine P, potentially through an electrophilic bromination at C23, isomerization to **48**, and a vinylogous S_N2' addition by water.



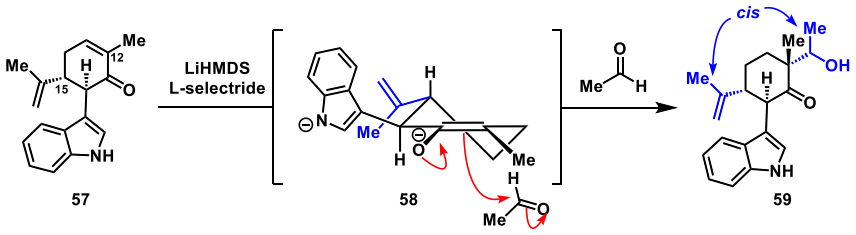
Scheme 4. Rawal's total synthesis of ambiguine P.

2.2 Retrosynthetic Analysis



Scheme 5. Retrosynthesis.

When considering a synthesis plan for the pentacyclic ambiguines, our intention was to devise one that was divergent and asymmetric such that the entire family can be accessed with enantiocontrol. Therefore, retrosynthetically (Scheme 5), we envisioned multiple pentacyclic congeners arising from common intermediate **49** via late-stage oxidation and/or chlorination. Pentacyclic isocyanide **49** could be accessed from **50**, which in the forward sense, would require olefination of the formyl group and conversion of the angular nitrile functionality to an isonitrile group. The C12 quaternary center in **50** would be installed using the primary amide of **51** as a directing group. To access the pentacyclic core of **52**, we envisioned sequential indole C3, C2, and C4 functionalizations, which ultimately took us back to readily available starting reagents (see **51** ⇒ **54** + **55** + **56**). Notably, to forge the seven-membered ring of the pentacyclic framework, a cobalt-mediated Nicholas alkylation at C2 of **53** would be employed, followed by Friedel–Crafts cyclization at C4 to build the C ring. The successful implementation of this strategy in the forward sense would provide access to all the target pentacyclic ambiguines.

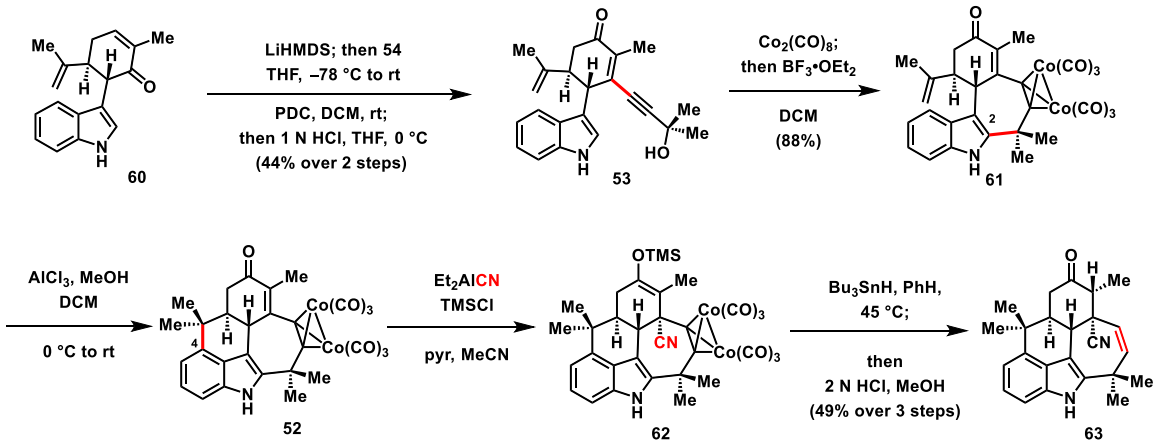


Scheme 6. Stereochemical outcome of a direct α-functionalization on carvone moiety.

The key synthetic challenge that had to be considered in preparing the pentacyclic ambiguine natural products lay in the diastereoselective α-functionalization at C12 (see **50** for numbering). The stereochemical outcome of this α-functionalization on related systems[11] is dictated by the stereochemistry at C15 that favors the *cis*-disposed stereodiad (Scheme 6), whereas

the *trans*-disposed grouping is required in our case. In our approach, we take advantage of a directed α-functionalization using the amide group in **51** to overcome the inherent diastereoselectivity.[13]

2.3 Synthesis of Ambiguine P



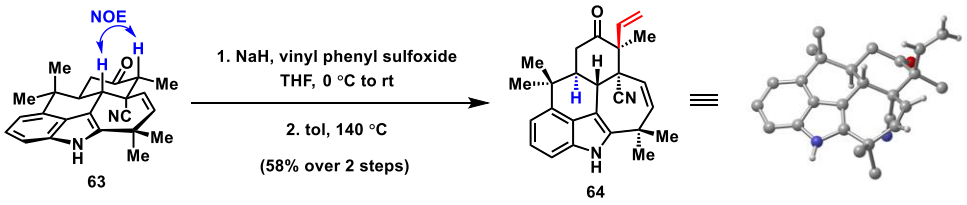
Scheme 7. Construction of the pentacyclic core.

Our synthesis commenced with the Cu(II)-mediated oxidative coupling of indole (**55**) with (*S*)-carvone (**56**) to afford C3 functionalized indole **60** (Scheme 7), following the precedent of Baran.[11] Subsequent 1,2-addition of propargylic alcohol **54** to the enone carbonyl of **60** and Babler–Dauben oxidative transposition[14] afforded enone **53** in 44% yield over the two steps. Cyclization to forge the seven-membered ring that is characteristic of the pentacyclic ambiguines was accomplished in excellent yield through an intramolecular Nicholas reaction[15] wherein the indole C2 site preferentially reacted over the C3 and C4 positions.

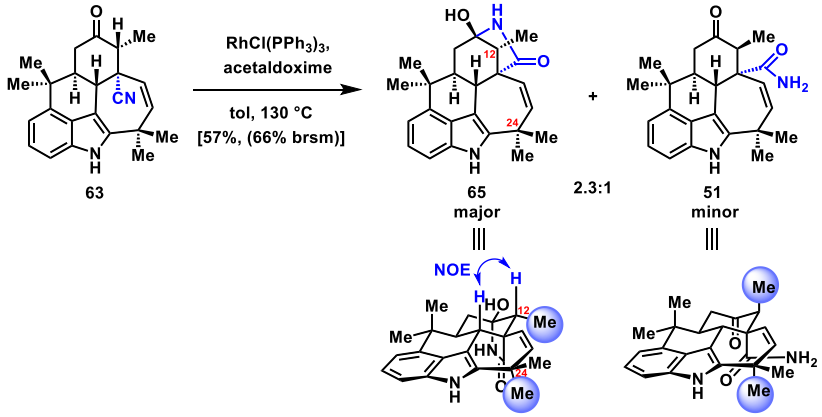
While site-selective Friedel–Crafts alkylation at the C4 position of the indole nucleus is often challenging due to competitive alkylation at the C2 and C3 positions,[16] we found that with the seven-membered E ring in place in **61**, the combination of 15 equivalents each of aluminum chloride and methanol successfully furnished the C ring in the desired pentacycle (**52**). All attempts to reduce the amount of aluminum chloride reagent were unsuccessful; lowering the amount of aluminum chloride while maintaining the starting reactant concentration gave no conversion and increasing the starting material concentration resulted in the formation of various side products that were not easily characterized. Because it was important to maintain the concentration of the reaction at 0.15 M with respect to aluminum chloride and 0.1 M to the starting material, this reaction could only be carried out on a 15 mmol scale at the maximum (1.5 L reaction mixture) and thus was the limiting step when scaling up.

Conjugate addition of cyanide to the enone moiety using Nagata's reagent[17] installed a nitrile group that would later serve both as a directing group and a surrogate for the isonitrile

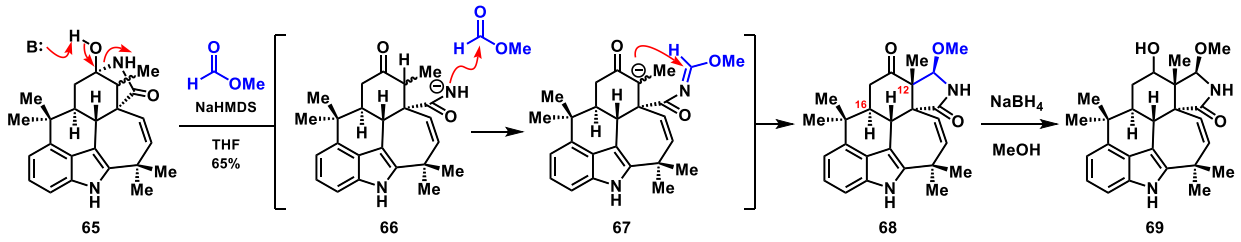
moiety. Concomitant trapping of the enolate that resulted from conjugate addition of the cyanide with TMSCl accomplished *in situ* protection of the carbonyl group to give **62**. At this stage, reductive removal of dicobalt using tributyltin hydride[18] followed by the acidic cleavage of the silyl protecting group yielded pentacycle **63** in 49% yield over three steps.



Scheme 8. Direct α-vinylation at C12



Scheme 9. Rhodium-catalyzed nitrile hydration.

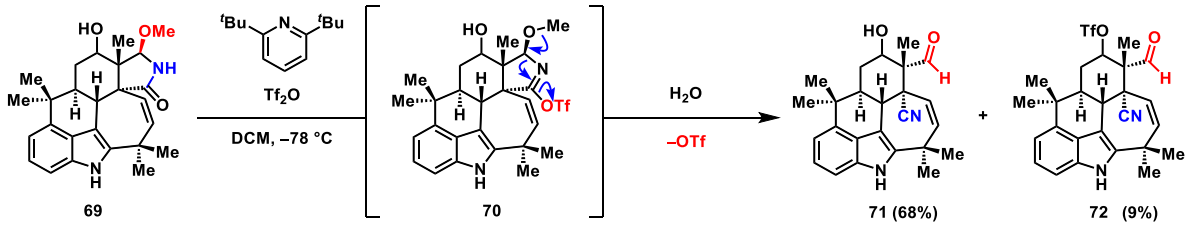


Scheme 10. Directed α-functionalization using methylformate.

With access to the key pentacycle (**63**) in gram quantities (up to 2.5 grams in a single pass) over a seven-step sequence from carvone, we sought to address the challenge of setting the C12 quaternary center. Not surprisingly, direct α-vinylation at C12 (Scheme 8) yielded the expected, undesired *cis*-disposed vinyl group (with respect to C15) in accord with Fürst–Plattner selectivity.[19] To overcome the inherent diastereoselectivity, we sought to hydrate the nitrile group to an amide, which could act as a directing group. We performed Rh(I)-catalyzed nitrile hydration using acetaldoxime as a surrogate for water[20] to obtain the amide (Scheme 9). On the basis of NMR

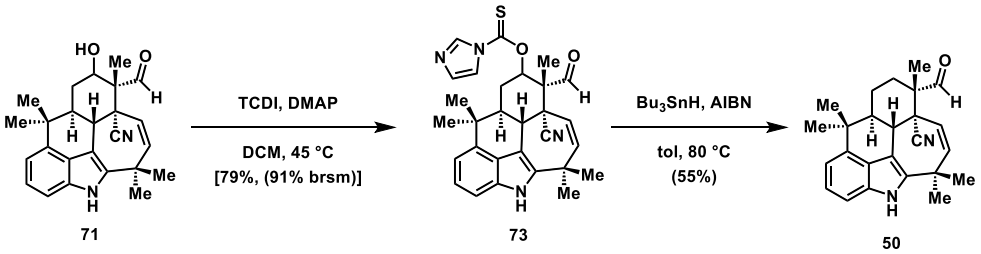
analysis, a mixture of **65** and **51** formed. Hemiamidal **65** arises from the cyclization of the primary amide onto the carbonyl group, which is presumably reinforced by the steric bulk of the α-disposed C12 methyl group.

A visiting scholar, Marco Hartmann found reaction conditions where methylformate could be used to functionalize the α-position (Scheme 10). The mixture of **65** and **51** was converged to the hemiamidal ether with methylformate under basic conditions in 54% yield, setting the C12 quaternary center with complete selectivity for the desired stereochemical outcome. Reduction of the carbonyl group with sodium borohydride generated alcohol **69**.



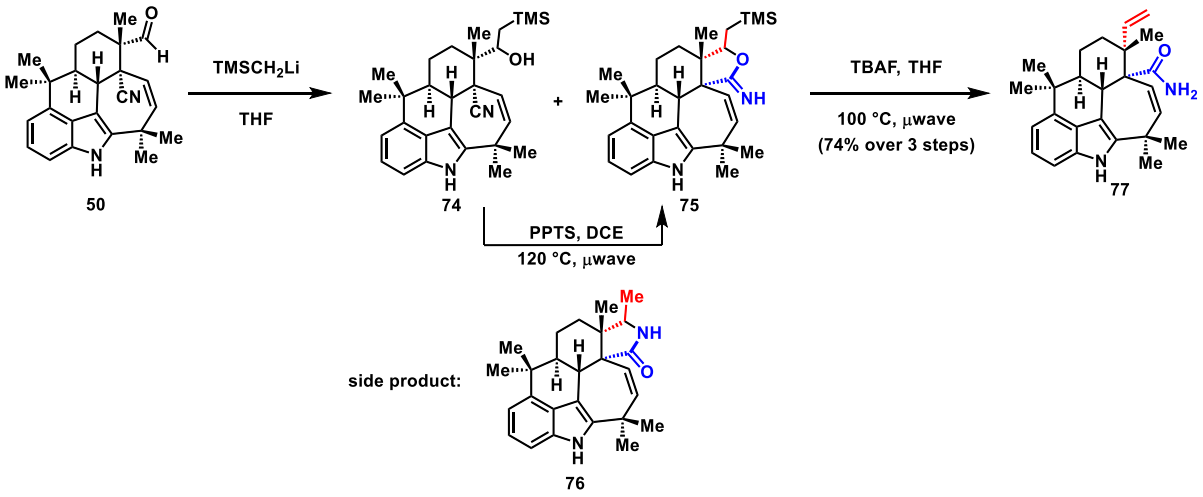
Scheme 11. Revealing the formyl group. ^{t}Bu = *tert*-butyl

The hemiamidal carbonyl of **69** was activated with triflic anhydride to form triflyl imidate intermediate **70** (Scheme 11). Upon addition of water, ring-opening, and ejection of the triflate furnished β-cyano aldehyde **71**.[21] In smaller scale reactions, 5 equivalents of triflic anhydride were used to effect the transformation, however, poor solubility of **69** in DCM often resulted in inconsistent yields as the scale increased. After screening several conditions, I discovered that using triflic anhydride as a cosolvent in combination with DCM gave consistently good yields, affording the desired product (**71**) in 68−71% yield along with 9% of triflated alcohol **72**.



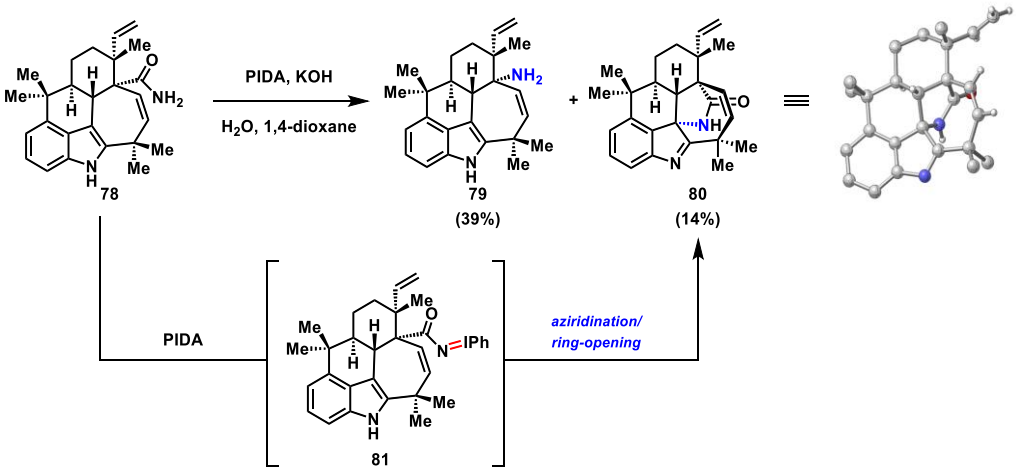
Scheme 12. Barton−McCombie deoxygenation.

At this stage, secondary alcohol **71** was converted to thiocarbamate **73** (Scheme 12), using 1,1'-thiocarbonyldiimidazole (TCDI). Compound **73** had to be immediately purified and subjected to the next reaction since the thiocarbamate was susceptible to reverting back to **71** by hydrolysis over time. Transforming **73** by Barton–McCombie deoxygenation[22] of the corresponding thiocarbamate intermediate gave **50** in 55% yield. Again, prompt purification of product **50** is necessary because reduction of the aldehyde to the primary alcohol by the residual organotin reagent occurs when the compound is left in crude form for prolonged periods of time.

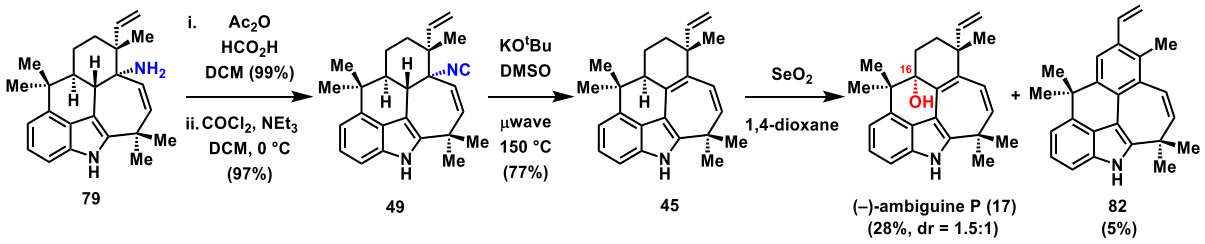


Scheme 13. Merging Peterson olefination with nitrile hydration.

While exploring the olefination and nitrile hydration sequence, we discovered that these two transformations could be achieved in a single step (Scheme 13). In the event, treatment of **50** with $TMSCH_2Li$ produced a secondary alkoxide, which engaged the nitrile group to afford **75** because of its proximity. To convert residual secondary alcohol **74** to imidate **75**, several conditions using AcOH or PPTS were tested and I found that the use of PPTS[23] under microwave irradiation gave the best result with minimal formation of the side product (**76**). Subsequent cleavage of the silyl group with TBAF yielded the primary amide and the vinyl group, effectively marrying the Peterson-type olefination[24] with nitrile hydration.



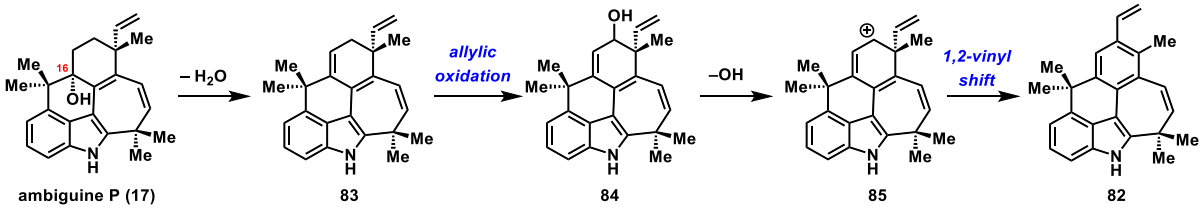
Scheme 14. Hoffman rearrangement and an aziridination/ring-opening side reaction.



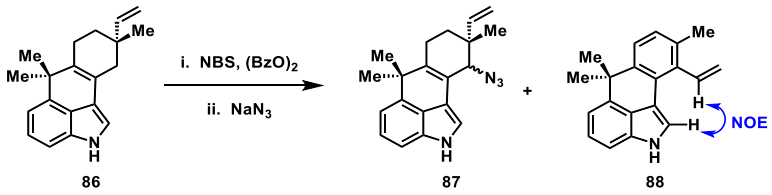
Scheme 15. Completion of ambiguine P.

At this stage, it was necessary to convert the primary amide at C11 to an isonitrile, a functional group that is present in the majority of ambiguine natural products. Hypervalent-iodine-mediated Hofmann rearrangement[25] of amide **78** progressed in 39% yield to give desired tertiary amine **79** along with indolenine **80** (Scheme 14), which presumably arose from competing aziridination of the indole C2–C3 double bond[26] followed by ring-opening. I observed rapid formation of **80** and the isocyanate intermediate (within 5 minutes after the addition of PIDA) by TLC and LCMS analyses, but the decarboxylation step was sluggish and the reaction mixture had to be stirred for more than 20 h. Interestingly, the isocyanate intermediate could be isolated, and because the isocyanate functional group is tertiary and neopentyl, it was stable enough to be fully characterized after purification using silica gel preparatory thin-layer chromatography.

Subjecting the intermediate tertiary amine to a formylation-dehydration sequence yielded pentacyclic isonitrile **49** (Scheme 15). Sequential elimination of the isonitrile and allylic oxidation using selenium dioxide gave ambiguine P (**17**) as a mixture of diastereomers (dr = 1.5:1 ratio in favor of **17**). An overoxidation side product was also observed, which presumably forms from the elimination of the C16 hydroxy group, allylic oxidation and subsequent ionization followed by a 1,2-vinyl shift (Scheme 16).[27] A similar Wagner−Meerwein rearrangement of the vinyl group was previously reported in Natsume's synthesis of the natural product hapalindole (Scheme 17).[28]



Scheme 16. Overoxidation/1,2-vinyl shift side reaction.



Scheme 17. Similar overoxidation/1,2-vinyl shift reported by Natsume and coworkers.

2.4 Conclusion and Distribution of Credit

In conclusion, the first total synthesis of a pentacyclic ambiguine has been achieved in 20 steps from C3-functionalized indole **60**, which is readily available in multigram quantities in a single step from commercial reagents.[11] Overall, our approach to the pentacyclic ambiguines highlights a rapid construction of the pentacyclic skeleton through sequential alkylative functionalizations of indole using robust C–C bond forming reactions as well as a novel application of an amide group to accomplish a stereoselective C12 functionalization. Ready access to pentacyclic isonitrile **49** sets the stage for late-stage derivatization to access other pentacyclic members of the ambiguine family that retain the isonitrile group.

Contributions. The synthesis of the intermediate containing the pentacyclic core (**68**) was primarily accomplished by Rebecca Johnson and these studies are detailed in her dissertation. Work on late-stage functional group manipulations to arrive at the isocyanide intermediate (**49**) was performed by Rebecca Johnson and me and is partially discussed in Rebecca Johnson's dissertation. My contributions to the scale-up, optimization, characterization of advanced intermediates and side-products are thoroughly discussed in this chapter. The synthesis, isolation, purification, and full characterization of ambiguine P were executed solely by me. Part of this work has been published in: *J. Am. Chem. Soc.* **2019**, *141*, 2233.

2.5 References

(1) (a) Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1992**, *57*, 857. (b) Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1998**, *61*, 1304. (c) Raveh, A.; Carmeli, S. *J. Nat. Prod*. **2007**, *70*, 196. (d) Mo, S.; Krunic, A.; Chlipala, G.; Orjala, J. *J. Nat. Prod.* **2009**, *72*, 894. (e) Mo, S.; Krunic, A.; Santarsiero, B. D.; Franzblau, S. G.; Orjala, J. *Phytochemistry* **2010**, *71*, 2116. (f) Walton, K.; Gantar, M.; Gibbs, P. D. L.; Schmale, M. C.; Berry, J. P. *Toxins* **2014**, *6*, 3568.

(2) (a) Moore, R. E.; Cheuk, C.; Patterson, G. M. L. *J. Am. Chem. Soc.* **1984**, *106*, 6456. (b) Moore, R. E.; Cheuk, C.; Yang, X. Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; Swartzendruber, J. K.; Deeter, J. B. *J. Org. Chem.* **1987**, *52*, 1036. (c) Klein, D.; Daloze, D.; Braekman, J. C.; Hoffmann, L.; Demoulin, V. *J. Nat. Prod*. **1995**, *58*, 1781. (d) Becher, P. G.; Keller, S.; Jung, G.; Sussmuth, R. D.; Juttner, F. *Phytochemistry* **2007**, *68*, 2493. (e) Kim, H.; Lantvit, D.; Hwang, C. H.; Kroll, D. J.; Swanson, S. M.; Franzblau, S. G.; Orjala, J. *Bioorg. Med. Chem.* **2012**, *20*, 5290.

(3) (a) Chandra, A.; Viswanathan, R.; Johnston, J. N. *Org. Lett.* **2007**, *9*, 5027. (b) Rafferty, R. J.; Williams, R. M. *Tetrahedron Lett.* **2011**, *52*, 2037. (c) Rafferty, R. J.; Williams, R. M. *Heterocycles* **2012**, *86*, 219.

(4) (a) Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature* **2007**, *446*, 404. (b) Maimone, T. J.; Ishihara, Y.; Baran, P. S. *Tetrahedron*, **2015**, *71*, 3652.

(5) Sahu, S.; Das, B.; Maji, M. S. *Org. Lett.* **2018**, *20*, 6485.

(6) Xu, J.; Rawal, V. H. *J. Am. Chem. Soc.* **2019**, *141*, 4820.

(7) (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc*. **1994**, *116*, 9935. (c) Kim, H.; Krunic, A.; Lantvit, D.; Shen, Q.; Kroll, D. J.; Swanson, S. M.; Orjala, J. *Tetrahedron* **2012**, *68*, 3205.

(8) Jimenez, J. I.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 569.

(9) (a) Doan, N. T.; Rickards, R.W.; Rothschild, J. M.; Smith, G. D. *J. Appl. Phycol.* **2000**, *12*, 409. (b) Doan, N. T.; Stewart, P. R.; Smith, G. D. *FEMS Microbiol. Lett.* **2001**, *196*, 135. (c) Asthana, R.; Srivastava, A.; Singh, A.; Singh, S.; Nath, G.; Srivastava, R.; Srivastava, B. *J. Appl. Phycol.* **2006**, *18*, 33. (d) Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241. (e) Zhang, X.; Smith, C. D. *Mol. Pharmacol.* **1996**, *49*, 288.

(10) (a) Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257. (b) Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, 9935. (c) Raveh, A.; Carmeli, S. *J. Nat. Prod.* **2007**, *70*, 196. (d) Hillwig, M. L.; Zhu, Q.; Liu, X. *ACS Chem. Biol.* **2014**, *9*, 372. (e) Li, S.; Lowell, A. N.; Yu, F. Raveh, A. Newmister, S. A.; Bair, N.; Schaub, J. M.; Williams, R. M.; Sherman, D. H. *J. Am. Chem. Soc.* **2015**, *137*, 15366. (f) Hillwig, M. L.; Zhu, Q.; Ittiamornkul, K.; Liu, X. *Angew. Chem. Int. Ed.* **2016**, *55,* 5780. (g) Liu, X.; Hillwig, M. L.; Koharudin, L. M. I.; Gronenborn, A. M. *Chem. Commun.* **2016**, *52*, 1737. (h) Zhu, Q.; Liu, X. *Chem. Commun.* **2017**, *53*, 2826. (i) Zhu, Q.; Liu, X. *Angew, Chem.*

Int. Ed. **2017**, *56*, 9062. (j) Wong, C. P.; Awakawa, T.; Nakashima, Y.; Mori, T.; Zhu, Q.; Liu, X.; Abe, I. *Angew. Chem. Int. Ed.* **2018**, *57*, 560. (k) Chen, C. C.; Hu, X.; Tang, X.; Yang, Y.; Ko, T. P.; Gao, J.; Zheng, Y.; Huang, J. W.; Yu, Z.; Li, L.; Han, S.; Cai, N.; Zhang, Y.; Liu, W.; Guo, R. T. *Angew. Chem. Int. Ed.* **2018**, *57*, 15060. (l) Li, S.; Newmister, S. A.; Lowell, A. N.; Zi, J.; Chappell, C. R.; Yu, F.; Hohlman, R. M.; Orjala, J.; Williams, R. M.; Sherman, D. A. *Angew. Chem. Int. Ed.* **2020**, *59*, 2.

(11) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450 (b) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17983.

(12) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964.

(13) For a previous example of a directed functionalization in the synthesis of the hapalindoles see: Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

(14) (a) Babler, J. H.; Coghlan, M. J *Synth. Commun.* **1976**, *6*, 469. (b) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(15) (a) Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21. (b) Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. (c) Ni, R.; Mitsuda, N.; Kashiwagi, T.; Igawa, K.; Tomooka, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 1190.

(16) For previous attempts of a Friedel-Crafts reaction on indole C-4 of related systems see: (a) Ref 3e. (b) Chandra, A.; Johnston, J. N. *Angew. Chem. Int. Ed.* **2011**, *50*, 7641. (c) Bonjouklian, R.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1988**, *53*,

(17) Nagata, W.; Yoshioka, M. *Org. Synth*. **1972**, *52*, 90

(18) Hosokawa, S.; Isobe, M. *Tetrahedron Lett*. **1998**, *39*, 2609.

(19) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta.* **1949**, *32*, 275.

(20) Lee, J.; Kim, M; Chang, S.; Lee, H. Y. *Org. Lett.* **2009**, *11*, 5598.

(21) Activation of amides using Tf_2O: (a) Charette, A.B.; Chua, P. *Synlett* **1998**, *163*. (b) Charette, A.B.; Grenon, M. *Can. J. Chem.* **2001**, *79*, 1694.

(22) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1,* **1975**, *0*, 1574.

(23) Xu, S.; Ciufolini, M.A. *Org. Lett.* **2015**, *17*, 2424.

(24) (a) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780. (b) Ager, D. J. *Synthesis* **1984**, *5*, 384.

(25) Zagulyaeva, A. A.; Banek, C. T.; Yusubov, M. S.; Zhdankin, V. V. *Org. Lett.* **2010**, *12*, 4644.

(26) Kumar, P. J. *Heterocycles* **1987**, *26*, 1257.

(27) For a theoretical study on the migratory aptitude of a vinyl group see: Osamura, Y.; Nakamura, K. *Tetrahedron Lett.* **1990**, *31*, 251.

(28) Natsume, M.; Muratake, H. *Tetrahedron* **1990**, *46*, 6331.

2.6 Experimental Section

General Procedures

1)Reagents and Solvents

Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon®-coated magnetic stir bars. Liquid reagents and solvents were transferred by syringe using standard Schlenk techniques. Reagents were purchased from Sigma-Aldrich, Acros Organics, Chem-Impex, Fisher Scientific, or Alfa Aesar. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), methanol (MeOH), NEt_3 were dried by passage over a column of activated alumina; dichloromethane (DCM) was distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Where stated, solutions were degassed using three cycles of freeze/pump/thaw (freezing the solution contained within a Schlenk flask in liquid nitrogen, opening the flask to vacuum for 5 min, then allowing the solution to thaw under vacuum).

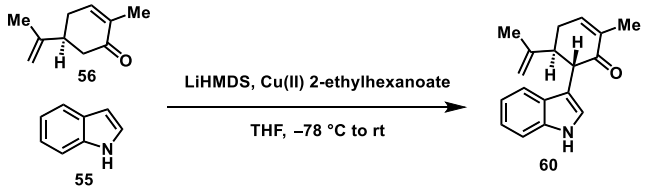
2) Reaction Monitoring/Purification

Reaction progress was monitored using a combination of thin layer chromatography (TLC) using SiliCycle silica gel 60 F-254 precoated plates (0.25 mm) and LC/MS. TLC plates were visualized by UV irradiation, anisaldehyde, cerium ammonium molybdenate (CAM), potassium permanganate, or iodine stain. LC/MS analysis was performed on a Shimadzu LCMS-2020 (UFLC) equipped with the LC20AD solvent delivery system, a SPD-20AV prominence UV/Vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 × 50 mm). Purifications were performed with a Yamazen® Smart S4 Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents and gradients were determined by inputting R_f values and using the corresponding Yamazen® generated conditions.

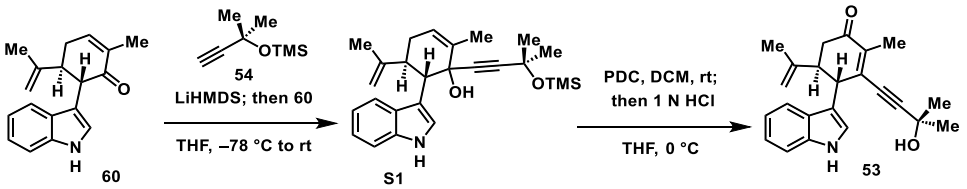
3) Instrumentation

Optical rotation was recorded on a Perkin Elmer Polarimeter 241 at the D line (1.0 dm path length), c = mg/mL, in $CHCl_3$ unless otherwise stated. ^1H and ^{13}C NMR experiments were performed on Bruker spectrometers operating at 300, 400, 500, 600, 700, or 900 MHz for ^1H and 75, 100, 125, 150, 176, or 226 MHz for ^{13}C experiments. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$ δ = 7.26 for ^1H NMR and δ = 77.16 for ^{13}C NMR; $(CD_3)_2CO$ δ = 2.05 for ^1H NMR and δ = 29.84 for ^{13}C NMR; $(CD_3)_2SO$ δ = 2.50 for ^1H NMR and δ = 39.52 for ^{13}C NMR; C_6D_6 δ = 7.16 for ^1H NMR and δ = 128.06 for ^{13}C NMR; CD_3OD δ = 3.31 for ^1H NMR and δ = 49.00 for ^{13}C NMR). Data are reported as follows: chemical shift (multiplicity, coupling

constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), ddq (doublet of doublets of quartets), m (multiplet), bs (broad singlet). IR spectra were recorded on a Bruker ALPHA Platinum ATR FT-IR spectrometer. Samples were loaded onto the diamond surface either in their solid form or as a solution in DCM (allowing DCM to dry thoroughly). Low and high-resolution mass spectral data were obtained from the University of California, Berkeley Mass Spectral Facility, on a VG 70-Se Micromass spectrometer for FAB, and a VG Prospec Micromass spectrometer for EI.



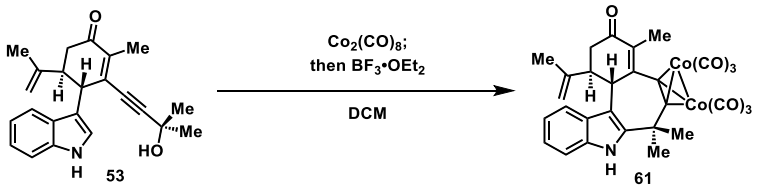
Enone 60: (Adapted from Baran et al.)[1] An oven-dried 2 L round-bottomed flask was charged with indole (**55**) (22.7 g, 194 mmol, 2.00 equiv) followed by (*S*)-carvone (**56**) (15 mL, 97 mmol, 1.0 equiv). To this mixture was added THF (484 mL) and the resulting solution was cooled in a dry ice/acetone bath to –78 °C. The reaction mixture was held at –78 °C while LHMDS (1.0 M in THF, 300 mL, 300 mmol, 3.1 equiv) was added via cannula transfer dropwise over 30 min. The resulting brownish solution was stirred at –78 °C for 1 h after which the flask was opened to the atmosphere and Cu(II) 2-ethylhexanoate (50.9 g, 145 mmol, 1.5 equiv) was added as a solid through a plastic funnel. The reaction mixture was quickly resealed with the septum and allowed to warm to rt overnight. The reaction mixture was quenched with ammonium chloride (sat. aq.) (500 mL) and the aqueous layer was extracted with ethyl acetate (3 x 500 mL). The organic layer was washed with brine (1 x 300 mL), dried over sodium sulfate, and the solvent was removed in vacuo. The crude product was purified via SiO_2 column chromatography eluting with 4:1 hexanes/ethyl acetate to afford pure product as an off-white solid (10.7 g, 40.2 mmol, 41.0%). Analytical data was identical in all aspects to that which was previously reported.[1]



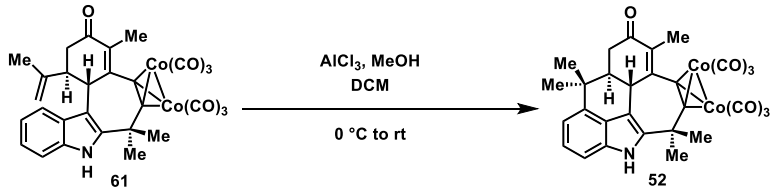
Allylic alcohol S1: To a solution of alkyne **54** (10.2 mL, 52.5 mmol, 2.1 equiv) in THF (130 mL) at –78 °C was added LHMDS (1.0 M in THF, 54 mL, 54 mmol, 2.2 equiv) dropwise over 10 min. This solution was allowed to stir at –78 °C for 1 h after which indole−carvone adduct **60** (6.6 g, 25 mmol, 1.0 equiv) was added as a solution in THF (15 mL) dropwise over 5 min. The reaction mixture was immediately taken out of the –78 °C bath and allowed to warm to rt. The reaction mixture was then quenched with ammonium chloride (sat. aq.) (200 mL) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined and washed with brine (200 mL), dried over sodium sulfate, and the solvent was removed in vacuo. The yellowish-

red crude reaction mixture was used immediately in the next step.

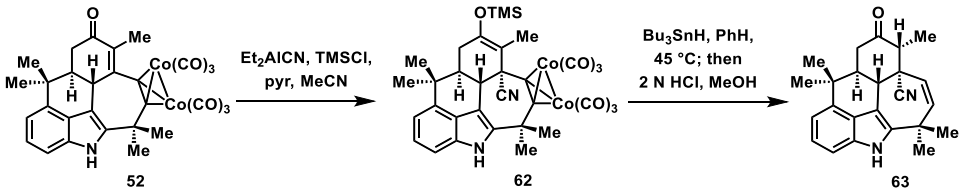
Tricycle 53: The crude product from the previous step (**S1**) was dissolved in DCM (250 mL) and PDC (14.1 g, 37.5 mmol, 1.5 equiv) was added. The reaction mixture was allowed to stir at rt overnight. The reaction mixture was then filtered through a plug of Celite® eluting with DCM and to the filtrate was added 2N HCl/MeOH (50 mL). After complete removal of the TMS group as indicated by TLC analysis (approx. 10 min), the reaction mixture was quenched with sodium bicarbonate (sat. aq.) (200 mL) and the aqueous layer was washed with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed in vacuo and the crude product was purified using SiO_2 column chromatography eluting with 2:1 hexanes/ethyl acetate then 1:1 hexanes/ethyl acetate to yield the product as a beige solid (3.8 g, 11 mmol, 44% over 2 steps). mp 115 °C (decomp) **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 4.75 - 4.64 (m, 2H), 4.12 (dd, *J* = 7.9, 2.2 Hz, 1H), 3.17 (td, *J* = 9.0, 4.5 Hz, 1H), 2.68 - 2.57 (m, 2H), 2.01 (d, *J* = 1.9 Hz, 3H), 1.72 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H). **^{13}C NMR**; (150 MHz, $CDCl_3$) δ 198.4, 145.4, 139.5, 138.1, 136.4, 127.5, 122.8, 122.3, 119.6, 119.2, 116.0, 113.1, 111.6, 109.0, 81.2, 65.5, 47.7, 41.9, 41.8, 30.7, 30.7, 20.4, 14.3. **IR** (thin film) 3324, 3260, 2979, 2850, 2220, 1640, 1456, 1340, 1167, 891, 739 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{23}H_{26}O_2N$ $[M+H]^+$: 348.1958. Found 348.1960. $[\alpha]_D$ = +151 (c 7.5 x 10^{-3}, $CHCl_3$).



Cobalt-complexed tetracycle 61: A 1 L flask was charged with propargylic alcohol **53** (2.0 g, 5.9 mmol, 1.0 equiv). To this flask was added DCM (60 mL) followed by $Co_2(CO)_8$ (2.4 g, 7.0 mmol, 1.2 equiv). The reaction mixture was allowed to stir at rt for 5 h. To this reaction mixture was added $BF_3 \cdot OEt_2$ (0.72 mL, 5.9 mmol, 1.0 equiv). After stirring for 5 min, the reaction mixture was quenched with sodium bicarbonate (100 mL) and the aqueous layers were extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine (sat. aq.) (100 mL), dried over sodium sulfate, and the solvent was removed in vacuo. The crude reaction mixture was purified using SiO_2 gel column chromatography eluting with hexanes then 2:1 hexanes/ethyl acetate. The product was isolated as a dark red solid (3.2 g, 5.2 mmol, 88%). mp >260 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.09 (dt, *J* = 19.6, 7.4 Hz, 2H), 4.82 (d, *J* = 13.3 Hz, 2H), 4.44 (s, 1H), 3.88 (d, *J* = 6.2 Hz, 1H), 3.23 (dd, *J* = 15.9, 5.1 Hz, 1H), 2.77 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.00 (s, 3H), 1.96 (s, 3H), 1.80 (s, 3H), 1.77 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 199.5, 198.3, 198.1, 154.1, 146.4, 141.6, 138.0, 134.4, 126.9, 121.4, 120.4, 120.1, 112.3, 112.0, 111.4, 110.8, 85.2, 44.7, 42.3, 42.2, 39.7, 30.4, 29.6, 21.7, 12.6. **IR** (thin film) 3306, 2974, 2090, 2052, 2012, 1645, 1568, 1437, 1323, 898 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{29}H_{24}O_7NCo$ $[M+H]^+$: 616.0211. Found 616.0222. We attempted to obtain optical rotations, however, at the wavelength we had access to (Na lamp, 584 nm), the transmittance was too low to obtain accurate rotations.



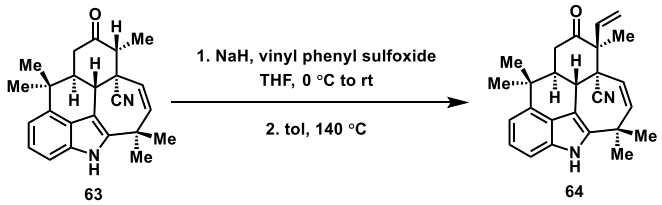
Cobalt-complexed pentacycle 52: A flame-dried 500 mL round-bottomed flask was brought into a glovebox and charged with $AlCl_3$ (3.0 g, 23 mmol, 15 equiv). The flask was fitted with a rubber septum and brought out of the glovebox. Freshly distilled DCM (150 mL) was added to the flask and the mixture was placed under a stream of N_2. The mixture was cooled to 0 °C and tetracycle **61** (0.923 g, 1.50 mmol, 1.0 equiv) was added as a solid immediately followed by the addition of MeOH (0.79 mL, 23 mmol, 15 equiv) via syringe. The reaction mixture was removed from the ice bath and allowed to warm to rt. After stirring for 5 h at rt, the reaction mixture was quenched by pouring into ice water (100 mL) and the organic layer was washed with water (3 x 100 mL) to remove excess aluminum reagent. The combined aqueous layer was then extracted with DCM (3 x 100 mL). The organic layers were combined, washed with sodium bicarbonate solution (sat. aq., 200 mL) brine (200 mL), dried over sodium sulfate, and the solvent was removed in vacuo. The crude product was subjected to the next reaction without purification.



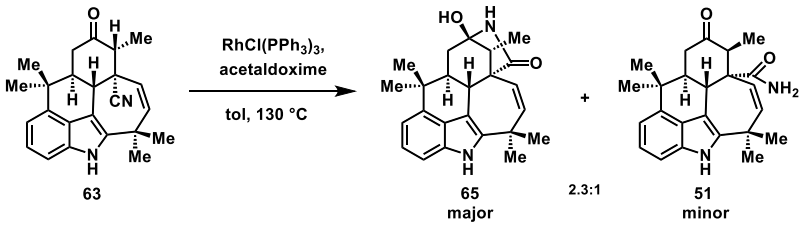
Silyl enol ether 62: Crude cobalt-complexed pentacycle **52** was dissolved in MeCN (15 mL) in a round-bottomed flask. To this solution was added Et_2AlCN (1.0 M in toluene, 4.4 mL, 4.4 mmol, 3.0 equiv) via syringe over 1 min. After 30 min of stirring at rt, TMSCl (0.89 mL, 6.9 mmol, 4.8 equiv) followed by pyridine (0.89 mL, 11 mmol, 7.6 equiv) was added via syringe. After another 30 minutes of stirring at rt, the reaction mixture was quenched by pouring into ice and sodium bicarbonate (sat. aq.) (50 mL). The organic layer was washed with brine (2 x 50 mL) and the combined aqueous layers were extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuo. The crude brown foam was immediately subjected to the next reaction without purification.

Nitrile ketone 63: Crude **62** was dissolved in benzene (15 mL) and the solution was placed in an oil bath pre-heated to 45 °C. $SnBu_3H$ (2.1 mL, 7.3 mmol, 5.0 equiv) was added in four equal portions every half hour totaling 2.5 h reaction time at 45 °C. After this time, the solvent was removed in vacuo and the crude product was filtered through a SiO_2 plug eluting with hexanes (500 mL). The SiO_2 plug was then washed with ethyl acetate (500 mL) and the solvent was removed in vacuo. The crude reaction mixture was dissolved in ethyl acetate (100 mL) and a 2N HCl/MeOH (50 mL) mixture was added. Following complete desilylation (as indicated by TLC), the mixture was quenched with sodium bicarbonate (sat. aq.) (100 mL) and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (100 mL), dried

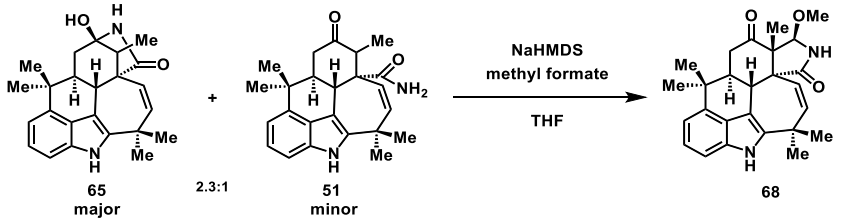
over sodium sulfate, and concentrated in vacuo. The crude reaction mixture was purified using SiO_2 column chromatography eluting with 2:1 hexanes/ethyl acetate to yield the desired product as a white solid (0.26 g, 0.72 mmol, 49% over 3 steps). mp >260 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.15 (d, *J* = 4.1 Hz, 2H), 7.01 (t, *J* = 4.0 Hz, 1H), 5.80 (d, *J* = 12.1 Hz, 1H), 5.68 (d, *J* = 12.1 Hz, 1H), 3.51 (d, *J* = 11.1 Hz, 1H), 2.82 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.71 (q, *J* = 6.6 Hz, 1H), 2.47 (t, *J* = 13.5 Hz, 1H), 2.29 (ddd, *J* = 14.1, 11.0, 3.2 Hz, 1H), 1.67 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.3, 143.1, 139.2, 135.9, 133.4, 127.6, 125.8, 122.9, 119.1, 113.2, 108.0, 106.4, 52.0, 49.9, 48.5, 44.0, 41.8, 38.2, 37.9, 33.3, 28.2, 24.6, 24.3, 10.3. **IR** (thin film) 3393, 2955, 2866, 2365, 1719, 1450, 1327, 776 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{24}H_{26}N_2O$ $[M+H]^+$: 358.2040 found = 358.2046. $[\alpha]_D$ –81.9 (c 4.7 x 10^{-3}, $CHCl_3$).



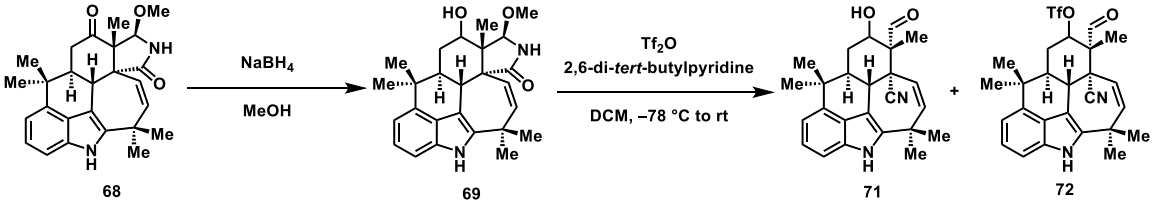
α-Functionalized nitrile ketone 64: To a 100 mL round-bottomed flask was added **63** (270 mg, 0.75 mmol, 1.0 equiv), phenyl vinyl sulfoxide (0.20 mL, 1.5 mmol, 2.0 equiv), and THF (20 mL). The resulting solution was cooled to 0 °C, then NaH (60% dispersion in mineral oil, 120 mg, 3.0 mmol, 5.0 equiv) was added. The ice bath was removed, and the reaction mixture was stirred for 1 h at rt. The reaction mixture was quenched with water (5 mL), and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (10 mL) followed by brine (10 mL), dried over magnesium sulfate, and concentrated in vacuo. The resulting crude compound was dissolved in toluene (20 mL) in a 10–20 mL microwave vial. The reaction mixture was stirred for 4 h at 140 °C, then cooled to rt and concentrated in vacuo. The product was purified by column chromatography eluting with 1:1 DCM: toluene to give an orange solid, which was recrystallized from DCM and hexanes to afford the vinylated product as a single diastereomer in 58% yield (168 mg, 58%). mp >260°C. See X-ray crystal structure data below**. ^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.17 – 7.13 (m, 2H), 7.03 – 6.99 (m, 1H), 6.30 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.81 (d, *J* = 12.4, 1H), 5.62 (d, *J* = 12.4 Hz, 1H), 5.47 (d, *J* = 10.8 Hz, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 3.74 (d, *J* = 11.3 Hz, 1H), 2.75 (dd, *J* = 13.7, 13.7 Hz, 1H), 2.69 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.35 (ddd, *J* = 14.3, 11.3, 4.0 Hz, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.19 (s, 3H). **^{13}C NMR** (150 MHz, CDCl3) δ 206.9, 143.7, 139.3, 136.2, 136.0, 133.5, 126.0, 124.2, 122.9, 120.6, 119.7, 113.1, 108.0, 106.3, 57.9, 51.8, 48.1, 39.9, 38.6, 38.4, 37.9, 33.1, 28.1, 24.6, 24.3, 18.5. **IR** (ATIR) 3355, 2966, 2237, 1713, 1469, 1328, 928, 773 cm^{-1}. **HRMS** (ESI) m/z calc'd for $C_{26}H_{28}ON_2{}^{39}K$ $[M+K]^+$ 428.1833, found 428.1840. $[\alpha]_D$ –63.8 (c 5.0 x 10^{-3}, $CHCl_3$).



Amide 51 and hemiamidal 65: Ketone **63** (260 mg, 0.72 mmol, 1.0 equiv) was added to a 25-mL round-bottomed flask. Toluene (2 mL) was added followed by acetaldoxime (freeze-pump-thawed (3x), 1.1 mL, 18 mmol, 25 equiv) via syringe. Wilkinson's catalyst, $RhCl(PPh_3)_3$ (0.14 mmol, 13 mg, 0.20 equiv), was added to the mixture and a reflux condenser flushed with N_2, was fitted on the flask. The setup was sealed with a septum with a N_2 inlet. The reaction mixture was placed in an oil bath preheated to130 °C and heated at reflux for 2.5 h at this temperature. After 2.5 h, the reaction flask was taken out of the oil bath and allowed to cool down to rt. The mixture was quenched with water (10 mL) and diluted with ethyl acetate (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. The crude mixture was concentrated in vacuo and purified using SiO_2 gel column chromatography on a Yamazen® automatic purification system using a gradient of 50% hexanes/ethyl acetate to 5% hexanes/ethyl acetate. The product was isolated as a slight white solid (**65**) and yellow foam (**51**) (150 mg, 0.41 mmol, 57%, 66% brsm). Both **51** and **65** are typically collected and subjected to the next step along with triphenylphosphine oxide but does not affect the efficiency of the subsequent steps. **Hemiamidal of lower polarity (65):** mp >260 °C. **^{1}H NMR** (600 MHz, CD_3OD) δ 9.96 (s, 1H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 5.72 (d, *J* = 13.2 Hz, 1H), 5.58 (d, *J* = 13.3 Hz, 1H), 3.21 (d, *J* = 11.3 Hz, 1H), 2.12 – 2.10 (m, 2H), 1.88 (td, *J* = 11.9, 5.5 Hz, 1H), 1.79 (t, *J* = 12.2 Hz, 1H), 1.67 (s, 3H), 1.45 (s, 3H), 1.40 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.14 (s, 3H). **^{13}C NMR** (151 MHz, CD_3OD) δ 176.5, 144.2, 141.5, 138.2, 135.6, 127.2, 123.1, 122.3, 112.3, 108.4, 107.3, 87.8, 59.1, 55.0, 49.8, 42.8, 39.8, 38.0, 37.7, 32.9, 31.1, 25.3, 25.2, 10.4. **IR** (thin film) 3287, 2963, 2927, 1693, 1660, 1450, 1362, 1306, 1263, 1121, 1053, 1022, 735 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{24}H_{28}O_2N_2Na$ $[M+Na]^+$: 399.2043. Found 399.2049. $[\alpha]_D$ –83.3 (c 1.5 x10^{-3}, $CHCl_3$). **Amide of higher polarity (51)**: **^{1}H NMR** (600 MHz, 10% $(CD_3)_2CO$ in CD_3OD) δ7.05 (d, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.02 (d, *J* = 13.0 Hz, 1H), 5.79 (d, *J* = 12.9 Hz, 1H), 3.64 (d, *J* = 11.2 Hz, 1H), 3.15 (ddd, *J* = 13.2, 11.1, 3.8 Hz, 1H), 2.70 – 2.67 (m, 2H), 2.51-2.46 (m, 1H), 1.67 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.18 (s, 3H), 1.03 (s, 3H). **^{13}C NMR** (151 MHz, 10% $(CD_3)_2CO$ in CD_3OD) δ 212.2, 175.6, 142.4, 141.0, 137.5, 135.4, 131.7, 127.3, 122.8, 112.5, 108.6, 107.4, 60.0, 52.9, 49.0, 46.9, 45.1, 42.4, 40.1, 38.3, 34.4, 30.0, 27.7, 24.4, 24.2, 10.1. **IR** (thin film) 3353, 2964, 2871, 2487, 1693, 1448, 1384, 1288, 1207, 746 cm^{-1}. $[\alpha]_D$ –26.7 (1.2 x10^{-3}, $CHCl_3$).



Hemiaminal ether 68: Mixture of **51** and **65** (330 mg, 0.87 mmol, 1.0 equiv) was dissolved in THF (8.7 mL) in a round-bottomed flask. To the solution was added NaHMDS (2.0 M in THF, 2.2 mL, 4.3 mmol, 5.0 equiv) at rt. After 10 min, methyl formate (2.6 mL, 43 mmol, 50 equiv) was added via syringe and the reaction mixture was allowed to stir for 10 min at rt. The reaction mixture was quenched with ammonium chloride (sat. aq.) (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (50 mL) and dried over sodium sulfate. The crude mixture was concentrated in vacuo and purified using SiO_2 gel column chromatography eluting with 2:1 hexanes/ethyl acetate then 1:1 hexanes/ethyl acetate to give the product as white solid (196 mg, 4.69 mmol, 54%). mp >260 °C **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 9.79 (s, 1H), 7.82 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.10 (d, *J* = 13.1 Hz, 1H), 5.60 (d, *J* = 13.1 Hz, 1H), 5.15 (s, 1H), 3.66 (d, *J* = 11.1 Hz, 1H), 3.38 (s, 3H), 2.88-2.76 (m, 4H), 2.59 (dd, *J* = 14.1, 3.0 Hz, 1H), 1.95 - 1.88 (m, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.08 (s, 3H). **^{13}C NMR** (101 MHz, $(CD_3)_2CO$) δ 211.4, 175.3, 141.1, 139.4, 136.9, 134.9, 127.8, 127.4, 122.0, 112.3, 108.3, 105.8, 87.2, 60.6, 56.3, 55.4, 46.3, 40.1, 39.4, 38.3, 38.0, 32.8, 28.9, 25.3, 24.6, 15.1. **IR** (thin film) 3401, 3365, 2964, 2931, 1708, 1452, 1364, 1086, 1052, 735 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{31}O_3N_2$ $[M+H]^+$: 419.2329. Found 419.2336. $[\alpha]_D$ –20.8 (c 2.6 x 10^{-3}, $CHCl_3$).

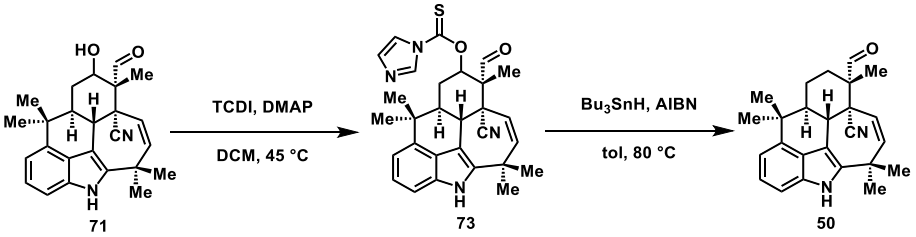


Hydroxy hemiaminal ether 69: Hemiaminal ether **68** (536 mg, 1.28 mmol, 1.0 equiv) was dissolved in MeOH (3 mL) in a round-bottomed flask and $NaBH_4$ (242 mg, 6.4 mmol, 5.0 equiv) was added all at once. After 1 h, the mixture was quenched with ammonium chloride solution (sat. aq., 30 mL) and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL) and dried over sodium sulfate. The crude mixture was concentrated in vacuo and isolated as an off-white solid. The crude product was taken forward to the next step without further purification.

β-Hydroxy aldehyde 71: To the round-bottomed flask containing crude alcohol **69** was added DCM (43 mL). The starting material does not fully dissolve and results in an off-white suspension. To this mixture, di-*tert*-butylpyridine (0.43 mL, 1.92 mmol, 1.5 equiv) was added via syringe and the reaction mixture was cooled to –78 °C. Tf_2O (12 mL) was added via syringe and the mixture was allowed to stir at –78 °C for 2.5 h at which time the reaction mixture was quenched with water (30 mL) at –78 °C. After stirring at –78 °C for 30 seconds, the flask was removed from the –78 °C bath and gradually warmed over 30 min. To the cold reaction mixture was added sodium

bicarbonate (sat. aq.) (100 mL) and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried over sodium sulfate. The crude mixture was concentrated in vacuo and purified using SiO_2 gel column chromatography on a Yamazen® automatic purification system. Pure aldehyde **71** was isolated as a white solid (340 mg, 0.880 mmol, 68% over 2 steps) along with triflate **72** as a white solid (60.0 mg, 0.120 mmol, 9%). **β-Hydroxy aldehyde 71 :** mp 218−222 °C (decomp). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.81 (s, 1H), 7.15 (d, *J* = 5.5 Hz, 2H), 7.02 (dd, *J* = 5.6, 2.5 Hz, 1H), 5.75 (d, *J* = 12.3 Hz, 1H), 5.50 (d, *J* = 12.3 Hz, 1H), 4.59 (dd, *J* = 11.6, 4.5 Hz, 1H), 3.28 (d, *J* = 11.4 Hz, 1H), 2.21 (dt, *J* = 12.7, 4.1 Hz, 1H), 2.14 - 2.10 (m, 1H), 2.01 (bs, 1H), 1.68 (q, *J* = 12.5 Hz, 1H), 1.61 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H), 1.15 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 204.1, 144.0, 140.0 135.7, 133.6, 126.0, 122.9, 122.8, 119.8, 113.0, 107.9, 105.7, 69.1, 56.1, 46.1, 45.4, 38.7, 38.2, 37.5, 32.9, 29.3, 28.1, 24.9, 24.6, 8.5. **IR** (thin film) 3408, 2966, 2930, 2867, 1727, 1471, 1450, 1333, 1084, 753 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for C25H29O2N2 $[M+H]^+$: 389.2224. Found 389.2229. $[\alpha]_D$ –165 (c 3.8 x 10^{-3}, $CHCl_3$).

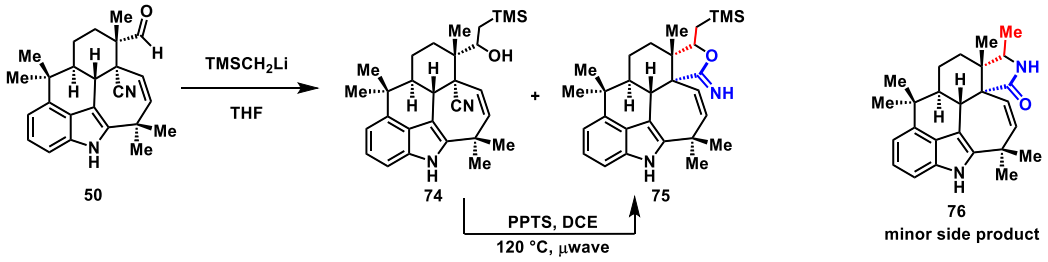
triflate 72: mp 134−141 °C (decomp). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.87 (br s, 1H), 7.20 – 7.14 (m, 2H), 7.03 (dd, *J* = 6.0, 2.1 Hz, 1H), 5.78 (d, *J* = 12.4 Hz, 1H), 5.77 (dd, *J* = 12.0, 4.4 Hz, 1H), 5.34 (d, *J* = 12.4 Hz, 1H), 3.33 (d, *J* = 11.4 Hz, 1H), 2.58 (ddd, *J* = 12.4, 4.8, 3.4 Hz, 1H), 2.23 (ddd, *J* = 13.3, 11.3, 3.4 Hz, 1H), 2.11 – 2.03 (m, 1H), 1.60 (s, 3H), 1.54 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.18 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 199.7, 144.8, 139.1, 135.9, 133.7, 125.7, 123.2, 121.2, 118.5, 118.4 (q, *J* = 319.35 Hz), 113.3, 108.2, 104.5, 86.6, 55.3, 46.2, 45.8, 38.8, 38.0, 37.8, 32.8, 28.0, 27.8, 24.8, 24.5, 9.2. **^{19}F NMR** (565 MHz, $CDCl_3$) δ −74.78. $[\alpha]_D$ –117 (c 1.3 x 10^{-3}, DCM).



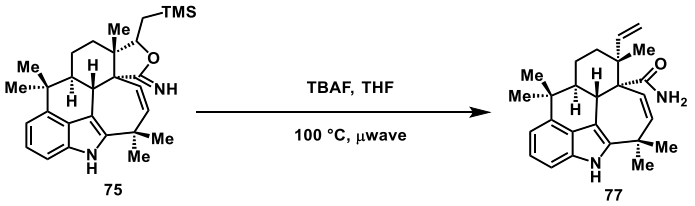
Thiocarbamate 73: Alcohol **71** (160 mg, 0.412 mmol, 1.0 equiv), DMAP (10 mg, 0.082 mmol, 0.2 equiv), in an oven-dried microwave vial were brought into a glovebox. TCDI (88 mg, 0.49 mmol, 1.0 equiv) and DCM (4 mL) were added and the vial was sealed. The reaction vessel was then removed from the glovebox and placed in an oil bath preheated to 45 °C and allowed to stir for 20 h. Once the vial had cooled to rt, the reaction mixture was concentrated in vacuo and immediately subjected to SiO_2 gel column chromatography on a Yamazen® automatic purification system. Pure thiocarbamate **73** was isolated as a white solid (160 mg, 0.32 mmol, 79%, 91% brsm). mp 245−254 °C (decomp). **^{1}H NMR** 183 (700 MHz, $(CD_3)_2CO$) δ 10.14 (br s, 1H), 10.04 (s, 1H), 8.36 (s, 1H), 7.74 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.48 (dd, *J* = 11.5, 4.6 Hz, 1H), 5.94 (d, *J* = 12.3 Hz, 1H), 5.58 (d, *J* = 12.3 Hz, 1H), 3.58 (d, *J* = 11.1 Hz, 1H), 2.76 - 2.73 (m, 1H), 2.19 (ddd, *J* = 13.9, 11.1, 3.1 Hz, 1H), 2.14 - 2.10 (m, 1H), 1.66 (s, 3H), 1.65 (s, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.20 (s, 3H). **^{13}C NMR** (176 MHz, $(CD_3)_2CO$) δ 201.9, 184.3, 145.6, 140.1, 137.6, 137.3, 135.0, 131.9, 126.6, 123.1, 122.6, 119.9, 119.1, 113.1, 108.9, 105.2, 81.9, 56.3, 47.4, 47.1, 39.6, 39.2, 38.3, 32.5, 27.8, 25.6, 25.1,

24.8, 10.5. **IR** (thin film) 3370, 2966, 2934, 1789, 1731, 1470, 1388, 1330, 1286, 1229 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{29}H_{31}O_2N_4S$ $[M+H]^+$:499.2162. Found 499.2152. $[\alpha]_D$ –73 (c 3.75 $x10^{-3}$, $CHCl_3$).

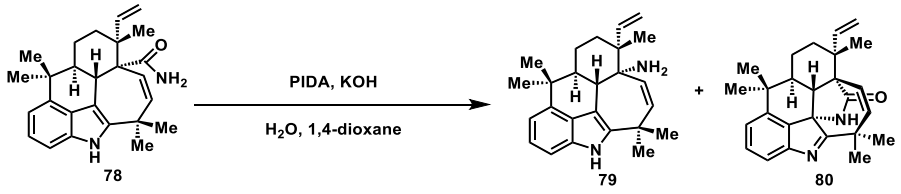
Deoxygenated aldehyde 50: Thiocarbamate **73** (160 mg, 0.32 mmol, 1.0 equiv) and AIBN (21 mg, 0.13 mmol, 0.4 equiv) were added as solids to an oven-dried round-bottomed flask. A N_2 inlet was placed in the septum and the flask was evacuated and backfilled with N_2 three times. Toluene (9 mL) was added via syringe, followed by $SnBu_3H$ (0.13 mL, 0.49 mmol, 1.5 equiv) and the reaction vessel was placed in an oil bath preheated to 80 °C. After 30 min at this temperature, the reaction mixture was allowed to cool to rt and the contents were concentrated in vacuo. The crude reaction mixture was immediately subjected to SiO_2 gel column chromatography on a Yamazen® automatic purification system. Aldehyde **50** was isolated as a white solid (66 mg, 55%). mp >260 °C. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.83 (s, 1H), 7.16 - 7.13 (m, 2H), 7.01 (dd, *J* = 6.4, 1.7 Hz, 1H), 5.71 (d, *J* = 12.5 Hz, 1H), 5.38 (d, *J* = 12.3 Hz, 1H), 3.31 (d, *J* = 11.0 Hz, 1H), 2.25 - 2.21 (m, 1H), 2.08 - 2.01 (m, 2H), 1.71 - 1.65 (m, 1H), 1.63-1.60 (m, 4H), 1.50 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 204.0, 143.7, 140.4, 135.6, 133.6, 126.0, 124.1, 122.7, 120.3, 112.8, 107.7, 106.5, 51.5, 47.5, 45.5, 38.7, 38.5, 37.4, 32.8, 29.6, 28.2, 24.9, 24.6, 19.5, 14.2. **IR** (thin film): 3369, 2964, 2929, 2868, 2251, 1725, 1451, 1169, 908, 731 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{29}ON_2$ $[M+H]^+$, 373.2274. Found 373.2278. $[\alpha]_D$ –141 (c 2.4 $x10^{-3}$, DCM).



Acetimidate 75: To a solution of **50** (79.7 mg, 0.214 mmol, 1.0 equiv) in THF (2.1 mL) was added $TMSCH_2Li$ (1.0 M solution in pentane, 1.1 mL, 1.07 mmol, 5.0 equiv). The solution was allowed to stir for 1 h at which time it was quenched with the addition of ammonium chloride (sat. aq.) (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to give a yellow foam likely consisting of **74** and **75**. The crude mixture was purified by SiO_2 gel preparative thin-layer chromatography (2:1 hexanes/ethyl acetate) to give **74** (39.3 mg, 0.0853 mmol, 40%) and **75** (44.2 mg, 0.0959 mmol, 45%), both as diastereomeric mixtures. The mixture of **74** was transferred to a microwave vial as a solution in DCE (2.4 mL). PPTS (107 mg, 42.6 mmol, 5.0 equiv) was added and the vial was sealed with a crimp-top cap. The vial was heated to 120 °C under microwave irradiation for 30 min. Once the vial had cooled to rt, the solution was poured into saturated aqueous sodium bicarbonate solution (5 mL) and the aqueous layer was extracted with DCM (3 x10 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude mixture of **75** as a yellow oil. The crude product was directly subjected to the next reaction without further purification.

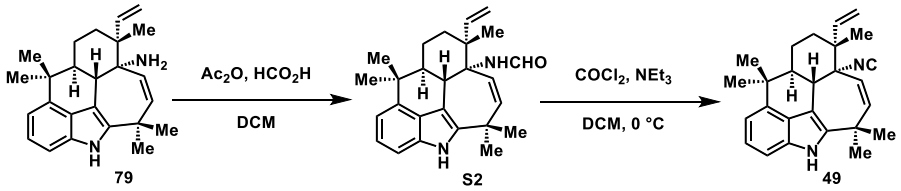


Amide 77: To a crude reaction mixture containing **75** in a microwave vial was added TBAF (1 M THF, 0.54 mL, 0.54 mmol, 3.0 equiv) and the vial was sealed. The resulting yellowish-brown solution was then heated to 100 °C under microwave irradiation for 1 h. Upon cooling to rt, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel column chromatography on a Yamazen® automatic purification system. Amide **77** was isolated as a glassy, off-white solid (61.5 mg, 0.158 mmol, 74% over 3 steps). mp >260 °C. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.11 – 7.02 (m, 2H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.16 (s, 1H), 5.98 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.84 (d, *J* = 13.1 Hz, 1H), 5.57 (d, *J* = 13.1 Hz, 1H), 5.27 (s, 1H), 5.17 (d, *J* = 17.4 Hz, 1H), 5.11 (d, *J* = 10.9 Hz, 1H), 3.36 (d, *J* = 11.3 Hz, 1H), 3.13 (ddd, *J* = 12.1, 3.6 Hz, 1H), 2.53 (ddd, *J* = 13.5, 4.4 Hz, 1H), 1.94 (dd, *J* = 13.1, 3.7 Hz, 1H), 1.62 (ddd, *J* = 13.4, 9.4 Hz, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.38 – 1.34 (m, 1H), 1.31 (s, 6H), 1.01 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 175.2, 146.2, 141.9, 140.2, 134.9, 133.8, 131.3, 126.7, 122.2, 1133, 112.2, 109.2, 107.2, 56.4, 43.5, 43.2, 38.9, 38.8, 37.3, 34.6, 33.8, 27.8, 24.3, 21.2, 19.3. **IR** (thin film) 3361, 3310, 3185, 2992, 1589, 1561, 1463, 1435 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{32}ON_2Na$ $[M+Na]^+$: 411.2407. Found 411.2409. $[\alpha]_D$ –196 (c 17.6 x10^{-3}, DCM).



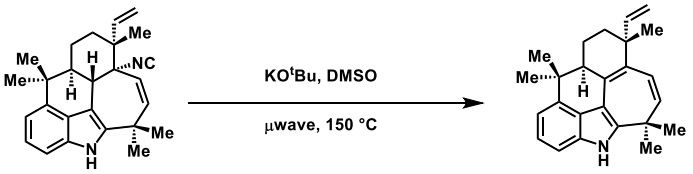
Vinyl amine 79 and Hofmann side product 80: Amide **78** (79 mg, 0.21 mmol, 1.0 equiv) was dissolved in 1,4-dioxane (4.1 mL) and H_2O (4.1 mL) was added. To this solution was added crushed KOH (402 mg, 7.18 mmol, 35 equiv) and the suspension was allowed to stir for 5 min at rt. At this time, PIDA (79 mg, 0.25 mmol, 1.2 equiv) was added and the solution turned light yellow. The suspension was allowed to stir at rt for 20 h at which time it was quenched with sodium bicarbonate (sat. aq.) (5 mL) and sodium thiosulfate (sat. aq.) (5 mL). After stirring for 5 min at rt, the mixture was diluted with ethyl acetate (10 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography eluting with a mixture of 10% acetone and 1% NH_4OH in DCM to yield the desired product (**79**, 29.0 mg, 0.0804 mmol, 39%)

as well as Hofmann side product **80** (9.1 mg, 0.028 mmol, 14%). **Amine product (79): ^{1}H NMR** (700 MHz, CD_3OD) δ 7.06 (d, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.20 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.93 (d, *J* = 13.1 Hz, 1H), 5.42 (d, *J* = 13.0 Hz, 1H), 5.19 - 5.15 (m, 2H), 3.41 (d, *J* = 11.4 Hz, 1H), 2.10 - 2.05 (m, 1H), 1.93 - 1.87 (m, 2H), 1.71 - 1.65 (m, 1H), 1.51 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.38 - 1.35 (m, 1H), 1.29 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (176 MHz, CD_3OD) δ 146.5, 142.0, 139.5, 137.0, 135.8, 134.8, 127.8, 122.8, 186 114.2, 112.4, 108.3, 107.1, 59.6, 46.3, 44.3, 41.1, 39.5, 38.0, 34.1, 32.9, 30.1, 25.1, 25.0, 22.3, 20.2. **IR** (thin film) 3500, 2963, 2926, 2854, 1467, 1449, 914, 744 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{33}N_2$ $[M+H]^+$: 361.2638. Found 361.2643. $[\alpha]_D$ –73.5 (c 2.0 x10^{-3}, MeOH). **Hofmann side product (80):** In a 4 mL vial, compound **80** (9 mg) was dissolved in a minimal amount of DCM (~0.5 mL). A layer of hexanes (~0.2 mL) was carefully added on top of the DCM solution. The mixture was lightly capped and allowed to crystallize in a freezer with minimal agitation. mp 118-122°C. See X-ray crystal structure data below. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.7 Hz, 1H), 7.27 (m, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.62 (d, *J* = 13.3 Hz, 1H), 5.45 (d, *J* = 13.3 Hz, 1H), 5.21 (d, *J* = 11.0 Hz, 1H), 5.17 – 5.14 (m, 2H), 2.35 (dd, *J* = 11.0, 1.6 Hz, 1H), 2.26 (ddd, *J* = 13.8, 10.9, 3.1 Hz, 1H), 1.91 (td, *J* = 13.4, 3.7 Hz, 1H), 1.84 (dq, *J* = 13.4, 3.4 Hz, 1H), 1.56 (m, 1H), 1.54 (s, 3H), 1.50 (dd, *J* = 13.1, 3.2 Hz, 1H), 1.47 (s, 3H) 1.46 (s, 3H), 1.13 (s, 3H), 0.94 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 192.9, 178.0, 155.5, 146.9, 144.6, 138.4, 131.5, 130.8, 128.1, 122.9, 117.3, 113.4, 70.0, 55.8, 47.6, 43.3, 42.6, 41.5, 38.1, 37.2, 31.7, 31.5, 27.3, 26.3, 20.3, 20.2. **IR** (thin film) 3223, 2966, 2927, 2854, 1697. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{31}ON_2$ $[M+H]^+$: 387.2431. Found 387.2437. $[\alpha]_D$ –216 (c 1.8 x10^{-3}, DCM).



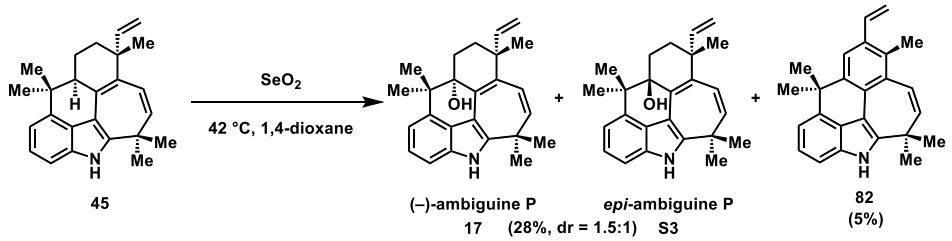
Formamide S2: To amine **79** (12 mg, 1.0 equiv) in a round-bottomed flask was added DCM (1 mL) followed by Ac_2O (56 µL, 0.59 mmol, 18 equiv) and formic acid (25 µL, 0.66 mmol, 20 equiv). This solution was allowed to stir at rt for 14 h. The solution was quenched with sodium bicarbonate (10 mL) and diluted with DCM (10 mL). The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, then concentrated in vacuo. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography eluting with a mixture of 2:1 hexanes/ethyl acetate to give the desired product (**S2**) as a clear film (13 mg, 0.033 mmol, 99%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 11.1 Hz, 1H), 7.95 (s, 1H), 7.18 - 7.04 (m, 2H), 6.97 (dd, *J* = 5.7, 2.6 Hz, 1H), 5.96 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.89 (d, *J* = 12.9 Hz, 1H), 5.82 (d, *J* = 11.7 Hz, 1H), 5.60 (d, *J* = 12.6 Hz, 1H), 5.27 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.5 Hz, 1H), 3.49 (d, *J* = 10.1 Hz, 1H), 1.92 - 1.88 (m, 1H), 1.81 - 1.77 (m, 1H), 1.72 - 1.64 (m, 2H), 1.50 - 1.47 (m, 1H), 1.47 (s, 3H) 1.40 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.11 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 166.5, 143.7, 141.5, 140.5, 135.8, 133.6, 129.0, 126.5, 122.3, 116.1, 112.4, 107.6, 106.0, 60.9, 45.5, 44.2, 39.6, 38.2, 37.5, 33.2, 33.0, 28.0, 24.6, 24.5, 20.6, 19.8. **IR** (thin film) 3297, 2965, 2926, 2868, 1669, 1453, 1337, 761, 739 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{32}ON_2Na$ $[M+Na]^+$: 411.2407. Found 411.2399. $[\alpha]_D$ –121 (c 3.5 x10^{-3}, $CHCl_3$)

Isonitrile (49): Crude formamide **S2** (6.8 mg, 0.018 mmol, 1.0 equiv) was dissolved in DCM (1 mL) and the reaction mixture was cooled to 0 °C. NEt_3 (49 µL, 0.035 mmol, 20 equiv) was added followed by phosgene (20% in toluene, 46 µL, 0.088 mmol, 5.0 equiv). After stirring for 10 min at 0 °C, the reaction mixture was quenched with sodium bicarbonate (5 mL) and diluted with DCM (5 mL). The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated in vacuo. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography eluting with a mixture of 2:1 hexanes/ethyl acetate to yield the desired product (**49**) as an off-white solid (6.3 mg, 0.017 mmol, 97%). mp 198−216 °C. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.12 (d, *J* = 4.0 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.23 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.67 (d, *J* = 12.6 Hz, 1H), 5.61 (d, *J* = 12.6 Hz, 1H), 5.28 (d, *J* = 10.9 Hz, 1H), 5.24 (d, *J* = 17.5 Hz, 1H), 3.37 (dt, *J* = 11.1, 3.3 Hz, 1H), 2.08 - 2.03 (m, 1H), 2.02 - 1.98 (m, 1H), 1.91 - 1.89 (m, 1H), 1.68 - 1.62 (m, 1H), 1.59 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.29 (s, 3H), 1.24 - 1.20 (m, 1H), 1.14 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 156.2, 143.8, 142.4, 140.9, 135.2, 133.6, 127.0, 126.6, 122.3, 115.2, 112.5, 107.5, 106.6, 67.6, 45.8, 43.2, 39.4, 38.3, 37.3, 33.7, 32.9, 27.9, 25.1, 24.6, 20.6, 17.7. **IR** (thin film) 3344, 2923, 2854, 2124, 1719, 1636, 1454, 730 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{30}N_2$ $[M–HNC+H]^+$: 344.2373. Found 344.2372. $[\alpha]_D$ –181 (c 3.5 x10^{-3}, DCM).



49 45

Deoxy-ambiguine P (45): Isonitrile **49** (3.5 mg, 0.0094 mmol, 1.0 equiv) and KO^{t}Bu (11 mg, 0.094 mmol) were placed in a 1 mL microwave vial with DMSO (0.5 mL), and subjected to microwave irradiation at 150 °C. Upon cooling to rt, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with H_2O (3 x 5 mL). The aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate and concentrated in vacuo. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography eluting with a mixture of 2:1 hexanes/ethyl acetate to yield the pure product as an off-white solid (2.5 mg, 0.0073 mmol, 77%). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.16 - 7.13 (m, 2H), 7.03 (dd, *J* = 5.3, 2.6 Hz, 1H), 5.93 (dd, *J* = 11.4, 1.0 Hz, 1H), 5.86 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.34 (dd, *J* = 11.4, 1.0 Hz, 1H), 5.09 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.03 (dd, *J* = 10.6, 1.4 Hz, 1H), 2.89 (dd, *J* = 11.2, 7.0 Hz, 1H), 2.00 - 1.96 (m, 1H), 1.95 - 1.89 (m, 1H), 1.73 - 1.69 (m, 1H), 1.66 - 1.63 (m, 1H), 1.65 (s, 3H) 1.54 (s, 3H), 1.41 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 149.2, 140.8, 138.1, 134.8, 132.9, 130.1, 129.4, 128.2, 125.5, 122.7, 113.4, 110.9, 110.3, 108.1, 46.7, 40.3, 39.6, 36.8, 35.3, 26.9, 25.7, 25.0, 23.7, 23.6, 19.8. **IR** (thin film): 3419, 3003, 2923, 2330, 1570, 1470, 909, 748 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{30}N_2$ $[M+H]^+$: 344.2373. Found 344.2372. $[\alpha]_D$ –15.5 (c 2.0 x 10^{-3} DCM).



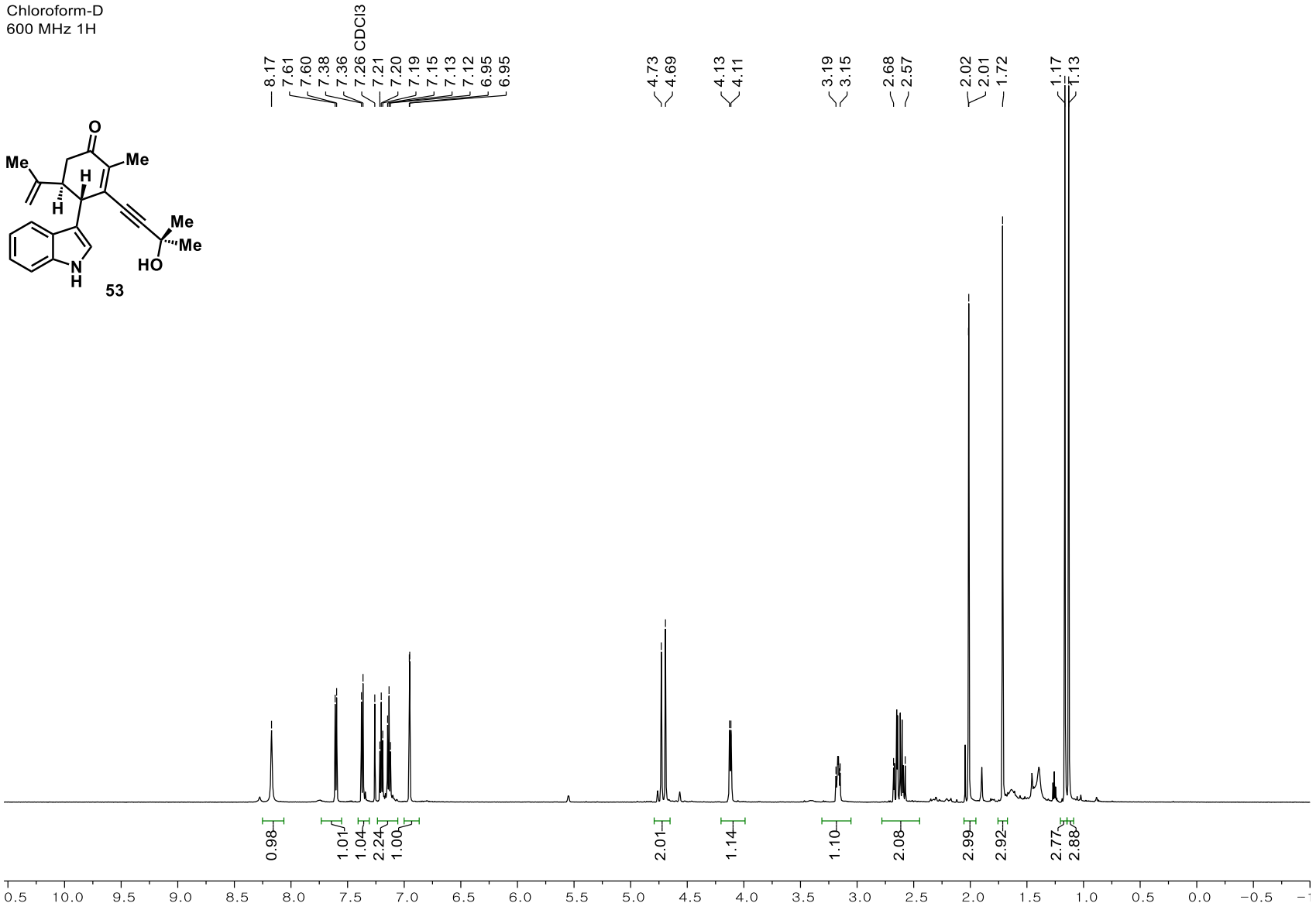
(–)-Ambiguine P (17): Deoxy-ambiguine P **45** (0.013 mmol, 4.4 mg, 1.0 equiv) was dissolved in 1,4-dioxane (0.05 M, 0.26 mL) and SeO_2 (0.026 mmol, 2.8 mg, 2.0 equiv) was added. The 4-mL vial was placed in a pre-heated aluminum heating block at 42 °C and allowed to stir at this temperature for 10 h. The vial was removed from the aluminum heating block and allowed to cool to rt. The crude mixture was quenched with saturated sodium thiosulfate solution, and the aqueous layer was extracted with ethyl acetate (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over sodium sulfate then concentrated in vacuo. The crude product was purified using Al_3O_2 preparatory thin-layer chromatography eluting multiple times with 2:1 hexanes/DCM until separation of the diastereomers was observed. Isolation of the bands gave (–)-ambiguine P (**17**) (0.8 mg, 0.002 mmol, 17%) and epi-ambiguine P (**S3**, 0.5 mg, 0.001 mmol, 11%) as white solids. Over-oxidation side product **82** (0.2 mg, 5 x 10^{-4} mmol, 5%) and starting material (**45**) (0.5 mg, 0.001, 11%) were also isolated from this mixture. **(–)-Ambiguine P (17): ^{1}H NMR** (900 MHz, CD_3OD) δ 7.16 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 8.0, 7.1 Hz, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 5.93 (d, *J* = 11.4 Hz, 1H), 5.89 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.40 (d, *J* = 11.4 Hz, 1H), 5.11 (dd, *J* = 10.6, 1.8 Hz, 1H), 4.93 (dd, *J* = 17.4, 1.8 Hz, 1H), 2.17 – 2.13 (m, 1H), 1.96 (ddd, *J* = 14.3, 13.2, 2.7 Hz, 1H), 1.79 (ddd, *J* = 13.4, 4.0, 2.7 Hz, 1H), 1.68 (s, 3H), 1.60 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.53 (s, 3H), 1.23 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H). **^{13}C NMR** (226 MHz, CD_3OD) δ 146.9, 142.1, 139.2, 134.9, 133.9, 133.5, 133.2, 128.6, 125.6, 123.5, 114.8, 114.6, 109.6, 108.8, 77.2, 45.9, 42.5, 36.7, 34.0, 29.2, 28.9, 27.5, 27.1, 26.4, 18.6. **IR** (thin film): 3331, 2966, 2349, 1458, 1318, 1032, 916, 751 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{30}ON$ $[M+H]^+$: 360.2322. Found 360.2319. $[\alpha]_D$ –48 (c 4.5 x 10^{-4}, MeOH) All spectroscopic data matches that for the natural product (**17**) as reported by Orjala et. al.[2] ***epi*-ambiguine P (S3): ^{1}H NMR** (900 MHz, CD_3OD) δ 7.16 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 5.89 (d, *J* = 11.4 Hz, 1H), 5.87 (dd, *J* = 17.6, 10.7 Hz, 1H), 5.34 (d, *J* = 11.4 Hz, 1H), 5.11 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.7, 1.4 Hz, 1H), 2.31 (td, *J* = 14.2, 3.3 Hz, 1H), 2.05 (td, *J* = 13.9, 3.2 Hz, 1H), 1.91 (dt, *J* = 13.7, 3.4 Hz, 1H), 1.66 (s, 3H), 1.56 (s, 3H), 1.49 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.39 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H). **^{13}C NMR** (226 MHz, CD_3OD) δ 150.0, 141.9, 139.0, 135.3, 135.0, 133.0, 131.9, 128.6, 125.6, 123.5, 114.9, 111.4, 109.6, 108.7, 77.0, 45.7, 41.5, 36.7, 34.1, 29.0, 27.6, 27.4, 26.5, 23.0, 18.5. IR (thin film) 3206, 2966, 2359, 1576, 1485, 902, 693 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{30}ON$ $[M+H]^+$: 360.2322. Found 360.2318. $[\alpha]_D$ +6.7 (c 3.0 x 10^{-4}, MeOH). **Aromatized product (82): ^{1}H NMR** (900 MHz, CD_3OD) δ 7.61 (s, 1H), 7.15 – 7.10 (m, 3H), 7.02 (d, *J* = 6.9 Hz, 1H), 6.64 (d, *J* = 12.5 Hz, 1H), 5.65 (d, *J* = 12.5 Hz, 1H), 5.59 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.27 (dd, *J* = 10.9, 1.5 Hz, 1H), 2.37 (s, 3H), 1.66 (s, 6H), 1.48 (s, 6H). **^{13}C NMR** (226 MHz, CD_3OD) δ 143.4, 140.5, 139.0, 137.7, 136.4, 135.1, 134.8, 132.9, 131.5, 130.0, 126.8, 126.3, 125.7, 124.1, 115.3, 114.6, 108.4, 107.7, 40.6, 38.2, 35.1, 30.5, 16.1. **IR** (thin film) 3432, 2963, 2923, 2858, 2349, 1570, 1457, 1125, 905, 752 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{26}N$ $[M+H]^+$: 340.2060. Found 340.2058.

References

1. Baran, P.S.; Richter, J.M. Direct Coupling of Indoles with Carbonyl Compounds: Short, Enantioselective, Gram-Scale Synthetic Entry into the Hapalindole and Fischerindole Alkaloid Families *J. Am. Chem. Soc.* **2004**, *126*, 7450.

2. Mo, S.; Krunic, A.; Chlipala, G.; Orjala, J. Antimicrobial ambiguine isonitriles from the cyanobacterium *Fischerella ambigua. J. Nat. Prod.* **2009**, *72*, 894.

2.7 Appendix to Chapter 2: Spectra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2.02
2.01
1.72
1.17
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Me
Me
H
H
O
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Me
HO
N
H
53
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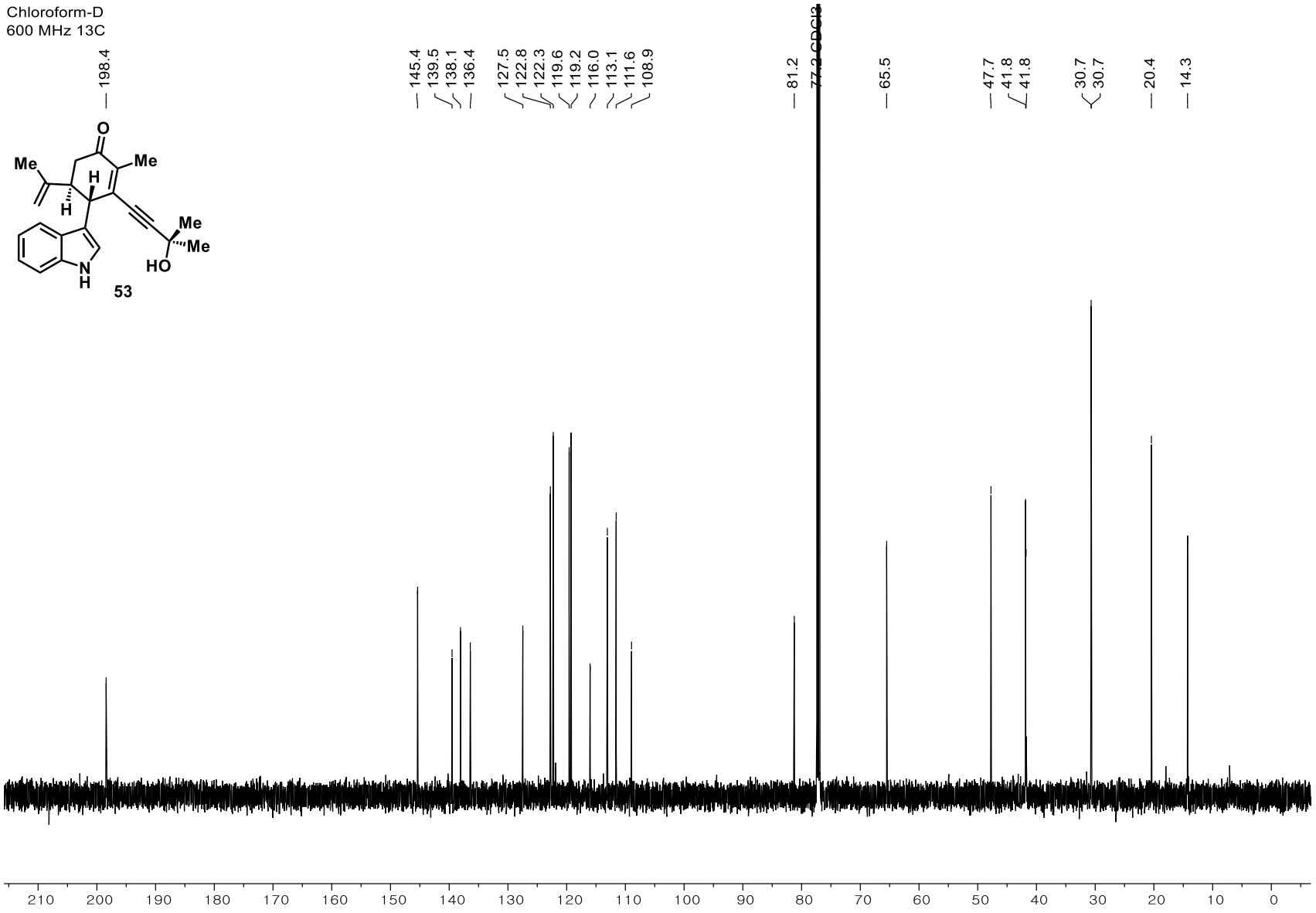
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H
Me
Me
HO
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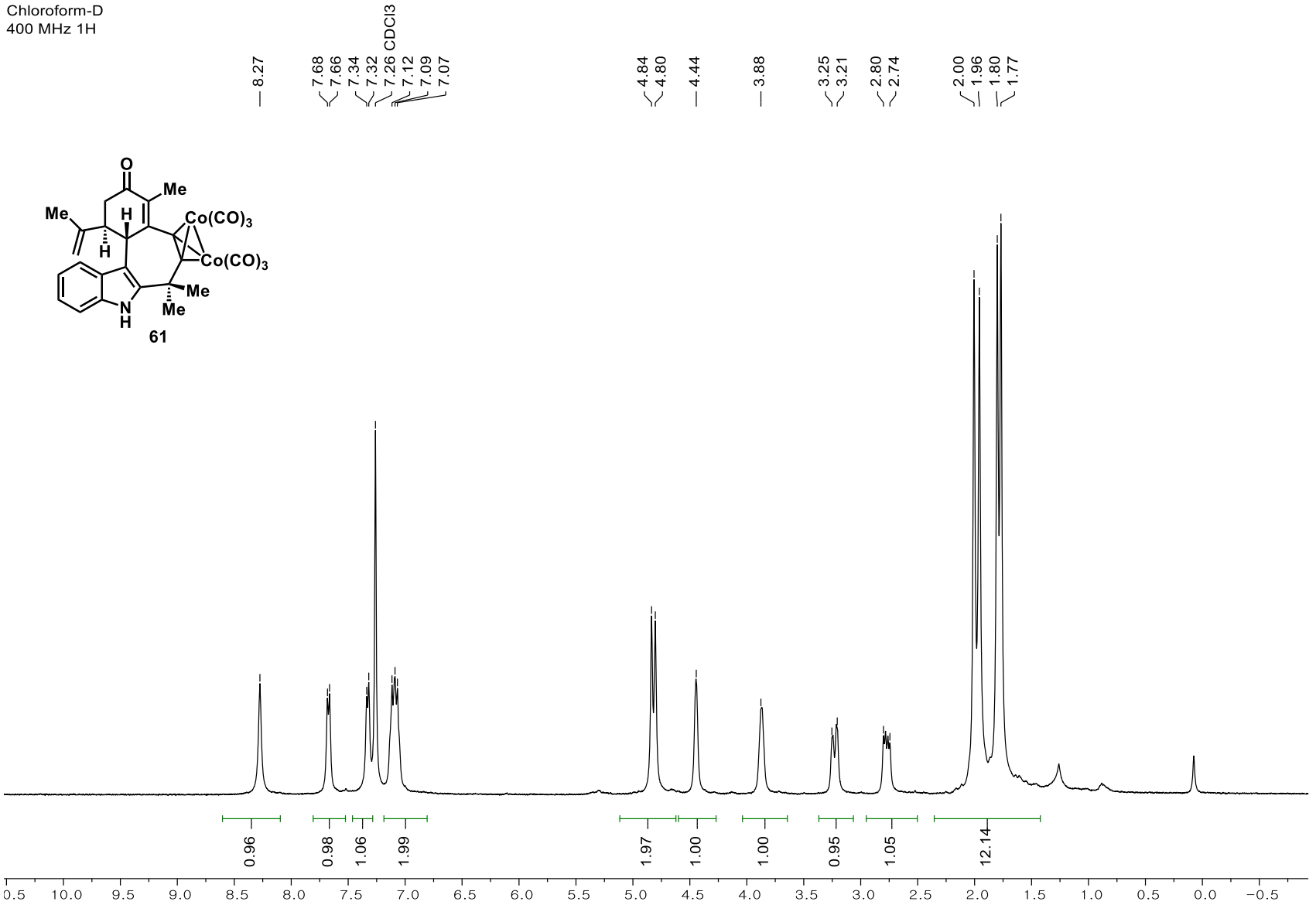
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2.74
2.00
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1.77
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H
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H
Co(CO)3
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1.00
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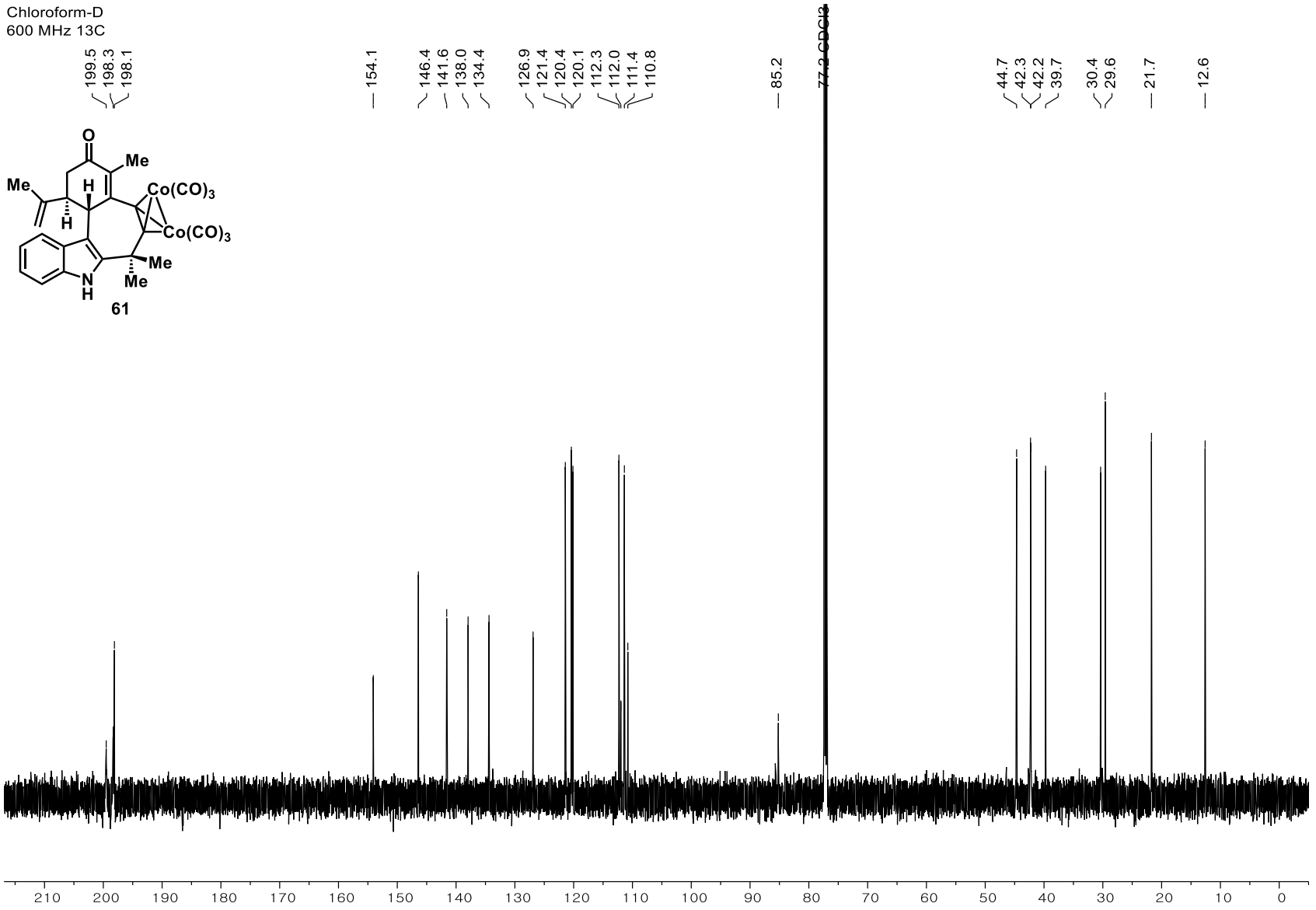
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120.4
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H
Co(CO)3
H
Co(CO)3
Me
N
H
Me
61
210
200
190
180
170
160
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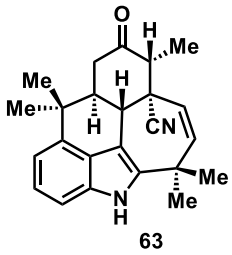
Chloroform-D
600 MHz 1H



63

Chloroform-D
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63

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119.1
113.2
108.0
106.4
77.2 CDCl3
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49.9
48.5
44.0
41.8
38.2
37.9
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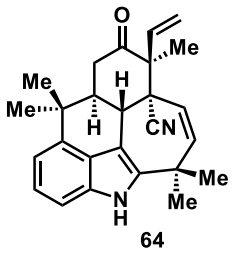

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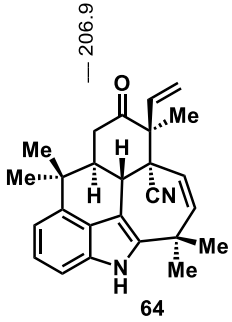
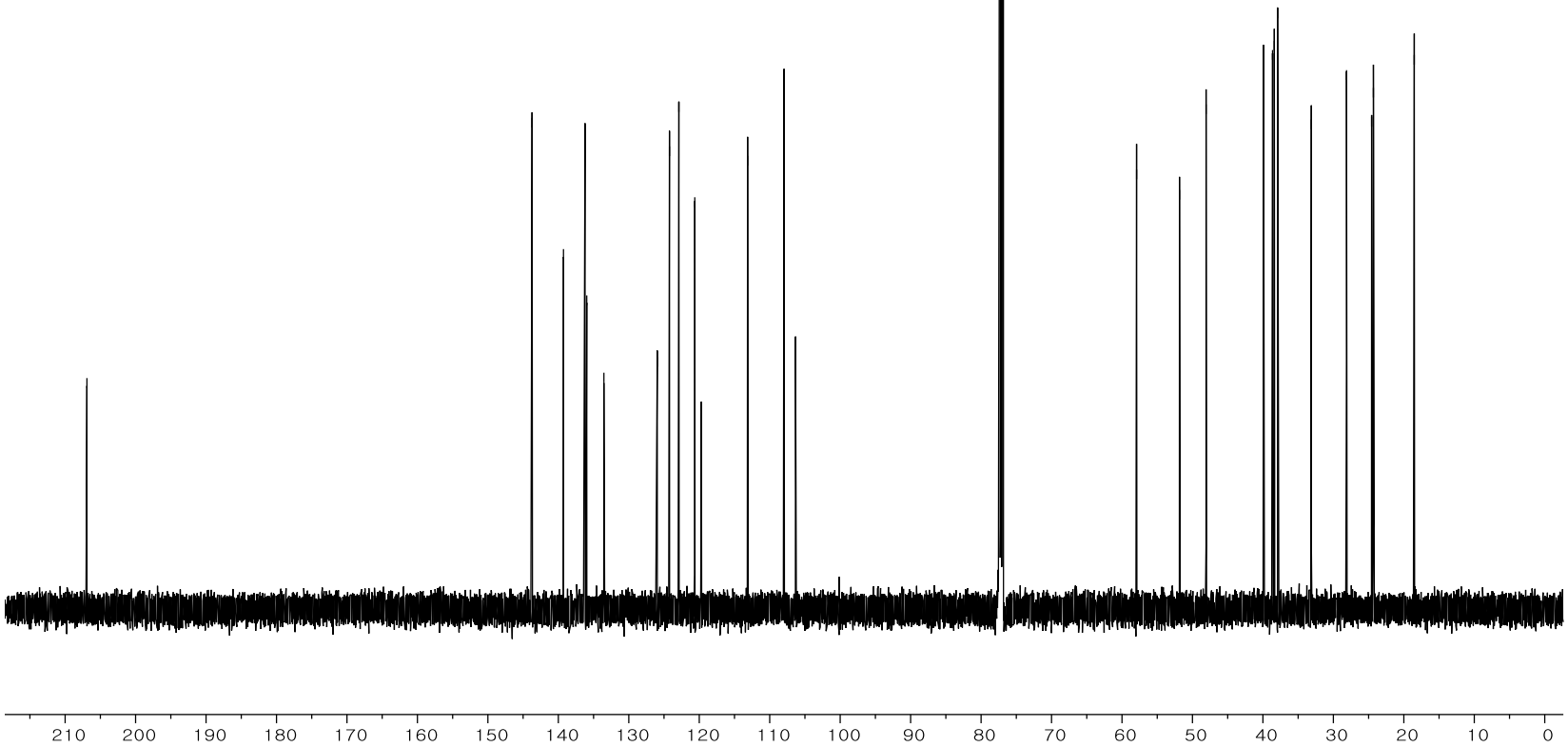
Chloroform-D
600 MHz 13C

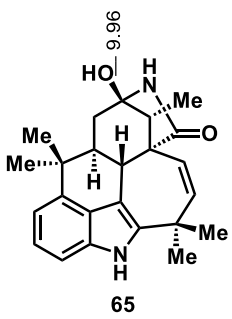


64

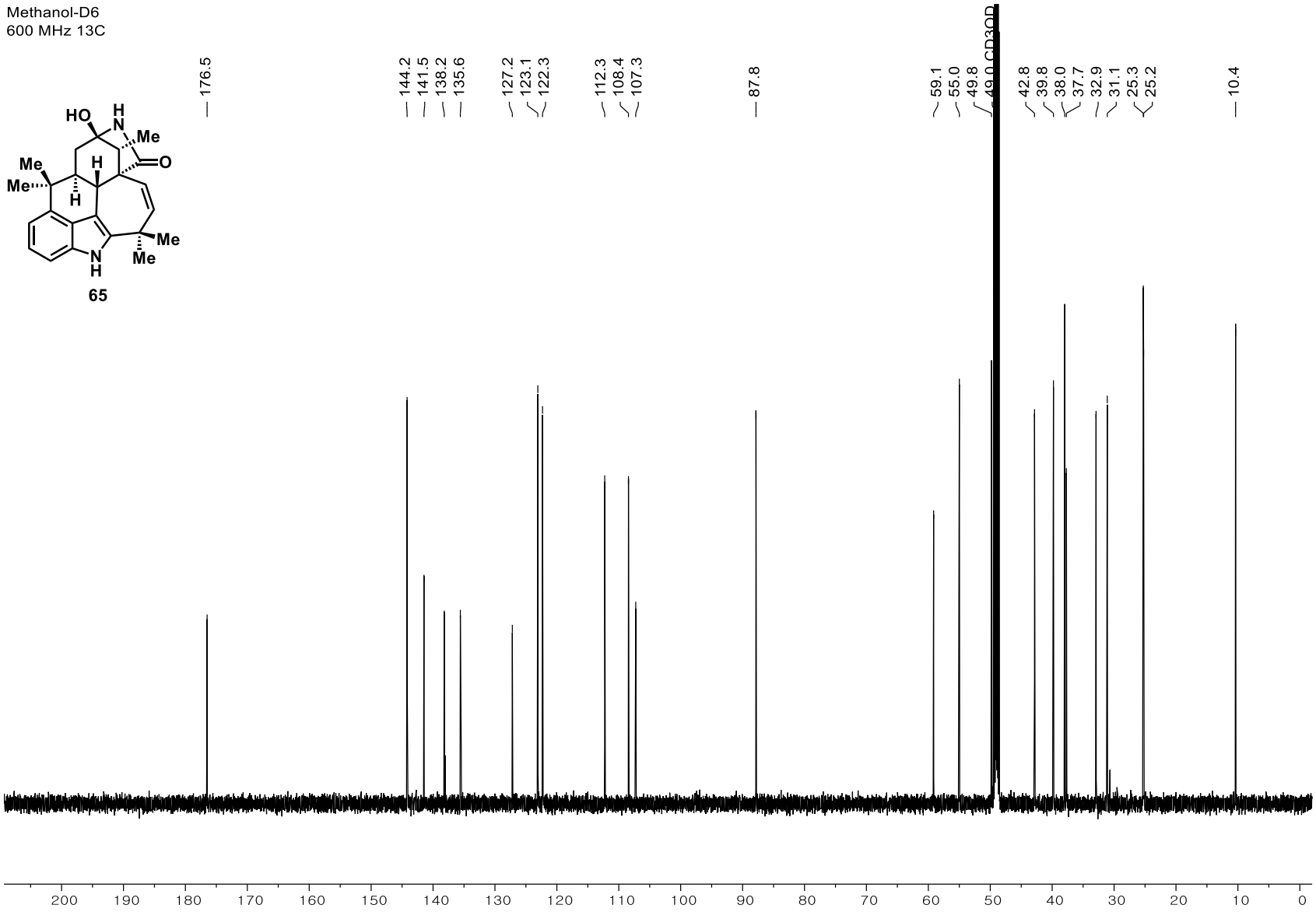
206.9
143.7
139.3
136.2
136.0
133.5
126.0
124.2
122.9
120.6
119.7
113.1
108.0
106.3
77.2 CDCl3
57.9
51.8
48.1
39.9
38.6
38.4
37.9
33.1
28.1
24.6
24.3
18.5



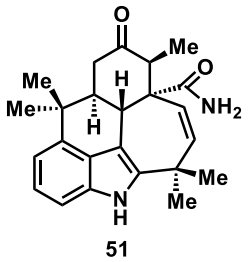
Methanol-D6
600 MHz 1H



65


Methanol-D6
600 MHz 13C
HO
H
N
Me
O
Me
Me
H
H
Me
Me
N
H
65
176.5
144.2
141.5
138.2
135.6
127.2
123.1
122.3
112.3
108.4
107.3
87.8
59.1
55.0
49.8
49.0 CD3OD
42.8
39.8
38.0
37.7
32.9
31.1
25.3
25.2
10.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Methanol-D6 + Acetone-D6
600 MHz 1H



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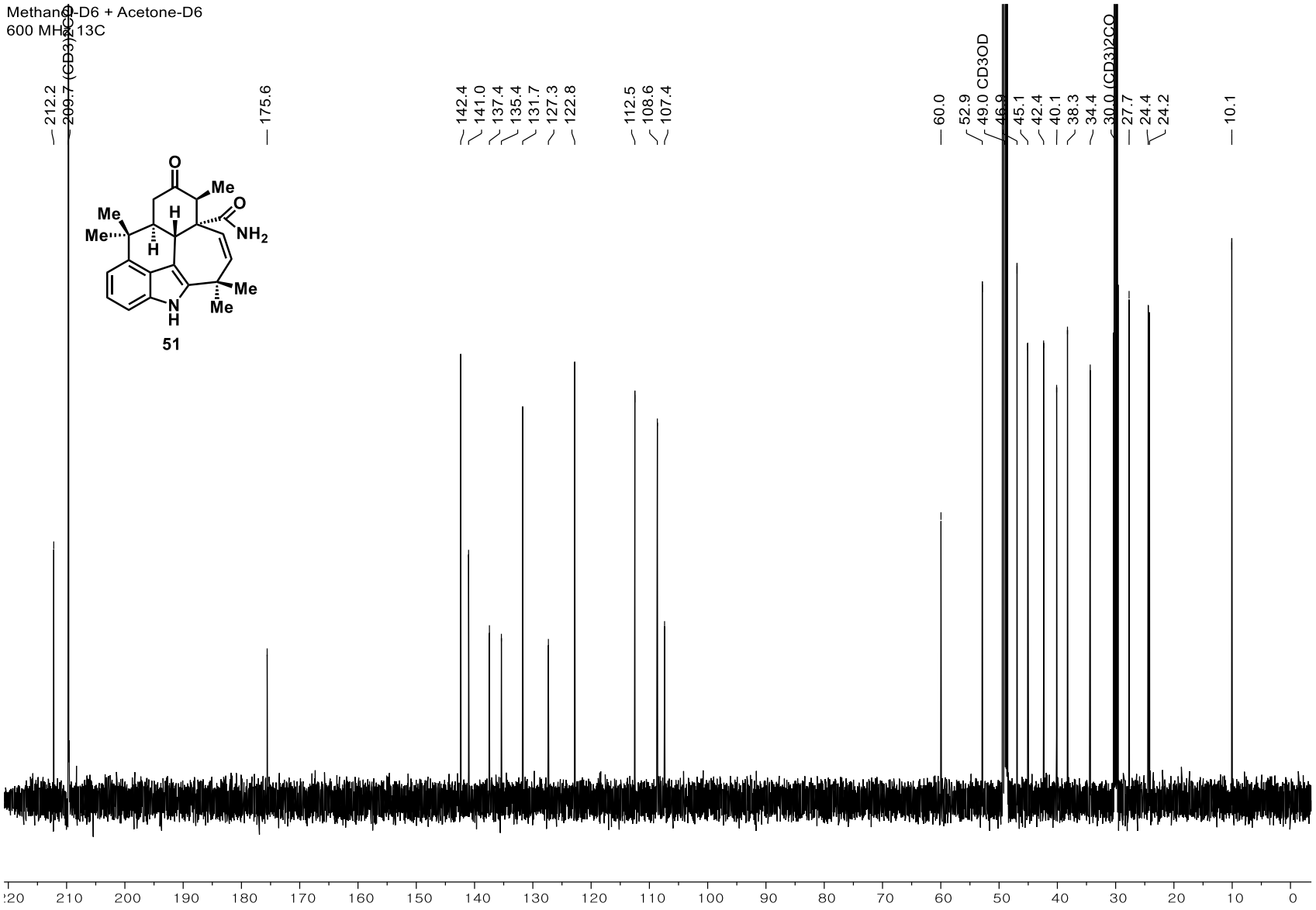
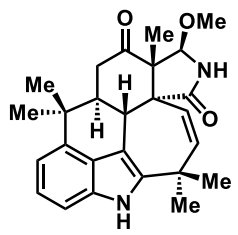

Methanol-D6 + Acetone-D6
600 MHz 13C
212.2
209.7 (CD3)2CO
175.6
142.4
141.0
137.4
135.4
131.7
127.3
122.8
112.5
108.6
107.4
60.0
52.9
49.0 CD3OD
46.9
45.1
42.4
40.1
38.3
34.4
30.0 (CD3)2CO
27.7
24.4
24.2
10.1
O
Me
O
Me
H
NH2
Me
H
Me
Me
N
H
Me
51
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Acetone-D6
400 MHz 1H



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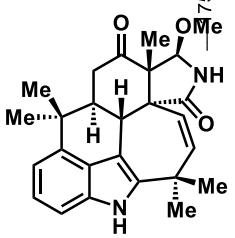
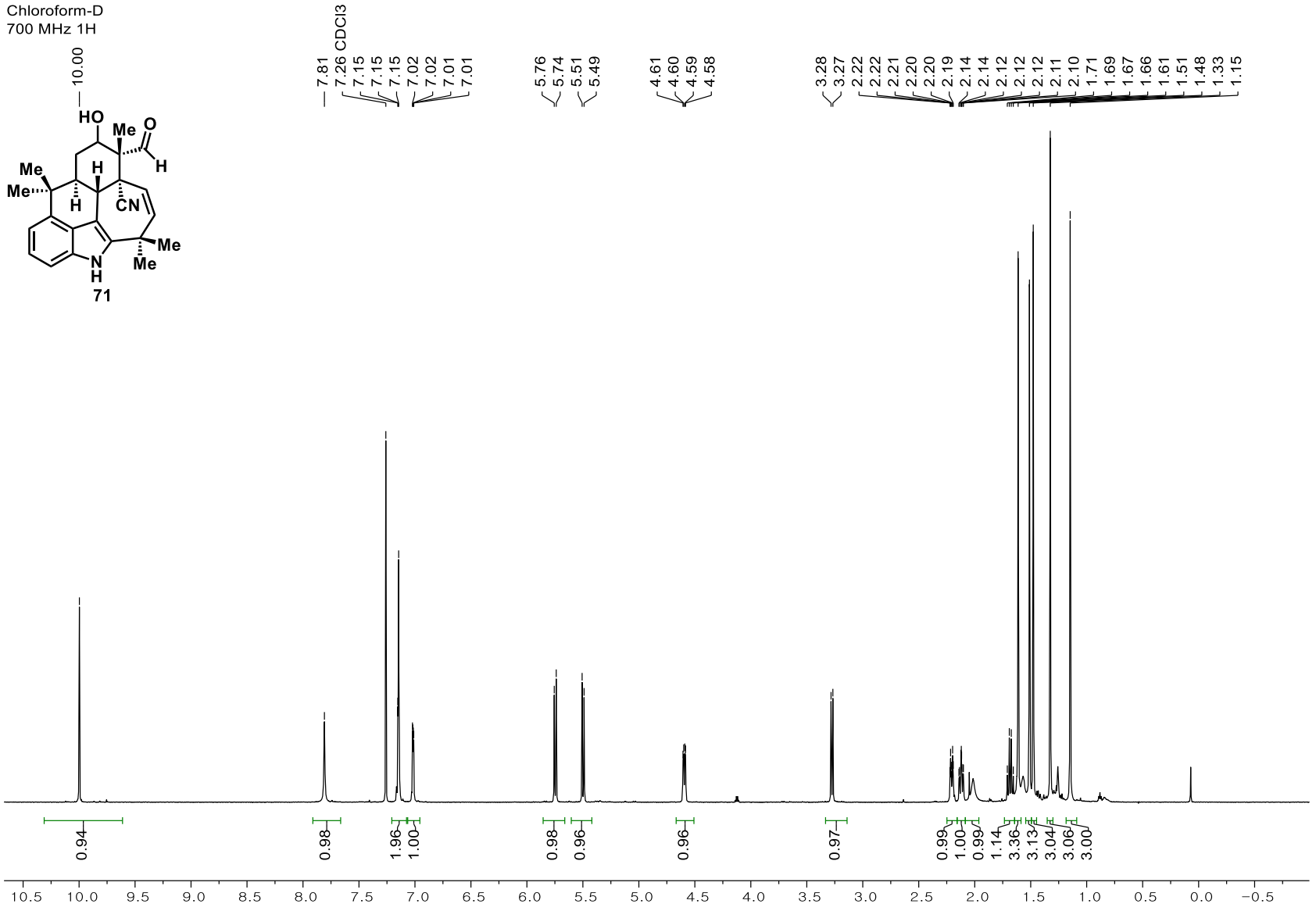
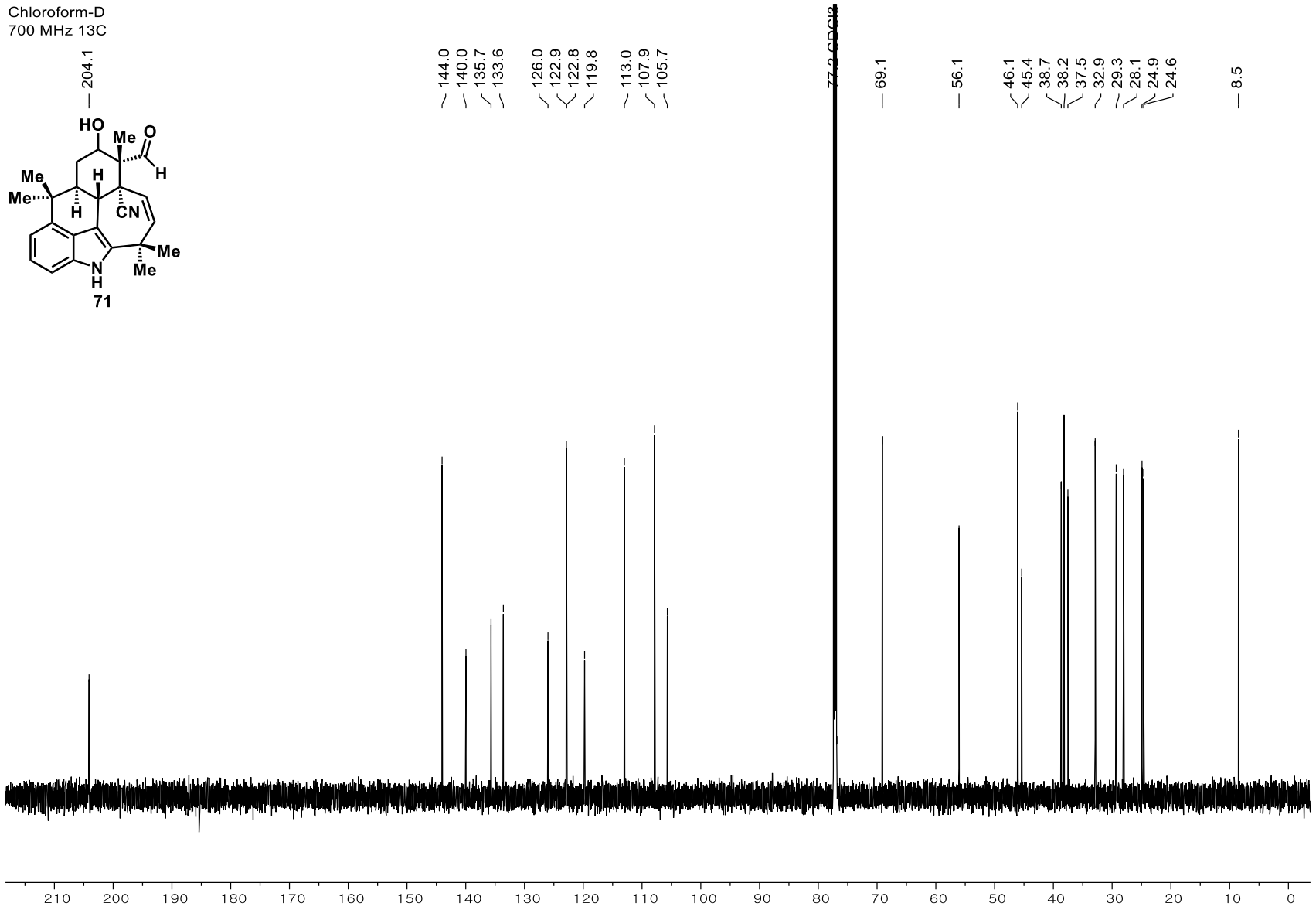
Acetone-D6
400 MHz, 13C

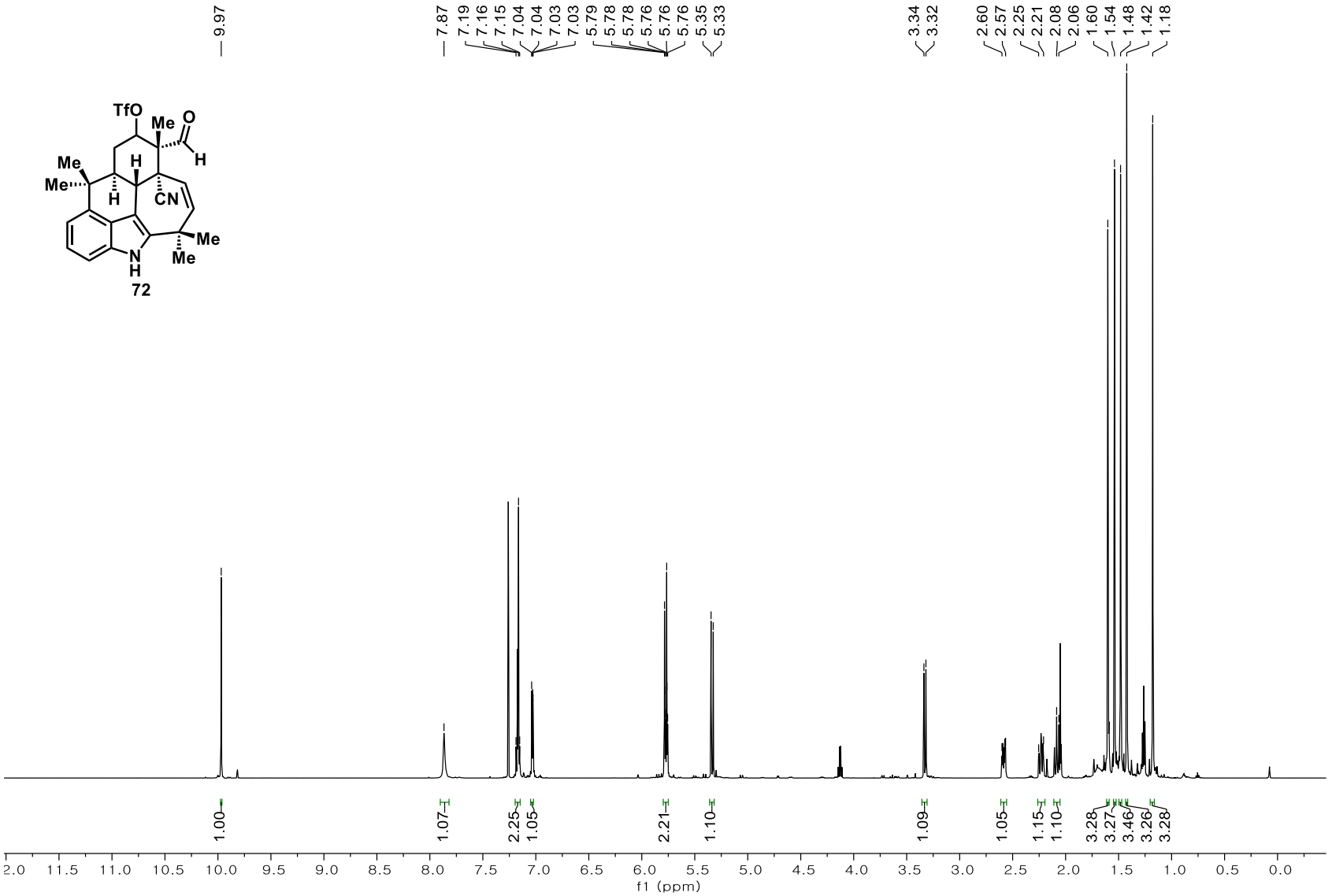


68

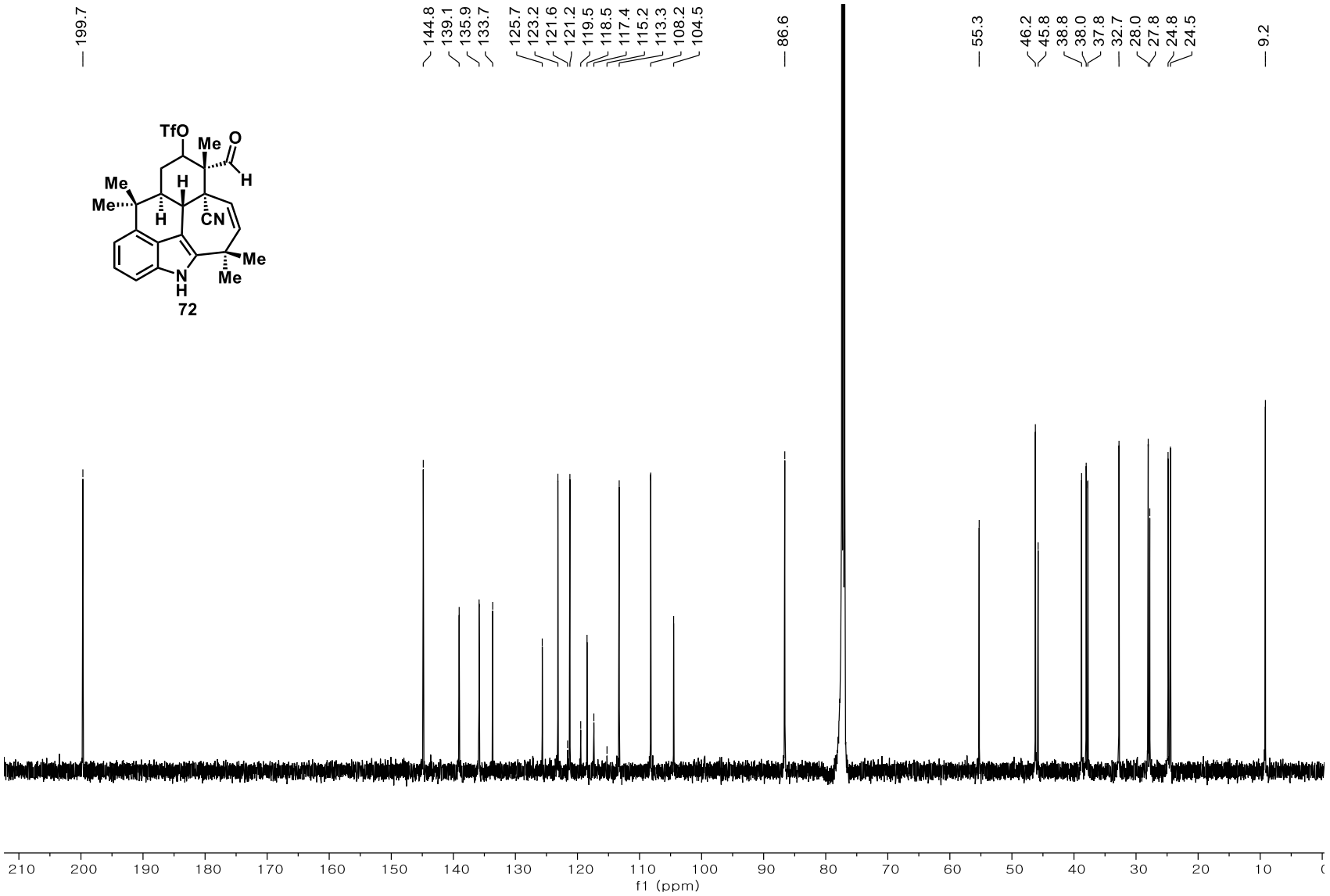

Chloroform-D
700 MHz 1H
10.00
HO
Me
O
H
Me
Me
H
H
CN
Me
Me
N
H
71
7.81
7.26 CDCl3
7.15
7.15
7.15
7.02
7.02
7.01
7.01
5.76
5.74
5.51
5.49
4.61
4.60
4.59
4.58
3.28
3.27
2.22
2.22
2.21
2.20
2.20
2.19
2.14
2.14
2.12
2.12
2.12
2.11
2.10
1.71
1.69
1.67
1.66
1.61
1.51
1.48
1.33
1.15
0.94
0.98
1.96
1.00
0.98
0.96
0.96
0.97
0.99
1.00
0.99
1.14
3.36
3.13
3.04
3.06
3.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5


Chloroform-D
700 MHz 13C
204.1
144.0
140.0
135.7
133.6
126.0
122.9
122.8
119.8
113.0
107.9
105.7
77.2 CDCl3
69.1
56.1
46.1
45.4
38.7
38.2
37.5
32.9
29.3
28.1
24.9
24.6
8.5
HO
Me
O
H
Me
Me
H
H
CN
Me
N
H
Me
71
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

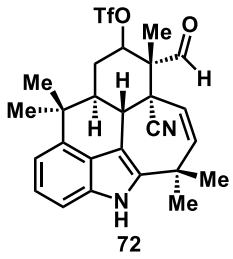
Ree4-42A.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



IV-36AB.2.fid — 13C{1H} starting parameters - HC 06/17/2019



IV-36AB.3.fid — 19F starting parameters - HC 06/17/2019 — No decoupling



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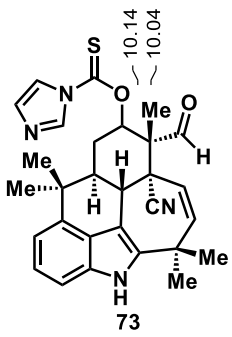
Acetone-D6
700 MHz 1H



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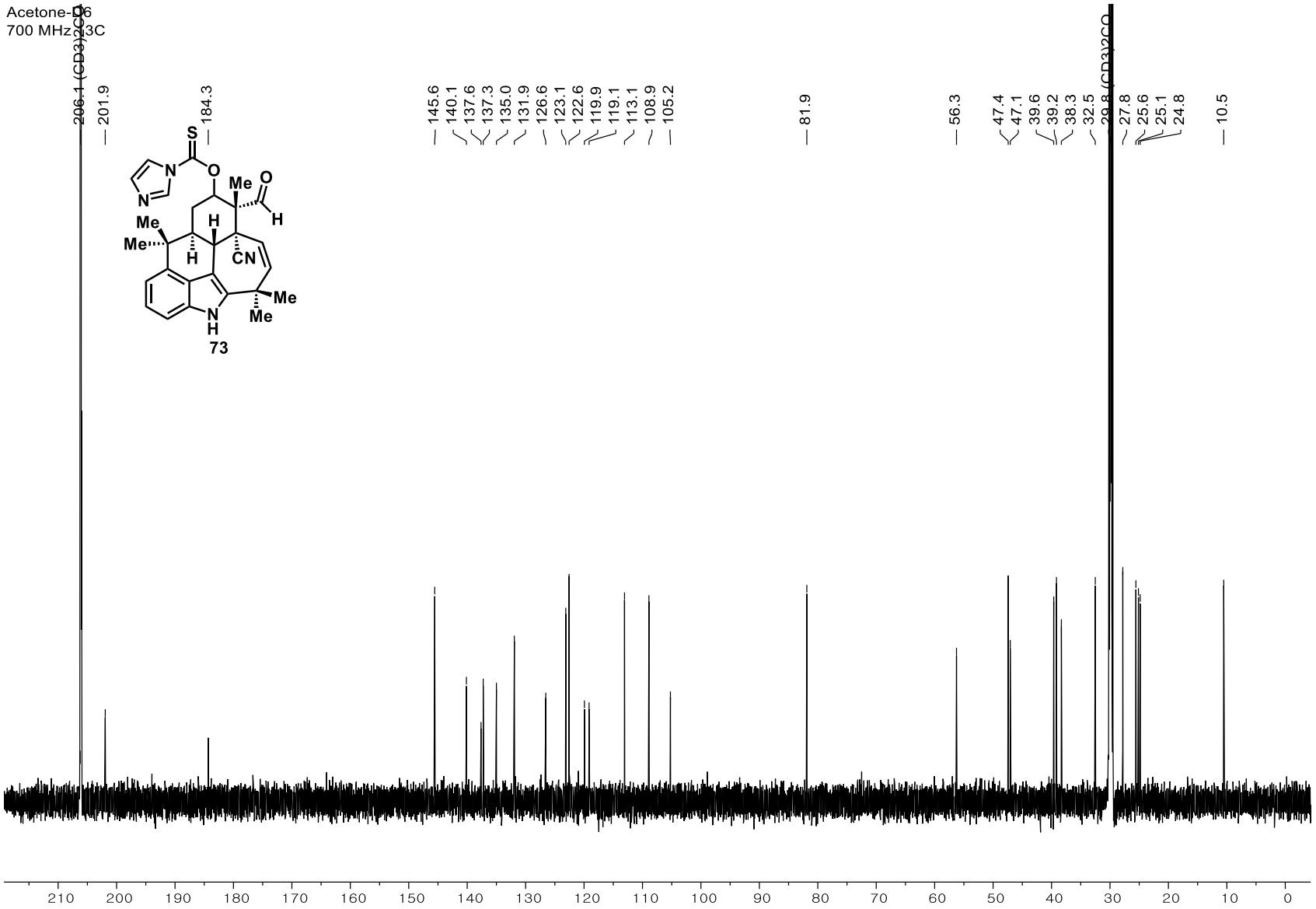
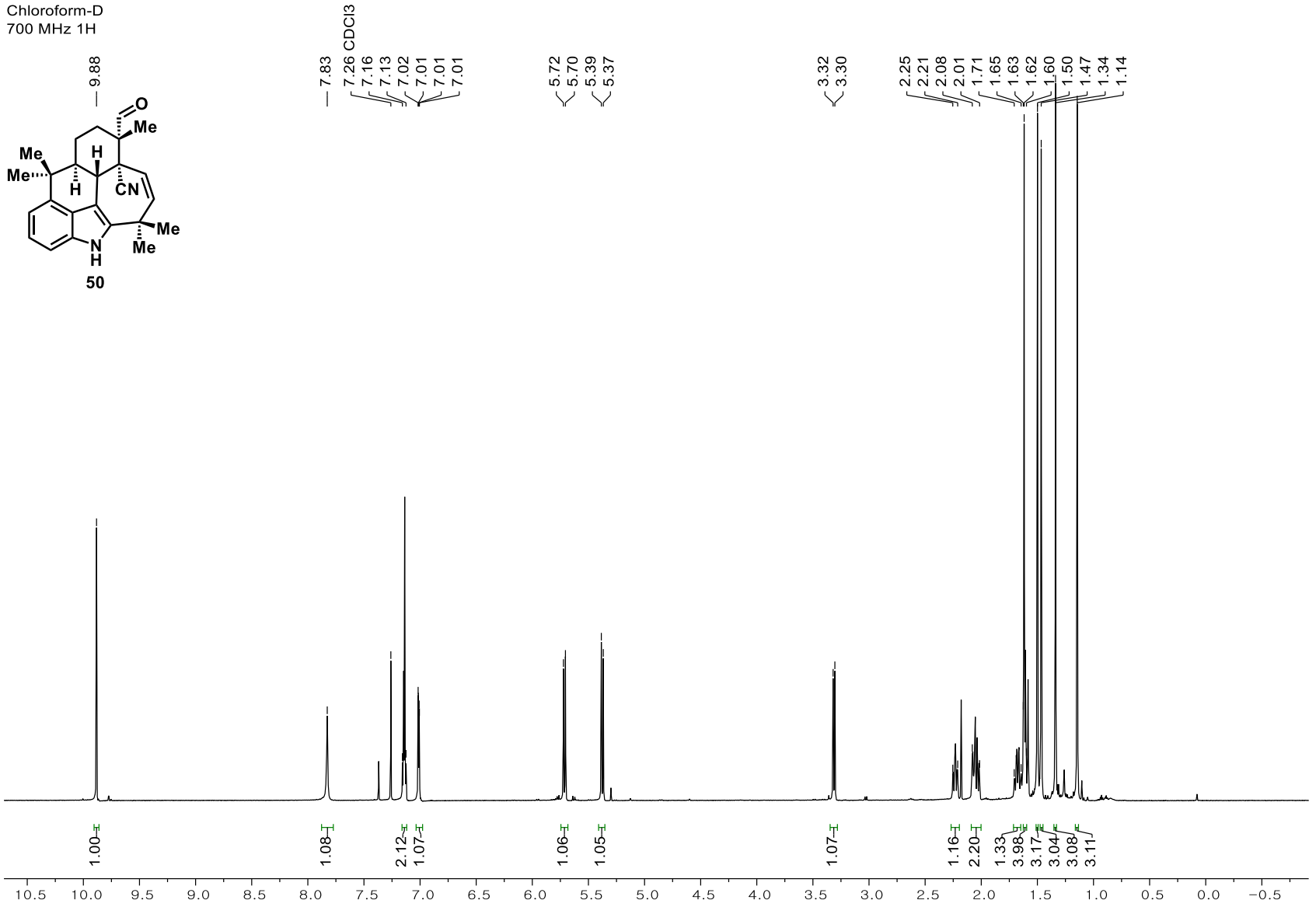
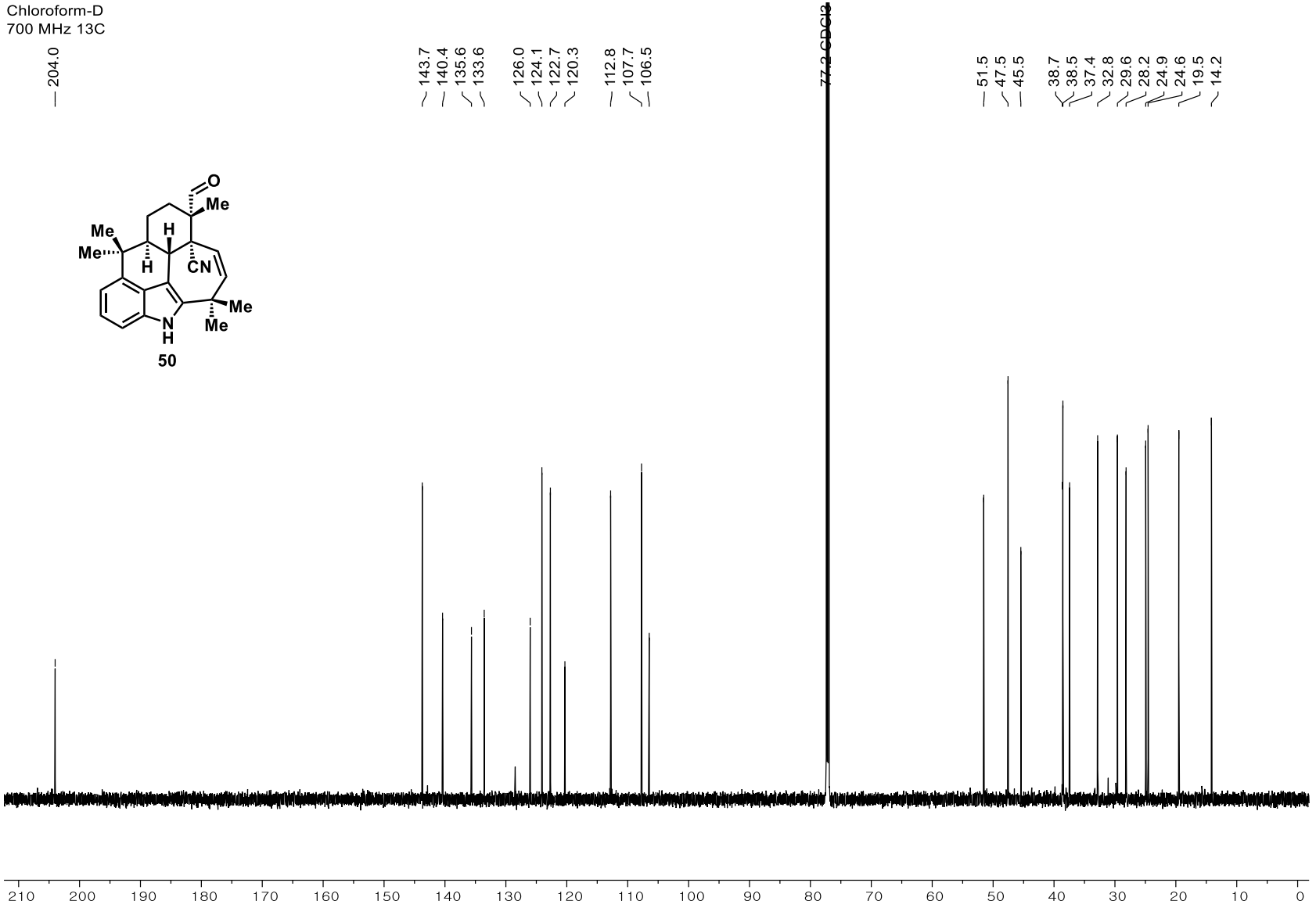
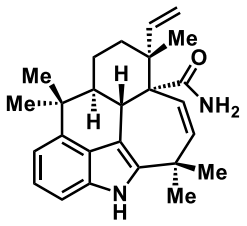

Acetone-D6
700 MHz, 13C
206.1 (CD3)2CO
201.9
184.3
145.6
140.1
137.6
137.3
135.0
131.9
126.6
123.1
122.6
119.9
119.1
113.1
108.9
105.2
81.9
56.3
47.4
47.1
39.6
39.2
38.3
32.5
29.8 (CD3)2CO
27.8
25.6
25.1
24.8
10.5
S
N
O
Me
O
H
Me
Me
H
H
CN
Me
N
H
Me
73
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


Chloroform-D
700 MHz 1H
9.88
7.83
7.26 CDCl3
7.16
7.13
7.02
7.01
7.01
7.01
5.72
5.70
5.39
5.37
3.32
3.30
2.25
2.21
2.08
2.01
1.71
1.65
1.63
1.62
1.60
1.50
1.47
1.34
1.14
O
Me
Me
Me
H
H
CN
Me
Me
N
H
50
1.00
1.08
2.12
1.07
1.06
1.05
1.07
1.16
2.20
1.33
3.98
3.17
3.04
3.08
3.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5


Chloroform-D
700 MHz 13C
204.0
143.7
140.4
135.6
133.6
126.0
124.1
122.7
120.3
112.8
107.7
106.5
77.2 CDCl3
51.5
47.5
45.5
38.7
38.5
37.4
32.8
29.6
28.2
24.9
24.6
19.5
14.2
O
Me
Me
Me
H
H
CN
Me
Me
N
H
50
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Chloroform-D
700 MHz 1H



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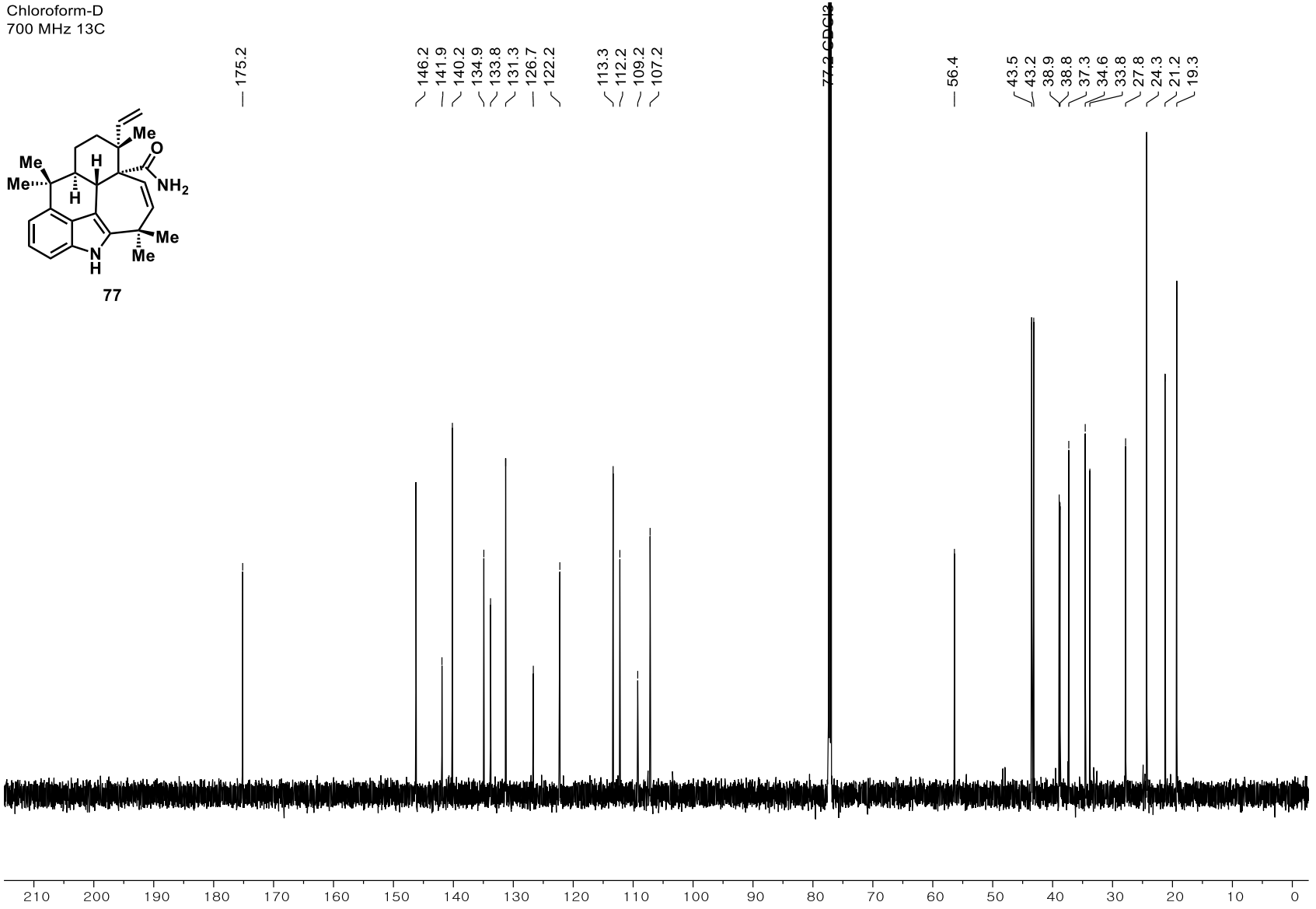
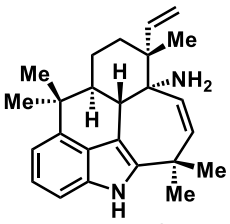

Chloroform-D
700 MHz 13C
175.2
146.2
141.9
140.2
134.9
133.8
131.3
126.7
122.2
113.3
112.2
109.2
107.2
77.2 CDCl3
56.4
43.5
43.2
38.9
38.8
37.3
34.6
33.8
27.8
24.3
21.2
19.3
Me
Me
Me
H
H
O
NH2
Me
Me
N
H
77
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Methanol-D6
700 MHz 1H



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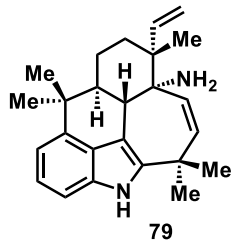
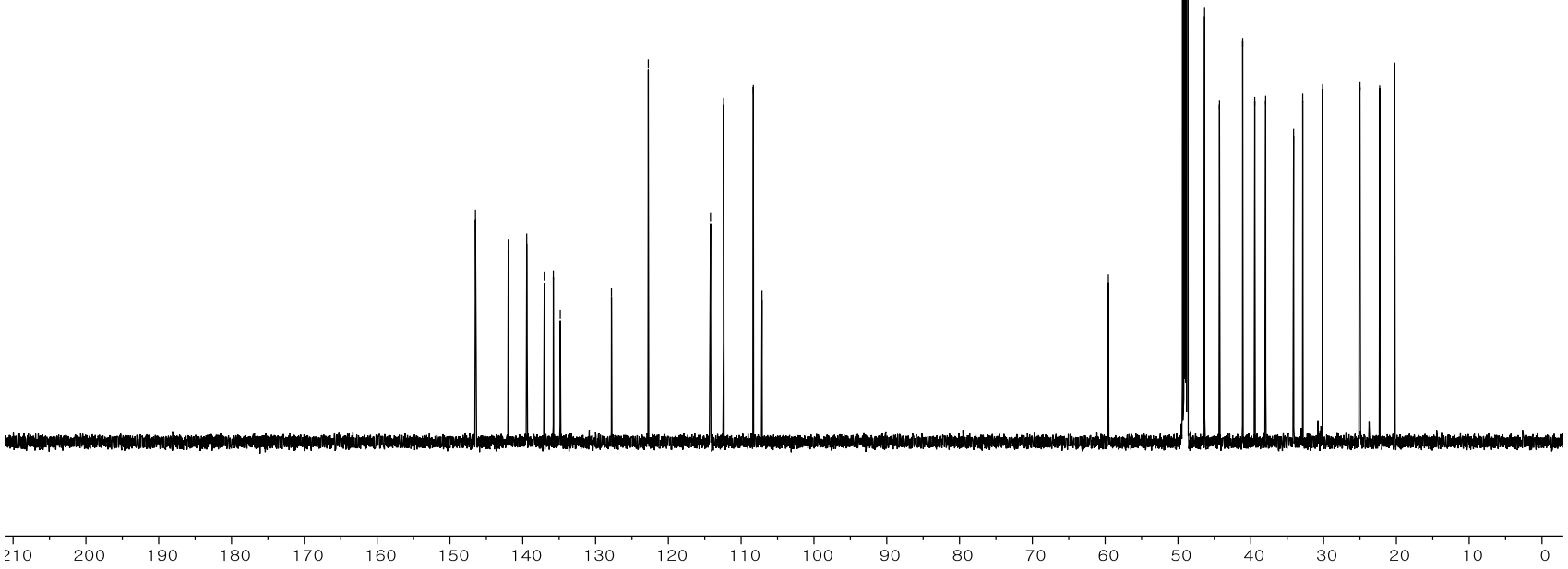
Methanol-D6
700 MHz 13C



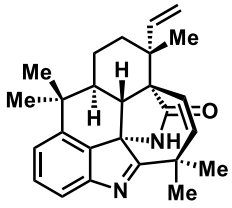
79

146.5
142.0
139.5
137.0
135.8
134.8
127.8
122.8
114.2
112.4
108.3
107.1
59.6
49.0 CD3OD
46.3
44.3
41.1
39.5
38.0
34.1
32.9
30.1
25.1
25.0
22.3
20.2

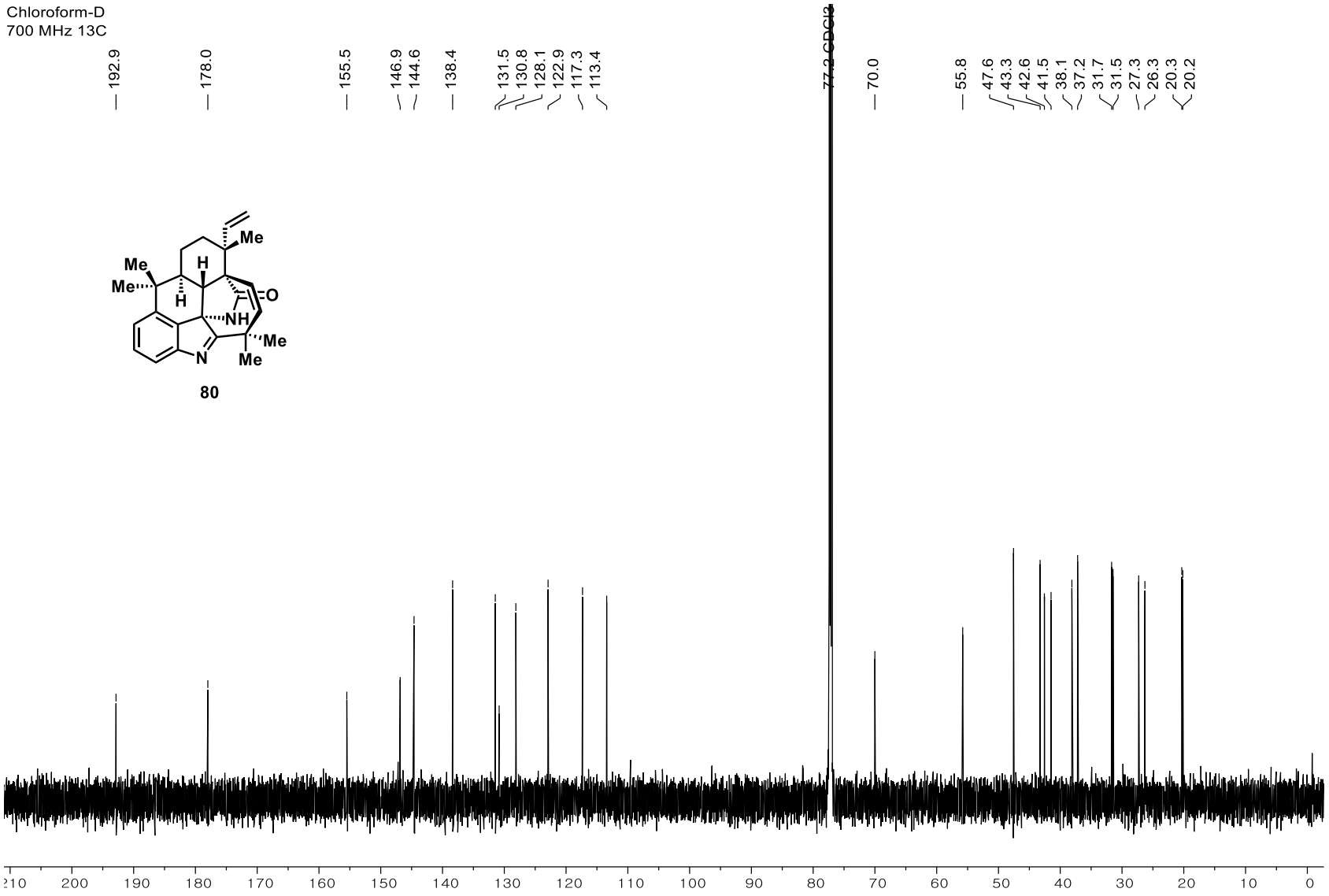


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

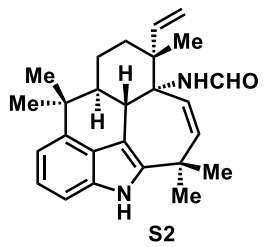
Chloroform-D
600 MHz 1H



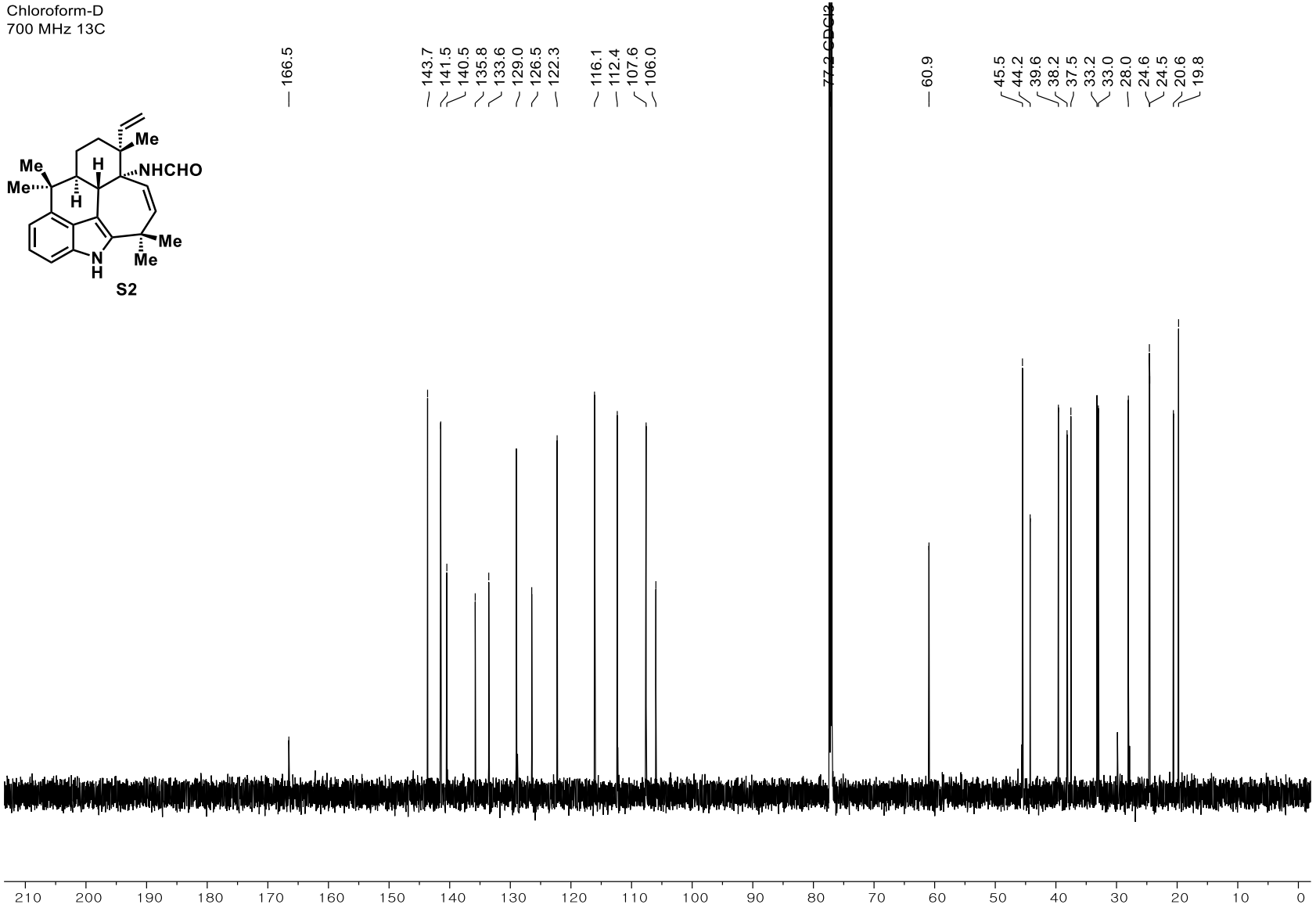
80


Chloroform-D
700 MHz 13C
192.9
178.0
155.5
146.9
144.6
138.4
131.5
130.8
128.1
122.9
117.3
113.4
77.2 CDCl3
70.0
55.8
47.6
43.3
42.6
41.5
38.1
37.2
31.7
31.5
27.3
26.3
20.3
20.2
Me
Me
Me
H
H
NH
O
N
Me
Me
80
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

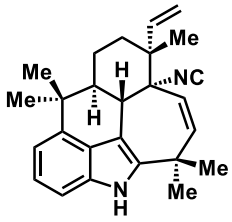
Chloroform-D
600 MHz 1H



S2


Chloroform-D
700 MHz 13C
166.5
143.7
141.5
140.5
135.8
133.6
129.0
126.5
122.3
116.1
112.4
107.6
106.0
77.2 CDCl3
60.9
45.5
44.2
39.6
38.2
37.5
33.2
33.0
28.0
24.6
24.5
20.6
19.8
Me
Me
Me
H
H
NHCHO
Me
Me
N
H
S2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

Chloroform-D
700 MHz 1H



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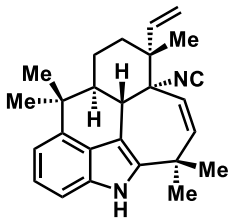
Chloroform-D
700 MHz 13C

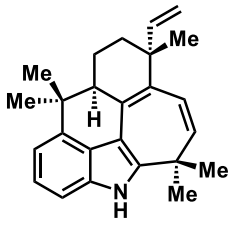


49

156.2
143.8
142.4
140.9
135.2
133.6
127.0
126.5
122.3
115.2
112.5
107.5
106.6
77.2 CDCl3
67.6
45.8
43.2
39.4
38.3
37.3
33.7
32.9
27.9
25.1
24.6
20.6
17.7

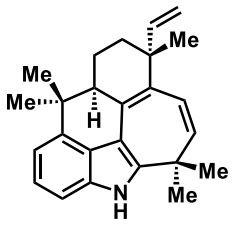
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

Chloroform-D
700 MHz 1H



45

Chloroform-D
700 MHz 13C



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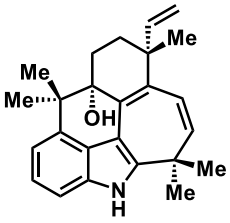
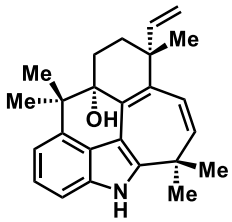
Methanol-D6
900 MHz 1H



ambiguine P (**17**)

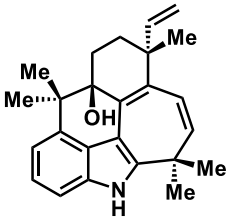
Methanol-D6
900 MHz 13C



ambiguine P (**17**)

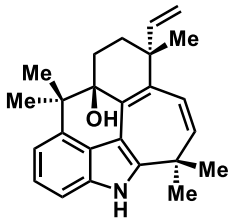
146.9
142.1
139.2
134.9
133.9
133.5
133.2
128.6
125.6
123.5
114.9
114.6
109.6
108.8
77.2
49.0 CD3OD
45.9
42.5
36.7
34.0
29.2
28.9
27.5
27.1
26.4
18.6

Methanol-D6
900 MHz 1H



epi-ambiguine P (**S3**)

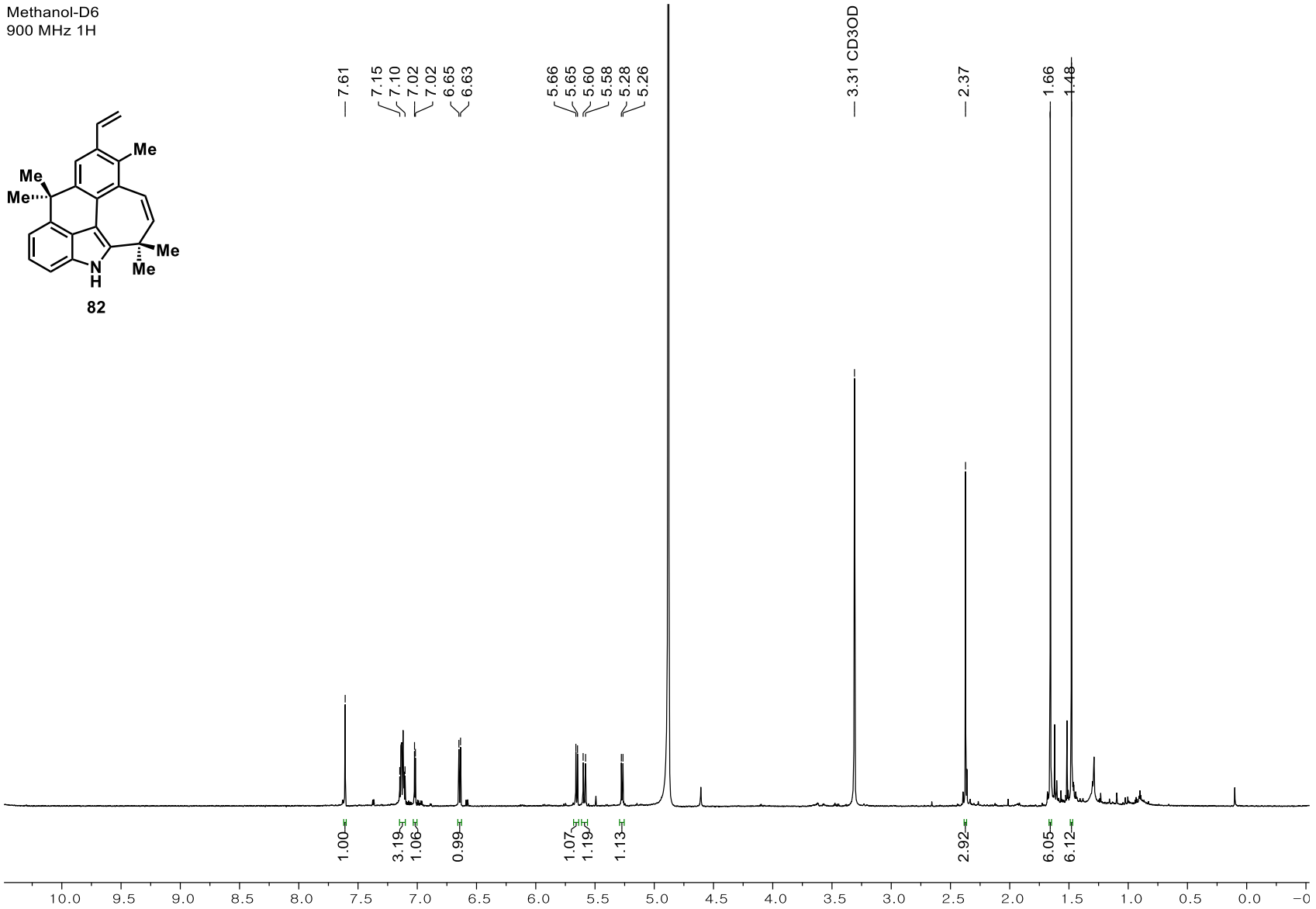
Methanol-D6
900 MHz 13C



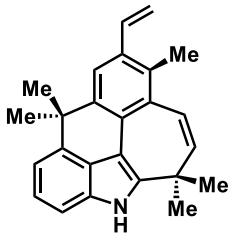
epi-ambiguine P (**S3**)

150.0
141.8
139.0
135.3
134.9
133.0
131.9
128.6
125.6
123.5
114.9
111.4
109.6
108.7
77.0
49.0 CD3OD
45.7
41.5
36.7
34.1
29.0
27.6
27.4
26.5
23.0
18.5

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Methanol-D6
900 MHz 1H
Me
Me
Me
Me
Me
N
H
82
7.61
7.15
7.10
7.02
7.02
6.65
6.63
5.66
5.65
5.60
5.58
5.28
5.26
3.31 CD3OD
2.37
1.66
1.48
1.00
3.19
1.06
0.99
1.07
1.19
1.13
2.92
6.05
6.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0

Methanol-D6
900 MHz 13C



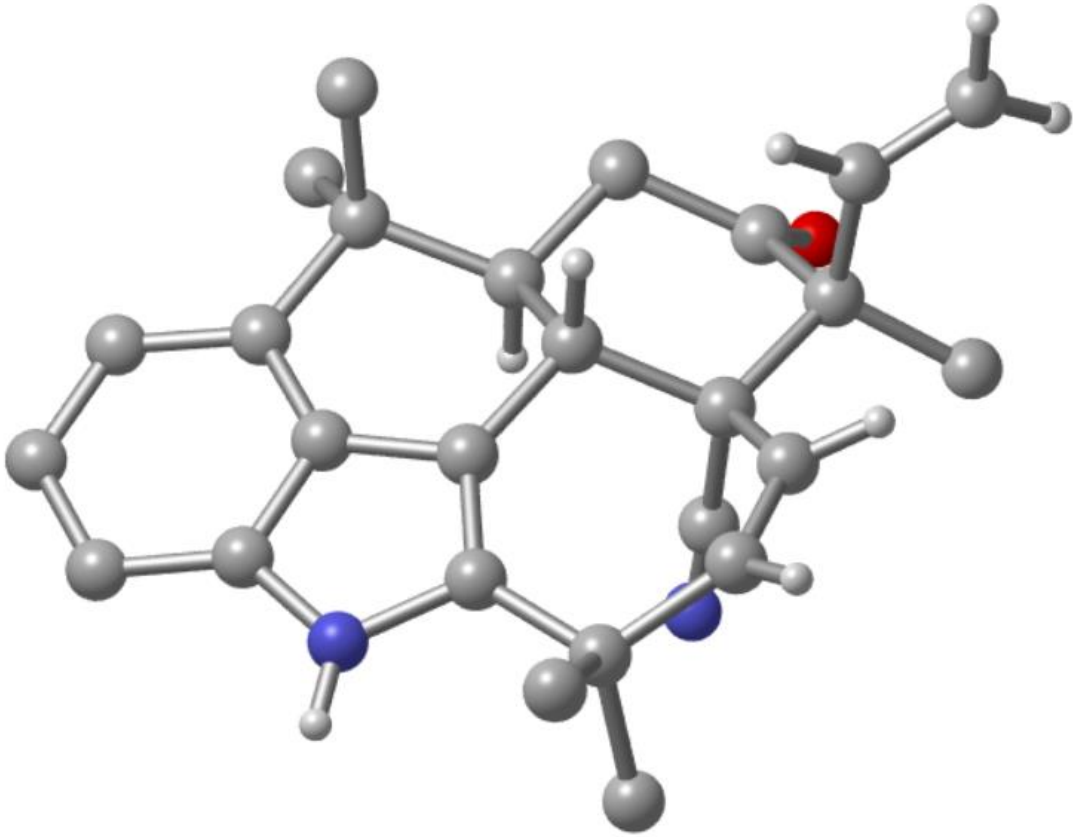
82

143.4
140.5
139.0
137.7
136.4
135.1
134.8
132.9
131.5
130.0
126.8
126.3
125.7
124.1
115.3
114.6
108.4
107.7
49.0 CD3OD
40.6
38.2
35.1
30.5
16.1

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

2.8 Appendix to Chapter 2: Xray Crystallographic Data

*1) Nitrile Ketone (**64**)*



A colorless needle 0.060 x 0.020 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 20 seconds per frame using a scan width of 2.0°. Data collection was 99.7% complete to 67.000° in . A total of 30752 reflections were collected covering the indices, -11<=*h*<=10, -15<=*k*<=15, -21<=*l*<=21. 3856 reflections were found to be symmetry independent, with an R_{int} of 0.0559. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a

riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Absolute stereochemistry was unambiguously determined to be *R* at C1 and *S* at C2, C5 and C18, respectively.

Table 1. Crystal data and structure refinement for sarpong135.

X-ray ID	sarpong135	
Sample/notebook ID	MLH-B1-115	
Empirical formula	C26 H28 N2 O	
Formula weight	384.50	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.2170(3) Å	α= 90°.
	b = 12.9842(4) Å	β= 90°.
	c = 17.6732(6) Å	γ = 90°.
Volume	2115.05(12) $Å^3$	
Z	4	
Density (calculated)	1.208 Mg/m^3	
Absorption coefficient	0.568 mm^{-1}	
F(000)	824	
Crystal size	0.060 x 0.020 x 0.020 mm^3	
Theta range for data collection	4.225 to 68.345°.	
Index ranges	-11<=h<=10, -15<=k<=15, -21<=l<=21	
Reflections collected	30752	
Independent reflections	3856 [R(int) = 0.0559]	
Completeness to theta = 67.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.809	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3856 / 0 / 267	
Goodness-of-fit on F^2	1.027	
Final R indices [I>2sigma(I)]	R1 = 0.0402, wR2 = 0.1002	
R indices (all data)	R1 = 0.0460, wR2 = 0.1044	
Absolute structure parameter	0.00(17)	
Extinction coefficient	n/a	

Largest diff. peak and hole	0.706 and -0.161 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sarpong135. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6365(3)	5390(2)	4145(2)	26(1)
C(2)	7261(3)	6419(2)	4006(2)	28(1)
C(3)	8779(3)	6098(2)	3729(2)	31(1)
C(4)	8813(3)	5400(2)	3054(2)	34(1)
C(5)	8003(3)	4392(2)	3216(2)	26(1)
C(6)	8158(3)	3597(2)	2553(2)	29(1)
C(7)	7337(3)	2622(2)	2764(1)	26(1)
C(8)	7577(3)	1644(2)	2483(2)	31(1)
C(9)	6756(3)	804(2)	2734(2)	34(1)
C(10)	5665(3)	904(2)	3270(2)	33(1)
C(11)	5380(3)	1894(2)	3532(2)	28(1)
C(12)	6201(3)	2732(2)	3278(1)	25(1)
C(13)	5667(3)	3642(2)	3633(1)	24(1)
C(14)	4544(3)	3346(2)	4094(2)	29(1)
C(15)	3544(3)	3933(2)	4615(2)	34(1)
C(16)	3691(3)	5083(2)	4525(2)	36(1)
C(17)	4804(3)	5679(2)	4344(2)	31(1)
C(18)	6419(3)	4637(2)	3458(1)	24(1)
C(19)	7052(3)	4845(2)	4786(2)	27(1)
C(20)	7416(3)	7054(2)	4731(2)	36(1)
C(21)	6545(3)	7024(2)	3368(2)	35(1)
C(22)	6538(4)	8021(3)	3290(2)	51(1)
C(23)	7536(4)	4012(2)	1812(2)	41(1)
C(24)	9770(3)	3338(3)	2439(2)	44(1)
C(25)	1951(3)	3651(3)	4424(2)	46(1)
C(26)	3836(4)	3629(3)	5447(2)	43(1)
N(1)	4384(2)	2283(2)	4032(1)	30(1)
N(2)	7626(3)	4404(2)	5260(1)	35(1)
O(1)	9871(2)	6387(2)	4044(1)	41(1)

Table 3. Bond lengths [Å] and angles [°] for sarpong135.

C(1)-C(19)	1.478(4)	C(14)-N(1)	1.393(4)
C(1)-C(17)	1.528(4)	C(14)-C(15)	1.508(4)
C(1)-C(18)	1.560(4)	C(15)-C(16)	1.508(4)
C(1)-C(2)	1.590(4)	C(15)-C(26)	1.545(4)
C(2)-C(21)	1.524(4)	C(15)-C(25)	1.551(4)
C(2)-C(20)	1.530(4)	C(16)-C(17)	1.324(4)
C(2)-C(3)	1.540(4)	C(16)-H(16)	0.9500
C(3)-O(1)	1.210(4)	C(17)-H(17)	0.9500
C(3)-C(4)	1.498(4)	C(18)-H(18)	1.0000
C(4)-C(5)	1.533(4)	C(19)-N(2)	1.144(4)
C(4)-H(4A)	0.9900	C(20)-H(20A)	0.9800
C(4)-H(4B)	0.9900	C(20)-H(20B)	0.9800
C(5)-C(18)	1.555(4)	C(20)-H(20C)	0.9800
C(5)-C(6)	1.568(4)	C(21)-C(22)	1.302(4)
C(5)-H(5)	1.0000	C(21)-H(21)	0.9500
C(6)-C(7)	1.521(4)	C(22)-H(22A)	0.9500
C(6)-C(23)	1.528(4)	C(22)-H(22B)	0.9500
C(6)-C(24)	1.536(4)	C(23)-H(23A)	0.9800
C(7)-C(8)	1.381(4)	C(23)-H(23B)	0.9800
C(7)-C(12)	1.393(4)	C(23)-H(23C)	0.9800
C(8)-C(9)	1.399(4)	C(24)-H(24A)	0.9800
C(8)-H(8)	0.9500	C(24)-H(24B)	0.9800
C(9)-C(10)	1.389(4)	C(24)-H(24C)	0.9800
C(9)-H(9)	0.9500	C(25)-H(25A)	0.9800
C(10)-C(11)	1.391(4)	C(25)-H(25B)	0.9800
C(10)-H(10)	0.9500	C(25)-H(25C)	0.9800
C(11)-N(1)	1.371(4)	C(26)-H(26A)	0.9800
C(11)-C(12)	1.399(4)	C(26)-H(26B)	0.9800
C(12)-C(13)	1.425(4)	C(26)-H(26C)	0.9800
C(13)-C(14)	1.372(4)	N(1)-H(1)	0.8800
C(13)-C(18)	1.499(4)		

C(19)-C(1)-C(17)	110.2(2)
C(19)-C(1)-C(18)	106.5(2)
C(17)-C(1)-C(18)	111.3(2)
C(19)-C(1)-C(2)	107.4(2)
C(17)-C(1)-C(2)	108.5(2)
C(18)-C(1)-C(2)	112.9(2)
C(21)-C(2)-C(20)	112.4(2)
C(21)-C(2)-C(3)	107.3(2)
C(20)-C(2)-C(3)	109.1(2)
C(21)-C(2)-C(1)	108.8(2)
C(20)-C(2)-C(1)	111.8(2)
C(3)-C(2)-C(1)	107.1(2)
O(1)-C(3)-C(4)	122.5(3)
O(1)-C(3)-C(2)	121.7(2)
C(4)-C(3)-C(2)	115.9(2)
C(3)-C(4)-C(5)	110.9(2)
C(3)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
C(5)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.0
C(4)-C(5)-C(18)	109.5(2)
C(4)-C(5)-C(6)	112.3(2)
C(18)-C(5)-C(6)	115.2(2)
C(4)-C(5)-H(5)	106.4
C(18)-C(5)-H(5)	106.4
C(6)-C(5)-H(5)	106.4
C(7)-C(6)-C(23)	108.5(2)
C(7)-C(6)-C(24)	109.4(2)
C(23)-C(6)-C(24)	109.1(3)
C(7)-C(6)-C(5)	108.6(2)
C(23)-C(6)-C(5)	111.9(2)
C(24)-C(6)-C(5)	109.3(2)
C(8)-C(7)-C(12)	116.7(2)
C(8)-C(7)-C(6)	126.6(2)

C(12)-C(7)-C(6)	116.7(2)
C(7)-C(8)-C(9)	121.1(3)
C(7)-C(8)-H(8)	119.5
C(9)-C(8)-H(8)	119.5
C(10)-C(9)-C(8)	122.3(3)
C(10)-C(9)-H(9)	118.8
C(8)-C(9)-H(9)	118.8
C(9)-C(10)-C(11)	116.8(3)
C(9)-C(10)-H(10)	121.6
C(11)-C(10)-H(10)	121.6
N(1)-C(11)-C(10)	132.9(3)
N(1)-C(11)-C(12)	106.4(2)
C(10)-C(11)-C(12)	120.6(3)
C(7)-C(12)-C(11)	122.4(2)
C(7)-C(12)-C(13)	129.2(2)
C(11)-C(12)-C(13)	108.4(2)
C(14)-C(13)-C(12)	106.9(2)
C(14)-C(13)-C(18)	135.4(3)
C(12)-C(13)-C(18)	117.6(2)
C(13)-C(14)-N(1)	108.1(2)
C(13)-C(14)-C(15)	133.0(3)
N(1)-C(14)-C(15)	119.0(2)
C(16)-C(15)-C(14)	112.4(2)
C(16)-C(15)-C(26)	109.7(3)
C(14)-C(15)-C(26)	110.2(2)
C(16)-C(15)-C(25)	107.2(3)
C(14)-C(15)-C(25)	109.1(3)
C(26)-C(15)-C(25)	108.1(3)
C(17)-C(16)-C(15)	132.4(3)
C(17)-C(16)-H(16)	113.8
C(15)-C(16)-H(16)	113.8
C(16)-C(17)-C(1)	129.9(3)
C(16)-C(17)-H(17)	115.1
C(1)-C(17)-H(17)	115.1
C(13)-C(18)-C(5)	108.3(2)

C(13)-C(18)-C(1)	111.4(2)
C(5)-C(18)-C(1)	111.9(2)
C(13)-C(18)-H(18)	108.4
C(5)-C(18)-H(18)	108.4
C(1)-C(18)-H(18)	108.4
N(2)-C(19)-C(1)	176.9(3)
C(2)-C(20)-H(20A)	109.5
C(2)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(2)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(22)-C(21)-C(2)	126.4(3)
C(22)-C(21)-H(21)	116.8
C(2)-C(21)-H(21)	116.8
C(21)-C(22)-H(22A)	120.0
C(21)-C(22)-H(22B)	120.0
H(22A)-C(22)-H(22B)	120.0
C(6)-C(23)-H(23A)	109.5
C(6)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(6)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(6)-C(24)-H(24A)	109.5
C(6)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(6)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(15)-C(25)-H(25A)	109.5
C(15)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(15)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5

H(25B)-C(25)-H(25C)	109.5
C(15)-C(26)-H(26A)	109.5
C(15)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(15)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
C(11)-N(1)-C(14)	110.2(2)
C(11)-N(1)-H(1)	124.9
C(14)-N(1)-H(1)	124.9

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for sarpong135. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	31(1)	25(1)	21(1)	1(1)	2(1)	0(1)
C(2)	39(2)	23(1)	23(1)	1(1)	0(1)	-1(1)
C(3)	38(2)	28(2)	27(1)	6(1)	3(1)	-6(1)
C(4)	36(2)	34(2)	34(2)	0(1)	9(1)	-6(1)
C(5)	28(1)	27(1)	22(1)	1(1)	3(1)	-1(1)
C(6)	31(1)	32(1)	23(1)	-1(1)	3(1)	2(1)
C(7)	26(1)	30(1)	22(1)	-2(1)	-6(1)	1(1)
C(8)	31(1)	34(2)	28(1)	-4(1)	-3(1)	5(1)
C(9)	38(2)	29(2)	35(2)	-6(1)	-10(1)	3(1)
C(10)	36(2)	29(1)	33(2)	1(1)	-12(1)	-5(1)
C(11)	30(1)	32(2)	23(1)	1(1)	-7(1)	-3(1)
C(12)	28(1)	26(1)	21(1)	0(1)	-5(1)	0(1)
C(13)	26(1)	25(1)	21(1)	1(1)	-1(1)	1(1)
C(14)	30(1)	32(2)	25(1)	1(1)	-2(1)	-2(1)
C(15)	29(1)	40(2)	33(2)	2(1)	6(1)	-3(1)
C(16)	34(2)	42(2)	30(2)	-4(1)	5(1)	6(1)
C(17)	35(2)	31(2)	28(1)	-1(1)	3(1)	6(1)

C(18)	29(1)	24(1)	19(1)	2(1)	0(1)	0(1)
C(19)	34(2)	28(1)	20(1)	-3(1)	5(1)	-2(1)
C(20)	45(2)	33(2)	29(1)	-2(1)	-1(1)	-3(1)
C(21)	45(2)	28(2)	32(2)	3(1)	-5(1)	-5(1)
C(22)	57(2)	36(2)	59(2)	8(2)	-21(2)	2(2)
C(23)	63(2)	38(2)	22(1)	1(1)	2(2)	1(2)
C(24)	33(2)	42(2)	56(2)	-16(2)	11(2)	-3(1)
C(25)	31(2)	52(2)	55(2)	-3(2)	7(2)	-4(2)
C(26)	44(2)	53(2)	32(2)	6(2)	13(1)	-2(2)
N(1)	31(1)	31(1)	29(1)	6(1)	2(1)	-8(1)
N(2)	45(1)	35(1)	25(1)	1(1)	-1(1)	5(1)
O(1)	39(1)	44(1)	40(1)	-2(1)	0(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sarpong135.

	x	y	z	U(eq)
H(4A)	9833	5245	2920	41
H(4B)	8359	5752	2617	41
H(5)	8486	4076	3666	31
H(8)	8311	1541	2113	37
H(9)	6953	142	2529	41
H(10)	5139	325	3450	39
H(16)	2817	5451	4616	43
H(17)	4601	6397	4337	37
H(18)	5911	4970	3021	29
H(20A)	8004	7667	4627	54
H(20B)	7891	6636	5121	54
H(20C)	6454	7264	4908	54
H(21)	6055	6636	2991	42
H(22A)	7012	8444	3652	61
H(22B)	6058	8326	2870	61
H(23A)	7649	3493	1414	61

H(23B)	8056	4640	1668	61
H(23C)	6504	4169	1880	61
H(24A)	10166	3047	2906	65
H(24B)	10302	3967	2308	65
H(24C)	9869	2836	2028	65
H(25A)	1295	4034	4759	70
H(25B)	1804	2910	4498	70
H(25C)	1745	3831	3897	70
H(26A)	4845	3789	5576	64
H(26B)	3664	2889	5512	64
H(26C)	3183	4016	5780	64
H(1)	3737	1914	4278	36

2) *Hoffman side product (**80**)*

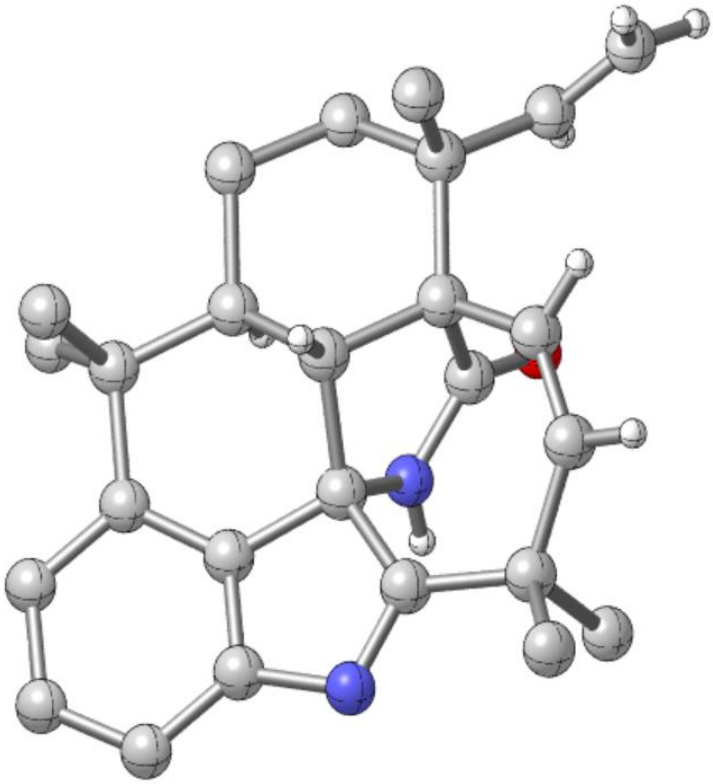


Table 1. Crystal data and structure refinement for hr001_sarpong.

Identification code	PIDAsidepdt	
Empirical formula	C27 H32 Cl2 N2 O	
Formula weight	471.44	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.92760(10) Å	α= 99.7130(10)°.
	b = 10.75250(10) Å	β= 104.8560(10)°.
	c = 12.95480(10) Å	γ = 110.2590(10)°.
Volume	1202.34(2) $Å^3$	
Z	2	
Density (calculated)	1.302 Mg/m^3	
Absorption coefficient	2.591 mm^{-1}	

F(000)	500
Crystal size	0.220 x 0.200 x 0.190 mm^3
Theta range for data collection	3.681 to 74.493°.
Index ranges	-12<=h<=12, -13<=k<=13, -16<=l<=16
Reflections collected	58641
Independent reflections	4913 [R(int) = 0.0411]
Completeness to theta = 74.000°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.83742
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4913 / 0 / 298
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0395, wR2 = 0.1062
R indices (all data)	R1 = 0.0397, wR2 = 0.1063
Extinction coefficient	n/a
Largest diff. peak and hole	0.413 and -0.501 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for hr001_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-1072(2)	2198(2)	5225(1)	33(1)
C(2)	162(2)	3369(2)	5555(1)	26(1)
C(3)	1326(2)	4073(1)	6717(1)	23(1)
C(4)	766(2)	3410(2)	7580(1)	29(1)
C(5)	1536(2)	5594(2)	7012(1)	26(1)
C(6)	2783(2)	6455(2)	8127(1)	27(1)
C(7)	4314(2)	6456(1)	8095(1)	21(1)
C(8)	5706(2)	7540(1)	9104(1)	23(1)
C(9)	5939(2)	9005(2)	9015(1)	31(1)
C(10)	5441(2)	7411(2)	10210(1)	30(1)
C(11)	7139(2)	7310(1)	9118(1)	23(1)
C(12)	8596(2)	8154(2)	9919(1)	29(1)
C(13)	9804(2)	7756(2)	10046(1)	30(1)
C(14)	9607(2)	6462(2)	9428(1)	28(1)
C(15)	8192(2)	5657(1)	8629(1)	24(1)
C(16)	7035(2)	6137(1)	8415(1)	21(1)
C(17)	5629(2)	4992(1)	7561(1)	20(1)
C(18)	4209(2)	4937(1)	7857(1)	20(1)
C(19)	2890(2)	3995(1)	6764(1)	20(1)
C(20)	3621(2)	4528(1)	5917(1)	20(1)
C(21)	2641(2)	2474(1)	6527(1)	24(1)
C(22)	3591(2)	1852(1)	6519(1)	26(1)
C(23)	5281(2)	2365(1)	6723(1)	24(1)
C(24)	5514(2)	2292(2)	5578(1)	30(1)
C(25)	5886(2)	1390(2)	7241(1)	32(1)
C(26)	6199(2)	3821(1)	7491(1)	22(1)
C(27)	699(2)	1729(2)	2886(1)	35(1)
Cl(1)	1733(1)	687(1)	3041(1)	49(1)
Cl(2)	-1291(1)	740(1)	2375(1)	40(1)
N(1)	7631(1)	4235(1)	8024(1)	25(1)

N(2)	5147(1)	5112(1)	6419(1)	20(1)
O(1)	2957(1)	4395(1)	4931(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for hr001_sarpong.

C(1)-C(2)	1.323(2)
C(1)-H(1A)	0.9500
C(1)-H(1B)	0.9500
C(2)-C(3)	1.5146(19)
C(2)-H(2A)	0.9500
C(3)-C(5)	1.5408(19)
C(3)-C(4)	1.5421(18)
C(3)-C(19)	1.5706(18)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(5)-C(6)	1.522(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-C(7)	1.5301(19)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.5558(19)
C(7)-C(18)	1.5722(17)
C(7)-H(7)	1.0000
C(8)-C(11)	1.5226(19)
C(8)-C(9)	1.5397(18)
C(8)-C(10)	1.5410(18)
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(16)	1.3797(19)
C(11)-C(12)	1.412(2)
C(12)-C(13)	1.389(2)
C(12)-H(12)	0.9500

C(13)-C(14)	1.404(2)
C(13)-H(13)	0.9500
C(14)-C(15)	1.380(2)
C(14)-H(14)	0.9500
C(15)-C(16)	1.4000(19)
C(15)-N(1)	1.4295(18)
C(16)-C(17)	1.4987(18)
C(17)-N(2)	1.4763(16)
C(17)-C(18)	1.5384(18)
C(17)-C(26)	1.5477(17)
C(18)-C(19)	1.5467(18)
C(18)-H(18)	1.0000
C(19)-C(21)	1.5298(17)
C(19)-C(20)	1.5467(17)
C(20)-O(1)	1.2369(16)
C(20)-N(2)	1.3454(18)
C(21)-C(22)	1.333(2)
C(21)-H(21)	0.9500
C(22)-C(23)	1.507(2)
C(22)-H(22)	0.9500
C(23)-C(26)	1.5139(19)
C(23)-C(25)	1.5414(19)
C(23)-C(24)	1.5520(19)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-N(1)	1.2850(19)
C(27)-Cl(2)	1.7632(17)
C(27)-Cl(1)	1.7653(17)
C(27)-H(27A)	0.9900
C(27)-H(27B)	0.9900
N(2)-H(2)	0.84(2)

C(2)-C(1)-H(1A)	120.0
C(2)-C(1)-H(1B)	120.0
H(1A)-C(1)-H(1B)	120.0
C(1)-C(2)-C(3)	127.24(14)
C(1)-C(2)-H(2A)	116.4
C(3)-C(2)-H(2A)	116.4
C(2)-C(3)-C(5)	107.12(11)
C(2)-C(3)-C(4)	111.45(12)
C(5)-C(3)-C(4)	108.59(11)
C(2)-C(3)-C(19)	110.78(11)
C(5)-C(3)-C(19)	110.04(11)
C(4)-C(3)-C(19)	108.81(11)
C(3)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(6)-C(5)-C(3)	112.57(11)
C(6)-C(5)-H(5A)	109.1
C(3)-C(5)-H(5A)	109.1
C(6)-C(5)-H(5B)	109.1
C(3)-C(5)-H(5B)	109.1
H(5A)-C(5)-H(5B)	107.8
C(5)-C(6)-C(7)	109.84(11)
C(5)-C(6)-H(6A)	109.7
C(7)-C(6)-H(6A)	109.7
C(5)-C(6)-H(6B)	109.7
C(7)-C(6)-H(6B)	109.7
H(6A)-C(6)-H(6B)	108.2
C(6)-C(7)-C(8)	113.43(11)
C(6)-C(7)-C(18)	109.92(11)
C(8)-C(7)-C(18)	115.71(11)
C(6)-C(7)-H(7)	105.6

C(8)-C(7)-H(7)	105.6
C(18)-C(7)-H(7)	105.6
C(11)-C(8)-C(9)	109.59(12)
C(11)-C(8)-C(10)	108.09(11)
C(9)-C(8)-C(10)	108.84(11)
C(11)-C(8)-C(7)	110.13(11)
C(9)-C(8)-C(7)	109.41(11)
C(10)-C(8)-C(7)	110.75(12)
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
C(8)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(16)-C(11)-C(12)	115.87(13)
C(16)-C(11)-C(8)	120.23(12)
C(12)-C(11)-C(8)	123.42(12)
C(13)-C(12)-C(11)	121.47(13)
C(13)-C(12)-H(12)	119.3
C(11)-C(12)-H(12)	119.3
C(12)-C(13)-C(14)	121.31(14)
C(12)-C(13)-H(13)	119.3
C(14)-C(13)-H(13)	119.3
C(15)-C(14)-C(13)	116.78(13)
C(15)-C(14)-H(14)	121.6
C(13)-C(14)-H(14)	121.6
C(14)-C(15)-C(16)	121.38(13)
C(14)-C(15)-N(1)	127.29(13)
C(16)-C(15)-N(1)	110.91(12)

C(11)-C(16)-C(15)	121.80(13)
C(11)-C(16)-C(17)	127.97(12)
C(15)-C(16)-C(17)	107.98(11)
N(2)-C(17)-C(16)	118.52(11)
N(2)-C(17)-C(18)	99.11(10)
C(16)-C(17)-C(18)	110.09(10)
N(2)-C(17)-C(26)	106.30(10)
C(16)-C(17)-C(26)	99.15(10)
C(18)-C(17)-C(26)	125.07(11)
C(17)-C(18)-C(19)	102.36(10)
C(17)-C(18)-C(7)	106.12(10)
C(19)-C(18)-C(7)	110.85(10)
C(17)-C(18)-H(18)	112.3
C(19)-C(18)-H(18)	112.3
C(7)-C(18)-H(18)	112.3
C(21)-C(19)-C(18)	113.68(11)
C(21)-C(19)-C(20)	104.82(10)
C(18)-C(19)-C(20)	99.20(10)
C(21)-C(19)-C(3)	108.06(11)
C(18)-C(19)-C(3)	113.10(10)
C(20)-C(19)-C(3)	117.73(11)
O(1)-C(20)-N(2)	124.53(12)
O(1)-C(20)-C(19)	127.26(12)
N(2)-C(20)-C(19)	108.12(11)
C(22)-C(21)-C(19)	132.43(13)
C(22)-C(21)-H(21)	113.8
C(19)-C(21)-H(21)	113.8
C(21)-C(22)-C(23)	133.82(13)
C(21)-C(22)-H(22)	113.1
C(23)-C(22)-H(22)	113.1
C(22)-C(23)-C(26)	113.79(11)
C(22)-C(23)-C(25)	109.00(12)
C(26)-C(23)-C(25)	108.29(12)
C(22)-C(23)-C(24)	107.87(12)
C(26)-C(23)-C(24)	109.80(11)

C(25)-C(23)-C(24)	107.95(11)
C(23)-C(24)-H(24A)	109.5
C(23)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(23)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(23)-C(25)-H(25A)	109.5
C(23)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(23)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
N(1)-C(26)-C(23)	120.53(12)
N(1)-C(26)-C(17)	113.69(12)
C(23)-C(26)-C(17)	124.98(12)
Cl(2)-C(27)-Cl(1)	112.08(9)
Cl(2)-C(27)-H(27A)	109.2
Cl(1)-C(27)-H(27A)	109.2
Cl(2)-C(27)-H(27B)	109.2
Cl(1)-C(27)-H(27B)	109.2
H(27A)-C(27)-H(27B)	107.9
C(26)-N(1)-C(15)	107.59(11)
C(20)-N(2)-C(17)	112.86(11)
C(20)-N(2)-H(2)	123.6(14)
C(17)-N(2)-H(2)	121.0(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for hr001_sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	31(1)	34(1)	30(1)	6(1)	11(1)	10(1)
C(2)	28(1)	31(1)	24(1)	8(1)	12(1)	14(1)
C(3)	26(1)	26(1)	21(1)	8(1)	11(1)	12(1)
C(4)	30(1)	36(1)	27(1)	12(1)	16(1)	14(1)
C(5)	30(1)	29(1)	25(1)	7(1)	9(1)	17(1)
C(6)	34(1)	27(1)	24(1)	4(1)	10(1)	18(1)
C(7)	31(1)	20(1)	17(1)	6(1)	9(1)	14(1)
C(8)	33(1)	21(1)	18(1)	4(1)	9(1)	14(1)
C(9)	41(1)	21(1)	31(1)	6(1)	12(1)	16(1)
C(10)	39(1)	33(1)	18(1)	5(1)	10(1)	17(1)
C(11)	32(1)	22(1)	17(1)	7(1)	9(1)	12(1)
C(12)	35(1)	26(1)	21(1)	3(1)	7(1)	11(1)
C(13)	30(1)	31(1)	22(1)	6(1)	5(1)	9(1)
C(14)	28(1)	33(1)	26(1)	11(1)	10(1)	14(1)
C(15)	31(1)	24(1)	21(1)	8(1)	12(1)	14(1)
C(16)	28(1)	21(1)	18(1)	8(1)	9(1)	11(1)
C(17)	28(1)	18(1)	17(1)	7(1)	10(1)	11(1)
C(18)	27(1)	20(1)	17(1)	7(1)	10(1)	12(1)
C(19)	26(1)	19(1)	18(1)	7(1)	11(1)	10(1)
C(20)	27(1)	16(1)	19(1)	6(1)	11(1)	10(1)
C(21)	29(1)	19(1)	25(1)	7(1)	13(1)	8(1)
C(22)	35(1)	17(1)	29(1)	7(1)	14(1)	10(1)
C(23)	33(1)	19(1)	24(1)	6(1)	13(1)	14(1)
C(24)	38(1)	27(1)	26(1)	4(1)	15(1)	15(1)
C(25)	45(1)	24(1)	33(1)	9(1)	15(1)	22(1)
C(26)	31(1)	20(1)	21(1)	8(1)	14(1)	14(1)
C(27)	38(1)	24(1)	37(1)	6(1)	13(1)	7(1)
Cl(1)	55(1)	50(1)	48(1)	18(1)	15(1)	30(1)
Cl(2)	38(1)	34(1)	38(1)	-2(1)	14(1)	7(1)
N(1)	30(1)	24(1)	26(1)	8(1)	12(1)	14(1)

N(2)	26(1)	21(1)	16(1)	7(1)	10(1)	10(1)
O(1)	27(1)	26(1)	17(1)	7(1)	9(1)	9(1)

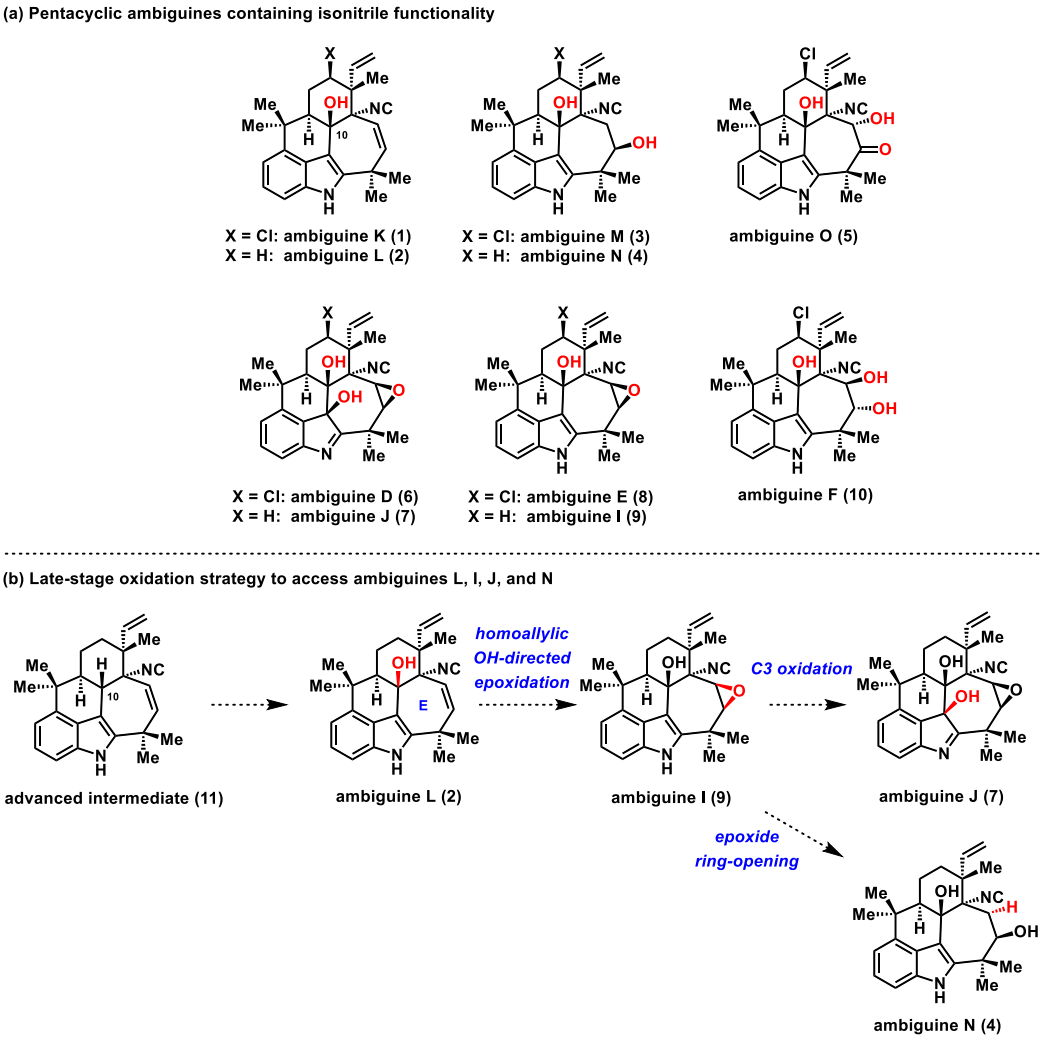
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for hr001_sarpong.

	x	y	z	U(eq)
H(1A)	-1305	1704	5744	39
H(1B)	-1726	1850	4469	39
H(2A)	338	3818	5000	31
H(4A)	527	2419	7360	43
H(4B)	-152	3541	7614	43
H(4C)	1568	3848	8314	43
H(5A)	1795	6000	6421	32
H(5B)	560	5629	7034	32
H(6A)	2525	6066	8727	32
H(6B)	2859	7415	8290	32
H(7)	4449	6757	7425	26
H(9A)	6142	9107	8325	46
H(9B)	6808	9688	9655	46
H(9C)	5017	9151	9008	46
H(10A)	4632	7710	10275	45
H(10B)	6387	7994	10834	45
H(10C)	5135	6445	10223	45
H(12)	8752	9014	10381	34
H(13)	10784	8372	10562	36
H(14)	10409	6156	9553	34
H(18)	4139	4552	8503	24
H(21)	1609	1853	6352	29
H(22)	3096	875	6346	31
H(24A)	5064	2847	5206	44
H(24B)	5017	1329	5115	44
H(24C)	6609	2653	5691	44
H(25A)	6966	1674	7321	48
H(25B)	5301	440	6756	48
H(25C)	5773	1436	7974	48

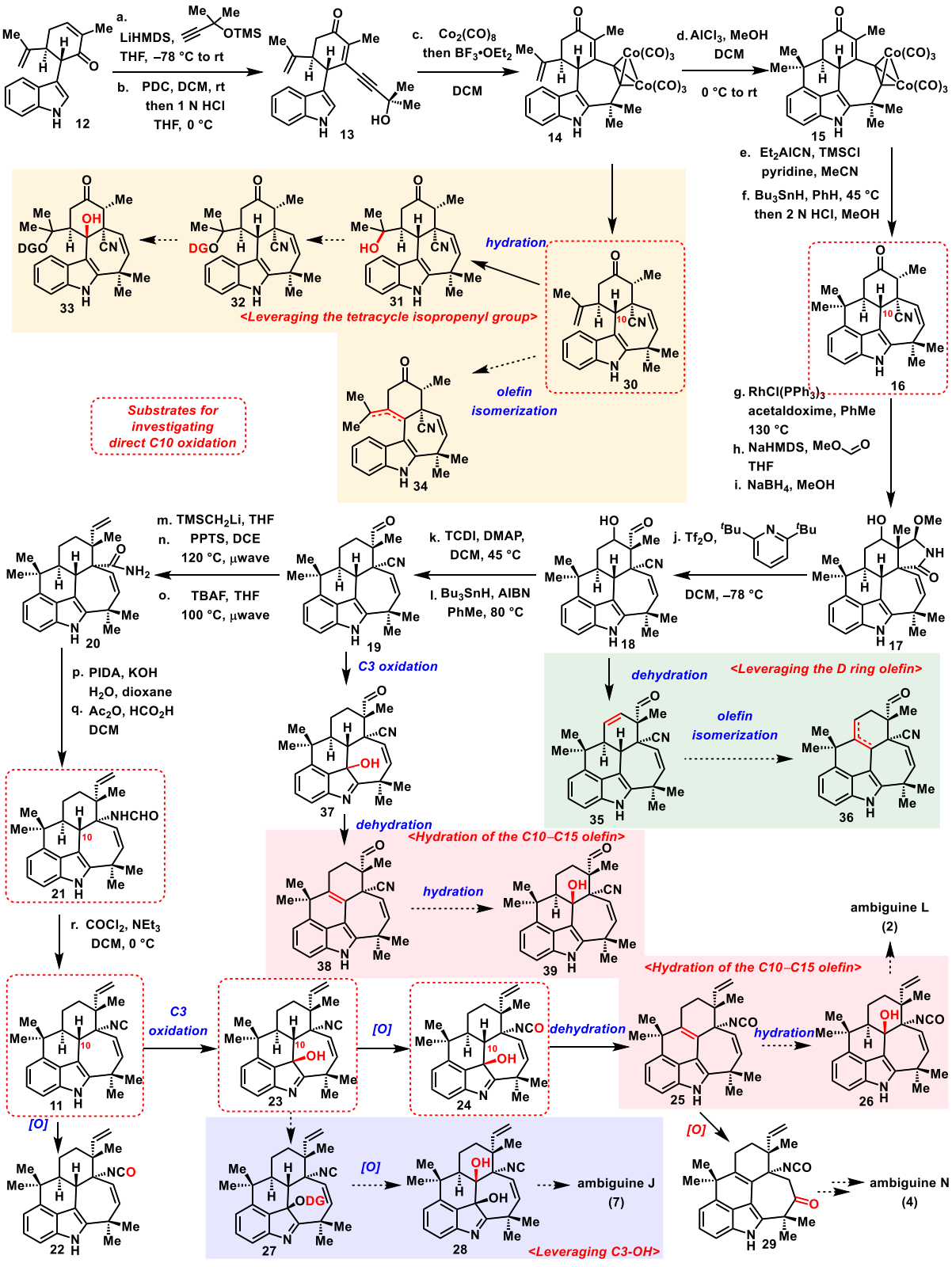
H(27A)	982	2393	3616	42
H(27B)	981	2266	2366	42
H(2)	5770(20)	5300(20)	6072(17)	37(5)

Chapter 3

Late-Stage Oxidation Efforts toward the Total Synthesis of Ambiguines Bearing the Isonitrile Functionality



Scheme 1. Late-stage diversification plans toward pentacyclic ambiguines.

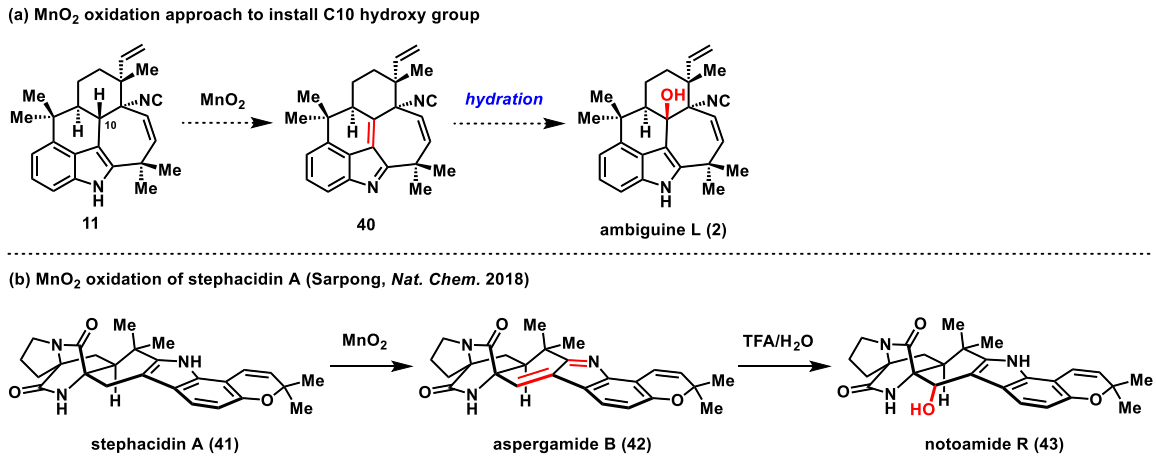


Scheme 2. Overview of the late-stage studies.

The Rawal group has reported syntheses of ambiguine P[1] and more recently of ambiguine G.[2] Their strategy highlights late-stage functionalization of the pentacyclic framework. Despite these advances in the total synthesis of the pentacyclic ambiguines, including our group's efforts[3] as described in Chapter 2, there still exists a synthesis gap in accessing isonitrile-bearing congeners, all of which possess C10 hydroxylation. Late-stage C–H oxidation methods are envisioned to play a critical role in incorporating the desired oxygen atoms.[4] In this chapter, I discuss the progress achieved in accessing those ambiguines with higher levels of oxygenation, including approaches aimed at C10-hydroxylation. Thus, I propose accessing a C10 hydroxylated intermediate en-route to ambiguine L (**2**, Scheme 1B), which would serve as a logical starting point (given it bears a synthetic handle) to facilitate further oxygenation(s) on the E ring characteristic of ambiguines I (**9**), J (**7**), and N (**4**).

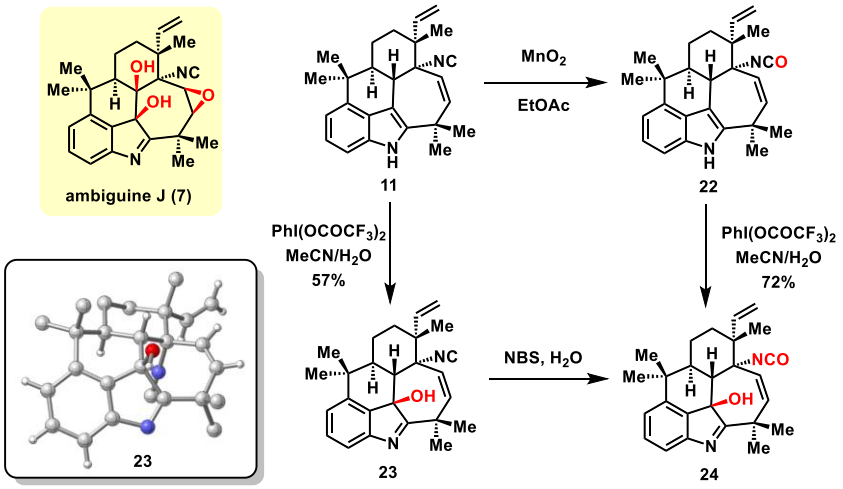
Scheme 2 depicts an overview of the forward synthesis route to advanced intermediate **11,** which was used in the synthesis of ambiguine P, and the synthetic studies that are discussed in this chapter.

3.1 Direct C−H Oxidation Strategies



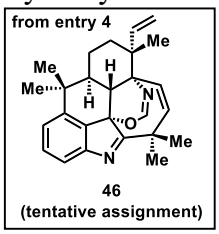
Scheme 3. MnO_2 oxidation approach.

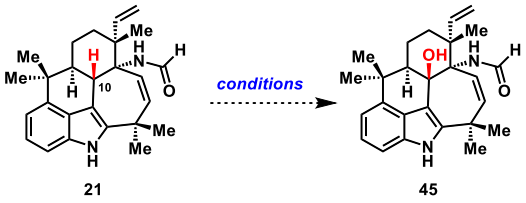
We envisioned oxidation of the indole component to give an α,β-unsaturated indolenine (**40**, Scheme 3A), hydration of which could give tertiary alcohol **2**. This approach is inspired by related precedent from our group on hydroxylating 2,5-diketopiperazine-containing indole alkaloids (Scheme 3B).[5]



Scheme 4. Oxidation outcomes for isonitrile **11**.

To test this hypothesis, common intermediate **11** was treated with manganese dioxide (Scheme 4). Instead of forming the α,β-unsaturated indolenine (**40**) as envisioned, oxidation of the isocyanide functional group to the isocyanate group was observed (**11** → **22**). This result suggests that isocyanide oxidation occurs preferentially over the other functional groups in this molecule. However, I found that the site of oxidation changed when the hypervalent iodine reagent, PIFA, was used. Instead of oxidizing the isocyanide, the indole was oxidized to the 3-hydroxyindolenine (**23**), which is featured in ambiguine J (**7**). This was confirmed by X-ray crystallography. Oxidation of the isocyanide to the isocyanate was again observed when the 3-hydroxyindolenine (**23**) was treated with NBS and water. This same product formed when isocyanate (**22**) was treated with PIFA.



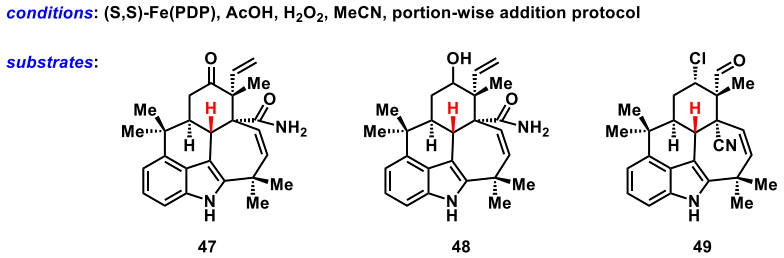


entry	conditions	results
1	$Rh_2(cap)_4$, TBHP, DCM, K_2CO_3, rt to 40 °C	decomp.
2	SeO_2, 1,4-dioxane, rt to110 °C	decomp.
3	DDQ, THF, H_2O, rt to 110 °C	no conversion
4	MnO_2, EtOAc, 65 °C	C3 oxidation
5	NBS, AIBN, CCl_4, 85 °C	bromination on indole

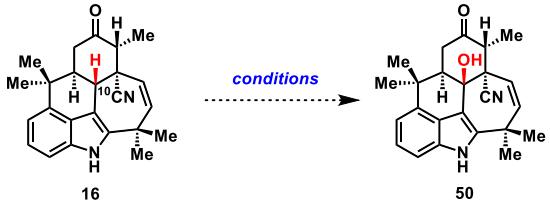
Table 1. Direct C10 oxidation attempts on formamide **21**.

Direct oxidation of earlier-stage intermediates that do not have the oxidation-sensitive isonitrile functional group was also attempted. Formamide **21**, the precursor to isonitrile **11**, was

subjected to several conditions for direct C10 oxidation (Table 1). $Rh_2(cap)_4$ catalyzed oxidation[6, 7] and selenium dioxide-mediated oxidation conditions,[6, 8] (entries 1 and 2) which are known to effect allylic and benzylic oxidations, did not lead to any conversion at room temperature and instead resulted in decomposition of the starting material at higher temperatures. Only minor consumption of the starting material was observed under DDQ benzylic oxidation conditions[8] (entry 3) even at high temperatures. In the absence of the isonitrile group, MnO_2 oxidized the indole motif at the C3 position (entry 4) which was then engaged by the formamide to yield cyclic imidate **46** (based on a tentative assignment using ^1H NMR spectroscopy and mass spectrometry). Radical bromination with NBS and AIBN resulted in aromatic bromination on the indole portion of the molecule (entry 5). Attempts to use White's catalyst[9] to effect late-stage C–H oxidation on various pentacyclic intermediates gave unreacted starting materials (Scheme 5).



Scheme 5. Late-stage aliphatic C−H oxidation attempts using White's catalyst.



entry	conditions	results
1	MnO_2, EtOAc, 65 °C	No conversion
2	TFDO, DCM, −15 °C	decomp.
3	CrO_3, $^nBu_4IO_4$, DCM, MeCN, −40 °C	multiple products
4	**51**, Ac_2O, DCM, MeCN, −40 °C	multiple products
5	**51**, H_5IO_6, Ac_2O, DCM, MeCN, −40 °C	decomp.

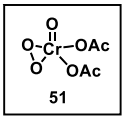
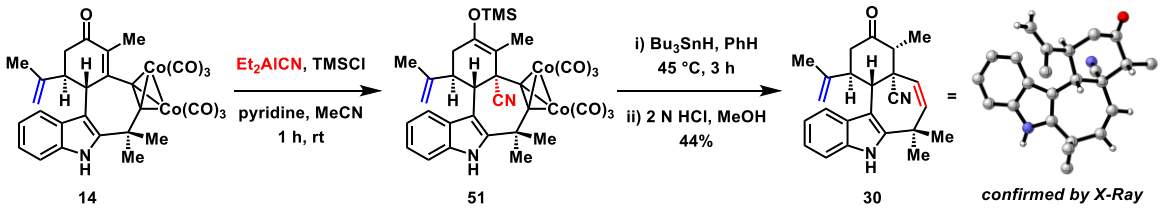


Table 2. Direct C10 oxidation attempts on ketone **16**.

Pentacyclic ketone **16**, a key intermediate in our synthesis that could be prepared in gram quantities, was chosen as another substrate to explore the late-stage oxidation (Table 2). MnO_2 failed to transform the substrate (entry 1) and TFDO converted the substrate to a complex mixture that could not be successfully separated (entry 2). Dioxiranes have been used in total syntheses to effect late-stage oxidation of tertiary C−H bonds,[4] however the presence of unsaturated bonds would render selective C10 oxidation difficult. A chromium [VI] catalyzed oxidation method,[10] which was reported to be more selective toward tertiary C−H oxidation was explored (entries 3−5). Fuchs and coworkers proposed the formation of Cr peroxy **51** from the reaction between CrO_3 and

periodate. When **51** was formed in situ from CrO_3 and $^nBu_4IO_4$ (entry 3), I observed formation of multiple products that were difficult to isolate. Most of the new compounds exhibited changes in the aromatic region of the NMR spectra, indicating that the indole portion of the molecule was chemoselectively oxidized under these conditions. A similar result was observed when preformed peroxy catalyst **51** was added to the reaction mixture (entry 4). When H_5IO_6 was added along with the preformed catalyst (entry 5), only decomposition was observed.

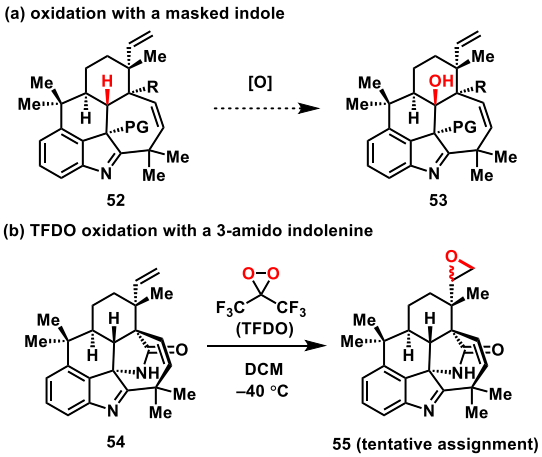


14 51 30

Scheme 6. Cyanide addition and reductive demetallation of tetracycle **14**.

I wondered whether oxidation of related tetracycles would give different results because they are less strained compared to the pentacycle frameworks. Tetracycle **30** was obtained by performing the cyanide addition and reductive demetallation on cobalt complex **14** (Scheme 6). Several oxidants including DDQ, PIDA, PIFA, DMDO, TFDO and MnO_2 gave no conversion of **30**. Some conversion was observed using mCPBA or trichloroperoxyacetic acid, which oxidized the indole portion of the molecule.

These results provide insight into the failure of direct C−H oxidation attempts at the C10 position as it appears the isocyanide and the indole moieties are more readily oxidized than the desired pseudobenzylic position.

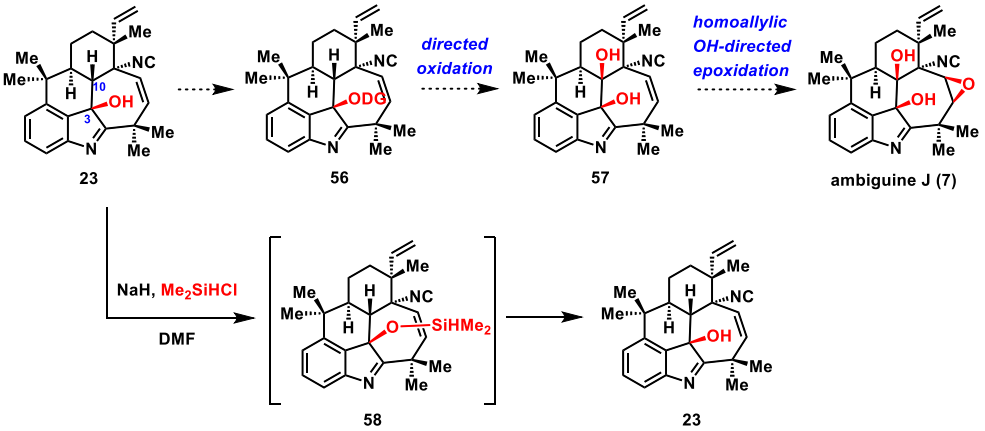


Scheme 7. TFDO oxidation on a masked-indole system.

To test if masking the indole C3 position would facilitate the direct C10 oxidation, I subjected 3-amido indolenine **54**, which is a side product from Hoffmann rearrangement (Scheme 2, **p**) to (bis)trifluoromethyl dioxirane (TFDO, Scheme 7). Without the electron-rich indole ring, I observed epoxidation of the monosubstituted alkene at the C12 position to a mixture of

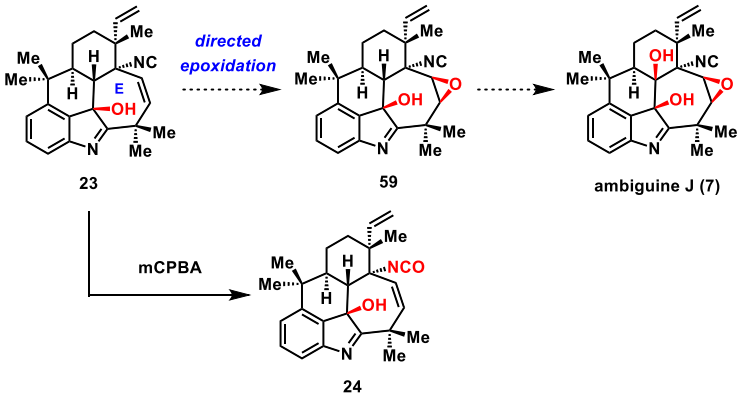
diastereomeric epoxides (**55**).

3.2 Leveraging Other Functional Groups



Scheme 8. Leveraging the C3 hydroxy group for C10 oxidation.

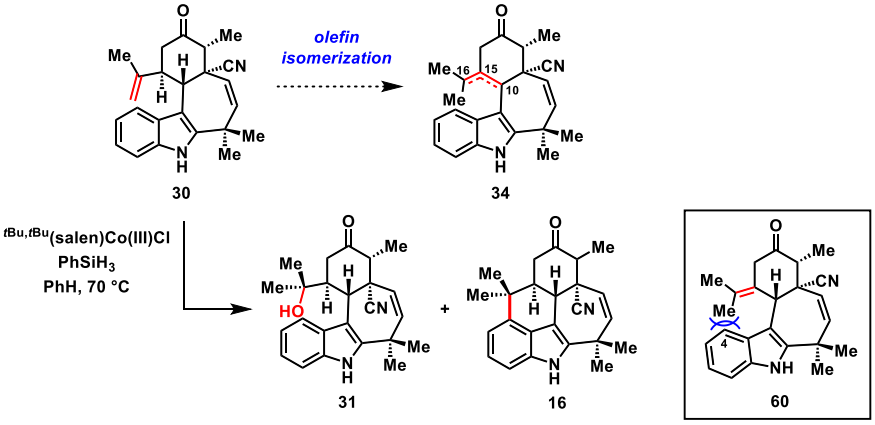
To avoid undesired oxidations of other functionalities, I sought to use the C3 hydroxy as a directing group for C10 aliphatic C–H oxidation by installing a tethering group (Scheme 8). However, tertiary alcohol **23** was largely unreactive toward carbamate or silyl ether formation. Modest conversion to dimethylsilane **58** was observed with chlorodimethylsilane as the silylating reagent, but silyl ether reverted back to starting material (**23**) upon aqueous workup.



Scheme 9. Attempted epoxidation on the E ring of **23**.

Unable to append a strong directing group to the hydroxy group of the hydroxyindolenine, I explored the possibility of leveraging the hydroxy group to direct epoxidation of the alkene in the seven-membered E ring and in the presence of the isonitrile group (Scheme 9). When treated with mCPBA,[11] the major product formed was the isocyanate (**24**) with no evidence of alkene epoxidation. $VO(acac)_2$ catalyzed TBHP epoxidation[12] was also attempted but resulted in

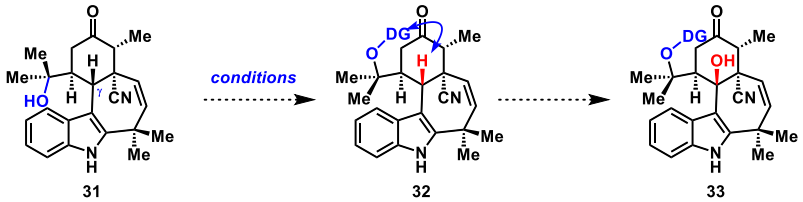
decomposition of **23**.



Scheme 10. Leveraging the isopropenyl group in **30**.

Another functionality that I envisioned utilizing is the isopropenyl group in tetracycle **30**. If the double bond of this substituent could be isomerized to the internal position (i.e. to form the C15−C16 olefin, Scheme 10), allylic oxidation would give the desired C10 hydroxy group. Following the Shenvi group's protocol for cobalt-catalyzed isomerization of terminal olefins,[13] two unexpected products, one arising from Mukaiyama hydration (**31**) and the other from a formal Friedel−Crafts cyclization (**16**) were isolated.[14] This suggests that the intended isomerization did not occur, potentially due to the steric clash between the C16 methyl group and C4 hydrogen atom that would develop should the isomerization have occured.

In an attempt to transform the hydroxy group of tertiary alcohol **31** into a suitable directing group for γ-oxidation (Table 3), the installation of three directing tethers was pursued. 2,2,2-Trifluoroethylisocyanate, which was used in the Baran group's eudesmane synthesis,[15, 16] did not react with our tertiary alcohol to form the carbamate tether (entry 1). Exposure of tertiary alcohol **31** to the Roisen group's conditions[17] did not lead to sulfamate formation (entry 2), whereas the use of *tert*-butylsulfamoylchloride led to elimination of the hydroxy group (see **30**; entries 3 and 4).



entry	conditions	results
1	CF_3CH_2NCO, pyr, DMAP, DCM, 0 °C to rt	no conversion
2	$CF_3CH_2NHSO_3H{\cdot}NEt_3$, $OPPh_3$, Tf_2O, DCM, 0 °C; NEt_3, DCM, −78 °C to rt	no conversion
3	^{t}BuNHSO$_2$Cl, NEt_3, DCM, 0 °C	dehydration (**30**)
4	^{t}BuNHSO$_2$Cl, NEt_3, DCM, −78 °C	dehydration (**30**)

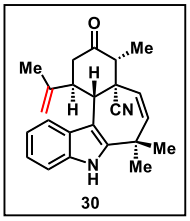
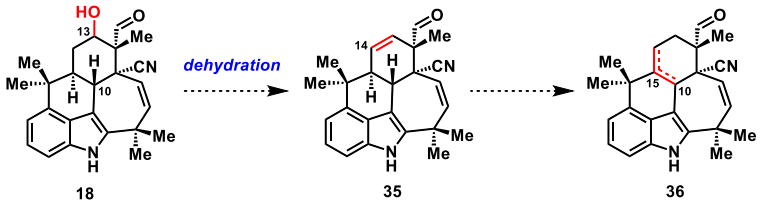
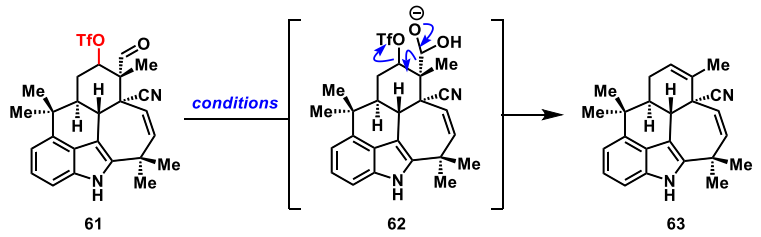


Table 3. Utilizing the hydroxy group to direct a γ-oxidation.



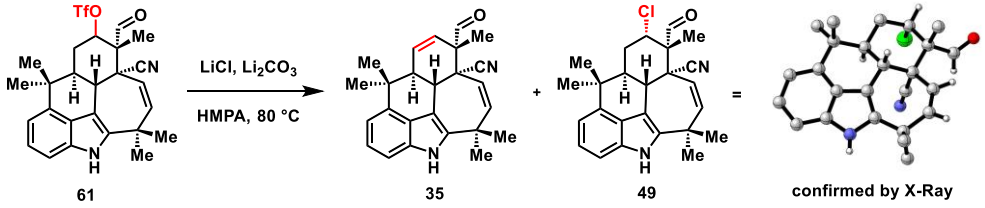
Scheme 11. Strategy to make use of C13 hydroxy group.

From the pentacyclic intermediate (**18**), I planned to eliminate the C13 hydroxy group to form the C13−C14 double bond, which could then be used as a synthetic handle to install the C10 hydroxy group (Scheme 11). Direct dehydration conditions using Martin's sulfurane or the Burgess reagent did not provide conversion to the desired alkene, so I investigated the elimination reaction with the triflyl derivative (**61**).



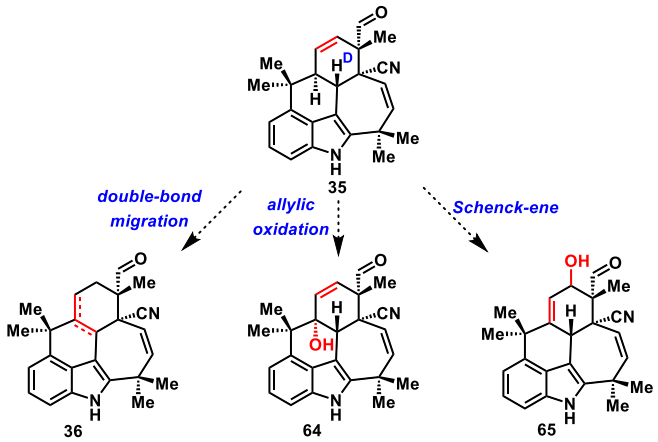
entry	conditions
1	DBU, THF, 50 °C
2	KO^{t}Bu, DMSO 40 °C
3	KOTMS, DMSO, 40 °C

Table 4. Grob fragmentation of aldehyde **61**.



Scheme 12. Triflate elimination using LiCl and Li_2CO_3

Several elimination conditions were tested and the use of bases including DBU, KO^{t}Bu and KOTMS resulted in Grob fragmentation of the β-triflate aldehyde (Table 4) even when the reactions were set up in a nitrogen-filled glove box to exclude moisture. This undesirable Grob fragmentation was suppressed with the use LiCl and Li_2CO_3 in HMPA solvent (Scheme 12), leaving the desired elimination reaction as the major pathway to yield alkene (**35**) along with a β-chlorinated side product (**49**).



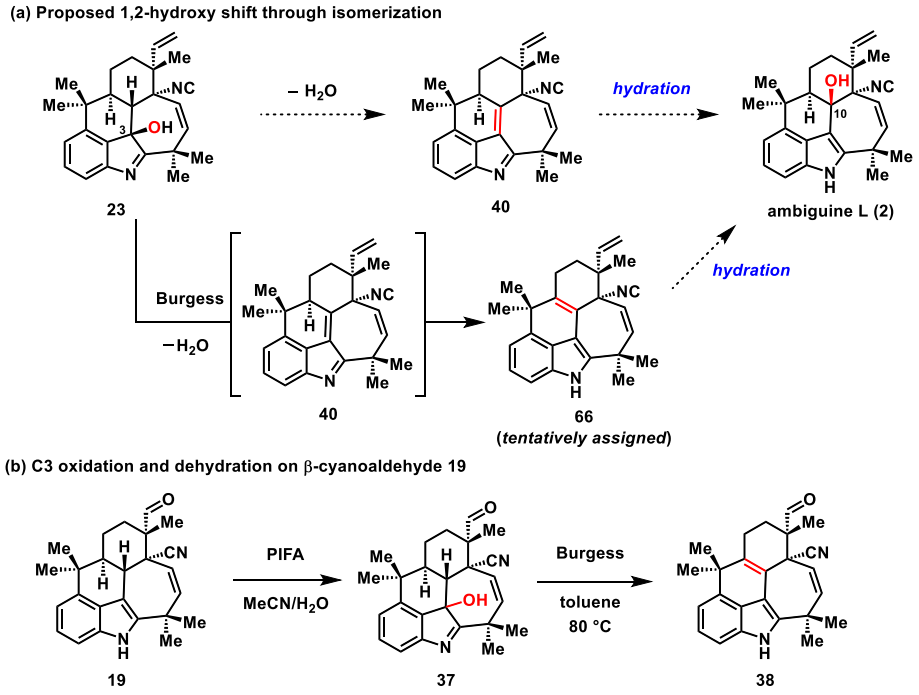
Scheme 13. The D-ring double bond as a synthetic handle.

Efforts to manipulate the double bond within the D ring by olefin isomerization (Table 5, entries 1−6), allylic oxidation (entries 7−9) and the Schenk-ene reaction (entries 10−13) were unsuccessful on β-cyanoaldehyde **35**. These experiments either yielded a complex mixture of products that could not be separated, decomposition to materials that were not discernable by NMR spectroscopy, or unreacted starting material.

entry	conditions	results
1	$RhCl_3 \cdot 3H_2O$, EtOH, 100 °C	decomp.
2	$Pd(MeCN)_4(BF_4)_2$, MeCN, rt	no conversion
3	$PdCl_2$, $TaCl_5$, THF, 60 °C	no conversion
4	AgOTf, PhCl, 130 °C	decomp.
5	Pd/C, H_2 (1 atm), EtOAc, rt	multiple products (reduction)
6	$^{t\text{Bu, }t\text{Bu}}$(salen)CoCl, $PhSiH_3$, PhH, 70 °C	no conversion
7	SeO_2, 1,4-dioxane, 45−80 °C	no conversion
8	SeO_2, TBHP, DCM, 45°C	no conversion
9	SeO_2, 1,4-dioxane, 100−140 °C, μwave	incomplete conversion, decomp.
10	TPP, O_2, hν, pyr; PPh_3, 15 °C	no conversion
11	TPP, O_2, hν, DCE; PPh_3, 15 °C	no conversion
12	Rose Bengal, O_2, hν, pyr; PPh_3, 15 °C	incomplete conversion, decomp.
13	Rose Bengal, O_2, hν, pyr, DCE; PPh_3, 15 °C	incomplete conversion

Table 5. Attempts to manipulate the D ring olefin of **35**.

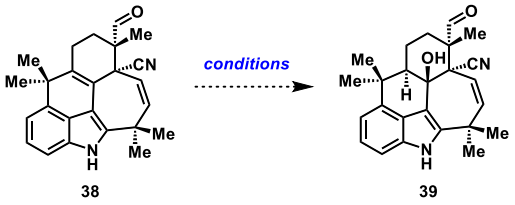
3.3 Attempts to Functionalize the C10−C15 Olefin



Scheme 14. Dehydration of 3-hydroxyindolenines **23** and **37**.

Alternatively, I envisioned that vicinal isomerization of the hydroxy group from **23** to **2** could be accomplished through a dehydration–hydration sequence (Scheme 14). Dehydration with the Burgess reagent, for example, would lead to α,β-unsaturated indolenine **40**, which could react with water in a conjugate addition fashion, ultimately leading to ambiguine L (**2**).

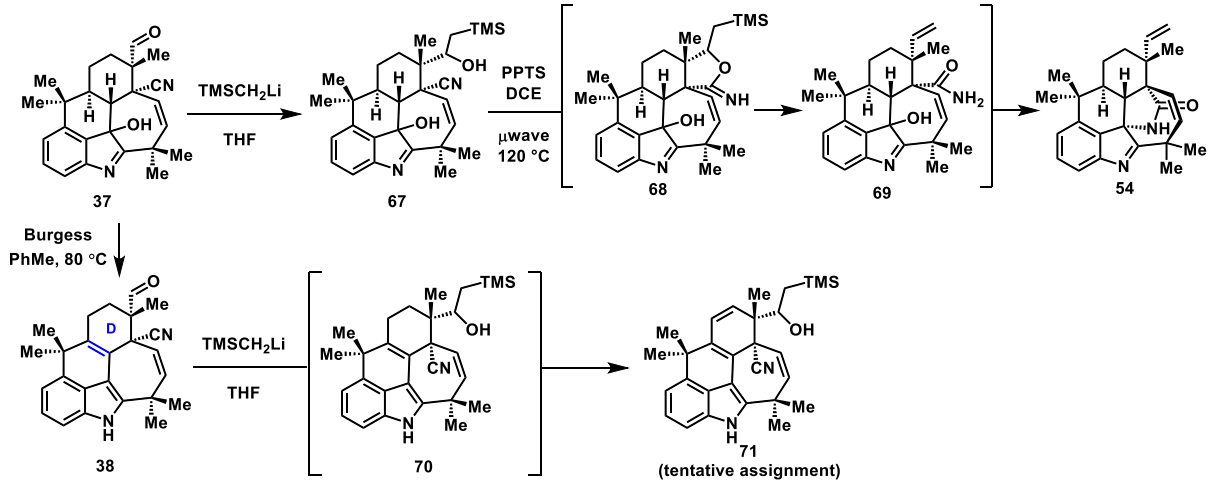
In practice, elimination of the alcohol proceeded as expected; however, rapid isomerization and rearomatization of the initially-formed α,β-unsaturated indolenine (**40**) to indole **66** occurred before the desired conjugate addition could take place (Scheme 14a). I recognized that from here, an olefin hydration reaction could introduce the final hydroxy group at C10. However, isocyanide **66** was isolated in only minute quantities, which was insufficient for full characterization. Thus, the same sequence was repeated on an earlier stage intermediate (**19**, Scheme 14b) to confirm the olefin isomerization.



entry	conditions	results
1	$Mn(dpm)_3$, O_2, $PhSiH_3$, ^iPrOH	multiple products, no aldehyde
2	$Co(acac)_2$, $PhSiH_3$, O_2, CF_3CH_2OH, ^iPrOH, 1,4-dioxane	no conversion
3	$Hg(OAc)_2$, THF, H_2O; NaOH, $NaBH_4$	no conversion

Table 6. Hydration attempts on alkene **38**

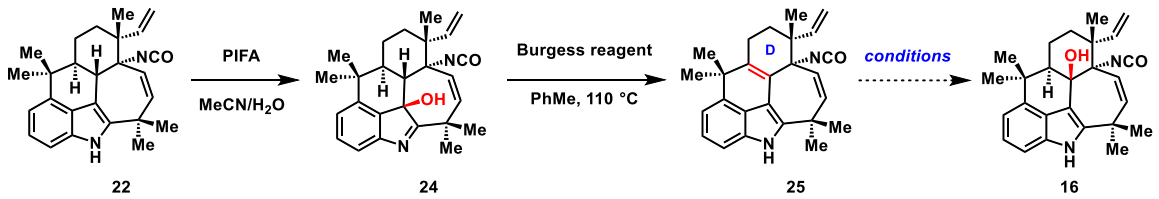
Mukaiyama hydration (Table 6, entries 1 and 2) and oxymercuration (entry 3) attempts on alkene **38** using well-established reaction conditions were unsuccessful. Speculating that the aldehyde functional group may be interfering with the Mukaiyama hydration, plans were made to transform the reactive aldehyde using the Peterson olefination sequence established earlier for the synthesis of ambiguine P (Scheme 2, **m** to **o**). $TMSCH_2Li$ addition into 3-hydroxyindolenine **37** proceeded smoothly (Scheme 15), and subsequent acid-mediated hydration provided imidate **68**, which spontaneously cyclized to the γ-lactam (**54**) upon olefination under microwave irradiation. Under these conditions, olefination occured in the absence of a fluoride source, furnishing a product arising from substitution of the tertiary alcohol. While the precise mechanism is speculative at this point, under strongly acidic conditions in aprotic DCE solvent, protonation of the indolenine should strongly disfavor the S_N1 pathway. Therefore, the final C–N bond formation could bear close resemblance to an unusual S_N2 substitution at the tertiary alcohol carbon center.[18] Further mechanistic analysis is warranted and probing the solvent effect would be a logical first step. Aldehyde **38**, in contrast to that (**19**) used in the successful synthesis of ambiguine P, contains an additional tetrasubstituted alkene (**38**, highlighted in blue). In this instance, the desired olefination product (**70**) was not isolated. When treated with $TMSCH_2Li$, multiple products formed, one of which has the D ring oxidized to bear a fully-conjugated system (**71**), presumably through the intermediacy of **70**.



Scheme 15. Olefination attempts on C3-hydroxyindolenine **37** and alkene **38**.

It was found that the isocyanate-bearing pentacycle (**22,** Table 7) undergoes the same C3-hydroxylation–dehydration transformation more effectively (or in a much cleaner fashion compared to the system depicted in Scheme 14a). As in the previous case, dehydration of the tertiary alcohol resulted in formation of the isomerized indole product from which I explored the aforementioned hydration reaction conditions. Gratifyingly, this alkenyl isocyanate (**25**) was formed in much higher quantities and was easier to purify compared to alkenyl isonitrile **66**. As such, I was able to perform the experiment reproducibly in up to a 50 mg scale, thus effectively preparing a substrate analogous to **38** but without the sensitive aldehyde functionality. As the protected form of the isonitrile, the isocyanate can be reduced at a later stage. Nonetheless, even

in the absence of the aldehyde component, various hydration conditions studied did not deliver the desired hydroxylated material.



entry	conditions	results
1	$Mn(dpm)_3$, O_2, $PhSiH_3$, $^{i}PrOH$, rt	decomp.
2	$Co(acac)_2$, O_2, $PhSiH_3$, 1,4-dioxane, CF_3CH_2OH, rt	decomp.
3	$^{t\text{Bu}, t\text{Bu}}$(salen)CoCl, $PhSiH_3$, PhH, rt	decomp.
4	H_2SO_4, 1,4-dioxane, H_2O, rt−60 °C	no conversion
5	H_2SO_4, THF, H_2O, rt−60 °C	no conversion
6	PPTS, H_2O, 1,4-dioxane, μwave, 100−120 °C	decomp.
7	*p*TsOH, THF, H_2O, rt−60 °C	no conversion
8	TFA, THF, H_2O, rt−60 °C	no conversion
9	TfOH, 1,4-dioxane, H_2O, 80 °C	no conversion
10	TfOH, DCE, AcOH, 80 °C	decomp.
11	TfOH, benzoic acid, DCE, 80 °C	decomp.

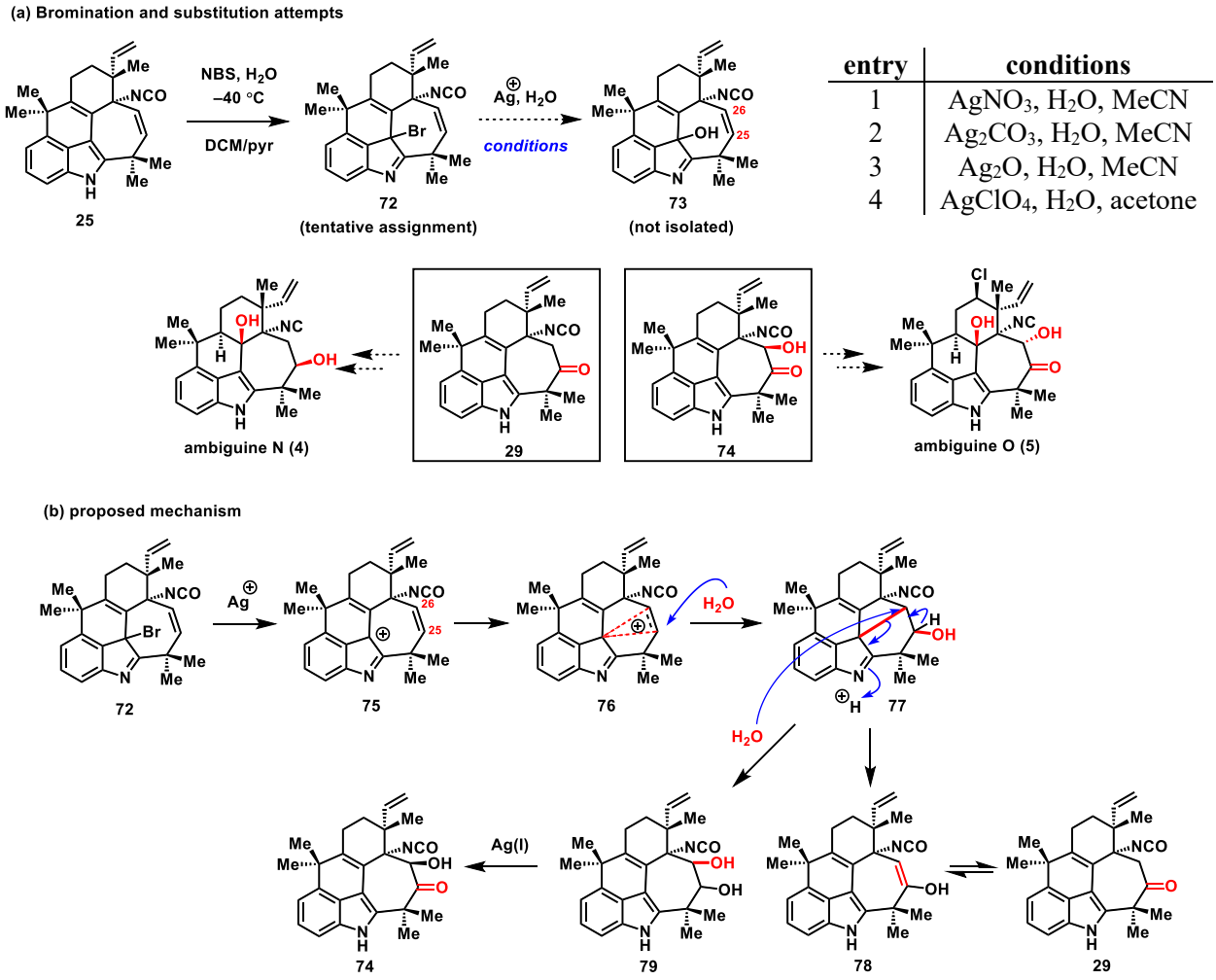
Table 7. Hydration attempts on **25**.

Since direct hydration protocols described in Table 7 were unsuccessful, I resorted to epoxidation conditions using TFDO and mCPBA. However, both reagents resulted in decomposition of the starting material (**25**). The highly conjugated nature of compound **25** likely contributes to its sensitivity to oxidizing conditions. Given the higher reactivity of the indole component, perhaps it would be possible to selectively oxidize the C3 position first, followed by epoxidation of the C10−C15 alkene. Attempts to selectively oxidize the C3 indole position with PIDA and PIFA led to decomposition of the starting material.

Although conventional hydroxylation conditions failed to yield the desired 3-hydroxylated product, treating alkene **25** with NBS at −40 °C gave 3-bromoindolenine **72** as one major product (Scheme 16a). This compound was found to be unstable and readily reverted back to starting material **25**. When directly subjected to silver salts in water, an unexpected transformation of the alkene occurred to produce ketone **29** and α-hydroxyketone **74** where the cycloheptane ring system was oxidized. All of the conditions that were explored gave similar reaction patterns and with multiple products. This serendipitous discovery provided access to oxygenation patterns reminiscent in ambiguines N (**4**) and O (**5**).

The mechanism of this unexpected transformation (Scheme 16b) is proposed to proceed through nonclassical carbocation **76**, which arises from the transannular engagement of the C25−C26 alkene with the C3 carbocation. Presumably, water attacks at C25, forming the ring-contracted hexacycle (**77**). The strained bond can break upon deprotonation at C25 to give enol **78**, which then tautomerizes to ketone **29**. In forming α-ketol **74**, the attack of a water molecule at C26 of intermediate **77** can result in diol (**79**). A final oxidation in the presence of excess Ag(I) could

oxidize the C25 hydroxy group to ketone **74**.



entry	conditions
1	$AgNO_3$, H_2O, MeCN
2	Ag_2CO_3, H_2O, MeCN
3	Ag_2O, H_2O, MeCN
4	$AgClO_4$, H_2O, acetone

Scheme 16. C3 Bromination and substitution attempts.

3.4 Conclusion and Outlook

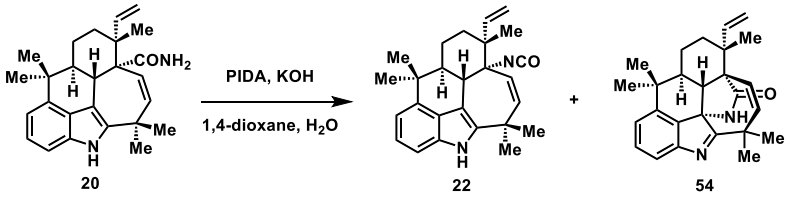
I have explored various strategies to install a hydroxy group that is common to most members of the ambiguine family. Late-stage oxidation of the pentacyclic scaffold has proven to be a challenge due to the presence of the oxidation-sensitive indole moiety. My experiments have also shown that the pentacyclic ambiguine scaffold does not react in a conventional manner, but

rather through unusual ring-forming pathways that involve substituting at a sterically-hindered tertiary alcohol and through non-classical carbocation intermediates. These outcomes attest to the long-standing synthetic challenge that this class of natural products pose. Despite these challenges, I have achieved the desired oxidation state at the C10 position through formation of an alkene, from which the seven-membered E ring of the pentacyclic ambiguines can be functionalized. The resulting C25 and C26 oxidation products map onto ambiguines N and O, respectively, paving way for their completion.

3.5 References

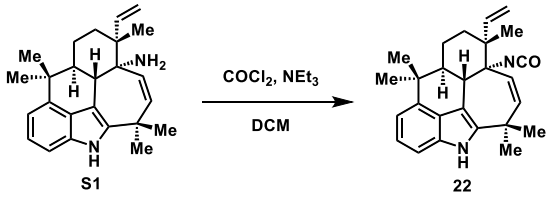
(1) Xu, J.; Rawal, V. H. *J. Am. Chem. Soc.* **2019**, *141*, 4820.
(2) Hu, L.; Rawal, V. H. *J. Am. Chem. Soc.* **2021**, *143*, 10872.
(3) Johnson, R. E.; Ree, H.; Hartmann, M.; Lang, L.; Sawano, S.; Sarpong, R. *J. Am. Chem. Soc.* **2019**, *141*, 2233.
(4) Qiu, Y.; Gao, S. *Nat. Prod. Rep.* **2016**, *33*, 562.
(5) Mukai, K.; Pereira de Sant'Ana, D.; Hirooka, Y.; Mercadi-Marin, E. V.; Stephens, D. E.; Kou, K. G. M.; Richter, S. C.; Kelley, N.; Sarpong, R. *Nat. Chem.* **2018**, *10*, 38.
(6) Nakamura, A.; Nakada, M. *Synthesis.* **2013**, *45*, 1421.
(7) Wang, Y.; Kuang, Y.; Wang, Y. *Chem. Commun*. **2015**, *51*, 5852.
(8) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.
(9) White, M. C.; Zhao, J. *J. Am. Chem. Soc.* **2018**, *140*, 13988.
(10) Lee, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, *124*, 13978.
(11) Glotter, E.; Zviely, M. *J. Chem. Soc. Perkin. Trans. 1.* **1986**, 321.
(12) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(13) Crossley, S. W. M.; Barabe, F.; Shenvi, R. A. *J. Am. Chem. Soc.* **2014**, *136*, 16788.
(14) Green, S. A.; Crossley, S. W. M.; Matos, J. L. M.; Vasquez-Cespedes, S.; Shevick, S. L.; Shenvi, R. A. *Acc. Chem. Res.* **2018**, *51*, 2628.
(15) Chen, K.; Baran, P. S. *Nature.* **2009**, *459*, 825.
(16) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247.
(17) Short, M. A.; Blackburn, J. M.; Roizen, J. L. *Angew. Chem. Int. Ed.* **2018**, *57*, 296.
(18) Barlose, C. L.; Ostergaard, N. L.; Bitsch, R. S.; Iversen, M. V.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2021**, *60*, 2.

3.6 Experimental Section



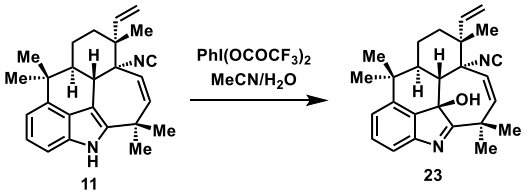
Isocyanate (22): Amide **20** (61.5 mg, 0.158 mmol, 1 equiv) was dissolved in 1,4-dioxane (1.6 mL) and H_2O (1.6 mL) was added. To this solution was added crushed KOH (44.2 mg, 0.790 mmol, 5 equiv) and the suspension was allowed to stir for 5 min at rt. At this time, PIDA (61.2 mg, 0.190 mmol, 1.2 equiv) was added and the solution turned light yellow. The suspension was allowed to stir at rt for 20 h, at which time it was quenched with sodium bicarbonate (sat. aq., 3 mL) and sodium thiosulfate (sat. aq.) (3 mL). After stirring for 5 min at rt, the mixture was diluted with ethyl acetate (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 4:1 hexanes/ethyl acetate) to yield the desired product (27.8 mg, 0.0719 mmol, 46%) as a yellow film along with a side product (**54**) resulting from indole oxidation (13.8 mg, 0.0357 mmol, 23%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (br s, 1H), 7.19 – 7.10 (m, 2H), 6.99 (dd, *J* = 4.0 Hz, 1H), 6.17 (dd, *J* = 17.5, 10.9 Hz, 1H), 5.81 (d, *J* = 12.8 Hz, 1H), 5.52 (d, *J* = 12.8 Hz, 1H), 5.26 – 5.13 (m, 2H), 3.43 (d, *J* = 10.9 Hz, 1H), 2.00 – 1.93 (m, 2H), 1.88 (ddd, *J* = 14.1, 3.7 Hz, 1H), 1.64 (ddd, *J* = 13.3, 3.8 Hz, 1H), 1.56 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H), 1.41 – 1.39 (m, 1H), 1.27 (s, 3H), 1.12 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.1, 141.1, 140.0, 135.8, 133.7, 130.0, 126.6, 124.2, 122.4, 114.5, 112.5, 107.5, 107.3, 67.3, 46.4, 44.4, 40.5, 38.4, 37.2, 34.2, 33.1, 30.2, 25.0, 24.6, 21.0, 18.5. **IR** (ATR, thin film) 3402, 2964, 2928, 2248, 1704, 1453, 797, 769 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{29}N_2O$ $[M-H]^-$: 385.2285. Found 385.2291. $[\alpha]_D$ −56.9 (c 0.65 x10^{-3}, DCM).

Alternative synthesis:

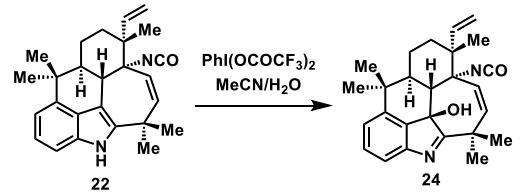


The amine (**S1**) (7.5 mg, 0.021 mmol, 1.0 equiv) was dissolved in DCM (0.7 mL) and the reaction mixture was cooled to 0 °C. NEt_3 (15 µL, 0.011 mmol, 5 equiv) was added followed by phosgene (20% in toluene, 29 µL, 0.042 mmol, 2 equiv). After stirring for 10 min at 0 °C, the reaction mixture was quenched with sodium bicarbonate (2 mL) and diluted with DCM (5 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic layers were washed with brine (3 mL), dried over sodium sulfate, and concentrated in vacuo. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 4:1 hexanes/ethyl

acetate) to yield the desired product (**14**) as a yellow film (5.4 mg, 0.014 mmol, 67%).

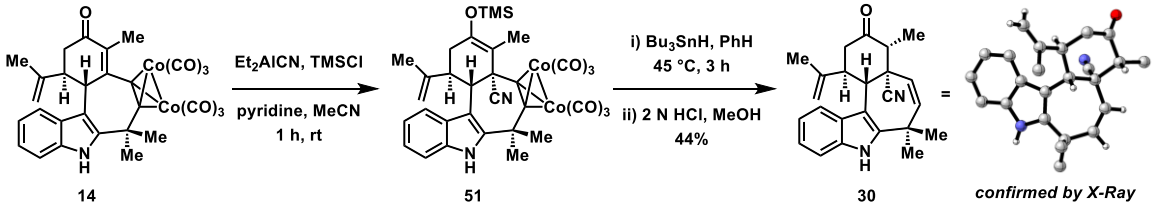


3-hydroxyindolenine (23): To a solution of **11** (13.8 mg, 3.72 x10^{-2} mmol) in MeCN (3.7 mL) and H_2O (3.7 mL) was added (bis(trifluoroacetoxy)iodo)benzene (24.0 mg, 5.59 x 10^{-2} mmol, 1.5 equiv). The reaction mixture was allowed to stir for 1h, at which time it was quenched with the addition of sodium bicarbonate and sodium thiosulfate (sat. aq., 5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) to give the desired product as a yellow foam (8.2 mg, 2.1 x10^{-2} mmol, 57%). See X-ray crystal structure data below. mp 176−178 °C. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.05 (dd, *J* = 17.4, 10.9 Hz, 1H), 5.73 (d, *J* = 12.3 Hz, 1H), 5.64 (d, *J* = 12.2 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 5.18 (d, *J* = 17.4 Hz, 1H), 2.93 (d, *J* = 12.1 Hz, 1H), 1.74 (ddd, *J* = 11.6, 10.6, 4.0 Hz, 1H), 1.68 (s, 2H), 1.62 (s, 2H), 1.58 – 1.48 (m, 1H), 1.46 (s, 2H), 1.43 – 1.37 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 190.7, 158.7, 153.2, 148.3, 142.6, 142.3, 135.8, 130.7, 124.6, 120.9, 118.4, 115.5, 84.6, 66.0, 51.9, 50.2, 43.8, 42.2, 38.5, 34.6, 33.6, 26.9, 25.0, 22.6, 21.1, 19.0. **IR** (ATR, thin film) 3332, 2972, 2120, 1734, 1639, 1558, 1444, 1003, 809, 735 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{31}N_2O$ $[M+H]^+$: 387.2431. Found 387.2429. $[\alpha]_D$ −27 (c 2.0 x10^{-3}, DCM).



Isocyanate (24): To a solution of SM (27.8 mg, 7.19 x10^{-2} mmol) in MeCN (2.4 mL) and H_2O (2.4 mL) was added (bis(trifluoroacetoxy)iodo)benzene (61.9 mg, 0.144 mmol, 2 equiv). The reaction mixture was allowed to stir for 1h, at which time it was quenched with the addition of sodium bicarbonate and sodium thiosulfate (sat. aq., 5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) to give the desired product as a yellow foam (20.8 mg, 5.17 x10^{-2} mmol, 72%). **^{1}H NMR** (700 MHz, CD_2Cl_2) δ 7.30 (dd, *J* = 7.6 Hz, 1H), 7.24 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.12 (dd, *J* = 7.7, 0.8 Hz, 1H), 6.05 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.96 (d, *J* = 12.2 Hz, 1H), 5.72 (d,

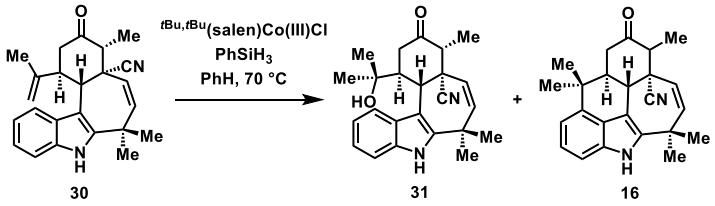
J = 12.2 Hz, 1H), 5.22 (dd, J = 10.9, 1.0 Hz, 1H), 5.18 (dd, J = 17.5, 1.0 Hz, 1H), 2.85 (d, J = 11.9 Hz, 1H), 1.89 (s, 1H), 1.76 (ddd, J = 11.9, 5.0, 4.2 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.51 – 1.46 (m, 2H), 1.44 (s, 3H), 1.31 (s, 3H), 1.30 (d, J = 0.8 Hz, 3H), 1.12 (ddd, J = 12.2, 3.4 Hz, 1H). **^{13}C NMR** (226 MHz, $CDCl_3$) δ 191.6, 153.2, 148.6, 142.9, 141.1, 136.1, 130.6, 127.9, 122.3, 120.7, 118.1, 116.3, 84.9, 65.4, 53.3, 50.8, 45.7, 42.0, 38.5, 34.4, 32.7, 28.6, 25.2, 22.5, 22.1, 21.1. **IR** (ATR, thin film) 3342, 2970, 2936, 2248, 1729, 1567, 1445, 1001, 806, 736 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{31}N_2O_2$ $[M+H]^+$: 403.2380. Found 403.2388. $[\alpha]_D$ −60 (c 0.2 x10^{-3}, DCM).



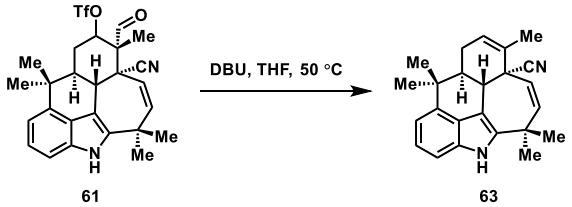
Silyl enol ether 51: Crude cobalt-complexed tetracycle **14** was dissolved in MeCN (20 mL) in a round-bottomed flask. To this solution was added Et_2AlCN (1.0 M in toluene, 6.0 mL, 6.0 mmol, 3 equiv) via syringe over 1 min. After stirring at rt for 30 min, TMSCl (1.2 mL, 9.6 mmol, 4.8 equiv) followed by pyridine (1.2 mL, 15 mmol, 7.6 equiv) were added via syringe. After stirring at rt for another 30 min, the reaction mixture was quenched by pouring into ice and sodium bicarbonate (sat. aq.) (50 mL). The organic layer was washed with brine (2 x 50 mL) and the combined aqueous layers were extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed in vacuo to give silyl enol ether **51** as a crude brown foam, which was immediately subjected to the next reaction without purification.

Ketonitrile 30: Crude **51** was dissolved in benzene (20 mL) and the resulting solution was placed in an oil bath pre-heated to 45 °C. $SnBu_3H$ (2.7 mL, 10 mmol, 5 equiv) was added in four equal portions every half hour at 45 °C, totaling 3 h reaction time. After this time, the solvent was removed in vacuo and the crude product was filtered through a SiO_2 plug eluting with hexanes (500 mL). The hexanes eluent contains the non-polar impurities, which was discarded. The SiO_2 plug was then washed with ethyl acetate (500 mL) and this was concentrated in vacuo. The resulting residue was redissolved in ethyl acetate (100 mL) and 2N $HCl_{(aq)}$/MeOH (1:1, 50 mL) mixture was added. Following complete desilylation (as indicated by TLC), the mixture was quenched with sodium bicarbonate (sat. aq.) (100 mL) and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine (100 mL), dried over sodium sulfate, and concentrated in vacuo. The crude reaction mixture was purified using SiO_2 column chromatography (eluting with 2:1 hexanes/ethyl acetate) to yield the desired product as a white solid (0.34 g, 0.94 mmol, 47% over 3 steps). In a 4 mL vial, the ketonitrile (15 mg) was dissolved in a minimal amount of DCM (~0.5 mL). A layer of hexanes (~0.2 mL) was carefully added on top of the DCM solution. The mixture was lightly capped and allowed to crystallize in a freezer with minimal agitation. mp >260 °C. See X-ray crystal structure data below. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.07 (ddd, J = 8.1, 6.9,

1.1 Hz, 1H), 7.01 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 5.74 (d, *J* = 12.2 Hz, 1H), 5.59 (d, *J* = 12.3 Hz, 1H), 4.90 (s, 1H), 4.76 (s, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 3.91 (ddd, *J* = 12.5, 3.9 Hz, 1H), 2.79 (dd, *J* = 13.3, 3.9 Hz, 1H), 2.64 (q, *J* = 6.6 Hz, 1H), 2.51 (dd, *J* = 13.1 Hz, 1H), 1.78 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 206.1, 144.8, 142.0, 140.5, 134.5, 127.6, 121.7, 121.2, 119.8, 117.7, 113.8, 111.0, 108.6, 51.2, 48.8, 48.1, 45.4, 45.1, 36.2, 29.2, 27.9, 19.8, 10.2. **IR** (ATR, thin film) 3382, 2972, 2928, 2232, 1714, 1492, 902, 728, 701 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{24}H_{26}N_2ONa$ $[M+Na]^+$:381.1937. Found 381.1941. $[\alpha]_D$ −208 (c 1.1 x10^{-3}, DCM).

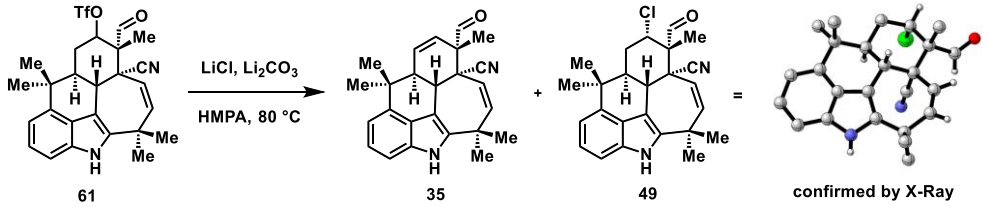


Cyano alcohol 31: To a 4 mL reaction vial charged with **30** (5.0 mg, 0.014 mmol) and the $^{t\text{Bu},t\text{Bu}}$(Salen)CoCl (0.9 mg, 1 μmol, 0.1 equiv) were added phenylsilane (1.9 μL, 0.015 mol, 1.1 equiv) and benzene (0.5 mL). The reaction mixture was stirred under air for 2 h and concentrated under reduced pressure. The crude mixture was purified using SiO_2 preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) to yield the desired product as a white solid (2.0 mg, 5.3 μmol, 38%), along with pentacycle **16** (1.6 mg, 4.5 μmol, 32%). mp 242−254 °C (decomp). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 5.68 (d, *J* = 12.2 Hz, 1H), 5.64 (d, *J* = 12.3 Hz, 1H), 4.29 (d, *J* = 3.7 Hz, 1H), 3.46 (ddd, *J* = 7.5, 3.8, 2.1 Hz, 1H), 3.38 (dd, *J* = 15.8, 7.5 Hz, 1H), 3.00 – 2.91 (m, 1H), 2.74 (q, *J* = 7.2 Hz, 1H), 1.64 (s, 6H), 1.42 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.17 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 210.8, 141.0, 140.4, 135.1, 127.8, 127.2, 121.5, 120.4, 120.1, 119.4, 112.5, 111.6, 73.5, 49.4, 44.7, 43.5, 40.8, 38.5, 37.0, 29.7, 29.0, 28.9, 28.9, 12.0. **IR** (ATR, thin film) 3385, 2975, 2931, 2230, 1712, 1457, 1321, 1125, 1067, 704 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{24}H_{28}N_2O_2Na$ $[M+Na]^+$: 399.2043. Found 399.2044. $[\alpha]_D$ −132 (c 1.0 x10^{-3}, DCM).



Alkene 63: To a solution of **61** (8.0 mg, 0.015 mmol, 1.0 equiv) in THF (0.3 mL) was added DBU (0.011 mL, 0.077 mmol, 5 equiv) and the reaction mixture was stirred at 50 °C for 3 h. The mixture was diluted with ethyl acetate (3 mL) and ammonium chloride solution (sat. aq., 3 mL) and the aqueous layer was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate and concentrated under reduced

pressure to give the crude product. Purification by SiO_2 gel preparatory thin-layer chromatography (4:1 hexanes/ethyl acetate) gave the product as a beige solid (3.4 mg ,0.010 mmol, 67%). mp 210−222 °C (decomp). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.16 – 7.10 (m, 2H), 6.99 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.85 (d, *J* = 12.0 Hz, 1H), 5.82 (d, *J* = 5.8 Hz, 1H), 5.71 (d, *J* = 12.0 Hz, 1H), 3.20 (d, *J* = 11.3 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.22 – 2.14 (m, 1H), 2.05 (ddd, *J* = 11.5, 5.8 Hz, 1H), 1.97 (s, 1H), 1.70 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 141.7, 140.3, 136.0, 133.4, 130.7, 128.1, 126.9, 125.9, 122.6, 121.5, 112.7, 108.0, 107.8, 47.2, 43.4, 42.0, 38.4, 37.0, 33.7, 28.0, 26.2, 24.9, 23.9, 19.3. **IR** (thin film) 3355, 2966, 2928, 2891, 2229, 1721, 1607, 1471, 1454, 1330, 771, 740, 723 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{24}H_{26}N_2Na$ $[M+Na]^+$: 365.1988. Found 365.1991. $[\alpha]_D$ +50.7 (c 0.75 x10^{-3}, DCM).

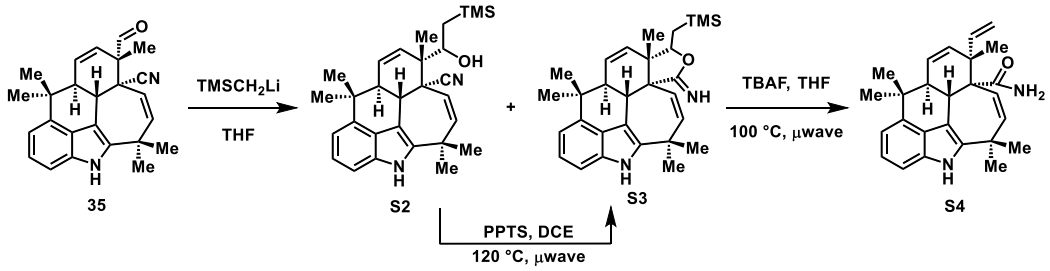


Alkene 35 + chloride 49: To a 4 mL reaction vial charged with the **61** (182 mg, 0.350 mmol) was added LiCl (148 mg, 3.50 mmol, 10 equiv), Li_2CO_3 (259 mg, 3.50 mmol, 10 equiv) and HMPA (0.7 mL) in the glovebox. The vial was sealed with a Teflon-lined cap and removed from the glovebox. The reaction mixture was stirred at 80 °C for 12 h and diluted with ethyl acetate (10 mL) and 1N $HCl_{(aq)}$ solution (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 x 10 mL). The combined organic extract was washed with brine (10 mL), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure. Purification by SiO_2 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) gave the desired product as a white solid (81.6 mg, 0.220 mmol, 63%) and the chloro compound **49** (48.4 mg, 0.119 mmol, 34%) as a white solid.

Alkene 35: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.76 (br s, 1H), 7.20 – 7.14 (m, 2H), 7.06 (dd, *J* = 6.3, 1.7 Hz, 1H), 6.26 (dd, *J* = 10.5, 2.0 Hz, 1H), 5.78 (d, *J* = 12.7 Hz, 1H), 5.70 (dd, *J* = 10.5, 3.0 Hz, 1H), 5.47 (d, *J* = 12.7 Hz, 1H), 3.52 (d, *J* = 10.9 Hz, 1H), 2.85 (ddd, *J* = 11.0, 2.3 Hz, 1H), 1.61 (s, 6H), 1.51 (s, 3H), 1.35 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 201.5, 143.7, 140.0, 135.7, 133.9, 130.3, 127.3, 126.2, 123.0, 122.8, 119.9, 113.8, 107.9, 105.9, 54.3, 49.5, 43.1, 38.7, 37.9, 35.5, 32.1, 29.4, 25.7, 25.1, 18.8. **IR** (ATR, thin film) 3373, 2966, 2929, 2865, 2232, 1727, 1470, 1452, 1365, 752 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{26}N_2ONa$ $[M+Na]^+$: 369.1972. Found 369.1982. $[\alpha]_D$ −102 (c 1.3 x10^{-3}, DCM).

Chloride 49: In a 4 mL vial, the chloro compound (15 mg) was dissolved in a minimal amount of DCM (~0.5 mL). A layer of hexanes (~0.2 mL) was carefully added on top of the DCM solution. The mixture was lightly capped and allowed to crystallize in a freezer with minimal agitation. mp >260 °C. See X-ray crystal structure data below. **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ 10.79 (s, 1H), 9.57 (br s, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 5.66 (d, *J* = 12.5 Hz, 1H), 5.57 (d, *J* = 12.4 Hz, 1H), 5.02 (dd, *J* = 3.2 Hz, 1H), 3.34 (d, *J* = 11.0 Hz, 1H), 2.29 (ddd, *J* = 15.5, 12.7, 3.3 Hz, 1H), 2.25 – 2.15 (m, 2H), 1.58 (s, 3H), 1.48 (s, 3H), 1.43

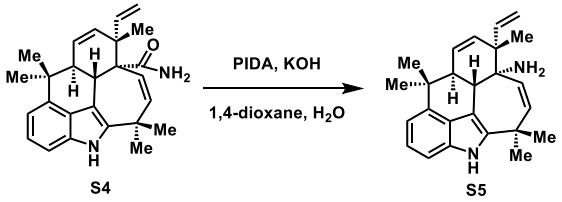
(s, 3H), 1.42 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (151 MHz, $(CD_3)_2SO$) δ 199.3, 141.2, 139.1, 136.7, 133.4, 125.6, 125.3, 121.5, 120.7, 111.6, 107.7, 104.2, 61.9, 54.7, 42.1, 41.5, 38.9, 38.4, 36.5, 32.1, 29.0, 26.6, 25.3, 24.3, 17.1. **IR** (ATR, thin film) 3324, 3228, 2966, 2926, 2123, 1829, 1622, 1453, 1334, 1171, 1032, 808, 640 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{27}N_2OClNa$ $[M+Na]^+$: 429.1704. Found 429.1705. $[\alpha]_D$ −154 (c 1.6 x10^{-3}, DCM).



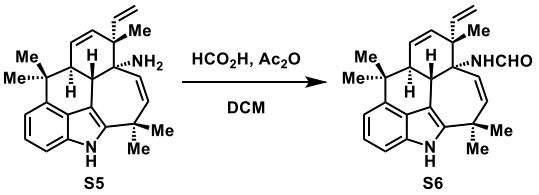
Acetimidate S3: To a solution of **35** (73.4 mg, 0.198 mmol, 1 equiv) in THF (2 mL) was added $TMSCH_2Li$ (1.0 M solution in pentane, 1.0 mL, 1.0 mmol, 5 equiv). The solution was allowed to stir for 1 h, at which time it was quenched with the addition of ammonium chloride (sat. aq.) (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to give a yellow foam. The crude mixture was transferred to a microwave vial (2.5–5 mL capacity) as a solution in DCE (5 mL). PPTS (249 mg, 0.990 mmol, 5 equiv) was added and the vial was sealed with a crimp-top cap. The vial was heated to 120 °C under microwave irradiation for 30 min. Once the vial had cooled to rt, the solution was poured into saturated aqueous sodium bicarbonate solution (5 mL) and the aqueous layer was extracted with DCM (3 x10 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude mixture of **S3** as a yellow oil. The crude product was directly subjected to the next reaction without further purification.

Amide S4: To a crude reaction mixture containing **S3** in a microwave vial was added TBAF (1 M THF, 2.0 mL, 2.0 mmol, 10 equiv) and the vial was sealed. The resulting yellowish-brown solution was then heated to 100 °C under microwave irradiation for 1 h. Upon cooling to rt, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel column chromatography on a Yamazen® automatic purification system. Amide **S4** was isolated as a yellow foam (35.0 mg, 0.0906 mmol, 46% over 3 steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.84 (br s, 1H), 7.17 – 7.08 (m, 2H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.44 (dd, *J* = 17.5, 10.9 Hz, 1H), 6.14 (br s, 1H), 5.97 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.78 (d, *J* = 13.4 Hz, 1H), 5.74 (dd, *J* = 10.4, 3.0 Hz, 1H), 5.63 (d, *J* = 13.4 Hz, 1H), 5.31 – 5.19 (m, 3H), 3.74 (d, *J* = 11.0 Hz, 1H), 2.88 (ddd, *J* = 10.9, 2.3 Hz, 1H), 1.58 (s, 3H), 1.55 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.5, 143.2, 141.0, 139.0, 136.3, 135.6, 134.1, 128.9, 126.3, 125.6, 122.7, 114.9, 113.2, 108.5, 107.5, 57.5, 47.3, 45.5, 38.8, 37.4, 35.7, 33.3, 28.8, 25.6, 24.7, 24.6. **IR** (ATR, thin film) 3485, 3327, 2966, 2927, 1668, 1577, 1469, 1452, 1338, 917, 749 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{30}N_2ONa$ $[M+Na]^+$: 409.2250.

Found 409.2253. $[\alpha]_D$ −111 (c 0.75 x10^{-3}, DCM).

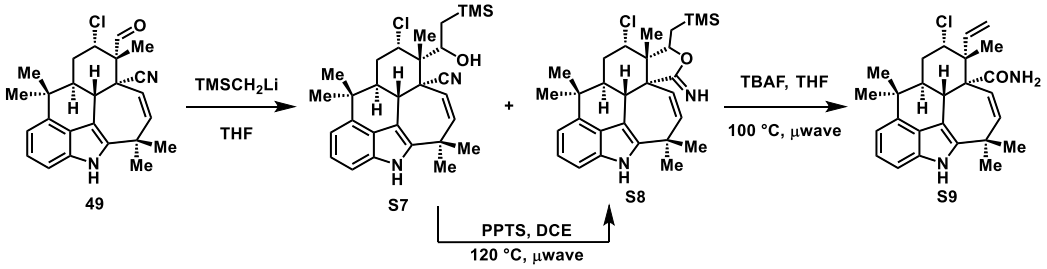


Amine S5: Amide **S4** (27.7 mg, 0.0717 mmol, 1 equiv) was dissolved in 1,4-dioxane (1.5 mL) and H_2O (1.5 mL) was added. To this solution was added crushed KOH (141 mg, 2.51 mmol, 35 equiv) and the suspension was allowed to stir for 5 min at rt. At this time, PIDA (27.7 mg, 0.0858 mmol, 1.2 equiv) was added and the solution turned light yellow. The suspension was allowed to stir at rt for 20 h at which time it was quenched with sodium bicarbonate (sat. aq., 3 mL) and sodium thiosulfate (sat. aq., 3 mL). After stirring for 5 min at rt, the mixture was diluted with ethyl acetate (5 mL) and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with a mixture of 10% acetone and 1% NH_4OH in DCM) to yield the desired product (12.0 mg, 0.0330 mmol, 46%) as a yellow film. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.70 (br s, 1H), 7.17 – 7.11 (m, 2H), 7.04 (dd, *J* = 6.7, 1.4 Hz, 1H), 6.24 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.95 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.85 (d, *J* = 13.2 Hz, 1H), 5.62 (dd, *J* = 10.5, 3.0 Hz, 1H), 5.42 (d, *J* = 13.2 Hz, 1H), 5.27 (dd, *J* = 1.8 Hz, 1H), 5.26 (dd, *J* = 30.4, 1.5 Hz, 1H), 3.57 (d, *J* = 10.9 Hz, 1H), 2.65 (ddd, *J* = 11.0, 2.3 Hz, 1H), 1.58 (s, 3H), 1.50 (s, 3H), 1.30 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 142.0, 141.2, 137.1, 135.7, 135.5, 134.2, 132.8, 127.1, 125.1, 122.5, 115.6, 113.3, 107.6, 107.4, 57.7, 46.8, 46.6, 38.3, 37.3, 37.1, 32.4, 31.1, 25.8, 25.2, 24.2. **IR** (ATR, thin film) 3416, 3293, 3027, 2965, 1468, 1449, 917, 750 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{31}N_2$ $[M+H]^+$: 359.2482. Found 359.2489. $[\alpha]_D$ −53 (c 1.0 x10^{-3}, DCM).



Formamide S6: To amine **S5** (3.0 mg, 8.4μmol, 1 equiv) in a round-bottomed flask was added DCM (0.5 mL) followed by Ac_2O (14 μL, 0.15 mmol, 18 equiv) and formic acid (6.3 μL, 0.17 mmol, 20 equiv). This solution was allowed to stir at rt for 14 h. The solution was quenched with sodium bicarbonate (5 mL) and diluted with DCM (5 mL). The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, then concentrated in vacuo. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) to give the desired product (**S9**) as a yellow film (1.0 mg, 2.6 μmol, 31%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 11.9 Hz, 1H), 7.73 (s, 1H), 7.18 – 7.10 (m, 2H), 7.02 (dd, *J* = 6.6, 1.4 Hz, 1H), 6.06 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.02 (dd, *J* = 10.5, 1.8 Hz, 1H), 5.92 (br d, *J* = 12.1 Hz, 1H), 5.74 (d, *J* = 13.3 Hz,

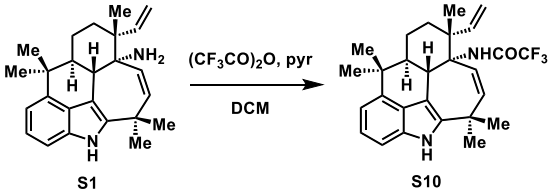
1H), 5.68 (d, *J* = 13.3 Hz, 1H), 5.65 (dd, *J* = 10.5, 2.9 Hz, 1H), 5.34 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.28 (dd, *J* = 17.4, 1.1 Hz, 1H), 3.67 (d, *J* = 11.0 Hz, 1H), 2.50 (ddd, *J* = 11.0, 2.4 Hz, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.2, 141.7, 140.6, 140.2, 135.6, 134.7, 134.2, 126.6, 126.5, 125.7, 122.7, 117.6, 113.4, 107.8, 106.3, 60.6, 47.4, 46.3, 38.6, 37.5, 36.9, 32.8, 29.1, 25.8, 24.9, 24.1. **IR** (ATR, thin film) 3303, 2966, 1669, 1451, 1296, 1164, 919, 783 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{29}N_2O$ $[M-H]^-$: 385.2285. Found 385.2291. $[\alpha]_D$ −143 (c 0.75 x10^{-3}, DCM).



Chloroacetimidate S8: To a solution of **49** (15 mg, 0.030 mmol, 1 equiv) in THF (2 mL) was added $TMSCH_2Li$ (1.0 M solution in pentane, 0.21 mL, 0.21 mmol, 7 equiv). The solution was allowed to stir for 1 h, at which time it was quenched with the addition of ammonium chloride (sat. aq., 5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to give a yellow foam. The crude mixture was transferred to a microwave vial (0.5–2 mL capacity) as a solution in DCE (1 mL). PPTS (38 mg, 0.15 mmol, 5 equiv) was added and the vial was sealed with a crimp-top cap. The vial was heated to 120 °C under microwave irradiation for 30 min. Once the vial had cooled to rt, the solution was poured into saturated aqueous sodium bicarbonate solution (5 mL) and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude **S8** as a yellow oil. The crude product was directly subjected to the next reaction without further purification.

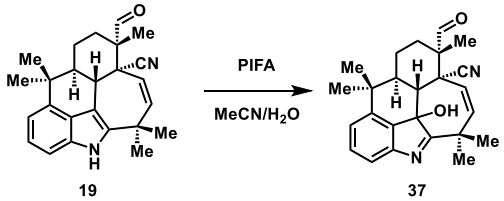
Chloroamide S9: To a crude reaction mixture containing **S8** in a microwave vial was added TBAF (1 M THF, 0.30 mL, 0.30 mmol, 10 equiv) and the vial was sealed. The resulting yellowish-brown solution was then heated to 100 °C under microwave irradiation for 1 h. Upon cooling to rt, the reaction mixture was diluted with ethyl acetate (5 mL) and washed with H_2O (5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 30% ethyl acetate in DCM). Chloroamide **S9** was isolated as a white solid (11.0 mg, 0.026 mmol, 87% over 3 steps). mp 246−250 °C (decomp). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.16 – 7.09 (m, 2H), 7.05 – 6.97 (m, 2H), 5.82 (d, *J* = 12.8 Hz, 1H), 5.48 (d, *J* = 12.8 Hz, 1H), 5.40 (br s, 2H), 5.32 (d, *J* = 11.1 Hz, 1H), 5.24 (d, *J* = 17.4 Hz, 1H), 5.15 (br s, 0H), 4.26

(dd, J = 3.3 Hz, 1H), 3.64 (d, J = 11.7 Hz, 1H), 3.12 (ddd, J = 11.8, 4.4 Hz, 1H), 2.43 – 2.29 (m, 2H), 1.52 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.09 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 175.3, 143.7, 140.8, 138.1, 135.7, 133.8, 131.4, 125.4, 122.8, 113.7, 112.7, 107.9, 107.7, 67.8, 54.7, 47.8, 34.0, 38.5, 37.4, 37.2, 33.0, 31.3, 28.7, 25.0, 24.3, 21.3. **IR** (ATR, thin film) 3483, 3362, 2964, 1674, 1579, 1454, 1332, 924, 767, 725 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{31}N_2OClNa$ $[M+Na]^+$: 445.2017. Found 445.2023. $[\alpha]_D$ −235 (c 0.80 x10^{-3}, DCM).



S1 S10

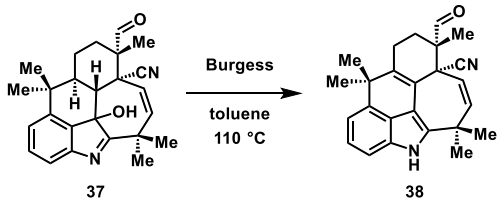
To a solution of **S1** (1.1 mg, 3.1 μmol, 1 equiv) dissolved in DCM (0.2 mL), pyridine (1.2 μL, 0.015 mmol, 5 equiv) and trifluoroacetic anhydride (4.3 μL, 0.031 mmol, 10 equiv) were added at rt. The reaction mixture was stirred for 40 h, then diluted with DCM (2 mL) and sodium bicarbonate solution (sat. aq., 2 mL). The aqueous layer was extracted with DCM (3 x 3 mL) and the combined organic layers were washed with brine, dried over sodium sulfate and concentrated in vacuo to yield the crude reaction product. The crude product was purified using SiO_2 gel preparatory thin-layer chromatography (eluting with 4:1 hexanes/ethyl acetate) to give the desired product (**S10**) as a beige solid (1.4 mg, 3.1 μmol, quant.). mp 206−215 °C (decomp). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 7.88 (br s, 1H), 7.13 – 7.07 (m, 2H), 6.98 (dd, J = 7.0, 1.0 Hz, 1H), 6.15 – 6.05 (m, 2H), 5.98 (d, J = 12.9 Hz, 1H), 5.57 (d, J = 12.9 Hz, 1H), 5.12 – 5.06 (m, 2H), 3.60 (d, J = 11.7 Hz, 1H), 1.95 (ddd, J = 13.1, 3.6 Hz, 1H), 1.82 (ddd, J = 13.6, 3.8 Hz, 1H), 1.72 (ddd, J = 13.0, 3.5 Hz, 1H), 1.61 (ddd, J = 12.2, 3.7 Hz, 1H), 1.54 – 1.51 (m, 1H), 1.50 (s, 3H), 1.40 (s, 3H), 1.32 (s, 6H), 1.10 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 155.7 (q, J = 35.0 Hz), 145.4, 140.8, 139.3, 136.7, 134.0, 127.1, 126.7, 122.6, 116.1 (q, J = 290.2 Hz), 113.0, 112.6, 107.9, 105.5, 63.4, 46.9, 45.8, 40.2, 38.4, 37.9, 33.3, 33.2, 28.6, 24.6, 24.5, 20.9, 19.9. **^{19}F NMR** (565 MHz, CD_2Cl_2) δ −76.2. **IR** (ATR, thin film) 3385, 2968, 1731, 1535, 1453, 1208, 1165, 916, 727 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{27}H_{30}N_2OF_3$ $[M-H]^-$: 455.2316. Found 455.2325. $[\alpha]_D$ −160 (c 1.1 x10^{-3}, DCM).



19 37

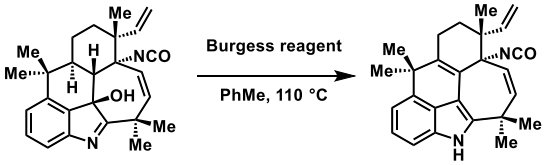
Cyano 3-hydroxyindolenine 37: To a solution of **19** (68.0 mg, 0.183 mmol) MeCN (3.7 mL) and H_2O (3.7 mL) was added (bis(trifluoroacetoxy)iodo)benzene (157 mg, 0.365 mmol, 2 equiv). The reaction mixture was allowed to stir for 1h at which time it was quenched with the addition of

sodium bicarbonate and sodium thiosulfate (sat. aq., 5 mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated in vacuo to yield the crude reaction product. The crude material was dissolved in DCM and was filtered through a cotton plug and concentrated. It was then triturated with cold diethyl ether (0.5 mL) to give the product as a white solid. The mother liquor was concentrated under reduced pressure and subjected to purification using Al_2O_3 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) to give the desired product (50.0 mg, 0.130 mmol, 70% combined) and the dehydrated side product (1.5 mg, 4.1 x10^{-3} mmol, 2%) both as white solids. mp >260 °C. **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 9.63 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 5.79 (d, *J* = 12.0 Hz, 1H), 5.40 (d, *J* = 12.0 Hz, 1H), 2.89 (d, *J* = 12.1 Hz, 1H), 2.09 (br s, 1H), 1.90 (ddd, *J* = 13.0, 3.7 Hz, 1H), 1.80 (ddd, *J* = 13.6, 4.0 Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.59 – 1.51 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.29 (ddd, *J* = 12.4, 3.4 Hz, 1H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 202.6, 190.1, 153.6, 148.6, 143.4, 136.2, 131.1, 122.3, 121.3, 120.0, 118.6, 85.1, 52.5, 52.2, 51.5, 42.8, 42.7, 39.1, 34.6, 30.3, 26.8, 25.0, 22.6, 20.4, 14.8. **IR** (ATR, thin film) 3419, 3373, 3037, 2970, 2938, 2726, 2225, 1727, 1616, 1456, 1328, 795, 756 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{26}N_2ONa$ $[M-H_2O+Na]^+$: 393.1937. Found 393.1943. $[\alpha]_D$ −157 (c 2.4 x10^{-3}, DCM).



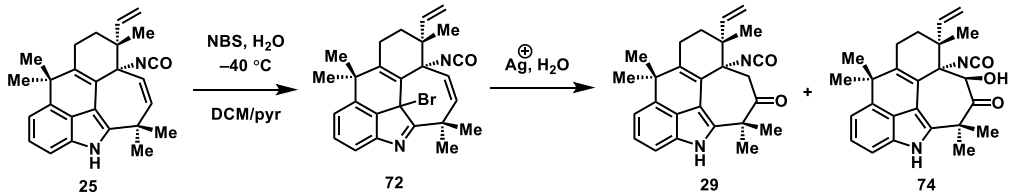
37 38

Cyano alkene 38: In a nitrogen-filled glovebox, to a 4 mL reaction vial charged with the starting material (8.0 mg, 2.1 x10^{-2} mmol) and a stir bar were added the Burgess Reagent (7.4 mg, 3.1 x10^{-2} mmol, 1.5 equiv) and toluene (0.4 mL). The vial was sealed with a Teflon-sealed cap, removed from the glovebox and heated to 110 °C for 4 h. The reaction mixture was then diluted with water (2 mL) and ethyl acetate (2 mL). The biphasic mixture was vigorously mixed and the layers separated. The aqueous layer was additionally extracted with ethyl acetate (3 x 2 mL), and the combined organic extract was dried over anhydrous sodium sulfate, then concentrated under reduced pressure. Purification by Al_2O_3 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) gave the desired product as a white solid (4.7 mg, 0.013 mmol, 62%). mp 135 °C (decomp). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 9.93 (s, 1H), 7.83 (br s, 1H), 7.19 (dd, *J* = 8.0, 7.4 Hz, 1H), 7.08 (dd, *J* = 8.0, 0.6 Hz, 1H), 6.99 (dd, *J* = 7.4, 0.6 Hz, 1H), 5.91 (d, *J* = 12.4 Hz, 1H), 5.36 (d, *J* = 12.4 Hz, 1H), 2.74 (ddd, *J* = 18.7, 6.8, 1.6 Hz, 1H), 2.54 (ddd, *J* = 18.6, 11.5, 6.9 Hz, 1H), 2.39 (ddd, *J* = 13.5, 11.6, 6.8 Hz, 1H), 1.71 (ddd, *J* = 13.4, 6.9, 1.6 Hz, 1H), 1.68 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.39 (s, 3H), 1.22 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 204.0, 145.3, 138.9, 138.0, 136.4, 133.1, 126.0, 124.6, 123.4, 122.0, 121.0, 114.9, 107.4, 106.8, 51.0, 42.1, 42.1, 37.8, 32.0, 31.79, 29.1, 27.6, 26.7, 21.4, 13.4. **IR** (ATR, thin film) 3372, 3050, 2968, 2931, 2869, 2225, 1726, 1471, 1456, 1301, 756, 735 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{25}H_{25}N_2O$ $[M-H]^-$: 369.1972. Found 369.1976. $[\alpha]_D$ −113 (c 0.75 x10^{-3}, DCM).



24 25

Isocyanate alkene 25: In a nitrogen-filled glovebox, to a 4 mL reaction vial with **24** (20.8 mg, 5.17 x10^{-2} mmol) and a stir bar were added the Burgess Reagent (24.6 mg, 0.103 mmol, 2 equiv) and toluene (2.6 mL). The vial was sealed with a Teflon-sealed cap, removed from the glovebox and heated to 110 °C for 4 h. The reaction mixture was then diluted with water (3 mL) and ethyl acetate (3 mL). The biphasic mixture was vigorously mixed and the layers separated. The aqueous layer was additionally extracted with ethyl acetate (3 x 5 mL), and the combined organic extract was dried over anhydrous sodium sulfate, then concentrated under reduced pressure. Purification by SiO_2 gel preparatory thin-layer chromatography (eluting with 2:1 hexanes/ethyl acetate) gave the desired product as a yellow film (9.0 mg, 0.023 mmol, 45%). **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 8.06 (br s, 1H), 7.24 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.19 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.05 (dd, *J* = 7.2, 0.7 Hz, 1H), 5.92 (d, *J* = 11.4 Hz, 1H), 5.88 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.44 (d, *J* = 11.4 Hz, 1H), 5.14 (dd, *J* = 17.5, 1.2 Hz, 1H), 5.07 (dd, *J* = 10.7, 1.2 Hz, 1H), 2.28 (td, *J* = 15.4, 14.9, 2.9 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.67 (s, 3H), 1.62 (dt, *J* = 12.5, 3.1 Hz, 1H), 1.59 (s, 3H), 1.40 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H). **^{13}C NMR** (151 MHz, CD_2Cl_2) δ 148.2, 141.3, 137.6, 135.7, 133.2, 133.1, 129.9, 127.6, 124.5, 123.5, 119.9, 114.9, 111.8, 109.2, 107.5, 67.3, 45.8, 40.6, 35.8, 33.5, 27.2, 26.8, 26.7, 25.7, 23.0, 19.1. **IR** (ATR, thin film) 3431, 2970, 2240, 1469, 912, 749 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{27}N_2O$ $[M-H]^-$: 383.2129. Found 383.2135. $[\alpha]_D$ 3.25 (c 4.0 x10^{-3}, DCM).



25 72 29 74

Isocyanoketone 29 + Isocyanoketol 74: A solution of **25** (6.0 mg, 0.016 mmol) in DCM (0.64 mL), pyridine (0.64 mL) and water (0.035 mL, 1.9 mmol, 120 equiv) was cooled to −40 °C in a dry ice bath with acetonitrile. *N*-bromosuccinimide (6.9 mg, 0.039 x10^{-3} mmol, 2.5 equiv) in acetonitrile (0.3 mL) was added dropwise to the solution of **25** and the resulting mixture was stirred for 1 h at −40 °C. The reaction was quenched with saturated aqueous sodium thiosulfate and sodium bicarbonate solutions. The biphasic mixture was vigorously mixed and the layers separated. The aqueous layer was additionally extracted with DCM (3 x 0.5 mL), and the combined organic extract was dried over anhydrous Na_2SO_4, then concentrated under reduced pressure to give crude **72**.

To a 4 mL vial containing Ag_2CO_3 (2.6 mg, 9.6 x10^{-3} mmol, 0.6 equiv) in water (0.1 mL) was added crude **72** in acetonitrile (0.4 mL). The reaction mixture was stirred for 70 min at rt, then

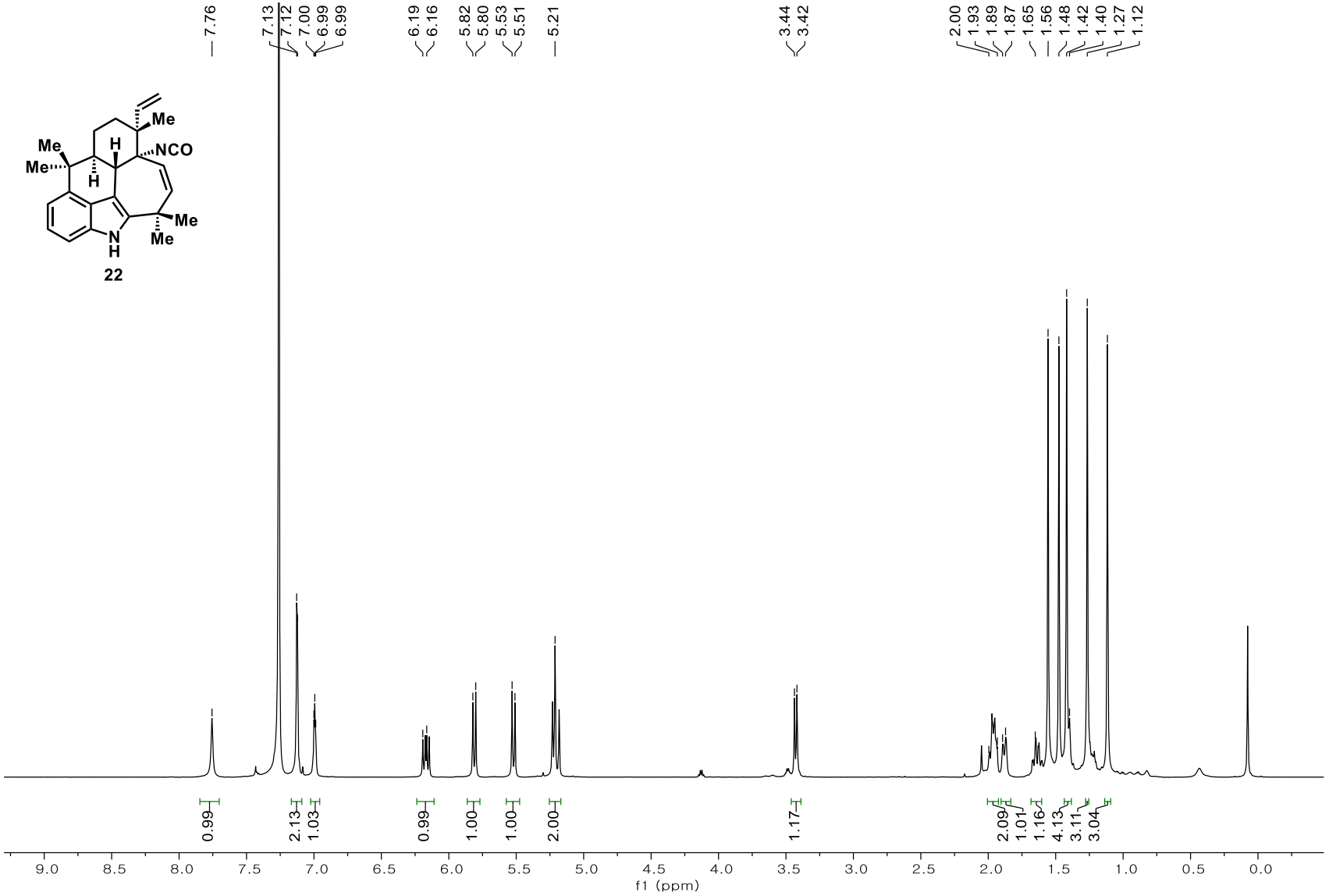
filtered through a pad of celite and sodium sulfate and washed with DCM. After concentration under reduced pressure, preparatory thin-layer chromatography on SiO_2 (eluting with 4:1 hexanes/ethyl acetate) gave **29** (1.6 mg, 4.0 x10^{-3} mmol, 25 %) and **74** (1.0 mg, 2.4 x10^{-3} mmol, 15%).

Isocyanoketone 29: ^{1}**H NMR** (900 MHz, CD_3Cl) δ 7.99 (s, 1H), 7.24 – 7.21 (m, 2H), 7.05 (dd, J = 5.0, 2.8 Hz, 1H), 5.92 (dd, J = 17.4, 10.6 Hz, 1H), 5.26 (dd, J = 10.6, 1.1 Hz, 1H), 5.19 (dd, J = 17.4, 1.1 Hz, 1H), 3.54 (d, J = 11.1 Hz, 1H), 3.21 (d, J = 11.1 Hz, 1H), 2.22 (ddd, J = 14.3, 13.9, 3.0 Hz, 2H), 1.97 – 1.88 (m, 2H), 1.63 (s, 3H), 1.60 – 1.59 (m, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.25 (s, 3H), 1.13 (s, 3H). ^{13}**C NMR** (226 MHz, $CDCl_3$) δ 206.7, 145.9, 138.0, 137.3, 133.8, 130.7, 129.1, 125.1, 124.1, 123.5, 115.0, 113.2, 108.8, 107.64, 66.5, 50.1, 45.3, 43.0, 41.9, 33.3, 27.8, 27.0, 26.6, 26.4, 21.0, 19.1. **IR** (ATR, thin film) 3374, 2967, 2238, 1732, 1713, 1468, 1169, 802 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{27}N_2O_2$ $[M–H]^-$: 399.2078. Found 399.2080. $[\alpha]_D$ +89 (c 0.65 x10^{-3}, DCM).

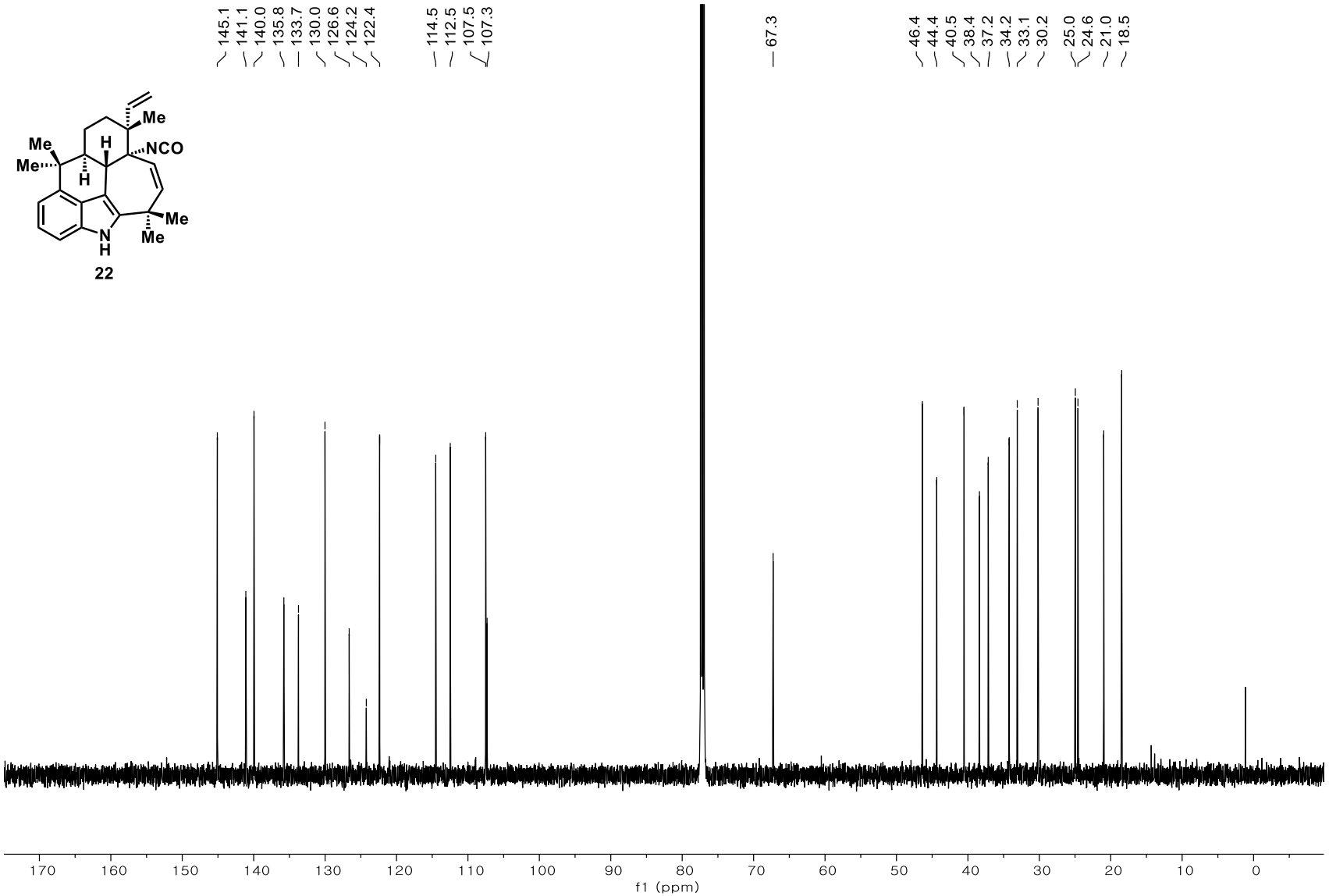
Isocyanoketol 74: ^{1}**H NMR** (900 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.26 – 7.24 (m, 2H), 7.08 (dd, J = 5.0, 2.8 Hz, 1H), 5.76 (dd, J = 17.4, 10.6 Hz, 1H), 5.29 (dd, J = 10.6, 1.1 Hz, 1H), 5.25 (dd, J = 17.4, 1.1 Hz, 1H), 4.85 (d, J = 9.5 Hz, 1H), 2.88 (d, J = 9.7 Hz, 1H), 2.22 (ddd, J = 13.9, 3.0 Hz, 1H), 1.97 (ddd, J = 13.5, 3.4 Hz, 1H), 1.93 (ddd, J = 14.0, 3.0 Hz, 1H), 1.77 (s, 3H), 1.60 (dd, J = 3.4 Hz, 1H), 1.59 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H). ^{13}**C NMR** (226 MHz, $CDCl_3$) δ 206.8, 144.7, 137.6, 137.2, 137.2, 133.8, 130.2, 125.2, 124.5, 123.4, 115.5, 114.4, 109.1, 105.6, 78.9, 66.3, 47.8, 45.5, 41.9, 33.2, 28.1, 27.8, 26.5, 25.8, 21.1, 19.2. **IR** (ATR, thin film) 3374, 2969, 2238, 1707, 1455, 1214, 1053, 761 cm^{-1}. **HRMS** (ESI) *m/z* calc'd for $C_{26}H_{27}N_2O_3$ $[M–H]^-$: 415.2027. Found 415.2032. $[\alpha]_D$ +157 (c 0.35 x10^{-3}, DCM).

3.7 Appendix to Chapter 2: Spectra

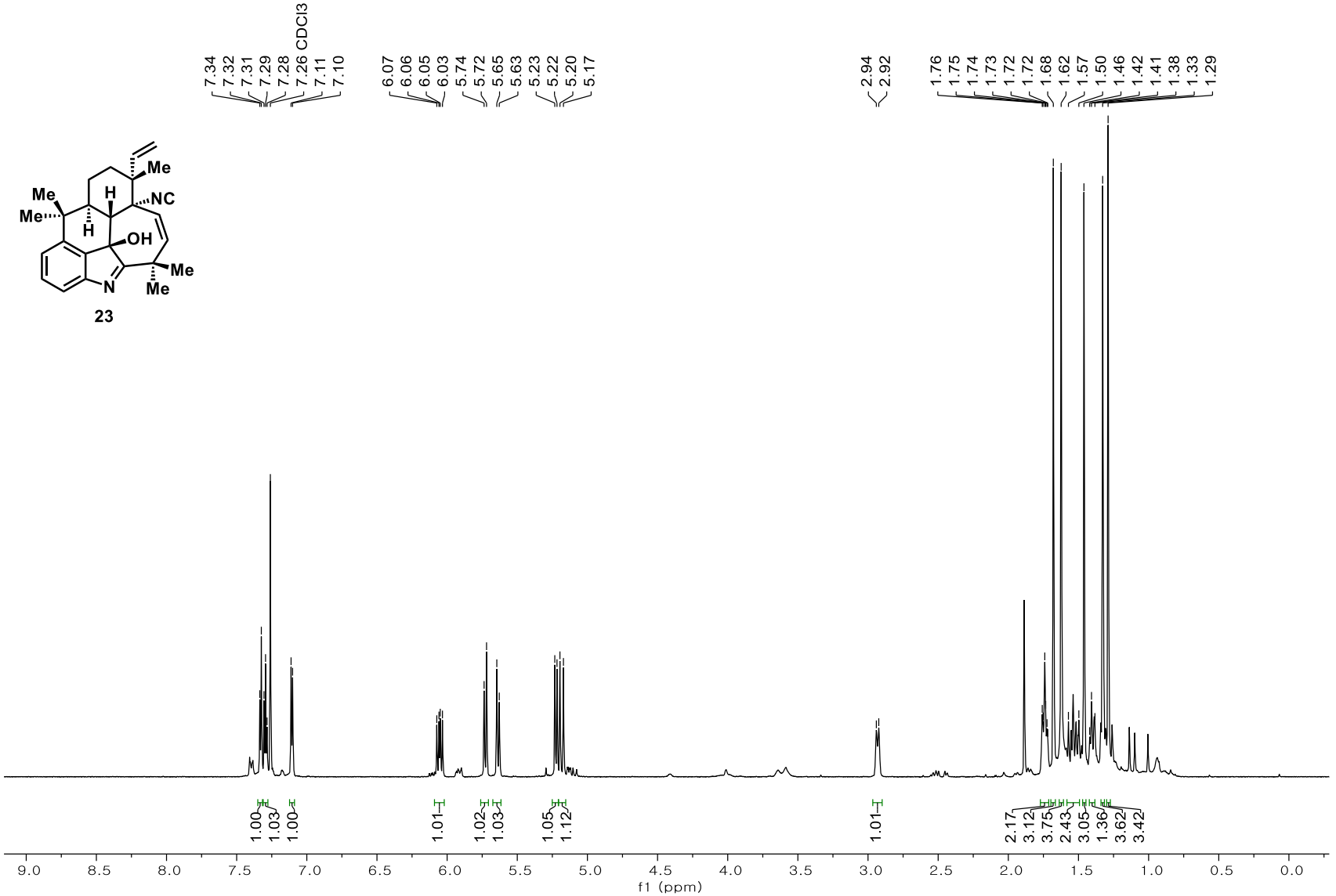
Ree5-136A.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



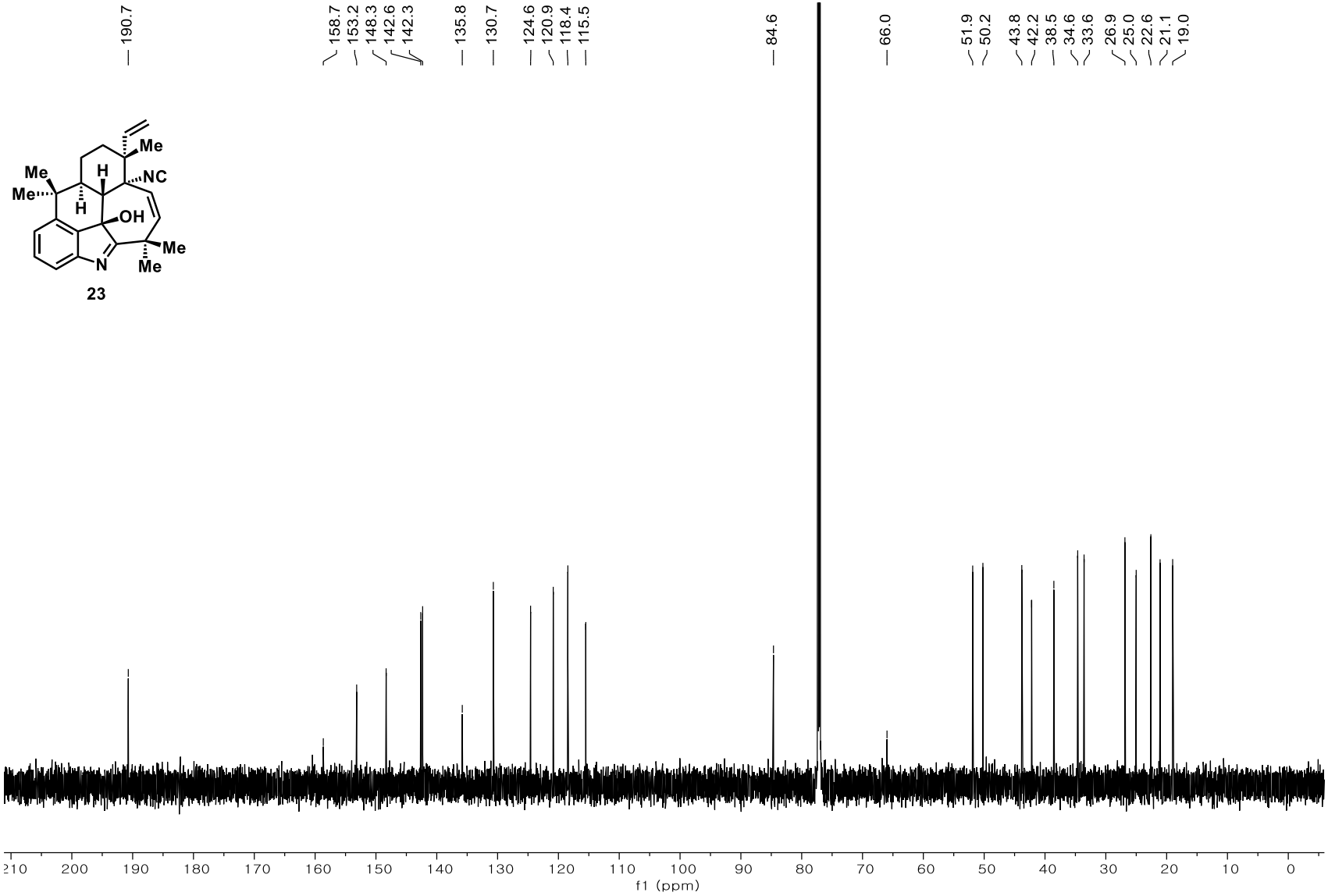
Ree5-136A.13.fid — 13C{1H} starting parameters - HC 06/17/2019



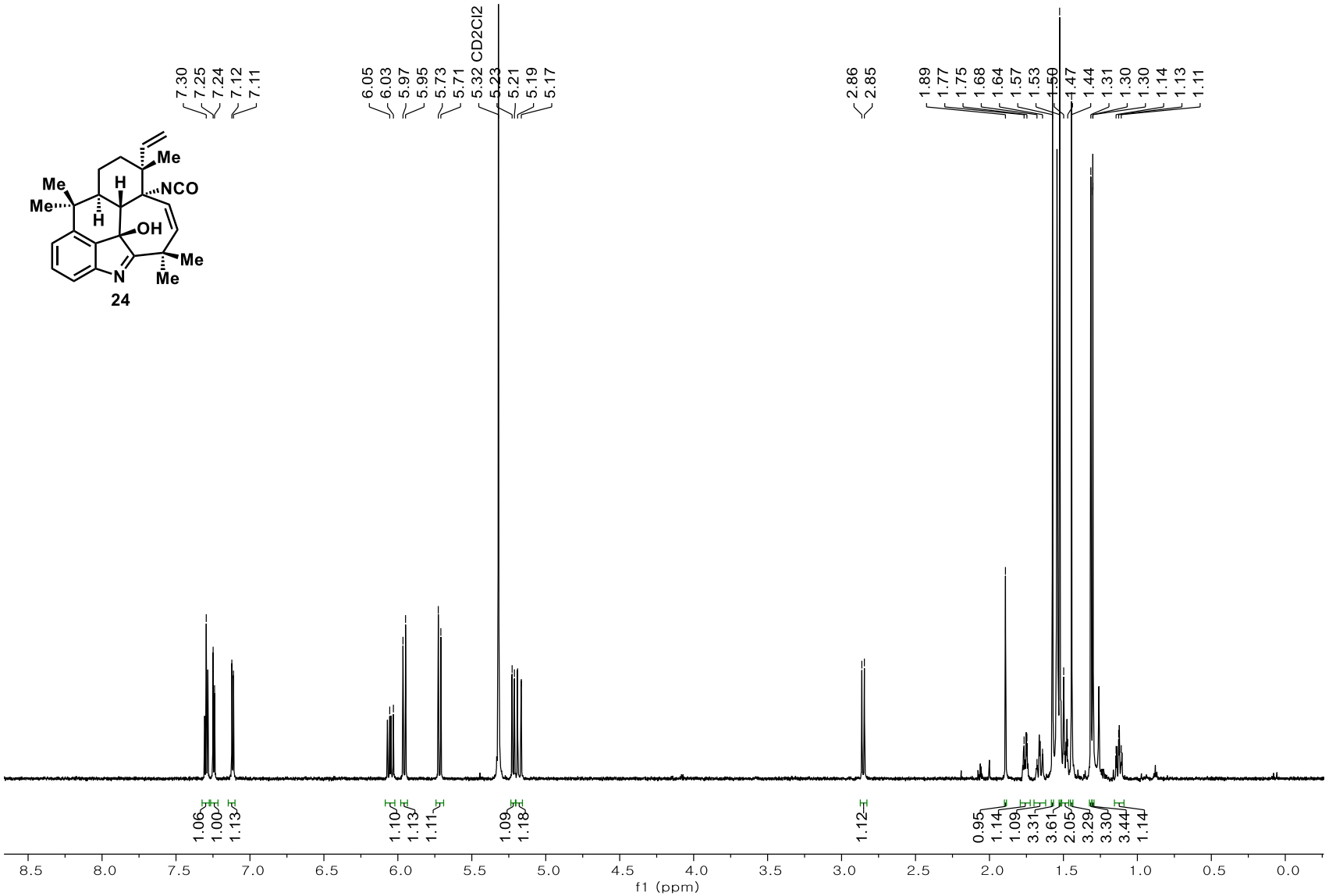
Ree3-124_d2_repurified.1.fid — AV-700 starting parameters for 1D 1H — TXI probe - HC 08/22/2018 — p1=14.88 us @ -6 dB (13 dB attenuator at the amplifier)

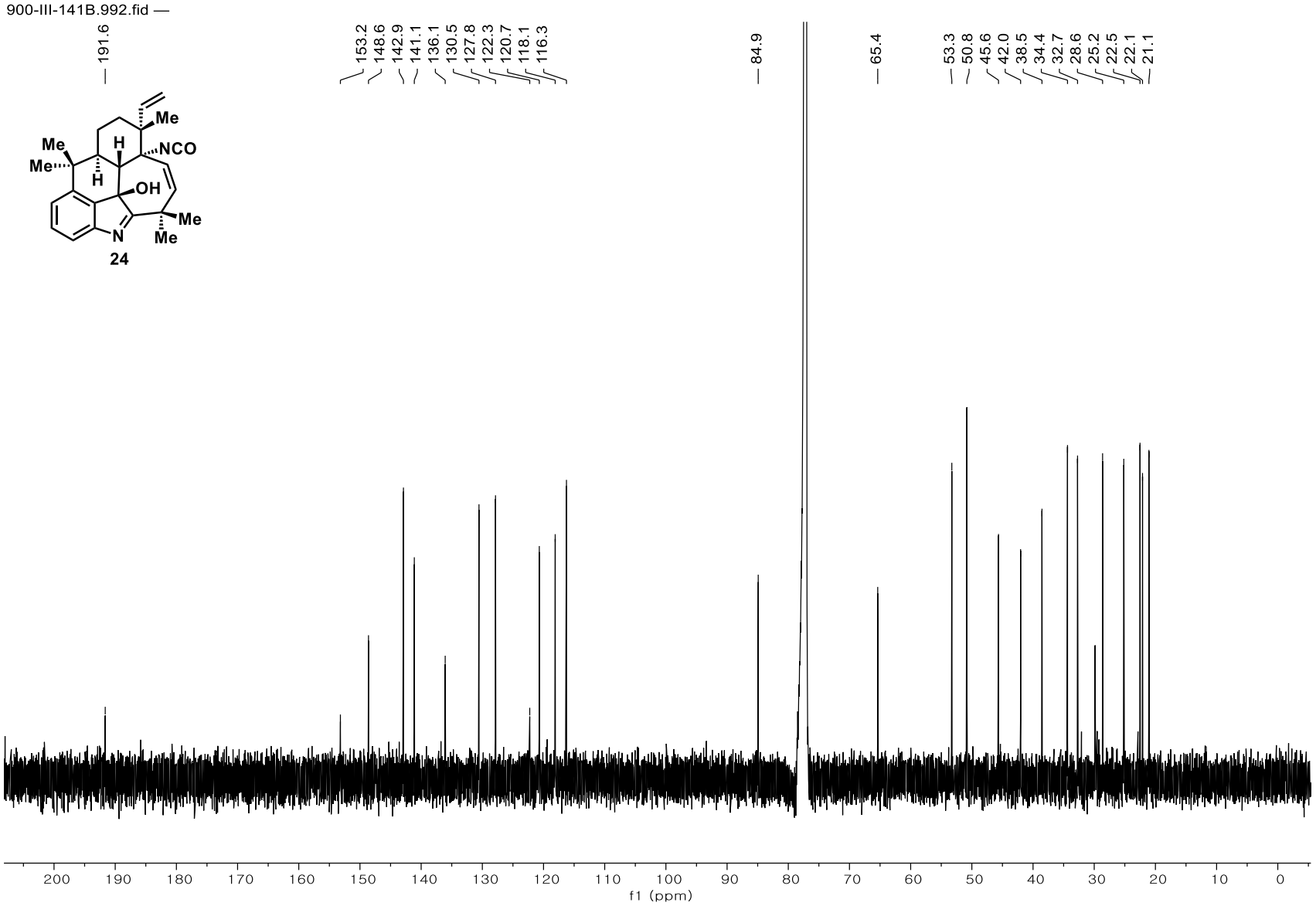


Ree3-124_d2_repurified.13.fid — AV-700 starting parameters for 1D 13C{1H} — TXI probe - HC 08/22/2018 — 13C p1=14.00 us @ -6 dB (6 dB attenuator at the amplifier)

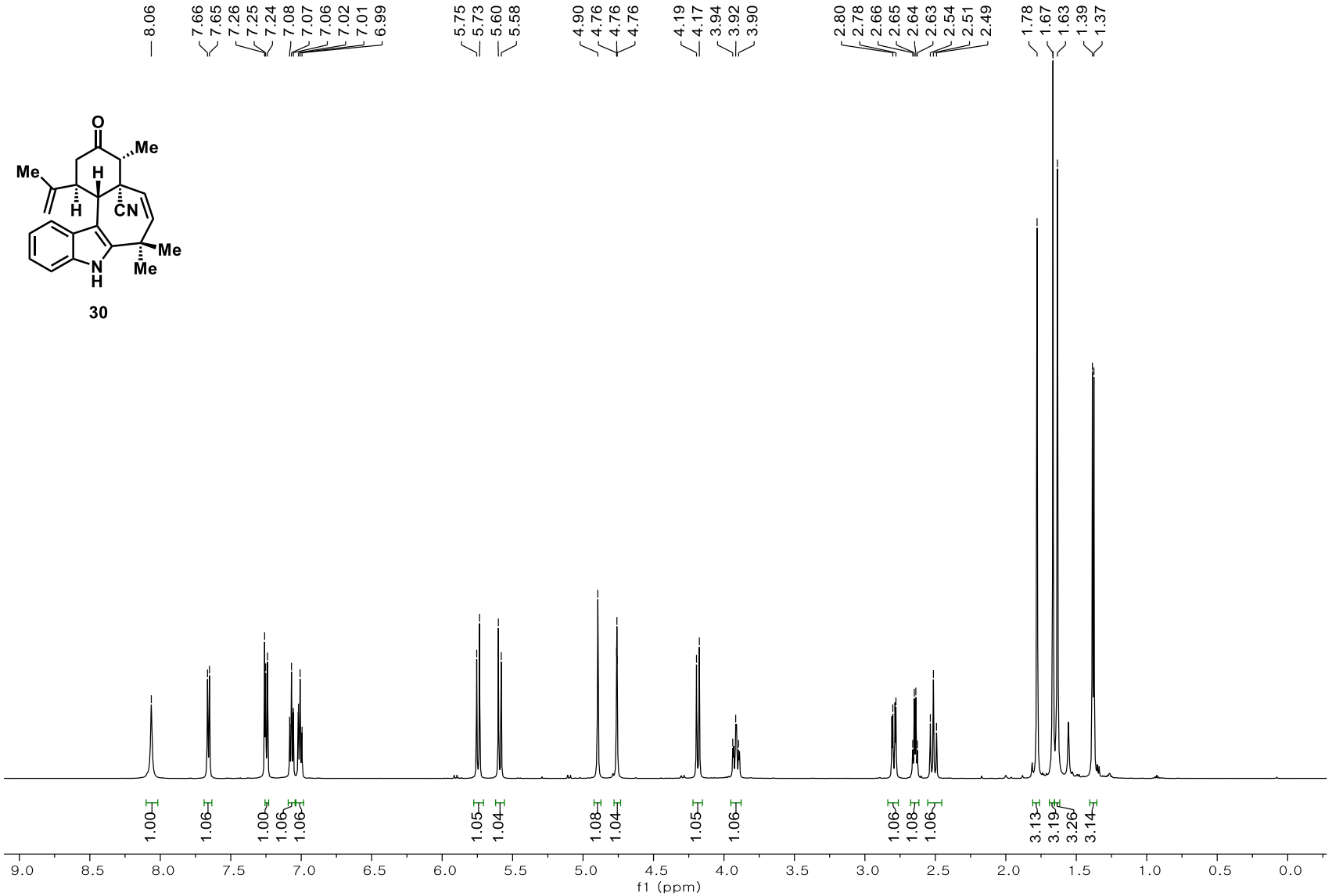


700-Ree5-127B-H.1.fid — AV-700 starting parameters for 1D 1H — CP-TXI probe - HC 10/03/2019 — p1=9.5 us @ -6 dB SGU1 (13 dB attenuator at the amplifier)



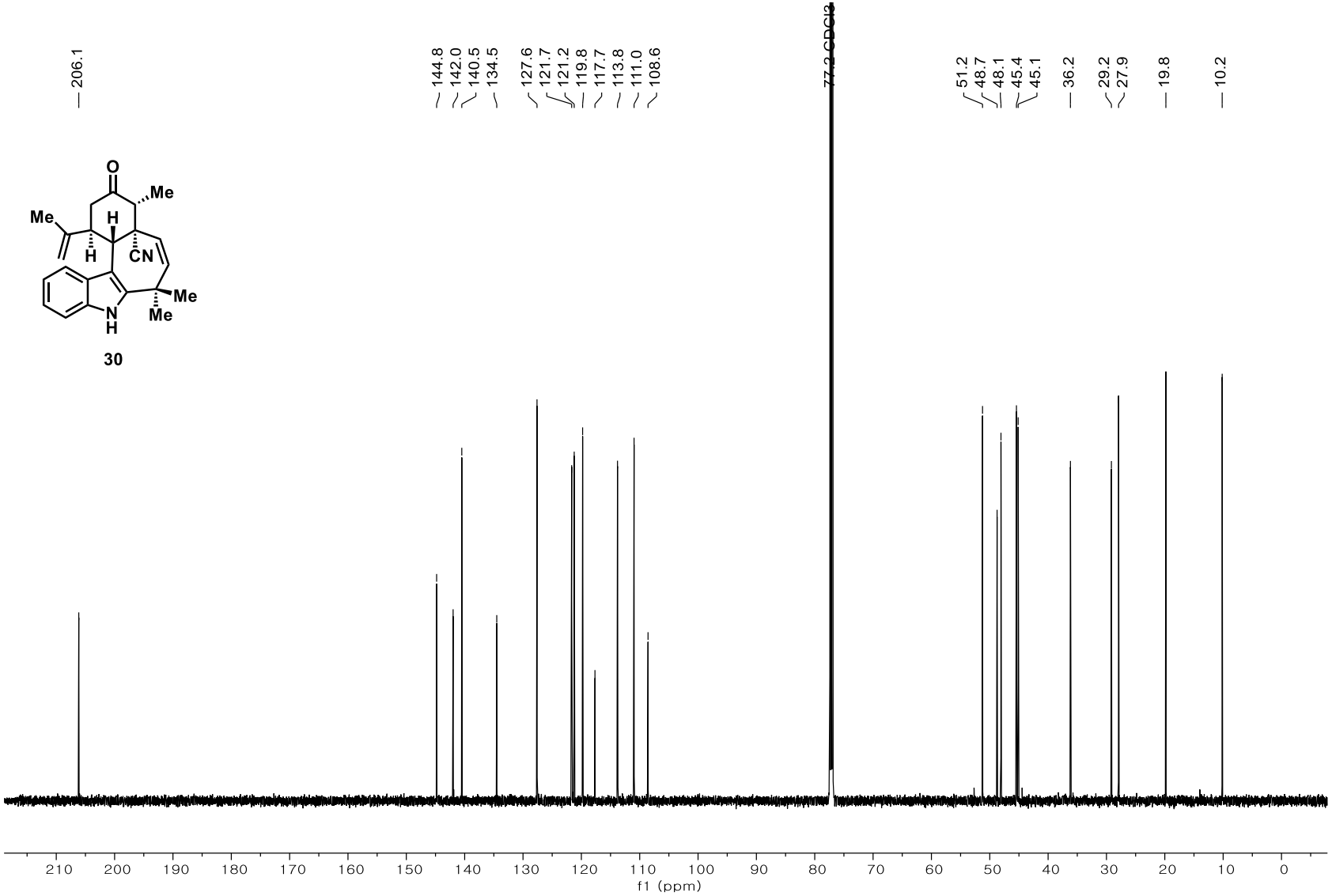

900-III-141B.992.fid
191.6
153.2
148.6
142.9
141.1
136.1
130.5
127.8
122.3
120.7
118.1
116.3
84.9
65.4
53.3
50.8
45.6
42.0
38.5
34.4
32.7
28.6
25.2
22.5
22.1
21.1
Me
Me
Me
H
H
NCO
OH
N
Me
Me
24
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Ree4-17-char.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling

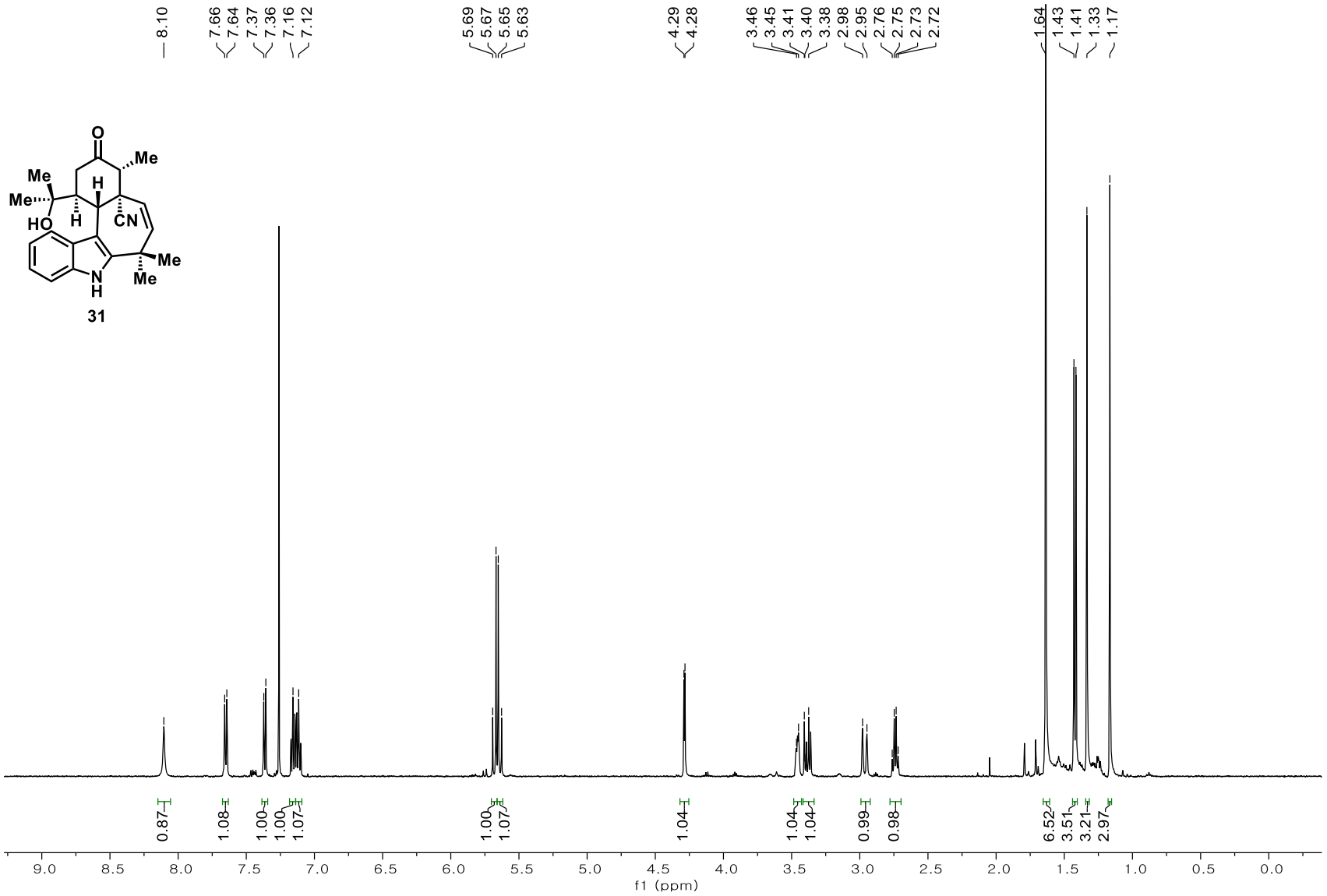


30

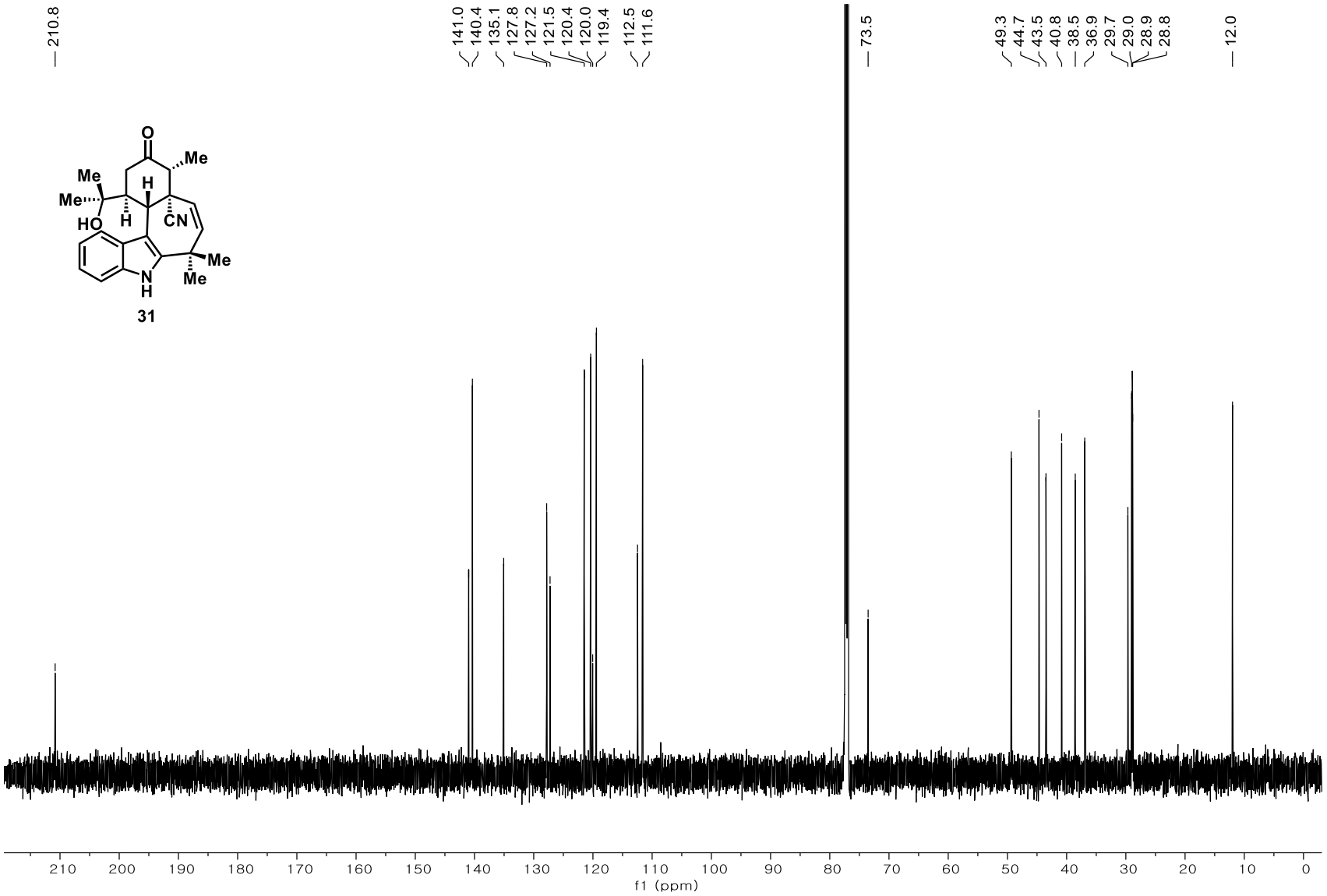
Ree4-17-char.2.fid — 13C{1H} starting parameters - HC 06/17/2019



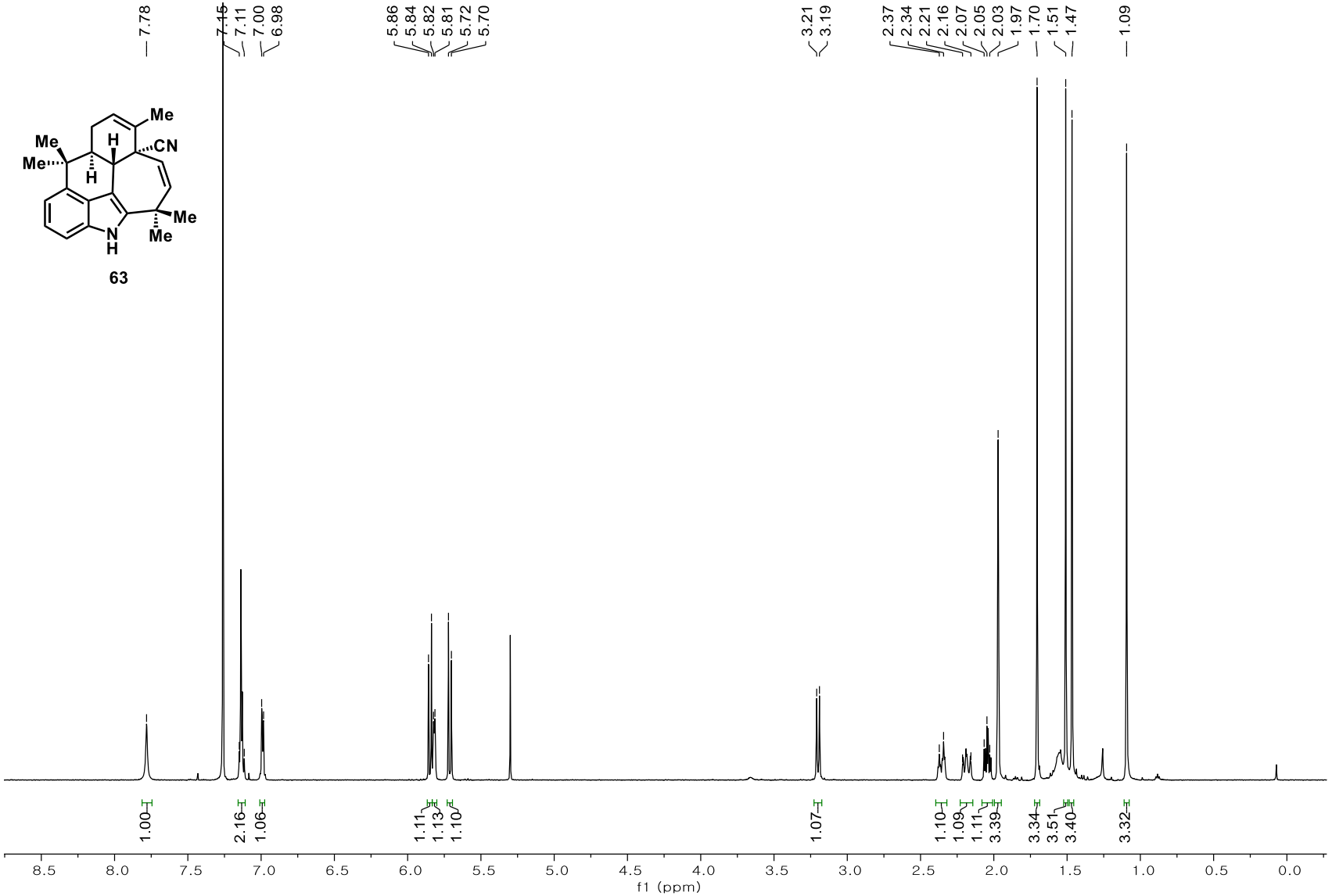
Ree4-104B.1.fid — AV-500 BBO probe — 1H 1D NMR



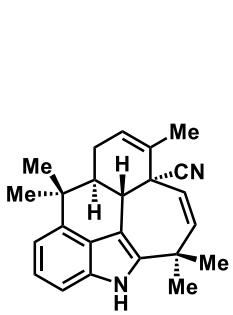
Ree4-104Bchar.13.fid — 13C{1H} starting parameters - HC 06/17/2019



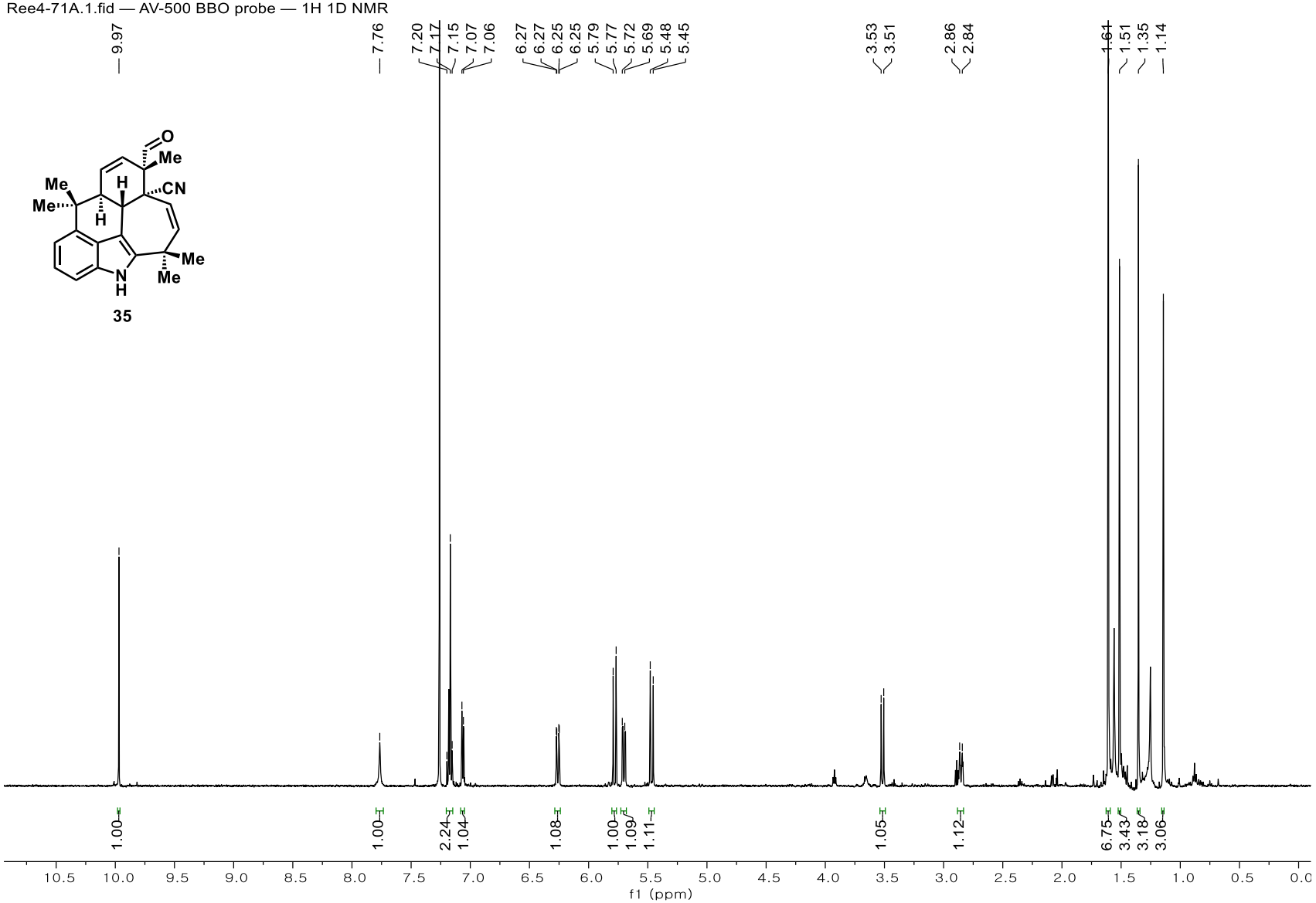
Ree4-44A-cdcl3-char.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



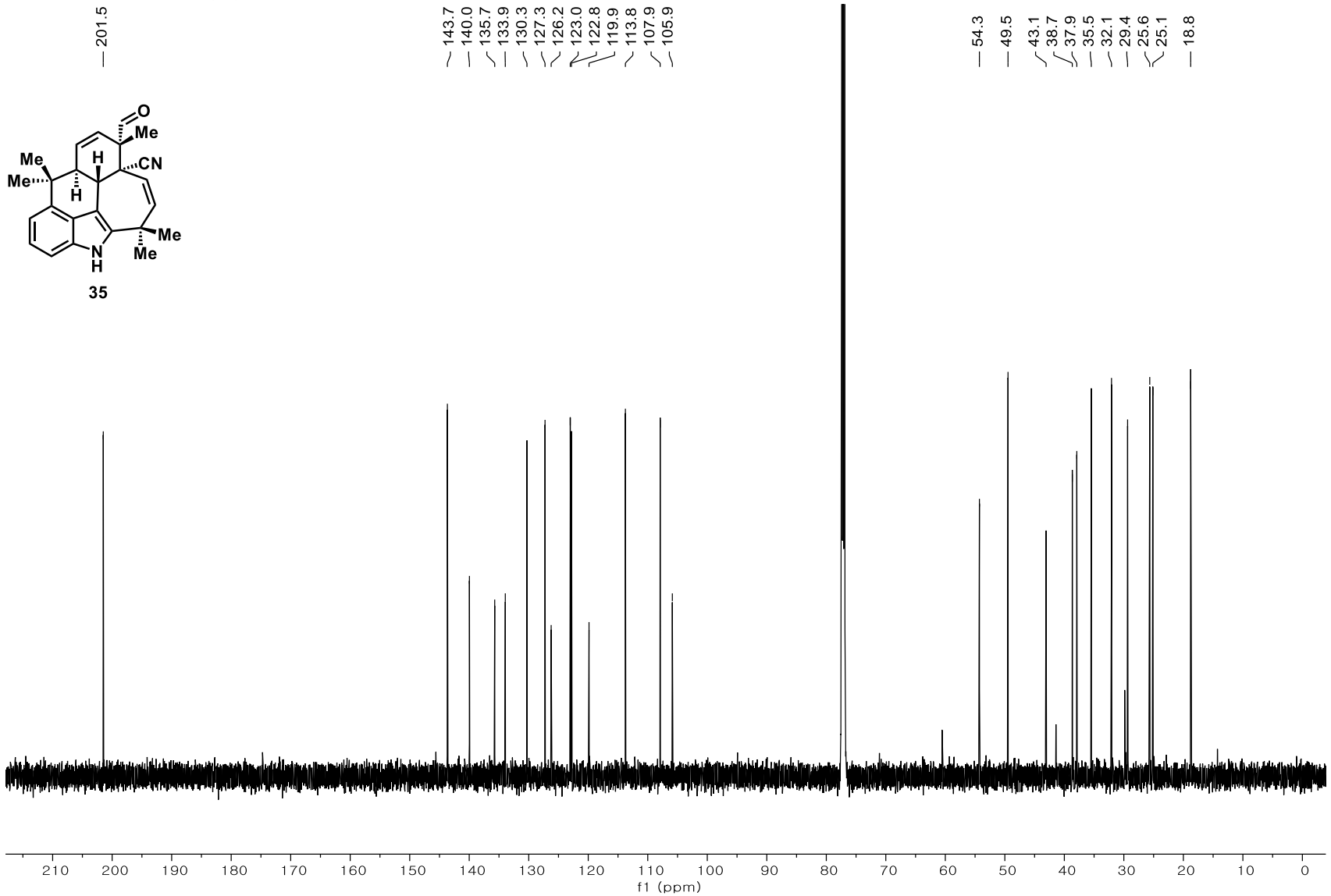
Ree4-44A-cdcl3-char.13.fid — 13C{1H} starting parameters - HC 06/17/2019



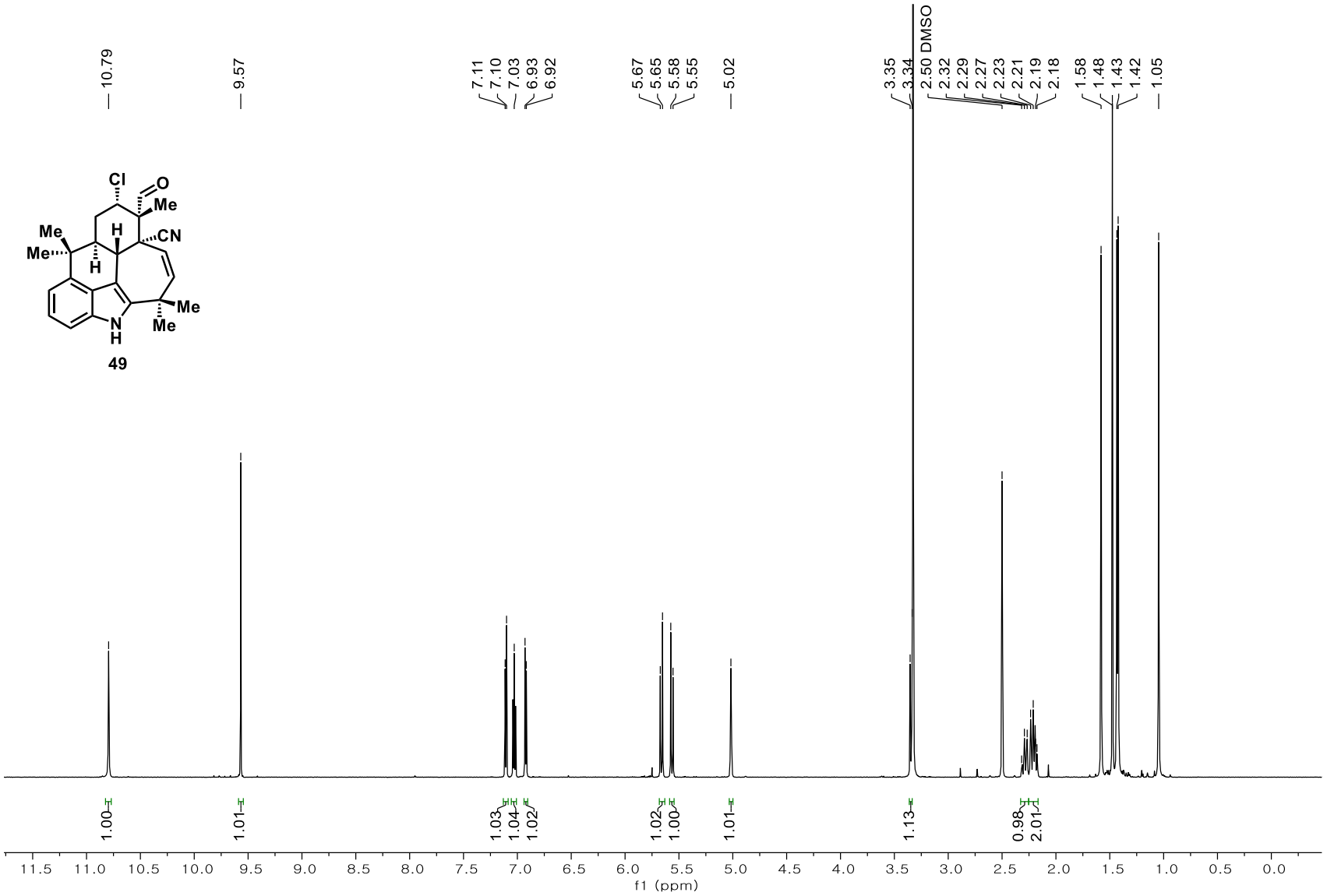
63


Ree4-71A.1.fid — AV-500 BBO probe — 1H 1D NMR
9.97
7.76
7.20
7.17
7.15
7.07
7.06
6.27
6.27
6.25
6.25
5.79
5.77
5.72
5.69
5.48
5.45
3.53
3.51
2.86
2.84
1.64
1.51
1.35
1.14
O
Me
Me
Me
H
H
CN
N
H
Me
Me
35
1.00
1.00
2.24
1.04
1.08
1.00
1.09
1.11
1.05
1.12
6.75
3.43
3.18
3.06
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Ree4-71A-13C.1.fid — 13C{1H} starting parameters - HC 06/17/2019

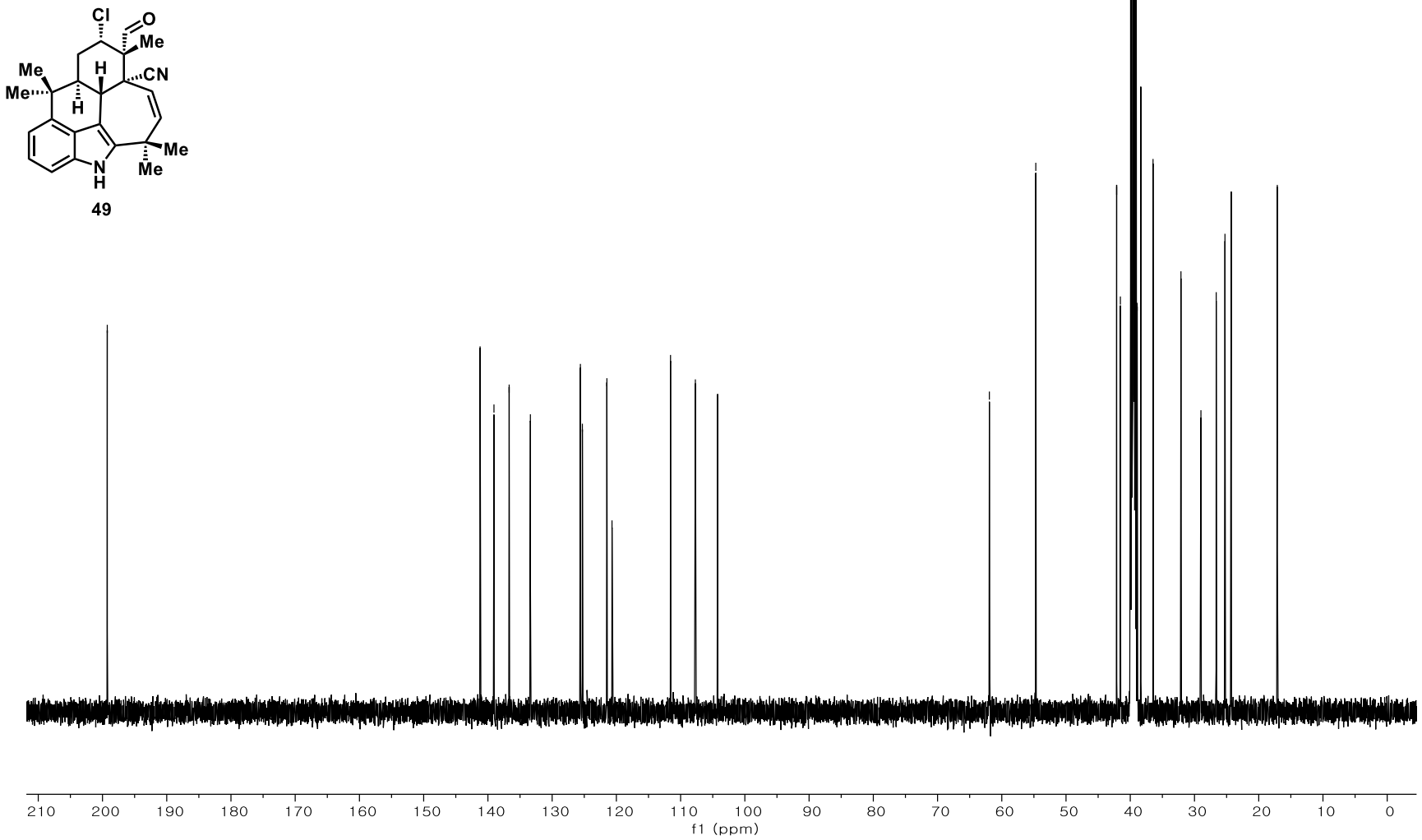


Ree4-75Brods-DMSO.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



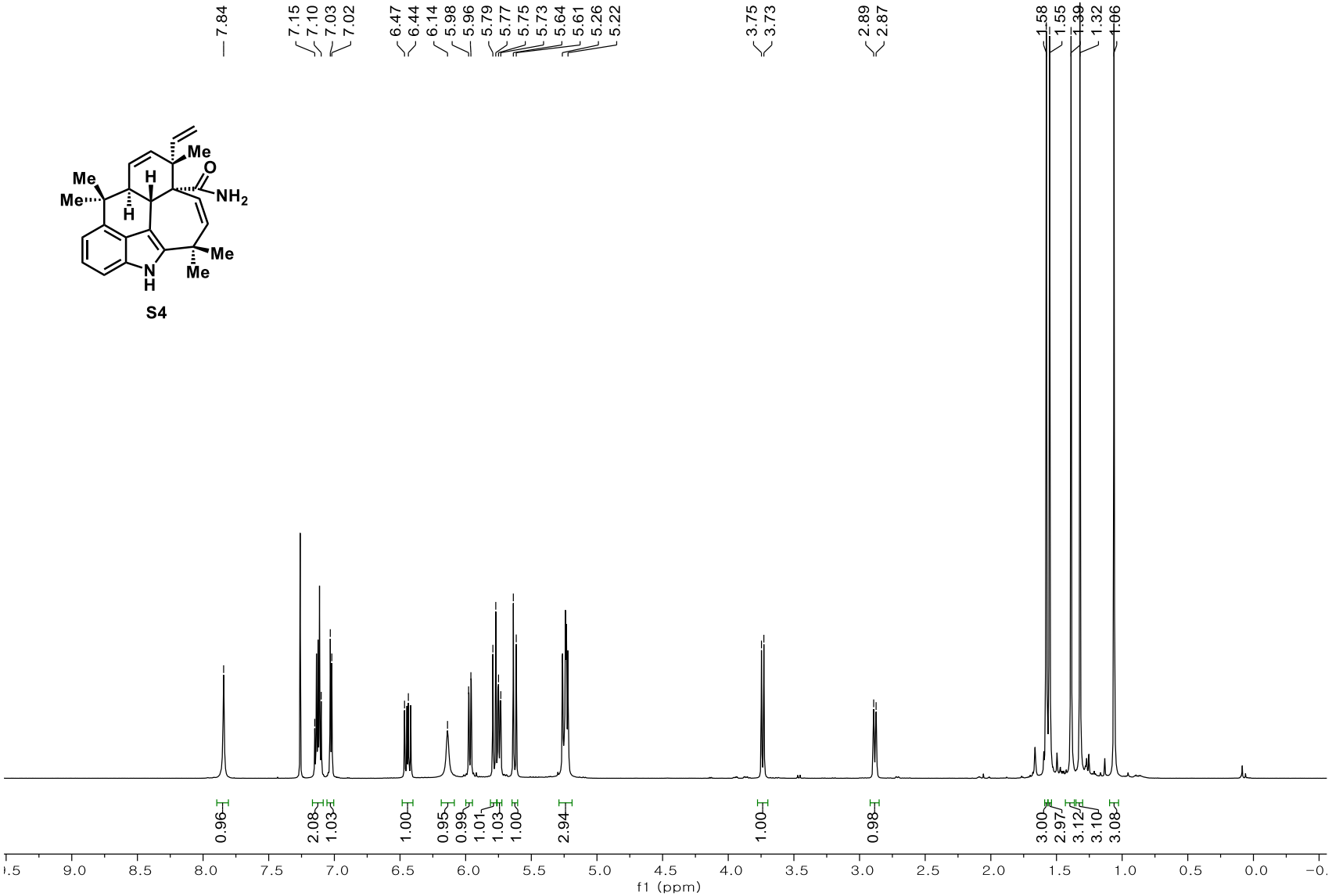
49

Ree4-75Brods-DMSO.13.fid — 13C{1H} starting parameters - HC 06/17/2019



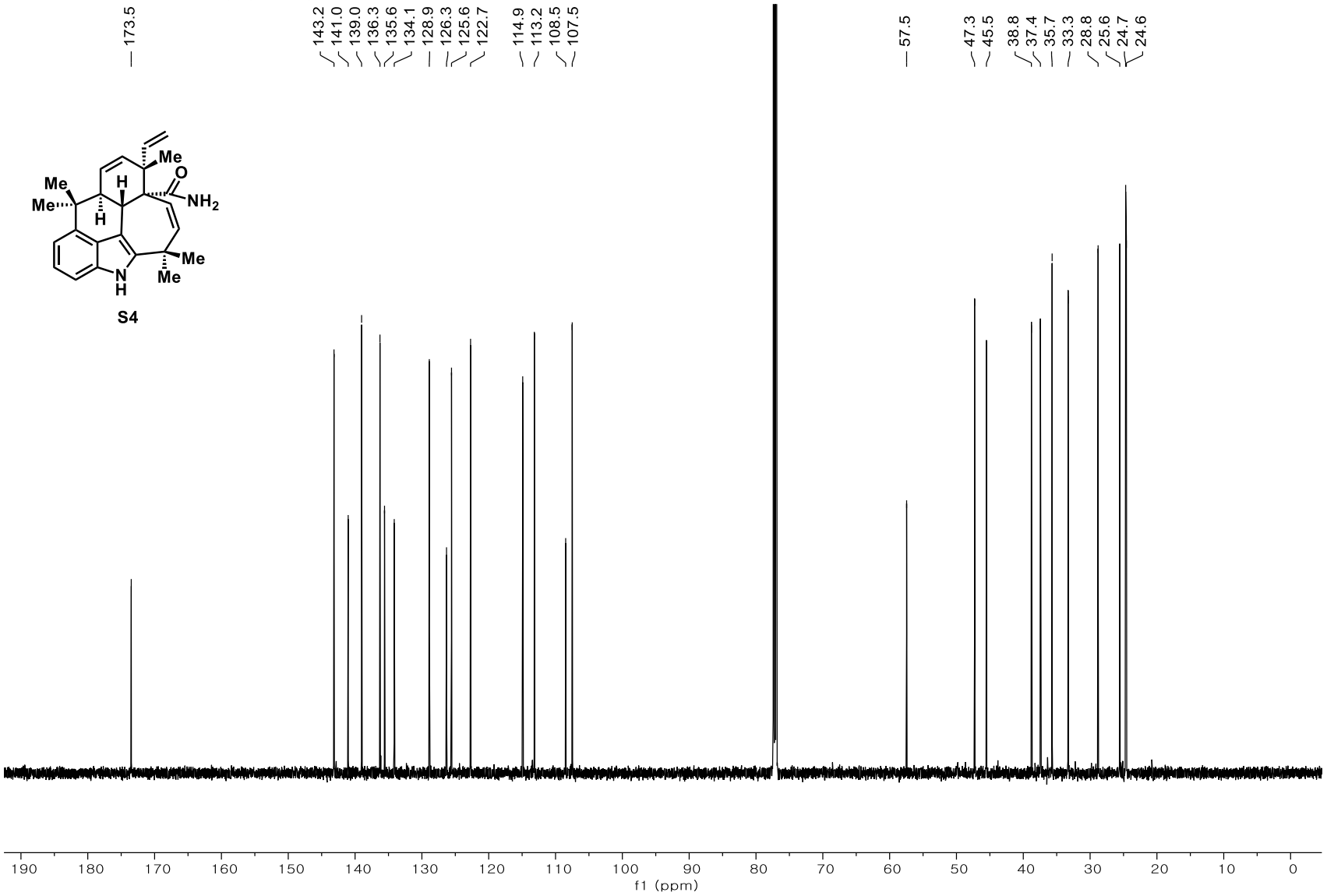
49

Ree4-148A char.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling

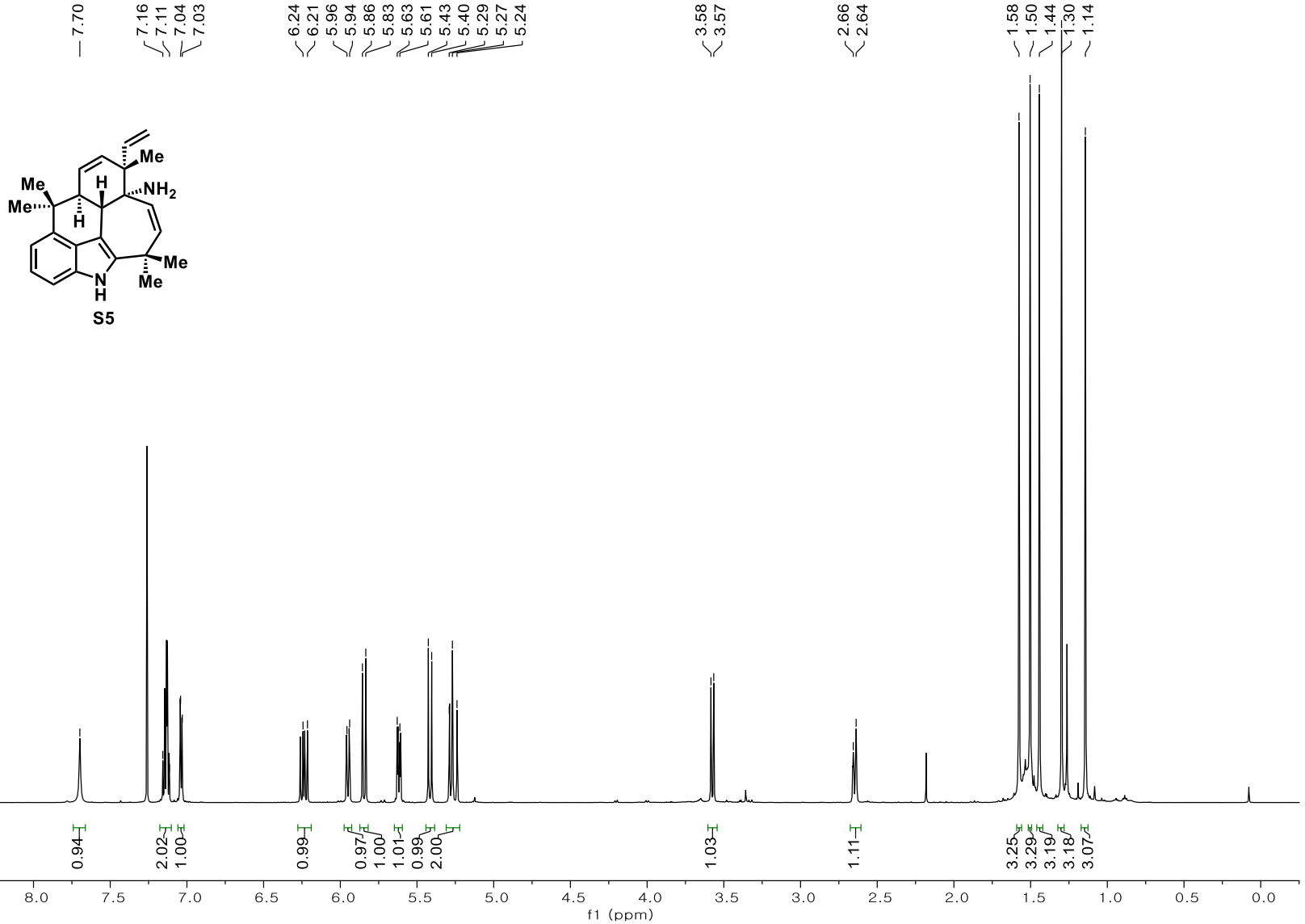


S4

Ree4-148A char.13.fid — 13C{1H} starting parameters - HC 06/17/2019

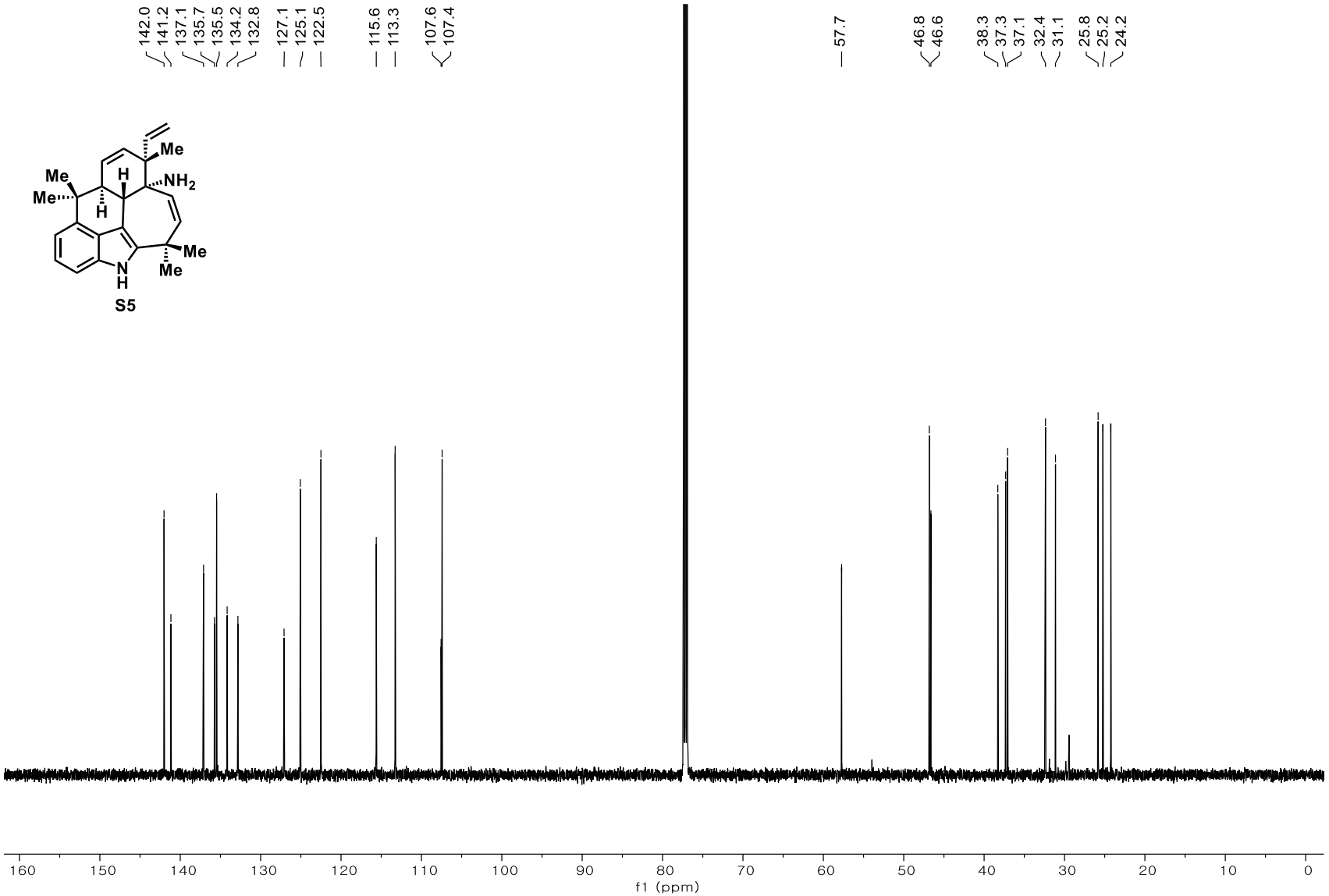


Ree4-163B-repurified.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



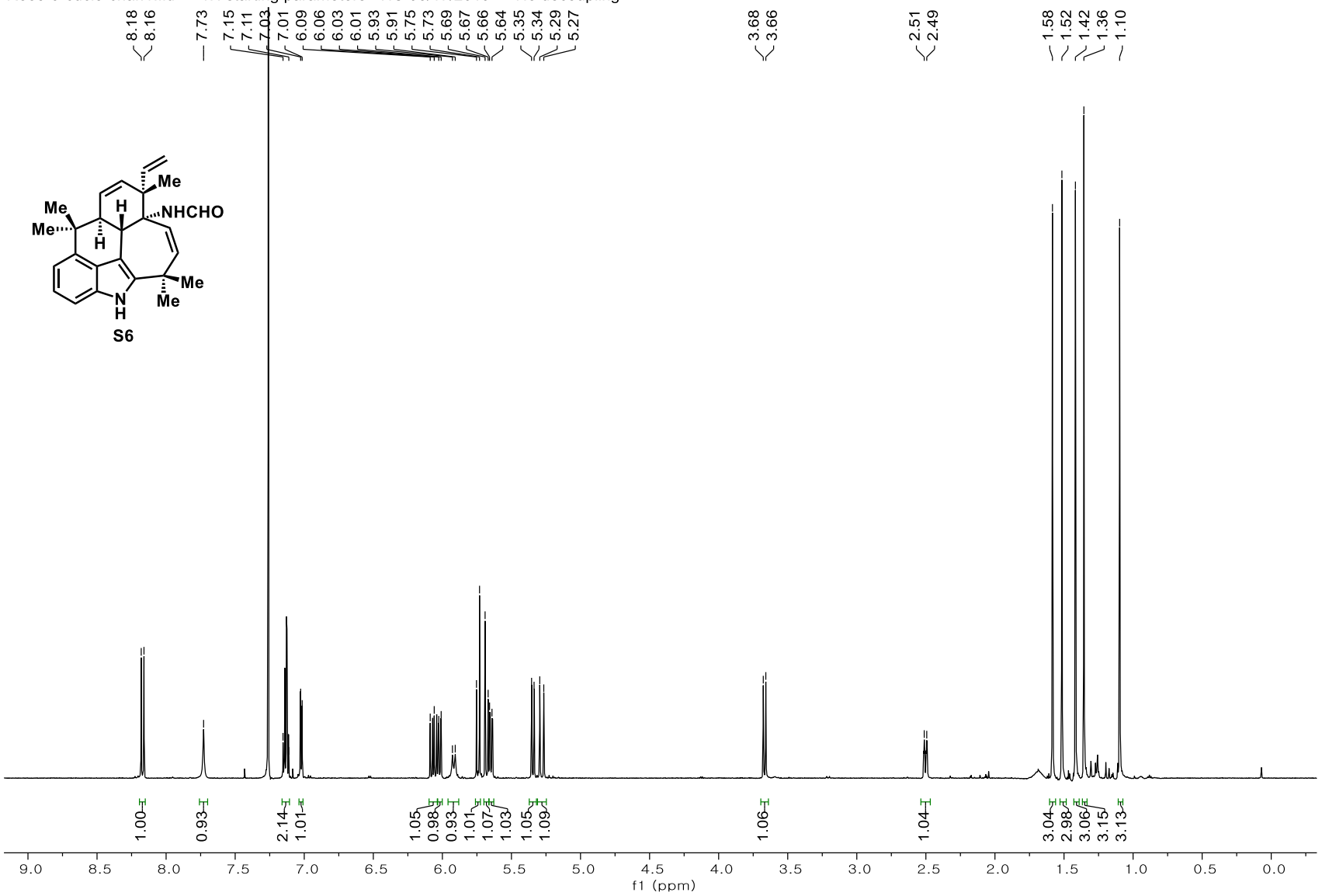
S5

Ree4-163B-repurified.13.fid — 13C{1H} starting parameters - HC 06/17/2019

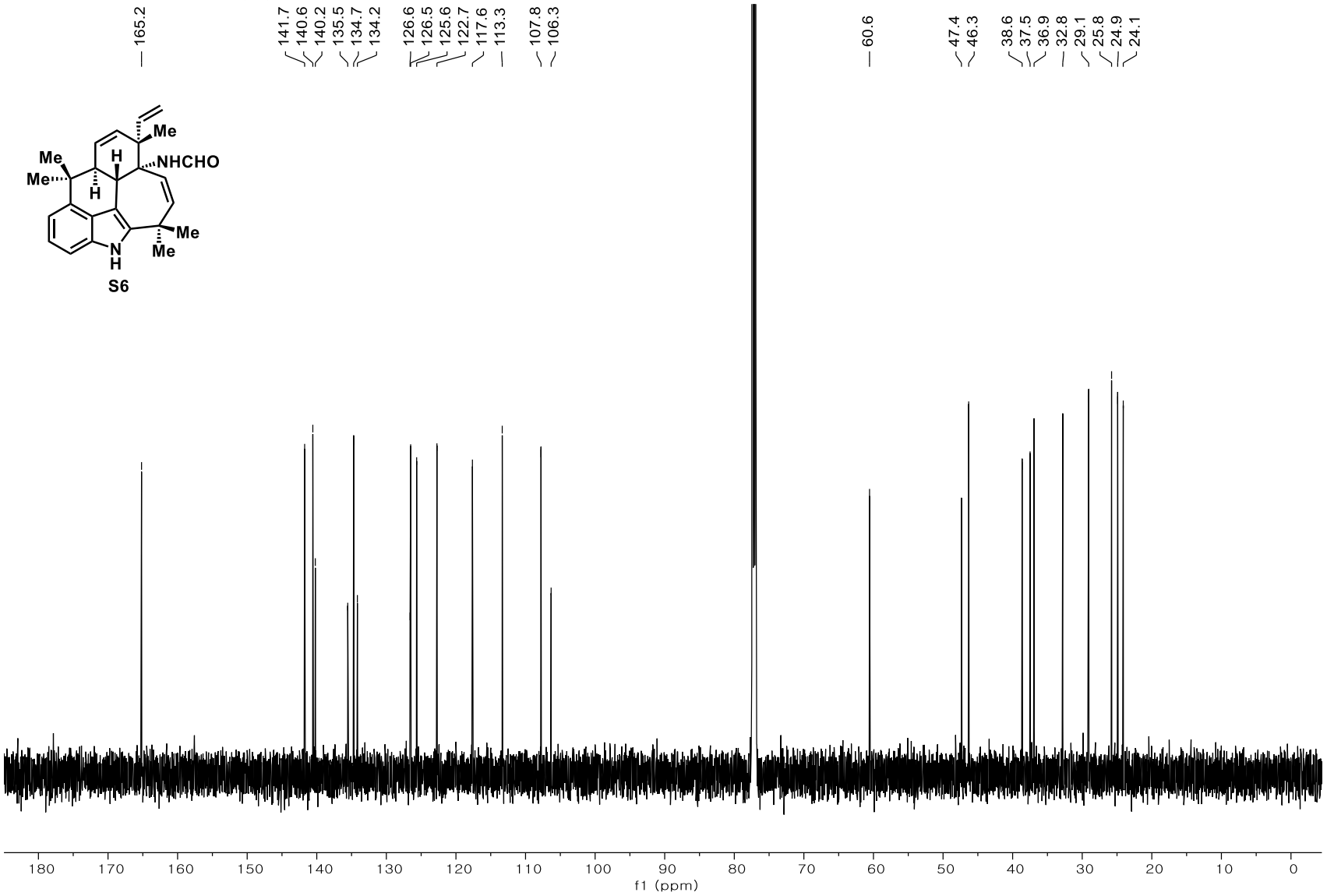


S5

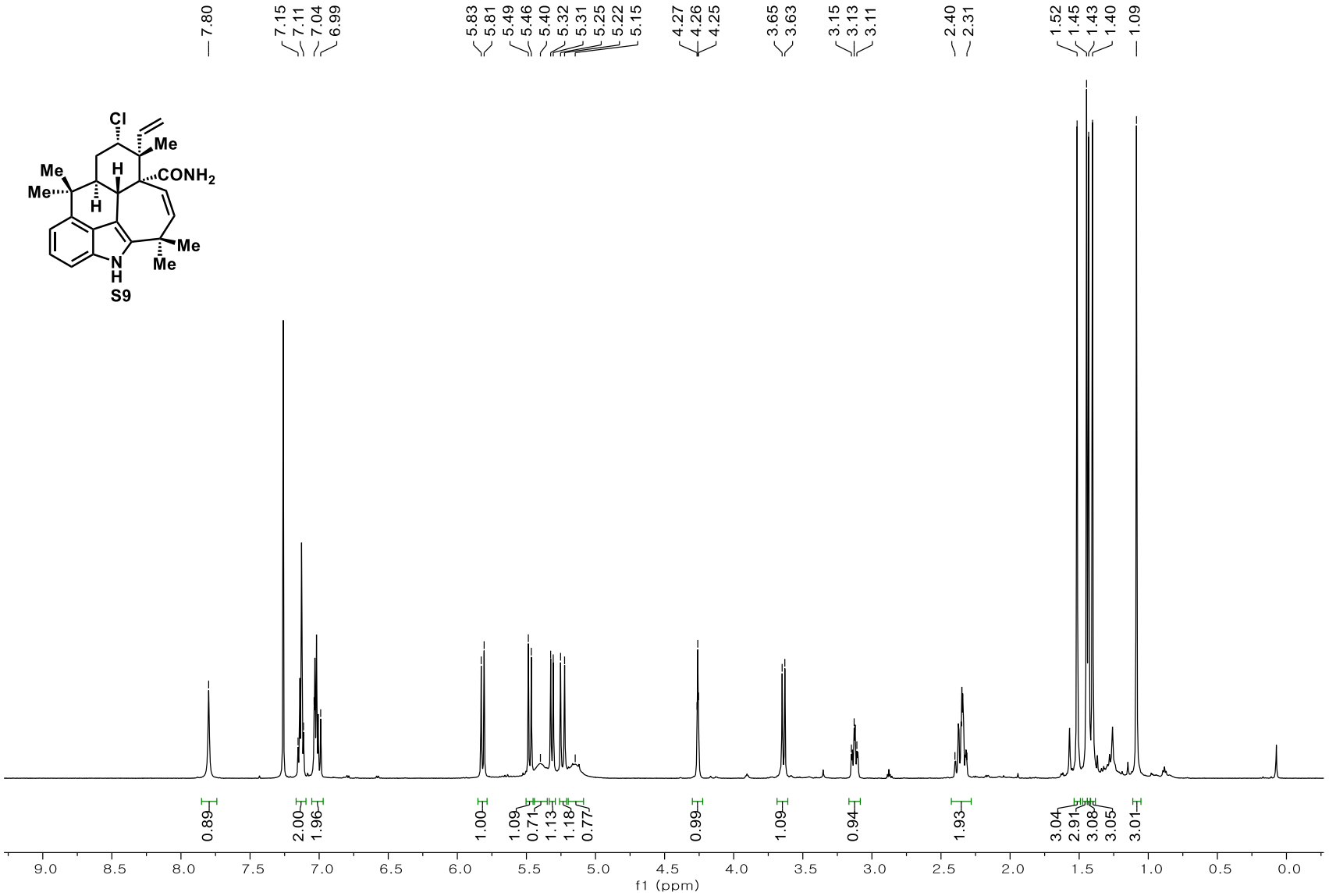
Ree5-9-cdcl3-char.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



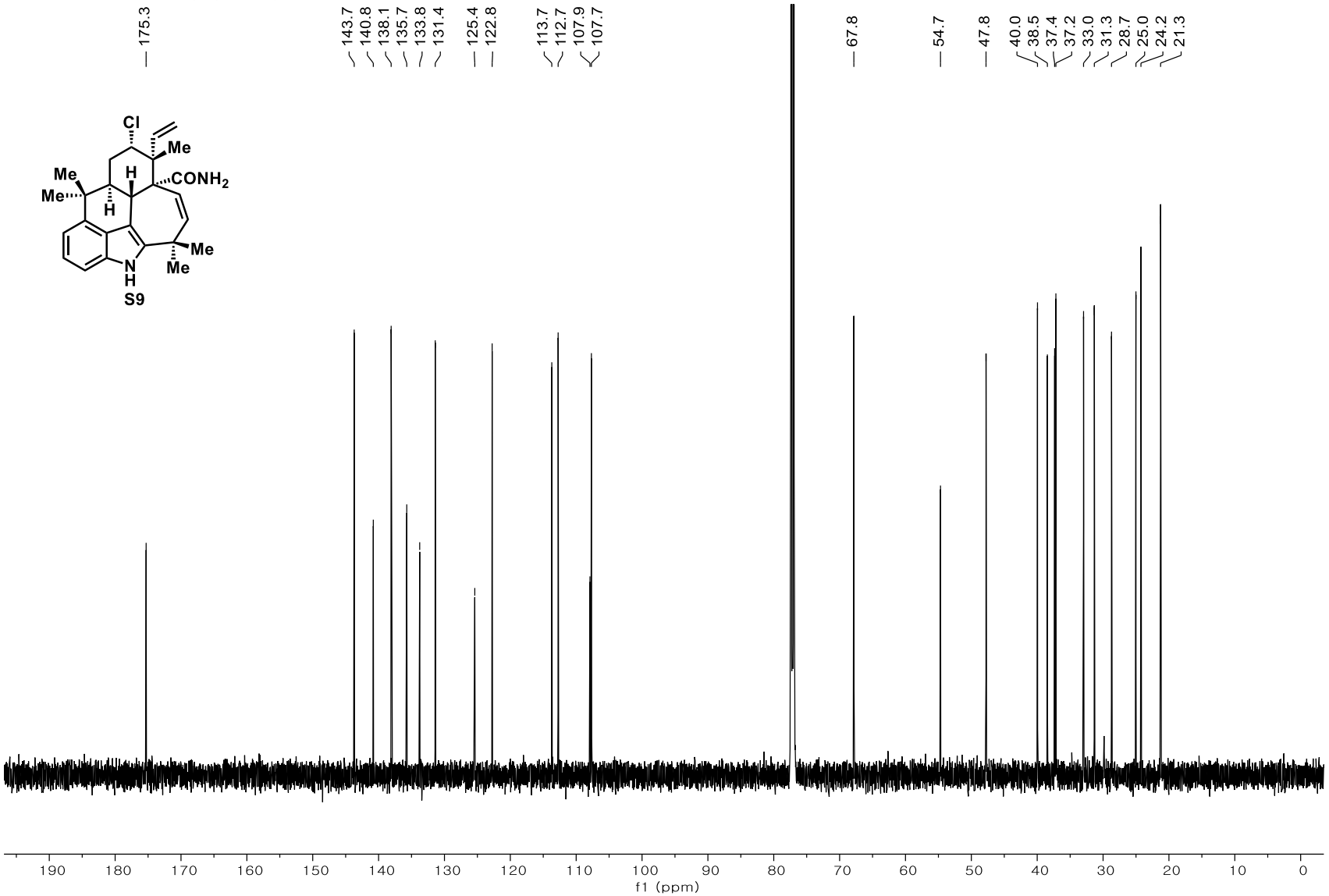
Ree5-9-cdcl3-char.13.fid — 13C{1H} starting parameters - HC 06/17/2019



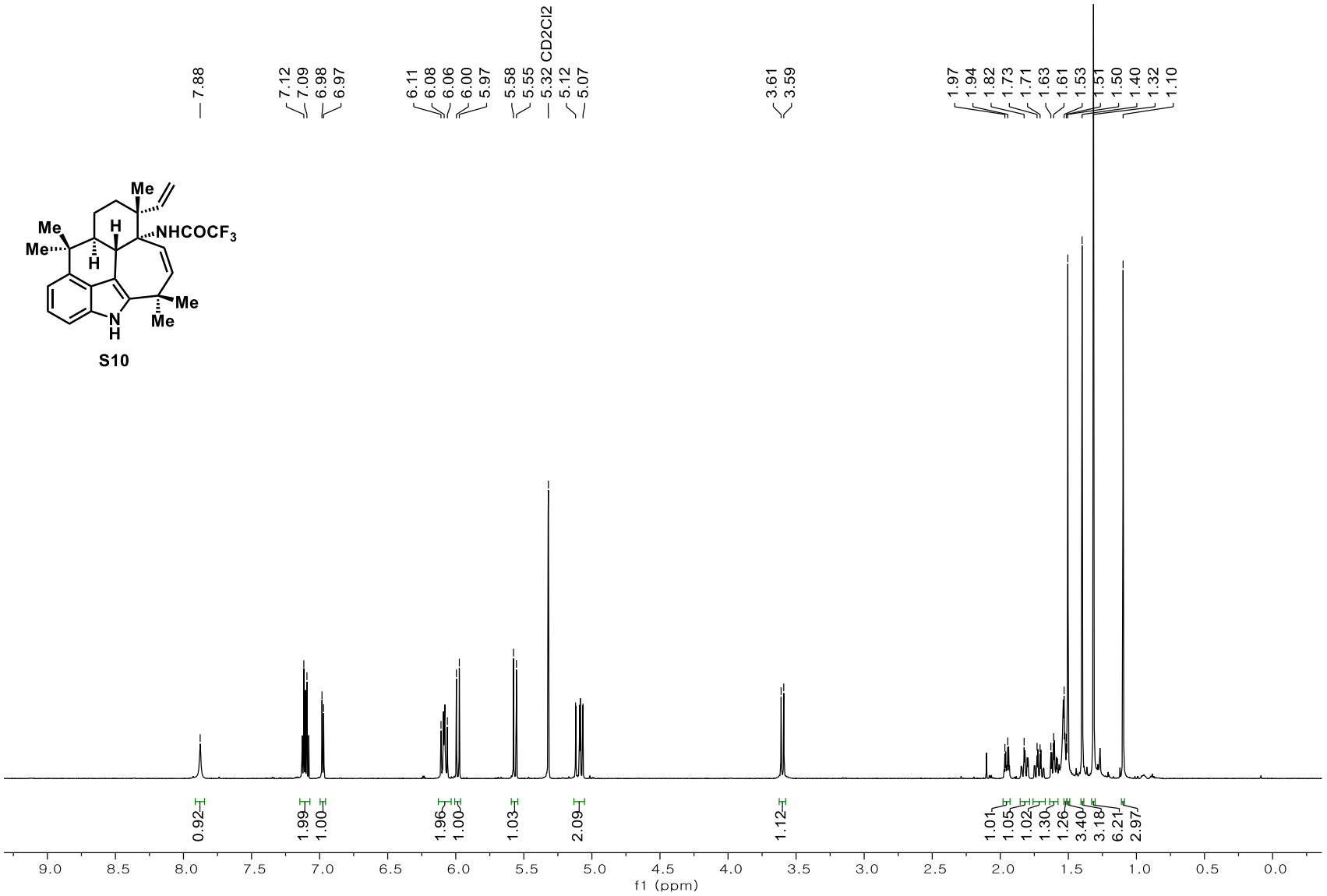
Ree4-161B.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



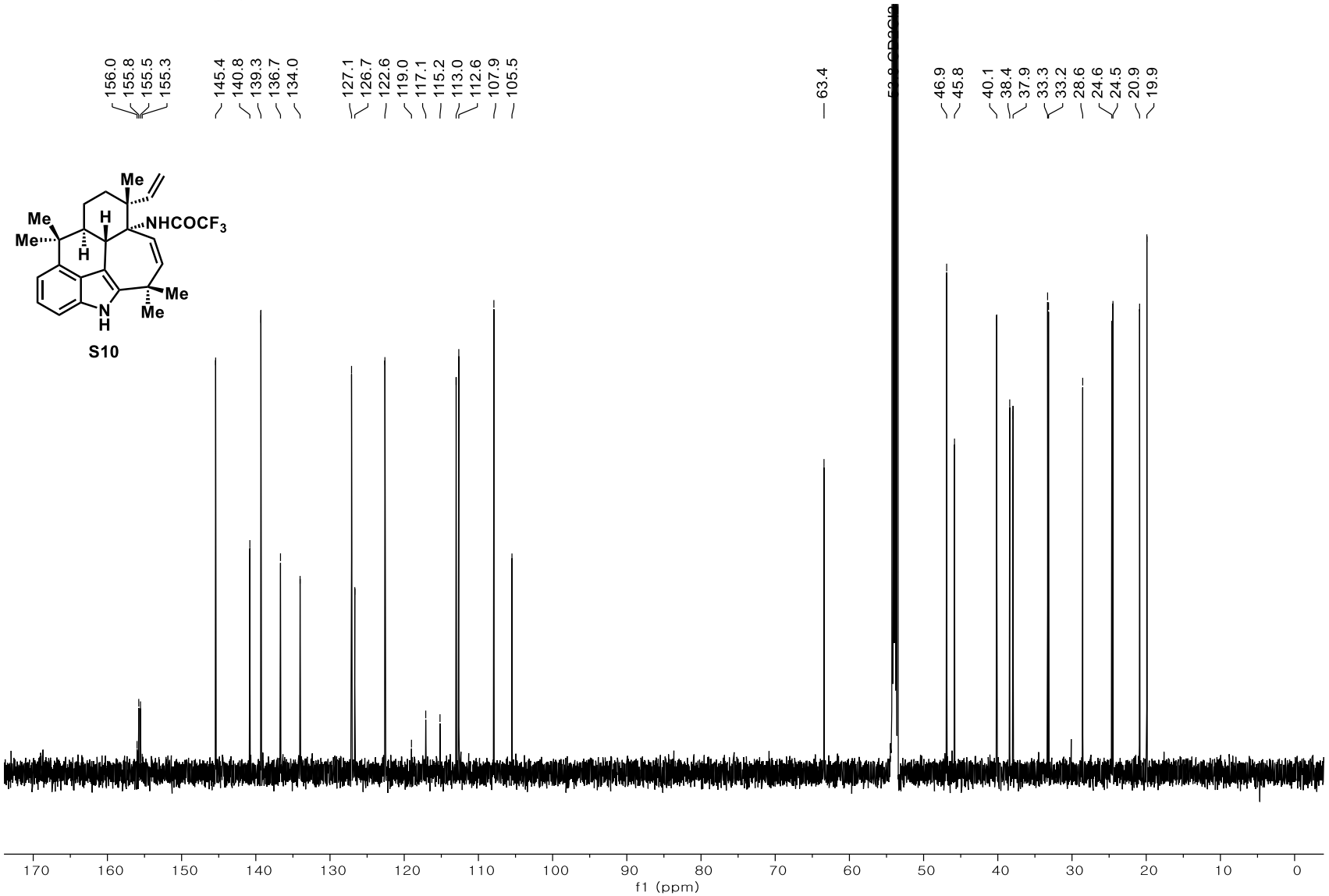
Ree4-161B.13.fid — 13C{1H} starting parameters - HC 06/17/2019



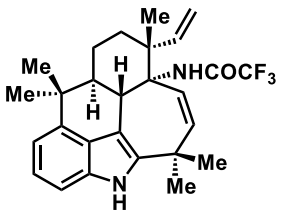
Ree5-110-dcm.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



Ree5-110-dcm.13.fid — 13C{1H} starting parameters - HC 06/17/2019

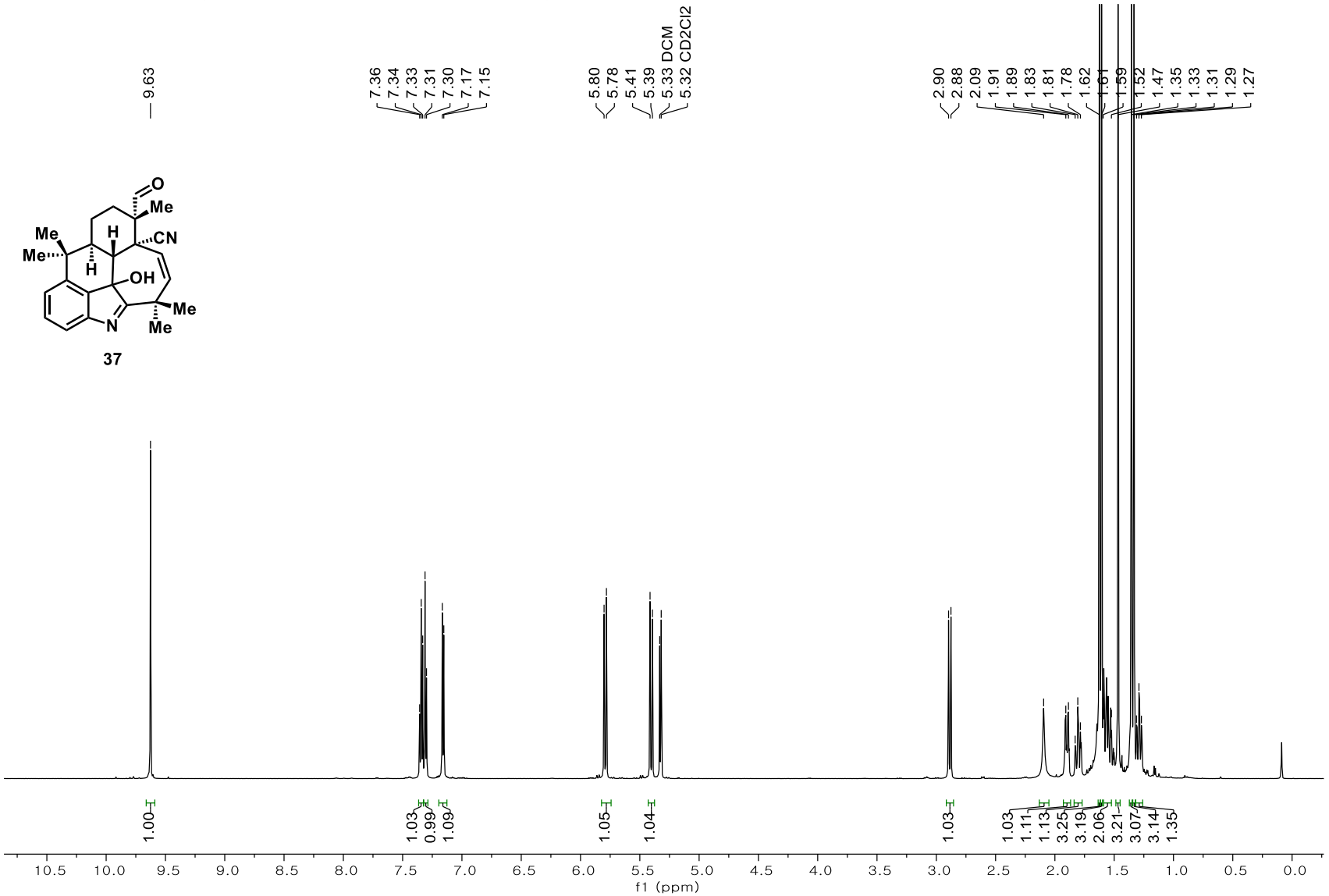


Ree5-110-dcm.19.fid — 19F starting parameters - HC 06/17/2019 — No decoupling



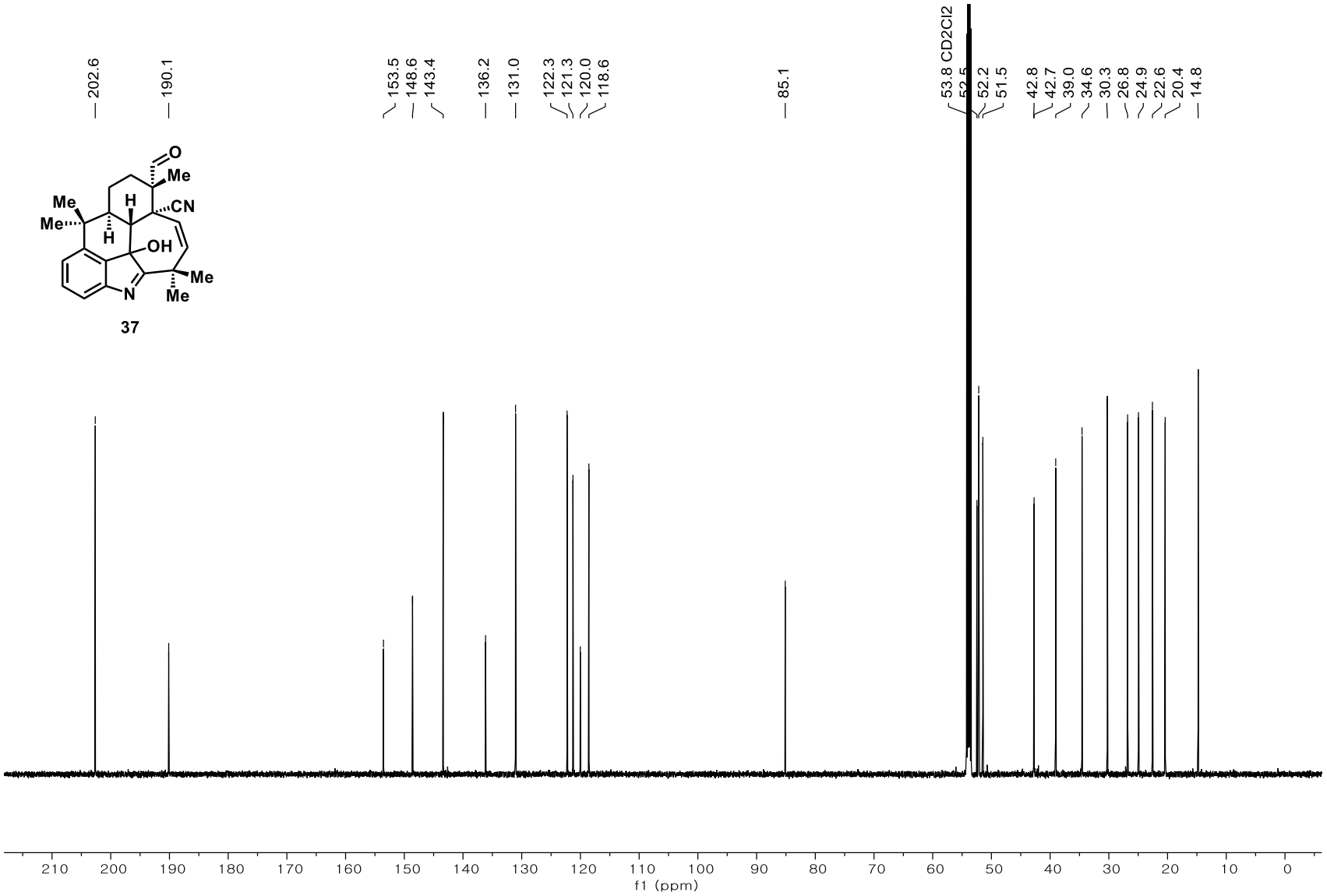
S10

Ree5-66.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling

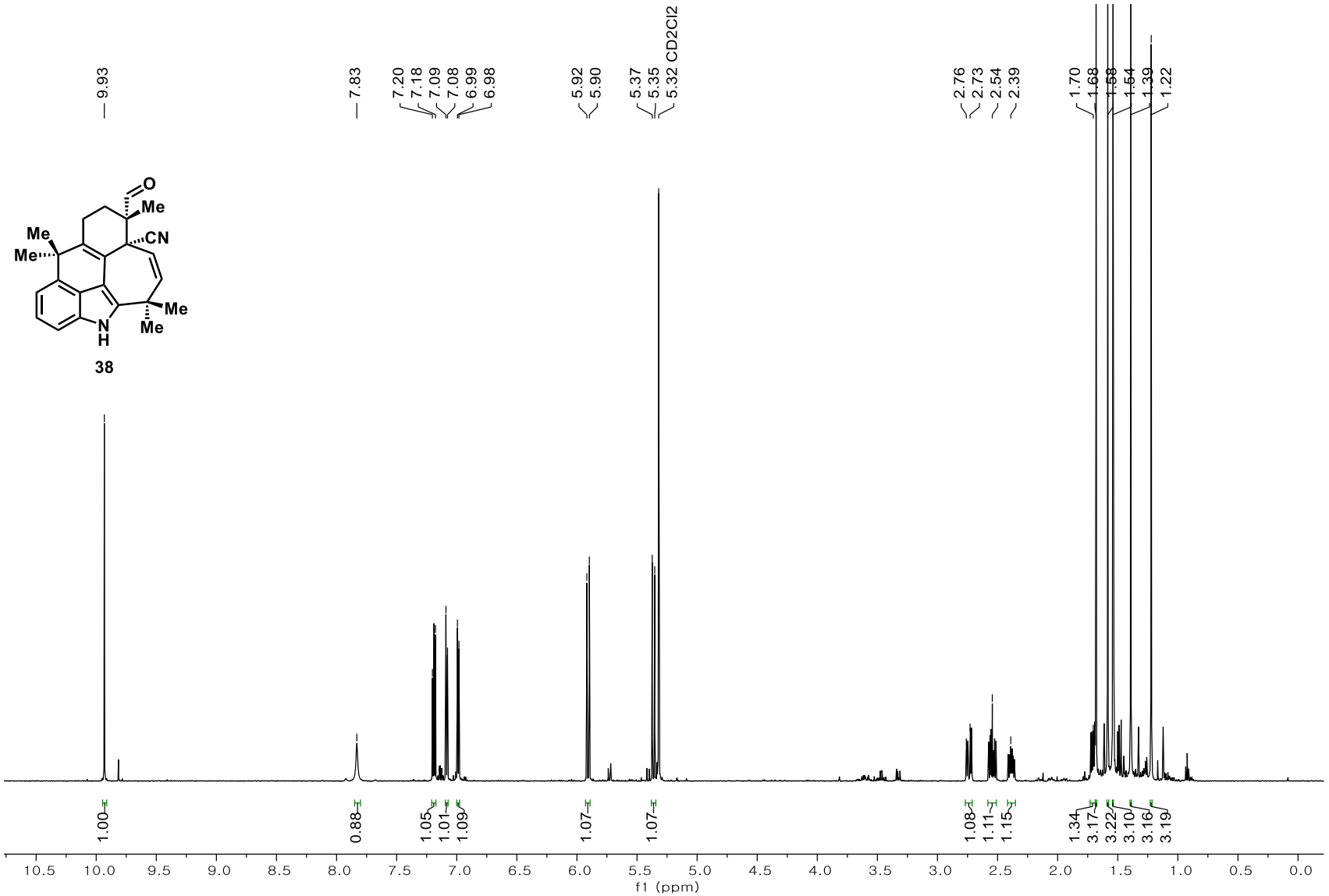


37

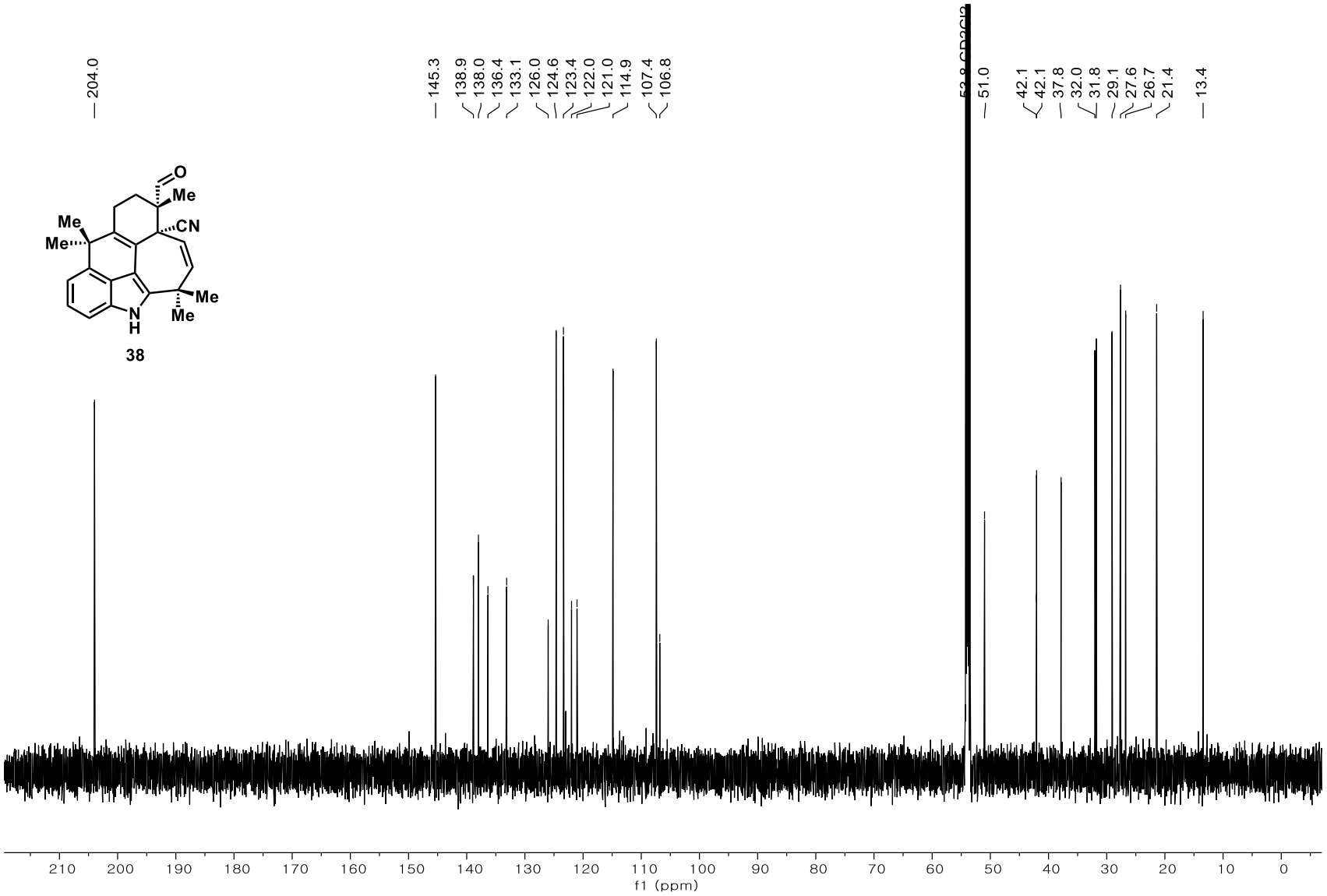
Ree5-66 -dcm.13.fid — 13C{1H} starting parameters - HC 06/17/2019



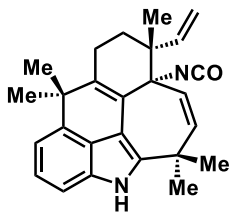
Ree6-69B.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



Ree6-69B.13.fid — 13C{1H} starting parameters - HC 06/17/2019

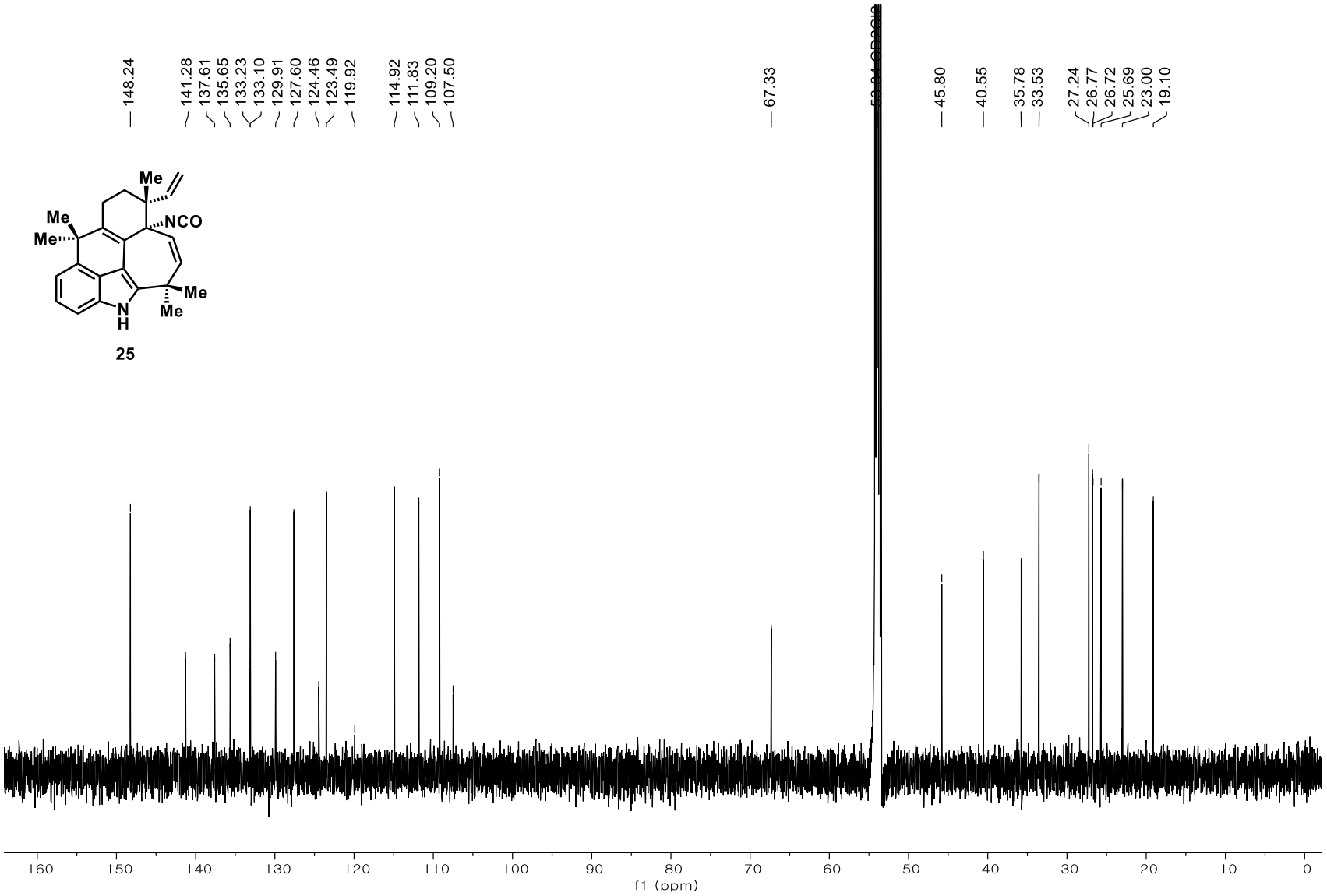


Ree5-126-cd2cl2.1.fid — 1H starting parameters - HC 06/17/2019 — No decoupling



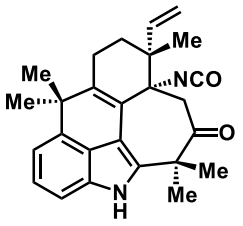
25

Ree5-126-cd2cl2.13.fid — 13C{1H} starting parameters - HC 06/17/2019



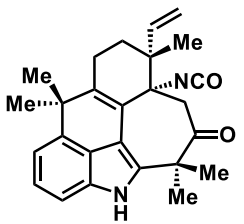
25

Ree6_004D.1.1.1r — 1H 1puls



29

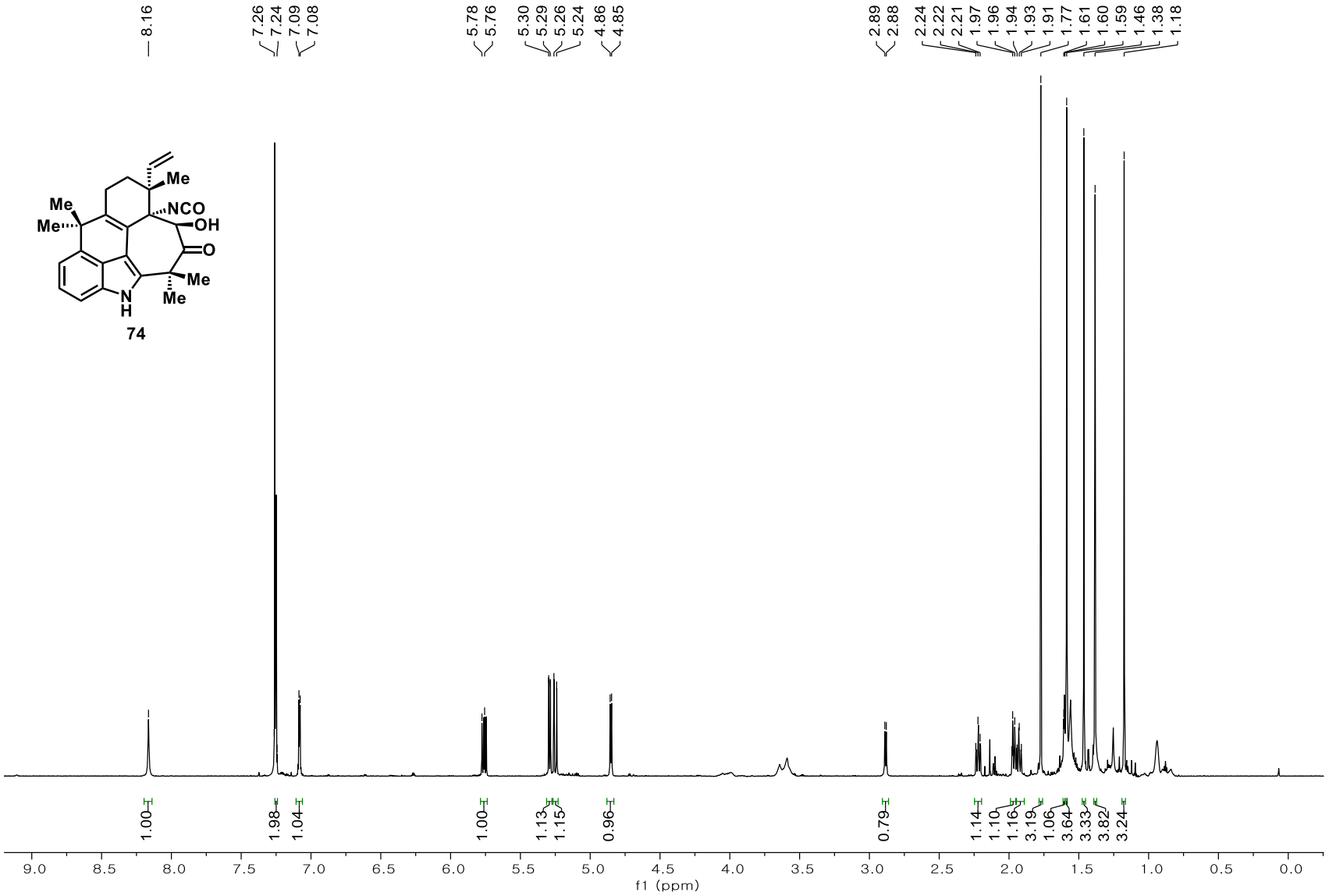
Ree6_004D.997.1.1r



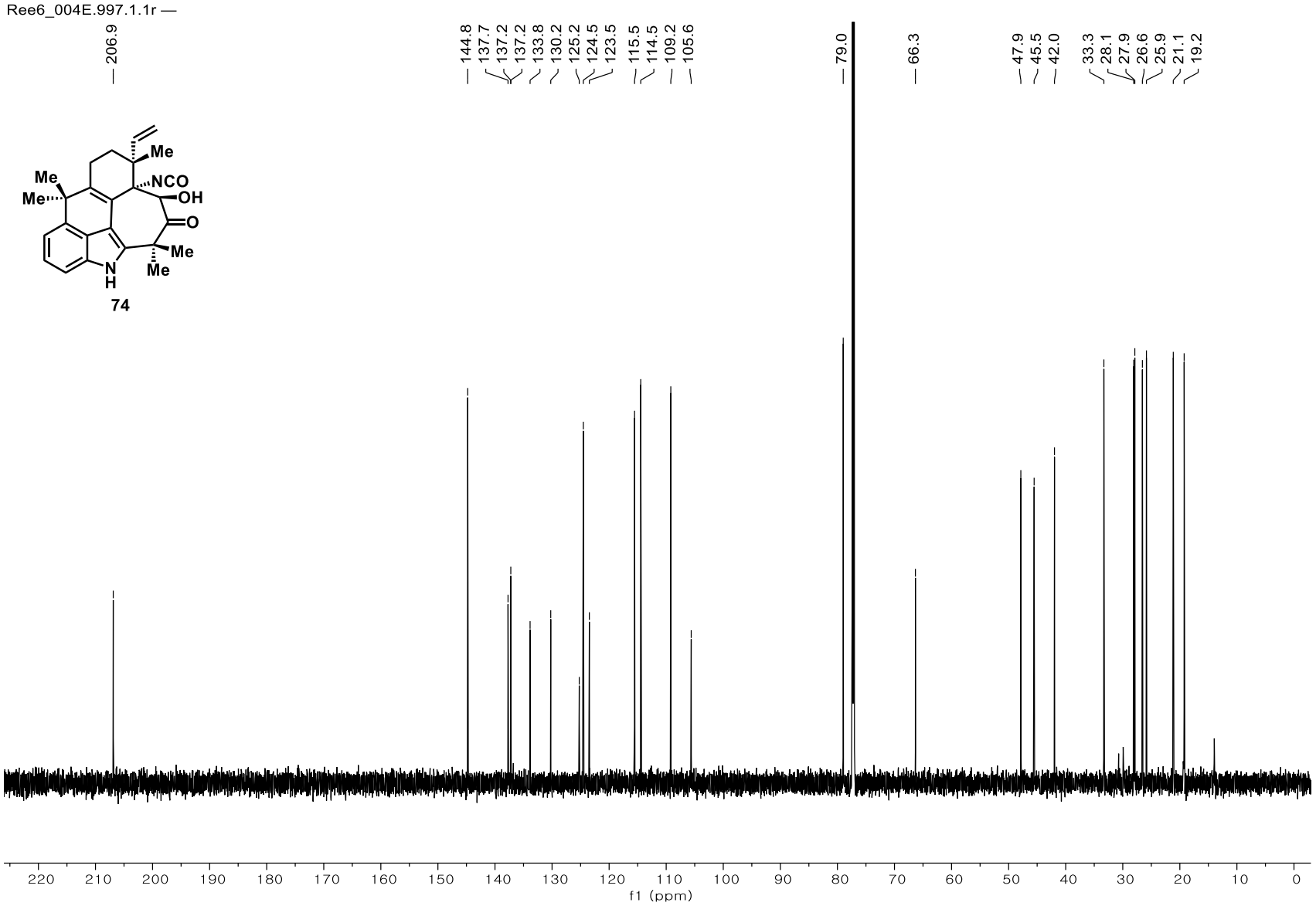
29

206.7, 145.9, 138.0, 137.3, 133.8, 130.7, 129.1, 125.1, 124.1, 123.5, 115.0, 113.2, 108.8, 107.6, 66.5, 50.0, 45.3, 43.0, 41.9, 33.3, 27.8, 27.0, 26.6, 26.4, 21.0, 19.1

Ree6_004E.1.1.1r — 1H 1puls

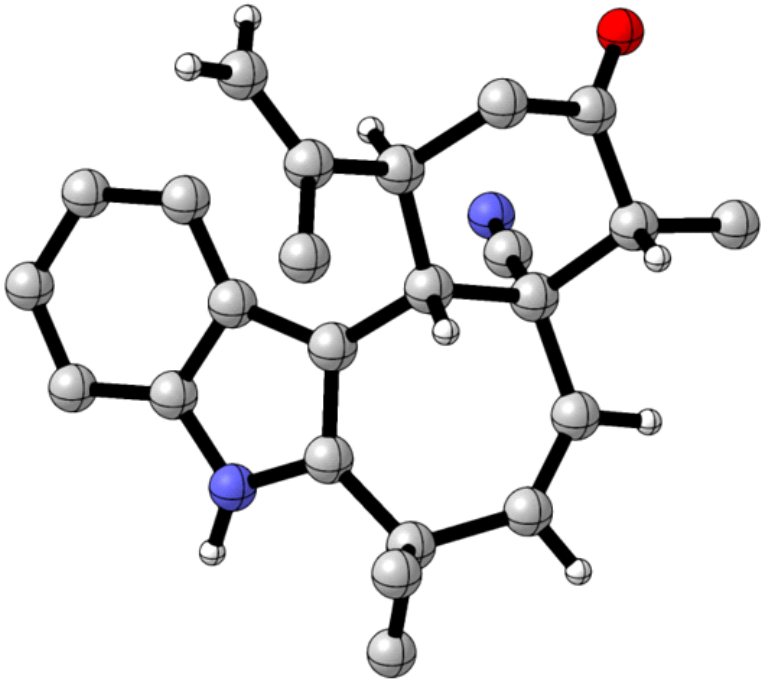


74


Ree6_004E.997.1.1r
206.9
144.8
137.7
137.2
137.2
133.8
130.2
125.2
124.5
123.5
115.5
114.5
109.2
105.6
79.0
66.3
47.9
45.5
42.0
33.3
28.1
27.9
26.6
25.9
21.1
19.2
Me
Me
Me
NCO
OH
O
Me
Me
N
H
74
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

3.8 Appendix to Chapter 2: Xray Crystallographic Data

*1) Nitrile ketone (**30**)*



A colorless block 0.32 x 0.21 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 33.00 mm and exposure time was 0.50 seconds per frame using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 21243 reflections were collected covering the indices -9<=h<=9, -18<=k<=18, -21<=l<=21. 4003 reflections were founded to be symmetry independent, with an R_{int} of 0.0268. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the CrysAlis^{Pro} 1.171.41.109a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1. Crystal data and structure refinement for HR09_Sarpong.

Identification code	HR09_Sarpong	
Empirical formula	C24 H26 N2 O	
Formula weight	358.47	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.62440(10) Å	α= 90°.
	b = 14.91490(10) Å	β= 90°.
	c = 17.2140(2) Å	γ = 90°.
Volume	1957.53(4) $Å^3$	
Z	4	
Density (calculated)	1.216 Mg/m^3	
Absorption coefficient	0.577 mm^{-1}	
F(000)	768	
Crystal size	0.320 x 0.210 x 0.100 mm^3	
Theta range for data collection	3.922 to 74.442°.	
Index ranges	-9<=h<=9, -18<=k<=18, -21<=l<=21	
Reflections collected	21243	
Independent reflections	4003 [R(int) = 0.0268]	
Completeness to theta = 74.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.93372	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4003 / 0 / 252	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0777	
R indices (all data)	R1 = 0.0296, wR2 = 0.0780	
Absolute structure parameter	-0.11(7)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.175 and -0.165 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for hr09_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4292(2)	3440(1)	4779(1)	28(1)
N(1)	2524(2)	5881(1)	8381(1)	22(1)
N(2)	666(2)	4080(1)	6106(1)	31(1)
C(1)	5037(2)	3602(1)	5389(1)	20(1)
C(2)	6273(2)	4368(1)	5492(1)	23(1)
C(3)	5403(2)	5067(1)	6040(1)	19(1)
C(4)	6711(2)	5831(1)	6154(1)	26(1)
C(5)	6803(3)	6479(1)	5626(1)	39(1)
C(6)	7954(2)	5781(1)	6824(1)	36(1)
C(7)	4789(2)	4649(1)	6809(1)	16(1)
C(8)	3753(2)	5307(1)	7303(1)	16(1)
C(9)	2898(2)	6147(1)	7103(1)	16(1)
C(10)	2612(2)	6663(1)	6428(1)	20(1)
C(11)	1696(2)	7459(1)	6477(1)	24(1)
C(12)	1030(2)	7780(1)	7185(1)	23(1)
C(13)	1243(2)	7289(1)	7857(1)	21(1)
C(14)	2166(2)	6481(1)	7800(1)	19(1)
C(15)	3462(2)	5175(1)	8082(1)	20(1)
C(16)	4074(3)	4418(1)	8595(1)	27(1)
C(17)	6007(3)	4570(1)	8824(1)	42(1)
C(18)	2977(4)	4385(2)	9351(1)	52(1)
C(19)	3867(2)	3514(1)	8213(1)	25(1)
C(20)	3624(2)	3248(1)	7485(1)	24(1)
C(21)	3748(2)	3751(1)	6713(1)	18(1)
C(22)	1990(2)	3945(1)	6393(1)	21(1)
C(23)	4674(2)	3085(1)	6125(1)	20(1)
C(24)	3671(3)	2220(1)	5961(1)	32(1)

Table 3. Bond lengths [Å] and angles [°] for hr09_sarpong.

O(1)-C(1)	1.2189(19)
N(1)-C(14)	1.368(2)
N(1)-C(15)	1.374(2)
N(1)-H(1)	0.88(2)
N(2)-C(22)	1.142(2)
C(1)-C(2)	1.491(2)
C(1)-C(23)	1.508(2)
C(2)-C(3)	1.554(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.527(2)
C(3)-C(7)	1.537(2)
C(3)-H(3)	1.0000
C(4)-C(5)	1.328(3)
C(4)-C(6)	1.495(3)
C(5)-H(5A)	0.9500
C(5)-H(5B)	0.9500
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(7)-C(8)	1.5190(19)
C(7)-C(21)	1.566(2)
C(7)-H(7)	1.0000
C(8)-C(15)	1.373(2)
C(8)-C(9)	1.4537(19)
C(9)-C(10)	1.411(2)
C(9)-C(14)	1.414(2)
C(10)-C(11)	1.381(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.404(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.378(2)
C(12)-H(12)	0.9500

C(13)-C(14)	1.399(2)
C(13)-H(13)	0.9500
C(15)-C(16)	1.509(2)
C(16)-C(19)	1.507(2)
C(16)-C(17)	1.543(3)
C(16)-C(18)	1.547(3)
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-C(20)	1.328(2)
C(19)-H(19)	0.9500
C(20)-C(21)	1.529(2)
C(20)-H(20)	0.9500
C(21)-C(22)	1.478(2)
C(21)-C(23)	1.584(2)
C(23)-C(24)	1.526(2)
C(23)-H(23)	1.0000
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800

C(14)-N(1)-C(15)	109.29(12)
C(14)-N(1)-H(1)	122.2(15)
C(15)-N(1)-H(1)	128.3(15)
O(1)-C(1)-C(2)	123.34(15)
O(1)-C(1)-C(23)	122.40(15)
C(2)-C(1)-C(23)	114.10(13)
C(1)-C(2)-C(3)	108.42(12)
C(1)-C(2)-H(2A)	110.0
C(3)-C(2)-H(2A)	110.0
C(1)-C(2)-H(2B)	110.0
C(3)-C(2)-H(2B)	110.0

H(2A)-C(2)-H(2B)	108.4
C(4)-C(3)-C(7)	113.02(13)
C(4)-C(3)-C(2)	107.45(12)
C(7)-C(3)-C(2)	112.42(12)
C(4)-C(3)-H(3)	107.9
C(7)-C(3)-H(3)	107.9
C(2)-C(3)-H(3)	107.9
C(5)-C(4)-C(6)	122.06(17)
C(5)-C(4)-C(3)	119.33(17)
C(6)-C(4)-C(3)	118.39(15)
C(4)-C(5)-H(5A)	120.0
C(4)-C(5)-H(5B)	120.0
H(5A)-C(5)-H(5B)	120.0
C(4)-C(6)-H(6A)	109.5
C(4)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
C(4)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(8)-C(7)-C(3)	112.26(12)
C(8)-C(7)-C(21)	110.38(12)
C(3)-C(7)-C(21)	114.22(11)
C(8)-C(7)-H(7)	106.5
C(3)-C(7)-H(7)	106.5
C(21)-C(7)-H(7)	106.5
C(15)-C(8)-C(9)	106.36(13)
C(15)-C(8)-C(7)	122.57(13)
C(9)-C(8)-C(7)	131.07(13)
C(10)-C(9)-C(14)	116.48(13)
C(10)-C(9)-C(8)	137.26(13)
C(14)-C(9)-C(8)	106.25(12)
C(11)-C(10)-C(9)	119.76(14)
C(11)-C(10)-H(10)	120.1
C(9)-C(10)-H(10)	120.1
C(10)-C(11)-C(12)	121.99(14)

C(10)-C(11)-H(11)	119.0
C(12)-C(11)-H(11)	119.0
C(13)-C(12)-C(11)	120.24(14)
C(13)-C(12)-H(12)	119.9
C(11)-C(12)-H(12)	119.9
C(12)-C(13)-C(14)	117.34(14)
C(12)-C(13)-H(13)	121.3
C(14)-C(13)-H(13)	121.3
N(1)-C(14)-C(13)	127.71(14)
N(1)-C(14)-C(9)	108.14(13)
C(13)-C(14)-C(9)	124.14(14)
C(8)-C(15)-N(1)	109.94(14)
C(8)-C(15)-C(16)	128.96(15)
N(1)-C(15)-C(16)	121.06(13)
C(19)-C(16)-C(15)	112.46(13)
C(19)-C(16)-C(17)	110.07(15)
C(15)-C(16)-C(17)	109.56(15)
C(19)-C(16)-C(18)	106.37(16)
C(15)-C(16)-C(18)	110.39(15)
C(17)-C(16)-C(18)	107.86(17)
C(16)-C(17)-H(17A)	109.5
C(16)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(16)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(16)-C(18)-H(18A)	109.5
C(16)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(16)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(20)-C(19)-C(16)	133.86(15)
C(20)-C(19)-H(19)	113.1
C(16)-C(19)-H(19)	113.1

C(19)-C(20)-C(21)	131.75(14)
C(19)-C(20)-H(20)	114.1
C(21)-C(20)-H(20)	114.1
C(22)-C(21)-C(20)	111.38(13)
C(22)-C(21)-C(7)	109.34(12)
C(20)-C(21)-C(7)	111.02(12)
C(22)-C(21)-C(23)	106.75(12)
C(20)-C(21)-C(23)	106.05(12)
C(7)-C(21)-C(23)	112.19(12)
N(2)-C(22)-C(21)	176.19(17)
C(1)-C(23)-C(24)	111.70(13)
C(1)-C(23)-C(21)	107.35(12)
C(24)-C(23)-C(21)	115.09(13)
C(1)-C(23)-H(23)	107.5
C(24)-C(23)-H(23)	107.5
C(21)-C(23)-H(23)	107.5
C(23)-C(24)-H(24A)	109.5
C(23)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(23)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for hr09_sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	37(1)	28(1)	20(1)	-4(1)	-7(1)	5(1)
N(1)	29(1)	23(1)	15(1)	0(1)	4(1)	6(1)
N(2)	21(1)	30(1)	40(1)	-2(1)	-6(1)	-1(1)
C(1)	22(1)	19(1)	18(1)	-4(1)	0(1)	7(1)
C(2)	26(1)	23(1)	21(1)	-3(1)	8(1)	0(1)
C(3)	21(1)	18(1)	19(1)	-2(1)	4(1)	-2(1)
C(4)	25(1)	21(1)	32(1)	-8(1)	15(1)	-4(1)
C(5)	48(1)	24(1)	44(1)	-5(1)	24(1)	-9(1)
C(6)	24(1)	35(1)	49(1)	-14(1)	4(1)	-11(1)
C(7)	16(1)	16(1)	16(1)	-2(1)	0(1)	0(1)
C(8)	16(1)	17(1)	16(1)	0(1)	0(1)	0(1)
C(9)	15(1)	17(1)	17(1)	-1(1)	0(1)	-2(1)
C(10)	22(1)	20(1)	18(1)	1(1)	0(1)	-2(1)
C(11)	26(1)	21(1)	24(1)	6(1)	-2(1)	0(1)
C(12)	21(1)	17(1)	31(1)	1(1)	-1(1)	3(1)
C(13)	20(1)	20(1)	24(1)	-3(1)	2(1)	1(1)
C(14)	19(1)	19(1)	18(1)	1(1)	0(1)	-1(1)
C(15)	24(1)	20(1)	17(1)	0(1)	-1(1)	4(1)
C(16)	44(1)	23(1)	15(1)	2(1)	-2(1)	9(1)
C(17)	58(1)	25(1)	43(1)	-4(1)	-31(1)	12(1)
C(18)	98(2)	38(1)	21(1)	12(1)	17(1)	26(1)
C(19)	33(1)	21(1)	21(1)	6(1)	1(1)	3(1)
C(20)	30(1)	19(1)	24(1)	3(1)	1(1)	-3(1)
C(21)	18(1)	17(1)	17(1)	0(1)	-1(1)	0(1)
C(22)	20(1)	18(1)	24(1)	-2(1)	2(1)	-3(1)
C(23)	22(1)	17(1)	21(1)	-1(1)	-2(1)	3(1)
C(24)	41(1)	20(1)	35(1)	-6(1)	4(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for hr09_sarpong.

	x	y	z	U(eq)
H(1)	2100(30)	5946(15)	8855(13)	36(6)
H(2A)	6532	4647	4982	28
H(2B)	7388	4154	5720	28
H(3)	4350	5315	5769	23
H(5A)	7680	6929	5668	46
H(5B)	5993	6492	5207	46
H(6A)	7296	5819	7312	53
H(6B)	8790	6279	6794	53
H(6C)	8592	5211	6806	53
H(7)	5873	4500	7110	19
H(10)	3049	6463	5941	24
H(11)	1510	7801	6019	28
H(12)	431	8338	7202	28
H(13)	782	7490	8339	26
H(17A)	6738	4573	8355	63
H(17B)	6393	4087	9170	63
H(17C)	6120	5147	9091	63
H(18A)	3163	4938	9647	78
H(18B)	3341	3869	9664	78
H(18C)	1731	4328	9219	78
H(19)	3922	3030	8571	30
H(20)	3317	2634	7435	29
H(23)	5832	2915	6354	24
H(24A)	2460	2365	5816	48
H(24B)	3670	1844	6428	48
H(24C)	4239	1897	5534	48

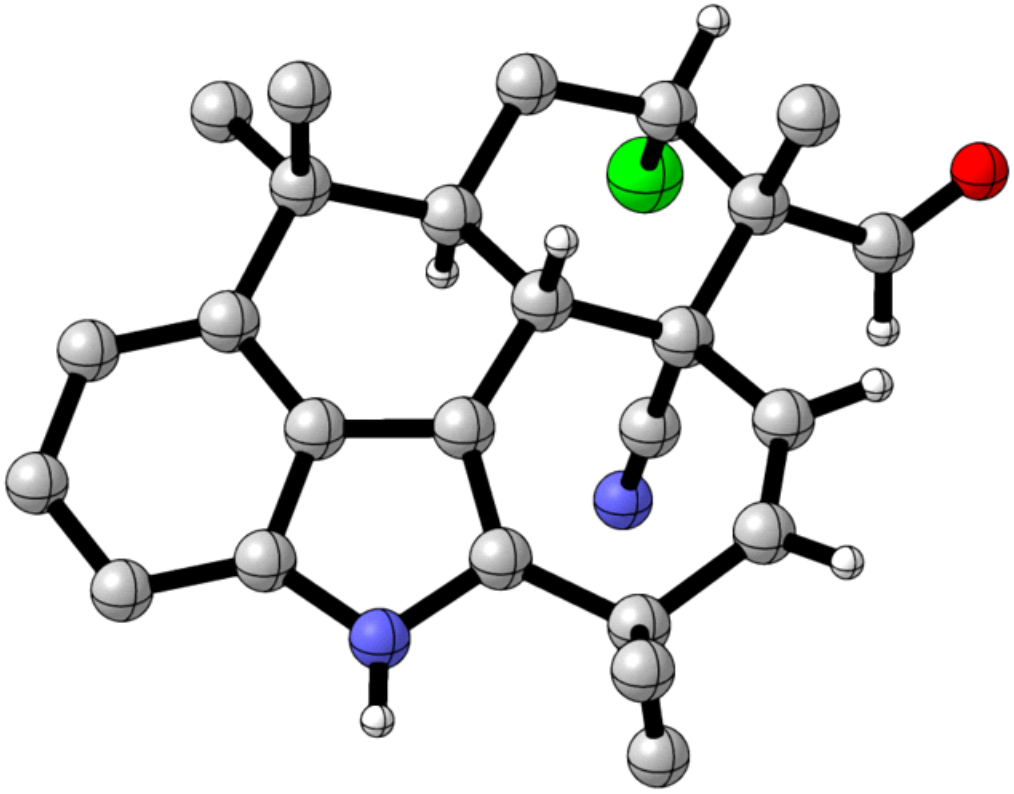
Table 6. Torsion angles [°] for hr09_sarpong.

O(1)-C(1)-C(2)-C(3)	111.01(17)
C(23)-C(1)-C(2)-C(3)	-64.40(17)
C(1)-C(2)-C(3)-C(4)	178.47(13)
C(1)-C(2)-C(3)-C(7)	53.50(17)
C(7)-C(3)-C(4)-C(5)	-152.10(15)
C(2)-C(3)-C(4)-C(5)	83.29(18)
C(7)-C(3)-C(4)-C(6)	33.13(19)
C(2)-C(3)-C(4)-C(6)	-91.48(17)
C(4)-C(3)-C(7)-C(8)	64.80(16)
C(2)-C(3)-C(7)-C(8)	-173.35(12)
C(4)-C(3)-C(7)-C(21)	-168.56(12)
C(2)-C(3)-C(7)-C(21)	-46.71(17)
C(3)-C(7)-C(8)-C(15)	-162.73(14)
C(21)-C(7)-C(8)-C(15)	68.59(18)
C(3)-C(7)-C(8)-C(9)	17.4(2)
C(21)-C(7)-C(8)-C(9)	-111.24(17)
C(15)-C(8)-C(9)-C(10)	-177.18(17)
C(7)-C(8)-C(9)-C(10)	2.7(3)
C(15)-C(8)-C(9)-C(14)	1.37(16)
C(7)-C(8)-C(9)-C(14)	-178.78(15)
C(14)-C(9)-C(10)-C(11)	1.5(2)
C(8)-C(9)-C(10)-C(11)	179.98(16)
C(9)-C(10)-C(11)-C(12)	0.1(2)
C(10)-C(11)-C(12)-C(13)	-1.6(2)
C(11)-C(12)-C(13)-C(14)	1.2(2)
C(15)-N(1)-C(14)-C(13)	-179.97(15)
C(15)-N(1)-C(14)-C(9)	0.12(18)
C(12)-C(13)-C(14)-N(1)	-179.34(15)
C(12)-C(13)-C(14)-C(9)	0.6(2)
C(10)-C(9)-C(14)-N(1)	177.98(13)
C(8)-C(9)-C(14)-N(1)	-0.92(16)
C(10)-C(9)-C(14)-C(13)	-1.9(2)
C(8)-C(9)-C(14)-C(13)	179.17(14)

C(9)-C(8)-C(15)-N(1)	-1.34(18)
C(7)-C(8)-C(15)-N(1)	178.79(13)
C(9)-C(8)-C(15)-C(16)	-179.07(16)
C(7)-C(8)-C(15)-C(16)	1.1(3)
C(14)-N(1)-C(15)-C(8)	0.79(19)
C(14)-N(1)-C(15)-C(16)	178.74(15)
C(8)-C(15)-C(16)-C(19)	-43.5(2)
N(1)-C(15)-C(16)-C(19)	138.98(16)
C(8)-C(15)-C(16)-C(17)	79.2(2)
N(1)-C(15)-C(16)-C(17)	-98.28(19)
C(8)-C(15)-C(16)-C(18)	-162.13(19)
N(1)-C(15)-C(16)-C(18)	20.4(2)
C(15)-C(16)-C(19)-C(20)	17.0(3)
C(17)-C(16)-C(19)-C(20)	-105.5(2)
C(18)-C(16)-C(19)-C(20)	137.9(2)
C(16)-C(19)-C(20)-C(21)	11.4(3)
C(19)-C(20)-C(21)-C(22)	-104.8(2)
C(19)-C(20)-C(21)-C(7)	17.3(3)
C(19)-C(20)-C(21)-C(23)	139.42(19)
C(8)-C(7)-C(21)-C(22)	55.24(15)
C(3)-C(7)-C(21)-C(22)	-72.37(15)
C(8)-C(7)-C(21)-C(20)	-68.05(15)
C(3)-C(7)-C(21)-C(20)	164.34(13)
C(8)-C(7)-C(21)-C(23)	173.48(12)
C(3)-C(7)-C(21)-C(23)	45.87(16)
O(1)-C(1)-C(23)-C(24)	14.6(2)
C(2)-C(1)-C(23)-C(24)	-169.98(14)
O(1)-C(1)-C(23)-C(21)	-112.49(16)
C(2)-C(1)-C(23)-C(21)	62.97(16)
C(22)-C(21)-C(23)-C(1)	68.62(15)
C(20)-C(21)-C(23)-C(1)	-172.51(13)
C(7)-C(21)-C(23)-C(1)	-51.14(15)
C(22)-C(21)-C(23)-C(24)	-56.41(17)
C(20)-C(21)-C(23)-C(24)	62.46(17)
C(7)-C(21)-C(23)-C(24)	-176.17(13)

Symmetry transformations used to generate equivalent atoms:

2) *Chloride (**49**)*



A colorless rod 0.20 x 0.11 x 0.08 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 100% complete to

74.000° in θ. A total of 20810 reflections were collected covering the indices -12<=h<=10, -15<=k<=15, -21<=l<=19. 4331 reflections were found to be symmetry independent, with an R_{int} of 0.0882. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the CrysAlis^{Pro} 1.171.40.68a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Table 1. Crystal data and structure refinement for HR007_Sarpong.

Identification code	HR007_Sarpong	
Empirical formula	C25 H27 Cl N2 O	
Formula weight	406.93	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 10.06480(10) Å	α= 90°.
	b = 12.1993(2) Å	β= 90°.
	c = 17.2537(2) Å	γ = 90°.
Volume	2118.47(5) Å^3	
Z	4	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	1.729 mm^{-1}	
F(000)	864	
Crystal size	0.200 x 0.110 x 0.080 mm^3	
Theta range for data collection	4.439 to 74.482°.	
Index ranges	-12<=h<=10, -15<=k<=15, -21<=l<=19	
Reflections collected	20810	
Independent reflections	4331 [R(int) = 0.0882]	
Completeness to theta = 74.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.83896	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	4331 / 0 / 271
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R1 = 0.0438, wR2 = 0.1228
R indices (all data)	R1 = 0.0447, wR2 = 0.1237
Absolute structure parameter	-0.004(11)
Extinction coefficient	n/a
Largest diff. peak and hole	0.196 and -0.362 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for hr007_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1814(3)	3649(2)	3458(2)	28(1)
C(2)	3207(3)	3519(2)	3808(2)	24(1)
C(3)	4055(3)	2940(2)	3186(2)	29(1)
C(4)	3112(3)	2769(2)	4521(2)	30(1)
C(5)	3833(3)	4641(2)	4044(1)	18(1)
C(6)	3116(3)	5150(2)	4701(2)	21(1)
C(7)	5248(3)	4416(2)	4338(2)	23(1)
C(8)	6234(3)	5091(2)	4517(2)	25(1)
C(9)	6367(3)	6320(2)	4525(2)	23(1)
C(10)	6230(3)	6684(3)	5381(2)	32(1)
C(11)	7782(3)	6597(3)	4232(2)	31(1)
C(12)	5362(2)	6914(2)	4042(1)	18(1)
C(13)	4381(3)	8449(2)	3575(1)	18(1)
C(14)	3967(3)	9510(2)	3381(2)	24(1)
C(15)	2928(3)	9592(2)	2864(2)	28(1)
C(16)	2280(3)	8670(2)	2550(2)	26(1)
C(17)	2653(2)	7621(2)	2756(2)	20(1)
C(18)	3720(2)	7535(2)	3273(1)	16(1)
C(19)	4333(2)	6566(2)	3572(1)	16(1)
C(20)	3770(2)	5472(2)	3358(1)	17(1)
C(21)	2299(3)	5631(2)	3089(2)	21(1)
C(22)	1728(3)	4522(2)	2836(2)	27(1)
C(23)	2095(3)	6537(2)	2460(2)	23(1)
C(24)	606(3)	6669(3)	2286(2)	40(1)
C(25)	2822(4)	6248(3)	1703(2)	33(1)
Cl(1)	550(1)	3904(1)	4192(1)	36(1)
N(1)	2598(3)	5577(2)	5212(1)	26(1)
N(2)	5380(2)	8053(2)	4043(1)	20(1)
O(1)	3066(3)	1795(2)	4483(2)	47(1)

Table 3. Bond lengths [Å] and angles [°] for hr007_sarpong.

C(1)-C(22)	1.515(4)
C(1)-C(2)	1.535(4)
C(1)-Cl(1)	1.822(3)
C(1)-H(1)	1.0000
C(2)-C(4)	1.535(4)
C(2)-C(3)	1.543(4)
C(2)-C(5)	1.562(4)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(3)-H(3C)	0.9800
C(4)-O(1)	1.191(4)
C(4)-H(4)	0.9500
C(5)-C(6)	1.481(3)
C(5)-C(7)	1.536(4)
C(5)-C(20)	1.560(3)
C(6)-N(1)	1.148(4)
C(7)-C(8)	1.326(4)
C(7)-H(7)	0.9500
C(8)-C(9)	1.506(4)
C(8)-H(8)	0.9500
C(9)-C(12)	1.497(4)
C(9)-C(11)	1.548(4)
C(9)-C(10)	1.549(4)
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-H(11A)	0.9800
C(11)-H(11B)	0.9800
C(11)-H(11C)	0.9800
C(12)-C(19)	1.382(3)
C(12)-N(2)	1.389(3)
C(13)-N(2)	1.376(4)
C(13)-C(18)	1.399(4)

C(13)-C(14)	1.400(4)
C(14)-C(15)	1.378(4)
C(14)-H(14)	0.9500
C(15)-C(16)	1.409(4)
C(15)-H(15)	0.9500
C(16)-C(17)	1.380(4)
C(16)-H(16)	0.9500
C(17)-C(18)	1.400(3)
C(17)-C(23)	1.525(4)
C(18)-C(19)	1.430(3)
C(19)-C(20)	1.496(3)
C(20)-C(21)	1.564(3)
C(20)-H(20)	1.0000
C(21)-C(22)	1.534(4)
C(21)-C(23)	1.564(4)
C(21)-H(21)	1.0000
C(22)-H(22A)	0.9900
C(22)-H(22B)	0.9900
C(23)-C(24)	1.537(4)
C(23)-C(25)	1.538(4)
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
N(2)-H(2)	0.82(4)

C(22)-C(1)-C(2)	113.9(2)
C(22)-C(1)-Cl(1)	109.4(2)
C(2)-C(1)-Cl(1)	112.4(2)
C(22)-C(1)-H(1)	106.9
C(2)-C(1)-H(1)	106.9
Cl(1)-C(1)-H(1)	106.9
C(4)-C(2)-C(1)	108.7(2)

C(4)-C(2)-C(3)	108.6(2)
C(1)-C(2)-C(3)	106.2(2)
C(4)-C(2)-C(5)	109.8(2)
C(1)-C(2)-C(5)	112.4(2)
C(3)-C(2)-C(5)	111.0(2)
C(2)-C(3)-H(3A)	109.5
C(2)-C(3)-H(3B)	109.5
H(3A)-C(3)-H(3B)	109.5
C(2)-C(3)-H(3C)	109.5
H(3A)-C(3)-H(3C)	109.5
H(3B)-C(3)-H(3C)	109.5
O(1)-C(4)-C(2)	123.6(3)
O(1)-C(4)-H(4)	118.2
C(2)-C(4)-H(4)	118.2
C(6)-C(5)-C(7)	105.9(2)
C(6)-C(5)-C(20)	106.8(2)
C(7)-C(5)-C(20)	113.8(2)
C(6)-C(5)-C(2)	111.7(2)
C(7)-C(5)-C(2)	107.7(2)
C(20)-C(5)-C(2)	110.8(2)
N(1)-C(6)-C(5)	177.3(3)
C(8)-C(7)-C(5)	131.3(2)
C(8)-C(7)-H(7)	114.4
C(5)-C(7)-H(7)	114.4
C(7)-C(8)-C(9)	133.4(3)
C(7)-C(8)-H(8)	113.3
C(9)-C(8)-H(8)	113.3
C(12)-C(9)-C(8)	114.6(2)
C(12)-C(9)-C(11)	109.6(2)
C(8)-C(9)-C(11)	107.3(2)
C(12)-C(9)-C(10)	109.4(2)
C(8)-C(9)-C(10)	106.6(2)
C(11)-C(9)-C(10)	109.3(2)
C(9)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10B)	109.5

H(10A)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(9)-C(11)-H(11A)	109.5
C(9)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(9)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(19)-C(12)-N(2)	108.5(2)
C(19)-C(12)-C(9)	133.2(2)
N(2)-C(12)-C(9)	118.3(2)
N(2)-C(13)-C(18)	106.6(2)
N(2)-C(13)-C(14)	133.0(3)
C(18)-C(13)-C(14)	120.4(2)
C(15)-C(14)-C(13)	116.7(3)
C(15)-C(14)-H(14)	121.7
C(13)-C(14)-H(14)	121.7
C(14)-C(15)-C(16)	122.8(3)
C(14)-C(15)-H(15)	118.6
C(16)-C(15)-H(15)	118.6
C(17)-C(16)-C(15)	121.0(3)
C(17)-C(16)-H(16)	119.5
C(15)-C(16)-H(16)	119.5
C(16)-C(17)-C(18)	116.3(2)
C(16)-C(17)-C(23)	128.1(2)
C(18)-C(17)-C(23)	115.5(2)
C(13)-C(18)-C(17)	122.8(2)
C(13)-C(18)-C(19)	108.6(2)
C(17)-C(18)-C(19)	128.6(2)
C(12)-C(19)-C(18)	106.3(2)
C(12)-C(19)-C(20)	134.6(2)
C(18)-C(19)-C(20)	119.0(2)
C(19)-C(20)-C(5)	112.1(2)

C(19)-C(20)-C(21)	108.7(2)
C(5)-C(20)-C(21)	110.1(2)
C(19)-C(20)-H(20)	108.6
C(5)-C(20)-H(20)	108.6
C(21)-C(20)-H(20)	108.6
C(22)-C(21)-C(20)	109.3(2)
C(22)-C(21)-C(23)	112.1(2)
C(20)-C(21)-C(23)	114.7(2)
C(22)-C(21)-H(21)	106.8
C(20)-C(21)-H(21)	106.8
C(23)-C(21)-H(21)	106.8
C(1)-C(22)-C(21)	113.3(2)
C(1)-C(22)-H(22A)	108.9
C(21)-C(22)-H(22A)	108.9
C(1)-C(22)-H(22B)	108.9
C(21)-C(22)-H(22B)	108.9
H(22A)-C(22)-H(22B)	107.7
C(17)-C(23)-C(24)	109.5(2)
C(17)-C(23)-C(25)	108.0(2)
C(24)-C(23)-C(25)	108.8(3)
C(17)-C(23)-C(21)	109.4(2)
C(24)-C(23)-C(21)	109.7(2)
C(25)-C(23)-C(21)	111.4(2)
C(23)-C(24)-H(24A)	109.5
C(23)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(23)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(23)-C(25)-H(25A)	109.5
C(23)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(23)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5

C(13)-N(2)-C(12)	110.0(2)
C(13)-N(2)-H(2)	126(2)
C(12)-N(2)-H(2)	124(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for hr007_sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	24(1)	26(1)	35(2)	-9(1)	5(1)	-9(1)
C(2)	23(1)	19(1)	28(1)	-2(1)	6(1)	-3(1)
C(3)	32(2)	22(1)	34(2)	-7(1)	10(1)	-2(1)
C(4)	32(2)	18(1)	38(2)	0(1)	10(1)	-2(1)
C(5)	20(1)	15(1)	20(1)	-1(1)	4(1)	1(1)
C(6)	22(1)	19(1)	22(1)	2(1)	2(1)	0(1)
C(7)	24(1)	19(1)	25(1)	3(1)	-2(1)	4(1)
C(8)	20(1)	27(1)	28(1)	3(1)	-4(1)	6(1)
C(9)	18(1)	24(1)	26(1)	-2(1)	-6(1)	2(1)
C(10)	33(2)	34(2)	29(2)	-2(1)	-14(1)	2(1)
C(11)	17(1)	32(2)	46(2)	-1(1)	-4(1)	0(1)
C(12)	15(1)	20(1)	20(1)	-2(1)	-1(1)	0(1)
C(13)	18(1)	18(1)	19(1)	0(1)	3(1)	0(1)
C(14)	23(1)	21(1)	29(1)	1(1)	8(1)	-1(1)
C(15)	28(1)	24(1)	31(1)	7(1)	6(1)	7(1)
C(16)	22(1)	30(2)	25(1)	5(1)	2(1)	6(1)
C(17)	14(1)	25(1)	19(1)	2(1)	2(1)	2(1)
C(18)	14(1)	20(1)	16(1)	1(1)	1(1)	1(1)
C(19)	14(1)	16(1)	18(1)	-1(1)	0(1)	2(1)
C(20)	14(1)	20(1)	18(1)	-2(1)	0(1)	0(1)
C(21)	14(1)	25(1)	23(1)	-3(1)	-2(1)	-2(1)
C(22)	23(1)	28(2)	32(1)	-5(1)	-2(1)	-7(1)
C(23)	16(1)	28(1)	24(1)	-1(1)	-6(1)	0(1)
C(24)	21(1)	42(2)	57(2)	7(2)	-18(2)	-1(1)
C(25)	47(2)	33(2)	19(1)	-3(1)	-4(1)	0(1)
Cl(1)	23(1)	38(1)	48(1)	-6(1)	12(1)	-7(1)
N(1)	33(1)	20(1)	25(1)	0(1)	9(1)	4(1)
N(2)	17(1)	19(1)	24(1)	-5(1)	-4(1)	-2(1)
O(1)	70(2)	23(1)	49(1)	1(1)	11(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for hr007_sarpong.

	x	y	z	U(eq)
H(1)	1586	2935	3206	34
H(3A)	3939	3312	2687	44
H(3B)	3773	2174	3139	44
H(3C)	4993	2967	3337	44
H(4)	3089	3100	5019	35
H(7)	5452	3661	4403	27
H(8)	7021	4722	4673	30
H(10A)	6488	7456	5429	48
H(10B)	6810	6232	5707	48
H(10C)	5306	6594	5548	48
H(11A)	7871	6368	3690	47
H(11B)	8439	6210	4549	47
H(11C)	7931	7389	4271	47
H(14)	4382	10141	3594	29
H(15)	2635	10301	2714	33
H(16)	1575	8772	2191	31
H(20)	4295	5169	2915	21
H(21)	1784	5866	3556	25
H(22A)	785	4622	2688	33
H(22B)	2214	4266	2371	33
H(24A)	131	6840	2767	60
H(24B)	259	5986	2067	60
H(24C)	479	7266	1913	60
H(25A)	2705	6843	1327	49
H(25B)	2454	5568	1489	49
H(25C)	3771	6148	1809	49
H(2)	5940(30)	8430(30)	4271(19)	20(8)

Table 6. Torsion angles [°] for hr007_sarpong.

C(22)-C(1)-C(2)-C(4)	170.1(2)
Cl(1)-C(1)-C(2)-C(4)	44.9(3)
C(22)-C(1)-C(2)-C(3)	-73.3(3)
Cl(1)-C(1)-C(2)-C(3)	161.58(19)
C(22)-C(1)-C(2)-C(5)	48.3(3)
Cl(1)-C(1)-C(2)-C(5)	-76.9(3)
C(1)-C(2)-C(4)-O(1)	80.4(4)
C(3)-C(2)-C(4)-O(1)	-34.7(4)
C(5)-C(2)-C(4)-O(1)	-156.3(3)
C(4)-C(2)-C(5)-C(6)	-53.6(3)
C(1)-C(2)-C(5)-C(6)	67.5(3)
C(3)-C(2)-C(5)-C(6)	-173.7(2)
C(4)-C(2)-C(5)-C(7)	62.4(3)
C(1)-C(2)-C(5)-C(7)	-176.5(2)
C(3)-C(2)-C(5)-C(7)	-57.8(3)
C(4)-C(2)-C(5)-C(20)	-172.5(2)
C(1)-C(2)-C(5)-C(20)	-51.4(3)
C(3)-C(2)-C(5)-C(20)	67.3(3)
C(6)-C(5)-C(7)-C(8)	-69.4(4)
C(20)-C(5)-C(7)-C(8)	47.6(4)
C(2)-C(5)-C(7)-C(8)	170.9(3)
C(5)-C(7)-C(8)-C(9)	1.6(5)
C(7)-C(8)-C(9)-C(12)	-19.8(5)
C(7)-C(8)-C(9)-C(11)	-141.7(3)
C(7)-C(8)-C(9)-C(10)	101.3(4)
C(8)-C(9)-C(12)-C(19)	-1.3(4)
C(11)-C(9)-C(12)-C(19)	119.3(3)
C(10)-C(9)-C(12)-C(19)	-120.9(3)
C(8)-C(9)-C(12)-N(2)	177.4(2)
C(11)-C(9)-C(12)-N(2)	-62.1(3)
C(10)-C(9)-C(12)-N(2)	57.7(3)
N(2)-C(13)-C(14)-C(15)	178.2(3)
C(18)-C(13)-C(14)-C(15)	-2.3(4)

C(13)-C(14)-C(15)-C(16)	1.1(4)
C(14)-C(15)-C(16)-C(17)	0.8(4)
C(15)-C(16)-C(17)-C(18)	-1.6(4)
C(15)-C(16)-C(17)-C(23)	-178.1(3)
N(2)-C(13)-C(18)-C(17)	-178.7(2)
C(14)-C(13)-C(18)-C(17)	1.6(4)
N(2)-C(13)-C(18)-C(19)	0.4(3)
C(14)-C(13)-C(18)-C(19)	-179.2(2)
C(16)-C(17)-C(18)-C(13)	0.4(4)
C(23)-C(17)-C(18)-C(13)	177.4(2)
C(16)-C(17)-C(18)-C(19)	-178.6(2)
C(23)-C(17)-C(18)-C(19)	-1.6(4)
N(2)-C(12)-C(19)-C(18)	0.7(3)
C(9)-C(12)-C(19)-C(18)	179.4(3)
N(2)-C(12)-C(19)-C(20)	-177.3(3)
C(9)-C(12)-C(19)-C(20)	1.5(5)
C(13)-C(18)-C(19)-C(12)	-0.7(3)
C(17)-C(18)-C(19)-C(12)	178.4(2)
C(13)-C(18)-C(19)-C(20)	177.7(2)
C(17)-C(18)-C(19)-C(20)	-3.2(4)
C(12)-C(19)-C(20)-C(5)	34.9(4)
C(18)-C(19)-C(20)-C(5)	-142.9(2)
C(12)-C(19)-C(20)-C(21)	156.9(3)
C(18)-C(19)-C(20)-C(21)	-20.9(3)
C(6)-C(5)-C(20)-C(19)	56.7(3)
C(7)-C(5)-C(20)-C(19)	-59.9(3)
C(2)-C(5)-C(20)-C(19)	178.6(2)
C(6)-C(5)-C(20)-C(21)	-64.6(3)
C(7)-C(5)-C(20)-C(21)	178.9(2)
C(2)-C(5)-C(20)-C(21)	57.4(3)
C(19)-C(20)-C(21)-C(22)	177.7(2)
C(5)-C(20)-C(21)-C(22)	-59.1(3)
C(19)-C(20)-C(21)-C(23)	50.8(3)
C(5)-C(20)-C(21)-C(23)	174.0(2)
C(2)-C(1)-C(22)-C(21)	-51.4(3)

Cl(1)-C(1)-C(22)-C(21)	75.4(3)
C(20)-C(21)-C(22)-C(1)	56.2(3)
C(23)-C(21)-C(22)-C(1)	-175.5(2)
C(16)-C(17)-C(23)-C(24)	-33.5(4)
C(18)-C(17)-C(23)-C(24)	150.0(3)
C(16)-C(17)-C(23)-C(25)	84.9(3)
C(18)-C(17)-C(23)-C(25)	-91.7(3)
C(16)-C(17)-C(23)-C(21)	-153.7(3)
C(18)-C(17)-C(23)-C(21)	29.7(3)
C(22)-C(21)-C(23)-C(17)	178.6(2)
C(20)-C(21)-C(23)-C(17)	-56.0(3)
C(22)-C(21)-C(23)-C(24)	58.5(3)
C(20)-C(21)-C(23)-C(24)	-176.1(2)
C(22)-C(21)-C(23)-C(25)	-62.1(3)
C(20)-C(21)-C(23)-C(25)	63.3(3)
C(18)-C(13)-N(2)-C(12)	0.0(3)
C(14)-C(13)-N(2)-C(12)	179.6(3)
C(19)-C(12)-N(2)-C(13)	-0.4(3)
C(9)-C(12)-N(2)-C(13)	-179.4(2)

Symmetry transformations used to generate equivalent atoms: