Approaches Towards a Total Synthesis of Daphenylline

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ABSTRACT

The following work describes the synthesis of advanced intermediates enroute to daphenylline. Construction of the ABCE tetracyclic skeleton of daphenylline was accomplished in thirteen steps with seven percent overall yield from commercially available (S)-carvone through [3,3]-allyl cyanate-to-isocyanate rearrangement, intramolecular Heck Reaction, and Intermolecular Diels-Alder/benzannulation strategies. Efforts towards the synthesis of daphenylline's D ring are discussed. A terse introduction to the scientific literature of daphniphyllum alkaloids and a comprehensive overview of selected approaches and all previous syntheses of daphenylline is given. Experimental procedures and spectroscopic data are provided for all new compounds.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

A	Angstrom(s)
p-ABSA	4-Acetamidobenzenesulfonyl azide
Ac	Acyl
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Anhyd.	Anhydrous
AZADOL	2-Azaadamantane-N-oxyl
9-BBN	9-Borabicyclo(3.3.1)nonane
BHT	Butylated hydroxytoluene
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
b.p	Boiling point
Bu	Butyl
n-BuLi	*n*-Butyllithium
s-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butyllithium
*m*CPBA	*meta*-Chloroperoxybenzoic acid
cod	Cyclooctadiene
CI	Chemical ionization
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
diglyme	Bis(2-methoxyethyl) ether
DIPEA	*N*,*N*-Diisopropylethylamine
DIPA	Diisopropylamine
DMAD	Dimethylacetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDC	*N*-(3-DimethylaminopropyI) carbodiimide
ee	Enantiomeric excess
EI	Electron ionization
ESI	Electrospray ionization
Et	Ethyl
F	Farad(s)
h	Hour(s)
HMDS	Hexamethyldisilane
HMPA	Hexamethylphosphoramide
HOBT	Hydroxybenzotriazole
HRMS	High-resolution mass spectrometry
IC	Inhibitory concentration

IR	Infrared spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide
PCC	Pyridinium chlorochromate
Ph	Phenyl
py	Pyridine
Pybox	Pyridine-2,6-bis(oxazoline)
LAH	Lithium aluminium hydride
LICA	Lithium *N*-isopropylcyclohexylamide
LDA	Lithium diisopropylamide
LDCA	Lithium dicyclohexylamide
Me	Methyl
min	Minute(s)
mL	Millilitre
mm	Millimetre
mmol	Millimol
m.p.	Melting point
MS	Molecular sieves
MsCl	Methanesulfonyl chloride
MW	Microwave
Mya	Million years ago
NDBCl	4-Chloro-7-nitrobenzofurazan
2-NPSC	2-Nitrophenylselenecyanate
Ns	Nitrobenzenesulfonamide

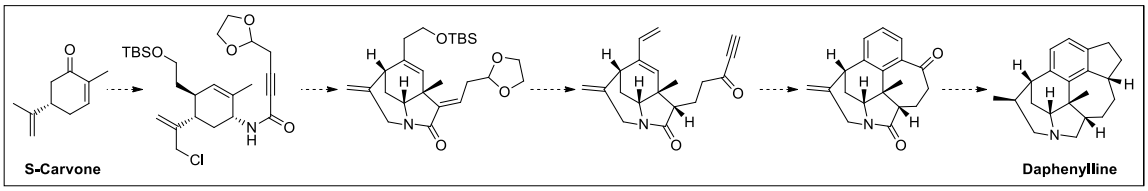
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
PCC	Pyridinium chlorochromate
PTSA, *p*TsOH	*para*-Toluenesulfonic acid
R_f	Retention factor
rt	Room temperature
TBAI	Tetra-*n*-butylammonium iodide
TBAF	Tetra-*n*-butylammonium fluoride
TBD	Triazabicyclodecene
TBDPS	*tert*-Butyldiphenylsilyl
tbs	tert-butylacetoacetate
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPSCl	Chlorotriisopropyl silane
TMS	Trimethylsilyl
(S)-tol-BINAP	(*S*)-2,2′-p-tolyl-phosphino-1,1′-binaphthyl
TPP	Triphenylphosphine
UV	Ultraviolet
V	Volt(s)

INTRODUCTION

Serturner's identification and isolation of the natural compounds present in opium, and the decades of work culminating in the elucidation of these compounds saw the growth of organic chemistry into the mature field it is today.[1,2] Total synthesis of these natural compounds was considered the ultimate confirmation of structure, and in 1956, Gates synthesized morphine[3] confirming the structure proposed[4] by Robinson in 1925. The field of synthetic organic chemistry has thus evolved into a challenge driven discipline where the community attempts to synthesize the most formidable and complex molecules.

The isolation and elucidation of daphniphylline and yuzurimine by Hirata in 1966[5–7] prompted intense investigation into the chemical components of the daphniphyllum genus. Since then, significant effort has been made to synthesize these highly complex compounds.[8–10]

The work in this thesis will focus on a method to synthesize the Daphniphyllum *macropodum* alkaloid daphenylline. A total synthesis of daphenylline will be pursued from (*S*)-carvone. The key steps in the synthesis will be the installation of the C4 nitrogen through a suprafacial [3,3]-sigmatropic rearrangement, a Finkelstein type nitrogen alkylation to construct the B ring, a Heck reaction to build the C ring, and an intramolecular Diels-Alder reaction/oxidative aromatization to construct the E and D rings simultaneously. Installation of the cyclopentene F-ring will finalize the synthesis of daphenylline.



CHAPTER 1: INTRODUCTION TO DAPHENYLLINE

1.1 Overview of Daphniphyllum Alkaloids

Daphniphyllum alkaloids are amine containing compounds isolated from species of the Daphniphyllum genus of plants. Named after Daphne – in Greek mythology a naiad associated with fresh water – the daphniphyllum genus consists of several dozen deciduous shrubs with a range of Eastern to Southeastern Asia. Species of the genus can be considered living fossils as daphniphyllum pollen from the Miocene epoch (23-5.3 Mya) has been discovered[11] in present-day Austria. The plants are sometimes used in traditional Chinese medicine[12] and the leaves are dried and smoked by the Ainu people[13]. Modern usefulness of these plants is generally ornamental.

The first record of isolation of any of the alkaloids found in the plant is a 1909 report[5] by S. Yagi who described the isolation of an alkaloid as a white amorphous powder from Daphniphyllum *macropodum* which he named daphnimacrin. Although Yagi offered a melting point (75-84 °C) and a molecular formula ($C_{27}H_{41}O_4N$), the molecular structure is still unknown.

Interest in the alkaloids of this genus reemerged in 1966 when a report by N. Sakabe, H. Irikawa, and Y. Hirata described the isolation of three new alkaloids[5] from the basic fraction of the methanolic extract of the leaves and bark of D. *macropodum*. They named these new compounds daphniphylline (**1.1**), neodaphniphylline (**1.2**) and yuzurimine (**1.3**). That same year, Hirata's group reported[6,7] the determination of the structures of the hydrobromide salts of daphniphylline and yuzurimine through X-ray diffraction studies.

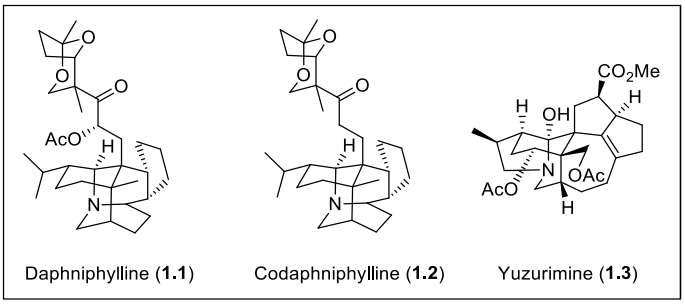


Figure 1.1 The First Three Alkaloids Isolated by Hirata's Group[6,7]

The unusual cage-like, highly sterically congested, contiguous stereocenter containing structures of these molecules continue to garner significant interest from the chemical community[8,9]. Although these compounds are alkaloids in the usual sense that they contain a basic amine group, it is more accurate to call them triterpenoids as they consist of six isoprene units and are theorized to be derived from squalene[14,15]. More than 320 unique members of this class have been isolated and more than 20 have been synthesized. Nine known classes of these compounds as well as some representative examples that have been synthesized are shown in Figure 1.2.[8–10]

Two groups, Yamamura's in 1973[15], and Heathcock's in 1989[14], have published potential biosynthetic pathways to these triterpenoids starting from squalene which are illustrated below in Figure 1.3. Yamada proposed an incomplete biosynthetic pathway resulting in daphniphylline type skeleton, while Heathcock proposed a skeletal cascade that results in a secodaphniphylline-type intermediate: protodaphniphylline which could be elaborated to the diverse classes of daphniphyllum alkaloids.

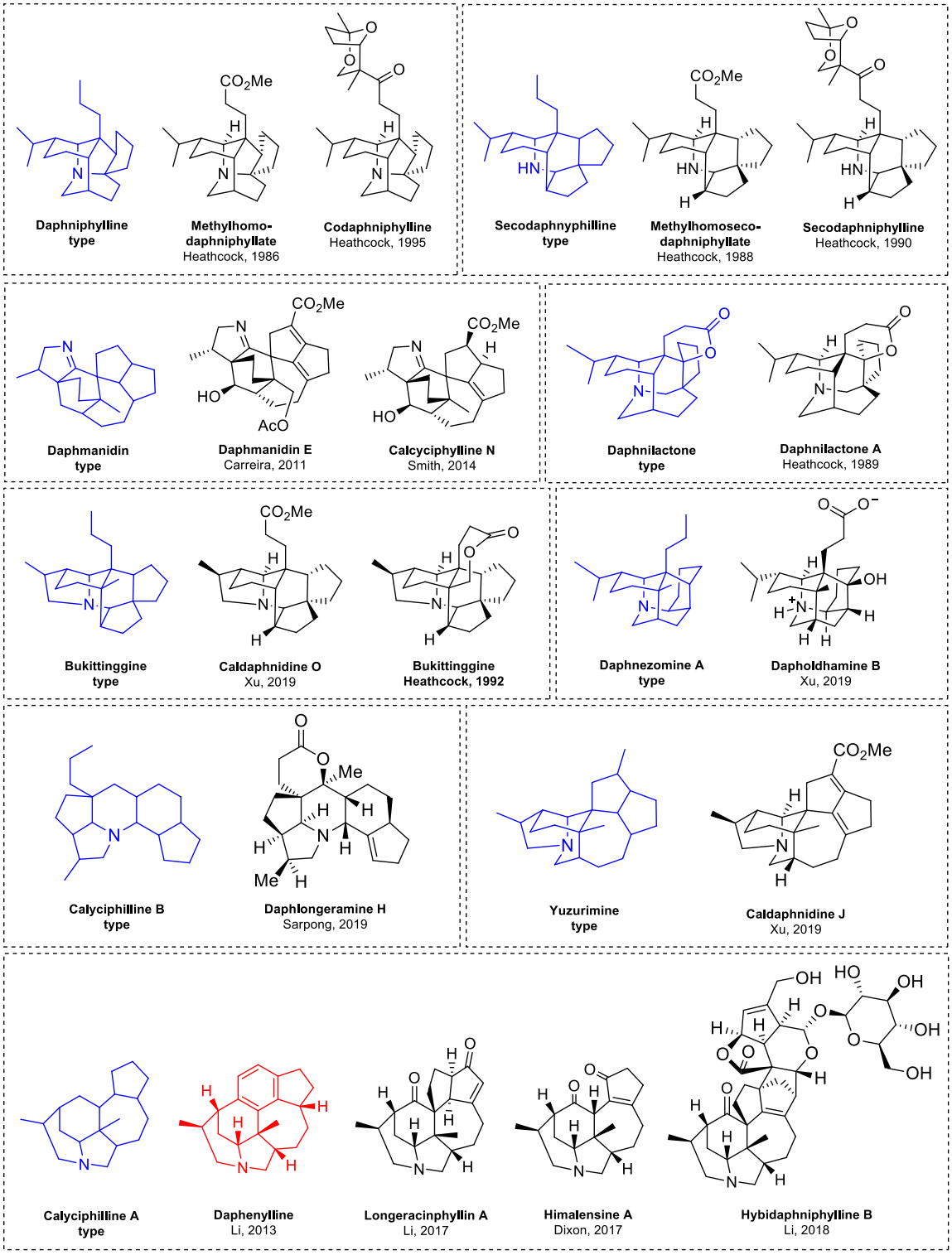


Figure 1.2 Selected Subgroups and Alkaloids of the Daphniphyllum Class[10]

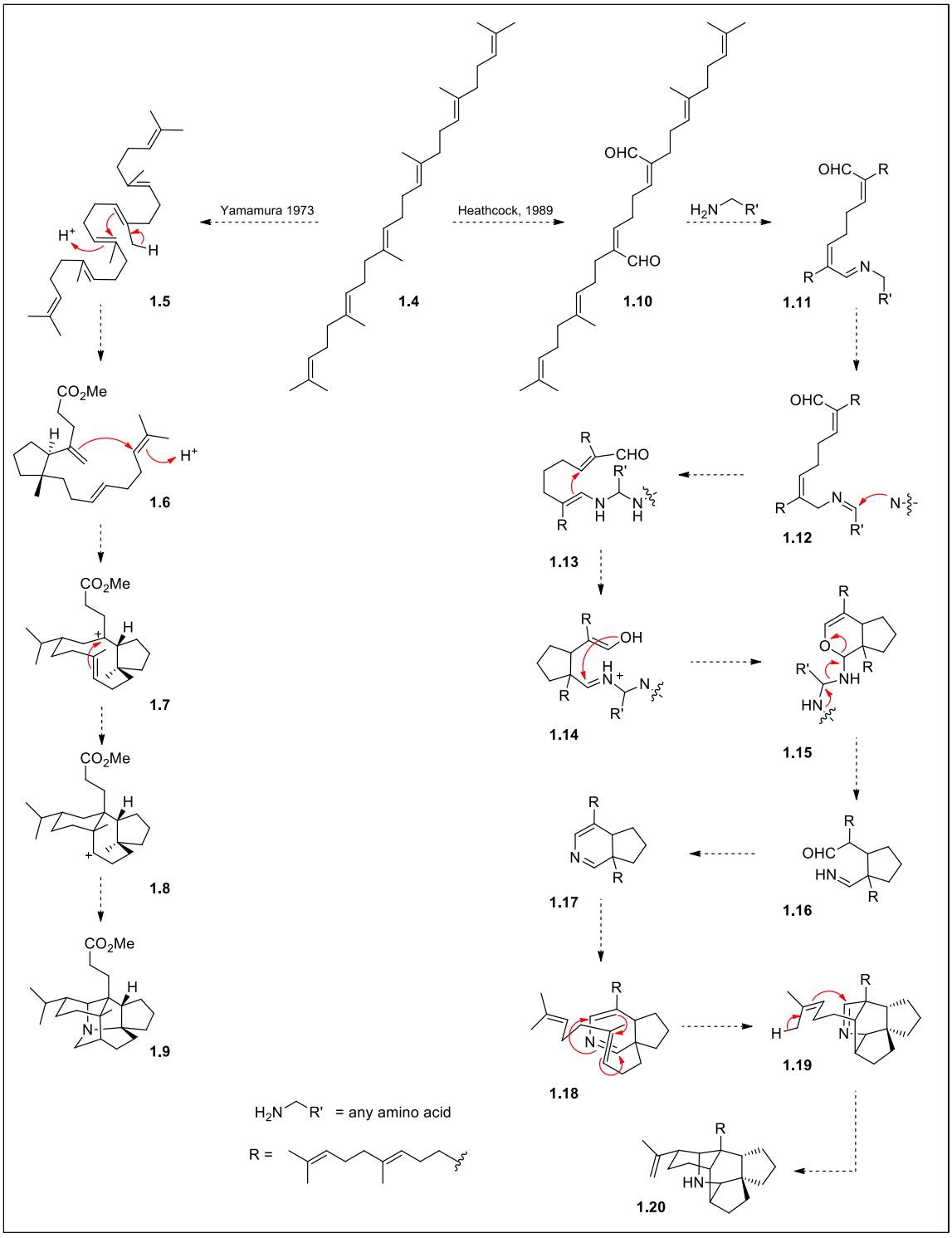
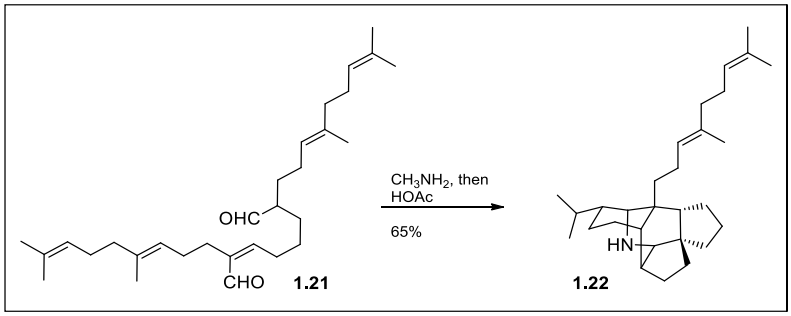


Figure 1.3 Two Proposed Biosynthetic Origins of Daphniphyllum Alkaloids[14,15]

Heathcock's group investigated the synthetic utility of his proposed biosynthesis. And in a striking example of biomimetic strategy, published a synthesis of protodaphniphylline in a single step from squalene-dialdehyde[14] (scheme 1.1). The synthesized protodaphniphylline was later elaborated to several natural daphniphyllum alkaloids evidently supporting his theorized biosynthesis.



Scheme 1.1 Heathcock's Biomimetic Synthesis of Protodaphniphylline[14]

1.2 Isolation and Elucidation of Daphenylline

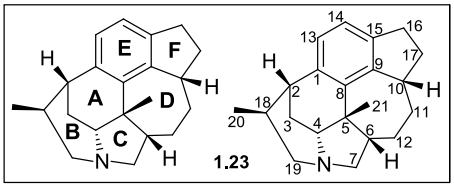


Figure 1.4 Ring and Carbon Identification Scheme of Daphenylline[16]

In 2009 a new daphniphyllum alkaloid[16] was isolated from daphniphyllum *longeracemosum* by Xiao-Jiang Hao and coworkers. Sixty kilograms of fruits were extracted with 95% ethanol, and the basic organic fraction was repeatedly chromatographed to yield 44 mg of a pure alkaloid. They determined the structure of this

new compound through NMR studies and the proposed structure was eventually confirmed by total synthesis (*vide supra*). This example was considered to be unique in the daphniphyllum class, as it is the only alkaloid with a six-membered aromatic ring – thus naming it daphenylline. The structure and identification scheme of daphenylline is shown above in Figure 1.4.

1.3 Proposed Biosynthesis of Daphenylline

The biosynthesis of daphenylline has never been thoroughly investigated, but as with all daphniphyllum alkaloids it is assumed to originate from squalene dialdehyde **1.10**. The skeletal rearrangement consisting of amino acid condensation, nitrogen assisted cyclization, aza-Diels-Alder, and aza-ene type reaction (*vide infra*) is presumed to provide protodaphniphylline **1.20**. It is assumed that daphnilongeranin C (**1.26**) is obtained *in vivo* from several complex rearrangements of protodaphniphylline, then a Wagner-Meerwein type alkyl shift and subsequent olefin isomerization, dehydration and elimination that could complete the biosynthesis of daphenylline.[17,18]

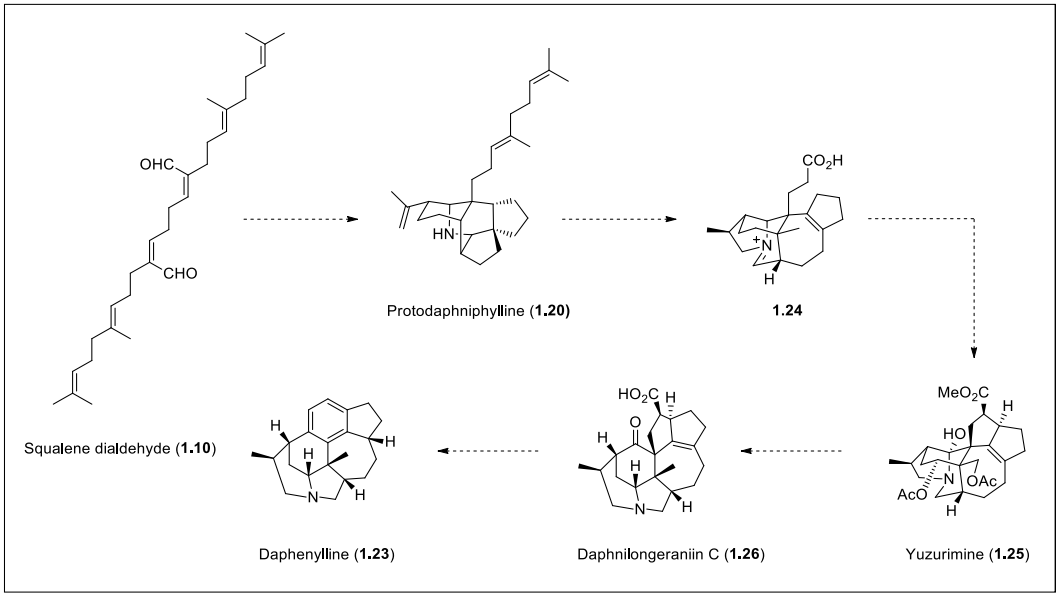


Figure 1.5 Possible Biosynthetic Pathway for Daphenylline[17]

Although some daphniphyllum alkaloids are promising anticancer and antiviral agents, daphenylline has a very high IC_{50} value versus human cancer cell lines (>40 μM versus HL-60, SMMC-7721, A-549, SKBR-3).[16,19] Efforts at the synthesis of daphenylline is thus limited to the challenge and scientific gain of exploring the construction of its unique scaffold.

CHAPTER 2: SELECTED APPROACHES TO DAPHENYLLINE

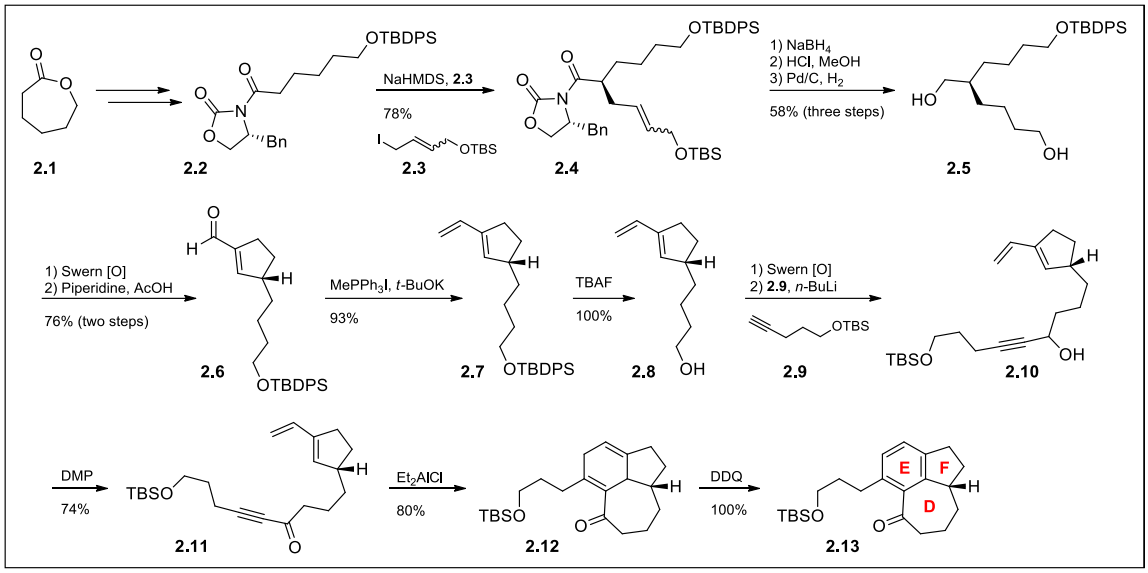
The scientific literature is rich with excellent approaches to the skeleton of daphenylline, and more generally the calyciphylline-A-type core. For brevity, only approaches with which the strategy in the discussion section (*vide supra*) is based upon are included here.

2.1 She's Synthesis of the DEF tricycle

In 2015, Xuegong She's group published[20] a stereocontrolled synthesis of daphenylline's all-carbon DEF tricycle in 18 steps through a Diels-Alder cycloaddition and oxidative aromatization pathway.

The previously known chiral oxazolidinone **2.2** was constructed in five steps from lactone **2.1**. Next, an Evans asymmetric allylation of **2.1** with allylic iodide **2.3** furnished protected allylic alcohol **2.4** with stereochemical control derived from the chiral oxazolidinone. Reduction, selective deprotection, and hydrogenation gave the saturated diol **2.5,** which after oxidation and intramolecular aldol condensation, yielded cyclopentene-al **2.6**. Deprotection and coupling of the aldehyde derived from **2.8** and the acetylide derived from alkyne **2.9** provided allylic alcohol **2.10** which yielded the key acetylenic ketone **2.11** after oxidation with Dess-Martin reagent.

The key [4+2] intramolecular cycloaddition proceeded only under Lewis acid catalyzed conditions, providing 1,4-cyclohexadiene **2.12,** which was easily aromatized in the presence of DDQ to the fused DEF [7,6,5]-tricycle of daphenylline.



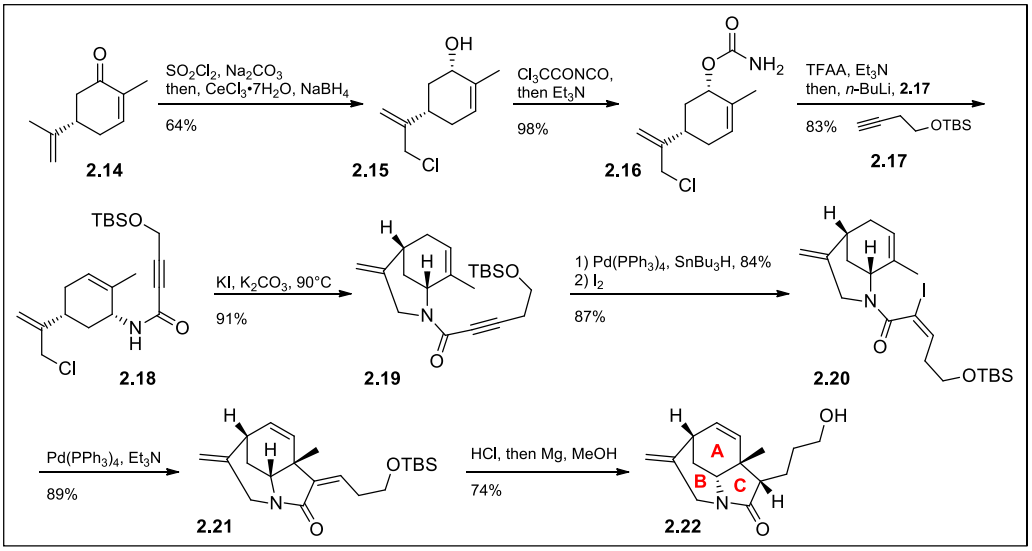
Scheme 2.1 Synthesis of the DEF Tricycle through Diels-Alder/Aromatization[20]

2.2 Hudlicky's Approach to the ABC tricyclic Core

In 2019 our group reported[21] a concise 7-step synthesis of the aza-[5,6,6] ABC tricycle of calyciphylline-A type alkaloids through a sigmatropic rearrangement/intramolecular Heck reaction strategy.

The required stereochemistry was derived from the chiral isopropene moiety of (*S*)-carvone **2.14** and transferred through a one pot chlorination/stereoselective reduction to **2.15.** A suprafacial [3,3] allyl cyanate to isocyanate sigmatropic rearrangement as first reported by Ichikawa was performed on the carbamate **2.16**, and the intermediate isocyanate was trapped with the lithium acetylide derived from alkyne **2.17**. Finkelstein-type nitrogen alkylation constructed daphenylline's B ring, and then an alkyne hydrostannylation, iodination-Heck reaction sequence provided the C ring of daphenylline. Reduction of the olefin of the unsaturated lactam by the action of

methanolic magnesium provided the aza-[5,6,6]-tricycle of daphenylline with the desired stereochemistry as the hydride can only be delivered from the less hindered α-face of the molecule.



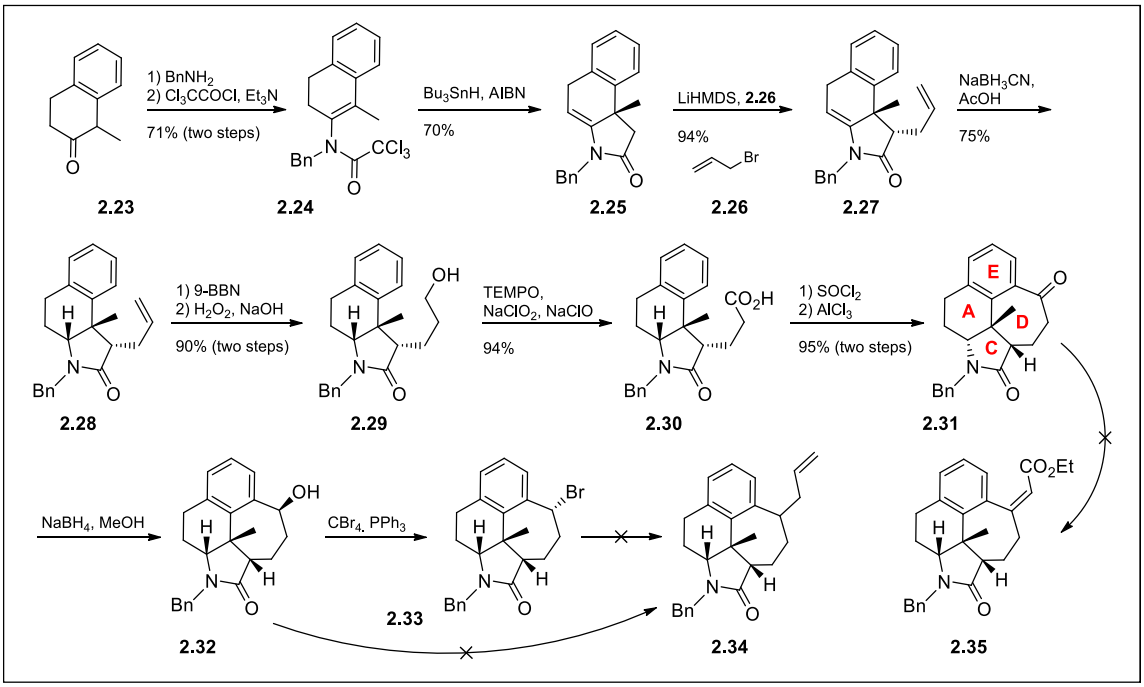
Scheme 2.2 [3,3]-Sigmatropic Rearrangement and Heck Reaction Strategy[21]

2.3 Bonjoch's Synthesis of the ACDEF Pentacyclic Core

Another approach[22] was completed by Josep Bonjoch's group in 2019. The ACDEF pentacyclic ring was synthesized in 22 steps from α-methyl-β-tetralone **2.23** through an acyl radical cyclization/successive Friedel-Crafts acylation pathway and by including the aromatic E-ring embedded in the starting tetralone.

Reaction of the 2-tetralone **2.23** with benzylamine provided an intermediate enamine which was treated with trichloroacetyl chloride to furnish the trichloroacetamide **2.24**. The acyl radical of **2.24** was generated in the presence of tributyltin hydride/AIBN and cyclization to the enamine olefin provided aza-[5,6,6] tricycle **2.25** on a multigram scale. The stereochemical outcome of this transformation is not discussed in the original

publication[22] and no enantiomeric excess is reported, however, it is probably determined by the geometrical configuration of a preferential rotational isomer. Base catalyzed allylation provided the enamide **2.27** with stereochemical outcome of the allylation controlled by the neighboring methyl group. Reduction of the enamide furnished amide **2.28** with delivery of the hydride to the β-face of the molecule. Hydroboration/oxidation of the vinyl sidechain of **2.28** provided the primary alcohol **2.29** which was oxidized to the acid **2.30** via a system of $NaClO_2$, NaClO and TEMPO. Finally, standard Friedel-Crafts acylation of the acyl chloride derived from **2.30** constructed the ketone-containing seven-membered ring to complete the synthesis of the ACDE tetracycle **2.31**.

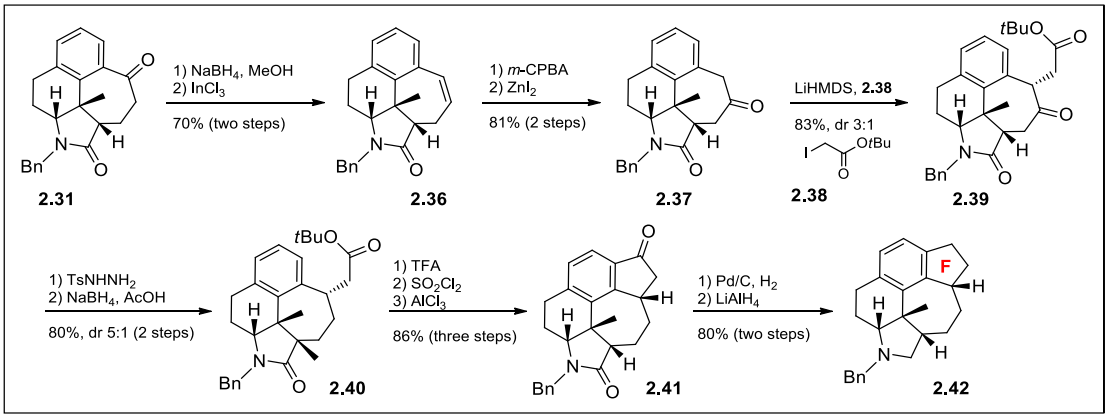


Scheme 2.3 Construction of the ACDE Tetracycle and Studies Toward the F-Ring[22]

The group next attempted to construct the five-membered F ring. The ketone of **2.31** was found to be unreactive to a Horner-Wadsworth-Emmons reaction, and the derived alcohol

2.32 and bromide **2.33** were not susceptible to allylation. The authors theorize that the underactivity of these compounds was the result of steric congestion from the C21 methyl, or because of easy enolization of the ketone **2.31** under basic conditions.[22]

They eventually found that exposure of the alcohol derived from ketone **2.31** to indium chloride forced eliminated to the olefin **2.36**. Construction of the five-membered F ring thus progressed via a circuitous route. Epoxidation of the olefin of **2.36**¸ and subsequent treatment with zinc iodide furnished ketone **2.37**. Alkylation of the enolate derived from **2.37** proceeded via attack from the less hindered α-face, then deoxygenation through the tosylhydrazone gave the ester **2.40**. Finally, hydrolysis, acid chloride formation, Friedel-Crafts acylation and deoxygenation completed construction of the ACDEF pentacycle **2.42** of daphenylline.



Scheme 2.4 Successful Synthesis of the F-Ring[22]

CHAPTER 3: TOTAL SYNTHESES OF DAPHENYLLINE

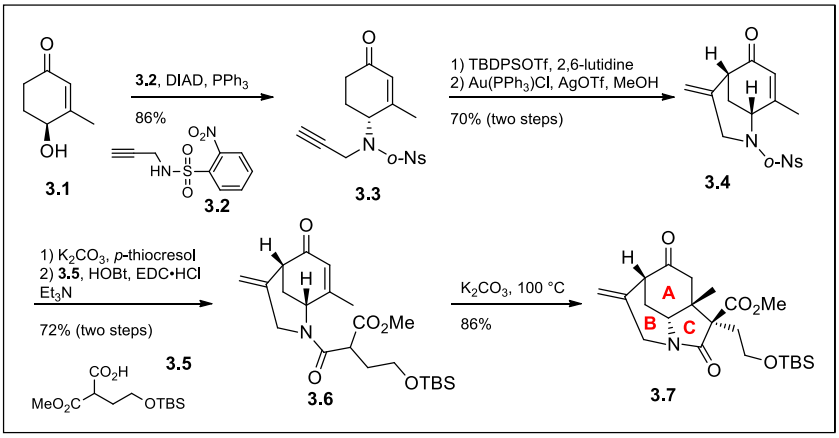
The structural complexity of daphenylline has attracted significant interest in synthesis of the compound. Since its discovery in 2009 there have been seven total syntheses[12,17–19,23–25] of the compound reported in the literature. Each one has approached the construction in a unique way. The challenging architecture has given rise to novel reaction pathways of great interest to the community of synthetic chemists. Each of the seven total syntheses are described here with a focus on the strategy used to construct daphenylline.

3.1 The First Total Synthesis of Daphenylline – Li (2013)

The first report of a total synthesis of daphenylline was reported[24] in the literature in 2013, only four years after the discovery and structural elucidation. Ang Li's published a total synthesis of daphenylline in 25 steps from methyl anisole through a strategy of gold catalyzed 6-exo-dig-enol-yne cyclization, intramolecular Michael addition, electrocyclic reaction, and radical cyclization. The starting chiral hydroxy-enone **3.1** was synthesized in six steps from commercially available methyl anisole and was the basis upon which the stereochemistry of daphenylline was elaborated.

The alcohol of the starting hydroxy-enone **3.1** was converted to *o*-nosyl-amine **3.3** through an aza-Mitsunobu reaction with protected propargyl amine **3.2**, the reversion of stereochemistry installing the C4 carbon-nitrogen bond with required stereochemistry. The enol ether derived from **3.3** was combined with the terminal alkyne sidechain through a gold catalyzed 6-*exo*-dig cyclization, creating the *cis*-fused aza-[6,6] AB bicycle **3.4** of daphenylline. Next, nosyl deprotection of **3.4**, and nitrogen acylation by EDC coupling with malonate derivative **3.5** provided α-amidoester **3.6** after which

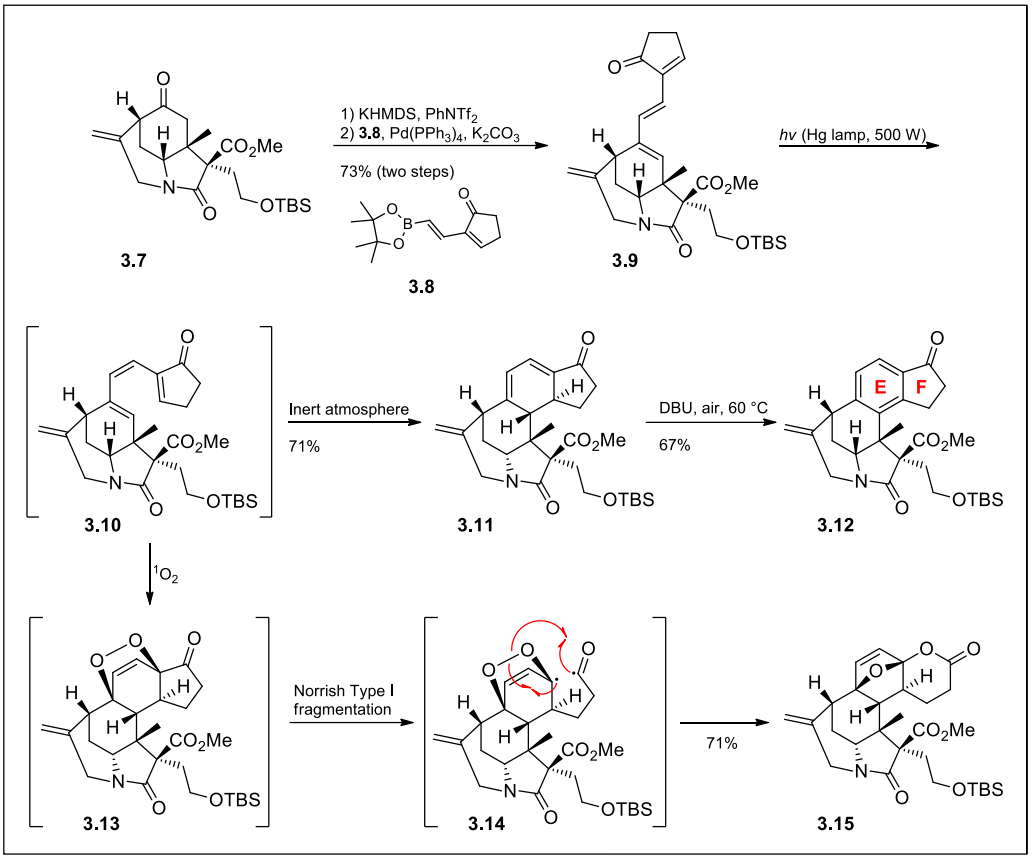
deprotonation with carbonate triggered the key Michael addition to produce the ABC tricycle **3.7**. The stereochemistry of each of these transformations is brought about from the chirality of the C4 carbon, as each cyclization proceeds from the bottom face of the molecule.



Scheme 3.1 Synthesis of the ABC Tricycle[24]

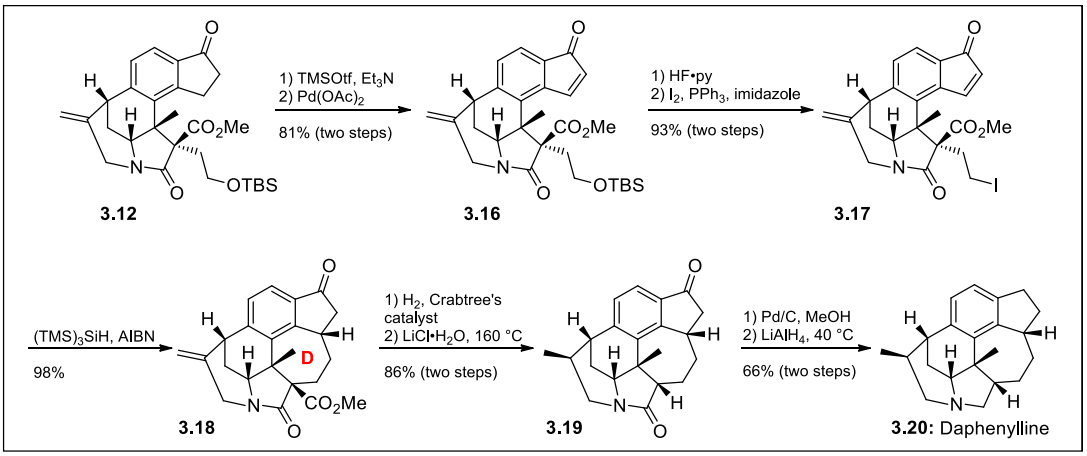
With the synthesis of the ABC tricycle with required stereochemistry completed, efforts were then focused on the aromatic E ring of daphenylline. The ketone of **3.7** was converted to enol-triflate, which was subsequently coupled with boronic ester **3.8** via a Suzuki reaction furnishing the triene **3.9**. Irradiation of the triene with UV light triggered *trans-cis* isomerization of the central π-bond, and subsequent electrocyclic cyclization provided the 1,3-cyclohexadiene **3.11**. Finally, aromatization of the diene was accomplished with the use of DBU under an atmosphere of air, accomplishing the synthesis of the ABCEF petacycle of daphenylline. The authors also attempted the electrocyclization in air in an effort to promote tandem oxidative aromatization, however, they proposed that a radical cyclization with singlet oxygen gave an intermediate

peroxide **3.13**, which undergoes a Norrish type I fragmentation and subsequent recombination to produce the isolated bridged ether **3.15**.



Scheme 3.2 Intramolecular Radical Cyclization of E Ring[24]

With the pentacycle **3.12** in hand, it only remained to install the seven-membered D ring. Saeguso-Ito oxidation converted the benzylic ketone of **3.12** to benzylic enone **3.16**, and then silyl ether deprotection, and Appel protocol provided the alkyl iodide **3.17**. Exposure of the iodide **3.17** to tin hydride and AIBN prompted radical cyclization of the side-chain to the enone and delivered the seven-membered- D-ring-containing ketone **3.19**. Finally, stereoselective hydrogenation of the exocyclic methylene, and deoxygenation of the ketone and lactam moiety completed the first-ever total synthesis of daphenylline.

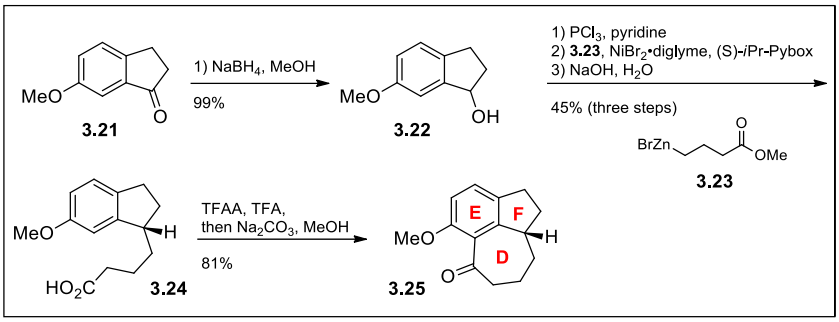


Scheme 3.3 Radical Closure of D Ring[24]

3.2 Fukuyama (2016)

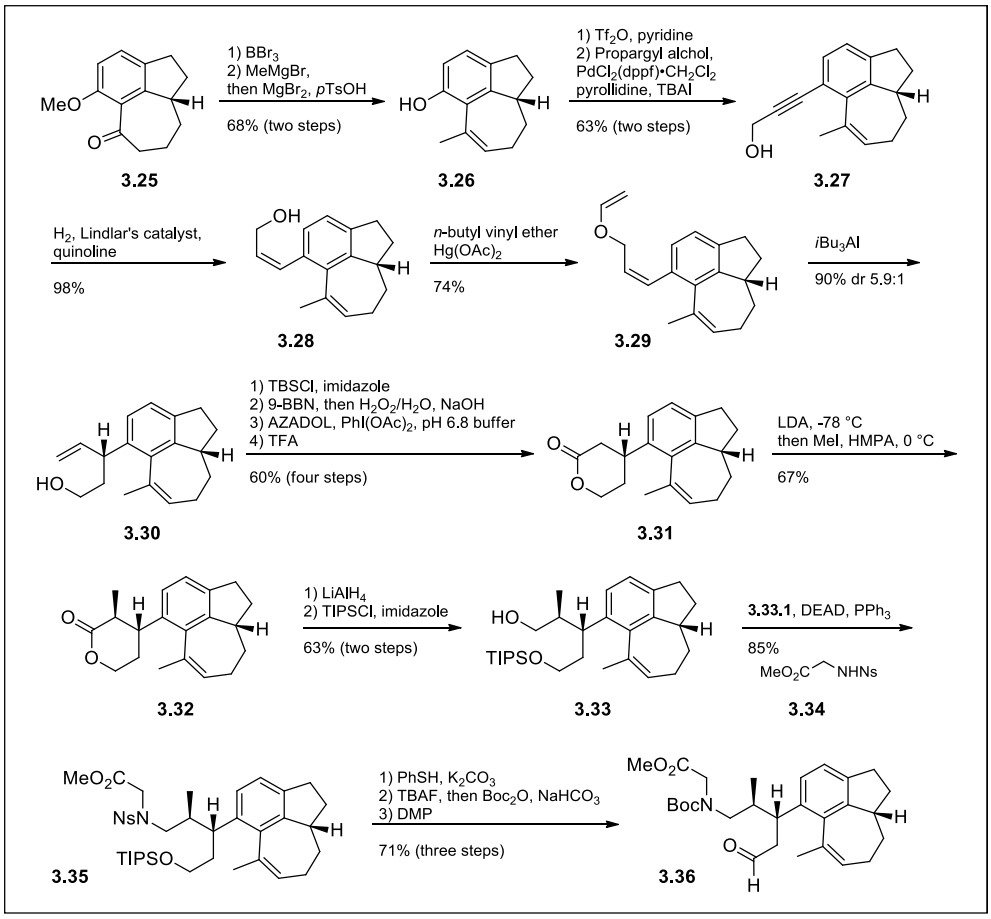
Three years after Li's seminal publication, Tohru Fukuyama's group reported[19] another total synthesis of daphenylline in 27 steps. The strategy was very different from that of Li's 2019 synthesis, as the E and F rings of daphenylline were present in the starting 6-methoxy-indenone **3.21**. A strategy of using Friedel-Crafts acylation to provide the seven-membered D ring, and intramolecular azomethine-ylide [3+2] cycloaddition was theorized to construct the ABC tricycle in a single transformation. The stereochemistry of the final molecule was derived from a stereoselective Negishi coupling which installed the C10 chiral center.

6-Methoxy-indenone **3.21** was reduced to indenol **3.22**, the alcohol of which was converted to alkyl chloride, then a stereoselective Negishi coupling with alkyl zinc **3.23** provided an ester which was hydrolyzed to carboxylic acid **3.24**. A Friedel-Crafts acylation by the action of trifluoroacetic anhydride constructed the seven-membered ring, completing the synthesis of the DEF tricycle of daphenylline.



Scheme 3.4 Synthesis of DEF Tricycle[19]

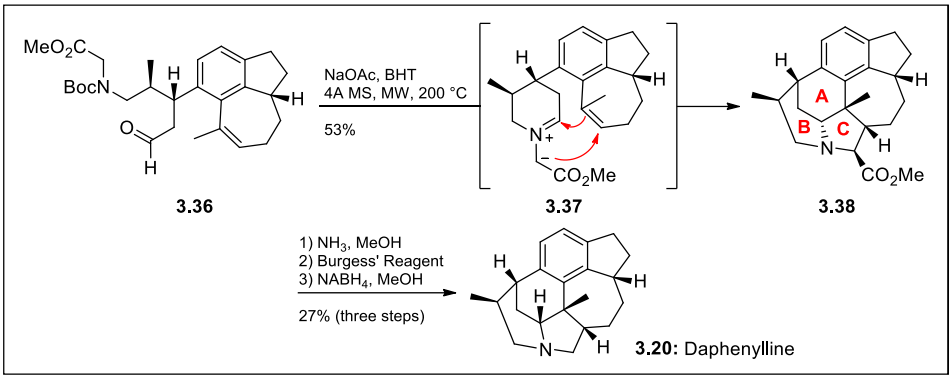
The next goal was to build the precursor to the anticipated azomethine cyclization. This was accomplished – albeit in a long series of transformations. Demethylation followed by a Grignard addition of methyl magnesium bromide and dehydration of the resultant tertiary alcohol gave the conjugated olefin **3.25**. Next, triflation of the phenol of **3.25** and subsequent Sonagashira coupling furnished the propargyl alcohol **3.27**, and following hydrogenation and allylation of the resulting alcohol provided the enol ether **3.29**. A Lewis acid promoted stereoselective Claisen rearrangement yielded the primary alcohol **3.30** which was protected, and then a hydroboration/oxidation of the terminal olefin, oxidation of the resultant ketone to acid, and acidic treatment provided the δ-lactam **3.31**. Methylation of the α-position, then global reduction produced a diol which was regioselectivity protected to the mono-TIPS-protected diol **3.33**. Finally, an aza-Mitsunobu reaction of the free alcohol with nosyl protected glycinate **3.34**, protecting group transformations and oxidation provided the key azomethine-ylide precursor **3.36**.



Scheme 3.5 Setup for Intramolecular Azomethine Ylide [3+2]-Cycloaddition[19]

Treatment of the Boc protected glycinate **3.36** with base and microwave irradiation triggered removal of the Boc group, and condensation of the free amine with the aldehyde producing an intermediate azomethine ylide **3.37,** which underwent an intramolecular [3+2] cycloaddition with the cyclic olefin to construct the ABC rings of daphenylline in a single step. Although a long series of transformations were required to build the precursor to this transformation, the significance of building three of daphenylline's rings in one transformation is not lost. The resulting hexacycle **3.38** was

decarboxylated in a three-step procedure culminating the second ever synthesis of daphenylline.



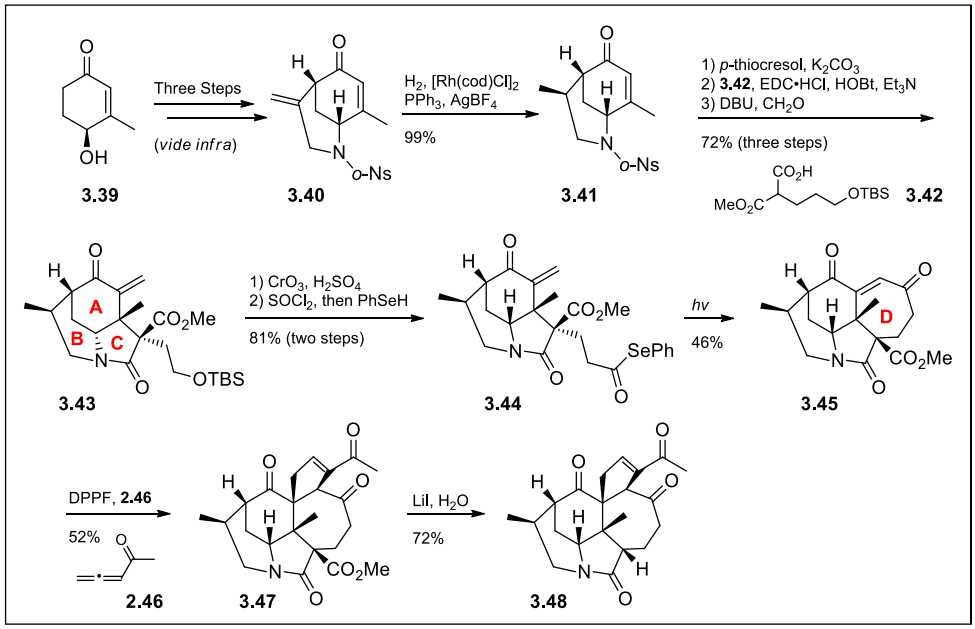
Scheme 3.6 Synthesis of ABC tricycle Through Azomethine Ylide Cycloaddition[19]

3.3 Li (2018)

In 2018 two total syntheses of daphenylline were published that were inspired by the Wagner-Meerwein rearrangement of the proposed biosynthesis of daphenylline. Ang Li's group reported[18] their second total synthesis of daphenylline through a key skeletal rearrangement related to the biosynthetic Wagner-Meerwein rearrangement that is supposed to construct daphenylline's E ring. The total synthesis was achieved in 16 steps from hydroxy-enone **3.30 (**22 steps from methyl anisole). Although not elaborated on in this text, the publication also elaborates daphnipaxianine A and himalenine D from common intermediates in the synthetic pathway.

This work commenced by constructing daphenylline's ABC tricycle in an analogous way to the Li's group previous 2013 synthesis. Aza-[6,6] bicycle **3.40** was made in three steps from hydroxy-enone **3.39** (nine steps from methyl anisole) as previously described (*vide infra*), and the exocyclic olefin was immediately stereoselectively hydrogenated. The

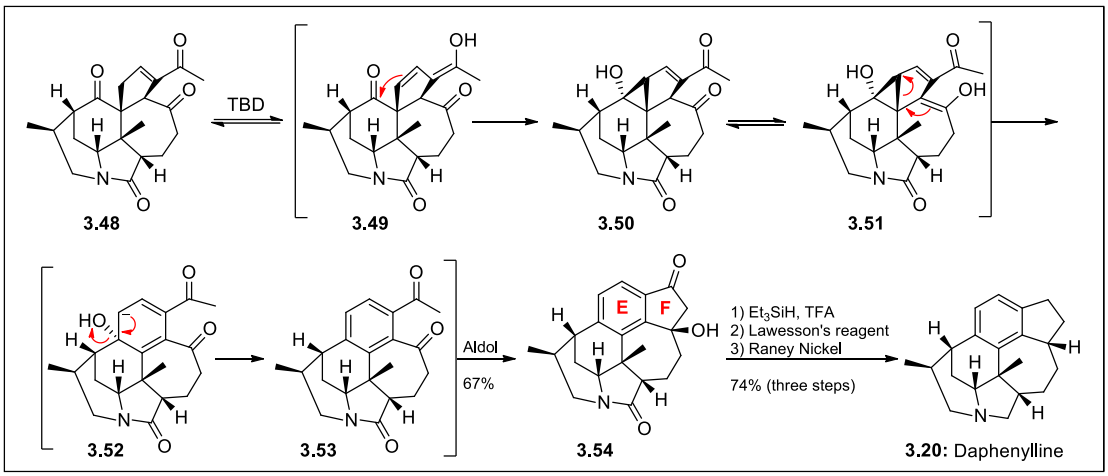
amine of the resultant bicycle **3.40** was nosyl deprotected, coupled with malonate derivative **3.42**, and the resultant α-amido ester underwent an intramolecular Michael addition and an aldol condensation with formaldehyde to provide the ABC tricycle **3.43**. One pot deprotection oxidation of the silyl ether sidechain of **3.42** gave an intermediate carboxylic acid which was converted to the acyl chloride and coupled with benzeneselenol to provide the acyl selenide **3.44**. Irradiation of the acyl selenide generated an acyl radical which combined with the exocyclic enone in a 7-*exo*-trig cyclization constructing the D-ring of enedione **3.43**. Next, [3+2] cycloaddition between the electron deficient enedione olefin of **3.42** and acylketene **3.46**, and subsequent Krapcho decarboxylation gave the fused-cyclopentene ABCD pentacycle **3.48**.



Scheme 3.7 Synthesis of ABCD Tetracycle[18]

Treatment of the fused cyclopentene triggered a series of transformations; the authors postulated that the dienol **3.49** originating from the enone **3.48** intramolecularly added to

the A-ring ketone**,** and the resultant fused cyclopropane was opened by the electron push from the enol **3.51** derived from the D-ring ketone. The resulting 1,3-cyclohexadine anion was dehydrated to furnish the aromatic ring containing **3.53**¸which underwent a tandem intramolecular aldol reaction to produce the ABCDEF hexacyclic skeleton of daphenylline **3.54**. Finally, a series of reductions and deoxygenations completed the third ever total synthesis of daphenylline.



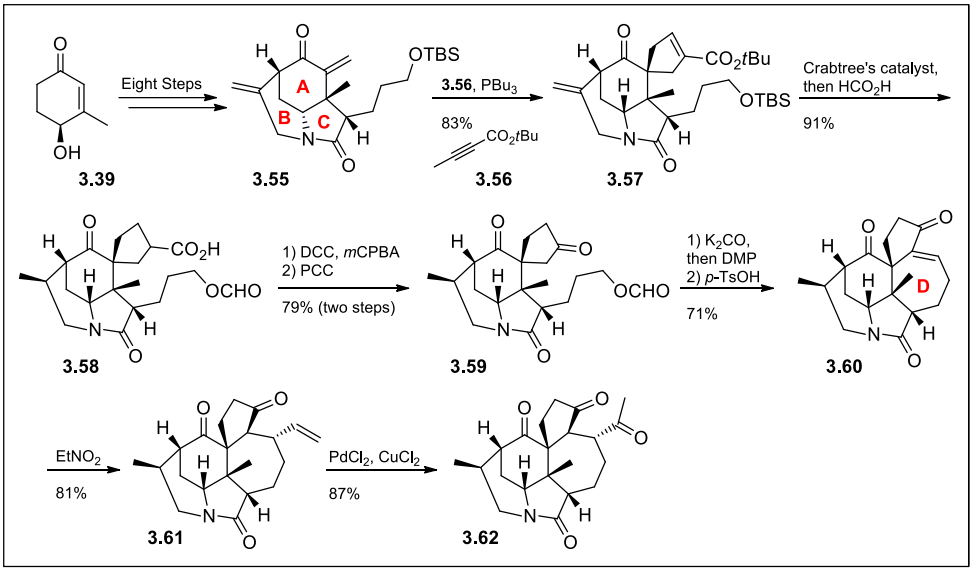
Scheme 3.8 Synthesis of E and F Ring Through Cyclopentane Rearrangement[18]

3.4 Zhai (2018)

Around the same time as the Li group reported their second total synthesis of daphenylline, Hongbin Zhai's group also reported[17] a bioinspired total synthesis of daphenylline (these publications[17,18] were reported together in the same issue of *Angewandte Chemie International Edition*). Although both syntheses were ingenious in their interpretation of the biosynthetic Wagner-Meerwein rearrangement, Zhai's approach is arguably more akin to the proposed biosynthesis, as an 1,2-alkyl migration constructed the E ring of daphenylline, and the precursor of the Wagner-Meerwein rearrangement was elaborated to daphnilongeranin B, which is the precursor to daphenylline in the proposed biosynthesis. Zhai's synthesis was completed in 24 steps from the oft-used hydroxy-enone **3.39** (30 steps from methyl anisole).

The hydroxy-enone **3.39** was elaborated to ABC tricycle **3.55** in an analogous fashion to Li's 2013 and 2018 syntheses[18,24]. Next, **3.56** underwent an intermolecular [3+2]-cycloaddition with acetylenic ester **3.56** in the presence of tributylphosphine to provide spirocycle **3.57**¸ and global stereoselective hydrogenation and treatment with formic acid gave the corresponding spirocycle **3.58**. Exposure of **3.58** to DCC and *m*CPBA gave a secondary alcohol, which was oxidized with PCC to provide the ketone **3.59** required for the synthesis of the seven-membered D ring. Treatment of ketone **3.59** with carbonate hydrolyzed the formate ester of the side chain, and Dess-Martin reagent provided an intermediate aldehyde which was cyclized with the spiro-ketone in an intramolecular aldol condensation completing construction of the ABCD skeleton (**3.60**) of daphenylline. Next, a Michael addition with nitroethane unexpectedly produced the

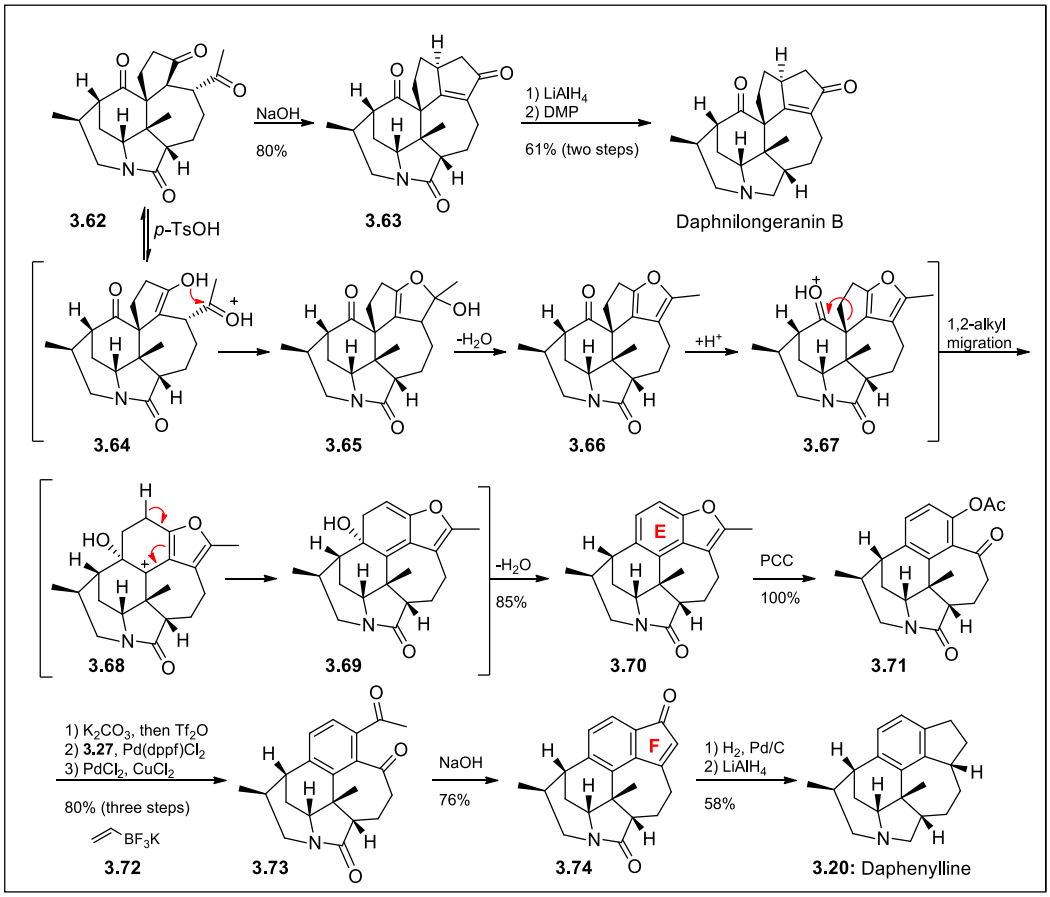
elimination product **3.61**, and Wacker-Tsuji Oxidation provided the pentacyclic triketone **3.62** required for the key Wagner-Meerwein rearrangement.



Scheme 3.9 Synthesis of ABCD Tetracycle[17]

In a remarkable example of divergent total synthesis, the triketone **3.62** was exposed to hydroxide in a solvent system of brine/methanol, and aldol condensation and olefin isomerization provided the enone **3.63**, which was deoxygenated in a two-step procedure finishing the synthesis of daphnilongeranin B. The triketone **3.62** was also exposed to *p*-toluenesulphonic acid the E-ring containing benzofuran **3.70** was isolated. The authors proposed that instead of an aldol condensation, as is the case when base is used, the oxygen of the enol **3.64** attacks the carbonyl carbon directly, and following dehydration, the intermediate furan **3.66** is obtained. Next, a Wagner-Meerwein rearrangement and deprotonation/aromatization produces the isolated benzofuran **3.70**. Oxidative cleavage of the furan provided acetate **3.71,** which was hydrolyzed, converted to the triflate, coupled with trifluoroborate **3.72** in a Suzuki-type reaction, and oxidized to the diketone

3.73 in a Wacker-Tsuji reaction. Finally, intramolecular aldol condensation and global reduction/deoxygenation completed the fourth total synthesis of daphenylline.



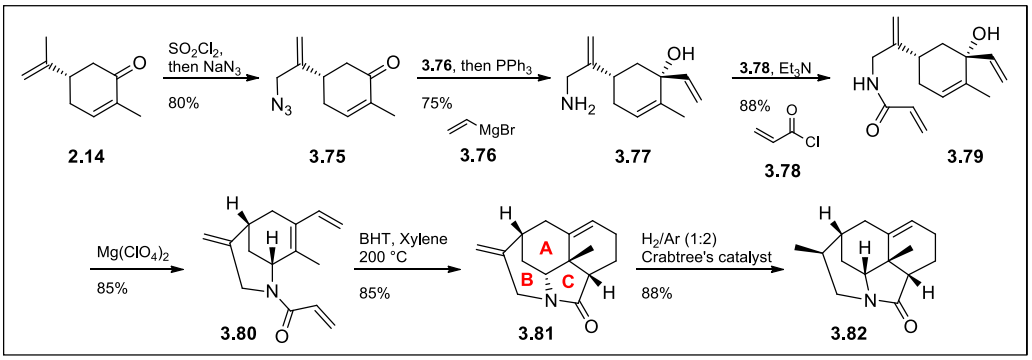
Scheme 3.10 Wagner-Meerwein Rearrangement and Intramolecular Aldol[17]

3.5 Qiu (2019)

Interest in daphenylline's unique architecture was then taken up by Fayang Qiu's group, who published two related total syntheses of daphenylline, a 19-step endeavor[25] in 2019 and a more concise 16-step construction[23] in 2021**.** Both syntheses used (*S*)-carvone as the chiral pool from which the stereochemistry of daphenylline was derived.

The 2019 synthesis[25] consisted of key steps of intramolecular allylic amination, intramolecular Diels-Alder cycloaddition, Robinson annulation/aromatization, and Friedel-Crafts acylation.

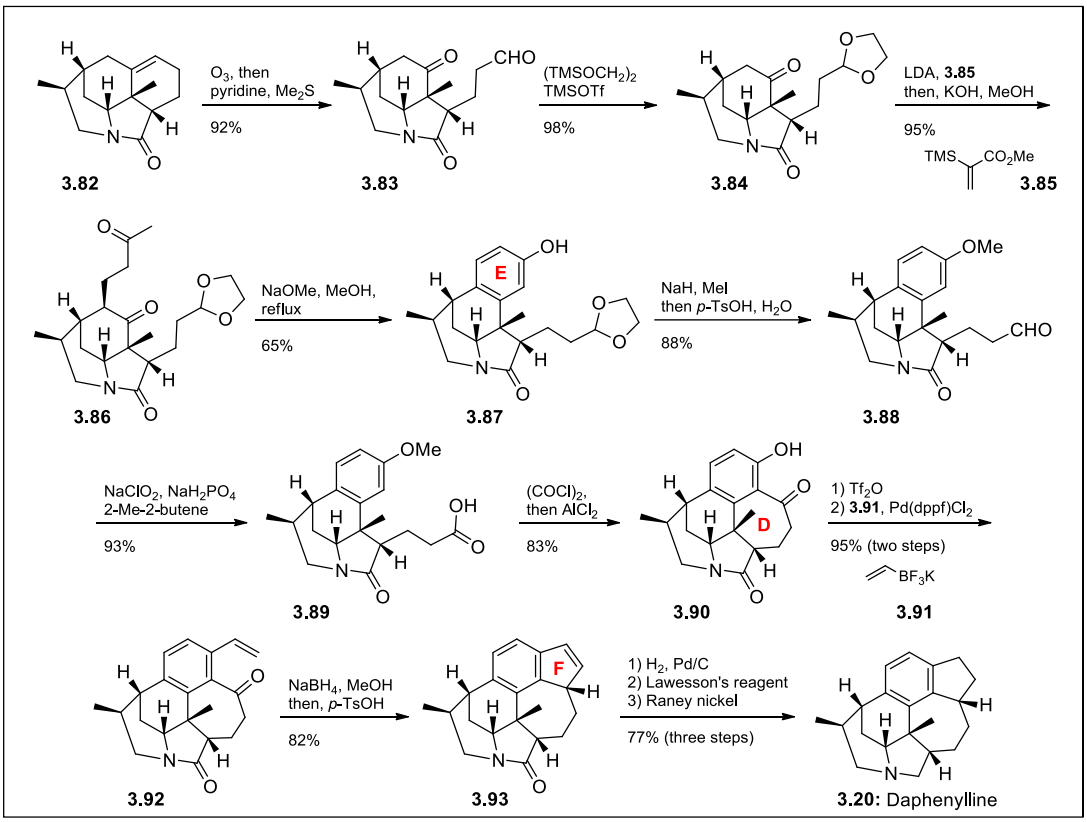
The isopropene moiety of (*S*)-carvone **2.14** was azidated through the intermediate allylic chloride in one pot, and then 1,2-Gringard addition of allyl Grignard reagent **3.76** and Staudinger reaction provided the amine **3.77**. Amidation with acryloyl chloride **3.78** gave the unsaturated amide **3.79**, which underwent allylic amination in the presence of catalytic $Mg(ClO_4)_2$ constructing the AB bicycle **3.80**. Next, intramolecular Diels-Alder cyclo-addition and stereoselective hydrogenation of the exocyclic olefin finished the construction of daphenylline's C-ring.



Scheme 3.11 Synthesis of ABC Tricycle[25]

The remaining olefin of **3.82** underwent ozonolysis, the resultant aldehyde was protected as an acetal (**3.84**), and the naked ketone was enolized and subjected to Stork-Ganem reagent yielding the diketone **3.82**. Treatment of **3.82** with sodium methoxide in methanol ender reflux prompted a tandem Robinson annulation/aromatization completing the synthesis of the E-ring and gave the phenol **3.87**. Next, the free phenol was capped with a methyl group, and the acetal was deprotected furnishing aldehyde **3.88**. Pinnick

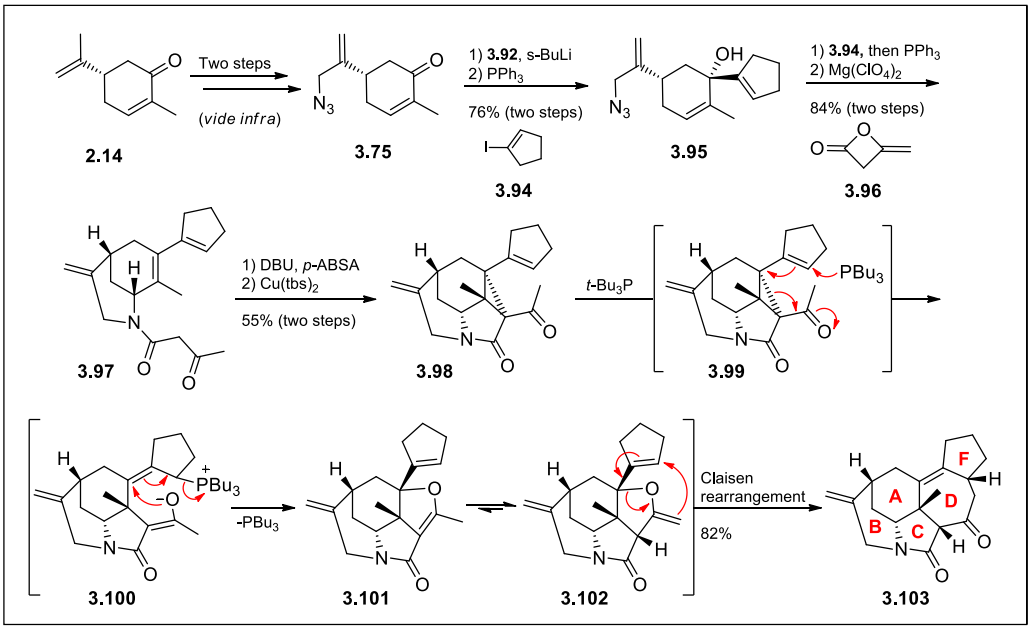
oxidation, and standard Friedel-Crafts acylation provided the D-ring containing ABCDE pentacyclic skeleton of daphenylline. Finally, O-demethylation, conversion of the phenol to triflate, and a Suzuki-type reaction afforded the styrene containing **3.92**, the ketone of which was reduced to an alcohol and a Nazarov-type cyclization using *para*-toluenesulphonic acid provided the F ring containing hexacycle **3.93**. Global reduction and deoxygenation resulted in the culmination of the fifth total synthesis of daphenylline.



Scheme 3.12 Synthesis of DEF Rings[25]

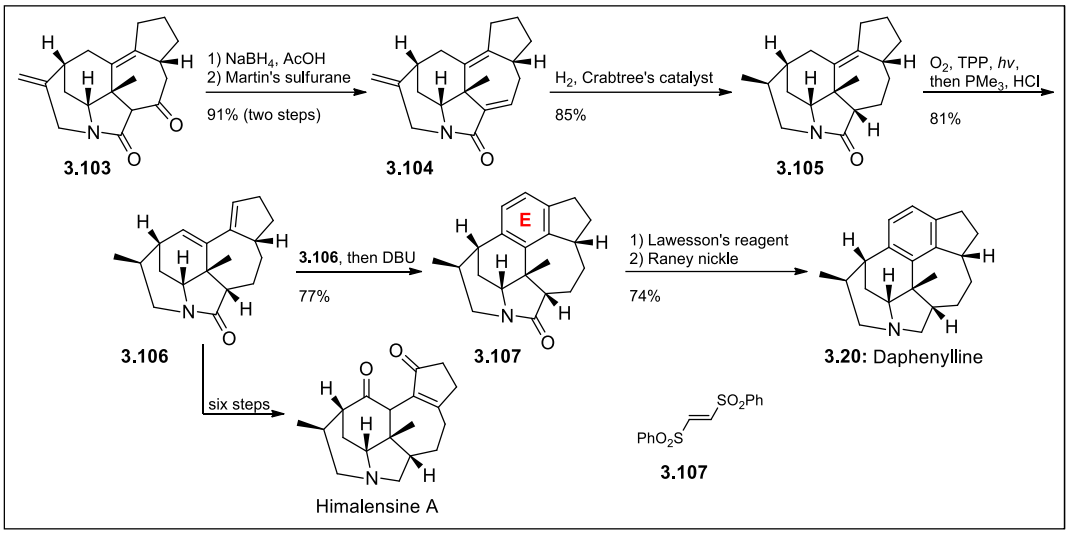
3.6 Qiu (2021)

In the Qiu Group's second publication[23], (*S*)-carvone was again azidated, but in a different tack from the previous publication, the carbonyl was attacked by the vinyl lithium derived from vinyl iodide **3.94**, and after a Staudinger reduction, the amine was amidated with diketene **3.96** and subsequent allylic amidation produced β-ketoamide **3.97**. A Regitz diazo transfer produced an intermediate diazo compound that underwent carbene cycloaddition in the presence of a copper catalyst installed the C-ring and cyclopropane moiety of **3.98**. Next, the allylic cyclopropane was treated with tri-*tert*-butyl phosphine triggering a series of transformations, probably including a cyclopropane opening, and Claisen rearrangement (scheme 3.13) to produce the D and E rings of daphenylline in a single step.



Scheme 3.13 Synthesis of ABCDF Pentacycle Through Cyclopropane Rearrangement[23]

The authors then turned their attention to the only remaining obstacle, installation of the aromatic E-ring. Reduction of the ketone in **3.103** to the corresponding alcohol, dehydration by the action of Martin's sulfurane, and hydrogenation of the electron deficient olefin produced the amide **3.105**. Allylic transpositional oxidation by Schenck-ene reaction afforded the diene **3.106.** Finally, a tandem Diel-Alder cycloaddition and elimination of the intermediate bis-phenyl selenide, followed by deoxygenation completed the sixth total synthesis of daphenylline. The authors also completed a total synthesis of himalensine A in six steps from the common diene **3.106**.[23]



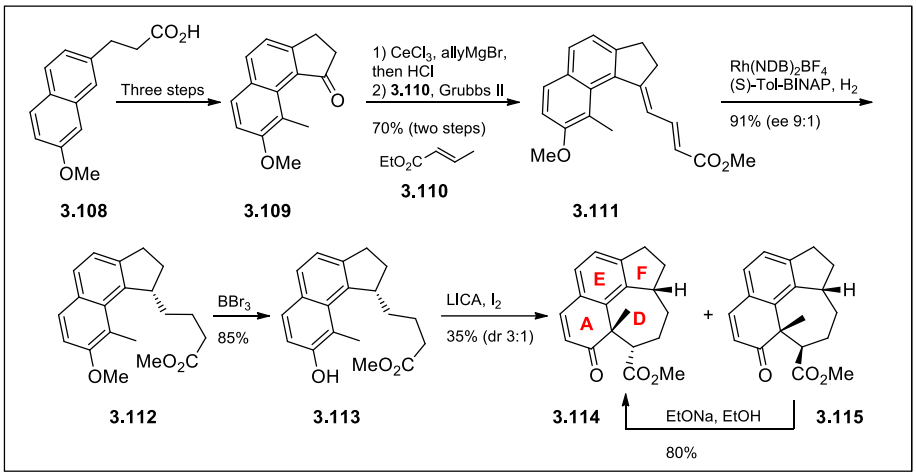
Scheme 3.14 Construction of the E-Ring through Diels-Alder/Elimination[23]

3.7 Lu (2022)

Hai-Hua Lu's group recently published another total synthesis of daphenylline[12] in 19 steps from the starting methoxy-naphthalene **3.109**. The stereochemistry of the key intramolecular oxidative dearomatization was directed by the chirality of the ester

sidechain precursor, which was introduced using a selective hydrogenation. A tandem triple reductive amination constructed the A and B rings.

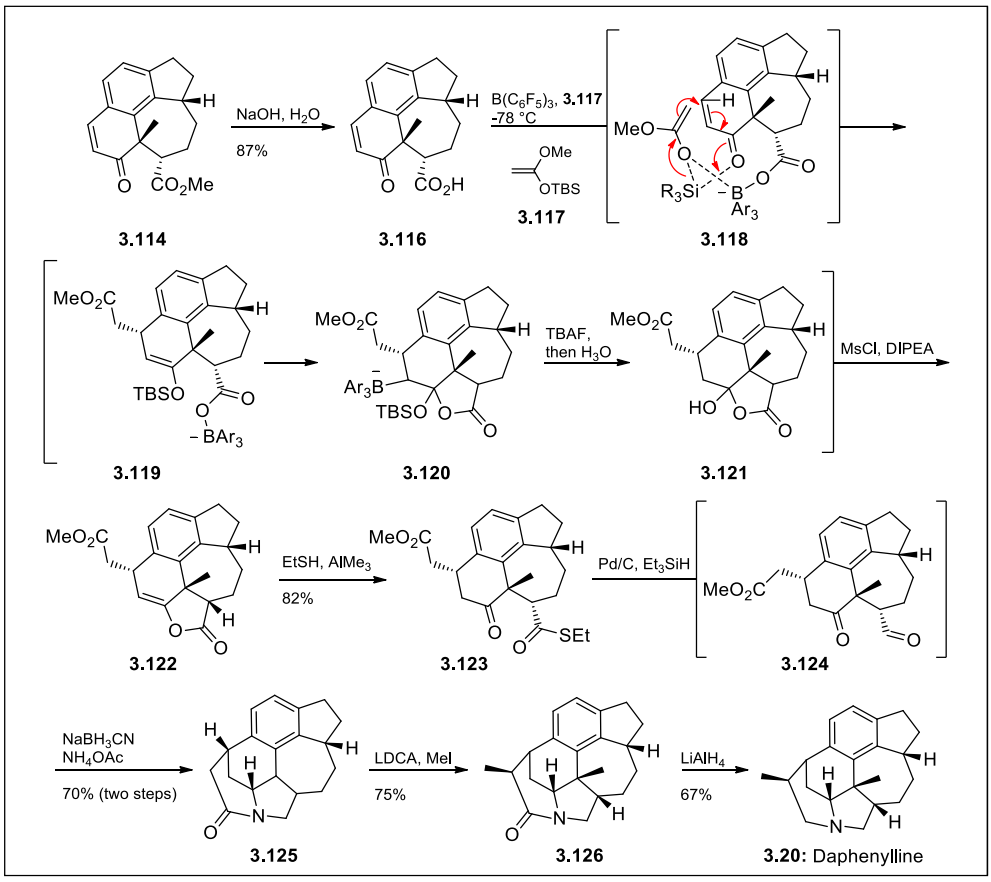
Tricycle **3.109** was produced in three steps from methoxy-naphthalene **3.108**, then reduction of the ketone, and attack to the resultant alcohol with allyl Grignard and Grubb's metathesis with ene-ester **3.110** furnished diene-ester **3.111.** A stereoselective reduction gave the aliphatic ester sidechain of **3.112**, then the key oxidative dearomatization provided the ADEF tetracycle **3.114.** Ten percent of the product had the undesired stereochemistry at the C6 position, however, the action of sodium ethoxide afforded the more stable isomer **3.114**.



Scheme 3.15 Synthesis of ADEF Tetracycle[12]

Hydrolysis of the methyl ester contained in **3.115** provided the corresponding carboxylic acid, which was subjected to silyl enol ether **3.117** in the presence of tris(pentafluoro-phenyl)borane. The Lewis-acid catalyzed Michael addition was presumably directed to the α-face via the carboxylic acid, which quenched the resultant silyl enol ether. Same pot silyl ether deprotection and acidic workup furnished the allylic lactam **3.122** with desired

ethyl ester sidechain. The lactam of **3.122** was opened with ethanethiol in the presence of a Lewis acid to provide the ketone containing thioester **3.123**. Fukuyama reduction of the thioester led to the intermediate aldehyde **3.124**, which underwent a three-fold reductive amination upon exposure to cyanoborohydride and ammonium acetate constructing the B and C rings of daphenylline in a single step. Finally, introduction of the methyl group and deoxygenation furnished daphenylline.



Scheme 3.16 Synthesis of the B and C Rings[12]

CHAPTER 4: Work Towards a Total Synthesis of Daphenylline

4.1 General Strategy

The following figure displays the generally accepted numbering scheme and ring labelling for daphenylline. Any discussions that include carbon numbering or ring identification refer to the system shown in Figure 4.1.

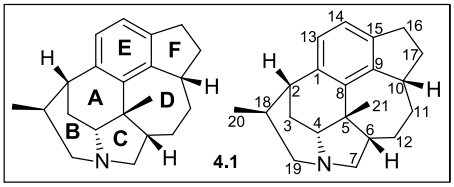


Figure 4.1 Daphenylline's Numbering System and Ring Labels[16]

With our group's 2019 work[21] on the construction of the calyciphylline-A type ABC system **4.6,** it was believed that a total synthesis of daphenylline (**4.1**) could be attained by combining our work with She's 2014 synthesis[20] of the all-carbon DEF tricycle **4.8** through a [4+2]-cycloaddition/aromatization sequence (Figure 4.2).

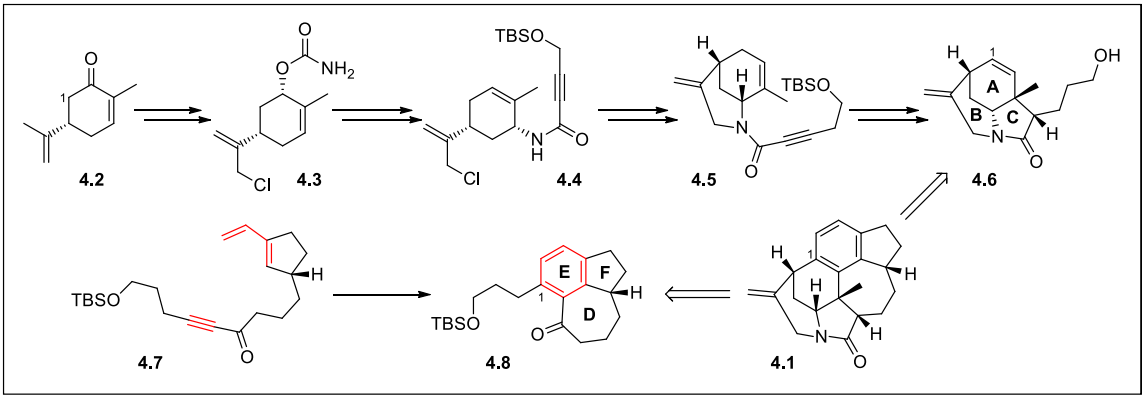


Figure 4.2 Proposed Strategy for the Synthesis of Daphenylline[20,21]

For an intramolecular [4+2] cycloaddition, it was clear that a diene and dienophile moiety would need to be installed on the aza-[5,6,6] tricyclic core (**4.6**, Figure 4.2). The previously investigated Heck coupling shown in Figure 4.3 revealed that the C5-C8 olefin isomerizes to C8-C1 during the course of the reaction. If a vinyl group or a functionality that may be elaborated to a vinyl group was present at C1, the olefin isomerization during the Heck coupling could complete construction of the diene moiety.

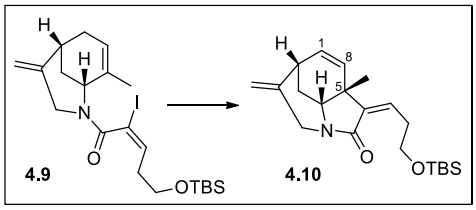


Figure 4.3 Olefin Isomerization During Intramolecular Heck Coupling[21]

The dienophile on the other hand, may originate from what was the primary alcohol sidechain. Oxidation of the primary alcohol **4.6** to an aldehyde, attack at the carbonyl with a lithium acetylide, and then oxidation of the resulting secondary alcohol might lead to an acetylenic ketone that would be an excellent dienophile.

During the course of our 2019 approach[21], it was found that that oxidation of the primary alcohol sidechain of **4.6** was sluggish and low yielding (ca. 50% yield). If a protected aldehyde functionality could be preinstalled as an acetal, access to the aldehyde, and eventually the acetylenic ketone should be readily accomplished.

The key [4+2] cycloaddition and aromatization sequence could build the D and E rings of the daphenylline skeleton in a single step. The final required F ring would either be

constructed as reported[22] by Bonjoch and coworkers (Figure 4.4) or in an improved novel synthetic pathway (*vide supra*, Section 4.12).

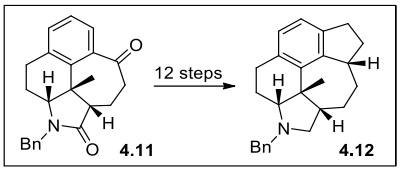


Figure 4.4 Bonjoch's 2019 Synthesis of the ACDEF Pentacycle[22]

With the general strategy set, the details began to emerge. As in our 2019 approach, (*S*)-carvone (**2**) would be the chiral pool starting material not only contributing the carbons consisting of daphenylline's A ring, but also the stereochemistry of the C2 carbon, and by extension, the stereoselectivity of the reduction determining chirality of the C4 carbon. Alkylation of (*S*)-carvone **4.2** with a protected ethanol moiety, reduction, and carbamate formation could provide **4.13**. Chemistry explored in our 2019 publication[21], including Ichikawa's protocol[26] for [3,3]-sigmatropic rearrangement of allyl-cyanate to isocyanate, entrapment of the intermediate isocyanate, Finkelstein type N-alkylation[27], hydrostannylation[28], iodination, Heck reaction, and stereoselective reduction of α,β-unsaturated lactam[21,29] may furnish tricycle **4.15**. A Greico-Sharpless olefination protocol[30,31], acetal deprotection, addition of acetylide and an oxidation may provide the diene/dienophile **4.18**, which would be subjected to a Lewis acid as described by She[20] to construct the tetracycle **4.19**. Finally, the F ring would be built as described by Bonjoch[22] or with new chemistry to complete a total synthesis of daphenylline **4.1**.

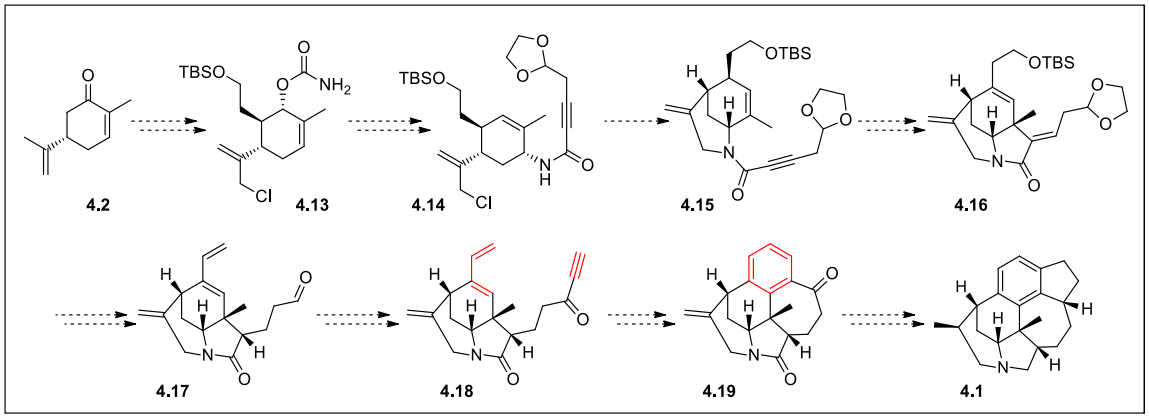


Figure 4.5 First Generation Strategy for the Synthesis of Daphenylline

The initial target was to build carbamate **4.13**, which would then be subjected to the [3,3]-sigmatropic ally-cyanate to isocyanate rearrangement discovered by Ichikawa[26], and elaborated in Hudlicky's formal synthesis of tetrodotoxin[32] and Hudlicky's 2019 approach to the calyciphylline A-type ABC skeleton[21].

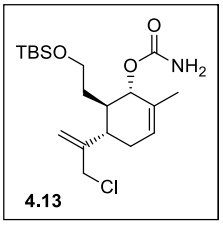


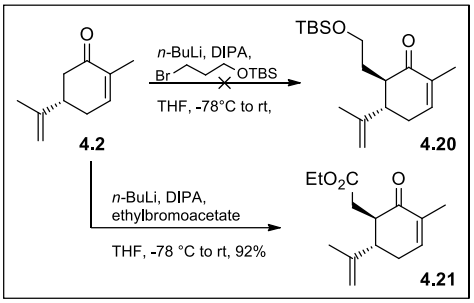
Figure 4.6 Short Term Target

4.2 Installation of the C1 Sidechain

The fact that a vinyl side chain may be directly added to the C1 carbon as described by Stenkamp[33] was considered, however, the resulting triene was unsuitable for this work because it was unstable, difficult to isolate, and would be incompatible with the chemistry we planned to explore. Instead it was decided to alkylate carvone at the C1

position with a protected ethanol sidechain, which could be elaborated to ethylene when desired by using Greico's procedure for the olefination of primary alcohols through the nitroaryl selenide[30,31] as used in Danishefsky's synthesis of taxol[34].

Alkylation at the C1 position of carvone is known and has been reported in the literature as proceeding through the enolate under kinetic control with subsequent treatment of electrophiles including methyl iodide[33], TBS protected bromomethanol[35], and others[36]. However, alkylation with TBS protected bromoethanol was complicated as none of the expected ketone **4.20** was isolated. Instead, we opted to alkylate C1 with ethyl bromoacetate as the resulting γ-keto ester **4.21** has previously been reduced to the diol[37]. Using an optimized procedure found in the literature, γ-ketoester **4.21** was obtained in 91%, an excellent yield.

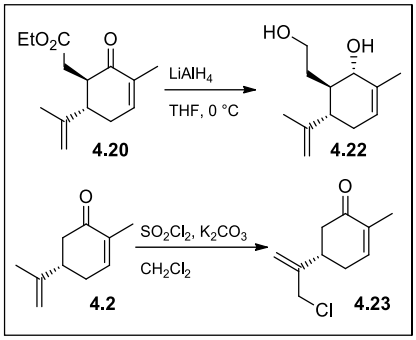


Scheme 4.1 Alkylation of (*S*)-Carvone at C1

4.3 Chlorination of the Isopropene Moiety

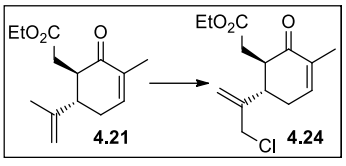
The γ-ketoester **4.21** is known to undergo stereoselective reduction to the diol **4.22**, and carvone **4.2** is known to undergo chlorination to allylic chloride **4.23**. These two transformations needed to be combined as chlorination of the isopropene moiety has never been reported on the γ-ketoester **4.21**. It was decided that chlorination of the allylic

position would be attempted *after* alkylation at C1, but *before* reduction to the diol, because the chlorination would likely not be compatible with the alcohol moieties, and the alkylation would likely not be compatible with an allylic chloride.



Scheme 4.2 Known Manipulations of Carvone

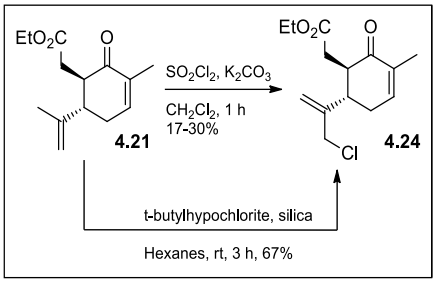
Chlorination of the isopropene sidechain of **4.21** was first attempted with the conditions published in the 2019 approach.[38,21] However, when **4.21** was exposed to sulfuryl chloride and potassium carbonate, very little of the desired compound was isolated as there are many possible sites of chlorination. Many conditions found in the literature[39,40] were screened (outlined in Figure 4.7). Notably, a chlorohydrin was produced whenever water was included in the reaction mixture (as evidenced by HNMR).



Entry	Conditions	Isolated yield
1	SO_2Cl_2, CH_2Cl_2 0° C to rt 3 h	17-30%
2	NaOCl, $InCl_3$ CH_2Cl_2/H_2O	13%
3	NaOCl, KH_2PO_4 CH_2Cl_2/H_2O	9%
4	TMSCl, DMSO CH_2Cl_2	No conversion
5	*t*-BuOCl, silica, anhyd. hexanes	67%

Figure 4.7 Attempted Chlorinations

Eventually, a chlorination method using *tert*-butyl hypochlorite and silica[41–43] was found, and the desired allylic chloride was isolated in an acceptable yield of 67%. When the reaction was attempted without silica, very little conversion of the starting material was observed. It was also found that water-free conditions were of utmost importance to limit production of the chlorohydrin side product.

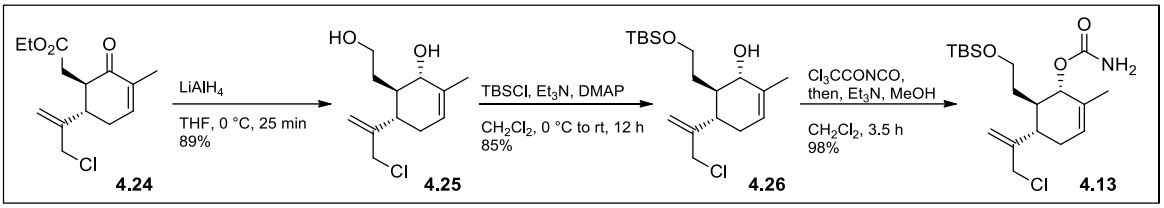


Scheme 4.3 Chlorination of γ-Keto Ester

4.4 Synthesis of the Aza-[5,6,6] Tricyclic Core

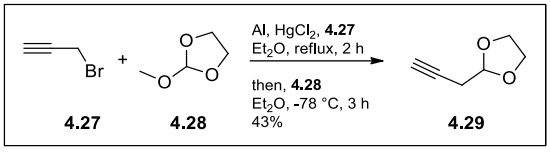
With the alkyl chloride in hand, the global reduction of **4.24** to the corresponding diol **4.25** was explored. Although the reduction of the corresponding non-chlorinated compound has been reported[37], it was unclear if the lithium aluminum hydride required for the reaction would also dehalogenate[44] the substrate. We were pleasantly surprised to find that the chloride moiety was sufficiently resistant to reduction as long as the reaction temperature was kept at or below 0 °C, and the reaction time was sufficiently short (ca. 25 minutes) to yield diol **4.25** in an excellent 89% yield. Global reduction with DIBAL-H was also attempted, however, the yield and diastereoselectivity were poor.

Direct silyl ether protection of the sterically more available alcohol[45] proceeded in excellent isolated yield (85%) under standard conditions, and then the resulting free alcohol of **4.26** was converted[21] to carbamate **4.13**.



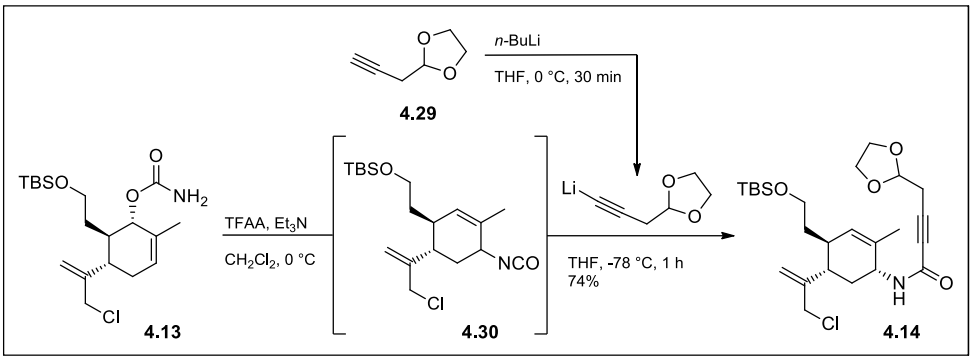
Scheme 4.4 Synthesis of Carbamate Target

With the precursor to the key suprafacial [3.3]-sigmatropic rearrangement available, the procedure[21] developed by our group was followed to install the amide with the required chirality. As discussed previously, we planned to build the amide with a sidechain containing a protected aldehyde. Interestingly, the aldehyde derived from dioxolane **25** is not commercially available, although the compound can be obtained in a round-about way from the Barbier reaction[46] of propargyl bromide **4.27** and methoxy-dioxolane **4.28**.



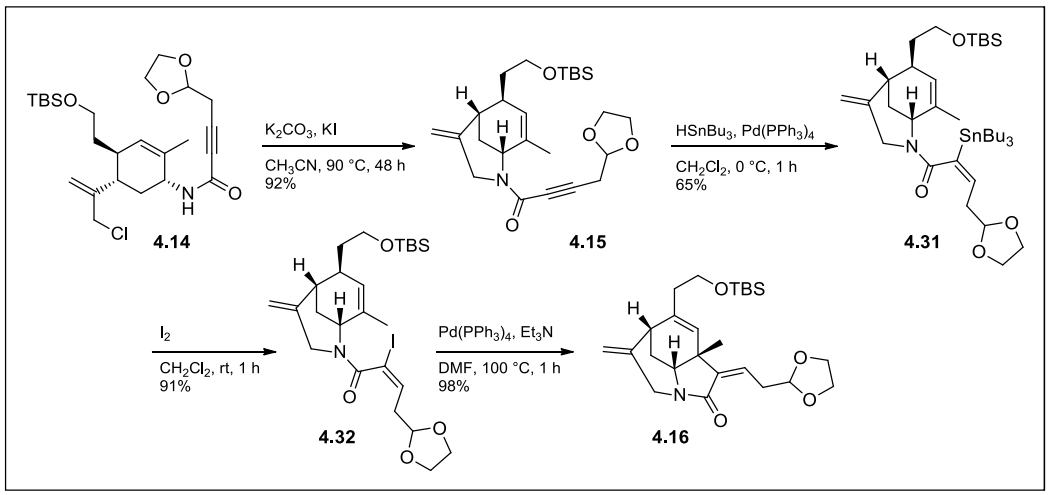
Scheme 4.5 Synthesis of C6 Sidechain Building Block

Ichikawa rearrangement of the carbamate **4.13** is uncomplicated, and the derived isocyanate **4.30** was successfully coupled with the acetylide generated from dioxolane **4.29** to produce the secondary amide **4.14**.



Scheme 4.6 One Pot [3,3]-Sigmatropic Rearrangement and Amidation

With secondary amide **4.14** available, repetition of previously explored[21] chemistry was accomplished. Finkelstein-type nitrogen alkylation[27], palladium catalyzed hydrostannylation[28], iodine quench, and intramolecular Mizoroki-Heck reaction provided the ABC tricycle **4.16** as the only product in excellent isolated yield (98%).



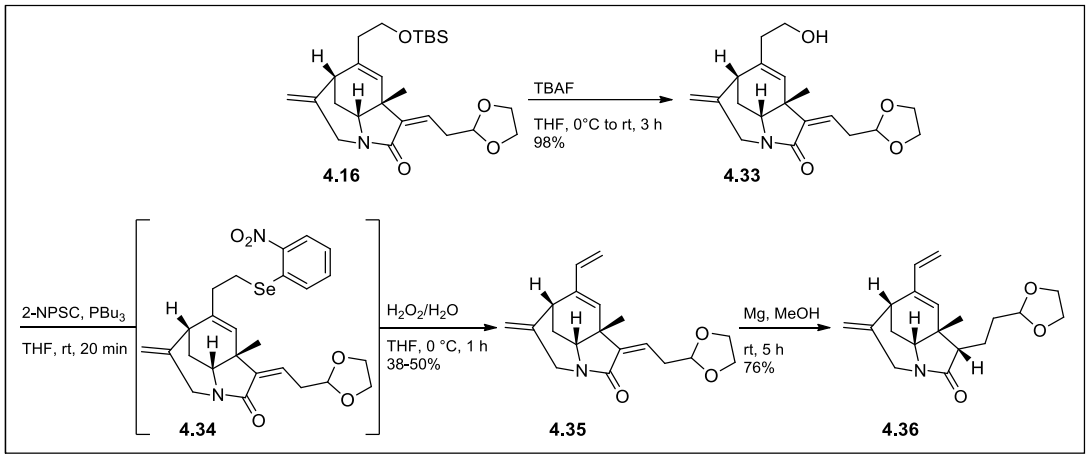
Scheme 4.7 Construction of the aza-[5,6,6] Tricycle

In order for the *N*-alkylation to take place, the nitrogen center and alkyl chloride must be proximal. As a consequence, any of the undesired epimer at C4 emanating from lithium aluminum hydride reduction, and possibly carried over to secondary amide **4.14** cannot

attack at the allylic chloride. As a result, tertiary amide **4.15** was obtained purely as a single diastereomer. The palladium catalyzed carbon-carbon coupling is quite effective; the high yield and fast reaction time were probably because of the proximity of the vinyl iodide and cyclic olefin in **4.32**.

4.5 Installation of Conjugated Diene

With the culmination of the construction of the tricycle **4.16**, it was time to apply Greico's olefination protocol to install the diene moiety necessary for intramolecular [4+2]-cycloaddition. The silyl ether of **4.16** was easily deprotected, and the resulting alcohol **4.33** was subjected to 2-nitrophenylselenocyanate in the presence of tri-*n*-butyl phosphine. The selenide **4.34** was obtained with almost quantitive conversion, and on exposure to aqueous hydrogen peroxide, the conjugated diene **4.35** was acquired. However, the yield and quality of the obtained diene varied drastically between batches. It was thought that because excess hydrogen peroxide was used, elimination of the selenide occurred in concert with a permutation of epoxidations, and many epoxidized products derived from **4.35** were produced, limiting the yield of the desired compound. Nevertheless, the α,β-unsaturated lactam **4.35** was efficiently converted to the saturated lactam **4.36** by the action of methanolic magnesium.[29] Only one product was formed during the hydrogenation because hydride can only be delivered from the α-face of the molecule. It is of the utmost importance that the C6-C2 bond is fully saturated, so that the dienophile on the C6 sidechain can reach the diene when they are both installed.



Scheme 4.8 Synthesis of the Diene by Greico Olefination Protocol

When a small amount of water was added to a concentrated solution of the unsaturated lactam **4.35** in methanol a turbid mixture was obtained, and upon standing, single crystals were obtained as long thin needles. To confirm our stereochemical assignment, a crystal structure of **4.35** (Figure 4.9) was obtained. Note that the carbon numbering of the diffraction result is different from the numbering scheme described at the beginning of this chapter in Figure 4.1.

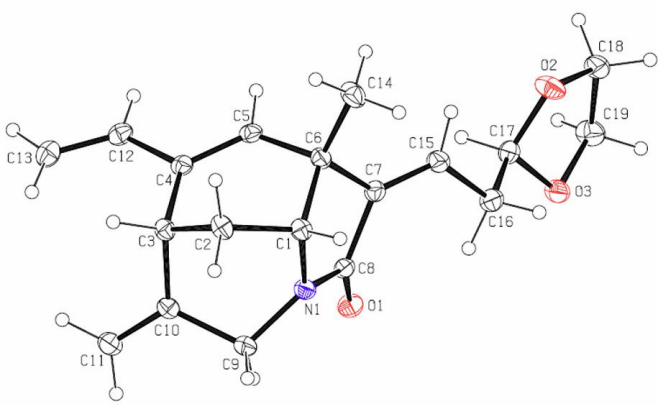
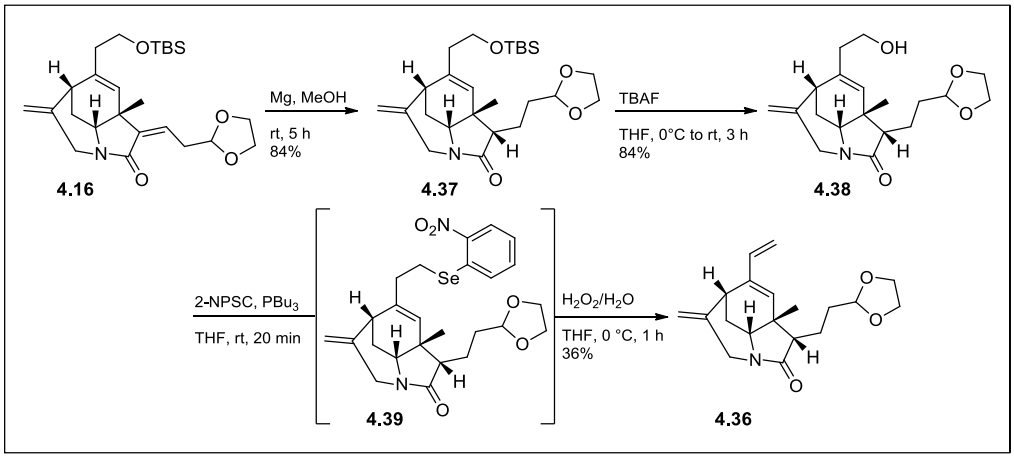


Figure 4.8 Crystal Structure of Diene **4.35**

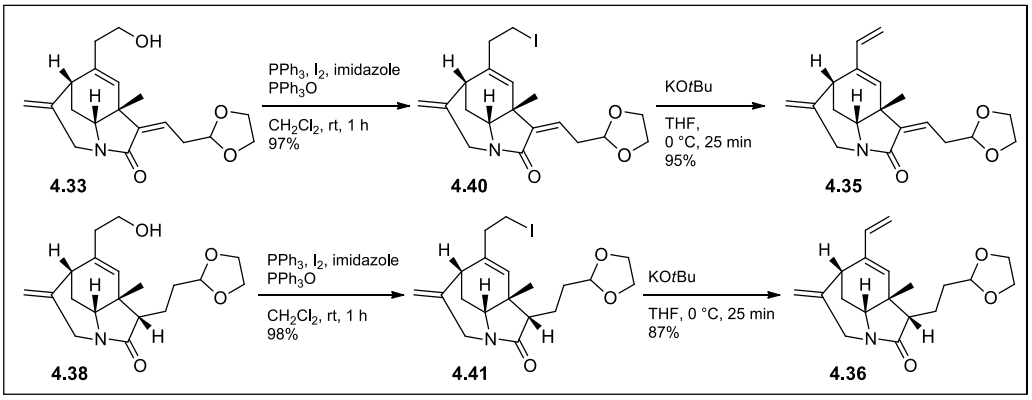
Although the synthesis of the desired conjugated diene **4.35** was achieved, the unpredictability and low yield of the Greico olefination procedure encouraged us to search for a more efficient protocol. The initial thought was to reduce the number of unsaturated carbon bonds in the molecule, reducing the probability of epoxidation during the selenide oxidation step. It was decided to reduce the unsaturated bond conjugated to the lactam first, and then attempt Greico olefination. Reduction of the unsaturated lactam of **4.16** to saturated lactam **4.37** proceeded well using methanolic magnesium[29], however, the outcome of selenide elimination was again unacceptable, and provided the conjugated diene **4.36** in very poor yield (36%). The electron poor unsaturated lactam was probably not an issue during oxidative elimination, as the electron rich C1-C12 and C18-C20 olefins are far more likely to undergo epoxidation with hydrogen peroxide.



Scheme 4.9 Greico Olefination Protocol on the Saturated Lactam

Because these intermediates are fairly advanced, and poor yields at this stage were intolerable, an alternative route was devised. The primary alcohol of tricycle **4.33** was converted to iodide by a modification of Appel's procedure[47,48], and the resulting alkyl

iodide **4.40** was eliminated with a non-nucleophilic base[48–51]. To our delight, clean elimination of the iodide was observed, and conjugated diene **4.35** was obtained in an excellent 95% yield. This iodination and elimination procedure was also applied to the saturated lactam **4.38**. Both proved to be excellent substrates for this protocol.

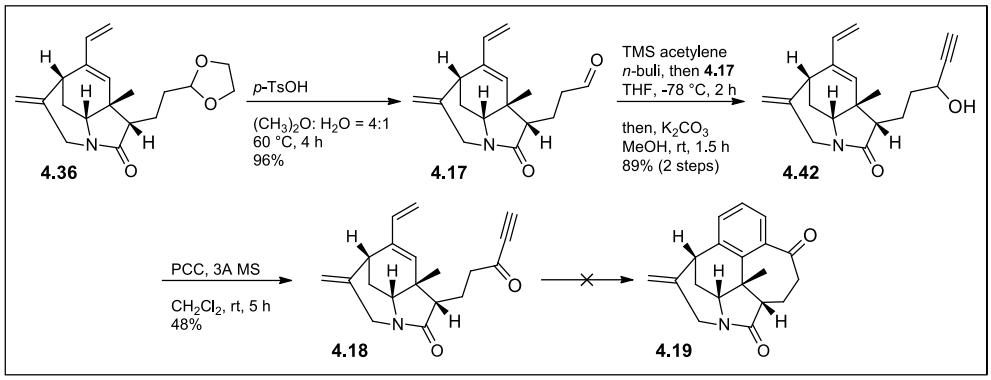


Scheme 4.10 Appel/Elimination Protocol for the Construction of the Diene

4.6 Attempts at an Intramolecular Diels-Alder Reaction

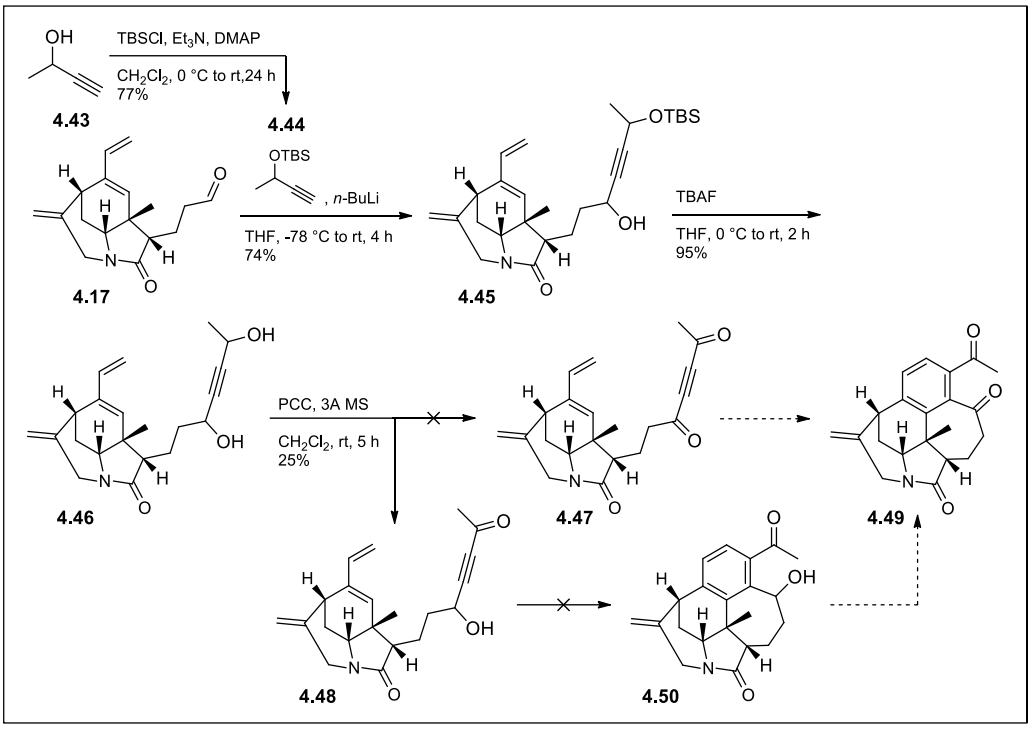
With the C6 sidechain free to rotate, and the diene installed, construction of the dienophile began. The acetal of **4.36** was deprotected without issue, and the resulting aldehyde **4.17** was subjected to trimethylsilane acetylide. After solvolysis, a diastereomeric mixture of propargyl alcohols **4.42** was obtained. Oxidation of the alcohol to acetylenic ketone was tenuous, and only pyridinium chlorochromate yielded the desired ketone **4.18** with a poor 48% yield, but in usable amounts.

With diene and dienophile functionalities present in the molecule, a [4+2]-cycloaddition was attempted. However, neither thermal conditions nor Lewis acid catalysts gave any of the desired tetracycle. Instead, decomposition of the substrate to many low weight molecular compounds was observed.



Scheme 4.11 Construction of Dienophile and Attempts at Intramolecular Diels Alder

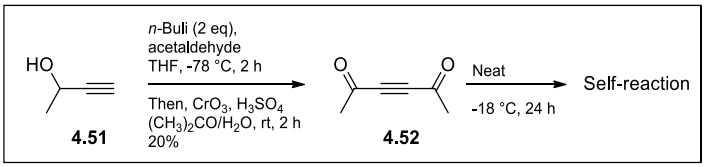
It was thought that perhaps either the dienophile or the diene was unreactive, and in an attempt to increase the reactivity of the dienophile, we tried to make the acetylenic diketone **4.47** by addition of the protected acetylide derived from **4.43** to aldehyde **4.17**. A benefit of this tactic is that the F ring could be synthesized by a simple aldol reaction of adduct **4.49.** The nucleophilic addition, and deprotection were straightforward but resulted in a spectroscopically complicated mixture of diastereomeric alcohols **4.46**. This mixture was subjected to oxidation with PCC, but only one of the alcohols was reactive to oxidation. Regardless, the resulting acetylenic monoketone **4.48** was subjected to thermal and Lewis acid catalyzed Diels-Alder conditions, but no pentacycle was isolated.



Scheme 4.12 More Efforts at Intramolecular Diels-Alder

4.7 Reactivity of the Diene

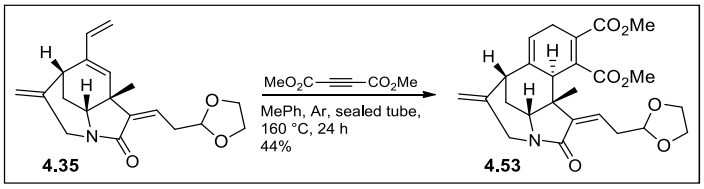
Changing tack, it was then decided to explore the reactivity of the diene. Would it add to dienophiles at all? It was decided to expose it to very reactive dienophiles. Acetylenic diketone **4.52** was made according to a known procedure[52]. The isolated ketone, however, proved unstable, and reacted with itself when stored overnight (ca. 24 h) in the freezer to afford a dark tar. Clearly this reagent was a little *too* reactive.



Scheme 4.13 Synthesis and Reactivity of 3-hexyne-2,5-dione

Instead, the conjugated diene **4.35** was exposed to dimethylacetylenedicarboxylate and it was found that thermal conditions were sufficient to produce the adduct **4.53**. The stereochemistry of the C8 methine was proposed through investigation of coupling constants and 2-D NOE spectra; it appeared that the dienophile approached from the α-face as one would expect.

With the reactivity of the diene of system **4.35** confirmed, it was speculated that the diene and dienophile in **4.18** were sufficiently reactive, however, they were too far apart in space for the necessary orbital overlap to occur. Preliminary attempts at aromatizing the 1,4-cyclohexadiene **4.53** with DDQ were unsuccessful but thought possible with further experimentation.



Scheme 4.14 Intermolecular Diels-Alder

4.8 Synthesis of Daphenylline's Tricyclic Core with C6 Methylene

The strategy was reassessed, and a new plan was designed. Perhaps if there was only a methylene sidechain at C6, prepared by the addition of acetylene to the isocyanate **4.30**, and cycloaddition of the conjugated diene **4.54** with some methyl ketone containing dienophile. Then, the enolate derived from the methyl ketone of **4.55** may add via conjugate addition to the unsaturated lactam producing the fused pentacycle **4.19**.

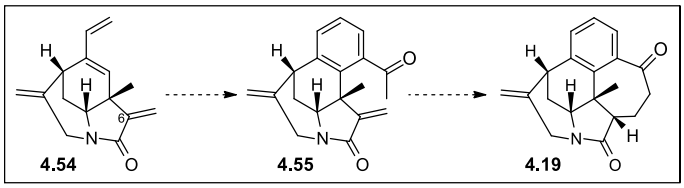
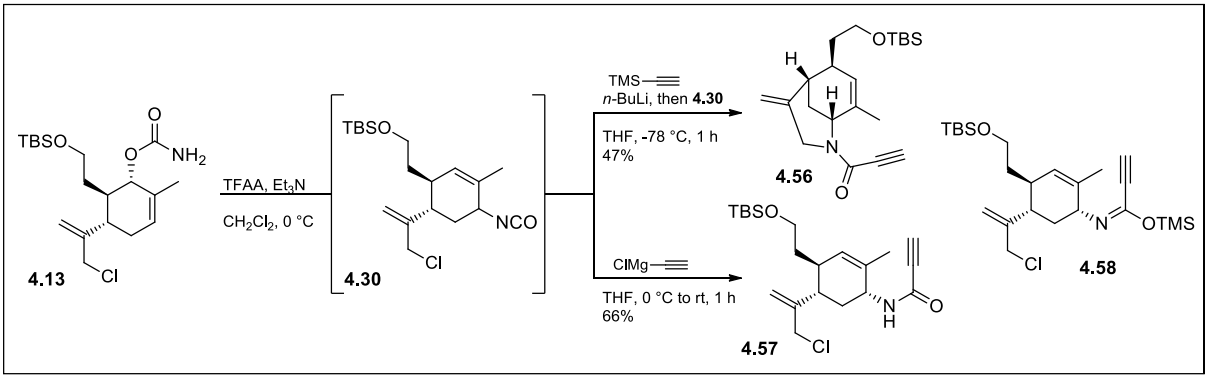


Figure 4.9 Intramolecular Conjugate Addition Strategy for the Synthesis of the D ring

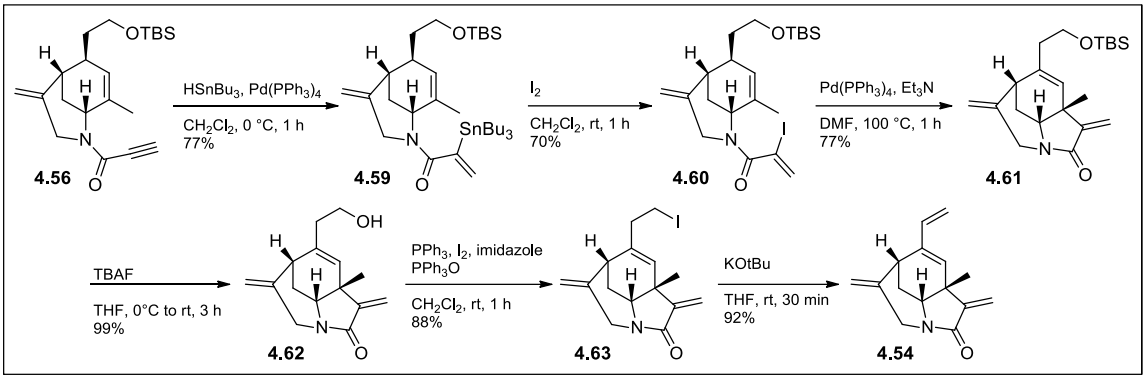
To our surprise, when isocyanate **4.30** was exposed to the lithium acetylide derived from TMS acetylene, the tertiary amide **4.56** was isolated. Evidently, the nitrogen attacked the allylic chloride in a tandem reaction. An alternative experiment was conducted in which isocyanate **4.30** was exposed to the Grignard reagent derived from acetylene, and only the secondary amide **4.57** was isolated. One explanation is that the tandem N-alkylation required the presence of trimethylsilane, as this phenomenon is only observed in cases where it is included, perhaps proceeding through an intermediate similar to **4.58**.



Scheme 4.15 Surprises During Entrapment of Isocyanate **26**

The bicyclic amide **4.56** was then subjected to the previously described hydrostannylation/iodination/Heck sequence furnishing the methylene lactam **4.61**. Silyl

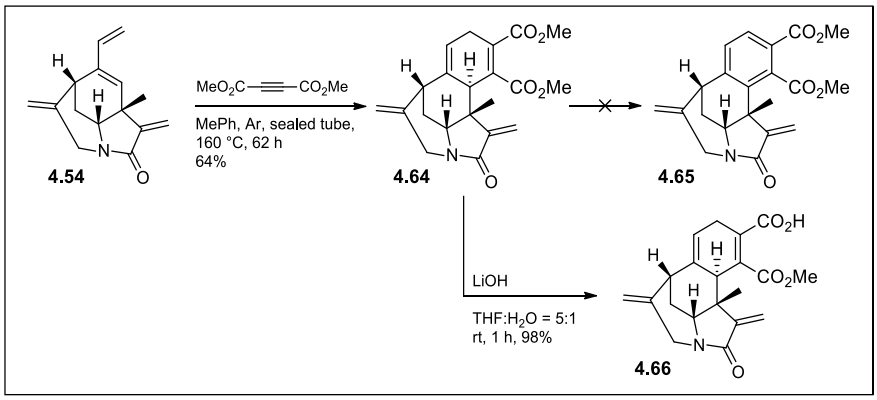
ether deprotection of **4.61**, and then the iodination/elimination protocol yielded the conjugated diene **4.54** with an excellent 33% yield over six steps.



Scheme 4.16 Synthesis of the C6 Methylene Containing ABC Tricycle

4.9 Intermolecular Diels Alder and Attempts at Aromatization

At this point, the conjugated diene **4.54** was exposed to dimethylacetylenedicarboxylate under optimized thermal conditions, resulting in 1,4-cyclohexadiene **4.64** with a good 64% yield. Many hours were spent in efforts to aromatize the E-ring to no avail. These trials are described below and in Figure 4.11. As an aside, base-mediated hydrolysis of **4.64** gave only the mono-acid **4.66**. We propose that the more available ester was easily hydrolyzed, and that charge-charge repulsion prevented hydrolysis of the second ester.



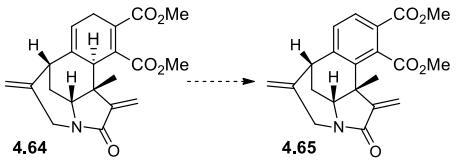
Scheme 4.17 Synthesis of the D ring

Because of the implied energy benefit, 1,4-cyclohexadiene diester **4.64** should be easily aromatized to the corresponding aromatic compound **4.65**, however, our experiments proved otherwise. Although used in previous approaches to daphenylline[53,24], classic oxidative aromatization conditions with quinone[54–56] failed to elicit any reaction of the substrate, even in refluxing toluene with long reaction times (Figure 4.11, entry 1). Classic dehydrogenation conditions[57] also failed to produce any of the desired aromatic compound (entry 2). Only a small fraction of the substrate isomerized to the trisubstituted olefin **4.67** presumably through the η-3 palladium complex. Several other conditions with literature precedent were attempted: Ruthenium/oxygen hydrogenation[58] (entry 3), palladium/acrylic acid hydrogen transfer[59] (entry 4), Dess-Martin periodinane mediated aromatization[60,61] (entry 4), and electrochemical aromatization[62] (entry 5) all failed to exhibit any reactivity.

Neat DBU in air has had success in aromatizing a similar 1,4-cyclohexadiene[24] to **4.64**, however, in our case, aromatization happened with cleavage of the C5-C8 carbon-carbon bond, as evidenced by the isolated tricycles **4.68** and **4.69** (entry 7). This phenomenon is

explored further in section 4.10. The 1,4-cyclohexadiene was also exposed to bromine in the hope that the electron rich C1-C13 olefin would be dibrominated, and elimination of two equivalents of hydrobromic acid could produce the desired aromatic compound. However, bromine preferentially attacked the more available C18-C20 methylene as evidenced by the isolated dibromides **4.70** and **4.71** (entry 8). In a similar vein, it was thought that generation of the dienolate by lithium diisopropylamide, and then bromine quench would produce the alkyl bromide at C14 (entry 9), however, a complex mixture of many products was obtained, likely with a significant amount of ring opened product similar to those obtained with DBU.

I will attempt to rationalize why **4.64** is resistant to aromatization. We believe that the fused bowl-like structure of the ABC tricycle constrained the 1,4-cyclohexadiene in such a way that the C14 and C8 carbons were bent out of plane, preventing any planarization of the E ring necessary for aromatization. This is evidenced by the fact that when non-nucleophilic base was used, deprotonation of C14 lead to breaking of the C5-C8 bond, relieving strain, and allowing aromatization.



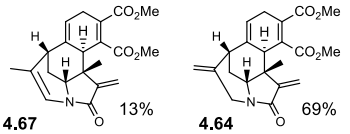
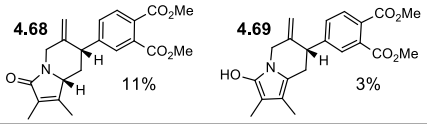
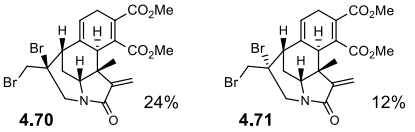
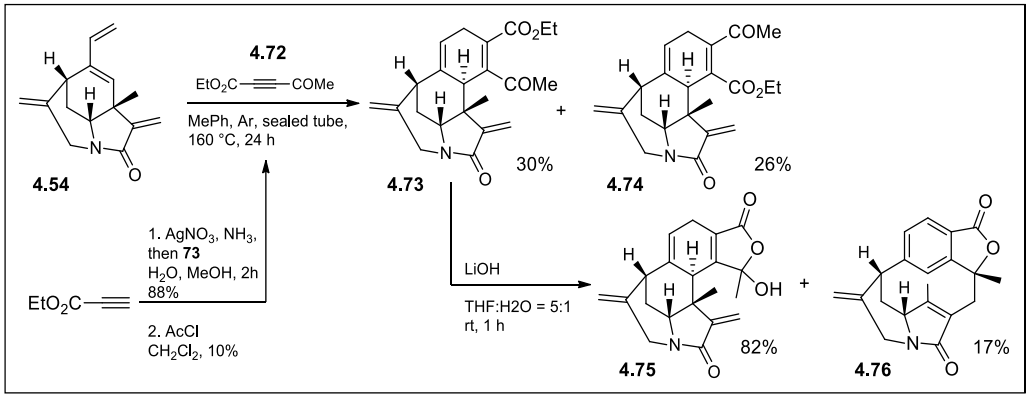
Entry	Conditions	Outcome
1	DDQ, MePh, Reflux, 48 h	No reaction
2	Pd/C, MePh, reflux 48 h	 4.67 13% 4.64 69%
3	Ru/C, O_2, H_2O, reflux, 24 h	No reaction
4	Pd/C, acrylic acid, water, reflux, 48 h	No reaction
5	DMP, CH_2Cl_2, rt, 24 h	No reaction
6	2,6-lutidine, TEMPO, $NaClO_4$ MeCN:H_2O = 19:1, 2.00 V, 2 F/mol	No reaction
7	DBU, neat, air, 6 h, rt	 4.68 11% 4.69 3%
8	Br_2, $CHCl_3$, -50 °C to rt, 1 h	 4.70 24% 4.71 12%
9	LDA, Br_2, THF, -78 °C, 1 h	Many unidentified products

Figure 4.10 Attempts at Aromatization of the E ring

4.10 Attempted Intramolecular Conjugate Addition

Even without aromatization of the E-ring, It was decided to test if a methyl ketone at the C9 position could add to the C12 position through a Michael addition. The asymmetric dienophile **4.72** was synthesized through the known silver acetylide[63]. We thought that the size discrepancy between the methyl ketone and ethyl ester moieties would give desirable regioselectivity in the resulting Diels-Alder adducts because of the steric congestion around the C8 carbon. However, the A-values of methyl ketone and ethyl

ester are quite similar (1.21 kcal/mol vs. 1.17 kcal/mol)[64] and the product distribution reflects this similarity (1.15:1, compounds **4.73**:**4.74**). We theorized that if the enolate of the methyl ketone **4.73** was formed, it would immediately attack the carbonyl carbon of the ester, so it was decided to first hydrolyze the ester to the carboxylate to reduce its electrophilicity, then make the corresponding enolate of the methyl ketone, which could attack the C6-C12 olefin of the α,β-unsaturated lactam. However, when the methyl ester **4.73** was subjected to hydrolysis, two products were obtained. The major product was hydroxy ester **4.75** derived from addition of the carboxylate to the methyl ketone, while the minor product was surprising; a cyclodecadiene **4.76** was generated from an unusual rearrangement analogous to those producing **4.68** and **4.69.** The proposed mechanism is shown in Figure 4.10. This was clearly a problem for the validity of this approach, as the most acidic proton is likely the methylene hydrogens at C14, and when deprotonation at this site occurred, the path of least resistance to the low energy well of an aromatized product was through cleavage of the C5-C8 carbon-carbon bond.



Scheme 4.18 Attempted Construction of the D-Ring

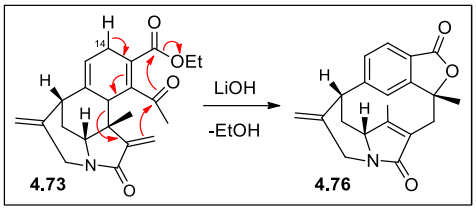


Figure 4.11 Proposed Mechanism of the Base Catalyzed Rearrangement

4.11 Benzannulation and Attempted Intermolecular Conjugate Addition

It was clear at this point that the E ring *must* be aromatized, and that traditional approaches of oxidative aromatization or dehydrogenation were not feasible for our substrates. Instead, it was theorized that a dienophile that contains two easily eliminated electron withdrawing groups could be used to generate compound **4.77** with an aromatized E ring without functionalization at C9 and C15. Michael addition of the Gilman reagent derived from 2-methyl-1,3-dioxolane to the unsaturated lactam of **4.77** could provide acetal **4.78**, which after stereoselective hydrogenation[17,18,23–25], acetal deprotection, oxidation[18,23], and Friedel-Crafts acylation[25,65] could generate the pentacyclic daphenylline skeleton **4.79**.

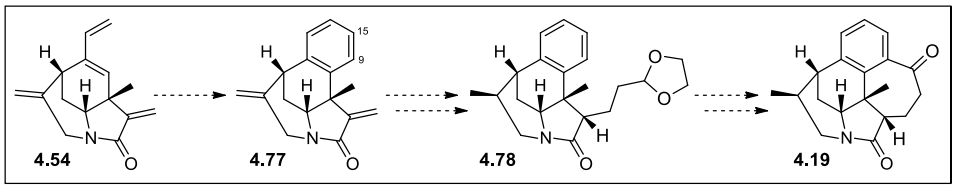


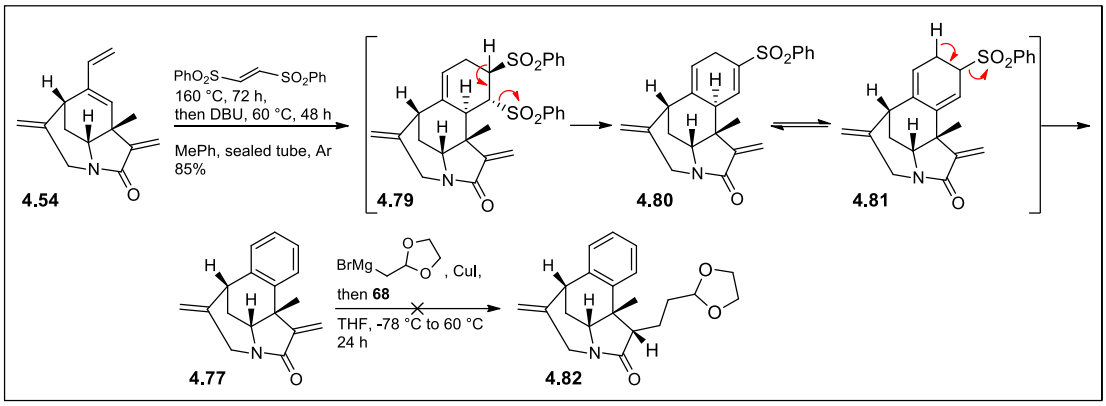
Figure 4.12 Strategy for the Synthesis of the D and E ring

A literature search revealed two possible tactics for the synthesis of the aromatic E ring. Bis-1,2-dichloroethylene has been used to generate aromatic compounds through [4+2]-

cycloadditions in the presence of triethylamine[66], however, the low reactivity of the dienophile requires very high reaction temperature and limits the scope of possible dienes[67]. The other tactic involved the use of bis-1,2-phenylsulfonylethylene, a dienophile with excellent reactivity. Although phenylsulfonyl is a poor leaving group, the acidity of the β-proton is greatly increased with the presence of the adjacent phenylsulfonyl moiety, which increases the rate of elimination of the first equivalent of phenylsulfonylate[68,69]. Subsequent isomerization and elimination are facilitated by the low energy of the aromatic product. Advantage of this phenomenon has been taken during several total syntheses[23,70].

[4+2]-Cycloaddition/elimination of conjugated diene **4.54** proceeded smoothy to the phenyl containing lactam **4.77** through the bis-phenylsulfonyl **4.79** in one pot. A possible mechanism is provided in scheme 4.21. A separate experiment that was terminated before the addition of DBU revealed that **4.79** was the major diastereomer produced from the [4+2]-cycloaddition as evidenced by NOE experiments (endo approach from the α-face).

Our attention was then turned to the installation of the 2-ethyl-1,3-dioxolane sidechain. The α,β-unsaturated lactam **4.77** was subjected to the Gilman reagent derived from the commercially available 2-methyl-1,3-dioxolane Grignard reagent. Unfortunately, **4.77** was wholly unreactive to the cuprate as no reaction was observed even after gentle heating of the reaction mixture. A review of the literature revealed that α,β-unsaturated lactams are usually inert to Michael addition unless some other electron withdrawing group is bound to the amide nitrogen.[71]



Scheme 4.19 Synthesis of the Aromatic E Ring

4.12 Synthesis of Daphenylline's ABCDE Pentacycle

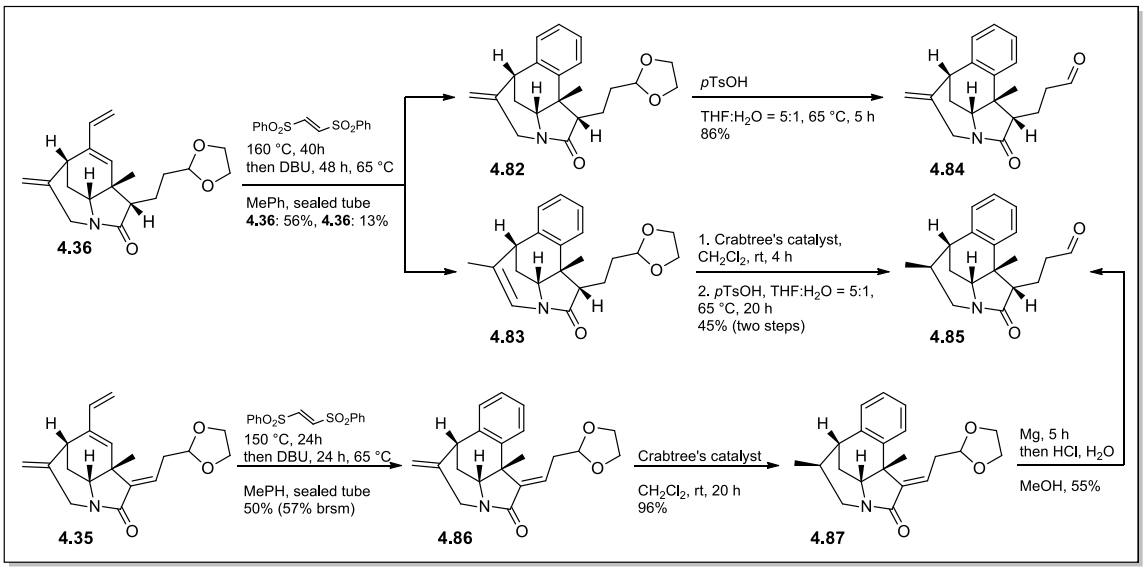
With the stable nature of the unsaturated lactam **4.77** revealed, attention was returned to the intermediates that failed to undergo intramolecular Diels-Alder. It was envisioned that the intermolecular Diels-Alder/benzannulation protocol developed with diene **4.54** could be instead applied to the dienes with preinstalled C6 sidechain (**4.36** and **4.35)** to provide the desired acetal **4.82**.

The Diels-Alder/benzannulation protocol proceeded smoothly with diene **4.36** to produce the phenyl containing **4.82**, although in lower yield compared to the analogous compound without C6 sidechain **4.54**, and with considerable side product of isomerized exocyclic olefin **4.83**. Clearly the freely rotating C6 sidechain does not endure as well in the required harsh conditions. Finally, hydrolysis of **4.82** cleanly produced the aldehyde with exocyclic olefin **4.84.**

The saturated aldehyde **4.85** was also prepared from the side product **4.83** through reduction with Crabtree's catalyst[17,18,23–25] and then acetal hydrolysis. Oddly, the aldehyde **4.85** and the saturated acetal intermediate were very difficult to visualize as

they weakly absorbed ultraviolet light and did not stain well in potassium permanganate, *p*-anisaldehyde, ninhydrin, chromic acid, phosphomolybdic acid, sulfuric acid/methanol, and ceric ammonium molybdate/sulfuric acid. This property extends to all compounds of this type without olefins, making chromatographic purifications difficult.

Nevertheless, aldehyde **4.85** was again assembled via a route one step shorter than the previously described pathway through Diels-Alder/benzannulation of tetraene **4.35**, reduction of resultant aromatic compound **4.86**, and a one pot magnesium/methanol reduction and acetal hydrolysis. It was envisioned that Crabtree's catalyst and hydrogen would reduce both the exocyclic and amido-conjugated olefins, however even with extended reaction time, only the non-conjugated C18-C20 olefin was hydrogenated.

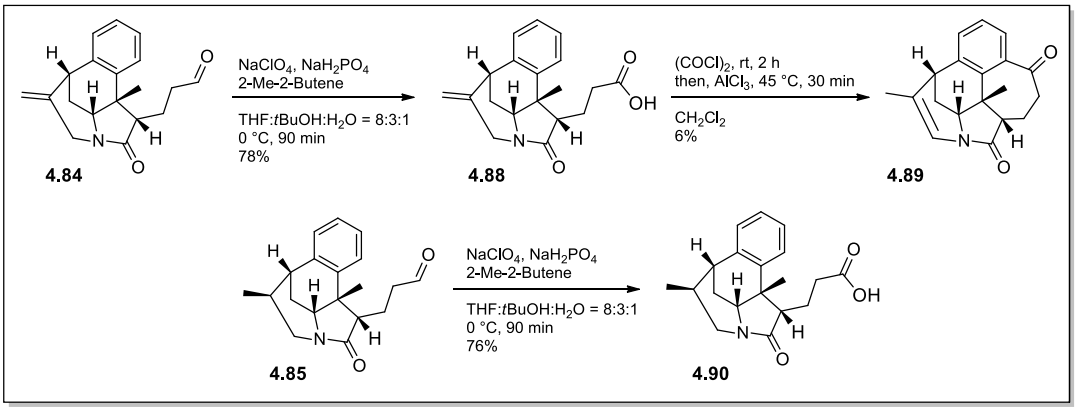


Scheme 4.20 Diels-Alder/Benzannulation and Preparation of Aldehydes **4.84** and **4.85**

Investigation of the key Friedel-Craft acylation for assembly of the D-ring was first attempted with the exocyclic olefin containing family of aldehyde **4.84**. The acid **4.88**

was smoothly prepared by Pinnick oxidation, then 'classic' Friedel-Crafts acylation conditions (oxalyl chloride then aluminum trichloride) successfully, albeit in an extremely poor 6% yield, gave the ABCDE pentacycle with isomerized olefin **4.89**. Examination of the carbon NMR of the crude reaction mixture revealed many products (>5) all of which contained a carbon signal in the range of 208-210 ppm suggesting that Friedel-Crafts acylation did indeed proceed but with subsequent side reactions that we speculate involved the exocyclic olefin. We believe that these exciting results can be greatly improved by performing Friedel-Crafts acylation on a substrate in which the exocyclic olefin is saturated.

The aldehyde **4.85** was also smoothly oxidized to the acid **4.90** via the Pinnick protocol. We are thrilled to continue investigation of these intermediates.

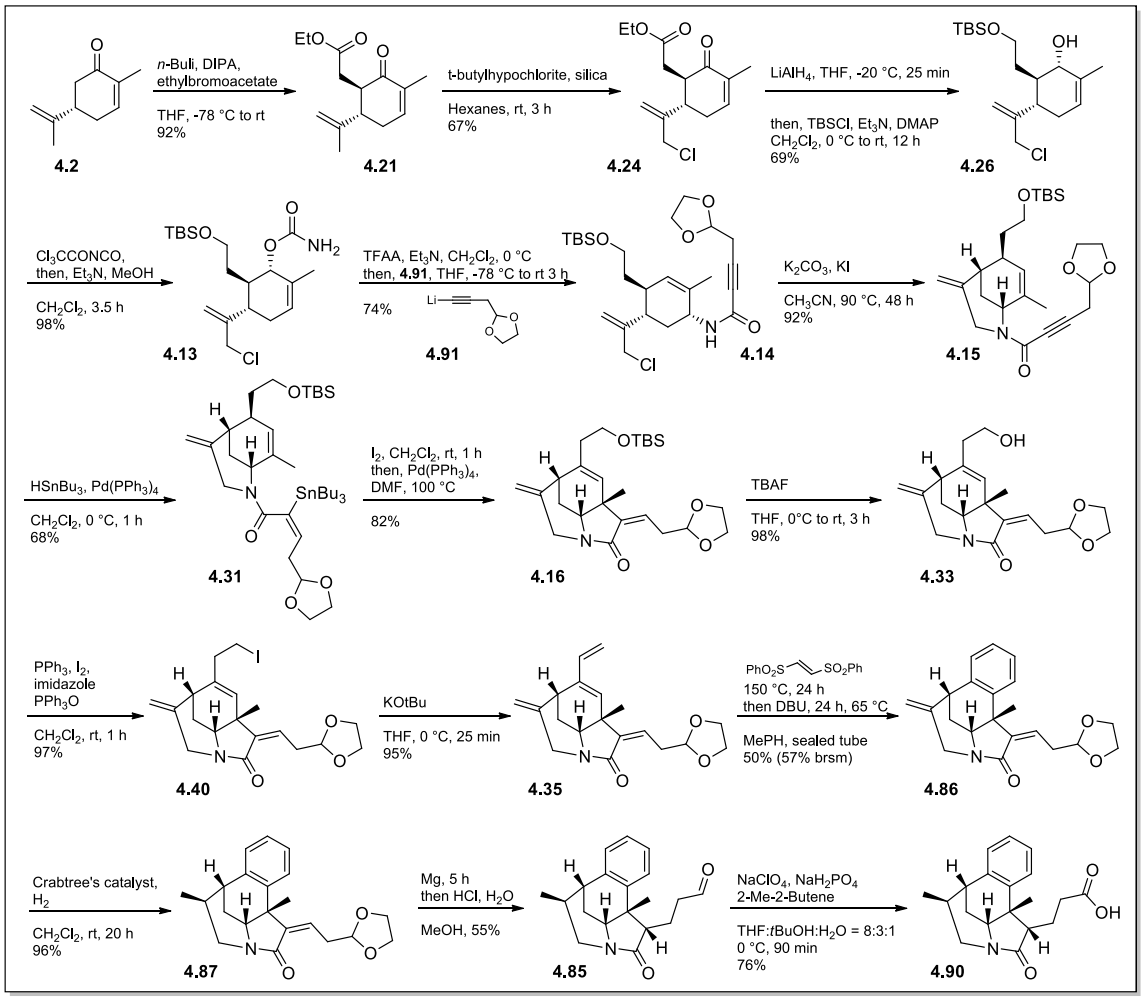


Scheme 4.21 Synthesis of C6 Carboxylic Acid Sidechain and Construction of D-Ring

4.13 Improvements

Throughout this investigation, we have continually been making improvements to the step count and the overall yield of the synthesis. The two largest developments follow. It was discovered that decreasing the temperature of the bis-reduction of **4.24** from 0 °C to

-20 °C (salt/ice cooling bath) lowered the mass contribution of side products (namely reduction of alkyl chloride) to such an extent that chromatography is no longer necessary. Secondly, the iodination and Heck reaction steps were combined, to prepare the tricycle **4.16** from the vinyl stannane **4.31** in one step without loss of yield. We suggest that in the future we will also be able to deprotect the silyl ether and quench the iodo-stannane byproduct in the same pot by addition of TBAF.



Scheme 4.22 Overall Progress on a Total Synthesis of Daphenylline

4.12 Future Work and Conclusions

We propose two distinct pathways to finalize a total synthesis of daphenylline. The first would include Friedel-Crafts acylation of **4.90**, a Horner-Wadsworth-Emmons reaction of the resultant ketone **4.19** with the appropriate stabilized phosphonium ylide, and reduction of the corresponding α,β-unsaturated ester to provide the C10 ester side-chain of **4.92**. Finally, basic hydrolysis, and another Friedel-Crafts acylation would give the hexacyclic ketone **4.93**. The alternative pathway to the hexacycle **4.93** could include the Friedel-Craft-type reaction of the aldehyde **4.85** to styrene **4.94** as discovered by Chida and coworkers[72–74]**,** then a protocol as including epoxidation, rearrangement with zinc iodide, alkylation, deoxygenation, hydrolysis and Friedel-Crafts acylation as reported by Bonjoch and coworkers[22] (*vide infra*). The common hexacyclic ketone **4.93** could be deoxygenated to furnish daphenylline.

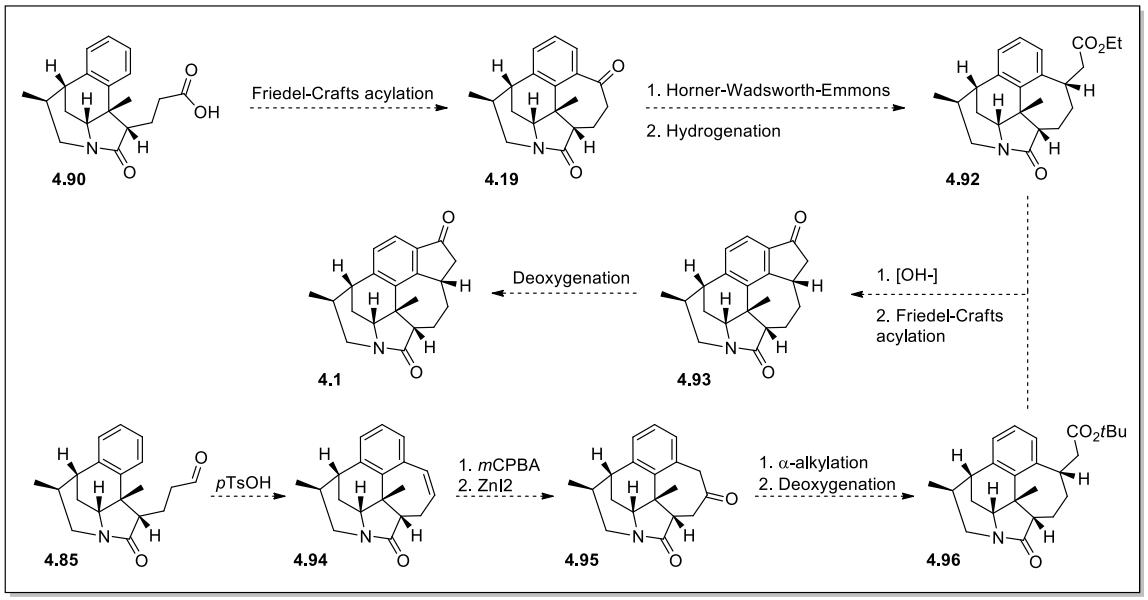


Figure 4.13 Proposed Completion of a Total Synthesis of Daphenylline

Construction of the ABCE tetracyclic skeleton of daphenylline (**4.86**) was accomplished in thirteen steps with seven percent overall yield from commercially available (S)-carvone through a strategy of [3,3]-allyl cyanate-to-isocyanate rearrangement, intramolecular Heck reaction, and Intermolecular Diels-Alder/benzannulation. Completion of a total synthesis of daphenylline is feasible through a two-fold intramolecular Friedel-Crafts acylation strategy.

EXPERIMENTAL SECTION

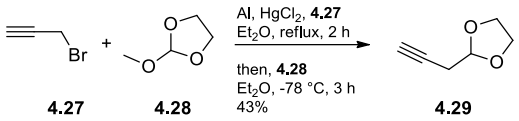
General Remarks

^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz Bruker Avance AV, 400 MHz Bruker Avance III, and 600 MHz Bruker Avance Neo spectrometers. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) referenced to the non-deuterated residual chloroform solvent peak at 7.26 ppm. Data for proton spectra are reported in the following format: Chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), quintet (qi), and multiplet (m)], coupling constants [Hz], integration). Chemical shifts for ^{13}C NMR are reported relative to the central line of the triplet at 77.16 ppm for chloroform-*d*. Melting points were recorded on a Hoover Unimelt apparatus and are not corrected. Analytical thin layer chromatography was performed on EMD Silica Gel 60 Å 250 μm plates with F-254 indicator, visualized with ultraviolet light and aqueous cerium ammonium molybdate stain. Retention factors are calculated as the ratio of the distance from the baseline to the center of the analyte and the distance of the baseline to the solvent front line. Column chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) silica. Optical rotations were measured on a Mandel Rudolph Research Analytical Polarimeter at 589 nm with a cell length of 50 mm. Infrared (IR) spectra were recorded on a Bruker ATR Fourier Transform Infrared Spectrometer and are reported in wavenumbers (cm^{-1}). Mass spectra and high-resolution mass spectra were obtained by the analytical division at Brock University and were performed on a Thermo Scientific Double Focusing Sector Mass Spectrometer or a Bruker HCT Plus Ion-Trap Mass Spectrometer. Combustion analyses were performed by Atlantic Microlabs in Atlanta Virginia. X-ray crystallographic analyses ware performed on an Oxford Cryostream

Variable Temperature apparatus at the X-ray Crystallography Laboratory at the University of Toronto.

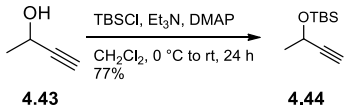
Tetrahydrofuran and toluene were freshly distilled from sodium and benzophenone, dichloromethane and acetonitrile were distilled from calcium hydride, and methanol was freshly distilled from barium oxide before use. When used as a reaction solvent, hexanes were distilled from potassium and stored over potassium mirror before use. HPLC grade hexanes were used for column chromatography to minimize grease content. Commercially redistilled diisopropylamine and triethylamine were purchased from Millipore-Sigma and stored in a desiccator over Drierite between uses. Potassium iodide and potassium carbonate were oven dried at 160 °C before use. *tert*-Butyl hypochlorite was freshly synthesized according to an *Organic Synthesis* procedure[75], and was stored at -21 °C over anhydrous calcium chloride before use. All other chemicals were purchased from Millipore-Sigma, Oakwood Chemicals or Alpha-Aesar and were used as-is unless otherwise noted. Care was taken to during storage and manipulation of the chemicals to avoid contact with moisture and air and they were stored at the temperature recommended by the manufacturer. All reactions are considered sensitive to moisture and air and were conducted under an inert atmosphere of argon using standard Schlenk techniques unless otherwise noted. All intermediates are considered unstable at room temperature and were stored long term (>1 day) at -21 °C. Chromatographic purifications were performed with silica as the stationary phase unless otherwise noted.

Experimental Procedures



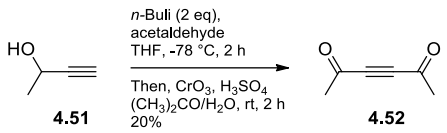
2-(prop-2-yn-1-yl)-1,3-dioxolane. To a suspension of aluminum powder (10.0 g, 370 mmol) and anhydrous diethyl ether (50 mL) in a 3 neck round bottom flask was added mercury (II) chloride (0.65 g, 2.40 mmol) with vigorous stirring at reflux. A solution of propargyl bromide (**4.27**) (26.0 mL, 242 mmol) in anhydrous diethyl ether (180 mL) was added dropwise via a pressure equalizing addition funnel. The rate of addition was adjusted to maintain a gentle reflux. After the addition was complete, the mixture was stirred at reflux for a further 70 minutes. Next, the suspension was cooled to -78° C and a solution of 2-methoxy-1,3-dioxolane (**4.28**) (15.3 mL, 161 mmol) in anhydrous diethyl ether (25 mL) was added dropwise via a syringe pump over 20 minutes. The mixture was stirred for three hours at -78° C, and then the reaction was quenched at -78° C by the slow consecutive addition of 150 mL distilled water and 100 mL of 1 M sodium hydroxide. The mixture was stirred for 30 minutes, then Celite was added, and the mixtures stirred again for 30 minutes. The resulting slurry was filtered through a thin layer of Celite. The organic phase was removed, dried over sodium sulfate, and concentrated to yield the crude residue which was purified by column chromatography (hexanes:ethyl acetate = 9:1) to give alkyne **4.29** (7.78 g, 69.4 mmol, 43%) as a colourless liquid. The spectroscopic and physical data are identical to those reported in the literature.[46]

4.29: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, *J* = 4.6 Hz, 1H), 4.07 – 3.98 (m, 2H), 3.97 – 3.87 (m, 2H), 2.56 (dd, *J* = 4.6, 2.7 Hz, 2H), 2.06 (t, *J* = 2.7 Hz, 1H).



(but-3-yn-2-yloxy)(tert-butyl)dimethylsilane. To a stirred solution of (±)-3-butyne-2-ol (**4.43**) (3.50 g, 49.9 mmol), triethylamine (7.70 mL, 54.9 mmol) and 4-dimethylaminopyridine (244 mg, 1.99 mmol) in dichloromethane (60 mL) at 0 °C was added tert-butyldimethylsilylchloride (8.25 g, 54.9 mmol) portion-wise. The mixture was allowed to gradually warm to room temperature and was stirred for 24 hours before it was quenched by the addition of 50 mL of distilled water. The organic phase was removed and dried over magnesium sulfate. Filtration, concentration, and flash column chromatography (hexanes: ethyl acetate = 5:1) furnished silyl ether **4.44** (7.07g, 38.4 mmol, 77%) as a colourless oil. The physical and spectroscopic data are similar to those found in the literature.[76]

4.44: Rf 0.7 (silica, hexanes: ethyl acetate = 4:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.51 (qd, J = 6.5, 2.0 Hz, 1H), 2.37 (d, J = 2.1 Hz, 1H), 1.42 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 86.61, 71.28, 58.93, 25.92, 25.47, 18.36, -4.53, -4.87.

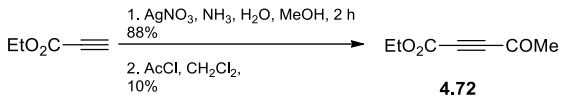


hex-3-yne-2,5-dione. To propargyl alcohol **4.51** (7.0 mL, 89.2 mmol), in tetrahydrofuran (200 mL) in a flame dried flask was added *n*-BuLi (2.5 M, 100 mL, 250 mmol) at -78 °C. The solution was stirred at -78 °C for 15 minutes, then it was allowed to warm to ca. -25 °C over 30 minutes and stirred at that temperature for a further 30 minutes. The mixture was cooled back down to -78 °C, and to the yellow solution of the di-anion was dropwise added acetaldehyde (7.5 mL, 134 mmol). The resulting mixture was allowed to warm to room temperature over one hour, then it was quenched by the addition of 120 mL saturated aqueous ammonium chloride. Organics were extracted with diethyl ether (3 x 100 mL), washed with brine (100 mL), dried over magnesium sulphate, filtered, and concentrated *in vacuo* to yield a crude residue which was used without further purification.

To the crude propargyl diol in acetone (240 mL) was added a freshly prepared solution of chromic acid (125 mmol, 34.1 mL = 12.5 g, 125 mmol chromium (IV) oxide, 10.8 mL concentrated sulfuric acid, 23.3 mL water), dropwise via an addition funnel until the characteristic brown/yellow colour of the endpoint persisted. The mixture was quenched with methanol (10 mL), and allowed to stir for 30 minutes, then allowed to stand for 30 minutes. The upper organic layer was decanted, and volatiles were evaporated *in vacuo* (Caution! The product has a low boiling point; a mild vacuum must be used). The resulting residue was dissolved in diethyl ether (200 mL), which was washed with 2 x 40 mL water, then 2 x 40 mL of brine. The organic layer was dried over sodium sulphate, and following filtration and concentration, a crude residue containing the diketone **0.3**

was obtained. Purification by flash column chromatography (hexanes: ethyl acetate = 3:1) furnished the pure diketone **0.3** (1.98 g, 18.0 mmol, 20%) as a yellow oil. The neat product decomposes at room temperature over the course of a few hours, and at -21 °C overnight. The product can be stored as a dilute solution in dichloromethane in the freezer for a few weeks maximum. The physical and spectroscopic data exactly match those found in the literature.[52,77]

4.52: Rf 0.5 (silica, hexanes/ethyl acetate = 2:1); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.42 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 182.97, 84.28, 32.49.

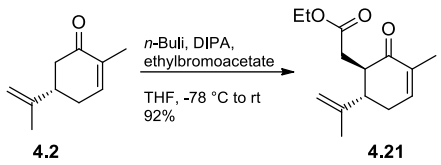


4.72

ethyl 4-oxopent-2-ynoate. To a solution of silver nitrate (3.40 g, 20.0 mmol) in water (40 ml) and methanol (70 ml) was added an aqueous solution of ammonia (28-30%) dropwise until the initially formed precipitate dissolved, then four more drops of the aqueous ammonia solution were added. Next, a solution of ethyl propriolate (2.10 ml, 20.7) mmol in methanol (5 ml) was added dropwise and the resulting solution was stirred at room temperature for three hours. The mixture was then twice extracted with chloroform (50 ml), and the organic phase was concentrated under reduced pressure yielding the intermediate silver acetylide as a grey explosive solid (3.60 g, 17.6 mmol, 88%) which was used without further purification.

The grey solid (3.59g, 17.5 mmol) was dissolved in dichloromethane (30 ml) and a solution of acetyl chloride (1.25 ml, 17.5 mmol) in dichloromethane (20 ml) was added in one portion at 0 °C. The resulting mixture was allowed to warm to room temperature, and stirred for seven hours, after which it was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the crude residue was purified by sequential Kuglerohr distillation and flash column chromatography (dichloromethane) to yield the acetylenic ketone **4.72** (250 mg, 1.78 mmol, 10%) as a colourless liquid. The spectroscopic data are similar to those found in the literature.[63]

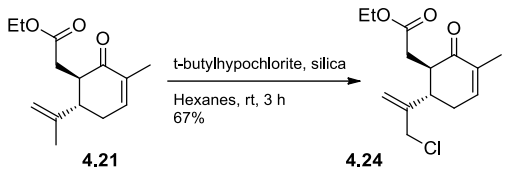
4.72: Rf 0.6 (silica, dichloromethane); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.30 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 182.62, 152.32, 80.92, 78.08, 63.13, 32.51, 14.06.



Ethyl-2-((1*R*,6*S*)-3-methyl-2-oxo-6-(prop-1-en-2-yl)cyclohex-3-en-1-yl)acetate. To a solution of diisopropylamine (19.7 mL, 0.141 mol) in tetrahydrofuran (250 mL) was added *n*-butyllithium solution (2.5 M in hexane, 56.2 mL, 0.141 mL) dropwise at 0° C. The solution of lithium diisopropylamide was cooled to -78° C, and (S)-carvone (**4.2**) (20.0 mL, 0.128 mol) was added dropwise over 20 minutes via a syringe pump. The resulting solution was stirred at -78° C for 50 minutes, and then to the yellow solution of the enolate was added a solution of ethylbromoacetate (17.0 mL, 0.153 mol) in tetrahydrofuran (35 mL) dropwise via a cannula. The resulting mixture was allowed to warm to room temperature and stirred for one hour. The wine-red mixture was quenched by the addition of 300 mL of saturated ammonium chloride, the organic phase was removed, and the aqueous phase was extracted three times with 200 mL of diethyl ether. The organic phases were combined, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield the crude red oil. The crude product was purified by column chromatography (hexanes: ethyl acetate = 9:1) to give the γ-ketoester **4.21** as a pale-yellow liquid (27.9 g, 0.118 mol, 92%). An analytical sample was prepared by Kuglerohr distillation (b.p. 140° C, 2.75 mmHg). The spectroscopic and physical data are similar to those found in the literature.[78,79,37]

4.21: R_f 0.3 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{21}$ -55.9° (c 1.03, $CHCl_3$); **IR** (neat): ν_{max} = 3076, 2979, 2924, 1732, 1670 cm^{-1};

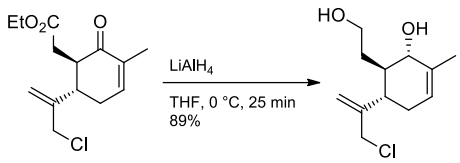
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (dd, J = 3.9, 1.5 Hz, 1H), 4.86 – 4.81 (m, 2H), 4.19 – 4.08 (m, 2H), 2.92 – 2.82 (m, 1H), 2.79 – 2.67 (m, 1H), 2.56 – 2.46 (m, 1H), 2.45 (d, J = 1.7 Hz, 1H), 2.43 (s, 1H), 2.35 – 2.22 (m, 1H), 1.79 – 1.75 (m, 3H), 1.71 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.95, 172.95, 145.14, 143.75, 134.97, 114.40, 60.52, 48.41, 46.54, 32.47, 31.39, 18.32, 16.12, 14.32; **HRMS** (EI, m/z): Calculated for $C_{14}H_{20}O_3$ $([M])^+$: 236.1407, found 236.1409; **MS** (EI, m/z (%)): 236.18 (3), 190.11 (43), 149.11 (100), 82.05 (77); analytically calculated for C 71.16, H 8.53, found C 71.32, H 8.72.



Ethyl-2-((1*R*,6*S*)-6-(3-chloroprop-1-en-2-yl)-3-methyl-2-oxocyclohex-3-en-1-yl)acetate. A stirred mixture of ester **4.21** (10.0 g, 42.3 mmol) in anhydrous hexanes (125 mL) and silica gel (20 g) was cooled to 0° C. Next, while avoiding exposure to intense light, *t*-butyl hypochlorite (5.04 mL, 44.4 mmol) was added dropwise via a syringe pump over ten minutes. The mixture was allowed to warm to room temperature and stirred for a further three hours. The solution was quenched by the addition of 50 mL of saturated aqueous sodium sulfite and diluted with 50 mL of ethyl acetate. the organic phase was removed, and the aqueous phase was extracted exhaustively with ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated under reduced pressure to furnish the crude yellow oil. The crude residue was purified by flash column chromatography (hexanes: ethyl acetate = 9:1) yielding chloro-ester **4.24** (7.70 g, 28.4 mmol, 67%) as a pale-yellow oil. An analytical sample was prepared by Kuglerohr distillation (b.p. 250° C, 1.75 mmHg).

4.24: $\boldsymbol{R_f}$ 0.2 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{21}$ +31.6° (c 1.06, $CHCl_3$); **IR** (neat): ν_{max} = 3083, 2982, 2927, 1727, 1669, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.73 – 6.67 (m, 1H), 5.38 (s, 1H), 5.18 (s, 1H), 4.13 (qd, J = 7.2, 0.6 Hz, 2H), 4.05 (s, 2H), 3.02 – 2.82 (m, 2H), 2.56 (d, J = 2.1 Hz, 1H), 2.54 (s, 1H), 2.53 – 2.42 (m, 2H), 1.79 (s, J = 1.8 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 199.28, 172.79, 145.72, 143.15, 135.20, 117.69, 60.64, 47.65, 47.02, 44.13, 33.24, 32.54, 16.10, 14.30; **HRMS** (EI, m/z): Calculated for $C_{14}H_{19}O_3Cl$ $([M])^+$: 270.1017, found 270.1016; **MS** (EI,

m/z (%)): 270.11 (4), 234.14 (86), 182.07 (100), 161.11 (67), 147.10 (38), 88.05 (27), 82.04 (26).

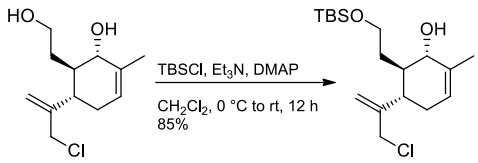


4.24 **4.25**

(1*S*,5*S*,6*R*)-5-(3-chloroprop-1-en-2-yl)-6-(2-hydroxyethyl)-2-methylcyclohex-2-en-1-ol. To a strongly stirred suspension of lithium aluminum hydride (3.18 g, 83.8 mmol) in tetrahydrofuran (140 mL) at 0° C was added dropwise a solution of chloro-ester **4.24** (7.55 g, 27.9 mmol) in tetrahydrofuran (30 mL) via a pressure equalizing funnel. After 25 minutes of stirring at 0° C, the reaction was quenched by the sequential slow addition of water (3.5 mL), 15% sodium hydroxide (3.5 mL), and again water (10 mL). The resulting mixture was stirred for 30 minutes, then anhydrous sodium sulphate was added to the grey paste and stirring was continued for another 30 minutes. The resulting white mixture was filtered through a short pad of Celite and chased with copious amounts of ethyl acetate. Concentration by rotary evaporation yielded a crude reside which was purified by flash chromatography (hexanes: ethyl acetate = 1:1) to give diol **4.25** (5.71 g, 24.7 mmol, 89%) as a colourless oil.

4.25: $\boldsymbol{R_f}$ 0.2 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ +22.5° (c 0.49, $CHCl_3$); **IR** (neat): ν_{max} = 3292 (br.), 3092, 3043, 2917, 1728, 1670, 752 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.59 – 5.48 (m, 1H), 5.31 (s, 1H), 5.07 (s, 1H), 4.06 – 4.03 (m, 2H), 3.95 – 3.82 (m, 2H), 3.71 – 3.62 (m, 1H), 3.19 (br. s, 2H), 2.39 – 2.28 (m, 1H), 2.23 – 2.01 (m, 2H), 2.01 – 1.90 (m, 1H), 1.87 – 1.80 (m, 1H), 1.77 (s, 3H), 1.46 (dtd, J = 14.8, 8.7, 4.0 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.59, 135.41, 123.49, 116.06, 76.04, 62.33, 47.66, 44.94, 43.47, 35.82, 32.85, 19.57; **HRMS** (EI, m/z): Calculated for $C_{12}H_{19}O_2Cl$ $([M])^+$: 230.1068, found 230.1070;

MS (EI, m/z): 230.08 (14), 195.12 (91), 177.12 (100), 149.10 (46), 135.08 (32), 110.07 (37); analytically calculated for C 62.47, H 8.30, found C 62.30, H 8.30.

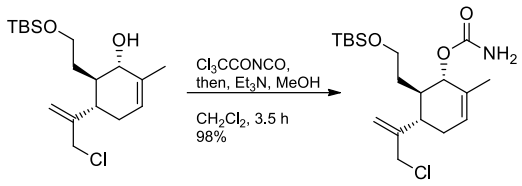


4.25 **4.26**

(1*S*,5*S*,6*R*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-ol. To diol **4.25** (3.28 g, 15.1 mmol) in dichloromethane (65 mL) at 0° C was sequentially added triethylamine (2.31 mL, 16.6 mmol), dimethylaminopyridine (74 mg, 0.60 mmol), and *t*-butyldimethylsilylchloride (2.39 g, 15.8 mmol). The reaction was gradually allowed to warm to ambient temperature, stirred overnight, and then quenched by the addition of 75 mL of distilled water. The organic phase was removed, and the aqueous phase was extracted three times with 35 mL dichloromethane. The organic phases were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the crude residue. Purification by flash column chromatography (hexanes: ethyl acetate = 19:1 ⟶ 9:1) yielded silyl ether **4.26** (4.40 g, 12.8 mmol, 85%) as a colourless oil.

4.26: $\boldsymbol{R_f}$ 0.4 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{21}$ +6.4° (c 0.89, $CHCl_3$); **IR** (neat): ν_{max} = 3412 (br.), 3086, 3040, 2954, 2930, 2887, 2860, 776 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.49 – 5.44 (m, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 4.33 (d, J = 3.5 Hz, 1H), 4.03 (s, 2H), 3.92 – 3.81 (m, 2H), 3.71 – 3.61 (m, 1H), 2.33 (td, J = 10.5, 5.4 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.95 – 1.79 (m, 2H), 1.77 (s, 3H), 1.49 – 1.35 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.95, 136.25, 122.34, 115.72, 75.34, 63.19, 47.57, 45.08, 43.36, 35.93, 32.80, 26.01, 19.74, 18.39, -5.28, -5.33; **HRMS** (EI, m/z): Calculated for $C_{18}H_{33}O_2ClSi$ $([M])^+$: 344.1933, found 344.1935;

MS (EI, m/z): 344.08 (9), 233.02 (60), 211.97 (53), 194.97 (46), 177.00 (58), 159.00 (100), 118.91 (41); analytically calculated for C 62.67, H 9.64, found C 62.86, H 9.80.

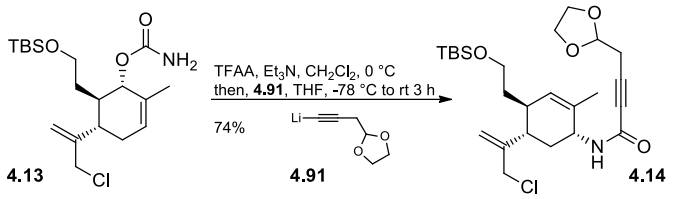


4.26 **4.13**

(1*S*,5*S*,6*R*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-yl carbamate. To a stirred solution of chloro-alcohol **4.26** (20.40 g, 59.1 mmol) in dichloromethane (180 mL) was dropwise added trichloroacetylisocyanate (7.80 mL, 65.0 mmol) at room temperature. After stirring for 30 minutes, methanol (180 mL) was added in one portion, and triethylamine (15.7 mL, 112.3 mmol) was added dropwise. After a further 3 hours of stirring, the reaction mixture was concentrated by *in vacuo* and then thrice triturated using dichloromethane to remove residual methanol and triethylamine. The crude residue was purified by flash column chromatography (hexanes: ethyl acetate = 9:1 → 3:1) to yield carbamate **4.13** (22.44 g, 57.8 mmol, 98%) as a colourless wax.

4.13: R_f 0.4 (silica, hexanes: ethyl acetate = 3:1); $[\alpha]_D^{21}$ -33.5° (c 1.72, $CHCl_3$); **IR** (neat): ν_{max} = 3506, 3441, 3345, 3272, 3200, 3085, 2953, 2930, 2887, 2858, 1712, 776 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.60 – 5.54 (m, 1H), 5.32 – 5.27 (m, 1H), 5.14 (d, J = 7.2 Hz, 1H), 5.08 (s, 1H), 4.74 (s, 2H), 4.09 (qd, J = 12.5, 0.5 Hz, 2H), 3.73 – 3.59 (m, 2H), 2.47 (td, J = 9.0, 5.7 Hz, 1H), 2.28 – 2.11 (m, 2H), 2.10 – 1.99 (m, 1H), 1.74 – 1.68 (m, 1H), 1.64 (s, 3H), 1.62 – 1.53 (m, 1H), 0.88 (s, J = 1.6 Hz, 9H), 0.04 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.19, 146.85, 132.73, 125.04, 116.01, 77.42, 61.39, 47.18, 41.72, 38.83, 34.48, 31.12, 26.12, 19.49, 18.46, -5.17, -5.19; **HRMS** (EI, m/z): Calculated for $C_{18}H_{33}O_2ClSi$ $([M\text{-}CONH])^+$: 344.1935, found 344.1930;

MS (EI, m/z (%)): 233.07 (32), 195.04 (100), 159.08 (74), 118.00 (60); analytically calculated for C 58.81, H 8.83, found C 58.56, H 8.84.



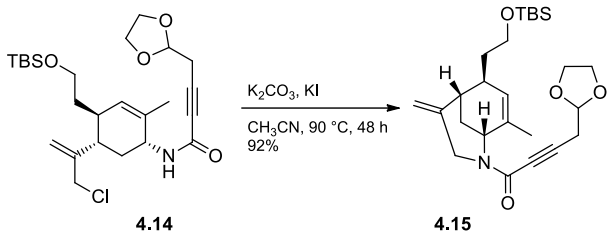
N-((1*R*,4*S*,5*S*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-yl)-4-(1,3-dioxolan-2-yl)but-2-ynamide. To a stirred solution of carbamate **4.13** (1.64 g, 4.23 mmol) dissolved in dichloromethane (60 mL), triethylamine (1.77 mL, 12.68 mmol) was added at room temperature and then the contents were cooled to 0 °C. Trifluoroaceticanhydride (0.69 mL, 5.07 mmol) was then added dropwise over 10 minutes, and the reaction was stirred for 30 minutes. Next, the mixture was filtered through a two-inch plug of silica, followed by flushing the silica with 60 mL of dichloromethane/petroleum ether (1:1). The resulting solution was concentrated under reduced pressure to yield the crude isocyanate intermediate.

Meanwhile, acetylide **4.91** was prepared by subjecting a stirred solution of the corresponding alkyne (1.18 mL, 10.57 mmol) in tetrahydrofuran (90 mL), a 0 °C, to *n*-butyllithium (2.5 M, 4.06 mL, 10.14 mmol) dropwise over 15 minutes, then stirring the resulting mixture for 60 minutes at 0 °C.

Then, a stirred solution of crude isocyanate intermediate in tetrahydrofuran (40 mL) was cooled to -78 °C. After cooling, the freshly prepared acetylide solution was added dropwise to the isocyanate via a cannula. After stirring for one hour at -78 °C, the mixture was quenched with saturated aqueous ammonium chloride (40 mL), diluted with ethyl acetate (40 mL), and the resulting solids were dissolved by adding a small amount of distilled water. The organics were removed, and the aqueous phase was extracted twice with ethyl acetate (50 mL). The organic layers were combined and dried over

sodium sulfate. After filtering, the organic phase was concentrated under reduced pressure to yield the crude product. The crude residue was purified by flash column chromatography (hexanes: ethyl acetate = 2:1 → 1:1) to furnish amide **4.14** (1.50 g, 3.11 mmol, 74%) as a pale-yellow oil.

4.14: **Rf** 0.5 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{21}$+92.5° (c 0.39, $CHCl_3$); **IR** (neat): ν_{max} = 3280 (br.), 3047, 2956, 2930, 2886, 2858, 2247, 2097, 1630, 729 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.92 – 5.61 (m, 1H), 5.61 – 5.46 (m, 1H), 5.32 – 5.23 (m, 1H), 5.15 – 5.03 (m, 2H), 4.66 – 4.52 (m, 1H), 4.10 – 3.99 (m, 4H), 3.98 – 3.81 (m, 3H), 3.65 (t, J = 6.1 Hz, 2H), 2.77 – 2.62 (m, 2H), 2.42 – 2.27 (m, 1H), 2.26 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 1.78 – 1.70 (m, 1H), 1.67 (s, J = 6.3 Hz, 3H), 1.55 – 1.41 (m, 1H), 1.35 – 1.26 (m, 1H), 0.88 (s, 9H), 0.03 (s, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$, mixture of rotamers) δ 157.10, 152.96, 146.95, 132.70, 129.49, 115.87, 101.54, 85.02, 81.77, 81.06, 74.90, 65.51, 61.83, 60.59, 49.84, 47.28, 43.42, 37.30, 35.98, 35.80, 26.07, 25.58, 19.82, 18.40, -5.20, -5.24; **HRMS** (CI, m/z): Calculated for $C_{25}H_{41}O_4NClSi$ ([M+H]+) 482.2488, found 482.2487; **MS** (CI, m/z): 482.24 (44), 446.24 (30), 390.17 (18), 314.12 (19), 195.01 (59), 161.04 (100), 111.03(81).

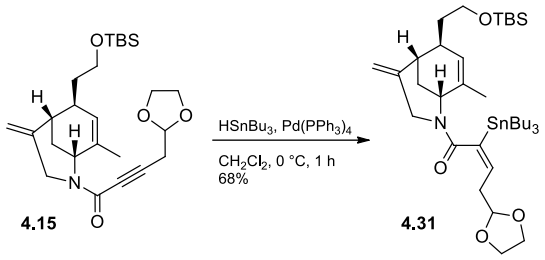


4.14 **4.15**

1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)-4-(1,3-dioxolan-2-yl)but-2-yn-1-one. To a stirred solution of amide **4.14** (924 mg, 1.92 mmol) in acetonitrile (50 mL) in a round bottom flask equipped with a reflux condenser was added potassium iodide (159 mg, 0.958 mmol) and potassium carbonate (530 mg, 3.83 mmol). The mixture was heated to 90 °C and left stirring for 48 hours, after which the reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL). Residual salts (if present) were dissolved with minimal distilled water and the mixture was diluted with ethyl acetate (20 mL). The organic phase was removed, and the aqueous phase was thrice extracted with ethyl acetate (20 mL), the organic layers were combined, dried over magnesium sulfate and then concentrated under reduced pressure to yield the crude product. The crude residue was purified by flash column chromatography (hexanes: ethyl acetate = 2:1 → 1:1) to yield tertiary amide **4.15** (784 mg, 1.76 mmol, 92%) as a colourless oil.

4.15: Rf 0.5 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{21}$ +128.7° (c 0.39, $CHCl_3$); **IR** (neat): ν_{max} = 3074, 2958, 2930, 2888, 2858, 2245, 1966, 1623 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.70 – 5.49 (m, 1H), 5.16 – 4.91 (m, 1H), 4.78 (s, 2H), 4.74 – 4.53 (m, 1H), 4.09 – 3.86 (m, 4H), 3.69 (t, J = 6.3 Hz, 2H), 3.55 – 3.34 (m, 1H), 2.80 – 2.64 (m, 2H), 2.52 (s, 1H), 2.16 (s, 1H), 1.95 – 1.53 (m, 8H), 0.89 (s, 9H), 0.05 (s, J = 6.5 Hz, 6H);

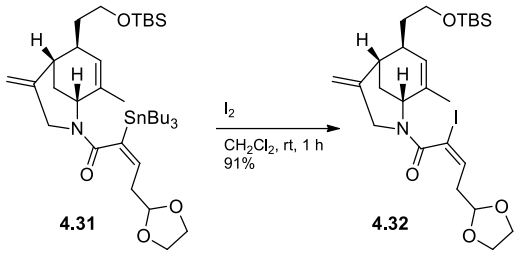
^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 152.50. 146.84, 145.91, 131.11, 130.71, 130.40, 130.32, 110.39, 109.62, 101.67, 87.29, 87.19, 65.54, 65.51, 61.30, 61.22, 52.94, 48.24, 46.78, 42.67, 39.82, 39.72, 38.24, 38.10, 37.49, 28.63, 28.01, 26.05, 25.91, 21.65, 21.23, 18.40, -5.18; **HRMS** (CI, m/z): Calculated for $C_{25}H_{39}O_4NSi$ ([M]+) 445.2643, found 445.2644; **MS** (CI, m/z (%)): 445.31 (100), 388.21 (97), 233.13 (34), 158.11 (34), 73.08 (55).



(*E*)-1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)-4-(1,3-dioxolan-2-yl)-2-(tributylstannyl)but-2-en-1-one. To a stirred solution of tertiary amide **4.15** (550 mg, 1.23 mmol) dissolved in degassed tetrahydrofuran (20 mL) was added tetrakis(triphenylphosphine)palladium(0) (114 mg, 0.0897 mmol) at room temperature. After five minutes of stirring, tributyltinhydride (0.35 mL, 1.30 mmol) was added dropwise at room temperature via a syringe pump over 20 minutes. The reaction was stirred for a further hour, and then the mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (hexanes: ethyl acetate = 9:1 → 3:1) to afford stannane **4.31** (587 mg, 0.797 mmol, 65%) as a colourless oil.

4.31: Rf 0.5 (silica, hexanes: ethyl acetate = 2:1); $[\alpha]_D^{21}$ +56.0° (c 0.76, $CHCl_3$); **IR** (neat): ν_{max} = 3072, 2956, 2928, 2856, 1727, 1601 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of rotamers) δ 5.94 – 5.68 (m, 1H), 5.68 – 5.61 (m, 1H), 5.06 (s, 1H), 4.90 (t, J = 4.7 Hz, 1H), 4.85 – 4.58 (m, 2H), 4.16 – 4.04 (m, 1H), 3.99 – 3.80 (m, 4H), 3.69 (t, J = 6.3 Hz, 2H), 2.60 – 2.18 (m, 3H), 2.18 – 2.08 (m, 1H), 1.89 – 1.80 (m, 1H), 1.71 (s, 3H), 1.66 – 1.55 (m, 4H), 1.55 – 1.39 (m, 6H), 1.31 (sx, J = 7.3 Hz, 6H), 1.12 – 0.93 (m, 6H), 0.93 – 0.84 (m, 18H), 0.05 (s, 6H);

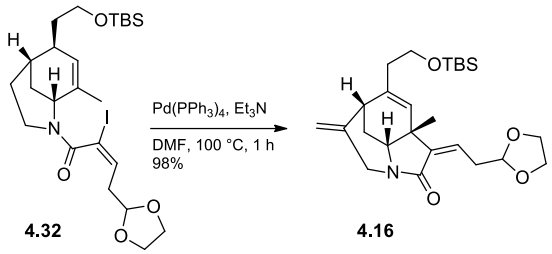
^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 171.61, 143.76, 134.37, 131.37, 129.81, 108.94, 103.31, 64.91, 61.17, 60.74, 58.61, 47.00, 45.90, 45.80, 39.84, 38.13, 37.45, 36.14, 35.60, 28.84, 27.32, 25.95, 25.91, 21.66, 18.26, 13.63, 10.24, -5.32; **HRMS** (EI, m/z): Calculated for $C_{37}H_{67}O_4NSiSn$ ([M]+) 737.3856, found 737.3839; **MS** (EI, m/z (%)): 680.43 (100), 312.85 (49), 207.91 (44), 165.88 (38); analytically calculated for C 60.32, H 9.17, found C 60.08, H 9.15.



(*E*)-1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)-4-(1,3-dioxolan-2-yl)-2-iodobut-2-en-1-one. To a stirred solution of stannane **4.31** (696 mg, 0.947 mmol) in dichloromethane (20 mL) was added iodine (252 mg, 0.995 mmol) in three portions. The solution was observed turning wine red and left stirring for 1 hour. The mixture was quenched with a minimal amount of 20% (w/w) aqueous sodium bisulfite and left stirring until the solution was decolorized. The mixture was extracted with 10 mL dichloromethane three times. The organic layers were combined, dried over magnesium sulfate, and then concentrated under reduced pressure to yield the crude product. The crude residue was purified by flash chromatography (silica with 10% potassium carbonate by weight, hexanes: ethyl acetate = 9:1) to yield the iodinated compound **4.32** (492 mg, 0.858 mmol, 91%) as a pale-yellow oil.

4.32: Rf 0.4 (silica, hexanes: ethyl acetate = 2:1); $[\alpha]_D^{21}$ +84.9° (c 1.8, $CHCl_3$); **IR** (neat): ν_{max} = 3074, 2954, 2929, 2880, 2857, 1626 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$, mixture of rotamers) δ 6.46 – 6.30 (m, 1H), 5.72 – 5.60 (m, 1H), 5.01 – 4.87 (m, 2H), 4.86 – 4.72 (m, 2H), 4.16 – 4.03 (m, 1H), 4.00 – 3.91 (m, 2H), 3.91 – 3.79 (m, 3H), 3.69 (t, J = 6.2 Hz, 2H), 2.59 – 2.28 (m, 3H), 2.24 – 2.12 (m, 1H), 1.97 – 1.73 (m, 2H), 1.71 (s, 3H), 1.68 – 1.57 (m, 2H), 0.89 (s, J = 2.6 Hz, 9H), 0.06 (s, 6H);

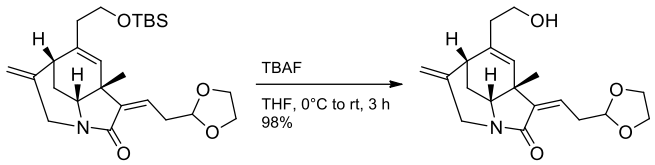
^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 165.09, 165.01, 146.15, 131.47, 131.05, 130.60, 123.43, 110.75, 102.30, 87.94, 87.51, 65.18, 61.28, 61.23, 60.77, 60.52, 53.56, 53.38, 48.81, 48.11, 43.29, 39.77, 39.73, 39.63, 38.33, 38.10, 37.46, 37.30, 36.20, 35.62, 32.99, 29.84, 29.81, 28.05, 28.01, 26.10, 26.07, 21.85, 21.48, 21.18, 18.46, 18.40, -5.17; **HRMS** (EI, m/z): Calculated for $C_{25}H_{40}O_4NISi$ ([M]+) 573.1766, found 573.1771; **MS** (EI, m/z (%)): 573.25 (33), 446.25 (100), 72.99 (77); analytically calculated for C 52.35, H 7.03, found C 52.81, H 7.21.



(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3a-methyl-8-methylene-3a,6,7,7a-tetrahydro-1,6-ethanoindol-2(3H)-one. To a stirred solution of vinyl iodide **4.32** (392 mg, 0.683 mmol) in dimethylformamide (10 mL) was added tetrakis(triphenylphosphine)palladium(0) (40 mg, 0.034 mmol), and triethylamine (0.48 mL, 3.42 mmol) at room temperature. The mixture was heated to 90 °C under reflux, and a colour change of the mixture from yellow to black was observed. The solution was left stirring for 45 minutes at 90° C and then it was filtered through a 6-inch plug of silica and chased with 90 mL of diethyl ether. The filtrate was collected and washed with a minimal amount of distilled water five times. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting oil was triturated three times with ethyl acetate to yield the crude product. The crude residue was purified by flash chromatography (hexanes: ethyl acetate = 4:1 → 2:1) to yield lactam **4.16** (297 mg, 0.666 mmol, 98%) as a yellow oil.

4.16: Rf 0.4 (silica, hexanes: ethyl acetate = 1:2); $[\alpha]_D^{21}$ -42.9° (c 0.13, $CHCl_3$); **IR** (neat): ν_{max} = 3073, 2955, 2931, 2888, 2859, 1693 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (t, J = 7.2 Hz, 1H), 4.96 (t, J = 4.7 Hz, 1H), 4.79 (s, 3H), 4.56 (d, J = 16.4 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.89 – 3.83 (m, 2H), 3.69 (d, J = 4.6 Hz, 1H), 3.65 (td, J = 13.2, 3.5 Hz, 2H), 3.61 (d, J = 16.3 Hz, 1H), 3.13 (ddd, J = 15.0, 8.1, 5.0 Hz, 1H), 3.00 (ddd, J = 15.3, 6.4, 4.5 Hz, 1H), 2.85 (s, 1H), 2.23 – 2.16 (m, 1H), 2.15 – 2.09 (m, 1H), 2.07 (ddd, J = 13.5, 5.0, 1.9 Hz, 1H), 1.77 (dd, J = 13.6, 3.4 Hz, 1H), 1.19 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.68, 144.48, 140.75, 137.82, 127.14, 126.54, 109.21, 103.92, 65.11, 65.08, 61.85, 57.17, 48.47, 40.98, 38.02, 37.79, 32.03, 26.05, 23.52, 18.79, 18.39, -5.17; **HRMS** (EI, m/z): Calculated for $C_{25}H_{39}O_4NSi$ ([M]+) 445.2643, found 445.2645; **MS** (EI, m/z (%)): 445.36 (48), 388.25 (100), 316. 20 (43); analytically calculated for C 67.38, H 9.01, found C 67.42, H 9.01.

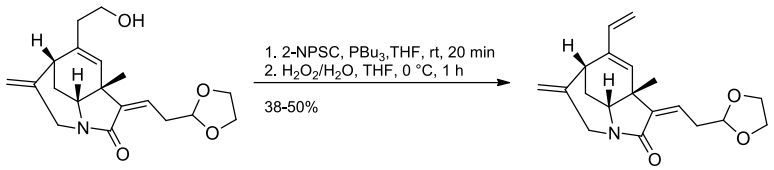


4.16 **4.33**

(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-hydroxyethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred solution of silyl ether **4.16** (344 mg, 0.772 mmol) in tetrahydrofuran (10 mL) was added tetra-N-butylammonium fluoride (1.0 M, 1.08 mL, 1.08 mmol) dropwise at 0° C. The mixture was warmed to room temperature and allowed to stir for three hours. The reaction mixture was diluted with ethyl acetate and quenched by the addition of 5 mL saturated aqueous ammonium chloride. The organic phase was removed and washed three times with 1 mL of distilled water. Organic phase was dried over sodium sulfate and filtered and concentrated to yield the crude residue which was purified by flash column chromatography (EtOAc) to furnish alcohol **4.33** (252 mg, 0.760 mmol, 98%) as a colourless oil.

4.33: Rf 0.3 (silica, ethyl acetate); $[\alpha]_D^{21}$ -28.9° (c 0.71, $CHCl_3$); **IR** (neat): ν_{max} = 3418 (br.), 2972, 2932, 2891, 1688, 1685, 1403, 1130 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.78 (dd, J = 7.7, 7.0 Hz, 1H), 4.96 (t, J = 4.6 Hz, 1H), 4.86 (s, 1H), 4.81 (d, J = 4.9 Hz, 2H), 4.58 (d, J = 16.5 Hz, 1H), 3.97 (dt, J = 12.9, 8.4 Hz, 2H), 3.87 (dt, J = 8.9, 8.5 Hz, 2H), 3.73 – 3.57 (m, 4H), 3.17 – 2.96 (m, 2H), 2.82 (s, 1H), 2.24 (qd, J = 14.7, 6.4 Hz, 2H), 2.10 (ddd, J = 13.7, 5.2, 2.2 Hz, 1H), 1.79 (dd, J = 13.6, 3.5 Hz, 1H), 1.59 (br. s, 1H), 1.21 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.61, 144.29, 140.43, 136.97, 127.84, 126.98, 109.55, 103.83, 65.11, 65.09, 60.44, 57.11, 48.54, 40.92, 38.01, 37.92, 32.02, 23.63, 18.81;

HRMS (EI, m/z): Calculated for $C_{19}H_{25}O_4N$ ([M]+) 331.1778, found 331.1776; **MS** (EI, m/z): 331.23 (100), 277.11 (41), 259.18 (23). 241.16 (24), 167.04 (14), 112.11 (23); analytically calculated for C 68.86, H 7.60, found C 68.91, H 7.75.

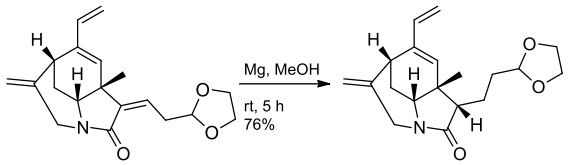


4.33 **4.35**

(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a solution of vigorously stirred alcohol **4.33** (190 mg, 0.573 mmol) in tetrahydrofuran (4 mL) was added 2-nitrophenylselenocyanate (143 mg, 0.631 mmol) at room temperature, next, tri-*n*-butyl phosphine (0.17 mL, 0.688 mmol) was added dropwise. After 20 minutes, the dark-red solution was concentrated, mounted on Celite, and filtered through a pad of silica (2:1 n-hexanes:ethyl acetate) to yield the intermediate selenide which was used without further purification. The intermediate selenide was dissolved in tetrahydrofuran (4 mL) and 30% hydrogen peroxide solution (0.51 mL) was added dropwise over five minutes. The mixture was stirred at room temperature for 30 minutes, then the aqueous phase was diluted by the addition of 5 mL of distilled water. The mixture was diluted further with 10 mL of ethyl acetate, the organic phase was removed, and the aqueous phase was extracted twice with 5 mL of ethyl acetate. The organic phases were combined, dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to yield pure diene **4.35** (89 mg, 0.28 mmol, 50%) as a yellow oil. The yellow oil crystallized under vacuum overnight, and recrystallization from ethanol and water gave colourless needles (mp. 170° C, EtOH: H_2O = 20:1).

4.35: Rf 0.6 (silica, ethyl acetate); $[\alpha]_D^{21}$ +95.3° (c 1.49, $CHCl_3$); **IR** (neat): ν_{max} = 2971, 2889, 1690, 1402, 1130 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (dd, J = 17.6, 11.0 Hz, 1H), 5.82 (dd, J = 7.8, 6.9 Hz, 1H), 5.31 (d, J = 17.6 Hz, 1H), 5.09 – 5.03 (m, 2H), 4.97 (t, J = 4.7 Hz, 1H), 4.93 – 4.90 (m, 1H), 4.83 (s, 1H), 4.53 (d, J = 16.3 Hz, 1H), 3.97 (dt, J = 12.9, 8.5 Hz, 2H), 3.87 (dt, J = 8.9, 8.4 Hz, 2H), 3.74 (d, J = 4.4 Hz, 1H), 3.64 (dt, J = 16.3, 2.4 Hz, 1H), 3.35 (s, J = 5.3 Hz, 1H), 3.18 – 2.97 (m, 2H), 2.15 (ddd, J = 13.7, 5.1, 2.4 Hz, 1H), 1.78 (dd, J = 13.7, 3.4 Hz, 1H), 1.22 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.33, 144.21, 140.01, 138.47, 137.87, 132.28, 127.30, 113.60, 110.38, 103.80, 65.08, 65.05, 57.26, 48.52, 41.28, 32.81, 32.04, 23.55, 18.76.; **HRMS** (EI, m/z): Calculated for $C_{19}H_{23}O_3N$ ([M]+) 313.1672, found 313.1673; **MS** (EI, m/z (%)): 313.25 (98), 241.20 (24), 73.07 (100); analytically calculated for C 72.82, H 7.40, found C 72.64, H 7.41.

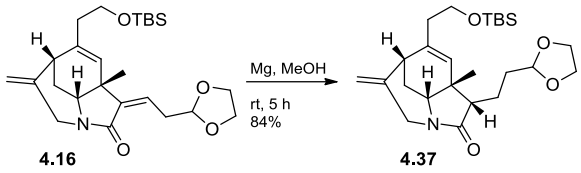


4.35 4.36

(3a*R*,6*S*,7a*R*)-3-(2-(1,3-dioxolan-2-yl)ethyl)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred solution of α,β-unsaturated lactam **4.35** (60 mg, 0.191 mmol) in methanol (5 mL) was added oven dried magnesium turnings (116 mg, 4.79 mmol) in three portions over two hours at room temperature. The mixture was stirred vigorously for another two hours, and then quenched by dropwise addition of 5M HCl until mixture was clear. Ethyl acetate (10 mL) and water (2 mL) were added, the organic phase was removed, and the aqueous phase was extracted twice with ethyl acetate (4 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to furnish the saturated lactam **4.36** (46 mg, 0.146 mmol, 76%) as a colourless oil.

4.36: Rf 0.6 (silica, ethyl acetate); $[\alpha]_D^{21}$ -106.4° (c 0.60, $CHCl_3$); **IR** (neat): ν_{max} = 2957, 2872, 1692, 1406, 1138, 1035, 896 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.16 (dd, J = 17.5, 11.0 Hz, 1H), 5.32 (d, J = 18.1 Hz, 2H), 5.07 (d, J = 11.0 Hz, 1H), 4.93 – 4.88 (m, 2H), 4.82 (s, 1H), 4.51 (d, J = 16.4 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.91 – 3.82 (m, 2H), 3.67 (d, J = 4.6 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.33 (s, J = 9.5 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.09 (ddd, J = 13.7, 5.1, 2.4 Hz, 1H), 1.80 – 1.50 (m, 4H), 1.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.83, 144.52, 140.61, 138.11, 129.37, 113.61, 110.27, 104.70, 65.01, 64.96, 57.86, 52.13, 48.04, 40.68, 33.39, 32.88, 23.51, 20.72, 19.27;

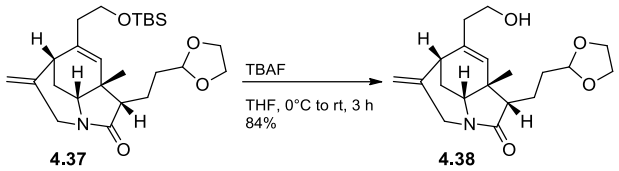
HRMS (EI, m/z): Calculated for $C_{19}H_{25}O_3N$ ([M]+) 315.1829, found 315.1830; **MS** (EI, m/z (%)): 315.22 (56), 243.18 (100), 73.09 (37).



(3*S*,3a*R*,6*S*,7a*R*)-3-(2-(1,3-dioxolan-2-yl)ethyl)-5-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred solution of α,β-unsaturated lactam **4.16** (400 mg, 0.898 mmol) in methanol (5 mL) was added oven dried magnesium turnings (327 mg, 13.5 mmol) in three portions over two hours at room temperature. The mixture was stirred vigorously for another three hours, and then quenched by dropwise addition of 5M HCl until the mixture was clear and excess magnesium had dissolved. Ethyl acetate (25 mL) and water (10 mL) were added, and the resulting mixture was filtered through a plug of cotton. the organic phase was removed, and the aqueous phase was extracted twice with ethyl acetate (10 mL). The organics were combined, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to furnish the saturated lactam **4.37** (339 mg, 0.757 mmol, 84%) as a colourless oil.

4.37: Rf 0.4 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{22}$ -164.7° (c 0.93, $CHCl_3$); **IR** (neat): ν_{max} = 2958, 2931, 2889, 1700, 1405, 1096, 837 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.01 (s, 1H), 4.89 (t, J = 4.5 Hz, 1H), 4.78 (s, 2H), 4.52 (d, J = 16.5 Hz, 1H), 4.02 – 3.90 (m, 2H), 3.90 – 3.78 (m, 2H), 3.72 – 3.58 (m, 3H), 3.54 – 3.45 (m, 1H), 2.82 (s, 1H), 2.29 – 2.07 (m, 4H), 2.00 (ddd, J = 13.5, 5.1, 2.1 Hz, 1H), 1.79 – 1.44 (m, 4H), 1.14 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.21, 144.86, 139.93, 123.81, 109.07, 104.74, 64.98, 64.93, 61.96, 57.79, 52.04, 47.70, 40.38, 38.38, 38.27, 32.92, 26.03, 23.45, 20.78, 19.20, 18.36, -5.21; **HRMS** (EI, m/z): Calculated for $C_{25}H_{41}O_4NSi$ ([M]+) 447.2799, found 447.2797; **MS** (EI, m/z (%)): 446.22 (2), 390.14 (100), 346.12 (9), 318.12 (6), 72.97 (3); analytically calculated for C 67.07, H 9.23, found C 67.22, H 9.42.

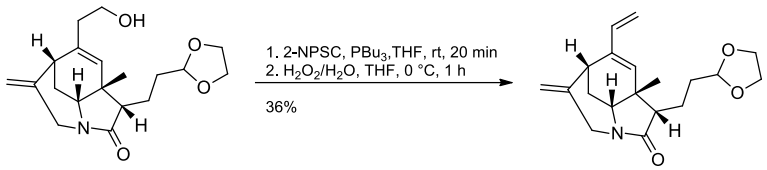


4.37 4.38

(3*S*,3a*R*,6*S*,7a*R*)-3-(2-(1,3-dioxolan-2-yl)ethyl)-5-(2-hydroxyethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred solution of silyl ether **4.37** (316 mg, 0.706 mmol) in tetrahydrofuran (7 mL) was added tetra-N-butylammonium fluoride (1.0 M, 1.06 mL, 1.06 mmol) dropwise at 0° C. The mixture was warmed to room temperature and allowed to stir for three hours. The reaction mixture was diluted with ethyl acetate (8 mL) and quenched by the addition of 4 mL saturated aqueous ammonium chloride. The organic phase was removed and washed three times with 1 mL of distilled water. The organic phase was dried over sodium sulfate and filtered and concentrated to yield the crude residue which was purified by flash column chromatography (ethyl acetate) to furnish alcohol **4.38** (197 mg, 0.591 mmol, 84%) as a colourless oil.

4.38: Rf 0.2 (silica, ethyl acetate); $[\alpha]_D^{22}$ -187.7° (c 0.73, $CHCl_3$); **IR** (neat): ν_{max} = 3428 (br.), 3076, 2982, 2974, 2935, 2888, 1677, 1397, 1143, 1040, 955 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.08 (s, 1H), 4.89 (t, J = 4.5 Hz, 1H), 4.82 – 4.78 (m, 2H), 4.54 (d, J = 16.6 Hz, 1H), 4.01 – 3.91 (m, 2H), 3.89 – 3.80 (m, 2H), 3.73 – 3.65 (m, 2H), 3.64 (d, J = 4.6 Hz, 1H), 3.54 – 3.47 (m, 1H), 2.78 (s, 1H), 2.35 – 2.14 (m, 4H), 2.03 (ddd, J = 13.6, 5.2, 2.2 Hz, 1H), 1.79 – 1.47 (m, 5H), 1.17 (s, 3H); ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 178.21, 144.62, 139.06, 124.62, 109.45, 104.67, 65.00, 64.95, 60.56, 57.73, 52.00, 47.85, 40.30, 38.66, 38.33, 32.88, 23.58, 20.76, 19.14;

HRMS (EI, m/z): Calculated for $C_{19}H_{27}O_4N$ ([M]+) 333.1935, found 333.1939; **MS** (EI, m/z (%)): 333.22 (14), 303.22 (29), 261.22 (43), 230.21 (100).

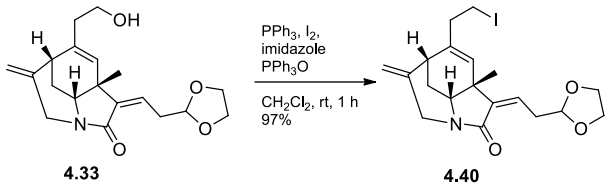


4.38 **4.36**

(3a*R*,6*S*,7a*R*)-3-(2-(1,3-dioxolan-2-yl)ethyl)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a solution of vigorously stirred alcohol **4.38** (186 mg, 0.558 mmol) in tetrahydrofuran (4 mL) was added 2-nitrophenylselenocyanate (140 mg, 0.614 mmol) at room- temperature. Next, tri-*n*-butyl phosphine (0.17 mL, 0.669 mmol) was added dropwise. After 20 minutes, the dark-red solution was concentrated, mounted on Celite, and filtered through a pad of silica (1:1 n-hexanes:ethyl acetate) to yield the intermediate selenide which was used without further purification. The intermediate selenide was dissolved in tetrahydrofuran (4 mL) and 30% hydrogen peroxide solution (0.57 mL) was added dropwise over five minutes. The mixture was stirred at room temperature for one hour, then the aqueous phase was diluted by the addition of 5 mL of distilled water. The mixture was diluted further with 10 mL of ethyl acetate, the organic phase was removed, and the aqueous phase was extracted twice with 5 mL of ethyl acetate. The organic phases were combined, dried over sodium sulfate, filtered, concentrated, and purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to yield pure diene **4.36** (63 mg, 0.20 mmol, 36%) as a colourless oil.

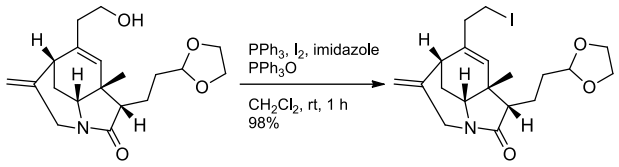
4.36: Rf 0.6 (silica, ethyl acetate); $[\alpha]_D^{21}$ -106.4° (c 0.60, $CHCl_3$); **IR** (neat): ν_{max} = 2957, 2872, 1692, 1406, 1138, 1035, 896 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (dd, J = 17.5, 11.0 Hz, 1H), 5.32 (d, J = 18.1 Hz, 2H), 5.07 (d, J = 11.0 Hz, 1H), 4.93 – 4.88 (m, 2H), 4.82 (s, 1H), 4.51 (d, J = 16.4 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.91 – 3.82 (m, 2H), 3.67 (d, J = 4.6 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.33 (s, J = 9.5 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.09 (ddd, J = 13.7, 5.1, 2.4 Hz, 1H), 1.80 – 1.50 (m, 4H), 1.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.83, 144.52, 140.61, 138.11, 129.37, 113.61, 110.27, 104.70, 65.01, 64.96, 57.86, 52.13, 48.04, 40.68, 33.39, 32.88, 23.51, 20.72, 19.27; **HRMS** (EI, m/z): Calculated for $C_{19}H_{25}O_3N$ ([M]+) 315.1829, found 315.1830; **MS** (EI, m/z (%)): 315.22 (56), 243.18 (100), 73.09 (37).



(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-iodoethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To free alcohol **4.33** (315 mg, 0.950 mmol) in dichloromethane (12 mL) was added a spatula tip of triphenylphosphine oxide followed by imidazole (252 mg, 3.71 mmol) and triphenylphosphine (1.23 g, 1.62 mmol). The mixture was stirred for 10 minutes, then iodine (362 mg, 1.43 mmol) was added in one portion, and the resulting solution was stirred at room temperature for one hour. The volatiles were removed *in vacuo* and the remaining residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to yield alkyl iodide **4.40** (405 mg, 0.918 mmol, 97%) as a colourless oil.

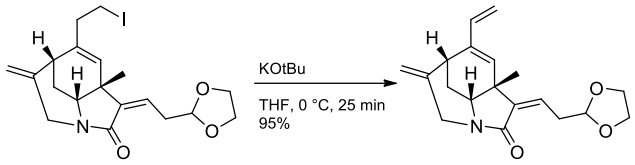
4.40: Rf 0.7 (silica, ethyl acetate); $[\alpha]_D^{22}$ -42.1° (c 0.90, $CHCl_3$); **IR** (neat): ν_{max} = 2957, 2930, 2885, 1686, 1398, 1127, 886 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.80 (t, *J* = 7.3 Hz, 1H), 4.97 (t, *J* = 4.6 Hz, 1H), 4.83 (d, *J* = 4.1 Hz, 2H), 4.77 (s, 1H), 4.58 (d, *J* = 16.5 Hz, 1H), 4.05 – 3.80 (m, 4H), 3.71 (d, *J* = 4.8 Hz, 1H), 3.61 (dt, *J* = 16.5, 2.3 Hz, 1H), 3.30 – 2.96 (m, 4H), 2.77 (s, 1H), 2.62 – 2.40 (m, 2H), 2.11 (ddd, *J* = 13.6, 5.1, 2.2 Hz, 1H), 1.81 (dd, *J* = 13.6, 3.5 Hz, 1H), 1.23 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.49, 144.31, 140.14, 138.77, 128.03, 127.12, 109.50, 103.81, 65.11, 65.09, 57.02, 48.54, 40.89, 38.73, 37.37, 32.02, 23.52, 18.58, 3.84. **HRMS** (EI, m/z): Calculated for $C_{19}H_{24}O_3NI$ ([M]+) 441.0795, found 441.0800; **MS** (EI, m/z (%)): 441.90 (9), 440.90 (51), 368.87 (14), 72.97(100).



4.38 **4.41**

(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-iodoethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To free alcohol **4.38** (107 mg, 0.323 mmol) in dichloromethane (4 mL) was added a spatula tip of triphenylphosphine oxide followed by imidazole (81 mg, 1.2 mmol) and triphenylphosphine (393 g, 0.516 mmol). The mixture was stirred for 10 minutes, then iodine (115 mg, 0.452 mmol) was added in one portion, and the resulting solution was stirred at room temperature for one hour. The volatiles were removed *in vacuo* and the remaining residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to yield alkyl iodide **4.41** (140 mg, 0.316 mmol, 98%) as a colourless oil.

4.41: Rf 0.3 (silica, hexanes; ethyl acetate = 1:1); $[\alpha]_D^{22}$ -137.7° (c 1.28, $CHCl_3$); **IR** (neat): ν_{max} = 2954, 2938, 2872, 1693, 1406 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.90 (t, J = 4.5 Hz, 1H), 4.80 (s, 1H), 4.76 (s, 1H), 4.54 (d, J = 16.6 Hz, 1H), 4.05 – 3.91 (m, 2H), 3.91 – 3.78 (m, 2H), 3.63 (d, J = 4.8 Hz, 1H), 3.54 – 3.46 (m, 1H), 3.31 – 3.12 (m, 2H), 2.73 (s, 1H), 2.64 – 2.41 (m, 2H), 2.31 – 2.14 (m, 2H), 2.04 (ddd, J = 13.5, 5.1, 2.1 Hz, 1H), 1.77 (dd, J = 13.7, 3.6 Hz, 1H), 1.74 – 1.46 (m, 3H), 1.19 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.02, 144.64, 140.92, 124.84, 109.40, 104.66, 65.01, 64.95, 57.63, 51.84, 47.88, 40.29, 39.00, 37.98, 32.88, 23.46, 20.55, 19.17, 3.94; **HRMS** (EI, m/z): Calculated for $C_{19}H_{26}O_3NI$ ([M]+) 443.0952, found 443.0949; **MS** (EI, m/z (%)): 442.95 (11), 244.11 (100).

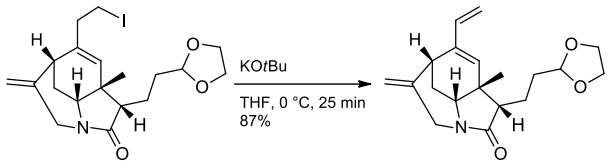


4.40 **4.35**

(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-iodoethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To alkyl iodide **4.40** (301 mg, 0.679 mmol) in tetrahydrofuran (8 mL) was added a freshly prepared solution of potassium *tert*-butoxide (1.0 M in tetrahydrofuran, 1.02 mL, 1.02 mmol) dropwise at 0 °C; A colourless precipitate was immediately observed. The mixture was stirred at 0 °C for 25 minutes, then quenched by the addition of distilled water (8 mL) and saturated aquous ammonium chloride (8 mL). The mixture was diluted with ethyl acetate (20 mL), then the organic phase was removed, and the aqueous phase was extracted five times with ethyl acetate (10 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to yield a crude residue which was purified by flash column chromatography (silica, hexanes: ethyl acetate = 1:1) to yield diene **4.35** (203 mg, 0.643 mmol, 95%) as a colourless solid (m.p 83-85 °C).

4.35: Rf 0.6 (silica, ethyl acetate); $[\alpha]_D^{21}$ +95.3° (c 1.49, $CHCl_3$); **IR** (neat): ν_{max} = 2971, 2889, 1690, 1402, 1130 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.13 (dd, J = 17.6, 11.0 Hz, 1H), 5.82 (dd, J = 7.8, 6.9 Hz, 1H), 5.31 (d, J = 17.6 Hz, 1H), 5.09 – 5.03 (m, 2H), 4.97 (t, J = 4.7 Hz, 1H), 4.93 – 4.90 (m, 1H), 4.83 (s, 1H), 4.53 (d, J = 16.3 Hz, 1H), 3.97 (dt, J = 12.9, 8.5 Hz, 2H), 3.87 (dt, J = 8.9, 8.4 Hz, 2H), 3.74 (d, J = 4.4 Hz, 1H), 3.64 (dt, J = 16.3, 2.4 Hz, 1H), 3.35 (s, J = 5.3 Hz, 1H), 3.18 – 2.97 (m, 2H), 2.15 (ddd, J = 13.7, 5.1, 2.4 Hz, 1H), 1.78 (dd, J = 13.7, 3.4 Hz, 1H), 1.22 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.33, 144.21, 140.01, 138.47, 137.87, 132.28, 127.30, 113.60, 110.38, 103.80, 65.08, 65.05, 57.26, 48.52, 41.28, 32.81, 32.04, 23.55, 18.76; **HRMS** (EI, m/z): Calculated for $C_{19}H_{23}O_3N$ ([M]+) 313.1672, found 313.1673; **MS** (EI, m/z (%)): 313.25 (98), 241.20 (24), 73.07 (100); analytically calculated for C 72.82, H 7.40, found C 72.64, H 7.41.

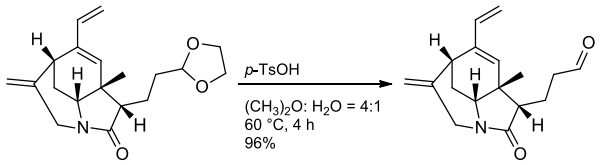


4.41 **4.36**

(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-iodoethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To alkyl iodide **4.41** (277 mg, 0.628 mmol) in tetrahydrofuran (10 mL) was added a freshly prepared solution of potassium *tert*-butoxide (1.0 M in tetrahydrofuran, 0.75 mL, 0.75 mmol) dropwise at 0 °C; A colourless precipitate was immediately observed. The mixture was stirred at 0 °C for 25 minutes, then quenched by the addition of distilled water (8 mL) and saturated aquous ammonium chloride (8 mL). The mixture was diluted with ethyl acetate (20 mL), then the organic phase was removed, and the aqueous phase was extracted five times with ethyl acetate (10 mL). The combined organics were dried over anhydrous magnesium sulfate, filtered, and concentrated to yield a crude residue which was purified by flash column chromatography (silica, hexanes: ethyl acetate = 1:1) to yield diene **4.36** (172 mg, 0.549 mmol, 87%) as a colourless oil.

4.36: Rf 0.6 (silica, ethyl acetate); $[\alpha]_D^{21}$ -106.4° (c 0.60, $CHCl_3$); **IR** (neat): ν_{max} = 2957, 2872, 1692, 1406, 1138, 1035, 896 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.16 (dd, J = 17.5, 11.0 Hz, 1H), 5.32 (d, J = 18.1 Hz, 2H), 5.07 (d, J = 11.0 Hz, 1H), 4.93 – 4.88 (m, 2H), 4.82 (s, 1H), 4.51 (d, J = 16.4 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.91 – 3.82 (m, 2H), 3.67 (d, J = 4.6 Hz, 1H), 3.58 – 3.49 (m, 1H), 3.33 (s, J = 9.5 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.09 (ddd, J = 13.7, 5.1, 2.4 Hz, 1H), 1.80 – 1.50 (m, 4H), 1.19 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.83, 144.52, 140.61, 138.11, 129.37, 113.61, 110.27, 104.70, 65.01, 64.96, 57.86, 52.13, 48.04, 40.68, 33.39, 32.88, 23.51, 20.72, 19.27;

HRMS (EI, m/z): Calculated for $C_{19}H_{25}O_3N$ ([M]+) 315.1829, found 315.1830; **MS** (EI, m/z (%)): 315.22 (56), 243.18 (100), 73.09 (37).



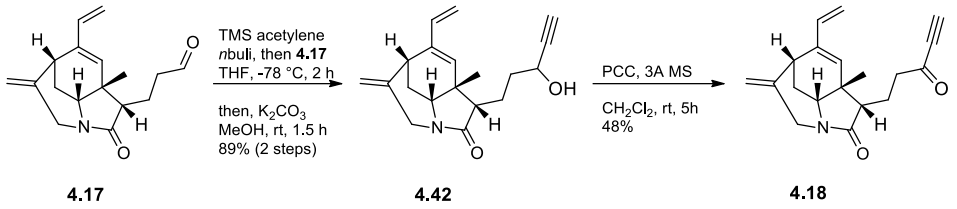
4.36 **4.17**

3-((3a*R*,6*S*,7a*R*)-3a-methyl-8-methylene-2-oxo-5-vinyl-2,3,3a,6,7,7a-hexahydro-1,6-ethanoindol-3-yl)propanal. To a stirred solution of acetal **4.36** (89 mg, 0.28 mmol) in acetone/water (4:1, 4 mL) under argon atmosphere was added *p*-toluenesulphonic acid (14 mg, 0.071 mmol). The mixture was heated to 60° C and stirred for four hours. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL), and then the mixture was diluted with ethyl acetate (5 mL). The organic phase was separated, and the aqueous phase was thrice extracted with ethyl acetate (5 mL). The organic phases were combined, dried over magnesium sulphate, filtered and concentrated. The resulting crude residue was purified by flash column chromatography (1:1 = hexanes:ethyl acetate) to yield aldehyde **4.17** as a white waxy solid (73 mg, 0.27 mmol, 96%) mp: 108-110° C (chloroform).

4.17: Rf 0.4 (silica, hexanes/ethyl acetate = 1:2); $[\alpha]_D^{21}$ -137.7° (c 0.19, $CHCl_3$); **IR** (neat): ν_{max} = 2933, 2904, 2821, 2723, 1715, 1682, 1407 cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 6.17 (dd, J = 17.5, 10.9 Hz, 1H), 5.38 – 5.27 (m, 2H), 5.10 (d, J = 11.0 Hz, 1H), 4.89 (d, J = 25.1 Hz, 2H), 4.50 (d, J = 16.3 Hz, 1H), 3.69 (d, J = 4.8 Hz, 1H), 3.55 (d, J = 16.3 Hz, 1H), 3.35 (s, 1H), 3.06 (ddd, J = 18.5, 8.1, 5.6 Hz, 1H), 2.72 (dt, J = 16.2, 7.4 Hz, 1H), 2.28 (dd, J = 10.8, 3.2 Hz, 1H), 2.11 (ddd, J = 13.8, 5.0, 2.2 Hz, 1H), 1.89 – 1.64 (m, 3H), 1.21 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.46, 177.72,

144.30, 140.93, 137.99, 128.93, 113.91, 110.50, 58.02, 51.37, 48.15, 42.92, 40.67, 33.40, 23.52, 20.45, 17.24;

HRMS (EI, m/z): Calculated for $C_{17}H_{21}O_2N$ ([M]+) 271.1567, found 271.1564; **MS** (EI, m/z (%)): 271.14 (28), 243.15 (64), 155.18 (135), 141.16 (27), 127.15 (43), 113.13 (49), 99.12 (55), 85.09 (100), 84.01 (72), 71.09 (89), 57.07(72).

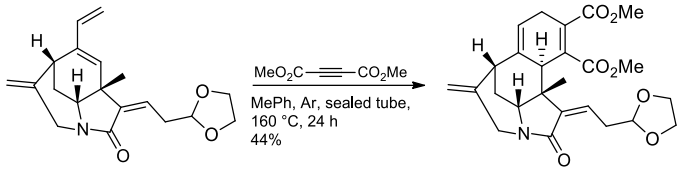


(3*S*,3a*R*,6*S*,7a*R*)-3a-methyl-8-methylene-3-(3-oxopent-4-yn-1-yl)-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a solution of trimethylsilylacetylene (11 µL, 0.072 mmol) in tetrahydrofuran (1.0 mL) at -78° C was added a 0.25 M solution of *n*-butyllithium (0.29 mL, 0.0719 mmol) dropwise. The mixture was stirred for one hour at -78° C, and then a solution of aldehyde **4.17** (15 mg, 0.055 mmol) in tetrahydrofuran (1.0 mL) was added dropwise. Then resulting mixture was stirred for 30 minutes at -78° C, then allowed to warm to room temperature over 30 minutes. Next, the mixture was quenched by the addition of 1 mL of distilled water, and diluted with 2 mL ethyl acetate, the organic phase was removed, and the aqueous phase was extracted twice with 1 mL ethyl acetate. The organic phases were combined, washed with brine, dried over magnesium sulphate, and concentrated.

The resulting residue was dissolved in methanol (1.0 mL), potassium carbonate (23 mg, 0.17 mmol) was added, and the mixture was stirred at room temperature for 90 minutes. The mixture was filtered through a pad of Celite and eluted with dichloromethane. The resulting solution was washed sequentially with saturated aqueous ammonium chloride and brine. The organic phase was dried over magnesium sulphate, filtered, and concentrated to yield the crude residue. The crude residue was purified by flash column chromatography (1:1 = n-hexane:ethyl acetate) to furnish a mixture of diastereomers of propargyl alcohol **4.42** (14.4 mg, 0.0484 mmol, 84%).

Next, alcohols **4.42** (6.9 mg, 0.023 mmol) were dissolved in dichloromethane (1.0 mL), a spatula tip of crushed 3 A molecular sieves and pyridinium chlorochromate (8 mg, 0.037 mmol) were added sequentially at room temperature. The mixture was stirred for five hours, and then filtered through a small plug of celite, eluting with dichloromethane. The eluent was concentrated and directly purified by column chromatography (pentane ⟶ pentane:ethyl acetate = 2:1 ⟶1:1) to furnish acetylenic ketone **4.18** (3.2 mg, 0.011 mmol, 48%) as a colourless oil.

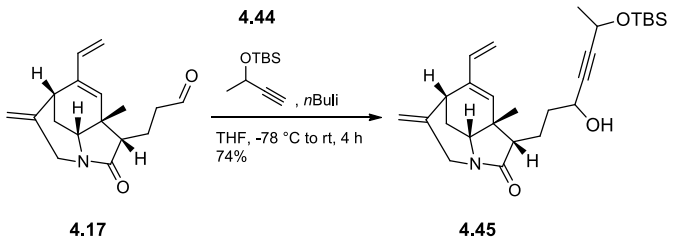
18: Rf 0.5 (silica, hexanes/ethyl acetate = 1:1); **IR** (neat): ν_{max} = 3203 (br.), 3088, 3007, 2956, 2938, 2898, 2870, 2088, 1683, 1648, 1410, 1107, 889 cm^{-1}; **1H NMR** (400 MHz, $CDCl_3$) δ 6.17 (dd, J = 17.6, 11.0 Hz, 1H), 5.34 (d, J = 17.6 Hz, 1H), 5.28 (s, 1H), 5.09 (d, J = 11.0 Hz, 1H), 4.93 (t, J = 1.1 Hz, 1H), 4.85 (s, 1H), 4.50 (d, J = 16.4 Hz, 1H), 3.69 (d, J = 4.5 Hz, 1H), 3.58 – 3.51 (m, 1H), 3.35 (s, 1H), 3.22 (ddd, J = 18.4, 8.3, 5.5 Hz, 1H), 3.20 (s, 1H), 2.88 (dt, J = 18.5, 7.7 Hz, 1H), 2.26 (dd, J = 11.0, 3.0 Hz, 1H), 2.11 (ddd, J = 13.7, 5.1, 2.3 Hz, 1H), 1.91 – 1.68 (m, 3H), 1.21 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 187.27, 177.58, 144.28, 140.92, 137.98, 128.90, 113.91, 110.49, 81.67, 78.53, 57.99, 51.08, 48.11, 44.11, 40.65, 33.39, 23.51, 20.41, 18.63; **HRMS** (EI, m/z): Calculated for $C_{19}H_{21}O_2N$ ([M]+) 295.1567, found 295.1562; **MS** (EI, m/z (%)): 295.16 (60), 167.10 (49), 158.17 (58), 157.14 (64), 149.09 (100), 143.15 (54), 113.20 (42).



4.35 4.53

(3α*R*,5*S*,9β*R*,*Z*)-dimethyl-1-(2-(1,3-dioxolan-2-yl)ethylidene)-9β-methyl-10-methylene-2-oxo-1,2,3α,4,5,7,9α,9β-octahydro-3,5-ethanobenzo[e]indole-8,9-dicarboxylate. Diene **4.35** (26 mg, 0.083 mmol) and dimethylacetlene dicarboxylate (18μL, 0.15 mmol) in toluene (1 mL) sparged with argon for 20 minutes in a sealed tube was heated to 160 °C (oil bath temperature) and stirred at this temperature for 24 hours. Next, volatiles were evaporated, and the resulting reside was purified by flash column chromatography (hexanes: ethyl acetate = 1:1 ⟶ 1:2) to yield Diels-Alder abduct **4.53** (17 mg, 0.037 mmol, 45%) as a pale-yellow oil.

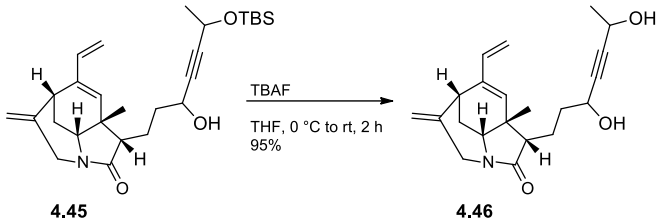
4.53: Rf 0.3 (silica, hexanes: ethyl acetate = 1:2); $[\alpha]_D^{22}$ +86.2° (c 0.82, $CHCl_3$); **IR** (neat): ν_{max} = 2952, 2925, 2895, 1725, 1692, 1257 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.66 – 5.62 (m, 1H), 5.59 (dd, J = 8.9, 5.4 Hz, 1H), 5.08 (s, 1H), 4.94 (t, J = 4.4 Hz, 1H), 4.87 (s, 1H), 4.53 (d, J = 15.5 Hz, 1H), 3.99 – 3.92 (m, 2H), 3.92 – 3.87 (m, 1H), 3.86 – 3.80 (m, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.45 (s, J = 8.5 Hz, 1H), 3.35 (t, J = 7.4 Hz, 1H), 3.27 – 3.05 (m, 3H), 2.77 (dddd, J = 20.9, 9.6, 5.9, 4.3 Hz, 2H), 2.18 (dt, J = 14.1, 3.7 Hz, 1H), 1.83 – 1.74 (m, 1H), 1.11 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.04, 168.84, 167.40, 143.66, 143.17, 137.69, 137.03, 130.88, 126.48, 117.18, 113.79, 103.52, 65.16, 65.11, 61.13, 54.97, 52.30, 52.07, 43.70, 43.10, 39.76, 32.36, 27.53, 26.37, 13.02; **HRMS** (EI, m/z): Calculated for $C_{25}H_{29}O_7N$ ([M]+) 455.1939, found 455.1945; **MS** (EI, m/z (%)): 445.15 (2), 279.08 (38), 166.96 (70), 148.97 (100), 113.06 (27).



(3*S*,3a*R*,6*S*,7a*R*)-3-(6-((tert-butyldimethylsilyl)oxy)-3-hydroxyhept-4-yn-1-yl)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred mixture of protected propargyl alcohol **4.44** (64 mg, 0.078 mL, 0.35 mmol) in tetrahydrofuran (2 mL) at -78 °C was added *n*-butyllithium dropwise. The mixture was stirred for one hour, then a solution of aldehyde **4.17** in tetrahydrofuran (1.5 mL) was added dropwise at -78 °C. The resulting mixture was stirred for 30 minutes, allowed to warm to room temperature over 30 minutes, then stirred at room temperature for two hours. The reaction was quenched with distilled water (2 mL) and diluted with of ethyl acetate (2mL). The organic phase was removed, and the aqueous phase was extracted four times with ethyl acetate (2 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to yield a crude residue which was purified by flash column chromatography (hexanes: ethyl acetate = 2:1) to furnish pure secondary alcohol **4.45** (93 mg, 0.20 mmol, 74%) as a colourless oil.

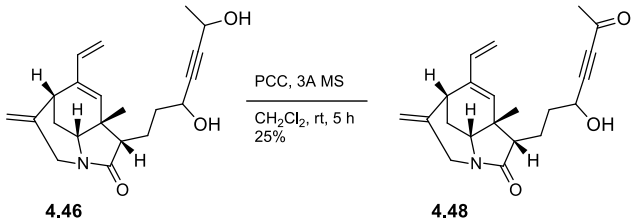
20 as a mixture of diastereomers: Rf 0.5, 0.4 (silica, hexanes: ethyl acetate = 1:1); **IR** (neat): ν_{max} = 3378 (br), 2925, 2954, 2929, 2856, 2099, 1676, 1100 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.34 (d, *J* = 17.5 Hz, 1H), 5.27 (s, 1H), 5.14 – 5.04 (m, 1H), 4.98 – 4.91 (m, 1H), 4.91 – 4.82 (m, 1H), 4.59 – 4.39 (m, 3H), 4.07 – 3.92 (m, 0.66H), 3.72 (d, *J* = 4.7 Hz, 0.66H), 3.69 (d, *J* = 4.7 Hz, 0.33H), 3.61 – 3.51 (m, 1H), 3.35 (s, 1H), 3.04 – 2.83 (m, 0.33H), 2.44 – 2.35 (m 0.33H), 2.26 (dd, *J* = 9.4, 2.4 Hz, 0.66H), 2.17 – 1.81 (m, 3H), 1.81 – 1.56 (m, 3H), 1.45 – 1.35 (m, 3H), 1.23 – 1.15 (m, 3H), 0.94 – 0.83 (m, 9H), 0.17 – 0.06 (m, 6H); **HRMS** (EI, m/z): Calculated for $C_{27}H_{41}O_3NSi$ ([M]+) 445.2850, found 445.28480; **MS** (EI, m/z (%)): 400.19 (10), 399.20 (30), 398.19 (100), 396.18 (31), 380.18 (7), 243.14 (7), 149.05 (6), 75.06 (18).



(3*S*,3a*R*,6*S*,7a*R*)-3-(3,6-dihydroxyhept-4-yn-1-yl)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred solution of silyl ether **4.45** (89 mg, 0.20 mmol) in tetrahydrofuran (4 mL) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.29 mL, 0.29 mmol) at 0 °C. The ice bath was removed, and the mixture was stirred for two hours at room temperature. The resulting solution was concentrated and purified directly by flash column chromatography (ethyl acetate) to yield diol **4.46** (65 mg, 0.19 mmol, 95%) as a white foam.

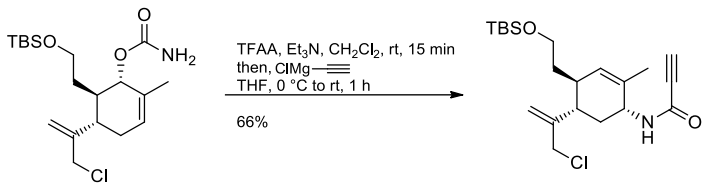
4.46 as mixture of diastereomers: Rf 0.4 (silica, ethyl acetate); **IR** (neat): ν_{max} = 3366 (br), 2976, 2955, 2932, 2870, 1672 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 5.27 (s, 1H), 5.14 – 5.06 (m, 1H), 4.97 – 4.91 (m, 1H), 4.88 – 4.83 (m, 1H), 4.59 – 4.40 (m, 3H), 4.33 (br. s, 0.66H), 3.73 (d, *J* = 4.6 Hz, 0.66H), 3.70 (d, *J* = 4.7 Hz, 0.33H), 3.61 – 3.53 (m, 1H), 3.42 (s, *J* = 14.4 Hz, 0.33H), 3.36 (s, 1H), 2.45 – 2.07 (m, 3H), 2.02 – 1.81 (m, 2H), 1.80 – 1.56 (m, 3H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.20 (s, 1H), 1.19 (s, 2H); **HRMS** (EI, m/z): Calculated for $C_{21}H_{27}O_3N$ ([M]+) 341.1985, found 341.1987; **MS** (EI, m/z (%)): 341.14 (29), 323.12 (35), 270.08 (100), 243.09 (48), 228.07 (48).



4.46 4.48

(3*S*,3a*R*,6*S*,7a*R*)-3-(3-hydroxy-6-oxohept-4-yn-1-yl)-3a-methyl-8-methylene-5-vinyl-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one. To a stirred mixture of diol **4.46** (65 mg, 0.19 mmol) in dichloromethane (5 mL) was added pyridinium chlorochromate (123 mg, 0.571 mmol). The mixture was stirred for four hours at room temperature, and then purified directly by flash column chromatography (hexanes: ethyl acetate = 2:1 ⟶ 1:1) to furnish a mixture of diastereomers of the acetylenic ketones **4.48** (16 mg, 0.047 mmol, 25%) as a colourless oil.

4.48 as mixture of diastereomers: Rf 0.3 (silica, hexanes: ethyl acetate = 1:1); **IR** (neat): ν_{max} = 3369 (br), 2956, 2926, 2870, 2209, 1672 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.39 – 5.30 (m, 1H), 5.28 (s, 0.38H), 5.25 (s, 0.62H), 5.15 – 5.07 (m, 1H), 4.98 – 4.82 (m, 2H), 4.65 (dd, *J* = 13.3, 6.7 Hz, 0.38H), 4.61 – 4.53 (m, 0.62H), 4.49 (d, *J* = 16.4 Hz, 1H), 3.75 (d, *J* = 4.7 Hz, 0.62H), 3.69 (d, *J* = 4.5 Hz, 0.38H), 3.62 – 3.50 (m, 1H), 3.40 – 3.32 (m, 1H), 2.37 – 2.32 (m, 1.86H), 2.30 – 2.23 (m,1.141H), 2.16 – 1.99 (m, 2H), 1.91 – 1.57 (m, 5H), 1.49 (d, *J* = 6.6 Hz, 1H), 1.22 – 1.17 (m, 3H); **HRMS** (EI, m/z): Calculated for $C_{21}H_{25}O_3N$ ([M]+) 339.1829, found 339.1826; **MS** (EI, m/z (%)): 339.12 (80), 321.10 (59), 296.09 (61), 270.08 (100), 243.09 (74), 242.09 (48), 228.08 (77), 174.06 (53), 158.06 (60).



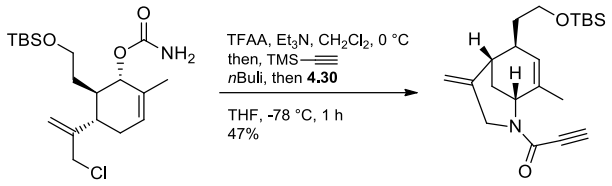
4.13 **4.57**

(1*R*,4*S*,5*S*)-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3chloroprop-1-en-2-yl)-2-methyl-N-(4.(trimethylsilyl)but-1-en-3-yn-2-yI)cyclohex-2-en-1-amine. To a stirred solution of carbamate **4.13** (1.42 g, 3.66 mmol) in dichloromethane (40 mL), triethylamine (1.53 mL, 11.0 mmol) was added at room temperature. The contents were cooled to 0 °C, and trifluoroacetic anhydride (0.60 mL, 4.4 mmol) was added dropwise over 10 minutes, and the resulting solution was stirred for 30 minutes. The mixture was concentrated to ca. 5 mL, then filtered through a two-inch plug of silica, eluted with dichloromethane: petroleum ether = 1:1 (100 mL). The eluent was concentrated *in vacuo* yielding the crude isocyanate as a colourless oil.

A stirred solution of the crude isocyanate intermediate in tetrahydrofuran (30 mL) was cooled to 0 °C, and a solution of ethynyl magnesium chloride (0.5 M in tetrahydrofuran, 8.78 mL, 4.39 mmol) was added dropwise over 30 minutes. The mixture was allowed to slowly warm to room temperature over one hour, then it was stirred for two further hours. The resulting solution was quenched with saturated aqueous ammonium chloride (20 mL), diluted with ethyl acetate (20 mL), and resulting solids (if present) were dissolved by adding a small amount of distilled water. The organics were removed, and the aqueous phase was extracted five times with ethyl acetate (20 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a crude residue which was purified by flash column chromatography (hexanes:

ethyl acetate = 3:1 ⟶ 2:1) to furnish secondary amide **4.57** (956 mg, 2.41 mmol, 66% mmol) as a yellow oil.

4.57: Rf 0.4 (silica, hexanes: ethyl acetate = 3:1); $[\alpha]_D^{21}$ +95.7° (c 1.80, $CHCl_3$); **IR** (neat): ν_{max} = 3289, 3247, 3044, 2953, 2929, 2857, 2110, 1635, 1536, 1256, 1099, 836, 776 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 6.01 – 5.48 (m, 2H), 5.39 – 3.91 (m, 4H), 3.65 (s, *J* = 5.1 Hz, 2H), 3.25 – 2.70 (m, 1H), 2.49 – 1.86 (m, 3H), 1.86 – 1.39 (m, 5H), 1.39 – 1.16 (m, 1H), 0.88 (s, 9H), 0.06 (d, *J* = 23.5 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 152.06, 146.96, 132.32, 129.77, 115.96, 77.34, 73.56, 60.57, 49.96, 47.31, 43.26, 37.08, 35.98, 35.79, 26.07, 19.80, 18.41, -5.20, -5.23; **HRMS** (EI, m/z): Calculated for $C_{17}H_{25}O_2NClSi$ ([M-C_4H_9]+) 338.1338, found 338.1339; **MS** (EI, m/z (%)): 340.12 (41), 338.13 (100), 233.13 (22), 159.12 (87), 75.07 (40).



4.13 **4.56**

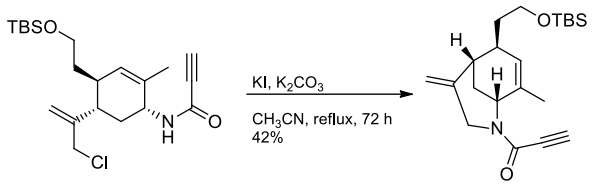
1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)prop-2-yn-1-one. To a stirred solution of carbamate **4.13** (2.53 g, 6.52 mmol) in dichloromethane (50 mL), triethylamine (2.70 mL, 19.6 mmol) was added at room temperature. The contents were cooled to 0 °C, and trifluoroacetic anhydride (1.07 mL, 7.82 mmol) was added dropwise over 10 minutes, and the resulting solution was stirred for 30 minutes. The mixture was concentrated to ca. 5 mL, then it was then filtered through a two-inch plug of silica, eluted with dichloromethane: petroleum ether = 1:1 (100 mL). The eluent was concentrated *in vacuo* yielding the crude isocyanate as a colourless oil.

Meanwhile, to a stirred solution of trimethylsilyl acetylene (1.73 mL, 16.30 mmol) in tetrahydrofuran (15 mL), at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 5.74 mL, 14.4 mmol) dropwise over 15 minutes, and the resulting mixture stirred for 60 minutes at 0 °C.

A stirred solution of the crude isocyanate intermediate in tetrahydrofuran (60 mL) was cooled to -78 °C, and the freshly prepared solution of lithium acetylide was added dropwise via a cannula. After stirring for one hour at -78 °C, the mixture was allowed to warm to room temperature over one hour, stirred overnight at room temperature, then quenched with saturated aqueous ammonium chloride (100 mL), diluted with ethyl acetate (100 mL), and resulting solids (if present) were dissolved by adding a small

amount of distilled water. The organics were removed, and the aqueous phase was extracted three times with ethyl acetate (40 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a crude residue which was purified by flash column chromatography (hexanes: ethyl acetate = 5:1 ⟶ 3:1) to furnish tertiary amide **4.56** (1.10 g, 3.05 mmol, 47% mmol) as a pale-yellow oil.

4.56: Rf 0.4 (silica, hexanes: ethyl acetate = 3:1); $[\alpha]_D^{22}$ +224.8° (c 0.64, $CHCl_3$); **IR** (neat): ν_{max} = 3213, 2952, 2928, 2856, 2102, 1622, 1418, 1098, 836, 775 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 5.72 – 5.62 (m, 1H), 4.93 (s, 0.40H), 4.79 (s, 2H), 4.74 (d, J = 15.2 Hz, 0.60H), 4.64 (s, 0.60H), 4.54 (d, J = 14.7 Hz, 0.40H), 3.95 (d, J = 14.6 Hz, 0.40H), 3.69 (t, J = 6.3 Hz, 2H), 3.49 (d, J = 15.2 Hz, 0.60H), 3.13 (s, 0.40H), 3.11 (s, 0.60H), 2.57 – 2.49 (m, 1H), 2.18 (s, 1H), 1.91 (dt, J = 12.7, 2.7 Hz, 0.60H), 1.84 (dt, J = 12.8, 2.6 Hz, 0.40H), 1.79 – 1.50 (m, 6H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 151.66, 151.50, 146.40, 145.58, 130.80, 130.69, 130.32, 110.64, 109.94, 79.13, 78.98, 76.06, 75.86, 61.22, 61.17, 53.14, 48.25, 46.95, 42.76, 39.72, 39.62, 38.19, 38.08, 37.41, 37.40, 28.63, 27.91, 26.03, 21.61, 21.21, 18.38, -5.20; **HRMS** (EI, m/z): Calculated for $C_{21}H_{33}O_2NSi$ ([M]+) 359.2274, found 359.2277; **MS** (EI, m/z (%)): 359.20 (6), 303.13 (25), 302.13 (100), 233.12 (17), 193.08 (18), 158.10 (24); analytically calculated for C 70.15, H 9.25, found C 70.16, H 9.45.

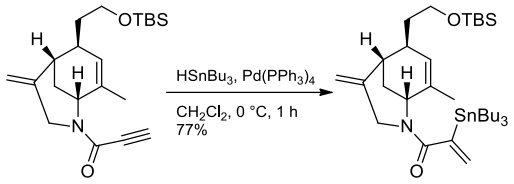


4.57 **4.56**

1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methy1-4methylene-2-azabicyclo[3.3.1]non-7-en-2-yI)prop-2-yn-1-one. To a stirred solution of amide **4.57** (820 mg, 2.07 mmol) in acetonitrile (35 mL) in a round bottom flask equipped with a reflux condenser was added potassium iodide (172 mg, 1.04 mmol) and potassium carbonate (572 mg, 4.14 mmol). The mixture was heated to reflux and stirred for 72 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL). Residual salts (if present) were dissolved with minimal distilled water and the mixture was diluted with ethyl acetate (20 mL). The organic phase was removed, and the aqueous phase was thrice extracted with ethyl acetate (20 mL), the organic layers were combined, washed with brine, dried over magnesium sulfate, and then concentrated under reduced pressure to yield the crude product. The crude residue was purified by flash column chromatography (hexanes:ethyl acetate = 4:1) to yield tertiary amide **4.56** (18 mg, 0.051 mmol, 42%) as colourless oil.

4.56: Rf 0.4 (silica, hexanes: ethyl acetate = 3:1); $[\alpha]_D^{22}$ +224.8° (c 0.64, $CHCl_3$); **IR** (neat): ν_{max} = 3213, 2952, 2928, 2856, 2102, 1622, 1418, 1098, 836, 775 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 5.72 – 5.62 (m, 1H), 4.93 (s, 0.40H), 4.79 (s, 2H), 4.74 (d, J = 15.2 Hz, 0.60H), 4.64 (s, 0.60H), 4.54 (d, J = 14.7 Hz, 0.40H), 3.95 (d, J = 14.6 Hz, 0.40H), 3.69 (t, J = 6.3 Hz, 2H), 3.49 (d, J = 15.2 Hz, 0.60H), 3.13 (s, 0.40H), 3.11 (s, 0.60H), 2.57 – 2.49 (m, 1H), 2.18 (s, 1H), 1.91 (dt, J = 12.7, 2.7 Hz, 0.60H), 1.84 (dt, J = 12.8, 2.6 Hz, 0.40H), 1.79 – 1.50 (m, 6H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, mixture of rotamers) δ 151.66, 151.50, 146.40, 145.58, 130.80, 130.69, 130.32, 110.64, 109.94, 79.13, 78.98, 76.06, 75.86, 61.22, 61.17, 53.14, 48.25, 46.95, 42.76, 39.72, 39.62, 38.19, 38.08, 37.41, 37.40, 28.63, 27.91, 26.03, 21.61, 21.21, 18.38, -5.20; **HRMS** (EI, m/z): Calculated for $C_{21}H_{33}O_2NSi$ ([M]+) 359.2274, found 359.2277; **MS** (EI, m/z (%)): 359.20 (6), 303.13 (25), 302.13 (100), 233.12 (17), 193.08 (18), 158.10 (24); analytically calculated for C 70.15, H 9.25, found C 70.16, H 9.45.

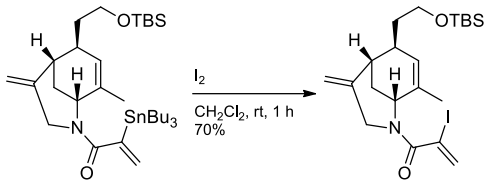


4.56 **4.59**

1-((1*R*,5*S*,6*S*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)-2-(tributylstannyl)prop-2-en-1-one. To a stirred solution of tertiary amide **4.56** (293 mg, 0.815 mmol) dissolved in degassed tetrahydrofuran (7 mL) was added tetrakis(triphenylphosphine)palladium(0) (33 mg, 0.039 mmol) at room temperature. After five minutes of stirring, tributyltinhydride (0.102 mL, 0.378 mmol) was added dropwise at room temperature via a syringe pump over 15 minutes. The reaction was stirred for a further hour, and then the mixture was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (hexanes → hexanes: ethyl acetate = 9:1) to afford stannane **4.59** (409 mg, 0.628 mmol, 77%) as a colourless oil.

4.59: Rf 0.7 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{20}$ +61.7° (c 1.28, $CHCl_3$); **IR** (neat): ν_{max} = 3071, 3035, 2954, 2927, 2855, 1617, 1560, 1425, 11008, 837, 775 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 5.95 (d, *J* = 2.3 Hz, 0.30H), 5.81 (d, *J* = 2.4 Hz, 0.70H), 5.65 (d, *J* = 3.7 Hz, 0.70H), 5.62 (d, *J* = 3.0 Hz, 0.30H), 5.55 (d, *J* = 2.3 Hz, 0.30H), 5.50 (d, *J* = 2.4 Hz, 0.70H), 5.01 (s, 0.70H), 4.84 – 4.73 (m, 0.90H), 4.71 (s, 0.70H), 4.61 (s, 0.70H), 4.29 (s, 0.30H), 4.20 (d, *J* = 14.6 Hz, 0.70H), 3.81 (d, *J* = 14.6 Hz, 0.70H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.47 (d, *J* = 14.8 Hz, 0.30H), 2.51 (s, 0.30H), 2.48 (s, 0.70H), 2.14 (m, 1H), 1.89 – 1.76 (m, 1H), 1.73 – 1.41 (m, 12H), 1.38 – 1.23 (m, 6H), 1.10 – 0.92 (m, 6H), 0.92 – 0.85 (m, 18H), 0.05 (s, 6H);

^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 173.57, 173.29, 151.15, 151.02, 147.56, 146.97, 131.62, 130.90, 130.56, 129.95, 128.40, 127.31, 109.87, 108.85, 61.36, 61.32, 52.12, 48.21, 46.27, 42.73, 39.94, 38.23, 37.56, 37.44, 29.02, 28.97, 27.48, 27.45, 26.06, 21.69, 21.50, 18.41, 13.79, 10.62, 10.39, -5.17; **HRMS** (EI, m/z): Calculated for $C_{29}H_{52}O_2NSiSn$ ([M-C_4H_9]+) 594.2781, found 594.2781; **MS** (EI, m/z (%)): 598.26 (14), 596.28 (19), 595.29 (32), 594.25 (100), 592.27 (70), 590.27 (32), 362.22 (23), 361.21 (76), 304.15 (78), 302.13 (45), 233.11 (26), 158.09 (37); analytically calculated for C 60.92, H 9.45, found C 61.52, H 9.67.



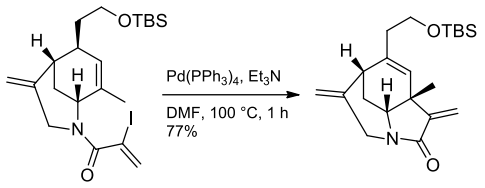
4.59 **4.60**

1-((1*R*,5*S*,6*S*)-6-(2-(tert-butyldimethylsilyl)oxy)ethyl)-8-methyl-4-methylene-2-azabicyclo[3.3.1]non-7-en-2-yl)-2-iodoprop-2-en-1-one. To a stirred solution of stannane **4.59** (1.48 g, 2.27 mmol) in dichloromethane (25 mL) was added iodine (606 mg, 2.39 mmol) in three portions over 30 minutes. The resulting wine-red solution was left stirring for 1 hour, it was quenched with a minimal amount of 20% (w/w) aqueous sodium bisulfite and left stirring until the solution decolorized. The organic phase was removed, and the aqueous phase was thrice extracted with dichloromethane (5 mL). The organic layers were combined, dried over magnesium sulfate, and concentrated under reduced pressure to yield a crude residue which was purified by flash column chromatography (silica, 10% potassium carbonate (w/w), hexanes: ethyl acetate = 5:1) to yield the iodinated compound **4.60** (956 mg, 1.96 mmol, 86 %) as a pale-yellow oil.

4.60: Rf 0.4 (silica, hexanes: ethyl acetate = 3:1);); $[\alpha]_D^{21}$ +125.3° (c 1.13, $CHCl_3$); **IR** (neat): ν_{max} = 3072, 2952, 2927, 2855, 1632, 1422, 1098, 834, 774 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, mixture of rotamers) δ 6.39 (d, *J* = 2.1 Hz, 0.50H), 6.32 (d, *J* = 2.1 Hz, 0.50H), 6.09 (d, *J* = 2.1 Hz, 0.50H), 6.03 (d, *J* = 2.2 Hz, 0.50H), 5.73 – 5.62 (m, 1H), 4.91 – 4.85 (m, 0.50H), 4.84 – 4.79 (m, 1H), 4.77 (s, 0.50H), 4.74 (s, 0.50H), 4.68 (d, *J* = 15.0 Hz, 0.50H), 4.21 – 4.15 (m, 0.50H), 4.06 (d, *J* = 14.5 Hz, 0.50H), 3.85 (d, *J* = 14.5 Hz, 0.50H), 3.68 (t, *J* = 6.3 Hz, 2H), 3.53 (d, *J* = 15.0 Hz, 0.50H), 2.53 (s, 0.50H), 2.49

(s, 0.50H), 2.25 – 2.12 (m, 1H), 1.89 – 1.78 (m, 1.50H), 1.72 – 1.63 (m, 3.50H), 1.63 – 1.51 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H).

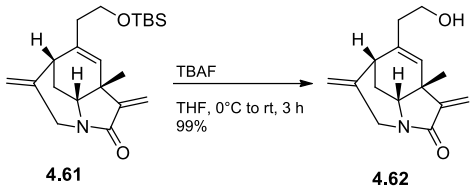
^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 166.27, 166.25, 146.48, 145.98, 131.29, 130.97, 130.56, 130.17, 129.60, 128.78, 110.76, 109.95, 96.21, 96.10, 61.23, 61.17, 53.27, 48.67, 47.19, 43.44, 39.71, 39.60, 38.39, 38.04, 37.39, 37.28, 28.23, 27.89, 26.03, 21.93, 21.77, 18.37, -5.20; **HRMS** (EI, m/z): Calculated for $C_{21}H_{34}O_2NISi$ ([M]+) 487.1398, found 487.1404; **MS** (EI, m/z (%)): 487.23 (47), 430.13 (100), 360.24 (44), 158.06 (29), 120.89 (53), 118.90 (82); analytically calculated for C 51.75, H 7.03, found C 51.76, H 7.09.



4.60 **4.61**

(3a*R*,6*S*,7a*R*)-5-(2-((tert-butyldimethylsily])oxy)ethyl)-3a-methyl-3,8-dimethylene-3a,6,7,7a-tetrahydro-1,6-ethanoindol-2(3H)-one. To a stirred solution of vinyl iodide **4.60** (895 mg, 1.84 mmol) in dimethylformamide (20 mL) was added triethylamine (1.28 mL, 9.18 mmol) and tetrakis(triphenylphosphine)palladium(0) (106 mg, 0.092 mmol) at room temperature. The mixture was heated to 100 °C and stirred for one hour. To the resulting black mixture, brine (100 mL) was added, then the mixture was extracted ten times with dichloromethane (10 mL), combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a crude residue which was purified by flash column chromatography (hexanes: ethyl acetate = 2:1 → 1:1) to yield lactam **4.61** (496 mg, 1.38 mmol, 75%) as a pale-yellow oil.

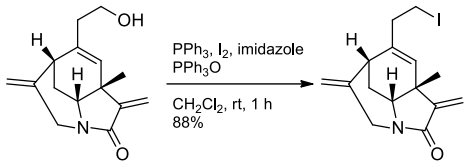
4.61: Rf 0.3 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{21}$ -61.7 (c 0.55, $CHCl_3$); **IR** (neat): ν_{max} = 3073, 2954, 2929, 2889, 2856, 1701, 1404, 1095, 836 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.20 (s, 1H), 4.86 – 4.76 (m, 3H), 4.58 (d, *J* = 16.4 Hz, 1H), 3.72 (d, *J* = 4.5 Hz, 1H), 3.70 – 3.60 (m, 3H), 2.88 (s, 1H), 2.26 – 2.06 (m, 3H), 1.79 (dd, *J* = 13.6, 3.5 Hz, 1H), 1.24 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.53, 148.57, 144.02, 138.38, 126.73, 112.93, 109.46, 61.78, 57.62, 47.96, 41.44, 38.00, 37.78, 26.03, 23.38, 18.50, 18.37, -5.20; **HRMS** (EI, m/z): Calculated for $C_{17}H_{24}O_2NSi$ ([M-C_4H_9]+) 302.1571, found 302.1566; **MS** (EI, m/z (%)): 302.19 (100).



4.61 4.62

(3a*R*,6*S*,*TaR*)-5-(2-hydroxyethyl)-3a-methyl-3,8-dimethylene-3a,6,7,7a-tetrahydro-1,6-ethanoindol-2(3H)-one.** To a stirred solution of silyl ether **4.61** (443 mg, 1.23 mmol) in tetrahydrofuran (12 mL) was added tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 1.85 mL, 1.85 mmol) dropwise at 0° C. The mixture was warmed to room temperature and allowed to stir for three hours. The reaction mixture was concentrated under reduced pressure and purified directly by flash column chromatography (EtOAc) to furnish alcohol **4.62** (299 mg, 1.22 mmol, 99%) as a pale rose oil.

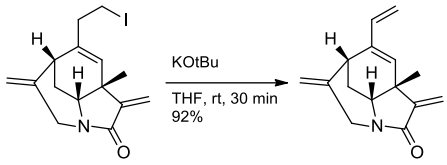
4.62: Rf 0.3 (silica, ethyl acetate); $[\alpha]_D^{21}$ -35.8 (c 0.96, $CHCl_3$); IR (neat): ν_{max} = 3410 (br.), 3073, 2957, 2934, 2896, 1678, 1660, 1417 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.22 (s, 1H), 4.89 – 4.75 (m, 3H), 4.57 (d, *J* = 16.4 Hz, 1H), 3.74 (d, *J* = 4.6 Hz, 1H), 3.70 – 3.59 (m, 3H), 2.83 (s, 1H), 2.31 – 2.07 (m, 3H), 1.87 (br. s, *J* = 13.0 Hz, 1H), 1.80 (dd, *J* = 13.7, 3.5 Hz, 1H), 1.26 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.50, 148.27, 143.76, 137.69, 127.16, 113.30, 109.78, 60.44, 57.58, 48.03, 41.38, 37.97, 37.84, 23.42, 18.49; **HRMS** (EI, m/z): Calculated for $C_{15}H_{19}O_2N$ ([M]+) 245.1410, found 245.1414; **MS** (EI, m/z (%)): 245.22 (26), 216.20 (17), 215.20 (100), 200.17 (15).



4.62 4.63

(3a*R*,6*S*,*T*a*R*)-5-(2-hydroxyethyl)-3a-methyl-3,8-dimethylene-3a,6,7,7a-tetrahydro-1,6-ethanoindol-2(3H)-one. To a stirred solution of alcohol **4.62** (300 mg, 1.22 mmol) in dichloromethane (12 mL) was added a spatula tip of triphenylphosphine oxide followed by imidazole (308 mg, 4.52 mmol) and triphenylphosphine (1.49 g, 1.96 mmol). The resulting mixture was stirred for ten minutes, then iodine (435 mg, 1.71 mmol) was added in one portion. The solution was stirred for one hour, then volatiles were removed, and the residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to furnish alkyl iodide **4.63** (383 mg, 1.08 mmol, 88%) as a colourless oil.

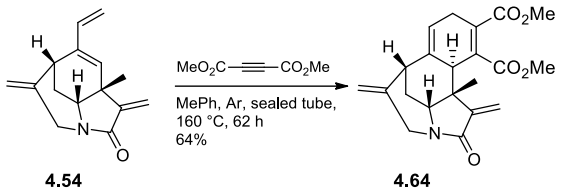
4.63: Rf 0.4 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{21}$ -57.7 (c 0.55, $CHCl_3$); **IR** (neat): ν_{max} = 3069, 2959, 2937, 2891, 1693, 1661, 1405 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (s, 1H), 5.23 (s, 1H), 4.89 – 4.73 (m, 3H), 4.59 (d, *J* = 16.5 Hz, 1H), 3.74 (d, *J* = 4.7 Hz, 1H), 3.66 (dt, *J* = 16.5, 2.3 Hz, 1H), 3.29 – 3.12 (m, 2H), 2.78 (s, 1H), 2.62 – 2.39 (m, 2H), 2.13 (ddd, *J* = 13.6, 5.1, 2.2 Hz, 1H), 1.83 (dd, *J* = 13.6, 3.4 Hz, 1H), 1.28 (s, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.32, 147.98, 143.83, 139.31, 127.65, 113.45, 109.76, 57.45, 48.04, 41.35, 38.73, 37.32, 23.39, 18.31, 3.63; **HRMS** (EI, m/z): Calculated for $C_{15}H_{18}ONI$ ([M]+) 355.0428, found 355.0426; **MS** (EI, m/z (%)): 355.03 (100), 228.13 (97), 200.10 (59); analytically calculated for C 50.72, H 5.11, found C 50.78, H 5.10.



4.63 **4.54**

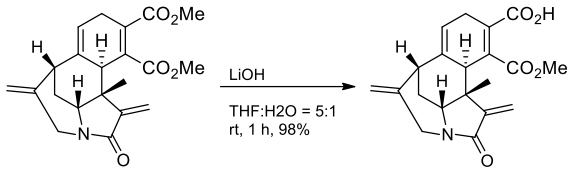
(3a*R*,6*S*,*T*a*R*)-5-(2-hydroxyethyl)-3a-methyl-3,8-dimethylene-3a,6,7,7a-tetrahydro-1,6-ethanoindol-2(3H)-one. To a stirred solution of alkyl iodide **4.63** (374 mg, 1.05 mmol) in tetrahydrofuran (10 mL) at 0 °C was dropwise added a solution of potassium tert-butoxide (1.0 M in tetrahydrofuran, 1.58 mL, 1.58 mmol). The mixture was stirred for 30 minutes at 0 °C, then water (10 mL) saturated aqueous ammonium chloride (10 mL) and ethyl acetate (10 mL) was added. The organic phase was removed, and the aqueous phase was extracted three times with ethyl acetate (20 mL). The combined organics were dried over magnesium sulphate, filtered, and concentrated yielding a crude residue which was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to yield diene **4.54** (221 mg, 0.971 mmol, 92%) as a white to pale yellow solid (m.p. 73-75 °C, CH_2Cl_2).

4.54: Rf 0.4 (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ 123.2 (c 1.02, $CHCl_3$); **IR** (neat): ν_{max} = 3085, 3004, 2960, 2937, 2893, 1695, 1659, 1410 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.91 (s, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.26 (s, 1H), 5.15 – 5.04 (m, 2H), 4.98 – 4.91 (m, 1H), 4.85 (s, 1H), 4.56 (d, *J* = 16.3 Hz, 1H), 3.78 (d, *J* = 4.4 Hz, 1H), 3.70 (dt, *J* = 16.3, 2.4 Hz, 1H), 3.38 (s, 1H), 2.19 (ddd, *J* = 13.7, 5.1, 2.4 Hz, 1H), 1.81 (dd, *J* = 13.8, 3.4 Hz, 1H), 1.29 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.19, 147.90, 143.80, 138.97, 137.76, 131.81, 113.95, 113.60, 110.64, 57.75, 48.05, 41.78, 32.85, 23.45, 18.53; **HRMS** (EI, m/z): Calculated for $C_{15}H_{17}ON$ ([M]+) 227.1305, found 227.1304; **MS** (EI, m/z (%)): 228.17 (16), 227.17 (100), 212.15 (20).



(3a*R*,5*S*,9a*R*,9b*R*)-dimethyl 9b-methyl-1,10-dimethylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-3,5-ethanobenzo[e]indole-8,9-dicarboxylate. Diene **4.54** (85 mg, 0.374 mmol) in toluene (1.5 mL) in a pressure tube was sparged with argon for ten minutes, was treated with dienophile (65 µL, 0.53) sealed, and heated to 160 °C (oil bath temperature). The mixture was stirred at this temperature for 62 hours, then volatiles were evaporated, and the resulting reside was purified directly by flash column chromatography (hexanes: ethyl acetate = 1:1 ⟶ 1:2) to yield Diels-Alder abduct **4.64** (88 mg, 0.238 mmol, 64%) as a white foam.

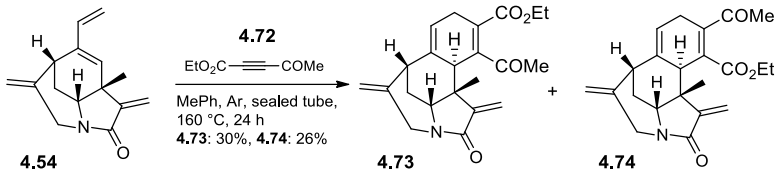
4.64: Rf 0.3 (silica, hexanes: ethyl acetate = 1:2); $[\alpha]_D^{22}$ +180.3° (c 0.83, $CHCl_3$); **IR** (neat): ν_{max} = 3077, 2950, 2990, 2874, 1725, 1699, 1258 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.82 (s, 1H), 5.69 – 5.64 (m, 1H), 5.09 (s, 1H), 5.03 (s, 1H), 4.90 (s, 1H), 4.53 (d, *J* = 15.4 Hz, 1H), 3.75 (d, *J* = 16.0 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.47 (d, *J* = 2.5 Hz, 1H), 3.34 (t, *J* = 7.5 Hz, 1H), 3.28 (s, 1H), 3.13 (ddd, *J* = 23.2, 8.4, 2.6 Hz, 1H), 2.84 (ddd, *J* = 23.2, 6.6, 4.2 Hz, 1H), 2.21 (dt, *J* = 14.1, 3.7 Hz, 1H), 1.82 (dt, *J* = 14.2, 2.1 Hz, 1H), 1.17 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.11, 168.92, 167.24, 150.55, 143.50, 137.28, 137.02, 130.92, 117.46, 113.96, 113.28, 61.36, 54.25, 52.32, 51.62, 44.19, 43.03, 39.65, 27.48, 26.16, 12.73; **HRMS** (EI, m/z): Calculated for $C_{21}H_{23}O_5N$ ([M]+) 369.1571, found 369.1570; **MS** (EI, m/z (%)): 369.18 (15), 337.13 (100) 322.11 (61), 251.16 (60), 155.23 (31), 141.22 (36), 127.20 (45), 113.19 (56).



4.64 4.66

(3a*R*,5*S*,9a*R*,9b*R*)-9-(methoxycarbonyl)-9b-methyl-1,10-dimethylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-3,5-ethanobenzo[e]indole-8-carboxylic acid. To diester **4.64** (11 mg, 0.030 mmol) in tetrahydrofuran: water = 1:1 (2 mL) was added lithium hydroxide monohydrate (6 mg, 0.14 mmol) at room temperature. The mixture was stirred for 90 minutes, then the volatiles were removed *in vacuo* and the remaining aqueous layer was acidified with 10% phosphoric acid to ca. pH 3. The aqueous phase was extracted four times with ethyl acetate (1 mL), combined organic phases were dried over magnesium sulphate, filtered, and concentrated, furnishing acid **4.66** (10 mg) as a white oil.

4.66: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.71 – 5.65 (m, 1H), 5.10 (s, 1H), 5.06 (s, 1H), 4.91 (s, 1H), 4.54 (d, *J* = 15.5 Hz, 1H), 3.75 (d, *J* = 15.6 Hz, 1H), 3.60 (s, 3H), 3.51 – 3.45 (m, 1H), 3.34 (t, *J* = 7.5 Hz, 1H), 3.29 (s, 1H), 3.12 (ddd, *J* = 23.2, 8.4, 2.4 Hz, 1H), 2.91 (ddd, *J* = 23.2, 6.7, 4.2 Hz, 1H), 2.21 (dt, *J* = 14.0, 3.6 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.19 (s, 3H).

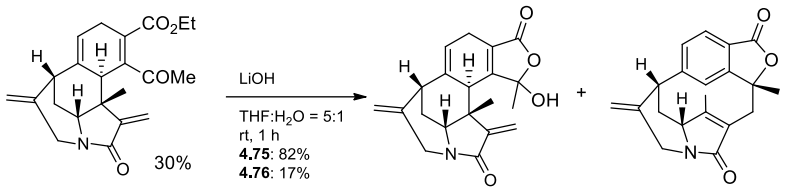


(3a*R*,5*S*,9a*R*,9b*R*)-ethyl-9-acetyl-9b-methyl-1,10-dimethylene-2-oxo-1,2,3a,4,5,7,9a ,9b-octahydro-3,5-ethanobenzo[e]indole-8-carboxylate; and **(3aR,5S,9aR,9bR)-ethyl-8-acetyl-9b-methyl-1,10-dimethylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-3,5-ethano benzo[e]indole-9-carboxylate.** Diene **4.54** (25 mg, 0.073 mmol) in toluene (1 mL) in a pressure tube was sparged with argon for ten minutes, treated with dienophile (19 mg, 0.13 mmol), sealed, and heated to 160 °C (oil bath temperature). The mixture was stirred at this temperature for 12 hours then it was cooled to room temperature and the flask was charged with another 19 mg (0.13 mmol) of dienophile. The mixture was heated back up to 160 °C and stirred for another 12 hours. The next morning, the volatiles were evaporated, and the resulting reside was purified directly by flash column chromatography (silica, hexanes: ethyl acetate = 1:1 ⟶ 1:2) to yield Diels-Alder adducts **4.73** (8 mg, 0.022 mmol, 30%), **4.74** (7 mg, 0.019 mmol, 26%) both as pale-yellow oils, and recovered diene **4.54** (9 mg, 0.026, 36%).

4.73: Rf 0.3 (silica, hexanes: ethyl acetate = 1:2); **IR** (neat): ν_{max} = 3072, 2979, 2961, 2932, 2904, 2873, 1691, 1256 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.90 (s, 1H), 5.73 – 5.68 (m, 1H), 5.13 (s, 1H), 5.02 (s, 1H), 4.94 (s, 1H), 4.56 (d, *J* = 15.4 Hz, 1H), 4.18 – 4.06 (m, 2H), 3.76 (dd, *J* = 15.4, 0.7 Hz, 1H), 3.48 (d, *J* = 2.9 Hz, 1H), 3.30 (s, 1H), 3.26 (t, *J* = 7.5 Hz, 1H), 3.13 (ddd, *J* = 23.1, 8.4, 2.6 Hz, 1H), 2.81 (ddd, *J* = 23.0, 6.6, 4.2 Hz, 1H), 2.21 (dt, *J* = 14.3, 3.8 Hz, 1H), 2.16 (s, 3H), 1.83 (dt, *J* = 14.3, 2.2 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.16 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 205.79, 172.42, 167.18, 149.70, 146.79, 143.82, 136.79, 127.96, 118.32, 116.85, 113.82, 61.47, 61.27, 54.66, 44.13, 43.24, 37.94, 29.68, 27.35, 26.01, 13.80, 12.57; **HRMS** (EI, m/z): Calculated for $C_{22}H_{25}O_4N$ ([M]+) 367.1778, found 367.1780; **MS** (EI, m/z (%)): 367.16 (13), 322.08 (23) 321.08 (100), 149.06 (25).

4.74: Rf 0.3 (silica, hexanes/ethyl acetate = 1:2); **IR** (neat): ν_{max} = 3076, 2979, 2963, 2933, 2902, 2873, 1699, 1254 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.68 – 5.65 (m, 1H), 5.11 (s, 1H), 4.99 (s, 1H), 4.91 (s, 1H), 4.55 (d, *J* = 15.5 Hz, 1H), 4.10 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.88 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.76 (dd, *J* = 15.4, 0.7 Hz, 1H), 3.47 (d, *J* = 2.3 Hz, 1H), 3.39 (t, *J* = 7.0 Hz, 1H), 3.30 (s, 1H), 3.11 (ddd, *J* = 22.8, 7.8, 2.5 Hz, 1H), 2.77 (ddd, *J* = 22.9, 6.2, 4.1 Hz, 1H), 2.26 (s, 3H), 2.23 (dt, *J* = 14.2, 3.6 Hz, 1H), 1.81 (dt, *J* = 14.2, 2.2 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.12 (s, 3H).**^{13}C NMR** (151 MHz, $CDCl_3$) δ 203.40, 172.07, 168.43, 151.12, 143.52, 142.75, 138.51, 130.38, 116.64, 114.00, 112.44, 61.21, 61.12, 54.68, 44.26, 43.12, 38.52, 28.77, 27.95, 26.64, 13.69, 12.74; **HRMS** (EI, m/z): Calculated for $C_{22}H_{25}O_4N$ ([M]+) 367.1778, found 367.1781; **MS** (EI, m/z (%)): 367.16 (3), 322.11 (23) 321.11 (100), 293.11 (17), 215.09 (35), 149.03 (18).



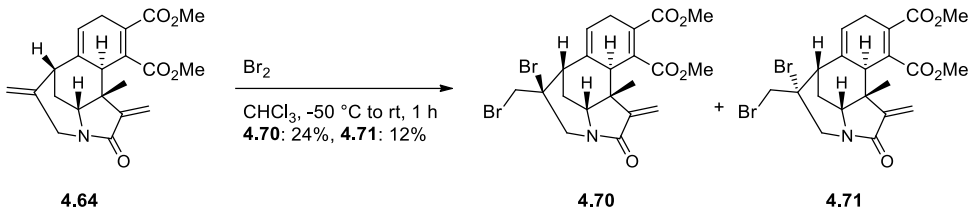
4.73 **4.75** **4.76**

(6*S*,7a*R*,10a*R*,10b*R*)-1-hydroxy-1,10a-dimethyl-10,12-dimethylene-6,7,7a,10,10a,10b-hexahydro-6,8-ethanoisobenzofuro[4,5-e]indole-3,9(1H,4H)-dione; and **(6*S*,10*R*,13-a*R*)-11,13a-dimethyl-7-methylene-7,8,13,13a-tetrahydro-2H-3,5-(epiethane[1,2]-diyli-dene)-6,10:9,12-dimethanofuro[2,3-f][1]azacyclododecine-2,14(6H,10H)-dione.** To keto-ester **4.73** (7 mg, 0.019 mmol) in tetrahydrofuran: water = 1:1 (1 mL) was added lithium hydroxide monohydrate (4 mg, 0.10 mmol) at room temperature. The mixture was stirred for 60 minutes, then the volatiles were removed *in vacuo* and the remaining aqueous layer was acidified with 10% phosphoric acid to ca. pH 3. The aqueous phase was extracted four times with ethyl acetate (1 mL), and the combined organic phases were dried over magnesium sulphate, filtered, and concentrated. The resulting residue was purified by column chromatography (silica, ethyl acetate) furnishing hydroxy-lactone **4.75** (5 mg, 0.019 mmol, 82%) and macrocycle **4.76** (1 mg, 0.003 mmol, 17%) both as off-white films.

4.75: Rf 0.2 (silica, dichloromethane: methanol = 95:5); $[\alpha]_D^{20}$ +145.7° (c 0.19, $CHCl_3$); **IR** (neat): ν_{max} = 3306 (br.), 3078, 2982, 2955, 2928, 22875, 2247, 1756, 1680, 1661, 1415, 907, 730 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.84 – 5.79 (m, 1H), 5.38 (s, 1H), 5.10 (s, 1H), 4.91 (s, 1H), 4.56 (d, *J* = 15.4 Hz, 1H), 3.77 (d, *J* = 15.5 Hz, 1H), 3.55 (d, *J* = 2.9 Hz, 1H), 3.42 (s, 1H), 3.38 (s, 1H), 3.22 (t, *J* = 7.6 Hz, 1H), 2.91 (dt, *J* = 7.2, 3.5 Hz, 2H), 2.25 (dt, *J* = 14.2, 3.8 Hz, 1H), 1.89 (dt, *J* = 14.2, 2.1 Hz, 1H), 1.56 (s, 3H), 1.21 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.79, 169.70, 158.16, 150.55, 143.68, 138.29, 130.26, 119.16, 116.01, 113.89, 106.14, 61.96, 54.25, 43.89, 43.19, 38.27, 25.57, 24.99, 22.40, 13.42; **HRMS** (EI, m/z): Calculated for $C_{20}H_{21}O_4N$ ([M]+) 339.1465, found 339.1465; **MS** (EI, m/z (%)): 339.10 (14), 321.09 (37), 211.20 (38), 197.18 (46), 183.16 (54), 169.15 (64), 155.15 (71), 141.14 (81), 127.12 (90), 113.10 (100), 111.09 (43).

4.76: Rf 0.3 (silica, dichloromethane: methanol = 95:5); $[\alpha]_D^{20}$ +6.3° (c 0.14, $CHCl_3$); **IR** (neat): ν_{max} = , 2979, 2963, 2933, 2902, 2873, 1699, 1254 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 5.43 (s, 1H), 5.21 (s, 1H), 4.94 (d, *J* = 16.5 Hz, 1H), 4.18 (s, 1H), 4.09 (d, *J* = 9.2 Hz, 1H), 3.97 (d, *J* = 16.4 Hz, 1H), 3.17 (d, *J* = 14.1 Hz, 1H), 2.57 (d, *J* = 14.2 Hz, 1H), 2.39 (ddd, *J* = 14.4, 9.3, 4.6 Hz, 1H), 2.07 (s, 3H), 1.69 (dd, *J* = 14.7, 1.9 Hz, 1H), 1.02 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.98, 169.93, 156.25, 153.75, 151.30, 142.87, 133.30, 128.28, 126.66, 125.69, 123.29, 116.37, 90.24, 59.93, 44.87, 42.86, 39.36, 29.64, 24.54, 11.44; **HRMS** (EI, m/z): Calculated for $C_{22}H_{19}O_3N$ ([M]+) 321.1359, found 321.1363; **MS** (EI, m/z (%)): 321.15 (3), 303.17 (20) 302.16 (96), 220.19 (44), 205.17 (100), 84.01 (30).



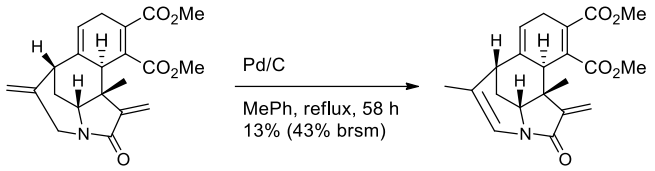
4.64 4.70 4.71

(3a*R*,5*S*,9a*R*,9b*R*,10*S*)-dimethyl 10-bromo-10-(bromomethyl)-9b-methyl-1-methylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-5,3-ethanobenzo[e]indole-8,9-dicarboxylate; and **(3a*R*,5*S*,9a*R*,9b*R*,10*R*)-dimethyl 10-bromo-10-(bromomethyl)-9b-methyl-1-methylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-5,3-ethanobenzo[e]-indole-8,9-dicarboxylate.** To diester **4.64** (8.0 mg, 0.022 mmol) in chloroform (1 mL) at -50 °C was added a 10% (m/m) solution of bromine in chloroform (0.02 mL, 0.025 mmol) dropwise. The mixture was allowed to warm to room temperature over one hour, then it was stirred overnight. The next morning, the reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1 mL), and the resulting mixture was thrice extracted with dichloromethane (1 mL). The combined organics were dried over magnesium sulfate, filtered, concentrated and the remaining crude residue was purified by column chromatography (silica, hexanes: ethyl acetate = 1:1) yielding dibromides **4.70** (2.7 mg, 0.0051 mmol, 24%) and **4.71** (1.4 mg, 0.0026 mmol, 12%) as colourless films.

4.70: Rf 0.4 (silica, hexanes: ethyl acetate = 1:2); **IR** (neat): ν_{max} = 2997, 2950, 2876, 1726, 1705, 1259, 731 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 – 5.85 (m, 1H), 5.83 (s, 1H), 5.08 (s, 1H), 4.64 (d, J = 15.0 Hz, 1H), 3.77 (d, J = 15.1 Hz, 1H), 3.74 (s, 3H), 3.73 – 3.67 (m, 2H), 3.64 (s, 3H), 3.52 (d, J = 4.3 Hz, 1H), 3.50 – 3.47 (m, 1H), 3.27 (dd, J = 8.9, 7.5 Hz, 1H), 3.16 (ddd, J = 23.5, 8.9, 2.9 Hz, 1H), 2.92 (ddd, J = 23.6, 7.5, 4.1 Hz, 1H), 2.47 (ddd, J = 14.5, 4.5, 2.7 Hz, 1H), 1.90 (ddd, J = 14.0, 3.8, 0.9 Hz, 1H), 1.21 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.14, 168.66, 166.45, 150.33, 137.19, 131.13, 129.56, 126.09, 113.68, 69.18, 60.65, 53.20, 52.78, 52.47, 51.83, 48.32, 42.06, 41.64, 27.64, 25.02, 15.27, 11.99**; HRMS** (EI, m/z): Calculated for $C_{21}H_{23}O_5NBr_2$ ([M]+) 526.9937, found 526.9943; **MS** (EI, m/z (%)): 337.02 (100), 321.99 (56), 251.01 (40), 148.96 (47).

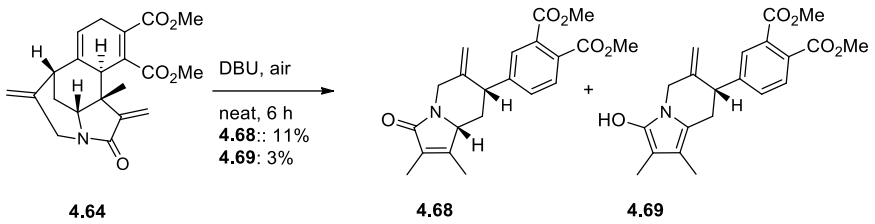
4.71: Rf 0.4 (silica, hexanes: ethyl acetate = 1:2); **IR** (neat): ν_{max} = 2991, 2951, 2931, 2876, 1724, 1705, 1259, 731 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.88 – 5.85 (m, 1H), 5.83 (s, 1H), 5.08 (s, 1H), 4.64 (d, J = 15.0 Hz, 1H), 3.77 (d, J = 15.1 Hz, 1H), 3.74 (s, 3H), 3.73 – 3.67 (m, 2H), 3.64 (s, 3H), 3.52 (d, J = 4.3 Hz, 1H), 3.50 – 3.47 (m, 1H), 3.27 (dd, J = 8.9, 7.5 Hz, 1H), 3.16 (ddd, J = 23.5, 8.9, 2.9 Hz, 1H), 2.92 (ddd, J = 23.6, 7.5, 4.1 Hz, 1H), 2.47 (ddd, J = 14.5, 4.5, 2.7 Hz, 1H), 1.90 (ddd, J = 14.0, 3.8, 0.9 Hz, 1H), 1.21 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.14, 168.66, 166.45, 150.33, 137.19, 131.13, 129.56, 126.09, 113.68, 69.18, 60.65, 53.20, 52.78, 52.47, 51.83, 48.32, 42.06, 41.64, 27.64, 25.02, 15.27, 11.99**; HRMS** (EI, m/z): Calculated for $C_{21}H_{23}O_5NBr_2$ ([M]+) 526.9937, found 526.9940; **MS** (EI, m/z (%)): 526.91 (3), 496.83 (42), 448.95 (32), 415.93 (30), 337.03 (100), 322.00 (66), 251.02 (42), 148.96 (54), 147.98 (85), 121.96 (49).



4.64 **4.67**

(3a*R*,5*S*,9a*R*,9b*R*)-dimethyl 9b,10-dimethyl-1-methylene-2-oxo-1,2,3a,4,5,7,9a,9b-octahydro-3,5-ethenobenzo[e]indole-8,9-dicarboxylate: To diester **4.64** (8.0 mg, 0.022 mmol) in toluene (0.5 mL) under atmosphere of argon, was added a spatula tip of palladium on carbon. The mixture was heated to reflux and allowed to stir at that temperature for 48 hours. Next, the volatiles were evaporated *in vacuo*, and the resulting residue was dissolved in ethyl acetate and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica, hexanes: ethyl acetate = 1:1) yielding recovered **4.64** (5.5 mg, 0.015 mmol, 69%) and the isomer **4.67** (1.0 mg, 0.003 mmol, 13%, 43% brsm) as a colourless film.

4.67: Rf 0.7 (silica, hexanes: ethyl acetate = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 1.4 Hz, 1H), 5.91 (s, 1H), 5.69 – 5.66 (m, 1H), 5.11 (s, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.42 – 3.38 (m, 1H), 3.30 – 3.24 (m, 1H), 3.15 (ddd, *J* = 23.2, 8.5, 2.6 Hz, 1H), 2.84 (ddd, *J* = 23.2, 6.7, 4.3 Hz, 1H), 2.78 (dd, *J* = 5.0, 2.8 Hz, 1H), 2.04 (ddd, *J* = 13.2, 3.1, 1.9 Hz, 1H), 1.98 (ddd, *J* = 13.0, 3.7, 3.1 Hz, 1H), 1.69 (d, *J* = 1.5 Hz, 3H), 1.16 (s, 3H).

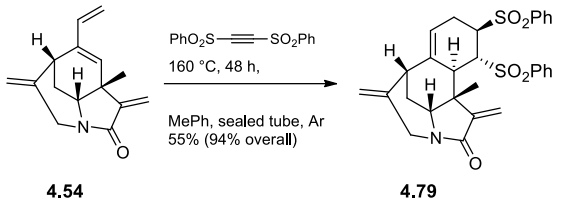


4.64 4.68 4.69

(*S*)-dimethyl-4-(3-hydroxy-1,2-dimethyl-6-methylene-5,6,7,8-tetrahydroindolizin-7-yl)phthalate; and **dimethyl 4-((7*S*,8a*R*)-3-hydroxy-1,2-dimethyl-6-methylene-3,5,6,7, 8,8a -hexahydroindolizin-7-yl)phthalate:** A mixture of diester **4.64** (12.4 mg, 0.0336 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.2 mL) was stirred under atmosphere of air for six hours. The mixture was then taken up in saturated aqueous ammonium chloride (1.5 mL) and the resulting suspension was extracted four times with ethyl acetate (1 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure, yielding a crude residue which was purified by sequential column chromatography (silica, 1:1 = hexanes: ethyl acetate) and preparatory thin layer chromatography (silica, 1:1 = hexanes: ethyl acetate) yielding aminohydrin **4.69** (0.4 mg, 0.001 mmol, 3%) and conjugated amide **4.68** (1.4 mg, 0.0038 mmol, 11%) both as off-white films.

4.69: **Rf 0.5** (silica, hexanes: ethyl acetate = 1:1); **IR** (neat) ν_{max} = 3235 (br.), 2953, 2924, 2853, 1727, 1703, 1686, 1435, 1291 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.33 – 7.30 (m, 1H), 5.06 (s, 1H), 4.74 (d, J = 14.5 Hz, 1H), 4.18 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (d, J = 13.5 Hz, 1H), 3.75 (d, J = 14.6 Hz, 1H), 2.32 (dd, J = 13.6, 3.9 Hz, 1H), 1.92 (s, 3H), 1.87 – 1.80 (m, 4H).

4.68: **Rf 0.5** (silica, hexanes: ethyl acetate = 1:1); **IR** (neat) ν_{max} = 2952, 2920, 2853, 1727, 1681, 1435, 1291 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 1.1 Hz, 1H), 7.34 (dd, *J* = 8.0, 1.3 Hz, 1H), 5.03 (s, 1H), 4.84 (d, *J* = 14.6 Hz, 1H), 4.16 (s, 1H), 3.93 – 3.88 (m, 7H), 3.68 (d, *J* = 14.4 Hz, 1H), 3.62 (d, *J* = 12.0 Hz, 1H), 2.30 (dt, *J* = 12.2, 3.4 Hz, 1H), 1.92 (s, 3H), 1.83 (s, 3H), 1.44 (dd, *J* = 24.6, 12.3 Hz, 1H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.82, 168.03, 167.70, 148.39, 147.17, 144.85, 144.60, 143.96, 132.60, 131.23, 129.33, 128.95, 112.38, 61.33, 52.73, 52.68, 47.15, 45.84, 36.89, 11.60, 8.67; **HRMS** (EI, m/z): Calculated for $C_{21}H_{23}O_5N$ ([M]+) 369.1571, found 369.1572; **MS** (EI, m/z (%)): 369.25 (25), 337.20 (44), 322.17 (24), 251.22 (30), 163.16 (51), 149.15 (100), 105.12 (63).

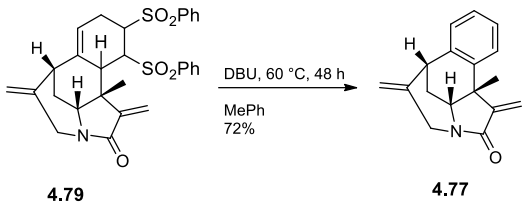


4.54 **4.79**

(3a*R*,5*S*,8*R*,9*R*,9a*R*,9b*R*)-9b-methyl-1,10-dimethylene-8,9-bis(phenylsulfonyl)-1,4,5,7,8,9,9a,9b-octahydro-3,5-ethanobenzo[e]indol-2(3aH)-one. Diene **4.54** (10.5 mg, 0.0462 mmol) and trans-1,2-bis(phenylsulfonyl)ethene (15.7 mg, 0.0508 mmol) in a pressure tube was dissolved in toluene (2 mL) and sparged with argon for 20 minutes. The apparatus was sealed, heated to 160 °C (oil bath temperature) and kept at that temperature for 48 hours. The volatiles were then evaporated under reduced pressure, and the resulting residue was purified by sequential column chromatography (silica, 1:1 = hexanes: ethyl acetate) and preparatory thin layer chromatography (silica, 1:1 – hexanes: ethyl acetate) to furnish trans-1,2-disulfonyl **4.79** (13.6 mg, 0.0254 mmol, 55%) and an inseparable mixture of stereoisomers of **4.79** (9.6 mg, 0.018 mmol, 39%, 94% overall) as colourless oils.

4.79: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:2); **IR** (neat) ν_{max} = 3066, 2927, 2811, 2243, 1697, 1665, 1307, 1143, 727 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.85 (m, 2H), 7.77 – 7.66 (m, 4H), 7.65 – 7.56 (m, 4H), 5.70 (dt, *J* = 5.4, 2.8 Hz, 1H), 5.16 (s, 1H), 5.11 (s, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 4.49 (d, *J* = 15.1 Hz, 1H), 4.42 – 4.36 (m, 1H), 4.07 (s, 1H), 3.75 (d, *J* = 15.1 Hz, 1H), 3.50 (d, *J* = 3.4 Hz, 1H), 3.33 (s, 1H), 2.81 (s, 1H), 2.47 – 2.31 (m, 2H), 2.19 (dt, *J* = 14.2, 3.8 Hz, 1H), 1.93 (d, *J* = 14.3 Hz, 1H), 1.36 (s, *J* = 13.2 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.13, 150.38, 144.16, 139.17, 137.29, 136.91, 134.31, 134.22, 129.92, 129.70, 129.67, 128.69, 116.92, 113.65, 113.28, 61.26, 57.15, 54.23, 51.97, 44.39, 43.40, 33.80, 24.25, 21.54, 15.79;

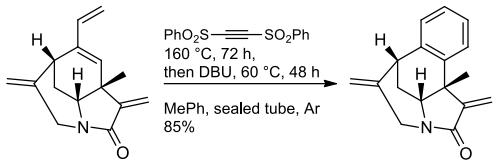
HRMS (EI, m/z): Calculated for $C_{29}H_{29}O_5NS_2$ ([M]+) 535.1482, found 535.1488; **MS** (EI, m/z (%)): 535.20 (1), 394.12 (54), 252.13 (100).



4.79 4.77

(3a*R*,5*S*,9b*R*)-9b-methyl-1,10-dimethylene-1,4,5,9b-tetrahydro-3,5-ethanobenzo[e]-indol -2(3aH)-one. To a mixture of stereoisomers of trans-1,2-disulfonyl **4.79** (21 mg, 0.039 mmol) in toluene (1.5 mL) sparged with argon for 15 minutes was added 1,8-diazabicyclo(5.4.0)undec-7-ene (35 µL, 0.24 mmol) at room temperature. The mixture was heated to 65 °C (oil bath temperature) and stirred for 24 hours. The volatiles were evaporated under reduced pressure, and the resulting crude residue was purified by column chromatography (silica, hexanes: ethyl acetate = 1:1) yielding pure aromatic lactam **4.77** (6.9 mg, 0.028, 72%) as a white crystalline solid (m.p. 125-127 °C, CH_2Cl_2).

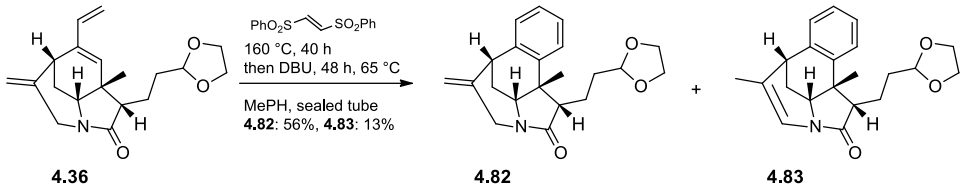
4.77: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ +27.5° (c 0.31, $CHCl_3$); **IR** (neat) ν_{max} = 3067, 3015, 2964, 2934, 2895, 2875, 1695, 1662, 1413, 761 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 3H), 7.12 – 7.08 (m, 1H), 5.87 (s, 1H), 5.50 (s, 1H), 5.09 (s, 1H), 4.82 (s, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 3.89 (d, *J* = 5.4 Hz, 1H), 3.78 (d, *J* = 16.4 Hz, 1H), 3.66 (s, 1H), 2.30 (ddd, *J* = 13.9, 5.4, 2.1 Hz, 1H), 2.10 (dd, *J* = 13.9, 3.5 Hz, 1H), 1.57 (s, *J* = 18.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.48, 150.52, 145.86, 139.18, 137.50, 129.19, 128.94, 127.78, 126.97, 112.52, 109.86, 58.62, 49.45, 41.17, 39.88, 22.59, 21.16; **HRMS** (EI, m/z): Calculated for $C_{17}H_{17}ON$ ([M]+) 251.1305, found 251.1308; **MS** (EI, m/z (%)): 251.26 (100), 236.23 (11), 142.21 (11), 69.30 (12).



4.54 **4.77**

(3a*R*,5*S*,9b*R*)-9b-methyl-1,10-dimethylene-1,4,5,9b-tetrahydro-3,5-ethanobenzo[e]indol-2(3aH)-one. Tetraene **4.54** (30 mg, 0.13 mmol) and trans-1,2-bis(phenylsulfonyl)ethene (45 mg, 0.15 mmol) in a pressure tube was dissolved in toluene (3 mL) and sparged with argon for 20 minutes. The apparatus was sealed, heated to 160 °C (oil bath temperature) and kept at that temperature for 72 hours. The apparatus was allowed to cool to room temperature, then 1,8-diazabicyclo(5.4.0)undec-7-ene (118 µL, 0.79 mmol) was added. The apparatus was again sealed, warmed to 60 °C and allowed to stir for 48 h. The resulting mixture was filtered through a pad of Celite which was washed with ethyl acetate (4 ml). The filtrate was concentrated, and the residue was purified by column chromatography (silica, hexanes: ethyl acetate = 1:1) to furnish lactam **4.77** (25 mg, 0.11 mmol, 85%) as a white crystalline solid (m.p. 125-127 °C).

4.77: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ +27.5° (c 0.31, $CHCl_3$); **IR** (neat) ν_{max} = 3067, 3015, 2964, 2934, 2895, 2875, 1695, 1662, 1413, 761 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 3H), 7.12 – 7.08 (m, 1H), 5.87 (s, 1H), 5.50 (s, 1H), 5.09 (s, 1H), 4.82 (s, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 3.89 (d, *J* = 5.4 Hz, 1H), 3.78 (d, *J* = 16.4 Hz, 1H), 3.66 (s, 1H), 2.30 (ddd, *J* = 13.9, 5.4, 2.1 Hz, 1H), 2.10 (dd, *J* = 13.9, 3.5 Hz, 1H), 1.57 (s, *J* = 18.7 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.48, 150.52, 145.86, 139.18, 137.50, 129.19, 128.94, 127.78, 126.97, 112.52, 109.86, 58.62, 49.45, 41.17, 39.88, 22.59, 21.16; **HRMS** (EI, m/z): Calculated for $C_{17}H_{17}ON$ ([M]+) 251.1305, found 251.1308; **MS** (EI, m/z (%)): 251.26 (100), 236.23 (11), 142.21 (11), 69.30 (12).

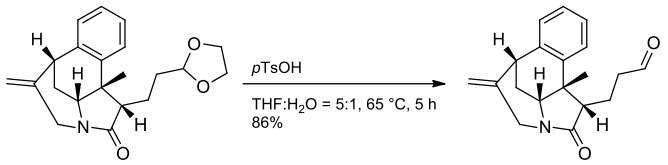


(1*S*,3a*R*,5*S*,9b*S*)-1-(2-(1,3-dioxolan-2-yl)ethyl)-9b-methyl-10-methylene-1,4,5,9b-tetrahydro-3,5-ethanobenzo[e]indol-2(3aH)-one and **(1*S*,3a*R*,5*S*,9b*S*)-1-(2-(1,3-dioxolan-2-yl)ethyl)-9b-methyl-10-methylene-1,4,5,9b-tetrahydro-3,5-ethanobenzo[e]indol-2(3aH)-one.** Triene **4.36** (200 mg, 0.634 mmol) and trans-1,2-bis(phenylsulfonyl)ethene (215 mg, 0.697 mmol) in a pressure tube was dissolved in toluene (6 mL) and sparged with argon for 20 minutes. The apparatus was sealed, heated to 160 °C (oil bath temperature) and kept at that temperature for 40 hours. The apparatus was allowed to cool to room temperature, then 1,8-diazabicyclo(5.4.0)undec-7-ene (0.57 mL, 3.80 mmol) was added. The apparatus was again sealed, warmed to 60 °C and allowed to stir for 48 h. The resulting mixture was concentrated, and the residue was purified by flash column chromatography (silica, hexanes: ethyl acetate = 1:1) to furnish lactam **4.82** (121 mg, 0.358 mmol, 46%) as a yellow foam and lactam **4.83** (29 mg, 0.084 mmol, 13%) as colourless crystals (m.p. 128-132 °C).

4.82: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ -91.6° (c 0.33, $CHCl_3$); **IR** (neat) ν_{max} = 3065, 2956, 2927, 2972, 1694, 1412, 1142 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 – 7.08 (m, 4H), 5.07 (s, 1H), 4.92 (dd, J = 4.9, 4.3 Hz, 1H), 4.79 (s, 1H), 4.58 (d, J = 16.5 Hz, 1H), 4.04 – 3.92 (m, 2H), 3.92 – 3.79 (m, 3H), 3.64 – 3.53 (m, 2H), 2.52 (dt, J = 16.8, 8.4 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.22 (ddd, J = 13.7, 5.4, 2.2 Hz, 1H), 1.98 (dd, J = 13.7, 3.6 Hz, 1H), 1.85 – 1.70 (m, 2H), 1.64 – 1.54 (m, 1H), 1.49 (s, J = 11.0 Hz, 3H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.40, 146.95, 140.72, 135.51, 130.12, 129.55, 126.84, 126.48, 109.11, 104.81, 65.02, 64.95, 59.59, 53.56, 50.18, 40.50, 39.99, 32.83, 23.73, 22.85, 20.52; **HRMS** (EI, m/z): Calculated for $C_{21}H_{25}O_3N$ ([M]+) 339.1829, found 339.1823; **MS** (EI, m/z (%)): 339.07 (17), 267.05 (100), 166.90 (58), 148.84 (98).

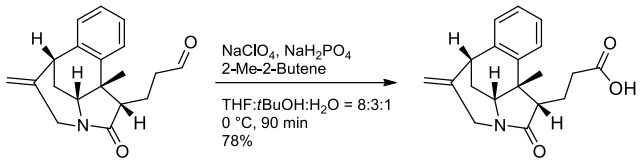
4.83: **Rf 0.5** (silica, hexanes: ethyl acetate = 1:1); $[\alpha]_D^{20}$ -154.6° (c 1.34, $CHCl_3$); **IR** (neat) ν_{max} = 3059, 2958, 2929, 2875, 1699, 1390, 1141 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.18 – 7.13 (m, 1H), 7.13 – 7.08 (m, 2H), 6.32 (d, J = 1.3 Hz, 1H), 4.95 (dd, J = 5.3, 3.9 Hz, 1H), 4.03 – 3.94 (m, 2H), 3.94 – 3.84 (m, 2H), 3.81 (dd, J = 5.7, 1.5 Hz, 1H), 3.22 – 3.18 (m, 1H), 2.70 (dd, J = 9.4, 4.4 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.19 (dd, J = 12.8, 3.9 Hz, 1H), 1.97 (ddd, J = 12.8, 5.9, 2.1 Hz, 1H), 1.91 (d, J = 1.6 Hz, 3H), 1.88 – 1.65 (m, 4H), 1.46 (s, J = 4.3 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.73, 137.58, 136.78, 131.86, 130.57, 129.28, 126.78, 126.44, 119.69, 104.79, 65.03, 64.96, 59.78, 56.05, 51.77, 39.76, 32.87, 27.39, 23.03, 20.75, 19.68; **HRMS** (EI, m/z): Calculated for $C_{21}H_{25}O_3N$ ([M]+) 339.1829, found 339.1828; **MS** (EI, m/z (%)): 338.91 (14), 266.95 (31), 250.92 (100), 166.93 (45), 152.93 (54).



4.82 4.84

3-((1*S*,3a*R*,5*R*,9b*S*,10*S*)-9b,10-dimethyl-2-oxo-1,2,3a,4,5,9b-hexahydro-5,3-ethanobenzo[e]indol-1-yl)propanal. The acetal **4.82** (94 mg, 0.28 mmol) was dissolved in tetrahydrofuran (4 mL) and water (1 mL), and *para*-toluenesulphonic acid (13 mg, 0.069 mmol) was added. The solution was heated to 65 °C and stirred for 5 hours, then it was cooled to room temperature and saturated aqueous sodium bicarbonate (2 mL) and water (2 mL) were added and the resulting biphasic mixture was extracted five times with ethyl acetate (5 mL). The combined organics were dried over magnesium sulphate, filtered, and concentrated to provide a crude residue which was purified by column chromatography (hexanes: ethyl acetate = 1:1 to furnish aldehyde **4.84** (70 mg, 0.24 mmol, 86%) as a white foam.

4.84: **Rf 0.4** (silica, hexanes: ethyl acetate = 1:2); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.81 (s, J = 13.7 Hz, 1H), 7.23 – 7.11 (m, 4H), 5.09 (s, 1H), 4.82 (s, J = 10.4 Hz, 1H), 4.56 (d, J = 16.5 Hz, 1H), 3.86 (d, J = 5.4 Hz, 1H), 3.63 – 3.57 (m, 2H), 3.04 (ddd, J = 18.5, 7.5, 5.7 Hz, 1H), 2.75 (dt, J = 15.1, 7.2 Hz, 1H), 2.50 (dd, J = 11.3, 2.7 Hz, 1H), 2.23 (ddd, J = 13.8, 5.4, 2.0 Hz, 1H), 2.09 (dtd, J = 13.6, 7.6, 3.1 Hz, 1H), 1.99 (dd, J = 13.8, 3.6 Hz, 1H), 1.63 – 1.55 (m, 1H), 1.52 (s, 3H); **^{13}C NMR** (151 MHz, CDCl3) δ 202.58, 176.36, 146.71, 140.75, 135.23, 129.97, 129.68, 127.03, 126.58, 109.34, 59.79, 52.77, 50.19, 42.79, 40.46, 39.97, 23.33, 22.90, 18.59; **HRMS** (EI, m/z): Calculated for $C_{19}H_{21}O_2N$ ([M]+) 295.1567, found 295.1570; **MS** (EI, m/z (%)): 295.02 (4), 267.04 (100).

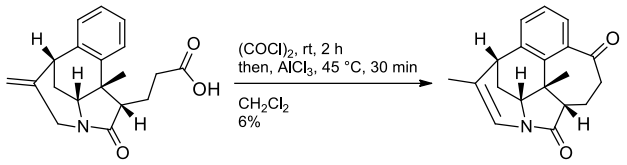


4.84 **4.88**

3-((1*S*,3a*R*,5*R*,9b*S*,10*S*)-9b,10-dimethyl-2-oxo-1,2,3a,4,5,9b-hexahydro-5,3-ethanobenzo[e]indol-1-yl)propanoic acid. To aldehyde **4.84** (65 mg, 0.22 mmol) in tetrahydrofuran (4 mL) , *tert*-butanol (1.5 mL), and water (0.5 mL) was added 2-Me-2-butene (0.19 mL, 1.76 mmol) and monobasic sodium phosphate monohydrate (91 mg, 0.66 mmol). The mixture was cooled to 0 °C and finely crushed sodium chlorite (75 mg, 0.66 mmol) was added. The mixture was stirred for 90 minutes at 0 °C, then saturated aqueous sodium thiosulfate (1.5 mL) was added and the resulting solution was stirred for ten minutes. The volatiles were removed *in vacuo* and the remaining aqueous phase was diluted with water (1 mL) and extracted five times with ethyl acetate (2 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to furnish a crude residue which was purified by column chromatography (hexanes: ethyl acetate: acetic acid = 1:2:0.01) to furnish the carboxylic acid **4.88** (54 mg, 0.17 mmol, 78%) as a colourless oil.

4.88: **Rf 0.1** (silica, hexanes: ethyl acetate: acetic acid = 1:2:0.01); **IR** (neat) ν_{max} = 3064 (br.), 2952, 2868, 2854, 1687, 1665, 1444, cm^{-1}; **^{1}H NMR** (300 MHz, CDCl3) δ 7.25 – 7.05 (m, 4H), 4.06 (dd, J = 13.4, 7.7 Hz, 1H), 3.82 (d, J = 5.4 Hz, 1H), 2.75 (ddd, J = 15.3, 7.7, 6.2 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.58 (dd, J = 11.3, 3.1 Hz, 1H), 2.44 (dd, J = 13.0, 10.4 Hz, 1H), 2.35 – 2.06 (m, 4H), 1.81 (dd, J = 13.9, 4.0 Hz, 1H), 1.72 – 1.57 (m, 1H), 1.52 (s, J = 2.9 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H);

HRMS (EI, m/z): Calculated for $C_{19}H_{23}O_3N$ ([M]+) 313.1672, found 313.1667; **MS** (EI, m/z (%)): 313.03 (44), 269.06 (72), 267.05 (50), 254.04 (59), 241.04 (100).

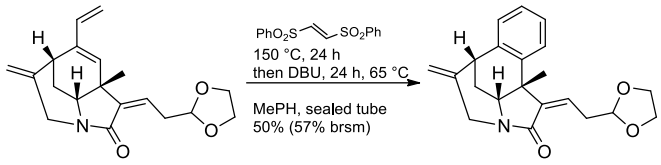


4.88 4.89

(2a*S*,2a1*S*,9*S*,10a*R*)-2a1,11-dimethyl-2a1,3,4,9,10,10a-hexahydro-2H-1-aza-1,9-ethenonaphtho[2,1,8-cde]azulene-2,5(2aH)-dione. To acid **4.88** (17 mg, 0.055 mmol) in dichloromethane (1 mL) was added a solution of oxalyl chloride in (2.0 M in dichloromethane, 0.11 mL, 0.22 mmol) dropwise at room temperature. The mixture was stirred at room temperature for two hours, then aluminum trichloride (29 mg, 0.22 mmol) was added in one portion and the resulting mixture was heated to reflux. After stirring for 45 minutes at reflux, the mixture was cooled to room temperature and saturated aqueous Rochelle's salt (5mL) was added. This biphasic mixture was stirred for several hours, then it was extracted five times with dichloromethane (2 mL). The combined organics were dried over magnesium sulfate, filtered and concentrated to furnish a crude residue which was purified by column chromatography (hexanes: ethyl acetate = 2:1 ⟶ 1:1) yielding ketone **4.98** (1 mg, 0.003 mmol, 6%) as a white film.

12: **Rf 0.4** (silica, hexanes: ethyl acetate = 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.3, 1.4 Hz, 1H), 7.28 – 7.22 (m, 2H), 6.41 (s, 1H), 3.86 (d, J = 5.4 Hz, 1H), 3.30 (s, 1H), 2.97 (dd, J = 11.5, 6.9 Hz, 1H), 2.87 (ddd, J = 19.7, 14.5, 2.1 Hz, 1H), 2.74 (ddd, J = 19.8, 4.8, 2.2 Hz, 1H), 2.37 (dt, J = 15.1, 7.0 Hz, 1H), 2.21 (dd, J = 13.0, 3.6 Hz, 1H), 2.01 (ddd, J = 12.7, 5.6, 1.9 Hz, 1H), 1.93 (s, 3H), 1.75 – 1.66 (m, 1H), 1.48 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.86, 179.61, 160.10, 141.90, 136.75, 136.74, 133.15, 128.59, 127.71, 119.92, 58.99, 53.45, 50.37, 39.54, 38.25, 26.75, 25.64, 23.03, 19.77; **HRMS** (EI, m/z): Calculated for $C_{19}H_{19}O_2N$ ([M]+) 292.1410, found 292.1410; **MS** (EI, m/z (%)): 292.97 (39), 179.95 (71), 165.98 (58), 164.98 (100), 151.98

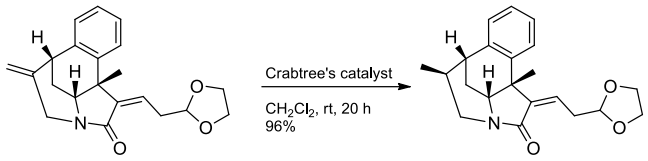


4.35 4.86

(3a*R*,5*S*,9b*R*,*E*)-1-(2-(1,3-dioxolan-2-yl)ethylidene)-9b-methyl-10-methylene-1,4,5,9b-tetrahydro-3,5-ethanobenzo[e]indol-2(3aH)-one. Tetraene **4.35** (730 mg, 2.33 mmol) and trans-1,2-(bisphenylsulfonyl)ethene (718 mg, 2.33 mmol) in a pressure tube was dissolved in toluene (25 mL) and sparged with argon for 20 minutes. The apparatus was sealed, heated to 150 °C (oil bath temperature) and kept at that temperature for 24 hours. The apparatus was allowed to cool to room temperature, then 1,8-diazabicyclo(5.4.0)undec-7-ene (2.09 mL, 14.0 mmol) was added. The apparatus was again sealed, warmed to 60 °C and allowed to stir for 24 h. The resulting mixture was concentrated, and the residue was purified by flash column chromatography (silica, hexanes: ethyl acetate = 2:1 ⟶ 1:1) to furnish unreacted starting material **4.35** (80 mg, 0.26 mmol, 13%) and lactam **4.86** (403 mg, 1.19 mmol, 50%, 57% based on recovered starting material) as an off-white solid (m.p. 139-140 °C) .

4.86: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); **IR** (neat) ν_{max} = 3066, 3013, 2963, 2937, 2887, 1686, 1403, 1135 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.20 – 7.11 (m, 3H), 7.11 – 7.05 (m, 1H), 6.09 (dd, J = 8.0, 6.8 Hz, 1H), 5.06 (s, 1H), 4.98 (t, J = 4.6 Hz, 1H), 4.80 (s, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.03 – 3.96 (m, 2H), 3.91 – 3.84 (m, 3H), 3.76 – 3.70 (m, 1H), 3.64 (s, 1H), 3.12 (ddd, J = 15.1, 8.2, 5.0 Hz, 1H), 3.00 (ddd, J = 15.2, 6.6, 4.3 Hz, 1H), 2.27 (ddd, J = 13.8, 5.4, 2.2 Hz, 1H), 2.08 (dd, J = 13.8, 3.4 Hz, 1H), 1.51 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.55, 146.25, 142.72, 139.06, 137.96, 129.09, 128.85, 127.63, 126.78, 126.09, 109.57, 103.86, 65.12, 65.10, 58.14, 49.91, 40.67, 39.92, 31.92, 22.70, 21.50; **HRMS** (EI, m/z): Calculated for $C_{21}H_{23}O_3N$ ([M]+) 337.1672, found 337.1667; **MS** (EI, m/z (%)): 336.99 (13), 193.99 (64), 149.00 (58), 125.08 (63), 113.08 (74), 111.07 (100).

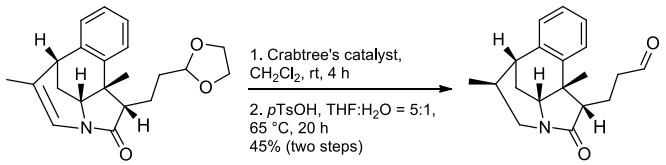


4.86 **4.87**

(3a*R*,5*R*,9b*R*,10*S*,*E*)-1-(2-(1,3-dioxolan-2-yl)ethylidene)-9b,10-dimethyl-1,4,5,9b-tetrahydro-5,3-ethanobenzo[e]indol-2(3aH)-one. To the aromatic compound **4.86** (99 mg, 0.293 mmol) in dichloromethane (5 mL) was added (1,5-Cyclooctadiene) (pyridine)(tricyclohexylphosphine)-iridium(I) hexafluorophosphate (Crabtree's catalyst) (5 mg, 0.005 mmol. The headspace was thrice purged and refilled with hydrogen, then the resulting mixture was stirred overnight. The next morning, the yellow solution was concentrated, and the resulting residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to cleanly provide the singly hydrogenated compound **4.87** (95 mg, 0.280 mmol, 96%) as a colourless oil.

4.87: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); **IR** (neat) ν_{max} = 3057, 3010, 2949, 2925, 2899, 2870, 1686, 1412, 1135 cm^{-1}; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.19 – 7.15 (m, J = 7.4 Hz, 1H), 7.12 (td, J = 14.9, 1.1 Hz, 1H), 7.07 (td, J = 14.9, 1.1 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 6.05 (dd, J = 8.1, 6.7 Hz, 1H), 4.97 (t, J = 4.6 Hz, 1H), 4.07 (dd, J = 13.5, 8.1 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.92 – 3.83 (m, 2H), 3.77 (d, J = 5.2 Hz, 1H), 3.13 (ddd, J = 15.1, 8.2, 5.0 Hz, 1H), 2.98 (ddd, J = 15.2, 6.5, 4.3 Hz, 1H), 2.67 (s, 1H), 2.51 (dd, J = 13.5, 10.4 Hz, 1H), 2.19 (ddd, J = 14.0, 5.2, 2.2 Hz, 1H), 2.17 – 2.10 (m, 1H), 1.87 (dd, J = 14.0, 3.6 Hz, 1H), 1.48 (s, J = 11.6 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.89, 143.10, 141.88, 138.03, 129.27, 128.82, 127.22, 126.83, 125.54, 103.89, 65.08, 65.07, 58.71, 49.61, 40.93, 39.25, 36.94, 31.86, 21.59, 20.08, 19.64; **HRMS** (EI, m/z): Calculated for $C_{21}H_{25}O_3N$ ([M]+) 339.1829, found 339.1829; **MS** (EI, m/z (%)): 338.99 (100), 267.10 (81), 241.01 (16), 219.04 (17).

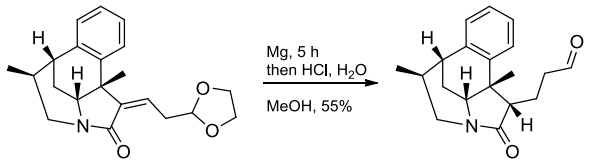


4.83 **4.85**

3-((1*S*,3a*R*,5*R*,9b*S*,10*S*)-9b,10-dimethyl-2-oxo-1,2,3a,4,5,9b-hexahydro-5,3-ethano-benzo[e]indol-1-yl)propanal. To the olefinic compound **4.83** (28 mg, 0.083 mmol) in dichloromethane (4 mL) was added (1,5-Cyclooctadiene)(pyridine)(tricyclohexyl-phosphine)-iridium(I) hexafluorophosphate (Crabtree's catalyst) (13 mg, 0.017 mmol. The headspace was thrice purged and refilled with hydrogen, then the resulting mixture was stirred for four hours. The yellow solution was concentrated, and the resulting residue was purified by flash column chromatography (hexanes: ethyl acetate = 1:1) to provide an inseparable mixture of aliphatic acetal and aliphatic free aldehyde (4.3:1) This mixture without further purification was dissolved in tetrahydrofuran (2.4 mL) and water (0.6 mL), and para-toluenesulphonic acid (3 mg, 0.014 mmol) was added. The solution was heated to 65 °C and stirred for 20 hours, then it was cooled to room temperature and saturated sodium bicarbonate (0.5 mL) and water (0.5 mL) were added and the resulting biphasic mixture was extracted five times with ethyl acetate (2 mL). The combined organics were dried over magnesium sulphate, filtered, and concentrated to provide a crude residue which was purified by column chromatography (hexanes: ethyl acetate = 1:1 to furnish aldehyde **4.85** as a colourless oil. (11 mg, 0.037 mmol, 45%) as a colourless oil.

4.85: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1);

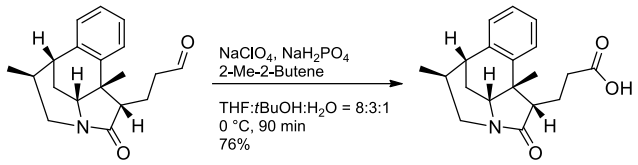
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.23 – 7.19 (m, 1H), 7.18 – 7.11 (m, 2H), 7.08 – 7.03 (m, 1H), 4.01 (dd, J = 13.5, 8.0 Hz, 1H), 3.77 (d, J = 5.4 Hz, 1H), 3.04 (ddd, J = 18.1, 7.4, 5.7 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.62 (s, 1H), 2.47 (dd, J = 11.2, 3.0 Hz, 1H), 2.39 (dd, J = 13.2, 10.7 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.16 (ddd, J = 13.9, 5.3, 2.1 Hz, 1H), 2.08 (dtd, J = 13.6, 7.6, 3.2 Hz, 1H), 1.78 (dd, J = 13.9, 3.8 Hz, 1H), 1.63 – 1.55 (m, 1H), 1.50 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 202.57, 175.63, 143.47, 135.17, 129.85, 129.45, 126.97, 126.09, 60.21, 52.69, 49.84, 42.74, 40.27, 39.71, 36.94, 23.35, 20.04, 19.69, 18.66.



3-((1*S*,3a*R*,5*R*,9b*S*,10*S*)-9b,10-dimethyl-2-oxo-1,2,3a,4,5,9b-hexahydro-5,3-ethanobenzo[e]indol-1-yl)propanal. To the unsaturated lactam **4.87** (25 mg, 0.074 mmol) in methanol (2 mL) was added magnesium turnings (27 mg, 1.1 mmol) in three portions over three hours with evolution of gas being observed shortly after each addition. The mixture was allowed to stir for an additional two hours, then it was acidified to approximately pH 2 by the addition of an aqueous solution of 3M hydrochloric acid. The resulting solution was stirred overnight, then water (2 ml) was added, and the biphasic mixture was extracted five times with ethyl acetate (1 ml). The organic washings were combined, dried over magnesium sulphate, filtered, and concentrated to furnish a crude residue which was purified by column chromatography (1hexanes: ethyl acetate = 1:1. To provide aldehyde **4.85** (12 mg, 0.040 mmol, 55%) as a colourless oil.

4.85: **Rf 0.3** (silica, hexanes: ethyl acetate = 1:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.23 – 7.19 (m, 1H), 7.18 – 7.11 (m, 2H), 7.08 – 7.03 (m, 1H), 4.01 (dd, J = 13.5, 8.0 Hz, 1H), 3.77 (d, J = 5.4 Hz, 1H), 3.04 (ddd, J = 18.1, 7.4, 5.7 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.62 (s, 1H), 2.47 (dd, J = 11.2, 3.0 Hz, 1H), 2.39 (dd, J = 13.2, 10.7 Hz, 1H), 2.27 – 2.20 (m, 1H), 2.16 (ddd, J = 13.9, 5.3, 2.1 Hz, 1H), 2.08 (dtd, J = 13.6, 7.6, 3.2 Hz, 1H), 1.78 (dd, J = 13.9, 3.8 Hz, 1H), 1.63 – 1.55 (m, 1H), 1.50 (s, 3H), 1.09 (d, J = 6.9 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 202.57, 175.63, 143.47, 135.17, 129.85, 129.45, 126.97, 126.09, 60.21, 52.69, 49.84, 42.74, 40.27, 39.71, 36.94, 23.35, 20.04, 19.69, 18.66.

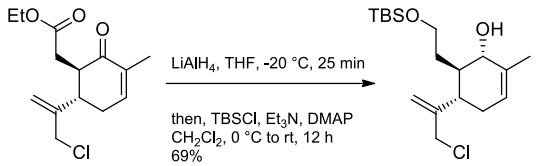


4.85 **4.90**

3-((1*S*,3a*R*,5*R*,9b*S*,10*S*)-9b,10-dimethyl-2-oxo-1,2,3a,4,5,9b-hexahydro-5,3-ethanobenzo[e]indol-1-yl)propanoic acid. To aldehyde **4.85** (10 mg, 0.034 mmol) in tetrahydrofuran (2 mL) , *tert*-butanol (0.75 mL), and water (0.25 mL) was added 2-Me-2-butene (30 µL, 0.10 mmol) and monobasic sodium phosphate monohydrate (14 mg, 0.10 mmol). The mixture was cooled to 0 °C and finely crushed sodium chlorite (11 mg, 0.10 mmol) was added. The mixture was stirred for 90 minutes, then saturated aqueous sodium thiosulfate (1 mL) was added and the resulting solution was stirred for ten minutes. The volatiles were removed *in vacuo* and the remaining aqueous phase was diluted with water (1 mL) and extracted five times with dichloromethane (2 mL). The combined organics were dried over magnesium sulfate, filtered, and concentrated to furnish a crude residue which was purified by column chromatography (hexanes: ethyl acetate: acetic acid = 1:2:0.01) to furnish the carboxylic acid **4.90** (9 mg, 0.029 mmol, 76%) as a colourless oil.

4.90: **Rf 0.1** (silica, hexanes: ethyl acetate: acetic acid = 1:2:0.01); **IR** (neat) ν_{max} = 3064 (br.), 2952, 2868, 2854, 1687, 1665, 1444, cm^{-1}; **^{1}H NMR** (300 MHz, CDCl3) δ 7.25 – 7.05 (m, 4H), 4.06 (dd, J = 13.4, 7.7 Hz, 1H), 3.82 (d, J = 5.4 Hz, 1H), 2.75 (ddd, J = 15.3, 7.7, 6.2 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.58 (dd, J = 11.3, 3.1 Hz, 1H), 2.44 (dd, J = 13.0, 10.4 Hz, 1H), 2.35 – 2.06 (m, 4H), 1.81 (dd, J = 13.9, 4.0 Hz, 1H), 1.72 – 1.57 (m, 1H), 1.52 (s, J = 2.9 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H);

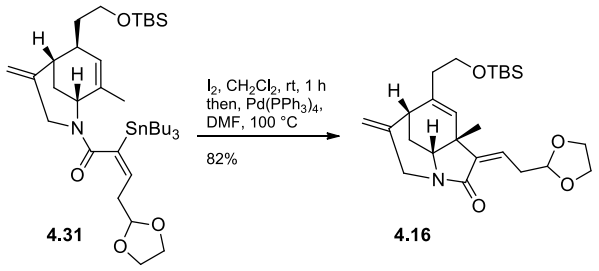
HRMS (EI, m/z): Calculated for $C_{19}H_{23}O_3N$ ([M]+) 313.1672, found 313.1667; **MS** (EI, m/z (%)): 313.03 (44), 269.06 (72), 267.05 (50), 254.04 (59), 241.04 (100).



4.24 **4.26**

(1*S*,5*S*,6*R*)-6-(2-((tert-butyldimethylsilyl)oxy)ethyl)-5-(3-chloroprop-1-en-2-yl)-2-methylcyclohex-2-en-1-ol. To a strongly stirred suspension of lithium aluminum hydride (2.37 g, 62.5 mmol) in tetrahydrofuran (100 mL) at -20 °C (salt/ice bath) was added dropwise a solution of chloro-ester **4.24** (5.64 g, 20.8 mmol) in tetrahydrofuran (30 mL) via a pressure equalizing funnel over ten minutes. The mixture was stirred for another 25 minutes at -20 °C, then the reaction was quenched by the sequential slow addition of water (3 mL), 15% sodium hydroxide (3 mL), and again water (5 mL). The resulting grey paste was stirred for 30 minutes, then anhydrous sodium sulphate was added and stirring was continued for another 30 minutes. The resulting white mixture was filtered through a short pad of Celite and chased with copious amounts of ethyl acetate. Concentration by rotary evaporation yielded a crude reside which was dissolved in dichloromethane (100 mL) and at 0° C was sequentially added triethylamine (3.19 mL, 22.9 mmol), dimethylaminopyridine (102 mg, 0.83 mmol), and *t*-butyldimethylsilylchloride (3.14 g, 20.8 mmol). The reaction was gradually allowed to warm to ambient temperature, stirred overnight, and then quenched by the addition of 75 mL of distilled water. The organic phase was removed, and the aqueous phase was extracted three times with 50 mL dichloromethane. The organic phases were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the crude residue. Purification by flash column chromatography (hexanes ⟶ hexanes: ethyl acetate = 19:1) yielded silyl ether **4.26** (4.91 g, 14.2 mmol, 68%) as a colourless oil.

4.26: $\boldsymbol{R_f}$ 0.4 (silica, hexanes: ethyl acetate = 4:1); $[\alpha]_D^{21}$ +6.4° (c 0.89, $CHCl_3$); **IR** (neat): ν_{max} = 3412 (br.), 3086, 3040, 2954, 2930, 2887, 2860, 776 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.49 – 5.44 (m, 1H), 5.29 (s, 1H), 5.04 (s, 1H), 4.33 (d, J = 3.5 Hz, 1H), 4.03 (s, 2H), 3.92 – 3.81 (m, 2H), 3.71 – 3.61 (m, 1H), 2.33 (td, J = 10.5, 5.4 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.95 – 1.79 (m, 2H), 1.77 (s, 3H), 1.49 – 1.35 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.95, 136.25, 122.34, 115.72, 75.34, 63.19, 47.57, 45.08, 43.36, 35.93, 32.80, 26.01, 19.74, 18.39, -5.28, -5.33; **HRMS** (EI, m/z): Calculated for $C_{18}H_{33}O_2ClSi$ $([M])^+$: 344.1933, found 344.1935; **MS** (EI, m/z): 344.08 (9), 233.02 (60), 211.97 (53), 194.97 (46), 177.00 (58), 159.00 (100), 118.91 (41); analytically calculated for C 62.67, H 9.64, found C 62.86, H 9.80.



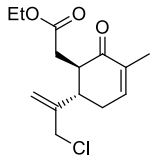
(3a*R*,6*S*,7a*R*,*Z*)-3-(2-(1,3-dioxolan-2-yl)ethylidene)-5-(2-((tert-butyldimethylsilyl) oxy)ethyl)-3a-methyl-8-methylene-3,3a,7,7a-tetrahydro-1,6-ethanoindol-2(6H)-one.

To the alkyl stannane **4.31** (552 mg, 0.750 mmol) in dichloromethane (10 mL) was added iodine (209 mg, 0.825 mmol) in three portions over 30 minutes. The blood red mixture was stirred for another 30 minutes, then 10% aqueous sodium bisulfite (5 mL) was added. The solution decolorized over ten minutes, then the organic phase was removed and the aqueous phase was extracted three times with dichloromethane (10 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a yellow oil which was dissolved in dimethylformamide (6 mL). To the solution was added triethylamine (0.52 mL, 3.75 mmol) and tetrakis(triphenylphosphine)palladium(0) (43 mg, 0.038 mmol). The mixture was heated to 100 °C and stirred for at that temperature for one hour. Next, the solution was cooled and distilled water (25 mL) was added. The resulting solution was extracted six times with diethyl ether (15 mL). The combined organics were washed with brine (10 mL), dried over magnesium sulfate, filtered, and concentrated to provide a crude residue which was purified by flash column chromatography (10% K_2CO_3 on silica; hexanes: ethyl acetate = 3:1) to furnish **4.16** as a yellow oil (274 mg, 0.615 mmol, 82%).

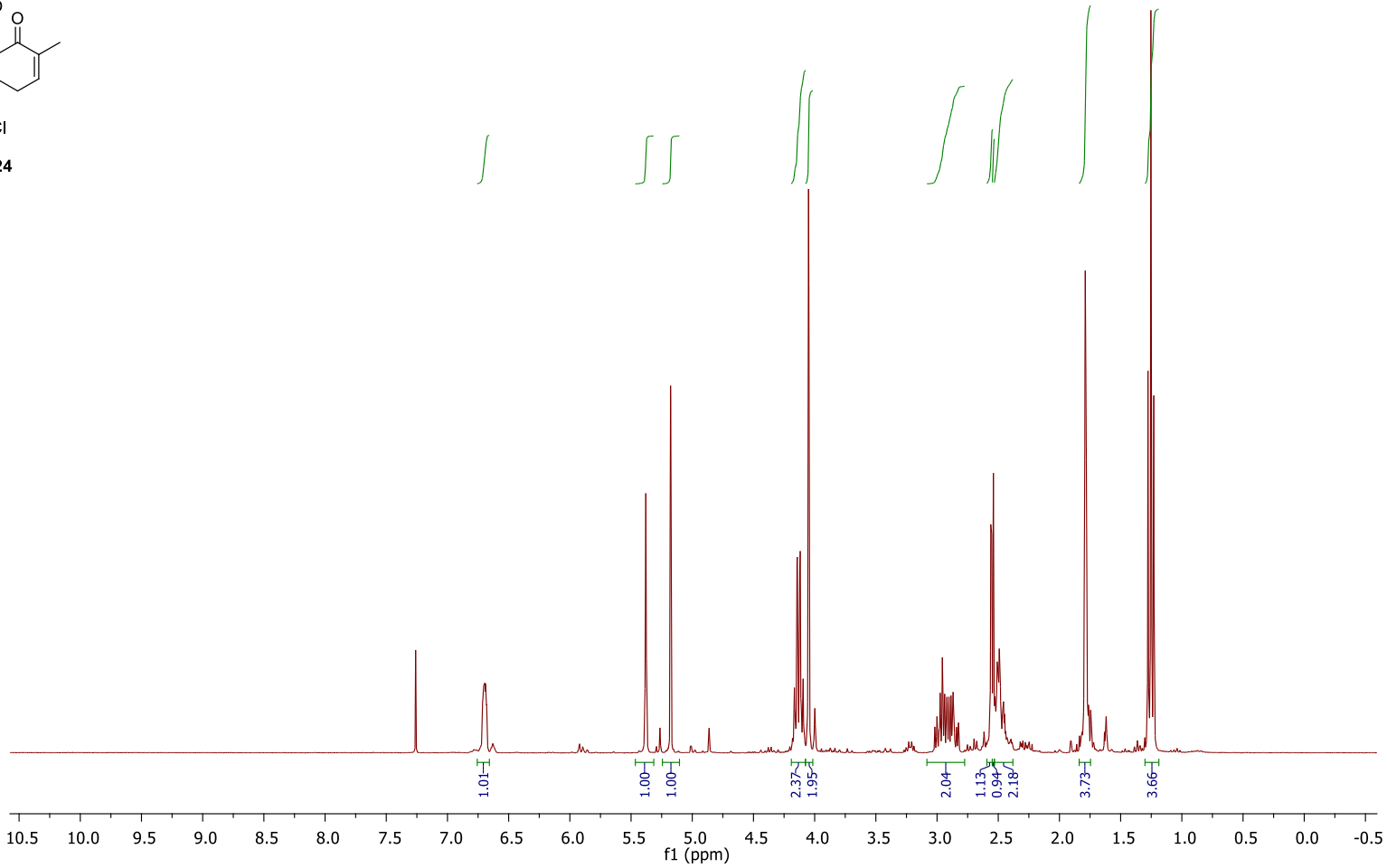
4.16: Rf 0.4 (silica, hexanes: ethyl acetate = 1:2); $[\alpha]_D^{21}$ -42.9° (c 0.13, $CHCl_3$); **IR** (neat): ν_{max} = 3073, 2955, 2931, 2888, 2859, 1693 cm^{-1};

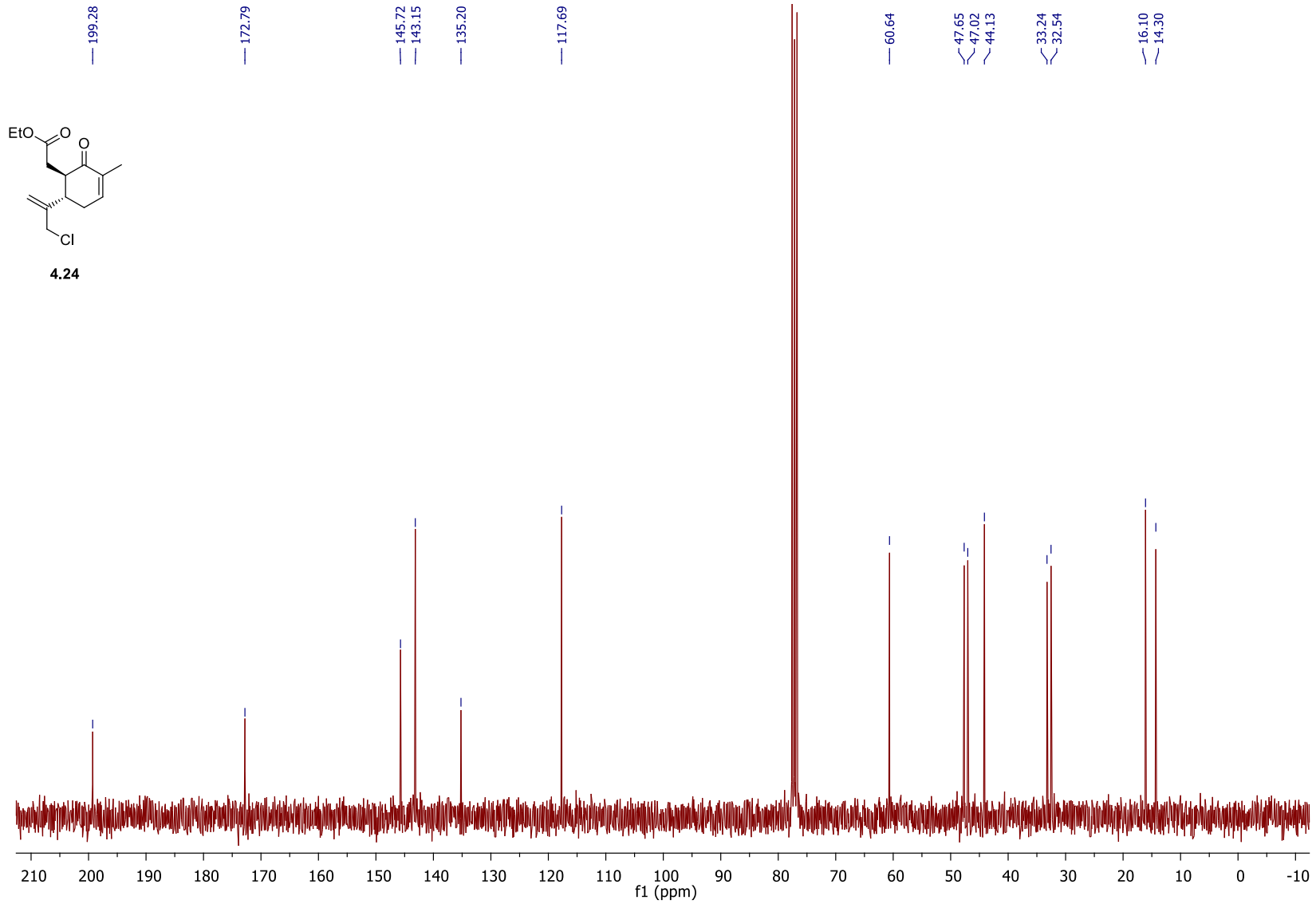
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (t, J = 7.2 Hz, 1H), 4.96 (t, J = 4.7 Hz, 1H), 4.79 (s, 3H), 4.56 (d, J = 16.4 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.89 – 3.83 (m, 2H), 3.69 (d, J = 4.6 Hz, 1H), 3.65 (td, J = 13.2, 3.5 Hz, 2H), 3.61 (d, J = 16.3 Hz, 1H), 3.13 (ddd, J = 15.0, 8.1, 5.0 Hz, 1H), 3.00 (ddd, J = 15.3, 6.4, 4.5 Hz, 1H), 2.85 (s, 1H), 2.23 – 2.16 (m, 1H), 2.15 – 2.09 (m, 1H), 2.07 (ddd, J = 13.5, 5.0, 1.9 Hz, 1H), 1.77 (dd, J = 13.6, 3.4 Hz, 1H), 1.19 (s, 3H), 0.87 (s, 9H), 0.03 (s, 6H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.68, 144.48, 140.75, 137.82, 127.14, 126.54, 109.21, 103.92, 65.11, 65.08, 61.85, 57.17, 48.47, 40.98, 38.02, 37.79, 32.03, 26.05, 23.52, 18.79, 18.39, -5.17; **HRMS** (EI, m/z): Calculated for $C_{25}H_{39}O_4NSi$ ([M]+) 445.2643, found 445.2645; **MS** (EI, m/z (%)): 445.36 (48), 388.25 (100), 316. 20 (43); analytically calculated for C 67.38, H 9.01, found C 67.42, H 9.01.

Selected Spectra



4.24

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145.72
143.15
135.20
117.69
60.64
47.65
47.02
44.13
33.24
32.54
16.10
14.30
EtO
O
O
Cl
4.24
210
200
190
180
170
160
150
140
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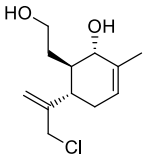
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


HO
OH
Cl

4.25

0.97
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1.06
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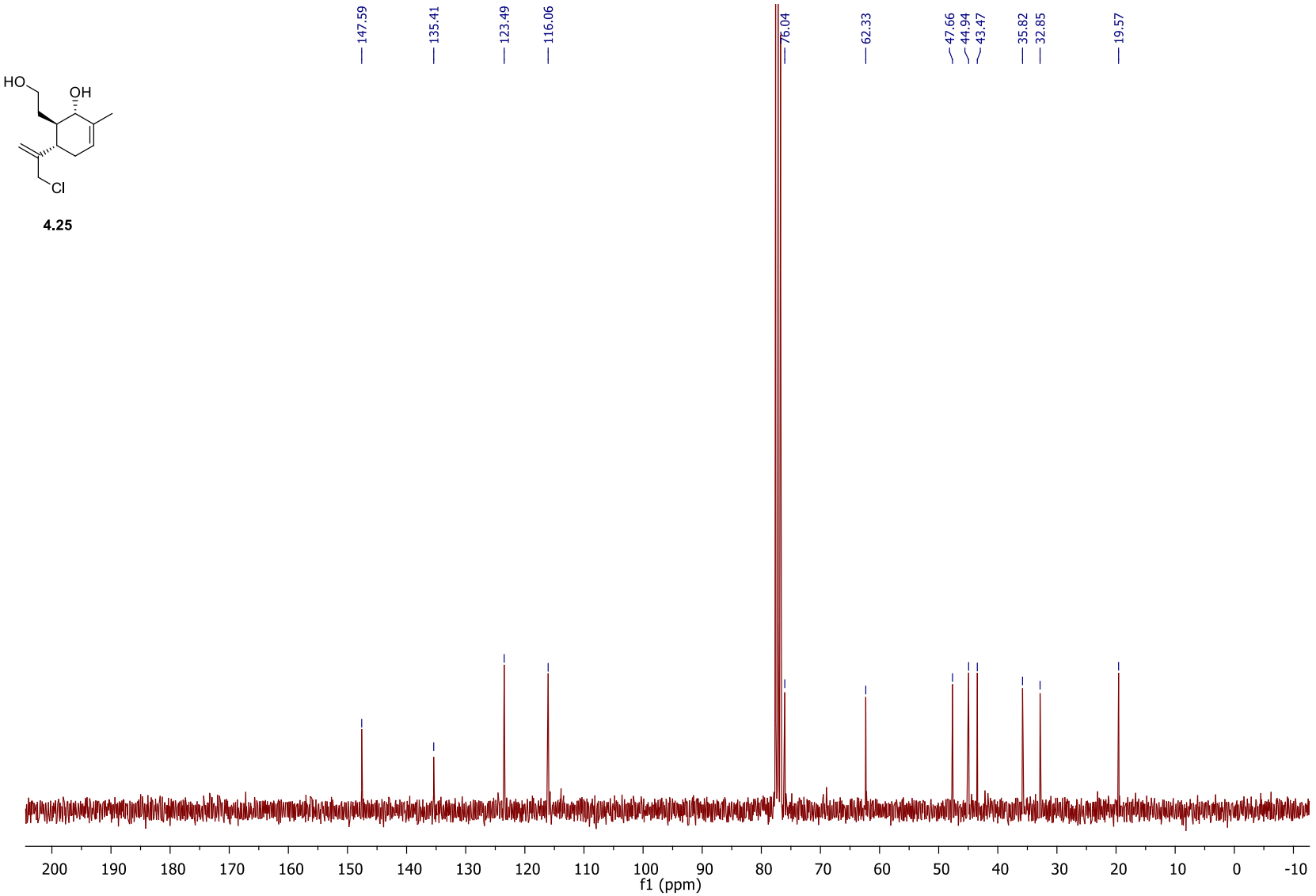
2.25
1.16
2.05
1.28
2.41
1.22
1.44
3.07
1.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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OH
Cl
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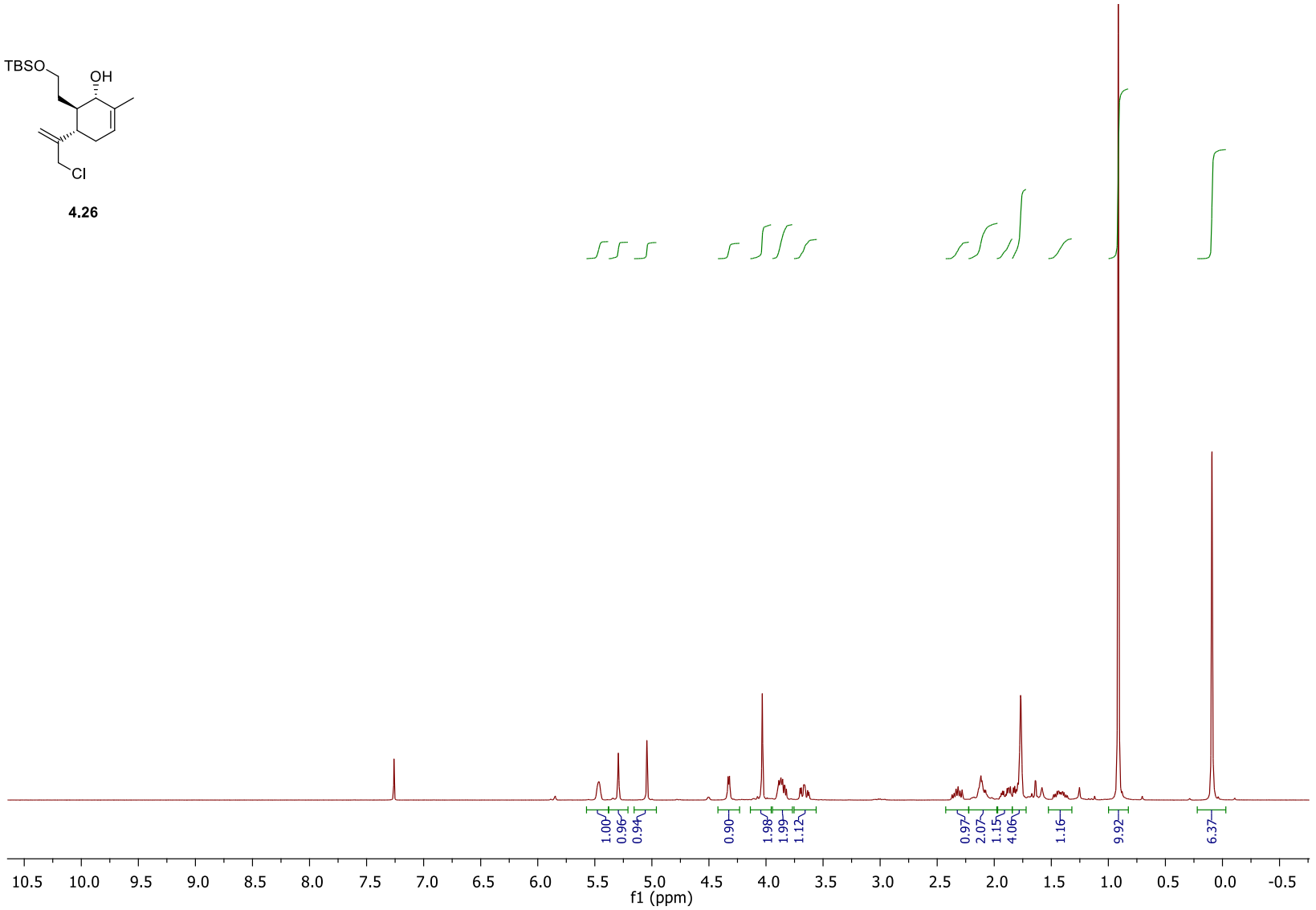
147.59
135.41
123.49
116.06
76.04
62.33
47.66
44.94
43.47
35.82
32.85
19.57
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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Cl
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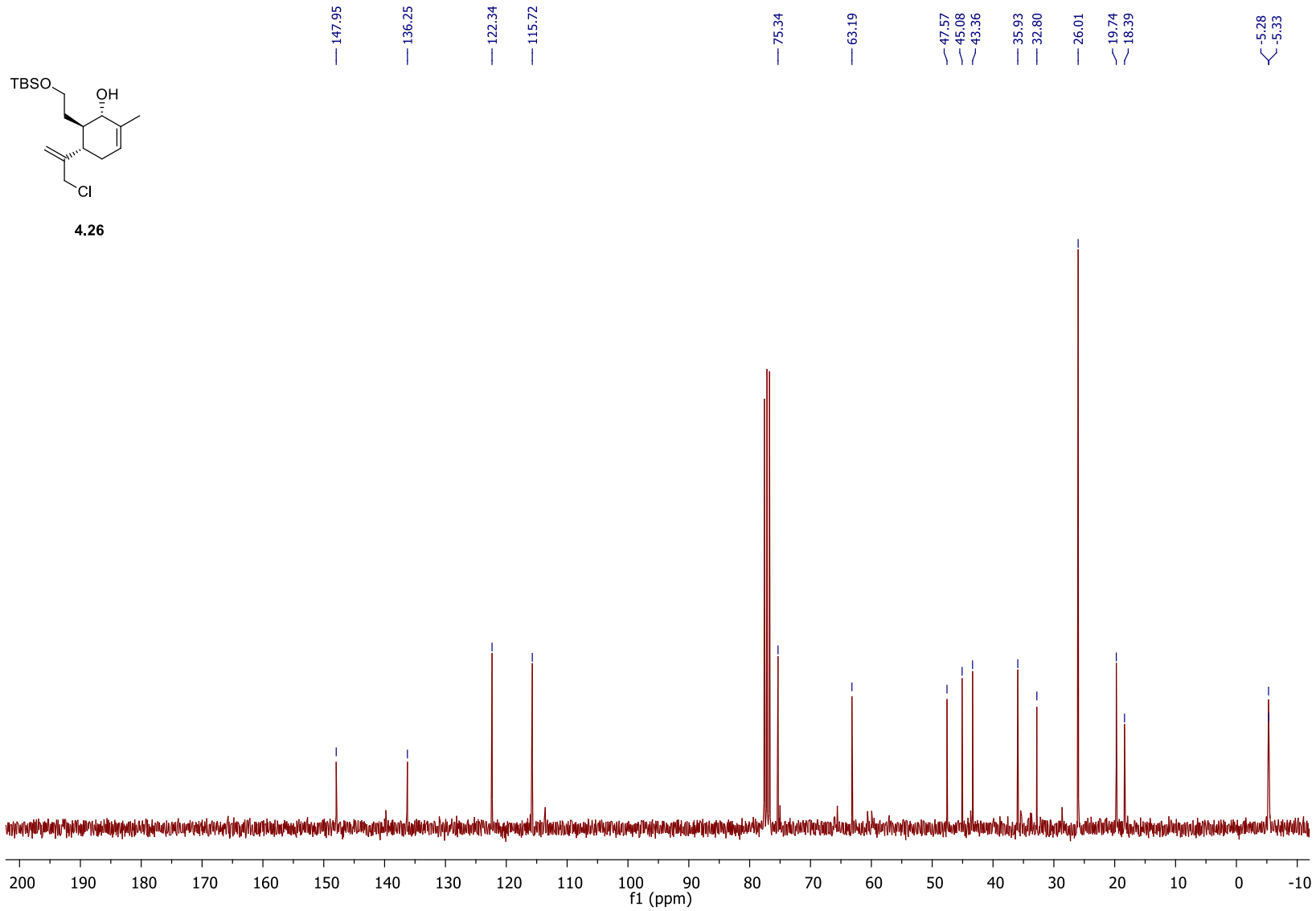
0.94
0.90
1.98
1.99
1.12
0.97
2.07
1.15
4.06
1.16
9.92
6.37
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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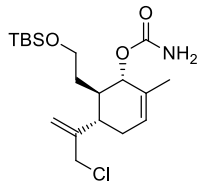
136.25
122.34
115.72
75.34
63.19
47.57
45.08
43.36
35.93
32.80
26.01
19.74
18.39
-5.28
-5.33
TBSO
OH
Cl
4.26
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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O
O
NH2
Cl

4.13

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1.18
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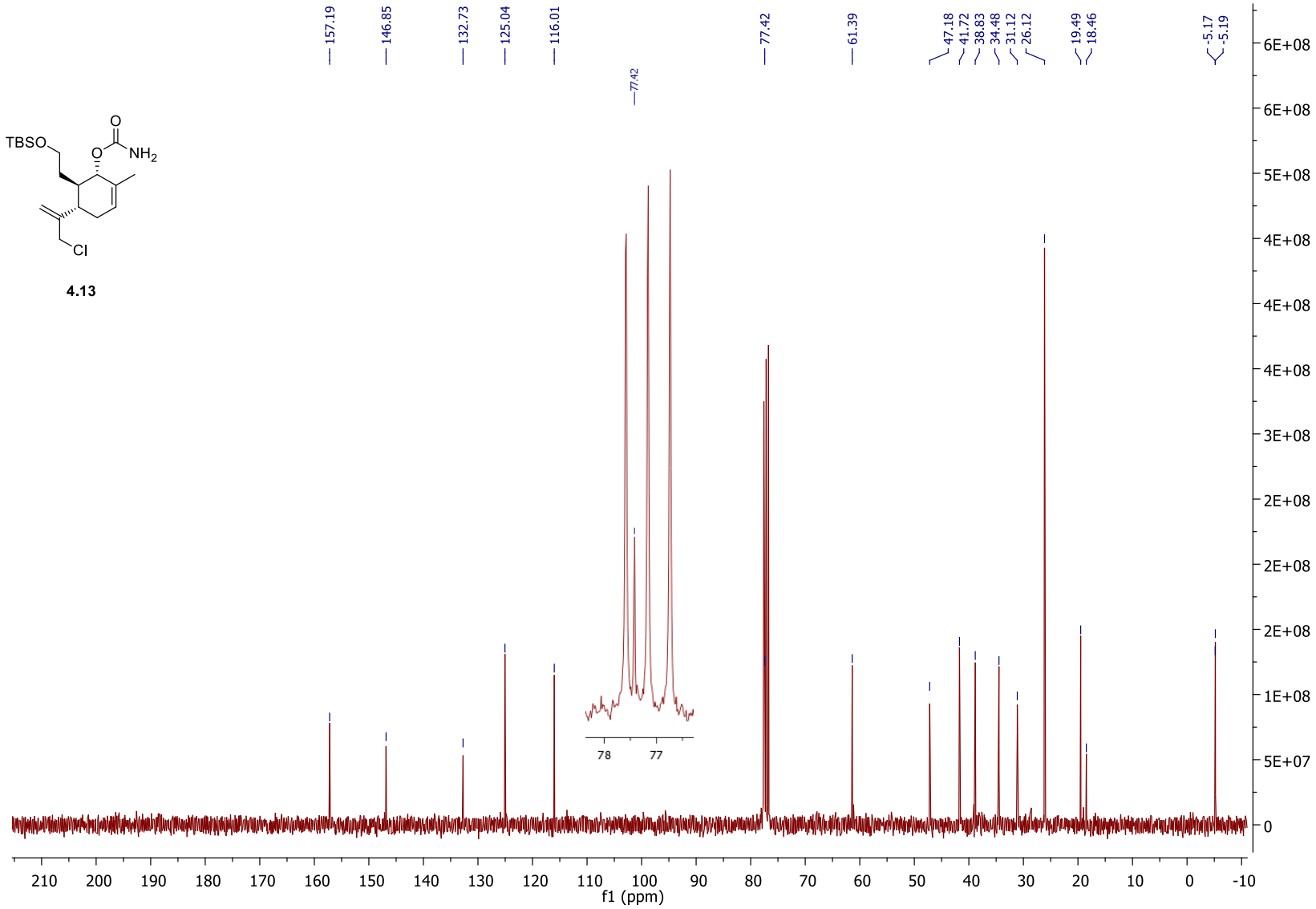
2.32
2.00
2.40
1.03
2.06
1.33
1.52
3.38
1.29
10.80
6.90
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


TBSO
O
O
NH2
Cl
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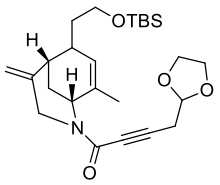
157.19
146.85
132.73
125.04
116.01
77.42
61.39
47.18
41.72
38.83
34.48
31.12
26.12
19.49
18.46
-5.17
-5.19
78
77
f1 (ppm)


OTBS
H
H
O
O
N
O

4.15

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4.62
4.37
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0.54
1.88
0.95
1.03
8.38
9.52
6.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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3.0
2.5
2.0
1.5
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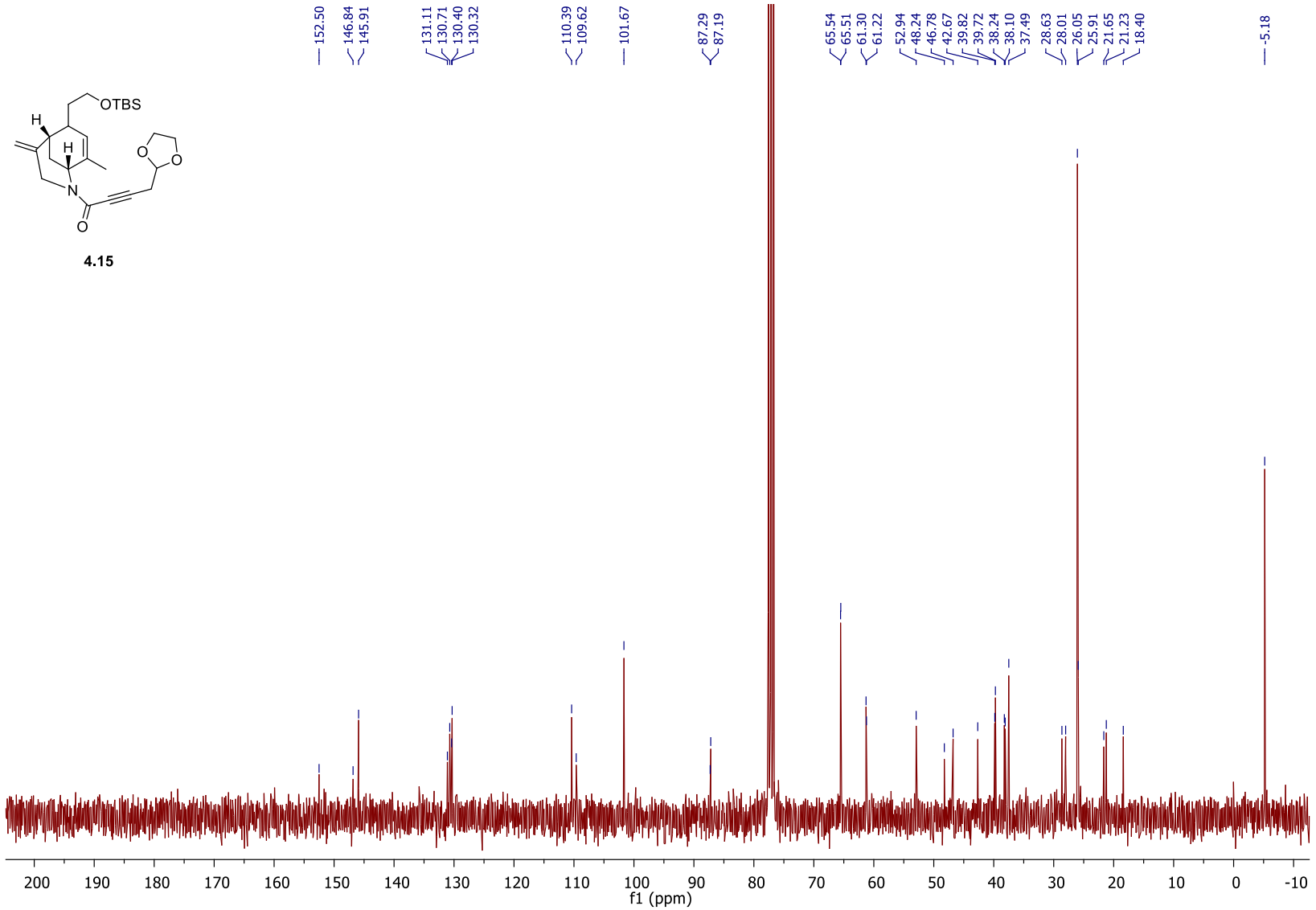
0.5
0.0
-0.5
f1 (ppm)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130.40
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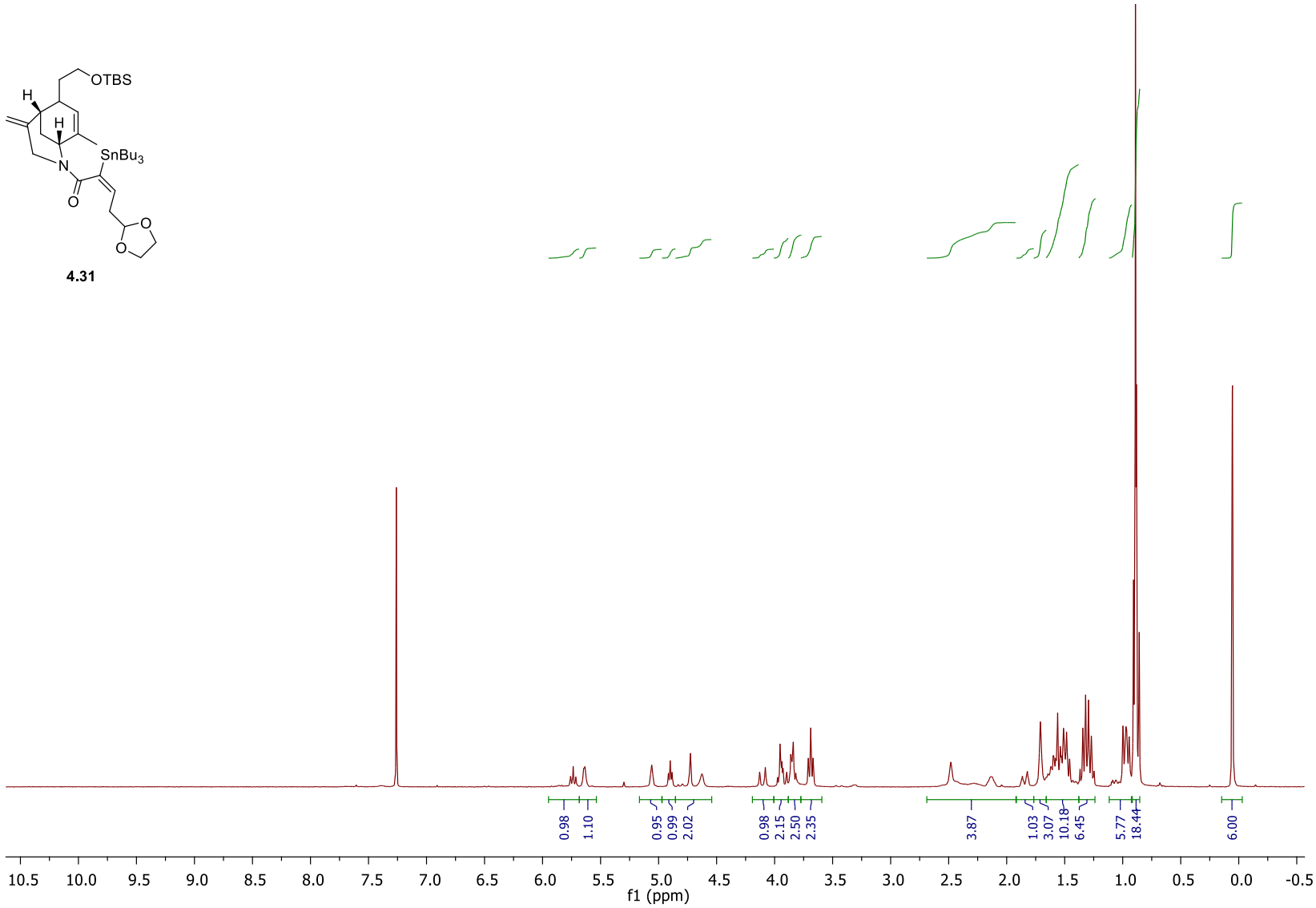
110.39
109.62
101.67
87.29
87.19
65.54
65.51
61.30
61.22
52.94
48.24
46.78
42.67
39.82
39.72
38.24
38.10
37.49
28.63
28.01
26.05
25.91
21.65
21.23
18.40
-5.18
OTBS
H
H
N
O
O
O
O
4.15
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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H
N
O
SnBu3
O
O
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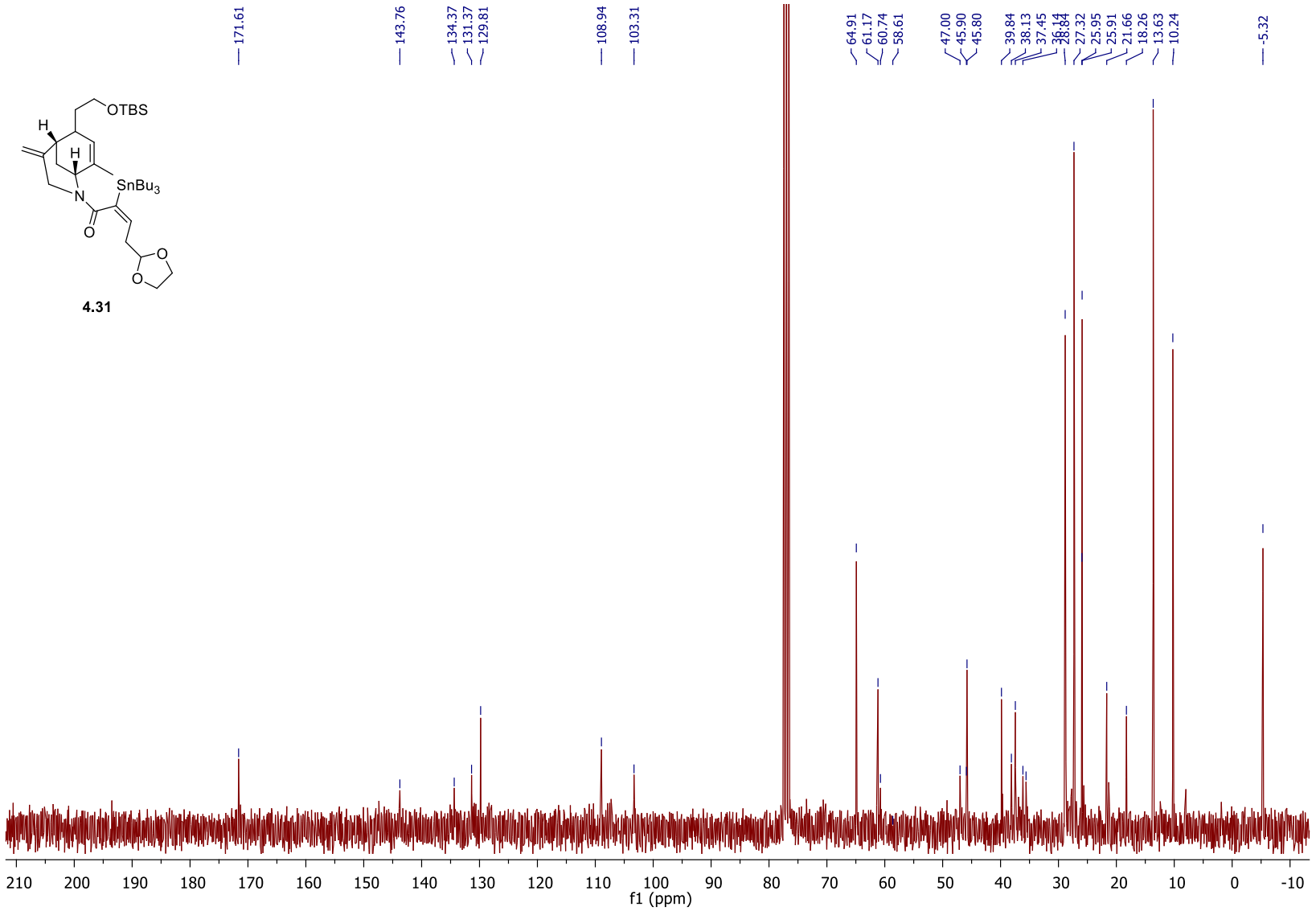
0.95
0.99
2.02
0.98
2.15
2.50
2.35
3.87
1.03
3.07
10.18
6.45
5.77
18.44
6.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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47.00
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45.80
39.84
38.13
37.45
36.14
28.84
27.32
25.95
25.91
21.66
18.26
13.63
10.24
-5.32
OTBS
H
H
N
O
SnBu3
O
O
4.31
210
200
190
180
170
160
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140
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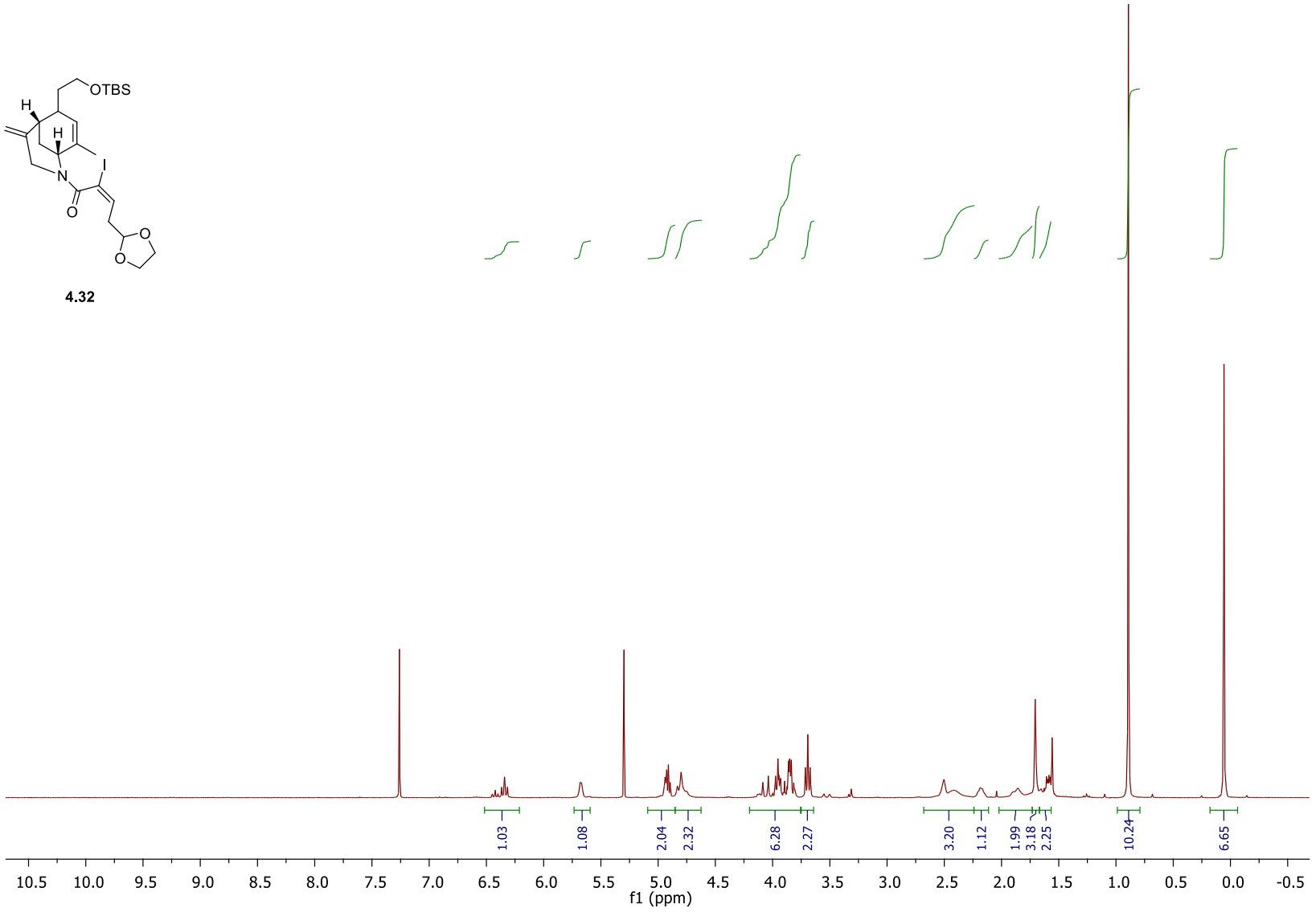
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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O
I
O
O
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1.03
1.08
2.04
2.32
6.28
2.27
3.20
1.12
1.99
3.18
2.25
10.24
6.65
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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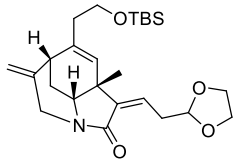
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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H
H
N
O
O
O

4.16

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3.15
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2.16
2.22
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2.03
1.15
1.06
1.08
1.04
1.08
1.06
1.09
1.15
3.25
10.15
6.36
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
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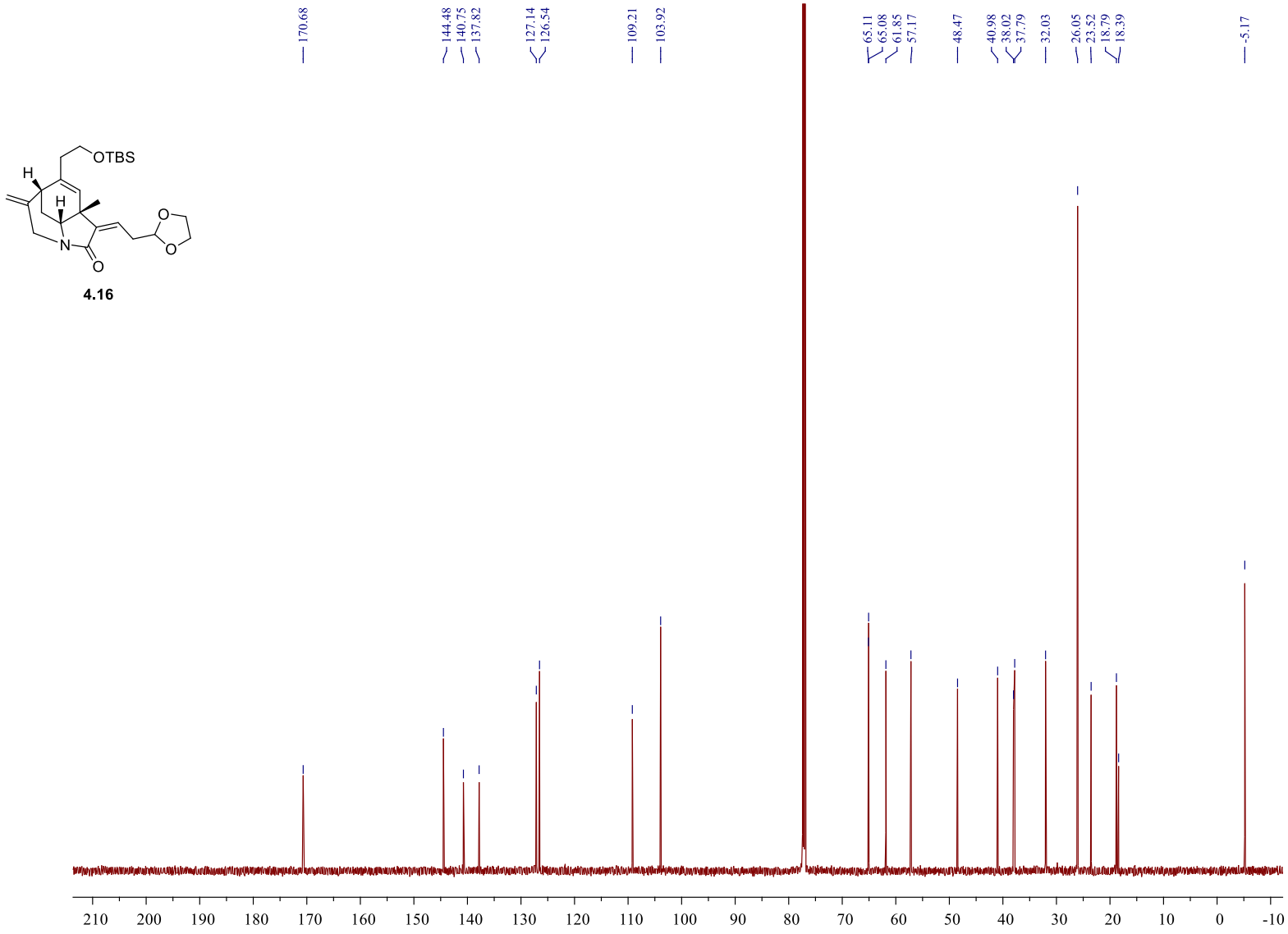
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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61.85
57.17
48.47
40.98
38.02
37.79
32.03
26.05
23.52
18.79
18.39
-5.17
OTBS
H
H
N
O
O
O
O
4.16
210
200
190
180
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130
120
110
100
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60
50
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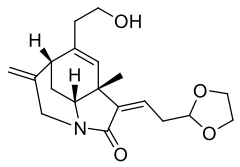
0
-10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H
N
O
O
O

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2.05
4.17
2.03
1.07
2.12
1.19
1.20
1.46
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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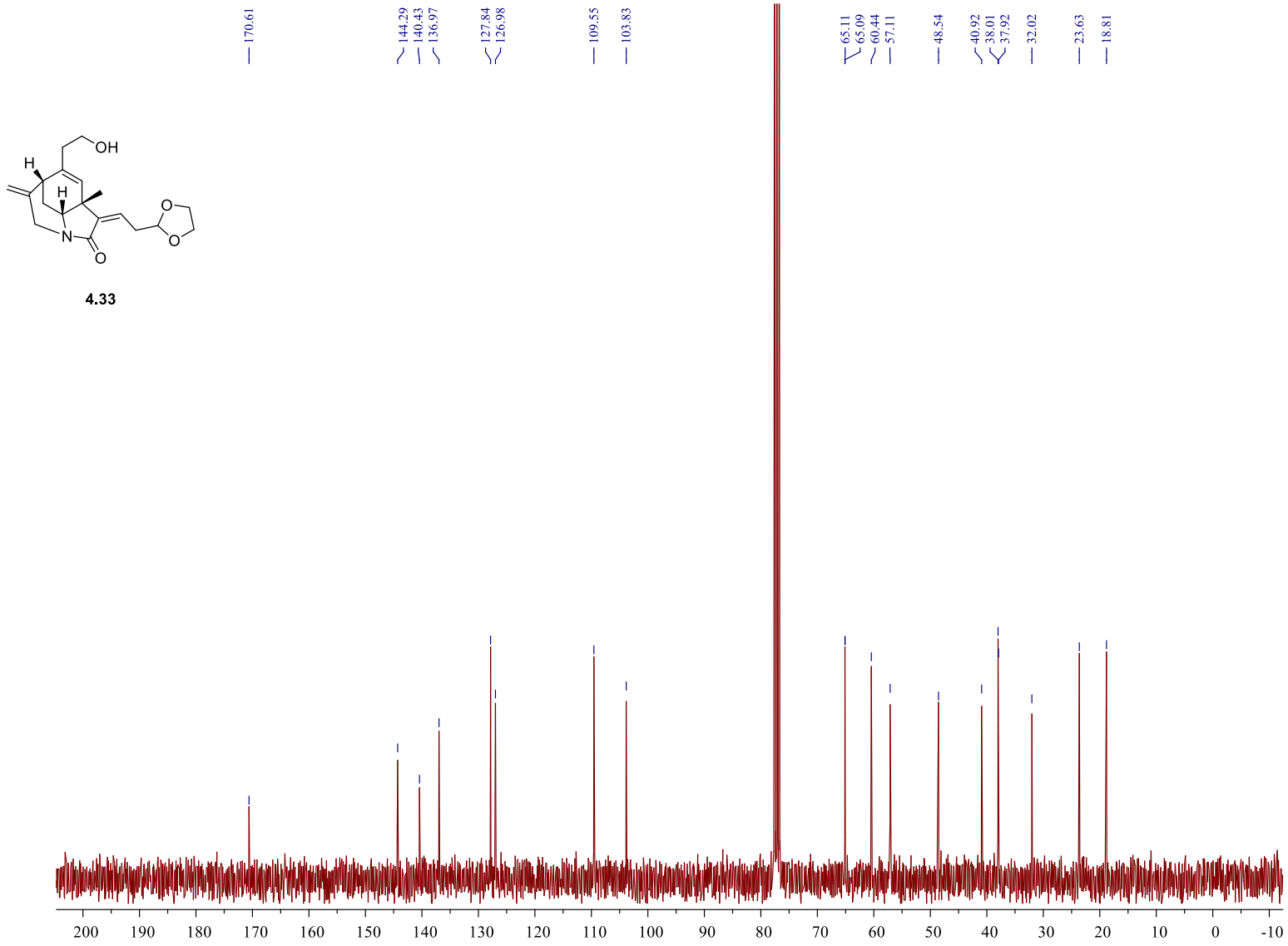
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48.54
40.92
38.01
37.92
32.02
23.63
18.81
OH
H
H
N
O
O
O
200
190
180
170
160
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90
80
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50
40
30
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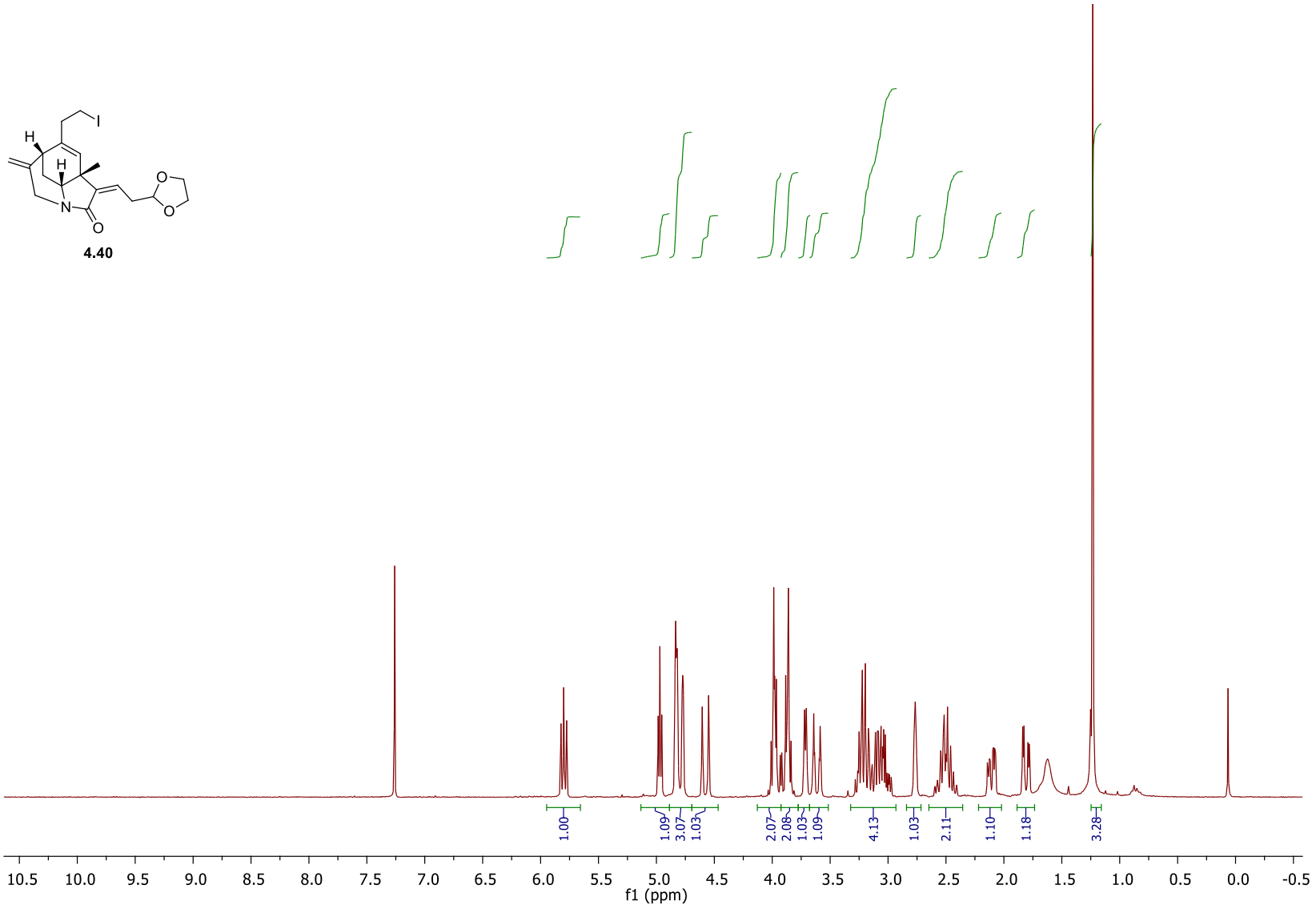
10
0
-10

4.33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1.09
4.13
1.03
2.11
1.10
1.18
3.28
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
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3.0
2.5
2.0
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0.5
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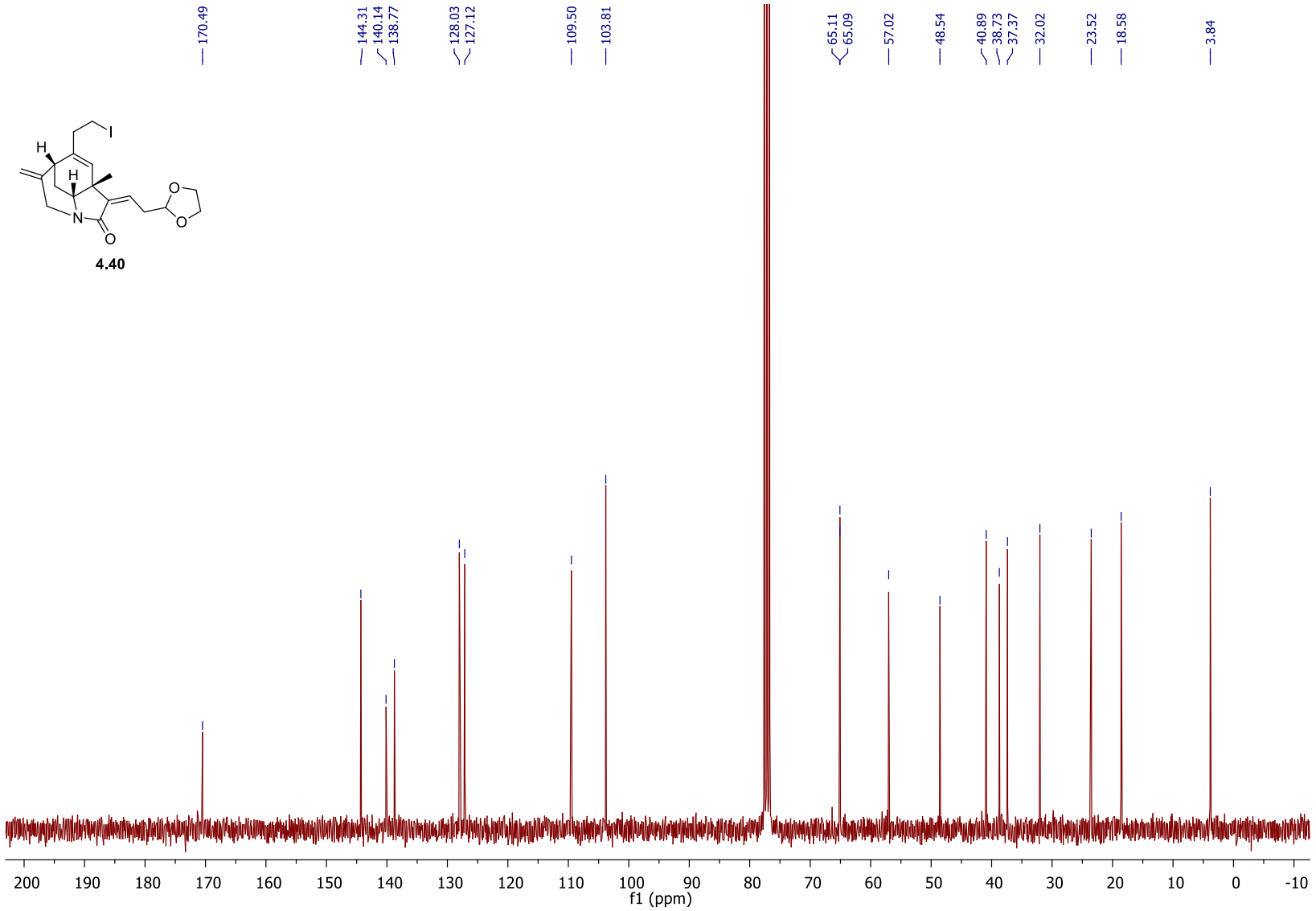
f1 (ppm)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103.81
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65.09
57.02
48.54
40.89
38.73
37.37
32.02
23.52
18.58
3.84
H
H
I
N
O
O
O
4.40
200
190
180
170
160
150
140
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120
110
100
90
80
70
60
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40
30
20
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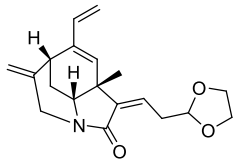
0
-10
f1 (ppm)


H
H
N
O
O
O

4.35

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0.91
1.00
1.89
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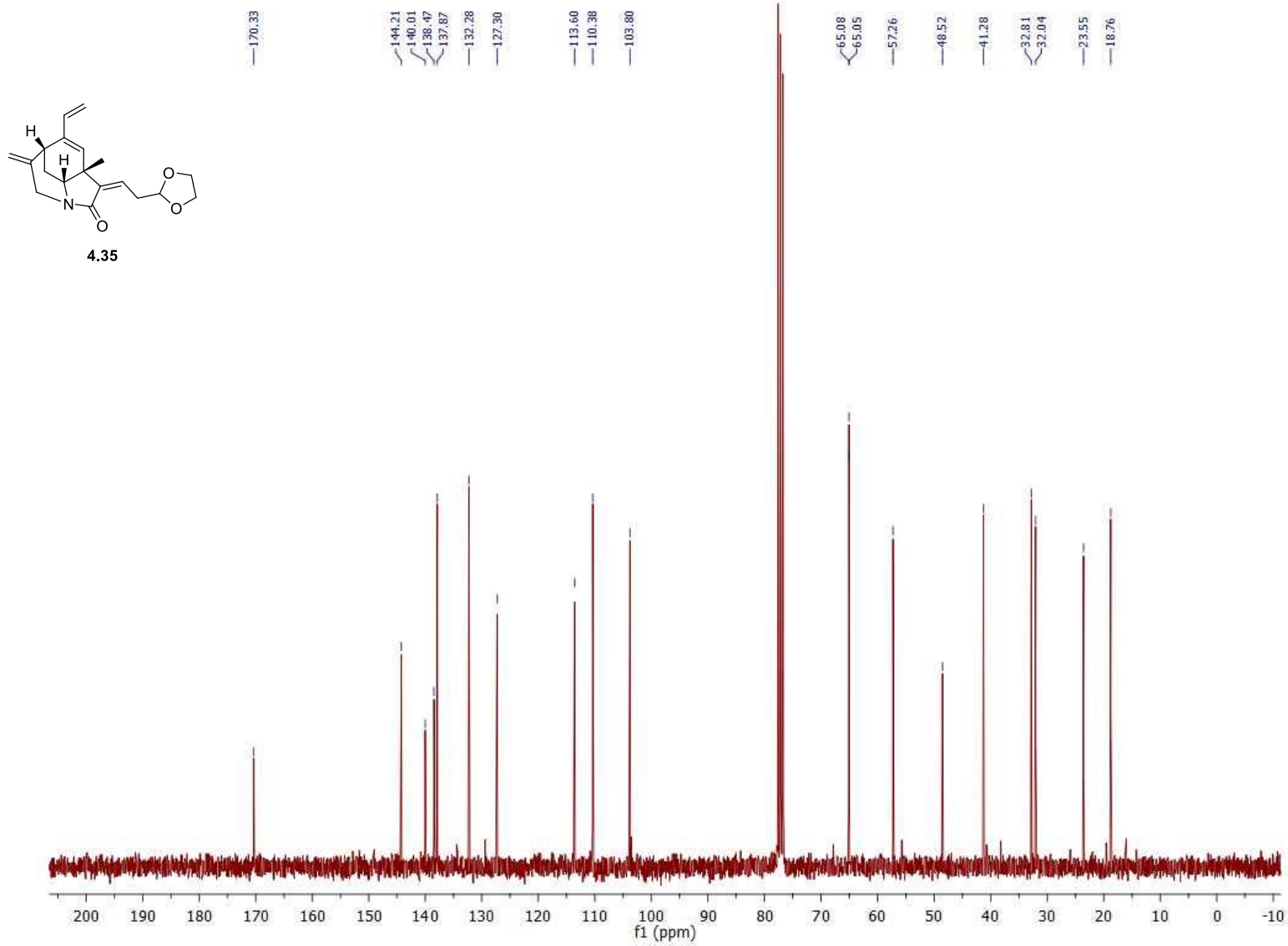
0.99
1.00
0.97
1.89
1.90
0.99
0.95
0.96
0.93
0.94
0.99
1.01
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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137.87
132.28
127.30
113.60
110.38
103.80
65.08
65.05
57.26
48.52
41.28
32.81
32.04
23.55
18.76
H
H
N
O
O
O
4.35
200
190
180
170
160
150
140
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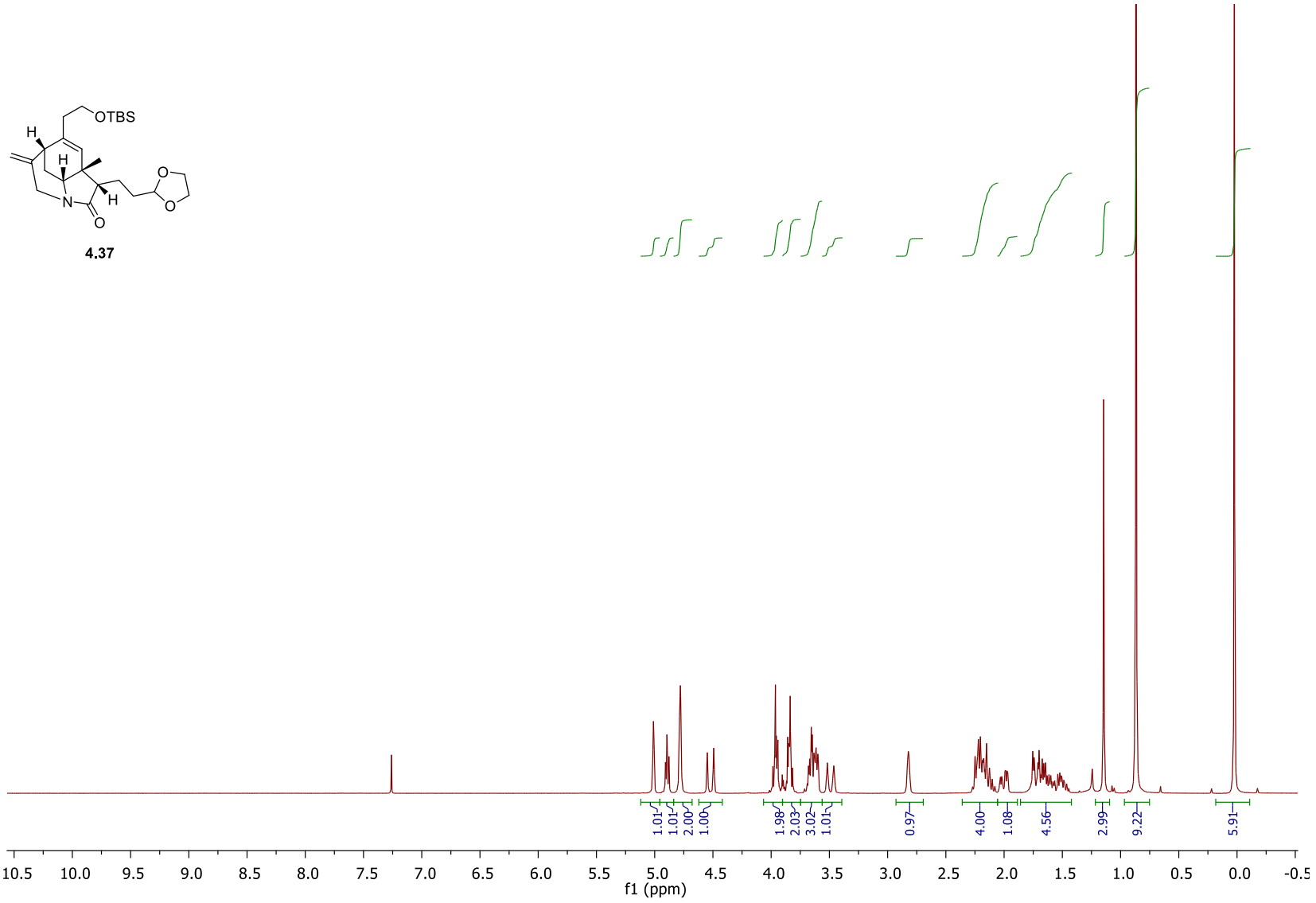
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OTBS
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O
H
O
O
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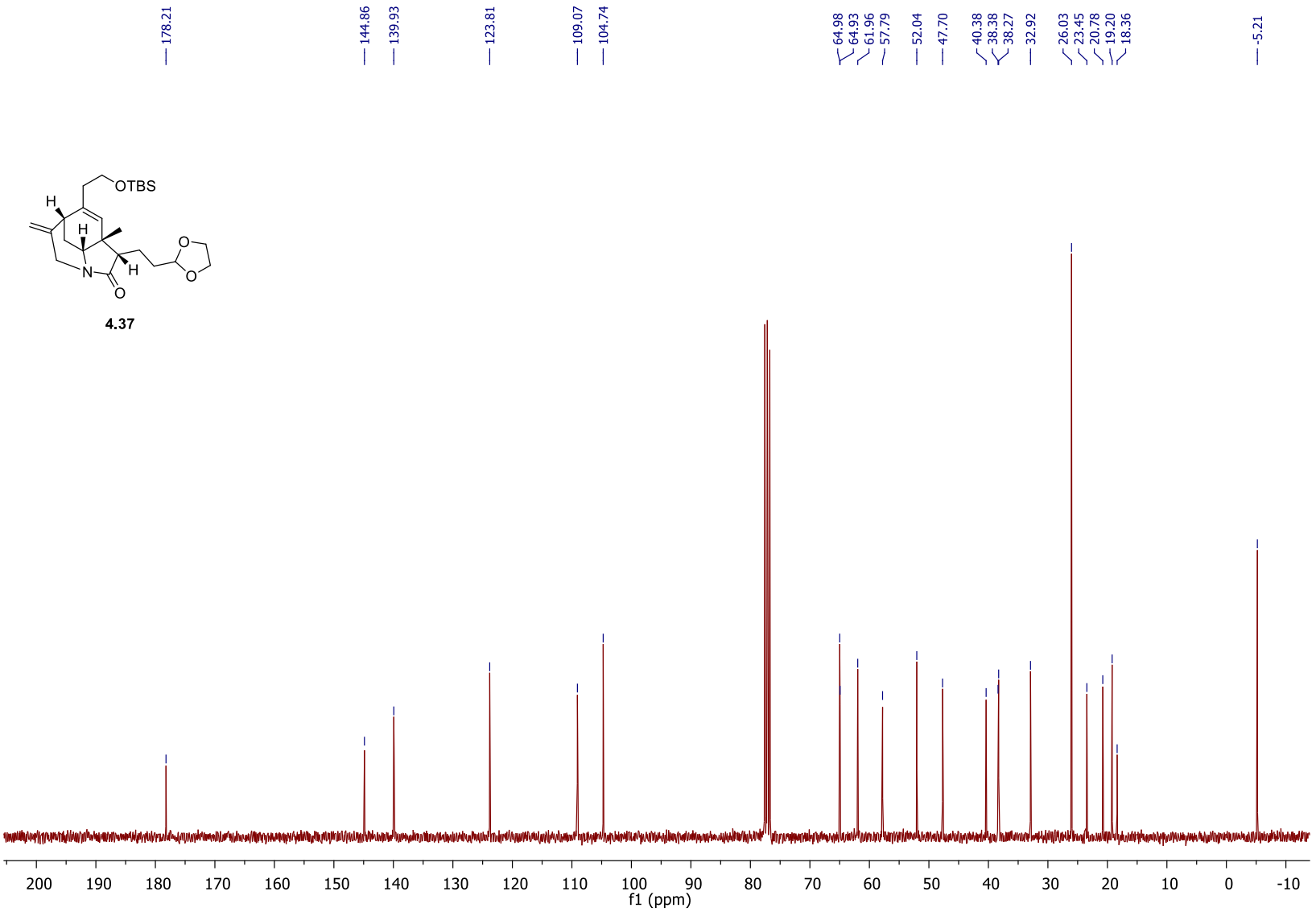
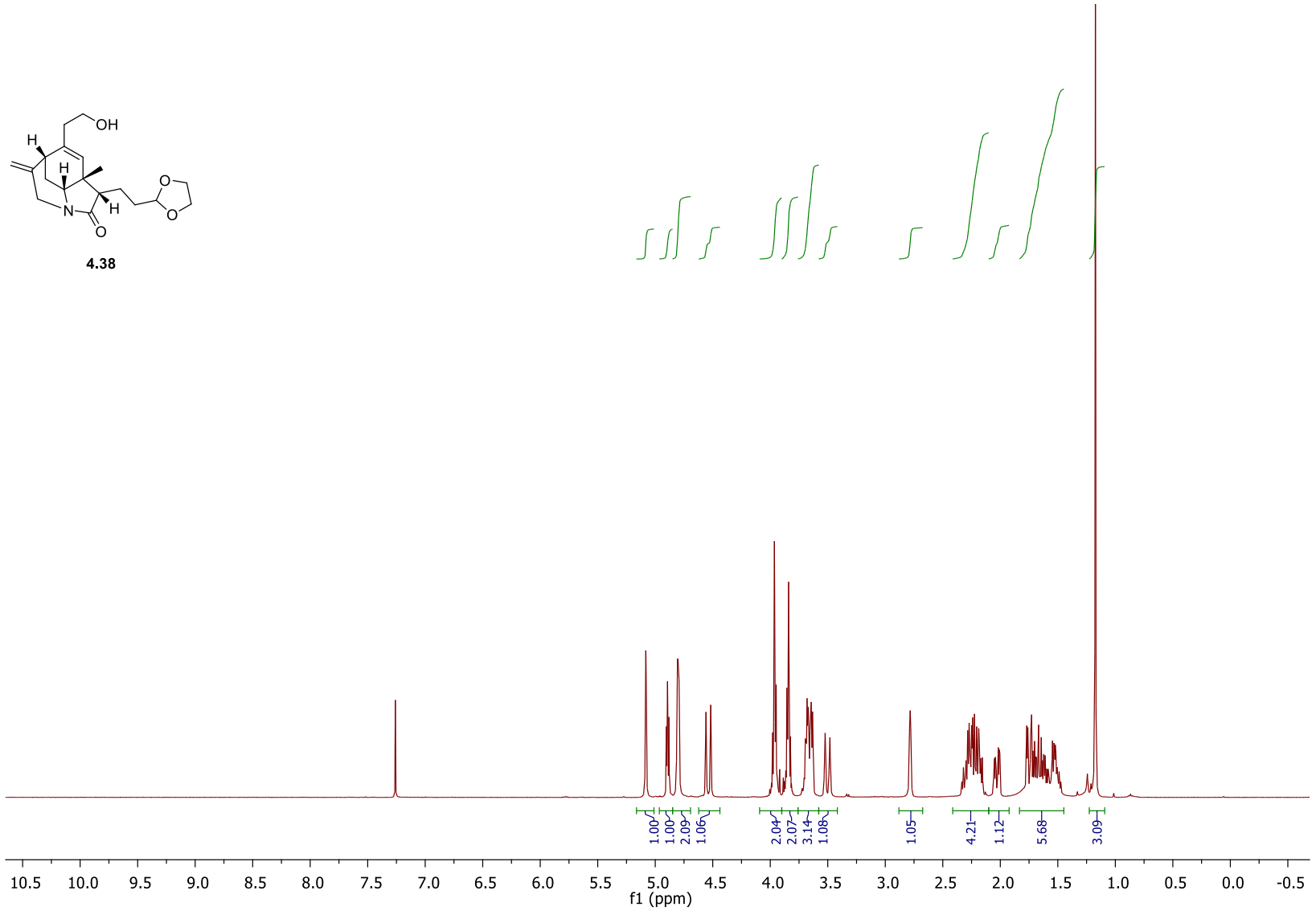
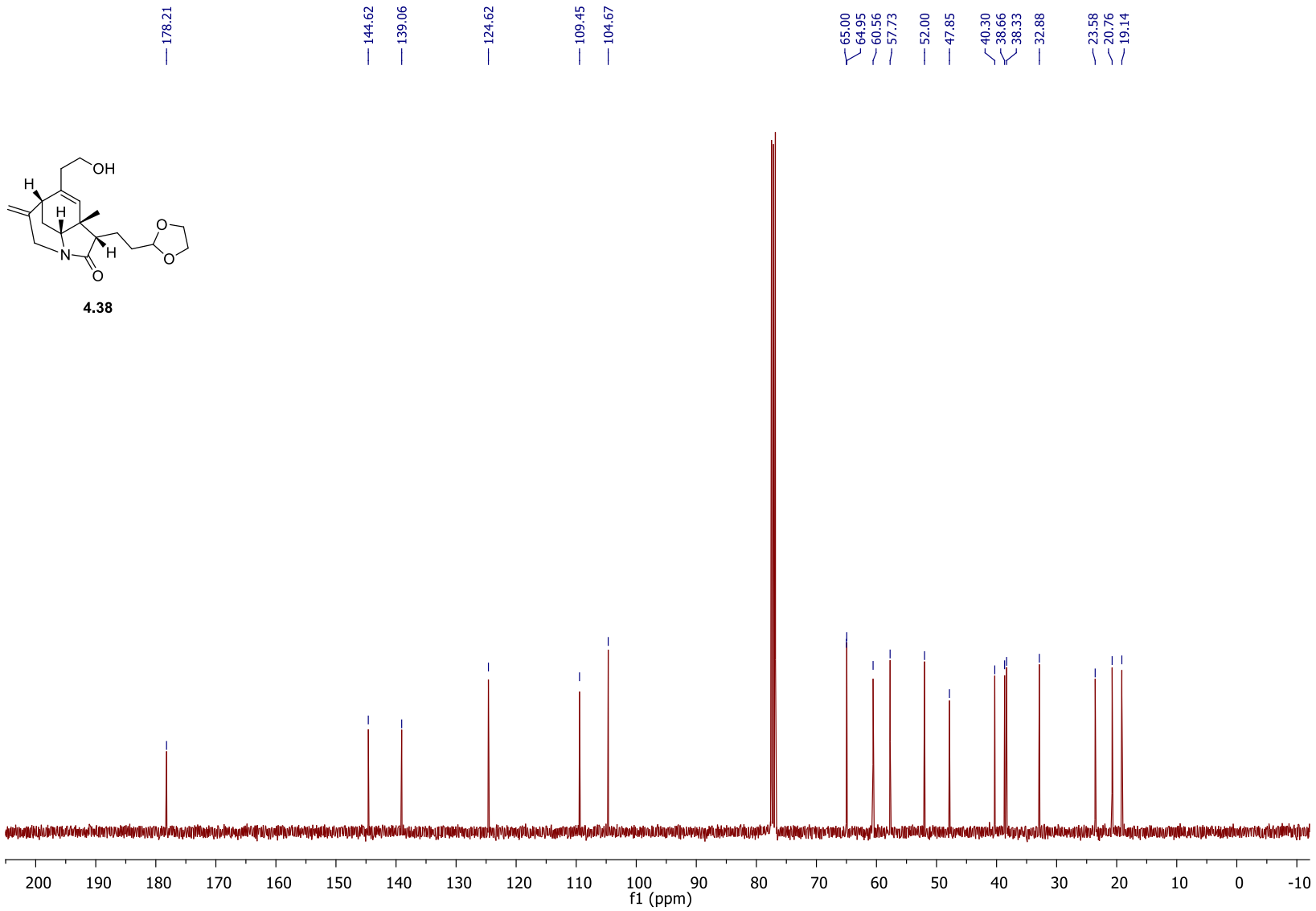
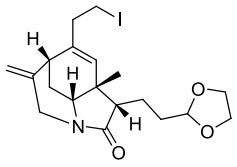
1.01
1.01
2.00
1.00
1.98
2.03
3.02
1.01
0.97
4.00
1.08
4.56
2.99
9.22
5.91
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


178.21
144.86
139.93
123.81
109.07
104.74
64.98
64.93
61.96
57.79
52.04
47.70
40.38
38.38
38.27
32.92
26.03
23.45
20.78
19.20
18.36
-5.21
OTBS
H
H
H
N
O
O
O
4.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
H
H
N
O
H
O
O
4.38
1.00
1.00
2.09
1.06
2.04
2.07
3.14
1.08
1.05
4.21
1.12
5.68
3.09
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
f1 (ppm)

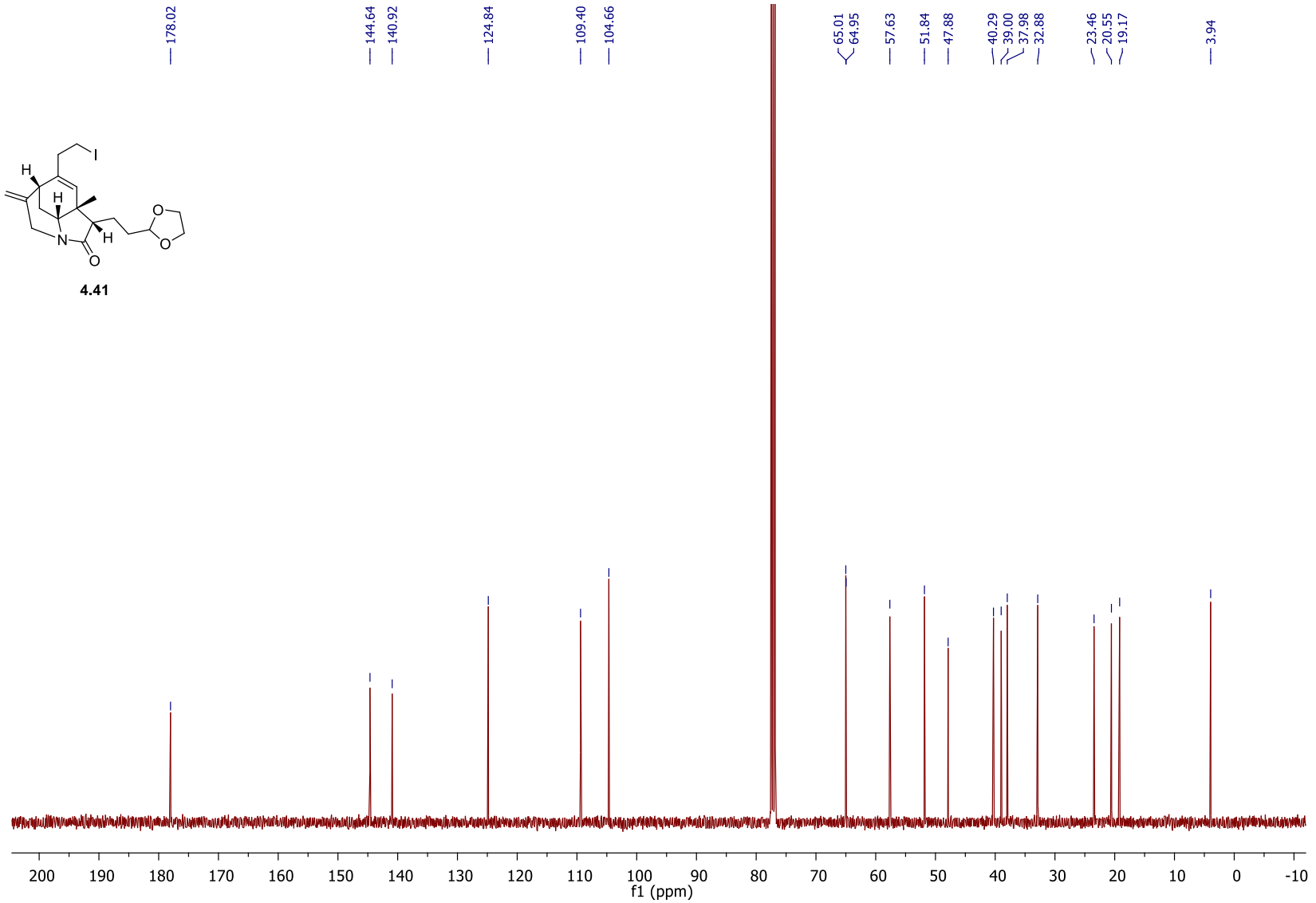

178.21
144.62
139.06
124.62
109.45
104.67
65.00
64.95
60.56
57.73
52.00
47.85
40.30
38.66
38.33
32.88
23.58
20.76
19.14
OH
H
H
N
O
H
O
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

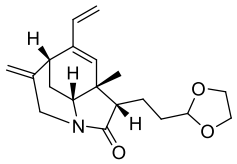
4.38


H
I
H
O
N
H
O
O

4.41

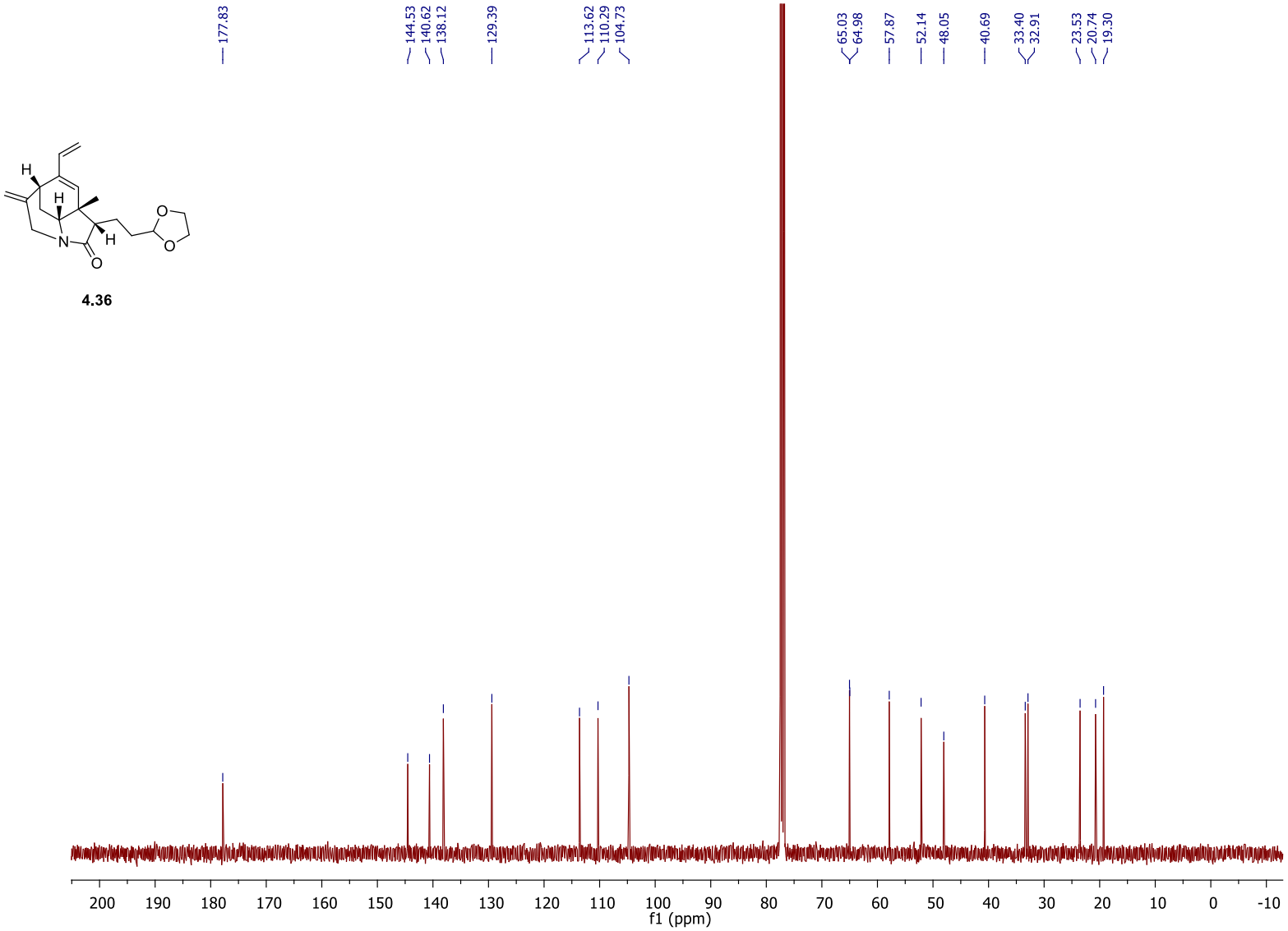
1.00
0.98
2.07
1.04
2.01
2.02
1.04
1.03
2.06
1.03
2.11
2.02
1.05
1.26
3.47
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

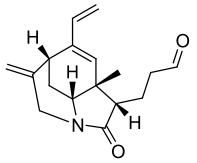

178.02
144.64
140.92
124.84
109.40
104.66
65.01
64.95
57.63
51.84
47.88
40.29
39.00
37.98
32.88
23.46
20.55
19.17
3.94
I
H
H
N
O
H
O
O
O
4.41
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
H
N
O
H
O
O

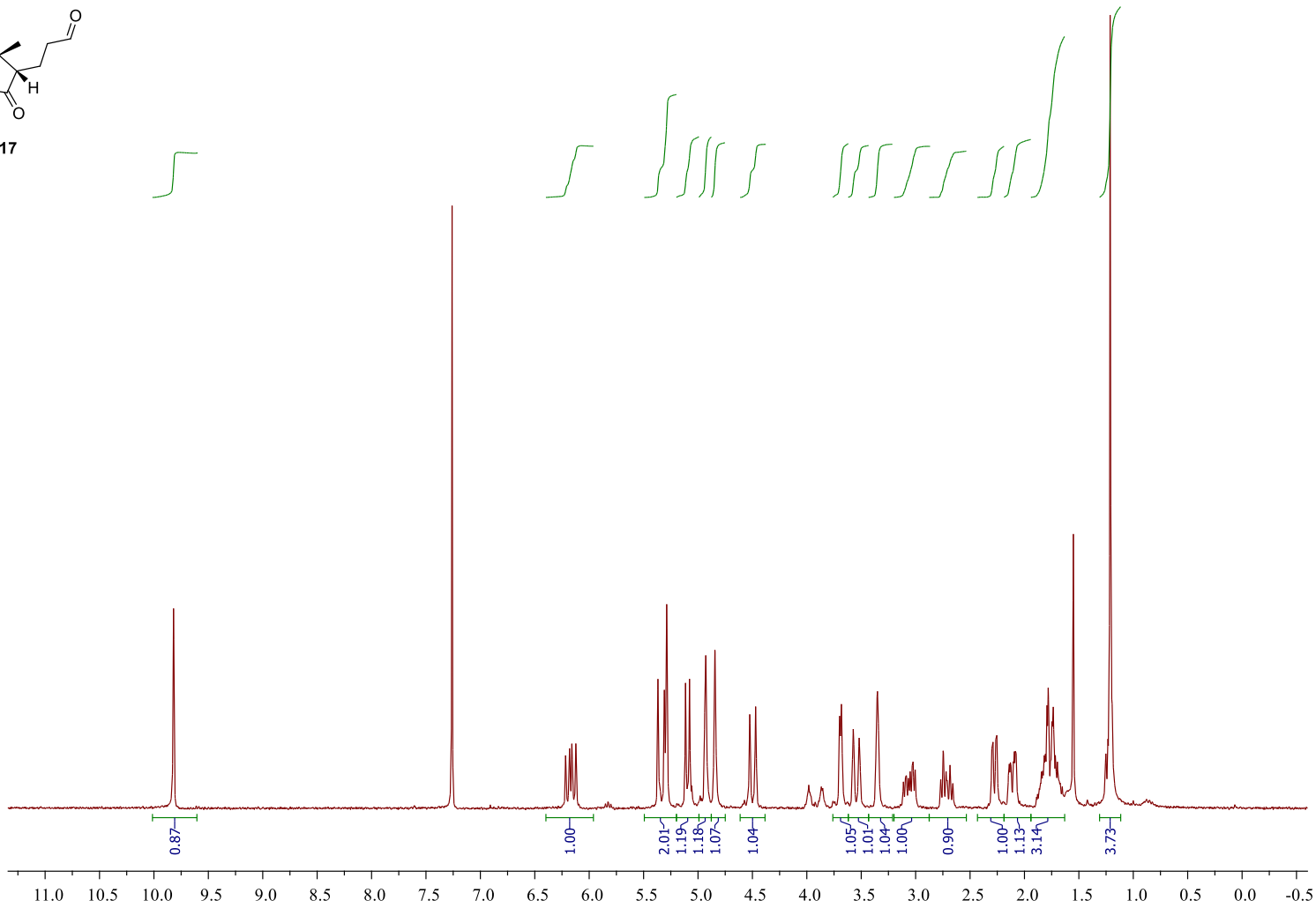
4.36

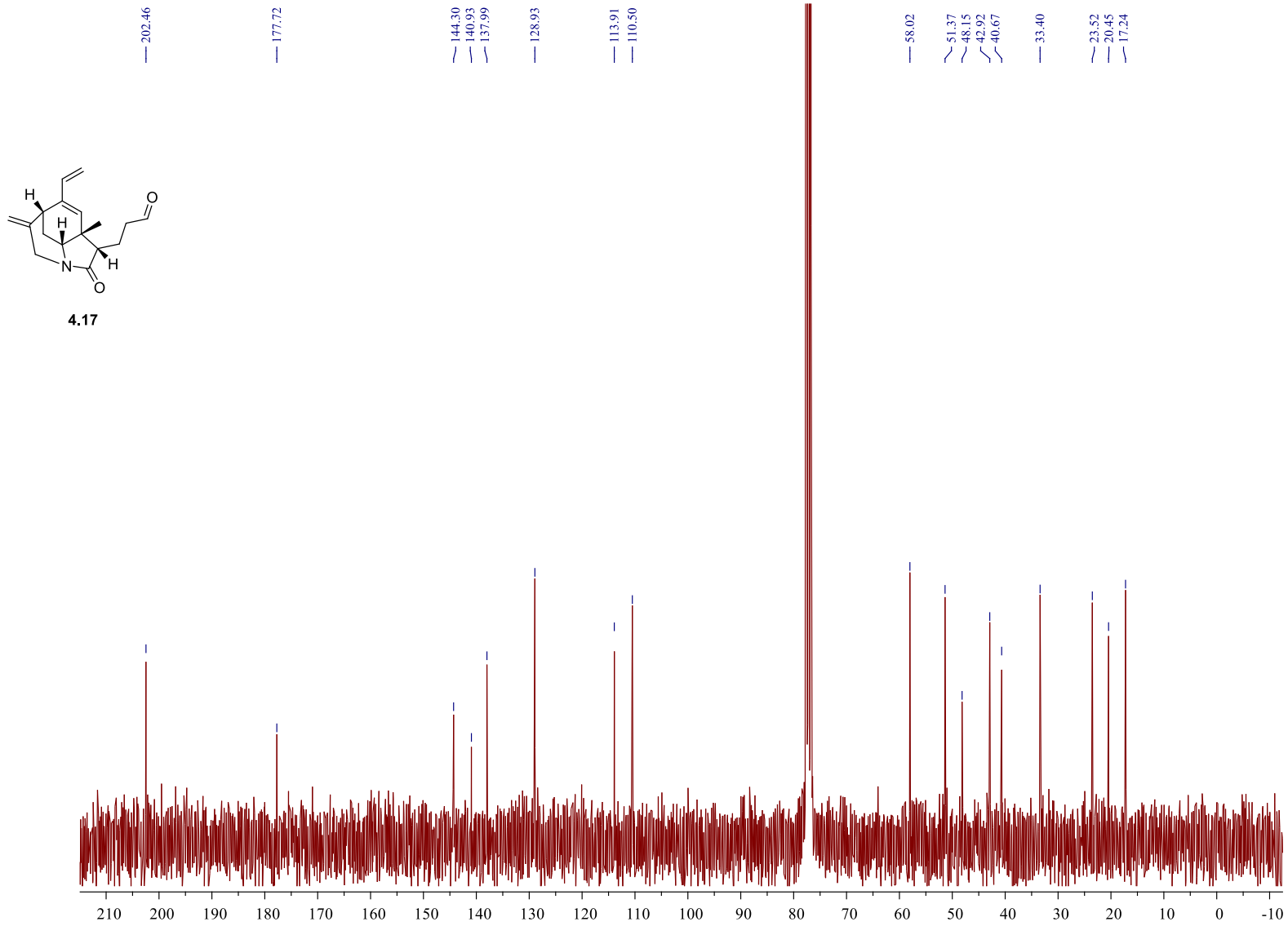
1.00
2.11
1.07
2.00
1.01
1.00
2.01
1.99
1.01
1.02
1.03
0.96
1.03
1.04
4.40
3.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


177.83
144.53
140.62
138.12
129.39
113.62
110.29
104.73
65.03
64.98
57.87
52.14
48.05
40.69
33.40
32.91
23.53
20.74
19.30
H
H
H
N
O
O
O
4.36
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

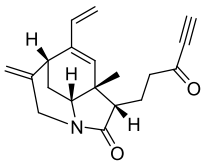

H
H
O
N
O
H

4.17


0.87
1.00
2.01
1.19
1.18
1.07
1.04
1.05
1.01
1.04
1.00
0.90
1.00
1.13
3.14
3.73
11.0
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

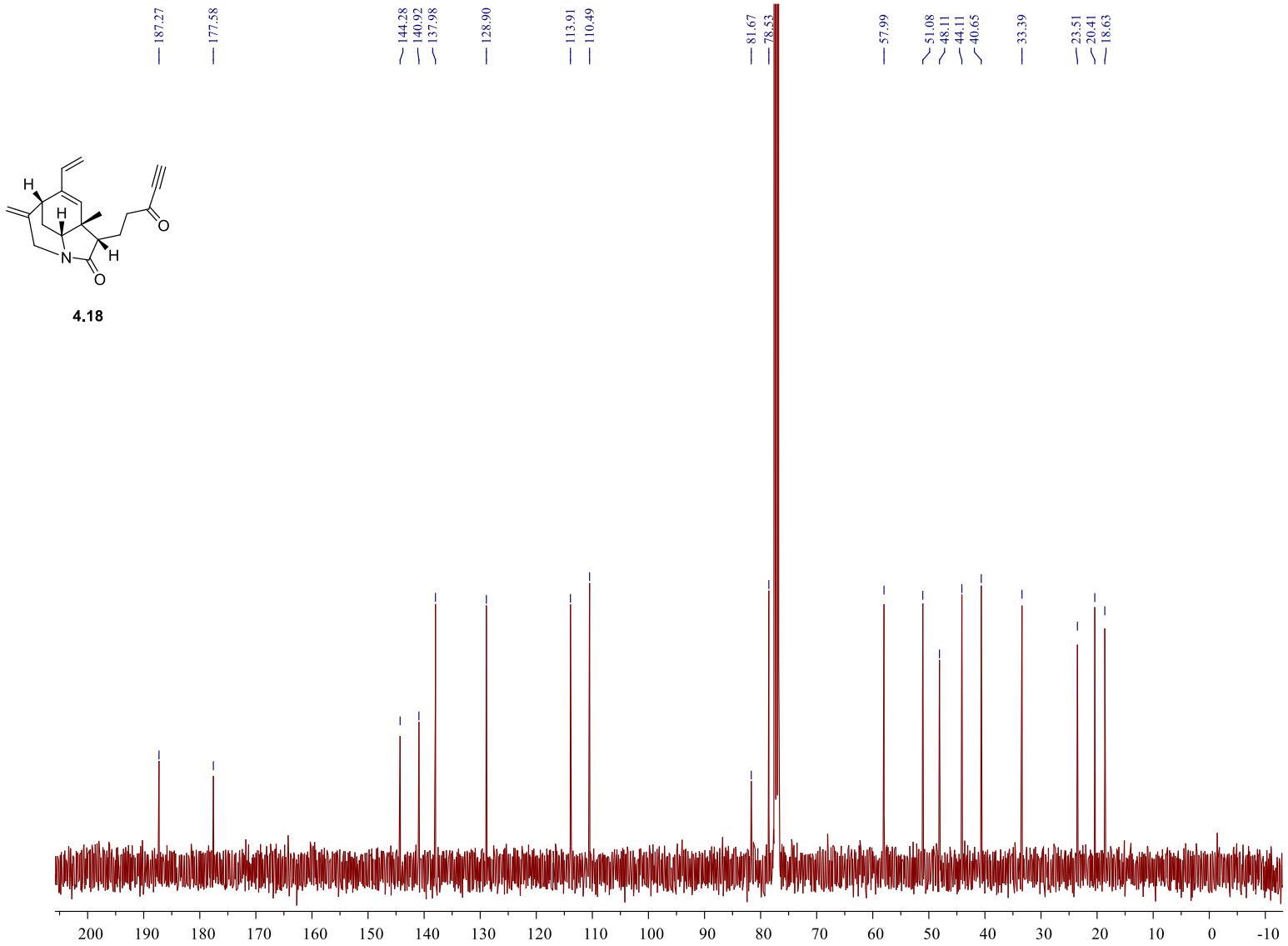

202.46
177.72
144.30
140.93
137.99
128.93
113.91
110.50
58.02
51.37
48.15
42.92
40.67
33.40
23.52
20.45
17.24
H
H
H
N
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

4.17

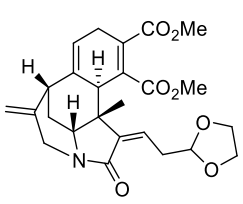

H
H
N
O
O
H

4.18

1.00
1.10
0.93
1.06
1.05
0.99
1.01
1.00
1.01
1.00
1.78
0.98
0.97
1.08
1.03
2.06
3.53
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

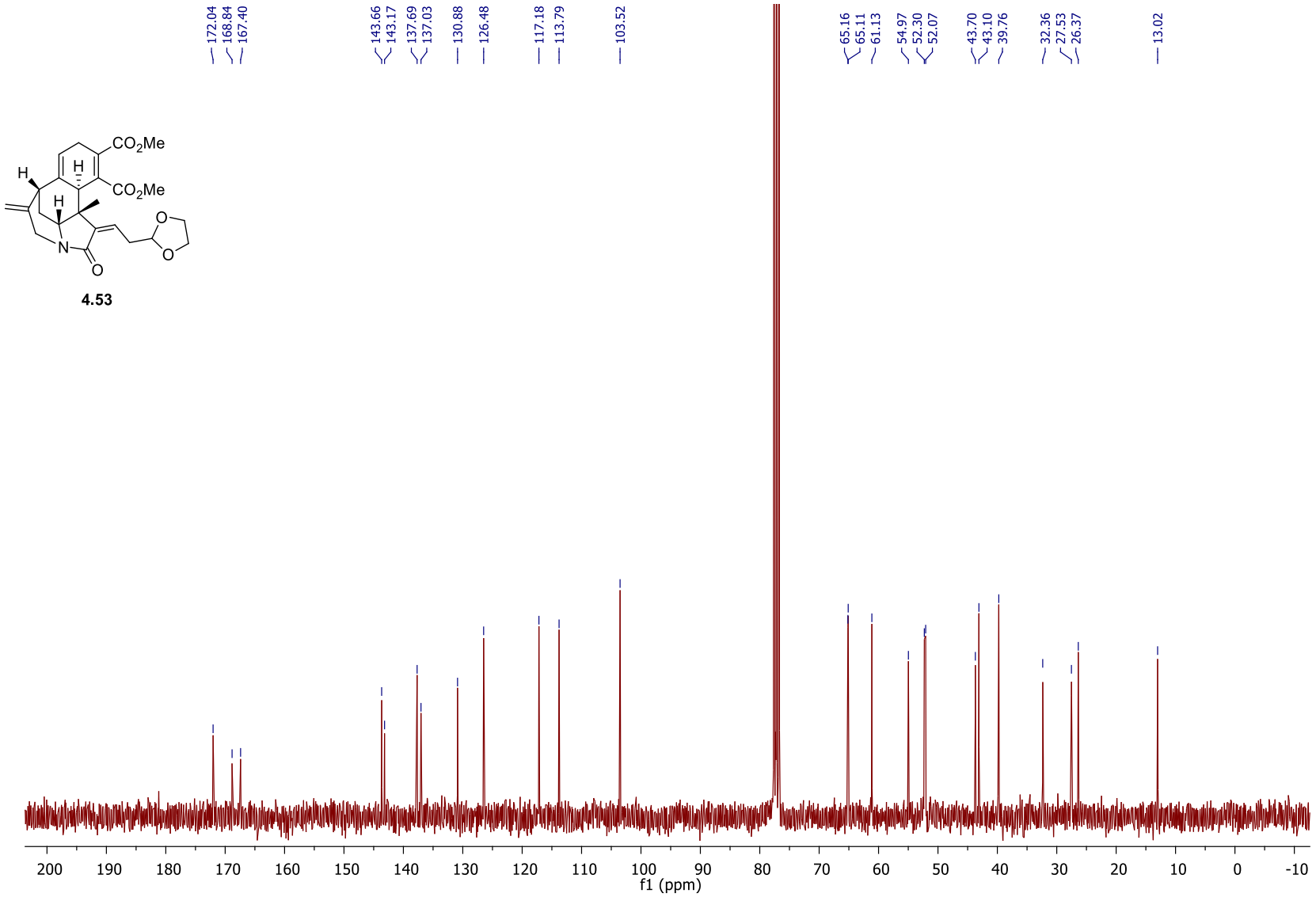

187.27
177.58
144.28
140.92
137.98
128.90
113.91
110.49
81.67
78.53
57.99
51.08
48.11
44.11
40.65
33.39
23.51
20.41
18.63
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

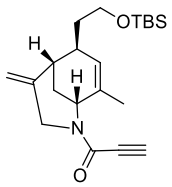
4.18


CO2Me
CO2Me
H
H
H
N
O
O
O
O

4.53

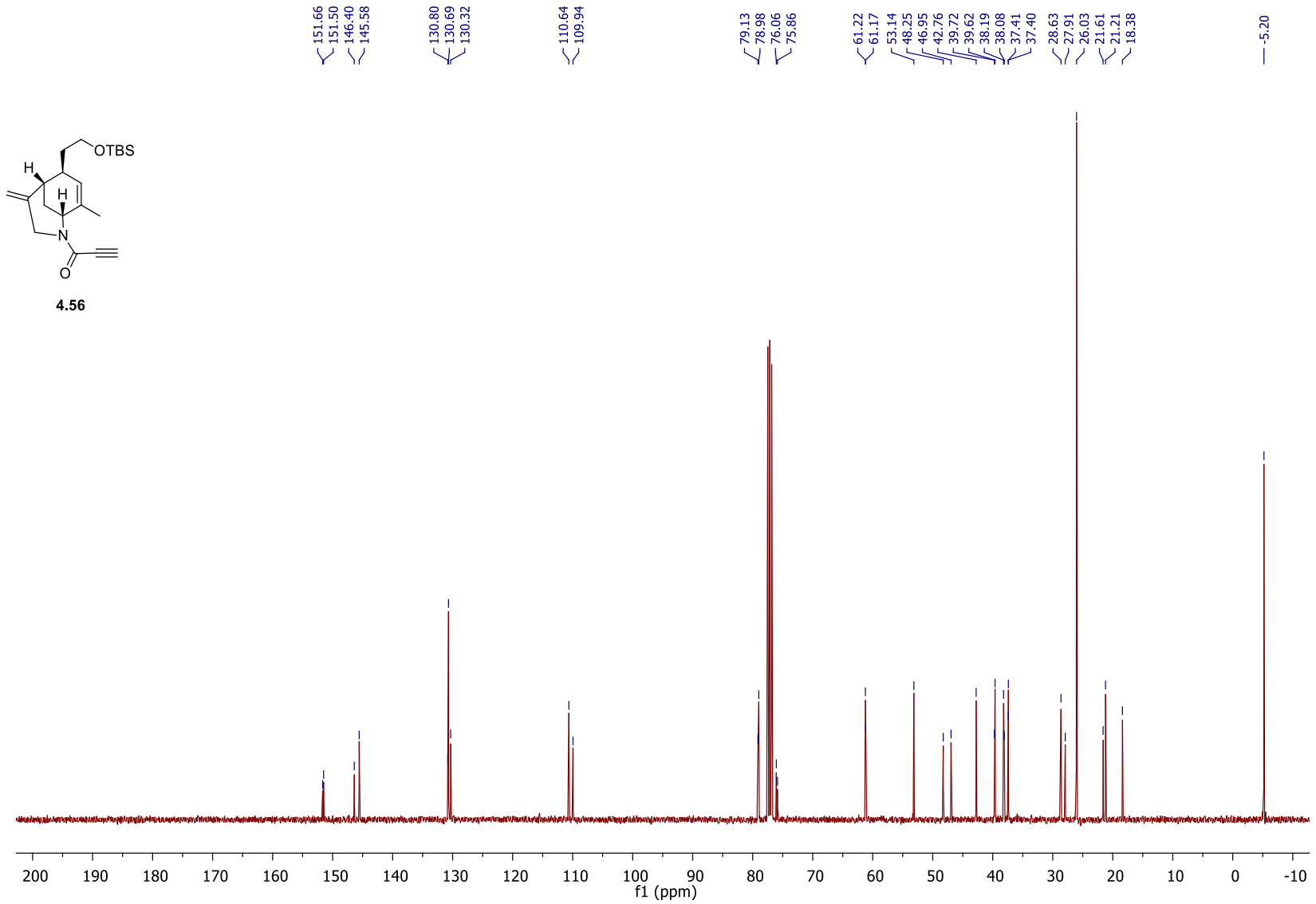
1.00
1.08
1.08
1.10
1.24
1.00
3.16
2.63
3.16
3.39
1.10
1.03
3.40
2.26
1.10
1.18
3.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

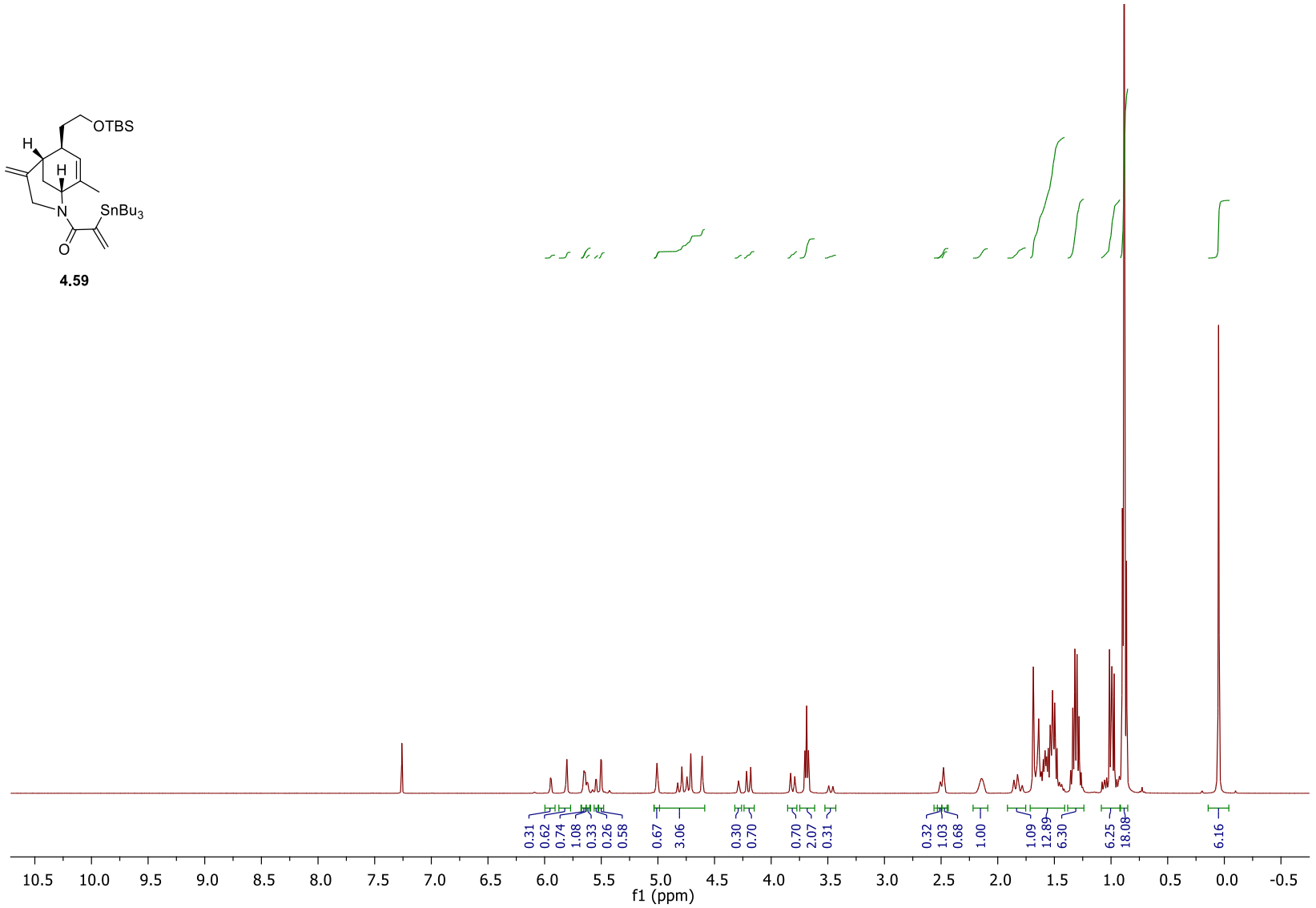

172.04
168.84
167.40
143.66
143.17
137.69
137.03
130.88
126.48
117.18
113.79
103.52
65.16
65.11
61.13
54.97
52.30
52.07
43.70
43.10
39.76
32.36
27.53
26.37
13.02
CO2Me
CO2Me
H
H
H
N
O
O
O
O
4.53
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

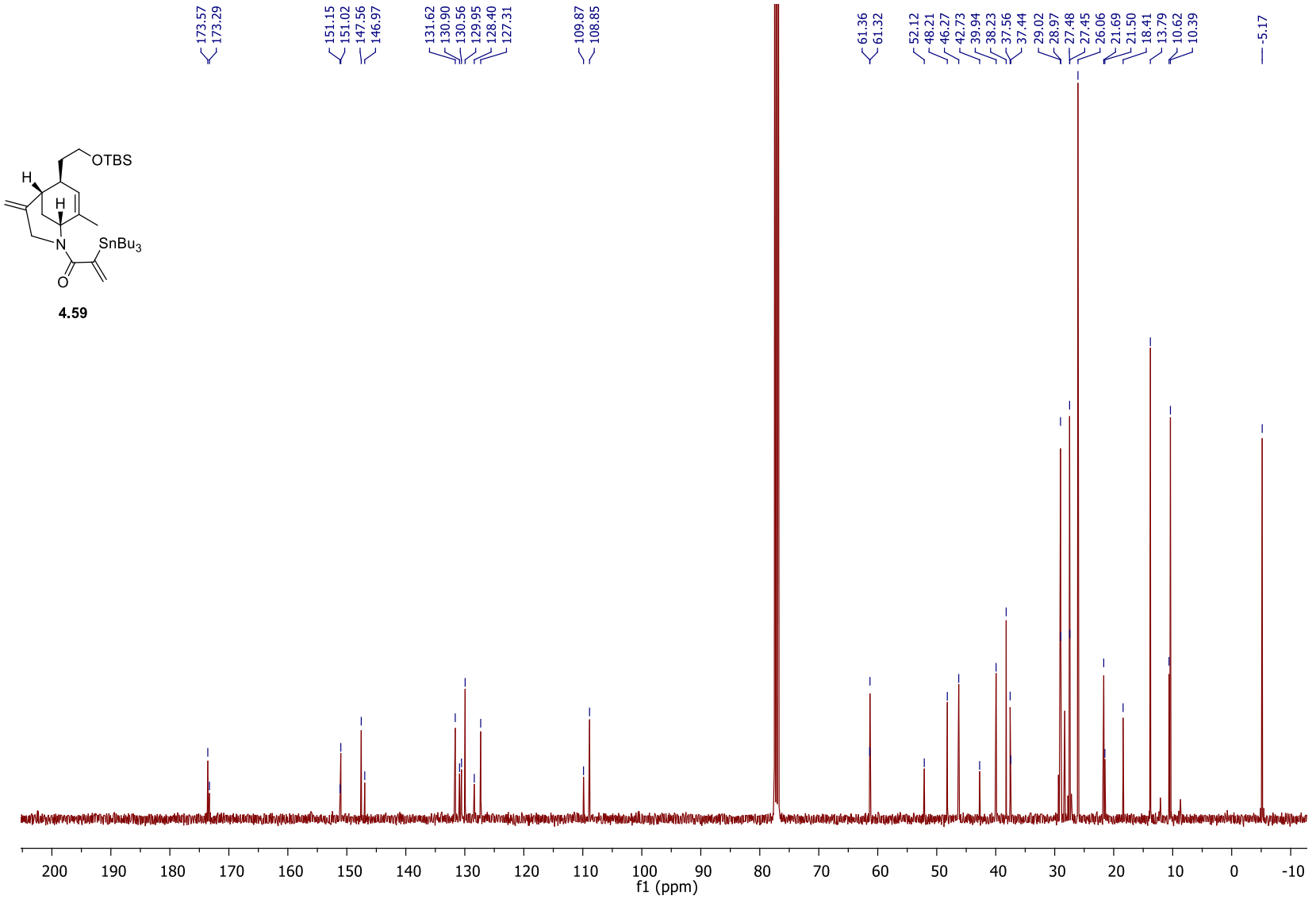

OTBS
H
H
N
O

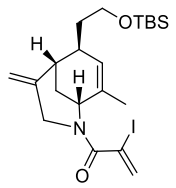
4.56

1.00
0.40
1.94
0.62
0.61
0.40
0.40
2.03
0.60
0.34
0.49
0.99
0.96
0.63
0.43
6.35
9.35
6.05
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
f1 (ppm)


151.66
151.50
146.40
145.58
130.80
130.69
130.32
110.64
109.94
79.13
78.98
76.06
75.86
61.22
61.17
53.14
48.25
46.95
42.76
39.72
39.62
38.19
38.08
37.41
37.40
28.63
27.91
26.03
21.61
21.21
18.38
-5.20
OTBS
H
H
N
O
4.56
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

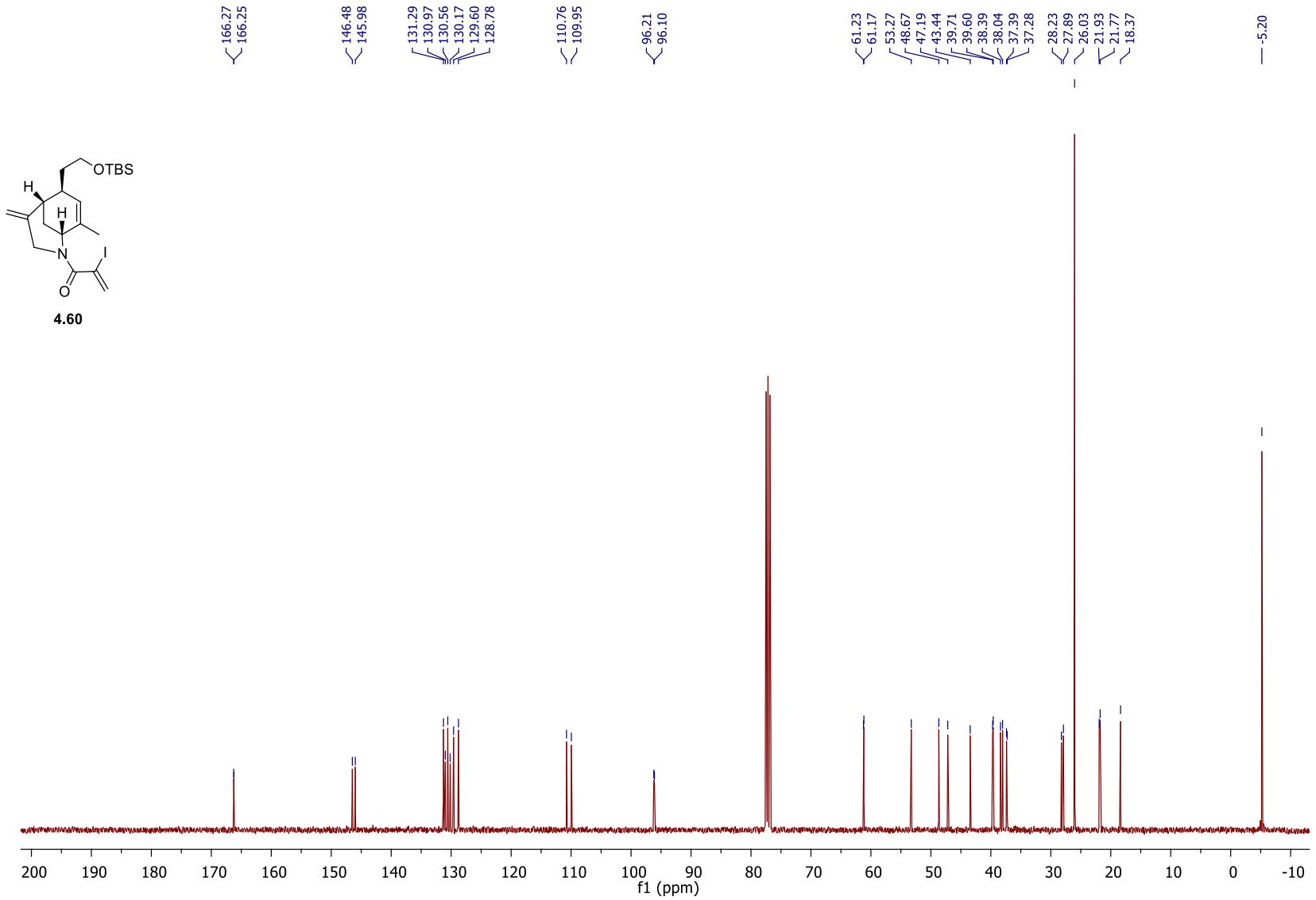

OTBS
H
H
N
SnBu3
O
4.59
0.31
0.62
0.74
1.08
0.33
0.26
0.58
0.67
3.06
0.30
0.70
0.70
2.07
0.31
0.32
1.03
0.68
1.00
1.09
12.89
6.30
6.25
18.08
6.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


173.57
173.29
151.15
151.02
147.56
146.97
131.62
130.90
130.56
129.95
128.40
127.31
109.87
108.85
61.36
61.32
52.12
48.21
46.27
42.73
39.94
38.23
37.56
37.44
29.02
28.97
27.48
27.45
26.06
21.69
21.50
18.41
13.79
10.62
10.39
-5.17
OTBS
H
H
N
SnBu3
O
4.59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

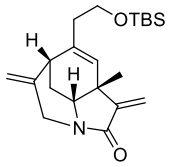

OTBS
H
H
N
I
O

4.60

0.49
0.50
0.48
0.50
0.94
0.48
0.95
0.51
0.47
0.48
0.46
0.50
0.49
2.00
0.48
0.48
0.49
0.94
1.49
3.45
1.97
9.05
5.82
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
f1 (ppm)

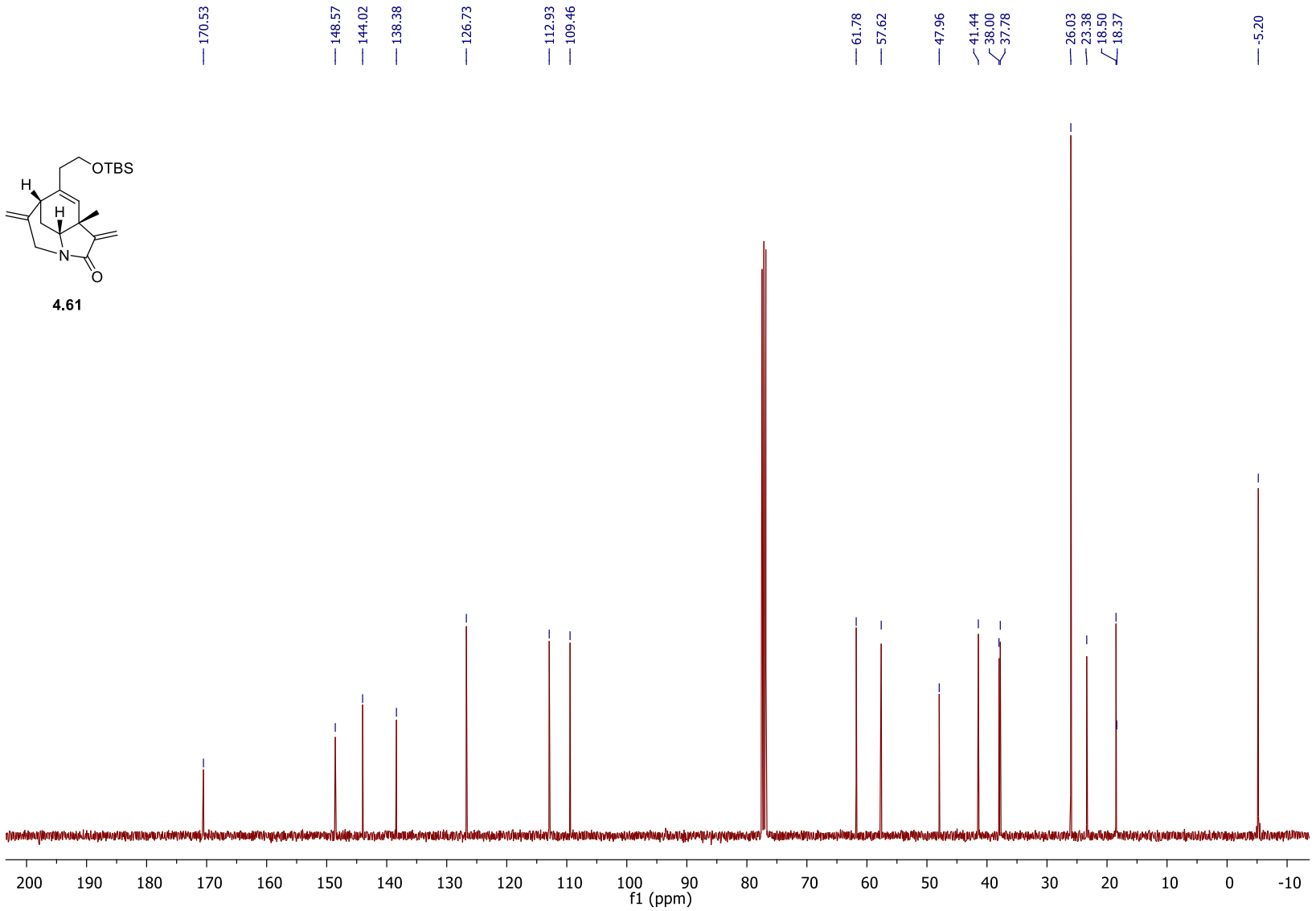

166.27
166.25
146.48
145.98
131.29
130.97
130.56
130.17
129.60
128.78
110.76
109.95
96.21
96.10
61.23
61.17
53.27
48.67
47.19
43.44
39.71
39.60
38.39
38.04
37.39
37.28
28.23
27.89
26.03
21.93
21.77
18.37
-5.20
OTBS
H
H
N
O
I
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

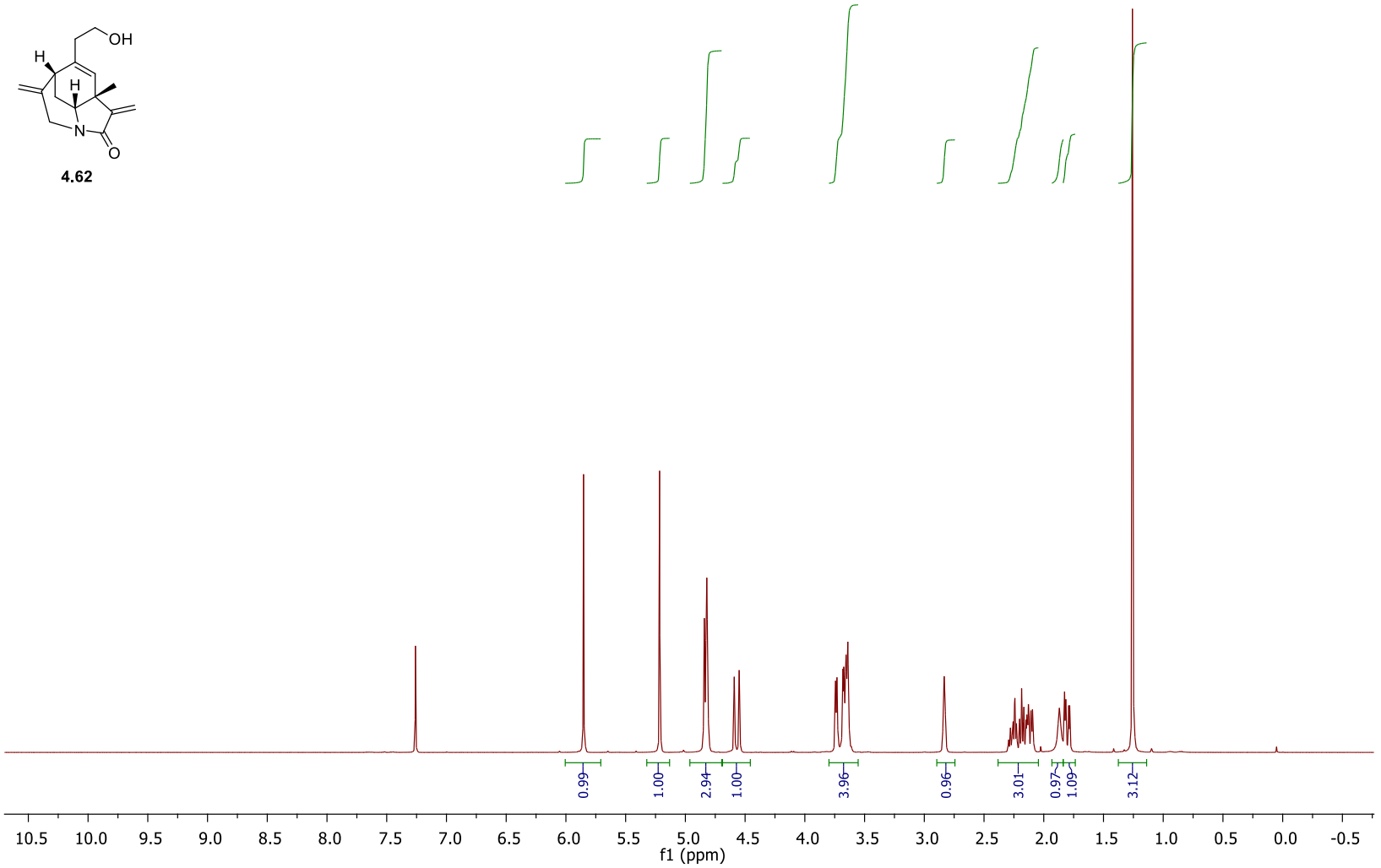
4.60

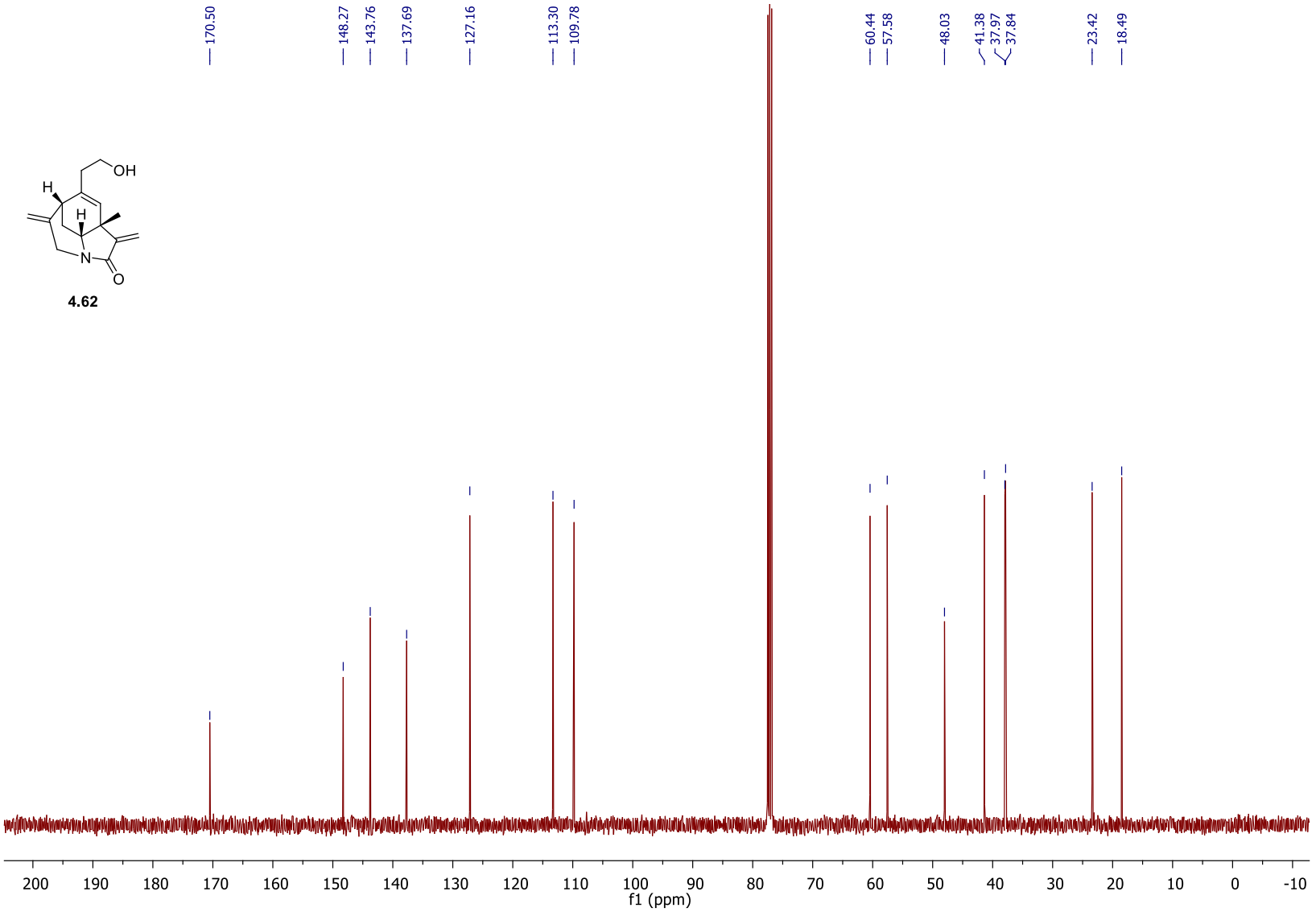

OTBS
H
H
N
O

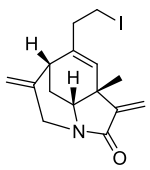
4.61

1.00
1.01
2.98
1.02
0.99
3.03
1.00
3.08
1.11
3.12
9.24
6.05
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
f1 (ppm)


170.53
148.57
144.02
138.38
126.73
112.93
109.46
61.78
57.62
47.96
41.44
38.00
37.78
26.03
23.38
18.50
18.37
-5.20
OTBS
H
H
N
O
4.61
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

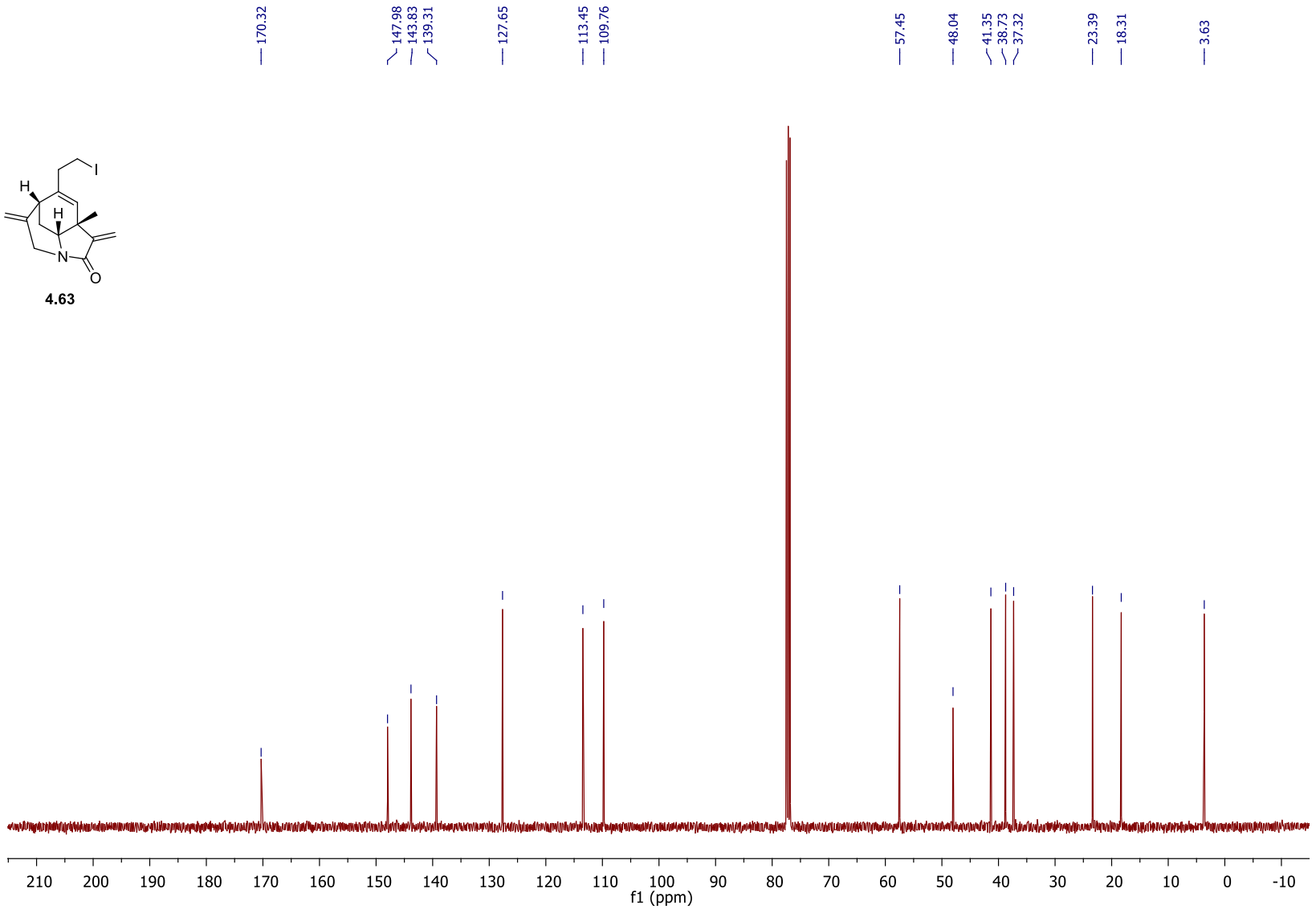

OH
H
H
N
O
4.62
0.99
1.00
2.94
1.00
3.96
0.96
3.01
0.97
1.09
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

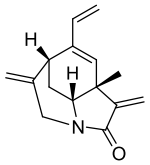

170.50
148.27
143.76
137.69
127.16
113.30
109.78
60.44
57.58
48.03
41.38
37.97
37.84
23.42
18.49
OH
H
H
N
O
4.62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
I
H
N
O

4.63

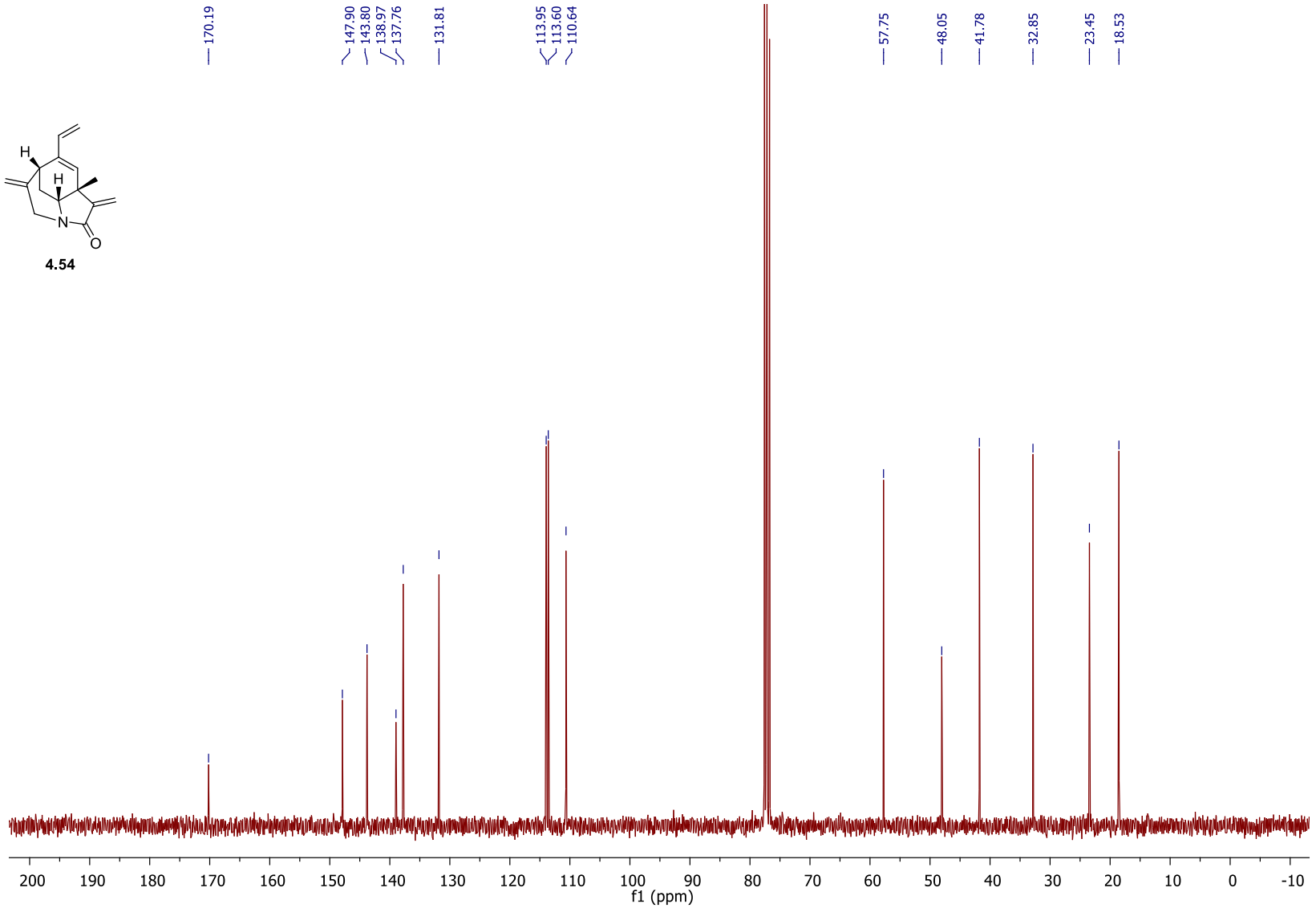
1.00
1.01
3.00
1.02
0.98
1.00
2.01
0.98
2.04
1.02
1.04
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

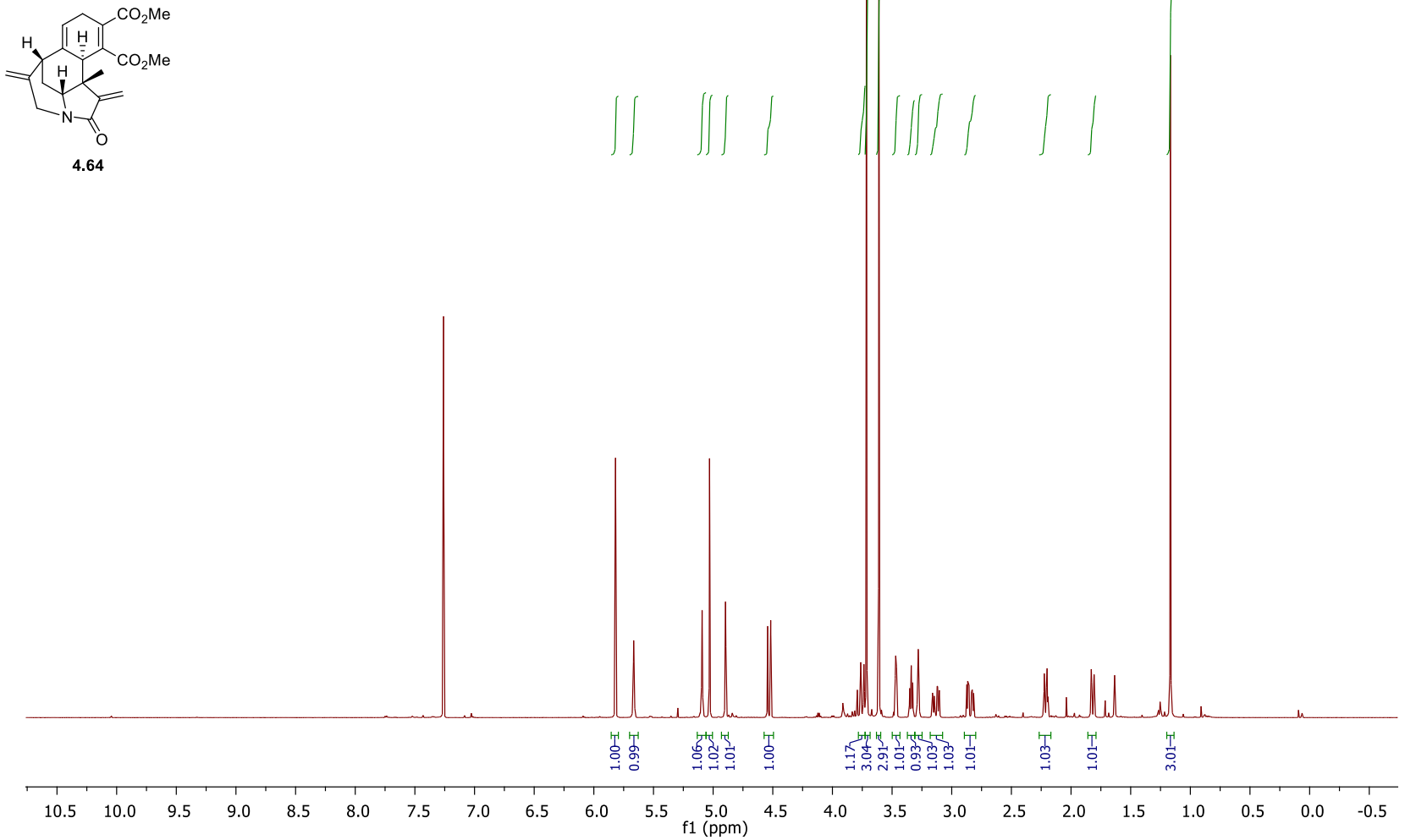

170.32
147.98
143.83
139.31
127.65
113.45
109.76
57.45
48.04
41.35
38.73
37.32
23.39
18.31
3.63
H
H
I
N
O
4.63
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

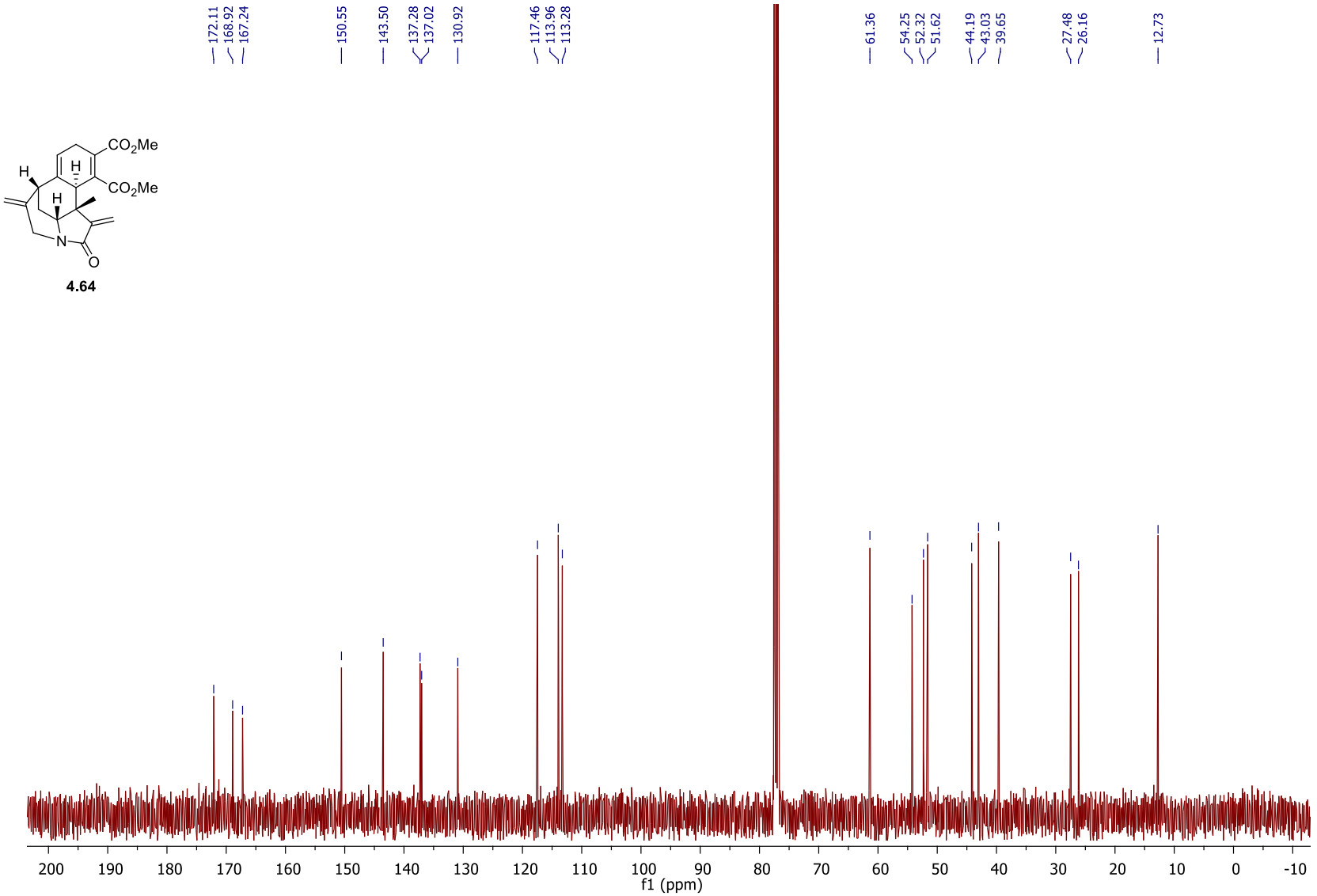

H
H
N
O

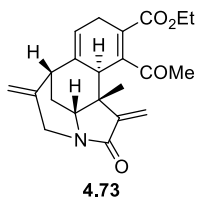
4.54

1.00
1.01
1.09
1.00
1.99
1.03
1.03
1.02
0.98
1.02
0.99
1.03
1.04
3.24
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
f1 (ppm)


170.19
147.90
143.80
138.97
137.76
131.81
113.95
113.60
110.64
57.75
48.05
41.78
32.85
23.45
18.53
H
H
N
O
4.54
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

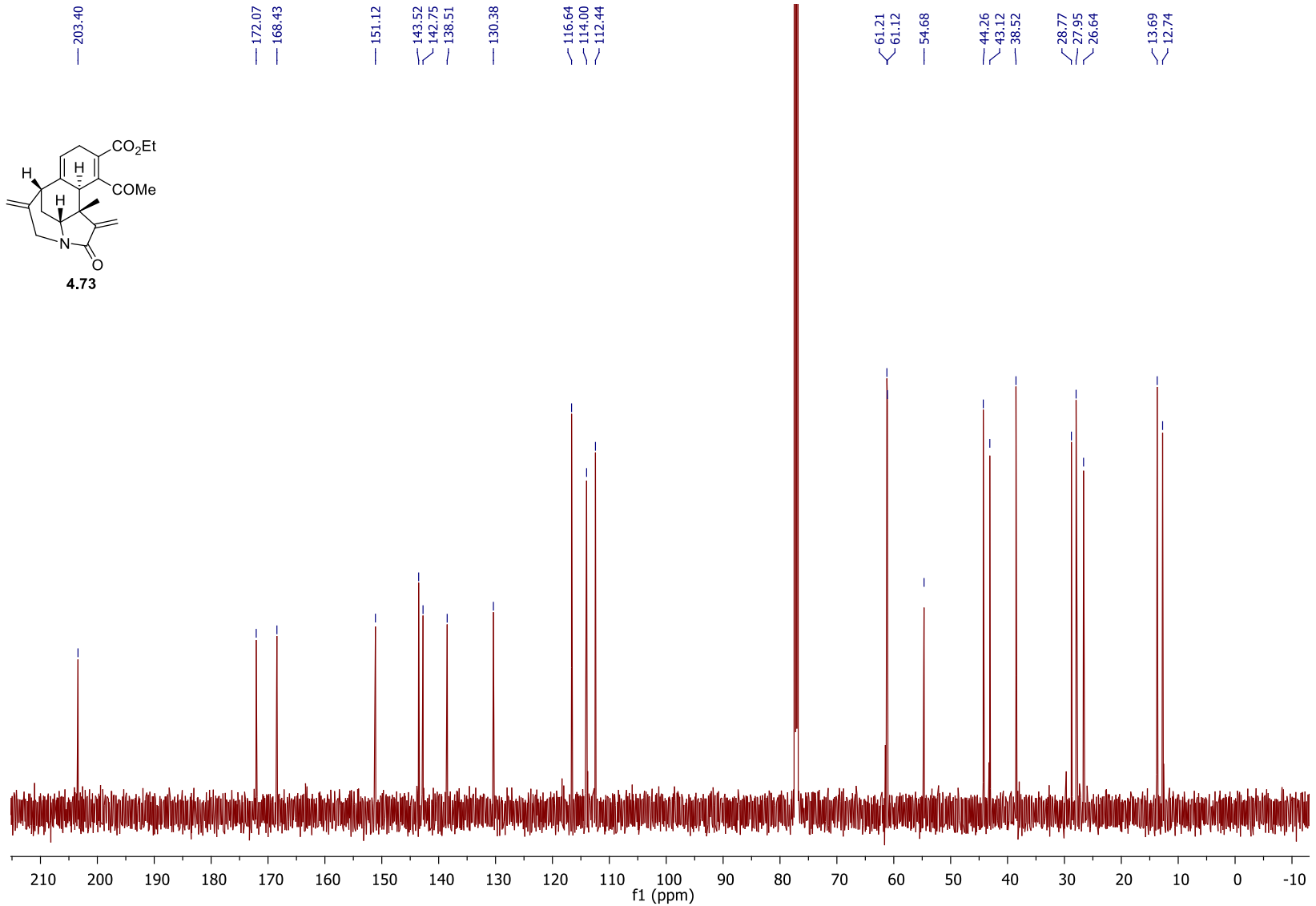

CO2Me
CO2Me
H
H
H
N
O
4.64
1.00
0.99
1.06
1.02
1.01
1.00
1.17
3.04
2.91
1.01
0.93
1.03
1.03
1.01
1.03
1.01
3.01
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

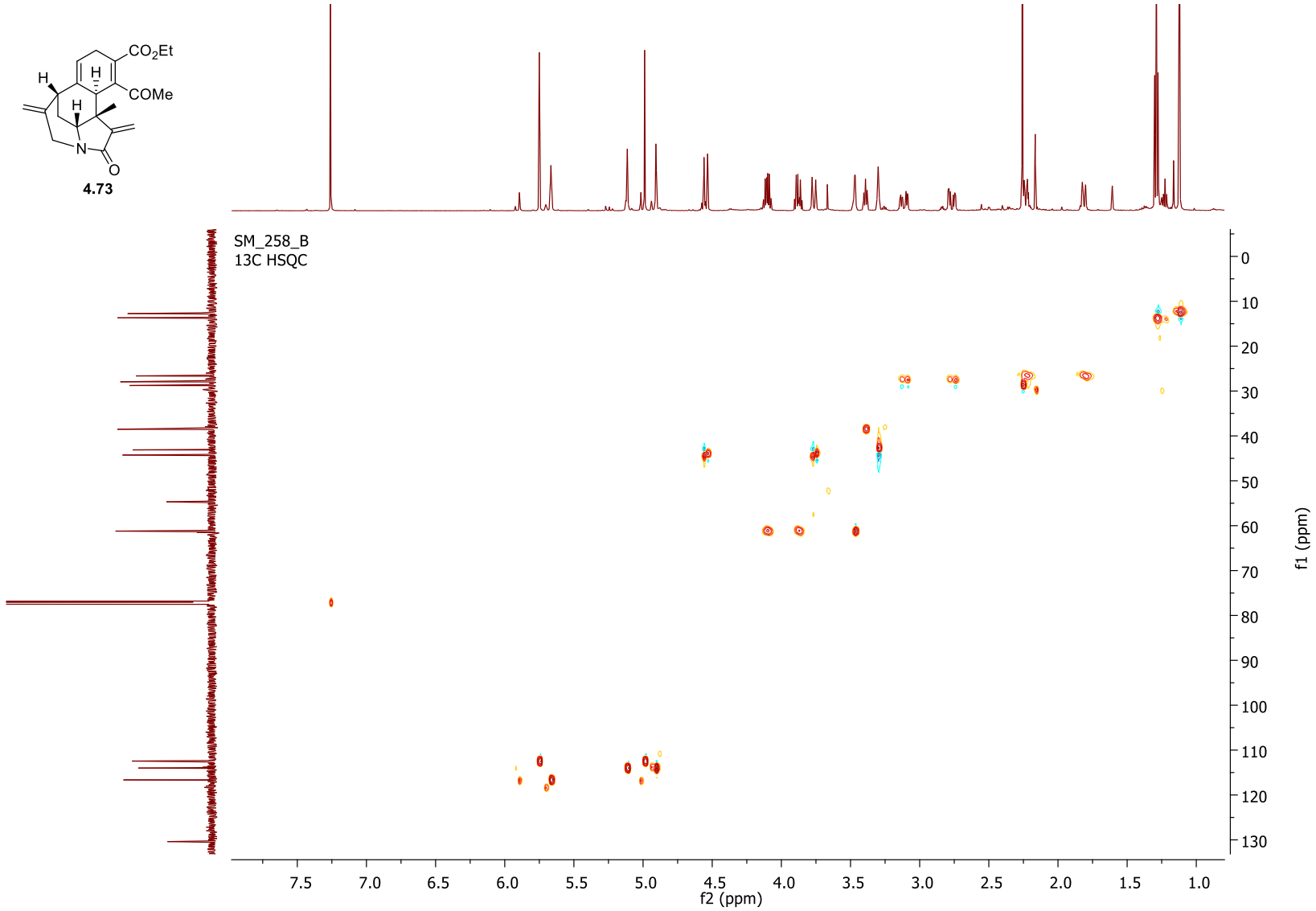

172.11
168.92
167.24
150.55
143.50
137.28
137.02
130.92
117.46
113.96
113.28
61.36
54.25
52.32
51.62
44.19
43.03
39.65
27.48
26.16
12.73
CO2Me
CO2Me
H
H
H
N
O
4.64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

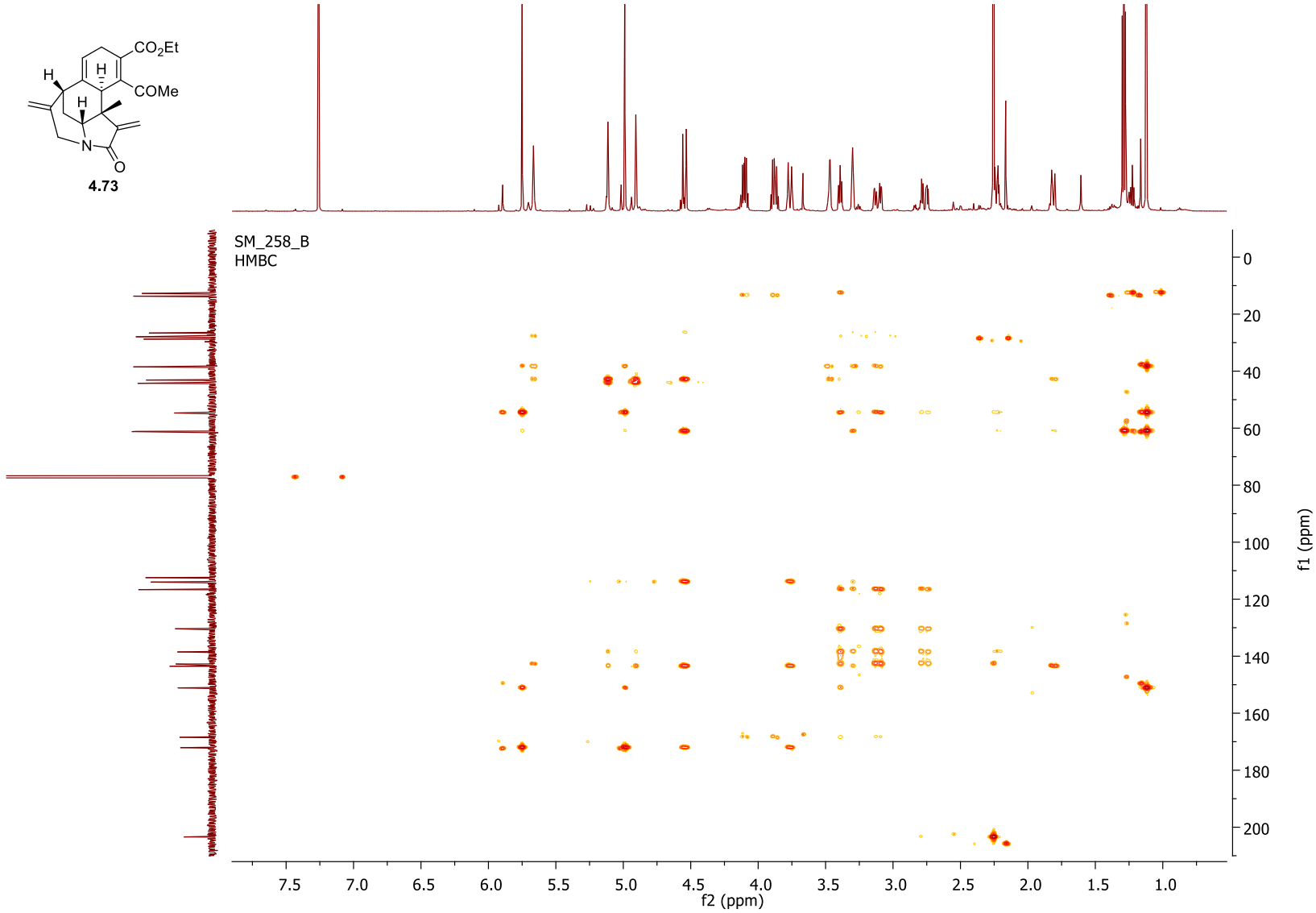

CO2Et
COMe
H
H
H
N
O

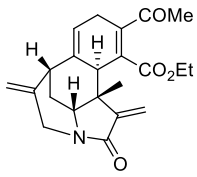
4.73

1.00
1.00
1.06
0.97
1.05
1.11
1.28
1.05
1.26
1.11
0.95
1.21
1.19
1.11
2.90
1.29
1.13
3.24
3.15
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
f1 (ppm)


203.40
172.07
168.43
151.12
143.52
142.75
138.51
130.38
116.64
114.00
112.44
61.21
61.12
54.68
44.26
43.12
38.52
28.77
27.95
26.64
13.69
12.74
CO2Et
COMe
H
H
H
N
O
4.73
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

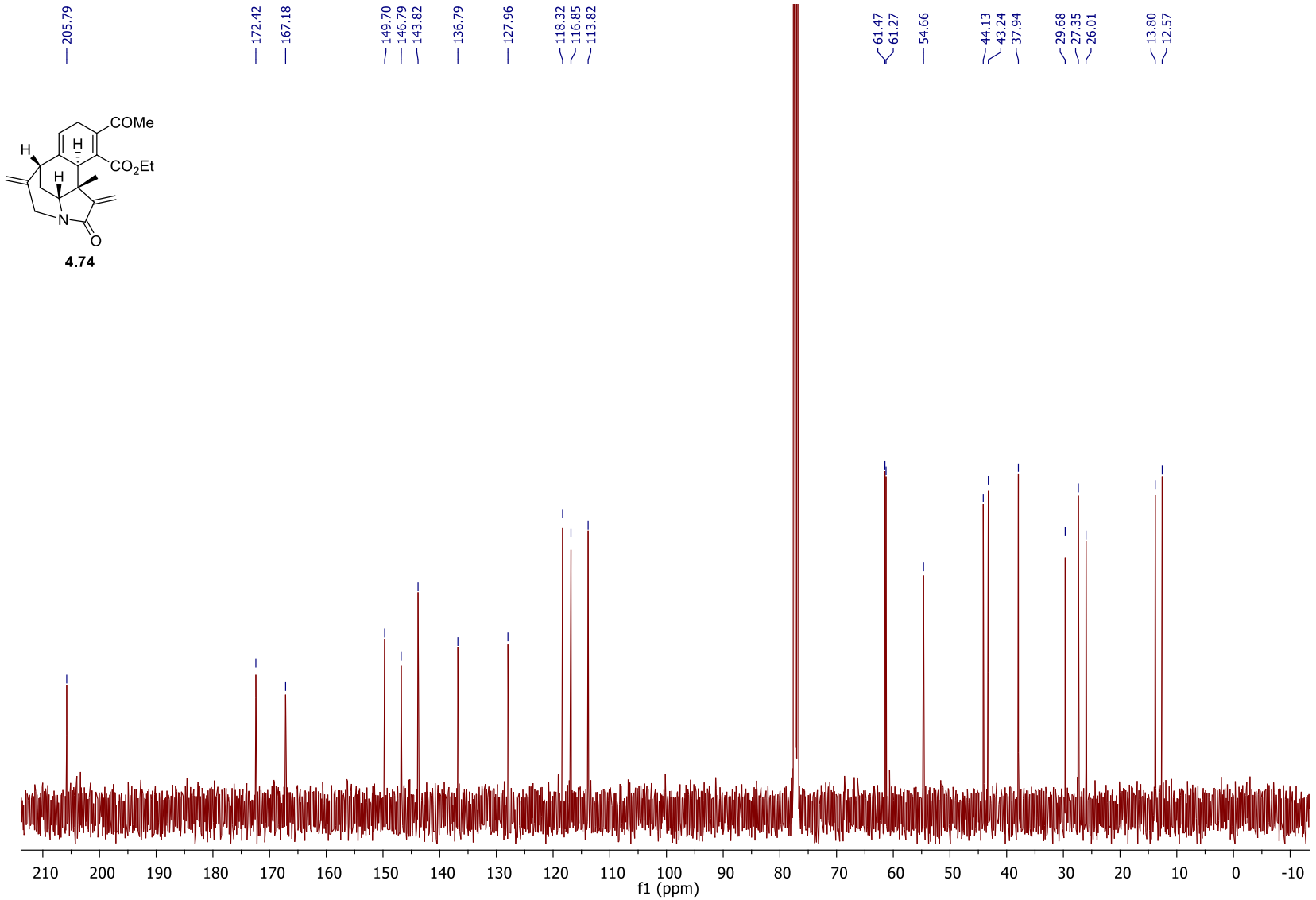

CO2Et
COMe
H
H
H
N
O
4.73
SM_258_B
13C HSQC
f2 (ppm)
f1 (ppm)

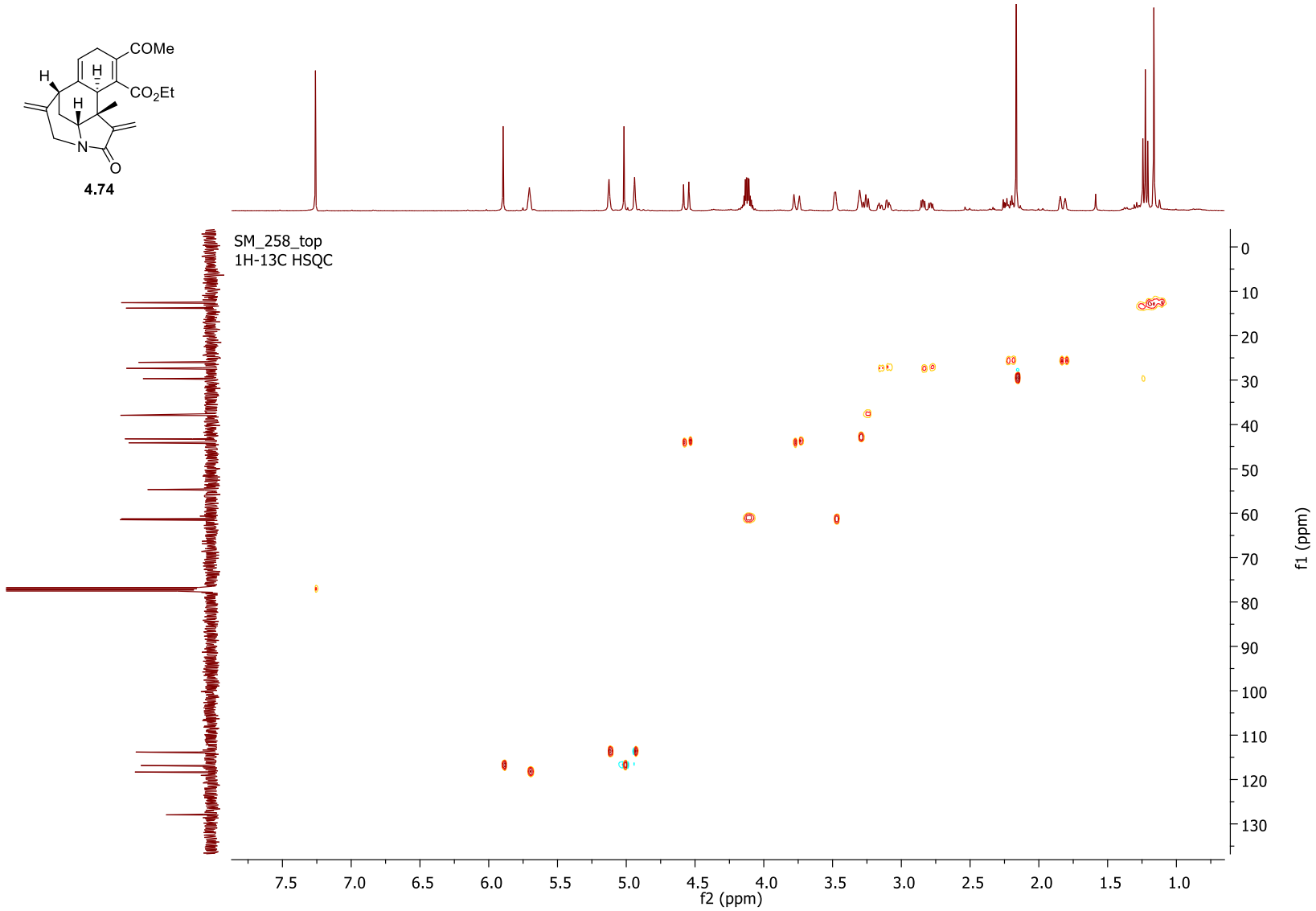

CO2Et
COMe
H
H
H
N
O
4.73
SM_258_B
HMBC
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
20
40
60
80
100
120
140
160
180
200

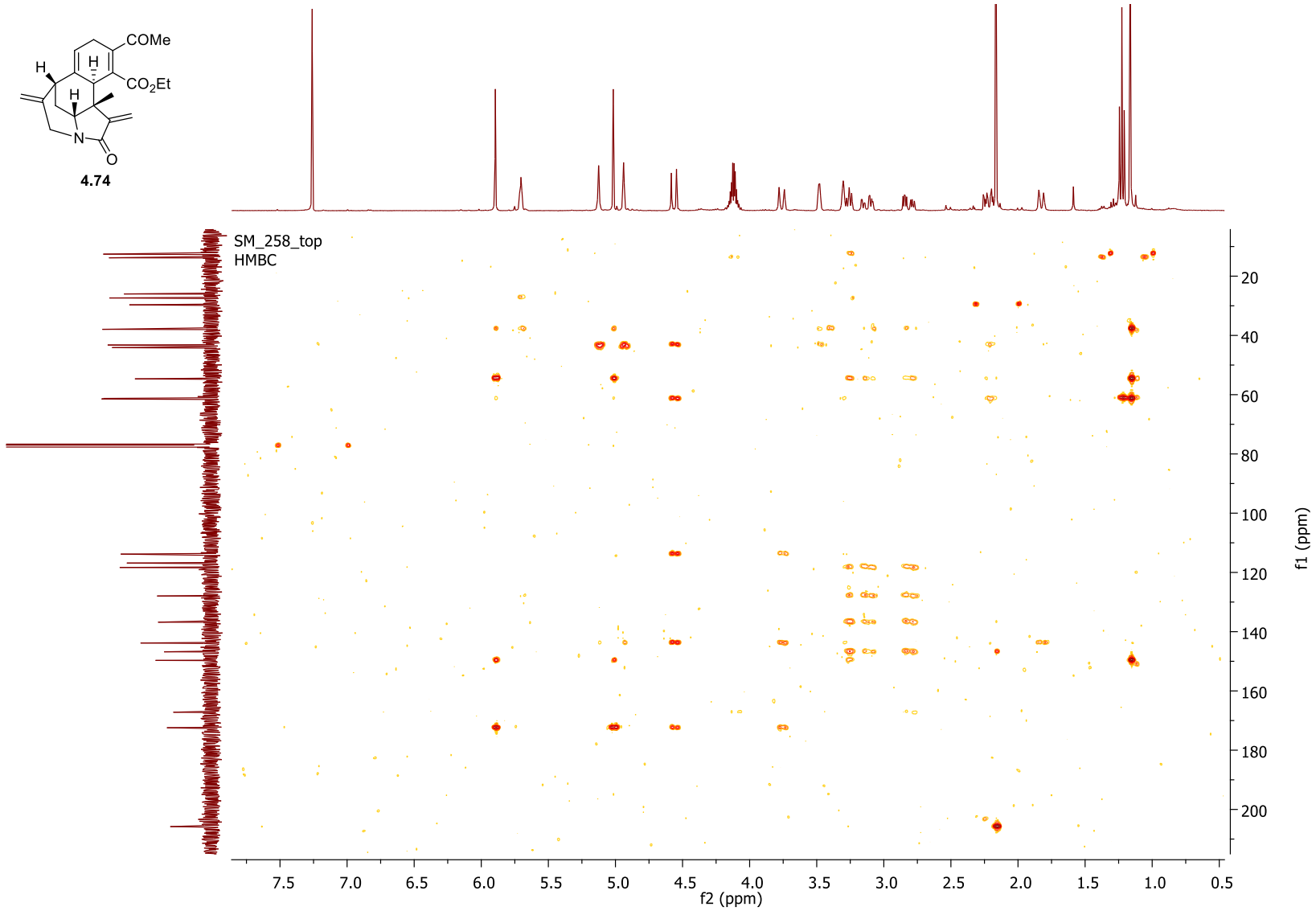

COMe
H
H
H
CO2Et
N
O

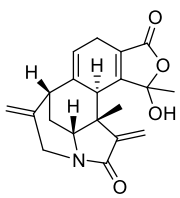
4.74

1.00
1.03
1.07
0.98
1.01
1.02
2.11
1.06
1.00
1.00
1.01
1.09
1.03
1.04
2.91
1.05
3.23
3.04
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
f1 (ppm)


205.79
172.42
167.18
149.70
146.79
143.82
136.79
127.96
118.32
116.85
113.82
61.47
61.27
54.66
44.13
43.24
37.94
29.68
27.35
26.01
13.80
12.57
COMe
CO2Et
H
H
H
N
O
4.74
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

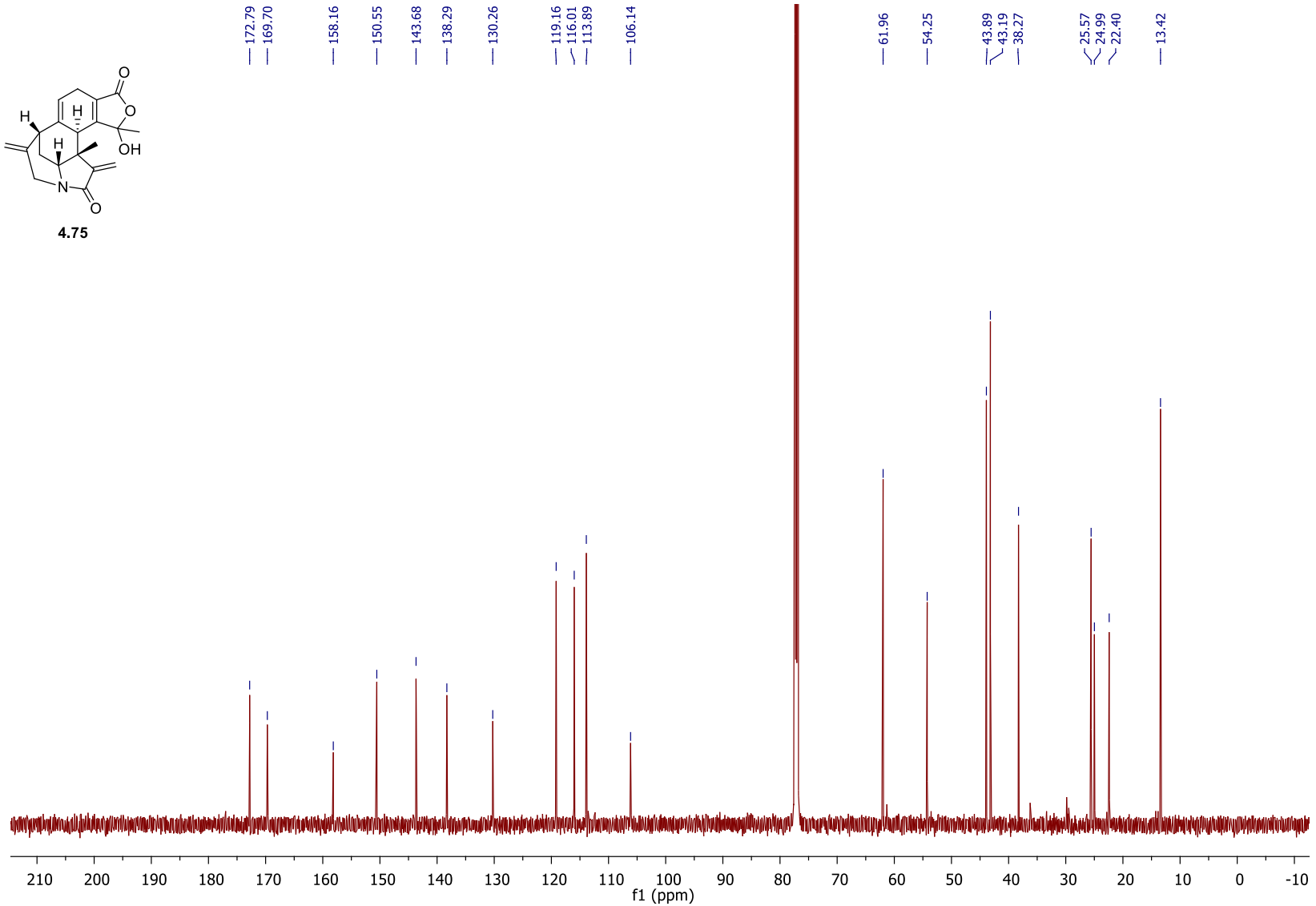

COMe
CO2Et
H
H
H
N
O
4.74
SM_258_top
1H-13C HSQC
f2 (ppm)
f1 (ppm)

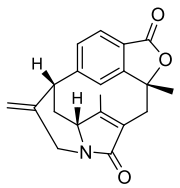

COMe
H
H
CO2Et
H
N
O
4.74
SM_258_top
HMBC
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
20
40
60
80
100
120
140
160
180
200
f1 (ppm)


O
O
H
H
H
OH
N
O

4.75

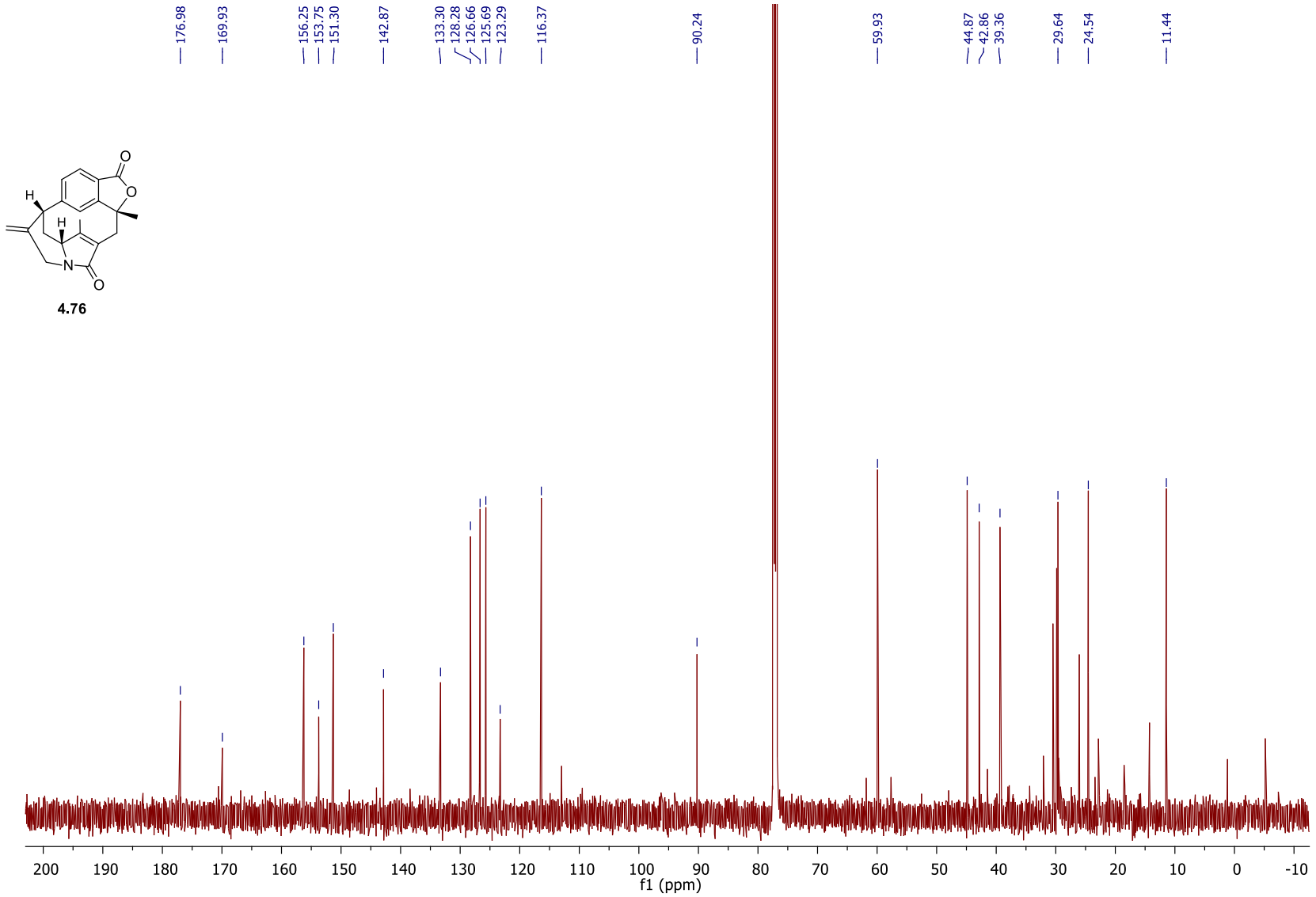
1.00
0.99
0.97
1.01
1.00
1.04
1.04
1.00
0.58
1.22
0.96
1.91
1.05
1.03
3.07
2.98
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

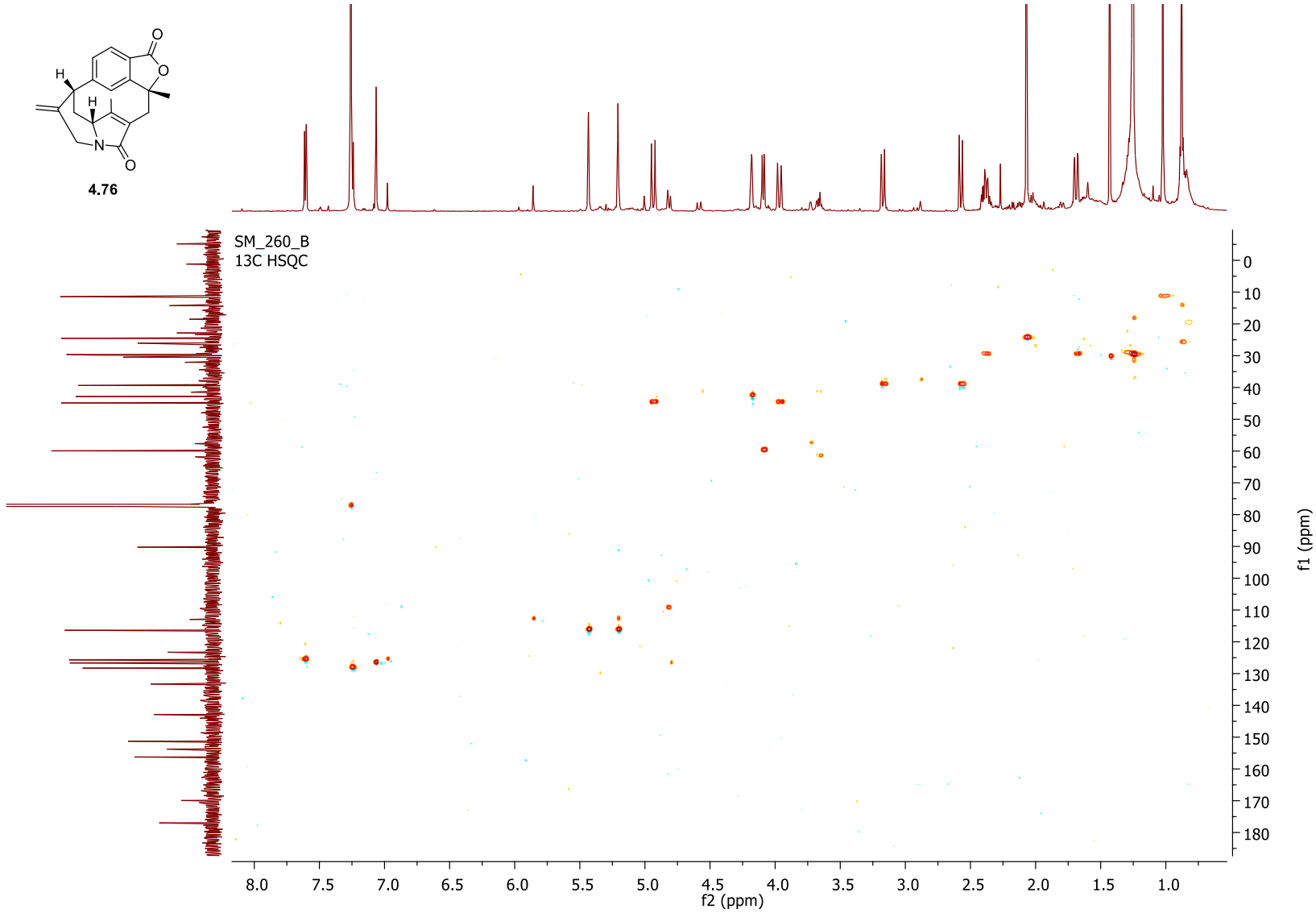

172.79
169.70
158.16
150.55
143.68
138.29
130.26
119.16
116.01
113.89
106.14
61.96
54.25
43.89
43.19
38.27
25.57
24.99
22.40
13.42
O
O
H
H
H
OH
N
O
4.75
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

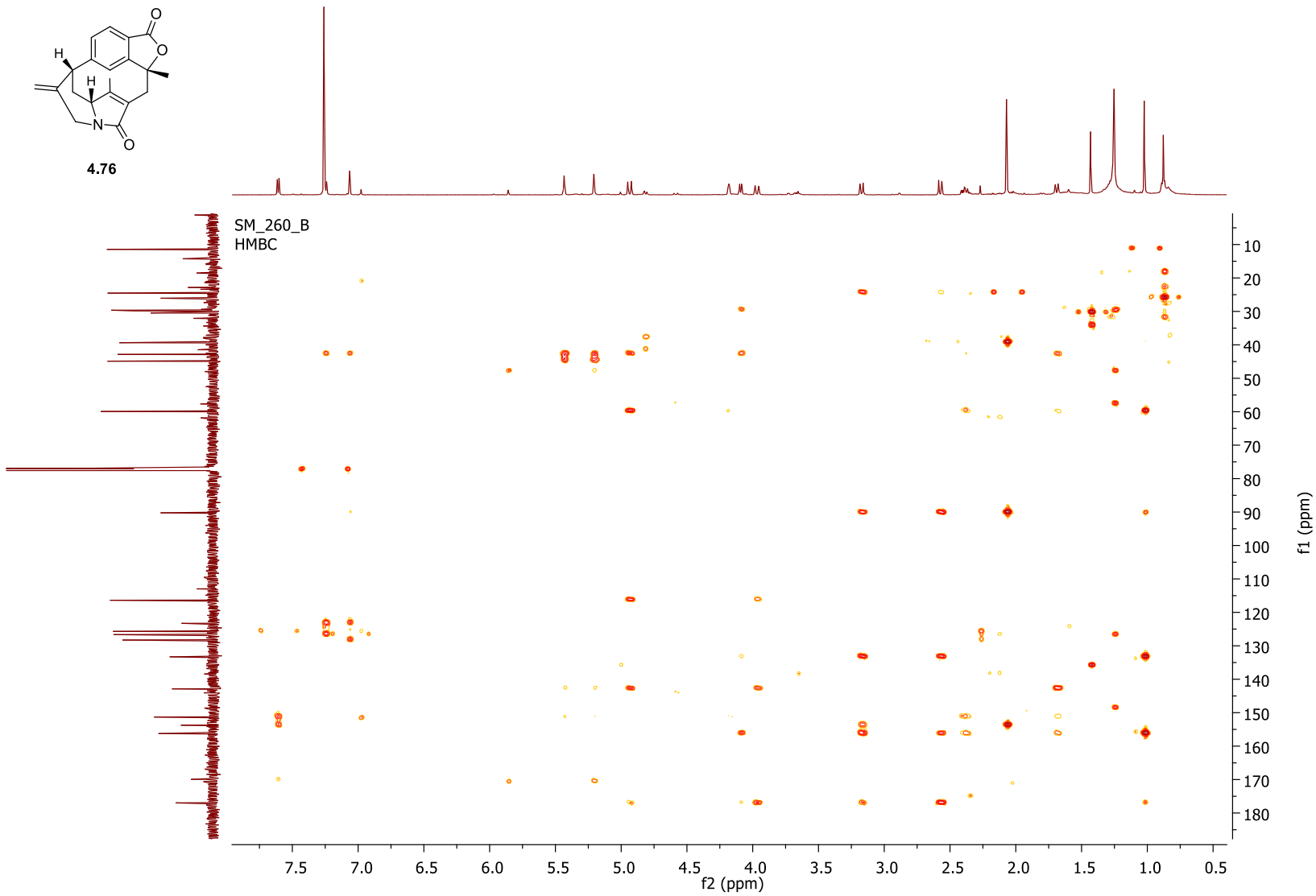

O
O
H
H
N
O

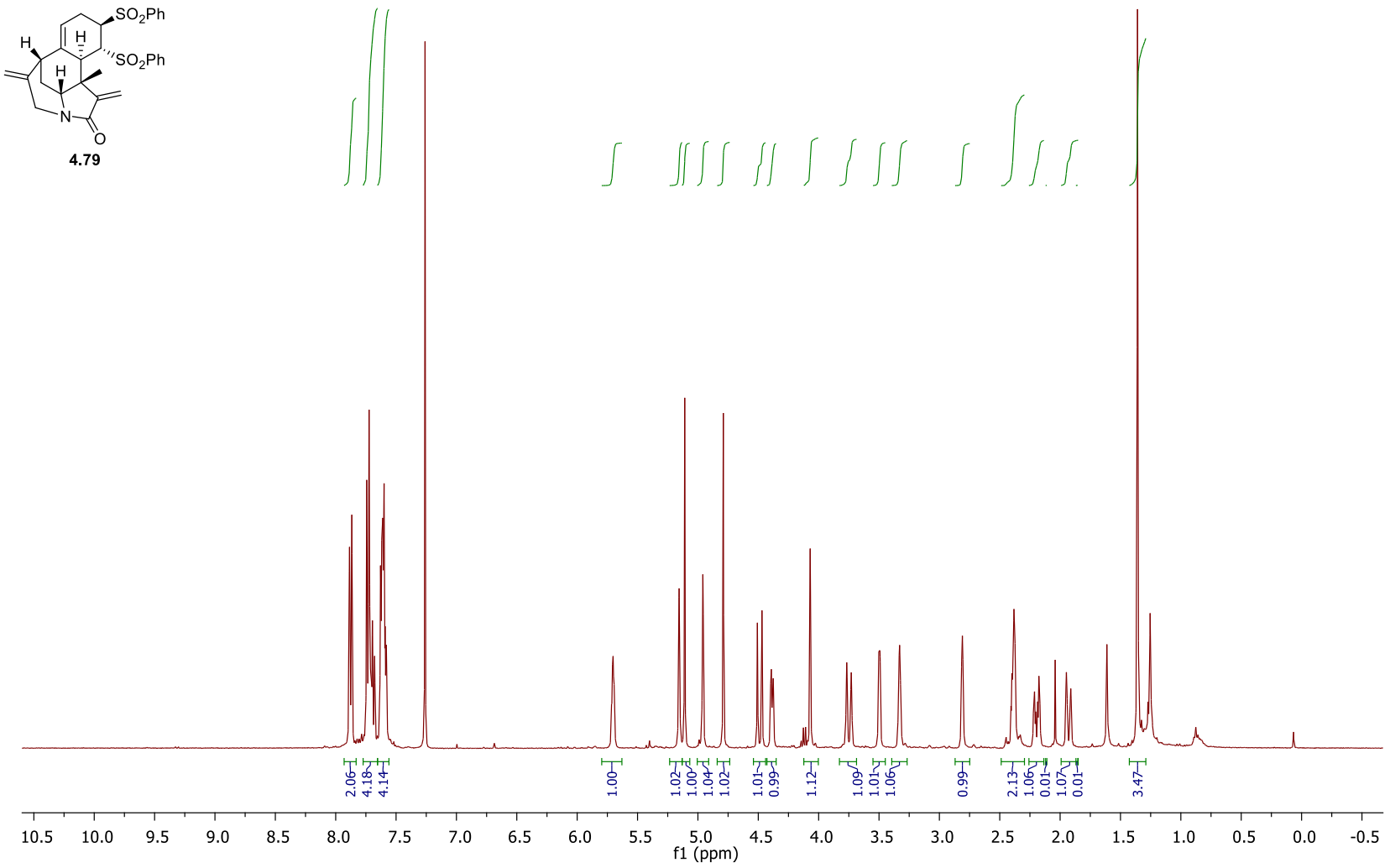
4.76

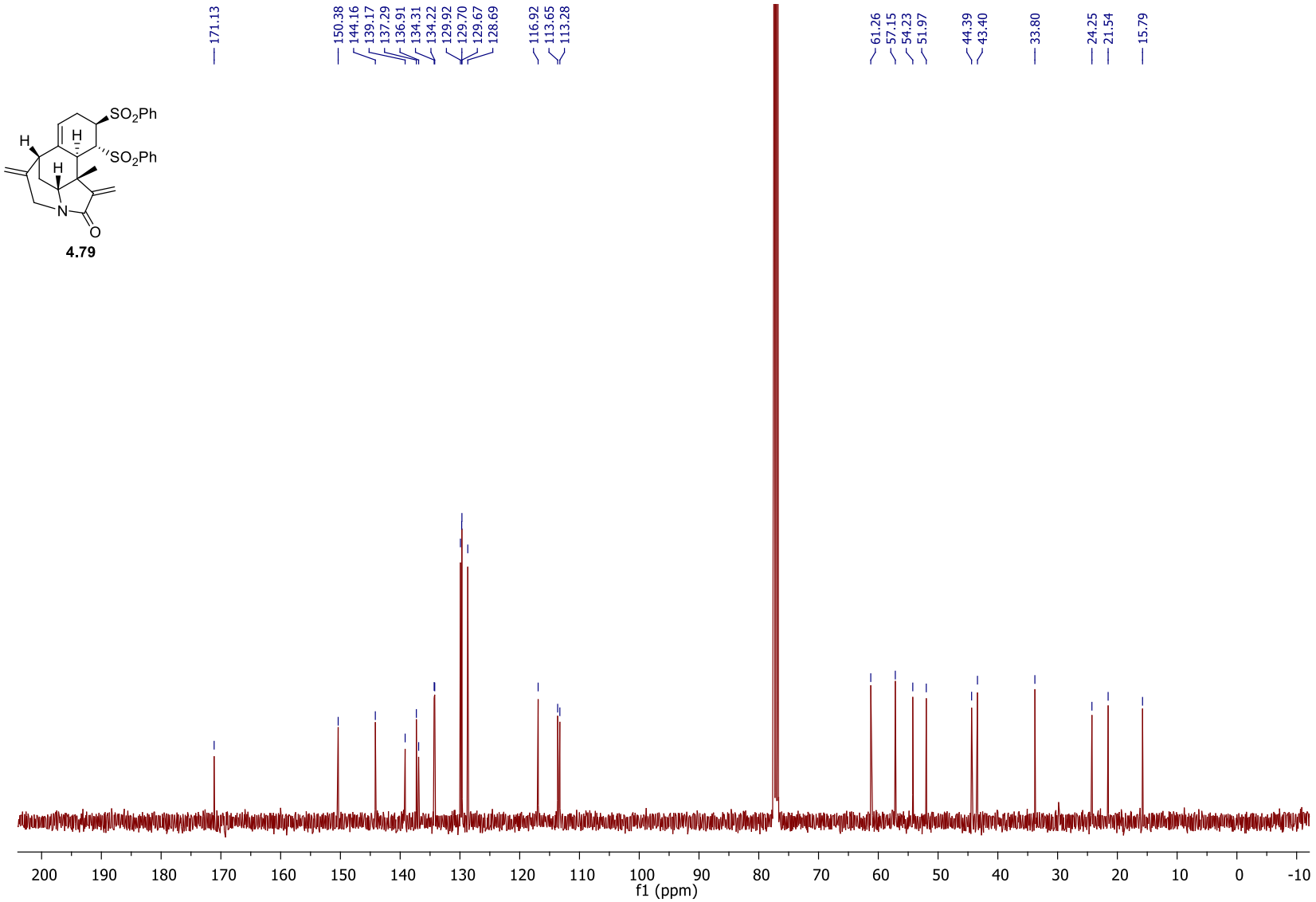
1.00
1.21
1.03
1.11
1.28
1.12
1.19
1.19
1.16
1.10
1.09
1.45
3.53
1.66
3.64
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

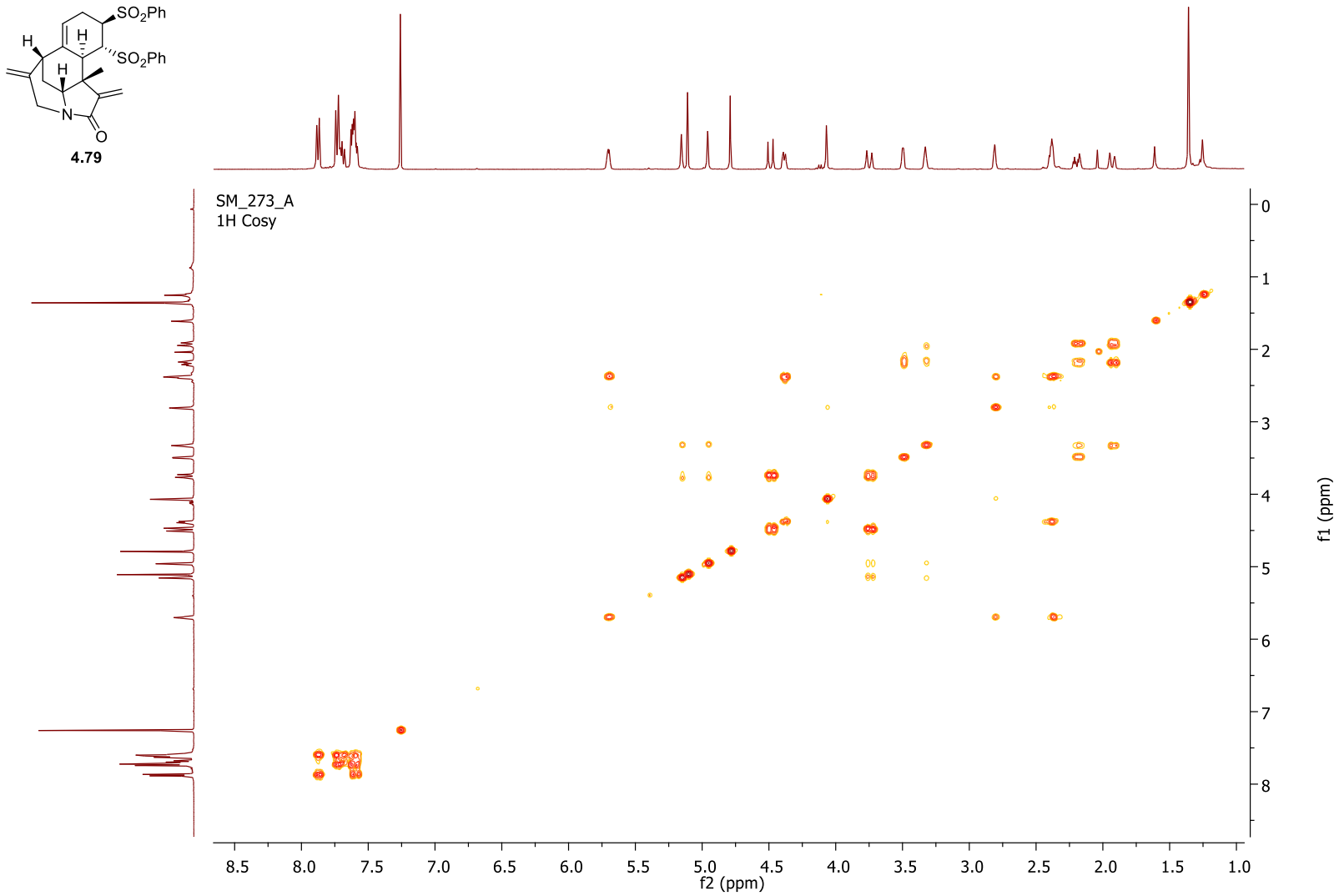

176.98
169.93
156.25
153.75
151.30
142.87
133.30
128.28
126.66
125.69
123.29
116.37
90.24
59.93
44.87
42.86
39.36
29.64
24.54
11.44
H
H
O
O
N
O
4.76
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

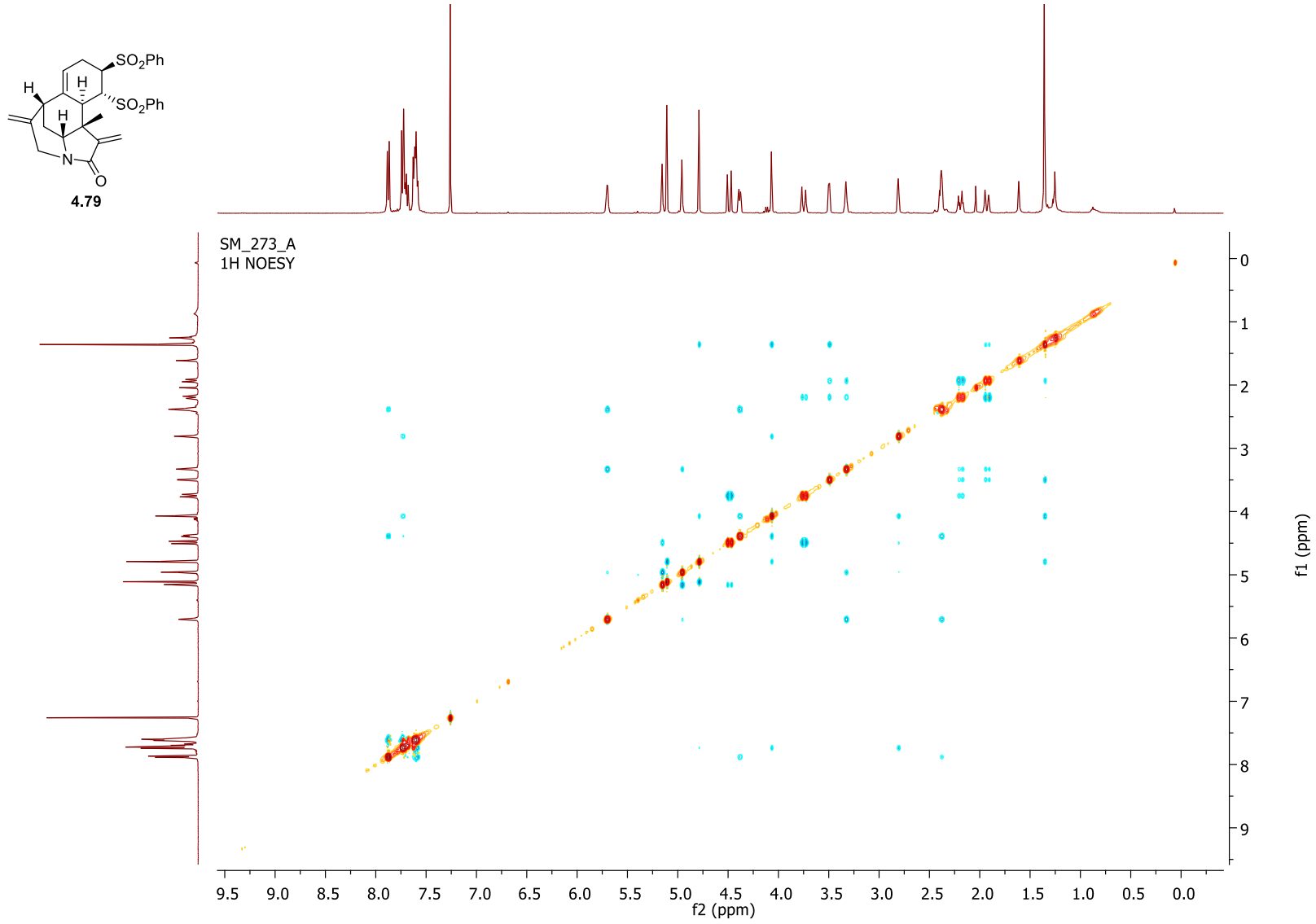

4.76
SM_260_B
13C HSQC
f2 (ppm)
f1 (ppm)

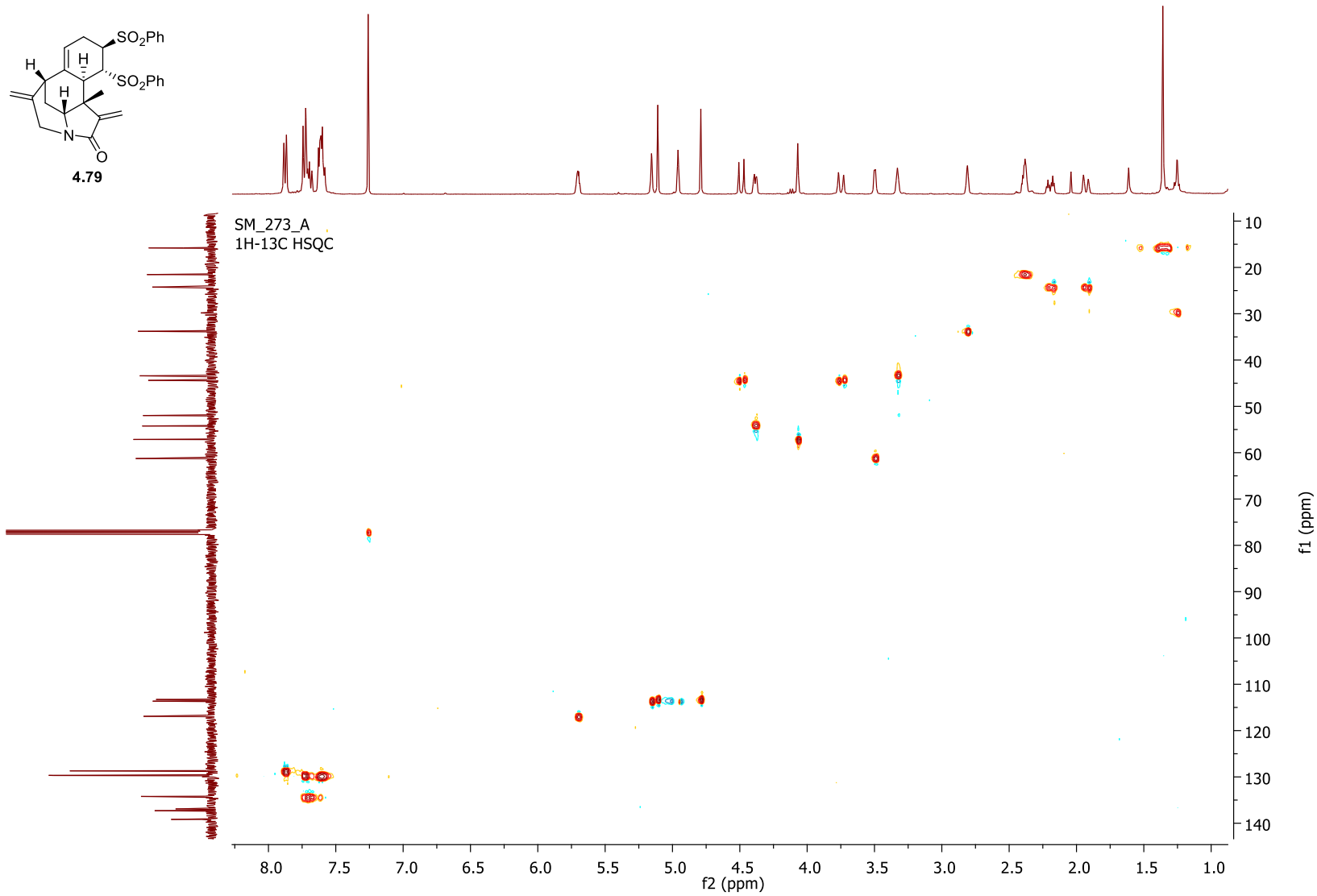

4.76
SM_260_B
HMBC
f2 (ppm)
f1 (ppm)

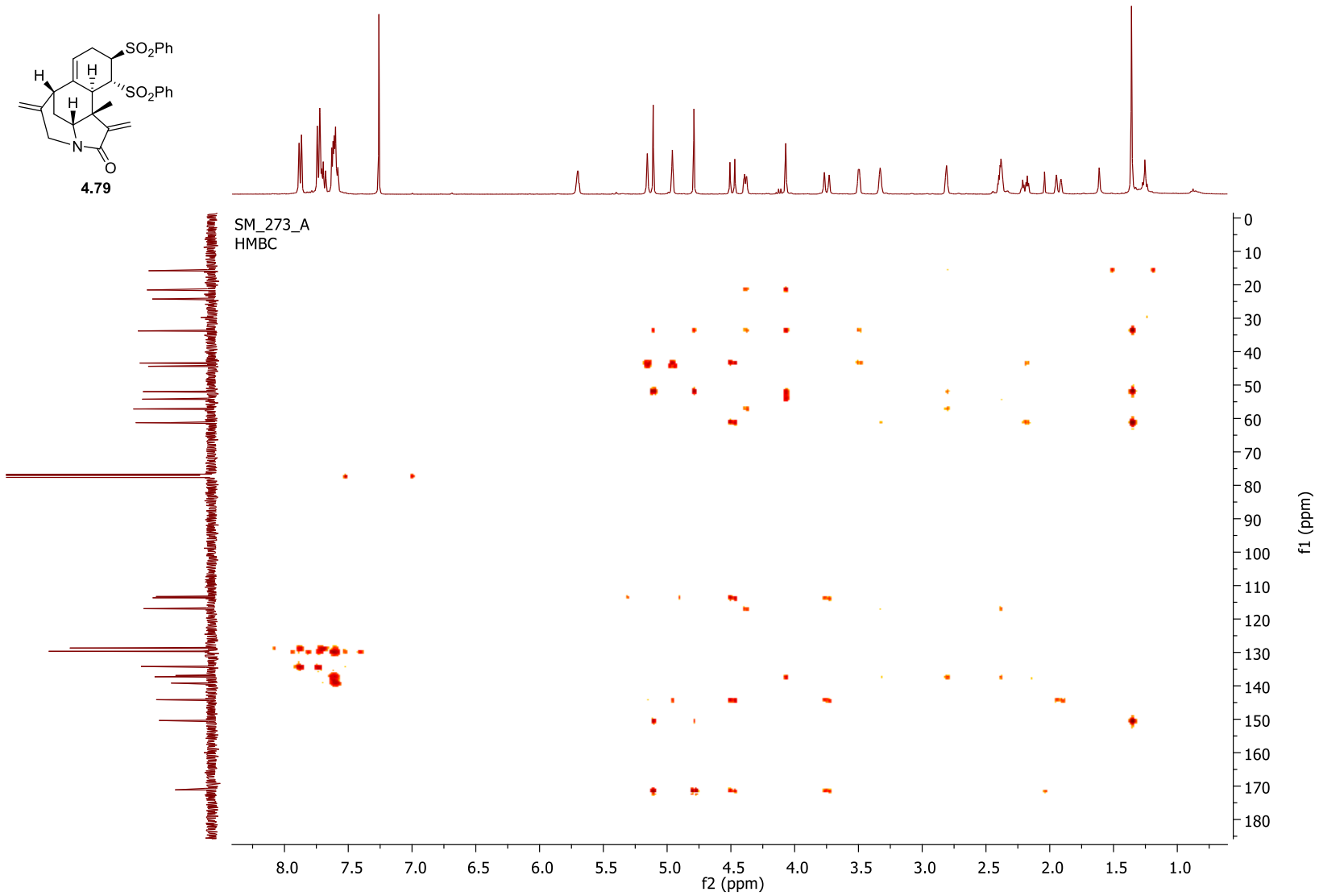

SO2Ph
SO2Ph
H
H
H
N
O
4.79
2.06
4.18
4.14
1.00
1.02
1.00
1.04
1.02
1.01
0.99
1.12
1.09
1.01
1.06
0.99
2.13
1.06
0.01
1.07
0.01
3.47
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

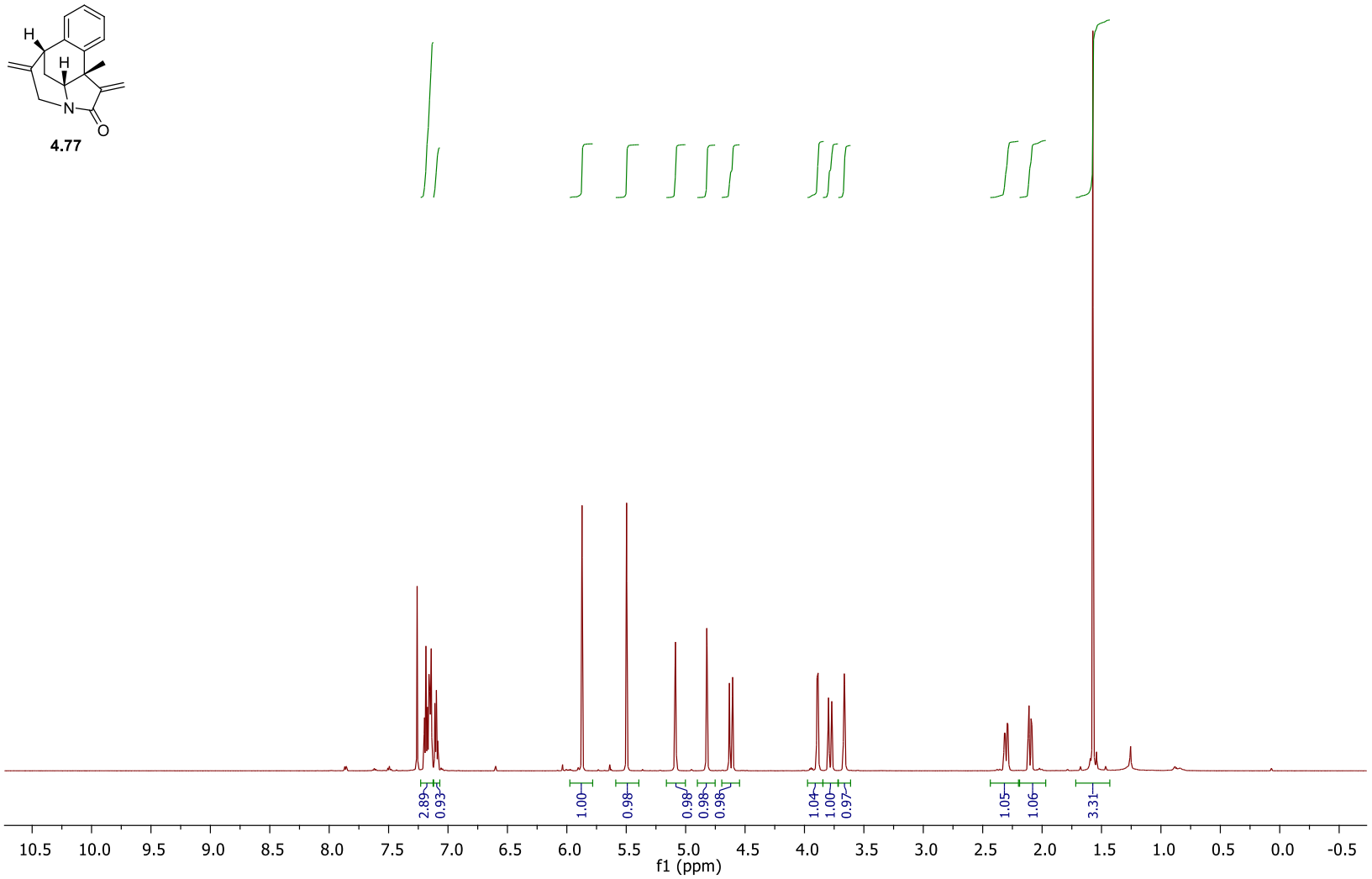

171.13
150.38
144.16
139.17
137.29
136.91
134.31
134.22
129.92
129.70
129.67
128.69
116.92
113.65
113.28
61.26
57.15
54.23
51.97
44.39
43.40
33.80
24.25
21.54
15.79
SO2Ph
SO2Ph
H
H
H
N
O
4.79
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

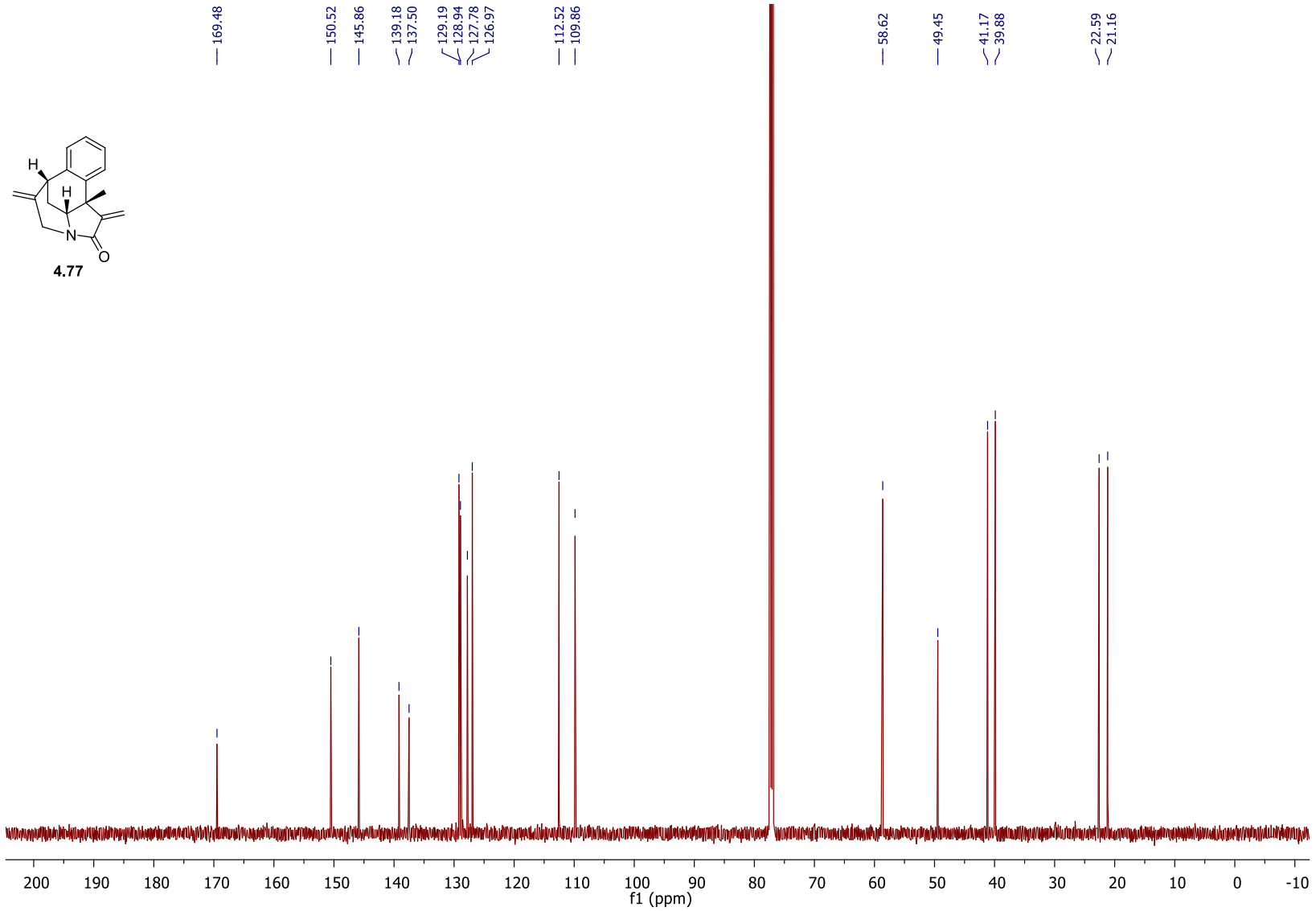

SO2Ph
SO2Ph
H
H
H
N
O
4.79
SM_273_A
1H Cosy
f2 (ppm)
f1 (ppm)

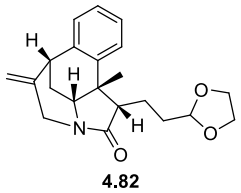

SO2Ph
SO2Ph
H
H
H
N
O
4.79
SM_273_A
1H NOESY
f2 (ppm)
f1 (ppm)


SO2Ph
SO2Ph
H
H
H
N
O
4.79
SM_273_A
1H-13C HSQC
f2 (ppm)
f1 (ppm)


SO2Ph
SO2Ph
H
H
H
N
O
4.79
SM_273_A
HMBC
f2 (ppm)
f1 (ppm)

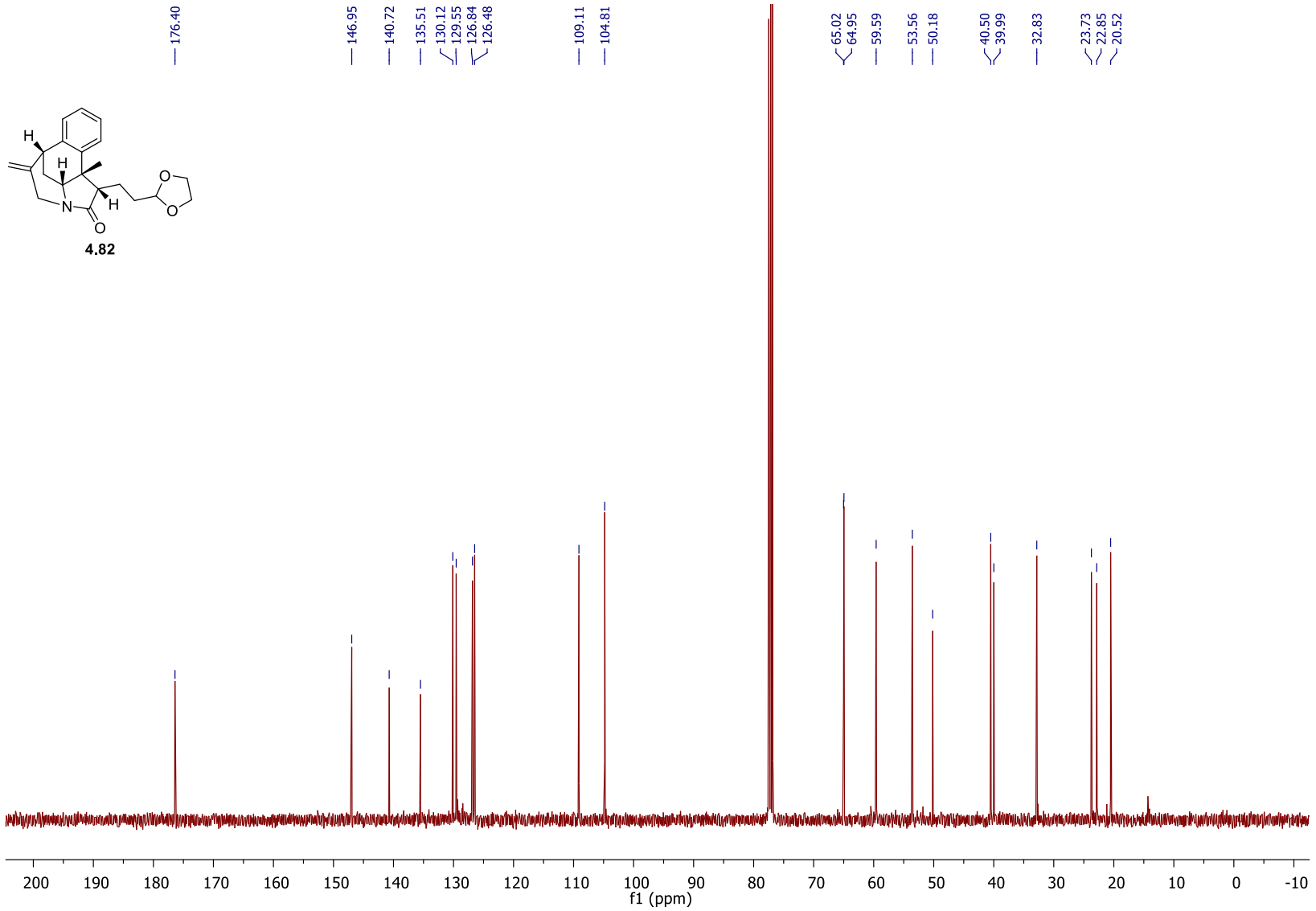

H
H
N
O
4.77
2.89
0.93
1.00
0.98
0.98
0.98
0.98
1.04
1.00
0.97
1.05
1.06
3.31
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

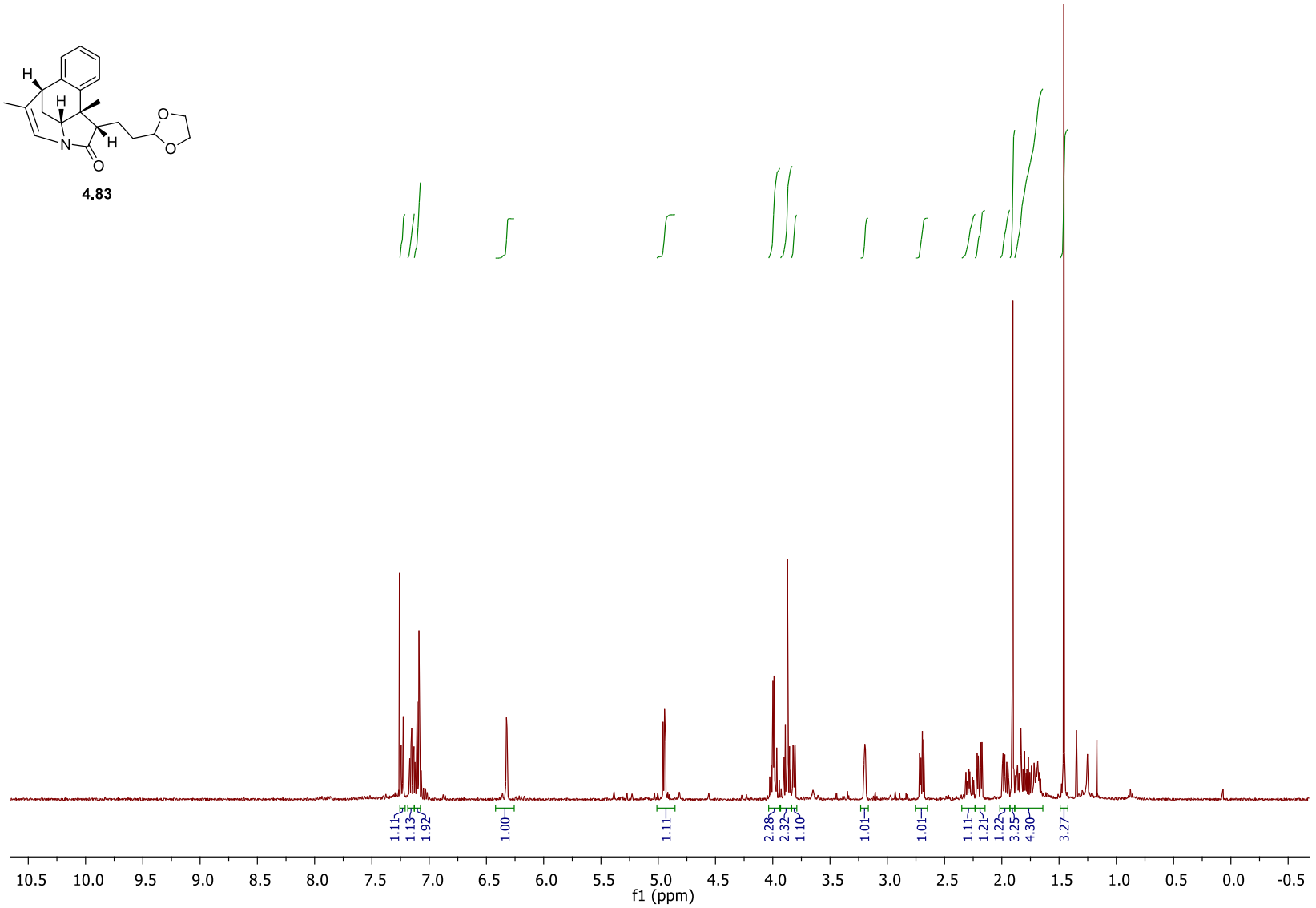

169.48
150.52
145.86
139.18
137.50
129.19
128.94
127.78
126.97
112.52
109.86
58.62
49.45
41.17
39.88
22.59
21.16
H
H
N
O
4.77
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

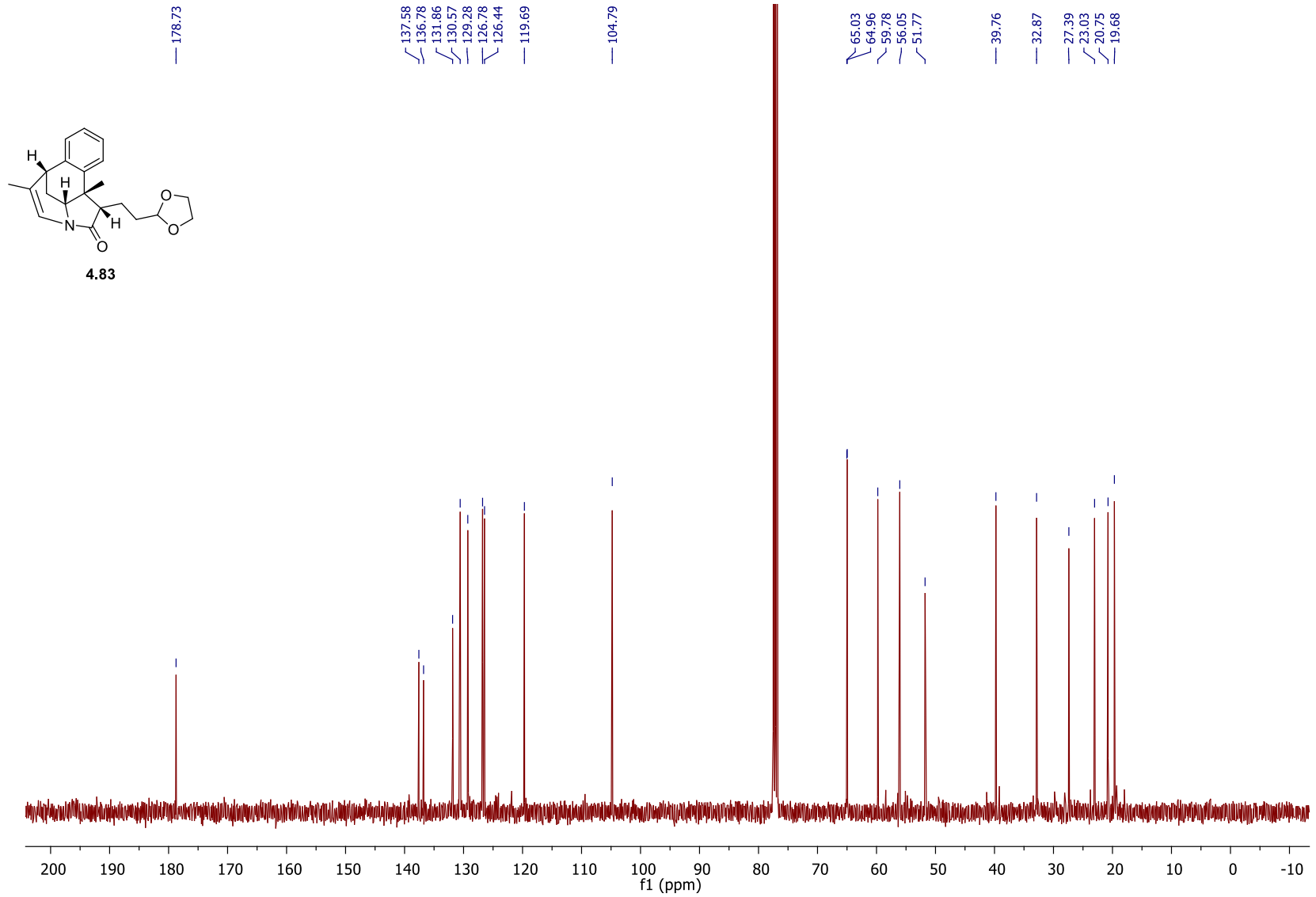

H
H
N
O
H
O
O

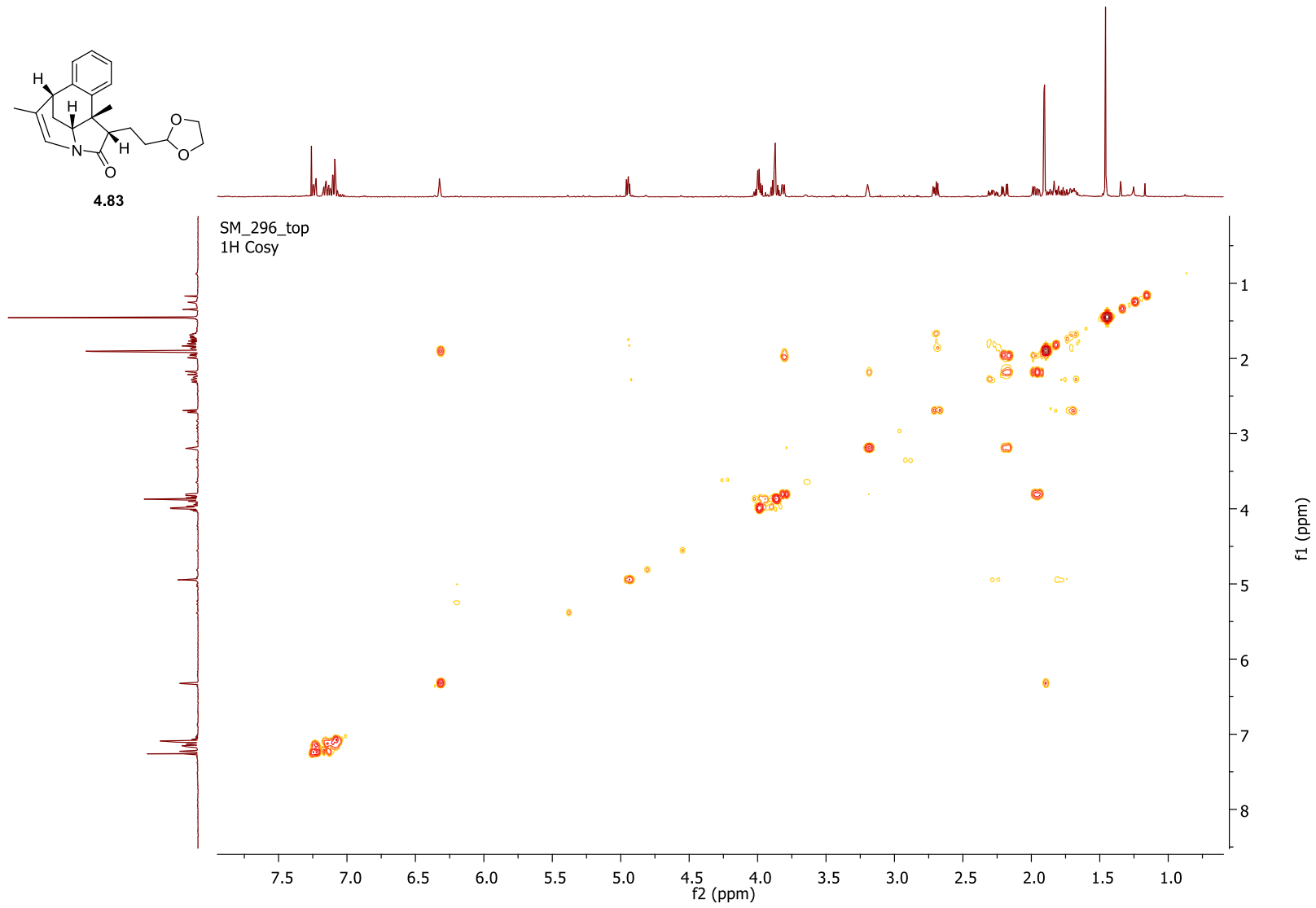
4.82

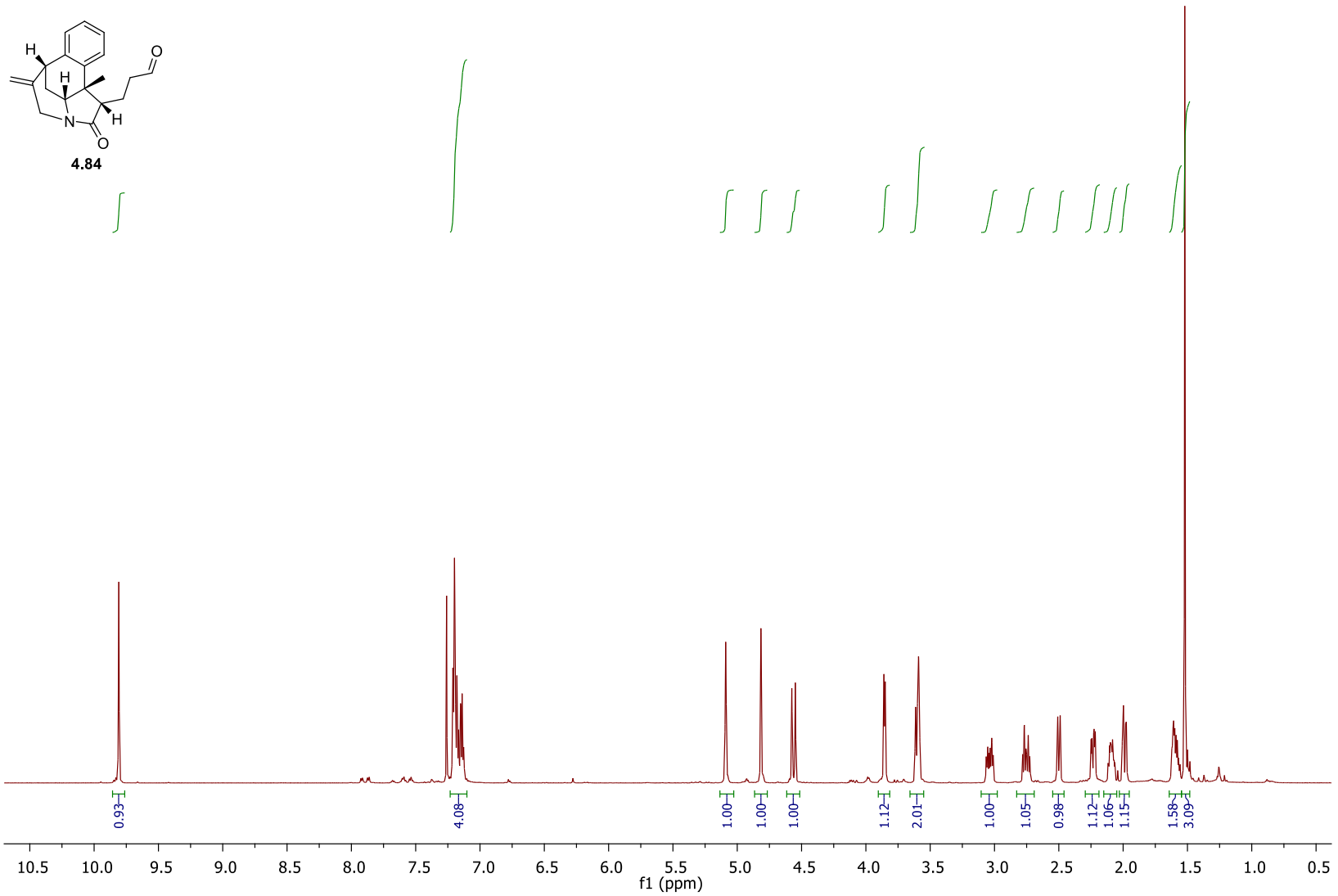
4.05
1.00
1.07
0.98
0.98
2.10
3.17
2.01
1.00
2.24
1.17
2.31
1.01
3.18
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

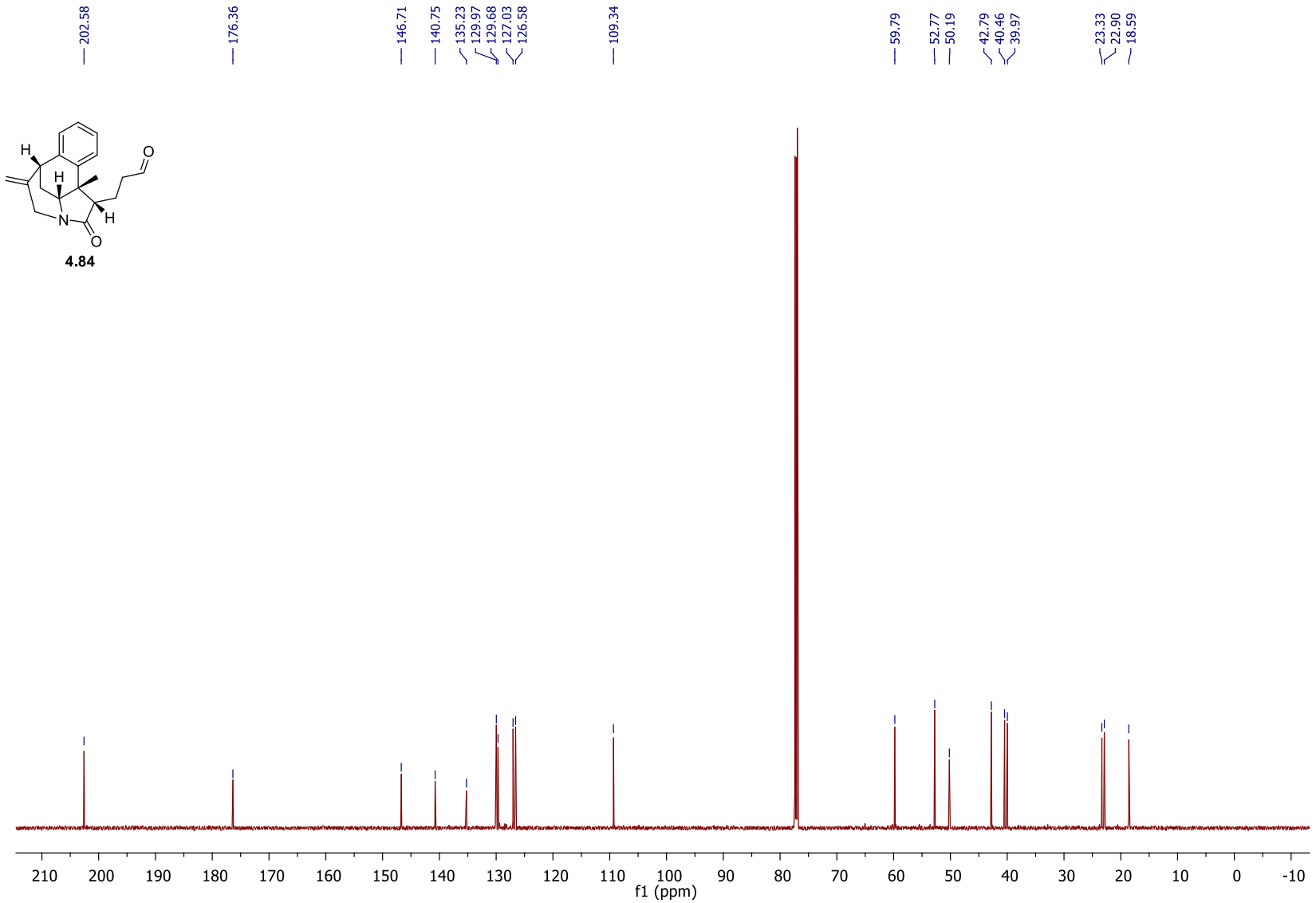

176.40
146.95
140.72
135.51
130.12
129.55
126.84
126.48
109.11
104.81
65.02
64.95
59.59
53.56
50.18
40.50
39.99
32.83
23.73
22.85
20.52
H
H
H
N
O
O
O
4.82
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

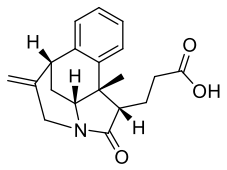

4.83
1.11
1.13
1.92
1.00
1.11
2.28
2.32
1.10
1.01
1.01
1.11
1.21
1.22
3.25
4.30
3.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


178.73
137.58
136.78
131.86
130.57
129.28
126.78
126.44
119.69
104.79
65.03
64.96
59.78
56.05
51.77
39.76
32.87
27.39
23.03
20.75
19.68
H
H
H
N
O
O
O
O
4.83
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


4.83
SM_296_top
1H Cosy
f2 (ppm)
f1 (ppm)

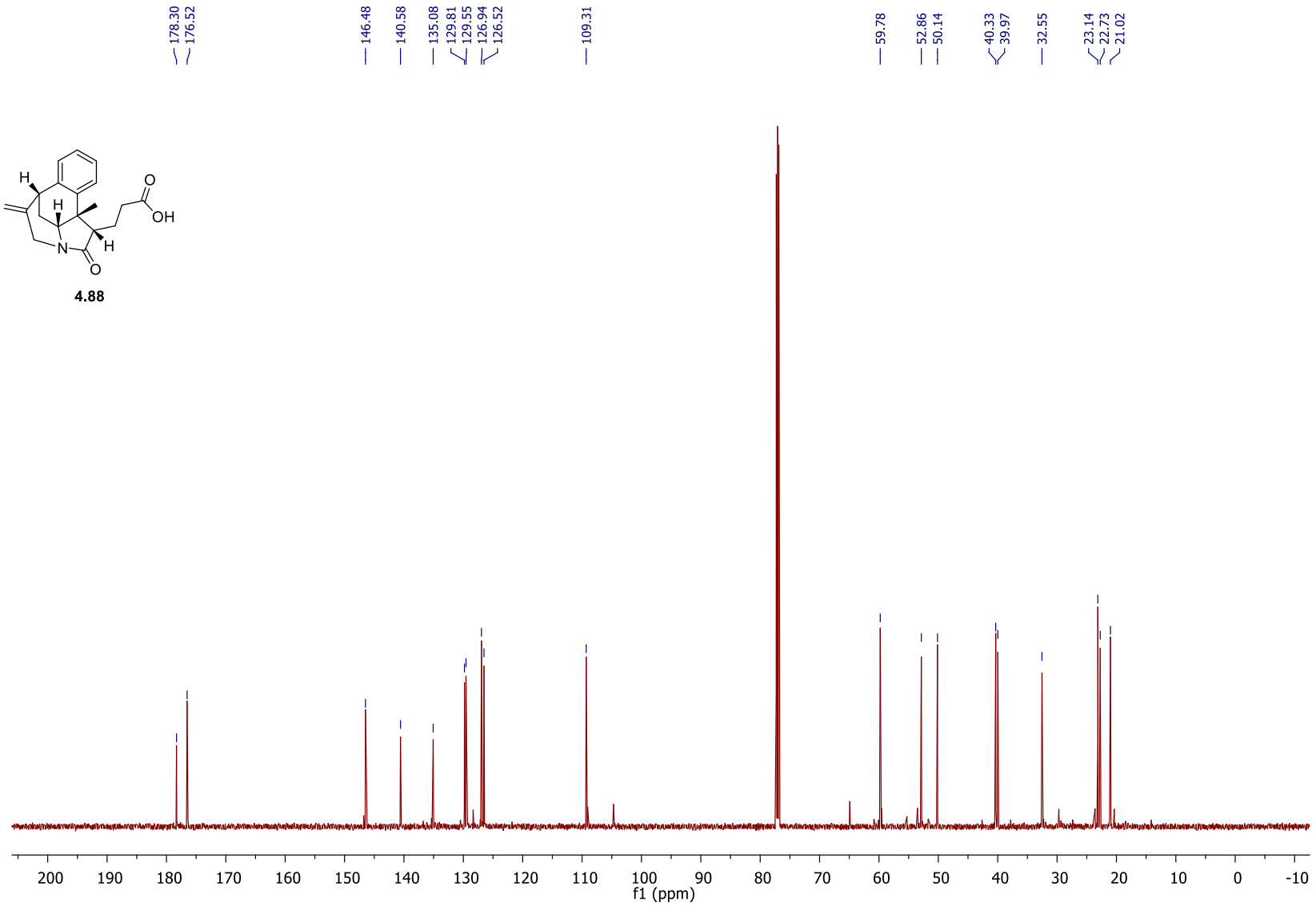

H
H
O
N
H
O
4.84
0.93
4.08
1.00
1.00
1.00
1.12
2.01
1.00
1.05
0.98
1.12
1.06
1.15
1.58
3.09
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


202.58
176.36
146.71
140.75
135.23
129.97
129.68
127.03
126.58
109.34
59.79
52.77
50.19
42.79
40.46
39.97
23.33
22.90
18.59
H
H
N
O
H
O
4.84
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

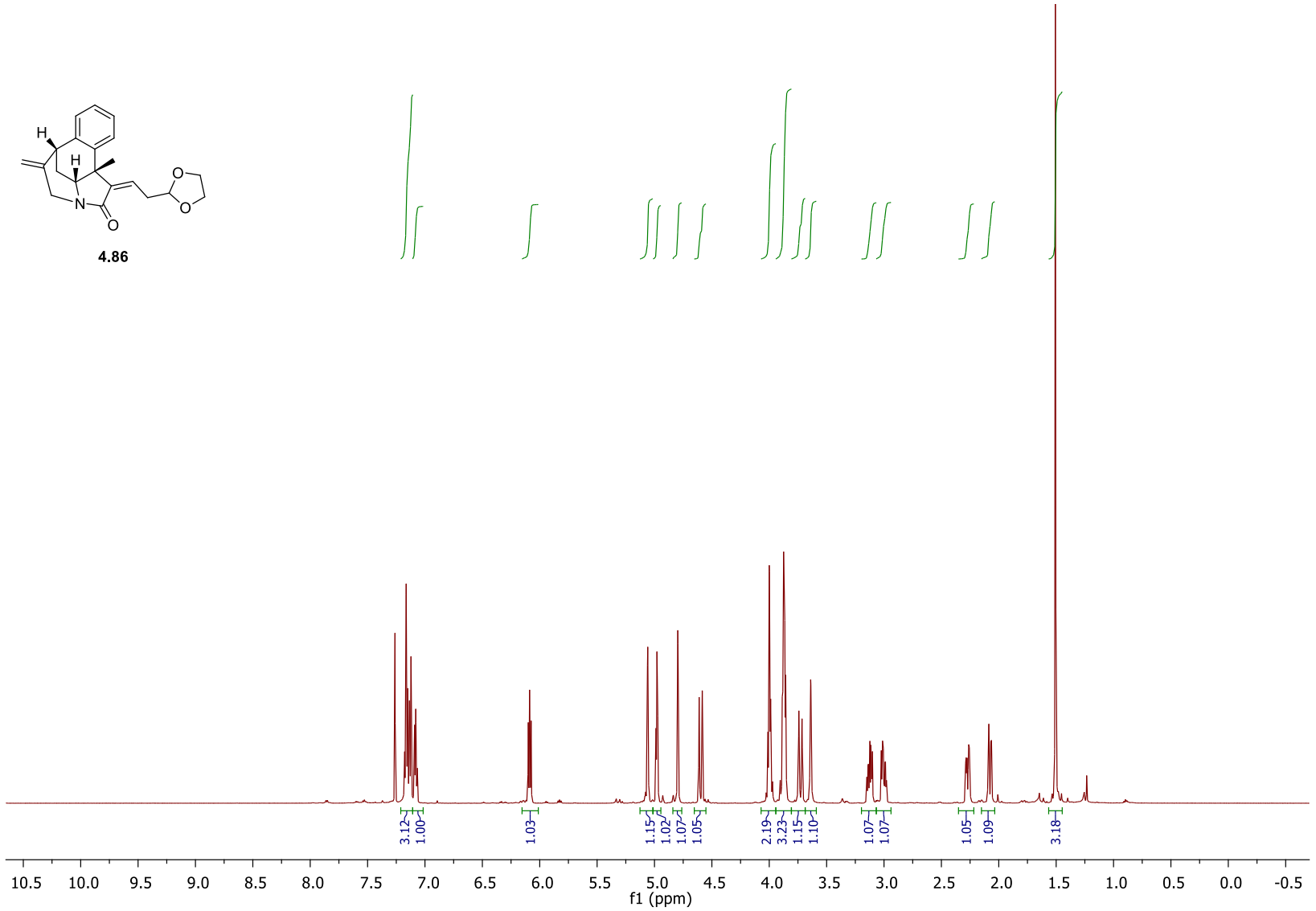

H
H
O
OH
N
H
O

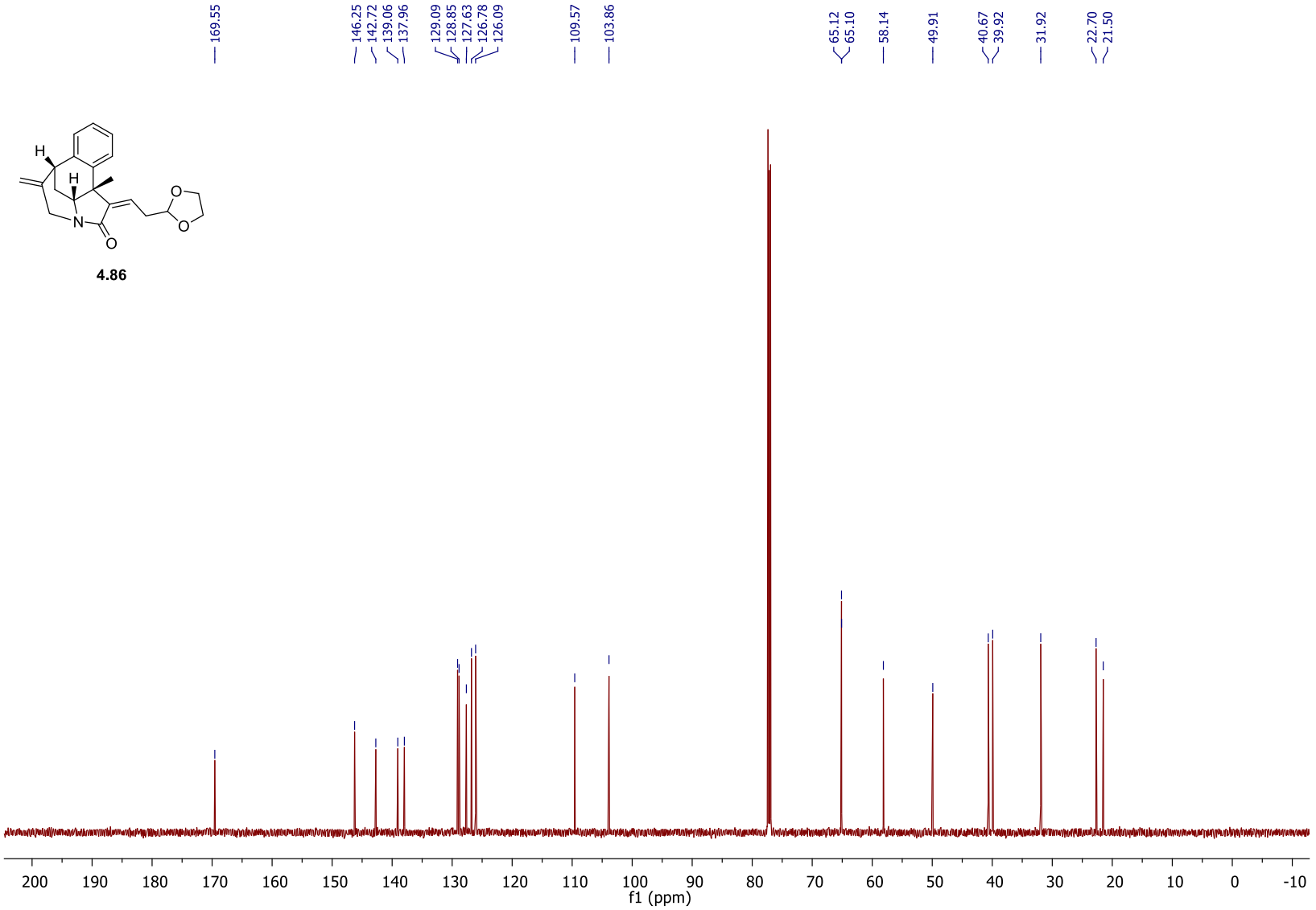
4.88

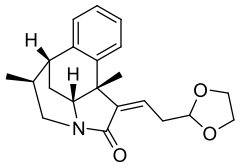
4.00
0.95
0.94
0.95
1.04
1.92
0.90
0.90
0.93
1.09
1.00
1.10
1.08
3.14
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


178.30
176.52
146.48
140.58
135.08
129.81
129.55
126.94
126.52
109.31
59.78
52.86
50.14
40.33
39.97
32.55
23.14
22.73
21.02
H
H
N
H
O
O
OH
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

4.88

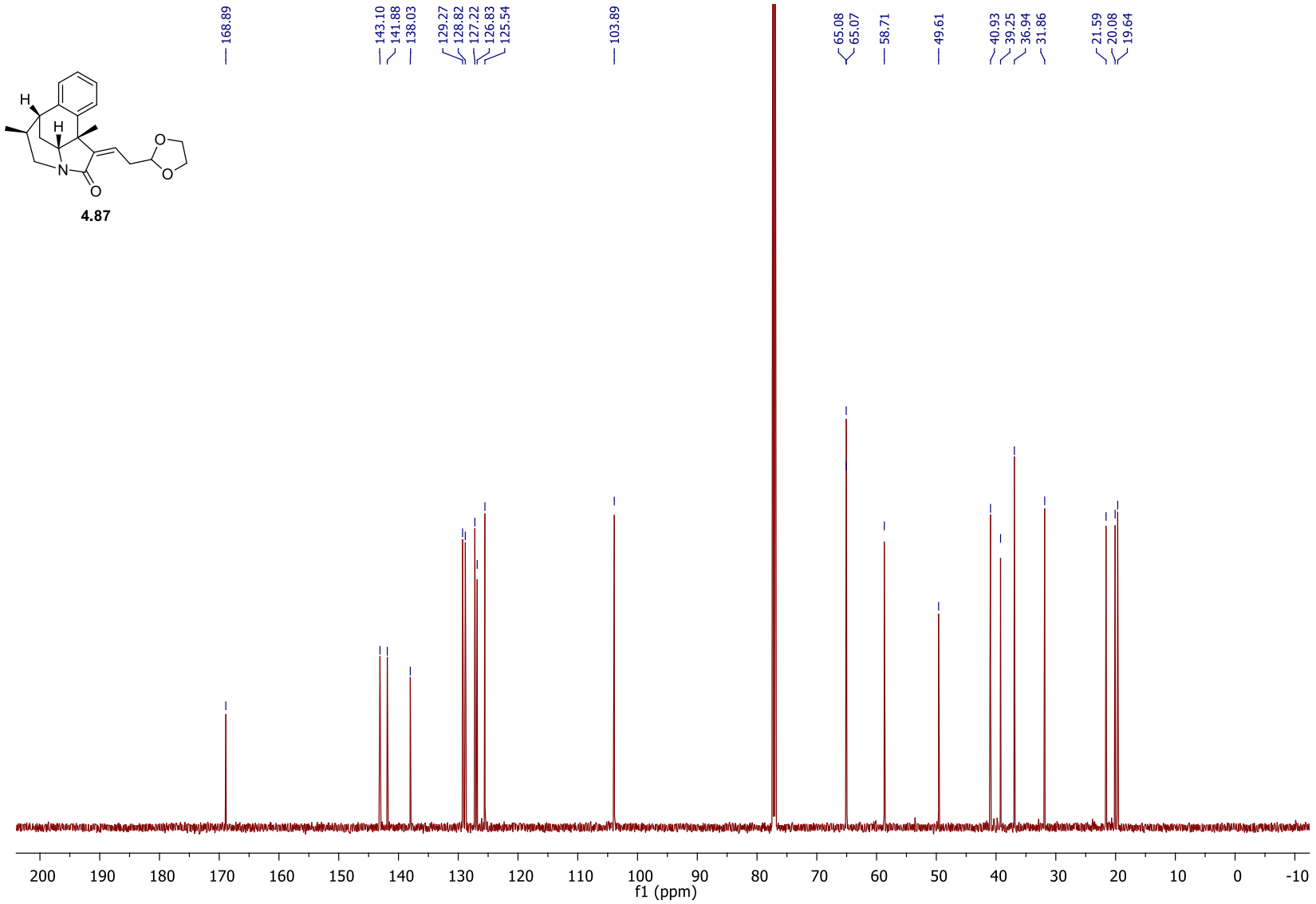

H
H
N
O
O
O
4.86
3.12
1.00
1.03
1.15
1.02
1.07
1.05
2.19
3.23
1.15
1.10
1.07
1.07
1.05
1.09
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


169.55
146.25
142.72
139.06
137.96
129.09
128.85
127.63
126.78
126.09
109.57
103.86
65.12
65.10
58.14
49.91
40.67
39.92
31.92
22.70
21.50
H
H
N
O
O
O
4.86
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


H
H
N
O
O
O

4.87

1.05
1.05
1.03
0.99
0.99
1.00
1.06
2.17
2.14
1.05
1.03
1.04
1.02
1.05
1.11
1.03
1.10
3.20
3.15
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
f1 (ppm)


168.89
143.10
141.88
138.03
129.27
128.82
127.22
126.83
125.54
103.89
65.08
65.07
58.71
49.61
40.93
39.25
36.94
31.86
21.59
20.08
19.64
H
H
N
O
O
O
4.87
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

VITA

Scott Miskey was born in Heerlen, Netherlands in 1994 to a Canadian military family serving at a NATO base in Germany. His family moved to Barrie, Ontario, Canada in 1999 where he completed his pre-university education. He obtained his Honours B.Sc. Degree in Chemistry and Mathematics at Brock University, Ontario, Canada in 2020 under the guidance of Prof. Tomas Hudlicky, and was given the opportunity to pursue a Master degree in the field of synthetic organic chemistry with his undergraduate advisor.

REFERENCES

(1) Butora, G.; Hudlicky, T. *Organic Synthesis: Theory and Applications*, 1st ed.; JAI Press, 1998.

(2) Wicks, C.; Hudlicky, T.; Rinner, U. In *the Alkaloids: Chemsitry and Biology*; Knölker, H.-J., Ed.; Elsevier Inc., 2021; pp 145–342.

(3) Gates, M.; Tschudi, G. *J. Am. Chem Soc.* **1955**, *78*, 1380–1393.

(4) Gulland, J. M.; Robinson, R. *Mem. Lit. Philisophical Soc. Manchester* **1925**, *69*, 79–86.

(5) Sakabe, N.; Irikawa, H.; Sakurai, H.; Hirata, Y. *Tetrahedron Lett.* **1966**, *7*, 963–964.

(6) Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1966**, *9*, 965–968.

(7) Sakurai, H.; Sakabe, N.; Hirata, Y. *Tetrahedron Lett.* **1966**, *7*, 6309–6314.

(8) Kobayashi, J.; Morita, H. *The Daphniphyllum Alkaloids*; Elsevier, 2003; Vol. 60.

(9) Zhong, J.; Wang, H.; Zhang, Q.; Gao, S. *The Chemistry of Daphniphyllum Alkaloids*; Hans-Joachim Knolker, Ed.; Elsevier Inc., 2021; Vol. 85.

(10) Guo, L. D.; Chen, Y.; Xu, J. *Acc. Chem. Res.* **2020**, *53*, 2726–2737.

(11) Grímsson, F.; Meller, B.; Bouchal, J. M.; Zetter, R. *Grana* **2015**, *54*, 85–128.

(12) Cao, M.-Y.; Ma, B.-J.; Gu, Q.-X.; Fu, B.; Lu, H.-H. *J. Am. Chem. Soc.* **2022**, *144*, 5750–5755.

(13) Christenhusz, M. J. M.; Fay, M. F.; Chase, M. W. *Plants of the World: An*

Illustrated Encyclopedia of Vascular Plants, 1st Ed.; Press, U. of C., Ed.; University of Chicago Press: Chicago, 2017.

(14) Heathcock, C. H. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 14323–14327.

(15) Niwa, H.; Hirata, Y.; Suzuki, K. T.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 2129–2132.

(16) Zhang, Y.; Di, Y. T.; Zhang, Q.; Mu, S. Z.; Tan, C. J.; Fang, X.; He, H. P.; Li, S. N.; Hao, X. J. *Org. Lett.* **2009**, *11*, 2357–2359.

(17) Chen, X.; Zhang, H.-J.; Yang, X.; Lv, H.; Shao, X.; Tao, C.; Wang, H.; Cheng, B.; Li, Y.; Guo, J.; Zhang, J.; Zhai, H. *Angew. Chem.* **2018**, *130*, 959–963.

(18) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. *Angew. Chem. Int. Ed.* **2018**, *57*, 952–956.

(19) Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2016**, *55*, 6067–6070.

(20) Li, H.; Qiu, Y.; Zhao, C.; Yuan, Z.; Xie, X.; She, X. *Chem. Asian J.* **2014**, *9*, 1274–1277.

(21) Baidilov, D.; Miskey, S.; Hudlicky, T. *Eur. J. Org. Chem.* **2019**, *2019*, 7590–7595.

(22) Jansana, S.; Diaba, F.; Bonjoch, J. *Org. Lett.* **2019**, *21*, 5757–5761.

(23) Wang, B.; Xu, B.; Xun, W.; Guo, Y.; Zhang, J.; Qiu, F. G. *Angew. Chem. Int. Ed.* **2021**, *60*, 9439–9443.

(24) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679–684.

(25) Xu, B.; Wang, B.; Xun, W.; Qiu, F. G. *Angew. Chem.* **2019**, *131*, 5810–5813.

(26) Ichikawa, Y. *Synlett* **1991**, No. 4, 238–240.

(27) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129.

(28) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3282.

(29) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287–5290.

(30) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1974**, *40*, 947–949.

(31) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485–1486.

(32) Baidilov, D.; Rycek, L.; Trant, J. F.; Froese, J.; Murphy, B.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2018**, *57*, 10994–10998.

(33) Raucher, S.; Gustavson, L. M.; Stenkamp, R. E. *J. Org. Chem.* **1987**, *52*, 2760–2762.

(34) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843–2859.

(35) Trost, B. M.; Krische, M. J.; V, S. U.; September, R. V; Synthesis, S. *J. Am. Chem. Soc.* **1996**, 233–234.

(36) Buchbauer, G.; Höfinghoff, J.; Froese, A. *Monatsh. Chem.* **1998**, *129*, 705–710.

(37) Juhl, M.; Nielsen, T. E.; Quement, S. Le; Tanner, D. *J. Org. Chem.* **2006**, *71*, 265–280.

(38) Hu, X.; Xu, S.; Maimone, T. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 1624–1628.

(39) Boualy, B.; El Firdoussi, L.; Ali, M. A.; Karim, A. *J. Braz. Chem. Soc.* **2011**, *22*, 1259–1262.

(40) Pisoni, D. S.; Gamba, D.; Fonseca, C. V.; Da Costa, J. S.; Petzhold, C. L.; De Oliveira, E. R.; Ceschi, M. A. *J. Braz. Chem. Soc.* **2006**, *17*, 321–327.

(41) Sato, W.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 141–142.

(42) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwakima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056–8066.

(43) Evans, A. P.; Chen, D. *Synthesis of Thapsigargin, Nortriloblide, and Analogs Therof*. CA 3057520, 2018.

(44) Jefford, C. W.; Kirkpatrick, D.; F, D. *J. Am. Chem. Soc.* **1972**, *94*, 8905–8907.

(45) Chen, H.; Plettner, E. *Tetrahedron Lett.* **2012**, *53*, 2059–2062.

(46) Cheng, X.; Micalizio, G. C. *J. Am. Chem. Soc.* **2016**, *138*, 1150–1153.

(47) Appel, R. *Angew. Chem. Int. Ed.* **1975**, *14*, 801–811.

(48) Ma, S.; Negishi, E. I. *J. Org. Chem.* **1997**, *62*, 784–785.

(49) Bradford, T. A.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2010**, *75*, 491–494.

(50) Delgado, M.; Martín, J. D. *J. Org. Chem.* **1999**, *64*, 4798–4816.

(51) Saglam, M. F.; Alborzi, A. R.; Payne, A. D.; Willis, A. C.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2016**, *81*, 1461–1475.

(52) Payne, A. D. *Tetrahedron* **2013**, *69*, 9316–9321.

(53) Deng, M.; Yao, Y.; Li, X.; Li, N.; Zhang, X.; Liang, G. *Org. Lett.* **2019**, *21*, 3290–3294.

(54) Doecke, C. W.; Garratt, P. J.; Shahriari-zavareh, H.; Zahler, R. *J. Org. Chem.* **1984**, *49*, 1412–1417.

(55) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826–5831.

(56) Muller, P.; Joly, D.; Mermoud, F. *Helv. Chim. Acta* **1984**, *67*, 105–112.

(57) Thirion, D.; Poriel, C.; Rault-Berthelot, J.; Barrière, F.; Jeannin, O. *Chem. - A Eur. J.* **2010**, *16*, 13646–13658.

(58) Yamamoto, Y.; Yamada, Y.; Sajiki, H.; Sawama, Y. *Bull. Chem. Soc. Jpn.* **2020**, *93*, 1419–1423.

(59) Yasukawa, N.; Yokoyama, H.; Masuda, M.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Green Chem.* **2018**, *20*, 1213–1217.

(60) Tissot, M.; Poggiali, D.; Hénon, H.; Müller, D.; Guénée, L.; Mauduit, M.; Alexakis, A. *Chem. - A Eur. J.* **2012**, *18*, 8731–8747.

(61) Earla, A.; Li, L.; Costanzo, P.; Braslau, R. *Polymer (Guildf).* **2017**, *109*, 1–12.

(62) Breton, T.; Liaigre, D.; Belgsir, E. M. *Electrochem. commun.* **2005**, *7*, 1445–1448.

(63) Yerino, L. V.; Osborn, M. E.; Mariano, P. S. *Tetrahedron* **1982**, *38*, 1579–1591.

(64) Ellel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*;

John Wiley and Sons Ltd: New York, 1994.

(65) Wang, W.; Li, G. P.; Wang, S. F.; Shi, Z. F.; Cao, X. P. *Chem. Asian J.* **2015**, *10*, 377–382.

(66) Ho, J. H.; Lin, Y. C.; Chou, L. T.; Chen, Y. Z.; Liu, W. Q.; Chuang, C. L. *Tetrahedron Lett.* **2013**, *54*, 1991–1993.

(67) McBee, E. T.; Rakoff, H.; Meyers, R. K. *J. Am. Chem. Soc.* **1955**, *77*, 4427–4428.

(68) Ballini, R.; Bosiea, G.; Chimiche, S.; Agostino, V. S. *Tetrahedron* **1996**, *52*, 10705–10710.

(69) Giovannini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron Lett.* **1998**, *39*, 5827–5830.

(70) Gil, J. A.; Arias, F.; Chahboun, R.; Alvarez-Manzaneda, E. *J. Org. Chem.* **2020**, *85*, 3799–3805.

(71) Byrd, K. M. *Beilstein J. Org. Chem.* **2015**, *11*, 530–562.

(72) Brousseau, J.; Xolin, A.; Barriault, L. *Org. Lett.* **2019**, *21*, 1347–1349.

(73) Varin, M.; Barré, E.; Iorga, B.; Guillou, C. *Chem. - A Eur. J.* **2008**, *14*, 6606–6608.

(74) Ichiki, M.; Tanimoto, H.; Miwa, S.; Saito, R.; Sato, T.; Chida, N. *Chem. - A Eur. J.* **2013**, *19*, 264–269.

(75) Mintz, M. J.; Walling, C. *Org. Synth.* **1969**, *49*, 9.

(76) Andrade, L. H.; Barcellos, T. *Org. Lett.* **2009**, *11*, 3052–3055.

(77) Bates, R. W.; Díez-Martín, D.; Kerr, W. J.; Knight, J. G.; Ley, S. V.; Sakellaridis,

A. *Tetrahedron* **1990**, *46*, 4063–4082.

(78) Si, L. L.; Shen, H. J.; Fang, L. C.; Huang, J.; Li, C. C.; Yang, Z. *Chem. Commun.* **2013**, *49*, 8806–8808.

(79) Liu, S.; Shen, H.; Yu, Z.; Shi, L.; Yang, Z.; Lan, Y. *Organometallics* **2014**, *33*, 6282–6285.