UNIVERSITY OF CALIFORNIA SAN DIEGO

Asymmetric Total Synthesis of Cylindrocyclophanes A and F through Cyclodimerization and a Ramberg–Bäcklund Reaction
and
Studies Directed Towards the Total Synthesis of CJ-16,264

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy

in

Chemistry

by

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Professor Emmanuel Theodorakis

2014

The dissertation of Henry Korman is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Chair

University of California, San Diego

2014

Dedication

This work is dedicated to my wife who has put up with me throughout the entirety of graduate school, and hopefully longer, and it is also dedicated to my family and friends… for much the same reason.

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List of Symbols and Abbreviations

Ac	acetyl
AcSH	thiol acetic acid
AcOH	acetic acid
$AlMe_3$	trimethyl aluminum
atm	atmospheres
Bu	butyl
BAIB	[bis(acetoxy)iodo]benzene
tBu	tert-butyl
°C	degrees Celsius
calcd	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	methylene chloride
CH_3OH	methanol
CuTC	copper(I)-thiophene-2-carboxylate
DIPEA	N,N-diisopropylethylamine
DCM	dichloromethane
DMAP	N,N-dimethylaminopyridine
DMSO	dimethylsulfoxide
DMF	N,N-dimethylformamide
DMP	Dess-Martin periodinane
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalents
Et	ethyl
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethyl amine
g	gram
h	hours
HCl	hydrochloric acid
HRMS	high-resolution mass spectrometry
IMDA	intramolecular Diels–Alder reaction
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
iPr	isopropyl
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar
Me	methyl
MeOH	methanol

MIC	minimum inhibitory concentration
MHz	megahertz
mL	milliliter
MsCl	mesyl chloride
µg	microgram
µL	microliter
µmol	micromole
mmol	millimole
MNBA	2-methyl-6-nitrobenzoic anhydride
*n*BuLi	n-butyllithium
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
PDC	pyridinium dichromate
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
*p*TSOH	para-toluenesulfonic acid
R_f	retention factor
(S)-CBS	(S)-(−)-2-methyl-CBS-oxazaborolidine
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetrabutylammonium fluoride
*t*BuLi	tert-butyl lithium
*t*BuOH	tert-butyl alcohol
TBS	t-butyldimethyl silyl
TEMPO	4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TRAP assay	telomeric repeat amplification protocol assay

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Acknowledgments

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Chapter 1 is a partial reprint of the material as it appears in "Asymmetric Total Synthesis of Cylindrocyclophanes A and F Through Cyclodimerization and a Ramberg–Bäcklund Reaction, K.C. Nicolaou, Y.-P. Sun, H. Korman, D. Sarlah, *Angew. Chem. Int. Ed.* **2010**, *49*, 5875–5878".

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Asymmetric Total Synthesis of Cylindrocyclophanes A and F Through Cyclodimerization and a Ramberg–Bäcklund Reaction, K.C. Nicolaou, Y.-P. Sun, H. Korman, D. Sarlah, *Angew. Chem. Int. Ed.* **2010**, *49*, 5875–5878

ABSTRACT OF THE DISSERTATION

Asymmetric Total Synthesis of Cylindrocyclophanes A and F through Cyclodimerization and a Ramberg–Bäcklund Reaction
and
Studies Directed Towards the Total Synthesis of CJ-16,264

by

Henry Korman

Doctor of Philosophy in Chemistry

University of California, San Diego, 2014

Professor K. C. Nicolaou, Chair

Cylindrocyclophanes A and F are naturally occurring cyclophanes with beautiful molecular architectures and important biological properties that have inspired numerous syntheses. Chapter 1 details the isolation and biological properties of these molecules, our retrosynthetic analysis, and asymmetric total syntheses of these molecules. The highlights of this synthesis includes a "head-to-tail" dimerization reaction and a Ramberg–Bäcklund olefination reaction to generate the [7.7]-paracyclophane found in these molecules.

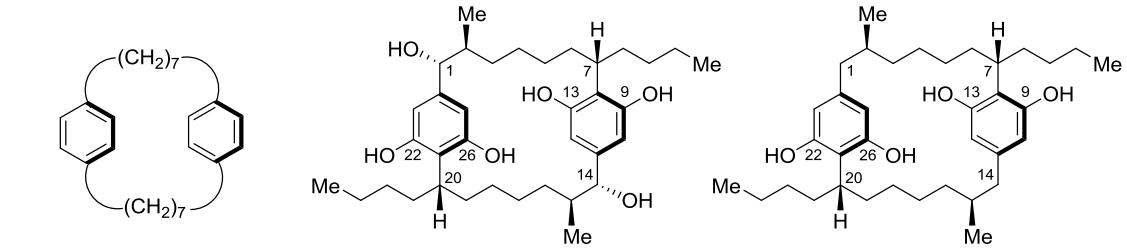
CJ-16,264, UCS1025A, and pyrrolizilactone belong to a unique class of natural products isolated from fungi, each containing a γ-hydroxypyrrolizidinone adjoined to a decalin. Their unique architectures, as well as their amazing biological activities, has inspired several syntheses of UCS1025A. There has been no report, to the best of our knowledge, of a successful synthesis of CJ-16,264 or pyrrolizilactone. Chapter 2 describes the isolation and biological properties of these molecules, our retrosynthetic

analysis, the synthesis of (±)-1-epi-CJ-16,264 and our significant contributions towards the synthesis CJ-16,264. The highlights of this synthesis include a double exo-selective IMDA (intramolecular Diels–Alder) reaction and a stereoselective Reformatsky–type cross coupling to generate the common scaffold of these molecules.

Chapter 1: Asymmetric Total Synthesis of Cylindrocyclophanes A and F through Cyclodimerization and Ramberg–Bäcklund Reaction

A. Introduction

1. Isolation and Biological Activity of Cylindrocyclophanes A and F



parent [7.7]-paracyclophane cylindrocyclophane A (**1.01**) cylindrocyclophane F (**1.02**)

Figure **1.01**: Structures of parent [7.7]paracyclophane and cylindrocyclophanes A (**1.01**) and F (**1.02**).

Due to their appealing architectures and unique chemical and physical properties, the bridged class of aromatic compounds known as cyclophanes (e.g. parent [7.7]-paracyclophane, Figure **1.01**) have been inspiring chemists ever since their introduction by Cram and Steinberg almost 60 years ago.[1] To the designed cyclophanes[2] were later added naturally occurring compounds, beginning in 1990 when Moore and co-workers reported the isolation of cylindrocyclophane A (**1.01**, Figure **1.01**) and its siblings from a blue-green algae belonging to *Cylindrospermum licheniforme* Kützing (ATTC 29204).[3a] Two years later, the same group isolated cylindrocyclophane F (**1.02**) from the same algae.[3b] These 22-membered [7.7]-paracyclophanes exhibit potent cytotoxicity against the KB and LoVo tumor cells lines (IC_{50} = 2–10 μg/mL). The unique molecular architectures and important biological properties of the cylindrocyclophane natural products elicited considerable research activities directed toward their total synthesis,[4–6] with two total

syntheses of such molecules, both employing head-to-tail cyclodimerizations, already reported.[4, 5]

2. Retrosynthetic Analysis of Cylindrocyclophanes A and F

Our own head-to-tail dimerization approach to this class of compounds was based on the Ramberg–Bäcklund olefination reaction to generate [7.7]-paracyclophane intermediate **1.03** from precursor **1.04** (Figure **1.02**) that culminated in an asymmetric total syntheses of cylindrocyclophanes A (**1.01**) and F (**1.02**).

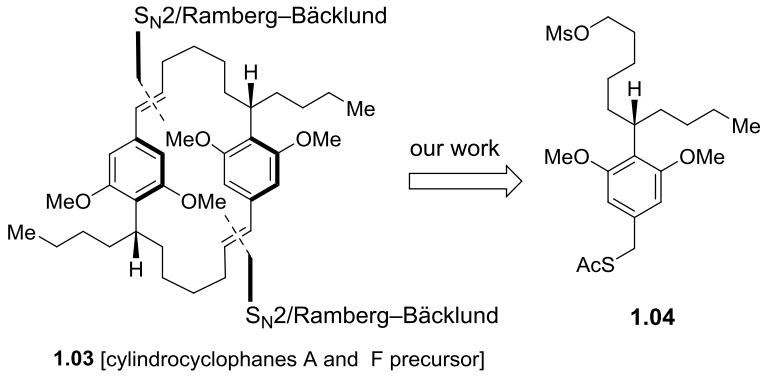


Figure **1.02**: Ramberg–Bäcklund approach to cylindrocyclophanes A (**1.01**) and F (**1.02**).

From a strategic perspective, it would be most desirable to construct the C2-symmetric cyclophane structural motif of these molecules through dimerization, preferably "head-to-tail", of two identical fragments. To this end, our approach envisioned a Ramberg–Bäcklund reaction of sulfone **1.05** as shown retrosynthetically in Figure **1.03**. Disassembly of **1.05** led to bifunctional monomeric unit **1.04**, which was traced back to aryl bromide **1.06** through asymmetric functionalization.

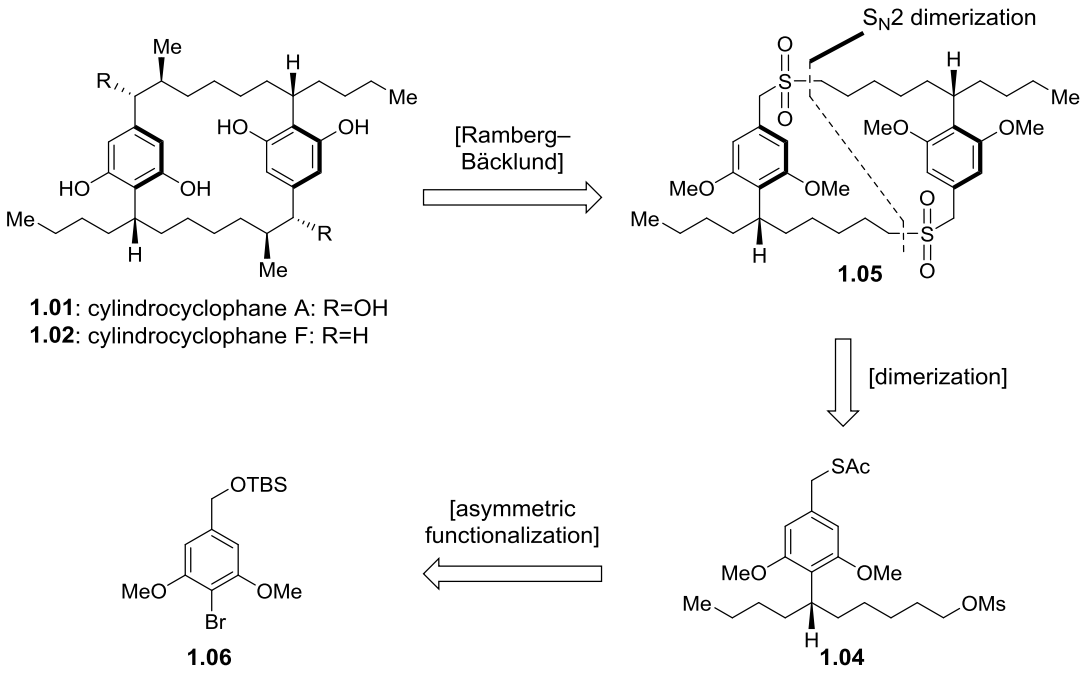


Figure **1.03**: Retrosynthetic analysis of cylindrocyclophanes A (**1.01**) and F (**1.02**).

B. Total Synthesis of Cylindrocyclophanes A and F

1. Synthesis of Cyclodimerization Precursor **1.04** and "Head-to-tail" Cyclodimerization

The enantioselective construction of the bifunctional precursor **1.04** commenced with bromide **1.06**[7] and proceeded as depicted in Figure **1.04**. Thus, addition of lithiated **1.06** (*n*BuLi) to pentanal yielded secondary alcohol **1.07** in 78% yield. Subsequent oxidation of the resulting alcohol with TEMPO/BAIB furnished benzylic ketone **1.08** in 98% yield. Treatment of **1.08** with the vinyl lithium derived from **1.09** (*t*BuLi) resulted in the formation of allyic alcohol **1.10**. A PDC-mediated oxidative allylic transposition of the resulting allylic alcohol gave desired vinyl ketone **1.11** in 57% as well as ketone **1.08** in 25% yield.[8] Enantioselective reduction of **1.11** with (*S*)-CBS furnished the expected chiral allylic alcohol (85%, 95% *ee*), which underwent hydroxy-directed hydrogenation

(CH_2Cl_2, 50 atm of H_2) in the presence of Crabtree's catalyst (9 mol %)[9] to afford alcohol **1.12** in 76% yield and 93% *ee* (*dr*>20:1). Deoxygenation of **1.12** was achieved through its mesylate which reacted with Super-H to generate, after desilylation (TBAF), benzylic alcohol **1.13** in 73% overall yield.

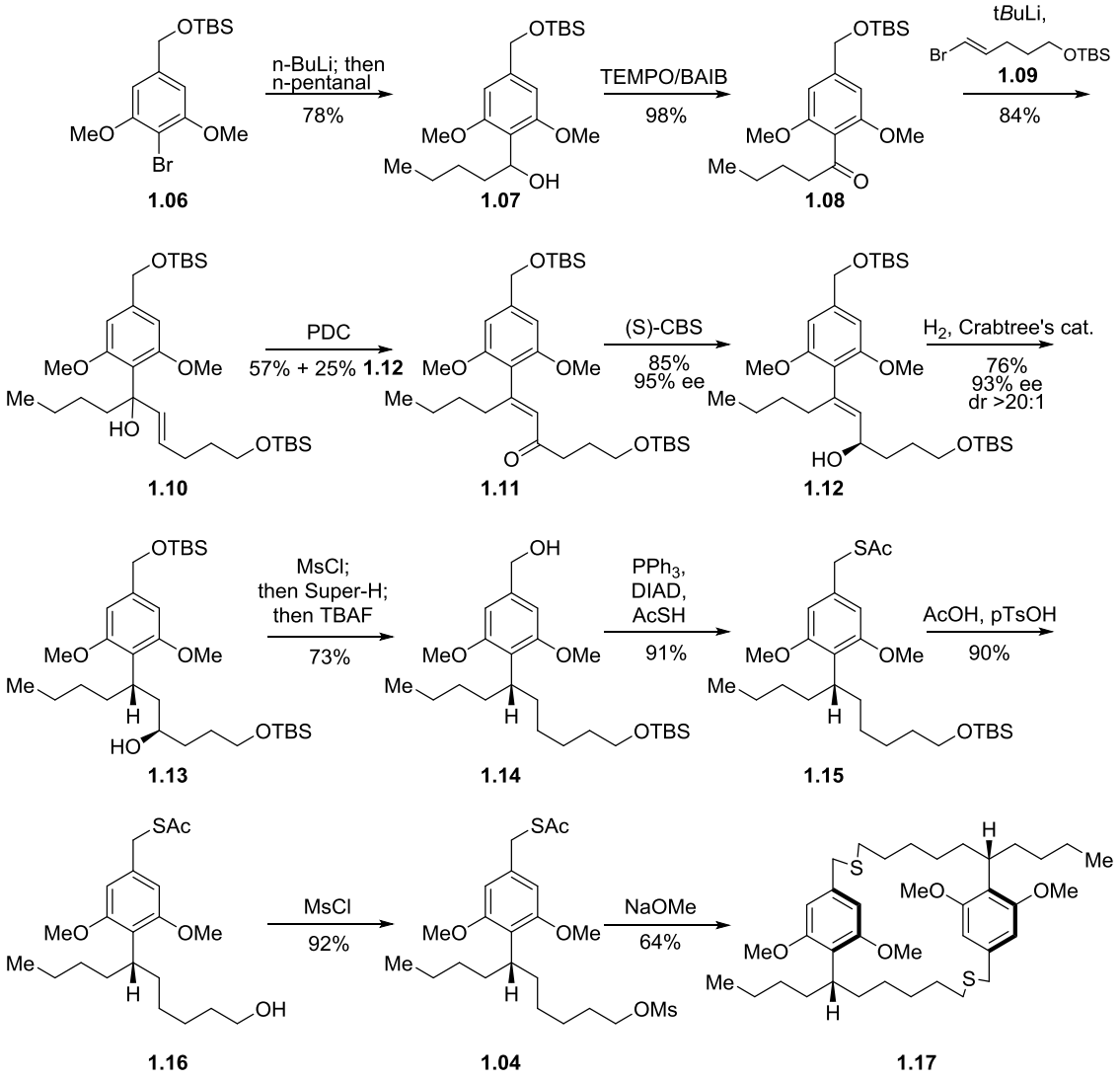


Figure **1.04**: Synthesis of macrocyclic bis(thioether) **1.17** from known bromide **1.06.**

Mitsunobu reaction of **1.13** with AcSH (Ph_3P, DIAD) furnished **1.15** in 91% yield. This was followed by a desilylation of **1.15** (*p*TsOH, AcOH, H_2O) in 90% yield. Subsequent mesylation (MsCl, Et_3N) of **1.16** led to thioacetate mesylate **1.04** in 92% overall yield. With the monomeric precursor **1.04** in hand, its dimerization to a [7.7]-paracyclophane **1.17** and further functionalization to the targeted cylindrocyclophanes became possible, and indeed was realized. The much anticipated cyclodimerization of **1.04** was brought about by treatment with NaOMe in MeOH at ambient temperature to afford the corresponding macrocyclic bis(thioether) **1.17** in 64% yield.

2. Synthesis of Cylindrocyclophane A and F

The oxidation of **1.17** with H_2O_2 (Figure **1.05**) in the presence of $(NH_4)_6Mo_7O_{24}$ furnished macrocyclic bis(sulfone) **1.05** in 80% yield. Treatment of the resulting sulfone **1.05** with alumina-impregnated KOH (KOH/Al_2O_3) in the presence of CF_2Br_2 in CH_2Cl_2/*t*BuOH (1:1) at 0→23 °C led to the expected bis(olefin) **1.18** in 70% yield (ca. 12:1 *EE*/*EZ* before complete isomerization to *EE*-**1.18** with $Pd[CH_3CN]_2Cl_2$).[10] Dihydroxylation of **1.18** with AD-mix-β ($MeSO_2NH_2$, *t*BuOH:H_2O, ambient temperature)[11] efficiently generated the corresponding tetraol, which was subsequently exposed to 1,1′-thiocarbonyldiimidazole and trapped as its bis(thionocarbonate) **1.19** in 62% yield in two steps. The bis(thionocarbonate) was selectively deoxygenated to diol **1.20** under Barton conditions (*n*Bu_3SnH, AIBN)[12] in 81% yield. Methylation of **1.20** (MsCl; then $AlMe_3$),[13] followed by deprotection of the phenolic groups (BBr_3), all in one pot, secured cylindrocyclophane F (**1.02**) in 71% overall yield.

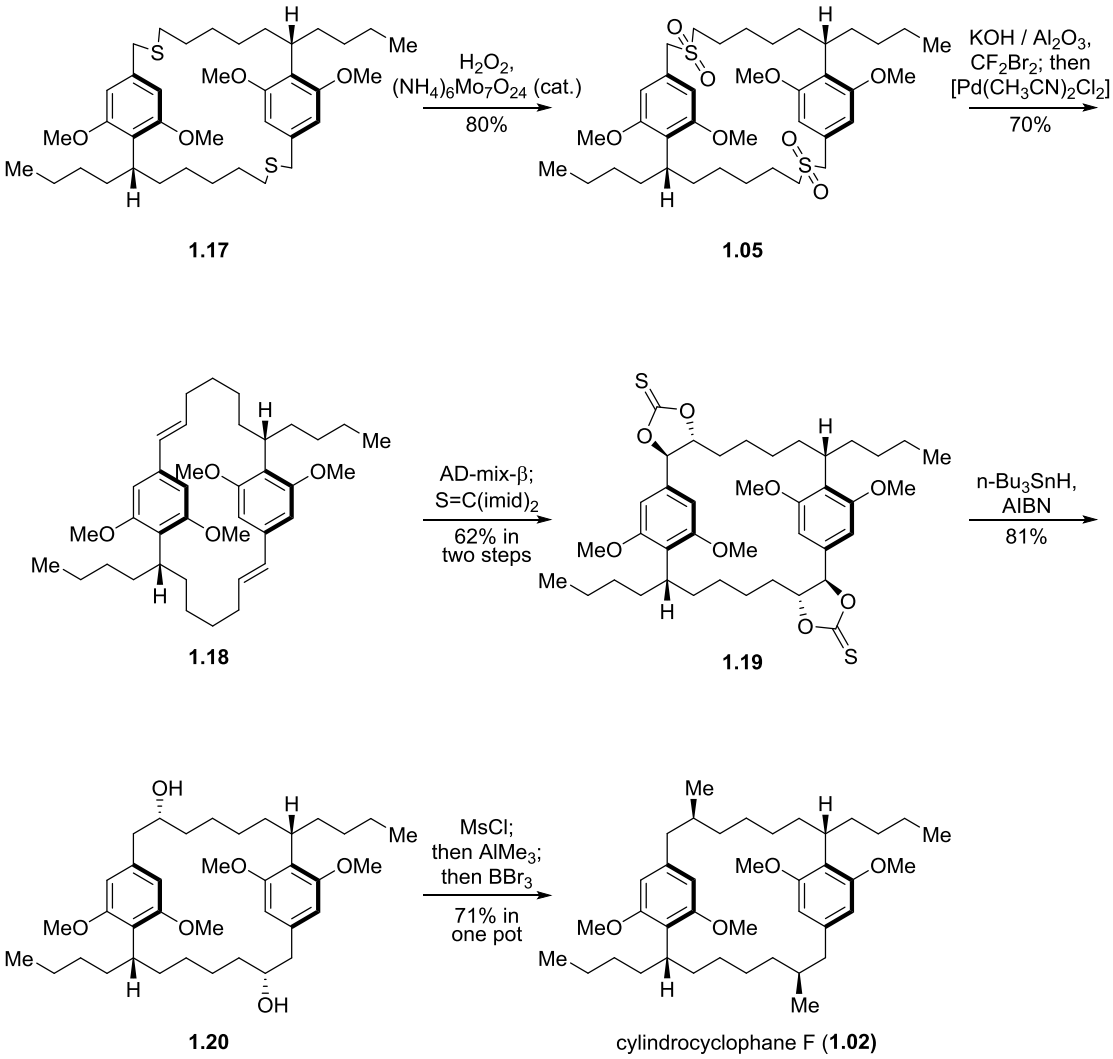


Figure **1.05**: Synthesis of cylindrocyclophane F (**1.02**) from known macrocyclic bis(thioether) **1.17**.

Oxidation of common intermediate **1.20** (DMP, Figure **1.06**), followed by enol triflate formation (KHMDS, Comins reagent) and subsequent Kumada-type coupling with MeMgBr in the presence of $[Fe(acac)_3]$,[14] led to bis(olefin) **1.21** (74% yield, single geometrical isomer). The latter compound served as a precursor in Hoye's total synthesis

of cylindrocyclophane A (hydroboration/deprotection).[5] The physical properties of synthetic cylindrocyclophane F (**1.02**) and **1.22** were in accord with those previously reported in the literature.[3b,5]

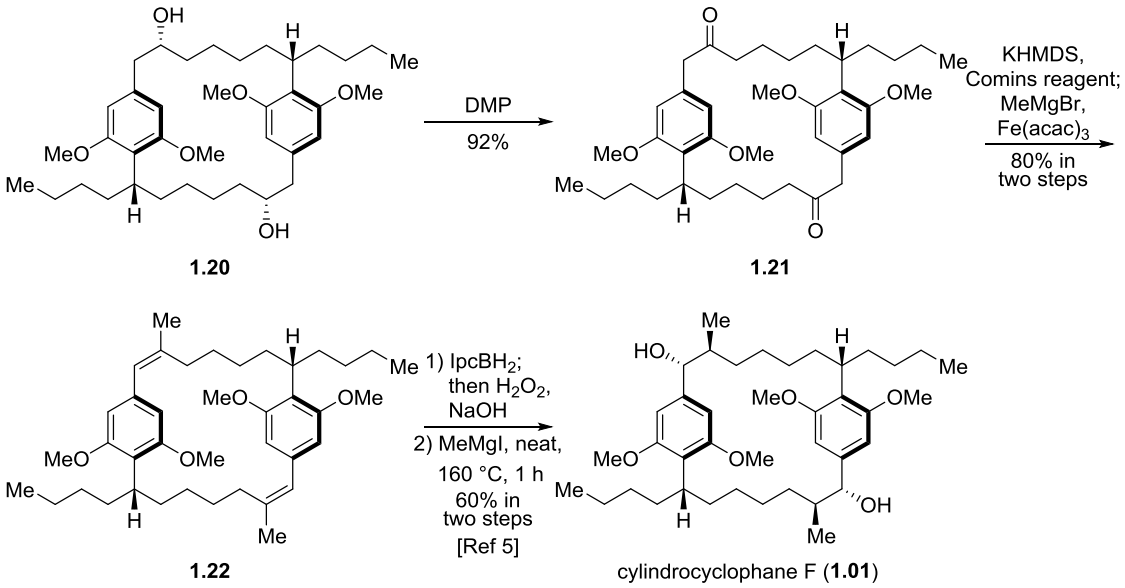


Figure **1.06**: Formal synthesis of cylindrocyclophane A (**1.01**) from common intermediate **1.20**.

C. Comparison with Previous Synthetic Approaches

A number of research groups have devised synthetic routes towards cylindrocyclophanes A and F.[4-6] The total synthesis of cylindrocyclophanes A and F by the Smith group[4] involved an elegant cross metathesis/ring closing metathesis (CM/RCM) head-to-tail cyclodimerization to cast the molecule's [7.7]-paracyclophane framework (Figure **1.07**).

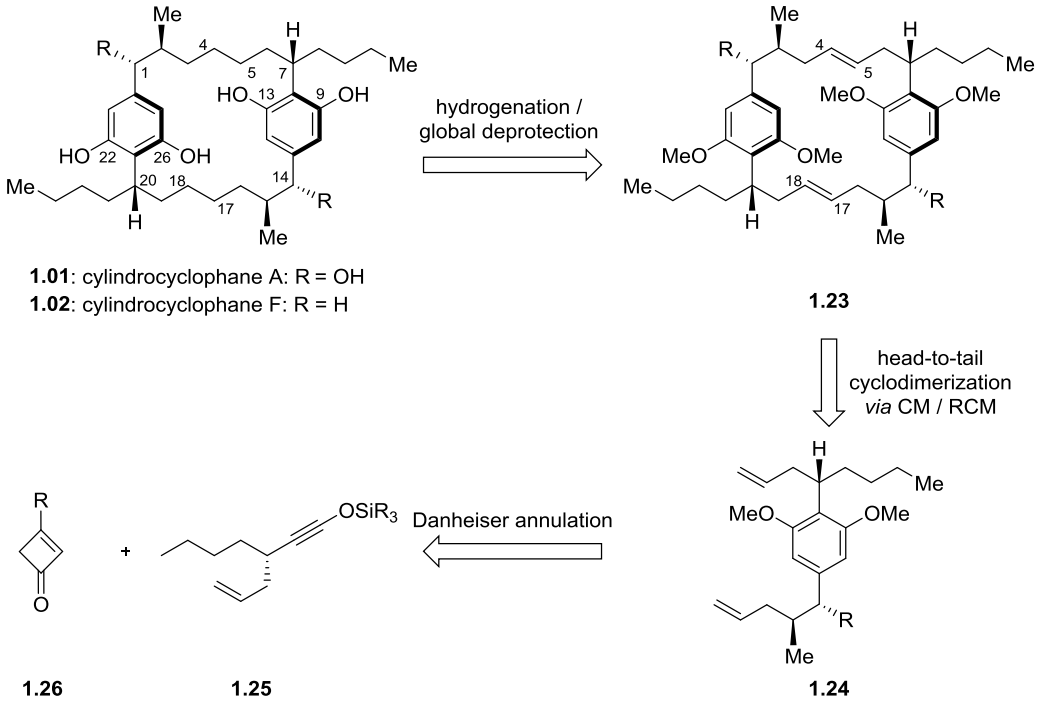


Figure **1.07**: CM/RCM approach to cylindrocyclophane A and F by Smith.

Thus, cylindrocyclophanes A and F are derived from **1.23** *via* a hydrogenation and global deprotection sequence. Dimer **1.23** is then derived from bis(olefin) **1.24** *via* a CM/RCM head-to-tail cyclodimerization to forming the C-4–C-5 and C-17–C-18 bonds needed to form the [7.7]-paracyclophane backbone. **1.24** is then available through a Danheiser annulation of ester **1.25** and siloxyalkyene **1.26**. This strategy made possible the total synthesis of cylindrocyclophane A in 16 steps and 8.1% overall yield and the total synthesis of cylindrocyclophane F in 11 steps in 22% overall yield.

The total synthesis of cylindrocyclophane A by the Hoye group[5] also involved a head-to-tail cyclodimerization strategy, though instead of using a CM/RCM approach, a double

Horner–Emmons reaction was instead employed to construct the [7.7]-paracyclophane backbone (Figure **1.08**).

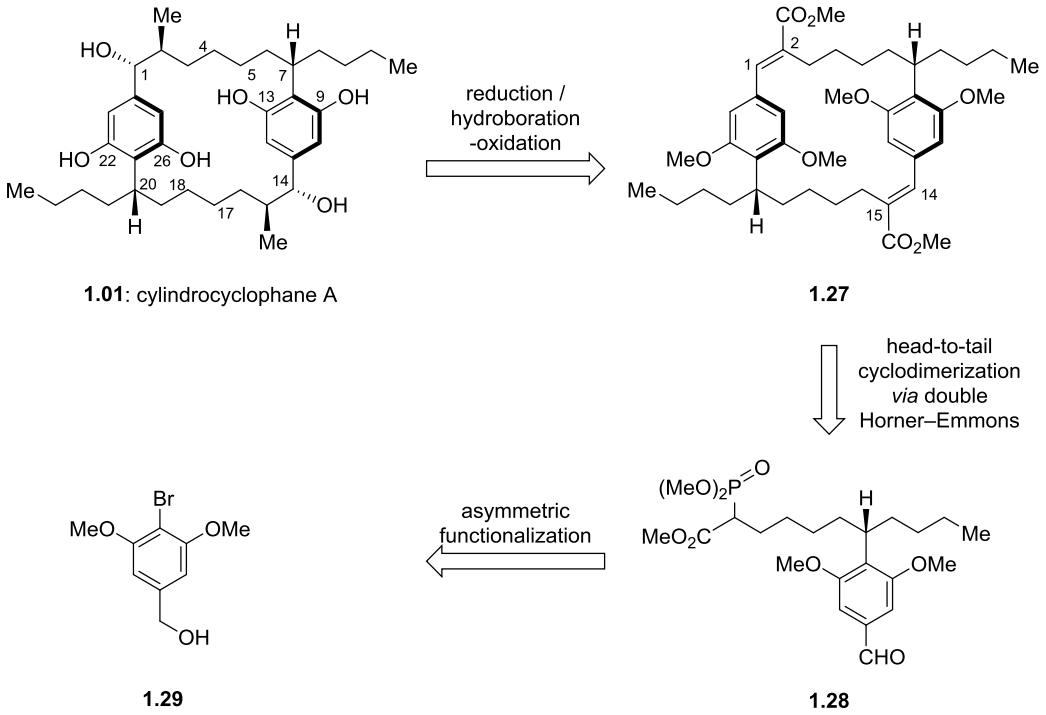


Figure **1.08**: Horner–Emmons approach to cylindrocyclophane A by Hoye.

Thus, cylindrocyclophane A is derived from precursor **1.27** over a reduction and hydroboration-oxidation sequence. Dimer **1.27** is then synthesized *via* a double Horner–Emmons cyclodimerization of **1.28**, creating C-1–C-2 and C-13–C-14 bonds to access the [7.7]-paracyclophane moiety. **1.28** is then derived from **1.29** over several synthetic steps. This alternate strategy by the Hoye group allowed the total synthesis of cylindrocyclophane A in 24 steps in 1.9% overall yield.

In our own approach, we also elected to employ a head-to-tail cyclodimerization strategy to access the [7.7]-paracyclophane skeleton (Figure **1.03**). Thus, cylindrocyclophanes A and F were both made available from common intermediate **1.18** *via* a Ramberg–Bäcklund reaction and subsequent functionalization. Bis(sulfone) **1.05** is derived from a cyclodimerization of thioacetate mesylate **1.04** and subsequent bis(oxidation) of the resulting macrocyclic bis(thioether). Thioacetate mesylate **1.04** was synthesized from known bromide **1.06** in several synthetic steps. This strategy to access the cylindrocyclophanes led to the synthesis of cylindrocyclophane F in 15 steps in 1.9% overall yield, and the formal synthesis of cylindrocyclophane A in 16 steps in 1.9% overall yield.

The synthetic strategies used in each of these three syntheses have their advantages and disadvantages. From a strategic standpoint, it would be highly desirable to construct the C_2-symmetric [7.7]-paracyclophane motif found in cylindrocyclophanes A and F through the cyclodimerization of two identical molecules. Indeed, all three synthetic approaches to the cylindrocyclophanes accomplish this goal, employing different methods to affect a head-to-tail cyclodimerization strategy to construct this cyclophane motif.

The Smith groups' synthesis created the C-4–C-5 and C-17–C-18 bonds of the [7.7]-paracyclophane system *via* a CM/RCM strategy, allowing for the cyclodimerization of a precursor already containing the requisite asymmetric functionalization at C-1, C-2, C-14, and C-15 found in the cylindrocyclophane backbone. This strategy is very efficient, producing cylindrocyclophanes A and F in the highest overall yield and shortest

step count of these three reported syntheses. However, because of the early incorporation of these functional groups, this synthetic strategy does not allow access of both cylindrocyclophane A and cylindrocyclophane F from a common intermediate. It would therefore be less convenient to use this synthetic approach during structure activity relationship (SAR) studies where late stage modifications to a common intermediate would be able to provide the most rapid access to a library of congeners.

The Hoye group employed a different C_2-symmetric strategy to the cylindrocyclophane backbone. In their synthesis of cylindrocyclophane A, they instead used a double Horner–Emmons olefination to create C-1–C-2 and C-14–C-15 bonds. While this approach was only reported to reach cylindrocyclophane A, it is conceivable that an intermediate like bis(enone) **1.27** could be used to access other relevant congeners in a SAR study. This synthesis required more synthetic transformations to arrive at cylindrocyclophane A than the other syntheses, and was also less efficient in overall yield. Nonetheless, this remarkable synthesis demonstrated the reliability of late stage double Horner–Emmons olefinations as a viable approach in the end game of natural product synthesis. This approach allowed us to believe that creating the C-1–C-2 and C-14–C-15 bonds of the cylindrocyclophane motif through another method would be a worthwhile strategy.

Our own approach constructed this [7.7]-paracyclophane backbone through the creation of C-1–C-2 and C-14–C-15 bonds, as the Hoye group did, but through the intermediacy of a 24-membered bis(sulfone) **1.05**. While our synthetic strategy led to the synthesis of cylindrocyclophanes A and F in a higher step count and lower overall yield

than the Smith groups' syntheses, we were able to access both cylindrocyclophanes A and F from a common intermediate and in a large enough amount (several miligrams) to begin a biological evaluation of these natural products. Late stage modifications to this common intermediate would allow the rapid construction of analogues of these natural products, thereby impacting SAR studies. Our approach also highlights the usefulness and robustness of the Ramberg–Bäcklund reaction in late stage synthetic transformations, especially as reliable synthetic method to synthesize strained ring systems.

D. Conclusions

The described chemistry constitutes a short and efficient total synthesis cylindrocyclophane F (**1.02**) and a formal total synthesis of cylindrocyclophane A (**1.01**) in their naturally occurring enantiomeric forms. The asymmetry was introduced through a CBS reduction of an enone followed by a hydroxyl-directed hydrogenation employing the Crabtree catalyst and deoxygenation. The crucial macrocyclodimerization was achieved through the use of the Ramberg–Bäcklund reaction, whose application to the synthesis of complex molecules is on the rise.[15]

E. Experimental Section

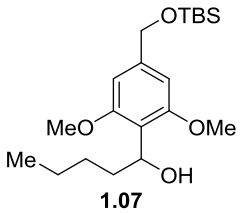
1. General Procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*, *N*′-dimethylformamide (DMF), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040 – 0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-400, DRX-500 or DRX- 600 instruments and calibrated using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm) as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray

ionization). Optical rotations were recorded on a Perkin–Elmer Model 343 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

2. Preparation of Compounds

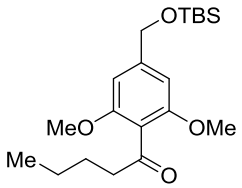
Alcohol 1.07: To a stirred solution of bromide **1.06** (11.34 g, 31.38 mmol) in THF (210 mL) at –78 °C was added *n*BuLi (16.3 mL, 40.8 mmol, 2.5 M in hexanes, 1.3 equiv) dropwise. After stirring at that temperature for 0.5 h, the reaction mixture was allowed to warm to –30 °C over 0.5 h. The solution was then cooled to –78 °C and pentanal (6.7 mL, 62.8 mmol, 2.0 equiv) was added dropwise. After being stirred for 1 h at 0 °C, the reaction mixture was carefully quenched with NH_4Cl (sat. aq., 100 mL). The resulting mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification of the resulting residue by flash column chromatography (silica gel, EtOAc:hexanes 1:20) gave alcohol **1.07** (9.01g, 24.5 mmol, 78% yield) as a colorless oil.



1.07

1.07: R_f = 0.38 (silica gel, EtOAc:hexanes 1:5); FT-IR (neat) ν_{max}= 3564, 2955, 2930, 2858, 1612, 1586, 1460, 1421, 1367, 1254, 1219,1119, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.54 (s, 2 H), 5.08 (ddd, *J* = 11.4, 7.8, 6.0 Hz, 1 H), 4.70 (s, 2 H), 3.82 (s, 6 H), 3.66 (d, *J* = 11.4 Hz, 1 H), 1.85 (m, 1 H), 1.66 (m, 1 H), 1.48–1.23 (m, 4 H), 0.95 (s, 9 H), 0.87 (t, *J* = 7.2 Hz, 3 H), 0.10 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 157.6, 142.0, 118.7, 101.8, 67.9, 64.9, 55.6, 37.4, 28.4, 25.9, 22.7, 18.4, 14.1, –5.2 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{35}O_4SiNa$ $(M+Na)^+$ 391.2275, found 391.2279.

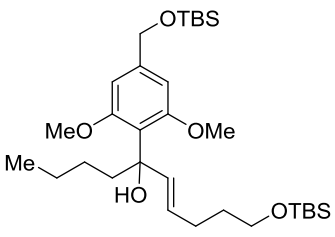
Ketone 1.08: To a stirred solution of alcohol **1.07** (500 mg, 1.3 mmol) in CH_2Cl_2 (15 mL) were added TEMPO (30 mg, 0.19 mmol, 0.15 equiv) and BAIB (502 mg, 1.56 mmol, 1.2 equiv.) at 23 °C. The resulting mixture was stirred for 12 h before it was quenched with $NaHCO_3$:NaS_2O_3:H_2O (1:1:1, sat. aq., 10 mL), and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. Purification of the resulting residue by flash column chromatography (silica gel, EtOAc:hexanes 1:7) gave ketone **1.08** (490 mg, 98% yield) as a yellow oil.



1.08

1.08: R_f = 0.50 (silica gel, EtOAc:hexanes 1:4); FT-IR (neat) ν_{max} = 2955, 2934, 2858, 1703, 1609, 1584, 1457, 1415, 1367, 1321, 1254, 1228, 1128, 1033, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.53 (s, 2 H), 4.71 (s, 2 H), 3.77 (s, 6 H), 2.73 (t, *J* = 7.2 Hz, 2 H), 1.64 (p, *J* = 3.6 Hz, 2 H), 1.36 (sext, *J* = 7.2 Hz, 2 H), 0.95 (s, 9 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 0.11 (s, 6 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 205.5, 156.7, 144.7, 119.2, 101.3, 64.8, 55.7, 44.5, 25.9, 25.7, 22.3, 18.4, 13.9, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{20}H_{35}O_4Si$ $(M+H)^+$ 367.2299, found 367.2310.

Alcohol 1.10: To a stirred solution of vinyl bromide **1.09** (3.06 g, 10.9 mmol) in Et_2O (20 mL) at – 78 °C was added *t*BuLi (13 mL, 1.7 M in pentane, 22.1 mmol) dropwise. The resulting yellow mixture was stirred for 0.5 h at 23 °C and cooled to –78 °C. A solution of ketone (**1.08**, 2.0 g, 5.46 mmol) in Et_2O (20 mL) was added dropwise and the resulting mixture was warmed up to 0 °C. After stirring for 30 min at 0 °C, the reaction mixture was quenched with NH_4Cl (sat. aq., 30 mL). The organic phase

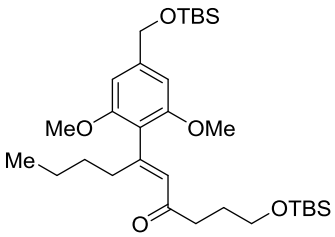


1.10

was separated and the aqueous phase was extracted with Et_2O (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified by flash column chromatography (silica gel, EtOAc:hexanes 1:7) to give the alcohol **1.10** as a colorless oil (2.6 g, 84% yield).

1.10: R_f = 0.55 (silica gel, EtOAc:hexanes 1:5); FT-IR (neat) ν_{max} = 3519, 2929, 2857, 1612, 1575, 1461, 1418, 1253, 1096, 833 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 6.58 (s, 2 H), 5.99 (s, 1 H), 5.90 (d, *J* = 15.5 Hz, 1 H), 5.59 (dt, *J* = 15.0, 7.0 Hz, 1 H), 4.70 (s, 2 H), 3.80 (s, 6H), 3.57 (t, *J* = 6.5 Hz, 2 H), 2.35 (m, 1 H), 2.07 (q, *J* = 9.5 Hz, 2 H), 1.63 (m, 3 H), 1.49–1.10 (m, 4 H), 0.95 (s, 9 H), 0.87 (s, 9 H), 0.85 (t, *J* = 7.5 Hz, 3 H), 0.11 (s, 6 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 157.9, 141.4, 137.4, 125.5, 120.3, 103.6, 78.5, 64.5, 62.6, 56.2, 41.6, 32.6, 28.4, 26.5, 25.9, 25.9, 23.2, 18.3, 18.3, 14.1, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{31}H_{58}O_5Si_2Na$ $(M+Na)^+$ 589.3715, found 589.3712.

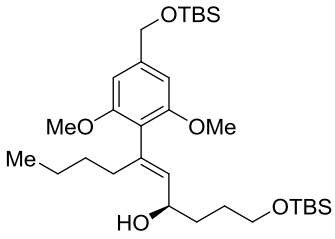
Enone 1.11: To a stirred suspension of PDC (3.2 g, 12.72 mmol) and activated molecular sieves (4 Å, 3.2 g) in CH_2Cl_2 (20 mL) at 23 °C was added dropwise a solution of allylic alcohol **1.10** (2.4 g 4.24 mmol) in CH_2Cl_2 (20 mL). The resulting dark brown mixture was stirred for 3 h at 23 °C before filtered through a pad of celite, and washed with EtOAc (80 mL). The combined organic layer was washed with $NaHCO_3$ (sat. aq., 2 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:20) to give the enone **1.11** as a colorless oil (1.36 g, 64% BORM over two steps) and recovered ketone **1.08** (388 mg, 25%).



1.11

1.11: R_f = 0.40 (silica gel, EtOAc:hexanes 1:15); FT-IR (neat) ν_{max} = 2954, 2857, 1686, 1614, 1578, 1462, 1415, 1363, 1254, 1227, 1126, 1099, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.56 (s, 2 H), 6.07 (s, 1 H), 4.74 (s, 2 H), 3.75 (s, 6 H), 3.64 (t, *J* = 9.0 Hz, 2 H), 2.87 (t, *J* = 10.2 Hz, 2 H), 2.55 (t, *J* = 10.8 Hz, 2 H), 1.83 (p, *J* = 10.8 Hz, 2 H), 1.28 (m, 4 H), 0.97 (s, 9 H), 0.88 (s, 9 H), 0.83 (t, *J* = 7.2 Hz, 3 H), 0.13 (s, 6 H), 0.04 (s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 200.8, 157.1, 154.8, 142.6, 127.6, 119.2, 101.4, 64.9, 62.4, 55.7, 41.0, 33.0, 30.2, 27.1, 25.9, 22.9, 18.4, 18.3, –5.2, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{31}H_{57}O_5Si_2$ $(M+H)^+$ 565.3739, found 565.3744.

Allylic Alcohol 1.12: To a stirred solution of enone **1.11** (3.0 g, 5.3 mmol) in toluene (80 mL) at – 78 °C was added dropwise (S)-CBS (1.6 mL, 1.0 M in toluene, 1.6 mmol). The resulting mixture was stirred for 15 min before catecholborane (10.6 mL, 1.0 M in THF, 10.6 mmol) was added via syringe pump over 2 h. The resulting mixture was allowed slowly to reach 0 °C over 12 h before being quenched with water (40 mL), stirred for 10 min, extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:5) to give allylic alcohol **1.12** as a colorless oil (2.55 g, 85% yield). Mosher ester analysis revealed 95% ee.

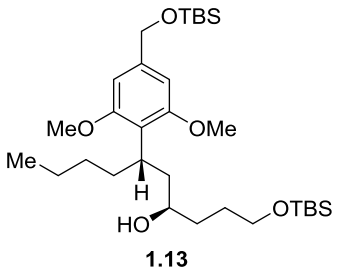


1.12

1.12: R_f = 0.30 (silica gel, EtOAc:hexanes 1:5); $[\alpha]_D^{25}$ = –12.3 (c =0.45 in CH_2Cl_2); FT-IR (neat) ν_{max} = 3439, 2929, 2857, 1608, 1578, 1462, 1415, 1254, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.53 (s, 2 H), 5.24 (d, *J* = 9.0 Hz, 1 H), 4.73 (s, 2 H), 4.57 (dt, *J* = 9.0, 6.0 Hz, 1 H), 3.74 (s, 6 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 2.34 (m, 2 H), 1.94 (s, 1 H), 1.72–1.57 (m, 4 H), 1.30–1.16 (m, 4 H), 0.96 (s, 9 H), 0.90 (s, 9 H), 0.82 (t, *J* = 7.2 Hz, 3

H), 0.12 (s, 6 H), 0.06 (s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 157.6, 141.6, 136.1, 133.2, 119.8, 101.5, 68.2, 65.0, 63.4, 55.7, 34.3, 31.3, 30.5, 28.9, 25.9, 25.9, 22.8, 18.4, 18.3, 14.0, –5.2, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{31}H_{58}O_5Si_2Na$ $(M+Na)^+$ 589.3715, found 589.3714.

Alcohol 1.13: To a stirred solution of alkene **1.12** (566 mg, 1.0 mmol) in CH_2Cl_2 (30 mL) at 23 °C was added Crabtree's catalyst (72 mg, 0.09 mmol). The resulting mixture was stirred for 4 h under H_2 (50 atm) before it was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:7) to give alcohol **1.13** as a colorless oil (430 mg, 76% yield). Mosher ester analysis revealed 93% ee.

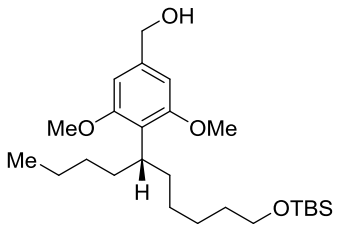


1.13

1.13: R_f = 0.40 (silica gel, EtOAc:hexanes 1:5); $[\alpha]_D^{25}$ = –12.0 (c = 0.5 in MeOH); FT-IR (neat) ν_{max} = 3451, 2929, 2857, 1609, 1584, 1462, 1421, 1255, 835 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.50 (s, 2 H), 4.70 (s, 2 H), 3.77 (s, 6 H), 3.60 (m, 2 H), 3.48 (m, 1 H), 3.35 (ddt, *J* = 9.6, 6.0, 3.6 Hz, 1 H), 2.13 (d, *J* = 3.0 Hz, 1 H), 2.02 (m, 1 H), 1.82 (m, 1 H), 1.73 (dt, *J* = 13.8, 6.0 Hz, 1 H), 1.58 (m, 4 H), 1.35 (m, 1 H), 1.23 (m, 2 H), 1.13 (m, 1 H), 1.02 (m, 1 H), 0.95 (s, 9 H), 0.88 (s, 9 H), 0.81 (t, *J* = 7.2 Hz, 3 H), 0.10 (s, 6 H), 0.04 (s, 3 H), 0.03 (s, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.5, 157.9, 140.6, 119.4, 102.0, 101.5, 71.2, 65.0, 63.7, 55.9, 55.2, 41.6, 33.8, 33.4, 32.0, 30.3, 29.0, 25.9, 25.9, 22.8, 18.4, 18.3, 14.1, –5.2, –5.4 ppm; HRMS (ESI-TOF) calcd for $C_{31}H_{61}O_5Si_2$ $(M+H)^+$ 569.4052, found 569.4063.

Benzylic Alcohol 1.14: To a stirred solution of alcohol **1.13** (568 mg, 1.0 mmol) in THF (10 mL) at 0 °C were added Et_3N (0.167 mL, 1.2 mmol) and MsCl (0.085 mL, 1.1 mmol)

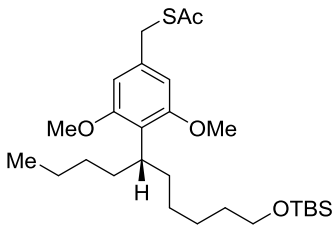
dropwise. The resulting mixture was stirred for 30 min before lithium triethylborohydride (4.0 mL, 1.0 M in THF, 4.0 mmol) was added. The mixture was heated to 80 °C for 4 h and then cooled to 0 °C. TBAF (3.0 mL, 1.0 M in THF, 3.0 mmol) was added and stirring was continued for 1 h at 0 °C. The reaction mixture was quenched with NH_4Cl (sat. aq., 15 mL), extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:2) to give benzylic alcohol **1.14** as a colorless oil (317 mg, 73% yield).



1.14

1.14: R_f = 0.35 (silica gel, EtOAc:hexanes 1:2); $[\alpha]_D^{25}$ = +3.0 (c = 1.0 in CH_2Cl_2); FT-IR (neat) ν_{max} = 3325,2929, 2857, 1608, 1583, 1462, 1421, 1374, 1254, 1131, 1098, 834 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.54 (s, 2 H), 4.65 (s, 2 H), 3.78 (s, 6 H), 3.54 (t, *J* = 6.6 Hz, 2 H), 3.27 (m, 1 H), 1.78 (m, 2 H), 1.68 (s, 1 H), 1.56 (m, 2 H), 1.44 (m, 2 H), 1.30–1.11 (m, 6 H), 1.02 (m, 2 H), 0.88 (s, 9 H), 0.81 (t, *J* = 7.2 Hz, 3 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.6, 158.9, 139.4, 121.3, 103.1, 102.8, 65.8, 63.4, 56.0, 55.3, 35.0, 33.6, 33.3, 32.9, 30.5, 28.0, 26.0, 22.9, 18.4, 14.1, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{25}H_{46}O_4SiNa$ $(M+Na)^+$ 461.3057, found 461.3079.

Thioacetate 1.15: To a stirred solution of PPh_3 (393 mg, 1.5 mmol) in THF (4 mL) at 0 °C was added dropwise DIAD (0.30 mL, 1.5 mmol). The resulting mixture was stirred for 20 min before a solution of HSAc (0.1 mL, 1.4 mmol) and alcohol **1.14** (357 mg, 0.mmol) in THF (8 mL) was added dropwise. The resulting mixture was stirred for 1 h before it was concentrated in vacuo. The residue was purified

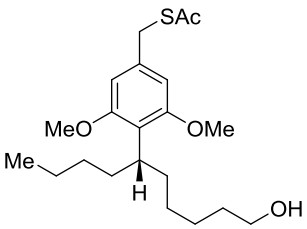


1.15

by flash column chromatography (silica gel, EtOAc: hexanes 1:10) to give thioacetate **1.15** as a yellow oil (378 mg, 91% yield).

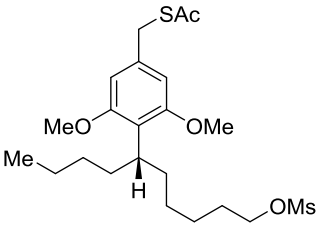
1.15: R_f = 0.60 (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{25}$ = +2.5 (c = 0.4 in CH_2Cl_2); FT-IR (neat) ν_{max} = 2929, 2857, 1693, 1605, 1583, 1462, 1421, 1253, 1131, 1098, 835 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.42 (s, 2 H), 4.08 (s, 2 H), 3.74 (s, 6 H), 3.54 (t, *J* = 6.6 Hz, 2 H), 3.22 (m, 1 H), 2.37 (s, 3 H), 1.74 (m, 2 H), 1.54 (m, 2 H), 1.44 (m, 2 H), 1.28–1.09 (m, 6 H), 1.02 (m, 2 H), 0.87 (s, 9 H), 0.81 (t, *J* = 7.2 Hz, 3 H), 0.02 (s, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.4, 159.7, 158.7, 135.6, 121.0, 104.9, 63.4, 56.0, 55.3, 35.0, 33.9, 33.5, 33.3, 32.9, 30.5, 30.4, 28.0, 26.0, 22.9, 18.4, 14.1, –5.3 ppm; HRMS (ESI-TOF) calcd for $C_{27}H_{49}O_4SSi$ $(M+H)^+$ 497.3115, found 497.3103.

Alcohol 1.16: To a stirred solution of thioacetate **1.15** (390 mg, 0.78 mmol) in HOAc (7.0 mL) and H_2O (1.0 mL) at 23 °C was added pTsOH (30 mg, 0.158 mmol, 0.2 equiv). The resulting mixture was stirred for 1 h before it was concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:2) to give alcohol **1.16** as a colorless oil (270 mg, 90% yield). **1.16**: R_f = 0.35 (silica gel, EtOAc:hexanes 1:2); $[\alpha]_D25$ = –2.8 (c = 0.7 in CH_2Cl_2); FT-IR (neat) ν_{max} = 3356,2929, 2856, 1691, 1605, 1583, 1455, 1421, 1232, 1129 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.43 (s, 2 H), 4.08 (s, 2 H), 3.75 (s, 6 H), 3.57 (t, *J* = 6.6 Hz, 2 H), 3.22 (m, 1 H), 2.37 (s, 3 H), 1.76 (m, 2 H), 1.55–1.43 (m, 4 H), 1.34–0.98 (m, 8 H), 0.81 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.4, 159.5, 158.7, 135.7, 120.9, 105.0, 63.1, 56.0, 55.4, 34.9, 33.9, 33.4, 33.3, 32.7, 30.5, 30.4, 27.9, 25.7, 22.9, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{21}H_{34}O_4SNa$ $(M+Na)^+$ 405.2070, found 405.2060.



1.16

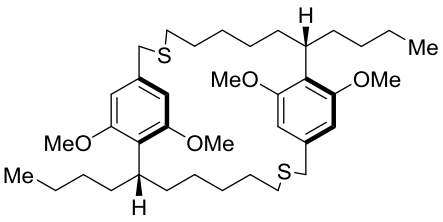
Mesylate 1.04: To a stirred solution of alcohol **1.16** (270 mg, 0.70 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added dropwise Et_3N (0.194 mL, 1.4 mmol) and MsCl (0.081 mL, 1.05 mmol). The resulting mixture was stirred for 30 min before it was quenched with NH_4Cl (sat. aq., 10 mL), extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:3) to give mesylate **1.04** as a colorless oil (298 mg, 92% yield).



1.04

1.04: R_f = 0.45 (silica gel, EtOAc:hexanes 1:2); $[\alpha]_D25$ = +3.6 (c = 0.6 in CH2Cl2); FT-IR (neat) ν_{max} = 2925, 2856, 1688, 1604, 1582, 1455, 1421, 1352, 1260, 1174 cm^{-1};^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.43 (s, 2 H), 4.15 (t, *J* = 6.6 Hz, 2 H), 4.08 (s, 2 H), 3.75 (s, 6 H), 3.23 (m, 1 H), 2.96 (s, 3 H), 2.37 (s, 3 H), 1.76 (m, 2 H), 1.67 (m, 2 H), 1.53 (m, 2 H), 1.37–0.98 (m, 8 H), 0.81 (t, *J* = 7.2 Hz, 3 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 195.4, 159.3, 158.7, 135.9, 120.5, 104.9, 104.7, 70.4, 56.0, 55.3, 37.3, 34.8, 33.9, 33.3, 33.2, 30.5, 30.4, 29.0, 27.5, 25.5, 22.8, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{22}H_{37}O_6S_2$ $(M+H)^+$ 461.2026, found 461.2046.

Cyclic disulfide 1.17: A stirred solution of thioacetate **1.04** (290 mg, 0.627 mmol) in MeOH (10 mL) was degassed by bubbling argon (balloon) through it for 20 min. To this solution was added a degassed solution of NaOMe (170 mg, 3.15 mmol) in MeOH (10 mL) at 23 °C. The resulting mixture was stirred for 36 h before being quenched with NH_4Cl (sat. aq., 20 mL), extracted with EtOAc (3 × 25 mL), dried over Na_2SO_4, and concentrated in vacuo. The

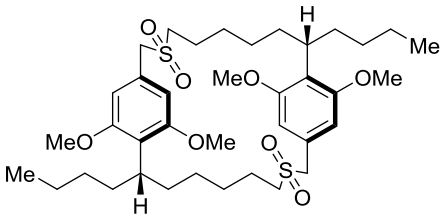


1.17

residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:15) to give cyclic disulfide **1.17** as a colorless viscous oil (128 mg, 64% yield).

1.17: R_f = 0.50 (silica gel, EtOAc:hexanes 1:10); $[\alpha]_D^{25}$ = +5.0 (c = 0.2 in CH_2Cl_2); FT-IR (neat) ν_{max} = 2925, 2854, 1605,1581, 1454, 1420, 1373, 1205, 1118 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.41 (s, 4 H), 3.71 (s, 12 H), 3.59 (s, 4 H), 3.23 (m, 2 H), 2.26 (t, *J* = 7.2 Hz, 4 H), 1.88 (m, 2 H), 1.74 (m, 2 H), 1.52 (m, 2 H), 1.44–1.11 (m, 16 H), 1.02 (m, 2 H), 0.92 (m, 4 H), 0.81 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.3, 158.7, 137.8, 119.8, 105.1, 104.6, 56.0, 55.2, 36.8, 34.8, 33.9, 33.3, 31.0, 30.5, 29.8, 29.0, 27.2, 22.9, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{38}H_{61}O_4S_2$ $(M+H)^+$ 645.4006, found 645.4010.

Cyclic disulfone 1.05: To a stirred solution of cyclic sulfide **1.17** (130 mg, 0.202 mmol) in EtOH (4 mL) at 0 °C were added H_2O_2 (0.20 mL, 2.06 mmol, 10.0 equiv) and ammonium molybdate tetrahydrate (75 mg, 0.061 mmol, 0.3 equiv). The resulting mixture was stirred at 23 °C for 12 h before it was quenched with $Na_2S_2O_3$ (sat. aq., 10 mL), extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes: CH_2Cl_2 1:3:2) to give cyclic disulfone **1.05** as a white amorphous solid (114 mg, 80% yield).

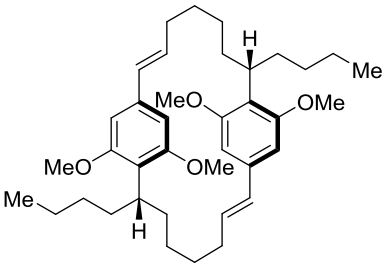


1.05

1.05: R_f = 0.40 (silica gel, EtOAc:hexanes 2:3); $[\alpha]_D^{25}$ = +3.5 (c = 0.2 in CH_2Cl_2); FT-IR (neat) ν_{max} = 2925, 2855, 1604, 1583, 1457, 1425, 1302, 1248, 1116 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.47 (s, 4 H), 4.13 (d, *J* = 14.4 Hz, 2 H), 4.07 (d, *J* = 14.4 Hz, 2 H), 3.72 (s, 12 H), 3.25 (m, 2 H), 2.68 (m, 4 H), 1.92 (m, 2 H), 1.68 (m, 6 H), 1.54–1.46 (m,

4 H), 1.35–1.09 (m, 10 H), 0.96 (m, 6 H), 0.81 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.6, 159.0, 127.3, 121.9, 106.8, 105.7, 59.7, 56.1, 55.4, 50.3, 34.8, 33.7, 32.8, 30.3, 28.3, 26.9, 22.8, 22.2, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{38}H_{61}O_8S_2$ $(M+H)^+$ 709.3802, found 709.3817.

Bis(olefin) 1.18: To a stirred solution of cyclic sulfone **1.05** (90 mg, 0.127 mmol) in



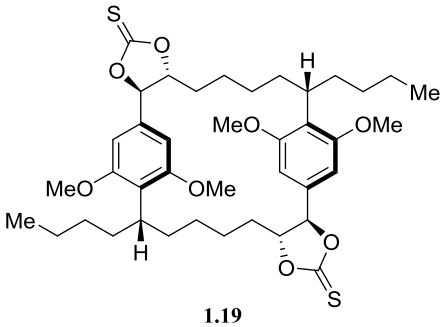
1.18

CH_2Cl_2/*t*BuOH (1:1, 6.0 mL) at 0 °C was added Al_2O_3/KOH (500 mg) and CF_2Br_2 (0.110 mL, 1.21 mmol). The resulting mixture was sealed and stirred at 23 °C for 2 h before being filtered, washed with EtOAc (30 mL), and concentrated in *vacuo*. The crude product was dissolved in CH_2Cl_2 (4.0 mL), $Pd(CH_3CN)2Cl_2$ (10 mg, 0.04 mmol) was added, and the resulting mixture was heated to 40 °C for 4 h before concentrated in *vacuo*. The residue was purified by flash column chromatography (silica gel, benzene:hexanes 3:7) to give bis(olefin) **1.18** as a colorless viscous oil (51 mg, 70% yield).

1.18: R_f = 0.60 (silica gel, EtOAc:hexanes 1:20); $[\alpha]_D^{25}$ = –2.4 (c = 0.4 in CH_2Cl_2); FT-IR (neat) ν_{max} = 2927, 2854, 1602, 1571, 1452, 1415, 1373, 1269, 1126 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.32 (s, 2 H), 6.26 (s, 2 H), 6.04 (d, *J* = 15.6 Hz, 2 H), 5.75 (dt, *J* = 15.6, 7.2 Hz, 2 H), 3.76 (s, 6 H), 3.75 (s, 6 H), 3.27 (m, 2 H), 2.13 (m, 4 H), 1.97 (m, 2 H), 1.88 (m, 2 H), 1.55 (m, 4 H), 1.39–1.15 (m, 10 H), 1.08 (m, 2 H), 0.98 (m, 4 H), 0.82 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.2, 158.8, 136.5, 130.4, 130.0, 119.8, 102.9, 101.4, 56.0, 55.2, 34.7, 33.8, 32.6, 31.8, 30.6, 28.2, 25.7, 22.9, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{38}H_{57}O_4$ $(M+H)^+$ 577.4251, found 577.4239.

Thiocarbonate 1.19: To a stirred solution of alkene **1.18** (30 mg, 0.052 mmol) in *t*BuOH/H_2O (2:1, 4.2 mL) at 23 °C were added AD-mix-β (300 mg) and $MeSO_2NH_2$ (5 mg, 0.052 mmol). The resulting mixture was stirred at 23 °C for 12 h before being quenched with Na_2SO_3 (400 mg), stirred for 45 min, extracted with EtOAc (3 × 15 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The resulting crude tetraol was used without further purification. To a stirred suspension of this tetraol in toluene (5.0 mL) at 23 °C was added 1,1′- thiocarbonyldiimidazole (92 mg, 0.52 mmol), and the resulting mixture was heated to 125 °C for 5 h before it was concentrated in *vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:4) to give thiocarbonate **1.19** as a yellow oil (23 mg, 62% yield in two steps).

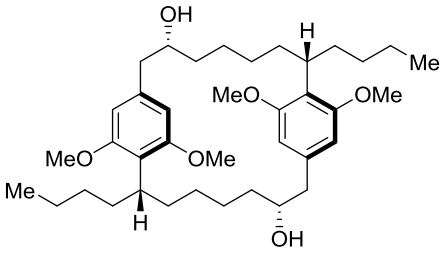
1.19: R_f = 0.30 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{25}$ = +55.7 (c = 1.0 in CH_2Cl_2); FT-IR



1.19

(neat) ν_{max} = 2930, 2857, 1800, 1605, 1586, 1460, 1426, 1239, 1129 cm^{-1}; 1H NMR (600 MHz, $CDCl_3$) δ = 6.43 (bs, 2 H), 6.26 (bs, 2 H), 5.22 (d, *J* = 7.2 Hz, 2 H), 4.46 (dt, *J* = 7.2, 6.0 Hz, 2 H), 3.76 (bs, 6 H), 3.75 (bs, 6 H), 3.31 (m, 2 H), 2.02–1.94 (m, 4 H), 1.78 (m, 2 H), 1.58–1.41 (m, 8 H), 1.30–1.14 (m, 8 H), 1.00 (m, 4 H), 0.92 (m, 2 H), 0.84 (t, *J* = 7.2 Hz, 6 H) ppm; 13C NMR (150 MHz, $CDCl_3$) δ = 191.4, 159.7, 159.4, 132.5, 123.0, 104.3, 100.4, 88.5, 87.6, 56.2, 55.4, 34.6, 33.4, 32.3, 32.1, 30.2, 26.4, 24.2, 22.7, 14.0 ppm; HRMS (ESI-TOF) calcd for $C_{40}H_{57}O_8S_2$ $(M+H)^+$ 729.3489, found 729.3495.

Diol 1.20: A stirred solution of thiocarbonate **1.18** (9.0 mg, 0.0124 mmol) in toluene (3.0 mL) was degassed by bubbling argon (balloon) through it for 20 min. To this solution at 23 °C were added dropwise nBu$_3$SnH (0.033 mL, 0.124 mmol) and a degassed solution of AIBN (4.0 mg, 0.0248 mmol) in toluene (0.3 mL). The resulting mixture was heated in a 100 °C oil bath for 1.5 h before being concentrated in *vacuo*. The resulting residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:2) to give diol **1.20** as an amorphous solid (6.1 mg, 81% yield).

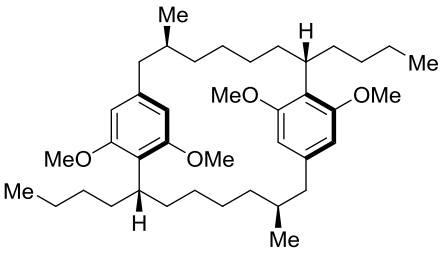


1.20

1.20: R_f = 0.40 (silica gel, EtOAc:hexanes 2:3); $[\alpha]_D^{25}$ = +9.0 (c = 0.3 in CH2Cl2); FT-IR (neat) ν_{max} = 3311, 2930, 2855, 1605, 1578, 1457, 1419, 1237, 1126 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.28 (s, 2 H), 6.25 (s, 2 H), 3.76 (bs, 6 H), 3.74 (bs, 6 H), 3.43 (m, 2 H), 3.24 (m, 2 H), 2.70 (dd, *J* = 15.6, 7.8 Hz, 2 H), 2.46 (dd, *J* = 15.6, 7.8 Hz, 2 H), 1.83 (m, 4 H), 1.48 (d, *J* = 5.4 Hz, 2 H), 1.45 (m, 2 H), 1.28–1.10 (m, 18 H), 0.82 (t, *J* = 8.4 Hz, 6 H), 0.75 (m, 2 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.3, 158.9, 137.4, 119.4, 106.0, 105.8, 73.2, 56.5, 55.3, 44.8, 36.0, 35.1, 33.6, 33.0, 30.6, 27.9, 26.4, 22.9, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{38}H_{61}O_6$ $(M+H)^+$ 613.4462, found 613.4487.

(–)-Cylindrocyclophane F (**1.02**): To a stirred solution of alcohol **1.20** (5 mg, 8.2 μmol) in CH_2Cl_2 (0.4 mL) at 0 °C were added dropwise Et_3N (6.0 μL, 0.043 mmol) and MsCl (3.0 μL, 0.043 mmol). The resulting mixture was stirred for 30 min at 0 °C before addition of $AlMe_3$ (2.0 M solution in heptanes, 20 μL, 0.04 mmol) at 0 °C. The resulting mixture was stirred for 10 min before addition of BBr_3 (1.0 M solution in CH_2Cl_2, 82 μL,

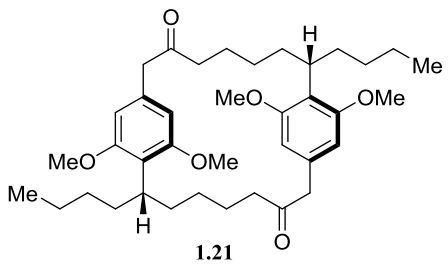
0.082 mmol). The resulting mixture was stirred for 5 h at 23 °C before it was quenched with H_2O (4 mL), extracted with CH_2Cl_2 (3 × 5 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc: hexanes 1:4) to give the (–)-cylindrocyclophane F (**1.02**) as a colorless solid (3.2 mg, 71% yield).



cylindrocyclophane F (**1.02**)

(–)-cylindrocyclophane F (**1.02**): R_f = 0.30 (silica gel, EtOAc:hexanes 1:4); $[\alpha]_D^{25}$ = –72.0 (c = 0.2 in MeOH), lit. $[\alpha]_D^{25}$ = –72.0 (c = 0.9 in MeOH); FT-IR (neat) ν_{max} = 3456, 2925, 2855, 1624, 1586, 1461, 1427, 1376, 1267, 1008 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ = 6.01 (bs, 2 H), 5.97 (bs, 2 H), 3.11 (m, 2 H), 2.57 (dd, *J* = 13.2, 3.6 Hz, 2 H), 2.01–1.88 (m, 4 H), 1.82 (dd, *J* = 13.2, 11.4 Hz, 2 H), 1.56 (m, 2 H), 1.51–0.90 (m, 18 H), 0.93 (d, *J* = 6.6 Hz, 6 H), 0.78–0.73 (m, 4 H), 0.81 (t, *J* = 7.2 Hz, 6 H), 0.64 (m, 2 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.2, 157.1, 140.9, 116.1, 110.0, 108.0, 45.9, 36.8, 36.7, 36.7, 35.6, 34.9, 31.8, 30.7, 30.2, 24.0, 20.8, 14.6 ppm; HRMS (ESI-TOF) calcd for $C_{36}H_{57}O_4$ $(M+H)^+$ 553.4251, found 553.4244.

Diketone 1.21: To a stirred solution of diol **1.20** (5.0 mg, 8.2 μmol) in CH_2Cl_2 (0.4 mL) at 2 °C were added $NaHCO_3$ (7 mg, 0.082 mmol) and Dess–Martin periodinane (17 mg, 0.04 mmol). The resulting solution was stirred for 1 h before it was quenched with $Na_2S_2O_3$ (sat. aq., 2 mL), extracted with EtOAc (3 × 4 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The

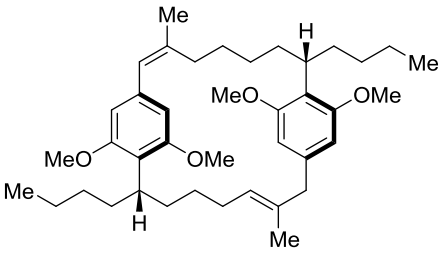


1.21

residue was purified by flash column chromatography (silica gel, EtOAc:hexanes 1:5) to give diketone **1.21** as an amorphous solid (4.6 mg, 92% yield).

1.21: R_f = 0.40 (silica gel, EtOAc:hexanes 1:3); $[\alpha]_D^{25}$ = +42.5 (c = 1.0 in CH_2Cl_2); FT-IR (neat) ν_{max} = 2929, 2854, 1710, 1605, 1583, 1455, 1422, 1234, 1142, 1103 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.29 (bs, 2 H), 6.25 (bs, 2 H), 3.69 (s, 12 H), 3.48 (d, *J* = 3.0 Hz, 4 H), 3.24 (m, 2 H), 2.12 (m, 4 H), 1.87–1.72 (m, 4 H), 1.55–1.39 (m, 6 H), 1.29–1.11 (m, 8 H), 1.02 (m, 2 H), 0.90 (m, 2 H), 0.80 (t, *J* = 8.4 Hz, 6 H), 0.57 (m, 2 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 209.3, 159.7, 159.2, 133.7, 120.1, 105.6, 56.4, 55.4, 51.4, 40.9, 34.9, 33.6, 33.4, 30.5, 27.9, 23.3, 22.8, 14.1 ppm; HRMS (ESI-TOF) calcd for $C_{38}H_{57}O_6$ $(M+H)^+$ 609.4149, found 609.4134.

Diene 1.22: To a stirred solution of diketone **1.21** (4.6 mg, 7.6 μmol) and Comins reagent (18 mg, 0.046 mmol) in THF (0.4 mL) at –78 °C was added KHMDS (0.5 M solution in toluene, 0.091 mL, 0.046 mmol). The resulting solution was stirred for 1 h before it was quenched with MeOH (0.2 mL) and $NaHCO_3$ (sat. aq., 2 mL), extracted with EtOAc (3 × 5 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The residue was used without further purification. To a stirred solution of the crude triflate obtained above in THF/NMP (0.5 mL/0.025 mL) at 0 °C were added $Fe(acac)_3$ (0.8 mg, 2.3 μmol) and MeMgBr (3.0 M solution in Et_2O, 25 μL, 0.075 mmol). The resulting mixture was stirred for 1 h before it was quenched with NH_4Cl (sat. aq., 2 mL), extracted with Et_2O (3 × 5 mL), dried over Na_2SO_4, and concentrated in *vacuo*. The residue was purified by

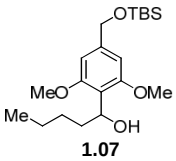


1.22

preparative TLC (silica gel, EtOAc:hexanes 1:30) to give diene **1.22** as a white solid (3.6 mg, 80% yield in two steps).

1.22: R_f = 0.65 (silica gel, EtOAc:hexanes 1:15); $[\alpha]_D^{25}$ = +41.0 (c /= 0.3 in CH_2Cl_2), lit. $[\alpha]_D^{25}$ = +40.6 (c = 0.36 in CH2Cl2); FT-IR (neat) ν_{max} = 2925, 2855, 1600, 1567, 1464, 1408, 1373, 1259, 1196, 1122 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ = 6.24 (bs, 4 H), 6.19 (bs, 2 H), 3.63 (bs, 6 H), 3.59 (bs, 6 H), 3.23 (m, 2 H), 2.09 (m, 4 H), 1.90 (m, 2 H), 1.84 (s, 6 H), 1.78 (m, 2 H), 1.52 (m, 4 H), 1.38 (m, 4 H), 1.31–1.13 (m, 6 H), 1.08 (m, 4 H), 0.89 (m, 2 H), 0.82 (t, *J* = 7.2 Hz, 6 H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ = 158.9, 140.5, 137.5, 125.3, 119.4, 105.8, 104.8, 56.2, 55.6, 35.2, 34.0, 33.6, 33.5, 30.8, 29.0, 28.9, 23.6, 23.1, 14.3 ppm; HRMS (ESI-TOF) calcd for $C_{40}H_{61}O_4$ $(M+H)^+$ 605.4564, found 605.4563.

3. List of Spectra



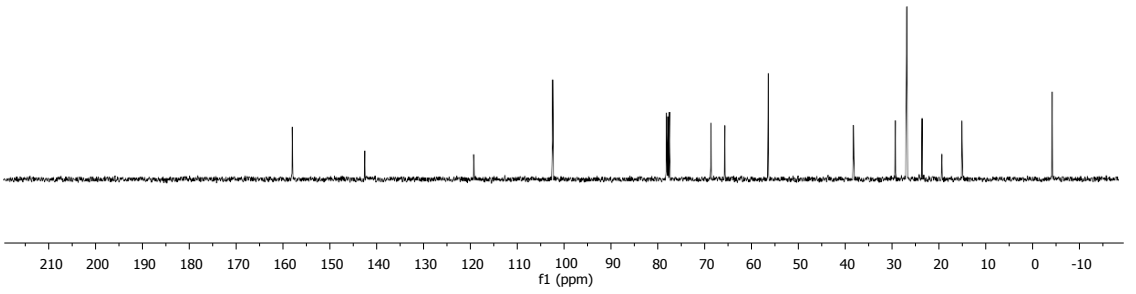
1.07

^{1}H NMR spectrum

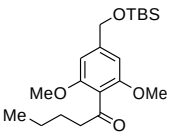
($CDCl_3$, 400 MHz)

^{13}C NMR spectrum

($CDCl_3$, 100 MHz)



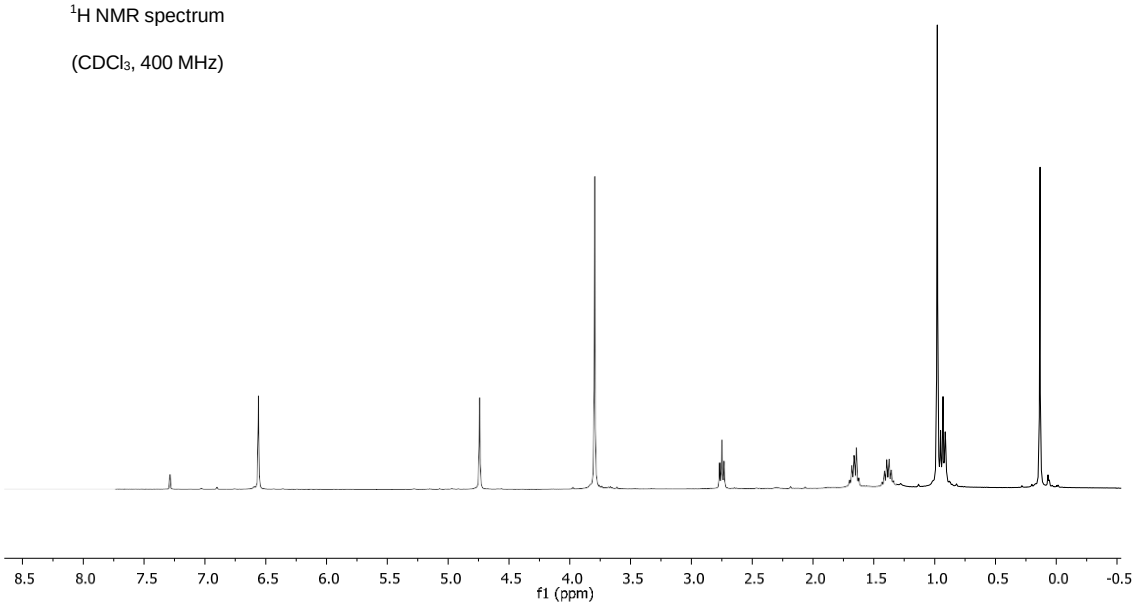
Spectra **1.01**: Compound **1.07**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.08

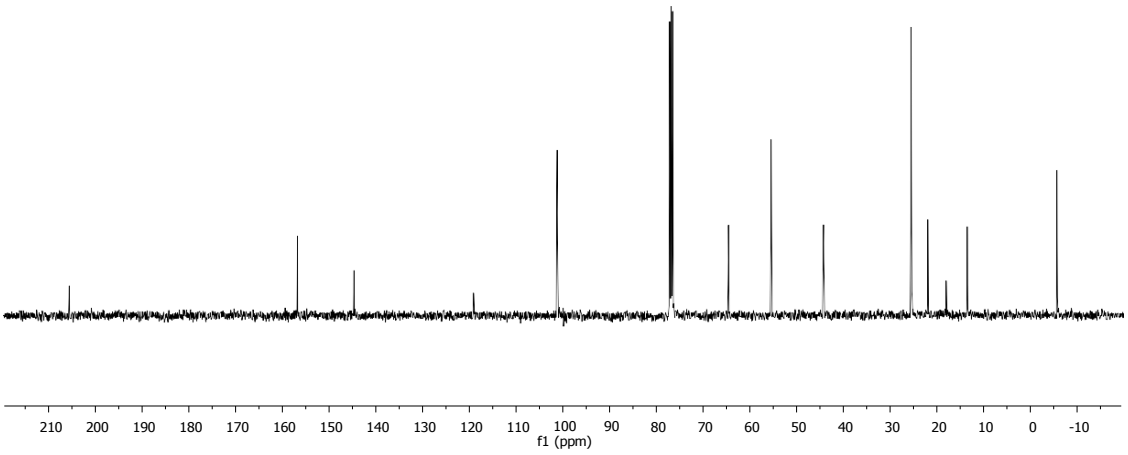
^{1}H NMR spectrum

($CDCl_3$, 400 MHz)

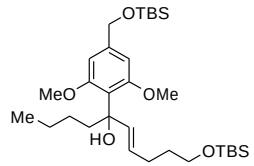


^{13}C NMR spectrum

($CDCl_3$, 100 MHz)



Spectra **1.02**: Compound **1.08**: ^{1}H NMR (top) and ^{13}C NMR (bottom)

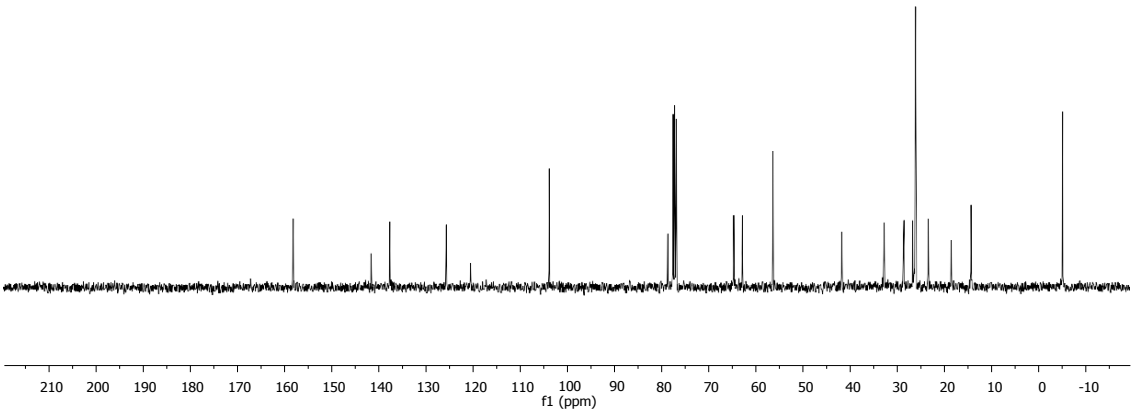


1.10

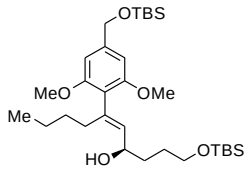
^{1}H NMR spectrum
($CDCl_3$, 500 MHz)

^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



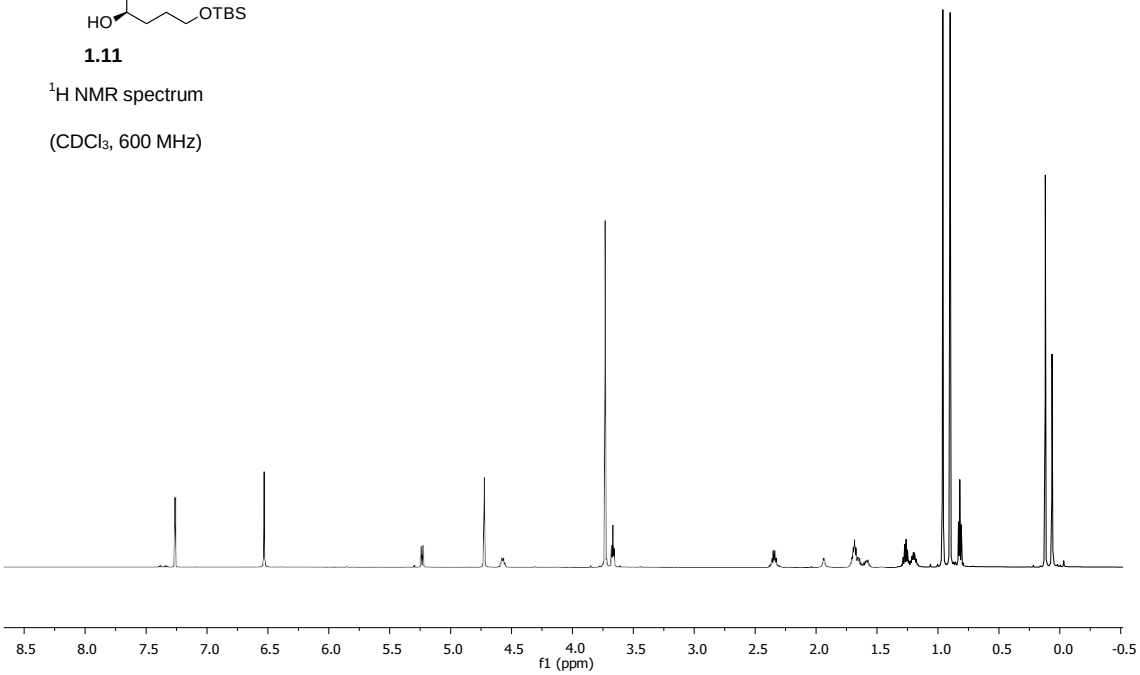
Spectra **1.03**: Compound **1.10**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.11

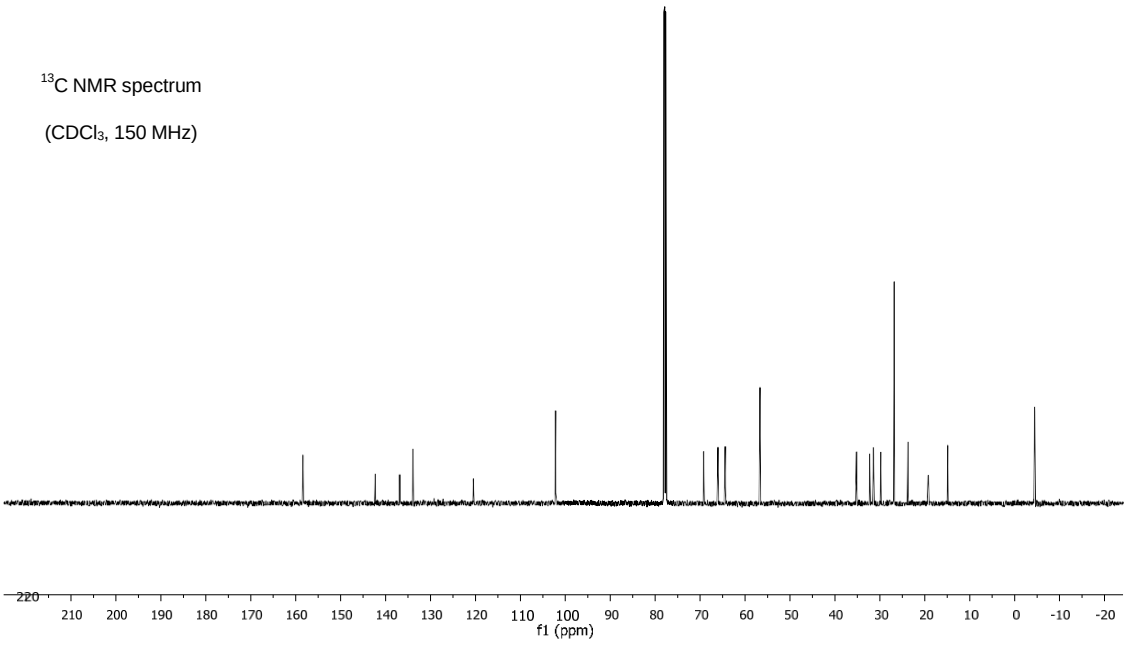
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

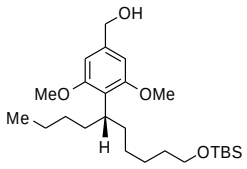


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.04**: Compound **1.11**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



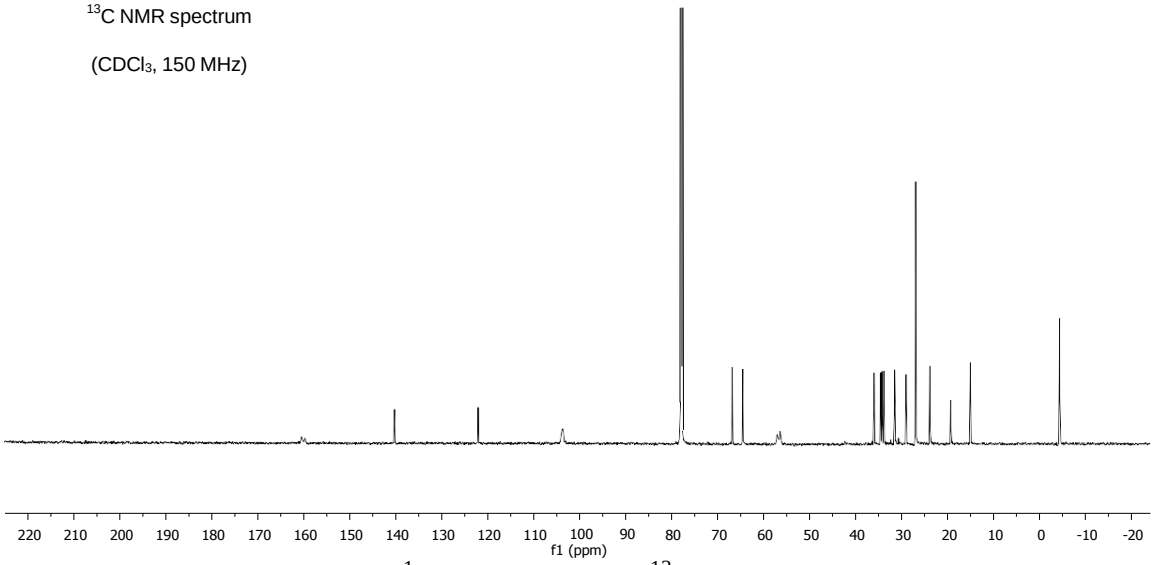
1.12

^{1}H NMR spectrum

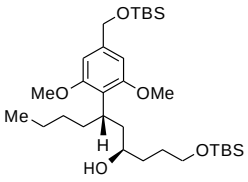
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.05**: Compound **1.12**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



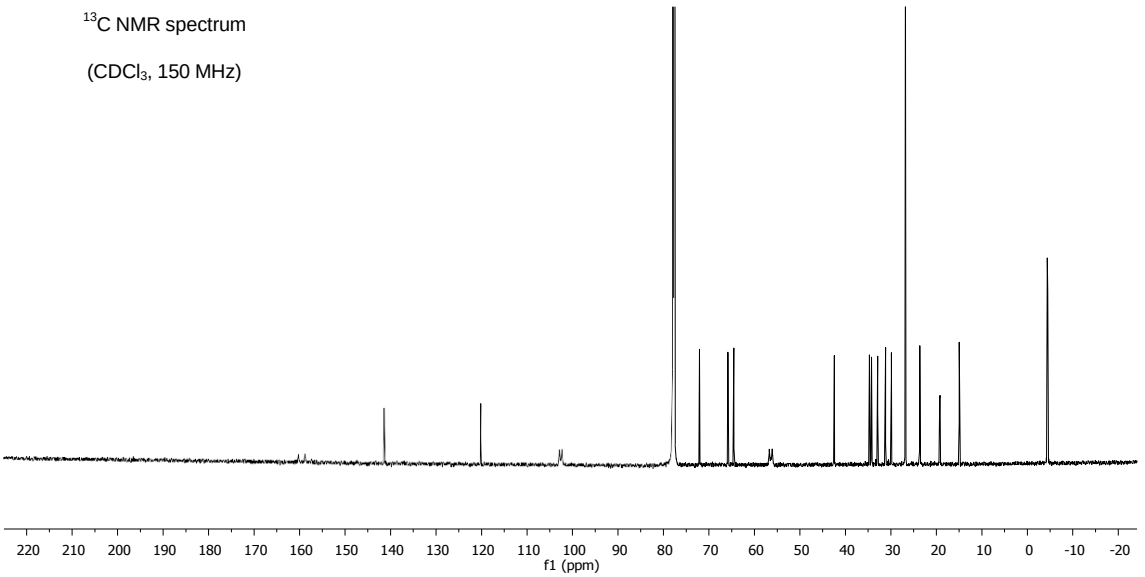
1.13

^{1}H NMR spectrum

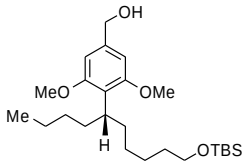
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.06**: Compound **1.13**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



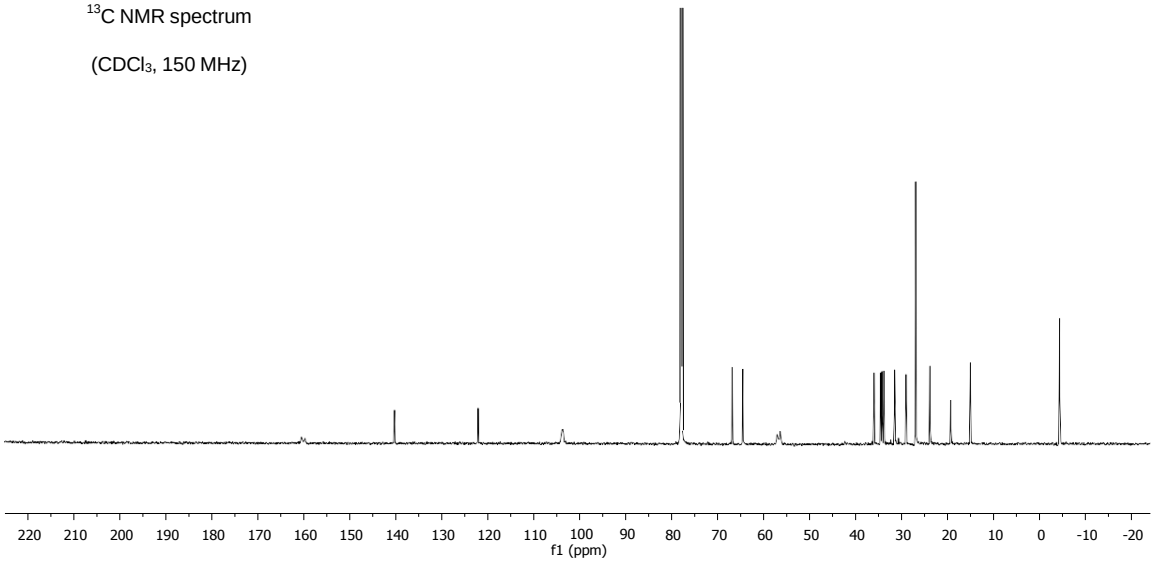
1.14

^{1}H NMR spectrum

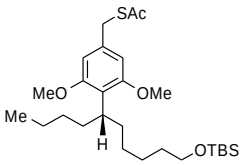
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.07**: Compound **1.14**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



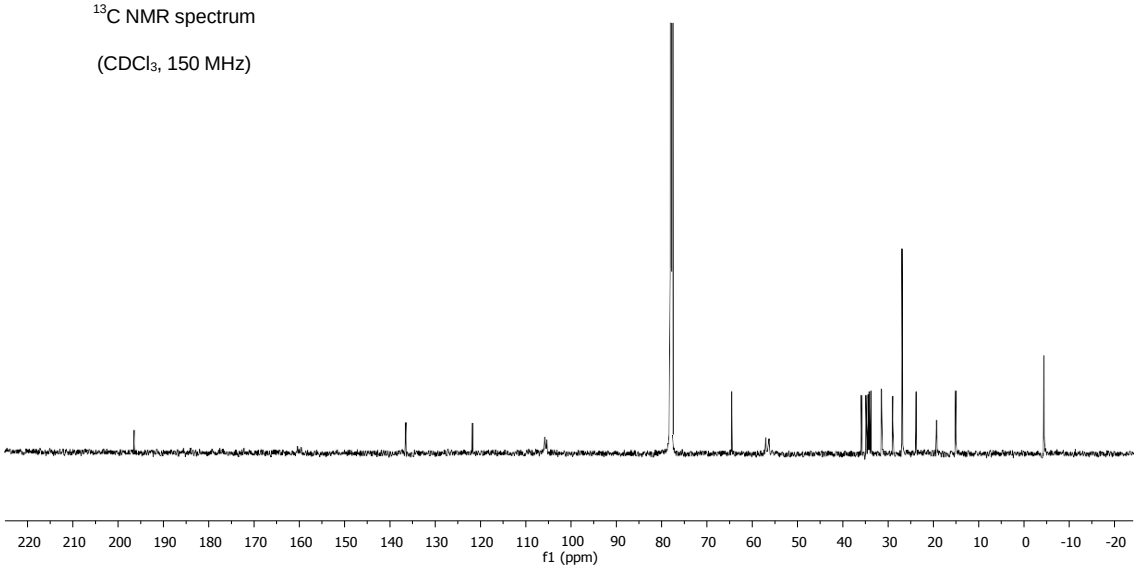
1.15

^{1}H NMR spectrum

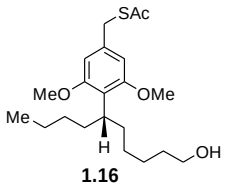
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.08**: Compound **1.15**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



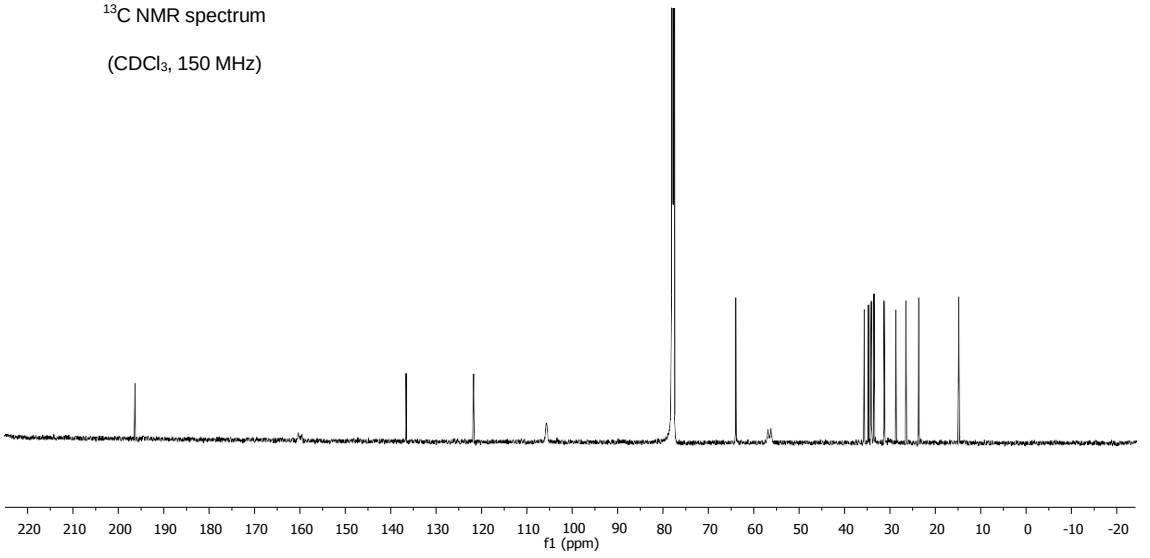
1.16

^{1}H NMR spectrum

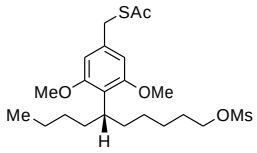
($CDCl_3$, 600 MHz)

^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



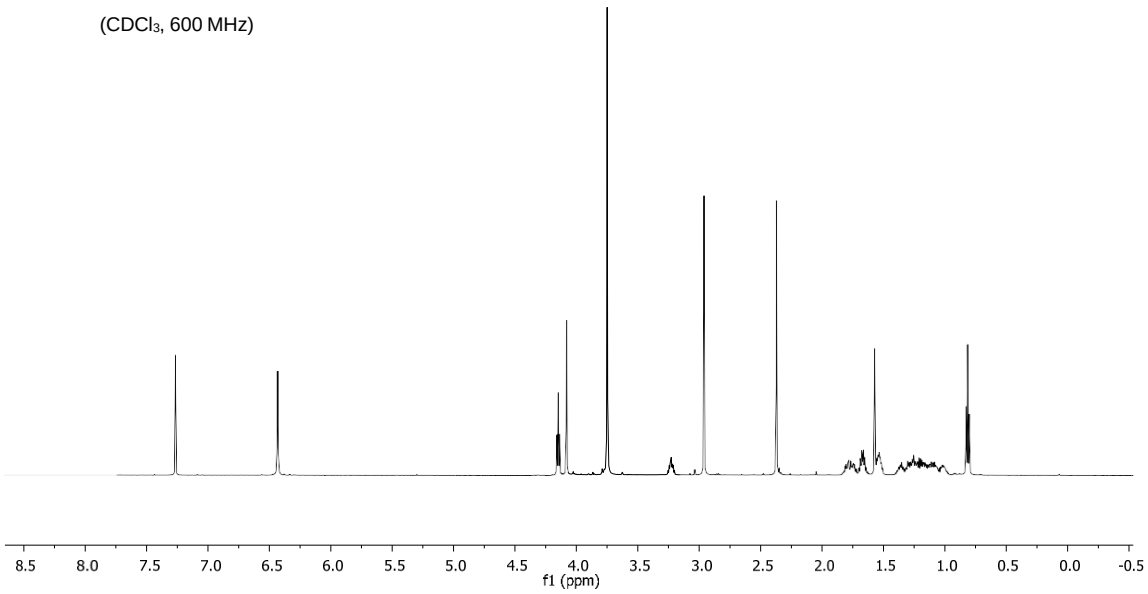
Spectra **1.09**: Compound **1.16**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.04

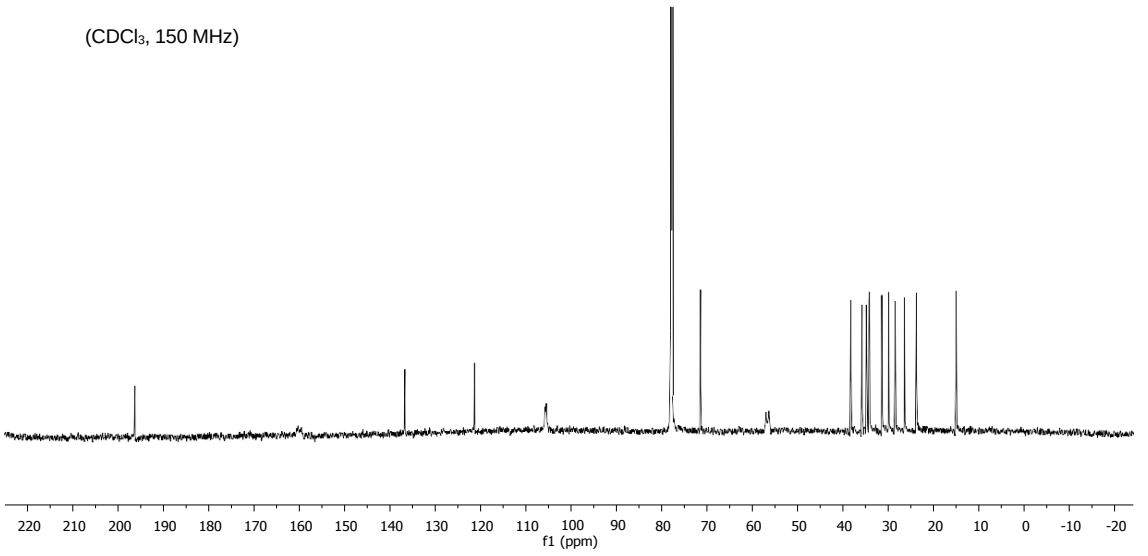
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

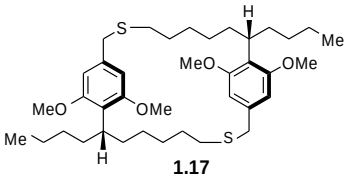


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



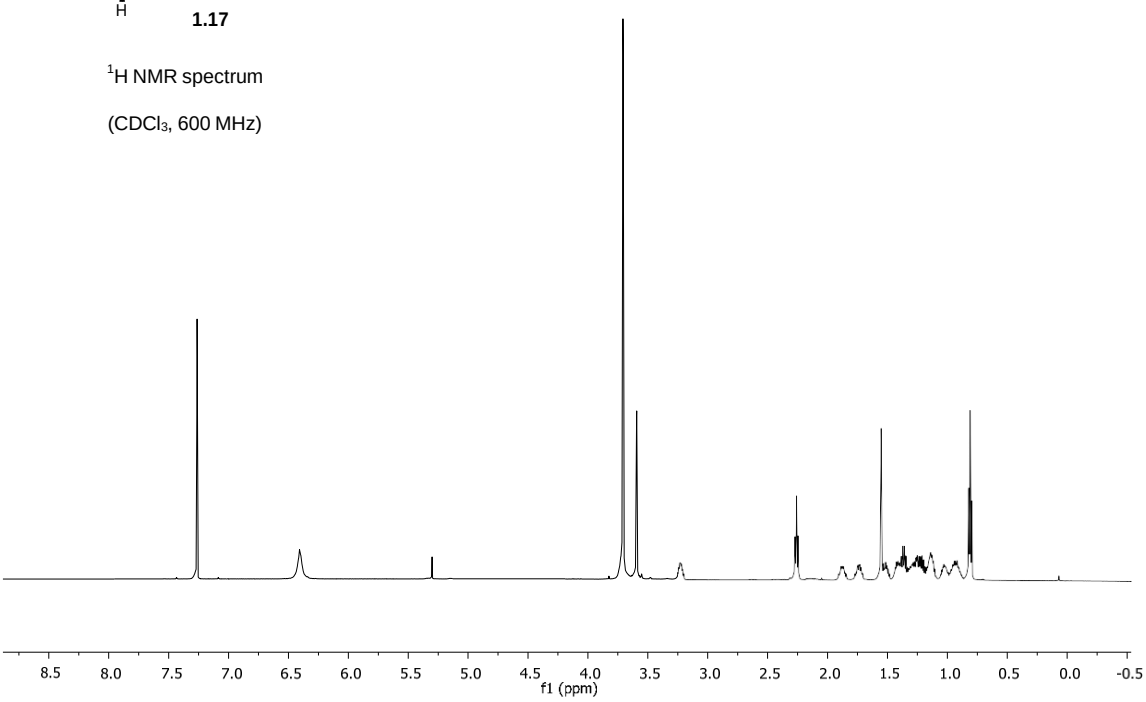
Spectra **1.10**: Compound **1.04**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.17

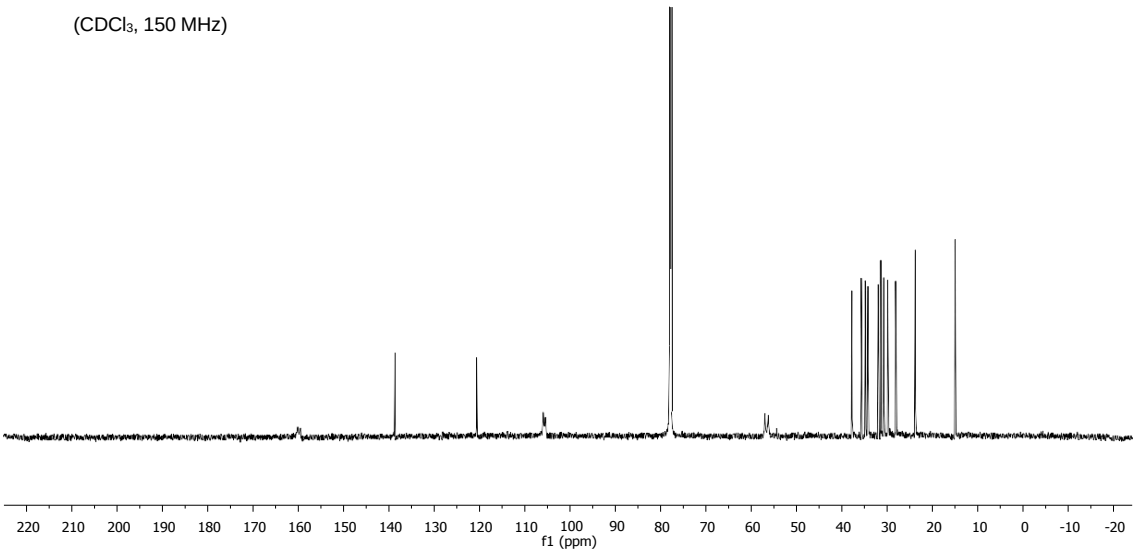
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

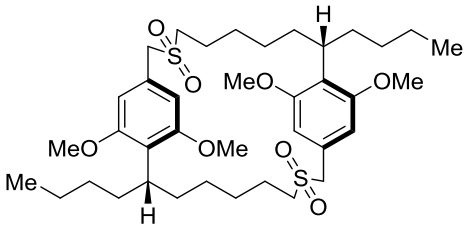


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



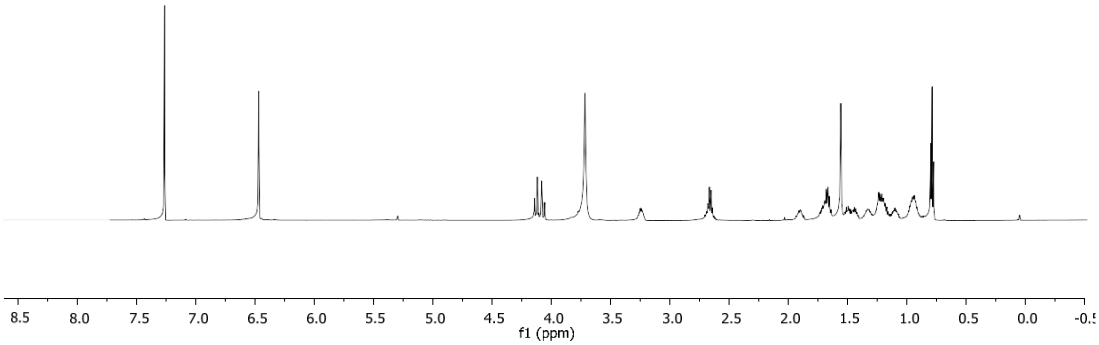
Spectra **1.11**: Compound **1.17**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.05

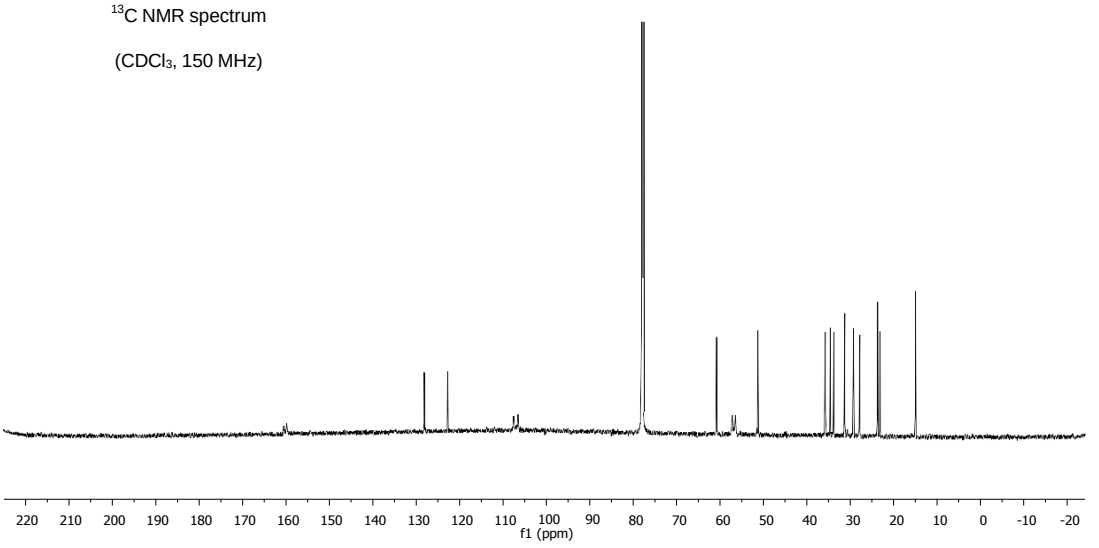
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

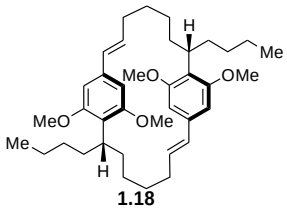


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



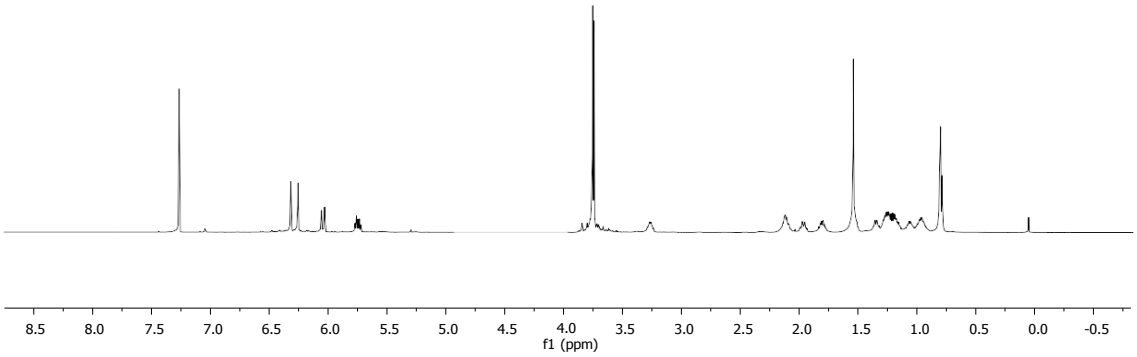
Spectra **1.12**: Compound **1.05**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.18

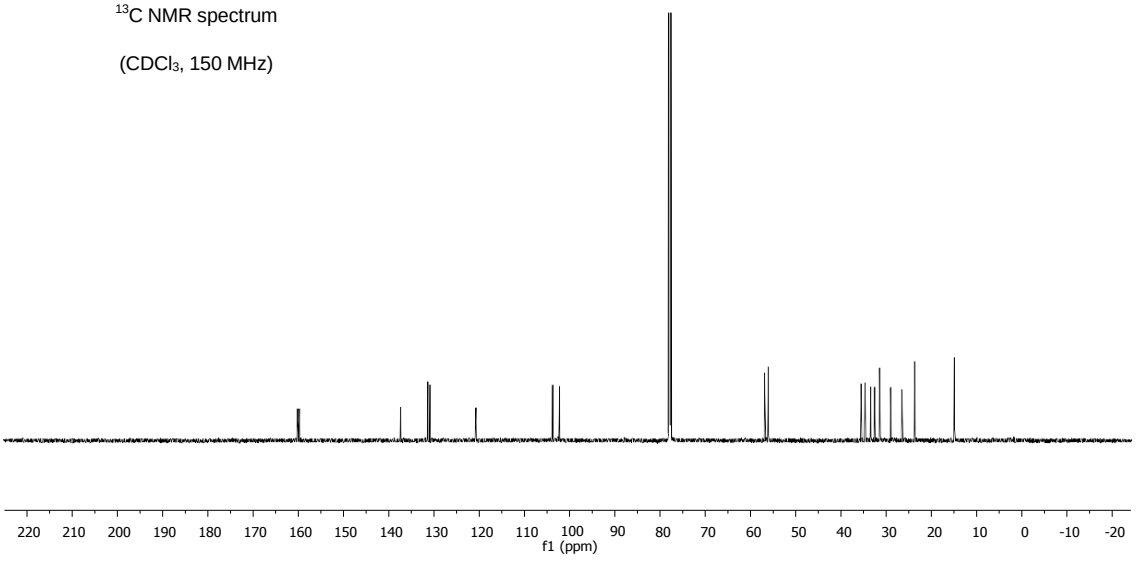
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

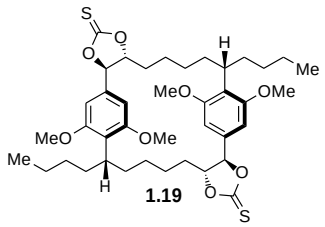


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



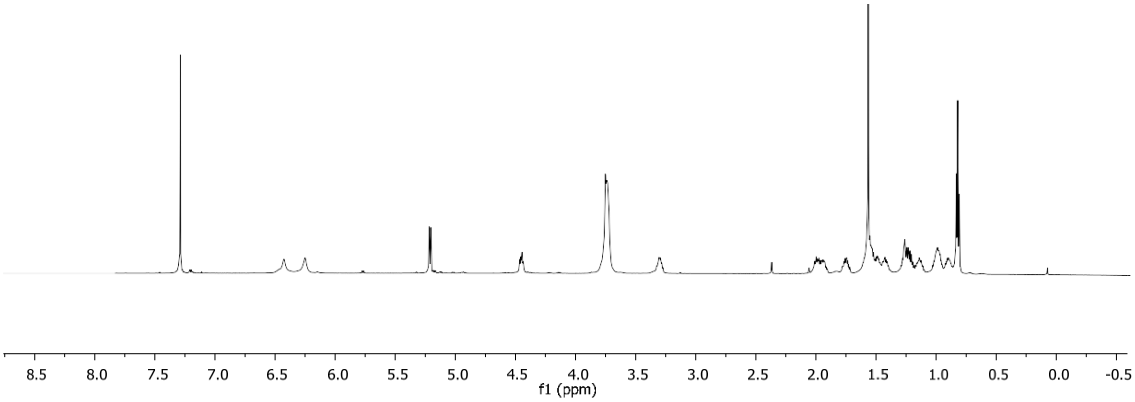
Spectra **1.13**: Compound **1.18**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.19

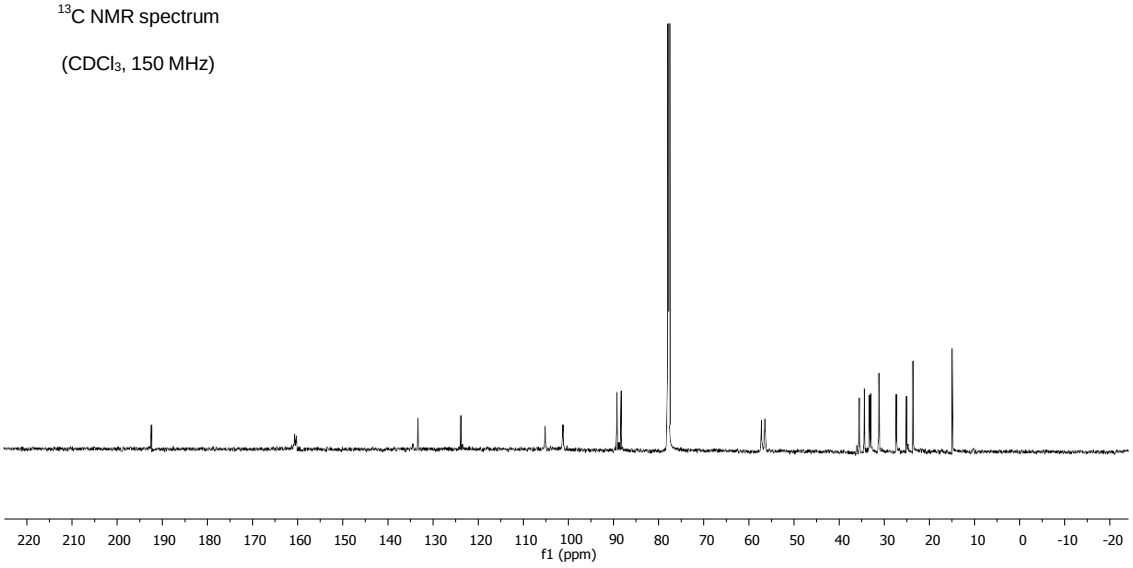
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

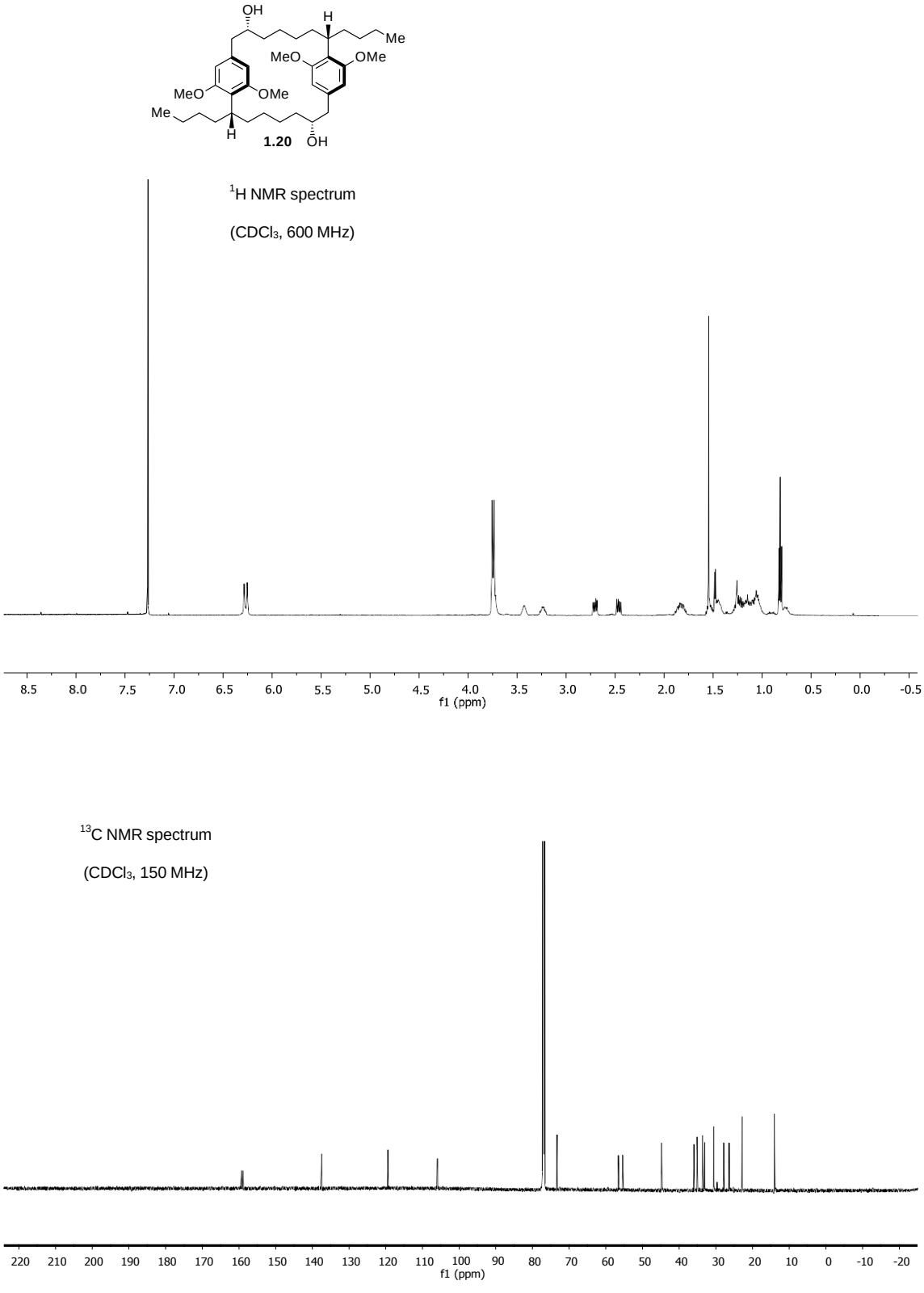


^{13}C NMR spectrum

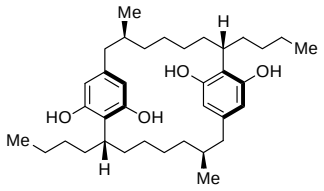
($CDCl_3$, 150 MHz)



Spectra **1.14**: Compound **1.19**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



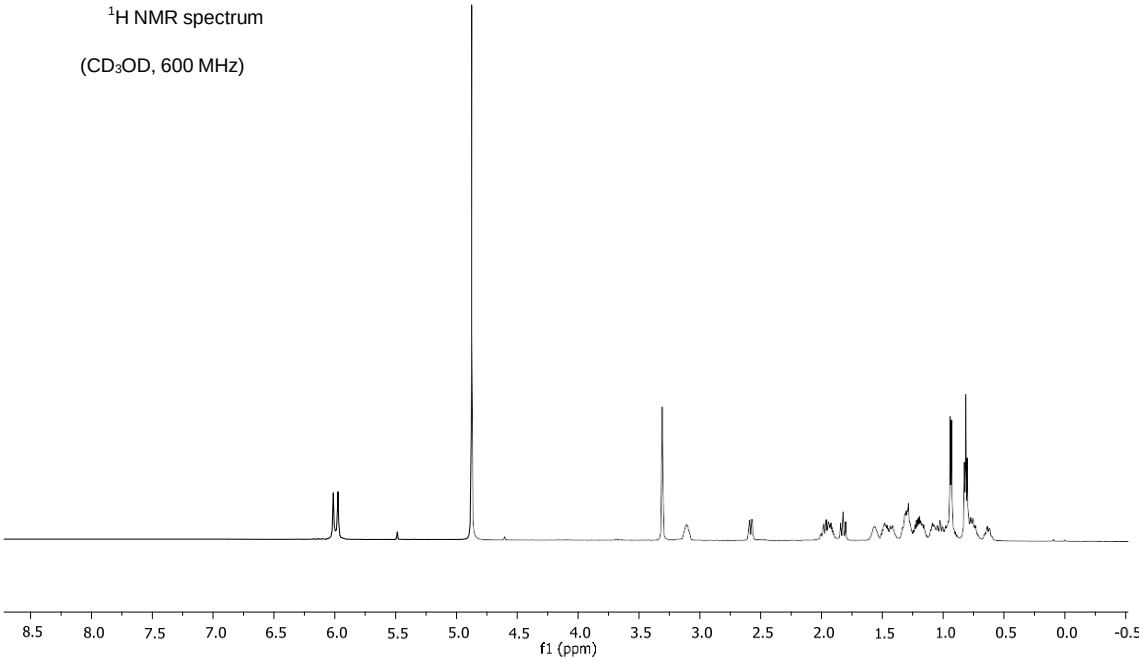
Spectra **1.15**: Compound **1.20**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.02

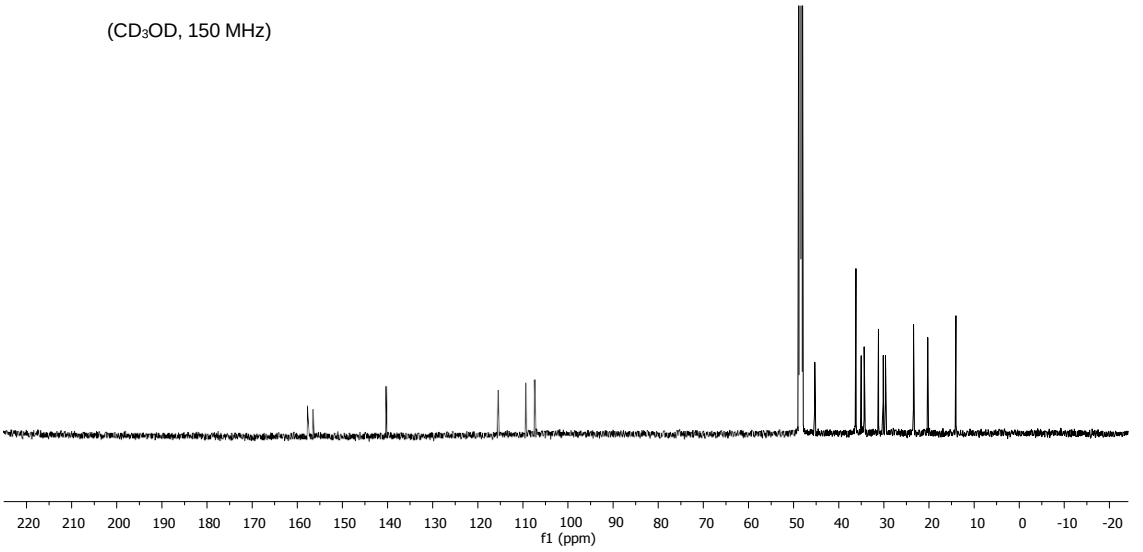
^{1}H NMR spectrum

(CD_3OD, 600 MHz)

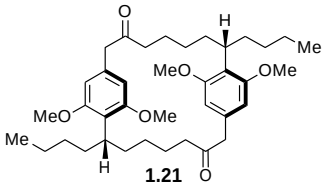


^{13}C NMR spectrum

(CD_3OD, 150 MHz)



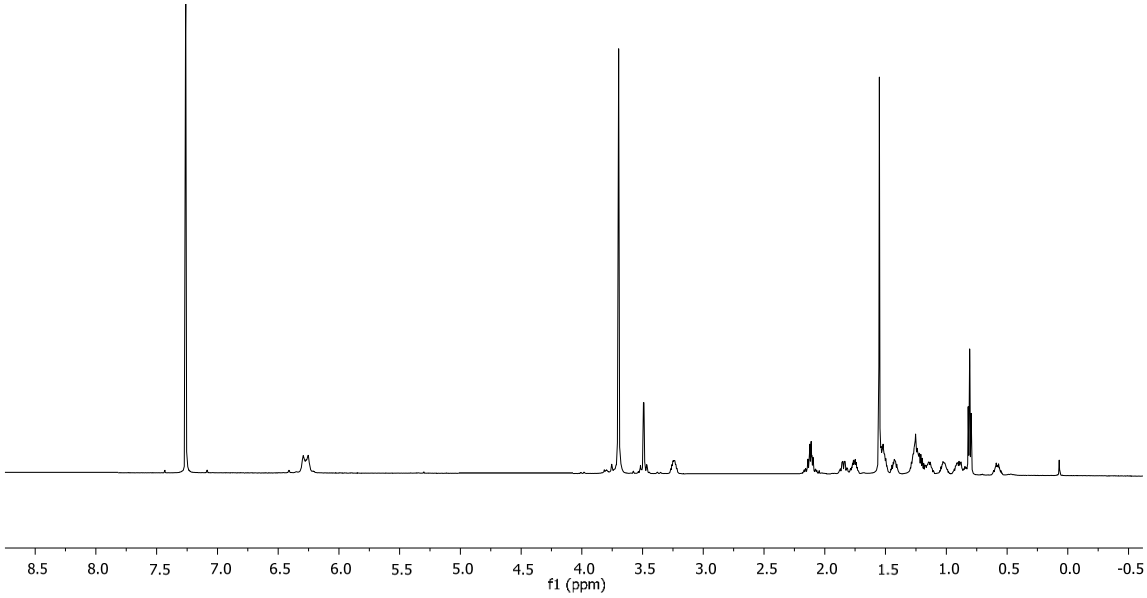
Spectra **1.16**: Compound **1.02**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.21

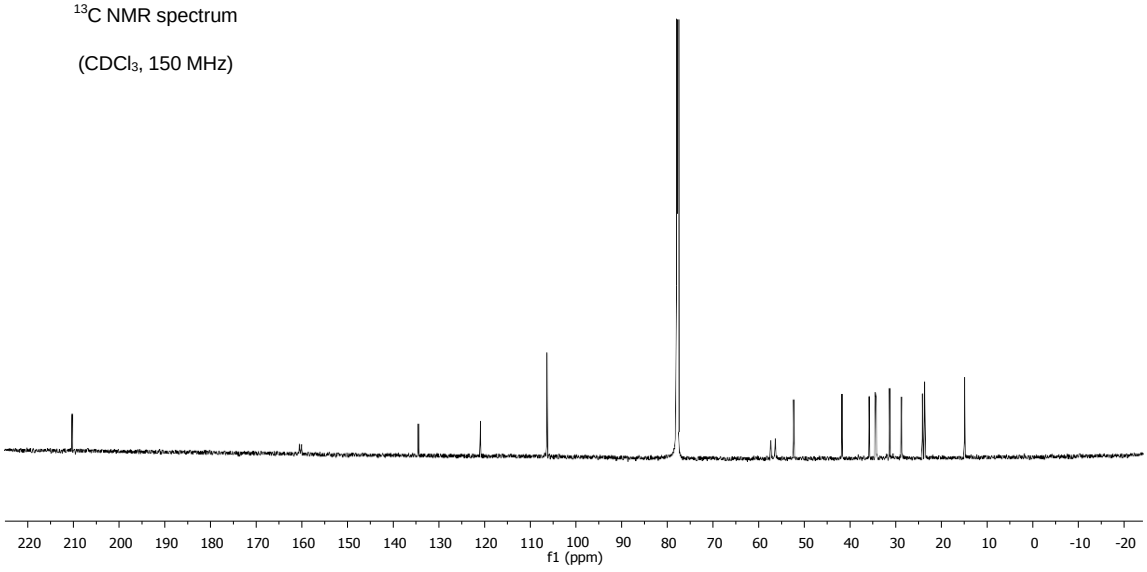
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)

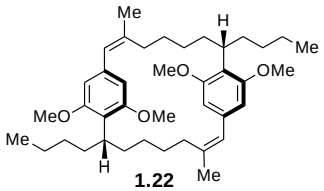


^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



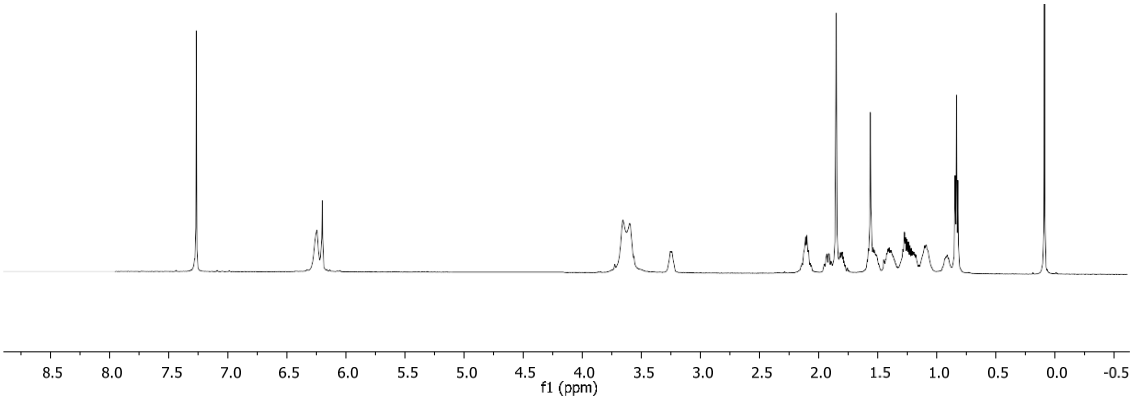
Spectra **1.17**: Compound **1.21**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



1.22

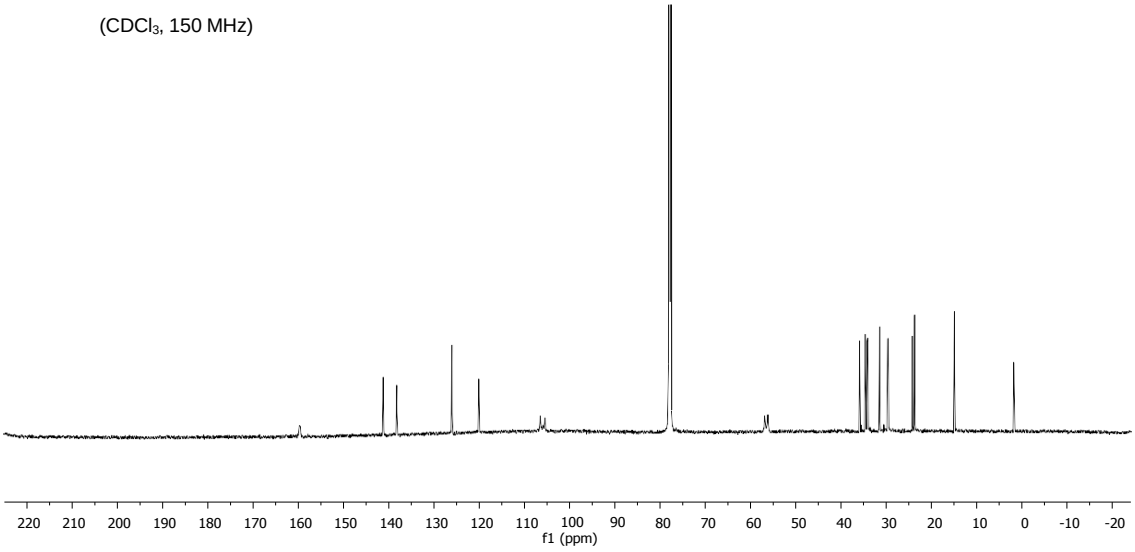
^{1}H NMR spectrum

($CDCl_3$, 600 MHz)



^{13}C NMR spectrum

($CDCl_3$, 150 MHz)



Spectra **1.18**: Compound **1.22**: ^{1}H NMR (top) and ^{13}C NMR (bottom)

Chapter 1 is a partial reprint of the material as it appears in "Asymmetric Total Synthesis of Cylindrocyclophanes A and F Through Cyclodimerization and a Ramberg–Bäcklund Reaction, K.C. Nicolaou, Y.-P. Sun, H. Korman, D. Sarlah, *Angew. Chem. Int. Ed.* **2010**, *49*, 5875–5878".

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Chapter 2: Studies Directed Towards the Total Synthesis of CJ-16,264 and Analogues

A. Introduction

1. Isolation and Biological Activity of CJ-16,264 and CJ-16,367

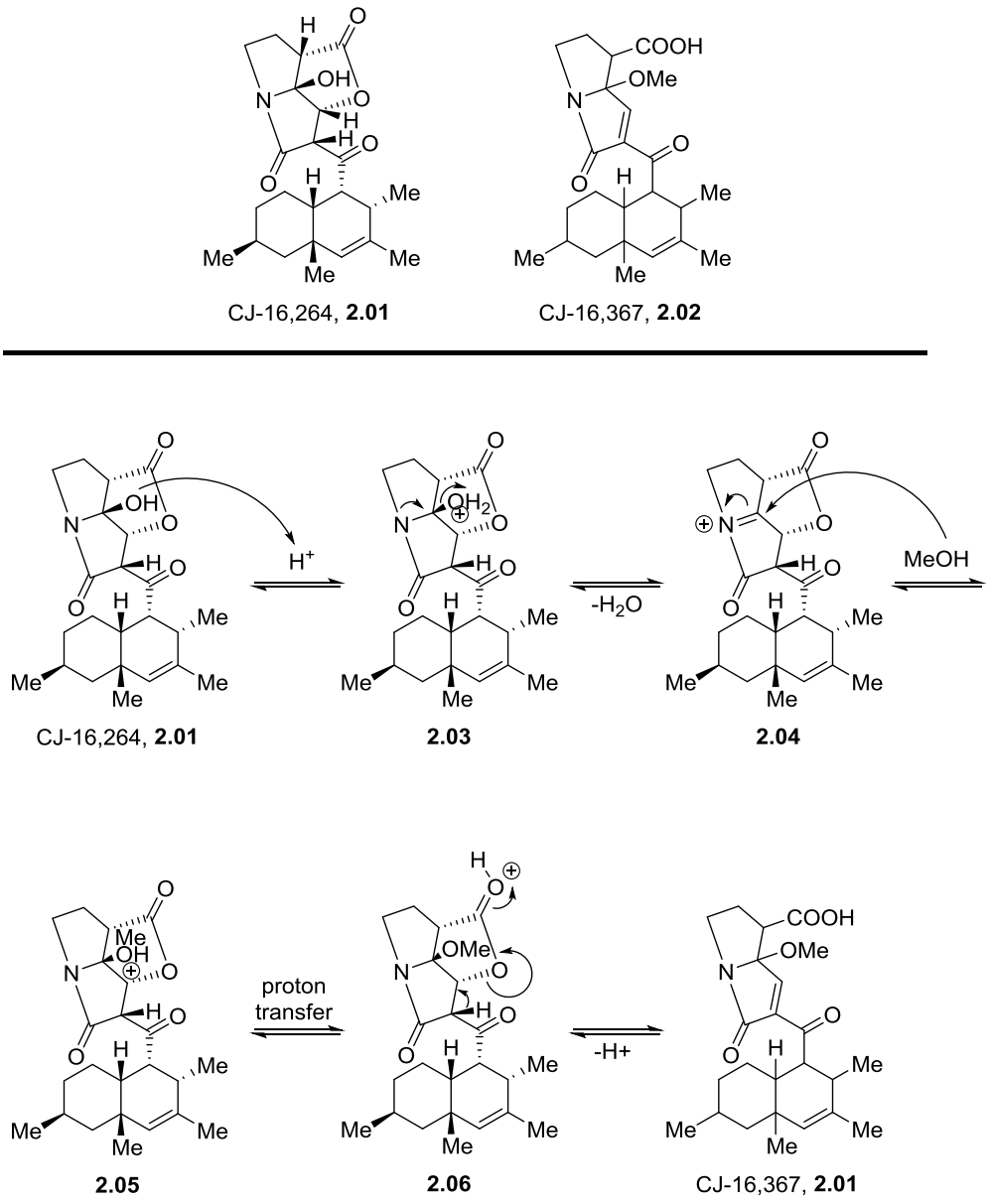


Figure **2.01**: Possible origin of CJ-16,367 (**2.01**) from CJ-16,264 (**2.02**).

In 2001, CJ-16,264 (**2.01**) and CJ-16,367 (**2.02**) were isolated from an unidentified fungus CL39457 (Figure **2.01**).[1] The structure of CJ-16,264 was found to contain a tricyclic γ-hydroxypyrrolizidinone adjoined to a *cis*-decalin. Similar in structure to CJ-16,264, CJ-16,367 contains a γ-methoxypyrrolizidinone acid also adjoined to a decalin. Interestingly, though the relative stereochemistry of **2.01** was assigned, there was no assignment of the relative stereochemistry of **2.02**. Having been subjected to a 0.5% TFA / MeOH solution, used as eluent during its isolation, it is possible that CJ-16,367 is not naturally produced by the fungus, but rather was formed from CJ-16,264 during purification, after it was isolated *via* methanolysis and elimination (Figure **2.01**).

CJ-16,264 was shown to inhibit the growth of multi-drug resistant (MDR) Gram-positive bacteria with a broad spectrum, inhibiting *Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Streptococcus pneumonia*, and *Entereococcus faecalis* as well Gram-negative bacteria *Moraxella catarrhalis* and *Esherichia coli* with MIC values ranging from 0.39 – 12.5 μg/mL. CJ-16,264 also showed broad antibacterial activities against these bacterial strains, though much weaker with MIC values ranging from 1.56 – 100 μg/mL. Both CJ-16,264 and CJ-16,367 showed cytotoxicity against HeLa cells with IC_{90} values reported as 8.0 μg/mL and 6.8 μg/mL, respectively.

2. Isolation and Biological Activity of UCS1025A, UCS1025B and Pyrrolizilactone

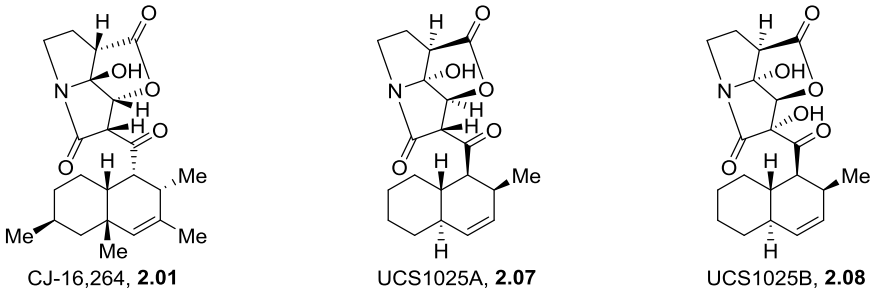


Figure **2.02**: CJ-16,264 (**2.01**) compared with UCS1025A (**2.07**) and UCS1025B (**2.08**).

UCS1025A and UCS1025B (**2.07** and **2.08**, Figure **2.02**), isolated from the fungus *Acremonium* sp. KY4917, were first described and tested for biological activities in 2000,[2] and then later assigned relative and absolute stereochemistries in 2002.[3] UCS1025A and UCS1025B, whose intriguing structures and interesting biological activities have led to considerable synthetic efforts towards their total synthesis,[4] are closely related to in structure to CJ-16,264. UCS1025A and UCS1025B were found to contain the almost the exact same γ-hydroxypyrrolizidinone moiety as found in CJ-16,264, though adjoined to less highly methylated *trans*-decalin (instead of adjoined to *cis*-decalin as in CJ-16,264). UCS1025A was discovered to have antibacterial activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and *Entercoccus hirae*, and Gram-negative bacterium *Proteus vulgaris* with a MIC from 1.3 – 5.2 μg/mL. UCS1025B was discovered to have much lower antibacterial activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and *Entercoccus hirae*, and

Gram-negative bacterium *Proteus vulgaris* with MIC values ranging from 42 – 83 μg/mL. UCS1025A was shown to have weak antiproliferative activity against humor tumor cell lines with IC_{50} values of cell lines ACHN, A4321, MCF-7 and T24 ranging from 21 – 58 μM, whereas UCS1025B exhibited no antiproliferative activity against these cell lines up to 100 μM.[2] UCS1025A was also shown to be a novel telomerase inhibitor with an IC_{50} value of 1.3 μM in a TRAP assay.[5]

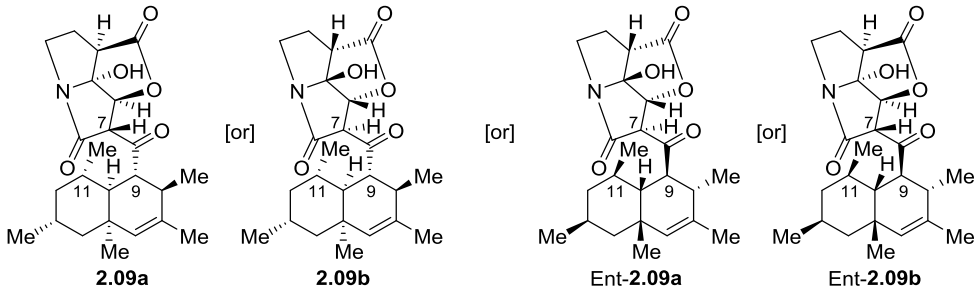


Figure **2.03**: Four possible structures of pyrrolizilactone (**2.09**), two diastereoisomers and their enantiomers.

In 2013, another very similar natural product to CJ-16,264, pyrrolizilactone (**2.09**, Figure **2.03**) was isolated from an uncharacterized fungus.[6] Much like CJ-16,264, pyrrolizilactone was also found to contain the exact same γ-hydroxypyrrolizidinone system adjoined to a highly methylated *cis*-decalin moiety. Pyrrolizilactone contains one additional methyl group at C-11, and is α-epimeric with CJ-16,264 at C-1. The configuration of the stereochemistries between the *cis*-decalin and pyrrolizidinone moieties of pyrrolizilactone were not be determined due to free rotation of the C-7–C-8 and C-9–C-8 bonds, a point that may have been overlooked in the structural assignment of CJ-16,264. Interestingly, pyrrolizilactone was not found to exhibit antibacterial

activity against *Escherichia coli* up to 30 µg/mg. Pyrrolizilactone did show some cytotoxicity against human tumor cell lines with IC_{50} values of 1.1 and 3.1 µg/mg for cell lines HL-60 and HeLa respectively.

3. Structural Considerations of CJ-16,264

UCS1025A was reported to exist as a mixture of **2.07** and **2.07b**, as well as elimination isomer **2.07c** (Figure **2.04**), though upon standing in $CDCl_3$, only **2.07** was observed.[3] This phenomenon was not reported for CJ-16,264 or pyrrolizilactone.

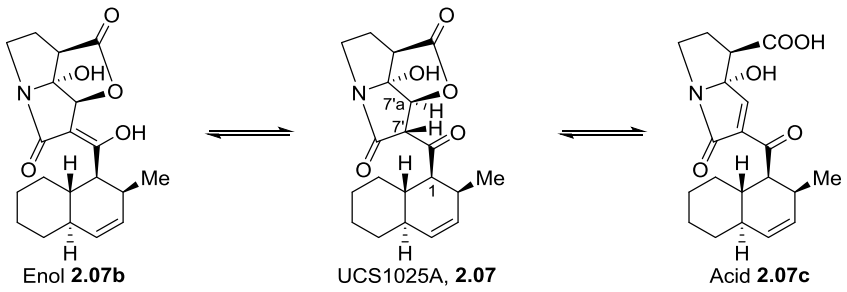


Figure **2.04**: Isomers of **2.07.**

Interestingly, the X-ray crystal structure obtained of UCS1025A furnished the structure of enol **2.07b**, and so the stereochemistry at H-7' was not able to be assigned by X-ray crystallography. Instead, the stereochemistry of H-7' was assigned on the basis of the coupling constant of the dihedral angle of H-7'–C-7'–C-7'a–H-7'a.

Thus, if H-7' and H-7'a were on the same side (in the syn-orientation, as in CJ-16,264's proposed structure **2.01**), there would be a vicinal coupling constant observed between these two hydrogens. Alternatively, if these two hydrogens are on the opposite

side (in an anti-orientation, as seen in structure **2.07**), then the dihedral angle between these hydrogens would be nearly 90°, and this would lead to a vicinal coupling constant of zero. On this basis, with a coupling constant of zero observed between these two hydrogens, it was determined that H-7' and H-7'a must exist in an anti-orientation, and the structure of UCS1025A was assigned as **2.07**. Similar logic later allowed the same anti-orientation of these hydrogens to be assigned for **2.09**.[6]

Examination of the ^{1}H-NMR spectrum of CJ-16,264 reveals H-7' as a sharp singlet at 4.09 ppm in d6-benzene, and H7'a as a sharp singlet at 4.23 ppm in d6-benzene.[1] These hydrogens also have a coupling constant of zero. It is therefore likely that the structure **2.01** has been misassigned for CJ-16,264 and H-7' and H-7'a should be anti in orientation, as opposed to having the syn-orientation as proposed in its isolation. It is also unlikely that, considering the similarity in the tricyclic γ-hydroxypyrrolizidinone motif found in CJ-16,264, UCS1025A and pyrrolizilactone, that H-7' (a readily enolizable hydrogen) would have a different orientation in these three natural products. This logic allows for 7'-epi-**2.01** (Figure **2.05**) to possibly be the true structure of CJ-16,264.

The relative and absolute stereochemistry of UCS1025A were assigned on the basis of X-ray crystallography, not on NOESY data.[3] In fact, though there was NOESY data obtained from the isolation of pyrrolizilactone, there was no attempt to assign the relative stereochemistries between its *cis*-decalin and pyrrolizidinone moieties.[6] The relative configuration of the stereochemistries between the *cis*-decalin and pyrrolizidinone moieties of CJ-16,264, however, were indeed assigned on the basis of

NOESY experiments.[1] The free rotation in the C-7–C-8 and C-9–C-8 bonds, however, may have been overlooked. It is therefore not possible to rule out 2'a-7'a-7'b-tris-epi-**2.01** as a possible true structure of CJ-16,264.

The NOESY data of CJ-16,264 do not show a correlation between the hydrogen on C-1 with either hydrogen on the two adjacent carbons, C-2 and C-8a. Though the lack of a NOESY correlation would not rule any of the possible structures in Figure **2.05**, it is possible that the stereocenter at C-1 could be inverted from the proposed structure of **2.01** to look more similar to the *cis*-decalin motif found in pyrrolizilactone. It should

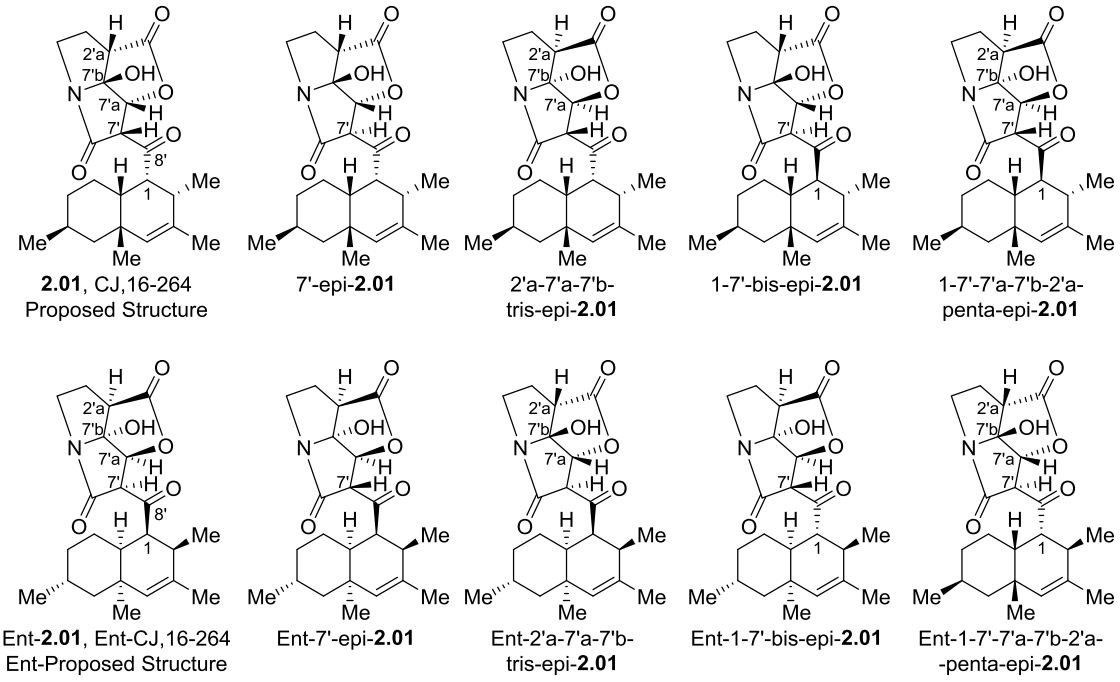


Figure **2.05**: Possible true structures of CJ-16,264.

therefore be possible that the additional structures of 1-7'-bis-epi-**2.01** and 1-7'-7'a-7'b-2'a-penta-epi-**2.01** could possibly be the true structure of CJ-16,264. Lastly, because the

absolute configuration of CJ-16,264 is unknown, these compounds' enantiomers may also be the true structure. Therefore, the true structure of CJ-16,264 may well be any of the structures in Figure **2.05**.

4. Retrosynthetic Analysis of CJ-16,264

The reported difficulty in executing the IMDA reaction of triene **2.10**[7] led us to wonder whether such a reaction was hindered by an unfavorable 1,4 steric repulsion between Me-4a and a hydrogen in the s-cis conformation (Figure **2.06**). It is conceivable this unfavorable steric interaction prevents the formation of a significant population of the s-cis conformation required for the diene moiety to be susceptible to undergo a Diels–Alder reaction. Thus, molecules with similar diene moieties, containing a methyl group in this position, may prove problematic when undergoing IMDA reactions.

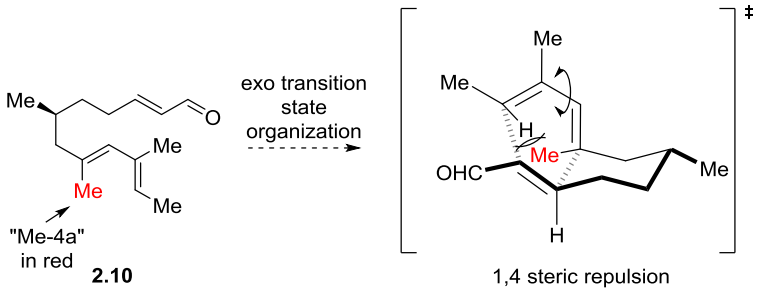


Figure **2.06**: Steric repulsion of Me-4a during exo transition state organization.

It was envisioned that a macrolactone such as **2.11** (Figure **2.07**) would force the diene and dienophile close enough together to overcome the steric difficulties present in such an IMDA system and force such an IMDA reaction to take place at a greater rate.

Because iodolactam **2.12** was ready available,[4a] the most conceivable retrosynthetic approach towards the total synthesis of CJ-16,264 was to use a similar disconnection as did Danishefsky and Hoye. Thus, CJ-16,264 leads to **2.12** and **2.13** *via* a BEt_3 mediated Reformatsky–type coupling. Then, aldehyde **2.13** would be available after functionalization from lactone **2.14**, derived from an IMDA of macrolactone **2.11**. Macrolide **2.11** would come from a macrolactonization reaction of seco acid **2.15**. Lastly, seco acid **2.15** would be derived from citronellal after several synthetic steps.

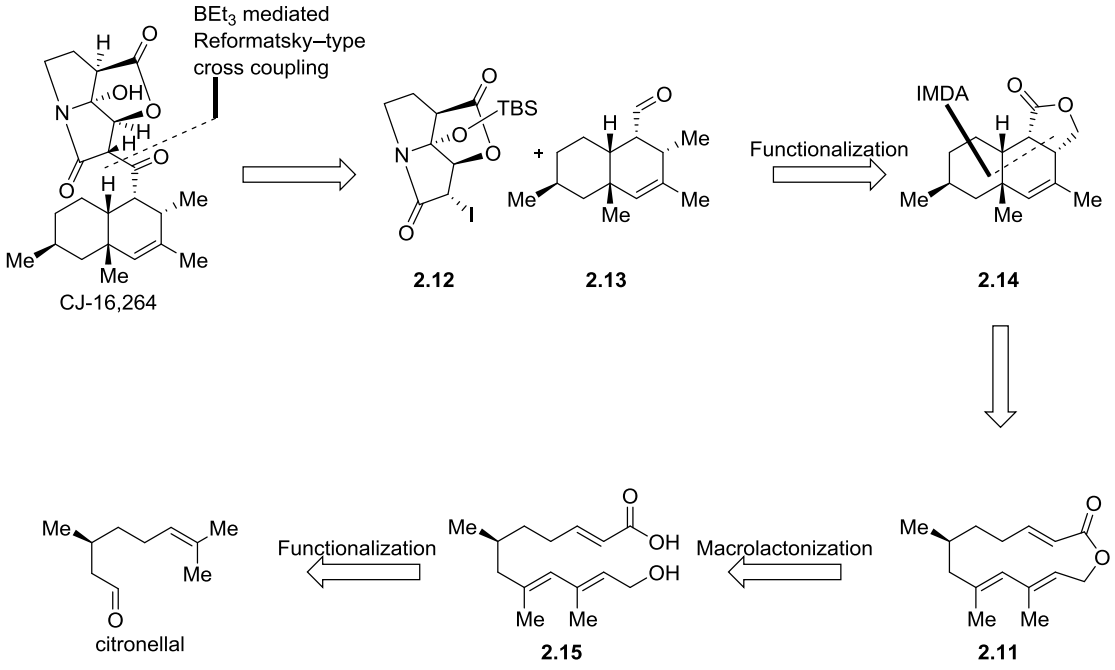


Figure **2.07**: Retrosynthetic analysis of CJ-16,264.

B. Synthesis

1. Total Synthesis of (±)-1-epi-CJ-16,264

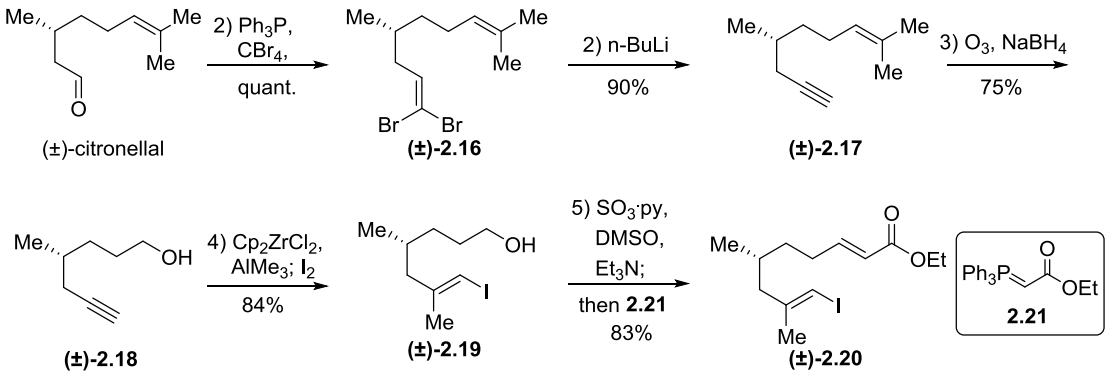


Figure **2.08**: Synthesis of **(±)-2.20** from citronellal.

Starting from (±)-citronellal, geminal dibromide **(±)-2.16**[8] was synthesized in quantitative yield when treated with Ph_3P and CBr_4 (Figure **2.08**). Subsequent conversion of **(±)-2.16** to enyne **(±)-2.17** was achieved with *n*Buli in 90% yield.[9] Enyne **(±)-2.17** was then converted to ynol **(±)-2.18** *via* a reductive ozonolysis with O_3 followed by treatment with $NaBH_4$ in 75% yield.[10] Ynol **(±)-2.18** was then subjected to Cp_2ZrCl_2 and Me_3Al, and then I_2 to generate **(±)-2.19** in 84% yield.[11] This alcohol was then oxidized to the aldehyde *via* the Parikh-Doering oxidation conditions (SO_3·py, DMSO, Et_3N),[12] and then treated with (carbethoxymethylene)triphenylphosphorane (**2.21**) in the same flask to generate ester **(±)-2.20** in 83% yield from **(±)-2.19**.

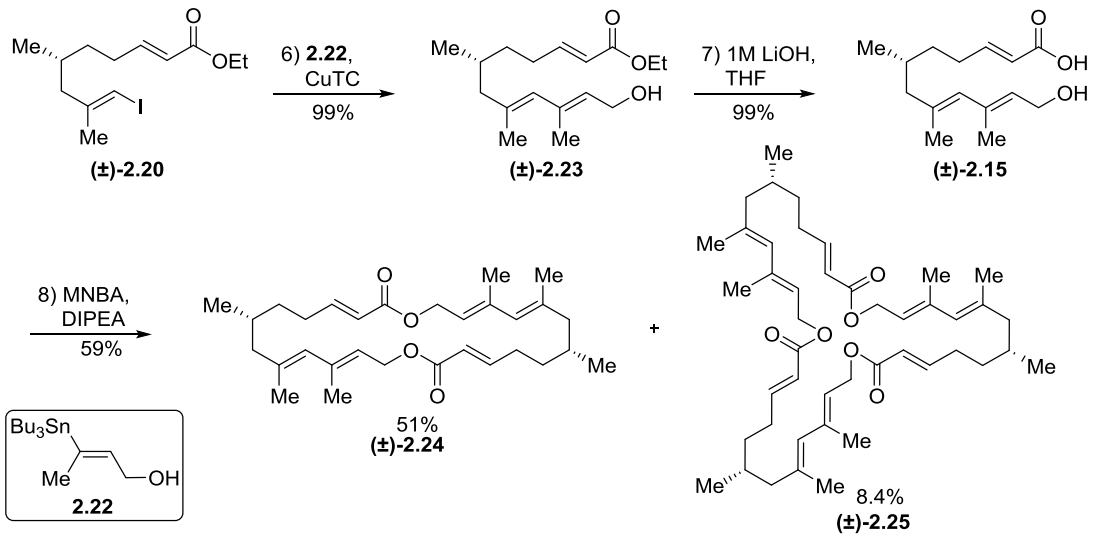


Figure **2.09**: Macrolactonization of seco acid **(±)-2.15** leads to dimer **(±)-2.24** and trimer **(±)-2.25**.

With ester **(±)-2.20** in hand, a CuTC mediated cross coupling[13] with stannane **2.22** produced triene ester **(±)-2.23** in 99% yield (Figure **2.09**). Subsequent hydrolysis of **(±)-2.23** led to the formation of seco acid **(±)-2.15** in 99%, which was then treated with MNBA and DIPEA[14] to create dimer **(±)-2.24** and trimer **(±)-2.45** in 51% and 8.4% yields respectively. Subjection of **(±)-2.15** to Yamaguchi macrolactonization conditions[15] (2,4,6-trinitrobenzoyl chloride, Et_3N) resulted in much lower and inconsistent yields of dimer **(±)-2.24** and trimer **(±)-2.25** (5-15% and <1-3% respectively). The expected monolactone **(±)-2.11** was not observed under any macrolactonization condition, despite literature precedent[16] for the formation of a similar monolactone using Yamaguchi macrolactonization conditions.

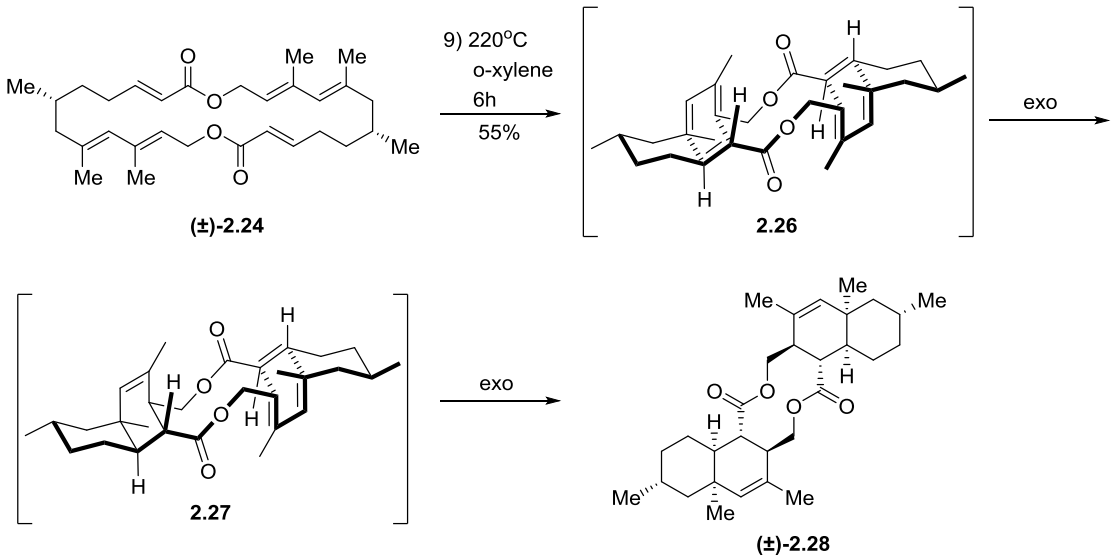


Figure **2.10**: Dimer **(±)-2.24** undergoes bis-exo IMDA reaction to form **(±)-2.28.**

Nonetheless, heating **(±)-2.24** in a sealed tube at 220ºC for 6 hours resulted in the formation of diastereoisomer **(±)-2.28** *via* a double exo-selective IMDA reaction in 55% yield, as well as decomposed materials (Figure **2.10**). An endo IMDA adduct was not isolated. X-ray crystallography was able to confirm the relative stereochemistry of **(±)-2.28**. When trimer **(±)-2.25** was treated with similar conditions it did not undergo an IMDA reaction, but rather underwent decomposition. It is possible that the structural flexibility contained with trimer **(±)-2.25** would reduce the ability of such large macrolide system to force the diene and dienophile close enough together to undergo the IMDA reaction. Upon heating **(±)-2.23** or **(±)-2.15**, only decomposition product was observed.

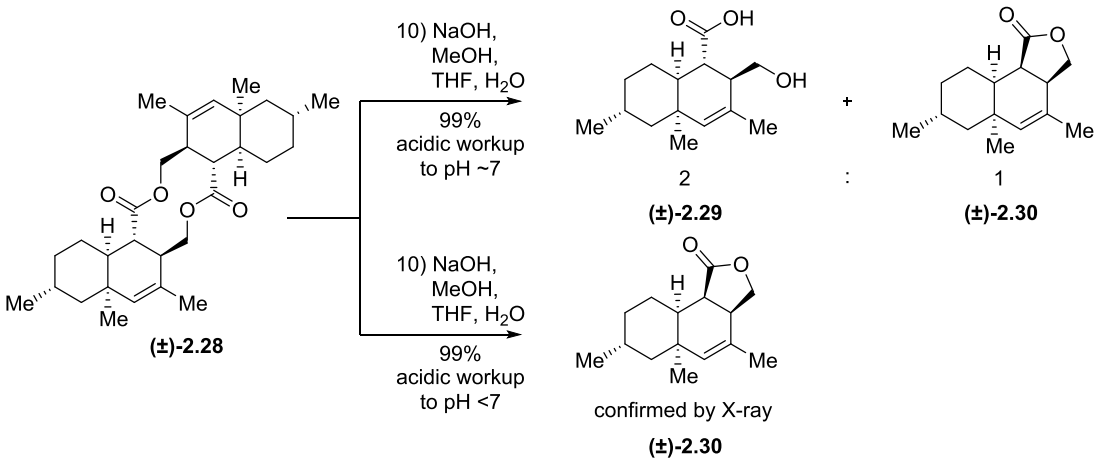


Figure **2.11**: Hydrolysis of **(±)-2.28** leads to **(±)-2.29** and **(±)-2.30**.

Treatment of with **(±)-2.28** with 1M NaOH in THF would return the starting material, even if subjected to higher temperatures (Figure **2.12**). Subjection of IMDA adduct **(±)-2.28** to NaOH, MeOH, and THF, and a subsequent workup to pH ~7 *via* slow addition of a 10% HCl solution resulted in a recovery of 2:1 mixture of hydrolysis product **(±)-2.29** and α-epimerized lactone **(±)-2.28** in 99% overall yield (Figure **2.11**). Interestingly, if the workup was allowed to continue for a longer period of time, only lactone **(±)-2.28** could be recovered.

Treatment of acid **(±)-2.29** with Me_3OBF_4 led to the formation of **(±)-2.31** in quantitative yield (Figure **2.12**). The deoxygenation of primary alcohol **(±)-2.31** proceeded in two steps. First, **(±)-2.31** was mesylated with MsCl and Et_3N to furnish **(±)-2.32** in 90% yield. Then, treatment of **(±)-2.32** with NaI and Zn at 100°C led to the formation of ester **(±)-2.33** in 83% yield.[17] Reduction of ester **(±)-2.33** with DIBAL-H

yielded alcohol **(±)-2.34** in quantitative yield. This was then oxidized to aldehyde **(±)-2.35** with DMP in 91% yield, which would enable us to try to the key coupling step.

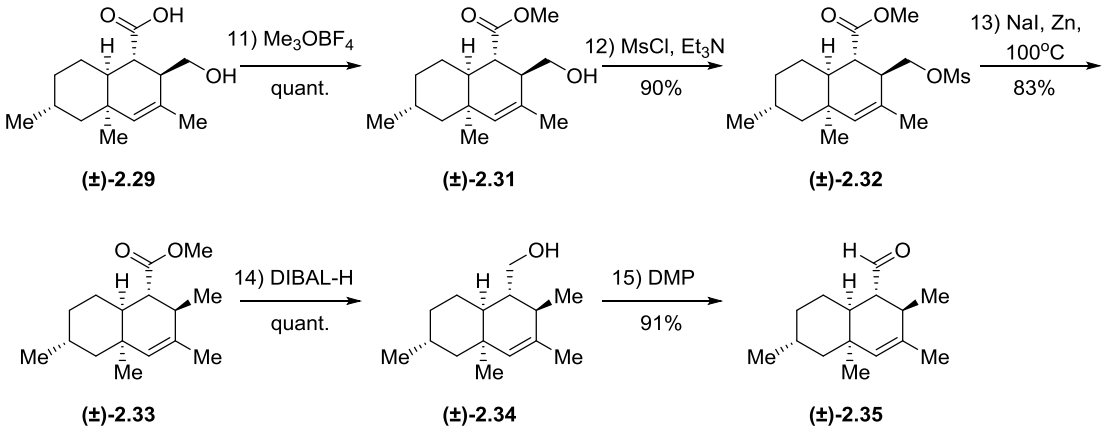


Figure **2.12**: Synthesis of aldehyde **(±)-2.35** from acid **(±)-2.29**.

When aldehyde **(±)-2.35** was treated with BEt_3 in the presence of iodide **(±)-2.12** (Figure **2.13**), two coupling products, **(±)-2.36** and **(±)-2.37** were isolated in an overall 95% yield in a ~2:1 ratio. The relative stereochemistries of **(±)-2.36** and **(±)-2.37** were confirmed by X-ray crystallography of TASF deprotected **(±)-2.38** and **(±)-2.39** (Figures **2.14** and **2.15**).

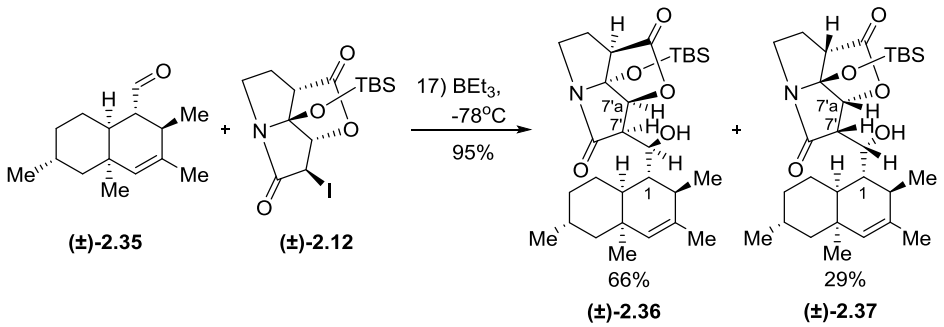


Figure **2.13**: BEt_3 mediated Reformatsky–type coupling of **(±)-2.35** and **(±)-2.12**.

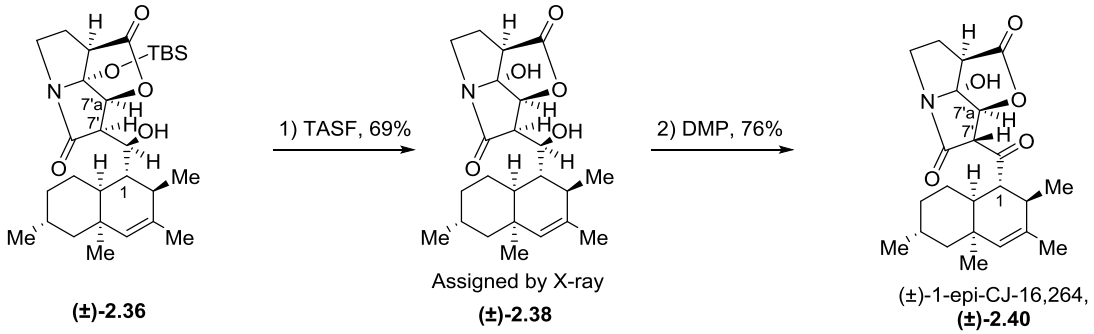


Figure **2.14**: Oxidation / deprotection sequence to reach (±)-1-epi-CJ-16,264, **(±)-2.40**.

Thus, with the major coupling product **(±)-2.36** in hand, it was possible to remove the TBS group with TASF to generate **(±)-2.38** in 69% yield (Figure **2.20**). Oxidation of this compound with DMP yielded **(±)-2.40**, the 1-α-epimer of CJ-16,264 in 76% yield.

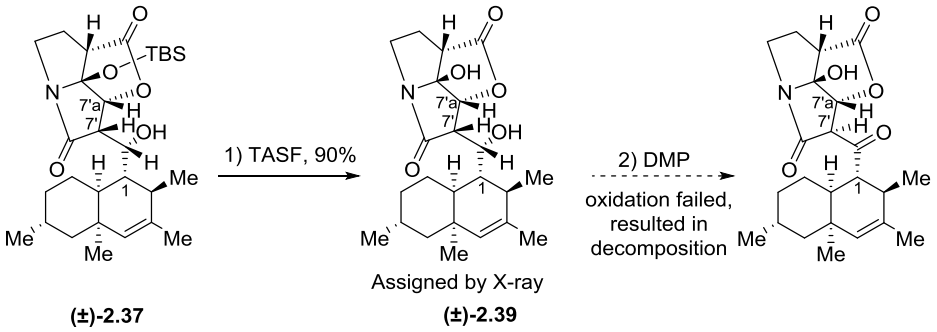


Figure **2.15**: Oxidation / deprotection sequence results in decomposition.

Unfortunately, similar treatment of the minor coupling product **(±)-2.37** with the same synthetic sequence in Figure **2.14** led to decomposition upon oxidation with DMP (Figure **2.15**). Studies towards completing this synthesis are currently underway in our laboratory.

2. Progress Towards Total Synthesis of CJ-16,264

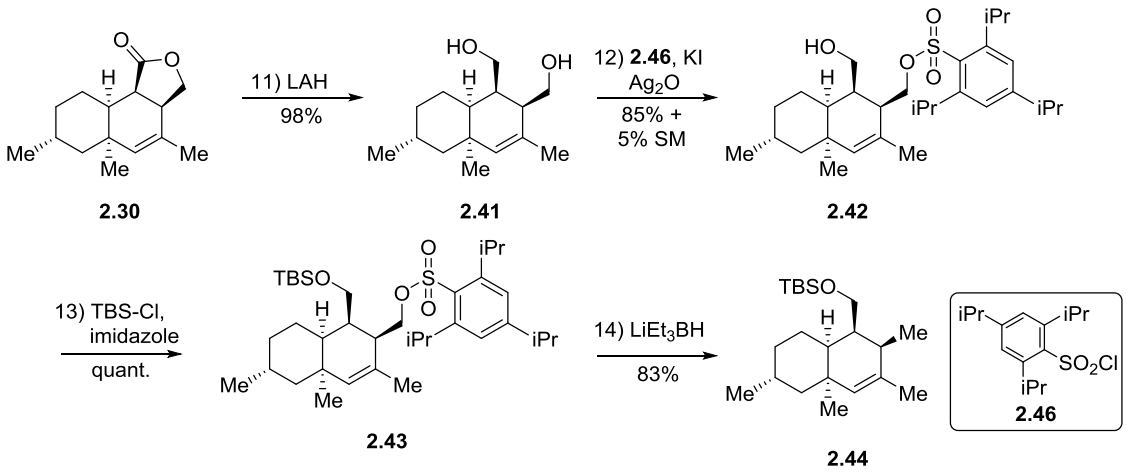
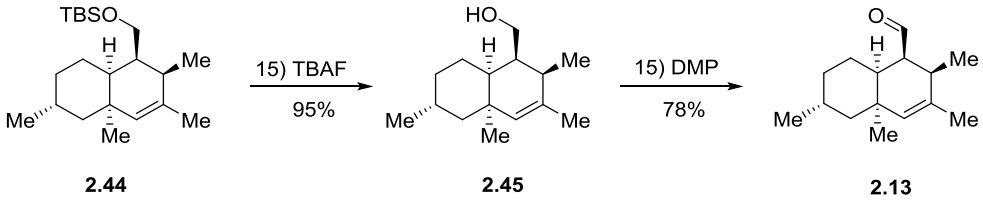


Figure **2.16**: Synthesis of **2.44** from **2.30**.

With the absolute configuration of CJ-16,264 unknown, its synthesis began with (R)-(+)-citronellal, which was available in plentiful supply in the laboratory. Thus, enantiopure lactone **2.30**, derived from R-(+)-citronellal and the same synthetic sequence shown above in the racemic synthesis, was treated with LAH to give diol **2.41** in 98% yield (Figure **2.16**). Diol **2.41** was then selectively monotosylated[18] using Ag_2O, KI, and bulky sulfonyl chloride **2.46** to give monosulfonate **2.42** in 85% yield, as well as a recovery of 5% of diol **2.41**. TBS protection of **2.42** led to the formation of **2.43** in quantitative yield, which was then reductively cleaved with $LiEt_3BH$ to furnish **2.44** in 83% yield.

Deprotection of **2.44** with TBAF in 95% yield, and a subsequent oxidation of resultant alcohol **2.45** yielded aldehyde **2.13** in 78% yield (Figure **2.17**).



2.44 **2.45** **2.13**

Figure **2.17**: Synthesis of aldehyde **2.13** from **2.44**.

With enantiopure aldehyde **2.13**, the stage was set for coupling with **(-)-2.12**, obtained from chiral HPLC separation of **(±)-2.12** (Figure **2.17**).[4a] This coupling led to the formation of one diastereoisomer, compound **2.47**. The absolute stereochemistry of **2.47** was confirmed by X-ray crystallography.

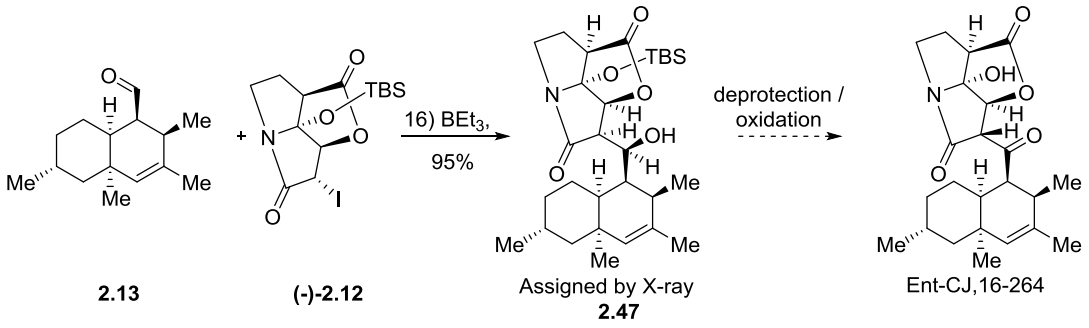


Figure **2.18**: Efforts toward ent-CJ-16,264.

Unfortunately, in my hands it was not possible to convert **2.47** to the nominal structure of Ent-CJ-16,264 via a deprotection / oxidation sequence (Figure **2.18**). Studies towards completing this synthesis are currently underway in our laboratory.

C. Medicinal Significance of CJ-16,264, UCS1025A, and Pyrrolizilactone

The emergence of antibiotic-resistant microbes has led to a considerable decline in effective treatment options of these pathogens.[19] As existing medicines become obsolete in the face of rapidly mutating microbes, the search for new biologically active natural products with novel mechanisms of action will help to serve as a continued source of potent medicines.

CJ-16,264 and UCS1025A were discovered to be broad spectrum inhibitors of multi-drug resistant bacteria, though pyrrolizilactone was not discovered to exhibit antibacterial properties.[1,2,6] The mechanism of action of this unique class of natural products against bacteria is not known. Containing a novel tricyclic γ-hydroxypyrrolizidinone adjoined to a highly decorated decalin, the similarities in the

structures of these natural products are remarkable. Is therefore intriguing that pyrrolizilactone did not exhibit antibiotic properties similar to CJ-16,264 and UCS1025A. To the best of our knowledge, there have been no reported studies examining the role that the substructures of these natural products play in eliciting antibacterial properties. The total synthesis of these natural products would render these natural products and congeners available for structure–activity relationship (SAR) studies to determine the moieties responsible for evoking antibacterial resistance. These important studies could lead to development of new antibacterial agents with a novel mechanism of action.

The telomeres of normal human cells progressively shorten upon cell division until the cells eventually reach senescence. Telomerase is a ribonucleoprotein enzyme that maintains chromosomes by adding DNA sequence repeats to their termini. In cancer cells, telomere length is maintained by telomerase, allowing the cells to avoid senescence and become immortal. The inhibition of telomerase has therefore become a popular strategy to treat cancer.[20] UCS1025A has been described to be able to inhibit telomerase,[5] though there is no known study to determine the telomerase inhibition properties of CJ-16,264 or pyrrolizilactone. The total synthesis of these natural products would also render these natural products and congeners available for structure–activity relationship (SAR) studies to determine the moieties responsible for telomerase inhibition. These studies could lead to development of new anticancer agents.

D. Comparison with Previous Synthetic Approaches

The beautiful and complex molecular architecture and remarkable biological activities of CJ-16,264, UCS1025A, and pyrrolizilactone make them very attractive

targets for total synthesis. As a result, there have been numerous synthetic studies and several total syntheses of UCS1025A.[4] Efforts towards its total synthesis have been reported in a thesis dissertation by Dr. Sizova of the Hoye laboratory.[7] To the best of our knowledge, there no reported synthetic efforts towards the total synthesis of pyrrolizilactone.

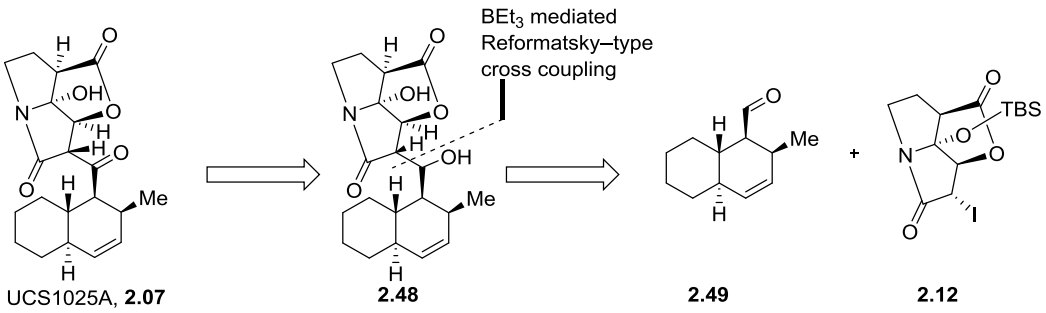


Figure **2.19**: Reformatsky–type approach to UCS1025A by Danishefsky.

The first reported total synthesis of UCS1025A,[4a] achieved by the Danishefsky group, involved a novel BEt_3 mediated Reformatsky–type cross coupling of aldehyde **2.49** and iodolactam **2.12**, and a subsequent deprotection and oxidation sequence to furnish UCS1025A (Figure **2.19**). While *trans*-decalin aldehyde **2.49** has previously been prepared,[21] both the racemic, as well as the enantiopure iodolactam **2.12** were both in several steps prepared in and in excellent yield from commercially available material. This synthetic strategy employed a highly efficient and novel late stage coupling that allowed efficient conversion of aldehyde **2.49** into UCS1025A in short order from previously synthesized material.

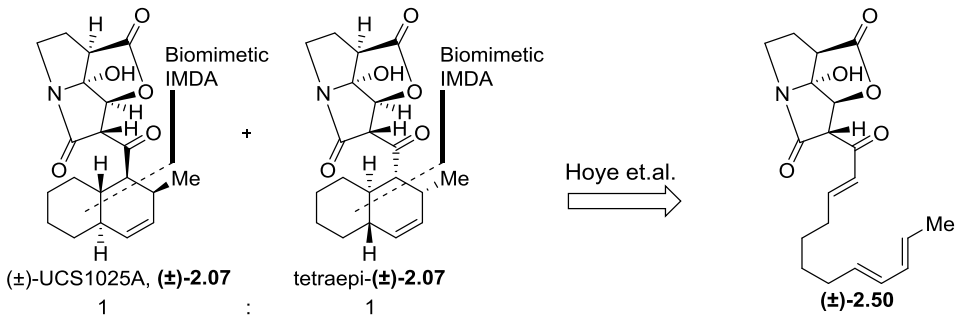


Figure **2.20**: Hoye's approach to (±)-UCS1025A.

The total synthesis of UCS1025A by the Hoye group[4b], published just months after Danishefsky's synthesis, instead employed a biomimetic strategy (Figure **2.20**). This synthetic strategy sought to explore whether enzymatic catalysis of a triene **(±)-2.50** would be necessary for this system to undergo an intramolecular Diels–Alder (IMDA) reaction, or if this reaction could occur in the laboratory under biologically relevant conditions. Their synthesis was highlighted by a remarkable and fast ($t_{1/2}$ = 10 min at room temperature) biomimetic IMDA reaction of triene **(±)-2.50** to yield **(±)-**UCS1025A**,** as well as tetraepi-**(±)-**UCS1025A**,** in a 1:1 ratio. While this synthesis did demonstrate that this IMDA would indeed take place extremely quickly, the chiral heterocyclic fragment of **(±)-2.50** did not impart diastereocontrol in the IMDA, resulting in the formation of the natural product UCS1025A and tetraepi-**(±)-2.07** in a 1:1 ratio.

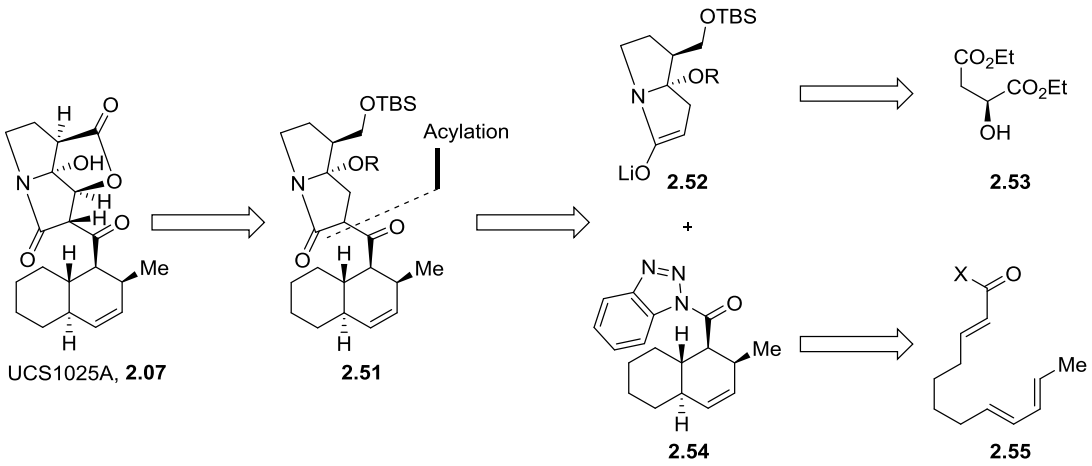


Figure **2.21**: Acetylation approach to UCS1025A by Uchida.

The total synthesis of UCS1025A was achieved by the Uchida group[4d] through a late stage acylation to bring together the framework of UCS1025A (Figure **2.21**). Thus, **2.51**, a suitable precursor to UCS1025A, was formed *via* coupling of enolate **2.52** with decalin **2.54**. *Trans*-decalin **2.54** was accessed through an IMDA reaction of triene **2.55**, and **2.52** was accessed in several steps from bis(ester) **2.53**. This strategy, though much more lengthy than the previous two syntheses, was able to achieve a stereocontrolled synthesis of UCS1025.

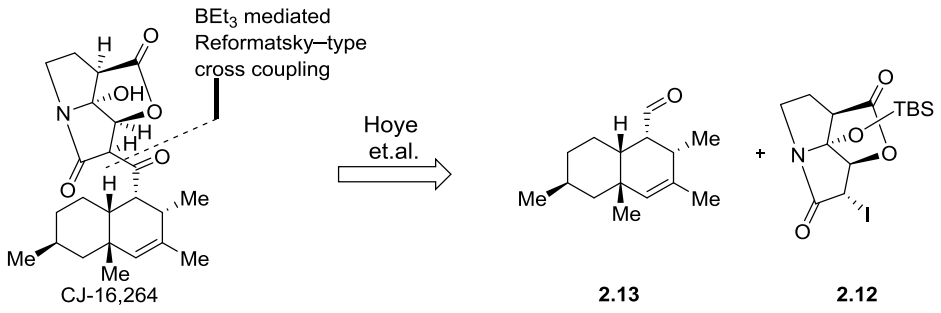


Figure **2.22**: Reformatsky–type approach to CJ-16,264 by Hoye.

While to the best of our knowledge a total synthesis of CJ-16,264 has not been reported, efforts towards its total synthesis have been reported in a thesis dissertation by Dr. Sizova of the Hoye laboratory.[7] Similar to the disconnection made by Danishefsky in their approach to UCS1025A, the Hoye approach involved a BEt_3 mediated Reformatsky–type coupling of iodolactam **2.17** and aldehyde **2.21.** (Figure **2.22**). Aldehydes **2.56**, **2.35**, and **2.13** were synthesized *via* an IMDA of triene **2.10** (Figure **2.23**), though this particular reaction was reported as difficult and low yielding.

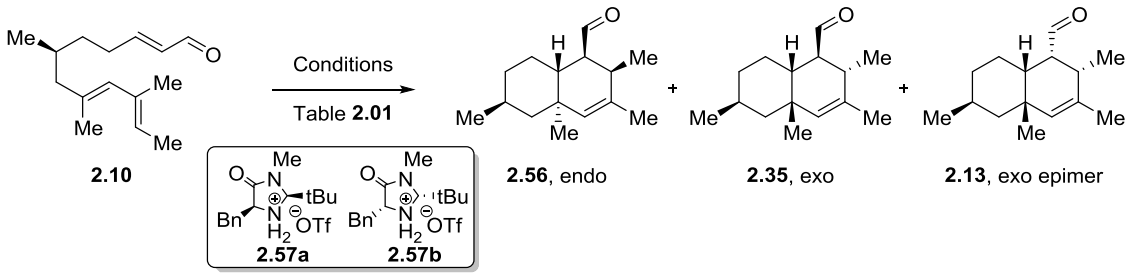


Figure **2.23**. IMDA reaction of triene **2.10**.

Table **2.01**

#	Conditions: catalyst, solvent	T (°C)	t1/2	dr 2.56 : 2.35 : 2.13; yield
1	Toluene, BHT (~2 mol%)	120	7d	31 : 60 : 9 ; (53%)
2	**2.57a**, CD_3CN/D2O	0	24h	63 : 37 : 0 ; (15%)
3	**2.57b**, CD_3CN/D2O	0	24h	40 : 7 : 53 ; (10%)

With aldehydes **2.35** and **2.13** in hand, 1-7'-bis-epi-**2.01**, 1-7'-7'a-7'b-2'a-penta-epi-**2.01**, 7'-epi-**2.01**, and 2'a-7'a-7'b-tris-epi-**2.01** were then targeted to be synthesized (Figure **2.24**). Of these compounds, only 1-7'-bis-epi-**2.01** was fully characterized by

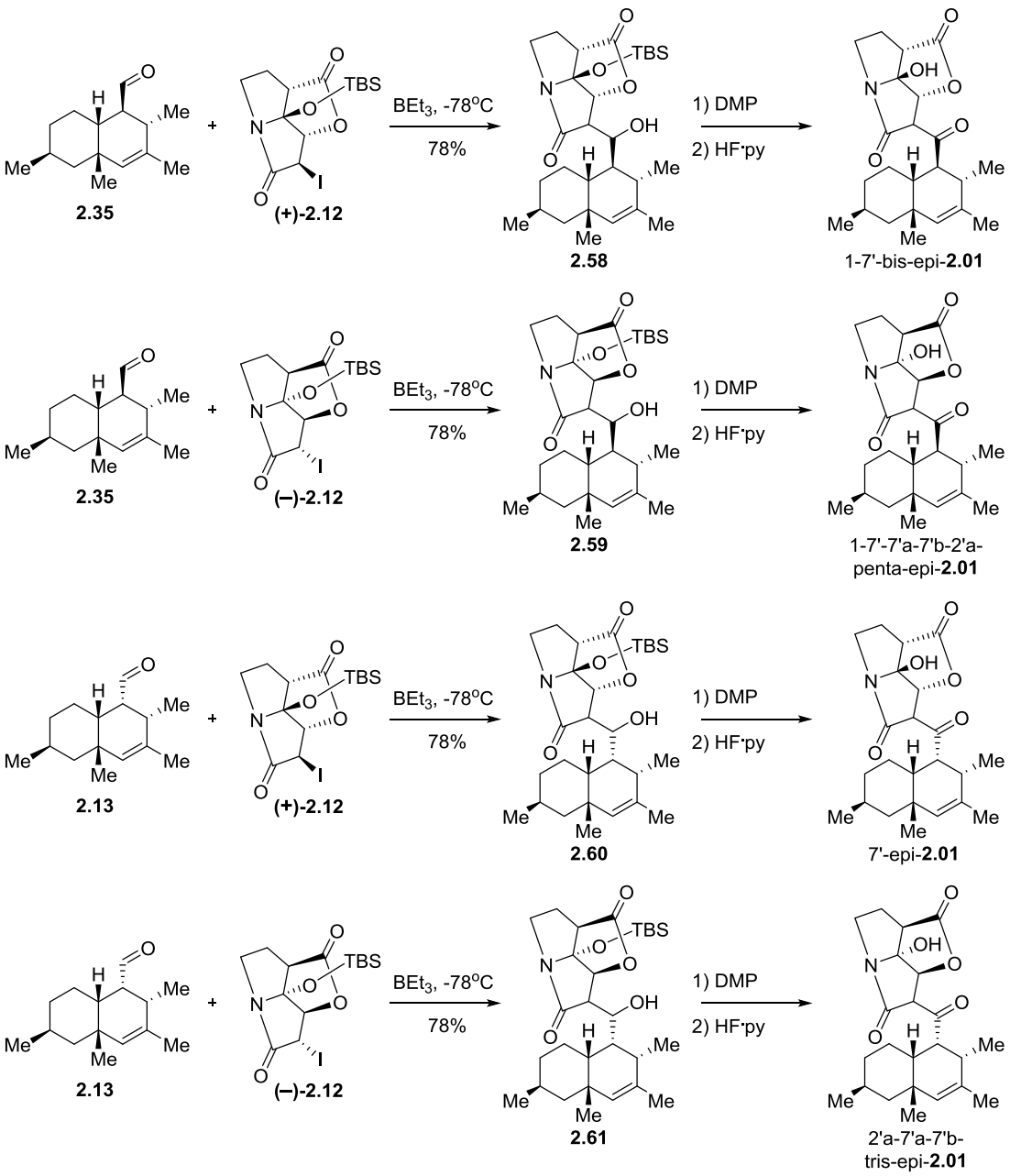


Figure **2.24**: Approach to CJ-16,264 and epimers by Hoye.

^{13}C-NMR, though none of these compounds matched the ^{1}H-NMR data provided for **2.01**, leaving the true structure of CJ-16,264 a mystery.

In our own strategy to synthesize CJ-16,264, we also elected to employ the BEt_3 mediated Reformatsky–type coupling of iodolactam **2.12** and aldehyde **2.13** (Figure **2.25**). We recognized that there would be difficulty in creating the *cis*-decalin system found in CJ-16,264, so our plan utilized a transannular IMDA of diolide **2.24** to reach the necessary *cis*-decalin in acceptable yield. While our synthesis did not reach the natural product, it did pave the way for future synthetic studies to synthesize CJ-16,264 (and even pyrrolizilactone).

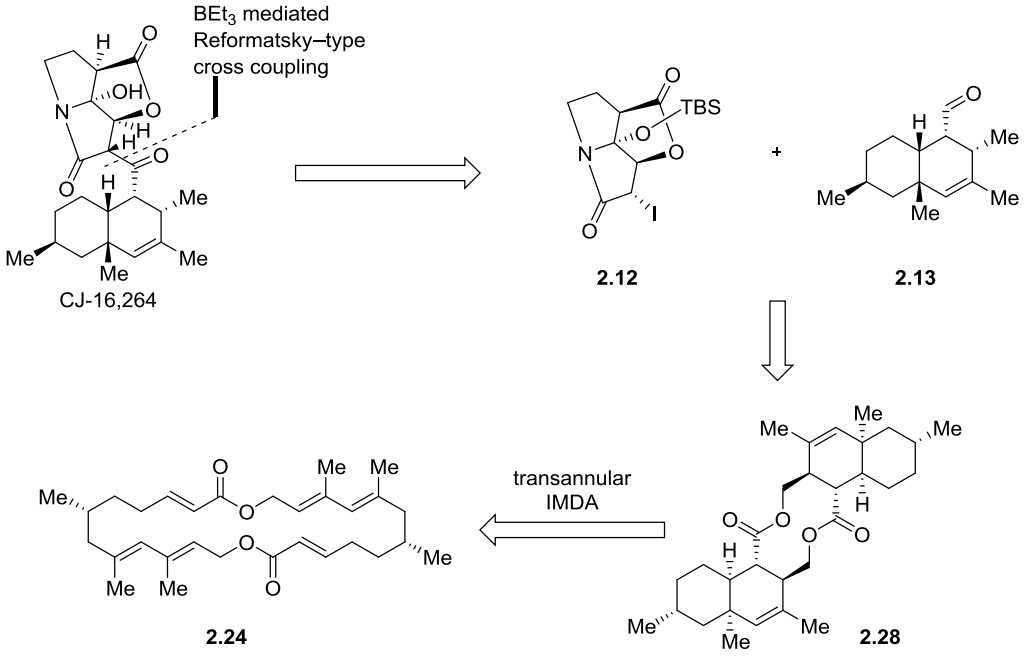


Figure **2.25**: Our own approach to CJ-16,264.

These reported synthetic endeavors each contain different synthetic strategies to access this class of natural products. The Danishefky synthesis introduces an interesting, highly efficient and reliable boron mediate Reformatsky–type coupling in their synthesis of UCS1025A. Late stage coupling of iodolactam **2.12** with a decalin aldehyde enables a

convenient disconnection for the synthesis of UCS1025A and congeners such as CJ-16,264 and pyrrolizilactone. The Uchida synthesis splendidly accesses UCS1025A by relying on a late stage acylation of a *trans*-decalin fragment with a lithium enolate. While this synthesis does present a completely unique way to access the pyrrolizidinone motif in UCS1025A, it is also requires a lengthy synthetic sequence to do so. The Hoye synthesis's biomimetic design beautifully demonstrates the spontaneity of an IMDA reaction to form UCS1025A, as well as another *trans*-decalin analogue. It has not been shown if this remarkably fast IMDA could be used to design a *cis*-decalin such as those found in CJ-16,264 and pyrrolizilactone. In our own approach to synthesize CJ-16,264, were indeed able to use a transannular approach to efficiently synthesize the *cis*-decalin motif found in both CJ-16,264 and pyrrolizilactone, and in an efficient step count and yield. Continuing with this approach, synthetic studies toward the total synthesis of CJ-16,264 and pyrrolizilactone are currently underway in our laboratories.

E. Conclusions

The described chemistry constitutes the efficient total synthesis of (±)-1-epi-CJ-16,264 and advanced intermediate **2.47** from citronellal. The ability to successfully synthesize the requisite methylated *cis*-decalin scaffold found in these molecules, as well as found in pyrrolizilactone, was demonstrated *via* a double exo-selective IMDA reaction of a sterically constrained macrolactone system. Though there has been a significant amount of interest demonstrated in the biological testing of previously synthesized UCS1025A,[5, 18] the biological testing of CJ-16,264 and pyrrolizilactone has been limited. The results of this synthetic work provide for the first time efficient access to the highly methylated cis-decalin scaffold found in CJ-16,264 and pyrrolizilactone. Their synthesis

would allow biological testing of this class of highly active compounds, thereby impacting the drug discovery progress. This may result in the development of new medicines.

F. Experimental Section

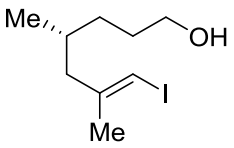
1. General Procedures

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, benzene, diethyl ether (Et_2O), *N*, *N*′-dimethylformamide (DMF), and methylene chloride (CH_2Cl_2) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040 – 0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-400, DRX-500 or DRX-600 instruments and calibrated using residual undeuterated solvent ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm) as an internal reference. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, m = multiplet, br = broad. Infrared (IR) spectra were recorded on a Perkin–Elmer 100 FT-IR spectrometer. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI-TOF (time of flight) mass spectrometer using MALDI (matrix-assisted laser desorption ionization) or ESI (electrospray ionization). Optical rotations were

recorded on a Perkin–Elmer Model 343 polarimeter at 589 nm, and are reported in units of 10^{-1} (deg cm^2 g^{-1}).

2. Preparation of Compounds

Alcohol 2.19: To a stirred suspension of Cp_2ZrCl_2 (11.58 g, 39.62 mmol, 1.0 equiv) in 1,2-dichloroethane (150 mL) was added a solution of $AlMe_3$ (2.0 M in hexanes, 40 mL, 80 mmol, 4.0 equiv). After stirring for 0.5 h at ambient temperature, alkyne **2.17** in 50 mL 1,2-dichloroethane was added. The resultant yellow solution was stirred at room temperature for 18 h at ambient temperature before it was cooled to -20°C and a solution of I_2 in THF (50 mL) was added. The reaction was then stirred for 1 h 0°C. The mixture was then slowly poured into water (100mL) at 0°C and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 2:8) providing pure alcohol **2.19** as a yellow oil (8.93 g, 33.3 mmol, 84% yield).

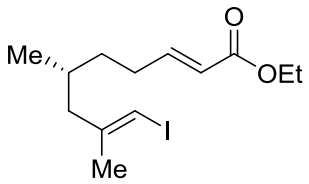


2.19

2.19: R_f = 0.26 (silica, Et_2O:hexanes, 1:1); $[\alpha]_D^{19}$ = –6.61 (*c* = 0.31, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ = 5.84 (d, J=1.0, 1H), 3.63 (td, J=6.6, 1.2, 2H), 2.21 (dd, J=13.3, 5.9, 1H), 2.02 (dd, J=13.5, 8.3, 1H), 1.80 (d, J=0.9, 3H), 1.67 – 1.60 (m, 2H), 1.35 (ddt, J=13.3, 10.8, 5.2, 2H), 1.18 – 1.10 (m, 2H), 0.84 (d, J=6.6, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 147.2, 75.5, 63.4, 47.7, 32.8, 31.0, 30.4, 23.9, 19.4; HRMS calcd for $C_9H_{18}IO^+$ [*M*+H^+] 269.0397 found 269.0402.

Ester 2.20: To a stirred solution of vinyl iodide **2.19** (10.17 g, 37.93 mmol, 1.0 equiv) in CH_2Cl_2/DMSO (3:1 150 mL) at 0 °C were added Et_3N (21.3 mL, 151.71 mmol, 4.0

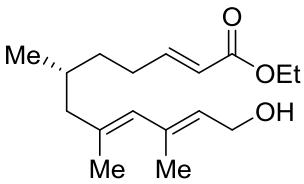
equiv), and SO_3•py (12.08 mg, 75.86 mmol, 2.0 equiv). The reaction mixture was warmed to ambient temperature and stirred for 1 h before carbethoxymethylene)triphenylphosphorane (26.43 g, 75.86 mmol, 2.0 equiv) was added. The resulting mixture was stirred for 4 hours before it was quenched with sat. NH_4Cl (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:19) providing pure enone **2.20** as a yellow oil (10.58 g, 31.47 mmol, 83% yield).



2.20

2.20: R_f = 0.58 (silica, EtOAc:hexanes, 3:7); $[\alpha]_D^{21}$ = –1.7 (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.94 (dt, J=15.6, 7.0, 1H), 5.86 – 5.85 (m, 1H), 5.81 (dt, J=15.6, 1.6, 1H), 4.19 (q, J=7.1, 2H), 2.31 – 2.22 (m, 1H), 2.22 – 2.13 (m, 2H), 2.02 (dd, J=13.5, 8.3, 1H), 1.79 (d, J=1.0, 3H), 1.66 (dq, J=8.3, 6.7, 1H), 1.48 – 1.41 (m, 1H), 1.29 (t, J=7.1, 3H), 1.27 – 1.21 (m, 1H), 0.84 (d, J=6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.8, 149.1, 146.9, 121.6, 60.3, 47.5, 34.9, 30.6, 29.8, 23.8, 19.2, 14.4; HRMS calcd for $C_{21}H_{22}IO_2^+$ [*M*+H^+] 337.0659 found 337.0654.

Triene 2.23: To a stirred solution of enone iodide **2.20** (2.42 g, 7.2 mmol, 1.0 equiv) and stannyl alcohol **2.22** (7.82 g, 21.6 mmol, 3.0 equiv) in DMF (degassed, 4 mL) at 0 °C was added CuTC (8.24 g, 43.19 mmol, 6.0 equiv). The reaction mixture was warmed to ambient temperature and stirred for 2.5 h before being diluted with EtOAc (20mL) and H_2O (20mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The resulting crude product was purified by flash column

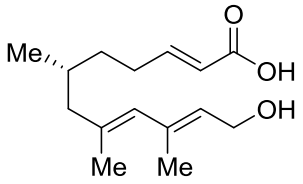


2.23

chromatography (silica gel, EtOAc:hexanes, 1:19) providing pure triene **2.23** as a yellow oil (2.01 g, 31.47 mmol, 99% yield).

2.23: R_f = 0.11 (silica, EtOAc:hexanes, 1:9); $[\alpha]_D^{23}$ = –6.5 (*c* = 0.74, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.03 – 6.94 (m, 1H), 5.84 (d, J=15.6, 1H), 5.63 (s, 1H), 5.50 (t, J=6.8, 1H), 4.27 (t, J=6.2, 2H), 4.21 (q, J=7.1, 2H), 2.34 – 2.16 (m, 2H), 2.06 (dd, J=13.1, 6.4, 1H), 1.85 (dd, J=13.1, 8.1, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.68 (dd, J=12.9, 6.8, 1H), 1.54 – 1.46 (m, 1H), 1.31 (t, J=7.1, 3H), 1.26 (t, J=5.6, 2H), 0.87 (d, J=6.6, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 166.9, 149.6, 136.5, 136.1, 129.8, 127.2, 121.4, 60.3, 59.7, 48.7, 35.1, 30.6, 29.9, 19.4, 18.0, 17.5, 14.4.; HRMS calcd for $C_{17}H_{29}O_3^+$ [M+H^+] 281.2111 found 281.1116.

Seco acid 2.15: To a stirred solution of **2.23** (2.1 g, 7.49 mmol, 1.0 equiv) in THF (35 mL) was added LiOH (1.0 M, 35 mL) at ambient temperature. After stirring for 18 h at 60 °C, the reaction was cooled to ambient temperature and quenched with HCl (10%, 1.0 M) until pH = 3, and then extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 8:2) providing pure seco acid **2.15** as a yellow oil (1.88 g, 7.54 mmol, 99% yield).

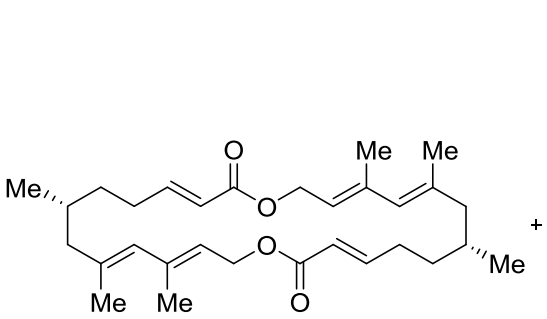


2.15

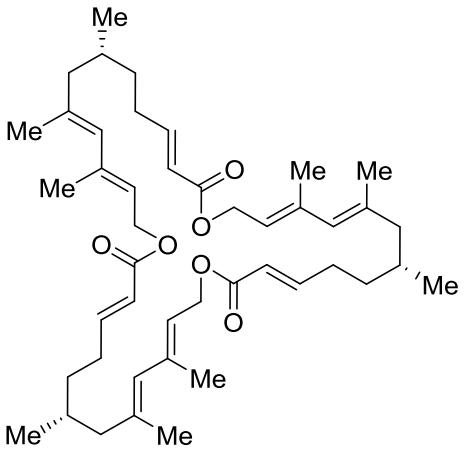
2.15: R_f = 0.32 (silica, EtOAc); $[\alpha]_D^{22}$ = -4.3 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.11 – 7.03 (m, 1H), 5.83 (dt, J=15.6, 1.5, 1H), 5.61 (s, 1H), 5.47 (t, J=6.9, 1H), 4.25 (d, J=6.9, 2H), 2.35 – 2.16 (m, 2H), 2.07 – 2.00 (m, 1H), 1.84 (dd, J=13.2, 8.1, 1H), 1.76 (s, 3H), 1.74 (d, J=1.2, 3H), 1.70 – 1.62 (m, 1H), 1.49 (ddd, J=14.9, 5.3, 3.7,

1H), 1.30 – 1.21 (m, 1H), 0.86 (d, J=6.6, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.6, 152.5, 136.5, 136.1, 129.8, 127.2, 120.4, 59.7, 48.6, 34.8, 30.6, 30.1, 19.4, 18.0, 17.5; HRMS calcd for $C_{15}H_{24}O_3Na^+$ [*M*+Na^+] 275.1618 found 275.1617.

Dimer 2.25 and Trimer 2.25: To a stirred solution of seco acid **2.15** (0.5 g, 1.98 mmol,



2.24



2.25

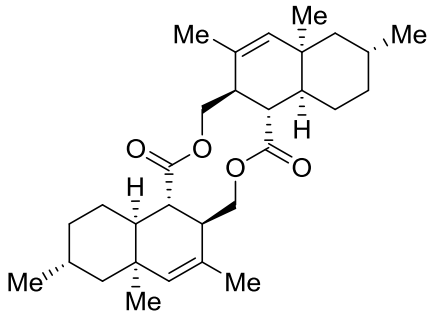
1.0 equiv) in CH_2Cl_2 (180 mL) were added Et_3N (0.57 mL, 3.46 mmol, 2.0 equiv), DMAP (24 mg, 0.19 mmol, 0.1 equiv), and then MNBA (1.03 g, 2.97 mmol, 1.5 equiv). After stirring for 5 h at ambient temperature, H_2O (30 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:19) providing pure diolide **2.24** as an amorphous solid (236 mg, 0.504 mmol, 51% yield) and pure triolide **2.25** as an amorphous solid (39 mg, 0.056 mmol, 8.4%).

For dimer 2.24: R_f = 0.39 (silica, EtOAc:hexanes, 2:8); $[\alpha]_D^{22}$ = +32.9 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.95 (dt, J=15.5, 6.8, 1H), 5.82 (d, J=15.7, 1H), 5.60 (s, 1H), 5.39 (t, J=6.8, 1H), 4.74 (qd, J=12.5, 6.8, 2H), 2.30 (td, J=15.3, 6.1, 1H), 2.10 (td,

J=15.0, 6.6, 1H), 2.02 (dd, J=13.0, 4.7, 1H), 1.86 (dd, J=13.2, 9.5, 1H), 1.79 (s, 3H), 1.69 (s, 3H), 1.66 – 1.63 (m, 1H), 1.52 – 1.48 (m, 1H), 1.13 – 1.05 (m, 1H), 0.90 (d, J=6.6, 3H); ^{13}C NMR (150 MHz, $CHCl_3$) δ = 166.8, 149.5, 138.4, 136.5, 129.7, 122.3, 121.5, 61.2, 49.0, 33. 2, 30. 1, 29.7, 20.2, 17.9, 17.6; HRMS calcd for $C_{30}H_{45}O_4H^+$ [M+H^+] 469.3312 found 469.3313.

For trimer 2.25: R_f = 0.30 (silica, EtOAc:hexanes, 2:8); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.95 (m, 1H), 5.83 (d, 1H, J = 15.5 Hz), 5.61 (s, 1H), 5.41 (t, 1H, J = 7.0 Hz), 4.72 (d, 2H, J = 7.0 Hz), 2.28 (m, 1H), 2.16 (m, 1H), 1.94-1.88 (m, 3H), 1.79 (s, 3H), 1.72 (s, 3H), 1.66 (m, 1H), 1.50 (m, 1H), 0.86 (d, 3H, J = 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ= 166.8, 149.7, 138.5, 136.6, 129.6, 122.3, 121.4, 61.3, 48.8, 34.3, 30.3, 29.9, 19.8, 18.1, 17.7; HRMS calcd for $C_{45}H_{66}O_6Na^+$ [M+Na^+] 725.4752 found 725.4753.

IMDA adduct 2.28: A solution of diolide **2.24** (87 mg, 0.186 mmol, 1.0 equiv) in o-xylene (degassed, 6 mL) was transferred into an oil bath preheated to 220 °C and stirred for 6 h. The resultant yellow solution was concentrated *in vacuo* and the resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:9) to provide pure IMDA adduct **2.28** as a white amorphous solid (48 mg, 0.102 mmol, 55% yield).

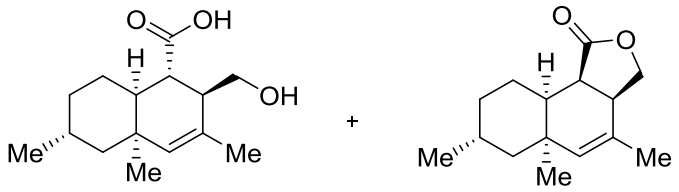


2.28

2.28: R_f = 0.46 (silica, EtOAc:hexanes, 2:8); $[\alpha]_D^{21}$ = –31.92 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.22 (s, 1H), 4.59 (dd, J=10.6, 4.5, 1H), 4.13 – 4.02 (m, 1H), 3.04 (t, J=10.8, 1H), 2.55 (t, J=9.9, 1H), 1.92 – 1.68 (m, 6H), 1.67 (s, 3H), 1.52 (dd, J=14.1,

5.4, 1H), 1.24 – 1.17 (m, 1H), 1.14 (d, J=4.5, 1H), 1.11 (s, 1H), 1.06 (s, 3H), 1.00 (d, J=7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.16, 136.68, 126.63, 66.86, 47.61, 42.02, 41.09, 40.57, 35.02, 28.99, 27.11, 22.26, 22.24, 21.81, 21.01; HRMS calcd for C17H23NO7Na+ [M+Na+] 376.1367 found 376.1367.

Acid 2.29 and Lactone 2.30: To a solution of IMDA adduct **2.28** (120 mg, .256 mmol, 1.0 equiv) in THF/MeOH/H_2O (4:2:1, 3 mL) was added NaOH (720 mg). It was then transferred into an oil bath preheated to 100 °C. After stirring for 3 h at 60 °C, the reaction was cooled to ambient temperature and quenched with HCl (10%) until pH ~ 7, and then extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude products were purified by flash column chromatography (silica gel, EtOAc:hexanes, 100% hexanes → 1:1) providing pure acid **2.29** (86 mg, 0.34 mmol, 66% yield) and pure lactone **2.30** as an amorphous solid (40 mg, 0.16 mmol, 33% yield). If the workup is modified to quench with HCl (10%) until pH < 3 and left to stir for 30 minutes, only lactone **2.30** would be isolated, in 99% yield.



2 : 1

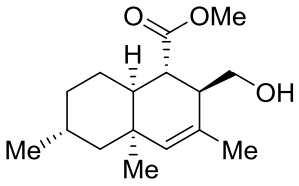
2.29 **2.30**

Acid 2.29:; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.23 (s, 1H, H-9), 3.90 (dd, 1H, *J* = 10.8, 4.0 Hz), 3.61 (t, 1H, *J* = 9.2 Hz), 2.86 (br s, 1H), 2.72 (t, 1H, *J* = 3.6 Hz), 2.11 (d, 1H, *J* = 10.8 Hz), 1.74 (s, 3H), 1.62 (m, 1H), 1.54 (m, 1H), 1.46-1.39 (m, 3H), 0.99-0.90 (m, 2H), 0.90 (s, 3H), 0.86 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.1, 134.1,

129.3, 64.6, 48.4, 46.0, 41.9, 40.3, 36.2, 33.9, 29.9, 29.4, 28.8, 22.4, 21.9; HRMS calcd for $C_{15}H_{23}O_3$ $[M-H]^-$ 251.1653 found 251.1654.

Lactone 2.30: R_f = 0.31 (silica, acetone:hexanes, 3:7); $[\alpha]_D^{21}$ = –9.7 (*c* = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 5.21 (d, J=1.5, 1H), 4.54 (dd, J=9.8, 8.7, 1H), 3.87 (dd, J=10.6, 8.6, 1H), 3.11 (dd, J=10.2, 5.8, 1H), 3.02 – 2.92 (m, 1H), 1.83 – 1.76 (m, 1H), 1.65 – 1.63 (m, 3H), 1.63 – 1.57 (m, 2H), 1.57 – 1.52 (m, 1H), 1.49 (dd, J=12.5, 3.5, 1H), 1.39 – 1.30 (m, 2H), 1.18 (dd, J=12.8, 3.6, 1H), 0.96 (s, 3H), 0.83 (d, J=6.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 180.3, 132.0, 128.7, 72.1, 49.4, 40.5, 40.4, 37.4, 36.7, 34.8, 29.4, 29.2, 25.8, 22.5, 20.9; HRMS calcd for $C_{15}H_{22}O_2Na^+$ [*M*+Na^+] 257.1517 found 257.1515.

Ester 2.31: To a solution of acid **2.29** (34 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) was added

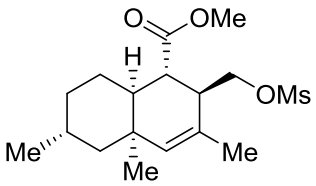


2.31

Me_3OBF_4 (22 mg, 0.15 mmol) and DIPEA (0.05 mL, 1.5 mmol). The reaction mixture was stirred at rt for 5 min. The mixture was concentrated under reduced pressure and purified by flash chromatography (silica gel, EtOAc:hexanes, 2:8) to give **2.31** (40 mg, quant.) as a colorless oil.

2.31: R_f = 0.5 (silica, EtOAc:hexanes, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ = 5.21 (s, 1H), 3.83 (dd, 1H, *J* = 10.8, 4.0 Hz), 3.70 (s, 3H), 3.61 (dd, 1H, *J* = 10.8, 7.6 Hz), 2.90 (br s, 1H), 2.70 (t, 1H, *J* = 4.0 Hz), 2.04 (m, 1H), 1.74 (s, 3H), 1.64 (m, 1H), 1.56-1.40 (m, 4H), 0.99-0.92 (m, 2H), 0.86 (d, 3H, *J* = 6.8 Hz), 0.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4, 132.9, 128.3, 63.4, 50.9, 46.9, 44.8, 40.9, 39.7, 34.9, 32.3, 28.7, 28.1, 27.5, 21.2, 20.7; HRMS calcd for $C_{16}H_{26}O_3Na$ $[M+Na]^+$ 289.1774 found 289.1776.

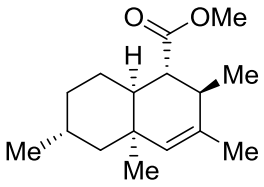
Mesylate 2.32: To a solution of **2.31** (75 mg, 0.28 mmol) in 3 mL CH_2Cl_2 at 0 °C was added TEA (0.1 mL, 0.84 mmol) and MsCl (0.05 mL, 0.56 mmol) under Ar. The reaction mixture was stirred at 0 °C for 3 h. The mixture was quenched with sat. NH_4Cl, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc:hexanes, 2:8) to give **2.32** (87 mg, 90%) as a colorless oil.



2.32

Mesylate 2.32: ^{1}H NMR (400 MHz, $CDCl_3$); δ = 5.26 (s, 1H), 4.34-4.25 (m, 2H), 3.71 (s, 3H), 3.18 (br s, 1H), 3.01 (s, 3H), 2.55 (br s, 1H), 2.08 (br d, 1H, *J* = 11.2 Hz), 1.77 (s, 3H), 1.62 (br d, 1H, *J* = 11.6 Hz), 1.53-1.36 (m, 4H), 0.96-0.91 (m, 2H), 0.84 (d, 3H, *J* = 6.4 Hz), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 176.4, 134.7, 127.9, 71.1, 52.3, 48.8, 46.3, 42.1, 37.6, 37.3, 36.2, 34.2, 30.2, 29.1, 28.9, 22.4, 22.6; HRMS calcd for $C_{17}H_{28}O_5SNa$ $[M+Na]^+$ 367.1550 found 367.1552.

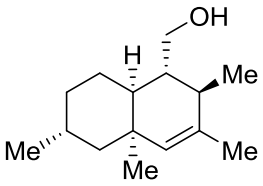
Ester 2.33: To a solution of **2.32** (124 mg, 0.36 mmol) in 3.6 mL DME was added NaI (540 mg, 3.60 mmol) and activated Zn dust (470 mg, 7.20 mmol). The reaction mixture was stirred at 90 °C for 24 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (100% hexanes) to give **2.32** (75 mg, 83%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.07 (s, 1H), 3.68 (s, 3H), 2.75 (m, 1H), 2.27 (t, 1H, *J* = 4.8 Hz), 1.97 (m, 1H), 1.69 (s, 3H), 1.66-1.35 (m, 5H), 1.07 (d, 3H, *J* = 7.2 Hz), 0.99-0.94 (m, 2H), 0.88 (d, 3H, *J* = 6.8 Hz), 0.86 (s, 3H); ^{13}C NMR (100 MHz,



2.33

$CDCl_3$) δ = 177.4, 133.1, 131.4, 51.8, 51.5, 47.6, 42.6, 36.0, 32.8, 29.6, 28.7, 28.5, 22.3, 21.9, 20.5; HRMS calcd for $C_{16}H_{27}O_2$ $[M+H]^+$ 251.2011 found 251.2006.

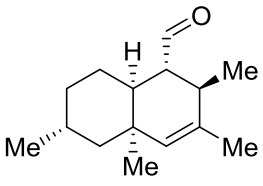
Alcohol 2.34: To a solution of **2.33** (86 mg, 0.34 mmol) in 1 mL CH_2Cl_2 at 0 °C was added DIBAL-H (1.4 mL, 1.37 mmol). The reaction mixture was stirred at 0 °C for 5 min. The mixture was quenched with 20% NaOH, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc:hexanes, 2:8) to give **2.34** (76 mg, quant.) as a colorless oil.



2.34

2.34: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.11 (s, 1H), 3.71-3.60 (m), 1.82 (m, 1H), 1.72 (m, 1H), 1.68 (s, 3H), 1.54 (m, 1H), 1.44-1.34 (m, 6H), 1.13 (d, 3H, *J* = 7.2 Hz), 0.90 (s, 3H), 0.87 (m, 1H), 0.82 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.3, 131.1, 68.8, 51.7, 50.4, 41.9, 36.3, 35.1, 34.2, 32.9, 31.1, 28.9, 22.6, 22.1, 21.7; HRMS calcd for $C_{15}H_{27}O^+$ [*M*+H^+] 223.2056 found 223.2063.

Aldehyde 2.35: To a solution of **2.34** (9.90 mg, 0.04 mmol) in 1.2 mL CH_2Cl_2 was added Dess-Martin Periodinane (DMP) (38 mg, 0.08 mmol). The reaction mixture was stirred at rt for 30 min. The mixture was quenched with sat. sodium thiosulfate and sat. sodium bicarbonate (1:1), extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% ethyl acetate in hexane) to give **2.35** (8.90 mg, 91%) as a colorless oil.

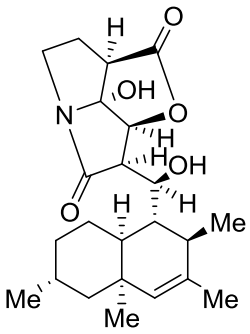


2.35

2.35: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.75 (s, 1H, 5.04 (s, 1H), 2.81 (m, 1H, 2.00-1.97 (m, 2H), 1.71 (s, 3H), 1.66-1.38 (m, 5H), 1.13 (d, 3H, *J* = 7.6 Hz), 0.94-0.88 (m, 2H), 0.85 (d, 3H, *J* = 6.4 Hz), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.1, 133.7, 130.1, 60.8, 49.6, 41.6, 36.4, 35.3, 31.8, 31.3, 29.2, 28.7, 22.6, 22.1, 21.5; HRMS calcd for $C_{15}H_{25}O$ [*M*+H^+] 221.1905 found 221.1907.

Diols 2.38 and **2.39**: General procedure for TASF deprotection: To a solution of **2.36** (10.3 mg, 0.02 mmol) in 0.8 mL THF at 0 °C was added TASF (11.0 mg, 0.04 mmol). The reaction mixture was stirred at 0 °C for 10 min. The mixture was quenched with H_2O, extracted with EtOAC, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, EtOAc:hexanes, 1:1) to give **2.38** (5.5 mg, 69%) as a white powder.

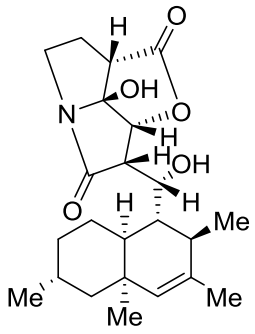
Diol 2.38: ^{1}H NMR (500 MHz, Acetone-d_6) δ = 6.29 (br s, 1H), 5.07 (d, 1H, *J* = 3.5),



2.38

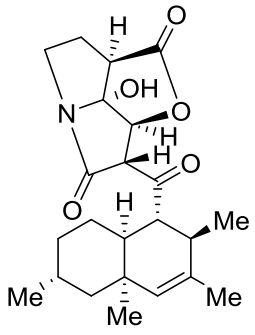
5.05 (s, 1H), 4.54 (d, 1H, *J* = 2.5), 4.04 (m, 1H), 3.76 (m, 1H), 3.36 (dd, 1H, *J* = 8.0, 4.0), 3.33-3.28 (m, 2H), 2.69 (m, 1H), 2.54 (m, 1H), 2.42 (m, 1H), 1.69 (s, 3H), 1.65 (br s, 1H), 1.58-1.53 (m, 2H), 1.48-1.40 (m, 3H), 1.35-1.28 (m, 3H), 1.18 (d, 3H, *J* = 7.5), 1.08 (s, 3H), 0.88 (m, 1H), 0.82 (d, 3H, *J* = 6.5); ^{13}C NMR (125 MHz, Acetone-d_6) δ = 176.7, 175.9, 135.6, 131.1, 100.2, 83.0, 73.4, 52.1, 51.6, 51.5, 49.1, 46.0, 42.2, 36.7, 36.1, 33.9, 30.6, 29.9, 29.6, 29.4, 23.4, 22.9, 22.7; HRMS calcd for $C_{23}H_{33}NO_5Na$ [*M*+Na^+] 426.2251 found 426.2254.

Diol 2.39: ^{1}H NMR (500 MHz, Acetone-d_6) δ = 6.34 (br s, 1H), 5.26 (s, 1H), 4.96 (d, 1H, *J* = 4.0), 4.66 (t, 1H, *J* = 1.5), 4.07 (m, 1H, H-8'), 3.77 (ddd, 1H, *J* = 11.5, 9.5, 6.5), 3.39 (dd, 1H, *J* = 10.0, 4.0), 3.34-3.28 (m, 2H), 2.71 (m, 1H), 2.44 (dddd, 1H, *J* = 13.5, 9.5, 4.5, 2.0), 2.29 (m, 1H), 1.76 (dd, 1H, *J* = 12.5, 5.0), 1.72 (s, 3H), 1.56-1.52 (m, 2H), 1.39-1.32 (m, 4H), 1.15 (m, 1H), 1.09 (d, 3H, *J* = 7.0), 0.98 (s, 3H), 0.87 (m, 1H), 0.83 (d, 3H, *J* = 6.5); ^{13}C NMR (125 MHz, Acetone-d_6) δ = 177.8, 175.9, 136.3, 132.7, 100.3, 82.7, 69.9, 66.2, 53.6, 53.5, 51.9, 50.1, 49.0, 42.1, 40.3, 37.1, 36.6, 36.4, 32.8, 30.6, 23.0, 21.9, 19.8; HRMS calcd for $C_{23}H_{33}NO_5Na$ [*M*+Na^+] 426.2251 found 426.2252.



2.39

(±)-1-epi-CJ-16,264 (**2.40**): To a solution of **2.38** (9.0 mg, 0.02 mmol) in 0.7 mL THF and DMF (one drop) was added TASF (48.0 mg, 0.17 mmol). The reaction mixture was stirred at rt for 30 min. The mixture was quenched with H_2O, extracted with EtOAC, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (50% ethyl acetate in hexane) to give **2.40** (5.0 mg, 70%) as a white solid.

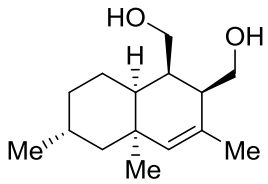


2.40

2.40: ^{1}H NMR (500 MHz, C_6D_6) δ = 5.03 (s, 1H, H-4), 4.99 (s, 1H), 4.09 (s, 1H), 3.98 (s, 1H), 3.46 (ddd, 1H, *J* = 12.5, 11.0, 5.0), 2.93 (br t, 1H, *J* = 3.5), 2.70 (ddd, 1H, *J* = 12.0, 10.5, 4.5), 2.65 (dd, 1H, *J* = 9.5, 1.5 Hz), 2.51 (br d, 1H, *J* = 11.0 Hz), 2.07 (br t, 1H, *J* = 3.5), 2.02 (dddd, 1H, *J* = 13.5, 9.5, 4.5, 2.0'), 1.86 (m, 1H), 1.62 (s, 3H), 1.56 (br d, 1H, *J*

= 13.0), 1.38-1.26 (m, 4H), 1.04-0.96 (m, 2H), 0.88 (d, 3H, *J* = 7.0), 0.88 (s, 3H), 0.83 (d, 3H, *J* = 6.5); ^{13}C NMR (125 MHz, C_6D_6) δ: 209.9, 174.0, 167.7, 133.1, 131.4, 100.9, 81.1, 63.7, 63.6, 48.9, 47.5, 41.8, 38.9, 37.1, 34.3, 31.9, 29.7, 29.6, 29.1, 28.9, 22.4, 21.7, 21.1; HRMS calcd for $C_{23}H_{31}NO_5Na$ [M+Na+] 424.2094 found 424.2099.

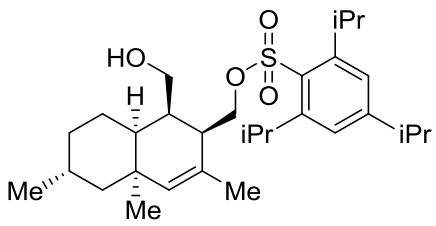
Diol 2.41: To a stirred solution of lactone **2.30** (30 mg, 0.128 mmol, 1.0 equiv) in THF (1.5 mL) at -78 °C was added a solution of LAH (3.5 M in THF, 0.2 mL, 0.65 mmol, 5.0 equiv). After stirring for 0.5 h at -78 °C the reaction was warmed to 0 °C and diluted with 1.0 mL Et_2O. To this reaction mixture were then added H_2O (0.03 mL), NaOH (15% aq., 0.03 mL), and then H_2O (0.03 mL). After stirring 10 min, the mixture was filtered through a short pad of Celite® and was concentrated *in vacuo*. The resulting crude product was purified by flash column chromatography (silica gel, acetone:hexanes, 2:8) providing diol **2.41** (30 mg, 0.126 mmol, 98% yield) as a white amorphous solid.



2.41

2.41: R_f = 0.18 (silica, acetone:hexanes, 3:7); $[\alpha]_D^{25}$ = +59.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.10 (d, J=1.5, 1H), 4.11 (d, J=11.3, 1H), 3.99 (dd, J=10.8, 8.1, 1H), 3.79 (dd, J=10.8, 1.7, 1H), 3.63 (dd, J=11.3, 4.6, 1H), 2.61 (dd, J=7.2, 4.0, 1H), 2.37 (t, J=7.6, 1H), 1.78 (d, J=0.9, 3H), 1.59 – 1.53 (m, 1H), 1.50 – 1.45 (m, 1H), 1.43 – 1.36 (m, 1H), 1.32 – 1.26 (m, 2H), 1.24 – 1.18 (m, 1H), 1.11 (qd, J=12.8, 3.5, 1H), 0.97 (s, 3H), 0.80 (d, J=6.5, 3H), 0.72 (ddd, J=24.7, 12.9, 3.2, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 133.6, 131.4, 64.9, 62.2, 50.2, 43.6, 42.4, 38.6, 37.4, 35.4, 31.2, 29.6, 25.2, 22.8, 22.7; HRMS calcd for $C_{15}H_{27}O_2^+$ [*M*+H^+] 239.2005 found 239.2014.

Hydroxy Sulfonate 2.42: To a solution of diol **2.41** in CH_2Cl_2 (3 mL) was added Ag_2O (14 mg, 0.06 mmol, 1.5 equiv), KI (1.3 mg, 0.008 mmol, 0.2 equiv), and 2,4,6-triisopropylbenzenesulfonyl chloride (13 mg, 0.044 mmol, 1.1 equiv) and stirred for 24 hours. The reaction mixture was then concentrated and the resulting crude product was purified by flash column chromatography (silica gel, acetone:hexanes, 30:70) providing pure hydroxyl sulfonate **2.42** as a yellow oil (17 mg, 0.034 mmol, 85% yield) and diol **2.41** (0.5 mg, 0.002 mmol, 5% recovered).



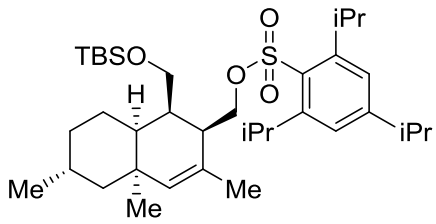
2.42

2.42: R_f = 0.45 (silica, acetone:hexanes, 3:7); $[\alpha]_D^{22}$ = +43.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CHCl_3$) δ = 7.19 (s, 2H), 5.10 (d, J=1.1, 1H), 4.39 (dd, J=10.6, 4.9, 1H), 4.13 (dt, J=13.5, 6.8, 2H), 4.06 (dd, J=10.6, 3.8, 1H), 3.94 (dd, J=11.2, 9.1, 1H), 3.63 (dd, J=11.3, 6.1, 1H), 2.91 (hept, J=6.9, 1H), 2.59 – 2.53 (m, 1H), 2.49 – 2.44 (m, 1H), 1.67 (s, 3H), 1.54 – 1.49 (m, 1H), 1.49 – 1.45 (m, 1H), 1.40 – 1.32 (m, 2H), 1.29 – 1.24 (m, 18H), 1.22 – 1.12 (m, 1H), 0.95 (s, 3H), 0.92 – 0.81 (m, 2H), 0.78 (d, J=6.5, 3H), 0.76 – 0.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 154.0, 151.0, 134.2, 131.1, 129.4, 123.9, 68.9, 63.4, 50.0, 40.8, 40.1, 39.3, 37.4, 35.0, 34.4, 31.0, 29.8, 29.7, 25.1, 24.9, 24.9, 23.7, 22.7, 22.4; HRMS calcd for $C_{30}H_{48}O_4SNa^+$ [M+Na+] 527.3171 found 527.3171.

Silyl Sulfonate 2.43: To a stirred solution of sulfonate **2.42** (18.5 mg, 0.0367 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 mL) were added imidazole (7.5 mg, 0.11 mmol, 3.0 equiv) and TBS-Cl (8.3 mg, 0.055 mmol, 1.5 equiv). After stirring for 0.5 h at ambient temperature, the reaction mixture was concentrated. The resulting crude product was purified by flash

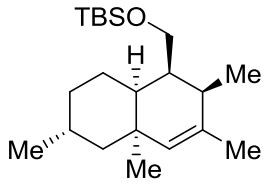
column chromatography (silica gel, acetone:hexanes, 1:19) providing pure silyl sulfonate **2.43** as a yellow oil (21.5 mg, 0.0348 mmol, 95% yield).

2.43: R_f = 0.46 (silica, acetone:hexanes, 1:9); $[\alpha]_D^{22}$ = +28.2 (*c* = 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.17 (s, 2H), 5.09 (d, J=1.3, 1H), 4.21 (dd, J=10.1, 4.1, 1H), 4.18 – 4.11 (m, 3H), 3.71 (dd, J=10.1, 6.8, 1H), 3.61 (dd, J=10.1, 8.4, 1H), 2.91 (hept, J=6.9, 1H), 2.46 (tt, J=7.7, 3.9, 1H), 2.33 (ddd, J=7.5, 4.0, 0.8, 1H), 1.67 (s, 3H), 1.53 – 1.47 (m, 2H), 1.45 (dd, J=9.0, 6.5, 2H), 1.36 (dd, J=12.9, 3.6, 2H), 1.28 – 1.23 (m, 18H), 1.18 (ddd, J=9.2, 5.7, 2.5, 1H), 0.93 (s, 3H), 0.85 (s, 9H), 0.79 (d, J=6.5, 3H), 0.74 – 0.65 (m, 1H), 0.01 (s, 3H), -0.01 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ = 153.7, 150.8, 134.2, 131.6, 129.9, 123.8, 68.5, 62.7, 50.2, 40.0, 39.5, 39.3, 37.2, 35. 1, 34.4, 31.0, 29.7, 26.0, 26.0, 25.8, 25.0, 24.9, 24.6, 23.7, 22.7, 22.5, 18.3, -3.4, -5.2, -5.3; HRMS calcd for $C_{36}H_{62}O_4SSiNa^+$ [M+Na^+] 641.4036 found 641.4037.



2.43

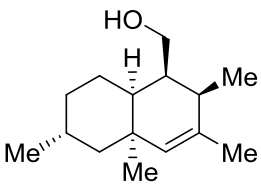
Silyl Decalin 2.44: A solution of silyl sulfonate **2.43** (7.7 mg, 0.0125 mmol, 1.0 equiv) and $LiBEt_3H$ (1.0 M in THF, 0.06 mL, .06 mmol, 5.0 equiv) in THF (0.12 mL) was heated under microwave irradiation at 80 °C for 4 min. The reaction mixture was then concentrated and the resulting crude product was purified by flash column chromatography (silica gel, acetone:hexanes, 1:19) providing pure silyl decalin **2.44** as a yellow oil (3.5 mg, 0.0104 mmol, 83% yield).



2.44

2.44: R_f = 0.55 (silica, acetone:hexanes, 1:9); $[\alpha]_D^{24}$ = +30.1 (*c* = .29, $CHCl_3$); ^{1}H NMR (500 MHz, cdcl3) δ = 5.01 (s, 1H), 3.75 (dd, J=9.6, 8.4, 1H), 3.60 (dd, J=9.8, 7.0, 1H), 2.34 (qd, J=7.7, 2.5, 1H), 2.16 (p, J=7.3, 1H), 1.69 (s, 3H), 1.55 (s, 1H), 1.47 (dt, J=13.2, 2.8, 1H), 1.40 (dd, J=7.0, 3.5, 1H), 1.37 (d, J=2.9, 1H), 1.36 (d, J=3.5, 1H), 1.31 – 1.26 (m, 2H), 0.98 (d, J=7.6, 3H), 0.95 (s, 3H), 0.90 (s, 9H), 0.80 (d, J=6.5, 4H), 0.73 – 0.64 (m, 1H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, CDCl3) δ = 136.0, 131.0, 64.1, 50.6, 41.6, 38.8, 37.2, 35.6, 33.9, 31.5, 29.7, 26.1, 25.1, 22.9, 22.5, 18.4, 14.1, -5.1, -5.2; HRMS calcd for $C_{21}H_{41}OSi$ [M+H^+] 337.2927 found 337.2925.

Hydroxy Decalin 2.45; To a stirred solution of silyl decalin **2.44** (3.5 mg, 0.0104 mmol, 1.0 equiv) in CH_2Cl_2 (0.1 mL) was added a solution of TBAF (1.0 M in THF, 0.016 mL, 0.016 mmol, 1.5 equiv). After stirring for 10 min at ambient temperature, the reaction mixture was then concentrated *in vacuo* and the resulting crude product was purified by flash column chromatography (silica gel, acetone:hexanes, 1:9) providing pure hydroxy decalin **2.45** as a white amorphous solid (2.2 mg, 0.00989 mmol, 95% yield).

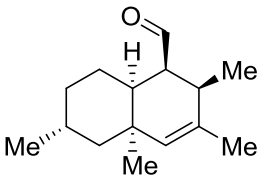


2.45

2.45: R_f = 0.18 (silica, acetone:hexanes, 1:9); $[\alpha]_D^{21}$ = +35.8 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.05 (s, 1H), 3.84 (dd, J=10.3, 8.2, 1H), 3.71 (dd, J=10.4, 7.2, 1H), 2.40 (qd, J=7.6, 2.5, 1H), 2.21 (p, J=7.5, 1H), 1.71 (s, 3H), 1.62 – 1.56 (m, 2H), 1.53 – 1.48 (m, 2H), 1.44 (d, J=3.6, 1H), 1.41 (s, 1H), 1.38 (d, J=3.2, 1H), 1.32 – 1.30 (m, 1H), 1.30 – 1.27 (m, 2H), 1.03 (d, J=7.6, 3H), 0.98 (s, 3H), 0.82 (d, J=6.6, 4H), 0.76 – 0.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 135.6, 131.0, 64.2, 50.5, 41.6, 39.0, 37.2,

35.5, 33.8, 31.5, 29.7, 25.1, 22.8, 22.4, 14.2; HRMS calcd for $C_{15}H_{27}O^+$ [M+H^+] 223.2056 found 223.2061.

Decalin aldehyde 2.13: To a stirred solution of hydroxy decalin **2.45** (2.2 mg, 0.00989 mmol, 1.0 equiv) in CH_2Cl_2 (0.3 mL) at 0°C was added DMP (8.4 mg, 0.0197, 2.0 equiv). The resulting mixture was stirred for 15 min before it was quenched with sat. aq. $NaHCO_3$/ sat. aq. $Na_2S_2O_3$ (1:1, 0.5 mL) and extracted with CH_2Cl_2 (3 × 0.5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, acetone:hexanes, 1: 9) providing pure decalin aldehyde **2.13** as a white amorphous solid (1.7 mg, 0.0077 mmol, 78% yield).

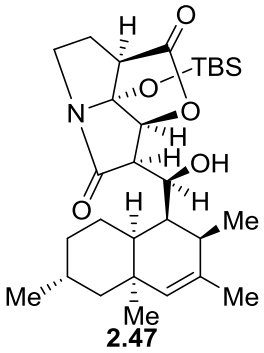


2.21

2.13: R_f = 0.50 (silica, acetone:hexanes, 1:9); $[\alpha]_D^{23}$ = +15.9 (c = 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.91 (s, 1H), 5.08 (d, J=1.2, 1H), 2.96 (dd, J=7.2, 3.1, 1H), 2.66 – 2.58 (m, 1H), 1.89 (d, J=12.7, 1H), 1.73 (s, 3H), 1.64 – 1.62 (m, 1H), 1.62 – 1.60 (m, 1H), 1.56 – 1.52 (m, 1H), 1.42 – 1.35 (m, 1H), 1.35 – 1.29 (m, 2H), 1.18 (d, J=7.4, 3H), 0.96 (s, 3H), 0.84 (d, J=6.5, 3H), 0.80 (m, J=12.4, 3.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 206.0, 134.7, 131.3, 51.1, 50.0, 40.2, 37. 0, 35.3, 32.5, 31.3, 29.8, 26.4, 22.8, 22.0, 16.5.; HRMS calcd for $C_{15}H_{25}O$ [M+H^+] 221.1905 found 221.1906.

Alcohols (±)-2.36, (±)-2.37, and 2.47: General procedure for Reformatsky-type coupling: To a stirred solution of decalin aldehyde **2.13** (3.4 mg, 0.0153 mmol, 1.0 equiv) and iodide **(–)-2.12** (19.5 mg, 0.046 mmol, 3.0 equiv) in toluene (0.3 mL) at -78°C was added BEt_3 (1.0 M in hexanes, 0.5 mL, 0.046 mmol, 3.0 equiv). The resulting mixture was

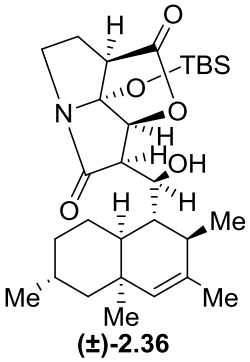
stirred for 1 h before H_2O was added (0.3 mL). The reaction was warmed to ambient temperature and extracted with Et_2O (3 × 0.5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting crude product was purified by flash column chromatography (silica gel, EtOAc:hexanes, 1:9) providing pure coupling product **2.47** as a white amorphous solid (7.6 mg, 0.0069 mmol, 95% yield).



2.47

2.47: R_f = 0.47 (silica, acetone:hexanes, 3:7); $[\alpha]_D^{19}$ = +5.08 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.04 (d, J=1.1, 1H), 4.78 (d, J=4.1, 1H), 4.34 – 4.28 (m, 1H), 3.91 – 3.84 (m, 1H), 3.62 (s, 1H), 3.39 – 3.29 (m, 2H), 3.12 (dd, J=8.6, 2.4, 1H), 2.68 – 2.50 (m, 2H), 2.49 – 2.43 (m, 1H), 2.18 – 2.11 (m, 1H), 2.00 (dd, J=13.3, 3.5, 1H), 1.71 (s, 3H), 1.66 – 1.56 (m, 2H), 1.53 (dd, J=13.1, 2.7, 1H), 1.42 (dd, J=12.1, 4.0, 1H), 1.36 – 1.29 (m, 2H), 1.20 (d, J=7.6, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.82 (d, J=6.5, 3H), 0.74 (ddd, J=15.5, 13.4, 3.4, 1H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.2, 174.8, 136.0, 130.8, 100.8, 82.9, 70.3, 50.7, 49.6, 49.3, 42.5, 40.9, 38.7, 37.9, 36.8, 35.8, 31.6, 29.9, 29.7, 29.0, 25.9, 25.5, 22.8, 22.3, 17.9, 15.7, -3.2, -3.5.; HRMS calcd for $C_{29}H_{48}NO_5Si^+$ [*M*+H+] 518.3296 found 518.3300.

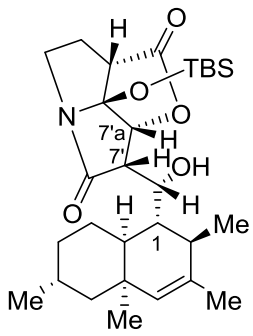
(±)-2.36: ^{1}H NMR (500 MHz, C_6D_6) δ: 5.20 (s, 1H), 4.81 (br d, 1H, *J* = 0.9), 4.41 (d, 1H, *J* = 3.8), 4.38 (dt, 1H, *J* = 8.5, 3.0), 3.40 (m, 1H, H-4'), 3.21 (dd, 1H, *J* = 8.7, 3.8), 2.81 (br d, 1H, *J* = 7.5), 2.64 (m, 1H), 2.35 (d, 1H, *J* = 8.3), 2.03 (m, 1H), 1.78 (s, 3H), 1.71-1.49 (m, 9H), 1.32 (s, 3H), 1.24 (d, 3H, *J* = 7.5), 0.96 (m, 1H), 0.90 (d, 3H, *J* = 7.0), 0.79 (br s, 9H), -0.12 (s, 3H), -0.22 (s,



(±)-2.36

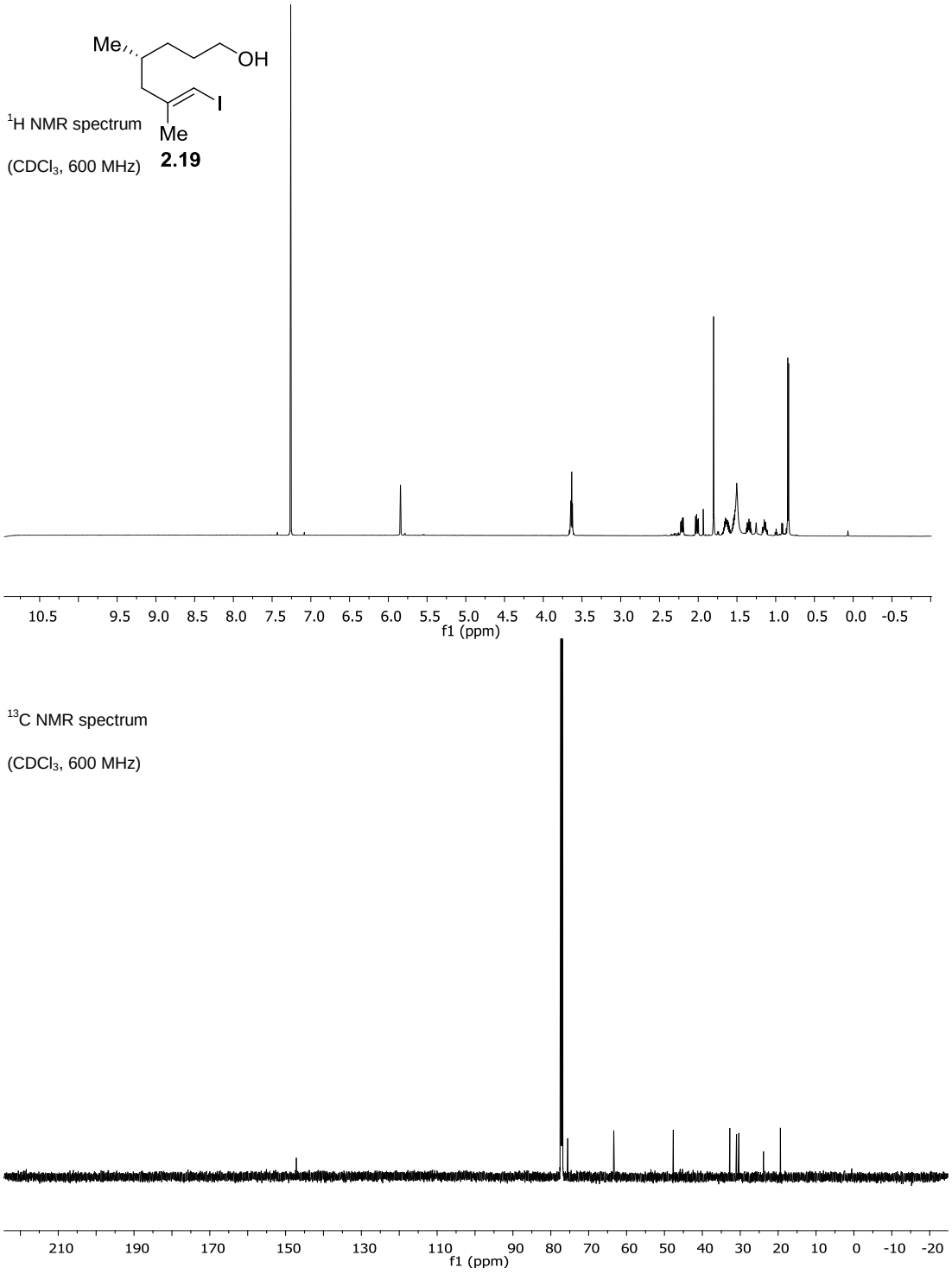
3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 177.1, 173.7, 134.6, 131.5, 100.4, 82.6, 73.0, 51.6, 51.3, 50.9, 49.2, 45.9, 42.5, 36.3, 35.4, 33.7, 30.7, 29.9, 29.4, 28.7, 25.4, 23.2, 22.8, 22.7, 17.8, -3.6, -4.0; HRMS *m/z* 540.3107 $[M+Na]^+$ (calcd for $C_{29}H_{47}NO_5SiNa$, 540.3116).

(±)-2.37: ^{1}H NMR (500 MHz, C_6D_6) δ: 5.40 (s, 1H), 4.87 (s, 1H), 4.40 (d, 1H, *J* = 10.0), 4.29 (d, 1H, *J* = 3.5), 3.42 (dt, 1H, *J* = 10.5, 7.5), 3.26 (dd, 1H, *J* = 10.0, 3.5), 2.65 (m, 1H), 2.57 (br t, 1H, *J* = 7.0), 2.33 (d, 1H, *J* = 8.5), 2.05 (ddd, 1H, *J* = 14.0, 9.0, 3.0), 1. 87 (dd, 1H, *J* = 12.5, 4.0), 1.77 (s, 3H), 1.73 (m, 1H), 1.67-1.61 (m, 2H), 1.53-1.45 (m, 2H), 1.36 (s, 3H), 1.32-1.28 (m, 2H), 1.15 (d, 3H, *J* = 7.0), 1.09 (m, 1H), 1.22 (m, 1H), 0.94 (d, 3H, *J* = 6.5), 0.79 (br s, 9H), -0.12 (s, 3H), -0.22 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ: 177.8, 173.7, 136.3, 132.6, 100.4, 82.1, 68.9, 53.3, 51.4, 49.7, 49.1, 42.2, 40.5, 37.2, 36.9, 36.0, 32.3, 30.3, 29.3, 28.6, 25.3, 22.9, 21.8, 19.3, 17.8, -3.7, -4.0; HRMS calcd for $C_{29}H_{48}NO_5Si^+$ [*M*+H+] 518.3296 found 518.3297.

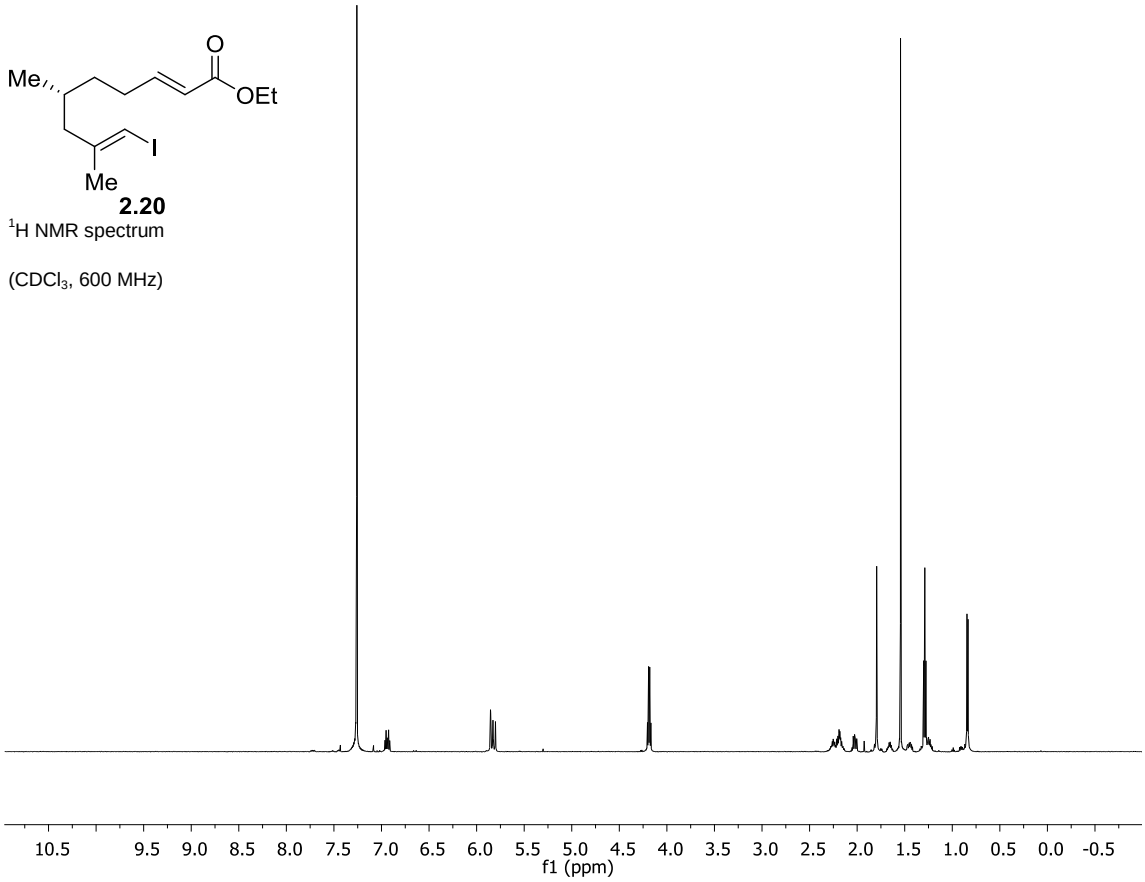


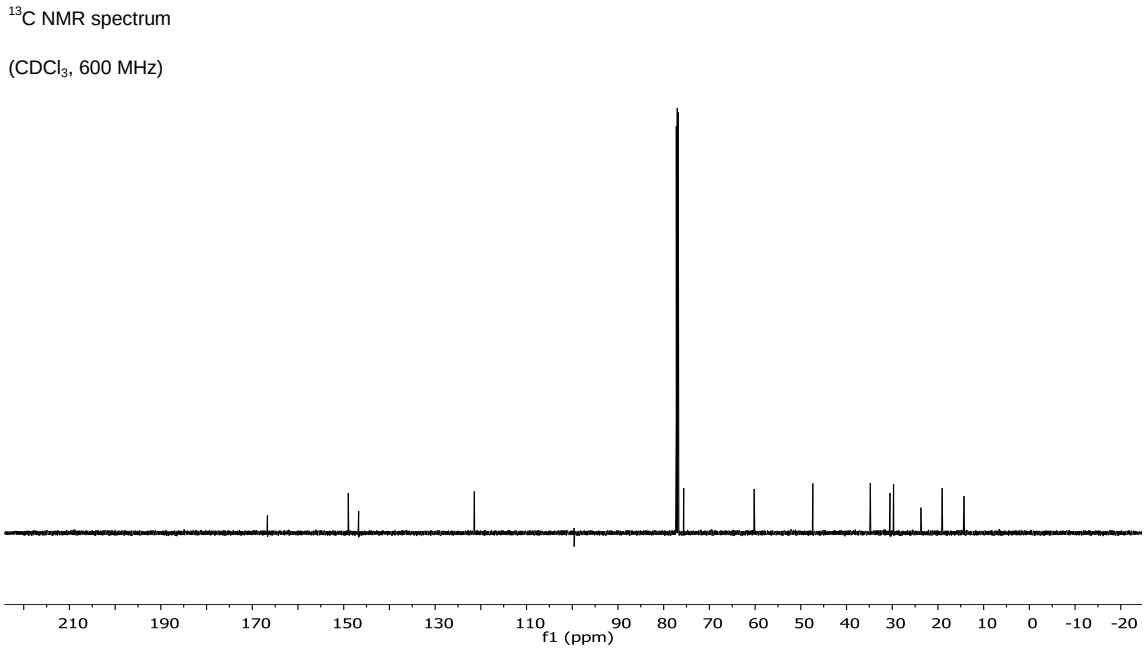
(±)-2.37

3. List of Spectra

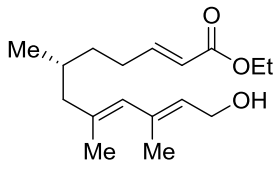


Spectra **2.01**: Compound **2.19**: ^{1}H NMR (top) and ^{13}C NMR (bottom)





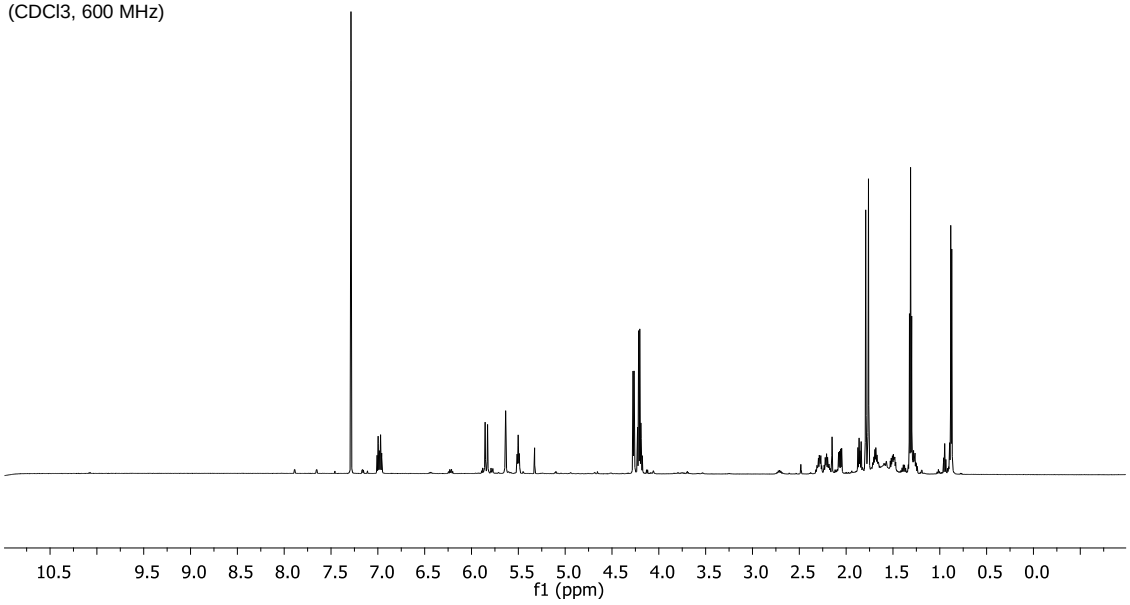
Spectra **2.02**: Compound **2.20**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.23

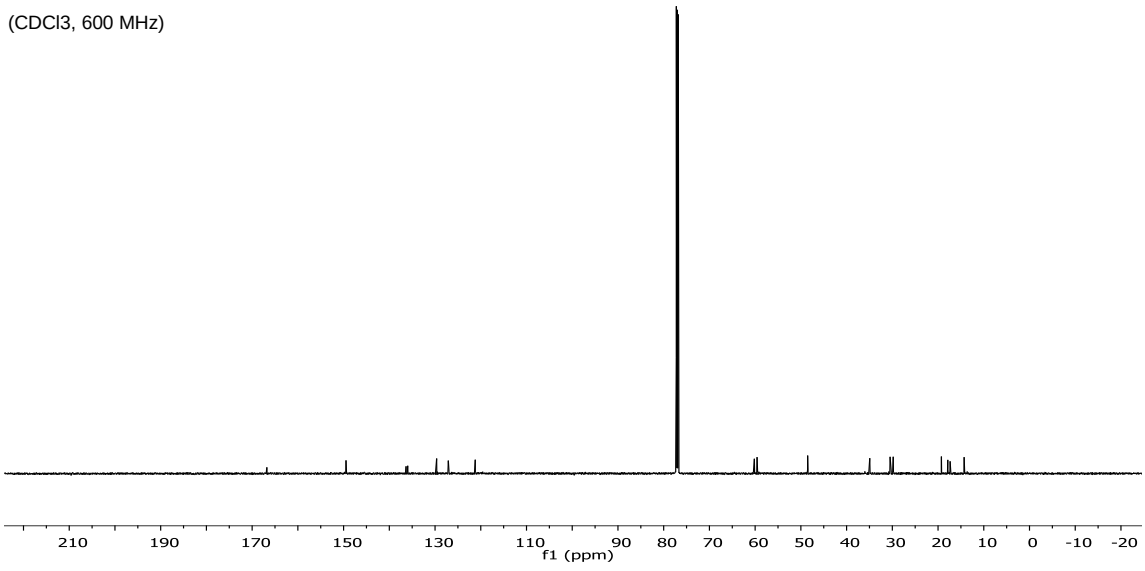
^{1}H NMR spectrum

(CDCl3, 600 MHz)

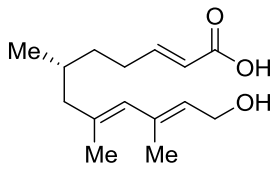


^{13}C NMR spectrum

(CDCl3, 600 MHz)



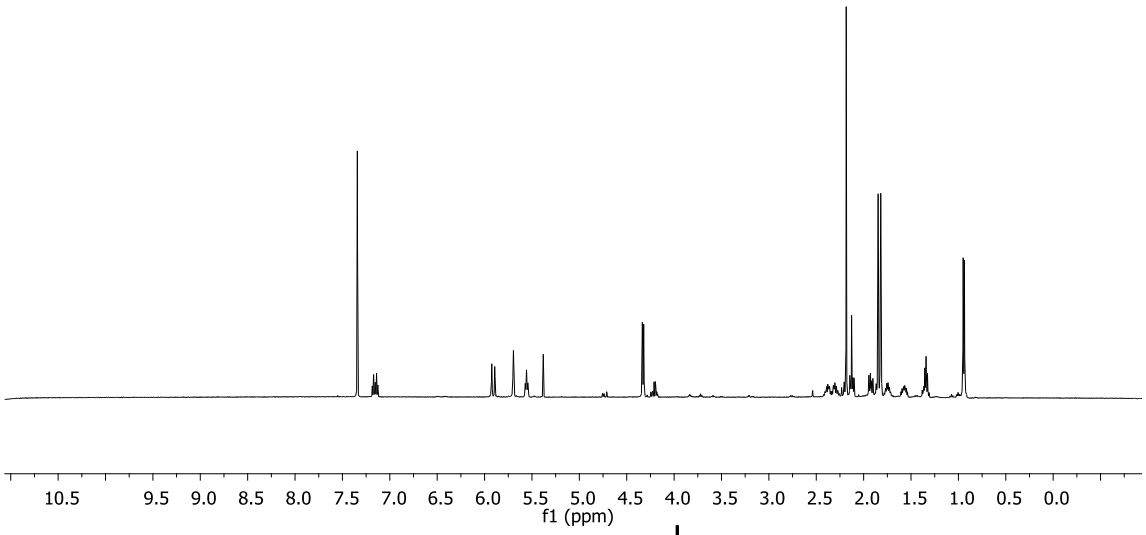
Spectra **2.03**: Compound **2.23**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.15

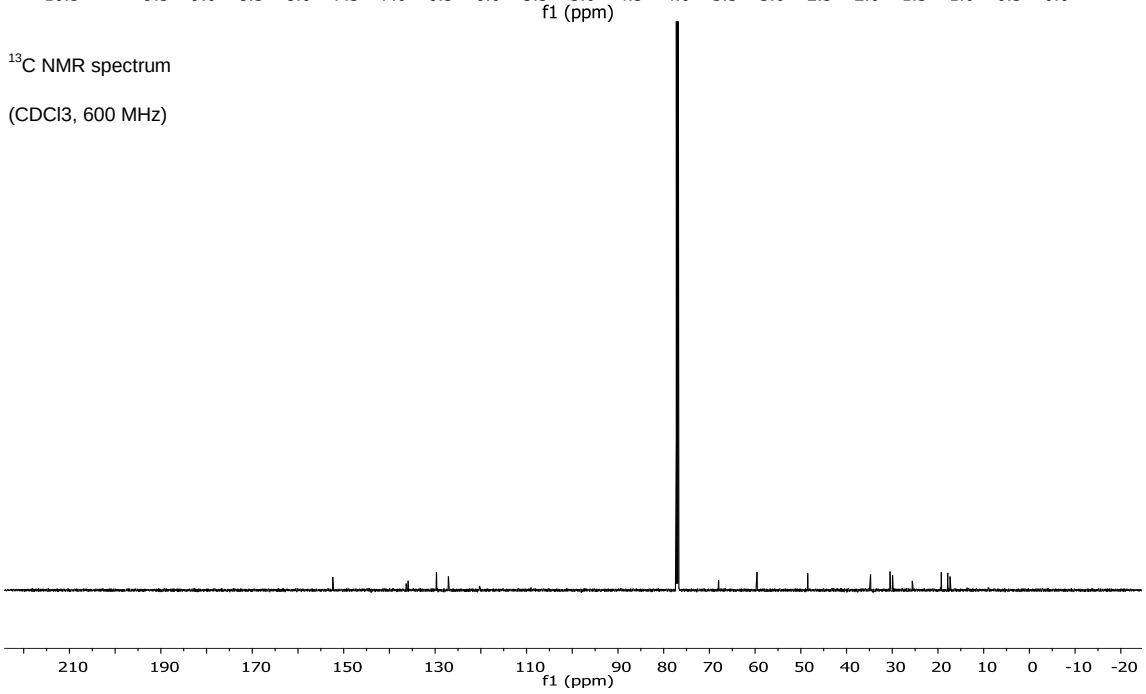
^{1}H NMR spectrum

(CDCl3, 600 MHz)

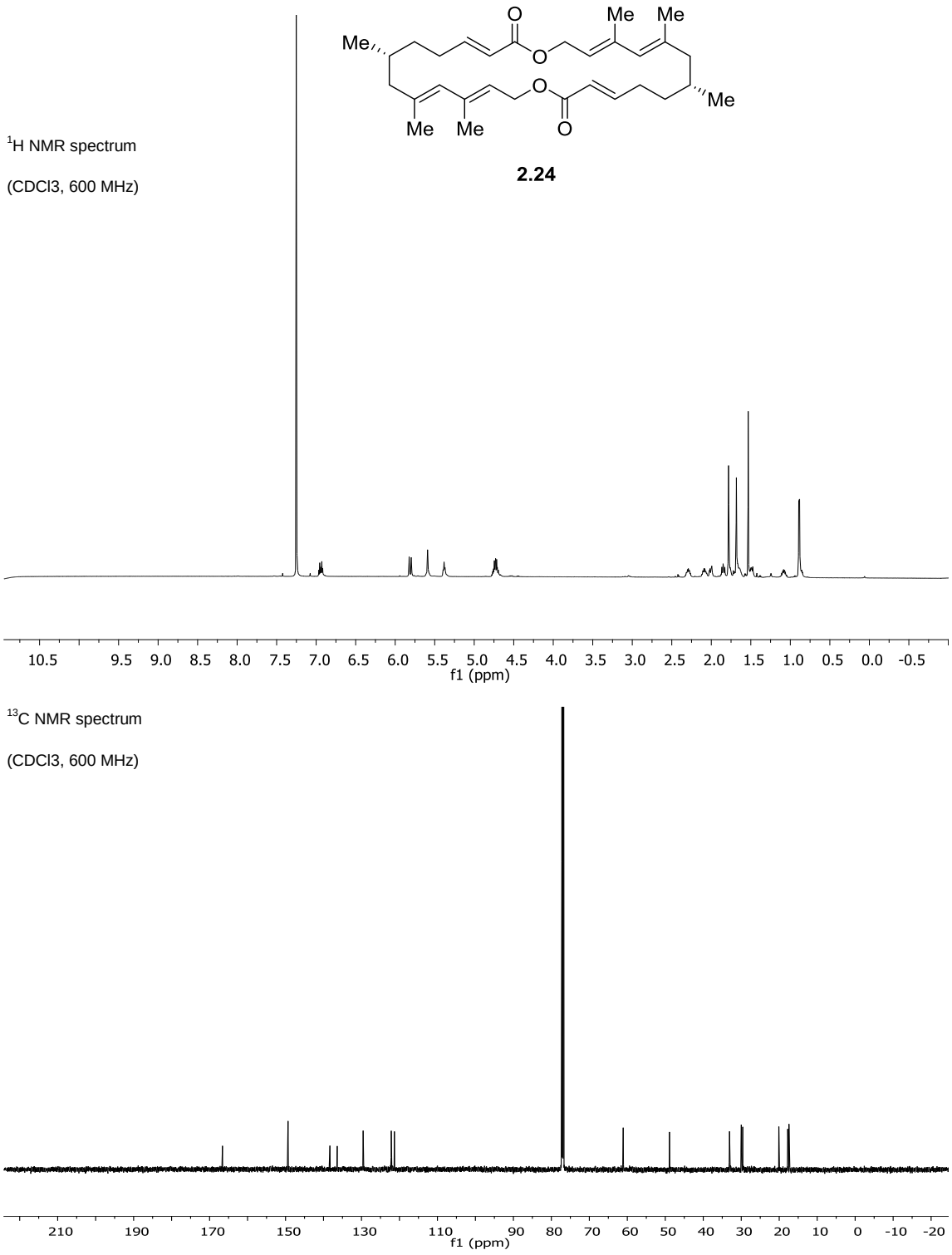


^{13}C NMR spectrum

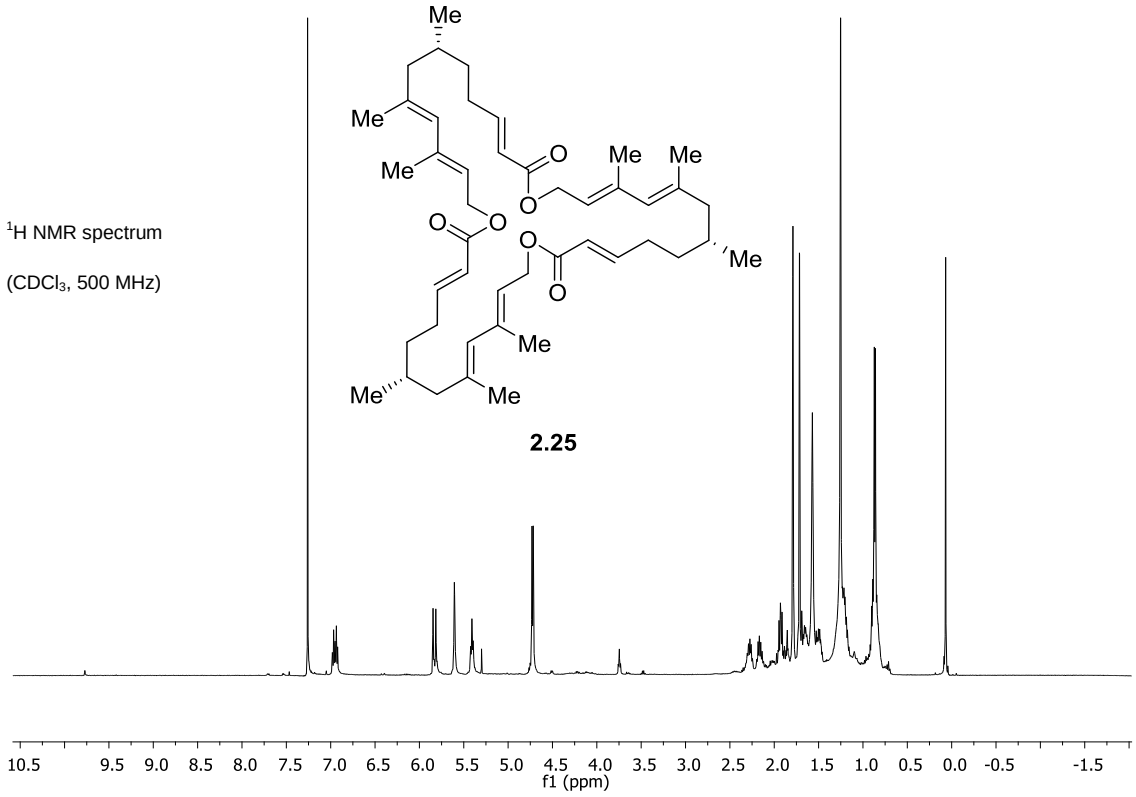
(CDCl3, 600 MHz)

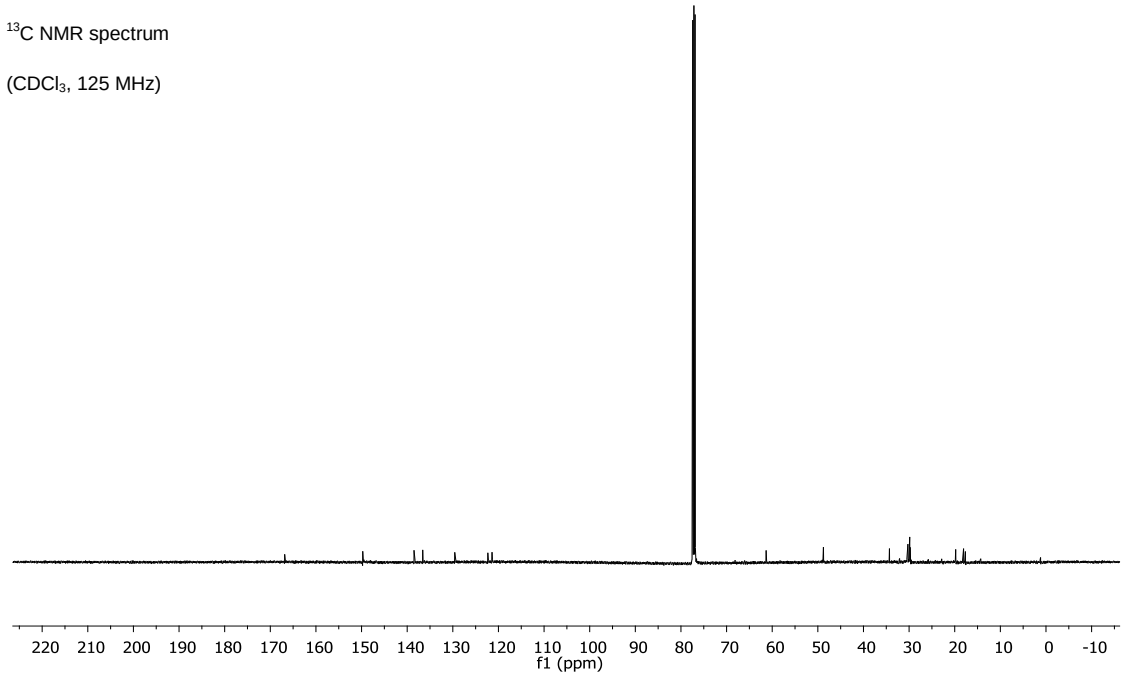


Spectra **2.04**: Compound **2.15**: ^{1}H NMR (top) and ^{13}C NMR (bottom)

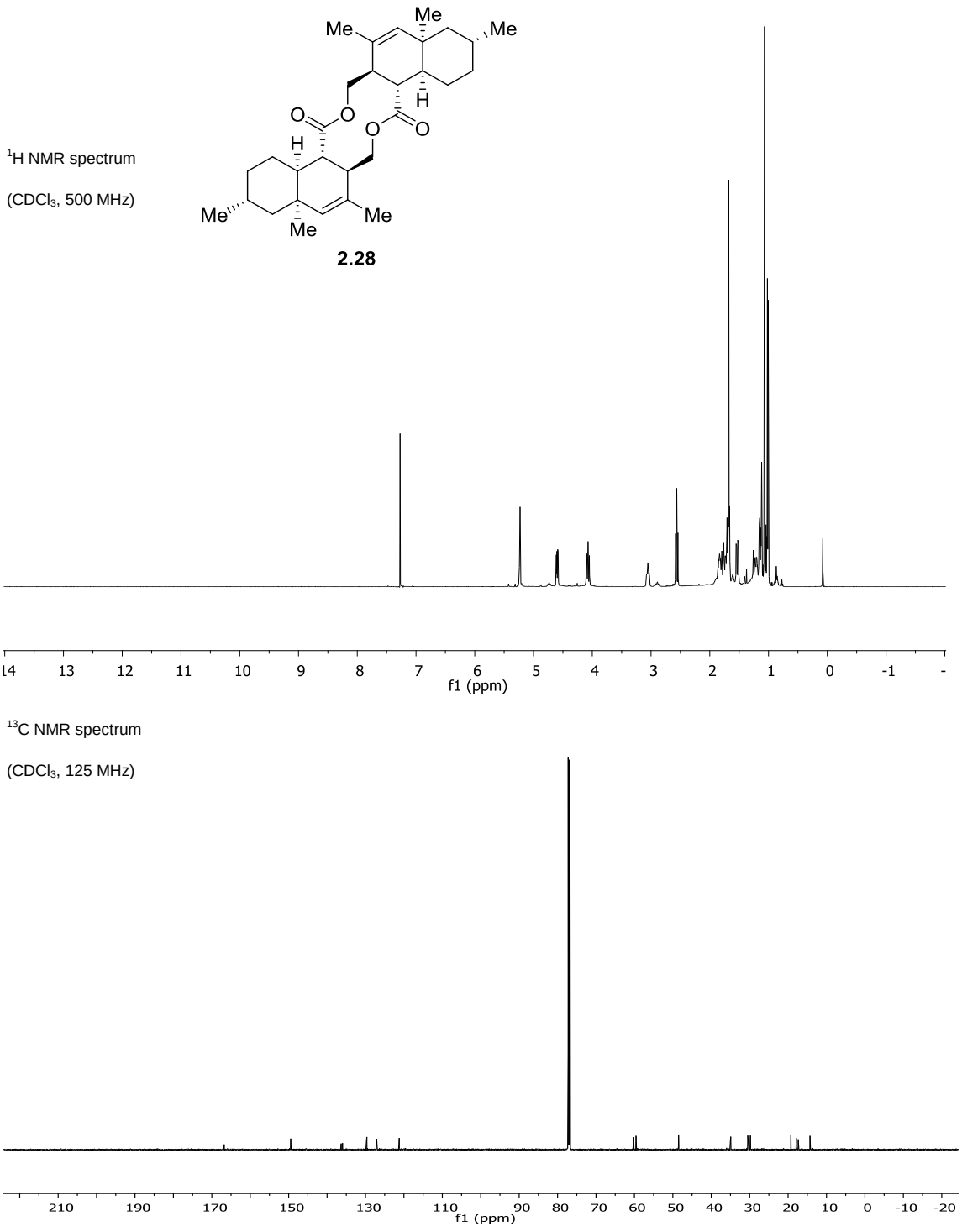


Spectra **2.05**: Compound **2.24**: ^{1}H NMR (top) and ^{13}C NMR (bottom)

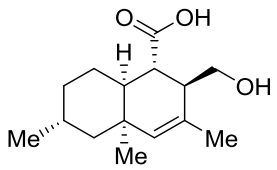




Spectra **2.06**: Compound **2.25**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



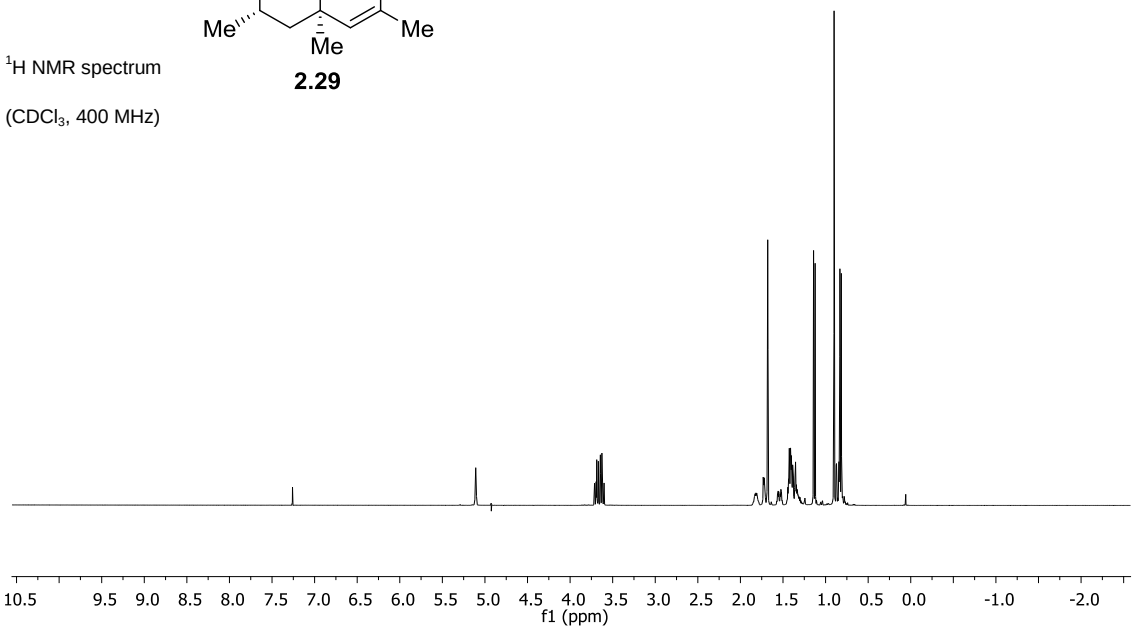
Spectra **2.07**: Compound **2.28**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.29

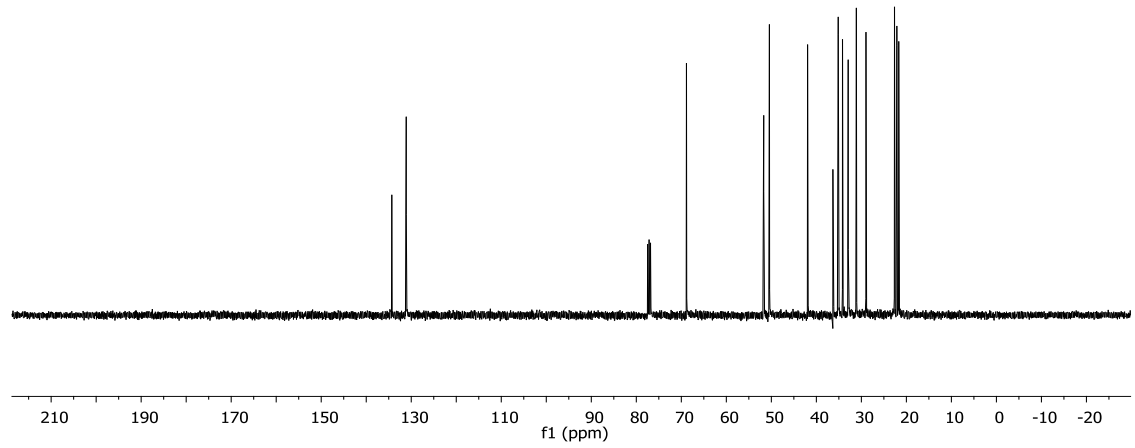
^{1}H NMR spectrum

($CDCl_3$, 400 MHz)

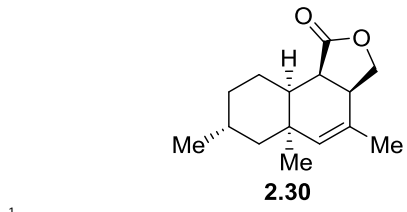


^{13}C NMR spectrum

($CDCl_3$, 400 MHz)



Spectra **2.08**: Compound **2.29**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



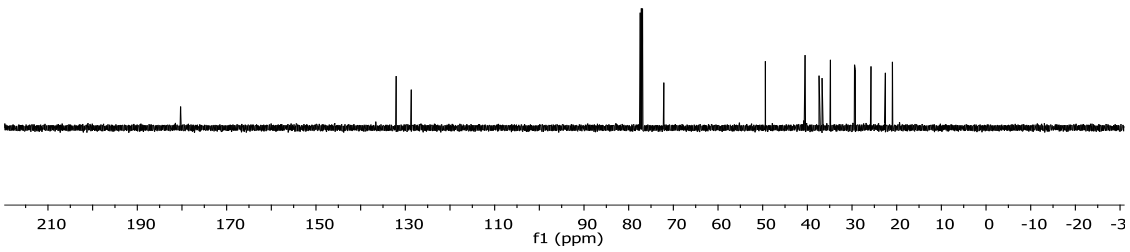
2.30

^{1}H NMR spectrum

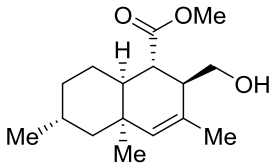
($CDCl_3$, 500 MHz)

^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



Spectra **2.09**: Compound **2.30**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



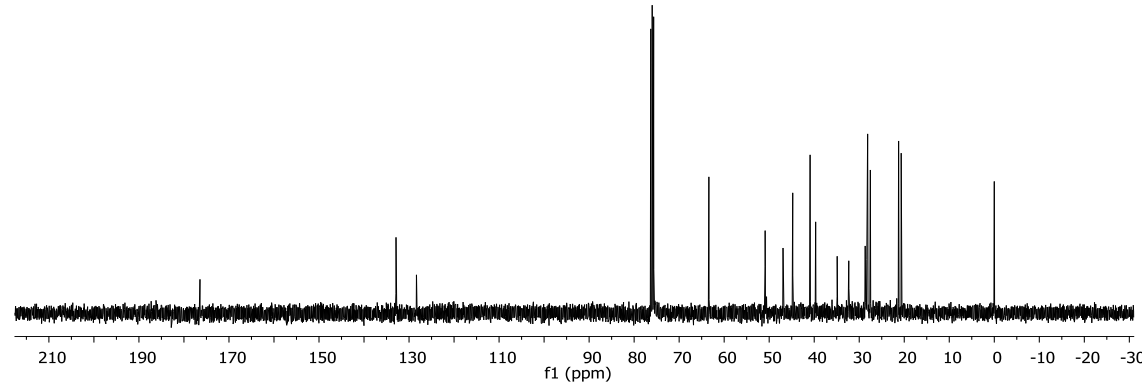
2.31

^{1}H NMR spectrum

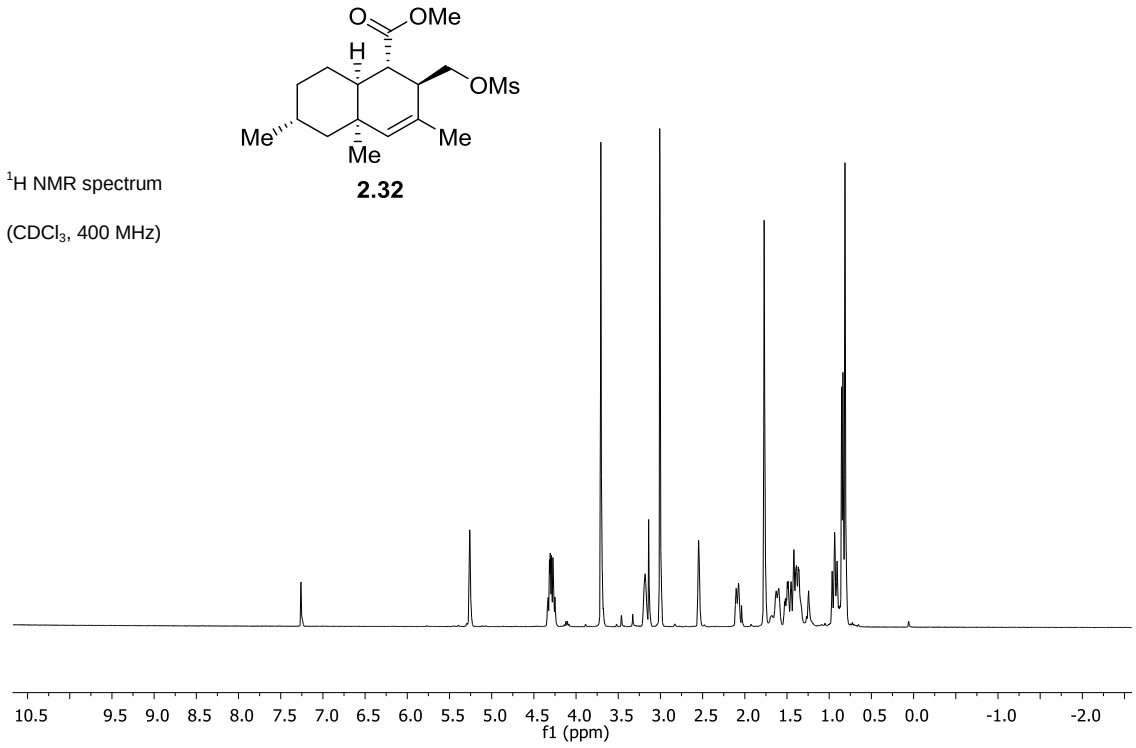
($CDCl_3$, 400 MHz)

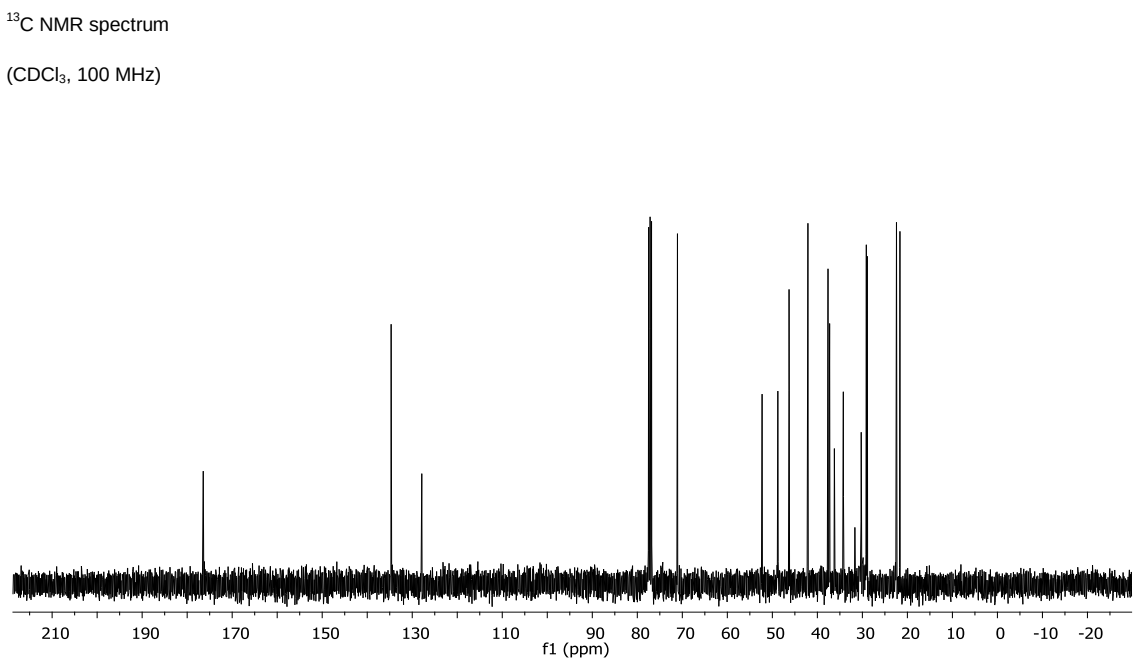
^{13}C NMR spectrum

($CDCl_3$, 100 MHz)

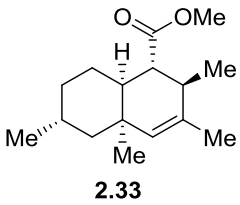


Spectra **2.10**: Compound **2.31**: ^{1}H NMR (top) and ^{13}C NMR (bottom)





Spectra **2.11**: Compound **2.32**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



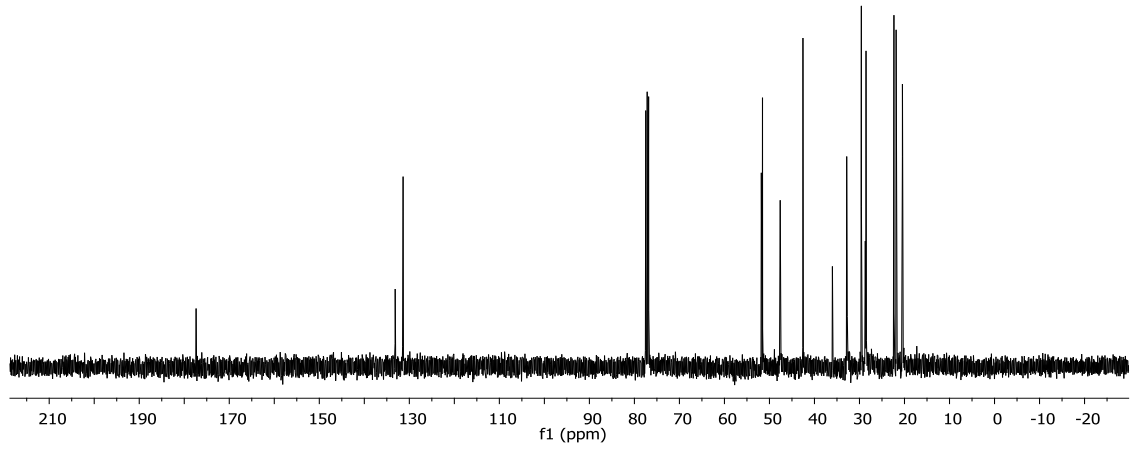
2.33

^{1}H NMR spectrum

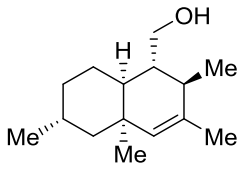
($CDCl_3$, 400 MHz)

^{13}C NMR spectrum

($CDCl_3$, 100 MHz)



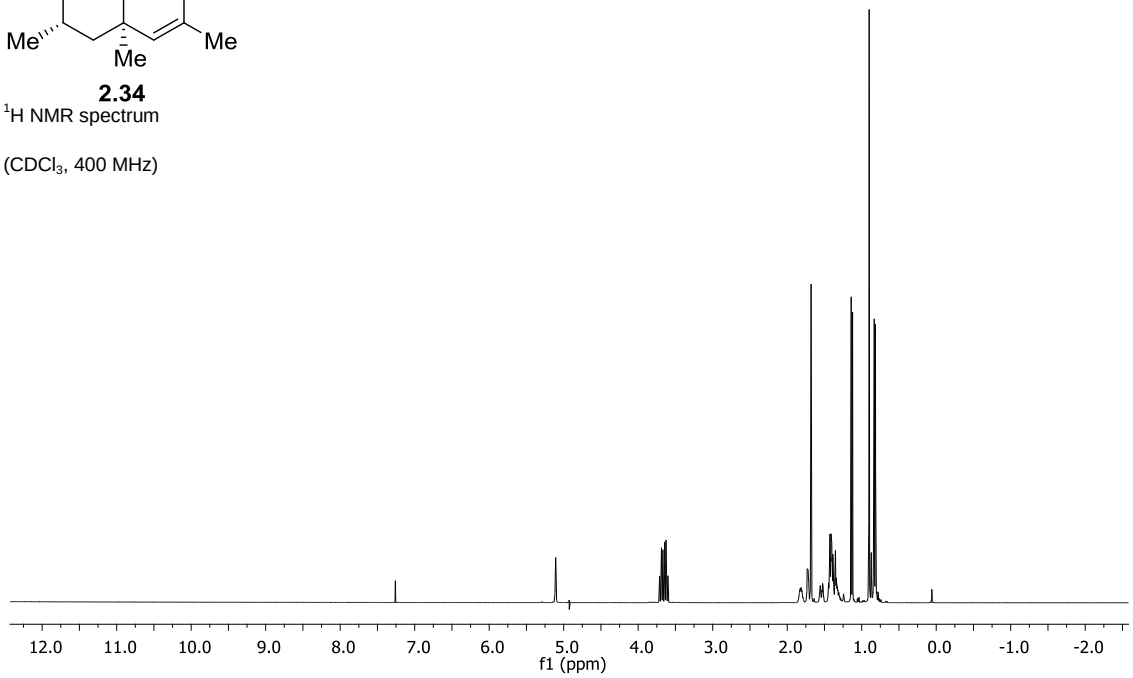
Spectra **2.12**: Compound **2.33**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.34

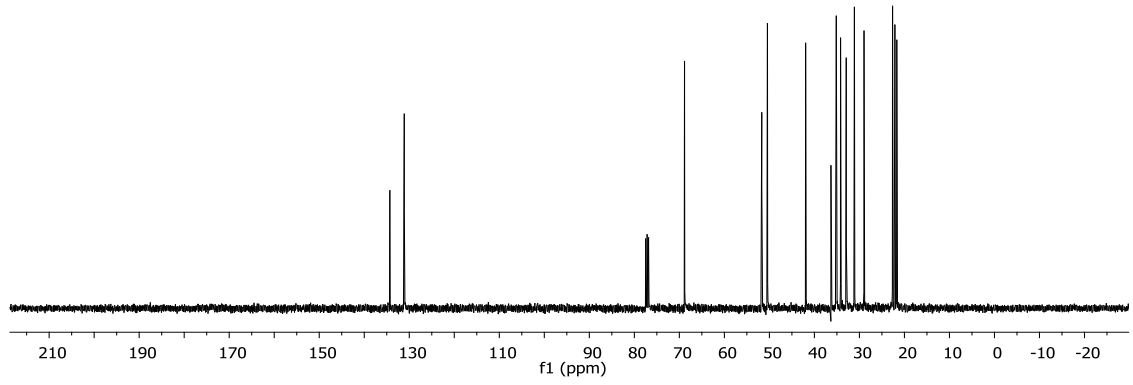
^{1}H NMR spectrum

($CDCl_3$, 400 MHz)

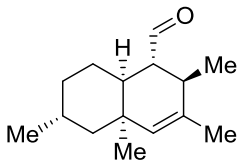


^{13}C NMR spectrum

($CDCl_3$, 100 MHz)



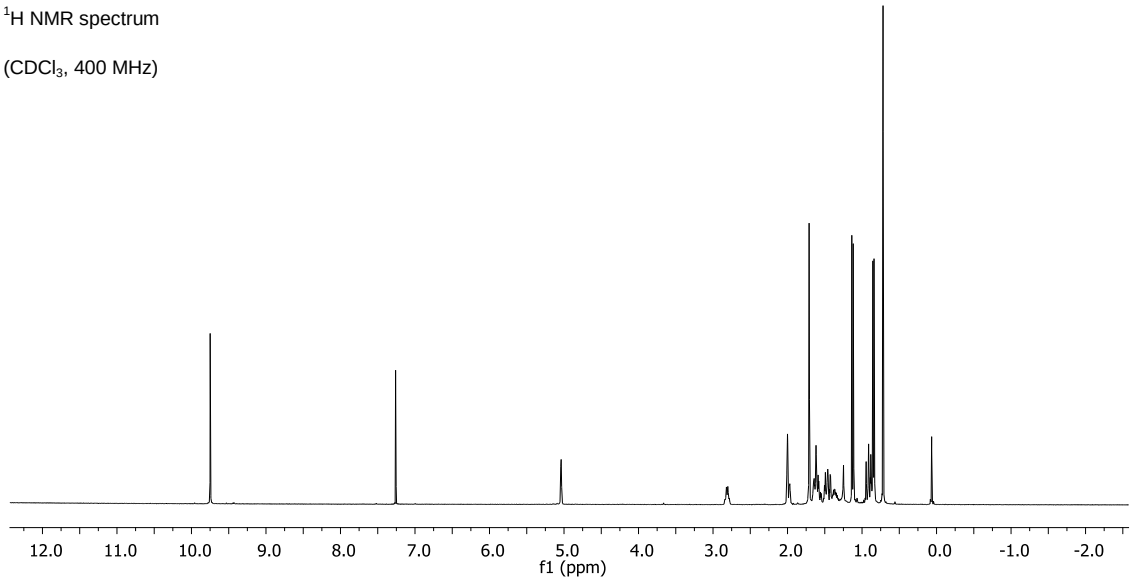
Spectra **2.13**: Compound **2.34**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.35

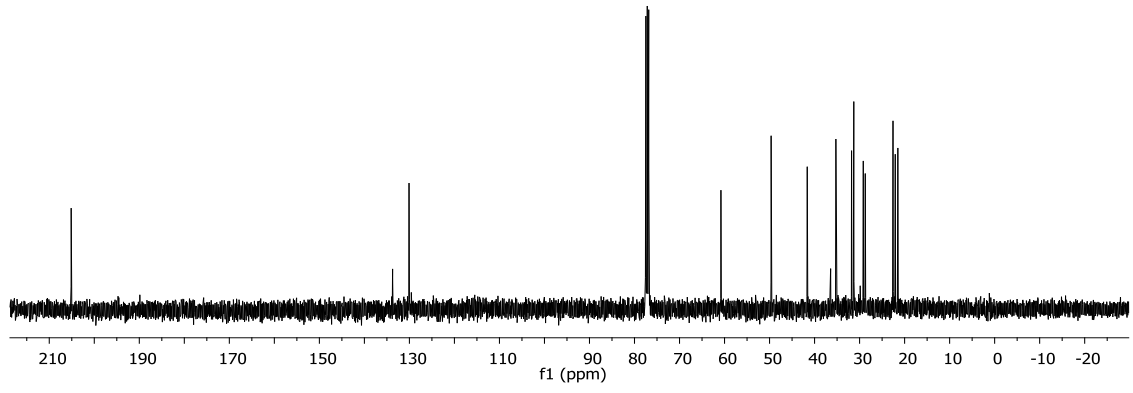
^{1}H NMR spectrum

($CDCl_3$, 400 MHz)

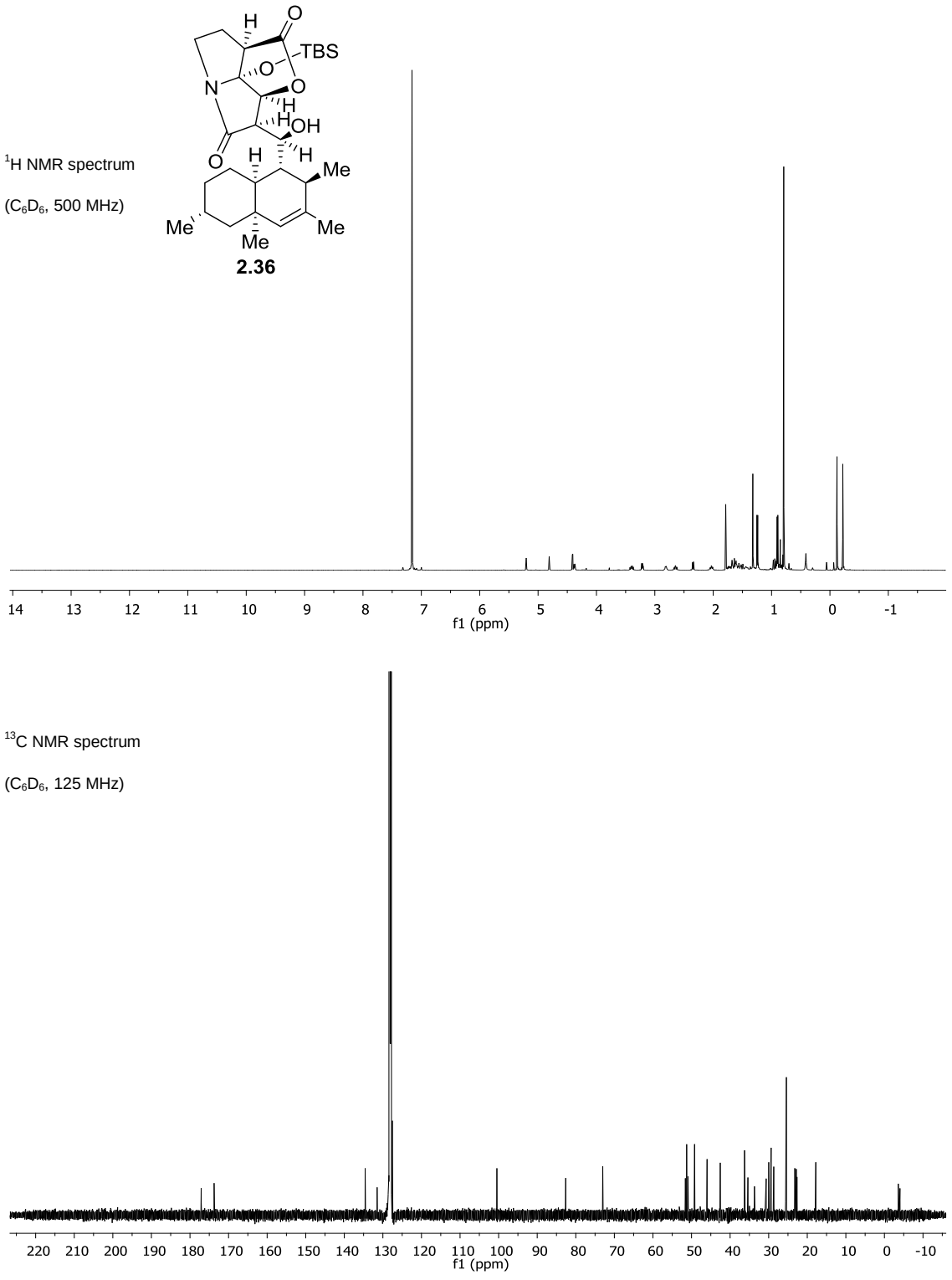


^{13}C NMR spectrum

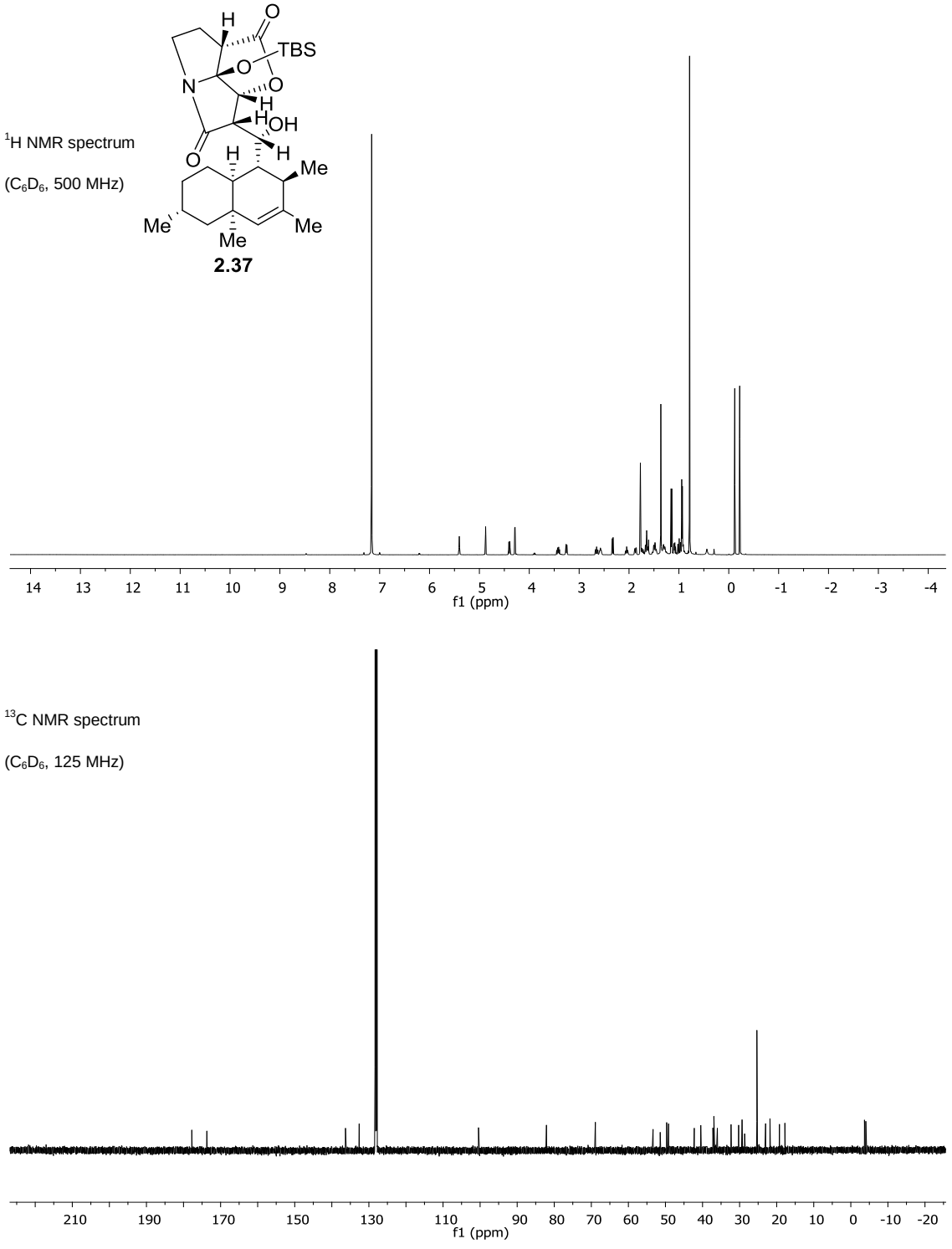
($CDCl_3$, 100 MHz)



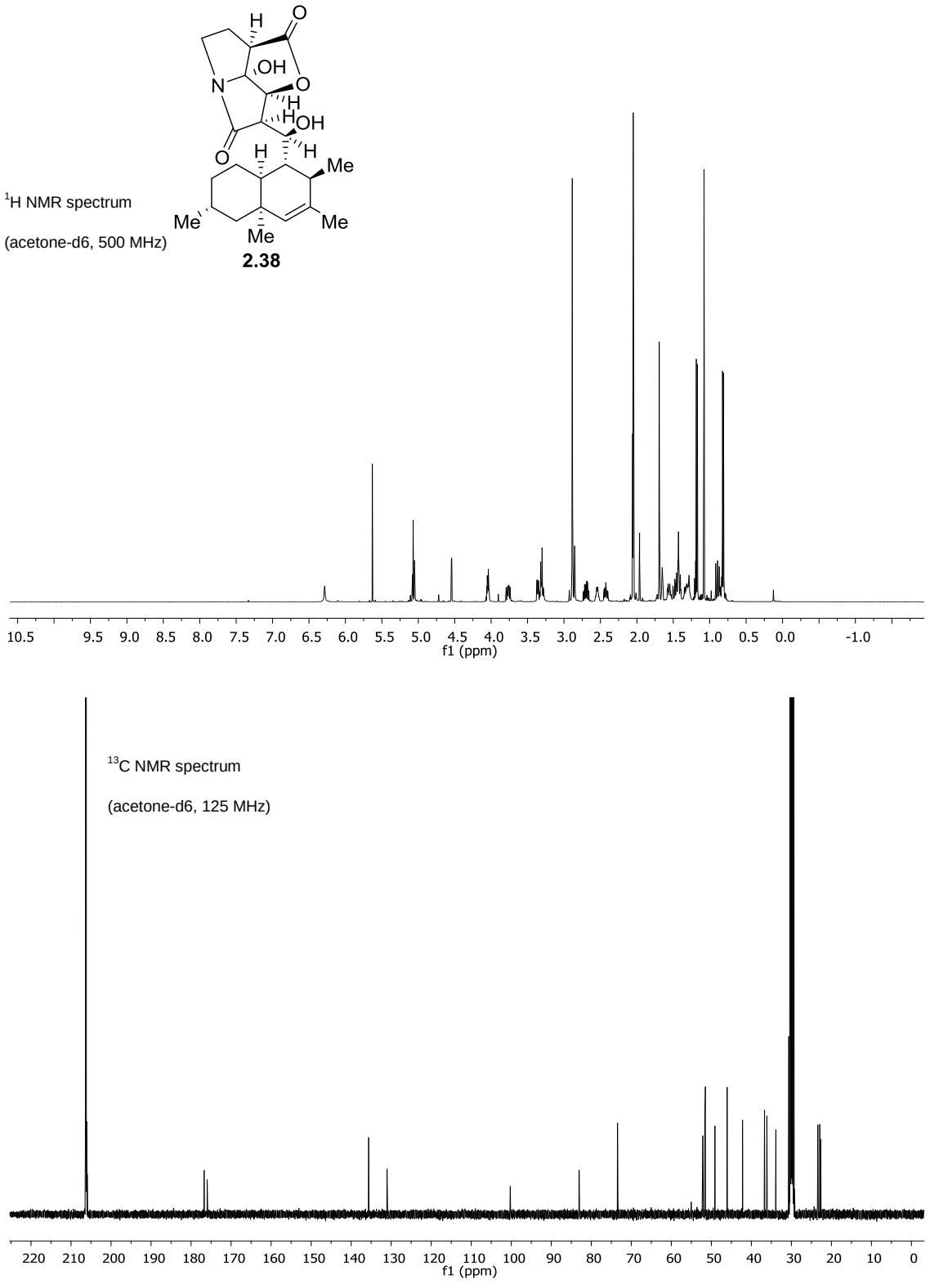
Spectra **2.14**: Compound **2.35**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



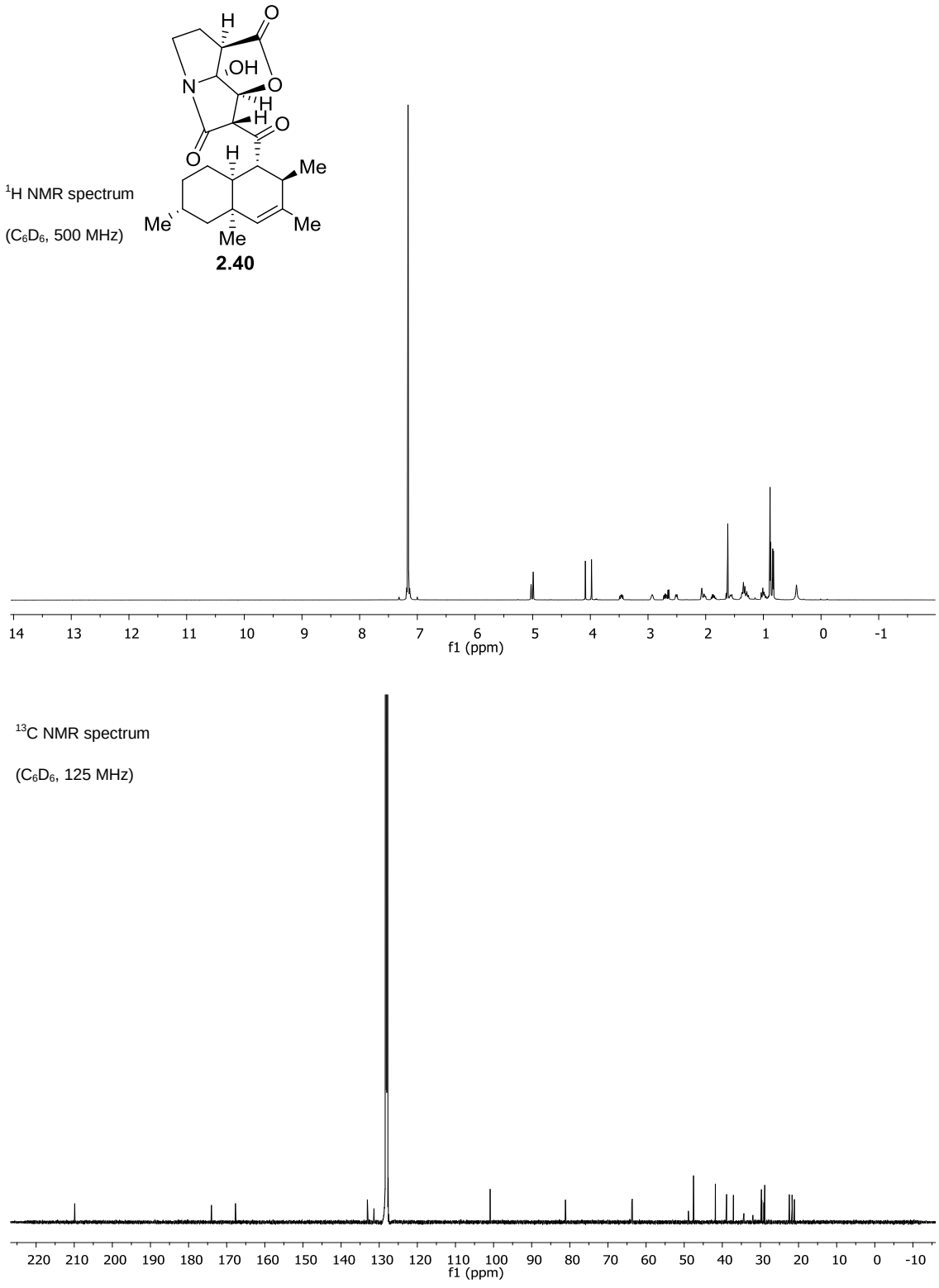
Spectra **2.15**: Compound **2.36**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



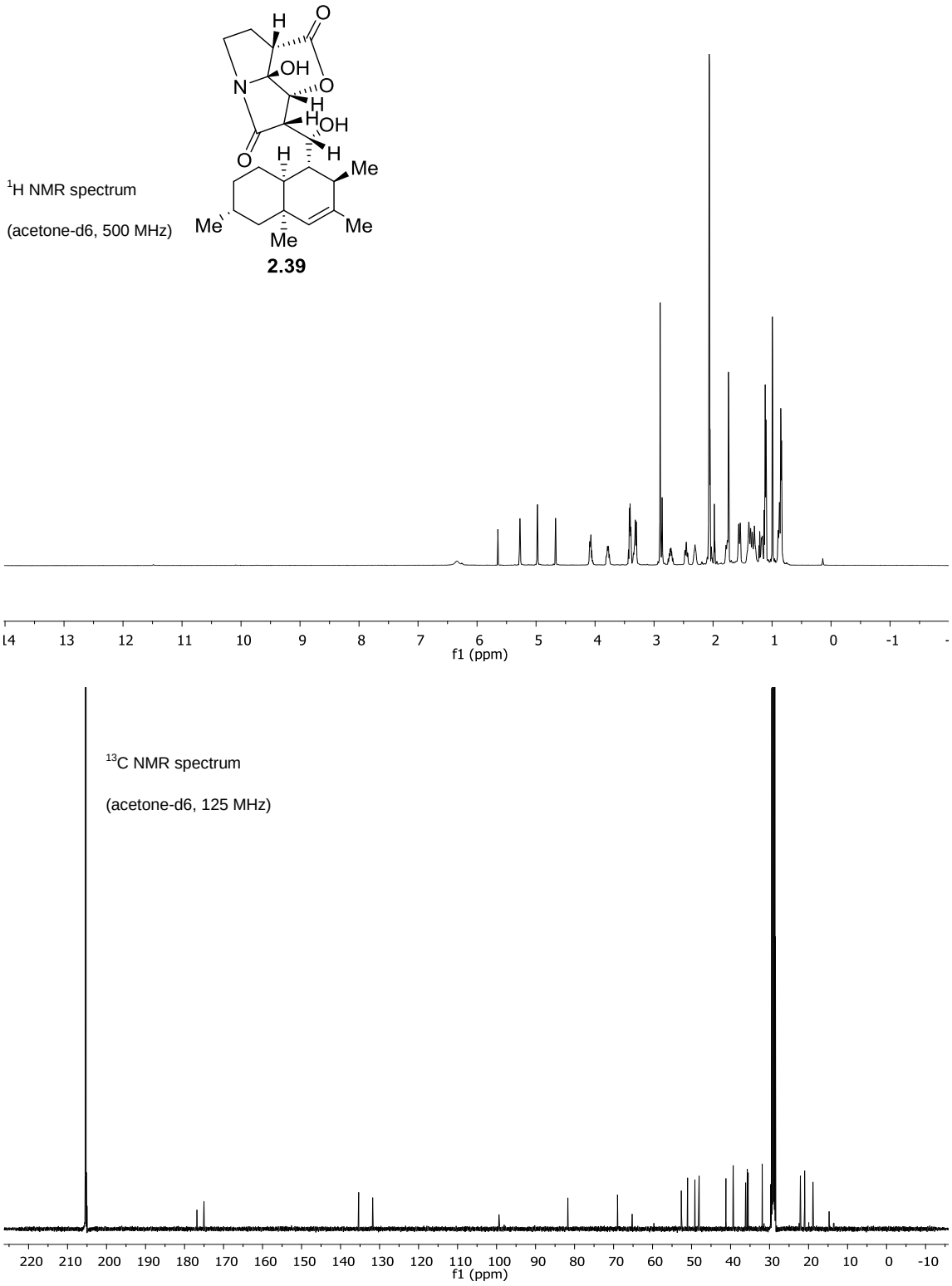
Spectra **2.16**: Compound **2.37**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



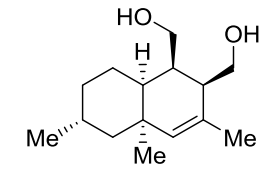
Spectra **2.17**: Compound **2.38**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



Spectra **2.18**: Compound **2.40**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



Spectra **2.19**: Compound **2.39**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



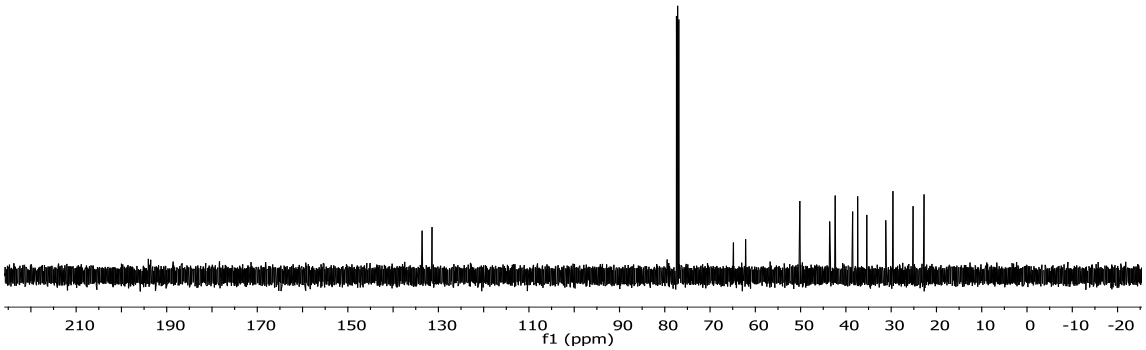
2.41

^{1}H NMR spectrum

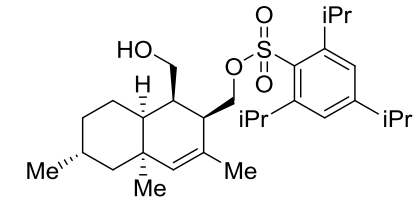
($CDCl_3$, 500 MHz)

^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



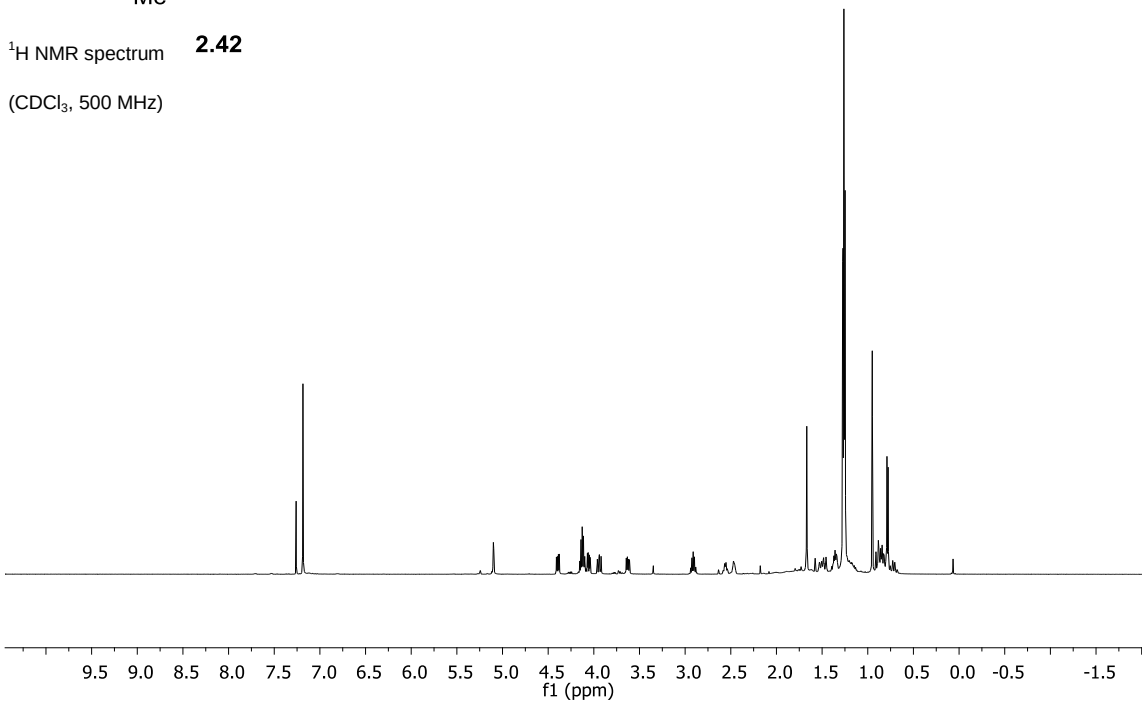
Spectra **2.20**: Compound **2.41**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.42

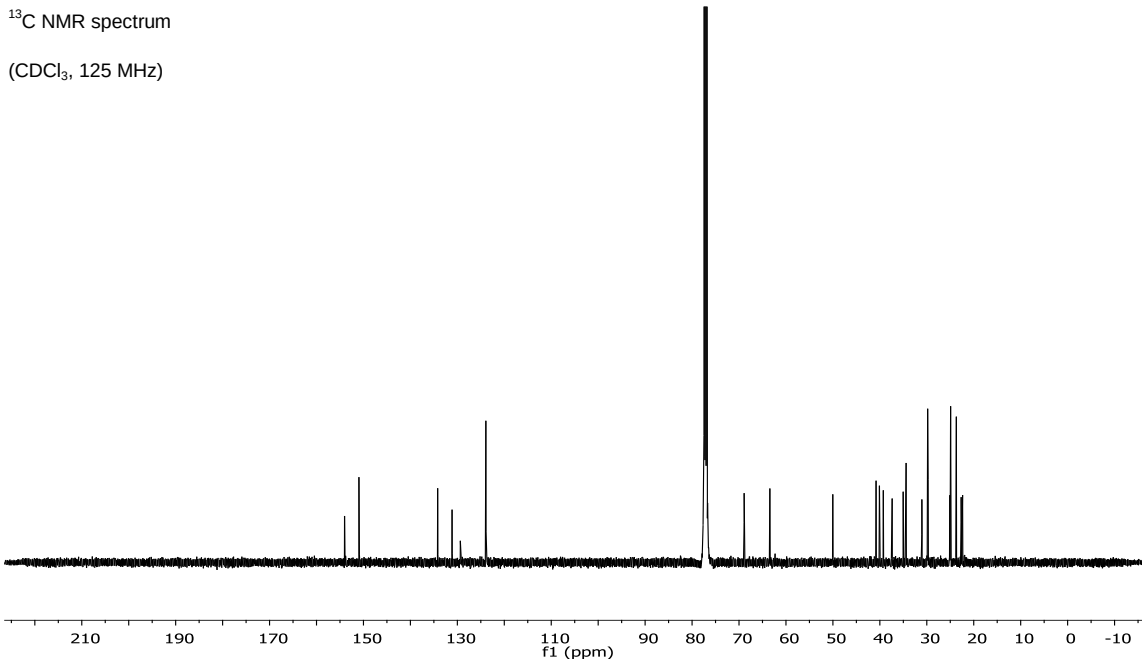
^{1}H NMR spectrum

($CDCl_3$, 500 MHz)

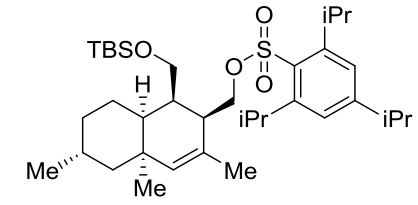


^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



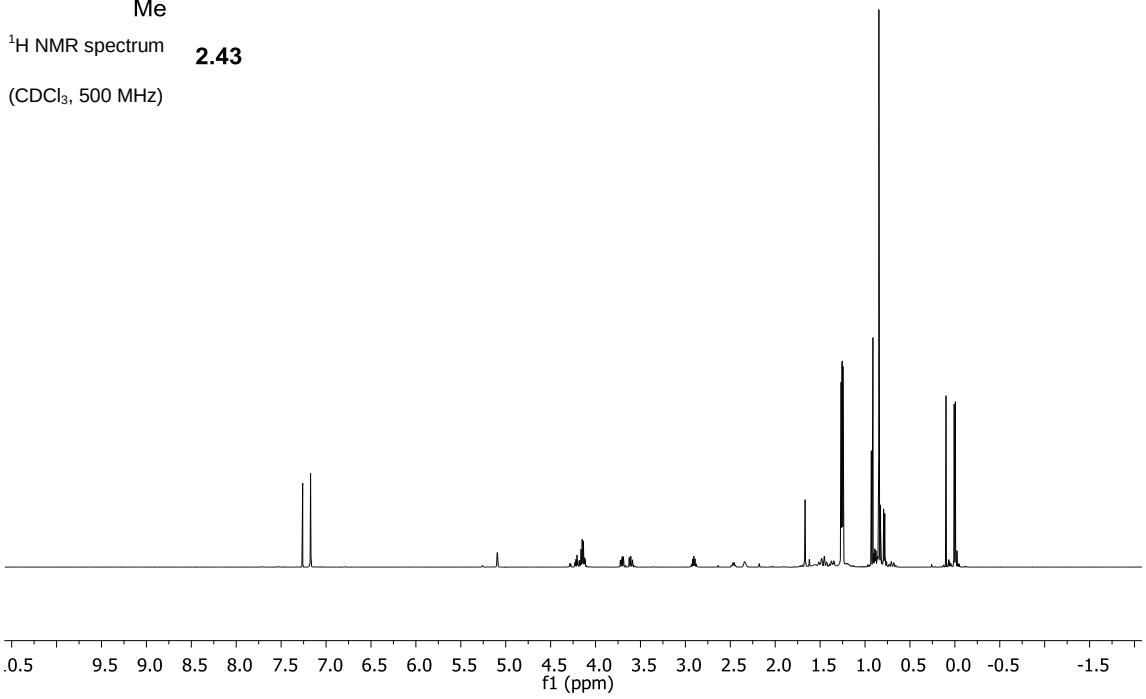
Spectra **2.21**: Compound **2.42**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.43

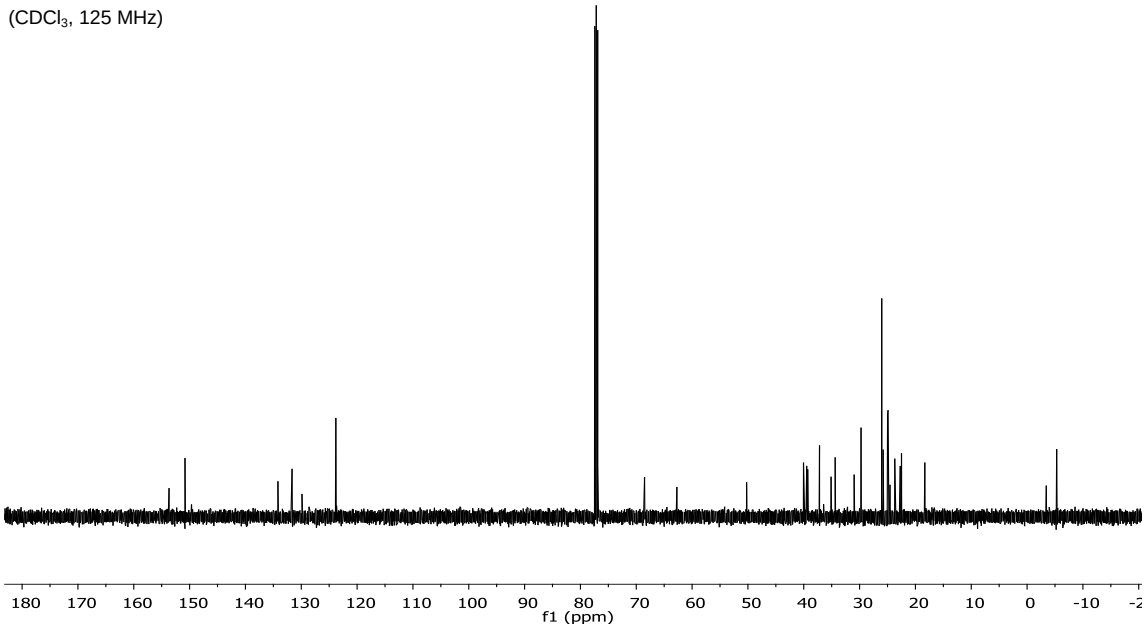
^{1}H NMR spectrum

($CDCl_3$, 500 MHz)

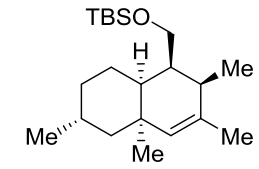


^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



Spectra **2.22**: Compound **2.43**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



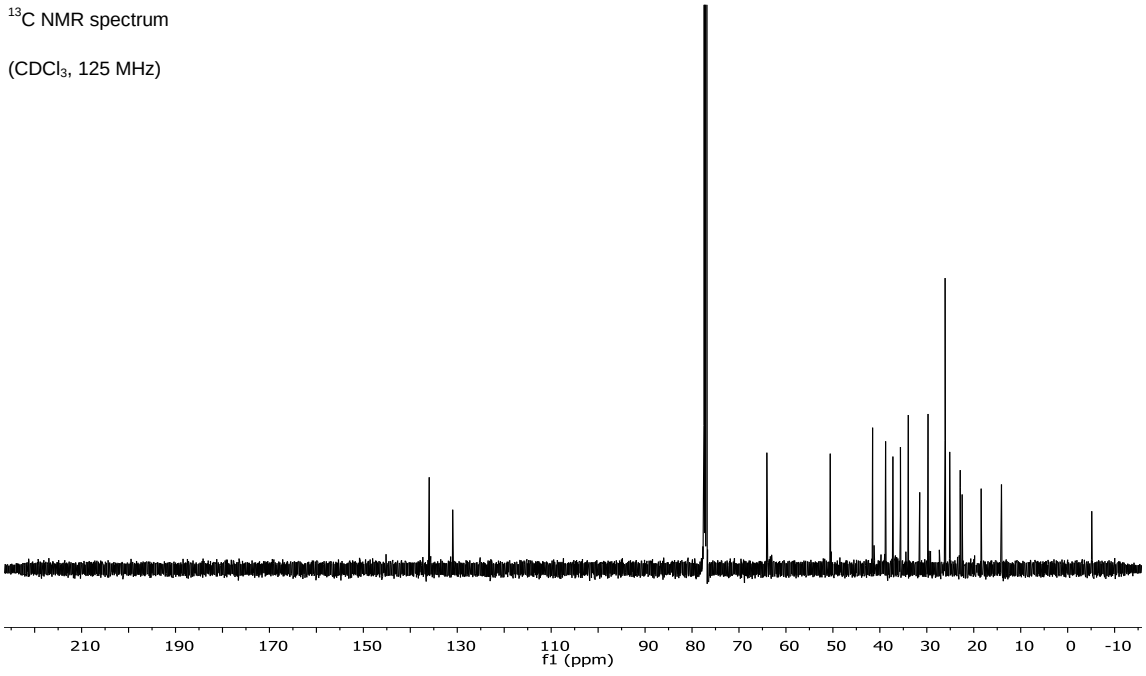
2.44

^{1}H NMR spectrum

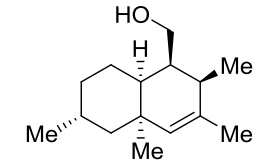
($CDCl_3$, 500 MHz)

^{13}C NMR spectrum

($CDCl_3$, 125 MHz)



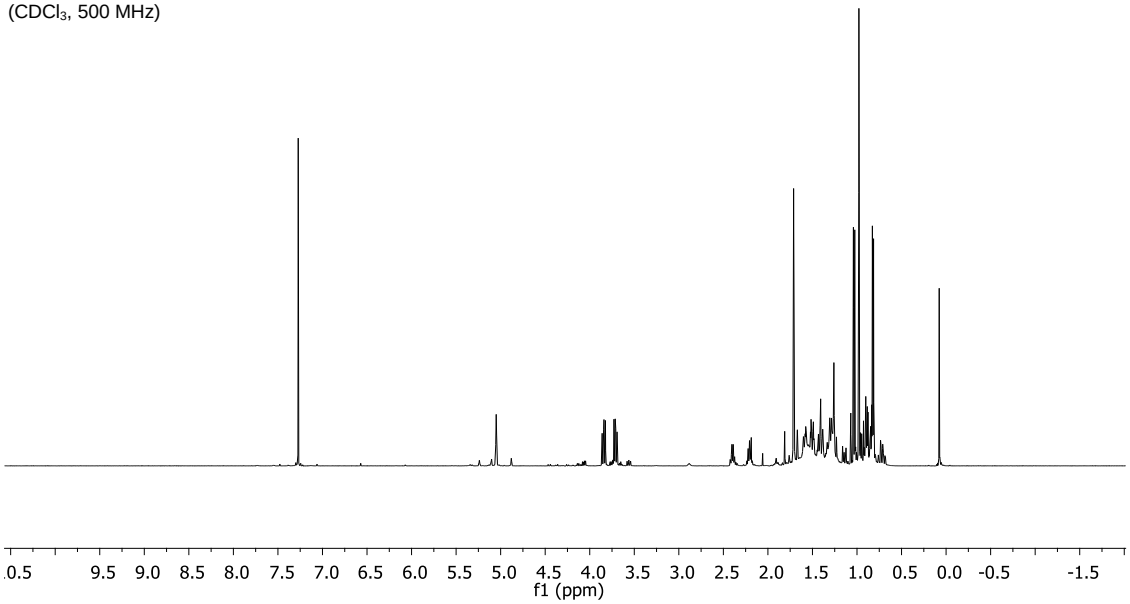
Spectra **2.23**: Compound **2.44**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



2.45

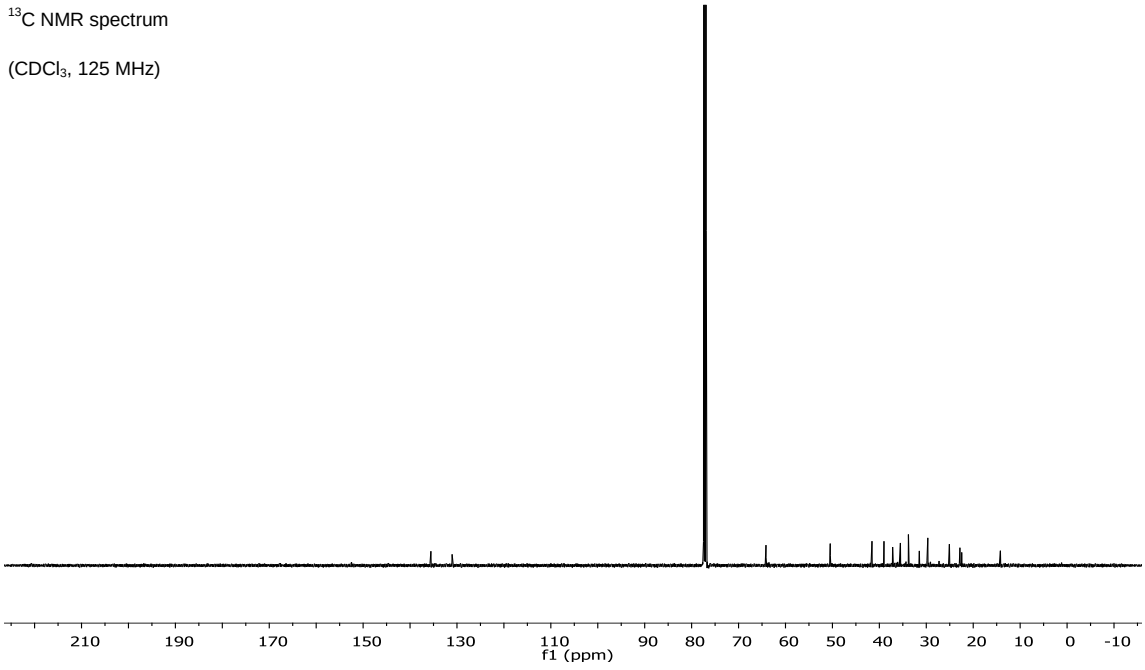
^{1}H NMR spectrum

($CDCl_3$, 500 MHz)

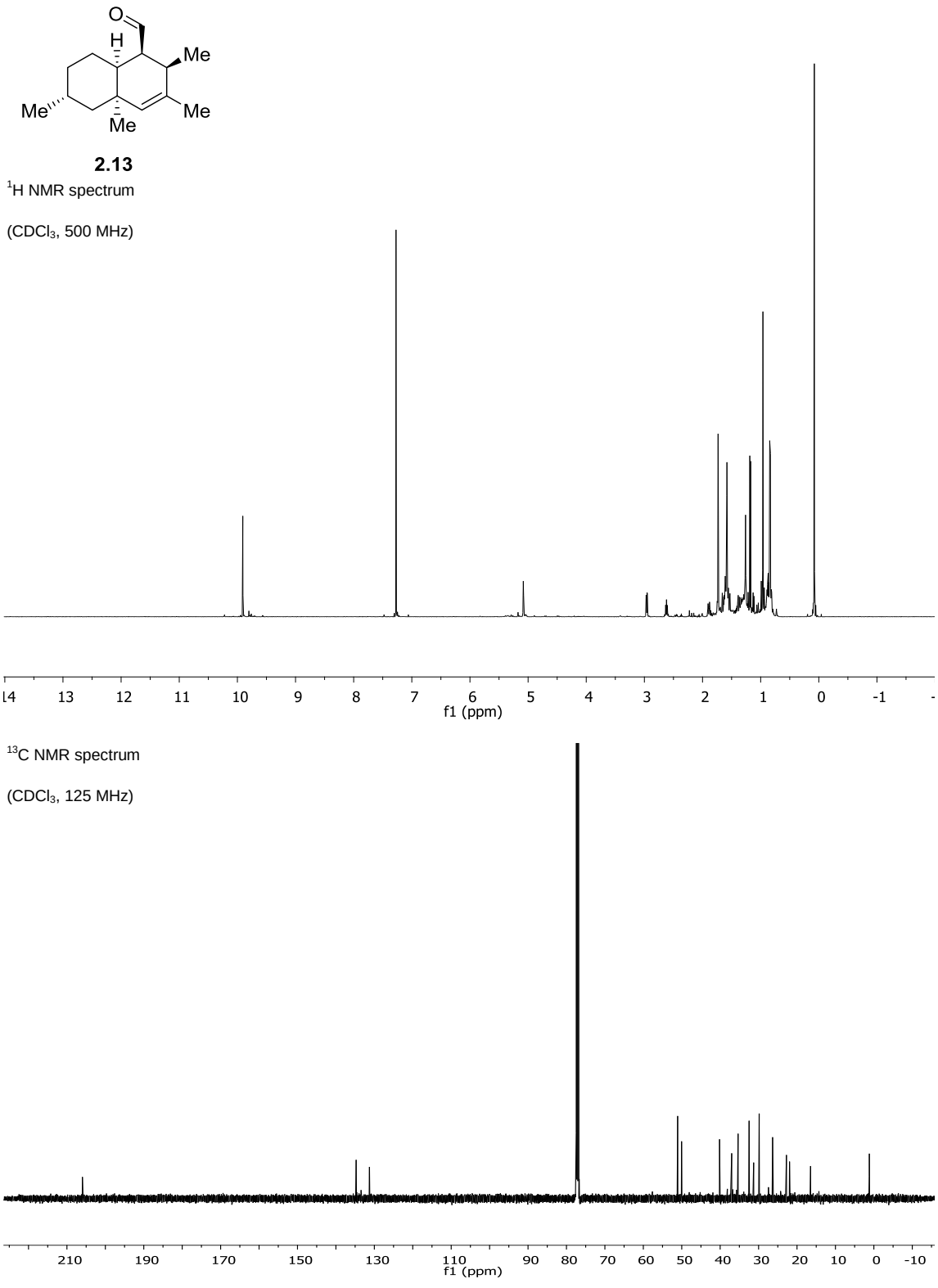


^{13}C NMR spectrum

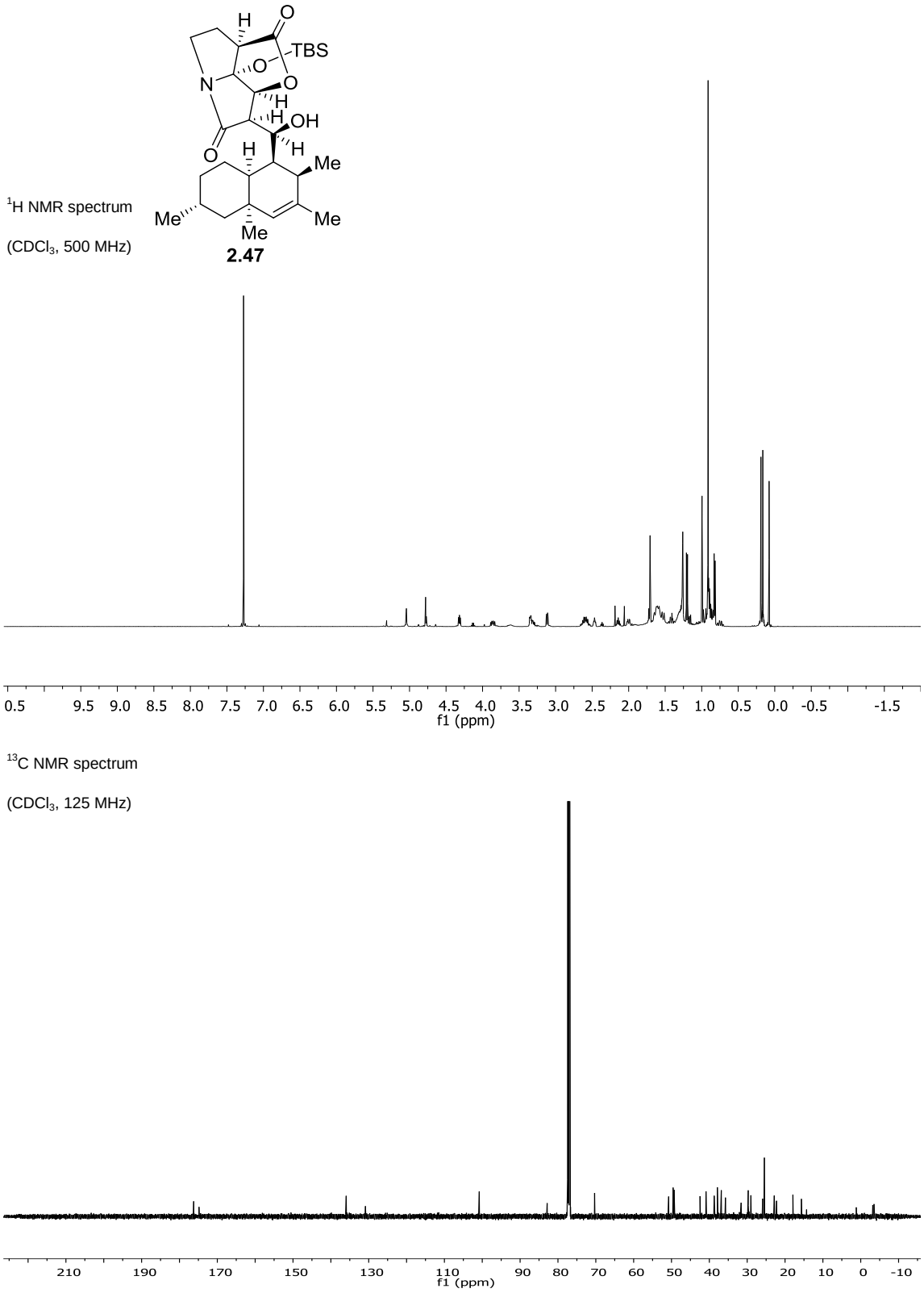
($CDCl_3$, 125 MHz)



Spectra **2.24**: Compound **2.45**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



Spectra **2.25**: Compound **2.13**: ^{1}H NMR (top) and ^{13}C NMR (bottom)



Spectra **2.26**: Compound **2.47**: ^{1}H NMR (top) and ^{13}C NMR (bottom)

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