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Determination of the Absolute Configuration of β-Chiral Primary Alcohols Using the Competing Enantioselective Conversion Method

Heteroatom-Directed Acylation of Secondary Alcohols to Assign Absolute Configuration

Total Synthesis of Illisimonin A

Osmate Esters are Crystalline Derivatives of Alkenes, Facilitating Structural Assignment via X-ray Analysis

DISSERTATION

submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Alexander Sunshine Burns

Dissertation Committee:

Professor Scott D. Rychnovsky, Chair

Professor Christopher D. Vanderwal

Professor Sergey V. Pronin

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DEDICATION

I met a traveller from an antique land,
Who said—"Two vast and trunkless legs of stone
Stand in the desert. . . . Near them, on the sand,
Half sunk a shattered visage lies, whose frown,
And wrinkled lip, and sneer of cold command,
Tell that its sculptor well those passions read
Which yet survive, stamped on these lifeless things,
The hand that mocked them, and the heart that fed;
And on the pedestal, these words appear:
My name is Ozymandias, King of Kings;
Look on my Works, ye Mighty, and despair!
Nothing beside remains. Round the decay
Of that colossal Wreck, boundless and bare
The lone and level sands stretch far away."

Ozymandias
Percy Bysshe Shelley, 1818

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LIST OF ABBREVIATIONS

	ngstroms
Ac	Acetyl
Atm	Atmosphere
Bn	Benzyl
Boc	tert-butoxycarbonyl
Bp	Boiling point
Bu	Butyl
BuLi	Butyllithium
°C	Degree Celsius
cat.	Catalytic
CSA	Camphorsulfonic acid
CI	Chemical ionization
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
δ	Chemical shift
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron-impact ionization
e.r.	Enantiomeric ratio
eq.	Equation
equiv.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
GC	Gas chromatography
h	hour(s)

HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i	iso
IR	Infrared spectroscopy
J	Coupling constant
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilazide
μ	micro
m	milli
M	Molar
m-CPBA	3-Chloroperoxybenzoic acid
min	minute(s)
Me	Methyl
MHz	Megahertz
MS	Mass spectrometer
N	nano
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser Effect
Ph	Phenyl
ppm	parts per million
rt r	oom temperature
sec	second(s)
t	tert
TBAF	tetra-*n*-butylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid

THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	4-Toluenesulfonyl
TsOH	4-Toluenesulfonic acid

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VITA

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PUBLICATIONS

7. **Burns, A. S.**; Dooley III, C.; Carlson, P. R.; Ziller, J. W.; Rychnovsky, S. D. Relative and absolute structure assignments of alkenes using crystalline osmate derivatives for X-ray analysis. *Org. Lett.* **2019**, *21*, 10125–10129.

6. **Burns, A. S.**; Rychnovsky, S. D. Total synthesis and structure revision of (–)-illisimonin A, a neuroprotective sesquiterpenoid from the fruits of *Illicium simonsii*. *J. Am. Chem. Soc.* **2019**, *141*, 13295–13300.

5. Brito, G. A.; Della-Felice, F.; Luo, G.; **Burns, A. S.**; Pilli, R. A.; Rychnovsky, S. D.; Krische, M. J. Catalytic enantioselective allylations of acetylenic aldehydes via 2-propanol-mediated reductive coupling. *Org. Lett.* **2018**, *20*, 4144–4147.

4. **Burns, A. S.**; Ross, C. C.; Rychnovsky, S. D. Heteroatom-directed acylation of secondary alcohols to assign absolute configuration. *J. Org. Chem.* **2018**, *83*, 2504–2515. *Featured article*.

3. **Burns, A. S.**; Wagner, A. J.; Fulton, J. L.; Young, K.; Zakarian, A.; Rychnovsky, S. D. Determination of the absolute configuration of β-chiral primary alcohols using the competing enantioselective conversion method. *Org. Lett*. **2017**, *19*, 2953–2956.

2. Piedra, F.-A.; Kim, T.; Garza, E. S.; Geyer, E. A.; **Burns, A.**; Ye, X.; Rice, L. M. GDP-to-GTP exchange on the microtubule end can contribute to the frequency of catastrophe. *Mol. Biol. Cell.* **2016**, *27*, 3515–3525.

1. Geyer, A. E.; **Burns, A.**; Lalonde, B. A.; Ye X.; Piedra, F.-A.; Huffaker, T. C.; Rice, L. M. A mutation uncouples the tubulin conformational and GTPase cycles, revealing allosteric control of microtubule dynamics. *eLife* **2015**;4:e10113.

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Funded research in the laboratory of Professor Luke Rice

UT Dallas/UT Southwestern Green Fellowship January 2014 – May 2014
Funded research in the laboratory of Professor Luke Rice

National Merit Scholar 2009

UNDERGRADUATE MENTORSHIP

Erdwin Orellana	December 2017 – June 2019
Christopher Ross	June 2017 – December 2017

ABSTRACT OF THE DISSERTATION

Determination of the Absolute Configuration of β-Chiral Primary Alcohols Using the Competing Enantioselective Conversion Method

Heteroatom-Directed Acylation of Secondary Alcohols to Assign Absolute Configuration

Total Synthesis of Illisimonin A

Osmate Esters are Crystalline Derivatives of Alkenes, Facilitating Structural Assignment via X-ray Analysis

By

Alexander Sunshine Burns

Doctor of Philosophy in Chemistry

University of California, Irvine, 2020

Professor Scott D. Rychnovsky, Chair

The first chapter details the development of a method for determining the absolute configuration of β-chiral primary alcohols that bear a π or heteroatom substituent on the stereocenter. The method relies on the rate differences of acylation using Birman's homobenzotetramisole acylation catalyst. An empirical relationship between the faster reacting catalyst system and absolute configuration of the substrate was developed. The method is applicable to primary carbinols appended to tertiary stereocenters that bear a directing group; directing groups include arenes, heteroarenes, enones, and halides.

The second chapter details the extension of the competing enantioselective conversion method to assign the absolute configuration of secondary alcohols bearing electron-withdrawing groups such

as halides and other heteroatoms. The level of selectivity is modest to good and is sufficient for determining configuration. A mathematical analysis identifies conditions for achieving maximum differences in conversion and, consequently, assigning configuration with greater confidence. The new method is effective for halohydrins and secondary−tertiary 1,2-diols and was used to confirm the configuration of two inoterpene natural products.

The third chapter details the completion of the first synthesis of (±)-illisimonin A. Notable steps in the route include a 1,3-dioxa-2-silacyclohexene templated Diels–Alder cycloaddition and type-3 semipinacol rearrangement to generate the trans-pentalene. The final step is an iron-catalyzed C-H oxidation. The synthetic route is robust, with 94 mg of racemic material prepared in a single pass. Classical resolution of a late stage intermediate enabled the synthesis of natural (–)-illisimonin A. The absolute configuration of (–)-illisimonin A was revised to 1S,4S,5S,6S,7R,9R,10R based on the X-ray structure of an heavy-atom analogue.

The fourth chapter details the use of osmium tetroxide and TMEDA to form stable crystalline adducts with alkenes. Osmate derivatization converted many liquid alkenes into solid crystalline compounds, enabling structure determination through X-ray analysis. Osmium, a heavy atom, facilitates the crystallographic analysis and the determination of the absolute configuration using common Mo X-ray sources. The utility of this method for assigning structures and absolute configurations was demonstrated on a number of unsaturated substrates that include simple alkenes, enones, enol ethers, and silyl enol ethers.

Chapter 1. Determination of the Absolute Configuration of β-Chiral Primary Alcohols Using the Competing Enantioselective Conversion Method

1.1 Abstract

A method for determining the absolute configuration of β-chiral primary alcohols that bear a π or heteroatom substituent on the stereocenter is described. The method relies on the rate differences of acylation using Birman's homobenzotetramisole acylation catalyst. An empirical relationship between the faster reacting catalyst system and absolute configuration of the substrate was developed. The method is applicable to primary carbinols appended to tertiary stereocenters that bear a directing group; directing groups include arenes, heteroarenes, enones, and halides.

1.2 Introduction

1.2.1 General background on absolute configuration and chirality

While often depicted in two dimensional representations, molecules actually exist in three spatial dimensions. Indeed, two molecules may have the same two-dimensional connectivity, but differ in their arrangement with respect to a third dimension. An example of this is shown in Figure 1-1. The two molecules have the same connectivity between atoms, but are not the same molecule. In this particular example, the molecules are enantiomers. Enantiomerism is a particular form of stereoisomerism in which two molecules are non-superimposable mirror images of each other. Enantiomers are special in that they have identical physical properties and only differ from one another in their interactions with other chiral substances.

The two substances shown in Figure 1-1 are asymmetric by virtue of a chiral atom. This is referred to as point chirality, and is the most well-known form of chirality in organic chemistry. It should be noted that this is not the only form of chirality. In addition, both axial and planar chirality exist. In the former, enantiomeric substances differ from one another in the arrangement of their atoms with respect to an axis. In the latter, they differ with respect to a plane. Enantiomers may even have multiple elements of chirality that define their structure. A molecule's absolute configuration refers to which enantiomer it is.

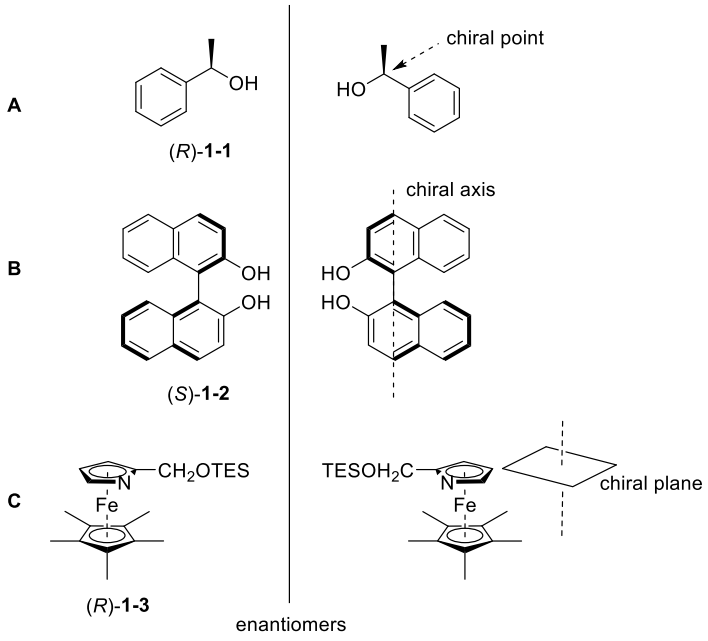


Figure 1-1. Different forms of molecular chirality. (A) Point chirality (B) Axial chirality (C) Planar chirality

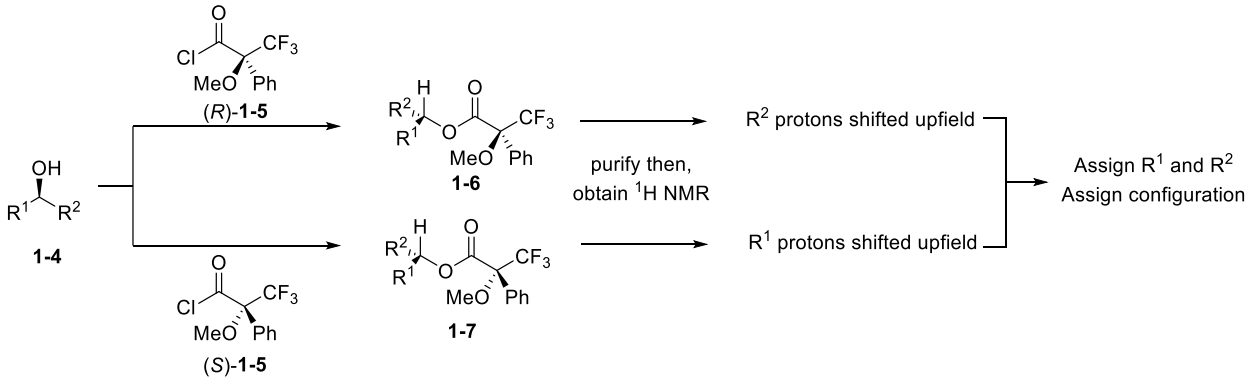
Synthetic chemists strive to make molecules with a defined structure. While much of the effort is aimed at developing ways to make these molecules, we have to determine what it is that we have made (or isolated). Generally, relative structure is determined through NMR spectroscopy along with IR spectroscopy and mass spectrometry.[1] In cases where this leads to ambiguity, x-ray crystallography is the gold standard for relative structural assignment.[2] While these techniques are not always conclusive, they are general for many classes of molecules. However, these

techniques (with some specific exceptions for x-ray crystallography) do not establish the absolute configuration of a molecule. To determine this, we have to probe its structure with some other outside form of chirality. Some of the most common techniques are discussed in the following section.

1.2.2 Common techniques for absolute configuration assignment

1.2.2.1 Chiral derivatization and NMR analysis

As noted earlier, the relative configuration of a molecule can often be assigned by NMR analysis. If a group of known chirality is installed onto an enantiomerically pure chiral molecule of unknown absolute configuration, one of two diastereomers is formed. As diastereomers have different physical properties, they may be distinguishable by NMR. If the relative relationship between these two moieties can be established, the absolute configuration of the molecule can be determined. One common example of this is Mosher's method, which is used to determine the configuration of chiral secondary alcohols.[3]



Scheme 1-1 Workflow scheme for the assignment of the absolute configuration of scalemic secondary alcohols using the advanced Mosher's method.

This method is outlined in Scheme 1-1. A scalemic secondary alcohol **1-4** is acylated with both enantiomers of Mosher's acid chlorides in separate reactions. The products are purified, their

proton NMR spectra are acquired, and peaks are assigned. Mosher's method relies on an empirically observed relationship that proton shifts of the R^2 substituents of many Mosher esters like **1-6** are shifted upfield relative to **1-7**. Conversely, the R^1 substituents of **1-6** are shifted downfield relative to **1-7**. It is proposed that **1-6** and **1-7** represent the lowest energy conformations of these molecules, and that the phenyl group shields the substituents which it eclipses. This method has been found to work on many different alcohols, and can be used to assign their configuration with some degree of confidence.

A few drawbacks and limitations should be noted for the method, however. Most critically, the method is not infallible and there are cases in which it is unsuccessful.[4] The method also requires the separate purification of two compounds, as well as assignment of all of the signals within the proton spectrum. This may require 2-D NMR analysis for more complicated substrates.

1.2.2.2 Circular dichroism

Circular dichoism (CD) is a type of spectroscopy that measures the differential absorption of left and right circularly polarized light. Chiral compounds will absorb left and right polarized light with different intensities. For vibrational circular dichroism (VCD), a spectrum for each enantiomeric compound will be calculated, typically using density-functional theory (DFT).[5] This spectrum can then be compared to an experimentally obtained spectrum. If one matches well, this indicates the absolute configuration of the molecule. As a spectrum has to be calculated for all energetically low-lying conformations, the calculations are much easier for rigid molecules, which is a drawback of the method. Electronic circular dichroism (ECD) can also be used to determine the absolute configuration of molecules with chromophore(s) near the stereocenter in question. This is not covered in detail in this text, but I would direct the reader to the following references for more information.[6]

1.2.2.3 X-ray crystallography

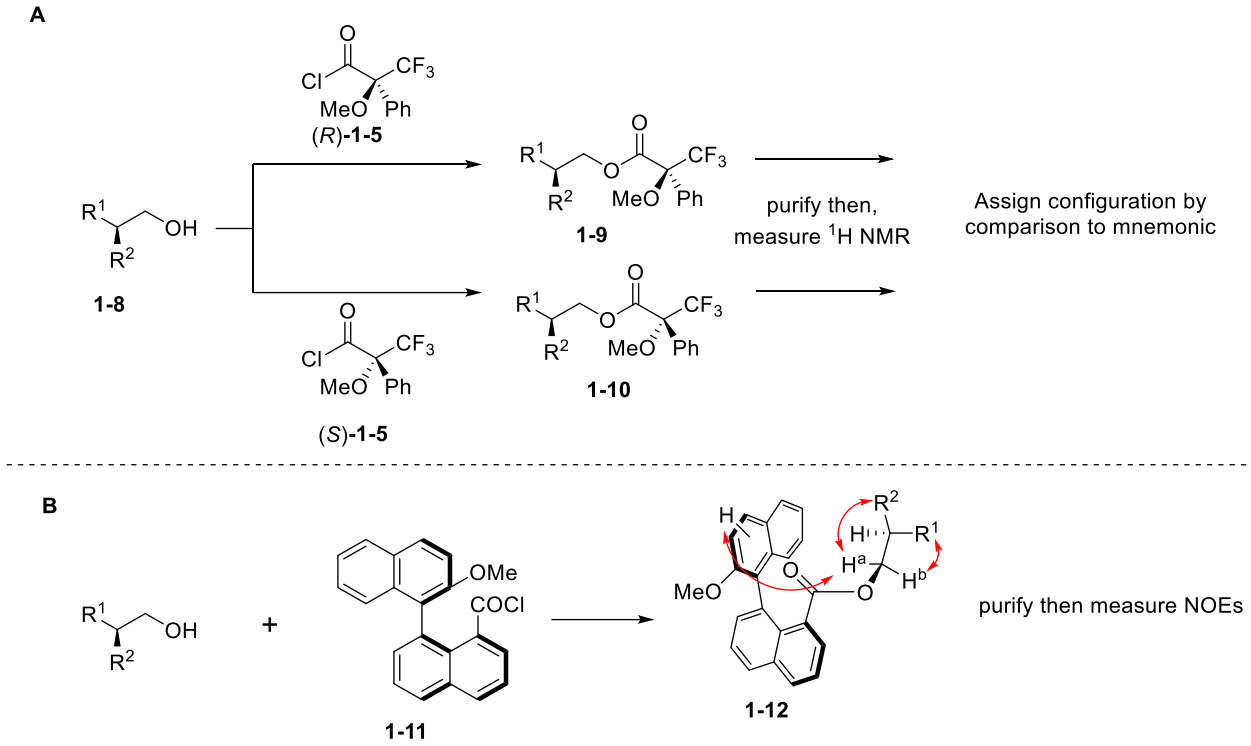
With maybe the exception of total synthesis, X-ray crystallography is the surest way to determine the absolute configuration of a molecule.[2] The first requirement for this technique is to grow crystals that are suitable for x-ray diffraction analysis. This process is not always trivial, and many compounds are not crystalline. Traditionally, determination of absolute stereochemistry with X-ray crystallography has required that there be a heavy atom (third row or below) within the molecule. However, there has been much work done in recent years which now allows the determination to be made for a molecule only containing light atoms.[7] The confidence in such an assignment is increased through the use of high quality crystals, high resolution data, high data redundancy, and a Cu-Kα radiation source.

1.2.3 Previous work on assigning the absolute configuration of β-chiral Primary Alcohols

Both the Riguerda[8] and Seebach[9] groups have extended the modified Mosher's method to β-chiral primary alcohols. An outline of Riguerda's approach is shown in Scheme 1-2A. The alcohol in question is acylated in separate reactions, and each product is purified. A ^{1}H NMR is measured, and the changes in chemical shift for each peak is tabulated. An empirical comparison analogous to that used in the modified Mosher's analysis for secondary alcohols is used to establish the absolute configuration of the alcohol in question. Seebach's approach is similar but instead is based upon analysis of the ^{19}F NMR.

The Fukushi group's approach to the problem is distinct.[10] An outline of their method is shown in Scheme 1-2B. β-chiral primary alcohols are acylated with binaphthyl derivatives such as **1-11**. ^{1}H NOESY spectra are obtained for the product, and the cross peaks are examined. Based upon the relative magnitudes of the NOEs, the absolute configuration of the alcohol in question can be

inferred by comparison to empirical data. The physical basis for the observed relationship can be rationalized by the confirmation shown for ester **1-12**.



Scheme 1-2 Other methods to assign the absolute configuration of β-chiral primary alcohols (A) Riguerda (B) Fukushi

1.2.4 Background on the competing enantioselective conversion method

The competing enantioselective conversion method (CEC) is a method developed by our laboratory to determine the absolute configuration of molecules, by exploiting rate differences of the molecule with two enantiomeric catalysts or reagents.[11] The CEC method is related to the Horeau method in that kinetic resolution catalysts are used to determine absolute configuration.[12] An example of a CEC method to assign the absolute configuration of secondary alcohols is shown in Figure 1-2.

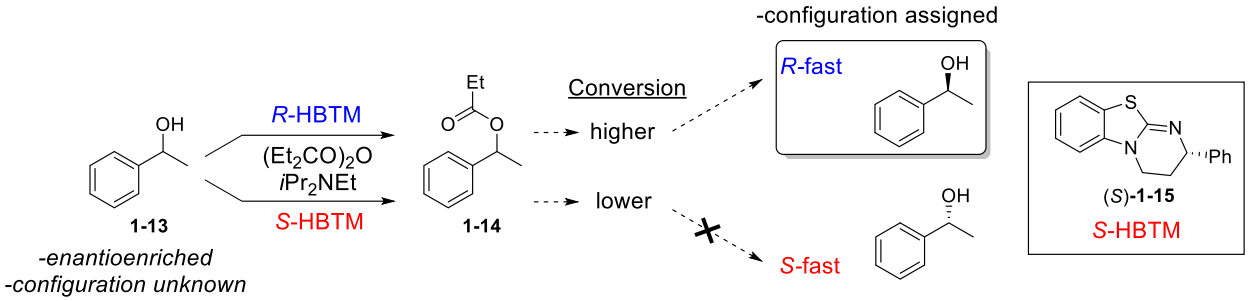


Figure 1-2 Workflow of a CEC method

Alcohol **1-13** is acylated in two separate reactions using either *R*-HBTM (homobenzotetramisole) or *S*-HBTM. The conversion for the *R*-HBTM reaction was higher. For previously tested substrates, if *R*-HBTM is the faster reaction, then the alcohol is pointed forward when the alcohol is drawn as depicted. Thus we can conclude that for this unknown substrate, the alcohol is pointed forward.

To date, a number of different substrate classes have been targeted by our lab. Methods for the determination of the absolute configuration of primary amines,[13] cyclic secondary amines,[14] lactams, oxazolidinones,[15] and secondary alcohols[11,16] have been reported. In theory, a CEC method could be developed for many other classes of substrates as long as: A. There is a kinetic resolution catalyst or reagent capable of resolving a class of substrates with predictable absolute selectivity and; B. The rate determining step of the kinetic resolution is also the enantiodetermining step of the reaction.

HBTM was developed by the Birman lab for the kinetic resolution of chiral secondary alcohols which have a π-bond containing group attached to the stereocenter.[17] Further background on this catalyst will be provided in chapter 2. HBTM had been previously used in CEC methods to assign the absolute configuration of secondary alcohols in our lab. Prior to my joining the lab, preliminary

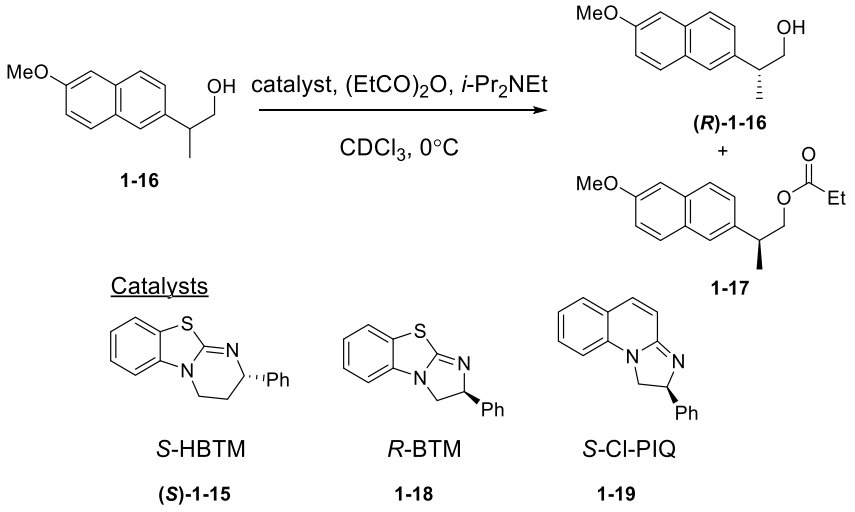
work was done by Dr. Alexander Wagner and Jennifer Fulton to determine if HBTM could be used in a CEC method to determine the absolute configuration of β-chiral primary alcohols.

1.3 Results

1.3.1 Kinetic resolution of β-chiral primary alcohols

We sought to determine if HBTM, or some other related catalyst would resolve β-chiral primary alcohols. The data is displayed in Table 1-1.

Table 1-1 Screening of Different Acylation Catalysts[a,b]

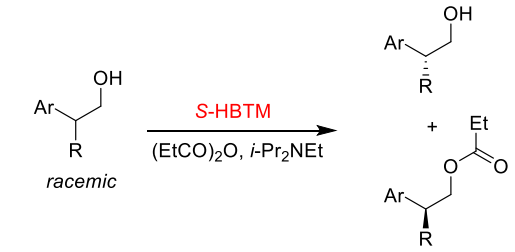


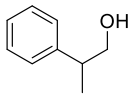
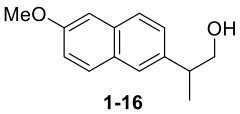
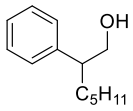
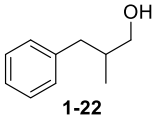
catalyst	ee-alcohol[c] (%)	ee-ester[c] (%)	conversion (%)	selectivity
S-HBTM	35.5	46.4	43	3.8
R-BTM	19.3	51.1	27	3.7
S-Cl-PIQ	2.52	50.5	4.8	3.1

[a.] Alcohol **1-16** (0.1 M), catalyst (10 mol%), and diisopropylethylamine (0.55 equiv) were combined in $CDCl_3$, followed by the addition of propionic anhydride (0.55 equiv) at 0 °C. The reaction was quenched after 15 min by the addition of MeOH [b.] Predominant enantiomers formed in the kinetic resolution of naphthyl alcohol **1-16** using *S*-Cl-PIQ and *R*-BTM are opposite that shown in the above scheme. [c.] The conversion and selectivity were calculated based upon the ee of the ester and remaining alcohol, which were determined using HPLC chiral analysis.

We were pleased to see that all three catalysts tested were able to resolve naphthyl alcohol **1-16** with comparable levels of selectivity. As the conversion was low when using *S*-Cl-PIQ, and BTM is known to be water sensitive, we elected to move forward with HBTM as our catalyst for further studies. Further optimizations were performed by others in the lab and are presented in the experimental section of this chapter.

Table 1-2 Kinetic Resolution of Racemic β-Chiral Primary Alcohols



substrate	conversion[b]	selectivity[b]
 **1-20**	49%	3.8
 **1-16**	52%	3.8
 **1-21**	35%	4.0
 **1-22**	30%	1.2

[a] The alcohol (0.1 M), *S*-HBTM (10 mol%), and diisopropylethylamine (DIPEA, 0.55 equiv) were combined in $CDCl_3$, followed by the addition of propionic anhydride (0.55 equiv) at 0 °C. The reaction was quenched after 15 min by the addition of MeOH. [b]The conversion and selectivity were calculated based upon the ee of the ester and remaining alcohol, which were determined using chiral HPLC analysis.

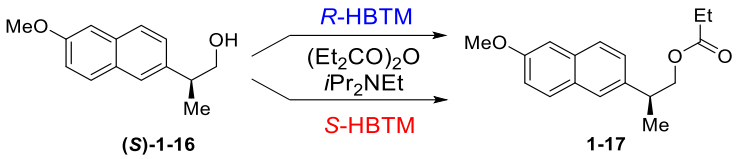
We aimed to minimally probe which different substrate classes would be amenable to kinetic resolution using this system. Those data are presented in Table 1-2. These experiments were carried out by Ms. Jennifer Fulton and Dr. Alexander Wagner.

Substrates **1-20**, **1-21**, and **1-16** all had approximately the same selectivity, and had aromatic "directing groups" attached to the primary carbinol stereocenter. Not surprisingly the conversion was dimished for alcohol **1-21** relative to **1-20**, and is likely due to the increased steric hindrance of a pentyl group relative to a methyl group. Alcohol **1-22** contains a methylene spacer between the stereocenter and the directing group, and was nearly unselective. This indicated that a CEC method for these substrates would be limited to primary alcohols with a "directing group" directly attached to the stereocenter. The selectivities for these kinetic resolutions are quite modest. This would not likely be a synthetically useful method for obtaining enantioenriched products. However, these selectivities are high enough to use in a CEC method to assign absolute stereochemistry.

1.3.2 CEC investigations

I next sought out to probe the kinetics of the acylation of these motifs using the system we developed. The order of the reaction was investigated in which conversion as a function of time was determined for the acylation of enantiopure **(*S*)-1-16**. The acylation of **(*S*)-1-16** was faster with *S*-HBTM, and the data demonstrated that a one-point NMR analysis of conversion would be sufficient to identify the faster reacting catalyst. Previous work on the HBTM catalyzed acylation of enantiopure secondary-alcohol (1*R*,2*S*)-2-phenylcyclohexanol showed that the reaction was first order in anhydride, alcohol, and HBTM. The data shown in Figure 2 are consistent with an apparent second order reaction (d[HBTM]/dt = 0) that is first order in both alcohol and anhydride. A reaction that is zeroth order in alcohol would be useless in a CEC assay of the alcohol's

configuration, as the enantiodetermining step is not the rate-determining step.



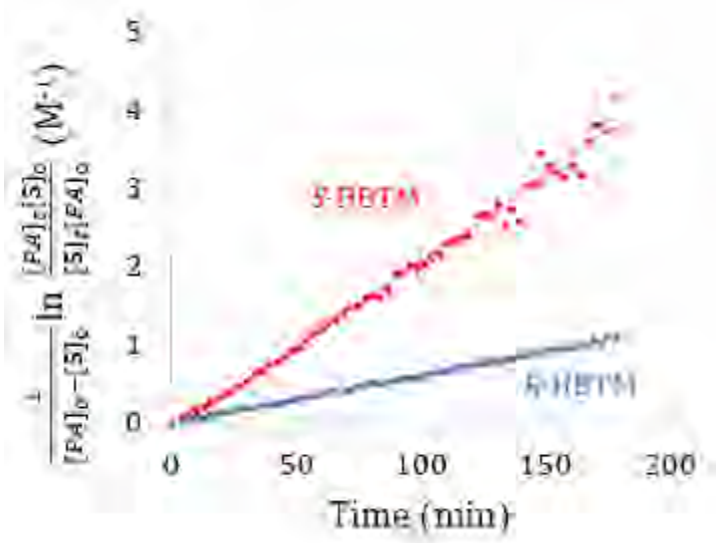
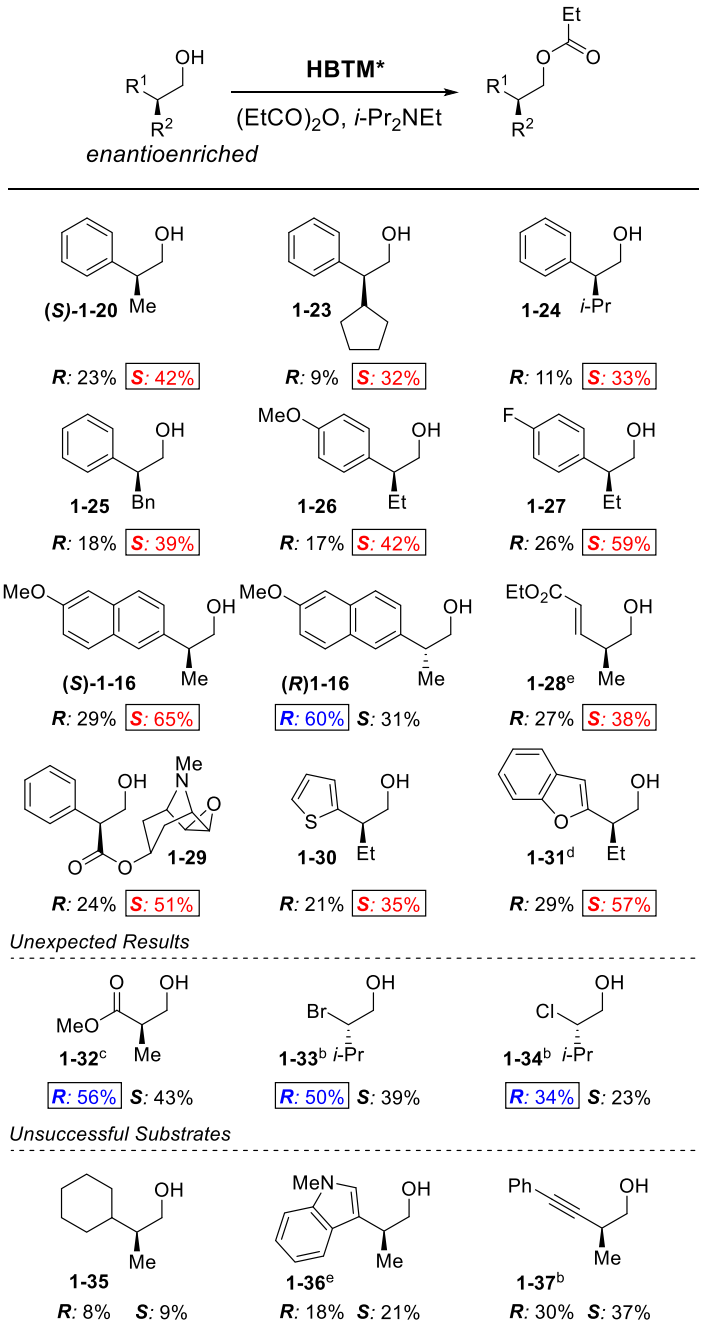


Figure 1-3 Reaction kinetics of acylation of **(*S*)-1-16** with both *R*- and *S*-HBTM.

Optically enriched alcohol (***S*)-1-16** was acylated with propionic anhydride (2 equiv) and 20 mol% of either *R*- or *S*-HBTM. Reaction progress is plotted using the integrated 2nd order rate law where $[A]_0 \neq [B]_0$. Propionic anhydride concentration was determined from alcohol concentration (d[**1-16**]/dt = d[PA]/dt). Selectivity factor (**s**) from the ratio of slopes: *S*-HBTM/*R*-HBTM = 0.0216/0.00602 = 3.6.

With all of the groundwork laid for a CEC method, I began to explore the substrate scope.[18] Most of the substrates were obtained by borane reduction of enantiomerically enriched carboxylic acids provided by the Zakarian group.



Scheme 1-3 CEC results for the conversion of β-chiral primary alcohols with *R*- and *S*-HBTM acylation system

[a] Optically enriched alcohols (0.015 M) were acylated with propionic anhydride (2 equiv) in the presence of *R*- or *S*-HBTM (10 mol %) and DIPEA (2 equiv) in $CDCl_3$ (400 µL total volume). After 30 min, the reactions were quenched by the addition of CD_3OD (50 µL). The reaction was diluted to 600 µL in $CDCl_3$, and % conversion was determined by ^1H NMR analysis. The results from run to run were reproducible [b]Percent conversions are the average of two

trials [c] CEC reaction run with 0.020 M alcohol and 20 mol % HBTM [d]For compound **1-31**, slightly overlapping peaks introduced small errors in the absolute values of the integrations. The relative conversions were consistent run to run. [e]The enantiomeric excess for all alcohols was ≥ 89%, except for **1-28** (83% ee) and **1-36** (84% ee).

Alcohols (*S*)-**1-20**, **1-23**, and **1-24** all have the same absolute stereochemistry with respect to their π, alkyl, and carbinol functionality. They were all acylated faster with *S*-HBTM indicating a correlation. Alcohol **1-25** was interesting in that it had two potential directing groups which have been known to steer selectivity for HBTM catalyzed acylations of chiral secondary alcohols. As the substrate was selective for *S*-HBTM, this indicates that the phenyl group (which is closer to the stereocenter) acts as a directing group. This was in line with the lack of selectivity in the kinetic resolution of alcohol **1-22**. (*R*) and (*S*)-**1-16** were each acylated with roughly equal and opposite selectivity with either enantiomer of HBTM, serving as a positive control for the CEC method. The method was also applied to scopolamine **1-29**, a natural product. We were pleased to see it react as expected, indicating that our method could have potential use for natural products chemists.

We next explored whether the method would work for other π-containing groups, and were met with mixed results. Thiophene **1-30** and benzofuran **1-31** were both acylated faster with *S*-HBTM indicating that these heteroaromatics act as directing groups in the same sense as all carbon aromatic groups. However indole **1-36** was unselective. While vinylogous ester **1-28** showed modest selectivity for acylation with *S*-HBTM, ester **1-32** displayed the opposite selectivity with respect to its π-containing group. We speculate that internal hydrogen bonding between the alcohol and ester carbonyl plays a role in this reversed selectivity. Alkyl alcohol **1-35** showed no selectivity for either catalyst, in line with our expectations that a π-group is required.

Most curious were halogens **1-33** and **1-34**. Both showed selectivity, albeit modest, for acylation with *R*-HBTM. This selectivity is in line with the halogen acting as a directing group, an observation that had not been made before this time. We believe that an electrostatic interaction between the dipole on the halogen and the positively, acylated catalyst lead to this selectivity. This is discussed in much greater detail in chapter 2.

1.3.3 Discussion

An examination of the substrates in Table 1-2 reveals a clear correlation between the absolute configuration of the substrate and the faster reacting catalyst, in many of the cases. We have summarized these trends in the mnemonic shown in Figure 1-4A. With the directing group pointed to the left, and the primary carbinol to the right, if *R*-HBTM is the catalyst in the faster reaction, the R group will be pointed into the plane of the page. If *S*-HBTM is the catalyst in the faster reaction, the R group will be pointed out of the plane of the page. The directing group can be an arene certain heteroarenes, an enone, or a halogen. Though the halogens and some other π-containing groups were selective, I am hesitant to recommend this as a method to confidently determine the absolute configuration of more complicated substrates which have these groups. I would only recommend this as a method for the more selective substrates which possess either an arene or a benzofuran.

Based upon this, we posit the transition-state model in Figure 1-4B, analogous to that proposed by Birman and Houk.[17] The substrate alcohol will approach the face of the catalyst which is not blocked by the phenyl ring. The directing group favorably interacts with the cationic-π system of the acylated catalyst. An unfavorable steric interaction between the R group and the catalyst accounts for the substrate's faster acylation with *S*-HBTM.

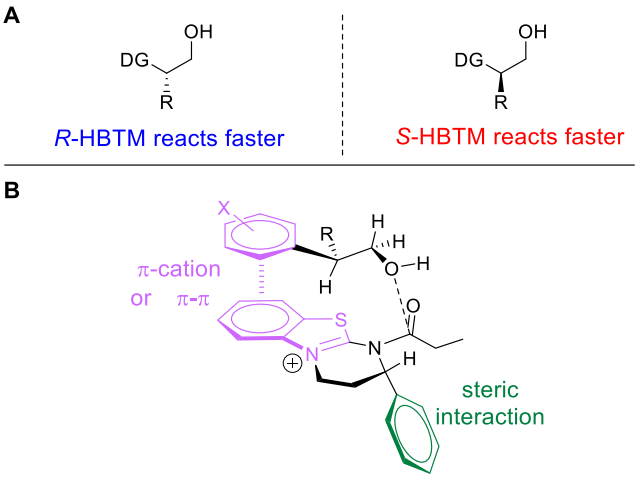


Figure 1-4 (A) Mnemonic for determining the absolute configuration of stereocenters β to a primary alcohol. Aryl groups, certain heteroaromatic and nonaromatic π systems, bromines, and chlorines act as directing groups. (B) Proposed transition state between chiral primary alcohols and acylated *S*-HBTM

1.4 Supporting information

1.4.1 General information

All kinetic resolution and CEC reactions were carried out under air. $CDCl_3$ was dried using Na_2SO_4 before use. All volumetric glassware and NMR tubes were oven-dried prior to use. ^1H NMR and ^{13}C and spectra were recorded at 500 MHz and 125 MHz at 298.0 K unless stated otherwise. Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^1H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using GC-CI-TOF. Enantiomeric excess was determined by HPLC on an Agilent Series 1100 HPLC instrument using a Chiralpak AD, Chiralcel OB-H, Chiralcel OJ, or Chiralcel OD column.

Unless otherwise stated, synthetic reactions were carried out in flame- or oven-dried glassware under an atmosphere of argon. All commercially available reagents were used as received unless

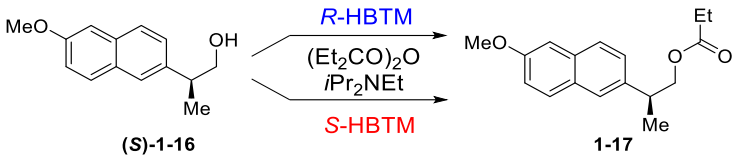
stated otherwise. Solvents were purchased as ACS grade or better and as HPLC-grade and passed though a solvent purification system equipped with activated alumina columns prior to use. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm, or by staining with *p*-anisaldehyde, potassium permanganate, phosphomolybdic acid, or vanillin. Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns. Compounds that only occur in the Supporting Information are numbered starting from **S1-1**.

1.4.2 Chemicals

All purchased chemicals were used without further purification unless otherwise noted. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Propionic anhydride was purchased from Sigma-Aldrich and distilled over CaH_2 prior to use. *N,N*-Diisopropylethylamine was distilled over CaH_2 prior to use. *R*-HBTM and *S*-HBTM were synthesized according to known literature procedure.[17] 2-Methyl-3-phenylpropan-1-ol **1-22** was synthesized according to known literature procedure.[19] *S*-Cl-PIQ **1-19** was synthesized according to known literature procedure.[20] *R*-BTM **1-18**, methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate, methyl (*R*)-2-(6-methoxynaphthalen-2-yl)propanoate, and methyl (*R*)-3-hydroxy-2-methylpropanoate **1-32** were purchased from TCI chemicals. 2-Phenylpropan-1-ol **1-20** and (*S*)-2-bromo-3-methylbutanoic acid were purchased from Sigma-Aldrich. Scopolamine hydrobromide trihydrate was purchased from Acros Organics.

1.4.3 Optimization of CEC reaction temperature and time

Table 1-3 CEC Optimization



[(***S***)-**1-16**] (M)	Time (min)	% conversion *R*-HBTM	*S*-HBTM
0.1	15	98	99
0.05	15	76	97
0.02	30	43	81
0.015	30	29	65
0.01	60	28	69

[a.] The alcohol **1-16** was acylated with propionic anhydride (2 equiv) in the presence of *R*- or *S*-HBTM (10 mol%) and DIPEA (2 equiv) in $CDCl_3$ (400 µL total volume). After the indicated time the reactions were quenched by the addition of CD_3OD (50 µL). After 90 min, reaction was concentrated and resuspended in 600 µL of $CDCl_3$, and % conversion was determined by proton NMR analysis

1.4.4 Kinetic Resolution Experimental

Stock Solutions:

S-HBTM-

An oven dried 2 mL volumetric flask was charged with *S*-HBTM (53.4 mg, 0.201mmol) and filled to the 2 mL mark with $CDCl_3$. The resulting 0.100 M solution of *S*-HBTM in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Propionic Anhydride-

An oven dried 10 mL volumetric flask was charged with propionic anhydride (355 µL, 2.78 mmol) and filled to the 10 mL mark with $CDCl_3$. The resulting 0.278 M solution of propionic anhydride in $CDCl_3$ was transferred to a flame-dried, capped 20 mL scintillation vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

General procedure:

The 0.1 M S-HBTM (0.50 mL, 0.05 mmol) and DIPEA (47.9 µL, 0.275 mmol) were added to 0.5 mmol of the corresponding alcohol. The mixture was subsequently diluted to a total volume of 4 mL with $CDCl_3$. This solution and the stock solution of propionic anhydride were cooled to 0 °C, before 0.278 M propionic anhydride (1.0 mL, 0.28 mmol) was added to the flask. After 15 min of stirring, MeOH (0.5 mL) was added to quench the reaction. A solution of 1N HCl (5 mL) was then added, and the mixture was transferred to a separatory funnel. The mixture was extracted with DCM (2 x 10 mL), and the organic extracts were combined and washed with saturated $NaHCO_3$ (5 mL). The organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*.

Calculations

Conversion and selectivity were calculated using the following formulas:

$$c(conversion) = \frac{ee_{SM}}{ee_{SM} + ee_{Pdt}}$$

$$s(selectivity) = \frac{\ln[(1-c)(1-ee_{SM})]}{\ln[(1-c)(1+ee_{SM})]}$$

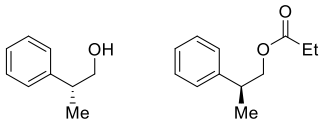
Derivatization procedure

In order to obtain enantiomeric excess for certain alcohol products from kinetic resolution, the following procedure was employed to derivatize them to the corresponding propionate esters as racemic reference samples:

The corresponding alcohol was dissolved in DCM (0.1 M) before DMAP (0.01 equiv), Et_3N (1.5 equiv), and propionic anhydride (1.5 equiv) were added. The reaction was stirred until the starting material had been consumed. A solution of 1N HCl was added, and the product was extracted with DCM (2x). Organic layers were combined and washed with saturated $NaHCO_3$ before being dried over anhydrous $MgSO_4$. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc/Hex) on silica to deliver the propionate ester.

Table 1-2 Experimental

Entry 1



(*R*)-1-20 S1-1

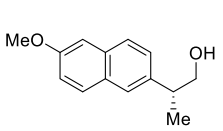
The products were separated by flash column chromatography (EtOAc/Hex) on silica to give the alcohol **(*R*)-1-20** as a clear oil 10.1 mg, 15%), and the ester ((*S*)-2-phenylpropyl propionate **S1-1**) as a clear oil (3.7 mg, 4%).

(*S*)-2-phenylpropyl propionate **S1-1**: Chiral HPLC analysis (Chiralcel OJ with OJ guard, 2% *i*-

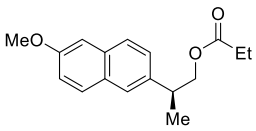
PrOH in *n*-hexane, 39 bar, 1.0 mL/min, UV detection at 254 nm, tS = 13.7 min, tR = 17.9 min) led to 44% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), δ 7.28-7.18 (m, 3H), δ 4.25-4.18 (dd, *J* = 10.6, 7.1 Hz, 1H), δ 4.13 (dd, *J* = 10.6, 7.5 Hz, 1H), δ 3.10 (app sex, *J* = 6.9 Hz, 1H), δ 2.29 (q, *J* = 7.6 Hz, 1H), δ 1.29 (t, *J* = 13.3 Hz, 2H), δ 1.10 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 143.4, 128.6, 127.4, 126.8, 69.3, 39.1, 27.7, 18.2, 9.3. HRMS (CI, CH_2Cl_2) m/z calcd for $C_{12}H_{20}NO_2$ $(M+NH_4)^+$ 210.1494, found 210.1489. Absolute configuration confirmed with HPLC analysis of the enantiopure (*S)*-2-phenylpropyl propionate.

(*R*)-2-phenylpropan-1-ol **(*R*)-1-20**: NMR spectra were consistent with starting alcohol. The alcohol was transformed to the propionate ester and separated via Chiral HPLC (Chiralcel OJ with OJ guard, 2% *i*-PrOH in *n*-hexane, 39 bar, 1.0 mL/min, UV detection at 254 nm, tS = 13.5 min, tR = 16.2 min) 41% ee.

Entry 2



(*R*)-1-16



1-17

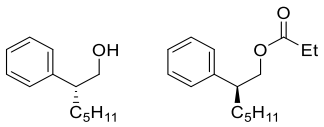
The products were separated by flash column chromatography (EtOAc/Hex) on silica to give the alcohol (*R*)-2-(6-methoxynaphthalen-2-yl)propan-1-ol **(*R*)-1-16** as a white solid (42.7 mg, 39%), and the ester (*S*)-2-(6-methoxynaphthalen-2-yl)propyl propionate **1-17** as a clear oil (72.6 mg, 53%).

(*S*)-2-(6-methoxynaphthalen-2-yl)propyl propionate **1-17**: Chiral HPLC analysis (Chiralcel OJ with OD guard, 5% *i*-PrOH in *n*-hexane, 20 bar, 1.0 mL/min, UV detection at 254 nm, tR = 26.22 min, tS = 30.80 min) 40% ee. NMR spectra were consistent with previously reported data.[21]

Absolute configuration confirmed with HPLC analysis of the enantiopure naproxen-derived ester ((*S*)-2-(6- methoxynaphthalen-2-yl)propyl propionate).

(*R*)-2-(6-methoxynaphthalen-2-yl)propan-1-ol **(*R*)-1-16**: NMR spectra were consistent with the starting alcohol. The alcohol was converted to the propionate ester and separated via Chiral HPLC (Chiralcel OJ with OD guard, 5% *i*-PrOH in *n*-hexane, 20 bar, 1.0 mL/min, UV detection at 254 nm, tR = 24.52 min, tS = 29.83 min) 52% ee.

Entry 3



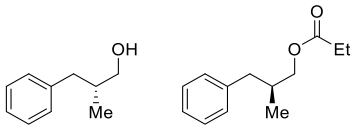
(*R*)-1-21 **S1-2**

The products were separated by flash column chromatography (EtOAc/Hex) on silica to give the alcohol, (*R*)-2-phenylheptan-1-ol **(*R*)-1-21** as a clear oil (42.8 mg, 45%), and the ester, (*S*)-2-phenylheptyl propionate **S1-2** as a clear oil (48.8 mg, 39%).

(*S*)-2-phenylheptyl propionate **S1-2**: Chiral HPLC analysis (Chiralcel OJ with OD guard, 1% *i*-PrOH in *n*-hexane, 13 bar, 0.5 mL/min, UV detection at 254 nm, tR = 12.94 min, tS = 14.68 min) led to 51% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, *2*H), δ 7.25-7.15 (m, 3H), δ 4.22 (dd, *J* = 10.9, 6.8 Hz, 1H), δ 4.19 (dd, *J* = 10.7, 7.3 Hz, 1H), δ 2.96-2.86 (m, 1H), δ 2.26 (q, *J* = 7.6 Hz, 1H), δ 1.78-1.68 (m, 1H), δ 1.65-1.54 (m, 1H), δ 1.34-1.14 (m, 6H), δ 1.07 (t, *J* = 7.6 Hz, 3H), δ 0.84 (t, *J* = 6.8 Hz, 3H). δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.6, 142.3, 128.5, 128.0, 126.7, 68.5, 45.1, 32.5, 31.9, 27.7, 27.0, 22.6, 14.1, 9.7. HRMS (CI, CH_2Cl_2) m/z calcd for $C_{16}H_{28}NO_2$ $(M+NH_4)^+$ 266.2120, found 266.2115. Absolute configuration inferred from analogy to previous substrates.

(*R*)-2-phenylheptan-1-ol **(*R*)-1-21**: NMR spectra were consistent with the starting alcohol. The alcohol was transformed to the propionate ester and separated via Chiral HPLC (Chiralcel OJ with OD guard, 1% *i*-PrOH in *n*-hexane, 12 bar, .5 mL/min, UV detection at 254 nm, tR = 13.53 min, tS = 14.98 min) 27% ee.

Entry 4



(*R*)-1-22 **S1-3**

The products were separated via flash column chromatography (3:1 Hex:EtOAc) to give the alcohol (*R*)-2-methyl-3-phenylpropan-1-ol **(*R*)-1-22** as a clear oil (13.5 mg, 18%), and the ester ((*S*)-2-methyl-3-phenylpropyl propionate) **S1-3** as a clear oil (27.2 mg, 26%).

(*S*)-2-methyl-3-phenylpropyl propionate **S1-3**: Chiral HPLC analysis (Chiralcel OJ with OD guard, 1% *i*-PrOH in *n*-hexane, 20 bar, 1.0 mL/min, UV detection at 254 nm, tR = 13.43 min, tS = 11.24 min) led to 6% ee. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), δ 7.20 (t, *J* = 7.4 Hz, 1H), δ 7.16 (d, *J* = 8.0 Hz, 2H), δ 3.98 (dd, *J* = 10.8, 6.1 Hz, 1H), δ 3.92 (dd, *J* = 10.8, 6.4 Hz, 1H), δ 2.74 (dd, *J* = 13.5, 6.3 Hz, 1H), δ 2.46 (dd, *J* = 13.5, 8.0 Hz, 1H), δ 2.34 (q, *J* = 7.6 Hz, 2H), δ 2.19-2.06 (m, *J* = 13.1, 6.5 Hz, 1H), δ 1.16 (t, *J* = 7.6 Hz, 3H), δ 0.93 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 140.1, 129.2, 128.4, 126.1, 68.6, 39.9, 34.7, 27.7, 16.8, 9.3. HRMS (CI, CH_2Cl_2) m/z calcd for $C_{13}H_{22}NO_2$ $(M+NH_4)^+$ 224.1651, found 224.1659.

(*R*)-2-methyl-3-phenylpropan-1-ol **(*R*)-1-22**: Chiral HPLC analysis (Chiralcel OD-H with OD-H guard, 10% *i*-PrOH in *n*-hexane, 20 bar, 1.0 mL/min, UV detection at 254 nm, tR = 9.46 min, tS

= 8.63 min) led to 3% ee. NMR spectra were consistent with starting alcohol. Absolute configuration assigned via reference to literature data.[22]

1.4.5 CEC experimental

1.4.5.1 Preparation of stock solutions

R-HBTM-

An oven dried 2 mL volumetric flask was charged with *R*-HBTM (8.5 mg, 0.032 mmol) and filled to the 2 mL mark with $CDCl_3$. The resulting 0.016 M solution of *R*-HBTM in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

S-HBTM-

An oven dried 2 mL volumetric flask was charged with *S*-HBTM (8.5 mg, 0.032 mmol) and filled to the 2 mL mark with $CDCl_3$. The resulting 0.016 M solution of *S*-HBTM in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Diisopropylethylamine (DIPEA)-

An oven dried 1 mL volumetric flask was charged with DIPEA (56 μL, 0.32 mmol) and filled to the 1 mL mark with $CDCl_3$. The resulting 0.32 M solution of DIPEA in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Propionic anhydride-

An oven dried 1 mL volumetric flask was charged with propionic anhydride (41 μL, 0.32 mmol)

and filled to the 1 mL mark with $CDCl_3$. The resulting 0.32 M solution of propionic anhydride in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

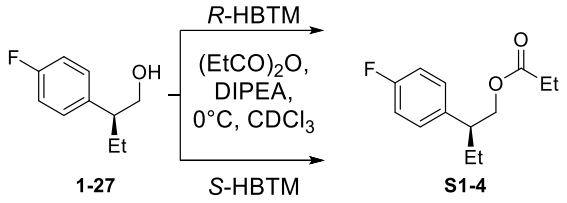
Substrate Alcohols-

An oven dried 1 mL volumetric flask was charged with the alcohol substrate and filled to the 1 mL mark with $CDCl_3$. The resulting alcohol solution in $CDCl_3$ was transferred to a flame-dried, capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C prior to use.

1.4.5.2 General CEC procedure (Scheme 1-3)

Two separate 2 mL capped glass dram vials were flame dried and allowed to cool to room temperature. Next 6 μmol of alcohol substrate as a solution in $CDCl_3$ was transferred to each vial. The reaction volume in each vial was diluted to 287.5 μL with $CDCl_3$. Next, 0.32 M DIPEA (37.5 μL, 12 μmol) was added to each flask. The flask was then was charged with either enantiomer of 0.016 M HBTM (37.5 μL, 0.60 μmol), and chilled to 0 °C in an ice-water bath. Cold 0.32 M propionic anhydride (37.5 μL, 12 μmol) was added to each vial bringing the total reaction volume to 400 μL. The reaction flasks were kept at 0 °C for 30 min, and the reactions were quenched by the addition of CD_3OD (50 μL). $CDCl_3$ (150 μL) was added to each mixture, which were subsequently transferred to NMR tubes. The ^{1}H-NMR spectrum was taken of each reaction to assay conversion. In some cases the reaction solvent was removed under reduced pressure and resuspended in $CDCl_3$ to eliminate interfering peaks. In these cases the mixture was allowed to stand at least 90 min to guarantee no remaining propionic anhydride remained.

1.4.5.3 Example CEC experiment:



Stock solutions

53.5 mM alcohol **1-27**

0.32 M DIPEA

0.016 M *R*-HBTM

0.016 M *S*-HBTM

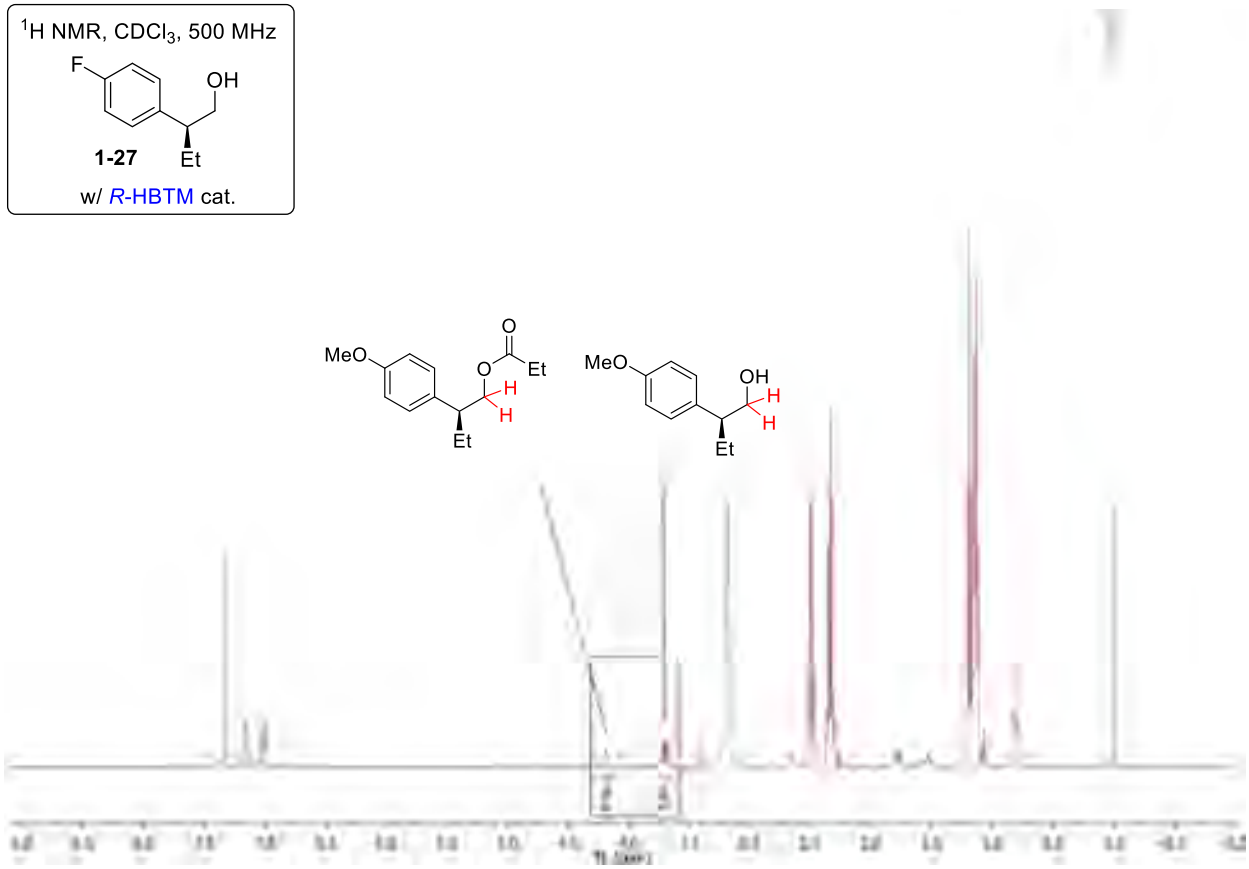
0.32 M Propionic Anhydride

	Reaction	[**1-27**] in reaction	$CDCl_3$	DIPEA	HBTM	Propionic Acid	Total Volume (µL)	Reaction Time
	1-27 with *R*-HBTM	0.015M		2 equiv	*R*- 10 mol%	2 equiv		30 min.
Volume Added (µL)		112	175.5	37.5	37.5	37.5	400	
	1-27 with *S*-HBTM	0.015M		2 equiv	*S*- 10 mol%	2 equiv		30 min.
Volume Added (µL)		112	175.5	37.5	37.5	37.5	400	

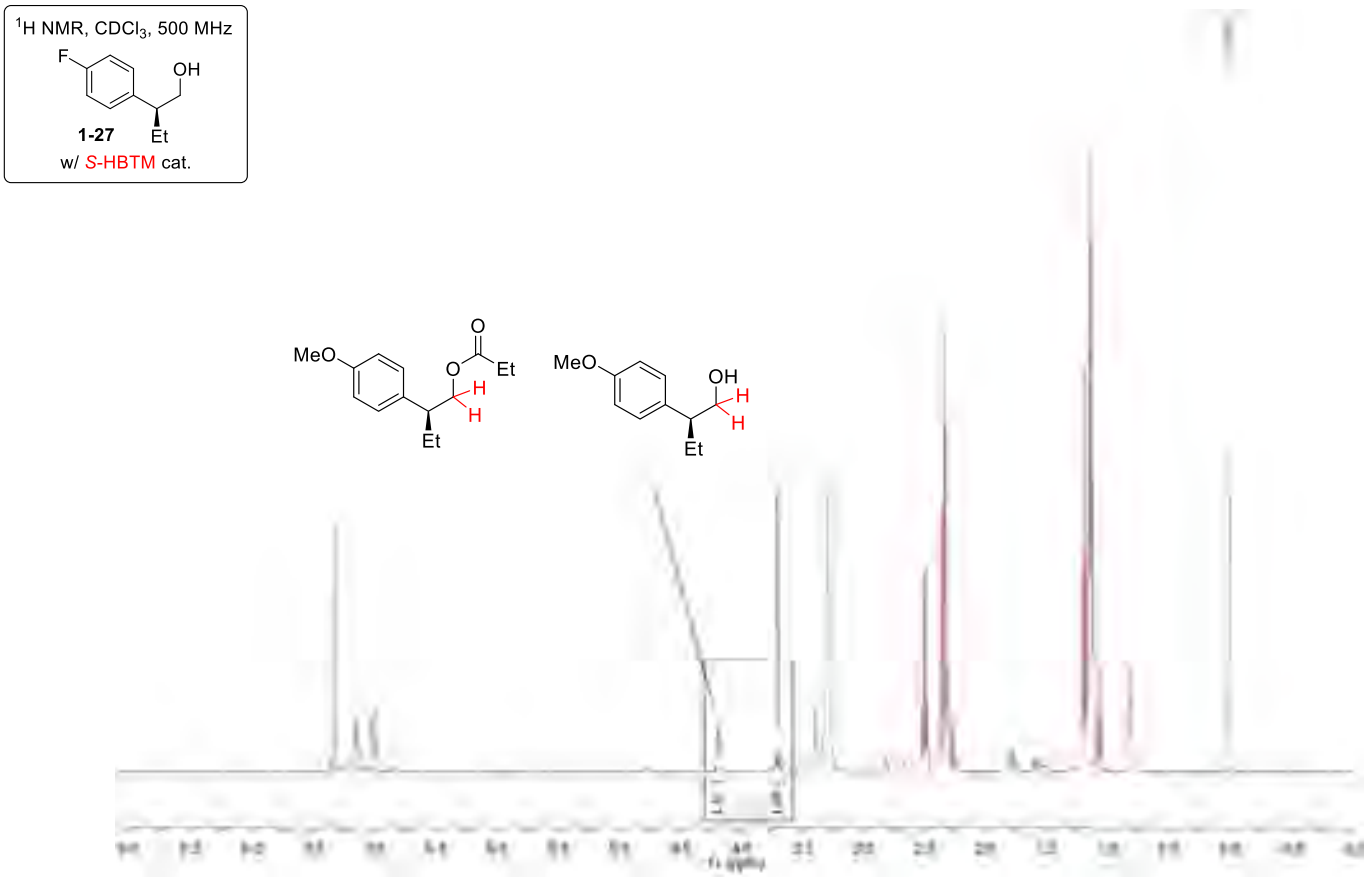
^{1}H NMR, $CDCl_3$, 500 MHz

1-27

w/ *R*-HBTM cat.



$$conversion = \frac{int._{methylene}\,(ester)}{int._{methylene}\,(ester) + int._{methylene}\,(alcohol)} = \frac{0.36}{0.36 + 1.00} = 26\%$$



$$conversion = \frac{int._{methylene}\,(ester)}{int._{methylene}\,(ester) + int._{methylene}\,(alcohol)} = \frac{1.42}{1.42 + 1.00} = 59\%$$

1.4.5.4 Table 1-3 experimental

Stock Solutions

Stock solutions in $CDCl_3$ were made following an analogous procedure for the preparation of stock solutions for Scheme 1-3, but with the following concentrations:

0.80 M DIPEA

0.04 M *R*-HBTM

0.04 M *S*-HBTM

0.80 M Propionic Anhydride

0.40 M alcohol **(*S*)-1-16**

[**(*S*)-1-16**] in reaction (M)	$CDCl_3$ added (µL)	**(*S*)-1-16** added (µL)	DIPEA Added (µL)	HBTM Added (µL)	Propionic Acid Added (µL)	Reaction Time (min)	CD_3OD Added (µL)
0.1	0	100	100	100	100	15	200
0.05	200	50	50	50	50	15	100
0.02	320	20	20	20	20	30	50
0.015	340	15	15	15	15	30	50
0.01	360	10	10	10	10	60	50

Two separate 2 mL capped glass dram vials were flame dried and allowed to cool to room temperature. Next stock solutions of alcohol **(*S*)-1-16**, DIPEA, and either *R*- or *S*-HBTM were transferred to the vials in the amounts indicated in the above table. Both reaction vials and propionic anhydride were cooled to 0 °C. The indicated volume of propionic anhydride solution was added to both reactions which were allowed to sit at 0 °C for the indicated amount of time before the addition of CD_3OD. The mixtures were allowed to sit at room temperature for 90 min before the solvent was removed *in vacuo*. The crude materials were resuspended in 600 µL of $CDCl_3$ and ^1H NMR was recorded.

1.4.6 NMR kinetics experimental

1.4.6.1 Preparation of stock solutions

The same stock solutions for *R*-HBTM, *S*-HBTM, DIPEA, propionic anhydride, and alcohol **5** were used as in a typical CEC experiment (Scheme 1-3).

1.4.6.2 Procedure for NMR kinetic experiment

$CDCl_3$ (413 µL), 0.32 M DIPEA (37.5 µL, 12 µmol), 0.016 M ***X***-HBTM (75 µL, 2.4 µmol), and 0.16 M **5** (37.5 µL, 6 µmol) were added to an NMR tube that was cooled to 0 °C in an ice bath. Next, chilled 0.32 M propionic anhydride (37.5 µL, 12 µmol) was added quickly, the tube was

mixed by inverting once with the open end covered by a nitrile glove. The NMR sample was placed in the spectrometer already chilled to 0 °C to collect ^{1}H NMR spectra at regular time intervals.

This experiment was run with *R*-HBTM, *S*-HBTM, as well as without catalyst ($CDCl_3$ was added to maintain the same reaction volume).

1.4.6.3 Tracking reaction progress

Reaction progress was followed by comparison of the integrations of the methylene protons from the ester product relative to that of the alcohol product. Conversion and alcohol concentration were calculated using the following formulas:

$$conversion = \frac{int._{methylene}\,(ester)}{int._{methylene}\,(ester) + int._{methylene}\,(alcohol)}$$

$$[OH]_t = [OH]_{t^0} * (1 - conversion_t)$$

$[OH]_t^0$ = 0.01 M; *R*-HBTM- 20 mol%

Time (min)	% conversion	[OH] (M)	Time (min)	% conversion	[OH] (M)
0.0	0.00	0.01000	89.8	59.18	0.00408
3.9	4.76	0.00952	92.7	60.63	0.00394
6.9	8.26	0.00917	95.7	60.32	0.00397
9.8	13.04	0.00870	98.7	61.54	0.00385
12.8	12.28	0.00877	101.6	63.50	0.00365
15.7	18.03	0.00820	104.6	63.64	0.00364
18.7	20.63	0.00794	107.5	64.79	0.00352
21.7	23.66	0.00763	110.5	64.79	0.00352
24.6	25.37	0.00746	113.5	66.89	0.00331
27.6	29.58	0.00704	116.4	67.95	0.00321
30.6	30.07	0.00699	119.4	68.25	0.00317
33.5	31.03	0.00690	122.3	69.04	0.00310
36.5	34.64	0.00654	125.3	69.14	0.00309
39.4	35.06	0.00649	128.3	70.85	0.00292
42.4	36.31	0.00637	131.2	70.33	0.00297
45.4	38.65	0.00613	134.2	70.93	0.00291
48.3	41.18	0.00588	137.2	72.45	0.00275
51.3	42.86	0.00571	140.1	72.90	0.00271
54.2	45.05	0.00549	143.1	73.40	0.00266
57.2	45.65	0.00543	146.0	74.55	0.00254
60.2	47.09	0.00529	149.0	74.16	0.00258
63.1	48.45	0.00515	152.0	75.49	0.00245
66.1	50.74	0.00493	154.9	75.73	0.00243
69.0	49.75	0.00503	157.9	76.13	0.00239
72.0	51.69	0.00483	160.8	76.64	0.00234
75.0	54.75	0.00452	163.8	76.19	0.00238
77.9	56.52	0.00435	166.8	77.58	0.00224
80.9	57.98	0.00420	169.7	78.99	0.00210
83.9	57.08	0.00429	172.7	77.63	0.00224
86.8	58.51	0.00415	175.6	80.20	0.00198

$[OH]_t^0$ = 0.01 M; *S*-HBTM- 20 mol%

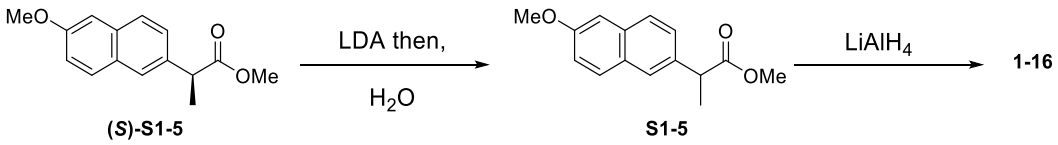
Time (min)	% conversion	[OH] (M)	Time (min)	% conversion	[OH] (M)
0.0	0.00	0.01000	89.8	91.90	0.00081
3.9	11.50	0.00885	92.7	92.27	0.00077
6.9	19.35	0.00806	95.7	92.80	0.00072
9.8	27.01	0.00730	98.7	92.35	0.00076
12.8	32.43	0.00676	101.6	93.03	0.00070
15.7	38.65	0.00613	104.6	93.30	0.00067
18.7	43.18	0.00568	107.5	93.94	0.00061
21.7	47.92	0.00521	110.5	94.67	0.00053
24.6	51.92	0.00481	113.5	94.76	0.00052
27.6	55.56	0.00444	116.4	95.06	0.00049
30.6	59.51	0.00405	119.4	95.14	0.00049
33.5	62.96	0.00370	122.3	96.37	0.00036
36.5	65.28	0.00347	125.3	96.41	0.00036
39.4	69.33	0.00307	128.3	96.36	0.00036
42.4	70.59	0.00294	131.2	96.86	0.00031
45.4	73.40	0.00266	134.2	95.88	0.00041
48.3	75.31	0.00247	137.2	96.56	0.00034
51.3	76.02	0.00240	140.1	96.06	0.00039
54.2	78.31	0.00217	143.1	97.51	0.00025
57.2	80.84	0.00192	146.0	97.64	0.00024
60.2	82.05	0.00180	149.0	98.35	0.00017
63.1	84.15	0.00158	152.0	98.11	0.00019
66.1	84.54	0.00155	154.9	97.90	0.00021
69.0	85.73	0.00143	157.9	97.74	0.00023
72.0	87.01	0.00130	160.8	98.11	0.00019
75.0	87.28	0.00127	163.8	97.84	0.00022
77.9	88.90	0.00111	166.8	98.59	0.00014
80.9	88.95	0.00110	169.7	98.88	0.00011
83.9	88.69	0.00113	172.7	98.89	0.00011
86.8	89.86	0.00101	175.6	98.78	0.00012

$[OH]_t^0$ = 0.01 M; HBTM- 0 mol%

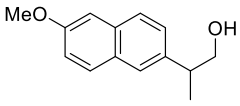
Time (min)	% conversion	[OH] (M)	Time (min)	% conversion	[OH] (M)
0.0	0.00	0.01000	89.8	0.00	0.01000
3.9	0.00	0.01000	92.7	0.00	0.01000
6.9	0.00	0.01000	95.7	0.00	0.01000
9.8	0.00	0.01000	98.7	0.00	0.01000
12.8	0.00	0.01000	101.6	0.00	0.01000
15.7	0.00	0.01000	104.6	0.00	0.01000
18.7	0.00	0.01000	107.5	0.00	0.01000

21.7	0.00	0.01000	110.5	0.00	0.01000
24.6	0.00	0.01000	113.5	0.00	0.01000
27.6	0.00	0.01000	116.4	0.00	0.01000
30.6	0.00	0.01000	119.4	0.00	0.01000
33.5	0.00	0.01000	122.3	0.00	0.01000
36.5	0.00	0.01000	125.3	0.00	0.01000
39.4	0.00	0.01000	128.3	0.00	0.01000
42.4	0.00	0.01000	131.2	0.00	0.01000
45.4	0.00	0.01000	134.2	0.00	0.01000
48.3	0.00	0.01000	137.2	0.00	0.01000
51.3	0.00	0.01000	140.1	0.00	0.01000
54.2	0.00	0.01000	143.1	0.00	0.01000
57.2	0.00	0.01000	146.0	0.00	0.01000
60.2	0.00	0.01000	149.0	0.00	0.01000
63.1	0.00	0.01000	152.0	0.00	0.01000
66.1	0.00	0.01000	154.9	0.00	0.01000
69.0	0.00	0.01000	157.9	0.00	0.01000
72.0	0.00	0.01000	160.8	0.00	0.01000
75.0	0.00	0.01000	163.8	0.00	0.01000
77.9	0.00	0.01000	166.8	0.00	0.01000
80.9	0.00	0.01000	169.7	0.00	0.01000
83.9	0.00	0.01000	172.7	0.00	0.01000
86.8	0.00	0.01000	175.6	0.00	0.01000

1.4.7 Substrate synthesis

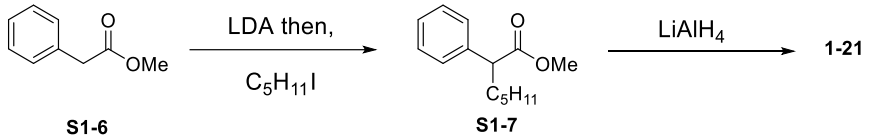


(*S*)-S1-5 S1-5

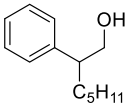


2-(6-Methoxynaphthalen-2-yl)propan-1-ol (1-16). Diisopropylamine (0.72 mL, 5.2 mmol) in THF (6.2 mL) was cooled to 0 °C and 2.14 M *n*-BuLi in hexanes (2.20 mL, 4.7 mmol) was added dropwise. The resulting LDA solution was stirred at 0 °C for 15 min and then cooled to –78 °C. A solution of methyl (S)-2-(6-methoxynaphthalen-2-yl)propanoate (1.0 g, 4.1 mmol) in THF (12.3 mL) was added dropwise and the reaction was stirred at –78 °C for 40 min before the addition of saturated NH_4Cl (aq) (8.2 mL). The reaction mixture was transferred to a separatory funnel and extracted with diethyl ether (3 x 50 mL). The organic

layers were combined and washed with 1M HCl (aq) (100 mL) followed by brine (100 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to afford a white solid (0.94 g, 94%). A 0.5 g sample of the resulting racemate was reduced with $LiAlH_4$ as is described for **(*S*)-1-16** to yield **1-16** as a white solid (0.36 g, 80%). Spectral data matched that of compound **(*S*)-1-16.**



S1-6 S1-7



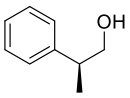
2-Phenylheptan-1-ol (1-21). Diisopropylamine (1.2 mL, 8.3 mmol) in THF (10 mL) was cooled to 0 °C and 2.14 M *n*-BuLi in hexanes (2.20 mL, 4.7 mmol) was added dropwise. The resulting LDA solution was stirred at 0 °C for 15 min and then cooled to –78 °C. A solution of methyl phenyl acetate (0.938 mL, 6.7 mmol) in THF (20 mL) was added dropwise and the reaction mixture was stirred at –78 °C for 40 min before the addition of iodopentane (1.3 mL, 10 mmol). The reaction mixture was warmed to 0 °C and stirred for 6 h, before the addition of saturated NH_4Cl (aq) (13 mL). The mixture was transferred to a separatory funnel and extracted with diethyl ether (3 x 75 mL). The organic layers were combined and washed with 1M HCl (aq) (75 mL) followed by brine (75 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/Hex) on silica to afford methyl 2-phenylheptanoate (**S1-7**) as a yellow oil (0.77 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.28 (m, 4H), δ 7.27-7.21 (m, 1H), δ 3.65 (s, 3H), δ 3.54 (t, *J* = 7.7 Hz, 1H), δ 2.13-1.99 (m, 1H), δ 1.84-1.60 (m, 1H), δ 1.41-1.06 (m, 6H), 0.86 (t, *J* = 5.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 139.4, 128.7, 128.0, 127.3, 52.0, 51.8, 33.7, 31.7, 27.4,

22.6, 14.1. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{14}H_{24}NO_2$ $[M + NH_4]^+$ 238.1807, found 238.1807.

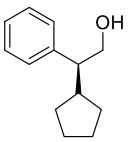
A solution of ester **S1-7** (0.60 g, 2.7 mmol) in diethyl ether (2.7 mL) was added dropwise to a suspension of $LiAlH_4$ (0.114 g, 3.02 mmol) in diethyl ether (6.3 mL) at 0 °C . The reaction mixture was stirred overnight, and the reaction was quenched by the addition of H_2O (11 mL). The reaction mixture was transferred to a separatory funnel and extracted with diethyl ether (3 x 50 mL). The organic layers were combined and washed with brine (50 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/Hex) on silica to afford **1-21** as a clear oil (0.42 g, 79%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.29 (m, 2H), δ 7.27-7.22 (m, 1H), δ 7.20 (m, 2H), δ 3.74 (dd, *J* = 10.7, 5.8 Hz, 1H), δ 3.67 (dd, *J* = 10.7, 8.0 Hz, 1H), δ 2.76 (tt, *J* = 9.2, 5.6 Hz, 1H), δ 1.68 (ddd, *J* = 15.2, 10.5, 5.4 Hz, 1H), δ 1.56 (ddd, *J* = 22.7, 11.6, 7.4 Hz, 1H), δ 1.38 (br s, 1H), δ 1.33-1.08 (m, 6H), δ 0.83 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 128.7, 128.2, 126.8, 67.7, 48.8, 32.1, 32.0, 27.1, 22.6, 14.1. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{13}H_{24}NO$ $[M + NH_4]^+$ 210.1858, found 210.1857.

1.4.7.1 General synthesis of enantiopure primary alcohols

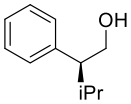
A 0.3 M solution of the enantioenriched carboxylic acid in THF was cooled to 0 °C in a flame dried reaction vessel equipped with a magnetic stir bar. Next 2 M BH_3·DMS (3 equiv) in THF was added dropwise. The reaction mixture was warmed to room temperature overnight under an atmosphere of argon, and the reaction was quenched with the addition of $NaHCO_3$ (aq). The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3x). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/Hex) on silica.



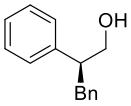
(*S*)-2-Phenylpropan-1-ol ((*S*)-1-20). (*S*)-2-Phenylpropanoic acid (20.0 mg, 0.133 mmol, 88% ee) was converted to **(*S*)-1-20** following the general procedure for the preparation of primary alcohols to afford a clear oil (7.5 mg, 41%); $[\alpha]_D^{21.6} = -11.5$ (c 0.75 $CDCl_3$). Spectral data matched those reported in the literature.[23]



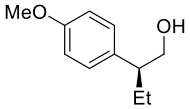
(*S*)-2-Cyclopentyl-2-phenylethan-1-ol (1-23). (*S*)-2-Cyclopentyl-2-phenylacetic acid (15.6 mg, 0.168 mmol, 96% ee) was converted to **1-23** following the general procedure for the preparation of primary alcohols to afford a clear oil (6.0 mg, 41%); $[\alpha]_D^{21.3}$ = 18.2 (c 0.60 $CDCl_3$). Spectral data matched those reported in the literature.[24]



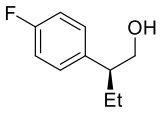
(*S*)-3-Methyl-2-phenylbutan-1-ol (1-24). (*S*)-3-Methyl-2-phenylbutanoic acid (25.0 mg, 0.140 mmol, 97% ee) was converted to alcohol **1-24** following the general procedure for the preparation of primary alcohols to afford a clear oil (8.9 mg, 39%); $[\alpha]_D^{22.1}$ = 11.5 (c 0.89 $CDCl_3$). Spectral data matched those reported in the literature.[24]



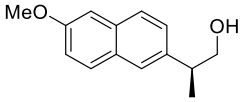
(*S*)-2,3-Diphenylpropan-1-ol (1-25). (*S*)-2,3-Diphenylpropanoic acid (25.0 mg, 0.110 mmol, 92% ee) was converted to **1-25** following the general procedure for the preparation of primary alcohols to afford a clear oil (13.0 mg, 55%); $[\alpha]_D^{22.2} = 77.5$ (c 0.54 $CDCl_3$). Spectral data matched those reported in the literature for the enantiomer of **9**.[25]



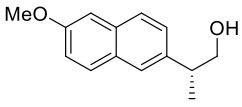
(*S*)-2-(4-Methoxyphenyl)butan-1-ol (1-26). (*S*)-2-(4-Methoxyphenyl)-butanoic acid (24.8 mg, 0.128 mmol, 89% ee) was converted to alcohol **1-26** following the general procedure for the preparation of primary alcohols to afford a clear oil (9.7 mg, 42%); $[\alpha]_D^{22.1}$ = 15.0 (c 0.97 $CDCl_3$). Spectral data matched those reported in the literature for the enantiomer of **10**.[26]



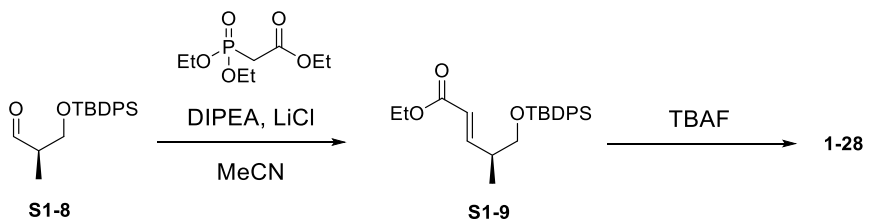
(*S*)-2-(4-Fluorophenyl)butan-1-ol (1-27). (*S*)-2-(4-Fluorophenyl)butanoic acid (24.1 mg, 0.132 mmol, 96% ee) was converted to alcohol **1-27** following the general procedure for the preparation of primary alcohols to afford a clear oil (9.0 mg, 40%); $[\alpha]_D^{22.1}$ = 18.2 (c 0.90 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.13 (m, 2H), δ 7.06-6.98 (m, 2H), δ 3.80-3.73 (m, 1H), δ 3.73-3.69 (m, 1H), δ 2.68 (tt, *J* = 10.9, 5.6 Hz, 1H), δ 1.81-1.69 (m, 1H), δ 1.59-1.48 (m, 1H), δ 1.37-1.17 (br s, 1H), δ 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (d, *J* = 244.3 Hz), 138.0 (d, *J* = 3.2 Hz), 129.6 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 21.1 Hz), 67.5, 49.9, 25.2, 12.0. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{10}H_{17}NO$ $[M + NH_4]^+$ 186.1288, found 186.1294.

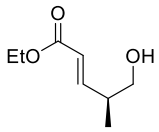


(*S*)-2-(6-Methoxynaphthalen-2-yl)propan-1-ol ((*S*)-1-16). Alcohol **(*S*)-1-16** was prepared from the $LiAlH_4$ reduction of methyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate as previously described.[21]

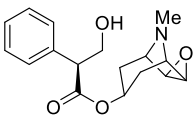


(*R*)-2-(6-Methoxynaphthalen-2-yl)propan-1-ol ((*R*)-1-16). Commercially available (*R*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (25 mg, 0.109 mmol) was converted to **(*R*)-1-16** following the general procedure for the preparation of primary alcohols to afford a white solid (13.7 mg, 57%); $[\alpha]_D^{21.7}$ = 18.3 (c 1.37 $CDCl_3$). Spectral data matched that of compound **(*S*)-1-16.**



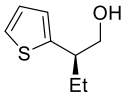


Ethyl (*S*,*E*)-5-Hydroxy-4-methylpent-2-enoate (1-28). A dry reaction flask was charged with a magnetic stir bar and dry LiCl (12.5 mg, 0.294 mmol). Under an atmosphere of argon, acetonitrile (3 mL), triethylphosphonoacetate (59 µL, 0.29 mmol, 1.2 equiv), and DIPEA (43 µL, 0.25 mmol) were added sequentially. Next (2*R*)-3-((*tert*-butyl(diphenyl)silyl)oxy)-2-methylpropanal[27] (**S1-8**) (80 mg, 0.25 mmol) was added and the reaction mixture was stirred under argon for 24 h.[28] The reaction was quenched by the addition of saturated NH_4Cl (aq) (5 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 5mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated in vacuo. After flash column chromatography (EtOAc/Hex) on silica, 75.6 mg of a clear oil containing known ethyl (*S,E*)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylpent-2-enoate (**S1-9**),[29] along with some amount of starting aldehyde. The mixture was dissolved in THF (0.5 mL) in a small reaction vessel. A 1 M solution of tetrabutylammonium fluoride (290 µL, 0.29 mmol) was added, and the solution was allowed to stir overnight. The mixture was diluted in water (5 mL), and extracted with diethyl ether (5 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography (Et_2O/Hex) on silica to afford alcohol **1-28** a clear oil (11.7 mg, 30% over 2 steps); $[\alpha]_D^{22.4}$ = -27.1 (c 0.59 $CHCl_3$) Spectral data matched those reported in the literature.[30] The reported rotation was in reasonable agreement with data: $[\alpha]_D^{21}$ = -21.6 (c 1.08 $CHCl_3$), 83% ee.[30]

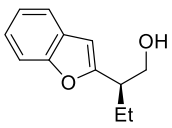


Scopolamine (1-29). Prior to use, the scopolamine hydrobromide trihydrate salt was transferred to a separatory funnel filled with DCM and saturated $NaHCO_3$ and extracted in DCM. The aqueous layer was washed with DCM (2x). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield the free-based **1-29**

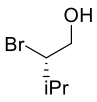
as a white solid.



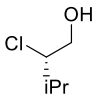
(*R*)-2-(Thiophen-2-yl)butan-1-ol (1-30). (*R*)-2-(Thiophen-2-yl)butanoic acid (25.0 mg, 0.147 mmol, 90% ee) was converted to alcohol **1-30** following the general procedure for the preparation of primary alcohols to afford a clear oil (7.3 mg, 32%); $[\alpha]_D^{23.0}$ = 14.9 (c 0.73 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.18 (m, 1H), δ 6.98 (dd, *J* = 5.1, 3.4 Hz, 1H), δ 6.92 – 6.86 (m, 1H), δ 3.78 (ddd, *J* = 11.0, 7.7, 5.4 Hz, 1H), δ 3.73-3.66 (m, 1H), δ 3.12-3.03 (m, 1H), δ 1.85-1.73 (m, 1H), δ 1.69-1.59 (m, 1H), δ 1.48 (t, *J* = 6.5 Hz, 1H), δ 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 126.9, 125.0, 123.9, 67.6, 46.1, 26.4, 12.0. HRMS (CI/CH_2Cl_2) m/z calcd for $C_8H_{13}OS$ $[M + H]^+$ 157.0682, found 157.0687.



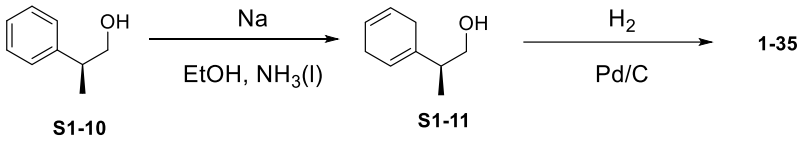
(*R*)-2-(Benzofuran-2-yl)butan-1-ol (1-31). (*S*)-2-(Benzofuran-2-yl)butanoic acid (24.2 mg, 0.118 mmol, 92% ee) was converted to alcohol **1-31** following the general procedure for the preparation of primary alcohols to afford a clear oil (7.4 mg, 33%); $[\alpha]_D^{21.1}$ = 17.8 (c 0.74 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), δ 7.52-7.46 (m, 2H), δ 7.33 - 7.28 (m, 1H), δ 7.25 - 7.21 (m, 1H), δ 3.93 - 3.82 (m, 2H), δ 2.99 – 2.91 (m, 1H), δ 1.92 - 1.82 (m, 1H), δ 1.77 (ddd, *J* = 16.0, 11.7, 7.4 Hz, 1H), δ 1.39 (br s, 1H), δ 0.94 (t, *J* = 7.4 Hz, 3H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 142.3, 127.5, 124.5, 122.5, 120.7, 120.3, 111.9, 65.6, 40.8, 23.9, 12.2. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{12}H_{14}O$ $[M]^+$ 190.0994 found 190.0994.

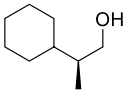


(*S*)-2-Bromo-3-methylbutan-1-ol (1-33). (*S*)-2-Bromo-3-methylbutanoic acid (200 mg, 1.11 mmol), was converted to **1-33** following the general procedure for the preparation of primary alcohols to afford a clear oil (123 mg, 66%); $[\alpha]_D^{21.5}$ = –3.4 (c 1.13 $CDCl_3$) Spectral data matched those reported in the literature.[31]



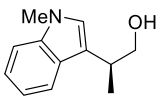
(*S*)-2-Chloro-3-methylbutan-1-ol (1-34). Alcohol **1-34** was synthesized according to known literature procedure.[32] The observed and literature optical rotations were in good agreement: $[\alpha]_D^{20.8} = -3.59$ (neat); $_{lit}[\alpha]_D^{20} = -3.58$ (neat), 98-99% ee.[33]



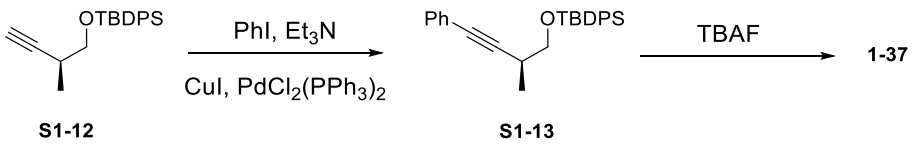


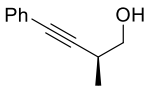
(*S*)-2-Cyclohexylpropan-1-ol (1-35). The conversion of (*S*)-2-phenylpropan-1-ol (**S1-10**) to (S)-2-(cyclohexa-1,4-dien-1-yl)propan-1-ol (**S1-11**) has been previously reported.[34] Alcohol **S1-10** (100 mg, 0.734 mmol) and EtOH (0.15 mL) were cooled to –78 °C in a dry round bottom equipped with a glass stir bar and gas condenser filled with dry ice/acetone. Next, ammonia (1 mL) was condensed into the round bottom. Freshly cut sodium (143 mg, 6.24 mmol) was added quickly, and the mixture quickly turned a deep blue. The reaction mixture was allowed to stir at –78 °C for 6 h before the reaction was quenched by the addition of saturated NH_4Cl (aq) (1 mL). The reaction mixture was allowed to warm to RT, diluted in brine, transferred to a separatory funnel, and extracted with DCM (3x). The organic extracts were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo to yield 76.8 mg of crude, clear oil, which was carried forward without further purification. The crude oil was dissolved in MeOH (5.4 mL) and transferred to a round bottom flask charged with a stir bar and 5% Pd/C (114 mg, 0.054 mmol). The reaction mixture was stirred under H_2 (g) (1 atm) overnight. The reaction mixture was then filtered through a pad of celite and purified by flash column chromatography (EtOAc/Hex) on silica to afford **1-35** as a clear oil (18.4 mg, 18% over 2 steps). Spectral data matched those reported in the literature for the enantiomer of **1-35**.[35] The synthetic sample and appropriate optical rotation

compared with the literature sample: $[\alpha]_D^{22.1}$ = –2.3 (c 1.36 $CHCl_3$), $_{lit}[\alpha]_D^{25}$ = 1.94 (c 2.3 $CHCl_3$)



(*S*)-2-(1-Methyl-1H-indol-3-yl)propan-1-ol (1-36). (*S*)-2-(1-Methyl-1H-indol-3-yl)propanoic acid (23.3 mg, 0.115 mmol, 84% ee) was converted to alcohol **1-36** following the general procedure for the preparation of primary alcohols to afford a pale yellow oil (7.9 mg, 36%); $[\alpha]_D^{21.2}$ = 4.2 (c 0.79 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), δ 7.31 (d, *J* = 8.2 Hz, 1H), δ 7.24-7.21 (m, 1H), δ 7.14-7.08 (m, 1H), δ 6.91 (s, 1H), δ 3.84-3.77 (m, 2H), δ 3.76 (s, 3H), δ 3.33-3.25 (m, 1H), δ 1.42 (br s, 1H), δ 1.39 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 127.3, 126.2, 121.9, 119.4, 119.0, 116.5, 109.5, 68.2, 34.0, 32.8, 17.6. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{12}H_{16}NO$ $[M + H]^+$ 190.1226, found 190.1232.





(*S*)-2-Methyl-4-phenylbut-3-yn-1-ol (1-37). (*S*)-*tert*-Butyl((2-methylbut-3-yn-1-yl)oxy)diphenylsilane (**S1-13**) was synthesized according to know literature procedure.[36] A flame-dried round bottom flask was charged with a stir bar, **S1-13** (100 mg, 0.310 mmol), PhI (40 µL, 0.357 mmol), and Et_3N (2 mL). Argon was bubbled through the solution for 30 min prior to the addition of CuI (12 mg, 0.062 mmol) and $PdCl_2(PPh_3)_4$ (44 mg, 0.062 mmol). The reaction mixture was stirred for 24 h before the addition of saturated NH_4Cl (aq) (5 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated in vacuo. After flash column chromatography (EtOAc/Hex) on silica, 59 mg of a clear oil containing (*S*)-*tert*-butyl((2-methyl-4-phenylbut-3-yn-1-yl)oxy)diphenylsilane (**S1-13**), along with 16 mol% of **S1-12**

(as determined by ^{1}H NMR analysis) were isolated. The product was dissolved in THF (0.4 mL) in a small reaction vessel. A 1 M solution of tetrabutylammonium fluoride (220 μL, 0.22 mmol) was added, and the reaction mixture was allowed to stir overnight. The solution was diluted in water, and extracted with diethyl ether (5x). The organic fractions were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **1-37** a clear oil (19.3 mg, 39% over 2 steps); $[\alpha]_D^{22.2}$ = –34.9 (c 1.93 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.37 (m, 2H), δ 7.33-7.22 (m, 3H), δ 3.70-3.57 (m, 2H), δ 2.90 (app sex, *J* = 6.7 Hz, 1H), δ 1.94 (br s, 1H), δ 1.27 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.8, 128.4, 128.1, 123.4, 91.2, 82.6, 67.0, 30.3, 17.2. HRMS (CI/CH_2Cl_2) m/z calcd for $C_{11}H_{12}O$ $[M]^+$ 160.0888 found 160.0890. HPLC chiral analysis (Chiralcel AD with AD guard, 2% *i*-PrOH in *n*-hexane, 1.0 mL/min, UV detection at 254 nm, tR = 15.16 min, tS = 17.07 min) resulted in an estimated enantiomeric excess of >99%. Racemic **1-37** was synthesized using the same procedure and used as a standard for HPLC analysis.

1.5 References

[1] Silverstein, R. M.; Webster, F. X.; Kiemle, D. J.; Bryce, D. L. *Spectrometric Identification of Organic Compounds*, 7th edition; Wiley: Hoboken, NJ, 2015.
[2] Flack, H. D.; Bernardinelli, G. *Chirality* **2008**, *20*, 681–690.
[3] (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543−2549. (b) For a detailed explanation of the advanced Mosher's method, see: Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc*. **2007**, *2*, 2451−2458.
[4] (a) El-Elimat, T.; Figueroa, M.; Raja, H. A.; Adcock, A. F.; Kroll, D. J.; Swanson, S. M.; Mansukh, C. W.; Pearce, C. J.; Oberlies, N. H. *Tetrahedron Lett.* **2014**, *54*, 4300–4302. (b) Ojika, M.; Itou, Y.; Sakagami, Y. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 1568–1573.
[5] (a) Freedman, T. B.; Cao, X.; Dukor, R. K.; Nafie, L. A. *Chirality* **2003**, *15*, 743–758. (b) Yang, G.; Xu, Y. *Top. Curr. Chem.* **2013**, *298*, 189–236.
[6] Harada, N.; Nakanishi, K.; Berova, N. In *Comprehensive Chiroptical Spectroscopy, Vol. 2: Applications in Stereochemical Analysis of Synthetic Compounds, Natural Products, and Biomolecules*, 1st ed.; Wiley: Hoboken, NJ, 2012; pp 115–166.
[7] Parsons, S. *Tetrahedron*: *Asymmetry* **2017**, *28*, 1304–1313.
[8] Latypov, S. K.; Ferreiro, M. J.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998,** *120*, 4741–4751.
[9] Ramón, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996,** *79*, 875–894.
[10] Fukui, H.; Fukushi, Y.; Tahara, S. *Tetrahedron Lett.* **2005,** *46*, 5089–5093.
[11] Wagner, A. J.; David, J. G.; Rychnovsky, S. D. *Org. Lett.* **2011**, *13*, 4470–4473.
[12] Horeau, A. *Tetrahedron Lett.* **1961**, *15*, 506–512.
[13] Miller, S. M.; Samame, R. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2012**, *134*, 20318–20321.
[14] Burtea, A.; Rychnovsky, S. D. *Org. Lett.* **2017**, *19*, 4195–4198.

[15] Perry, M. A.; Trinidad, J. V.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 472–475.
[16] Wagner, A. J.; Miller, S. M.; King, R. P.; Rychnovsky, S. D. *J. Org. Chem.* **2016**, *81*, 6253–6265.
[17] Birman, V. B.; Li, X. *Org. Lett.* **2008**, 10, 1115−1118.
[18] A brief optimization of conditions to run CEC reactions is given in section 1.4.3
[19] Arjona, O.; Pérez-Ossorio, R.; Pérez-Rubaicaba, A.; Quiroga, M. L**.** *J. Chem. Soc., Perkin Trans. 2*, **1981**, 597–603.
[20] Birman, V.B.; Jiang, H., *Org. Lett.* **2005**, 7, 3445–3447.
[21] Koul, S.; Koul, J. L., Singh, B.; Kapoor, M.; Parshad, R.; Manhas, K.S.; Taneja, S.C.; Qazi, G.N. *Tetrahedron Asymmetry* **2005**, *16*, 2575–2591.
[22] Bert, K.; Noël, T; Kimpe, W.; Goeman, J. L.; Van der Eycken, J. *Org. Biomol. Chem.* **2012**, *10*, 8539–8550.
[23] Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2010**, 132, 3612–3620.
[24] Xie, J-H.; Zhou, Z-T.; Kong, W-L.; Zhou, Q-L. *J. Am Chem. Soc.* **2007**, 129, 1868–1869.
[25] Wang, Q.; Liu, X.; Liu, X.; Li, B.; Nie, H.; Zhang, S.; Chen, W. *Chem. Commun.* **2014**, 50, 978–980.
[26] Wang, X-N.; Lv, H.; Huang, X-L.; Ye, S. *Org. Biomol. Chem.* **2009**, 7, 346–350.
[27] Fürstner, A.; Kattnig, E.; Lepage, O., *J. Am. Chem. Soc.* **2006**, *128*, 9194–9204.
[28] Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Satai, T. *Tetradedron Lett.* **1984**, 25, 2183–2186.
[29] Pasqua, A. E.; Ferrari, F. D.; Crawford, J. J.; Rodolfo, M. *Tetrahedron Lett*. **2012**, 53, 2114–2116.
[30] Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. *Tetrahedron Lett.* **1997**, 38, 3419–3422.
[31] Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 41, 4821–4823.
[32] Birk, C.; Voss, J. *Tetrahedron* **1996**, 52, 12745–12760.
[33] Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316–318.
[34] Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, 36, 9129–9132.
[35] Lee, S.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2013**, 135, 7126–7129.
[36] Trost, B. M.; Papillon, J. P. N. *J. Am. Chem. Soc.* **2004**, 126, 13618–13619.

Chapter 2. Heteroatom-Directed Acylation of Secondary Alcohols to Assign Absolute Configuration

2.1 Abstract

Birman's HBTM catalyst is effective for the enantioselective acylation and kinetic resolution of benzylic secondary alcohols. The enantioselective acylation has now been extended to secondary alcohols bearing electron-withdrawing groups such as halides and other heteroatoms. The level of selectivity is modest to good and is sufficient for determining configuration using the competing enantioselective conversion method. A mathematical analysis identifies conditions for achieving maximum differences in conversion and, consequently, assigning configuration with greater confidence. The new method is effective for halohydrins and secondary−tertiary 1,2-diols and was used to confirm the configuration of two inoterpene natural products.

2.2 Introduction

Our previous investigations into assigning the absolute configuration of β-chiral primary alcohols led us to the observation that halides acted as directing groups in the same sense as aromatic and other π-containing groups (see chapter 1). This prompted us to wonder whether these, or other heteroatoms, would act as directing groups for a CEC method for secondary alcohols. These motifs are found in both medicinally relevant molecules, as well as natural products. A few examples are shown in Figure 2-1. Such a method would be of use to the fields of medicinal, synthetic, and natural products chemistry.

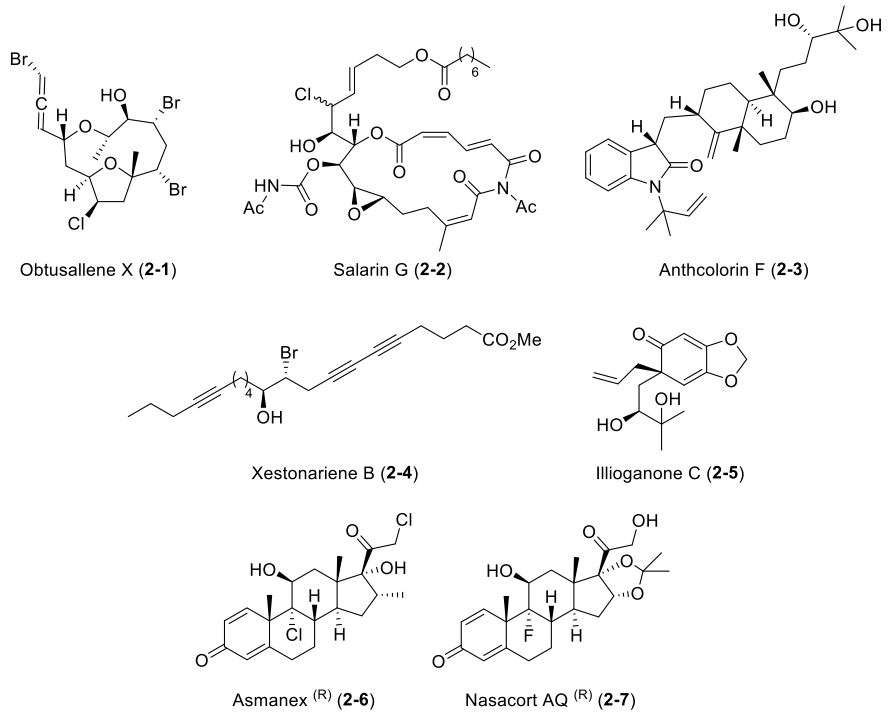


Figure 2-1 Examples of natural products and medicinally relevant molecules containing α-heteroatom bearing secondary alcohols

2.2.1 Other methods to assign the configuration of α-heteroatom bearing secondary alcohols

Perhaps the most common method to assign the configuration of chiral secondary alcohols, including those that bear an α-heteroatom, is Mosher's method. As this was discussed in detail in chapter 1, I will not delve into it here.

A subset of these molecules are 1,2-diols. One of the more common methods for absolute stereochemical assignment is complexation with $Mo_2(OAc)_4$ and analysis of the CD spectrum of the resulting complex, known as Snatzke's method.[37]

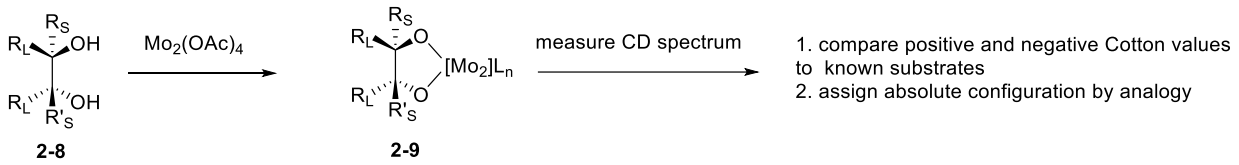


Figure 2-2 Snatzke's method

Snatzke's method is an empirical method in which a 1,2-diol, such as **2-8**, is treated with $Mo_2(OAc)_4$, and form a metal complex such as, **2-9**. The generated cyclic complex has reduced conformational freedom. It has been demonstrated for many different 1,2-diols, (1'-2', 2'-2', 1'-3', and 2'-3' diols) that different configurations of the substituents lead to positive or negative bands in the ICD (induced circular dichroism) spectrum, depending on the absolute configuration of the 1,2-diol. By comparison of an experimental ICD spectrum to an analogous substrate, one can infer the absolute configuration of the substrate.

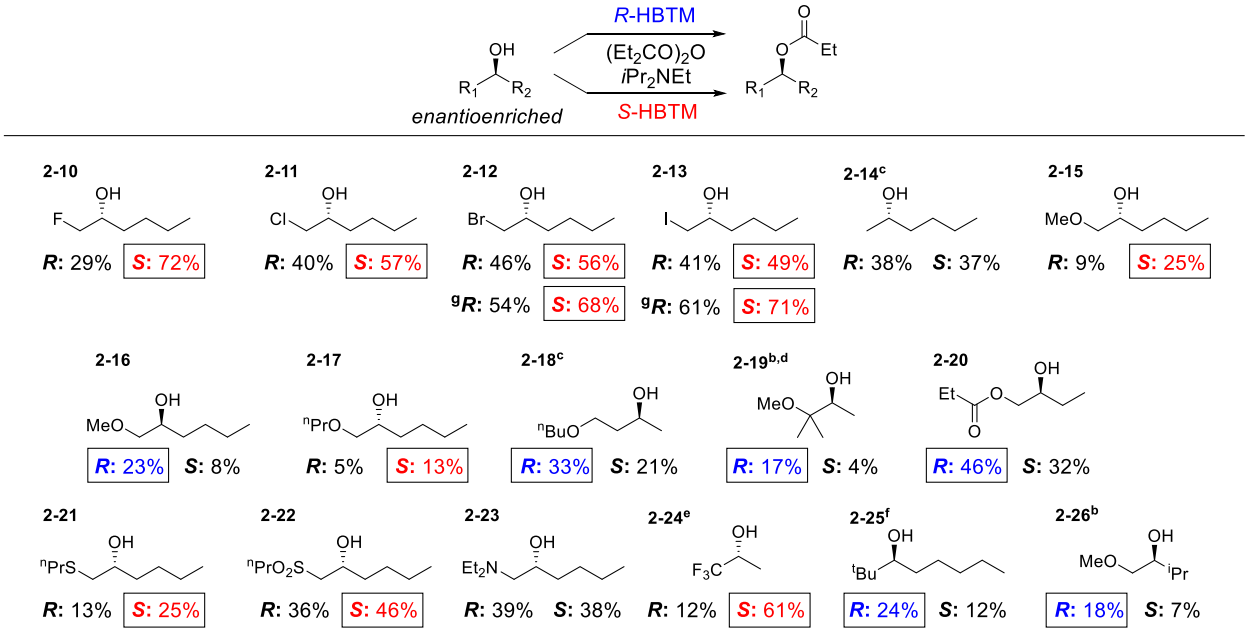
2.3 Results

I am grateful to Mr. Christopher C. Ross. Many of the CEC experiments were carried out by him under my supervision.

2.3.1 CEC investigations

We began by determining the differences in conversion for the acylation of a series of vicinal halo-alcohols, Scheme 2-1. Fluoro alcohol **2-10** was remarkably selective for acylation with *S*-HBTM, consistent with the fluoromethyl substituent acting as a directing group in the same sense as an aromatic group. Chloride **2-11**, bromide **2-12**, and iodide **2-13** all reacted faster with *S*-HBTM, and the differences in conversion decreased down the group. Not surprisingly, aliphatic alcohol **2-14** showed no appreciable selectivity for acylation with *R*- or *S*-HBTM. The rates of acylation were also reduced relative to the substrates bearing a halide.

Scheme 2-1 [a] CEC Results for the Conversion of Secondary Alcohols Bearing a Vicinal Heteroatom



[a] Optically enriched alcohols (0.1 M) were acylated with propionic anhydride (1.3 equiv) in the presence of *R*- or *S*-HBTM (10 mol%) and *i*-Pr_2NEt (1.2 equiv) in $CDCl_3$ (100 µL total volume). After 30 min, the reactions were diluted to 600 µL in $CDCl_3$, and percent conversion was determined by proton NMR analysis. The faster reaction is boxed. The results from run to run were reproducible.[38] [b]60 min reaction time. [c]120 min reaction time. [d]CEC reaction run with 0.15 M alcohol. [e]CEC reaction run with 0.01 M alcohol [f]CEC reaction run with 0.35 M alcohol for 240 min. [g] CEC reaction run with propionic anhydride (3 equiv) and 0.075 M alcohol.

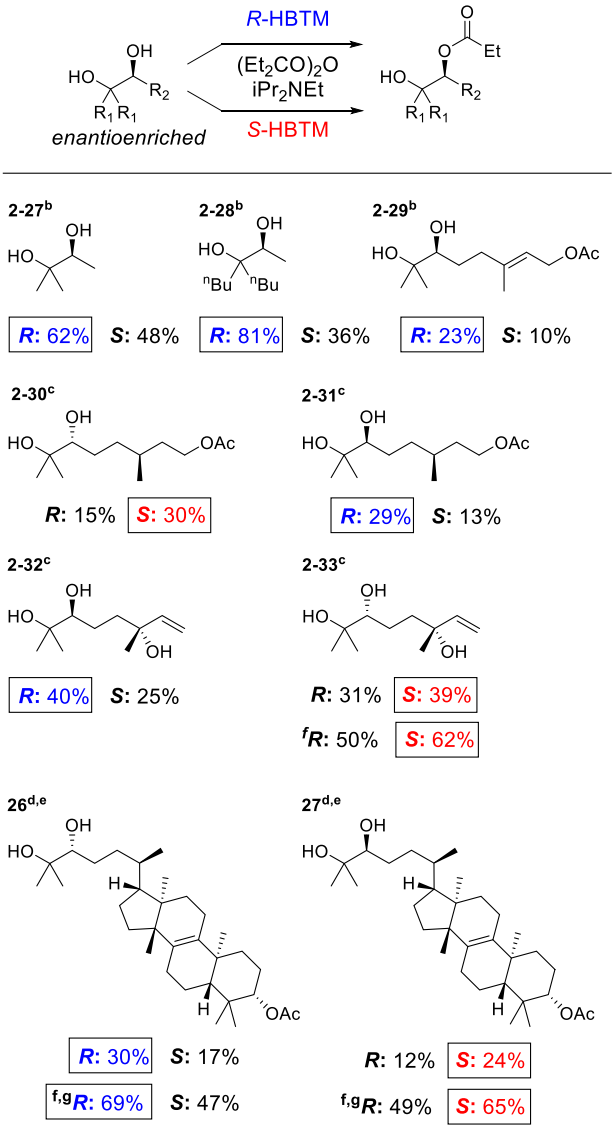
Next, we turned our attention toward oxygen containing directing groups. Enantiomeric primary ethers **2-15** and **2-16** displayed approximately equal and opposite reactivity for acylation by *S*- or *R*-HBTM. Slightly bulkier *n*-propyl ether **2-17** was slower to acylate than the other ethers, and tertiary ether **2-19** was substantially slower to acylate compared to the less congested ether-alcohols. Homovicinal ether **2-18** was acylated faster with *R*-HBTM, with the ether β to the stereogenic alcohol acting as the directing group, demonstrating that heteroatoms further removed than the α position can act as directing groups in simple cases. Notably, alcohol **2-18** displayed relatively slow rates of acylation, on par with aliphatic alcohol **2-14**.

Thioether **2-21** was moderately faster than its oxygen counterpart **2-17**, but still selective for *S*-HBTM. In contrast, tertiary amine **2-23** was acylated at the same rate with both *R*- and *S*-HBTM. This substrate showed a high level of acylation in the absence of HBTM (27%), indicating that most of the observed acylation product arose from an unselective background reaction. None of the other substrates investigated showed any significant background acylation in the absence of HBTM. The acylation of trifluoromethyl alcohol **2-24** was much faster and more selective than any of the previous substrates, requiring more dilute reaction conditions to obtain conversions measurably less than completion. Acylation of the *tert*-butyl alcohol **2-25** was very surprising; it acylated faster with *R*-HBTM, albeit at drastically slower overall rates relative to the heteroatom-bearing substrates. Having explored the range of heteroatoms that could serve as directing groups, and probed the effects of some substitutions on selectivity and conversion, we next investigated 2°-3° diols as substrates.

Results for 2°-3° diols are presented in Scheme 2-2. We were gratified to see selectivity for diols **2-27** and **2-28**, whose acylation was consistent with the tertiary alcohol acting as a directing group. Curiously, the acylation of diol **2-28** was faster than ether analog **2-19**, but less selective. A number of dihydroxylated monoterpenes were tested with the method. Geraniol derived **2-29** displayed good selectivity for *R*-HBTM. Diastereomeric diols **2-30** and **2-31**, derived from citronellol, demonstrated roughly equal and opposite reactivity with both enantiomers of HBTM. Diastereomeric triols **2-32** and **2-33** did not show completely complementary reactivity with *R*- and *S*-HBTM, demonstrating that other stereogenic centers within a molecule can influence the level of selectivity. However, the preferred catalyst in both cases faithfully predicted the configuration of the secondary alcohol in question. We were pleased to successfully apply the

method to complex diols **2-34** and **2-35**, which correspond to the acylated natural products inoterpene A and B, respectively.[39]

Scheme 2-2 CEC results for the conversion of chiral 2°-3° diols[a]

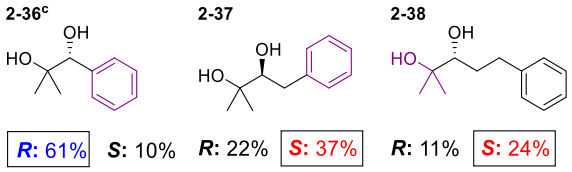


[a] Refer to the corresponding caption in Scheme 2-1. [b] 60 min reaction time. [c] 120 min reaction time. [d] Total volume of CEC reactions was 50 µL. [e] CEC reaction run with 0.04 M alcohol. [f]Propionic anhydride (3 equiv). [g] 3.5 h reaction time.

Given that π groups are excellent directors for the acylation of secondary alcohols, we wanted to determine how far an aromatic ring would have to be located from the stereocenter to have the

tertiary alcohol override its directing effect. The experiments are presented in Scheme 2-3. While the faster reaction was dictated by the phenyl group and the benzyl group in **2-36** and **2-37**, respectively, the acylation of compound **2-38** was directed by the tertiary alcohol, based on the observed faster acylation with *S*-HBTM. If the arene is γ to the stereogenic alcohol, a vicinal tertiary alcohol will direct the faster reaction, and thus facilitate a configuration assignment. Understanding the relative directing effect of different substituents will allow configuration assignments to be made with a wide variety of structures.

Scheme 2-3 CEC results for the conversion of 2°-3° diols with an aromatic ring present[a,b]



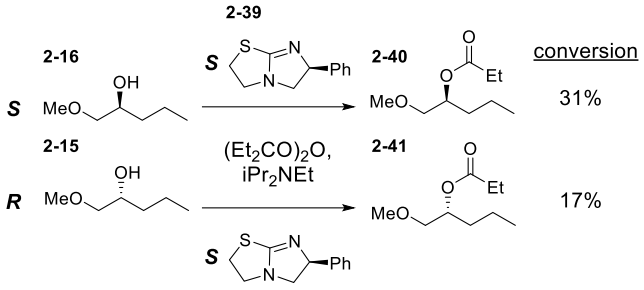
[a] Refer to the corresponding caption in Scheme 1. [b] The directing group is highlighted in purple. [c] CEC reaction run with 0.04 M alcohol.

During the course of our investigations, we determined that running CEC reactions to higher conversions, and with greater equivalents of anhydride led to greater differences in conversion. This effect is analyzed in detail in the discussion section, *vida infra*. A handful of substrates were run under these optimized conditions, and the results are shown in Schemes 2-1 and 2-2. In all cases, we obtained larger differences in conversion. The increases were relatively modest for the less selective substrates **2-12**, **2-13**, and **2-33**. For 2°-3° diols **2-34** and **2-35**, larger improvements in differences in conversion were obtained, as would be predicted for more selective reactions.

Tetramisole **2-39** is a simpler analog of HBTM, featuring a 5,5- rather than 5,6-ring system. It is a selective acylation catalyst for benzylic alcohols. We wanted to determine if it would display rate differences in the acylation of vicinal heteroatom bearing secondary alcohols. Because tetramisole is only commercially available as the *S*-enantiomer (structurally analogous to *R*-HBTM), we

probed its selectivity by reaction with two enantiomeric substrates (Scheme 4). Tetramisole was substantially slower to acylate **2-16** and **2-15** than HBTM, but showed the same absolute sense of selectivity.

Scheme 2-4 Selective acylations reactions catalyzed by (*S*)-tetramisole[a]



[a] The alcohol (0.5 M), *i*-PrNEt$_2$ (2 equiv), and *S*-tetramisole (20 mol%) were combined in $CDCl_3$ at RT, followed by propionic anhydride (2 equiv). After 2 h, both reactions (100 µL total volume) were diluted with $CDCl_3$ (500 µL), and conversion was determined by ^{1}H NMR analysis.

The above results are consistent with the previously developed mnemonic for secondary alcohols that bear a π-group, Figure 3. With the better polar or π-directing group oriented to the left, and the other group pointed to the right, if *R*-HBTM is the faster reaction, then the alcohol is pointed forward. Inversely, if *S*-HBTM is the faster reaction, then the alcohol points backward.

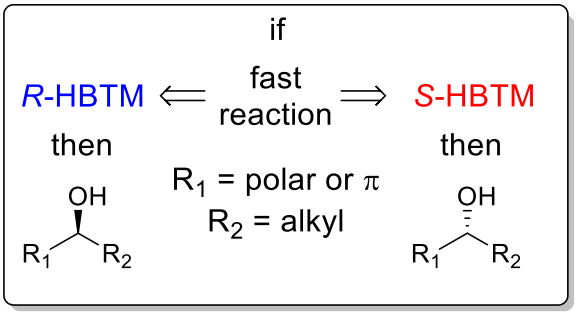


Figure 2-3 Mnemonic to predict the configuration of secondary alcohols with heteroatom substitution.

2.3.2 Discussion

Clearly the selectivity of HBTM for secondary alcohols without π-systems cannot be rationalized by π-π or π-cation interactions.[40] Because these substrates are selective in the same fashion as π-bearing substrates, it is reasonable to hypothesize they interact with HBTM with a similar transition-state geometry. This geometry implies that there would be a favorable interaction between the polar group of the substrate and the cationic acylated catalyst in the rate-determining step of the reaction. An examination of the selectivity trends within the halogen series of alcohols Scheme 2-1 provides a clue to the origin of this proposed interaction. If the interaction were mainly dispersive in nature, one would predict that iodo-alcohol **2-13** would be the most selective of the series. As fluoro-alcohol **2-10** is the most selective, this points toward a primarily electrostatic interaction. Because fluorine is the most electronegative element, the carbon-fluorine bond is polarized, placing a partial negative charge on the fluorine. It is reasonable to expect that this would interact favorably with the cationic catalyst, adopting a conformation during acylation that places the alkyl group in the least crowded environment. A hypothetical transition state geometry for the fast-reacting catalyst-alcohol combination is presented in Figure 2-4.

Possible transition state:

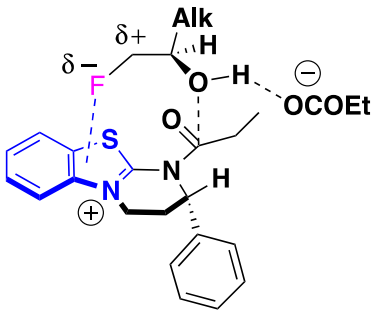


Figure 2-4 Proposed favorable dipole-charge interactions in the preferred transition state

Scheme 2-4 reports the selectivities of aromatic HBTM and aliphatic tetramisole with both π and heteroatom bearing secondary alcohols. The selectivities for 1-phenylpropan-1-ol are taken from the kinetic resolution of the racemate as reported by Birman and coworkers.[41] The selectivities for alcohols **2-15** and **2-16** are calculated based upon the conversions from our CEC method. For both substrates, the overall rates are much faster with HBTM, but the selectivities are comparable for the same substrate. Tetramisole and HBTM display the same sense of selectivity for aromatic substrates and polar substrates. These similarities are consistent with the vicinal heteroatom-bearing alcohols interacting with acylated HBTM and acylated tetramisole in a similar fashion.

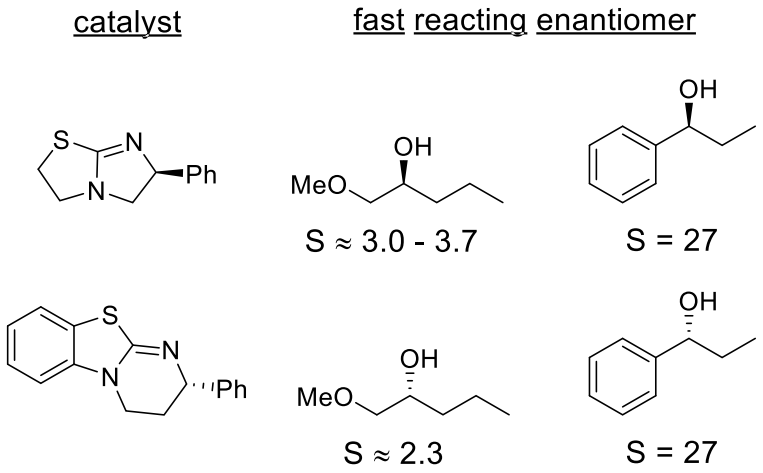


Figure 2-5 Comparison of selectivity for acylation reactions with tetramisole and HBTM

In considering the acyl transfer reactions, there are two trends of interest: overall reaction rate and selectivity. While the two correlate to some extent, there are several exceptions. To visualize the data, a few representative examples of the substrates, calculated selectivities and the rates for the faster reaction are plotted in Figure 2-6.[42] The selectivities and rates are estimated from one-point CEC data, and there is some error expected in these numbers, as there is some small variability when measuring the level of conversion for a CEC reaction.[38] Regardless, they quantify some interesting trends in reactivity and selectivity.

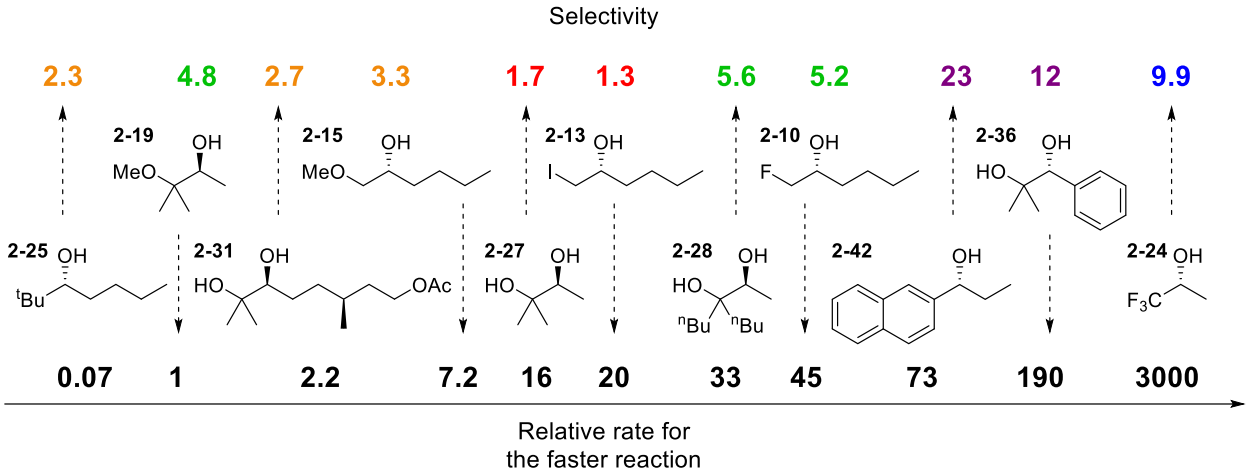


Figure 2-6 Comparison of the rates of reaction for the fast enantiomer and the selectivity of the acylation

The slowest substrate investigated was neopentylic alcohol **2-25**. It is curious that it displays the same sense of selectivity as if the *tert*-butyl group were treated as the "directing group." It is hard to imagine that the *tert*-butyl group interacts favorably with the catalyst in the same fashion as the other alcoholic substrates bearing additional heteroatoms. Thus, the selectivity cannot be rationalized solely upon electronic arguments.

It appears increasing the steric bulk of the non-directing group slows the rate of conversion (e.g. **2-27** vs. **2-31**). Similarly, increasing the steric bulk of the directing group slows down the rate of conversion (e.g. **2-19** vs. **2-15**). Curiously though, dibutyl alcohol **2-28** reacts about twice as fast as its dimethyl counterpart **2-27**, with the favored catalyst. The bulky butyl groups may restrict the diol to a more favorable conformation for acylation. Notably, dibutyl alcohol **2-28** was roughly three times more selective than dimethyl alcohol **2-27**.

In comparing ethers to alcohols, alcohol **2-27** reacts an order of magnitude faster than analogous ether **2-19** with the matched catalyst. Ether **2-19** is over twice as selective as **2-27**. This effect is consistent with the enhanced selectivity with relatively hydrophobic directing groups (**2-19**, **2-25**, **2-28**).

Naphthyl alcohol **2-42**[11] was included to show how this new class of substrates compares to π-bearing alcohols. Its acylation was faster than most of the non-π alcohols for the matched catalyst. It was also substantially more selective than any of the other entries. Surprisingly, it was two times slower than the presumably more sterically congested diol **2-36**, and forty times slower than trifluoromethyl alcohol **2-24**. Because trifluoromethyl is strongly electron withdrawing, the reactive alcohol becomes more acidic. Deprotonation of the alcohol is predicted to take place in the transition state,[17] which suggests that alcohol acidity would be an important factor in the reaction rate. Alcohols **2-24** (CF_3), **2-10** (CH_2F), **2-12** (CH_2Br, relative rate = 25), **2-13** (CH_2I) and **2-14** (CH_3; relative rate = 3.2) are expected to have decreasing acidity, and they demonstrate an ordered decrease in reaction rate (Figure 6). The importance of alcohol acidity in acyl transfer rates has been previously reported.[43]

2.3.3 Kinetic analysis

In the previously developed CEC method for secondary alcohols bearing π-groups, HBTM was quite selective for a particular enantiomer of substrate alcohol, leading to large differences in conversion. In contrast, the current investigation exploits smaller selectivities, leading to smaller differences in conversion between two parallel reactions. Consequently, the assignment of the faster reaction may become more challenging. While more trials could increase the confidence in assigning the faster reaction, this is disadvantageous because it requires more material and labor. Another, more attractive solution would be to increase the absolute difference in observed conversion. Given that the method focuses on the use of enantioselective acylation catalysts, we considered the underlying kinetics. Let us first consider the hypothetical scenario where the reaction is simply first order in alcohol and zeroth order in all other reaction components.

2.3.3.1 First order assumption

If the HBTM catalyzed acylation of a chiral alcohol were first order in alcohol, and zeroth order in all other components, the reaction rate is governed by the following equation:

$$-\frac{d[OH]}{dt} = k[OH] \quad (\mathbf{2.1})$$

The integrated rate law for a first order reaction is:

$$[A]_t = [A]_0 e^{-kt}$$

Conversion is given by the following equation:

$$conv = 1 - \frac{[OH]_t}{[OH]_0} = 1 - \frac{[OH]_0 e^{-kt}}{[OH]_0} = 1 - e^{-kt} \quad (\mathbf{2.2})$$

Thus for the two parallel reactions:

$$conv_{fast} = 1 - e^{-k_{fast}t} \quad (\mathbf{2.3})$$

$$conv_{slow} = 1 - e^{-k_{slow}t} \quad (\mathbf{2.4})$$

The difference in conversion between the two parallel reactions is given by the following equation:

$$Diff.\,in\,conv. = e^{-k_{slow}t} - e^{-k_{fast}t} = e^{-k_{slow}t} - e^{-Sk_{slow}t} \quad (\mathbf{2.5})$$

Where

$$Selectivity\ (S) = \frac{k_{fast}}{k_{slow}} \quad (\mathbf{2.6})$$

Because we want to maximize difference in conversion, we are interested in the point where the difference in conversion switches from increasing to decreasing. We want to find where its derivative with respect to time is zero.

$$\frac{d}{dt}(Difference\ in\ conv.) = 0$$

$$-k_{slow}e^{-k_{slow}t} + Sk_{slow}e^{-Sk_{slow}t} = 0$$

$$k_{slow}e^{-k_{slow}t} = Sk_{slow}e^{-Sk_{slow}t} \quad (\mathbf{2.7})$$

A few algebraic manipulations lead to the following relationship, which holds true at maximum difference in conversion:

$$k_{slow}t = \frac{-\ln(S)}{(1-S)} \quad (\mathbf{2.8})$$

Substituting equation **2.8** into equation **2.3**:

$$Conv_{fast} = 1 - e^{-S*\frac{-\ln(S)}{(1-S)}}$$

$$Conv_{fast} = 1 - e^{\frac{S\ln(S)}{(1-S)}}$$

At maximum difference in conversion

$$Conv_{fast} = 1 - S^{\frac{S}{1-S}} \quad (\mathbf{2.9})$$

Substituting equation **2.8** into equation **2.4**:

$$Conv_{slow} = 1 - e^{-1*\frac{-\ln(S)}{(1-S)}}$$

At maximum difference in conversion

$$Conv_{slow} = 1 - S^{\frac{1}{1-S}} \quad (\mathbf{2.10})$$

Thus for two parallel first order reactions, the maximum difference in conversion is governed by the following equation:

$$Diff.in\ conv. = S^{\frac{1}{1-S}} - S^{\frac{S}{1-S}} \quad (\mathbf{2.11})$$

2.3.3.2 Second order assumption

If the HBTM catalyzed acylation of a chiral alcohol were first order in alcohol, first order in anhydride, and d[HBTM]/dt = 0, the reaction rate is governed by the following equation:

$$-\frac{d[OH]}{dt} = k[OH][anhydride] \quad (\mathbf{2.12})$$

If

$$[OH]_0 = [anhydride]_0$$

and

$$\frac{d[OH]}{dt} = \frac{d[anhydride]}{dt}$$

Then equation **2.12** becomes:

$$-\frac{d[OH]}{dt} = k[OH]^2 \quad (\mathbf{2.13})$$

The integrated rate law for this second order equation is:

$$\frac{1}{[OH]_t} = \frac{1}{[OH]_0} + kt$$

Conversion is given by the following equation:

$$conv = 1 - \frac{[OH]_t}{[OH]_0} = 1 - \frac{1 \Big/ \left(\frac{1}{[OH]_0} + kt\right)}{[OH]_0} = 1 - \frac{1}{\frac{[OH]_0}{[OH]_0} + [OH]_0 kt}$$

$$conv = 1 - \frac{1}{1 + [OH]_0 kt} \quad (\mathbf{2.14})$$

Thus for the two parallel reactions:

$$conv_{fast} = 1 - \frac{1}{1 + [OH]_0 k_{fast} t} \quad (\mathbf{2.15})$$

$$conv_{slow} = 1 - \frac{1}{1 + [OH]_0 k_{slow} t} \quad (\mathbf{2.16})$$

The difference in conversion between the two parallel reactions is given by the following equation:

$$Diff.in\ conv. = conv_{fast} - conv_{slow} = \frac{1}{1 + [OH]_0 k_{slow} t} - \frac{1}{1 + [OH]_0 S k_{slow} t} \quad (\mathbf{2.17})$$

Where

$$Selectivity\ (S) = \frac{k_{fast}}{k_{slow}} \quad (\mathbf{2.6})$$

Because we want to maximize difference in conversion, we are interested in the point where the difference in conversion switches from increasing to decreasing. We want to find where its derivative with respect to time is zero.

$$\frac{d}{dt}(Diff.in\ conv.) = 0$$

$$\frac{-[OH]_0 k_{slow}}{(1 + [OH]_0 k_{slow} t)^2} + \frac{[OH]_0 S k_{slow}}{(1 + [OH]_0 S k_{slow} t)^2} = 0$$

$$\frac{1}{(1 + [OH]_0 k_{slow} t)^2} = \frac{S}{(1 + [OH]_0 S k_{slow} t)^2} \quad (\mathbf{2.18})$$

A few algebraic manipulations lead to the following relationship, which holds true at maximum difference in conversion:

$$[OH]_0 k_{slow} t = \frac{1}{\sqrt{S}} \quad (\mathbf{2.19})$$

Substituting equation **2.19** into equation **2.15**:

$$Conv_{fast} = 1 - \frac{1}{1 + S * S^{-1/2}} = 1 - \frac{1}{1 + \sqrt{S}} \quad (\mathbf{2.20})$$

Substituting equation **2.19** into equation **2.16**:

$$Conv_{slow} = 1 - \frac{1}{1 + \sqrt[-2]{S}} \quad (\mathbf{2.21})$$

Thus for two parallel second order reactions, the maximum difference in conversion is governed by the following equation:

$$Diff.\,in\,conv. = \frac{1}{1 + \sqrt[-2]{S}} - \frac{1}{1 + \sqrt{S}} \quad (\mathbf{2.22})$$

2.3.3.3 Analysis and application of kinetics to CEC

We have previously determined that the determined that the HBTM catalyzed acylation of (1*R*,2*S*)-2-phenylcyclohexanol was first order in anhydride, catalyst, and alcohol.[44] Rapid pre-equilibrium between the catalyst and the acylated catalyst prior to the rate determining acylation of the alcohol leads to this interesting behavior. Because the concentration of HBTM remains constant, the reaction can be treated as an apparent second order reaction.

Figure 2-7 shows a plot of equations **2.9**, **2.10**, and **2.11**, which govern the maximum difference in difference for a first order reaction. It is interesting to note that these values are solely a function of the two rate constants, i.e., selectivity. Figure 2-7 shows that as selectivity increases, so does the maximum difference in the conversions of the two parallel reactions. Thus, more selective reactions lead to greater differences in conversion and consequently more confidence in a stereochemical assignment. Another implication of Figure 2-7 is that the maximum difference in

conversion is observed when the fast reaction reaches higher conversions. For instance, at S = 2 for a first order set of reactions, the fast reaction runs to 75% conversion at the point of maximum difference in conversion. Many of our CEC reactions from Schemes 2-1 and 2-2 were only run to low conversions, suggesting room for improvement.

Figure 2-7 Conversion and maximum difference in conversion were plotted as a function of selectivity assuming perfect first order behavior, according to equations **2.9**, **2.10**, and **2.11**.

Figure 2-8 shows the maximum differences in conversion that can be obtained from a CEC reaction, if the reaction is first order or second order in alcohol. As the selectivity of the two reactions increases, a first order reaction will give higher maximum differences in conversion. While we cannot change the mechanism of our CEC reactions, increasing the equivalents of the anhydride relative to the alcohol would push the reaction rate from a second-order reaction towards an apparent first-order reaction. We tested this prediction experimentally.

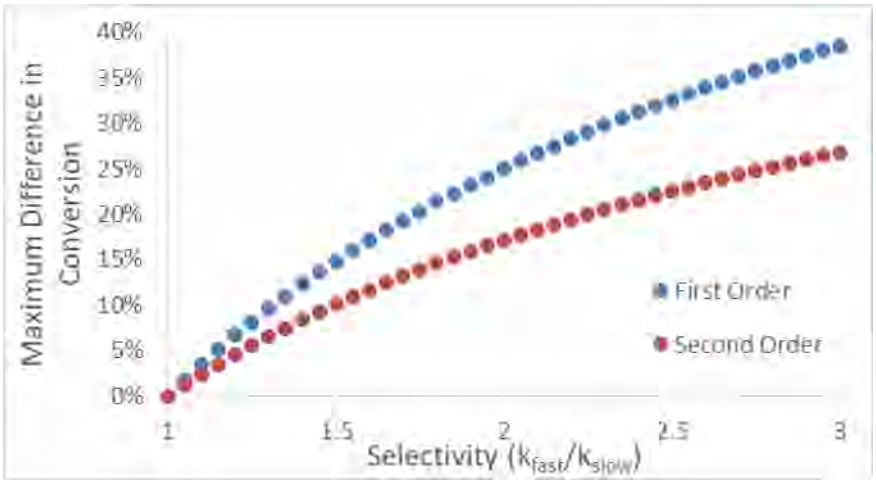
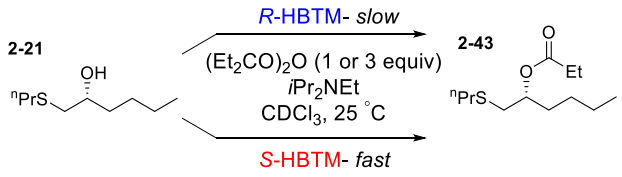


Figure 2-8 Maximum difference in conversion was plotted as a function of selectivity, assuming perfect first- or second-order behavior, according to eqs **2.11** and **2.22**.

Figure 2-9 shows the experimental conversion of alcohol **2-21** to ester with *R*- or *S*-HBTM, with different equivalents of anhydride. The difference in conversion was plotted against the conversion of the fast reaction in order to compare different reactions regardless of variations in absolute rates. In the first experiment, one equivalent of propionic anhydride relative to **2-43** was employed, and a maximum difference in conversion of around 21% was obtained, when the fast reaction was around 60% conversion. Under more "first-order conditions," with 3 equivalents of propionic anhydride, a maximum difference of around 26% was obtained when the fast reaction approached 80% conversion. These experiments confirm the mathematical analysis and demonstrate that the measured difference in conversion can be enhanced by a judicious choice of reaction conditions.



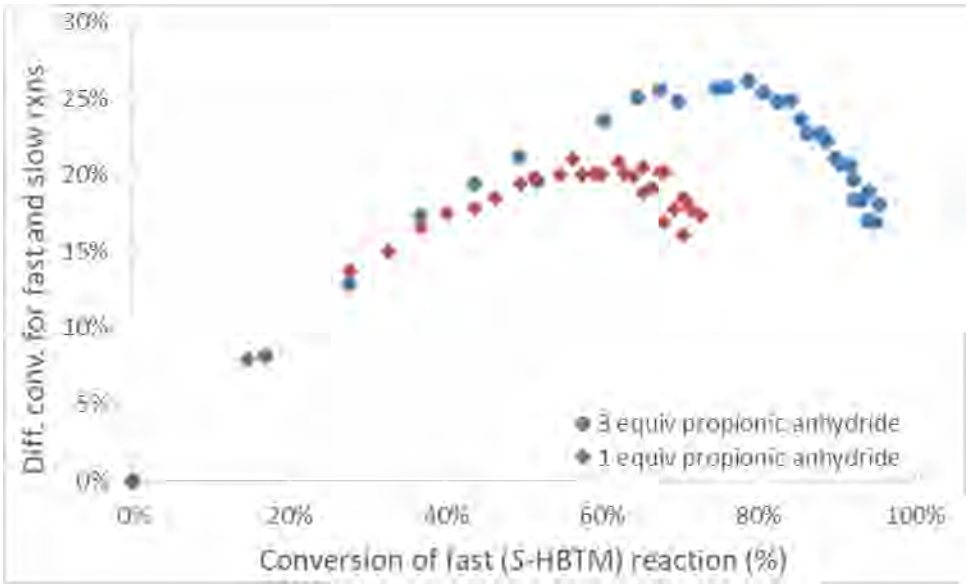


Figure 2-9 Difference in conversion of slow and fast CEC reactions with 1.0 and 3.0 equiv of propionic anhydride. The larger amount of propionic anhydride shifts the kinetics toward pseudo-first order dependence, and leads to a greater observed difference in conversion between the slow and fast reactions.

Thus the following two changes in reaction conditions will lead to greater differences in conversion, and subsequently greater confidence in stereochemical assignments:

•Running the faster reaction to higher conversions, with ca. 70–80% conversion appropriate for most situations.

•Running the CEC reactions with more equivalents of anhydride, pushing the reaction toward more "first-order" kinetics. Operationally, 3 equivalents of anhydride is sufficient to show enhanced differences in conversion.

Several substrates were run under these improved conditions in Schemes 2-1 and 2-2.[45] In all cases, the improved conditions lead to enhanced differences in conversion between the fast and slow acylation reactions. These changes increase the reliability of measured differences in selectivity and thus the confidence in configuration assignments using the CEC strategy.

2.3.4 Conclusions

In summary, we have developed a method to determine the absolute configuration of secondary alcohols that bear a vicinal heteroatom. The method uses the kinetic resolution catalyst HBTM. The method relies upon the previously unappreciated modest selectivities of HBTM for substrates that contain an electron-withdrawing heteroatom, rather than a π-system. Good substrates for the method were those containing ethers, thioethers, esters, fluorides, and chlorides. Less selective substrates include sulfones, bromides, and iodides. The method was unselective for tertiary amines, and unhindered aliphatic alcohols. Differences of 10% or greater in conversion are recommended for credible assignments of absolute configuration. We applied this method to the assignment of a number of 2°-3° vicinal diols.

Our data is consistent with the heteroatom directing group interacting with HBTM via an electrostatic interaction, though the details are not fully clear at this time. This selectivity would be an interesting area to investigate in the future using computational modeling.

We presented a new kinetic treatment of the competing enantioselective conversion method and mathematically determined optimal conditions to observe the largest difference in rates between two parallel reactions. To evaluate these predictions, we followed the reaction progress of two parallel reactions under specific second-order conditions, or pseudo first-order conditions. As predicted by the model, the first-order conditions led to higher differences in conversion. These modified conditions were applied to several substrates and resulted in greater differences in conversion. These new conditions will enhance the reliability of configuration assignments using the CEC strategy.

2.4 Supporting information

2.4.1 General information

All volumetric glassware and NMR tubes were oven-dried prior to use. The ^{1}H NMR and ^{13}C and spectra were recorded at 298.0 K. Chemical shifts (δ) were referenced to tetramethylsilane (0 ppm) for ^{1}H NMR, and $CDCl_3$ (77.16 ppm) for ^{13}C NMR. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sex = sextet, oct = octet, m = multiplet, app. = apparent, br. = broad), coupling constant(s) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using GC-ESI-TOF.

Unless otherwise stated, synthetic reactions were carried out in flame- or oven-dried glassware under an atmosphere of argon. All commercially available reagents were used as received unless stated otherwise. Solvents were purchased as ACS grade or better and as HPLC-grade and passed through a solvent purification system equipped with activated alumina columns prior to use. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm, or by staining with *p*-anisaldehyde, potassium permanganate, phosphomolybdic acid, or vanillin. Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns using ethyl acetate/hexanes gradients (0% EtOAc to 100% EtOAc).

2.4.2 Chemicals

All purchased chemicals were used without further purification unless otherwise noted. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Propionic anhydride was purchased from Sigma-Aldrich and distilled over CaH_2 prior to use. *N,N*-Diisopropylethylamine was distilled over CaH_2 prior to use. *R*-HBTM,[46] *S*-HBTM,[46] (*R*)-2-butyloxirane,[47] (S)-2-butyloxirane,[47] (*R*)-2-(*tert*-

butyl)-oxirane,[47] *O*-acetyl lanosterol,[48] and (*S*)-3-methylbutane-1,2-diol[49] were synthesized according to known literature procedure. (*R*)-1,1,1-Trifluoropropan-2-ol (**16**), AD-mix alpha, AD-mix beta, Methyl (*S*)-(–)-lactate, and (*S*)-butane-1,3-diol were purchased from Sigma-Aldrich. (*S*)-Butane-1,2-diol was purchased from ArkPharm. (*R*)-Ethyl 2-hydroxy-4-phenylbutanoate was purchased from Alfa Aesar. The absolute configuration of Compound **21** was assigned based on the reported rotation.[5061] The absolute configuration of compounds **26** and **27** were assigned based on the optically pure starting material used in the synthesis and by matching spectra with the known diastereomerically pure products.[51] The absolute configurations of all other compounds in Schemes 1-3 were assigned based on the configurations of known starting materials, or by Sharpless asymmetric dihydroxylation reactions that had previously been reported.

2.4.3 General CEC procedure

All CEC reactions were run under an atmosphere of air without stirring. $CDCl_3$ was used without further purification or drying.

Preparation of stock solutions.

***R*-HBTM solution**: A glass dram vial was charged with *R*-HBTM (10.0 mg, 0.0376 mmol) and $CDCl_3$ 1.50 mL (or 0.375 mL) was added. The resulting 0.025 M (or 0.100 M) solution of *R*-HBTM in $CDCl_3$ was capped. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

***S*-HBTM solution**: A glass dram vial was charged with *S*-HBTM (10.0 mg, 0.0376 mmol) and $CDCl_3$ 1.50 mL (or 0.375 mL) was added. The resulting 0.025 M (or 0.100 M) solution of *S*-HBTM in $CDCl_3$ was capped. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Diisopropylethylamine solution: A 1.00 mL volumetric flask was charged with *i*-Pr_2NEt (418 µL, 2.40 mmol) and filled to the 1 mL mark with $CDCl_3$. The resulting 2.40 M solution of *i*-Pr_2NEt in $CDCl_3$ was transferred to a capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Propionic anhydride solution: A 1.00 mL volumetric flask was charged with propionic anhydride (166 µL, 1.30 mmol) and filled to the 1 mL mark with $CDCl_3$. The resulting 1.30 M solution of propionic anhydride in $CDCl_3$ was transferred to a capped glass dram vial. The cap was wrapped in Parafilm® and stored at –20 °C for no longer than 3 weeks prior to use.

Substrate alcohol solutions: A dram vial was charged with an alcohol substrate (75.0 µmol), followed by $CDCl_3$ (250 µL) to make a ca. 0.30 M solution.

General CEC procedure: The 0.30 M alcohol solution (33.5 µL, 10 µmol) was added to two separate dram vials followed by additional $CDCl_3$ (11.5 µL). Next, 2.40 M *i*-Pr_2NEt solution (5.0 µL, 12 µmol) was added to each flask. The flask was then was charged with either enantiomer of 0.025 M HBTM (40 µL, 1.0 µmol). Propionic anhydride solution (1.30 M, 10 µL, 13 µmol) was added to each vial bringing the total reaction volume to 100 µL. The reaction flasks were capped, and allowed to sit for a given period of time before being diluted with $CDCl_3$ (500 µL).[52] Each diluted reaction mixture was transferred to an NMR tube, and a ^{1}H-NMR spectrum was taken of each sample to assay conversion.

General CEC procedure optimized to higher conversion: The 0.30 M alcohol (33.5 µL, 10 µmol) was added to two separate dram vials followed by additional $CDCl_3$ (21 µL). Next, 2.40 M *i*-Pr_2NEt solution (12.5 µL, 30.0 µmol) was added to each flask. The flask was then charged with either enantiomer of 0.10 M HBTM (10 µL, 1.0 µmol). The propionic anhydride (1.30 M, 23 µL, 30 µmol) was added to each vial bringing the total reaction volume to 100 µL. The reaction flasks

were capped, and allowed to sit for a given period of time[53] before being diluted with $CDCl_3$ (500 μL). Each reaction mixture was transferred to an NMR tube, and the ^{1}H-NMR spectrum was taken of each sample to assay conversion.

2.4.4 NMR time course experiments

Sample procedure: Stock solutions of *i*-Pr_2NEt, propionic anhydride, alcohol **13**, and HBTM in $CDCl_3$ were made following the general procedure outlined earlier. The NMR reactions are prepared by combining $CDCl_3$ (130 μL), 2.5 M *i*-Pr_2NEt (60 μL, 0.15 mmol), 0.15 M *R*-HBTM (100 μL, 0.015 mmol), and 0.6 M **13** (250 μL, 0.15 mmol) in an NMR tube. Propionic anhydride (2.50 M, 60 μL, 0.15 mmol) was added. The top of the NMR tube was covered with a nitrile glove and inverted once. The reaction time was measured from this point. The NMR tube was loaded into a spectrometer preheated to 298.0 K. ^{1}H scans were taken at regular intervals, and conversion was determined at each time point.

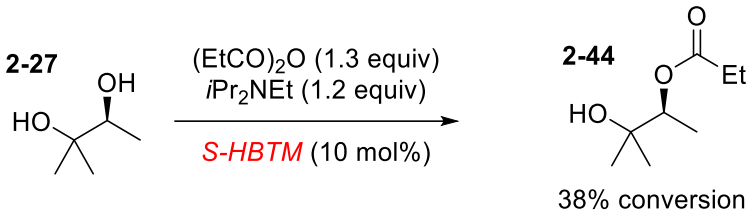
2.4.5 Determination of conversion

A full discussion of the determination of conversion for a CEC experiment can be found in chapter 1. Here I would like to include some further details on common problems that might be encountered, and general solutions.

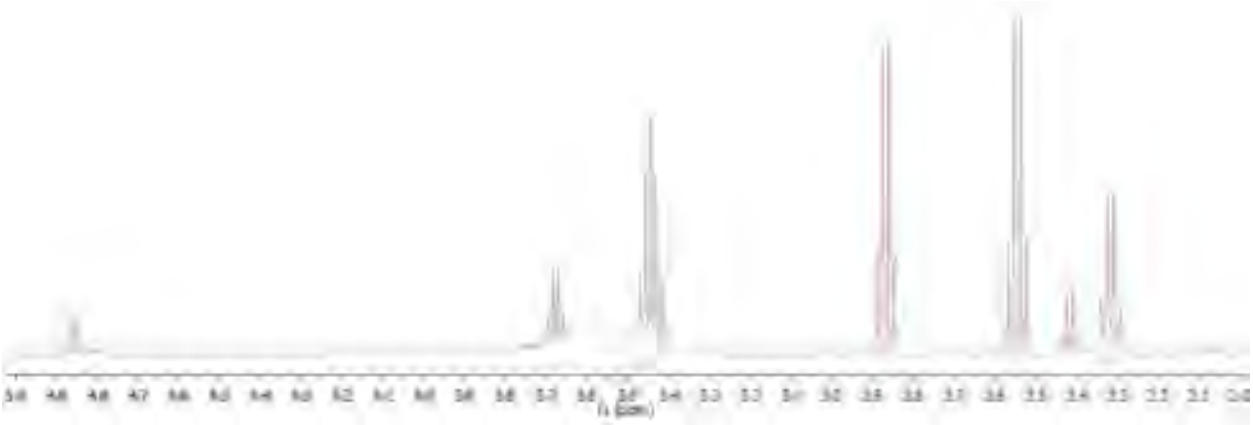
2.4.5.1 Bulk water in the NMR

Because HBTM is relatively moisture stable, we began running our analyses under an atmosphere of air, taking no steps to exclude atmospheric moisture. In some of our CEC NMRs, there was a broad peak, usually between 3-5 ppm, which obscured other peaks. In all cases we were able to find two identical sets of peaks in both reactions to determine conversion that were not covered by this large broad peak. However, we later realized that this peak corresponded to bulk (rather than monomeric) water in the NMR.[54] Shown below is a severe example of this contamination. The

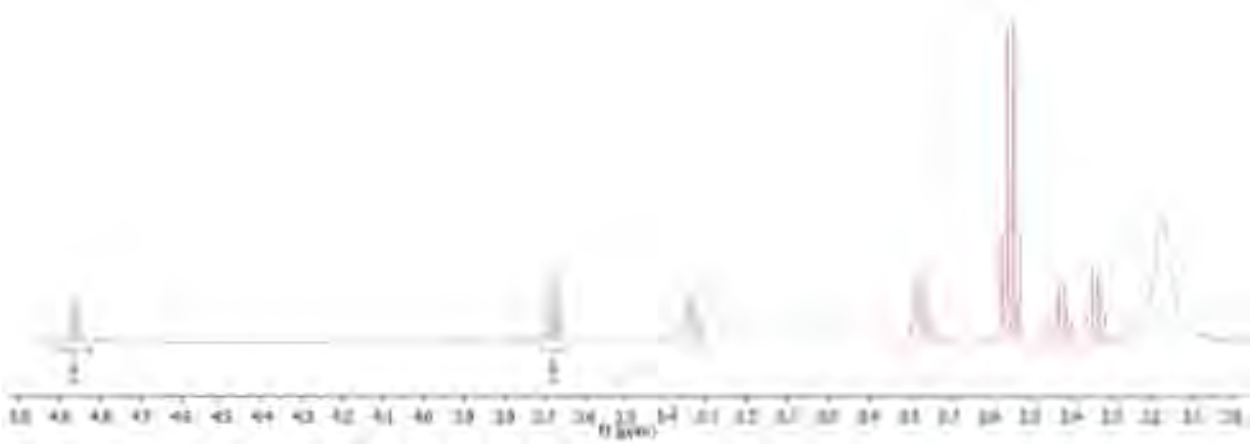
bulk water can be shifted to what we believe is monomeric water by the addition of a small amount of dry silica gel (around 10 mg).



Before the addition of silica



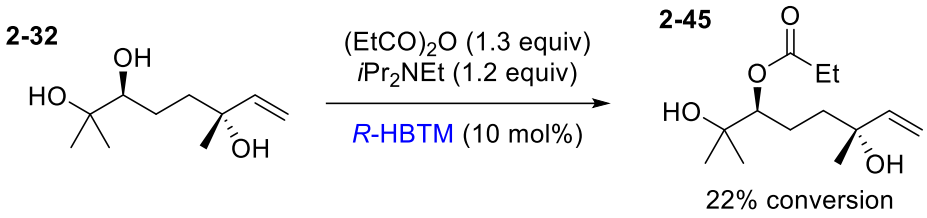
After the addition of silica



2.4.5.2 *i*-Pr$_2$NEt peak obscuring other peaks

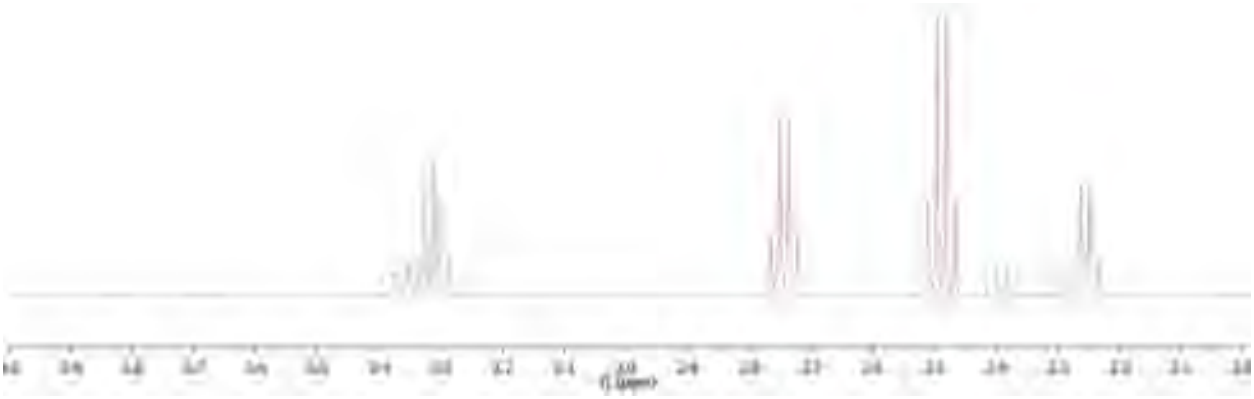
The methine septet, and methylene quartet of *i*-Pr$_2$NEt move downfield during the course of a CEC reaction as conversion increases. This shift can be explained by the net protonation state of *i*-Pr$_2$NEt. Propionic acid is released as a by-product of the acylation of the secondary alcohol, which protonates the *i*-Pr$_2$NEt. In all cases we were able to find two identical sets of peaks in both

reactions to determine conversion, which were not obscured by these peaks. However, these peaks can be shifted further downfield by the addition of propionic acid.



The peak corresponding to the methine proton of *i*-Pr$_2$NEt partially overlapped with a peak corresponding to the starting alcohol, which could be used to calculate reaction conversion. Propionic acid (1.2 equiv) was added to the reaction mixture, shifting the *i*-Pr$_2$NEt further downfield. Shown below are the appropriate regions of the ^{1}H NMR spectrum before and after the addition of propionic acid.

Before addition of propionic acid



After addition of propionic acid

2.4.6 Calculation of selectivity and rate constants for CEC reactions

Our CEC reactions are first order in anhydride, alcohol, and HBTM. Because d[HBTM]/dt = 0, the reactions can be treated as second order, according to the following integrated rate equation where $[PA]_0 \neq [OH]_0$:

$$k't = \frac{1}{[PA]_0 - [OH]_0} \ln \frac{[PA]_t [OH]_0}{[OH]_t [PA]_0} \quad (\mathbf{2.23})$$

However, since the reaction is third order:

$$k' = [HBTM]k \quad (\mathbf{2.24})$$

The expression for the third order rate constant for a CEC reaction is given by:

$$k = \frac{1}{t[HBTM] * ([PA]_0 - [OH]_0)} \ln \frac{[PA]_t [OH]_0}{[OH]_t [PA]_0} \quad (\mathbf{2.25})$$

At a given conversion, where the alcohol is the limiting reagent:

$$[OH]_t = (1 - conversion) * [OH]_0 \quad (\mathbf{2.26})$$

$$[PA]_t = [PA]_0 - ([OH]_0 - [OH]_t) \quad (\mathbf{2.27})$$

The values for these parameters are given in schemes 2-1, 2-2, and 2-3, and are compiled here:

Substrate	$[OH]_0$ (M)	$[PA]_0$ (M)	[HBTM] (M)	t (h)	$conversion_{fast}$	$conversion_{slow}$
2-10	0.1	0.13	0.01	0.5	0.72	0.29
2-11	0.1	0.13	0.01	0.5	0.57	0.40
2-12	0.1	0.13	0.01	0.5	0.56	0.46
2-12	0.075	0.225	0.0075	0.5	0.68	0.54
2-13	0.1	0.13	0.01	0.5	0.49	0.41
2-13	0.075	0.225	0.0075	0.5	0.71	0.61
2-14	0.1	0.13	0.01	2	0.38	0.37
2.15	0.1	0.13	0.01	0.5	0.25	0.09
2-16	0.1	0.13	0.01	0.5	0.23	0.08
2-17	0.1	0.13	0.01	0.5	0.13	0.05
2-18	0.1	0.13	0.01	2	0.33	0.21
2-19	0.15	0.195	0.015	1	0.17	0.04
2-20	0.1	0.13	0.01	0.5	0.46	0.32
2-21	0.1	0.13	0.01	0.5	0.25	0.13
2-22	0.1	0.13	0.01	0.5	0.46	0.36
2-23	0.1	0.13	0.01	0.5	0.39	0.38
2-24	0.01	0.013	0.001	0.5	0.61	0.12
2-25	0.35	0.455	0.035	4	0.24	0.12
2-26	0.1	0.13	0.01	1	0.18	0.07
2-27	0.1	0.13	0.01	1	0.62	0.48
2-28	0.1	0.13	0.01	1	0.81	0.36
2-29	0.1	0.13	0.01	1	0.23	0.10
2-30	0.1	0.13	0.01	2	0.30	0.15
2-31	0.1	0.13	0.01	2	0.29	0.13
2-32	0.1	0.13	0.01	2	0.40	0.25
2-33	0.1	0.13	0.01	2	0.37	0.28
2-33	0.1	0.30	0.01	2	0.62	0.50
2-34	0.1	0.13	0.01	2	0.29	0.15
2-34	0.1	0.30	0.01	3.5	0.69	0.47
2-35	0.1	0.13	0.01	2	0.22	0.12
2-35	0.1	0.30	0.01	3.5	0.65	0.49
2-36	0.04	0.052	0.004	0.5	0.61	0.1
2-37	0.1	0.13	0.01	0.5	0.37	0.22
2-38	0.1	0.13	0.01	0.5	0.24	0.11
2-42	0.1	0.13	0.004	0.75	0.71	0.08

Using these values, we have calculated rate constants and selectivities for the substrates in schemes 1-3. These are based upon one point analyses, so there is some error expected in these numbers.

Example calculation for substrate **2-10**:

Fast reaction:

$$[OH]_t = (1 - conversion) * [OH]_0 = (1 - 0.72) * 0.1 = 0.028\ M$$

$$[PA]_t = [PA]_0 - ([OH]_0 - [OH]_t) = 0.13 - (0.1 - 0.028) = 0.058\ M$$

$$k = \frac{1}{t[HBTM] * ([PA]_0 - [OH]_0)} \ln \frac{[PA]_t [OH]_0}{[OH]_t [PA]_0}$$

$$k_{fast} = \frac{1}{0.5 * 0.01 * (0.13 - 0.1)} \ln \frac{0.058 * 0.1}{0.028 * 0.13} = 3106\ M^{-2} h^{-1}$$

Slow reaction:

$$[OH]_t = (1 - conversion) * [OH]_0 = (1 - 0.29) * 0.1 = 0.071\ M$$

$$[PA]_t = [PA]_0 - ([OH]_0 - [OH]_t) = 0.13 - (0.1 - 0.071) = 0.101\ M$$

$$k = \frac{1}{t[HBTM] * ([PA]_0 - [OH]_0)} \ln \frac{[PA]_t [OH]_0}{[OH]_t [PA]_0}$$

$$k_{slow} = \frac{1}{0.5 * 0.01 * (0.13 - 0.1)} \ln \frac{0.101 * 0.1}{0.071 * 0.13} = 601\ M^{-2} h^{-1}$$

Selectivity:

$$Selectivity\ (S) = \frac{k_{fast}}{k_{slow}} = \frac{3106}{601} = 5.2$$

Substrate	k_{fast} ($M^{-2}h^{-1}$)	Relative k_{fast}	k_{slow} ($M^{-2}h^{-1}$)	Relative k_{slow}	Selectivity
2-10	3106	45	601	8.8	5.2
2-11	1779	26	954	14	1.9
2-12	1717	25	1196	17	1.4
2-12*	1569	23	1028	15	1.5
2-13	1335	20	992	15	1.3
2-13*	1721	25	1270	19	1.4
2-14	220	3.2	212	3.1	1.0
2.15	494	7.2	150	2.2	3.3
2-16	444	6.5	132	1.9	3.4
2-17	226	3.3	80.5	1.2	2.8
2-18	718	11	397	5.8	1.8
2-19	68.4	1	14.2	0.21	4.8
2-20	1196	17	687	10	1.7
2-21	494	7.2	226	3.3	2.2
2-22	1196	17	814	12	1.5
2-23	917	13	882	13	1.0
2-24	205454	3000	20656	300	9.9
2-25	4.79	0.070	2.11	0.031	2.3
2-26	165	2.4	57.4	0.84	2.9
2-27	1065	16	644	9.4	1.7
2-28	2283	33	407	6.0	5.6
2-29	222	3.2	84.4	1.2	2.6
2-30	157	2.3	66.5	0.97	2.4
2-31	150	2.2	56.5	0.83	2.7
2-32	239	3.5	124	1.8	1.9
2-33	212	3.1	143	2.1	1.5
2-33*	184	2.7	128	1.9	1.4
2-34	150	2.2	66.5	0.97	2.3
2-34*	130	1.9	66.4	0.97	2.0
2-35	105	1.5	51.6	0.75	2.0
2-35*	115	1.7	70.7	1.0	1.6
2-36	12841	190	1055	15	12
2-37	847	12	420	6.1	2.0
2-38	469	6.9	187	2.7	2.5
2-42	4976	73	221	3.2	23

*Values calculated from trials using 3 equiv of propionic anhydride

2.4.7 NMR time course data

Reaction conditions:

0.25 M **2-21**

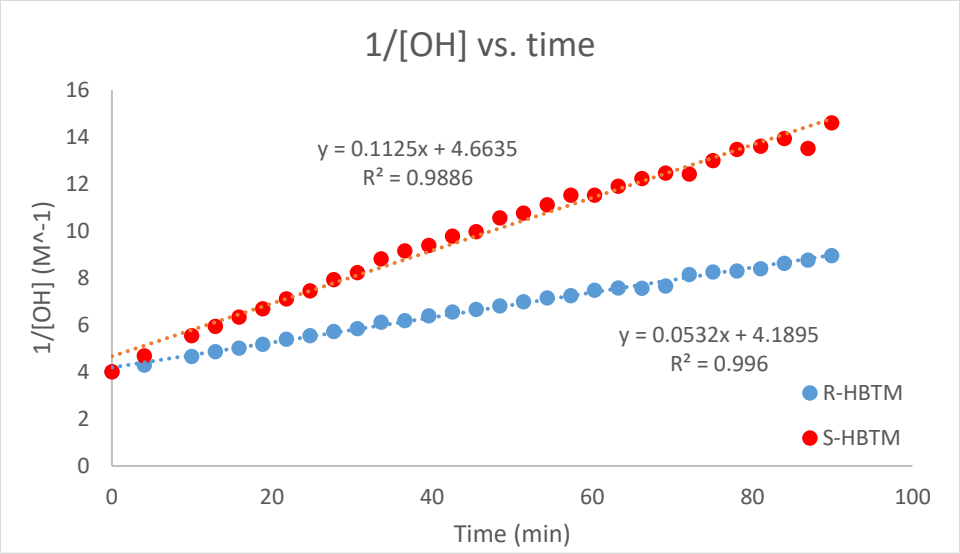
0.25 M *i*-Pr_2NEt

0.25 M Propionic Anhydride

0.025 M HBTM

	R-HBTM	*S*-HBTM		*R*-HBTM	*S*-HBTM
Time (min)	Conversion		Difference in Conversion	1/[OH] (M^{-1})*	
0	0	0	0	4.00	4.00
4.03	0.068	0.147	0.079	4.29	4.69
6.99	-	0.219	-	-	5.12
9.96	0.141	0.278	0.137	4.66	5.54
12.92	0.177	0.327	0.15	4.86	5.94
15.88	0.202	0.368	0.166	5.01	6.33
18.84	0.227	0.402	0.175	5.17	6.69
21.80	0.259	0.437	0.178	5.40	7.10
24.76	0.278	0.463	0.185	5.54	7.45
27.72	0.301	0.495	0.194	5.72	7.92
30.68	0.316	0.514	0.198	5.85	8.23
33.65	0.346	0.546	0.2	6.12	8.81
36.61	0.353	0.563	0.21	6.18	9.15
39.57	0.374	0.574	0.2	6.39	9.39
42.53	0.39	0.591	0.201	6.56	9.78
45.49	0.399	0.599	0.2	6.66	9.98
48.45	0.413	0.621	0.208	6.81	10.55
51.41	0.427	0.628	0.201	6.98	10.75
54.37	0.441	0.64	0.199	7.16	11.11
57.33	0.448	0.653	0.205	7.25	11.53
60.30	0.465	0.653	0.188	7.48	11.53
63.26	0.472	0.664	0.192	7.58	11.90
66.22	0.471	0.673	0.202	7.56	12.23
69.18	0.477	0.679	0.202	7.65	12.46
72.14	0.509	0.678	0.169	8.15	12.42
75.10	0.515	0.692	0.177	8.25	12.99
78.06	0.518	0.703	0.185	8.30	13.47
81.02	0.523	0.706	0.183	8.39	13.61
83.98	0.536	0.713	0.177	8.62	13.94
86.95	0.543	0.704	0.161	8.75	13.51
89.91	0.553	0.726	0.173	8.95	14.60

* $[OH]_t$ calculated according to equation **2.26**


1/[OH] vs. time
y = 0.1125x + 4.6635
R² = 0.9886
y = 0.0532x + 4.1895
R² = 0.996
R-HBTM
S-HBTM
1/[OH] (M^-1)
Time (min)
0
2
4
6
8
10
12
14
16
0
20
40
60
80
100

Reaction conditions:

0.15 M **2-21**

0.45 M *i*-Pr_2NEt

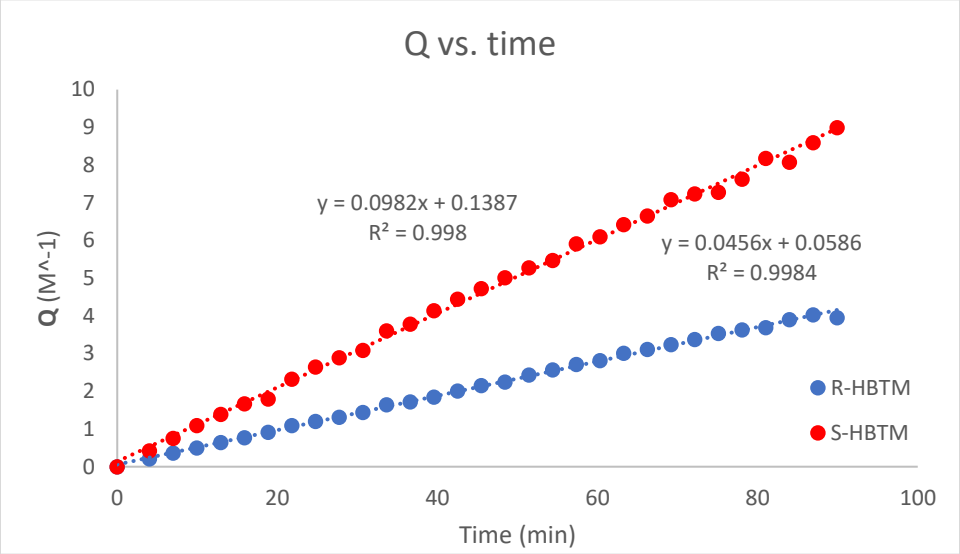
0.45 M Propionic Anhydride

0.015 M HBTM

	R-HBTM	*S*-HBTM		*R*-HBTM	*S*-HBTM
Time (min)	Conversion		Difference in Conversion	Q (M^{-1})*	
0	0	0	0	0	0.00
4.03	0.087	0.169	0.082	0.21	0.42
6.99	0.147	0.276	0.129	0.36	0.75
9.96	0.195	0.368	0.173	0.50	1.09
12.92	0.242	0.436	0.194	0.64	1.39
15.88	0.281	0.493	0.212	0.77	1.67
18.84	0.321	0.517	0.196	0.91	1.80
21.80	0.367	0.602	0.235	1.09	2.32
24.76	0.395	0.645	0.25	1.20	2.65
27.72	0.419	0.674	0.255	1.31	2.89
30.68	0.448	0.696	0.248	1.44	3.09
33.65	0.489	0.745	0.256	1.64	3.60
36.61	0.503	0.76	0.257	1.72	3.78
39.57	0.526	0.787	0.261	1.85	4.14
42.53	0.553	0.807	0.254	2.00	4.44
45.49	0.576	0.824	0.248	2.15	4.72
48.45	0.591	0.84	0.249	2.25	5.01
51.41	0.617	0.853	0.236	2.43	5.28
54.37	0.635	0.862	0.227	2.57	5.47
57.33	0.653	0.88	0.227	2.71	5.91
60.30	0.665	0.887	0.222	2.81	6.10
63.26	0.687	0.898	0.211	3.00	6.42
66.22	0.698	0.905	0.207	3.11	6.65
69.18	0.711	0.917	0.206	3.24	7.08
72.14	0.724	0.921	0.197	3.37	7.24
75.10	0.739	0.922	0.183	3.53	7.28
78.06	0.747	0.93	0.183	3.63	7.63
81.02	0.752	0.941	0.189	3.69	8.18
83.98	0.769	0.939	0.17	3.90	8.07
86.95	0.779	0.948	0.169	4.03	8.59
89.91	0.773	0.954	0.181	3.95	8.99

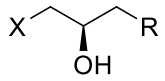
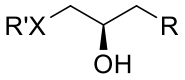
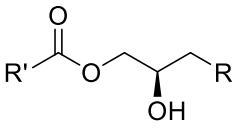
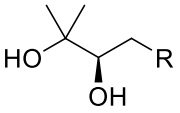
*$[PA]_t$ and $[OH]_t$ calculated according to equations **2.27** and **2.26**

$$Q = \frac{1}{[PA]_0 - [OH]_0} \ln \frac{[PA]_t [OH]_0}{[OH]_t [PA]_0}$$



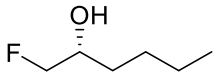
2.4.8 Estimated optimal conditions for classes of substrates

Based upon our data, we would recommend using the optimized "first-order" conditions, which employ 3 equivalents of propionic anhydride, as detailed in the experimental section of the manuscript. To obtain levels of conversion for the faster reaction nearing 80%, we estimate these reaction times for the following classes of substrates.

	[OH] (M)	run time (min)
 X= F, Cl, Br, I	0.075	30
 X = O, S	0.1	90
	0.1	30
	0.1	120

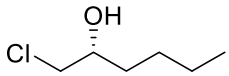
If the non-directing group has alpha-branching, or is particularly bulky, the run times should be increased.

2.4.9 Compound synthesis and characterization

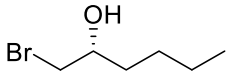


(*R*)-1-Fluorohexan-2-ol (2-10). $Et_3N{\cdot}3HF$ (240 µL, 1.5 mmol) and (*R*)-2-butyloxirane (180 µL, 1.5 mmol) were placed into a 2 mL reaction tube. The vessel was sealed under an atmosphere of air and heated to 130 °C for 4 h in an oil bath. The reaction mixture was allowed to cool to ambient temperature and then transferred to a separatory funnel. The sample was diluted with 1 M NH_4OH (aq) (5 mL), and the resulting mixture was extracted with DCM (3 x 5 mL). The organic layers were combined and washed with 1 M HCl (aq) (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The

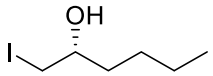
crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-21** (19.5 mg) as a clear oil; ^{1}H NMR showed minor impurities. $[\alpha]_D^{22}$ = 3.5 (*c* 0.37 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (ddd, *J* = 47.0, 9.4, 3.0 Hz, 1H), 4.28 (ddd, *J* = 48.2, 9.4, 6.9 Hz, 1H), 3.94-3.82 (m, 1H), 1.99 (br d, *J* = 4.3 Hz, 1H), 1.52-1.41 (m, 3H), 1.41-1.28 (m, 3H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 87.2 (d, *J* = 168.2 Hz), 70.7 (d, *J* = 18.5 Hz), 31.7 (d, *J* = 6.6 Hz), 27.6, 22.8, 14.1. HRMS (ESI, MeOH) m/z calcd for $C_6H_{13}FONa$ $(M+Na)^+$ 143.0843, found 143.0836.



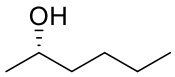
(*R*)-1-Chlorohexan-2-ol (2-11). Alcohol **2-11** was synthesized from (*R*)-2-butyloxirane according to the literature procedure.[55] $[\alpha]_D^{22}$ = −1.9 (c 0.80 $CHCl_3$).



(*R*)-1-Bromohexan-2-ol (2-12). Alcohol **2-12** was synthesized from (*R*)-2-butyloxirane according to the literature procedure.[55] $[\alpha]_D^{23}$ = −7.9 (c 0.38 $CHCl_3$).

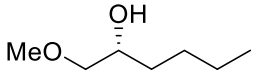


(*R*)-1-Iodohexan-2-ol (2-13). Alcohol **2-13** was synthesized from (*R*)-2-butyloxirane according to the literature procedure.[55] $[\alpha]_D^{23}$ = −6.0 (c 0.77 $CHCl_3$).

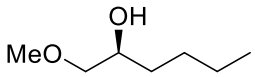


(*S*)-Hexan-2-ol (2-14). (*R*)-2-Butyloxirane (120 μL, 1.0 mmol) was added to a suspension of $LiAlH_4$ (42 mg, 1.1 mmol) in Et_2O (5 mL) at 0 °C. After stirring for 2 h, 1:1 THF:water (5 mL) was added slowly. The reaction mixture was transferred to a separatory funnel, and saturated NH_4Cl (aq) (5 mL) was added. The mixture was extracted in Et_2O (3 x 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-14** (38.4 mg, 38%) as a clear oil; $[\alpha]_D^{23}$ = 12.5 (*c* 0.48 $CDCl_3$). Spectral data matched

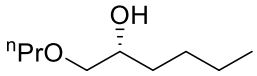
those reported in the literature.[56] The observed rotation was in reasonable agreement with reported data: $[\alpha]_D^{25}$ = 11.8 (*c* 0.56 $CHCl_3$), >98% ee.



(*R*)-1-Methoxypentan-2-ol (2-15). (*R*)-2-Butyloxirane (156 µL, 1.3 mmol) and NaOMe 25% (w/w) in MeOH (1 mL) were stirred under an atmosphere of air, at ambient temperature, and monitored by TLC for the disappearance of starting material. After 4 h, saturated NH_4Cl (aq) (5 mL) was added to the reaction. The reaction mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **7**(126.8 mg, 73.9%) as a pale yellow oil; $[\alpha]_D^{23}$ = −6.8 (*c* 0.55 $CHCl_3$). Spectral data matched those reported in the literature.[57]

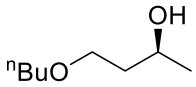


(*S*)-1-Methoxypentan-2-ol (2-16). Ether **2-16** was synthesized from (*S*)-2-butyloxirane following the same procedure used for ether **7**. $[\alpha]_D^{22}$ = 8.0 (*c* 0.59 $CHCl_3$).

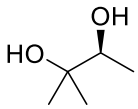


(*R*)-1-Propoxyhexan-2-ol (2-17). NaH (60% suspension in mineral oil) (80 mg, 2.0 mmol) and 1-propanol (1 mL) were stirred at ambient temperature for 5 min before the addition of (*R*)-2-butyloxirane (120 µL, 1.0 mmol). The reaction flask was heated to 55 °C in an oil bath overnight. Saturated NH_4Cl (aq) (5 mL) was added to the reaction mixture. The mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-17** (122.3 mg, 76%) as a pale yellow oil; $[\alpha]_D^{22}$ = −6.3 (c 0.58 $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 3.80-3.74 (m, 1H), 3.51-3.37 (m, 3H), 3.25 (dd, *J* = 9.5, 8.1 Hz, 1H), 2.36 (br d, *J*

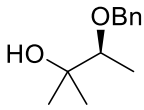
= 3.2 Hz, 1H), 1.61 (app. sex, *J* = 7.1 Hz, 2H), 1.51-1.39 (m, 3H), 1.39-1.27 (m, 3H), 0.98-0.85 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 75.2, 73.2, 70.1, 33.0, 27.9, 23.0, 22.9, 14.2, 10.7. HRMS (ESI, MeOH) m/z calcd for $C_9H_{20}O_2Na$ $(M+Na)^+$ 183.1356, found 183.1353.



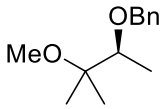
(*S*)-4-Butoxybutan-2-ol (2-18). A 10 mL round bottom flask was charged with NaH (60% suspension in mineral oil) (44 mg, 1.1 mmol) and NaI (166 mg, 1.11 mmol) and cooled to 0 °C. (*S*)-butane-1,3-diol (100 mg, 1.11 mmol) in THF (2.2 mL) was added dropwise. After stirring for 5 min, 1-bromobutane (152 mg, 1.11 mmol) was added. The reaction flask was covered with aluminum foil and allowed to warm to RT overnight. Saturated NH_4Cl (aq) (5 mL) was added to the reaction flask. The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-18** (14.3 mg, 9%) as a clear oil; $[\alpha]_D^{24}$ = –3.3 (*c* 1.43 $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05-3.94 (m, 1H), 3.66 (dt, *J* = 9.6, 4.9 Hz, 1H), 3.59 (td, *J* = 9.1, 4.1 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 1.79-1.64 (m, 2H), 1.56 (dt, *J* = 14.6, 6.6 Hz, 2H), 1.42-1.31 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 71.3, 70.2, 68.2, 38.1, 31.9, 23.4, 19.5, 14.0. HRMS (ESI, MeOH) m/z calcd for $C_8H_{18}O_2Na$ $(M+Na)^+$ 169.1200, found 169.1196.



(*S*)-2-Methylbutane-2,3-diol (2-27). Alcohol **2-27** was synthesized according to the literature procedure.[58] $[\alpha]_D^{22}$ = 4.8 (*c* 1.00 $CDCl_3$). Spectral data was consistent with literature report.[59] The enantiomeric excess of **2-27** was determined to be 96% by Mosher's ester analysis of the mono-MTPA esters, using a modified literature procedure, employing only 1 equivalent of the corresponding *R* and *S* acid chlorides.[3]

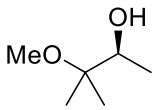


(*S*)-3-(Benzyloxy)-2-methylbutan-2-ol (2-46). A sample of alcohol **2-27** (500 mg, 4.80 mmol) in THF (9.6 mL) was cooled to 0 °C before the addition of NaH (60% suspension in mineral oil) (182 mg, 4.56 mmol). After 5 min, benzyl bromide (0.54 mL, 4.6 mmol) was added to the reaction flask, which was allowed to warm to ambient temperature overnight. Saturated NH_4Cl (aq) (20 mL) was added to quench the reaction. The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 20 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-46** (441 mg, 47%) as a clear oil; $[\alpha]_D^{22}$ = 60.4 (*c* 1.10 $CDCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.32 (m, 4H), 7.31-7.27 (m, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.37 (q, *J* = 6.3 Hz, 1H), 2.49 (s, 1H), 1.19 (s, 3H), 1.18-1.15 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.7, 128.5, 127.78, 127.76, 82.0, 72.9, 71.5, 26.2, 23.9, 14.2. HRMS (ESI, MeOH) m/z calcd for $C_{12}H_{18}O_2Na$ $(M+Na)^+$ 217.1200, found 217.1205.

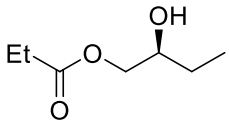


(*S*)-(((3-Methoxy-3-methylbutan-2-yl)oxy)methyl)benzene (2-47). The alcohol **2-46** (405 mg, 2.09 mmol) and THF (4 mL) were cooled to 0 °C before the addition of NaH (60% suspension in mineral oil) (83 mg, 2.1 mmol). After 5 min, methyl iodide (195 µL, 3.13 mmol) was added to the reaction flask, which was allowed to warm to ambient temperature overnight. Saturated NH_4Cl (aq) (10 mL) was added to quench the reaction. The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford ether **2-47** (190 mg, 44%) as a clear oil; $[\alpha]_D^{22}$ = 39.1 (*c* 1.52 $CDCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.30 (m, 4H), 7.29-7.24 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 3.41 (q, *J* = 6.3 Hz,

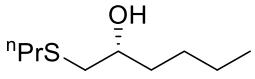
1H), 3.22 (s, 3H), 1.20 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.14 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.2, 128.4, 127.7, 127.5, 80.1, 77.4, 71.7, 49.7, 22.2, 20.4, 14.0. HRMS (ESI, MeOH) m/z calcd for $C_{13}H_{20}O_2Na$ $(M+Na)^+$ 231.1356, found 231.1348.



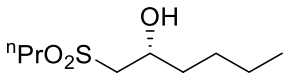
(*S*)-3-Methoxy-3-methylbutan-2-ol (2-19). The benzyl ether **2-47** (165 mg, 0.79 mmol) and THF (4 mL) were combined in a round bottom flask. The catalyst, 5% Pd/C (169 mg, 0.079 mmol), was added to the reaction flask, which was stirred under H_2 (1 atm) overnight. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated in vacuo and purified by flash column chromatography (Et_2O/pentanes) on silica to afford alcohol **2-19** (41.7 mg, 44%) as a clear oil; $[\alpha]_D^{23}$ = –1.9 (c 4.17 $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (qd, J = 6.4, 1.9 Hz, 1H), 3.27 (s, 3H), 2.61 (d, J = 1.7 Hz, 1H), 1.18-1.14 (m, 6H), 1.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 77.8, 72.7, 49.2, 20.8, 18.1, 17.0. HRMS (ESI, MeOH) m/z calcd for $C_6H_{14}O_2Na$ $(M+Na)^+$ 141.0887, found 141.0885.



(*S*)-2-Hydroxybutyl propionate (2-20). (*S*)-Butane-1,2-diol (150 mg, 1.66 mmol), DMAP (51 mg, 0.42 mmol), Et_3N (460 µL, 3.3 mmol), and CH_2Cl_2 (3 mL) were combined in a reaction flask and cooled to 0 °C. Propionic anhydride (210 µL, 1.7 mmol) was added, and the reaction was stirred at 0 °C for 3 h before warming to room temperature overnight. Saturated NH_4Cl (aq) (10 mL) was added to the solution. The reaction mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford ester **2-20** (95.8 mg, 39%) as a clear oil; $[\alpha]_D^{23}$ = 7.3 (*c* 1.41 $CDCl_3$). Spectral data was consistent with literature report.[60]

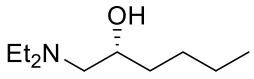


(*R*)-1-(Propylthio)hexan-2-ol (2-21). NaH (60% suspension in mineral oil) (240 mg, 6.0 mmol) and propane-1-thiol (3 mL, 30 mmol) were stirred at ambient temperature for 5 min before the addition of (*S*)-2-butyloxirane (360 µL, 3.0 mmol). After 20 min, saturated NH_4Cl (aq) (5 mL) was added to quench the reaction. The reaction mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **2-21** (383 mg, 73%) as a pale yellow oil; $[\alpha]_D^{23}$ = –47.7 (*c* 0.39 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73-3.66 (m, 1H), 2.81 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.63-2.54 (m, 3H), 2.50 (dd, *J* = 13.6, 9.1 Hz, 1H), 1.74-1.63 (m, 2H), 1.61-1.47 (m, 3H), 1.47-1.33 (m, 3H), 1.06 (t, *J* = 7.3 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 69.3, 40.5, 36.1, 34.4, 28.1, 23.3, 22.9, 14.2, 13.6. HRMS (ESI, MeOH) m/z calcd for $C_9H_{20}OSNa$ $(M+Na)^+$ 199.1128, found 199.1126.

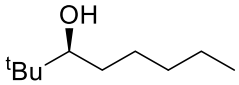


(*R*)-1-(Propylsulfonyl)pentan-2-ol (2-22). A sample of mCPBA (67% w/w) (180 mg, 0.70 mmol) in CH_2Cl_2 (1.5 mL) was cooled to 0 °C under an atmosphere of air. A solution of sulfide **2-21** (41.3 mg, 235 mmol) in CH_2Cl_2 (1.5 mL) was added. The reaction mixture was monitored by TLC for the consumption of starting material. After 45 min, saturated Na_2SO_3/$NaHCO_3$ (aq) (10 mL) was added to the solution. The reaction mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford sulfone **2-22** (22.1 mg, 45%) as a white crystalline solid. mp 73-75°C. $[\alpha]_D^{22}$ = –15.4 (*c* 0.37 $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35-4.23 (m, 1H), 3.14-2.99 (m, 4H), 2.90 (d, *J* = 3.0 Hz, 1H), 1.95 -1.84 (app. sex., *J* = 7.6 Hz, 2H), 1.66-1.56 (m, 1H), 1.55 – 1.47 (m, 1H), 1.47 – 1.41 (m, 1H), 1.40 – 1.29 (m,

3H), 1.10 (t, J = 7.4 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.4, 59.0, 56.4, 36.6, 27.4, 22.6, 15.9, 14.1, 13.3. HRMS (ESI, MeOH) m/z calcd for $C_9H_{20}O_3SNa$ $(M+Na)^+$ 231.1026, found 231.1027.

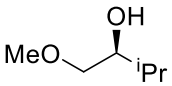


(*R*)-1-(Diethylamino)hexan-2-ol (2-23). Diethylamine (0.37 mL, 3.6 mmol) in THF (1.6 mL) was cooled to –78 °C and 2.59 M *n*-BuLi in hexanes (1.16 mL, 3.00 mmol) was added dropwise. The reaction mixture was warmed to 0 °C and then cooled to –78 °C. (*R*)-2-Butyloxirane (180 µL, 1.50 mmol) was added dropwise, and the reaction mixture was warmed to 0 °C. After stirring for an additional hour, the reaction was quenched by the addition of saturated $NaHCO_3$ (aq) (5 mL). The reaction mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, concentrated in vacuo, and dried under high vacuum to afford **2-23** (75.3 mg, 29%) as a pale yellow oil; $[\alpha]_D^{21}$ = –65.2 (*c* 0.34 $CDCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.57 (ddd, J = 10.9, 7.1, 3.6 Hz, 1H), 2.69-2.60 (m, 2H), 2.53-2.45 (m, 2H), 2.42 (dd, J = 12.6, 3.1 Hz, 1H), 2.24 (dd, J = 12.5, 10.6 Hz, 1H), 1.53-1.39 (m, 2H), 1.39-1.29 (m, 4H), 1.02 (t, J = 7.1 Hz, 6H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 66.8, 59.8, 47.2, 34.9, 28.1, 23.1, 14.2, 12.2. HRMS (ESI, MeOH) m/z calcd for $C_{10}H_{23}NONa$ $(M+Na)^+$ 196.1672, found 196.1668.

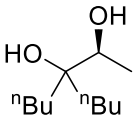


(*S*)-2,2-Dimethyloctan-3-ol (2-25). A suspension of CuI (220 mg, 1.2 mmol) in THF (2.6 mL) was cooled to –40 °C. A solution of *n*-BuLi (2.59 M, 1.6 mL, 4.2 mmol) in hexanes was added dropwise, and the reaction mixture was stirred vigorously for 30 min. (*R*)-2-(*tert*-Butyl)-oxirane (106 mg, 1.06 mmol) as a solution in THF (1.8 mL) was added, and the reaction flask was warmed to –20 °C for 3 h before the addition of saturated $NaHCO_3$ (aq) (5 mL). The reaction mixture was transferred to a separatory funnel and extracted

with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, concentrated in vacuo, and dried under high vacuum to afford alcohol **2-25** (103.8 mg, 62%) as a clear oil; $[\alpha]_D^{23}$ = –26.8 (*c* 0.80 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (ddd, *J* = 10.5, 5.2, 1.6 Hz, 1H), 1.60-1.46 (m, 2H), 1.37-1.20 (m, 6H), 0.94-0.86 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 80.2, 35.1, 32.1, 31.7, 26.9, 25.9, 22.9, 14.2. HRMS (ESI, MeOH) m/z calcd for $C_{10}H_{22}ONa$ $(M+Na)^+$ 181.1563, found 181.1557.

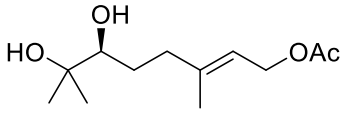


(*S*)-1-Methoxy-3-methylbutan-2-ol (2-26). NaH (60% suspension in mineral oil) (178 mg, 4.4 mmol) in THF (5 mL) was cooled to 0 °C. (*S*)-3-Methylbutane-1,2-diol (420 mg, 4.0 mmol) in THF (3 mL) was added dropwise and the mixture was stirred for 5 min. MeI (250 µL, 4.0 mmol) was added. The reaction flask was covered in aluminum foil, and allowed to react for 48 h at ambient temperature. Saturated NH_4Cl (aq) (10 mL) was added to quench the reaction. The reaction mixture was transferred to a separatory funnel and extracted ethyl acetate (3 x 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-26** (97.4 mg, 20%) as a pale yellow oil; $[\alpha]_D^{23}$ = 17.5 (*c* 1.10 $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53-3.48 (m, 1H), 3.46 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.39 (s, 3H), 3.30 (dd, *J* = 9.3, 8.4 Hz, 1H), 2.33 (br. s, 1H), 1.71 (app. oct., *J* = 6.8 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 75.3, 75.1, 59.1, 31.0, 18.8, 18.3. HRMS (ESI, MeOH) m/z calcd for $C_6H_{14}O_2Na$ $(M+Na)^+$ 141.0887, found 141.0894.

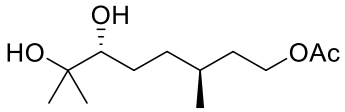


(*S*)-3-Butylheptane-2,3-diol (2-28). Methyl (*S*)-(–)-lactate (280 µL, 2.9 mmol) in THF (5.8 mL) was cooled to –78 °C and 2.59 M *n*-BuLi in hexanes (3.45 mL, 8.93 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h before the addition

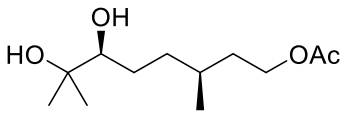
of saturated NH_4Cl (aq) (20 mL). The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **2-28** (138 mg, 25%) as an amorphous white solid; $[\alpha]_D^{22}$ = 1.5 (*c* 1.27 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (app p, *J* = 5.8 Hz, 1H), 1.90 (d, *J* = 5.1 Hz, 1H), 1.73 (s, 1H), 1.62-1.42 (m, 3H), 1.40-1.19 (m, 9H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 6.5 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 76.2, 71.8, 35.8, 34.1, 25.7, 25.6, 23.63, 23.56, 17.4, 14.23, 14.22. HRMS (ESI, MeOH) m/z calcd for $C_{11}H_{24}O_2Na$ $(M+Na)^+$ 211.1669, found 211.1662.



(*S,E*)-6,7-Dihydroxy-3,7-dimethyloct-2-en-1-yl acetate (2-29). Acetate **2-29** was synthesized according to the literature procedure for enantiomeric **2-29**;[61] $[\alpha]_D^{23}$ = –25.8 (*c* 0.95 $CHCl_3$); Literature for (*R,E*): $[\alpha]_D^{23}$ = 26.8 (*c* 1.0 $CHCl_3$), 97% ee. The estimated enantiomeric excess of **2-29**, based upon optical rotation, is 94%.

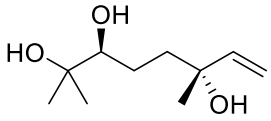


(3*S*,6*R*)-6,7-Dihydroxy-3,7-dimethyloctyl acetate (2-30). Diol **2-30** was synthesized according to the literature procedure.[62] The minor diastereomer was not observed by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17-4.06 (m, 2H), 3.33 (ddd, *J* = 10.2, 3.9, 1.7 Hz, 1H), 2.16 (d, *J* = 4.3 Hz, 1H), 2.04 (s, 3H), 1.88 (s, 1H), 1.74-1.62 (m, 2H), 1.59-1.49 (m, 2H), 1.48-1.40 (m, 1H), 1.31-1.18 (m, 5H), 1.17 (s, 3H), 0.94 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.4, 79.1, 73.3, 63.0, 35.4, 34.2, 30.2, 29.2, 26.7, 23.3, 21.2, 19.7. HRMS (ESI, MeOH) m/z calcd for $C_{12}H_{24}O_4Na$ $(M+Na)^+$ 255.1567, found 255.1568.

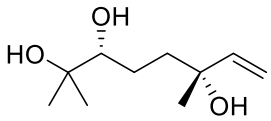


(3*S*,6*S*)-6,7-Dihydroxy-3,7-dimethyloctyl acetate (2-31). Diol **2-31** was synthesized according to the literature procedure.[62] The minor diastereomer was not observed by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (ddd, *J* = 10.9,

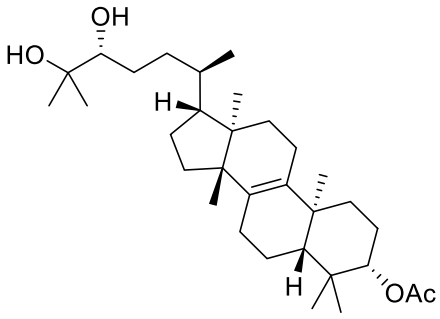
7.1, 6.3 Hz, 1H), 4.09 (app. dt, *J* = 10.9, 7.0 Hz, 1H), 3.33 (d, *J* = 10.0 Hz, 1H), 2.34 (br s, 1H), 2.05 (br s, 1H), 2.05 (s, 3H), 1.71-1.63 (m, 1H), 1.57 (td, *J* = 12.6, 6.7 Hz, 1H), 1.52-1.42 (m, 3H), 1.42-1.30 (m, 2H), 1.22 (s, 3H), 1.16 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.5, 78.7, 73.3, 63.0, 35.9, 33.9, 29.8, 29.0, 26.7, 23.3, 21.2, 19.5. HRMS (ESI, MeOH) m/z calcd for $C_{12}H_{24}O_4Na$ $(M+Na)^+$ 255.1567, found 255.1567.



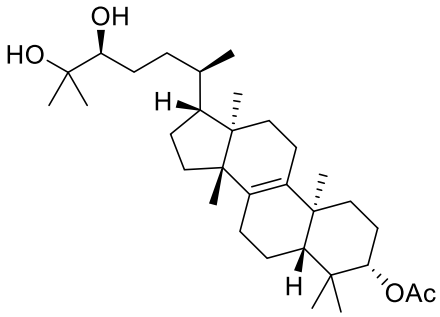
(3*S*,6*R*)-2,6-Dimethyloct-7-ene-2,3,6-triol (2-32). Triol **2-32** was synthesized according to the literature procedure.[62] The diastereomeric excess of **2-32** was 95% as determined by ^{1}H NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.24 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.09 (dd, *J* = 10.8, 1.3 Hz, 1H), 3.36 (dd, *J* = 10.5, 2.0 Hz, 1H), 2.04 (br. s, 1H), 1.87-1.78 (m, 1H), 1.73-1.62 (m, 2H), 1.62-1.54 (m, 1H), 1.46-1.36 (m, 1H), 1.31 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 112.3, 79.3, 73.32, 73.31, 39.1, 29.0, 26.7, 26.1, 23.4. HRMS (ESI, MeOH) m/z calcd for $C_{10}H_{20}O_3Na$ $(M+Na)^+$ 211.1305, found 211.1305.



(3*R*,6*R*)-2,6-Dimethyloct-7-ene-2,3,6-triol (2-33). Triol **2-33** was synthesized according to the literature procedure.[62] The diastereomeric excess of **2-33** was 94% as determined by ^{1}H NMR analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 5.06 (d, *J* = 10.8 Hz, 1H), 3.37 (dd, *J* = 10.5, 1.7 Hz, 1H), 3.14 (br s, 1H), 2.31 (br s, 2H), 1.80 (ddd, *J* = 14.2, 9.0, 5.5 Hz, 1H), 1.66 (ddd, *J* = 14.2, 8.5, 6.0 Hz, 1H), 1.44-1.36 (m, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.3, 111.9, 78.8, 73.32, 73.30, 39.1, 28.0, 26.7, 26.0, 23.4. HRMS (ESI, MeOH) m/z calcd for $C_{10}H_{20}O_3Na$ $(M+Na)^+$ 211.1305, found 211.1309.

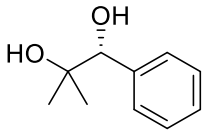


24(*S*)-3β-Acetoxyl-24,25-dihydroxy-5α-lanost-8-ene (2-34). AD-mix alpha (174 mg), $K_2OsO_4 \cdot 2H_2O$ (2 mg, 5 μmol), $(DHQ)_2PHAL$ (2 mg, 3 μmol), methanesulfonamide (12 mg, 0.13 mmol), *t*-BuOH (0.7 mL), and H_2O (0.7 mL) were combined in a round-bottom flask under an atmosphere of air. The flask was cooled to 0 °C, and *O*-acetyl lanosterol (58 mg, 12 mmol) was added. The heterogeneous mixture was stirred rapidly for 6 days. $Na_2S_2O_3$ (0.6 g) was added, and the reaction flask was allowed to warm to room temperature over 30 min. After the removal of *t*-BuOH under reduced pressure, the reaction mixture was extracted with EtOAc (3 x 5mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **2-34** (23.5 mg, 38%) as a white solid. The diastereomeric excess of **2-34** was 86% as determined by ^1H NMR analysis. Spectral data was consistent with that reported in the literature.[63]

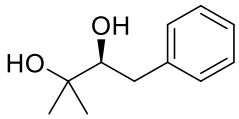


24(*R*)-3β-Acetoxyl-24,25-dihydroxy-5α-lanost-8-ene (2-35). AD-mix beta (181 mg), $K_2OsO_4 \cdot 2H_2O$ (2 mg, 5 μmol), $(DHQD)_2PHAL$ (2 mg, 3 μmol), methanesulfonamide (12 mg, 0.13 mmol), *t*-BuOH (0.7 mL), and H_2O (0.7 mL) were combined in a round-bottom flask under an atmosphere of air. The flask was cooled to 0 °C, and *O*-acetyl lanosterol (60 mg, 0.13 mmol) was added. The heterogeneous mixture was stirred rapidly for 6 days. $Na_2S_2O_3$ (0.6 g) was added, and the reaction flask was allowed to warm to room temperature over 30 min. After the removal of *t*-BuOH under reduced pressure, the reaction mixture was extracted with EtOAc (3 x 5mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude mixture was

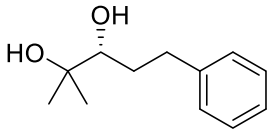
purified by flash column chromatography (EtOAc/Hex) on silica to afford **2-35** (26.1 mg, 41%) as a white solid. The diastereomeric excess of **2-35** was 92% as determined by ^{1}H NMR analysis. Spectral data was consistent with that reported in the literature.[63]



(*R*)-2-Methyl-1-phenylpropane-1,2-diol (2-36). Diol **2-36** was synthesized according to the literature procedure.[64] $[\alpha]_D^{24}$ = –16.7 (*c* 0.93 EtOH). The observed rotation was in reasonable agreement with reported value: $[\alpha]_D^{24}$ = –18.8 (*c* 1.00 EtOH).



(*S*)-3-Methyl-1-phenylbutane-2,3-diol (2-37). Diol **2-37** was synthesized according to the literature procedure.[65] $[\alpha]_D^{23}$ = –55.1 (*c* 0.72 $CHCl_3$). The observed rotation was in reasonable agreement with literature value: $[\alpha]_D^{20}$ = –59.0 (*c* 0.86 $CHCl_3$).



(*R*)-2-Methyl-5-phenylpentane-2,3-diol (2-38). (*R*)-Ethyl 2-hydroxy-4-phenylbutanoate (500 mg, 2.4 mmol) in THF (5 mL) was cooled to 0 °C before the dropwise addition of 3 M MeMgCl in THF (3.2 mL, 9.6 mmol). The reaction was stirred at 0 °C for 3 h before the slow addition of 1 M HCl (aq) (10 mL). The reaction mixture was transferred to a separatory funnel and extracted DCM (3 x 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford diol **2-38** (345 mg, 74%) as a clear oil; $[\alpha]_D^{21}$ = 45.3 (*c* 2.15 $CDCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.24-7.17 (m, 3H), 3.39 (d, *J* = 10.6 Hz, 1H), 2.95 (ddd, *J* = 14.3, 9.5, 4.7 Hz, 1H), 2.67 (ddd, *J* = 13.7, 9.5, 7.1 Hz, 1H), 2.34 (s, 1H), 1.98 (s, 1H), 1.82 -1.75 (m, 1H), 1.69-1.61 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.2, 128.61, 128.58, 126.0, 78.0, 73.3, 33.6, 33.1, 26.7, 23.4. HRMS (ESI, MeOH) m/z calcd for $C_{12}H_{18}O_2Na$ $(M+Na)^+$ 217.1200, found 217.1191.

2.5 References

[37] (a) Snatzke, G.; Wagner, U.; Wolff, H. P. *Tetrahedron* **1981**, *37*, 349−361. (b) Di Bari, L.; Pescitelli, G.; Pratelli, C.; Pini, D.; Salvadori, P. *J. Org. Chem.* **2001**, *66*, 4819−4825.

[38] Most CEC reactions were run in duplicate. The trial showing the smallest difference in conversion is reported. The duplicate trial showed a small change in the difference in conversion: considering all examples, the median change was 1%.

[39] Nakamura, S.; Iwami, J.; Matsuda, H.; Mizuno, S.; Yoshikawa, M. *Tetrahedron* **2009**, *65*, 2443–2450.

[40] Birman's original report (Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115–1118) and later work by Shiina demonstrated enantioselective HBTM acylations with substrates containing esters and azides. Both functional groups have π-bonds, but a polar component may be important in the observed selectivity. Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem.-Eur. J*. **2010**, *16*, 167–172.

[41] (a) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351–1354. (b) Li, X.; Jiang, H.; Uffman, E. W.; Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem.* **2012**, *77*, 1722–1737.

[42] A complete tabulation of selectivities and rates is presented in the supplementary information.

[43] Wayman, K. A.; Sammakia, T. *Org. Lett.* **2003**, *5*, 4105–4108.

[44] Wagner, A. J.; Rychnovsky, S. D. *Org. Lett.* **2013**, *15*, 5504–5507.

[45] Some reactions were run at a different overall concentration or for a different length of time to offset the overall rate increase expected from increasing the amount of anhydride. Varying the overall concentration or reaction time will not affect relative conversions between reactions, at a given conversion for either reaction.

[46] Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115–1118.

[47] Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307–1317.

[48] Ignatenko, V. A.; Tochtrop, G. P. *J. Org. Chem.* **2013**, *78*, 3821–3831.

[49] McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378–8379.

[50] Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 7409–7416.

[51] Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925–6928.

[52] A 6-fold dilution reduces the rate of conversion 36-fold for the 3rd order reaction.

[53] As discussed, the preferred reaction conversions are typically 70-80% for the fast reacting catalyst. Some guidelines for estimating reaction times are included in the Supporting Information.

[54] Silverstein, R. M.; Webster, F. X.; Kiemle, D. J.; Bryce, D. L. *Spectrometric Identification of Organic Compounds*, 7th edition; Wiley: Hoboken, NJ, 2015, p. 153.

[55] Kotsuki, H.; Shimanouchi, R. O.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709–2722.

[56] Kalinowska, I. M.; Szawkalo, J.; Krawczyk, K. K.; Maurin, J. K.; Czarnocki, Z. *Synthesis* **2011**, *11*, 1809–1813.

[57] Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688.

[58] Dubé, D.; Brideau, C.; Deschênes, D.; Fortin, R.; Friesen, R. W.; Gordon, R.; Girard. Y.; Riendeau, D.; Savoie, C.; Chan, C.-C. *Bioorg. & Med. Chem. Lett.* **1999**, *9*, 1715–1720.

[59] Tartaglia, S.; Pace, F.; Scafato, P.; Rosini, C. *Org. Lett*. **2008**, *10*, 3421–3424.

[60] Janssen, A. J. M.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1991**, *47*, 7409–7416.

[61] Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869.

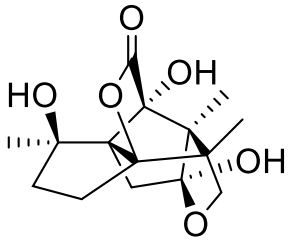
[62] Vidari, G.; Giori, A.; Dapiaggi, A.; Lanfranchi, G. *Tetrahedron Lett.* **1993**, *34*, 6925–6928.

[63] Kavtaradze, L. K.; Manley-Harris, M.; Nicholson, B. K. *Steroids* **2004**, *69*, 227–233.

[64] Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585–4588. The authors give two procedures for the synthesis. We followed the procedure for Grignard addition into *R*-methyl mandelate.

[65] Terashima, S.; Tseng, C. C.; Hayashi, M.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 758–764.

Chapter 3. Total Synthesis of Illisimonin A



3.1 Abstract

Illisimonin A is a neurotrophic sesquiterpenoid, originally isolated from the fruits of *Illicium simonsii* and has a previously unreported tricyclic carbon framework. It incorporates a highly strained trans-pentalene ring system. We completed the first synthesis of (±)-illisimonin A. Notable steps in the route include a 1,3-dioxa-2-silacyclohexene templated Diels-Alder cycloaddition and type-3 semipinacol rearrangement to generate the trans-pentalene. The final step is an iron-catalyzed C-H oxidation. The synthetic route is robust, with 94 mg of racemic material prepared in a single pass. Resolution of an intermediate enabled the synthesis of natural (–)-illisimonin A. The absolute configuration of (–)-illisimonin A was revised to 1*S*,4*S*,5*S*,6*S*,7*R*,9*R*,10*R* based on the X-ray structure of a heavy-atom analogue.

3.2 Introduction

3.2.1 Structure and bioactivity of the illicium sesquiterpenoids

The *Illicium* genus is a group of flowering shrubs and small trees indigenous to central and northern America, as well as eastern Asia.[66] These plants have produced a wide variety of sesquiterpenoids, which can be classified on the basis of their carbon skeletons. Many of the different carbon skeletons of these sesquiterpenoids are shown in figure 3-1.[67] Around 100 members of the *seco*-prezizaane class have been identified, and many are popular synthetic targets due, in large part, to their intriguing bioactivity.

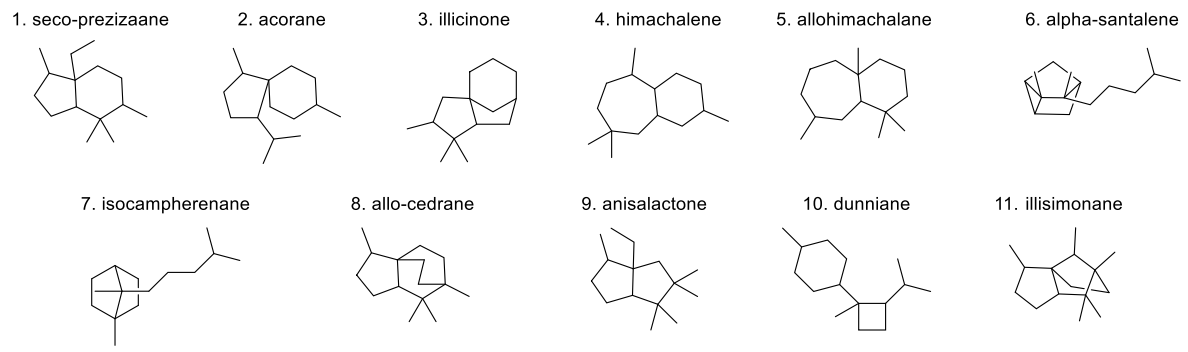


Figure 3-1 Different carbon skeletons for the *Illicium* sesquiterpenoids

The flowers of the Japanese star anise, *Illicium anisatin* have been known to be toxic for many centuries.[66] In 1968, the structure of anisatin **3-2**, the principle toxin of the Japanese star anise, was determined through chemical and degradative methods.[68] Ingestion of anisatin can cause convulsions, or death in high enough doses. Its mechanism of action is likely the same as that of the better studied natural product, picrotoxinin **3-6** (not an *Illicium* sesquiterpenoid).[69] Both molecules act as non-competitive antagonists of GABA gated chloride channels. GABA (gamma amino butyric acid) is the principle inhibitory neurotransmitter in the developed central nervous system.[70] Antagonism of an inhibitory signal is net excitatory, and can lead to depolarization of a neuron. This can lead to an increase in action potential firing, and convulsions of the organism.[71]

In the early nineties, the research group of Fukuyama initiated a program searching for exogenous, small-molecule neurotrophic factors. Guided by phenotypic cell-based assays, his group identified isodunnianin **3-5**, isolated from *Illicium tashiroi*. The molecule enhanced neurite outgrowth in primary cultures of rat fetal neurons at 10 μM.[72] Over the next two decades, his group and others identified many small-molecule neurotrophic factors from the *Illicium* genus, and other plants, some of which are shown in Figure 3-2.

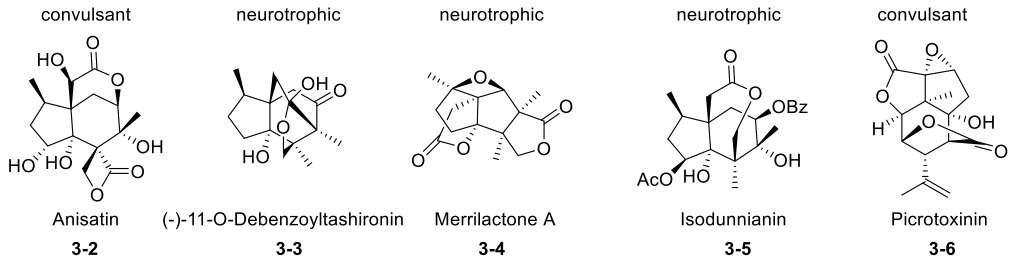


Figure 3-2 Neurotrophic and convulsant sesquiterpenoids

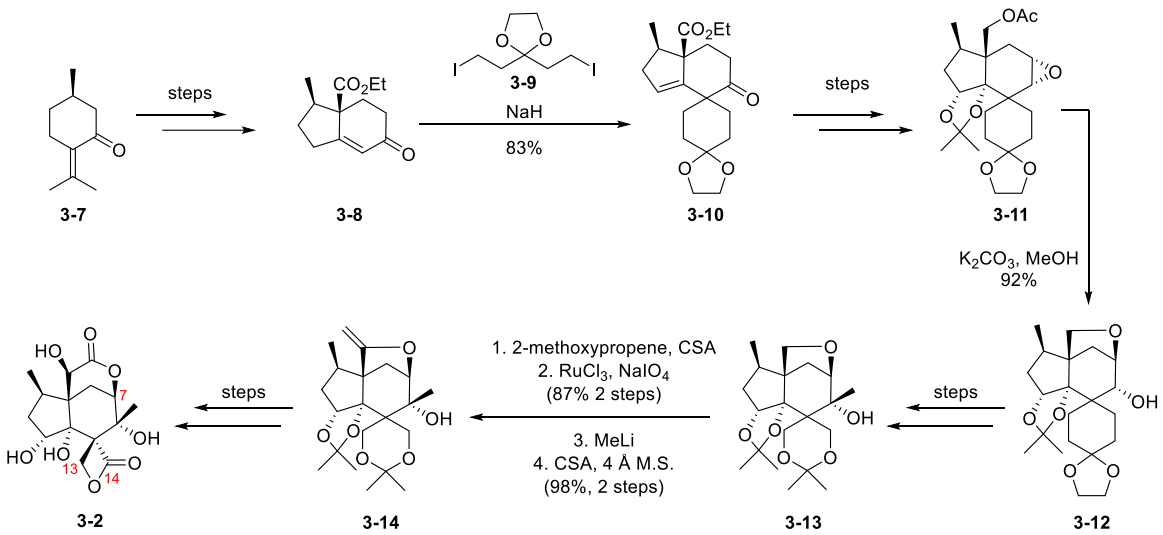
These molecules are neurotrophic; that is they promote the survival and/or growth of neural cells. This property was identified through phenotypic screens, and the exact mechanism of action remains unclear. The Shenvi group and collaborators at Eli Lily have made recent strides to attempt to understand the bioactivity of these molecules.[71] Interestingly, both the "neurotrophic" and the "convulsant" sesquiterpenoids antagonize $GABA_A$ channels. The neurotrophic molecules, however, bind to these channels with a much lower potency. This has led to the "sweet spot" hypothesis that this low potency leads to a minor, but persistent antagonism of these channels. This in turn leads to a minor decrease in intracellular chloride concentration, leading to a slight depolarization of the neuron. This could increase calcium influx, leading to an increase in the production of neurotrophic factors, ultimately leading to the neurotrophic phenotype. While this is one possible explanation, the argument is far from airtight. There still remains much work to be done in this area to understand how these fascinating molecules work.

3.2.2 Selected synthetic work towards the Illicium sesquiterpenoids

There has been a great deal of synthetic work directed at the *Illicium* sesquiterpenoids, which cannot all be covered here. I have chosen to highlight a handful of the strategies used to target these molecules. I would direct the reader to this non-exhaustive list of publications for more information on previous syntheses of the *Illicium* sesquiterpenoids.[73,74,75,76]

In 1982 the Woodward lab published synthetic studies toward anisatin.[77] Three years after that, Kende's group published a 24 step synthesis of 8-deoxyanisatin, an anisatin analog which lacked the α-hydroxy group on the δ-lactone.[78] However, the first total synthesis of an *Illicium* sesquiterpenoid would have to wait until 1990, when the Yamada group prepared (–)-anisatin in 40 steps.

3.2.2.1 Yamada's (–)-anisatin[79]

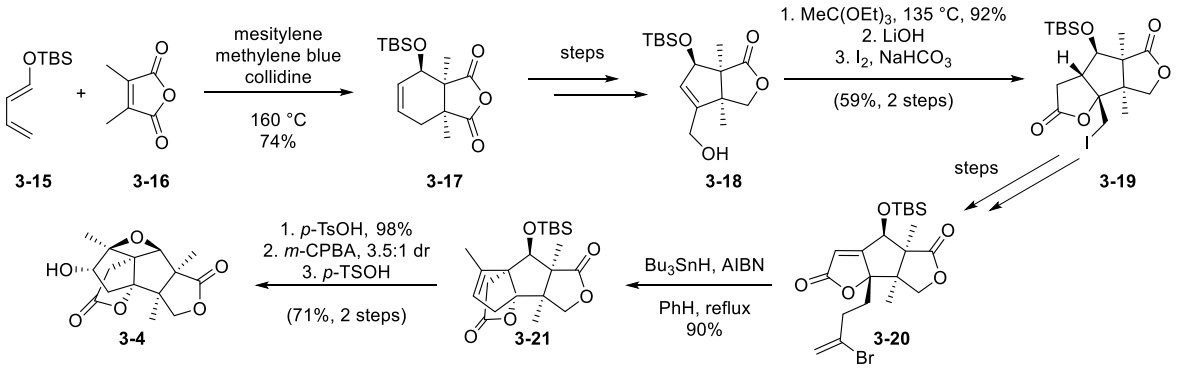


Scheme 3-1 Outline of Yamada's (–)-anisatin synthesis

Pulegone **3-7** was converted into bicycle **3-8** in several steps, including a Robinson annulation. The C-13 and C-14 carbons were installed via a surprisingly effective double α-alkylation of an extended enolate to yield ketal **3-10**. Unfortunately, they were added along with several other carbons which were oxidatively excised further on in the sequence. The C_7-O bond was installed via intramolecular epoxide opening with an alkoxide producing **3-12**. Finally the fifteenth carbon was installed as a methylene unit in enol ether **3-14**. Ultimately, the synthesis was completed with a number of other oxidative manipulations. Though lengthy by today's standards, Yamada's synthesis stands as a landmark.

While the *seco*-prezizaanes are the most well represented class of *Illicium* sesquiterpenoids (both in numbers and amount of synthetic effort), the *allo*-cedrane and anisalactone family are popular in their own right. Merrilactone A **3-4** was isolated in 2000, and displayed potent neurotrophic activity.[67e] This along with an densely functionalized pentacyclic core, including an oxetane, spurred many groups to work on its synthesis. Just two years later, Danishefsky and Birman reported their inaugural racemic synthesis of merrilactone A.

3.2.2.2 Birman and Danishefsky's merrilactone A[80]



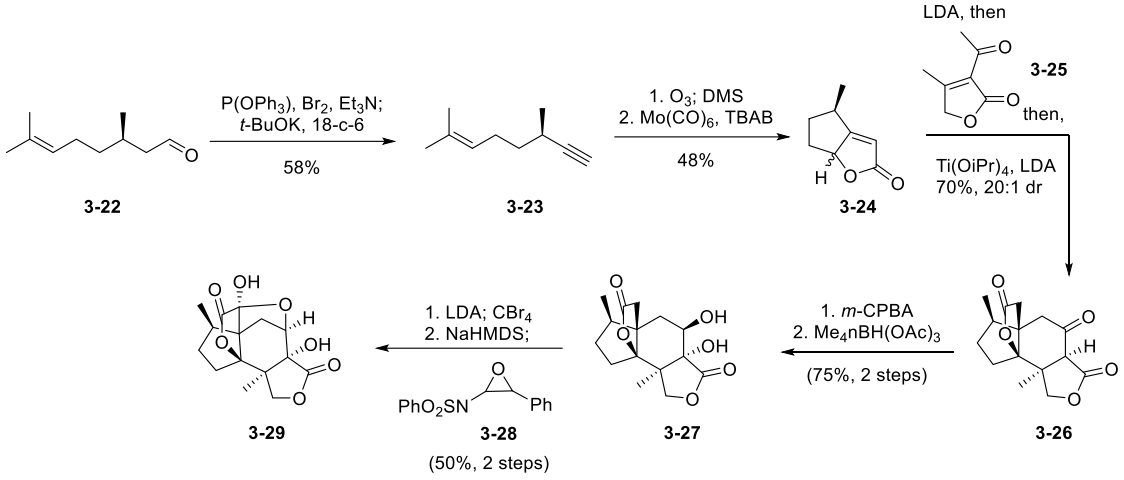
Scheme 3-2 Outline of Birman and Danishefsky's merrilactone A synthesis

Birman and Danishefsky tackled the pair of vicinal quaternary stereocenters in the opening transformation of the synthesis. A thermal Diels–Alder cycloaddition united diene **3-15** with dimethyl maleic anhydride **3-16** in good yield. Several transformations led to allylic alcohol **3-18**. A Johnson–Claisen rearrangement produced an γ,δ-unsaturated ester in 1.8:1 desired:undesired diastereoselectivity. Hydrolysis followed by iodolactonization gave lactone **3-19**. After some functional group manipulations, the final quaternary center was set via a radical 5-*exo*-*trig* cyclization to yield tetracycle **3-21**. Isomerization of the alkene and diastereoselective epoxidation generated the final intermediate. The oxetane was formed through intramolecular epoxide opening

as was established by Fukuyama in his semi-synthesis of merrilactone A.[81] In all, this synthesis was 19 steps from commercial materials.

Jiadefenolide **3-29** was isolated in 2009, and due to its potent activity, became a popular target.[82] The groups of Theodorakis, Sorensen, Patterson, Zhang, and Gademann published syntheses prior to 2015.[74] However, later that year, the Shenvi lab published an unbelievably expedient synthesis.

3.2.2.3 Shenvi's jiadefenolide[83]



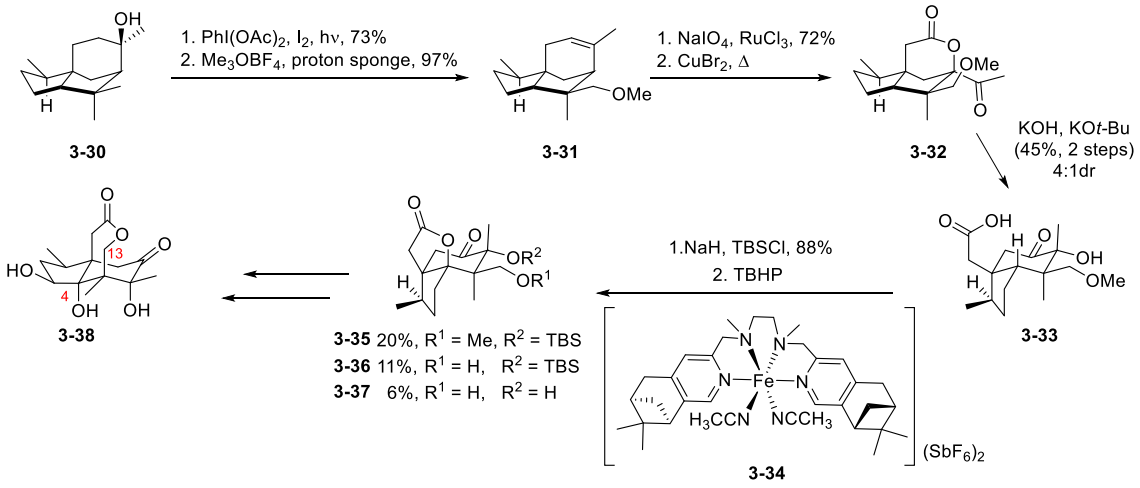
Scheme 3-3 Shenvi's (–)-jiadefenolide synthesis

Citronellal **3-22**, which bears the secondary methyl stereocenter contained in jiadefenolide, was first converted to alkyne **3-23**. After ozonolysis of the alkene, an intramolecular hetero-Pauson–Khand reaction forged bicycle **3-24**. Notably, an aldehyde took the place of the usual alkene. In a remarkable double Michael addition, lactone **3-24** and β-keto lactone **3-25** (available in 2 steps from commercially available material) were united with excellent yield and diastereoselectivity. In a handful of manipulations, **3-27** was converted to (–)-jiadefenolide. In total, the synthesis was 8 steps in its LLS, and was amenable to the gram scale production of this molecule.

Recently, the Maimone lab has been pursuing a unique strategy toward the *seco*-prezizaanes. [84] They identified (–)-cedrol as a potential starting material. They recognized that through several

oxidations, and a skeletal rearrangement, they could convert this cheap starting material into many of the members of the *seco*-prezizaanes.

3.2.2.4 Maimone's pseudoanisatin[85]



Scheme 3-4 Outline of Maimone's pseudoanisatin synthesis

Leveraging the tertiary alcohol contained within cedrol **3-30**, C_{13} is oxidized under Suarez conditions. After eliminating the tertiary ether with concomitant protection of the primary alcohol, the alkene is exhaustively oxidized to the ketone-acid. An α-oxidation of the methyl ketone with $CuBr_2$, delivers δ-lactone **3-32**. In the key step, the octahydropentalene is isomerized to the more stable hydrindane **3-33** in an α-ketol rearrangement. C_4 was oxidized using a modified White's catalyst and *tert*-butyl hydroperoxide as the stoichiometric oxidant. This step proved rather challenging, and after significant optimization, delivered a mixture of oxidized products **3-35**, **3-36**, and **3-37** in 37% overall yield. A series of manipulations led to pseudoanisatin **3-38** in a total of 12 steps from cedrol.

3.2.3 Isolation and bioactivity of illisimonin A

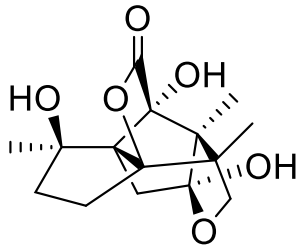


Figure 3-3 Illisimonin A

In October of 2017, Yu and Qu reported the isolation and neurotrophic activity of illisimonin A **3-1**, from the fruits of *Illicium simonsii*.[86] Through extensive 2-D NMR analysis, they assigned the relative structure as that shown. The molecule contains the first example of a tricyclo[5.2.1.$0^{1,6}$] carbon skeleton within a sesquiterpenoid.

In addition to an unprecedented architecture, illisimonin A was demonstrated to be protective against oxygen-glucose deprivation induced cell injury in SH-SY5Y cells, with an EC_{50} of 28 μM. Unfortunately, illisimonin A was isolated in a vanishingly small quantity. Through extensive purification, 4.0 mg was isolated from 96 kg of the fruits of *Illicium simonsii*. Intrigued by the unique structure of illisimonin A and the bioactivity, we set about to develop a laboratory synthesis of the precious molecule.

3.3 Synthesis of illisimonin A

3.3.1 Structural considerations

Despite its low molecular weight, illisimonin A contains significant complexity. The molecule has 7 contiguous fully substituted stereocenters. Its central cyclopentane ring is fully substituted at every carbon, including two vicinal quaternary centers. However, most interestingly, the molecule contains an embedded trans-octahydropentalene, which adds significant strain to the molecule.

Trans bicyclo[3.3.0]octane systems are significantly more strained than their cis counterparts.[87] According to Shenvi *et. al.*, only around 30 natural products have been isolated with this motif.[88] Of those, only five (excluding illisimonin A) have been synthesized in the laboratory.[89] We were

curious how much strain energy this motif added within the context of the full tricyclic core. Professor Scott Rychnovsky performed DFT calculations which indicated that the parent hydrocarbon for the trans 5-5 containing tricycle was approximately 7 kcal/mol more unstable than its cis counterpart.[90]

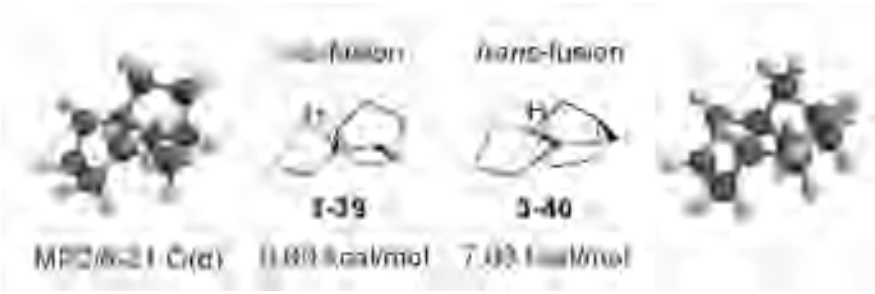
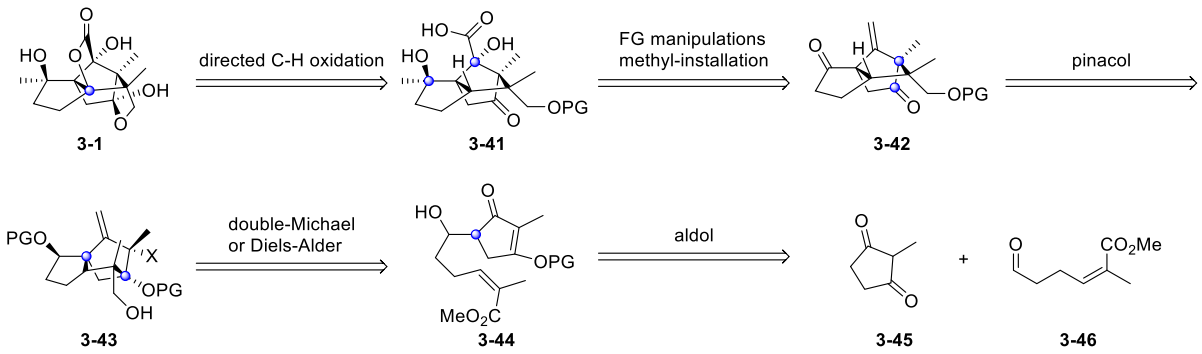


Figure 3-4 Strain energy of illisimonin A's trans-octahydropentalene containing tricycle, relative to isomeric cis-octahydropentalene containing tricycle

3.3.2 Retrosynthesis

While many retrosyntheses were proposed for illisimonin A by myself, Professor Rychnovsky, and other members of the lab, the retrosynthesis discussed below was my initial plan of attack when I began working on illisimonin A in the laboratory. All three of the key steps would actually find their way into our final synthesis of the molecule, though many of the details were modified throughout the course of our campaign.

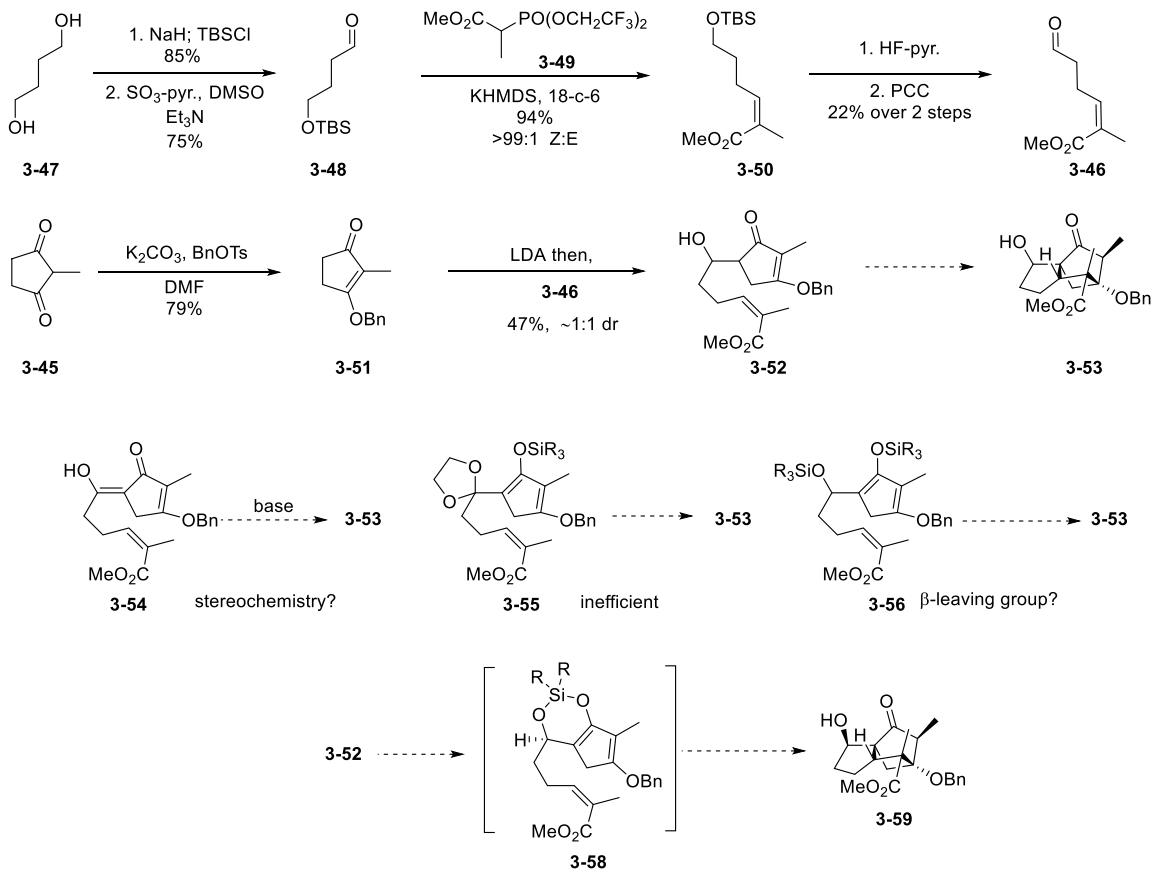


Scheme 3-5 Initial retrosynthetic analysis for illisimonin A

Illisimonin contains several tertiary oxygens. I envisioned excision of the bridging lactone via a White acid-directed C-H oxidation.[91] This had close precedent in Maimone's pseudoanisatin synthesis,[85] and gave **3-42** after some functional group manipulations. The semi-pinacol rearrangement has been used in numerous syntheses to construct strained ring systems and congested bonds.[92] Disconnection of the C5-C6 bond via a semipinacol rearrangement leads to tricycle **3-43** after the application of additional routine transforms. This transformation had the potential to take a cis-5,5 tricycle to a trans-5,5 system, along with installation of the vicinal quaternary centers. I imagined that two of the rings within **3-43** or a similar structure could be constructed by a Diels-Alder or double Michael reaction. Finally alcohol **3-44** could be traced back to **3-45** and **3-46** via an aldol reaction.

3.3.3 Secondary alcohol route

The synthesis of aldehyde **3-46** began with the known two-step conversion of diol **3-47** to aldehyde **3-48**. Installation of the Z-alkene proceeded in excellent yield and stereoselectively. Finally, a low yielding deprotection, oxidation sequence delivered aldehyde **3-46**. Much of the mass balance can be attributed to dimerization of deprotected alcohol **3-50** to an ester during the Corey-Suggs oxidation. This is a known side reaction for chromium-based oxidations. Its formation may be minimized by running the reaction under more dilute conditions as well as adding the alcohol slowly to the oxidant.[93]



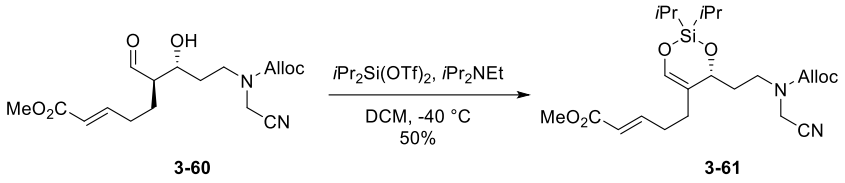
Scheme 3-6 Initial aldol reaction, and potential routes to forge tricycle

2-methyl-cyclopenta-1,3-dione **3-45** was *O*-alkylated with benzyl tosylate to yield vinylogous ester **3-51**, which was joined with aldehyde **3-46** in a non-diastereoselective aldol coupling. With this material in hand, we had some ideas about how to forge the tricycle. One possibility was to treat a 1,3-dione, such as **3-54**, with base. While this could work in theory, the diastereoselectivity was unpredictable.

We next targeted a Diels–Alder reaction using **3-55** as a starting material. However, we were never able to selectively ketalize the exocyclic ketone of a precursor to dione **3-55**. Another idea was to generate bis-silylated diene **3-56**, and cyclize it. While this had the potential to work, we feared both elimination of the protected secondary alcohol, and also the diastereoselectivity was

questionable. Professor Scott Rychnovsky suggested using a silacycle, such as **3-58**, to perform a Diels–Alder cycloaddition.

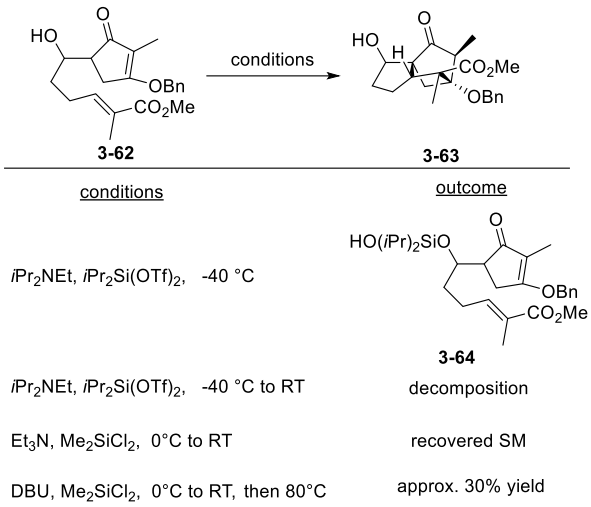
While this still had a potential retro-aldol available to it, the diastereoselectivity appeared to be well templated. A simple literature search turned up very little in terms of the generation of these silacycles from aldol products.[94] However, there was one very nice example of such a strategy in the Belanger lab's work on the calyciphylline type B alkaloids, Scheme 3-7.[95]



3-60 **3-61**

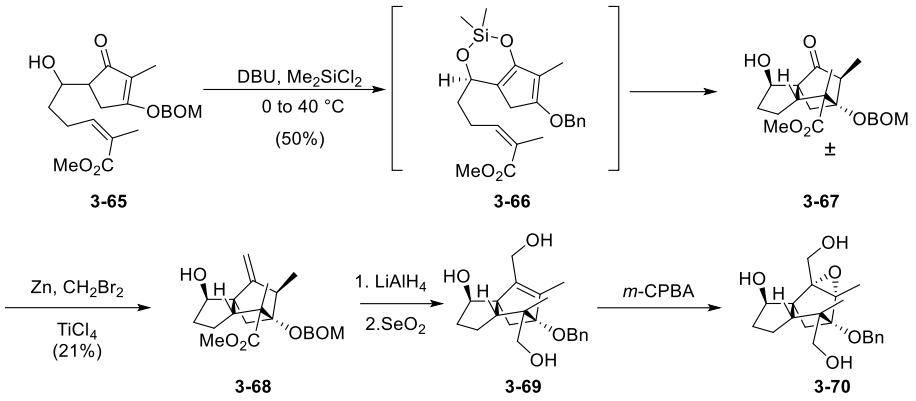
Scheme 3-7 Belanger's silacycle

β-hydroxy aldehyde **3-60** was treated with diisopropylsilyl ditriflate in the presence of Hunig's base, forming the 1,3-dioxa-2-silacyclohexene **3-61**. Though retro-aldol was a side reaction in this transformation, they were still able to generate synthetically useful amounts of **3-61**. Armed with this precedent, I began investigating whether this could be used in the context of my synthesis.



Scheme 3-8 Silacycle Diels–Alder cycloaddition investigations

I initially investigated the reaction on aldol product with the E-α,β-unsaturated ester **3-62**. Employing Belanger's original conditions, I isolated silanol **3-64** as the major product. Warming of the reaction led to extensive decomposition. Hypothesizing that the steric congestion of the bulky silyl groups and base shut down productive reactivity, I next attempted the reaction with dimethylsilyl dichloride and triethylamine. This led only to recovered starting material. As it seemed unlikely that initial silylation of the secondary alcohol was not occurring, I reasoned that the enolization was the problem. I thought that a stronger base could improve this, and thus switched to DBU. Finally, this led to isolation of Diels-Alder adduct **3-63** in approximately 30% yield. Though many other conditions were screened after this initial hit, the best conditions still employed the same reagents and solvent. Only number of equivalents and temperature were ultimately modified to improve the yield to 50% with the corresponding aldol product **3-65**. As the benzyl group had been difficult to remove under hydrogenolytic conditions, a benzyloxymethylene (BOM) was selected for milder deprotection options later on in the synthesis.



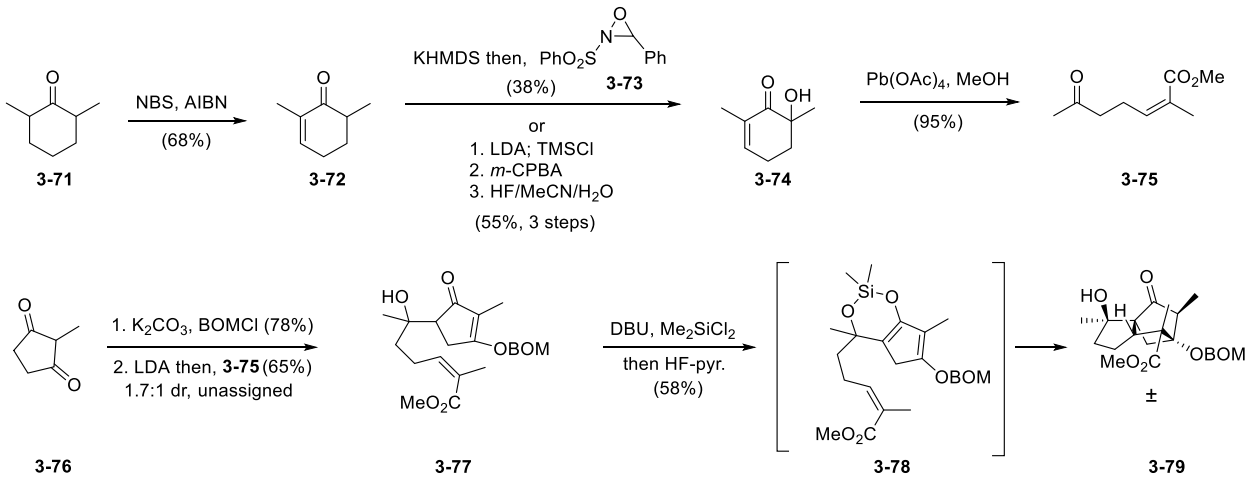
Scheme 3-9 Unexpected allylic rearrangement

Next, I began attempting to install a leaving group to test the critical pinacol rearrangement. Methylenation of the congested ketone was successful in low yield, employing the Lombardo modification of the Takai methylenation.[96] Next, I attempted to install a tertiary allylic alcohol as my leaving group for my pinacol rearrangement. When alkene **3-68** was treated with selenium dioxide, rather than delivering a tertiary allylic alcohol, rearranged tetrasubstituted allylic alcohol **3-69** was isolated. Riley oxidation of positions adjacent to quaternary centers is known to sometimes proceed with rearrangement of the alkene.[97] While unexpected, I realized that the allylic alcohol could be epoxidized, and that this could undergo a type-3 semipinacol rearrangement, reorganizing the bonds appropriately, while installing a tertiary alcohol found within the natural product.

3.3.4 Tertiary alcohol route

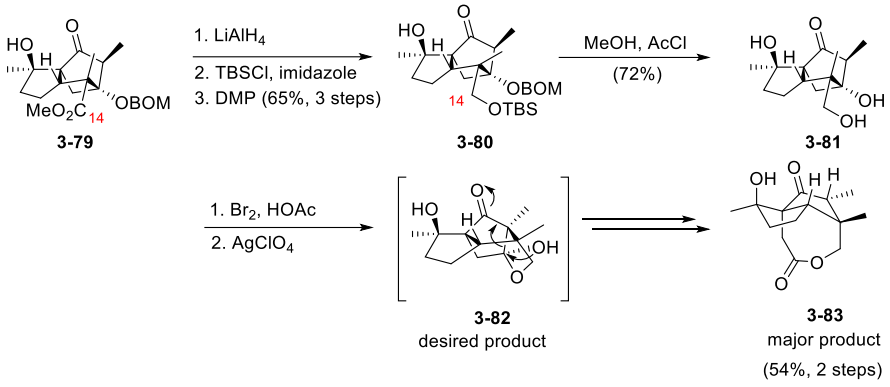
My initial retrosynthesis envisioned a late stage installation of the C15 methyl group through an organometallic addition to a ketone. However, the expected diastereoselectivity for such a transformation was not obvious. In the silacycle templated Diels-Alder reaction to form tricycle **3-67**, the C1 secondary alcohol had the correct stereochemistry that the C1 tertiary alcohol has in the natural product. Professor Sergey Pronin pointed out that if the same reaction was carried out

on a substrate with a tertiary alcohol, this would lead to the same motif as in illisimonin A. Though I was concerned about the potential for a retro-aldol fragmentation, the advantage of such an approach was quite appealing.



Scheme 3-10 Diels–Alder reaction with tertiary alcohol

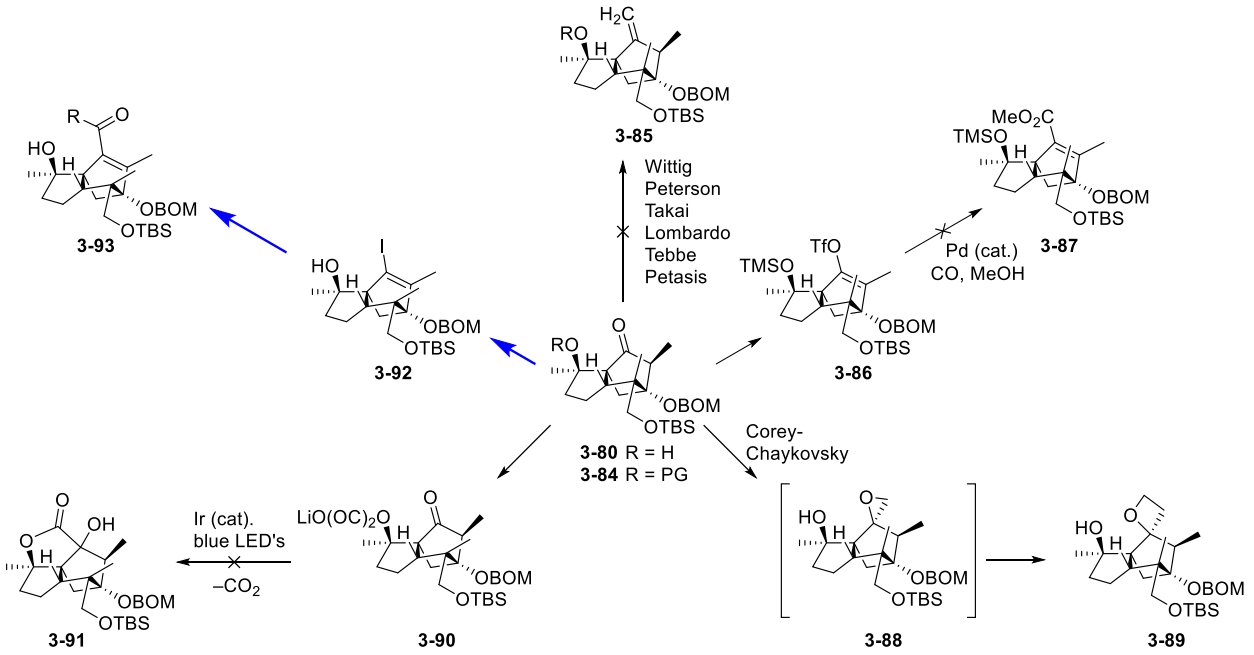
The ketone electrophile **3-75** was prepared in a 3-step known procedure,[98] or a higher yielding 5-step sequence, Scheme 3-10. It was then coupled with the BOM-protected diketone in acceptable yield and low diastereoselectivity. Using almost the same conditions as optimized for the secondary alcohol substrate **3-52**, tricycle **3-79** was generated through a silacycle templated Diels–Alder reaction. Remarkably, this transformation establishes 5 new stereocenters and two rings, with exquisite diastereoselectivity. It should be noted that one of the stereocenters generated in the aldol addition is ablated prior to cycloaddition. The exact mechanism of this transformation is currently being studied in the lab and results will be reported in due course.



Scheme 3-11 Semipinacol rearrangement, and undesired fragmentation

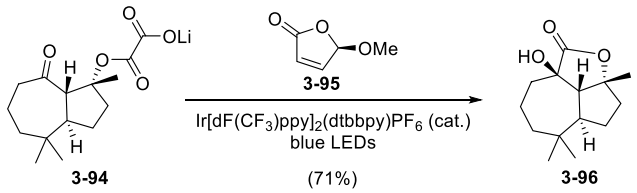
Next, C14 was reduced to the primary alcohol oxidation state, as it exists in the natural product. This was most easily accomplished by global reduction of ester **3-79** with lithium aluminum hydride ($LiAlH_4$), mono-TBS protection of the less sterically congested primary alcohol, and reoxidation of the secondary alcohol back to the ketone to deliver protected alcohol **3-80** in good yield over 3 steps. After acid mediated bis-deprotection, a bromide was introduced alpha to the ketone with elemental bromine in the presence of acetic acid. Treatment of this crude product with silver perchlorate generated trans 5-5 containing lactone **3-83**, rather than the expected lactol **3-82**. This can be most easily rationalized through the intermediacy of lactol **3-82**, followed by a retro-Claisen type fragmentation.

While this result was interesting in that the strained trans 5-5 ring system could be obtained, it was a dead-end with respect to the synthesis of illisimonin A. One way to avoid the undesired fragmentation would be to remove the ketone. Because there is a carbon in this position in the natural product, methylenation appeared to be a good way to move forward with this strategy. Unfortunately, the methylenation of ketone **3-80** or protected analogs was unsuccessful under a plethora of standard conditions.[99] This was rather unfortunate, as ketone **3-59**, differing by only a methyl group, had previously been methylenated albeit in low yield.



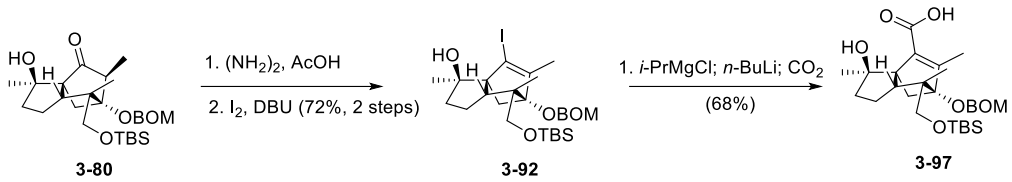
Scheme 3-12 Installation of the final carbon

Next, I attempted to install the carbon through palladium catalyzed carbonylative methoxylation of triflate **3-86**, Scheme 3-12. All attempts either led to recovered starting material, or decomposition. Surprisingly, Corey–Chaykovsky homologation led to mainly oxetane **3-89**, rather than epoxide **3-88**, even when employing only one equivalent of the sulfonium or sulfoxonium ylide. While oxetanes are a known side product of the Corey–Chaykovsky reaction, they typically require more forcing conditions, as ketones are more electrophilic than epoxides. I believe that ketone **3-80** is less reactive to the nucleophilic ylide than epoxide **3-88**, due to the high steric hindrance around the ketone.



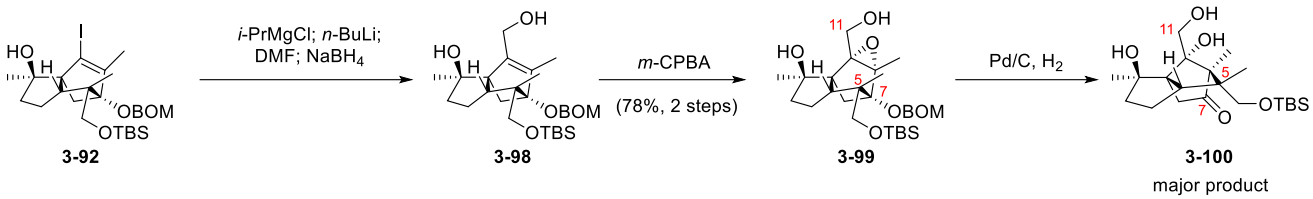
Scheme 3-13 Overman's unexpected acyl-oxy radical addition into a ketone

At the suggestion of Dr. Alex Burtea, I attempted to capitalize on an observation made by the Overman lab *en route* to cheloviolenes A and B. They were attempting to couple butenolide **3-95** with a tertiary radical generated from the photoredox catalyzed double decarboxylation of lithium oxalate **3-94**. Surprisingly, they observed tricycle **3-96** as the major product. Apparently the substrate only underwent mono-decarboxylation, and the acyloxy radical performed a 5-exo trig addition to a ketone. Unfortunately, this transformation did not occur in my system, and only proto-deoxalation was observed.



Scheme 3-14 Barton vinyl iodide synthesis and subsequent lithiation

Professor Rychnovsky suggested to install a vinyl iodide, perform a lithium/halogen exchange, and quench the vinyllithium with a one carbon electrophile. Gratifyingly, this idea proved to be an effective solution for our synthesis. Employing Barton's method, vinyl iodide **3-92** was synthesized from the corresponding hydrazone. Deprotonation of the tertiary alcohol with isopropylmagnesium chloride was followed by lithium halogen exchange with *n*-butyllithium. The organolithium was then treated with CO_2, which furnished α,β-unsaturated acid **3-97** after acidic workup. Unfortunately, all attempts to epoxidize the acid were unsuccessful.[100] Given the difficulty of epoxidizing a tetrasubstituted, electron-deficient olefin, I elected to try the epoxidation on the corresponding primary alcohol. Though this approach is suboptimal from the standpoint of redox efficiency, it allowed me to push forward with the synthesis.

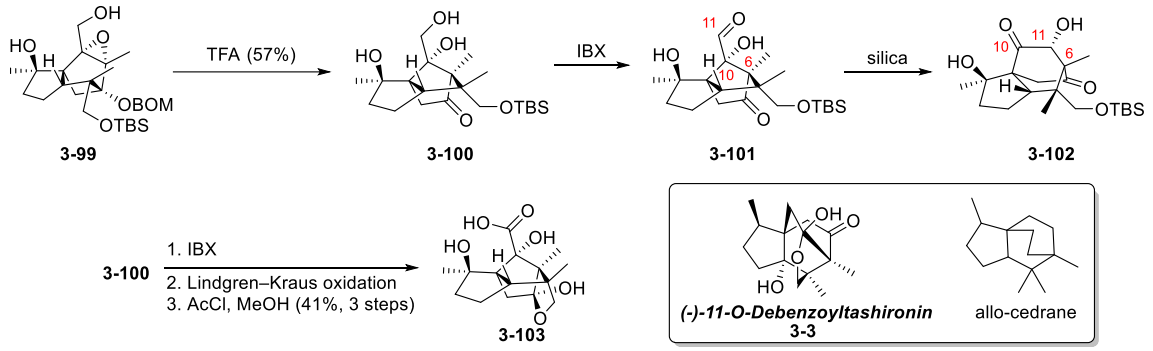


Scheme 3-15 Epoxidation and facile semi-pinacol rearrangement

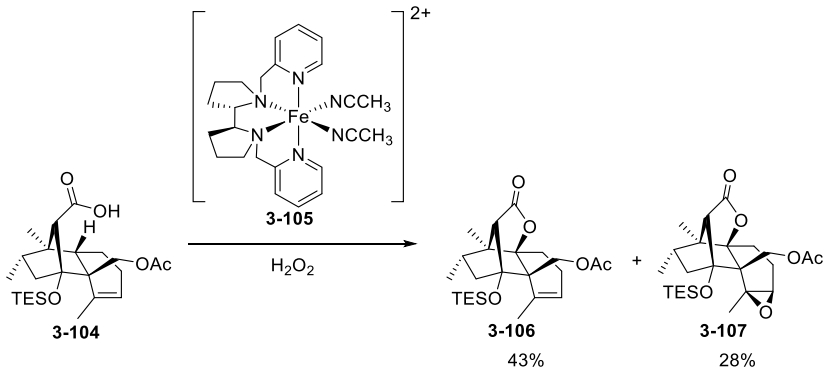
Thus, the final carbon was installed using a Bouveault aldehyde synthesis, and the resultant formyl group was reduced *in situ* using sodium borohydride. After a work-up, allylic alcohol **3-98** was easily epoxidized with *m*-CPBA. At this juncture, I removed the BOM protecting group under standard hydrogenolytic conditions. Surprisingly, in addition to removal of the protecting group, the semi-pinacol rearrangement occurred, possibly due to trace acid impurities on the palladium on carbon. Though competing hydride migration from the primary alcohol was a concern, only small amounts of an aldehyde were seen in the crude NMR. Evidently, the rigid conformation of the molecule facilitates selective migration of the $\sigma_{C5\text{-}C7}$ bond over the $\sigma_{C11\text{-}H}$. After a short screen, it was found that this transformation could easily be accomplished by treatment of epoxide **3-99** with substoichiometric amounts of TFA in chloroform. Having established the two vicinal quaternary centers and trans-octahydropentalene contained within illisimonin A, three oxidations and a deprotection separated us from our target.

Sequential oxidation of the C11 carbon in **3-100** to the aldehyde and then to the carboxylic acid was accomplished using standard chemistry.[101] When attempting to purify α-hydroxy aldehyde **3-101** by column chromatography, rearrangement to α-hydroxy ketone **3-102** occurred. The rearrangement could be avoided by taking the material forward directly without chromatographic purification. While the transformation can be rationalized as a retro-aldol/aldol sequence, it is likely due to an α-ketol rearrangement, as rearrangements of strained α-hydroxy aldehydes and ketones catalyzed by silica have been reported in the literature.[102] The facile isomerization to the

more stable [2.2.2]-bicycle highlights the strain contained within illisimonin A's ring system. It is interesting to note that the isolation team proposed that the illisimonane skeleton could arise from a carbocation shift of the *allo*-cedrane skeleton.[86] The interconversion of α-hydroxy carbonyl **3-101** to **3-102**, which bears the *allo*-cedrane skeleton, is the reverse of the proposed biosynthetic step.



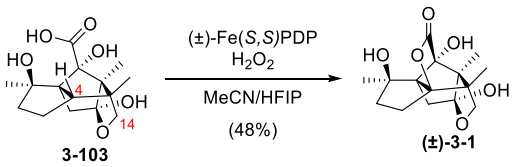
Scheme 3-16 α-ketol rearrangement and functional group manipulations



Scheme 3-17 Snyder's late stage, acid-directed C-H oxidation

After deprotection of the primary alcohol with methanolic HCl, only a C-H oxidation remained to complete the synthesis. As the C4 methine was doubly neopentylic, steric hindrance could block oxidation. However, Snyder recently described an acid-directed White oxidation of a comparably congested C-H bond in his scaparvin B-D syntheses, Scheme 3-17 Snyder's late stage, acid-directed C-H oxidation.[103] Our gamble was rewarded when acid **3-103** was oxidized to to natural product **3-1**

using White's FePDP catalyst with hydrogen peroxide as the stoichiometric oxidant. Some points about this reaction warrant further discussion. HFIP was included to improve the solubility of acid **3-103** and may also play a role in suppressing the undesired oxidation of the C14 methylene by electronically deactivating the position through hydrogen bond donation.[104] The rigid conformation of **3-103** likely aids in the high reactivity for the C4 methine. We speculate that strain release in the transition state may also enhance the reactivity at this position.[105] The reaction proved to be effective after minimal optimization. We were pleased to obtain 94 mg of natural product **3-1** from 196 mg of acid **3-103** in our largest reaction.



Scheme 3-18 Completion of the synthesis of racemic illisimonin A

3.3.5 Absolute configuration reassignment

The proton and carbon NMR spectra for synthetic and natural illisimonin A were in agreement, thus confirming its relative structure as that assigned by the isolation team. The isolation team also assigned the absolute configuration of illisimonin A on the basis of experimental and calculated electronic circular dichroism (ECD) spectra. However, the absolute stereochemistry of illisimonin A was at odds with other members of the *Illicium* sesquiterpenoids. Shown below are two representative examples. In all cases, if C1 is oxidized, the hydroxyl is α when depicted as shown. Additionally, if only C13 or C14 is oxidized, it is always C13. However, with the assigned absolute configuration, C14 of illisimonin A was oxidized. Mindful of these discrepancies, we set out to independently assign the absolute configuration of illisimonin A. To do this, we needed to

obtain enantioenriched illisimonin A, or its enantiomer, and independently verify the absolute stereochemistry of that sample.

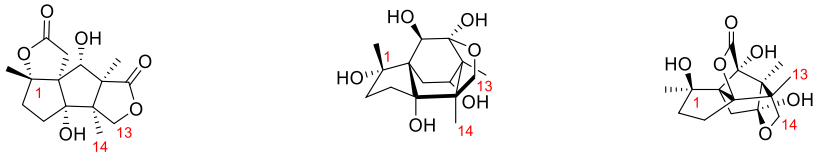
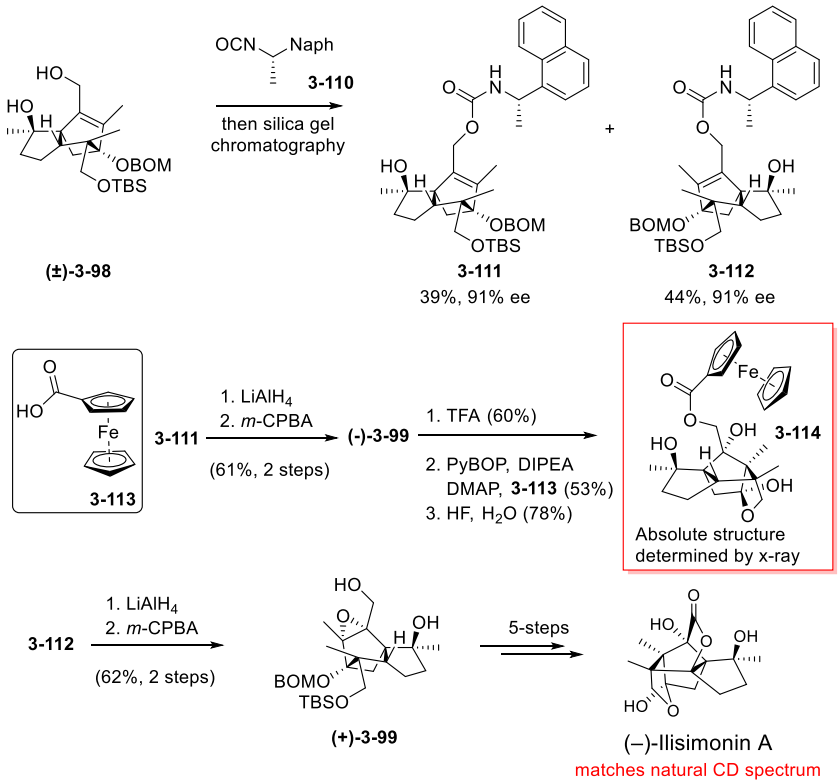


Figure 3-5 Oxidation discrepancies between illisimonin A and other members of the *illicium* sesquiterpenoids

Initial attempts at obtaining an enantioenriched intermediate focused on kinetic resolutions of racemic allylic alcohol **3-98**. Sharpless asymmetric epoxidation, HBTM catalyzed kinetic resolution, and enzymatic resolutions were all unsuccessful at delivering products in high enantioenrichment.[106] After exploring a handful of chiral auxiliaries for alcohols, it was found that intermediate allylic alcohol **(±)-3-98** could be resolved by derivatizing with (*S*)-1-(1-naphthyl)ethyl isocyanate **3-110** and separating the diastereomers by silica gel chromatography.[107] The lower R_f diastereomer **3-111** was deprotected, converted to the epoxide **(–)-3-99** and rearranged upon treatment with TFA. Esterification of the C11 alcohol with ferrocenecarboxylic acid **3-113** added a heavy atom suitable for absolute configuration determination using X-ray crystallography with a molybdenum X-ray source.[108] A suitably crystalline compound was found with removal of the TBS group to generate lactol **3-114**. X-ray analysis allowed the absolute configuration of **3-114** to be assigned to the 1*R* series. The higher R_f diastereomer **3-112**, inferred to have the 1*S* configuration, was deprotected and taken on to (–)-illisimonin A using the previously developed sequence. The CD of this synthetic material matched that reported for the

natural product.[86] Thus the absolute configuration of the natural product, (–)-illisimonin A, is therefore revised to 1*S*,4*S*,5*S*,6*S*,7*R*,9*R*,10*R*.



Scheme 3-19 Revision of the absolution configuration of (–)-illisimonin A

3.4 Summary

We report the first synthesis of (±)-illisimonin A. The NMR data for synthetic illisimonin A matched that reported for the natural product, confirming its relative configuration. An enantioselective synthesis of (–)-illisimonin A, combined with an X-ray structure, led to a revision of the absolute configuration of the natural product. Notable steps in the synthetic route include a 1,3-dioxa-2-silacyclohexene templated Diels-Alder cycloaddition and type-3 semipinacol rearrangement. The final step is a White, acid-directed C-H oxidation. The route is effective, and has enabled the preparation of 165 mg of (±)-Illisimonin A. This material will be valuable in exploring its neurotrophic bioactivity.

3.5 Supporting Information

3.5.1 General Information

Many of the details contained within this chapter have been previously published. The NMR spectra not included for the characterized compounds can be found in this publication.[90] Compounds which only occur in the supporting information are numbered starting from **S3-1**

Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of tripets, dq = doublet of quartets, ddq = doublet of doublet of quartets, app. = apparent), coupling constant(s) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using ESI-TOF.

Unless otherwise stated, synthetic reactions were carried out in flame- or oven-dried glassware

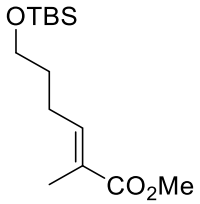
under an atmosphere of argon. All commercially available reagents were used as received unless stated otherwise. Solvents were purchased as ACS grade or better and as HPLC-grade and passed through a solvent purification system equipped with activated alumina columns prior to use. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm, or by staining with potassium permanganate or Hanessian's stain.[109] Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns unless otherwise stated. Electrospray ionization mass spectrometry (ESI-MS) was analyzed in positive mode with flow injection. Circular dichroism was carried out on a Jasco J-810 spectropolarimeter with a 0.1 cm cell at room temperature with the following parameters: speed 50 nm/min; D.I.T. 2 sec; bandwidth 5 nm.

3.5.2 Chemicals

All purchased chemicals were used without further purification unless otherwise noted. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Fe(*R,R*)PDP and Fe(*S,S*)PDP were prepared as described, and stored in a nitrogen filled glove box prior to use.[91a]

3.5.3 Compound Characterization

3.5.3.1 Racemic section- All compounds reported in this section are either achiral or racemic



methyl (E)-6-((tert-butyldimethylsilyl)oxy)-2-methylhex-2-enoate (S3-1): To a solution of methyl 2-(triphenyl-λ^5-phosphaneylidene)propanoate[110] (24.4 g, 70.0 mmol) in DCM (400 mL) was added aldehyde **3-48**[111] (11.8 g, 58.3 mmol). After stirring for 8 h, silica gel (40 g)

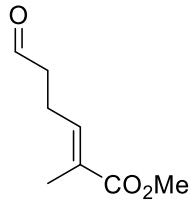
was added, and the solvent was removed in vacuo. The crude mixture was chromatographed on silica gel with (5% EtOAc in hex) to afford **3-48** as a clear oil (14.2 g, 89%, 41:1 E:Z).

$\mathbf{R}_f$ = 0.26 (EtOAc:Hex, 1:19), visualized with Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (td, *J* = 7.5, 1.3 Hz, 1H), 3.73 (s, 3H), 3.63 (t, J = 6.2 Hz, 2H), 2.25 (q, 7.5 Hz, 2H), 1.84 (s, 3H), 1.65 (app. p, *J* = 6.9 Hz, 2H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (126 MHz, CDCl3) δ 168.8, 142.4, 127.9, 62.5, 51.8, 31.8, 26.0, 25.3, 18.4, 12.5, –5.2.

HRMS (ESI, MeOH) calculated for $C_{14}H_{28}O_3SiNa$ $(M+Na)^+$ 295.1700, found 295.1709.



methyl (E)-2-methyl-6-oxohex-2-enoate (S3-2): ester **S3-1** (14.2 g, 52.1 mmol), pyridine (20 mL), and THF (100 mL) were cooled to 0 °C. HF-pyridine (~70% HF) (7 mL, 0.27 mol) was added slowly over a period of 10 minutes. The reaction was monitored by TLC for consumption of starting material. After 4 h, no starting material remained. The reaction vessel was opened to air and H_2O (20 mL) was added. Solid $NaHCO_3$ was added carefully until bubbling ceased. The mixture was transferred to a separatory funnel. H_2O (100 mL) was added, and the mixture was extracted with DCM (3 x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield 12.2 g of crude material which was used without further purification.

The crude alcohol was dissolved in DCM (50 mL), and PCC (17 g, 79 mmol) was added in 3 portions over 20 minutes, and the reaction was stirred at ambient temperature overnight. The following day, the reaction mixture was passed through a plug of silica and washed with DCM several times. The filtrate was concentrated in vacuo. The crude mixture was purified by flash

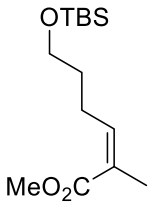
column chromatography (DCM/Hex) on silica to afford **S3-2** (2.91 g, 33% over 2 steps) as a clear oil.

$\mathbf{R_f}$ = 0.44 (EtOAc:Hex, 1:2), visualized with Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (t, *J* = 1.1 Hz, 1H), 6.69 (tq, *J* = 7.4, 1.4 Hz, 1H), 3.74 (s, 3H), 2.62 (t, *J* = 7.2, 2H), 2.50 (app. q, *J* = 7.3 Hz, 2H), 1.87 (q, *J*= 1.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 168.4, 139.7, 129.1, 51.9, 42.7, 21.3, 12.6.

HRMS (ESI, MeOH) calculated for $C_8H_{12}O_3Na$ $(M+Na)^+$ 179.0679, found 179.0679.



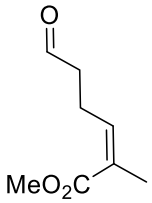
methyl (Z)-6-((tert-butyldimethylsilyl)oxy)-2-methylhex-2-enoate (3-50): Methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate[112] (2.76 g, 8.31 mmol) and 18-crown-6 (10.8 g, 41.6 mmol) in THF (140 mL) was cooled to -78 °C. KHMDS (1.66 g, 8.31 mmol) as a solution in THF (15 mL) was added. Next, aldehyde **3-48** (1.68 g, 8.31 mmol) as a solution in THF (5 mL) was added. After 30 min., NH_4Cl (aq) (50 mL) was added and the reaction was allowed to warm to ambient temperature. The mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **3-50** (2.12 g, 94%, >99:1 Z:E) as a clear oil.

$\mathbf{R_f}$ = 0.58 (EtOAc:Hex, 1:9), visualized by UV

^{1}H NMR ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (tq, *J* = 7.4, 1.4 Hz, 1H), 3.73 (s, 3H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.51 (app. q, *J* = 7.5 Hz, 2H), 1.90 (q, *J* = 1.4 Hz, 3H), 1.63 (app. p, *J* = 7.1Hz, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 143.2, 127.1, 63.0, 51.3, 32.7, 26.4, 26.1, 20.8, 18.5, –5.2.

HRMS (ESI, MeOH) calculated for $C_{14}H_{28}O_3SiNa$ $(M+Na)^+$ 273.1881, found 273.1858.



methyl (Z)-2-methyl-6-oxohex-2-enoate (3-46): A solution of ester **3-50** (2.29 g, 8.4 mmol), pyridine (3 mL), in THF (17 mL) was cooled to 0 °C. HF-pyridine (~70% HF) (1.1 mL, 42 mmol) was added slowly over a period of 10 minutes. The reaction was monitored by TLC for consumption of starting material and was allowed to run overnight. The reaction vessel was opened to air and H_2O (5 mL) was added. Solid $NaHCO_3$ was added carefully until bubbling ceased. The mixture was transferred to a separatory funnel. H_2O (20 mL) was added, and the mixture was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield 1.33 g of crude material which was used without further purification.

The crude alcohol was dissolved in DCM (25 mL), and PCC (3.62 g, 16.8 mmol) was added in 3 portions over 20 minutes, and the reaction was stirred at ambient temperature overnight. The following day, the reaction mixture was passed through a plug of silica to remove most of the chromium by-products. The plug of silica was washed with DCM several times. The filtrate was concentrated in vacuo. The crude mixture was purified by flash column chromatography

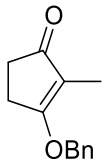
(DCM/Hex) on silica to afford **3-46** (284 mg, 22% over 2 steps) as a clear oil, corrected for the 6 mol% of DCM.

$\mathbf{R_f}$ = 0.33 (EtOAc:Hex, 3:17), visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.95 (t, *J* = 7.1 Hz, 1H), 3.75 (s, *J* = 5.8 Hz, 3H), 2.78 (q, *J* = 7.4 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 1.90 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.8, 168.2, 140.6, 128.7, 51.5, 43.5, 22.5, 20.7.

HRMS (ESI, MeOH) calculated for $C_8H_{12}O_3SNa$ $(M+Na)^+$ 179.0679, found 179.0674.



3-(benzyloxy)-2-methylcyclopent-2-en-1-one (3-51). 2-methylcyclopenta-1,3-dione (2.67 g, 23.8 mmol), K_2CO_3 (9.86 g, 71.3 mmol), and benzyl tosylate (9.36 g, 35.7 mmol) were combined in a round-bottom flask. DMF (36 mL) was added and the reaction was stirred at ambient temperature for 24 h. EtOAc (50 mL) was added, and the reaction mixture was transferred to a separatory funnel and washed with H_2O (3 x 50 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford a red oil. The oil crystallized under high-vacuum overnight to yield **3-51** (3.82 g, 79%) as an orange-crystalline solid.

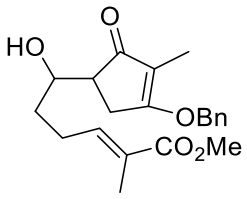
$\mathbf{R_f}$ = 0.22 (EtOAc:Hex, 3:1), visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.31 (m, 5H), 5.24 (s, 2H), 2.78–2.61 (m, 2H), 2.47–2.34 (m, 2H), 1.69 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.3, 183.6, 136.1, 128.9, 128.6, 127.1, 117.0, 70.9, 33.7, 25.4, 6.3.

HRMS (ESI, MeOH) calculated for $C_{13}H_{14}O_2Na$ $(M+Na)^+$ 225.0887, found 225.0895.

m.p. 42-44 °C



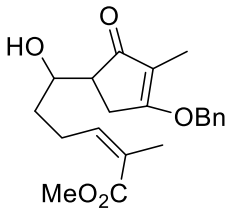
methyl (E)-6-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-6-hydroxy-2-methylhex-2-enoate (3-65): Diisopropylamine (0.34 mL, 2.4 mmol) in THF (1.6 mL) was cooled to -78 °C. A solution of *n*-BuLi (2.50 M, 0.80 mL, 2.0 mmol) was added dropwise. The reaction mixture was warmed to 0 °C for 5 min. then cooled to -78 °C. Cyclopentenone **7** (407 mg, 2.01 mmol) as a solution in THF (1.6 mL) was added. After 1 h, the reaction was warmed to -40 °C for 15 minutes before being cooled back to -78 °C. Aldehyde **S3-2** (314 mg, 2.01 mmol) was added as a solution in THF (1.6 mL). After 30 min., the reaction was quenched by the addition of citric acid (aq, 10% w/v) (5 mL), and allowed to warm to ambient temperature. The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **3-65** (506 mg, 70%, ~1:1 dr unassigned) as an orange oil.

$\mathbf{R_f}$ = 0.51 (EtOAc:Hex, 3:2), visualized by UV

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45–7.33 (m, 10H), 6.78–6.72 (m, 2H), 5.26 (s, 2H), 5.25 (s, 2H), 4.13 (dt, *J* = 9.9, 3.2 Hz, 1H), 3.734 (s, 3H), 3.731 (s, 3H), 2.79 (ddd, *J* = 17.3, 7.1, 1.5 Hz, 1H), 2.69–2.63 (m, 2H), 2.63–2.60 (m, 1H), 2.46 (ddd, *J* = 9.7, 7.1, 2.8 Hz, 1H), 2.42–2.22 (m, 6H), 1.85 (s, 3H), 1.84 (s, 3H), 1.68 (s, 3H), 1.67 (s, 3H), 1.61–1.54 (m, 3H), 1.52–1.44 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 206.6, 184.5, 183.71, 168.8, 168.7, 141.9, 141.6, 135.8, 135.6, 129.04, 128.98, 128.8, 128.7, 128.30, 128.28, 127.21, 127.20, 117.3, 116.3, 72.0, 71.5, 71.3, 69.8, 51.86, 51.85, 50.5, 48.9, 34.5, 33.2, 29.0, 26.8, 25.4, 24.3, 12.5, 12.3, 6.2, 6.1.

HRMS (ESI, MeOH) calculated for $C_{21}H_{26}O_5Na$ $(M+Na)^+$ 381.1673, found 381.1673.



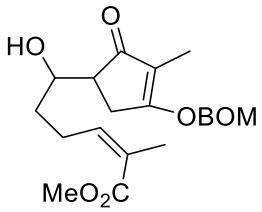
methyl (Z)-6-(4-(benzyloxy)-3-methyl-2-oxocyclopent-3-en-1-yl)-6-hydroxy-2-methylhex-2-enoate (3-52): Diisopropylamine (75 µL, 0.53 mmol) in THF (0.35 mL) was cooled to -78 °C. A solution of *n*-BuLi (2.50 M, 0.18 mL, 0.44 mmol) was added dropwise. The reaction mixture was warmed to 0 °C for 5 min. then cooled to -78 °C. Cyclopentenone **3-51** (89 mg, 0.44 mmol) as a solution in THF (0.35 mL) was added. After 1 h, the reaction was warmed to -40 °C for 15 minutes before being cooled back to -78 °C. Aldehyde **3-46** (69 mg, 0.44 mmol) was added as a solution in THF (0.35 mL). After 30 min., the reaction was quenched by the addition of citric acid (aq, 10% w/v) (2 mL), and allowed to warm to ambient temperature. The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford **3-51** (89 mg, 56%, ~1:1 dr unassigned), corrected for the 18 mol% DCM it contains.

R_f = 0.51 (EtOAc:Hex, 3:2), visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.33 (m, 10H), 5.99–5.90 (m, 2H), 5.28–5.22 (m, 4H), 4.70 (br s, 1H), 4.15–4.07 (m, 1H), 3.77–3.70 (m, 7H), 3.13 (br s, 1H), 2.84–2.51 (m, 8H), 2.45–2.33 (m, 2H), 1.92–1.87 (m, 6H), 1.70–1.66 (m, 6H), 1.65–1.60 (m, 1H), 1.59–1.53 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.9, 206.2, 184.2, 183.8, 169.1, 168.8, 142.8, 142.4, 136.1, 135.8, 129.0, 128.9, 128.8, 128.6, 128.3, 127.8, 127.3, 127.2, 117.0, 116.5, 71.7, 71.3, 71.1, 68.9, 51.7, 51.5, 50.5, 49.0, 34.3, 34.2, 28.8, 26.8, 25.9, 25.3, 20.78, 20.77, 6.3, 6.1.

HRMS (ESI, MeOH) calculated for $C_{21}H_{26}O_5Na$ $(M+Na)^+$ 381.1673, found 381.1668.



alcohol 3-65: Diisopropylamine (0.35 mL, 2.5 mmol) in THF (1.6 mL) was cooled to -78 ℃. A solution of *n*-BuLi (2.50 M, 0.82 mL, 2.1 mmol) was added dropwise. The reaction mixture was warmed to 0 ℃ for 5 min. then cooled to –78 ℃. Cyclopentenone **S3-3** (475 mg, 2.05 mmol) as a solution in THF (1.6 mL) was added. After 1 h, the reaction was warmed to –40 ℃ for 15 minutes before being cooled back to –78 ℃. Aldehyde **3-46** (320 mg, 2.05 mmol) was added as a solution in THF (1.6 mL). After 30 min., the reaction was quenched by the addition of citric acid (aq, 10% w/v) (6 mL), and allowed to warm to ambient temperature. The reaction mixture was transferred to a separatory funnel and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex) on silica to afford alcohol **3-52** (630 mg) as a yellow oil (approx. 79%), which contained some impurities which were carried on to the next step without further purification.

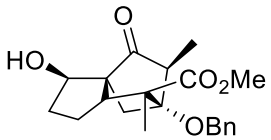
R_f = 0.23, 60% EtOAc in hexanes, visualized by UV

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 10H), 5.95 (t, *J* = 7.8 Hz, 1H), 5.92 (t, *J* = 8.3 Hz, 1H), 5.38–5.34 (m, 1H), 5.32–5.27 (m, 3H), 4.75–4.67 (m, 4H), 4.11 (dt, *J* = 8.5, 3.7 Hz, 1H),

3.74–3.71 (m, 1H), 3.70 (s, 6H), 3.16 (d, *J* = 3.9 Hz, 1H), 2.88–2.69 (m, 4H), 2.65– 2.51 (m, 4H), 2.46–2.35 (m, 2H), 1.89 (s, 3H), 1.88 (s, 3H), 1.65–1.53 (m, 10H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 208.3, 206.6, 182.6, 182.3, 168.9, 168.7, 142.7, 142.4, 136.6, 136.5, 128.7, 128.6, 128.3, 128.2, 128.10, 128.07, 128.04, 127.6, 118.1, 117.6, 92.1, 91.9, 71.6, 71.3, 71.1, 68.7, 51.6, 51.4, 50.4, 48.9, 34.3, 34.2, 28.3, 26.1, 25.8, 25.2, 20.70, 20.69, 6.0, 5.9.

HRMS (ESI, MeOH) calculated for $C_{22}H_{28}O_6Na$ $(M+Na)^+$ 411.1778, found 411.1777.



(±) methyl (3R,3aS,5S,6R,7S,7aR)-6-(benzyloxy)-3-hydroxy-5,7-dimethyl-4-oxooctahydro-3a,6-methanoindene-7-carboxylate (3-64): Alcohol **3-63** (34 mg, 0.095 mmol) in DCM (0.5 mL) was cooled to 0 °C. DBU (40 µL, 0.26 mmol), then Me_2SiCl_2 (20 µL, 0.16 mmol) was added, and the reaction was allowed to warm to ambient temperature overnight. The following day, DMF (1 mL) was added, and a stream of argon was passed over the reaction for 20 minutes to evaporate the DCM. The reaction was heated to 80 °C for 2 h, and then allowed to cool to ambient temperature. Saturated $NaHCO_3$ (aq) (5 mL) was added. The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex), to afford **3-64** (12.5 mg) as an orange solid. The product contained minor impurities as evidenced by ^{1}H NMR.

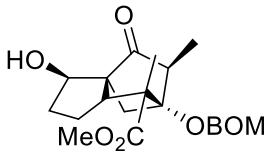
R_f = 0.25 (EtOAc:Hex, 3:7), visualized with Hanessian's stain

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.35 (m, 4H), 7.32–7.28 (m, 1H), 4.69 (d, *J*= 11.9 Hz, 1H), 4.58 (d, *J*= 11.9 Hz, 1H), 4.37–4.35 (m, 1H), 4.32 (br. s, 1H), 3.70 (s, 3H), 3.26–3.21 (m, 1H),

2.85 (q, *J*= 7.5 Hz, 1H), 2.09–1.99 (m, 2H), 1.93–1.82 (m, 3H), 1.68–1.58 (m, 1H), 1.43 (s, 3H), 1.00 (d, *J*= 7.4 Hz, 3H)

^{13}C NMR (151 MHz, $CDCl_3$) δ 216.4, 176.5, 138.7, 128.6, 127.7, 126.9, 88.5, 74.0, 67.6, 64.0, 53.1, 52.2, 51.0, 47.9, 39.4, 36.6, 23.0, 20.3, 8.4.

HRMS (ESI, MeOH) calculated for $C_{21}H_{26}O_5Na$ $(M+Na)^+$ 381.1673, found 381.1668.



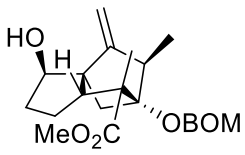
tricycle 3-67: Alcohol **3-65** (630 mg, 1.62 mmol) in DCM (10 mL) was cooled to 0 °C in a pressure vial. DBU (0.69 mL, 4.9 mmol), then Me_2SiCl_2 (0.31 mL, 2.4 mmol) was added, and the reaction was sealed. After 30 minutes, the reaction was heated to 40 °C overnight then allowed to warm to ambient temperature overnight. Saturated $NaHCO_3$ (aq) (10 mL) was added. The reaction mixture was transferred to a separatory funnel and extracted with DCM (3 x 5 mL). The organic extracts were transferred to an Erlenmeyer flask, and silica gel (ca. 1g) was added. The flask was stirred open to air for one hour. The silica was filtered off, and washed with MeOH (2 x 2 mL). The filtrate was concentrated in vacuo. The crude mixture was purified by flash column chromatography (EtOAc/Hex), to afford tricycle **3-67** (325 mg, approx. 50%) as an orange oil. The product contained minor impurities as evidenced by ^{1}H NMR.

R_f = 0.38 (EtOAc:Hex, 3:7), visualized with Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.05 (d, *J* = 7.6 Hz, 1H), 4.83 (d, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.43–4.40 (m, 1H), 4.26 (s, 1H), 3.71 (s, 3H), 3.00 (q, *J* = 7.2 Hz, 1H), 2.95 (d, *J* = 10.0 Hz, 1H), 2.23 (ddd, *J* = 9.6, 7.2, 2.0 Hz, 1H), 2.11–2.03 (m, 2H), 2.00 (dd, *J* = 9.9, 2.1 Hz, 1H), 1.88–1.77 (m, 1H), 1.52–1.46 (m, 1H), 1.45 (s, 3H), 1.30 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) 13C NMR (126 MHz, CDCl3) δ 217.8, 174.0, 137.5, 128.7, 128.0, 127.9, 92.5, 89.2, 74.2, 70.2, 65.1, 57.5, 57.0, 55.7, 51.9, 40.7, 35.9, 25.4, 21.8, 10.2.

HRMS (ESI, MeOH) calculated for $C_{22}H_{28}O_6Na$ $(M+Na)^+$ 411.1778, found 411.1785.



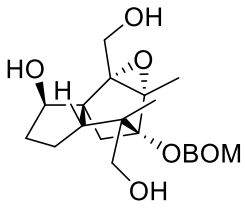
Alkene 3-68. A mixture of Zn, $TiCl_4$, and CH_2Br_2 in THF at –5 °C was prepared as described in the literature.[96] Ketone **3-67** (45 mg, 0.12 mmol) as a solution in CH_2Cl_2 was added, and the mixture was warmed to ambient temperature and stirred for 45 min. H_2O (5 mL) was added slowly, followed by Et_2O (5 mL). The mixture was filtered, and the filtrate was transferred to a separatory funnel and the organic layer was collected, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica (60 % EtOAc in hexanes) to yield **3-68** as a yellow oil (9.4 mg, 21%).

R_f = 0.47 (30% EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4H), 7.30–7.27 (m, 1H), 5.38 (d, *J* = 3.3 Hz, 1H), 4.99 (d, *J* = 7.4 Hz, 1H), 4.80 (d, *J* = 7.4 Hz, 1H), 4.74 (d, *J* = 2.7 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 6.5 Hz, 1H), 4.40–4.35 (m, 1H), 3.66 (s, 3H), 3.04–2.98 (m, 1H), 2.57 (d, *J* = 9.2 Hz, 1H), 2.27–2.19 (m, 1H), 2.07 (ddd, *J* = 9.8, 7.8, 2.2 Hz, 1H), 1.97–1.89 (m, 1H), 1.80 (dd, *J* = 9.2, 2.3 Hz, 1H), 1.73–1.66 (m, 1H), 1.53 (s, 1H), 1.44 (s, 3H), 1.43–1.36 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 174.7, 155.6, 138.1, 128.6, 128.0, 127.8, 102.8, 92.5, 90.1, 76.1, 69.8, 60.3, 59.1, 58.4, 51.5, 49.7, 43.6, 37.3, 25.3, 22.2, 13.8.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{30}O_5Na$ 409.1986; Found 409.1987.



Epoxide 3-70. Alkene **3-68** (5.6 mg, 0.015 mmol) was dissolved in THF (0.4 mL). $LiAlH_4$ (6 mg, 0.015 mmol) was added, and the mixture was stirred for 1 h. before being quenched by the addition of saturated Rochelle's salt (1 mL) (aq) and stirred for an addition 30 min. The solution was transferred to a separatory funnel and extracted with Et_2O (3 x 2 mL), and the organic extracts were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude alcohol was taken forward to the next step without further purification.

The crude alcohol was dissolved in CH_2Cl_2 (0.2 mL) under argon. SeO_2 (5 mg, 0.045 mmol) was added, and the reaction was stirred for 2 h. H_2O (1 mL) was added, and the mixture was transferred to a separatory and washed with CH_2Cl_2 (3 x 1 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude allylic alcohol **3-69** was taken forward to the next step without further purification.

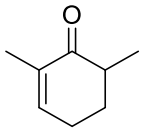
The crude allylic alcohol was dissolved in CH_2Cl_2 (0.2 mL). *m*-CPBA (ca. 70 % with H_2O) (7 mg, ca. 0.028 mmol) was added. After 120 min, saturated $NaHCO_3$ (0.5 mL) and saturated $Na_2S_2O_3$ (0.5 mL) were added, and the mixture was stirred for 1 h. Next, the mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with $CHCl_3$ (2 x 1 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography on silica (67 % EtOAc in hexanes), to afford epoxide **3-70** (mass not determined).

$\mathbf{R_f}$ = 0.25 (67% EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.89 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 11.9 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.22 (d, *J* = 4.7 Hz, 1H), 4.21 (d, *J* = 3.9 Hz, 1H), 3.94 (d, *J* = 11.5 Hz, 1H), 3.60 (d, *J* = 12.5 Hz, 1H), 3.43–3.38 (m, 1H), 2.91–2.82 (m, 1H), 2.17–2.13 (m, 1H), 2.07–2.01 (m, 1H), 1.92 (dd, *J* = 9.6, 2.7 Hz, 1H), 1.89–1.74 (m, 2H), 1.46 (s, 3H), 1.18 (s, 3H).[113]

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 128.7, 128.0, 127.8, 93.2, 92.2, 72.8, 70.5, 69.8, 63.1, 59.8, 59.0, 53.7, 47.3, 35.9, 33.2, 23.5, 22.8, 20.5, 13.1.[114]

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{30}O_6Na$ 413.1935; Found 413.1935.



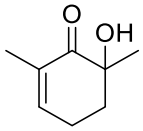
2,6-Dimethylcyclohex-2-en-1-one (3-72). This compound was prepared following a literature procedure modified for safety and reproducibility.[115] A 3-neck, 1-L round bottom flask was equipped with two reflux condensers and a large magnetic stir bar to allow efficient stirring. An argon line was placed in one of the condensers, and an outlet attached to a bubbler was placed in the other. Argon was passed through the reaction flask throughout the course of the reaction. The flask was charged with 2,6-dimethylcyclohexanone **3-71** (cis:trans mixture) (30.0 mL, 0.219 mol), N-bromosuccinimide (43.1 g, 0.242 mol), AIBN (150 mg, 0.913 mmol), and DCE (180 mL). The flask was heated with a heat gun until the reaction initiated (vigorous exotherm and generation of gas), at which time the heat was removed. After ca. 5-10 min, the bromination was complete, and the reaction mixture had cooled down below the boiling point of DCE. The solution was then heated to reflux in an oil bath overnight (ca. 15 h). The following morning, the mixture was

allowed to cool to RT, transferred to a separatory funnel, and washed successively with saturated $Na_2S_2O_3$ (aq) (200 mL), 2M NaOH (aq) (3 x 200 mL) and then brine (200 mL). Each aqueous phase was extracted one additional time with $CHCl_3$ (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The resulting oil was then purified by short path distillation to yield 19.57 g of a clear oil containing product **3-72** along with 5 mol% of 2,6-dimethylcyclohexanone **3-71** and 1.5 mol% DCE. (corrected yield: 18.42 g, 68%). Spectral data was consistent with literature report. The mixture was taken on to the next step without additional purification.

$\mathbf{R_f}$ = 0.29 (5% EtOAc in hexanes) visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68–6.60 (m, 1H), 2.37–2.27 (m, 3H), 1.99 (dddd, *J* = 9.0, 5.8, 4.8, 1.1 Hz, 1H), 1.73–1.70 (m, 3H), 1.70–1.63 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 202.6, 144.6, 135.1, 41.7, 31.3, 25.4, 16.2, 15.3.



6-Hydroxy-2,6-dimethylcyclohex-2-en-1-one (3-74). This compound was prepared using a modified literature procedure.[115b] A 1-L round bottom flask was charged with solid KHMDS (34.33 g, 172.1 mmol). THF (500 mL) was added and the flask was cooled to –78 °C. A solution of 2,6-dimethylcyclohex-2-en-1-one (**3-72**) (20.33 g, 163.7 mmol) in THF (200 mL) was cooled to –78 °C, and then added to the base via canula over a period of 10 min. The reaction mixture was then stirred for an additional 45 min.

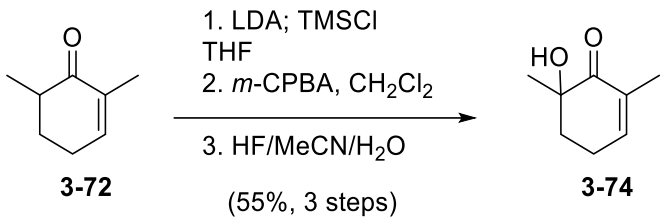
In a separate 2-L round bottom flask, (±)-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine **3-73** (44.9 g, 171.9 mmol) in THF (300 mL) was cooled to –78°C. The potassium enolate was added via canula over a period of 10 min, and the solution was then stirred for an additional 45 min. Saturated

NH_4Cl (800 mL) was added, and the reaction mixture was allowed to warm to RT, and transferred to a separatory funnel. The organic layer was collected, and the aqueous layer was washed with Et_2O (2 x 300 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. 1:1 Et_2O:pentanes (125 mL) was added to the crude reaction mixture, and the slurry was then placed in a –25 °C freezer for at least one hour. The resulting solids were filtered off, and washed with cold 1:1 Et_2O:pentanes (3 x 75 mL). The filtrate was concentrated *in vacuo*, and the orange liquid was then purified by short-path distillation, yielding a mixture of product and benzaldehyde. The mixture was then purified by flash column chromatography on silica (25% EtOAc in hexanes, until the benzaldehyde eluted, then 60% EtOAc in hexanes), to afford **S4** (8.73 g, 38%) as a pale yellow oil. Spectral data was consistent with literature.

R_f = 0.30 (20% EtOAc in hexanes), visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69–6.63 (m, 1H), 3.73 (s, 1H), 2.42–2.36 (m, 2H), 2.11–1.98 (m, 2H), 1.80 (s, 3H), 1.28 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 203.4, 145.7, 132.8, 73.2, 35.9, 24.5, 24.3, 15.9.



3-72 **3-74**

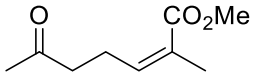
An alternative 3-step procedure was developed to access 3-74: Diisopropylamine (26.7 mL, 156 mmol) in THF (250 mL) was cooled to –78 °C. *n*-BuLi (2.30 M in hexanes) (75.2 mL, 173 mmol) was added over 5 min. The solution was warmed to 0 °C for 5 min then back to –78 °C. Enone **3-72** (18.42 g, 148.3 mmol) containing an additional 5 mol% of 2,6-dimethylcyclohexanone (**3-71**) and 1.5 mol% DCE was added dropwise over a period of 5 min. The solution was stirred

for an additional 15 min. TMSCl (24.0 mL, 189 mmol) was added, and the reaction mixture was allowed to warm to RT over 45 min. The solvent was removed via a rotary evaporator. Pentanes (300 mL) were added, and the solids were filtered off and washed with additional pentanes (100 mL). The filtrate was transferred to a separatory funnel, and washed with acetonitrile (500 mL). The acetonitrile layer was washed with pentanes (5 x 100 mL). The combined pentane washes were concentrated *in vacuo*, and the crude silyl enol ether was used without further purification.

The crude silyl enol ether was dissolved in CH_2Cl_2 (800 mL; used directly from the bottle without attempt to further dry the solvent). This solution was placed in a 3-L RB flask equipped with overhead stirrer, and was open to the atmosphere.[116] Solid $NaHCO_3$ (38 g, 0.45 mol) was added. *m*-CPBA (ca. 70% with H_2O) (38.5 g, ca. 156 mmol) was added portionwise to the stirred solution of silyl enol ether over a period of 30 min. After the starting material had been consumed (as verified by TLC analysis), saturated $Na_2S_2O_3$ (800 mL) was added and the solution was stirred for 30 min until all solids dissolved. The mixture was transferred to a separatory funnel, and the organic layer was collected. The aqueous layer was washed with $CHCl_3$ (2 x 200 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude silyl alcohol was used without further purification.

HF:MeCN:H_2O (1:8:1 by volume) (150 mL) was added to crude silyl alcohol under an atmosphere of air. After 20 min, all of the starting material had been consumed as judged by TLC analysis. Saturated $NaHCO_3$ (aq) (100 mL) was added slowly to the reaction mixture. Solid $NaHCO_3$ was added in approximately 1 gram portions to the vigorously stirred reaction mixture until bubbling had ceased. The mixture was then stirred for an additional 5 min, then transferred to a separatory funnel. H_2O (200 mL) was added followed by Et_2O (300 mL). The organic layer was collected, and the aqueous layer was washed with additional Et_2O (2 x 100 mL). The combined organic

extracts were washed with brine (200 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified via flash column chromatography on silica (10 – 30% EtOAc in hexanes gradient) to afford alcohol **3-74** (11.46 g, 55%) as a yellow oil. The product was modestly volatile.



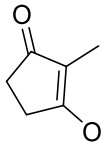
Methyl (Z)-2-methyl-6-oxohept-2-enoate (3-75). Ketone **7** was synthesized using a modified literature procedure.[115b] $Pb(OAc)_4$ (42.2 g, 95.3 mmol) was dissolved in benzene (540 mL) and MeOH (200 mL). Alcohol **3-74** (11.11 g, 79.4 mmol) as a solution in benzene (100 mL) was added to the solution, and the mixture was heated to 40 ℃ for 3 h. After the starting material was consumed as verified by TLC, the stir bar was removed, and most of the solvent was removed under reduced pressure. Once solid began to crash out, silica gel (75 g) was added, and the remaining solvent was removed on the rotary evaporator. Complete removal of the solvent was necessary, and could be achieved either through prolonged evaporation times (30 min), or an additional azeotrope of the solvent/silica mixture with CH_2Cl_2 (150 mL).

A slurry of silica gel (200 g) and 40% EtOAc in hexanes mixture was added to a column. The product and lead impregnated silica was loaded on top of the plug, and 40% EtOAc in hexanes mixture (1.5 L) was passed through the plug. The solvent was transferred to a separatory funnel, and washed with saturated $NaHCO_3$ (aq) (500mL). The organic layer was dried over Na_2SO_4, and concentrated *in vacuo* to yield alcohol **3-75** as a pale yellow oil (12.76 g, 95%). Spectral data was consistent with the literature.

$\mathbf{R_f}$ = 0.46 (25% EtOAc in hexanes), visualized by UV or $KMnO_4$

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (tq, *J* = 7.6, 1.5 Hz, 1H), 3.73 (s, 3H), 2.68 (app. q, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.14 (s, *J* = 7.6 Hz, 3H), 1.87 (q, *J* = 1.3 Hz, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 208.1, 168.3, 141.3, 128.1, 51.4, 43.2, 29.9, 24.0, 20.7.



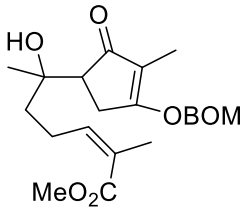
3-((Benzyloxy)methoxy)-2-methylcyclopent-2-en-1-one (S3-3). 2-Methylcyclopenta-1,3-dione (**3-76**) (12.60 g, 69.7 mmol), K_2CO_3 (29 g, 0.20 mol), and BOMCl (approximately 78% by NMR analysis) (15.0 mL, ca. 83.7 mmol) were combined in a round-bottom flask. DMF (157 mL) was added and the reaction mixture was stirred at ambient temperature for 24 h. EtOAc (150 mL) was added, and the reaction mixture was transferred to a separatory funnel and washed with H_2O (2 x 150 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was diluted with CH_2Cl_2 (150 mL) and washed with H_2O (4 x 150 mL) to remove most of the remaining DMF. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was purified by flash column chromatography (55% EtOAc in hexanes) on silica to afford **S3-3** (12.60 g, 78%) as an orange oil which would reversibly solidify in a –20 °C freezer.

$\mathbf{R_f}$ = 0.27 (60% EtOAc in hexanes), visualized by UV

^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 5.30 (s, 2H), 4.70 (s, 2H), 2.77–2.65 (m, 2H), 2.46–2.36 (m, 2H), 1.63 (s, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 205.7, 182.1, 136.6, 128.6, 128.2, 128.0, 118.1, 91.7, 71.1, 33.6, 24.8, 6.0.

HRMS (ESI/TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}O_3$ 233.1173; Found 233.1176.



Aldol adduct 3-77. Diisopropylamine (5.12 mL, 36.3 mmol) was dissolved in THF (56 mL) and cooled to –78 °C. *n*-BuLi (2.17 M in hexanes) (14.0 mL, 30.4 mmol) was added. The solution was warmed to 0 °C for 5 min, then cooled back to –78 °C. Cyclopentenone **S3-3** (7.04 g, 30.3 mmol) as a solution in THF (56 mL) was added over a period of 5 min. After 1 h, the reaction mixture was warmed to –40 °C for 15 min then cooled back to –78 °C. Ketone **7** (5.41 g, 31.8 mmol) as a solution in THF (10 mL) was added rapidly. After 30 min, saturated NH_4Cl (aq) (100 mL) was added, and the mixture was allowed to warm to RT. The mixture was transferred to a separatory funnel, and the organic layer was collected. The aqueous layer was washed with Et_2O (2 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and passed through a small plug of silica. The silica was washed with EtOAc (150 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica (25 – 70% EtOAc in hexanes gradient), to afford **3-77** (8.06 g, 65%) as a 1.7:1 mixture of diastereomers. The mixture contained some minor impurities which were taken forward to the next step. Each diastereomer could be isolated by further silica chromatography.

Major diastereomer:

$\mathbf{R_f}$ = 0.36 (33% EtOAc in hexanes), visualized by UV

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 5.98 (t, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 6.9 Hz, 1H), 5.31 (d, *J* = 7.0 Hz, 1H), 4.80 (s, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 3.69 (s, 3H), 2.88 (dd, *J* = 17.7, 7.1 Hz, 1H), 2.69 (dd, *J* = 7.0, 2.5 Hz,

1H), 2.66–2.51 (m, 2H), 2.35 (d, J = 17.8 Hz, 1H), 1.88 (s, 3H), 1.62 (s, 3H), 1.60–1.45 (m, 2H), 1.00 (s, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 209.2, 182.8, 168.5, 143.4, 136.5, 128.8, 128.5, 128.2, 127.1, 118.6, 92.2, 73.7, 71.5, 51.5, 51.3, 40.4, 28.7, 23.8, 22.7, 20.8, 5.9.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{30}O_6Na$ 425.1935; Found 425.1929.

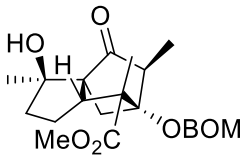
Minor diastereomer:

R_f = 0.18 (33% EtOAc in hexanes), visualized by UV

^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.94 (t, J = 7.3 Hz, 1H), 5.34 (s, 2H), 4.74 (d, J = 11.8 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.37 (s, 1H), 3.71 (s, 3H), 2.86 (ddd, J = 17.7, 7.1, 1.4 Hz, 1H), 2.67 (dd, J = 7.1, 2.7 Hz, 1H), 2.63–2.45 (m, 2H), 2.49 (d, J = 18.2 Hz, 1H), 1.87 (s, 3H), 1.62 (s, 3H), 1.44–1.39 (m, 2H), 1.16 (s, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) 208.2, 182.6, 168.6, 143.5, 136.6, 128.8, 128.5, 128.2, 127.1, 118.8, 92.2, 73.9, 71.5, 54.3, 51.4, 36.1, 28.6, 25.2, 23.9, 20.8, 5.9.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{30}O_6Na$ 425.1935: Found 425.1916.



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Diels–Alder adduct 3-79. Aldol **3-77** (diastereomeric mixture; 8.06 g, 20.0 mmol) was placed in a 500 mL round bottom flask equipped with a magnetic stir bar, and fitted with a rubber septum. The flask was evacuated, and then back-filled with argon. CH_2Cl_2 (180 mL) was added, and the solution was cooled to 0 °C. DBU (17.0 mL, 120 mmol) then Me_2SiCl_2 (5.0 mL, 40 mmol) were added to the flask. The rubber septum was then quickly exchanged for a greased glass stopper, and the neck of the flask was wrapped in Teflon tape, then parafilm. A

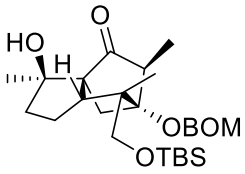
Keck clamp was added to secure the stopper. After 30 min at 0 °C, the solution was heated to 40 °C overnight (ca. 15 h). The following morning, the reaction flask was allowed to cool to room temperature. The stopper was exchanged for a rubber septum. Pyridine (9.4 mL, 0.12 mol) then 70% HF in pyridine (2.32 mL, 89 mmol)[117] were added, and the reaction mixture was stirred for 1 h. Saturated $NaHCO_3$ (aq) (50 mL) was added slowly to the solution. Solid $NaHCO_3$ was added in portions to the vigorously stirred reaction mixture until bubbling had ceased. The reaction mixture was then stirred for an additional 5 min, then transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with $CHCl_3$ (2 x 50 mL). The combined organic layers were washed with saturated $CuSO_4$ (aq) (150 mL), which was back extracted with $CHCl_3$ (50 mL). The combined organic extracts were dried over $MgSO_4$, and passed through a small plug of silica. The silica was washed with Et_2O (150 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica (10 – 30% EtOAc in hexanes gradient), to afford **3-79** (4.65 g, 58%) as an orange oil.

$\mathbf{R_f}$ = 0.30 (20% EtOAc in hexanes), visualized by Hanessian's stain.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.06 (d, *J* = 7.7Hz, 1H), 4.84 (d, *J* = 7.7 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.27 (s, 1H), 3.71 (s, 3H), 3.04 (d, *J* = 10.0 Hz, 1H), 2.96 (q, *J* = 7.1 Hz, 1H), 2.34 (ddd, *J* = 10.8, 6.0, 2.1 Hz, 1H), 2.15–2.03 (m, 1H), 1.95 (dd, *J* = 9.9, 2.2 Hz, 1H), 1.87–1.79 (m, 2H), 1.53–1.43 (m, 1H), 1.43 (s, 3H), 1.30 (d, *J* = 7.1Hz, 3H), 1.30 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) 217.8, 174.1, 137.5, 128.7, 128.07, 128.05, 92.4, 89.0, 79.7, 70.2, 68.2, 58.2, 57.1, 56.1, 51.9, 40.5, 40.3, 25.1, 24.5, 21.8, 10.2.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{30}O_6Na$ 425.1935: Found 425.1942.



Silyl ether 3-80. A suspension of $LiAlH_4$ (3.44 g, 85.9 mmol) in diethyl ether (100 mL) was cooled to 0 °C. A solution of ketone **3-79** (8.64 g, 21.5 mmol) in diethyl ether (100 mL) was added via canula over the course of 10 min. After 1 h, saturated Rochelle's salt (aq) (20 mL) was added very slowly until the bubbling had ceased. Then an additional 280 mL of the Rochelle's salt solution was added, and the mixture was stirred vigorously for 2 h. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with diethyl ether (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude triol which was used without further purification.

The crude triol, imidazole (14.6 g, 0.251 mol), DMAP (2.63 g, 21.5 mmol), TBSCl (13.0 g, 86.2 mmol), and DMF (120 mL) were combined in a round bottom flask and stirred at RT for 4 h. No attempt was made to exclude moisture or air from the reaction. The reaction mixture was transferred to a separatory funnel and diluted with saturated NH_4Cl (aq) (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O (2 x 500 mL), and the aqueous washes were back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the mono-protected triol which was used without further purification.

To the crude product was added $NaHCO_3$ (16 g, 0.19 mol) and CH_2Cl_2 (200 mL). No attempt was made to exclude moisture or air from the mixture. Dess-Martin periodinane (13.7 g, 32.3 mmol) was added, and the reaction mixture was stirred at RT overnight (ca. 15 h). The following morning, saturated $Na_2S_2O_3$ (aq) (300 mL) was added and the mixture was stirred for 2 h, before being transferred to a separatory funnel. The organic layer was collected. The aqueous layer was washed

with $CHCl_3$ (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and passed through a small plug of silica. The silica was washed with ethyl acetate (300 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica (0 – 20 % EA in hexanes gradient), to afford **3-80** (6.81 g, 65% over 3 steps) as a colorless oil which solidified to a white crystalline solid upon storage in the freezer.

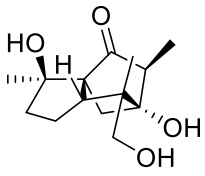
$\mathbf{R_f}$ = 0.70 (25% EtOAc in hexanes), visualized by Hanessian's stain.

^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 4.96 (d, *J* = 7.5 Hz, 1H), 4.86 (d, *J* = 7.5 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 1H), 3.71 (d, *J* = 10.2 Hz, 1H), 3.57 (d, *J* = 10.3 Hz, 1H), 2.88 (q, *J* = 7.1 Hz, 1H), 2.51 (d, *J* = 9.5 Hz, 1H), 2.20 (ddd, *J* = 9.9, 7.5, 2.2 Hz, 1H), 2.10–1.96 (m, 2H), 1.86 (ddd, *J* = 12.7, 8.6, 3.8 Hz, 1H), 1.80 (dd, *J* = 9.3, 2.0 Hz, 1H), 1.78–1.72 (m, 1H), 1.29 (s, 3H), 1.27 (d, *J* = 7.1 Hz, 3H), 1.03 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) 219.1, 137.5, 128.7, 128.1, 127.9, 92.1, 87.8, 79.9, 70.2, 68.2, 66.9, 56.5, 55.2, 49.3, 40.7, 39.8, 26.0, 24.8, 23.7, 22.4, 18.2, 10.3, –5.5, –5.6.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{44}O_5SiNa$ 511.2851; Found 511.2834.

Melting Point: 85 – 88 °C



Triol 3-81. Protected triol **3-80** (30.3 mg, 0.0620 mmol) was dissolved in MeOH (0.5 mL). The solution was cooled to 0 °C. Acetyl chloride (0.1 mL) was added dropwise, and the reaction mixture was stirred for 30 min. Saturated $NaHCO_3$ (aq) (1 mL) was added slowly. The reaction mixture was transferred to a separatory funnel, and washed with Et_2O (3 x 1 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude

residue was purified by flash column chromatography on silica (0 – 100% EtOAc in hexanes gradient), to afford triol **3-81** (11.4 mg, 72%) as a white solid.

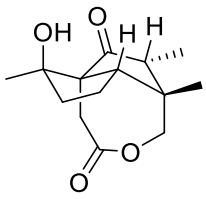
$\mathbf{R}_f$ = 0.56 (100% EA), visualized by Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.42 (d, *J* = 1.8 Hz, 1H), 4.12 (dd, *J* = 10.5, 3.8 Hz, 1H), 3.59 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.71 (t, *J* = 4.5 Hz, 1H), 2.64 (q, *J* = 7.2 Hz, 1H), 2.31 (ddd, *J* = 10.3, 6.3, 1.7 Hz, 1H), 2.22 (d, *J* = 10.1 Hz, 1H), 1.97 – 1.81 (m, 2H), 1.79–1.69 (m, 1H), 1.64–1.58 (m, 1H), 1.58 (dd, *J* = 10.1, 1.8 Hz, 1H), 1.29 (s, 3H), 1.28 – 1.23 (m, 6H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) 218.7, 85.5, 79.4, 71.4, 68.0, 58.1, 55.7, 44.6, 44.2, 40.9, 24.6, 22.8, 20.9, 10.1.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{22}O_4Na$ 277.1411; Found 277.1414.

Melting Point: 138–140 °C



Lactone 3-83. Triol **3-81** (11.4 mg, 0.0449 mmol) was dissolved in Et_2O (50 µL) and THF (150 µL) and cooled to 0 °C. No attempt was made to exclude air or moisture. A solution of bromine (100 µL, 1.88 mmol), acetic acid (200 µL, 3.49 mmol), THF (2 mL), and Et_2O (2 mL) was made. 100 µL of this solution (ca. 4.35 µL, 0.0783 mmol Br_2) was added to the chilled solution of triol **3-81**, and the reaction mixture was stirred for 20 min. Saturated $NaHCO_3$ (aq) (0.5 mL) and saturated $Na_2S_2O_3$ (0.5 mL) was added. The mixture was transferred to a separatory funnel, and extracted with EtOAc (3 x 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude bromide, which was used without further purification.

A suspension of $AgClO_4$ (22 mg, 0.106 mmol) in THF (0.4 mL) was made under an atmosphere

of argon. A solution of the crude bromide in THF (0.1 mL) was added. After 20 min saturated $NaHCO_3$ (1 mL) and EA (1 mL) were added. The crude mixture was filtered through a cotton plug. The filtrate was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was extracted with additional EA (2 x 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica (60 % EtOAc in hexanes) to yield **3-83** as a white solid (6.1 mg, 54% over 2 steps)

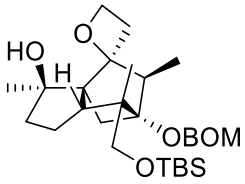
R_f = 0.43 (80% EtOAc in hexanes), visualized by Hanessian's stain

Melting Point: 170–175 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (d, *J* = 13.4 Hz, 1H), 3.98 (dd, *J* = 13.4, 1.3 Hz, 1H), 3.10 (dd, *J* = 12.9, 6.9 Hz, 1H), 2.76 (dd, *J* = 15.0, 0.9 Hz, 1H), 2.63 (d, *J* = 14.9 Hz, 1H), 2.44 (q, *J* = 7.3 Hz, 1H), 2.21 (ddd, *J* = 15.3, 9.1, 6.5 Hz, 1H), 2.08–2.02 (m, 1H), 1.79–1.73 (m, 1H), 1.74 (s, 1H), 1.66 (app. tdd, *J* = 12.5, 10.9, 6.4 Hz, 1H), 1.49 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) 213.6, 171.0, 77.0, 69.0, 64.2, 62.1, 54.7, 42.6, 40.6, 35.1, 24.7, 23.1, 16.4, 8.8.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{20}O_4Na$ 275.1254; Found 275.1258.



Oxetane 3-89. To a solution of Me_3SOI (32.3 mg, 0.147 mmol) in dry DMSO (0.2 mL) was added 60% NaH (5.9 mg, 0.147 mmol). After 30 minutes, ketone **3-80** (24 mg, 0.049) as a solution in THF (0.1 mL) was added. The reaction was stirred overnight. Crude TLC analysis indicated significant starting material along with a major, more polar spot. The reaction was quenched by the addition of saturated NH_4Cl (aq) (2 mL), and the mixture was transferred to

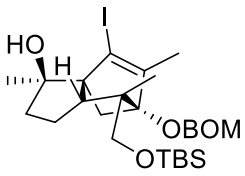
a separatory funnel and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography on silica (0 – 100% EtOAc in hexanes gradient) to yield **3-89** as a yellow oil (7.5 mg, 30% over 2 steps).

R_f = 0.30 (20% EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 4.79 (d, *J* = 7.4 Hz, 1H), 4.77 (d, *J* = 7.4 Hz, 1H), 4.64 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 3.93–3.79 (m, 2H), 3.65 (d, *J* = 9.7 Hz, 1H), 3.54 (d, *J* = 9.7 Hz, 1H), 2.34 (ddd, *J* = 12.4, 5.6, 1.5 Hz, 1H), 2.15 (q, *J* = 7.6 Hz, 1H), 2.04–1.86 (m, 4H), 1.70–1.64 (m, 2H), 1.43–1.31 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 1.15 (d, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.0, 128.6, 128.0, 127.9, 91.1, 89.6, 79.2, 72.3, 69.8, 67.9, 59.1, 58.7, 50.3, 49.3, 48.9, 46.0, 38.2, 33.0, 26.1, 25.8, 22.2, 20.8, 18.3, 9.1, -5.4, -5.5.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{20}O_4Na$ 275.1254; Found 275.1258.



Vinyl Iodide 3-92. Ketone **3-80** (6.35 g, 13.0 mmol), $(NH_2)_2 \cdot H_2O$ (19.7 mL, 0.402 mol), AcOH (4.4 mL, 110 mmol), and EtOH (29 mL) were combined in a 100 mL, 1-neck round bottom flask equipped with condenser. No attempt was made to exclude air or moisture. The mixture was heated to reflux for 4 h, then allowed to cool to RT. The crude mixture was transferred to a separatory funnel along with H_2O (300 mL) and Et_2O (75 mL). The organic layer was collected. The aqueous layer was washed with additional Et_2O (2 x 75 mL). The combined organic layers washed with brine (50 mL), dried over $MgSO_4$, and passed through a small plug of silica. The silica was washed with ethyl acetate (300 mL). The filtrate was concentrated *in vacuo*

and the hydrazone was used without further purification.

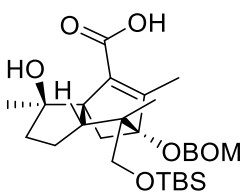
The crude hydrazone was azeotroped twice with dry benzene to get rid of any residual water, and then left under high vacuum for at least 30 min. Next, the flask of crude hydrazone was placed under argon, and THF (150 mL) and DBU (18.9 mL, 0.127 mol) were added. A solution of I_2 (12.8 g, 50.4 mmol) in THF (90 ml) was prepared in a separate flask. This solution was added to the reaction dropwise until the yellow color of iodine persisted for longer than 30 sec.[118] The reaction was then stirred for an additional 10 min. Saturated $Na_2S_2O_3$ (aq) (150 mL) was added, the mixture was transferred to a separatory funnel and the mixture was washed with Et_2O (3 x 75 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and passed through a small plug of silica. The silica was washed with additional Et_2O (200 mL). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica (0 – 15% EtOAc in hexanes gradient), to afford **3-92** (5.62 g, 72% over 2 steps) as a colorless oil.

$\mathbf{R_f}$ = 0.46 (10% EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.27 (m, 5H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.71 (d, *J* = 7.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.73 (d, *J* = 10.4 Hz, 1H), 2.49 (s, 1H), 2.04–1.95 (m, 2H), 1.93–1.77 (m, 4H), 1.75 (s, 3H), 1.73–1.65 (m, 1H), 1.34 (s, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.064 (s, 3H), 0.056 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.0, 137.8, 128.6, 127.93, 127.89, 95.5, 93.3, 92.2, 78.8, 69.9, 66.8, 64.7, 52.6, 51.7, 49.9, 40.9, 26.0, 23.8, 22.5, 22.2, 18.3, 17.2, -5.4, -5.5.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{43}IO_4SiNa$ 621.1868; Found 621.1888.



Carboxylic acid 3-97. Vinyl iodide **3-92** (188 mg, 0.334 mmol) was

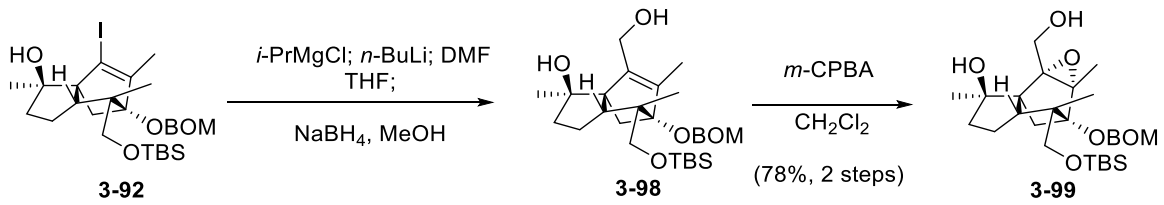
azeotroped twice with dry benzene, and then left under high vacuum for at least 30 min. Next, THF (3 mL) was added and the flask was cooled to 0 °C. *i*-PrMgCl (2 M in diethyl ether) (0.31 mL, 0.67 mmol) was added. After 10 min the flask was cooled to –78 °C, and *n*-BuLi (2.17 M in hexanes) (0.29 mL, 0.67 mmol) was added. After 20 min, a balloon containing CO_2 and affixed with a long needle was placed in the reaction flask, and CO_2 was bubbled through as the reaction warmed to ambient temperature over 30 minutes. Saturated NH_4Cl (aq) (5 mL) was added and the reaction mixture was transferred to a separatory funnel. The mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude acid was purified by flash column chromatography on silica (0 – 10 % MeOH in CH_2Cl_2 gradient) to afford **3-97** (118 mg, 68%) as a white foamy solid.

R_f = 0.42 (10% MeOH in CH_2Cl_2), visualized by Hanessian's stain

^{1}H NMR (600 MHz, MeOD) δ 7.36–7.26 (m, 5H), 4.83 (d, *J* = 7.0 Hz, 1H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.69 (d, *J* = 12.8 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 3.82 (d, *J* = 10.2 Hz, 1H), 3.80 (d, *J* = 10.4 Hz, 1H), 2.14 (s, 3H), 2.06–1.88 (m, 4H), 1.82–1.71 (m, 3H), 1.29 (s, 3H), 0.91 (s, 9H), 0.88 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, MeOD) δ 170.0, 168.1, 139.1, 133.4, 129.4, 128.8, 128.7, 95.0, 93.5, 78.7, 70.8, 68.3, 65.4, 54.6, 52.64 50.3, 40.8, 26.4, 23.6, 23.5, 22.6, 19.1, 15.7, -5.3, -5.4.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{44}O_6SiNa$ 539.2800; found 539.2826.



Vinyl iodide **3-92** (5.62 g, 9.38 mmol) was azeotroped twice with dry benzene, and then left under high vacuum for at least 30 min. Next, THF (30 mL) was added and the flask was cooled to 0 °C.

i-PrMgCl (2 M in diethyl ether) (9.20 mL, 18.4 mmol) was added. After 10 min the flask was cooled to –78 °C, and *n*-BuLi (2.25 M in hexanes) (12.5 mL, 28.1 mmol) was added. After 20 min, DMF (4.35 mL, 56.3 mmol) was added, and the flask was allowed to warm to RT over 60 min. MeOH (136 mL), then $NaBH_4$ (2.85 g, 75.1 mmol) were added. After 10 min saturated NH_4Cl (aq) was added dropwise until bubbling had ceased. Additional saturated NH_4Cl (aq) (200 mL) was added and the reaction mixture was transferred to a separatory funnel. The mixture was extracted with CH_2Cl_2 (3 x 80 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude allylic alcohol which was used without further purification. The crude allylic alcohol could be purified on by flash column chromatography on silica (0 – 100 % EtOAc in hexanes gradient).

CH_2Cl_2 (48 mL) was added to the crude allylic alcohol. No attempt was made to exclude air or moisture. *m*-CPBA (ca. 70 % with H_2O) (4.55 g, ca. 18.4 mmol) was added in two portions. After 30 min, saturated $NaHCO_3$ (75 mL) and saturated $Na_2S_2O_3$ (75 mL) were added, and the mixture was stirred for 1 h. Next, the mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with $CHCl_3$ (2 x 75 mL). The combined organic layers were dried over $MgSO_4$ and passed through a small plug of silica. The silica was washed with EtOAc (200 mL), concentrated *in vacuo* and purified by flash column chromatography on silica (0 – 100 % EtOAc in hexanes gradient), to afford **3-99** (4.05 g, 83% over 2 steps) as a foamy white solid.

Epoxy Alcohol 3-99

$\mathbf{R_f}$ = 0.42 (40% EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.32–7.33 (m, 1H), 4.82 (d, *J* = 6.7 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 12.5 Hz,

1H), 3.68 (d, *J* = 10.2 Hz, 1H), 3.62 (d, *J* = 10.2 Hz, 1H), 3.56 (d, *J* = 12.5 Hz, 1H), 2.13 (ddd, *J* = 10.6, 5.4, 2.6 Hz, 1H), 2.02–1.93 (m, 1H), 1.91–1.84 (m, 3H), 1.80–1.74 (m, 1H), 1.44 (s, 3H), 1.37 (d, *J* = 9.5 Hz, 1H), 1.35 (s, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) 137.8, 128.6, 127.9, 127.8, 91.7, 90.0, 78.7, 69.8, 66.4, 63.2, 63.1, 62.4, 59.1, 53.2, 50.2, 40.9, 32.5, 25.9, 24.4, 23.1, 22.7, 18.2, 13.2, –5.44 –5.55

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{46}O_6SiNa$ 541.2956; found 541.2935.

Melting Point: 100 – 102 °C

Allylic Alcohol 3-98

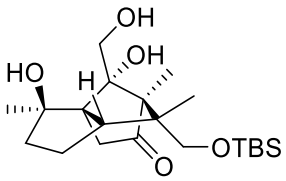
R_f = 0.28 (30% EtOAc in hexanes), visualized by Hanessian's stain

^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.81 (d, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 7.0 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.22 (d, *J* = 12.8 Hz, 1H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.73 (d, *J* = 10.0 Hz, 1H), 3.52 (br. s, 1H), 2.53 (br. s, 1H), 2.03–1.88 (m, 3H), 1.86–1.78 (m, 3H), 1.71 (s, 3H), 1.63 (dd, *J* = 7.9, 2.2 Hz, 1H), 1.36 (s, 3H), 0.90 (s, *J* = 2.7 Hz, 9H), 0.88 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 142.1, 140.3, 138.0, 128.6, 127.9, 127.9, 93.8, 92.1, 79.4, 69.7, 67.4, 64.3, 57.6, 54.5, 50.4, 50.3, 42.7, 26.0, 25.0, 23.1, 22.1, 18.3, 11.5, -5.37, -5.44.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{46}O_5SiNa$ 525.3007; found 525.3006.

Melting Point: 122 – 126 °C



Cyclopentanone triol 3-100. A solution of TFA (530 µL, 6.93 mmol) in $CHCl_3$ (41 mL) was added to epoxide **3-99** (4.05 g, 7.80 mmol). The solution was stirred for 40 h. No attempt was made to exclude moisture or air. Et_3N (1.71 mL, 12.3 mmol) was added, and

the solution was concentrated *in vacuo.* The crude residue was purified by flash column chromatography on silica (0 – 100% EtOAc in hexanes gradient), to afford **17** (1.77 g, 57%) as a white solid.

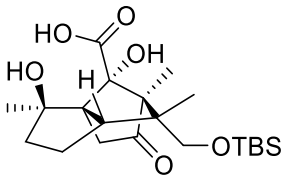
$\mathbf{R}_f$ = 0.21 (40 % EtOAc in hexanes), visualized by Hanessian's stain

^{1}H NMR (500 MHz, $CDCl_3$)[119] δ 4.38 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.29 (dd, *J* = 9.9, 3.2 Hz, 1H), 3.34 (app. t, *J* = 10.6 Hz, 1H), 3.28 (s, 1H), 3.21 (d, *J* = 10.1 Hz, 1H), 3.12 (d, *J* = 10.1 Hz, 1H), 2.91 (ddd, *J* = 11.9, 8.2, 1.5 Hz, 1H), 2.72 (s, 1H), 2.51 (dd, *J* = 17.5, 1.7 Hz, 1H), 2.13 (ddd, *J* = 14.6, 11.2, 3.2 Hz, 1H), 2.09 (d, *J* = 17.5 Hz, 1H), 1.96 (ddd, *J* = 14.9, 9.1, 5.8 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.51 (ddd, *J* = 24.4, 12.1, 5.8 Hz, 1H), 1.34 (s, 3H), 1.00 (s, 3H), 0.88 (s, 3H), 0.85 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 213.6, 84.1, 76.6, 69.8, 66.0, 63.2, 60.6, 51.6, 45.1, 39.5, 39.4, 25.9, 25.0, 23.5, 19.6, 18.2, 6.4, -5.6, -5.7.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{38}O_5SiNa$ 421.2381; found 421.2363.

Melting Point: 142 – 146 °C



Carboxylic acid S3-4. Alcohol **3-100** (0.64 g, 1.6 mmol) was dissolved in dry DMSO (11 mL). IBX (2.56 g, 9.15 mmol) was added and the reaction was stirred at RT overnight (ca. 15 h). The following morning, H_2O (30 mL) was added, generating a white precipitate. The mixture was filtered, and the precipitate was washed with CH_2Cl_2 (30 mL). The filtrate was transferred to a separatory funnel, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were washed with H_2O (50 mL) then saturated $NaHCO_3/Na_2S_2O_3$ (aq) (50 mL). Each aqueous layer was extracted

with additional CH_2Cl_2 (2 x 15 mL). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and carried on to the next step without additional purification.

To the crude aldehyde **3-101** was added acetone (7 mL), H_2O (9 mL), 2-methyl-2-butene (3.32 mL, 31.4 mmol), and 2 M NaH_2PO_4 (aq) (8.83 mL, 17.7 mmol). To the mixture was added solid $NaClO_2$ (80% technical grade) (2.19 g, 17.6 mmol). No attempt was made to exclude air from the reaction. The mixture was stirred vigorously for 45 min, then pH 2.5 buffer (30 mL) was added and the mixture was transferred to a separatory funnel.[120] The mixture was extracted with EtOAc (5 x 15 mL). The combined organic extracts were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography on silica (0 – 10% MeOH:formic acid (20:1) in CH_2Cl_2 gradient), to afford impure acid **S3-4** (580 mg) as a white foamy solid. The product was taken on to the next step without further purification.

The product could be purified by further chromatography, and characterization of the resulting white solid product is given below.

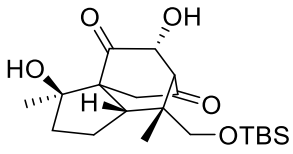
R_f = 0.27 (90% CH_2Cl_2 : 9% MeOH : 1% formic acid), visualized by Hanessian's stain

^{1}H NMR (500 MHz, CD_3OD) δ 3.28 (d, *J* = 10.2 Hz, 1H), 3.23 (d, *J* = 10.3 Hz, 1H), 3.13 (app. td, *J* = 10.0, 1.6 Hz, 1H), 2.55 (dd, *J* = 17.8, 1.5 Hz, 1H), 2.28 (d, *J* = 17.8 Hz, 1H), 2.15–2.00 (m, 2H), 1.76 (app. dtd, *J* = 12.8, 8.6, 4.4 Hz, 1H), 1.64 (app. qd, *J* = 12.0, 6.0 Hz, 1H), 1.37 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 0.89 (s, 9H), 0.014 (s, 3H), 0.010 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, CD_3OD) δ 214.6, 176.0, 86.4, 77.3, 74.3, 67.8, 63.9, 52.9, 45.2, 41.5, 41.0, 26.3, 24.2, 22.6, 19.8, 19.0, 8.2, -5.7[121].

HRMS (ESI/TOF) m/z: $[M-H]^-$ Calcd for $C_{21}H_{35}O_6Si$ 411.2208; found 411.2213.

Melting Point: 136 – 140 °C



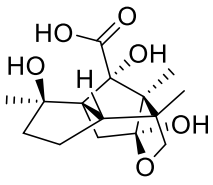
Tricycle 3-102: When crude aldehyde **3-101** was subjected to flash column chromatography on silica (0 – 100% ethyl acetate in hexanes gradient), the aldehyde was not recovered. Instead the major product is tricycle **3-102**, which was isolated along with some impurities. As the product was not on the path to Illisimonin A **3-1**, we did not attempt further purification.

$\mathbf{R}_f$ = 0.30 (50% ethyl acetate in hexanes), visualized by Hanessian's stain

^{1}H NMR see below

^{13}C{^{1}H} NMR see below

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{36}O_5SiNa$ 419.2225; found 419.2244.



Lactol 3-103: AcCl (1.20 mL, 16.8 mmol) was added slowly to MeOH (28.8 mL). When the solution had cooled to room temperature, it was added to impure acid **S3-4** (580 mg), and the solution was stirred at room temperature for 4.5 hours. No attempt was made to exclude air or moisture from this reaction. The solvent was removed *in vacuo*, and the crude residue was purified by flash column chromatography on silica (0 – 20% MeOH:formic acid (20:1) in CH_2Cl_2 gradient), to afford lactol **3-103** (196 mg, 41% over 3 steps) as a white foamy solid.

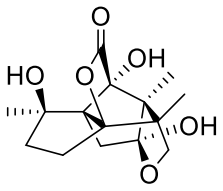
$\mathbf{R}_f$ = 0.42 (84% CH_2Cl_2 : 15% MeOH : 1% formic acid), visualized by Hanessian's stain

^{1}H NMR (500 MHz, CD_3OD) δ 3.65 (d, J = 8.6 Hz, 1H), 3.48 (d, J = 8.6 Hz, 1H), 3.08 (app. td, J = 9.3, 1.4 Hz, 1H), 2.41 (dd, J = 12.8, 1.6 Hz, 1H), 2.08 (ddd, J = 14.3, 11.1, 3.4 Hz, 1H), 2.00 (ddd, J = 14.8, 11.1, 3.4 Hz, 1H), 1.78 (d, J = 12.9 Hz, 1H), 1.66–1.59 (m, 1H), 1.59–1.50 (m, 1H), 1.31 (s, 3H), 1.08 (s, 3H), 1.00 (s, 3H).

$^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD) δ 176.0, 111.8, 86.6, 77.0, 70.5, 66.2, 64.0, 54.1, 45.4, 45.1, 44.5, 24.6, 20.7, 19.4, 7.0.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_6Na$ 321.1309; found 321.1312.

Melting Point: 175 – 180 °C



Illisimonin A 3-1: Lactol **3-103** (196 mg, 0.657 mmol) was azeotroped in HFIP:MeCN (3:1) three times to remove any traces of methanol. HFIP (2.84 mL) was added to the flask containing lactol **3-103** and a stir bar. The flask was left open to air.

Approximately racemic White's catalyst was prepared by mixing equal amounts of Fe(*R,R*)PDP and Fe(*S,S*)PDP.

The following solutions were made open to air:

5.52 mL MeCN + 200 μL H_2O_2 30% w/w in H_2O

4.77 mL MeCN + 169.2 mg Fe(PDP)

4.32 mL of the H_2O_2 solution (ca. 1.48 mmol) and 4.32 mL of the Fe(PDP) solution (ca. 0.164 mmol) were added dropwise, concurrently via syringe pump to the stirred solution of lactol **3-103** over 45 min.[122] After this period, isopropanol (300 μL, 3.92 mmol) was added, and the crude reaction mixture was concentrated onto silica gel, and purified by flash column chromatography on silica (0 – 50% acetone in hexanes gradient then 50 % acetone in hexanes isocratic), to afford natural product **3-1** (93.9 mg, 48%) as a white solid.

The same reaction was performed starting from lactol **3-103** (107.6 mg, 0.3607 mmol), and yielded natural product **3-1** (50.2 mg, 47%).

$\mathbf{R_f}$ = 0.32 (10% MeOH in CH_2Cl_2), visualized by Hanessian's stain

$\mathbf{R_f}$ = 0.34 (60% acetone in hexanes), visualized by Hanessian's stain

^{1}H NMR see below

^{13}C{^{1}H} NMR see below

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{20}O_6Na$ 319.1153; found 319.1164.

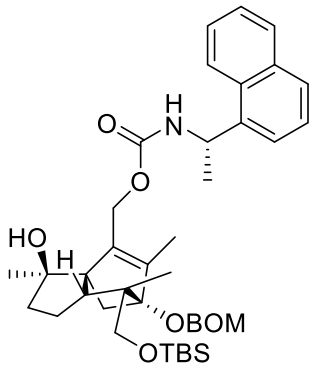
Melting Point: Illisimonin A **3-1** turned from a white solid to a yellowish-brown solid around 165 °C, then liquefied between 169 – 175 °C

3.5.3.2 Enantioenriched section- Compounds reported in this section are enantioenriched

Carbamates (-)-3-111 and (+)-3-112. Allylic alcohol **(±)-3-98** (340 mg, 0.676 mmol), DMAP (5 mg, 0.04 mmol), (S)-1-(1-isocyanatoethyl)naphthalene[123] (146 mg, 0.745 mmol), and dry PhMe (1.6 mL) were combined in a sealed tube and heated to 110 °C for 6 h, then allowed to cool to RT. The solvent was removed in vacuo, and the mixture of diastereomers was isolated by flash column chromatography on silica (10 – 30% EtOAc in hexanes).

$\mathbf{R_f}$ = 0.47 (30% EtOAc in hexanes), visualized by UV

The mixture of diastereomers were partially separated by additional flash column chromatography on silica (0 – 10% Et_2O in CH_2Cl_2). The mixed fractions were resubjected to the same chromatography conditions two additional times. Carbamate **(+)-3-112** (208.8 mg, 44%) was isolated as a white foamy solid. Carbamate **(-)-3-111** (186.4 mg, 39%) was isolated as a white foamy solid. Additionally a mixture of the two diastereomers (18.4 mg, 4%) was recovered.



Carbamate (-)-3-111

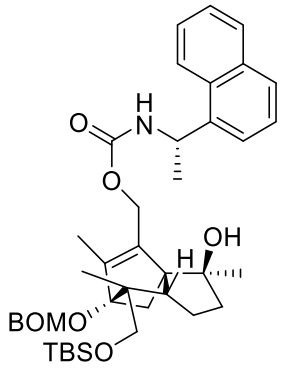
R_f = 0.43 (10% Et_2O in CH_2Cl_2), visualized by UV

^{1}H NMR (600 MHz, $CDCl_3$)[124] 8.09 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.52–7.47 (m, *J* = 7.0 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.38–7.27 (m, 5H), 5.69–5.61 (m, 1H), 5.00 (d, *J* = 7.7 Hz, 1H), 4.91 (d, *J* = 12.3 Hz, 1H), 4.86 (d, *J* = 12.5 Hz, 1H), 4.80 (d, *J* = 6.9 Hz, 1H), 4.73–4.69 (m, 2H), 3.78 (d, *J* = 9.8 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 2.65 (s, 1H), 1.99–1.90 (m, 1H), 1.87–1.74 (m, 7H), 1.68–1.61 (m, 5H), 1.55 (s, 1H), 1.26 (s, 3H), 0.90 (s, 9H), 0.84 (s, 3H), 0.061 (s, 3H), 0.055 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.2, 147.7, 138.4, 137.9, 135.9, 134.1, 131.0, 129.0, 128.6, 128.5, 127.9, 127.9, 126.7, 125.9, 125.3, 123.4, 122.4, 93.8, 92.1, 78.5, 69.7, 67.4, 64.2, 60.0, 54.1, 50.8, 50.0, 46.8, 42.0, 26.0, 24.6, 23.1, 22.0, 21.5, 18.4, 11.8, -5.37, -5.43.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{42}H_{57}NO_6SiNa$ 722.3848; Found 722.3863.

$[\alpha]_D^{20.9}$ = –58.1 (c 1.36 $CDCl_3$).



Carbamate (+)-3-111

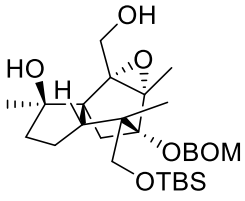
$\mathbf{R}_f$ = 0.48 (10% Et_2O in CH_2Cl_2), visualized by UV

^{1}H NMR (600 MHz, $CDCl_3$) [124] δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.49 (m, 2H), 7.46–7.43 (m, 1H), 7.38–7.27 (m, 5H), 5.70–5.62 (m, 1H), 5.01 (d, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 12.3 Hz, 1H), 4.83 (d, *J* = 12.4 Hz, 1H), 4.80 (d, *J* = 6.7 Hz, 1H), 4.73–4.68 (m, 2H), 4.55 (d, *J* = 11.8 Hz, 1H), 3.77 (d, *J* = 9.9 Hz, 1H), 3.73 (d, *J* = 9.9 Hz, 1H), 2.68 (s, 1H), 2.06–1.89 (m, 1H), 1.88–1.73 (m, 6H), 1.70–1.52 (m, 6H), 1.22 (s, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 155.4, 147.6, 138.4, 137.9, 136.0, 134.0, 131.0, 128.9, 128.6, 128.5, 127.9, 127.9, 126.6, 125.9, 125.4, 123.4, 122.5, 93.8, 92.1, 78.5, 69.7, 67.3, 64.1, 60.1, 54.1, 50.6, 50.0, 46.8, 42.0, 29.8, 26.0, 24.6, 23.1, 22.1, 21.5, 18.3, 11.8, -5.4, -5.5.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{42}H_{57}NO_6SiNa$ 722.3848; Found 722.3844.

$[\alpha]_D^{20.7}$ = 59.8 (c 1.27 $CDCl_3$).

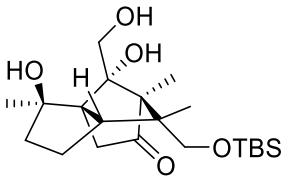


Epoxide (-)-3-99. Carbamate **(-)-3-111** (186 mg, 0.265 mmol) was dissolved in Et_2O (3 mL). $LiAlH_4$ (33 mg, 0.823 mmol) was added. The reaction was stirred at ambient temperature. After 4.5 h, TLC analysis showed no more starting material. Saturated Rochelle's salt (aq) (3 mL) was added very slowly until the bubbling had ceased. The mixture was stirred vigorously for 2 h. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with diethyl ether (2 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield the crude alcohol which was used without further purification.

The crude product was dissolved in CH_2Cl_2. No attempt was made to exclude air or moisture from

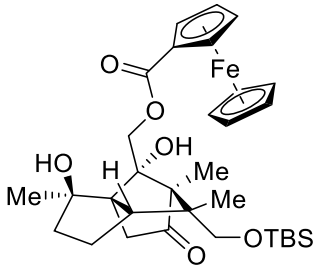
the reaction. *m*-CPBA (203 mg, 0.823 mL) was added. After 30 min., TLC analysis showed no more starting material. saturated $NaHCO_3$ (3 mL) and saturated $Na_2S_2O_3$ (3 mL) were added, and the mixture was stirred for 1 h. Next, the mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with $CHCl_3$ (2 x 75 mL). The combined organic layers were dried over concentrated *in vacuo* and purified by flash column chromatography on silica (0 – 100 % EtOAc in hexanes gradient), to afford epoxide **(-)-3-99** (83.6 mg, 61%) as a foamy white solid. The enantiomeric excess of the product was determined to be 90%, by HPLC chiral analysis (Chiralcel AD-H with AD guard, 2% *i*-PrOH in *n*-hexane, 1.0 mL/min, UV detection at 215 nm, t_{major} = 18.6 min, t_{minor} = 22.8 min).

$[\alpha]_D^{22.1}$ = –56.6 (c 1.95 $CDCl_3$).



Cyclopentanone triol (+)-3-100. Epoxide **(-)-3-99** (163 mg, 0.314 mmol) was converted to cyclopentanone triol **(+)-3-100** (75.4 mg, 60%) following the same procedure for cyclopentanone triol **(±)-3-100**.

$[\alpha]_D^{21.5}$ = 4.6 (c 4.00 $CHCl_3$).



Ferrocene (+)-S3-5. Cyclopentanone triol **(+)-3-100** (75.4 mg, 0.189 mmol), DIPEA (0.17 mL, 0.978 mmol), DMAP (37 mg, 0.303 mmol), and CH_2Cl_2 (1.13 mL) were combined in a flask. PyBOP (271 mg, 0.521 mmol) was added, and the reaction was stirred overnight. The following morning, saturated NH_4Cl (aq) (5 mL) was added. The mixture was

transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography on silica (0 – 30 % EtOAc in hexanes gradient), to afford ferrocene **(+)-S3-5** (59.1 mg, 53%) as a foamy orange solid.

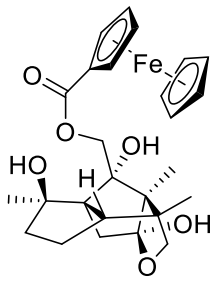
R_f = 0.39 (33% EtOAc in hexanes), visualized by Hanessian's stain or UV.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 – 4.75 (m, 4H), 4.49–4.45 (m, 2H), 4.25 (s, 5H), 3.25 (d, *J* = 10.1 Hz, 1H), 3.18 (d, *J* = 10.1 Hz, 1H), 3.04 (t, *J* = 9.8 Hz, 1H), 2.60 (s, 1H), 2.58 (d, *J* = 17.5 Hz, 1H), 2.49 (s, 1H), 2.17 (d, *J* = 17.6 Hz, 1H), 2.11–2.00 (m, 2H), 1.86 – 1.78 (m, 1H), 1.53 (ddd, *J* = 18.8, 11.6, 6.4 Hz, 1H), 1.44 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H), 0.87 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 212.7, 172.3, 83.2, 75.9, 72.2, 71.7, 70.2, 70.1, 69.6, 66.3, 63.9, 63.5, 51.6, 43.4, 39.6, 39.3, 25.9, 25.0, 23.4, 19.3, 18.2, 7.1, -5.60, -5.64.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{32}H_{46}FeO_6SiNa$ 633.2306; Found 633.2330.

$[\alpha]_D^{21.7}$ = 3.5 (c 1.41 $CHCl_3$).



(+)-29

Lactol (+)-3-114. To ferrocene **(+)-S3-5** (59.1 mg, 0.0969 mmol) was added THF (0.4 mL), MeCN (0.4 mL), and 49% HF (aq) (0.2 mL). The solution was stirred overnight. The following morning silica gel (0.2 g) was added, and the mixture was stirred for 1 h. The solvent was removed *in vacuo*, and the impregnated silica was purified by flash column chromatography on silica (0 – 100 % EtOAc in hexanes gradient), to afford lactol **(+)-3-114** (37.3

mg, 78%) as an orange solid. Crystals were grown for x-ray diffraction by liquid/liquid diffusion using $CHCl_3$ (solvent) and pentanes (antisolvent).

R_f = 0.19 (50% EtOAc in hexanes), visualized by Hanessian's stain or UV.

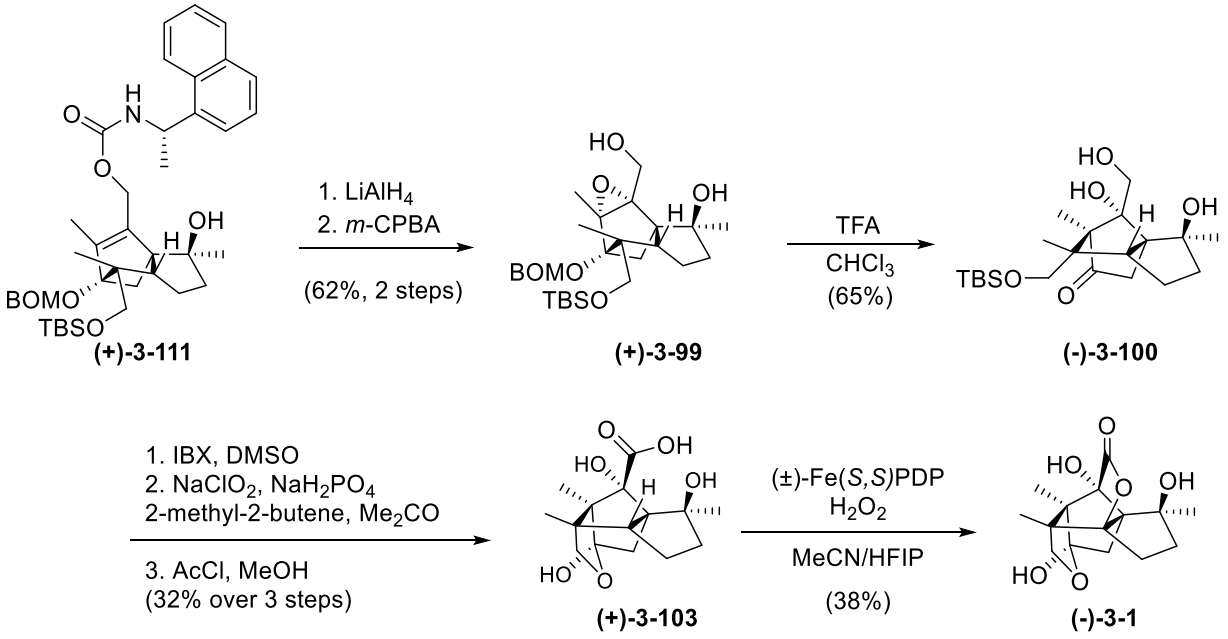
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 2H), 4.72 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.45 (m, 2H), 4.26 (s, 5H), 3.72 (d, *J* = 8.7 Hz, 1H), 3.53 (d, *J* = 8.7 Hz, 1H), 3.18–3.03 (br s, 1H), 2.96 (t, *J* = 9.6 Hz, 1H), 2.80 (br s, 1H), 2.75 (br s, 1H), 2.36 (dd, *J* = 13.2, 1.8 Hz, 1H), 2.11–1.99 (m, 2H), 1.87 (d, *J* = 13.2 Hz, 1H), 1.73–1.65 (m, 1H), 1.54 (m, 1H), 1.42 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 171.8, 111.5, 83.0, 75.8, 72.0, 70.2, 70.2, 70.1, 70.1, 69.8, 63.8, 63.2, 62.9, 53.1, 43.4, 43.3, 25.1, 21.8, 18.7, 6.2.

HRMS (ESI/TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{32}FeO_6Na$ 519.1442; Found 519.1461.

Melting Point: 155 – 160 °C

$[\alpha]_D^{21.8}$ = 64.5 (c 1.96 $CHCl_3$).



Epoxide (+)-3-99. Carbamate **(+)-3-111** (192 mg, 0.274 mmol) was converted to epoxide **(+)-3-99** (87.7 mg, 62%) following the same procedure previously detailed for epoxide **(-)-3-99**. The enantiomeric excess of the product was determined to be 91%, by HPLC chiral analysis (Chiralcel AD-H with AD guard, 2% *i*-PrOH in *n*-hexane, 1.0 mL/min, UV detection at 215 nm, t_{minor} = 18.9 min, t_{major} = 22.2 min).

$[\alpha]_D^{21.2}$ = 59.9 (c 1.00 $CDCl_3$).

Cyclopentanone triol (-)-3-100. Epoxide **(+)-3-99** (85 mg, 0.16 mmol) was converted to cyclopentanone triol **(-)-3-100** (42.5 mg, 65%) following the same procedure for cyclopentanone triol **(±)-3-100.**

$[\alpha]_D^{21.8}$ = –10.1 (c 0.91 $CHCl_3$).

Carboxylic acid (+)-3-103. Cyclopentanone triol **(-)-3-100** (42.0 mg, 0.105 mmol) was converted to carboxylic acid **(+)-18** (10.0 mg, 32% over 3 steps) following the same procedure for carboxylic acid **(±)-3-103.**

$[\alpha]_D^{22.0}$ = 3.7 (c 1.00 MeOH).

(-)-Illisimonin A. Carboxylic acid **(+)-3-1** (10.0 mg, 0.335 mmol) was converted to (-)-illisimonin A (3.8 mg, 38%) following the same procedure for (±)-illisimonin A.

$[\alpha]_D^{22.0}$ = –12.4 (c 0.35 MeOH).

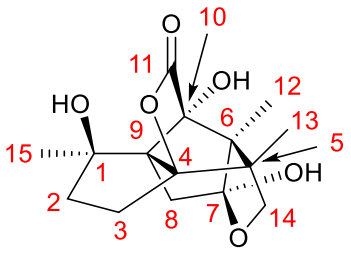
$[\alpha]_{577}^{22.1}$ = –14.8 (c 0.35 MeOH).

$[\alpha]_{546}^{22.1}$ = –17.2 (c 0.35 MeOH).

$[\alpha]_{435}^{22.1}$ = –35.1 (c 0.35 MeOH).

[α]$_D^{22.1}$ = –44.0 (c 0.35 MeOH).

3.5.4 Illisimonin A comparison



3.5.4.1 Illisimonin A spectral comparison

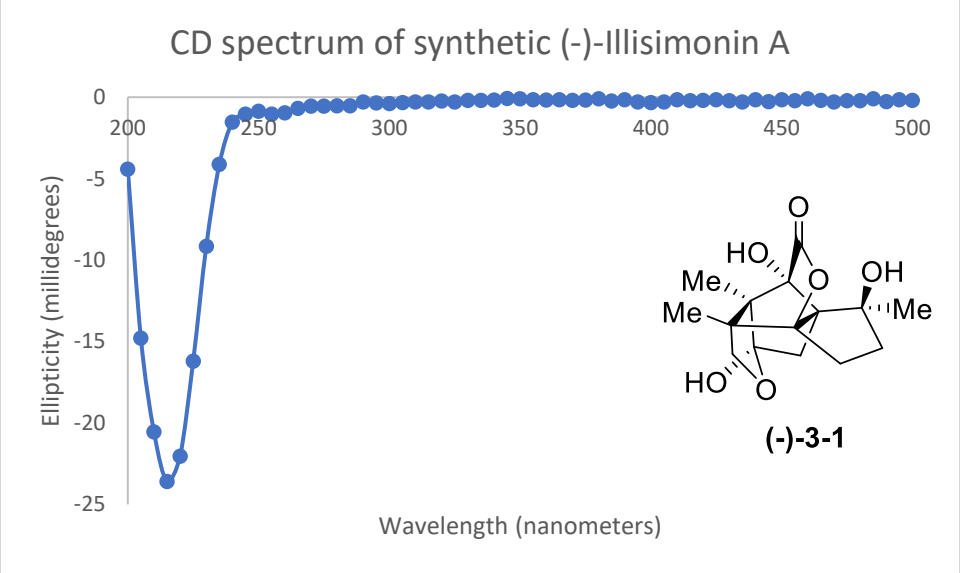
Position	Isolation ^{1}H NMR (500 MHz, CD_3OD)	Synthetic ^{1}H NMR (500 MHz, CD_3OD)
2α	2.25 (ddd, *J* = 14.0, 10.5, 3.5 Hz, 1H)	2.25 (ddd, *J* = 14.0, 10.6, 3.3 Hz, 1H)
2β	2.36 (d app. t, *J* = 14.0, 8.5 Hz, 1H)	2.37 (d app. t, *J* = 14.2, 8.7 Hz, 1H)
3α	2.03 (ddd, *J* = 14.5, 10.5, 8.5 Hz, 1H)	2.02 (ddd, *J* = 14.3, 10.3, 8.5 Hz, 1H)
3β	1.91 (ddd, *J* = 14.5, 8.5, 3.5 Hz, 1H)	1.91 (ddd, *J* = 14.3, 8.9, 3.1 Hz, 1H)
8α	1.97 (d, *J* = 14.5 Hz, 1H)	1.97 (d, *J* = 14.3 Hz, 1H)
8β	2.30 (d, *J* = 14.5 Hz, 1H)	2.31 (d, *J* = 14.3 Hz, 1H)
12	0.91 (s, 3H)	0.91 (s, 3H)
13	1.03 (s, 3H)	1.03 (s, 3H)
14α	3.79 (d, *J* = 10.0 Hz, 1H)	3.79 (d, *J* = 10.1 Hz, 1H)
14β	3.55 (d, *J* = 10.0 Hz, 1H)	3.55 (d, *J* = 10.1 Hz, 1H)
15	1.27 (s, 3H)	1.27 (s, 3H)

Position	Isolation $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD)	Synthetic $^{13}C\{^1H\}$ NMR (151 MHz, CD_3OD)
1	76.7	76.7
2	46.5	46.5
3	23.1	23.1
4	104.9	104.9
5	52.8	52.8
6	63.9	63.9
7	111.5	111.5
8	39.0	39.1
9	71.0	71.0
10	88.4	88.4
11	177.6	177.6

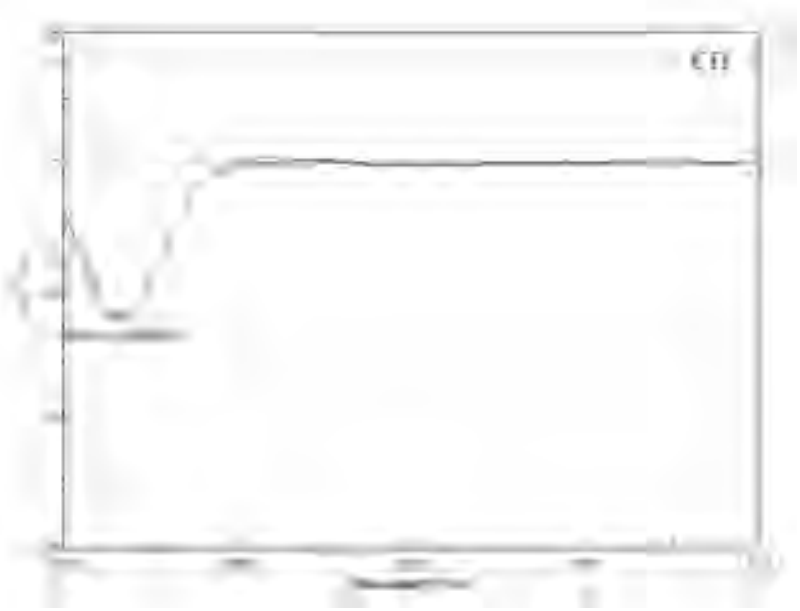
12	6.0	5.9
13	16.7	16.7
14	69.7	69.7
15	28.1	28.1

3.5.4.2 (-)-Illisimonin A circular dichroism

Measurements were carried out in a 0.1 cm cuvette, at room temperature, at 0.79 mg/mL concentration in MeOH.

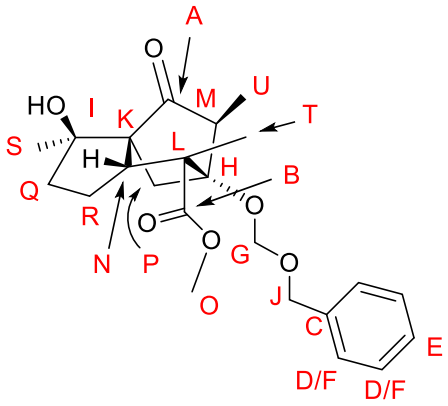


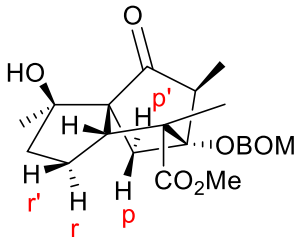
Literature circular dichroism spectrum:[86]

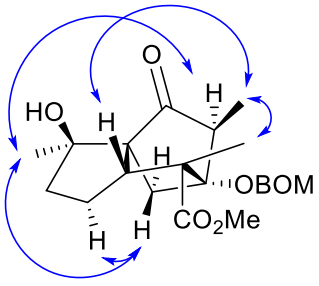


3.5.5 *NMR assignments of compounds **3-79**, **3-83**, **3-100**, and **3-102***

The relative structure of **3-79** was assigned on the basis of ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY NMR as well as HRMS analysis. Shown below are the chemical shift assignments:







Important NOE correlations

Discussion: The correlations between methine **n**, methyl **t**, and methyl **u** were strong indicators of the relative stereochemistry about those three stereocenters. The NOE observed between methyl **S** and methine **m** further confirmed the stereochemistry at carbon **M**, and established the

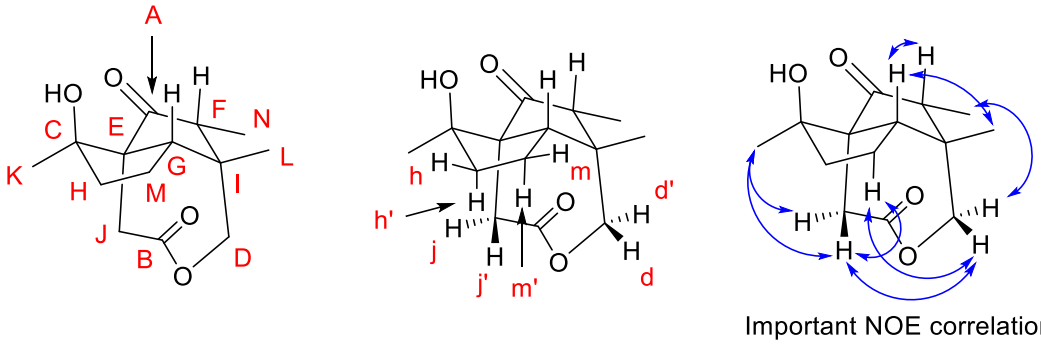
configuration of carbon **I**. The observed stereochemistry is consistent with a Diels-Alder templated through silacycle **3-78**. The stereochemistry at carbon **M** can be rationalized by protonation from the less hindered alpha face of the resulting silyl-enol ether from the Diels-Alder. Tricycle **3-79** was ultimately taken on to natural product **3-1**, further confirming our structure assignment.

δ (ppm)	Splitting	J (Hz)	Integration	Assignment
7.38–7.28	m		5H	d-f
5.06	d	7.7	1H	g
4.84	d	7.7	1H	g’
4.68	d	11.7	1H	j
4.62	d	11.7	1H	j’
4.27	s		1H	O-H
3.71	s		3H	o
3.04	d	10.0	1H	p
2.96	q	7.1	1H	m
2.34	ddd	10.8, 6.0, 2.1	1H	n
2.15–2.03	m		1H	r
1.95	dd	9.9, 2.2	1H	p’
1.87–1.79	m		2H	q, q’
1.53–1.43	m		1H	r’
1.43	s		3H	t
1.30	d	7.1	3H	u
1.30	s		3H	s

δ (ppm)	Assignment
217.8	A
174.1	B
137.5	C
128.7	D
128.07	E
128.05	F
92.4	G
89.0	H
79.7	I
70.2	J
68.2	K
58.2	L
57.1	M
56.1	N

51.9	O
40.5	P
40.3	Q
25.1	R
24.5	S
21.8	T
10.2	U

The relative structure of **3-83** was assigned on the basis of ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY NMR as well as HRMS analysis. Shown below are the chemical shift assignments:

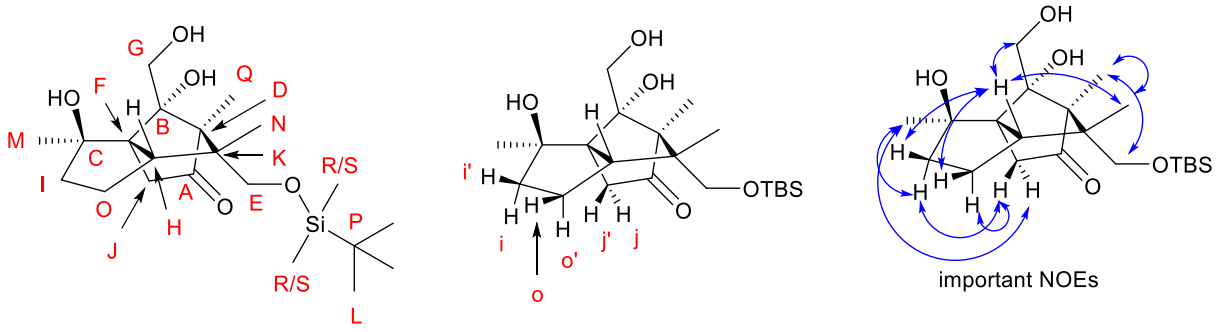


Discussion: The NOE between methines **f** and **g** were helpful in establishing the stereochemistry at carbon **F**. The rest of the structure was consistent with the bromination/semi-pinacol/retro-Claisen sequence from intermediate **3-81**, whose structure can be traced back to tricycle **3-79** through standard transformations.

δ (ppm)	Splitting	J (Hz)	Integration	Assignment
4.42	d	13.4	1H	d
3.98	dd	13.4, 1.3	1H	d’
3.10	dd	12.9, 6.9	1H	g
2.76	dd	15.0, 0.9	1H	j
2.63	d	14.9	1H	j’
2.44	q	7.3	1H	f
2.21	ddd	15.3, 9.1, 6.5	1H	h
2.08–2.02	m		1H	h’
1.79–1.73	m		1H	m
1.66	app. tdd	12.5, 10.9, 6.4	1H	m’
1.46	s		3H	k
1.22	s		3H	n
1.14	s		3H	l

δ (ppm)	Assignment
213.6	A
171.0	B
77.0	C
69.0	D
64.2	E
62.1	F
54.7	G
42.6	H
40.6	I
35.1	J
24.7	K
23.1	L
16.4	M
8.8	N

The relative structure of **3-100** was assigned on the basis of ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY NMR as well as HRMS analysis. Shown below are the chemical shift assignments:



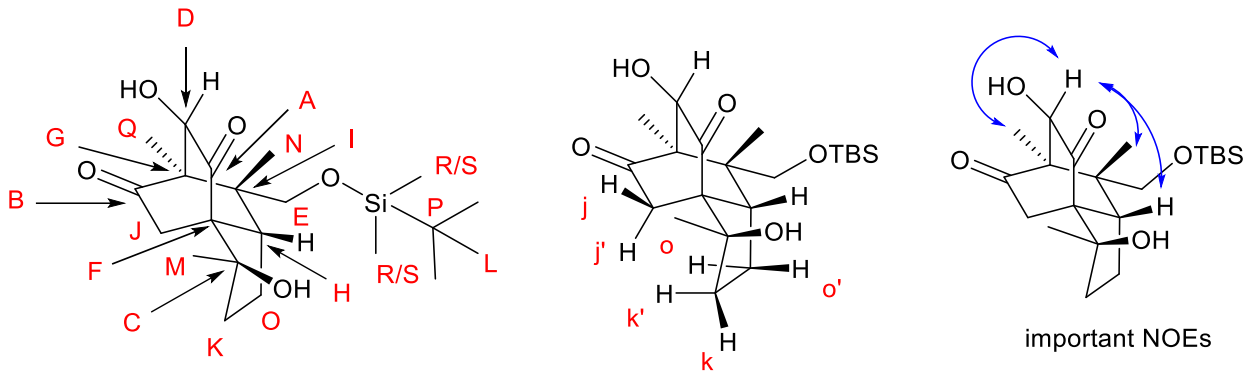
Discussion: The NOE's between methylene protons **g**, methine **h**, and methyl **n**, as well as between methylene **g'** and methyl **q** were helpful in establishing the configuration of carbon **B**. The appearance of a ketone (**A**), where there previously had been none was helpful in confirming the desired semipinacol rearrangement had taken place. Finally, intermediate **3-100** was taken forward to natural product **3-1**, further confirming its relative structure.

δ (ppm)	Splitting	J (Hz)	Integration	Assignment
4.40	d	11.4	1H	g
4.19	br s		1H	O-H

3.35	d	11.7	1H	g’
3.28	br s		1H	O-H
3.22	d	10.0	1H	e
3.13	d	10.1	1H	e’
2.92	ddd	12.0, 8.1, 1.7	1H	h
2.52	dd	17.5, 1.9	1H	j
2.45	br s		1H	O-H
2.14	ddd	14.8, 11.3, 3.4	1H	i
2.09	d	17.4	1H	j’
1.96	ddd	14.9, 9.1, 5.8	1H	i’
1.86	m		1H	o
1.53	m		1H	o’
1.36	s		3H	m
1.01	s		3H	n
0.89	s		3H	q
0.86	s		9H	l
-0.02	s		3H	r/s
-0.03	s		3H	r/s

δ (ppm)	Assignment
213.3	A
84.1	B
76.7	C
69.8	D
66.0	E
63.1	F
60.6	G
51.6	H
45.3	I
39.5	J
39.4	K
25.9	L
25.0	M
23.5	N
19.7	O
18.2	P
6.4	Q
-5.6	R
-5.7	S

The relative structure of **3-102** was assigned on the basis of ^{1}H, ^{13}C, COSY, HSQC, HMBC, and NOESY NMR as well as HRMS analysis. Shown below are the chemical shift assignments:



Discussion: Most important to structure determination were the NOEs between proton **d**, and methyls **q** and **n**, and methine **h**. The structure is consistent with an alpha-ketol rearrangement of aldehyde **3-101** which can be traced back to primary alcohol **3-100** (whose structure was earlier established) through simple IBX oxidation.

δ (ppm)	Splitting	J (Hz)	Integration	Assignment
4.08	s		1H	d
3.50	d	10.8	1H	e
3.46	d	10.8	1H	e’
2.88	br s		1H	O-H
2.77	app. t	9.8	1H	h
2.70	d	18	1H	j
2.17–2.11	m		1H	o
2.12	dd	17.8, 1.9	1H	j’
2.05–1.96	m		1H	o’
1.92	ddd	15.3, 9.7, 5.8	1H	k
1.84–1.76	m		1H	k’
1.37	s		3H	m
1.12	s		3H	q
1.00	s		3H	n
0.87	s		9H	l
0.05	s		3H	r/s
0.03	s		3H	r/s

δ (ppm)	Assignment
214.4	A
206.8	B
79.2	C

74.8	D
66.6	E
60.0	F
57.2	G
46.2	H
42.2	I
38.8	J
38.2	K
26.0	L
24.4	M
22.3	N
20.6	O
18.5	P
9.0	Q
-5.9	R
-6.0	S

3.6 References

[66] Fukuyama, Y.; Huang, J.-M. *Studies in Nat. Prod. Chem.* **2005**, *32*, 395–427.

[67] (a) Song, T.-F.; Zhang, W.-F.; Xia, X.-H.; Shen, Y.-H.; Liu, C.-M.; Lin, S.; Jin, L-H. ;Li, H.-L. *Arch. Pharm. Res.* **2009**, *32*, 1233–1236. (b) Y.; Shida, N.; Kodama, M.; Chaki, H.; Yumagi, T. *Chem. Pharm. Bull.* **1995**, *43*, 2270–2272. (c) Ngo, K.-S.; Brown, G. D. *Tetrahedron* **1999**, 55, 759–770. (e) Huang, J.-m.; Yokoyama, R.; Yang, C.-s.; Fukuyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6111–6114. (f) Sy, L.-K.; Brown, G. D. *Phytochemistry* **1998**, *47*, 301–302.

[68] Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199–229.

[69] Schmidt, T. J. *Curr. Org. Chem*., **1999**, *3*, 577–608.

[70] Augustine, G. J *Neuroscience*, 6th ed.; Purves, D., Ed.; Oxford University Press: Oxford, 2018; pp 33–190.

[71] (a) Shenvi, R. A. *Nat. Prod. Rep.* **2016**, *33*, 535-539. (b) Witkin, J. M.; Shenvi, R. A.; Li, X.; Gleason, S. D.; Weiss, J.; Morrow, D.; Catow, J. T.; Wakulchik, M.; Ohtawa, M.; Lu, H.-H.; Martinez, M. D.; Schkervantz, J. M.; Carpenter, T. S.; Lightstone, F. C.; Cerne, R. *Biochem. Pharm.* **2018**, *155,* 61–70.

[72] Fukuyama, Y.; Shida, N.; Kodama, M. *Planta Med.* **1993**, *59*, 181–183.

[73] For a review on the synthetic work towards the *Illicium* sesquiterpenoids up to 2009, see: Urabe, D.; Inoue, M. *Tetrahedron* **2009**, *65*, 6271–6289.

[74] For a review on recent syntheses of the seco-prezizaane class, see: Condakes, M. L.; Novaes, L. F. T.; Maimone, T. J. *J. Org. Chem.* **2018**, *83*, 14843–14852.

[75] For syntheses of the *allo*-cedrane, (±)-11-*O*-debenzoyltashironin, see: (a) Cook, S. P.; Polara, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16440–16441. (b) Mehta, G.; Maity, P. A. *Tetrahedron Lett.* **2011**, *52*, 1749–1752. (c) Ohtawa, M.; Krambis, M. J.; Cerne, R.; Schkeryantz, J. M.; Witkin, J. M.; Shenvi, R. A. *J. Am. Chem. Soc.* **2017**, *139*, 9637–9644.

[76] For syntheses of the anislactone, merrilactone, see: (a) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080–2081. (b) Inoue, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc.* **2003**, *125*, 10772–10773. (c) Mehta, G.; Singh, S. R. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 953–955. (d) He, W.; Huang, J.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 498–499. (e) Shi, L.; Meyer, K.; Greaney, M. F. *Angew. Chem. In.t Ed.* **2010**, *49*, 9250–9253. (f) Chen, J.; Gao, P.; Yu, F.; Yang, Y.; Zhu, S.; Zhai, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 5897–5899. (g) Liu, W.; Wang, B. *Chem. Eur. J.* **2018**, *24*, 16511–16515.

[77] Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111–5113.

[78] Kende, A. S.; Chen, J. *J. Am. Chem. Soc*. **1985**, *107*, 7184–7186.

[79] Niwa, H.; Nishiwaki, M.; Tsukada, I.; Ishigaki, T.; Ito, S.; Wakamatsu, K.; Mori, T.; Ikagawa, M.; Yamada, K. *J. Am. Chem. Soc.* **1990**, *112*, 9001–9003.
[80] Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *124,* 2080–2081.
[81] Huang, J.-M.; Yang, C.-S.; Tanaka, T.; Fukuyama, Y *Tetrahedron,* **2001,** *57,* 4691–4698.
[82] M. Kubo, C. Okada, J.-M. Huang, K. Harada, H. Hioki, Y.Fukuyama, *Org. Lett.* **2009**, *11*, 5190–5193.
[83] Lu, H.-H.; Martinez, M. D.; Shenvi, R. A. *Nat. Chem.* **2015**, *7*, 604–607.
[84] Hung, K.; Condakes, M. L.; Novaes, L. F. T.; Harwood, S. J.; Morikawa, T.; Yang, Z.; Maimone, T. J. *J. Am. Chem. Soc.* **2019**, *141*, 3083–3099.
[85] Hung, K.; Condakes, M. L.; Morikawa, T.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 16616−16619.
[86] Ma, S.-G.; Li, M.; Lin, M.-B.; Li, L.; Liu, Y.-B.; Qu, J.; Li, Y.; Wang, X.-J.; Wang, R.-B.; Xu, S.; Hou, Q.; Yu, S.-S. *Org. Lett.* **2017**, *19*, 6160−6163.
[87] Allinger, N. L.; Hirsch, J. A.; Miller, M. A.; Tyminski, I. J.; Van Catledge, F. A. *J. Am. Chem. Soc.* **1968**, *90*, 1199−1210.
[88] Pronin, S. V.; Shenvi, R. A. *Nat. Chem.* **2012**, *4*, 915−920.
[89] (a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 5505−5506. (b) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed*. **2010**, *49*, 1095−1098. (c) Hu, P.; Snyder, S. A. *J. Am. Chem. Soc.* **2017**, *139*, 5007−5010.
[90] For a full discussion of these calculations, see our paper: Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295–13300.
[91] (a) Chen, M. S.; Science, M. W. *Science* **2007**, *318*, 783–787. (b) Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721–9726. (c) White, M. C.; Zhao, J. *J. Am. Chem. Soc.* **2018**, *140*, 13988–14009.
[92] Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556.
[93] (a) Ermolenko, L.; Sasaki, N. A.; Potier, P. *Synlett* **2001**, *10*, 1565–1566. (b) Papaioannou, D.; Francis, G. W.; Aksnes, D. W.; Brekke, T.; Maartmann-Moe, K. *Acta Chem. Scand.* **1990**, *44*, 90–95. (c) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones*, Springer: New York, **2006**.
[94] (a) Ryu, I.; Murai, S.; Shinonaga, A.; Horiike, T.; Sonoda, N. *J. Org. Chem.* **1978**, *43*, 780−782. (b) Singh Batra, M.; Brunet, E. *Tetrahedron Lett.* **1993**, *34*, 711−714. (c) Dietz, W.; Schwerdtfeger, Y.; Klingebiel, U.; Noltemeyer, M. Z. Naturforsch., B. *J. Chem. Sci*. **2007**, *62*, 1371−1376.
[95] Boissarie, P.; Belanger, G. *Org. Lett.* **2017**, *19*, 3739−3742.
[96] Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296.
[97] Yuan, L.; Zhang, C.; Sun, H.; Liu, Q.; Huang, J.; Sheng, L.; Lin, B.; Wang, J.; Chen, L. Bio. *Med. Chem. Lett*., **2016**, *26*, 769–773.
[98] Banwell, M. G.; Jury, J. C. *Org. Prep. Proced. Int.* **2004**, 36, 87−91.
[99] (a) *Org. React.* **1993**, *43*, 1–90. (b) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281–283.
[100] (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 867−868. (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.
[101]Several one-step oxidations were attempted, but none were successful at generating the α-hydroxy acid, leading either to decomposition or no reaction. Conditions investigated include Jones oxidation, O_2/Pt, and TPAP/NMO/H_2O.
[102] (a) Miller, T. C. *J. Org. Chem.* **1969**, *34*, 3829–3833. (b) Creary, X.; Inocencio, P. A.; Underiner, T. L.; Kostromin, R. *J. Org. Chem.* **1985**, *50*, 1932–1938.
[103] Ye, Q.; Qu, P.; Snyder, S. A. *J. Am. Chem. Soc.* **2017**, *139*, 18428–18431.
[104] Bietti, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 16618–16637.
[105] To rationalize the selective oxidation of axial vs. equatorial hydrogens in cyclohexanes, relief of 1,3-diaxial strain in the transition state has been proposed as an explanation. We reason that relief of the trans-pentalene ring strain in the rate limiting transition state of the C-H oxidation may similarly be a factor in our system. (a) Chen, K.; Eschenmoser, A.; Baran, P. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 9705–9708. (b) Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374.
[106] (a) Pfenninger, A. *Synthesis*. **1986,** *2*, 89–116. (b) Li, X.; Jiang, H.; Uffman, E. W. Guo, L.; Zhang, Y.; Yang, X.; Birman, V. B. *J. Org. Chem*. **2012**, *77*, 1722–1737.
[107] (a) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904–3906. (b) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169–2175. (c) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4111–4117.
[108] Holstein, P. M.; Holstein, J. J.; Escudero-Adán, E. C.; Baudoin, O.; Echavarren, A. M. *Tetrahedron Asymm.* **2017**, *28*, 1321–1329.
[109] Khadem, El, H.; Hanessian, S. *Anal. Chem.* **1958**, *30*, 1965–1965.
[110] Handa, M.; Scheidt, K. A.; Bossart, M.; Zheng, N.; Roush, W. R. *J. Org. Chem.* **2008**, *73*, 1031–1035.

[111] Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J.-S.; Kim, H.-J.; Lee, S.-G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321–6329.
[112] Lifchits, O.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 10227–10229.
[113] There are two additional aliphatic protons expected in the region 1.5-0.5ppm. As there were significant impurities in this region, their location could not be determined.
[114] The peak belonging to the CH_0 carbon of the phenyl ring could not be distinguished from the noise.
[115] (a) Kende, A. S.; Fludzinski, P.; Hill, J. H.; Swenson, W.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 3551–3562. (b) Banwell, M. G.; Jury, J. C. *Org. Prep. Proced. Int.* **2004**, *36*, 87–91.
[116] On smaller scale, the reaction could be run using a magnetic stirrer. On larger scale, the viscous reaction mixture could not be efficiently stirred without overhead stirring.
[117] BOM cleavage was a major side reaction in the absence of extra pyridine.
[118] Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59–63.
[119] The chemical shifts and splitting for this compound varied at the hydroxyl protons and hydroxyl-methylene protons, depending on the sample, and presumably its concentration and water content. A different sample was used for the 2-D analysis shown in the structural assignments section.
[120] The buffer was prepared by making a 100 mL aqueous solution of $KHSO_4$ (3.2 g, 24 mmol) and NaH_2PO_4 (10 g. 83 mmol) as described in: Xu, C.; Han, A.; Reisman, S. E. *Org. Lett.* **2018**, *20*, 3793–3796.
[121] This peak corresponds to two overlapping diastereomeric methyls from the TBS moiety.
[122] Vermeulen, N. A.; Chen, M. S.; White, C. *Tetrahedron* **2009**, *65*, 3078–3084.
[123] Chen, K.-F.; Tai, W.-T.; Hsu, C.-Y.; Huang, J.-W.; Liu, C.-Y.; Chen, P.-J.; Kim, I.; Shiau, C.-W. *Eur. J. Med. Chem.* **2012**, *55*, 220–227.
[124] The spectrum is a mixture of rotamers. For clarity, we tabulated only the major rotamer.

Chapter 4. Osmate esters are crystalline derivatives of alkenes, facilitating structural assignment via x-ray analysis

4.1 Abstract

Osmium tetroxide and TMEDA form stable crystalline adducts with alkenes. The structure of liquid alkenes can be determined through X-ray analysis of these derivatives. Osmium, a heavy atom, facilitates the crystallographic analysis and the determination of the absolute configuration using common Mo X-ray sources. The utility of this method for assigning structures and absolute configurations was demonstrated on a number of unsaturated substrates that include simple alkenes, enones, enol ethers, and silyl enol ethers.

4.2 Motivation

In chapter 3, I described the synthesis of the *Illicium* sesquiterpenoid, illisimonin A.[125] The proposed absolute configuration, which had been assigned on the basis of electronic circular dichroism (ECD) calculations, was at odds with other *Illicium* natural products.[126] To address this structural question, I needed to synthesize and independently determine the absolute configuration of (–)-illisimonin A **3-1**. I derivatized an advanced, racemic intermediate with a chiral auxiliary, and separated the resultant diastereomers. I took forward one of the diastereomers to natural (–)-illisimonin A whose ECD spectrum matched the authentic material. Unfortunately, the diastereomers were not crystalline, and to address this, a suitable crystalline derivative was sought. After much experimentation, I found that ferrocene ester **3-114** was crystalline, allowing the establishment of its absolute structure through x-ray diffraction analysis, reversing the absolute configuration (–)-illisimonin A by inference.

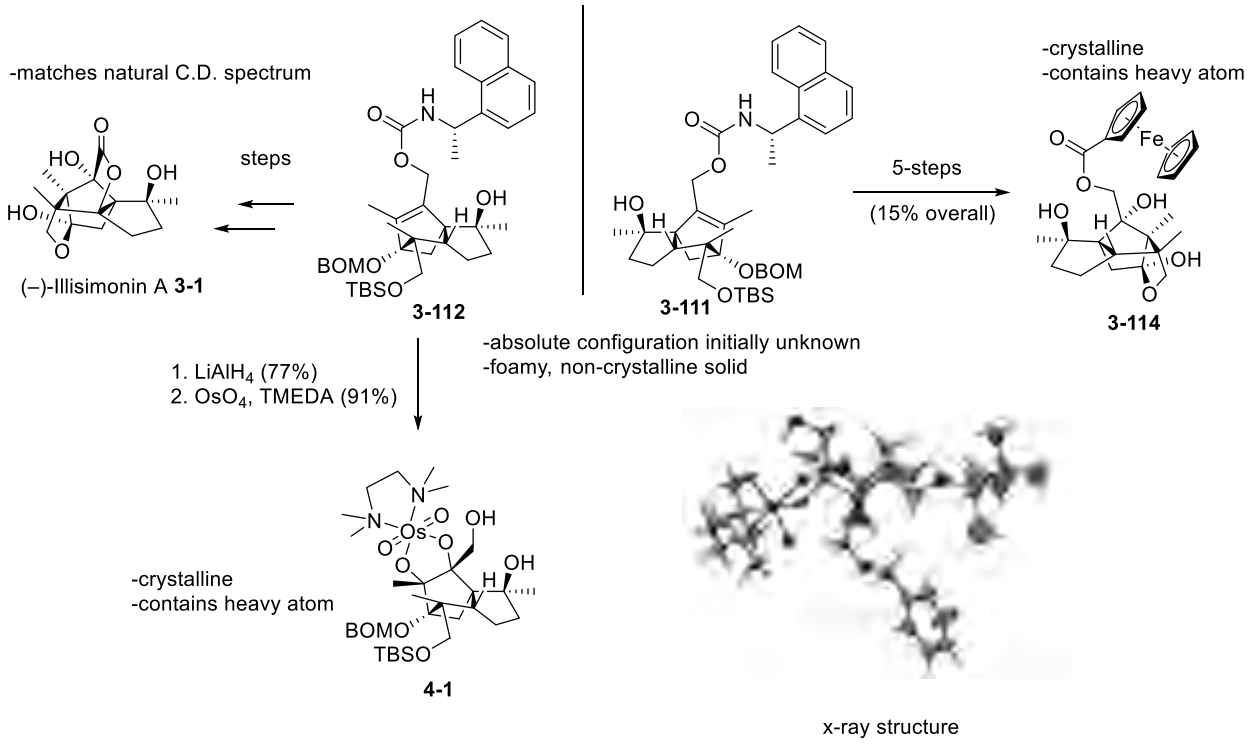


Figure 4-1 Determination and revision of the absolute configuration of (−)-illisimonin A. Our published assignment was based on ferrocene ester **3-114**, whose absolute configuration was determined through X-ray crystallography. Osmate ester **4-1** prepared in fewer steps and still carrying protecting groups, was analyzed by crystallography and provided a more direct means to assign the absolute configuration of the natural product.

Strategically, I wanted to install a heavy atom which would enable our in-house x-ray facility to determine absolute configuration. I took advantage of the reactivity of a primary alcohol, acylating with ferrocene carboxylic acid, a source of iron.[127] However, that molecule was not sufficiently crystalline in my hands, and the greasy silyl protecting group had to be removed before I was able to obtain suitable crystals. We later found a more concise, and tactically unique solution to this problem. Treatment of allylic alcohol **(–)-3-98** with stoichiometric amounts of osmium tetroxide and TMEDA formed the isolable, chromatographable osmate ester **4-1**. This substance was readily crystalline, despite having a TBS ether, and would have addressed the problem in a more straightforward manner than ferrocene derivative **3-114**.

4.3 Background

As discussed in chapters 1 and 2, the determination of the absolute configuration of molecules is a non-trivial and substrate dependent task. With the exception of perhaps total synthesis, X-ray crystallography is the least ambiguous method for absolute structure determination. Absolute configuration can be determined from the Flack parameter.[128] Traditionally, to have low uncertainty in the Flack parameter, and thus confidence in the assignment, a heavy-atom has been required for sufficient anomalous scattering.[129] There has been major progress in the determination of the absolute configuration of solely light-atom containing structures, but this work best with Cu Kα radiation, high quality crystals, and high data redundancy.[130]

Obtaining an appropriate crystal for X-ray analysis can prove to be quite difficult for many compounds. To start, the substance needs to be a crystalline solid. An exception to this is the crystalline sponge method, in which a liquid substance is absorbed into the cavities in a metal complex, and the resultant, compound-metal framework's structure can be determined through X-ray diffraction.[131] Another strategy for dealing with liquid substances is to crystallize them at low temperatures.[132] While these strategies have been successful at tackling problems other methods could not, their utilization is far from routine and often requires significant expertise to execute. A more common approach to converting a liquid substance into a crystalline solid at room temperature has been the derivatization of the substance, *vide infra*.

Alcohols, amines, carboxylic acids, ketones, and aldehydes have all been derivatized to render them more crystalline. Alcohols and amines are traditionally acylated with 4-bromobenzoyl chloride or 4-nitrobenzoyl chloride, with the former providing a heavy atom enabling absolute structure determination. More recently, acylation with ferrocene carboxylic acid has facilitated the

crystallization of otherwise liquid alcohols.[133] Carboxylic acids may be converted to amine salts, and ketones and aldehydes have been transformed into 3,5-$(NO_2)_2$-phenylhydrazones.

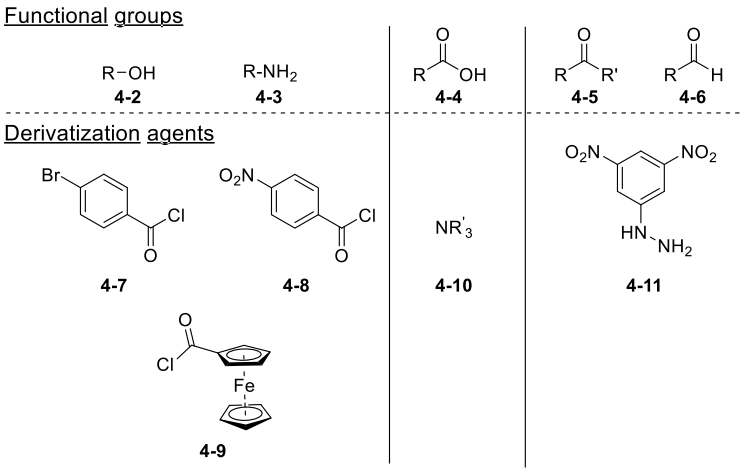


Figure 4-2 Common strategies for producing crystalline compounds by derivatizing functional groups

Osmium tetroxide and amines have been known to form crystalline compounds for decades. However, there is only one example, of which we are aware, that such a strategy was used for the purpose of determining the structure of the alkene. The first crystal structure of a derivative of buckminsterfullerene was that of its complex with osmium tetroxide and 4-*tert*-butylpyridine.[134] Aside from that, X-ray structures of crystalline osmate esters have been used to determine the stereoselectivity[135] or regioselectivity[136] of the osmylation or rationalize the use of chiral ligands in stoichiometric enantioselective osmylations.[137] Additionally, several X-ray structures of osmate esters with nucleosides and nucleotides have shed light on the interaction of osmium tetroxide with DNA and RNA.[138]

The high chemoselectivity and reactivity of osmium tetroxide-amine complexes make them ideal candidates for derivatization agents. In particular, the OsO_4-TMEDA (tetramethylethylenediamine) complex is estimated to be 100 times more reactive than the OsO_4-pyridine complex, and reacts with alkenes at cryogenic temperatures.[135] The dihydroxylation can

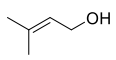
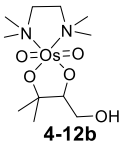
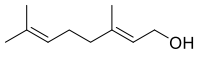
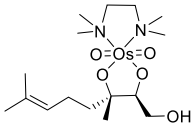
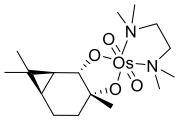
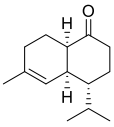
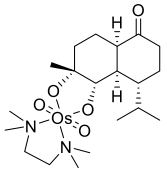
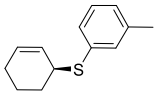
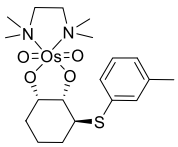
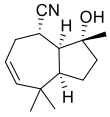
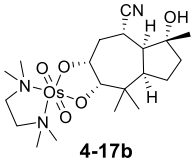
be directed by hydrogen bonding, and often reacts with good diastereoselectivity. The high toxicity and cost of osmium tetroxide is a drawback of preparative, stoichiometric osmylations. However, the milligram quantities of osmium tetroxide required for these reactions can be safely handled in a properly ventilated fume hood. Additionally, Fisher Scientific currently (December 2019) sells osmium tetroxide at $58/g, rendering the cost of osmium tetroxide negligible on this scale. We set about to determine what other liquid and/or chiral alkenes could be functionalized and crystallized as osmate esters.

4.4 Results and Discussion

To evaluate the utility of this method, we initially examined commercially available, liquid alkenes. The results are shown in Table 4-1. The osmylation of prenol (**4-12a**), geraniol (**4-13a**), and (+)-2-carene (**4-14a**), all proceeded in good yield. The products were purified using flash column chromatography (CH_2Cl_2/MeOH) on silica. The solid products were readily crystallized using vapor diffusion, and their structures determined by single crystal X-ray diffraction. For geraniol, osmylation occurs proximal to the allylic alcohol, in accord with the hydroxyl-directing effect reported by Donohoe.[135] The melting point of the geraniol osmate **4-13b** is 61 °C higher than the corresponding ferrocene carboxylate ester, indicating enhanced crystallinity.[133a] In the case of (+)-2-carene osmate **4-14b**, the absolute configuration was confirmed by the Flack method.[130]

Decalin **4-15a**,[139] and allylic sulfide **4-16a**[140] are both oils. They react under standard conditions (OsO_4 and TMEDA at –78 °C in CH_2Cl_2) to form osmate esters in good yields. The structures and absolute configurations were determined by X-ray crystallography. Sulfide **4-16a** is a compelling example of the utility of our methodology. Its absolute stereochemistry was originally inferred by analogy to a model substrate synthesized using the same enantioselective method. From 14 mg of

the sulfide, we prepared 36 mg of the osmate ester that crystallized on the first attempt, providing conclusive experimental evidence of its proposed absolute configuration.

Alkene	Yield	Osmate	mp
 **4-12a** achiral oil	59%	 **4-12b**	135 °C (dec)
 **4-13a** achiral oil	60%	 **4-13b**	100-103 °C
4-14a enantiopure oil	85%	 **4-14b**	180 °C (dec)
 **4-15a** racemic oil	93%	 **4-15b**	87-92 °C
 **4-16a** enantiopure oil	91%	 **4-16b**	170 °C (dec)
 **4-17a** enantiopure solid mp = 59-63 °C	97%	 **4-17b**	231 °C (dec)

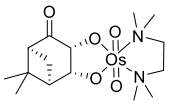
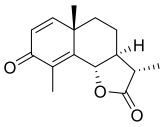
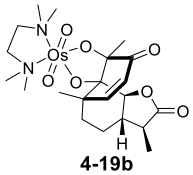
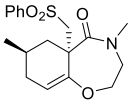
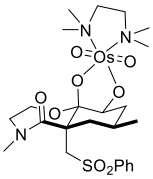
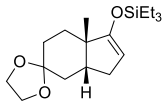
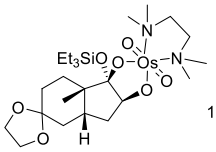
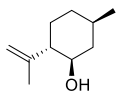
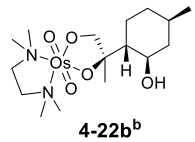
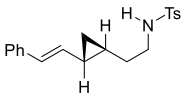
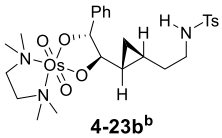
Alkene	Yield	Osmate	mp
4-18a enantiopure oil	81%	 **4-18b**	192 °C (dec)
 **4-19a** enantiopure solid mp = 172 °C	87%	 **4-19b**	202 °C (dec)
 **4-20a** racemic oil	76%	 **4-20b**	182–185 °C
 **4-21a** enantiopure oil	-	 **4-21b**	170 °C (dec)
 **4-22a** enantiopure oil	87% 1.3:1 dr	 **4-22b**[b]	84–87 °C
 **4-23a** racemic oil	68% 2.4:1 dr	 **4-23b**[b]	90-93 °C

Table 4-1 Alkenes and derived crystalline osmate-TMEDA esters

Verbenone (**4-18a**), an oil, and the solid dienone α-santonin (**4-19a**) were both osmylated and the adducts readily crystallized, highlighting the method's applicability to electron deficient alkenes. The chemoselectivity of the OsO_4/TMEDA system in the osmylation of α-santonin was notable,

as a lack of selectivity could lead to lower yields and perhaps necessitate further purification.[141] The selectivity of OsO_4 additions has been extensively documented.[142]

Alkene **4-17a**[143] reacted with the osmium complex selectively and the adduct **4-17b** crystallized readily. Initially the crystals were twinned, but changing solvents resulted in untwinned crystals. X-ray crystallographic analysis resulted in a full structure with absolute configuration.

The dihydroxylation of enol ethers and silyl enol ethers typically leads to isolation of alpha hydroxy ketones.[144] We sought to investigate whether the osmate esters of these motifs would be kinetically stable and crystalline. Enol ether **4-20a** formed a stable, crystalline osmate ester. Even silyl enol ether **4-21a** formed a moderately stable osmate ester. While we did note some unidentified decomposition over time, the TES ether osmate **4-21b** could be crystallized directly from the crude reaction mixture, without prior chromatography.[145]

One drawback of the functionalization of alkenes is the possible generation of diastereomers. Initially, we investigated substrates that gave high diastereoselectivity. In theory a single diastereomer could be selectively crystallized out of a mixture, but we did not have much success with roughly equimolar mixtures of diastereomeric osmates. However, we were able to separate diastereomeric osmates when the osmate group was proximal to the other stereocenters. Thus, (–)-isopulegol (**4-22a**) and vinylcyclopropane **4-23a** were osmylated to form diastereomeric mixtures. The diastereomers were separated by silica gel chromatography prior to crystallization.

Several alkenes did not result in useful osmate crystals, and these cases are presented in Table 4-2. Several were unreactive with OsO_4-TMEDA, including benzothiophene **4-29**. Chloroalkene **4-27a** did react, but the osmate was not stable. A few examples formed stable osmates, but did not crystallize in our hands. In the case of lanosterol **4-31a**, the osmate esters were inseparable by

chromatography. The osmate derivatization and crystallization strategy was successful for most but not all substrates.

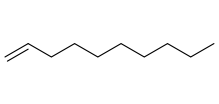
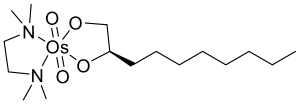
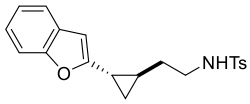
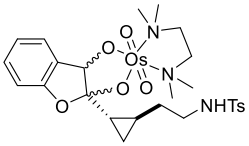
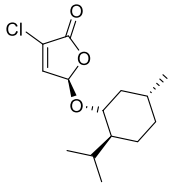
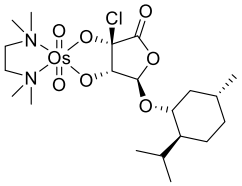
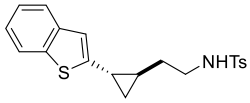
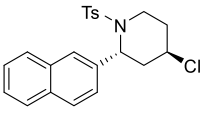
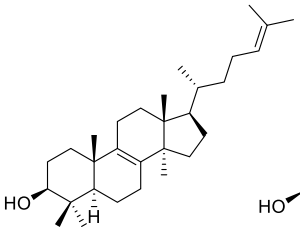
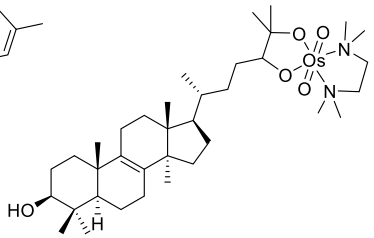
Alkene	Product	Reason for failure
 **4-24a**	 **4-24b**	Product was oil
 **4-25a**	 **4-26b**	Product was amorphous solid; it did not crystallize in our hands
 **4-27a**	 **4-28b**	Product decomposed upon purification and isolation
 **4-29**	N/A	No reaction
 **4-30**	N/A	No reaction
 **4-31a**	 **4-31b**	Product was formed in a 1:1 dr. The mixture was not separable on chromatography and did not crystallize.

Table 4-2 Table of unsuccessful substrates

4.5 Summary

Derivatization of alkenes with OsO_4-TMEDA is a mild and efficient procedure. It offers a tactically distinct alternative from traditional functionalization strategies which rely on alcohols, amines, ketones, and carboxylic acids. The examples in Table 1 demonstrate that the reaction is compatible with alcohols, cyclopropanes, ketones, sulfides, nitriles, acetals, lactones, amides, sulfones and silyl ethers. Dichloromethane is the standard solvent, but reactions run in THF and MeOH gave >80% yields from verbenone (**4-18a**), demonstrating that more polar substrates could be derivatized under these conditions. The reagents add 370 au to the alkenes. For precious samples, the increase in mass of the osmate esters simplifies crystallization.

This method has the following advantages and limitations:

1. Liquid alkenes can be converted to solid, crystalline substances suitable for x-ray crystallography.
2. The osmium contained within these complexes greatly facilitates the assignment of absolute configuration by increased anomalous scattering.
3. Due to the increased electron density of osmium, the crystals of these compounds needed for satisfactory structure assignment can be smaller and of poorer quality than those comprised of only light atom elements.
4. The osmate esters are brown, aiding in their detection within chromatographic fractions.
5. Mixtures of diastereomeric osmates can be generated. The separation and/or selective crystallization of a single diastereomeric complex can be difficult and is on a case by case basis.

4.6 Acknowledgements and contributions

Professor Scott Rychnovsky suggested using an osmium tetroxide-amine complex as a derivatization agent to obtain X-ray quality crystals of an illisimonin A intermediate. He also should be credited for proposing that this be explored as a general method for structure determination, as well as providing advice throughout these studies. Much of the literature exploration was done by him. Charles Dooley and Paul Carlson participated in the design of experiments as well as the synthesis of osmate esters. I have only included the synthesis of compounds which I made. The synthesis of the remainder of compounds was carried out by them, and is described in our communication.[146] Dr. Joseph Ziller, Sunny Sun, and Dan Huh are responsible for obtaining and solving the x-ray crystal structures of the osmate esters. I thank Ryan Davison, Kirsten A. Hewitt, Dr. Nicholas Weires, Dr. Jonathan Chung, Dr. Matthias Göhl, Nicholas Foy, and Ryan Kozlowski for providing us with alkenes for testing.

4.7 Supporting information

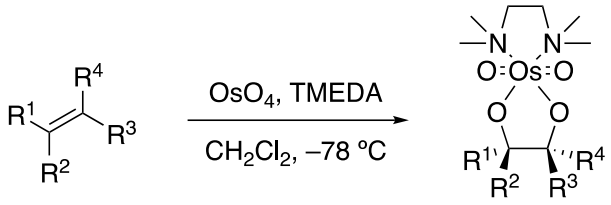
4.7.1 General information

Chemical shifts (δ) were referenced to either TMS or the residual solvent peak. The ^{1}H NMR spectra data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets, dt = doublet of tripets, dq = doublet of quartets, ddq = doublet of doublet of quartets, app. = apparent), coupling constant(s) in hertz (Hz), and integration. High-resolution mass spectrometry was performed using ESI-TOF. An internal standard was used to calibrate the exact mass of each compound. For accuracy, the peak selected for comparison was that which most closely matched the ion intensity of the internal standard. The isotope of osmium which corresponds to the nominal mass of this peak is denoted.

Unless otherwise stated, synthetic reactions were carried out under an atmosphere of argon. All commercially available reagents were used as received unless stated otherwise. Solvents were purchased as ACS grade or better and as HPLC-grade and passed through a solvent purification system equipped with activated alumina columns prior to use. Thin layer chromatography (TLC) was carried out using glass plates coated with a 250 μm layer of 60 Å silica gel. TLC plates were visualized with a UV lamp at 254 nm, or by staining with Hanessian's stain. Liquid chromatography was performed using forced flow (flash chromatography) with an automated purification system on prepacked silica gel (SiO_2) columns unless otherwise stated. Electrospray ionization mass spectrometry (ESI-MS) was analyzed in positive mode with flow injection. Optical rotations were performed on a JACSO P-1010 spectrometer using a glass 50 mm cell with the sodium D-line at 589 nm.

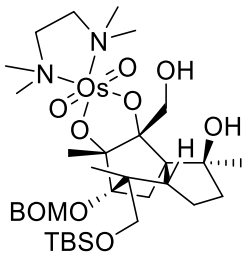
All purchased chemicals were used without further purification unless otherwise noted. $CDCl_3$ was purchased from Cambridge Isotope Laboratories. Tetramethylethane diamine (TMEDA) was distilled over calcium hydride into a storage Schlenk under an atmosphere of argon, which was stored in a desiccator. Osmium tetroxide was purchased as a pure solid from Fisher Scientific and used without further purification.

4.7.2 General procedure: osmate ester formation[147]



Reactions were set up open to air in non-flame dried glassware, and the mixture was subsequently placed under argon prior to the addition of osmium tetroxide. To a solution of alkene in dichloromethane was added TMEDA (1.1 equiv). The solution was cooled to –78 °C, and OsO_4 (1 equiv) was added as a solution in dichloromethane. Reactions were run at concentrations anywhere from 0.01–0.3 M. The clear solution turned red upon addition of OsO_4, then brown/black as the osmium complex reacted with the alkene. When the starting material was consumed as indicated by TLC (generally less than 15 min), the reaction was allowed to warm to room temperature, and the solvent was removed *in vacuo*. The crude material was purified by flash column chromatography (0 – 20% MeOH in CH_2Cl_2) to yield the brown osmate ester. The osmate esters were most often crystallized by vapor diffusion for X-ray crystallographic analysis.

4.7.3 Compound synthesis and characterization



Illisimonin osmate ester (4-1): Allylic alcohol **3-98** (27.5 mg, 0.0547 mmol) was converted to osmate **4-1** (43.1 mg, 91% yield) following the general procedure outlined above. Osmate **4-1** was a brown solid when initially concentrated down CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor Diffiusion	$CDCl_3$	Pentanes	poor quality crystals which unambiguously provided connectivity and absolute stereochemistry, but had a high degree of disorder and thermal instability
2	Vapor Diffusion	3:1 THF:CH_2Cl_2	Cyclopentane	X-ray quality crystals

R_f : 0.40 (10% MeOH in CH_2Cl_2, visualized by UV)

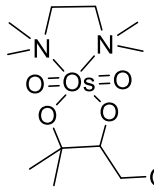
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.29 (m, 4H), 7.25–7.23 (m, 1H), 5.02 (d, *J* = 6.5 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.73 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.03 (d, *J* = 11.2 Hz, 1H), 3.77 (d, *J* = 9.8 Hz, 1H), 3.68 (d, *J* = 9.8 Hz, 1H), 3.47 (br. s, 1H), 3.13–3.02 (m, 4H), 2.87–2.84 (m, 1H), 2.84 (s, 3H), 2.82 (s, 3H), 2.81 (s, 3H), 2.79 (s, 3H), 2.06–1.98 (m, 1H), 1.92–1.81 (m, 3H), 1.76 (d, *J* = 10.1 Hz, 1H), 1.56–1.45 (m, 1H), 1.34 (s, 3H), 1.26 (s, 6H), 0.87 (s, 9H), –0.01 (s, 3H), –0.04 (s, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.6, 128.4, 127.5, 127.4, 103.8, 99.5, 94.6, 92.4, 79.2, 70.2, 68.3, 65.4, 64.6, 63.8, 61.9, 52.6, 52.4, 52.2, 51.7, 51.1, 48.6, 44.1, 34.9, 29.7, 27.5, 26.0, 21.4, 18.3, 17.3, –5.3, –5.5.

Melting Point: 186–189 °C

HRMS : *m / z* calcd for $C_{35}H_{62}N_2O_9{}^{187}OsSiNa$ $(M + Na)^+$: 892.3678, found 892.3706.

$[\alpha]^{22}_D$ –137.2 (*c* 2.39, $CDCl_3$)



3-Methylbut-2-en-1-ol osmate ester (4-12b): Prenol **4-12a** (10 mg, 0.12 mmol) was converted to osmate **4-12b** (31.1 mg, 59% yield) following the general procedure outlined above. Osmate **4-12b** was a brown foam when initially concentrated from CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor diffusion	$CHCl_3$	pentanes	X-ray quality crystals

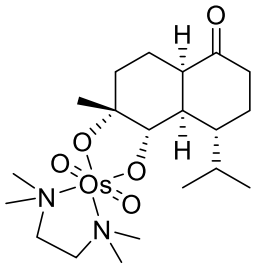
R_f : 0.37 (15% MeOH/CH_2Cl_2, UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.90 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.87 (dd, *J* = 10.1, 8.3 Hz, 1H), 3.77 (dd, *J* = 10.1, 2.6 Hz, 1H), 3.11–3.02 (m, 4H), 2.84 (s, 3H), 2.84 (s, 3H), 2.83 (s, 3H), 2.83 (s, 3H), 1.43 (s, 3H), 1.27 (s, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 94.5, 86.9, 64.7, 64.0, 63.2, 52.04, 52.03, 51.2, 51.1, 26.8, 22.1.

Melting Point: decomposed at 135 °C

HRMS *m / z* calcd for $C_{11}H_{26}N_2O_5{}^{190}OsNa$ $(M + Na)^+$: 479.1321, found 479.1329.



(±)-4-Isopropyl-6-methyl-3,4,4a,7,8,8a-hexahydronaphthalen-1(2*H*)-one osmate ester (4-15b): Ketone **4-15a**[139] (24 mg, 0.12 mmol) was converted to osmate **4-15b** (63.4 mg, 93% yield) following the general procedure outlined above. Osmate **4-15b** was a brown foam when initially concentrated from CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor diffusion	3:1 Et_2O:CH_2Cl_2	*n*-pentane	X-ray quality crystals

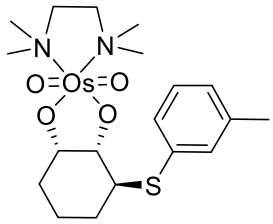
R_f : 0.32 (10% MeOH in CH_2Cl_2, visualized by UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.32 (d, *J* = 9.6 Hz, 1H), 3.14–3.07 (m, 2H), 3.00–2.91 (m, 2H), 2.81 (s, 3H), 2.78 (s, 3H), 2.82–2.70 (m, 2H), 2.74 (s, 3H), 2.72 (s, 3H), 2.69–2.64 (m, 1H), 2.32–2.23 (m, 2H), 2.20–2.08 (m, 2H), 2.02–1.88 (m, 3H), 1.87–1.79 (m, 1H), 1.52–1.44 (m, 1H), 1.24 (s, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 214.9, 90.8, 87.2, 64.3, 63.9, 52.0, 51.8, 50.9, 50.3, 45.6, 41.3, 40.9, 38.2, 32.7, 27.9, 26.5, 23.2, 22.3, 20.5, 20.0.

Melting Point: 87–92 °C

HRMS *m / z* calcd for $C_{20}H_{38}N_2O_5{}^{186}OsNa$ $(M + Na)^+$: 595.2212, found 595.2223.



(*S*)-Cyclohex-2-en-1-yl(*o*-tolyl)sulfane osmate ester (4-16b): Allylic thiol **4-16a**[140] (14 mg, 0.069 mmol) was converted to osmate **4-16b** (35.8 mg, 91% yield) following the general procedure outlined above. Osmate **4-16b** was a brown solid when initially concentrated from CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor diffusion	3:1 Et_2O:CH_2Cl_2	*n*-pentane	X-ray quality crystals

R_f: 0.44 (10% MeOH/CH_2Cl_2, UV)

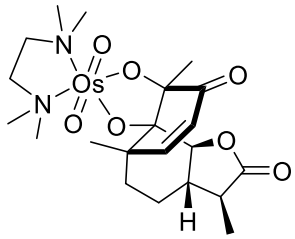
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.27 (m, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 4.49 (app. q, *J* = 4.1 Hz, 1H), 3.78–3.72 (m, 2H), 3.13–3.06 (m, 2H), 3.06–2.98 (m, 2H), 2.88 (s, 3H), 2.83 (s, 3H), 2.80 (s, 3H), 2.78 (s, 3H), 2.28 (s, 3H), 2.30–2.25 (m, 1H), 2.08–2.01 (m, 1H), 1.97 (ddt, *J* = 14.6, 11.1, 4.1 Hz, 1H), 1.69–1.60 (m, 1H), 1.60–1.52 (m, 1H), 1.51–1.42 (m, 1H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 138.1, 135.9, 133.3, 129.6, 128.4, 127.1, 89.6, 88.3, 64.5, 64.4, 52.2, 51.9, 51.3, 51.2, 48.7, 31.2, 29.8, 21.4, 20.8.

Melting Point: decomposed at 170 °C

HRMS *m / z* calcd for $C_{19}H_{32}N_2O_4{}^{186}OsSNa$ $(M + Na)^+$: 593.1514, found 593.1506.

$[\alpha]^{21}_D$ –610.4 (*c* 0.49, $CHCl_3$)



(–)-alpha-Santonin osmate ester (4-19b): (–)-alpha-Santonin **4-19a** (30 mg, 0.12 mmol) was converted to osmate **4-19b** (65.2 mg, 87% yield) following the general procedure outlined above. Osmate **4-19b** was a brown solid when initially concentrated from CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor diffusion	$CHCl_3$	pentanes	Insoluble oil
2	Vapor diffusion	1:4 CH_2Cl_2:THF	Pentanes	Very small crystals
3*	Vapor diffusion	1:4 CH_2Cl_2:THF	Pentanes	Extremely small crystals
4	Vapor diffusion	1:4 CH_2Cl_2:THF	Pentanes	X-ray quality crystals

*This trial used twice the volume of solvent as trial 2.

R_f: 0.47 (10% MeOH in CH_2Cl_2, visualized by UV)

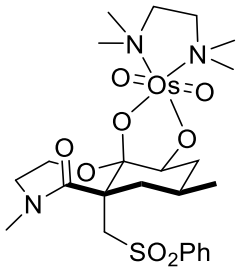
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (d, *J* = 10.4 Hz, 1H), 5.84 (d, *J* = 10.3 Hz, 1H), 4.21 (d, *J* = 12.2 Hz, 1H), 3.03–2.95 (m, 4H), 2.87 (s, 3H), 2.83 (s, 3H), 2.81 (s, 3H), 2.67 (s, 3H), 2.45 (app. qd, *J* = 12.2, 3.9 Hz, 1H), 2.16 (dq , *J* = 12.3, 6.9 Hz, 1H), 1.92 (dq, *J* = 12.7, 3.4 Hz, 1H), 1.85 (s, 3H), 1.79 (app. dd, *J* = 8.1, 3.3 Hz, 2H), 1.66–1.56 (m, 1H), 1.42 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.7, 178.9, 155.1, 124.7, 92.3, 89.2, 88.7, 64.3, 63.9, 52.0, 51.9, 51.8, 51.3, 49.0, 44.2, 41.5, 37.5, 24.6, 24.1, 22.8, 12.7.

Melting Point: decomposed at 202 °C

HRMS *m / z* calcd for $C_{21}H_{34}N_2O_7{}^{186}OsNa$ $(M + Na)^+$: 635.1797, found 635.1800.

$[\alpha]^{22}_D$ +585.1 (*c* 1.07, $CHCl_3$)



Sulfone osmate (4-20b): (±)-Sulfone **4-20a** (9.5 mg, 0.03mmol) was converted to osmate **4-20b** (14.8 mg, 76% yield) following the general procedure outlined above. Osmate **4-20b** was a brown solid when initially concentrated from CH_2Cl_2/MeOH fractions.

Crystallization attempts				
	Method	Solvent	Antisolvent	Result
1	Vapor diffusion	THF	*n*-pentane	amorphous solids
2	Vapor diffusion	$CHCl_3$	*n*-pentane	amorphous solids
3	Vapor diffusion	CH_2Cl_2	Et_2O	amorphous solids
4	Slow evaporation	3:1 PhH: CH_2Cl_2	N/A	oily solids
5	Vapor diffusion	3:1 PhH: CH_2Cl_2	Et_2O	X-ray quality crystals

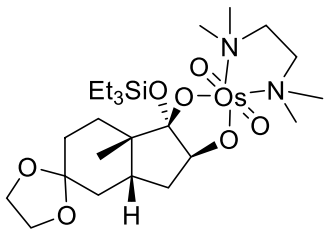
R_f : 0.55 (10% MeOH/CH_2Cl_2, UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 4.48 (d, *J* = 16.5 Hz, 1H), 4.08 (app. d, *J* = 13.4 Hz, 1H), 3.93 (app. t, *J* = 12.1 Hz, 1H), 3.70–3.65 (m, 2H), 3.60 (app. dt, *J* = 13.5, 2.3 Hz, 1H), 3.13–2.98 (m, 4H), 2.95 (s, 3H), 2.86 (s, 3H), 2.84 (s, 3H), 2.80 (s, 3H), 2.74 (s, 3H), 1.85 (app. d, *J* = 14.3 Hz, 1H), 1.63 (app. q, *J* = 12.5 Hz, 1H), 1.59–1.51 (m, 2H), 1.50–1.42 (m, 1H), 0.68 (d, *J* = 6.1 Hz, 3H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 171.6, 140.9, 133.7, 129.2, 128.5, 110.5, 90.0, 65.0, 64.0, 60.2, 56.5, 54.3, 52.5, 52.2, 52.0, 51.9, 51.3, 39.5, 37.4, 35.9, 24.4, 21.8.

Melting Point: 182–185 °C

HRMS *m / z* calcd for $C_{24}H_{39}N_3O_8{}^{192}OsSNa$ $(M + Na)^+$: 744.1965, found 744.1982.



Silyl ether osmate ester 4-21b: Silyl enol ether **4-21a** (35.3 mg, 0.109 mmol) and TMEDA (17 μL, 0.114 mmol) were dissolved in 3:1 Et_2O:CH_2Cl_2 (0.5 mL), and cooled to –78 °C. 0.36 M OsO_4 in 3:1 Et_2O:CH_2Cl_2 (0.30 mL, 0.109 mmol) was added. After 30 min, the reaction was allowed to warm to room temperature. The crude reaction mixture was filtered through a 0.45 μm nylon filter into an uncapped, clean dram vial, placed in a larger scintillation vial. *n*-Pentane was placed in the outer vial, and the scintillation vial was sealed. After letting the vapor diffuse into the inner chamber overnight, crystals had formed which were submitted for X-ray diffraction.

R_f : 0.49 (10% MeOH in CH_2Cl_2, visualized by UV)

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.83 (d, *J* = 7.7 Hz, 1H), 4.00-3.91 (m, 2H), 3.85 (app. t, *J* = 6.1 Hz, 2H), 3.13–3.06 (m, 2H), 3.05–2.99 (m, 2H), 2.83 (s, 3H), 2.80 (s, 3H), 2.77 (s, 6H), 2.71 (td, *J* = 13.2, 7.7 Hz, 1H), 2.27 (dt, *J* = 12.8, 6.5 Hz, 1H), 1.86–1.79 (m, 1H), 1.73 (dd, *J* = 14.3, 5.8 Hz, 1H), 1.65–1.59 (m, 3H), 1.56 (app. d, *J* = 14.3 Hz, 1H), 1.48 (app. d, *J* = 14.3 Hz, 1H), 1.03 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.71–0.61 (m, 6H).

^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 123.8, 109.6, 97.2, 64.5, 64.4, 63.9, 63.4, 51.8, 51.7, 51.17, 51.15, 48.8, 42.8, 36.5, 33.6, 31.3, 29.8, 16.9, 7.5 (3C), 6.2 (3C).

Melting Point: decomposed at 170 °C

HRMS *m / z* calcd for $C_{24}H_{48}N_2O_7{}^{186}OsSiNa$ $(M + Na)^+$: 713.2662, found 713.2667.

$[\alpha]^{22}_D$ –52.4 (*c* 1.66, $CDCl_3$)

4.7.4 Suggested starting point:

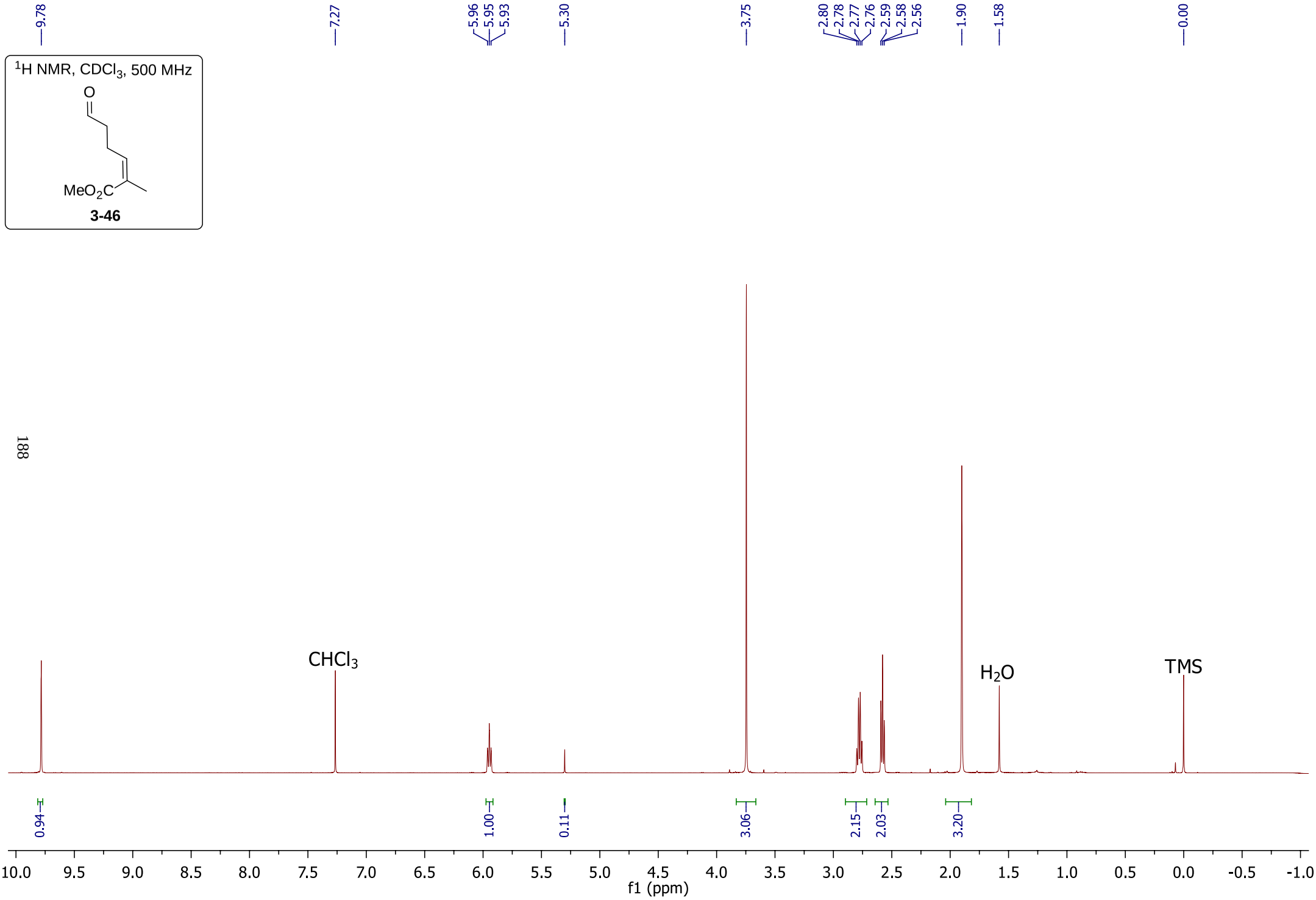
If you are interested in utilizing this methodology to crystallize a substrate, we suggest performing the reaction on 10-20 mg of substrate in dichloromethane, as shown in the general procedure. The osmate esters are generally very soluble in dichloromethane and chloroform, but these solvents are more likely to lead to non-crystalline products in attempted crystallizations. We found that crystallization solvents employing ether or THF were generally more likely to lead to x-ray quality crystals than those that only used CH_2Cl_2 or chloroform. We suggest the following starting procedure for crystallization:

Dissolve ca. 30 mg purified osmate ester in CH_2Cl_2, and filter into a clean dram vial. Remove the solvent in vacuo. Add CH_2Cl_2 (100 μL) until substance has dissolved. Add Et_2O (300 μL) for less polar substances, or THF (300 μL) for more polar substances. Make sure the compound is still soluble in the mixture. Place the dram vial in a scintillation vial and add n-pentane (faster crystallization) or cyclopentane (slower crystallization) to the outer chamber. Seal the chamber, and place in a relatively vibrationless area. Check after 3 hours up to 4 days later. For sensitive substrates, we suggest performing the reaction in the same manner as compound **4-21b**.

4.8 References

[125] Burns, A. S.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2019**, *141*, 13295–13300.
[126] (a) Ma, S.-G.; Li, M.; Lin, M.-B.; Li, L.; Liu, Y.-B.; Qu, J.; Li, Y.; Wang, X.-J.; Wang, R.-B.; Xu, S.; Hou, Q.; Yu, S.-S. *Org. Lett.* **2017**, *19*, 6160−6163. (b) Kouno, I.; Mori, K.; Okamoto, S.; Sato, S. *Chem. Pharm. Bull.* **1990**, *38*, 3060−3063. (C) Schmidt, T. J.; Müller, E.; Fronczek, F. R. *J. Nat. Prod*. **2001**, *64*, 411−414.
[127] Holstein, P. M.; Holstein, J. J.; Escudero-Adán, E. C.; Baudoin, O.; Echavarren, A. M. *Tetrahedron Asymm.* **2017**, *28*, 1321–1329.
[128] Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876–881.
[129] (a) Hooft, R. W. W.; Straver, L. H.; Spek, A. L. *J. Appl. Cryst.* **2008***, 41,* 96–103. (b) Parsons, S.; Wagner, T.; Presly, O.; Wood, P. A.; Cooper, R. I. *J. Appl. Cryst.* **2012***, 45,* 417–429.
[130] (a) Flack, H. D.; Bernardinelli, G. *Chirality* **2008**, *20*, 681–690. (b) Parsons, S. *Tetrahedron Asymmetry* **2017**, *28*, 1304–1313.

[131] Inokuma, Y.; Yoshioka, S.; Ariyoshi, J.; Arai, T.; Hitora, Y.; Takada, K.; Matsunaga, S.; Rissanen, K.; Fujita, M. *Nature* **2013**, *495*, 461–466.
[132] Boese, R. *Z. Kristallog.* **2014***, 229,* 595–601.
[133] (a) Holstein, P. M.; Holstein, J. J.; Escudero-Adán, E. C.; Baudoin, O.; Echavarren, A. M. *Tetrahedron Asymm.* **2017**, *28*, 1321–1329. (b) Shibata, T.; Arai, Y.; Takami, K.; Tsuchikama, K.; Fujimoto, T.; Takebayashi, S.; Takagi, K. *Adv. Synth. Catal*. **2006**, *348*, 2475–2483.
[134] Hawkins, J. M.; Meyer, A.; Lewis, T. A.; Loren, S.; Hollander, F. J. *Science* **1991**, *252*, 312–313.
[135] (a) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946–7956. (b) Donohoe, T. J.; Blades, K.; Helliwell, M.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett*. **1998**, *39*, 8755–8758. (c) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Org. Biomol. Chem.* **2003**, *1*, 2173–2186. (d) Prangé, T.; Pascard, C. *Acta Crystallogr. Sect. B* **1977**, *33*, 621–623. (e) Wallis, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 8207–8223. (f) Groy, T. L.; Hartman, R. F.; Rose, S. D. *Acta Crystallogr. Sect. C* **1991***, 47,* 273–275. (g) Herrmann, W. A.; Eder, S. J.; Scherer, W. *Angew. Chem. Int. Ed.* **1992**, *31*, 1345–1347. (h) Herrmann, W. A.; Roesky, P. W.; Elison, M.; Artus, G.; Oefele, K.. *Organometallics* **1995**, *14*, 1085–1086.
[136] (a) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573–576. (b) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834–5835. (c) Pearlstein, R. M.; Blackburn, B. K.; Davis, W. M.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1990**, *29*, 639–641. (d) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sanceau, J. Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991–1993. (e) Donohoe, T. J.; Harris, R. M.; Butterworth, S.; Burrows, J. N.; Cowley, A.; Parker, J. S. *J. Org. Chem.* **2006**, *71*, 4481–4489.
[137] (a) Conn, J. F.; Kim, J. J.; Suddath, F. L.; Blattmann, P.; Rich, A. *J. Am. Chem. Soc.* **1974**, *96*, 7152–7153. (b) Umemoto, T.; Okamoto, A. *Org. Biomol. Chem.* **2008**, *6*, 269–271. (c) Sugizaki, K.; Ikeda, S.; Yanagisawa, H.; Okamoto, A. *Org. Biomol. Chem.* **2011**, *9*, 4176–4176.
[138] (a) Conn, J. F.; Kim, J. J.; Suddath, F. L.; Blattmann, P.; Rich, A. *J. Am. Chem. Soc.* **1974**, *96*, 7152–7153. (b) Umemoto, T.; Okamoto, A. *Org. Biomol. Chem.* **2008**, *6*, 269–271. (c) Sugizaki, K.; Ikeda, S.; Yanagisawa, H.; Okamoto, A. *Org. Biomol. Chem.* **2011**, *9*, 4176–4176.
[139] Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992–3993.
[140] Yang, X.-H.; Davison, R.; Dong, V. M. *J. Am. Chem. Soc.* **2018**, *140*, 10443.
[141] The reactivity of the tetrasubstituted alkene in □-santonin has previously been noted for the dihydroxylation with potassium permanganate: Paknikar, S. K.; Malik, B. L.; Bates, R. B.; Caldera, S.; Wijayaratne, T. V. *Tetrahedron Lett.* **1994**, *35*, 8117–8118.
[142] (a) Schroeder, M. *Chem. Rev.* **1980**, *80*, 187–213. (b) Donohoe, T. J.; Bataille, Carole J. R.; Innocenti, P. *Org. React.* **2012**, *76*, 1–48.
[143] Slutskyy, Y.; Jamison, C. R.; Zhao, P.; Lee, J.; Rhee, Y. H.; Overman, L. E. *J. Am. Chem. Soc*. **2017**, *139*, 7192–7195.
[144]McCormick, J. P.; Tomasik, W.; Johnson, M. W *Tetrahedron Lett.* **1981**, *22*, 607–610.
[145] There was some disorder in the crystal structure of **4-21b** for the TES and TMEDA alkyl groups. The absolute and relative structure of the core was unambiguous.
[146] Burns, A. S.; Dooley III, C.; Carlson, P. R.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2019**, *21*, 10125–10129.
[147] Donohoe, T. J.; Blades, K.; Helliwell, M.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett*. **1998**, *39*, 8755–8758.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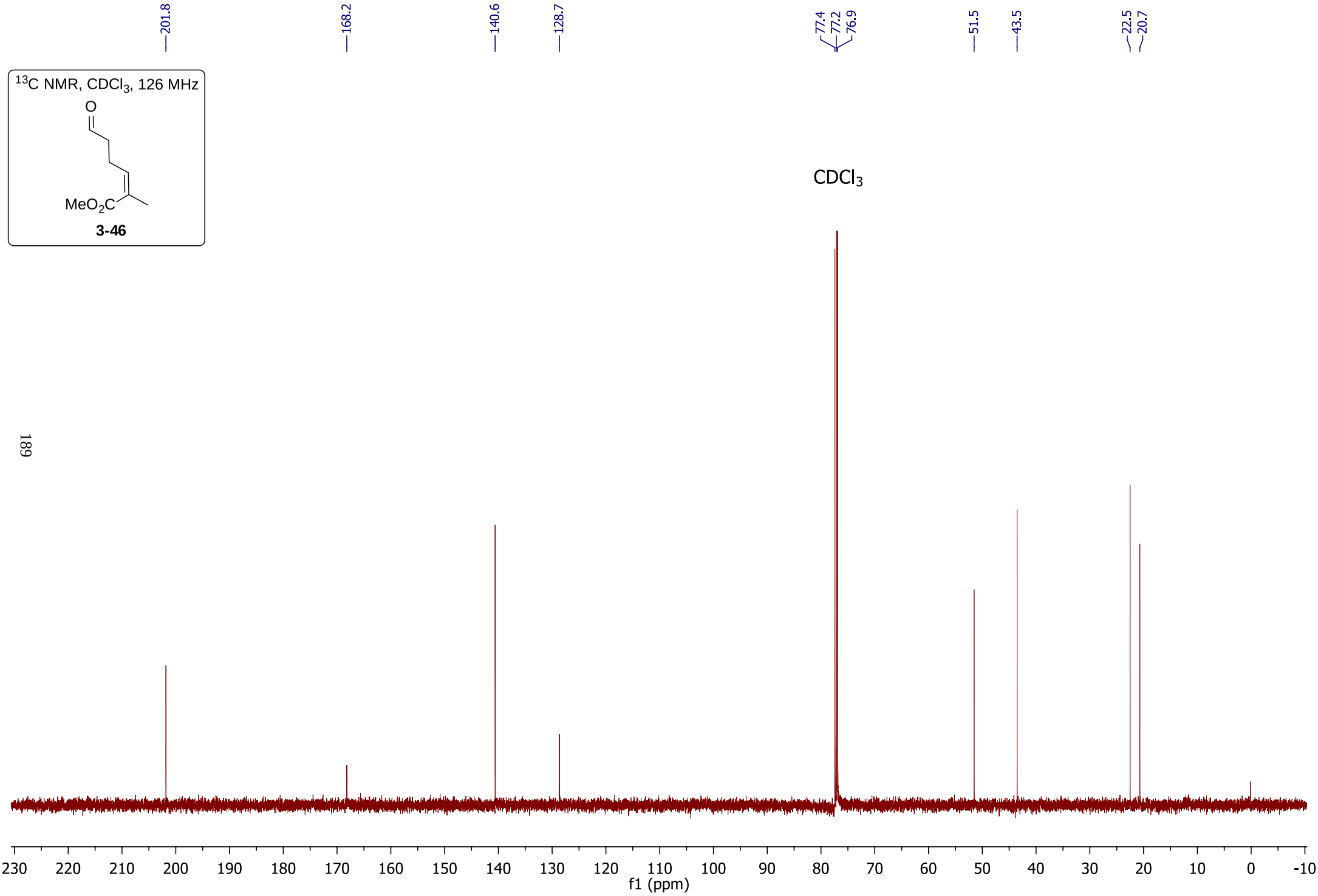
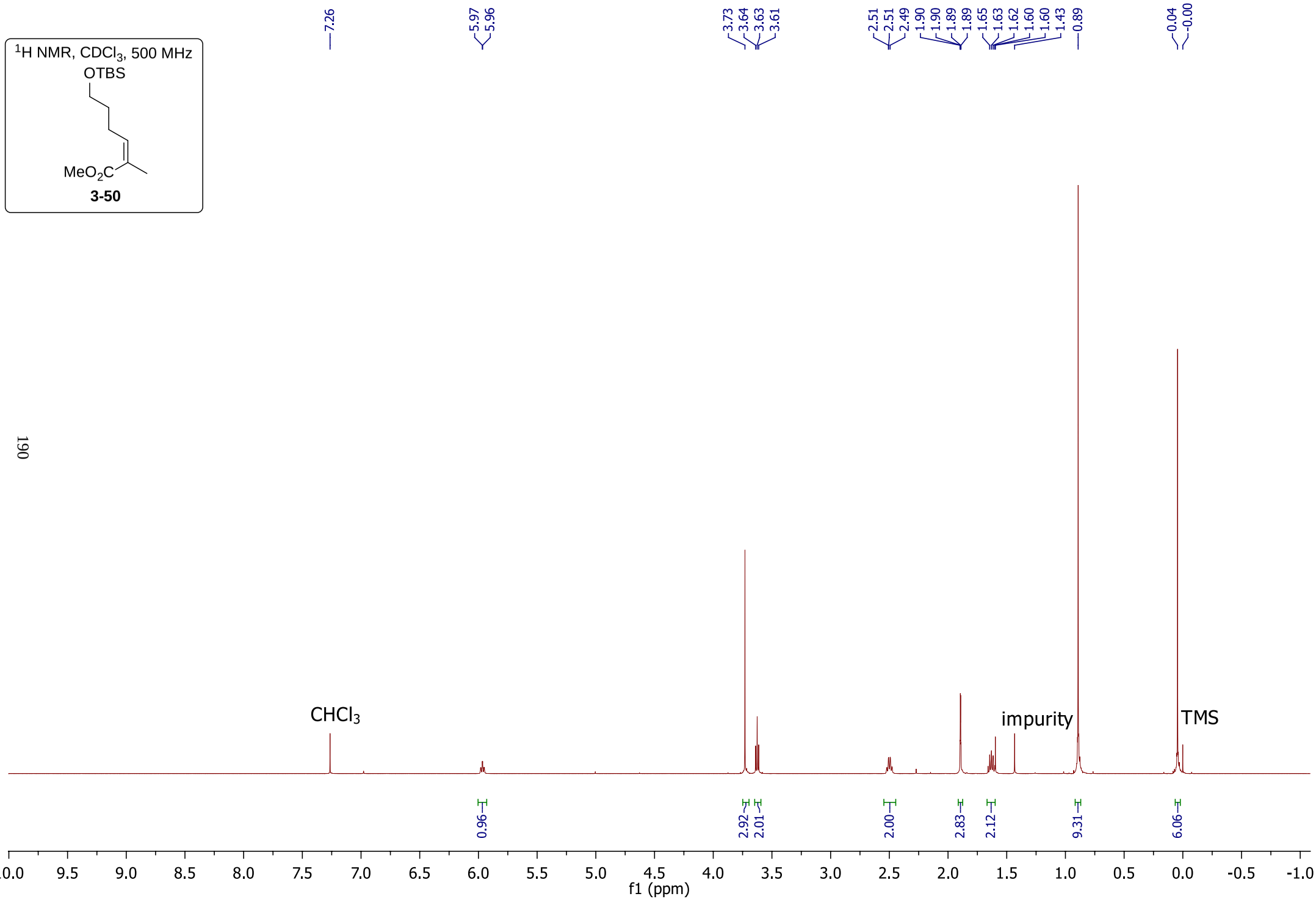
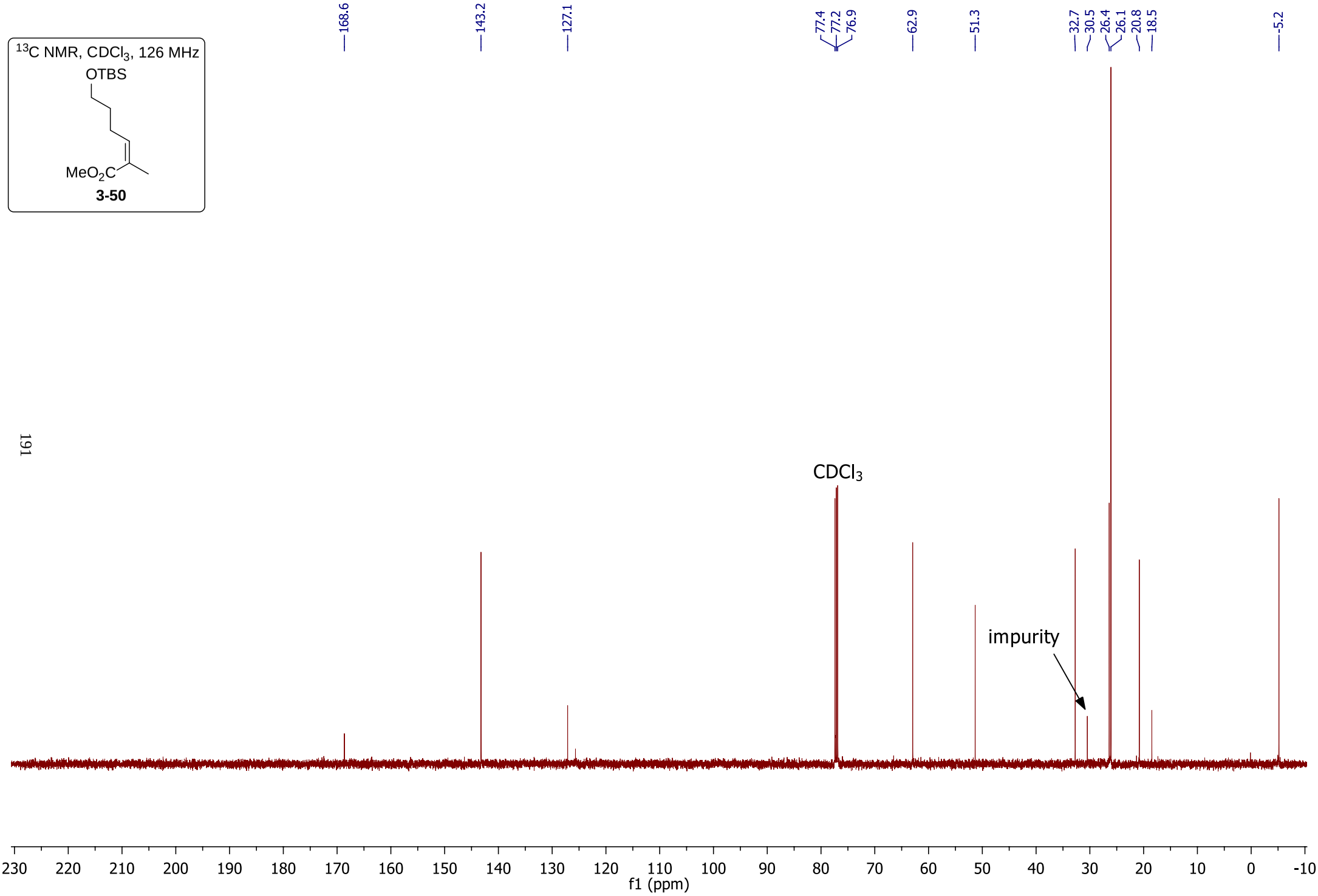
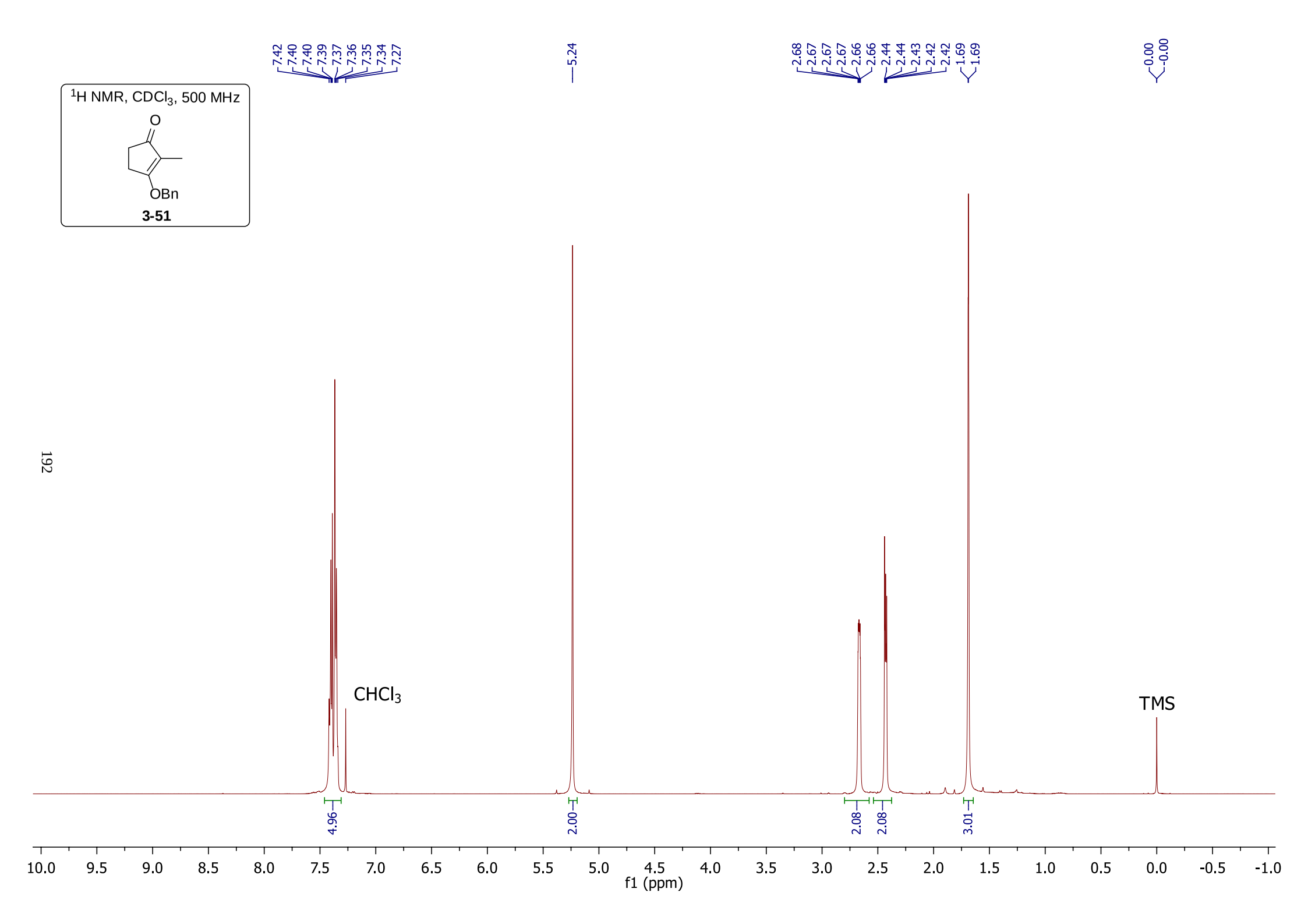
7.27
5.96
5.95
5.93
5.30
3.75
2.80
2.78
2.77
2.76
2.59
2.58
2.56
1.90
1.58
0.00
^{1}H NMR, $CDCl_3$, 500 MHz
O
MeO_2C
3-46
188
$CHCl_3$
H_2O
TMS
0.94
1.00
0.11
3.06
2.15
2.03
3.20
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


201.8
168.2
140.6
128.7
77.4
77.2
76.9
51.5
43.5
22.5
20.7
^{13}C NMR, $CDCl_3$, 126 MHz
O
MeO_2C
3-46
$CDCl_3$
189
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


^{1}H NMR, $CDCl_3$, 500 MHz
OTBS
MeO_2C
3-50
7.26
5.97
5.96
3.73
3.64
3.63
3.61
2.51
2.51
2.49
1.90
1.90
1.89
1.89
1.65
1.63
1.62
1.60
1.60
1.43
0.89
0.04
-0.00
190
$CHCl_3$
impurity
TMS
0.96
2.92
2.01
2.00
2.83
2.12
9.31
6.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


^{13}C NMR, $CDCl_3$, 126 MHz
OTBS
MeO_2C
3-50
168.6
143.2
127.1
77.4
77.2
76.9
62.9
51.3
32.7
30.5
26.4
26.1
20.8
18.5
-5.2
$CDCl_3$
impurity
f1 (ppm)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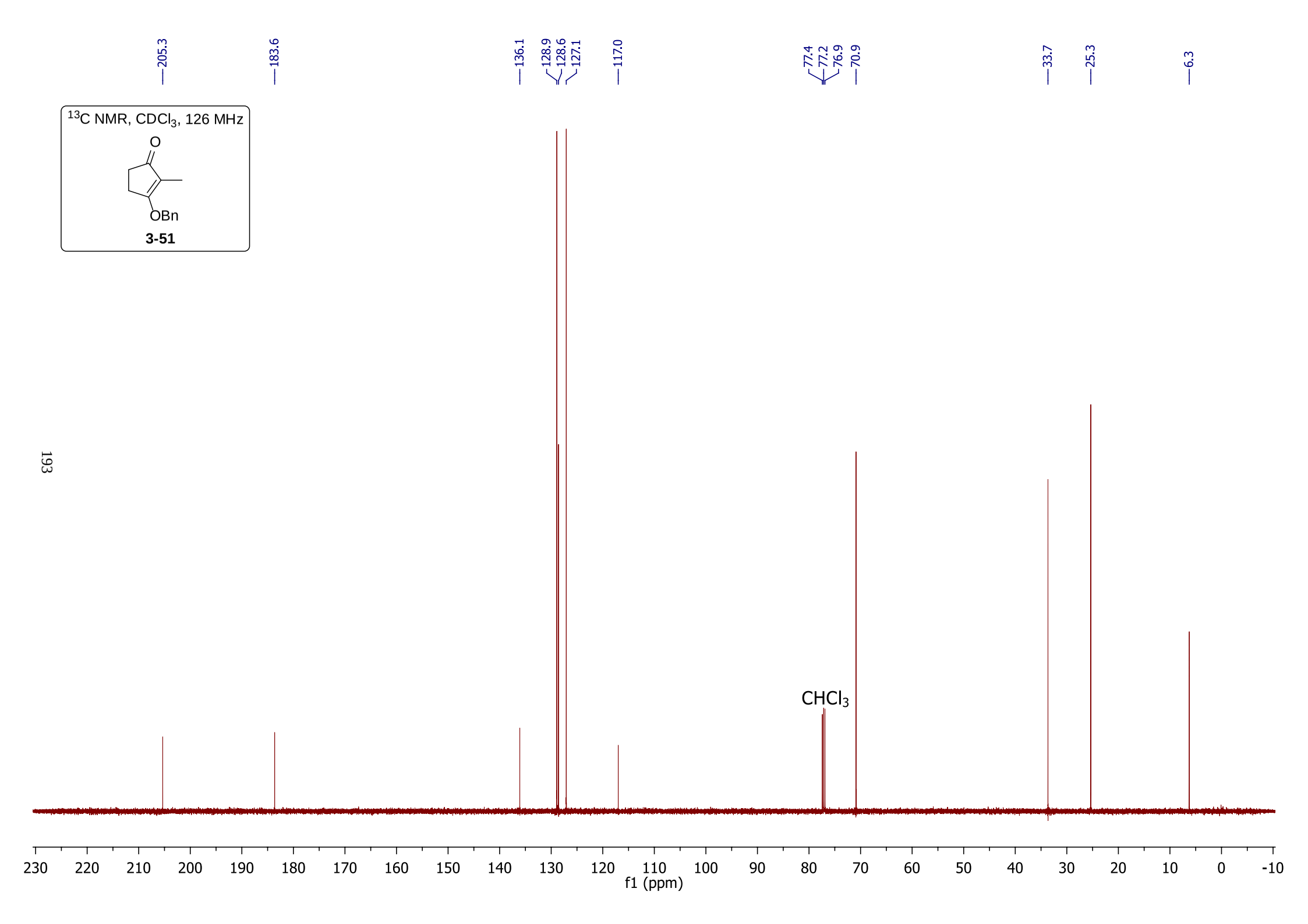
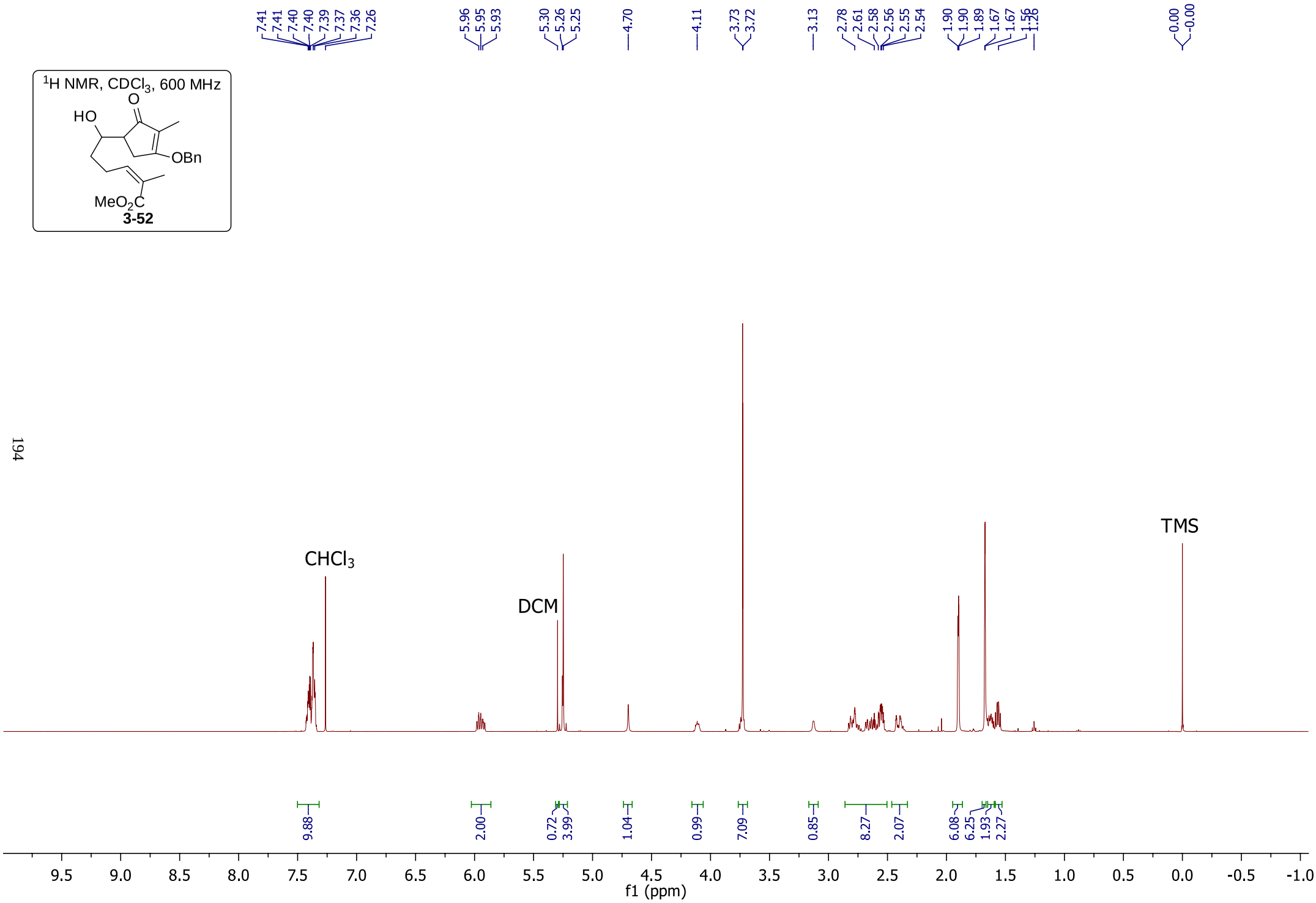
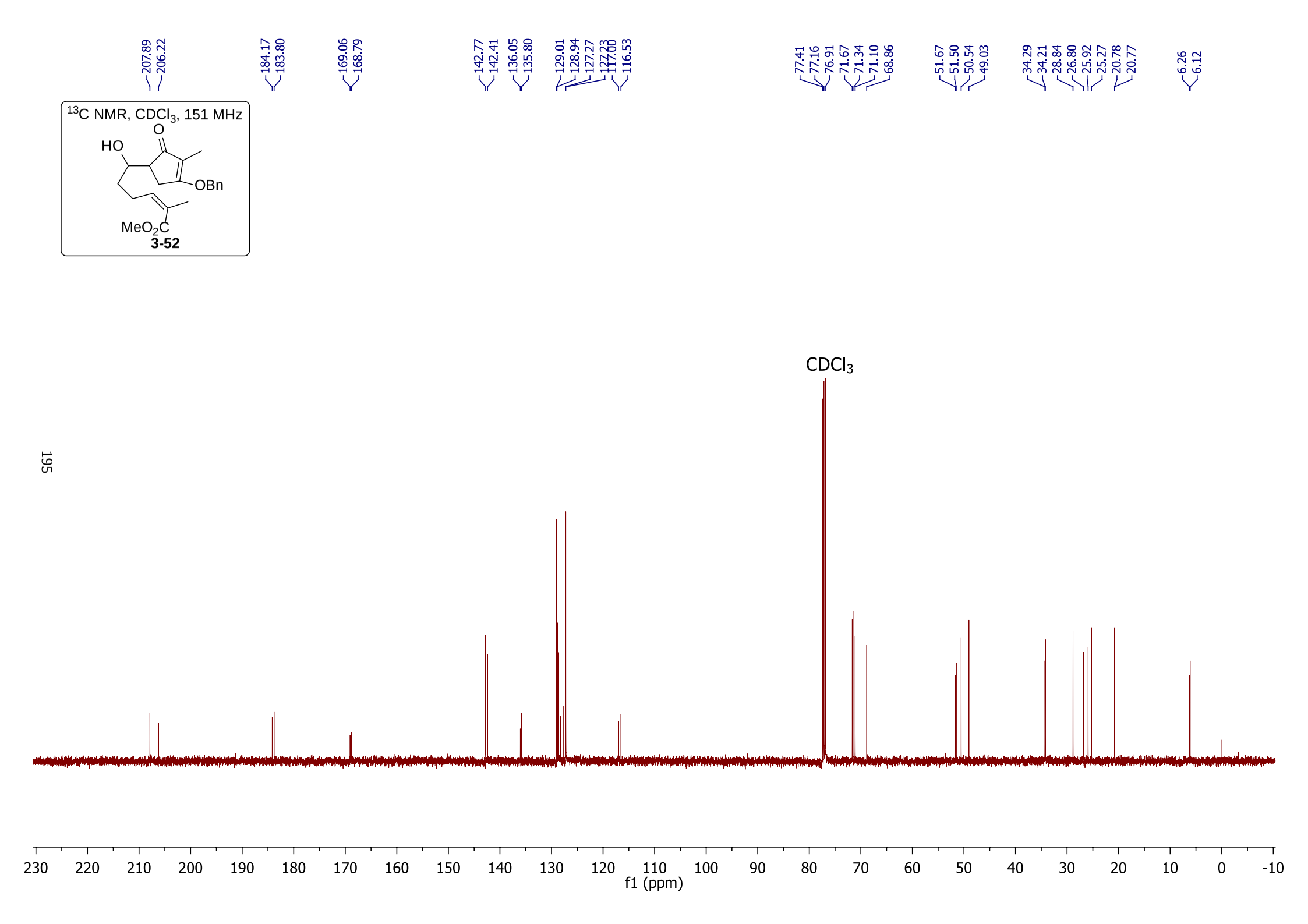
7.40
7.39
7.37
7.36
7.35
7.34
7.27
5.24
2.68
2.67
2.67
2.67
2.66
2.66
2.44
2.44
2.43
2.42
2.42
1.69
1.69
0.00
-0.00
^{1}H NMR, $CDCl_3$, 500 MHz
O
OBn
3-51
192
$CHCl_3$
TMS
4.96
2.00
2.08
2.08
3.01
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


205.3
183.6
136.1
128.9
128.6
127.1
117.0
77.4
77.2
76.9
70.9
33.7
25.3
6.3
13C NMR, CDCl3, 126 MHz
O
OBn
3-51
193
CHCl3
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

^{1}H NMR, $CDCl_3$, 600 MHz

3-52

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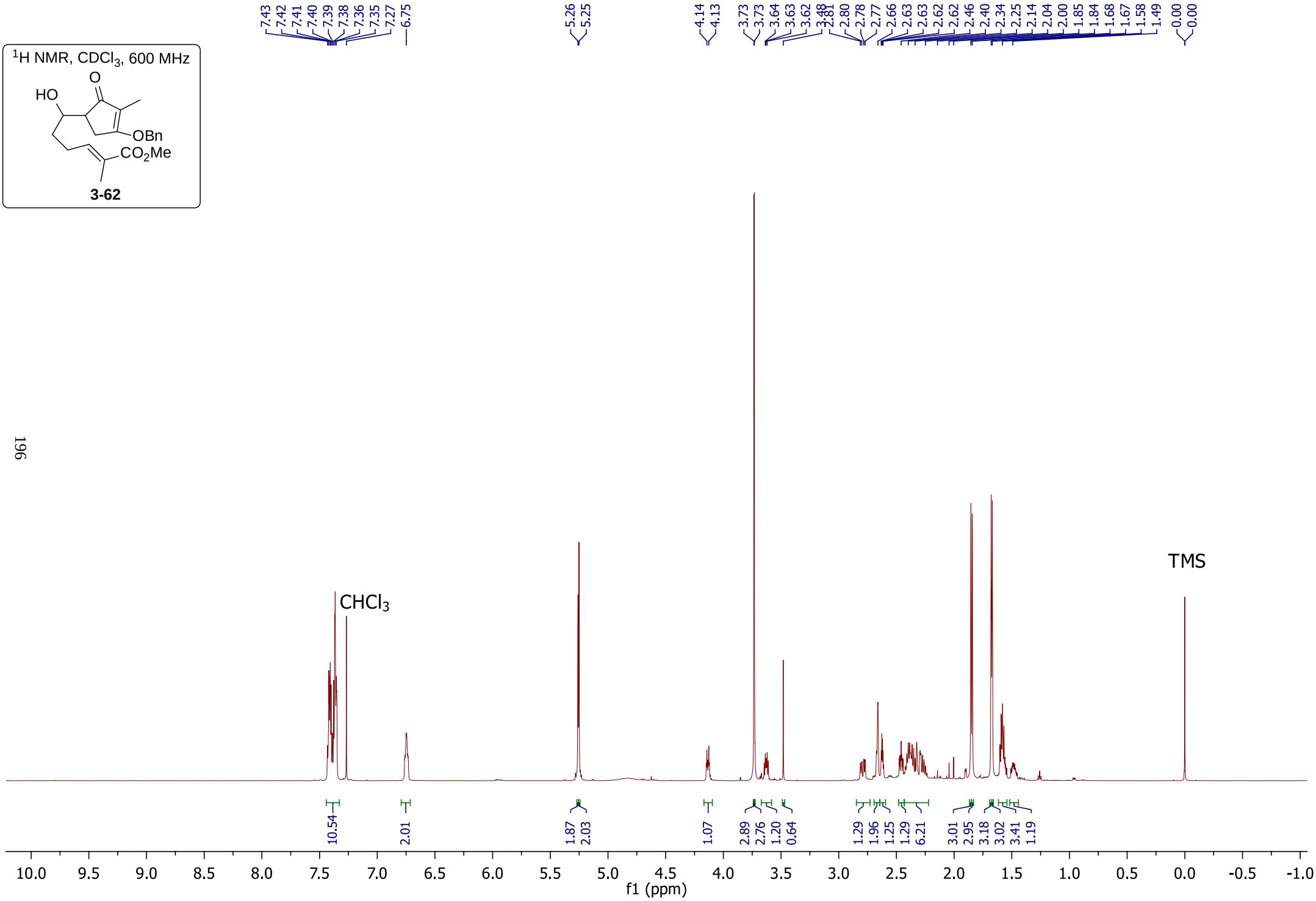
184.17
183.80
169.06
168.79
142.77
142.41
136.05
135.80
129.01
128.94
127.27
127.23
117.00
116.53
77.41
77.16
76.91
71.67
71.34
71.10
68.86
51.67
51.50
50.54
49.03
34.29
34.21
28.84
26.80
25.92
25.27
20.78
20.77
6.26
6.12
13C NMR, CDCl3, 151 MHz
HO
O
OBn
MeO2C
3-52
CDCl3
195
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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6.75
5.26
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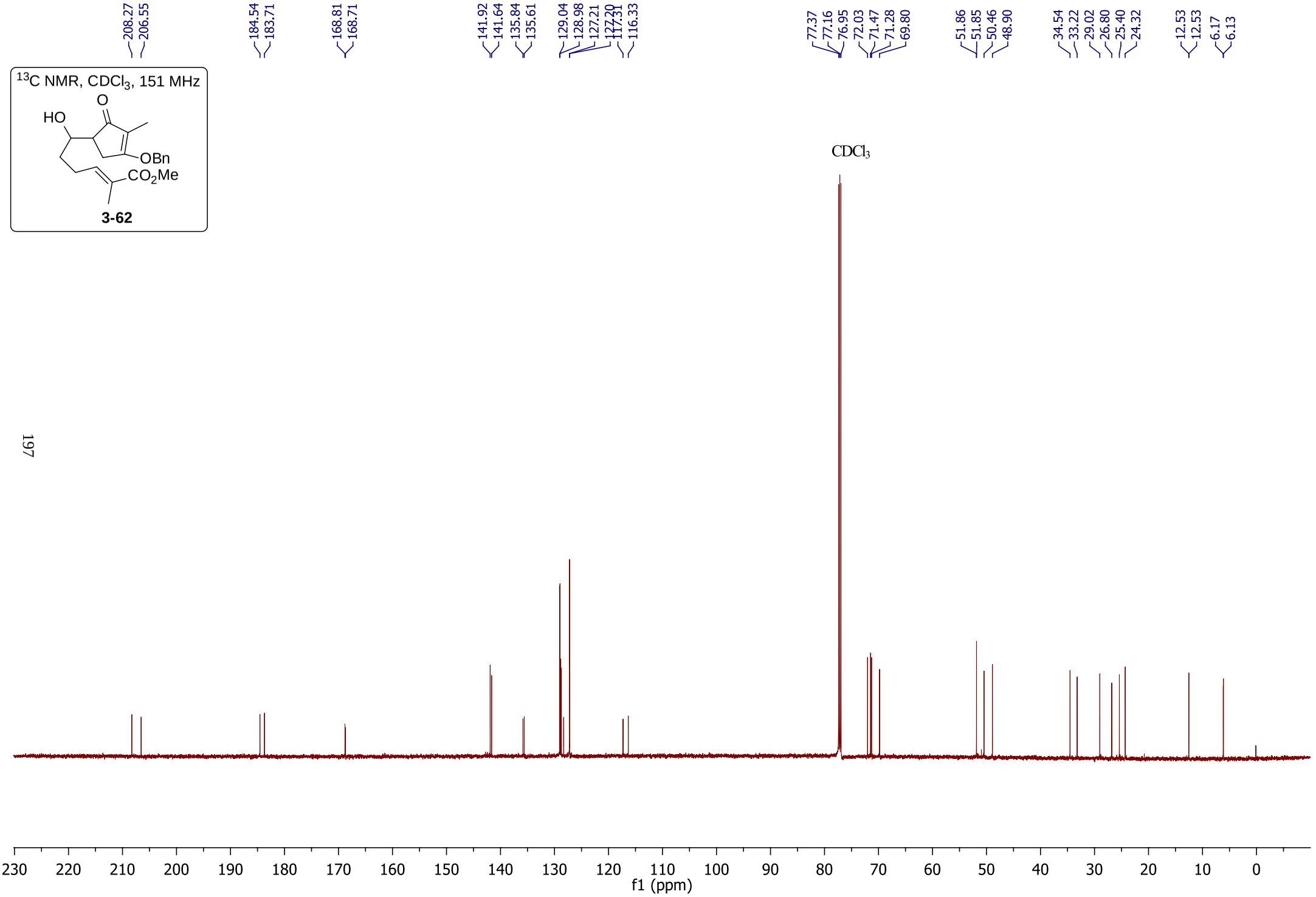
4.14
4.13
3.73
3.73
3.64
3.63
3.62
3.48
2.81
2.80
2.78
2.77
2.66
2.63
2.63
2.62
2.62
2.46
2.40
2.34
2.25
2.14
2.04
2.00
1.85
1.84
1.68
1.67
1.58
1.49
0.00
0.00
1H NMR, CDCl3, 600 MHz
HO
O
OBn
CO2Me
3-62
CHCl3
TMS
10.54
2.01
1.87
2.03
1.07
2.89
2.76
1.20
0.64
1.29
1.96
1.25
1.29
6.21
3.01
2.95
3.18
3.02
3.41
1.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)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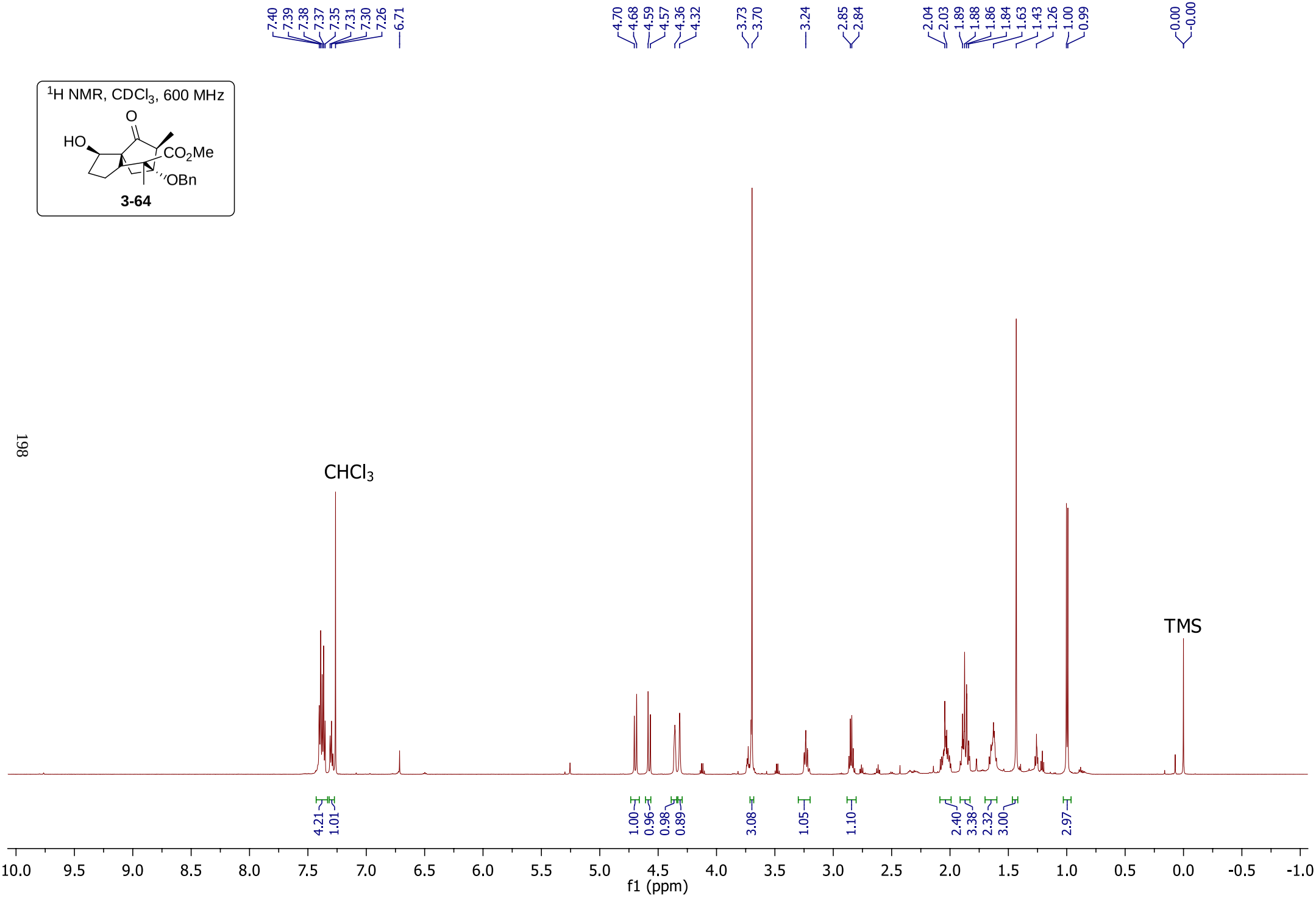
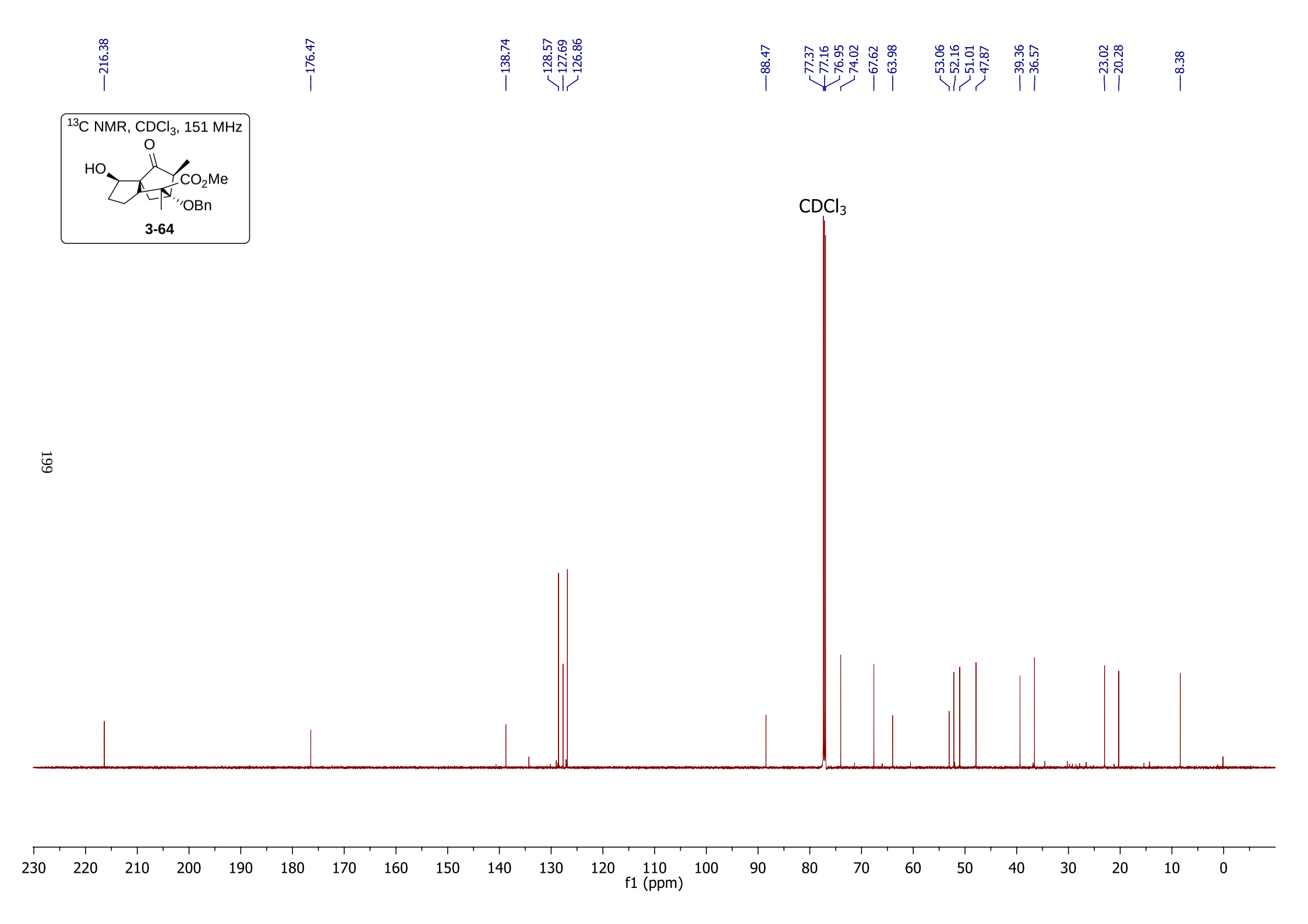
184.54
183.71
168.81
168.71
141.92
141.64
135.84
135.61
129.04
128.98
127.21
127.20
117.31
116.33
77.37
77.16
76.95
72.03
71.47
71.28
69.80
51.86
51.85
50.46
48.90
34.54
33.22
29.02
26.80
25.40
24.32
12.53
12.53
6.17
6.13
13C NMR, CDCl3, 151 MHz
HO
O
OBn
CO2Me
3-62
CDCl3
197
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

^{1}H NMR, $CDCl_3$, 600 MHz

3-64

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176.47
138.74
128.57
127.69
126.86
88.47
77.37
77.16
76.95
74.02
67.62
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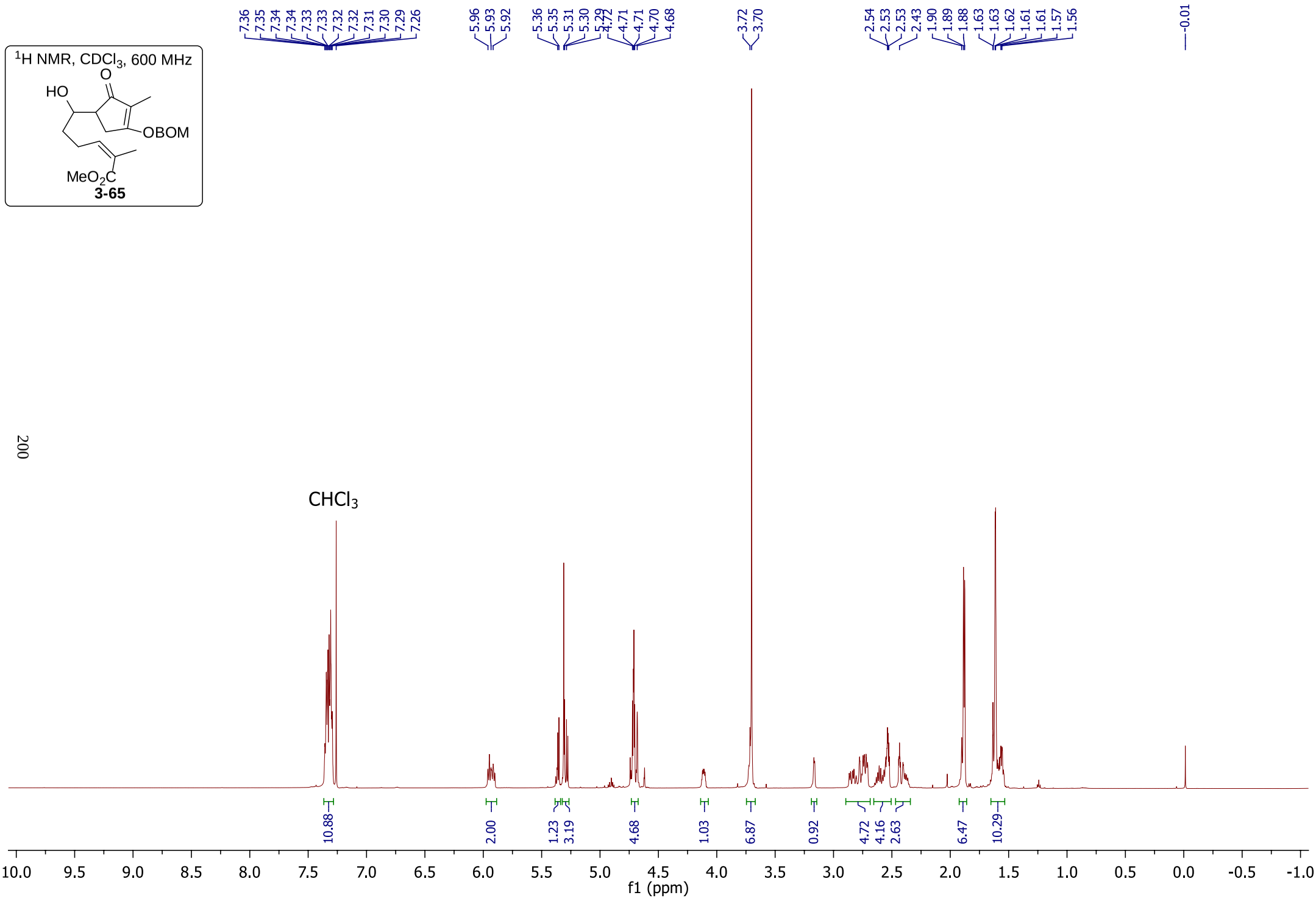
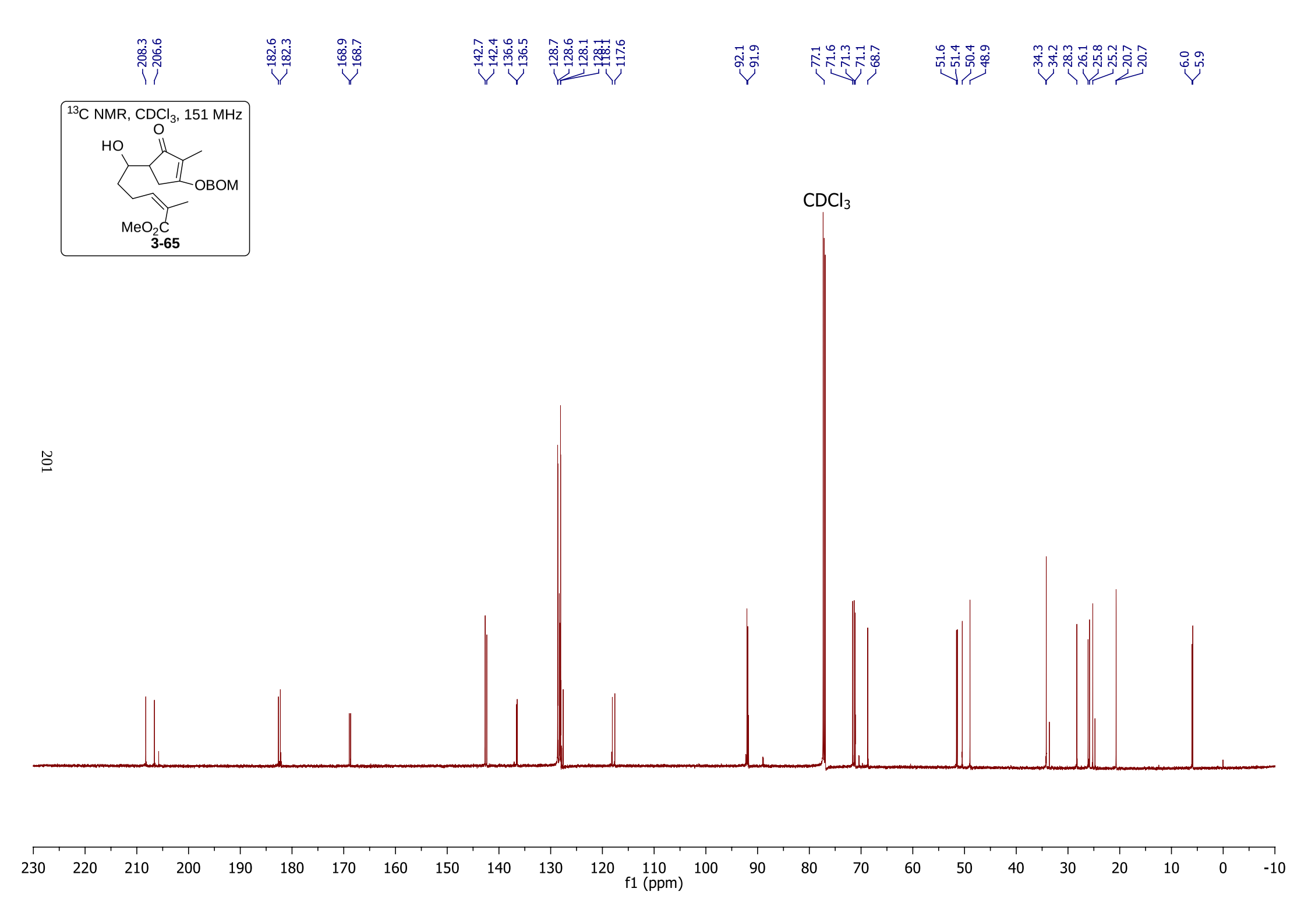
53.06
52.16
51.01
47.87
39.36
36.57
23.02
20.28
8.38
13C NMR, CDCl3, 151 MHz
HO
O
CO2Me
OBn
3-64
CDCl3
199
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


^{1}H NMR, $CDCl_3$, 600 MHz
HO
O
OBOM
MeO_2C
3-65
7.36 7.35 7.34 7.34 7.33 7.33 7.32 7.32 7.31 7.30 7.29 7.26
5.96 5.93 5.92
5.36 5.35 5.31 5.30 5.29 4.72 4.71 4.71 4.70 4.68
3.72 3.70
2.54 2.53 2.53 2.43 1.90 1.89 1.88 1.63 1.63 1.62 1.61 1.61 1.57 1.56
-0.01
200
$CHCl_3$
10.88 2.00 1.23 3.19 4.68 1.03 6.87 0.92 4.72 4.16 2.63 6.47 10.29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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206.6
182.6
182.3
168.9
168.7
142.7
142.4
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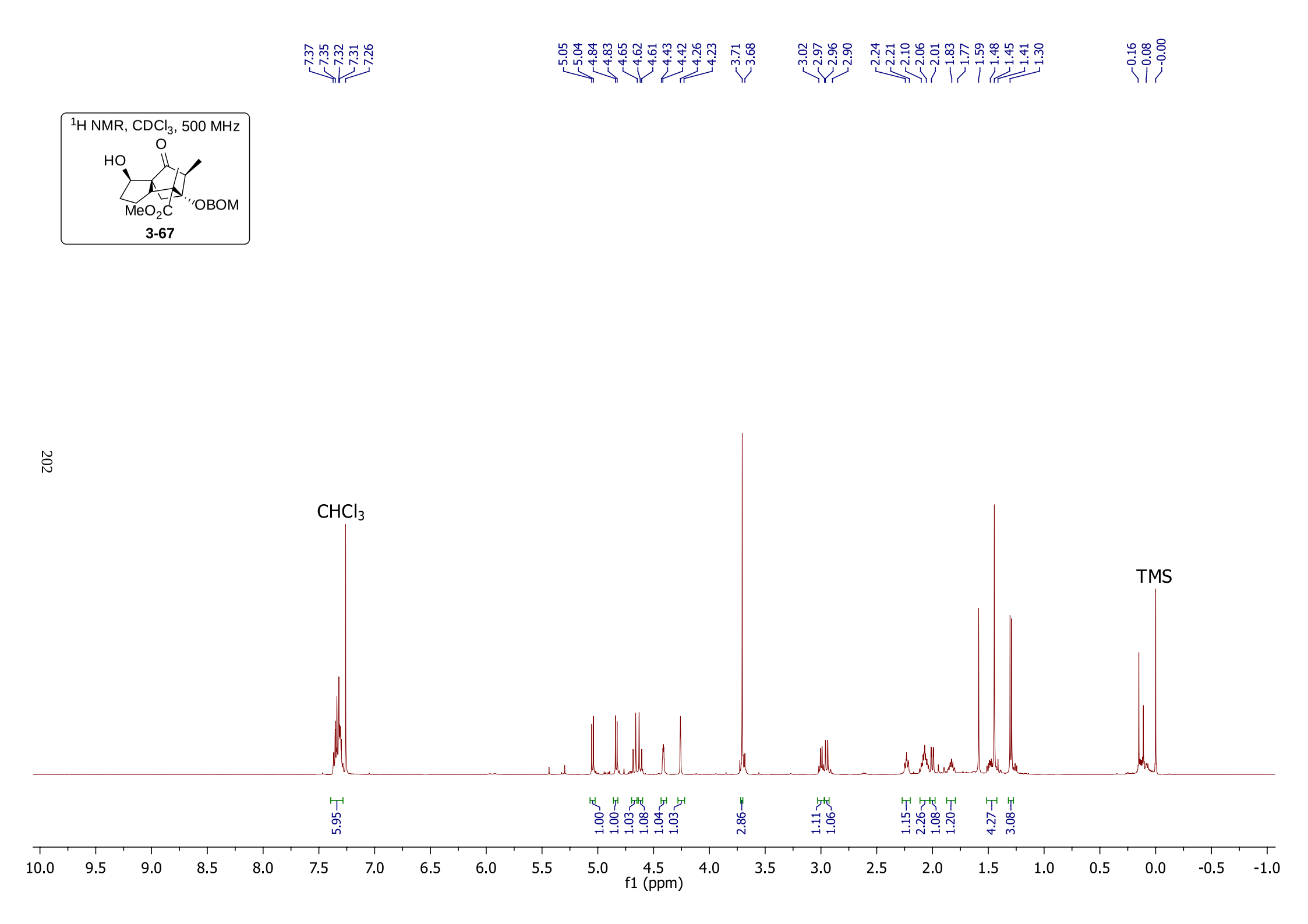
136.5
128.7
128.6
128.1
118.1
117.6
92.1
91.9
77.1
71.6
71.3
71.1
68.7
51.6
51.4
50.4
48.9
34.3
34.2
28.3
26.1
25.8
25.2
20.7
20.7
6.0
5.9
^{13}C NMR, $CDCl_3$, 151 MHz
HO
O
OBOM
MeO_2C
3-65
$CDCl_3$
201
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.37
7.35
7.32
7.31
7.26
5.05
5.04
4.84
4.83
4.65
4.62
4.61
4.43
4.42
4.26
4.23
3.71
3.68
3.02
2.97
2.96
2.90
2.24
2.21
2.10
2.06
2.01
1.83
1.77
1.59
1.48
1.45
1.41
1.30
0.16
0.08
-0.00
^{1}H NMR, $CDCl_3$, 500 MHz
HO
O
MeO_2C
OBOM
3-67
202
$CHCl_3$
TMS
5.95
1.00
1.00
1.03
1.08
1.04
1.03
2.86
1.11
1.06
1.15
2.26
1.08
1.20
4.27
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
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5.0
4.5
4.0
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2.5
2.0
1.5
1.0
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0.0
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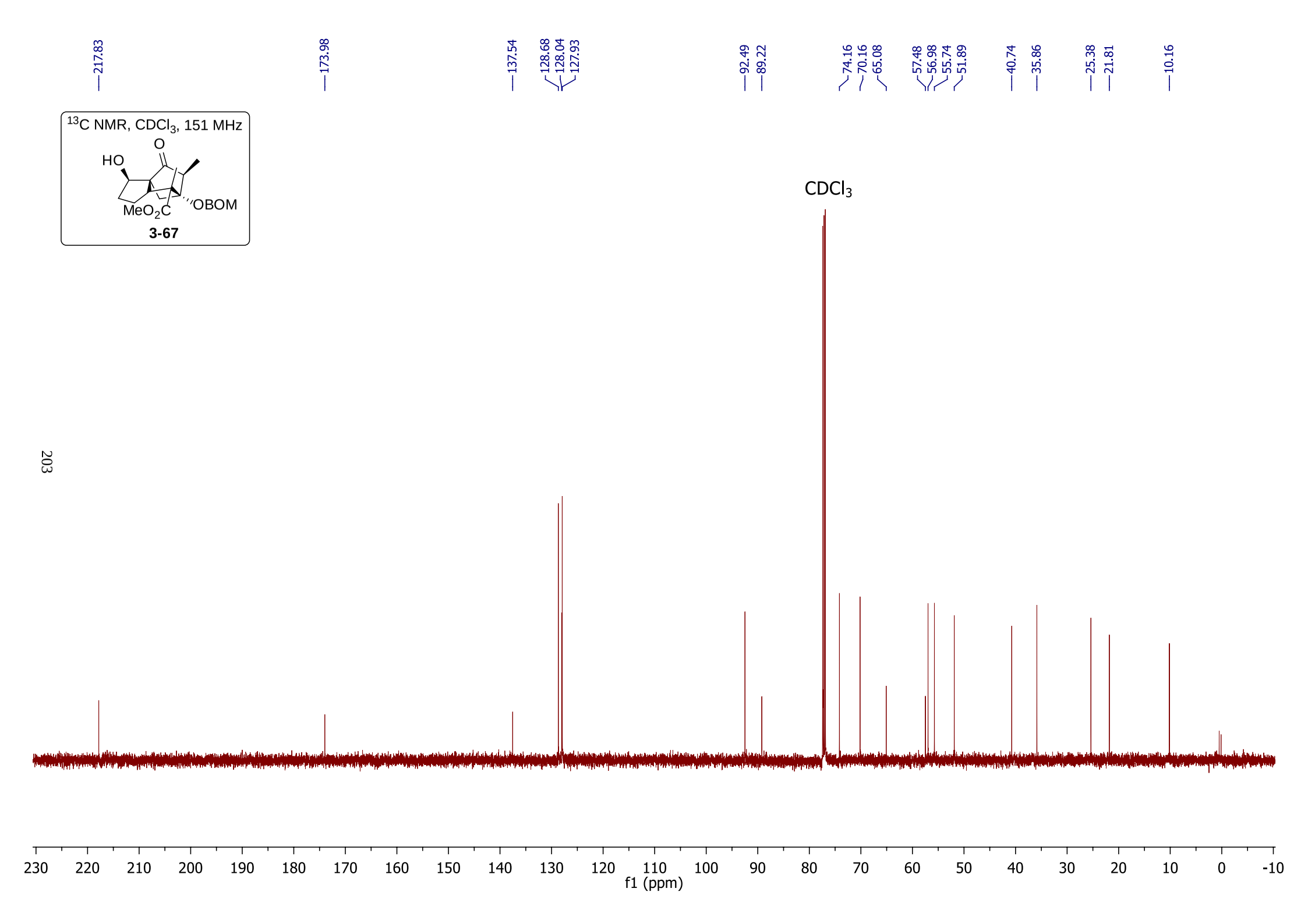
-1.0
f1 (ppm)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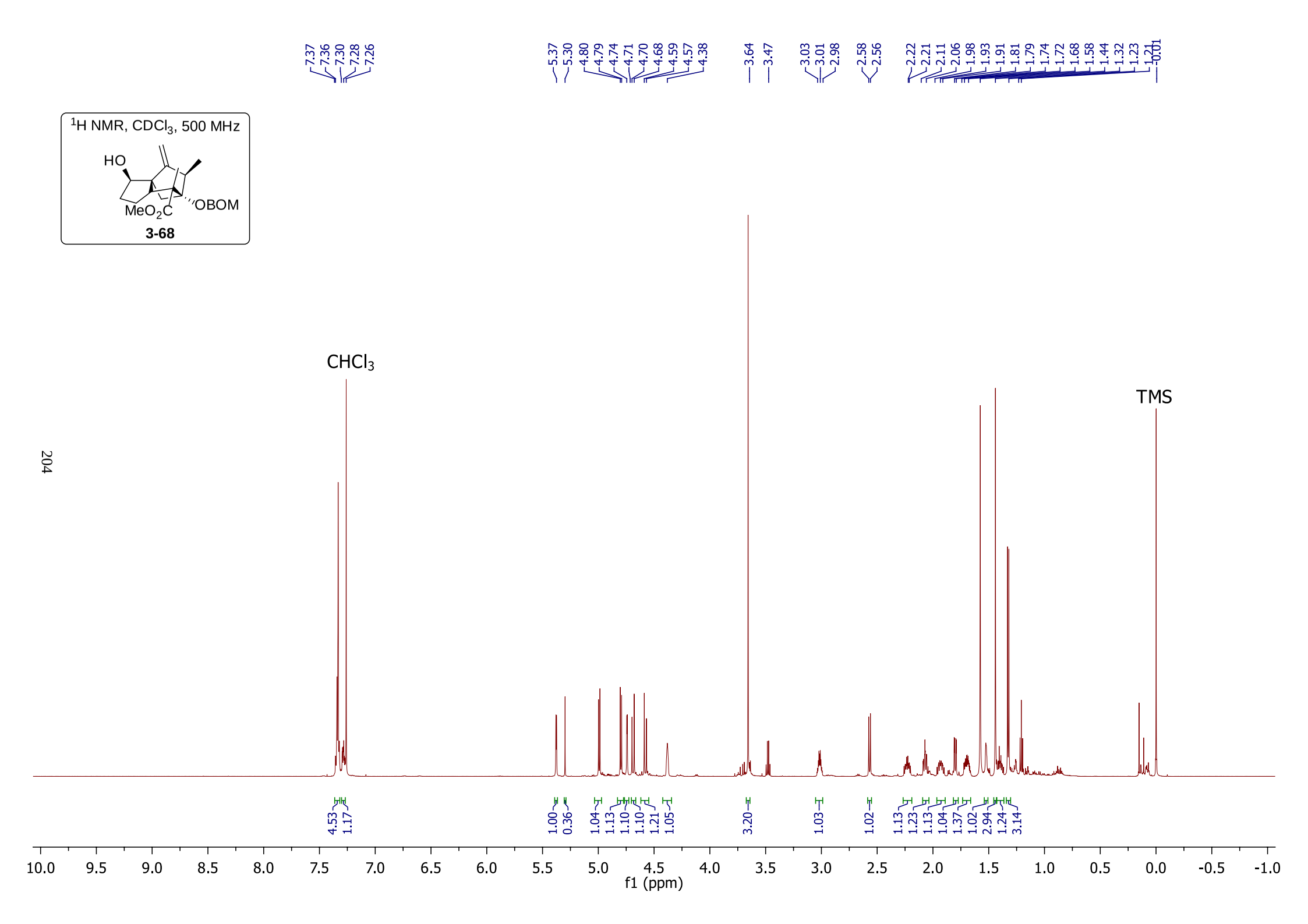
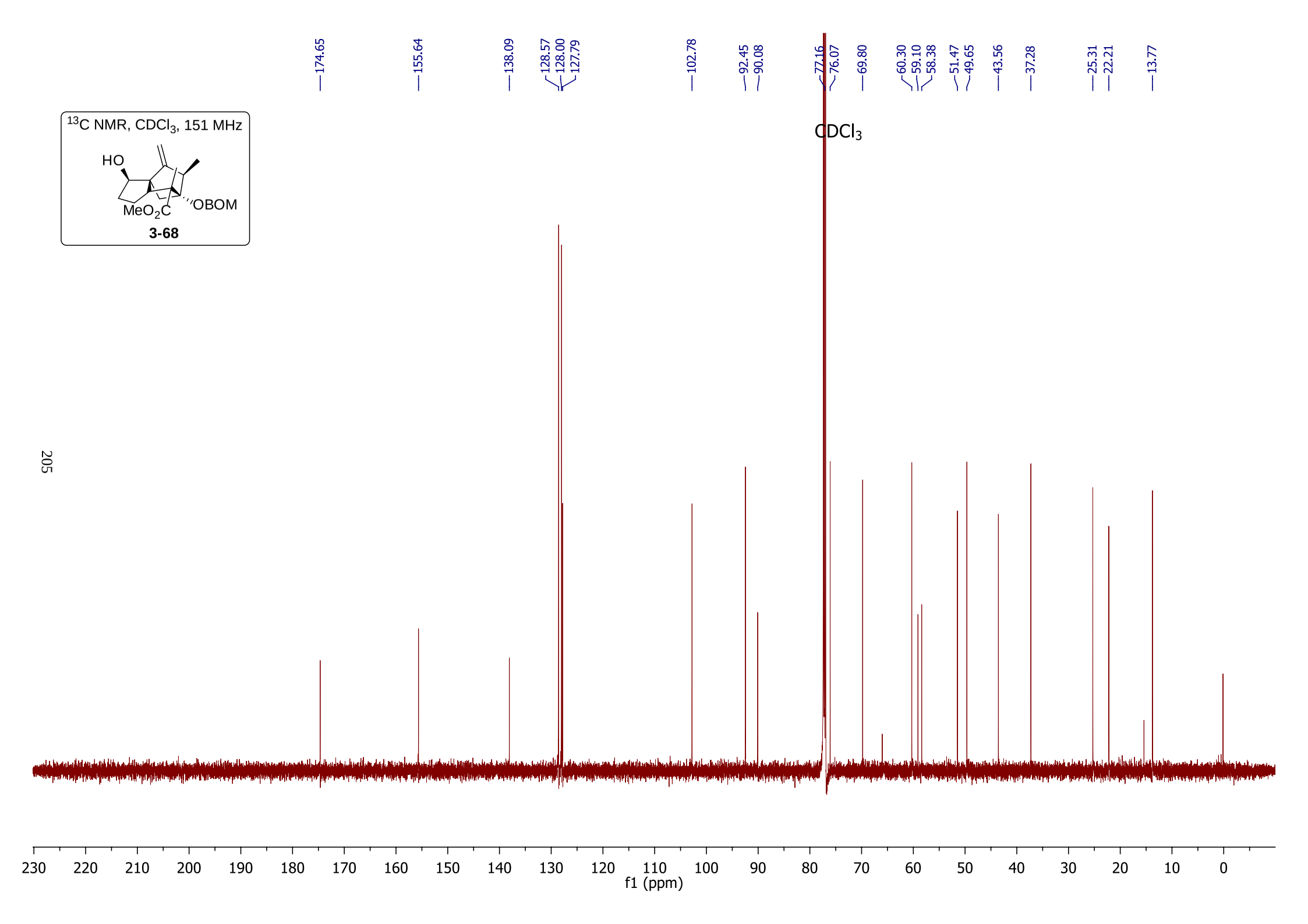
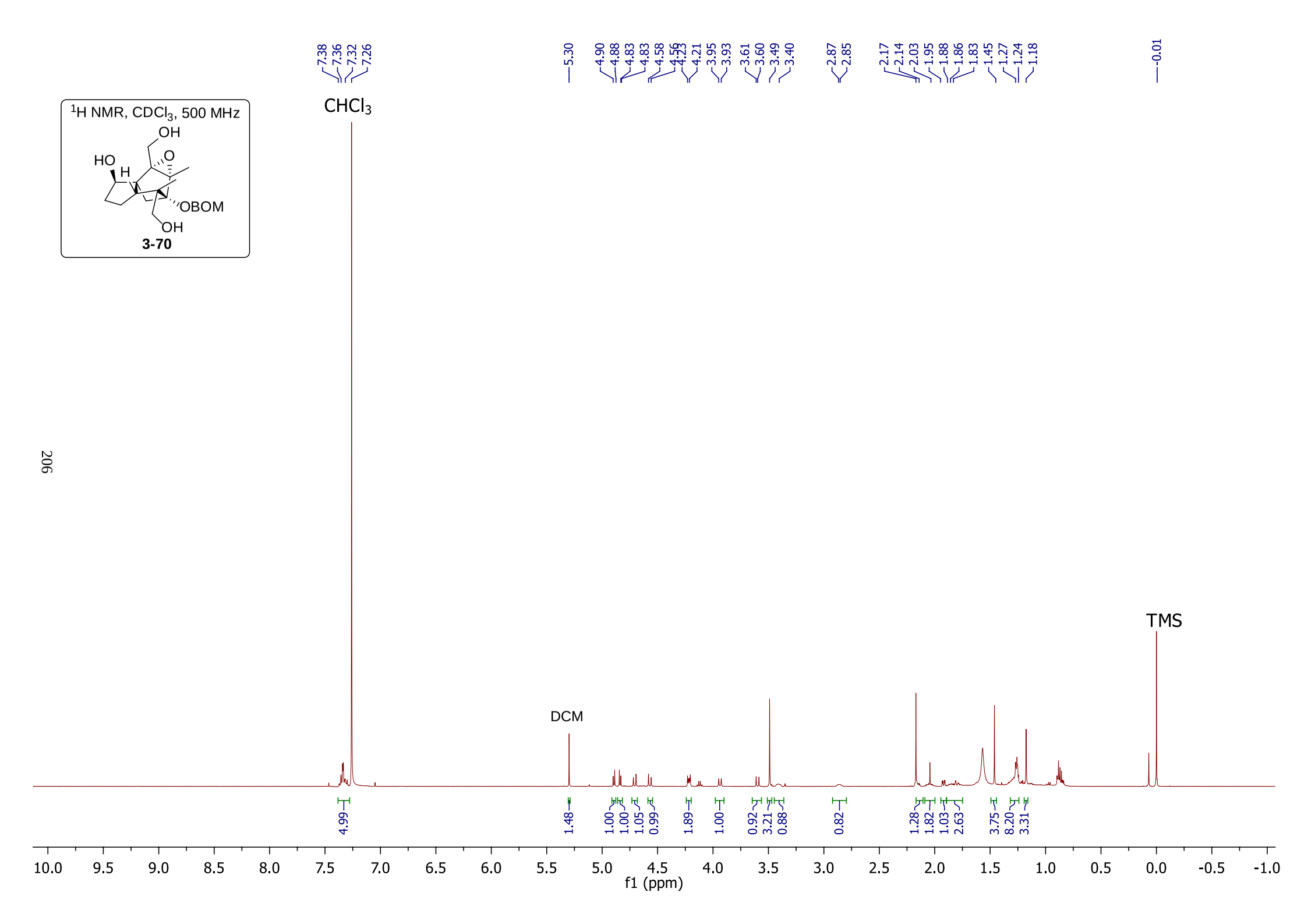
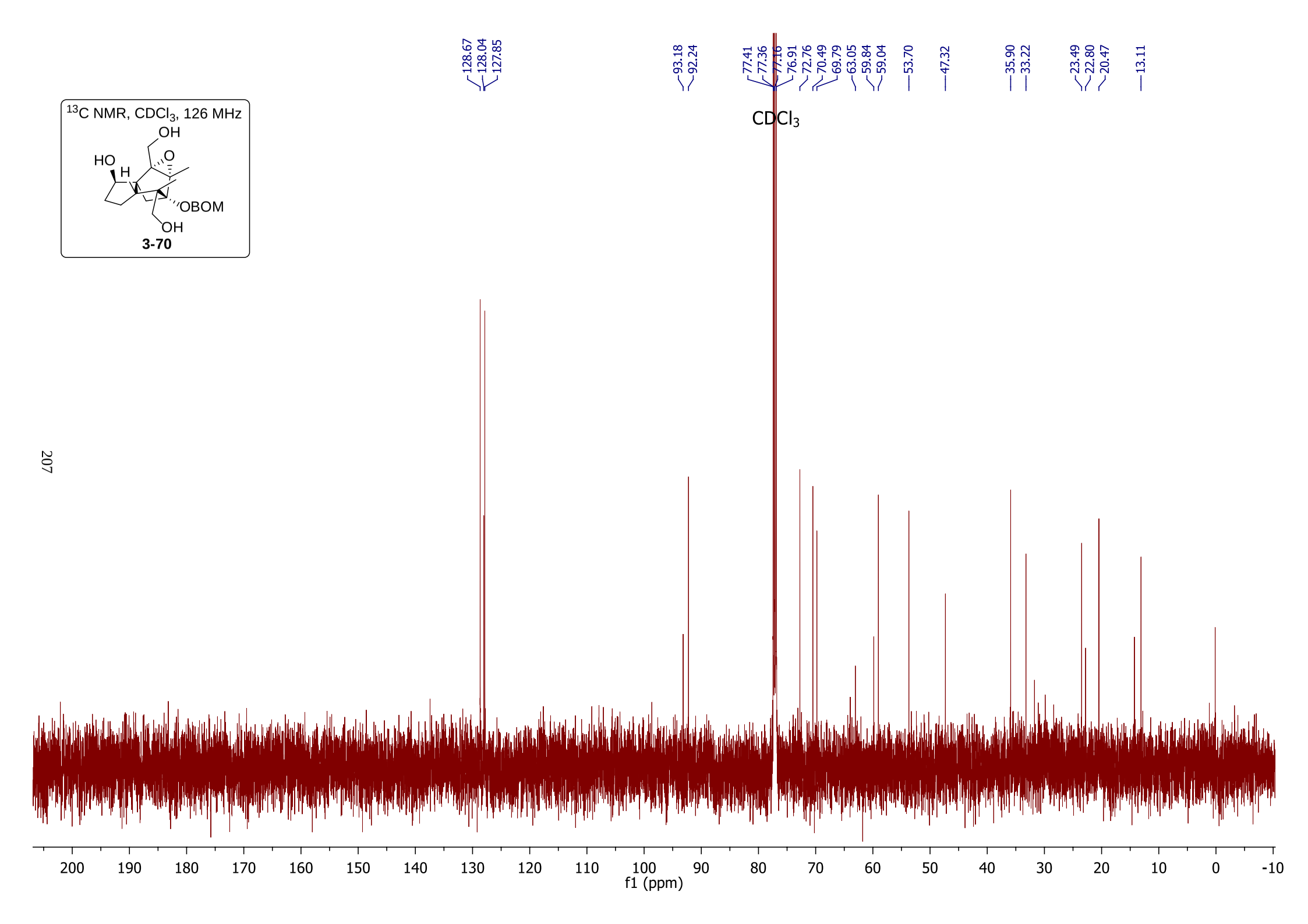
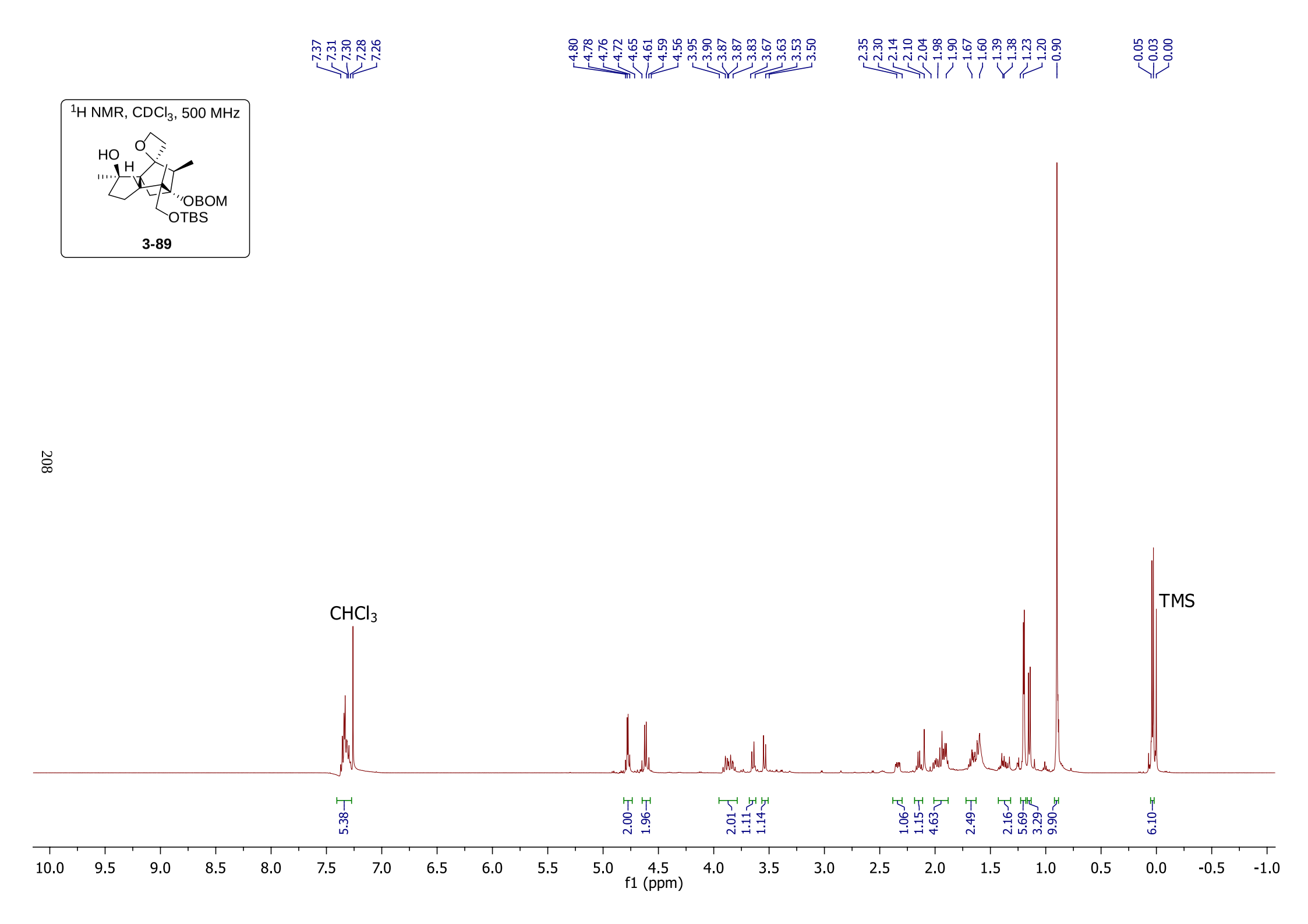
127.93
92.49
89.22
74.16
70.16
65.08
57.48
56.98
55.74
51.89
40.74
35.86
25.38
21.81
10.16
^{13}C NMR, $CDCl_3$, 151 MHz
HO
O
MeO_2C
OBOM
3-67
$CDCl_3$
203
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

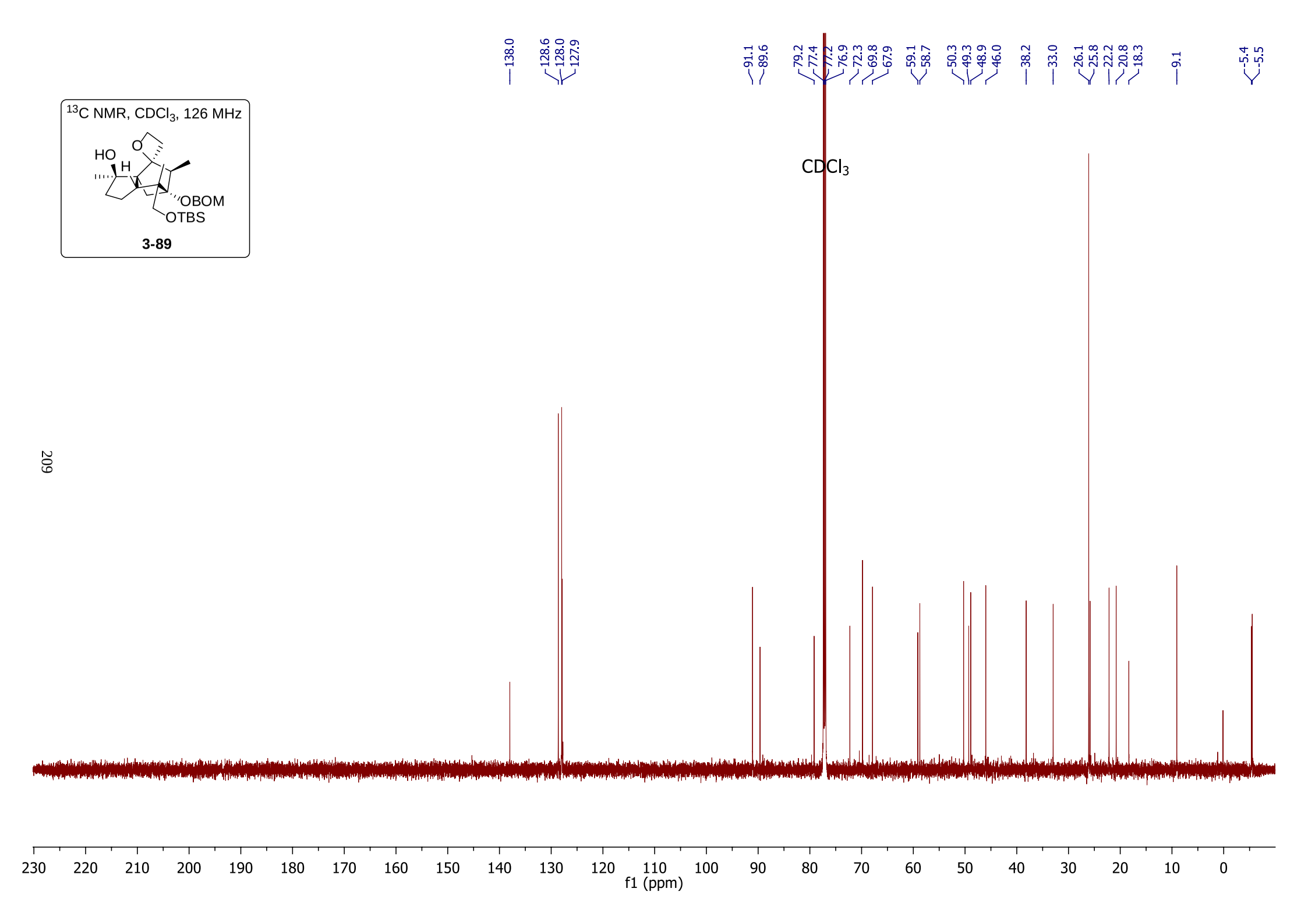

^{1}H NMR, $CDCl_3$, 500 MHz
HO
MeO_2C
OBOM
3-68
$CHCl_3$
TMS
204
f1 (ppm)

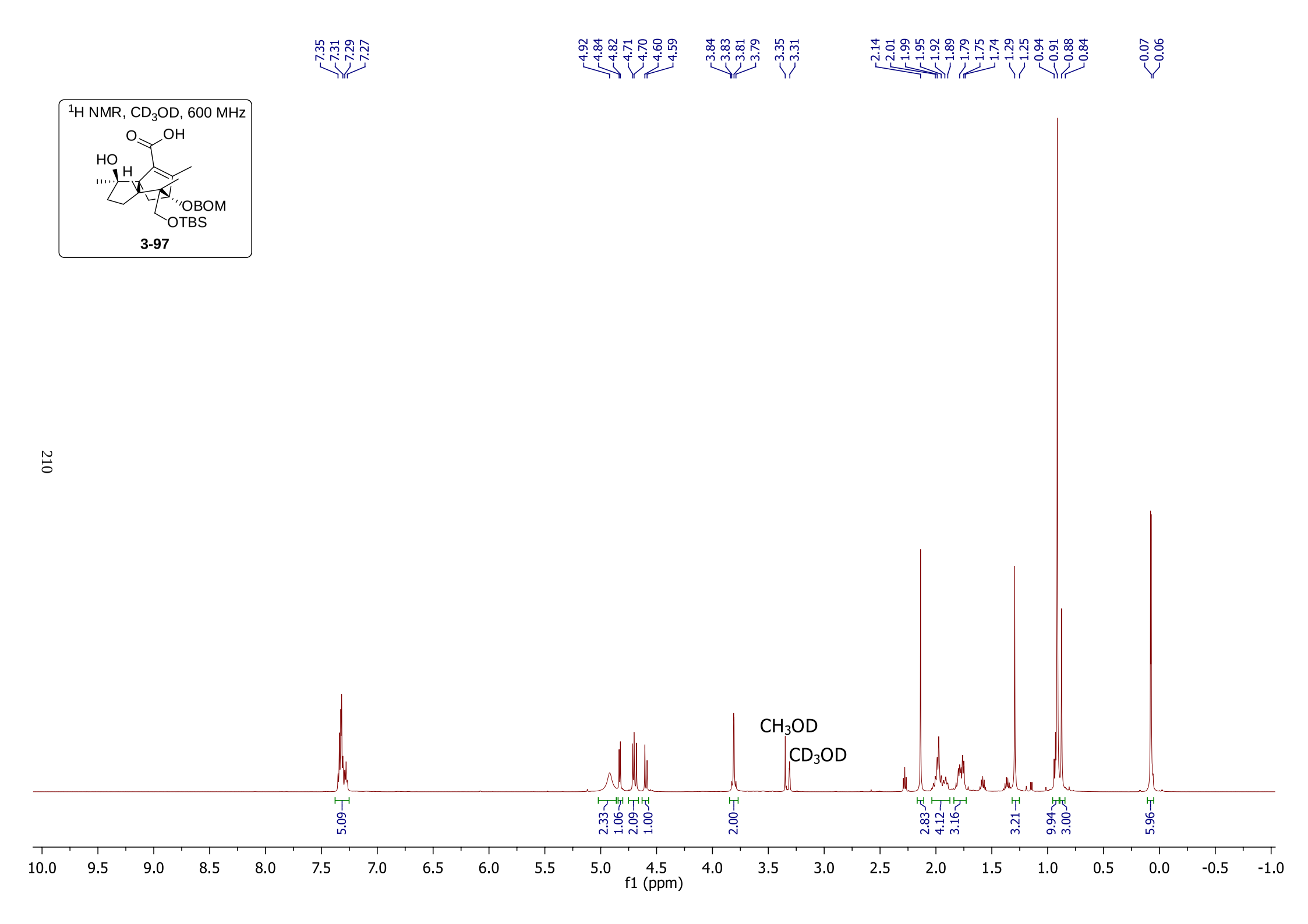

174.65
155.64
138.09
128.57
128.00
127.79
102.78
92.45
90.08
77.16
76.07
69.80
60.30
59.10
58.38
51.47
49.65
43.56
37.28
25.31
22.21
13.77
CDCl3
13C NMR, CDCl3, 151 MHz
HO
MeO2C
OBOM
3-68
205
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

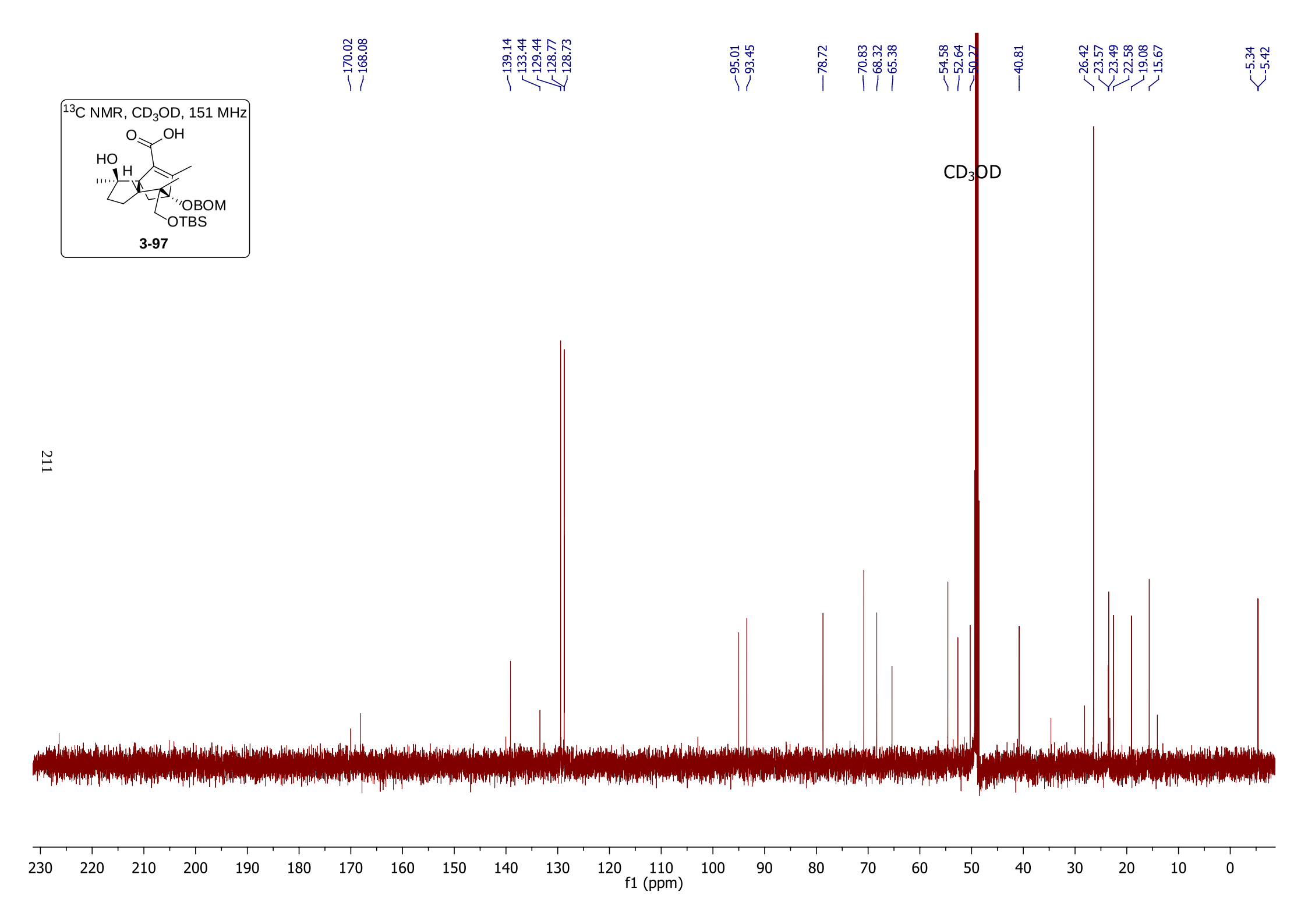

^{1}H NMR, $CDCl_3$, 500 MHz
OH
HO
H
O
OBOM
OH
3-70
$CHCl_3$
DCM
TMS
7.38
7.36
7.32
7.26
5.30
4.90
4.88
4.83
4.83
4.58
4.56
4.53
4.21
3.95
3.93
3.61
3.60
3.49
3.40
2.87
2.85
2.17
2.14
2.03
1.95
1.88
1.86
1.83
1.45
1.27
1.24
1.18
-0.01
4.99
1.48
1.00
1.00
1.05
0.99
1.89
1.00
0.92
3.21
0.88
0.82
1.28
1.82
1.03
2.63
3.75
8.20
3.31
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)
206

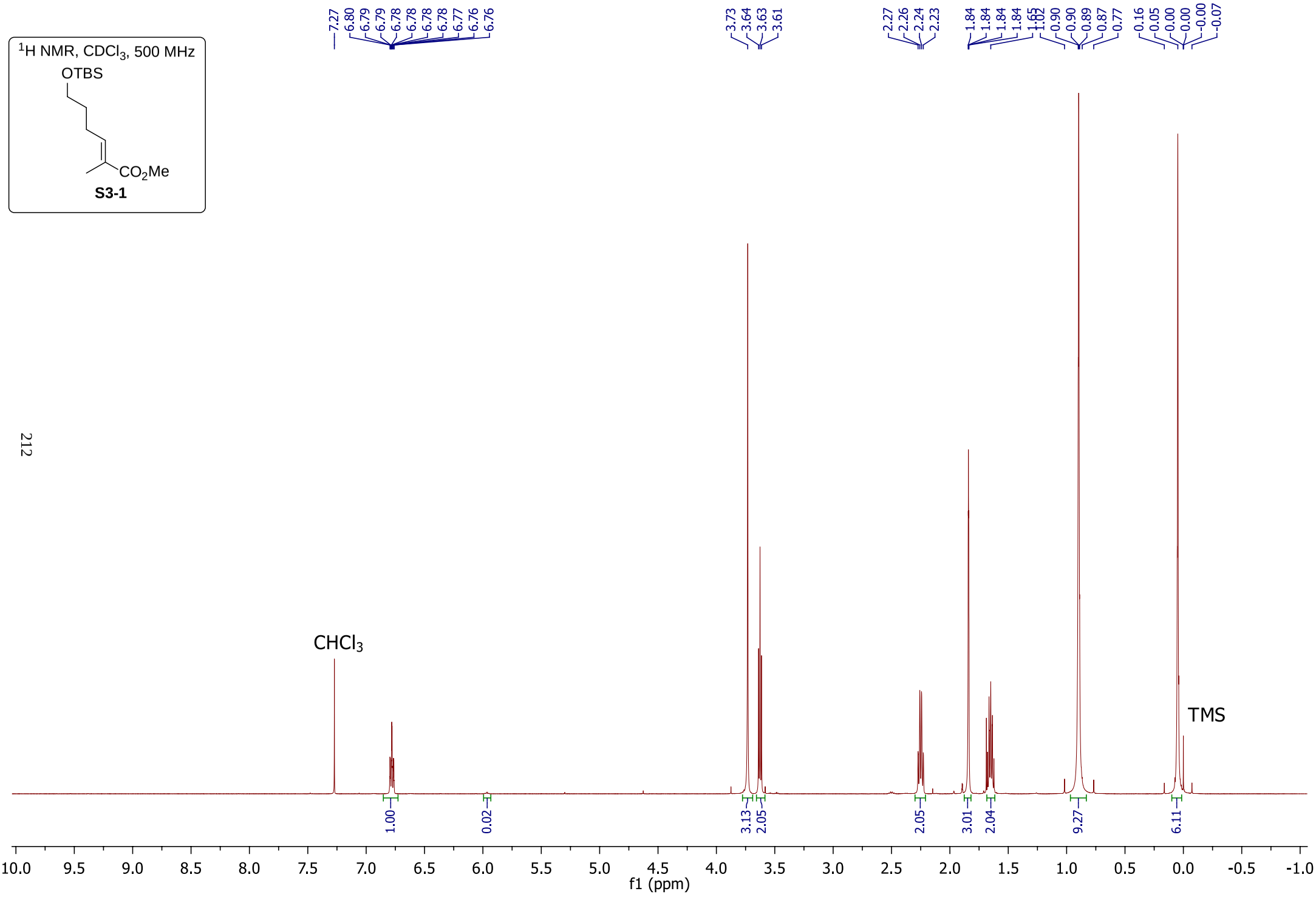

^{13}C NMR, $CDCl_3$, 126 MHz
OH
HO
H
O
OBOM
OH
3-70
128.67
128.04
127.85
93.18
92.24
77.41
77.36
77.16
76.91
72.76
70.49
69.79
63.05
59.84
59.04
53.70
47.32
35.90
33.22
23.49
22.80
20.47
13.11
$CDCl_3$
207
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

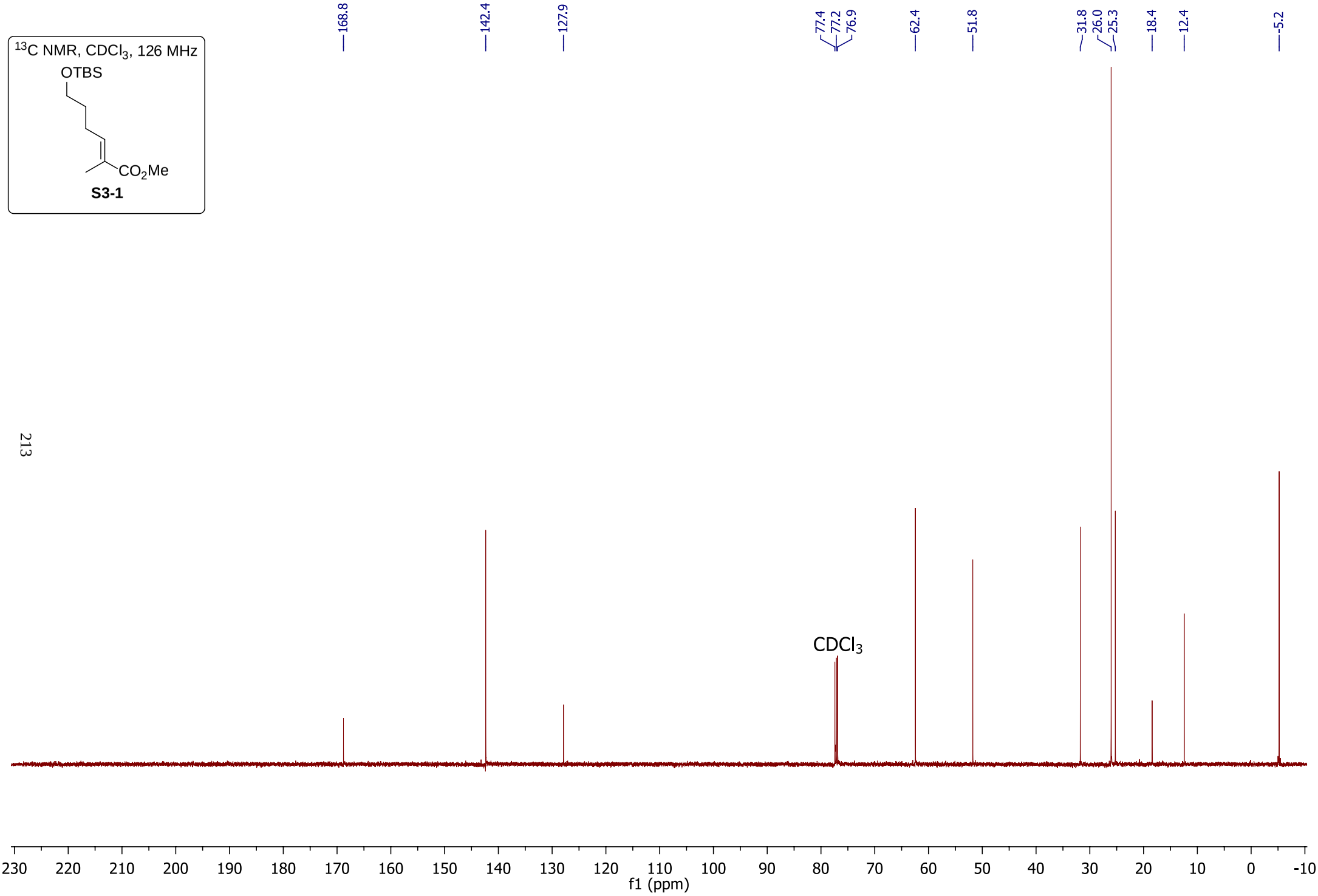

7.37
7.31
7.30
7.28
7.26
4.80
4.78
4.76
4.72
4.65
4.61
4.59
4.56
3.95
3.90
3.87
3.87
3.83
3.67
3.63
3.53
3.50
2.35
2.30
2.14
2.10
2.04
1.98
1.90
1.67
1.60
1.39
1.38
1.23
1.20
0.90
0.05
0.03
0.00
^{1}H NMR, $CDCl_3$, 500 MHz
HO
H
O
OBOM
OTBS
3-89
208
$CHCl_3$
TMS
5.38
2.00
1.96
2.01
1.11
1.14
1.06
1.15
4.63
2.49
2.16
5.69
3.29
9.90
6.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

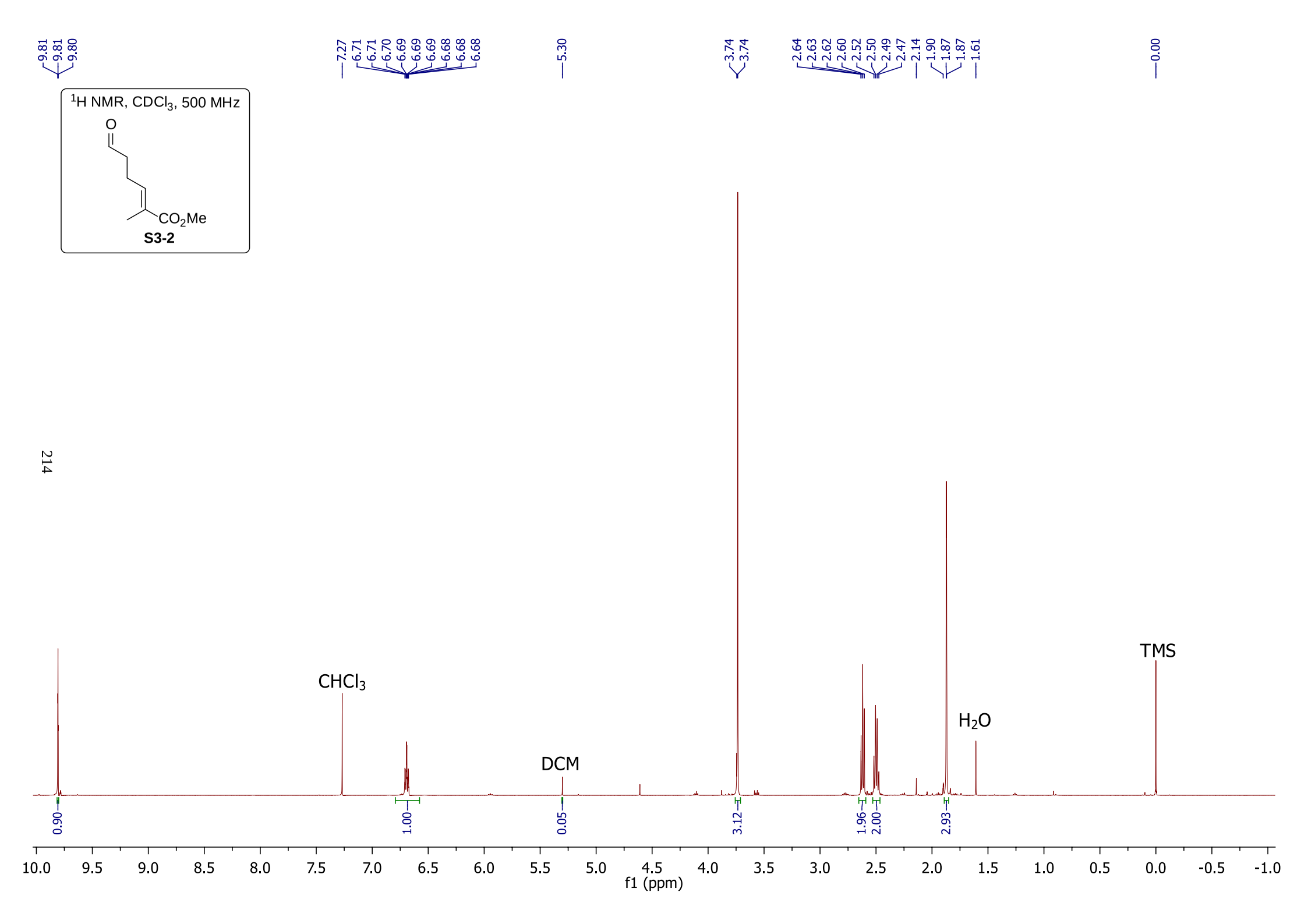

138.0
128.6
128.0
127.9
91.1
89.6
79.2
77.4
77.2
76.9
72.3
69.8
67.9
59.1
58.7
50.3
49.3
48.9
46.0
38.2
33.0
26.1
25.8
22.2
20.8
18.3
9.1
-5.4
-5.5
CDCl3
13C NMR, CDCl3, 126 MHz
HO
H
O
OBOM
OTBS
3-89
209
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

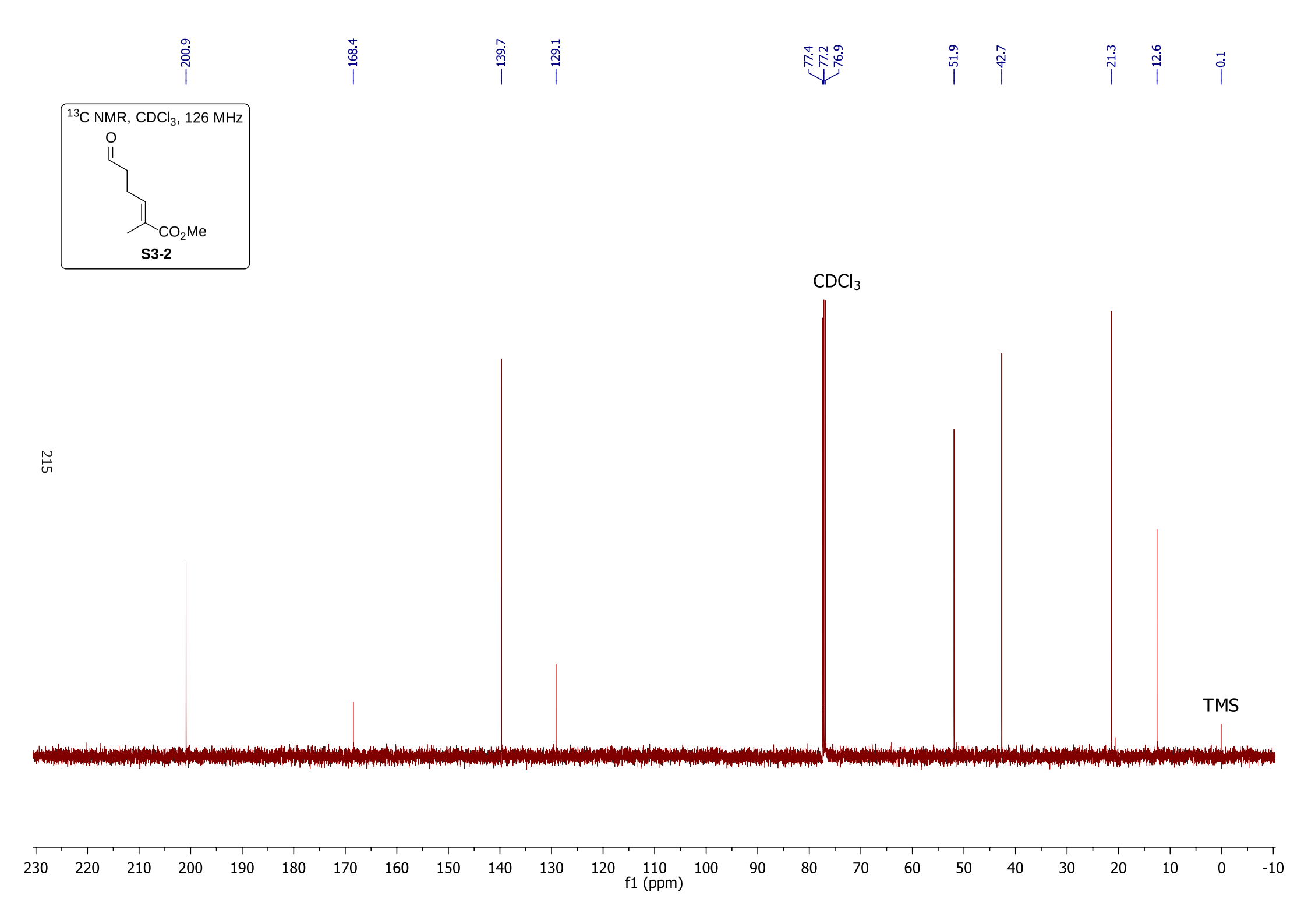

^{1}H NMR, CD_3OD, 600 MHz
O
OH
HO
H
OBOM
OTBS
3-97
7.35
7.31
7.29
7.27
4.92
4.84
4.82
4.71
4.70
4.60
4.59
3.84
3.83
3.81
3.79
3.35
3.31
2.14
2.01
1.99
1.95
1.92
1.89
1.79
1.75
1.74
1.29
1.25
0.94
0.91
0.88
0.84
0.07
0.06
CH_3OD
CD_3OD
5.09
2.33
1.06
2.09
1.00
2.00
2.83
4.12
3.16
3.21
9.94
3.00
5.96
210
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


170.02
168.08
139.14
133.44
129.44
128.77
128.73
95.01
93.45
78.72
70.83
68.32
65.38
54.58
52.64
50.27
40.81
26.42
23.57
23.49
22.58
19.08
15.67
-5.34
-5.42
CD3OD
13C NMR, CD3OD, 151 MHz
O
OH
HO
H
OBOM
OTBS
3-97
211
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


^{1}H NMR, $CDCl_3$, 500 MHz
OTBS
CO_2Me
S3-1
7.27
6.80
6.79
6.79
6.78
6.78
6.78
6.78
6.77
6.76
6.76
3.73
3.64
3.63
3.61
2.27
2.26
2.24
2.23
1.84
1.84
1.84
1.84
1.65
1.62
0.90
0.90
0.89
0.87
0.77
0.16
0.05
0.00
0.00
-0.00
-0.07
212
$CHCl_3$
TMS
1.00
0.02
3.13
2.05
2.05
3.01
2.04
9.27
6.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


^{13}C NMR, $CDCl_3$, 126 MHz
OTBS
CO_2Me
S3-1
168.8
142.4
127.9
77.4
77.2
76.9
62.4
51.8
31.8
26.0
25.3
18.4
12.4
-5.2
213
$CDCl_3$
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


9.81
9.81
9.80
7.27
6.71
6.71
6.70
6.69
6.69
6.69
6.68
6.68
6.68
5.30
3.74
3.74
2.64
2.63
2.62
2.60
2.52
2.50
2.49
2.47
2.14
1.90
1.87
1.87
1.61
0.00
^{1}H NMR, $CDCl_3$, 500 MHz
O
CO_2Me
S3-2
214
$CHCl_3$
DCM
H_2O
TMS
0.90
1.00
0.05
3.12
1.96
2.00
2.93
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)


200.9
168.4
139.7
129.1
77.4
77.2
76.9
51.9
42.7
21.3
12.6
0.1
^{13}C NMR, $CDCl_3$, 126 MHz
O
CO_2Me
S3-2
$CDCl_3$
TMS
215
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)