Stony Brook University

Part I. Stereospecific Synthesis of Vinyl Iodides: Iododesilylation of Homoallylic Alcohol Derivatives

Part II. Model Studies, A Formal Synthesis of (-)-Englerin A, and the Total Synthesis and Biological Evaluation of New Englerin Analogs

A Dissertation Presented

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Daniel Elliott

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Daniel Elliott

We, the dissertation committee for the above candidate for the

Doctor of Philosophy degree, hereby recommend

acceptance of this dissertation.

Kathlyn A. Parker – Dissertation Advisor
Professor, Department of Chemistry

Dale Drueckhammer - Chairperson of Defense
Professor, Department of Chemistry

Francis Johnson – Third Member
Professor, Department of Chemistry

Roland Lau – Outside Member
President, Apex Scientific, Inc.

This dissertation is accepted by the Graduate School

Charles Taber
Dean of the Graduate School

Abstract of the Dissertation

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Part I.

Vinyl iodides with defined geometry are important chemical building blocks. Their preparation by iododesilylation of the corresponding vinyl silane is an attractive method. Kishi et al. have shown that if iododesilylation is carried out with N-iodosuccinimide (NIS) in an acetonitrile/chloroacetonitrile mixture, one obtains vinyl iodides in which the geometry of the olefin is highly retained. By carrying out iododesilylation with NIS in hexafluoroisopropanol, Zakarian et al. have shown that the olefin geometry is also retained, but to a larger degree. Previously, the Parker group has applied this methodology to a synthetic study of trisubstituted vinyl iodides. Therein, they found that if iododesilylation was carried out with NIS in DMSO, one obtains products in which the geometry of the olefin had been highly inverted. To obtain a more thorough understanding of the scope and limitations of the methodology, we extended this

study to disubstituted homoallylic alcohol derivatives. The results obtained should be useful for the synthesis of polypropionates containing a disubstituted homoallylic alcohol moiety.

Part II.

In 2008 Beutler et al. isolated the guaiane sesquiterpene (-)-englerin A (EA) from the stem bark of *Phyllanthus engleri*, a species indigenous to east Africa. In an NCI 60 cell panel, EA displayed selective and potent activity against human renal cancer cell lines. This fact, combined with the limited response that kidney cancers display to standard chemotherapy, has made EA an important new drug lead. Although there have now been EA syntheses published by 11 research laboratories, little work has been done in the area of analog synthesis. The majority of EA analogs synthesized for structure activity relationship studies have been those in which the ester side chains have been altered. There has been little synthetic work revealing the necessity of the EA core structure for cytotoxicity. By utilizing chemistry that has been developed in our laboratories, we have completed a second-generation formal synthesis of EA. In addition, a late stage synthetic intermediate that permits the synthesis of analogs with core modifications was synthesized. By way of this intermediate, we have completed the total synthesis of two new analogs with modification at C-4.

To Grandma Bea

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List of Abbreviations

β	beta
μm	micrometer
ºC	celcius degree
Å	Angstrom
A498	renal cancer cell line
Ac	acetyl
ACHN	renal cancer cell line
Ac_2O	acetic anyhydride
AgOAc	silver acetate
Atm	atmosphere
app t	apparent triplet
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
bp	boiling point
Bu	butyl
Bz	benzoyl
br d	broad doublet
br s	broad singlet
br t	broad triplet
CB	catecholborane
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
cm^{-1}	reciprocal centimeter
COD	1,5-cyclooctadiene
cp	cyclopentadienyl
CSA	camphorsulfonic acid
cy	cyclohexyl
d	doublet
dd	doublet of doublet
dddd	doublet of doublet of doublet of doublet
d.r.	(dr) diastereomeric ratio
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIPCl	B-chlorodiisopinocampheylborane
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine

DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dq	doublet of quartet
EA	englerin A
e.e. (ee)	enantiomeric excess
EI	electron impact
e.r. (er)	enantiomeric ratio
ESI	electrospray
Et	ethyl
Et_2O	ethyl ether
EtOAc	ethyl acetate
FPP	farnesyl pyrophosphate
g	gram
G II	Grubbs second generation catalyst
GI_{50}	concentration for 50% growth
h	hour(s)
hex	hexanes
HF	hydrofluoric acid
HFIP	hexafluoroisopropanol
HI	hydroiodic acid
HPLC	high performance liquid chromatography
Hz	hertz
IC_{50}	concentration for 50% inhibition
in vacuo	under vacuum
ipc	isopinocampheyl
*i*Pr	isopropyl
IR	Infrared spectroscopy
J	first order coupling constant
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
L	liter
LDA	lithium diisopropylamide
m	multiplet
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl

MeCN	acetonitrile
MeLi	methyllithium
MEM	methoxyethoxymethyl
MeMgBr	methyl magnesiumbromide
MeOH	methanol
MHz	megahertz
min	minute
mg	milligram
mL	milliliter
mmol	millimole
mmpp	magnesium monoperoxyphthalate
mol	mole
MOM	methoxymethyl
m.p.	melting point
MS	mass spectroscopy
m/z	mass-charge ratio
NaOMe	sodium methoxide
NaHMDS	sodium 1,1,1,3,3,3-hexamethyldisilazide
*n*BuLi	*n*-Butyllithium
NHK	Nozaki-Hiyami-Kishi
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMA	phosphomolybdenic acid
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl
PTSA (TsOH)	*p*-toluenesulfonic acid
Py	pyridine
q	quartet
RCC	renal cell carcinomara
RCM	ring closing metathesis
RRCM	relay ring closing metathesis
r.t. (rt)	room temperature
s	singlet
SAR	structure-activity relationship
sat.	saturated

t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyl-diphenyl silyl
TBHP	*tert*-butyl hydroperoxide
TBS (TBDMS)	*tert*-butyl-dimethyl silyl
TEA	triethylamine
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropyl silyl
TLC	thin layer chromarography
TMS	trimethyl silyl
TPAP	tetra-*n*-propylammonium perruthenate
tq	triplet of quartets
Ts	*p*-toluenesulfonyl
UO31	renal cancer cell line

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Chapter 1

Stereospecific Synthesis of Vinyl Iodides

1.1 Introduction

Vinyl iodides are important building blocks in the total syntheses of complex molecules. They are often employed in Suziki, Negishi, Heck, and Stille cross coupling reactions, as well as the Nozaki-Hiyama-Kishi (NHK) addition reaction.[1] Although modern organic synthesis relies heavily on the use of vinyl iodides of increasing complexity, at the present time there are few ways in which they may be prepared. In order to expand the synthetic utility of these reactions, the discovery of new methods for the stereospecific synthesis of vinyl iodides is of great interest.

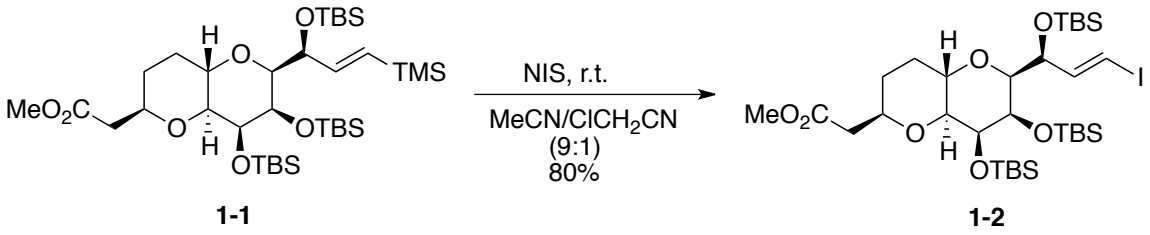
One useful procedure for the synthesis of vinyl iodides is through iododesilylation of the corresponding vinyl silane.[2] Vinyl silanes are attractive precursors to vinyl iodides - they are easy to handle and relatively nontoxic. In addition they may be prepared stereospecifically. With a geometrically defined vinyl silane, iododesilylation offers an attractive method of vinyl iodide synthesis. However, this necessitates reaction conditions that will either favor a net retention or inversion of olefin geometry.

At the present time there are a number of available reaction conditions that will effect iododesilylation, including IBr in CH_2Cl_2[3], I_2 in CH_2Cl_2[4], ICl in CCl_4[5], as well as N-iodosuccinimide (NIS) in a variety of solvent systems.[6] NIS is a popular reagent. It is an easily handled crystalline solid and it is also a fairly mild source of I^+. At the same time, the remarkable effect that solvent has on iododesilylation carried out with NIS allows one to tune a reaction in favor of inversion or retention of olefin geometry in the product vinyl iodide.

1.1.1 Iododesilylation of Disubstituted Allylic Alcohol Derivatives with NIS

The use of NIS in an acetonitrile mixture to effect iododesilylation was first shown by Kishi et al. during work on the synthesis of the C1-C13 portion of Halichondrin B.[6a] When they attempted the transformation of vinyl silane **1-1** to the desired vinyl iodide **1-2** (Scheme 1-1), the authors reported that standard literature methods failed. Either substrate decomposition was observed or reactions led to the recovery of starting material. This prompted the authors to

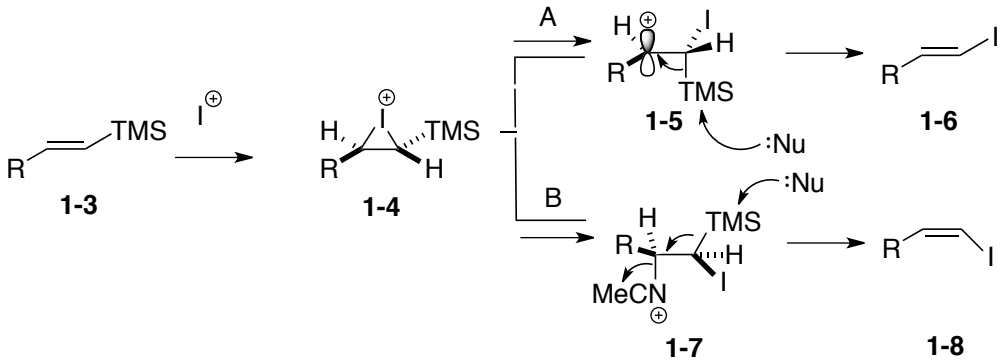
develop a new methodology. Eventually, the authors succeeded by using five equivalents of NIS in a 9:1 acetonitrile/monochloroacetonitrile mixture as solvent.



1-1 **1-2**

Scheme 1-1. Iododesilylation in Kishi's Synthesis of the C1-C13 Stretch of Halichondrin B

With the successful conversion of vinyl silane **1-1** to vinyl iodide **1-2**, Kishi and co-workers investigated the generality of this methodology. An iododesilylation study was performed on a series of simple vinyl silanes and allylic alcohol derivatives in acetonitrile and an acetonitrile/monochloroacetonitrile mixture. In Kishi's report, a simple mechanism was proposed (Scheme 1-2).



1-3 **1-4** **1-5** **1-6** **1-7** **1-8**

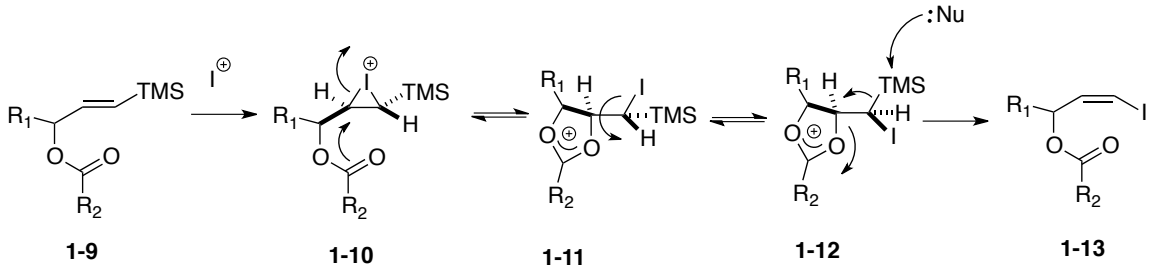
Scheme 1-2 . Mechanism of Iododesilylation Proposed by Kishi et al.

As shown above, the initial step in the reaction is believed to be the formation of an iodonium ion via interaction of the pi electrons of the olefin and the iodinating agent. After iodonium ion formation there are two possible reaction pathways.

In pathway A, the iodonium ion can open up to form a silicon stabilized beta carbonium ion.[7] This intermediate can then rotate along the shortest path to allow maximum hyperconjugative stablization of the carbonium ion by the silyl group. Elimination of TMS is believed to occur in an *anti* fashion, which leads to product in which the olefin geometry is retained.

If the solvent participates in the reaction (pathway B), one can obtain product mixtures in which the geometry has been both retained and inverted. This result is observed more often in unhindered substrates, and it is believed to be caused by iodonium ion opening at the beta position followed by elimination of the silicon substituent and the solvent molecule. The net result from this *anti* addition-*anti* elimination sequence is inversion of geometry in the product vinyl iodide.

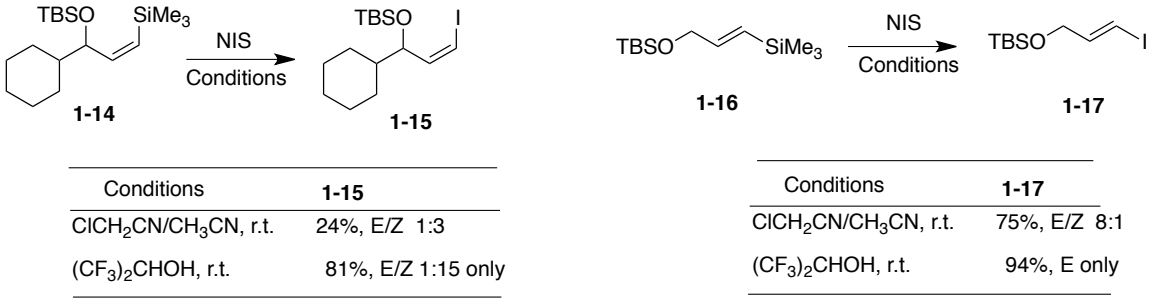
For substrates that contain an allylic substituent that can participate in the nucleophilic opening of the iodonium ion (e.g. acylated alcohols), inversion of olefin geometry can occur (pathway C). This is illustrated in Scheme 1-3.



Scheme 1-3. Neighboring Group Participation Leading to Inversion of Olefin Geometry in Iododesilylation (Pathway C)

After the initial studies performed by Kishi and co workers, Zakarian et al. showed that by changing the solvent system to hexafluoroisopropanol (HFIP), one that is both non-nuclophilic and very polar, a higher degree of retention of geometry in unhindered simple vinyl silanes could be achieved (Figure 1-1).[6b] The authors believe that the low nucleophilicity of HFIP causes the reaction to proceed through a pathway where solvent does not participate. In other words, pathway A becomes favorable. When iododesilylation was carried out on allylic

silyl ethers, good yields and an overall retention of olefin geometry in both (*E*) and (*Z*)-substrates were obtained.



Conditions	1-15
$ClCH_2CN/CH_3CN$, r.t.	24%, E/Z 1:3
$(CF_3)_2CHOH$, r.t.	81%, E/Z 1:15 only

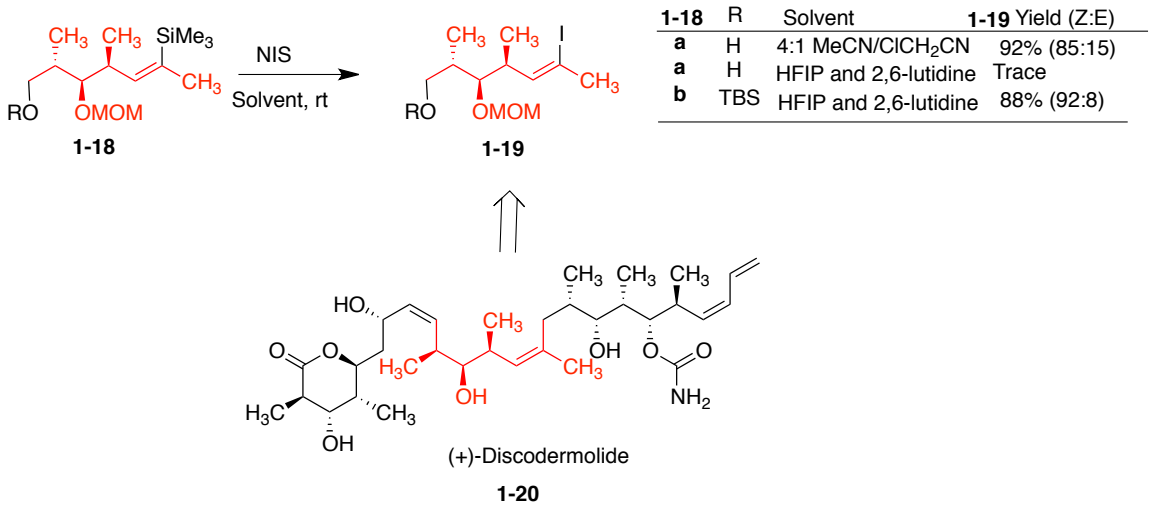
Conditions	1-17
$ClCH_2CN/CH_3CN$, r.t.	75%, E/Z 8:1
$(CF_3)_2CHOH$, r.t.	94%, E only

Figure 1-1. Iododesilylation of Allylic Silyl Ethers by Zakarian et al.

1.1.2 Iododesilylation of Homoallylic Alcohol Derivatives with NIS

1.1.2.1 Iododesilylation in the Parker Laboratory: Trisubstituted Homoallylic Alcohol Derivatives and a Key Intermediate of the Marine Polyketide (+)-Discodermolide

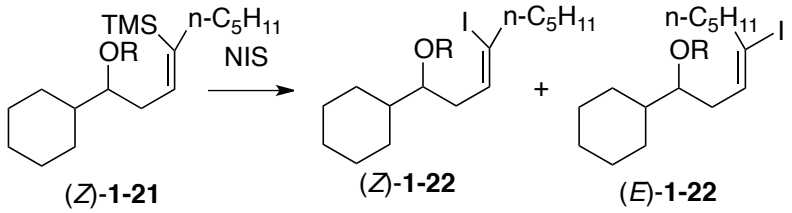
In our laboratories iododesilylation was utilized during the synthesis of a key intermediate of the potent microtubule stabilizing agent (+)-discodermolide, **1-20**.[8] When Xie, Denton, and Parker treated unprotected (*Z*)-vinyl silane **1-18a** with NIS in a 4:1 MeCN/$ClCH_2CN$ solvent mixture, they obtained vinyl iodide **1-19a** in very high yield and with retention of olefin geometry. In an attempt to improve the ratio of isomers observed, the solvent was replaced with HFIP containing 2,6-lutidine. This gave a complex mixture of products with only trace amounts of the desired iodoolefin. The treatment of TBS ether **1-18b**, however, with NIS in HFIP containing 2,6-lutidine, gave the desired vinyl iodide in good yield and with an improved ratio of geometric isomers (Scheme 1-4).



Scheme 1-4. Iododesilylation of a Trisubstituted Homallylic Alcohol Derivative Utilized in the Synthesis of a Key Discodermolide Intermediate

The completion of this study demonstrated the utility of iododesilylation chemistry in a relatively complex system. It also demonstrated that the nature of the protecting group and the solvent system play a crucial role in dictating the outcome of the reaction. The free alcohol **1-18a** could be converted smoothly to iodoolefin **1-19a** in an MeCN/$ClCH_2CN$ mixture. However, when the solvent system was replaced with HFIP, in order to carry out iododesilylation effectively, protection of the free hydroxyl group was required. To apply this methodology to future total syntheses, it would be beneficial to know what protecting groups can be utilized under a particular set of iododesilylation conditions.

Thus with the intention of exploring the generality of this iododesilylation chemistry, we performed a study in a model system containing a (*Z*)- trisubstituted homoallylic vinyl silane moiety.[9] We were curious to see, in addition to the free alcohol, how the MOM, TBS, and acetate protected derivatives would behave. Iododesilyation conditions that followed Zakarian's protocol (NIS with HFIP and 2,6-lutidine) and a modification of Kishi's protocol (NIS with 4:1 MeCN/$ClCH_2CN$) were screened. In hopes of promoting inversion of olefin geometry, iododesilylation with NIS in DMSO, was also investigated. The model system and the results of this study are shown in Table 1-1.



(*Z*)-**1-21** (*Z*)-**1-22** (*E*)-**1-22**

Substrate	Yield (ratio of (***Z***)-**1-22** to (***E***)-**1-22**) Rxn time (h)		
	HFIP	MeCN/$ClCH_2CN$ (4:1)	DMSO
a (R = H)	0% 1.5	82% (86:14)[a] 18	85% (15:85) 67
b (R = TBS)	72% (97:3) 0.5	53% (72:28) 2	94% (4:96) 117
c (R = MOM)	75% (97:3) 0.5	87% (82:18) 19	86% (3:97) 6
d (R = Ac)	94% (5:95) 0.5	48% (7:93) 17	43% (E) only 18

[a] Solvent was neat MeCN

Table 1-1. Parker and Denton's Iododesilylation of Model Trisubstituted Homoallylic Alcohol Derivatives

Treatment of the free alcohol **1-21a** with NIS in HFIP containing 2,6- lutidine gave a mixture of products containing none of the expected (*Z*)-olefin. This is not surprising considering that we observed a similar result during the iododesilylation of intermediate **1-18**. Treatment of the TBS and MOM protected derivatives, **1-21b** and **1-21c**, under the same iododesilylation conditions however, gave (*Z*)-vinyl iodides (*Z*)-**1-22b** and (*Z*)-**1-22c** almost exclusively, indicating that pathway A is dominant.

The acetate, **1-21d**, gave almost exclusively (*E*)- product. This result suggests that the homoallylic acetate group participates in the reaction, adding to the iodonium ion in an anti fashion followed by elimination anti to the TMS group (pathway C).

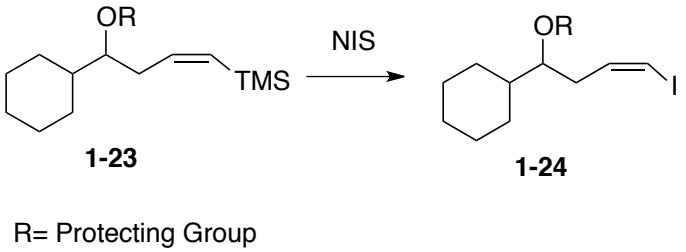
When iododesilylation was carried out in a 4:1 MeCN\$ClCH_2CN$ mixture, the alcohol, TBS, and MOM ethers, **1-21a-c**, gave product mixtures in which the major component was the (*Z*)-olefin. The acetate **1-21d**, once again, afforded only the (*E*)-product.

All reactions carried out in DMSO converted the (*Z*)-substrate to the inverted (*E*)-

iodoolefin, suggesting a high degree of solvent participation (Pathway B).

1.1.2.3 Iododesilylation of Disubstituted Homoallylic Alcohol Derivatives

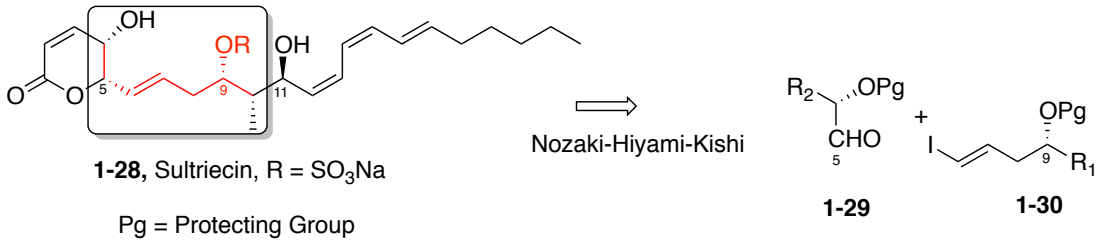
In order to obtain a more thorough understanding of the scope and limitations of this new methodology, we extended the iododesilylation study to a model disubstituted homoallylic alcohol system (Scheme 1-5).



Scheme 1-5. Model System for the Study of Iododesilylation of Disubstituted Homoallylic Alcohol Derivatives

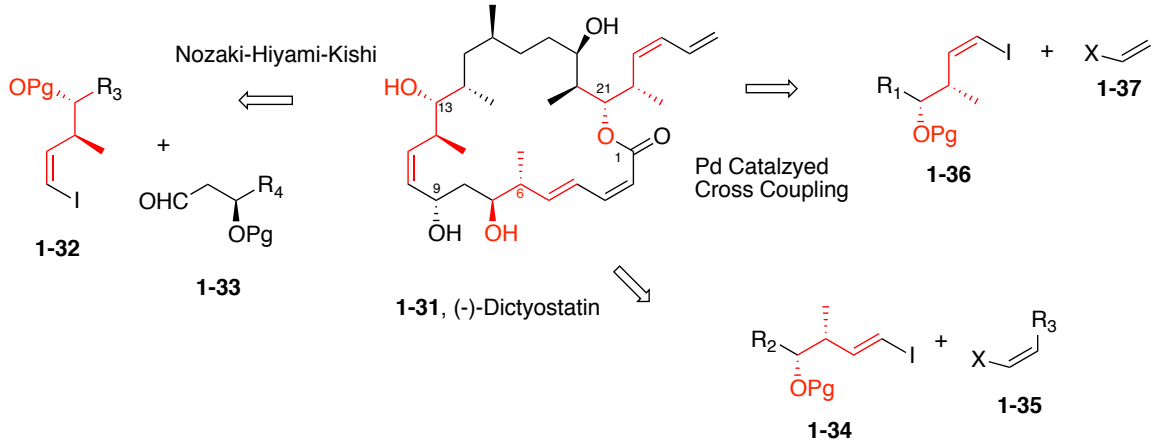
Vinyl iodides of the type shown in Scheme 1-5 could, in principle, be used to construct key fragments in the total synthesis of compounds containing a disubstituted homoallylic alcohol moiety. This substitution pattern is present in some biologically interesting polyketide natural products.

For example, one could envision coupling aldehyde **1-29** with vinyl iodide **1-30** via a Nozaki-Hiyami-Kishi (NHK) reaction in the synthesis of the C_6-C_{10} fragment of Sultriecin (**1-28)**, Scheme 1-6. Sultriecin is a highly potent and selective inhibitor of protein phosphatase 2A. It was also found to exhibit potent in vivo antitumor activity against the P388 leukemia and B16 melanoma cancer cell lines.[10]



Scheme 1-6. Retrosynthetic Analysis of Sultriecin

(-)-Dictyostatin (**1-31**), a compound structurally similar to (+)-discodermolide, possesses three disubstituted homoallylic alcohol moieties (Scheme 1-7). The conjugated diene between C_2 and C_5 or C_{23} and C_{26} could be the product of a palladium catalyzed cross-coupling reaction. In addition, the C_9-C_{13} fragment could be envisaged as the product of an NHK reaction between aldehyde **1-33** and vinyl iodide **1-32**. Like (+)-discodermolide, (-)-dictyostatin derives its biological activity through the stabilization of cancer cell microtubules.[11]

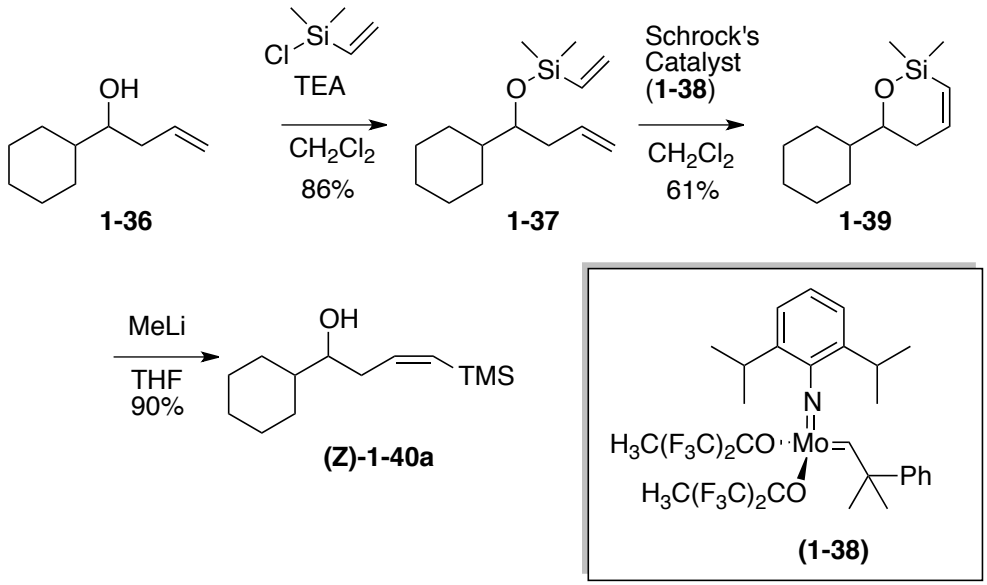


Scheme 1-7. (-)-Dictyostatin Retrosynthetic Analysis

1.2 Results and Discussion

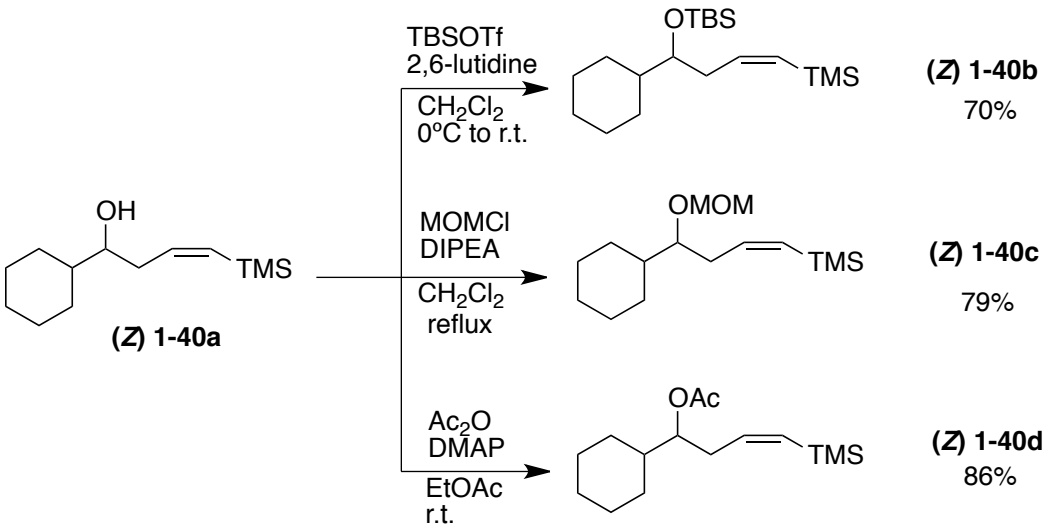
1.2.1 Synthesis of Model Disubstituted Homoallylic Alcohol Substrates

The preparation of (*Z*) substrates began with the synthesis of alcohol **(*Z*)-1-40a**. This alcohol is a known compound and it was prepared via a modification of the method of Barrett[12] through ring opening of dihydrooxasiline **1-39** with methylithium, (Scheme 1-8).



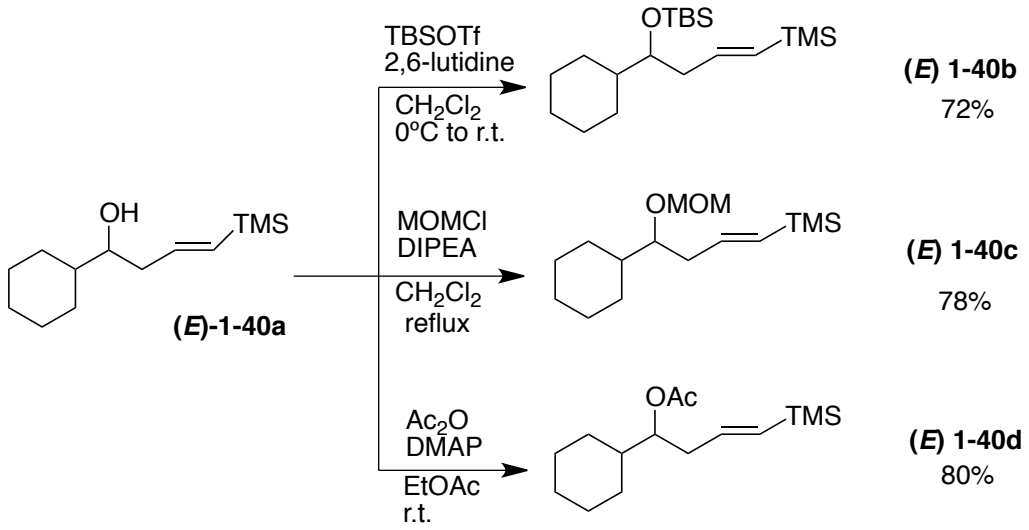
Scheme 1-8. Synthesis of Dihydrooxasiline **1-39** and Vinyl Silane (***Z***)**-1-40a**

With alcohol (***Z***)**-1-40a** in hand we obtained substrates **(*Z*)-1-40b-d** by applying the appropriate protection reactions (Scheme 1-9).



Scheme 1-9. Synthesis of Model (*Z*)-Homoallylic Alcohol Derivatives (***Z***)-**1-40b-d**

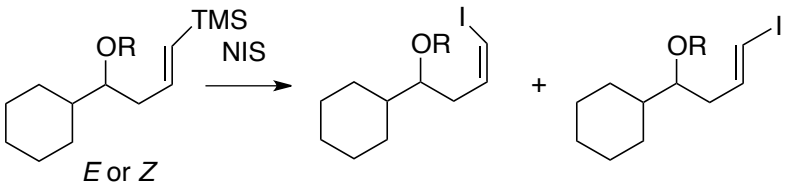
The preparation of the (*E*)-substrates began with the synthesis of alcohol **(*E*)-1-40a**. This is a known compound and it was prepared by the addition of allyltrimethyl silane to cyclohexane carboxaldehyde.[13] This alcohol was functionalized in the same fashion as alcohol **(*Z*)-1-40a** to give substrates **(*E*)-1-40b-d** (Scheme 1-10).



Scheme 1-10. Synthesis of Model (*E*)-Homoallylic Alcohol Derivatives **(*E*)-1-40a-d**

1.2.2 Iododesilylation Results of Model Disubstituted Homoallylic Alcohol Substrates

With the model compounds in hand, we screened iododesilylation conditions (Table 1-2). The geometry of the vinyl iodide product was analyzed by ^{1}H NMR spectroscopy.



Substrate **1-40**	Yield (ratio of (***Z***)-**1-41** to (***E***)-**1-41**)		
	HFIP	MeCN/$ClCH_2CN$ (4:1)	DMSO
a (R = H)			
E	Trace	15% (*Z*) 26% (*E*)	56%(*Z*) 12%(*E*)
Z	14% (*Z*) 9%(*E*)	37% (*Z*) 14% (*E*)	5%(*Z*) 18%(*E*)
b (R = TBS)			
E	47 % (1:6) **82%[a](*E* only)**	64% (1:7.4)	63% (8.5:1)
Z	80% (9:1) **96%[a] (9:1)**	60% (15.3:1)	47% (1:9.9)
c (R = MOM)			
E	Trace	50% (4.3:1)	31% (12.1:1)
Z	Trace	55% (1:2)	36% (1:7.3)
d (R = Ac)			
E	Trace	88% (20.7:1)	Trace
Z	Trace	69% (1:14.6)	Trace

a: Reaction carried out with 3 eq NIS, 3 eq 2,6-lutidine and 0.4 eq AgOAc, in 1:1 HFIP/$CDCl_3$

Table 1-2. Yields and Stereoselectivities of Vinyl Iodides **1-41a-d** as a Function of Solvent

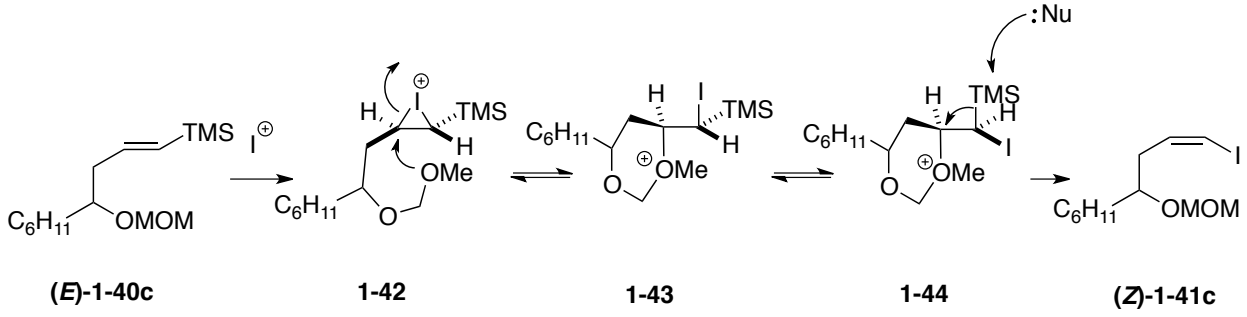
The free homoallylic alcohols, **(*E*)-1-40a** and **(*Z*)-1-40a**, upon treatment with NIS in HFIP containing 2,6-lutidine, gave a mixture of products containing very little of the desired iodoolefin. This is analogous to what was observed for the reaction of the (Z)-trisubstituted homoallylic alcohol **(Z)-1-21a**.

HFIP mediated iododesilylation of substrates **(*Z*)-1-40b** and **(*E*)-1-40b,** in which a TBS protected alcohol is present, gave the desired vinyl iodide with very high yield and with retention of geometry. During the course of this study, we found that by employing a modified procedure of Vilarrasa[14], in which the additive AgOAc was used, higher yields and retention of olefin

geometry in the desired (*E*) or (*Z*) vinyl iodide were observed. The authors believe that silver salts buffered with base can scavage I_2 and HI, both of which can be formed when NIS is used. For silyl ether bearing substrates the presence of these species can lead to substrate decomposition and lower overall product yield.

After iododesilylation of both MOM (**(*E*)-1-40c**) and **(*Z*)-1-40c**) and acetate (**(*E*)-1-40d** and **(*Z*)-1-40d**) protected alcohols in HFIP containing 2,6-lutidine, ^{1}H NMR analysis of the crude reaction mixture revealed a complex mixture of products containing only trace amounts of the desired vinyl iodide. This is in contrast to the HFIP mediated iododesilylation of trisubstituted vinyl silanes. Denton and Parker showed that trisubstituted substrates bearing a MOM and acetate protecting group, **(*Z*)-1-21c-d**, gave good yields of vinyl iodides in which the geometry of the olefin was largely retained (Table 1-1).

In a 4:1 $CH_3CN/ClCH_2CN$ mixture, treatment of unprotected alcohol substrates **(*Z*)** or **(*E*)-1-40a** gave product mixtures with only modest yields and stereoselectivities. Substrates bearing a TBS protecting group **(*Z*)** and **(*E*)-1-40b**, gave vinyl iodides in good yields and with an overall retention of olefin geometry. Substrates **(*Z*)** and **(*E*)-1-40c-d** bearing an acetate and MOM protecting group, in contrast, gave vinyl iodides where the geometry of the olefin had inverted. This suggests a large degree of neighboring group participation (pathway C). This is shown for MOM ether **(*E*)-1-40c** in Scheme 1-11 below.



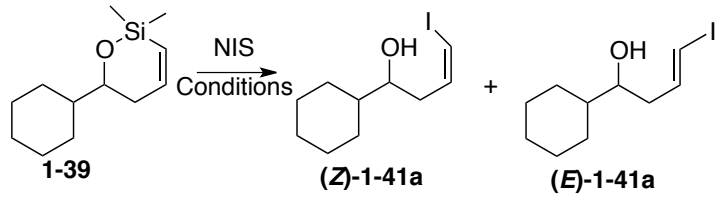
(*E*)-1-40c **1-42** **1-43** **1-44** **(*Z*)-1-41c**

Scheme 1-11. Neighboring Group Participation of MOM Ether Leading to Inversion of Olefin Geometry

As anticipated, when we carried out iododesilylation of substrates **(*E*)** and **(Z)-1-40-a-c** in DMSO, vinyl iodides were obtained in which the geometry of the olefin was largely inverted. This is consistent with previous results and suggests a high degree of solvent participation

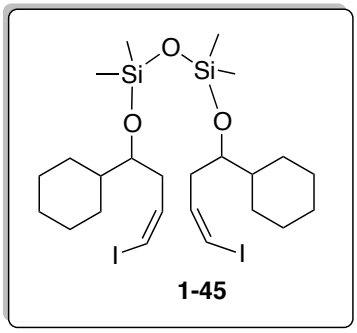
(pathway B). However, substrates **(*Z*)** and **(*E*)-1-40d**, bearing an acetate protecting group, gave mixtures of products under the same reaction conditions. ^{1}H NMR analysis of the crude reaction mixture showed only trace amounts of the desired iodoolefin..

After performing our study of protected alcohols, we were curious to see if we could obtain alcohol **(*Z*)** or **(*E*)-1-41a** directly from dihydrooxasiline **1-39** (Table 1-3).



1-39 **(*Z*)-1-41a** **(*E*)-1-41a**

Conditions	1)1:1 HFIP/$CDCl_3$ 2) HF-Py	1)DMSO
Yield	58% **(*Z*)-1-41a** 6% **(*E*)-1-41a**	65% **(*E*)-1-41a only**



1-45

Table 1-3. Yields and Stereoselectivies from Iododesilylation of Dihydrooxasiline **1-39** in HFIP and DMSO.

Treatment of dihydrooxasiline **1-39** with NIS in DMSO gave alcohol **(*E*)-1-41a** exclusively after stirring for 6 days at room temperature. Application of the HFIP protocol, however, gave dimeric intermediate **1-45** (presumably due to trace amounts of water). This was cleaved with HF-Pyridine to give the corresponding free alcohol **(*Z*)-1-41a** with retention of olefin geometry.

1.3 Conclusion

The results of this model study indicate that TBS protected disubstituted homoallylic alcohol derivatives, when subjected to iododesilylation with NIS in HFIP containing 2,6-lutidine or in a 4:1 MeCN/$ClCH_2CN$ solvent mixture give vinyl iodides with retention of olefin geometry (Pathway A). Moreover, for iododesilylation conducted in HFIP containing 2,6-lutidine, application of Vilarrasa's protocol improves both the yield and stereoselectivity of the vinyl iodides obtained.

In contrast to what we observed during the iododesilylation study of trisubstituted

homoallylic alcohol derivatives (Denton and Parker), iododesilylation of acetate and MOM protected disubstituted homoallylic alcohol derivatives in HFIP gives rise to mixtures of products containing very small amounts of iodoolefin. However, upon switching to a 4:1 MeCN/$ClCH_2CN$ mixture iododesilylation of these substrates gave vinyl iodides in good yield. Also noteworthy is that the acetate bearing substrates gave the inverted product almost exclusively. This result indicates a large degree of neighboring group participation (Pathway C).

For all substrates, when iododesilylation is performed in DMSO, the olefin geometry is largely inverted. This is consistent with a large degree of solvent participation (Pathway B).

(*Z*) or (*E*) disubstituted iodoolefinic homoallylic alcohols can be obtained directly from dihydrooxasilines by treatment with NIS in either HFIP containing AgOAc and 2,6-lutidine or in DMSO. This protocol offers a complementary approach to the synthesis of vinyl iodides requiring protecting groups that may not be compatible with the conditions of iododesilylation.

1.4 Experimental Section

General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. NIS was recrystallized from carbon tetrachloride. HPLC grade hexane and EtOAc, were used in chromatography. Diethyl ether (Et_2O) was distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or KMnO4 aq. solution and then heating.

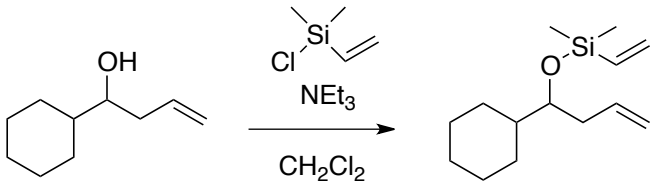
Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were

scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for 1H and 126 MHz for 13C), Varian Inova-400 (400 MHz for 1H and 101 MHz for 13C), or Gemini-2300 (300 MHz for 1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimental Procedure/Characterization

* - Indicates that a reaction was performed by undergraduate researcher Kenneth Kan

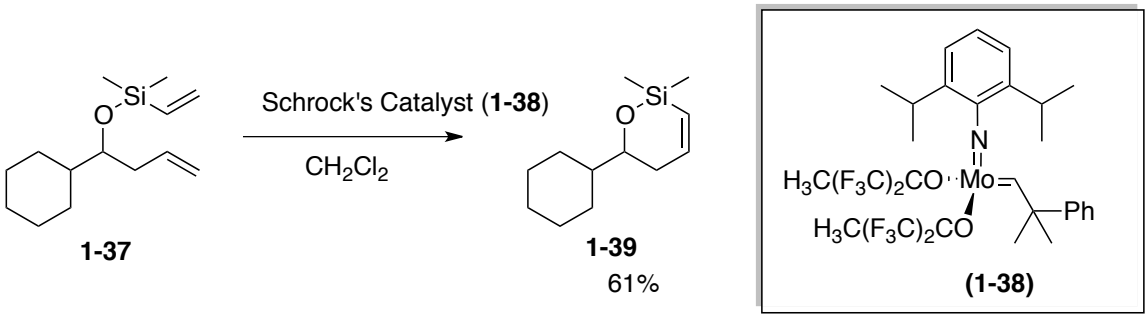
**- Indicates that a reaction was performed by Daniel Elliott and undergraduate researcher Stefani Jones



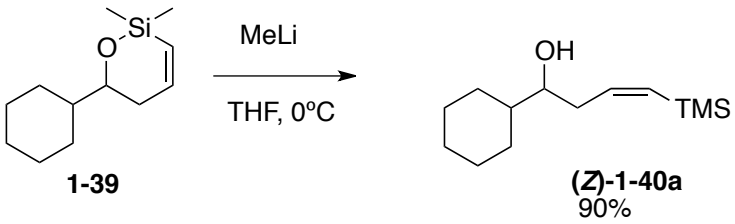
1-36 **1-37** 86%

Silyl Ether 1-37. To a stirred solution of alcohol **1-36**[15] (2.107 g, 13.66 mmol) in methylene chloride (20 mL) was added triethylamine (3.6 mL, 26 mmol) followed by chloro(dimethyl)vinylsilane (3.5 mL, 25 mmol). After 1.5 h, the solution was diluted with methylene chloride (20 mL) and washed with sat. NH_4Cl solution (2 x 15 mL) followed by sat. $NaHCO_3$ solution (10 mL). The organic solution was dried over $MgSO_4$, filtered, and

concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 20:1) to give silyl ether **1-37** (2.81 g, 86%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (dd, *J* = 20.4, 14.9 Hz, 1H), 6.02 – 5.94 (m, 1H), 5.87 – 5.78 (m, 1H), 5.75 (dd, *J* = 20.4, 3.9 Hz, 1H), 5.09 – 4.95 (m, 2H), 3.46 (q, *J* = 5.7 Hz, 1H), 2.46 – 2.04 (m, 2H), 1.87 – 1.55 (m, 5H), 1.44 – 0.80 (m, 6H), 0.17 (s, 6H). The data were consistent with literature values.[12]

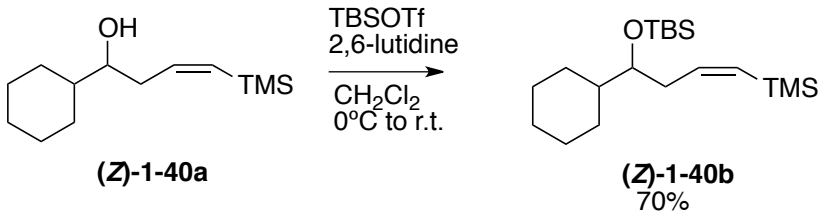


Dihydrooxasiline 1-39. A Schlenk flask was charged with silyl ether **1-37** (0.559 g, 2.34 mmol) followed by freshly distilled methylene chloride (30 mL). The solution was degassed via three freeze-pump-thaw cycles. The reaction vessel was transferred to a glove box and the Schrock Catalyst (**1-38**) was added in one portion (100 mg, 0.13 mmol). The reaction was kept under Ar and allowed to stir at room temperature. After 18h an additional portion of the Schrock catalyst (**1-38**) was added (100 mg, 0.13 mmol). After 3 days the reaction mixture was concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 10:1) followed by Kugelrohr distillation (bath temp 100ºC, pressure = 0.5 mmHg) to give dihydrooxasiline **1-39** as a colorless oil (299 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (dt, *J* = 14.2, 4.2 Hz, 1H), 5.72 (dt, *J* = 14.2, 1.9 Hz, 1H), 3.61 (q, *J* = 6.5 Hz, 1H), 2.19 – 2.10 (m, 2H), 2.00 – 1.89 (m, 1H), 1.78 – 1.60 (m, 5H), 1.43 – 0.90 (m, 6H), 0.17 (s, 3H), 0.15 (s, 3H). The data were consistent with literature values.[12]



Alcohol (*Z*)-1-40a. To a stirred solution of dihydrooxasiline **1-39** (350 mg, 1.66 mmol) in THF

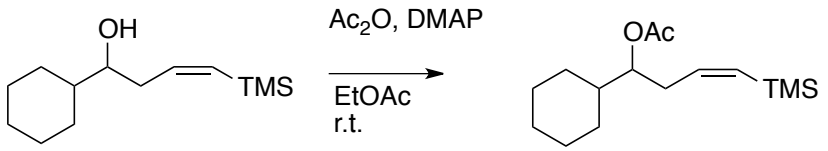
(25 mL) at 0ºC was added methyllithium (1.6 mL, 1.6M in ether, 2.6 mmol). The solution was allowed to slowly warm to room temperature. After 3.5h, sat. NH_4Cl solution (5 mL) and diethyl ether (10 mL) were added. The aqueous layer was extracted with diethyl ether (50 mL in three portions). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to Kugelrohr distillation (bath temperature = 130ºC, pressure = 0.5 mmHg) to give alcohol **(*Z*)-1-40a** (339 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (ddd, *J* = 14.5, 8.5, 6.5 Hz, 1H), 5.70 (d, *J* = 14.1 Hz, 1H), 3.45 – 3.38 (m, 1H), 2.39 – 2.30 (m, 1H), 2.29 – 2.20 (m, 1H), 1.89 – 1.63 (m, 5H), 1.47 (d, *J* = 3.9 Hz, 1H), 1.43 – 1.31 (m, 1H), 1.31 – 0.98 (m, 5H), 0.13 (s, 9H). The data were consistent with literature values.[12]



(*Z*)-1-40a **(*Z*)-1-40b** 70%

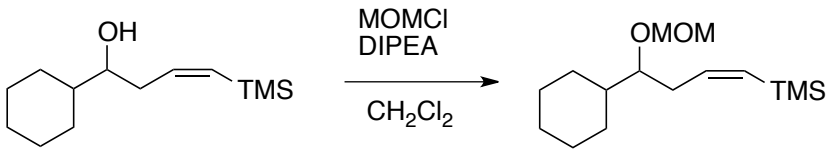
TBS ether (*Z*)-1-40b. To a stirred solution of alcohol **(*Z*)-1-40a** (92 mg, 0.41 mmol) and 2,6-lutidine (0.15 mL, 1.3 mmol) in methylene chloride (3.5 mL) at 0ºC was added t-butyldimethylsilyl triflate (0.30 ml,1.3 mmol) . The reaction mixture was allowed to warm to room temperature. After 24 hours the reaction mixture was diluted with methylene chloride (15 mL) and washed with sat. $NaHCO_3$ solution (3 x 5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 100:1) to afford TBS ether **(*Z*)-1-40b** (98 mg, 70%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (dt, *J* = 14.2, 7.1 Hz, 1H), 5.53 (dt, *J* = 14.2, 1.5 Hz, 1H), 3.53 – 3.46 (m, 1H), 2.29 – 2.23 (m, 2H), 1.80 – 1.59 (m, 5H), 1.43 – 1.30 (m, 1H), 1.29 – 0.94 (m, 5H), 0.88 (s, 9H), 0.11 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 146.2, 130.0, 76.3, 43.5, 37.6, 28.9, 28.1, 26.8, 26.5, 26.5, 26.0, 18.2, 0.2, -4.1, -4.5. IR (neat) νmax: 2929, 2855, 1606. HRMS [EI+] calc for $C_{23}H_{35}Si$ $[M]^+$ 339.25081, found 339.25442.



(*Z*)-1-40a **(*Z*)-1-40c**
86%

Acetate (*Z*)-1-40c. To a solution of alcohol **(*Z*)-1-40a** (25 mg, 0.11 mmol) and DMAP (174 mg, 1.42 mmol) in ethyl acetate (3 mL) was added acetic anhydride (0.06 mL, 0.6 mmol). The solution was allowed to stir at room temperature for 1.5 hrs. The reaction mixture was diluted with methylene chloride (30 mL), washed with sat. $NaHCO_3$ solution (10 mL) followed by 10% citric acid solution (2 x 10 mL). The organic solution was washed with an additional portion of sat. $NaHCO_3$ solution (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude residue was subjected to column chromatographed (Hex/EtOAc = 30:1) to afford acetate **(*Z*)-1-40c** (25 mg, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (dt, *J* = 14.2, 7.2 Hz, 1H), 5.57 (dt, *J* = 14.2, 1.4 Hz, 1H), 4.81 (q, *J* = 6.3 Hz, 1H), 2.41 – 2.34 (m, 2H), 1.80 – 1.62 (m, 5H), 1.57 – 1.45 (m, 1H), 1.29 – 0.95 (m, 5H), 0.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 143.9, 131.6, 41.2, 35.2, 29.0, 28.2, 26.3, 26.1, 26.0, 21.1, 0.2. IR (neat) νmax: 2930, 2854, 1739, 1608, 1451, 1370, 1247, 1180. HRMS [ES+] calc for $C_{15}H_{28}O_2NaSi$ $[M+Na]^+$ 291.1756, found 291.1761

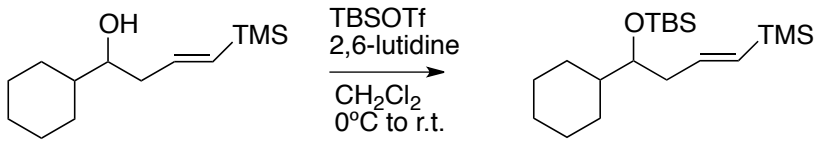


(*Z*)-1-40a **(*Z*)-1-40d**
79%

MOM ether (*Z*)-1-40d. To a solution of alcohol **(*Z*)-1-40a** (47 mg, 0.21 mmol) in methylene chloride (5 mL) was added N,N-Diisopropylethylamine (0.40 mL, 2.3 mmol). The solution was cooled to 0ºC and then chloromethyl methyl ether was added in one portion (0.07 mL, 0.9 mmol). The solution was allowed to warm to room temperature and was then brought to reflux.

After 2 hours the solution was allowed to cool to room temperature and quenched with sat. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic solution was washed with 10% citric acid (2 x 10 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 50:1 to 20:1) to give MOM ether **(*Z*)-1-40d** as a colorless oil.

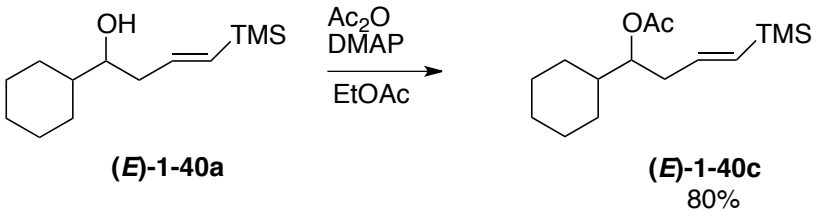
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dt, *J* = 14.2, 7.1 Hz, 1H), 5.57 (dt, *J* = 14.2, 1.5 Hz, 1H), 4.64 (J_{AB} = 6.9 Hz, 2H), 3.43 – 3.34 (m, 4H), 2.38 – 2.32 (m, 2H), 1.82 – 1.62 (m, 5H), 1.56 – 1.45 (m, 1H), 1.30 – 0.97 (m, 5H), 0.12 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 130.6, 96.2, 81.9, 55.6, 41.6, 35.2, 29.0, 28.4, 26.6, 26.4, 0.1. IR (neat) νmax: 2928, 2853, 1605, 1451, 1043, 838. HRMS [ES+] calc for $C_{15}H_{30}O_2NaSi$ $[M+Na]^+$ 293.1913 found 293.1911



(*E*)-1-40a **(*E*)-1-40b** 72%

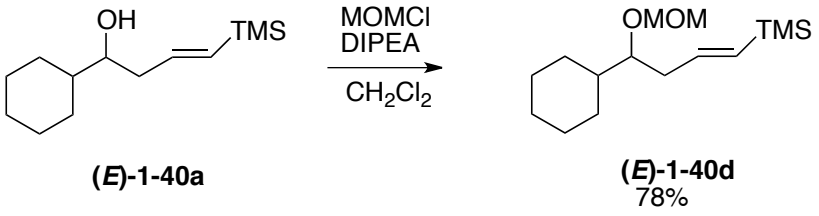
TBS ether (*E*)-1-40b.* To a stirred solution of alcohol **(*E*)-1-40a**[13] (187 mg, 0.83 mmol) and 2,6-lutidine (0.28 mL, 2.4 mmol) in methylene chloride (5 mL) at 0ºC was added a solution of *t*-butyldimethylsilyl triflate (0.28 mL, 1.24 mmol) in methylene chloride (1 mL) . The reaction mixture was allowed to warm to room temperature. After 10 minutes the reaction mixture was quenched with sat. $NaHCO_3$ (5 mL). The reaction mixture was diluted with methylene chloride (30 mL) and washed with 10% citric acid solution (3 x 10 ml). The organic solution was washed with an additional portion of sat. $NaHCO_3$ (5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (hexanes) to afford TBS ether **(*E*)-1-40b** (202 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (dt, *J* = 18.6, 6.7 Hz, 1H), 5.64 (d, *J* = 18.6 Hz, 1H), 3.48 (q, *J* = 5.5 Hz, 1H), 2.27 – 2.23 (m, 2H), 1.78 – 1.61 (m, 5H), 1.38 – 1.30 (m, 1H), 1.23 – 0.93 (m, 5H), 0.88 (s, 9H), 0.04 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 132.0, 76.1, 43.4, 41.6, 28.7, 28.2, 26.8, 26.5, 26.5, 26.0,

18.2, -1.2, -4.2, -4.4. IR (neat) νmax: 2929, 2855, 1248, 863, 836. HRMS [ES+] calc for $C_{19}H_{40}ONaSi_2$ $[M+Na]^+$ 363.2515 found 363.2521



(*E*)-1-40a **(*E*)-1-40c** 80%

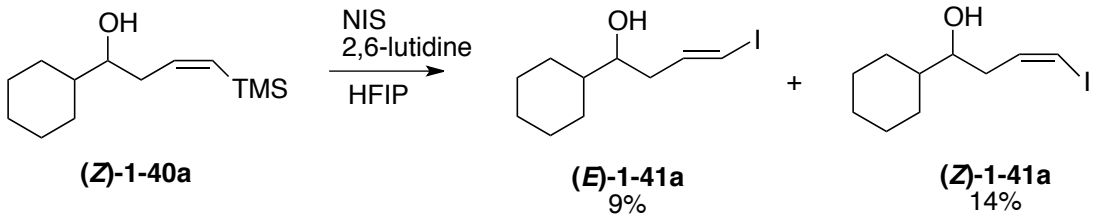
Acetate (*E*)-1-40c.** To a solution of alcohol **(*E*)-1-40a** (99 mg, 0.44 mmol) and DMAP (323 mg, 2.64 mmol) in ethyl acetate (10 mL) was added acetic anhydride (0.17 mL, 1.8 mmol). The solution was allowed to stir at room temperature overnight. The reaction mixture was quenched with water (10 mL), and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic solution was washed with 10% citric acid (3 x 10 mL) followed by sat. $NaHCO_3$ solution (3 x 10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by Kugelrohr distillation (0.5 mmHg, Bath Temp = 120ºC) to afford acetate **(*E*)-1-40c** (94 mg, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 18.5, 7.5, 5.7 Hz, 1H), 5.69 (dt, *J* = 18.5, 1.3 Hz, 1H), 4.79 (ddd, *J* = 8.3, 6.3, 4.3 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.34 – 2.23 (m, 1H), 1.81 – 1.61 (m, 5H), 1.55 – 1.41 (m, 1H), 1.28 – 0.93 (m, 5H), 0.03 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δC 170.67, 142.27, 142.24, 133.49, 133.46, 133.43, 41.03, 39.05, 39.01, 29.01, 28.19, 26.37, 26.09, 26.00, 21.07, 21.02, -1.32. IR (neat) νmax: 2929.08, 2854.09, 1739.49, 1618.85, 1244.60. HRMS [ES+] calc for $C_{15}H_{28}O_2NaSi$ $[M+Na]^+$ 291.1756 found 291.1758



(*E*)-1-40a **(*E*)-1-40d** 78%

MOM ether (*E*)-1-40d.* To a solution of alcohol **(*E*)-1-40a** (123 mg, 0.54 mmol) in methylene chloride (5 mL) was added N,N-Diisopropylethylamine (0.47 mL, 2.7 mmol). The solution was cooled to 0ºC and then chloromethyl methyl ether was added in one portion (0.08 mL, 1 mmol). The solution was allowed to warm to room temperature and allowed to reflux overnight. After

cooling to room temperature the reaction was quenched with sat. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic solution was washed with 10% citric acid (2 x 10 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 100:1) to give MOM ether **(*E*)-1-40d** (115 mg, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 18.6, 6.6 Hz, 1H), 5.72 (dt, *J* = 18.6, 1.4 Hz, 1H), 4.64 (J_{AB} = 6.9 Hz, 2H), 3.44 – 3.35 (m, 4H), 2.41 – 2.27 (m, 2H), 1.83 – 1.61 (m, 5H), 1.53 – 1.42 (m, 1H), 1.30 – 0.95 (m, 5H), 0.04 (s, 9H). ^{13}C NMR (126 MHz, CDCl3) δ 143.7, 132.6, 95.9, 81.4, 55.7, 41.3, 38.9, 28.6, 28.5, 26.6, 26.38, 26.35, -1.24. IR (neat) νmax: 2928, 2853, 1616, 1450, 1247. HRMS [ES+] calc for $C_{15}H_{30}O_2NaSi$ $[M+Na]^+$ 293.1913 found 293.1911.



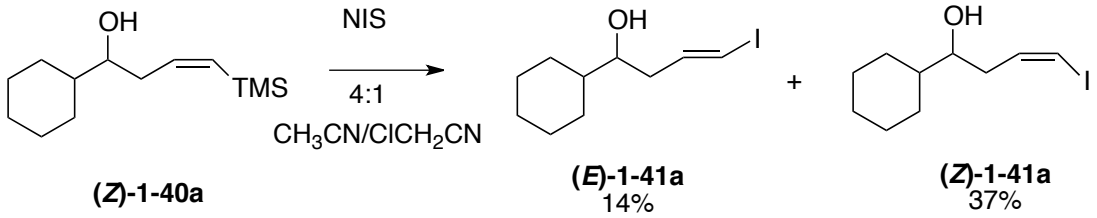
(*Z*)-1-40a **(*E*)-1-41a** 9% **(*Z*)-1-41a** 14%

General Procedure for the Iododesilylation of Alcohols in HFIP containing 2,6-lutidine (Procedure A). Alcohols (*E*)-1-41a and (*Z*)-1-41a. To a stirred solution of alcohol **(*Z*)-1-40a** (18 mg, 0.079 mmol) in HFIP (1 mL) was added NIS in one portion (68 mg, 0.30 mmol). The solution was allowed to stir in the absence of light for 2 hours. The reaction mixture was quenched with sat. sodium thiosulfate solution (2 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL in three portions). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 20:1 then 10:1) to give alcohol **(*E*)-1-41a** (2 mg, 9%) as a white solid and alcohol **(*Z*)-1-41a** (3 mg, 14%) as a pale yellow oil.

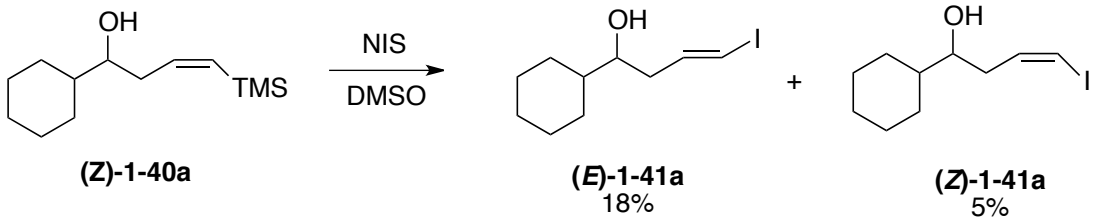
Alcohol (*E*)-1-41a: mp: 51-52ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (dt, *J* = 14.6, 7.5 Hz, 1H), 6.12 (dt, *J* = 14.6, 1.3 Hz, 1H), 3.44 – 3.38 (m, 1H), 2.29 (dddd, *J* = 14.5, 7.2, 3.6, 1.4 Hz, 1H), 2.21 – 2.13 (m, 1H), 1.87 – 1.61 (m, 5H), 1.45 (d, *J* = 4.7 Hz, 1H), 1.40 – 0.95 (m, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 143.3, 77.0, 74.5, 43.1, 40.8, 29.1, 27.9, 26.4, 26.2, 26.0. IR (neat) νmax: 3307, 2849, 1607, 1444. HRMS [EI+] calc for $C_{10}H_{17}OI$ $[M]^+$ 280.03245 found

280.03427.

Alcohol (*Z*)-1-41a ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 – 6.30 (m, 2H), 3.56 – 3.49 (m, 1H), 2.44 – 2.25 (m, 2H), 1.94 – 1.63 (m, 5H), 1.42 (d, *J* = 5.1 Hz, 1H), 1.40 – 0.97 (m, 6H).^{13}C NMR (101 MHz, CDCl3) δ 138.4, 84.4, 75.0, 43.4, 39.6, 29.1, 28.0, 26.4, 26.2, 26.1. IR (neat) νmax: 3382, 2923, 2851, 1449. HRMS [EI+] calc for $C_{10}H_{17}OI$ $[M]^+$ 280.03245 found 280.03258.

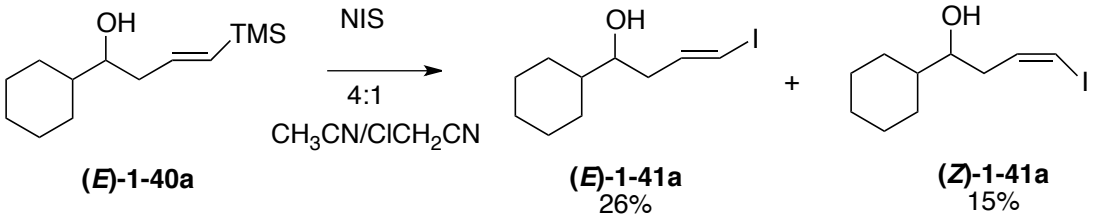


General Procedure for the Iododesilylation of Alcohols in 4:1 MeCN/$ClCH_2CN$ (Procedure B). Alcohols (*E*)-1-41a and (*Z*)-1-41a. To a stirred solution of alcohol **(*Z*)-1-40a** (20 mg, 0.09 mmol) in a 4:1 MeCN/$ClCH_2CN$ mixture (1 mL) was added NIS in one portion (65 mg, 0.29 mmol). The solution was allowed to stir in the absence of light for 2 hours. The reaction mixture was quenched with sat. sodium thiosulfate solution (2 mL) and diluted with CH_2Cl_2 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL in three portions). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 20:1 to 10:1) to give alcohol **(*E*)-1-41a** (3 mg, 14%) and alcohol **(*Z*)-1-41a** (9 mg, 37%).

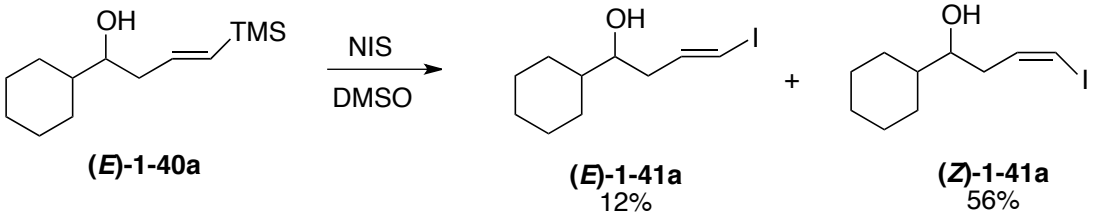


General Procedure for the Iododesilylation of Alcohols in DMSO (Procedure C). Alcohols (*E*)-1-41a and (*Z*)-1-41a. To a stirred solution of alcohol **(*Z*)-1-40a** (21 mg, 0.093 mmol) in DMSO (1 mL) was added NIS in one portion (66 mg, 0.29 mmol). The solution was allowed to stir in the absence of light for 24 hours. The reaction mixture was quenched with sat. sodium

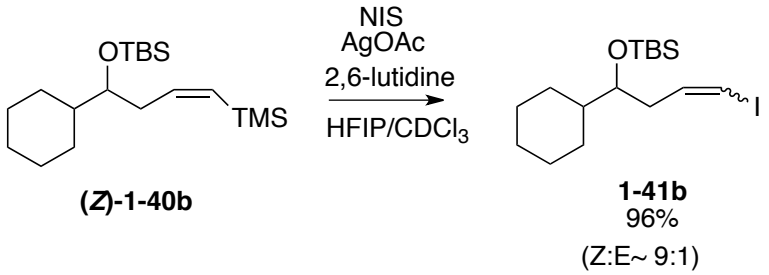
thiosulfate solution (2 mL) and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL in three portions). The combined organic solution was washed with water (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 20:1 then 10:1) to give alcohol **(*E*)-1-41a** (5 mg, 18%) and alcohol **(*Z*)-1-41a** (1 mg, 5%).



Alcohols (*E*)-1-41a and (*Z*)-1-41a.** Application of procedure B to compound **(*E*)-1-40a** (60 mg, 0.26 mmol), after 45 hours gave alcohol **(*E*)-1-41a** (20 mg, 26%) as an off white solid and alcohol **(*Z*)-1-41a** (11 mg, 15%) as a colorless oil.



Alcohols (*E*)-1-41a and (*Z*)-1-41a.* Application of procedure C to compound **(*E*)-1-40a** (21 mg, 0.93 mmol), after 19 hours gave alcohol **(*E*)-1-41a** (3 mg, 12%) as an off white solid and alcohol **(*Z*)-1-41a** (15 mg, 56%) as a colorless oil.

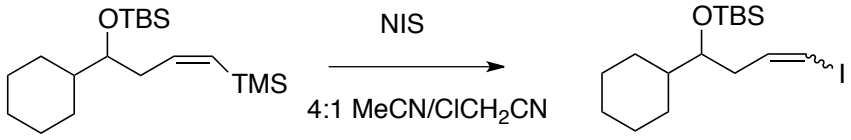


(*Z*)-1-40b

1-41b
96%
(Z:E~ 9:1)

General Procedure for the Iododesilylation of TBS Protected Alcohols in HFIP containing 2,6-lutidine and AgOAc (Procedure D). TBS ether (*Z*)-1-41b. To a stirred solution of TBS ether **(*Z*)-1-40b** (10 mg, 0.029 mmol), 2,6-lutidine (0.01 mL, 0.1 mmol), silver acetate (2 mg, 0.01 mmol), in a 1:1 mixture of hexafluoroisopropanol and chloroform-d (1mL) was added NIS in one portion (23 mg, 0.10 mmol). The solution was allowed to stir in the absence of light for 10 minutes. The reaction mixture was quenched with saturated sodium thiosulfate (2 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic solution was washed with 10% citric acid (2 x 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 100:1 to afford TBS ether **1-41b** (10 mg, 96%) as a 9:1 (*Z*:*E*) mixture of stereoisomers; the mixture could be recrystallized in chloroform to give a white solid (mp 123-125ºC).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (dt, *J* = 14.7, 7.6 Hz, 1H, mn), 6.32 – 6.22 (m, 2H, mj), 5.99 (dt, *J* = 14.7, 1.4 Hz, 1H, mn), 3.55 (q, *J* = 5.5 Hz, 1H, mj), 3.44 (q, *J* = 5.5 Hz, 1H, mn), 2.37 – 2.24 (m, 2H, mj, mn), 2.21 – 2.17 (m, 2H, mj, mn), 1.81 – 1.59 (m, 5H, mj, mn), 1.36 – 0.93 (m, 6H, mj, mn), 0.89 (s, 9H, mj, mn), 0.05 (s, 3H, mj), 0.04 (s, 3H, mj), 0.03 (s, 3H, mn), 0.02 (s, 3H, mn); mj = major isomer, mn = minor isomer. ^{13}C NMR (major isomer) (126 MHz, CDCl3) δ 138.6, 83.3, 75.0, 43.1, 39.4, 29.0, 28.4, 26.6, 26.41, 26.36, 25.9, 18.1, -4.3, -4.5. IR (neat) νmax 2928, 2854, 1256. HRMS [EI+] calc for $C_{16}H_{30}OISi$ $[M]^+$ 393.11110 found 393.11140.



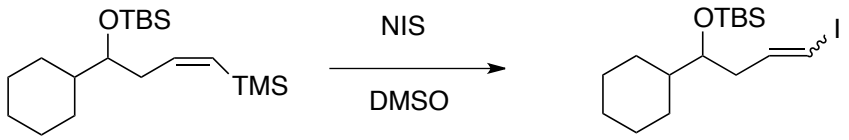
(*Z*)-1-40b

1-41b
60%
(Z:E~ 15.3:1)

General Procedure for the Iododesilylation of TBS Protected Alcohols in 4:1

MeCN/$ClCH_2CN$ (Procedure E). TBS ether (*Z*)-1-41b. To a stirred solution of TBS ether **(*Z*)-1-40b** (20 mg, 0.059 mmol), in a 4:1 MeCN/$ClCH_2CN$ mixture (1 mL) was added NIS in one portion (45 mg, 0.20 mmol). The solution was allowed to stir in the absence of light for 3 hours. The reaction mixture was quenched with saturated sodium thiosulfate (2 mL) and diluted with diethyl ether (5 mL). The aqueous solution was extracted with diethyl ether (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (100:1 Hexanes/EtOAc) to afford unreacted TBS ether **(*Z*)-1-40b** (1 mg) and TBS ether **1-41b** (13 mg, 60% yield based on recovered starting material) as a 15.3:1 (*Z*:*E*) mixture of stereoisomers; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.6, 7.5 Hz, 1H, mn), 6.32 – 6.22 (m, 2H, mj), 5.99 (dt, *J* = 14.6 Hz, 1.3 Hz 1H, mn), 3.55 (q, *J* = 5.5 Hz, 1H, mj), 3.44 (q, *J* = 5.5 Hz, 1H, mn), 2.40 – 2.23 (m, 2H, mj), 2.22 – 2.16 (m, 2H, mn), 1.87 – 1.56 (m, 5H, mj,mn), 1.42 – 0.92 (m, 6H, mj,mn), 0.89 (s, 9H, mj,mn), 0.05 (s, 3H, mj), 0.04 (s, 3H, mj), 0.03 (s, 3H, mn), 0.03 (s, 3H, mn); mj = major isomer, mn = minor isomer. IR (neat) νmax: 2928, 2854, 1256.



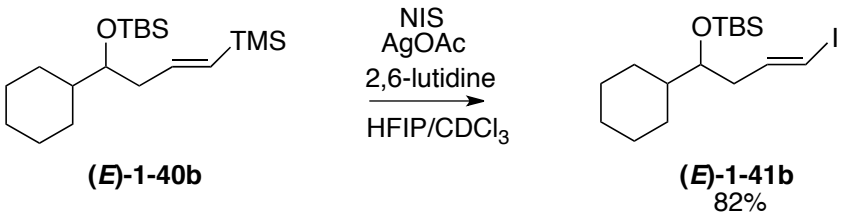
(*Z*)-1-40b

(E)-1-41b
47%
(Z:E~ 1:9.9)

General Procedure for the Iododesilylation of TBS Protected Alcohols in DMSO (Procedure F): TBS ether (*E*)-1-41b. To a stirred solution of TBS ether **(*Z*)-1-40b** (20 mg, 0.059 mmol) in DMSO (1 mL) was added NIS in one portion (38 mg, 0.17 mmol). The solution was allowed to stir in the absence of light for 6 hours. The reaction mixture was quenched with sat. sodium thiosulfate solution (3 mL) and diluted with ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic solution was washed with water (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was subjected to column chromatography (100:1 Hexanes/EtOAc) to give TBS ether **(*E*)-1-41b** (11 mg, 47%) as a 1:9.9 (*Z*:*E*) mixture of stereoisomers; colorless oil.

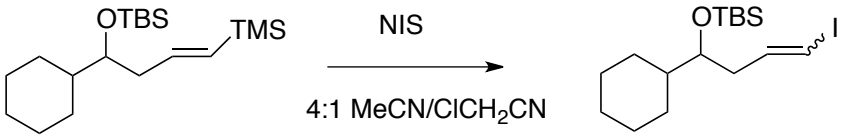
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.6, 7.5 Hz, 1H, mj), 6.32 – 6.22 (m, 2H, mn), 5.99

(dt, *J* = 14.6, 1.3 Hz, 1H, mj), 3.55 (q, *J* = 5.6 Hz, 1H, mn), 3.44 (q, *J* = 5.5 Hz, 1H, mj), 2.40 – 2.23 (m, 2H, mn), 2.22 – 2.16 (m, 2H, mj), 1.87 – 1.56 (m, 5H, mn, mj), 1.42 – 0.92 (m, 6H, mn, mj), 0.89 (s, 9H, mn, mj), 0.05 (s, 3H, mn), 0.04 (s, 3H, mn), 0.03 (s, 3H, mj), 0.03 (s, 3H, mj); mj = major isomer, mn = minor isomer. IR (neat) νmax: 2927, 2854, 1258.



(*E*)-1-40b **(*E*)-1-41b** 82%

TBS ether (*E*)-1-41b. Application of procedure D to compound **(*E*)-1-40b** (21 mg, 0.062 mmol) gave, after 40 minutes, TBS ether **(*E*)-1-41b** (20 mg, 82%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.3, 7.5 Hz, 1H), 5.99 (dt, *J* = 14.3, 1.3 Hz, 1H), 3.44 (q, *J* = 5.4 Hz, 1H), 2.22 – 2.16 (m, 2H), 1.80 – 1.58 (m, 5H), 1.40 – 0.90 (m, 6H), 0.89 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 143.8, 76.0, 75.3, 43.1, 40.5, 28.7, 28.3, 26.7, 26.4, 26.4, 25.9, 25.7, 18.1, -4.2, -4.5. IR (neat) νmax: 2927, 2854, 1255.

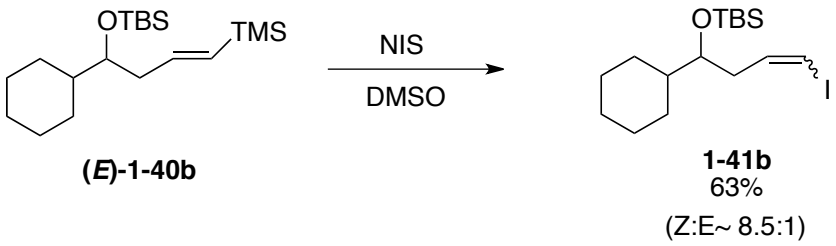


(*E*)-1-40b **1-41b** 64% (Z:E~ 1:7.4)

TBS ether (*E*)-1-41b.** Application of procedure E to compound **(*E*)-1-40b** (45 mg, 0.13 mmol), gave after 24 hours TBS ether **1-41b** (33 mg, 64% yield) as a 1:7.4 (*Z*:*E*) mixture of stereoisomers; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.6, 7.5 Hz, 1H, mj), 6.32 – 6.22 (m, 2H, mn), 5.99 (dt, *J* = 14.6 Hz, 1.3 Hz 1H, mj), 3.55 (q, *J* = 5.5 Hz, 1H, mn), 3.44 (q, *J* = 5.5 Hz, 1H, mj), 2.40 – 2.23 (m, 2H, mn), 2.22 – 2.16 (m, 2H, mj), 1.87 – 1.56 (m, 5H, mn, mj), 1.42 – 0.92 (m, 6H, mn, mj), 0.89 (s, 9H, mn, mj), 0.05 (s, 3H, mn), 0.04 (s, 3H, mn), 0.03 (s, 3H, mj), 0.03 (s, 3H,

mj); mj = major isomer, mn = minor isomer. IR (neat) νmax: 2927, 2854, 1255.

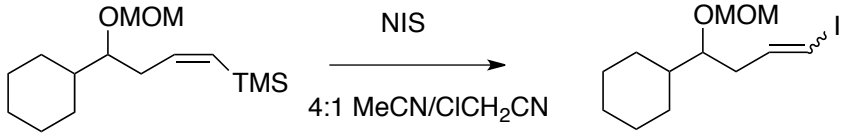


(*E*)-1-40b

1-41b
63%
(Z:E~ 8.5:1)

TBS ether (*Z*)-1-41b.** Application of procedure F to compound **(*E*)-1-40b** (43 mg, 0.13 mmol) gave after 23 hours TBS ether **1-41b** (32 mg, 63% yield) as a 8.5:1 (*Z*:*E*) mixture of stereoisomers; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (dt, *J* = 14.5, 7.4 Hz, 1H, mn), 6.32 – 6.22 (m, 2H, mj), 5.99 (dt, *J* = 14.6 Hz, 1.3 Hz 1H, mn), 3.55 (q, *J* = 5.5 Hz, 1H, mj), 3.44 (q, J=5.5 Hz, 1H, mn), 2.40 – 2.23 (m, 2H, mj), 2.22 – 2.16 (m, 2H, mn), 1.87 – 1.56 (m, 5H, mj,mn), 1.42 – 0.92 (m, 6H, mj, mn), 0.89 (s, 9H, mj,mn), 0.05 (s, 3H, mj), 0.04 (s, 3H, mj), 0.03 (s, 3H, mn), 0.03 (s, 3H, mn); mj = major isomer, mn = minor isomer. IR (neat) νmax: 2928, 2854, 1256.



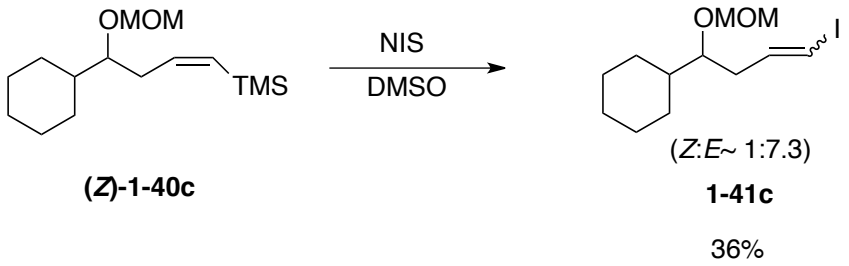
(*Z*)-1-40c

1-41c
(*Z*:*E*~ 1:2)
55%

General Procedure for the Iododesilylation of MOM Protected Alcohols in 4:1 MeCN/$ClCH_2CN$ (Procedure G): MOM ether (*E*)-1-41c. To a stirred solution of MOM ether **(*Z*)-1-40c** (10 mg, 0.037 mmol), in a 4:1 MeCN/$ClCH_2CN$ mixture (0.5 mL) was added NIS in one portion (28 mg, 0.12 mmol). The solution was allowed to stir in the absence of light for 43 hours and then quenched with saturated sodium thiosulfate (2 mL). The reaction mixture was diluted with ether (5 mL) and the aqueous layer was extracted with ether (3 x 7 mL). The combined organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude

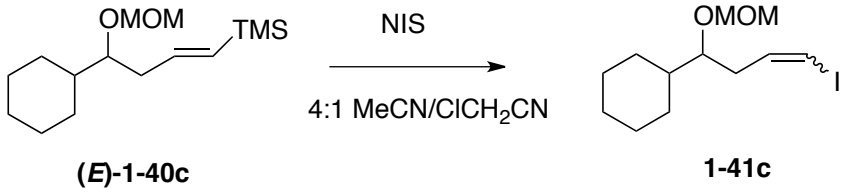
residue was chromatographed (100:1 to 30:1 Hexanes/EtOAc) to afford MOM ether **1-41c** (7 mg, 55% yield) as a 1:2 (*Z*:*E*) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.51 (m, 1H, mj), 6.34 – 6.27 (m, 2H, mn), 6.07 (dt, *J* = 14.4, 1.4 Hz, 1H, mj), 4.63 (s, 2H, mj), 4.65 (J_{AB} = 6.9 Hz, 2H, mn), 3.40 – 3.33 (m, 4H, mj,mn), 2.45 – 2.21 (m, 2H, mj,mn), 1.88 – 1.61 (m, 5H, mj,mn), 1.52 – 1.41 (m, 1H, mj,mn), 1.31 – 0.93 (m, 5H, mj,mn); mj = major isomer, mn = minor isomer. IR (neat) νmax: 2925, 2852, 1039. HRMS [ES+] calc for $C_{12}H_{21}O_2NaI$ $[M+Na]^+$ 347.0484 found 347.0489.



General Procedure for the Iododesilylation of MOM Protected Alcohols in DMSO (Procedure H): MOM ether (*E*)-1-41c. To a stirred solution of MOM ether **(*Z*)-1-40c** (14 mg, 0.052 mmol), in DMSO (1 mL) was added NIS in one portion (43 mg, 0.19 mmol). The solution was allowed to stir in the absence of light for 17 hours and was quenched with saturated sodium thiosulfate (5 mL). The reaction mixture was diluted with methylene chloride (5 mL) and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was washed with water (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was chromatographed (50:1 Hexanes/EtOAc) and then subjected to Kugelrohr distillation (pressure = 0.5 mmHg, bath temp = 150ºC) to afford MOM ether **1-41c** (6 mg, 36% yield) as a 1:7.3 (*Z*:*E*) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.51 (m, 1H, mj), 6.34 – 6.27 (m, 2H, mn), 6.07 (dt, *J* = 14.4, 1.4 Hz, 1H, mj), 4.63 (s, 2H, mj), 4.65 (J_{AB} = 6.9 Hz, 2H, mn), 3.40 – 3.33 (m, 4H, mj,mn), 2.45 – 2.21 (m, 2H, mj,mn), 1.88 – 0.93 (m, 11H, mj,mn); mj = major isomer, mn = minor isomer. IR (neat) νmax 2925, 2852, 1039.



(*E*)-1-40c

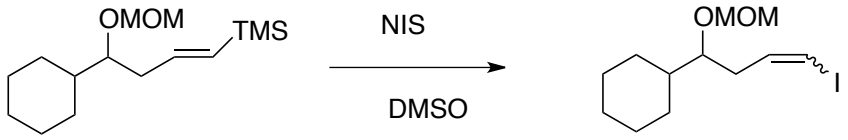
1-41c

(*Z*:*E*~ 4.3:1)

50%

MOM ether (*Z*)-1-41c.* Application of general procedure G to compound **(*E*)-1-40c** (10 mg, 0.038 mmol), after 4 hours gave MOM ether **1-41c** (6 mg, 50%) as a 4.3:1 (Z:E) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.51 (m, 1H, mn), 6.34 – 6.27 (m, 2H, mj), 6.07 (dt, *J* = 14.4, 1.4 Hz, 1H, mn), 4.63 (s, 2H, mn), 4.65 (J_{AB} = 6.9 Hz, 2H, mj), 3.40 – 3.33 (m, 4H, mj, mn), 2.45 – 2.21 (m, 2H, mj, mn), 1.88 – 0.99 (m, 11H, mj, mn); mj = major, mn = minor. IR (neat) νmax: 2925, 2852, 1040.



(*E*)-1-40c

1-41c

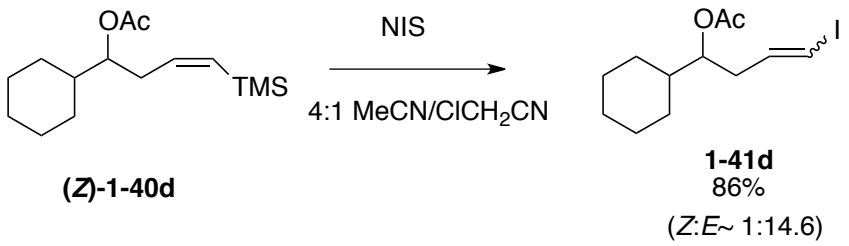
(*Z*:*E*~ 12.1:1)

31%

MOM ether (*Z*)-1-41c.** Application of general procedure H to compound **(*E*)-1-40c** (5.2 mg, 0.018 mmol), after 20 hours gave MOM ether **1-41c** (1.9 mg, 31%) as a 12.1:1 (*Z*:*E*) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 – 6.51 (m, 1H, mn), 6.34 – 6.27 (m, 2H, mj), 6.07 (dt, *J* = 14.5, 1.4 Hz, 1H, mn), 4.63 (s, 2H, mn), 4.65 (J_{AB} = 6.9 Hz, 2H, mj), 3.40 – 3.33 (m, 4H, mj, mn), 2.45 – 2.21 (m, 2H, mj, mn), 1.88 – 0.90 (m, 11H); mj = major, mn = minor. IR (neat)

νmax: 2925, 2852, 1040.

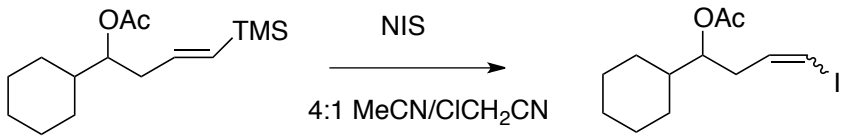


(*Z*)-1-40d

1-41d
86%
(*Z*:*E*~ 1:14.6)

General Procedure for the Iododesilylation of Acetate Protected Alcohols in 4:1 MeCN/ClCH$_2$CN (Procedure I): Acetate (*E*)-1-41d. To a stirred solution of acetate **(*Z*)-1-40d** (10 mg, 0.04 mmol), in a 4:1 MeCN/ClCH$_2$CN mixture (1 mL) was added NIS in one portion (27 mg, 0.12 mmol). The solution was allowed to stir in the absence of light for 36 hours. The reaction mixture was quenched with saturated sodium thiosulfate (3 mL). The aqueous solution was extracted with methylene chloride (3 x 20 mL). The organic solution was washed with sat. $NaHCO_3$ (3 x 10 mL), dried over $MgSO_4$, and then filtered. The solvent was removed in vacuo and the crude residue was chromatographed (50:1 Hexanes/EtOAc) and then subjected to Kugelrohr distillation (0.5 Torr, bath temp 150ºC) to afford acetate **1-41d** (32 mg, 63% yield) as a 1:14.6 (*Z*:*E*) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 – 6.40 (m, 1H, mj), 6.31 (dt, *J* = 7.9, 1.4 Hz, 1H, mn), 6.22 – 6.13 (m, 1H, mn), 6.08 (dt, *J* = 14.4, 1.3 Hz, 1H, mj), 4.88 – 4.80 (m, 1H, mn), 4.77 – 4.70 (m, 1H, mj), 2.46 – 2.37 (m, 2H, mn), 2.40 – 2.18 (m, 2H, mj), 2.04 (s, 3H, mj,mn), 1.81 – 1.42 (m, 5H, mj,mn), 1.31 – 0.90 (m, 5H, mj,mn); mj = major, mn = minor. ^{13}C NMR (major) (126 MHz, $CDCl_3$) δ 170.7, 141.8, 75.8, 40.5, 37.7, 28.8, 28.1, 26.2, 25.9, 25.8, 21.1. IR (neat) νmax 2927, 2853, 1738, 1235 HRMS [ES+] calc for $C_{12}H_{19}O_2NaI$ $[M]^+$ 345.0328 found 345.0327.



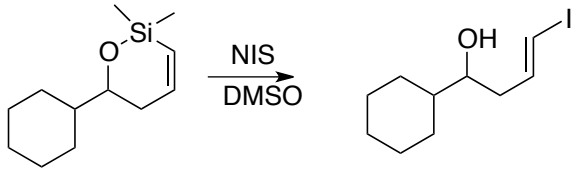
(*E*)-1-40d

1-41d

(Z:E~ 20.7:1)

88%

Acetate 1-41d.** Application of general procedure I to acetate **(*E*)-1-40d** (50 mg, 0.19 mmol), gave, after stirring for 24 hours, acetate **1-41d** (53 mg, 88% yield) as a 20.7:1 (*Z*:*E*) mixture of stereoisomers; colorless oil. A small amount of silicon containing byproduct was present. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 – 6.40 (m, 1H, mn), 6.31 (dt, *J* = 7.9, 1.4 Hz, 1H, mj), 6.22 – 6.13 (m, 1H, mj), 6.08 (dt, *J* = 14.4, 1.3 Hz, 1H, mn), 4.88 – 4.80 (m, 1H, mj), 4.77 – 4.70 (m, 1H, mn), 2.46 – 2.37 (m, 2H, mj), 2.40 – 2.18 (m, 2H, mn), 2.04 (s, 3H, mj, mn), 1.81 – 1.42 (m, 5H, mj,mn), 1.31 – 0.90 (m, 5H, mj,mn); mj = major, mn = minor. ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 137.1, 84.6, 76.2, 41.0, 36.9, 29.0, 28.3, 26.3, 26.0, 25.9, 21.1. IR (neat) νmax: 2928, 2853, 1738, 1611.

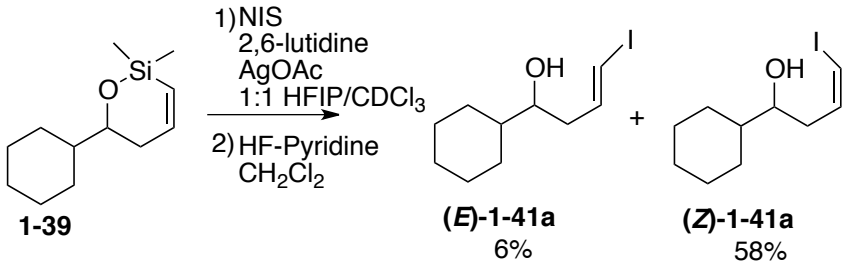


1-39

(E)-1-41a

65%

Alcohol (*E*)-1-41a. Application of general procedure C to oxasiline **1-39** (49 mg, 0.23 mmol), gave alcohol **(*E*)-1-41a** (42 mg, 65%) after stirring for 6 days, as an off- white solid.



1-39 **(*E*)-1-41a** 6% **(*Z*)-1-41a** 58%

Alcohols (*E*)-1-41a and (*Z*)-1-41a. To a stirred solution of oxasiline **1-39** (27 mg, 0.13 mmol) in a 1:1 HFIP/$CDCl_3$ mixture (2 ml) were added AgOAc (8 mg, 0.05 mmol) and 2,6-lutidine (0.03 mL, 0.3 mmol). NIS was added (69 mg, 0.31 mmol) and the solution was allowed to stir at room temperature in the absence of light. After 10 minutes sat. sodium thiosulfate was added (3 mL). The solution was diluted with methylene chloride (30 mL) and washed with 10% citric acid (3 x 10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was taken up in CH_2Cl_2 (2 mL) and 0.2 mL HF•Pyridine was added. After 5 min the reaction mixture was quenched sat. $NaHCO_3$ (30 mL)and diluted with CH_2Cl_2 (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic solution was washed with sat. $NaHCO_3$ (3 x 10 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was chromatographed (20:1 Hexanes/EtOAc) to give alcohol **(*E*)-1-41a** (2 mg, 6%) as an off white solid and alcohol **(*Z*)-1-41a** (21 mg, 58%) as a colorless oil.

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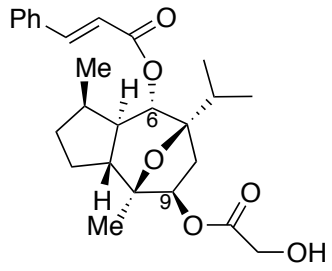
Chapter 2

(-)-Englerin A : Background

2.1 Introduction

2.1.1 The Discovery of (-)-Englerin A

In 2008 Beutler and coworkers isolated the guaiane sesquiterpene (-)-englerin A (EA) (**2-1**, Figure 2-1) from the stem bark of *Phyllanthus engleri*[1], a species indigenous to east Africa. The structure of (-)-EA was elucidated from data obtained through multiple 1D and 2D NMR experiments. EA's compact architecture and dense array of functionality immediately caught the attention of the synthetic community. The trans fused 5,7 ring system of EA contains a bridging oxygen, six stereocenters and two ester side chains. In addition EA showed both potent and selective activity against renal cancer cells in the NCI60 cell panel. Preliminary toxicity studies showed that mice were highly tolerant. These desirable biological properties in combination with the absence of effective chemotherapy for the treatment of renal cell carcinoma make (-)-EA a potential anti-cancer candidate. Accordingly there have been, to date, numerous synthetic undertakings.[2]

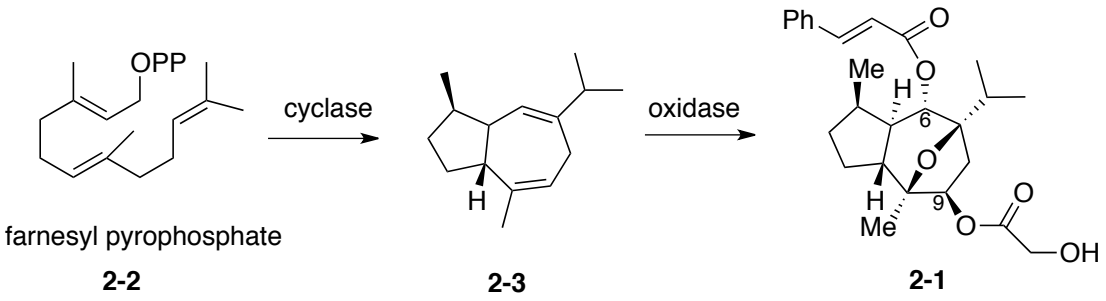


2-1

Figure 2-1. (-)-Englerin A (**2-1**)

2.1.2 The Biosynthesis of (-)-EA

(-)-EA is a member of a family of natural products known as sesquiterpenes; a subset of the vast and diverse terpene family. The sesquiterpenes are comprised of three isoprene units and are believed to be biosynthetically derived from farnesyl pyrophosphate (FPP). In the case of the guaiane type sesquiterpenes, nature's cyclase enzymes convert FPP (**2-2**) to the hydroazulene 5,7 scaffold (**2-3**) through a series of cationic cyclizations and hydride shifts (Scheme 2-1). Subsequent oxidations and functional group manipulations are believed to be responsible for conversion to EA.[3]



farnesyl pyrophosphate
2-2

2-3

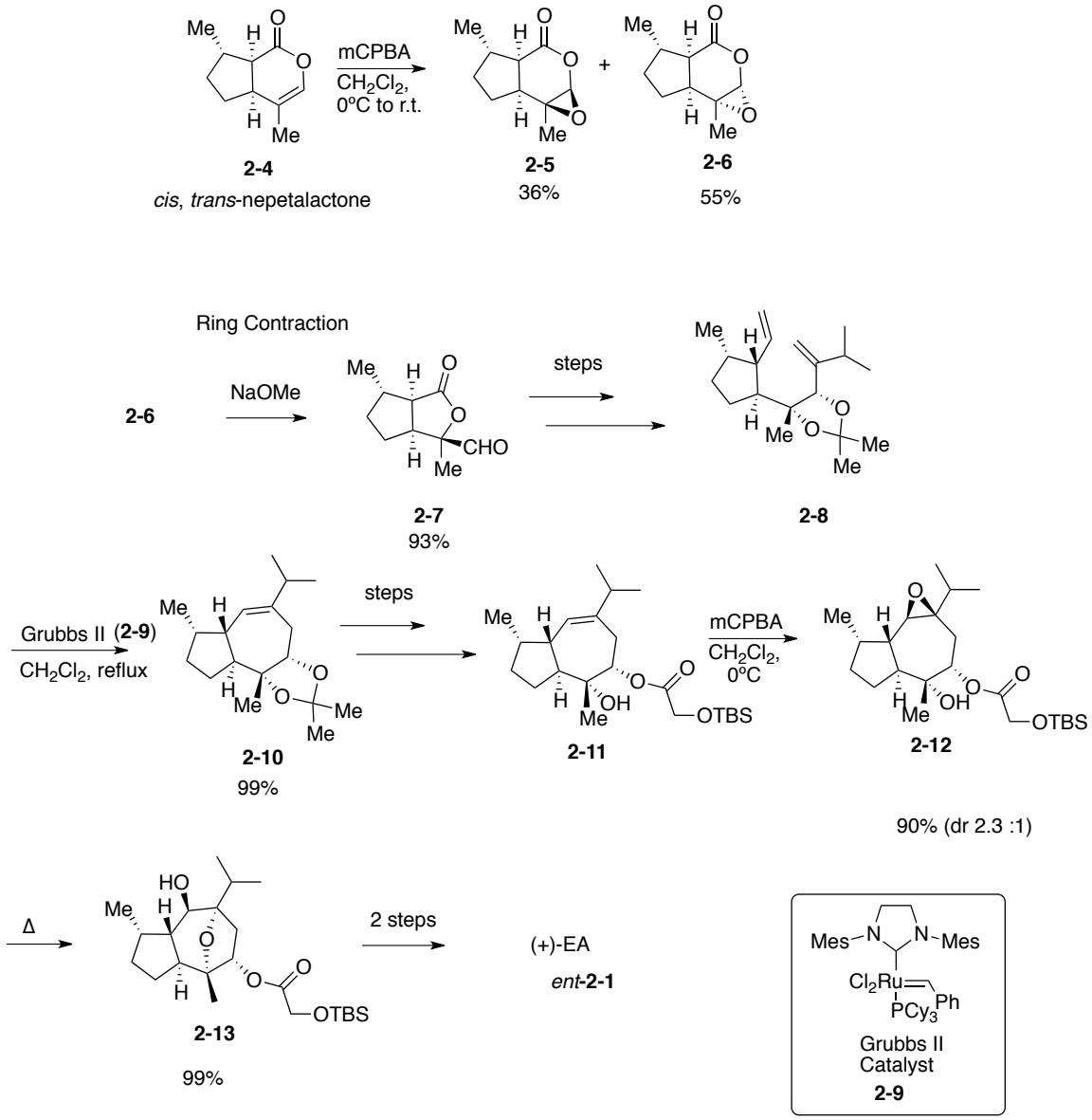
2-1

Scheme 2-1. Proposed Biosynthesis of (-)-EA (**2-1**)

This plausible biosynthetic pathway has inspired many of the current solutions to the englerin problem.

2.2 The Previous Syntheses of Englerin A

In 2009 Christmann and coworkers completed the first total synthesis of EA.[4] Their synthesis, which started from *cis*,*trans*-(+)-nepetalactone (**2-4**), utilized a ring closing metathesis (RCM)/ stereoselective epoxidation strategy (Scheme 2-2).

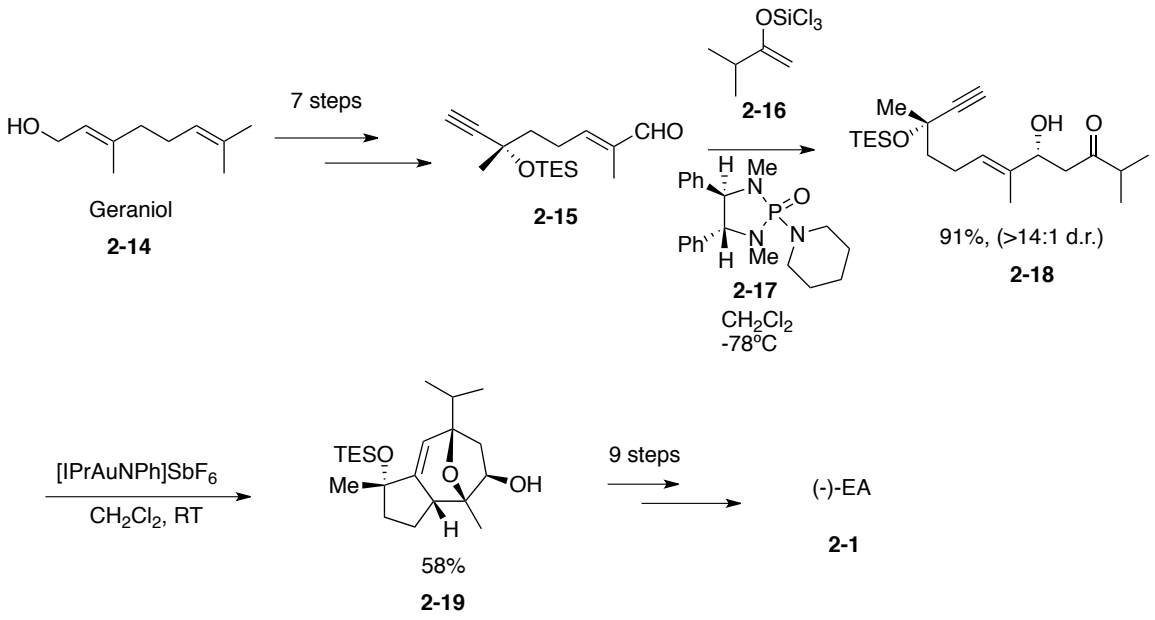


Scheme 2-2. Synthesis of (+)-EA (*ent*-**2-1**) by Christmann et al.

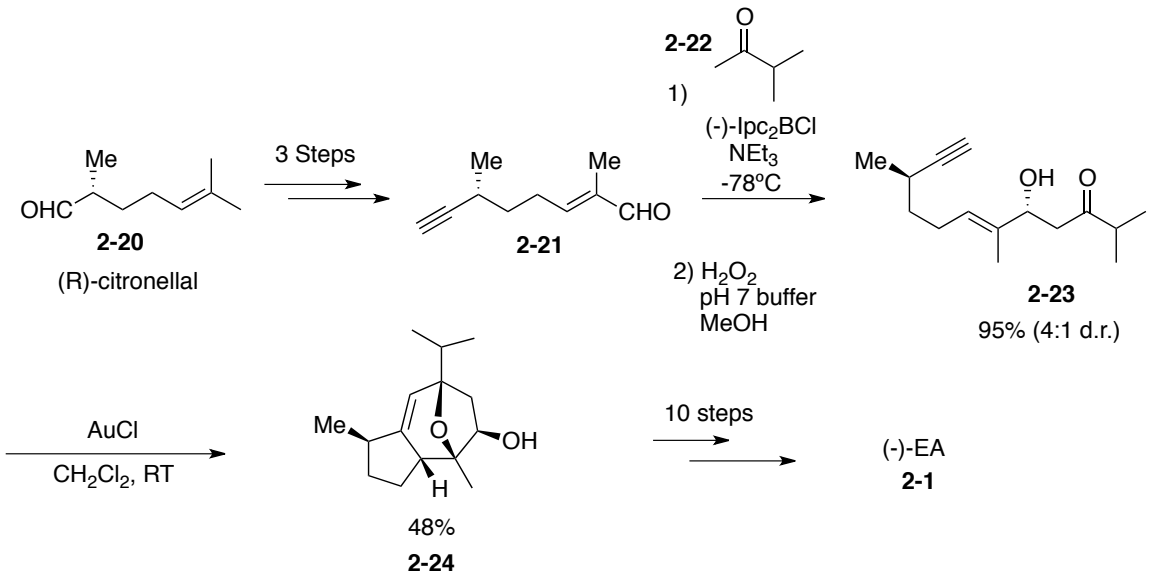
The completion of the 15-step synthesis, which was ultimately that of the unnatural (+)-antipode *ent*-**2-1**, established the absolute configuration of the natural product. In addition it

provided the groundwork for a later, second generation synthesis in which a number of new analogs were prepared and subjected to SAR studies (see section 2.2).

Shortly after Christmann's seminal work, the research groups of Ma[5] and Echavarren[6] completed EA total syntheses that utilized a gold catalyzed [2+2+2] cycloaddition as a key step. In each of these approaches a complex acyclic intermediate was transformed directly into the guaiane framework in a single step (Schemes 2-3 and 2-4).

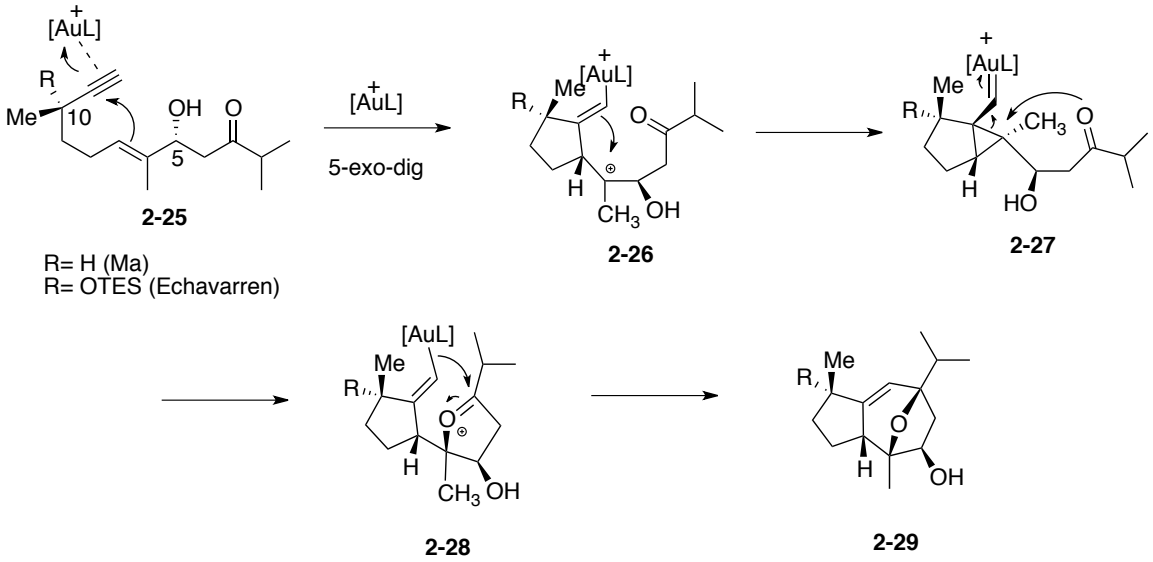


Scheme 2-3. Synthesis of EA (**2-1**) by Echavarren et al.



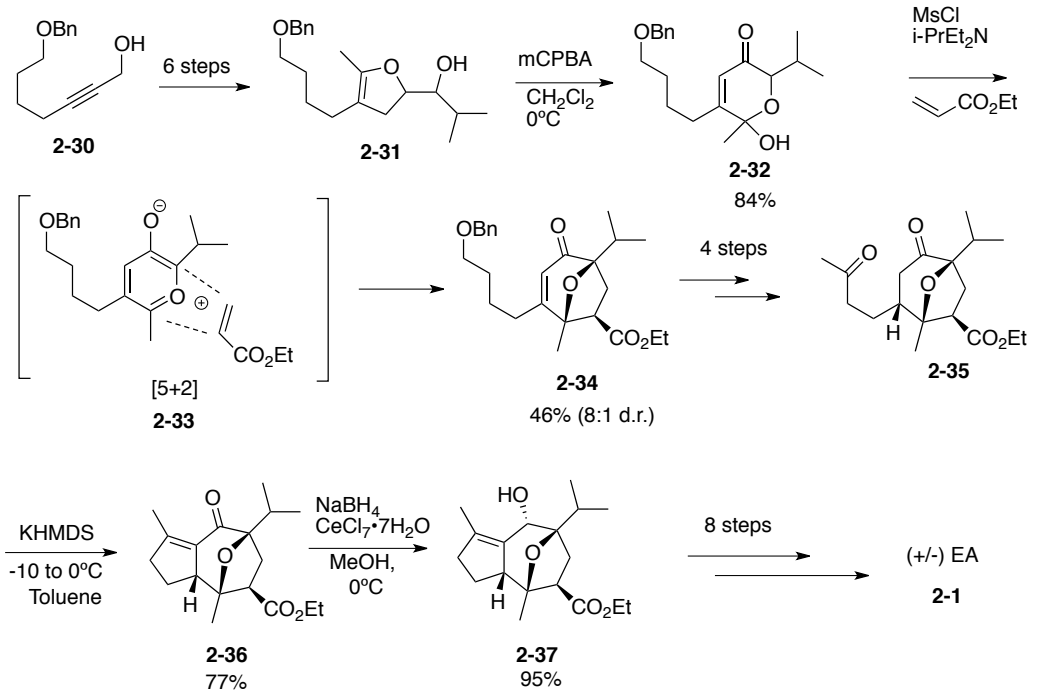
Scheme 2-4. Synthesis of EA (**2-1**) by Ma et al.

According to the mechanism proposed by Ma (Scheme 2-5) the reaction cascade from ketone **2-23** to alcohol **2-24** is initiated by a 5-exo-dig cyclization to form the *anti*-cylopropyl gold carbene intermediate **2-26**. Intramolecular attack of the cyclopropyl moiety by the carbonyl oxygen produces oxonium ion **2-28**. This undergoes a final Prins cyclization to give rise to alcohol **2-29**. It is believed that the high degree of asymmetric induction is imparted by the chiral center at C-10.



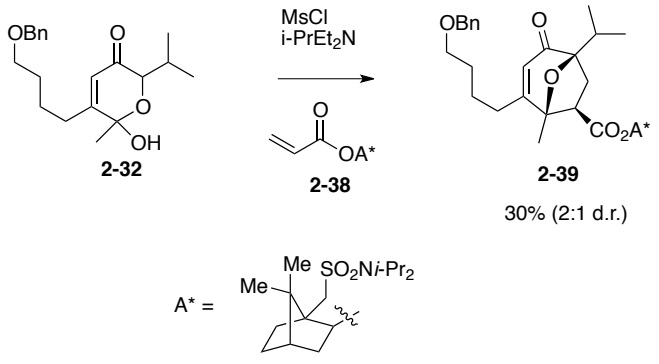
Scheme 2-5. Mechanism Proposed for Au Catalyzed [2+2+2] cycloaddition

Shortly thereafter, Nicolaou [7] and coworkers published an EA total synthesis based on a [5+2] cycloaddition between an oxopyrilium cation and ethyl acrylate.[8] This approach differed from earlier works in that the oxabicyclic system was established before construction of the cyclopentane ring (Scheme 2-6).



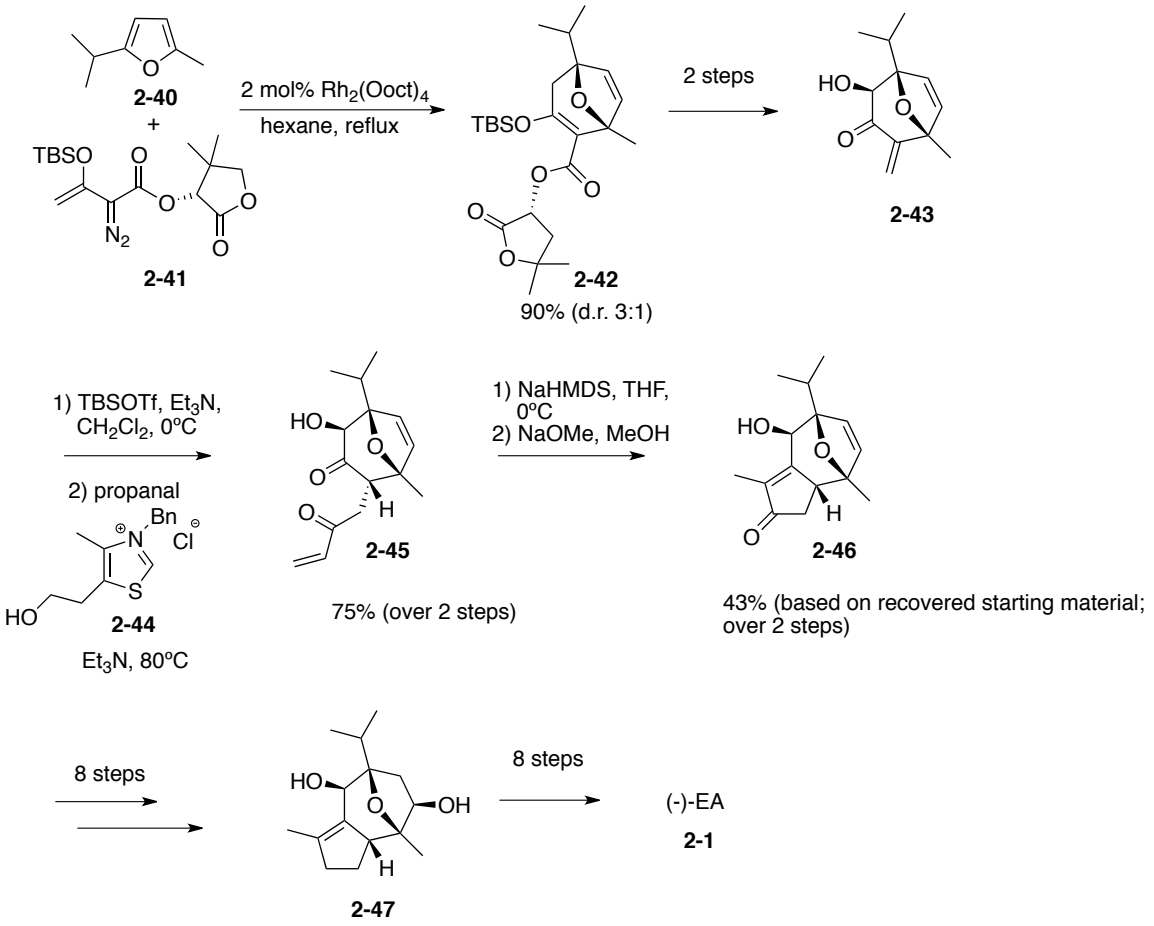
Scheme 2-6. Synthesis of (+/-)-EA (**2-1**) by Nicolaou et al.

After an intramolecular aldol cyclization furnished the cyclopentane ring, an additional nine steps gave racemic EA (**2-1**) (24 steps from commercially available materials). The key [5+2] cyclization step was later modified with a chiral sulfonamide acrylate (**2-38**) to render the synthesis asymmetric (Scheme 2-7).



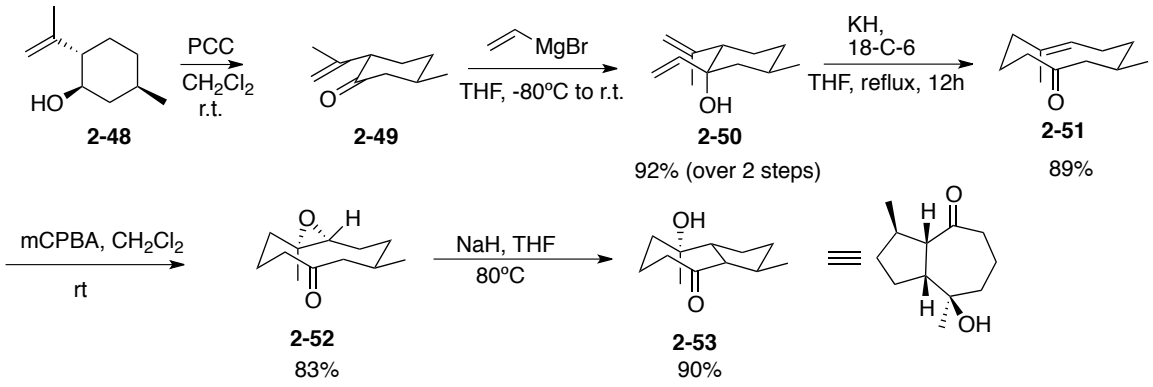
Scheme 2-7. Asymmetric [5+2] Cycloaddition with a Chiral Sulfonamide Acrylate (**2-38**) in the Total Synthesis of (-)-EA (**2-1**) by Nicolaou et al.

A formal synthesis from the Theodorakis group used a strategy similar to that of Nicolaou in that the oxabicyclic core was constructed initially (Scheme 2-8).[9] To provide the core, a Davies [4+3] Rh catalyzed cycloaddition[10] was employed. Furan **2-40** and chiral diazo ester **2-41** were coupled to give intermediate **2-42** in a highly regioselective fashion. This intermediate was elaborated in four steps to give diketone **2-45**. After an intramolecular aldol reaction, as in the Nicoloau synthesis, the cyclopentene ring was constructed (**2-45** → **2-46**). An additional eight steps was required to intersect Ma's total synthesis at a point eight steps from EA (**2-47**).



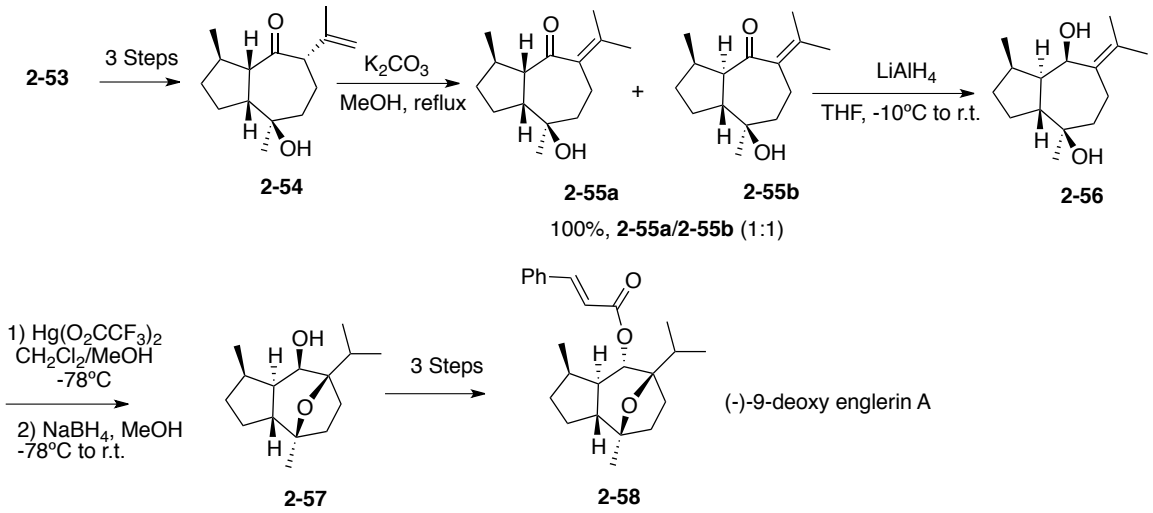
Scheme 2-8. Formal Synthesis of (-)-EA (**2-1**) by Theodorakis et al.

In 2011 Maier and coworkers published the total synthesis of 9-deoxy-englerin A.[11] The synthesis of this compound began with the commercially available monoterpene (-)-isopulegol, **2-48** (Scheme 2-9). After an oxidation, vinylation, and an anionic oxy cope rearrangement, compound **2-51** was constructed. The 10-membered ring was then converted into a 5,7 ring system by way of an intramolecular epoxide opening with the enolate of ketone **2-52**.



Scheme 2-9. Synthesis of the 5,7 Ring System of (-)-9-deoxy-englerin A (**2-58**) by Maier et al.

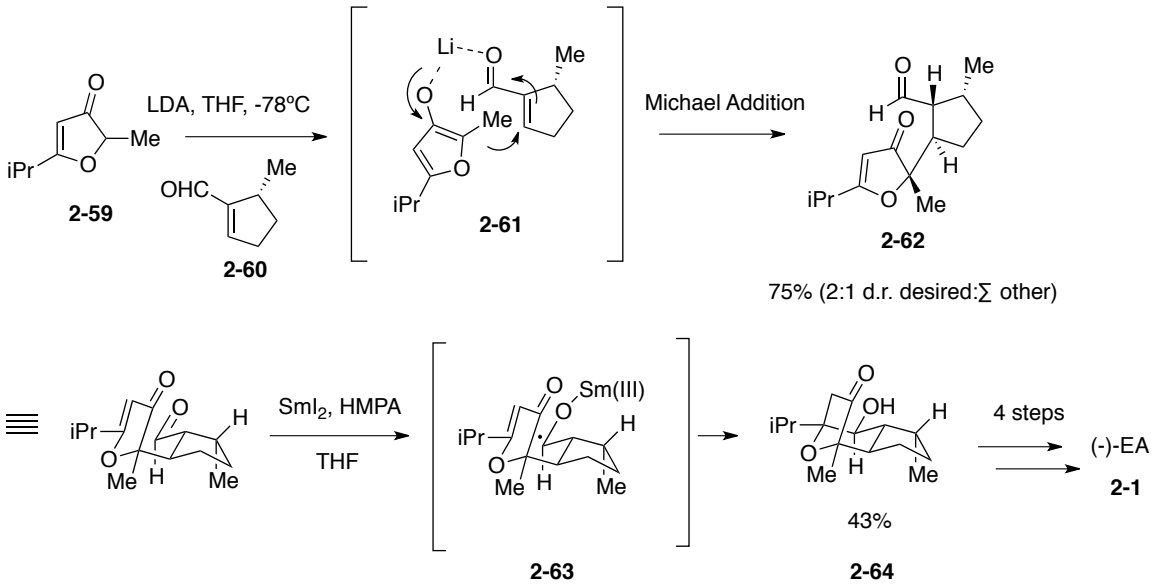
After a three step sequence from alcohol **2-53** to introduce the latent isopropyl moiety, ketone **2-54** was subjected to base catalyzed epimerization conditions (Scheme 2-10). This was necessary to establish the requisite *trans* fused 5,7-ring system and isomerize the exocyclic olefin. Although this gave a 1:1 mixture of *cis* and *trans* diastereomers (**2-55a** and **2-55b)**, they were separable by column chromatography and the *cis* isomer was resubjected to the epimerization conditions. After an additional reduction and a $Hg(O_2CCF_3)_2/NaBH_4$ etherification sequence (**2-56** → **2-57**), the authors completed the synthesis of analog **2-58** in three additional steps.



Scheme 2-10. Synthesis of (-)-9-Deoxy-englerin A (**2-58**) by Maier et al.

Upon completion of the synthesis, a test of analog **2-58** against the A-498 renal cell line revealed that it was inactive. This confirmed the necessity of the glycolate residue at the C-9 position for biological activity.

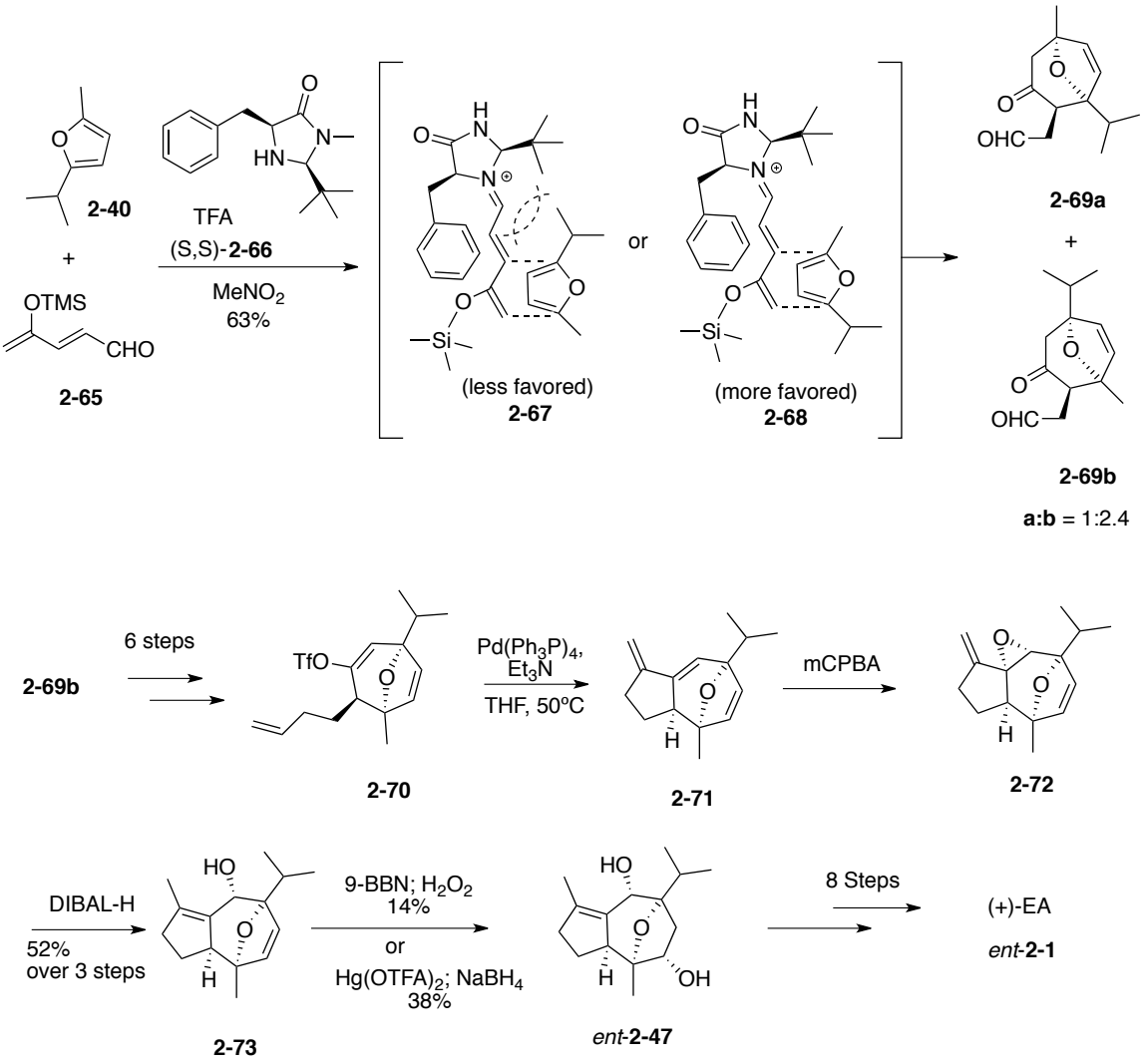
Later in 2011, Chain and coworkers published a remarkable synthesis of EA that required only eight steps from commercially available starting materials.[12] The core of the natural product was rapidly assembled through two carbonyl-enabled bond-forming reactions (Scheme 2-11).



Scheme 2-11. Synthesis of EA (**2-1**) by Chain et al.

In the first key step, an LDA mediated intermolecular Michael condensation of 3-furanone (**2-59**) and 5-methyl-cyclopentenecarboxaldehyde (**2-60**) gave aldehyde **2-62** with good diastereoselectivity. Subsequent samarium iodide-promoted reductive cyclization afforded compound **2-64**, an intermediate from Ma's EA total synthesis.

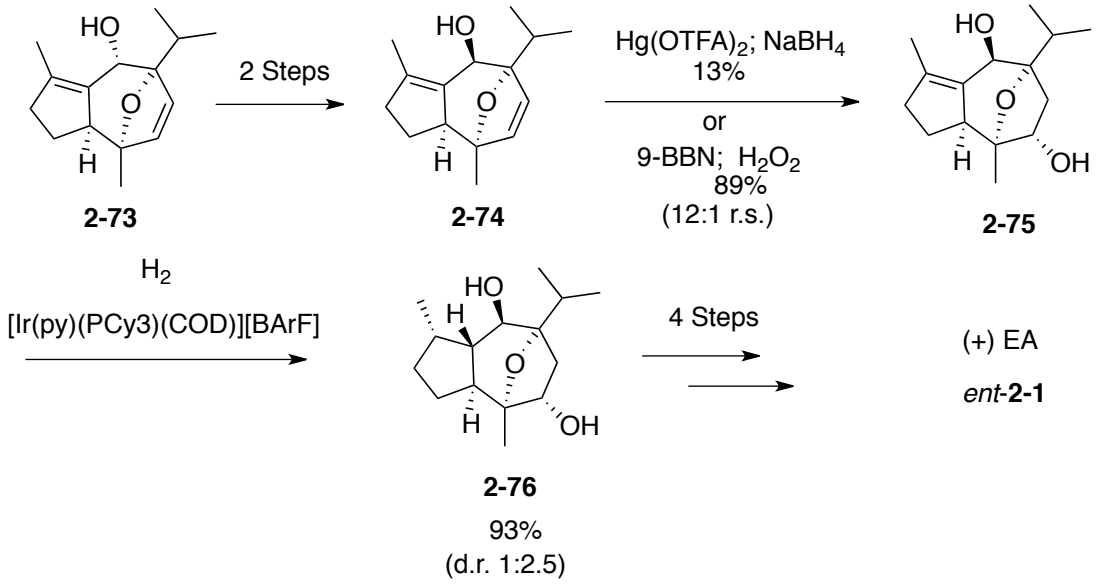
Not long after Chain's synthesis, Sun and coworkers published a formal synthesis of (+)-EA (Scheme 2-12).[13] The completion of this work was a culmination of previous synthetic efforts in accessing guaiane scaffolds.[14] To this end, they utilized a [4+3] organocatalytic cycloaddition.



Scheme 2-12. Formal Synthesis of (+)-EA (*ent*-**2-1**) by Sun et al.

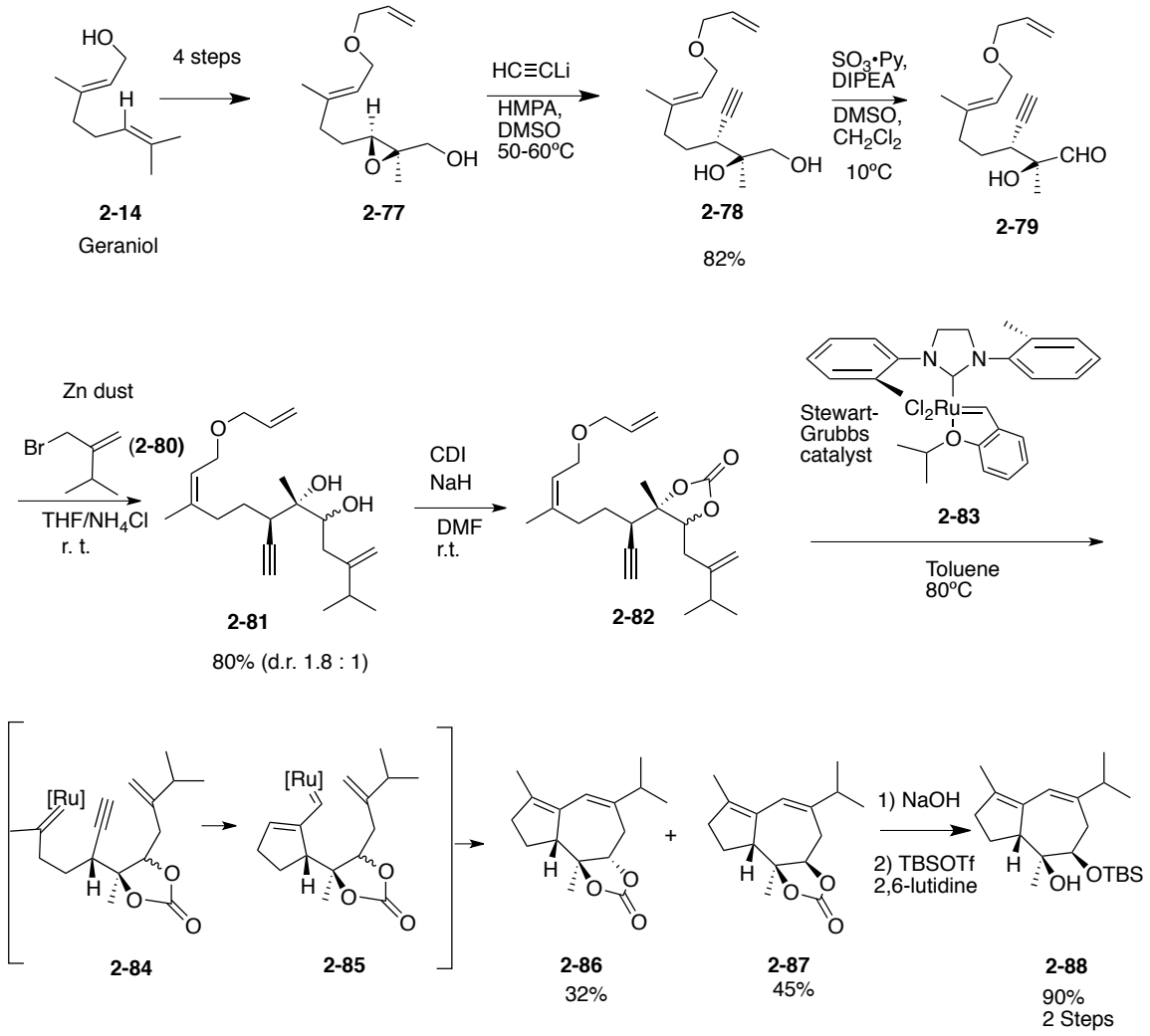
To effect cycloaddition Sun and coworker's employed a modified form of Harmata's conditions.[15] Furan **2-40** was condensed with dienal **2-65** to give oxabicycle **2-69b** as the major product. After conversion to vinyl triflate **2-70** in six steps, an intramolecular Heck reaction was used to construct the cyclopentane ring of compound **2-71**. This intermediate then was subjected to an epoxidation/SN2'-type reduction sequence. A final oxidation step with either 9-BBN/H_2O_2 or $Hg(OTFA)_2$/$NaBH_4$ gave diol *ent*-**2-47**, an intermediate from Ma's total synthesis.[5]

Sun and coworkers later published a full account of their work.[16] This included a summary of their previous formal synthesis. In addition, the authors described the completion of a new (+)-EA (*ent*-**2-1**) total synthesis from synthetic intermediate **2-73** (Scheme 2-13).



Scheme 2-13. Total Synthesis of (+)-EA (*ent*-**2-1**) by Sun et al.

In 2012, Parker and Lee described a fundamentally different solution to the englerin problem.[17] Their unique approach exploited relay ring closing metathesis (RRCM)[18] in combination with the powerful and commercially available Grubbs olefin metathesis catalyst **2-83.** [19]

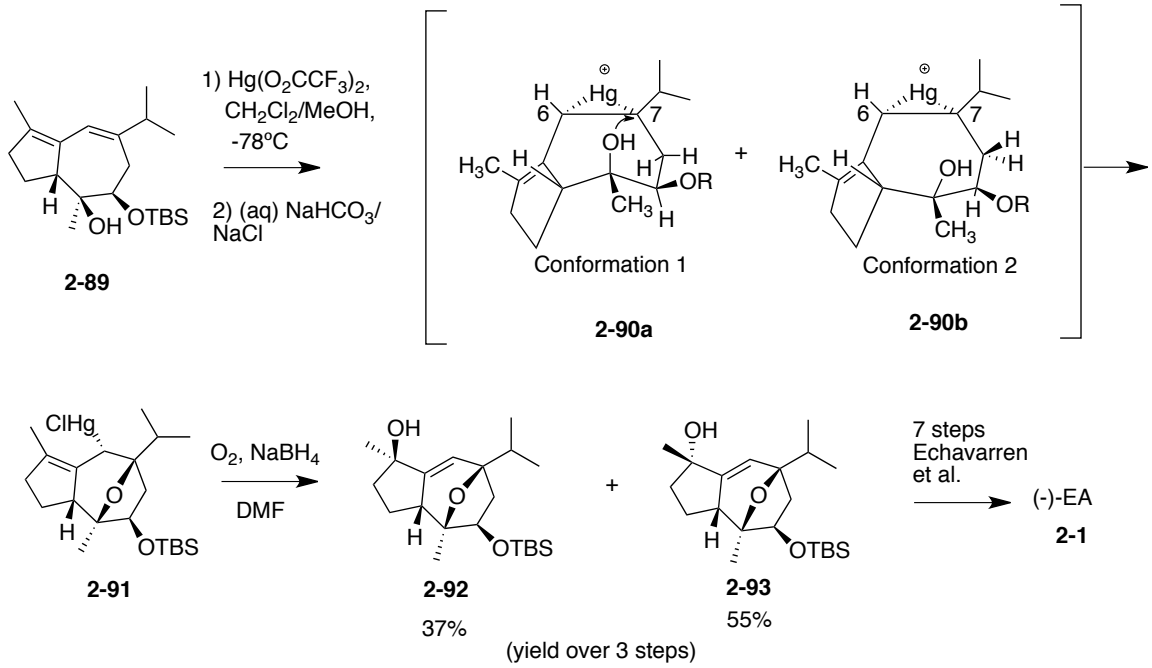


Scheme 2-14. Ene-Yne-Ene Metathesis for the Rapid Construction of the EA Hydroazulene Framework by Lee and Parker

Beginning with geraniol (**2-14**), Lee and Parker prepared the metathesis precursor **2-82** in eight steps (Scheme 2-14). Key transformations in this sequence included an alkynylation of a 2-substituted 2,3-epoxy alcohol and a stereoselective Barbier reaction. By incorporating an allyl ether "relay" into metathesis substrate **2-82**, Lee and Parker guided the directionality of ring closing metathesis to give hydroazulenes **2-86** and **2-87** exclusively.

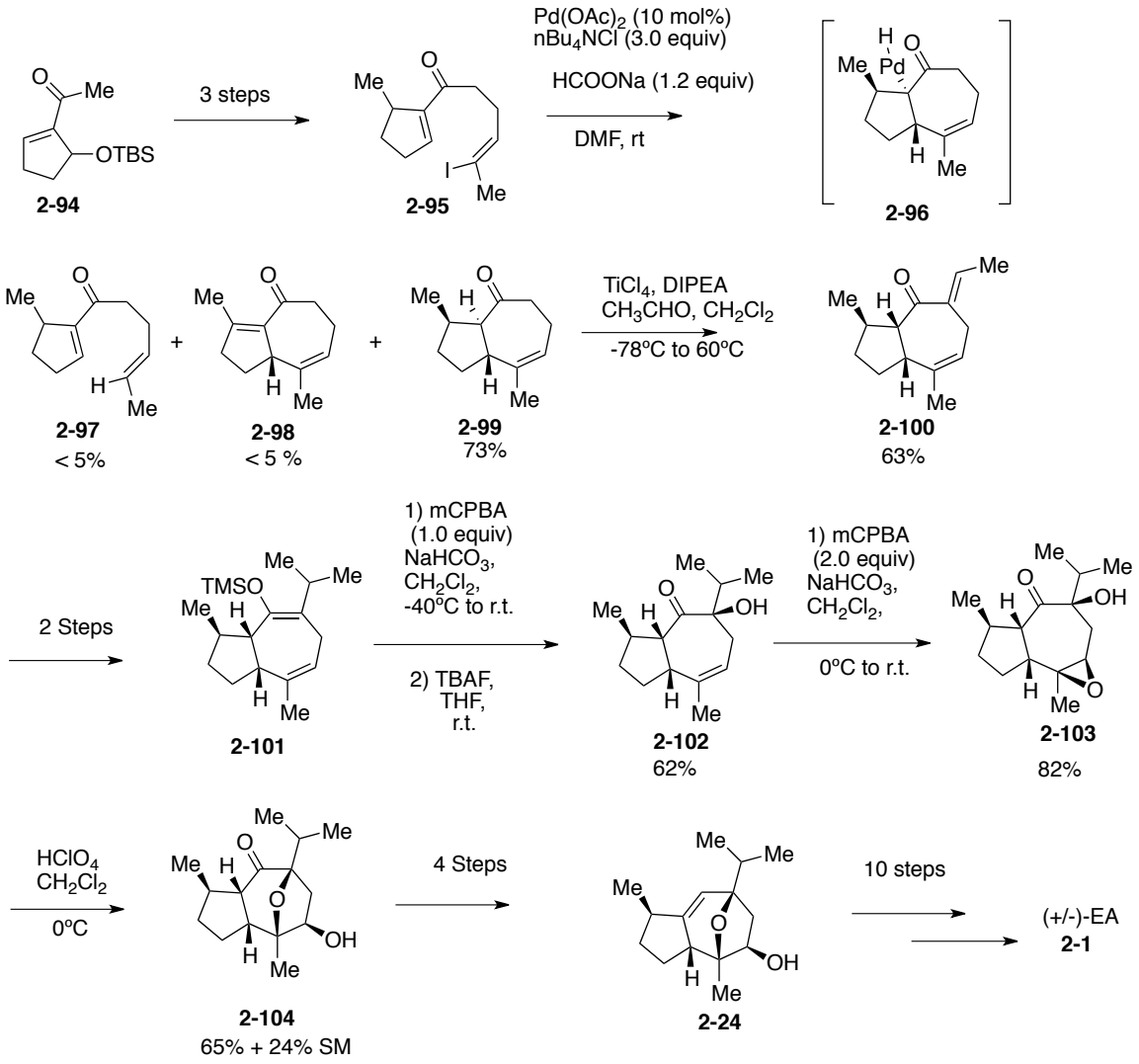
To construct the C-7-C-10 oxygen bridge, Lee and Parker effected a regio- and stereoselective etherification reaction with $Hg(O_2CCF_3)_2$ (Scheme 2-15). The authors postulated

that intramolecular attack by the internal hydroxyl nucleophile could only occur at C-7, as the most stable conformation of bridged cation **2-90** could not adopt a position that would permit attack at C-6. Oxidative demercuration of alkyl mercurial **2-91** gave two epimeric alcohols (**2-92** and **2-93**), one of which is an intermediate from the Echavarren[6] total synthesis.



Scheme 2-15. Formal Synthesis of (-)-EA (**2-1**) by Lee and Parker

The three most recent published syntheses of EA (Cook[20], Hatekayama[21], and Metz[22]) share a similar design feature- they all proceed with construction around the five membered ring.

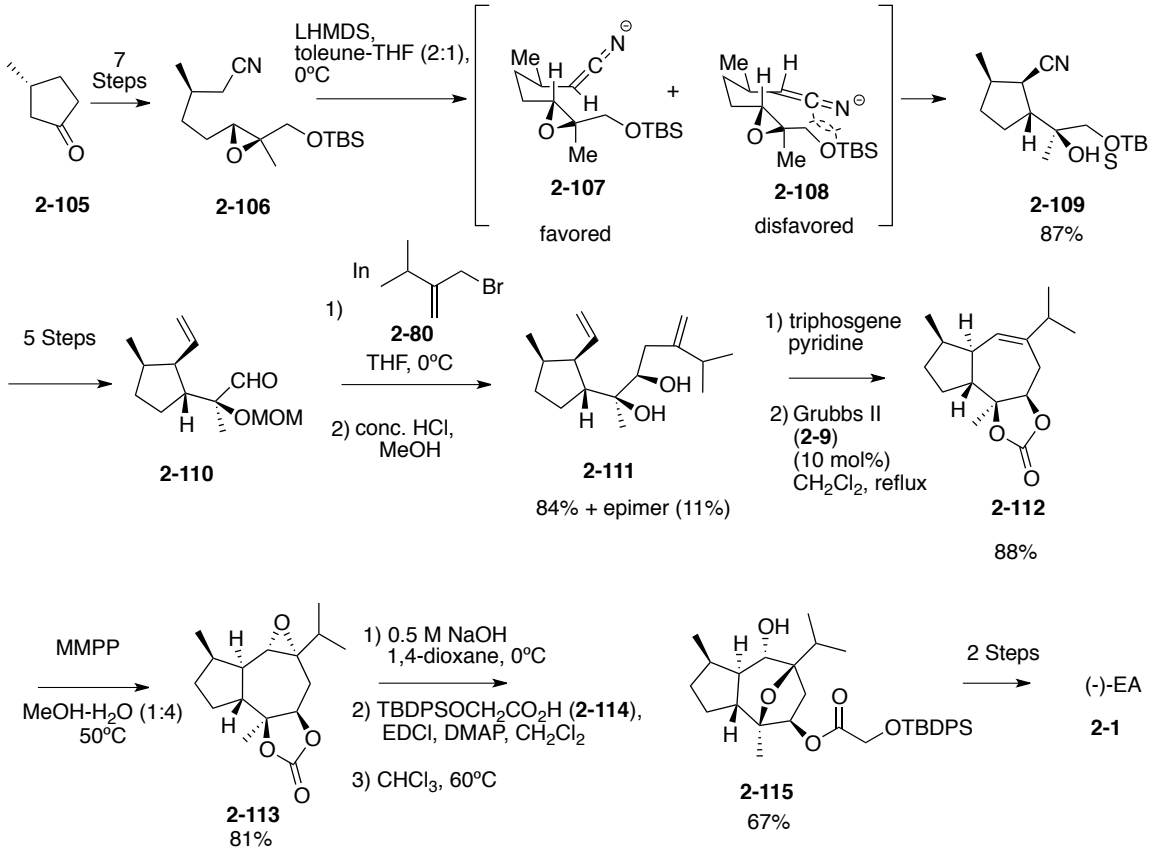


Scheme 2-16. Formal Synthesis of (+/-)-EA (**2-1**) by Cook et al.

The synthesis of Cook and coworkers proceeds by way of the known ketone **2-94** (Scheme 2-16). Through a reductive Heck reaction they converted vinyl iodide **2-95** into ketone **2-99**, a product containing the *trans*-hydroazulene ring system. Careful optimization of reaction conditions allowed them to minimize formation of compound **2-98**, a product that results from *syn* beta hydride elimination. Although the authors successfully applied their unique variant of the Heck reaction to part of the EA problem, their original goal was forced to be modified. Installation of the isopropyl group led to the problem of epimerization at C-3, which resulted in the formation of the more stable *cis* fused ring system (compound **2-100**). After a lengthy series

of manipulations, the author's were able to prepare alcohol **2-24**, an intermediate from Ma's synthesis.[5]

The Hatekayama EA solution begins with a seven-step synthesis of epoxy nitrile **2-106** from commercially available ketone **2-105** (Scheme 2-17). With this substrate the authors effect a stereoselective Stork epoxy nitrile cyclization[23] and, in doing so, obtain compound **2-109**, an intermediate that contains the cyclopentane ring and four of the required stereocenters in EA.

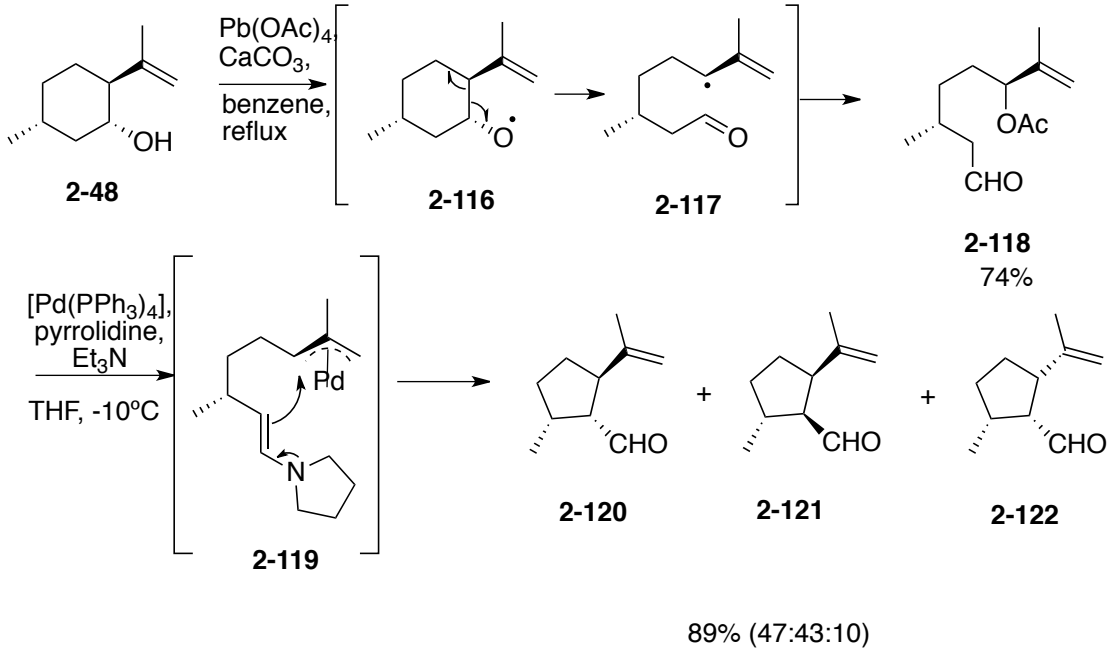


Scheme 2-17. Total Synthesis of (-)-EA (**2-1**) by Hatakeyama et al.

After five additional steps, an indium-mediated stereoselective Barbier reaction of a MOM protected aldehyde **2-110** and allyl bromide **2-80** was adopted. This gave diol **2-111** as an ~8:1 mixture of diastereomers, presumably through a non-chelation Felkin-Ahn transition state.[24]

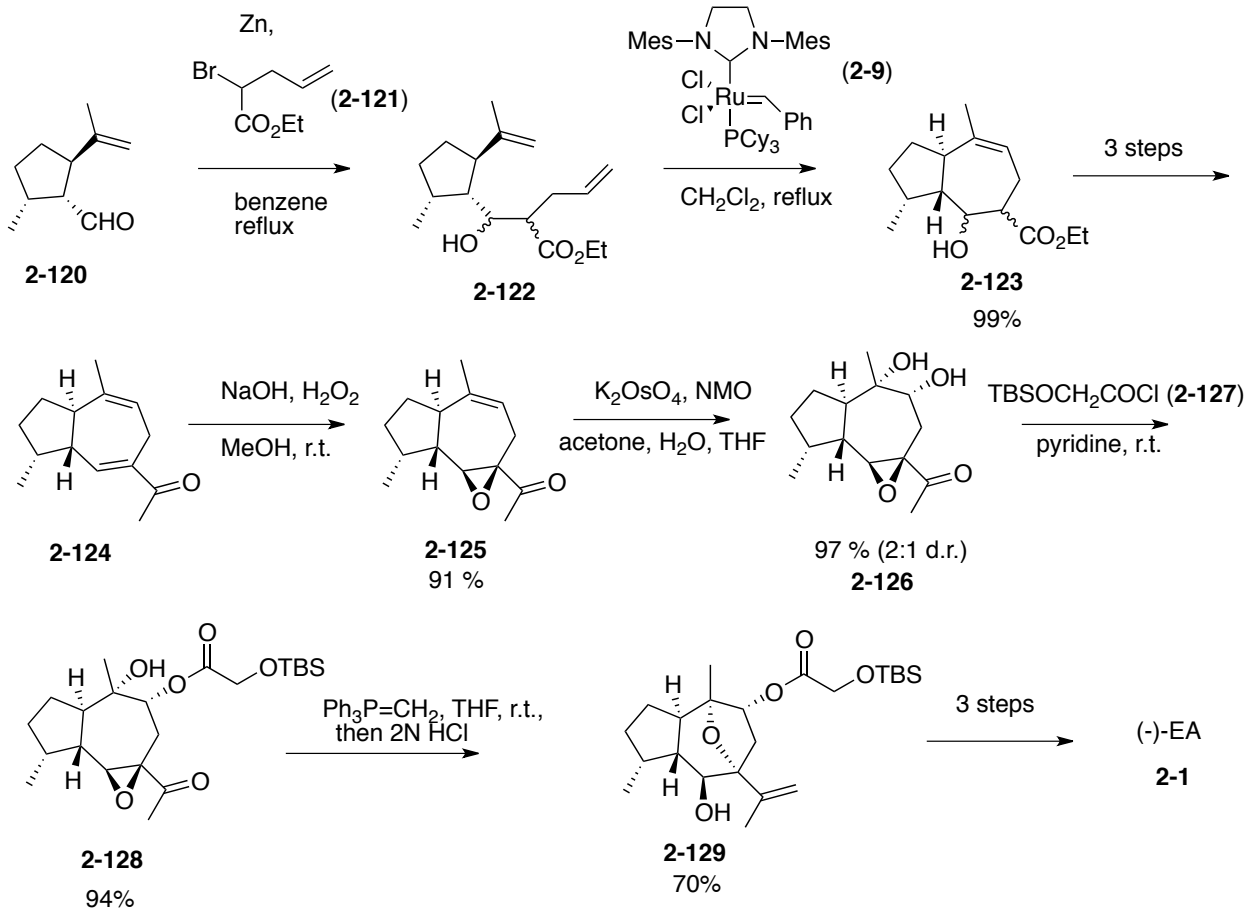
At this point the authors intersected the Christmann synthesis. Rather than adopt Christmann's protocol, diol **2-111** was protected as the corresponding carbonate prior to ring closing metathesis. This intermediate, in turn, was epoxidized in a highly diastereoselective manner. After carbonate hydrolysis and esterification of the less hindered alcohol with acid **2-114**, completion of the synthesis was straightforward. EA was finished in 24 steps and in 14% overall yield**.**

The Metz synthesis begins with the transformation of (-)-isopulegol (**2-48**) into the monoterpene (-)-photocitral A (**2-120**), a starting material with three stereogenic centers that are in the same configuration as the cyclopentane ring of EA (Scheme 2-18). This starting material was prepared in two steps - a lead tetraacetate induced fragmentation of alcohol **2-48** to aldehyde **2-118**, followed by an organocatalytic Tsuji-Trost reaction sequence. The diastereomeric aldehydes **2-120** - **2-122** were separable by column chromatography.



Scheme 2-18. Preparation of (-)-Photocitral (**2-120**) from (-)-Isopulegol (**2-48**) by Metz et al.

With aldehyde **2-120** in hand, a Reformatsky reaction /ring-closing metathesis sequence was used to construct the 5,7 hydroazulene framework (**2-123**) (Scheme 2-19). After three additional steps to form the unsaturated ketone **2-124**, a nucleophilic epoxidation of the less electron rich double bond was achieved. The remaining olefin was subjected to a substrate controlled diastereoselective dihydroxylation to give compound **2-126**. This was smoothly converted to EA in five steps.



Scheme 2-19. Total Synthesis of (-)-EA (**2-1**) by Metz et al.

2.3 The Previous Syntheses of Englerin Analogs

Although there have now been EA syntheses published by a total of eleven different research laboratories, very little work has been done in the area of analog synthesis. The majority of published SAR data are on englerin analogs in which the C-6 cinnamate and C-9 ester side chains have been modified.

The first SAR data published from an analog of EA was presented in the report of Nicolaou and coworkers.[7] Therein they described the synthesis of racemic englerin B acetate (**2-131**) and an englerin analog in which the cinnamate side chain had been reduced (**2-130**). The GI_{50} values of these analogs were measured against the ACHN, A498, and UO31 renal cancer cell lines and compared to that measured from synthetic (+/-)-EA (Figure 2-2).

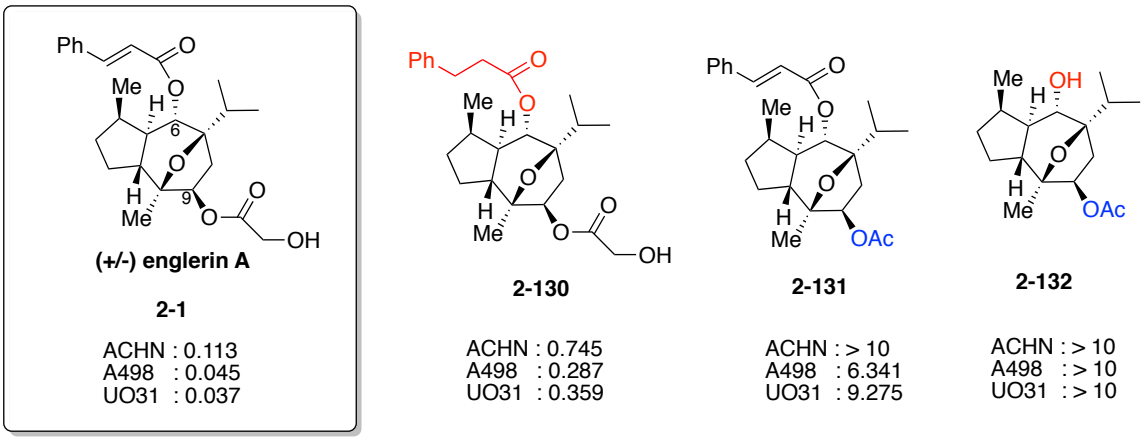


Figure 2-2. GI_{50} Value of Englerin Analogs in Selected Renal Cancer Cell Lines; Nicolaou et al.

As shown above, the analog bearing a hydrogenated cinnamate **2-130** retained activity but it was mitigated. This suggests that this region can tolerate some structural flexibility. Compounds **2-131** and **2-132** had essentially lost all of their biological activity. This was the

first piece of evidence that suggested that both the cinnamate and glycolate moieties of EA are important.

In a follow up report by Chan and coworkers, a large library of racemic englerin analogs was synthesized and subjected to SAR studies.[25] These analogs contained structural modifications to the C-6 cinnamate (Figure 2-3) and C-9 glycolate side chains (Figure 2-4).

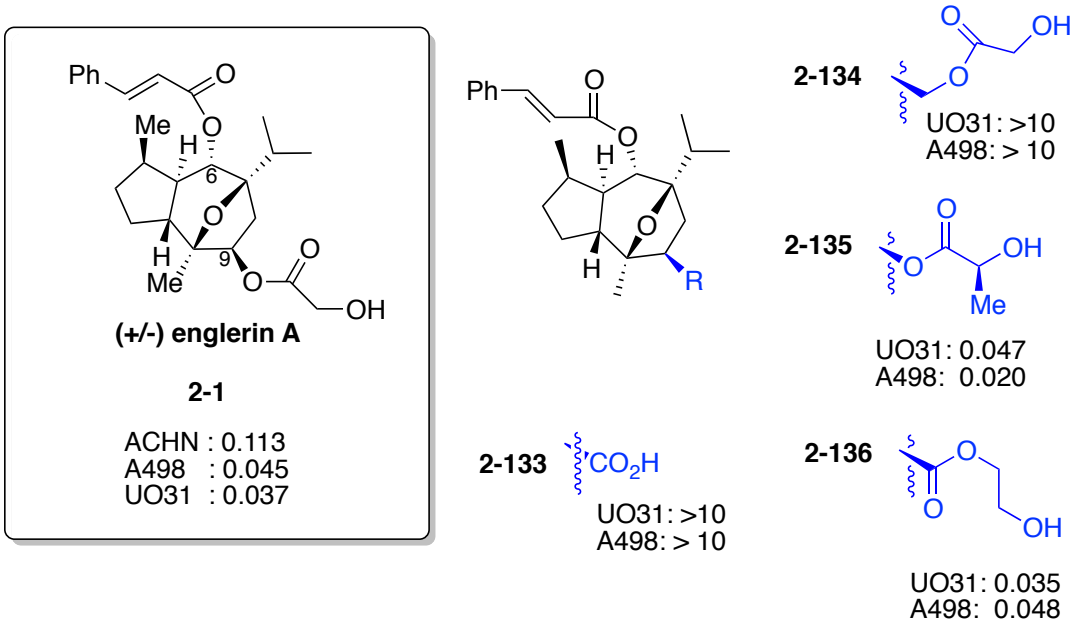


Figure 2-3. GI_{50} Values of Synthetic Englerin Analogs with Modified C-9 Glycolate Side Chains; Chan et al.

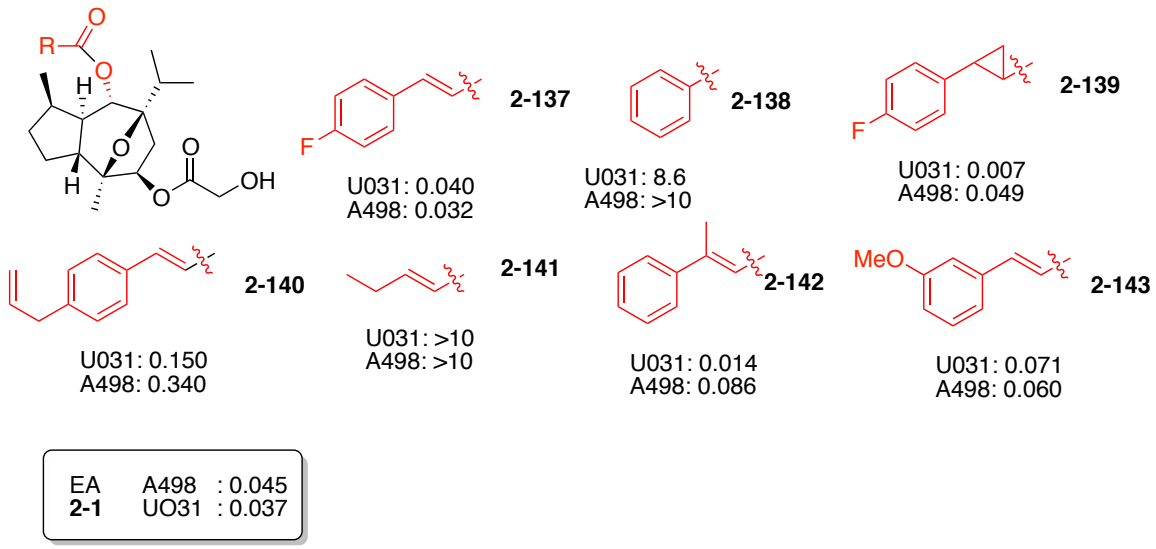


Figure 2-4. GI_{50} Values of Synthetic Englerin Analogs with Modified C-6 Cinnamate Side Chains; Chan et al.

Two of the four analogs containing structural modification to the glycolate region (compounds **2-133** and **2-134)** showed significant loss of cytotoxicity. In the reversed glycolate and lactate analogs, (compounds **2-136** and **2-135)** cytotoxicity was retained. Structural changes made to the cinnamate moiety appeared to be tolerated without loss of activity, and the majority of analogs (excluding **2-138** and **2-141**) retained biological activity.

In 2011 Christmann and coworkers published a second generation total synthesis of (-)-EA in which a number of key steps were optimized.[26] In addition they synthesized new analogs with a profile comparable to that of EA (**2-144** through **2-146**) (Figure 2-5). By diverting their synthesis at an early intermediate they synthesized truncated C-6 analogs **2-150** and **2-151** (Scheme 2-20)**.** The SAR data obtained with these compounds suggested that the isopropyl group was necessary for binding.

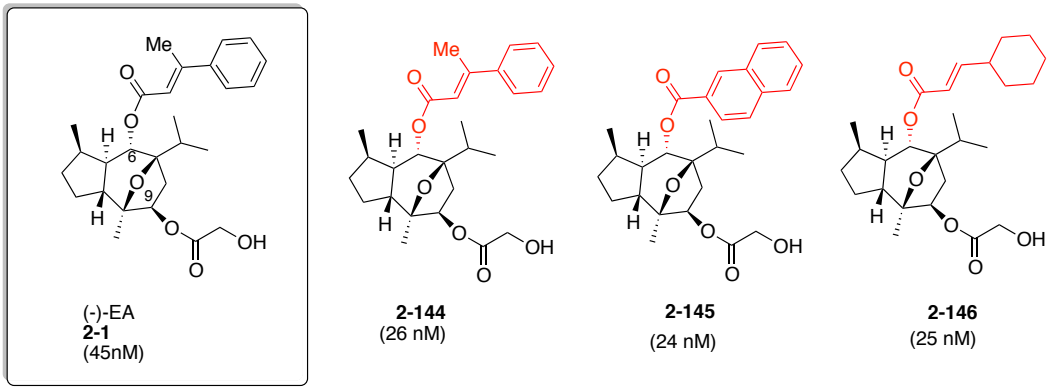
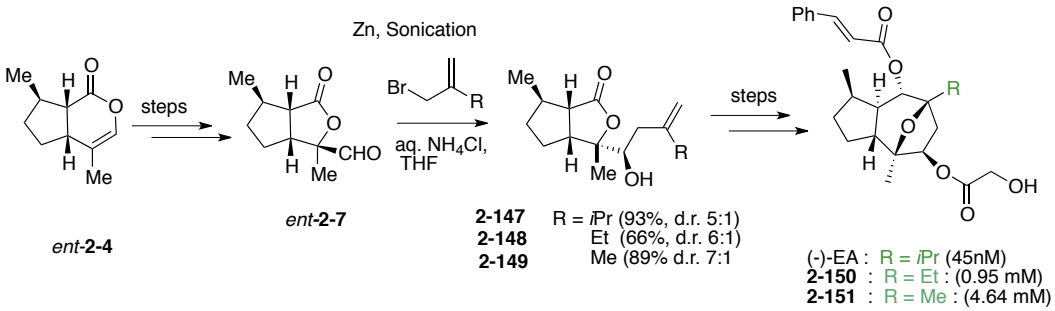
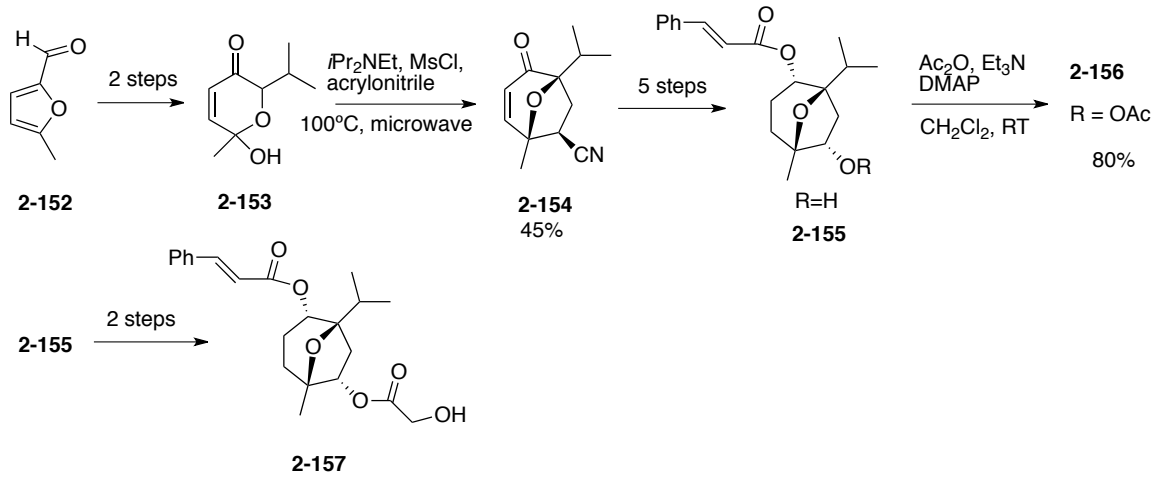


Figure 2-5. Synthetic Englerin Analogs with an IC_{50} value comparable to that of EA; Christmann et al.



Scheme 2-20. IC_{50} Values of Synthetic Englerin Analogs – Variation of the C-6 Isopropyl Moiety; Christmann et al.

Lastly, three bicyclic analogs (compounds **2-155**, **2-156**, and **2-157**) of englerin were synthesized by Theodorakis et al.[27] This was accomplished with a key [5+2] cycloaddition reaction; the same methodology that was applied in Nicolaou's EA synthesis[7] (Scheme 2-21).



Scheme 2-21. Synthesis of Bicyclic Englerin Analogs by Theodorakis et al.

Biological evaluation of these analogs (**2-155**-**2-157**) against the A498 renal cancer cell revealed that they were inactive.

2.4 Mechanism of Action Studies

In the past four years since the discovery of (-)-EA, many elegant total syntheses have been accomplished. Indeed considerable headway has been made in tackling englerin's synthetic challenges. Still, if englerin A were ever to advance to a clinical setting, its mechanism of action must be established. Although this problem has already begun to be addressed, much remains in question.

The first investigation of the possible mechanism of action of EA was reported by Ramos et al.[28] From studies conducted with synthetic EA, they found that EA specifically induces cell death in renal cancer cell lines but does not affect normal kidney cells. They also proposed that

the mechanism of cell death was through necrosis and that it was coincident with the production of reactive oxygen species and calcium influx.

Later in 2013 Neckers[29] and coworkers published a study suggesting that an EA initiated cascade begins by binding protein kinase C theta. This, in turn, activates two opposing metabolic pathways. One pathway is activated by the phosphorylation of insulin receptor substrate 1 (IRS1). When phosphorylated, IRS1 dissociates from the insulin receptor, ultimately lowering the uptake of glucose by the cancer cell. The other pathway involves the activation of heat shock factor 1 (HSF1). The stimulation of this transcription factor enforces glucose dependence. The net result is a metabolic catastrophe in which cell death results from the simultaneously "starvation and addiction to glucose."

In a recent report by Batova et al.[30] researchers concluded that protein kinase C theta may not be the target and that EA likely induces cell death by multiple mechanisms. The authors stated that the experiments demonstrating inhibition of glucose uptake were performed using EA at 10μM, a concentration 200-fold higher than the IC_{50} value of EA. The authors believe that the effects of EA on glucose uptake occur at higher concentrations and are likely the result of off-target effects. In addition, by examining histone-associated DNA fragments of cells treated with EA they confirmed that EA did induce apoptosis in addition to necrosis.

2.5 Conclusion

Although the mechanism of action of EA is still in question and being debated, the preclinical evaluation of EA remains highly positive. The next challenge appears to be the application of the now established chemical methods to unravel the chemical biology of EA.

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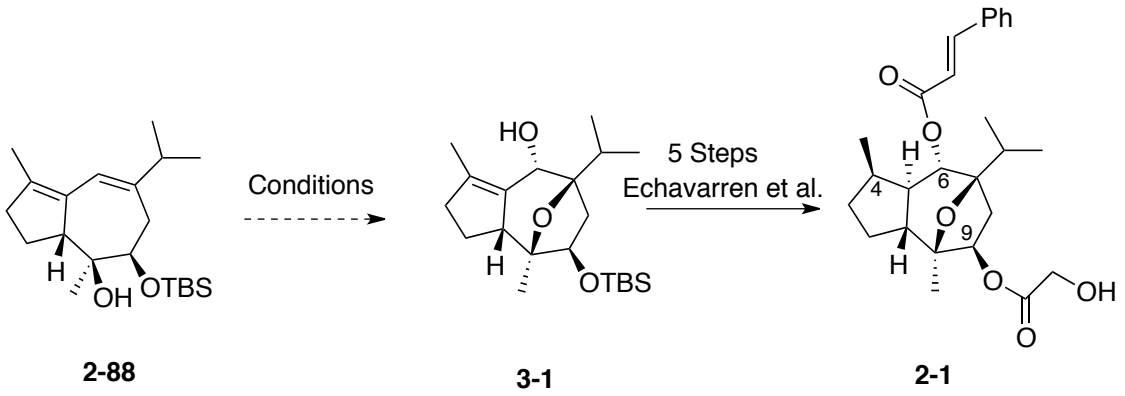
Chapter 3

Model Studies

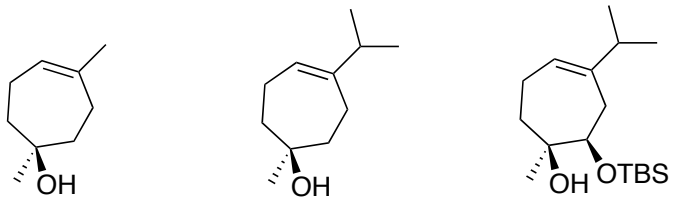
3.1 Introduction

The motivation for this portion of work on the englerin project came in early 2011. At that time the development of the Parker group's first generation EA synthesis was steadily underway. Based on the group's synthetic design, the completion of the total synthesis required an etherification reaction (**2-88** → **3-1**) that contained two important features. First, the transformation had to differentiate between the two olefins of the hydroazulene intermediate **2-88**. Second, the C7-C10 oxygen bridge and the adjacent C-6 carbon-oxygen bond needed to be constructed in a *trans* orientation. The goal at the outset of this project was to accomplish this transformation in a single step, thereby converting hydroazulene **2-88** into the known englerin intermediate **3-1**.[1] This could be converted to (-)-EA, (**2-1**) in five additional steps (Scheme 3-1).



Scheme 3-1. Desired Conversion of Hydroazulene **2-88** to Alcohol **3-1**; Lee and Parker's Synthesis of (-)-EA (**2-1**)

Although the intramolecular etherification of cyclohepten-4-ols has been effected by both halogens[2] and mercury salts[3], we could not find an example where the requisite oxa-bridge was formed adjacent to a new C-O bond. Thus we pursued the study of model compounds in which this transformation could be investigated (Figure 3-1). Our initial intention was that the etherification products of these model compounds might be elaborated to new analogs. Through SAR studies, we could potentially discover active analogs.



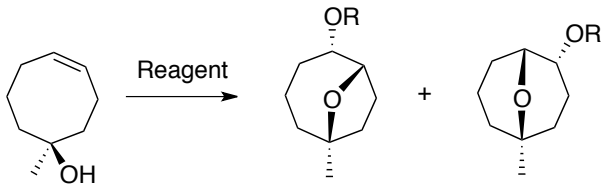
3-2 **3-3** **3-4**

Figure 3-1. Model Compounds for Etherification Studies

3.1.1 Oxidative Cyclization in a Cycloocten-4-ol System by Kim and Schlecht

We viewed a number of methods as attractive candidates for carrying out the transannular etherification reaction. When we began, the methods reported by Kim and Schlecht appeared to be the most appealing.[4]

Kim and Schlecht reported the transannular hydroxyetherification of cycloocten-4-ol (**3-5**) with a number of oxidizing agents, namely $Pb(OAc)_4$/benzene, $PhI(OAc)_2$/HOAc, $PhI(OH)OTs/CH_2Cl_2$ and $PHI(OTf)_2/CH_2Cl_2$. The combined yields of the regioisomeric products were excellent. In addition, the reaction was highly selective for trans addition (Table 3-1).

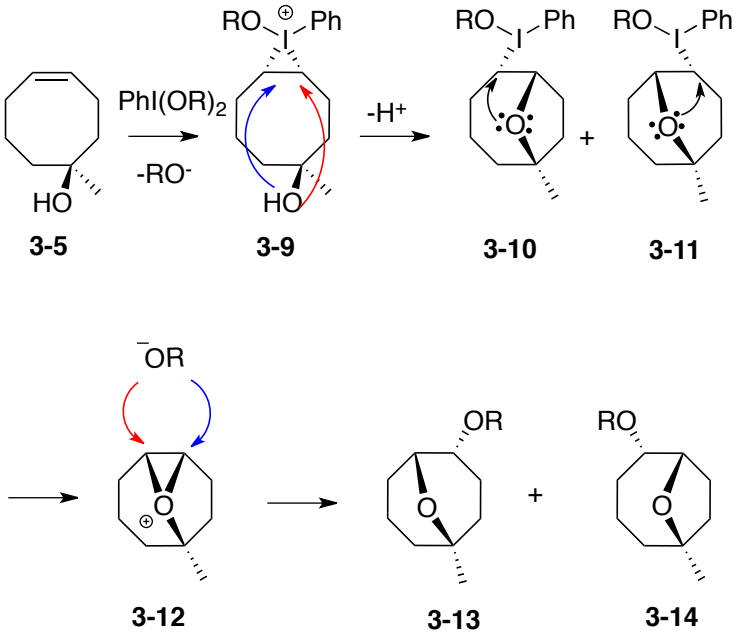


3-5 **a** **b**

Reagent	R	Solvent	Temp	Product	Overall Yield (%,a + b)
$PhI(O_2CCF_3)_2$	$COCF_3$	CH_2Cl_2	RT	**3-6**	75%
$PhI(OAc)_2$	Ac	HOAc	Reflux	**3-7**	87%
PhI(OH)(OTs)	Ts	CH_2Cl_2	RT	**3-8**	55%
$Pb(OAc)_4$	Ac	Benzene	Reflux	**3-7**	----

Table 3-1. Oxidative Cyclization of a Model Cycloocten-4-ol by Kim and Schlecht

In their report, the authors proposed a simple mechanism (Scheme 3-2). After initial formation of iodonium ion **3-9**, a transannular nucleophilic attack by the hydroxyl group occurs, giving intermediates **3-10** and **3-11**. Collapse of the iodonium ion leads to the formation of oxonium ion **3-12** which can be opened from two sides to give a mixture of regioisomers (**3-13** and **3-14**).



Scheme 3-2. Proposed Mechanism for *trans*-Etherification

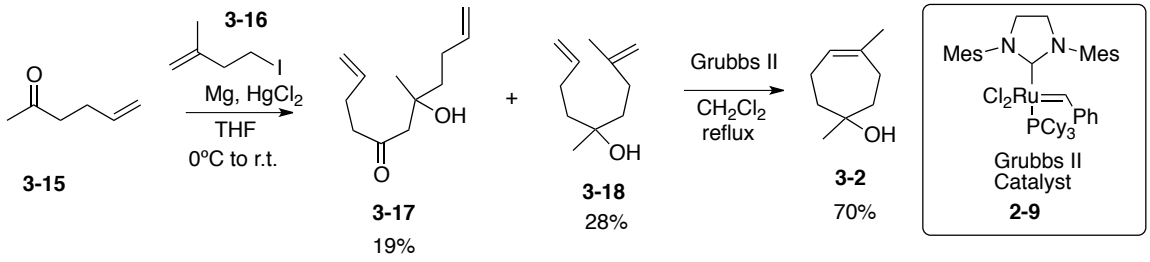
In the context of the englerin synthesis this methodology could, in principle, construct the desired C7-C10 oxygen bridge and adjacent C-6 substituent with the appropriate oxidation state and relative stereochemistry.

3.2 Results and Discussion

3.2.1 Synthesis of Model Cyclohepten-4-ols

The investigation of the Schlecht methodology began with the synthesis of model cycloheptenols **3-2** through **3-4**.

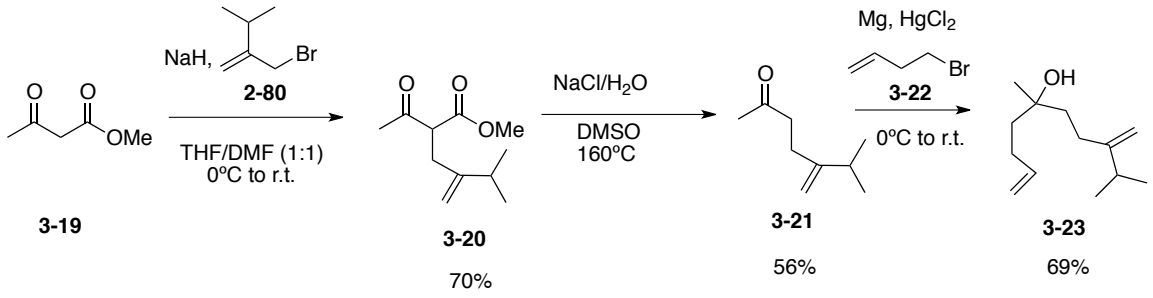
Alcohol **3-2** was prepared in 2 steps from commercially available 5-hexen-2-one (**3-15**) (Scheme 3-3).



Scheme 3-3. Synthesis of Model Compound **3-2**

Treatment of 5-hexen-2-one (**3-15**) with the Grignard reagent prepared from 4-iodo-2-methyl-1-butene (**3-16**) gave alcohol **3-18** in addition to some aldol product (**3-17**). Alcohol **3-2** was obtained upon treatment of diene **3-18** with Grubb's 2nd Generation catalyst (**2-9**) in refluxing methylene chloride.

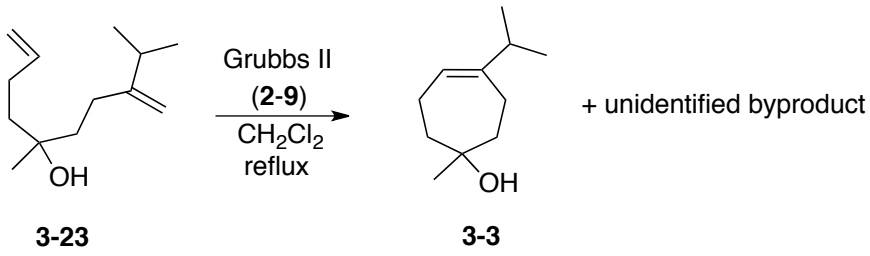
In order to construct compound **3-3** with ring closing metathesis (RCM) chemistry, diene **3-23** was prepared (Scheme 3-4).



Scheme 3-4. Synthesis of Diene **3-23**

Monoalkylation of methyl acetoacetate **3-19** with 3-bromo-2-isopropylpropene (**2-80**) followed by Krapcho decarbalkoxylation[5] of **3-20** gave ketone **3-21** in 56% yield. Treatment of this ketone with the Grignard reagent prepared from homoallyl bromide (**3-22**) provided diene **3-23**.

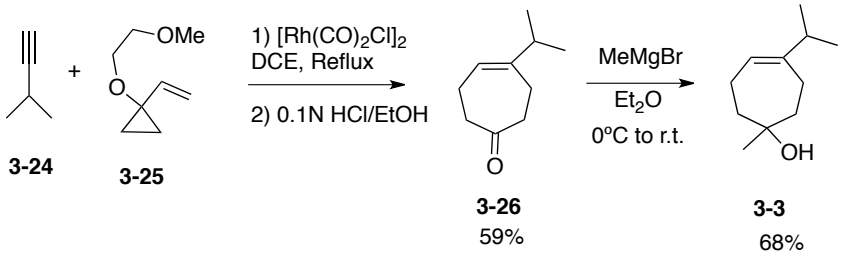
Attempted RCM of diene **3-23** met with difficulty (Scheme 3-5). The reaction conditions that promoted smooth ring closure in diene **3-18** were not effective when applied to diene **3-23**. Conversion proceeded sluggishly and appeared to produce a number of byproducts. Attempted isolation of the desired product using silica gel chromatography gave compound **3-3** but it was contaminated with an inseparable byproduct. In light of this we decided to prepare alcohol **3-3** by another means. The method of Wender[6] was chosen.



Scheme 3-5. Attempted Synthesis of Alcohol **3-3** by RCM of Diene **3-23**

By applying Wender's [5+2] cycloaddition strategy, alcohol **3-3** was obtained in three steps from commercially available starting materials (Scheme 3-6). Rhodium (I) catalyzed condensation of isopropylacetylene (**3-24**) with 1-(2-methyoxyethoxy)-1-vinylcyclopropane (**3-**

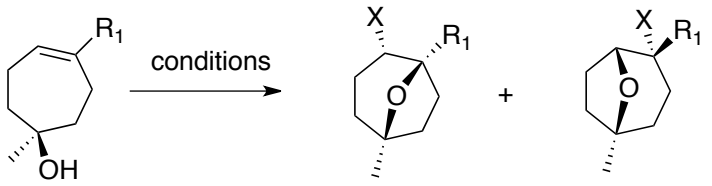
25) followed by enol ether hydrolysis gave ketone **3-26** in 59% yield (over two steps). Subsequent methylation gave alcohol **3-3** in 68% yield.



Scheme 3-6. Synthesis of Alcohol **3-3** by a [5+2] Cycloaddition

3.2.2 Oxidative Cyclization of Model Cyclohepten-4-ols **3-2** and **3-3**

With cycloheptenols **3-2** and **3-3** in hand, we began investigating Schlecht's etherification conditions. We also screened etherification promoted by NIS and thallium(III) trifluoroacetate. The results are summarized in Table 3-2.



3-2 R_1 = Me
3-3 R_1 = *i*Pr

a **b**

Entry	R_1	Conditions	X	Product	Yield % (a:b)
1	Me	$PhI(O_2CCF_3)_2$[a]	OH¶	**3-27**	74% (1:2.7)
2	Me	Pb(OAc)4 [b]	OAc	**3-28**	59% (1:1)
3	Me	NIS[c]	I	**3-29**	74% (1:0)
4	Me	PhI(OH)OTs[a]	OTs	**3-30**	14% (1:0)
5	*i*Pr	$PhI(O_2CCF_3)_2$[a]	OH¶	**3-31**	15% a + 30% (0.7:1)
6	*i*Pr	$Tl(O_2CCF_3)_2$[d]	OH	**3-31**	61% (1:1.5)
7	*i*Pr	Pb(OAc)4 [b]	OAc	**3-32**	50% a + 7% b
8	*i*Pr	NIS[c]	I	**3-33**	84% (1:0)

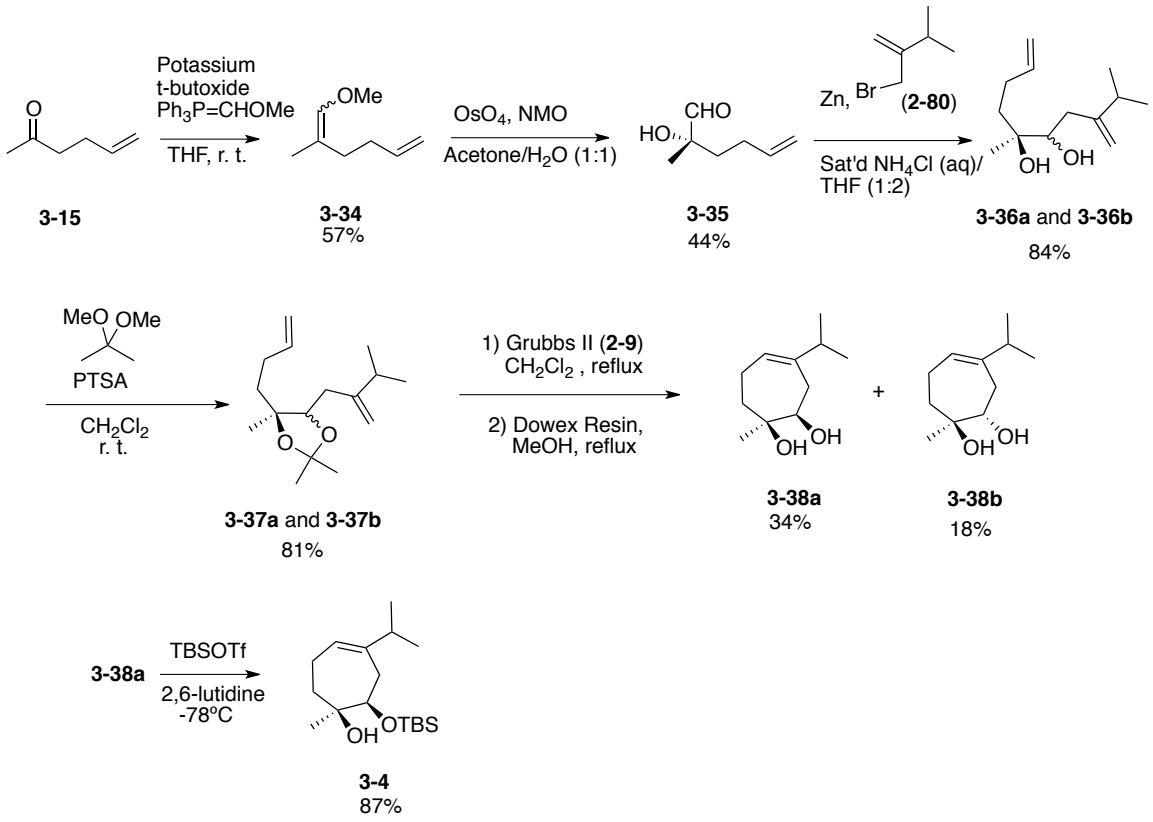
a: CH_2Cl_2, r. t. ; b: Toluene , reflux c: CH_2Cl_2, 0°C, d: THF/H_2O (1:1), r. t.
¶ The trifluoroacetates were hydrolyzed in (MeOH/$NaHCO_3$) and isolated as the corresponding alcohols.

Table 3-2. Oxidative Cyclization Results of Model Compounds **3-2** and **3-3**

The results from our initial experiments were promising. With four of the five reagents screened, namely $PhI(O_2CCF_3)_2$**,** $Tl(O_2CCF_3)_3$, $Pb(OAc)_4$, and NIS, the yields of the ring-closed products were satisfactory. Motivated by these results, we proceeded to synthesize model compound **3-4**.

3.2.3 Synthesis of Model Cyclohepten-4-ol **3-4**

We anticipated that the incorporation of an OTBS group *cis* to the nucloephilic hydroxyl group may interfere with the desired ring closure. The etherification results obtained from compound **3-4** would provide better insight into what we may encounter in the real system (**2-84**).

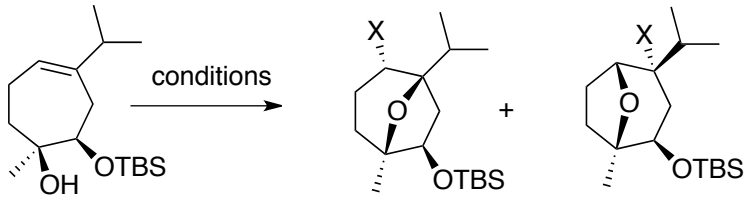


Scheme 3-7. Synthesis of Model Compound **3-4**

Thus model compound **3-4** was prepared in seven steps from 5-hexen-2-one (**3-15**), Scheme 3-7. Wittig olefination with (methoxymethyl)triphenyl-phosphonium chloride gave enol ether **3-34** as a mixture of stereoisomers. This was oxidized with osmium tetroxide to give aldehyde **3-35** which, in turn, was allylated with the Barbier reagent prepared from zinc and 2-bromomethyl-3-methyl-1-butene (**2-80**). This procedure gave an inseparable mixture of diastereomers **3-36a** and **3-36b**. The alcohols were protected as their corresponding acetonides and subjected to ring closing metathesis using the Grubbs 2nd generation catalyst (**2-9**). After an acid catalyzed deprotection with Dowex resin in wet methanol, diols **3-38a** and **3-38b** were separated by column chromatography. TBS protection of the *cis* isomer **3-38a** under kinetically controlled conditions with 1.5 equivalents of *tert*-butyldimethylsilyl triflate gave alcohol **3-4**.

3.2.4 Oxidative Cyclization of Model Cyclohepten-4-ol **3-4**

With the same etherification procedures optimized for alcohols **3-2** and **3-3**, we treated alcohol **3-4** with $PhI(O_2CCF_3)_2$**,** $Tl(O_2CCF_3)_3$, $Pb(OAc)_4$, and NIS to promote ring closure (Table 3-3). We also investigated oxymercuration conditions with $Hg(O_2CCF_3)_2$.



3-4 **a** **b**

Entry	Conditions	X	Product	Yield % (a:b)
1	$PhI(O_2CCF_3)_2$[a]	OH¶	**3-39**	30% **a** + 21%**b**
2	$Tl(O_2CCF_3)_2$[d]	OH	**3-39**	0%
3	Pb(OAc)4 [b]	OAc	**3-40**	< 10% (10:1)
4	NIS[c]	I	**3-41**	89% (1:0)
5	$Hg(O_2CCF_3)_2$[e]	HgCl§	**3-42**	83% (1:0)

a: CH_2Cl_2, r. t. ; b: Toluene , reflux; c: CH_2Cl_2, 0°C; d: THF/H_2O (1:1), r. t.; e: CH_2Cl_2, -78ºC to -40ºC
¶ The trifluoroacetates were hydrolyzed in (MeOH/$NaHCO_3$) and isolated as the corresponding alcohols.
§ The alkyl mercurial trifluoroacetate was treated with (aq) NaCl/$NaHCO_3$ and isolated as the corresponding mercurial chloride.

Table 3-3. Oxidative Cyclization Results of Model Compound **3-4**

While oxidative ring closure with $PhI(O_2CCF_3)_2$ appeared to be equally as effective in model **3-4** as it was in models **3-2** and **3-3**, this was not the case for reactions run with either $Pb(OAc)_4$ or $Tl(O_2CCF_3)_2$. After treatment of alcohol **3-3** with $Pb(OAc)_4$ in boiling toluene for 24 hours, ^{1}H NMR analysis of the crude reaction mixture revealed a number of products. In addition to starting material, as well as a major unidentified product, a small amount (< 10%) of the desired ring closed product was present. $Tl(O_2CCF_3)_2$ proved equally inefficient. After

stirring for four days at room temperature ^{1}H NMR analysis of the crude reaction mixture showed a mixture of products in which the major component was deprotected starting material. NIS, $Hg(O_2CCF_3)_2$, and $PhI(O_2CCF_3)_2$ all proceeded to give cyclized products.

3.3 Conclusion

The extension of the Kim and Schlecht oxidative cyclization methodology to model cycloheptenol systems was partially successful. For model compounds **3-2** and **3-3**, only the most reactive hypervalent iodine reagent, namely $PhI(O_2CCF_3)_2$, gave cyclized products in good yield. Lead tetraacetate, NIS, and thallium trifluoroacetate were also effective in promoting ring closure. Moreover, a trend was observed – bulkier nucleophiles promoted ether bridge formation at the more substituted carbon.

In the case of model compound **3-4**, in which a TBS protected alcohol was incorporated adjacent to the nucleophilic hydroxyl group, ring closure was less efficient. We believe that this effect is steric in origin and is evidenced by the reduced effectiveness of both $Tl(O_2CCF_3)_2$ and $Pb(OAc)_4$ in promoting ring closure. $Hg(O_2CCF_3)_2$, $PhI(O_2CCF_3)_2$, and NIS, were again effective in promoting ring closure.

With the results of this study to serve as a guideline, Lee and Parker screened etherification conditions with hydroazulene (**2-88**). As was shown in chapter 2-2, $Hg(O_2CCF_3)_2$ was the only reagent that could effect ring closure.

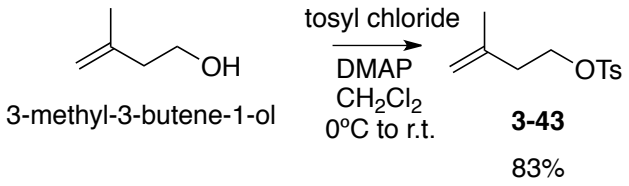
3.4 Experimental Section

General Information

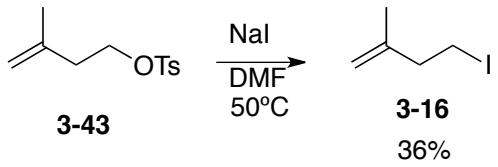
All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. $Pb(OAc)_4$ was recrystallized from glacial acetic acid. NIS was recrystallized from carbon tetrachloride. HPLC grade hexane and EtOAc, were used in chromatography. Diethyl ether (Et_2O) was distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or KMnO4 aq. solution and then heating.

Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for 1H and 126 MHz for 13C), Varian Inova-400 (400 MHz for 1H and 101 MHz for 13C), or Gemini-2300 (300 MHz for 1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimental Procedure/Characterization

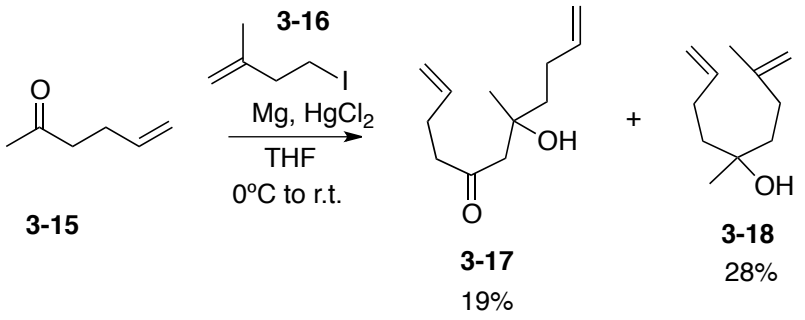


Tosylate 3-43. To a stirred solution of 3-methyl-3-butene-1-ol (10.02 g, 0.1161 mol) in methylene chloride (600 mL) was added DMAP (13.68 g, 0.1120 mol). The solution was placed in an ice bath, and then tosyl chloride was added in one portion (22.34 g, 0.1172 mol). The solution was allowed to slowly warm to room temperature overnight. The reaction mixture was poured into a separation funnel and then washed with sat. NH_4Cl solution (4 x 100 mL). The organic solution was dried over $MgSO_4$ and then filtered. Removal of the volatiles in vacuo gave tosylate **3-43**, (23.3 g, 83%) as a yellow oil. The crude residue was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.38 – 7.31 (m, 2H), 4.80 – 4.66 (m, 2H), 4.12 (t, *J* = 6.8 Hz, 2H), 2.45 (s, 2H), 2.38 – 2.32 (m, 2H), 1.66 (s, 1H). The data were consistent with literature values.[7]



Iodide 3-16. To a stirred solution of tosylate **3-43** (11.40 g, 47.44 mmol) in anhydrous DMF (50 mL) was added sodium iodide in one portion (10.87 g, 72.53 mmol). The reaction mixture was heated to 50ºC and it was maintained at that temperature for 3 hours. After cooling to room temperature the reaction mixture was poured into water (100 mL) and diluted with methylene chloride (100 mL). The aqueous layer was extracted with methylene chloride (3 x 100 mL). The

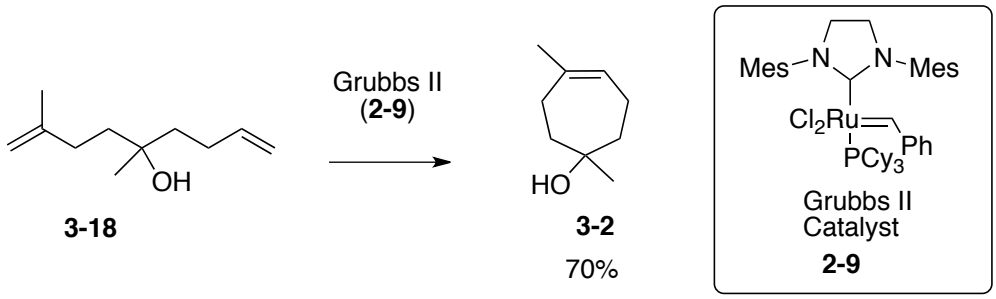
combined organic solution was washed with water (3 x 100 mL), dried over $MgSO_4$ and then filtered. Solvent was removed in vacuo. The crude residue was purified by distillation (boiling point 35ºC, pressure = 0.3 mmHg) to give a fraction that was still contaminated with some DMF. This was partitioned between 0.2N HCl (50 mL) and pentane (15 mL). The organic layer was washed with water (2 x 10 mL). The combined aqueous solution (washings) was extracted with pentane (2 x 25 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo to give iodide **3-16** (3.327 g, 36%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88 – 4.74 (m, 2H), 3.31 – 3.22 (m, 2H), 2.59 (br t, J = 7.4 Hz 2H), 1.74 (br s, 3H). The data were consistent with literature values.[7]



Alcohol 3-18. A 3 neck round bottom flask was charged with magnesium turnings (1.01 g, 41.1 mmol) followed by freshly distilled THF (30 mL). Iodide **3-16** was added (3.23 g, 16.5 mmol) dropwise in THF (5 mL) followed by $HgCl_2$ (21 mg, 0.077 mmol). The solution was allowed to reflux for 3 hours. The solution was cooled to 0ºC and then 5-hexen-2-one (**3-15**) was added (1.206 g, 12.29 mmol) dropwise in THF (5 mL). The solution was allowed to stir for 20 min and was then quenched by pouring into cold sat. NH_4Cl solution (200 mL). The aqueous layer was extracted with ether (3 x 100mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 10:1) to give alcohol **3-18** (0.579 g, 28%) in addition to some aldol product **3-17** (0.461 g, 19%). Alcohol **3-18** was purified further by Kugelrohr distillation (bath temp 100ºC, pressure = 0.5 mmHg) to give a colorless oil (0.512 g, 25%).

^{1}H NMR (400 MHz, $CDCl_3$ δ 5.86 (ddt, J = 17.1, 10.2, 6.6 Hz, 1H), 5.05 (dq, J = 17.1, 1.7 Hz, 1H), 4.96 (ddt, J = 10.2, 2.0, 1.3 Hz, 1H), 4.75 – 4.68 (m, 2H), 2.19 – 2.00 (m, 4H), 1.75 (s, 3H), 1.67 – 1.51 (m, 4H), 1.41 (s, 1H), 1.20 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 146.2, 138.9,

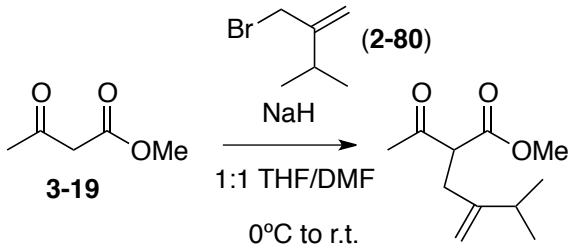
114.4, 109.8, 72.6, 40.9, 39.8, 32.1, 28.4, 26.8, 22.6. IR (neat) νmax: 3382, 3076, 2971, 2937, 2856, 1642, 1449, 1375, 910, 886. HRMS [EI+] calc for $C_{11}H_{20}O$ $[M]^+$ 168.15142, found 168.15234



3-18 **3-2** 70% **2-9**

Alcohol 3-2. To a refluxing solution of alcohol **3-18** (396 mg, 2.35 mmol) in CH_2Cl_2 (100 mL) was added Grubbs II catalyst (**2-9**) (204 mg, 0.240 mmol). After 4 hours the reaction mixture was allowed to cool to room temperature and was filtered through a pad of silica gel. The silica gel pad was washed with hexanes/ethyl acetate solution (2:1 v/v, 75 mL). After removal of solvent in vacuo, the crude residue was subjected to column chromatography (5:1 Hex/EtOAc) followed by Kugelrohr distillation (bath temp 60ºC, pressure = 0.5 mmHg) to give alcohol **3-2** as a colorless oil (231 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 – 5.47 (m, 1H), 2.35 – 2.16 (m, 2H), 1.94 – 1.82 (m, 2H), 1.72 – 1.54 (m, 7H), 1.28 (s, 1H), 1.24 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 140.0, 125.1, 73.5, 40.7, 39.6, 30.4, 28.4, 25.9, 22.8. IR (neat) νmax: 3363, 3042, 2964, 2926, 2852, 1438, 951 HRMS [EI+] calc for $C_9H_{16}O$ $[M]^+$ 140.12012, found 140.12083

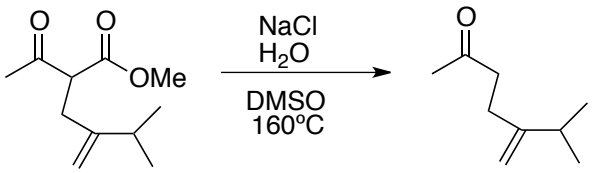


3-19 **3-20** 70%

Ester 3-20. To a stirred solution of 60% NaH (0.371 g, 9.29 mmol) in 1:1 THF/DMF (10 mL) was added methyl acetoacetate (1.0 g, 8.6 mmol) dropwise at 0ºC. After addition was complete,

2-bromo-methyl-3-methyl-1-butane (**2-80**) (1.37 g, 8.38 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 3 hours and the solution was quenched with water (50 mL). The reaction mixture was extracted with ether (3 x 50 mL). The combined organic solution was washed with water (5 x 100 mL), dried over $MgSO_4$ and then filtered. Solvent was removed in vacuo. The crude residue was subjected to column chromatography (25:1 Hex/EtOAc) to give compound **3-20** (1.16 g, 70%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (br s, 1H), 4.64 (br s, 1H), 3.76 – 3.69 (m, 4H), 2.59 (d, *J* = 7.7 Hz, 2H), 2.33 – 2.12 (m, 4H), 1.04 (d, *J* = 1.0 Hz, 3H), 1.02 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 202.6, 170.0, 152.1, 108.1, 58.3, 52.4, 34.0, 32.5, 29.0, 21.7. IR (neat) νmax: 2927, 1720, 1746, 1644 HRMS [ES+] calc for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1154, found 221.1158

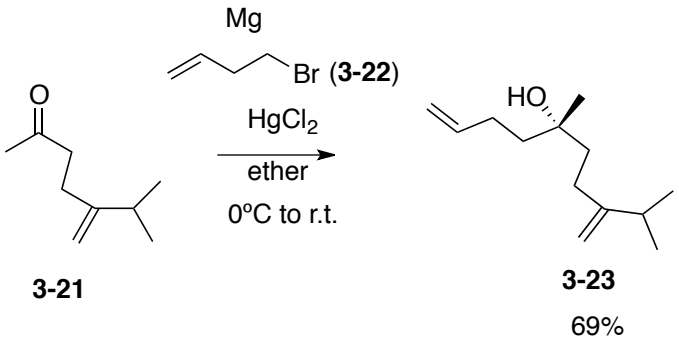


3-20 **3-21**

56%

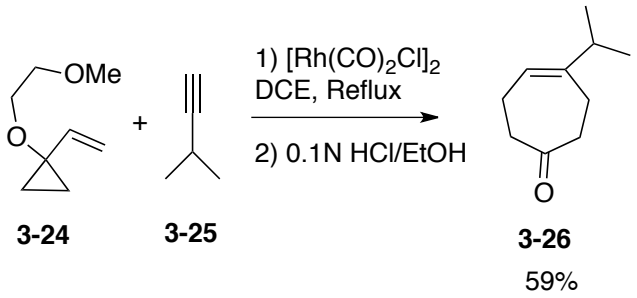
Ketone 3-21. Decarbalkoxylation of ester **3-20** was performed according to the method of Krapcho.[5] To a stirred solution of ester **3-20** (3.26 g, 16.4 mmol) in DMSO (30 mL) were added NaCl (1.12, 19.2 mmol) and water (0.60 mL, 33 mmol). The solution was heated to 160ºC. After 2.5 hours the solution was cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. $NaHCO_3$ solution (5 x 20 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (30:1 Hex/EtOAc) followed by Kugelrohr distillation (bath temp 120ºC, pressure = 0.5 mmHg) to give ketone **3-21** (1.28 g, 56%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (br s, 1H), 4.62 (br s, 1H), 2.63 – 2.55 (m, 2H), 2.34 – 2.18 (m, 3H), 2.16 (s, 3H), 1.04 (d, *J* = 6.9 Hz, 6H). IR (neat) νmax 3084, 2963, 2874, 1718, 1644



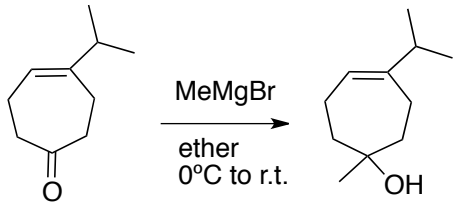
Alcohol 3-23. A 3 neck round bottom flask was charged with magnesium turnings (888 mg, 36.5 mmol) followed by freshly distilled ether (30 mL). 4-bromo-1-butene (**3-22**) (3.77 g, 27.9 mmol) was added dropwise in ether (2 mL) followed by $HgCl_2$ (250 mg, 0.913 mmol). The solution was allowed to reflux for 3 hours. The solution of Grignard reagent was then cooled to 0ºC and ketone **3-21** (1.28 g, 9.13 mmol) was added dropwise in ether (2 mL). The solution was allowed to slowly warm to room temperature overnight. The reaction was quenched by pouring into cold sat. NH_4Cl solution (40 mL). The aqueous layer was extracted with ether (3 x 50 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 20:1) followed by Kugelrohr distillation (bath temp =160ºC, pressure = 0.5 mmHg) to give alcohol **3-23** (1.23 g, 69%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.14 – 4.91 (m, 2H), 4.76 (br s, 1H), 4.71 (br s, 1H), 2.35 – 2.01 (m, 5H), 1.69 – 1.53 (m, 4H), 1.27 (br s, 1H), 1.21 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 156.2, 131.0, 114.4, 106.4, 72.7, 41.0, 40.5, 34.0, 28.6, 28.4, 26.8, 21.9. IR (neat) νmax 3383, 3079, 2964, 2872, 1642 HRMS [EI+] calc for $C_{13}H_{24}O$ $[M]^+$ 196.18272, found 196.18322



Ketone 3-26. To a stirred solution of $[Rh(CO)_2Cl]_2$ (28 mg, 0.072 mmol) in dichloroethane (7 mL) were added 1-(2-methyoxyethoxy)-1-vinylcyclopropane (**3-24**) (0.52 mL, 0.48 g, 3.4 mmol) followed by 3-methyl-1-buytne (**3-25**) (0.55 mL, 5.4 mmol). The solution was allowed to reflux for an hour and then an additional portion of $[Rh(CO)_2Cl]_2$ was added (7 mg, 0.02 mmol). The solution was allowed to reflux for an additional 30 min and then it was cooled to 0ºC. HCl was added (1 mL of a 0.1N solution in 95:5 v/v EtOH/H_2O) and the solution was allowed to slowly warm to room temperature over 2 hours. The reaction mixture was diluted with methylene chloride (30 mL) and transferred to a separation funnel. The reaction mixture was washed with water (3 x 10 mL), dried over $MgSO_4$, filtered and then concentrated in vacuo. The crude residue was subjected to column chromatography (Hex/EtOAc = 30:1) to give ketone **3-26** (341 mg, 59%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 – 5.56 (m, 1H), 2.58 – 2.51 (m, 4H), 2.34 – 2.23 (m, 5H), 1.00 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 213.4, 147.8, 121.2, 43.0, 42.6, 37.1, 25.0, 23.7, 21.30. IR (neat) νmax 2960, 1709 HRMS [EI+] calc for $C_{10}H_{16}O$ $[M]^+$ 152.12012, found 152.1217

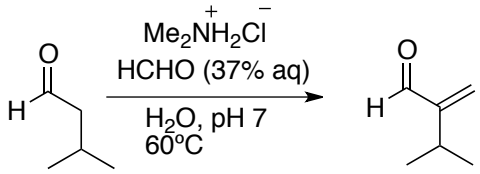


3-26 **3-3**

68%

Alcohol 3-3. To a stirred solution of MeMgBr (1.5 mL, 3M in ether, 4.5 mmol) in 2 mL diethyl ether was added ketone **3-26** (341 mg, 2.24 mmol) in ether (1 mL) dropwise at 0ºC. The reaction mixture was allowed to slowly warm to room temperature until TLC analysis indicated the disappearance of starting material. The reaction mixture was quenched with sat. NH_4Cl solution (5 mL) and diluted with ether (10 mL). The aqueous layer was extracted with ether (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by Kugelrohr distillation (bath temp 140ºC, pressure = 0.5 mmHg) to give alcohol **3-3** (256 mg, 68%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 – 5.48 (m, 1H), 2.34 – 2.14 (m, 3H), 1.96 – 1.81 (m, 2H), 1.67 – 1.46 (m, 4H), 1.31 (s, 1H), 1.23 (s, 3H), 0.96 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 150.0, 122.5, 73.4, 40.3, 40.3, 36.8, 30.7, 24.3, 22.4, 21.3, 21.2. IR (neat) νmax 3365, 2960, 2928, 2861, 1464, 1117 HRMS [EI+] calc for $C_{11}H_{20}O$ $[M]^+$ 168.15142, found 168.15298



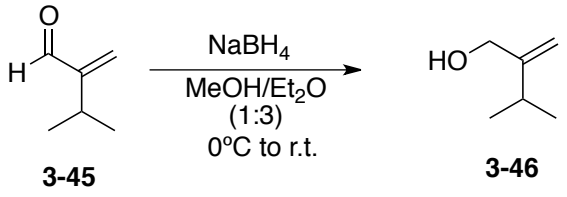
3-44 **3-45**

64%

Aldehyde 3-45. This compound was prepared according to the method of Breit.[8] A solution of dimethylamine hydrochloride (129.3 g, 1.586 mol) in formaldehyde (37% (aq), 120 mL) was prepared, and the pH was adjusted to 7 by the addition of sodium bicarbonate. Isovaleraldehye (freshly distilled from *para*-toluene sulfonic acid) was added (112.9 g, 1.311 mol), and the solution was allowed to stir at 60ºC for two days. The reaction mixture was subjected to steam distillation until organic material no longer separated from the distillate. The biphasic distillate

was transferred to a separation funnel and the aqueous layer was extracted with ether (3 x 80 mL). The combined organic solution was dried over $MgSO_4$ and filtered. The organic solution was subjected to fractional distillation to remove solvent and to isolate aldehyde **3-45** (82.4 g, 64%) as a colorless oil; boiling point 109ºC at 1 atm.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 6.24 (s, 1H), 5.95 (s, 1H), 2.87 – 2.72 (m, 1H), 1.07 (d, J = 6.9 Hz, 6H). The data were consistent with literature values.[9]



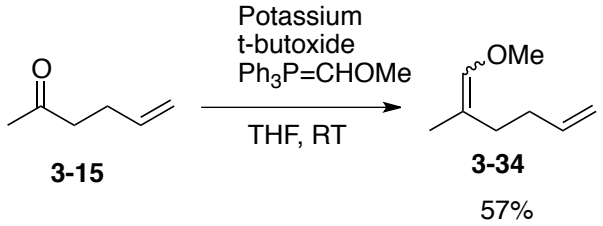
3-45 **3-46**

74%

Alcohol 3-46. A stirred solution of aldehyde **3-45** (82.4 g, 0.840 mol) in a 3:1 (v/v) solution of ether/methanol (830 mL) was cooled to 0ºC. Sodium borohydride was added slowly in portions over 10 minutes (31.7 g, 0.840 mol) and the reaction mixture was allowed to slowly warm to room temperature over 2 hours. The reaction mixture was carefully concentrated in vacuo to remove excess solvent (gentle heating; note the volatility of the product). The reaction mixture was diluted with methylene chloride (300 mL), placed in an ice bath, and then sat. NH_4Cl solution was added (200 mL). The biphasic reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was filtered through a glass frit. The filter was washed with methylene chloride (200 mL) and the filtrate was transferred to a separation funnel. The aqueous layer was extracted with methylene chloride (3 x 100 mL). The combined organic solution was dried over $MgSO_4$ and then filtered. The resulting solution was concentrated in vacuo (again gentle heating; note the volatility of the product). The crude oil was subjected to vacuum distillation (pressure = 13 mmHg) to give alcohol **3-46** (62.3 g, 74%) as a colorless oil; boiling point 55-57ºC.

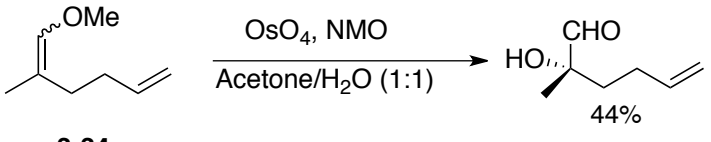
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 – 4.98 (m, 1H), 4.91 – 4.88 (m, 1H), 4.13 (br d, J = 6.2 Hz, 2H), 2.33 (hept, J = 6.9 Hz, 1H), 1.47 – 1.33 (m, 1H), 1.07 (d, J = 6.9 Hz, 6H). The data were consistent with literature values.[10]

2-bromo-methyl-3-methyl-1-butane (**2-80**) was prepared from this alcohol according to Barton et al.[11]



Enol ether 3-34. To a stirred solution of (methoxymethyl)triphenyl phosphonium chloride (55.8 g, 0.163 mol) in THF (100 mL) was added 20% potassium *t*-butoxide solution in THF (100 mL, 18.6 g, 0.166 mol). An additional portion of THF was added (40 mL) and the solution became slightly warm and dark red. After stirring for 40 minutes, 5-hexen-2-one (**3-15**) (8.01 g, 81.5 mmol) was added in THF (2 mL) followed by an additional portion of THF (8 mL). After 15 hours the reaction was quenched with 25% ammonium sulfate solution (500 mL). The solution was filtered through a pad of celite. At this point three layers appeared – the 'bottom' aqueous layer, a middle layer, and the 'top' organic layer. The middle layer was discarded. The aqueous layer was extracted with pentane (1 x 50 mL). The combined organic solution was washed once with 25% ammonium sulfate solution (50 mL), dried over $MgSO_4$ and filtered. The solvent was removed by distillation at ambient pressure. Vacuum distillation (pressure = 74 mmHg) of the crude residue gave enol ether **3-34** (boiling point 140ºC, 5.87 g, 57%) as a colorless oil; ~1:1.2 mixture of stereoisomers.

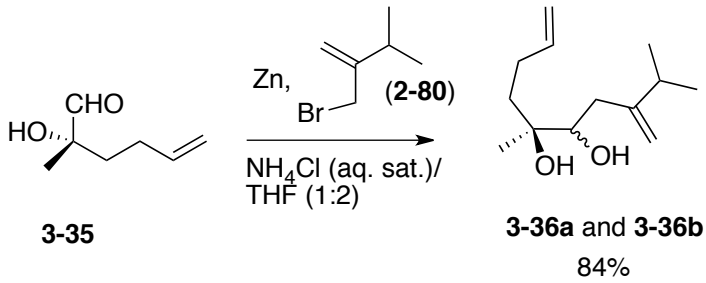
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.73 (m, 2H), 5.07 – 4.90 (m, 2H), 3.54 (s, 3H), 3.51 (s, 3H), 2.21 – 2.07 (m, 2H), 2.01 – 1.91 (m, 2H), 1.59 (d, J = 1.4 Hz, 3H), 1.53 (d, J = 1.5 Hz, 3H). IR (neat) νmax 3077.12, 2929.81, 2840.77, 1685.37, 1640.90, 1451.03, 1238.11, 1205.63, 1138.08



3-34 **3-35**

Aldehyde 3-35. To a stirred solution of enol ether **3-34** (2.018 g, 15.99 mmol) in 9:1 acetone/H_2O (200 mL) was added N-methylmorpholine N-oxide (NMO) (2.28 g, 19.5 mmol). Once the NMO had dissolved, OsO_4 solution was added (8.0 g, 2.5 wt% in *t*-butanol, 0.79 mmol) and the solution was allowed to stir at room temperature. After 20 hours the reaction mixture was poured into a biphasic solution of sat. sodium sulfite (100 mL) and methylene chloride (50 mL). This solution was transferred to a separation funnel and the aqueous layer was extracted with methylene chloride (3 x 50 mL). The combined organic solution was washed with 10% citric acid (3 x 50 mL), sat. $NaHCO_3$ (1 x 75 mL), dried over $MgSO_4$ and then filtered. Solvent was removed by distillation at ambient pressure. The crude residue was subjected to vacuum distillation (pressure = 10 mmHg) to give aldehyde **3-35** (903 mg, boiling point 65-66ºC, 44%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 5.78 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.07 – 4.95 (m, 2H), 3.16 (s, 1H), 2.25 – 2.13 (m, 1H), 2.01 – 1.91 (m, 1H), 1.81 – 1.75 (m, 2H), 1.31 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 203.6, 137.6, 115.4, 77.7, 36.4, 27.4, 22.8. IR (neat) νmax 3435, 3079, 2978, 2936, 1733, 1642. HRMS [ES+] calc for $C_7H_{12}O_2Na$ $[M+Na]^+$ 151.0735, found 151.0742

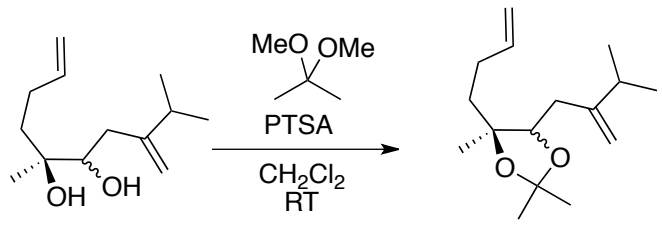


3-35

3-36a and **3-36b**
84%

Alcohols 3-36a and 3-36b. To a stirred solution of aldehyde **3-35** (4.09 g, 31.9 mmol) and 2-bromo-methyl-3-methyl-1-butane (**2-80**) (15.60 g, 95.64 mmol), in 1:2 sat. NH_4Cl solution/THF (240 mL) at 0ºC, was added zinc dust in one portion (8.935 g, 0.137 mol). The solution was allowed to slowly warm to room temperature. After 20 hours the reaction mixture was filtered through a pad of celite. The celite pad was washed with additional ethyl acetate. The biphasic mixture was transferred to a separation funnel, and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (5:1 to 2:1 Hex/EtOAc) to give alcohols **3-36a** and **3-36b** (5.68 g, 84%) as an inseparable mixture of diastereomers; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) 1H NMR (400 MHz, $CDCl_3$) δ 5.92 – 5.77 (m, 2H), 5.09 – 4.79 (m, 8H), 3.58 – 3.47 (m, 2H), 2.42 – 1.95 (m, 14H), 1.78 – 1.39 (m, 4H), 1.19 (s, 3H), 1.12 (s, 3H), 1.05 (d, J = 6.6 Hz, 6H), 1.02 (d, J = 6.8 Hz, 6H). IR (neat) νmax 3435, 3079, 2962, 2870, 1641. HRMS [ES+] calc for $C_{13}H_{124}O_2Na$ $[M+Na]^+$ 235.1674, found 235.1675



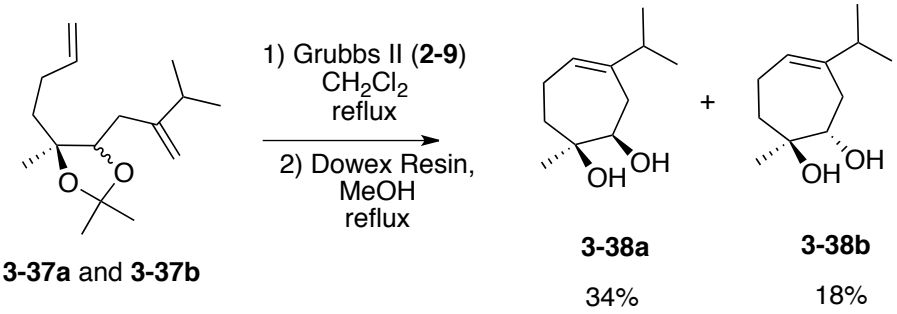
3-36a and **3-36b**

3-37a and **3-37b**
81%

Acetonides 3-37a and 3-37b. To a stirred solution of alcohols **3-36a** and **3-36b** (5.68 g, 26.8 mmol) in methylene chloride (500 mL) were added 2,2-dimethoxypropane (6.6 mL, 54 mmol) and p-toluenesulfonic acid monohydrate (0.51 g, 2.7 mmol). After stirring for 23 hours at room temperature, the reaction mixture was washed with sat. $NaHCO_3$ (4 x 100 mL). The organic

solution was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was subjected to column chromatography (30:1 Hex/EtOAc) followed by Kugelrohr distillation (bath temp 130ºC, pressure = 0.5 mmHg) to give acetonides **3-37a** and **3-37b** (5.48g, 81%) as an inseparable mixture of diastereomers; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 – 5.78 (m, 2H), 5.07 – 5.01 (m, 2H), 4.97 – 4.93 (m, 2H), 4.90 – 4.87 (m, 4H), 4.00 – 3.88 (m, 2H), 2.34 – 2.06 (m, 8H), 1.72 – 1.51 (m, 4H), 1.44 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.34 – 1.27 (m, 2H), 1.22 (s, 3H), 1.12 (s, 3H), 1.07 (d, *J* = 3.1 Hz, 6H), 1.06 (d, *J* = 3.1 Hz, 6H). IR (neat) νmax 3080, 2982, 2964, 2934, 2872, 1642, 1377. HRMS [ES+] calc for $C_{16}H_{28}O_2Na$ $[M+Na]^+$ 275.1987, found 275.1991



3-37a and **3-37b**

3-38a 34%

3-38b 18%

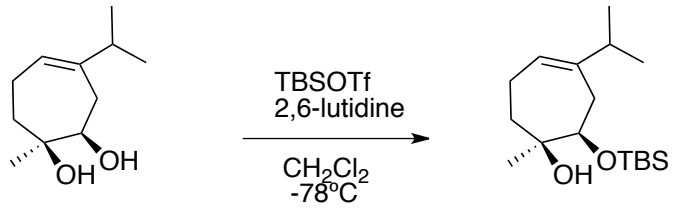
Diols 3-38a and 3-38b. A stirred solution of acetonides **3-37a** and **3-37b** (1.030 g, 4.081 mmol) in methylene chloride (550 mL) was brought to reflux. Grubbs 2nd generation catalyst (**2-9**) was added (831 mg, 0.979 mmol), and the solution was allowed to reflux for 34 hours. The reaction mixture was concentrated in vacuo, and the crude residue was partially purified by column chromatography (35:1 Hex/EtOAc). The resulting oil was dissolved in methanol (20 mL) and water (1 mL) and dowex exchange resin was added (360 mg). The solution was allowed to reflux under argon for 2 days. After cooling to room temperature the reaction mixture was filtered through a celite pad. The resulting filtrate was partitioned between methylene chloride (40 mL) and brine (40 mL). The aqueous layer was extracted with methylene chloride (5 x 40 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography to give *cis* diol **3-38a** (253 mg, 34%) and *trans* diol **3-38b** (134 mg, 18 %) as colorless oils.

Diol 3-38a:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (t, *J* = 6.2 Hz, 1H), 3.47 – 3.41 (m, 1H), 2.67 – 2.59 (m, 1H), 2.31 (s, 1H), 2.29 – 2.18 (m, 2H), 2.08 (d, *J* = 15.0 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.72 – 1.62 (m, 1H), 1.62 – 1.54 (m, 1H), 1.27 (s, 3H), 0.99 (d, *J* = 4.8 Hz, 3H), 0.98 (d, *J* = 4.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 144.1, 124.5, 74.6, 74.5, 37.5, 36.9, 32.9, 26.4, 22.3, 21.3, 21.2. IR (neat) νmax 3391, 2960, 2932, 2868, 1463. HRMS [ES+] calc for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207.1361, found 207.1369

Diol 3-38b:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 – 5.57 (m, 1H), 3.42 (t, *J* = 6.3 Hz, 1H), 2.31 – 2.19 (m, 3H), 2.16 – 2.06 (m, 1H), 2.00 – 1.79 (m, 3H), 1.77 – 1.67 (m, 1H), 1.53 – 1.43 (m, 1H), 1.28 (s, 3H), 1.04 – 0.90 (m, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 145.0, 123.9, 76.5, 76.3, 39.1, 37.2, 33.1, 22.5, 21.2, 20.8. IR (neat) νmax 3401, 2959, 2921, 2868, 1464. HRMS [ES+] calc for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207.1361 found 207.1369

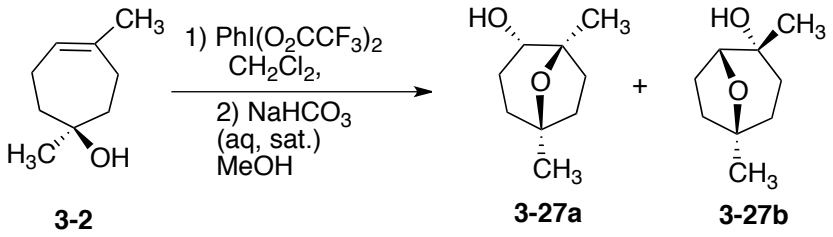


3-38a **3-4**

87%

Alcohol 3-4. To a stirred solution of diol **3-38a** (298 mg, 1.62 mmol) in methylene chloride (9 mL) was added 2,6-lutidine (0.57 mL, 4.9 mmol). The solution was cooled to -78ºC and then a solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.56 mL, 2.4 mmol) was added in CH_2Cl_2 (3 mL). After 10 minutes the reaction was quenched with sat. $NaHCO_3$ (3 mL) and the biphasic mixture was allowed to warm to room temperature. The aqueous layer was extracted with methylene chloride (3 x 5 mL). The combined organic solution was washed with 10% citric acid (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (100:1 Hex/EtOAc) to give alcohol **3-4** (422 mg, 87%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.55 – 5.51 (m, 1H), 3.43 (dd, *J* = 10.8, 1.9 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.64 (d, *J* = 1.2 Hz, 1H), 2.29 (ddd, *J* = 15.5, 10.1, 6.1 Hz, 1H), 2.20 (hept, *J* = 6.8 Hz, 1H), 1.89 – 1.70 (m, 3H), 1.58 – 1.48 (m, 1H), 1.18 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 144.3, 124.3, 76.0, 74.3, 37.5, 36.9, 33.6, 28.5, 25.9, 22.2, 21.6, 21.2, -3.9, -4.8. IR (neat) νmax 3572, 2957, 2858, 1463, 1252. HRMS [ES+] calc for $C_{17}H_{34}O_2NaSi$ $[M+Na]^+$ 321.2226 found 321.2235

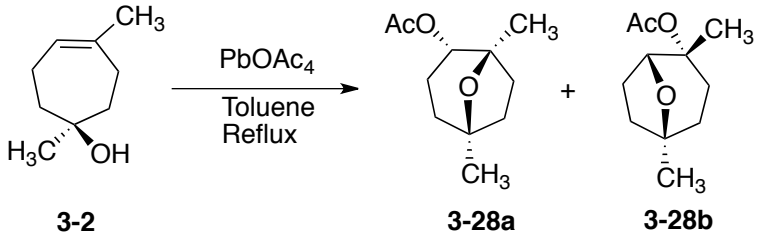


3-2 **3-27a** **3-27b**

74% (a:b, 1:2.7)

Alcohols 3-27a and **3-27b.** To a stirred solution of alcohol **3-2** (25 mg, 0.18 mmol) in methylene chloride (2 mL) was added $PhI(O_2CCF_3)_2$ (64 mg, 0.15 mmol). An additional portion of $PhI(O_2CCF_3)_2$ was added (29 mg, 0.067 mmol) after 5 minutes. After stirring at room temperature for 29 hours, the reaction mixture was diluted with methylene chloride (15 mL), washed with 10% NaI (5 mL) and sat. sodium thiosulfate (5 mL). The combined solution of aqueous washes was extracted once with methylene chloride (10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was dissolved in a 1:1 MeOH/$NaHCO_3$ solution (14 mL) and allowed to stir at room temperature for 72 hours. The reaction mixture was diluted with methylene chloride (10 mL) and transferred to a separation funnel. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (2:1 Hex/EtOAc) to give alcohols **3-27a** and **3-27b** (21 mg, 74%) as an inseparable mixture of regioisomers; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (d, *J* = 7.3 Hz, 1H), 3.54 – 3.47 (m, 1H), 2.13 – 1.40 (m, 18H), 1.37 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H). IR (neat) νmax 3421, 2967, 2932, 2873, 1450, 1376. HRMS [EI+] calc for $C_9H_{16}O_2$ $[M]^+$ 156.11503 found 156.11666

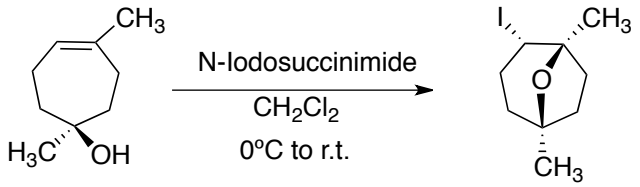


3-2 **3-28a** **3-28b**

59% (1:1)

Acetates 3-28a and 3-28b. To a stirred solution of alcohol **3-2** (23 mg, 0.16 mmol) in toluene (5 mL) was added $Pb(OAc)_4$ (103 mg, 0.232 mmol) and the solution was allowed to reflux for 1 hour. After cooling to room temperature the reaction mixture was quenched with ethylene glycol (5 mL). The reaction mixture was diluted with toluene (15 mL), washed with water (5 mL), 10% NaI solution (5 mL), and sat. sodium bicarbonate solution (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give acetates **3-28a** and **3-28b** (19 mg, 59%) as an inseparable mixture of regioisomers; colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (dd, *J* = 10.0, 5.8 Hz, 1H), 4.29 (d, *J* = 6.8 Hz, 1H), 2.19 – 1.41 (m, 25H), 1.30 (s, 6H), 1.23 (s, 3H). IR (neat) νmax 2970, 2933, 2877, 1739, 1372, 1250, 1236. HRMS [EI+] calc for $C_{11}H_{18}O_3$ $[M]^+$ 198.12560 found 198.12621

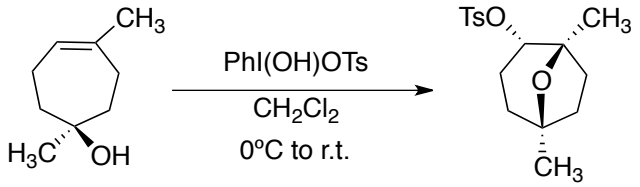


3-2 **3-29**

74%

Iodide 3-29. To a stirred solution of alcohol **3-2** (21 mg, 0.15 mmol) in methylene chloride (2 mL) was added NIS (48 mg, 0.21 mmol) at 0ºC. The solution was allowed to slowly warm to room temperature and stirred for 20 hours. The reaction mixture was quenched with sat. sodium thiosulfate solution (3 mL) and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (10:1 Hex/EtOAc) to give iodide **3-29** (29 mg, 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22 (ddd, J = 9.0, 7.9, 1.4 Hz, 1H), 2.48 – 2.27 (m, 3H), 1.95 – 1.56 (m, 4H), 1.49 (s, 3H), 1.37 – 1.31 (m, 1H), 1.26 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 84.0, 81.3, 40.5, 39.9, 36.5, 34.1, 32.8, 28.0, 26.8. IR (neat) νmax 2969, 2929, 2872, 1474, 1449, 1375, 1283, 1148, 1106, 1096. HRMS [EI+] calc for $C_9H_{15}OI$ $[M]^+$ 266.01680 found 266.01665



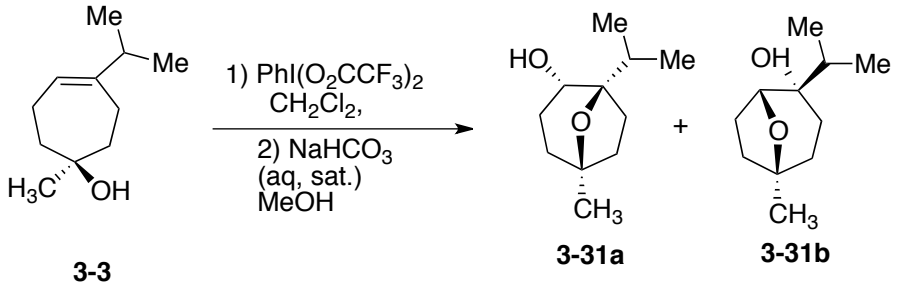
3-2 **3-30**

14%

Tosylate 3-30. To a stirred solution of alcohol **3-2** (20 mg, 0.14 mmol) in methylene chloride (2 mL) was added hydroxy(tosyloxy)iodo benzene (87 mg, 0.22 mmol) in one portion. The suspension was allowed to stir at room temperature for 21 hours. The reaction mixture was diluted with methylene chloride (15 mL) and washed with 10% NaI (5 mL) and sat. sodium

thiosulfate (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (10:1 Hex/EtOAc) to give tosylate **3-30** (6 mg, 14%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (br d, J = 8.3 Hz, 2H), 7.33 (br d, J = 8.0 Hz, 2H), 4.25 (dd, J = 10.5, 6.0 Hz, 1H), 2.44 (s, 3H), 2.09 (ddd, J = 13.1, 9.8, 5.2 Hz, 1H), 2.03 – 1.94 (m, 1H), 1.84 – 1.47 (m, 6H), 1.26 (s, 3H), 1.04 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 134.2, 129.8, 127.9, 82.8, 81.6, 81.0, 37.1, 36.0, 32.4, 25.9, 25.8, 23.1, 21.6. IR (neat) νmax 2970, 2932, 2877, 1598, 1366, 1189, 1176, 984. HRMS [ES+] calc for $C_{22}H_{22}O_4NaS$ $[M+Na]^+$ 333.1137 found 333.1146



3-3 **3-31a** **3-31b**

15% **3-31a** + 30% (**a**:**b**, 0.7:1)

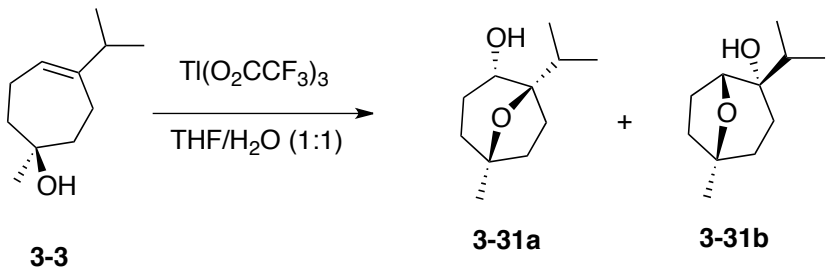
Alcohols 3-31a and **3-31b**. To a stirred solution of alcohol **3-3** (20 mg, 0.12 mmol) in methylene chloride (2 mL) was added phenyliodine bis(trifluoroacetate) in one portion (57 mg, 0.13 mmol). The solution was allowed to stir at room temperature for 24 hours and then an additional portion of phenyliodine bis(trifluoroacetate) was added (10 mg, 0.02 mmol). The solution was allowed to stir for an additional 3 hours and was quenched with sat. sodium thiosulfate (3 mL). The aqueous layer was extracted with methylene chloride (3 x 5 mL). The combined organic solution was concentrated in vacuo. The crude residue was dissolved in 1:1 MeOH/sat. $NaHCO_3$ (10 mL) and was allowed to stir overnight. The reaction mixture was diluted with ether (50 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR analysis of the crude mixture of alcohols revealed a 1:0.6 ratio of **a**:**b**. The crude mixture was then subjected to column chromatography (5:1 Hex/EtOAc) to give alcohol **3-31a** (3 mg, 15%) as a colorless oil along with a mixed fraction of **3-31a** and **3-31b** (7 mg, 30%) as a colorless oil; **a**:**b** (0.7:1).

Alcohol 3-31a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (dt, *J* = 9.7, 5.4 Hz, 1H), 1.99 – 1.37 (m, 9H), 1.26 (s, 3H), 1.22 (d, *J* = 5.1 Hz, 1H), 1.02 (app t, *J* = 6.5 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 86.7, 80.2, 70.2, 37.1, 36.1, 32.7, 28.5, 28.0, 26.0, 18.1, 17.1. IR (neat) νmax 3427, 2967, 2935, 2875, 1456, 1377.

Alcohols 3-31a and 3-31b (mixed fraction):

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (dd, *J* = 7.5, 2.1 Hz, 1H, mj), δ 3.82 (dt, *J* = 9.7, 5.4 Hz, 1H, mn), 2.32 (hept, *J* = 6.9 Hz, 1H, mj), 2.14 – 1.33 (m, 19H, mj, mn), 1.31 (s, 3H, mj), 1.27 (s, 3H, mn), 1.02 (app t, *J* = 7.3 Hz, 6H, mn), 0.96 (d, *J* = 6.9 Hz, 3H, mj), 0.91 (d, *J* = 7.0 Hz, 3H, mj). ^{13}C NMR (126 MHz, CDCl3) δ 86.7 mn, 80.2 mn, 80.1 mj, 79.0 mj, 72.4 mj, 70.2 mn, 37.0 mn, 36.1 mn, 35.5 mj, 35.0 mj, 32.7 mn, 29.0 mj, 28.5 mn, 28.0 mn, 27.9 mj, 26.2 mj, 26.0 mn, 25.5 mj, 18.1 mn, 17.1 mn, 16.5 mj, 16.1 mj. mj = major; mn = minor IR (neat) νmax 3445, 2967, 2929, 2878, 1472, 1378. HRMS [ES+] calc for $C_{11}H_{20}O_2Na$ $[M+Na]^+$ 207.1361 found 207.1357



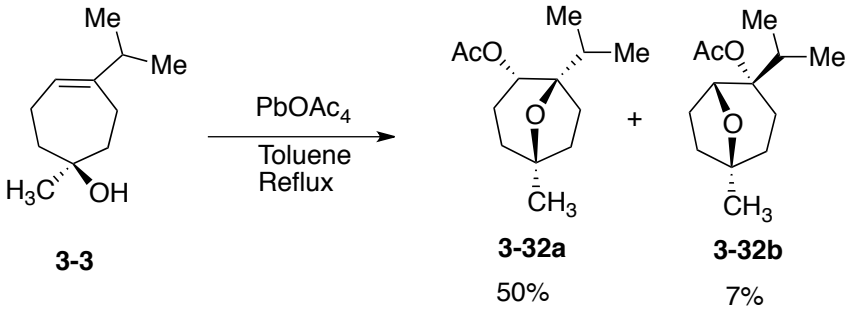
3-3 **3-31a** **3-31b**

61% (a:b, 1:1.5)

Alcohols 3-31a and **3-31b.** To a stirred solution of alcohol **3-3** (20 mg, 0.12 mmol) in 1:1 THF/H_2O (2 mL) was added thallium (III) trifluoroacetate (81 mg, 0.15 mmol) and the solution was allowed to stir at room temperature (Note: the solution turned red upon addition of the Tl(III) reagent). After stirring for 22 hours the solution was quenched with sat. $NaHCO_3$ (2 mL) (Note after conversion of Tl(III) to Tl(I) the solution became colorless) and diluted with ether (10 mL). The aqueous layer was extracted with ether (20 mL in three portions) and the

combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (5:1 Hex/EtOAc) to give alcohols **3-31a** and **3-31b** (13 mg, 61%) as a mixture of regioisomers (**a**:**b**, 1:1.5); colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, *J* = 7.1 Hz, 1H, mj), 3.89 – 3.76 (m, 1H, mn), 2.31 (hept, *J* = 6.9 Hz, 1H, mj), 2.16 – 1.34 (m, 18H, mj, mn), 1.31 (s, 3H, mj), 1.26 (s, 3H, mn), 1.02 (d, *J* = 4.8 Hz, 3H, mn), 1.00 (d, *J* = 4.6 Hz, 3H, mn), 0.95 (d, *J* = 6.9 Hz, 3H, mj), 0.91 (d, *J* = 7.0 Hz, 3H, mj). mj = major isomer; mn = minor isomer. IR (neat) νmax 3448, 2967, 2932, 2877, 1473, 1379.



3-3 **3-32a** 50% **3-32b** 7%

Acetates 3-32a and Acetates 3-32b. To a stirred solution of alcohol **3-3** (22 mg, 0.13 mmol) in toluene (1.5 mL) was added $Pb(OAc)_4$ (81 mg, 0.18 mmol) and the reaction mixture was brought to reflux. After stirring for 1.5 hours the reaction mixture was cooled to room temperature and ethylene glycol was added (3 mL). The reaction mixture was diluted with diethyl ether (30 mL) followed by saturated sodium thiosulfate (10 mL) and then transferred to a separation funnel. The organic layer was washed with sat. sodium thiosulfate (3 x 5 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give acetates **3-32a** (15 mg, 50%) and **3-32b** (2 mg, 7%) as colorless oils.

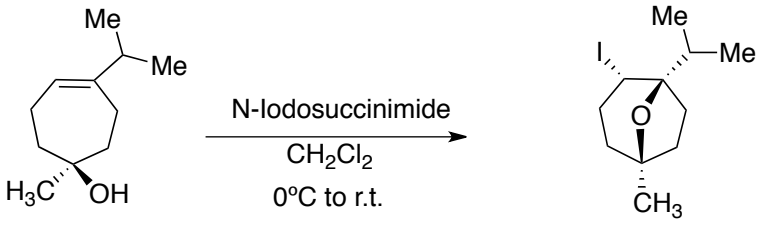
Acetate 3-32a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.10 – 1.95 (m, 5H), 1.86 – 1.41 (m, 7H), 1.27 (s, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 170.2, 85.6, 80.7, 72.2, 36.7, 35.9, 33.4, 29.5, 26.0, 24.9, 21.4, 18.0, 17.1. IR (neat)

νmax 2970, 2938, 2879, 1742, 1456, 1375, 1242. HRMS [ES+] calc for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1467 found 249.1462

Acetate 3-32b:

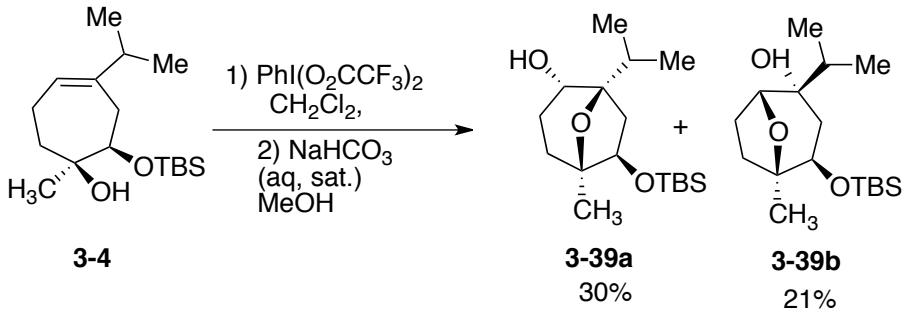
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70 (br d, *J* = 7.3 Hz, 1H), 2.51 (hept, *J* = 7.0 Hz, 1H), 2.40 (ddt, *J* = 14.0, 4.7, 2.1 Hz, 1H), 2.12 – 1.35 (m, 10H), 1.30 (s, 3H), 1.04 (d, *J* = 2.6 Hz, 3H), 1.02 (d, *J* = 2.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 170.1, 85.2, 80.4, 77.8, 36.1, 34.7, 31.2, 26.8, 26.8, 25.7, 22.1, 18.1, 17.6. IR (neat) νmax 2969, 2933, 2872, 2851, 1739, 1251



3-3 **3-33** 84%

Iodide 3-33. A stirred solution of alcohol **3-3** (42 mg, 0.25 mmol) in methylene chloride (3 mL) was cooled to 0ºC. N-Iodosuccinimide was added in one portion (85 mg, 0.38 mmol), and the solution was allowed to slowly warm to room temperature. After stirring for one hour the reaction mixture was quenched with sat. sodium thiosulfate (3 mL). The aqueous layer was extracted with methylene chloride (3 x 7 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (10:1 Hex/EtOAc) to give iodide **3-33** (59 mg, 80%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35 (t, *J* = 8.7 Hz, 1H), 2.42 – 2.33 (m, 2H), 2.22 – 2.12 (m, 1H), 2.08 (hept, *J* = 7.3 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.75 – 1.56 (m, 2H), 1.36 (br d, *J* = 13.1 Hz, 1H), 1.21 (s, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 87.2, 81.2, 40.6, 38.9, 36.6, 34.1, 33.6, 29.2, 26.7, 16.8, 16.3. IR (neat) νmax 2970, 2943, 2875, 2844, 1479, 1366. HRMS [EI+] calc for $C_{11}H_{19}OI$ $[M]^+$ 294.04810 found 294.04695



3-4 **3-39a** 30% **3-39b** 21%

Alcohols 3-39a and 3-39b. To a stirred of alcohol **3-4** (111 mg, 0.37 mmol) in methylene chloride (2 mL) was added phenyliodine bis(trifluoroacetate) (224 mg, 0.52 mmol). The reaction was allowed to stir at room temperature for 16 hours and was quenched with sat. sodium thiosulfate (3 mL). The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was washed with sat. sodium bicarbonate (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was dissolved in 1:1 sat. $NaHCO_3$/ MeOH (30 mL) and was allowed to stir at room temperature. After 23 hours the reaction mixture was concentrated in vacuo. The aqueous solution was extracted with methylene chloride (3 x 33 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (8:1 Hex/EtOAc) to give alcohol **3-39a** (35 mg, 30%) and alcohol **3-39b** (25 mg, 21%) as colorless oils.

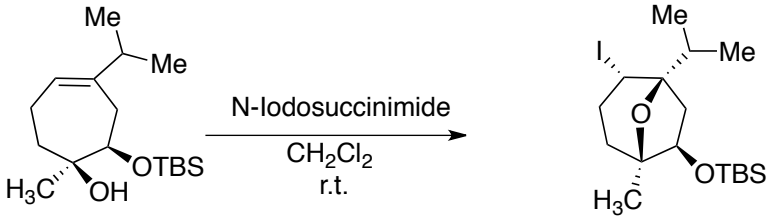
Alcohol 3-39a:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.74 (dd, *J* = 10.5, 5.7 Hz, 1H), 2.32 (dd, *J* = 13.9, 7.3 Hz, 1H), 1.97 – 1.82 (m, 2H), 1.65 – 1.23 (m, 5H), 1.16 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 6H), 0.89 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 85.7, 83.2, 76.8, 69.1, 40.7, 34.7, 32.3, 27.8, 25.8, 21.0, 18.1, 18.0, 17.0, -4.6, -5.0. IR (neat) νmax 3418, 2957, 2931, 2857, 1472, 1297, 1095. HRMS [ES+] calc for $C_{23}H_{29}O_2$ $[M]^+$ 337.2164 found 337.2168

Alcohol 3-39b:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (br d, *J* = 6.0 Hz, 1H), 3.43 (dd, *J* = 4.3, 2.0 Hz, 1H), 2.72 (hept, *J* = 7.0 Hz, 1H), 2.11 – 1.86 (m, 3H), 1.74 – 1.52 (m, 3H), 1.26 (s, 3H), 0.96 – 0.88 (m, 15H), 0.07 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 82.6, 78.9, 72.8, 72.2, 34.9, 34.4, 30.3, 25.9, 24.9, 22.1, 18.0, 17.2, 16.0, -4.4, -5.3. IR (neat) νmax 3460, 2961, 2858, 1471, 1372, 1254, 1096, 1052. HRMS [ES+] calc for $C_{23}H_{29}O_2$ $[M]^+$ 337.2168 found 337.2165

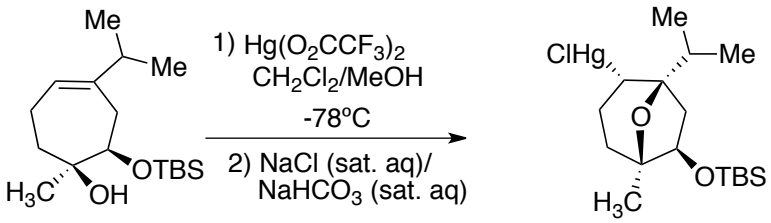


3-4 **3-41**

89%

Iodide 3-41. To a stirred solution of alcohol **3-4** (19 mg, 0.064 mmol) in methylene chloride (2 mL) was added NIS in one portion (20 mg, 0.087 mmol). After stirring for 23 hours the solution was quenched with sat. sodium thiosulfate (1.5 mL). The aqueous layer was extracted with methylene chloride (3 x 7 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (50:1 Hex/EtOAc) to give iodide **3-41** (24 mg, 89%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 11.9, 5.3 Hz, 1H), 4.01 (d, *J* = 7.0 Hz, 1H), 2.53 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.34 (dt, *J* = 15.4, 5.9 Hz, 1H), 2.17 (qd, *J* = 13.2, 5.7 Hz, 1H), 2.07 (hept, *J* = 6.8 Hz, 1H), 1.76 (d, *J* = 14.5 Hz, 1H), 1.68 (td, *J* = 13.4, 6.0 Hz, 1H), 1.34 (dd, *J* = 13.5, 5.3 Hz, 1H), 1.11 (s, 3H), 1.00 – 0.96 (m, 6H), 0.89 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 86.2, 84.4, 77.1, 41.4, 39.0, 37.6, 33.4, 33.4, 25.7, 21.5, 18.1, 16.6, 16.3, -4.6, -5.1. IR (neat) νmax 2930, 2857, 1472, 1257, 1090. HRMS [ES+] calc for C_{17}-$H_{33}O_2SiINa$ $[M+Na]^+$ 447.1192 found 447.1190



3-4 **3-42**

83%

Alkyl Mercurial 3-42. A stirred solution of alcohol **3-4** (12 mg, 0.040 mmol) in methylene chloride (2 mL) and methanol (0.1 mL) was cooled to -78ºC. Mercury (II) trifluoroacetate was added (20 mg, 0.047 mmol) and the solution was allowed to stir for 10 minutes. An additional portion of mercury (II) trifluoroacetate was added (3 mg, 0.01 mmol) and the solution was allowed to stir for 5 minutes. The reaction mixture was quenched with sat. $NaHCO_3$ (2 mL) and NaCl (2 mL). The biphasic solution was stirred vigorously and allowed to warm to room temperature. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (20:1 to 10:1 Hex/EtOAc) to give alkyl mercurial **3-42** (18 mg, 83%) as an amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 7.2, 2.4 Hz, 1H), 2.68 (dd, *J* = 12.2, 5.7 Hz, 1H), 2.23 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.14 – 2.01 (m, 2H), 1.88 (ddd, *J* = 13.5, 2.5, 1.4 Hz, 1H), 1.81 (hept, *J* = 6.8 Hz, 1H), 1.61 – 1.47 (m, 2H), 1.13 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 87.5, 84.4, 57.7, 47.9, 38.0, 37.2, 25.8, 25.8, 21.5, 18.4, 18.1, 17.3, -4.6, -5.0. IR (neat) νmax 2956, 2931, 2857, 1472, 1463, 1385, 1368, 1251, 1102, 1086.

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Chapter 4

Synthesis and Biological Evaluation of "High Risk-High Gain" Analogs

4.1 Introduction

During the course of our group's work on the EA project, we became curious as to what structural features of the EA core scaffold were essential for biological activity. At that time, there was little published SAR data from analogs with core modification. In the report by Chan and Chen[1], two analogs were prepared that contained a one-carbon homologation at C-9. In addition, Christmann et al. prepared analogs in which the C-7 isopropyl group was truncated.[2] Aside from these, the vast majority of analogs studied only contained structural modifications to the C-6 glycolate and C-9 cinnamate ester side chains.[1-3] This is illustrated graphically in Figure 4-1.

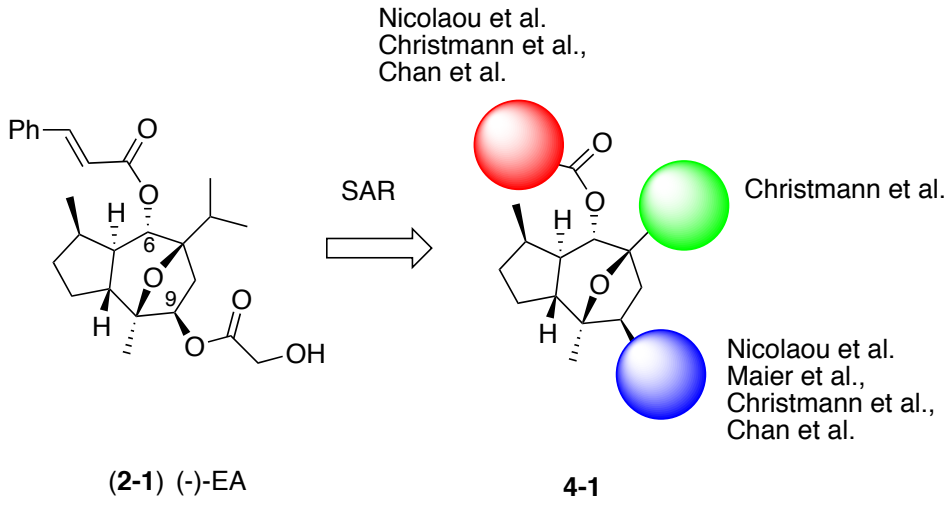


Figure 4-1. Graphical Description of EA Analogs Prepared and Subjected to SAR Studies

With only limited SAR data available, we postulated that analogs containing a mono or bicyclic core might contain the active pharmacophore for binding – so long as the cinnamate and glycolate moieties were present. To test this hypothesis, we embarked on a "high risk, high gain" strategy in which we synthesized EA analogs that, in a stepwise fashion, would incorporate features of the tricyclic core.

4.2 Results and Discussion

4.2.1 Synthesis and Biological Evaluation of Englerin Analog **4-2**

In collaboration with our colleague, Dale Drueckhammer, we designed a series of simple mono- and bicyclic englerin analogs with the HostDesigner[4] program. This program functions by scanning a virtual library of structures that are computer generated with molecular mechanics. The search identifies compounds with key bond vectors that have the same spacing and orientation as those in the parent compound. With regard to EA, we searched for compounds in which two C-O bonds could be superimposed on the C6-O and C9-O bonds. The program gave us six "hits" (Figure 4-2) and we synthesized and tested one of them (**4-2**) (Scheme 4-1).

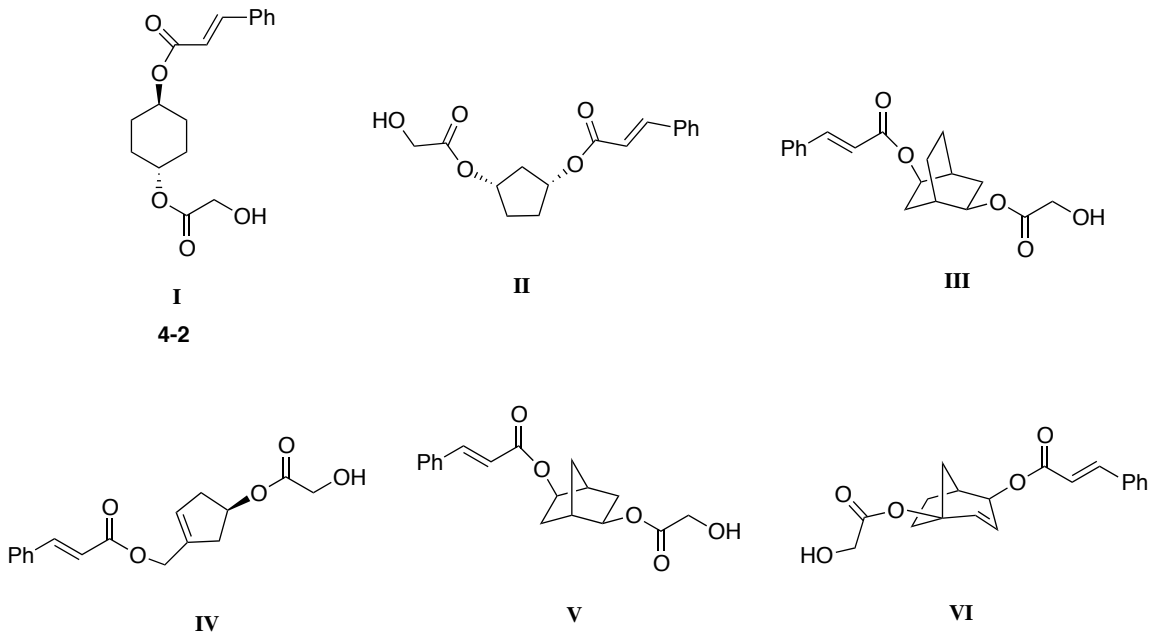
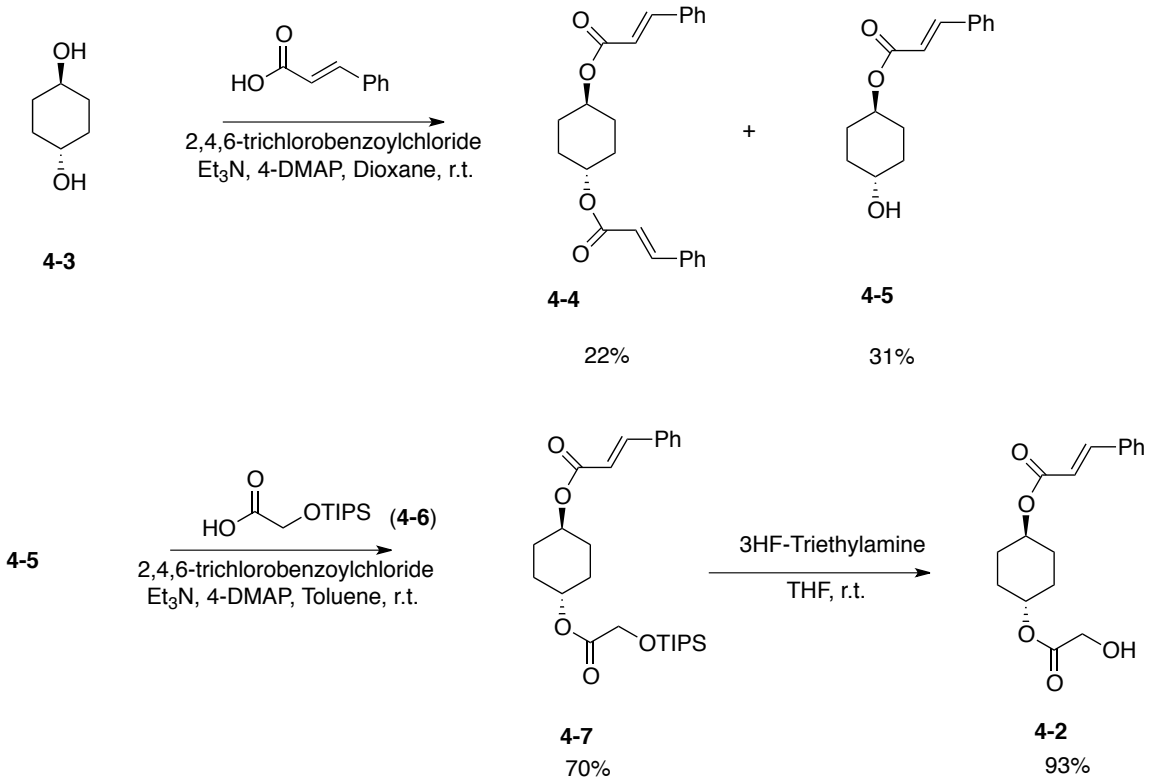


Figure 4-2. Simple Englerin Analog "Hits" Designed with HostDesigner



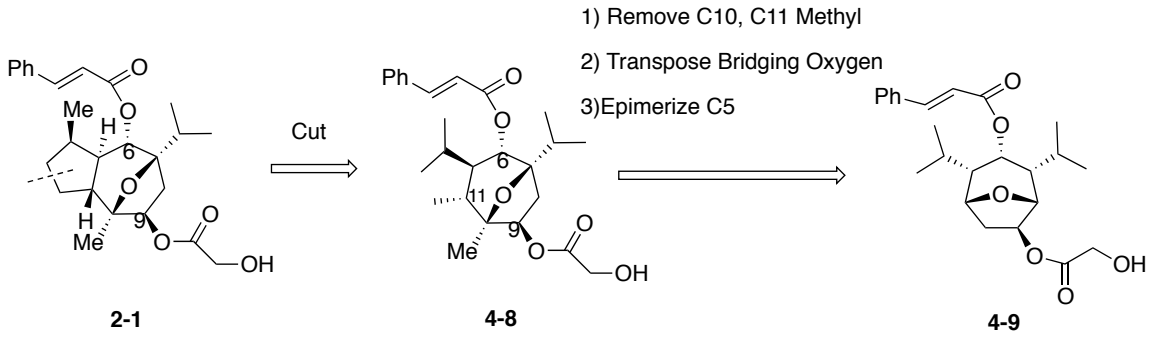
Scheme 4-1. Synthesis of Englerin Analog **4-2**

Englerin analog **4-2** was prepared in three steps starting from commercially available *trans*-1,4-cyclohexane diol (**4-3**). Esterification of diol **4-3** with *trans*-cinnamic acid under Yamaguchi[5] conditions gave a statistical mixture of products from which alcohol **4-5** was isolated. Diester **4-2** was obtained after a Yamaguchi esterification of alcohol **4-5** with ester **4-6** followed by desilylation. In the NCI 60 cell panel compound **4-2** did not display selective cytotoxicity.

The biological data obtained from this analog led us to believe that more features of the core of EA were likely important for activity. Thus the synthesis of simple structures that only contained the ester side chains of EA was probably not sufficient for identifying an active analog. Rather then focus our studies on the remaining analogs **II-VI**, we decided to prepare analogs with a core that, we thought, might more closely "mimic" that of EA.

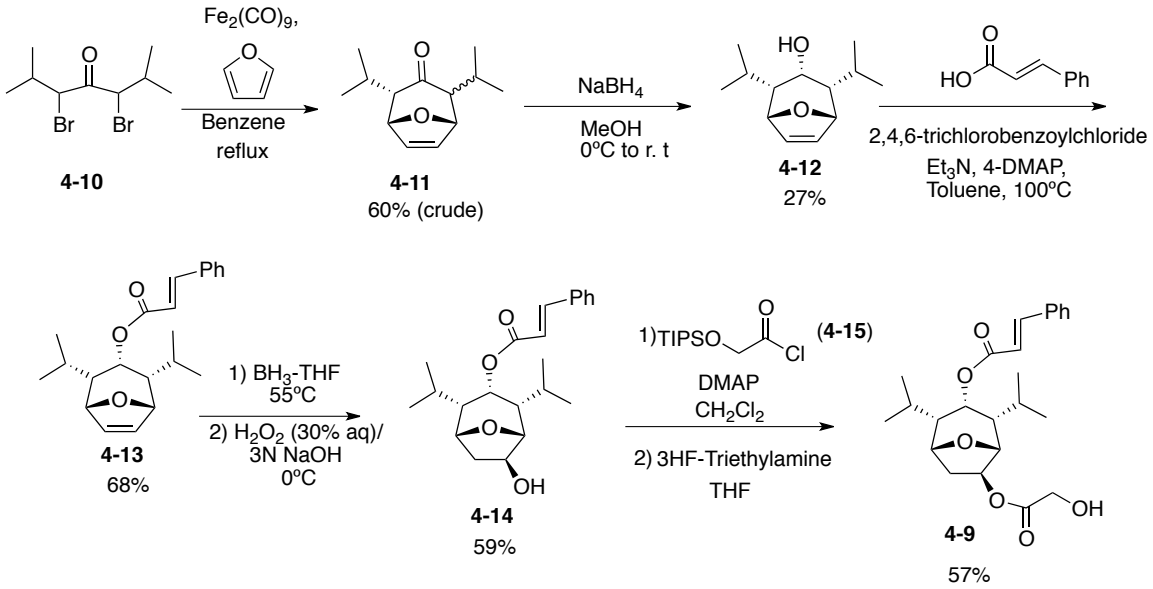
4.2.2 Synthesis and Biological Evaluation of Englerin Analog **4-9**

Although we viewed compound **4-8** as an attractive bicyclic analog, we decided to prepare englerin analog **4-9** instead (Scheme 4-2). We justified this decision based on the postulation that the C-5 and C-7 isopropyl groups in analog **4-9** may induce a conformation of the cinnamate ester that is favorable for binding. We also wondered if the location of the bridging oxygen and the other substituents on the cycloheptane ring were important.



Scheme 4-2. Rational Design of Analog **4-9**

Since there are many structural differences between compounds **4-8** and **4-9**, we were uncertain as to whether or not compound **4-9** would display selective cytotoxicity. However, its synthesis was quite short, and the result obtained from this experiment would be informative. Thus, we proceeded nonetheless (Scheme 4-3).

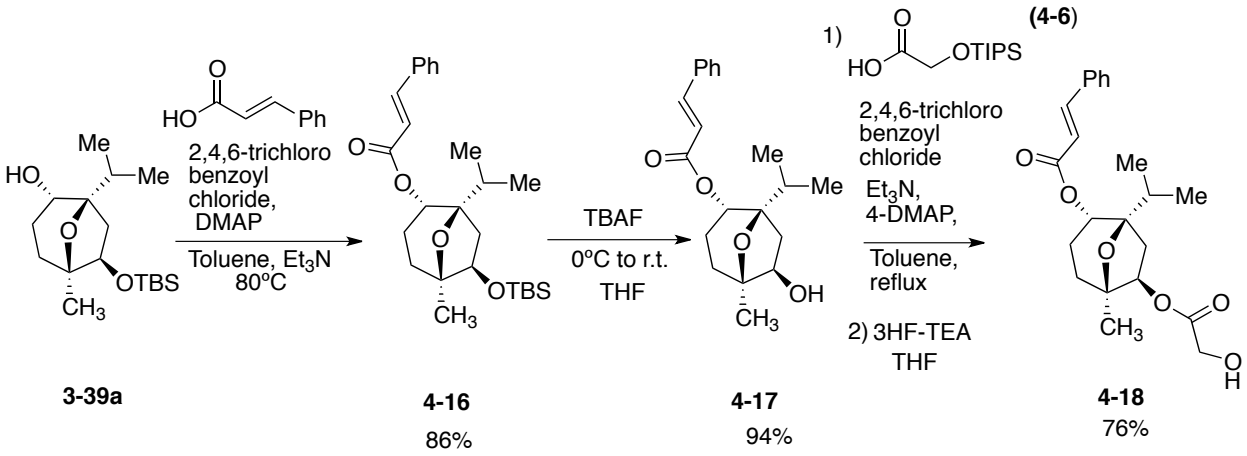


Scheme 4-3. Synthesis of Englerin Analog **4-9**

The synthesis of compound **4-9** began with a $Fe_2(CO)_9$ induced reductive cyclization reaction of ketone **4-10**[6] and furan.[7] The crude reaction product (**4-11**) was reduced with $NaBH_4$ to give compound **4-12** in 27% yield (from **4-11**) after silica gel chromatography. Esterification of alcohol **4-12** with cinnamic acid under Yamaguchi conditions[5] followed by a chemoselective hydroboration gave alcohol **4-14** in 59% yield. Installation of the glycolate ester gave analog **4-9** in 75% yield for two steps. Analog **4-9** did not display bioactivity in the NCI60 cell panel.

4.2.3 Synthesis and Biological Evaluation of Englerin Analog **4-18**

The last bicyclic analog prepared was compound **4-18** (Scheme 4-4). This was obtained by functionalizing alcohol **3-39a**, a product obtained during our etherification studies (Chapter 3).



Scheme 4-4. Synthesis of Englerin Analog **4-18**

The synthesis of compound **4-18** from alcohol **3-39a** was straightforward. Yamaguchi esterification of alcohol **3-39a** with cinnamic acid followed by a TBAF induced TBS deprotection gave alcohol **4-17**. Esterification with TIPS protected glycolic acid (**4-6**) followed by TIPS deprotection with HF-TEA gave the desired englerin analog **4-18** in 76% yield (over 2 steps).

Racemic analog **4-18** was submitted to our collaborator at the NCI for biological testing and did not exhibit any selective cytotoxicity. Subsequent to this test, Theodorakis et al. reported a similar finding after screening the chiral analog **2-151** against the A498 renal cell line.[8]

4.3 Conclusion

The biological evaluation of our "high-risk, high-gain" analogs **4-2**, **4-9**, and **4-18**, provided us with valuable insight into the active pharmacophore of the englerin scaffold. The lack of activity observed for the mono and bicyclic analogs motivated us to begin the synthesis of analogs containing the tricyclic core of EA. At this point in time our group had completed a formal synthesis of EA[9], and we were conveniently set up to utilize our established synthetic approach for this purpose.

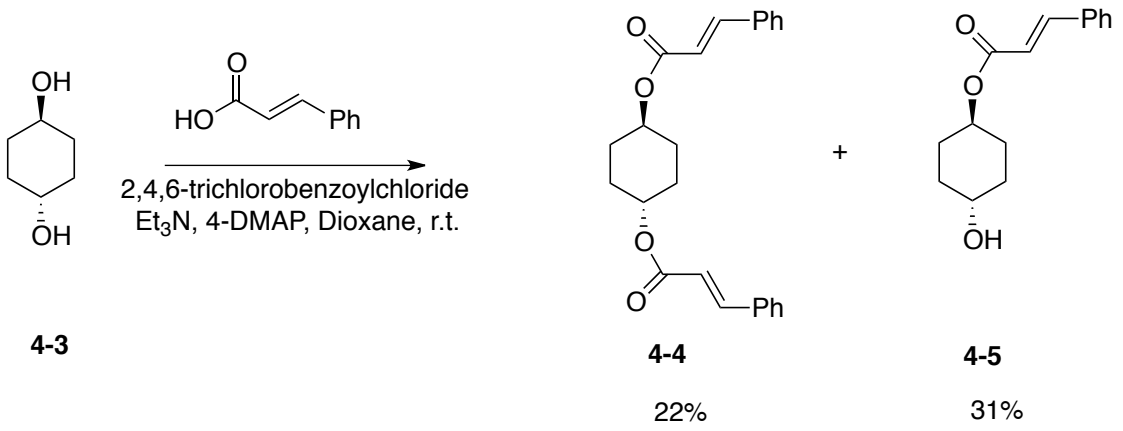
4.4 Experimental Section

General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. TIPS protected glycolic acid (**4-6**)[10] was provided as a gift from Iwao Ojima's research group. HPLC grade hexane and EtOAc, were used in chromatography. Reagent grade dioxane and benzene were stored under calcium hydride and used directly. Diethyl ether (Et_2O) was distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdic acid (PMA) in ethanol and then heating.

Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for 1H and 126 MHz for 13C), Varian Inova-400 (400 MHz for 1H and 100 MHz for 13C), or Gemini-2300 (300 MHz for 1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimental Procedure/Characterization



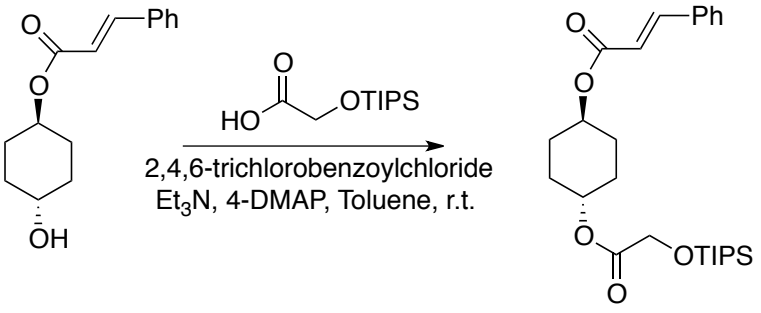
4-3 **4-4** 22% **4-5** 31%

Alcohol 4-5. To a stirred solution of cinnamic acid (141 mg, 0.952 mmol) and triethylamine (0.36 mL, 2.6 mmol) in dioxane (2 mL) was added 2,4,6-trichlorobenzoylchloride (0.175 mL, 1.12 mmol). The solution was allowed to stir at room temperature for 1 hour and then a solution of trans-1,4-cyclohexane diol (113 mg, 0.973 mmol) in dioxane (5 mL) was added followed by 4-DMAP (275 mg, 2.45 mmol). The reaction mixture turned yellow and became cloudy. After stirring for 4 hours sat. $NaHCO_3$ was added (1.5 mL) followed by diethyl ether (30 mL). The organic solution was washed with sat. $NaHCO_3$ (2 x 10 mL) followed by 10% citric acid (3 x 7 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (2:1 Hex/EtOAc to 100% EtOAc) to give diester **4-4** (79 mg, 22%) and alcohol **4-5** (83 mg, 31%) as white solids.

Diester 4-4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 16.0 Hz, 2H), 7.61 – 7.49 (m, 4H), 7.44 – 7.36 (m, 6H), 6.44 (d, J = 16.0 Hz, 2H), 5.05 – 4.93 (m, 2H), 2.20 – 2.02 (m, 5H), 1.82 – 1.61 (m, 5H).

Alcohol 4-5: m.p.: 92-94ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 16.0 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.42 – 7.36 (m, 3H), 6.42 (d, J = 16.0 Hz, 1H), 4.92 – 4.84 (m, 1H), 3.81 – 3.72

(m, 1H), 2.12 – 1.98 (m, 5H), 1.64 – 1.41 (m, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 166.4, 144.6, 134.4, 130.2, 128.9, 128.0, 118.5, 71.8, 69.0, 32.3, 28.7. IR (neat) νmax: 3400, 2942, 2863, 1708, 1637. HRMS [ES+] calc for $C_{15}H_{18}O_3Na$ $[M+Na]^+$ 269.1154, found 269.1154



4-5

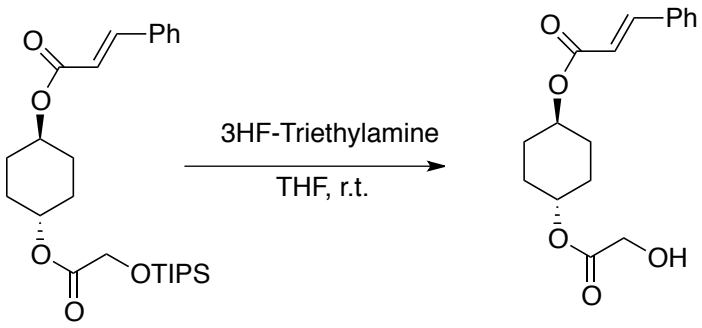
4-7

70%

Diester 4-7. To a stirred solution of TIPS protected glycolic acid (**4-6**) (54 mg, 0.23 mmol) and triethylamine (0.06 mL, 0.4 mmol) in toluene (1.5 mL) was added 2,4,6,-trichlorobenzoylchloride (0.040 mL, 0.25 mmol). The reaction mixture was allowed to stir at room temperature for 30 minutes and the solution became heterogeneous. A solution of alcohol **4-5** (29 mg, 0.10 mmol) was added in toluene (1 mL) followed by DMAP (43 mg, 0.35 mmol). The color of the reaction mixture became yellow upon addition of DMAP. After stirring for 24 hours, the reaction mixture was quenched with sat. $NaHCO_3$ (3 mL). The reaction mixture was diluted with diethyl ether (30 mL) and transferred to a separation funnel. The organic layer was washed with sat. $NaHCO_3$ (3 x 10 mL) followed by 10% citric acid (3 x 10 mL). The organic solution was then dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (30:1 to 20:1 Hex/EtOAc) to give diester **4-7** (34 mg, 70%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 16.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.43 – 7.34 (m, 3H), 6.42 (d, J = 15.9 Hz, 1H), 5.01 – 4.89 (m, 2H), 4.31 (s, 2H), 2.10 – 1.99 (m, 4H), 1.70 – 1.55 (m, 4H), 1.20 – 1.04 (m, 21H). ^{13}C NMR (101 MHz, CDCl3) δ 171.1, 166.4, 144.7, 134.4,

130.3, 128.9, 128.0, 118.4, 71.4, 70.9, 62.3, 28.0, 17.8, 11.9. IR (neat) νmax: 2945, 2866, 1760, 1713, 1638. HRMS [ES+] calc for $C_{26}H_{40}O_5NaSi$ $[M+Na]^+$ 483.2542, found 483.2543

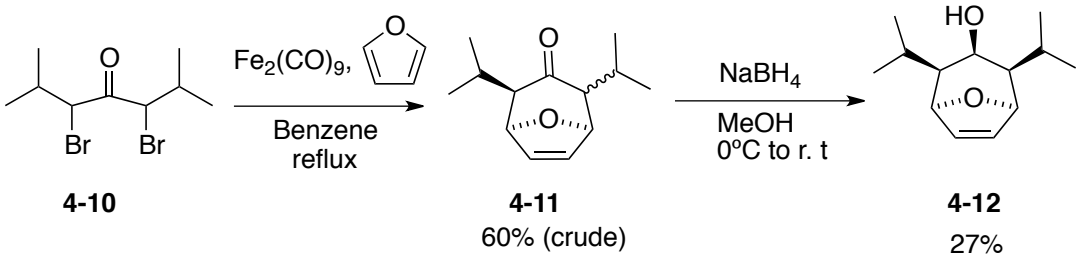


4-7 **4-2**

93%

Analog 4-2. To a solution of diester **4-7** (26 mg, 0.056 mmol) in THF (2 mL) was added triethylamine trihydrofluoride (37 wt%, 0.014 ml). After stirring for 4 days at room temperature, the reaction mixture was diluted with ether (20 mL) and transferred to a separation funnel. The organic layer was washed with sat. $NaHCO_3$ (1 x 5 mL), sat. NH_4Cl (3 x 5 mL), dried over $MgSO_4$, filtered and then concentrated in vacuo. The crude residue was subjected to column chromatography (2:1 Hex/EtOAc) to give compound **4-2** (16 mg, 93%) as a white solid.

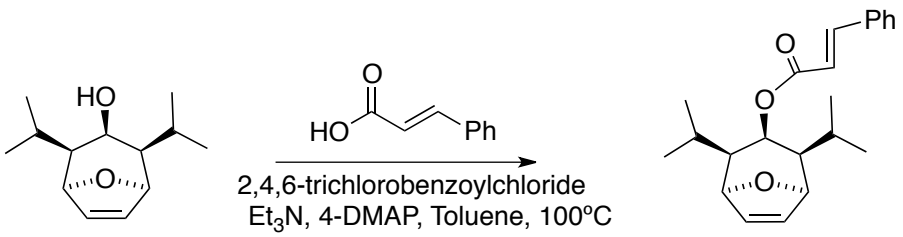
m.p.: 105 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.43 – 7.35 (m, 3H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.03 – 4.90 (m, 2H), 4.15 (d, *J* = 5.4 Hz, 2H), 2.39 (t, *J* = 5.4 Hz, 1H), 2.05 (d, *J* = 9.9 Hz, 4H), 1.71 – 1.60 (m, 4H). ^{13}C NMR (75 MHz, CDCl3) δ 172.9, 166.4, 144.8, 134.3, 130.3, 128.9, 128.1, 118.3, 72.6, 70.6, 60.7, 27.9. IR (neat) νmax 3521, 2956, 2863, 1732, 1698, 1635. HRMS [ES+] calc for $C_{17}H_{20}O_5Na$ $[M+Na]^+$ 327.1208 found 327.1205



Alcohol 4-12. To a stirred solution of ketone **4-10** (5.006 g, 16.67 mmol) in benzene (40 mL) was added diironnonacarbonyl (6.854 g, 18.84 mmol) followed by furan (12.13 mL, 166.8 mmol). After refluxing for 24 hours the solution was diluted with ether and then filtered through a pad of celite. The filtrate was concentrated in vacuo and the crude residue subject to Kugelrohr distillation (bath temp 150ºC, pressure = 0.5 mmHg) to give ketone **4-11** (2.07 g, 60%) which was used in the next step without further purification.

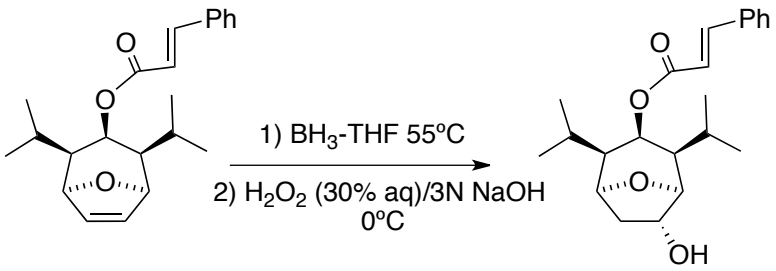
To a stirred solution of ketone **4-11** (1.036 g, 4.974 mmol) in MeOH (10 mL) was added sodium borohydride (2.46 g, 65.0 mmol) in small increments at 0ºC. An additional portion of MeOH was added (10 mL) and the solution was allowed to slowly warm to room temperature. After stirring for 30 minutes the reaction was quenched with sat. NH_4Cl solution (15 mL). The reaction mixture was diluted with ether (30 mL) and transferred to a separation funnel. The aqueous layer was extracted with ether (3 x 30 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (20:1 to 10:1 Hex/EtOAc) to give alcohol **4-12** (279 mg, 27%) as a white solid.

m.p.: 90-92ºC ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (s, 2H), 4.79 (d, *J* = 3.1 Hz, 2H), 4.07 – 3.98 (m, 1H), 1.78 – 1.64 (m, 4H), 1.60 (dt, *J* = 11.0, 3.9 Hz, 1H), 1.02 (d, *J* = 6.6 Hz, 6H), 0.98 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 135.7, 79.9, 68.0, 50.6, 25.8, 21.1, 20.8. IR (neat) νmax 3395, 3078, 2977, 2957, 2900, 2869, 1469. HRMS [ES+] calc for $C_{13}H_{23}O_2$ $[M+H]^+$ 211.1698 found 211.1701



Ester 4-13. To a stirred solution of cinnamic acid (422 mg, 2.85 mmol) and triethylamine (0.8 mL, 6 mmol) in toluene (10 mL) was added 2,4,6,-trichlorobenzoylchloride (0.49 mL, 3.1 mmol). After stirring at room temperature for 1 hour a solution of alcohol **4-12** (145 mg, 0.69 mmol) in toluene (13 mL) was added followed by DMAP (476 mg, 3.90 mmol). After stirring at 100ºC for 4 days the solution was cooled to room temperature and then pyridine (5 mL) and water (10 mL) were added. After 20 hours the reaction mixture was diluted with ether (50 mL) and transferred to a separation funnel. The organic layer was washed with 10% citric acid (50 mL in 4 portions) sat. $NaHCO_3$ (50 mL in 4 portions), dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the crude residue was subjected to column chromatography (100% Hexane to 5:1 Hex/EtOAc) to give ester **4-13** (160 mg, 68%) as a yellow oil containing a minor byproduct. An analytical sample was obtained by additional chromatography.

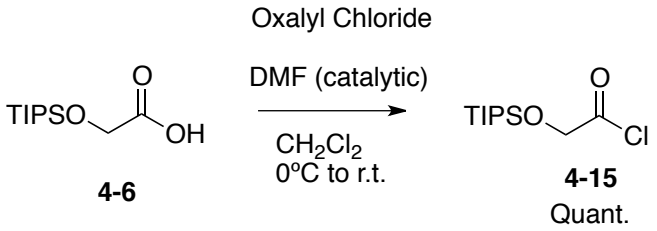
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 16.0 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.46 – 7.35 (m, 3H), 6.37 (d, J = 16.0 Hz, 1H), 6.34 (s, 2H), 5.67 (t, J = 4.4 Hz, 1H), 4.79 (d, J = 3.1 Hz, 2H), 1.87 (ddd, J = 9.6, 4.4, 3.1 Hz, 2H), 1.53 – 1.42 (m, 2H), 0.95 (dd, J = 7.7, 6.6 Hz, 12H). ^{13}C NMR (101 MHz, CDCl3) δ 166.4, 144.8, 134.4, 133.2, 130.3, 129.0, 128.1, 118.5, 79.7, 69.8, 49.7, 25.7, 21.9, 20.7. IR (neat) νmax 2960, 2872, 2360, 2342, 1707, 1636. HRMS [ES+] calc for $C_{22}H_{29}O_3$ $[M+H]^+$ 341.2117 found 341.2115



4-13 **4-14** 59%

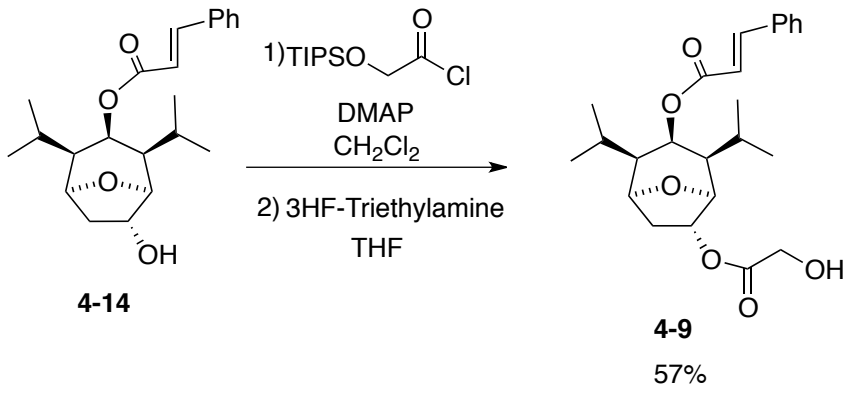
Alcohol 4-14. To a stirred solution of ester **4-13** (15.0 mg, 0.044 mmol) in THF (0.5 mL) was added borane tetrahydrofuran complex (1M, 0.15mL, 0.15 mmol) at 0ºC. The reaction mixture was warmed to room temperature and allowed to stir for 6 hours. An additional portion of borane tetrahydrofuran complex was added (1M, 0.05 mL, 0.05 mmol) and the solution was allowed to stir for 24 hours. The reaction mixture was heated to 55ºC for an additional 4 hours at which point TLC analysis indicated the disappearance of starting material. The reaction mixture was cooled to 0ºC and then 3N NaOH was added (3 μL) along with 30% H_2O_2 solution (3 μL). After 3 hours the reaction mixture was diluted with ether (30 mL), dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography (2:1 to 1:1 Hex/EtOAc) to give alcohol **4-14** (9.1 mg, 59%) as a sticky oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.46 – 7.38 (m, 3H), 6.41 (d, *J* = 16.0 Hz, 1H), 5.61 (t, *J* = 3.6 Hz, 1H), 4.69 (t, *J* = 6.6 Hz, 1H), 4.58 (dd, *J* = 8.1, 3.5 Hz, 1H), 4.25 (d, *J* = 3.5 Hz, 1H), 2.84 (dd, *J* = 13.5, 7.4 Hz, 1H), 1.84 – 1.34 (m, 6H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 165.8, 145.5, 134.1, 130.6, 129.0, 128.2, 117.6, 84.5, 76.5, 73.2, 69.0, 50.1, 49.5, 39.2, 25.5, 25.3, 21.4, 21.3, 20.9, 20.6. IR (neat) νmax 3405, 2962, 2872, 1712, 1635, 1155.



Acid chloride 4-15. To a stirred solution of TIPS protected glycolic acid (**4-6**) (510 mg, 2.19 mmol) in methylene chloride (10 mL), was added DMF (0.04 mL). The solution was cooled to 0ºC and then oxalyl chloride was added in one portion (0.24 mL, 0.36 g, 2.8 mmol). The solution was allowed to slowly warm to room temperature overnight. Concentration of the reaction mixture in vacuo gave acid chloride **4-15** (0.58 g). The crude residue was used without further purification.

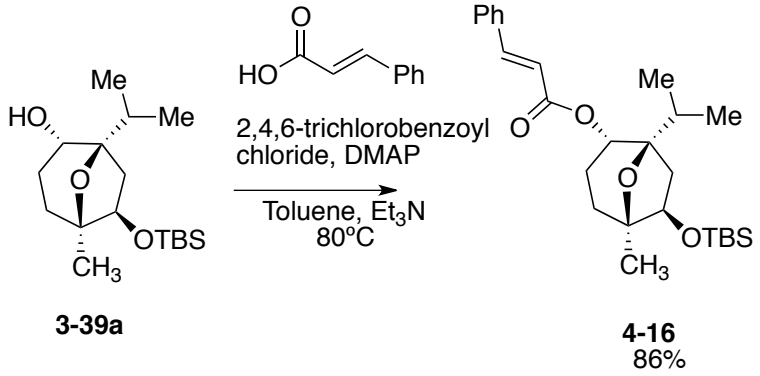
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (s, 2H), 1.37 – 1.00 (m, 21H).



Analog 4-9. To a stirred solution of alcohol **4-14** (6.6 mg, 0.018 mmol) in methylene chloride (1 mL) was added DMAP (13 mg, 0.11 mmol) followed by a solution of TIPS protected glycolic acid chloride (21 mg, 0.089 mmol) in methylene chloride (1mL). After stirring for 2 hours the reaction was quenched with sat. $NaHCO_3$ (3 mL). The reaction mixture was diluted with methylene chloride (30 mL) and transferred to a separation funnel. The organic layer was washed with 10% citric acid solution (3 x 7 mL), sat. $NaHCO_3$ solution (3 x 7 mL), dried over $MgSO_4$, and then filtered. After removal of the solvent in vacuo, the resulting residue was

partially purified by column chromatography (20:1 Hex/EtOAc) to give the crude TIPS protected diester. This intermediate was dissolved in 1 mL THF and then triethylamine trihydrofluoride (37 wt%, 0.02 ml) was added. After standing for 68 hours at room temperature, the reaction mixture was quenched with sat. $NaHCO_3$ solution (1 mL) and diluted with ether (10 mL). Brine was added (5 mL), and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (2:1 Hex/EtOAc) to give englerin analog **4-9** (4.7 mg, 57% over 2 steps) as an oil.

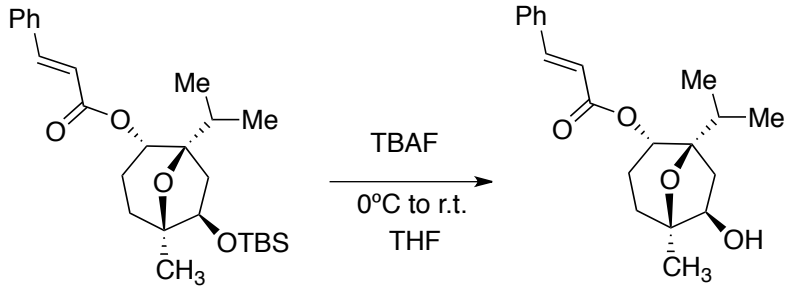
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 16.1 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.45 – 7.38 (m, 3H), 6.44 (d, *J* = 16.1 Hz, 1H), 5.73 (dd, *J* = 7.2, 2.5 Hz, 1H), 5.66 (t, *J* = 3.5 Hz, 1H), 4.59 (dd, *J* = 8.0, 3.3 Hz, 1H), 4.39 (d, *J* = 3.5 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 2H), 2.90 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.37 (t, *J* = 5.5 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.70 – 1.56 (m, 3H), 1.49 – 1.38 (m, 1H), 1.01 – 0.97 (m, 9H), 0.91 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 173.3, 165.6, 145.5, 134.1, 130.6, 129.0, 128.3, 117.5, 80.9, 76.4, 68.8, 60.8, 50.1, 36.1, 25.4, 25.3, 21.4, 21.2, 20.8, 20.5. IR (neat) νmax 3445, 2962, 2918, 2869, 1741, 1711, 1635. HRMS [ES+] calc for $C_{24}H_{32}O_6Na$ $[M+Na]^+$ 439.2097 found 439.2095



Ester 4-16. To a stirred solution of cinnamic acid (23 mg, 0.16 mmol) and triethylamine (0.05 mL, 0.3 mmol) in toluene (1 mL) was added 2,4,6-trichlorobenzoylchloride (26 μL, 0.17 mmol). After stirring for one hour at room temperature, a solution of alcohol **3-39a** (23 mg, 0.073 mmol) in toluene (2 mL) was added followed by DMAP (25 mg, 0.21 mmol) and the reaction mixture was brought to 80ºC. After 1 hour TLC analysis showed complete consumption of starting material. The reaction mixture was allowed to cool to room temperature and then sat. $NaHCO_3$

solution was added (5 mL). The reaction mixture was diluted with ether (10 mL) and transferred to a separation funnel. The aqueous layer was extracted with ether (3 x 7 mL). The combined organic solution was washed with 10% citric acid (3 x 5 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give ester **4-16** (28 mg, 86%) as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.44 – 7.35 (m, 3H), 6.38 (d, *J* = 16.0 Hz, 1H), 4.97 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.03 (dd, *J* = 7.3, 2.4 Hz, 1H), 2.51 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.18 – 2.07 (m, 1H), 1.87 (h, *J* = 6.9 Hz, 1H), 1.79 – 1.61 (m, 2H), 1.56 – 1.32 (m, 2H), 1.19 (s, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 166.0, 144.9, 134.3, 130.3, 128.9, 128.1, 118.2, 84.8, 83.7, 76.7, 71.1, 42.4, 34.3, 33.2, 25.8, 24.4, 21.0, 18.1, 18.0, 17.0, -4.6, -5.0. IR (neat) νmax 2931, 2856, 1713, 1638. HRMS [ES+] calc for $C_{26}H_{40}O_4NaSi$ $[M+Na]^+$ 467.2594 found 467.2585



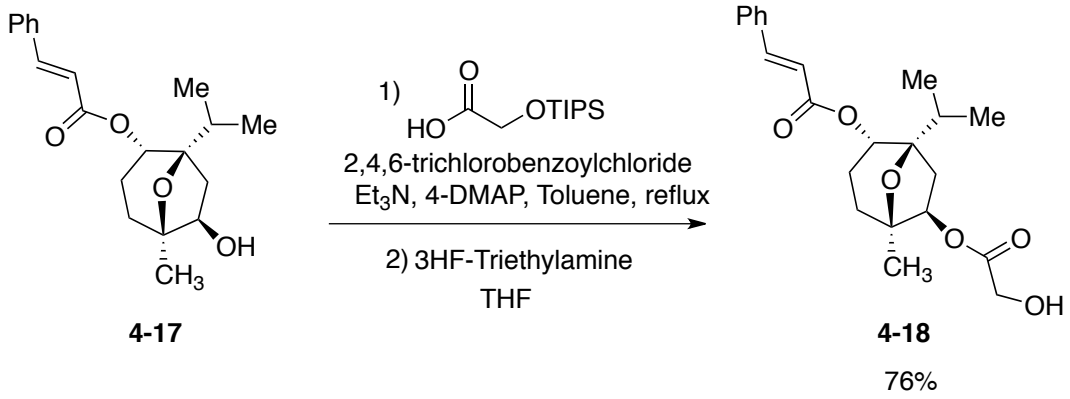
4-16 **4-17** 94%

Alcohol 4-17. To a stirred solution of ester **4-16** (39 mg, 0.087 mmol) in THF (5 mL) was added TBAF (1M in THF, 0.17 mL, 0.17 mmol) at 0ºC. The solution was allowed to slowly warm to room temperature. After 24 hours the reaction mixture was quenched with sat. NH_4Cl solution (1 mL). The reaction mixture was diluted with ether (30 mL) and transferred to a separation funnel. The organic layer was washed with sat. NH_4Cl (3 x 7 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (3:1 to 2:1 Hex/EtOAc) to give alcohol **4-17** (27 mg, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.42 – 7.36 (m, 3H), 6.39 (d, *J* = 16.0 Hz, 1H), 4.99 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.08 (dd, *J* = 7.5, 2.0 Hz, 1H),

2.65 (dd, *J* = 14.6, 7.5 Hz, 1H), 2.13 (dtd, *J* = 13.3, 5.8, 1.7 Hz, 1H), 1.90 (hept, *J* = 7.0 Hz, 1H), 1.78 – 1.65 (m, 2H), 1.57 (ddd, *J* = 13.7, 5.9, 1.8 Hz, 1H), 1.40 (tdd, *J* = 13.3, 10.4, 5.9 Hz, 1H), 1.26 (s, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 165.9, 145.0, 134.3, 130.4, 128.9, 128.1, 118.1, 84.7, 83.3, 76.8, 71.0, 41.7, 34.1, 33.0, 24.3, 20.6, 17.9, 17.0. IR (neat) νmax 3458, 2971, 2936, 1708, 1636, 1173. HRMS [ES+] calc for $C_{20}H_{26}O_4Na$ $[M+Na]^+$ 353.1729 found 353.1725



4-17 **4-18**

76%

Englerin Analog 4-18. To a stirred solution of TIPS protected glycolic acid (**4-6**) (22 mg, 0.095 mmol) and triethylamine (0.02 mL, 0.2 mmol) in toluene (1.5 mL) was added 2,4,6-trichlorobenzoylchloride (14 μL, 0.087 mmol). The reaction mixture was allowed to stir at room temperature. After two hours a solution of alcohol **4-17** (13 mg, 0.039 mmol) in toluene (1 mL) was added via pipette. An additional amount of toluene (1.5 mL) was added to rinse the pipette and the reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was quenched with sat. $NaHCO_3$ (3 mL), diluted with ether (30 mL), and transferred to a separation funnel. The organic layer was washed with 10% citric acid (3 x 5 mL), sat. $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, partial purification by column chromatography (30:1 Hex/EtOAc) gave the crude TIPS protected ester. This intermediate was dissolved in THF (1 mL) and then triethylamine trihydrofluoride (37 wt%, 0.01 ml) was added. After standing for 48 hours at room temperature, the reaction mixture was diluted with ether (20 mL) and washed with sat. $NaHCO_3$ (1 x 5 mL) followed by sat. NH_4Cl solution (3 x 5 mL). The organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (2:1 Hex/EtOAc) to give englerin analog **4-18** (10 mg, 65% over 2 steps) as an oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 16.0 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.42 – 7.37 (m, 3H), 6.38 (d, *J* = 16.0 Hz, 1H), 5.26 (dd, *J* = 7.9, 2.6 Hz, 1H), 5.03 (dd, *J* = 10.5, 5.8 Hz, 1H), 4.20 (d, *J* = 5.4 Hz, 2H), 2.70 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.35 (t, *J* = 5.5 Hz, 1H), 2.23 – 2.16 (m, 1H), 1.89 (h, *J* = 6.9 Hz, 1H), 1.82 (br d, *J* = 14.8 Hz, 1H), 1.75 – 1.64 (m, 2H), 1.52 – 1.42 (m, 1H), 1.21 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 172.9, 165.8, 145.2, 134.3, 130.4, 128.9, 128.1, 118.0, 85.2, 82.4, 79.7, 70.4, 60.6, 38.8, 34.2, 33.2, 24.4, 20.3, 17.9, 17.0. IR (neat) νmax 3467, 2968, 2932, 2878, 1746, 1710, 16361171, 1122, 1095. HRMS [ES+] calc for $C_{22}H_{28}O_6Na$ $[M+Na]^+$ 411.1784 found 411.1788 The data were consistent with literature values.[8]

References:

1. Chan, K. P.; Chen, D. Y.-K., Chemical Synthesis and Biological Evaluation of the Englerin Analogues. *ChemMedChem* **2011,** *6*, 420-423.

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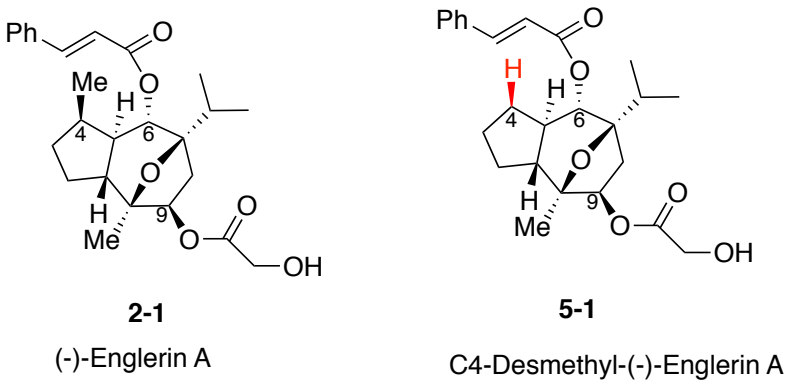
Chapter 5

A Formal Synthesis of (-)-Englerin A, and the Total Synthesis and Biological Evaluation of C4-Desmethyl Englerin A and C4-Ethyl Englerin A

5.1 Introduction

After the biological evaluation of our mono- and bicyclic analogs revealed the necessity of substituents around 7-membered ring of EA (Chapter 4), we decided to approach our SAR study in a more traditional manner. To this end we began the preparation of tricyclic analogs with fewer drastic structural alterations.

Initially, our curiosity brought us to question the importance that the C-4 methyl substituent had on the observed cytotoxicity of englerin. By exploiting chemistry developed in our laboratories,[1] and with the goal of answering this question, we embarked on an analog total synthesis. Our goal was to synthesize and screen compound **5-1**, in which the C-4 methyl group of EA has been replaced with a hydrogen (Figure 5-1).



2-1

(-)-Englerin A

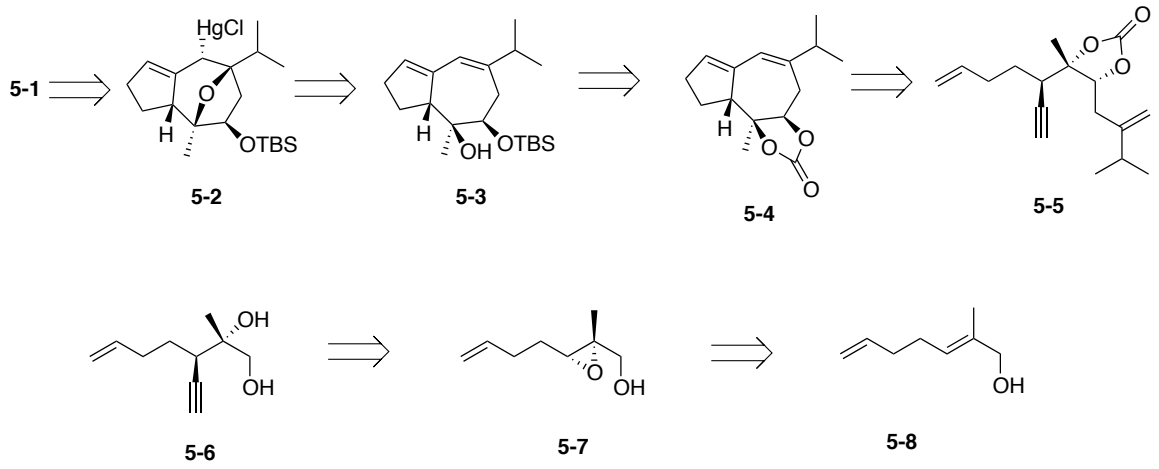
5-1

C4-Desmethyl-(-)-Englerin A

Figure 5-1. Structural Comparison of (-)-Englerin A (**2-1**) and C4-Desmethyl (-)-Englerin A (**5-1**)

5.1.1 Retrosynthetic Analysis of C4-Desmethyl-(-)-EA (**5-1**)

To accomplish this task, an appropriate synthesis was designed (Scheme 5-1).



Scheme 5-1. Retrosynthetic Analysis of C4-Desmethyl (-)-EA (**5-1**)

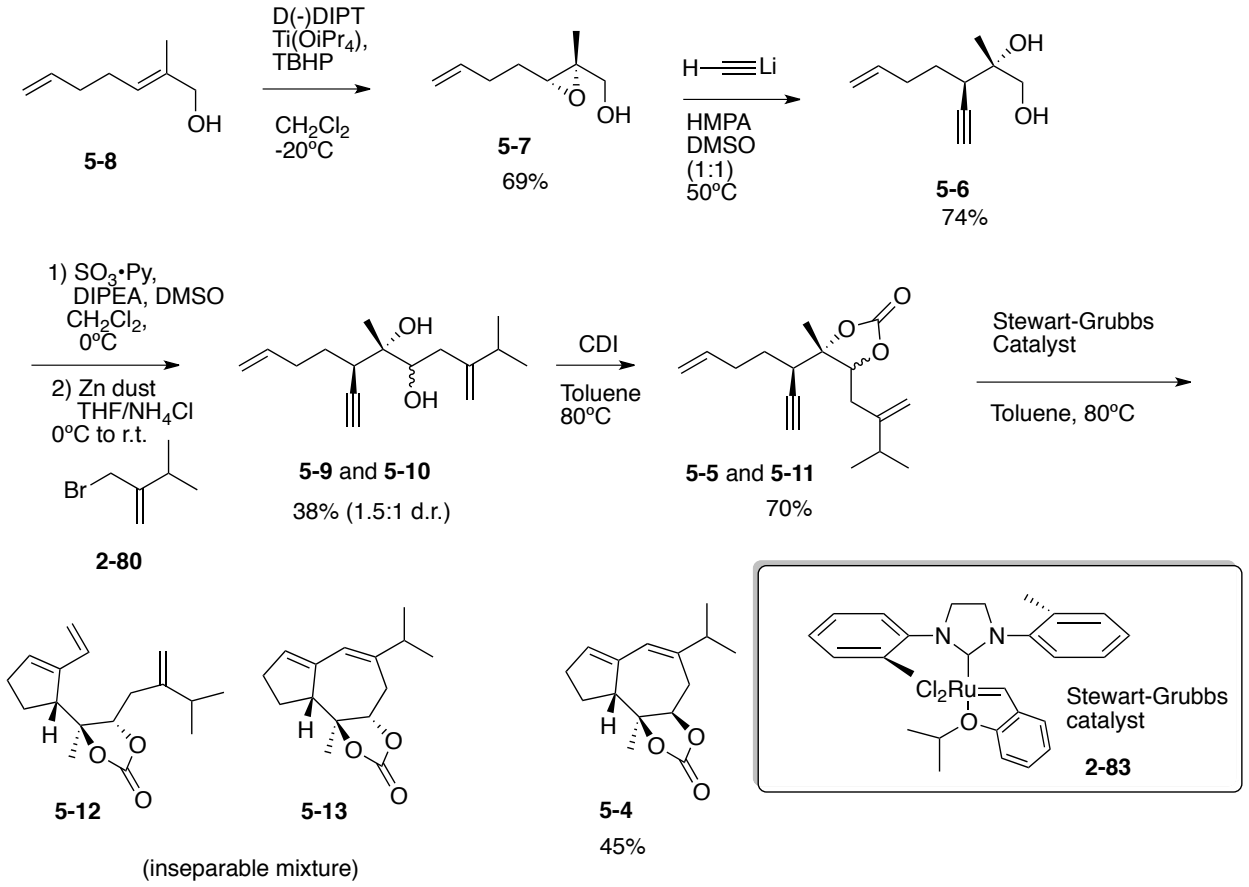
Alkyl mercurial **5-2**, by analogy to the synthesis of compound **2-91** by Lee and Parker (Chapter 2, page 51), could be obtained from alcohol **5-3**. By utilizing our recently developed ene-yne-ene metathesis chemistry we anticipated that hydroazulene **5-4** could be readily obtained from carbonate **5-5**. This compound would not require a relay "tether," as initiation of metathesis would occur at the desired and less substituted monosubstituted olefin.[2] The alkynylation of the known epoxy alcohol **5-7** would provide the requisite diol **5-6**.

5.2. Results and Discussion

5.2.1 Total Synthesis of C4-Desmethyl-(-)-EA (**5-1**)

5.2.1.1 Synthesis of Hydroazulene **5-15**

The synthesis of analog **5-1** began with the known alcohol **5-8** (Scheme 5-2). This was prepared according to the method of Taber.[3] Sharpless asymmetric epoxidation[4] followed by alkynylation with the lithium acetylide ethylene diamine complex gave diol **5-6**. Parikh-Doering oxidation[5] and subsequent alkylation of the crude aldehyde gave an inseparable mixture of diasteremeric diols **5-9** and **5-10**. The diols were protected as their corresponding carbonates and treated with the Stewart-Grubbs catalyst[6] (**2-83**) in hot toluene. After 36 hours, TLC analysis indicated that the starting material had disappeared and that two new, more polar products were present. After silica gel chromatography, ^{1}H NMR analysis revealed that the more polar of the two products was the desired diastereomer **5-4**, which was isolated in 45% yield. The other product appeared to represent an inseparable mixture of the partially cyclized product **5-12** and the undesired diastereomer **5-13**.



Scheme 5-2. Synthesis of Hydroazulene **5-4**

Although the completion of the synthesis of hydroazuluene **5-4** proceeded as anticipated, at this point, we felt compelled to make some improvements.

First we were not satisfied with the selectivity of the Barbier reaction. As was the case in our group's first formal englerin synthesis[1], this reaction proceeded with only modest diastereoselectivity (ca. 1.5:1 d.r. in favor of the desired alcohol **5-9**). In addition, when the metathesis reaction was conducted with the (inseparable) mixture of carbonates **5-5** and **5-11**, a large catalyst loading (0.3 equivalents) and long reaction times were necessary (36 hours). We speculated that the reason for this was do to consecutive unsuccessful ring closure events of triene **5-12** to hydroazulene **5-13**. We believe that the formation of hydroazulene **5-13** is less favorable (compared to **5-4**) because the preferred conformation of the corresponding ruthenium carbene **5-14** is inhibitory to ring closure (Figure 5-2).

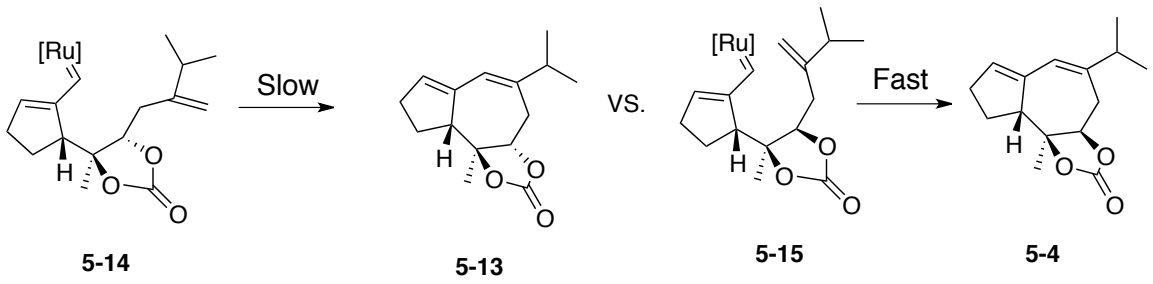
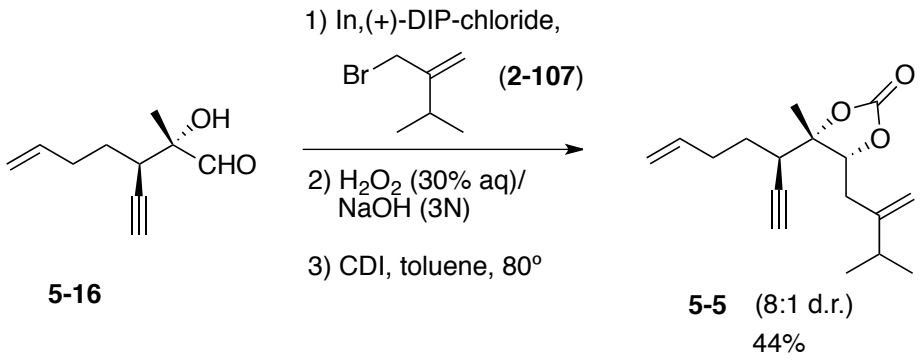


Figure 5-2. Comparison of Ring Closure Rates: Ruthenium Carbene **5-14** vs. Ruthenium Carbene **5-15**

5.2.1.2 Optimization of the Barbier Reaction

In an effort to improve the ratio of isomers obtained during allylation, we considered a number of literature methods for asymmetric allylation induced by chiral reagents.[7] As it turned out, the first protocol we screened was very successful. This procedure, developed by Singaram and coworkers, utilized an indium mediated Barbier reaction to prepare Brown's allyl diisopinocampheylborane reagent.[8]

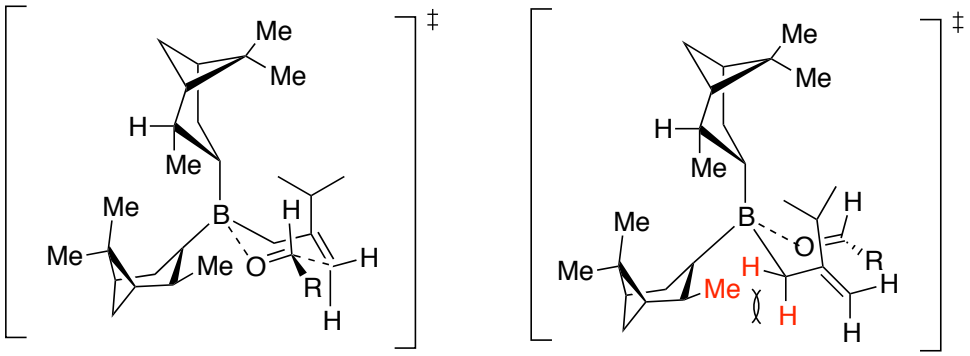


Scheme 5-3. Optimization of the Barbier Reaction through an Indium Mediated Brown Allylboration

The asymmetric allyation of aldehyde **5-16** effected by our modified version of this protocol, gave an 8:1 mixture of diastereomers in favor of carbonate **5-5** (Scheme 5-3). In the

context of the EA synthesis this methodology was attractive for two reasons. First, the allyl indium reagent prepared from 2-bromomethyl-3-methyl-1-butene (**2-80**) and In metal is a known compound and was utilized in a previous englerin synthesis.[9] Second the active allylating reagent could be prepared in a single step from commercially available (+)-B-chlorodiisopinocampheylborane, and allyl halide **2-80**, a compound which we had prepared in large quantities. Although the reaction workup produced a large amount of terpenol byproduct, the majority of this could be easily removed by Kugelrohr distillation. After a partial purification by column chromatography, the crude diol was protected as the corresponding carbonate **5-5**, which was isolated in 44% yield after silica gel chromatography.

Although the literature contains examples of boron-mediated allylation and crotylations of aldehydes in the presence of remote hydroxyl groups[10], to our knowledge, this is the first and only example in which this type of transformation is performed directly on an alpha-hydroxy aldehyde.



5-17a
Favored

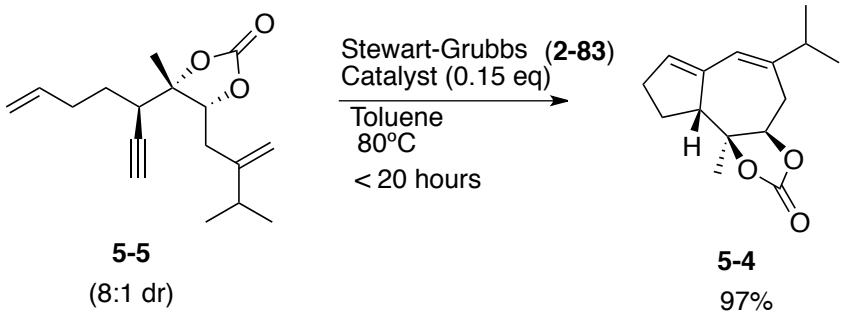
5-17b
Disfavored

Figure 5-3. Proposed Transition State for Asymmetric Allylation (Brown's Model)

The favorable diastereoselectivity observed is presumed to be the result of a Zimmerman-Traxler[11] chair-like transition state shown in Figure 5-3.[12] What differentiates the two is that in the higher energy transition state **(5-17b)** an unfavorable steric interaction exists between the chiral ligand and the allylic methylene group. In both transition states (**5-17a** and **5-17b)**, the R

group of the aldehyde occupies an equatorial position thereby minimizing the repulsive 1,3 diaxial interactions with the isopropyl group of the allyl moiety.

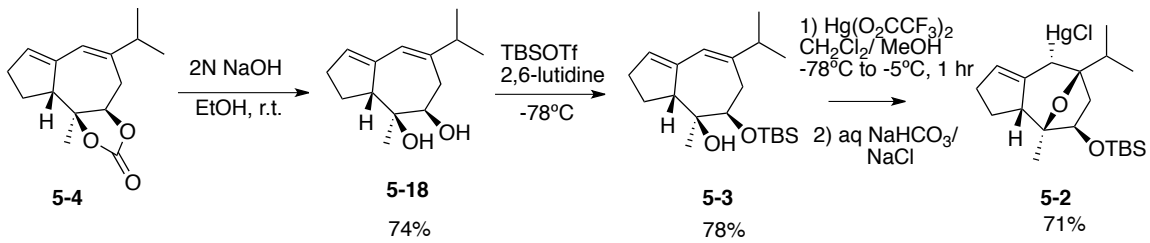
With the allylation/protection sequence optimized, we found that ene-yne-ene metathesis proceeded smoothly with 0.15 equivalents of catalyst in less than 20 hours (Scheme 5-4).



Scheme 5-4. Improved Conditions for Ene-Yne-Ene Metathesis of Carbonate **5-5**

5.2.1.3 Synthesis of Alkyl Mercurial Intermediate **5-2**

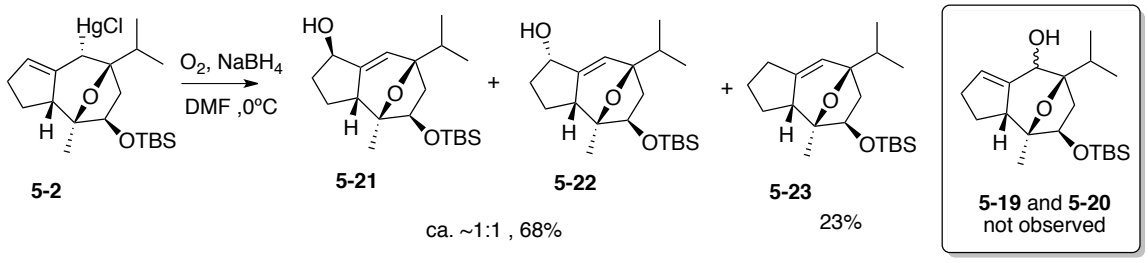
From this point on, synthesis of compound **5-2**, proceeded smoothly. Hydrolysis of carbonate **5-4** in basic ethanol followed by TBS protection under kinetically controlled conditions gave alcohol **5-3.** According to the oxymercuration protocol of Lee and Parker, compound **5-3** was smoothly converted to the corresponding ring closed product **5-2** in 71% yield (Scheme 5-5).



Scheme 5-5. Synthesis of Alkyl Mercurial **5-2**

5.2.1.4 Oxidative Demercuration of Alkyl Mercurial Intermediate **5-2**

With compound **5-2** in hand, we proceeded with oxidative demercuration (Scheme 5-6). Although we had hoped to obtain a diastereomeric mixture of alcohols **5-19** and **5-20,** instead alcohols **5-21** and **5-22** were isolated. In both of these alcohols the allylic substitution pattern reversed. In addition, the reduced product **5-23** was also isolated in 23% yield. A small sample of the alcohols was separated by column chromatography, and a crystal structure of compound **5-21** was obtained (Figure 5-4).



Scheme 5-6. Oxidative Demercuration of Alkyl Mercurial **5-2**

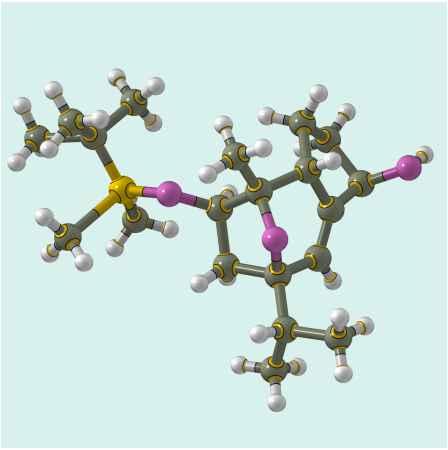
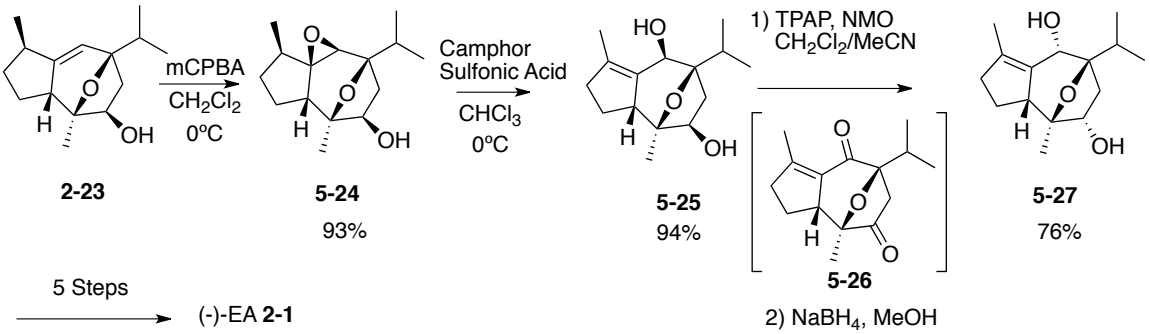


Figure 5-4. X-ray Structure of Alcohol **5-21**

5.2.1.5 Completion of the Synthesis of C4-Desmethyl (-)-Englerin A (**5-1**)

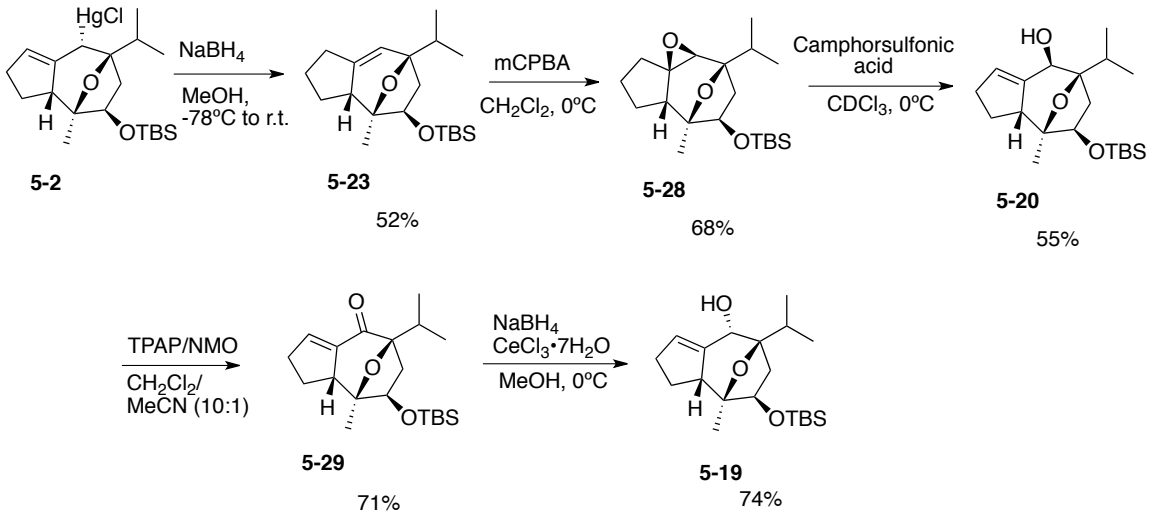
At this point, we decided to exploit the resemblance between compound **5-23** and alcohol **2-23**, a synthetic intermediate from Ma's EA total synthesis.[13] By employing an epoxidation-isomerization sequence, Ma and coworkers completed their EA total synthesis from compound **2-23** in nine steps (Scheme 5-7).



Scheme 5-7. Completion of the Total Synthesis of (-)-EA (**2-1**) by Ma et al.

By analogy, it appeared as though the completion of the desired analog **5-1**, might be rapidly achieved by partial adoption of this protocol.

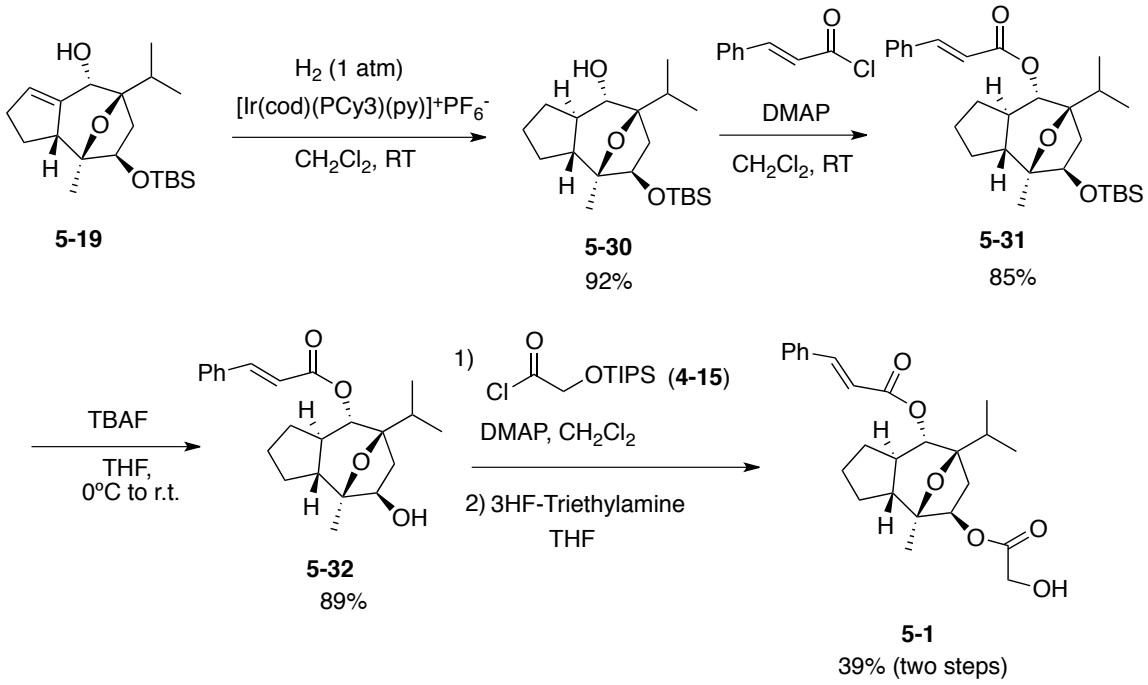
Thus alkyl mercurial **5-2** was reduced to compound **5-23**, by employing Maier's conditions.[14] The correction of the oxidation pattern and stereochemistry following Ma's protocol proceeded smoothly as well (Scheme 5-8).



Scheme 5-8. Synthesis of Alcohol **5-19**

Epoxidation of compound **5-23** gave compound **5-28**, a product in which oxidation occurred exclusively from the convex face. With camphorsulfonic acid as a catalyst, the rearrangement of epoxide **5-28** to allylic alcohol **5-20** proceeded as expected. An oxidation (**5-20→ 5-29**) followed by a stereoselective Luche[15] reduction gave alcohol **5-19**.

With the appropriately functionalized alcohol **5-19** in hand, completion of the synthesis from this point was straightforward (Scheme 5-9). Stereoselective hydrogenation in the presence of Crabtree's catalyst[16] afforded the C4-monodesmethyl englerin core **5-30**, exclusively. Esterification with cinnamoyl chloride (**5-30→5-31**), followed by a TBS deprotection gave alcohol **5-32**. This product was subjected to esterification with TIPS protected glycolic acid chloride (**4-15**) followed by HF-pyridine induced desilylation to give englerin intermediate **5-1**.



Scheme 5-9. Completion of the Synthesis of C4-Desmethyl (-)-Englerin A (**5-1**)

5.2.2 Biological Evaluation of C4-Desmethyl-EA (**5-1**)

After completion of the synthesis of analog **5-1**, we submitted a sample to our colleague John Beutler at the NCI for testing. The resulting bar graphs (Figure 5-5) and dose inhibition curves are shown below.

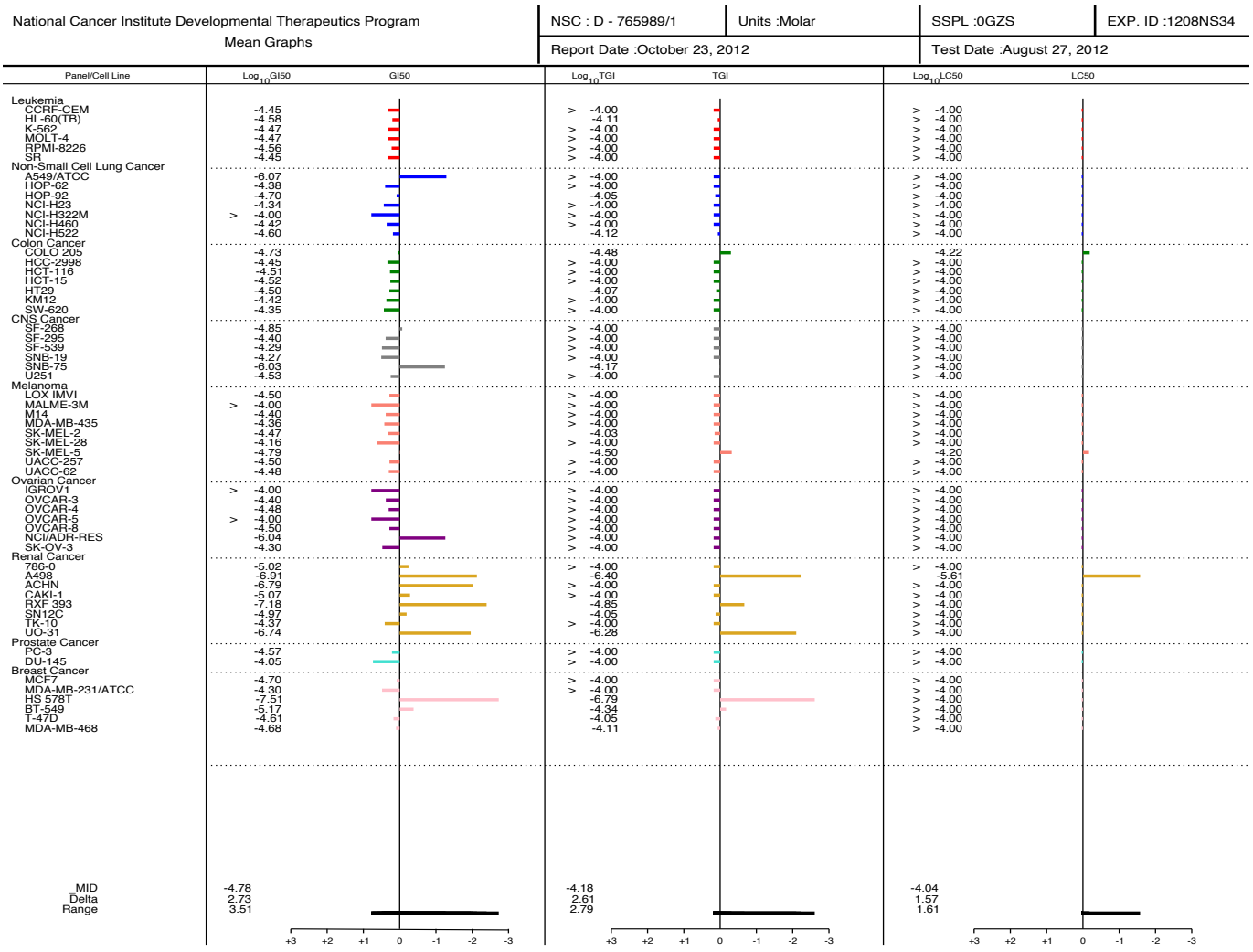


Figure 5-5. Biological Evaluation of C4-Desmethyl (-)-EA (**5-1**) in the NCI 60 panel

As shown in the bar graphs above, the selective cytotoxicity displayed by compound **5-1** on the renal cancer cell lines is quite good. In four of the six renal cell lines screened, namely A498, ACHN, RXF 393, and UO-31 the measured GI_{50} values are all around 10^{-7}. The compound also appears to display cytotoxicity in a few cell lines that are not associated with RCC (non small cell lung cancer A549/ATCC, CNS cancer SNB-75, ovarian NCI/ADR-RES, and breast cancer line MDA-MB-231/ATCC). The dose-response curves are shown below (Figure 5-6).

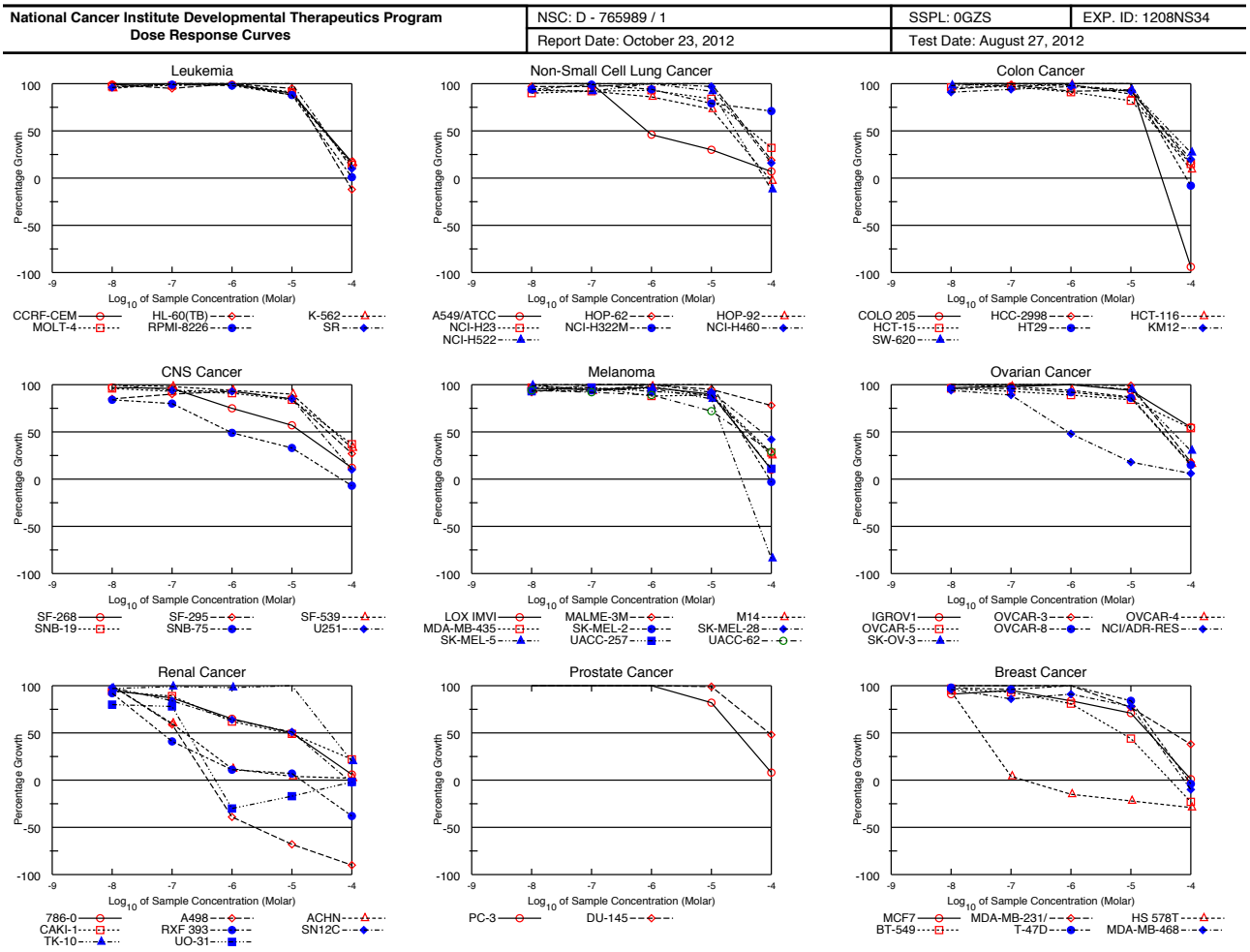


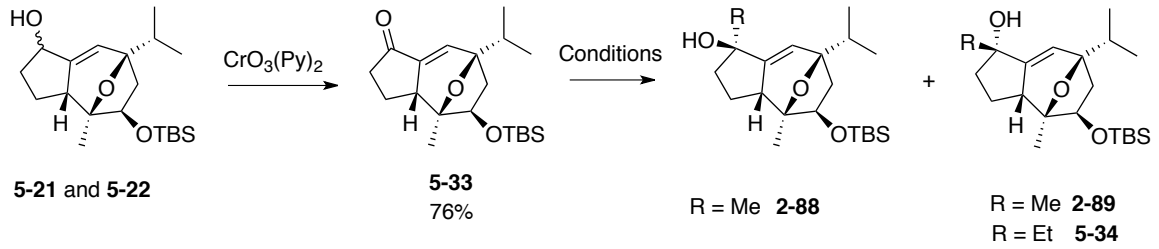
Figure 5-6. Dose Response Curves of C4-Desmethyl (-)-EA (**5-1**) in the NCI 60 panel

5.2.3 Formal Synthesis of (-)-Englerin A (**2-1**)

After synthesizing compounds **5-21** and **5-22**, we wondered if we could make use of the "reversed" allylic substitution pattern. If this mixture of epimeric alcohols could be oxidized to

the corresponding alpha beta unsaturated ketone, in principle the carbonyl could acts as a handle for introducing alkyl substituents at C-4 (vide infra).

In pursuit of this idea, we treated the mixture of epimeric alcohols **5-21** and **5-22** with the Collins reagent. The oxidation proceeded both cleanly and rapidly to afford the highly crystalline alpha beta unsaturated ketone **5-33** (Scheme 5-10). With this compound in hand, we screened alkylation conditions (Scheme 5-10 and Table 5-1).



Scheme 5-10. Synthesis of Ketone **5-33** and Screening of 1,2-Addition Reactions

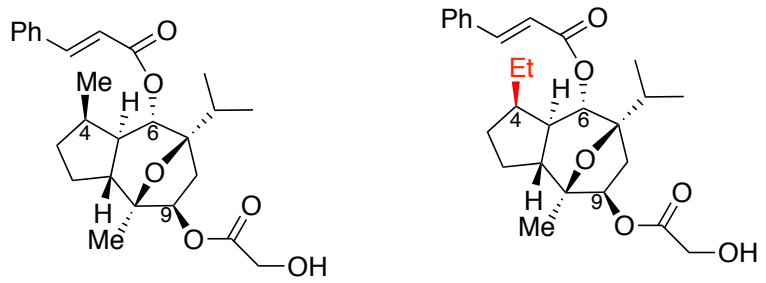
Entry	Conditions	R	Result	
1	MeLi, THF, -78ºC to r.t.	Me	**2-88** 28%	**2-89** 40%
2	MeMgBr, 0ºC to r.t.	Me	**2-88** 18%	**2-89** 69%
3	EtMgBr, 0ºC to r.t.	Et	**5-34** 87%	

Table 5-1. Results of 1,2-Addition Reactions to Ketone **5-33**

Treatment of ketone **5-33** with methyllithium gave approximately a 1:1.5 mixture of alcohols **2-88** along with epimer **2-89**. The latter is a known intermediate from the EA total synthesis by Echavarren and coworkers.[17] When we performed alkylation with MeMgBr, the formation of the desired alcohol **2-89** increased (the ratio was roughly 4:1). Treatment of ketone **5-33** with the bulkier Grignard reagent EtMgBr gave alcohol **5-34**, exclusively.

5.2.4 Total Synthesis of C4-Ethyl (-)-EA (**5-35**)

With the biological results of our C4-desmethyl analog (**5-1**) now recently acquired, we wondered what would happen if we performed the opposite structural modification to EA. That is, we wondered how a one-carbon homologation of the C-4 methyl group might affect cytotoxicity? With alcohol **5-34** in hand we were set up to synthesize the C4-ethyl analog of englerin A (**5-35**) with which we could answer this question (Figure 5-7).



2-1

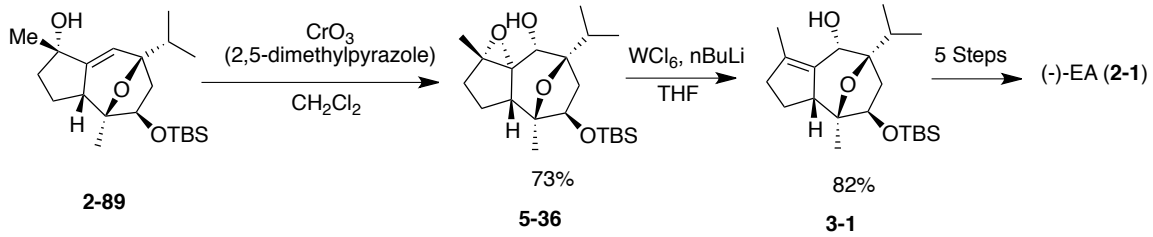
(-)-Englerin A

5-35

C4-Ethyl-(-)-Englerin A

Figure 5-7. Structural Comparison of (-)-Englerin A (**2-1**) and C4-Desmethyl (-)-Englerin A (**5-35**)

Since the analogous methyl alcohol **2-89**, is a synthetic intermediate from the EA total synthesis by Echavarren and coworkers[17] (Scheme 5-11), it followed that we might apply similar methodology to complete the synthesis of analog **5-35**.



2-89

73%

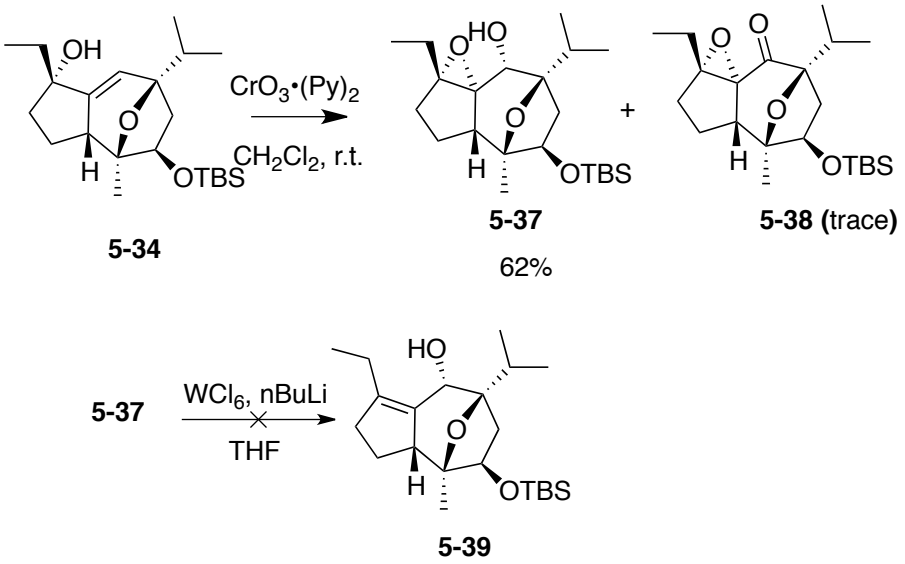
5-36

82%

3-1

Scheme 5-11. Completion of the Synthesis of (-)-EA (**2-1**) by Echavarren et al.

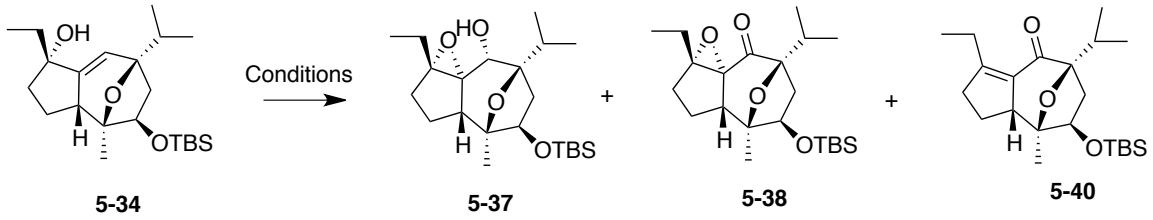
Thus we oxidized alcohol **5-34** with the Collins reagent to give epoxy alcohol **5-37** along with a trace amount of epoxy ketone **5-38**. Contrary to what we expected, exposure of this compound to Sharpless deoxygenation conditions[18] (WCl_6, nBuLi) did not give any of the desired allylic alcohol **5-39**. In our hands this reaction gave a complex mixture (Scheme 5-12).



Scheme 5-12. Attempted Deoxygenation of Alcohol **5-37**

5.2.4.1 Screening of Oxidative Transposition Conditions of Tertiary Allylic Alcohol **5-34**

In search of a solution to this problem, we screened alternative conditions that we hoped would effect the oxidative transposition of allylic alcohol **5-34** to alpha-beta unsaturated ketone **5-40** (Scheme 5-13, Table 5-2). This compound could then be easily converted to the desired allylic alcohol **5-39** through a simple Luche[15] reduction.



5-34 **5-37** **5-38** **5-40**

Scheme 5-13. Screening of Oxidative Transposition Conditions of Allylic Alcohol **5-34**

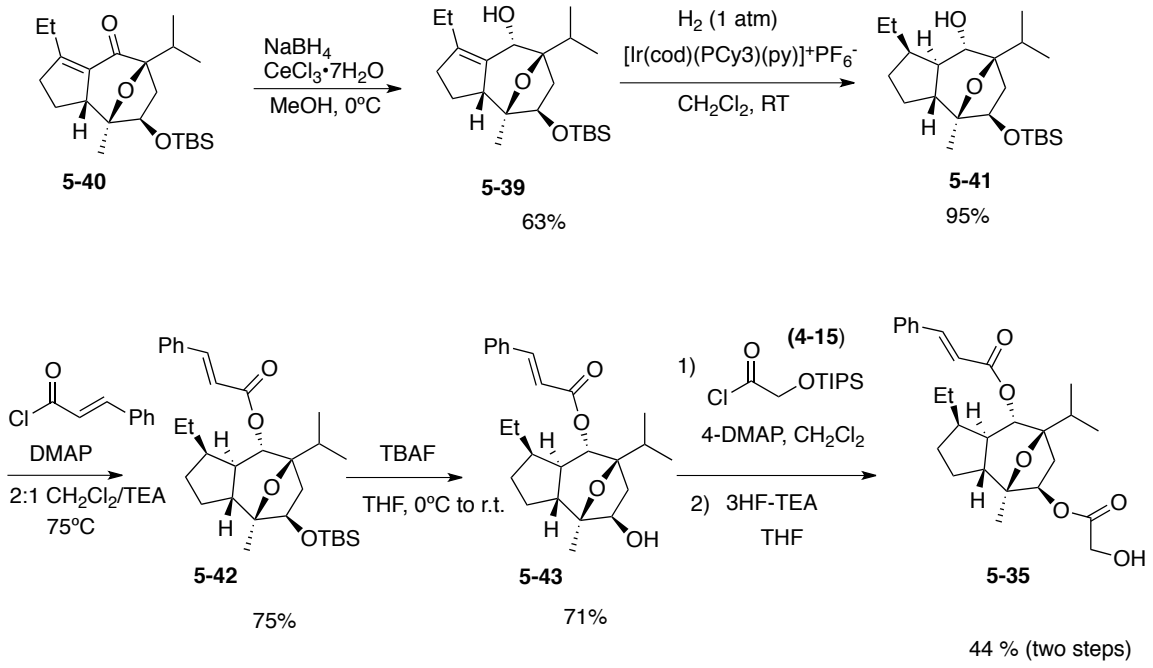
Entry	Conditions	Result
1	PCC, pyridine, silica gel, r.t.	50% **5-37** Trace (**5-38** and 5-**40**)
2	PDC, CH_2Cl_2, reflux	23% **5-40** 47% **5-37** + some dehydration
3	SO_3•Py, -78ºC to r.t.	dehydration
4	Dess-Martin Reagent, 0ºC to r.t.	dehydration
5	$TEMPO^+BF_4^-$, 1:1 MeCN/H_2O, 60ºC	**5-34** recovered + some decomposition

Table 5-2. Results from Attempted Oxidative Transposition of Alcohol **5-34**

Standard chromium-(VI)-based oxidative transposition conditions[19] gave epoxy alcohol **5-32** as the major product. Oxidation with PDC gave a small amount of the desired alpha beta unsaturated ketone **5-40**. Alternative oxidizing conditions such as Dess-Martin periodinane, SO_3•Py[20], and $TEMPO^+BF_4^-$[21] were uniformly unsuccessful- either starting material was recovered or substrate dehydration was observed.

5.2.4.2 Completion of the Synthesis of C4-Ethyl-(-)-EA (**5-35**)

Rather than continue to screen reaction conditions, we decided to move byproduct **5-40** forward. Although at this stage in the synthesis we were working with very small quantities of material, the chemistry was robust enough such that the synthesis of analog **5-35** was feasible (Scheme 5-14).



Scheme 5-14. Synthesis of C4-Ethyl (-)-Englerin A (**5-35**)

Thus Luche[15] reduction of ketone **5-40** gave allylic alcohol **5-39** which was reduced stereoselectively with the Crabtree catalyst.[16a] This gave the highly crystalline C4-ethyl englerin core (**5-41**). We were able to solve the crystal structure of this compound and confirm the relative stereochemistry at the 5,7 ring junction (Figure 5-8).

The synthesis of analog **5-35** was completed in 4 additional steps. Esterification of alcohol **5-41** with cinnamic acid followed by a TBAF-induced TBS deprotection gave alcohol **5-**

43. Esterification with TIPS-protected glycolic acid chloride (**4-15**) followed by TIPS deprotection gave englerin analog **5-35**.

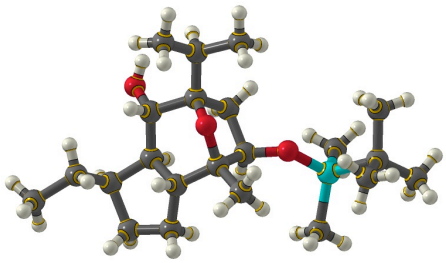


Figure 5-8. X-ray Structure of Alcohol **5-41**

5.2.5 Biological Evaluation of C4-Ethyl (-)-EA (**5-35**)

We submitted a sample of C4-ethyl-EA (**5-35**) to our colleague John Beutler at the NCI for testing. The resulting dose inhibition curves (Figure 5-9) and bar graphs (Figure 5-10) are shown below.

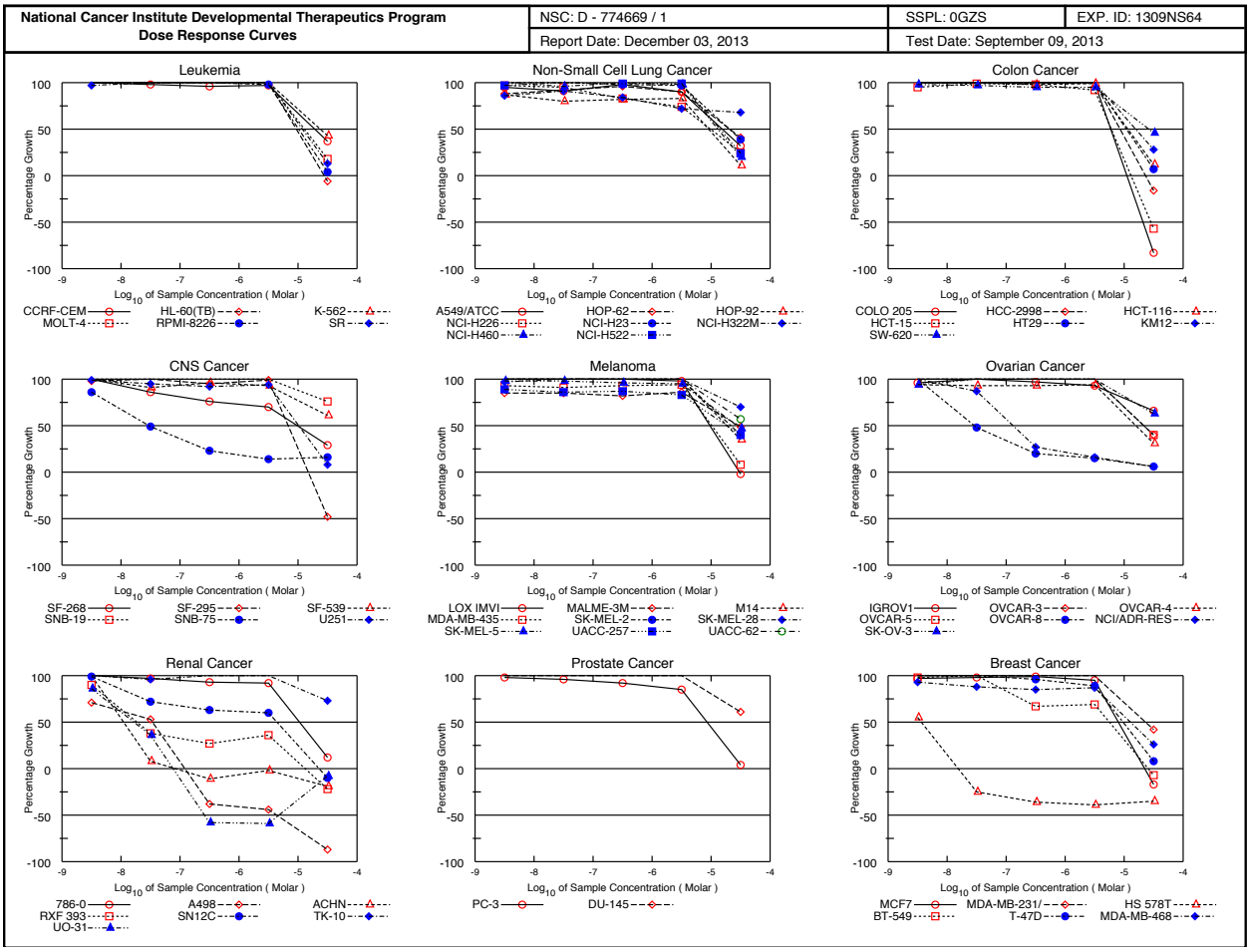


Figure 5-9. Dose Response Curves of C4-Ethyl (-)-EA (**5-35**) in the NCI 60 panel

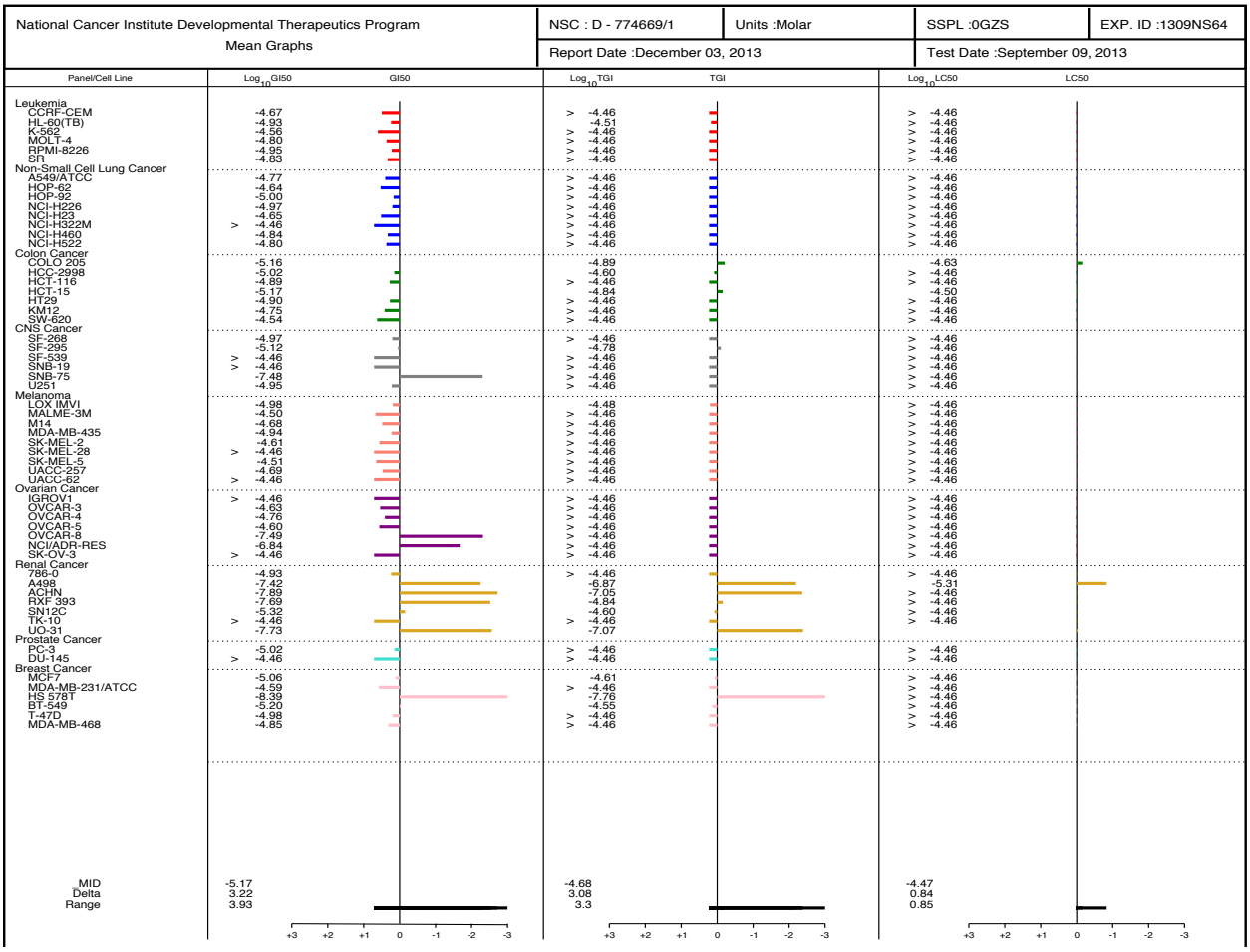
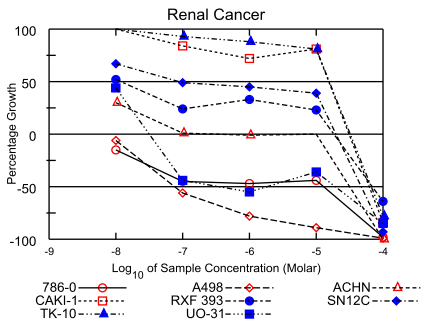


Figure 5-10. Biological Evaluation of C4-Ethyl (-)-EA (**5-35**) in NCI 60 panel

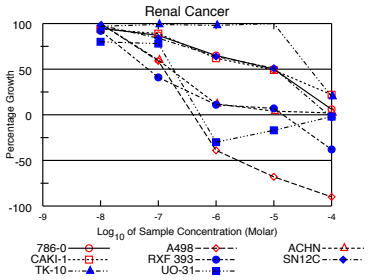
Like the desmethyl analog **5-1**, the ethyl analog **5-35** displays selective cytotoxicity in four of the six renal cancer cell lines. Cytotoxicity in cell lines not associated with RCC was also displayed (CNS cancer SNB-75, Ovarian Cancer OVCAR-8 and NCI/ADR-RES, Breast Cancer HS 578T).

5.2.6 Comparison of the Cytotoxicity of EA analogs **5-1** and **5-35** with Englerin A (**2-1**)



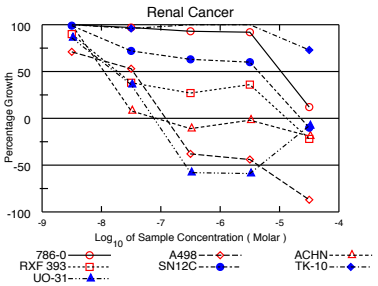
(-)-englerin A

2-1



C4-desmethyl (-)-englerin A

5-1



C4-ethyl (-)-englerin A

5-35

Figure 5-11. Dose-response curves for cytotoxic activity of englerin A (**2-1**), C4-desmethyl englerin A (**5-1**), and C4-ethylenglerin A (**5-35**) against the renal cancer cell lines in the NCI-60 panel.

When compared to EA (**2-1**) the dose response curves obtained from englerin analogs **5-1** and **5-30** allow one to draw an interesting conclusion (Figure 5-11). While truncation of the C-4 methyl group from EA's core causes roughly a 10-fold decrease in cytotoxicity, a one-carbon homologation has essentially no deleterious effect. We hypothesize that this may arise from two possible scenarios:

In one scenario the C-4 methyl group may influence the conformation of the C-6 cinnamate ester side chain in such a way that is favorable for target binding. Alternatively, the methyl group itself may be involved in binding to the protein target. If this scenario is the case, the data suggests that homologation of the methyl group by one carbon does not disrupt this interaction.

To more confidently answer these questions, the synthesis of C-4 extended chain analogs must be accomplished and the compounds must be subjected to cytotoxicity studies. This task is currently underway in our laboratories.

5.3 Conclusion

The completion of our second generation englerin formal synthesis has provided access to a late stage synthetic intermediate (**5-2**) that permits the synthesis of englerins with modifications to the core. By way of this intermediate two new englerin analogs, namely C4-desmethyl-(-)-englerin A (**5-1**), and C4-ethyl-(-)-englerin A (**5-35**) were synthesized. The SAR data obtained from these compounds by screening in the NCI 60 cell panel provided new insight into the active englerin pharmacaphore, specifically around C-4.

5.4 Experimental Section

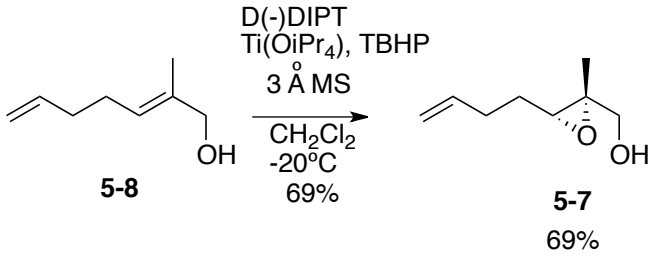
General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane and EtOAc, were used in chromatography. Diethyl ether (Et_2O) was distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol.

Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were

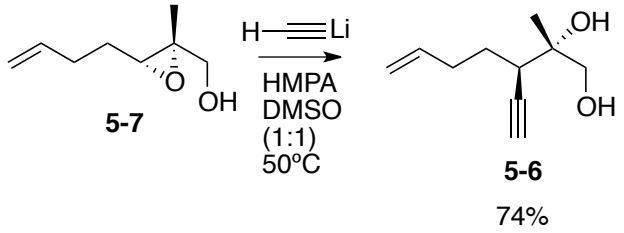
scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for 1H and 126 MHz for 13C), Varian Inova-400 (400 MHz for 1H and 101 MHz for 13C), or Gemini-2300 (300 MHz for 1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

Experimental Procedure/Characterization



Epoxy Alcohol 5-7. To a stirred solution of allylic alcohol **5-8** (12.009 g, 95.16 mmol), and 3Å molecular sieves (4 g) in methylene chloride (420 mL) was added (−)-diisopropyl D-tartrate (3.771 g, 16.10 mmol). After stirring for 10 minutes the solution was cooled to -20ºC and then a solution of titanium (IV) isopropoxide (3.025 g, 10.64 mmol) in methylene chloride (20 mL) was added. An additional portion of methylene chloride was added (20 mL) and the temperature of the solution was kept between -20ºC and -30ºC. After stirring for 1 hour, tertbutylhydroperoxide solution was added (5.5 M in decane, 39.0 mL, 215 mmol) slowly, and the solution was allowed to stir overnight at -20ºC. The reaction mixture was quenched by adding water (32 mL) and the solution was allowed to slowly warm to 0ºC. A solution of NaOH/NaCl was added (8.3M NaOH, 0.95 M NaCl, 5 mL) and the reaction mixture was allowed to warm to room temperature. The heterogeneous mixture was filtered through a pad of celite, and the filter cake was washed

with ether. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was subjected to column chromatography (5:1 Hex/EtOAc) to give epoxy alcohol **5-7** (9.335 g, 69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.07 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.04 – 4.98 (m, 1H), 3.68 (dd, *J* = 12.2, 4.4 Hz, 1H), 3.57 (dd, *J* = 12.2, 8.6 Hz, 1H), 3.06 (t, *J* = 6.3 Hz, 1H), 2.37 – 2.11 (m, 2H), 1.79 – 1.58 (m, 2H), 1.29 (s, 3H). The data was in agreement with the literature.[4] The enantiomeric excess was determined to be 90% based on ^{1}H NMR analysis of the known (+)-MTPA ester.[22]

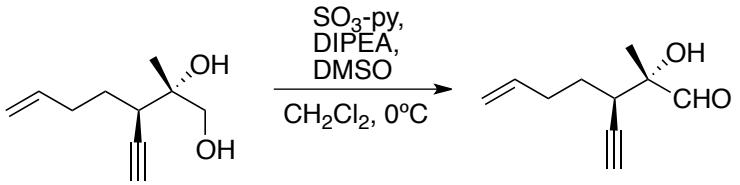


5-7 **5-6** 74%

Diol 5-6. To a stirred solution of lithium acetylide ethylene diamine complex (32.85 g, 356.8 mmol) in a 1:1 (v/v) solution of HMPA/DMSO (220 mL) was added a solution of epoxy alcohol **5-7** (10.607 g, 74.59 mmol) in HMPA/DMSO (10 mL). An additional portion of HMPA/DMSO was added (10 mL) and the temperature of the solution was brought to 50ºC. After stirring for 5 hours an additional portion of lithium acetylide ethylene diamine complex was added (5.478 g, 59.50 mmol). The reaction mixture was stirred for 40 minutes, after which, TLC analysis indicated complete consumption of starting material. The reaction mixture was allowed to cool to room temperature and was then poured slowly into an ice cold solution of sat. NH_4Cl (100 mL). An additional portion of sat. NH_4Cl was added (150 mL), and the solution was partitioned between EtOAc (500 mL) and sat. LiCl solution (400 mL). The biphasic mixture was transferred to a separation funnel and allowed to stand overnight. Once the layers cleanly separated, the aqueous layer was extracted with EtOAc (5 x 400 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was a mixture of product and HMPA/DMSO. To remove the solvent, the crude reaction mixture was subjected to multiple chromatographies (2:1 Hex/EtOAc). Once enough of the solvent was removed, an additional chromatography (2:1 Hex/EtOAc) gave diol **5-6** (9.340 g, 74%) as a brown solid. This

was used in the next step without further purification. An analytical sample was obtained by recrystallization from 1:1 hexane/ether.

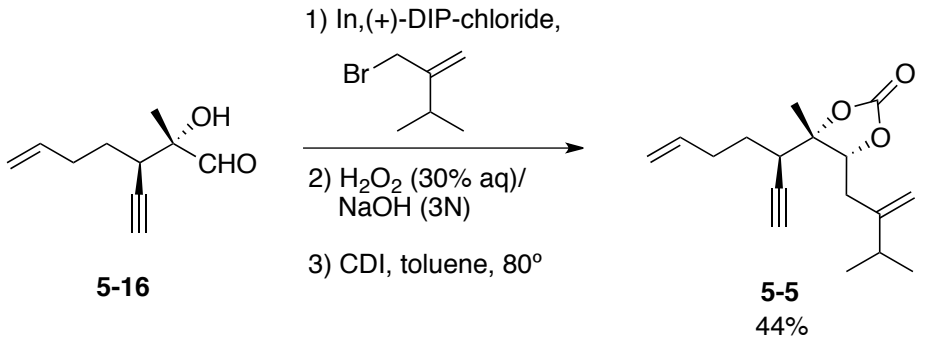
mp: 50-53ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.2, 10.3, 6.9 Hz, 1H), 5.08 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.02 – 4.98 (m, 1H), 3.82 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.51 (dd, *J* = 10.9, 6.8 Hz, 1H), 2.58 (dt, *J* = 11.9, 3.0 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.18 – 2.08 (m, 3H), 1.90 – 1.75 (m, 2H), 1.58 – 1.48 (m, 1H), 1.22 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 137.9, 115.2, 84.3, 74.1, 71.8, 68.6, 38.8, 32.0, 27.7, 19.9. IR (neat) νmax: 3392, 3304, 3074, 2977, 2935, 2869, 2118, 1040.63. HRMS [ES+] calc for $C_{10}H_{16}O_2Na$ $[M+Na]^+$ 191.1048, found 191.1053



5-6 **5-16**
52%

Aldehyde 5-16. The oxidation of diol **5-6** was performed according to the method of Parikh and Doering.[5] A stirred solution of diol **5-6** (6.389 g, 37.98 mmol), N,N-diisopropylethylamine (26 mL, 0.15 mol), and dimethylsulfoxide (21.0 mL, 296 mmol) in methylene chloride (300 mL) was cooled to 0ºC. Sulfur trioxide pyridine complex was added (15.174 g, 95.34 mmol) and the solution was allowed to stir 0ºC for 1.5 hours. The reaction mixture was transferred to a separation funnel and washed with 10% citric acid (3 x 50 mL) followed by sat. $NaHCO_3$ (1 x 100 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 Hex/EtOAc) followed by Kugelrohr distillation (bath temp = 135ºC, pressure = 1.4 mmHg) to give aldehyde **5-16** (3.260 g, 52%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.0 Hz, 1H), 5.77 (dddd, *J* = 17.3, 10.2, 7.4, 5.9 Hz, 1H), 5.07 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.02 – 4.99 (m, 1H), 3.21 (s, 1H), 2.57 (ddd, *J* = 11.4, 3.8, 2.5 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.26 (d, *J* = 2.5 Hz, 1H), 2.18 – 2.08 (m, 1H), 1.71 – 1.53 (m, 2H), 1.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.4, 137.2, 115.7, 81.8, 78.2, 73.3, 38.4, 31.3, 28.1, 19.8. IR (neat) νmax: 3437, 3300, 3078, 2935, 2116, 1732



5-16

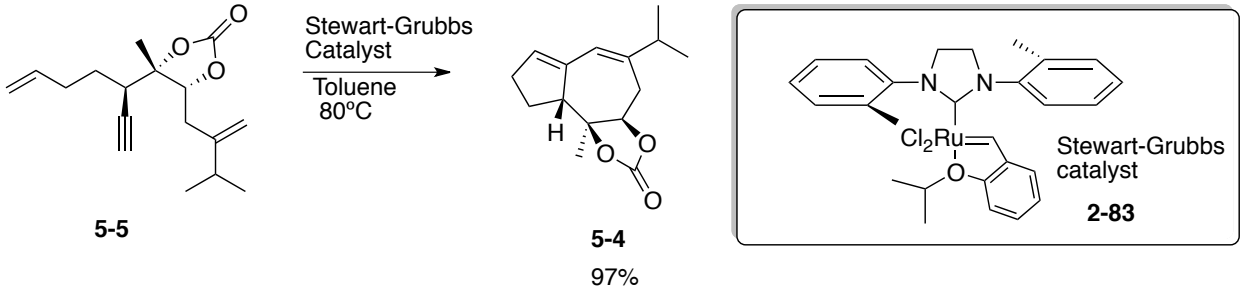
5-5
44%

Carbonate 5-5. The allylation protocol was conducted by employing a modified procedure of Singaram et al.[8]

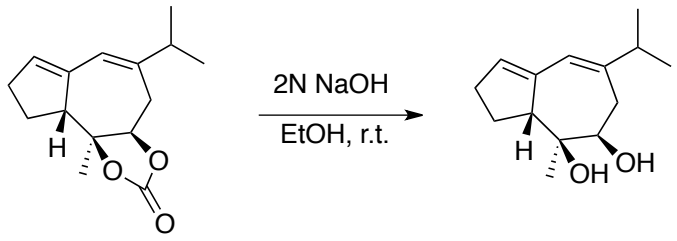
To a solution of indium powder (6.490 g, 56.52 mmol) in freshly distilled THF (15 mL) was added a solution of (+)-B-Chlorodiisopinocampheylborane (weighed in a glove bag) (17.809 g, 55.52 mmol) in THF (40 mL). 2-Bromo-methyl-3-methyl-1-butene (**2-80**) was added (9.047 g, 55.48 mmol) and the solution was allowed to stir at room temperature under a positive pressure of argon. After stirring for 1 hour the reaction mixture became very dark and the solution was diluted with hexanes (55 mL). After stirring for 30 minutes a bright orange precipitate appeared and the solution was filtered under argon. The filtrate was cooled to -78ºC and the reaction mixture became heterogeneous. A solution of aldehyde **5-16** (3.260 g, 19.61 mmol) in THF (5 mL) was added dropwise, and the solution was allowed to stir at -78ºC for one hour. After slowly warming to room temperature over an additional hour, the reaction mixture was concentrated in vacuo. The crude residue was dissolved in THF (100 mL) and then a 1:1 (v/v) solution of 3N NaOH/H_2O_2 (30% aq) (100 mL) was added. The reaction mixture was allowed to stir at room temperature. After 24 hours the reaction mixture was diluted with brine (100 mL), and then extracted with ether (4 x 100 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to Kugelrohr distillation (bath temp 100ºC, P =1.4 mmHg) to remove excess terpenol. The crude residue (distilland) was partially purified by column chromatography (20:1 to 10:1 Hex/EtOAc) to give the diol intermediate. The diol was dissolved in toluene (350 mL) and then 1,1'-carbonydiimidazole was added (26 g, 0.16 mol) and the solution was heated to 80ºC. After stirring for 6 hours the reaction mixture was cooled to room temperature and poured slowly into a cold solution of 10% citric acid (200 mL). The reaction mixture was diluted with ether (200

mL) and then transferred to a separation funnel. The aqueous layer was extracted with ether (4 x 100 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (50:1 to 10:1 Hex/EtOAc) to give carbonate **5-5** (2.371 g, 44%) as a white solid. ^{1}H NMR analysis revealed an ~8:1 ratio of diastereomers.

mp: 70-72ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dddd, *J* = 17.3, 10.2, 7.4, 6.0 Hz, 1H), 5.10 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.07 – 5.02 (m, 1H), 4.96 (s, 1H), 4.88 (s, 1H), 4.48 (dd, *J* = 11.5, 2.0 Hz, 1H), 2.84 (d, *J* = 15.1 Hz, 1H), 2.77 (dt, *J* = 11.5, 2.9 Hz, 1H), 2.48 – 2.27 (m, 3H), 2.25 (d, *J* = 2.5 Hz, 1H), 2.22 – 2.10 (m, 1H), 1.93 – 1.83 (m, 1H), 1.73 – 1.61 (m, 1H), 1.59 (s, 3H), 1.07 (d, *J* = 5.1 Hz, 3H), 1.05 (d, *J* = 5.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 153.5, 149.6, 137.0, 116.0, 110.7, 85.7, 85.0, 82.0, 73.5, 35.2, 33.8, 33.6, 31.3, 28.6, 21.6, 21.5, 20.6. IR (neat) νmax: 3263, 3082, 2963, 2874, 1032. HRMS [ES+] calc for $C_{17}H_{24}O_3Na$ $[M+Na]^+$ 299.1623, found 299.1621



Hydroazulene 5-4. A stirred solution of carbonate **5-5** (2.371 g, 8.577 mmol) in toluene (300 mL) was heated to 80ºC. The Stewart-Grubbs catalyst (**2-83**) was added in one portion (757 mg, 1.327 mmol) and the solution was allowed to stir for 16 hours at 80ºC. After cooling to room temperature the solvent was removed in vacuo. The crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give hydroazulene **5-4** (2.076 g, 97%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.68 (s, 1H), 4.29 (dd, *J* = 12.2, 3.8 Hz, 1H), 3.62 (d, *J* = 9.3 Hz, 1H), 2.98 (t, *J* = 13.7 Hz, 1H), 2.45 – 2.27 (m, 4H), 2.21 – 2.12 (m, 1H), 2.09 – 2.00 (m, 1H), 1.37 (s, 3H), 1.03 (d, *J* = 3.8 Hz, 3H), 1.01 (d, *J* = 3.9 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 153.8, 140.6, 134.0, 131.9, 122.3, 86.7, 84.6, 49.6, 37.3, 31.3, 30.5, 25.1, 21.3, 20.8, 20.7. IR (neat) νmax: 2960, 1800.

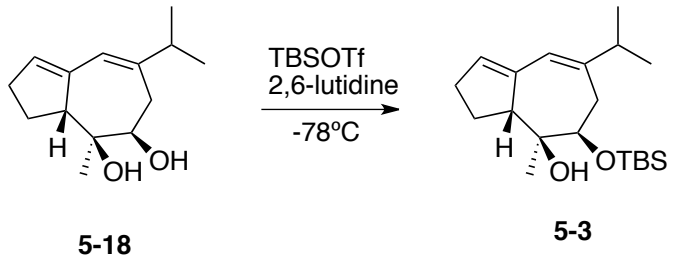


5-4 **5-18**

74%

Diol 5-18. To a stirred solution of carbonate **5-4** (2.076 g, 8.360 mmol) in ethanol (50 mL) was added 2N NaOH (50 mL). The solution was allowed to stir for 5 minutes and was quenched with sat. NH_4Cl solution (100 mL). The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic solution was dried over $MgSO_4$ and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (5:1 to 2:1 Hex/EtOAc) to give diol **5-18** (1.374 g, 74%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.56 (s, 1H), 3.53 – 3.38 (m, 1H), 3.27 – 3.13 (m, 1H), 3.09 – 2.98 (m, 1H), 2.88 – 2.64 (m, 2H), 2.44 – 2.17 (m, 3H), 2.15 – 1.89 (m, 3H), 1.13 (s, 3H), 0.99 (d, J = 6.8 Hz, 6H). ^{13}C NMR (75 MHz, CDCl3) δ 145.7, 141.5, 129.7, 120.7, 77.3, 76.3, 51.9, 37.4, 34.6, 31.4, 26.1, 21.3, 20.9, 20.7. IR (neat) νmax: 3382, 3034, 2960, 2928, 2870, 2846 HRMS [ES+] calc for $C_{12}H_{17}N_6$ $[M]^+$ 245.1515, found 245.1514



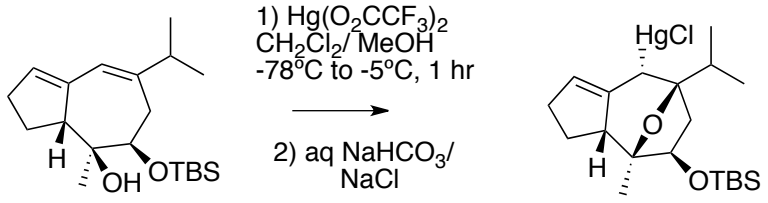
5-18 **5-3**

78%

TBS ether 5-3. A stirred solution of diol **5-18** (1.374 g, 6.179 mmol) and 2,6-lutidine (2.15 mL, 18.6 mmol) in methylene chloride (120 mL) was cooled to -78ºC. A solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.84 mL, 8.01 mmol) in methylene chloride (60 mL) was added and the solution was allowed to stir at -78ºC for 5 minutes. The reaction mixture was quenched with sat. $NaHCO_3$ solution (30 mL) and allowed to warm to 0ºC. The reaction

mixture was transferred to a separation funnel and the organic layer was washed with 10% citric acid (3 x 30 mL) followed by sat. $NaHCO_3$ (1 x 10 mL). The organic solution was then dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give TBS ether **5-3** (1.616 g, 78%) as a colorless oil.

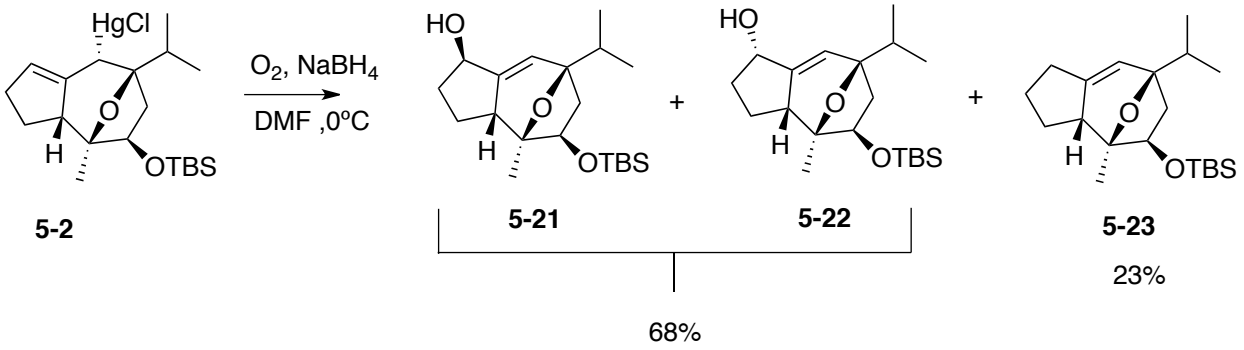
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.03 (br s, 1H), 5.58 (br s, 1H), 3.47 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.11 (s, 1H), 3.05 (br d, *J* = 9.5 Hz, 1H), 2.88 (dd, *J* = 16.6, 10.3 Hz, 1H), 2.44 – 2.22 (m, 3H), 2.21 – 2.10 (m, 1H), 2.09 – 1.96 (m, 1H), 1.84 (d, *J* = 16.7 Hz, 1H), 1.07 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 146.4, 142.0, 129.3, 121.0, 78.8, 75.7, 51.7, 37.5, 34.7, 31.7, 26.4, 25.9, 21.7, 21.5, 21.0, 18.0, -3.9, -4.8. IR (neat) νmax: 3417, 2956, 2930, 2857, 1723, 652, 1471, 1254, 1076, 837. HRMS [ES+] calc for $C_{20}H_{37}O_2Si$ $[M+H]^+$ 337.2563, found 337.2562



5-3 **5-2** 71%

Alkyl mercurial 5-2. A stirred solution of alcohol **5-3** (1.616 g, 4.802 mmol) in methylene chloride (200 mL) was cooled to -78ºC. A solution of mercury trifluoroacetate (2.56 g, 5.76 mmol) in methylene chloride (10 mL) and methanol (0.4 mL) was added and the solution was allowed to warm to -5ºC over one hour. The solution was quenched by pouring into a 1:1 sat. $NaHCO_3$/ sat. NaCl solution (200 mL). The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with methylene chloride (100 mL in 3 portions). The combined organic solution was washed with $NaHCO_3$ sat. (50 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (50:1 to 10:1 Hex/EtOAc) to give alkyl mercurial **5-2** (1.943 g, 71%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (m, 1H), 4.03 (dd, *J* = 7.3, 2.5 Hz, 1H), 3.11 (s, 1H), 2.71 (ddd, *J* = 10.6, 5.3, 2.0 Hz, 1H), 2.36 – 2.28 (m, 2H), 2.10 – 1.98 (m, 2H), 1.90 (hept, *J* = 6.9 Hz, 1H), 1.80 (dt, *J* = 13.2, 2.2 Hz, 1H), 1.45 (dq, *J* = 13.3, 8.9 Hz, 1H), 1.15

(s, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 143.5, 127.1, 88.2, 87.9, 73.2, 60.4, 57.3, 49.0, 36.5, 30.5, 25.74, 25.70, 25.2, 19.4, 18.7, 18.0, 17.7, -4.6, -5.0. IR (neat) νmax: 2956, 2931, 2856, 1471, 1463, 1256, 1090, 912, 835

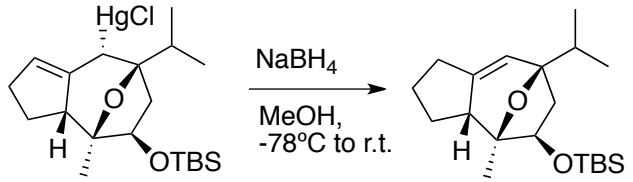


Alcohols 5-21 and **5-22** and **TBS ether 5-23.** A stirred solution of $NaBH_4$ (62.0 mg, 1.64 mmol) in DMF (4 mL) was cooled to 0ºC. A stream of oxygen gas was bubbled through the solution for an hour while stirring. To the resulting solution was added a solution of alkyl mercurial **5-2** (320 mg, 0.560 mmol) dropwise by syringe pump at 0ºC for 1 hour. During this time, oxygen bubbling was continued. When addition was complete, the resulting mixture was slowly warmed to room temperature over 2 hours (oxygen bubbling continued). The reaction mixture was slowly poured into a solution of 1N HCl (150 mL) and then methylene chloride was added (100 mL). The biphasic solution was filtered through a celite pad which was washed with methylene chloride (100 mL). The filtrate was transferred to a separation funnel and the aqueous layer was extracted with methylene chloride (100 mL in 3 portions). The combined organic solution was washed with 10% citric acid (150 mL in 5 portions) followed by sat. $NaHCO_3$ solution (3 x 50 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 to 2:1 Hex/EtOAc) to give TBS ether **5-23** (44 mg, 23%) and a ~1:1 mixture of epimeric alcohols **5-21** and **5-22** (135 mg, 68%). A small sample of each alcohol was isolated for characterization.

TBS ether 5-23 (colorless oil): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (d, *J* = 2.3 Hz, 1H), 4.09 (dd, *J* = 7.3, 5.6 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.36 – 2.25 (m, 2H), 2.17 – 2.08 (m, 1H), 1.87 (hept, *J* = 6.9 Hz, 1H), 1.83 – 1.60 (m, 3H), 1.53 (dd, *J* = 11.5, 5.6 Hz, 1H), 1.26 (s, 3H), 1.22 – 1.10 (m, 1H), 0.93 (app t, *J* = 7.1 Hz, 6H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 141.9, 120.0, 85.1, 83.1, 73.4, 52.0, 51.3, 34.2, 29.2, 26.5, 25.8, 23.5, 21.1, 18.0, 17.8, 17.7, -4.5, -4.9. IR (neat) νmax 2958, 2929, 2857, 1472, 1385, 1366, 1254, 1109, 1090, 1072, 877, 837, 775 HRMS [ES+] calc for $C_{20}H_{36}O_2NaSi$ $[M+Na]^+$ 359.2382, found 359.2386

Alcohol 5-22 (faster moving isomer) (pale yellow oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (t, *J* = 2.3 Hz, 1H), 4.53 (t, *J* = 6.3 Hz, 1H), 4.11 (dd, *J* = 7.3, 5.7 Hz, 1H), 2.67 (td, *J* = 9.5, 2.8 Hz, 1H), 2.33 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.05 – 1.82 (m, 3H), 1.79 – 1.68 (m, 1H), 1.64 – 1.50 (m, 2H), 1.43 – 1.31 (m, 1H), 1.23 (s, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 145.2, 120.9, 85.2, 83.5, 73.3, 71.9, 51.0, 49.3, 34.5, 34.2, 25.7, 22.8, 20.8, 18.0, 17.8, 17.7, -4.5, -5.0. IR (neat) νmax 3402, 2958, 2857, 1471, 1387, 1367, 1255, 1097 HRMS [ES+] calc for $C_{20}H_{36}O_3NaSi$ $[M+Na]^+$ 375.2331, found 375.2338

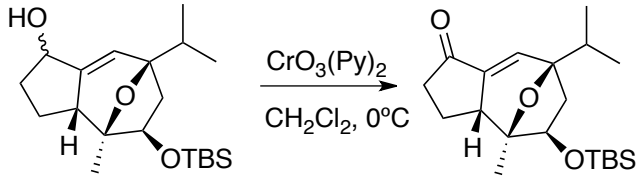
Alcohol 5-21 (slower moving isomer) (colorless crystals, mp 135ºC): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (d, *J* = 2.6 Hz, 1H), 4.47 – 4.40 (m, 1H), 4.03 (dd, *J* = 7.3, 5.7 Hz, 1H), 3.00 (td, *J* = 9.2, 2.6 Hz, 1H), 2.29 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.02 – 1.85 (m, 3H), 1.72 – 1.62 (m, 1H), 1.56 (dd, *J* = 11.7, 5.7 Hz, 1H), 1.47 (d, *J* = 3.5 Hz, 1H), 1.27 (s, 3H), 1.26 – 1.17 (m, 1H), 0.95 (t, *J* = 6.8 Hz, 6H), 0.87 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 123.9, 85.2, 83.1, 73.7, 73.3, 50.8, 48.3, 33.99, 33.93, 25.7, 23.4, 20.9, 18.0, 17.7, 17.7, -4.5, -5.0. IR (neat) νmax 3364, 2959, 2930, 2857, 1472, 1463, 1386, 1367, 1255, 1097, 1034, 876, 837. HRMS [ES+] calc for $C_{20}H_{36}O_3NaSi$ $[M+Na]^+$ 375.2331, found 375.2338



5-2 **5-23**

52%

TBS ether 5-23. A stirred solution of crude alkyl mercurial **5-2** (504 mg, 0.882 mmol) in methanol (50 mL) was cooled to -78ºC. Sodium borohydride (1.569 g, 41.47 mmol) was added in one portion and the solution was allowed to slowly warm to room temperature overnight. The reaction mixture was filtered through a celite pad and concentrated in vacuo. The crude residue was partitioned between ether (10 mL) and sat. NH_4Cl solution (30 mL) and the aqueous layer was extracted with ether (50 mL in three portions). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (Hex to 100:1 Hex/EtOAc) to give TBS ether **5-23** (153 mg, 52%) as a colorless oil.



5-21 and **5-22** **5-33**

76%

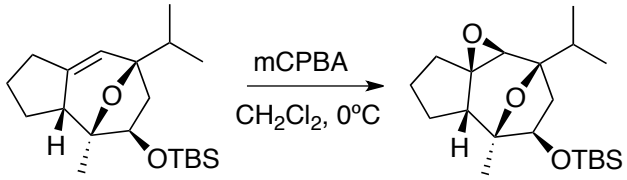
Ketone 5-33.

Preparation of the Collins reagent: A stirred solution of chromium trioxide (656 mg, 6.56 mmol) in methylene chloride (16 mL) was cooled to 0ºC. Pyridine was added (1.1 mL, 13.7 mmol) and the solution was allowed to slowly warm to room temperature over one hour.

A stirred solution of the alcohols **5-21** and **5-22** (239 mg, 0.68 mmol) in methylene chloride (14 mL) was cooled to 0ºC. An aliquot of the Collins reagent solution was added (10 mL, 41 mmol) and the solution was allowed to stir for 10 minutes. The reaction mixture was diluted with methylene chloride (50 mL) and filtered through a pad of silica gel. The silica gel pad was

washed with EtOAc. The resulting filtrate was concentrated in vacuo and the crude residue was subjected to column chromatography (20:1 Hex/EtOAc) to give ketone **5-33** (180 mg, 76%) as a white solid.

mp: 107-110ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 3.0 Hz, 1H), 4.14 (dd, *J* = 7.4, 5.7 Hz, 1H), 3.06 (ddd, *J* = 10.9, 7.4, 2.9 Hz, 1H), 2.45 – 2.22 (m, 3H), 2.12 (dt, *J* = 12.3, 8.0 Hz, 1H), 1.98 (hept, *J* = 6.7 Hz, 1H), 1.65 (dd, *J* = 12.3, 5.7 Hz, 1H), 1.49 – 1.35 (m, 1H), 1.32 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 205.6, 137.5, 133.9, 85.4, 84.1, 72.7, 50.4, 48.7, 38.4, 34.0, 25.7, 21.9, 20.0, 18.0, 17.8, 17.7, -4.5, -4.9. IR (neat) νmax 2959, 2929, 2883, 2857, 1721, 1648 HRMS [ES+] calc for $C_{20}H_{35}O_3Si$ $[M+H]^+$ 351.2355, found 351.2352

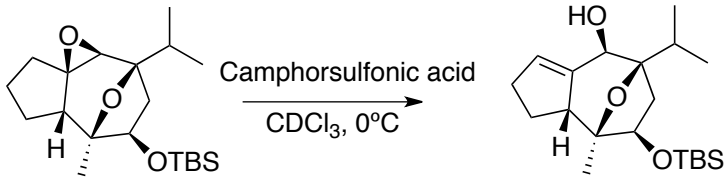


5-23 **5-28**

68%

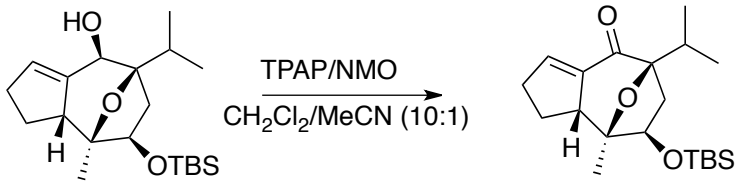
Epoxide 5-28. A stirred solution of TBS ether **5-23** (125 mg, 0.371 mmol) in methylene chloride (12 mL) was cooled to 0ºC. mCPBA was added in one portion (77% max, 102 mg, 0.45 mmol) and the solution was allowed to stir for 1.5 hours. The reaction mixture was quenched with sat. sodium thiosulfate (5 mL) and the aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was washed with sat. $NaHCO_3$ (3 x 7 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography to give epoxide **5-28** (88 mg, 68%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (dd, *J* = 7.6, 5.4 Hz, 1H), 2.95 (s, 1H), 2.29 – 2.18 (m, 2H), 2.05 – 1.93 (m, 2H), 1.92 – 1.84 (m, 1H), 1.81 – 1.73 (m, 2H), 1.72 – 1.64 (m, 1H), 1.60 (dd, *J* = 12.7, 5.4 Hz, 1H), 1.35 – 1.26 (m, 1H), 1.16 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 84.4, 80.9, 72.9, 63.5, 58.1, 47.3, 43.7, 33.4, 32.3, 27.2, 25.7, 23.8, 21.0, 18.1, 18.0, 17.3, -4.5, -5.0. IR (neat) νmax 2959, 2932, 2857, 1471, 1450, 1387, 1368, 1252, 1118, 1089. HRMS [ES+] calc for $C_{20}H_{37}O_3Si$ $[M+H]^+$ 353.2512, found 353.2512



5-28 **5-20** 55%

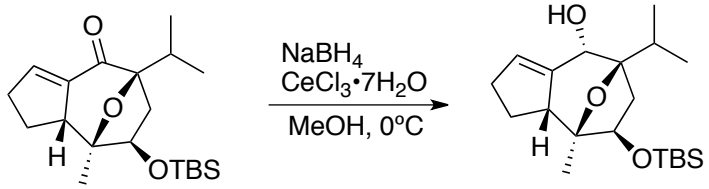
Alcohol 5-20. A stirred solution of epoxide **5-28** (85 mg, 0.24 mmol) in chloroform-d (5 mL) was cooled to 0ºC. Camphorsulfonic acid (6 mg, 0.02 mmol) was added in one portion and the solution was kept at 0ºC for the remainder of the reaction. After 4 hours ^{1}H NMR analysis indicated complete consumption of starting material. The reaction mixture was quenched with sat. $NaHCO_3$ (5 mL), diluted with methylene chloride (10 mL) and transferred to a separation funnel. The aqueous layer was extracted with methylene chloride (3 x 10 mL). The combined organic solution was washed with sat. $NaHCO_3$ (2 x 10 mL), dried over $MgSO_4$, and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 to 5:1 Hex/EtOAc) to give alcohol **5-20** (47 mg, 55%) as a white solid.; mp: 62-65ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 2.4 Hz, 1H), 3.99 (d, *J* = 9.7 Hz, 1H), 3.89 (dd, *J* = 6.7, 2.4 Hz, 1H), 3.00 – 2.92 (m, 1H), 2.45 – 2.26 (m, 3H), 2.14 (d, *J* = 9.7 Hz, 1H), 2.04 (dtd, *J* = 13.9, 9.2, 3.0 Hz, 1H), 1.67 – 1.61 (m, 2H), 1.44 – 1.34 (m, 1H), 1.19 (s, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 141.9, 127.3, 88.8, 87.2, 72.0, 69.3, 51.1, 39.4, 31.4, 28.2, 25.7, 24.2, 19.5, 18.0, 17.7, 16.1, -4.6, -5.0. IR (neat) νmax 3446, 2956, 2930, 2856, 1254 HRMS [ES+] calc for $C_{20}H_{36}O_3NaSi$ $[M+Na]^+$ 375.2331, found 375.2328



5-20 **5-29**

71%

Ketone 5-29. To a stirred solution of alcohol **5-20** (18 mg, 0.051 mmol) in a 10:1 CH_2Cl_2/MeCN mixture (10:1) was added 3Å molecular sieves (50 mg) followed by N-methylmorpholine N-oxide (29 mg, 0.25 mmol). Tetrapropylammonium perruthenate was added (5 mg, 0.01 mmol) and the solution was allowed to stir at room temperature. After 1.5 hours the reaction mixture was concentrated in vacuo and the crude residue was subjected to column chromatography (10:1 Hex/EtOAc) to give ketone **5-29** (13 mg, 71%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, *J* = 2.8 Hz, 1H), 4.21 (dd, *J* = 7.5, 4.1 Hz, 1H), 3.31 – 3.19 (m, 1H), 2.58 – 2.34 (m, 2H), 2.30 – 2.03 (m, 3H), 1.90 (dd, *J* = 13.9, 4.2 Hz, 1H), 1.59 – 1.47 (m, 1H), 1.27 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 6H), 0.89 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 198.6, 140.4, 139.3, 89.6, 87.2, 72.0, 55.6, 45.2, 32.0, 30.4, 27.4, 25.7, 19.9, 18.0, 18.0, 17.2, -4.5, -5.0. IR (neat) νmax 2958, 2931, 2857, 1701, 1618, 1253. HRMS [ES+] calc for $C_{20}H_{35}O_3Si$ $[M+H]^+$ 351.2355, found 351.2347

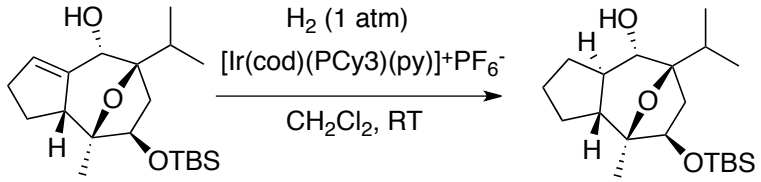


5-29 **5-19**

74%

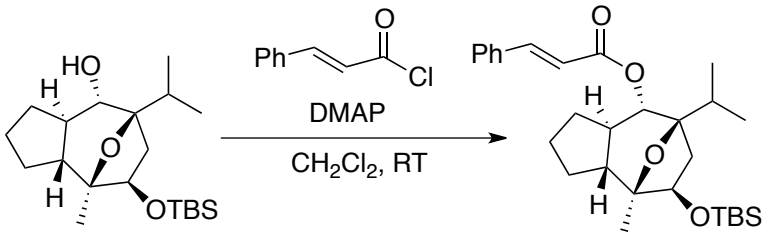
Alcohol 5-19. To a stirred solution of ketone **5-29** (15 mg, 0.043 mmol) and cerium(III) chloride heptahydrate (63 mg, 0.17 mmol) in methanol (3 mL) was added sodium borohydride (9 mg, 0.2 mmol) at 0ºC. After stirring for 20 minutes at 0ºC the reaction mixture was quenched with sat. NH_4Cl (3 mL) and diluted with methylene chloride (10 mL). The aqueous layer was extracted with methylene chloride (3 x 10 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 Hex/EtOAc)

to give alcohol **5-19** (11 mg, 74%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 – 5.52 (m, 1H), 4.24 (s, 1H), 3.86 (dd, *J* = 7.5, 2.2 Hz, 1H), 2.80 – 2.72 (m, 1H), 2.45 – 2.35 (m, 2H), 2.11 – 1.93 (m, 3H), 1.56 – 1.49 (m, 2H), 1.47 – 1.38 (m, 1H), 1.16 (s, 3H), 1.06 (d, *J* = 3.4 Hz, 3H), 1.05 (d, *J* = 3.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 145.1, 121.6, 87.7, 86.0, 73.1, 71.9, 54.8, 41.0, 32.1, 31.9, 25.8, 25.0, 19.3, 18.1, 18.0, 17.3, -4.6, -5.0. IR (neat) νmax 3419, 2956, 2930, 2856, 1472, 1385, 1255. HRMS [ES+] calc for $C_{20}H_{36}O_3NaSi$ $[M+Na]^+$ 375.2331, found 375.2336



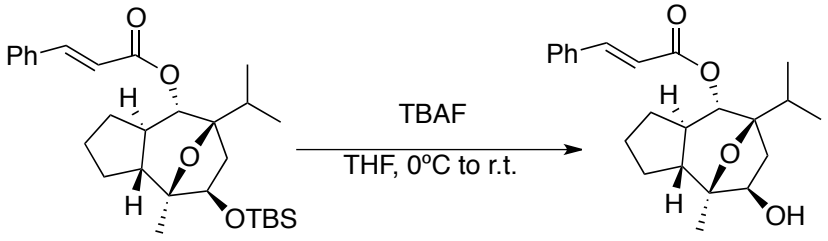
5-19 **5-30** 92%

Alcohol 5-30. A round bottom flask was charged with alcohol **5-19** (13 mg, 0.037 mmol) and purged with hydrogen gas. Methylene chloride was added (2 mL) followed by the Crabtree catalyst $[Ir(cod)(PCy3)(py)]^+PF_6^-$ (30 mg, 0.037 mmol). A stream of hydrogen gas was bubbled through the solution and the reaction vessel was equipped with a hydrogen balloon. The reaction mixture was allowed to stir at room temperature under a hydrogen atmosphere (1 atm). After 4 hours the reaction mixture was concentrated in vacuo. The crude residue was subjected to column chromatography (7:1 Hex/EtOAc) to give alcohol **5-30** (12 mg, 92%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (dd, *J* = 7.6, 2.5 Hz, 1H), 4.10 (t, *J* = 7.2 Hz, 1H), 2.56 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.25 (td, *J* = 9.4, 4.2 Hz, 1H), 1.97 – 1.69 (m, 4H), 1.57 – 1.31 (m, 5H), 1.13 (s, 3H), 1.04 (d, *J* = 3.6 Hz, 3H), 1.02 (d, *J* = 3.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 86.9, 83.9, 73.3, 70.3, 47.2, 44.4, 40.4, 34.2, 28.0, 27.3, 25.8, 25.1, 20.5, 18.2, 18.1, 17.6, -4.6, -5.0. IR (neat) νmax 3445, 2956, 2880, 2853, 1472, 1256, 1085, 1063. HRMS [EI+] calc for $C_{20}H_{38}SiO_3$ $[M]^+$ 354.25903, found 354.25841



5-30 **5-31** 85%

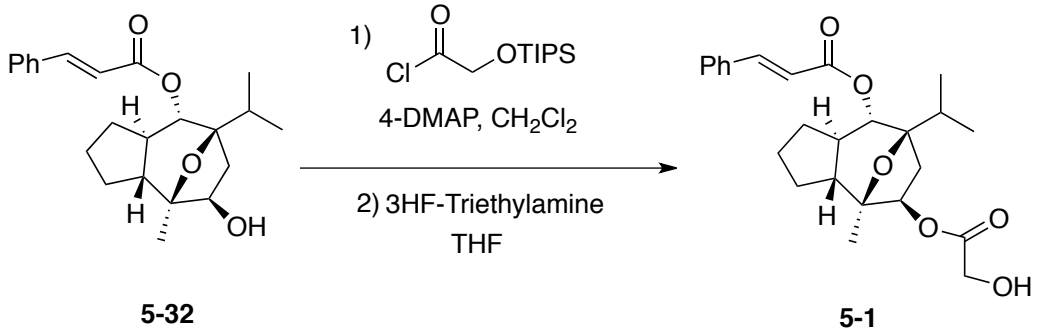
Ester 5-31. To a stirred solution of alcohol **5-30** (8.6 mg, 0.025 mmol) and DMAP (24 mg, 0.20 mmol) in methylene chloride (2 mL) was added (*E*)-cinnamoyl chloride (15 mg, 0.090 mmol). After stirring for 3 hours at room temperature an additional portion of cinnamoyl chloride was added (12 mg, 0.073 mmol). After stirring for 5 hours the reaction mixture was quenched with sat. $NaHCO_3$ solution (2 mL). Pyridine was added (1mL) and the solution was stirred vigorously for 1 hour. The reaction mixture was diluted with methylene chloride (40 mL) and transferred to a sepration funnel. The organic layer was washed with 10% citric acid (3 x 10 mL) followed by sat. $NaHCO_3$. The organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was subjected to column chromatography to give ester **5-31** (10 mg, 85%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.43 – 7.37 (m, 3H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.22 (dd, *J* = 8.7, 1.4 Hz, 1H), 4.22 (dd, *J* = 7.5, 2.6 Hz, 1H), 2.77 – 2.64 (m, 2H), 2.33 (td, *J* = 9.6, 4.1 Hz, 1H), 1.97 – 1.85 (m, 2H), 1.83 – 1.75 (m, 1H), 1.67 (ddd, *J* = 14.1, 2.7, 1.5 Hz, 1H), 1.54 – 1.35 (m, 4H), 1.16 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 166.1, 144.9, 134.3, 130.3, 128.9, 128.1, 118.1, 87.3, 82.7, 73.2, 72.1, 46.8, 42.1, 41.1, 35.0, 28.8, 27.3, 25.8, 24.9, 20.6, 18.2, 18.1, 17.5, -4.6, -4.9. IR (neat) νmax 2956, 2932, 2882, 2857, 1712, 1637, 1254, 1168. HRMS [ES+] calc for $C_{29}H_{45}O_4Si$ $[M+H]^+$ 485.3087, found 485.3089



5-31 **5-32**

89%

Alcohol 5-32. A solution of ester **5-31** (10 mg, 0.021 mmol) in THF (1 mL) was cooled to 0ºC. Tetrabutylammonium fluoride was added (1M, 0.15 mL, 0.15 mmol) and the solution was allowed to slowly warm to room temperature. After standing for 5 hours the reaction mixture was quenched with sat. NH_4Cl solution (2 mL). The reaction mixture was diluted with ether (10 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography to give alcohol **5-32** (6.8 mg, 89%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.43 – 7.37 (m, 3H), 6.43 (d, *J* = 16.0 Hz, 1H), 5.24 (dd, *J* = 8.8, 1.4 Hz, 1H), 4.25 (td, *J* = 7.7, 2.4 Hz, 1H), 2.88 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.75 – 2.65 (m, 1H), 2.36 (td, *J* = 9.9, 4.2 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.83 – 1.73 (m, 1H), 1.66 (dt, *J* = 14.8, 1.9 Hz, 1H), 1.56 – 1.37 (m, 5H), 1.23 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 166.1, 145.1, 134.3, 130.4, 128.9, 128.1, 117.9, 86.9, 82.7, 73.4, 71.8, 46.6, 41.5, 41.0, 34.7, 28.7, 27.3, 24.9, 20.3, 18.1, 17.4. IR (neat) νmax 3460, 2962, 2934, 2878, 1709, 1694, 1634, 1174. HRMS [ES+] calc for $C_{23}H_{30}O_4Na$ $[M+Na]^+$ 393.2042, found 393.2043



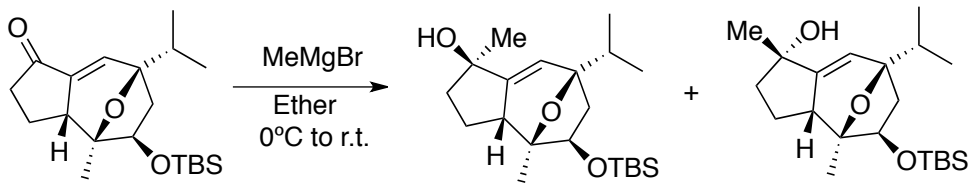
5-32 **5-1**

39% (two steps)

Englerin Analog 5-1. A stirred solution of alcohol **5-32** (5.5 mg, 0.015 mmol) and DMAP (36 mg, 0.29 mmol) in methylene chloride (0.8 mL) was cooled to 0ºC (ice bath). A solution of

TIPS protected glycolic acid chloride (52 mg, 0.22 mmol) was added in methylene chloride (1 mL) and the ice bath was removed. After stirring for 30 minutes, the reaction mixture was quenched with sat. $NaHCO_3$ (5 mL). The reaction mixture was diluted with methylene chloride (30 mL) and transferred to a separation funnel. The organic layer was washed with 10% citric acid (2 x 10 mL) followed by sat. $NaHCO_3$ (2 x 10 mL). The organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent the crude residue was partially purified by column chromatography (100:1 to 10:1 Hex/EtOAc) to give the TIPS protected ester. This intermediate was dissolved in THF (1 mL) and then triethylamine trihydrofluoride (37 wt%, 0.01 ml) was added. The solution was allowed to stand at room temperature. After 24 hours the reaction mixture was quenched with sat. $NaHCO_3$ (5 mL). The reaction mixture was diluted with ether (20 mL) and an additional portion of sat. $NaHCO_3$ solution was added (10 mL). The aqueous layer was extracted with ether (4 x 10 mL), dried over $MgSO_4$ and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (5:1 to 2:1 Hex/EtOAc) to give englerin analog **5-1** (2.5 mg, 39% over two steps) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.43 – 7.37 (m, 3H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.46 (dd, *J* = 8.1, 2.8 Hz, 1H), 5.27 (dd, *J* = 8.8, 1.4 Hz, 1H), 4.19 (d, *J* = 4.3 Hz, 2H), 2.89 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.79 – 2.67 (m, 1H), 2.40 – 2.30 (m, 2H), 2.00 – 1.84 (m, 3H), 1.78 (ddd, *J* = 14.9, 2.8, 1.4 Hz, 1H), 1.64 – 1.39 (m, 4H), 1.15 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 173.1, 166.0, 145.3, 134.2, 130.5, 128.9, 128.1, 117.7, 86.2, 83.1, 77.1, 71.3, 60.6, 46.8, 40.9, 38.4, 35.0, 28.7, 27.0, 25.0, 20.0, 18.2, 17.4. IR (neat) νmax 3418, 2961, 2923, 2848, 1737, 1710, 1636, 1169, 1093 HRMS [ES+] calc for $C_{25}H_{32}O_6Na$ $[M+Na]^+$ 451.2097, found 451.2094



5-33 **2-88** **2-89**

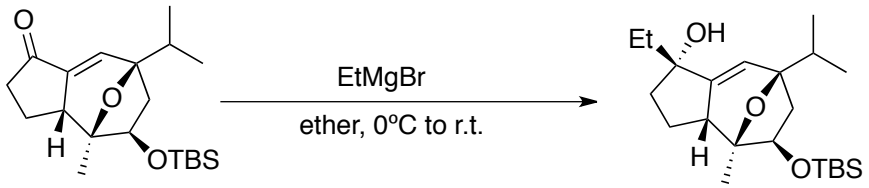
18% 69%

Alcohols 2-88 and **2-89**. A stirred solution of methyl magnesium bromide (3 M, 0.1 mL, 0.3 mmol) diluted with ether (0.5 mL) was cooled to 0ºC. A solution of ketone **5-33** (29 mg, 0.083 mmol) was added dropwise in ether (1.5 mL) and the reaction mixture was allowed to warm to room temperature. After stirring for 1 hour the reaction mixture was quenched with sat. NH_4Cl solution (5 mL) and diluted with EtOAc (5 mL). The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 to 5:1 Hex/EtOAc) to give alcohol **2-89** (21 mg, 69%) and alcohol **2-88** (5 mg, 18%) as colorless oils.

Alcohol 2-89: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 2.7 Hz, 1H), 4.12 (dd, *J* = 7.0, 5.8 Hz, 1H), 2.82 – 2.72 (m, 1H), 2.32 (dd, *J* = 11.7, 7.3 Hz, 1H), 1.91 (h, *J* = 6.9 Hz, 1H), 1.82 – 1.70 (m, 3H), 1.60 – 1.52 (m, 1H), 1.46 – 1.40 (m, 1H), 1.36 (s, 3H), 1.26 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

Alcohol 2-88: 1H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.8 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.13 – 2.99 (m, 1H), 2.26 (dd, *J* = 11.6, 7.3 Hz, 1H), 2.05 – 1.43 (m, 7H), 1.37 (s, 3H), 1.26 (s, 3H), 0.95 (app t, *J* = 7.2 Hz, 6H), 0.88 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H).

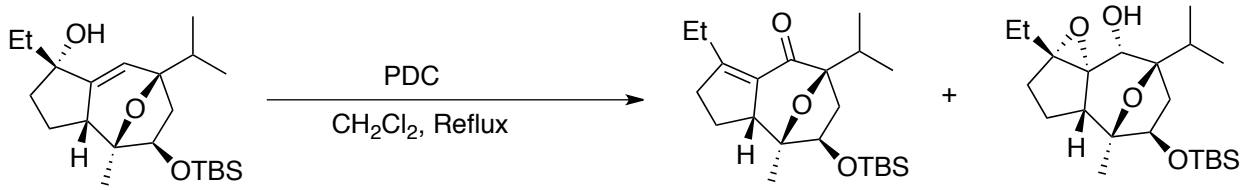
The data were consistent with reported values.[1]



5-33 **5-34**

87%

Alcohol 5-34. A stirred solution of ethyl magnesium bromide (prepared according to Moyer[23]) (2.44 M, 0.3 mL, 0.7 mmol) diluted with ether (2.5 mL) was cooled to 0ºC. A solution of ketone **5-33** (62 mg, 0.18 mmol) was added dropwise in ether (0.5 mL) and the reaction mixture was allowed to warm to room temperature. After stirring for 10 minutes the reaction mixture was quenched with sat. NH_4Cl solution (5 mL) and diluted with ether (10 mL). The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (15:1 Hex/EtOAc) to give alcohol **5-34** (59 mg, 87%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 2.7 Hz, 1H), 4.15 (dd, *J* = 7.3, 5.6 Hz, 1H), 2.69 (ddd, *J* = 10.6, 7.8, 2.8 Hz, 1H), 2.33 (dd, *J* = 11.6, 7.3 Hz, 1H), 1.91 (hept, *J* = 6.8 Hz, 1H), 1.84 – 1.53 (m, 6H), 1.42 – 1.35 (m, 2H), 1.25 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.92 – 0.85 (m, 12H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 147.4, 120.4, 85.0, 83.4, 80.3, 73.3, 51.0, 50.7, 38.8, 34.1, 33.0, 25.8, 23.3, 20.8, 18.0, 17.8, 17.6, 8.4, -4.5, -4.9. IR (neat) νmax 3460, 2960, 2930, 2879, 2857, 1463, 1255, 1102, 1088. HRMS [ES+] calc for $C_{22}H_{40}O_3NaSi$ $[M+Na]^+$ 403.2644, found 403.2645



5-34
87%

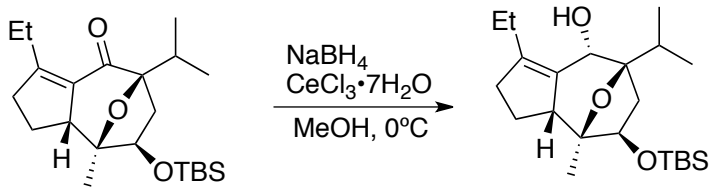
5-40
23%

5-37
47%

Ketone 5-40 and Epoxy Alcohol 5-37. To a stirred solution of alcohol **5-34** (59 mg, 0.16 mmol) in methylene chloride (20 mL) was added pyridinium dichromate (153 mg, 0.41 mmol) and the solution was brought to reflux. After stirring for one hour the reaction mixture was cooled and filtered through a pad of silica gel. The silica gel pad was washed with of EtOAc. After concentration of the filtrate in vacuo the crude residue was subjected to column chromatography (100:1 to 5:1 Hex/EtOAc) to give ketone **5-40** (13 mg, 22%) and epoxy alcohol **5-37** (29 mg, 47%) as oils. Ketone **5-40** was contaminated with a small amount of dehydration product. An analytical sample was obtained by performing additional chromatography.

Ketone 5-40: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.24 (dddd, *J* = 10.9, 7.6, 3.5, 1.8 Hz, 1H), 2.69 – 2.43 (m, 3H), 2.42 – 2.33 (m, 1H), 2.19 (hept, *J* = 6.8 Hz, 1H), 2.07 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.96 (dtd, *J* = 12.5, 7.7, 1.4 Hz, 1H), 1.88 (dd, *J* = 13.7, 4.0 Hz, 1H), 1.47 – 1.33 (m, 1H), 1.25 (s, 3H), 1.06 – 1.01 (m, 9H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 199.4, 160.1, 130.0, 89.5, 87.1, 72.1, 56.7, 45.4, 35.6, 30.4, 29.7, 25.7, 22.8, 19.8, 18.1, 18.0, 17.3, 12.5, -4.5, -5.0. IR (neat) νmax 2958, 2930, 2857, 1692, 1621, 1462, 1253, 1117, 1077

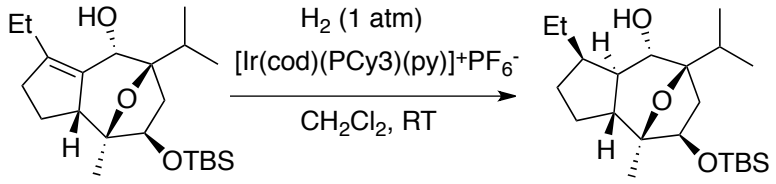
Epoxy Alcohol 5-37: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26 (dd, *J* = 7.3, 2.4 Hz, 1H), 4.03 (dd, *J* = 10.2, 1.4 Hz, 1H), 2.53 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.18 (d, *J* = 10.2 Hz, 1H), 2.05 – 1.86 (m, 4H), 1.82 – 1.73 (m, 1H), 1.61 – 1.44 (m, 4H), 1.16 (s, 3H), 1.07 (d, *J* = 1.9 Hz, 3H), 1.05 (d, *J* = 1.7 Hz, 3H), 1.02 (t, *J* = 7.6 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 86.4, 85.9, 72.6, 71.2, 69.0, 66.9, 49.4, 41.3, 33.0, 29.3, 25.8, 22.6, 19.9, 19.3, 18.1, 18.1, 17.2, 10.1, -4.6, -5.0. IR (neat) νmax 3348, 2958, 2930, 2883, 2858, 1664, 1593, 1472, 1388, 1315, 1256. HRMS [EI+] calc for $C_{22}H_{40}O_4Si$ $[M]^+$ 396.26959, found 396.26977



5-40 **5-39**

63%

Allylic Alcohol 5-39. A stirred solution of ketone **5-40** (8.9 mg, 0.024 mmol) and cerium(III) chloride heptahydrate (35 mg, 0.093 mmol) was cooled to 0ºC. Sodium borohydride was added (4.2 mg, 0.11 mmol) and the solution was allowed to stir for 10 minutes. The reaction mixture was quenched with sat. NH_4Cl solution (1 mL) and stirred vigorously for 5 minutes. The reaction mixture was diluted with methylene chloride (10 mL) and transferred to a separation funnel. The aqueous layer was extracted with methylene chloride (3 x 7 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the crude residue was subjected to column chromatography to give allylic alcohol **5-39** (5.6 mg, 63%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 – 4.34 (m, 1H), 3.90 (dd, *J* = 7.4, 2.1 Hz, 1H), 2.72 – 2.65 (m, 1H), 2.49 – 2.26 (m, 4H), 2.14 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.95 (hept, *J* = 7.0 Hz, 1H), 1.86 (dtd, *J* = 13.2, 8.6, 3.1 Hz, 1H), 1.55 (dt, *J* = 13.7, 1.8 Hz, 1H), 1.41 (d, *J* = 6.7 Hz, 1H), 1.30 – 1.19 (m, 1H), 1.12 (s, 3H), 1.06 – 1.00 (m, 9H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 131.9, 87.1, 85.7, 73.6, 73.0, 56.3, 41.3, 35.7, 31.2, 25.8, 23.5, 21.9, 19.1, 18.1, 18.0, 17.2, 13.7, -4.6, -5.0. IR (neat) νmax 3446, 2959, 2930, 2857, 1589, 1463, 1258

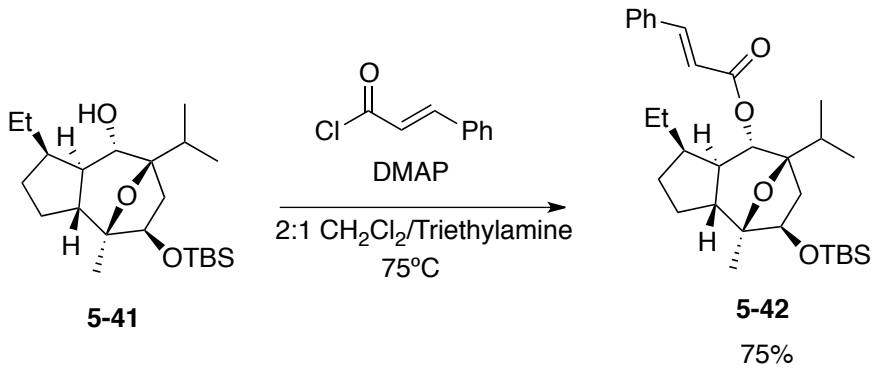


5-39 **5-41**

95%

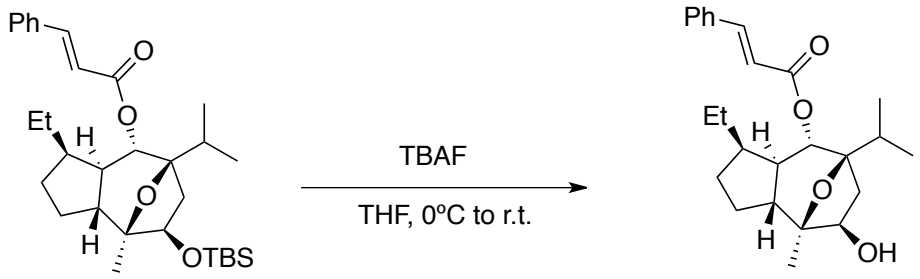
Alcohol 5-41. A round bottom flask was charged with alcohol **5-39** (4.0 mg, 0.011 mmol) and purged with hydrogen gas. Methylene chloride was added (1.5 mL) followed by the Crabtree catalyst $[Ir(cod)(PCy3)(py)]^{+}PF_6^{-}$ (30 mg, 0.037 mmol). A stream of hydrogen gas was bubbled through the solution and the reaction vessel was equipped with a hydrogen balloon. The reaction mixture was allowed to stir at room temperature under a hydrogen atmosphere. After 3 hours the reaction mixture was concentrated in vacuo. The crude residue was subjected to column chromatography (30:1 to 10:1 Hex/EtOAc) to give alcohol **5-41** (12 mg, 92%) as a white solid.

m.p.: 83-85ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89 (dd, *J* = 7.4, 2.6 Hz, 1H), 3.66 (dd, *J* = 10.2, 4.6 Hz, 1H), 2.30 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.04 – 1.91 (m, 2H), 1.90 – 1.82 (m, 1H), 1.70 – 1.58 (m, 2H), 1.57 – 1.48 (m, 2H), 1.41 – 1.22 (m, 3H), 1.21 (d, *J* = 4.6 Hz, 1H), 1.15 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 1.03 – 0.95 (m, 1H), 0.93 – 0.85 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 85.48, 85.45, 72.86, 70.81, 48.60, 48.01, 42.26, 38.30, 32.17, 28.20, 26.07, 25.78, 23.58, 19.66, 18.38, 18.11, 17.43, 12.22, -4.62, -5.02. IR (neat) νmax 3441, 2959, 2930, 2854, 1463, 1385, 1258, 1095. HRMS [ES+] calc for $C_{22}H_{42}O_3NaSi$ $[M+Na]^{+}$ 405.2801, found 405.2801



Ester 5-42. A vial was charged with alcohol **5-41** (4.0 mg, 0.010 mmol) and DMAP (12 mg, 0.10 mmol). A 2:1 (v/v) mixture of methylene chloride and triethylamine (0.6 mL) was added followed by cinnamoyl chloride (21 mg, 0.13 mmol). The vial was capped and placed in an oil bath that was preheated to 75ºC. After stirring for 5 hours the reaction mixture was cooled to room temperature and then diluted with methylene chloride (40 mL). The reaction mixture was washed with 10% citric acid (3 x 10mL), sat. $NaHCO_3$ (3 x 10 mL), dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (50:1 to 30:1 Hex/EtOAc) to give ester **5-42** (4.0 mg, 75%) as an oil.

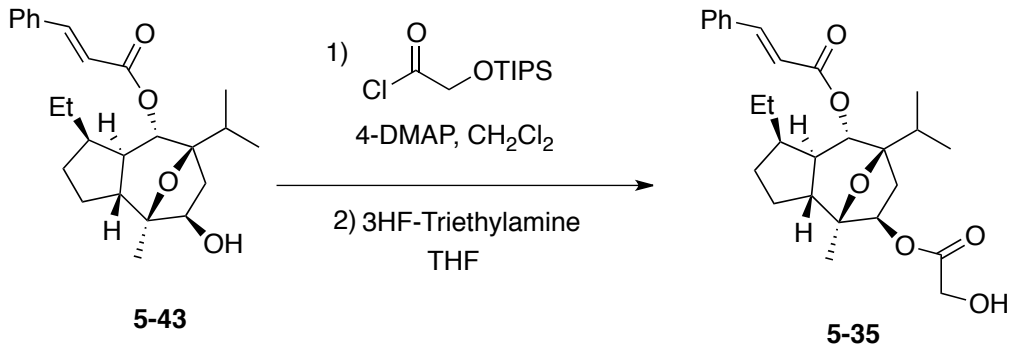
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.42 – 7.36 (m, 3H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.14 (d, *J* = 10.3 Hz, 1H), 4.00 (dd, *J* = 7.5, 2.7 Hz, 1H), 2.49 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.87 (hept, *J* = 6.9 Hz, 1H), 1.81 – 1.66 (m, 5H), 1.56 (s, 3H), 1.18 (s, 3H), 1.10 (dd, *J* = 10.3, 7.3 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.93 – 0.85 (m, 10H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.08 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 165.7, 144.8, 134.4, 130.3, 128.9, 128.1, 118.3, 85.7, 85.1, 72.8, 71.6, 48.2, 47.1, 43.5, 38.9, 33.0, 27.2, 25.8, 25.2, 22.7, 19.7, 18.3, 18.1, 17.6, 12.1, -4.58, -4.96. IR (neat) νmax 2959, 2925, 2896, 2851, 1716, 1636, 1333, 1259. HRMS [ES+] calc for $C_{31}H_{49}O_4Si$ $[M+H]^+$ 513.3400, found 513.3412



5-42

5-43
71%

Alcohol 5-43. A solution of ester **5-42** (4.0 mg, 0.0078 mmol) in THF (1 mL) was cooled to 0ºC. Tetrabutylammonium fluoride was added (1M, 0.15 mL, 0.15 mmol) and the solution was allowed to slowly warm to room temperature. After standing for 3 hours the reaction mixture was quenched with sat. NH_4Cl solution (1.5 mL). The reaction mixture was diluted with methylene chloride (30 mL) and transferred to a separation funnel. The organic layer was washed with 10% citric acid (3 x 10 mL), dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the crude residue was subjected to column chromatography to give alcohol **5-43** (2.2 mg, 71%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.42 – 7.36 (m, 3H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.15 (dd, *J* = 10.4, 0.8 Hz, 1H), 4.04 (td, *J* = 7.6, 2.7 Hz, 1H), 2.64 (dd, *J* = 14.5, 7.6 Hz, 1H), 1.88 (hept, *J* = 7.0 Hz, 1H), 1.83 – 1.66 (m, 5H), 1.64 – 1.39 (m, 2H), 1.38 (d, *J* = 7.5 Hz, 1H), 1.28 – 1.23 (m, 4H), 1.20 – 1.11 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.97 – 0.92 (m, 1H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 165.6, 145.0, 134.3, 130.4, 128.9, 128.1, 118.1, 85.3, 85.1, 73.1, 71.5, 48.2, 47.0, 42.9, 38.9, 32.8, 27.2, 25.0, 22.6, 19.2, 18.2, 17.6, 12.0. IR (neat) νmax 3431, 2960, 2928, 2874, 1710, 1636, 1334, 1170. HRMS [ES+] calc for $C_{25}H_{35}O_4$ $[M+H]^+$ 399.2535, found 399.2533



5-43 **5-35**

44 % (two steps)

Englerin Analog 5-35. A stirred solution of alcohol **5-43** (2.0 mg, 0.0050 mmol) and DMAP (18 mg, 0.15 mmol) in methylene chloride (0.4 mL) was cooled to 0ºC (ice bath). A solution of TIPS protected glycolic acid chloride (15 mg, 0.062 mmol) was added in methylene chloride (0.2 mL) and the ice bath was removed. After stirring for 30 minutes, the reaction mixture was quenched with sat. $NaHCO_3$ (2 mL). The reaction mixture was diluted with methylene chloride (30 mL) and transferred to a separation funnel. The organic layer was washed with 10% citric acid (3 x 5 mL) followed by sat. $NaHCO_3$ (3 x 5 mL). The organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent the crude residue was partially purified by column chromatography (100:1 to 20:1 Hex/EtOAc) to give the TIPS protected ester. This intermediate was dissolved in THF (1 mL) and then triethylamine trihydrofluoride (37 wt%, 0.05 ml) was added. The solution was allowed to stand at room temperature. After 24 hours the reaction mixture was diluted with ether (2 mL) and quenched with sat. $NaHCO_3$ (2 mL). The reaction mixture was diluted with additional ether (30 mL) and transferred to a separation funnel. The organic layer was washed with sat. $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$ and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 to 5:1 Hex/EtOAc) to give englerin analog **5-35** (1.0 mg, 44%) as an oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.43 – 7.36 (m, 3H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.22 (dd, *J* = 7.9, 3.0 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.20 (d, *J* = 5.5 Hz, 2H), 2.68 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.33 (t, *J* = 5.5 Hz, 1H), 1.89 (hept, *J* = 6.7 Hz, 1H), 1.84 – 1.67 (m, 5H), 1.65 – 1.55 (m, 1H), 1.45 (dt, *J* = 11.8, 7.8 Hz, 1H), 1.35 – 1.20 (m, 2H), 1.19 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H), 0.95 – 0.91 (m, 1H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 173.08, 165.55, 145.15, 134.24, 130.42,

128.91, 128.12, 117.96, 85.59, 84.53, 76.46, 70.99, 60.63, 48.33, 47.22, 39.84, 38.92, 32.99, 27.09, 24.80, 22.56, 18.96, 18.20, 17.47, 12.01. HRMS [ES+] calc for $C_{27}H_{37}O_6$ $[M+H]^+$ 457.2590, found 457.2588

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Chapter 6

Studies Towards the Synthesis of C10-Desmethyl (-)-Englerin A

6.1 Introduction

Aside from the C-4 methyl group and its effect upon the cytotoxicity of EA (**2-1**), we also wondered about the influence of the C-10 methyl group.

At the outset of this work, we knew that the adjacent C9 glycolate moiety was essential for biological activity.[1] Thus, we hypothesized that the C10 methyl group may influence the conformation of this ester group and, in doing so, may also be of importance. To answer this question we embarked on a total synthesis of C10-desmethyl-(-)-englerin A (**6-1**) (Figure 6-1).

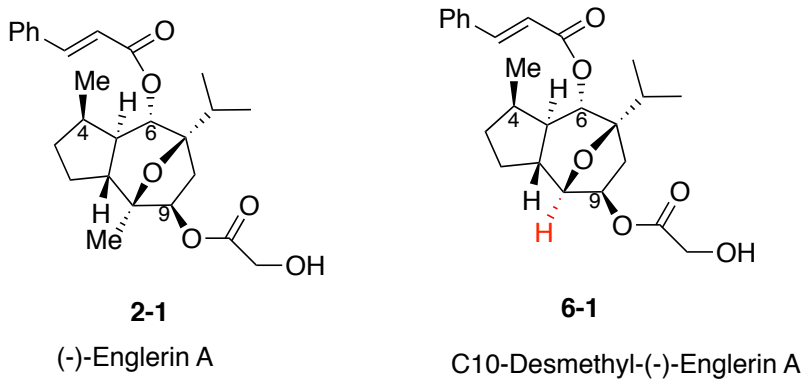
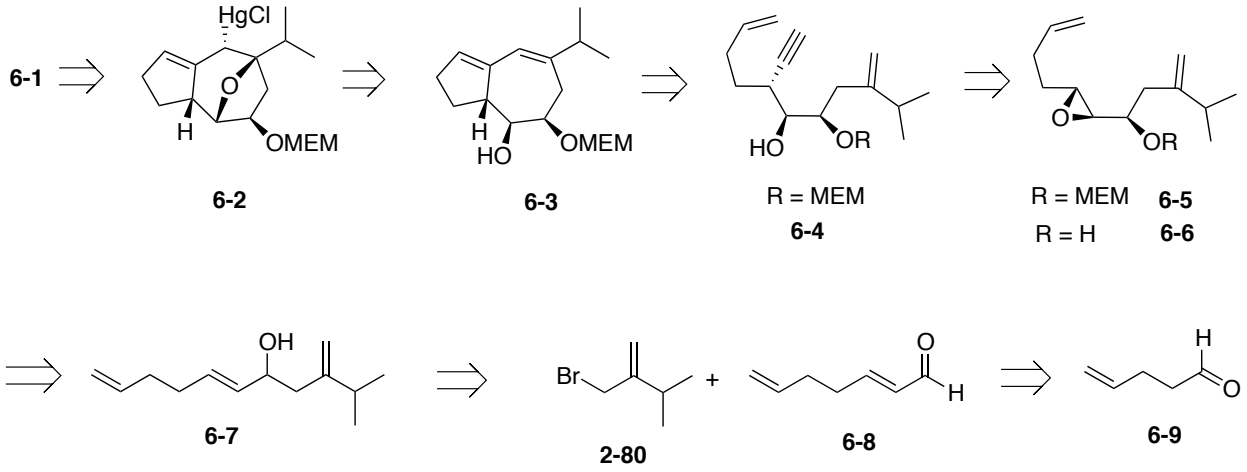


Figure 6-1. Structural Comparison of (-)-Englerin A (**2-1**) to C10-Desmethyl (-)-Englerin A (**6-1**)

6.1.1 Synthetic Design of C10-Desmethyl (-)-EA (**6-1**)

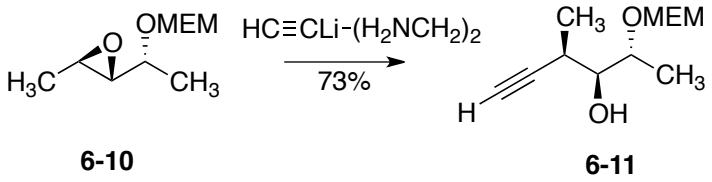
By analogy to our previous work, we designed the synthesis of analog (**6-1**) by way of a alkyl mercurial intermediate **6-2** (Scheme 6-1).



Scheme 6-1. Retrosynthetic Analysis of C10-Desmethyl-(-)-EA (**6-1**)

This would require that it be prepared from hydroazulene **6-3** which, in turn, would come from the addition of lithium acetylide to MEM protected epoxy alcohol **6-5**. We were confident that the alkynylation of this intermediate would proceed smoothly based on earlier work conducted by Parker and Chang.[2]

In 2005 Parker and Chang showed that *trans*-MEM protected *erythro*-epoxy alcohol **6-10** could be opened at the distal end to give alkynol **6-11** in good yield (Scheme 6-2).



Scheme 6-2. Alkynylation of *trans*-MEM Protected *erythro*-Epoxy Alcohol **6-10** with the Lithium Acetylide Ethylene Diamine Complex

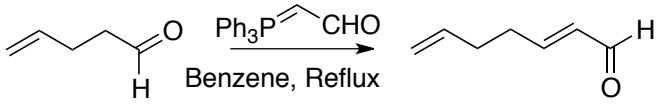
The substitution pattern present in compound **6-11** is identical to what is present in ene-yne-ene **6-4**. Therefore, this methodology appeared to offer a rapid entry into the hydroazuleune framework.

Thus we envisioned that the desired epoxy alcohol intermediate (**6-6**) would be derived from the Sharpless asymmetric epoxidation/kinetic resolution[3] of alcohol **6-7**. This in turn, could be synthesized by coupling aldehyde **6-8** with the Barbier reagent prepared from allyl halide **2-80**. Aldehyde **6-8** would be prepared by homologation of compound **6-9**.

6.2 Results and Discussion

6.2.1 Synthesis of MEM protected Epoxy Alcohol **6-5**

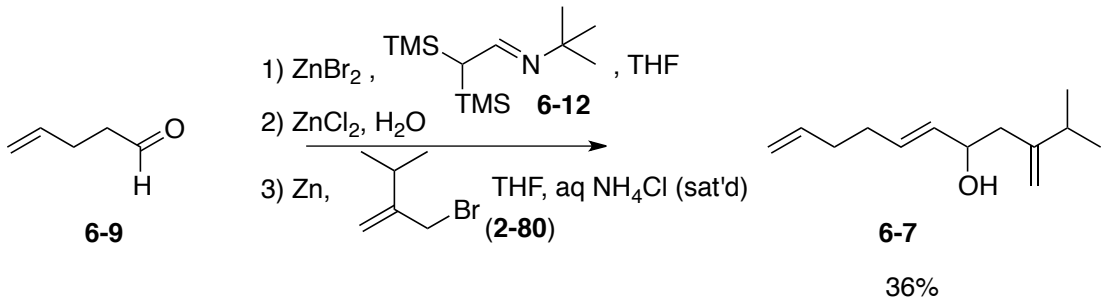
The synthetic route to MEM ether **6-5** began from the known aldehyde **6-9**, prepared according to the method of Whittaker.[4] Our initial plan was to homologate this to the corresponding alpha beta unsaturated compound **6-8** through Wittig chemistry.[5] However we soon abandoned this approach because the isolation of product proved to be problematic. Fractional distillation of the crude reaction mixture afforded only very small amounts (13% yield) of clean aldehyde **6-8**. Additional fractions isolated from distillation were contaminated with what was presumed to be overhomologated product.



6-9 **6-8** 13%

Scheme 6-3. Synthesis of Aldehyde **6-8**

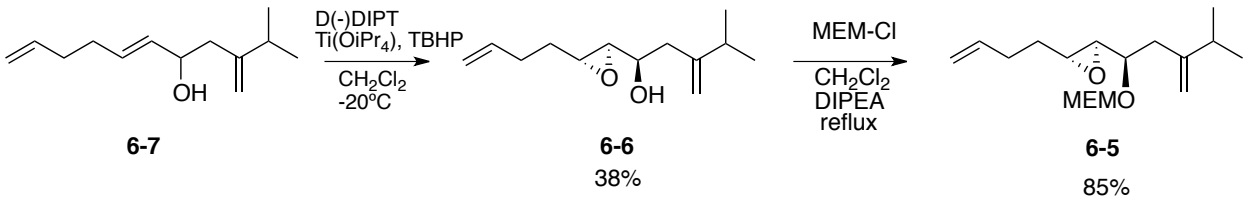
In light of this negative result, we explored a homologation alternative that utilized a Lewis acid - aldimine combination[6] (Scheme 6-4). Since the desired aldehyde **6-8** is volatile, we attempted a one-pot homologation-alkylation protocol. This would prevent any loss of compound that could occur during workup and isolation**.**



Scheme 6-4. Synthesis of Allylic Alcohol **6-7** via a One-Pot Lewis Acid/Aldimine Homologation-Barbier Allylation Strategy

The homologation of aldehyde **6-9** with aldimine **6-12**, $ZnBr_2$ followd by aqueous $ZnCl_2$, proceeded smoothly. In addition, aldehyde **6-8** was alkylated in situ with the Barbier reagent prepared from Zn and 2-bromomethyl-3-methyl-1-butene (**2-80**). This gave the desired allylic alcohol **6-7** in acceptable yield.

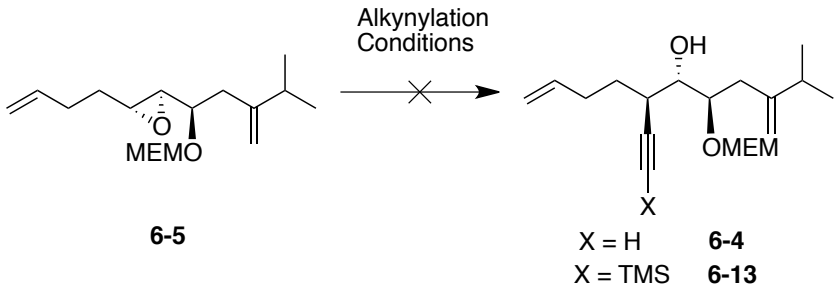
Once the racemic allylic alcohol **6-7** was in hand, subsequent Sharpless asymmetric epoxidation/kinetic resolution (**6-7→6-6**) followed by MEM protection gave protected epoxy alcohol **6-5** (Scheme 6-5).



Scheme 6-5. Synthesis of MEM Protected Epoxy Alcohol **6-5**

6.2.2 Attempted Alkynylation of Epoxide **6-5**

At this point, we screened reaction conditions in hopes of effecting alkynylation of protected epoxy alcohol **6-5** (Scheme 6-6). Unfortunately, all of the conditions screened, including the lithium acetylide ethylene diamine complex, were entirely ineffective. Either starting material was recovered or the reaction conditions produced a mixture of products that were not readily identifiable (Scheme 6-6 and Table 6-1).



Scheme 6-6. Unsuccessful Attempt at Alkynylating Epoxide **6-5**

X	Reaction Conditions	Result
H	Li-acetylide (12 eq.), HMPA/DMSO, rt -> 75ºC 2-2.5 days	No reaction (SM recovered)
TMS	TMS-acetylene (5 eq.), sodium amide (4 eq.), HMPA/DMSO, rt, 5hrs	No reaction (SM recovered)
TMS	TMS-acetylene (5 eq.), n-BuLi (5 eq.), Et_2AlCl (5 eq.), Toluene, -78ºC -> 0ºC -> RT, 2 hrs	No SM, mixture of unidentifiable products
H	Sodium acetylide (3 eq.) DMSO RT -> 90ºC (1 day)	No SM, mixture of unidentifiable products
H	Sodium acetylide (9 eq.) potassium t-butoxide (1.5 eq) HMPA/DMSO RT -> 65ºC 11 days	No reaction (SM recovered)

Table 6-1. Results from the Attempted Alkynylation of Epoxide **6-5**.

Although this result is surprising, an exhaustive SciFinder search of the transformation shown in Figure 6-2 (**I→II)** gave only 4 hits relevant to acyclic substrates.[2, 7] Remarkably all of

these alkynylation examples were of *erythro-trans* epoxy alcohol derivatives of the type III (Figure 6-2).

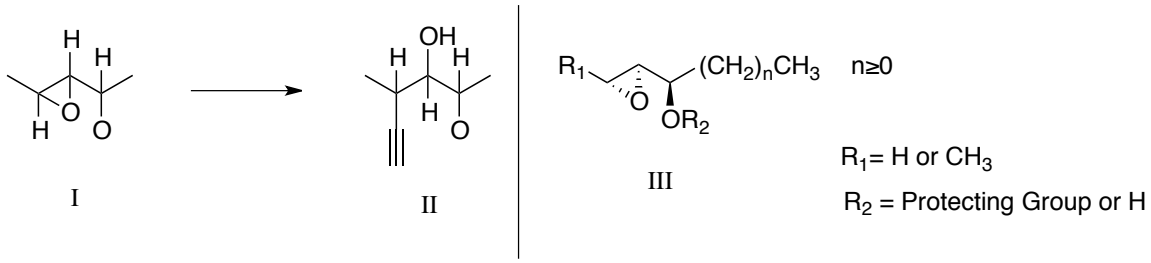
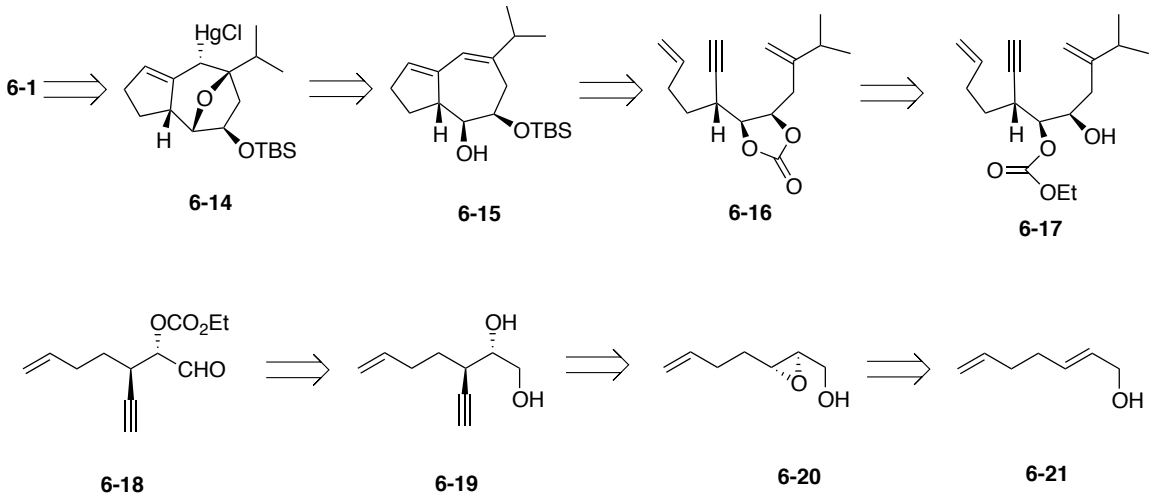


Figure 6-2. Examples of Disubstituted *trans*-Epoxy Alcohols Known to Undergo Alkynylation

To the best of our knowledge, there are no examples of alkynylations at the 3-position of acyclic *trans*-epoxy alcohols with extended chains on both ends.

6.2.3 Redesign of the Synthetic Strategy

To bypass this hurdle, we redesigned our synthetic strategy. Our second approach proceeded by way of *trans* disubstituted epoxide **6-14**, in which a primary alcohol was present at the 1-position. In an early report, Suzuki and coworkers demonstrated that epoxides of this type could be smoothly alkynylated at the 3-position.[7a] Since then there have been many examples in the literature that have demonstrated the successful application of this methodology.



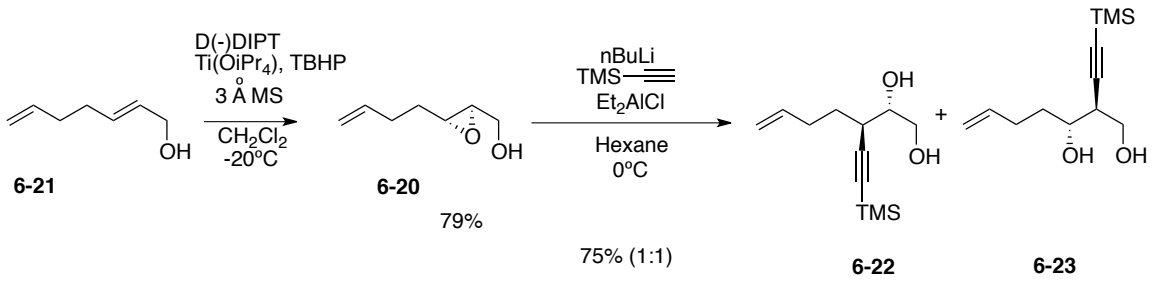
Scheme 6-7. Second Approach: Retrosynthetic Analysis

We decided to plan our second approach to analog **6-1** from alkylmercurial **6-14**, in which the C9 alcohol is protected as a TBS ether. This, like the analogous alkyl mercurial **5-2**, would be derived from the corresponding hydroazulene (**6-15**). The remainder of the synthetic intermediates were also designed to resemble, as closely as possible, what was successfully applied in synthesis of the analogous alkyl mercurial **5-2** (Chapter 5). We felt that this would expedite the synthesis of analog **6-1** by allowing us to use chemistry that we were familiar with.

Thus hydroazulene **6-15** would be derived from a metathesis reaction of carbonate protected ene-yne-ene **6-16**. We envisioned that this substrate could be prepared by an intramolecular carbonate esterification reaction of alcohol **6-17**. We planned on preparing this alcohol via an asymmetric allylation of aldehyde **6-18**, which in turn, could be derived from diol **6-19**. This diol appeared to be readily available through alkynylation of the known epoxy alcohol **6-20**[8] which could be furnished from alcohol **6-21**.

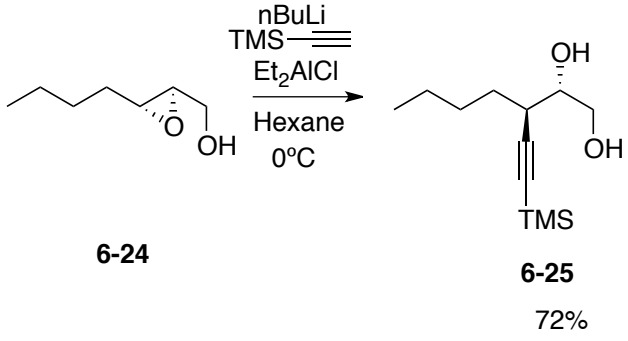
6.2.3.1 Synthesis of Diol **6-19**

The synthesis of diol **6-19** began by way of the known allylic alcohol **6-21**, which we prepared according to a modified version of Naruta's protocol.[9] Although the Sharpless asymmetric epoxidation reaction proceeded smoothly as expected,[8] subsequent alkynylation following Suzuki's organoaluminum[7a] protocol gave a 1:1 mixture of inseparable 1,2 and 1,3-diols **6-22** and **6-23** (Scheme 6-8).



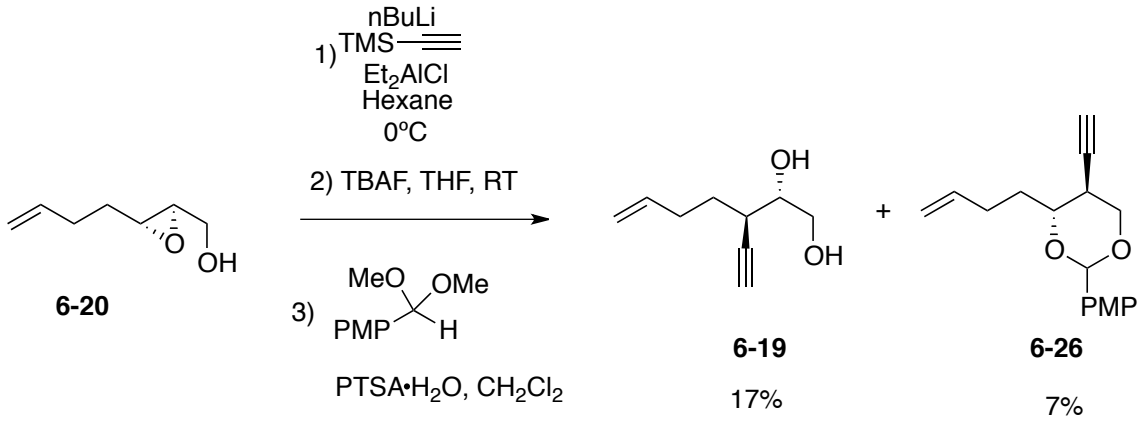
Scheme 6-8. Synthesis of Epoxy Alcohol **6-20** and Alkynylation Following Suzuki's Protocol

Admittedly, the lack of regioselectivity observed in this reaction was not at all anticipated. Suzuki et al. reported that the alkynylation of epoxy alcohol **6-24** underwent addition at the 3 position to give the corresponding 1,2-diol **6-25**, exclusively (Scheme 6- 9).



Scheme 6-9. TMS-Acetylide Opening of Epoxy Alcohol **6-24** by Suzuki et al.

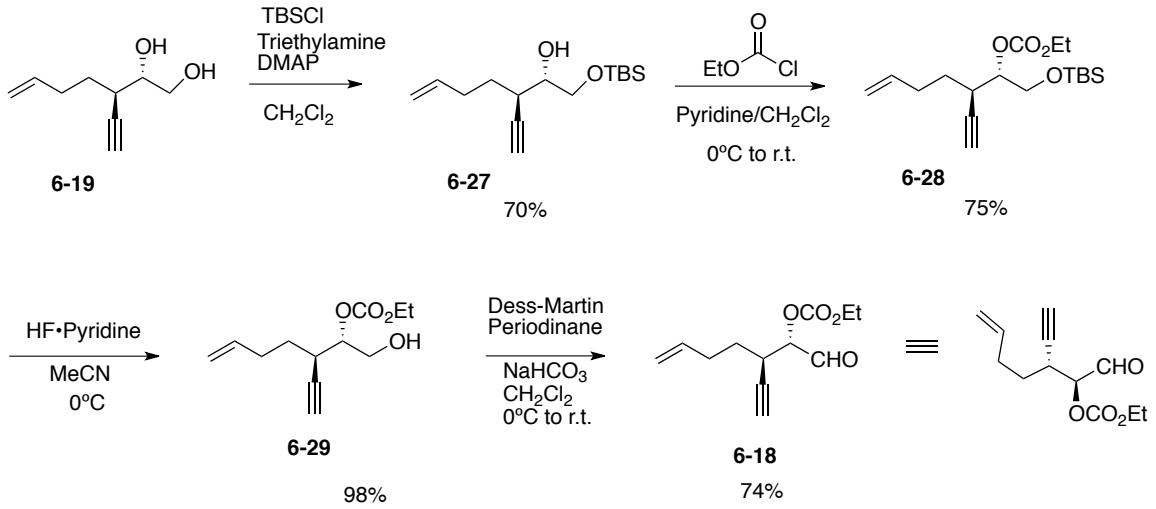
We managed to achieve separation of the 1,2 and 1,3-diols by exploiting the difference in hydrolytic susceptibilities of their corresponding PMP acetals (Scheme 6-10). After TMS deprotection with TBAF, the 1,2 and 1,3 diols were treated with *p*-anisaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid monohydrate monohydrate. This gave, after workup, a mixture of the diol **6-19** and acetal **6-26**; these were easily separated by silica gel chromatography (Scheme 6-10).



Scheme 6-10. Synthesis and Isolation of Diol **6-19**

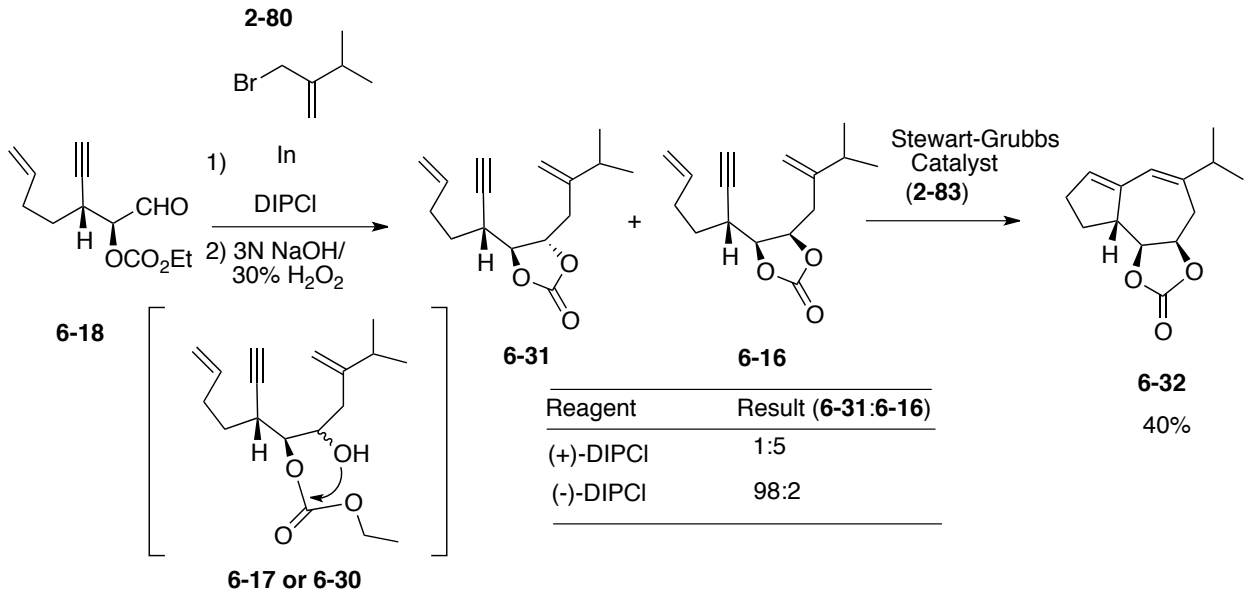
6.2.3.2 Synthesis of Hydroazulene **6-15**

After successful isolation of diol **6-19**, TBS protection of the primary alcohol gave compound **6-27**. Carbonate protection (**6-27→6-28**) followed by desilylation with HF-Pyridine gave alcohol **6-29**. This was oxidized with buffered Dess-Martin periodinane to give aldehyde **6-18** in 74% yield.



Scheme 6-11. Synthesis of Aldehyde **6-18**

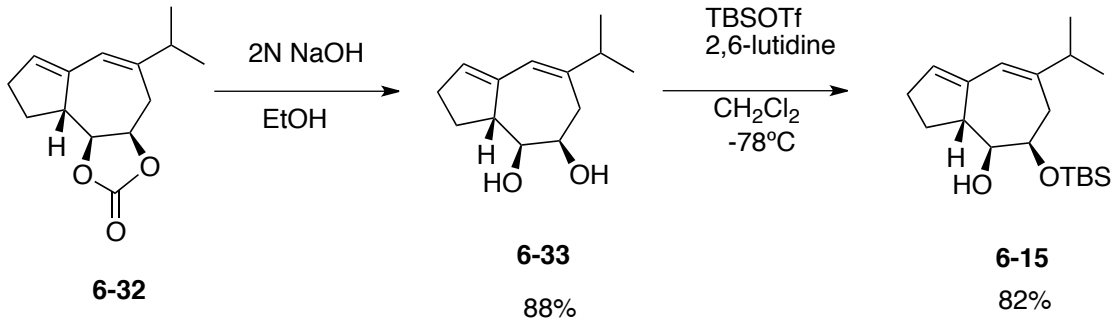
Once aldehyde **6-18** was in hand, we screened allylation conditions according to Singaram's protocol.[10] Since we could not determine, a priori, which chiral reagent would give the desired diastereoselectivity, we prepared allylation reagents from both (+) and (-) DIP-chloride (Scheme 6-12).



Scheme 6-12. Synthesis of Hydroazulene **6-32**

Evidently the desired *cis*-carbonate **6-16**, obtained upon allylation with the reagent prepared from (+)-DIPCl, came from the "mismatched" reagent-substrate combination. The undesired *trans* carbonate **6-31** was obtained almost exclusively upon switching to (-)-DIPCl. Remarkably, in both allylation cases the cyclic carbonate (**6-16** or **6-31**) was obtained directly after work-up by a spontaneous intramolecular carbonate esterification reaction of **6-17** or **6-30**.

After partial purification of carbonate **6-16** by silica gel chromatography, treatment with the Stewart-Grubbs catalyst (**2-79**) in hot toluene gave hydroazulene **6-32** in 40% yield (over 3 steps).

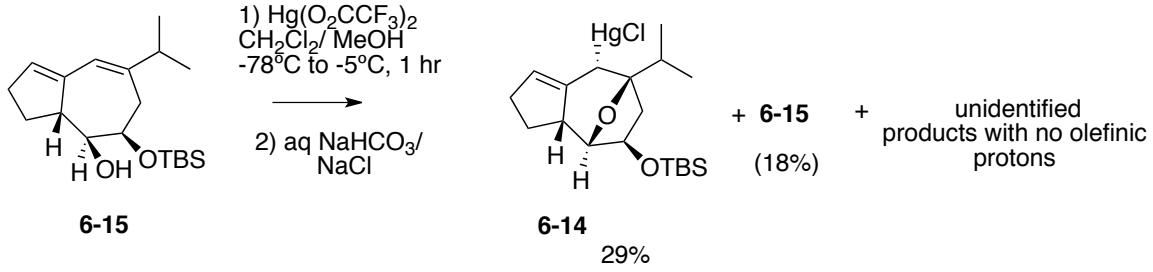


6-32 **6-33** 88% **6-15** 82%

Scheme 6-13. Synthesis of Hydroazulene **6-15**

With hydroazulene **6-32** in hand, carbonate hydrolysis (**6-32→ 6-33)** followed by monoprotection of the less hindered alcohol gave compound **6-15** exclusively (Scheme 6-13). It followed that we proceed with oxymercuration to establish the C7-C10 ether bridge.

6.2.3.3 Synthesis of Alkyl Mercurial **6-14**

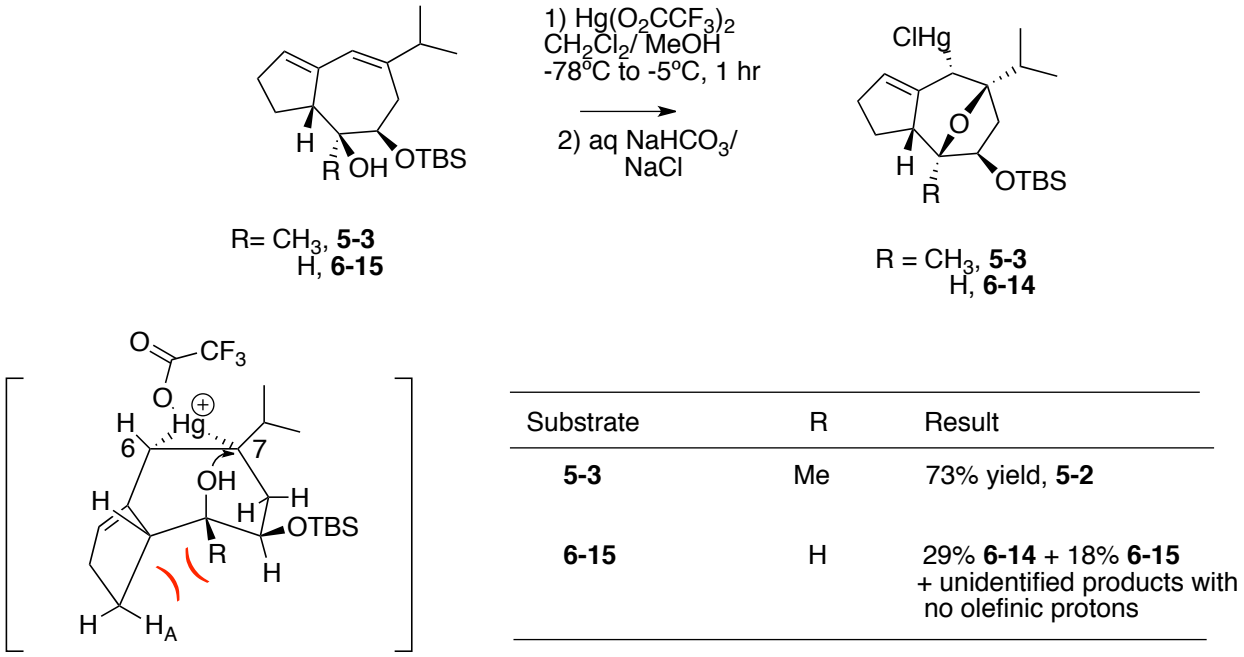


Scheme 6-14. Oxymercuration of Alcohol **6-15**

In contrast to what we observed during the oxymercuration of alcohol **5-3**, treatment of hydroazulene **6-15** with 1.3 eq of $Hg(O_2CCF_3)_2$ gave a mixture of products (Scheme 6-14). After workup and column chromatography, the desired ring closed product **6-14** was obtained in 29% yield along with 18% of recovered starting material. In addition, a fraction was isolated that appeared to contain a mixture of two products. ^{1}H NMR analysis of this fraction indicated the absence of any olefinic protons.

Treatment of hydroazulene **6-15** with excess mercuric trifluoroacetate (~2 equivalents) did not offer any improvement, and ultimately gave rise to the formation of a complex mixture of products (as indicated by crude ^{1}H NMR and TLC analysis).

We rationalized this result based on a "peri" steric interaction between H_A on the cyclopentene ring and the nearby "R" group (Figure 6-3). It appears as though removal of the C10 methyl group eliminates a repulsive interaction that otherwise favors ring closure.



Substrate	R	Result
5-3	Me	73% yield, **5-2**
6-15	H	29% **6-14** + 18% **6-15** + unidentified products with no olefinic protons

Figure 6-3. Comparison of Oxymercuration of Hydroazulene **5-13** and Hydroazulene **6-15**

The ^{1}H NMR spectrum of the major byproduct isolated from this reaction lacked olefinic signals. Thus we believe this scenario gives rise to the formation of products in which both olefins of hydroazulene **6-15** have been oxidized. That is, a second addition of $Hg(O_2CCF_3)_2$ to the remaining cycloheptene olefin of compound **6-14** occurs.

6.3 Conclusion

The synthetic utility of our group's ene-yne-ene metathesis approach has been demonstrated by the successful construction of the C10-desmethyl hydroazulene intermediate **6-15**.

The removal of the C10 methyl group caused a significant decrease in the efficiency of the construction of the C10-C7 oxa-bridge, ultimately lowering the yield of the desired ring closed product **6-14**. This result, although disappointing, is not surprising. We rationalize this observation based on a steric interaction.

The completion of analog **6-1** by way of intermediate **6-14** is currently underway in our laboratories.

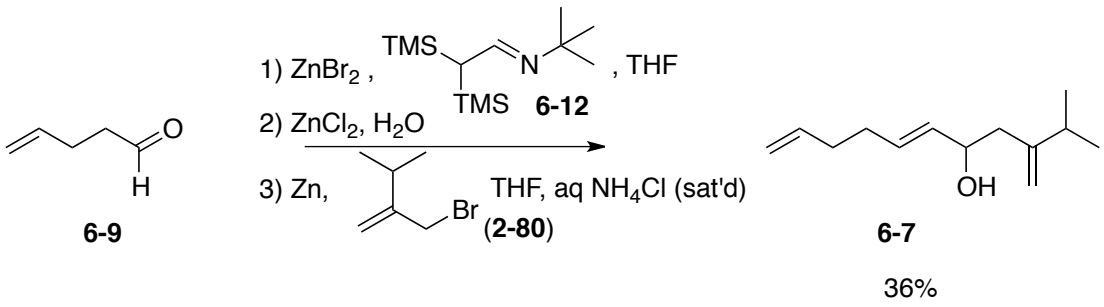
6.4 Experimental Section

General Information

All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC grade hexane and EtOAc, were used in chromatography. Diethyl ether (Et_2O) was distilled from sodium-benzophenone ketyl under argon gas. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin layer chromatography (TLC) performed on Whatman precoated PE SIL G/UV 250 μm layer polyester-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol.

Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh). Infrared spectra were recorded with a Perkin-Elmer 1600 Series FT-IR instrument. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-500 (500 MHz for 1H and 126 MHz for 13C), Varian Inova-400 (400 MHz for 1H and 101 MHz for 13C), or Gemini-2300 (300 MHz for 1H) spectrometer. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-d. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-d set at 77.00 ppm. High-resolution mass spectra were obtained on a Micromass Q-Tof Ultima spectrometer by the Mass Spectrometry Laboratory at the University of Illinois Urbana Champaign.

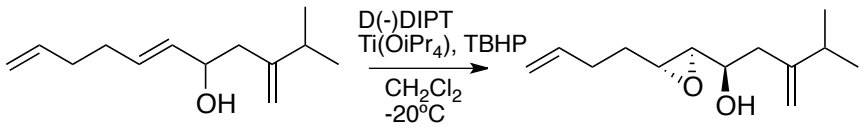
Experimental Procedure/Characterization



Alcohol 6-7. To a stirred solution of aldehyde (prepared by the method of Whittaker[4]) **6-9** (1.010 g, 12.00 mmol) in THF (34 mL) was added anhydrous $ZnBr_2$ (0.243 g, 1.08 mmol). After complete dissolution of the $ZnBr_2$, imine **6-12** (3.192 g, 31.11 mmol) (prepared according to the method of Bellassoued [6]) was added dropwise in THF (6 mL) over 5 minutes. After stirring for 5 hours at room temperature $ZnCl_2$ was added (3.24 g, 24.0 mmol) in 1:1 H_2O/ether (40 mL). After addition of $ZnCl_2$ a precipitate appeared immediately. The solution was allowed to stir for 1 hour and was then placed in an ice bath. 2-Bromo-methyl-3-methyl-1-butene was added (**2-80**) (5.81 g, 35.6 mmol) followed by sat. NH_4Cl solution (20 mL). At this point the solution became homogeneous. Zn dust was added (3.24 g, 49.6 mmol) and the solution was allowed to stir overnight and slowly warm to room temperature. The reaction mixture was filtered through a celite pad and the filtrate was transferred to a separation funnel. The aqueous layer was extracted with methylene chloride (3 x 20 mL). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography to give alcohol **6-7** (848 mg, 36%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 18.4, 9.8, 6.1 Hz, 1H), 5.75 – 5.64 (m, 1H), 5.50 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.02 (br d, *J* = 17.2 Hz, 1H), 4.96 (br d, *J* = 10.1 Hz, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 4.25 – 4.15 (m, 1H), 2.33 – 2.16 (m, 4H), 2.16 – 2.11 (m, 3H), 1.80 (d, *J* = 2.4 Hz, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 138.1, 132.7, 131.0, 114.7, 110.0, 70.3, 43.3, 33.5, 33.3, 31.5, 21.9, 21.6. IR (neat) νmax:

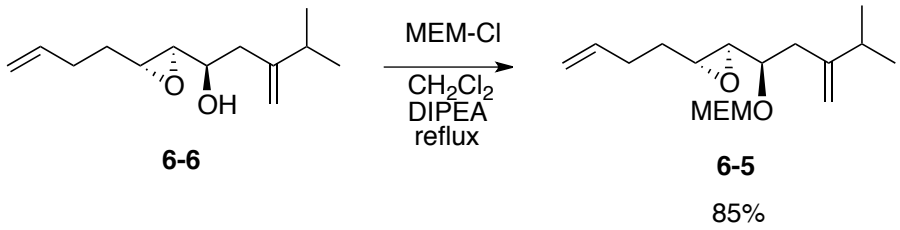
3362, 3079, 2962, 2928, 2872, 1641, 970, 911. HRMS [ES+] calc for $C_{13}H_{22}ONa$ $[M+Na]^+$ 217.1568, found 217.1561



6-7 **6-6**
38%

Epoxide 6-6. To a stirred solution of allylic alcohol **6-7** (147 mg, 0.76 mmol), and 3Å molecular sieves (50 mg) in methylene chloride (2 mL) was added (−)-diisopropyl D-tartrate (28 mg, 0.12 mmol). After stirring for 10 minutes the solution was cooled to -20ºC and then a solution of titanium (IV) isopropoxide (23 mg, 0.079 mmol) in methylene chloride (2 mL) was added. The solution was allowed to stir for one hour with the temperature kept between -20ºC and -30ºC. *Tert*-butylhydroperoxide solution was added (5.5 M in decane, 85 μL, 0.47 mmol) in methylene chloride (1 mL), and the solution was allowed to stir overnight at -20ºC. The reaction mixture was quenched by adding water (0.4 mL) and the solution was allowed to slowly warm to 0ºC. A solution of NaOH/NaCl was added (8.3M NaOH, 0.95 M NaCl, 0.08 mL) and the reaction mixture was allowed to warm to room temperature. The heterogeneous mixture was filtered through a pad of celite, and the celite pad was washed with methylene chloride. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was subjected to column chromatography to give epoxy alcohol **6-6** (61 mg, 38%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.06 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.92 (s, 1H), 4.84 (s, 1H), 3.90 – 3.75 (m, 1H), 3.02 (t, *J* = 5.9 Hz, 1H), 2.82 – 2.77 (m, 1H), 2.37 (dd, *J* = 14.5, 4.6 Hz, 1H), 2.31 – 2.14 (m, 4H), 2.01 (d, *J* = 2.3 Hz, 1H), 1.66 (q, *J* = 7.0 Hz, 2H), 1.05 (app t, *J* = 5.9 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 151.6, 137.5, 115.3, 109.8, 67.5, 60.7, 55.2, 39.2, 33.5, 30.9, 30.2, 21.8, 21.6. IR (neat) νmax: 3447, 3080, 2962, 2930, 2872, 1642, 911. HRMS [ES+] calc for $C_{13}H_{22}O_2Na$ $[M+Na]^+$ 233.1517, found 233.1525

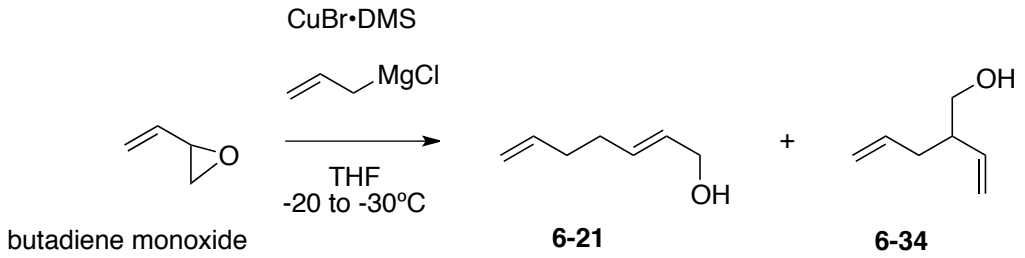


6-6 **6-5**

85%

Epoxide 6-5. To a stirred solution of epoxy alcohol **6-6** (99 mg, 0.48 mmol) in methylene chloride (4 mL) was added diisopropylethylamine (0.20 mL, 150 mg, 1.2 mmol) followed by 2-methoxyethoxymethyl chloride (80 μL, 87 mg, 0.70 mmol). The solution was brought to reflux and allowed to stir for 4 hours. After cooling to room temperature the reaction mixture was quenched with sat. $NaHCO_3$ solution (5 mL), and diluted with methylene chloride (40 mL). The organic layer was washed with sat. NH_4Cl solution (3 x 10 mL), dried over $MgSO_4$, and then filtered. After removal of the solvent in vacuo the crude residue was purified by column chromatography (10:1:0.5 Hex/EtOAc/triethylamine) to give epoxide **6-5** (120 mg, 85%) as a colorless oil.

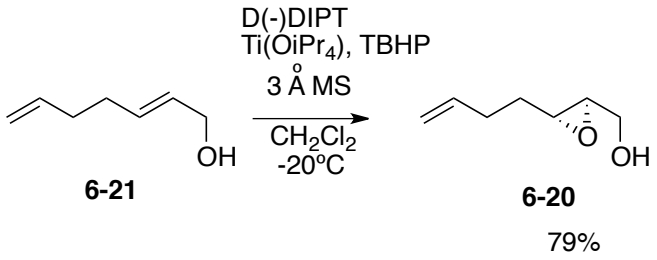
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.99 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.86 – 4.81 (m, 2H), 4.78 (d, *J* = 7.1 Hz, 1H), 4.66 (d, *J* = 7.1 Hz, 1H), 3.71 – 3.60 (m, 3H), 3.52 (dd, *J* = 5.1, 4.2 Hz, 2H), 3.37 (s, 3H), 2.98 (ddd, *J* = 6.8, 4.8, 2.2 Hz, 1H), 2.72 (dd, *J* = 5.5, 2.2 Hz, 1H), 2.43 – 2.12 (m, 5H), 1.76 – 1.54 (m, 2H), 1.04 (d, *J* = 4.2 Hz, 3H), 1.02 (d, *J* = 4.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 151.5, 137.5, 115.2, 109.5, 94.7, 74.9, 71.7, 67.0, 59.5, 59.0, 56.9, 38.1, 33.4, 31.2, 30.1, 21.7, 21.5. IR (neat) νmax: 3080, 2962, 2930, 2876, 1641, 1456, 1111, 1048, 1024, 911. HRMS [ES+] calc for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2042, found 321.2043



71% (**6-21**:**6-34**, 6.8:1)

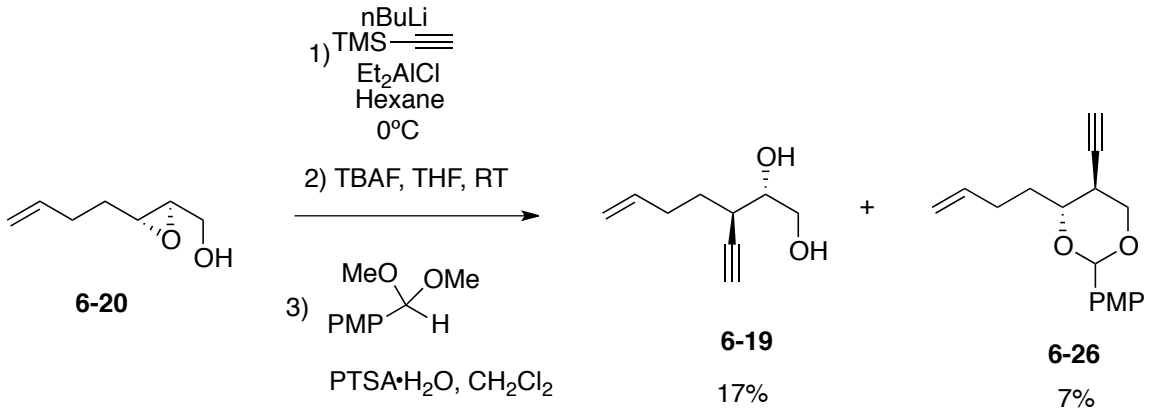
Allylic Alcohol 6-21. This compound was prepared according to a modified procedure by Naruta.[9] A stirred solution of butadiene monoxide (25 g, 0.36 mol) in THF (250 mL) was cooled to -30ºC. Copper bromide-dimethylsulfide complex was added (2.47 g, 12.0 mmol) and the solution was allowed to stir for 2 hours with the temperature kept between -20ºC and -30ºC. Allyl magnesium chloride solution was added dropwise over one hour (2M in THF, 270 mL, 540 mmol), and the solution was allowed to stir for 12 hours. After warming to room temperature over one hour the reaction mixture was poured into sat. NH_4Cl solution (300 mL). After the phases separated, the aqueous layer was extracted with ether (3 x 150 mL). The combined organic solution was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was subjected to Kugelrohr distillation (0.5 mmHg, bath temp 130ºC) to give an inseparable mixture of alcohols **6-21** and **6-34** (28.427 g, 71%) along with a small amount of minor contaminants; colorless oil. This mixture was used directly in the next step without further purification. The ratio of **6-21** to **6-34** was obtained by ^{1}H NMR analysis.

Major Isomer, Compound 6-21: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 – 5.49 (m, 3H), 5.06 – 4.99 (m, 1H), 4.99 – 4.95 (m, 1H), 4.09 (d, J = 4.6 Hz, 2H), 2.21 – 2.10 (m, 4H), 1.35 (br s, 1H). The data was consistent with the literature.[11]



Epoxide 6-20. To a stirred solution of allylic alcohol **6-21** (28.43 g, 253.4 mmol), and 3Å molecular sieves (20 g) in methylene chloride (800 mL) was added (−)-diisopropyl D-tartrate (9.131 g, 38.98 mmol). After stirring for 10 minutes the solution was cooled to -20ºC and then a solution of titanium (IV) isopropoxide (7.626 g, 26.83 mmol) in methylene chloride (20 mL) was added. An additional portion of methylene chloride was added (380 mL) and the solution was allowed to stir for one hour with the temperature kept between -20ºC and -30ºC. *Tert*-butylhydroperoxide solution was added (5.5 M in decane, 93.5 mL, 514 mmol) slowly, and the solution was allowed to stir overnight at -20ºC. The reaction mixture was quenched by adding water (60 mL) and the solution was allowed to slowly warm to 0ºC. A solution of NaOH/NaCl was added (8.3M NaOH, 0.95 M NaCl, 10 mL) and the reaction mixture was allowed to warm to room temperature. The heterogeneous mixture was filtered through a pad of celite, and the celite pad was washed with methylene chloride. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was subjected to column chromatography (5:1 Hex/EtOAc) to give epoxy alcohol **6-20** (25.976 g, 80%) as a yellow oil along with a small amount of a minor byproduct. This mixture was used directly in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.12 – 4.96 (m, 2H), 3.91 (ddd, *J* = 12.5, 5.5, 2.6 Hz, 1H), 3.63 (ddd, *J* = 12.7, 7.3, 4.2 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.31 – 2.13 (m, 2H), 1.68 (td, *J* = 7.5, 5.7 Hz, 2H), 1.26 (s, 1H). The data were in agreement with the literature.[8] The enantiomeric excess was determined to be 86% based on ^{1}H NMR analysis of the known (+)-MTPA ester.[8]



Alcohol 6-19. A stirred solution of trimethylsilyl acetylene (173 mL, 1.22 mol) in *n*-hexane (250 mL) was cooled to -40ºC and then *n*BuLi was added slowly (2.5 M, 405 mL, 1.0 mol). Once the addition was complete the reaction flask was transferred to an ice bath. After stirring for 20 minutes, the reaction vessel was cooled to -40ºC and diethylaluminum chloride solution was added slowly (1.0 M, 608 mL, 0.61 mol). Once addition was complete the solution was allowed to warm to room temperature. After stirring for one hour the reaction vessel was cooled to 0ºC (ice bath) and then a solution of epoxy alcohol **6-20** (25.976 g, 202.70 mmol) in *n*-hexane (20 mL) was added slowly. The solution was allowed to warm to room temperature overnight. The reaction was quenched by slowly pouring into cold 1N HCl solution (300 mL). After the quench was complete the biphasic solution was filtered through a celite pad, which was subsequently washed with ether. The filtrate was transferred to a separation funnel and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic solution was dried over $MgSO_4$, filtered, and then concentrated in vacuo. The crude residue was partially purified by column chromatography (4:1 Hex/EtOAc) to give the intermediate TMS protected alkynes. ^{1}H NMR analysis of the crude residue showed ~1:1 ratio of 1,2 and 1,3-diols. This mixture was dissolved in THF (200 mL), cooled to 0ºC and then TBAF solution was added (1.0 M in THF, 150 mL, 0.15 mol). The solution was allowed to slowly warm to room temperature over 6 hours. The reaction mixture was quenched with sat. NH_4Cl solution (200 mL) and the aqueous layer was extracted with EtOAc (250 mL in three portions). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was partially purified by column chromatography (2:1 Hex/EtOAc) to give the deprotected diol intermediates.

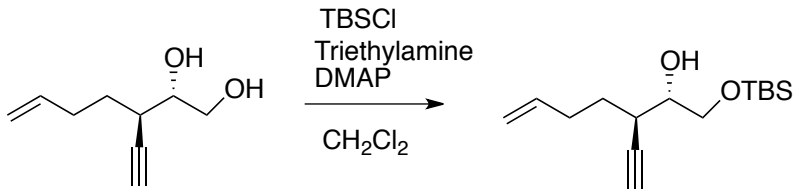
This mixture was taken up in methylene chloride (350 mL) and then p-anisaldehyde dimethyl acetal was added (19.1 g, 0.105 mol). *P*-toluenesulfonic acid monohydrate (2.0 g, 11 mmol) was added in three portions over 6 hours (6.0 g total, 33 mmol) and at that point ^{1}H NMR analysis of an aliquot of the reaction mixture revealed complete hydrolysis of the 1,2-PMP acetal. The reaction was quenched with sat. $NaHCO_3$ (250 mL) and transferred to a separation funnel. The organic phase was washed with sat. $NaHCO_3$ (2 x 50 mL) and the combined aqueous phase was extracted with EtOAc (200 mL in three portions). The combined organic solution was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (20:1 Hex/EtOAc to 100% EtOAc) to give three fractions. The first fraction contained the 1,3- PMP acetal **6-26** (3.758 g, 7%). The second fraction contained a mixture of anisaldehyde and **6-26** (14.968 g). The third fraction contained the 1,2-diol **6-19** (5.415 g, 17%).

PMP acetal 6-26: An analytical sample was obtained by recrystallization from 1:1 ether/isopropyl alcohol. mp: 75-76ºC; white crystals.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.37 (m, 2H), 6.97 – 6.85 (m, 2H), 5.86 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.46 (s, 1H), 5.07 (dd, *J* = 17.4, 1.8 Hz, 1H), 5.00 (br d, *J* = 10.3 Hz, 1H), 4.33 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.84 – 3.78 (m, 4H), 3.73 (td, *J* = 9.5, 2.6 Hz, 1H), 2.67 (dddd, *J* = 10.9, 9.8, 4.8, 2.4 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.28 – 2.18 (m, 1H), 2.16 (d, *J* = 2.4 Hz, 1H), 2.10 – 2.01 (m, 1H), 1.79 – 1.70 (m, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 160.0, 138.1, 130.6, 127.2, 114.9, 113.6, 101.1, 80.1, 79.6, 72.5, 70.2, 55.3, 32.9, 32.7, 29.1. IR (neat) νmax: 3281, 1640, 1615, 1520, 1252, 1132, 830. HRMS [ES+] calc for $C_{17}H_{21}O_3$ $[M+H]^+$ 273.1491, found 273.1493

1,2-Diol 6-19. An analytical sample was obtained by recrystallization from 1:1 ether/hexanes. mp: 62-65ºC.

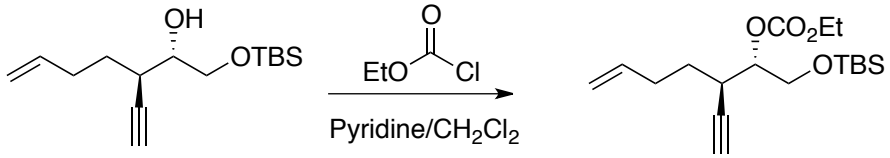
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.07 (br d, *J* = 17.1 Hz, 1H), 5.02 – 4.96 (m, 1H), 3.87 (dd, *J* = 11.2, 3.0 Hz, 1H), 3.77 – 3.62 (m, 2H), 2.61 – 2.10 (m, 6H), 1.83 – 1.72 (m, 1H), 1.62 – 1.51 (m, 1H). ^{13}C NMR (126 MHz, CDCl3) δ 137.7, 115.3, 83.5, 73.4, 72.1, 64.7, 34.9, 31.1, 29.8. IR (neat) νmax: 3297, 3079, 2958, 2921, 2870, 2838, 2110. HRMS [ES+] calc for $C_9H_{14}O_2Na$ $[M+Na]^+$ 177.0891, found 177.0893



6-19 **6-27** 70%

TBS ether 6-27. To a stirred solution of alcohol **6-19** (4.064 g, 26.35 mmol), triethylamine (4.45 mL, 31.9 mmol), and DMAP (169 mg, 1.38 mmol) was added *tert*-butyldimethylsilylchloride (4.755 g, 31.55 mmol) in one portion. After stirring for 10 days at room temperature the reaction mixture was washed with 10% citric acid (3 x 100 mL), dried over $MgSO_4$, and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (50:1 Hex/EtOAc) to give TBS ether **6-27** (4.979 g, 70%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.00 – 4.96 (m, 1H), 3.85 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.71 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.57 (ddd, *J* = 8.5, 6.2, 3.5 Hz, 1H), 2.56 (s, 1H), 2.50 (dddd, *J* = 10.5, 8.4, 3.9, 2.4 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.21 – 2.12 (m, 1H), 2.11 (d, *J* = 2.5 Hz, 1H), 1.86 (dddd, *J* = 13.3, 9.6, 7.0, 3.9 Hz, 1H), 1.61 – 1.51 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 138.0, 115.0, 84.0, 73.1, 71.5, 65.0, 34.4, 31.1, 29.8, 25.9, 18.3, -5.37, -5.43. IR (neat) νmax: 3565, 3467, 3311, 3078, 2955, 2929, 2885, 2858, 1642, 1472, 1464, 1362, 1255, 1115, 837, 778. HRMS [ES+] calc for $C_{15}H_{28}O_2NaSi$ $[M+Na]^+$ 291.1756, found 291.1756

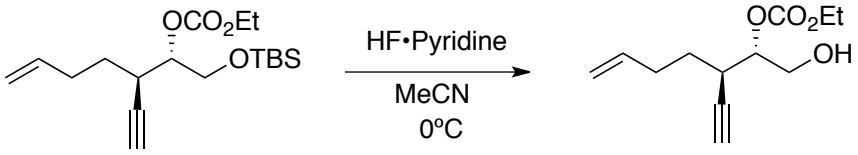


6-27 **6-28** 75%

Carbonate 6-28. A stirred solution of alcohol **6-27** (4.117 g, 15.33 mmol) in 4:1 pyridine/CH_2Cl_2 solution (100 mL) was cooled to 0ºC. Ethyl chloroformate was added dropwise (14.6 mL, 153 mmol) and the solution was allowed to slowly warm to room temperature. After

stirring for 24 hours the reaction mixture was diluted with methylene chloride (80 mL) and washed with 10% citric acid (6 x 30 mL). The organic solution was dried over $MgSO_4$ and concentrated in vacuo to give carbonate **6-28** (3.927 g, 75%) as a pale red oil. The crude residue was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.99 – 4.96 (m, 1H), 4.75 (ddd, *J* = 7.8, 6.3, 3.5 Hz, 1H), 4.20 (qd, *J* = 7.1, 4.0 Hz, 2H), 3.94 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.84 (dd, *J* = 11.2, 6.3 Hz, 1H), 2.78 (dddd, *J* = 10.4, 7.8, 4.1, 2.5 Hz, 1H), 2.39 – 2.30 (m, 1H), 2.20 – 2.10 (m, 2H), 1.73 – 1.63 (m, 1H), 1.55 (dddd, *J* = 13.0, 10.4, 9.3, 5.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 137.6, 115.3, 82.7, 79.0, 71.9, 64.0, 62.7, 32.3, 31.1, 29.5, 25.8, 18.2, 14.2, -5.47, -5.53. IR (neat) νmax: 3311, 3077, 2955, 2930, 2884, 2858, 1747, 1258, 837. HRMS [ES+] calc for $C_{18}H_{33}O_4[M+H]^+$ 341.2148, found 341.2146

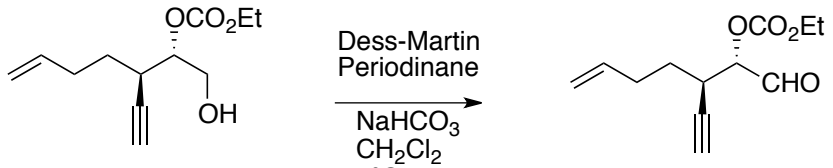


6-28 **6-29**

98%

Alcohol 6-29. A stirred solution of carbonate **6-28** (3.927 g, 11.53 mmol) in acetonitrile (180 mL) was cooled to 0ºC. HF-Py was added (~70% HF, 18.4 mL) and the solution was allowed to stir for 1.5 hours. The reaction mixture was poured into a biphasic solution of 1:1 methylene chloride/sat. $NaHCO_3$ (400 mL). The aqueous layer was extracted with methylene chloride (200 mL in three portions). The combined organic solution was washed with 10% citric acid (200 mL in 4 portions) followed by sat. $NaHCO_3$ (200 mL in 4 portions). The combined organic solution was dried over $MgSO_4$ and then filtered. Removal of the solvent in vacuo gave alcohol **6-29** (2.547 g, 98%) as a pale yellow oil. The crude product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 0H), 5.07 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.02 – 4.97 (m, 1H), 4.73 (ddd, *J* = 8.0, 5.4, 3.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.02 – 3.90 (m, 2H), 2.83 (tdd, *J* = 7.9, 4.2, 2.5 Hz, 1H), 2.41 – 2.30 (m, 1H), 2.25 – 2.11 (m, 2H), 1.94 – 1.84 (m, 1H), 1.74 – 1.49 (m, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 155.0, 137.3, 115.5, 82.2, 79.5, 72.4, 64.4, 62.9, 32.5, 31.0, 30.0, 14.2. IR (neat) νmax: 3436, 3295, 3078, 2980, 2934, 2873, 1745, 1641, 1397, 1375, 1261. HRMS [ES+] calc for $C_{12}H_{18}O_4Na[M+Na]^+$ 249.1103, found 249.1102

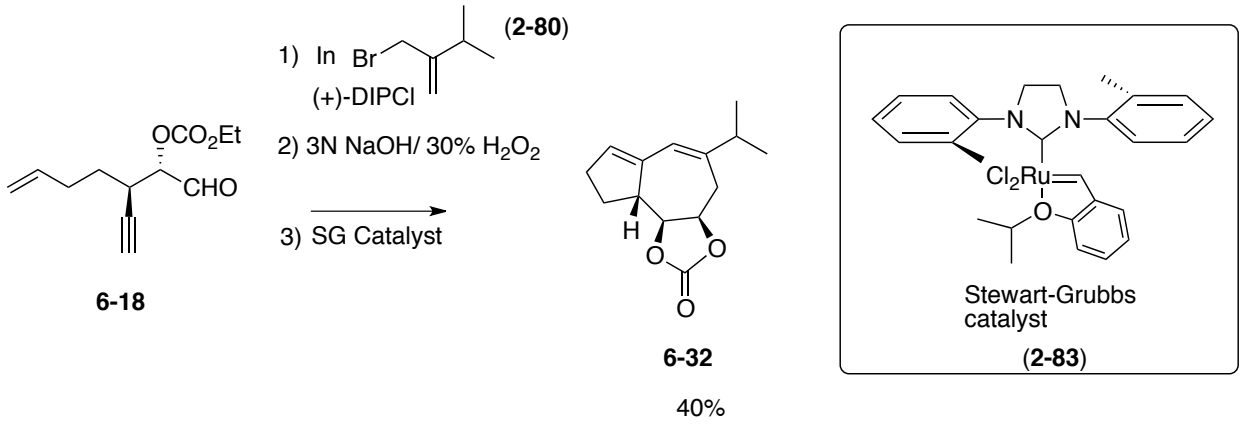


6-29 **6-18**

74%

Aldehyde 6-18. To a stirred solution of alcohol **6-29** (4.323 g, 19.11 mmol) in methylene chloride (80 mL) was added $NaHCO_3$ (35.499 g, 422.57 mmol). The reaction mixture was cooled to 0ºC and then Dess-Martin periodinane was added in one portion (10.58 g, 24.94 mmol). The heterogeneous mixture was allowed to slowly warm to room temperature. After stirring for 1.5 hours the reaction mixture was diluted with methylene chloride (100 mL) and transferred to a separation funnel. The organic layer was washed with sat. $NaHCO_3$ (6 x 50 mL), dried over $MgSO_4$, and then filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (10:1 to 5:1 Hex/EtOAc) to give aldehyde **6-18** (3.179 g, 74%) as a pale yellow oil.

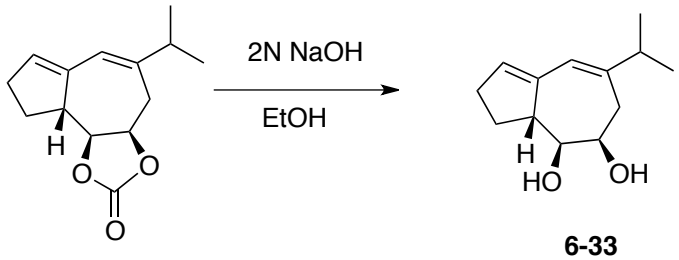
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 0.8 Hz, 1H), 5.77 (dddd, *J* = 17.3, 10.2, 7.2, 6.0 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.04 – 4.98 (m, 1H), 4.91 (d, *J* = 6.4 Hz, 1H), 4.31 – 4.21 (m, 2H), 2.96 – 2.89 (m, 1H), 2.40 – 2.31 (m, 1H), 2.25 (d, *J* = 2.5 Hz, 1H), 2.23 – 2.13 (m, 1H), 1.78 – 1.64 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 154.4, 136.8, 116.0, 81.0, 80.6, 73.3, 65.0, 31.8, 30.7, 29.5, 14.1. IR (neat) νmax: 3291, 3080, 2983, 2932, 2844, 1741, 1373, 1260. HRMS [ES+] calc for $C_4H_{17}N_6O_3Si[M]^+$ 225.1131, found 225.1133



Carbonate 6-32. The allylation portion of this reaction sequence was performed according to a modified procedure of Singaram et al.[10] To a suspension of indium powder (3.147 g, 27.41 mmol) in freshly distilled THF (7 mL) was added a solution of (+)-B-chlorodiisopinocampheylborane (weighed in a glove bag) (8.581 g, 26.75 mmol) in THF (20 mL). 2-Bromo-methyl-3-methyl-1-butene (**2-80**) was added (4.386 g, 26.90 mmol) and the solution was allowed to stir at room temperature under a positive pressure of argon. After stirring for 1 hour the reaction mixture became very dark and the solution was diluted with hexanes (54 mL). After stirring for 30 minutes a bright orange precipitate appeared and the solution was filtered under argon. The filtrate was cooled to -78ºC and the reaction mixture became heterogeneous. A solution of aldehyde **6-18** (3.179 g, 14.18 mmol) in THF (27 mL) was added dropwise, and the solution was allowed to stir at -78ºC for one hour and then slowly warm to room temperature. After stirring at room temperature for 5 hours the reaction mixture was concentrated in vacuo and then dissolved in THF (100 mL). The solution was cooled to -78ºC and then a solution of 1:1 3N NaOH (aq)/30% H_2O_2 (aq) (100 mL) was added while stirring. The reaction mixture was allowed to slowly warm to room temperature. After 18 hours the reaction mixture was diluted with ether (100 mL) and brine (100 mL) and transferred to a separation funnel. The aqueous layer was extracted with ether (3 x 100 mL). The combined organic solution was dried over $MgSO_4$ and then filtered. After removal of the solvent in vacuo the crude residue was partially purified by column chromatography (30:1 Hex/EtOAc) to give the intermediate carbonate (3.448 g, 93%). ^{1}H NMR analysis revealed a ~5:1 mixture of diastereomers in addition to the presence of some terpene byproducts. This intermediate was dissolved in toluene (440 mL) and then the temperature of the solution was brought to 80ºC. The Stewart-Grubbs catalyst was added in one portion (1.51 g, 2.64 mmol) and the solution was

allowed to stir at 80ºC for 19 hours. The reaction mixture was cooled to room temperature and the solvent was removed in vacuo. The crude residue was subjected to column chromatoghraphy (30:1 to 20:1 Hex/EtOAc) to give carbonate **6-32** (1.229 g, 40%) as a white solid; mp: 88-93ºC.

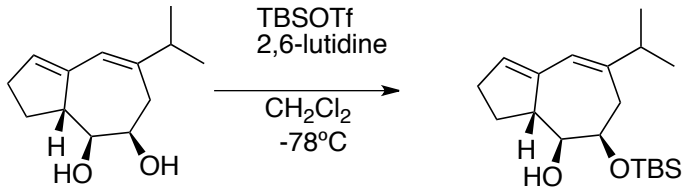
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.71 (d, *J* = 2.5 Hz, 1H), 4.73 (ddd, *J* = 12.2, 8.4, 3.7 Hz, 1H), 4.50 (dd, *J* = 10.9, 8.4 Hz, 1H), 3.48 – 3.36 (m, 1H), 2.97 (t, *J* = 13.2 Hz, 1H), 2.51 – 2.24 (m, 5H), 1.95 – 1.84 (m, 1H), 1.03 (d, *J* = 3.4 Hz, 3H), 1.02 (d, *J* = 3.4 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 154.1, 140.4, 139.0, 132.6, 122.3, 82.5, 77.9, 46.2, 37.4, 30.8, 30.1, 28.5, 20.78, 20.76. IR (neat) νmax: 2957, 1771, 1058. HRMS [ES+] calc for $C_{14}H_{18}O_3Na[M+Na]^+$ 257.1154, found 257.1153



6-32 **6-33** 88%

Diol 6-33. To a stirred solution of carbonate **6-32** (1.229 g, 5.246 mmol) in ethanol (30 mL) was added 2N NaOH (30 mL). The reaction mixture was stirred for 10 minutes and was quenched with sat. NH_4Cl solution (100 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and transferred to a separation funnel. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was subjected to column chromatography (5:1 to 2:1 Hex/EtOAc) to give diol **6-33** (0.966 g, 88%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (s, 1H), 5.55 (d, *J* = 2.4 Hz, 1H), 3.81 (ddd, *J* = 10.1, 4.4, 2.1 Hz, 1H), 3.64 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.31 (br s, 2H), 2.89 – 2.80 (m, 1H), 2.73 (dd, *J* = 16.2, 9.9 Hz, 1H), 2.44 – 2.33 (m, 1H), 2.32 – 2.14 (m, 3H), 1.99 (d, *J* = 16.6 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.00 (d, *J* = 1.6 Hz, 3H), 0.98 (d, *J* = 1.5 Hz, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 145.26, 141.18, 129.85, 120.52, 76.18, 72.11, 48.77, 37.33, 33.67, 30.64, 29.94, 21.25, 20.93. IR (neat) νmax: 3382, 3036, 2959, 2929, 2870, 2847, 1065, 1028. HRMS [ES+] calc for $C_{13}H_{20}O_2Na[M+Na]^+$ 231.1361, found 231.1360

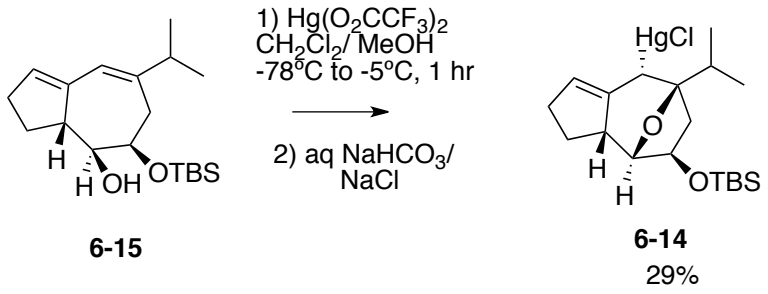


6-33 **6-15**

82%

TBS ether 6-15. A stirred solution of diol **6-33** (966 mg, 4.64 mmol) and 2,6-lutidine (1.6 mL, 14 mmol) in methylene chloride (230 mL) was cooled to -78ºC. A solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.28 mL, 5.57 mmol) in methylene chloride (50 mL) was added and the solution was allowed to stir at -78ºC for 5 minutes. The reaction mixture was quenched with sat. $NaHCO_3$ solution (100 mL) and allowed to warm to 0ºC. The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with methylene chloride (100 mL in three portions). The combined organic solution was washed with 10% citric acid (3 x 50 mL) followed by sat. $NaHCO_3$ (1 x 50 mL). The organic solution was then dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (30:1 Hex/EtOAc) to give TBS ether **6-15** (1.228 g, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.55 (s, 1H), 3.76 (ddd, *J* = 10.4, 4.9, 1.6 Hz, 1H), 3.60 (dd, *J* = 8.4, 4.9 Hz, 1H), 3.08 (d, *J* = 1.3 Hz, 1H), 2.93 – 2.76 (m, 2H), 2.51 – 2.39 (m, 1H), 2.36 – 2.18 (m, 3H), 2.02 – 1.93 (m, 1H), 1.77 (d, *J* = 16.5 Hz, 1H), 1.02 (d, *J* = 5.3 Hz, 3H), 1.01 (d, *J* = 5.2 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 146.6, 141.2, 129.5, 120.7, 75.9, 73.7, 49.1, 37.4, 33.3, 30.9, 29.8, 25.8, 21.6, 21.0, 18.0, -4.5, -5.0. IR (neat) νmax: 3552, 2956, 2929, 2856, 1464, 1255, 1075. HRMS [ES+] calc for $C_{19}H_{34}O_2NaSi[M+Na]^+$ 345.2226, found 345.2220.



6-15 **6-14** 29%

Alkyl Mercurial 6-14. A stirred solution of alcohol **6-15** (37 mg, 0.11 mmol) in methylene chloride (4 mL) was cooled to -78ºC. A solution of mercury trifluoroacetate (78 mg, 0.18 mmol) in methylene chloride (1 mL) and methanol (0.02 mL) was added and the reaction mixture was allowed to warm to 0ºC over 30 minutes. The reaction was quenched by adding a 1:1 sat. $NaHCO_3$ sat. NaCl solution (4 mL). The reaction mixture was transferred to a separation funnel and the aqueous layer was extracted with methylene chloride (30 mL in 3 portions). The combined organic solution was washed with $NaHCO_3$ sat. (2 x 10 mL), dried over $MgSO_4$, and filtered. After removal of the solvent in vacuo the crude residue was subjected to column chromatography (30:1 to 10:1 Hex/EtOAc) to give recovered starting material **6-15** (15 mg, 19%), and alkyl mercurial **6-14** (18 mg, 29%) as a brown oil. A fraction was isolated (24 mg) that contained no olefinic protons.

Alkyl Mercurial **6-14**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (m, 1H), 4.25 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.10 (d, *J* = 5.0 Hz, 1H), 3.15 (s, 1H), 2.85 (m, 1H), 2.39 – 2.33 (m, 1H), 2.12 – 2.03 (m, 1H), 2.03 – 1.91 (m, 2H), 1.86 – 1.78 (m, 1H), 1.57 – 1.48 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 143.2, 127.1, 90.2, 88.1, 72.9, 60.3, 50.9, 47.8, 36.5, 31.0, 25.8, 24.6, 18.8, 18.0, 17.6, -4.5, -4.7. IR (neat) νmax: 2954, 2928, 2855, 1471, 1254

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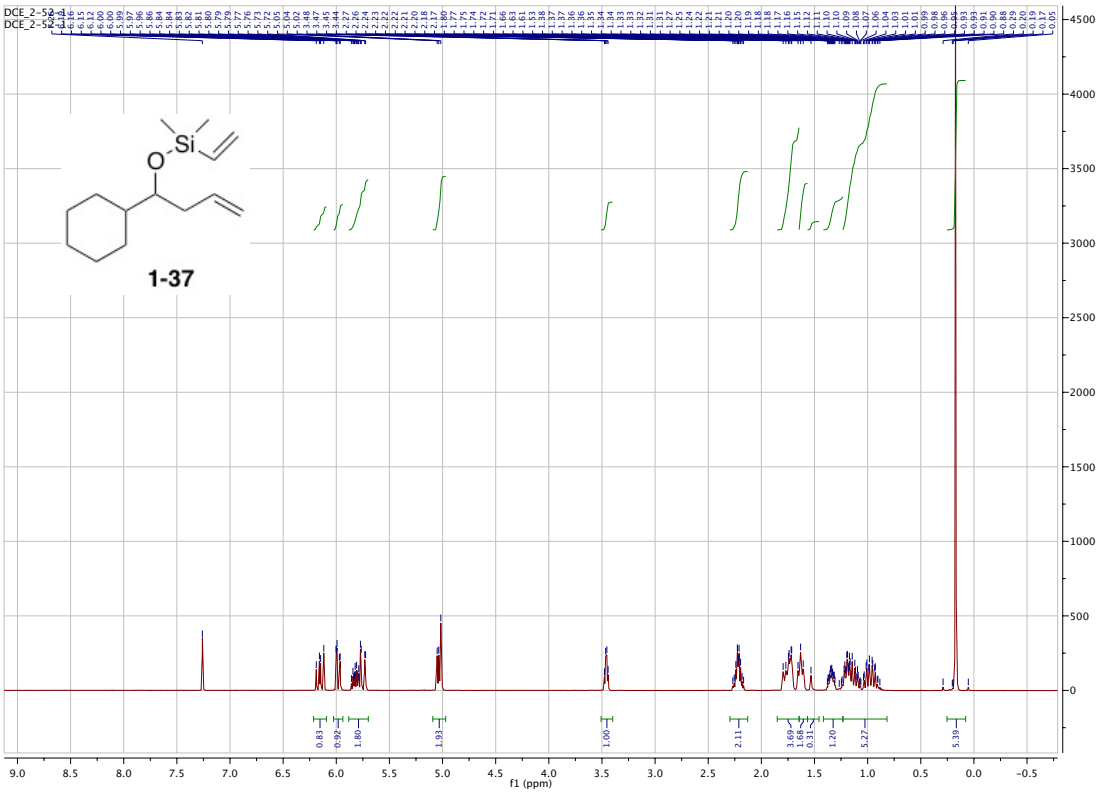
Appendix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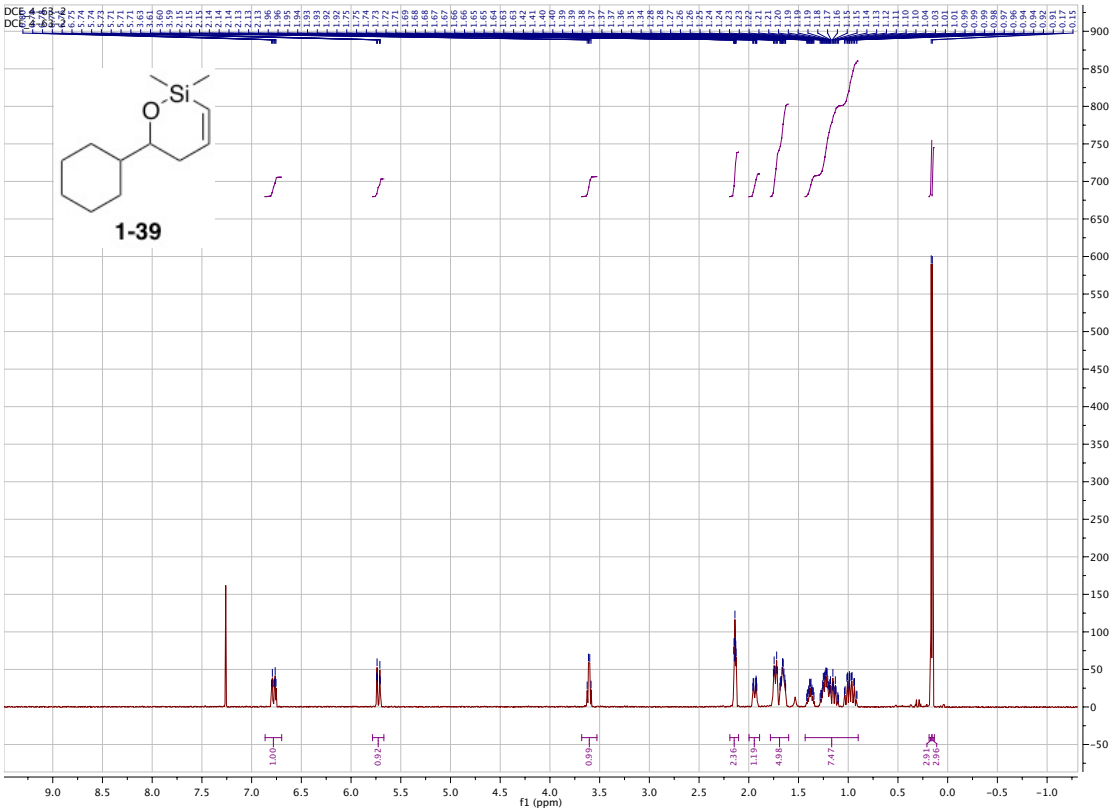
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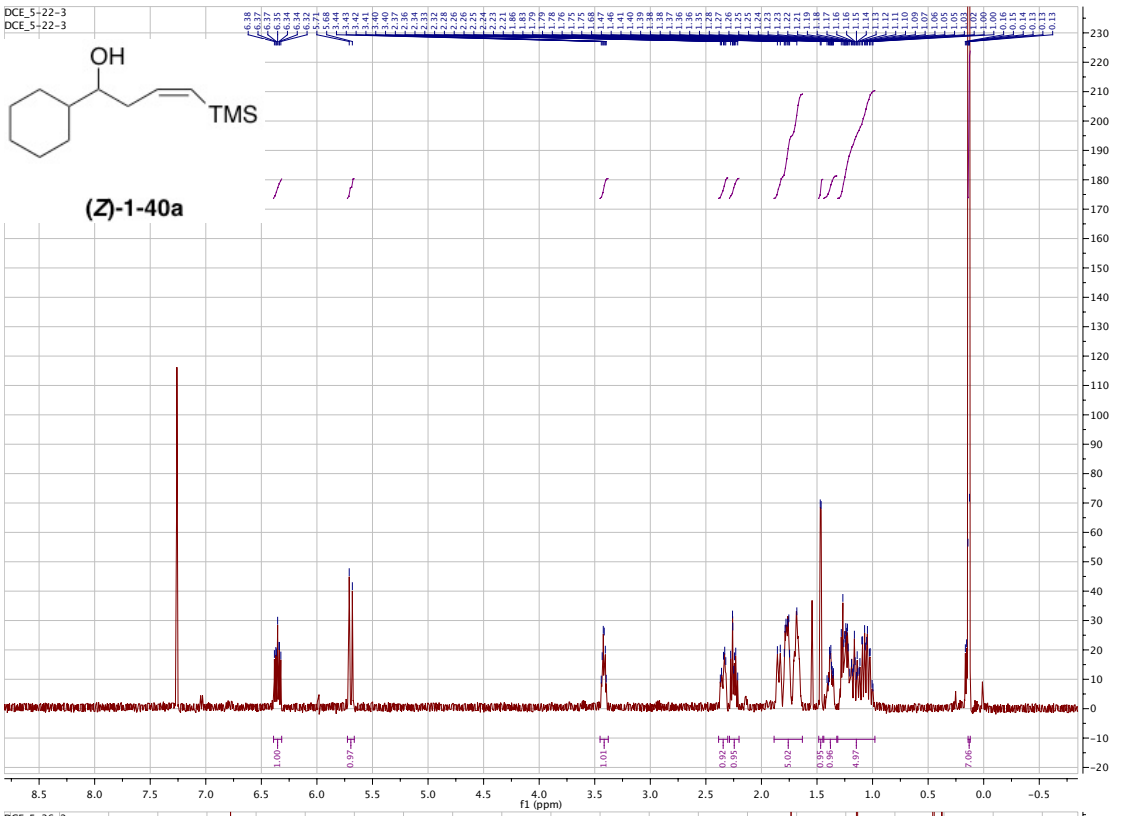
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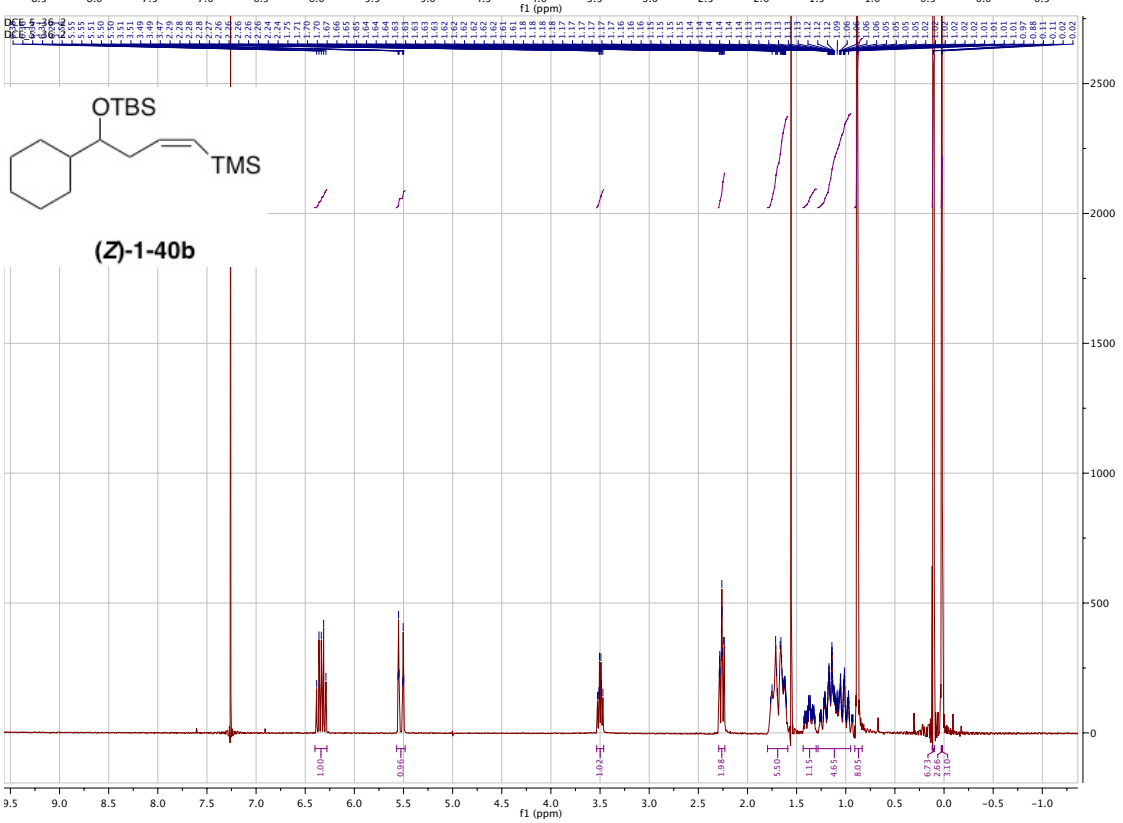
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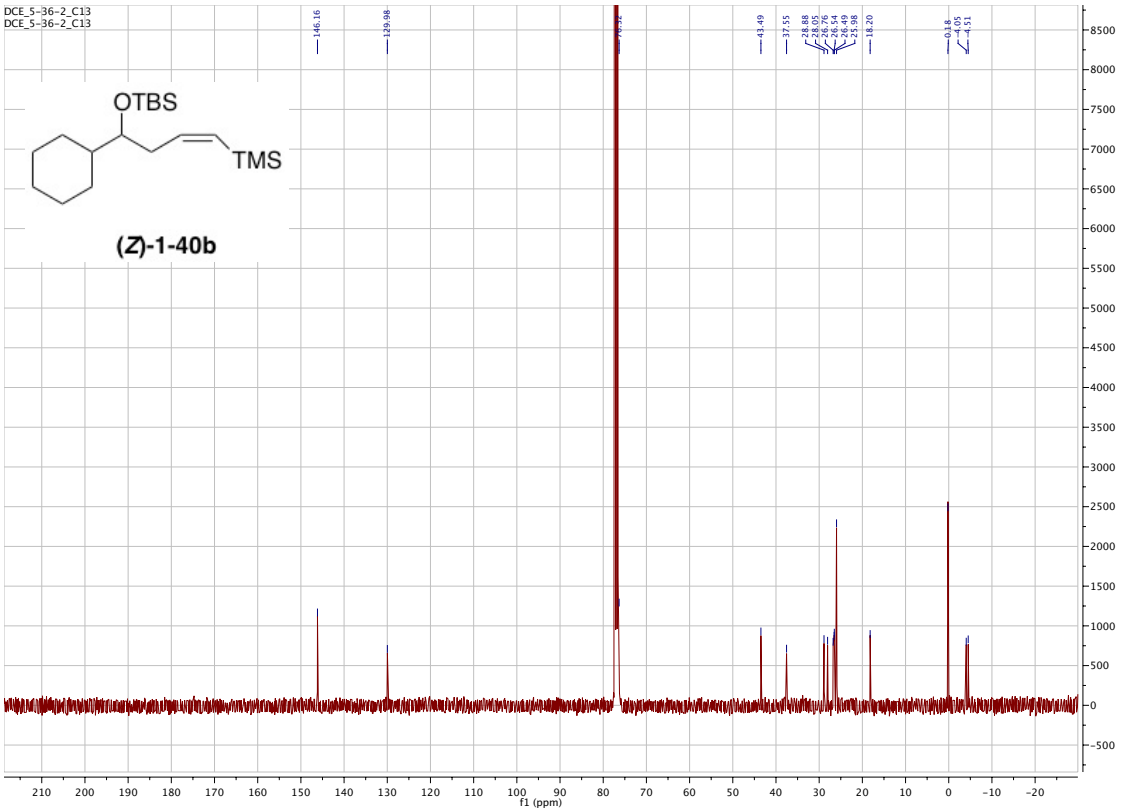
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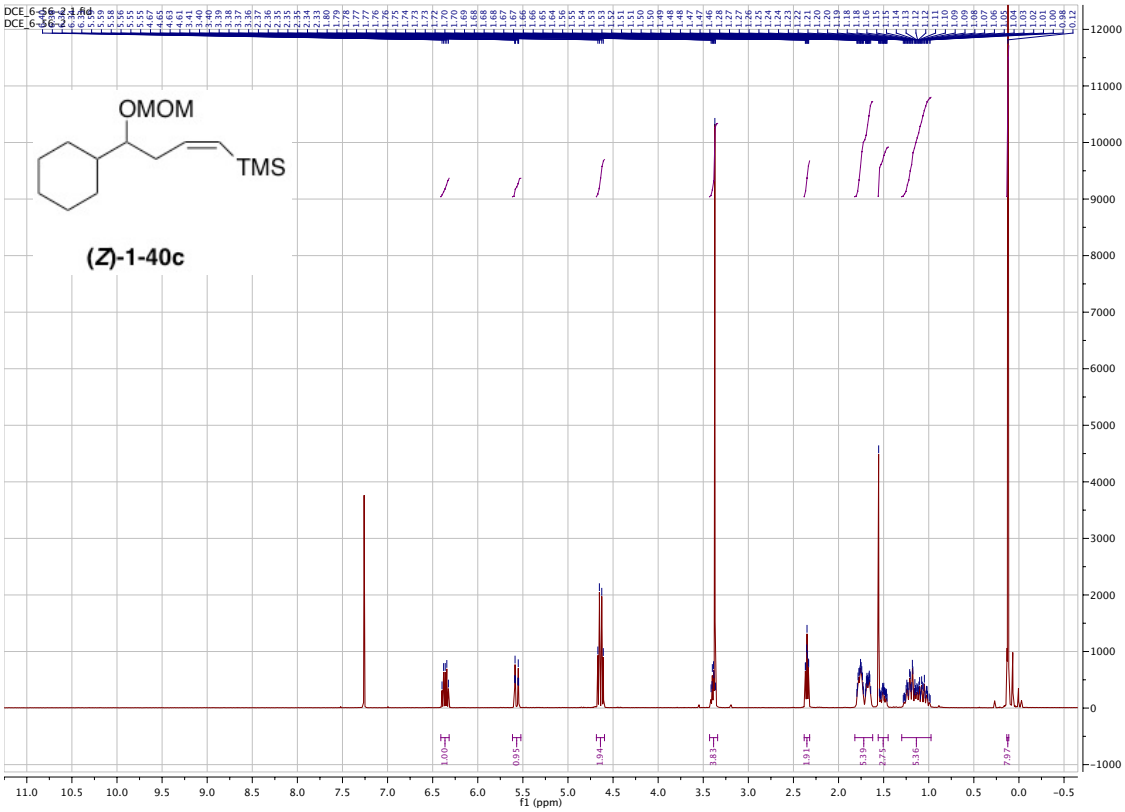
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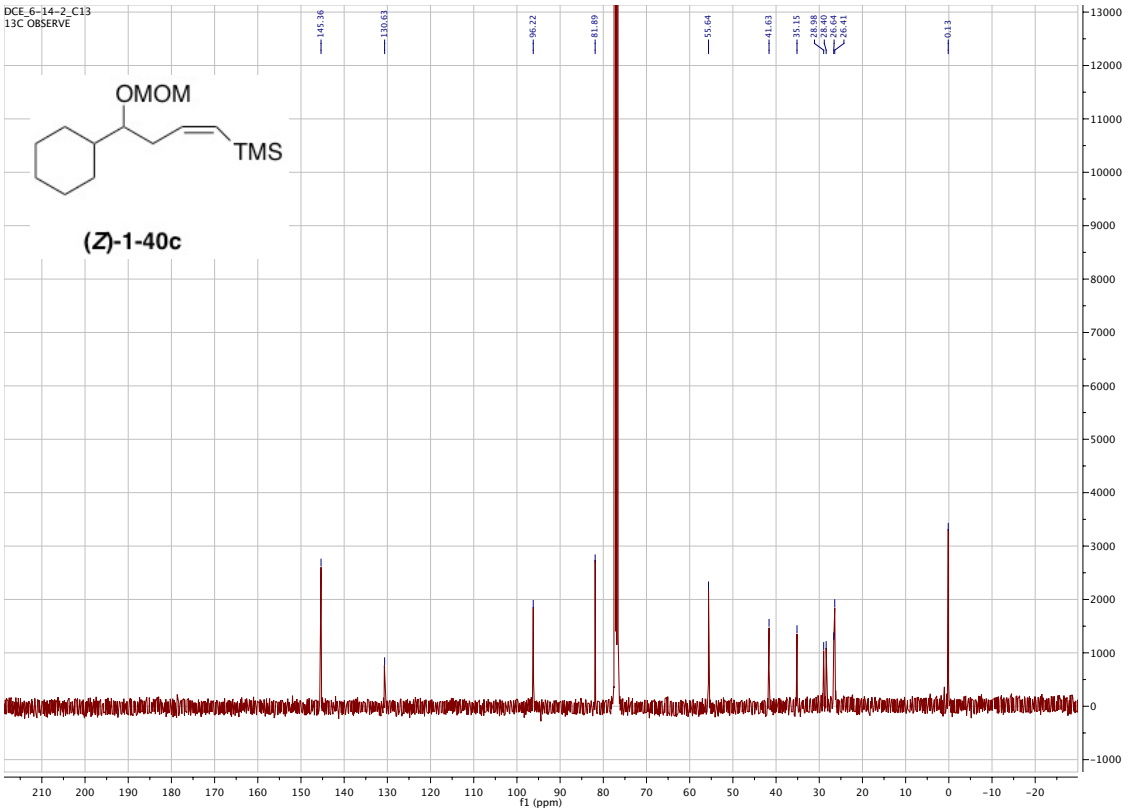
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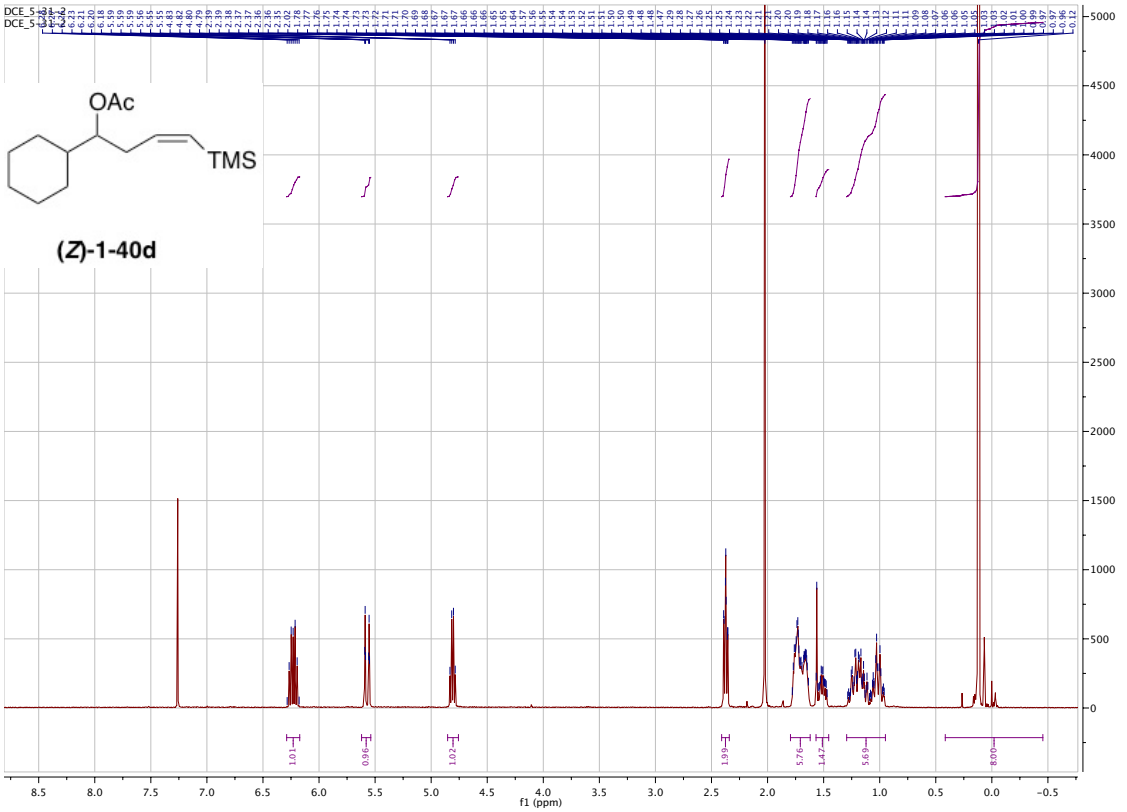
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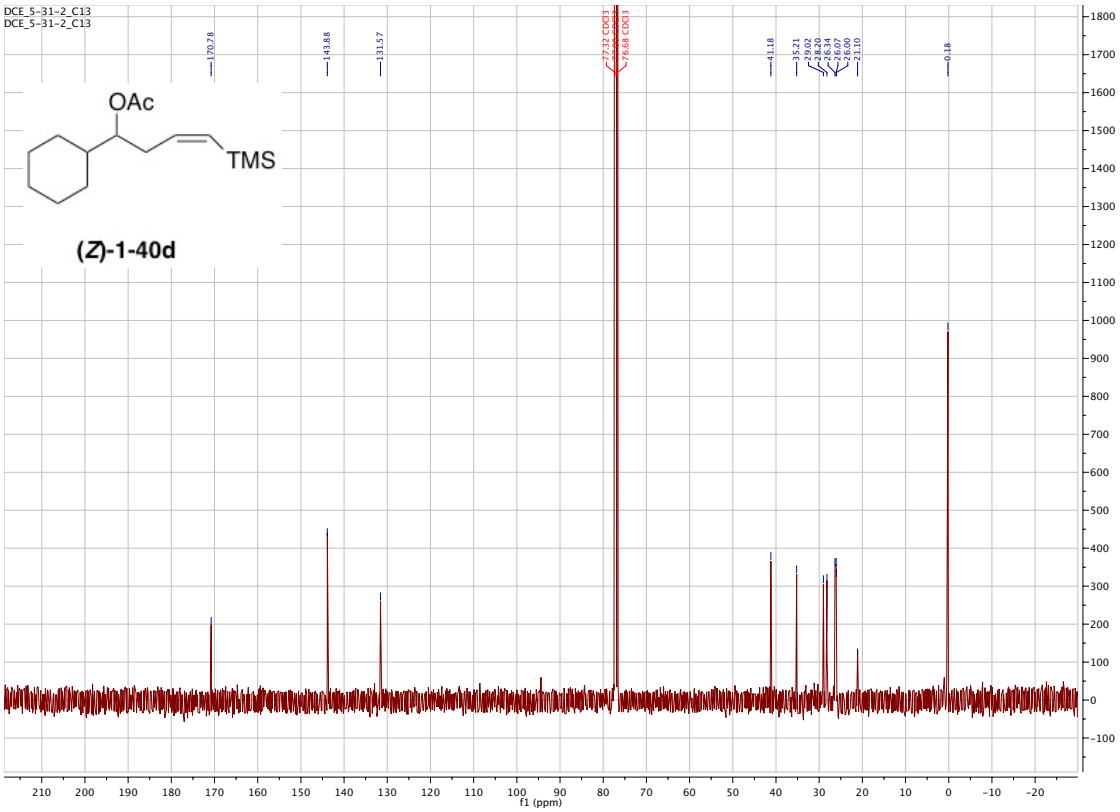
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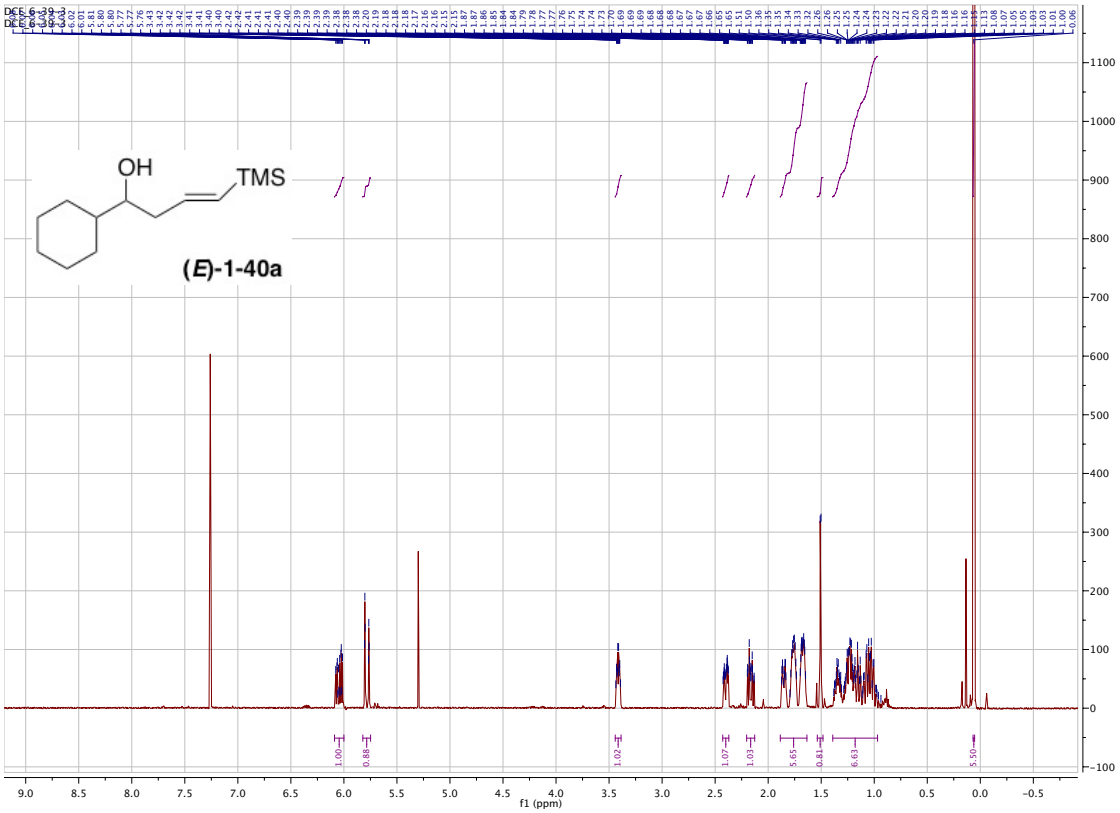
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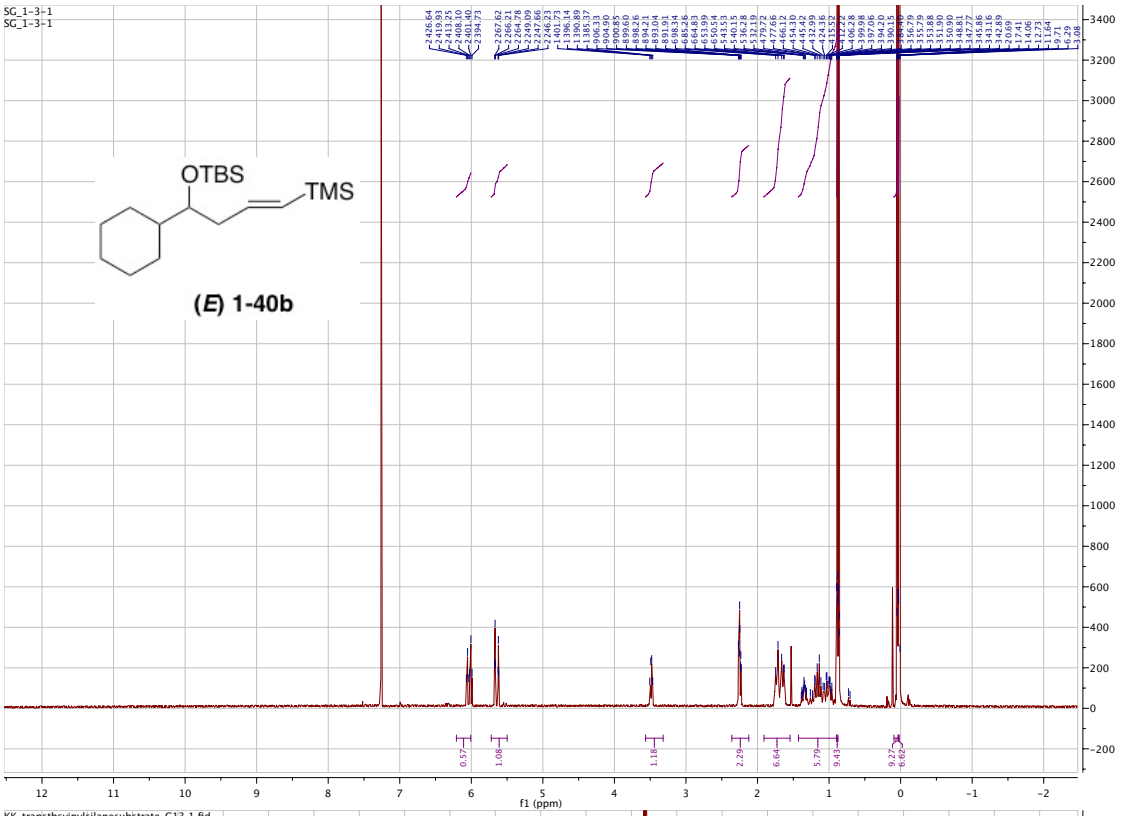
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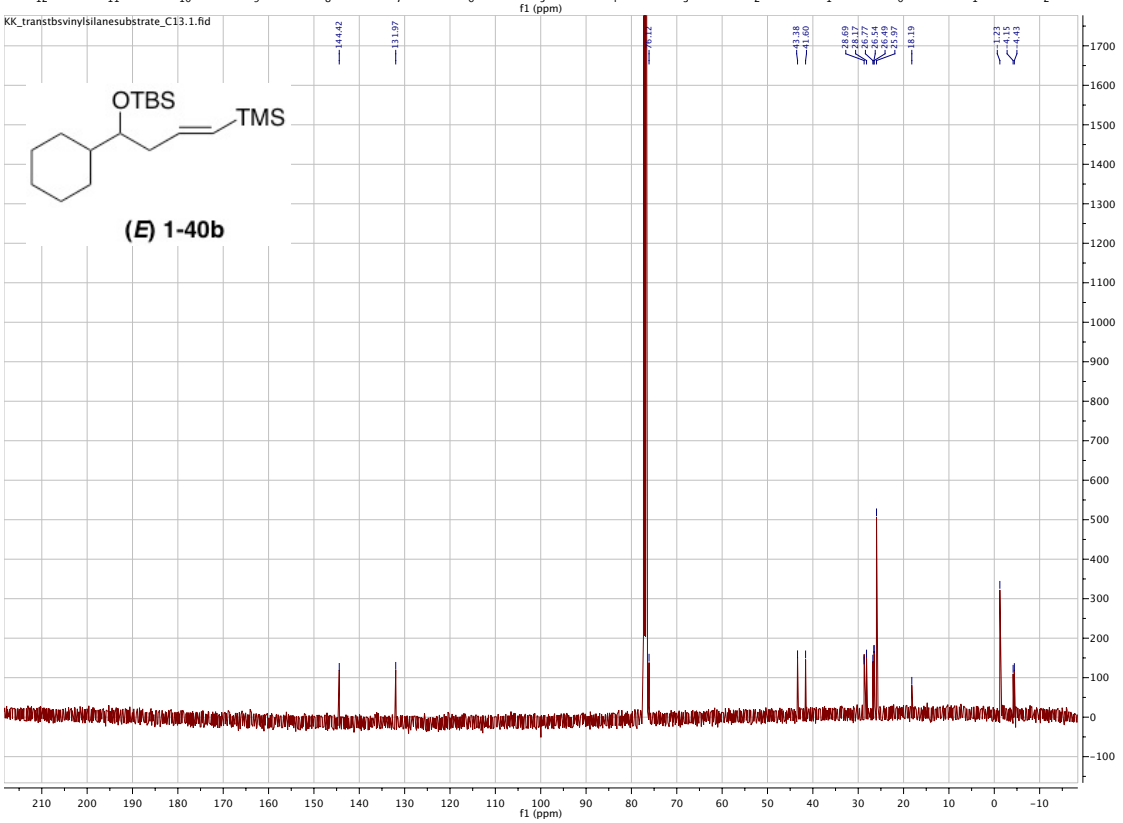
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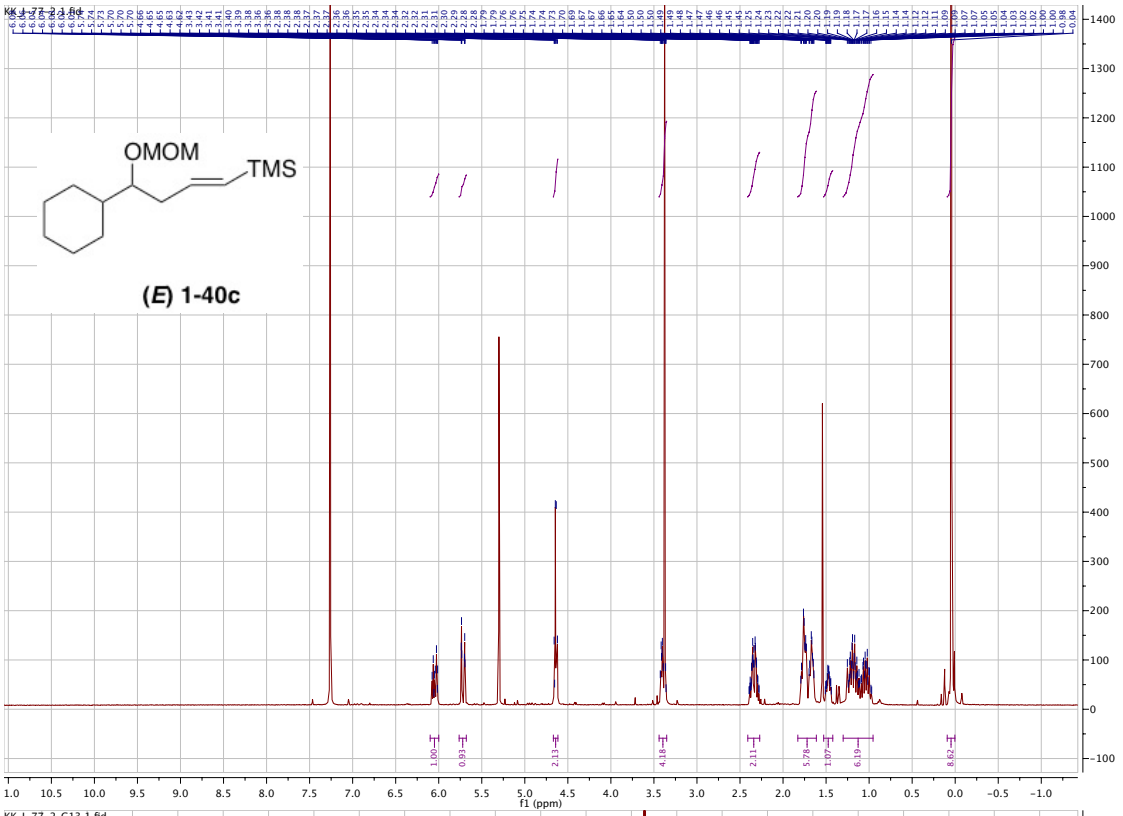
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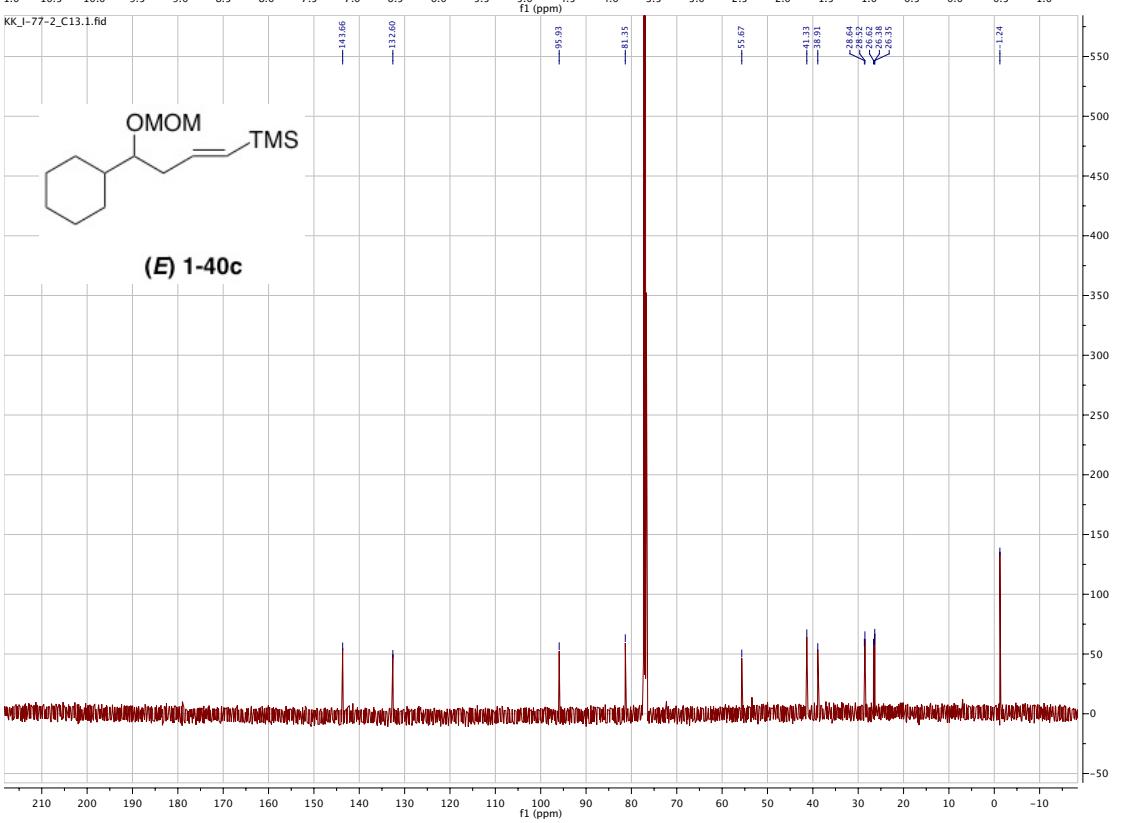
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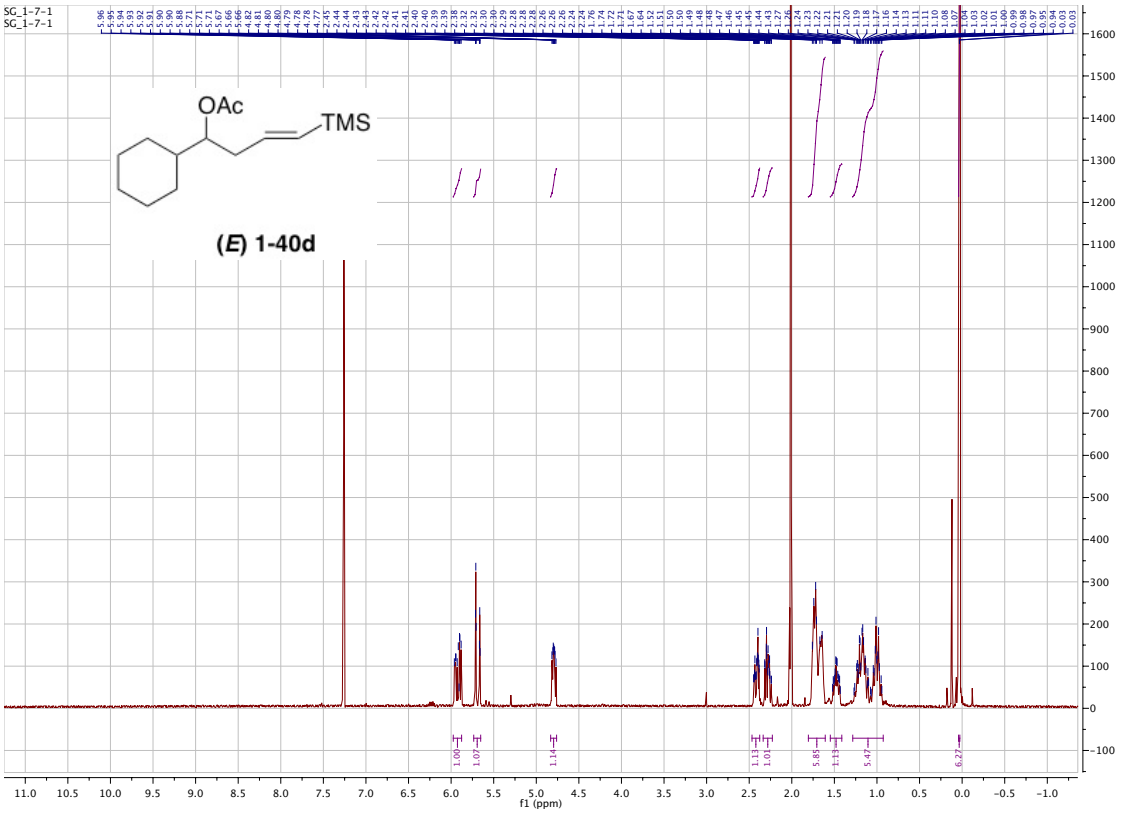
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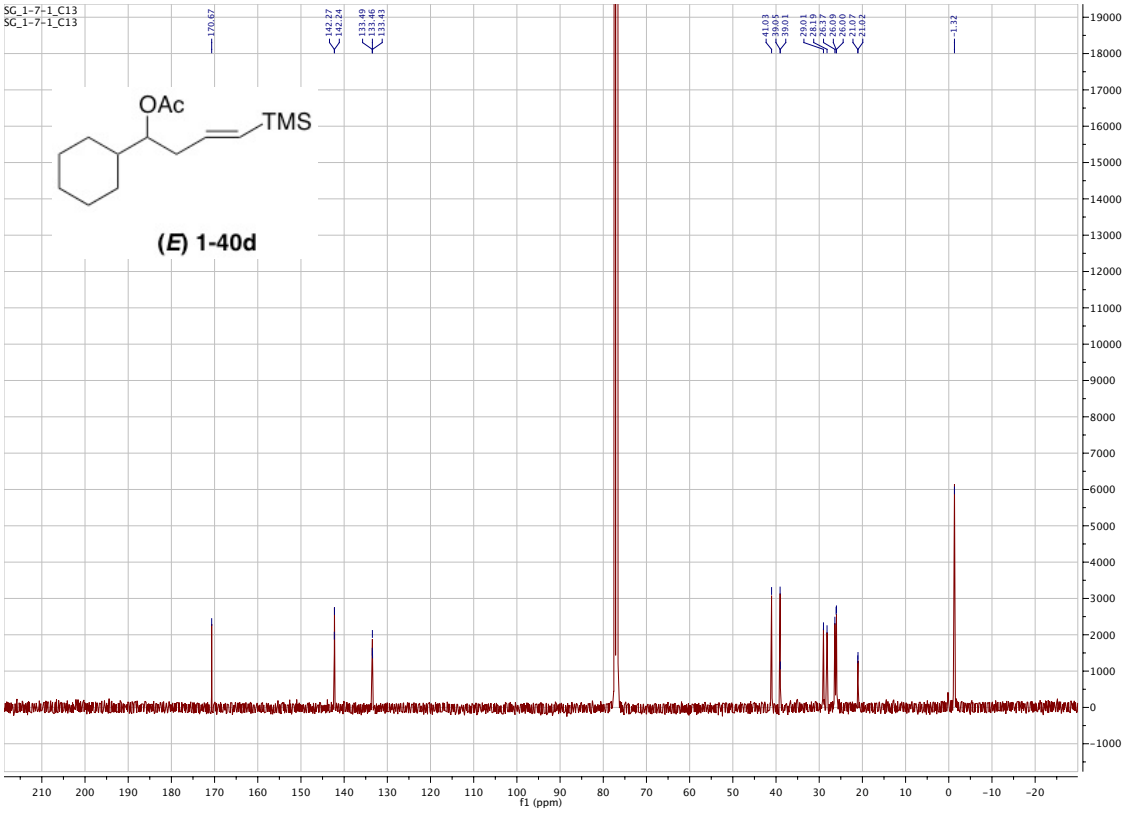
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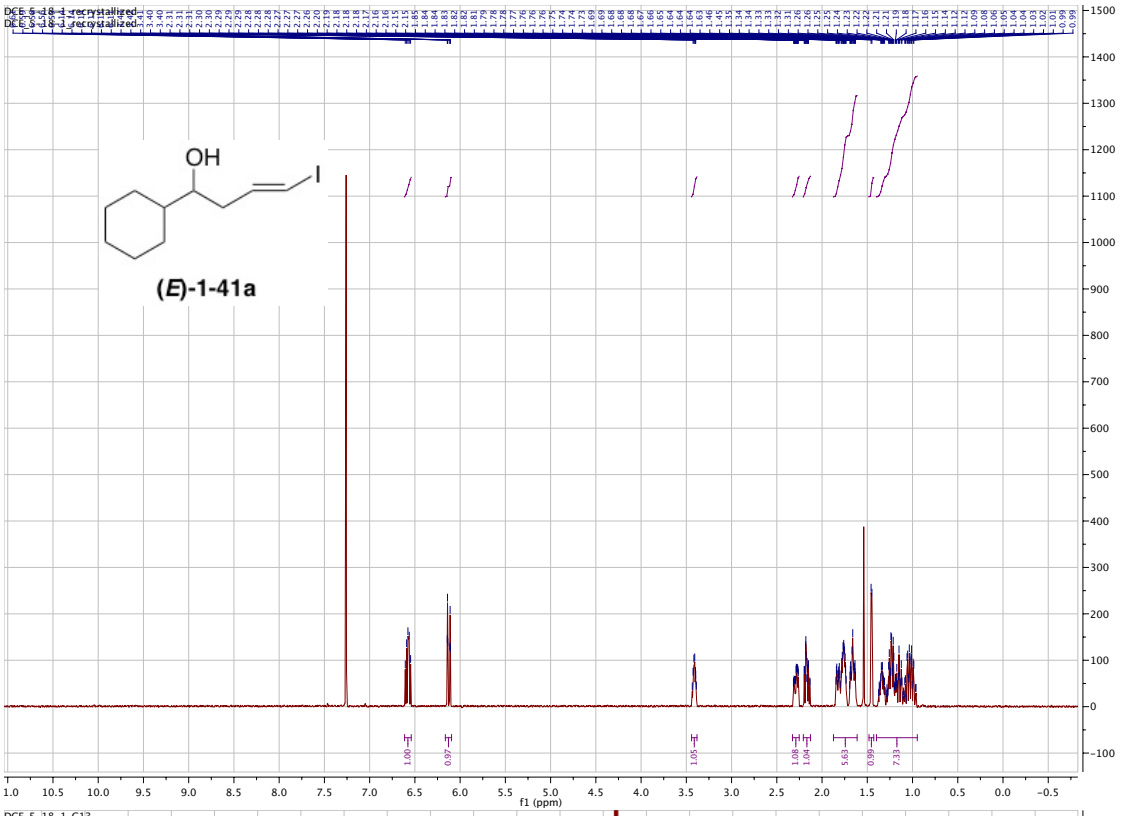
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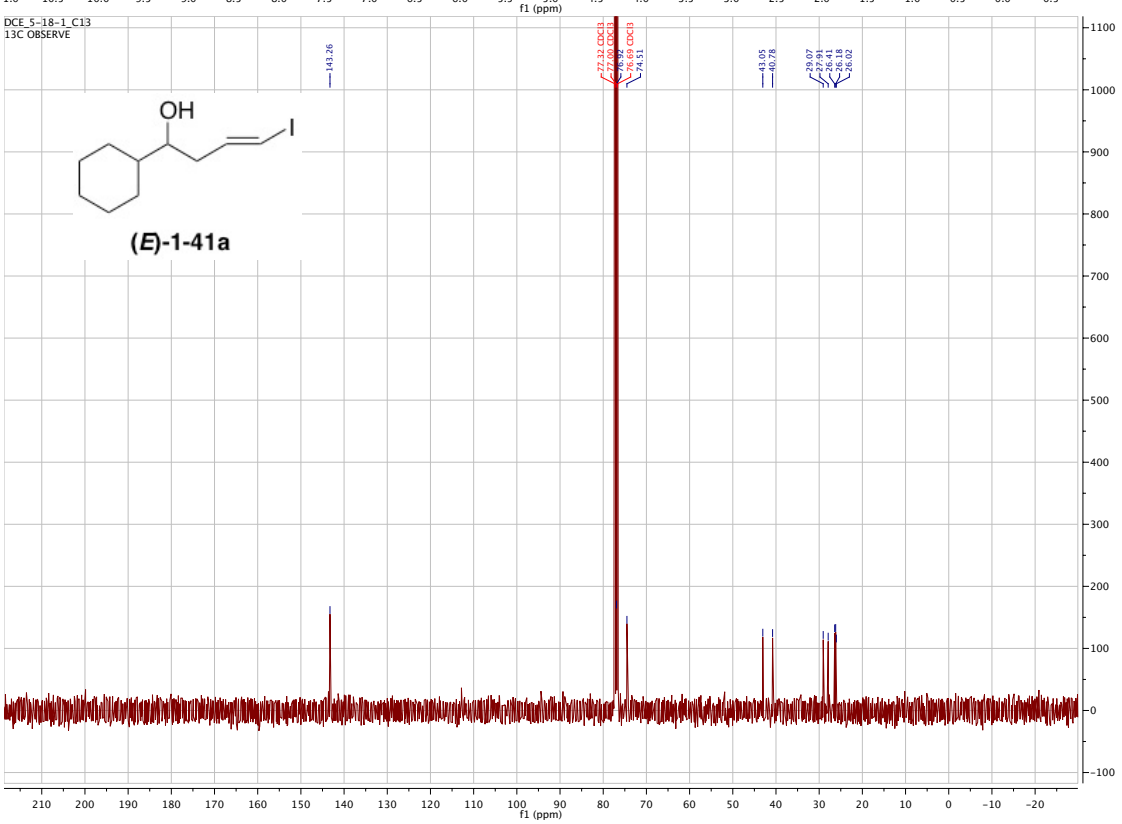
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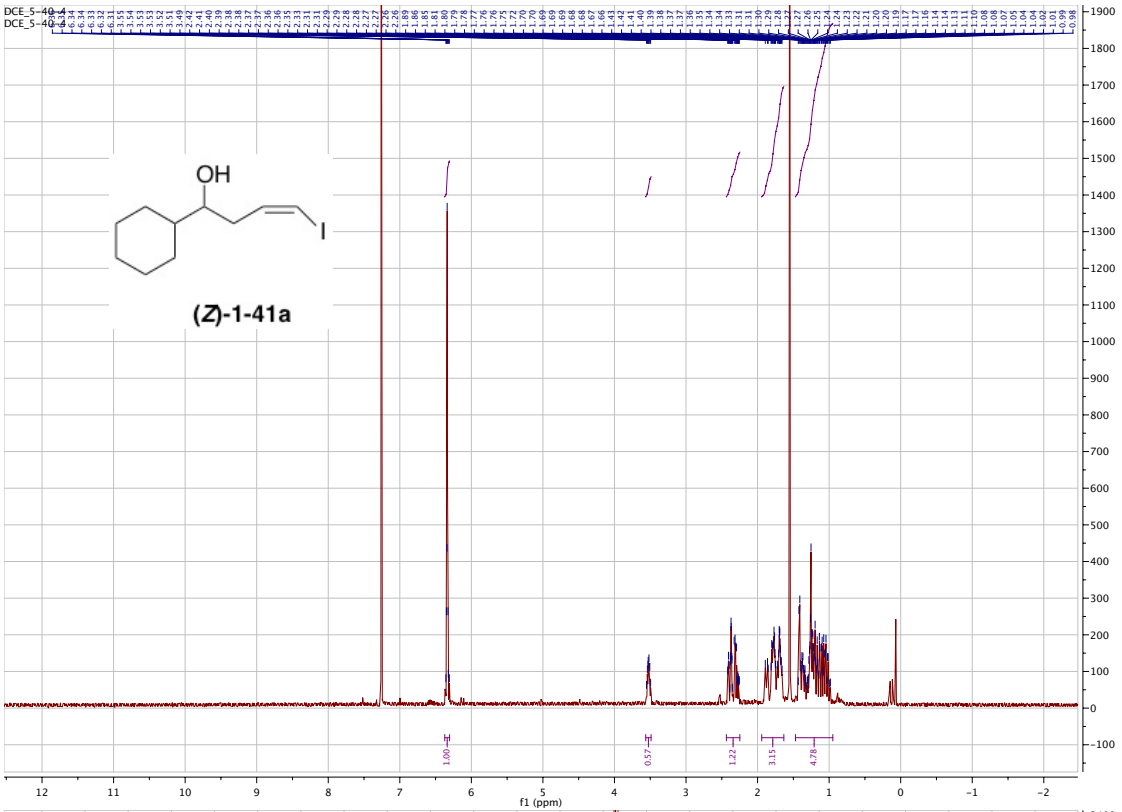
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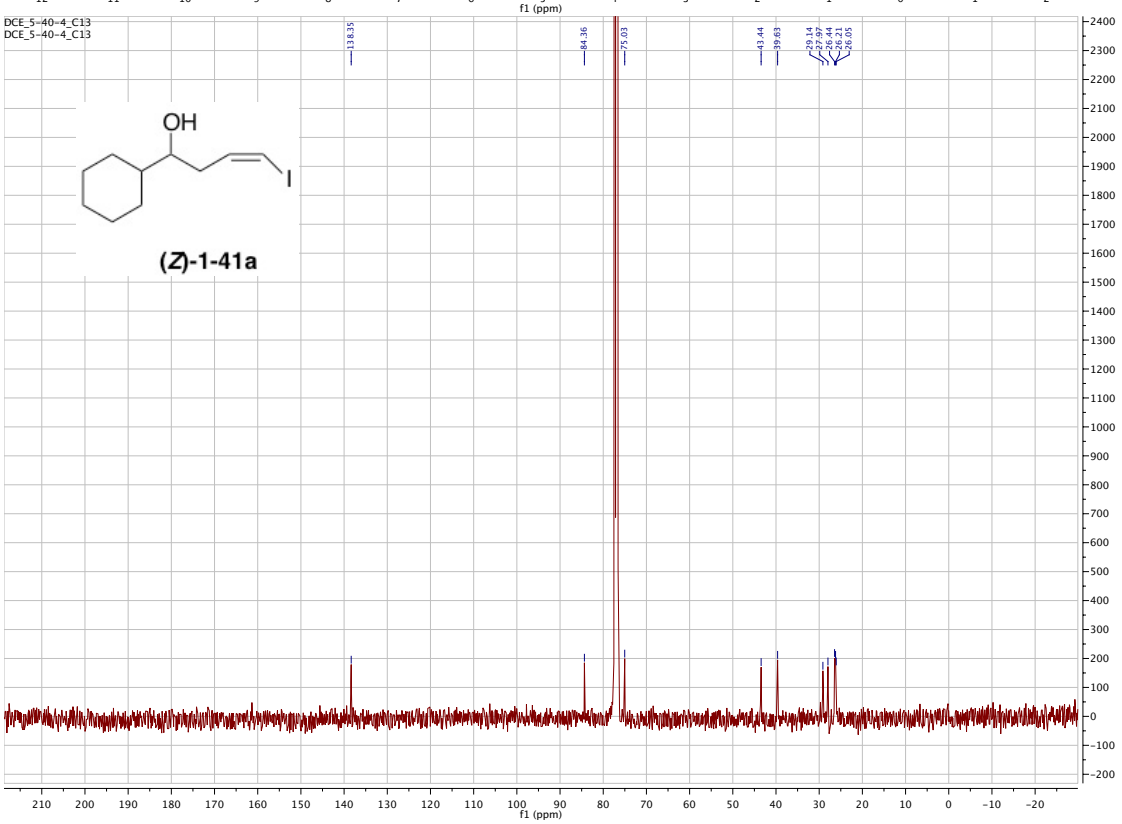
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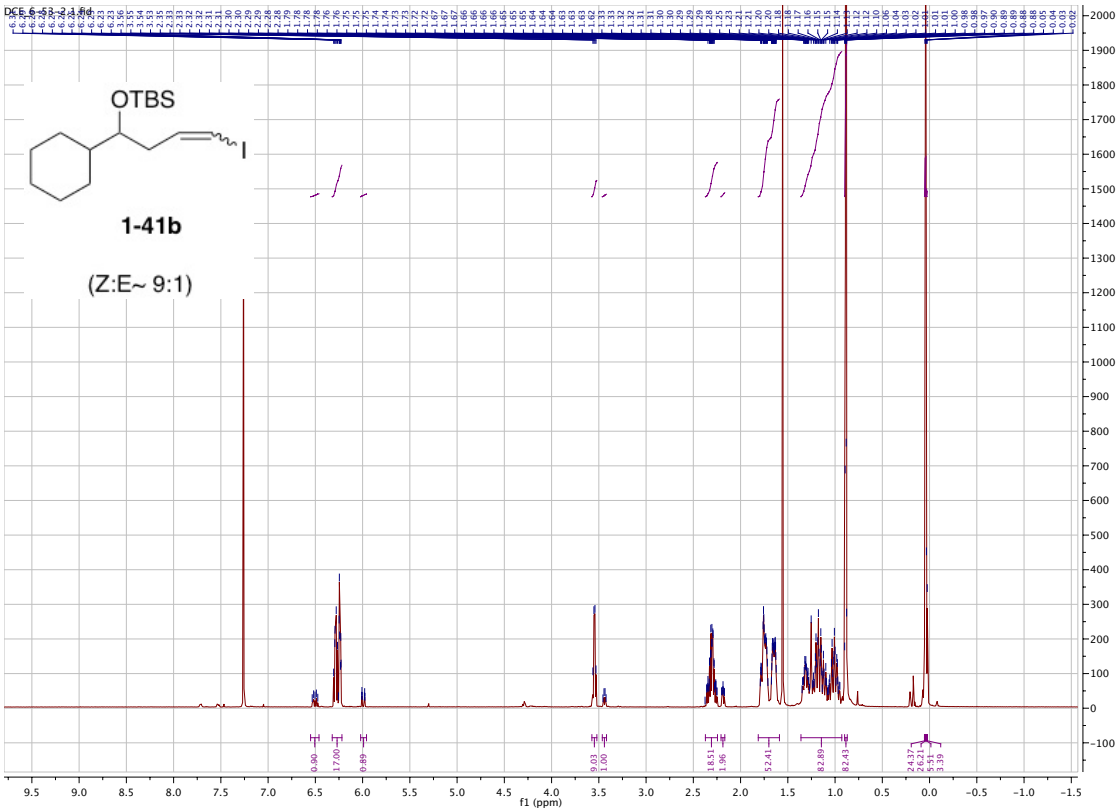
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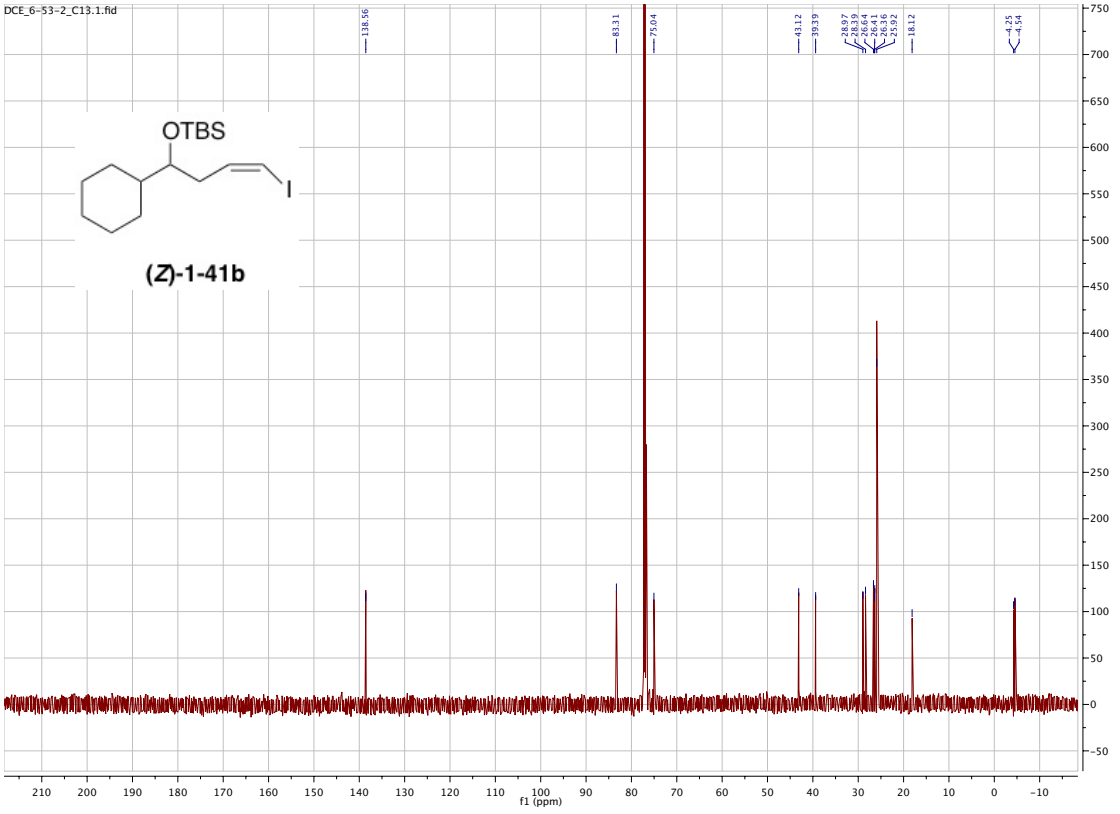
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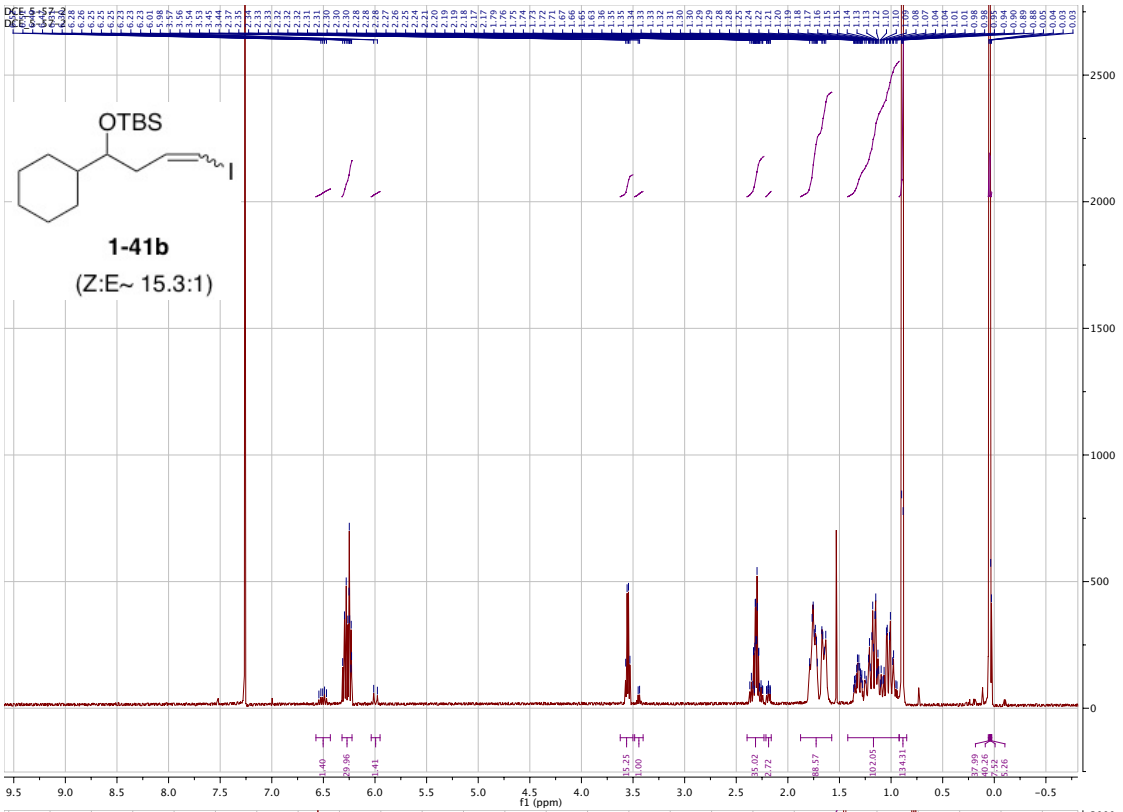
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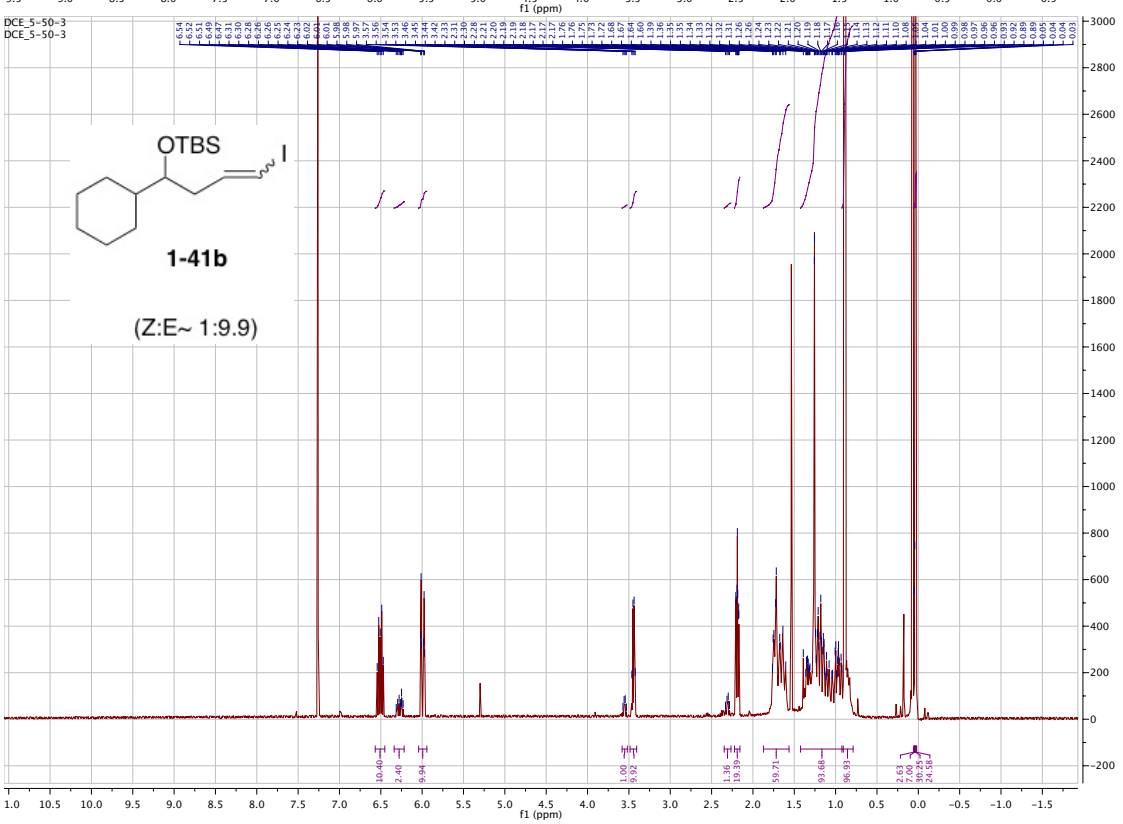
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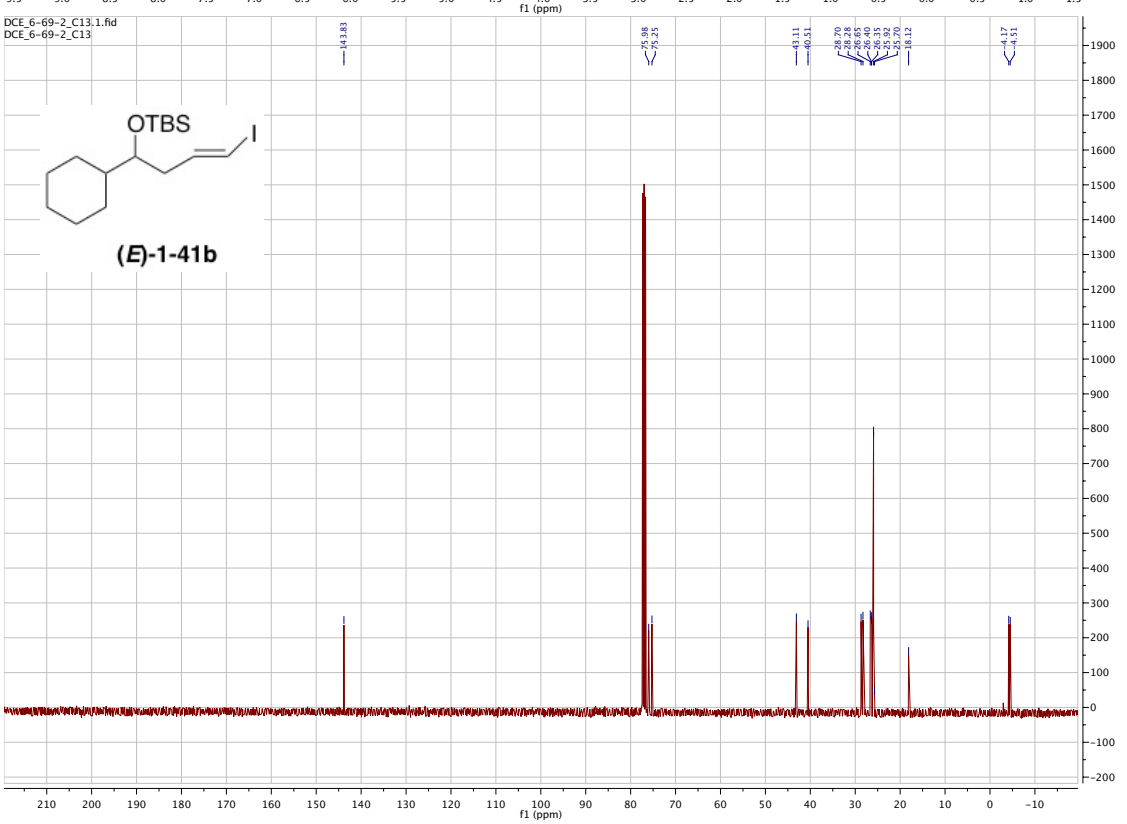
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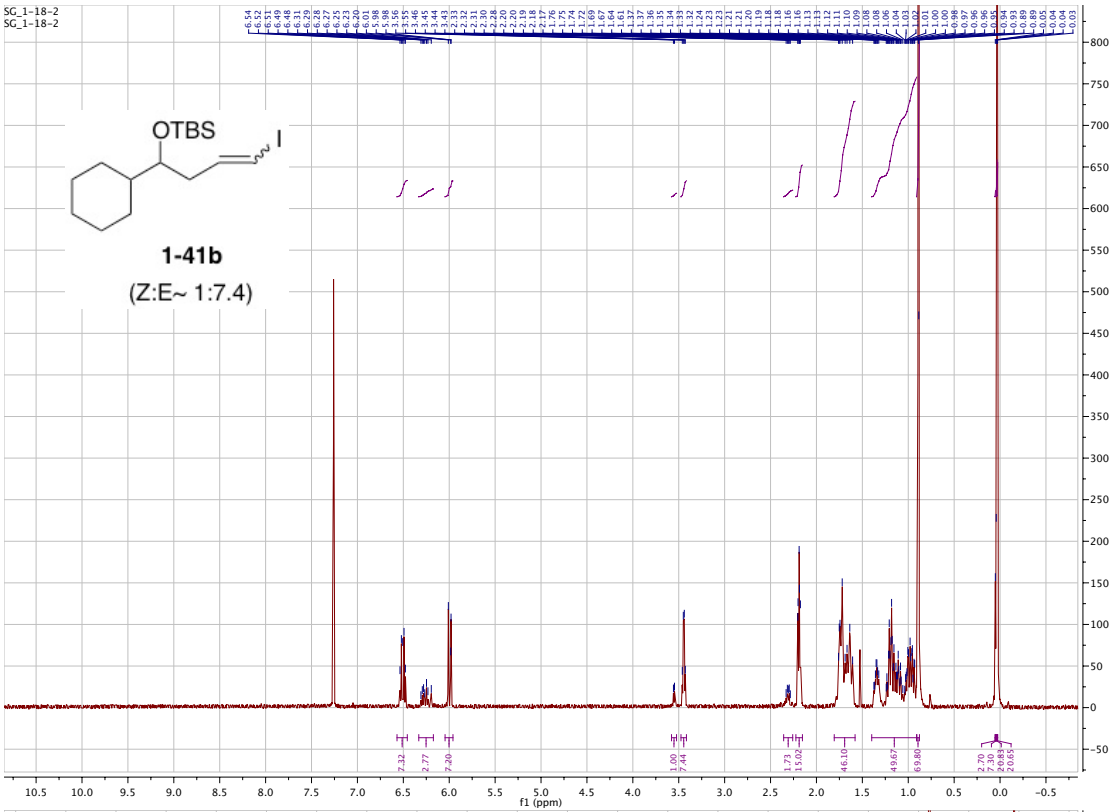
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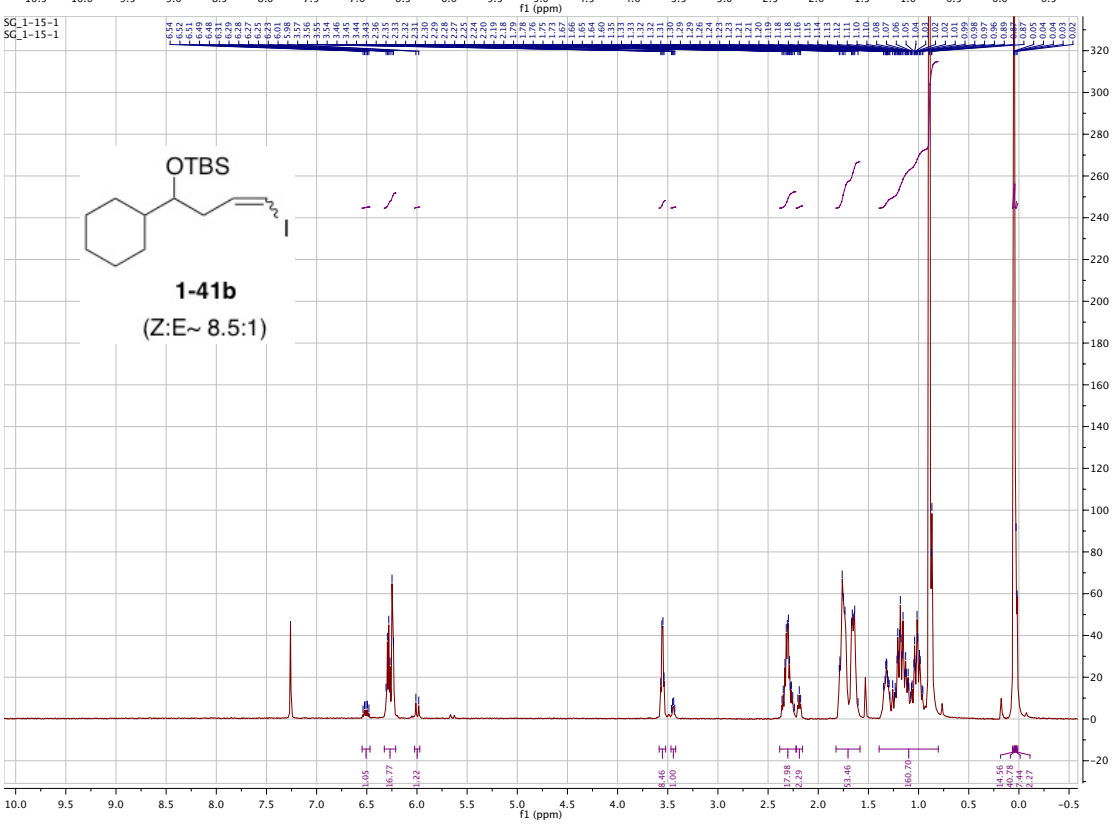
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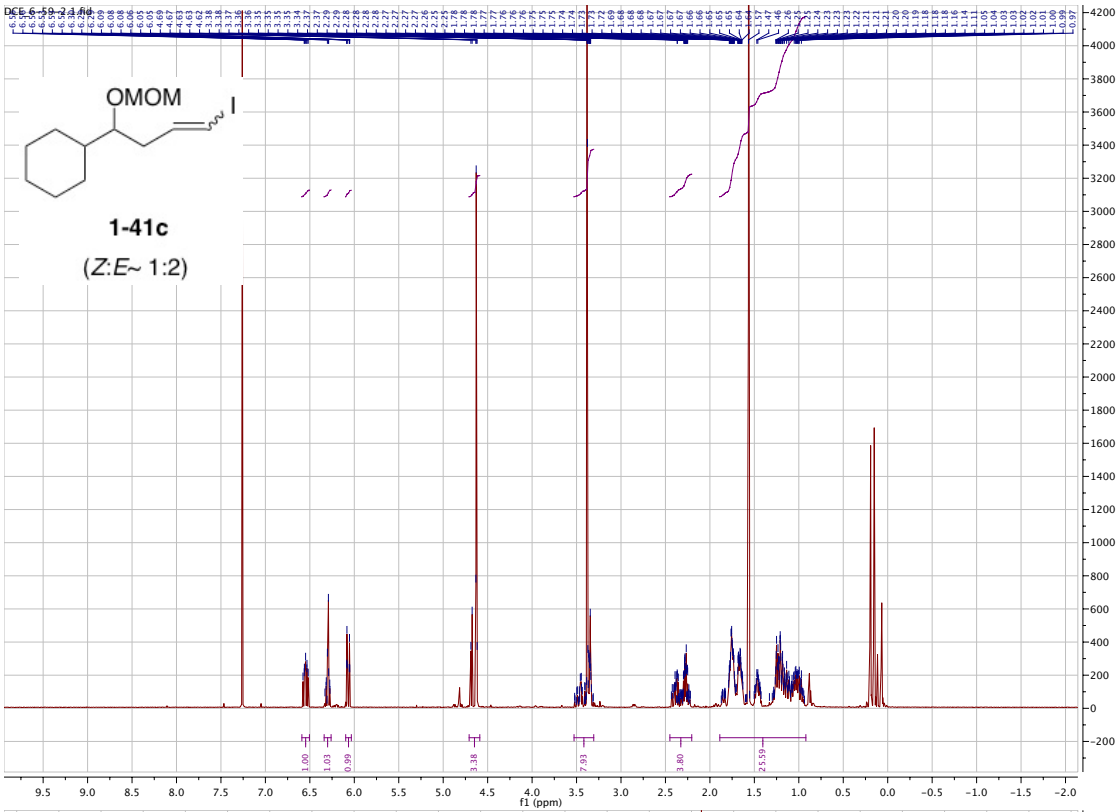
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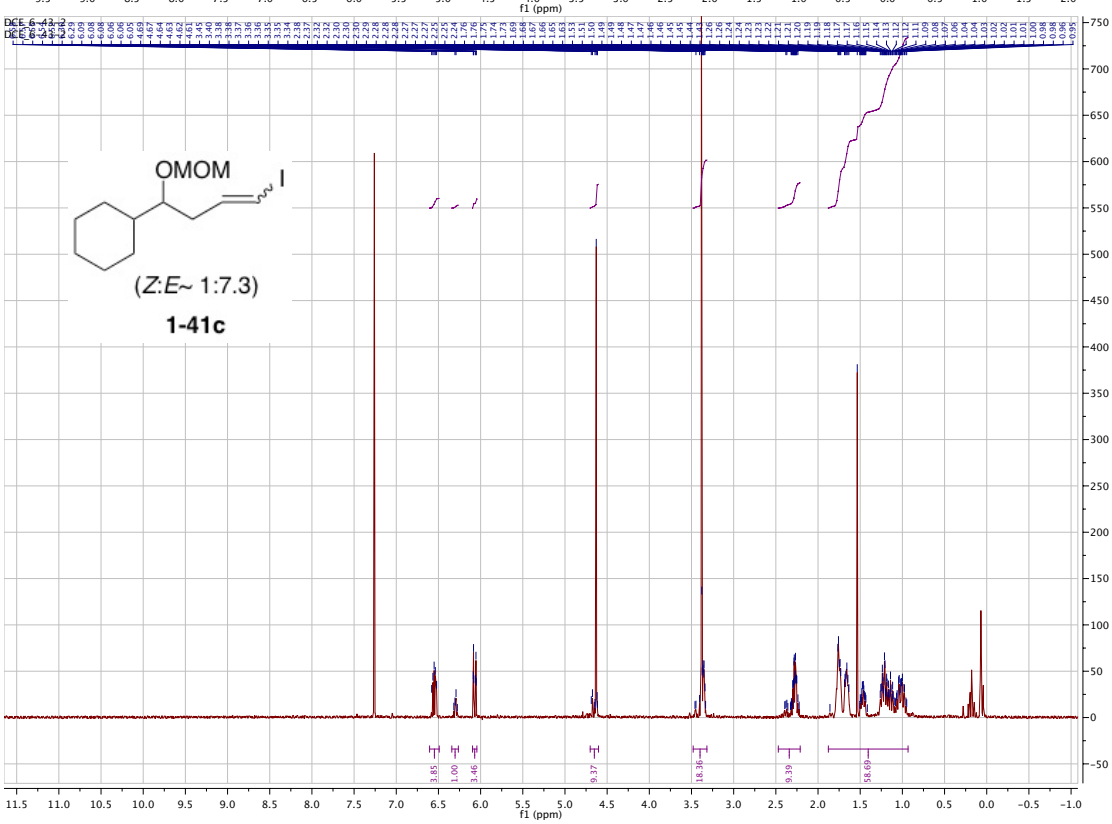
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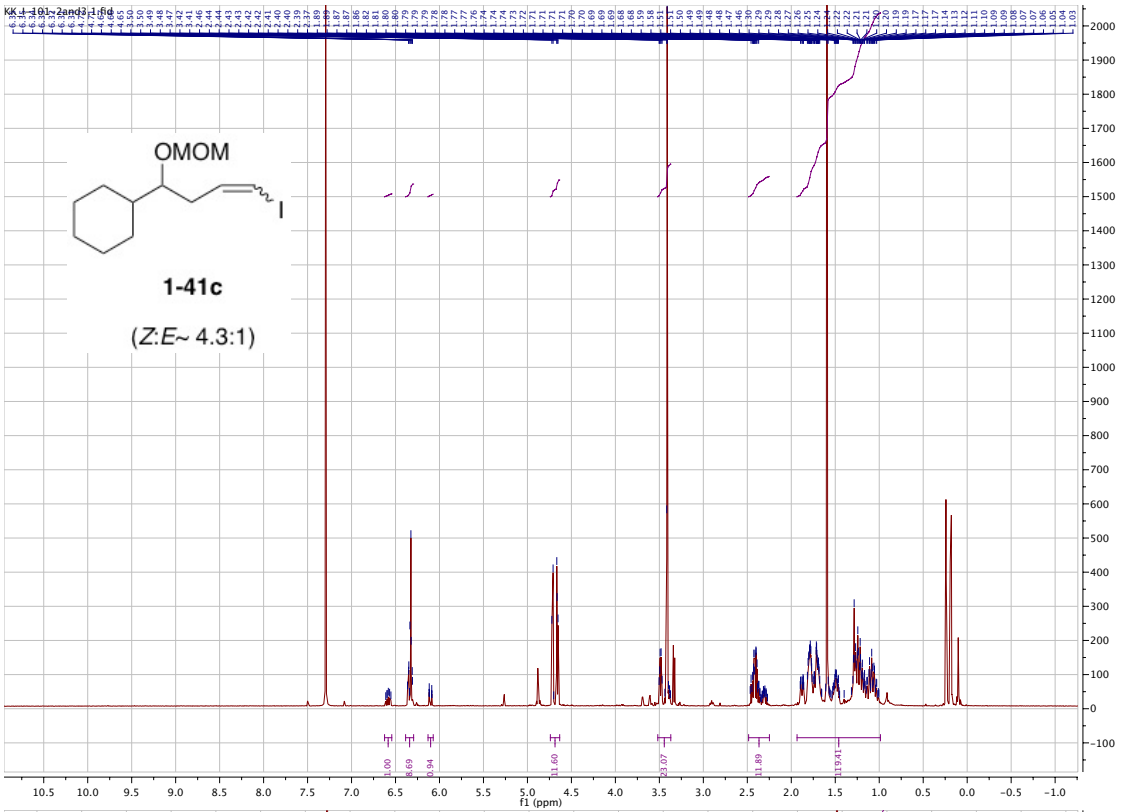
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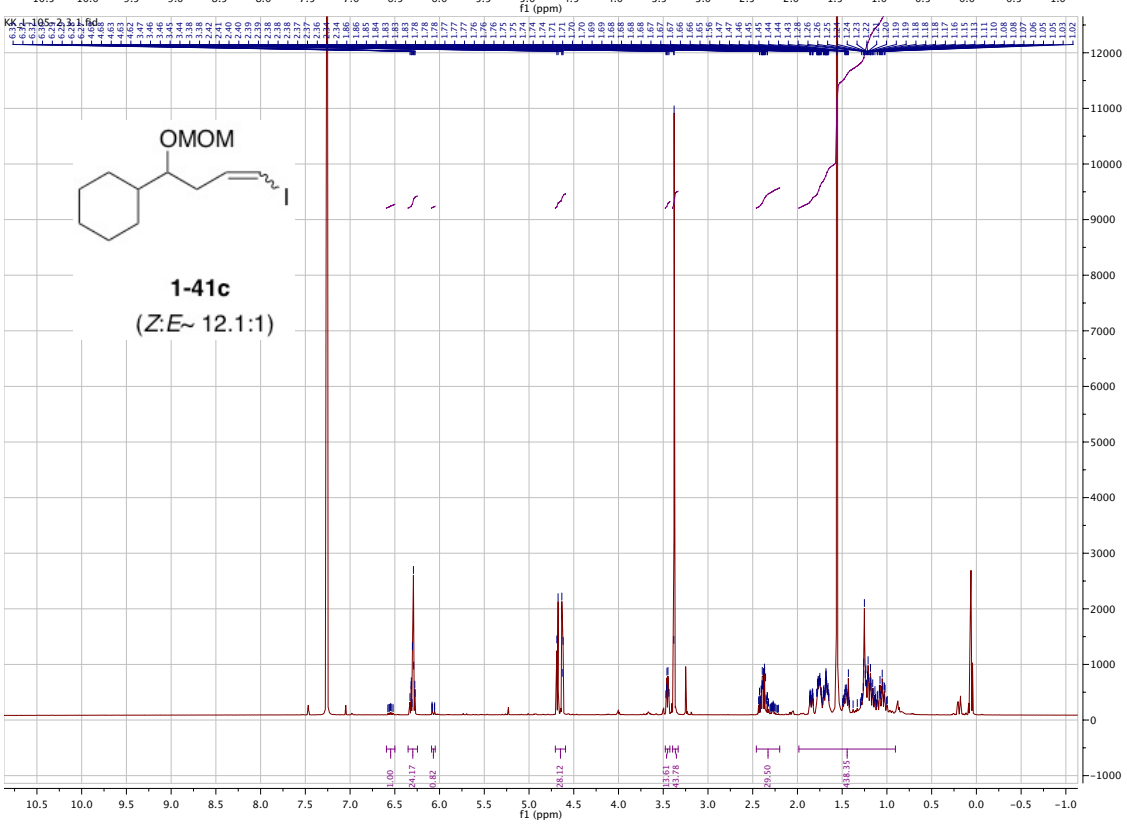
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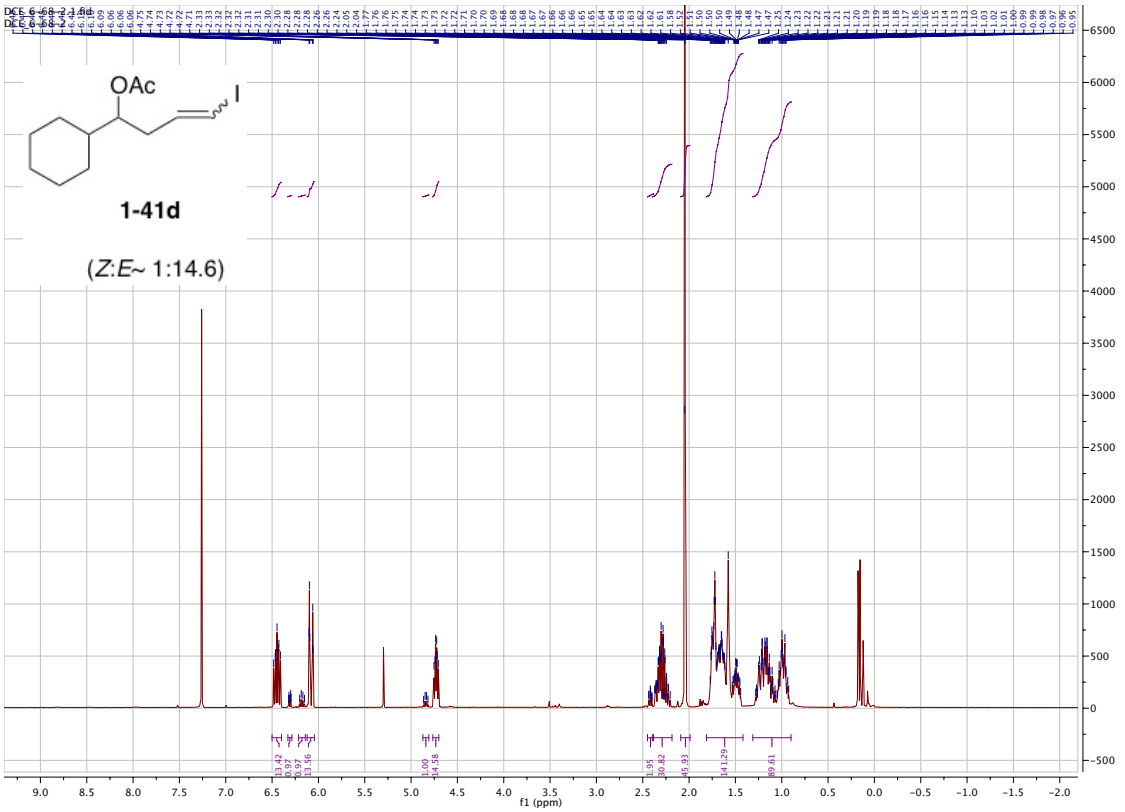
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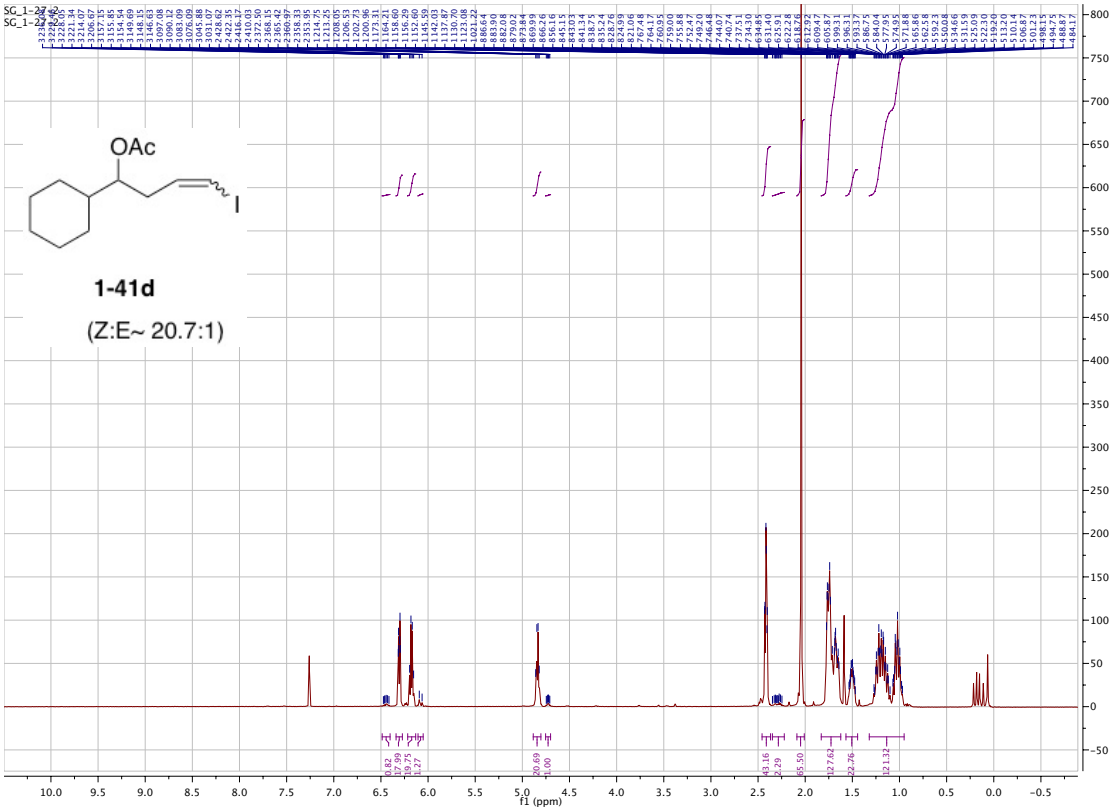
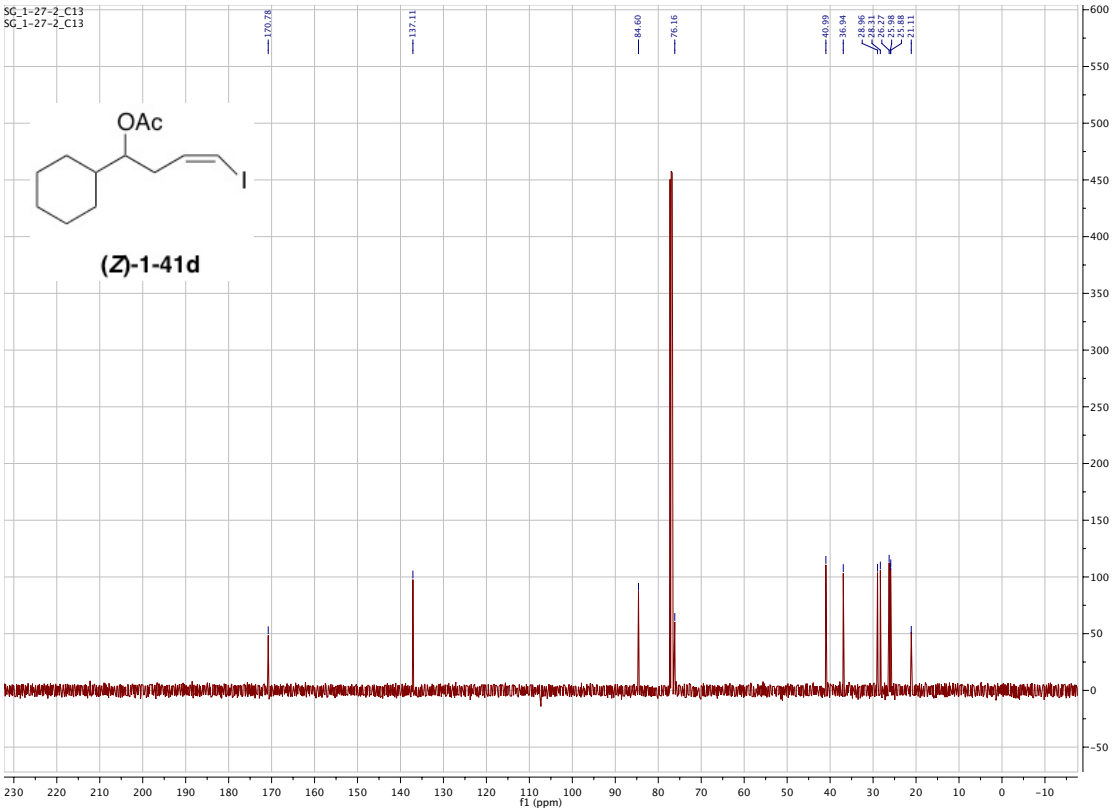
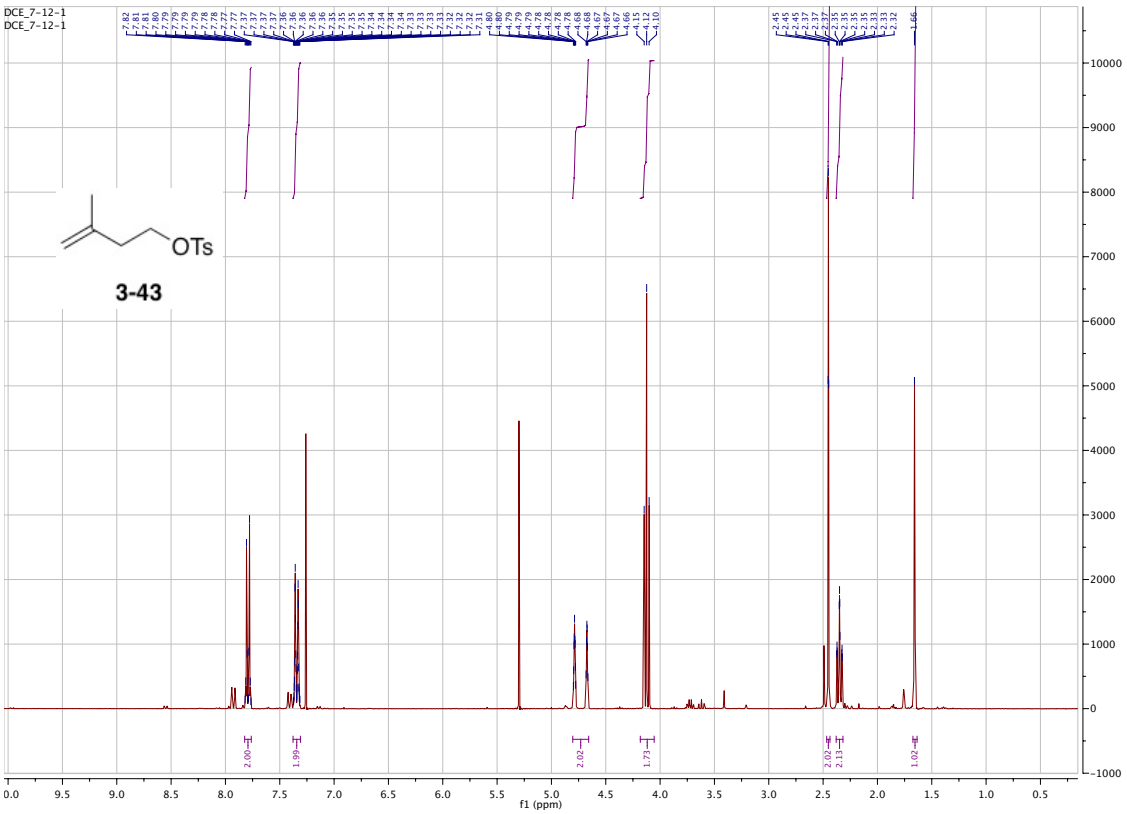
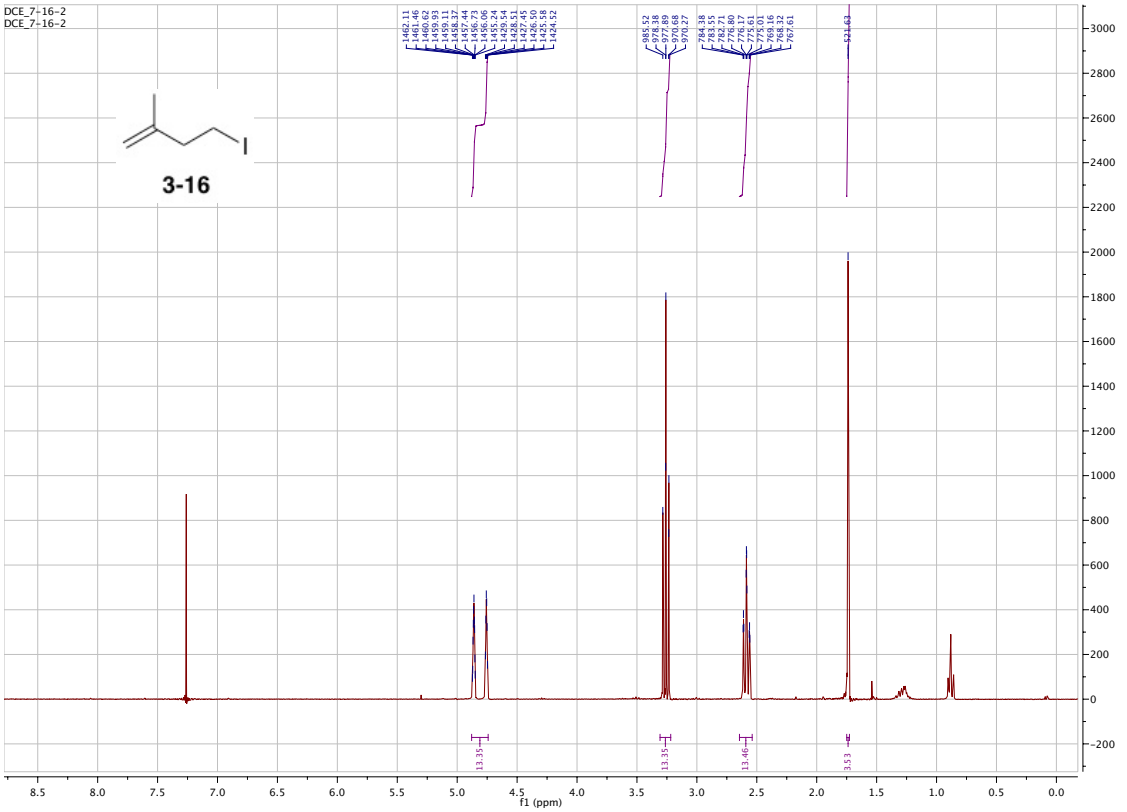
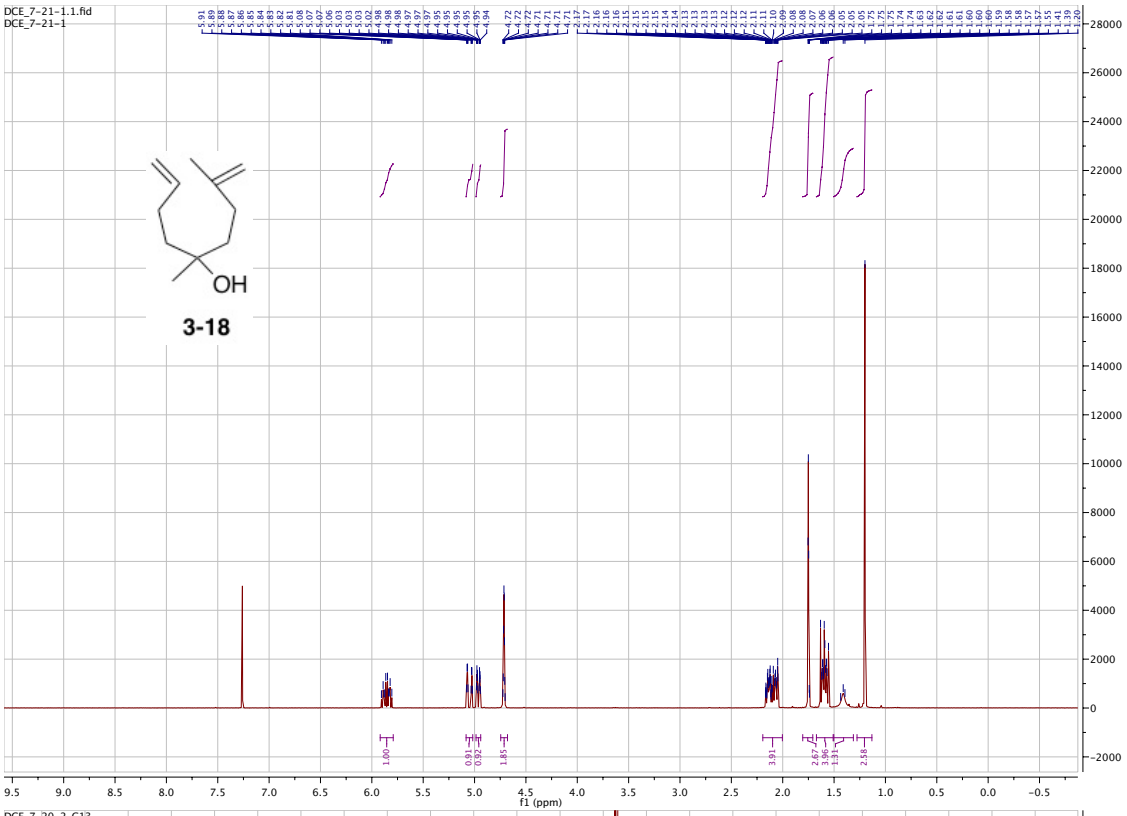
f1 (ppm)

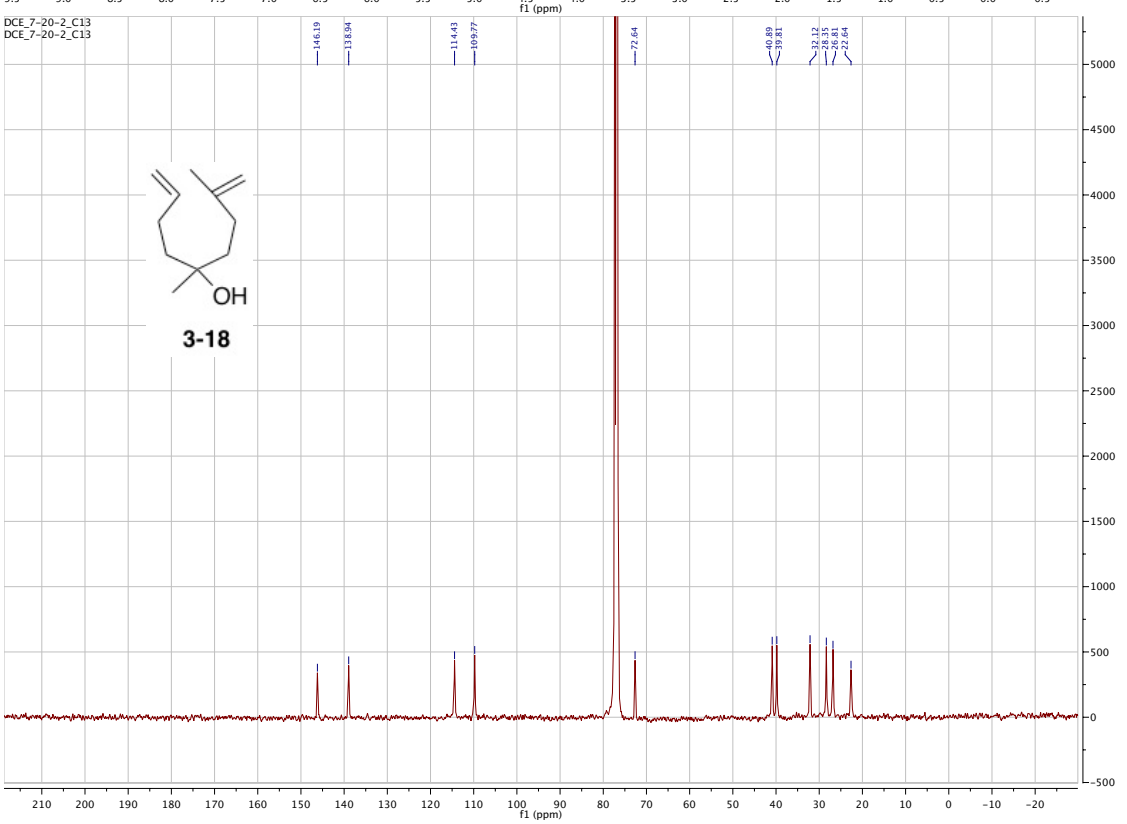

OAc
I
1-41d
(Z:E~ 20.7:1)
f1 (ppm)

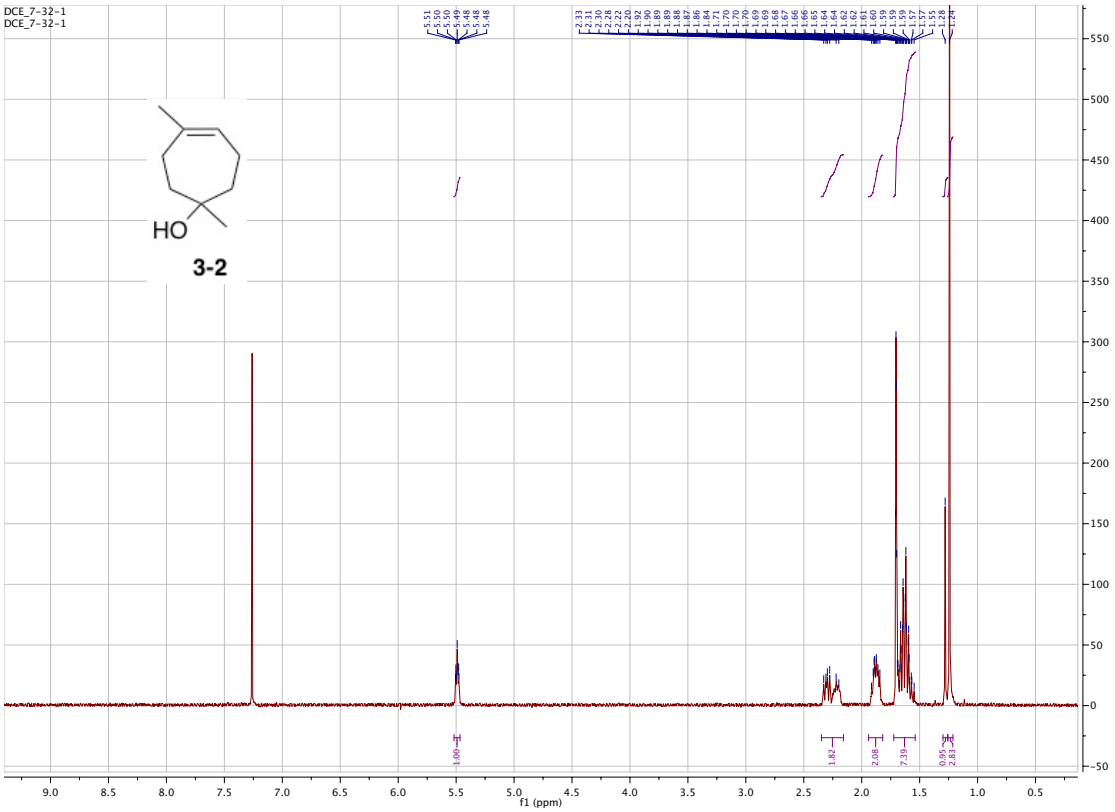

SG_1-27-2_C13
SG_1-27-2_C13
170.78
137.11
84.60
76.16
40.99
36.94
28.96
28.31
26.27
25.98
25.88
21.11
OAc
I
(Z)-1-41d
f1 (ppm)

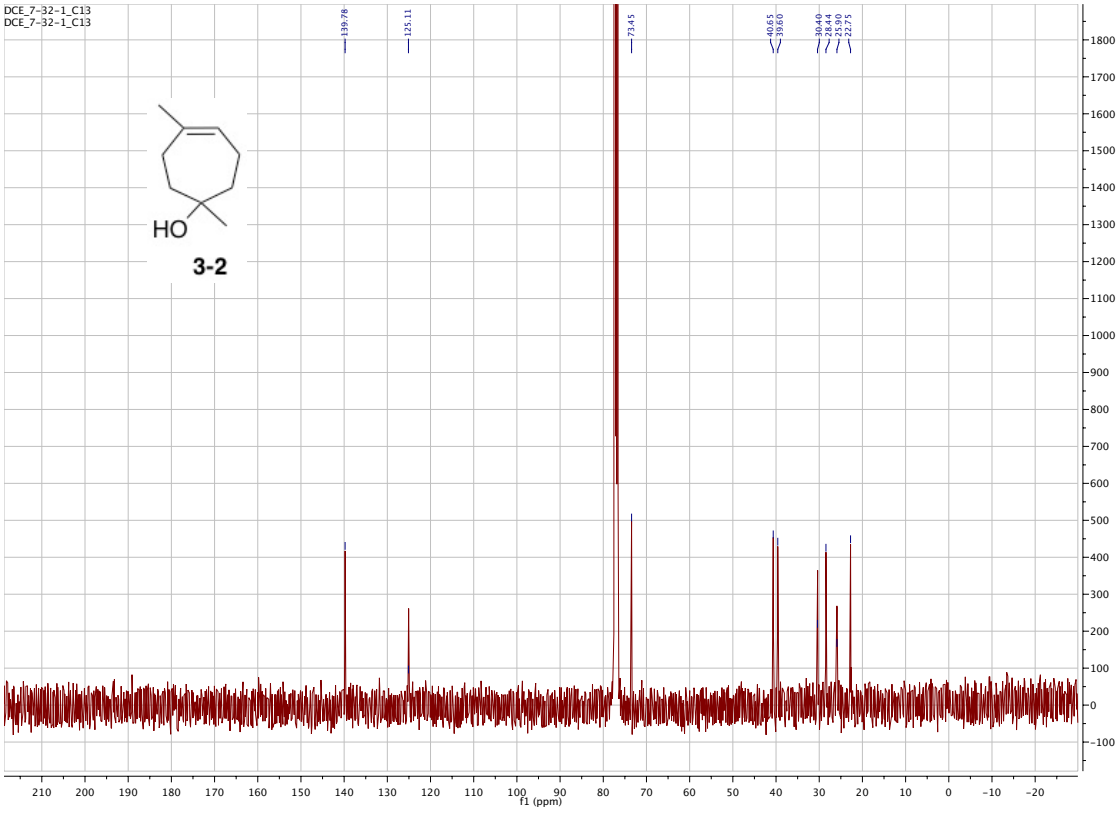

DCE_7-12-1
DCE_7-12-1
OTs
3-43
f1 (ppm)

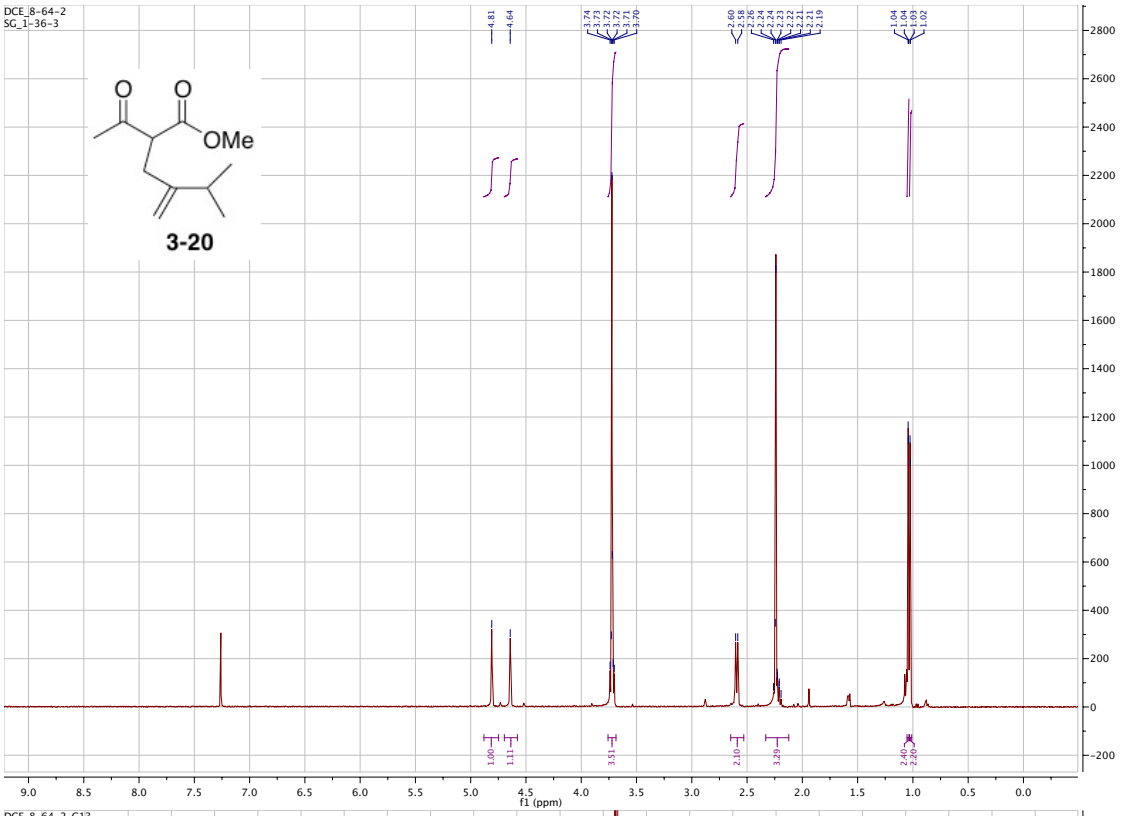

DCE_7-16-2
DCE_7-16-2
I
3-16
f1 (ppm)

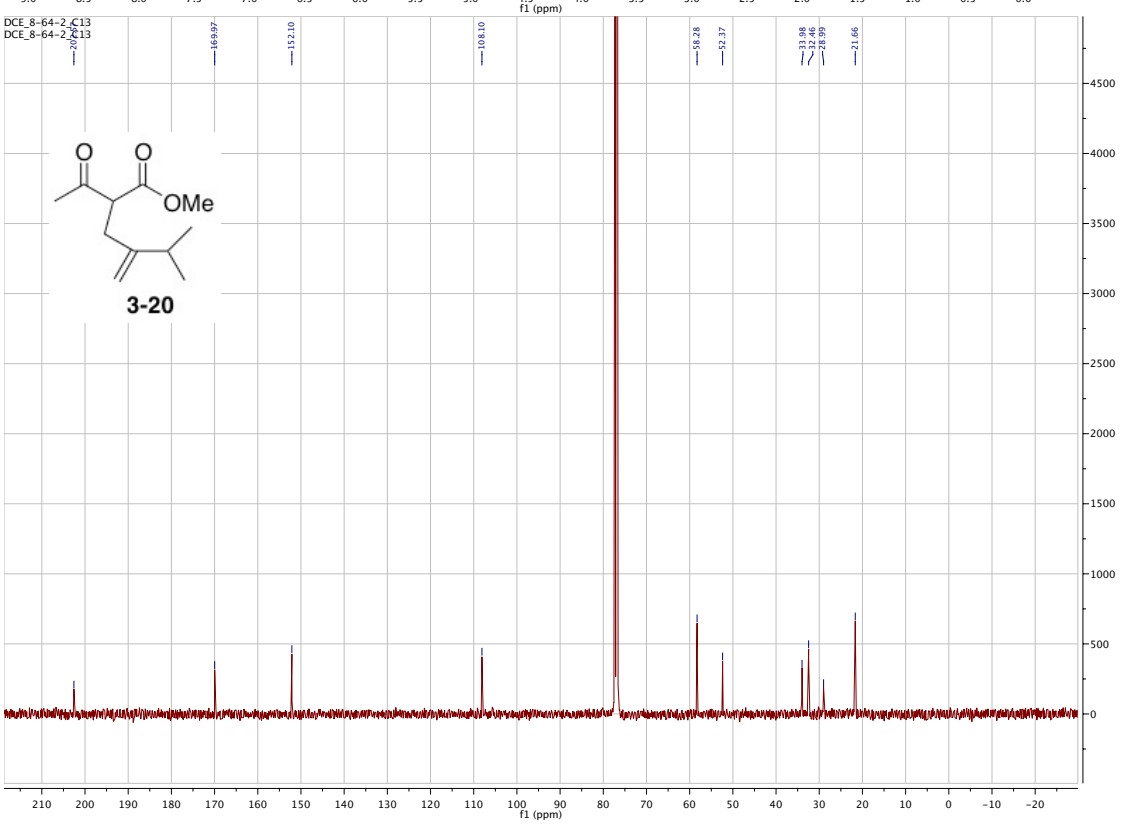

DCE_7-21-1.1.fid
DCE_7-21-1
OH
3-18
f1 (ppm)

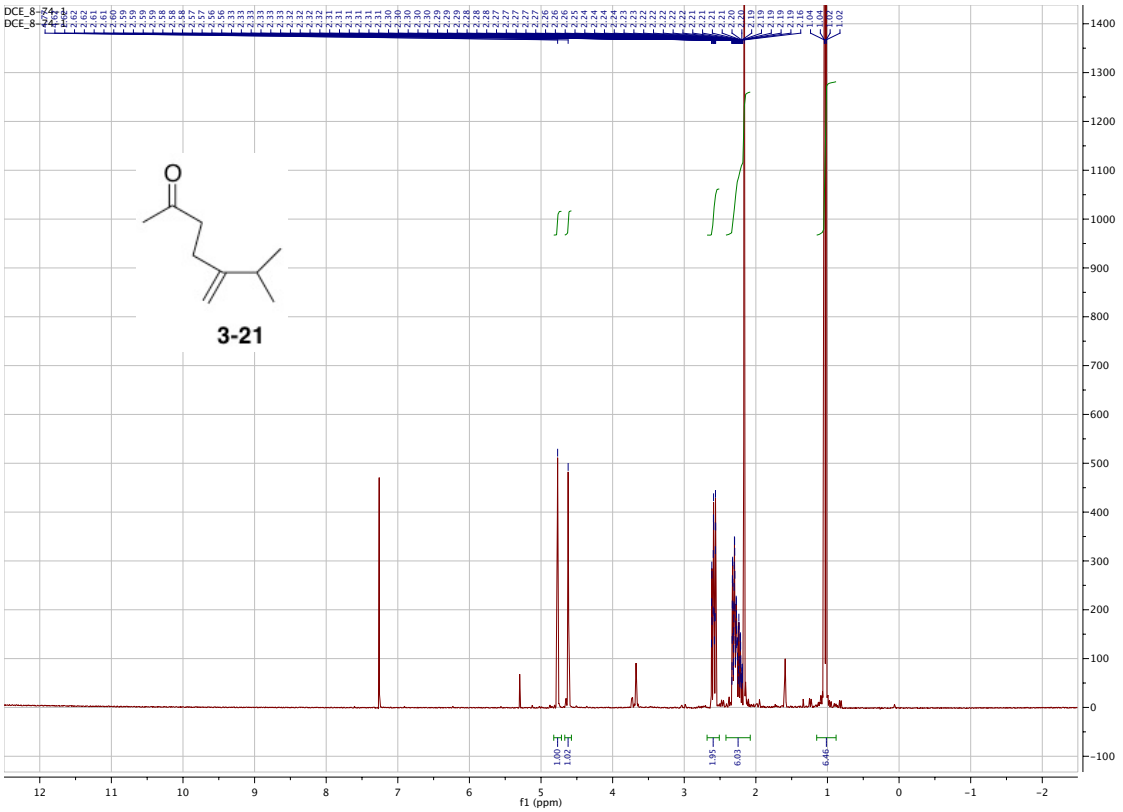

DCE_7-20-2_C13
DCE_7-20-2_C13
146.19
138.94
114.43
109.77
72.64
40.89
39.81
32.12
28.35
26.81
22.64
OH
3-18
f1 (ppm)

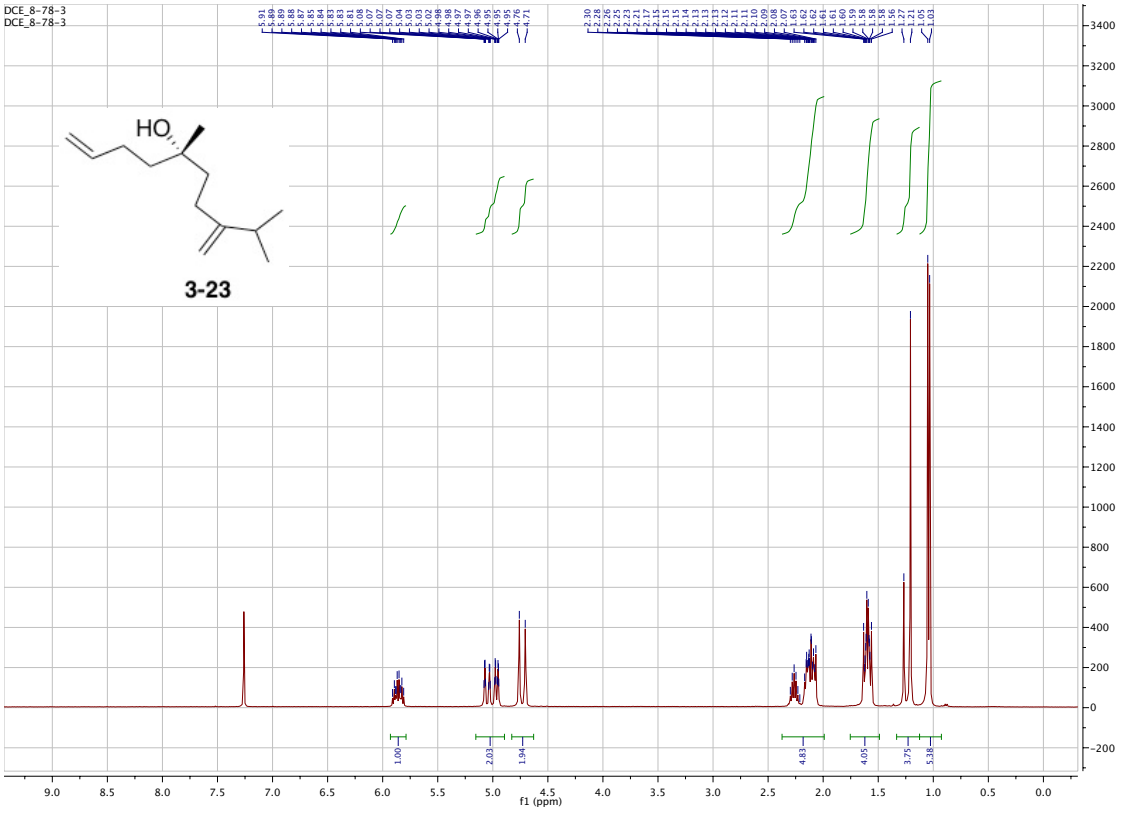

DCE_7-32-1
DCE_7-32-1
HO
3-2
f1 (ppm)

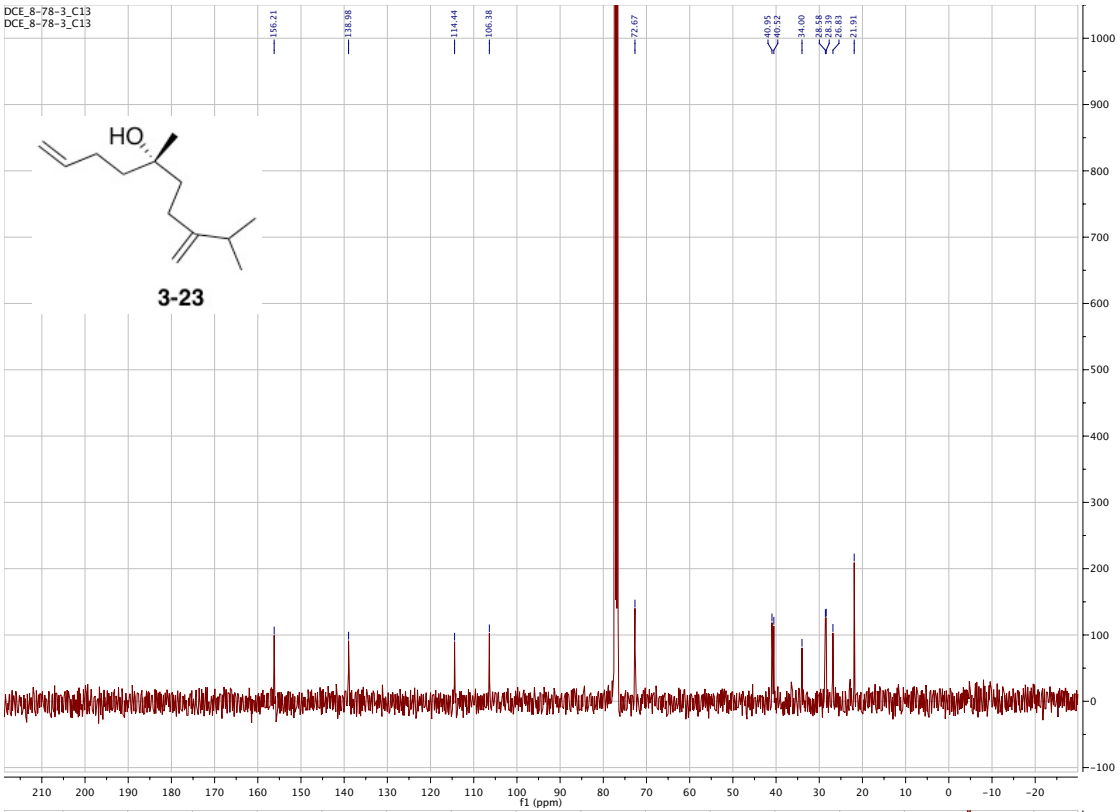

DCE_7-32-1_C13
DCE_7-32-1_C13
139.78
125.11
73.45
40.65
39.60
30.40
24.44
23.90
22.75
HO
3-2
f1 (ppm)

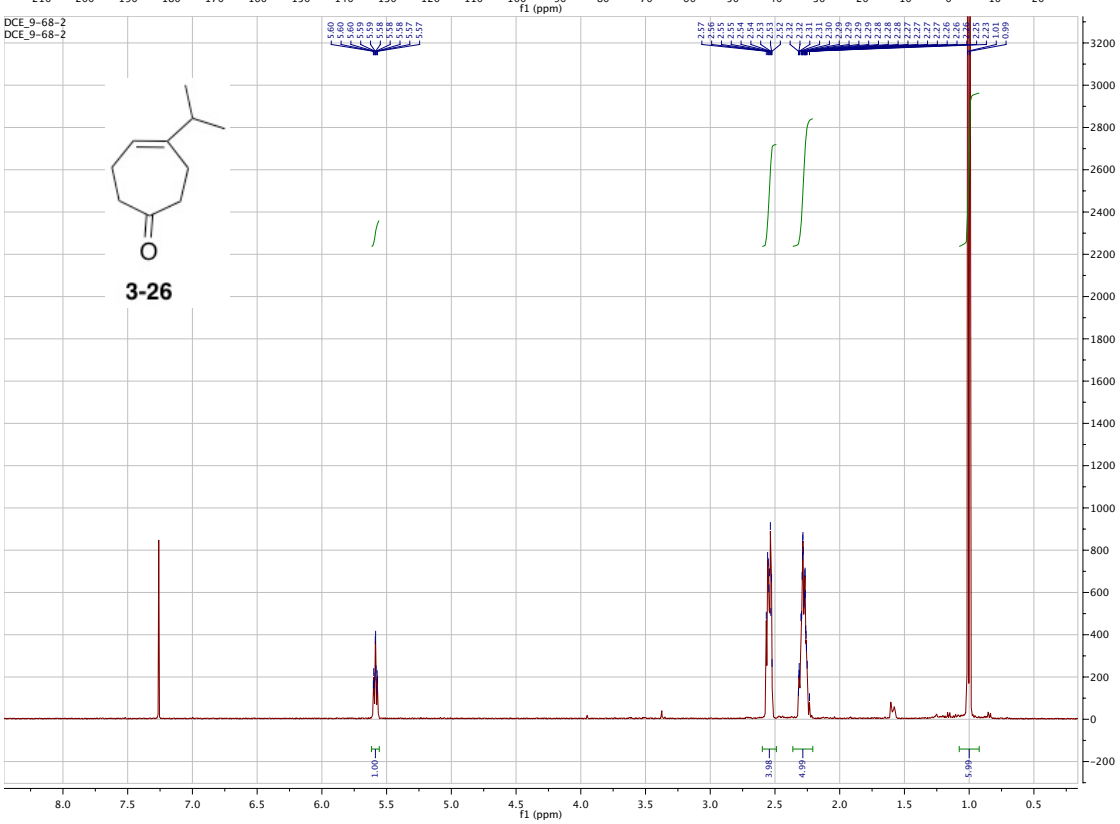

DCE_8-64-2
SG_1-36-3
OMe
3-20
f1 (ppm)

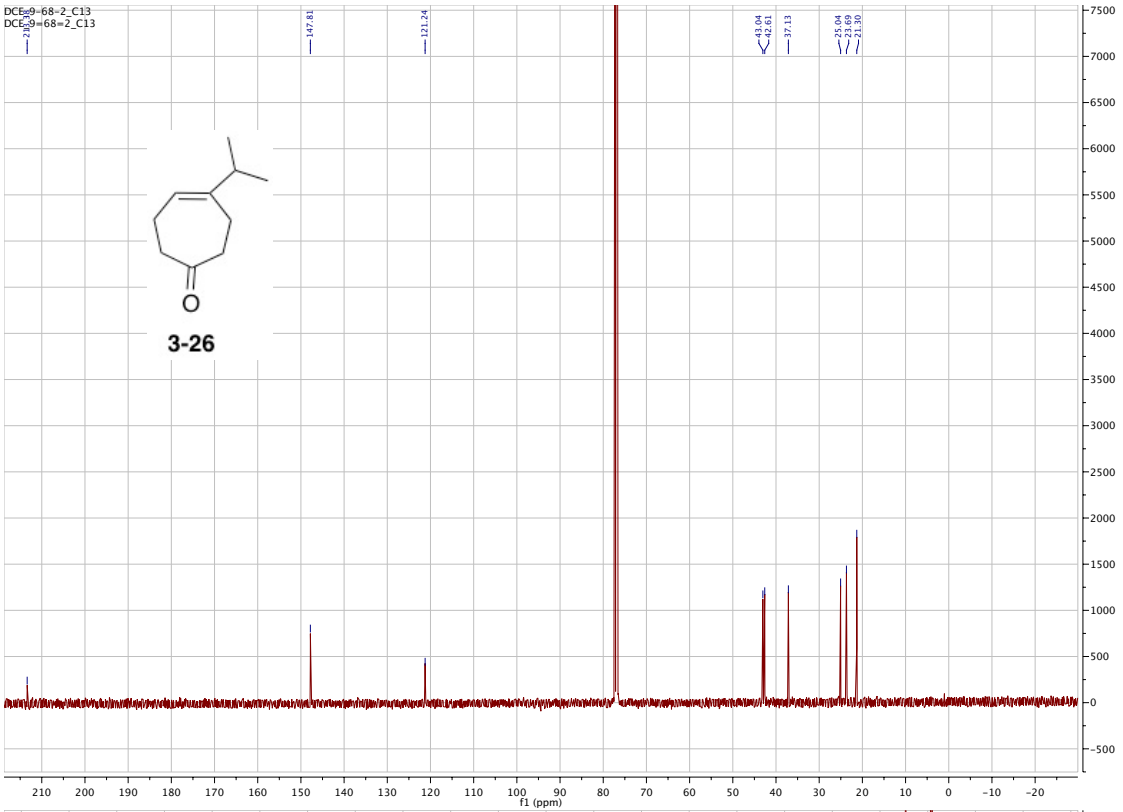

DCE_8-64-2_C13
DCE_8-64-2_C13
OMe
3-20
f1 (ppm)

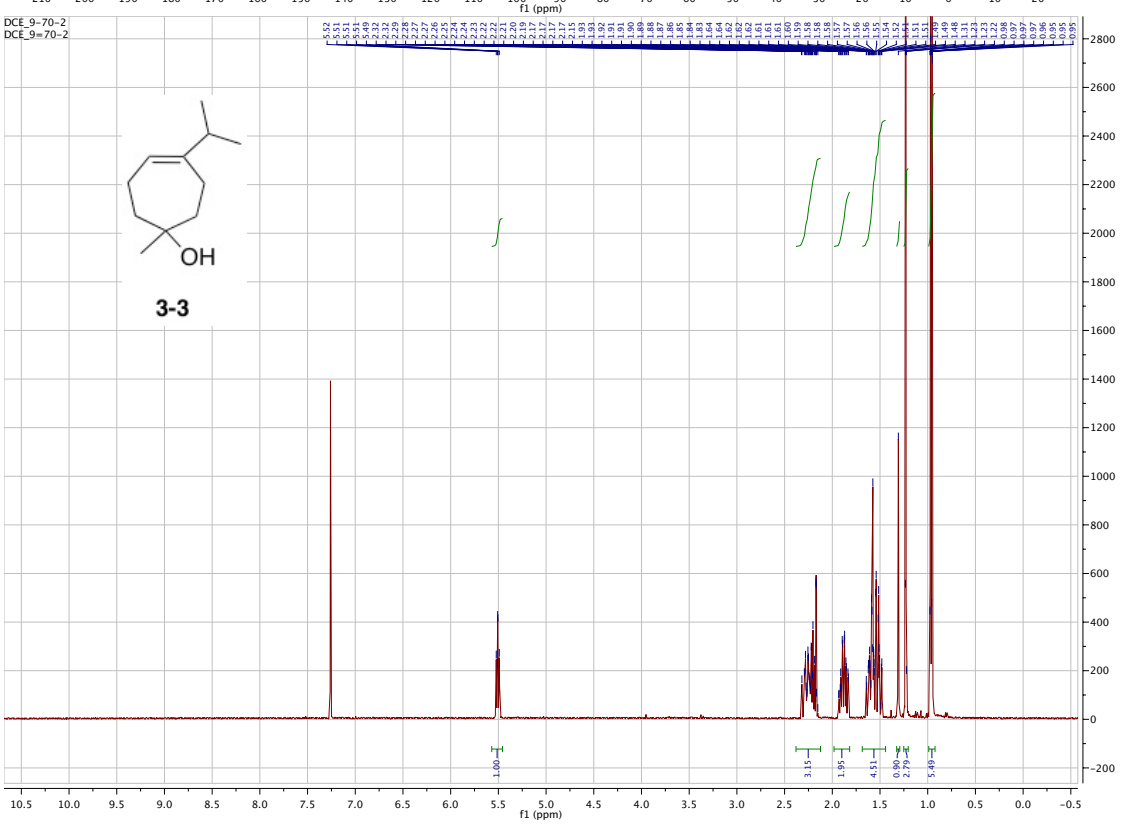

O
3-21
f1 (ppm)

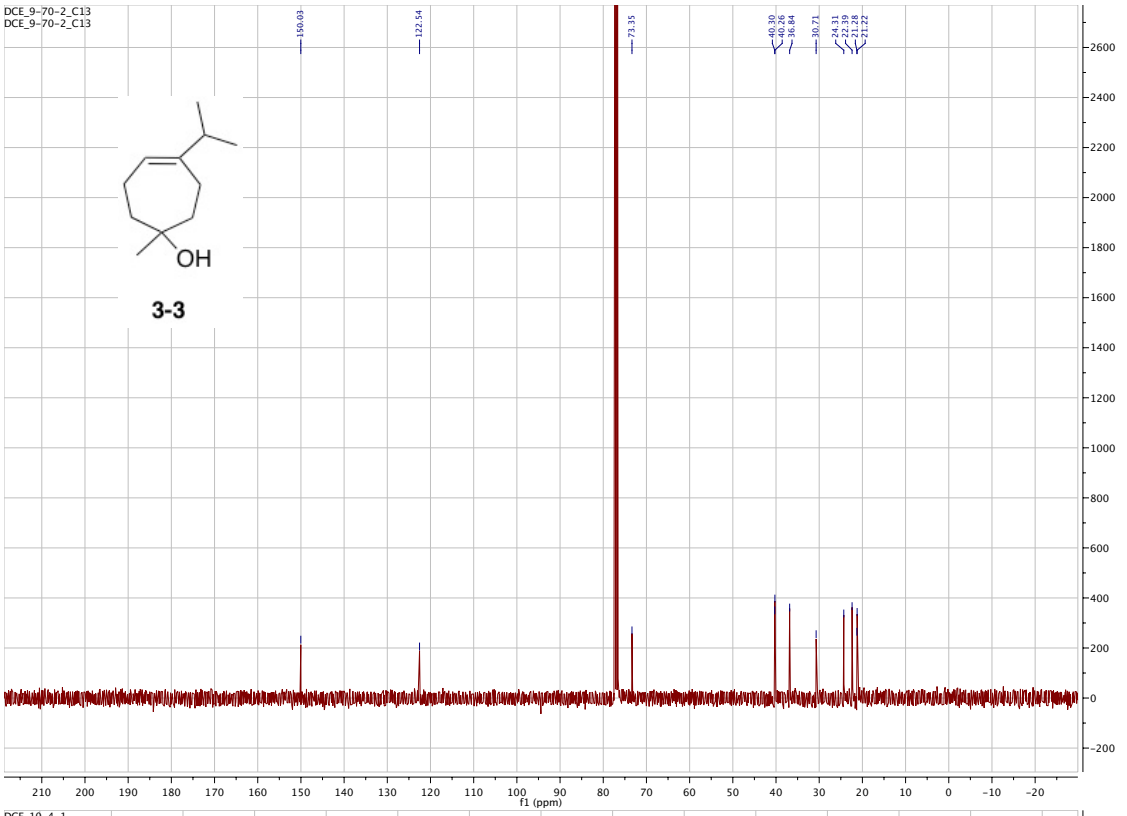

HO
3-23
f1 (ppm)

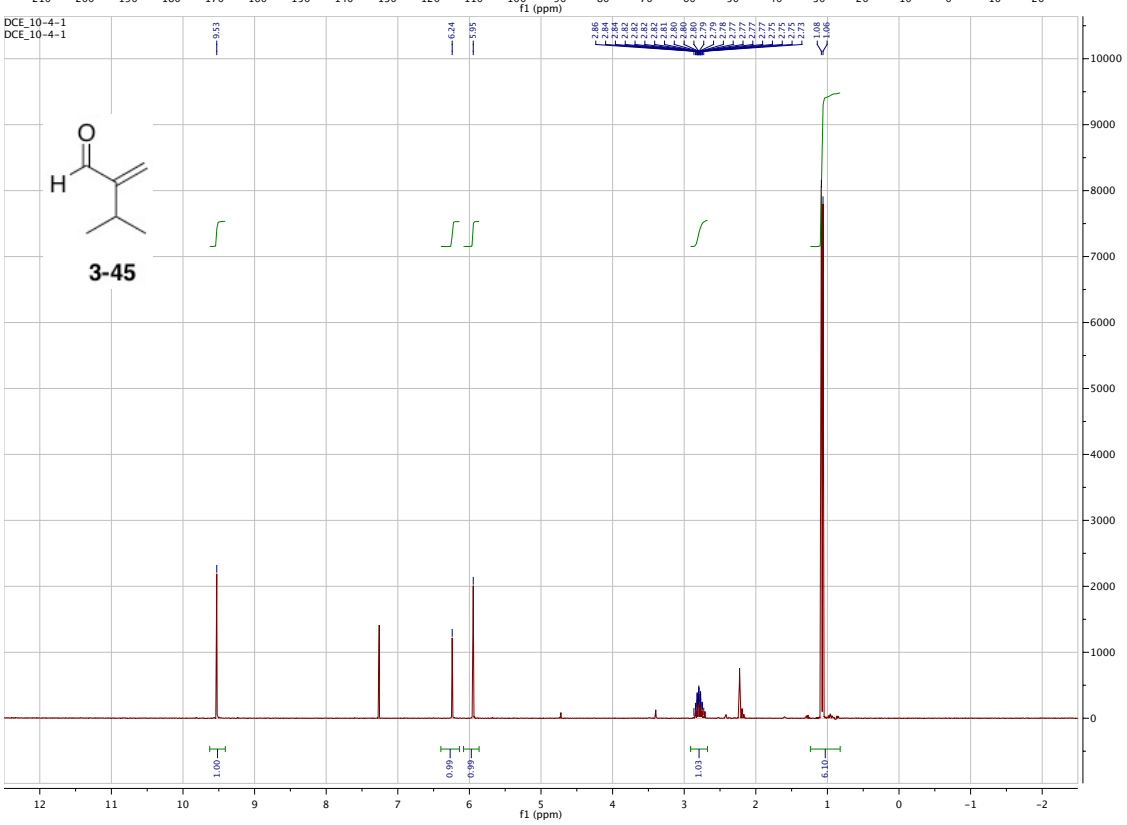

DCE_8-78-3_C13
DCE_8-78-3_C13
156.21
138.98
114.44
106.38
72.67
40.95
40.52
34.00
28.58
28.39
26.83
21.91
HO
3-23
f1 (ppm)

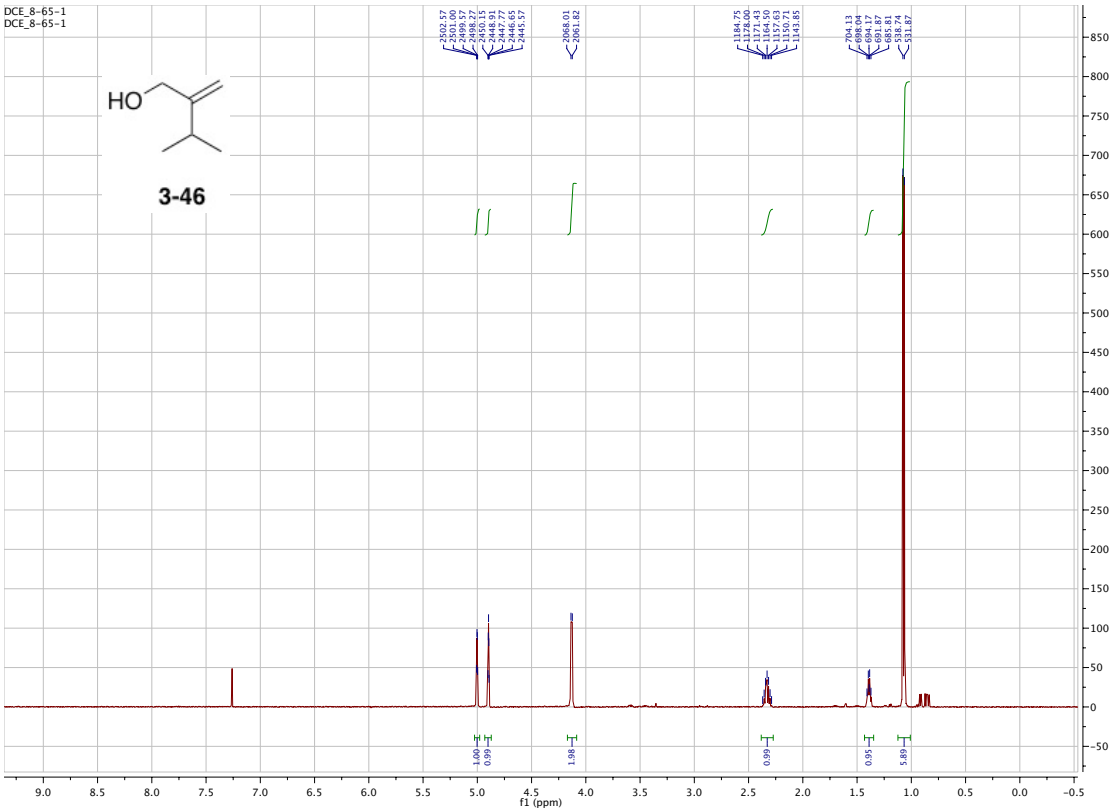

DCE_9-68-2
DCE_9-68-2
O
3-26
1.00
3.98
4.99
5.99
f1 (ppm)

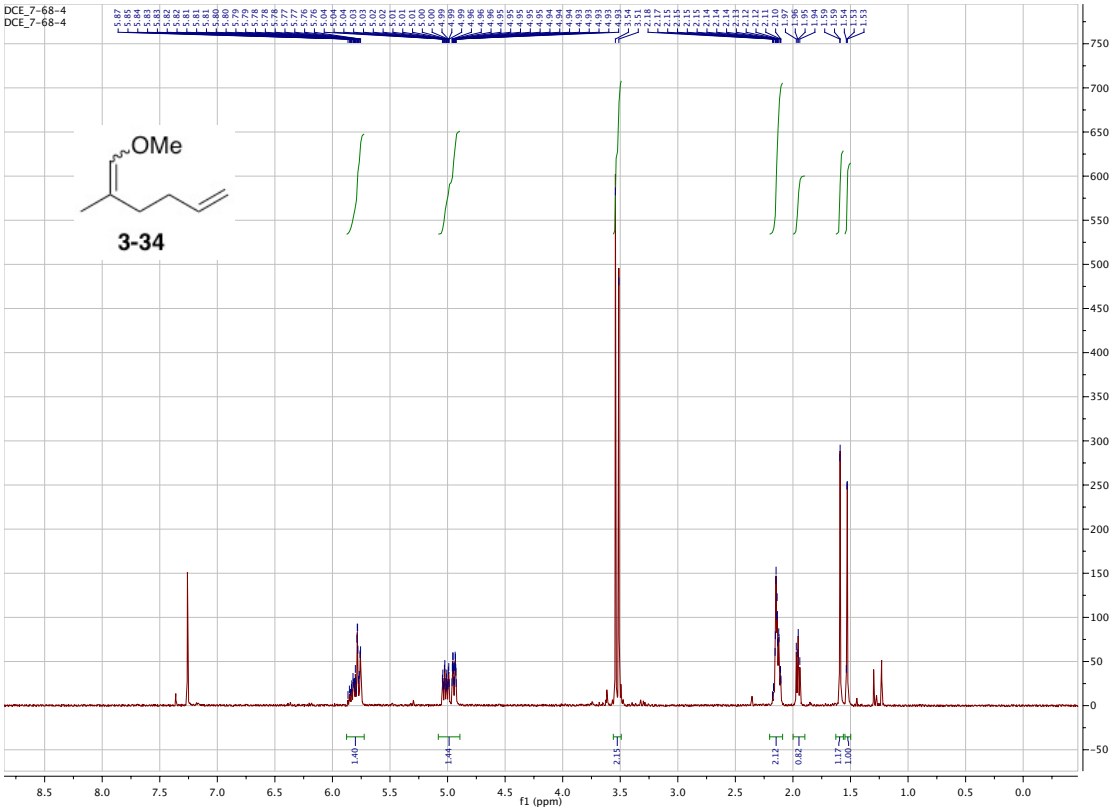

DCE_9-68-2_C13
DCE_9=68=2_C13
147.81
121.24
43.04
42.61
37.13
25.04
23.69
21.30
O
3-26
f1 (ppm)

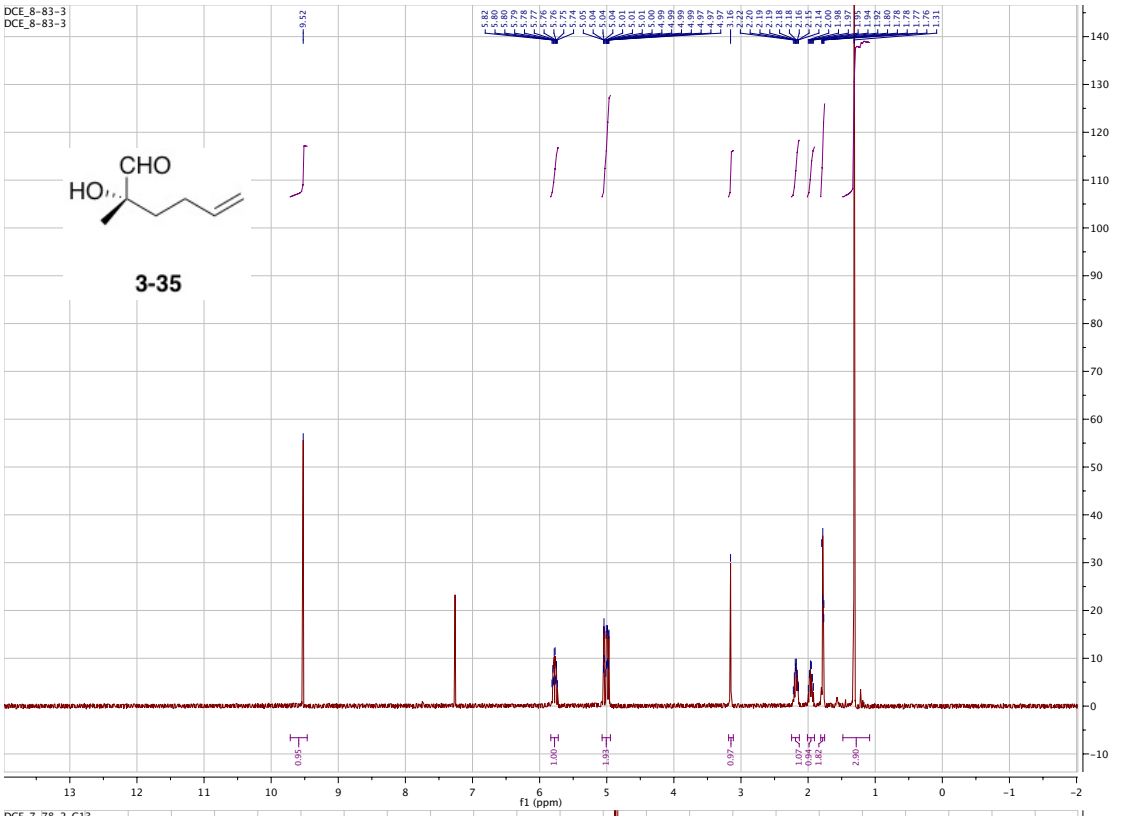

DCE_9-70-2
DCE_9=70-2
OH
3-3
1.00
3.15
1.95
4.51
0.90
2.79
5.49
f1 (ppm)

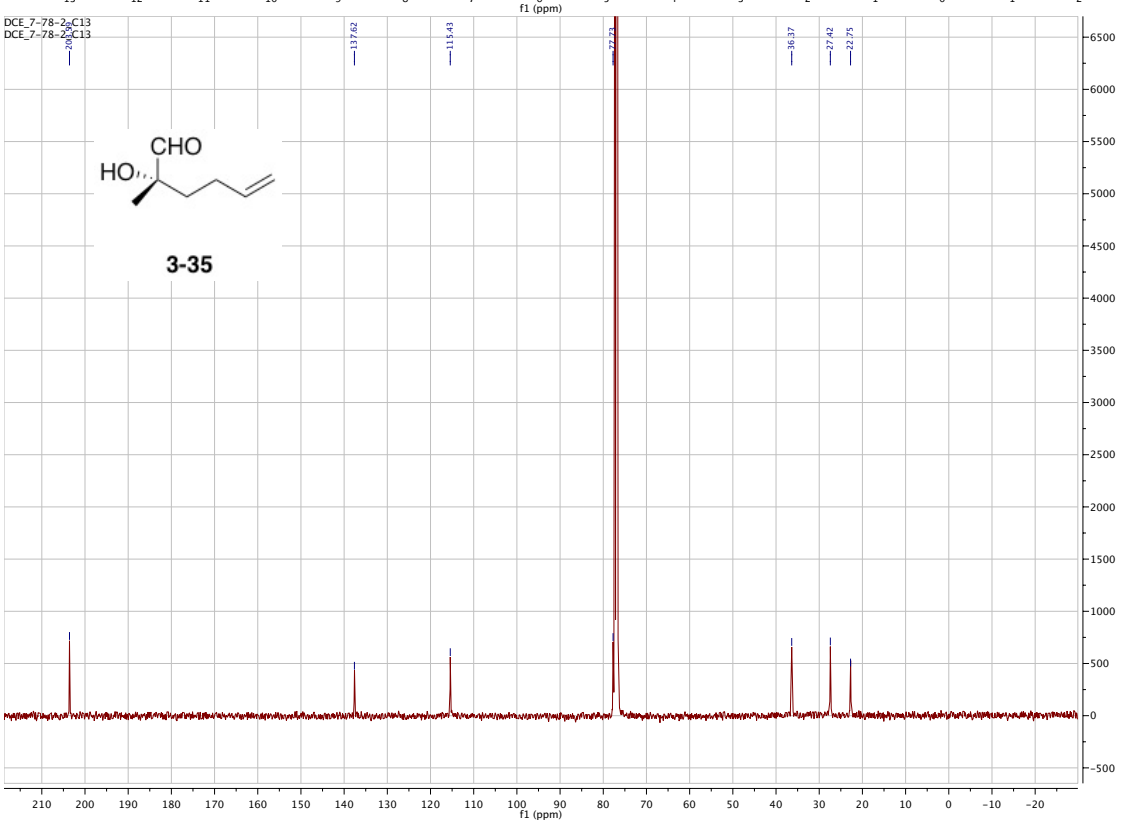

DCE_9-70-2_C13
DCE_9-70-2_C13
150.03
122.54
73.35
40.30
40.26
36.84
30.71
24.31
22.39
21.38
21.22
OH
3-3
f1 (ppm)

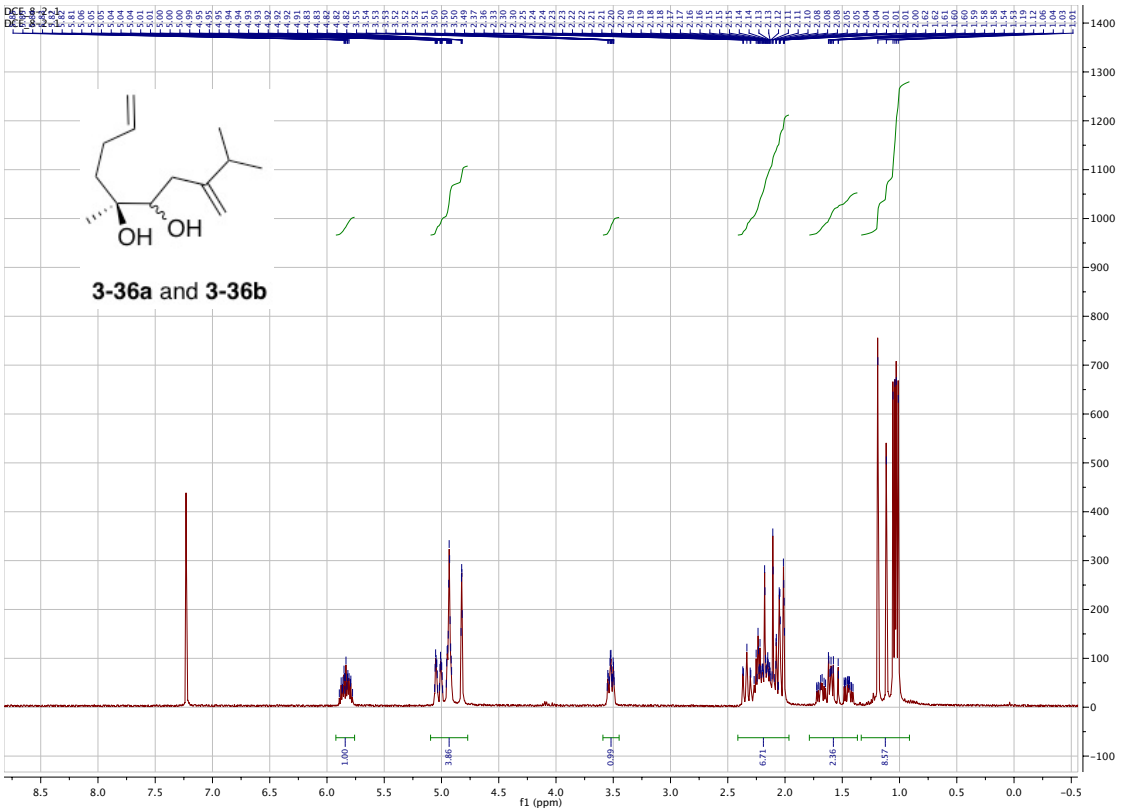

DCE_10-4-1
DCE_10-4-1
9.53
6.24
5.95
1.08
1.06
O
H
3-45
1.00
0.99
0.99
1.03
6.10
f1 (ppm)

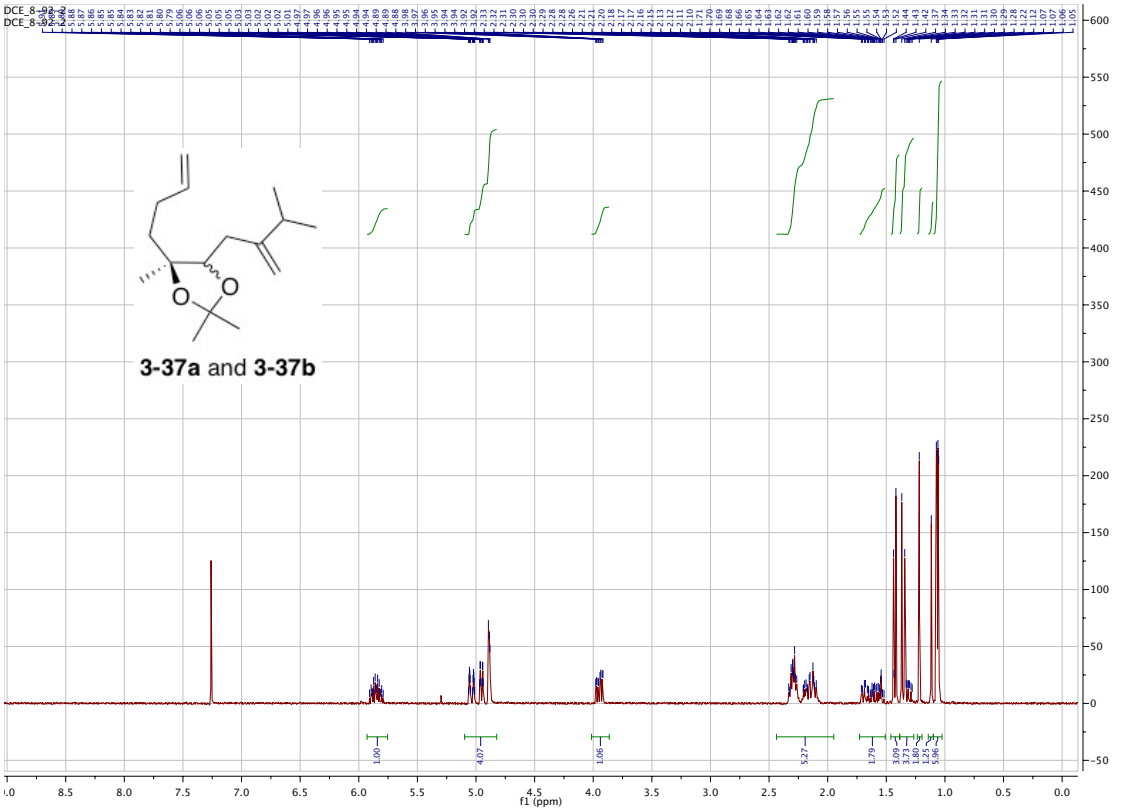

DCE_8-65-1
DCE_8-65-1
HO
3-46
f1 (ppm)

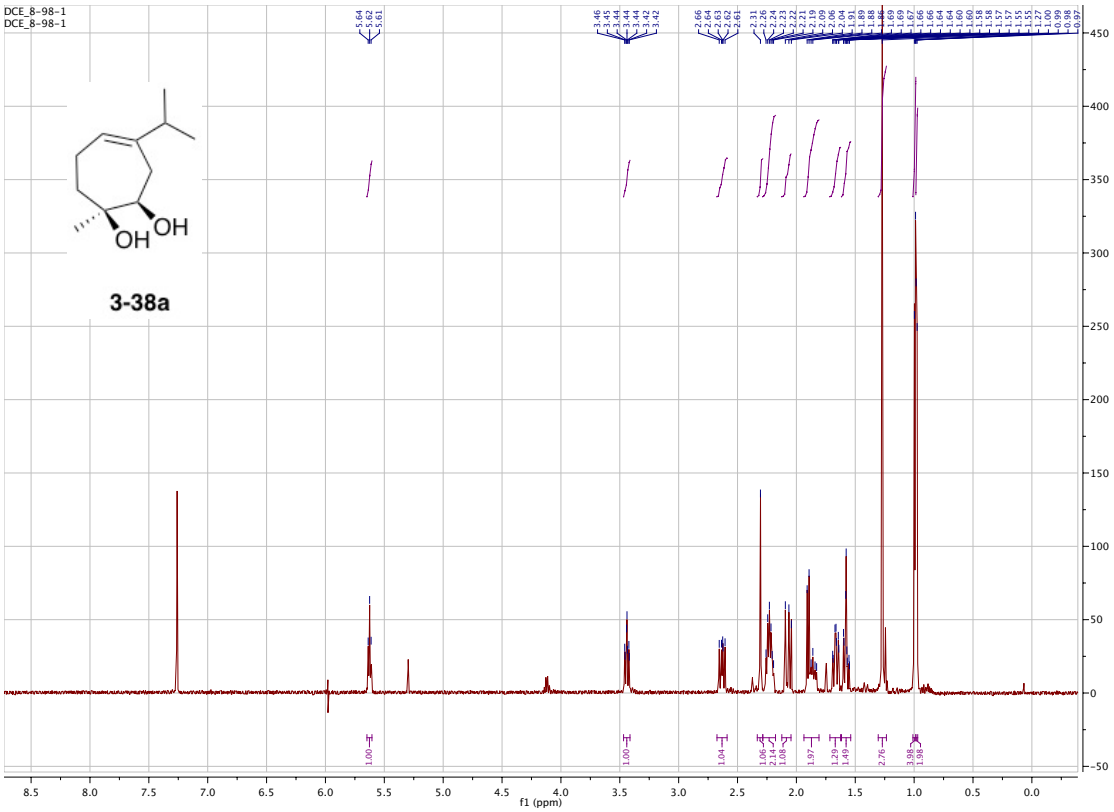

DCE_7-68-4
DCE_7-68-4
OMe
3-34
f1 (ppm)

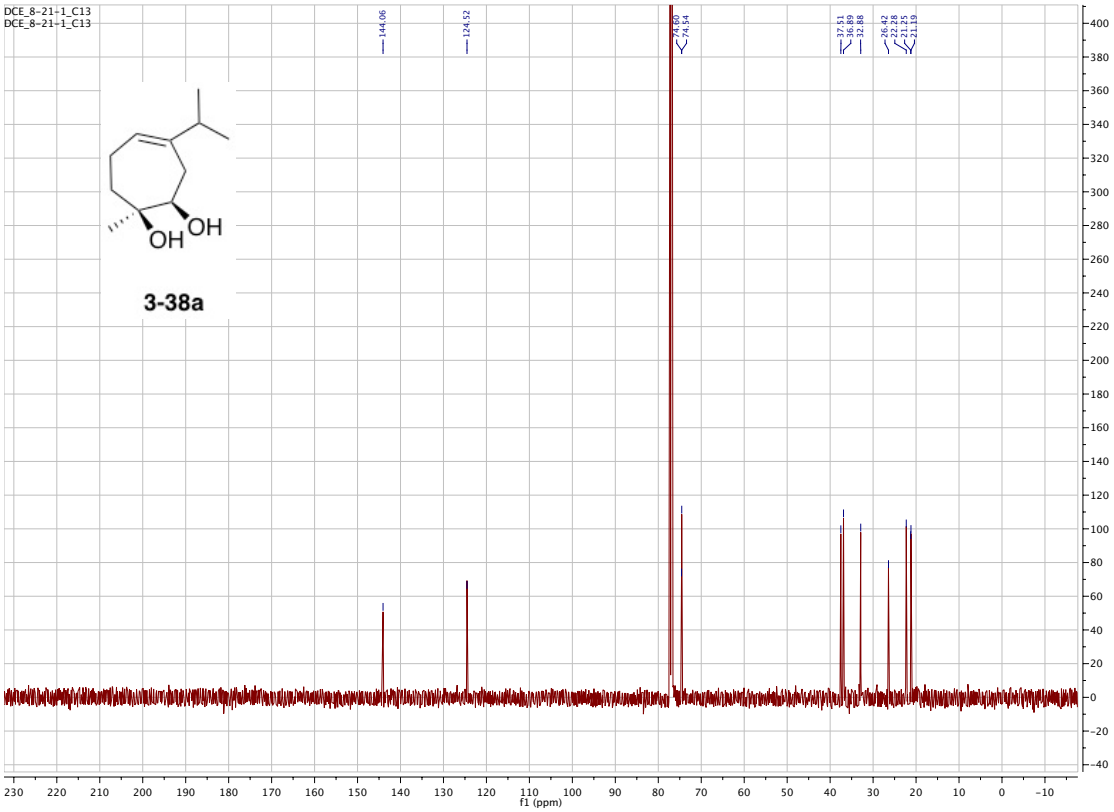

DCE_8-83-3
DCE_8-83-3
CHO
HO
3-35
f1 (ppm)

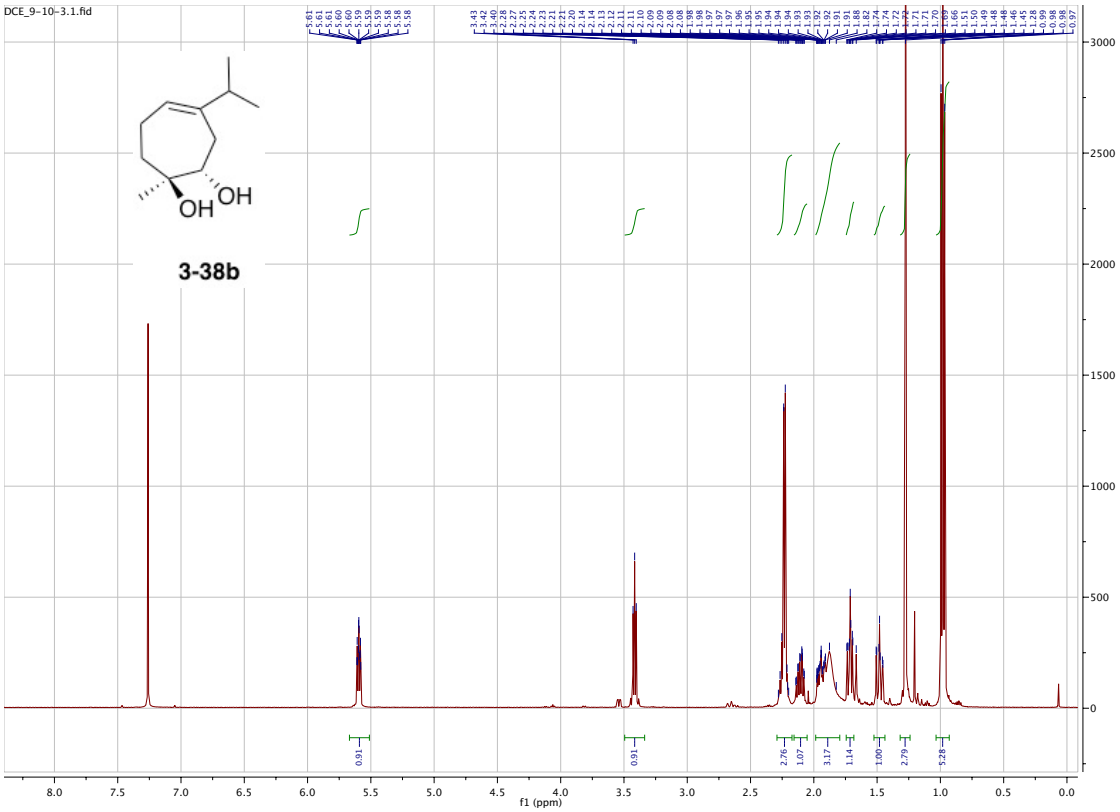

DCE_7-78-2_C13
DCE_7-78-2_C13
CHO
HO
3-35
f1 (ppm)

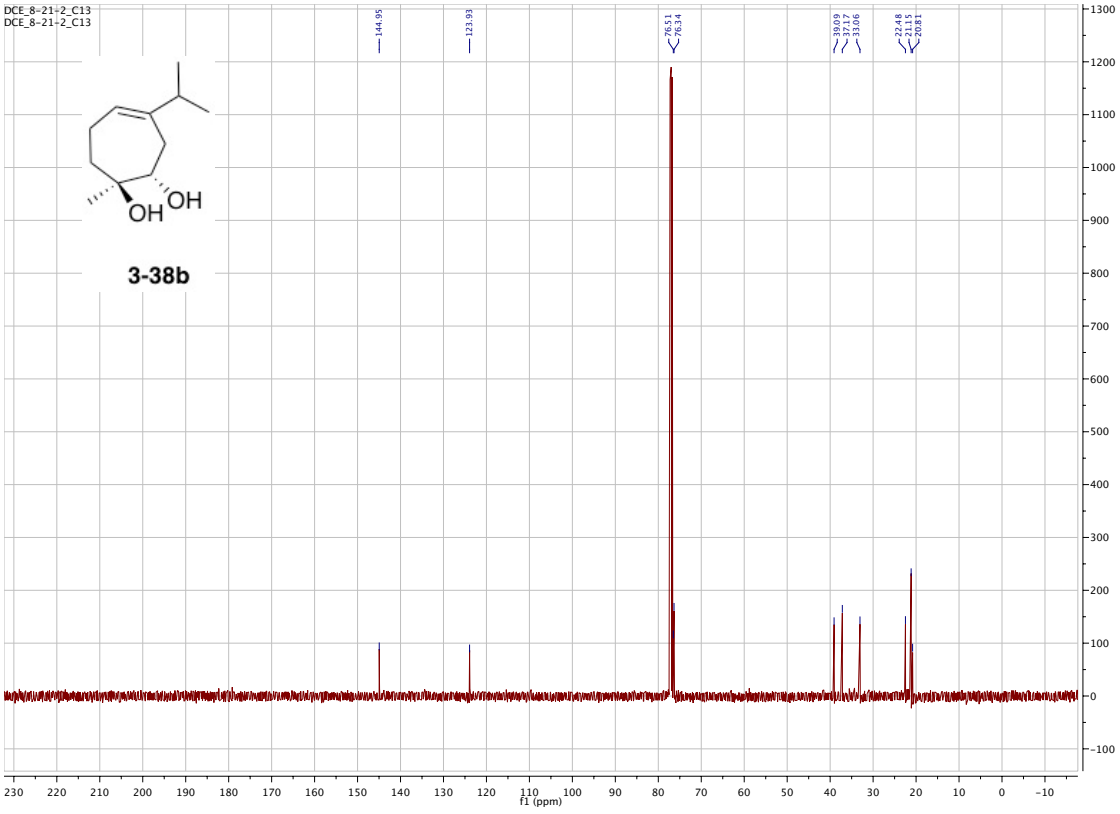

OH
OH
3-36a and 3-36b
f1 (ppm)

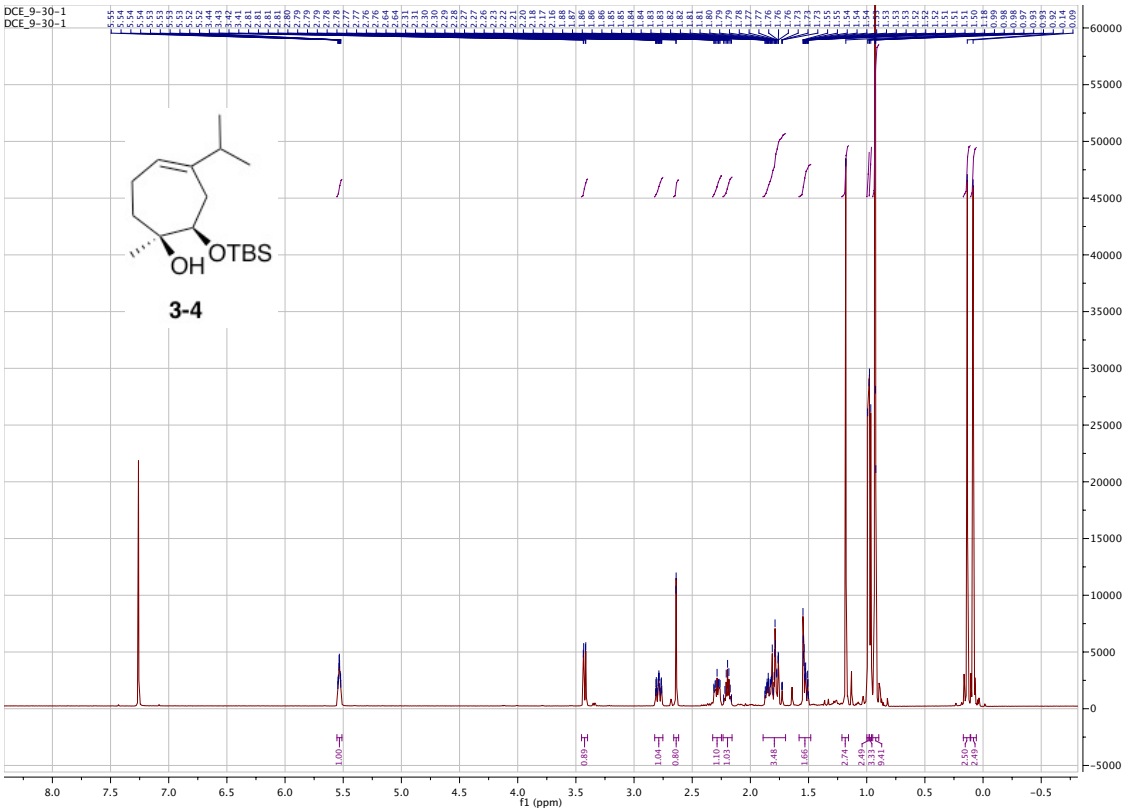

O
O
3-37a and 3-37b
f1 (ppm)

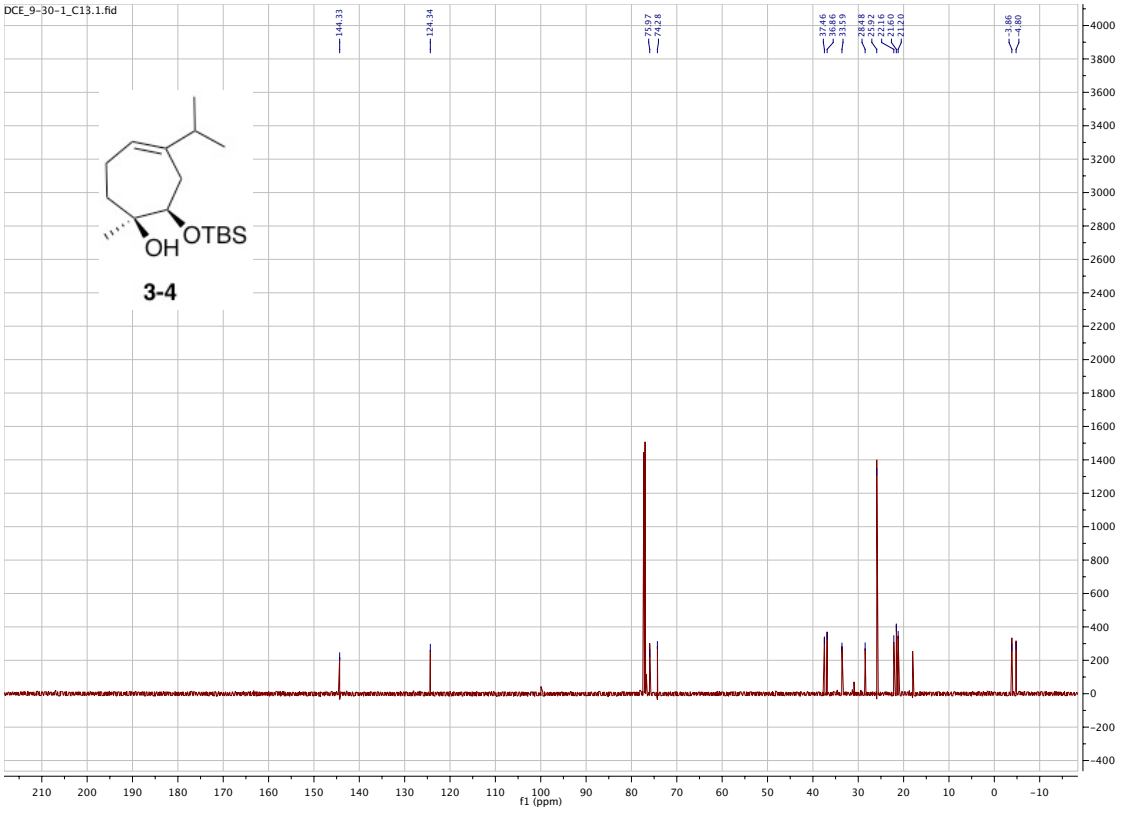

DCE_8-98-1
DCE_8-98-1
OH
OH
3-38a
f1 (ppm)

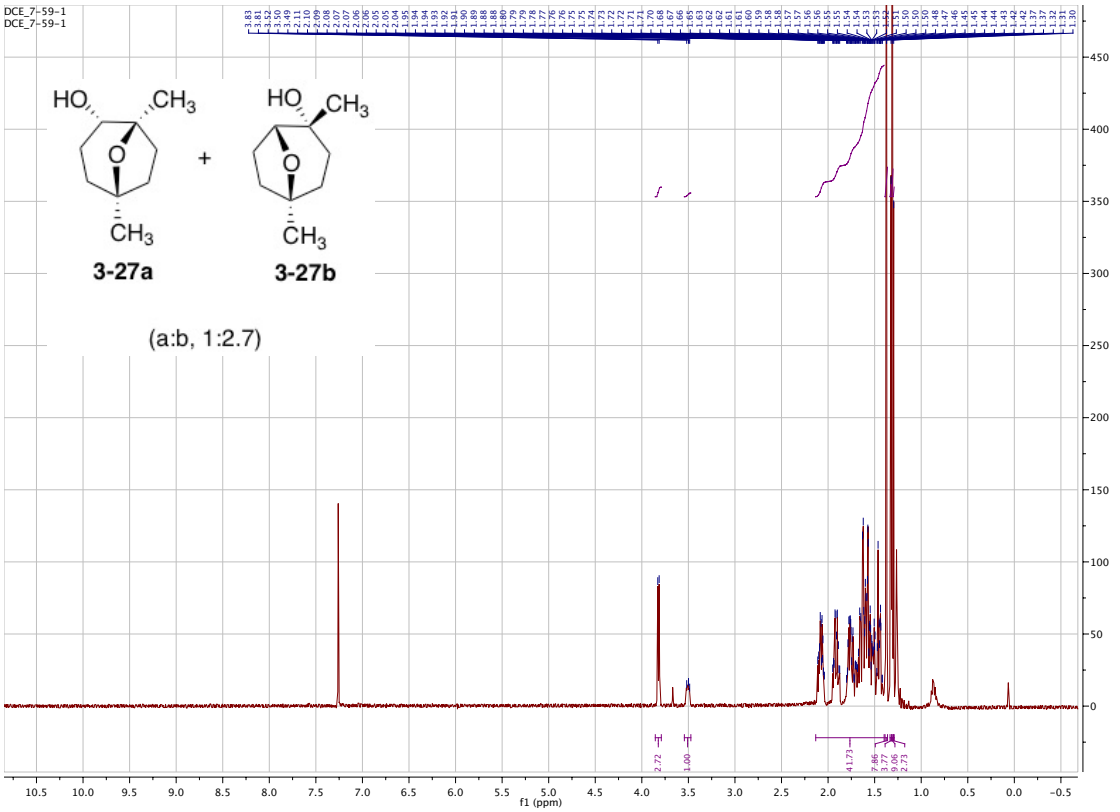

DCE_8-21+1_C13
DCE_8-21+1_C13
144.06
124.52
74.60
74.34
37.51
36.89
32.88
26.42
22.28
21.25
21.19
OH
OH
3-38a
f1 (ppm)

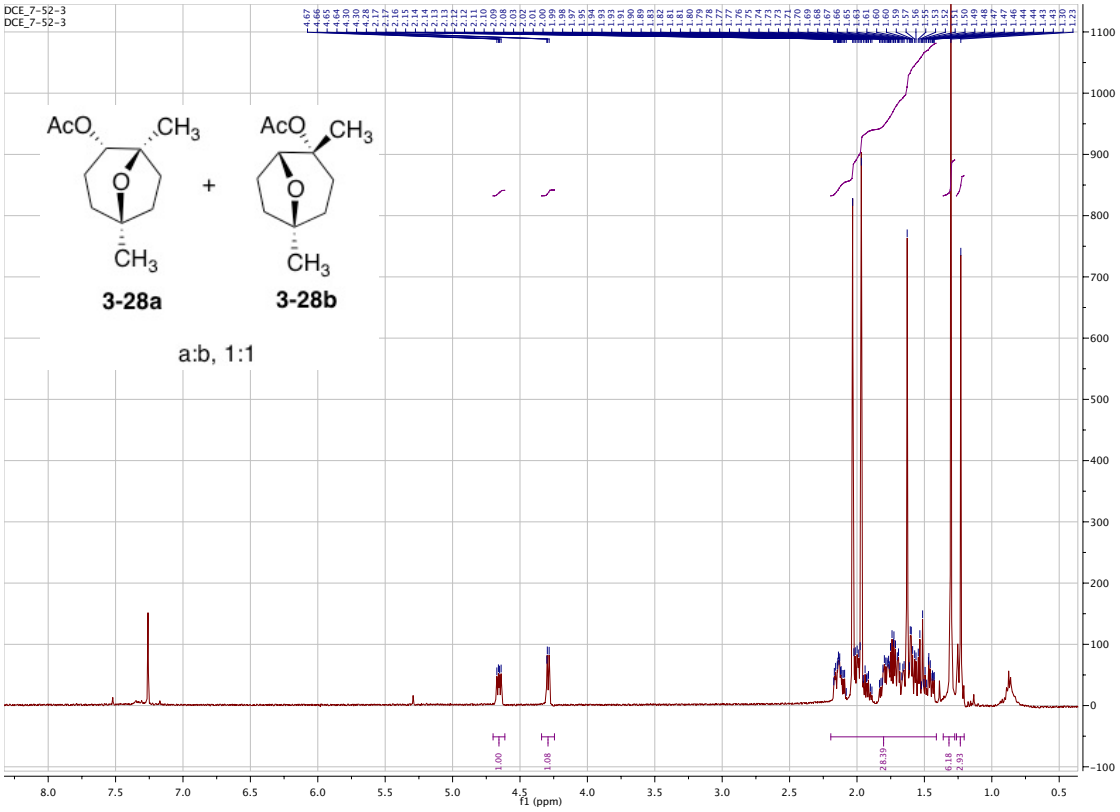

DCE_9-10-3.1.fid
OH
OH
3-38b
f1 (ppm)

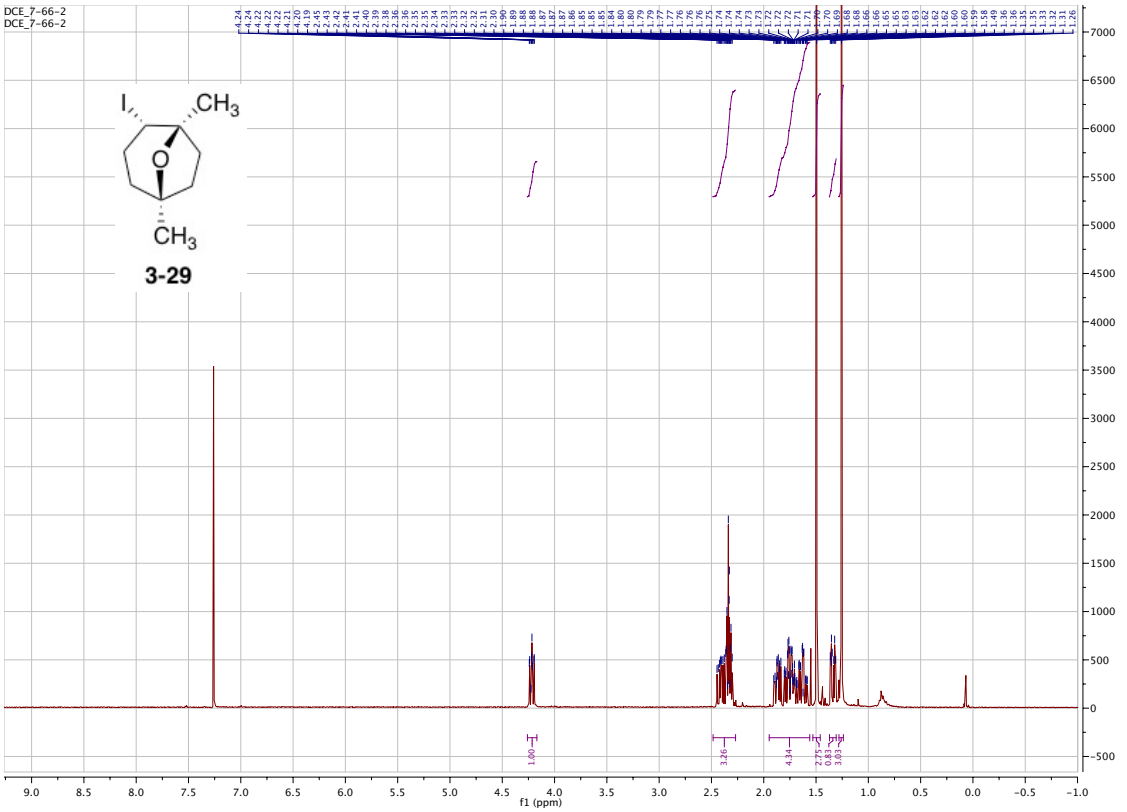

DCE_8-21-2_C13
DCE_8-21-2_C13
144.95
123.93
76.51
76.34
39.09
37.17
33.06
22.48
21.15
20.81
OH
OH
3-38b
f1 (ppm)

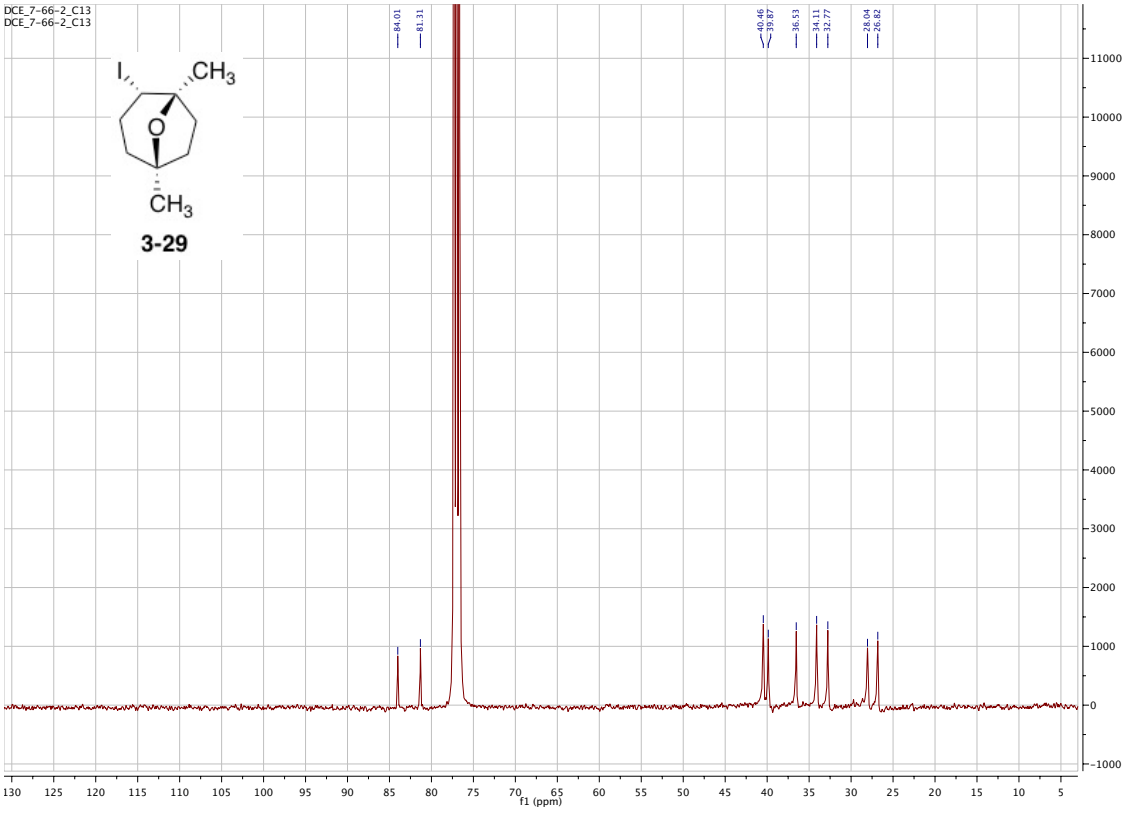

DCE_9-30-1
DCE_9-30-1
OH
OTBS
3-4
f1 (ppm)


DCE_9-30-1_C13.1.fid
144.33
124.34
75.97
74.68
37.46
36.86
35.59
28.48
25.92
24.16
21.60
21.20
13.86
4.80
OH
OTBS
3-4
f1 (ppm)

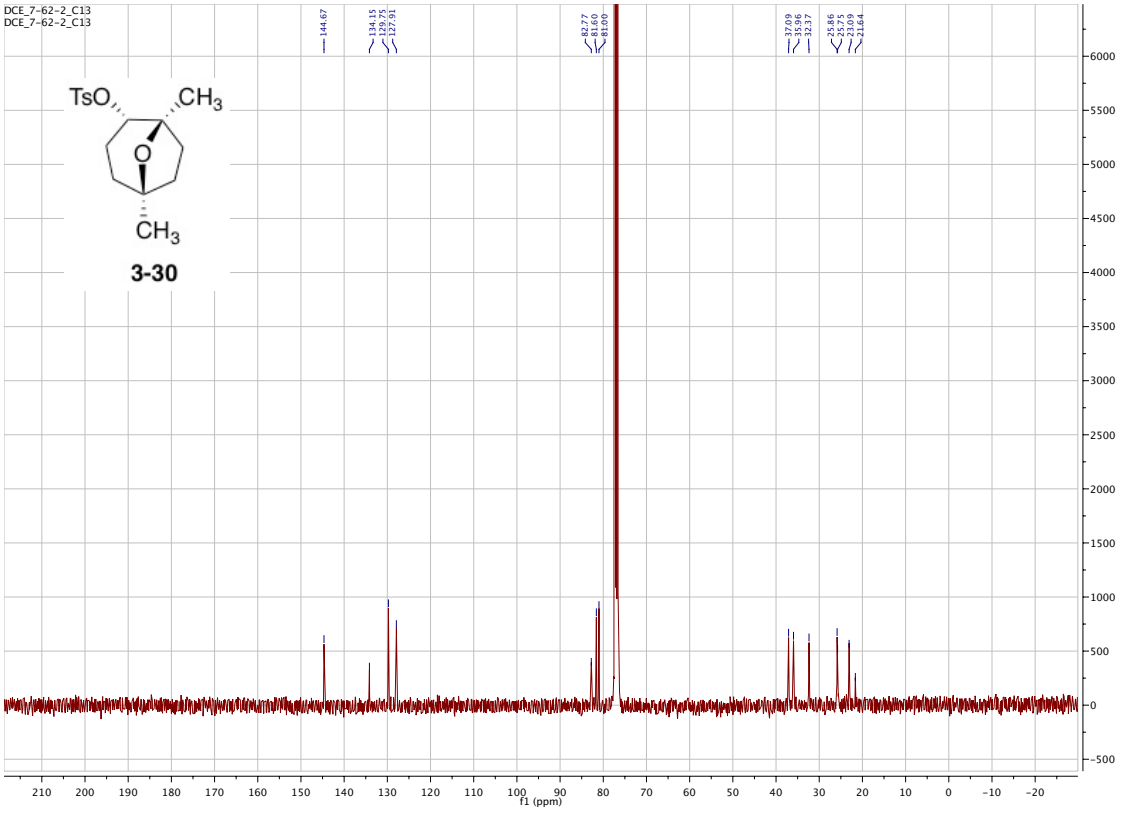

DCE_7-59-1
DCE_7-59-1
HO
CH3
O
CH3
+
HO
CH3
O
CH3
3-27a
3-27b
(a:b, 1:2.7)
f1 (ppm)

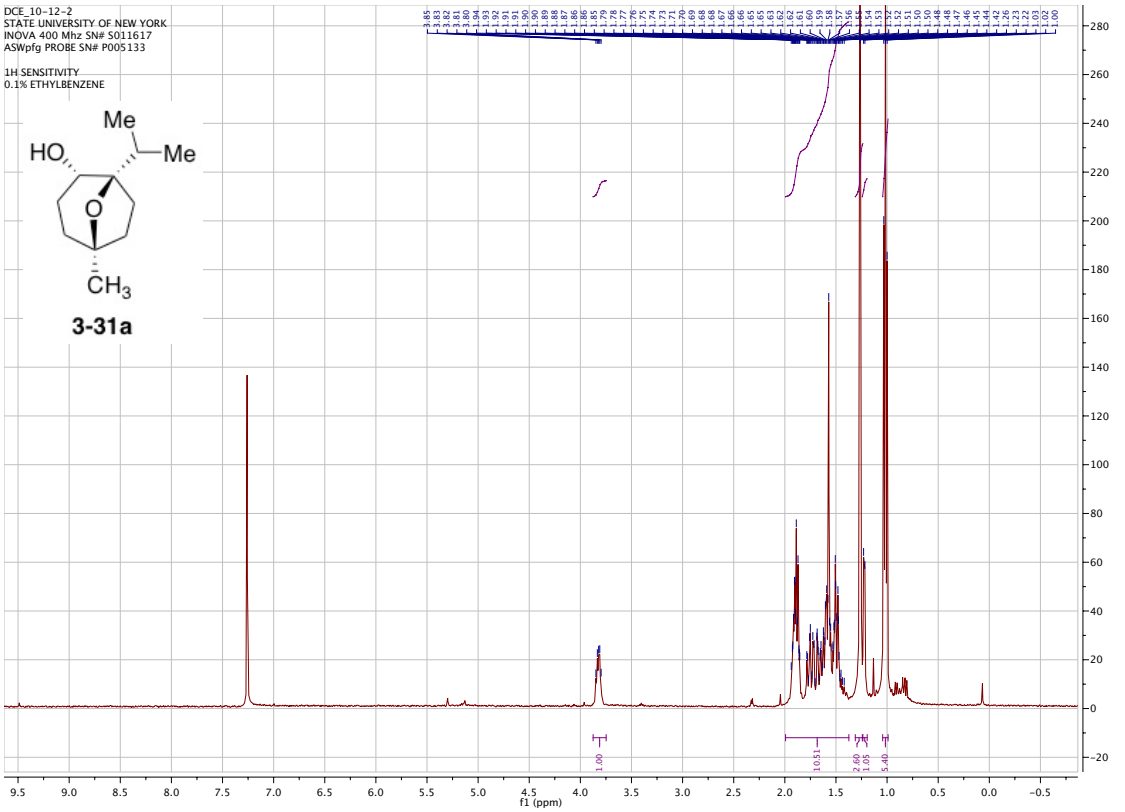

DCE_7-52-3
DCE_7-52-3
AcO
CH3
O
CH3
+
AcO
CH3
O
CH3
3-28a
3-28b
a:b, 1:1
f1 (ppm)

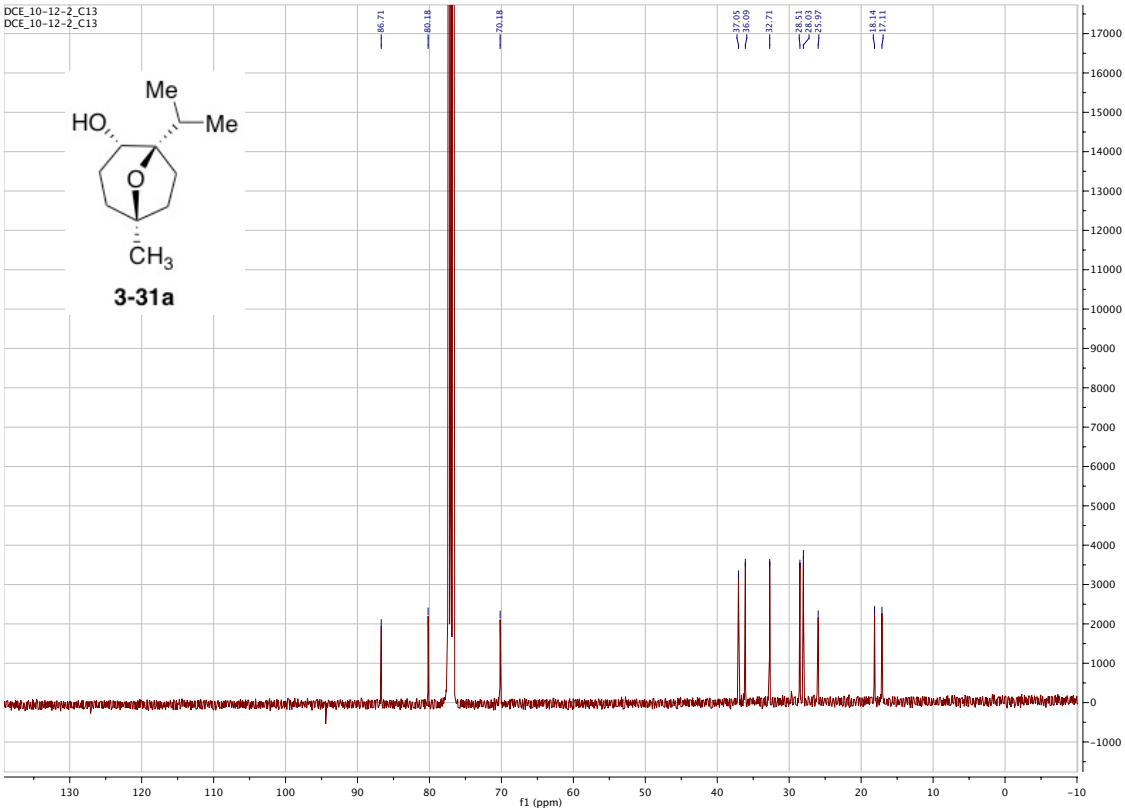

DCE_7-66-2
DCE_7-66-2
I
CH3
O
CH3
3-29
f1 (ppm)

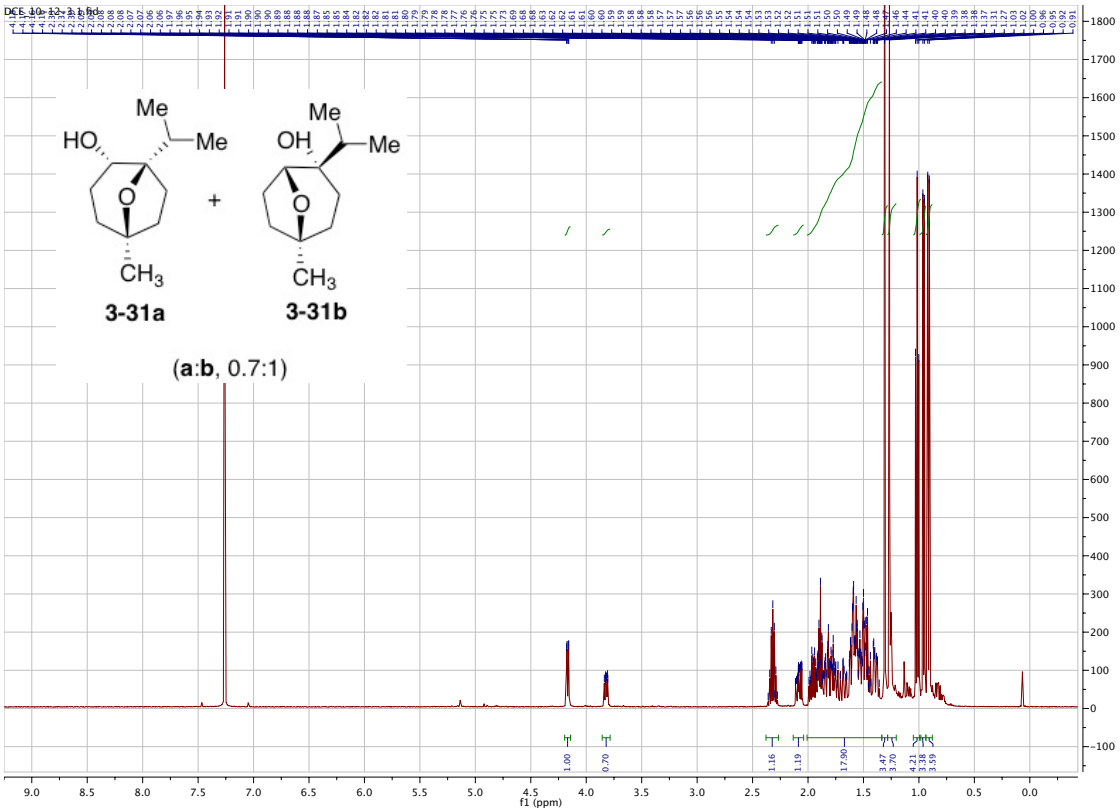

DCE_7-66-2_C13
DCE_7-66-2_C13
84.01
81.31
40.46
39.87
36.53
34.11
32.77
28.04
26.82
I
CH3
O
CH3
3-29
f1 (ppm)

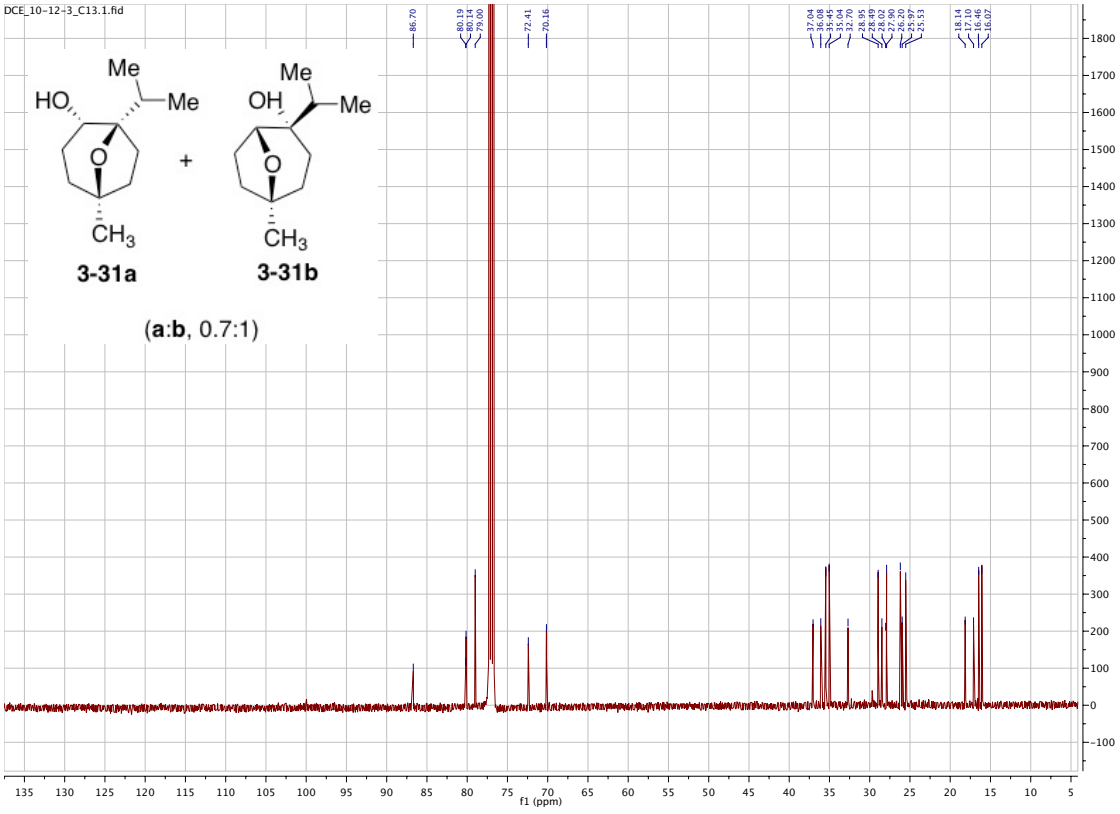

DCE_7-62-2
DCE_7-62-2
TsO
CH3
O
CH3
3-30
f1 (ppm)

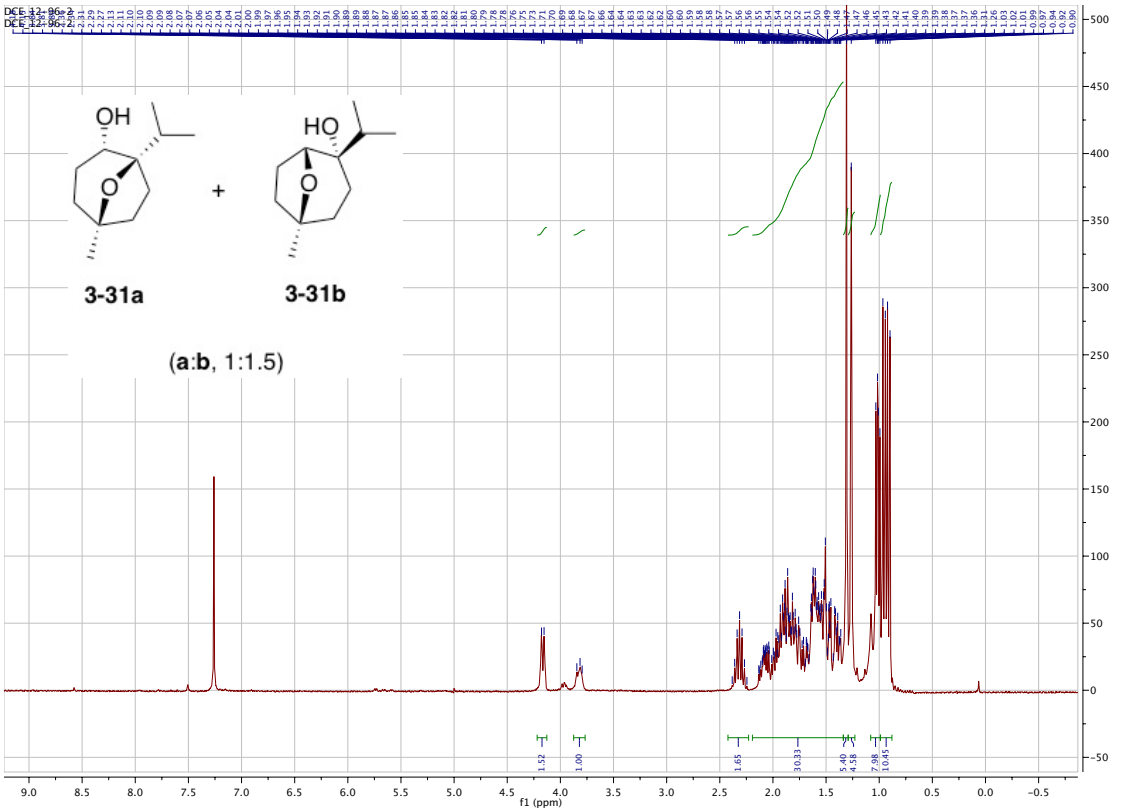

DCE_7-62-2_C13
DCE_7-62-2_C13
TsO
CH3
O
CH3
3-30
f1 (ppm)

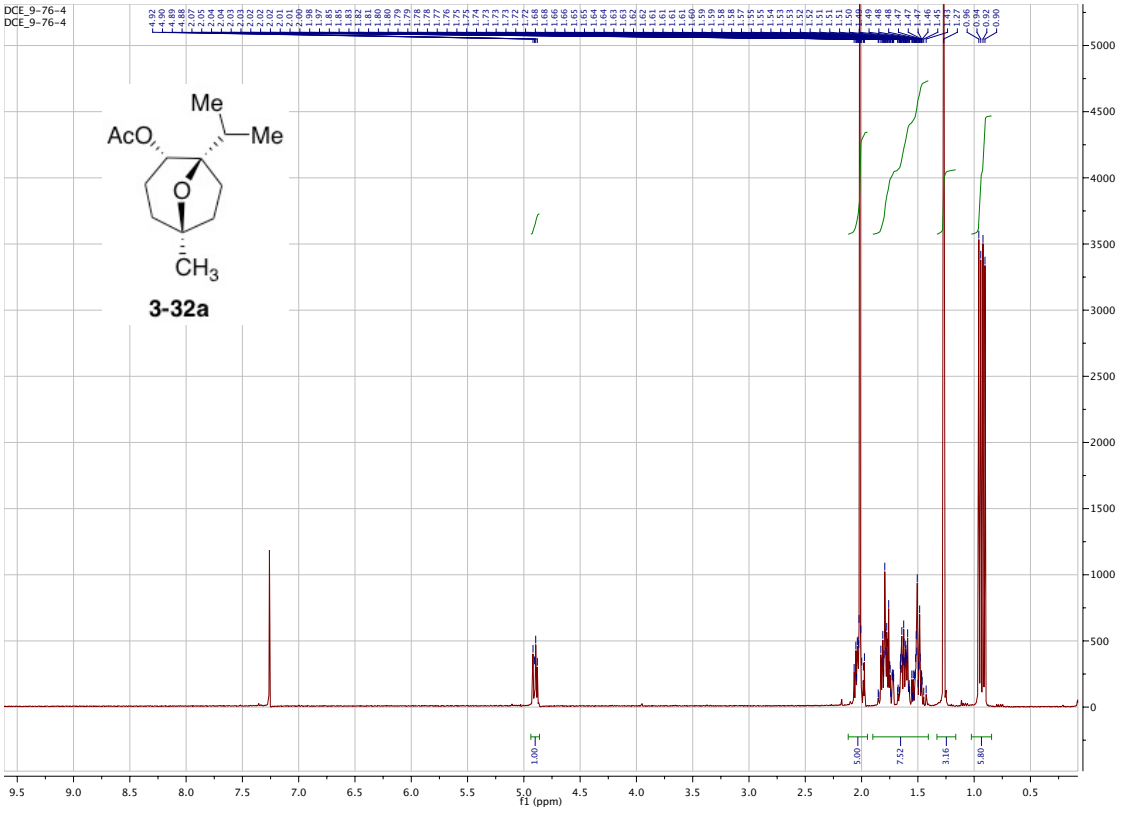

DCE_10-12-2
STATE UNIVERSITY OF NEW YORK
INOVA 400 Mhz SN# S011617
ASWpfg PROBE SN# P005133
1H SENSITIVITY
0.1% ETHYLBENZENE
Me
HO
Me
O
CH3
3-31a
f1 (ppm)

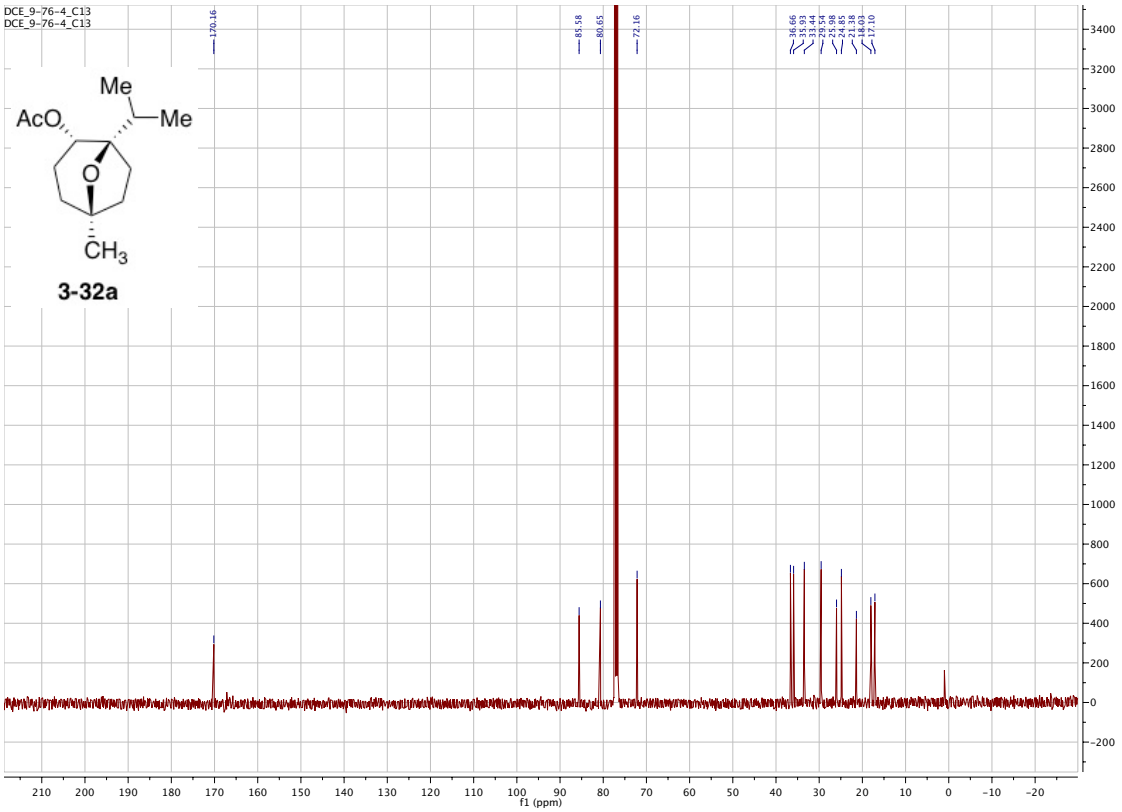

DCE_10-12-2_C13
DCE_10-12-2_C13
Me
HO
Me
O
CH3
3-31a
f1 (ppm)

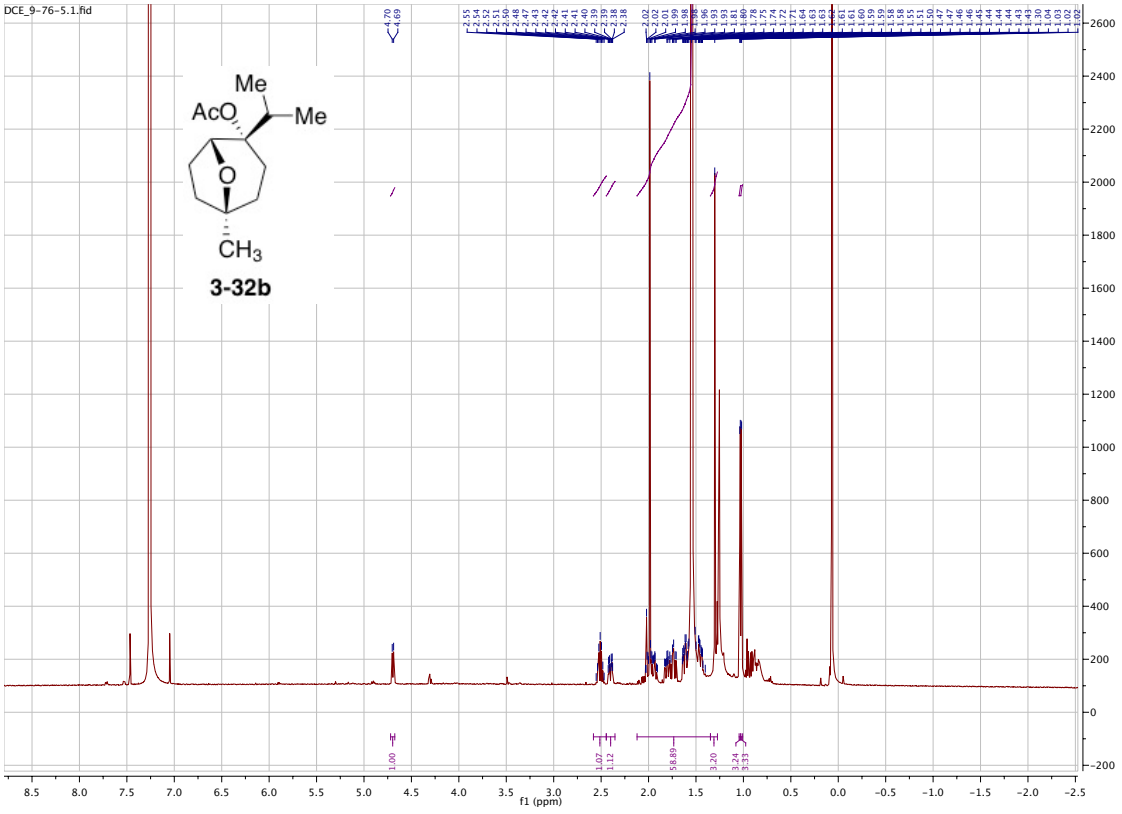

Me
HO
Me
O
CH3
+
Me
OH
Me
O
CH3
3-31a
3-31b
(a:b, 0.7:1)
f1 (ppm)

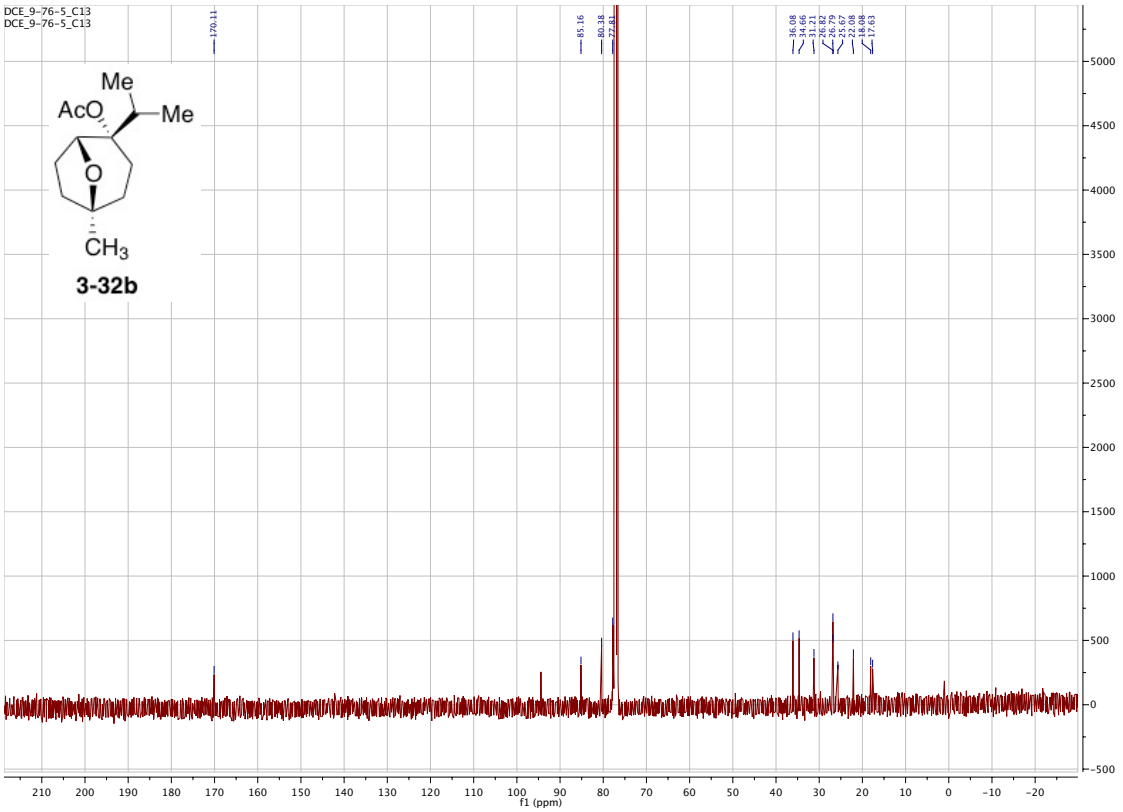

Me
HO
Me
O
CH3
+
Me
OH
Me
O
CH3
3-31a
3-31b
(a:b, 0.7:1)
f1 (ppm)

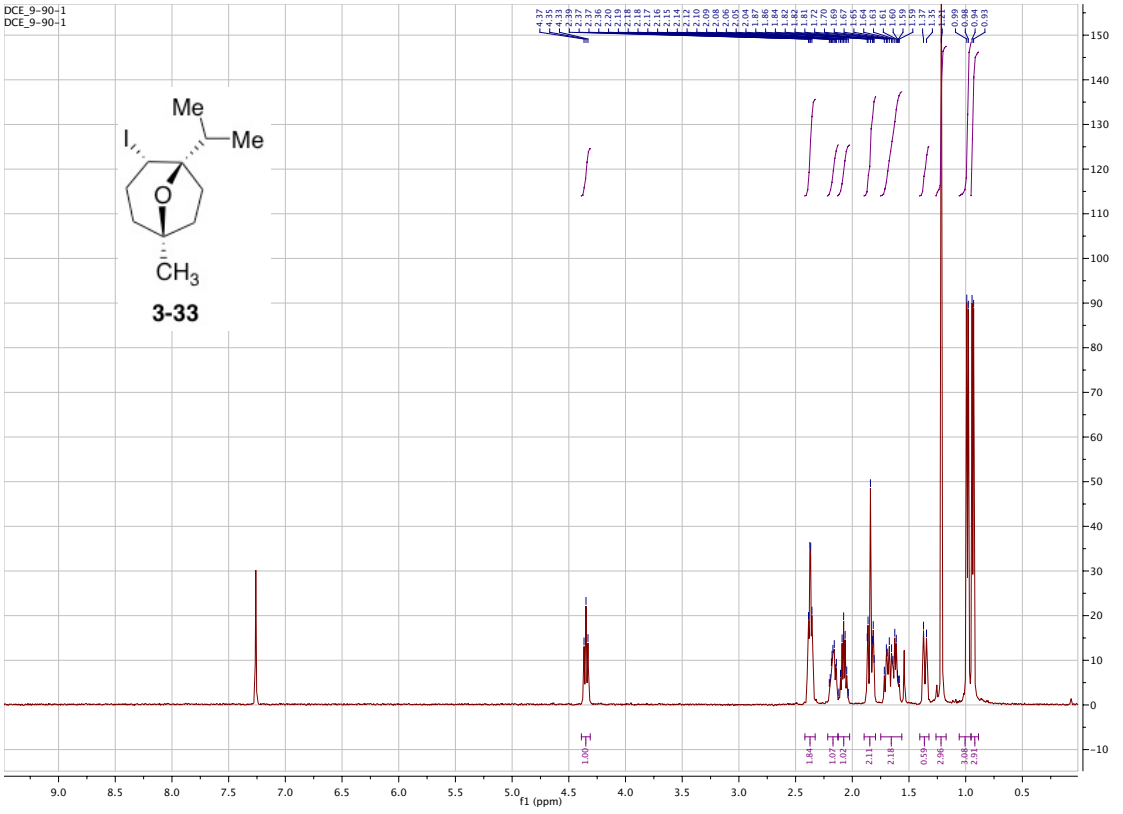

OH
O
HO
O
3-31a
3-31b
(a:b, 1:1.5)
f1 (ppm)

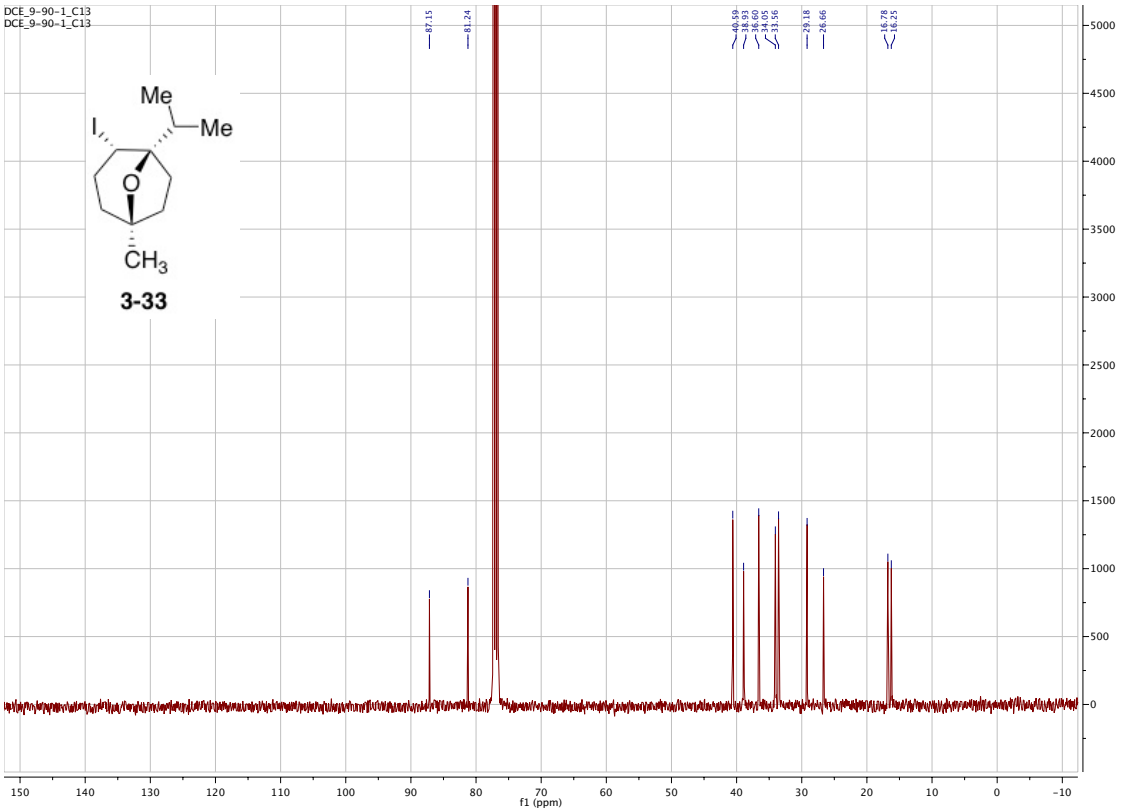

Me
Me
AcO
O
CH3
3-32a
f1 (ppm)

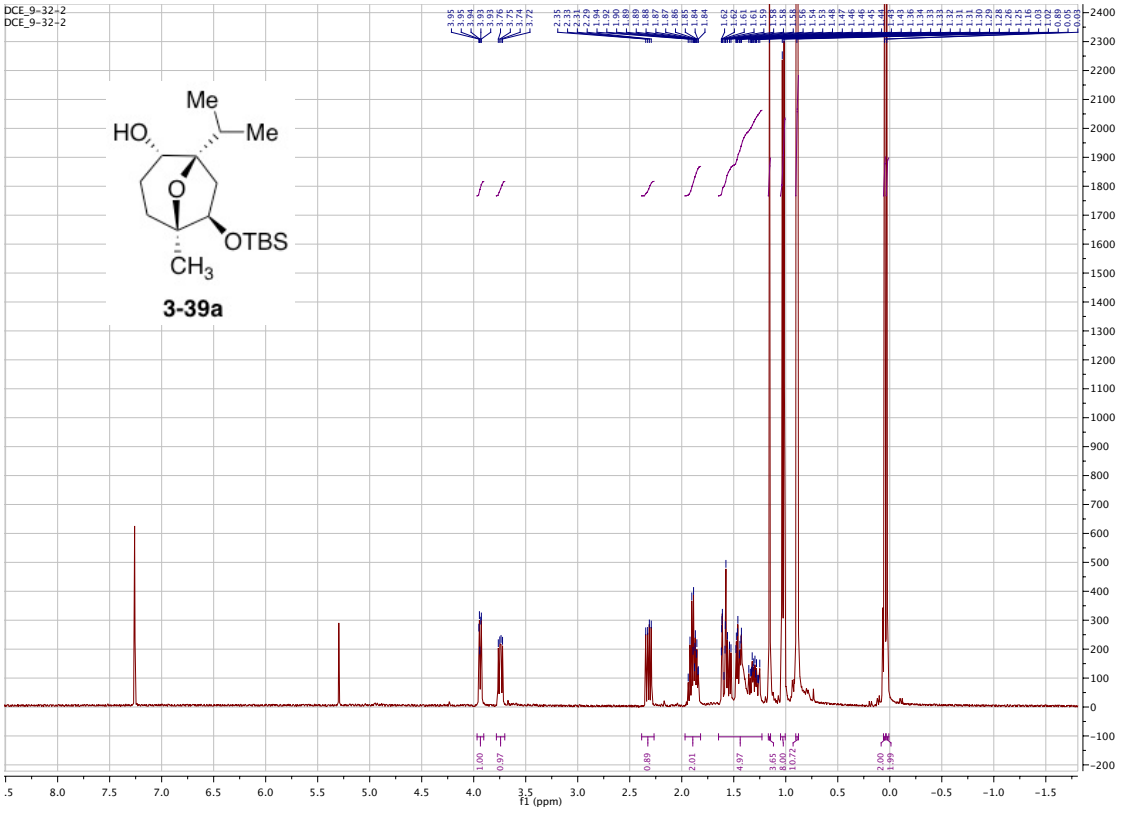

DCE_9-76-4_C13
DCE_9-76-4_C13
Me
AcO
Me
O
CH3
3-32a
170.16
85.58
80.65
72.16
36.66
35.93
33.44
29.54
25.98
24.55
21.38
18.03
17.10
f1 (ppm)

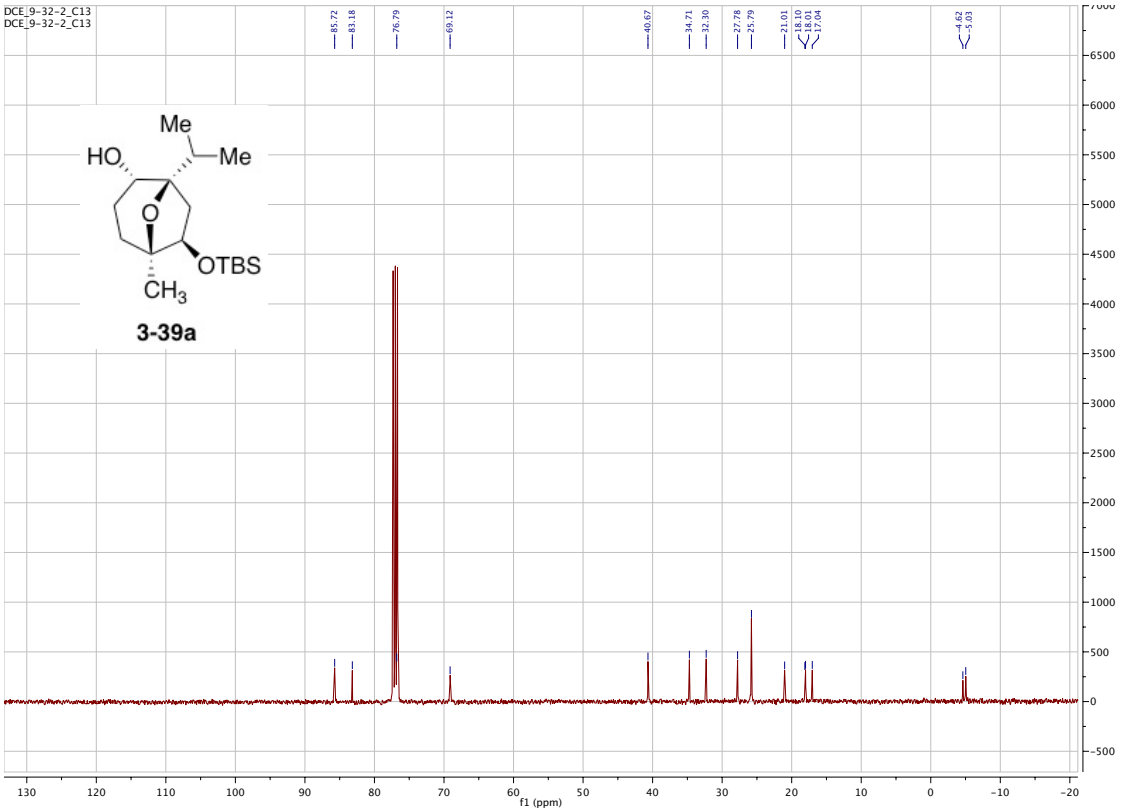

DCE_9-76-5.1.fid
Me
AcO
Me
O
CH3
3-32b
4.70
4.69
1.00
1.07
1.12
5.89
3.20
3.24
3.35
f1 (ppm)

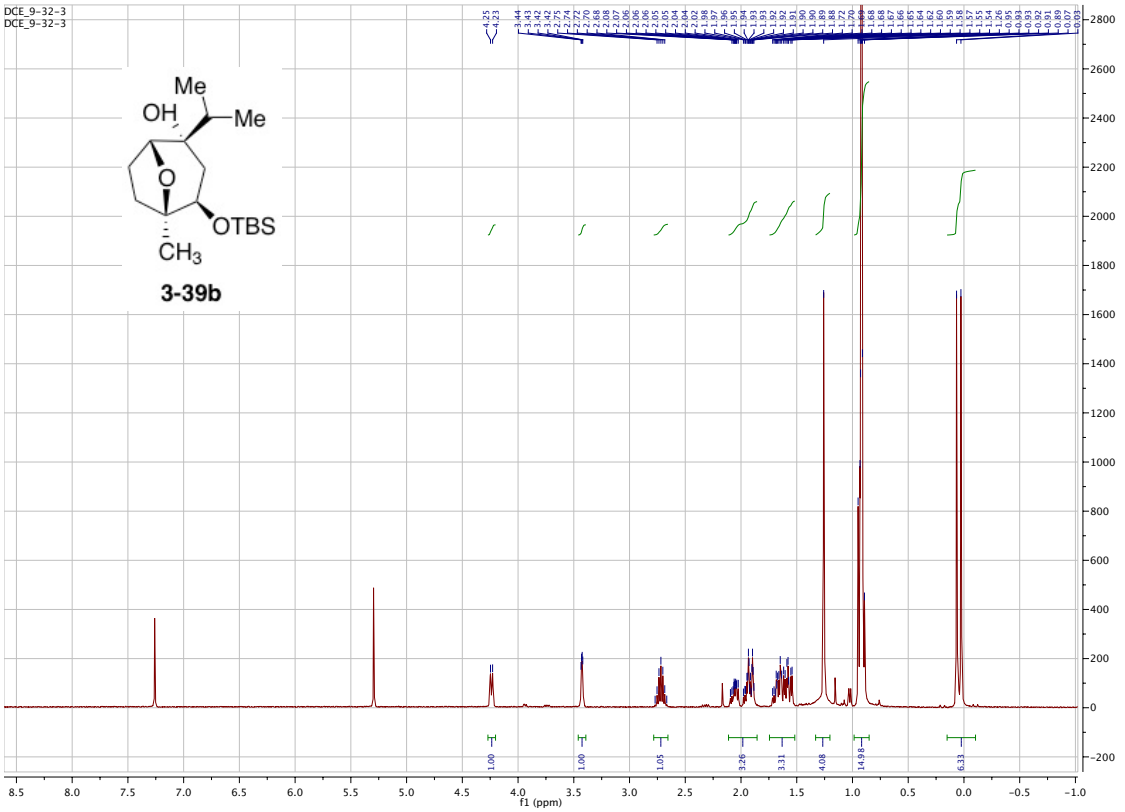

DCE_9-76-5_C13
DCE_9-76-5_C13
Me
AcO
Me
O
CH3
3-32b
170.11
85.16
80.38
77.81
36.08
34.66
31.21
26.82
26.79
25.67
22.08
18.08
17.63
f1 (ppm)

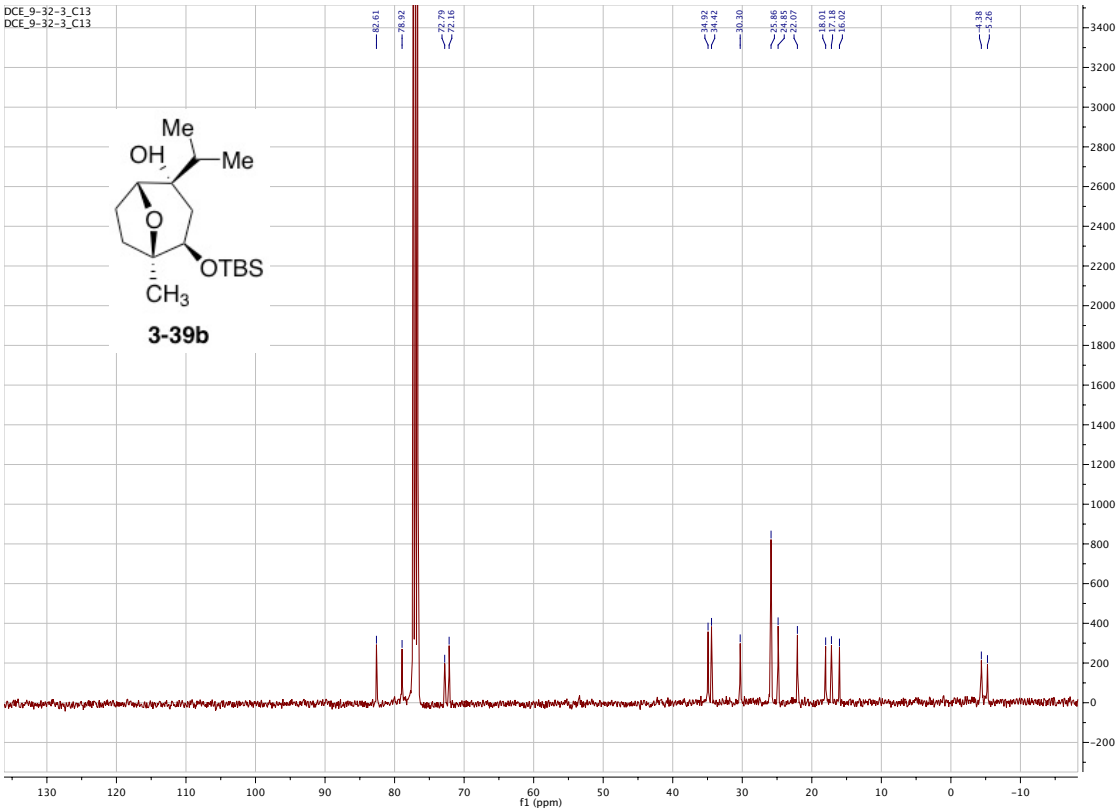

DCE_9-90-1
DCE_9-90-1
Me
I
Me
O
CH3
3-33
f1 (ppm)

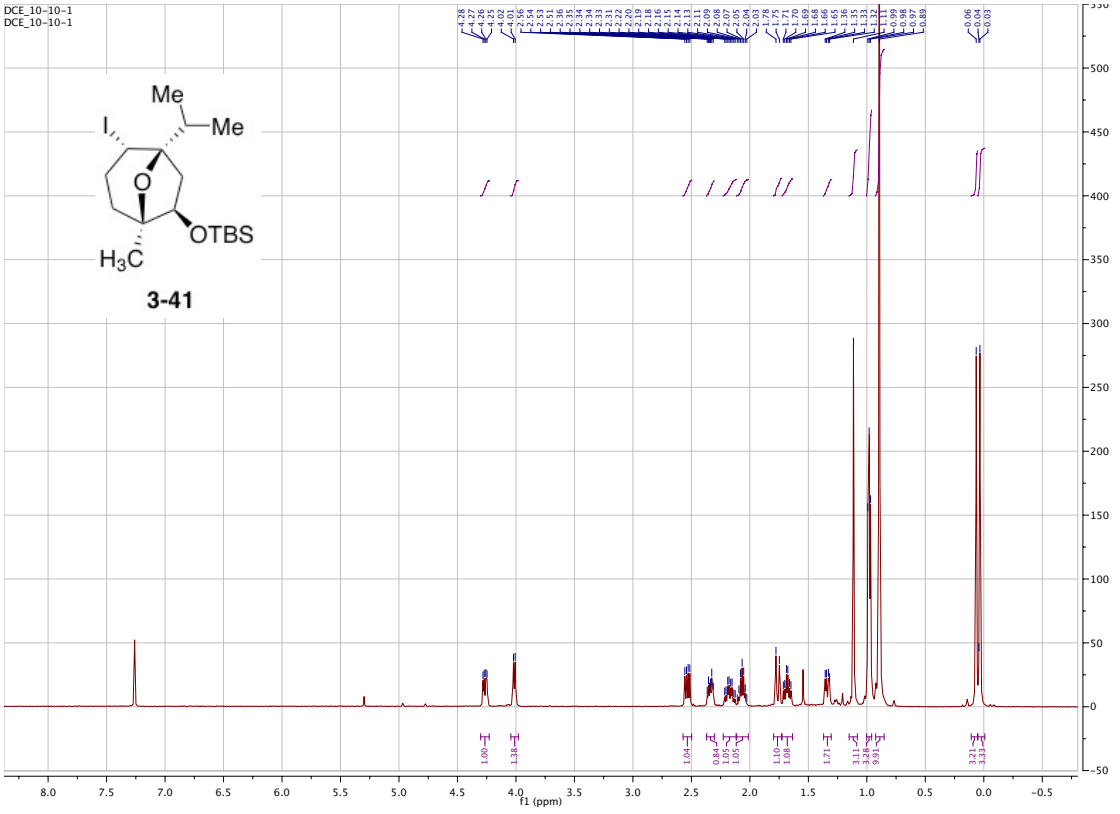

DCE_9-90-1_C13
DCE_9-90-1_C13
87.15
81.24
40.59
38.83
38.60
34.05
33.56
29.18
26.66
16.78
16.25
Me
Me
I
O
CH3
3-33
f1 (ppm)

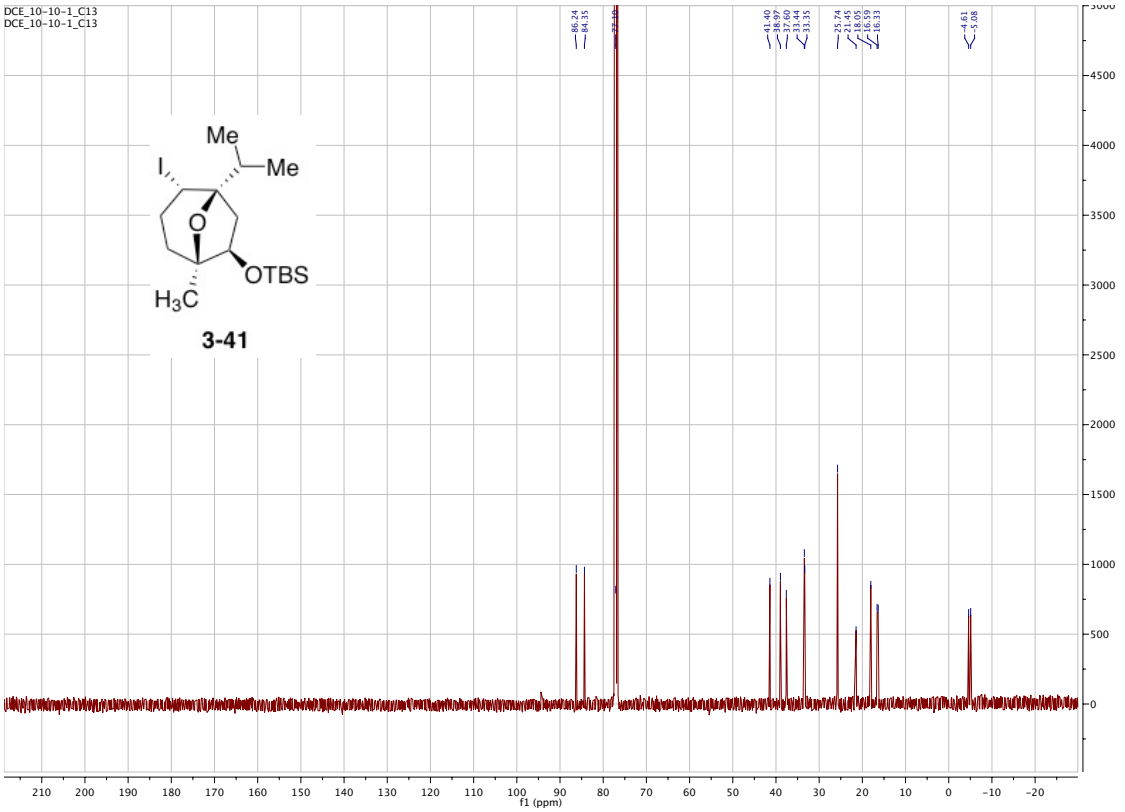

DCE_9-32-2
DCE_9-32-2
Me
Me
HO
O
OTBS
CH3
3-39a
f1 (ppm)

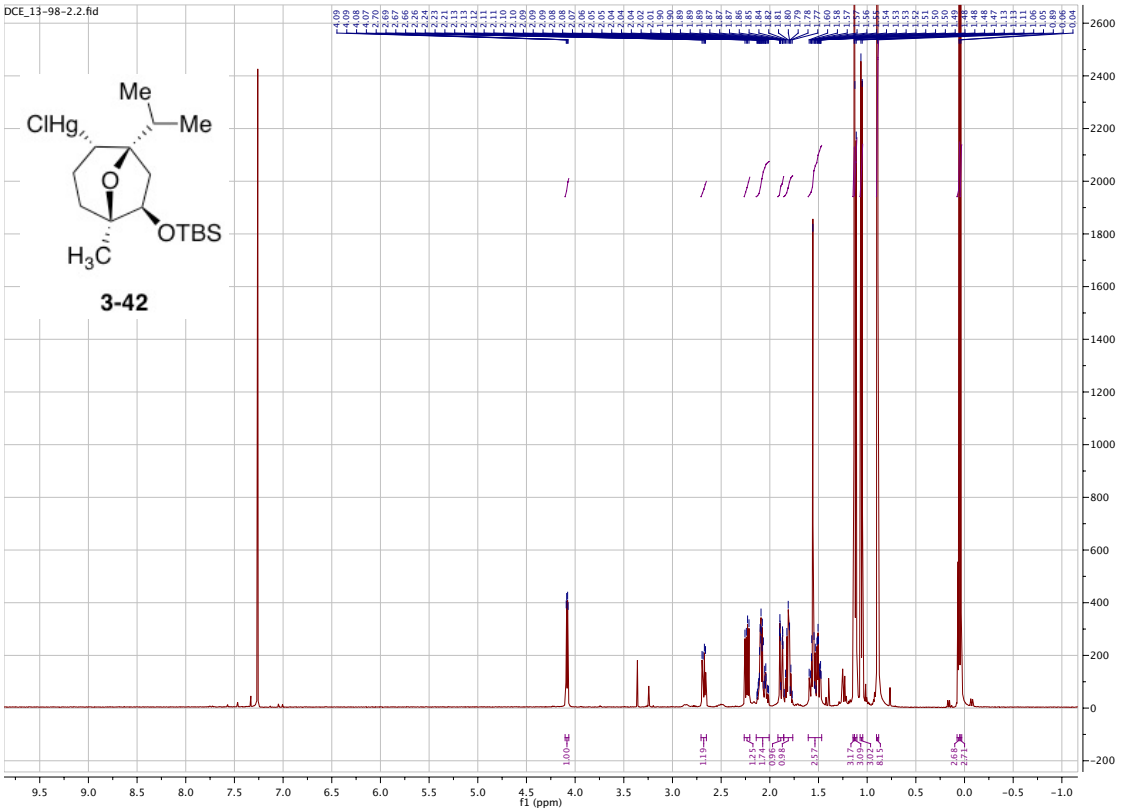

DCE_9-32-2_C13
DCE_9-32-2_C13
85.72
83.18
76.79
69.12
40.67
34.71
32.30
27.78
25.79
21.01
18.10
18.01
17.04
-4.62
-5.03
Me
HO
Me
O
OTBS
CH3
3-39a
f1 (ppm)

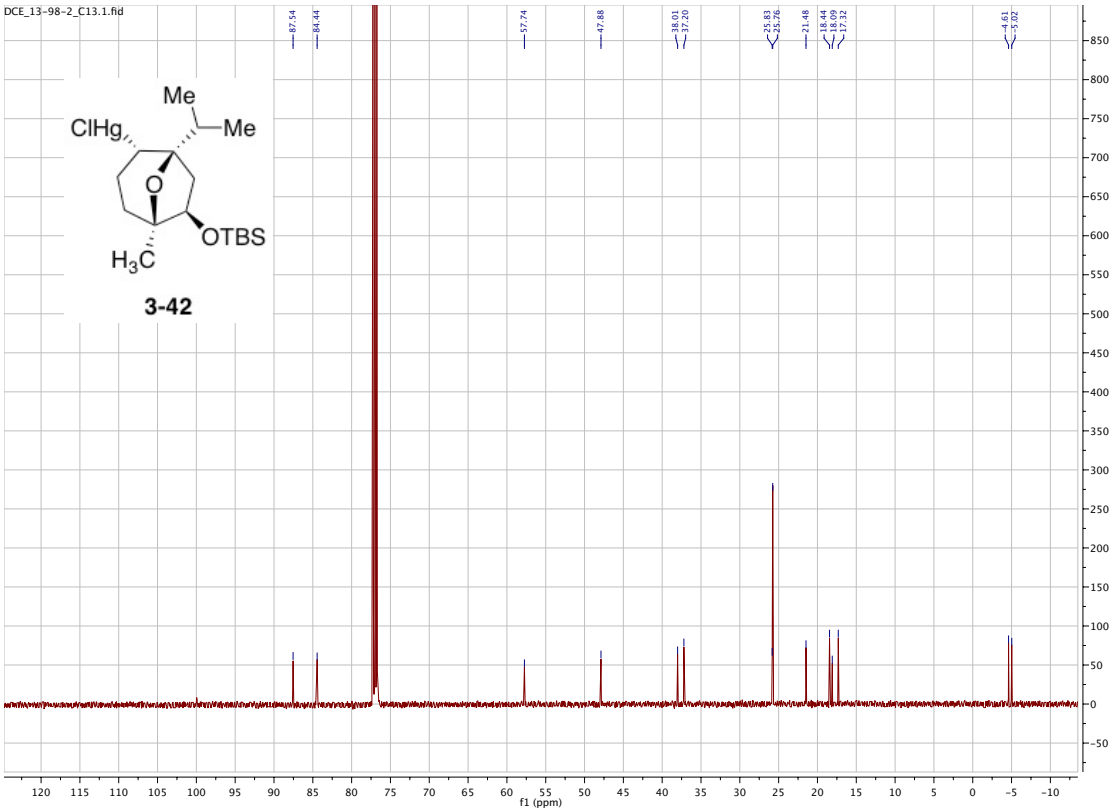

DCE_9-32-3
DCE_9-32-3
Me
OH
Me
O
OTBS
CH3
3-39b
f1 (ppm)


DCE_9-32-3_C13
DCE_9-32-3_C13
Me
OH
Me
O
OTBS
CH3
3-39b
f1 (ppm)

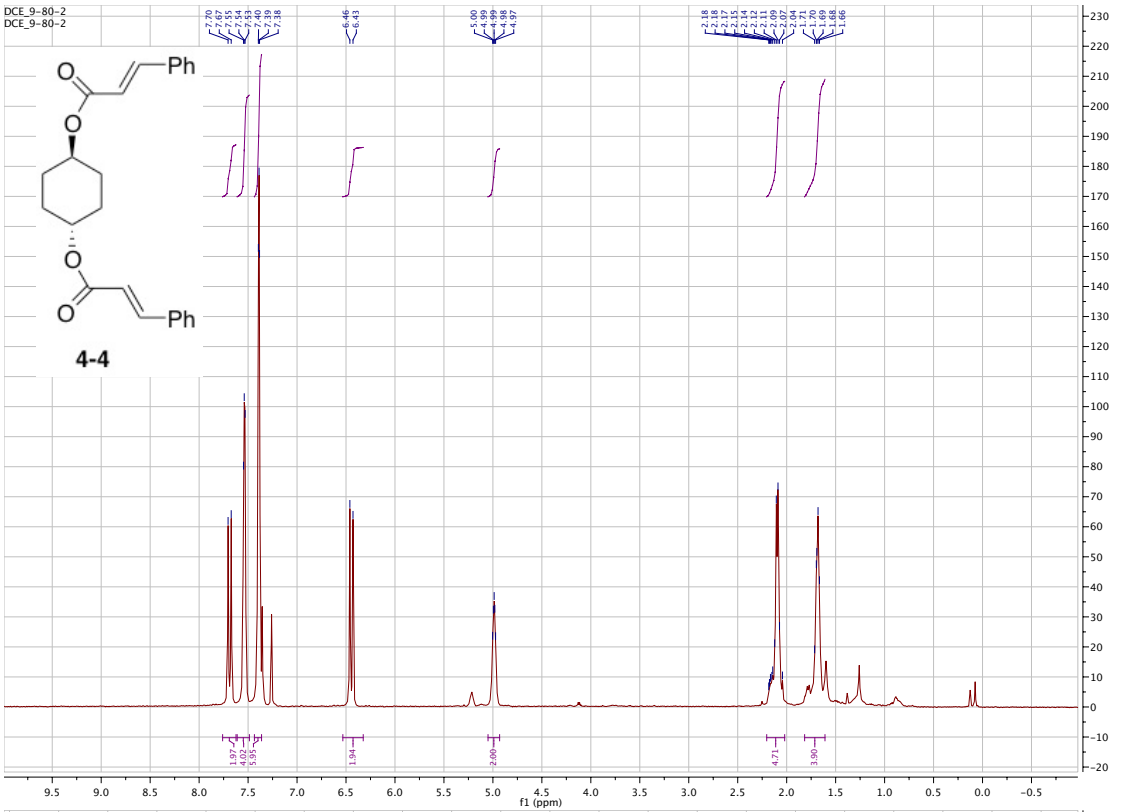

DCE_10-10-1
DCE_10-10-1
Me
I
Me
O
OTBS
H3C
3-41
f1 (ppm)

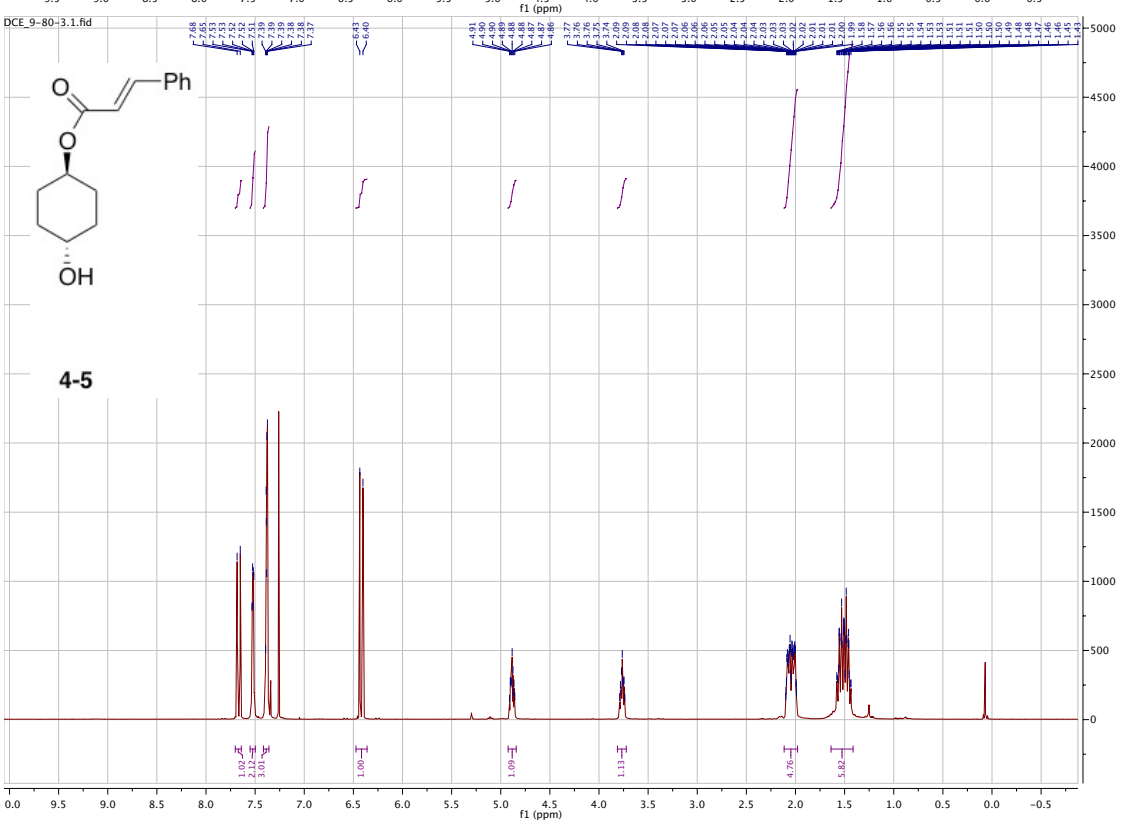

DCE_10-10-1_C13
DCE_10-10-1_C13
Me
Me
I
O
OTBS
H3C
3-41
f1 (ppm)

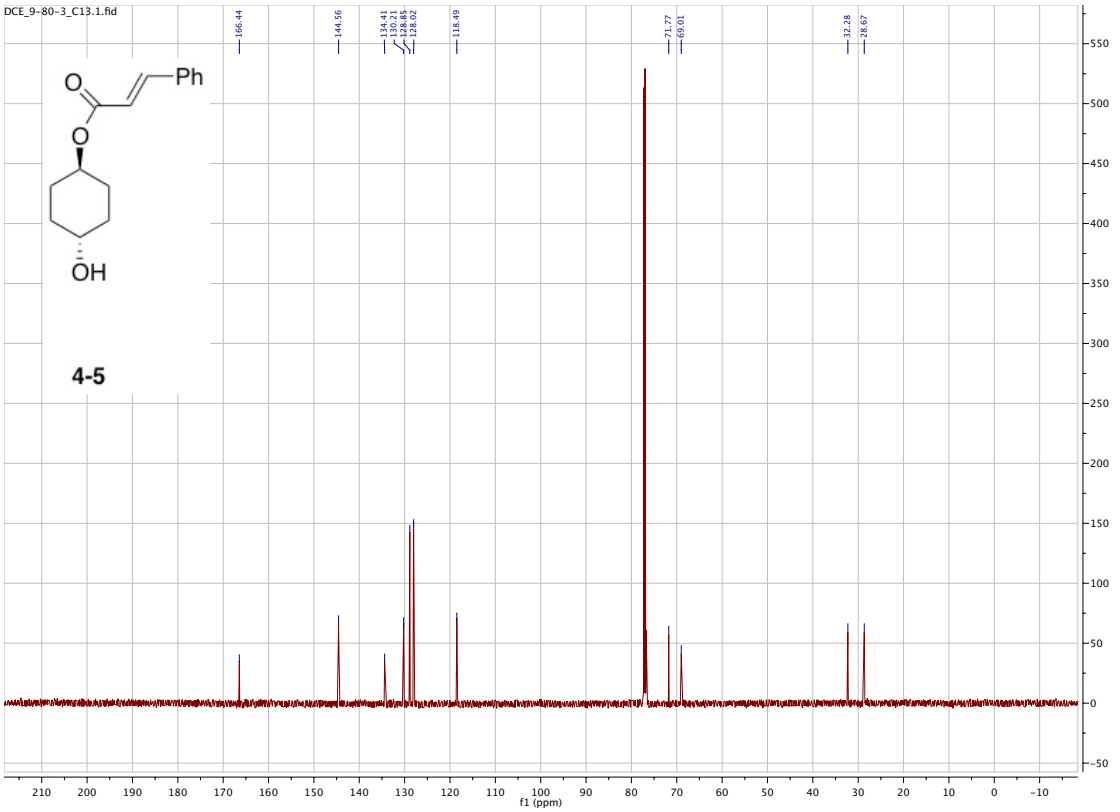

DCE_13-98-2.2.fid
Me
Me
ClHg
O
OTBS
H3C
3-42
f1 (ppm)

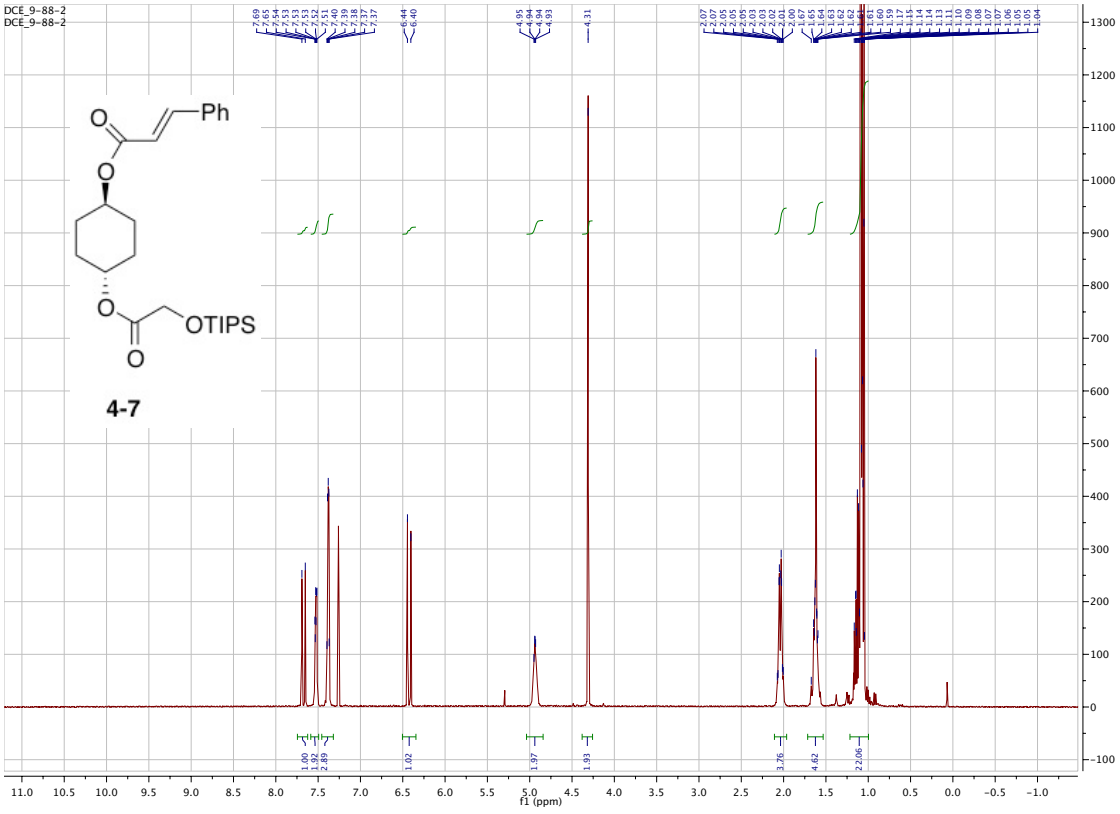

DCE_13-98-2_C13.1.fid
87.54
84.44
57.74
47.88
38.01
37.20
25.83
25.76
21.48
18.44
18.09
17.32
-4.61
-5.02
Me
ClHg
Me
O
OTBS
H3C
3-42
f1 (ppm)

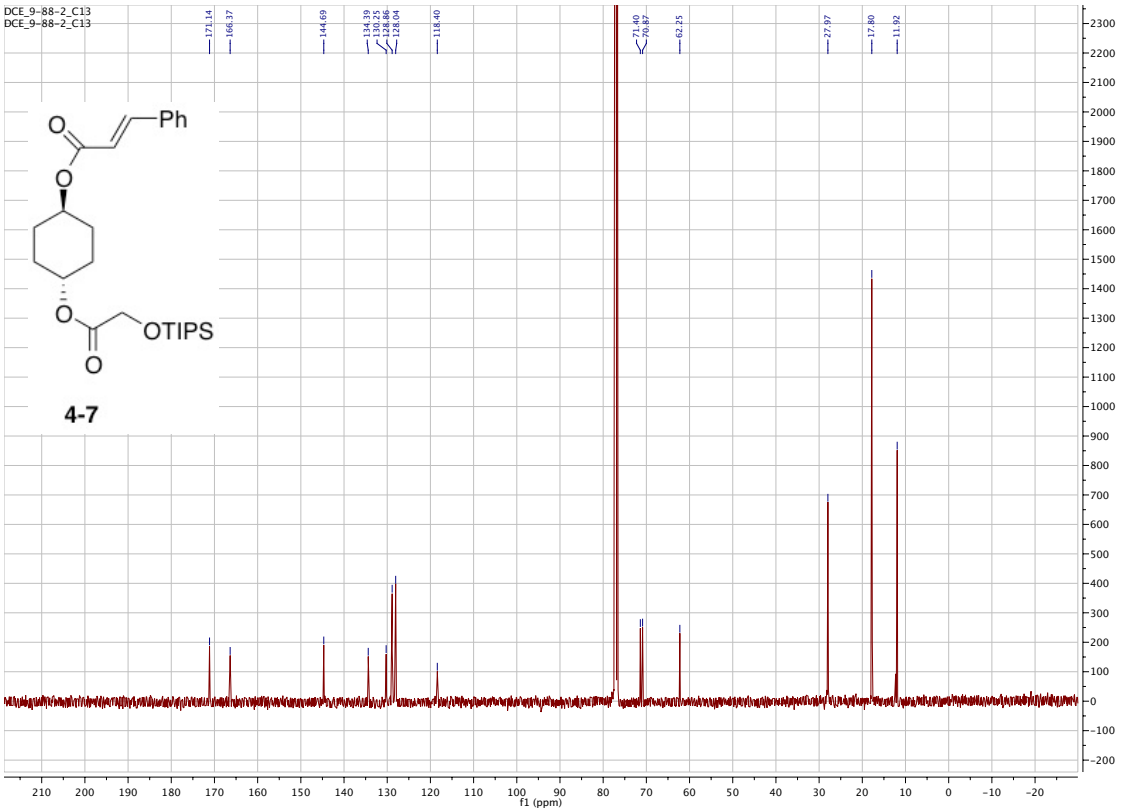
Chapter 4

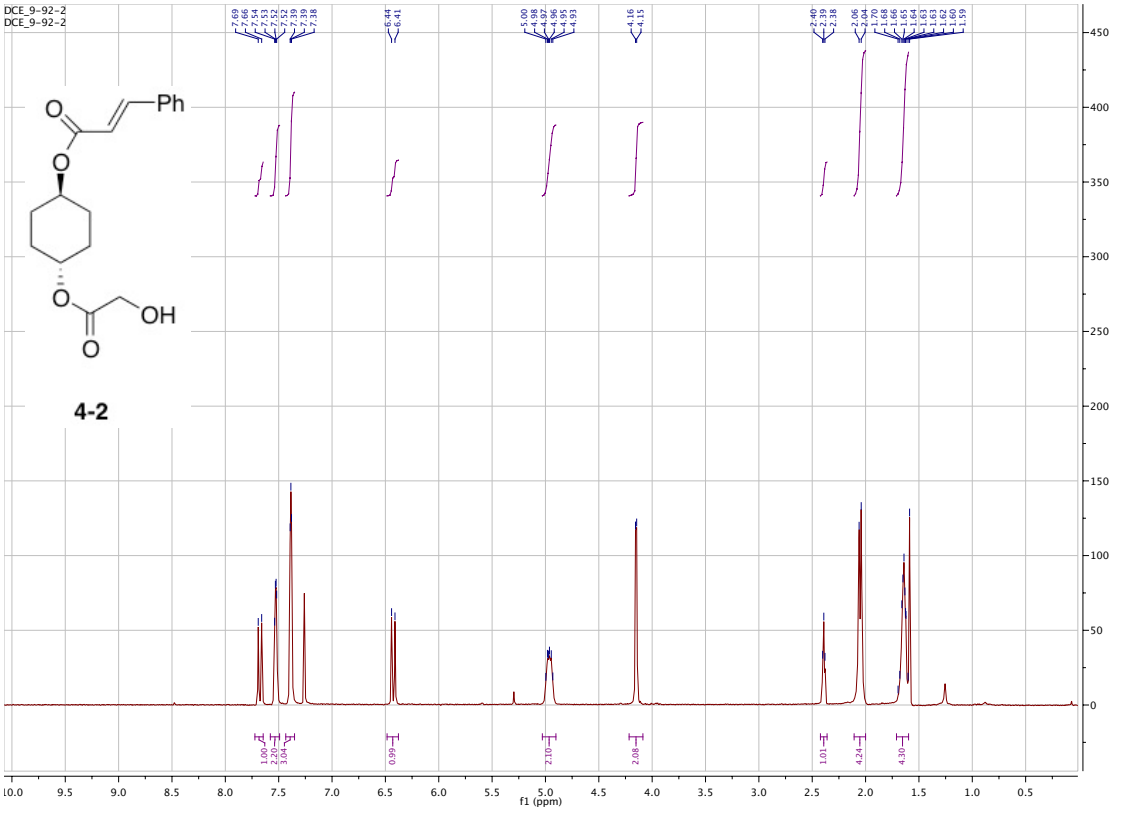

DCE_9-80-2
DCE_9-80-2
Ph
O
O
O
O
Ph
4-4
f1 (ppm)

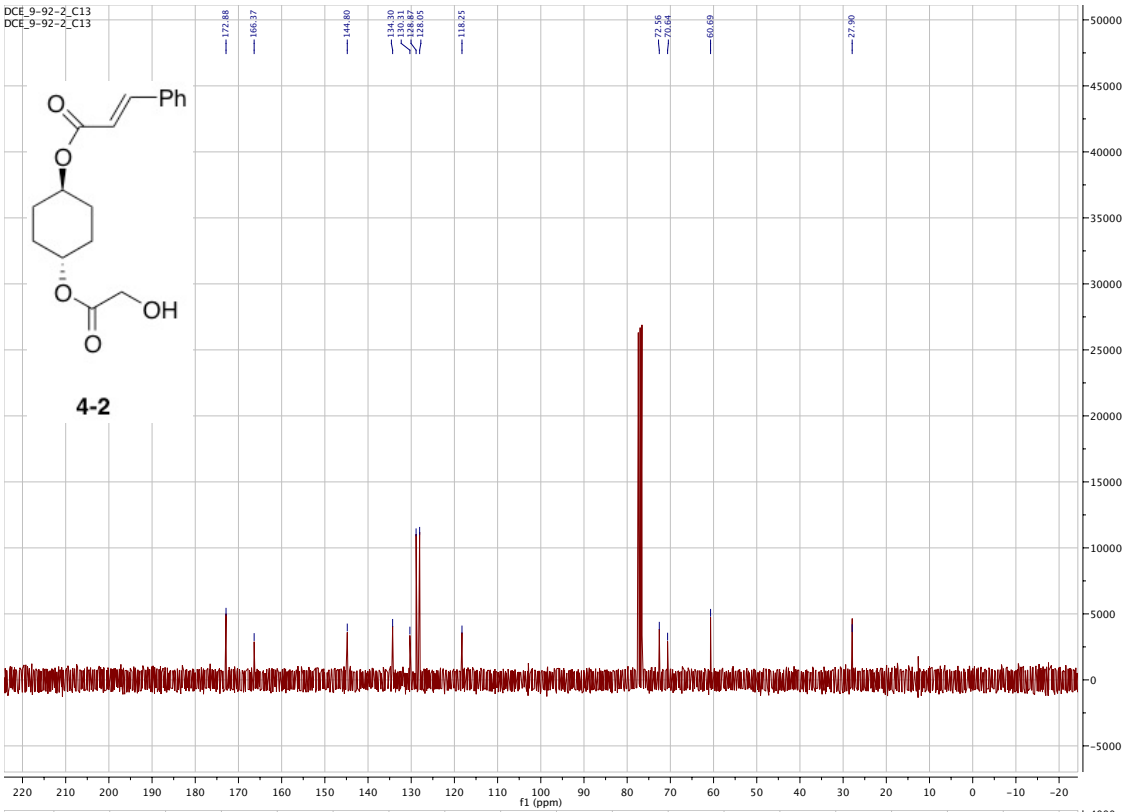

DCE_9-80-3.1.fid
Ph
O
O
OH
4-5
f1 (ppm)

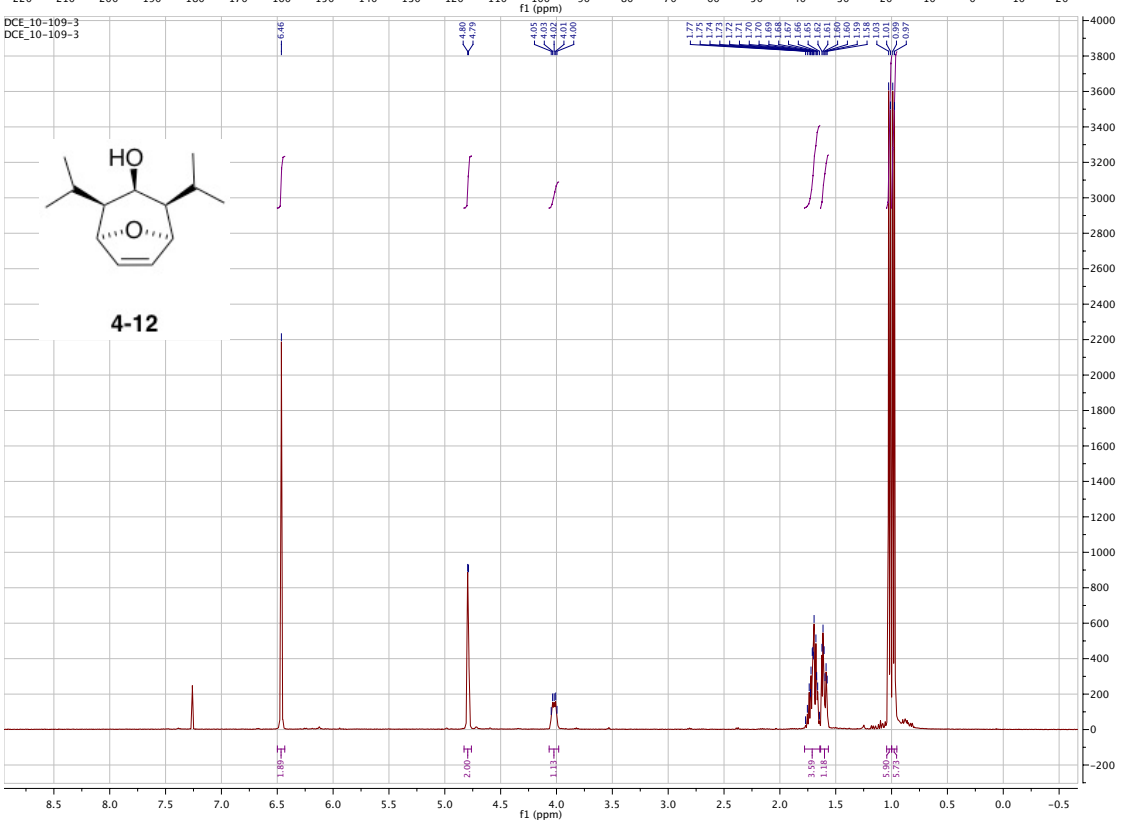

DCE_9-80-3_C13.1.fid
166.44
144.56
134.41
130.21
128.85
128.02
118.49
71.77
69.01
32.28
28.67
O
Ph
O
OH
4-5
f1 (ppm)

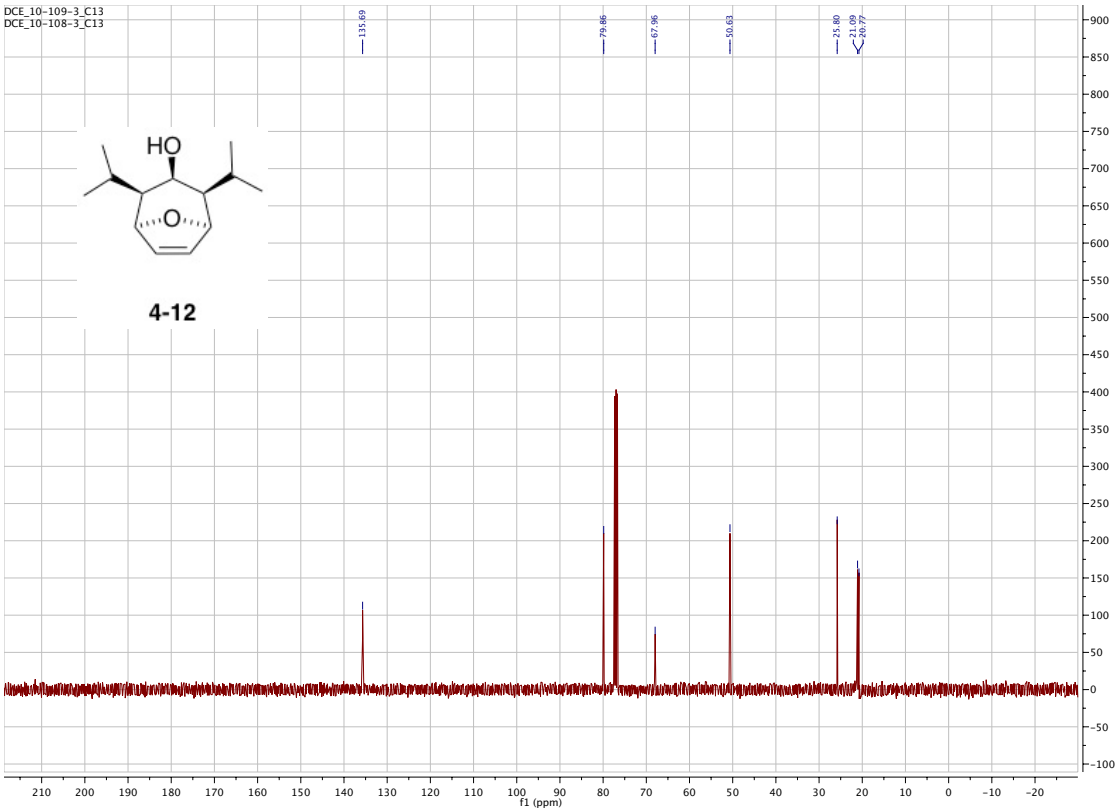

DCE_9-88-2
DCE_9-88-2
7.69
7.65
7.54
7.53
7.53
7.52
7.51
7.40
7.39
7.38
7.37
7.37
6.44
6.40
4.95
4.94
4.94
4.93
4.31
2.07
2.07
2.05
2.05
2.05
2.03
2.03
2.02
2.01
2.00
1.67
1.66
1.63
1.62
1.62
1.61
1.60
1.59
1.17
1.15
1.14
1.14
1.13
1.11
1.10
1.09
1.08
1.07
1.07
1.06
1.05
1.05
1.04
O
Ph
O
O
OTIPS
O
4-7
1.00
1.02
1.89
1.02
1.97
1.93
3.76
4.82
22.06
f1 (ppm)

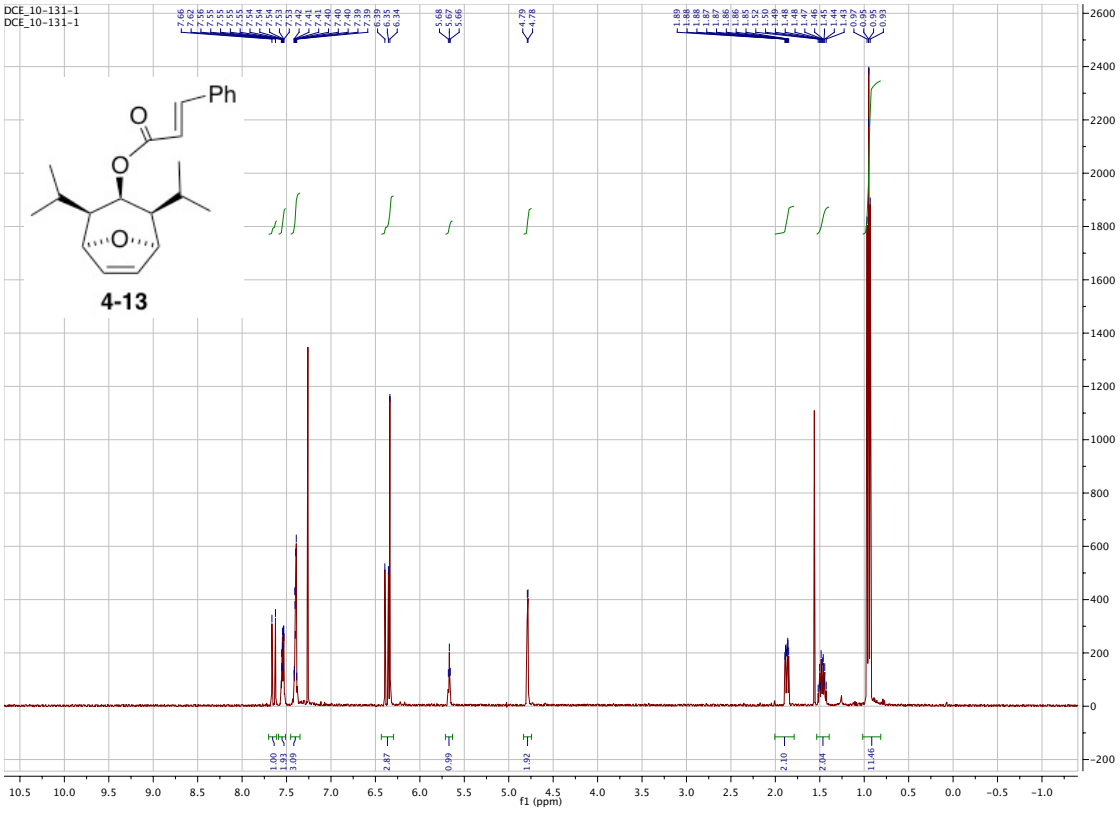

DCE_9-88-2_C13
DCE_9-88-2_C13
171.14
166.37
144.69
134.39
130.25
128.86
128.04
118.40
71.40
70.87
62.25
27.97
17.80
11.92
Ph
O
O
O
OTIPS
O
4-7
f1 (ppm)

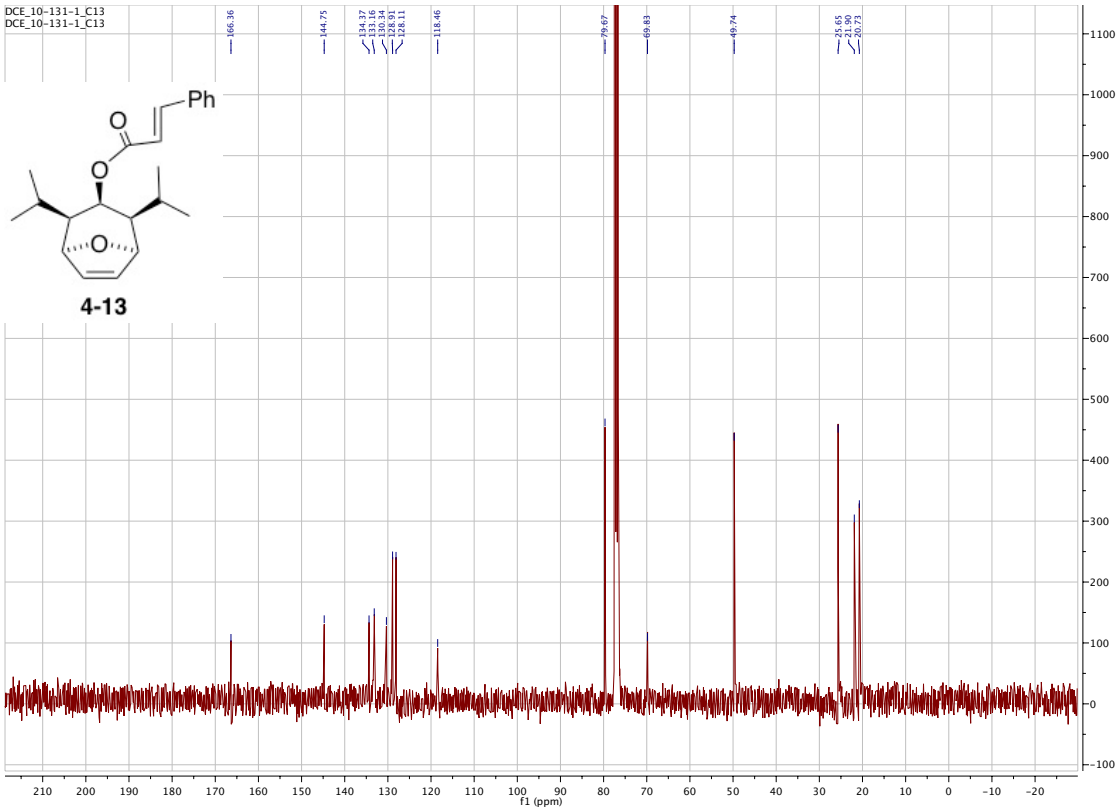

DCE_9-92-2
DCE_9-92-2
7.69
7.66
7.54
7.51
7.52
7.32
7.39
7.38
6.44
6.41
5.00
4.98
4.97
4.96
4.95
4.93
4.16
4.15
2.40
2.39
2.38
2.06
2.04
1.70
1.68
1.66
1.65
1.64
1.63
1.62
1.60
1.59
Ph
O
O
O
OH
O
4-2
1.00
2.20
3.04
0.99
2.10
2.08
1.01
4.24
4.30
f1 (ppm)

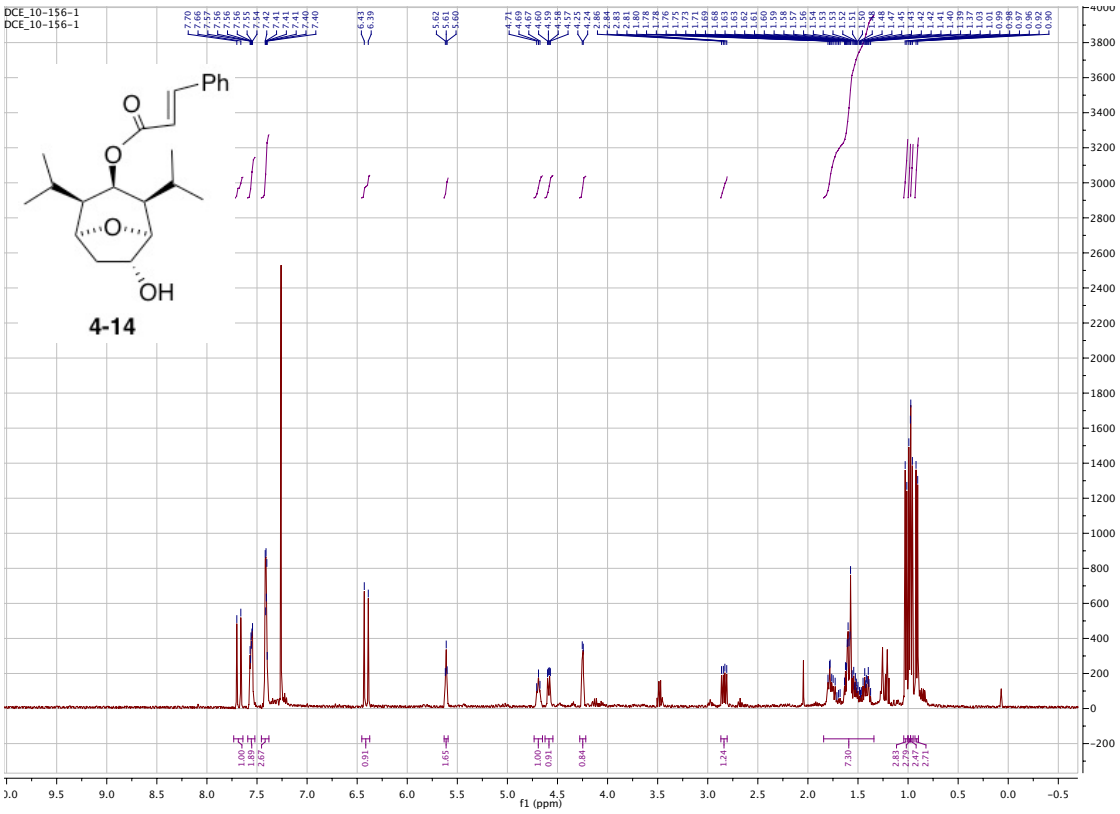

DCE_9-92-2_C13
DCE_9-92-2_C13
172.88
166.37
144.80
134.30
130.31
128.87
128.05
118.25
72.56
70.64
60.69
27.90
Ph
O
O
O
O
OH
4-2
f1 (ppm)

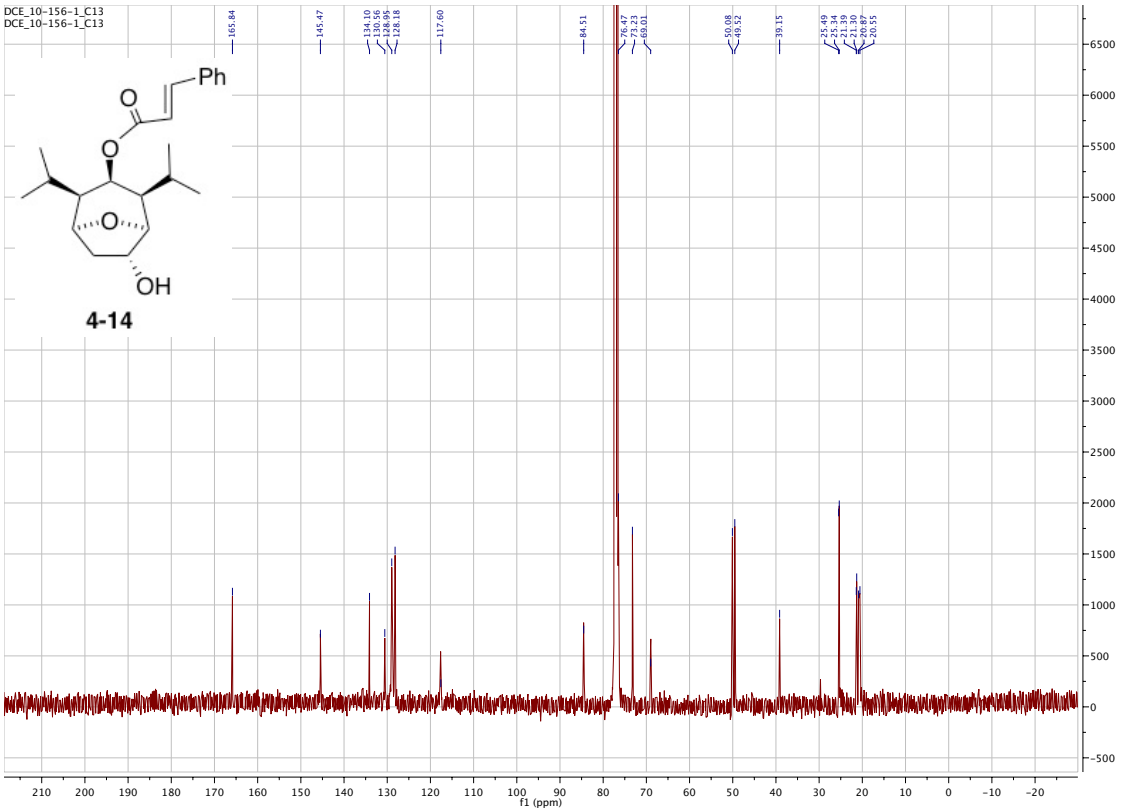

DCE_10-109-3
DCE_10-109-3
6.46
4.80
4.79
4.05
4.03
4.02
4.01
4.00
1.77
1.75
1.74
1.73
1.72
1.71
1.70
1.70
1.69
1.68
1.67
1.66
1.65
1.62
1.61
1.60
1.60
1.58
1.58
1.03
1.01
1.00
0.97
HO
O
4-12
1.89
2.00
1.13
3.59
1.18
5.00
5.75
f1 (ppm)

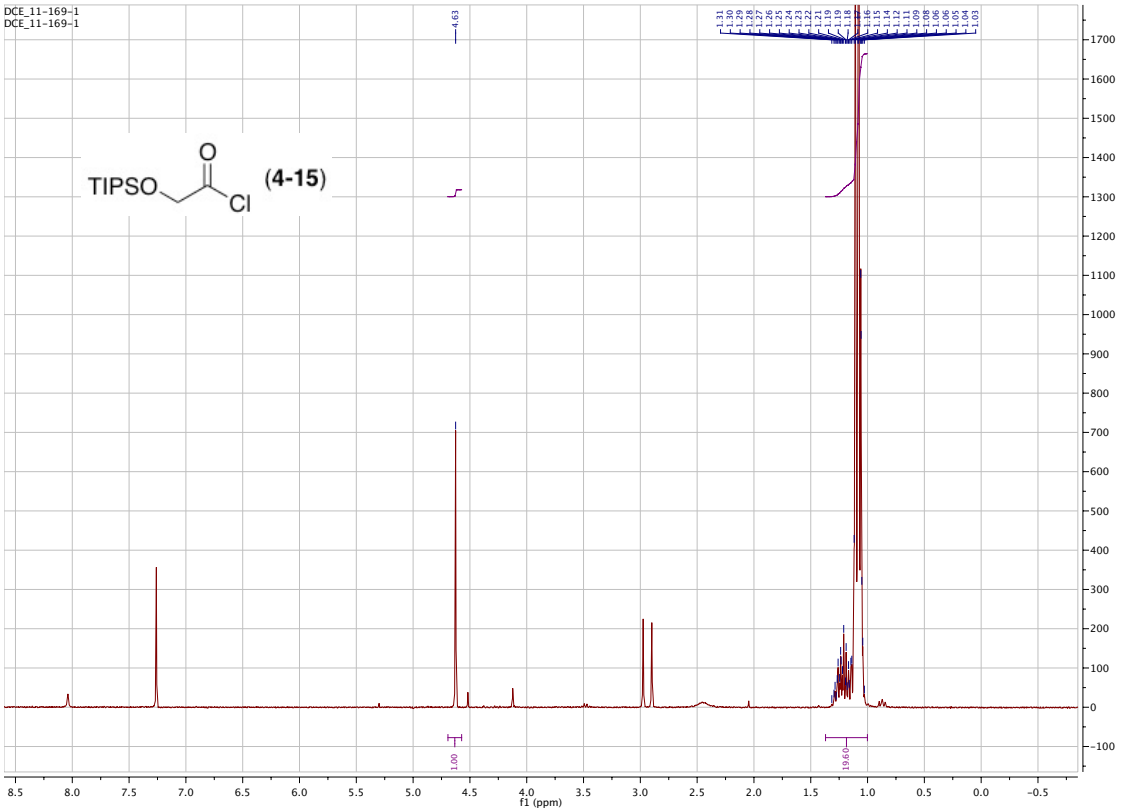

DCE_10-109-3_C13
DCE_10-108-3_C13
135.69
79.86
67.96
50.63
25.80
21.09
20.77
HO
O
4-12
f1 (ppm)

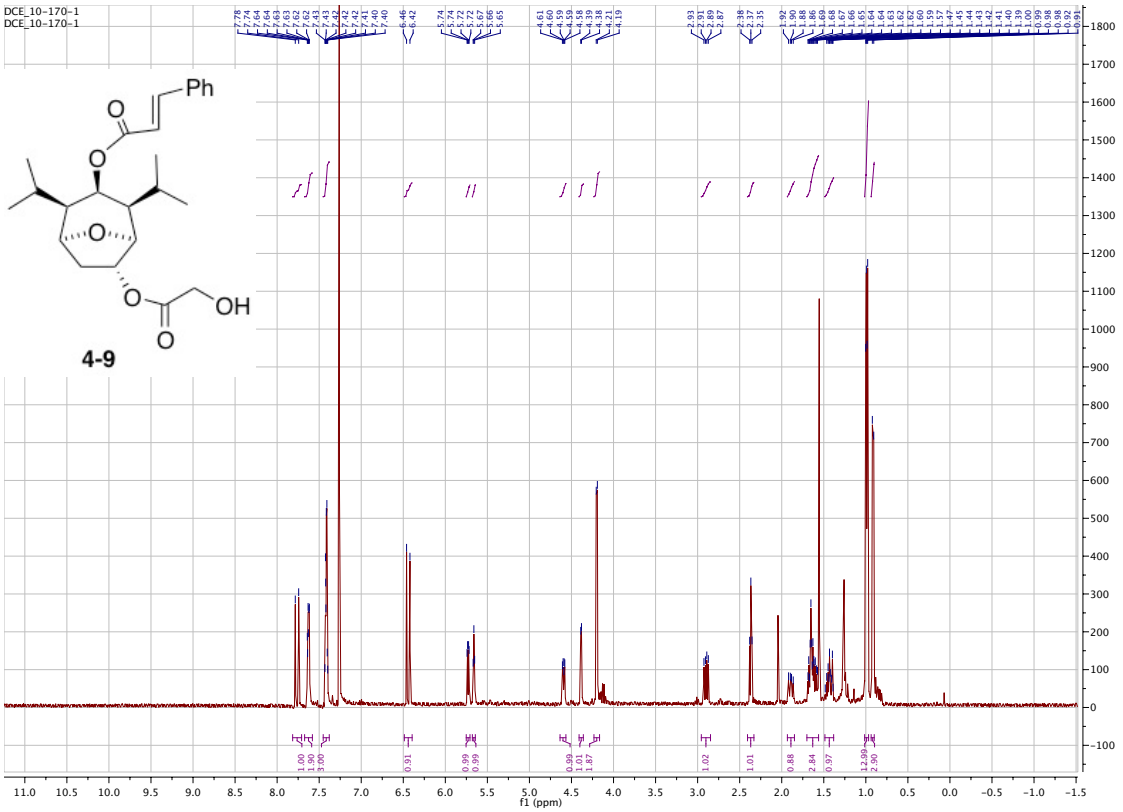

DCE_10-131-1
DCE_10-131-1
Ph
O
O
O
4-13
f1 (ppm)

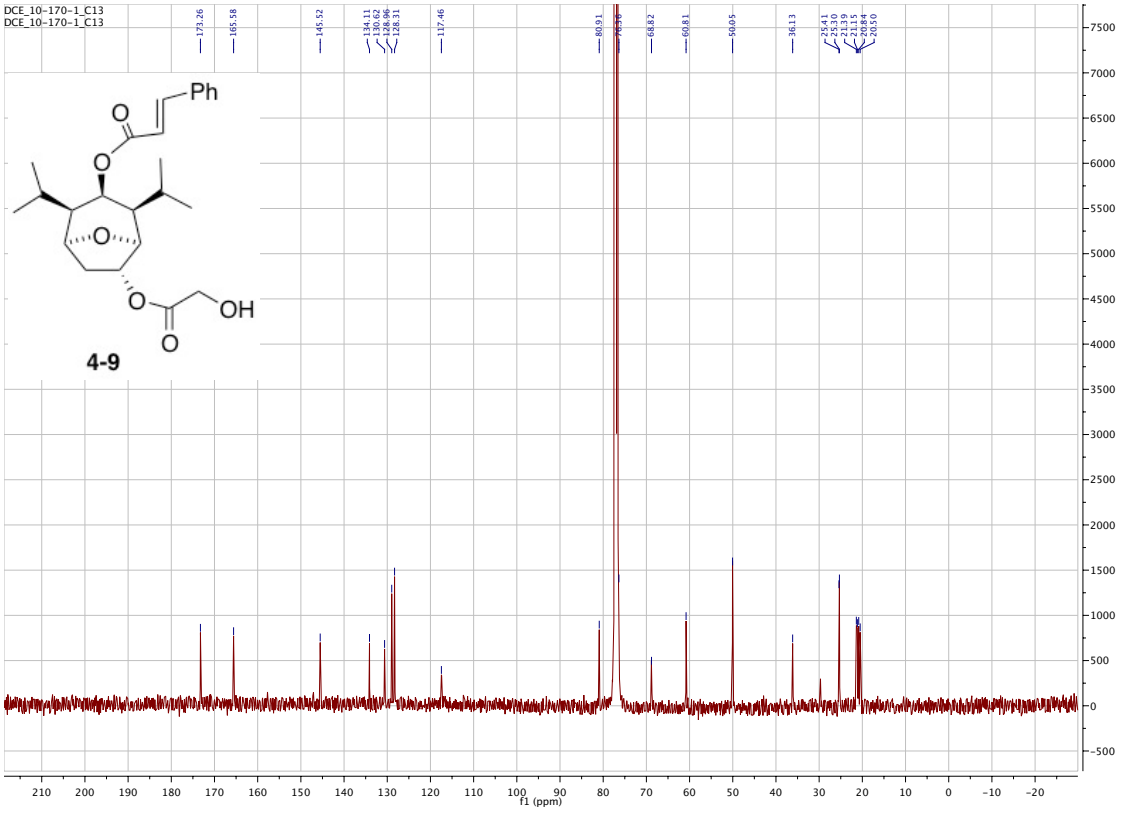

DCE_10-131-1_C13
DCE_10-131-1_C13
166.36
144.75
134.37
133.16
130.34
130.01
128.11
118.46
79.67
69.83
49.74
25.65
21.90
20.73
Ph
O
O
O
4-13
f1 (ppm)

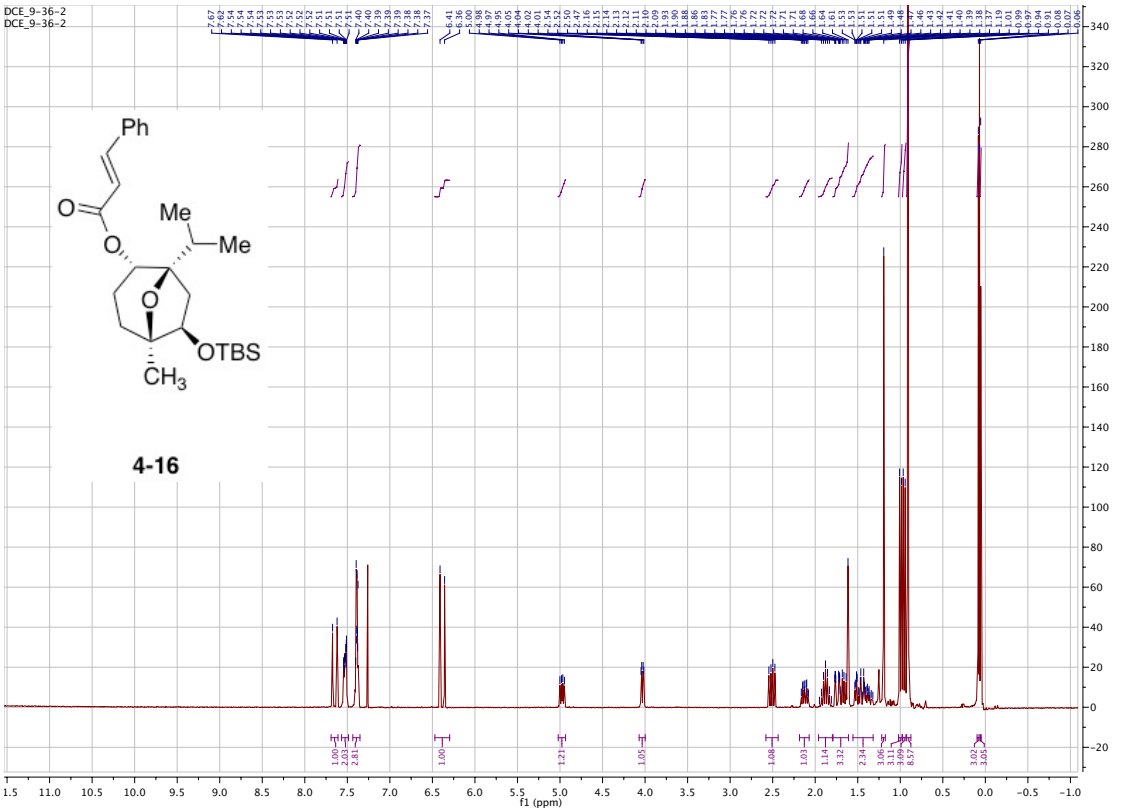

DCE_10-156-1
DCE_10-156-1
Ph
O
O
O
OH
4-14
f1 (ppm)

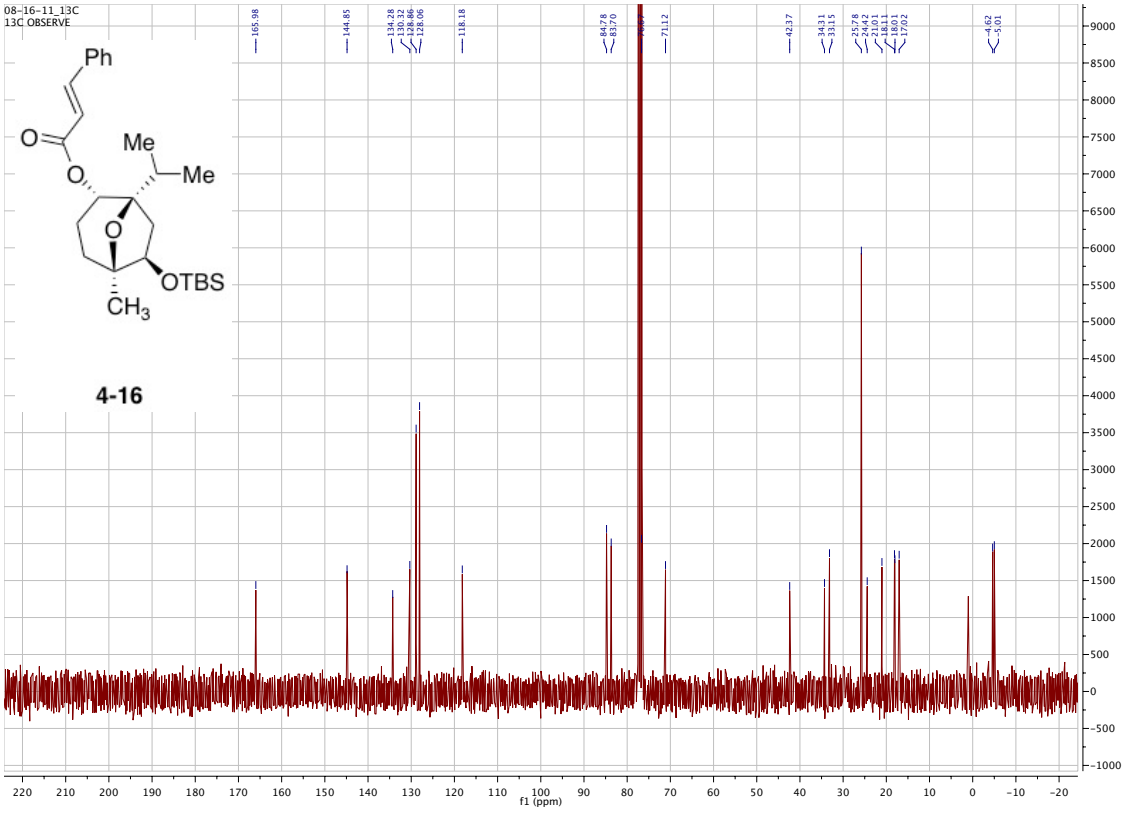

DCE_10-156-1_C13
DCE_10-156-1_C13
165.84
145.47
134.10
130.56
128.95
128.18
117.60
84.51
76.47
73.23
69.01
50.08
49.52
39.15
25.49
25.34
21.39
21.30
20.87
20.55
Ph
O
O
O
OH
4-14
f1 (ppm)

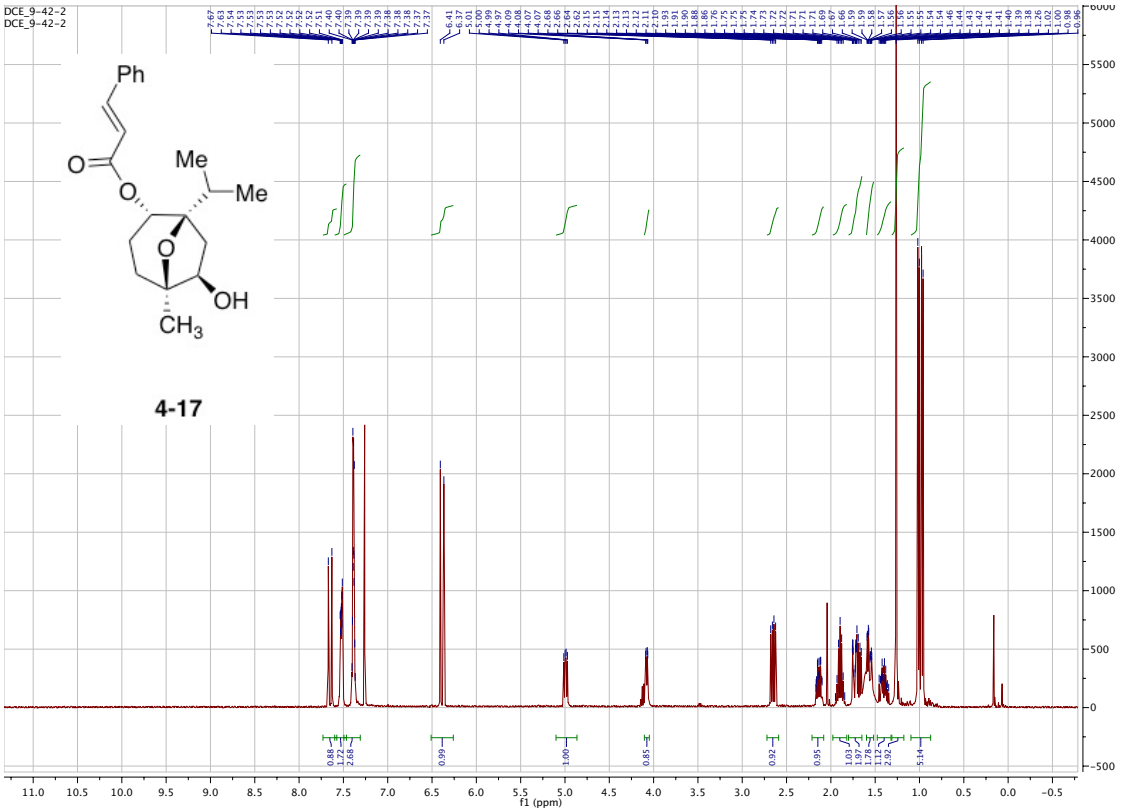

DCE_11-169-1
DCE_11-169-1
4.63
TIPSO
O
Cl
(4-15)
1.00
19.60
f1 (ppm)

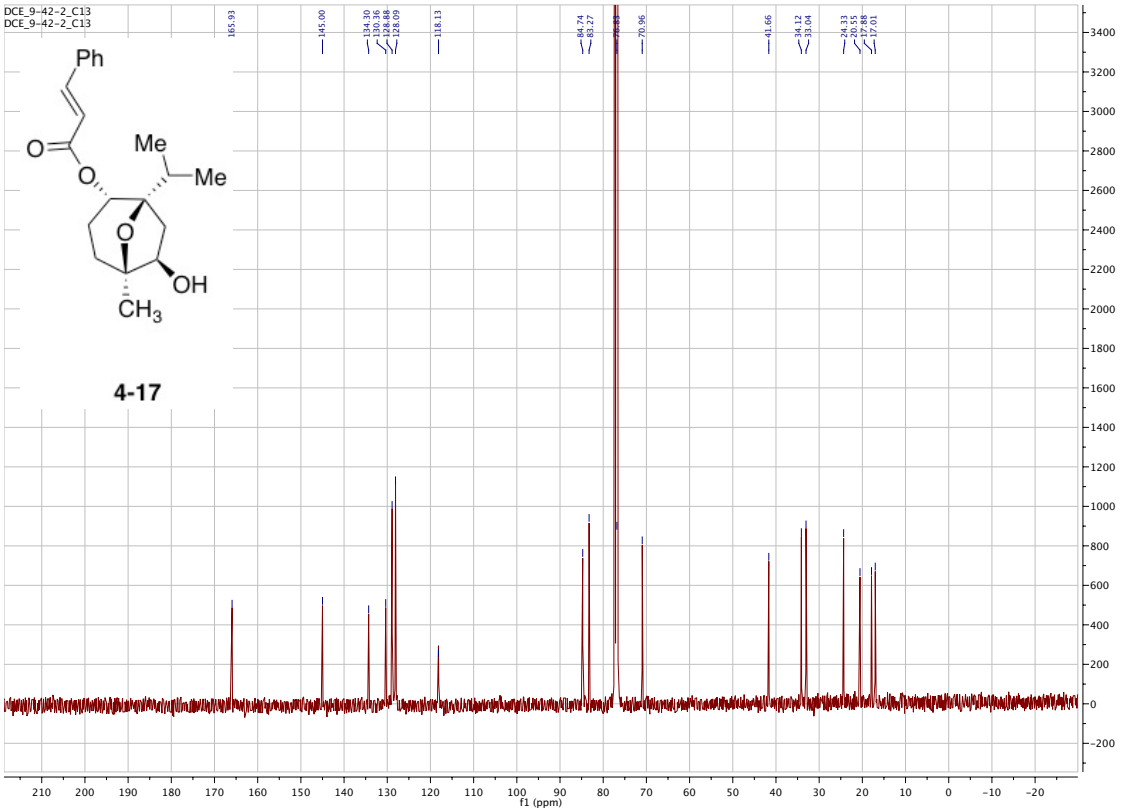

DCE_10-170-1
DCE_10-170-1
Ph
O
O
O
O
O
OH
O
4-9
f1 (ppm)

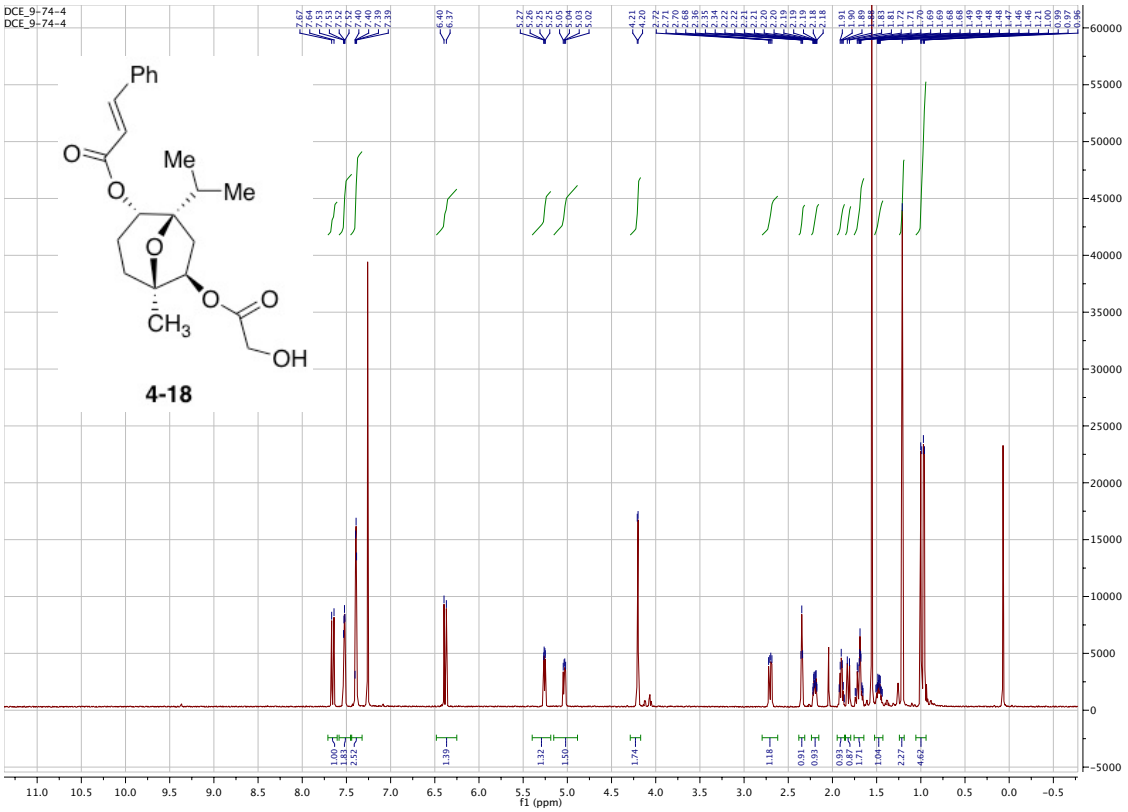

DCE_10-170-1_C13
DCE_10-170-1_C13
Ph
O
O
O
O
O
OH
O
4-9
f1 (ppm)

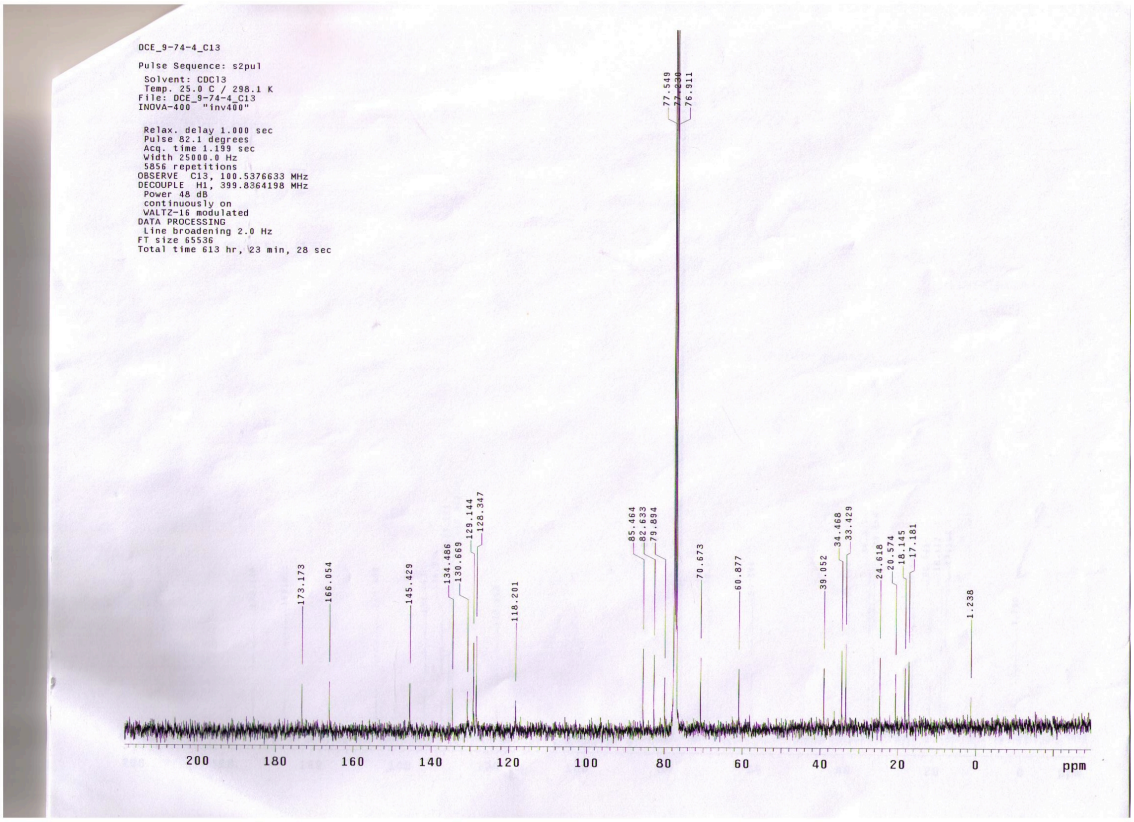

DCE_9-36-2
DCE_9-36-2
Ph
O
O
Me
Me
O
OTBS
CH3
4-16
f1 (ppm)

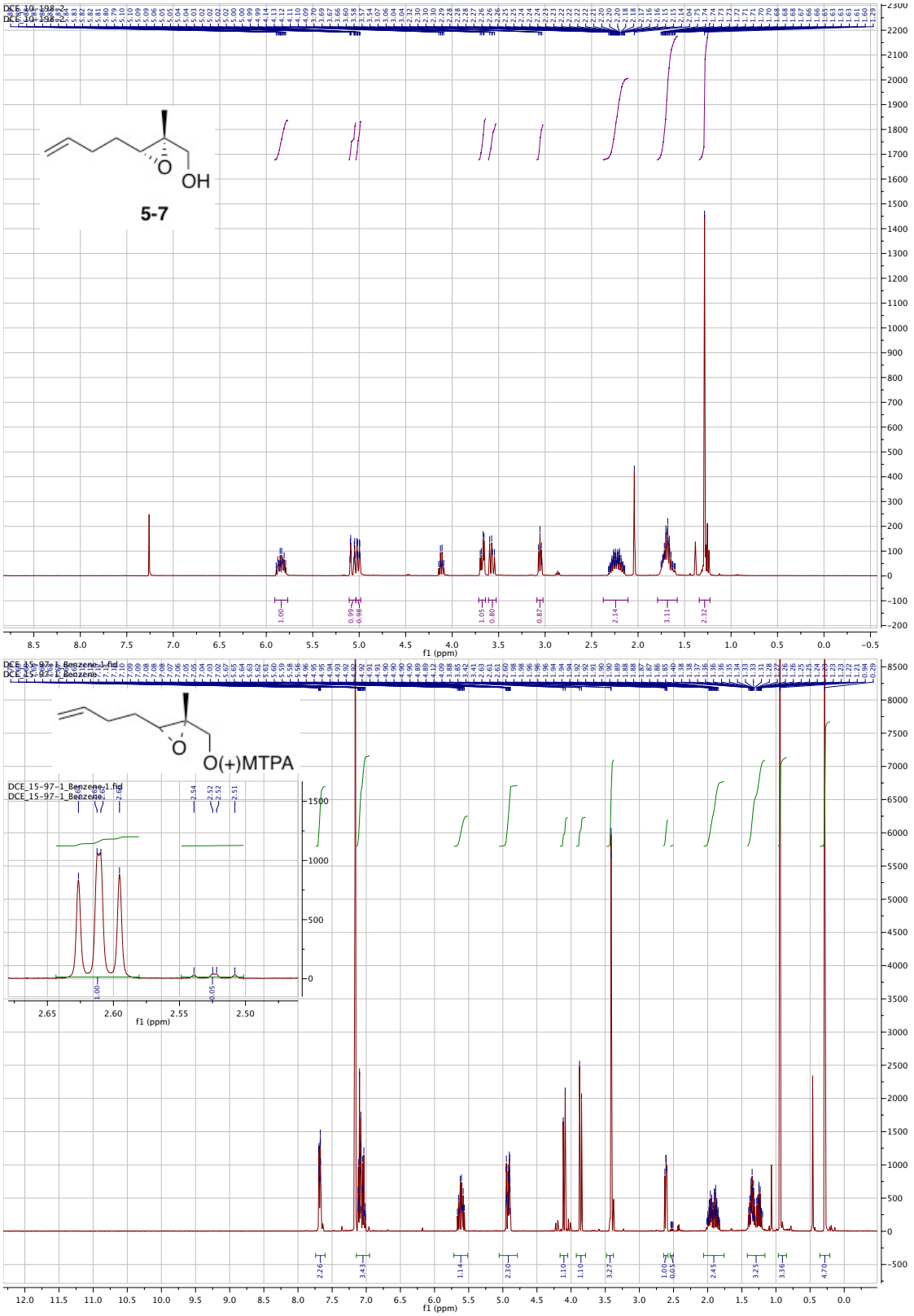

08-16-11_13C
13C OBSERVE
Ph
O
O
Me
Me
O
OTBS
CH3
4-16
f1 (ppm)

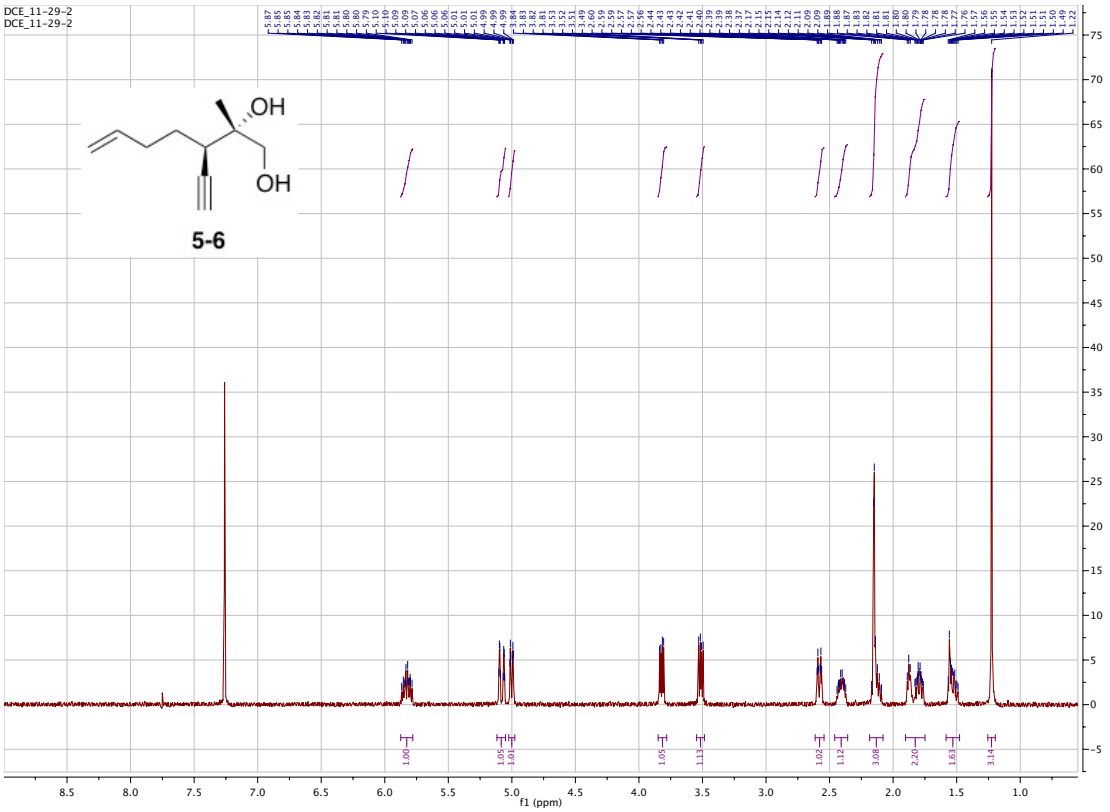

DCE_9-42-2
DCE_9-42-2
Ph
O
O
Me
Me
O
OH
CH3
4-17
f1 (ppm)

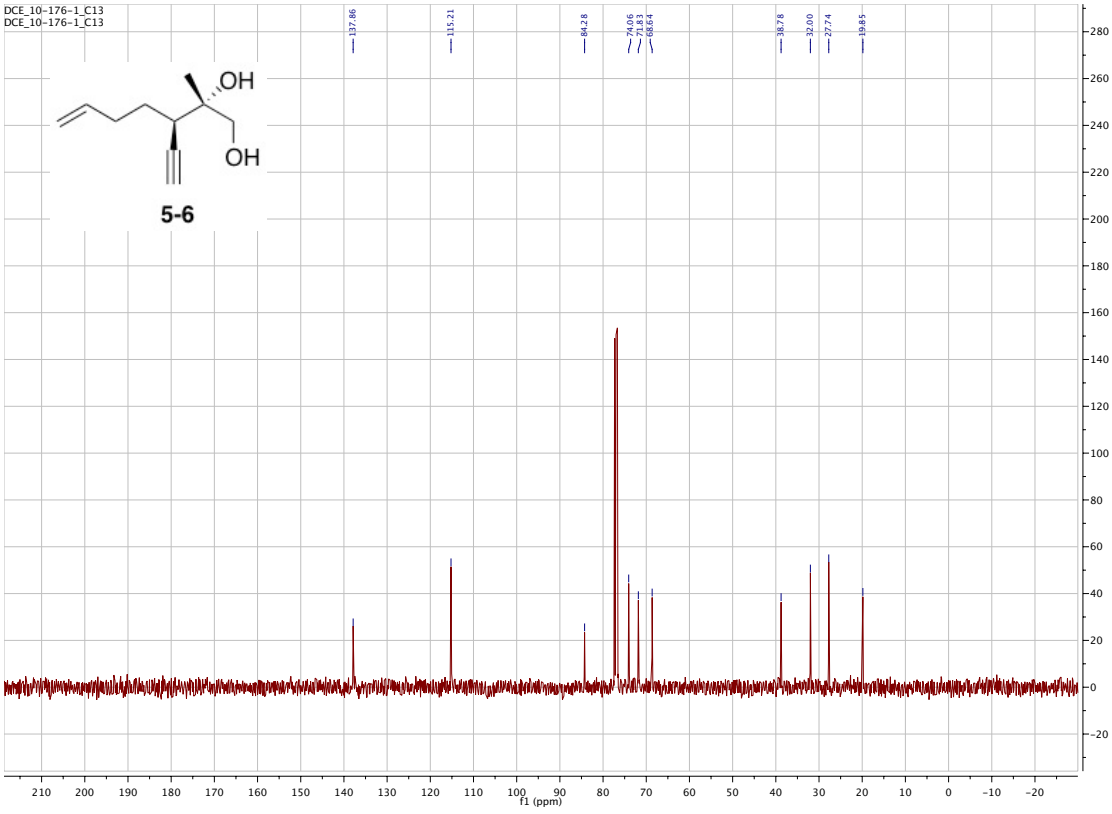

DCE_9-42-2_C13
DCE_9-42-2_C13
Ph
O
O
Me
Me
O
OH
CH3
4-17
165.93
145.00
134.30
130.36
128.88
128.09
118.13
84.74
83.27
76.83
70.96
41.66
34.12
33.04
26.33
20.35
17.88
17.01
f1 (ppm)

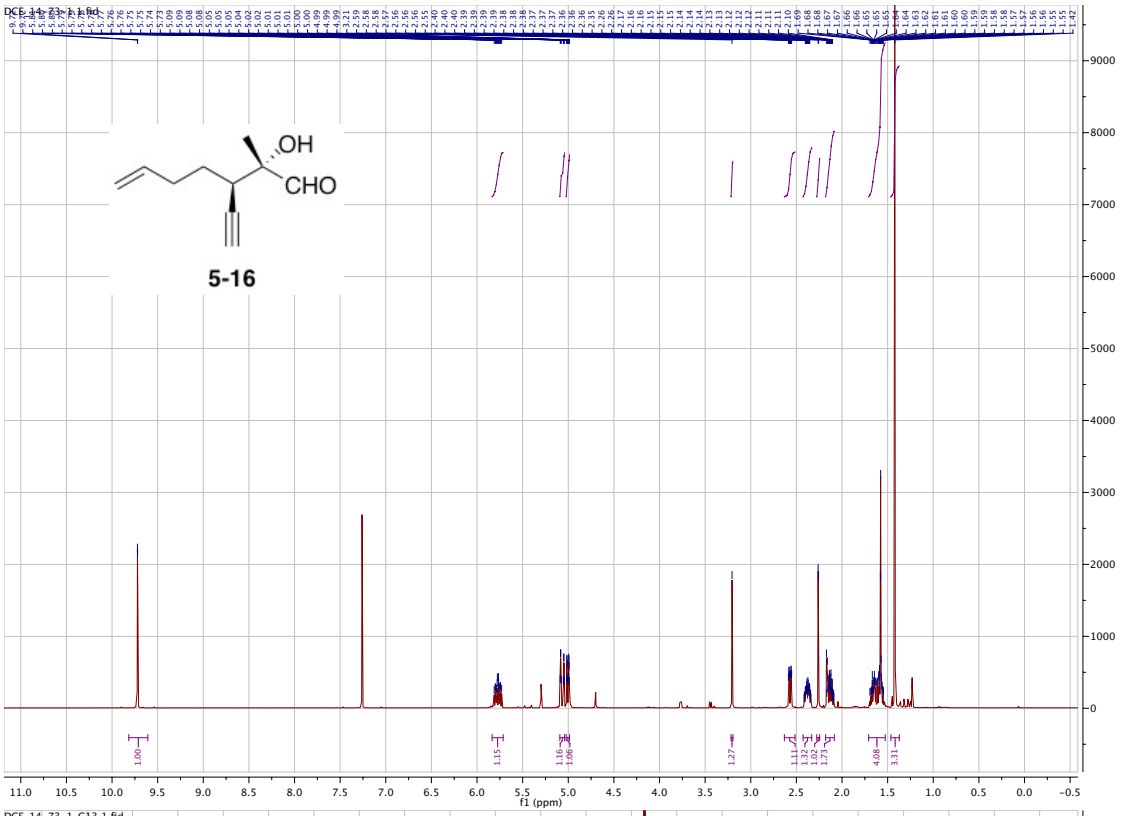

DCE_9-74-4
DCE_9-74-4
Ph
O
O
Me
Me
O
O
O
CH3
OH
4-18
f1 (ppm)

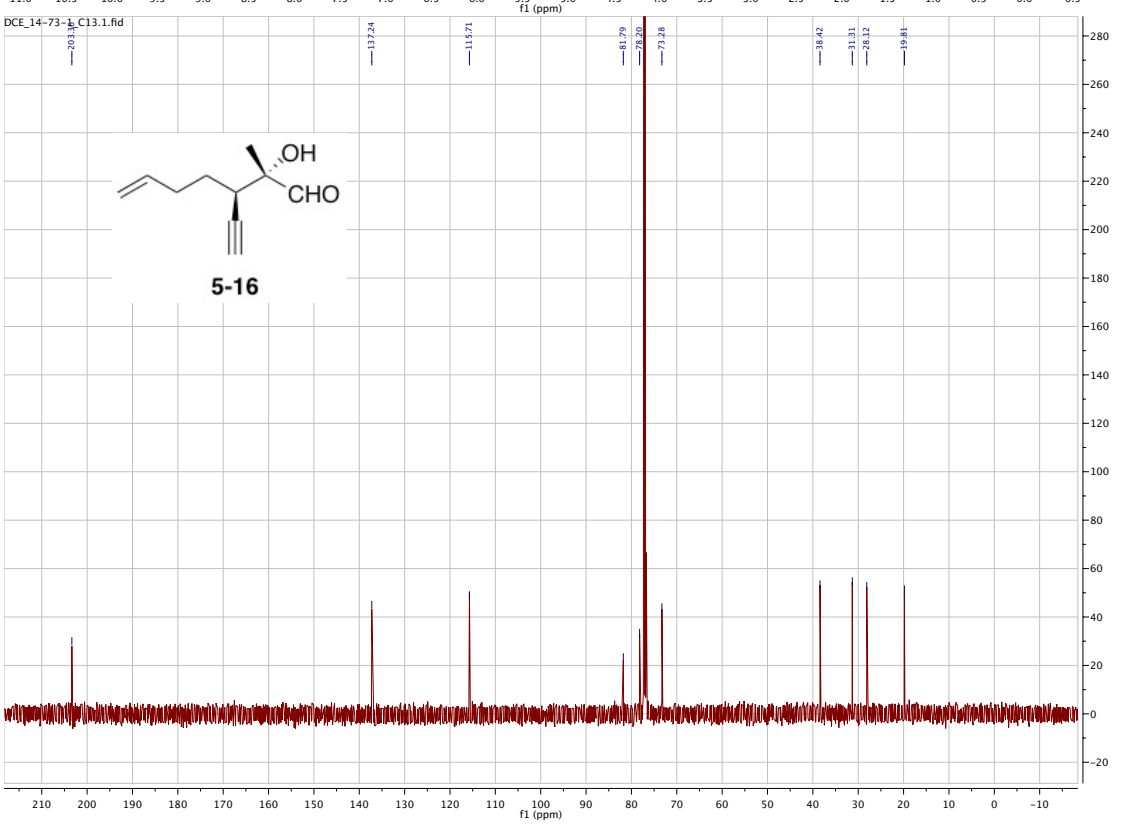

DCE_9-74-4_C13
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: DCE_9-74-4_C13
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
5856 repetitions
OBSERVE C13, 100.5376633 MHz
DECOUPLE H1, 399.8364198 MHz
Power 48 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 613 hr, 23 min, 28 sec
77.548
77.230
76.911
173.173
166.054
145.429
134.486
130.669
129.144
128.347
118.201
85.464
82.633
79.894
70.673
60.877
39.052
34.468
33.429
24.618
20.574
18.145
17.181
1.238
ppm

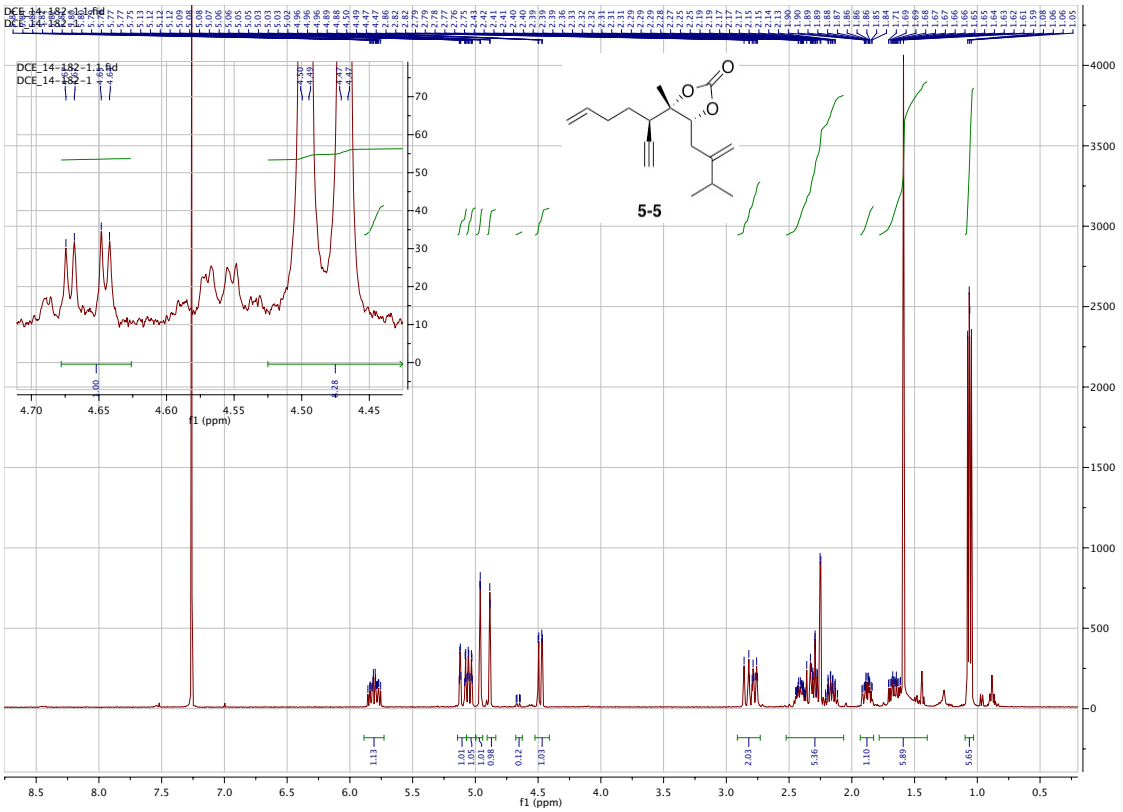

5-7
O(+)MTPA
f1 (ppm)

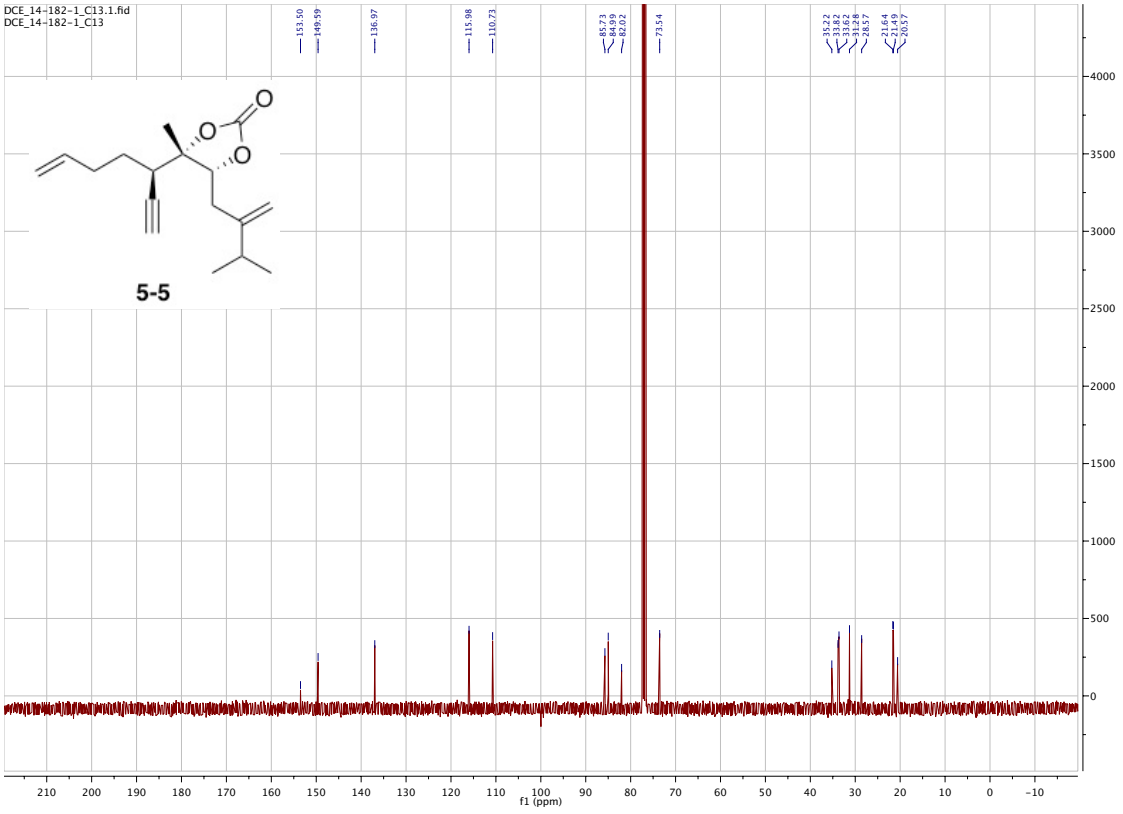

DCE_11-29-2
DCE_11-29-2
OH
OH
5-6
f1 (ppm)

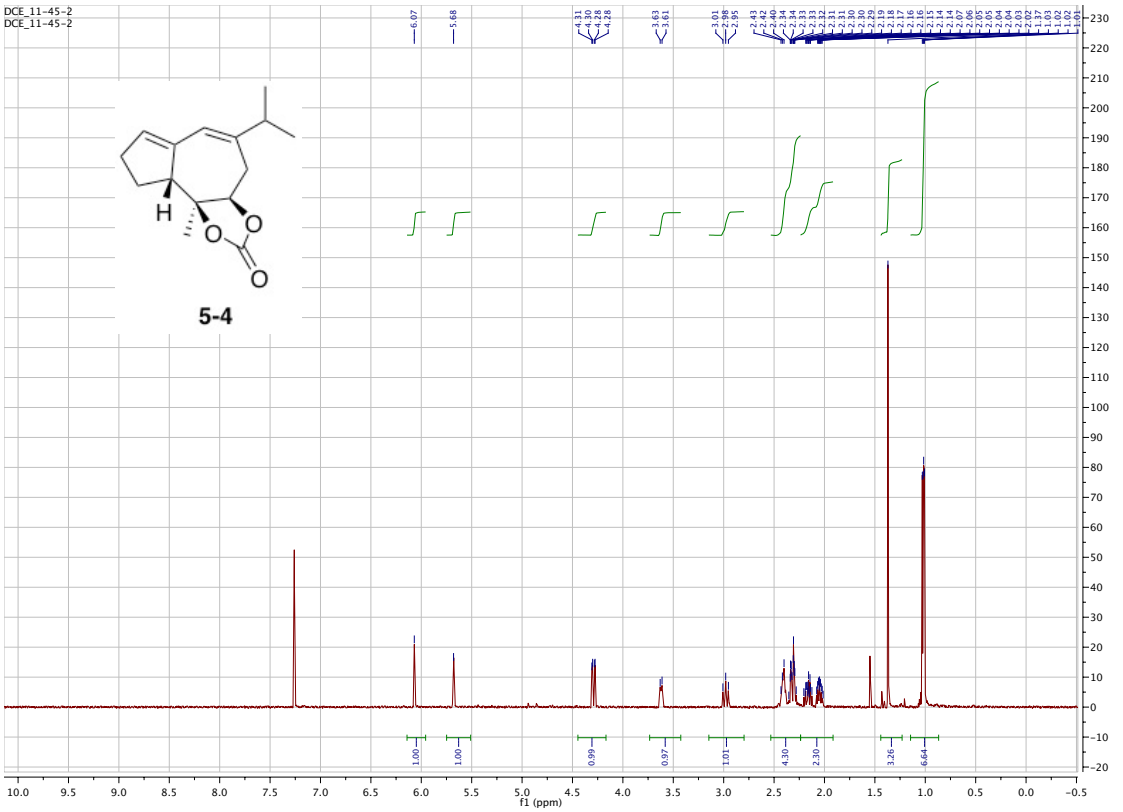

DCE_10-176-1_C13
DCE_10-176-1_C13
137.86
115.21
84.28
74.06
71.83
68.64
38.78
32.00
27.74
19.85
OH
OH
5-6
f1 (ppm)

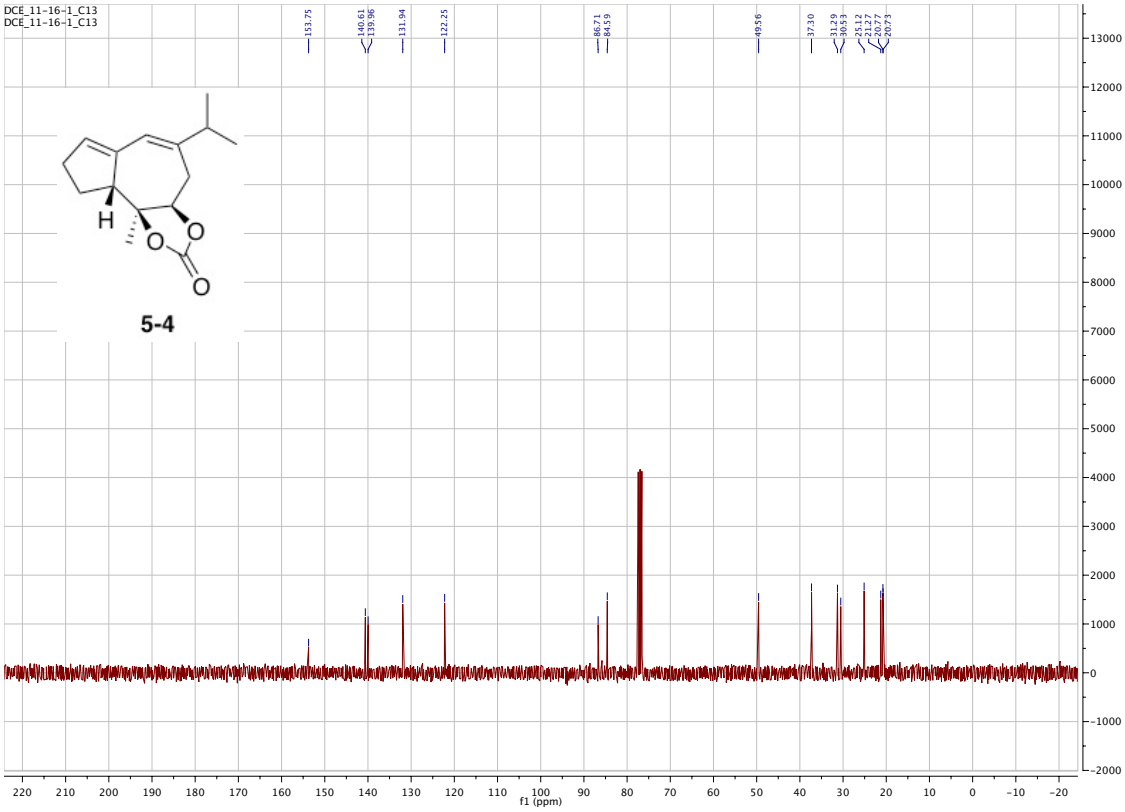

OH
CHO
5-16
f1 (ppm)

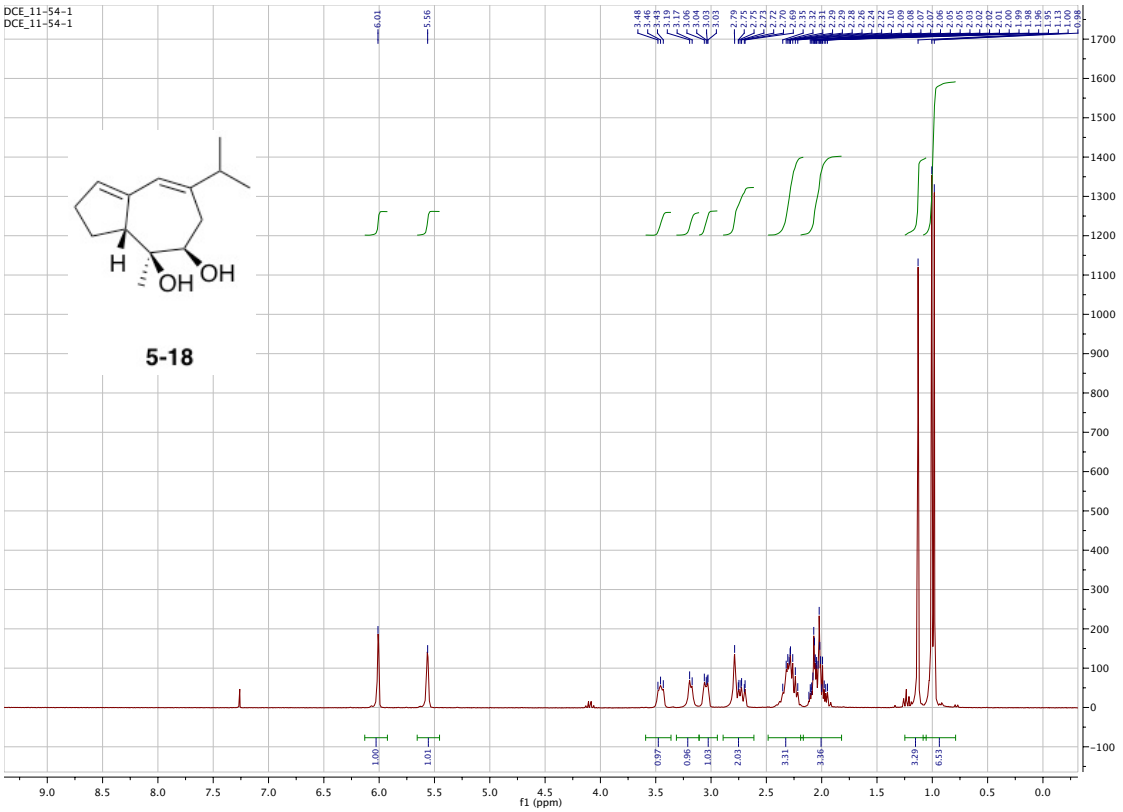

OH
CHO
5-16
f1 (ppm)

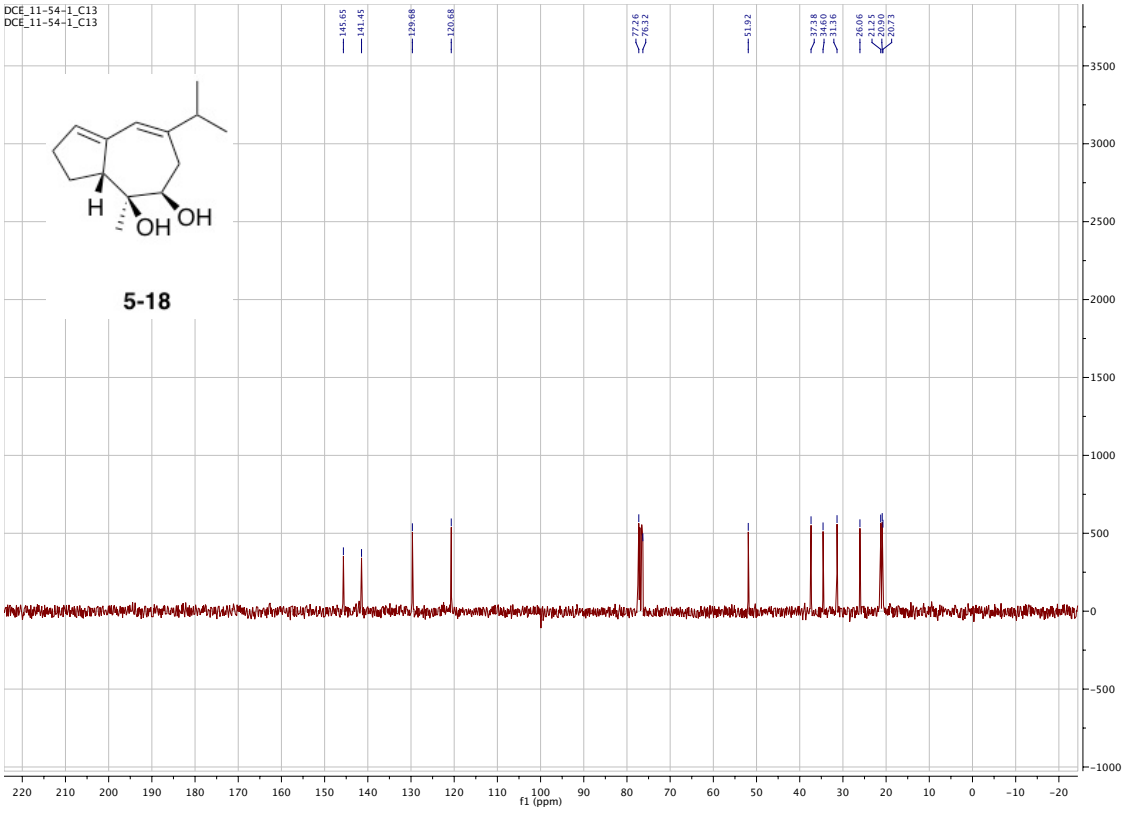

DCE_14-182-1.1.fid
DCE_14-182-1
5-5
f1 (ppm)

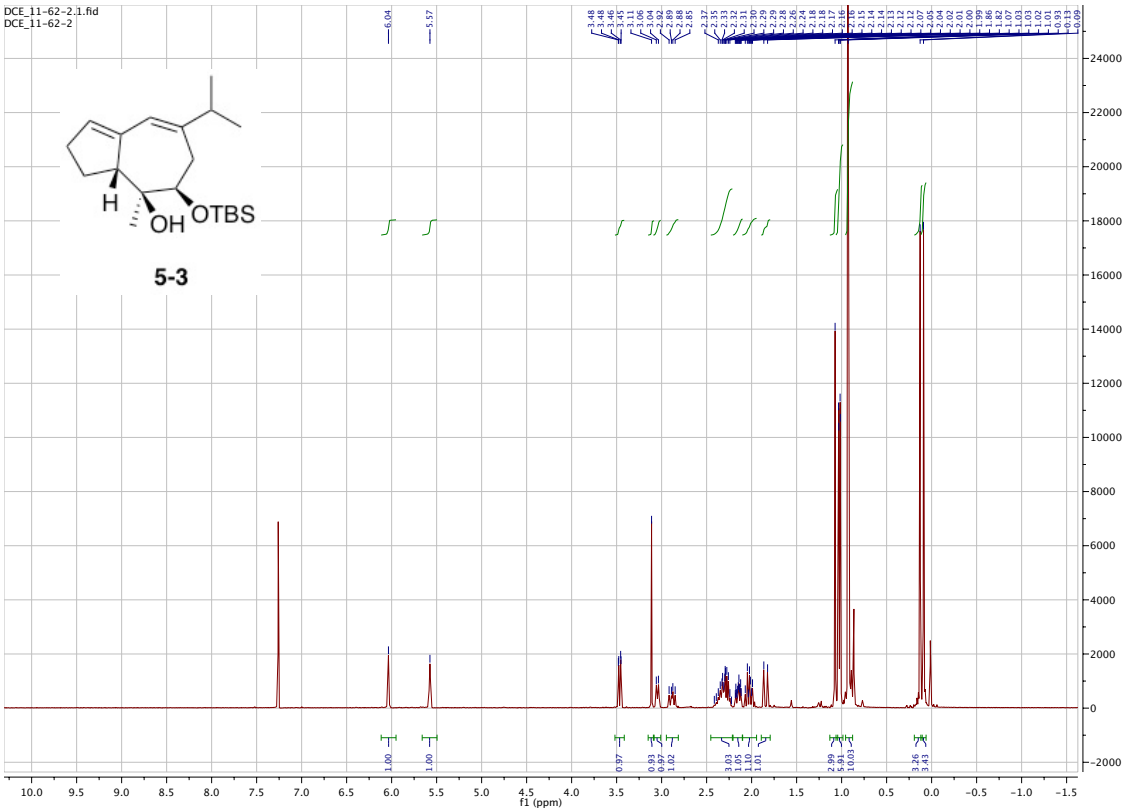

DCE_14-182-1_C13.1.fid
DCE_14-182-1_C13
153.50
149.59
136.97
115.98
110.73
85.73
84.99
82.02
73.54
35.22
33.82
33.62
28.48
26.57
21.64
21.49
20.57
5-5
f1 (ppm)

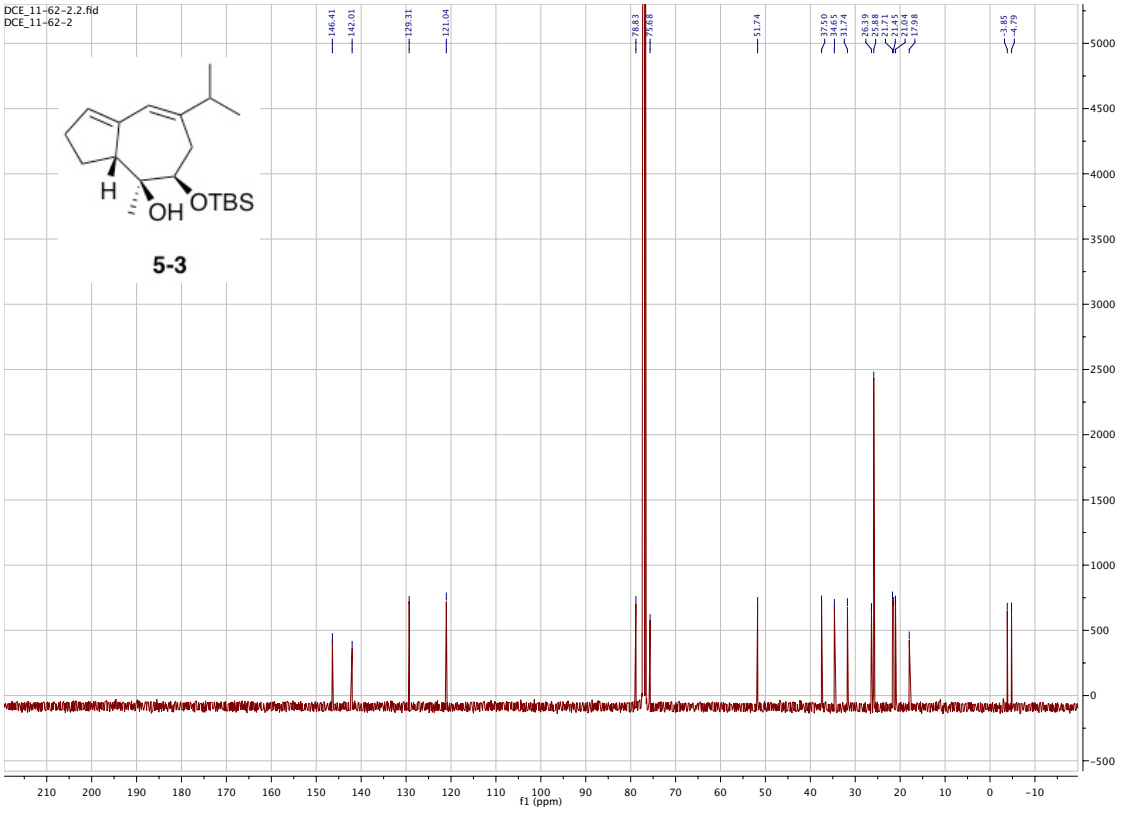

DCE_11-45-2
DCE_11-45-2
5-4
f1 (ppm)

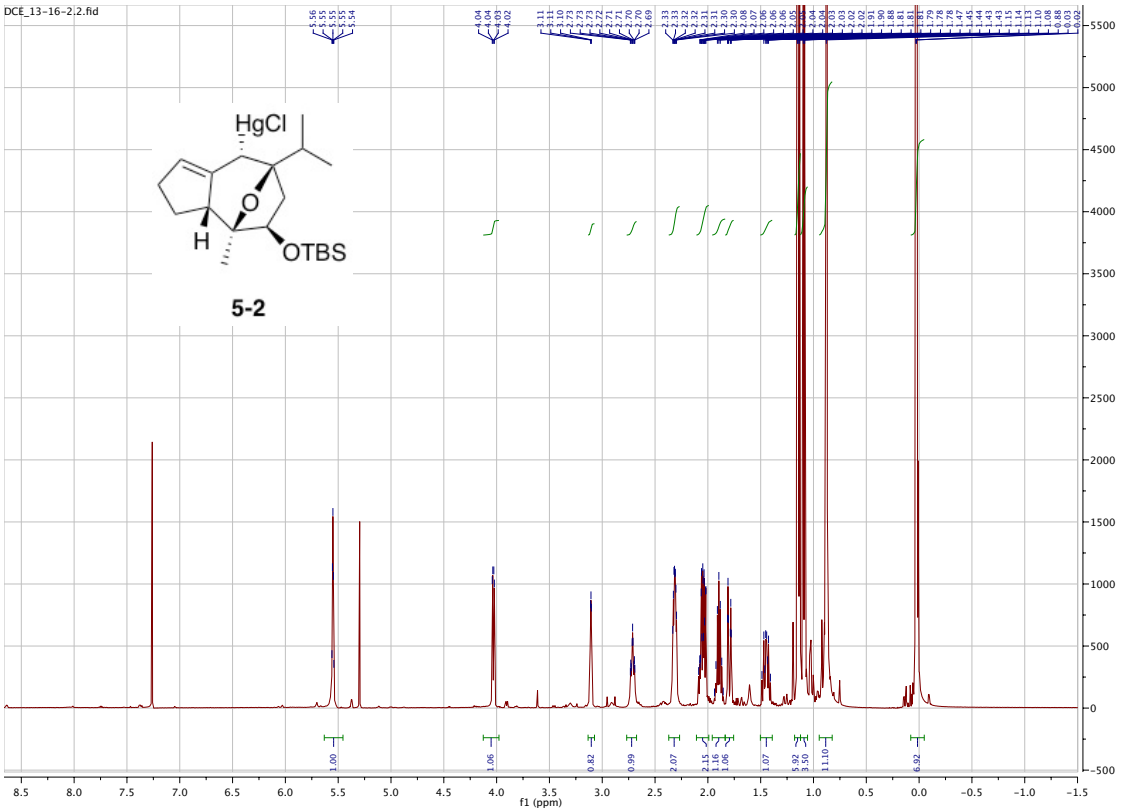

DCE_11-16-1_C13
DCE_11-16-1_C13
5-4
f1 (ppm)

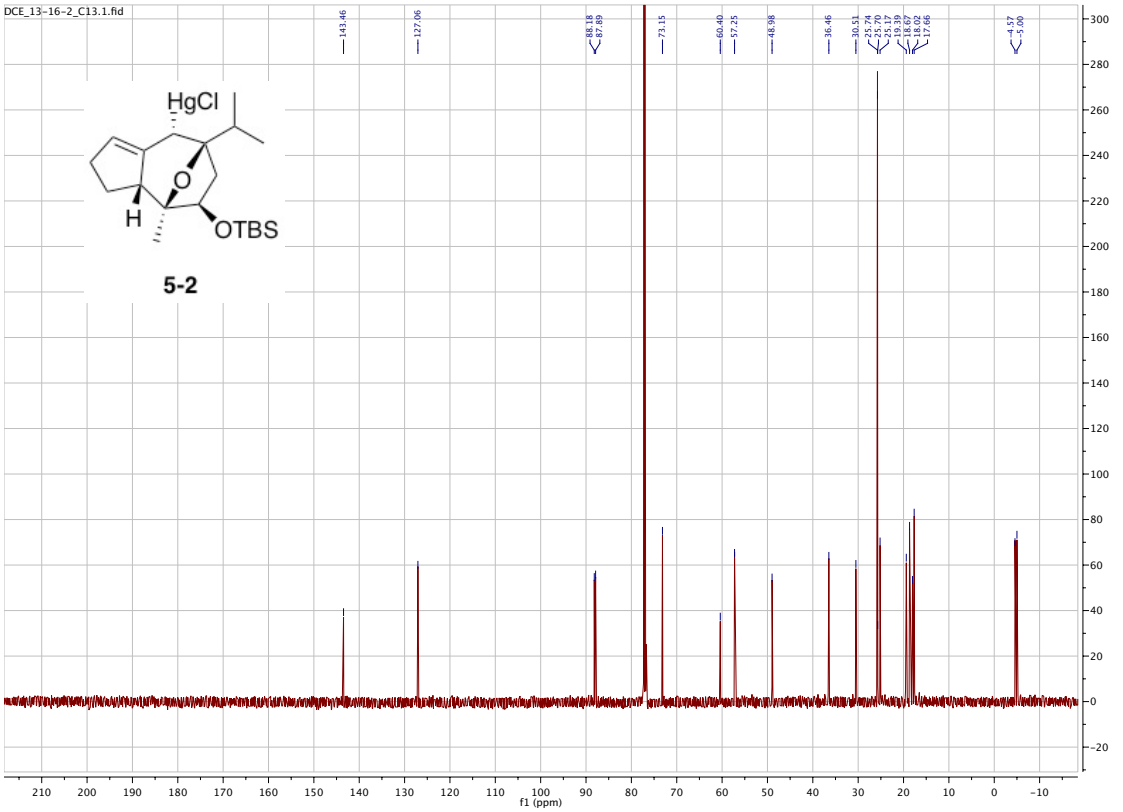

DCE_11-54-1
DCE_11-54-1
6.01
5.56
H
OH
OH
5-18
f1 (ppm)

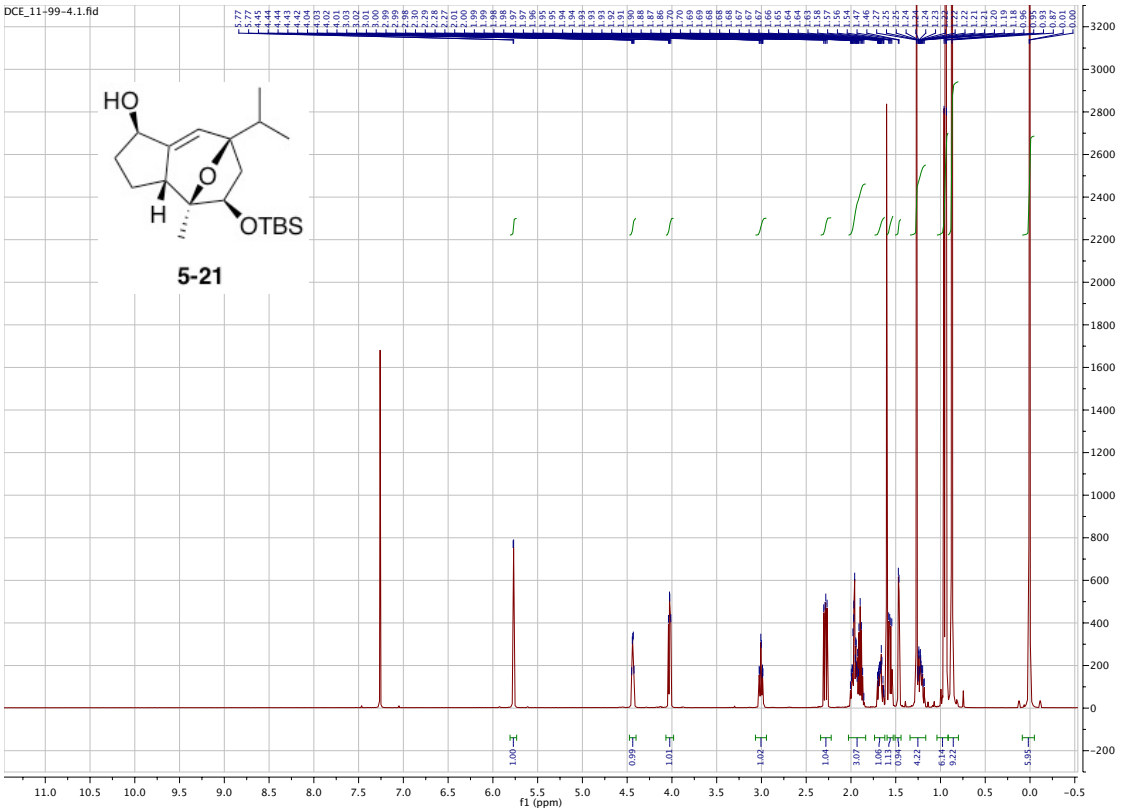

DCE_11-54-1_C13
DCE_11-54-1_C13
145.65
141.45
129.68
120.68
77.26
76.32
51.92
37.38
34.60
31.36
26.06
21.25
20.50
20.73
H
OH
OH
5-18
f1 (ppm)

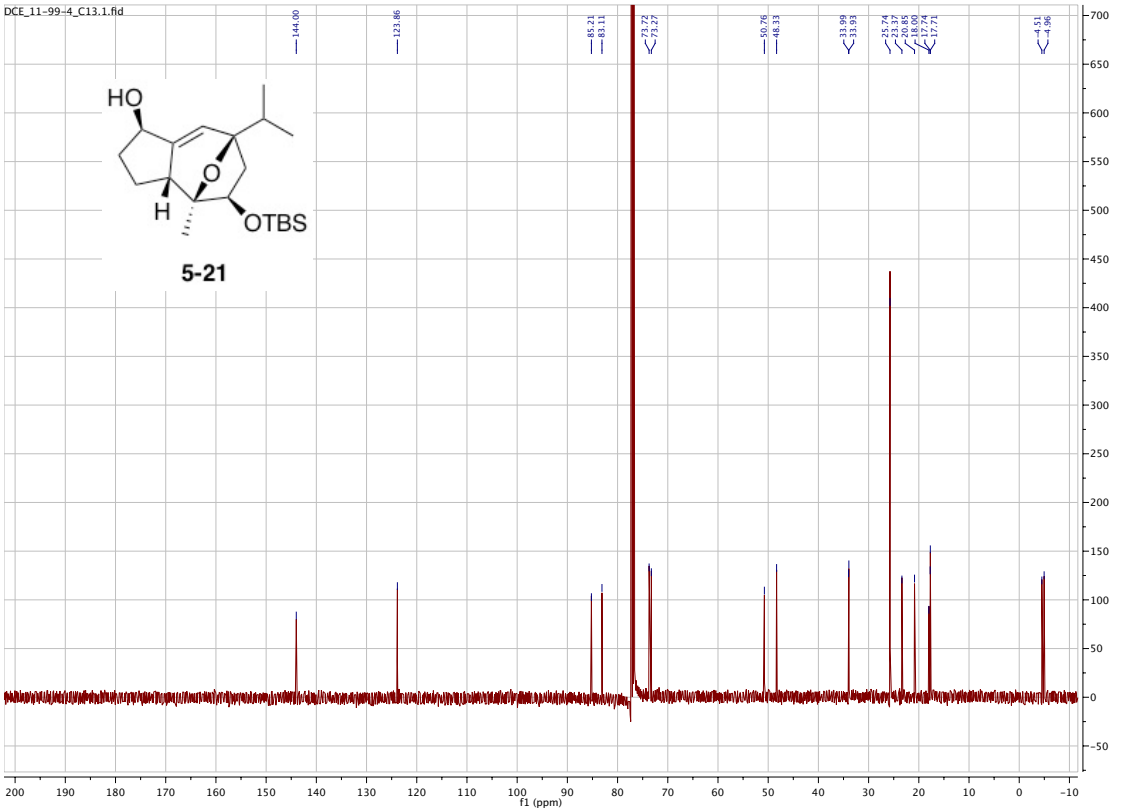

DCE_11-62-2.1.fid
DCE_11-62-2
H
OH
OTBS
5-3
f1 (ppm)

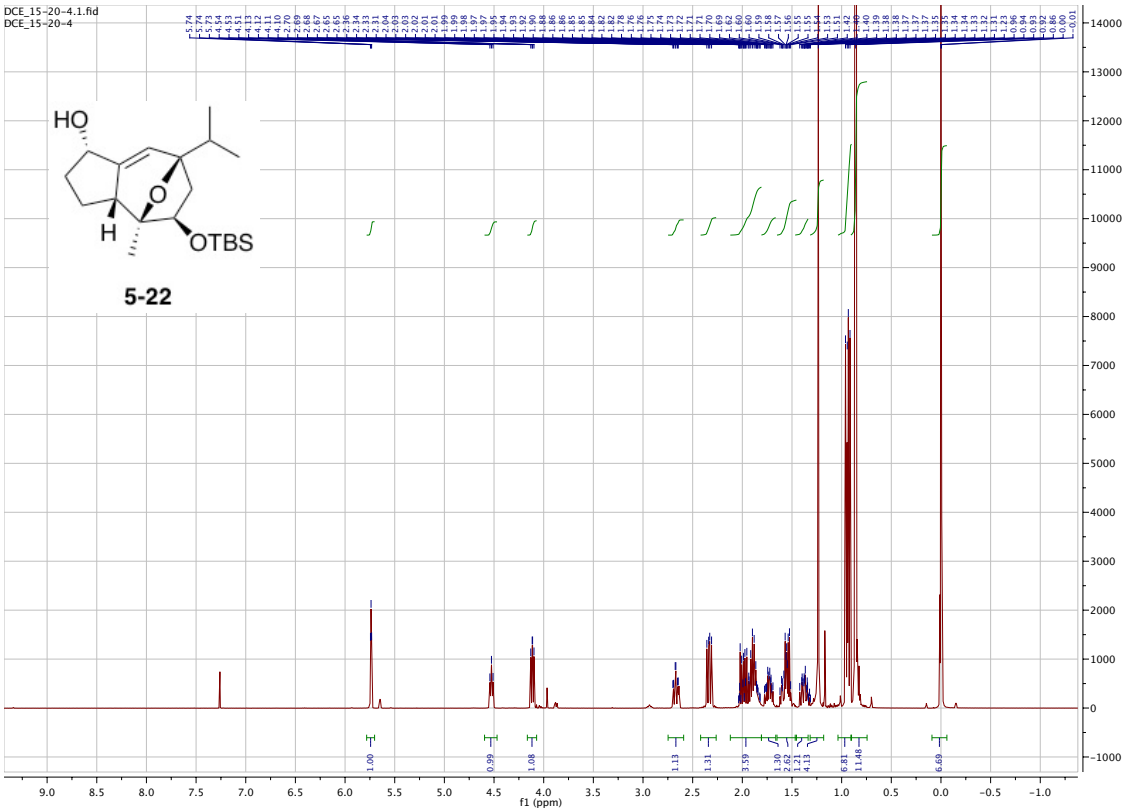

DCE_11-62-2.2.fid
DCE_11-62-2
H
OH
OTBS
5-3
f1 (ppm)

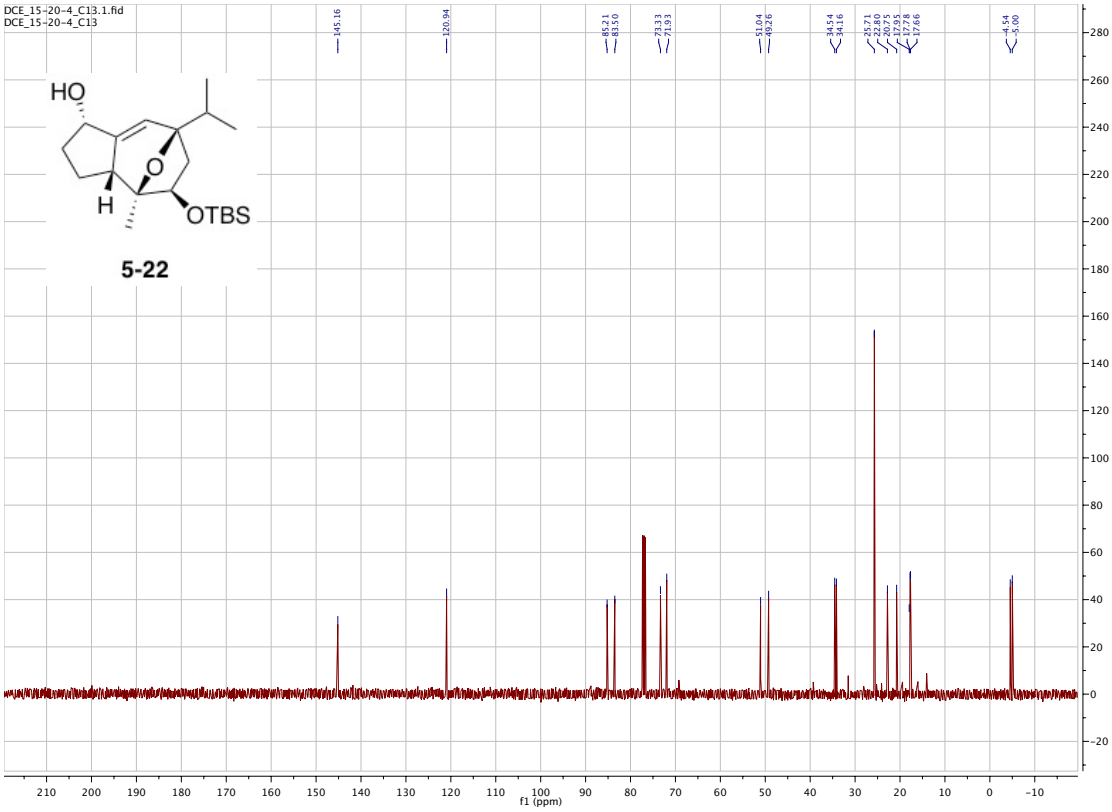

DCE_13-16-2_2.fid
HgCl
O
H
OTBS
5-2
f1 (ppm)

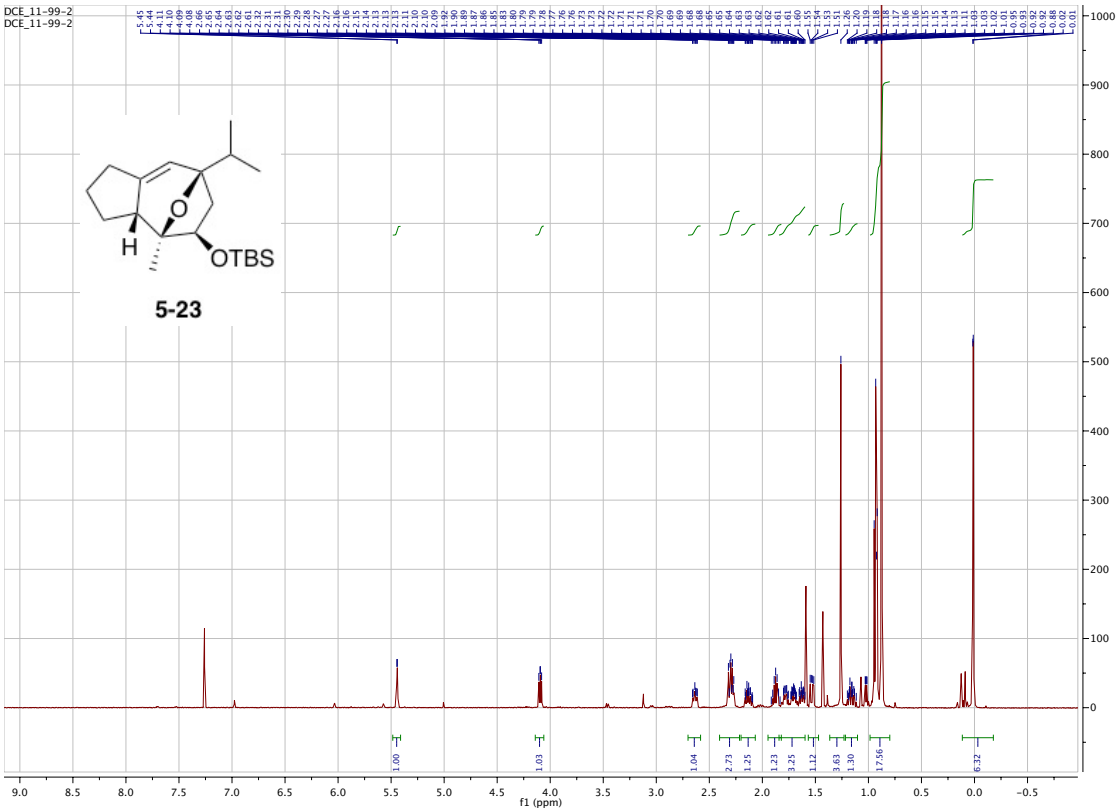

DCE_13-16-2_C13_1.fid
HgCl
O
H
OTBS
5-2
f1 (ppm)

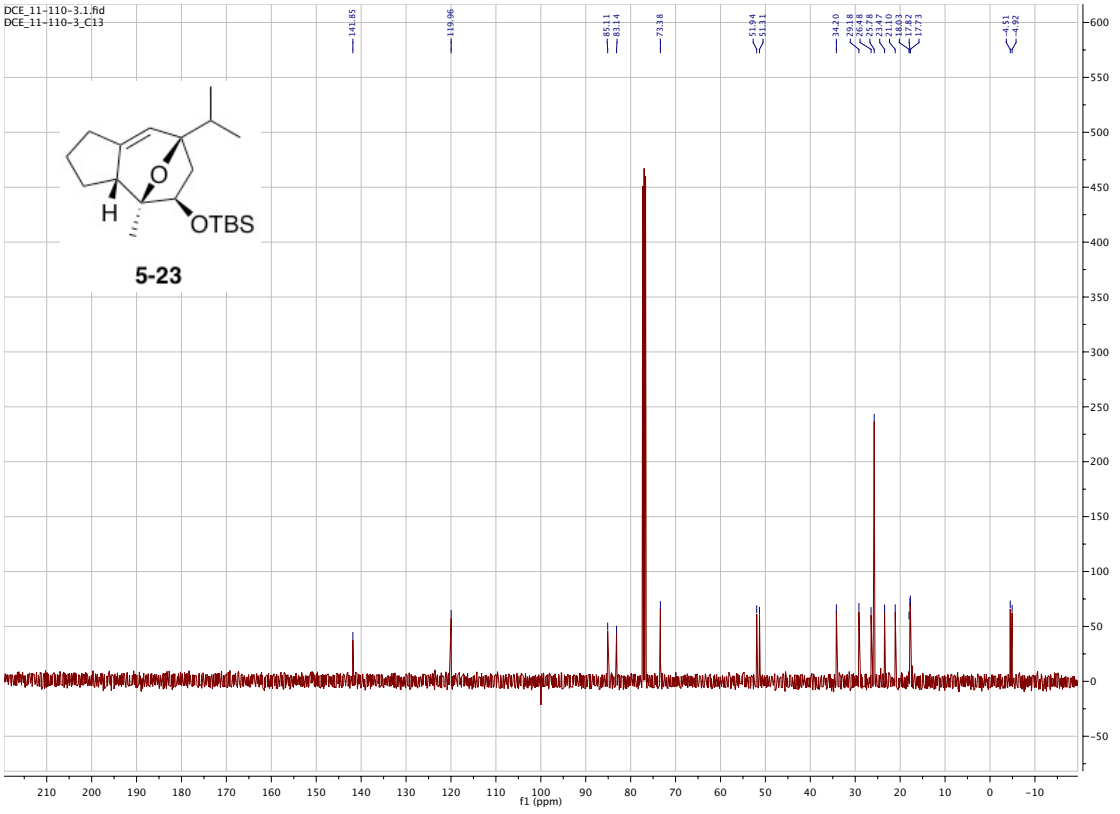

DCE_11-99-4.1.fid
HO
O
H
OTBS
5-21
f1 (ppm)

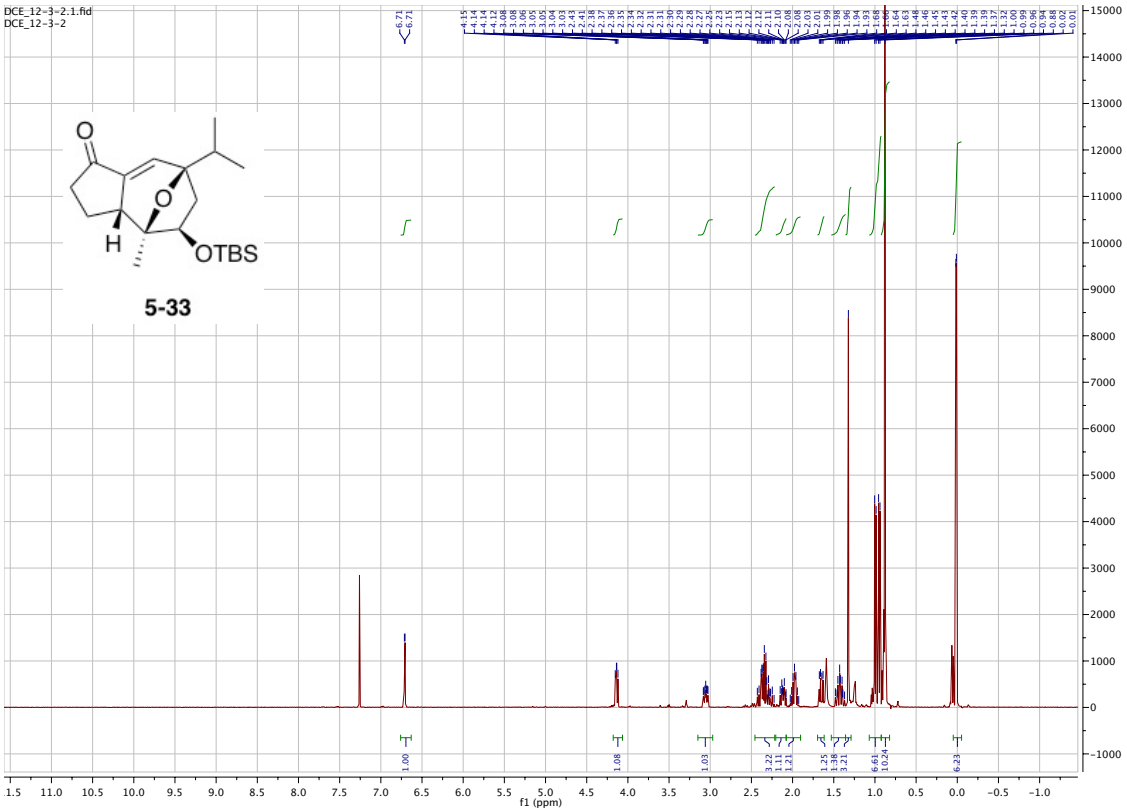

DCE_11-99-4_C13.1.fid
HO
O
H
OTBS
5-21
f1 (ppm)

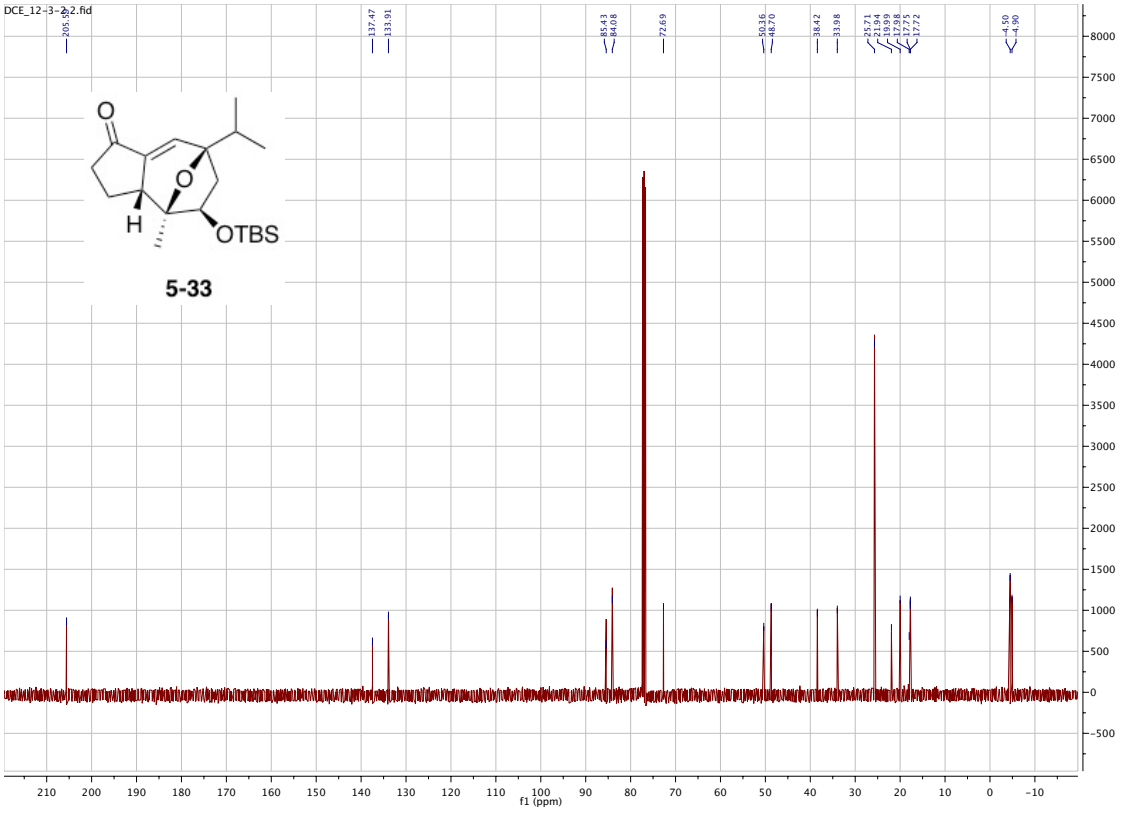

DCE_15-20-4.1.fid
DCE_15-20-4
HO
O
H
OTBS
5-22
f1 (ppm)

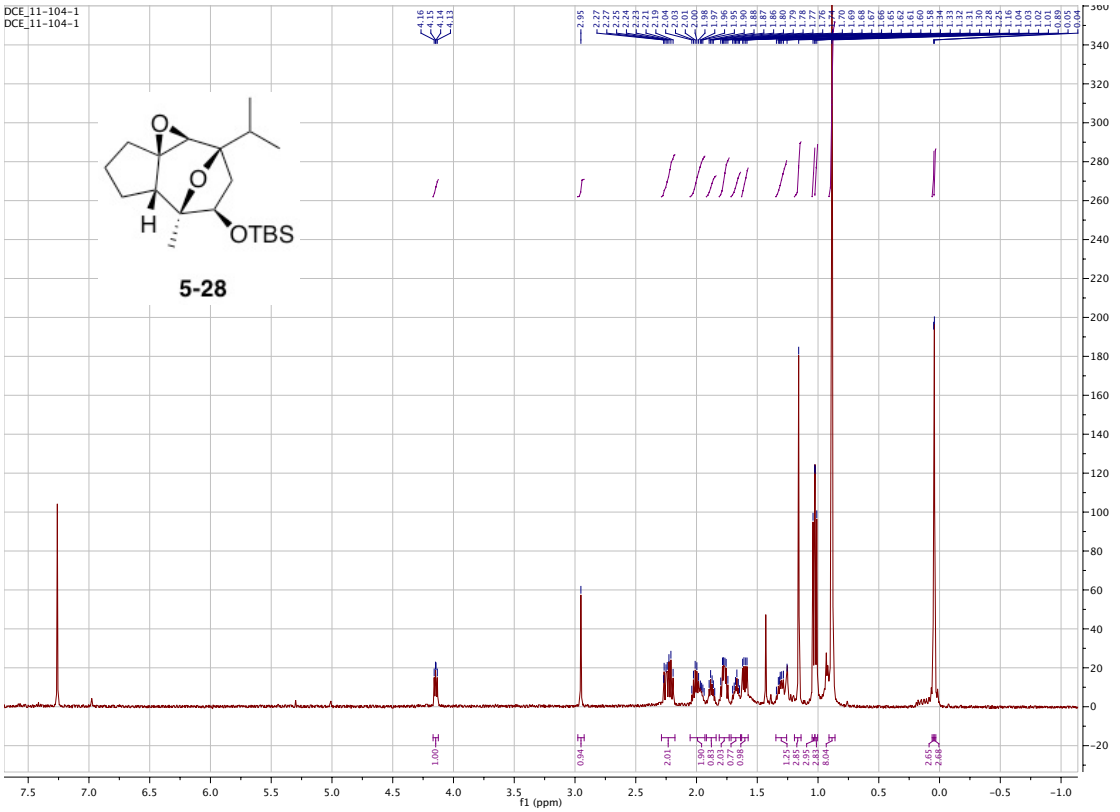

DCE_15-20-4_C13.1.fid
DCE_15-20-4_C13
HO
O
H
OTBS
5-22
f1 (ppm)

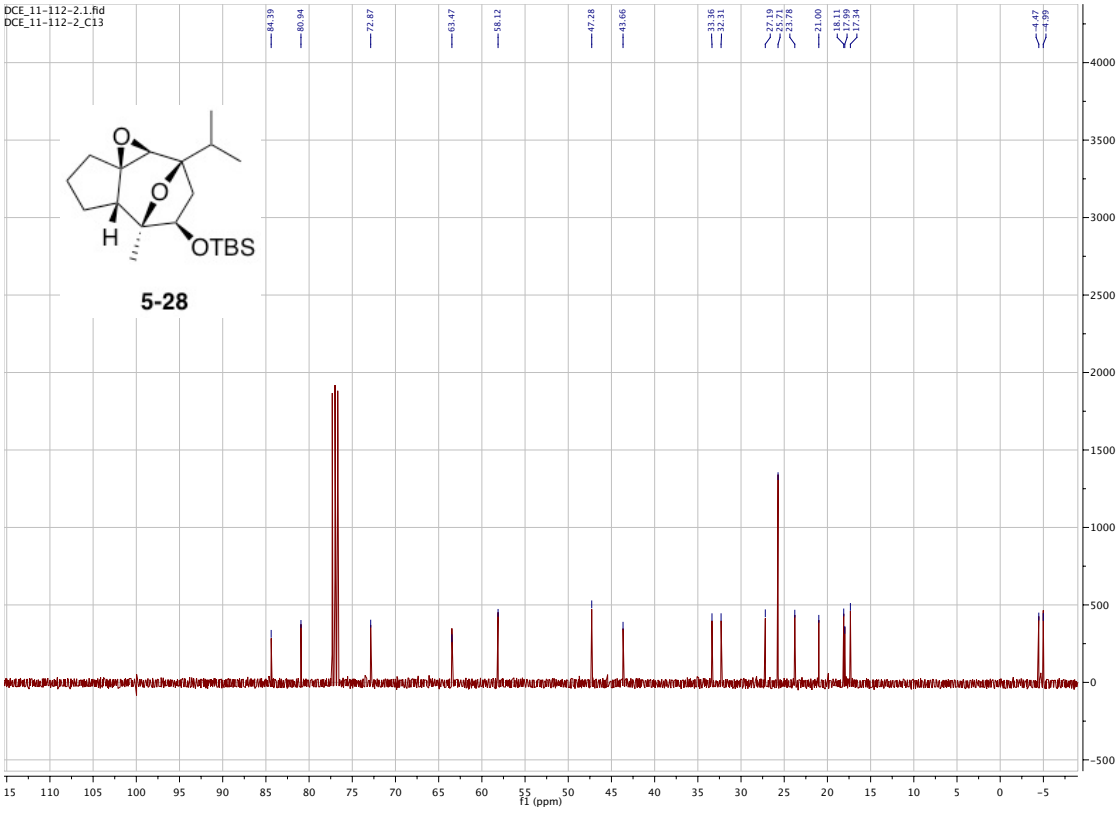

DCE_11-99-2
DCE_11-99-2
O
H
OTBS
5-23
f1 (ppm)

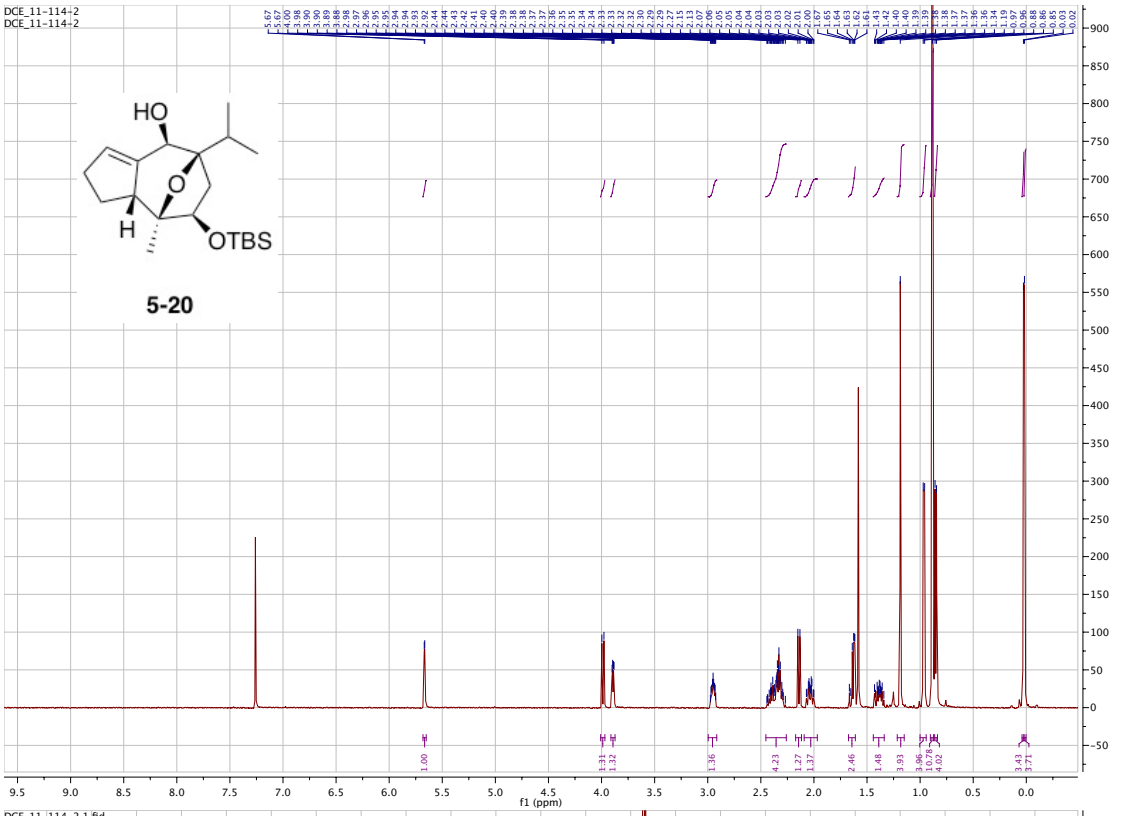

DCE_11-110-3.1.fid
DCE_11-110-3_C13
O
H
OTBS
5-23
f1 (ppm)

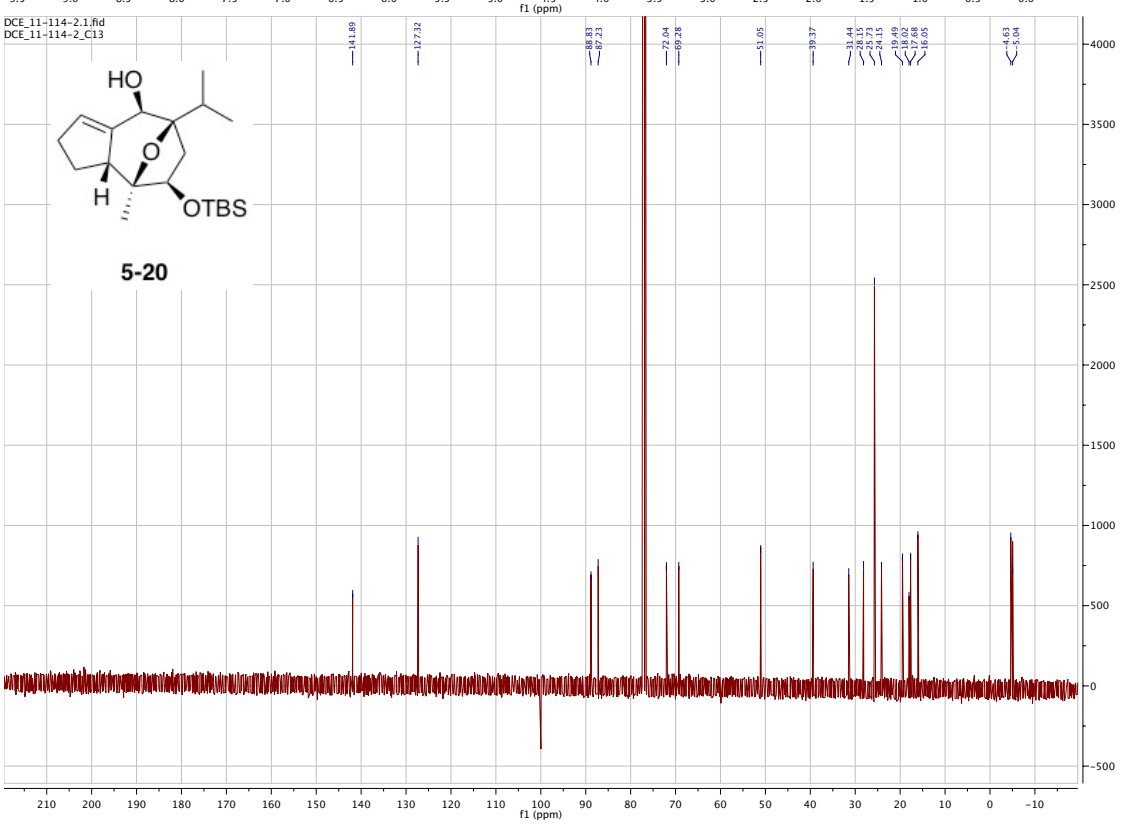

DCE_12-3-2.1.fid
DCE_12-3-2
O
O
H
OTBS
5-33
f1 (ppm)

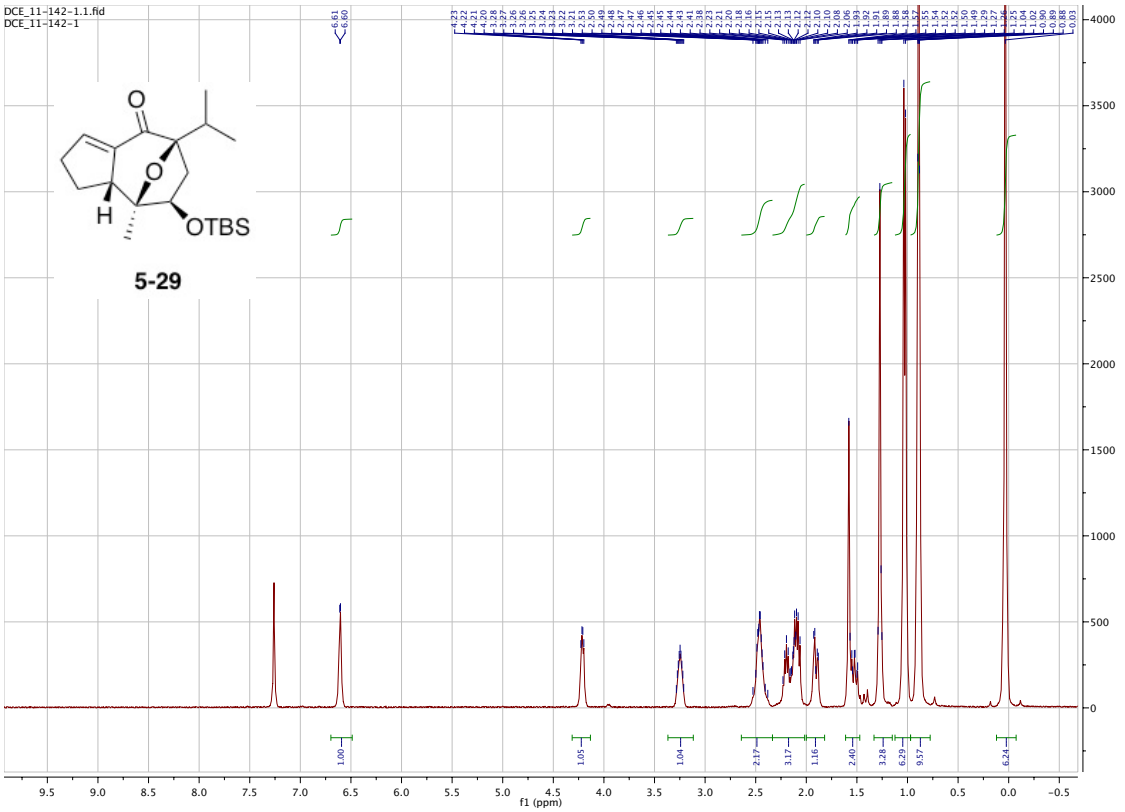

DCE_12-3-2.2.fid
O
O
H
OTBS
5-33
f1 (ppm)

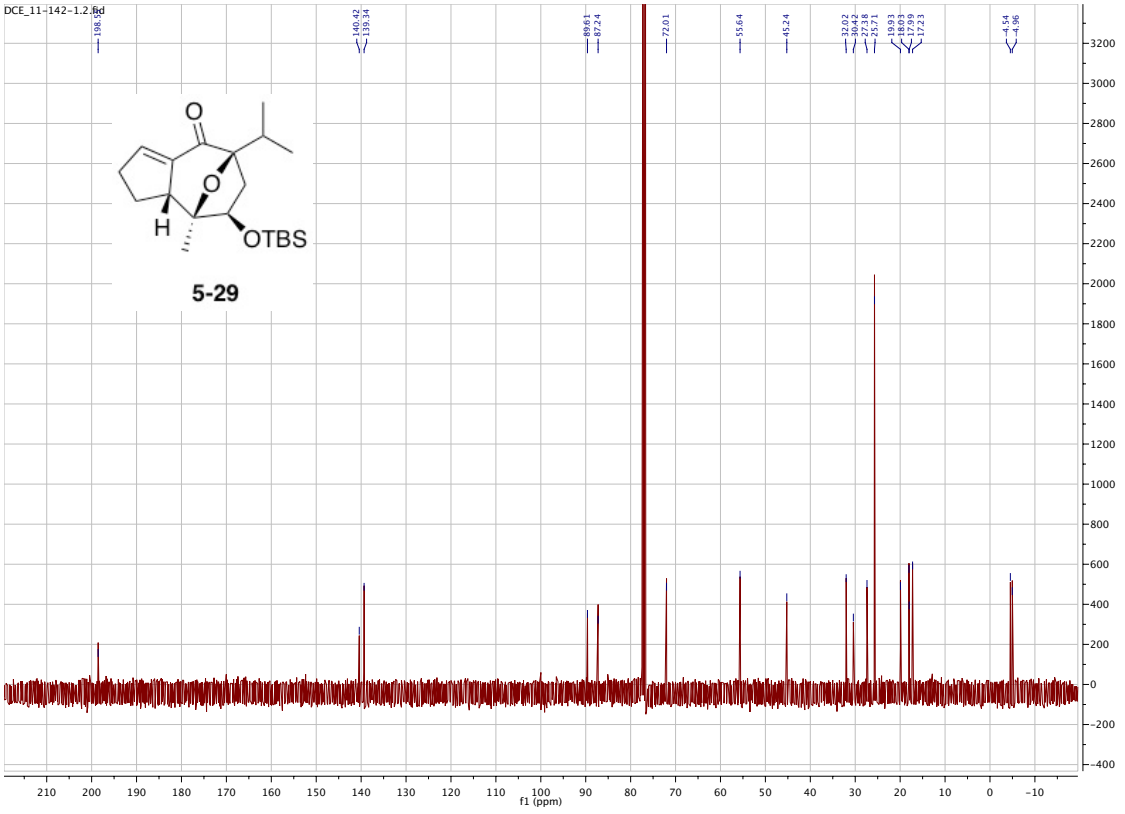

DCE_11-104-1
DCE_11-104-1
O
O
H
OTBS
5-28
f1 (ppm)

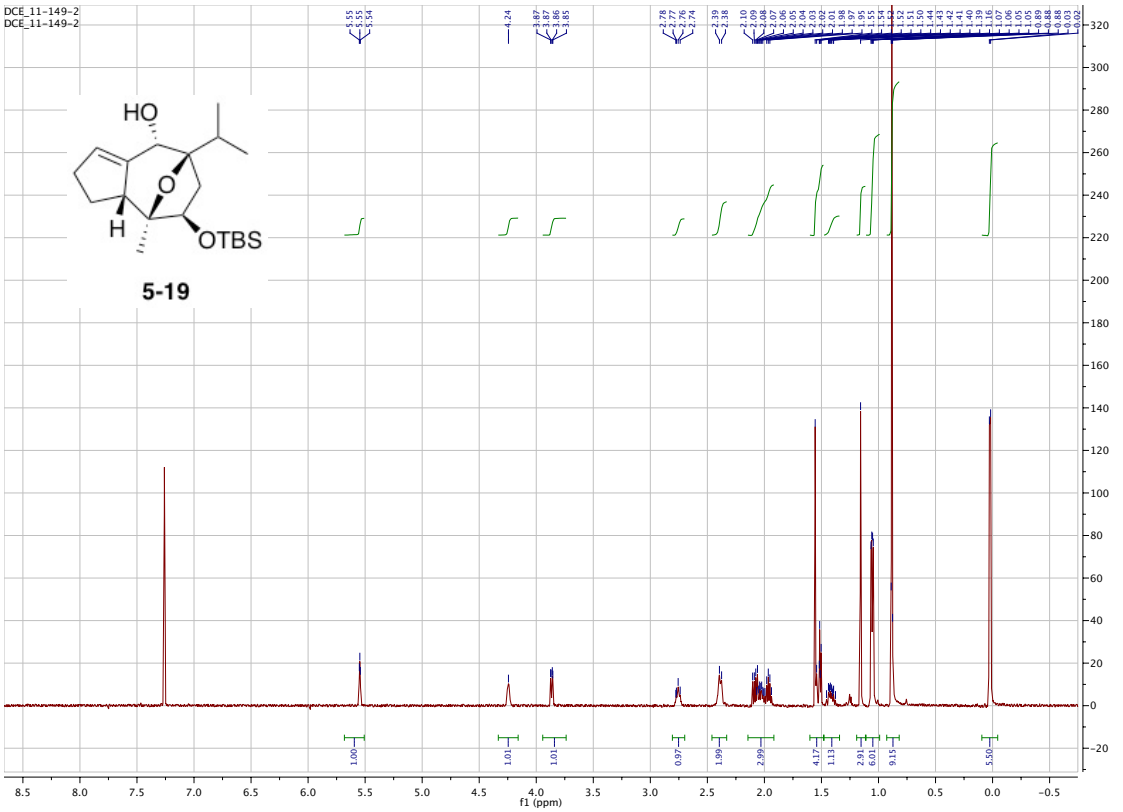

DCE_11-112-2.1.fid
DCE_11-112-2_C13
O
O
H
OTBS
5-28
f1 (ppm)

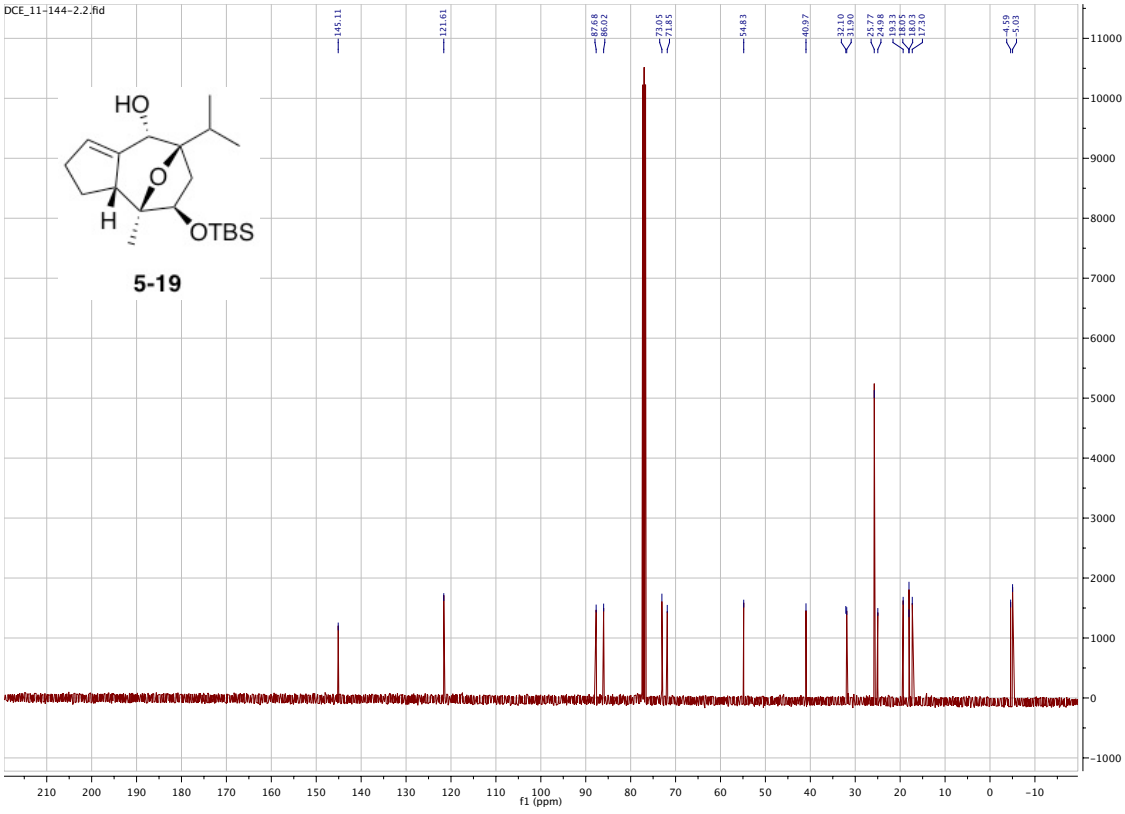

DCE_11-114-2
DCE_11-114-2
HO
O
H
OTBS
5-20
f1 (ppm)

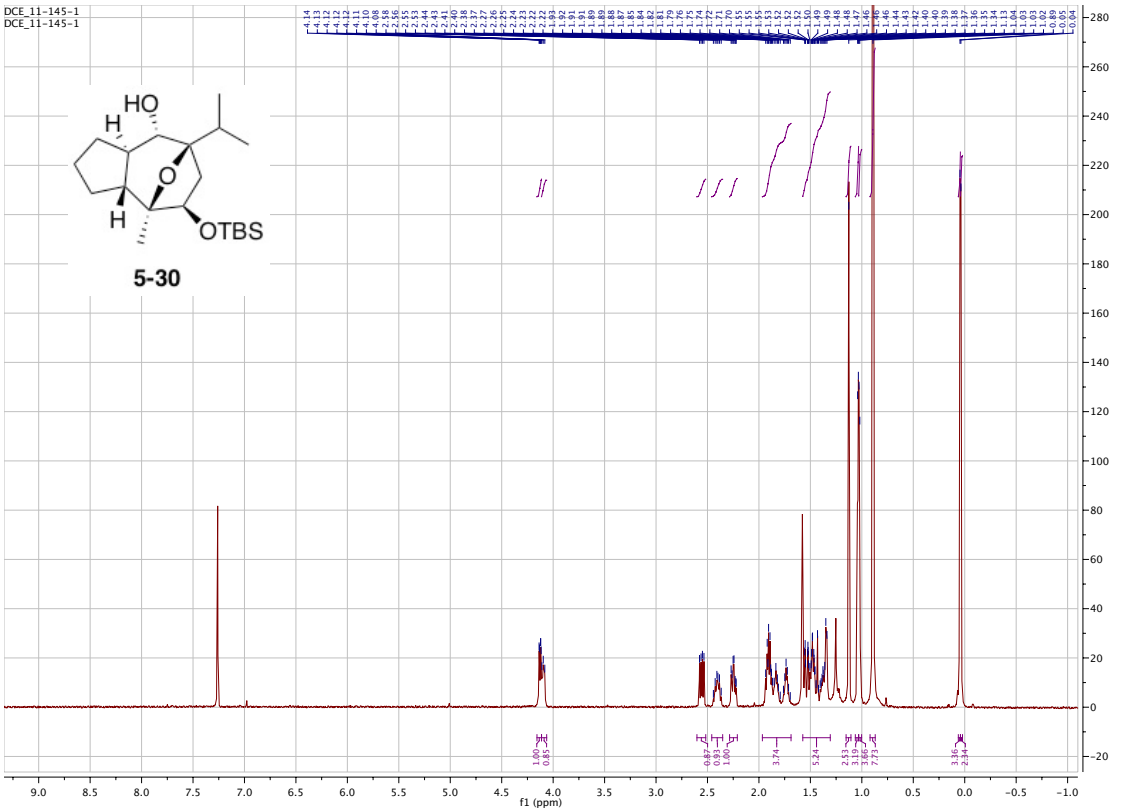

DCE_11-114-2.1.fid
DCE_11-114-2_C13
HO
O
H
OTBS
5-20
f1 (ppm)

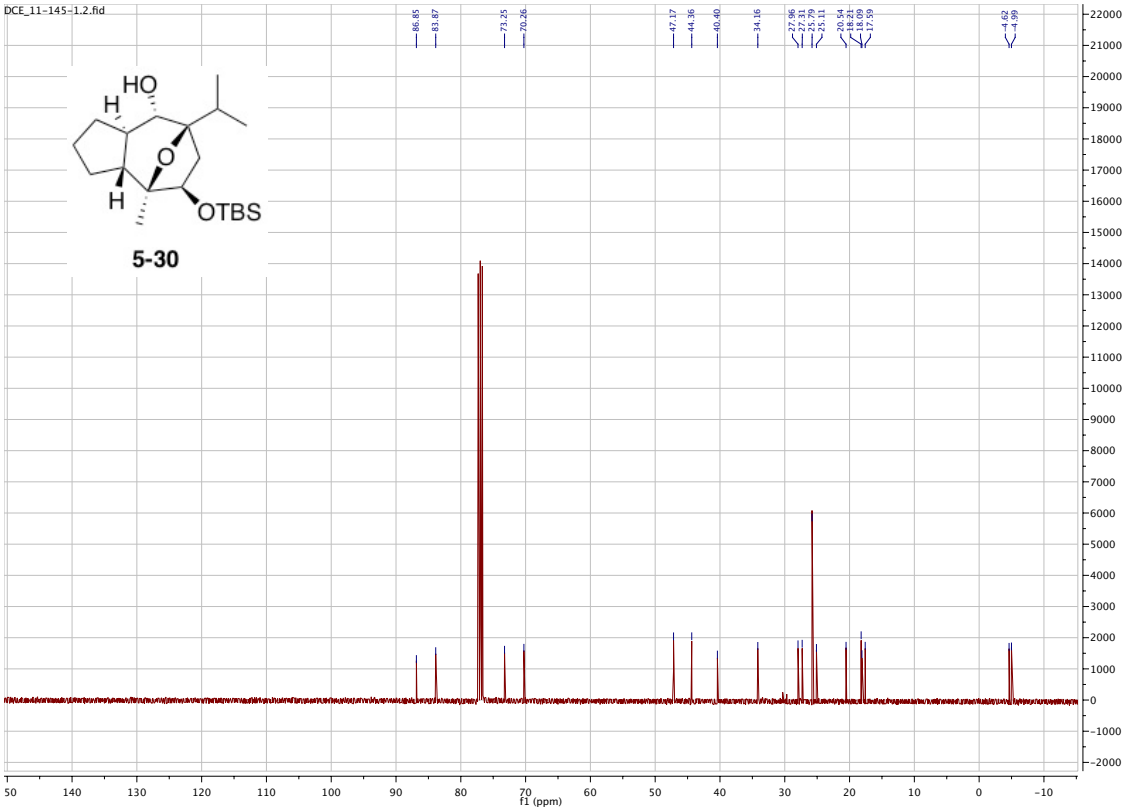

DCE_11-142-1.1.fid
DCE_11-142-1
O
O
H
OTBS
5-29
f1 (ppm)

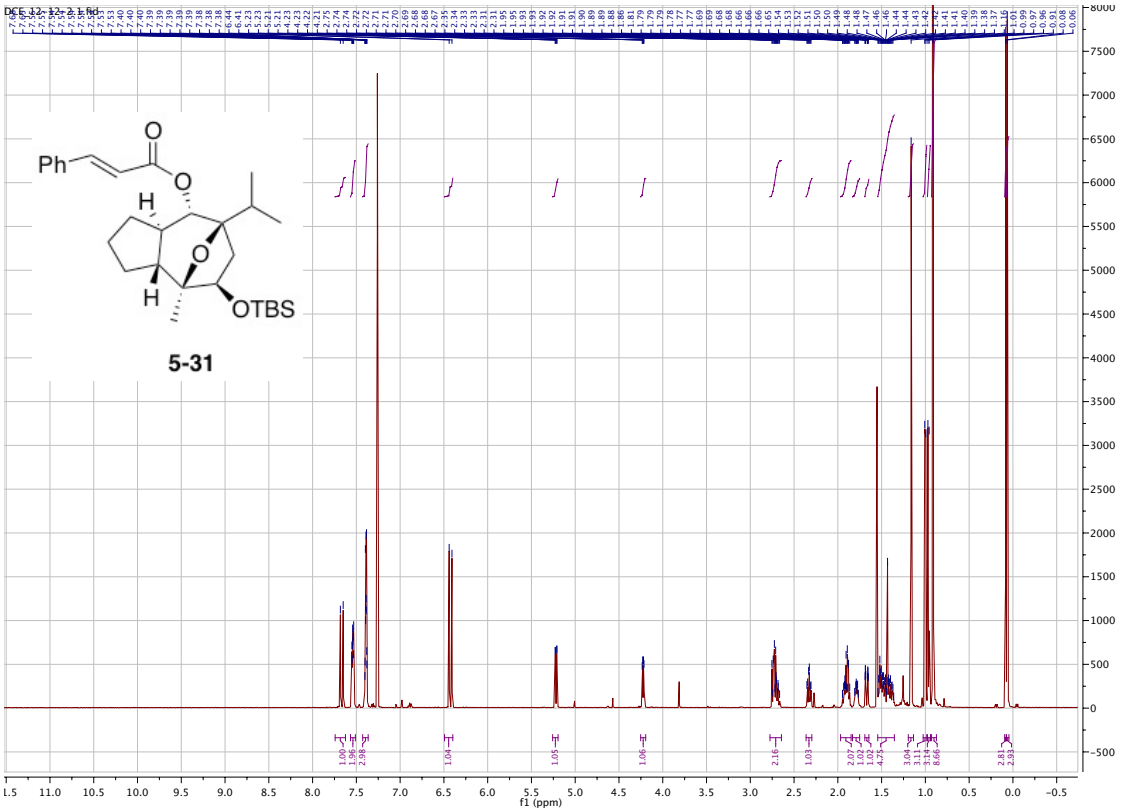

DCE_11-142-1.2.fid
O
O
H
OTBS
5-29
f1 (ppm)

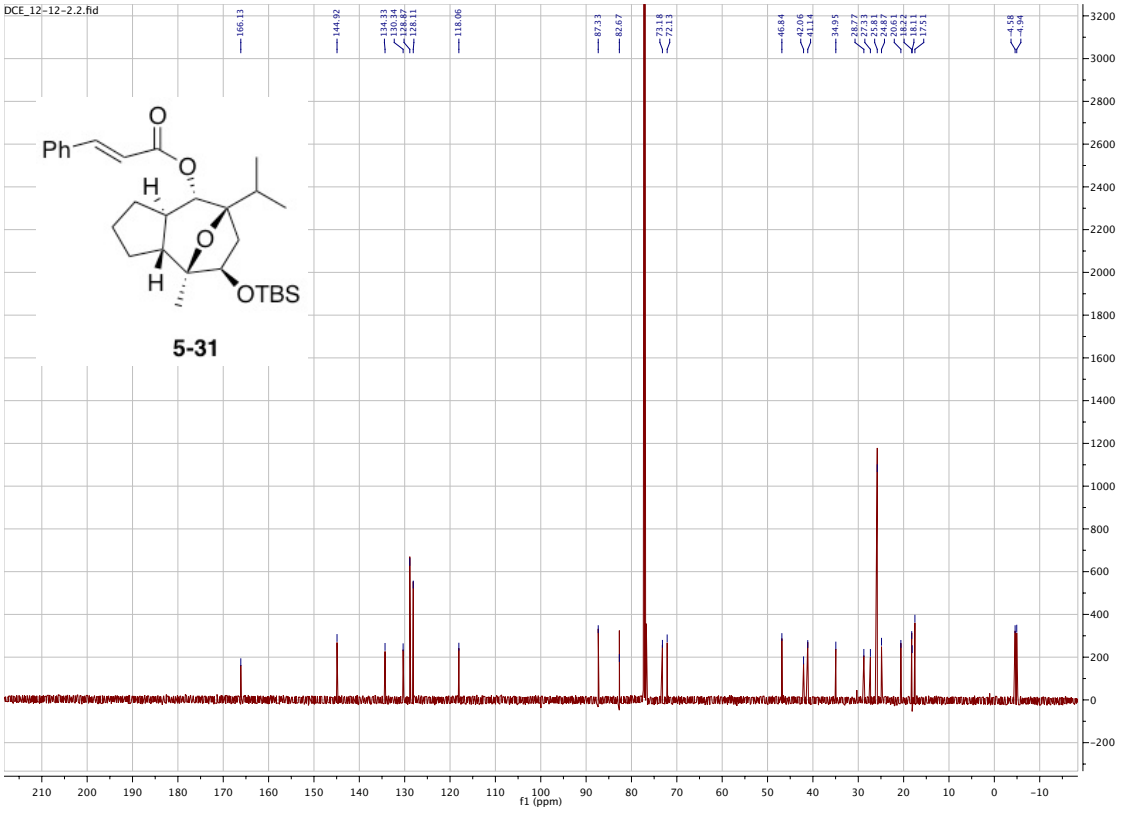

DCE_11-149-2
DCE_11-149-2
HO
O
H
OTBS
5-19
f1 (ppm)

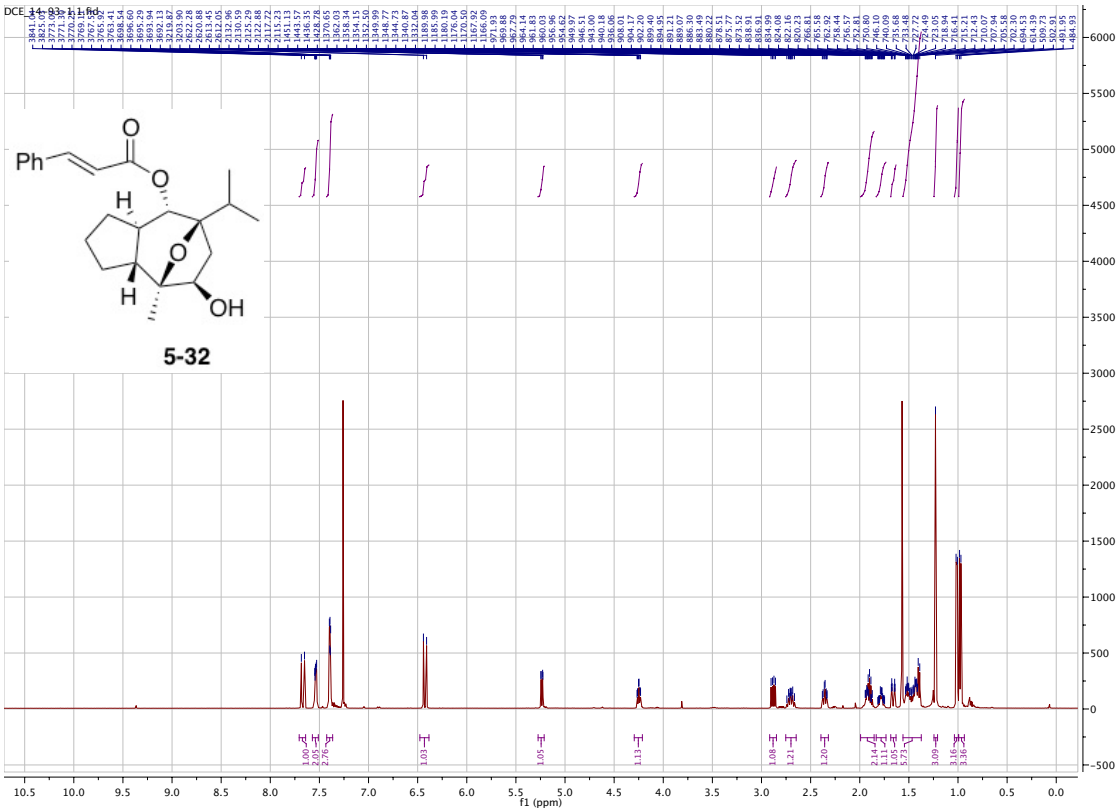

DCE_11-144-2.2.fid
HO
O
H
OTBS
5-19
145.11
121.61
87.68
86.02
73.05
71.85
54.83
40.97
32.10
31.90
25.77
24.98
19.33
18.05
14.03
17.30
-4.59
-5.03
f1 (ppm)

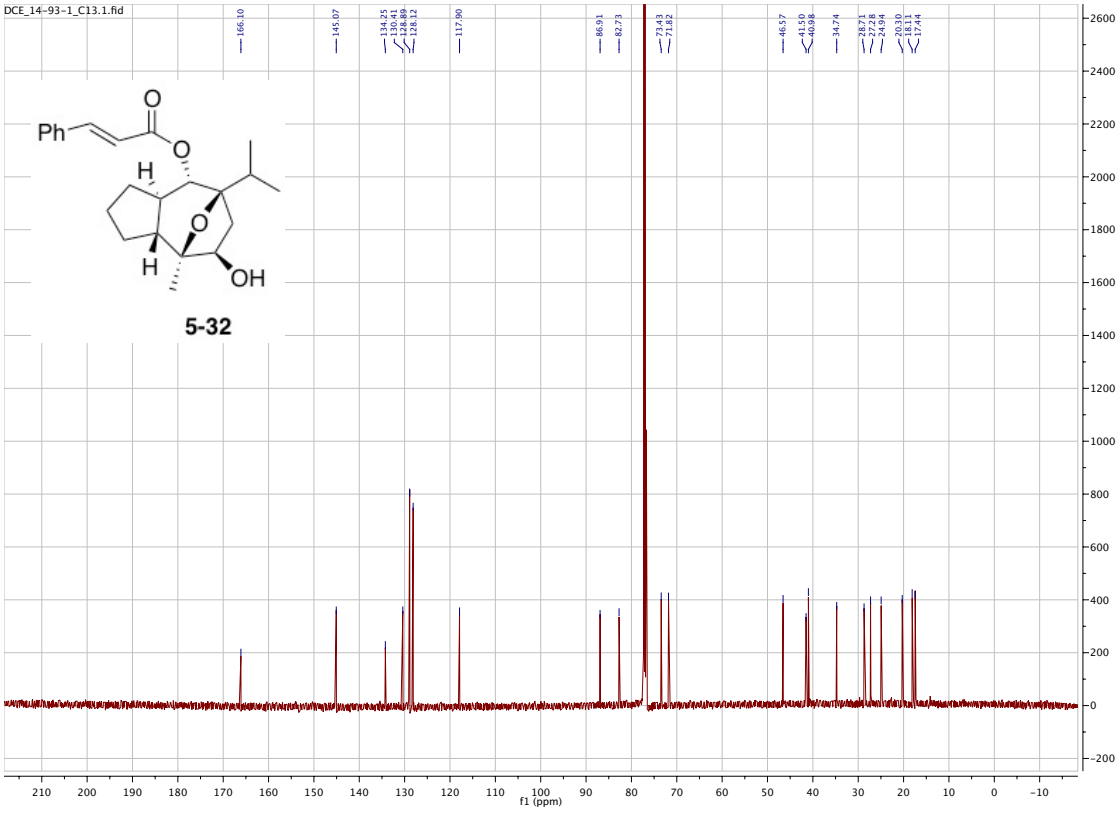

DCE_11-145-1
DCE_11-145-1
HO
H
O
H
OTBS
5-30
f1 (ppm)

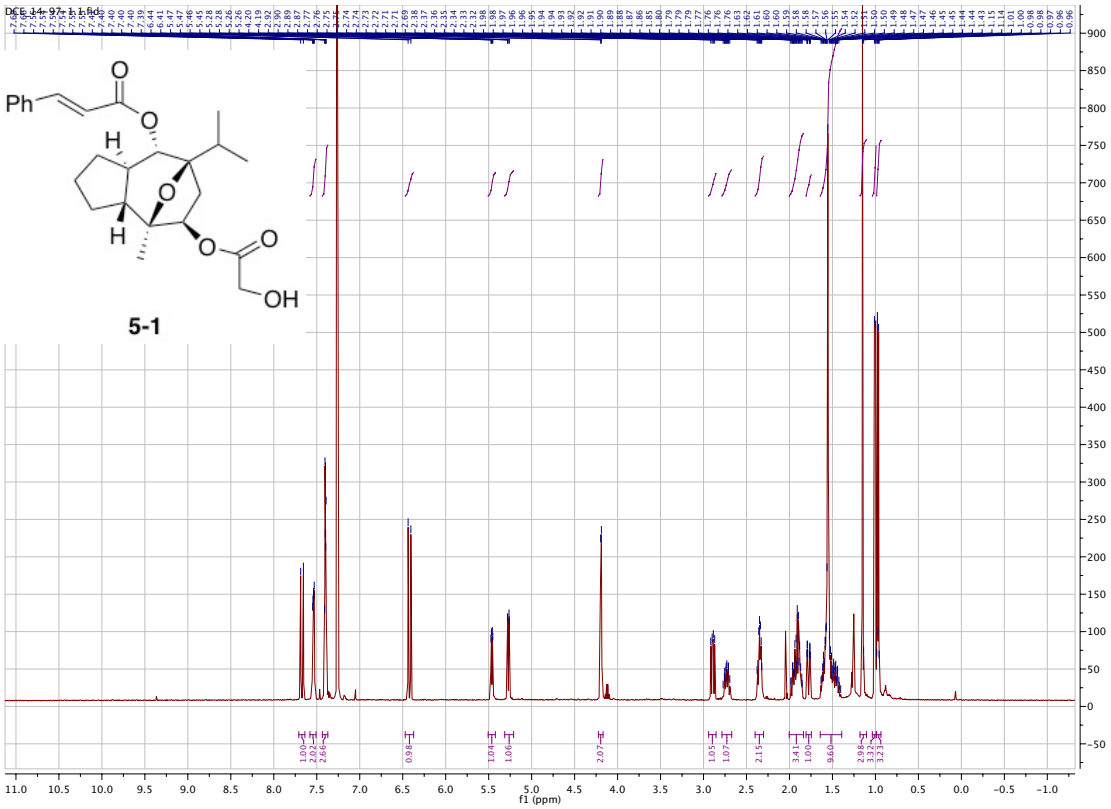

DCE_11-145-1.2.fid
HO
H
O
H
OTBS
5-30
f1 (ppm)

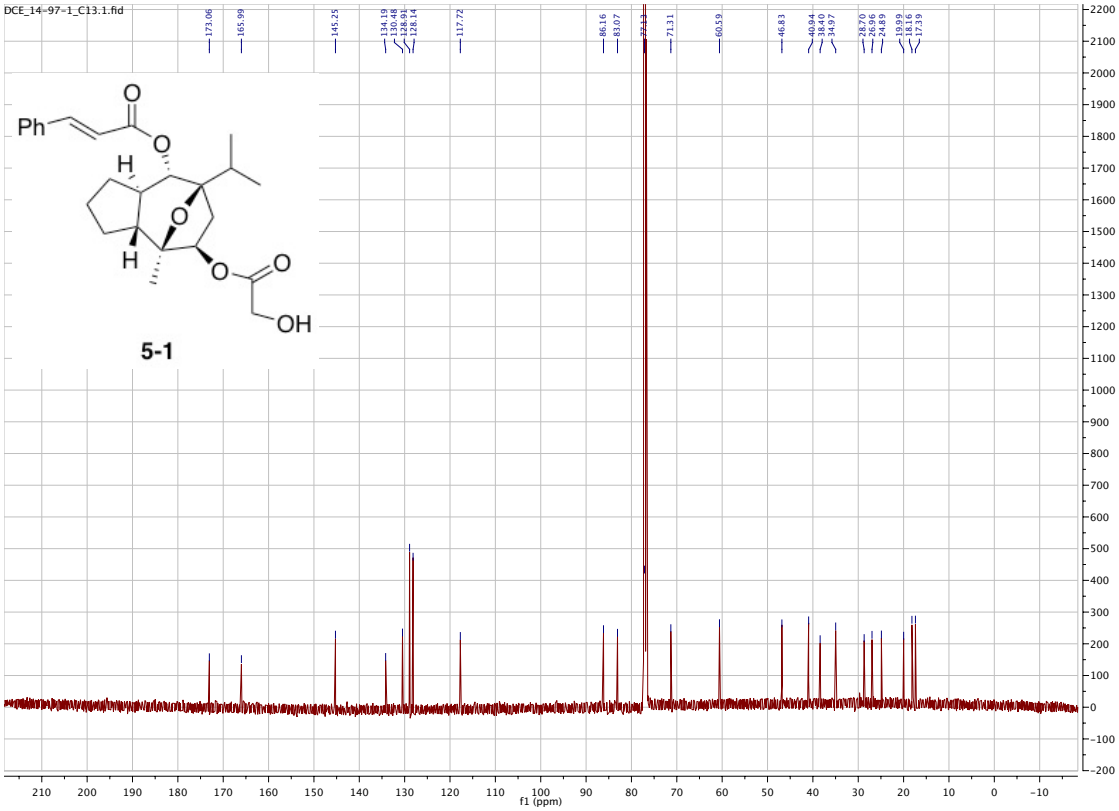

DCE_12-12-2.1.fid
Ph
O
O
H
O
H
OTBS
5-31
f1 (ppm)

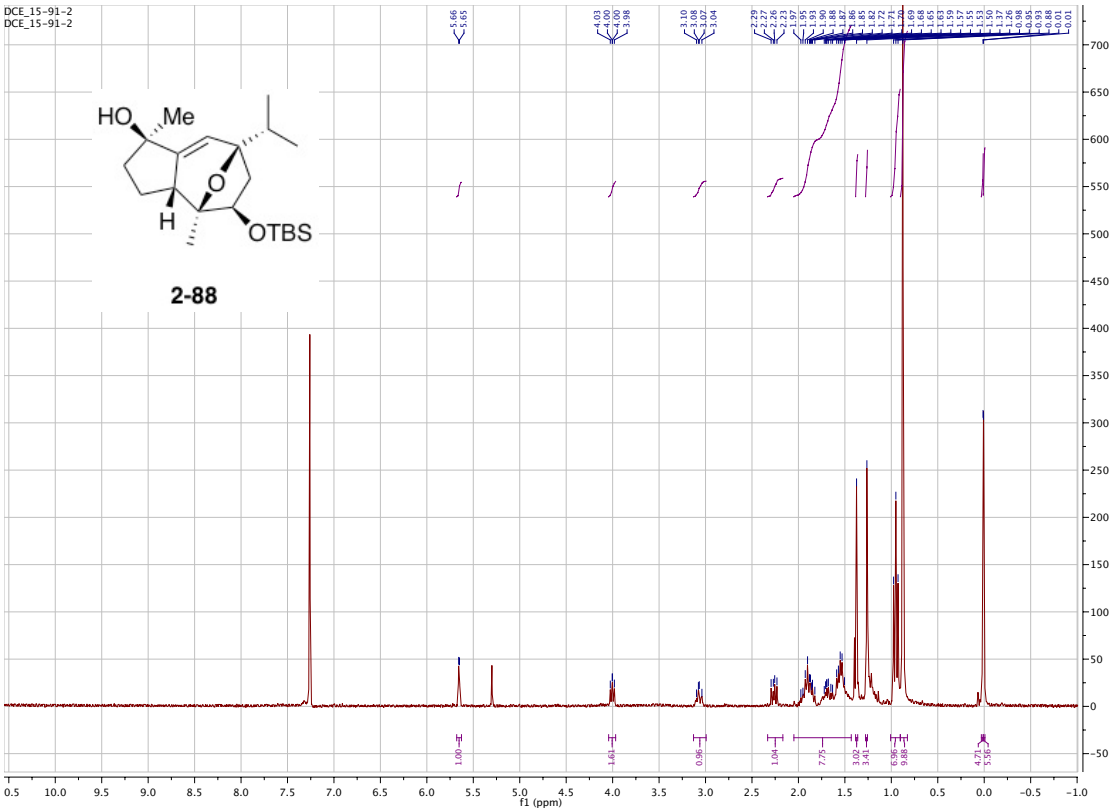

DCE_12-12-2.2.fid
166.13
144.92
134.33
130.44
128.47
128.11
118.06
87.33
82.67
73.18
72.13
46.84
42.06
41.14
34.95
28.77
27.33
25.81
24.87
20.61
18.22
15.11
12.51
4.58
4.34
Ph
O
O
H
O
H
OTBS
5-31
f1 (ppm)

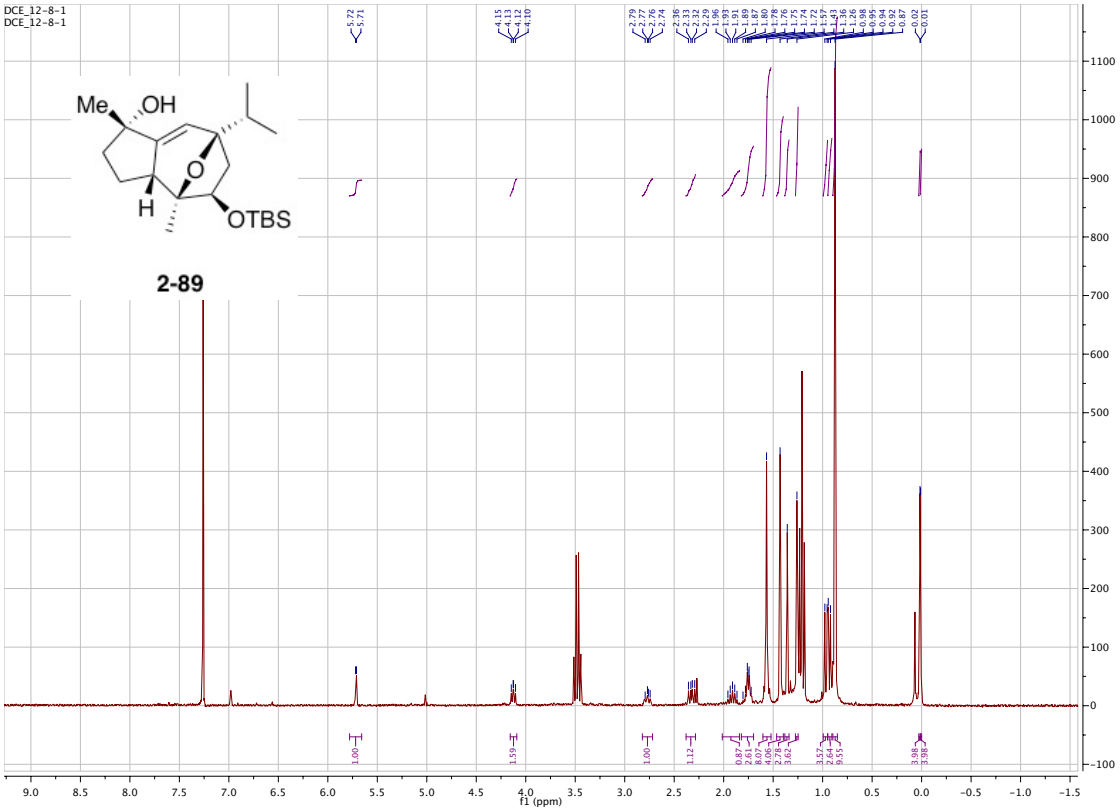

DCE_14-93-1.fid
Ph
O
O
H
O
H
OH
5-32
f1 (ppm)

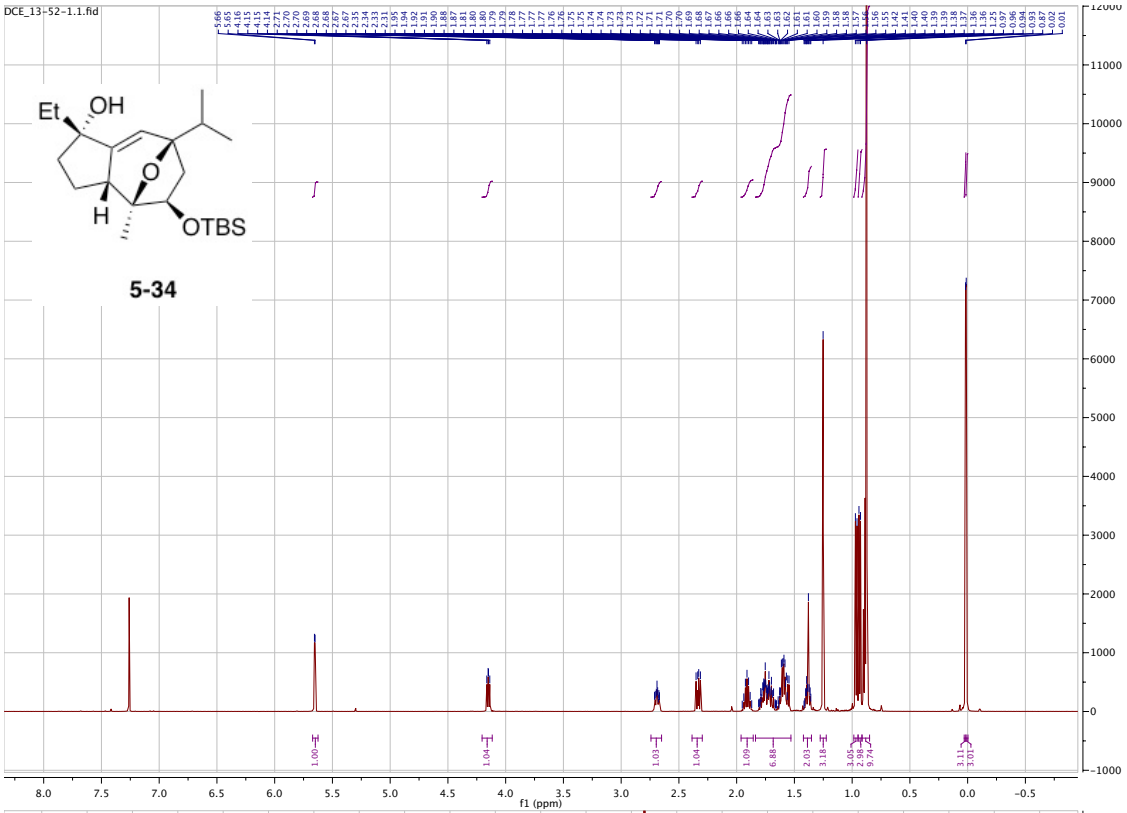

DCE_14-93-1_C13.1.fid
166.10
145.07
134.25
130.41
128.89
128.12
117.90
86.91
82.73
73.43
71.82
46.57
41.50
40.08
34.74
28.71
27.28
24.94
20.10
18.11
17.44
Ph
O
O
H
O
H
OH
5-32
f1 (ppm)

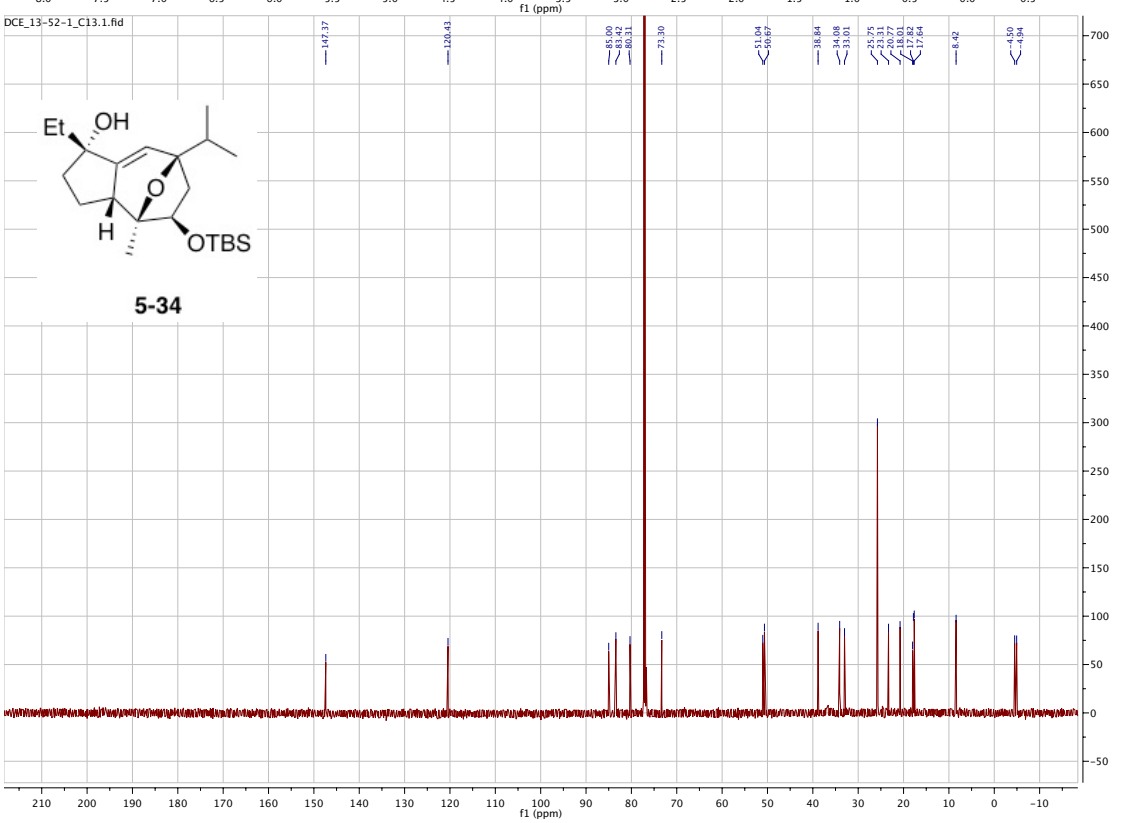

Ph
O
O
H
O
H
O
O
OH
5-1
f1 (ppm)

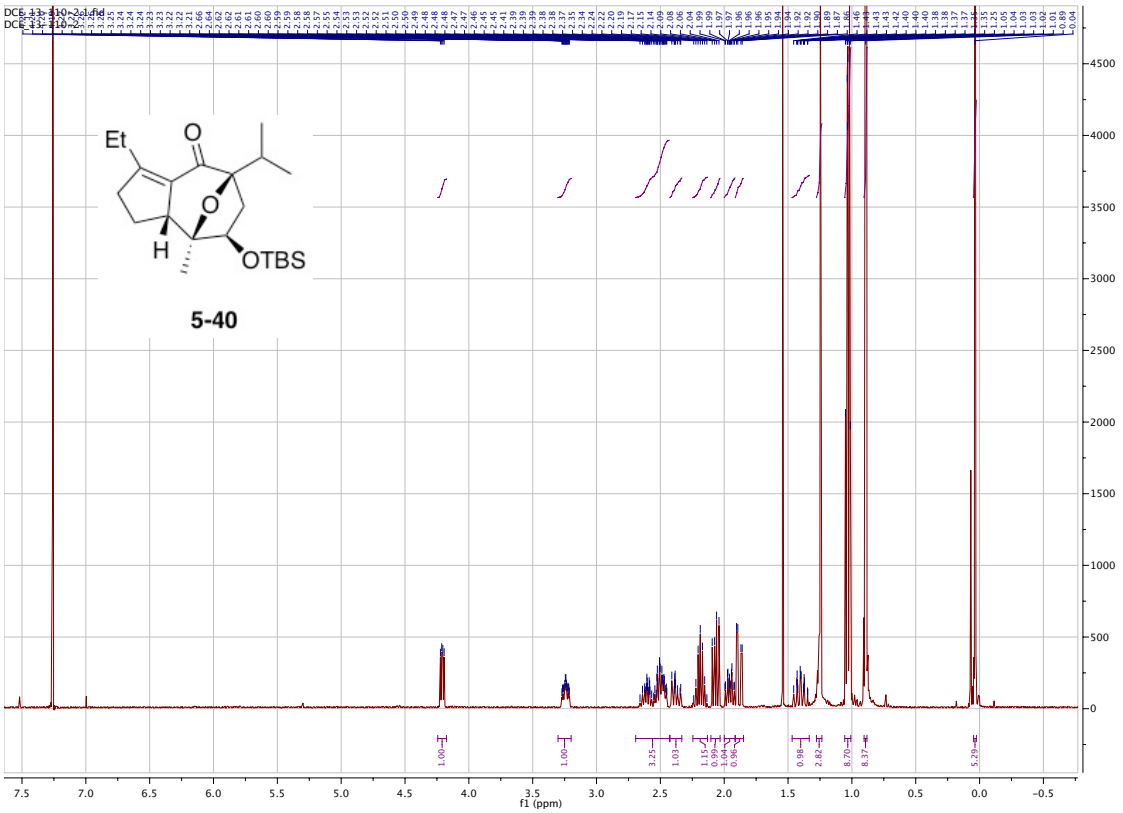

DCE_14-97-1_C13.1.fid
173.06
165.99
145.25
134.19
130.44
128.91
128.14
117.72
86.16
83.07
77.13
71.31
60.59
46.83
40.94
38.40
34.97
28.70
26.96
24.88
19.89
18.15
17.39
Ph
O
O
H
O
H
O
O
OH
5-1
f1 (ppm)

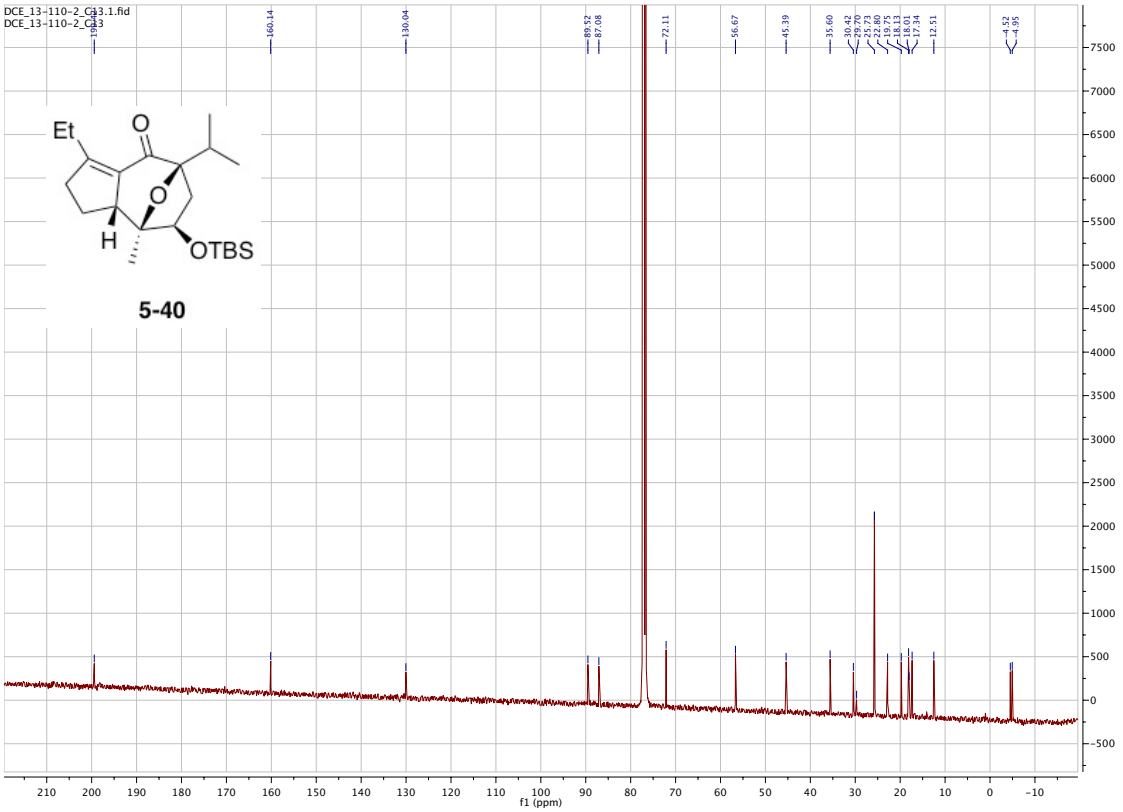

DCE_15-91-2
DCE_15-91-2
HO
Me
O
H
OTBS
2-88
f1 (ppm)

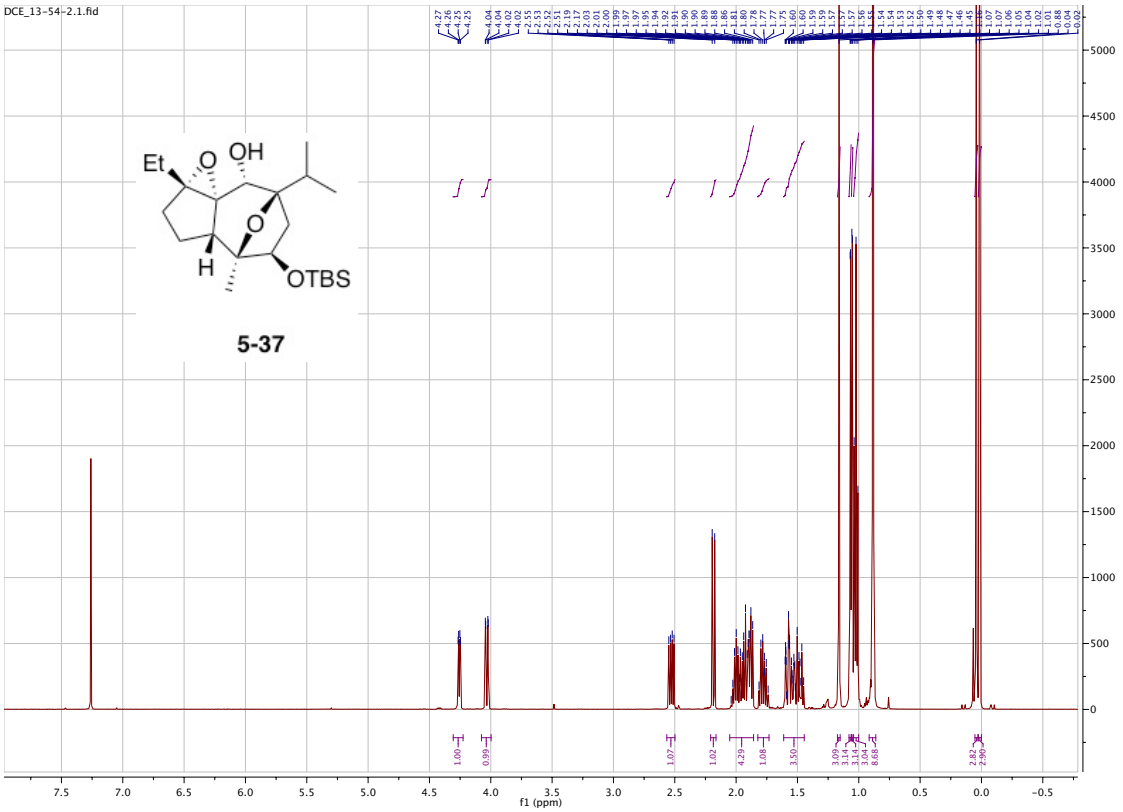

DCE_12-8-1
DCE_12-8-1
Me
OH
O
H
OTBS
2-89
f1 (ppm)

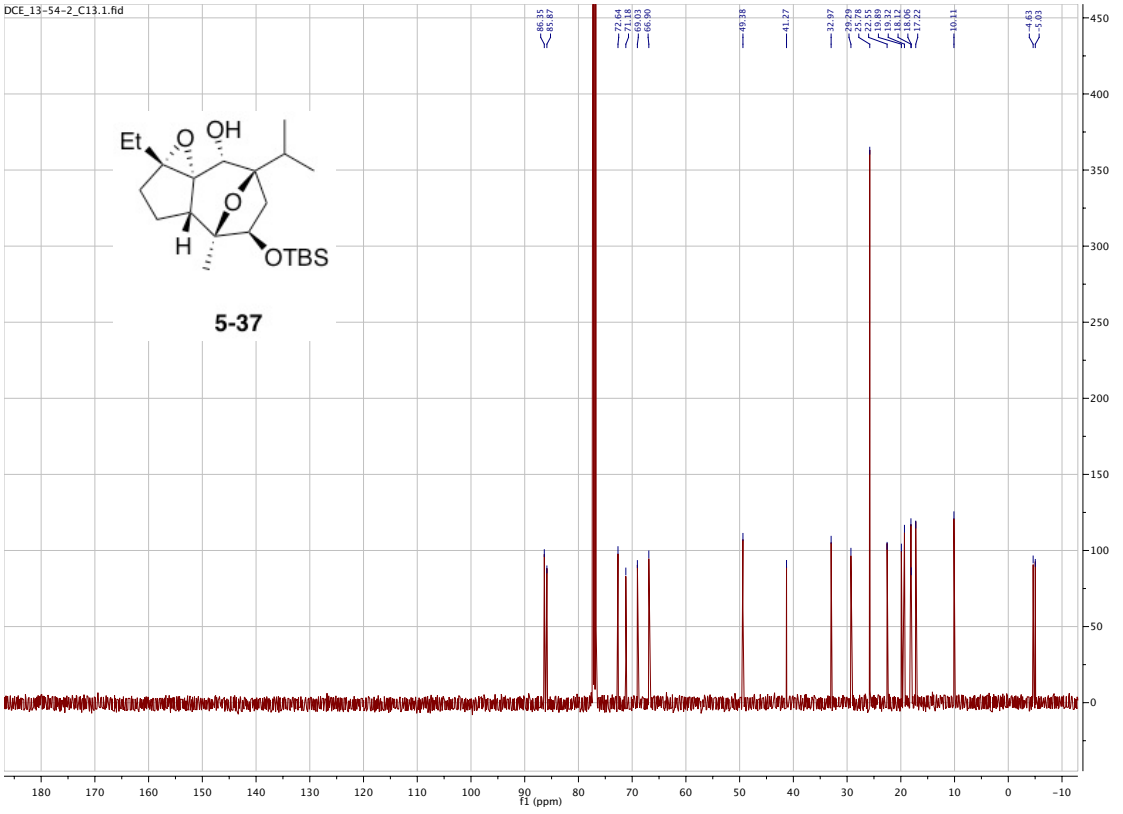

DCE_13-52-1.1.fid
Et
OH
O
H
OTBS
5-34
f1 (ppm)

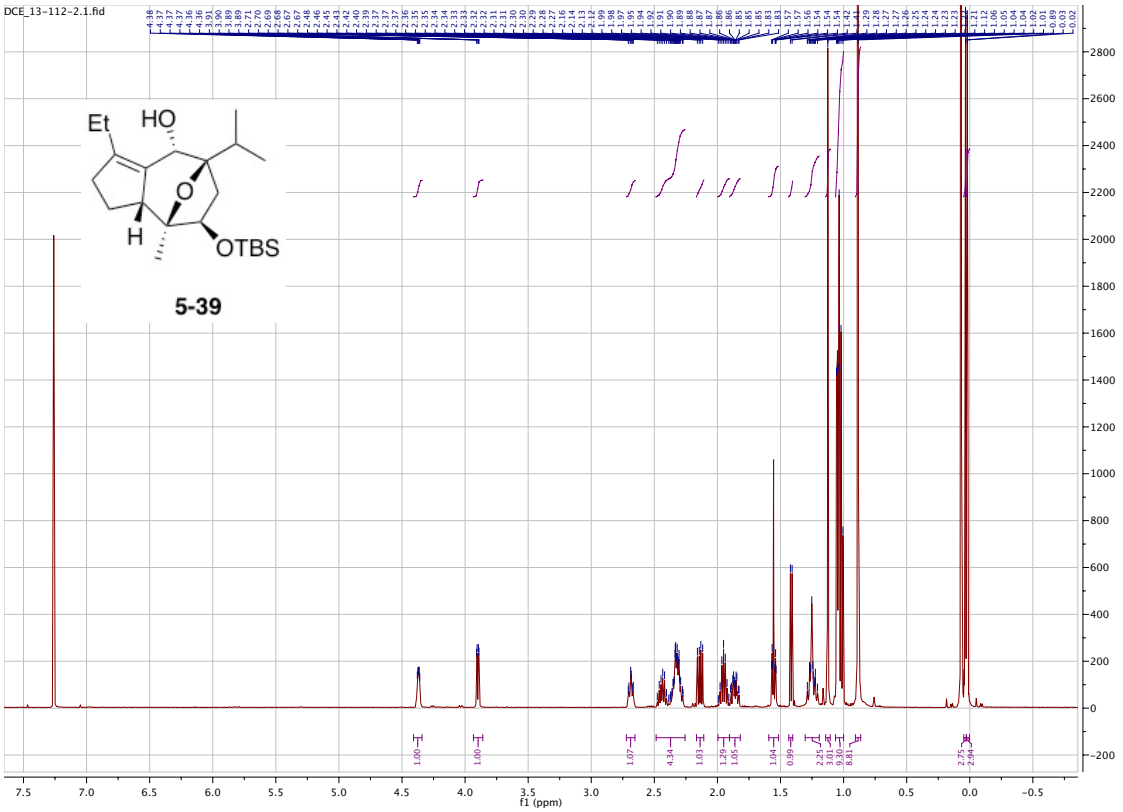

DCE_13-52-1_C13.1.fid
Et
OH
O
H
OTBS
5-34
f1 (ppm)

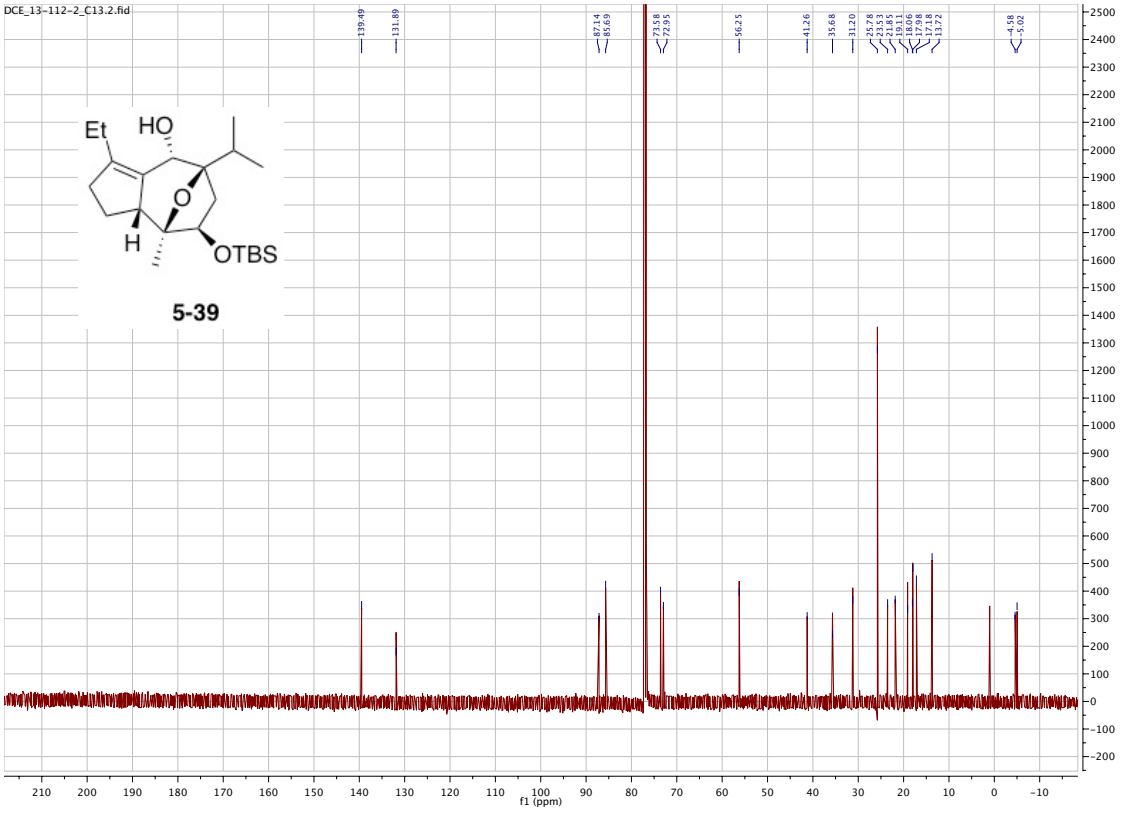

Et
O
O
H
OTBS
5-40
f1 (ppm)

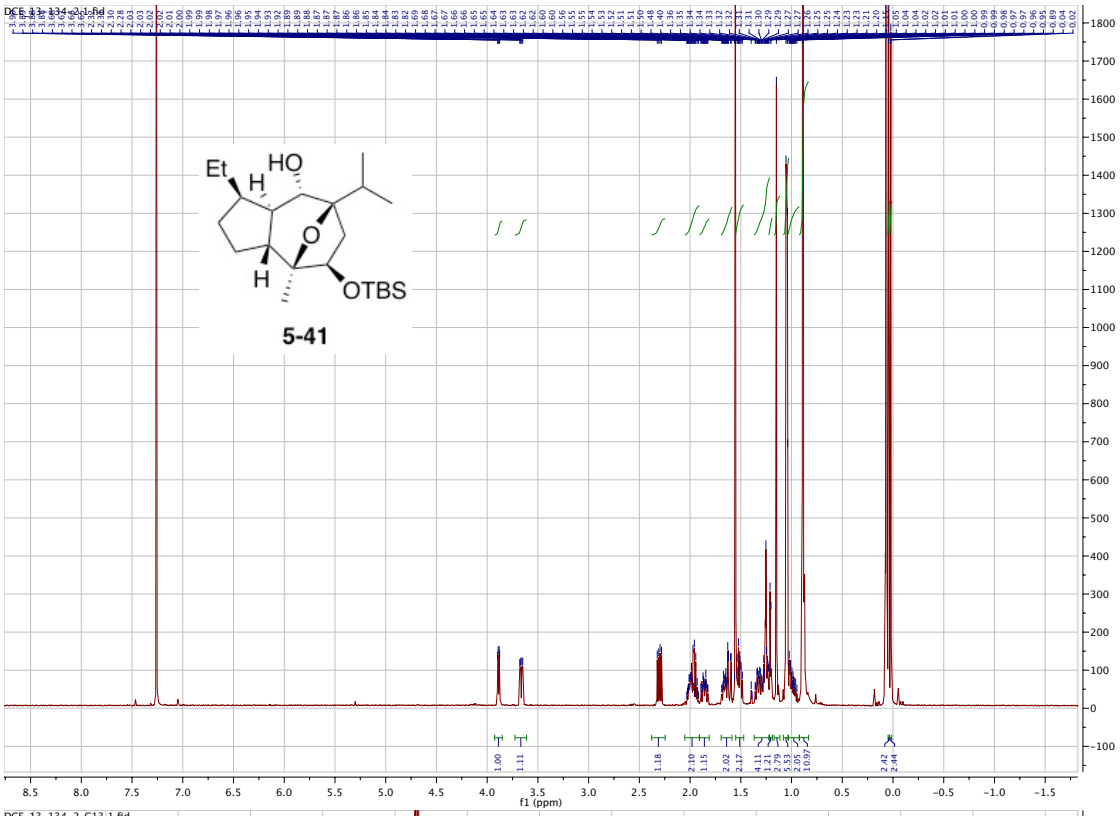

Et
O
O
H
OTBS
5-40
f1 (ppm)

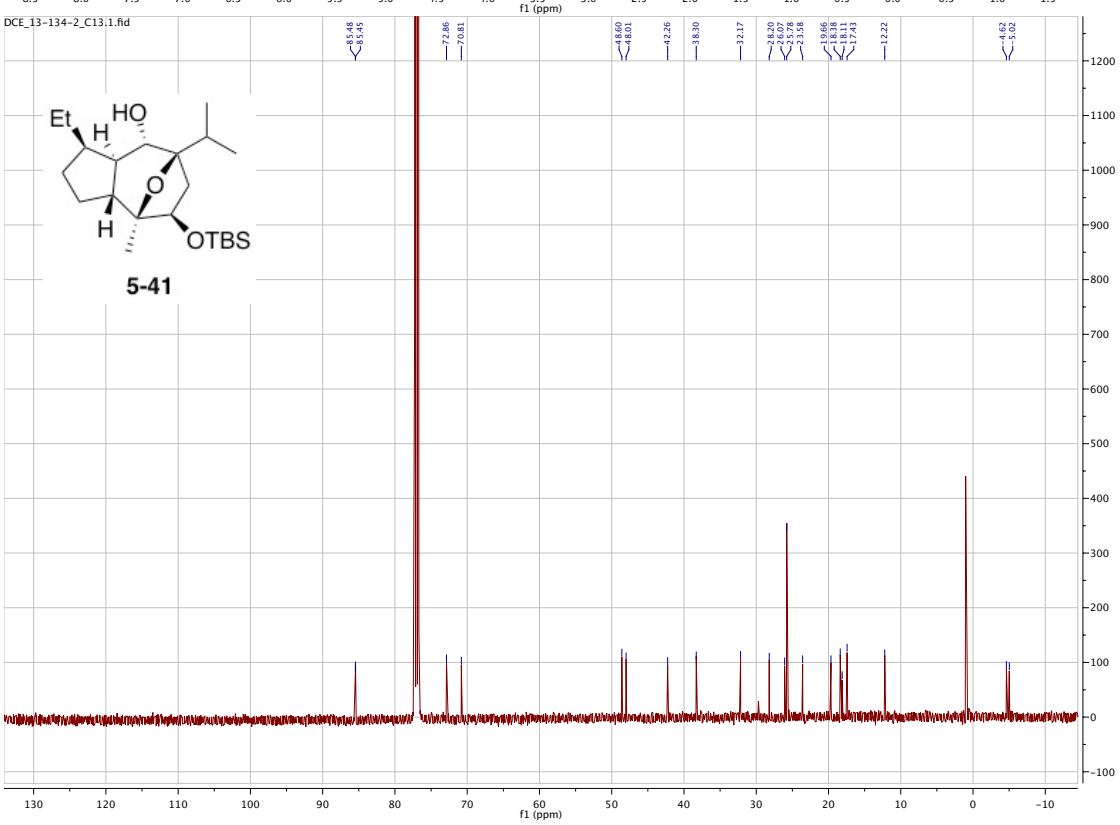

DCE_13-54-2.1.fid
Et
O
OH
O
H
OTBS
5-37
f1 (ppm)

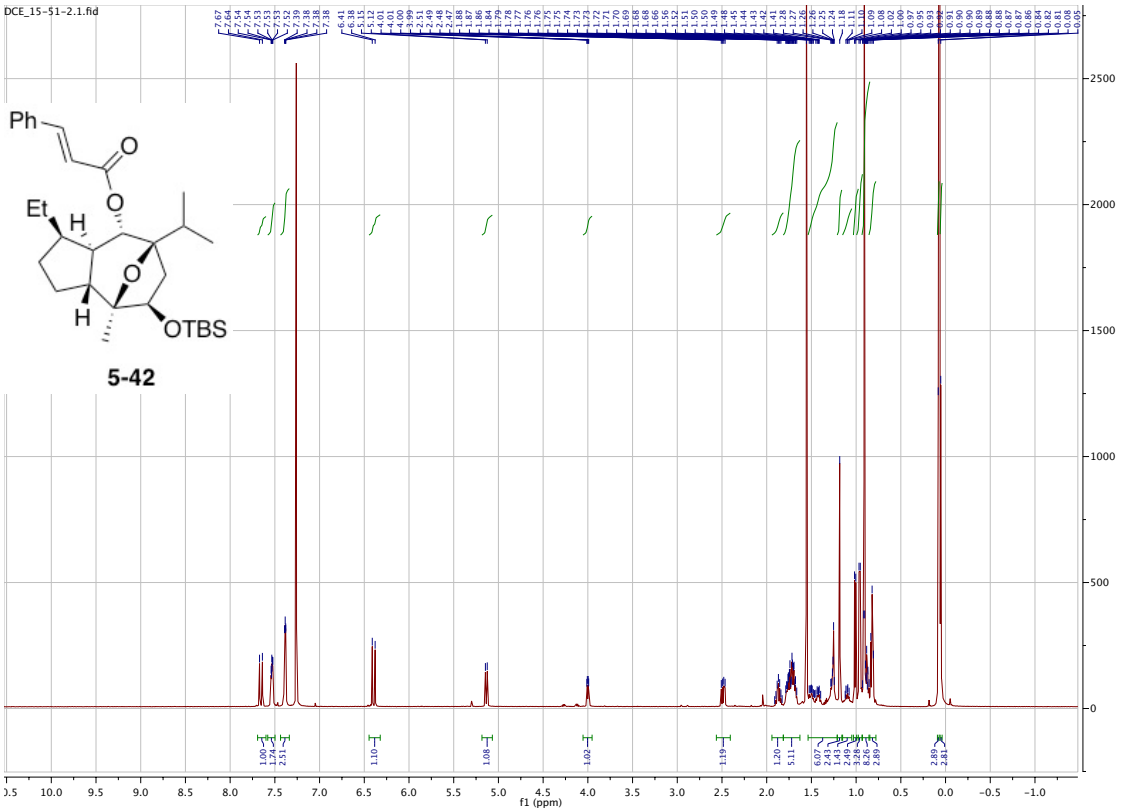

DCE_13-54-2_C13.1.fid
Et
O
OH
O
H
OTBS
5-37
f1 (ppm)

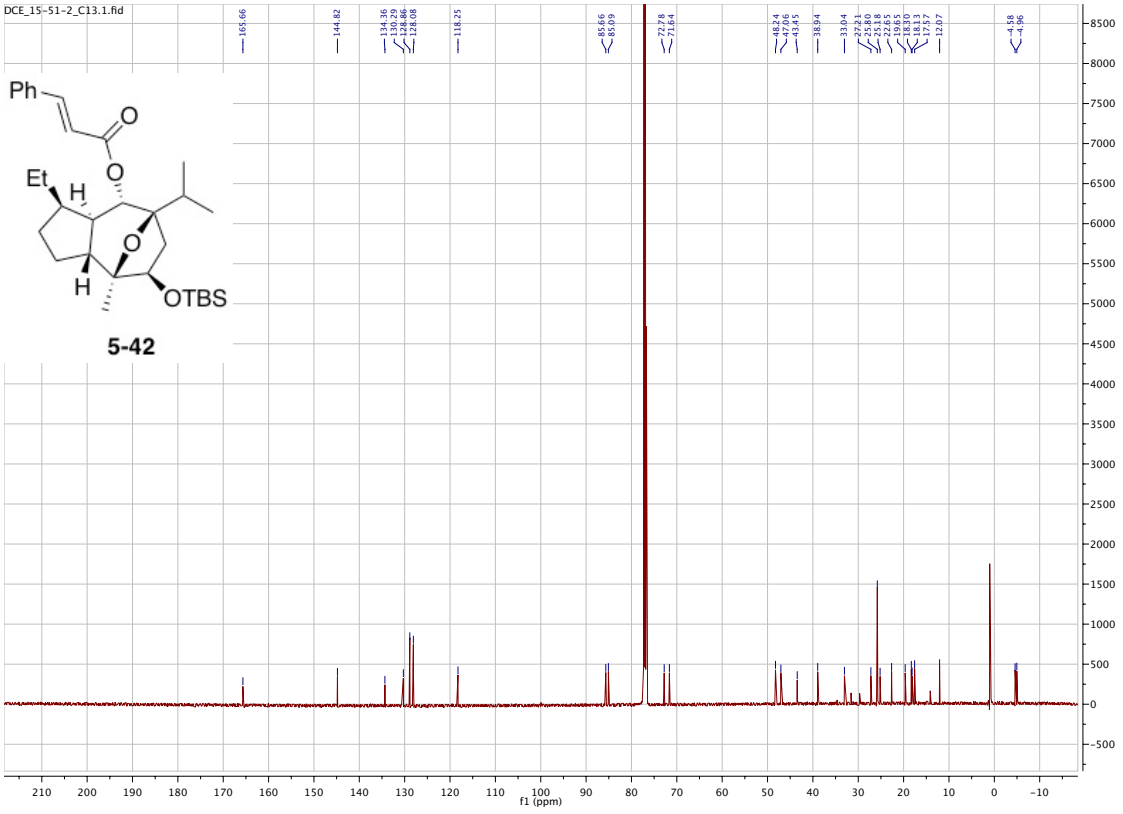

DCE_13-112-2.1.fid
Et
HO
O
H
OTBS
5-39
f1 (ppm)

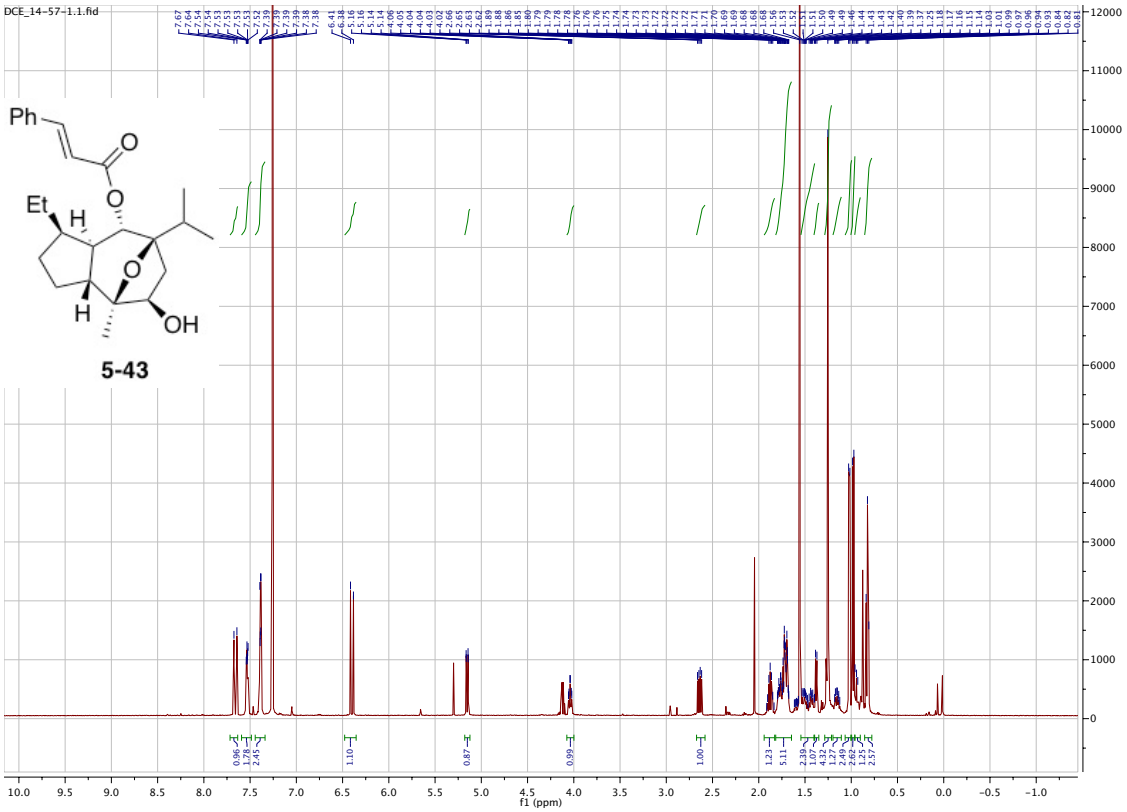

DCE_13-112-2_C13.2.fid
Et
HO
O
H
OTBS
5-39
f1 (ppm)

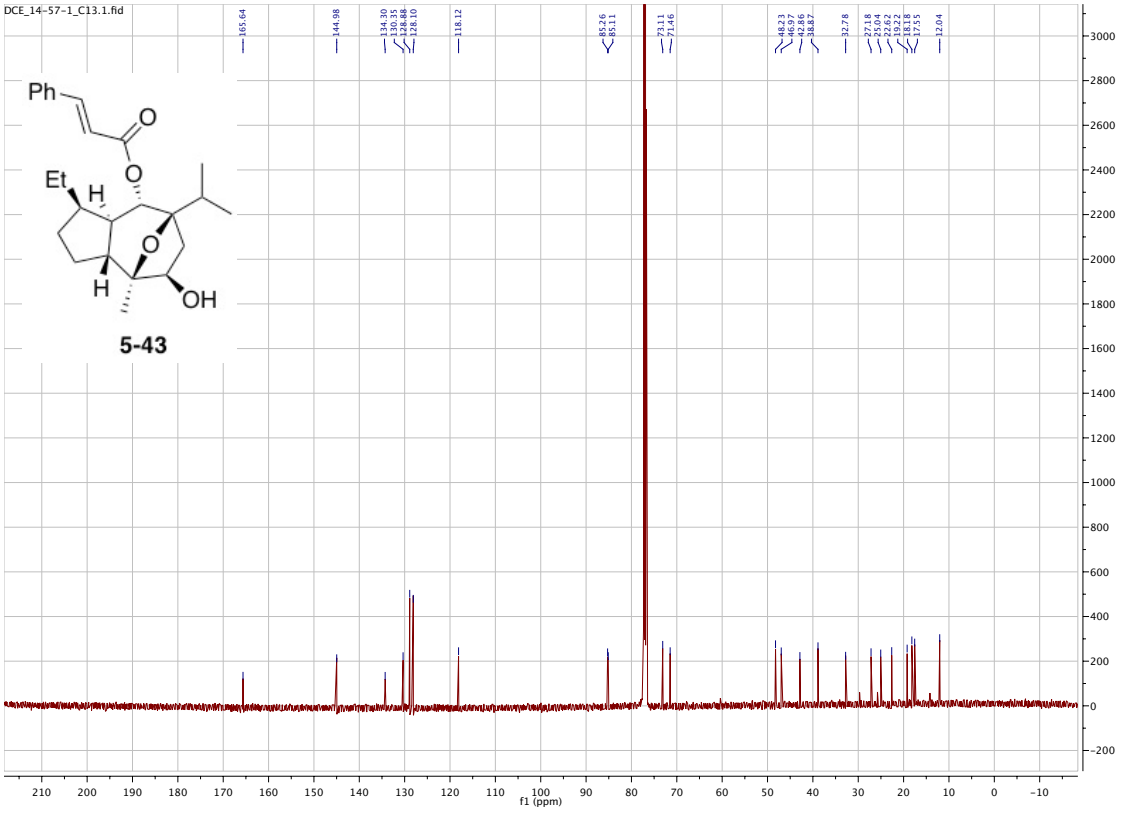

Et
H
HO
O
H
OTBS
5-41
f1 (ppm)

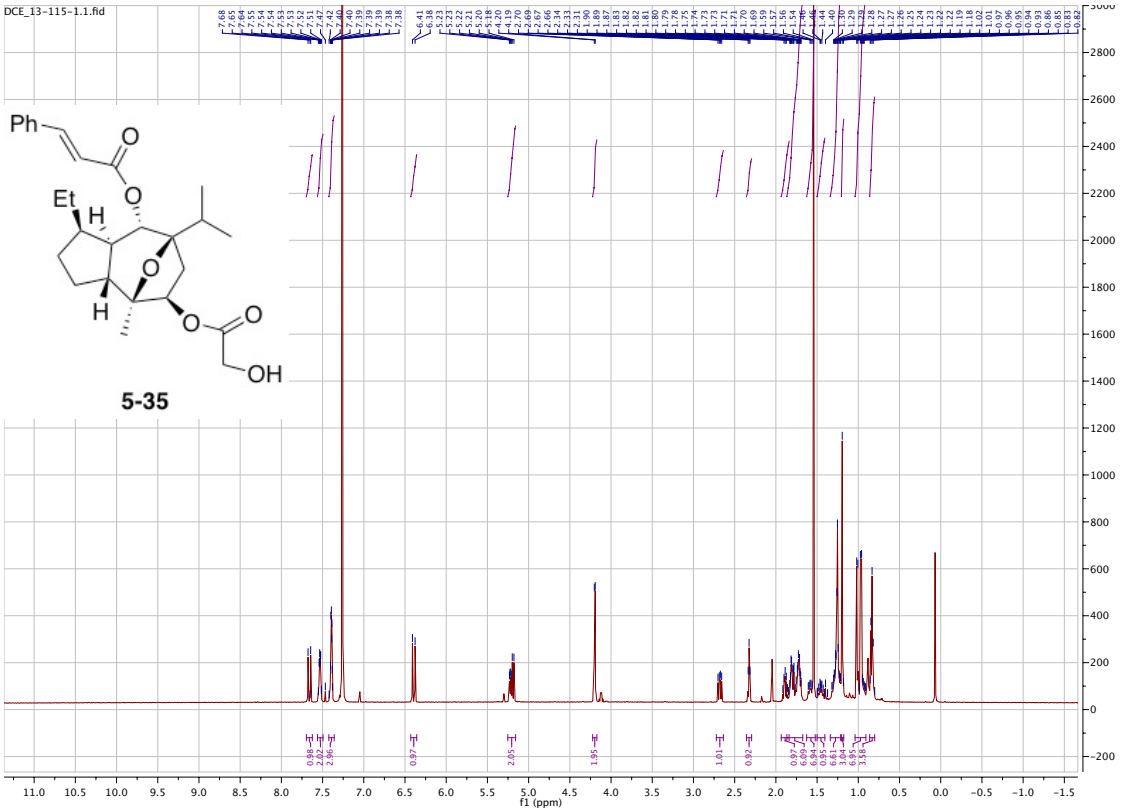

DCE_13-134-2_C13|1.fid
Et
H
HO
O
H
OTBS
5-41
f1 (ppm)

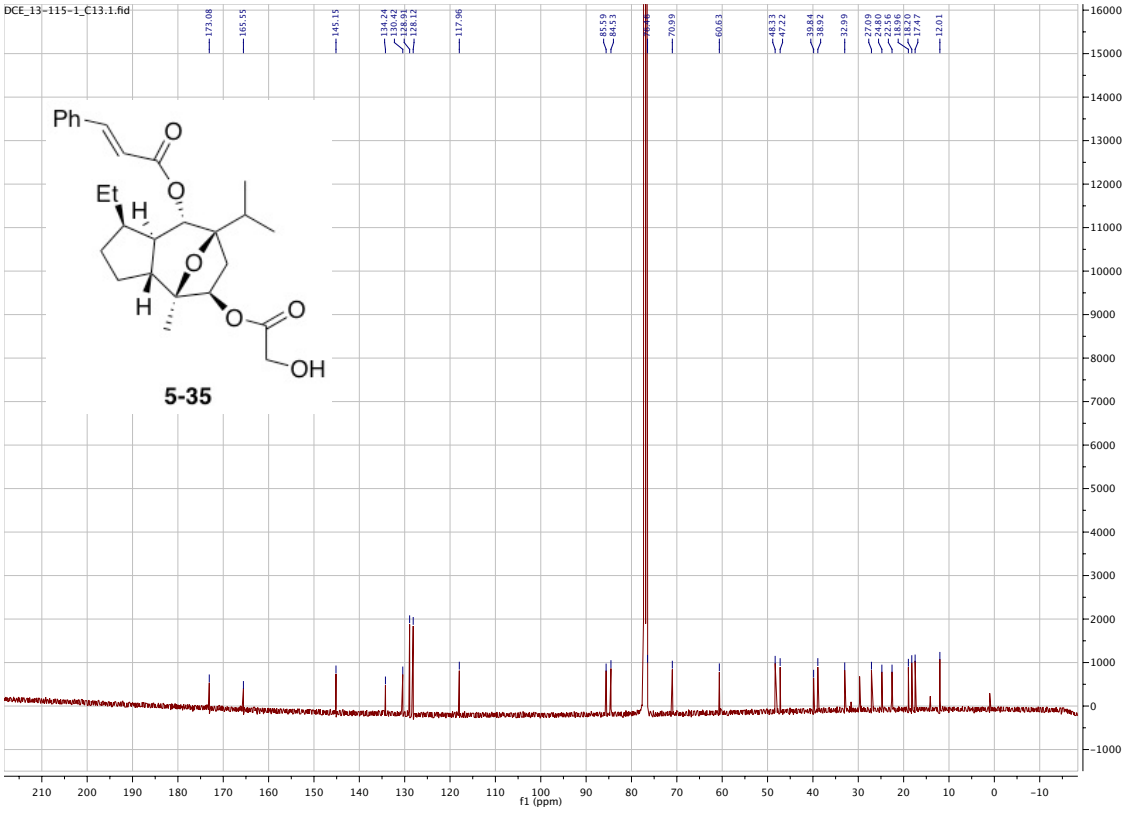

DCE_15-51-2.1.fid
Ph
O
O
Et
H
O
H
OTBS
5-42
f1 (ppm)

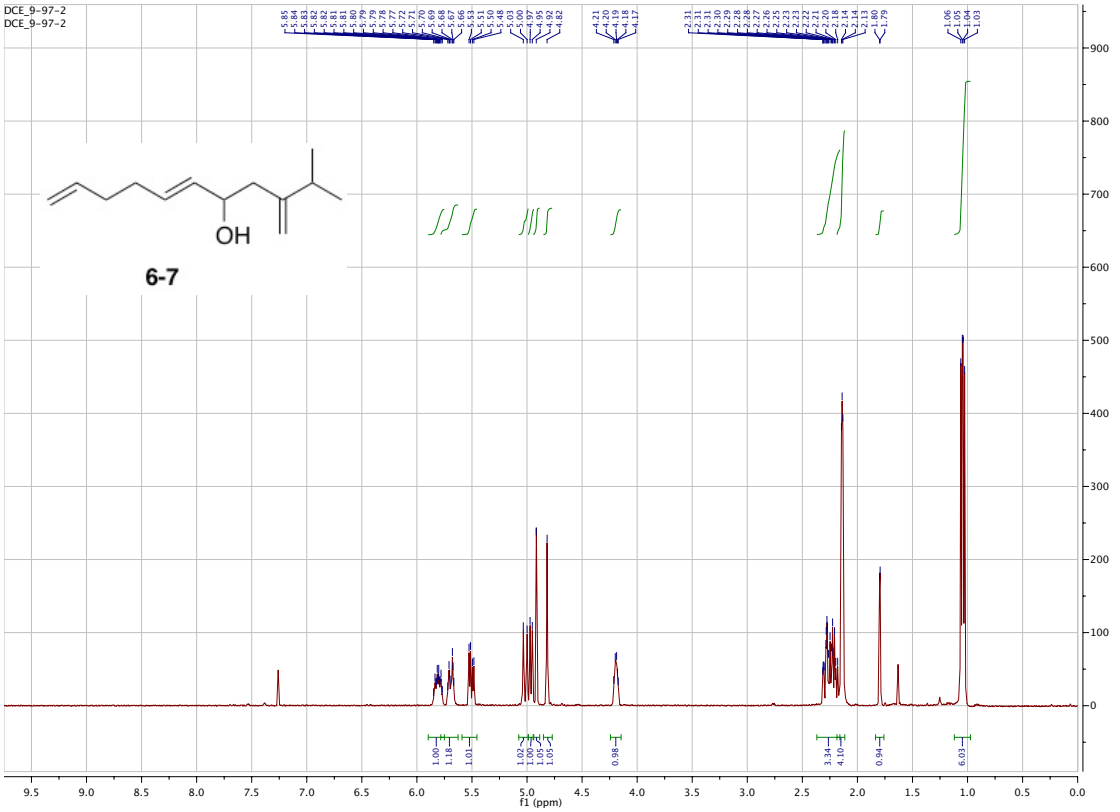

DCE_15-51-2_C13.1.fid
Ph
O
O
Et
H
O
H
OTBS
5-42
f1 (ppm)

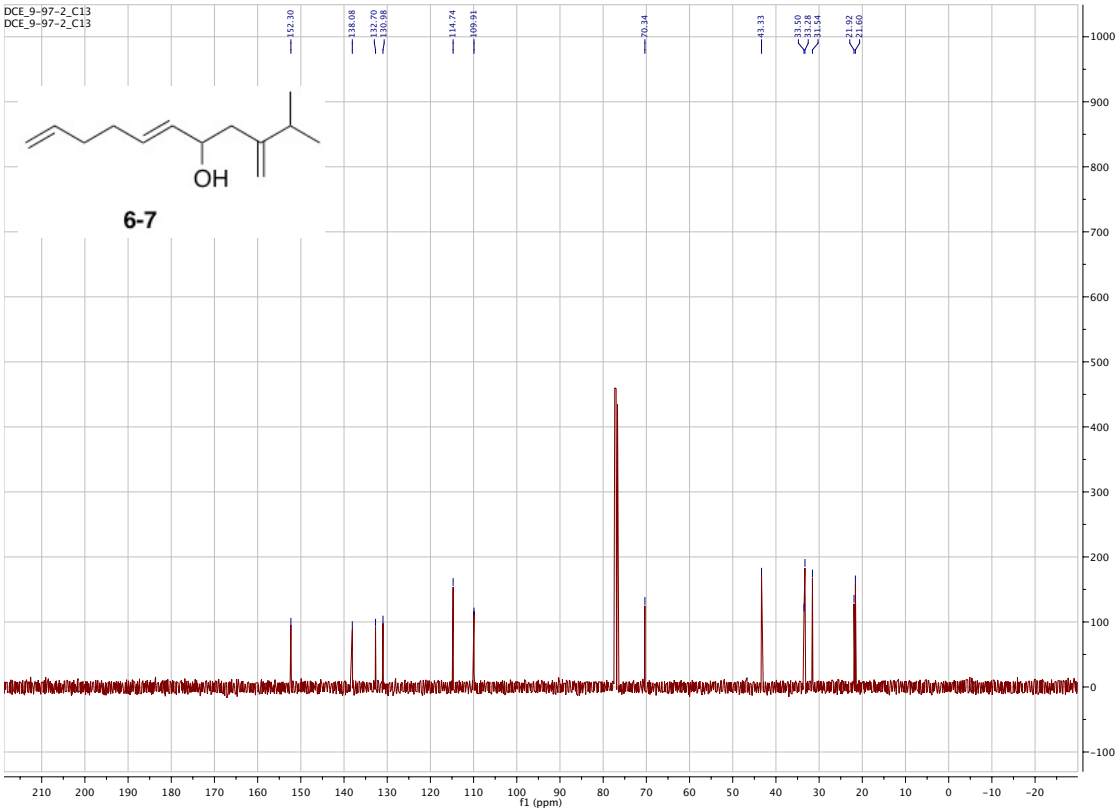

DCE_14-57-1.1.fid
Ph
O
O
Et
H
O
H
OH
5-43
f1 (ppm)

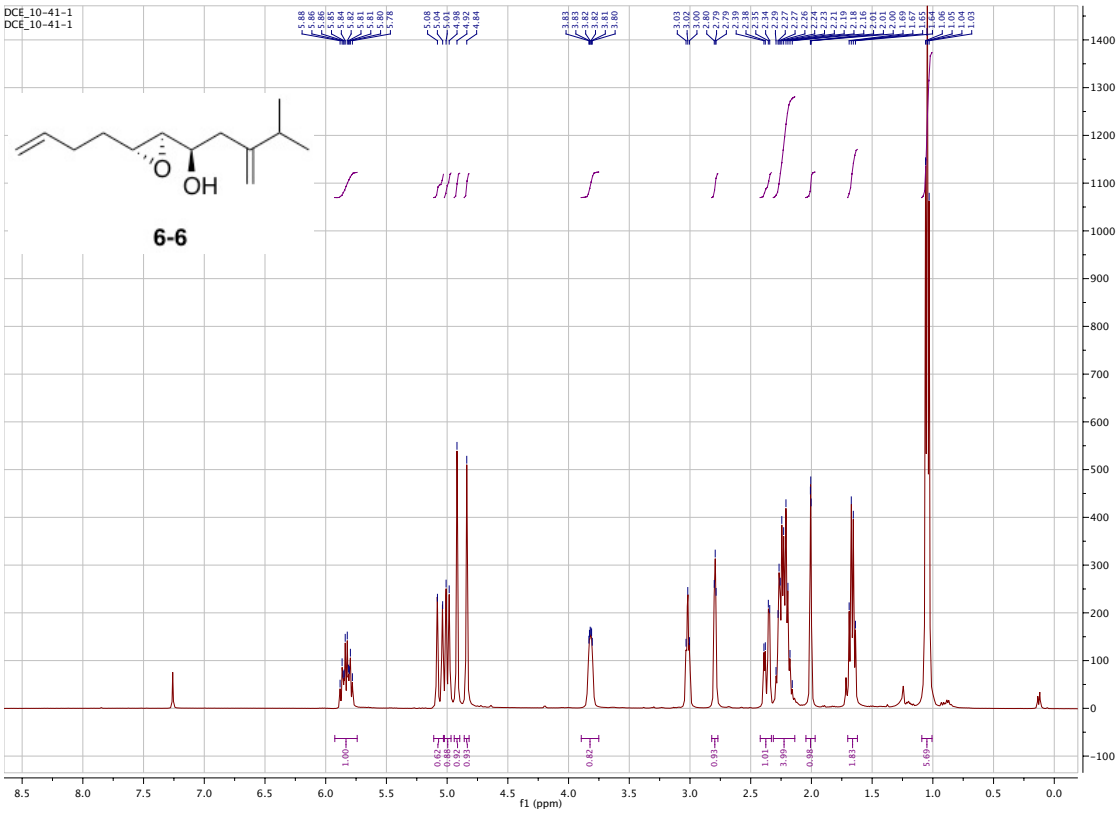

DCE_14-57-1_C13.1.fid
165.64
144.98
134.30
130.35
128.48
128.10
118.12
85.26
85.11
73.11
71.46
48.23
46.97
46.66
44.87
32.78
27.18
25.04
23.62
23.22
18.18
17.55
12.04
Ph
O
O
Et
H
O
H
OH
5-43
f1 (ppm)

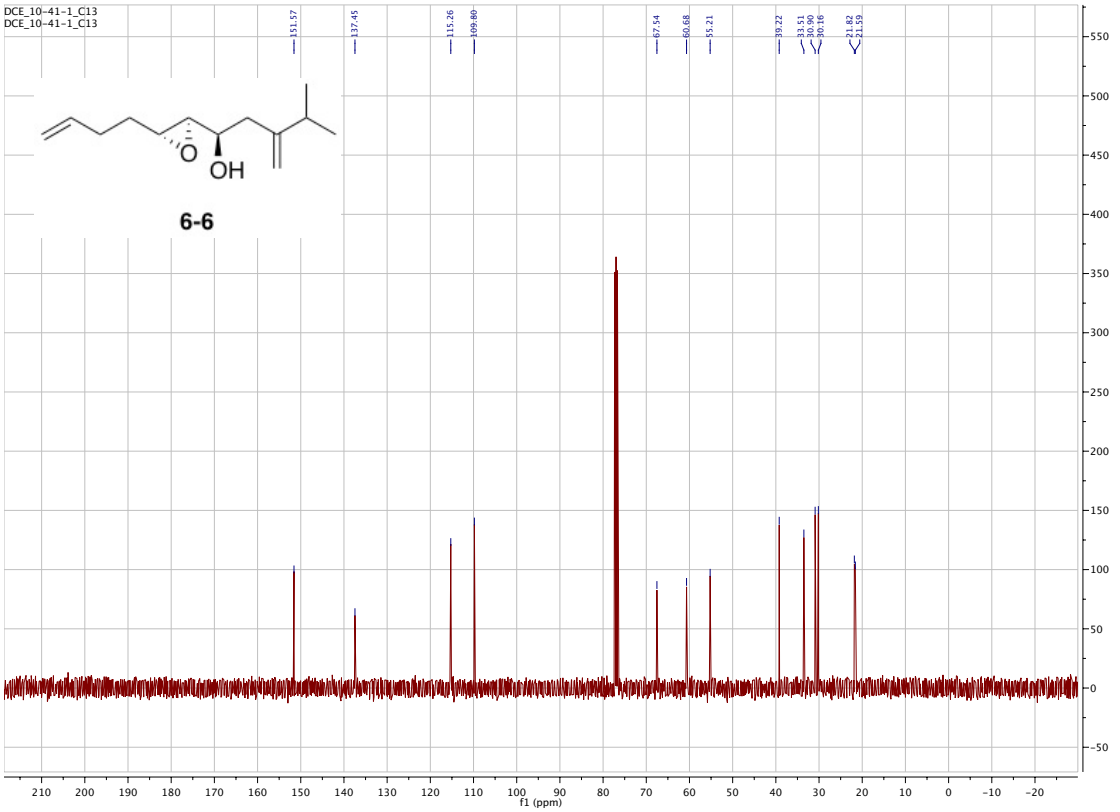

DCE_13-115-1.1.fid
Ph
O
O
Et
H
O
H
O
O
OH
5-35
f1 (ppm)

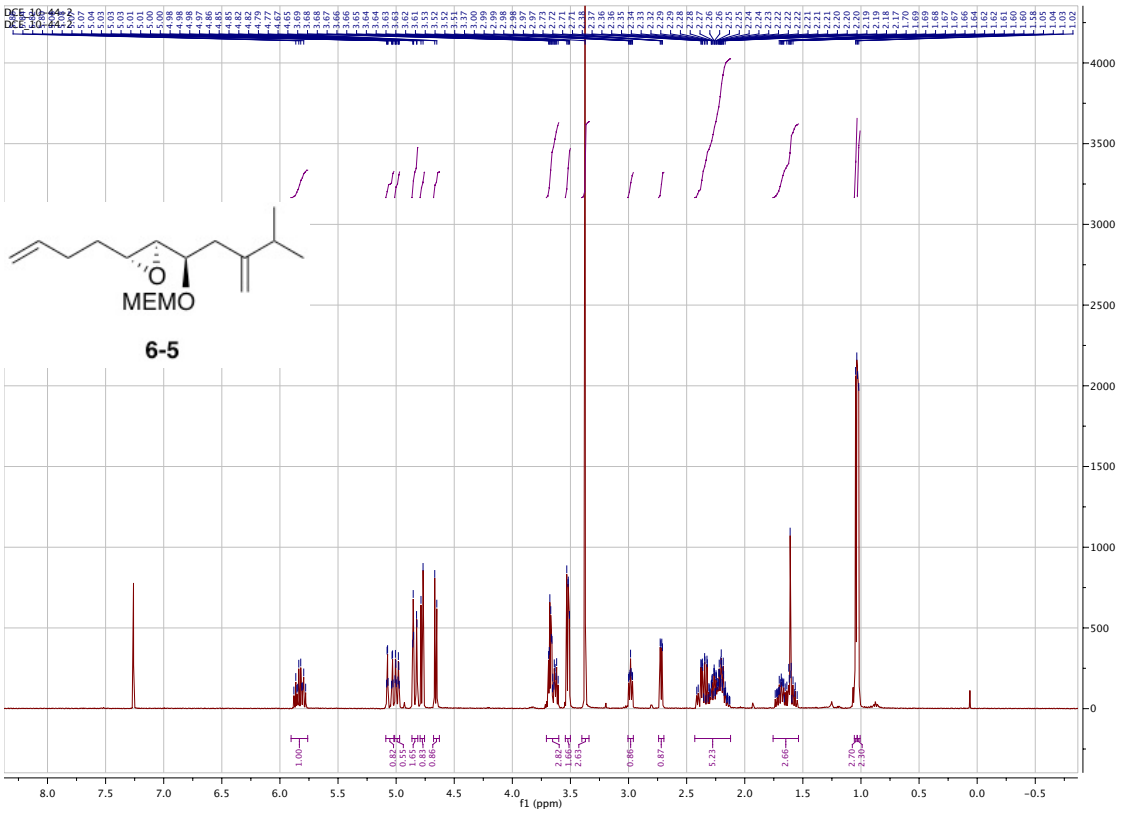

DCE_13-115-1_C13.1.fid
Ph
O
O
Et
H
O
H
O
O
OH
5-35
f1 (ppm)

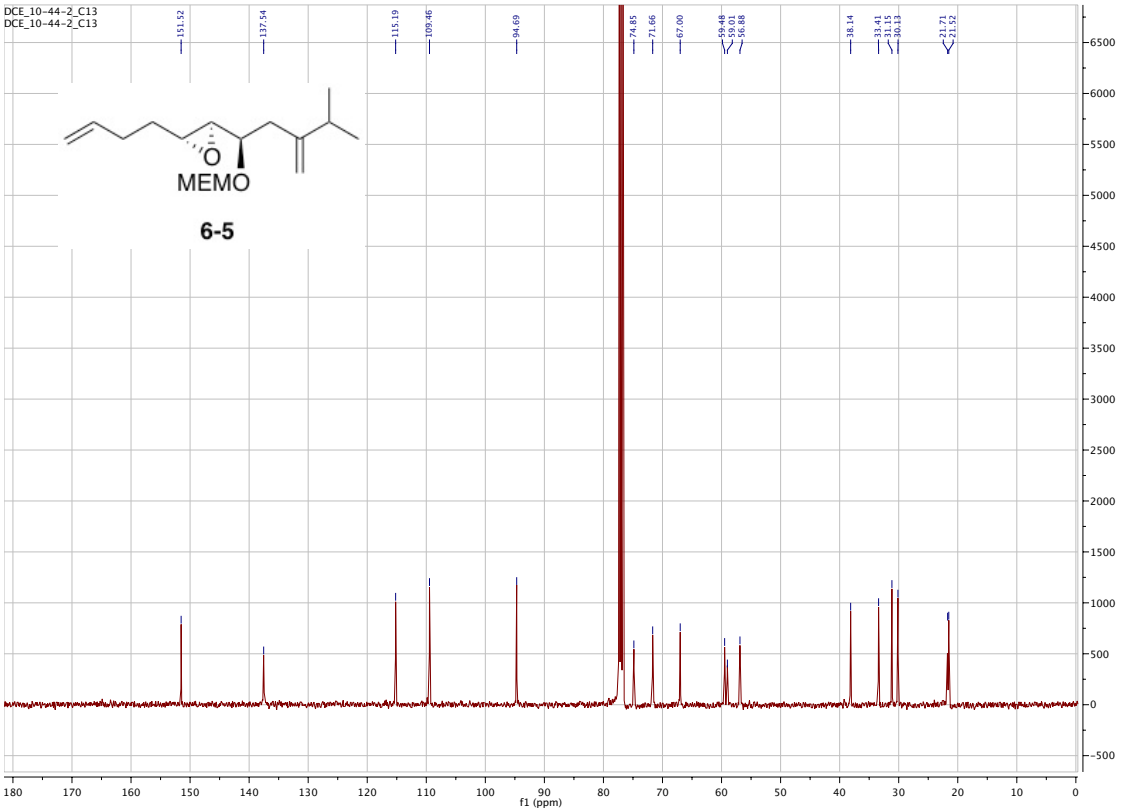

DCE_9-97-2
DCE_9-97-2
OH
6-7
f1 (ppm)

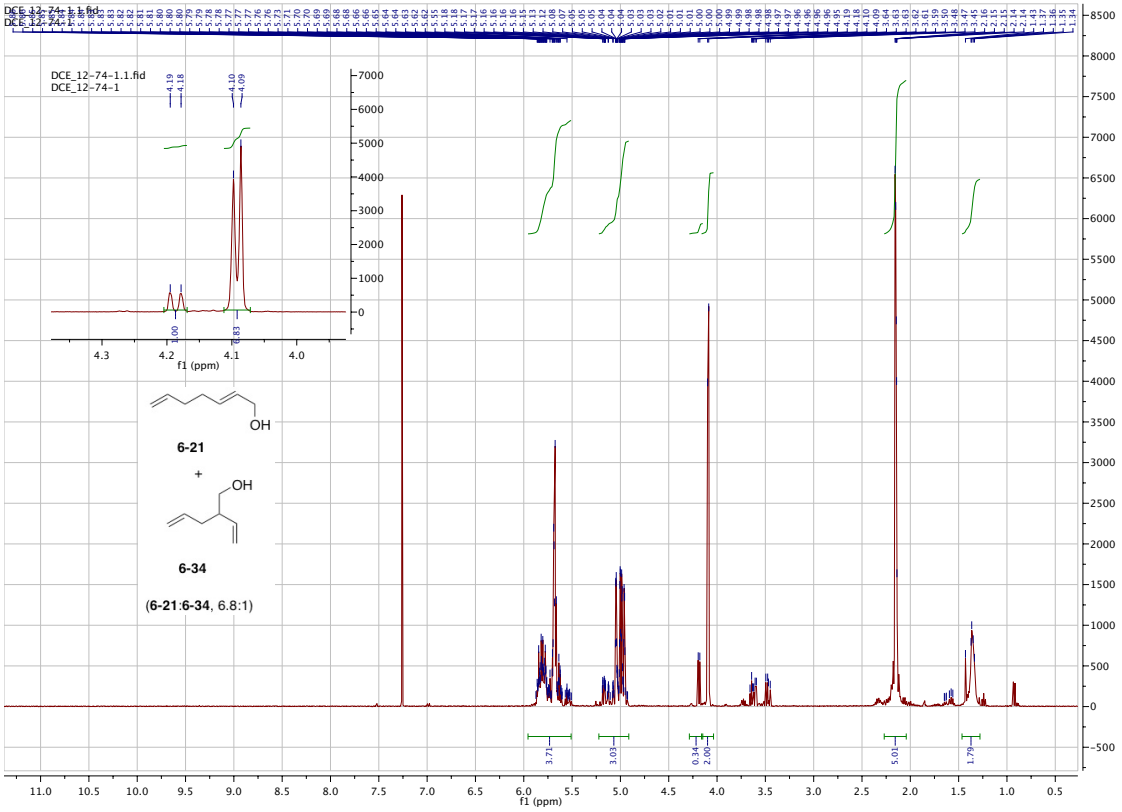

DCE_9-97-2_C13
DCE_9-97-2_C13
OH
6-7
f1 (ppm)

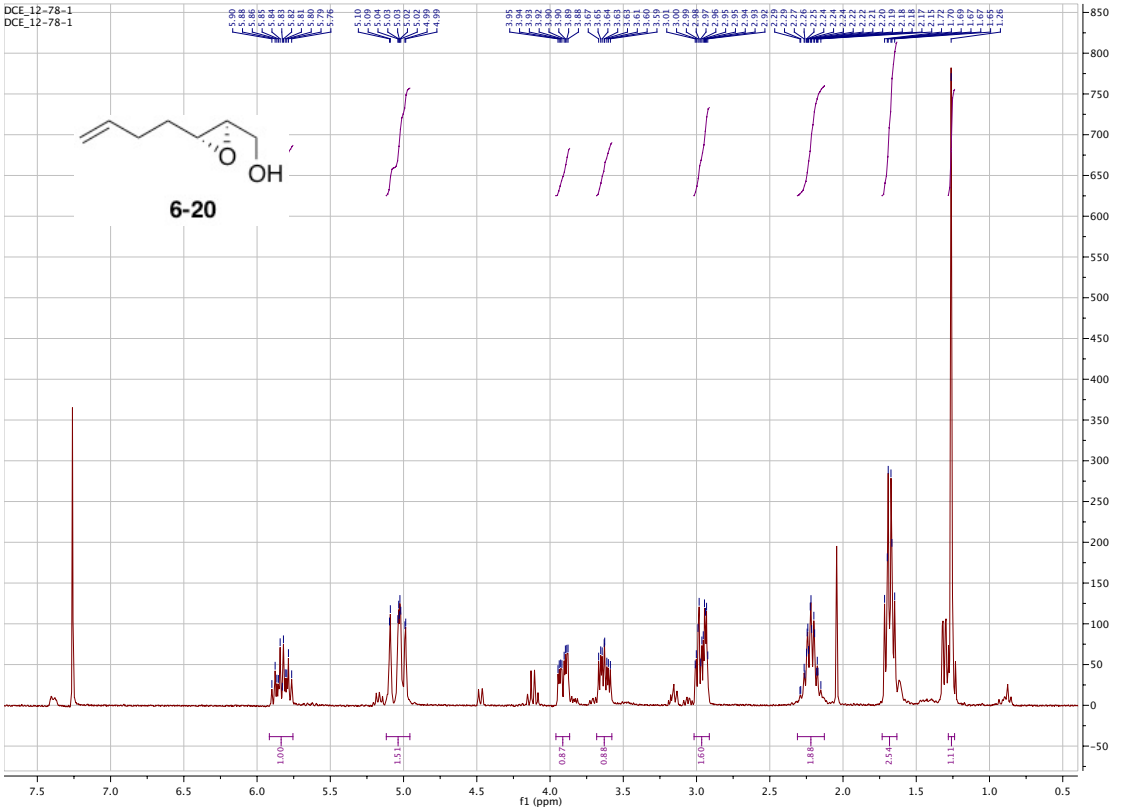

DCE_10-41-1
DCE_10-41-1
O
OH
6-6
f1 (ppm)

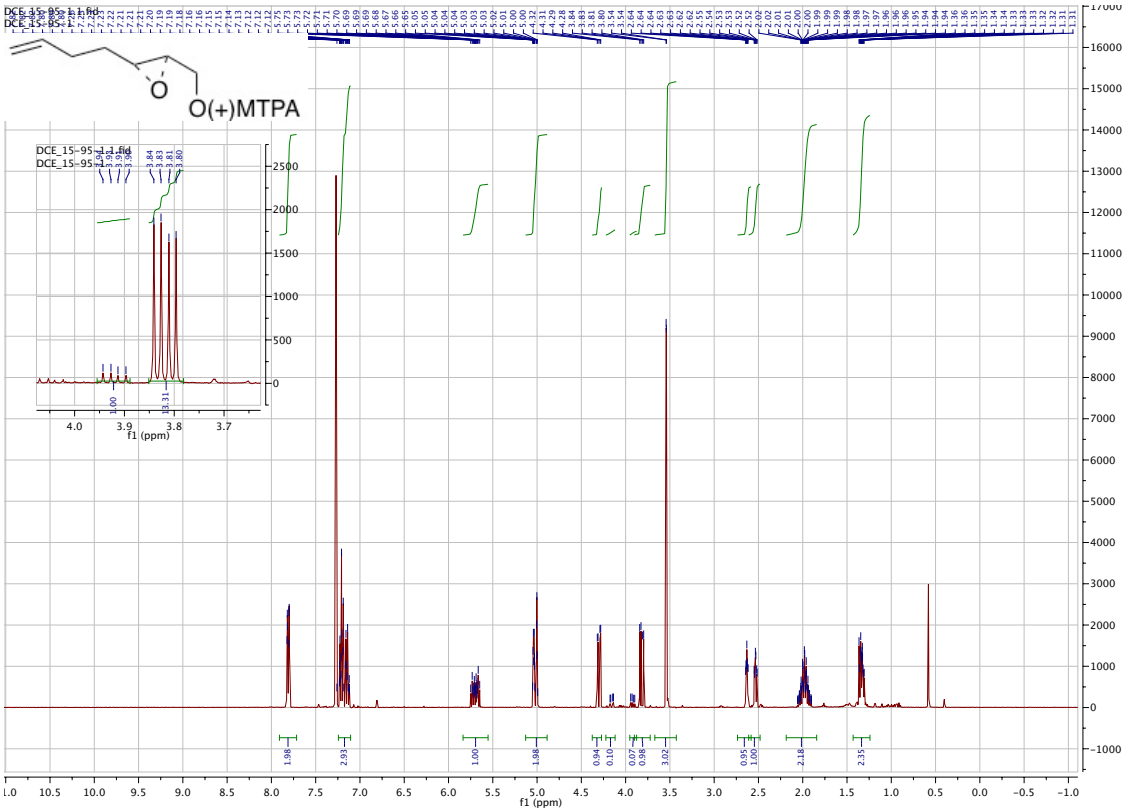

DCE_10-41-1_C13
DCE_10-41-1_C13
151.57
137.45
115.26
109.80
67.54
60.68
55.21
39.22
33.51
30.90
30.16
21.82
21.59
O
OH
6-6
f1 (ppm)

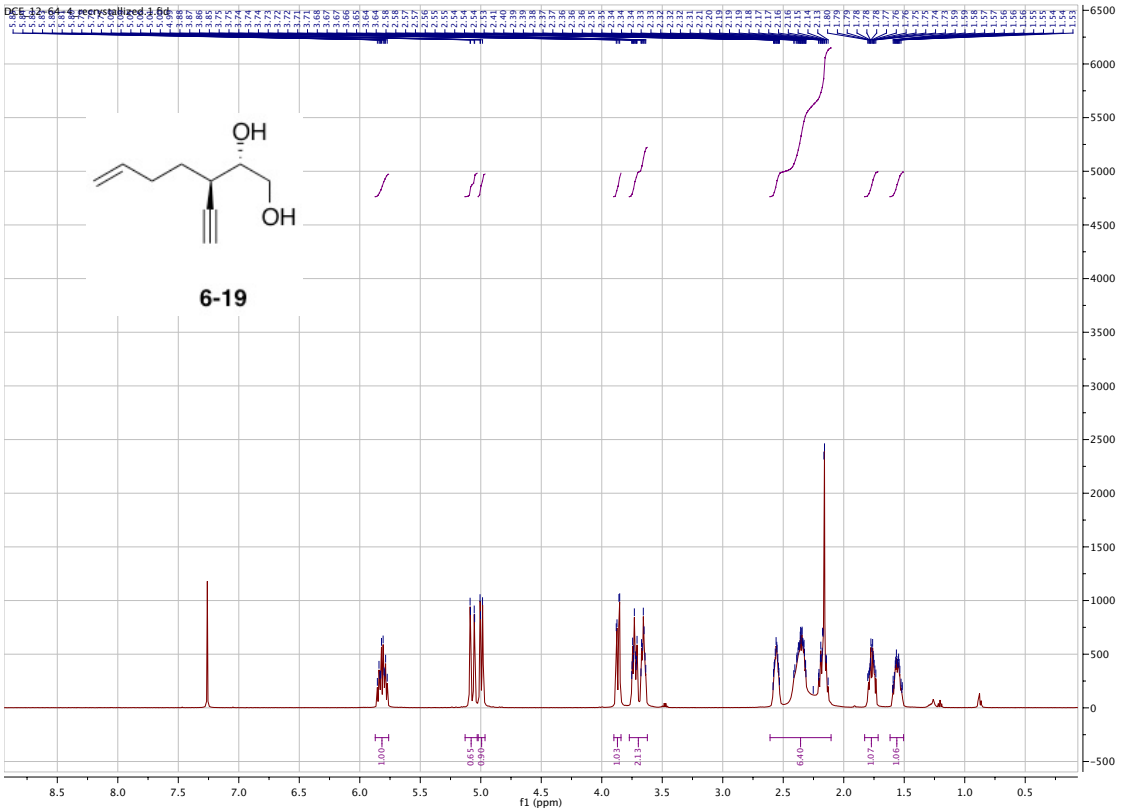

MEMO
6-5
f1 (ppm)

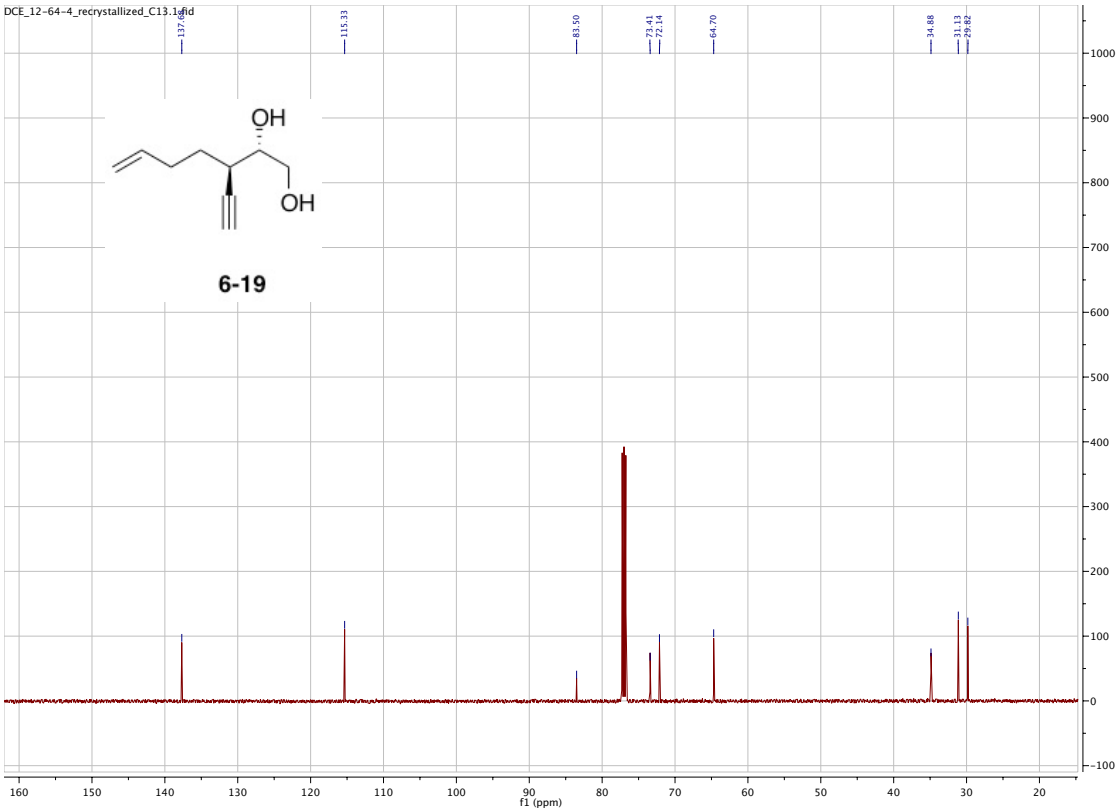

MEMO
6-5
f1 (ppm)

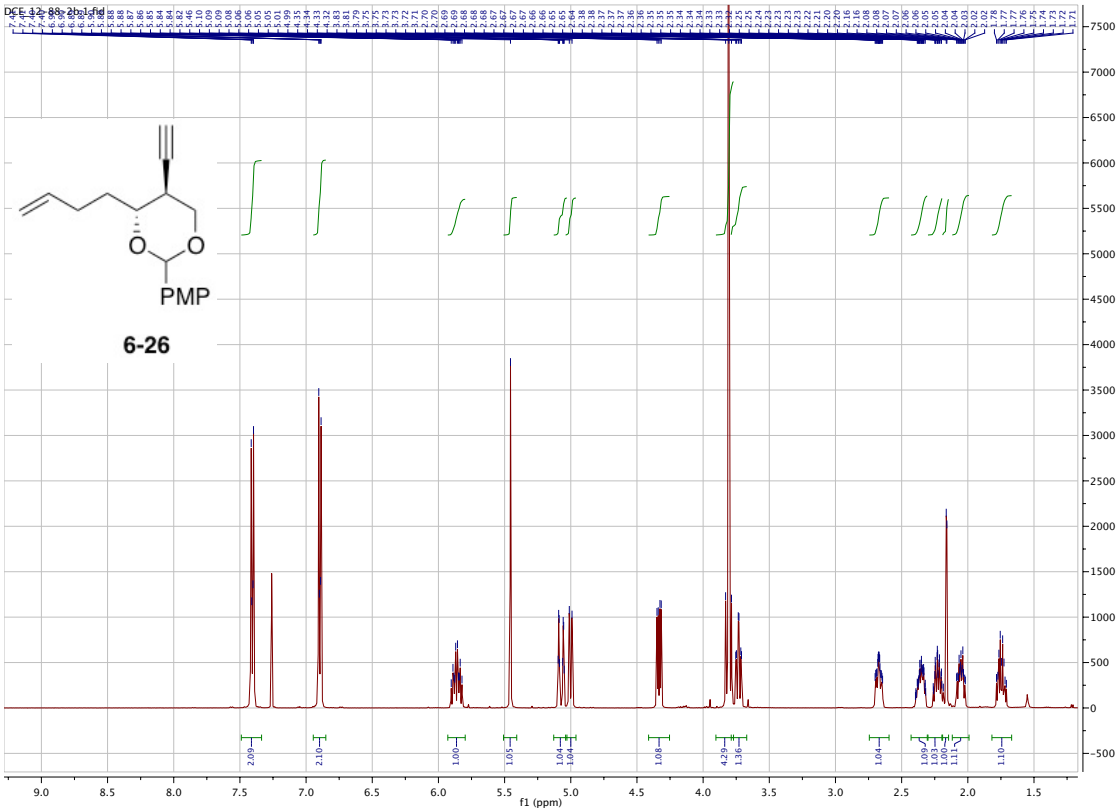

DCE_12-74-1.1.fid
DCE_12-74-1
6-21
+
6-34
(6-21:6-34, 6.8:1)
f1 (ppm)

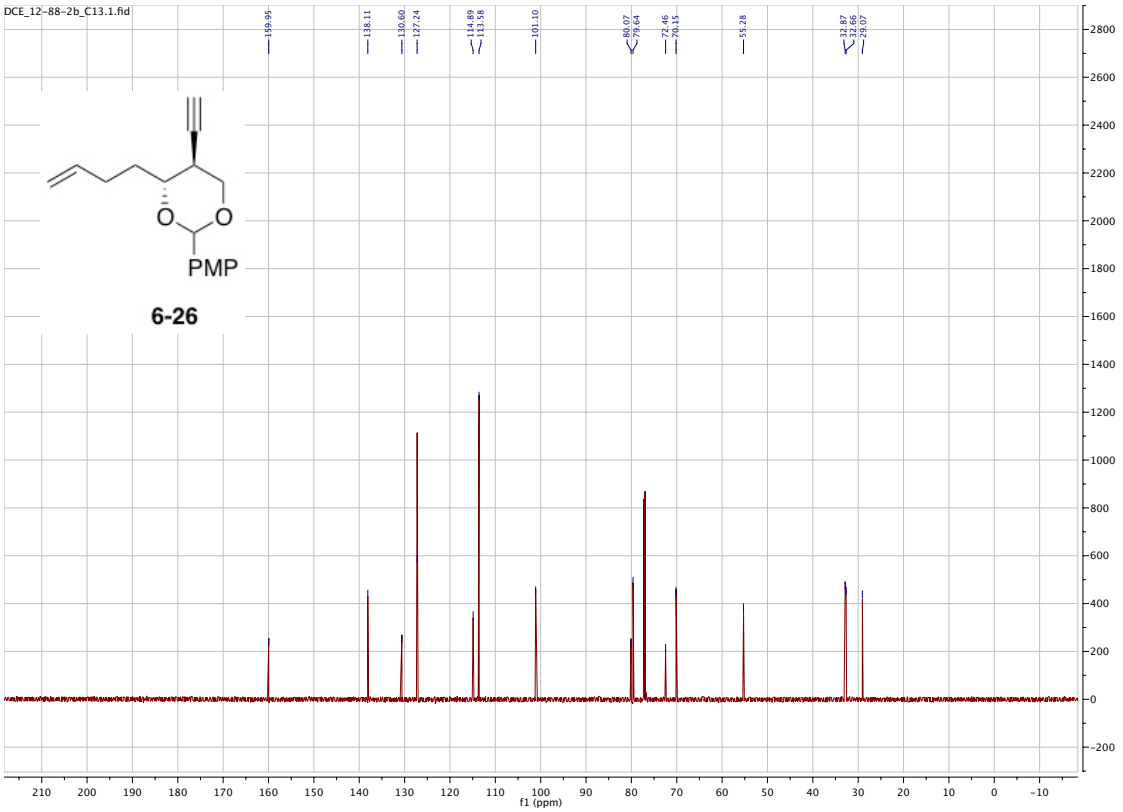

DCE_12-78-1
DCE_12-78-1
6-20
f1 (ppm)

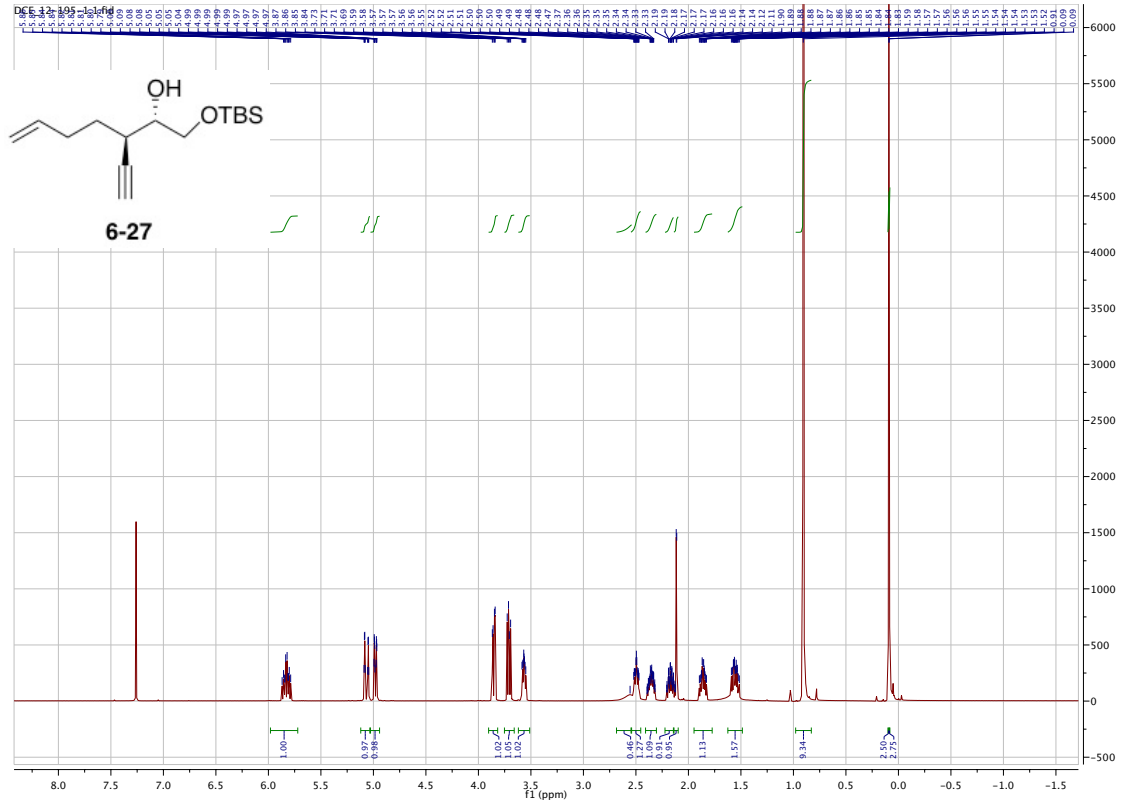

O(+)MTPA
f1 (ppm)

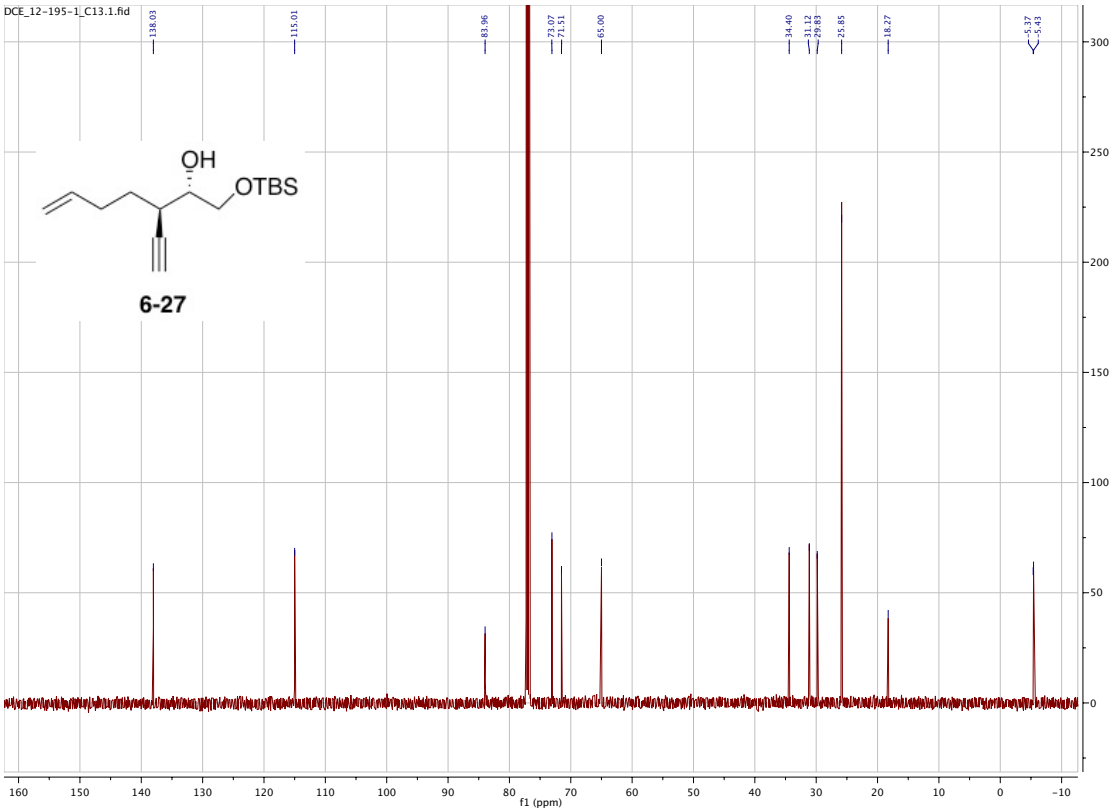

OH
OH
6-19
f1 (ppm)

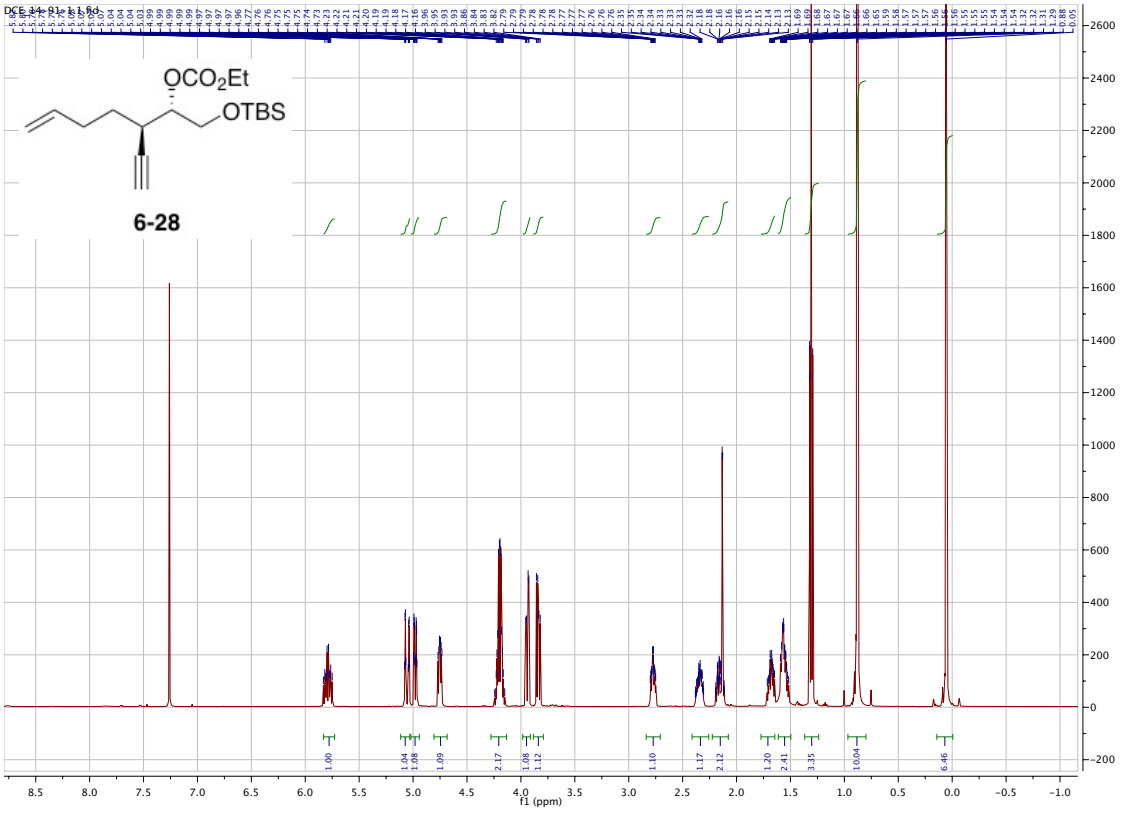

DCE_12-64-4_recrystallized_C13.1.fid
137.68
115.33
83.50
73.41
72.14
64.70
34.88
31.13
29.02
OH
OH
6-19
f1 (ppm)

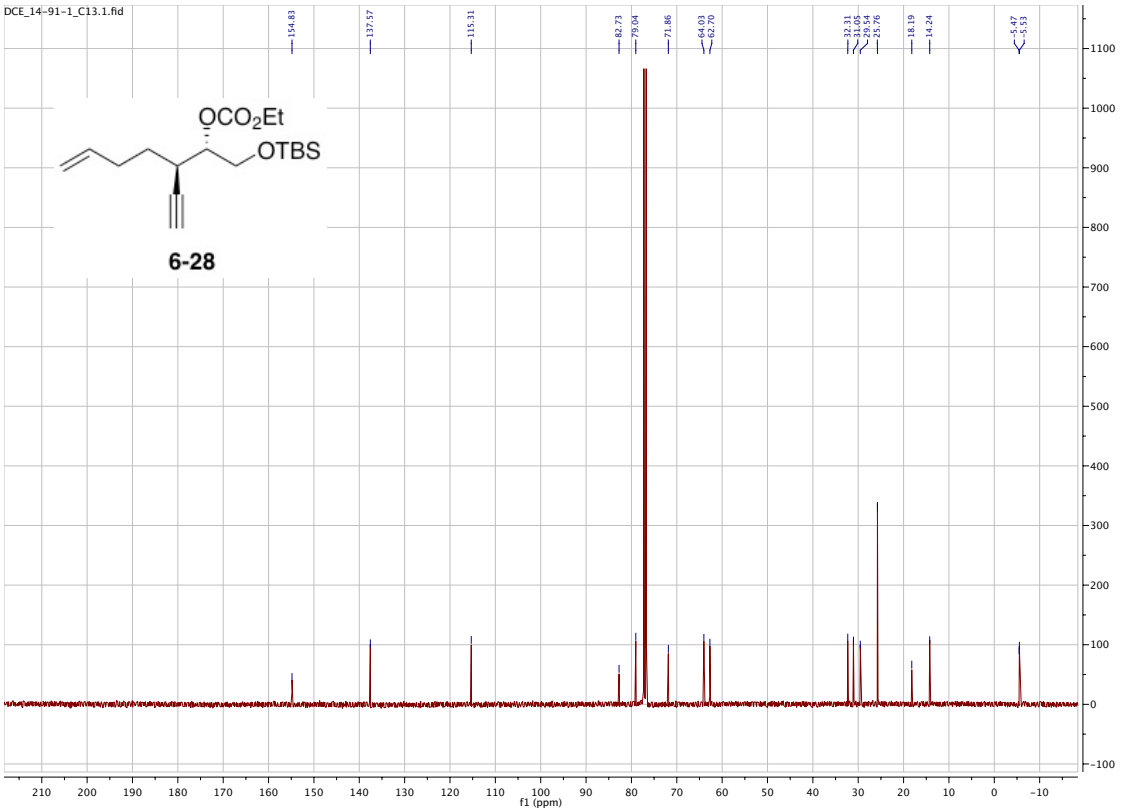

O
O
PMP
6-26
f1 (ppm)

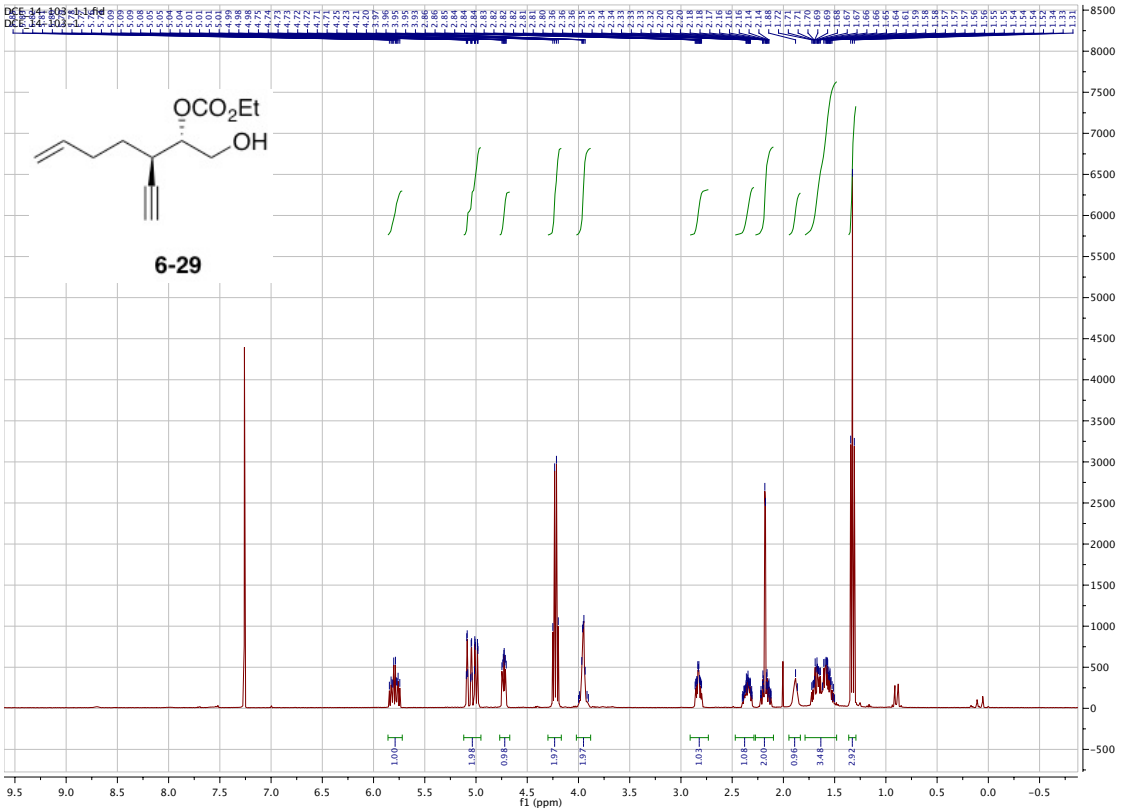

DCE_12-88-2b_C13.1.fid
159.95
138.11
130.60
127.24
114.89
113.58
101.10
80.07
79.64
72.46
70.15
51.28
32.67
32.60
29.07
O
O
PMP
6-26
f1 (ppm)

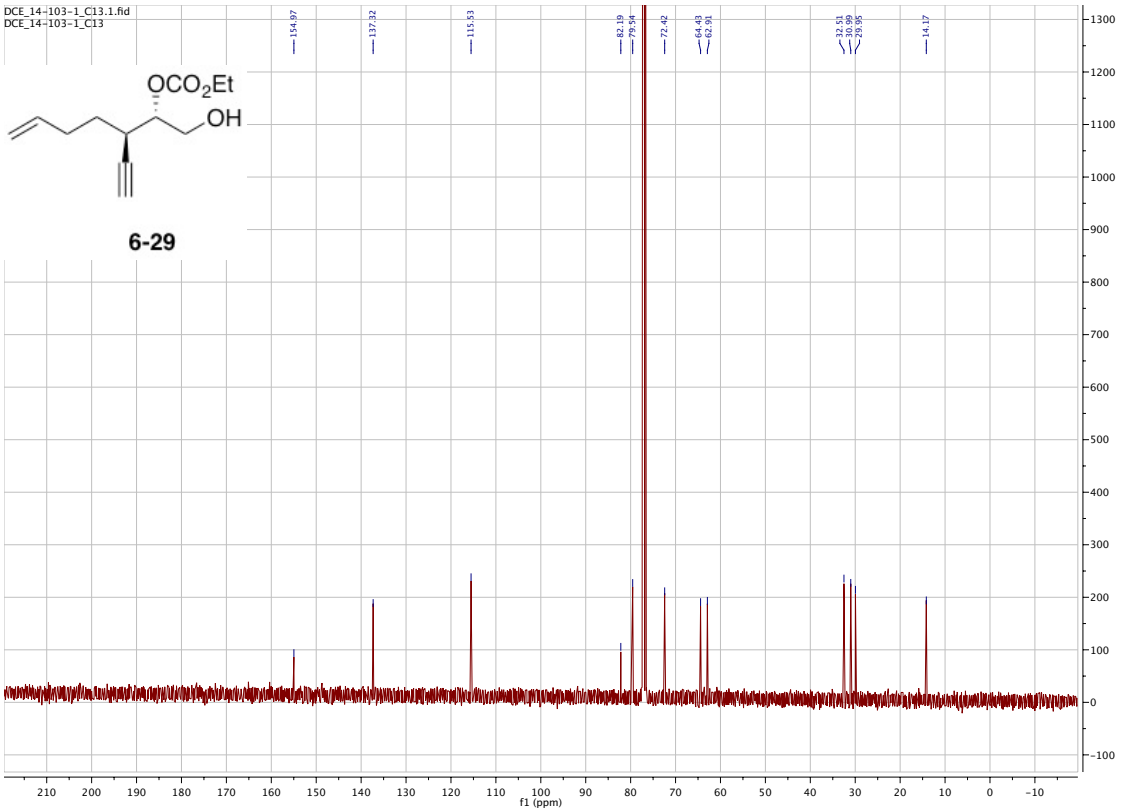

OH
OTBS
6-27
f1 (ppm)

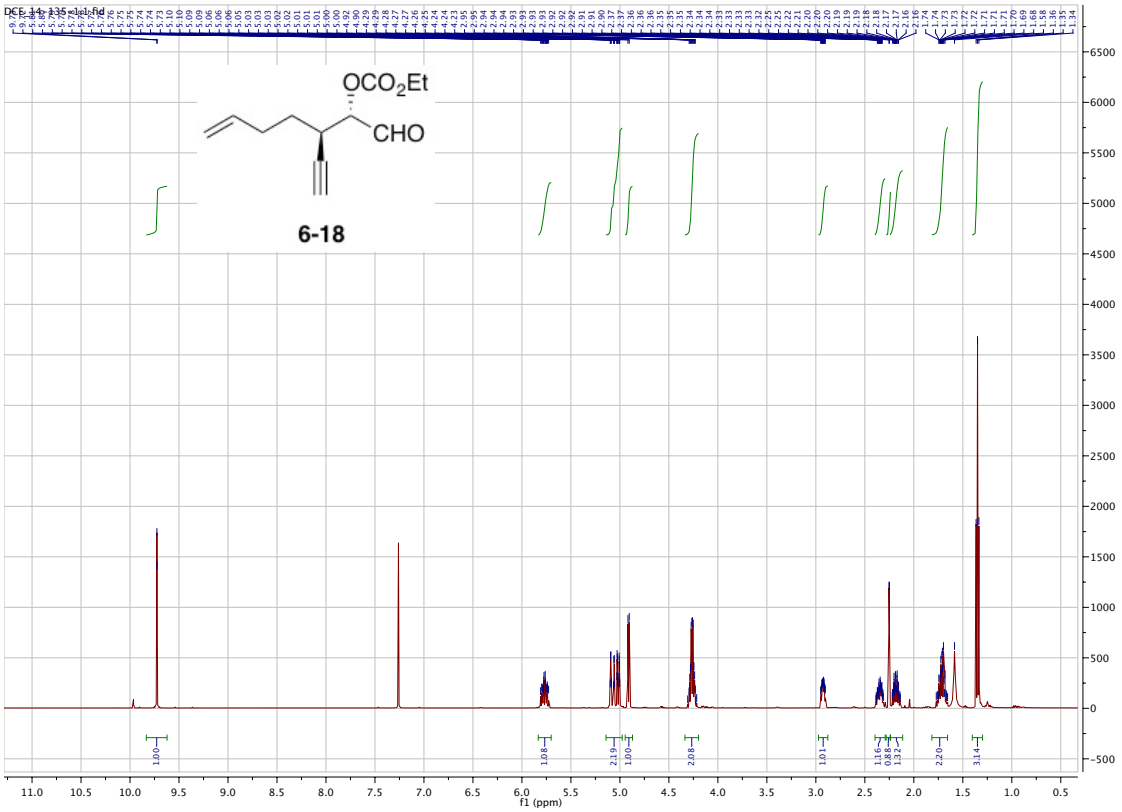

DCE_12-195-1_C13.1.fid
OH
OTBS
6-27
f1 (ppm)

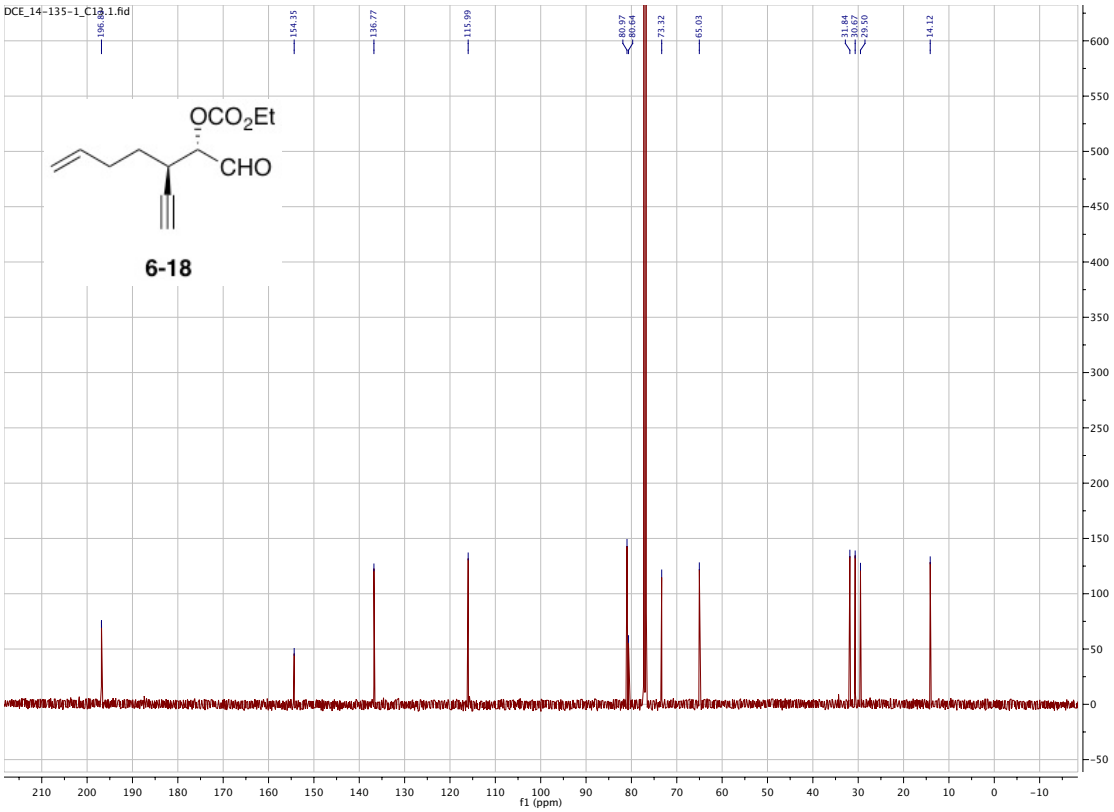

OCO2Et
OTBS
6-28
f1 (ppm)

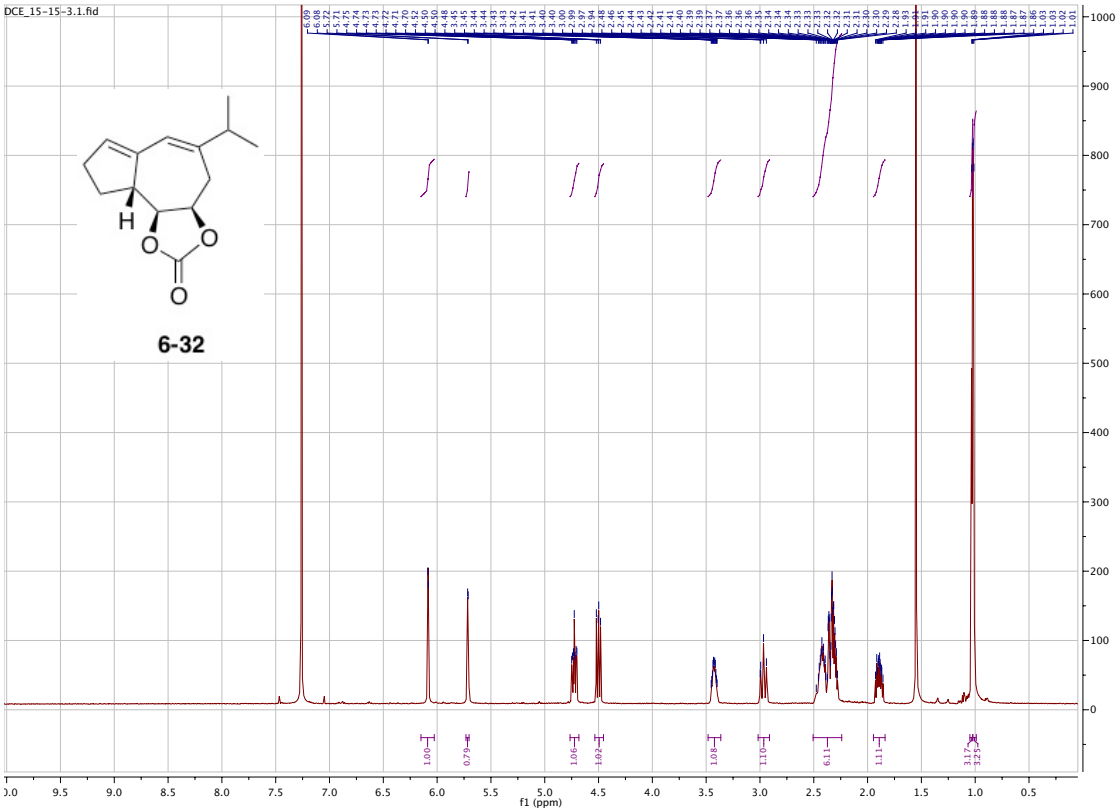

DCE_14-91-1_C13.1.fid
OCO2Et
OTBS
6-28
f1 (ppm)

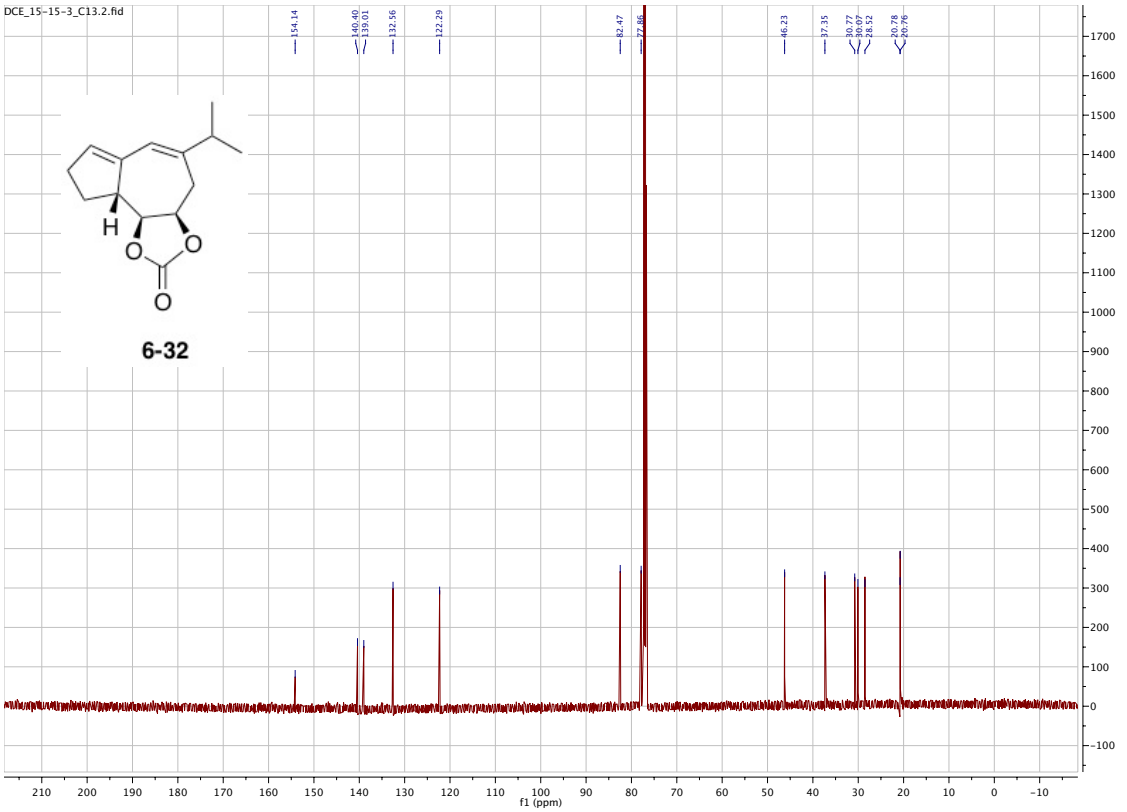

OCO2Et
OH
6-29
f1 (ppm)

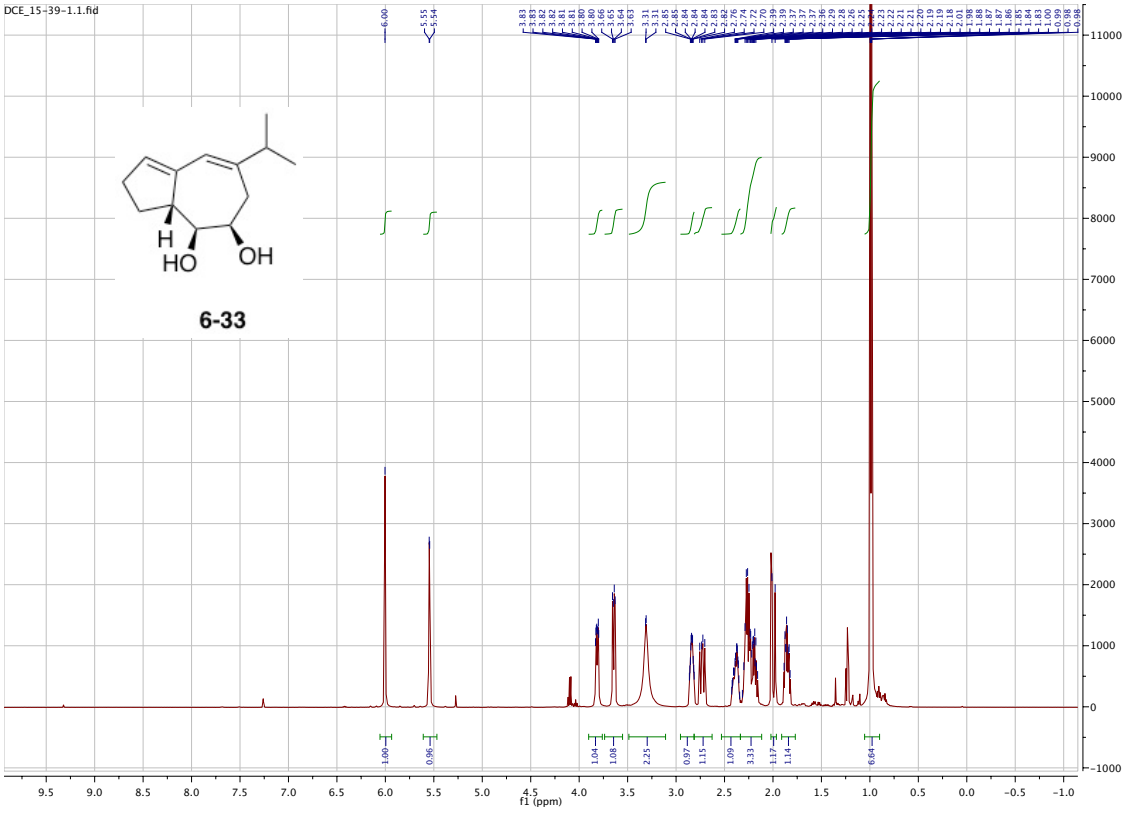

DCE_14-103-1_C13.1.fid
DCE_14-103-1_C13
OCO2Et
OH
6-29
154.97
137.32
115.53
82.19
79.34
72.42
64.43
62.91
32.51
30.99
29.95
14.17
f1 (ppm)

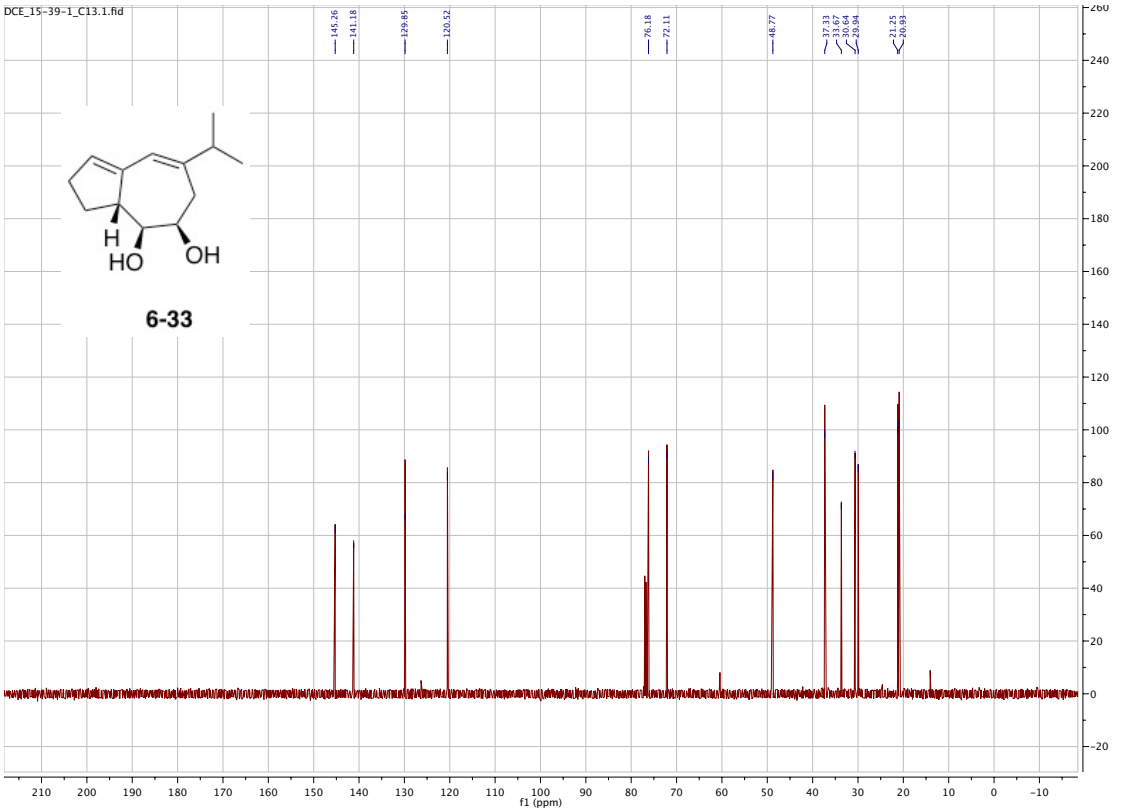

OCO2Et
CHO
6-18
f1 (ppm)

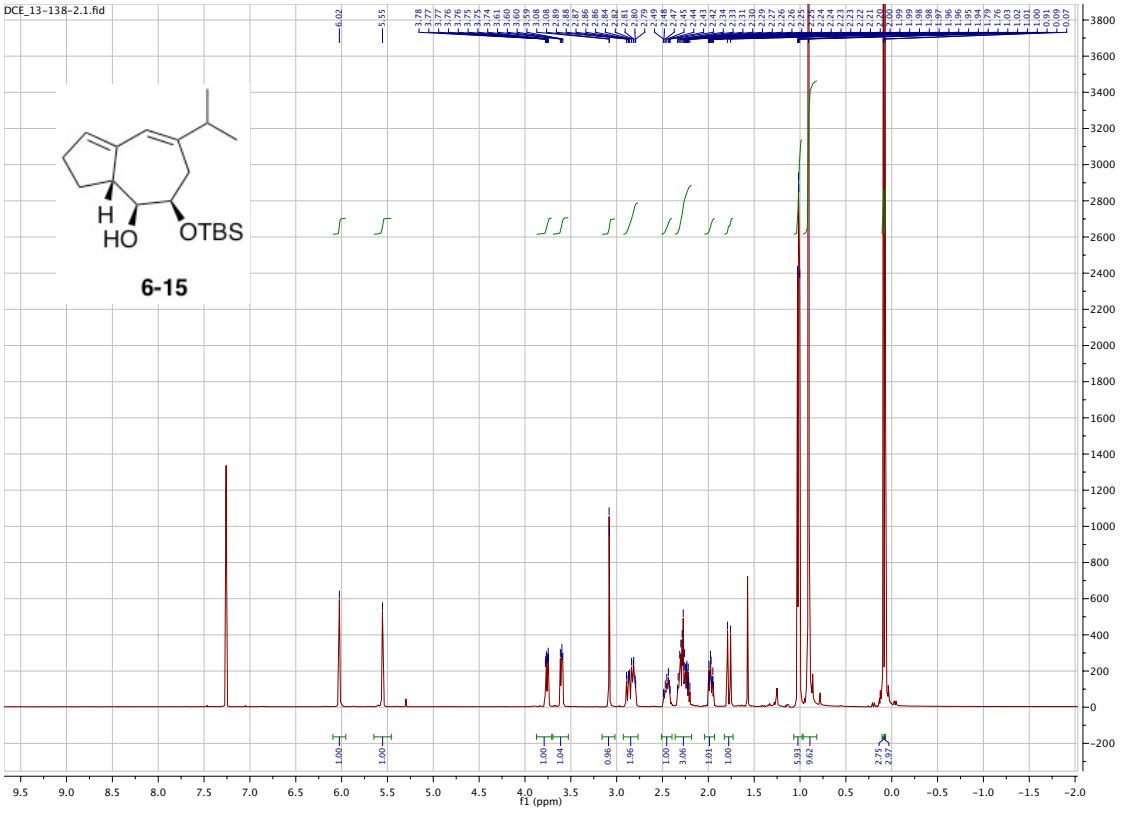

DCE_14-135-1_C13.1.fid
196.38
154.35
136.77
115.99
80.97
80.64
73.32
65.03
31.84
30.67
29.50
14.12
OCO2Et
CHO
6-18
f1 (ppm)

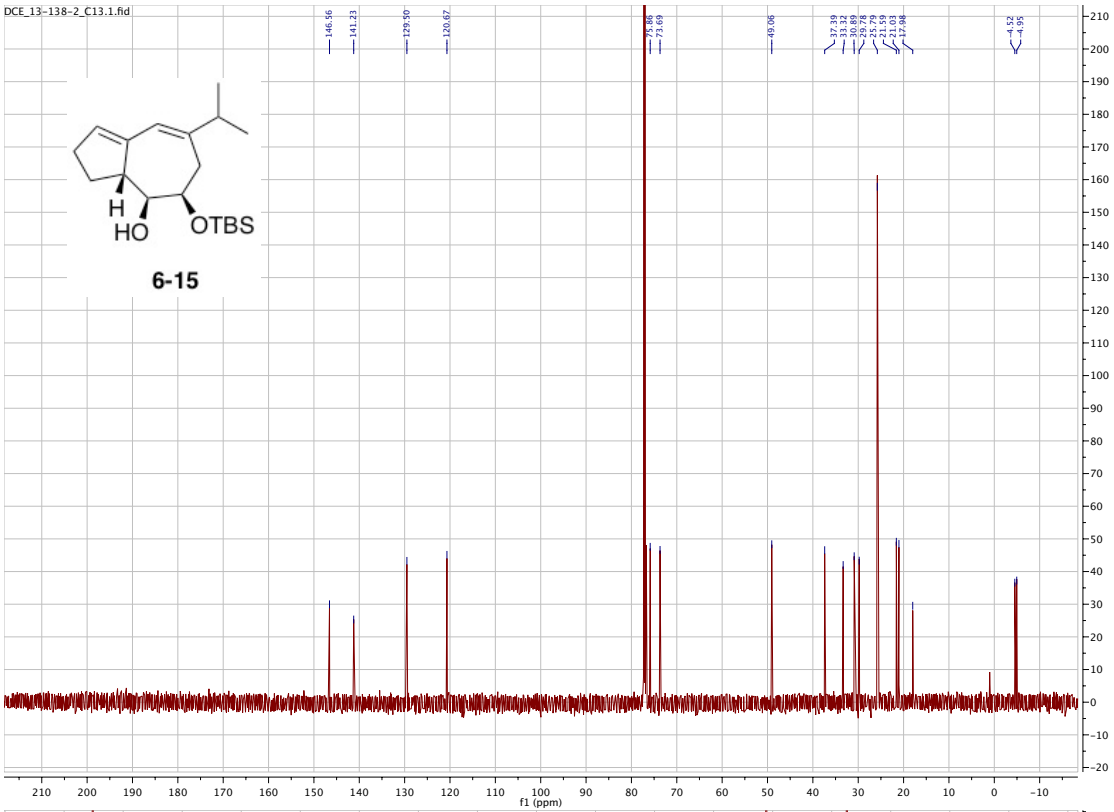

DCE_15-15-3.1.fid
H
O
O
O
6-32
f1 (ppm)

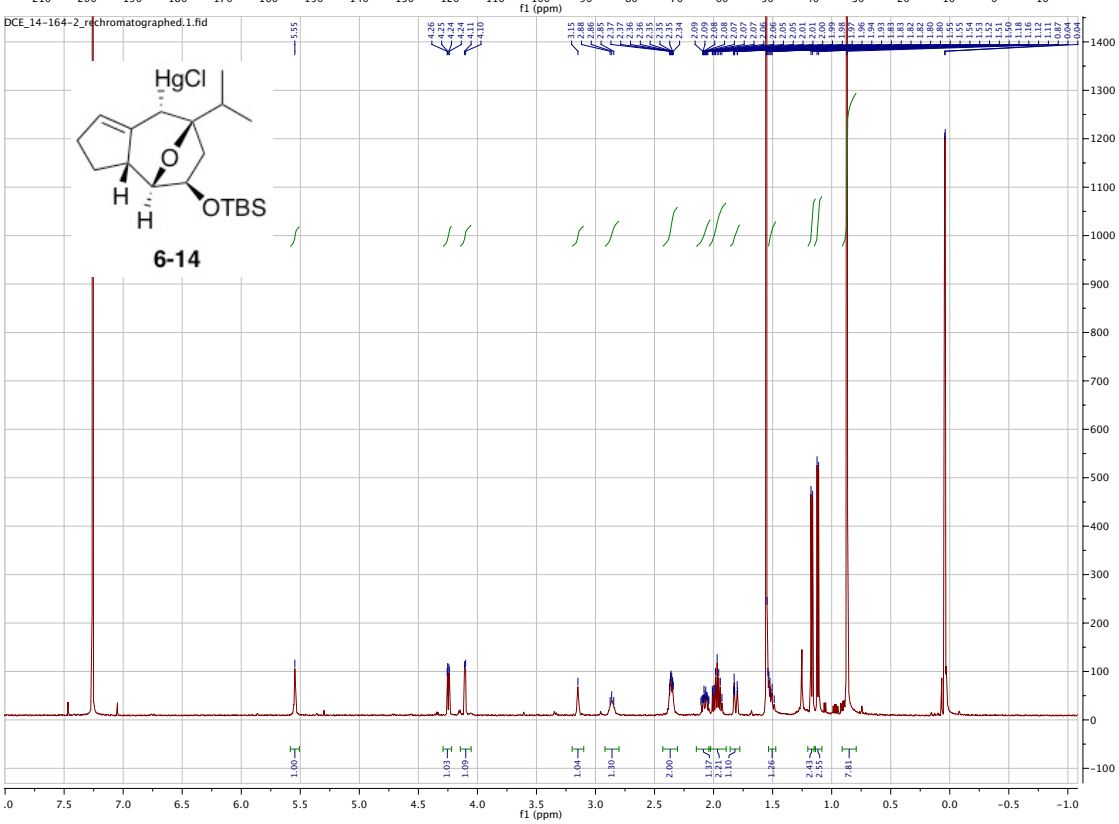

DCE_15-15-3_C13.2.fid
154.14
140.40
139.01
132.56
122.29
82.47
77.86
46.23
37.35
30.77
30.07
28.52
20.78
20.76
H
O
O
O
6-32
f1 (ppm)

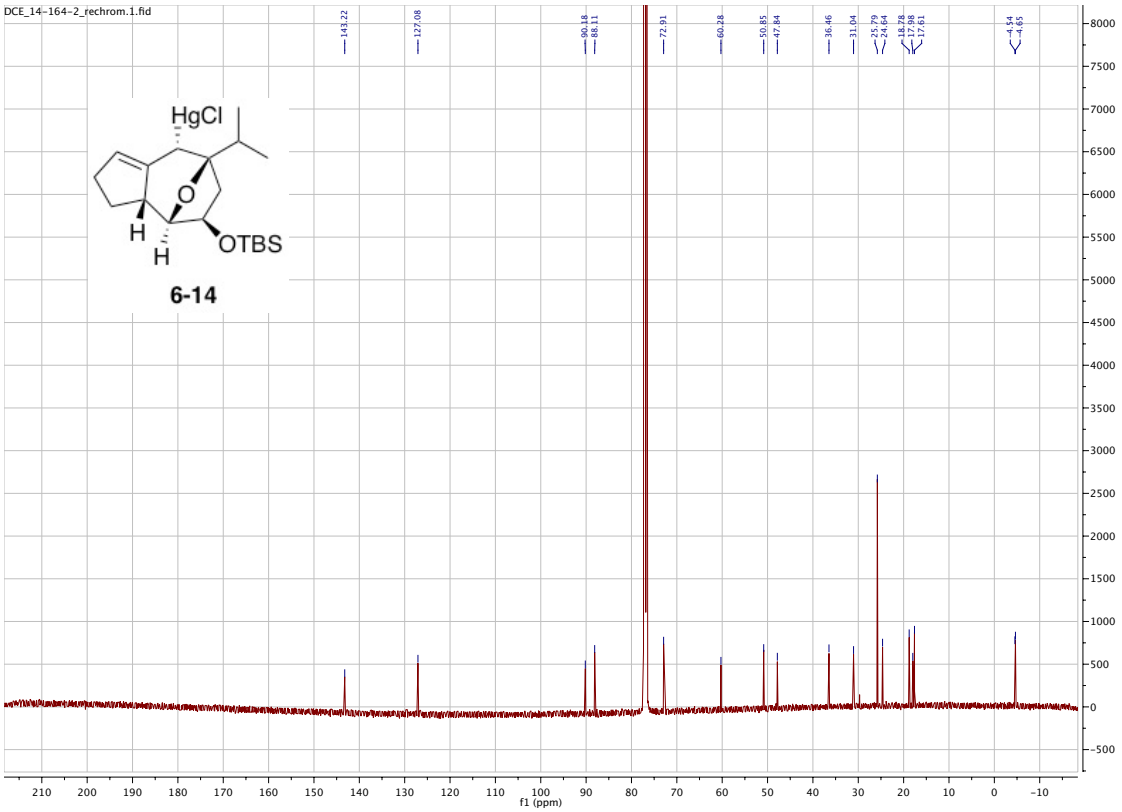

DCE_15-39-1.1.fid
6.00
5.51
5.44
H
HO
OH
6-33
f1 (ppm)


DCE_15-39-1_C13.1.fid
145.26
141.18
129.85
120.52
76.18
72.11
48.77
37.33
33.67
30.64
29.94
21.25
20.93
H
HO
OH
6-33
f1 (ppm)


DCE_13-138-2.1.fid
6.02
5.55
H
HO
OTBS
6-15
f1 (ppm)


DCE_13-138-2_C13.1.fid
146.56
141.23
129.50
120.67
75.88
73.69
49.06
37.39
33.32
30.88
29.78
25.79
21.59
21.03
17.98
-4.52
-4.95
H
HO
OTBS
6-15
f1 (ppm)


DCE_14-164-2_rechromatographed.1.fid
HgCl
O
H
H
OTBS
6-14
f1 (ppm)


DCE_14-164-2_rechrom.1.fid
143.22
127.08
90.18
88.11
72.91
60.28
50.85
47.84
36.46
31.04
25.79
24.64
18.28
17.98
17.61
-4.54
-4.65
HgCl
O
H
H
OTBS
6-14
f1 (ppm)