Stony Brook University

Part I.

One-Pot Synthesis of Secondary Alcohols and One-Pot Asymmetric Synthesis of Secondary Propargylic Alcohols

Part II.

Redox Isomerization of Secondary Propargylic Alcohols to Enones

Part III.

Synthesis Study towards C9-C14 Fragment of (+)-Discodermolide

Part IV.

Asymmetric Synthesis of *Anti, Anti*-Stereotriad Building Blocks for Polypropionate Natural Products

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Abstract of Dissertation

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Part I. Chiral secondary propargyl alcohols are versatile building blocks for fine chemicals, pharmaceuticals, and natural products. A convenient method for asymmetric synthesis of secondary propargyl alcohols is highly demanded. Based on preliminary study, asymmetric synthesis of secondary propargyl alcohols in one-pot was designed and achieved by applying Zn-catalyzed enantioselective alkynylation directly with the aldehyde products of substitution reaction of methyl formate with nucleophiles. Various chiral alcohols with different substitutions have been synthesized successfully with good yield and high enantiomeric excess.

Part II. A convenient conversion of secondary propargyl alcohols to α,β-enones is highly in demand because the diverse applications of α,β-enones in synthesis and the facile access to propargyl alcohols. Recently, the transition metals such as Pd, Ru, Rh and

Ir were used to catalyze the highly atom economical isomerization of propargyl alcohols to α,β-enals and α,β-enones. However, such isomerizations are less well studied compare with the well established isomerizations of allylic alcohols. In this project, Trost's two-metal (ruthenium, indium) catalysis system was carefully optimized to promote the isomerization of secondary propargyl alcohols to α,β-enones, with tetraethylammonium hexafluorophosphate additive. To our knowledge, the first example of isomerization of dialkynyl alcohols to enynones catalyzed by a transition metal complex is reported here.

Part III. (+)-Discodermolide, a marine sponge natural product that stabilizes microtubules and maintains activity against multidrug resistant cell lines, is currently in clinical trials as an anticancer drug developed by Novartis Pharmaceuticals. Most of the completed total syntheses of (+)-discodermolide have relied on the Roche ester as the source of chirality and enantioselective chain extensions for construction of the building blocks. In our retro-synthetic plan towards (+)-discodermolide, the disconnections at C8-C9, C14-C15 generated three fragments. While my colleagues concentrated on the C1-C8 fragment and C15-C24 fragment, my work focuses on the synthesis of the C9-C14 moiety. The C9-C14 fragment was successful synthesized in 12 steps with 26.8 % over all yield. The chirality source, (-)-N-methylephedrine, is inexpensive and the auxiliary is recoverable.

Part IV. Polypropionate subunits are present in a great number of biological active natural products such as antibiotics, antitumors, antifungals, or antiparasitics. A widespread strategy to synthesize these structures involves the disconnection of polypropionate chains into shorter subunits, such as stereotriad building blocks bearing alternate methyl and hydroxyl groups. Starting from inexpensive, commercially available achiral starting materials, a powerful protocol was developed to construct *anti*, *anti*-stereotriad building blocks. With further modifications, the (2*R*,3*R*,4*R*)-3-(tert-butyldimethylsilyloxy)-2,4,6-trimethylheptanoic acid (TBS-TMHEA) segment of Callipeltin A, the Segment B2 of Miyashita's total synthesis of Scytophycin C, and the TES-PMB protected piece of Paterson's synthesis approach of Aplyronines were synthesized from these stereotriads.

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List of Abbreviations

δ	Chemical Shift
Ac	Acetyl
AcOH	Acetic acid
aq.	Aqueous
Ar	Aryl
Atm	Atmosphere
br	Broad
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
n-Bu	*n*-Butyl
t-Bu	*tert*-Butyl
Bu	Butyl
Bz	Benzoyl
BzCl	Benzoyl Chloride
^{13}C-NMR	Carbon Nuclear Magnetic Resonance
cm^{-1}	Reciprocal Centimeter
COSY	Homonucleare (^{1}H-^{1}H) Correlation Spectroscopy
Cp	Cyclopentandienyl
CP*	1,2,3,4,5-Pentamethylcyclopenta-1,3-dienyl
CSA	Camphorsulfonic Acid
d	Doublet
dd	Doublet of Doublet
dr	Diastereomeric Ratio
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Methyl Sulfoxide
E	Entgegen (Opposite)
ee	Enantiomeric Excess
eq.	Eqiuvalent(s)
Et	Ethyl
Et2O	Diethyl Ether
EtOAc	Ethyl Acetate
g	Gram(s)

h	Hour(s)
HMPA	Hexamethylphosphoramide
^{1}H-NMR	Proton Nuclear Magnetic Resonance
hν	Irradiation with Light
HWE	Horner-Wadsworth-Emmons
Hz	Herz
*i*Pr	Isopropyl
IR	Infrared Spectroscopy
J	First Order Coupling Constant (NMR)
l	Liter
LAH	Lithium Aluminium Hydride
LDA	Lithium Diisopropylamide
LHMDS	Lithium 1,1,1,3,3,3-Hexamethyldisilazide
m	Multiplet
mCPBA	*meta*-Chloroperoxybenzoic Acid
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute(s)
mL	Milliliter
mmol	Millimole
mol	Mole
MOM	Methoxymethyl
mp	Melting Point
MS	Mass Spectrometry
NaHMDS	Sodium 1,1,1,3,3,3-Hexamethyldisilazide
NMO	4-Methylmopholine N-Oxide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
$PhCH_3$	Toluene
PMB	*para*-Methoxy Benzyl
PMP	*para*-Methoxy Phenyl
ppm	Parts per Million (NMR)
Pr	Propyl
Py	Pyridine
q	Quartet

Rf	Retention Factor
rt	Room Temperature
s	Singlet
t	Time, or triplet (NMR)
TBAF	Tetra-N-butylammonium Fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
Tf	Trifluoromethane Sulfonate
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
THP	Tetrahedropyranyl
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium Perruthenate
Ts	*para*-Toluenesulfonyl (tosyl)
UV	Ultraviolet
Z	Zusammen (Together)

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Qiuzhe Xie
Stony Brook University, October 2007

PART ONE

ONE-POT SYNTHESIS OF SECONDARY ALCOHOLS AND ONE-POT ASYMMETRIC SYNTHESIS OF SECONDARY PROPARGYLIC ALCOHOLS

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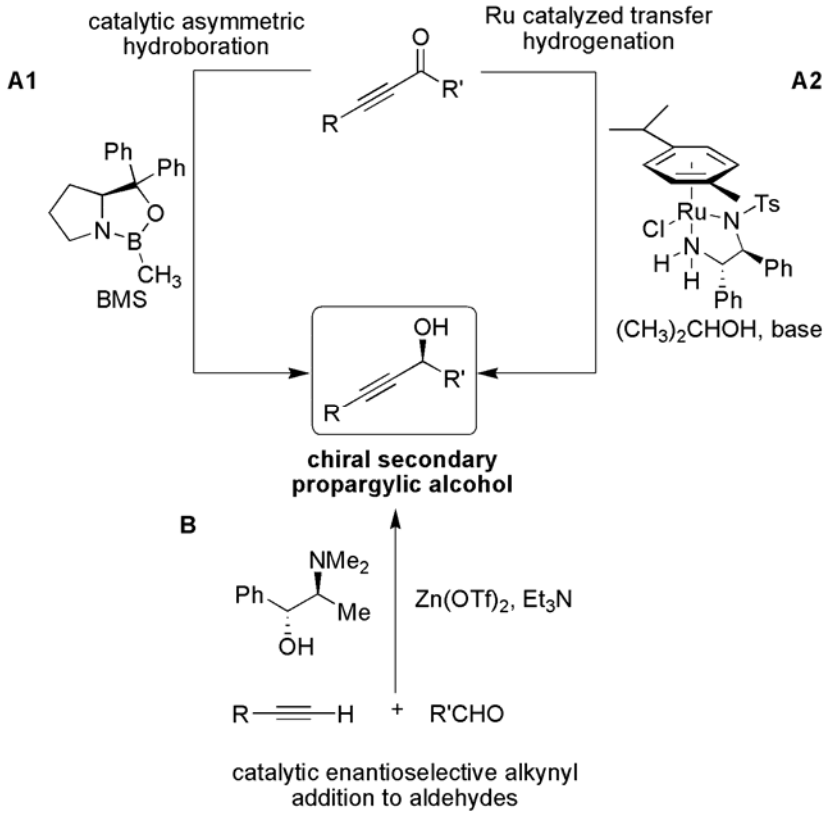
1.1 INTRODUCTION

Chiral secondary propargylic alcohols are versatile building blocks for fine chemicals, pharmaceuticals, and natural products. A convenient synthesis of chiral secondary propargylic alcohols will attract a large amount of interest. Different approaches to chiral secondary propargylic alcohols were developed by researchers. There are two major protocols: the asymmetric reduction of α,β-ynones, via either the catalytic asymmetric hydroboration (**A1** in Scheme **1-1**) or transition metal-catalyzed transfer hydrogenation (**A2** in Scheme **1-1**), and the catalytic enantioselective alkynyl addition to aldehydes (**B** in Scheme **1-1**). While excellent yields and enantioselectivities are obtained by each of these methods, the difficulty in purifying and storing the unstable aldehydes or the difficulty in obtaining *α,β*-acetylenic ketones has been an obstacle for applying these protocols.[1]



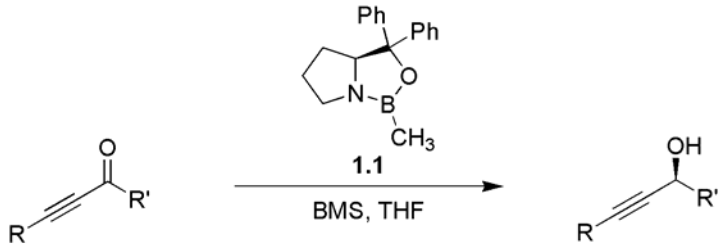
Scheme 1-1 Summary of previous protocols**Error! Bookmark not defined.**

1.1.1 Asymmetric Reduction of Alkynyl Ketones

In 1996, Parker's group reported the first reduction of conjugated alkynyl ketones with borane methyl sulfide (BMS) in the presence of chiral oxazaborolidine (**1.1**, Scheme

[1] Frantz, D. E.; Fassler, R. ; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807

1-2).[2] Secondary propargylic alcohols were synthesized with enantioselectivities at relatively low temperature in short time (Table **1-1**).

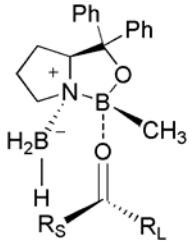


Scheme 1-2 Asymmetric reduction of alkynyl ketones

Table 1-1 Asymmetric reduction of alkynyl ketones

Entry	R	R'	Yield	ee
1	Ph	CH_3	80%	71%
2	Ph	CH_2CH_3	84%	88%
3	Ph	$(CH_2)_5CH_3$	84%	82%
4	Ph	$CH(CH_3)_2$	85%	94%
5	Ph	*c*-C_6H_{11}	92%	96%
6	H	$(CH_2)_6CH_3$	54%	95%
7	H	*c*-C_6H_{11}	81%	98%

The general mechanistic picture proposed by Corey[3] could explain the observed high enantioselectivity. The alkynyl substituent is considered to adopt the position of the sterically smaller group R_S and the bulkier group occupies the R_L position in the suggested transition state assembly. Then, hydride ion transfer sets the stereochemistry (Scheme **1-3**).



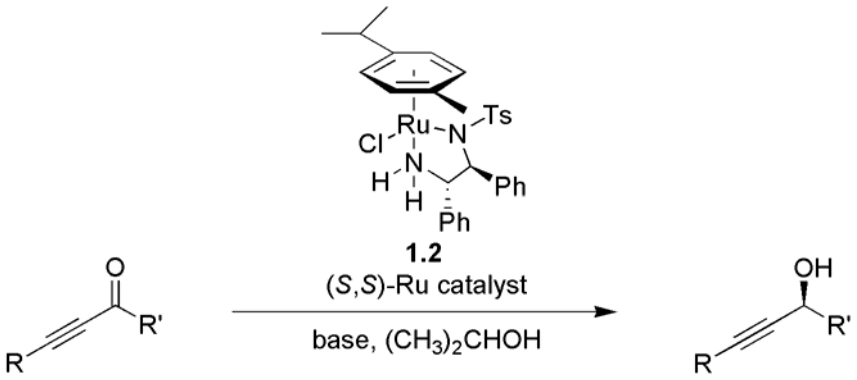
Scheme 1-3 Transition state assembly proposed by Corey

1.1.2 Asymmetric Transfer Hydrogenation of *α,β*-Acetylenic Ketones

In 1997, Noyori and coworkers published the first asymmetric transfer hydrogenation of *α,β*-acetylenic ketones using chiral Ru(II) catalysts (**1.2**) and 2-propanol as the

[2] Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*(9), 3214-3217.
[3] Corey E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.***1987**, *109*, 5551.

hydrogen donor (Scheme **1-4**, Table **1-2**). Structurally diverse acetylenic ketones were reduced to propargylic alcohols with high chemoselectivity and enantioselectivity.[4] In this reaction, 2-propanol acts as a safe, inexpensive, easy to handle solvent and reductant at the same time. This reversible process is forced to completion by removing acetone, the oxidation product of 2-propanol, from the reaction mixture.



Scheme 1-4 Asymmetric transfer hydrogenation of *α*,*β*-acetylenic ketones

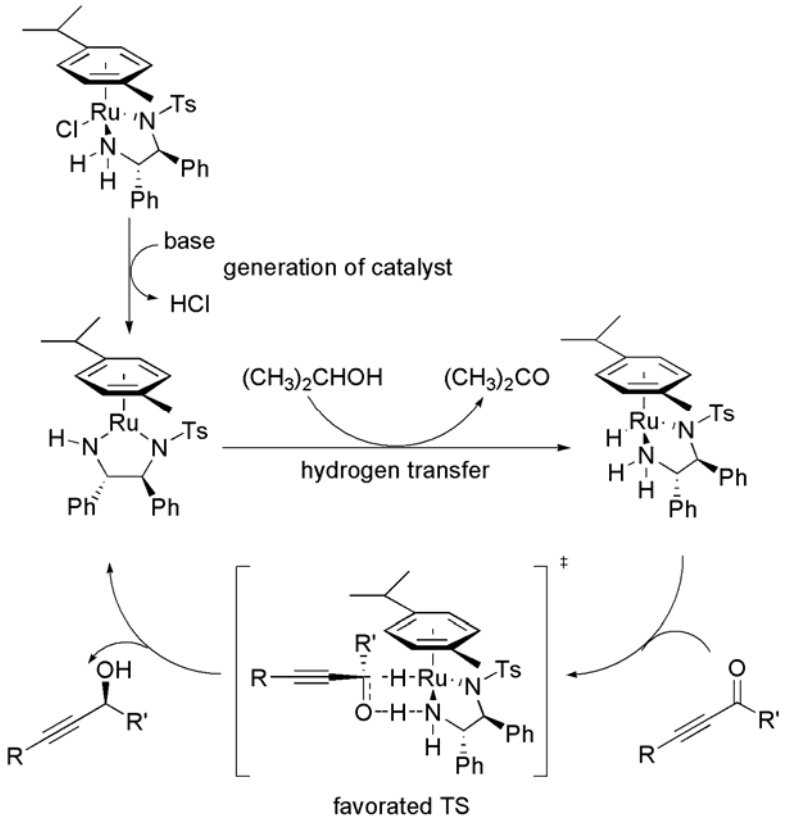
Table 1-2 Asymmetric transfer hydrogenation of *α*,*β*-acetylenic ketones

Entry	R	R'	Yield	Ee
1	Ph	Me	99%	98%
2	Ph	Et	97%	97%
3	Ph	*i*-Pr	98%	99%
4	Ph	*c*-C_6H_{11}	99%	98%
5	*n*-C_4H_9	Me	70%	98%
6	$Si(CH_3)_3$	Me	86%	96%

Noyori et al. established the identity of the catalyst precursors and true active intermediate species involved in the [Ru(arene)(TsDPEN)] catalyzed transfer hydrogenation process (Scheme **1-5**).[5]

[4] a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* 1997, *119*, 8738-8739. b) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* 2003, *345*, 67-77

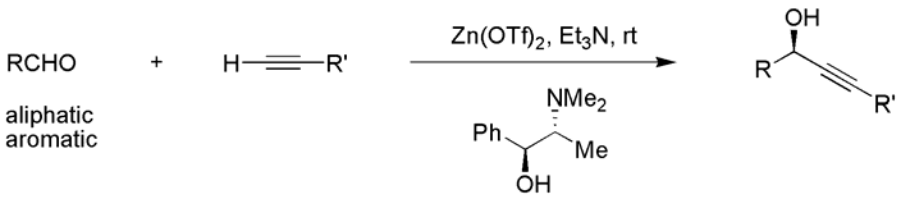
[5] a) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288. b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931-7944



Scheme 1-5 Proposed mechanism for Ru(II)-catalyzed transfer hydrogenation by Noyori

1.1.3 Carreira's N-Methylephedrine-directed Enantioselective Synthesis of Chiral Asymmetrical Secondary Alcohols

Eric M. Carreira and coworkers developed a synthetic method to synthesize chiral secondary propargylic alcohols by addition of alkynes to aldehydes with a zinc catalyst in a chiral environment (Scheme **1-6**, Table **1-3**).



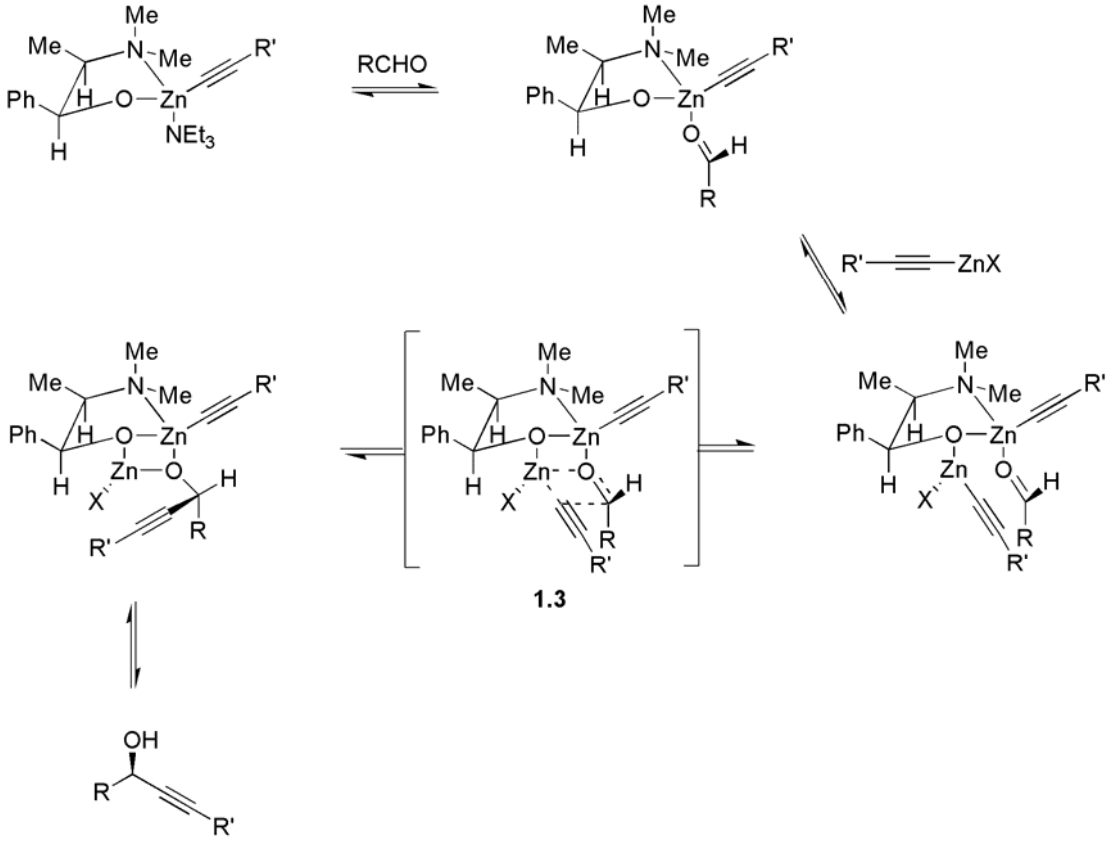
Scheme 1-6 Enantioselective synthesis of chiral asymmetric secondary propargylic alcohols

Table 1-3 Enantioselective synthesis of chiral asymmetric secondary propargylic alcohols

Entry	R	R'	Yield	ee
1	*c*-C_6H_{11}	Ph	99%	96%
2	*i*-Pr	Ph	95%	90%

3	*t*-Bu	Ph	99%	94%
4	*c*-C_6H_{11}	Me_3Si	93%	98%
5	Ph	Ph	53%	94%
6	Ph	$Ph(CH_2)_2$	52%	96%
7	PhCH=CH	$Ph(CH_2)_2$	39%	80%

A currently accepted Noyori-type mechanism [6] proposed by Marshall for N-methylephedrine-directed addition reaction could rationalize the stereochemical outcome of this addition process (Scheme **1-7**).[7] First, one equivalent of acetylide and one equivalent of N-methylephedrine anion coordinate to Zn(II). After the carbonyl group exchange with the Et_3N ligand, another equivalent of alkynyl zinc adds to the complex. A highly organized two-metal-center transition state (**1.3**) was proposed in which both electrophilic and nucleophilic components are activated. Then, the chiral propargylic alcohol product is released and the catalytic system is regenerated.



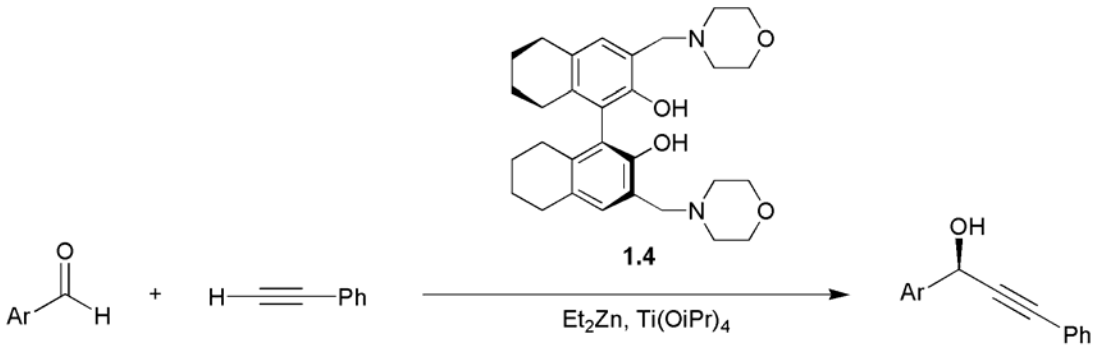
Scheme 1-7 Proposed mechanism for Carreira's enantioselective synthesis

1.1.4 BINOL-directed Titanium-catalyzed Alkynylation Reactions

[6] Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327-6335.

[7] Mashall, J. A.; Eidam, P. *Org. Lett*. **2004**, *6*, 445.

BINOLs and partially hydrogenated BINOLs were demonstrated to be effective ligands for titanium-catalyzed alkynylation reactions[8]. H_8-BINOL (**1.4**) has shown enhanced chiral induction over BINOL presumably because of the increased steric interaction between the two partially hydrogenated naphthalene rings in H_8-BINOL. 3,3'-Functionalized octahydro-BINOL **1.4** was synthesized by Pu and coworkers[8e] who revealed the potential of this ligand for asymmetric reactions. High enantioselectivity has been observed by a preliminary study of a combination of this ligand with Et_2Zn and $Ti(O^iPr)_4$ in the asymmetric addition of phenylacetylene to aromatic aldehydes (Scheme **1-8**).



Scheme 1-8 3,3'-Functionalized octahydro-BINOL-directed titanium-catalyzed alkynylation reactions

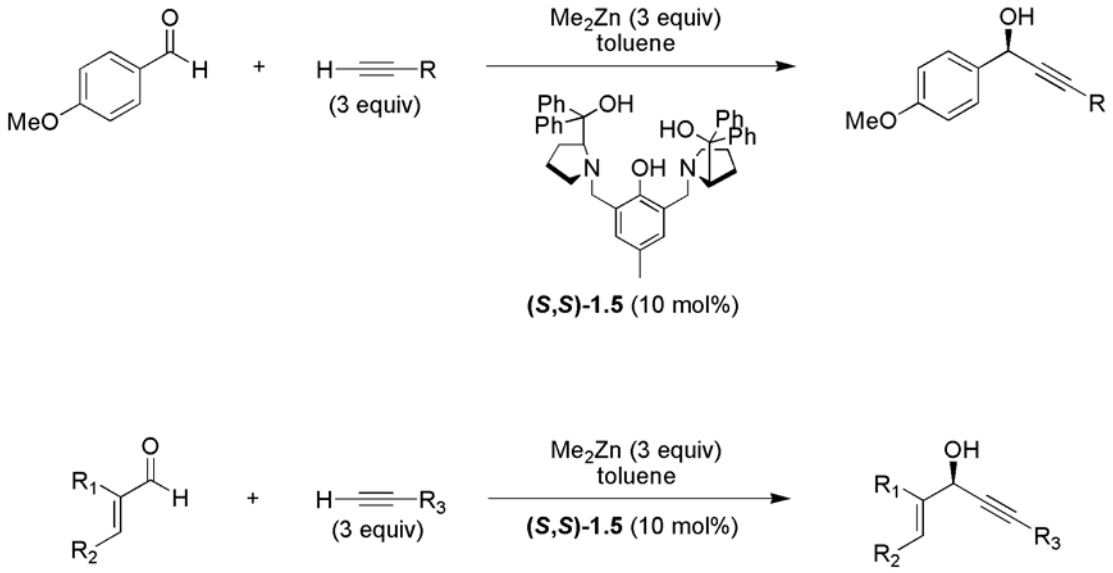
1.1.5 Dinuclear Zn-Catalyzed Asymmetric Alkynylation of Unsaturated Aldehydes

In 2005, Trost reported a practical and general alkynylation of aromatic and α,β-unsaturated aldehydes using their proline-derived bimetallic catalyst system (10 mol% of ligand **1.5** and three equivalents of dimethylzinc , Scheme **1-9**),[9] which has led to a number of efficient, catalytic, enantioselective transformations[10]. This complex successfully catalyzed alkylation of relatively unstable substrates by avoiding of stoichiometric or catalytic titanium consumption, which was often required by other chiral inducing reagent.

[8] (a) Liu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172. (b) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636.(c) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855. (d) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (e) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427. (f) Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-C. *J. Org. Chem.* **2003**, *68*, 7921.

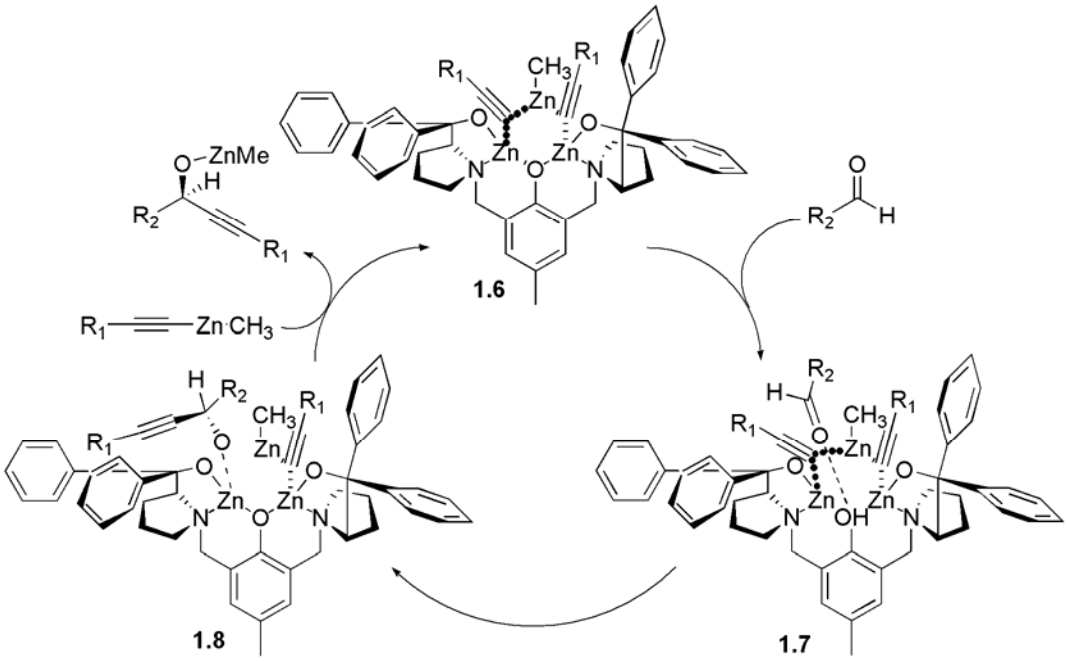
[9] Trost, B. M.; Weiss, A. H.; Wangelin, A. J. *J. Am. Chem.Soc.* **2006**, *128*, 8.

[10] (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (d) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (e) Trost, B. M.; Mino, T. *J. Am. Chem. Soc*. **2003**, *125*, 2410. (f) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc*. **2004**, *126*, 2660. (g) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc*. **2005**, *127*, 8602.



Scheme 1-9 Dinuclear Zn-catalyzed asymmetric alkynylation of unsaturated aldehydes

A catalytic cycle was proposed by Trost to rationalize the observed absolute stereo chemistry (Scheme **1-10**). First, two equivalents of zinc alkynylide are coordinated to the complex to form the intermediate **1.6**. Then, the coordination of the aldehyde to the most sterically accessible site forms intermediate **1.7**. Next, alkyne transfer sets the stereochemistry in intermediate **1.8**. The alkoxide of the product was provided by transmetalation to another molecular zinc alkynylide and the catalyst system was also regenerated.

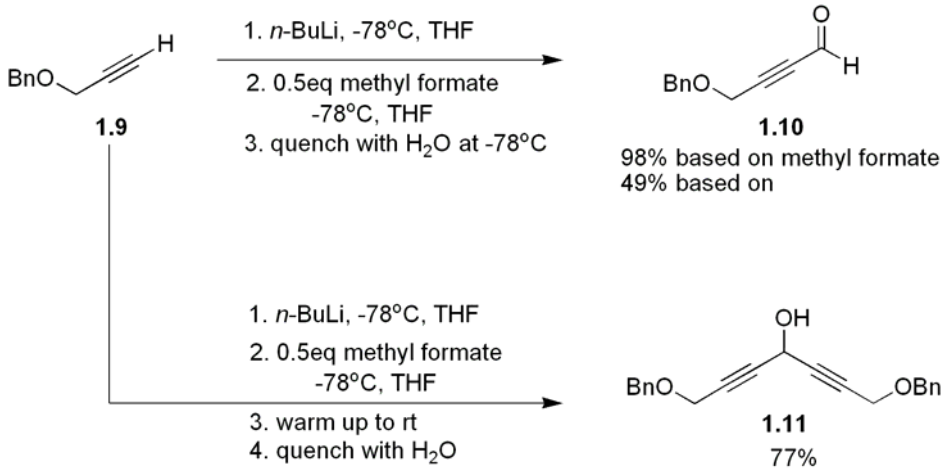


Scheme 1-10 Proposed catalytic cycle

1.2 RESULTS AND DISCUSSION

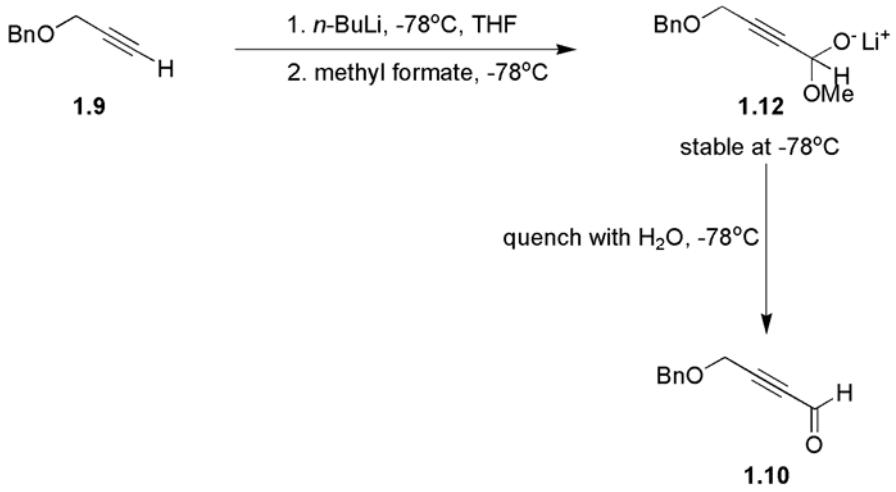
1.2.1 Cold-Quench Protocol

In the preliminary study of symmetrical secondary propargyl alcohol synthesis, when we treated two equivalents of terminal alkyne (**1.9**) anion with one equivalent of methyl formate at low temperature (-78 ^{o}C) and quenched the reaction mixture directly at low temperature without warming up, we obtained high yield aldehyde (**1.10**) without any alcohol formation. High yield of symmetrical secondary alcohol (**1.11**) could be obtained by warming up the reaction mixture to room temperature before quenching (Scheme **1-11**). Similar results were obtained by reacting other organometallic compounds with methyl formate.



Scheme 1-11 Alkynyl addition with different procedure

Presumably, the addition product of the first equivalent of alkynyl anion to methyl formate could survive the strongly basic conditions at the low temperature, and didn't react with excess alkynyl anion. We proposed that the tetrahedral intermediate (**1.12**) is stable at low temperature and will not release aldehyde (**1.10**) by eliminating methoxy anion until warming up (Scheme **1-12)**.

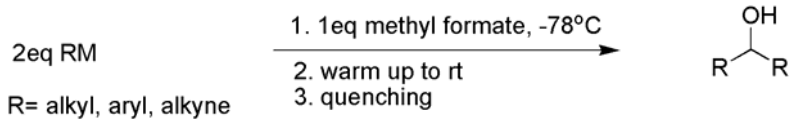


Scheme 1-12 Proposed tetrahedron intermediate

1.2.2 One-Pot Synthesis of Secondary Alcohols

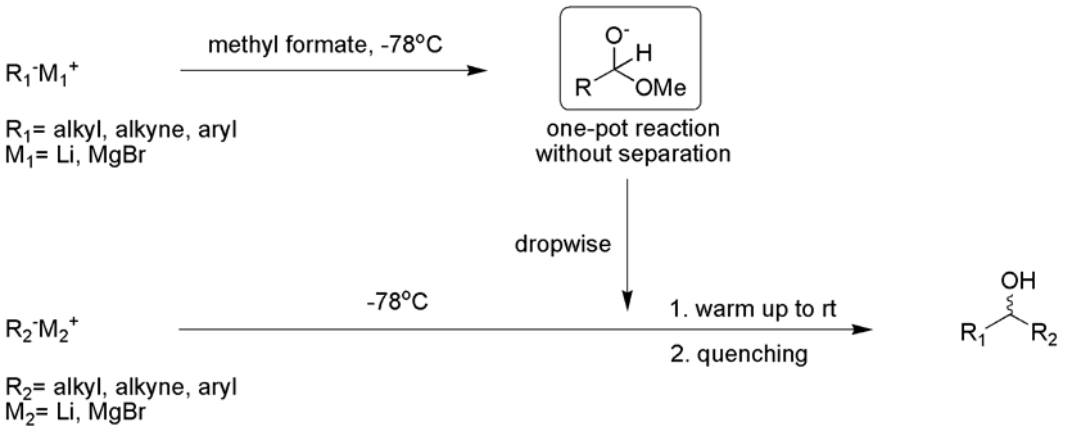
On the basis of the discovery that the outcome of nucleophilic addition of methyl formate could be controlled by the temperature and quenching timing, one-pot protocols of secondary alcohols synthesis were designed as follows.

To synthesize symmetrical secondary alcohols, two equivalents of nucleophile will be added to one of equivalent methyl formate at low temperature (-78°C). Then the resulting mixture will be warmed up to room temperature. After the consumption of starting material, the reaction mixture will be quenched with water at room temperature (Scheme **1-13**). The results of symmetrical secondary alcohol synthesis with different substitution groups will be discussed in the next section.



Scheme 1-13 Symmetrical secondary alcohol synthesis

To synthesize unsymmetrical secondary alcohols, one equivalent of nucleophile R_1M_1 will be added to one equivalent of methyl formate at low temperature (-78°C). After the consumption of starting material, the resulting mixture will be added dropwise to a pre-cooled solution of one equivalent of the other nucleophile R_2M_2. Then the resulting mixture will be warmed up to room temperature. After the addition is complete, the reaction mixture will be quenched with water at room temperature (Scheme **1-14**). The results of unsymmetrical secondary alcohol synthesis with different substitution groups will be discussed the section **1.2.2.2**.

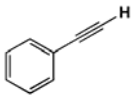
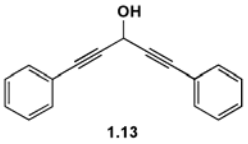
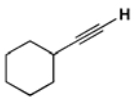
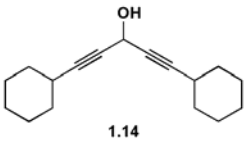
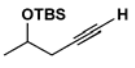
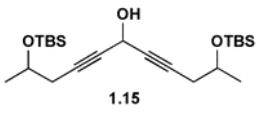
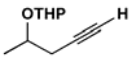
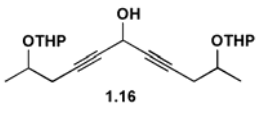
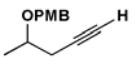
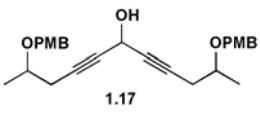


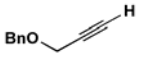
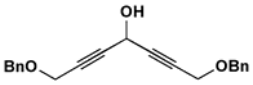
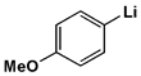
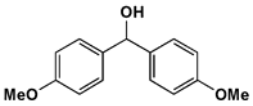
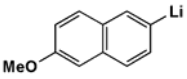
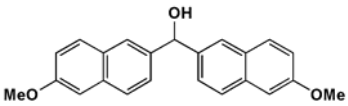
Scheme 1-14 Unsymmetrical secondary alcohol synthesis in one-pot

1.2.2.1 Symmetrical Secondary Alcohol Synthesis

Symmetrical secondary alcohols with different substitution groups were synthesized using the designed protocol. Dialkynyl alcohols were synthesized in 58-77% yields (Table **1-4**, entry 1-6); diaryl alcohols were synthesized in 62-71% yields (Table **1-4**, entry 7, 8). Dialkynyl alcohols with different protecting groups (TBS, THP, PMB) at different positions (α and β hydroxyl group) will be used as substrates for next chapter's redox isomerization study.

Table 1-4 Symmetrical secondary alcohol synthesis

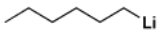
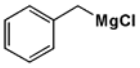
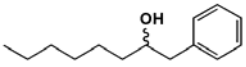
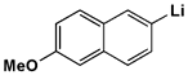
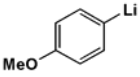
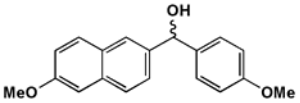
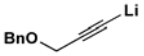
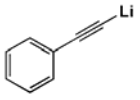
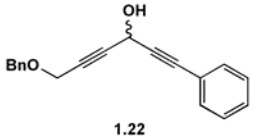
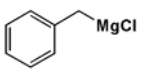
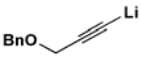
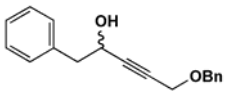
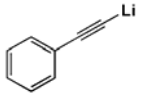
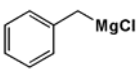
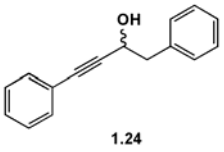
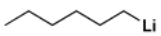
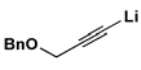
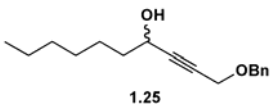
Entry	Nucleophile	Product	Yield
1		 1.13	77%
2		 1.14	68%
3		 1.15	68%
4		 1.16	58%
5		 1.17	58%

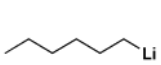
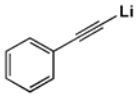
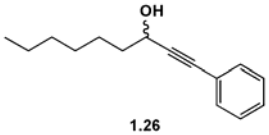
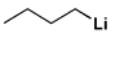
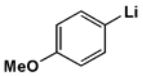
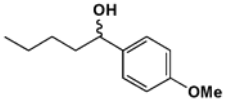
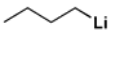
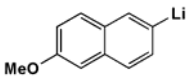
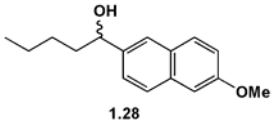
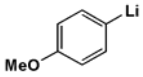
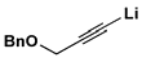
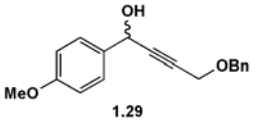
6		 1.11	72%
7		 1.18	71%
8		 1.19	62%

1.2.2.2 Unsymmetrical Secondary Alcohols Synthesis

Unsymmetrical secondary alcohols with different substitution patterns were synthesized using the designed protocol. The successful synthesis of alkyl-alkyl (Table **1-5**, entry 1), aryl-aryl (entry 2), alkyne-alkyne (entry 3), alkyl-alkyne (entry 4-7), alkyl-aryl (entry 8-9) and alkyne-aryl (entry 10) disubstituted unsymmetrical secondary alcohol displayed the wide applicability of the designed protocol.

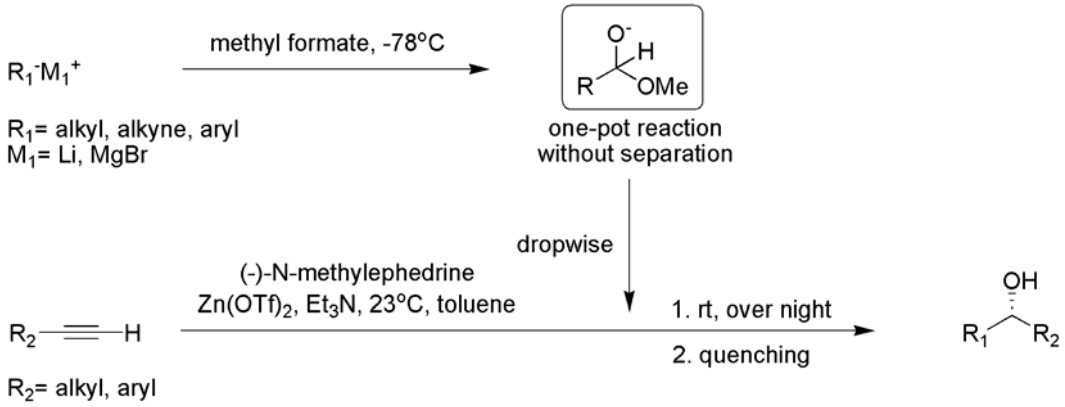
Table 1-5 One-Pot unsymmetrical secondary alcohol synthesis

Entry	Nucleophile #1	Nucleophile #2	Product	Yield
1			 1.20	79%
2			 1.21	73%
3			 1.22	75%
4			 1.23	40%
5			 1.24	63%
6			 1.25	76%

7			 1.26	74%
8			 1.27	46%
9			 1.28	52%
10			 1.29	87%

1.2.3 One-Pot Asymmetric Synthesis of Secondary Propargylic Alcohols

In order to synthesis chiral secondary propargylic alcohols in one-pot, the following protocol was designed (Scheme **1-15**). First, one equivalent of nucleophile RM is added to one equivalent of methyl formate at low temperature (-78°C). After the consumption of starting material, the resulting mixture is added dropwise to a toluene solution of zinc triflate, TEA, (-)-N-methylephedrine and alkyne at room temperature. Then as a result of increased temperature, the new formed aldehyde RCHO in the reaction mixture will simultaneously react with alkyne under the guidance of (-)-N-methylephedrine directed zinc catalyst. The target chiral secondary propargylic alcohols will be obtained after work up. The other enantiomer will be provided if (+)-N-methylephedrine is used.

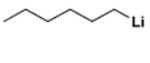
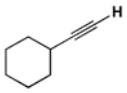
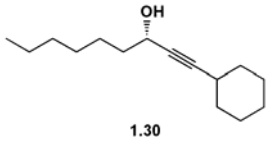
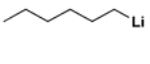
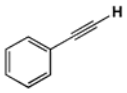
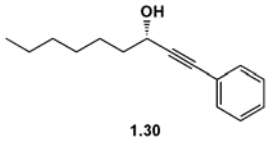
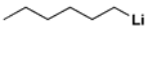
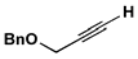
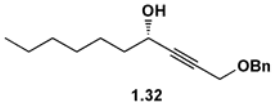
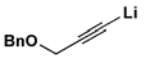
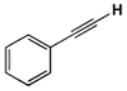
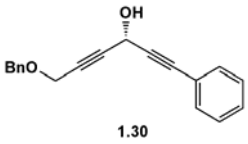
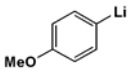
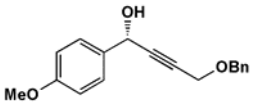
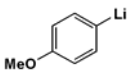
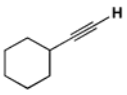
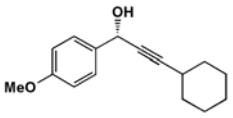
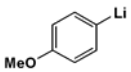
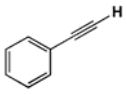
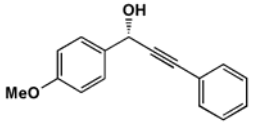
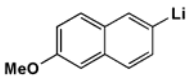
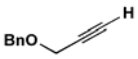
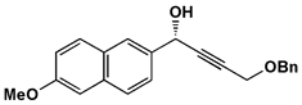


Scheme 1-15 Chiral secondary propargylic alcohol synthesis in one-pot

The results of asymmetrical secondary alcohol synthesis using this protocol are shown in table **1-6**. A wide applicability of the designed protocol was displayed by the good yields and high enantiomeric excess achieved in the synthesis of chiral propargylic alcohols with different substituent groups: alkyl-alkyl (table **1-6**, entry 1), alkyl-aryl

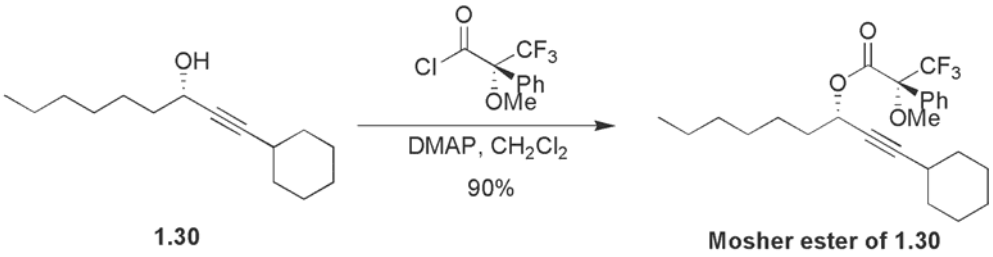
(entry 2), alkyl-alkoxymethylene (entry 3), alkoxymethylene -aryl (entry 4). The aryl-alkyl approach (entry 5 and 6), diaryl (entry 7) and alkyl-alkoxymethylene (entry 8) did not provide desired product probably due to the lack of reactivity of aryl aldehyde in the enantioselective alkynylation step.

Table 1-6 Asymmetrical approach of secondary propargylic alcohols synthesis in one-pot.

Entry	Nucleophile	Alkyne	Target Molecule	Yield	ee
1			 **1.30**	80%	99%
2			 **1.30**	71%	96%
3			 **1.32**	73%	90%
4			 **1.30**	75%	93%
5				0%	N/A
6				0%	N/A
7				0%	N/A
8				0%	N/A

1.2.4 Determination of Enantiomeric Composition of Alcohols by Making Mosher's Ester

The enantioselectivity of the asymmetric reactions discussed above was evaluated by making Mosher's ester and comparing the ^{1}H NMR integration of the different isomers (Scheme **1-16**). Careful integration showed that high enantiomeric excess was obtained by our one-pot strategy of asymmetric secondary alcohols synthesis. Synthesis of Mosher's ester of alcohol **1.30** is shown in Scheme **1-16**.



Scheme 1-16 Synthesis of Mosher's ester

1.3 CONCLUSION

Based on our cold-quench discovery, strategies leading to the synthesis of symmetrical secondary alcohols, unsymmetrical secondary alcohols and asymmetric secondary propargylic alcohols were designed. Various alcohols with different substitution groups have been successfully synthesized with moderate to good yield. Chiral secondary propargylic alcohols were obtained in high enantiomeric excess. Enantiomeric excesses were determined by carefully measuring the integration of the ^{1}H NMR of the related Mosher's esters.

1.4 EXPERIMENTAL SECTION

1.4.1 General Information

Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Lancaster, Alfa Aesar or Acros Organics. Liquid reagents were purified by distillation prior to use. Unless otherwise noted, solid reagents were used without further purification.

All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solutions and

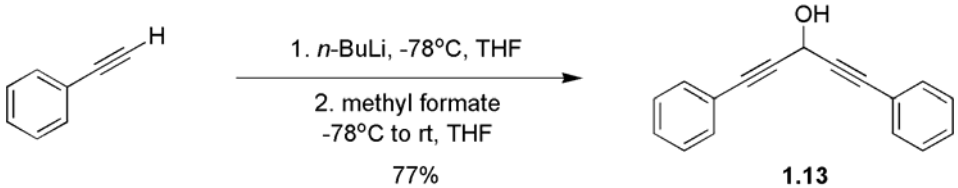
anhydrous solvents were transferred via standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. In general, the residual solvent was removed on a vacuum line at 1-1.5 torr. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. Diisopropylethylamine and triethylamine were distilled from sodium. The extracts were dried over Na_2SO_4 unless otherwise noted.

All experiments were monitored by thin layer chromatography (TLC) performed on EM Science precoated silica gel 60 F-254 glass supported plates with 0.25 mm thickness. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or to iodine vapor or by staining with a 10 % solution of phosphomolybdenic 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 Galaxy Series FT-IR 3000 infrared spectrophotometer. 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-600 (600 MHz for ^1H), Varian Inova-500 (500 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H, 100 MHz for ^{13}C), or Gemini-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). For complex multiplets, the chemical shift is given for the center of the multiplet. Coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectra were obtained with a Micromass 70-VSE spectrometer.

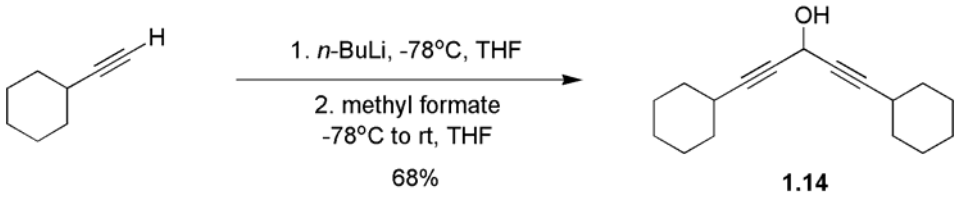
1.4.2 Experimental Procedures

1.4.2.1 Symmetrical Secondary Alcohols

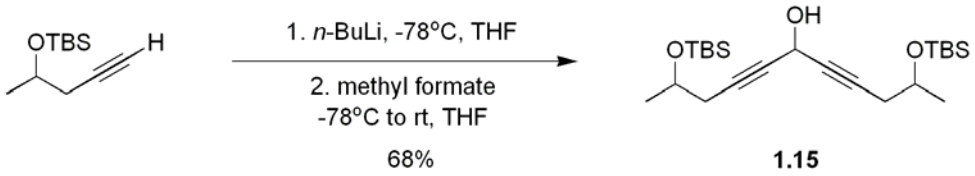


1,5-Diphenylpenta-1,4-diyn-3-ol (1.13) A sample of cyclohexylacetylene (1g, 9.80

mmol) was dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (3.92 mL, 2.50 M, 9.80 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (0.303 mL, 4.90 mmol) THF solution at -78 ^{o}C. Then the resulting mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.13** (882 mg, 77%) as a colorless oil. ^{1}H NMR (300 MH, $CDCl_3$) δ 7.45-7.53 (m, 4H), 7.29-7.39 (m, 6H), 5.59 (d, *J*= 7.6 Hz, 1H), 2.41 (d, *J*= 7.6 Hz, 1H); IR (neat) ν_{max} 3250 (br, s), 1488, 1442, 1300, 1031, 1013, 755, 689.

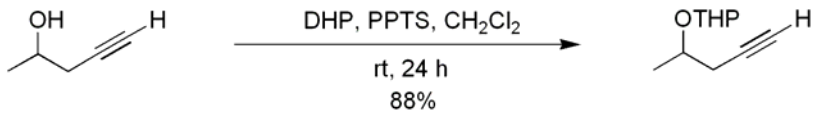


1,5-Dicyclohexylpenta-1,4-diyn-3-ol (1.14) A sample of cyclohexylacetylene (560 mg, 5.20 mmol) was dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (2.28 mL, 2.28 M, 5.20 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (0.160 mL, 2.6 mmol) THF solution at -78 ^{o}C. Then the resulting mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.14** (430 g, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.13-5.10 (dt, *J*= 7.2, 1.8 Hz, 1H), 2.44-2.37 (m, 2H), 2.04 (s, 1H), 1.81-1.23 (m, 20H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.4, 79.9, 42.7, 40.4, 36.6, 25.8, 25.3, 23.7, 21.7, 18.1, 17.8, 14.2, -4.1, -4.6; IR (neat) ν_{max} 3080, 2955, 2929, 2858, 1710, 1463, 1254, 1074, 836, 775.



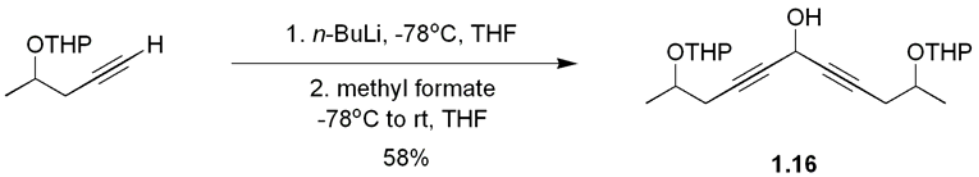
2,2,3,3,5,13,15,15,16,16-Decamethyl-4,14-dioxa-3,15-disilaheptadeca-7,10-diyn-9-ol (1.15) A sample of tert-butyldimethyl(pent-4-yn-2-yloxy)silane (506 mg, 2.55 mmol) was

dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (1.02 mL, 2.50 M, 2.55 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (0.079 mL, 1.28 mmol) THF solution at -78 ^{o}C. Then the resulting mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 4: 1) to give alcohol **1.15** (17.1 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (dt, *J*= 6.8, 2.0 Hz, 1H), 3.93 (tq, *J*= 6.9, 6.0 Hz, 1H), 2.39-2.33 (ddd, *J*= 16.48, 5.84, 2.04 Hz, 2H), 2.29-2.22 (ddd, *J*= 16.4, 7.0, 2.0 Hz, 2H), 2.18 (d, *J*= 7.1 Hz, 1H), 1.19 (d, *J* = 6.0 Hz, 6H), 0.86 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H). IR (neat) ν_{max} 3399 (br, s), 2956, 2931, 2857, 1463, 1256, 1083, 836, 776.



1.16S

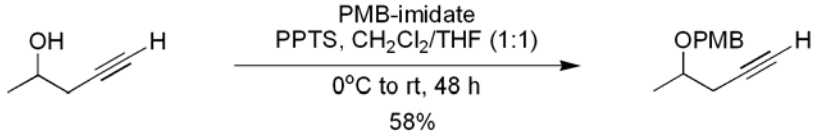
2-(pent-4-yn-2-yloxy)-tetrahydro-2H-pyran (1.16S) To a solution of pent-4-yn-2-ol (400 mg, 4.76 mmol) and PPTS (59.8 mg, 0.238 mmol) in CH_2Cl_2 (20 ml), a sample of DHP (440mg, 5.24 mmol) was added. Then the reaction mixture was stirred at room temperature for 24 h. After that, the mixture was poured into ether (40 mL) and water (50 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution, water and brine. Then the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give alkyne **1.16S** (704 mg, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77-4.70 (m, 1H), 3.99-86 (m, 2H), 3.53-3.46 (m, 1H), 2.60-2.26 (m, 2m), 2.04-1.96 (m, 1H), 1.87-1.49 (m, 6H), 1.33-1.24 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 97.4, 96.4, 70.5, 70.2, 69.3, 30.6, 30.5, 26.7, 25.3, 25.0, 20.6, 19.3, 19.1, 18.5.



1.16

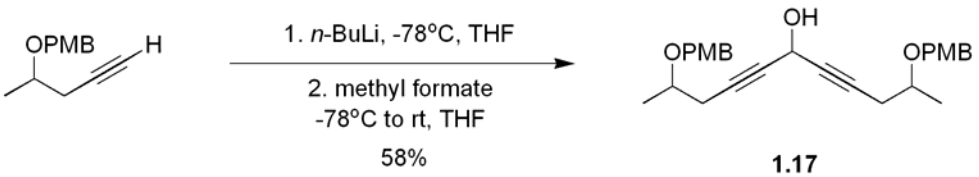
2,10-bis(tetrahydro-2H-pyran-2-yloxy)undeca-4,7-diyn-6-ol (1.16) A sample of **2.9** (200 mg, 1.09 mmol) was dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (0.524 mL, 2.50 M, 1.31 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (0.041 mL, 0.66 mmol) THF solution at -78 ^{o}C. Then the resulting mixture was stirred at –78 °C

for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.16** (125 mg, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10-5.08 (m, 1H), 4.78-4.73 (m, 2H), 3.99-3.87 (m, 4H), 3.54-3.50 (m, 2H), 3.35-3.29 (m, 1H), 2.65-2.30 (m, 4H), 1.86-1.55 (m, 12H), 1.31-1.24 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 97.9, 96.85, 96.81, 96.8, 81.82, 81.76, 81.42, 81.36, 79.8, 71.2, 70.8, 62.7, 62.5, 62.4, 52.3, 52.22, 52.19, 31.0, 30.9, 27.5, 26.2, 25.52, 25.50, 21.3, 19.8, 19.5, 19.2.



1.17S

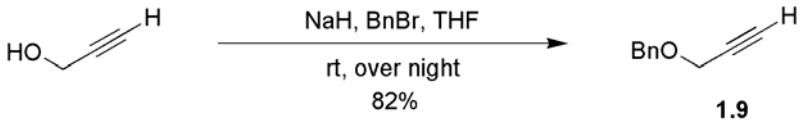
1-Methoxy-4-((pent-4-yn-2-yloxy)methyl)benzene (1.17S) A sample of pent-4-yn-2-ol (200 mg, 2.38 mmol) and PPTS (59.8mg, 0.238 mmol) was dissolved in THF/CH_2Cl_2 (20 mL, 1:1). Then the resulting solution was cooled to 0°C. To this solution, PMB-imidate (750mg, 2.62 mmol) was added slowly. After that, the reaction mixture was stirred at 0°C for 3 h and room temperature for 40 h. Then the reaction mixture was diluted with ethyl ether (50 mL) and washed with saturated $NaHCO_3$ aqueous solution, saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, H_2O and Brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give alkyne **1.17S** (306 g, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 4.50 (s, 2 H), 3.80 (s, 3 H), 3.74–3.65 (m, 1 H), 2.53-2.45 (ddd, J = 16.5, 5.1, 2.7 Hz, 1 H), 2.35 (ddd, J = 16.5, 6.9, 2.4 Hz, 1 H), 2.01 (t, J = 2.7 Hz, 1 H), 1.29-1.31 (d, J = 6 Hz, 3 H); IR (neat) ν_{max} 3291, 2973, 2932, 2911, 2868, 2837, 1613, 1513, 1248, 1097, 1035, 822, 639.



1.17

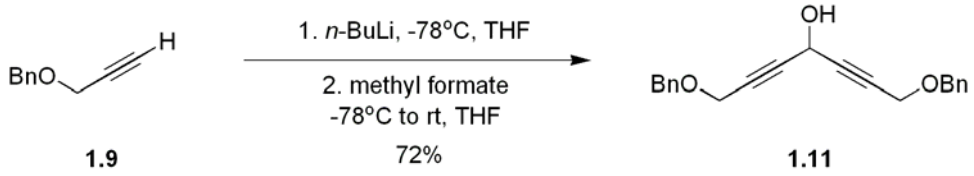
2,10-Bis(4-methoxybenzyloxy)undeca-4,7-diyn-6-ol (1.17) A sample of **1.17S** (100 mg, 0.454 mmol) was dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (0.218 mL, 2.50 M, 0.545 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (16 mg, 0.273 mmol) THF solution at -78^{o}C. Then the resulting mixture was stirred at –78 °C for two

more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give alcohol **1.17** (62 mg, 58%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.25 (m, 4H), 6.90-6.85 (m, 4H), 5.11-5.08 (m, 1H), 4.49 (s, 4H), 3.79 (s, 6H), 3.69-3.61 (m, 2H), 2.58-2.32 (m, 4H), 1.28-1.26 (d, *J*= 6.0 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.14, 130.50, 129.22, 113.77, 81.83, 79.49, 72.83, 70.34, 55.24, 52.43, 26.31, 19.69.



1.9

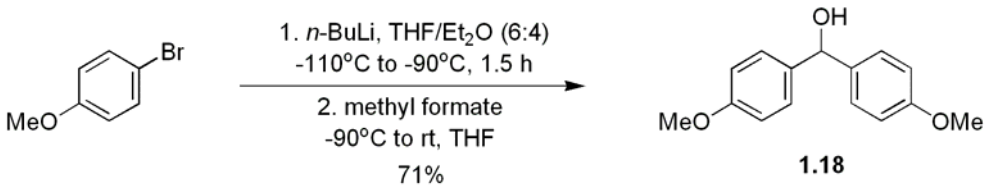
((Prop-2-ynyloxy)methyl)benzene (1.9) A sample of prop-2-yn-1-ol (8.03 g, 143 mmol) was dissolved in THF (80 mL) and the resulting solution was cooled to 0^{o}C. To this solution, a sample of NaH (3.79 g, 158 mmol) was added slowly at 0°C. Then the reaction mixture was stirred at 0°C for 1 h. After that, a sample of benzyl bromide (24.5 g, 143 mmol) was added dropwise at 0^{o}C. The resulting mixture was stirred at 0°C for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 20: 1) to give alkyne **1.9** (17.1 g, 82%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.22 (m, 5H), 4.5 (s, 2H), 4.12 (s, 1H), 2.45 (t, *J*= 2.7 Hz, 2H); IR (neat) ν_{max} 3289, 2857, 1454, 1355, 1083..



1.9 **1.11**

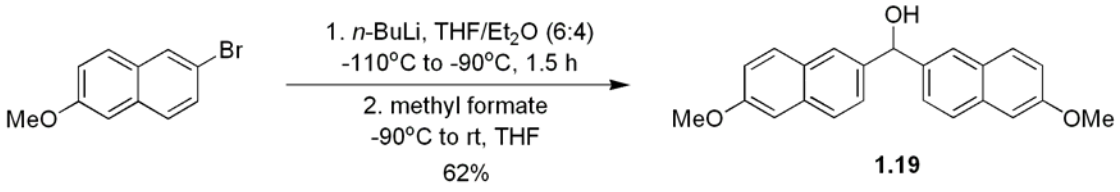
1,7-Bis(benzyloxy)hepta-2,5-diyn-4-ol (1.11) A sample of **1.9** (2.00 g, 13.7 mmol) was dissolved in THF (30 mL) and the resulting solution was cooled to -78 ^{o}C. To this solution, a sample of *n*-BuLi (6.01 mL, 2.28 M, 13.7 mmol) was added slowly at –78 °C. Then the reaction mixture was stirred at –78 °C for 2 h. After that, the reaction mixture was cannula transferred to a pre-cooled methyl formate (0.423 mL, 6.8 mmol) THF solution at -78 ^{o}C. Then the resulting mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to

column chromatography (HE: EA= 7: 1) to give alcohol **1.11** (1.57 g, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H), 5.24 (br, 1H), 4.61 (s, 4H), 4.24-4.23 (d, *J*= 1.5 Hz, 4H), 2.48-2.45 (d, *J*= 6.6 Hz, 1H); IR (neat) ν_{max} 3404, 3033, 2863, 1453, 1355, 1233, 1093.



1.18

Bis(4-methoxyphenyl)methanol (1.18) A sample of 1-bromo-4- methoxybenzene (151 mg, 0.808 mmol) was dissolved in THF/ether (6:4, 10 mL) and the resulting solution was cooled to -110 ^{o}C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then a sample of *n*-BuLi (0.354 mL, 2.28 M, 0.808 mmol) was added slowly at –110 °C. After that, the reaction mixture was stirred at –90 °C for 1.5 h. Then the reaction mixture was cannula transferred to a pre-cooled methyl formate (24 mg, 0.404 mmol) THF solution at -78 ^{o}C. The resulting mixture was stirred at –78 °C for 1/2 h and then warmed up to room temperature for 2 h. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.18** (70 mg, 71%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.25 (d, *J*= 8.7 Hz, 4H), 6.88-6.85 (d, *J*= 8.7 Hz, 4H), 5.70 (s, 1H), 3.78 (s, 6H), 2.89 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.63, 136.34, 127.59, 113.57, 75.02, 55.05. IR (solid with KBr) ν_{max} 3325 (br s), 2959, 2934, 2838, 1611, 1511, 1251, 1172, 1031, 813, 776, 554.



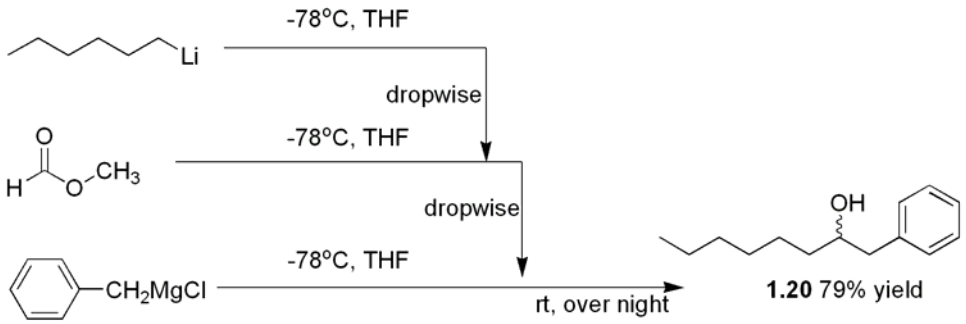
1.19

Bis(6-methoxynaphthalen-2-yl)methanol (1.19) A sample of 6-methoxy-naphthalenebromide (192 mg, 0.808 mmol) was dissolved in THF/ether (6:4, 10 mL) and the resulting solution was cooled to -110 ^{o}C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then a sample of *n*-BuLi (0.354 mL, 2.28 M, 0.808 mmol) was added slowly at –110 °C. After that, the reaction mixture was stirred at –90 °C for 1.5 h. Then the reaction mixture was cannula transferred to a pre-cooled methyl formate (24 mg, 0.404 mmol) THF solution at -78 ^{o}C. The resulting mixture was stirred at –78 °C for 1/2 h and then warmed up to room temperature for 2 h. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer

were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.19** (86 mg, 62%) as a colorless oil. ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.74-7.67 (m, 4H), 7.44-7.40 (m, 2H), 7.17-7.11 (m, 4H), 6.09 (s, 1H), 3.91 (s, 6H), 2.51 (s, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.71, 138.88, 133.99, 129.52, 128.62, 127.15, 125.46, 125.06, 118.92, 105.64, 76.34, 55.26. IR (solid with KBr) ν_{max} 3371 (br, s), 2957, 2938, 2903, 1631, 1605, 1484, 1390, 1266, 1231, 1195, 1168, 1029, 897, 854, 816, 475.

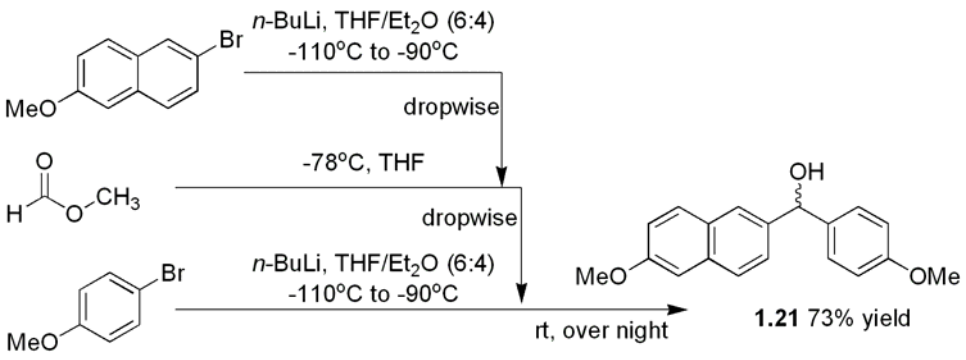
1.4.2.2 Unsymmetrical Secondary Alcohols

1.4.2.2.1 Alkyl- Alkyl



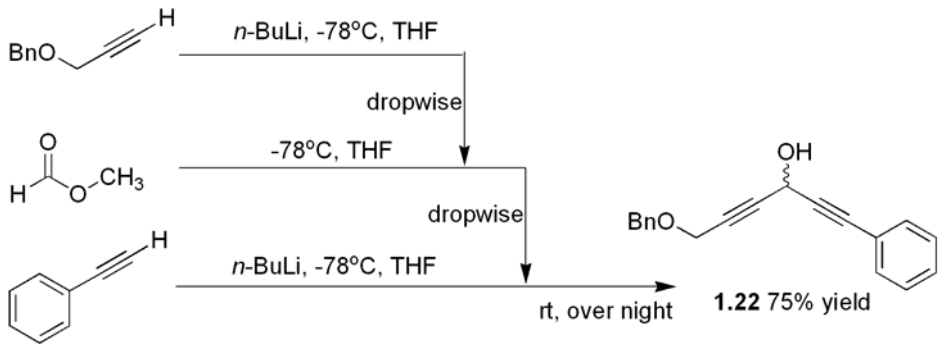
1-Phenyloctan-2-ol (1.20) A hexyllithium THF solution (0.543 mL, 1.0 M, 0.543 mmol) was added dropwise to a pre-cooled methyl formate (34.2 mg, 0.570 mmol) THF solution at -78 ^{o}C. The resulting mixture was stirring for 2 h at -78 °C to afford solution **A**. At the same time, a sample of benzyl magnesium chloride (0.272 mL, 2.0 M, 0.543 mmol) THF solution was cooled to -78 ^{o}C. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give alcohol **1.20** (88.4 mg, 79%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.26-7.21 (m, 3H), 3.82-3.78 (m, 1H), 2.85-2.62 (AB, 2H), 1.63 (bs, 1H), 1.54-1.51 (m, 2H), 1.39-1.26 (m, 8H), 0.92-0.89 (t, *J*= 6.4 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 138.8, 129.5, 128.6, 126.5, 72.9, 44.3, 37.1, 32.1, 29.6, 26.0, 22.9, 14.3. IR (neat) ν_{max} 3376(br, s), 2929, 2857, 1495, 1455, 1080, 1032, 744, 699.

1.4.2.2.2 Aryl-Aryl



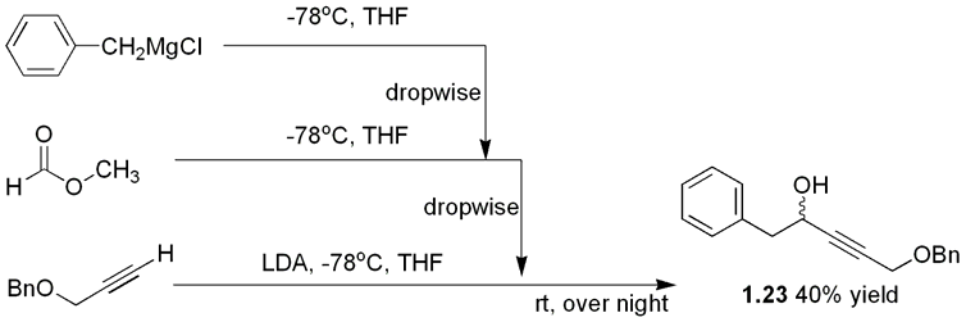
(6-Methoxynaphthalen-2-yl)(4-methoxyphenyl)methanol (1.21) A sample of 2-bromo-6-methoxynaphthalene (80 mg, 0.337 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110 ^{o}C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.148 mL, 2.5 M, 0.371 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate (22.3 mg, 0.371 mmol) solution at -78 ^{o}C. The resulting mixture was stirred for 2 h at -78^{o}C to afford solution **A**. At the same time, a sample of 1-bromo-4-methoxybenzene (63.0 mg, 0.337 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110 ^{o}C. Then *n*-BuLi (0.148 mL, 2.5 M, 0.371 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give alcohol **1.21** (72.4 mg, 73%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.73-7.67 (m, 2H), 7.39-7.37 (dd, *J*= 8.4, 1.6 Hz, 1H), 7.32-7.30 (d, *J*= 8.8 Hz, 2H), 7.18-7.15 (dd, *J*= 9.2, 2.8 Hz, 1H), 7.121-7.116 (d, *J*= 2.0 Hz, 1H), 6.88-6.85 (d, *J*= 8.8 Hz, 2H), 5.89 (s, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 2.63 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 159.0, 157.7, 139.3, 136.2, 134.0, 129.6, 128.7, 128.1, 127.2, 125.5, 124.8, 119.0, 113.9, 105.8, 76.0, 55.5, 55.4. IR (solid in KBr) ν_{max} 3285 (br, s), 2961, 2939, 1607, 1509, 1257, 1169, 1031, 854, 817.

1.4.2.2.3 Alkyne – Alkyne



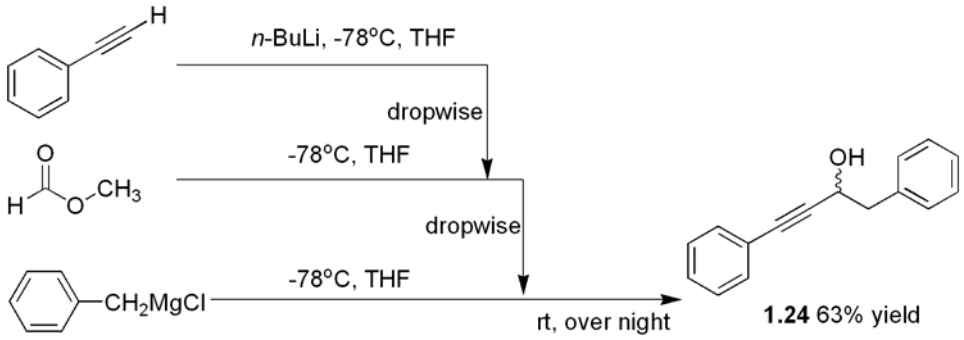
6-(Benzyloxy)-1-phenylhexa-1,4-diyn-3-ol (1.22) To a **1.9** (650mg, 4.45 mmol) THF solution at -78 ^{o}C, a pre-cooled LDA (2.97 mL, 1.8M, 5.34 mmol) THF solution was cannula transferred at -78 ^{o}C. Then the resulting mixture was stirred for 2 h at -78^{o}C. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate (267 mg, 4.45 mmol) solution at -78 ^{o}C. The resulting mixture was stirred for 2 h at -78^{o}C to afford solution **A**. At the same time, to an ethynylbenzene (476 mg, 4.67 mmol) THF solution at -78 ^{o}C, an aliquot of LDA (3.11 mL, 1.8 M, 5.61 mmol) was added slowly at –78 °C. Then the resulting mixture was stirred for 2 h at -78^{o}C. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.22** (920 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.38-7.29 (m, 8H), 5.42-5.40 (d, *J*= 7.6 Hz, 1H), 4.63 (s, 2H), 4.26 (d, *J*= 1.6 Hz, 2H), 2.32-2.30 (d, *J*= 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.77, 128.82, 128.38, 128.24, 128.07, 127.86, 85.73, 84.58, 83.62, 80.82, 71.84, 57.34, 52.80. IR (neat) ν_{max} 3375 (br, s), 3063, 3032, 2856, 1620, 1489, 1454, 1443, 1386, 1354, 1301, 1262, 1164, 1123, 1085, 1071, 1030.

1.4.2.2.4 Alkyne – Alkyl

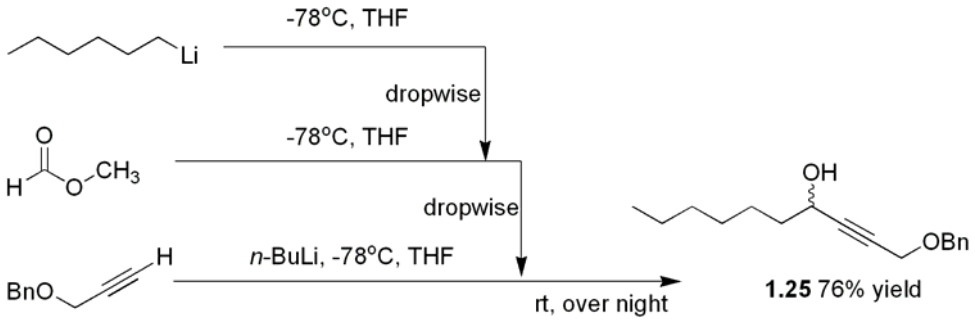


5-(Benzyloxy)-1-phenylpent-3-yn-2-ol (1.23) To a methyl formate (103 mg, 1.72 mmol) THF solution at -78^{o}C, a pre-cooled benzyl magnesium chloride solution (0.860 mL, 2.0 M, 1.72 mmol) THF solution was cannula transferred at -78 ^{o}C. Then the resulting

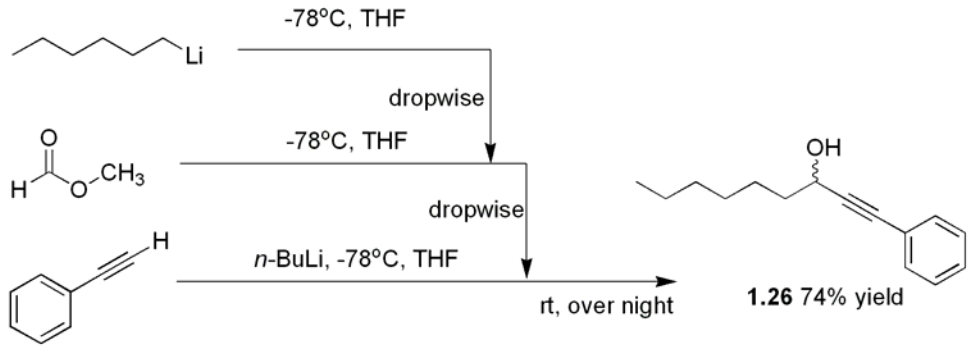
mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, to a 209 mg **1.9** (1.43 mmol) THF solution at -78 °C, a pre-cooled LDA (1.59 mL, 1.8 M, 0.912 mmol) THF solution was cannula transferred. Then the mixture was stirred for 2 h at -78°C. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.23** (150 mg, 40%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.33 (m, 10H), 4.73-4.71 (m, 1H), 4.63 (s, 2H), 4.28-4.27 (d, *J*= 1.5 Hz, 2H), 3.12-3.10 (d, *J*= 6.6 Hz, 2H), 2.49-2.47 (d, *J*= 5.7 Hz, 1H). IR (neat) ν_{max} 3094 (br, s), 3029, 2924, 2858, 1495, 1454, 1354, 1121, 1071, 1031, 740, 700.



1,4-Diphenylbut-3-yn-2-ol (1.24) To an ethynylbenzene (93 mg, 0.912 mmol) THF solution at -78 °C, a pre-cooled *n*-BuLi (58.4 mg, 0.912 mmol) THF solution was cannula transferred at -78°C. Then the resulting mixture was stirred for 2 h at -78 °C. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate (57.4 mg, 0.957 mmol) solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a sample of benzyl magnesium chloride (0.502 mL, 2.0M, 1.00 mmol) THF solution was cooled to -78 °C. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.24** (128 mg, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.30 (m, 10H), 4.90-4.89 (m, 1H), 3.21-3.18 (dd, *J*= 6.0, 0.9 Hz, 1H), 2.20 (br s, 1H).



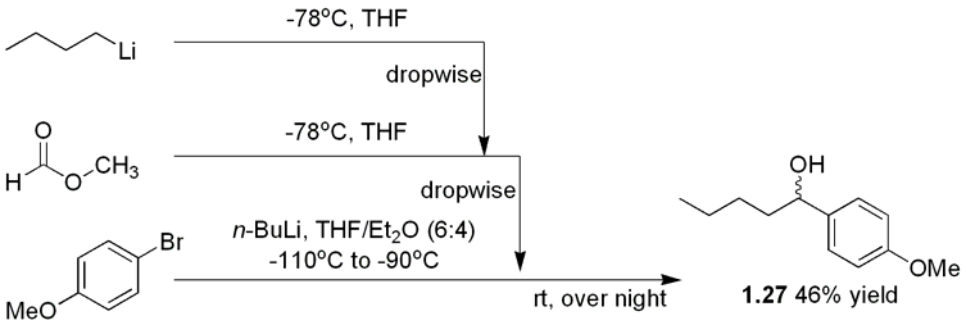
1-(Benzyloxy)dec-2-yn-4-ol (1.25) To a methyl formate (57 mg, 0.95 mmol) THF solution at -78°C, a pre-cooled hexyllithium (0.435 mL, 2.3 M, 1.00 mmol) THF solution was cannula transferred. Then the mixture was stirred for 2 h at -78 °C to afford solution **A**. At the same time, a 146 mg (1.00 mmol) of **1.9** was dissolved in THF (30 mL) and cooled to -78 °C. Then an aliquot of *n*-BuLi (0.625 mL, 1.6M, 1.00 mmol) was added slowly at –78 °C. The resulting mixture was stirred at –78 °C for 2 h. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.25** (198 mg, 76%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.60 (s, 2H), 4.44-4.39 (t, *J*= 6.6 Hz, 1H), 4.21 (d, *J*= 1.5 Hz, 2H), 2.16 (br, 1H), 1.75-1.67 (m, 2H), 1.48-1.30 (m, 8H), 0.91-0.87 (m, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 137.33, 128.37, 128.03, 127.82, 87.81, 80.51, 71.54, 62.40, 57.35, 37.69, 31.68, 28.87, 25.07, 22.51, 14.00; IR (neat) ν_{max} 3399 (br s), 2952, 2928, 2857, 1455, 1345, 1107, 1071, 1027, 738, 698.



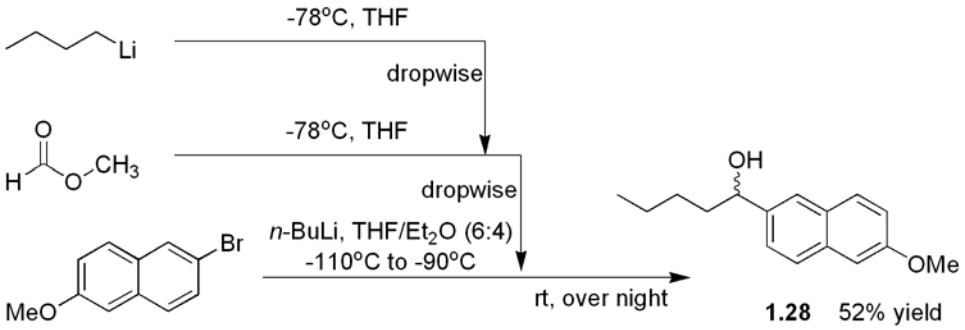
1-Phenylnon-1-yn-3-ol (1.26) To a methyl formate (57 mg, 0.95 mmol) THF solution at -78°C, a pre-cooled hexyllithium (0.435 mL, 2.3 M, 1.00 mmol) THF solution was cannula transferred. Then the mixture was stirred for 2 h at -78 °C to afford solution **A**. At the same time, a 102 mg (1.00 mmol) of ethynylbenzene was dissolved in THF (30 mL) and cooled to -78 °C. Then an aliquot of *n*-BuLi (0.625 mL, 1.6M, 1.00 mmol) was added slowly at –78 °C. The resulting mixture was stirred at –78 °C for 2 h. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was

warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.26** (159 mg, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.26 (m, 5H), 4.61-4.58 (t, *J*= 6.8 Hz, 1H), 2.02 (m, 1H), 1.83-1.77 (m, 2H), 1.54-1.29 (m, 8H), 0.90-0.87 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.57, 128.22, 128.17, 122.63, 84.75, 72.04, 62.99, 37.98, 31.88, 29.03, 25.68, 22.66, 14.16.

1.4.2.2.5 Aryl – Alkyl

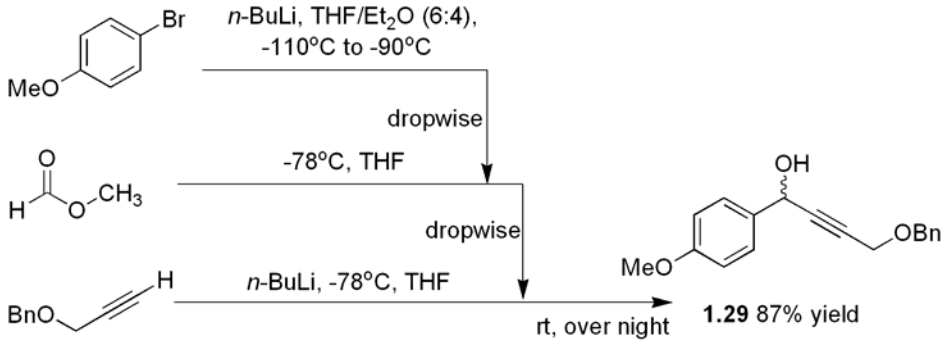


1-(4-Methoxyphenyl)pentan-1-ol (1.27) An *n*-BuLi THF solution (0.351 mL, 2.3 M, 0.808 mmol) was added dropwise to a pre-cooled methyl formate (49 mg, 0.808 mmol) THF solution at -78 °C. The resulting mixture was stirring for 2 h at -78 °C to afford solution **A**. At the same time, a sample of 1-bromo-4-methoxybenzene (152 mg, 0.808 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110 °C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.27** (72 mg, 46%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J*= 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.57 (t, *J* = 6.7 Hz, 1H), 3.78 (s, 3H), 2.23-2.04 (br s, 1H), 1.88-1.56 (m, 2H), 1.48-1.13 (m, 4H), 0.87 (t, *J*= 6.9 Hz, 3H).



1-(6-Methoxynaphthalen-2-yl)pentan-1-ol (1.28) An *n*-BuLi THF solution (0.351 mL, 2.3 M, 0.808 mmol) was added dropwise to a pre-cooled methyl formate (49 mg, 0.808 mmol) THF solution at -78 °C. The resulting mixture was stirring for 2 h at -78 °C to afford solution **A**. At the same time, a sample of 2-bromo-6- methoxynaphthalene (192 mg, 0.808 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110 °C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.28** (102 mg, 52%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.67 (m, 3H), 7.46-7.42 (m, 1H), 7.18-7.13 (m, 2H), 4.78-4.74 (t, *J*= 6.9 Hz, 1H), 3.91 (s, 3H), 2.27 (s, 1H), 1.87-1.77 (m, 2H), 1.39-1.24 (m, 4H), 0.92-0.87 (t, *J*= 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 157.50, 139.96, 133.98, 129.32, 128.61, 127.00, 124.63, 124.49, 118.80, 105.59, 74.69, 55.21, 38.55, 27.96, 22.57, 13.97; IR (solid with KBr) ν_{max} 3379 (br s), 2953, 2934, 2870, 1608, 1510, 1465, 1433, 1389, 1265, 1229, 1173, 1158, 1033, 855, 817.

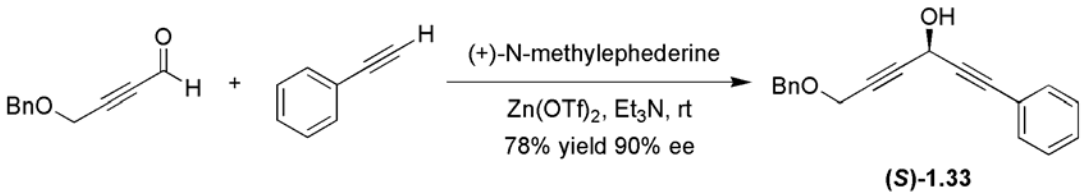
1.4.2.2.6 Aryl-Alkyne



4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-ol (1.29) A sample of 1-bromo-4-methoxybenzene (187 mg, 1.00 mmol) was dissolved in THF/ether (6:4, 10 mL) and the

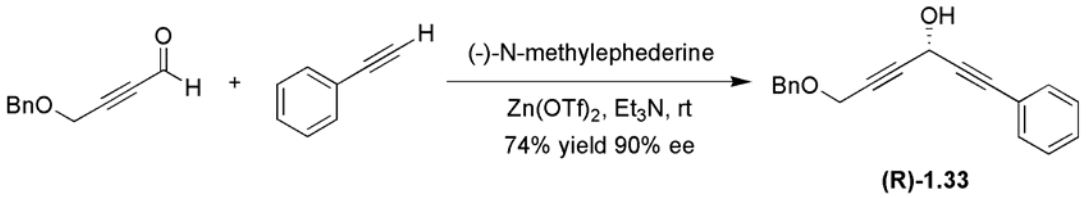
solution was cooled down to -110°C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.625 mL, 1.6 M, 1.00 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate (60 mg, 1.00 mmol) solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 161mg (1.10 mmol) of **1.9** was dissolved in THF (30 mL) and cooled to -78 °C. Then an aliquot of *n*-BuLi (0.687 mL, 1.6M, 1.10 mmol) was added slowly at –78 °C. The resulting mixture was stirred at –78 °C for 2h. Then solution **A** was added dropwise via cannula transfer. After stirring to homogeneous, the mixture was warming up to room temperature over night. Then the solution was diluted in ethyl acetate (40 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The organic layer were combined, washed with brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.29** (245 mg, 87%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.36-7.29 (m, 4H), 6.93-6.89 (m, 2H), 5.46 (br, 1H), 4.61 (s, 2H), 4.26 (d, *J*= 1.6 Hz, 2H), 3.81 (s, 3H), 2.66-2.64 (d, *J*= 4.2 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.45, 137.15, 132.67, 128.28, 127.95, 127.89, 127.74, 113.82, 86.55, 82.25, 71.62, 60.07, 57.40, 55.27; IR (neat) ν_{max} 3368 (br s), 2929, 2855, 2838, 1620, 1512, 1249, 1085, 1072, 1047, 1033.

1.4.2.3 Enantioselective Additions of Terminal Alkynes to Aldehydes



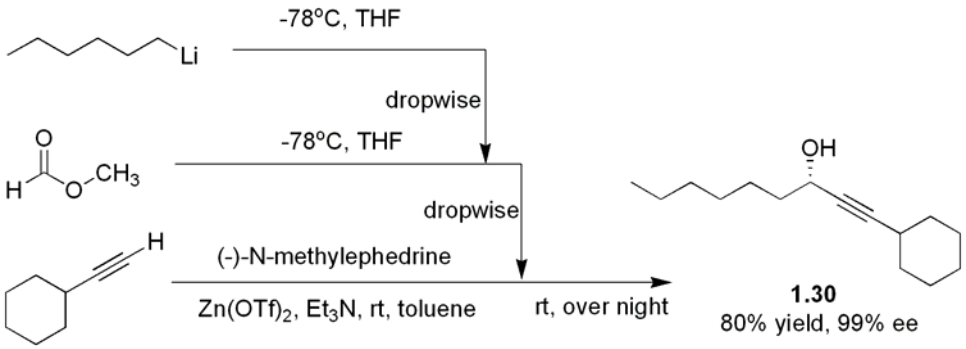
(*S*)-6-(Benzyloxy)-1-phenylhexa-1,4-diyn-3-ol ((*S*)-1.33) A 10 mL flask was charged with $Zn(OTf)_2$ (200 mg, 0.55 mmol) and (-)-N-methylephedrine (107 mg, 0.60 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (61 mg, 0.60 mmol). The resulting mixture was stirred at 23°C for 2 h before the ethynylbenzene (51 mg, 0.50 mmol) was added by syringe in one portion. After 15 min of stirring a 87mg of 4-(benzyloxy)but-2-ynal (0.50 mmol) was added in one portion by syringe. Then the mixture was kept stirring for another 2 h. After that, the reaction was quenched by the addition of saturated NH_4Cl aqueous solution (20 mL). The resulting mixture was poured into a separatory funnel containing ethyl acetate (30 mL). The layers were separated and the organic layer was washed with 10 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.33** (107 mg, 78%, 90% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.38-7.29 (m, 8H), 5.42-5.40 (d, *J*= 7.6 Hz, 1H), 4.63 (s, 2H), 4.26 (d, *J*= 1.6 Hz, 2H), 2.32-2.30 (d, *J*= 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.77, 128.82, 128.38, 128.24, 128.07, 127.86,

85.73, 84.58, 83.62, 80.82, 71.84, 57.34, 52.80. IR (neat) ν_{max} 3375 (br, s), 3063, 3032, 2856, 1620, 1489, 1454, 1443, 1386, 1354, 1301, 1262, 1164, 1123, 1085, 1071, 1030.



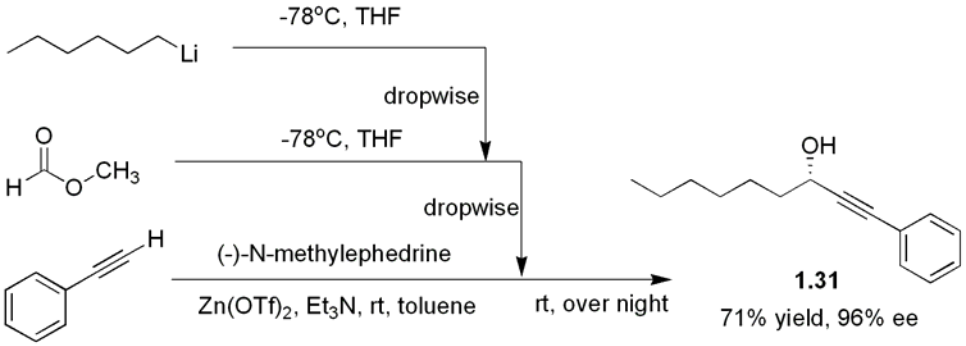
(*R*)-6-(Benzyloxy)-1-phenylhexa-1,4-diyn-3-ol (1.33) A 10 mL flask was charged with $Zn(OTf)_2$ (200 mg, 0.55 mmol) and (-)-N-methylephedrine (107 mg, 0.60 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (61 mg, 0.60 mmol). The resulting mixture was stirred at 23°C for 2 h before the ethynylbenzene (51 mg, 0.50 mmol) was added by syringe in one portion. After 15 min of stirring a 87mg of 4-(benzyloxy)but-2-ynal (0.50 mmol) was added in one portion by syringe. Then the mixture was kept stirring for another 2 h. After that, the reaction was quenched by the addition of saturated NH_4Cl aqueous solution (20 mL). The resulting mixture was poured into a separatory funnel containing ethyl acetate (30 mL). The layers were separated and the organic layer was washed with 10 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.33** (103 mg, 74%, 90% ee) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.38-7.29 (m, 8H), 5.42-5.40 (d, *J*= 7.6 Hz, 1H), 4.63 (s, 2H), 4.26 (d, *J*= 1.6 Hz, 2H), 2.32-2.30 (d, *J*= 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.77, 128.82, 128.38, 128.24, 128.07, 127.86, 85.73, 84.58, 83.62, 80.82, 71.84, 57.34, 52.80. IR (neat) ν_{max} 3375 (br, s), 3063, 3032, 2856, 1620, 1489, 1454, 1443, 1386, 1354, 1301, 1262, 1164, 1123, 1085, 1071, 1030.

1.4.2.4 One-Pot Enantioselective Synthesis of Secondary Propargylic Alcohols

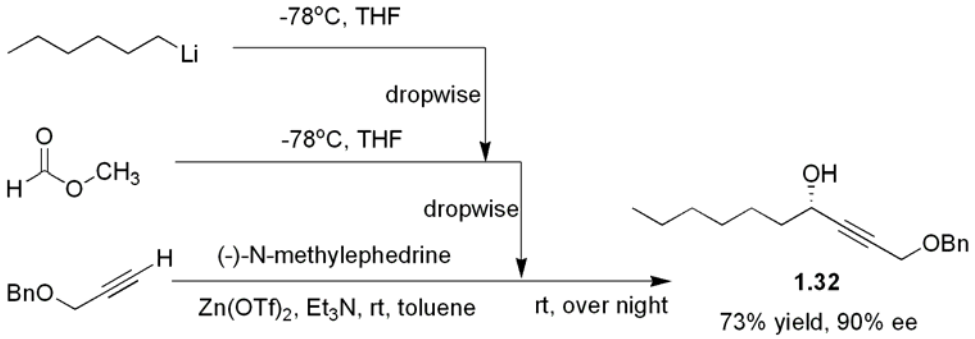


(*S*)-1-Cyclohexylnon-1-yn-3-ol (1.30) To a methyl formate (66 mg, 1.10 mmol) THF solution at -78°C, a pre-cooled hexyllithium THF solution (0.435 ml, 2.3M, 1.00 mmol) was cannula transferred. Then the mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the

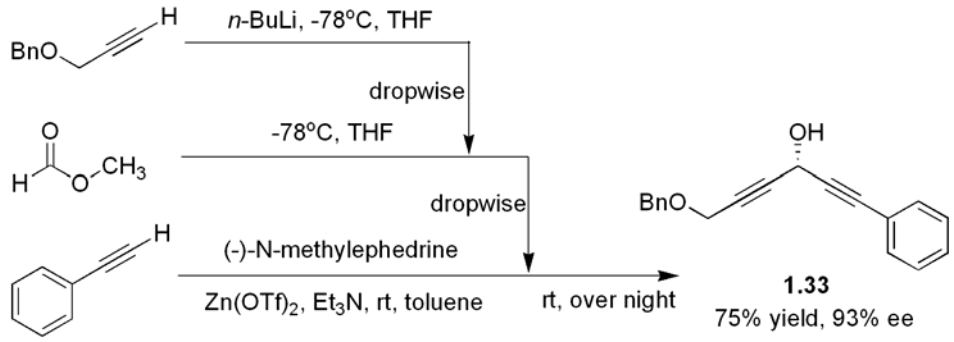
flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before ethynylcyclohexane (108 mg, 0.50 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with 30 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.30** (178 mg, 80%, 99% ee) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37-4.32 (d, *J*= 6.6, 1.8 Hz, 4H), 2.42-2.36 (m, H), 1.81-1.57 (m, 5H), 1.49-1.29 (m, 14H), 0.90-0.86 (t, *J*= 6.3 Hz, 1H); IR (neat) ν_{max} 3341 (br s), 2929, 2855, 2838, 1449, 1042, 1029.



(*S*)-1-Phenylnon-1-yn-3-ol (1.31) To a methyl formate (66 mg, 1.10 mmol) THF solution at -78°C, a pre-cooled hexyllithium THF solution (0.435 ml, 2.3M, 1.00 mmol) was cannula transferred. Then the mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before ethynylbenzene (102 mg, 1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with 30 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.31** (154 mg, 71%, 96% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.26 (m, 5H), 4.61-4.58 (t, *J*= 6.8 Hz, 1H), 2.02 (m, 1H), 1.83-1.77 (m, 2H), 1.54-1.29 (m, 8H), 0.90-0.87 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.57, 128.22, 128.17, 122.63, 84.75, 72.04, 62.99, 37.98, 31.88, 29.03, 25.68, 22.66, 14.16.

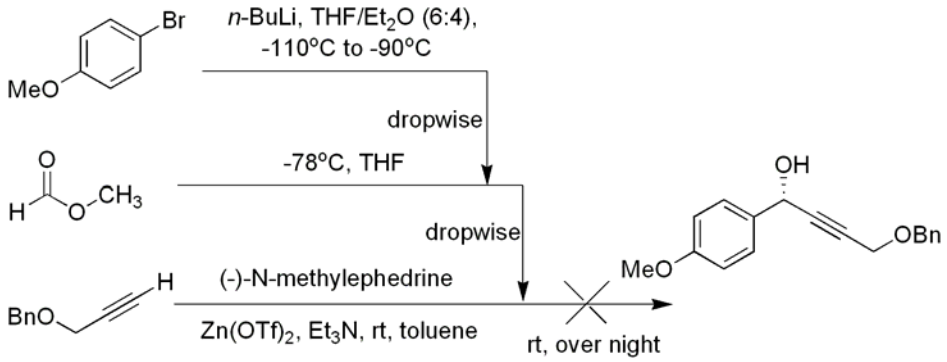


(*S*)-1-(Benzyloxy)dec-2-yn-4-ol (1.32) To a methyl formate (66 mg, 1.10 mmol) THF solution at -78°C, a pre-cooled hexyllithium THF solution (0.435 ml, 2.3M, 1.00 mmol) was cannula transferred. Then the mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before alkyne **1.9** (146 mg, 1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with 30 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.32** (190 mg, 73%, 90% ee) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 4.60 (s, 2H), 4.44-4.39 (t, *J*= 6.6 Hz, 1H), 4.21 (d, *J*= 1.5 Hz, 2H), 2.16 (br, 1H), 1.75-1.67 (m, 2H), 1.48-1.30 (m, 8H), 0.91-0.87 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 137.33, 128.37, 128.03, 127.82, 87.81, 80.51, 71.54, 62.40, 57.35, 37.69, 31.68, 28.87, 25.07, 22.51, 14.00; IR (neat) ν_{max} 3399 (br s), 2952, 2928, 2857, 1455, 1345, 1107, 1071, 1027, 738, 698.



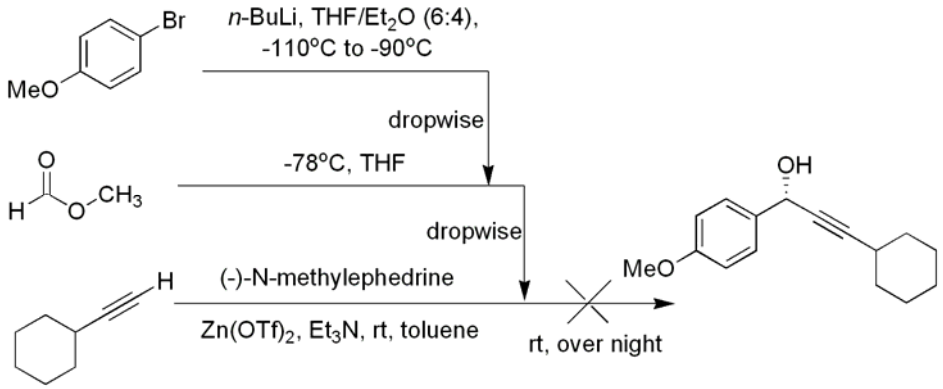
(*R*)-6-(Benzyloxy)-1-phenylhexa-1,4-diyn-3-ol (1.33) To a **1.9** (146 mg, 1.00 mmol) THF solution at -78°C, a pre-cooled *n*-BuLi THF solution was cannula transferred. Then

the mixture was stirred for 2 h at -78°C. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-Methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before the ethynylbenzene (102 mg, 1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with 30 mL brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 7: 1) to give alcohol **1.33** (209 mg, 75%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.38-7.29 (m, 8H), 5.42-5.40 (d, *J*= 7.6 Hz, 1H), 4.63 (s, 2H), 4.26 (d, *J*= 1.6 Hz, 2H), 2.32-2.30 (d, *J*= 7.6 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.77, 128.82, 128.38, 128.24, 128.07, 127.86, 85.73, 84.58, 83.62, 80.82, 71.84, 57.34, 52.80. IR (neat) ν_{max} 3375 (br, s), 3063, 3032, 2856, 1620, 1489, 1454, 1443, 1386, 1354, 1301, 1262, 1164, 1123, 1085, 1071, 1030.

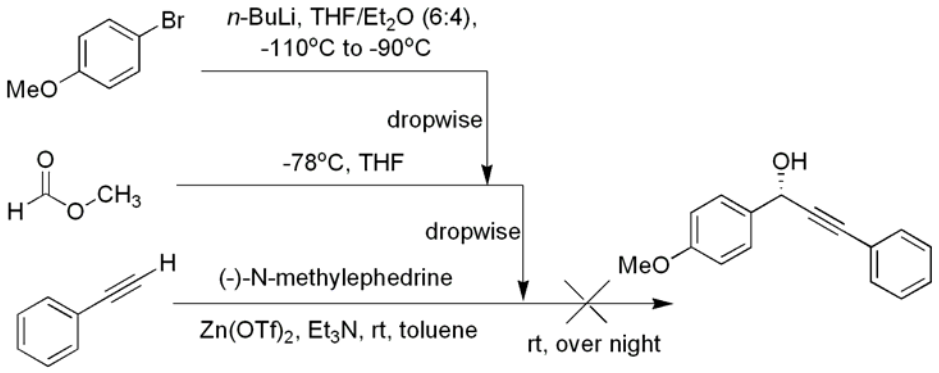


One-pot approach towards (S)-4-(benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-ol A sample of 1-Bromo-4-methoxy-benzene (187 mg, 1.00 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110°C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.687 mL, 1.6 M, 1.10 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before a 146 mg of **1.9** (1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was

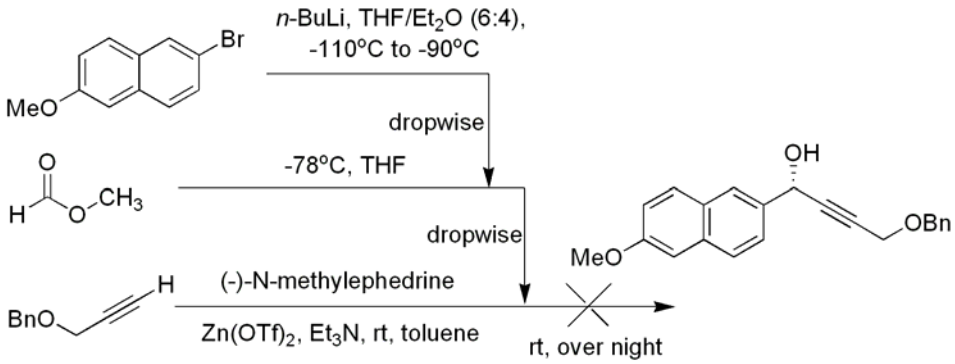
kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The TLC and NMR analysis of the resulting oil showed that no desired product was produced. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give 4-methoxybenzaldehyde (118 mg, 81%) as a pale yellow oil.



One-pot approach towards (S)-3-cyclohexyl-1-(4-methoxyphenyl)prop-2-yn-1-ol A sample of 1-Bromo-4-methoxy-benzene (187 mg, 1.00 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110°C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.687 mL, 1.6 M, 1.10 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before a 108 mg of ethynylcyclohexane (1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The TLC and NMR analysis of the resulting oil showed that no desired product was produced. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give 4-methoxybenzaldehyde (108 mg, 74%) as a pale yellow oil.



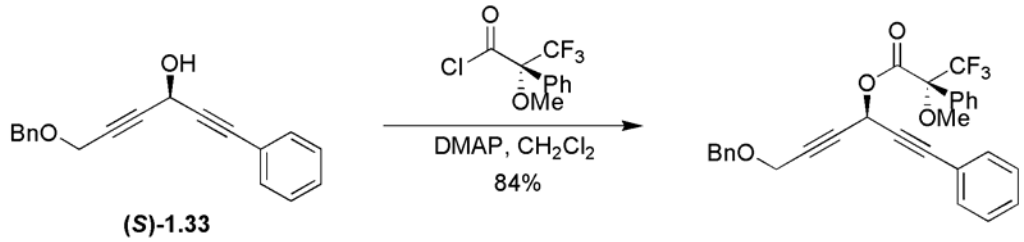
One-pot approach towards (*S*)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol A sample of 1-Bromo-4-methoxy-benzene (187 mg, 1.00 mmol) was dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110°C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.687 mL, 1.6 M, 1.10 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-methylephedrine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before a 102 mg of ethynylbenzene (1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The TLC and NMR analysis of the resulting oil showed that no desired product was produced. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give 4-methoxybenzaldehyde (106 mg, 73%) as a pale yellow oil.



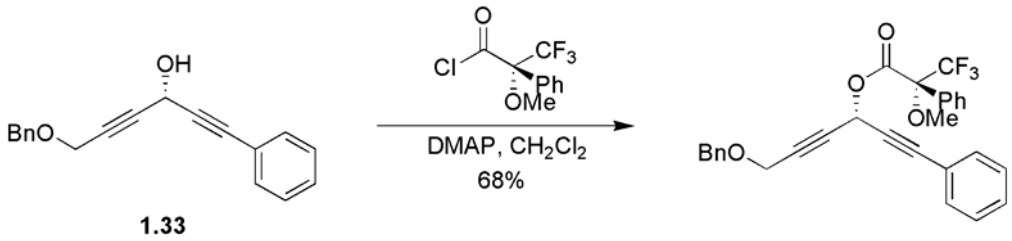
One-pot approach towards (S)-4-(benzyloxy)-1-(6-methoxynaphthalen-2-yl)but-2-yn-1-ol A sample of 2-bromo-6-methoxynaphthalene (187 mg, 1.00 mmol) was

dissolved in THF/ether (6:4, 10 mL) and the solution was cooled down to -110°C. The –110 °C bath was prepared by adding liquid N_2 to a mixture of 100 mL methanol, 100 mL hexanes and 50 mL acetone. Then *n*-BuLi (0.687 mL, 1.6 M, 1.10 mmol) was added slowly at –110 °C. The reaction mixture was stirred at –90 °C for 1.5 h. After that, the reaction mixture was added dropwise to a pre-cooled methyl formate solution at -78 °C. The resulting mixture was stirred for 2 h at -78°C to afford solution **A**. At the same time, a 10 mL flask was charged with $Zn(OTf)_2$ (400 mg, 1.10 mmol) and (-)-N-Methylephederine (215 mg, 1.20 mmol) and purged with Argon for 15 min. To the flask was added toluene (5 mL) and triethylamine (121 mg, 1.20 mmol). The resulting mixture was stirred at 23°C for 2 h before a 146 mg of **1.9** (1.00 mmol) was added by syringe in one portion. After 15 min of stirring the solution **A** was added dropwise via cannula transfer. Then the mixture was kept stirring over night at room temperature. Then the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The reaction mixture was poured into a separatory funnel containing ether (40 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The TLC and NMR analysis of the resulting oil showed that no desired product was produced. The resulting oil was subjected to column chromatography (HE: EA= 10: 1) to give 6-methoxy-2-naphthaldehyde (153 mg, 82%) as a pale yellow oil.

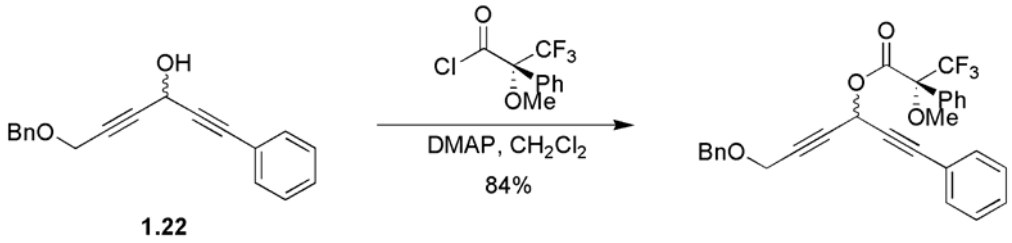
1.4.2.5 Preparation of Mosher's Esters



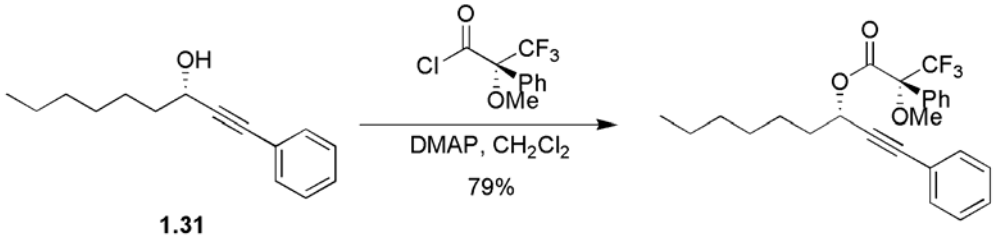
(*R*)-((*S*)-6-(benzyloxy)-1-phenylhexa-1,4-diyn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of (*S*)-1.33) A sample of 20 mg **(*S*)-1.33** (0.072 mmol) and a sample of 18 mg N, N-dimethyl aminol pyridine (0.145 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (0.027 mL, 37 mg, 0.145mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (32 mg, 84%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.59-7.57(m, 2H), 7.49-7.46 (m, 2H), 7.40-7.28 (m, 11H), 6.55-6.53 (t, *J*= 1.6 Hz, 0.04H), 6.53-6.51 (t, *J*= 1.6 Hz, 0.96H), 4.61 (s, 1.92H), 4.59 (s, 0.08H), 4.27 (d, *J*= 1.5 Hz, 1.93H), 4.24 (d, *J*= 1.5 Hz, 0.07H), 3.65 (s, 3H).



(*R*)-((*R*)-6-(benzyloxy)-1-phenylhexa-1,4-diyn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.33) A sample of 20 mg **1.33** (0.072 mmol) and a sample of 18 mg N, N-dimethyl aminol pyridine (0.145 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (0.027 mL, 37 mg, 0.145mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (26 mg, 68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59-7.57(m, 2H), 7.49-7.46 (m, 2H), 7.40-7.28 (m, 11H), 6.55-6.53 (t, *J*= 1.6 Hz, 0.96H), 6.53-6.51 (t, *J*= 1.6 Hz, 0.04H), 4.61 (s, 0.07H), 4.59 (s, 1.93H), 4.27 (d, *J*= 1.5 Hz, 0.07H), 4.24 (d, *J*= 1.5 Hz, 1.93H), 3.65 (s, 3H).

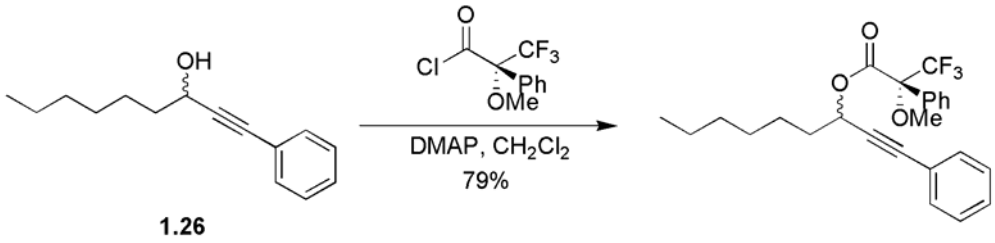


(*R*)-6-(Benzyloxy)-1-phenylhexa-1,4-diyn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.22) A sample of 50 mg (*S*)-**2.17** (0.181 mmol) and a sample of 89 mg N, N-dimethyl aminol pyridine (0.725 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (183 mg, 0.725mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (75 mg, 84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.32 (m, 15H), 6.57-6.56 (t, *J*= 1.8 Hz, 1H), 4.61 (s, 1H), 4.59 (s, 1H), 4.27 (d, *J*= 1.5 Hz, 1H), 4.24 (d, *J*= 1.5 Hz, 1H), 3.65 (s, 3H).



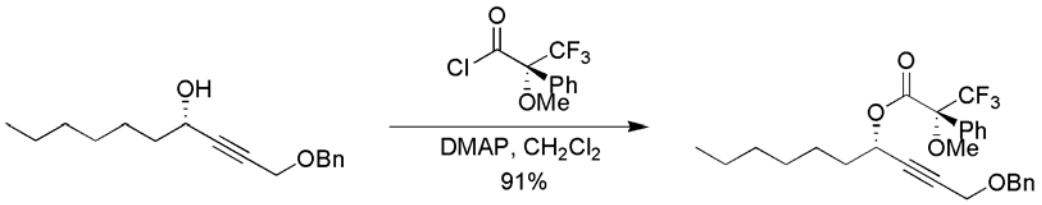
1.31

(*R*)-((*S*)-1-Phenylnon-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.31) A sample of 20 mg **1.31** (0.093 mmol) and a sample of 23 mg N, N-dimethyl aminol pyridine (0.185 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (47 mg, 0.185 mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (32 mg, 79%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.59 (d, *J*= 7.0 Hz, 1.96H), 7.57-7.56 (d, *J*= 7.0 Hz, 0.04H), 7.44-7.26 (m, 8H), 5.80-5.78 (t, *J*= 6.5 Hz, 0.98H), 5.76-5.74 (t, *J*= 6.5 Hz, 0.02H), 3.62-3.59 (d, *J*= 15.3 Hz, 3H), 1.97-1.84 (m, 2H), 1.43-1.19 (m, 8H), 0.89-0.86 (t, *J*= 7.0 Hz, 3H).



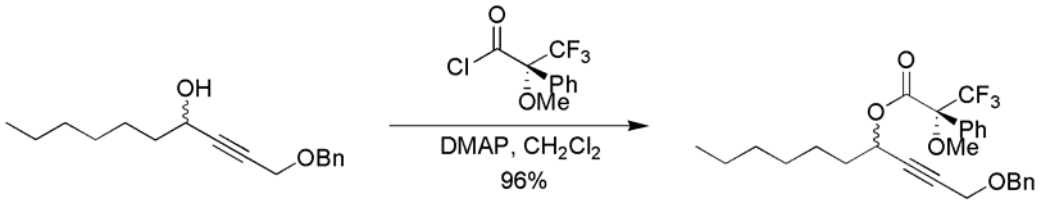
1.26

(*R*)-1-Phenylnon-1-yn-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.26) A sample of 10 mg **1.26** (0.046 mmol) and a sample of 17 mg N, N-dimethyl aminol pyridine (0.139 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (35 mg, 0.139 mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (16 mg, 79%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.59 (d, *J*= 7.0 Hz, 1H), 7.57-7.56 (d, *J*= 7.0 Hz, 1H), 7.44-7.26 (m, 8H), 5.80-5.78 (t, *J*= 6.5 Hz, 0.5H), 5.76-5.74 (t, *J*= 6.5 Hz, 0.5H), 3.62-3.59 (d, *J*= 15.3 Hz, 3H), 1.97-1.84 (m, 2H), 1.43-1.19 (m, 8H), 0.89-0.86 (t, *J*= 7.0 Hz, 3H).



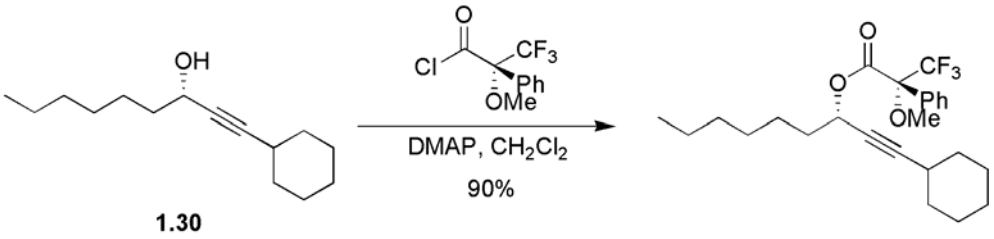
1.32

(*R*)-((*S*)-1-(Benzyloxy)dec-2-yn-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpro- panoate (Mosher ester of 1.32) A sample of 20 mg **1.32** (0.077 mmol) and a sample of 20 mg N, N-dimethyl aminol pyridine (0.164 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (40 mg, 0.158 mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (33 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.39-7.36 (m, 3H), 7.35-7.30 (m, 5H), 5.63-5.60 (t, *J*= 6.4 Hz, 1H), 4.57 (s, 1.90H), 4.55 (s, 0.10H), 4.22-4.21 (d, *J*= 1.6 Hz, 1.90H), 4.19-4.18 (d, *J*= 1.6 Hz, 0.10H), 3.59 (s, 3H), 1.83-1.78 (2H, m), 1.35-1.19 (m, 8H), 0.88-0.85 (t, *J*= 6.8 Hz, 3H).



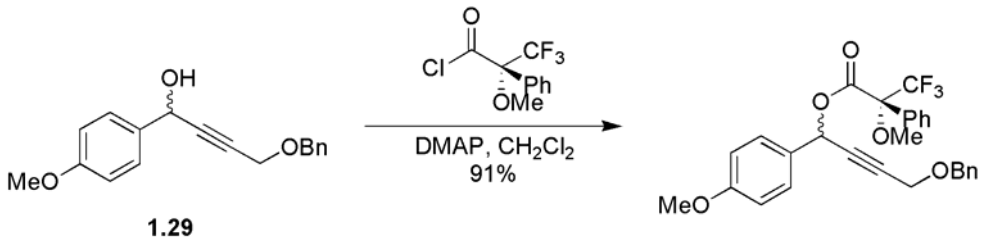
1.25

(*R*)-1-(Benzyloxy)dec-2-yn-4-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.25) A sample of 20 mg **1.25** (0.077 mmol) and a sample of 20 mg N, N-dimethyl aminol pyridine (0.164 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (40 mg, 0.158 mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (35 mg, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.39-7.36 (m, 3H), 7.35-7.30 (m, 5H), 5.63-5.60 (t, *J*= 6.4 Hz, 0.5H), 5.60-5.57 (t, *J*= 6.4 Hz, 0.5H), 4.57 (s, 1H), 4.55 (s, 1H), 4.21 (d, *J*= 1.6 Hz, 1H), 4.18 (d, *J*= 1.6 Hz, 1H), 3.59 (s, 1.5H), 3.56 (s, 1.5H), 1.83-1.78 (m, 2H), 1.35-1.19 (m, 8H), 0.88-0.85 (t, *J*= 6.8 Hz, 3H).



1.30

(*R*)-((*S*)-1-Cyclohexylnon-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropa- noate (Mosher ester of 1.30) A sample of 10 mg **1.30** (0.045 mmol) and a sample of 22 mg N, N-dimethyl aminol pyridine (0.180 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (44 mg, 0.180 mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (18 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 2H), 7.40-7.35 (m, 3H), 5.58-5.54 (td, *J*= 6.8, 1.6 Hz, 1H), 2.42 (br s, 1H), 1.78-1.68 (m, 6H), 1.56-1.21 (m, 14H), 0.88-0.85 (t, *J*= 6.4 Hz, 3H).



1.29

(*R*)-4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-ynyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher ester of 1.29) A sample of 20 mg **1.29** (0.071 mmol) and a sample of 18 mg N, N-dimethyl aminol pyridine (0.145 mmol) were dissolved in CH_2Cl_2 (2 mL) and (*R*)-2-methoxy-2-trifluoromethyl phenyl acetyl chloride (0.027 mL, 37 mg, 0.145mmol) were added. After 2 h stirring at room temperature, water (5 mL) and EtOAc (20 mL) were added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution (20 mL), saturated NH_4Cl aqueous solution (20 mL) and brine (20 mL). The resulting solution was dried over $MgSO_4$ and filtered through a silica column using HE: EA (7:1) solution as eluent to provide the Mosher's ester (32 mg, 91%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 4.56 (s, 1H), 4.270-4.266 (d, *J*= 1.6 Hz, 1H), 4.239-4.234 (d, *J*= 2.0 Hz, 1H).

PART TWO

REDOX ISOMERIZATION OF SECONDARY PROPARGYLIC ALCOHOLS TO ENONES

2.1 INTRODUCTION

2.1.1 Previous Protocols for obtaining Enones from Secondary Propargyl Alcohols

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2.1 INTRODUCTION

A convenient conversion of secondary propargyl alcohols to α,β-enones is in high demand because of the diverse applications of α,β-enones in synthesis and the facile access to propargyl alcohols. The Meyer-Schuster[11] and Rupe[12] rearrangement provide such a isomerization but with 1,3 or 1,2 shift of oxygen. Methods of transformation that keep the oxidation pattern are usually multistep process or have a special requirement of substrate[13]. Recently, the transition metals such as Pd[14], Ru[15], Rh[16] and Ir[17] were used to catalyze the highly atom economical isomerization of propargyl alcohols to α,β-enals and α,β-enones. However, such isomerizations are less well studied compared to the well established isomerizations of allylic alcohols. In this project, Trost's two-metal (ruthenium, indium) catalysis system was carefully optimized to promote the isomerization of secondary propargyl alcohols to α,β-enones, with tetraethylammonium hexafluorophosphate additive. To our knowledge, the first example of isomerization of dialkynyl alcohols to enynones catalyzed by a transition metal complex is reported in this chapter.

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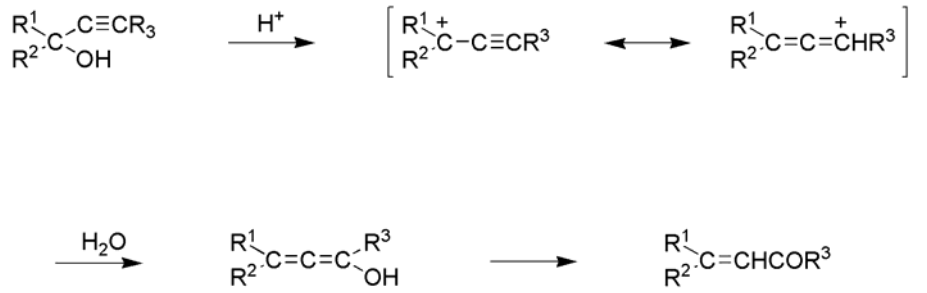
[17] Ma, D.; Lu, X. *Tetrahedron Lett.* **1989**, *30*, 2109.

2.1.1 Previous Protocols for obtaining Enones from Secondary Propargyl Alcohols

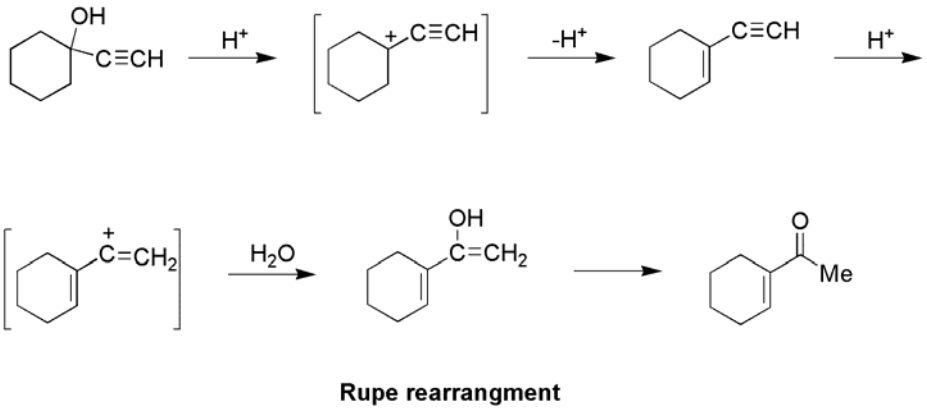
2.1.1.1 The Meyer-Schuster and Rupe Rearrangements

The first example of a Meyer-Schuster rearrangement was reported in 1922. The 1,3 oxygen shift acid-catalyzed isomerization of secondary and tertiary α-acetylenic alcohols to α,β-unsaturated carbonyl compounds was achieved. The products are aldehydes when the acetylenic group is terminal, otherwise, they are ketones.

Rupe and colleagues discovered the 1,2 oxygen shift rearrangement in 1924. The tertiary α-acetylenic alcohols were converted to enones as major products. The mechanisms of these two acid-catalyzed rearrangements were shown in Scheme **2-1**.



Meyer-Schuster rearrangement

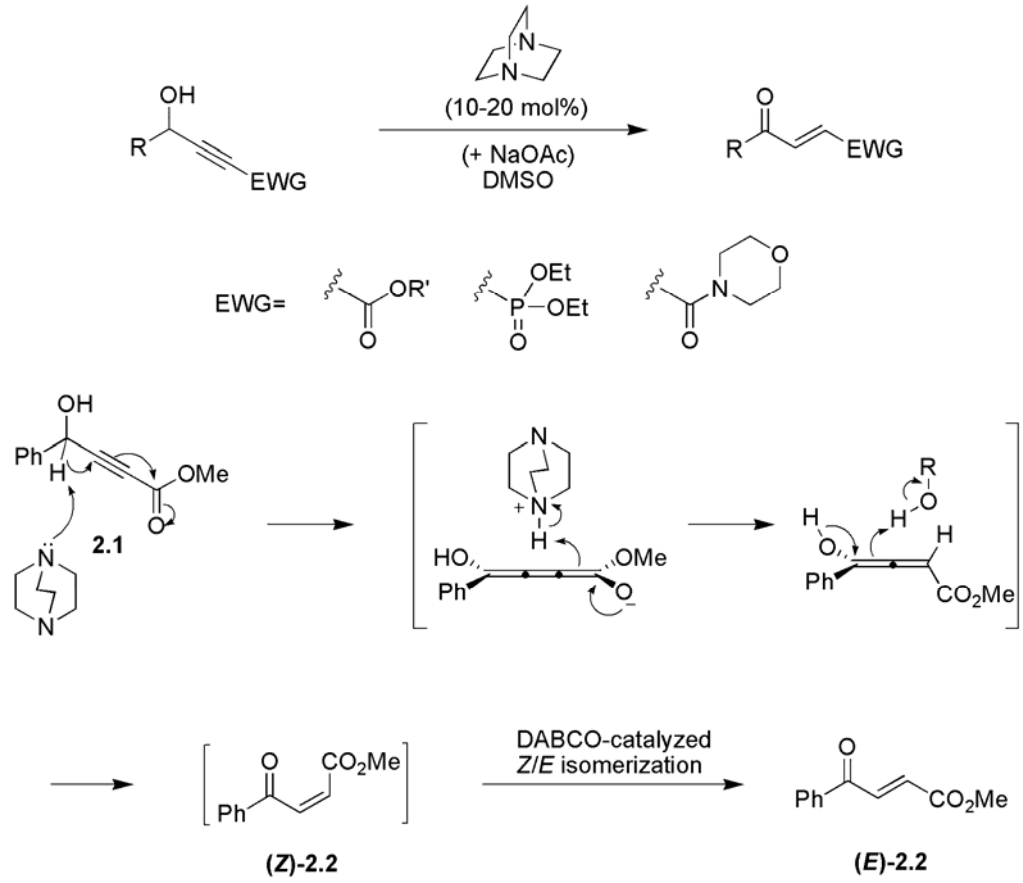


Rupe rearrangment

Scheme 2-1 Meyer-Schuster11 and Rupe12 rearrangements'

2.1.1.2 Base-Catalyzed Stereoselective Isomerization of Electron-Deficient Propargyl Alcohols to *E*-Enones

Nineham and Raphael [18] first reported an isomerization of methyl 4-hydroxy-4-phenylbut-2-ynoate **2.1** to (*E*)-methyl 4-oxo-4-phenylbut-2-enoate **2.2** with excess Et_3N at 23 ^oC in 1949. Presumably, the isomerization of (*Z*)-**2.2** to (*E*)-**2.2** at elevated temperature in the presence of Et_3N is the cause of the high trans-selectivity.[19] In 2006, the Koide group reported the isomerization of electron-deficient propargyl alcohols conjugated with an ester, amide or phosphonate to *E*-enones under mild conditions (Scheme **2-2**). [20] A Catalytic amount of 1,4-diazabicyclo- [2.2.2]octane (DABCO) was found to be effective in most cases among weak bases. The proposed mechanism is shown as follows.



Scheme 2-2 Mechanism of DABCO-catalyzed redox isomerization

[18] Nineham, A. W.; Raphael, R. A. *J. Chem. Commun*. **1949**, 118-121.
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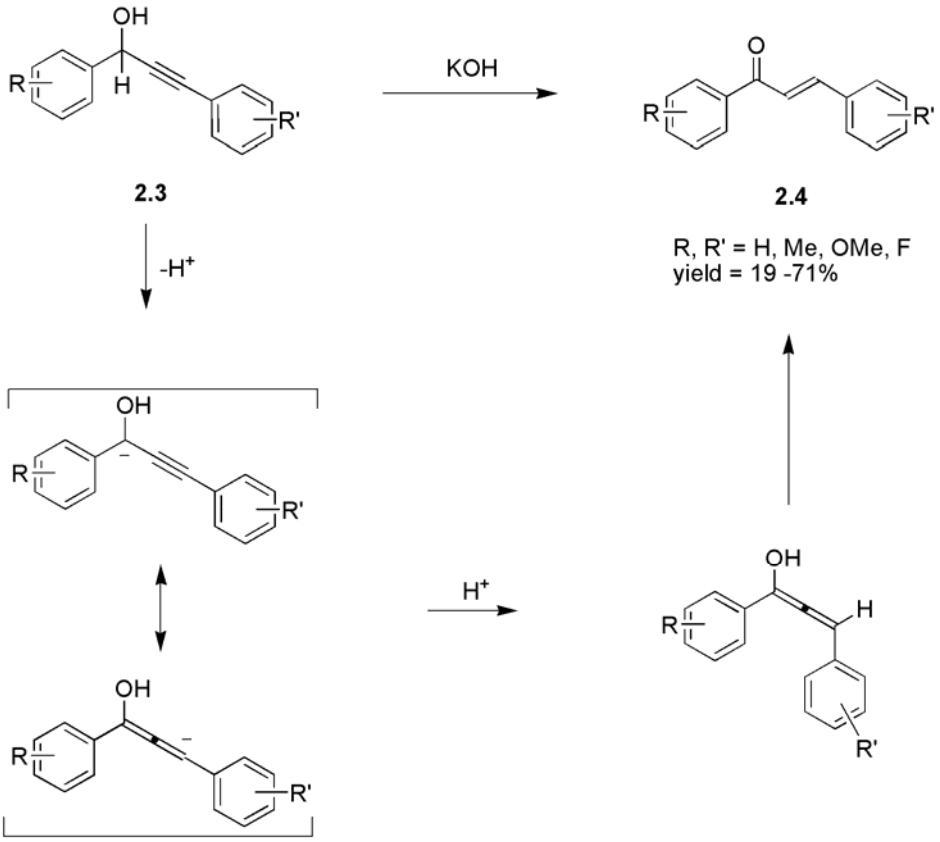
[20] Sonye, J. P.; Koide, K. *J. Org. Chem.* **2006**, *71*(16), 6254-6257.

2.1.1.3 Isomerization of 1,3-Diarylprop-2-yn-1-ols (2.3) to Chalcones in the Presence of Potassium Hydroxide

In 2005, Shim and coworkers reported that 1,3-diarylprop-2-yn-1-ols (**2.3**) isomerized to chalcones (**2.4**) in the presence of potassium hydroxide[21]. They screened a series of 1,3-diarylprop-2-yn-1-ols (**2.3**) with various substitutions on the aromatic rings. They found that the product yields were considerably affected by substituents on the aromatic ring attached to the carbon bearing the hydroxyl group. However, the yields were not significantly affected by the electronic nature and position of the substituent on the aromatic ring attached to the acetylenic carbon. The reaction was proposed to go through intermediates shown in Scheme **2-3**.



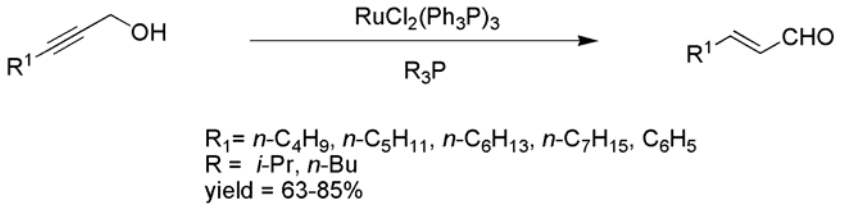
Scheme 2-3 KOH-catalyzed Isomerization of 1,3-diarylprop-2-yn-1-ols to chalcones

2.1.1.4 Ru-catalyzed Isomerization of Prop-2-ynols to Enals

In 1989, Lu and Ma reported the first example of isomerization of prop-2-ynols to the (*E*)-enals with a transition metal catalyst complex (Scheme **2-4**).[c] They found $RuCl_2(Ph_3P)_3$ and aliphatic phosphine ligands mixture catalyze these isomerization in moderate to good yield. The approach of using Ph_3P as the ligand or the approach in the

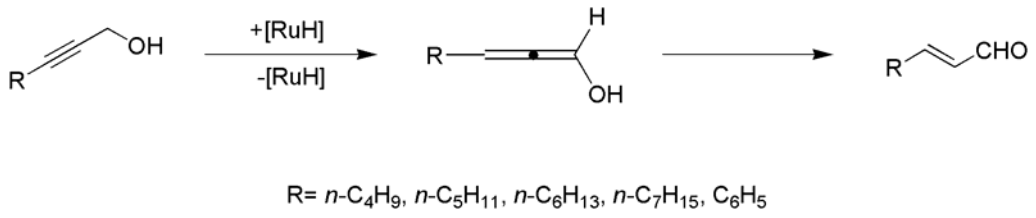
[21] Cho, C. S.; Seok, H. J.; Shim, S. C. *Bull. Korean Chem. Soc.* **2005**, *26*(7), 1107-1108

absence of a ligand failed to produce target enals. These results showed the aliphatic phosphine ligands played an important role in this Ru-catalyzed isomerization. It is also found that prop-2-ynols with an alkyl group are more reactive that those with an aryl group.



Scheme 2-4 Ru-catalyzed isomerization of prop-2-ynols to enals15[c]

The researchers proposed a mechanism (Scheme **2-5**) which is similar to that of the isomerization of 2-ynones to dienones[22], one of their previous studies. At first, ruthenium hydride species were probably formed from prop-2-ynols and the ruthenium catalyst, $RuCl_2(Ph_3P)_3$. Then 1,2-dienols were formed after the addition and elimination of Ru-H sequentially. After that, the 1,2-dienols will further isomerize to the target molecule, *α*,*β*-unsaturated aldehydes.

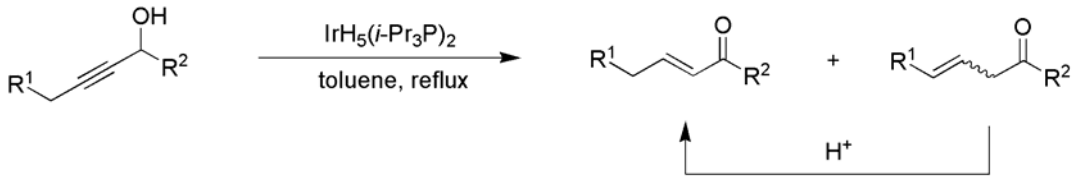


Scheme 2-5 Mechanism of Ru-catalyzed isomerization proposed by Lu15[c]

2.1.1.5 Ir and Pd-catalyzed Isomerization of Propargyl Alcohols to Enones

In the same year, 1989, Lu and Ma also reported the first example of transition metal catalyzed isomerization of secondary propargyl alcohols to *α*,*β*-enones.17 $IrH_5(i\text{-}Pr_3P)_2$ complex was found effective to catalyze this isomerization. Two isomers, (*E*)-*α*,*β*-enones and *β*,*γ*-enones were separated from the reaction mixture in the ratio of about 4 to 1 (Scheme **2-6**, Table **2-1**). Although the *β*,*γ*-enones could not be further isomerized to *α*,*β*-enones under the present reaction condition, pure (*E*)-α,β-enones could be obtained by treating the reaction products with acids.

[22] (a) Ma, D.; Lin, Y.; Lu, X.; Yu, Y. *Tetrahedron Lett.,* **1988**, *29*, 1045; (b) Ma, D.; Yu, Y.; Lu, X. *J. Org. Chem.,* **1989**, *54*, 1105.

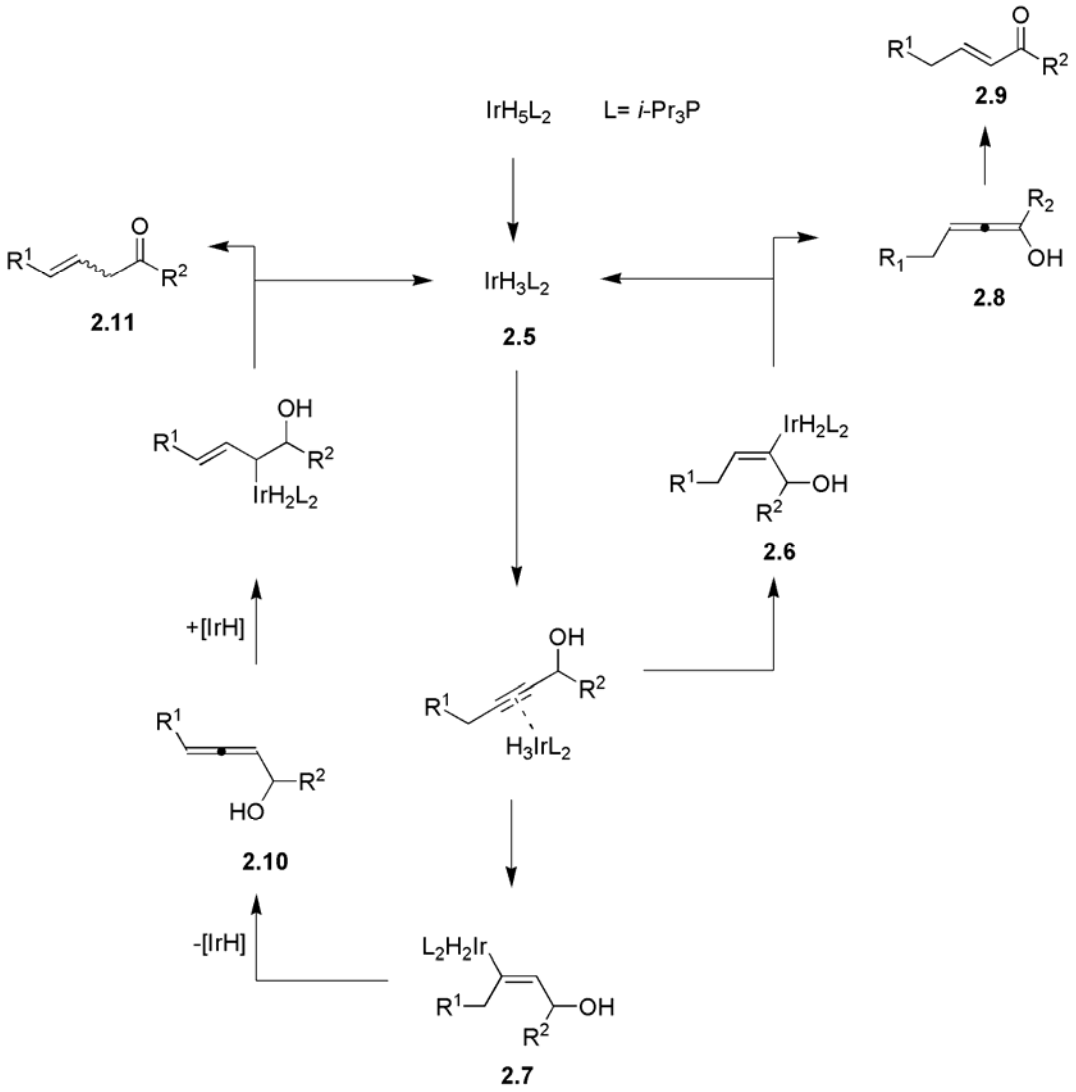


Scheme 2-6 Ir-catalyzed isomerization of secondary propargyl alcohols17

Table 2-1 Isomerization of propargyl alcohols by $IrH_5(i\text{-}Pr_3P)_2$17

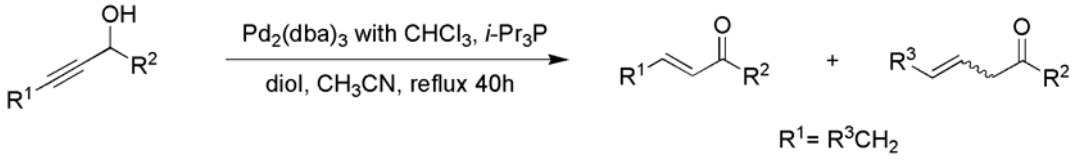
Entry	***R^1***	***R^2***	***Time (h)***	***Yield (%)***	***2:3***
1	*n*-C_6H_{13}	Me	28	90%	81:19
2	*n*-Pr	Et	28	91%	81:19
3	*n*-Pr	Et	40	70%	80:20
4	*n*-C_4H_9	Me	24	92%	78:22
5	*n*-Pr	Me	24	90%	76:24
6	*i*-Pr	Me	2	88%	83:17
7	Et	Et	28	87%	80:20
8	*n*-Pr	Ph	30	85%	85:15

The researchers proposed this reaction may proceed through a process of intramolecular hydrogen transfer as follows (Scheme **2-7**). First, the metal complex **2.5** will coordinate with the triple bond, then intermediates **2.6** and **2.7** will be formed by the insertion of the triple bond to the Ir-H bond. After that, a β-elimination of **2.6** may give dienol like structure **2.8** which will isomerize to the *α,β*-enones **2.9** and regenerate the metal complex **2.5** to complete the catalytic cycle. While the β-elimination of **2.7** may provide allenic alcohol **2.10**, then addition and elimination of iridium hydride will complete the catalytic cycle and produce *β,γ*-enones **2.11**.



Scheme 2-7 Mechanism of Ir-catalyzed isomerization proposed by Lu17

In 1992, Lu and coworkers reported similar results that was obtained from isomerization of alkyne-mono-ols catalyzed by a palladium(0) complex and diols (Scheme **2-8**, Table **2-2**).14 The addition of a catalytic amount of ethane-1,2-diol was found to be effective to promote the $Pd_2(dba)_3{\cdot}CHCl_3$ catalyzed isomerization smoothly under milder conditions.



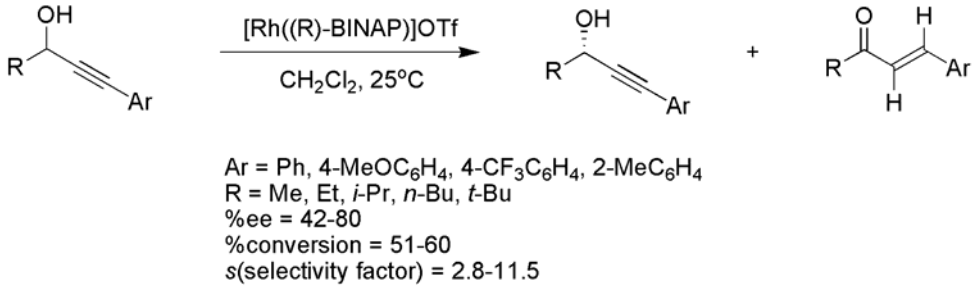
Scheme 2-8 Pd-catalyzed isomerization of alkynemono-ols14

Table 2-2 Isomerization of alkynemono-ols by $Pd_2(dba)_3 \cdot CHCl_3$ and ethane-1,2-diol14

Entry	R^1	R^2	*Time (h)*	*Yield (%)*	*2:3*
1	*n*-C_4H_9	Me	65	85%	77:23
2	*n*-C_5H_{11}	Me	65	82%	84:16
3	*n*-C_6H_{13}	Me	65	88%	79:21
4	*n*-C_4H_9	*p*-MePh	40	90%	78:22
5	Ph	Et	40	89%	-

2.1.1.6 Kinetic Resolution of Secondary Propargyl Alcohols

In 2005, Tanaka's group [23] developed a cationic rhodium(I)/BINAP complex-catalyzed isomerization of secondary propargyl alcohols to *α,β*-enones (Scheme **2-9**). A kinetic resolution of secondary alcohols was also reported using chiral catalyst. The asymmetric version of this reaction provided a selectivity factor up to 11.5. The selectivity was affected by the steric demand of the alkyl groups and the aryl ring. The electronic nature of the aromatic substituent also had a moderate effect on the selectivity factor. Although this transition metal catalyzed kinetic resolution isomerization has high potential, the conversion and selectivity still need to be optimized.

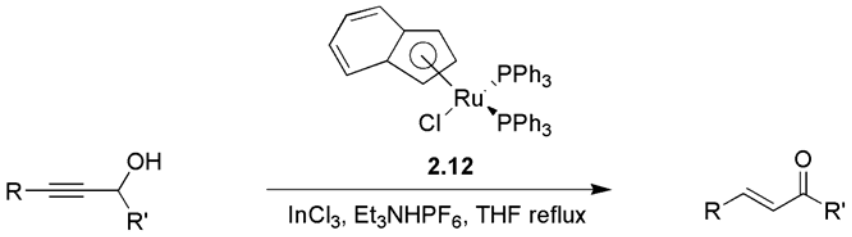


Scheme 2-9 Kinetic resolution of secondary propargyl alcohols23

2.1.2 Two-Metal Catalyst System for Redox Isomerization of Propargyl Alcohols to Enals and Enones

Inspired by the Trost group's previous development of a ruthenium-catalyzed system for isomerization of allylic alcohols, Barry M. Trost and Robert C. Livingston[15d] developed an extremely simple, practical, and efficient Ru-In catalyst system for the redox isomerization of propargyl alcohols to enals and enones. In a typical reaction, a mixture of the propargyl alcohol, indenylbis (triphenylphosphine) ruthenium chloride (**2.12**), indium trichloride, and triethylammonium hexafluorophosphate (in conjunction with ammonium hexafluorophosphate for synthesis of enals) in THF was heated to reflux temperature to give the enals and enones in 67-88% yields with extraordinary chemoselectivity (Scheme **2-10**, Table **2-3**).

[23] Tanaka, K.; Shoji, T. *Org. Lett.* **2005**, *7*(16), 3561-3563.

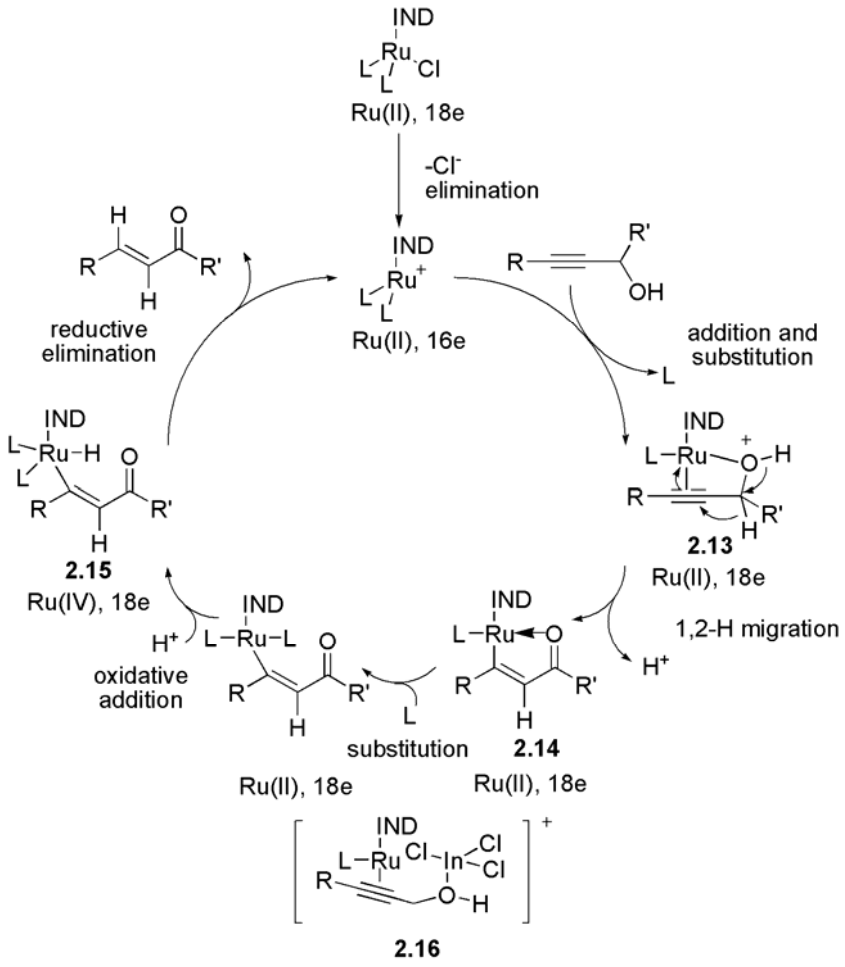


Scheme 2-10 Two-metal catalyzed redox isomerization of propargyl alcohols15[d]

Table 2-3 Two-metal catalyzed redox isomerization of propargyl alcohols15[d]

Entry	R	R'	Time (h)	Yield (%)
1	$Ph(CH_2)_3$	H	1.25	88
2	$PhC(=O)(CH_2)_3$	H	1.5	80
3	$PhCH(OAc)(CH_2)_3$	H	1.5	87
4	$PhCH(OH)(CH_2)_6$	H	1.5	86
5	$CH_3(CH_2)_3C{\equiv}C(CH_2)_6$	H	1.5	83
6	$(CH_3)_2C{=}CH$	H	1.5	67
7	n-$C_{10}H_{21}$	CH_2CH_2Ph	24	86
8	n-C_4H_9	$(CH_2)_8CH{=}CH_2$	24	83

The mechanism proposed by Trost is shown in Scheme **2-11**. First, the propargyl alcohol coordinates to Ru(II) to form some species like **2.13**. Then, complex **2.14** is formed after the a 1,2-H migration. Then, ligand substitution and oxidative addition forms a Ru(IV) complex like **2.15**. A reductive elimination then restores the Ru(II) catalyst and provides *α,β*-unsaturated carbonyl compounds as the product. The role of the indium salt remains unanswered. It could promote formation of the ruthenium cation by serving as a chloride scavenger or relieve the strain associated with **2.13** by forming an indium-bridged species like **2.16.**



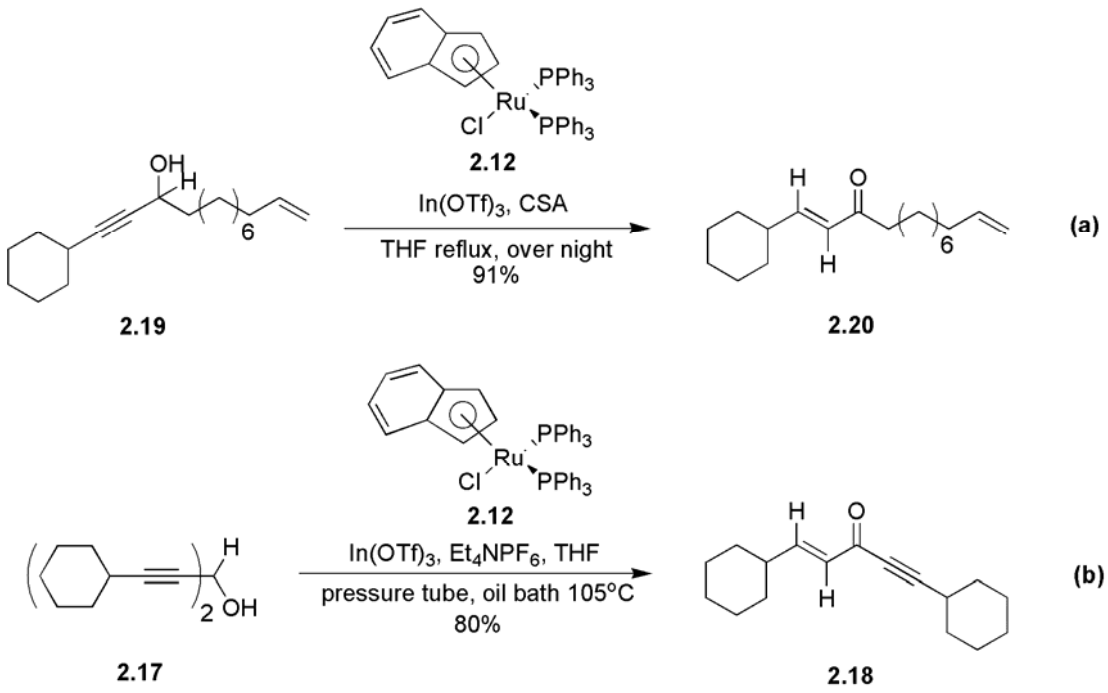
Scheme 2-11 Mechanism for redox isomerization of propargyl alcohols proposed by Trost15[d]

2.2 RESULTS AND DISCUSSION

Although several examples of transition metal catalyzed isomerization of secondary alcohols to *α,β*-enones were reported[14,15,17], some challenging substrates such as dialkynyl alcohols have not been studied yet. In order to optimize the redox isomerization of secondary propargyl alcohols to *α,β*-enones and achieve the redox isomerization of dialkynyl alcohols to enynones, Trost's two-metal (ruthenium, indium) catalysis system was carefully optimized using different additives. The stability of protecting groups under the optimized reaction condition was also tested.

2.2.1 Redox Isomerization of Secondary Propargyl Alcohols to Enones

Using dialkynyl **2.17** (same as **1.14**, see Scheme **2-12** and Table **2-4**) as the test substrate, our studies began with the indenylruthenium complex (**2.12)** and indium trifluoromethanesulfonate**,** which was reported to be very effective for the isomerization of propargyl alcohols. Under the reported conditions for secondary propargyl alcohols (Scheme **2-12**, eq **a**)15[d] , which is co-catalyzed by a Bronsted acid (such as CSA, boric acid, or ammonium hexafluorophosphate) in THF at reflux, **2.18** was not produced and the starting material decomposed after 12 h. Because of the known sensitivity of the dialkynyl alcohols, a basic additive (triethylamine), a neutral additive (tetraethylammonium hexafluorophosphate) or no additive were used to cocatalyze the isomerization. There was no significant improvement for the approach using triethylamine or the approach in the absence of a ligand compared to the reported condition. Remarkably, adding tetraethylammonium hexafluorophosphate to the original catalyst system in THF at reflux temperature led to complete consumption of starting material **2.17 (1.14)** within 16 h and provided the target enynone product **2.18** in 80% yield (Scheme **2-12**, eq **b**).

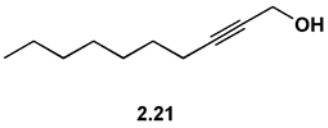
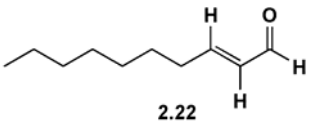
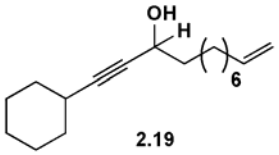
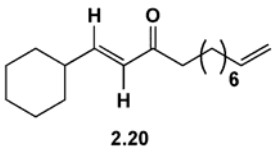
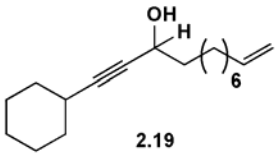
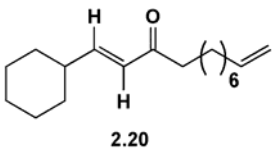
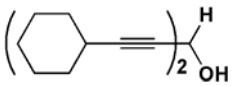
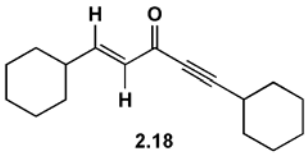
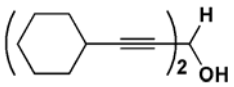
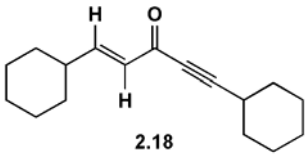
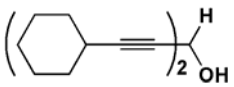
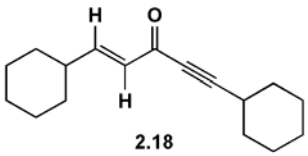
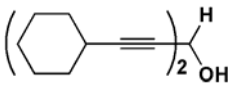
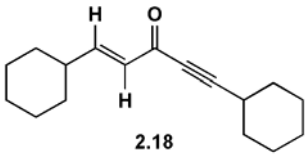
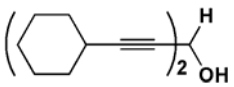
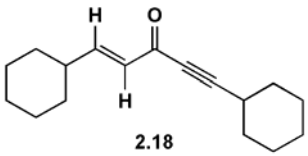


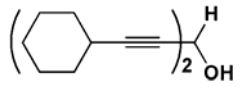
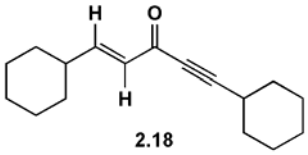
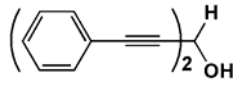
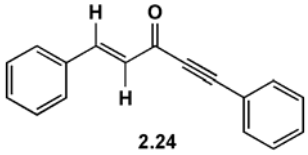
Scheme 2-12 Redox isomerization of secondary propargyl alcohols to enones

Table **2-4** summarizes our results. For the synthesis of the *α,β*-unsaturated aldehyde **2.22** (Table **2-4**, entry **1**), use of 5 mol % of tetraethylammonium hexafluorophosphate salts gave 95% yield in 16h. Reaction with internal propargyl alcohol **2.19** produced enone **2.20** in 61% yield with boric acid (Table **2-1**, entry **2**) and 91% yield with CSA (Table **2-1**, entry **3**). For the isomerization of dialkynyl alcohol **2.17 (1.14)** to enynone **2.18**, acidic additive (boric acid, CSA or ammonium hexafluorophosphate), basic additive

(triethylamine) or no additive led to no desired product formation (Table **2-1**, entries **4-9**). Remarkably, use of tetraethylammonium hexafluorophosphate alone proved beneficial (Table **2-1**, entry **10**). The fact that the highly reactive enynone product is isolated in good yield (80%) indicates high chemoselectivity of this redox isomerization reaction. However, isomerization of phenyl acetylenic alcohol **2.23 (1.13)** provided polymer like product instead of the target enynone **2.24** under this condition.

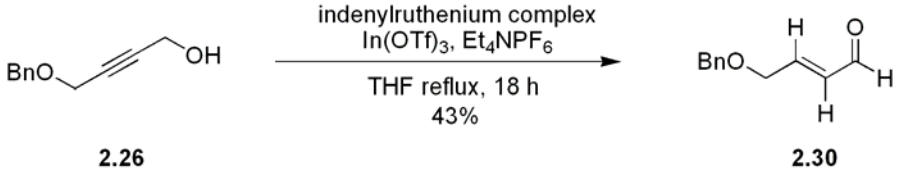
Table 2-4 Redox isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds

Entry	Substrate	Target Molecule	Additive	Yield
1	 2.21	 2.22	Et_4NPF_6	95%
2	 2.19	 2.20	boric acid	61%
3	 2.19	 2.20	CSA	91%
4	 2.17	 2.18	boric acid	0%
5	 2.17	 2.18	CSA	0%
6	 2.17	 2.18	NH_4PF_6	0%
7	 2.17	 2.18	none	0%
8	 2.17	 2.18	Et_3N	0%

9	 **2.17**	 **2.18**	Et_4NPF_6	80%
10	 **2.23**	 **2.24**	Et_4NPF_6	0%

2.2.2 Protecting Group Stability under Optimized Rearrangement Condition

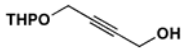
Although the isomerization of dialkynyl alcohol **2.17 (1.14)** provides enynone **2.18** in good yield under the optimized condition, the high temperature and long reaction time remains a hindrance for applying this method to natural product synthesis. Substrates with different protecting groups (TBS, THP, PMB, Bn, PIV) at different positions (α and β hydroxyl group) were tested with the optimized condition. The only substrate that yielded the target molecule under optimized conditions was the benzyl protected diol **2.26** (Table **2-5**, entry **2**, scheme **2-13**) with a relative short heating period (18 h). The desired product enone **2.30** was isolated in 43% yield. None of the isomerization approaches of dialkynyl alcohols bearing protecting groups yield desired enynone products. Further modification of conditions and search for suitable protecting groups will be the focus of future study.

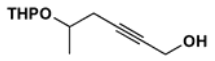
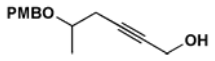
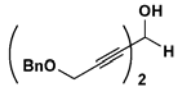
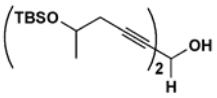
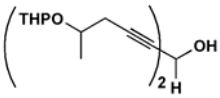
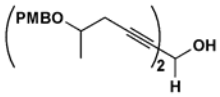


2.26 **2.30**

Scheme 2-13 Redox isomerization of benzyl protected diol **2.26**

Table 2-5 Stability tests of protecting groups

Entry	Starting Material	T (°C)	t (h)	Results
1	 **2.25**	80	48	S.M. decomposed No T.M. observed
2	 **2.26**	80	18	43% T.M.
3	 **2.27**	80	18	S.M. decomposed No T.M. observed

4	 2.28	80	48	S.M. decomposed No T.M. observed
5	 2.29	80	48	S.M. decomposed No T.M. observed
6	 1.11	105	72	S.M. decomposed No T.M. observed
7	 1.15	105	72	S.M. decomposed No T.M. observed
8	 1.16	105	72	S.M. decomposed No T.M. observed
9	 1.17	105	72	S.M. decomposed No T.M. observed

2.3 CONCLUSION

Tetraethylammonium hexafluorophosphate was found to be a useful additive for the isomerization of dialkynyl alcohols to enynones. Base on this discovery, Trost's two-metal (ruthenium, indium) catalysis system was carefully optimized. The first example of redox isomerization of dialkynyl alcohols to enynones catalyzed by a transition metal complex was achieved with good yield. Substrates with different protecting groups (TBS, THP, PMB) at different positions (α and β hydroxyl group) were tested with the optimized condition, but none could tolerate the optimized condition. Further modification of conditions will be the focused of future study.

2.4 EXPERIMENTAL SECTION

2.4.1 General Information

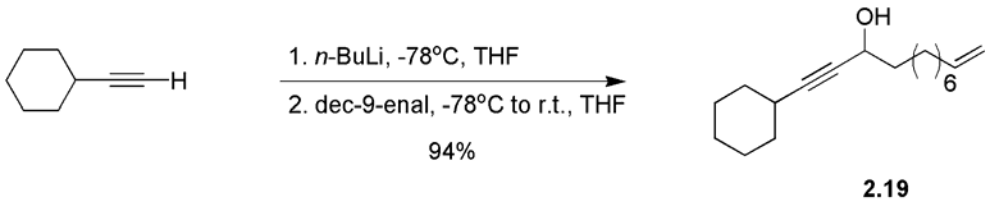
Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Lancaster, Alfa Aesar or Acros Organics. Liquid reagents were purified by distillation prior to use. Unless otherwise noted, solid reagents were used without further purification.

All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. In general, the residual solvent was removed on a vacuum line at 1-1.5 torr. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. Diisopropylethylamine and triethylamine were distilled from sodium. The extracts were dried over Na_2SO_4 unless otherwise noted.

All experiments were monitored by thin layer chromatography (TLC) performed on EM Science precoated silica gel 60 F-254 glass supported plates with 0.25 mm thickness. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or to iodine vapor or by staining with a 10 % solution of phosphomolybdenic acid (PMA) in ethanol and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

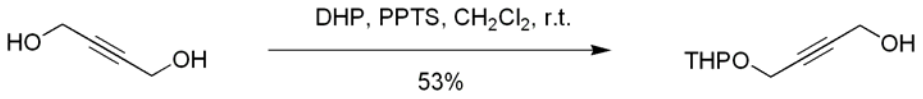
Infrared spectra were recorded with a Galaxy Series FT-IR 3000 infrared spectrophotometer. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), Varian Inova-500 (500 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H, 100 MHz for ^{13}C), or Gemini-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). For complex multiplets, the chemical shift is given for the center of the multiplet. Coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectra were obtained with a Micromass 70-VSE spectrometer.

2.4.2 Experimental Procedures



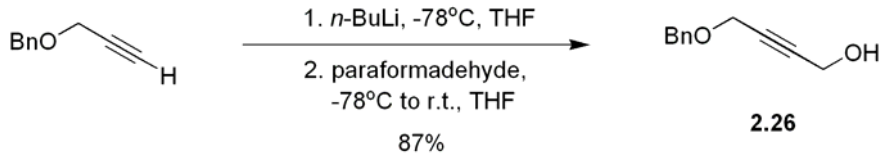
2.19

1-Cyclohexyldodec-11-en-1-yn-3-ol (2.19) A 1.0 g (9.24 mmol) of cyclohexylacetylene was dissolved in THF (30 mL), *n*-BuLi (4.08 mL, 2.5 M, 10.2 mmol) was added slowly at –78 °C. After that, the reaction mixture was stirred at –78 °C for 2 hours. Then a 1.72g of dec-9-enal (10.2 mmol) was added dropwise. The reaction mixture was stirred at –78 °C for 2 hours afterwards. Then it was allowed to warm up to room temperature and stirred overnight. To the resulting solution was added ethyl acetate (20 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and the resulting solution was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Then the residue was subjected to flash chromatography (HE: EA= 7:1) to give **2.19** (2.43 g, 94%) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 5.85-5.75 (ddt, *J*= 17.2, 8.4, 6.8 Hz, 1H), 5.00-4.90 (m, 2H), 4.39-4.32 (t, *J*= 6.4 Hz, 1H), 2.41-2.35 (m, 1H), 2.07-2.00 (m, 2H), 1.88 (br s, 1H), 1.78-1.77 (m, 2H), 1.72-1.59 (m, 3H), 1.52-1.28 (m, 17H). ^{13}C NMR (400 MHz, $CDCl_3$): *δ* 139.27, 114.2, 89.7, 81.5, 62.9, 38.5, 34.1, 32.9, 29.73, 29.70, 29.6, 29.5, 29.4, 29.24, 29.19, 29.13, 25.5, 25.08; IR (neat) ν_{max} 3351 (br), 3076, 2918, 2857, 1640, 1449, 1025, 1014, 994, 909, 738.

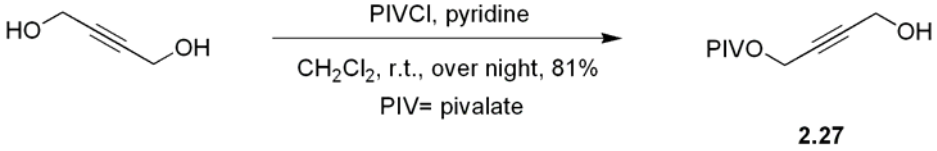


2.25

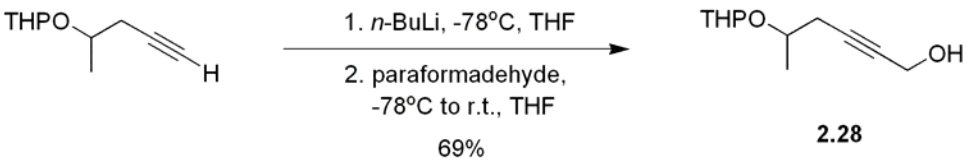
4-(Tetrahydro-2H-pyran-2-yloxy)but-2-yn-1-ol (2.25) To a solution of 2-butyne-1,4-diol (1.0 g, 11.6 mmol) and PPTS (145 mg, 0.58 mmol) in CH_2Cl_2 (20 mL), 3,4-dihydro-2*H*-pyran (781 mg, 9.28 mmol) was added. The reaction was stirred at r.t. for 16 h. Then the mixture was poured into ether and the resulting solution was washed with water, 5% $NaHCO_3$ (aq), water and brine. Then the organic solution was dried over $MgSO_4$ and concentrated. Then the residue was subjected to flash chromatography (HE: EA= 4:1) to give **2.25** (796 mg, 53% yield) as a colorless oil. ^{1}H-NMR (300MHz, $CDCl_3$) *δ* 4.81-4.78 (t, *J*= 3.0 Hz, 1H), 4.37-4.21 (m, 4H), 3.86-3.79 (m, 1H), 3.56-3.49 (m, 1H), 2.06-2.02 (t, *J*= 5.7 Hz, 1H), 1.76-1.50 (m, 6H); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 96.9, 84.3, 81.6, 61.9, 54.3, 51.1, 30.2, 25.3, 18.9; IR (neat) ν_{max} 3412 (br), 2944, 2869, 1442, 1390, 1345, 1264, 1202, 1130, 1119, 1023, 902.



4-(Benzyloxy)but-2-yn-1-ol (2.26) A sample of ((prop-2-ynyloxy)methyl)benzene **1.9** (522 mg, 3.58 mmol) was dissolved in THF (20 mL). To this solution, *n*-BuLi (1.57 mL, 2.50 M, 3.93 mmol) was added slowly at –78 °C. The reaction mixture was stirred at –78 °C for 2h. Then paraformadehyde (118 mg, 3.93 mmol) was added. After that, the reaction mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. To the resulting solution was added ethyl acetate (20 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and the resulting solution was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to flash chromatography on silica gel (HE: EA= 4: 1) to give **2.26** (548 mg, 87%) as a colorless oil. ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.37-7.33 (m, 5H), 4.60 (s, 2H), 4.33-4.32 (t, *J*= 1.8 Hz, 2H), 4.22-4.21 (t, *J*= 1.8 Hz, 2H), 1.64 (s, 1H); IR (neat) ν_{max} 3368 (br), 2860, 1453, 1441, 1353, 1123, 1071, 1015, 743, 699.

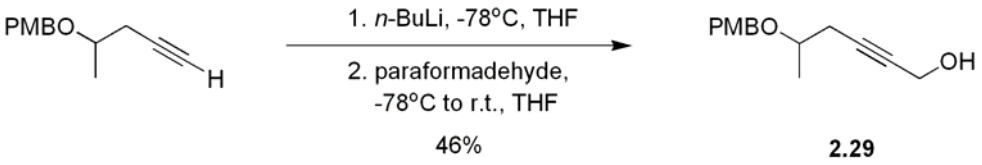


((4-Hydroxybut-2-ynyloxy)iodophosphino)vanadium (2.27) To a solution of 2-butyne-1,4-diol (2.0 g, 23.2 mmol) and pyridine (5 ml) in CH_2Cl_2 (20 mL), pivaloyl chloride (2.52 g, 20.9 mmol) was added dropwise. The reaction was stirred at r.t. for 16 h. Then the mixture was poured into ether and the resulting solution was washed with water, 5% $NaHCO_3$ (aq), water and brine. Then the organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography (HE: EA= 5: 1) to give **2.27** (2.87 g, 81% yield). ^{1}H-NMR (300MHz, $CDCl_3$) δ 4.70-4.69 (t, *J*= 1.5 Hz, 2H), 4.32-4.29 (dt, *J*= 6.3, 1.5 Hz, 2H), 1.80-1.65 (t, *J*= 6.3 Hz, 1H), 1.22 (s, 9H); IR (neat) ν_{max} 3425 (br), 2975, 2973, 2911, 2874, 1726, 1481, 1461, 1398, 1368, 1281, 1147, 1023, 965.

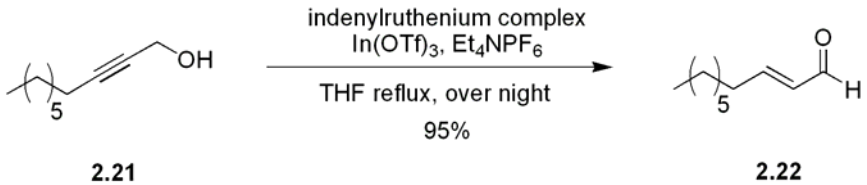


5-(Tetrahydro-2H-pyran-2-yloxy)hex-2-yn-1-ol (2.28) A sample of 2-(pent-4-yn-2-yloxy)-tetrahydro-2H-pyran (200 mg, 1.19 mmol) was dissolved in THF (20 mL). To this solution, *n*-BuLi (0.524 mL, 2.50 M, 1.31 mmol) was added slowly at –78 °C. The reaction mixture was stirred at –78 °C for 2h. Then paraformadehyde (39.3 mg, 1.31

mmol) was added. After that, the reaction mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. To the resulting solution was added ethyl acetate (20 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and the resulting solution was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Then the residue was subjected to flash chromatography (HE: EA= 4:1) to give **2.28** (150 mg, 69%) as pale yellow oil (a mixture of two diastereomers). ^{1}H-NMR (400MHz, $CDCl_3$) δ 4.74-4.66 (m, 1H), 4.20 (s, 2H), 3.93-3.83 (m, 2H), 3.48-3.46 (m, 1H), 2.57-2.32 (m, 3H), 1.83-1.65 (m, 6H), 1.56-1.47 (m, 4H), 1.29-1.19 (m, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 97.8, 97.1, 83.3, 82.8, 80.3, 80.2, 71.2, 62.8, 62.7, 51.32, 51.28, 31.2, 31.1, 27.7, 26.2, 25.7, 25.6, 21.3, 19.9, 19.8, 19.3; IR (neat) ν_{max} 3413 (br), 2940, 2869, 1453, 1441, 1378, 1352, 1341, 1201, 1123, 1074, 1022, 995.

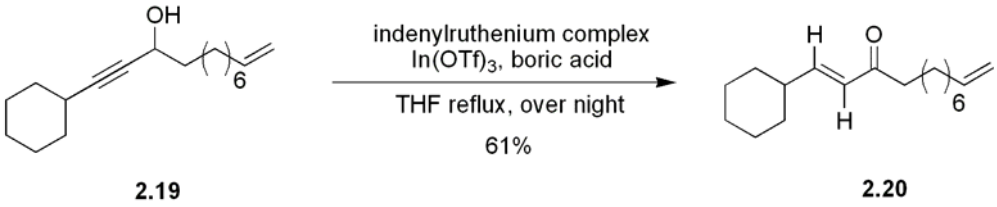


5-(4-Methoxybenzyloxy)hex-2-yn-1-ol (2.29) A sample of 1-methoxy-4-((pent-4-yn-2-yloxy)methyl)benzene (100 mg, 0.454 mmol) was dissolved in THF (20 mL). To this solution at –78 °C, *n*-BuLi (0.200 mL, 2.50 M, 0.499 mmol) was added slowly. After that, the reaction mixture was stirred at –78 °C for 2 h. Then paraformadehyde (15 mg, 0.499 mmol) was added. After that, the reaction mixture was stirred at –78 °C for two more hours and then warmed up to room temperature over night. To the resulting solution was added ethyl acetate (20 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and the resulting solution was washed with brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Then the residue was subjected to flash chromatography (HE: EA= 4:1) to give to give **2.29** (52 mg, 46%) as a pale yellow oil. ^{1}H-NMR (300MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 6.90-6.85 (m, 2H), 4.49 (s, 2H), 4.22 (br s, 2H), 3.78 (s, 3H), 3.69-3.62 (m, 1H), 2.54-2.35 (m, 2H), 2.16 (br s, 1H), 1.29-1.27 (d, *J*= 6.3 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$): δ 159.5, 130.8, 129.6, 114.1, 83.2, 80.5, 73.2, 70.6, 55.6, 51.5, 26.6, 19.9.



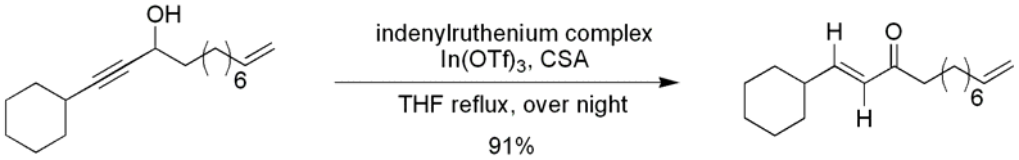
(*E*)-Dec-2-enal (2.22) A 37 mg (0.240 mmol) sample of 2-decyn-1-ol **2.21** was dissolved in 15 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 54 mg indium (III) trifluoromethanesulfonate (0.096 mmol, 40 mol%), 10 mg

chloro(indenyl)bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.012 mmol, 5 mol%), and 4 mg tetraethylammonium hexafluorophosphate (0.012 mmol, 5 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated to reflux. The reaction was monitored by TLC. After disappearance of starting material, the solvent was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then subjected to flash chromatography (HE: EA= 30: 1) to give **2.22** (35 mg, 95% yield) as a colorless oil. ^{1}H-NMR (300MHz, $CDCl_3$) δ 9.49-9.52 (d, *J*= 7.9 Hz, 1H), 6.80-6.88 (dt, *J*= 15.7, 6.9 Hz, 1H), 6.08-6.15 (ddt, *J*= 15.6, 7.9, 1.5 Hz, 1H), 1.77-1.87 (m, 2H), 1.24-1.39 (m, 10H), 0.87-0.92 (d, *J*= 7.7 Hz, 3H).



2.19 **2.20**

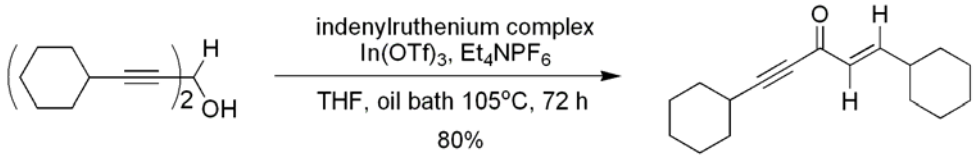
(*E*)-1-cyclohexyldodeca-1,11-dien-3-one (2.20, isomerization of alcohol 2.19 using boric acid as additive) A 45 mg (0.164 mmol) sample of alcohol **2.19** was dissolved in 15 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 5 mg indium (III) trifluoromethanesulfonate (0.0082 mmol, 5 mol%), 7 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.0082 mmol, 5 mol%), and 5 mg boric acid (0.066 mmol, 40 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated to reflux. The reaction was monitored by TLC. After disappearance of starting material, the solvent was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA= 20: 1) to give **2.20** (27 mg, 61% yield) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) *δ* 6.78-6.70 (dd, *J*= 15.9, 6.6 Hz, 1H), 6.05-5.99 (dd, *J*= 16.2, 1.5 Hz, 1H), 5.84-5.73 (ddt, *J*= 16.8, 10.0, 6.4 Hz, 1H), 5.01-4.88 (m, 2H), 2.53-2.48 (t, *J*= 6.8 Hz, 2H), 2.13-2.10 (m, 1H), 2.04-1.99 (m, 2H), 1.76-1.56 (m, 7H), 1.37-1.12 (m, 15H). ^{13}C NMR (400 MHz, $CDCl_3$): *δ* 201.3, 152.1, 139.2, 127.9, 114.2, 40.8, 40.4, 34.0, 32.1, 29.63, 29.55, 29.3, 29.2, 26.2, 26.0, 24.6; IR (neat) ν_{max} 2927, 2854, 1696, 1675, 1627, 1449, 981, 909.



2.19 **2.20**

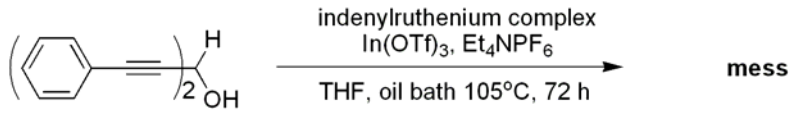
(*E*)-1-cyclohexyldodeca-1,11-dien-3-one (2.20, isomerization of alcohol 2.19 using

CSA as additive) A 45 mg (0.164 mmol) sample of alcohol **2.19** was dissolved in 15 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 5 mg indium (III) trifluoromethanesulfonate (0.0082 mmol, 5 mol%), 7 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.0082 mmol, 5 mol%), and 3 mg camphorsulfonic acid (0.0082 mmol, 5 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated to reflux. The reaction was monitored by TLC. After disappearance of starting material, the solvent was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 20: 1) to give **2.20** (41 mg, 91% yield) as a colorless oil.



2.17 **2.18**

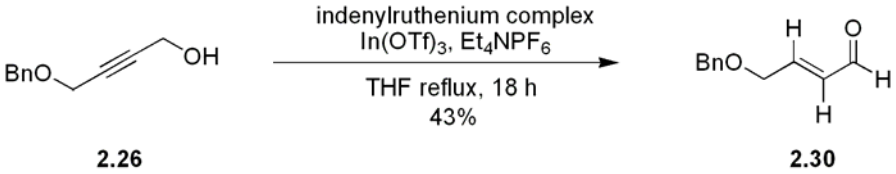
(*E*)-1,5-dicyclohexylpent-1-en-4-yn-3-one (2.18) A 40 mg (0.162 mmol) sample of alcohol **2.17** was dissolved in 6 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 90 mg indium (III) trifluoromethanesulfonate (0.162 mmol, 100 mol%), 14 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.016 mmol, 10 mol%), and 500 mg tetraethylammonium hexafluorophosphate (1.82 mmol, 11.2 eq, will be saturated in 6mL of THF). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube in an oil bath at 105 ^{o}C. After 72 h, the solvent was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 20: 1) to give **2.18** (32.4 mg, 80% yield) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 6.73-6.67 (dd, *J*= 15.6, 2.0 Hz, 1H), 6.55-6.50 (d, *J*= 15.6 Hz, 1H), 2.58-2.47 (m, 2H), 1.95-1.19 (m, 20H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 202.2, 135.3, 125.7, 124.2, 105.3, 49.5, 32.5, 31.6, 30.5, 30.3, 29.9, 28.6, 26.1, 26.0, 25.9, 25.8, 25.0; IR (neat) ν_{max} 2930, 2854, 1713, 1684, 1667, 1628, 1593, 1449, 1265, 1242,1066, 1010, 963.



2.23 (1.13)

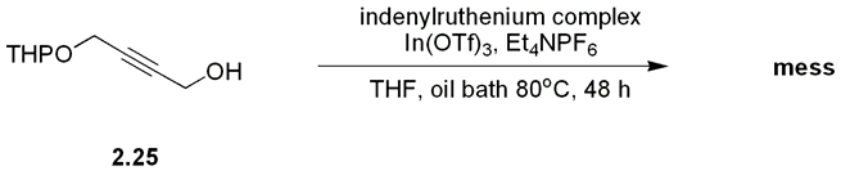
Isomerization approach of alcohol 2.23 (1.13) A 38 mg (0.162 mmol) sample of alcohol **2.23 (1.13)** was dissolved in 6 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 90 mg indium (III) trifluoromethanesulfonate (0.162 mmol, 100 mol%), 14 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.016 mmol, 10 mol%), and 500 mg tetraethylammonium

hexafluorophosphate (1.82 mmol, 11.2 eq, will be saturated in 6mL of THF). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube in an oil bath at 105 ^{o}C. After 72 h, the reaction mixture turned to gel-like polymer. The polymer was dried under reduce pressure. Then the residue was characterized with NMR. No vinyl proton was shown on ^{1}H NMR.



2.26 **2.30**

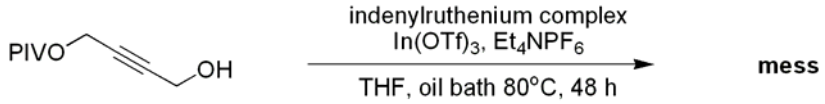
(E)-4-(Benzyloxy)but-2-enal (2.30) A 42 mg (0.240 mmol) sample of 4-(benzyloxy)but-2-yn-1-ol **2.26** was dissolved in 15 mL of freshly distilled THF. Then the resulting solution was added to a solid mixture of 54 mg indium (III) trifluoromethanesulfonate (0.096 mmol, 40 mol%), 10 mg chloro(indenyl)bis-(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.012 mmol, 5 mol%), and 4 mg tetraethylammonium hexafluorophosphate (0.012 mmol, 5 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated to reflux. The reaction was monitored by TLC. After disappearance of starting material, the solvent was removed *in vacuo*. The residue was filtered through a short plug of Florisil with ether and then subjected to flash chromatography (HE: EA= 20: 1) to give **2.30** (18 mg, 43% yield) as a colorless oil. ^{1}H-NMR (400MHz, $CDCl_3$) δ 9.60-9.58 (d, *J*= 8.1 Hz, 1H), 7.38-7.31 (m, 5H), 6.90-6.82 (dt, *J*= 15.6, 3.9 Hz, 1H), 6.46-6.37 (ddt, *J*= 15.6, 7.8, 1.8 Hz, 1H), 4.60 (s, 2H), 4.31-4.29 (dd, *J*= 3.9, 2.1 Hz, 1H); IR (neat) ν_{max} 2928, 2856, 1723, 1692, 1453, 1204, 1113, 1025, 970, 742, 699.



2.25

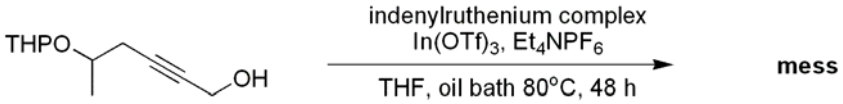
Isomerization approach of alcohol 2.25 A 39 mg (0.240 mmol) sample of **2.25** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 54 mg indium (III) trifluoromethanesulfonate (0.096 mmol, 40 mol%), 10 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.012 mmol, 5 mol%), and 80 mg tetraethylammonium hexafluorophosphate (0.240 mmol, 100 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 80 ^{o}C. After 48 hours, the solvent was removed *in vacuo*. The residue was filtered

through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 20: 1) to separate the components. Two major fractions were collected and no aldehyde proton, vinyl proton or THP group was shown on ^{1}H NMR of these two fractions.



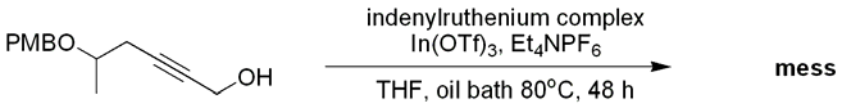
2.27

Isomerization approach of alcohol 2.27 A 80 mg (0.471 mmol) sample of **2.27** was dissolved in 20 mL freshly distilled THF. The solution was added to a solid mixture of 106 mg indium (III) trifluoromethanesulfonate (0.188 mmol, 40 mol%), 81 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.094 mmol, 20 mol%), and 116 mg tetraethylammonium hexafluorophosphate (0.471 mmol, 100 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 80 ^{o}C. After 48 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 20: 1) to separate the components. The major fraction colleted does not have aldehyde proton or vinyl proton based on the H^1 NMR analysis and no carbonyl group was shown on the FT-IR spectrum either.



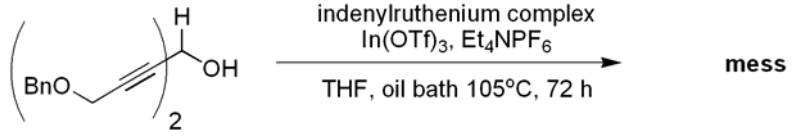
2.28

Isomerization approach of alcohol 2.28 A 48 mg (0.240 mmol) sample of **2.28** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 54 mg indium (III) trifluoromethanesulfonate (0.096 mmol, 40 mol%), 10 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.012 mmol, 5 mol%), and 80 mg tetraethylammonium hexafluorophosphate (0.240 mmol, 100 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 80 ^{o}C. After 48 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 20: 1) to separate the components. Two major fractions were collected. A slight vinyl proton and THP group signal was shown on ^{1}H NMR of the first fraction. However none of the two fractions has aldehyde proton based on ^{1}H NMR analysis.



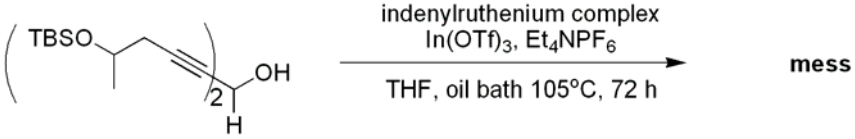
2.29

Isomerization approach of alcohol 2.29 A 52 mg (0.210 mmol) sample of **2.29** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 47 mg indium (III) trifluoromethanesulfonate (0.084 mmol, 40 mol%), 9 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.010 mmol, 5 mol%), and 58 mg tetraethylammonium hexafluorophosphate (0.210 mmol, 100 mol%). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 80°C. After 48 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and the filtrate was concentrated in *vacuo*. The crude ^{1}H NMR of the resulting residue shows a little PMB group signal but no vinyl proton signal. No target molecule or starting material was separated using TLC plate.



1.11

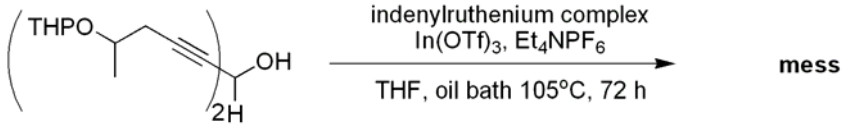
Isomerization approach of alcohol 1.11 A 100 mg (0.313 mmol) sample of **1.11** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 176 mg indium (III) trifluoromethanesulfonate (100 mol%), 54 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.0625, 20 mol%), and 500 mg tetraethylammonium hexafluorophosphate (saturated). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 105°C. After 72 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 10: 1) to separate the components. The major fraction colleted does not have aldehyde proton or vinyl proton based on the H^{1} NMR analysis and no carbonyl group was shown on the FT-IR spectrum either.



1.15

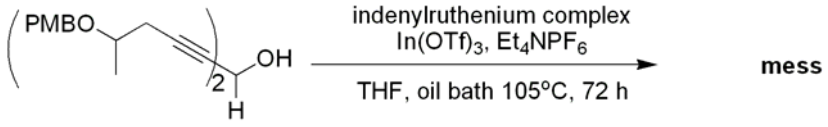
Isomerization approach of alcohol 1.15 A 20 mg (0.047 mmol) sample of **1.15** was

dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 26 mg indium (III) trifluoromethanesulfonate (100 mol%), 4 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (10 mol%), and 500 mg tetraethylammonium hexafluorophosphate (saturated). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 105°C. After 72 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 10: 1) to separate the components. The major fraction colleted does not have aldehyde proton or vinyl proton based on the H^1 NMR analysis and no carbonyl group was shown on the FT-IR spectrum either.



1.16

Isomerization approach of alcohol 1.16 A 46 mg (0.116 mmol) sample of **1.16** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 65 mg indium (III) trifluoromethanesulfonate (0.116 mmol, 100 mol%), 10 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.012 mmol, 10 mol%), and 500 mg tetraethylammonium hexafluorophosphate (saturated). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 105°C. After 72 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA = 10: 1) to separate the components. Two major fractions were collected and none of them has vinyl proton or THP group based on ^{1}H NMR analysis.



1.17

Isomerization approach of alcohol 1.17 A 32 mg (0.068 mmol) sample of **1.17** was dissolved in 6 mL freshly distilled THF. The solution was added to a solid mixture of 38 mg indium (III) trifluoromethanesulfonate (0.068 mmol, 100 mol%), 6 mg chloro(indenyl) bis(triphenylphosphine) ruthenium (II), dichloromethane adduct (0.007 mmol, 10 mol%), and 500 mg tetraethylammonium hexafluorophosphate (saturated). After addition of the substrate, the homogeneous red solution was stirred for several minutes at room temperature and gradually heated in the pressure tube with oil bath at 105°C. After 72 hours, the solvent was removed *in vacuo.* The residue was filtered through a short plug of Florisil with ether and then subjected to preparative TLC (HE: EA

= 10: 1) to separate the components. The two major fractions collected do not have aldehyde proton or vinyl proton based on the H^1 NMR analysis and no carbonyl group was shown on the FT-IR spectrum either.

PART THERE

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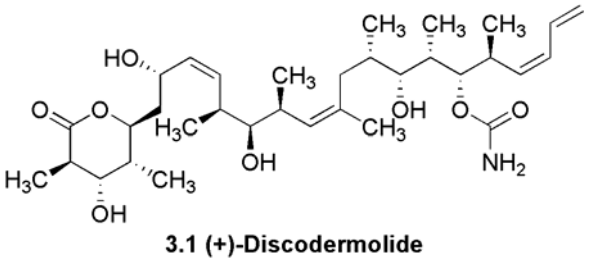
3.4 EXPERIMENTAL SECTION

3.1 INTRODUCTION

3.1.1 Background of (+)-Discodermolide

(+)-Discodermolide (**3.1**, Figure **3-1**), a marine sponge natural product that stabilizes microtubules and maintains activity against multidrug resistant cell lines, advanced to Phase I examination before being discontinued by Novartis due to excessive drug toxicity. Some analogues of discodermolide are still advancing in preclinical studies.[24]



3.1 (+)-Discodermolide

Figure 3-1 Structure of (+)-discodermolide

Discodermolide was first reported to be isolated from the Caribbean sponge *Discodermia dissoluta* by Gunasekera and co-workers at the Harbor Branch Oceanographic Institute in 1990. The sponge was collected at Lucay, Grand Bahama Island at a depth of 33 m. It was extracted by methanol/toluene (3:1) to yield an extract that was partitioned between ethyl acetate and water. Crystalline discodermolide was purified by silica gel and reversed-phase chromatography from the ethyl acetate soluble material. The isolation yield was 0.002% (w/w from frozen sponge). Therefore, extraction is an impractical method for procuring enough of the compound for clinical trials.[25]

The structure of discodermolide was elucidated by an x-ray crystallographic study and by extensive NMR spectroscopic studies, including a combination of 1H, 13C, COSY experiments, 2D C-H correlation experiments, 2D long-range C-H correlation experiments and decoupling experiments. It was shown that discodermolide contains a U-shaped linear polypropionate backbone. There are a lactone carbonyl, one carbamate carbonyl, seven secondary methyls, one olefinic methyl, two methylenes, six oxygen-bearing methine carbons, seven carbon methines, a monosubstituted double bond, two disubstituted double bonds, a trisubstituted double bond, and at least three exchangeable protons. The most important feature for synthesis is a common stereo triad (methyl, hydroxyl and methyl) that is repeated three times (C2-C4, C10-C12 and C18-C20) in the molecule. Later, the absolute configuration was established during the

[24] Dunlap, W. C.; Battershill, C. N.; Liptrot, C. H.; Cobb, R. E.; Bourne, D. G.; Jaspars, M.; Long, P. F.; Newman, D. J. *Methods*, **2007**, *42*, 358-376.
[25] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. Additions and corrections *J. Org. Chem.* **1991**, *56*, 1346.

Schreiber group's synthetic work.[26]

(+)-Discodermolide acts upon microtubules by stabilizing the heterodimer composed of α- and β-tubulin subunits and blocks cells at the G2/M phase of the cell cycle in a manner similar to that of paclitaxel (**3.2** Taxol, a clinically important anticancer drug of Bristol-Myers Squibb.). The binding activity of (+)-discodermolide is about 100 times greater than that of paclitaxel.[27] (+)-Discodermolide's ability to competitively inhibit paclitaxel binding to microtubules strongly suggests the existence of a common binding site. Through rationalizing the extensive structure–activity relationship data pertinent to (+)-discodermolide and paclitaxel, Ojima, Danishefsky and co-workers proposed a common pharmacophore that unites these two compounds (Figure **3-2**).[28,29] Unlike other microtubule-stabilizing agents (MSA), such as epothilones and eleutherobin, (+)-discodermolide encounters 37-fold less resistance than paclitaxel in paclitaxel-resistant cells, and 21-fold less resistance in cells containing β-tubulin mutations at the paclitaxel binding site. (+)-Discodermolide has also been shown to act synergistically with paclitaxel. The toxicity of (+)-discodermolide will be amplified by 20 fold in the presence of a low concentration of paclitaxel.[30]

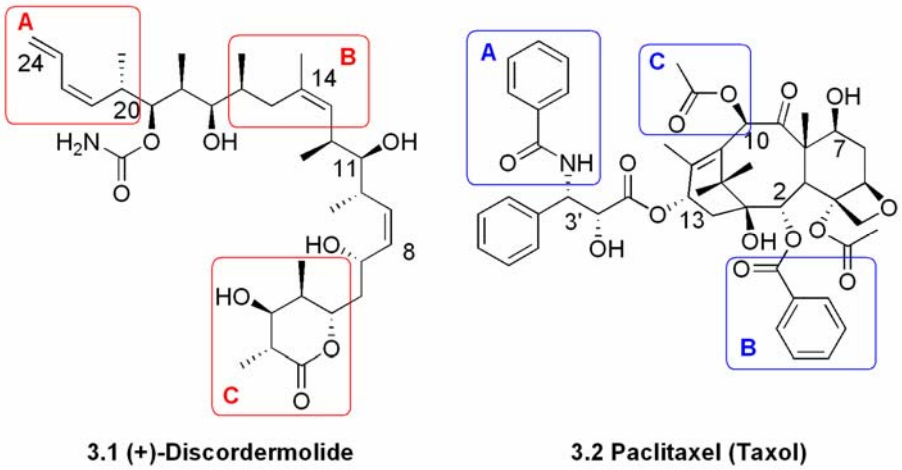


Figure 3-2 Structures of discodermolide and paclitaxel (Taxol). Labeled boxed regions are predicted areas of common overlap.

3.1.2 Previous Total Syntheses of (+)-Discodermolide

Due to the ability of (+)-discodermolide to escape the multidrug resistance (MDR)

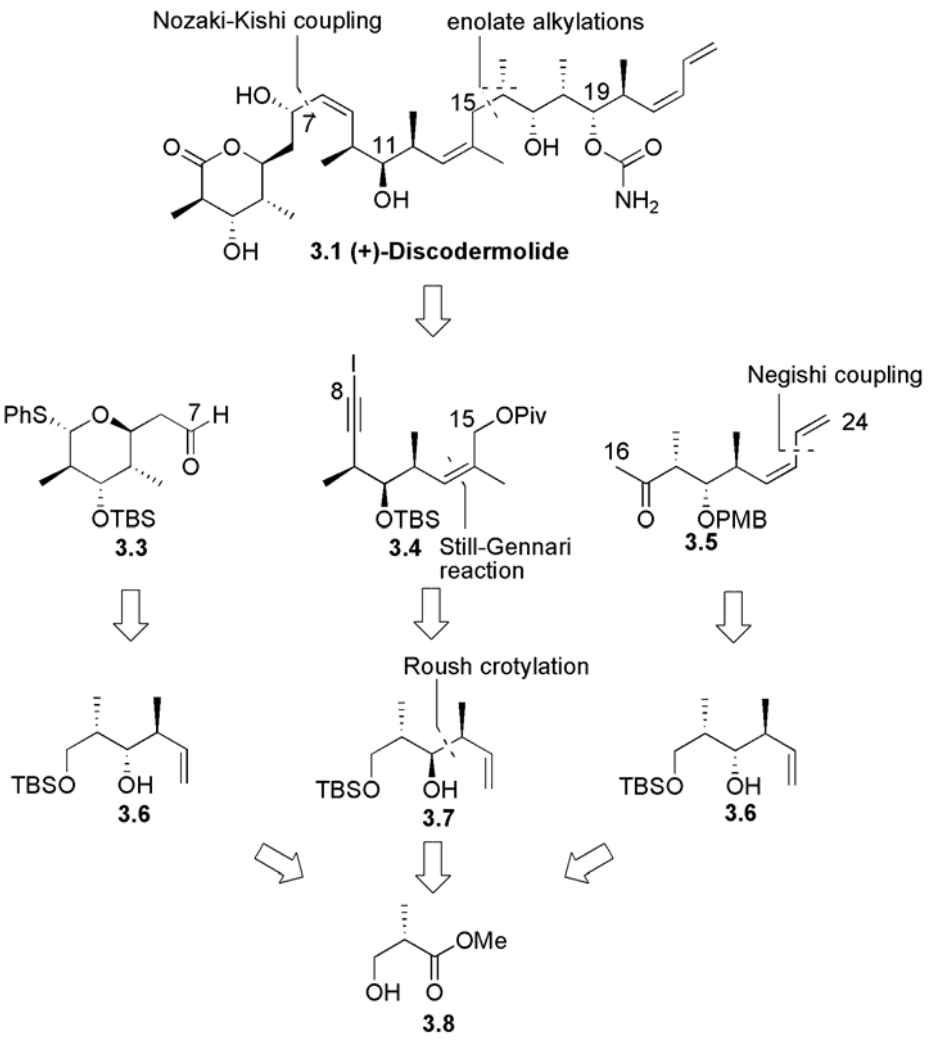
[26] (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621. (b) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11054.
[27] (a) Kowalski, R. J., Giannakakou, P., Gunasekera, S. P., Longley, R. E., Day, B. W., Hamel, E. *Mol. Pharmacol*. **1997**, *52*, 613-622. (b) Huang, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol*. **1996**, *3*, 287
[28] Xia, S., Kenesky, C. S.; Rucker, P. V.; Smith, A. B. III; Orr, G. A.; Horwitz, S. B. *Biochemistry* **2006**, *45*, 11762
[29] Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; Danishefsky, S. J., *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4256
[30] Martello, L. A.; McDaid, H. M.; Regl, D. L.; Yang, C. P.; Meng, D.; Pettus, T. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, A. B. III; Horwitz, S. B. Clin. *Cancer Res.* **2000**, *6*, 1978.

pathway (by way of an ATP-binding cassette[31]) coupled with its synergism with paclitaxel, (+)-discodermolide stands as an attractive lead compound for drug discovery. In 1999, Novartis Pharmaceuticals Corp. licensed discodermolide to develop it as a new-generation anticancer drug. To date, nine different research groups have accomplished total syntheses of discodermolide; however many of these syntheses use the expensive starting material Roche ester as a chirality source and suffer from steps that are not practical on a larger scale. Five selected previous total syntheses are presented here.

3.1.2.1 Schreiber Synthesis of (+)-Discodermolide[32]

The first total synthesis of discodermolide was accomplished by Schreiber's group. In a convergent approach (Scheme **3-1**), the polypropionate backbone of discodermolide was divided into three fragments of similar complexity. These three subunits **3.3**, **3.4**, and **3.5** were retrosynthetically reduced to the homoallylic alcohols **3.6** and **3.7**. The Roush asymmetric crotylation of a chiral aldehyde derivative from Roche ester **3.8** established the stereotriads in intermediates **3.6** and **3.7**. The Nozaki-Kishi coupling of fragments **3.3** and **3.4** resulted a dr = 2:1 stereoselectivity at C7. The minor epimer could be efficiently recycled. The resulting piece was elaborated and coupled with fragment **3.5** by enolate alkylation. The methyl group on C16 was introduced by alkylation with dr = 3:1. This total synthesis approach afforded discodermolide in 4.3% overall yield and with a longest linear sequence of 24 steps.

[31] Locher, K. P. Curr. Opin. Struct. Biol. 2004, 14, 426-431.
[32] (a) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chen. Soc.* **1996**, *118*, 11054. (b) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 12621



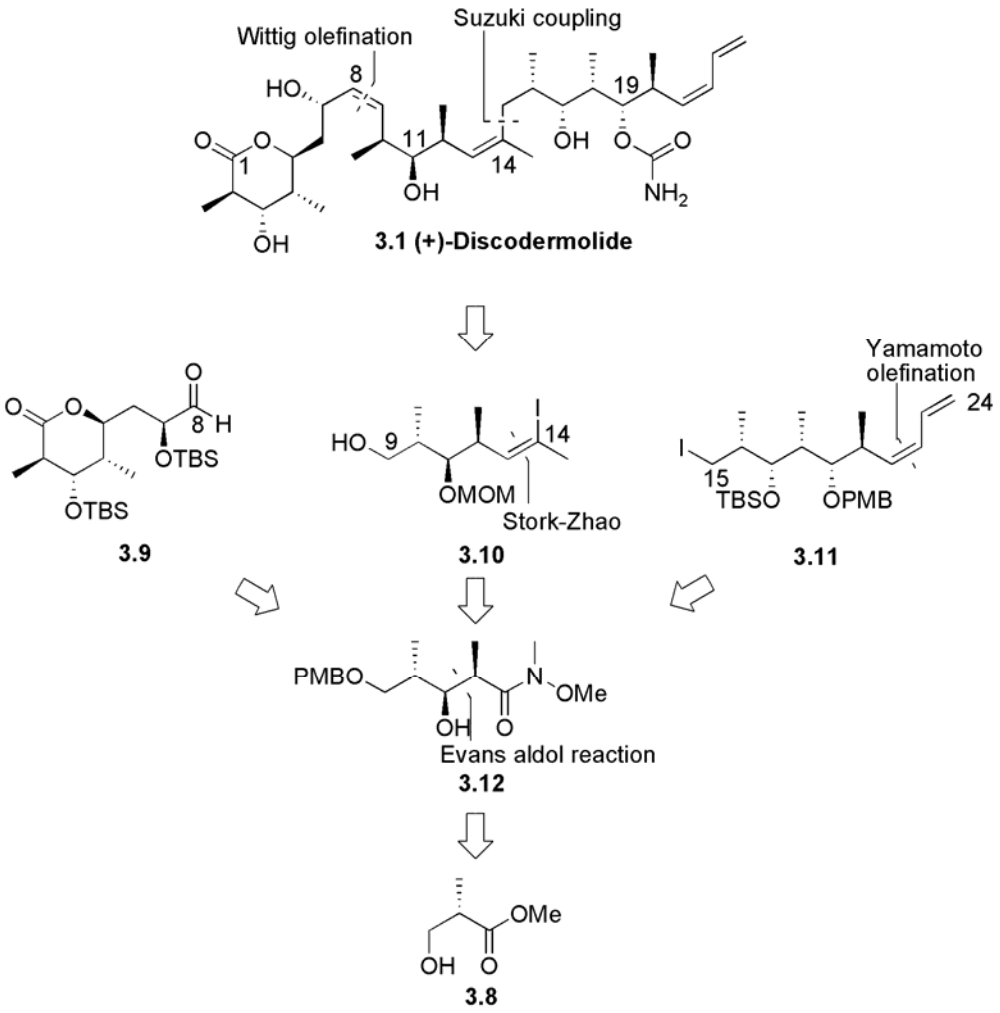
Scheme 3-1 Schreiber strategy for the total synthesis of (+)-discodermolide (**3.1**)

3.1.2.2 Smith Synthesis of (+)-Discodermolide[33]

The Smith group developed four generations of approaches to the total synthesis of discodermolide. An efficient, convergent and stereoselective fourth-generation total synthesis of discodermolide was revised (Scheme **3-2**). In this approach, disconnections at C8-C9, C14-C15 generated three fragments **3.9**, **3.10** and **3.11**, all of them were derived from common precursor **3.12**. The (*Z*)-alkenyl iodide in compound **3.10** was constructed by Stork-Zhao reaction with a moderate yield (40%). Compound **3.9**, **3.10** and **3.11** were coupled together by Wittig olefination and Suzuki coupling. A Yamamoto olefination efficiently established the terminal diene with correct stereostructure. The stereotriad in common precursor **3.12** was configured by Evans syn-aldol protocol from Roche ester. The fourth generation of Smith's synthesis proceeded in 9.0% yield over a

[33] (a) Smith, A. B. III; Qiu, Y. P.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (b) Smith, A. B. III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett.* **1999**, *1*, 1823. (c) Smith, A. B. III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (d) Smith, A. B. III; Freeze, B. S.; Brouard, I.; Hireose, T. *Org. Lett.* **2003**, *5*, 35. (e) Smith, A. B. III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett*. **2005**, *7*, 1825.

17-step longest liner sequence.



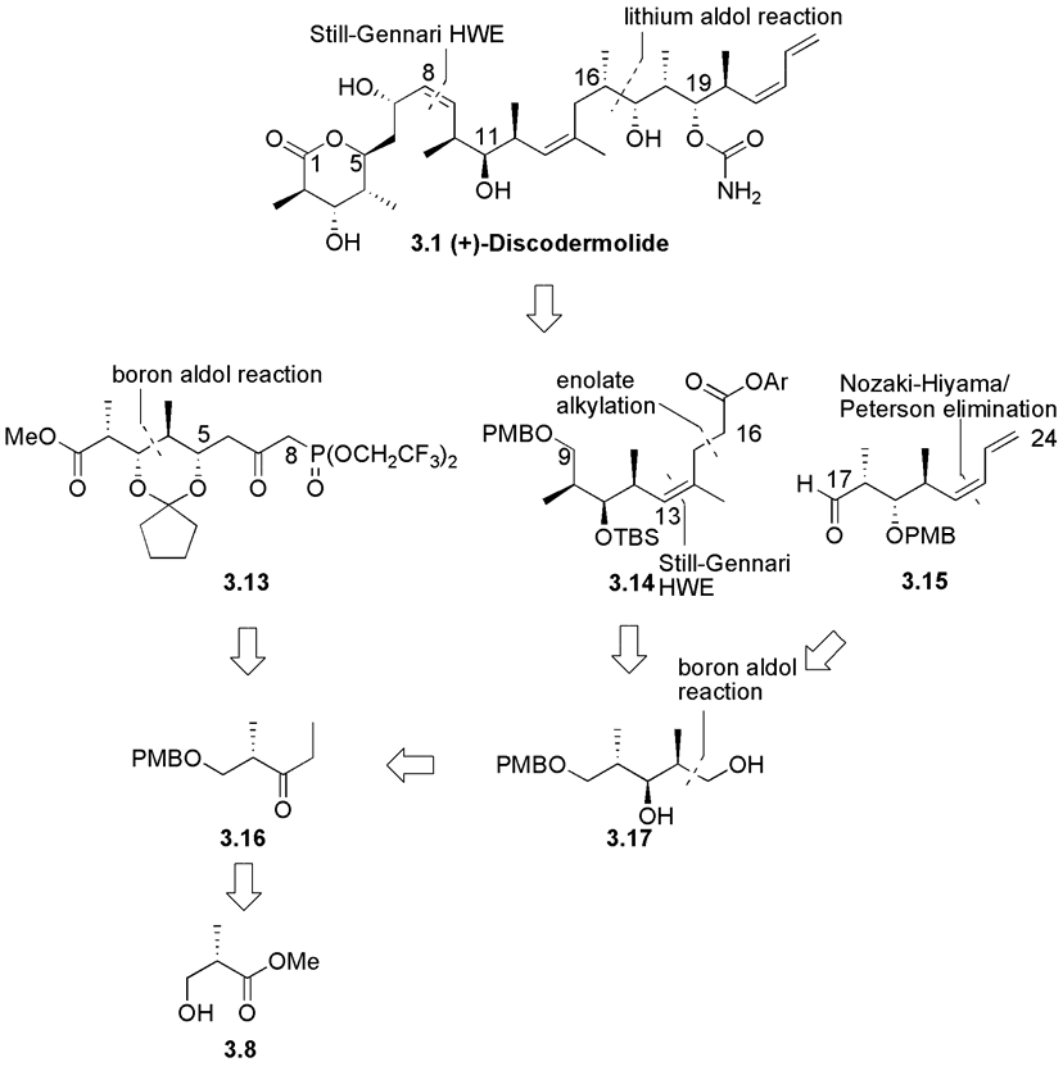
Scheme 3-2 Smith strategy for the total synthesis of (+)-discodermolide (**3.1**)

3.1.2.3 Paterson Synthesis of (+)-Discodermolide[34]

Three generations of strategies to synthesis (+)-discodermolide was developed by Paterson and co-workers. The use of chiral reagents (chiral auxiliaries) and the length of sequence were greatly reduced in the third generation synthesis (Scheme **3-3**) relative to those of the two precious generations. In this third-generation synthesis, fragments **3.14** and **3.15** were first assembled by a lithium-mediated aldol reaction with dr = 6:1. The resulting advanced intermediate was modified and was coupled with fragment **3.13** by a

[34] (a) Paterson, I.; Florence, G.J.; Gerlach, K.; Scott, J. P. *Angew. Chem. Int. Ed.* **2000**, *39*, 377. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535. (c) Paterson, I; Delgado, O; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35. (d) Paterson, I.; Lyothier, I.; *Org. Lett.* **2004**, *6*, 4933. (e) Paterson, I.; Lyothier, I. *J. Org. Chem.* **2005**, *70*, 5494.

Still-Gennari type Horner-Wadsworth-Emmons (HWE) reaction. Both intermediate **3.14** and **3.15** were derived from a common precursor **3.17** and both **3.17** and **3.13** were both synthesized from PMB protected β-hydroxyl ketone **3.16**. Compound **3.16** was produced from modification of Roche ester **3.8** in 5 steps. It was claimed that the Paterson's third generation approach afforded discodermolide in 11.1% overall yield and with a longest linear sequence of 21 steps.



Scheme 3-3 Paterson strategy for the total synthesis of (+)-discodermolide (**3.1**)

3.1.2.4 The Novartis Group's Synthesis of Discodermolide[35]

The chemical and analytic development group of Novartis Pharmaceuticals Corp. reported two formal syntheses and one large-scale total synthesis of (+) discodermolide by using a hybridized Novartis-Smith-Paterson synthetic route (Scheme **3-4**). Mickel and co-workers achieved 60 grams of (+)-discodermolide in 36 steps with a longest liner sequence of 26 steps. In this convergent approach, retrosynthetic disconnections at C6-C7 generated fragments **3.18** and **3.19**. Further disconnection of **3.19** at C8-C9, C14-C15, and C21-C22 generated two fragments **3.20** and **3.21**. Compounds **3.18**, **3.20** and **3.21** were all envisioned to arise from the common precursor **3.12** of the Smith synthesis, which was configured by Evans syn-aldol protocol from the chirality source Roche ester. The (*Z*)-alkenyl iodide in compound **3.20** was introduced by Stork-Zhao reaction and then coupled with **3.21** by Suzuki coupling reaction. Paterson's Still-Gennari type HWE reaction strategy to establish the C8-C9 *cis*-double bond and Nozaki-Hiyama/Peterson elimination strategy to establish the terminal diene were adopted to construct the advanced intermediate **3.19**. A facile boron aldol reaction was used to couple **3.18** and **3.19** to achieve (+)-discodermolide. Although sufficient material for early-stage human clinical trials was produced, there are still unsolved problems, such as the difficulty of scaling up the boron aldol reaction and consumption of large amount Roche ester. Also, the final steps of the approach need to be kept simple.

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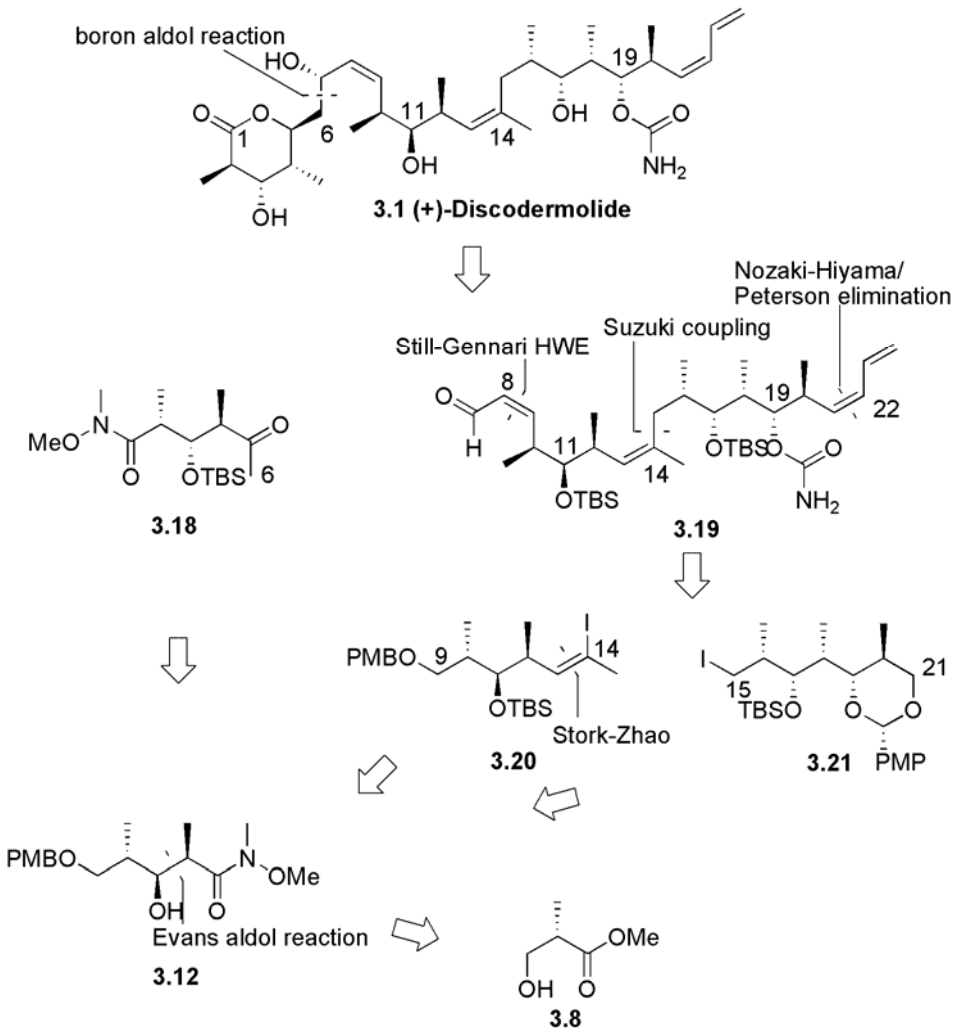
[35] (a) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-weibel, M.; Berod, B.; Schaer, K.; Gamboni, R.; Chen, S.; Chen, W.; Jagoe, C. T.; Kinder, F. R. Jr.; Loo, M.; Prasad, K.; Repic, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 92. (b) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Grimler, D.; Koch, G.; Daeffler, R.; Osmani, A.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chaudhary, A.; Chen, S.; Chen, W.; Hu, B.; Jagoe, C. T.; Kim, H.-Y.; Kinder, F. R., Jr.; Liu, Y.; Lu, Y.; McKenna, J.; Prashad, M.; Ramsey, T. M.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 101. (c) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Grimler, D.; Koch, G.; Kuesters, E.; Daeffler, R.; Osmani, A.; Seeger-Weibel, M.; Schmid, E.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, S.; Chen, W.; Geng, P.; Jagoe, C. T.; Kinder, F. R. Jr.; Lee, G. T.; McKenna, J.; Ramsey, T. M.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. De*v. **2004**, *8*, 107. (d) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Daeffler, R.; Osmani, A.; Bixel, D.; Loiseleur, O.; Cercus, J.; Steler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G. P.; Chen, W.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R. Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 113. (e) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev.* **2004**, *8*, 122.



Scheme 3-4 Novartis strategy for the total synthesis of (+)-discodermolide (**3.1**)

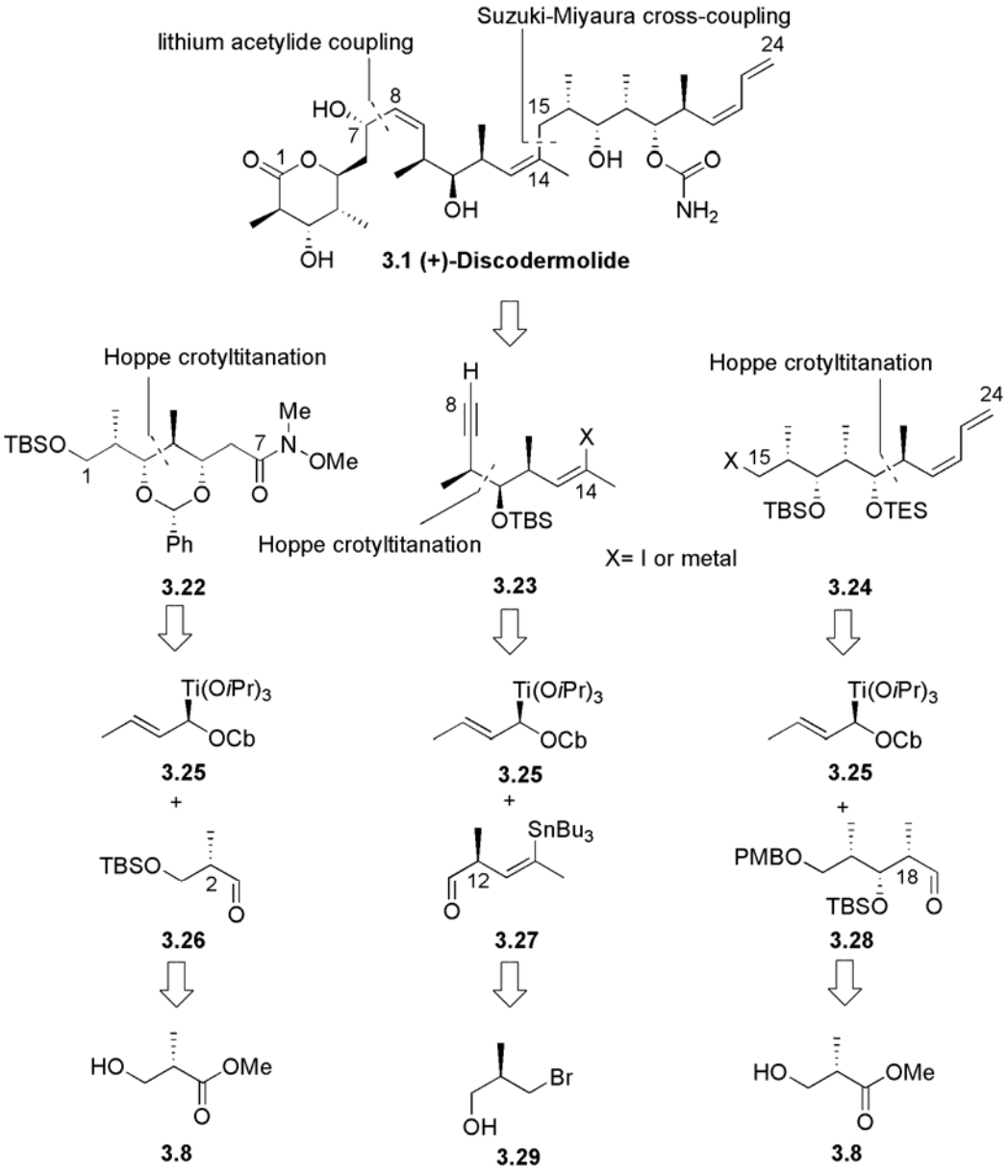
3.1.2.5 The Ardisson Group's Synthesis of Discodermolide[36]

Recently, the Ardisson group at Universite de Cergy-Pontoise (collaborated with Sanofi Aventis) reported total synthesis of (+) discodermolide by a synthetic route shown in Scheme **3-5**. Ardisson and co-workers synthesized (+)-discodermolide in 1.6% overall yield with a longest liner sequence of 21 steps. In this convergent approach, retrosynthetic disconnections at C7-C8 and C14-C15 generated three fragments **3.22, 3.23** and **3.24**. All of these three *syn-anti* stereotriad containing subunits were constructed by an allylation reaction developed by Hoppe[37] of enantioenriched *R*-α-oxygenated crotyltitanium **3.25** with α-(*S*)-methyl aldehydes **3.26**, **3.27** and **3.28**. Both of α-(*S*)-methyl aldehydes **3.26** and **3.28** were obtained from Roche ester **3.8**. Aldehyde **3.27** was obtained from

[36] de Lemos, E.; Poree, F.-H.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem. Int. Ed. Engl.* **2007**, *11*, 1917-1921

[37] a) Hoppe, D. *Angew. Chem.* **1984**, *96*, 930 – 946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932 – 948; b) Hoppe, D.; Zschage, O. *Angew. Chem.* **1989**, *101*, 67 – 69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69 – 71; c) Hoppe, D.; Zschage, O. *Tetrahedron* **1992**, *48*, 8389 – 8392.

commercial available (R)-3-bromo-2-methylpropan-1-ol **3.29**. The *Z*-*O*-enecarbamate groups in the produced triads of crotyltitanation reaction were directly transformed to either a triple bond or terminal *Z* diene functions. The trisubstituted *Z* double bond between C7 and C8 was constructed by dyotropic rearrangement. The C14-C15 σ bond was formed by a Suzuki-Miyaura cross-coupling reaction.

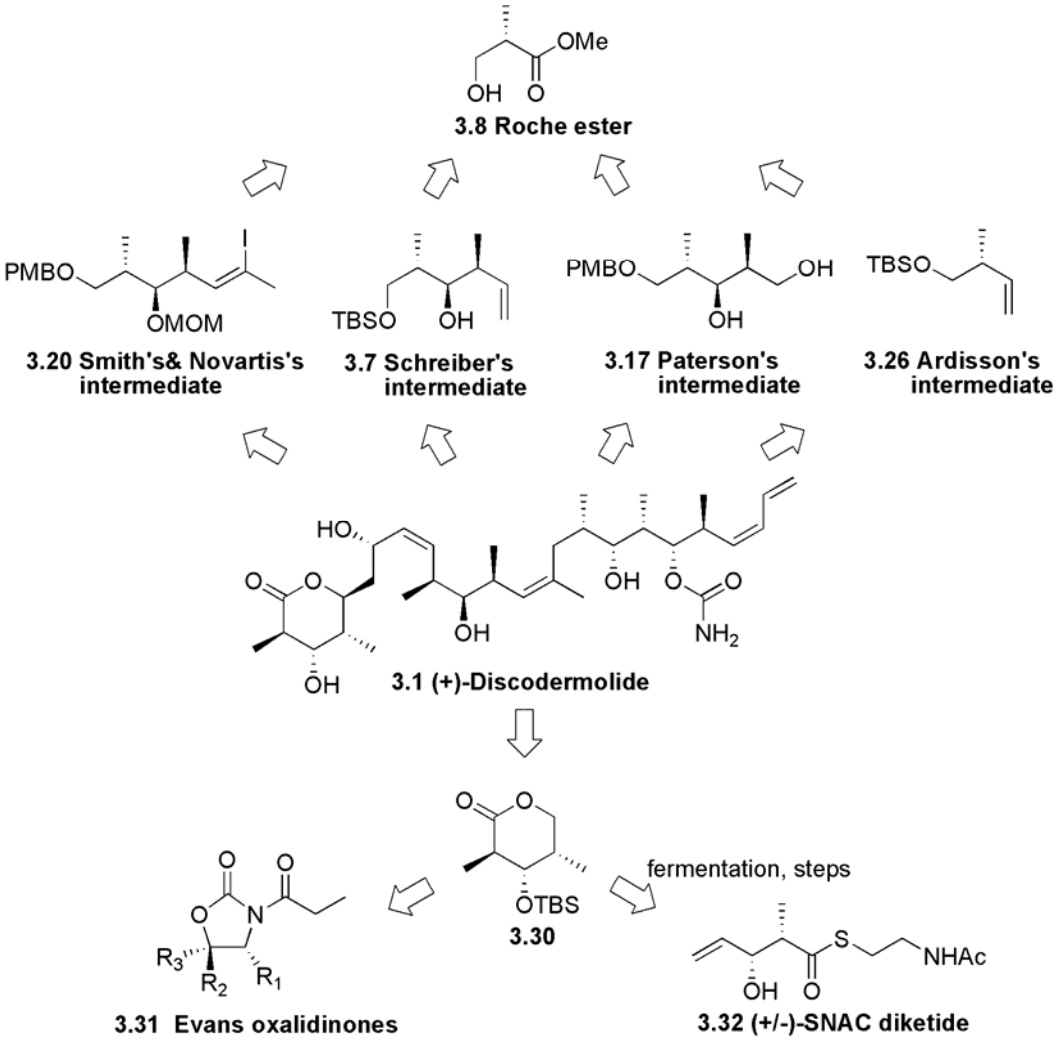


Scheme 3-5 Ardisson strategy for the total synthesis of (+)-discodermolide (**3.1**)

3.1.2.6 Chirality Sources Used in Previous Syntheses of (+)-Discodermolide

All of the completed total syntheses of (+)-discodermolide have relied on the Roche ester as the source of chirality and enantioselective chain extensions for construction of the building blocks. Most syntheses required additional chiral reagents or chiral

auxiliaries (Scheme **3-6**). There are two recent studies that demonstrated the applications of other chirality sources. In almost simultaneous disclosures, Dias[38] and Day[39] and later the Novartis group[40] have described the use of recoverable auxiliaries **3.31** as the sources of chiral induction in Evans aldol condensations with methacrolein. The resulting stereodiads were then converted to the stereotriad-containing lactone **3.30** which has been converted to common precursors of the Smith and Novartis syntheses.[33, 35b] Recently, Burlingame and co-workers at Kosan prepared this key lactone by chemical modification of a precursor which was produced from synthetic racemic "diketide thioesters" **3.32**[41] via fermentation using bacteria with modified 6-dEB PKS genes.[42]



Scheme 3-6 Chirality sources used in previous synthesis of (+)-discodermolide""""

[38] Dias, L. C.; Bau, R. Z.; de Sousa, M. A.; Zukerman-Schpector, J.*Org. Lett*. **2002**, *4*, 4325.

[39] Day, B. W.; Kangani, C. O.; Avor, K. S. *Tetrahedron: Asymmetry* **2002**, *13*, 1161.

[40] Loiseleur, O.; Koch, G.; Wagner, T. *Org. Process Res. Dev.* **2004**, *8*, 597.

[41] Burlingame, M. A.; Mendoza, E.; Ashley, G. A. *Tetrahedron Lett*. **2004**, *45*, 2961.

[42] Regentin, R.; Kennedy, J.; Wu, N.; Carney, J. R.; Licari, P.; Galazzo, J.; Desai, R. *Biotechnol. Prog*. **2004**, *20*, 122.

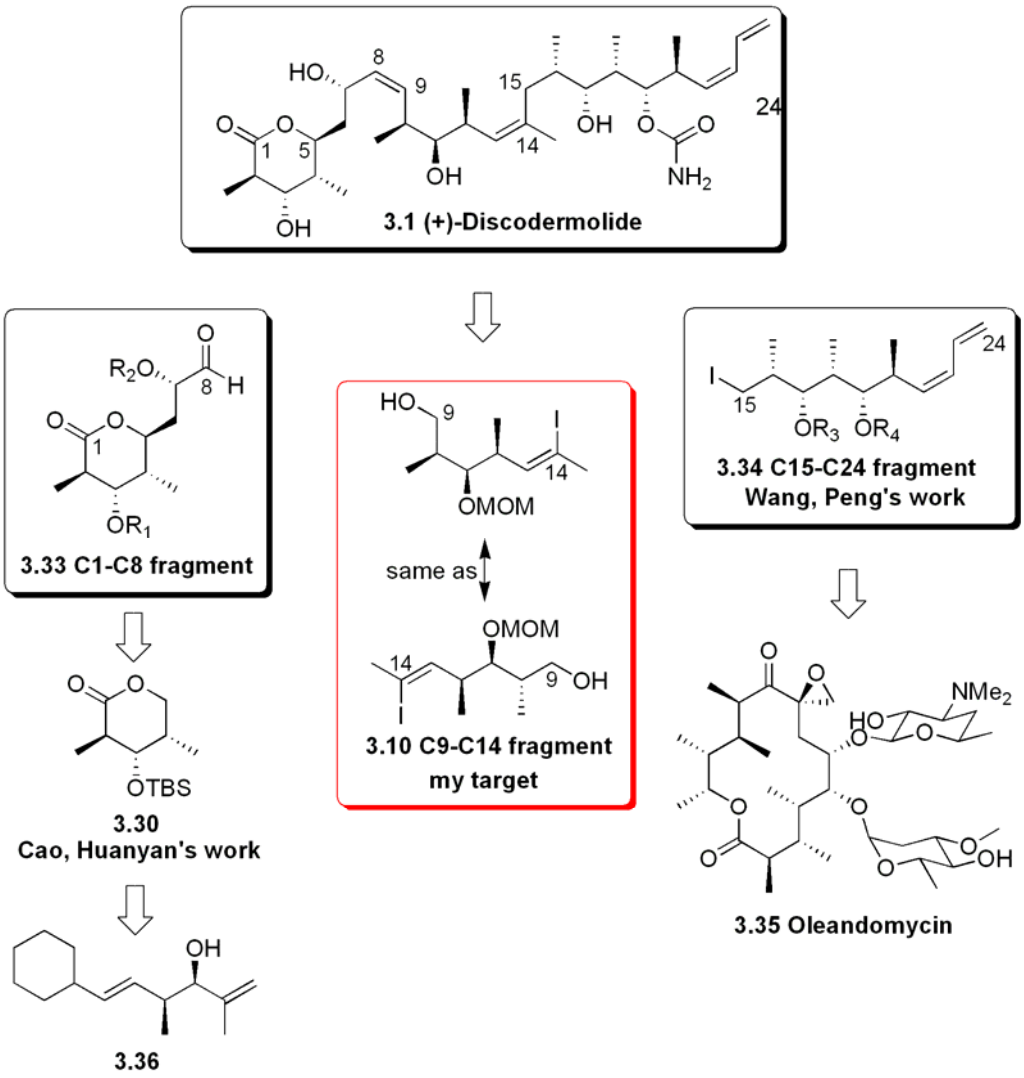
3.1.3 Our Strategy

Considering the complex molecular structure of (+)-discodermolide, a convergent strategy will be the first choice to keep the synthesis sequence short and efficient. Our strategy is based on the disconnections at C8-C9 (same as Smith and Paterson's strategy), C14-C15 generated three fragments **3.33**, **3.10** and **3.34**. The C8-C9 *cis*-double bound could later be established by a Wittig olefination (Smith's strategy) or Still-Gennari HWE reaction (Paterson's strategy). The C14-C15 carbon bound could later be constructed by Suzuki or Negishi coupling (Smith or Ardisson's strategy, Scheme **3-7**).

Our initial plan was to prepare stereopentad **3.34** from degradation of oleandomycin **3.35** followed by semisynthesis. The project of synthesis of the C15-C24 piece **3.34** was completed by Dr. Peng Wang, one of my colleagues in Parker's group.

The C1-C8 piece **3.33** was synthesized by another colleague Dr. Huanyan Cao.[43] The key intermediate lactone **3.30** was synthesized from allylic alcohol **3.36** which was derived from cyclohexanecarboxaldehyde. The sequence provided lactone **3.30** in 7 steps with 41% yield over all. According to Novartis groups' recently work and Smith's previous total synthesis, lactone **3.30** could be further modified to the C1-C8 fragment **3.33** in 6 steps with 45% yield. While my colleagues concentrated on the C1-C8 fragment (**3.33**) and C15-C24 fragment (**3.34**), my work focuses on the synthesis of the C9-C14 stereotriad moiety (**3.10**). The synthesis of C9-C14 fragment **3.10** will be discussed in the following part.

[43] Parker, K. A.; Cao, H. *Org. Lett*. **2006**, *16*, 3541-3544.

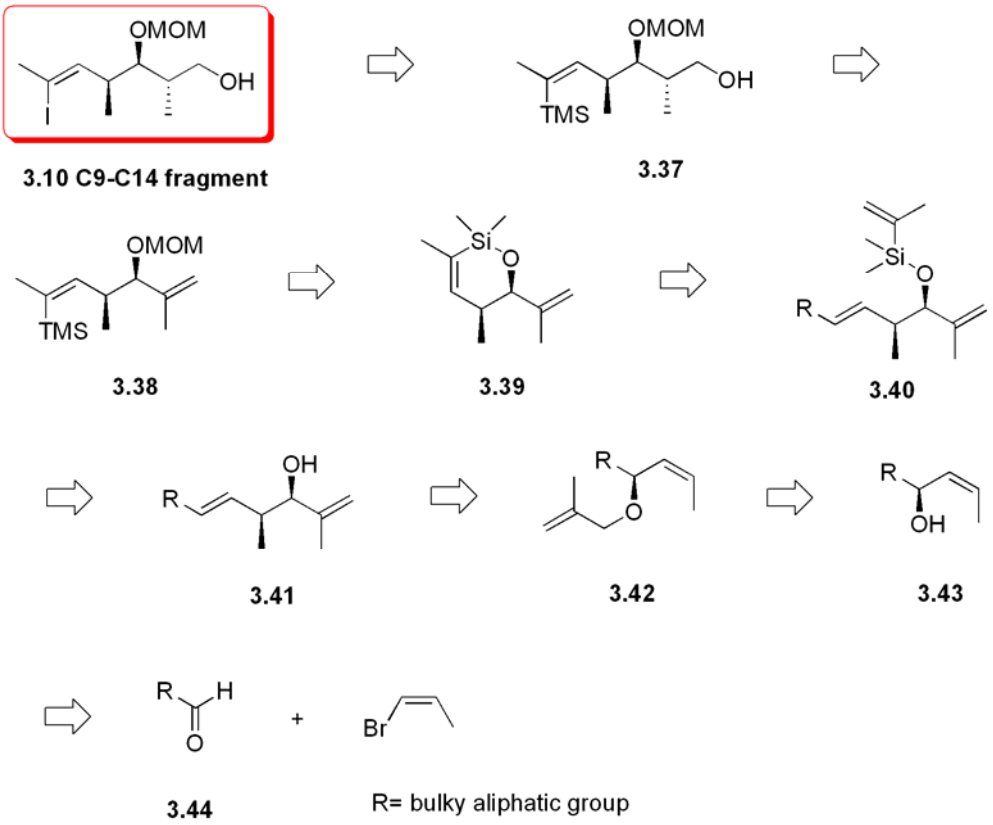


Scheme 3-7 Our strategy towards synthesis of (+)-discodermolide (**3.1**)

3.1.3.1 Retrosynthetic Strategy of the C9-C14 Fragment 3.10

Our retrosynthetic strategy of the C9-C14 fragment **3.10** of discodermolide is shown in Scheme **3-8**. The C9-C14 fragment **3.10** could be conveniently obtained by iododesilylation of MOM protected *syn*, *anti*-stereotriad **3.37**, which could be obtained from MOM protected *syn*-allylic alcohol **3.38** by stereoselective hydroboration followed by oxidation. MOM protected *syn*-allylic alcohol **3.38** could be constructed by MOM protection of the related alcohol which could be obtained by nucleophilic ring-opening addition of methyllithium with *syn*-allylic dihydro oxasiline **3.39**. The *syn*-allylic dihydro oxasiline **3.39** could be constructed by ring-closing metathesis of *syn*-allylic silyl ether **3.40**, which could be obtained by silylation of *syn*-allylic alcohol **3.41**. It was reported that *syn*-allylic alcohol **3.41** with two stereo centers could be constructed from (*S*)-diallylic ether **3.42**, which underwent the [2,3]-Wittig rearrangement in basic conditions to form **3.41**. A bulky aliphatic group at the allyl position of the (*Z*)-olefin (i.e. bulky R) in the (*S*)-diallylic ether **3.42** would improve the stereo selectivity of the

rearrangement step. Simple alkylation of (*S*, *Z*)-allyl alcohol **3.43** with 3-chloro-2-methylprop-1-ene could produce (*S*)-diallylic ether **3.42** handily. Enantioselective addition of (*Z*)-1-bromoprop-1-ene to aldehyde **3.44** could provide (*S*,*Z*)-allyl alcohol **3.43** conveniently. The *β* carbon of aldehyde **3.44** needs to be tertiary or quaternary substituted to give high enantioselectivity.[44]



Scheme 3-8 Retrosynthetic strategy of the C9-C14 fragment **3.10**

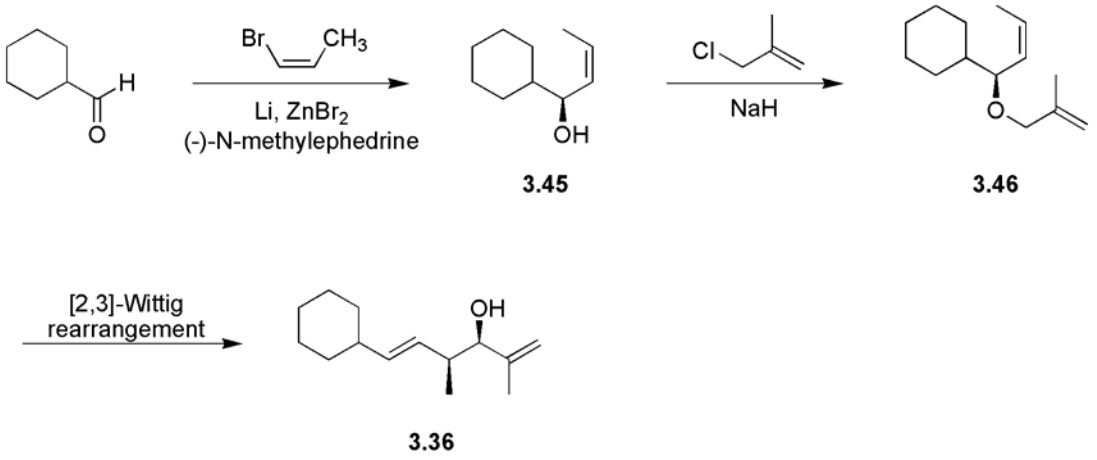
3.2 RESULTS AND DISCUSSION

3.2.1 Synthesis of (*syn*, *E*)-allyl alcohol 3.36

In 2006, Parker and Cao reported a convenient synthesis of (*syn*, *E*)-allyl alcohol **3.36** from cyclohexanecarbaldehyde by a 3-step sequence: catalytic enantioselective addition, alkylation and [2,3]-Wittig rearrangement sequentially (Scheme **3-9**). Our initial plan was

[44] Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

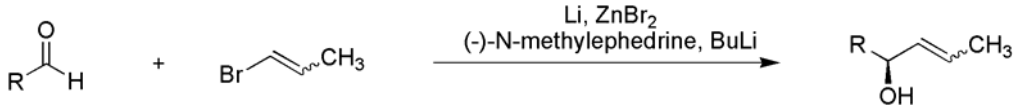
designed to adopt this strategy and construct the C9-C14 fragment from precursor **3.36** (eg. to **3.41** in Scheme **3-8**). An attempt to demonstrate this approach was carried out in the racemic series. Detailed background and results will be discussed in the following sections.



Scheme 3-9 Synthesis of (*syn*, *E*)-allyl alcohol **3.36** by Parker and Cao

3.2.1.1 Synthesis of (*S*,*Z*)-Allyl Alcohol 3.45

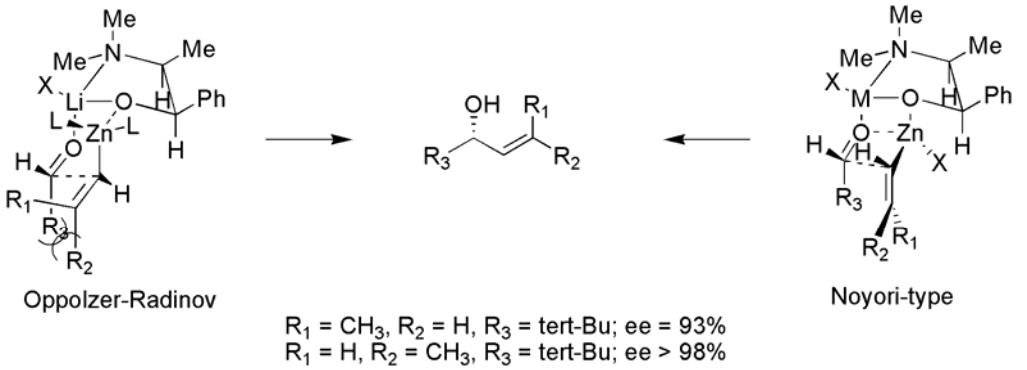
In 1991, Oppolzer and co-workers reported that a catalytic enantioselective addition of 1-propenyl zinc bromide with (-)-N-methylephedrine as ligand to an aldehyde could produce a chiral secondary alcohol with good yield and high ee (Scheme **3-10**).



Scheme 3-10 Zinc catalyzed enantioselective addition

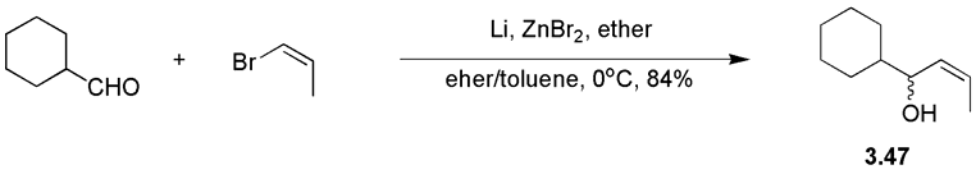
Oppolzer and Radinov suggested the cyclic Zimmerman-Traxler-type transition state to explain the high enantioselectivity of the addition reaction. Although this arrangement is consistent with the enantioselectivity observed, it can't explain the following results: the addition of (*Z*)-1-propenylzinc bromide ($R^1 = CH_3$, $R^2 = H$) to pivaldehyde ($R^3 = t$-Bu) provides an adduct of lower ee than the corresponding addition of (*E*)-1-propenylzinc bromide ($R^1 = H$, $R^2 = CH_3$). A currently accepted Noyori-type mechanism[45] proposed by Marshall for N-methylephedrine-directed addition reaction could explain this observation (Scheme **3-11**).[46]

[45] Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327-6335.
[46] Mashall, J. A.; Eidam, P. *Org. Lett*. **2004**, *6*, 445.



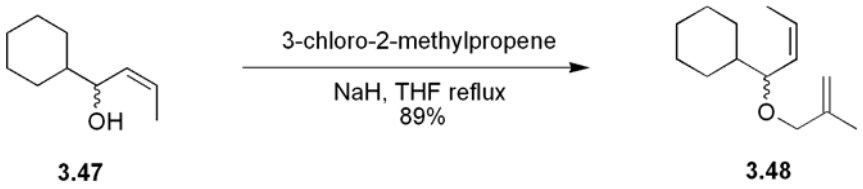
Scheme 3-11 Transition states proposed by researchers

In our synthesis, we used cyclohexanecarboxaldehyde-derived intermediates for convenience in handling. Also, for easy handling in large-scale synthesis, the large excess Li powder used in Oppozler's procedure was reduced to one equivalent. The (*Z*)-allylic alcohol **3.47** was synthesized in 84% yield (Scheme **3-12**).



Scheme 3-12 Synthesis of (*Z*)-allylic alcohol **3.47**

(*Z*)-Allylic alcohol **3.47** was then converted to (*Z*)-diallylic ether **3.48** by etherification (alkylation) with 3-chloro-2-methylpropene. The substrate of [2,3]-Wittig rearrangement was obtained in 89% yield (Scheme **3-13**).

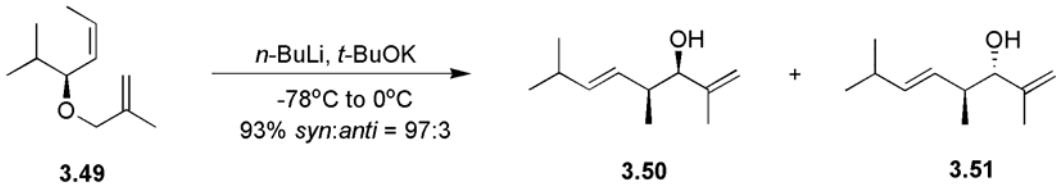


Scheme 3-13 Alkylation with 3-chloro-2-methylpropene

3.2.1.2 [2,3]-Wittig Rearrangement

In 1985, the Midland group reported a diastereoslective [2,3]-Wittig rearrangement to generate chiral alcohols with two stereo centers from (*Z*)-allylic ether (Scheme **3-14**). They reported that treatment of (*S*,*Z*)-allylic ether **3.49** with base resulted exclusively in

the (*E*)-alcohols with good yield. The ratio between *syn* product **3.50** and *anti* product **3.51** was about 97:3.[47]

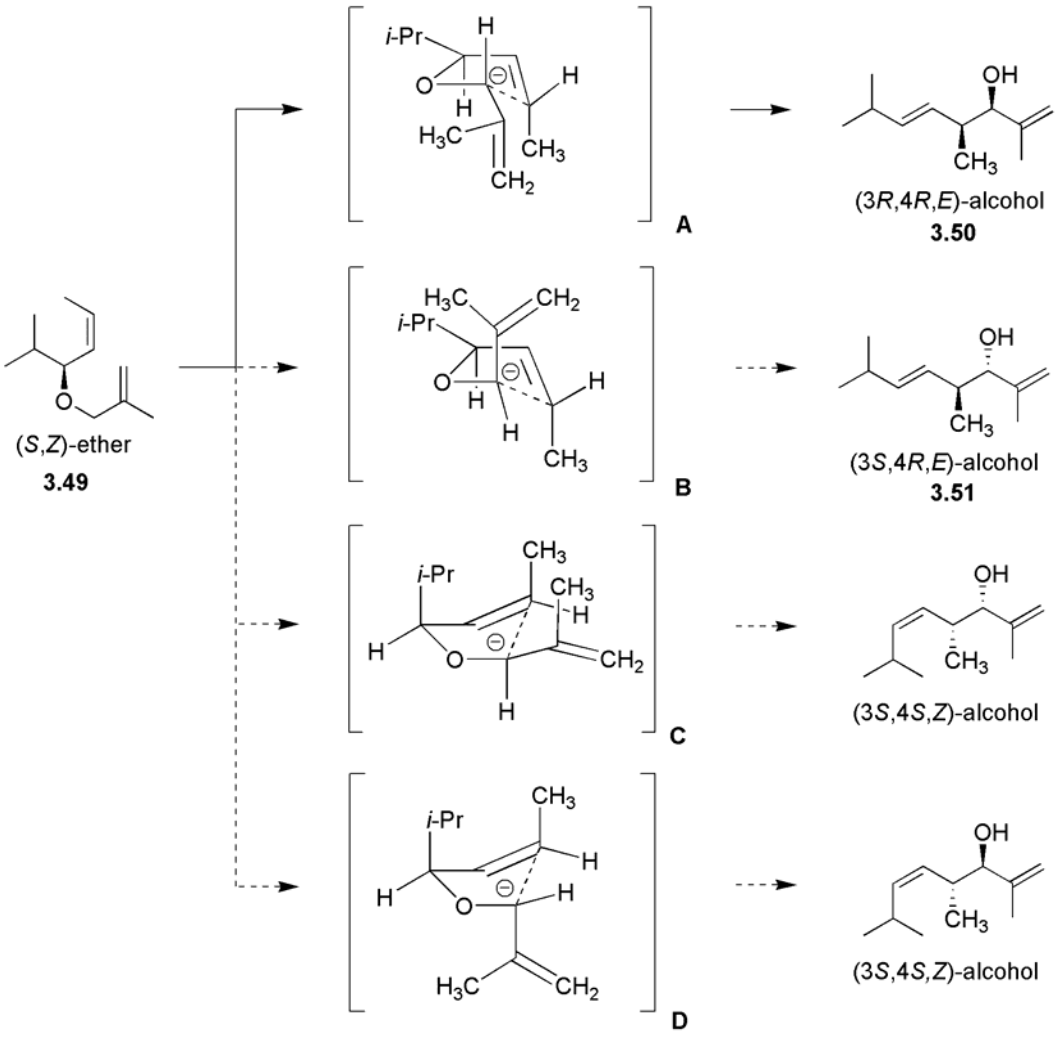


Scheme 3-14 [2,3]-Wittig rearrangement of diallylic ether reported by Midland

In the 1980's, Nakai and co-workers proposed a five-membered cyclic transition states for the [2,3]-Wittig rearrangement.[48] According to the five-membered cyclic transition state theory, there could be four transition states during the rearrangement (Scheme **3-15**). Transition state **A** and **B** are favored over transition states **C** and **D** because the isopropyl group is at the less hindered equatorial positions. This explains the exclusive formation of *E* products. Transition state A is favored in further comparison with transition state B because the isopropenyl group is at the less hindered equatorial position. This explains the high selectivity of *syn* product over *anti* product. Therefore, transition state **A** leads to the major product (3*R*,4*R*,*E*)-alcohol **3.50**.

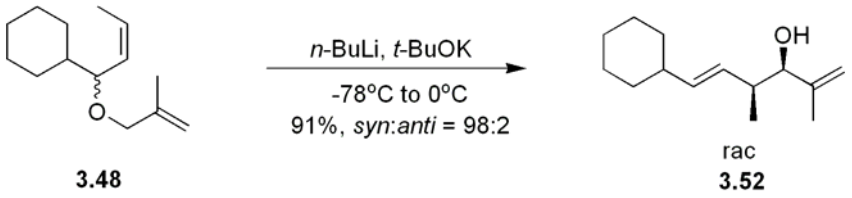
[47] Tsai, D. J.-S.; Midland, M. M. ***J. Am. Chem. Soc.* 1985, *107,*** 3915-3918

[48] (a) Mikami, K.; Azuma, K.-I.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303-2308. (b) Mikami, K.; Azuma, K.; Nakai, T. *Chem. Lett.* **1983**, 1379-1382. (c) Sayo, N.; Kitahara, E.; Nakai, T. *Chem. Lett.* **1984**, 259-262.



Scheme 3-15 Comparison of possible transition states

Typical [2,3]-Wittig rearrangement conditions were applied to (*Z*)-allylic ether **3.48** in our racemic approach. Results similar to those of Midland were obtained. Thus, (*syn*, *E*)-alcohol **3.52** was the major product (91% yield). The ratio of the *syn*/*anti* diastereomers of this rearrangement, as judged by analysis of the ^{1}H NMR spectrum, was 98:2, which is higher than the 97:3 diastereoselectivity obtained by Midland from the rearrangement of (*S*,*Z*)-allylic ether **3.49**. The bulky cyclohexyl substituent in (*Z*)-allylic ether **3.48** could be the factor that leads to better selectivity (Scheme **3-16**).

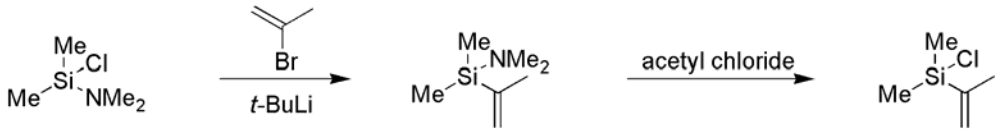


Scheme 3-16 Synthesis of (*syn*,*E*)-allyl alcohol

3.2.2 Silylation

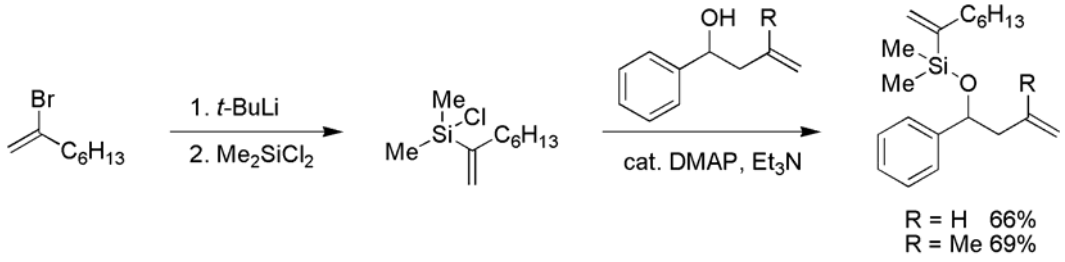
3.2.2.1 Previous Protocols for Allyloxydimethyl(prop-1-en-2-yl)silane Synthesis

In 2000, Robertson and co-workers [49] developed a protocol to synthesize chlorodimethyl(prop-1-en-2-yl)silane by displacement of chloride ion from commercially available chloro-N,N,1,1-tetramethylsilanamine with 2-propenyllithium followed by conversion of the dimethylamino substituent to chloride (Scheme **3-17**).



Scheme 3-17 Silylation protocol reported by Robertson

In 2001, Denmark's group [50] reported a protocol to synthesize silyl ethers by silylation of the alcohol with chlorodimethyl(oct-1-en-2-yl)silane. This reagent was prepared by displacement of one of the two chloride ions in commercially available dichlorodimethylsilane with oct-1-en-2-yllithium. The target silyl ether was obtained in 69% yield (Scheme **3-18**).



Scheme 3-18 Silylation protocol reported by Denmark

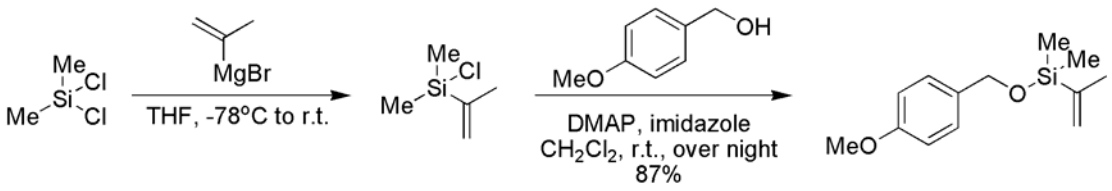
3.2.2.2 Optimized Allyloxydimethyl(prop-1-en-2-yl)silane Synthesis

Because of the easy access of dichlorodimethylsilane and Grignard reagent (low cost, commercially available), the Denmark's protocol was used for easy handling in the large scale synthesis. Using various ratios of reagents, we designed a model system (Scheme **3-19**) to further optimize the Denmark group's protocol for better yield. The (4-methoxybenzyloxy)dimethyl(prop-1-en-2-yl)silane was successfully synthesized in 87% yield.

---

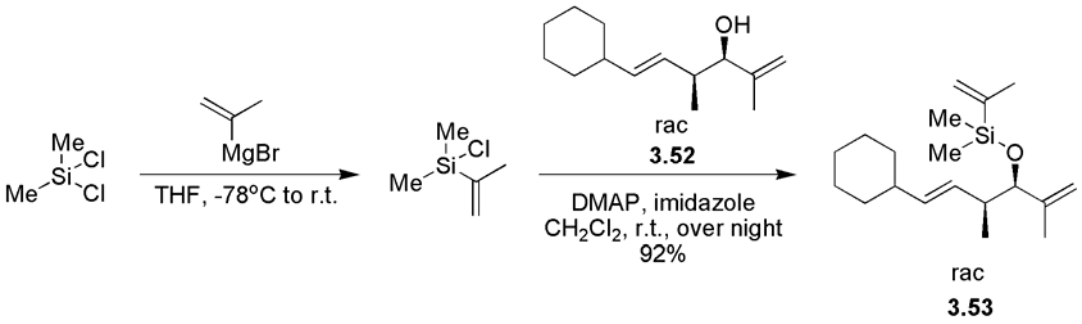
[49] Robertson, J.; O'Connor, G.; Sardharwala, T.; Middleton, D. S. *Tetrahedron*, **2000**, *56*, 8309-8320

[50] a) Denmark, S. E.; Yang S.-M. *Tetrahedron* **2004**, *60*, 9695–9708 b) Denmark, S. E.; Yang S.-M. *Org. Lett.* **2001**, *3*, 1749-1752



Scheme 3-19 Model study of silylation with Denmark's protocol

The best condition was found as follows. First, one of the two chloride ions in dichlorodimethylsilane was displaced by prop-1-en-2-ylmagnesium bromide. Then the resulting chlorodimethyl-(prop-1-en-2-yl)silane was treated with *syn*-allylic alcohol **3.52** to produce the target molecule, *syn*-allylic silyl ether **3.53** in good yield (92%). Therefore, four equivalents of dichlorodimethylsilane and six equivalent of prop-1-en-2-ylmagnesium bromide are used to make sure there will be excess of chlorodimethyl-(prop-1-en-2-yl)silane reacting with alcohol to afford better yield (Scheme **3-20**).

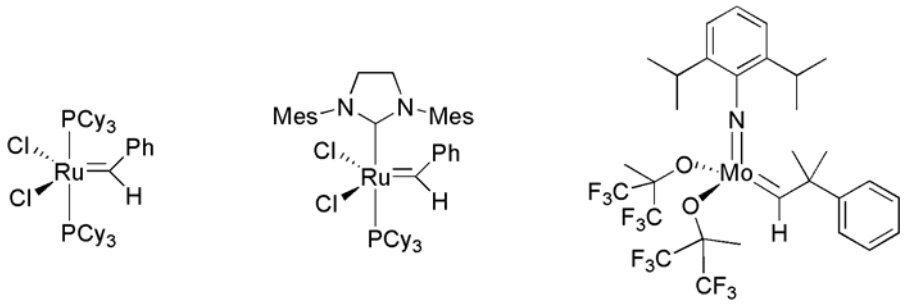


Scheme 3-20 Synthesis of *syn*-allylic silyl ether **3.53**

3.2.3 Ring Closing Metathesis (RCM)

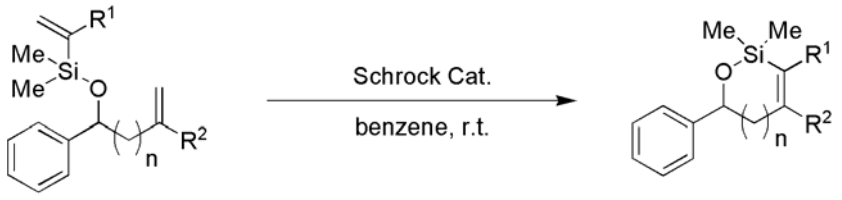
3.2.3.1 RCM of Silyl Ether Reported by Denmark's Group

In 2001, Denmark's group reported the ring closing metathesis (RCM) reaction of silyl ether **3.54** using molybdenum complex **3.55** (Figure **3-3**) as catalyst (Scheme **3-21**). Their initial studies using Grubbs alkylidene complex **3.56** (first generation) and **3.57** (second generation) did not yield any desired product that was observed by ^{1}H NMR analysis. On the other hand, Schrock's catalyst **3.55** proved efficient in the RCM reaction. A good yield (89-95%) of desired product **3.58** was obtained at room temperature. With a mono substituted alkene or vinylsilane, the RCM process proceeded slowly compared to unsubstituted precursor although ultimately to completion. Substrates with substitution on both the alkene and vinylsilane did not undergo the RCM process presumably due to the significant increase in steric crowding (Table **3-1**).



3.56 3.57 3.55

Figure 3-3 Representative catalysts for RCM



3.54 3.58

Scheme 3-21 RCM of silyl ether reported by Denmark's group

Table 3-1 RCM of silyl ether reported by Denmark's group

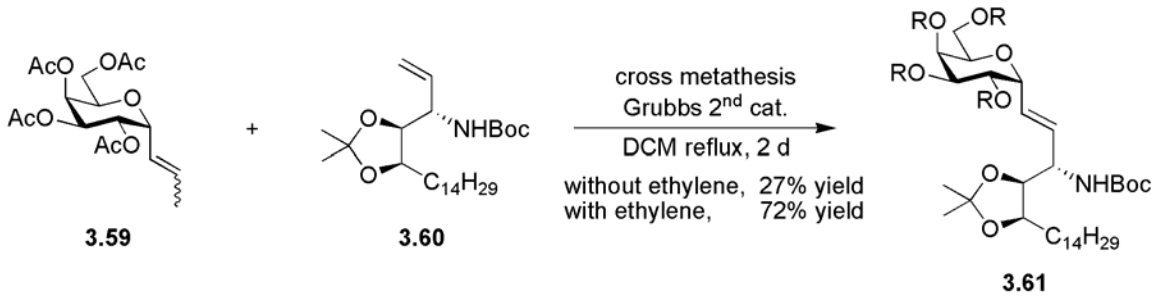
Entry	n	R^1	R^2	Cat. mol%	Time, h	Yield, %
1	0	H	H	7.0	3	89
2	1	H	H	5.0	1	95
3	1	H	Me	8.0	15	91
4	1	C_6H_{13}	H	7.0	12	90
5	1	C_6H_{13}	Me	-	-	-
6[c]	2	H	H	7.0	12	81

[a] Reactions were performed in 0.1 M concentration.
[b] Yields of analytically pure materials.
[c] 91% conversion was observed by ^{1}H NMR analysis.

3.2.3.2 Ethylene-Promoted Olefin Cross Metathesis (CM)

In the Franck group's second–generation synthesis of α-C-galactosylceramide derivatives[51], ethylene was used to promote CM of C-(1-propenyl)-sugar **3.59** with the terminal olefin form of the sphingosine side chain **3.60**. The desired product **3.61** was synthesized in 72% yield in the presence of ethylene compared with 27% yield in the absence of ethylene. The researchers proposed that ethylene probably improved ruthenocyclobutane intermediate formation (Scheme **3-22**).

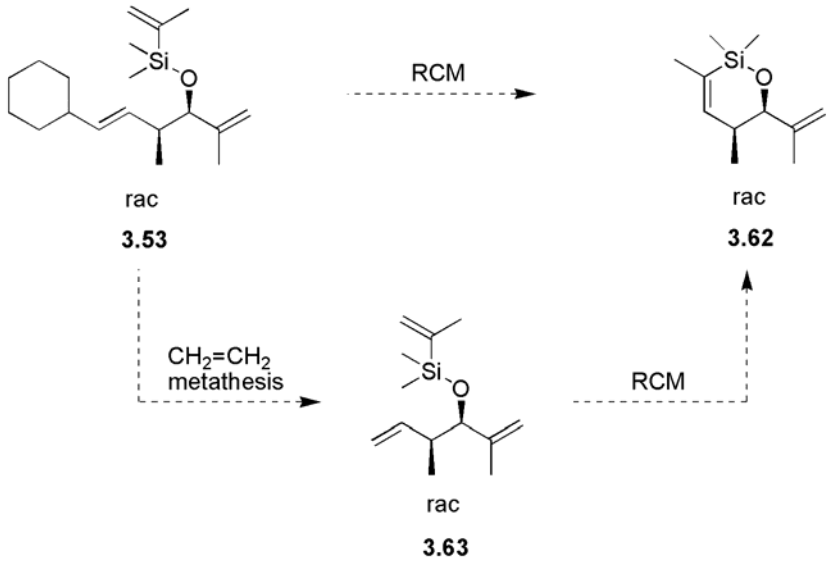
[51] Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077-4080



Scheme 3-22 Ethylene-promoted olefin CM

3.2.3.3 RCM Approach of Silyl Ether 3.53

On the basis of Denmark's protocol and considering the discrimination between forming trisubstituted and tetrasubstituted alkene, an approach of RCM reaction of *syn*-allylic silyl ether **3.53** was designed to produce *syn*-dihydro oxasiline **3.62**. The initial plan was designed to construct the desired product directly from *syn*-allylic silyl ether substrate with RCM catalyst. The back up plan is to treat the substrate with ethylene and metathesis catalyst to produce the terminal primary alkene **3.63** by CM first and then remove the ethylene atmosphere to finish the RCM reaction, a procedure consistent with the Franck group's results (Scheme **3-23**).



Scheme 3-23 Designed RCM of *syn*-allylic silyl ether **3.53**

Unfortunately, both of these approaches did not yield any desired product **3.49** based on the 1H NMR analysis and most of starting material **3.53** was recovered. All variations in conditions, including change of solvent (CH_2Cl_2 or benzene) and/or temperature (r.t. or reflux) were unsuccessful. Even the metathesis of starting material with ethylene failed to promote the CM reaction (Table **3-2**).

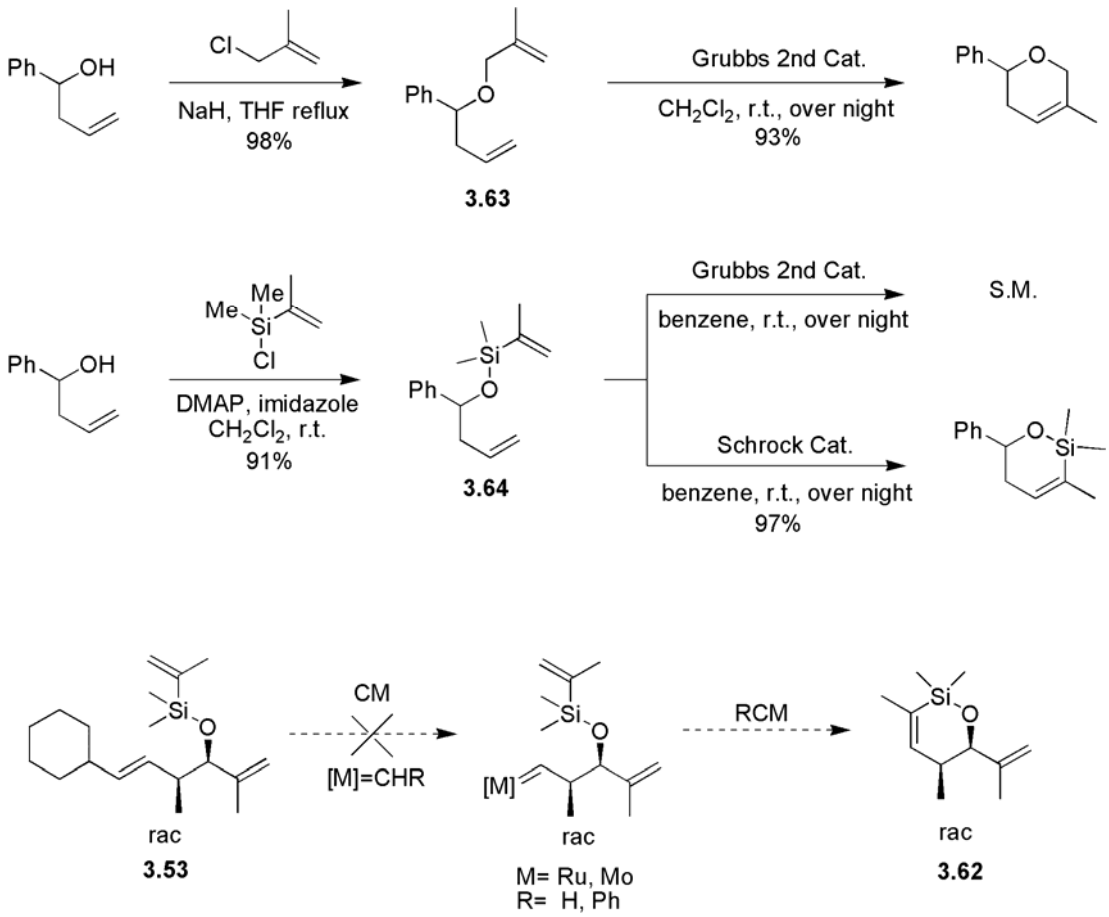
Table 3-2 RCM of *syn*-allylic silyl ether **3.53**

Entry	Catalyst	Additive	Solvent	T (^{o}C)	Time (h)	Results
1	Schrock Cat.	none	CH_2Cl_2	r.t.	12	S.M. recovered
2	Schrock Cat.	none	CH_2Cl_2	reflux	12	S.M. recovered
3	Schrock Cat.	none	benzene	r.t.	12	S.M. recovered
4	Schrock Cat.	none	benzene	reflux	12	S.M. recovered
5	Grubbs 2nd Cat.	none	CH_2Cl_2	reflux	12	S.M. recovered
6	Grubbs 2nd Cat.	none	benzene	reflux	12	S.M. recovered
7	Schrock Cat.	ethylene	CH_2Cl_2	reflux	24	S.M. recovered
8	Schrock Cat.	ethylene	benzene	reflux	24	S.M. recovered
9	Grubbs 2nd Cat.	ethylene	CH_2Cl_2	reflux	24	S.M. recovered
10	Grubbs 2nd Cat.	ethylene	benzene	reflux	24	S.M. recovered

3.2.3.4 Model RCM Study of Simplified Substrates

In order to overcome the problematic ring closing metathesis step, several simplified model substrates were designed and synthesized to discover an effective protocol for this transformation.

The results of RCM of simplified model substrates are shown in Scheme **3-24**. Although Grubbs 2nd generation catalyst proved to be effective to catalyze the RCM of (1-(2-methylallyloxy)but-3-enyl)benzene **3.63**, the approach of using Grubbs 2nd generation catalyst to catalyze the metathesis of vinylsilyl ether diene **3.64** did not yield the target 1,2-oxasilinane either. On the other hand, ring closing metathesis of vinylsilyl ether diene **3.64** using Schrock's catalyst provided the desired product in high yield (97%). These results are consistent with Denmark's results that the Schrock's catalyst is more active than Grubbs 2nd generation catalyst to catalyze RCM of the sterically more demanding vinylsilyl ether dienes (Scheme **3-24**, top).



Scheme 3-24 Model RCM study of simplified substrates

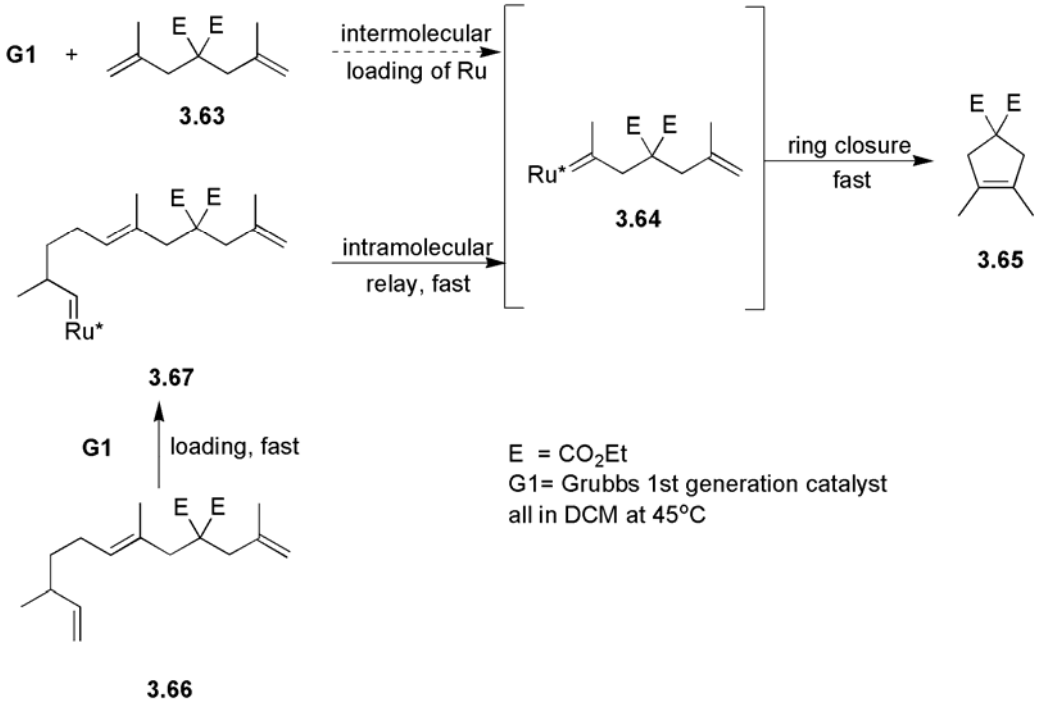
Based on ring closing metathesis study of the simplified model compound, it is most likely that at least the Schrock's catalyst are able to catalyze the RCM to form the tri-substituted double bond and dihydro oxasiline structure in the desired product **3.62**. Presumably, it is the difficulty to produce the metal carbene intermediate (Scheme **3-24**, bottom) from the disubstituted olefin in silyl ether **3.53** that hindered the metathesis progress. The two substituent groups at both β positions of the disubstituted double bond make the double bond sterically hindered. This is also consistent with the fact that the starting material was recovered in the initial metathesis approaches using different catalysts with or without ethylene promotion.

3.2.3.5 Relay Ring-Closing Metathesis (RRCM)

3.2.3.5.1 Hoye Strategy of Relay Ring-Closing Metathesis (RRCM)

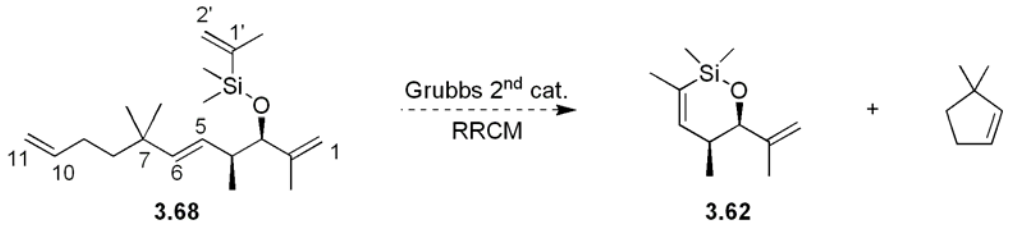
In 2004, Hoye's group reported a novel relay ring-closing metathesis (RRCM) strategy to circumvent the reactivity or selectivity problems of ring-closing metathesis by rationally designing modifications of imperfect RCM substrates (sterically hindered or

electronically deactivated).[52] Their example of RRCM involved the cyclization of diene **3.63**, which is known to be unreactive with the first generation of Grubbs catalyst **G1**. **G1** is not sufficiently active to form metal carbene **3.64** directly with the geminally substituted terminal alkene.[53] In contrast, the modified relay substrate **3.66** cyclized smoothly to the cyclopentene derivative **3.65**. The terminal monosubstituted olefin is essential to promote the RCM progress by forming metal carbene **3.67** with G1 rapidly and triggering the cyclization of the side chain. The resulting metal carbene **3.64**, which was not obtained with simple substrate, lead to the desired product **3.65** (Scheme **3-25**).



Scheme 3-25 Hoye's Strategy of RRCM

3.2.3.5.2 Rationally Designed Substrate for RRCM

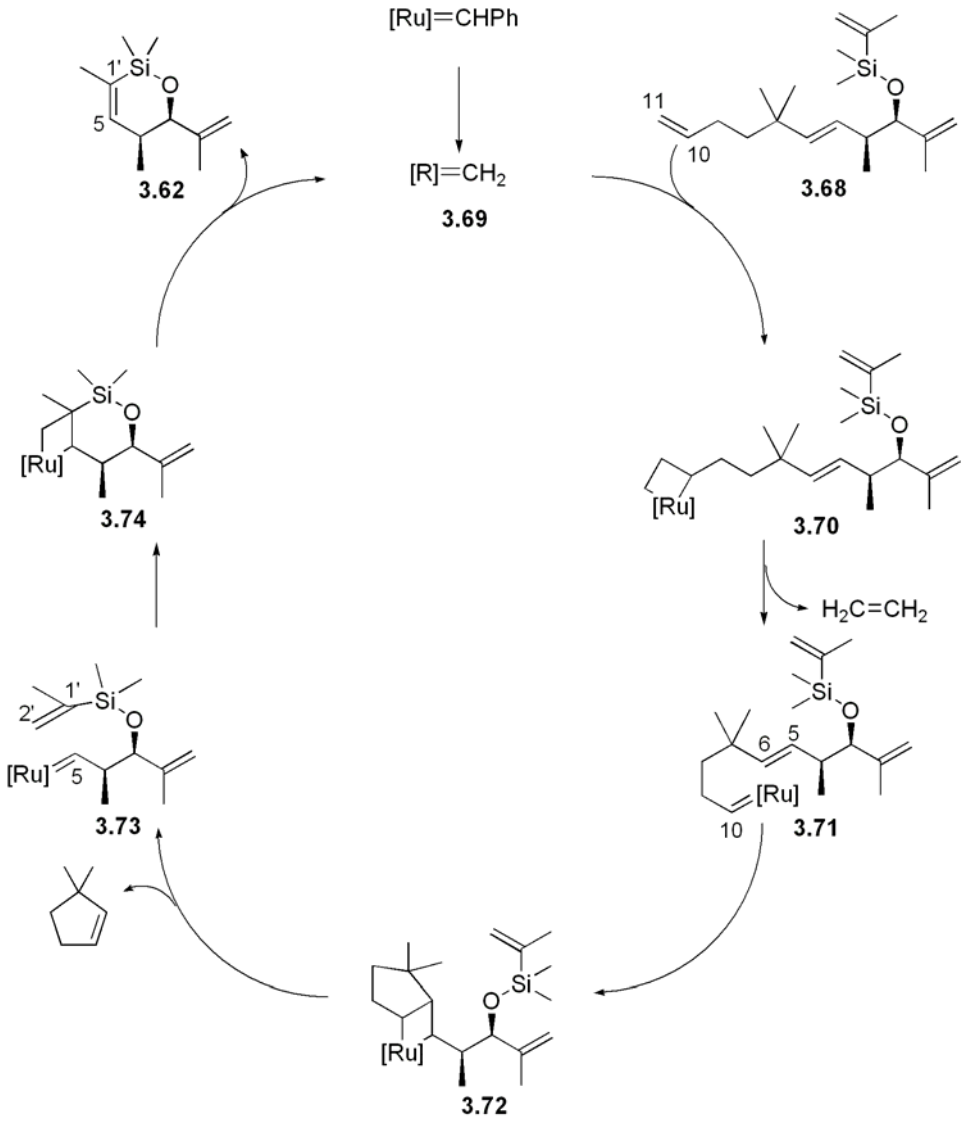


Scheme 3-26 Rationally designed substrate **3.68** for RRCM

On the basis of Hoye's strategy of RRCM, we designed substrate **3.68** to overcome

[52] Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210-10211.
[53] Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484-2489.

the difficulty of constructing dihydro oxasiline intermediate **3.62** (Scheme **3-26**). Presumably, the terminal C10-C11 olefin in **3.68** will react with the catalyst complex rapidly to form the first metal carbene at the C10 position. Then a ruthenocyclobutane structure will form with the C5-C6 olefin. A CM process is triggered to close a five-membered ring which leads to a side product, 3,3-dimethylcyclopent-1-ene. The resulting C5 metal carbene will form the second ruthenocyclobutane structure with the C1'-C2'olefin. Cleavage of the resulting ruthenocyclobutane will complete the catalytic cycle by forming the desired dihydro oxasiline product **3.62** and restoring the catalytic complex at the same time. The proposed catalytic cycle is shown in detail in Scheme **3-27**.

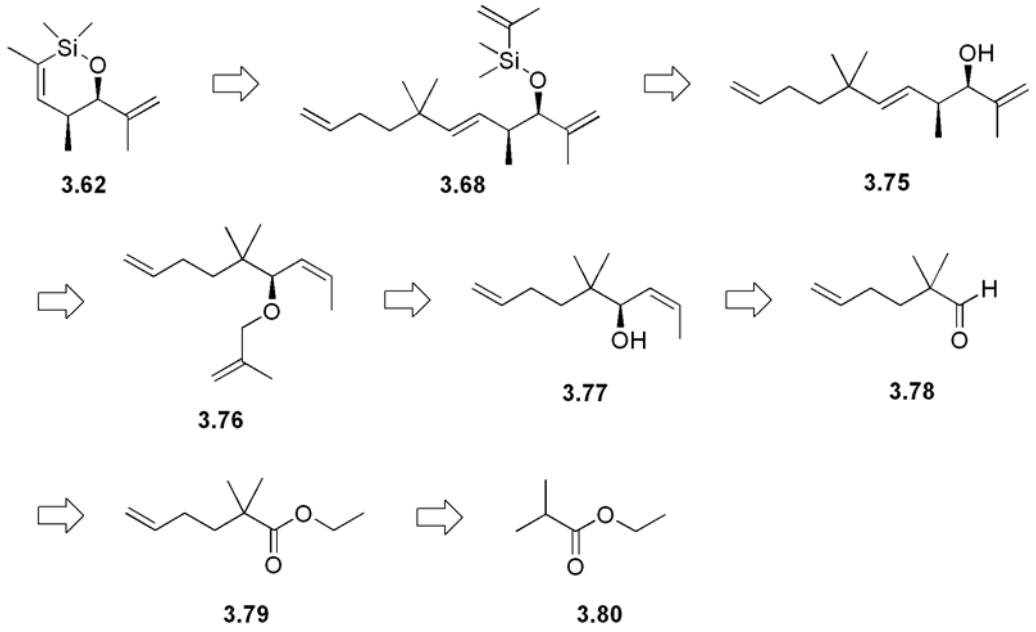


Scheme 3-27 Catalytic cycle of the designed RRCM

3.2.3.5.3 Retrosynthetic Strategy of the Relay Metathesis Substrate 3.68

Our retrosynthetic strategy of the relay metathesis substrate **3.68** is shown in Scheme

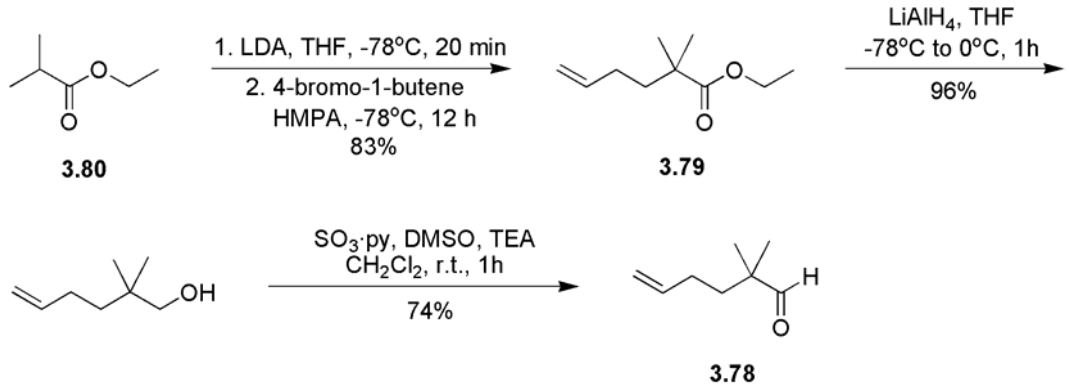
3-28. The *syn*-allylic silyl ether **3.68** could be obtained by silylation of *syn*-trienol **3.75**, which could be constructed by standard [2,3]-Wittig rearrangement of (*S*)-diallylic ether **3.76**. Simple alkylation of (*S*)-dienol **3.77** with 3-chloro-2-methylprop-1-ene could produce (*S*)-diallylic ether **3.76** handily. Stereoselective addition of (*Z*)-1-bromoprop-1-ene to hexenal **3.78** could provide (*S)*-dienol **3.77** conveniently. Presumably, the quaternary *β* carbon of hexenal **3.78** will benefit the enantioselectivity of the alkenylation step. Another nice feature of this design is that it does not introduce an unnecessary chiral center into any of the intermediates. The hexenal **3.78** could be synthesized by oxidation of related hexenol which could be obtained from reduction of ethyl hexenoate **3.79**. Alkylation of ethyl isobutyrate **3.80** with 4-bromobut-1-ene could provide ethyl hexenoate **3.79** conveniently.



Scheme 3-28 Retrosynthetic strategy of **3.68**

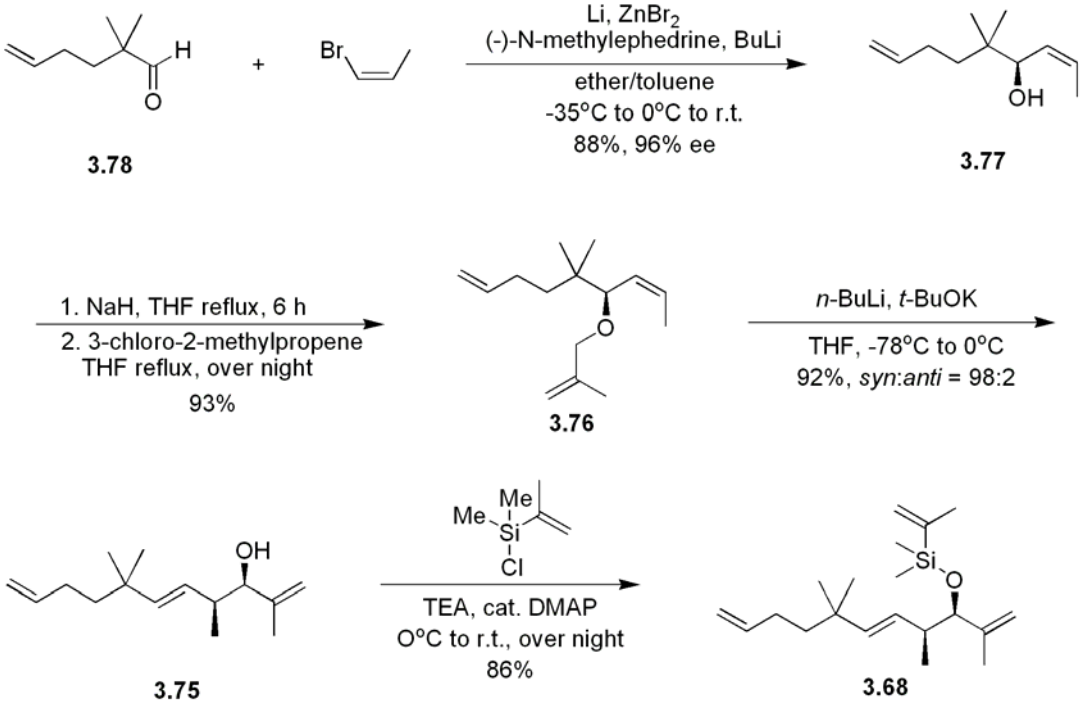
3.2.3.5.4 Asymmetric Synthesis of Relay Metathesis Substrate 3.68

Alkylation of ethyl isobutyrate **3.80** with 4-bromobut-1-ene afforded ethyl 2,2-dimethylhex-5-enoate **3.79** in 83% yield. Then hexenoate **3.79** was reduced by LAH to produce the related hexenol with 96% yield. Oxidation of the resulting alcohol with sulfur trioxide pyridine complex afforded the related hexenal **3.78** in 74% yield. All of these compounds, **3.80**, **3.79** and **3.78**, are volatile and need to be handled carefully to avoid evaporation (Scheme **3-29**).



Scheme 3-29 Hexenal **3.78** synthesis

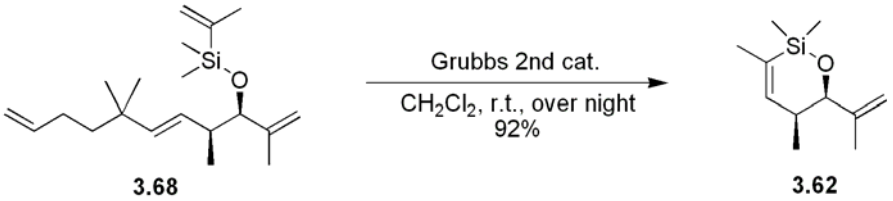
Enantioselective addition of *Z*-propenylzinc bromide to aldehyde **3.78** in the presence of (-)-N-methylephedrine produced the *cis* allylic alcohol **3.77** in 88% yield and 96% ee. Alkylation with 3-chloro-2-methylpropene afforded ether **3.76** in 97% yield. Application of standard [2,3]-Wittig rearrangement conditions afforded (3*R*,4*S*,*E*)-allylic alcohol **3.75** (92% yield). The ratio of the *anti*/*syn* diastereomers of this rearrangement product was, as judged by analysis of the ^{1}H NMR spectrum, 98:2. Treatment of allylic alcohol **3.75** with the pretreated mixture of dichlorodimethyl- silane and prop-1-en-2-ylmagnesium bromide gave the silyl ether **3.68** in 86% yield (Scheme **3-30**).



Scheme 3-30 Silyl ether **3.68** synthesis

3.2.3.5.5 Relay Metathesis of Substrate 3.68

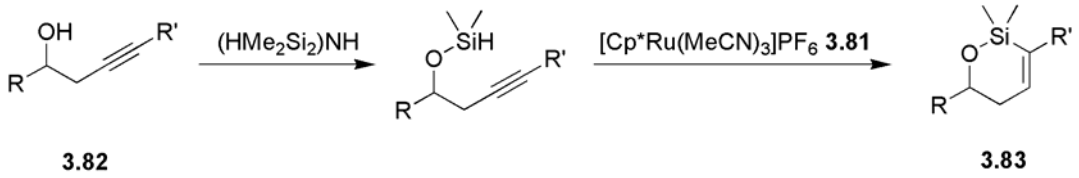
With substrate silyl ether **3.68** in hand, the stage was set for the designed relay metathesis. After stirring under argon overnight with Grubbs 2nd generation catalyst, the desired product, dihydro oxasiline **3.62** was isolated in 92% yield (Scheme **3-31**).



Scheme 3-31 RRCM of **3.68**

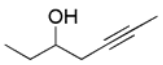
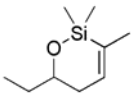
3.2.4 Construction of Model Compounds with the Trost Intramolecular Hydrosilylation

The Trost group reported the selective intramolecular hydrosilylation catalyzed by a cationic ruthenium complex, $[Cp^*Ru(MeCN)_3]PF_6$ (**3.81**).[54] This reaction gives us another option to construct the dihydro oxasiline containing building blocks for the study of the subsequent reactions of oxasiline ring opening and iododesilylation. In this one-pot reaction, homopropargylic alcohols **3.82** were silylated in neat tetramethyldisilazane (TMDS) and subjected to reduced pressure to remove TMDS. The endo-dig product **3.83** the result of a net trans addition, was produced by treating the residue with the ruthenium complex in methylenecholoride (Scheme **3-32**). A variety of substitution patterns and functionality are tolerated (Table **3-3**). A model compound **3.87** was designed and synthesized.

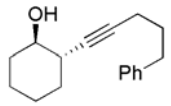
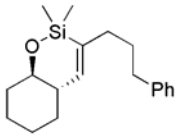
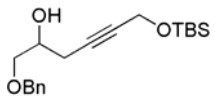
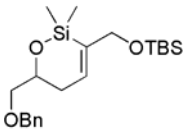
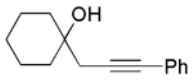
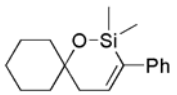
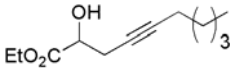
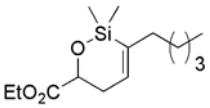


Scheme 3-32 $[Cp^*Ru(MeCN)_3]PF_6$ (**3.81**) catalyzed intramolecular hydrosilylation

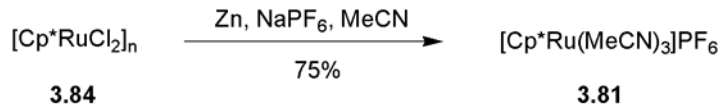
Table 3-3 $[Cp^*Ru(MeCN)_3]PF_6$ (**3.81**) catalyzed intramolecular hydrosilylation

Entry	Alkyne	Cat.	Product	Yield
1		1%		79%

[54] Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30-31

2		1%		85%
3		1%		86%
4		5%		95%
5		3%		77%

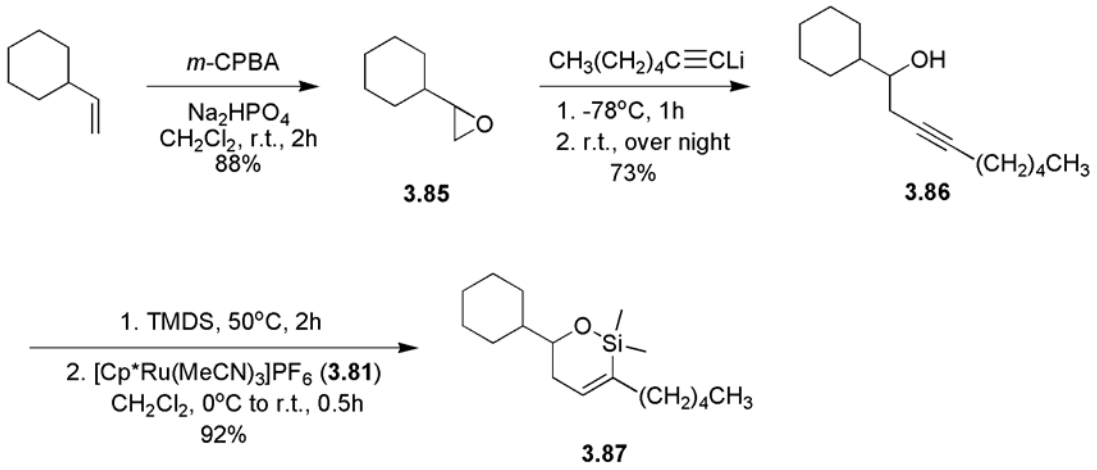
The ruthenium complex **3.81** was prepared by a protocol that was reported by Bruneau's group in 2004.[55] The commercially available $[Cp^*RuCl_2]_n$ (**3.84**) was reduced by zinc metal in acetonitrile and then KPF_6 was added. After that, the solution was cooled down and the resulting crystals were collected and purified (Scheme **3-33**).



Scheme 3-33 Synthesis of $[Cp^*Ru(MeCN)_3]PF_6$ (**3.81**) complex

The model compound **3.87** was designed and synthesized as follows. First, vinylcyclohexane was oxidized to 2-cyclohexyloxirane **3.85** by *m*-CPBA. Then the epoxide ring was opened by nucleophilic addition of hept-1-ynyllithium. The resulting homopropargylic alcohol **3.86** was silylated and treated with the ruthenium complex **3.81**. A high yield (92%) of dihydro oxasiline **3.87** was obtained (Scheme **3-34**).

[55] Mbaye, M. D.; Demerseman, B.; Renaud, J.-L.; Toupet, L.; Bruneau, C. *Adv. Synth. Catal*, **2004**, *346*, 835-841.



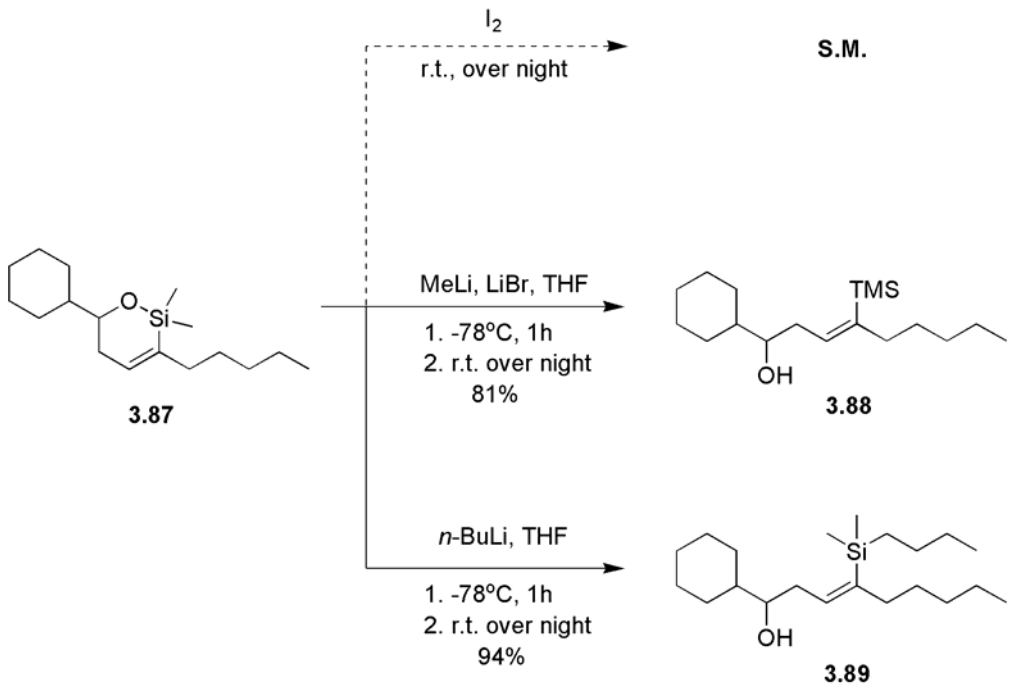
Scheme 3-34 Synthesis of model compound dihydro oxasiline **3.60**

3.2.5 Nucleophilic Opening of Dihydro oxasiline Ring

3.2.5.1 Model Study of Ring Opening Reaction of Dihydro oxasiline Ring

Initially, the model compound dihydro oxasiline **3.87** was treated with I_2 at room temperature to open the six-membered ring. Unfortunately, no desired ring opening product was obtained. Almost all of the starting material was recovered (Scheme **3-35**).

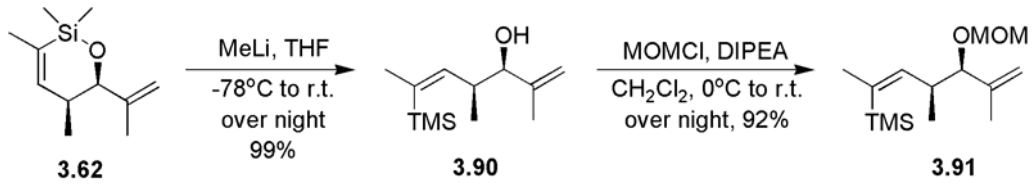
The model compound dihydro oxasiline **3.87** was then treated with aliphatic lithium reagents to open the six-membered ring by nucleophilic addition of aliphatic anion to the silyl group and cleavage of the O-Si bond. The resulting lithium oxides were then quenched with water to produce the *δ*-hydoxyl vinyl silane **3.88** and **3.89** in high yield. (Scheme **3-35**).



Scheme 3-35 Ring opening study of dihydro oxasiline **3.60**

3.2.5.2 Nucleophilic Ring Opening of Dihydro oxasiline 3.62

Application of the same protocol with dihydro oxasiline **3.62** resulted in 99% yield of desired product, dienol **3.90**. Then the hydroxyl group in dienol **3.90** was protected by MOM with standard conditions to give MOM protected vinyl silane **3.91** in 92% yield (Scheme **3-36**).

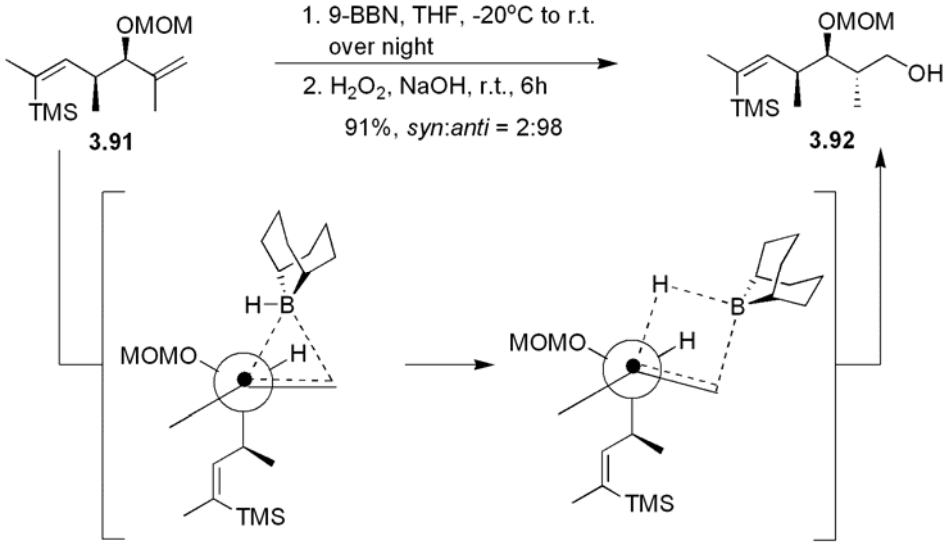


Scheme 3-36 Nucleophilic ring opening and MOM protection of **3.62**

3.2.6 Stereoselective Hydroboration and Oxidation

With precursors in hand, diastereoselective hydroboration of the terminal olefin group in the *syn*-allylic MOM ether **3.91** followed by oxidation generated terminal alcohol **3.92** containing the *syn*, *anti*-stereotriad in high yield and high diastereoselectivity (Scheme **3-37**, the diastereometric ratios were measured by careful integration of the ^{1}H NMR specturm).[56]

[56] Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *8*, 2487-2489



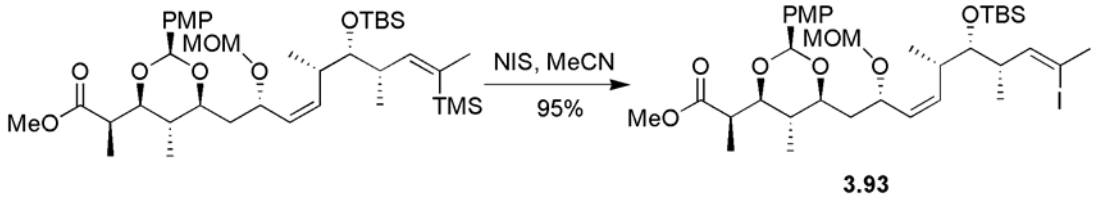
Scheme 3-37 Stereoselective hydroboration of **3.91**

The stereoselectivity of this hydroboration reaction could be explained by a simple model. Among all the possible transition states, the two structures shown in Scheme **3-37** would be the most likely ones that the reaction undergo because they have the smallest substituent (H) oriented over the face of the transition-state ring. The borane would approach from the less hindered side of olefinic π system and then the resulting less sterically encumbered transition state would lead to the selected *anti*- product.

3.2.7 Iodo Olefin Synthesis by Iododesilylation

3.2.7.1 Iododesilylation of Model Compounds with Various Reagents

In 1989, Kishi reported a useful iododesilylation protocol to effectively transform vinyl silyl ether to vinyl iodide using *N*-iodosuccinimide (NIS).[57] Then, this protocol was modified and used by Panek's group in their total synthesis of (+)-discodermolide.[58] The transformation was successful and yielded vinyl iodide **3.93** in 95% yield. (Scheme **3-38**).

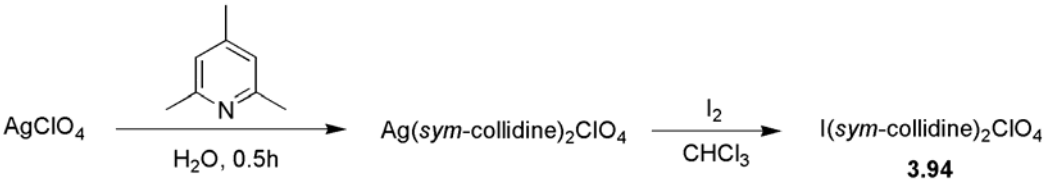


Scheme 3-38 Iododesilylation step in Panek's synthesis of (+)-discodermolide

[57] Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647-8650.

[58] (a) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc.* 2005, *127*, 5596. (b) Arefolov, A.; Paanek, J. S. *Org. Lett.* 2002, *4*, 2397.

We also prepared a more powerful iodonium reagent I(*sym*-collidine)$_2$ClO$_4$ (**3.94**) using the Morgan group's procedure[59]. First, *sym*-collidine reacted with silver perchlorate in aqueous conditions to give silver di-*sym*-collidine perchlorate as a precipitate. Then the resulting precipitate was dried and reacted with iodine to provide the highly reactive iodonium di-*sym*-collidine prechlorate (**3.94**). (Scheme **3-39**)

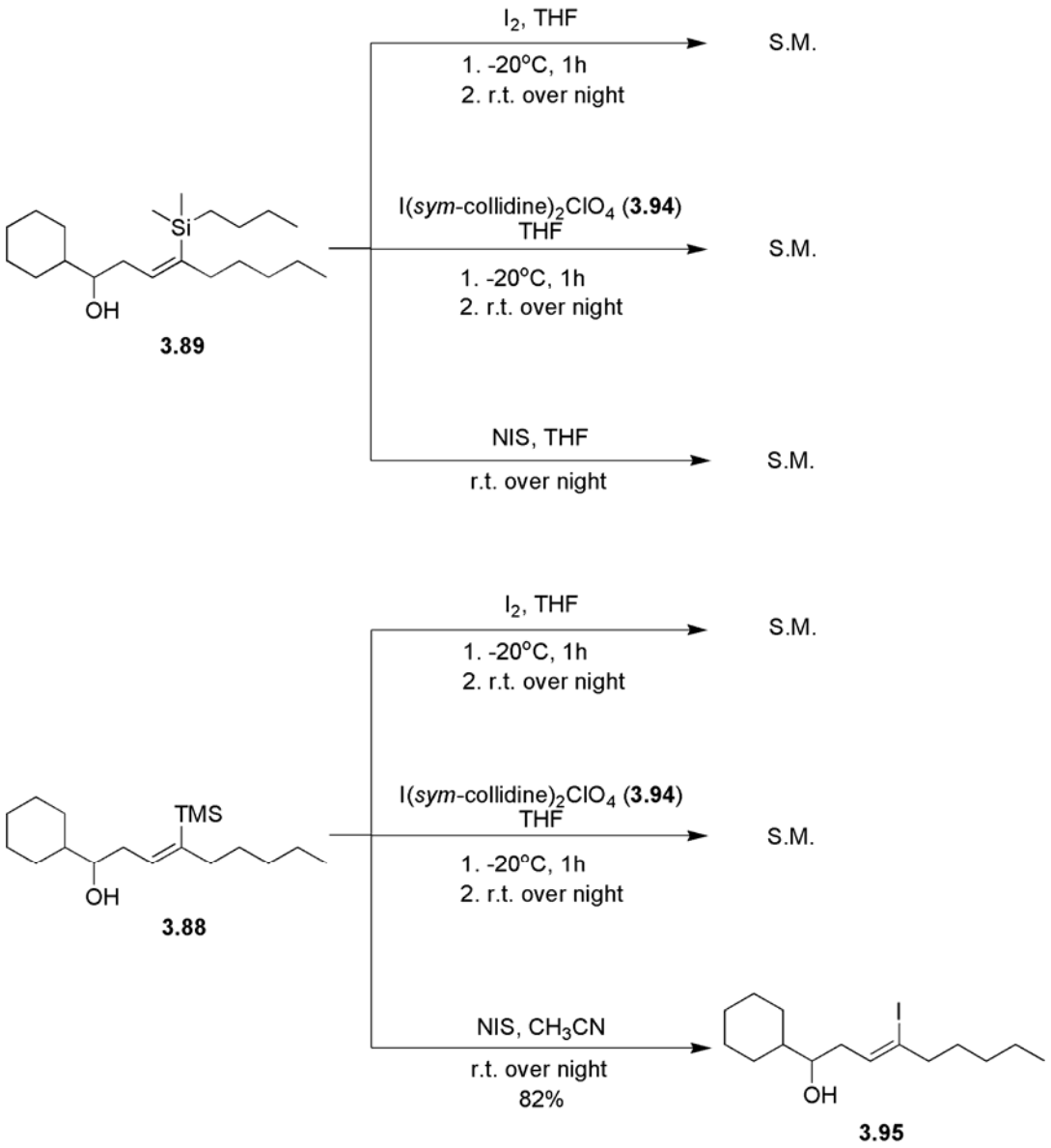


Scheme 3-39 Synthesis of iodonium di-*sym*-collidine prechlorate (**3.94**)

Silyl ether **3.88** and **3.89**, products of ring opening reaction of dihydro oxasiline **3.87**, were used as substrates for model study of iododesilylation. The results showed that vinyl silyl ether **3.88** was effectively transformed to vinyl iodide **3.95** in 82% yield with *Z*/*E* = 7:1 regioselectivity by using *N*-iodosuccinimide (NIS)[60] in acetonitrile (Scheme **3-40**).

[59] Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190-2198

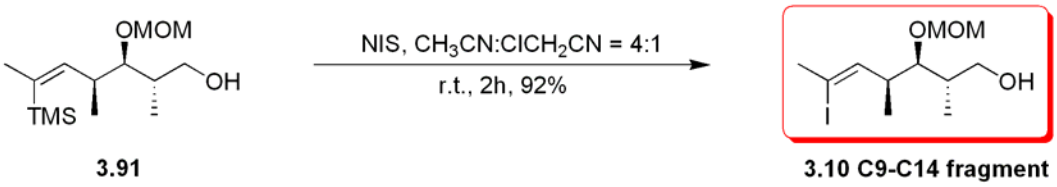
[60] NIS was used directly without recrystallization.



Scheme 3-40 Model study of iododesilylation

3.2.7.2 Iododesilylation of Vinyl Silane 3.91

Vinyl silane **3.91** was treated with NIS in acetonitrile at room temperature. The desired product, C9-C14 fragment **3.10** of discodermolide, was obtained with *Z*/*E* selectivity about 3.2/1. The addition of chloroacetonitrile and recrystallization of NIS were found to benefit the regioselectivity, a 92% yield and 5.5/1 selectivity was achieved by using purified NIS in a 4:1 mixture of acetonitrile and chloroacetonitrile (Scheme **3-41**).



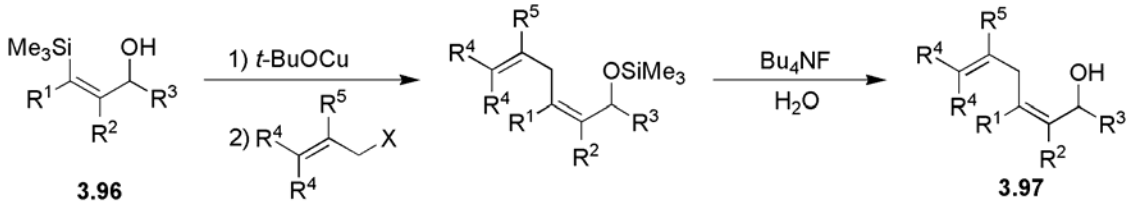
3.91 3.10 C9-C14 fragment

Scheme 3-41 Iododesilylation of vinyl silane **3.91**

3.2.8 Model Study of Future Coupling, Cross-Coupling Approach of (*Z*)-*δ*-trimethylsilyl Allylic Alcohols with Allylic Halides

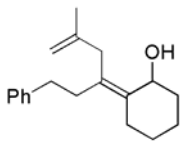
3.2.8.1 Copper(I) *tert*-Butoxide-Promoted Cross-Coupling of (*Z*)-γ-trimethylsilyl Allylic Alcohols with Allylic Halides

In 2002, the Takeda group developed the copper(I) *tert*-butoxide promoted 1,4 C^{sp2}-to-O silyl migration of (*Z*)-γ-trimethylsilyl allylic alcohols (**3.96**) (Scheme **3-42,** Table **3-4**).[61] Presumably, the vinylcopper intermediates react with allylic halides to afford the cross-coupling products (**3.97**) with complete retention of configuration. (Scheme **3-43**). Synthesis of geometrically well-defined tri- and tetrasubstituted olefins was achieved by using this reaction with stereoselectively synthesized starting material. This reaction has high potential to be used in the late stage of our synthesis of (+)-discodermolide as a coupling method of well designed pieces. There are two advantages of this reaction: first, the problematic step of vinyl iodide formation will be circumvented; secondly, the free alcohol group will be protected by a silyl group at the same time of coupling.

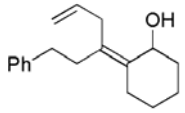
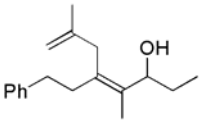
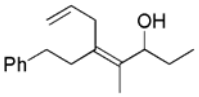
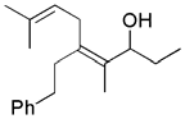
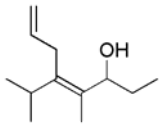
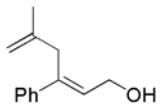
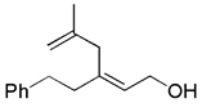


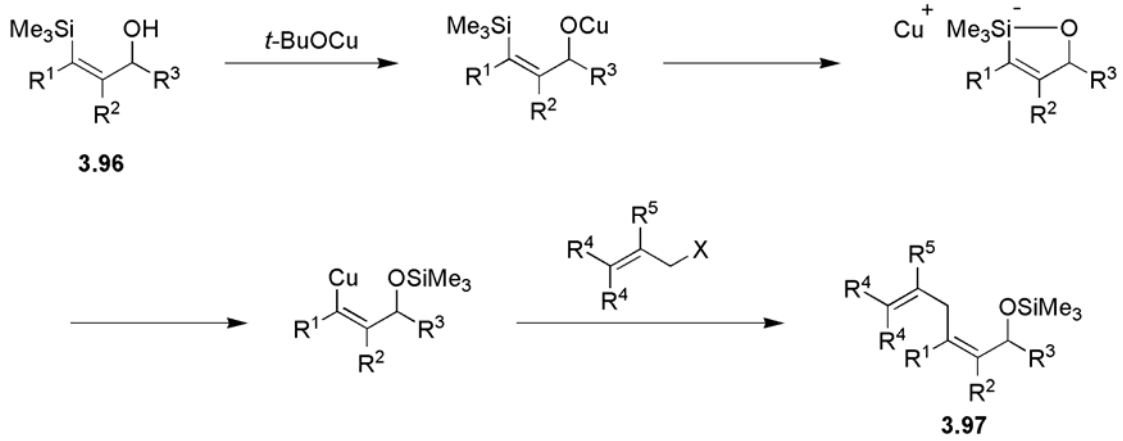
Scheme 3-42 Cross-Coupling of (*Z*)-γ-trimethylsilyl Allylic Alcohols with Allylic Halides

Table 3-4 Cross-coupling of (*Z*)-γ-trimethylsilyl allylic alcohols with allylic halides

Entry	R^1	R^2	R^3	R^4	R^5	Product	Yield
1	$Ph(CH_2)_2$	$-(CH_2)_4-$		H	Me		84%

[61] Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem*. **2002**, *67*, 8450.

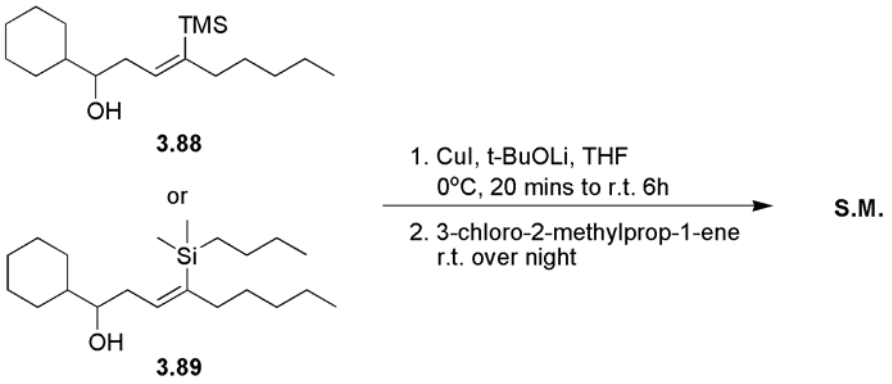
2	$Ph(CH_2)_2$	$-(CH_2)_4-$		H	H		88%
3	$Ph(CH_2)_2$	Me	Et	H	Me		85%
4	$Ph(CH_2)_2$	Me	Et	H	H		80%
5	$Ph(CH_2)_2$	Me	Et	Me	H		75%
6	*i*-Pr	H	Ph	H	H		76%
7	Ph	H	H	H	Me		74%
8	$Ph(CH_2)_2$	H	H	H	Me		73%



Scheme 3-43 Possible intermediates proposed by Takeda

3.2.8.2 Cross-Coupling Approach of Model (*Z*)-*δ*-trimethylsilyl Allylic Alcohols with Allylic Halides

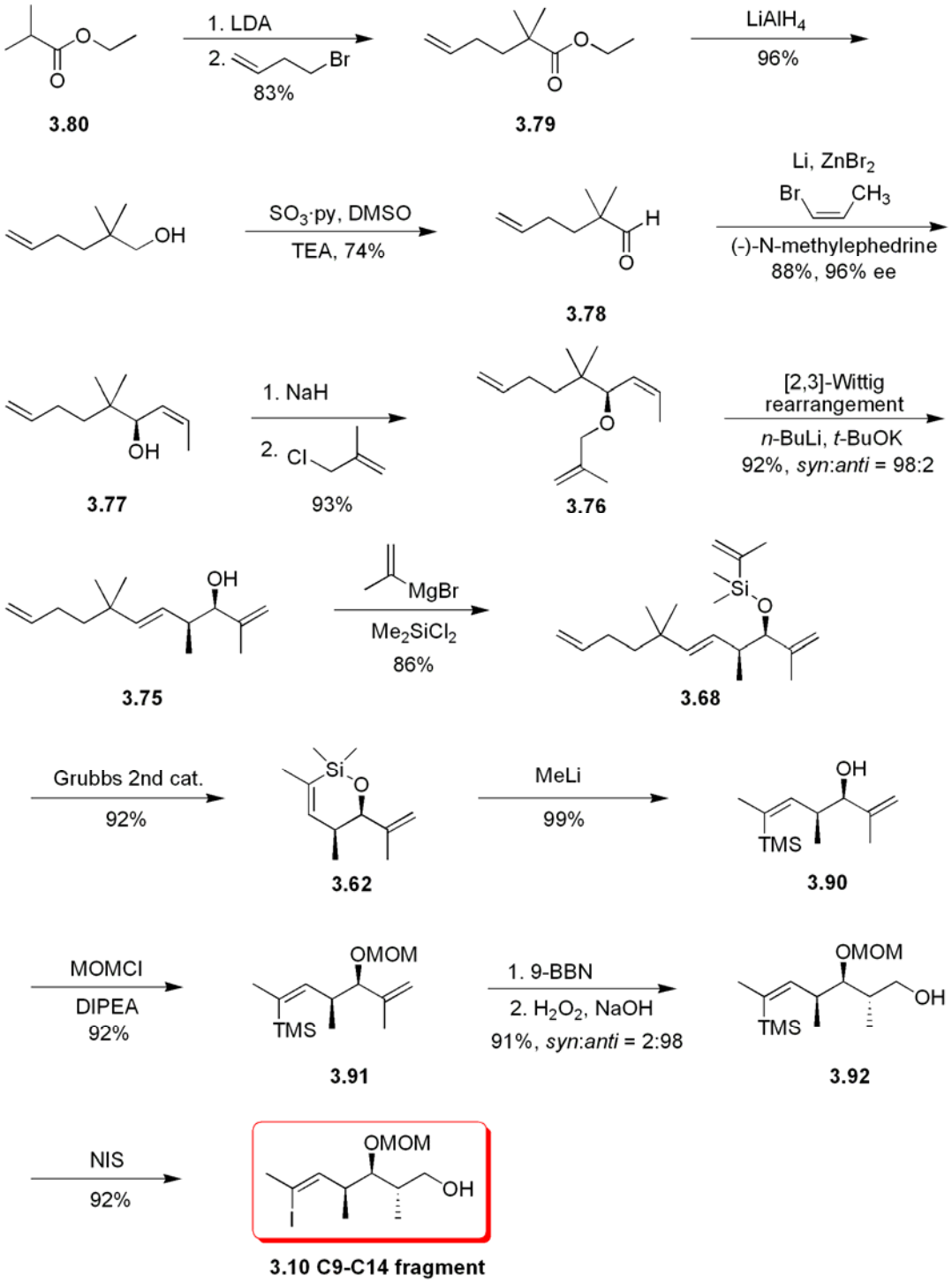
This migration-cross-coupling reaction was applied with model compounds, (*Z*)-4-(trimethylsilyl)but-3-en-1-ol derivatives **3.88** and **3.89**. Unfortunately, these reactions did not yield the target 1,5 C^{sp2}-to-O silyl migration and cross-coupling product. Almost all of the starting material was recovered instead (Scheme **3-44**). The extra methylene group between the hydroxyl group and the silyl group probably cause the lack of reactivity.



Scheme 3-44 Model study of 1,5 C^{sp2}-to-O silyl migration reaction

3.3 CONCLUSION

The C9-C14 fragment **3.10** of (+)-discodermolide was prepared from dihydro oxasiline **3.62** by ring opening nucleophilic addition, diastereoselective hydroboration and iododesilylation sequentially. The precursor, dihydro oxasiline **3.62**, was successfully achieved by a rationally designed relay metathesis of the related silyl ether **3.68**. The silyl ether **3.68** was readily available by the catalytic asymmetric synthesis of a chiral (Z)-allylic alcohol and then elaboration by methallylation, 2,3-Wittig rearrangement and silylation. Overall, the C9-C14 fragment **3.48** was successful synthesized in 12 steps with 26.8 % yield (Scheme **3-35**). The chirality source, (-)-N-methylephedrine, is inexpensive and the auxiliary is recoverable (Scheme 3-45).



Scheme 3-45 Synthesis of C9-C14 fragment **3.10**

3.4 EXPERIMENTAL SECTION

3.4.1 General Information

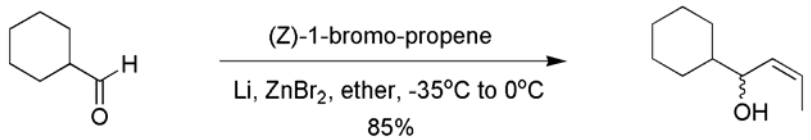
Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Lancaster, Alfa Aesar or Acros Organics. Liquid reagents were purified by distillation prior to use. Unless otherwise noted, solid reagents were used without further purification.

All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. In general, the residual solvent was removed on a vacuum line at 1-1.5 torr. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. Diisopropylethylamine and triethylamine were distilled from sodium. The extracts were dried over Na_2SO_4 unless otherwise noted.

All experiments were monitored by thin layer chromatography (TLC) performed on EM Science precoated silica gel 60 F-254 glass supported plates with 0.25 mm thickness. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or to iodine vapor or by staining with a 10 % solution of phosphomolybdenic acid (PMA) in ethanol and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

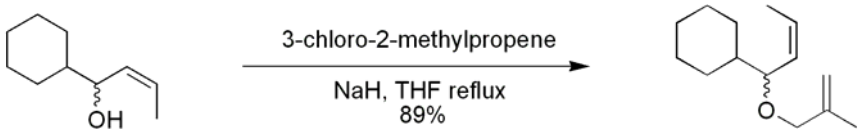
Infrared spectra were recorded with a Galaxy Series FT-IR 3000 infrared spectrophotometer. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), Varian Inova-500 (500 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H, 100 MHz for ^{13}C), or Gemini-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). For complex multiplets, the chemical shift is given for the center of the multiplet. Coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectra were obtained with a Micromass 70-VSE spectrometer.

3.4.2 Experimental Procedures



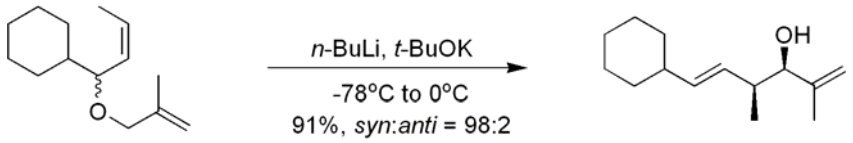
3.47

(*Z*)-1-Cyclohexylbut-2-en-1-ol (3.47) Parker and Cao's procedure was used here. To the lithium powder (1.19 g, 169.3 mmol) under argon was added dry ether (50 mL) and the suspension was cooled to –35 ºC. With stirring, a solution of (*Z*)-1-bromo-propene (10.0 g, 82.6 mmol) was added dropwise. The mixture was stirred at -35ºC for 2 h and treated dropwise with zinc bromide solution (20.4 g, 90.9 mmol, in 40 mL ether). The solution was stirred for 2 h at 0 ºC and cyclohexanecarboxaldehyde (8.81 g, 78.5mmol) was added neat. After stirring for 1 h at 0 ºC, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether. The organic phase was washed with a second portion of the ammonium chloride solution, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA= 10: 1) gave alcohol **3.47** (10.29 g, 85%) as clear liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (dqd, J = 10.2, 6.8, 1.3 Hz, 1H), 5.36 (ddq, J = 10.2, 9.4, 1.8 Hz, 1H), 4.14 (dd, J = 8.4 Hz, 1.0 Hz, 1H), 1.90 (m, 1H), 1.80-1.58 (m, 8H), 1.58-0.80 (m, 6 H).



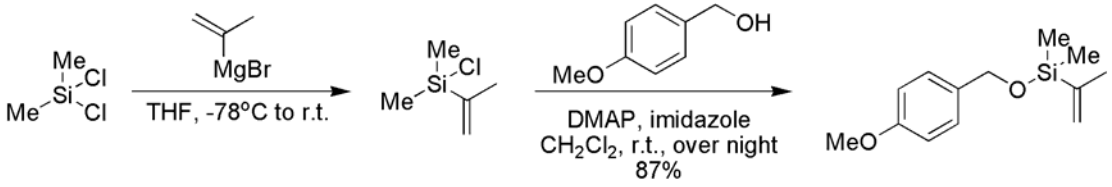
3.47 **3.48**

(*Z*)-(1-(2-Methylallyloxy)but-2-enyl)cyclohexane (3.48) Parker and Cao's procedure was used here. A 100-mL reaction flask was charged with 95% sodium hydride (1.97 g, 82.0 mmol) and 20 mL of dry THF. Alcohol **3.47** (1.81 g, 11.7 mmol) in 10 mL of THF was added dropwise followed by 3-chloro-2-methylpropene (3.18 g, 35.1 mmol). The reaction mixture refluxed overnight and cooled to room temperature. A 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA= 30: 1) produced compound **3.48** (2.18 g, 89%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.73 (dqd, J= 10.2, 6.8, 1.3 Hz, 1H), 5.24 (ddq, J= 10.2, 9.4, 1.8 Hz, 1H), 4.93 (m, 1H), 4.85 (m, 1H), 3.90 (d, J= 12.6 Hz, 1H), 3.80 (m, 1H), 3.69 (d, J= 12.4 Hz, 1H), 1.96 (m, 1H), 1.73 (s, 3H), 1.70-1.65 (m, 5H), 1.62 (dd, J= 7.1, 2.0 Hz, 3H), 1.58-0.80 (m, 6H).

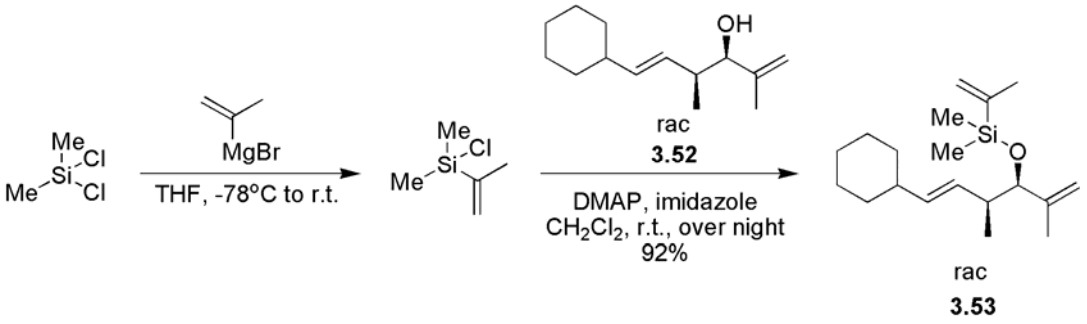


3.48 **rac 3.52**

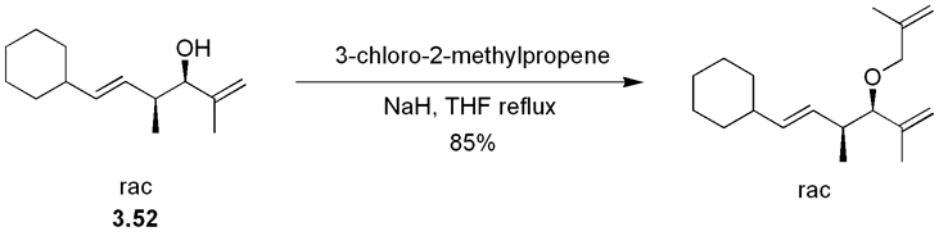
(*syn*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-ol (3.52) Parker and Cao's procedure was used here. A sample of Potassium *tert*-butoxide (1.0 M in THF, 11.5 mL, 11.5 mmol) was added to a flask under argon and an additional 5.0 mL of THF was added. The solution was cooled to –78 ºC and ether **3.48** (2.18 g, 10.5 mmol) was added. Then a sample of *n*-butyllithium (2.5 M in THF, 5.04 mL, 12.6 mmol) was slowly added. The mixture was warmed to –20 ºC over 4 h and the stirred 12 h at –20 ºC and 2 h at 0 ºC. The reaction was quenched with water and then extracted with ether. The organic phase was dried over $MgSO_4$, filtered and concentrated. Chromatography (HE: EA= 10:1) gave alcohol **3.52** (1.98 g, 91%, *syn*:*anti*= 98:2) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.40 (dd, *J*= 16.2, 6.6 Hz, 1H), 5.31 (dd, *J*= 16.2, 6.6 Hz, 1H), 4.92 (m, 1H), 4.86 (m, 1H), 3.87 (d, *J*= 6.0 Hz, 1H), 2.33 (m, 1H), 1.90 (m, 1H), 1.69 (s, 3H), 1.68-1.65 (m, 5H), 1.32-1.05 (m, 6H), 0.97 (d, *J*= 6.9 Hz, 3H); IR (neat) ν_{max} 3412 (broad), 2965, 2924, 2851, 1448, 979, 968, 896.



(4-Methoxybenzyloxy)dimethyl(prop-1-en-2-yl)silane To a -78^{o}C solution of dichlorodimethylsilane (706 mg, 5.43 mmol) in THF, a pre-cooled -78^{o}C solution of prop-1-en-2-ylmagnesium bromide (0.5 M, 13.0 mL, 6.52 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78^{o}C for 1/2 h and then warmed up to r.t. over 2 h. Then the resulting solution was cannula transferred to a pre-mixed solution of (4-methoxyphenyl)-methanol (500 mg, 3.62 mmol), DMAP (112 mg, 0.905 mmol) and imidazole (616 mg, 9.05 mmol) in CH_2Cl_2 at room temperature. Then, the reaction mixture was stirred at room temperature over night. After that, the reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 40 ml). Then the combined organic layers are washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine. The resulting organic solution was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 30:1) to yield (4-methoxybenzyloxy)dimethyl- (prop-1-en-2-yl)silane as a colorless oil (749 mg, 87%).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H), 6.96-6.92 (m, 2H), 5.75-5.72 (m, 1H), 5.48-5.46 (m, 1H), 4.69 (s, 2H), 3.87 (s, 3H), 1.92-1.89 (m, 3H), 0.281 (s, 6H); IR (neat) ν_{max} 2935, 2909, 2857, 2836, 1612, 1512, 1301, 1248, 1174, 1073, 1036,821.

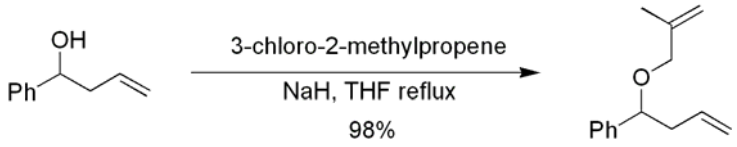


((*syn*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yloxy)dimethyl(prop-1-en-2-yl)silane (3.53) To a -78°C solution of dichlorodimethylsilane (1.70 g, 13.1 mmol) in THF, a pre-cooled -78°C solution of prop-1-en-2-ylmagnesium bromide (0.5 M, 39.2 mL, 19.6 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78°C for 1/2 h and then warmed up to r.t. over 2 h. Then the resulting solution was cannula transferred to a pre-mixed solution of *syn*-allylic alcohol **3.52** (680 mg, 3.27 mmol), DMAP (200 mg, 1.64 mmol) and imidazole (1.11 g, 16.4 mmol) in CH_2Cl_2 at room temperature. Then, the reaction mixture was stirred at room temperature over night. After that, the reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 40 ml). Then the combined organic layers are washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine. The resulting organic solution was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE: EA= 30:1) to yield **3.53** (924 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61-5.59 (m, 1H), 5.35-5.28 (m, 2H), 5.22-5.14 (m, 1H), 4.79-4.76 (m, 2H), 3.74-3.72 (d, *J*= 7.2 Hz, 1H), 2.47-2.17 (m, 1H), 1.95-1.44 (m, 11H), 1.31-0.96 (m, 9H), 0.16-0.15 (d, *J*= 3.3 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.27, 146.22, 135.45, 130.19, 126.10, 112.05, 81.63, 40.94, 40.75, 33.24, 33.18, 26.37, 26.19, 22.17, 17.69, 16.43, -1.84, -2.07; IR (neat) ν_{max} 3071, 3048, 3013, 2955, 2926, 2853, 1449, 1370, 1251, 1067, 895, 868, 831, 782.



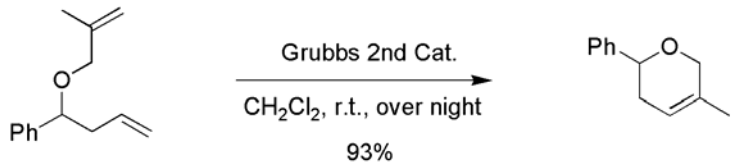
((*syn*,*E*)-3,5-Dimethyl-4-(2-methylallyloxy)hexa-1,5-dienyl)cyclohexane A 100-mL reaction flask was charged with 95% sodium hydride (403 mg, 16.8 mmol) and 20 mL of dry THF. A sample of **3.52** (500 mg, 2.40 mmol) in 10 mL of THF was added dropwise followed by 3-chloro-2-methylpropene (653 g, 7.20 mmol). The reaction mixture was heated at reflux temperature overnight and then cooled to room temperature. A 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL). The combined organic layers were dried

over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA= 30: 1) produced ((*syn*,*E*)-3,5-dimethyl-4-(2-methyl- allyloxy)hexa-1,5-dienyl)cyclohexane (534 mg, 85%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36-5.29 (dd, *J*= 15.6, 6.6 Hz, 1H), 5.20-5.12 (dd, *J*= 16.5, 7.8 Hz, 1H), 4.94 (s, 1H), 4.91 (s, 1H), 4.86 (s, 1H), 4.80 (s, 1H), 3.86-3.82 (d, *J*= 12.3 Hz, 1H), 3.64-3.60 (d, *J*= 12.3 Hz, 1H), 3.33-3.30 (d, *J*= 8.7 Hz, 1H), 2.33-2.21 (m, 1H), 1.95-1.77 (m, 1H), 1.74-1.53 (m, 10H), 1.30-0.95 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.64, 142.61, 135.66, 129.70, 114.42, 111.94, 87.78, 72.08, 40.61, 39.52, 33.11, 33.07, 26.23, 26.04, 19.74, 17.42, 17.03.



3.63

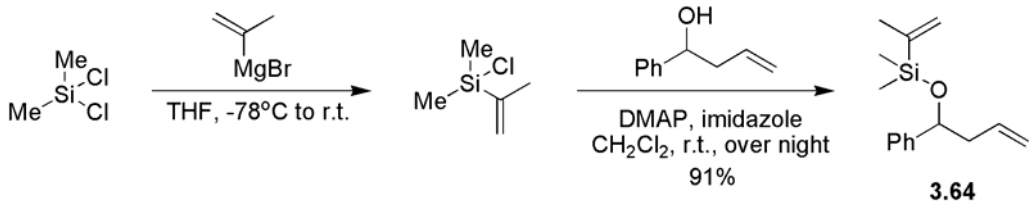
(1-(2-Methylallyloxy)but-3-enyl)benzene (3.63) A 100-mL reaction flask was charged with 95% sodium hydride (1.13 g, 47.3 mmol) and 20 mL of dry THF. Then a sample of 1-Phenylbut-3-en-1-ol (1.0 g, 6.75 mmol) in 10 mL of THF was added dropwise followed by 3-chloro-2-methylpropene (1.83 g, 20.2 mmol). The reaction mixture was refluxed overnight and cooled to room temperature. After that, 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA= 30: 1) produced allylic ether **3.63** (1.33 g, 98%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 5.87-5.73 (ddt, *J*= 17.3, 10.2, 6.9 Hz, 1H), 5.08-5.00 (m, 2H), 4.94 (s, 1H), 4.87 (s, 1H), 4.33-4.29 (dd, *J*= 7.5, 6.0 Hz, 1H), 3.84-3.64 (AB, 2H), 2.65-2.37 (m, 2H), 1.73 (s, 3H); IR (neat) ν_{max} 3076, 3028, 2977, 2934, 2913, 2857, 1656, 1642, 1493, 1452, 1090, 907, 759, 701.



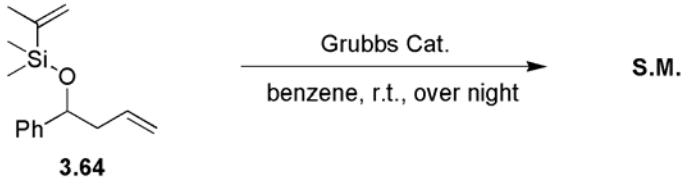
3.63

5-Methyl-2-phenyl-3,6-dihydro-2H-pyran In an oven-dried, 10-mL flask was placed Grubbs 2nd generation catalyst (17 mg, 0.020 mmol). Then 5 ml of freshly distilled and degassed CH_2Cl_2 was added. The allylic ether **3.63** (40 mg, 0.198 mmol) was added sequentially to the flask. The red-brown solution was stirred at room temperature under argon for over night. When the reaction was complete, the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a short column of silica gel and was further eluted (HE: EA= 30:1). The filtrate was concentrated in vacuo followed by Kugelrohr distillation to afford 5-methyl-2-phenyl-3,6-dihydro-2H-pyran (32 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.33 (m, 5H), 5.70-5.68 (m, 1H), 4.62-4.61 (dd, *J*= 9.6, 3.9 Hz, 1H), 4.40-4.23 (m, 2H), 2.47-2.28 (m, 2H), 1.76 (s, 3H);

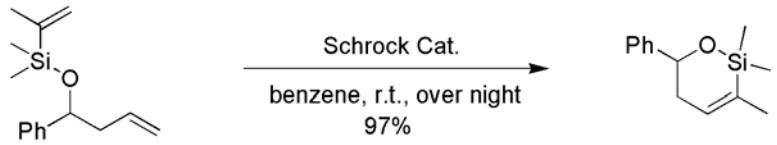
^{13}C NMR (300 MHz, $CDCl_3$) δ 142.50, 133.08, 128.29, 127.36, 125.83, 118.73, 75.65, 69.76, 32.82, 18.51; IR (neat) ν_{max} 3032, 2972, 2922, 1721, 1451, 1123,1091, 1044, 1029, 700.



Dimethyl(1-phenylbut-3-enyloxy)(prop-1-en-2-yl)silane (3.64) To a -78^{o}C solution of dichlorodimethylsilane (3.51 g, 27.0 mmol) in THF, a pre-cooled -78^{o}C solution of prop-1-en-2-ylmagnesium bromide (0.5 M, 81.0 mL, 40.5 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78^{o}C for 0.5 h and then warmed up to r.t. over 2 h. The resulting solution was cannula transferred to a pre-mixed solution of 1-phenylbut-3-en-1-ol (1.00 g, 6.75 mmol), DMAP (412 mg, 3.38 mmol) and imidazole (2.30 g, 33.8 mmol) in CH_2Cl_2. Then, the reaction mixture was stirred at r.t. over night. The reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 40 ml). The organic layers are combined, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, brine, died over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to column chromatography (HE: EA= 30:1) to yield allylic silyl ether **3.64** as a colorless oil (1.51 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (m, 5H), 5.80-5.70 (ddt, *J*= 17.2, 10.4, 6.8 Hz, 1H), 5.60-5.58 (dq, *J*= 3.6, 1.6 Hz, 1H), 5.34-5.32 (dq, *J*= 3.6, 1.2 Hz, 1H), 5.04-4.98 (m, 2H), 4.68-4.64 (dd, *J*= 7.2, 5.6 Hz, 1H), 2.52-2.40 (m, 2H), 1.76-1.75 (dd, *J*= 1.6, 1.2 Hz, 1H), 0.12(s, 3H), 0.07 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.9, 144.5, 135.0, 127.9, 127.0, 126.4, 125.9, 116.8, 75.1, 45.1, 22.0, -1.9, -2.1; IR (neat) ν_{max} 2952, 1451, 1252, 1089, 1067, 921, 830, 784, 699.

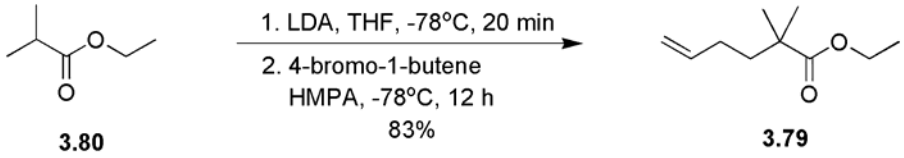


Metathesis Approach of 3.64 with Grubbs 2nd Generation Catalyst In an oven-dried, 10-mL flask was placed Grubbs 2nd generation catalyst (243 mg, 0.286 mmol). Then 5 ml of freshly distilled and degassed benzene was added. The silyl ether **3.64** (704 mg, 2.86 mmol) was added sequentially to the flask. The yellow-brown solution was stirred at room temperature over night. Then the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a short column of silica gel and was further eluted (HE: EA= 30:1). The filtrate was concentrated in vacuo to give the starting material back based on TLC and ^{1}H NMR analysis.



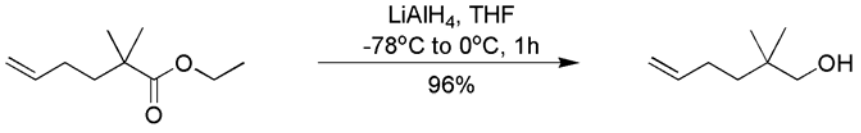
3.64

2,2,3-Trimethyl-6-phenyl-5,6-dihydro-2H-1,2-oxasiline In an oven-dried, 10-mL flask was placed Schrock catalyst (22 mg, 0.029 mmol). Then 5 ml of freshly distilled and degassed benzene was added. The silyl ether **3.64** (36 mg, 0.147 mmol) was added sequentially to the flask. The yellow-brown solution was stirred at room temperature over night. Then the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a short column of silica gel and was further eluted (HE: EA= 30:1). The filtrate was concentrated in vacuo. Then the resulting oil was subjected to column chromatography (HE: EA= 30:1) to yield **3.64** as a colorless oil (31 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 6.40-6.39 (m, 1H), 4.94-4.91 (dd, *J*= 10.4, 3.2 Hz, 1H), 2.43-2.25 (m, 2H), 1.78 (br s, 3H), 0.26(s, 3H), 0.25 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.4, 139.3, 135.2, 128.2, 127.0, 125.5, 73.7, 38.8, 20.3, -1.5, -1.7; IR (neat) ν_{max} 2955, 2920, 2851, 1613, 1451, 1443, 1250, 1051, 965, 824, 80, 699.



3.80 **3.79**

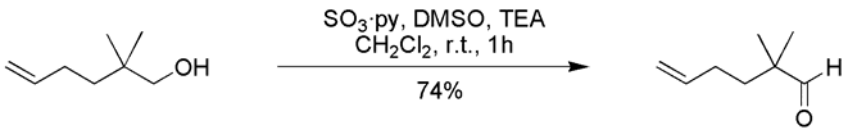
Ethyl 2,2-dimethylhex-5-enoate (3.79) A solution of ethyl isobutyrate **3.80** (14.34 g, 123.5 mmol) in THF (50 mL) was added slowly to a THF (100 mL) solution of LDA (2.0 M, 68.5 mL, 135.9 mmol) at –78 °C and stirred for 20 min. The resulting solution was treated with a solution of 4-bromo-1-butene (20.50 g, 148.0 mmol) in HMPA (25 mL) and stirred at –78 °C for 12 h. Aqueous HCl (2 N, 100 mL) was added and the resulting mixture was extracted with ether (4 x 50 mL). The combined organic fractions were washed with water (4 x 50 mL) and saturated $NaHCO_3$ (2 x 50 mL), dried, and concentrated. The oily residue was distilled under vacuum to give ethyl 2,2-dimethyl-5-hexenoate **3.79** (17.20 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (ddt, *J*= 16.4, 10.0, 6.4 Hz, 1H), 5.02-4.91 (m, 2H), 4.14-4.09 (q, *J*= 7.2 Hz, 2H), 2.68-2.61 (m, 2H), 1.64-1.59 (m, 2H), 1.27-1.22 (t, *J*= 6.8 Hz, 3H), 1.18 (s, 6H).



3.79

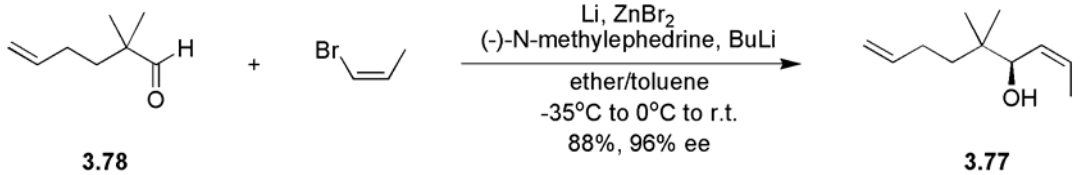
2,2-Dimethylhex-5-en-1-ol To a suspension of $LiAlH_4$ (3.27 g, 86.1 mmol) in THF (100

mL) at -78 °C was added **3.79** (12.20 g, 71.8 mmol) in 50 mL of THF over 20 min. The -78 °C bath was replaced with an ice bath, and the reaction mixture was stirred for 1 h. The reaction was quenched by careful addition of H_2O at 0 °C. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organics were dried, filtered, and concentrated. The resulting oil was subjected to column chromatography (HE: EA= 7:1) to yield alcohol 2,2-dimethylhex-5-en-1-ol as a colorless oil (8.86 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88-5.78 (ddt, *J*= 16.8, 10.0, 6.4 Hz, 1H), 5.05-4.99 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.95-4.91 (ddt, *J*= 10.0, 2.0, 1.2 Hz, 1H), 3.34-3.32 (d, *J*= 4.2 Hz, 2H), 2.06-1.99 (m, 2H), 1.58 (s, 1H), 1.36-1.32 (m, 2H), 0.89 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.4, 113.9, 71.8, 37.9, 35.1, 28.4, 23.9; IR (neat) ν_{max} 3349, 3077, 2957, 2934, 2871, 1641, 1473, 1389, 1364, 1049, 908.



3.78

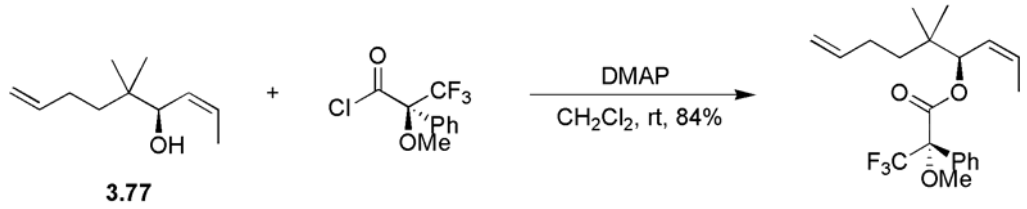
2,2-Dimethylhex-5-enal (3.78) To a solution of 2,2-dimethylhex-5-en-1-ol (5.105 g, 39.8 mmol) in 150 mL of CH_2Cl_2 were added DMSO (30 mL), Et_3N (12.09 g, 119.5 mmol), and SO_3·py (9.51 g, 59.7 mmol). The clear, light yellow solution was stirred for 0.5 h, after which time more SO_3·py (3.17 g, 19.9 mmol) was added. The reaction mixture was stirred for an additional 0.5 h, diluted with CH_2Cl_2, and washed twice with 1 N HCl aqueous solution and once with saturated $NaHCO_3$ aqueous solution. The organic layer was dried, filtered, and concentrated to provide an oil that was purified by flash column chromatography (1:2 hexanes:Et_2O) to afford aldehyde **3.78** (3.72 g, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 5.82-5.72 (ddt, *J*= 16.8, 10.0, 6.4 Hz, 1H), 5.03-4.98 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.96-4.93 (ddt, *J*= 10.0, 1.6, 1.6 Hz, 1H), 2.00-1.94 (m, 2H), 1.58-1.54 (m, 2H), 1.06 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.6, 130.0, 127.6, 113.8, 73.4, 37.8, 37.7, 28.4, 22.5, 22.3, 15.4.



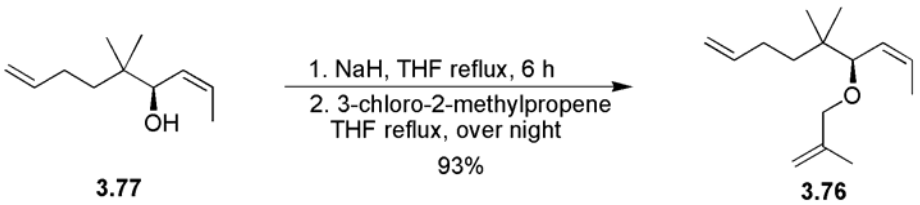
3.78 **3.77**

(*R*,*Z*)-5,5-Dimethylnona-2,8-dien-4-ol (3.77) To the lithium powder (319 mg, 45.5 mmol) under argon was added dry ether (20 mL) and the suspension was cooled to –35 ºC. With stirring, a solution of (*Z*)-1-bromo-propene (3.36 g, 27.7 mmol) was added dropwise. The mixture was stirred at -35ºC for 2 h and treated dropwise with zinc bromide solution (6.54 g, 29.1 mmol, in 30 mL ether). The reaction mixture was stirred for an additional 1 h at 0 ºC and then a solution of lithium (-)-N-methylephedrate, prepared by the addition of n-butyllithium (2.5 M in hexanes, 11.6 mL, 29.1 mmol) to a solution of

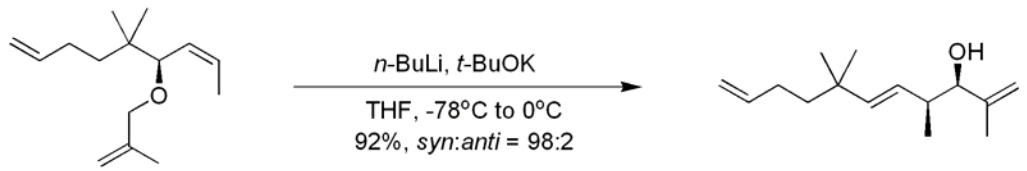
(-)-N-methylephedrine (5.22 g, 29.1 mmol) in toluene (20 mL) at 0 ºC, was added by cannula. The solution was stirred for 1 h at 0 ºC and aldehyde **3.78** (2.80 g, 22.2 mmol) was added neat. After stirring for 1 h at 0 ºC, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution. The organic phase was separated and the aqueous phase was extracted with ether (3 x 30 mL). The organic phases were combined, washed with a second portion of the NH_4Cl solution, dried (MgSO4), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **3.77** (3.24 g, 88%, 96% ee. according to NMR study of Mosher ester) as clear liquid. (-)-N-methylephedrine was recovered quantitatively from the aqueous phases by basification to pH=12 with 2 N NaOH solution and extraction into ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (ddt, *J*= 16.8, 10.0, 6.8 Hz, 1H), 5.70-5.62 (dqd, *J*= 11.2, 6.8, 0.8 Hz, 1H), 5.52-5.45 (ddq, *J*= 11.2, 9.2, 2.0 Hz, 1H), 5.04-4.98 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.94-4.90 (ddt, *J*= 10.4, 2.0, 1.2 Hz, 1H), 4.20-4.17 (dd, *J*= 9.6, 3.2 Hz, 1H), 3.75-3.68 (m, 1H), 2.07-2.02 (m, 2H), 1.70-1.67 (dd, *J*= 7.2, 2.0 Hz, 3H), 1.61 (s, 1H), 1.48-1.27 (m, 2H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.6, 130.0, 127.6, 113.8, 73.4, 37.8, 37.7, 28.4, 22.5, 22.3, 15.4; IR (neat) ν_{max} 3396 (br), 2963, 2937, 1640, 1470, 1451, 1384, 1364, 1047, 1032, 994, 908, 720.



(*S*)-((*R*,*Z*)-5,5-Dimethylnona-2,8-dien-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenyl-propanoate A sample of chiral allylic alcohol **3.77** (20 mg, 0.120 mmol) and DMAP (29 mg, 0.241 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (61 mg, 0.241 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 20: 1) through a silica gel column to give Mosher ester as a colorless oil (39 mg, 84%) for ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 2H), 7.41-7.36 (m, 3H), 5.88-5.80 (dq, *J*= 11.2, 7.2 Hz, 1H), 5.78-5.68 (ddt, *J*= 16.8, 10.0, 6.4 Hz, 1H), 5.61-5.58 (d, *J*= 10.0 Hz, 1H), 5.57-5.52 (t, *J*= 10.0 Hz, 0.02H), 5.49-5.43 (ddt, *J*= 10.0, 1.6, 1.6 Hz, 0.98H), 5.00-4.90 (m, 2H), 3.559-3.557 (d, *J*= 0.8 Hz, 3H), 2.02-1.95 (m, 2H), 1.82-1.80 (dd, *J*= 6.8, 1.6 Hz, 3H), 1.38-1.19 (m, 2H), 0.87 (s, 3H), 0.86 (s, 3H).

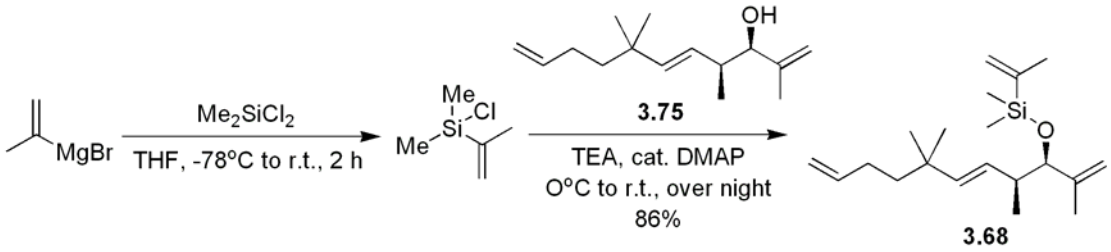


(*R*,*Z*)-5,5-Dimethyl-6-(2-methylallyloxy)nona-1,7-diene A 100-mL round bottom flask was charged with 95% sodium hydride (794 mg, 33.1 mmol) and 20 mL of dry THF. Alcohol **3.77** (1.10 g, 6.62 mmol) in 10 mL of THF was added dropwise followed by 3-chloro-2-methylpropene (4.20 g, 46.3 mmol). The reaction mixture refluxed over night and cooled to room temperature. A 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) produced compound **XXX** (1.35 g, 93%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.72 (m, 2H), 5.37-5.30 (ddq, *J*= 11.6, 10.0, 2.0 Hz, 1H), 5.02-4.96 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.93-4.89 (m, 2H), 4.85-4.84 (dq, *J*= 1.6, 0.8 Hz, 1H), 3.90-3.62 (AB, 2H), 3.79-3.76 (dd, *J*= 10.0, 0.8 Hz, 1H), 2.07-1.99 (m, 2H), 1.73 (s, 3H), 1.67-1.64 (dd, *J*= 6.8, 2.0 Hz, 3H), 1.52-1.27 (m, 2H), 0.91 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.0, 139.8, 128.7, 128.4, 113.6, 111.4, 79.8, 72.0, 38.1, 37.8, 28.5, 23.2, 23.0, 19.9, 13.8; IR (neat) ν_{max} 3076, 3019, 2972, 2938, 2920, 2871, 1657, 1641, 1451, 1382, 1364, 1105, 1083, 1058, 992, 905, 724.

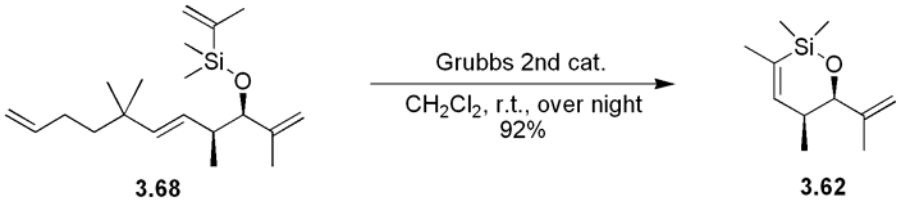


3.76 **3.75**

(3*R*,4*S*,*E*)-2,4,7,7-Tetramethylundeca-1,5,10-trien-3-ol (3.75) A sample of Potassium *tert*-butoxide (1.0 M in THF, 6.09 mL, 6.09 mmol) was added to a flask under argon and an additional 20 mL of THF was added. The solution was cooled to –78 ºC and ether **3.76** (1.22 g, 5.54 mmol) was added. Then a sample of *n*-butyllithium (2.5 M in THF, 2.66 mL, 6.65 mmol) was slowly added. The mixture was warmed to –20 ºC over 4 h and the stirred 12 h at –20 ºC and 2 h at 0 ºC. The reaction was quenched with water and then extracted with ether. The organic phase was dried over $MgSO_4$, filtered and concentrated. Chromatography (HE: EA = 20:1) gave alcohol **3.75** (1.12 g, 92%, *syn*:*anti*= 98:2) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.74 (ddt, *J*= 16.8, 10.4, 6.8 Hz, 1H), 5.41-5.37 (dd, *J*= 15.6, 0.8 Hz, 1H), 5.24-5.18 (dd, *J*= 16.0, 7.6 Hz, 1H), 5.00-4.94 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.92-4.88 (m, 2H), 4.85-4.84 (dq, *J*= 2.8, 1.2 Hz, 1H), 3.87-3.85 (dd, *J*= 6.4, 3.6 Hz, 1H), 2.38-2.29 (dqd, *J*= 13.6, 6.8, 0.8 Hz, 1H), 1.96-1.90 (m, 2H), 1.70-1.69 (m, 3H), 1.61-1.60 (d, *J*= 4.0 Hz, 1H), 1.35-1.31 (m, 2H), 1.01-0.99 (d, *J*= 6.8 Hz, 3H), 0.962 (s, 3H), 0.959 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.9, 140.0, 139.5, 128.3, 113.7, 111.9, 79.5, 42.3, 40.3, 35.7, 29.2, 27.5, 272, 18.3, 15.4; IR (neat) ν_{max} 3391, 3075, 2961, 2928, 2869, 1641, 1453, 1384, 1364, 1023, 981, 904.

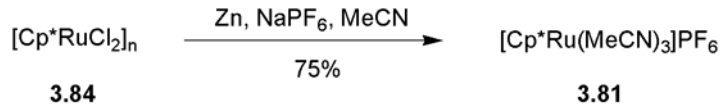


Dimethyl(prop-1-en-2-yl)((3*R*,4*S*,*E*)-2,4,7,7-tetramethylundeca-1,5,10-trien-3-yloxy)silane (3.68) To a -78°C solution of dichlorodimethylsilane (2.05 g, 15.8 mmol) in THF, a pre-cooled -78°C solution of prop-1-en-2-ylmagnesium bromide (0.5 M, 47.4 mL, 23.7 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78 °C for 0.5 h and then warmed up to r.t. over 2 h. Then the resulting solution was cannula transferred to a pre-mixed solution of *syn*-allylic alcohol **3.75** (870 mg, 3.95 mmol), DMAP (241 mg, 1.98 mmol) and imidazole (1.34 g, 19.75 mmol) in CH_2Cl_2 at room temperature. Then, the reaction mixture was stirred at room temperature over night. After that, the reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 40 ml). Then the combined organic layers are washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution and brine. The resulting organic solution was dried over $MgSO_4$ and concentrated in *vacuo*. The resulting oil was subjected to column chromatography (HE:EA= 30:1) to yield **3.68** (1.08 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.74 (ddt, *J*= 16.8, 10.4, 6.8 Hz, 1H), 5.61-5.59 (dq, *J*= 4.0, 2.0 Hz, 1H), 5.36-5.34 (dq, *J*= 4.0, 1.2 Hz, 1H), 5.30-5.26 (dd, *J*= 15.6, 0.6 Hz, 1H), 5.12-5.06 (dd, *J*= 15.6, 8.4 Hz, 1H), 4.99-4.94 (ddt, *J*= 17.2, 1.6, 1.6 Hz, 1H), 4.91-4.87 (ddt, *J*= 10.4, 2.4, 1.2 Hz, 1H), 4.78-4.77 (dq, *J*= 0.8, 0.8 Hz, 1H), 4.75-4.74 (dq, *J*= 2.8, 1.6 Hz, 1H), 3.74-3.72 (d, *J*= 7.6 Hz, 1H), 2.25-2.17 (m, 1H), 1.95-1.88 (m, 2H), 1.84-1.82 (m, 3H), 1.64-1.63 (dd, *J*= 1.2, 0.8 Hz, 3H), 1.32-1.27 (m, 2H), 0.99-0.97 (d, *J*= 6.4 Hz, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.3, 139.7, 138.8, 128.8, 126.1, 113.5, 112.2, 81.7, 65.9, 42.4, 41.4, 35.6, 29.2, 27.5, 27.2, 22.2, 17.5, 17.0, 15.4, -1.8, -2.1; IR (neat) ν_{max} 2959, 1641, 1451, 1383, 1368, 1251, 1067, 900, 871, 830, 781.

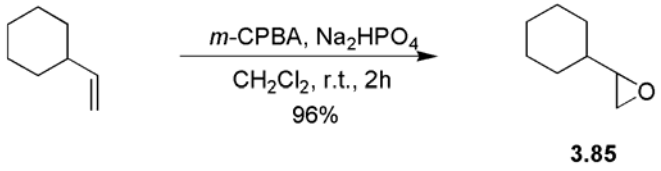


(5*S*,6*R*)-2,2,3,5-Tetramethyl-6-(prop-1-en-2-yl)-5,6-dihydro-2H-1,2-oxasiline (3.62) In an oven-dried, 10-mL flask was placed Grubbs 2nd generation catalyst (215 mg, 0.252 mmol). Then 30 ml of freshly distilled and degassed CH_2Cl_2 was added. The silyl ether **3.68** (800 mg, 2.52 mmol) was added sequentially to the flask. The yellow-brown solution was stirred at room temperature under Ar over night. Then the solvent was removed by rotary evaporation to give a brown residue, which was filtered through a

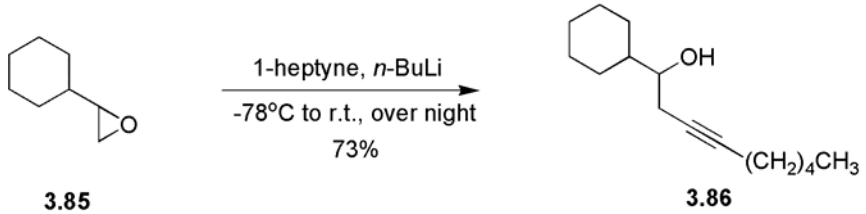
short column of silica gel and was further eluted with ether. Then the filtrate was concentrated in vacuo. The resulting oil was subjected to column chromatography (HE) to yield **3.62** as a colorless oil (453 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44-6.42 (d, *J*= 6.4 Hz, 1H), 5.134-5.132 (d, *J*= 0.8 Hz, 1H), 4.903-4.899 (d, *J*= 1.6 Hz, 1H), 4.33 (s, 1H), 2.29-2.27 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.01-0.94 (m, 1H), 0.82-0.80 (d, *J*= 7.2 Hz, 3H), 0.20 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.4, 144.9, 133.2, 110.1, 76.1, 35.6, 20.2, 19.9, 13.2, -1.58, -1.69; IR (neat) ν_{max} 2963, 1654, 1613, 1448, 1257, 1076, 1008, 876, 782.



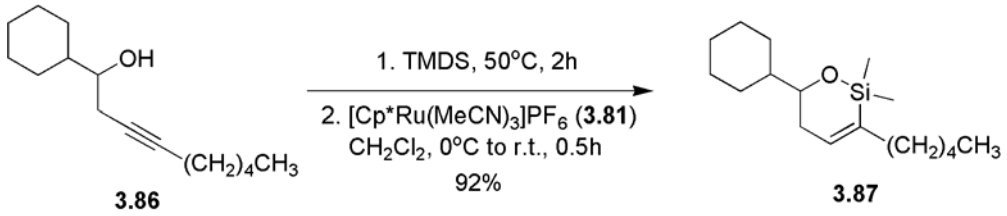
[Cp*Ru(MeCN)$_3$]PF$_6$ (3.81) A mixture consisting of [Cp*RuCl$_2$]$_n$ (**3.84**, 120 mg, 0.391 mmol), NaPF$_6$ (92 mg, 0.548 mmol), and acetonitrile (5 mL) was stirred overnight and then heated to reflux to be filtered. The hot dark-orange filtrate deposited orange crystals upon cooling to 0^{o}C. The crystals were collected, then washed with methanol (20 mL) and diethyl ether (30 mL), and finally dried under vacuum to yield complex **3.81** as a orange crystal (147 mg, 75%).



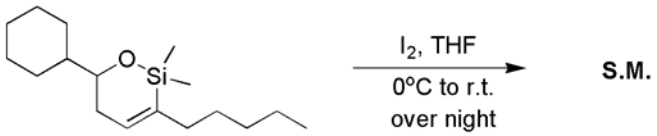
2-Cyclohexyloxirane (3.85) A sample of vinylcyclohexane (1.0 g, 9.07 mmol) was added dropwise through an addition funnel to a cold solution of *m*-CPBA (2.30 g, 75%, 9.98 mmol) and Na_2HPO_4 (1.55 g, 10.9 mmol) in CH_2Cl_2 (30 ml). After 1.75 h at room temperature, more *m*-CPBA (2.0 g) and CH_2Cl_2 (20 ml) added to the flask. The mixture was stirred overnight at room temperature. The solids were filtered off and the filtrate was treated with Na_2SO_3 aqueous solution and extracted with ether. The organics were washed (H_2O, brine, sat. Na_2CO_3 aq) and dried over Na_2SO_4. The solvents were removed by distillation at atmospheric pressure and the crude product was purified by distillation under reduced pressure to yield desired epoxide **3.85** as a colorless oil (1.10 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68-2.74 (m, 2H), 2.52 (dd, *J*= 3.4, 4.4 Hz, 1H), 0.6-2.10 (m, 11H).



1-Cyclohexylpent-3-yn-1-ol (3.86) A sample of 1-heptyne (420mg, 4.37 mmol) was dissolved in THF and cooled down to -78°C. Then a sample of *n*-BuLi THF solution (2.5 M, 1.75 mL, 4.37 mmol) was added. After 2 h stirring at -78 oC, the reaction mixture was cannula transferred to a pre-cooled -78°C solution of epoxide **3.85** (500 mg, 3.97 mmol) in THF. The resulting mixture was stirred at -78°C for 1 h and then warmed up to r.t. overnight. The reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 30 ml). The organic layers are combined, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, brine, died over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to column chromatography (HE: EA= 7:1) to yield alcohol **3.86** as a colorless oil (614 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.46-3.38 (m, 1H), 2.45-2.38 (ddt, *J*= 16.5, 4.5, 2.3 Hz, 1H), 2.34-2.26 (ddt, *J*= 16.5, 7.5, 2.4 Hz, 1H), 2.19-2.13 (m, 2H), 2.04-0.88 (m, 21H); IR (neat) ν_{max} 3401 (br), 2937, 2855, 1450, 1102, 1037, 988, 892.

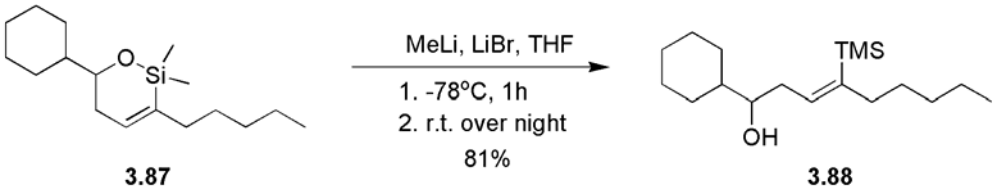


6-Cyclohexyl-2,2-dimethyl-3-pentyl-5,6-dihydro-2H-1,2-oxasiline (3.87) A round-bottomed flask was charged with alcohol **3.86** (500 mg, 2.25 mmol) under Ar at room temperature. To the neat alcohol was added 1,1,3,3-tetramethyldisilazane (901 mg, 6.76 mmol) and the flask heated to 50 °C for 2 h. Next, the flask was cooled to ambient temperature and placed under vacuum for 45 min to remove the excess silazane. An Ar atmosphere was then re-introduced and the residue taken up in CH_2Cl_2 (3.0 mL). The flask was cooled to 0 °C and solid [Cp*Ru(MeCN)$_3$]PF$_6$ (**3.81**) (5.4 mg, 0.011mmol) was added to the solution. The flask was allowed to warm to room temperature, and after 15 min, the solution was diluted with ether (10 mL) and filtered through a short plug of florisil, washing with additional ether (100 mL). The volatile components were then removed under reduced pressure and the resulting residue purified on a florisil column (HE: EA= 30:1) to afford the desired dihydro oxasiline **3.87** (583 mg, 92%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41-6.38 (dd, *J*= 6.9, 1.8 Hz, 1H), 3.63-3.57 (q, *J*= 6.6 Hz, 1H), 2.21-2.17 (td, *J*= 4.8, 1.2 Hz, 2H), 2.13-2.08 (t, *J*= 7.5 Hz, 2H), 2.03-1.98 (d, *J*= 13.8 Hz, 1H), 1.83-1.70 (m, 4H), 1.48-1.18 (m, 10H), 1.10-0.93 (m, 5H), 0.24 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 139.71, 139.35, 75.82, 43.93, 35.34, 32.76, 31.74, 29.25, 29.03, 28.72, 26.62, 26.23, 26.11, 22.52, 14.06, -0.75, -0.91; IR (neat) ν_{max} 2959, 2852, 1449, 1371, 1252, 1064, 1032, 896, 869, 830, 782.



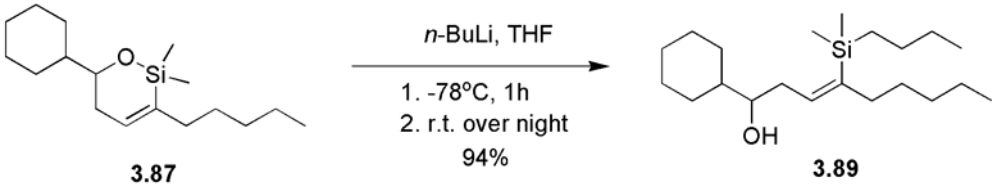
3.87

Ring Opening Approach of 3.87 with Iodine A sample of dihydro oxasiline **3.87** (20 mg, 0.071 mmol) was dissolved in THF (10 mL) and cooled down to 0 ^{o}C. Then a sample of I_2 (36 mg, 0.142 mmol) was added in one portion and the mixture was warmed up to room temperature and stirred overnight. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^{1}H NMR analysis of the residue showed starting material was recovered.



3.87 3.88

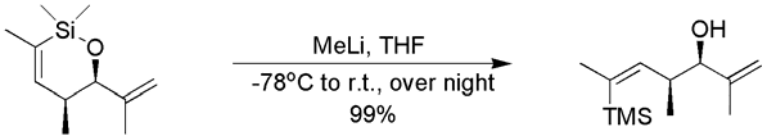
(*Z*)-1-Cyclohexyl-4-(trimethylsilyl)non-3-en-1-ol (3.88) To a -78^{o}C solution of **3.87** (118 mg, 0.418 mmol) in THF, a pre-cooled -78^{o}C solution of MeLi·LiBr (2.2 M, 0.285 mL, 0.628 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78^{o}C for 1 h and then warmed up to r.t. overnight. The reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 30 ml). The organic layers are combined, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, brine, died over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to column chromatography (HE: EA= 7:1) to yield alcohol **3.88** as a colorless oil (101 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00-5.95 (dd, *J*= 8.1, 6.9 Hz, 1H), 3.40-3.39 (d, *J*= 3.6 Hz, 1H), 2.31-2.09 (m, 2H), 2.09-2.05 (t, *J*= 7.2 Hz, 2H), 1.85-1.66 (m, 5H), 1.46-1.45 (d, *J*= 3.0 Hz, 1H), 1.43-0.86 (m, 16H), 0.15 (s, 9H).



3.87 3.89

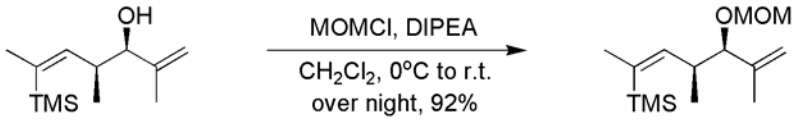
(*Z*)-4-(Butyldimethylsilyl)-1-cyclohexylnon-3-en-1-ol (3.89) To a -78^{o}C solution of **3.87** (100 mg, 0.355 mmol) in THF, a pre-cooled -78^{o}C solution of *n*-BuLi (2.5 M, 0.213 mL, 0.532 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78^{o}C for 1 h and then warmed up to r.t. overnight. The reaction was quenched

by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 30 ml). The organic layers are combined, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, brine, died over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to column chromatography (HE: EA= 7:1) to yield alcohol **3.89** as a colorless oil (114 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01-5.96 (t, *J*= 7.2 Hz, 1H), 3.40-3.39 (br d, *J*= 3.3 Hz, 1H), 2.30-2.17 (m, 2H), 2.08-2.03 (t, *J*= 7.2 Hz, 2H), 1.85-1.66 (m, 5H), 1.46-1.45 (br d, *J*= 13.3 Hz, 1H), 1.43-0.85 (m, 22H), 0.66-0.60 (m, 2H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.30, 138.71, 75.65, 43.29, 38.65, 36.55, 31.74, 30.64, 30.31, 29.15, 28.08, 26.60, 26.56, 26.36, 26.28, 26.21, 22.55, 16.42, 14.10, 13.80, -1.32, -1.48; IR (neat) ν_{max} 3400 (br), 2955, 2925, 2854, 1470, 1249, 835, 817.



3.62 **3.90**

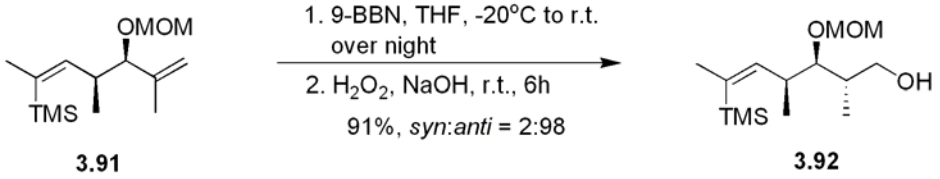
(3*R*,4*S*,*Z*)-2,4-Dimethyl-6-(trimethylsilyl)hepta-1,5-dien-3-ol (3.90) To a -78 ^{o}C solution of **3.62** (86 mg, 0.438 mmol) in THF, a pre-cooled -78 ^{o}C solution of MeLi (1.6 M, 0.548 mL, 0.877 mmol) in THF was added dropwise by cannula transfer. The resulting mixture was stirred at -78^{o}C for 1 h and then warmed up to r.t. over night. The reaction was quenched by saturated NH_4Cl aqueous solution and diluted with ether. The aqueous layer was extracted by ether (3 x 20 ml). The organic layers are combined, washed with saturated NH_4Cl aqueous solution, saturated $NaHCO_3$ aqueous solution, brine, died over $MgSO_4$, and concentrated in vacuo. The resulting oil was subjected to column chromatography (HE:EA= 7:1) to yield alcohol **3.90** as a colorless oil (92 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93-5.90 (dd, *J*= 10.0, 1.6 Hz, 1H), 4.96 (s, 1H), 4.87 (s, 1H), 3.91-3.90 (d, *J*= 4.8 Hz, 1H), 2.59-2.53 (m, 1H), 1.754-1.750 (d, *J*= 1.6 Hz, 3H), 1.70 (s, 3H), 1.64 (br s, 1H), 0.94-0.93 (d, *J*= 6.8 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 146.3, 144.6, 134.2, 111.2, 79.2, 39.0, 24.9, 19.2, 15.7, 0.17; IR (neat) ν_{max} 3393, 2954, 2896, 1650, 1617, 1450, 1371, 1249, 1029, 1009, 990, 898, 836, 755, 688.



3.90 **3.91**

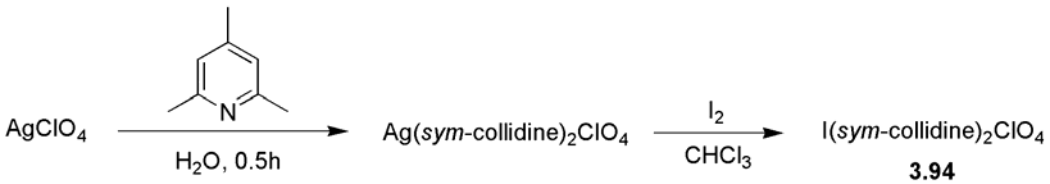
((4*S*,5*R*,*Z*)-5-(Methoxymethoxy)-4,6-dimethylhepta-2,6-dien-2-yl)trimethylsilane (3.91) A sample of MOMCl (279.5 mg, 263 µL, 3.47 mmol) was added drop wise *via* syringe to a solution of allylic alcohol **3.90** (92 mg, 0.434 mmol) in 5 mL of CH_2Cl_2 at 0 ºC, followed by addition of *i*-Pr_2NEt (448 mg, 3.47 mmol). The resulting mixture was stirred at 0 ºC for 2 h and then at ambient temperature over night. A saturated solution of

Na_2CO_3 (10 mL) was added to quench the reaction. The aqueous phase was extracted with ether (3 x 20 mL) and the organic phases were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave MOM ether **3.91** as a colorless oil (102.2 mg, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79-5.77 (dd, *J*= 10.0, 1.0 Hz, 1H), 4.92 (br s, 1H), 4.90 (br s, 1H), 4.62-4.48 (AB, 2H), 3.75-3.74 (d, *J*= 7.5 Hz, 1H), 3.38 (s, 3H), 2.57-2.55 (m, 1H), 1.723-1.720 (d, *J*= 1.5 Hz, 1H), 1.62 (s, 3H), 1.04-1.02 (d, *J*= 7.0 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 144.5, 142.9, 133.3, 114.3, 93.9, 84.0, 55.8, 38.3, 30.9, 24.8, 17.9, 0.10; IR (neat) ν_{max} 2953, 2889, 1650, 1619, 1451, 1249, 1153, 1097, 1034, 837.



3.91 **3.92**

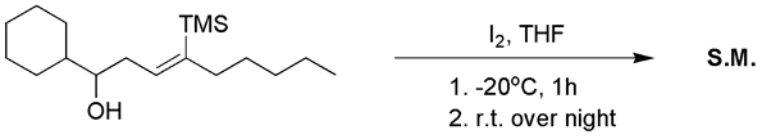
(2*S*,3*R*,4*S*,*Z*)-3-(Methoxymethoxy)-2,4-dimethyl-6-(trimethylsilyl)hept-5-en-1-ol (3.92) To the MOM ether **3.91** (44 mg, 0.172 mmol) in 5 mL of THF was added 9-BBN (0.5 M in THF, 0.413 mL, 0.206 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued over night. TLC showed the completion of the reaction. Then 2 mL of 3 N NaOH (aq) was added and this was followed by 2 mL of 30 wt% H_2O_2 (aq). The resulting mixture was stirred for 6 h at room temperature and then poured into 20 mL of ether and 20 mL of brine. The aqueous phase was extracted with ether and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **3.92** as a colorless oil (43 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.82 (dd, *J*= 10.4, 1.6 Hz, 1H), 4.65 (s, 2H), 3.87-3.81 (dd, *J*= 11.2, 3.6 Hz, 1H), 3.50-3.48 (dd, *J*= 11.6, 4.0 Hz, 1H), 3.32-3.29 (dd, *J*= 8.0, 4.4 Hz, 1H), 2.61-2.58 (s, 1H), 2.18-2.10 (m, 1H), 1.75-1.74 (d, *J*= 1.2 Hz, 3H), 1.01-0.99 (d, *J*= 7.2 Hz, 3H), 0.95-0.93 (d, *J*= 6.8 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 145.28, 134.07, 99.36, 86.73, 64.95, 56.41, 37.60, 34.78, 27.47, 22.73, 15.08, 0.07; IR (neat) ν_{max} 3436, 2956, 2930, 2857, 1615, 1453, 1248, 1145, 1095, 1031, 999, 836.



3.94

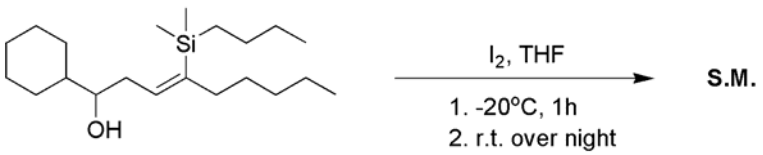
Iodonium Di-*Sym*-collidine Perchlorate (3.94) A sample of *sym*-Collidine (3.51 g, 28.95 mmol) was added with vigorous stirring to a solution of silver perchlorate (2.00g, 9.65 mmol) in 100ml of water to give a white precipitate. After washing repeatedly with water, the product was washed with ethanol and ether and finally dried under vacuum over phosphorous pentoxide. The yield was 4.12 g (95%).

A sample of powdered iodine (848 mg, 3.34 mmol) was added to a suspension of the silver di-*sym*-collidine perchlorate (1.50 g, 3.34 mmol), in about 200 ml of chloroform and 5 ml of *sym*-Collidine. After shaking for 15 min, the yellow precipitate of silver iodide was removed by filtration through a bed of Celite, and the iodonium complex crystallized directly from the filtrate on standing in the cold. The mother liquid gave further fine white crystals on the addition of ether. The combined crystals were dried under high vacuum. The yield of iodonium complex **3.94** was 1.48g (94%).



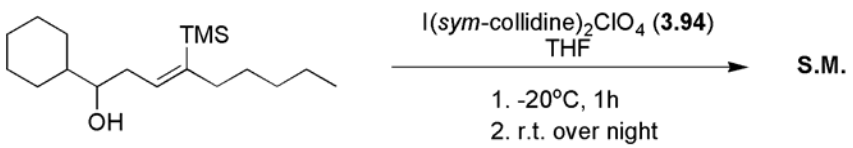
3.88

Iododesilylation Approach of 3.88 with Iodine A sample of vinyl silane **3.88** (10 mg, 0.037 mmol) was dissolved in THF (2mL) and cooled down to -20°C. Then a sample of I_2 (26 mg, 0.101 mmol) was added in one portion and the mixture was stirred in the absence of light for 1 h at -20°C. After that, the reaction mixture was warmed up to room temperature and stirred overnight in the absence of light. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^1H NMR analysis of the residue showed starting material was recovered.



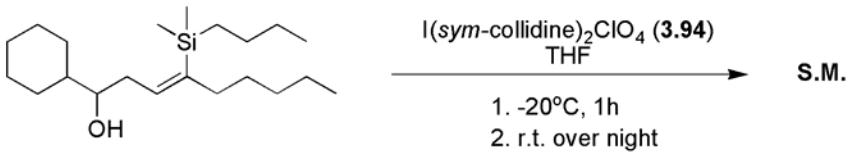
3.89

Iododesilylation Approach of 3.89 with Iodine A sample of vinyl silane **3.89** (38.0 mg, 0.112 mmol) was dissolved in THF (2mL) and cooled down to -20°C. Then a sample of I_2 (113 mg, 0.447 mmol) was added in one portion and the mixture was stirred in the absence of light for 1 h at -20°C. After that, the reaction mixture was warmed up to room temperature and stirred overnight in the absence of light. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^1H NMR analysis of the residue showed starting material was recovered.



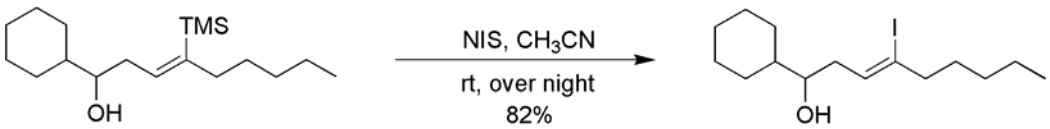
3.88

Iododesilylation Approach of 3.88 with Iodonium Complex 3.94 A sample of vinyl silane **3.88** (10 mg, 0.034 mmol) was dissolved in THF (2mL) and cooled down to -20°C. Then a sample of I(*sym*-collidine)$_2$ClO$_4$ (**3.94**, 32 mg, 0.067 mmol) was added in one portion and the mixture was stirred in the absence of light for 1 h at -20°C. After that, the reaction mixture was warmed up to room temperature and stirred overnight in the absence of light. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^{1}H NMR analysis of the residue showed starting material was recovered.



3.89

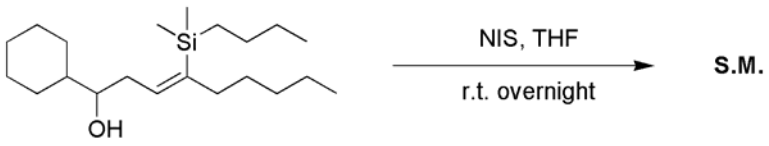
Iododesilylation Approach of 3.89 with Iodonium Complex 3.94 A sample of vinyl silane **3.89** (20 mg, 0.071 mmol) was dissolved in THF (2mL) and cooled down to -20°C. Then a sample of I(*sym*-collidine)$_2$ClO$_4$ (**3.94**, 37 mg, 0.078 mmol) was added in one portion and the mixture was stirred in the absence of light for 1 h at -20°C. After that, the reaction mixture was warmed up to room temperature and stirred overnight in the absence of light. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^{1}H NMR analysis of the residue showed starting material was recovered.



3.88 **3.95**

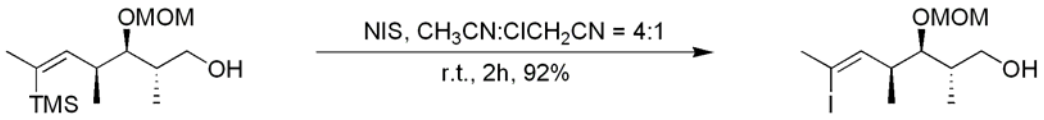
(*Z*)-1-cyclohexyl-4-iodonon-3-en-1-ol (3.95) A sample of vinyl silane **3.88** (71 mg, 0.240 mmol) was dissolved in CH_3CN (10mL). A sample of *N*-Iodosuccinimide (216 mg, 0.959 mmol) was added in one portion and the mixture was stirred in the absence of light for overnight. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

resulting residue was subjected to preparative TLC plate to yield vinyl iodide **3.95** (69 mg, 82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64-5.61 (t, *J*= 6.4 Hz, 1H), 3.51-3.45 (m, 1H), 2.51-2.47 (t, *J*= 7.2 Hz, 2H), 2.40-2.20 (m, 2H), 1.88-0.97 (m, 18H), 0.91-0.88 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.29, 112.08, 75.37, 45.37, 43.41, 41.41, 30.45, 29.22, 29.09, 28.05, 26.54, 26.32, 26.16, 22.48, 14.11; IR (neat) ν_{max} 3394, 2926, 2853, 1640, 1449, 1085, 1059, 1034, 985.



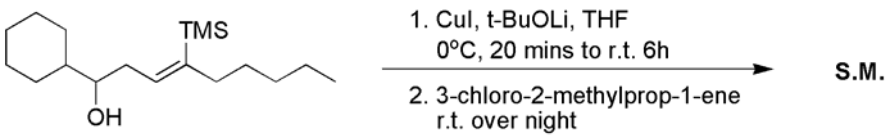
3.89

Iododesilylation Approach of 3.89 with NIS A sample of vinyl silane **3.89** (20.0 mg, 0.0588 mmol) was dissolved in THF (2mL). A sample of *N*-Iodosuccinimide (26.5 mg, 0.118 mmol) was added in one portion and the mixture was stirred in the absence of light for overnight. The reaction mixture was diluted with 50% aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. TLC and ^{1}H NMR analysis of the crude showed starting material was recovered.



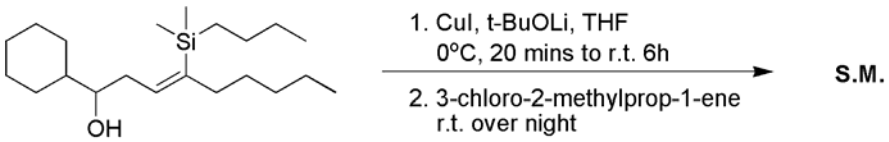
3.91 **3.10**

(2*S*,3*R*,4*S*,*Z*)-6-Iodo-3-(methoxymethoxy)-2,4-dimethylhept-5-en-1-ol (3.10) A sample of vinyl silane **3.91** (8.1 mg, 0.027 mmol) was dissolved in CH_3CN (1mL). A sample of *N*-Iodosuccinimide (12.3 mg, 0.055 mmol) was added in one portion and the mixture was stirred in the absence of light for 2 h. The reaction mixture was diluted with saturated aqueous $Na_2S_2O_3$ (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was subjected to preparative TLC plate (HE:EA= 20:1) to yield vinyl iodide **3.10** (8.3 mg, 92%, *Z*:*E*= 5.5:1) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35-5.32 (dd, *J*= 8.8, 1.6 Hz, 1H), 4.64 (s, 2H), 3.86-3.81 (ddd, *J*= 11.2, 5.6, 3.6 Hz, 1H), 3.57-3.44 (m, 2H), 3.43 (s, 3H), 2.69-2.66 (dd, *J*= 7.6, 2.0 Hz, 1H), 2.66-2.61 (m, 1H), 2.48 (d, *J*= 1.2 Hz, 3H), 1.82-1.79 (m, 1H), 1.07-1.05 (d, *J*= 6.8 Hz, 3H), 1.02-1.00 (d, *J*= 6.8 Hz, 3H).



3.88

Cross-Coupling Approach of Alcohol 3.88 A sample of CuI (12 mg, 0.065 mmol) and DMF (1 mL) were placed in a flask and cooled to 0 °C. Then, a sample of lithium *tert*-butoxide (1 M in THF, 0.071 mL, 0.071 mmol) was added under argon and the mixture was stirred for 20 min at room temperature. After that, a DMF (1 mL) solution of alcohol **3.88** (20 mg, 0.059 mmol) and a DMF (1 mL) solution of 3-chloro-2-methylprop-1-ene (6.4 mg, 0.071 mmol) were successively added to the mixture. After stirring for 2 h at room temperature, the reaction was quenched by addition of 3.5% NH_3 aqueous solution. The organic materials were extracted with ether, dried over Na_2SO_4, and concentrated. TLC and ^1H NMR analysis showed that starting material was recovered.



3.89

Cross-Coupling Approach of Alcohol 3.89 A sample of CuI (12 mg, 0.065 mmol) and DMF (1 mL) were placed in a flask and cooled to 0 °C. Then, a sample of lithium *tert*-butoxide (1 M in THF, 0.071 mL, 0.071 mmol) was added under argon and the mixture was stirred for 20 min at room temperature. After that, a DMF (1 mL) solution of alcohol **3.89** (20 mg, 0.059 mmol) and a DMF (1 mL) solution of 3-chloro-2-methylprop-1-ene (6.4 mg, 0.071 mmol) were successively added to the mixture. After stirring for 2 h at room temperature, the reaction was quenched by addition of 3.5% NH_3 aqueous solution. The organic materials were extracted with ether, dried over Na_2SO_4, and concentrated. TLC and ^1H NMR analysis showed that starting material was recovered.

PART FOUR

ASYMMETRIC SYNTHESIS OF *ANTI*, *ANTI*-STEREOTRIAD BUILDING BLOCKS FOR POLYPROPIONATE NATURAL PRODUCTS

4.1 INTRODUCTION

4.1.1 Polypropionate Natural Products

4.1.2 Anti, Anti Stereotriad Building Blocks for Polypropionate Natural Products

4.1.3 Polypropionate Natural Products Bearing *Anti*, *Anti*-Stereotriad

4.1.4 Miyashita's Total Synthesis of Scytophycin C (4.4)

4.1.4.1 Miyashita's Synthesis of Segment B2 (4.14)

4.1.5 TMHEA (4.5)

4.1.5.1 Lipton Synthesis of TMHEA (4.5)

4.1.5.2 D'Auria Synthesis of TMHEA (4.5)

4.1.6 Paterson's Synthesis Approach of Aplyronies (4.1)

4.1.6.1 Paterson's Synthesis of TES-PMB Piece (4.36)

4.1.7 Previous Protocols for Construction of *Anti*, *Anti*-Stereotriad

4.1.7.1 Enantioselective Crotylboration/Hydroboration

4.1.7.2 Chemoenzymatic Enantioselective Synthesis

4.1.7.3 Diastereoselective Palladium-Catalyzed Formate Reduction of Allylic Carbonates

4.1.7.4 Crotylation with Crotyltrifluorosilanes

4.2 RESULTS AND DISCUSSION

4.2.1 Synthesis of *Anti*, *Anti*-Stereotriads

4.2.1.1 Retrosynthetic Plan for *Anti*, *Anti*-Stereotriads

4.2.1.2 Catalytic Asymmetric Synthesis of (*S*,*E*)-Allylic Alcohol 4.48

4.2.1.3 [2,3]-Wittig Rearrangement

4.2.1.4 Regioselective Carbocupration and Protection

4.2.1.5 Stereoselective Hydroboration and Oxidation

4.2.1.6 Completion of the Synthesis of *Anti*, *Anti*-Stereotriads (4.52, 4.57)

4.2.2 Synthesis of Segment B2 (4.14)

4.2.2.1 Retrosynthetic Plan for Segment B2 (4.14)

4.2.2.2 Completion of the Synthesis of Segment B2 (4.14)

4.2.3 Synthesis of TBS-TMHEA (4.23)

4.2.3.1 Retrosynthetic Plan for TBS-TMHEA (4.23)

4.2.3.2 Benzyl Protection of the Primary Hydroxyl Group
4.2.3.2.1 TBS Migration under Basic Condition
4.2.3.2.2 Previous Reported TBS Migration with Similar Substrate
4.2.3.2.3 Benzyl Protection under Acidic Condition
4.2.3.3 Ozonolysis and Wittig Reaction
4.2.3.4 Hydrogenation, Hydrogenolysis and Oxidation
4.2.3.5 Completion of the Synthesis of TBS-TMHEA (4.23)
4.2.4 Synthesis of TES-PMB piece 4.36
4.2.4.1 Retrosynthetic Plan for TES-PMB piece 4.36
4.2.4.2 Synthetic Approach towards TES-PMB piece
4.2.4.2.1 PMB protection
4.2.4.2.2 Oxidative-Cleavage Approach towards TBS-PMB piece 4.36

4.3 CONCLUSION

4.4 EXPERIMENTAL SECTION

4.1 INTRODUCTION

Polypropionate subunits are present in a great number of biologically active natural products having antibacterial, antitumor, antifungal, antiparasitic, or immunomodulator activity.[62] A widespread retrosynthetic strategy for preparing these structures involves the disconnection of polypropionate chains into shorter subunits, such as stereotriad building blocks bearing alternate methyl and hydroxyl groups. Efficient syntheses of appropriately protected and functionalized stereotriads from inexpensive materials are needed.

4.1.1 Polypropionate Natural Products

Polyketides are perhaps the most attractive subgroup of natural products for synthetic organic chemists, since they exhibit the largest diversity in structural complexity and biological activities. Polyketides biosynthesized from propionate precursors belong to an important subclass called polypropionates. Most of these natural products are available in only minute quantities from their biological source: for example, aplyronine A[63] (**4.1**) is isolated in only 2.5 $\times 10^{-5}$% yield based on wet weight from marine sponge *Aplysia kurodai*. Isolation from biological sources, such as sponges, faces not only practical difficulties but also ecological difficulties. Therefore, the supply problem for biological and pharmaceutical testing can only be solved by obtaining sufficient quantities of these natural products from total synthesis.

4.1.2 *Anti*, *Anti*-Stereotriad Building Blocks for Polypropionate Natural Products

Stereotriads bearing alternate methyl and hydroxyl groups are important building blocks to construct polypropionate chains. In Hoffman's feature article,[64] the researchers pointed out that among the four individual stereochemical triads A-D (Figure **4-1**), stereotriad D is the only one that is not easily obtained. Yet many of polypropionate nature products of synthetic interest contain this stereotriad, such as aplyronine (**4.1**), triandamycin[65], rifamycin[66], ionomycin[67], denticulatin[68], siphonarin[69], zincophorin[70],

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muamvatin[71], calyculin[72], baconipyrone[73], swinholide (**4.2**)[74], crocacin[75], dolabriferol[76], baconipyrone[77], siserrone[13,78], sanglifehrin[79], mycalolide (**4.3**)[80], scytophycin (**4.4**)[81], callipeltin (**4.5**)[82], and neamphamide (**4.6**) [83]. Several high potential polypropionate subunit containing natural products are introduced in the following part. The *anti*, *anti*-stereotriad fragments in aplyronine A (**4.1**), swinholide A (**4.2**), mycalolide B (**4.3**), scytophycin (**4.4**), callipeltin A (**4.5**), callipeltin D (**4.7**), and neamphamide (**4.6**) are enclosed within a red box.

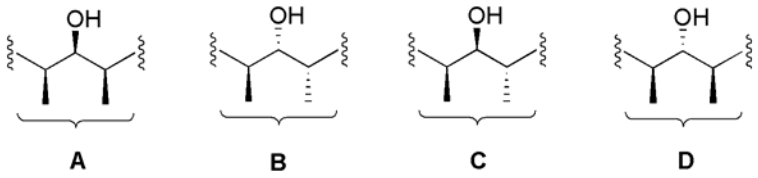

Figure 4-1 Four individual sterochemical triads A-D

4.1.3 Polypropionate Natural Products Bearing *Anti*, *Anti*-Stereotriad

Aplyronine A (**4.1**, Figure **4-2**), an antitumor macrolide isolated from *Aplysia kurodai*, interacts with actin, one of the two major components (the other is tubulin.) of

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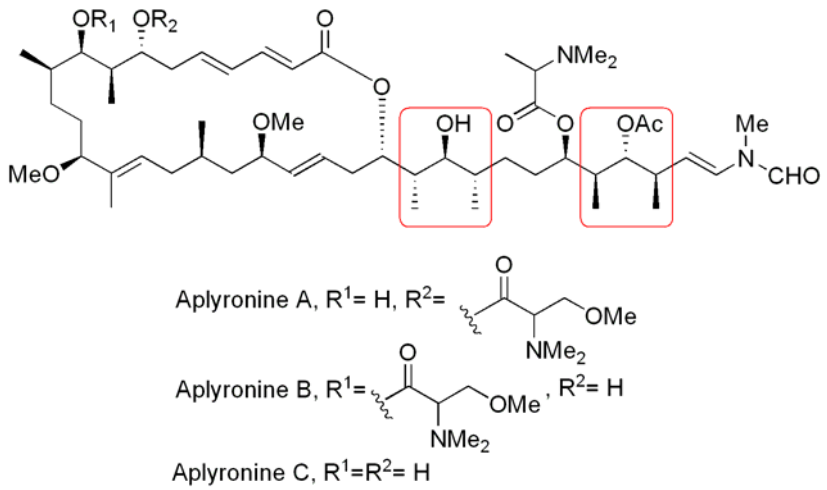
the cytoskeleton in eukaryotic cells. Actin controls and standardizes various cell functions such as muscle contraction, cell motility, cell division, cell adhesion and intracellular transportation.[84] Actin exists as a dynamic equilibrium mixture of two forms; monomeric soluble global actin (G-actin; about 43 kDa) and helical filamentous actin (F-actin).[85] Aplyronine A (**4.1**) sequesters G-actin by forming a 1:1 complex. Aplyronine A (**4.1**) not only inhibits polymerization of G-actin but also severs polymerized F-actin to G-actin.[86] The total synthesis of aplyronine A (**4.1**) was achieved by Yamada's group in 1994[87] and Paterson's group at 2002[88].



4.1 Aplyronines

Figure 4-2 Structure of aplyronines (**4.1**)

Swinholide A (**4.2**, Figure **4-3**), a cytotoxic macrolide, was first reported by Carmely and Kashman in 1985 from Okinawan marine sponge *Theonella swinhoei*. Further structure related studies have shown that swinholide A (**4.2**) is a dimer containing a twisted saddle shaped 44-membered dilactone ring in the solid phase.[89,90] Swinholide A (**4.2**) is a potent cancer cell growth inhibitor with IC_{50} values ranging from 0.37 nM to 1.0 μM against several cancer cell lines such as L1210 and KB[91]. The cytotoxic role of

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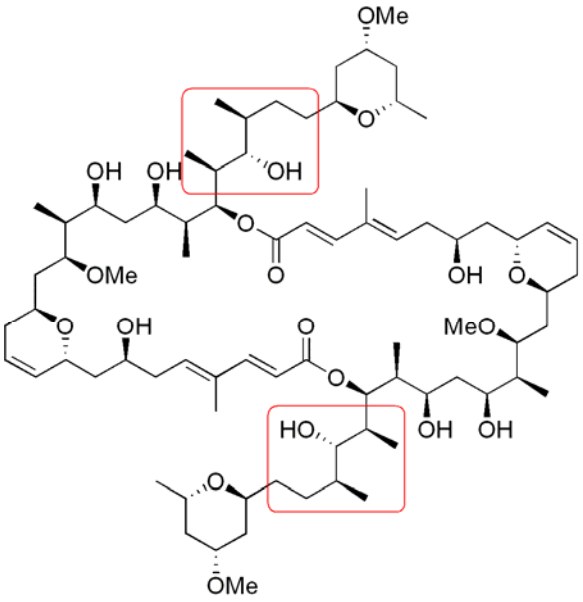
swinholide A (**4.2**) is to disrupt the actin cytoskeleton. Swinholide A (**4.2**) inhibits polymerization of G-actin by sequestrating G-actin: one molecule of dimeric swinholide A (**4.2**) binds simultaneously to two molecules of G-actin and forms a tertiary complex with the two side chains of the macrolide (C-21/C-21' to C-27/C-27').[92] In contrast to the other bistheonellides, Swinholide A (**4.2**) also causes breakage of F-actin strands[93]. Two groups have accomplished total syntheses of swinholide A (**4.2**): Paterson's group in 1994[94] and Nicolaou's group in 1996[95].



4.2 Swinholide A

Figure 4-3 Structure of swinholide A (**4.2**)

Mycalolide B (**4.3**, Figure **4-4**) is a cytotoxic and antifungal macrolide isolated from a sponge of the genus *Mycale* sp. Mycalolide B (**4.3**) has effects on actin that are similar to those of aplyronine A (**4.1**)[96] and also inhibits actomyosin Mg^{2+}-ATPase[97]. The total

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Munro, M. H. G.; Pannell, L. K. *J. Org. Chem.* **1997**, *62*, 2635-2639. (d) Sakai, R.; Higa, T.; Kashman, Y. *Chem. Lett.* **1986**, 1499-1502. (e) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Sakai, R.; Higa, T.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 6225-6228. (f) Tanaka, J.; Higa, T.; Motomasa, K.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2967-2970. (g) Todd, J. S.; Alvi, K. A.; Crews, P. *Tetrahedron Lett.* **1992**, *33*, 441-442.

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synthesis of (-)-mycalolide A (**4.8**), which is short of the 2,3-di-*O*-methyl-$_D$-glyceroyl group at C30, has been achieved by Panek's group in 2000[98].

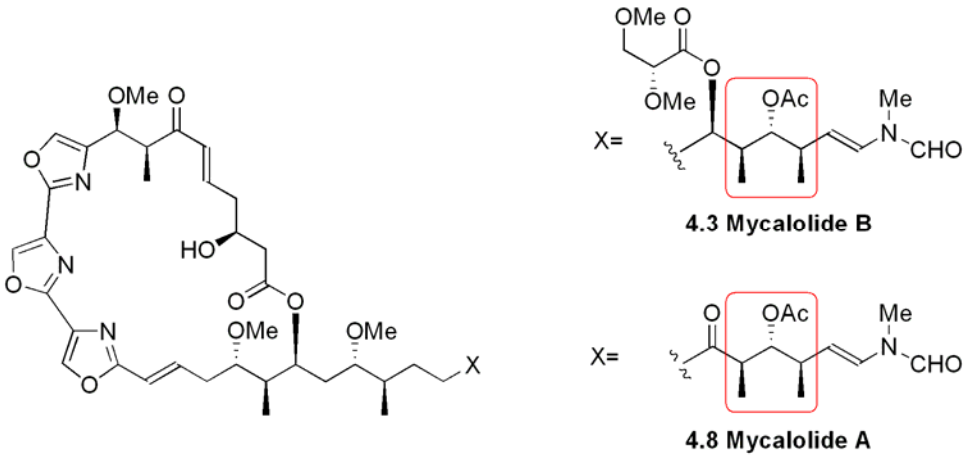

Figure 4-4 Structure of mycalolide B (**4.3**) and mycalolide A (**4.8**)

Scytophycin C (**4.4**, Figure **4-5**), a polyoxygenated 22-membered macrolide first isolated by Moore et al. in 1986 from the cultured terrestrial blue-green alga *Scytonema pseudohofmanni*, has exhibited potent cytotoxicity against a variety of human carcinoma cell lines as well as broad-spectrum antifungal activity[81b,c,99]. It has also been found that the scytophycins inhibit actin polymerization and induce the depolimerization of F-actin *in vitro*. Thus, this class of macrolides has potential therapeutic value for the treatment of drug-resistant cancers[100]. The total synthesis of scytophycin C (**4.4**) was achieved by Paterson's group in 1997[101] and Miyashita's group in 2003.

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[97] Hori, M.; Saito, S.; Shin, Y.; Ozaki, H.; Fusetani, N.; Karaki, H. *FEBS Lett.* **1993**, *322*, 151–154.

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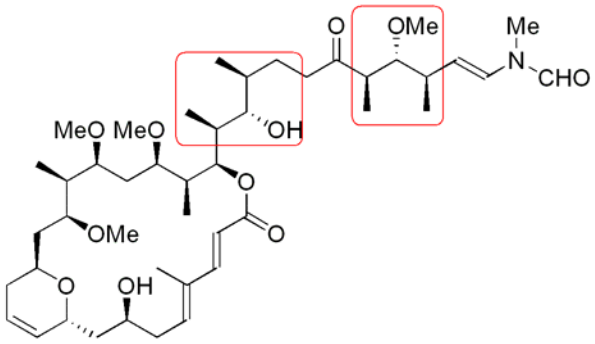
[101] Paterson, I.; Watson, C.; Yeung, K.-S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*(3), 452-453.



4.4 Scytophycin C

Figure 4-5 Structure of scytophycin C (**4.4**)

The callipeltins (callipeltin A **4.5**, callipeltin D **4.7**, Figure **4-6**) from *Callipelta sp.* and *Latrunculia sp.*, neamphamide A (**4.6**, Figure **4-7**) from *Neamphius huxleyi*, and the papuamides from *Theonella sponges*[102] are a series of cyclic depsipeptides that have recently been described from a number of marine sponges. These compounds have been reported to exhibit potent antiviral, antifungal, cytotoxic, anti-HIV, and sodium inophore properties.[103] This group of peptides contains some unique structural subunits, such as unusual amino acid residues and N-terminal polyketide derived moieties. These peptidic metabolites have attracted significant interest among synthetic chemists because of their distinctive structural features and remarkable biological effects. However, synthesis of the intact natural products has not been achieved yet.

[102] Ford, P. W.; Gustafson, K. R.; McKee, T. C.; Shigematsu, N.; Maurizi, L. K.; Pannell, L. K.; Williams, D. E.; de Silva, E. D.; Lassota, P.; Allen, T. M.; Van Soest, R.; Andersen, R. J.; Boyd, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 5899-5909.

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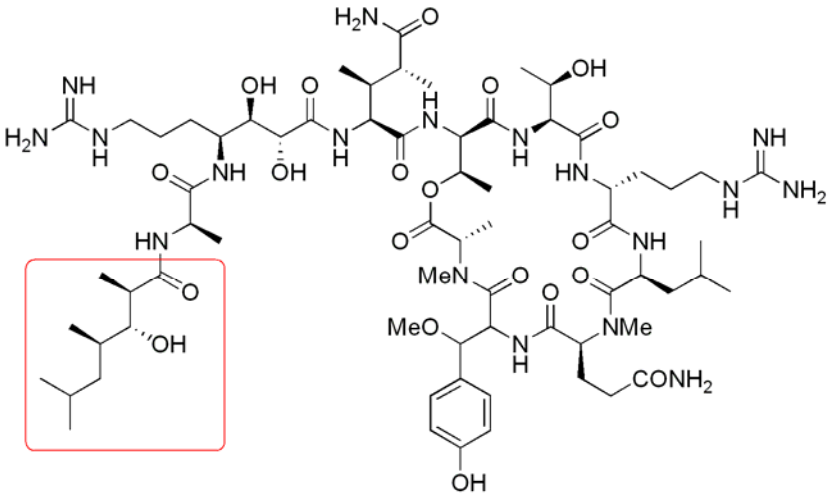
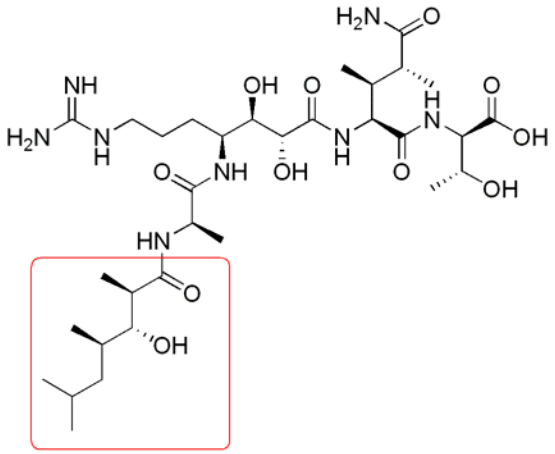


4.5 Callipeltin A



4.7 Callipeltin D

Figure 4-6 Structure of callipeltin A (**4.5**) and callipeltin D (**4.7**)

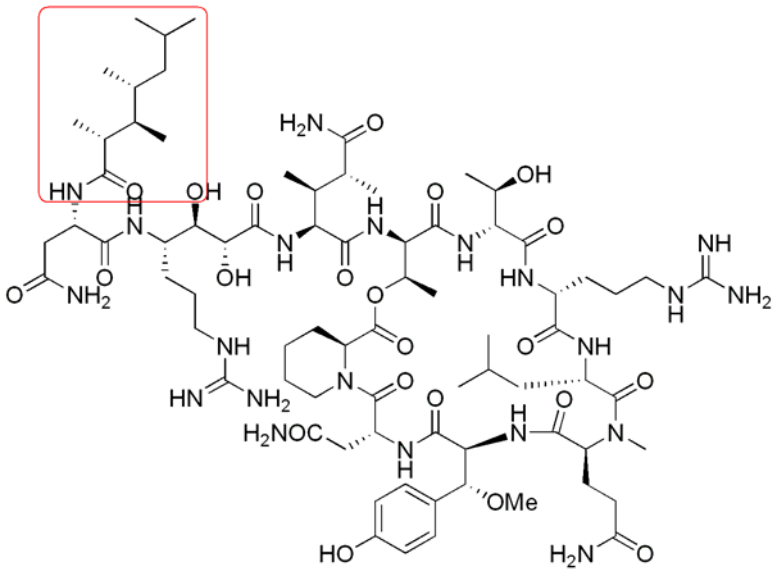
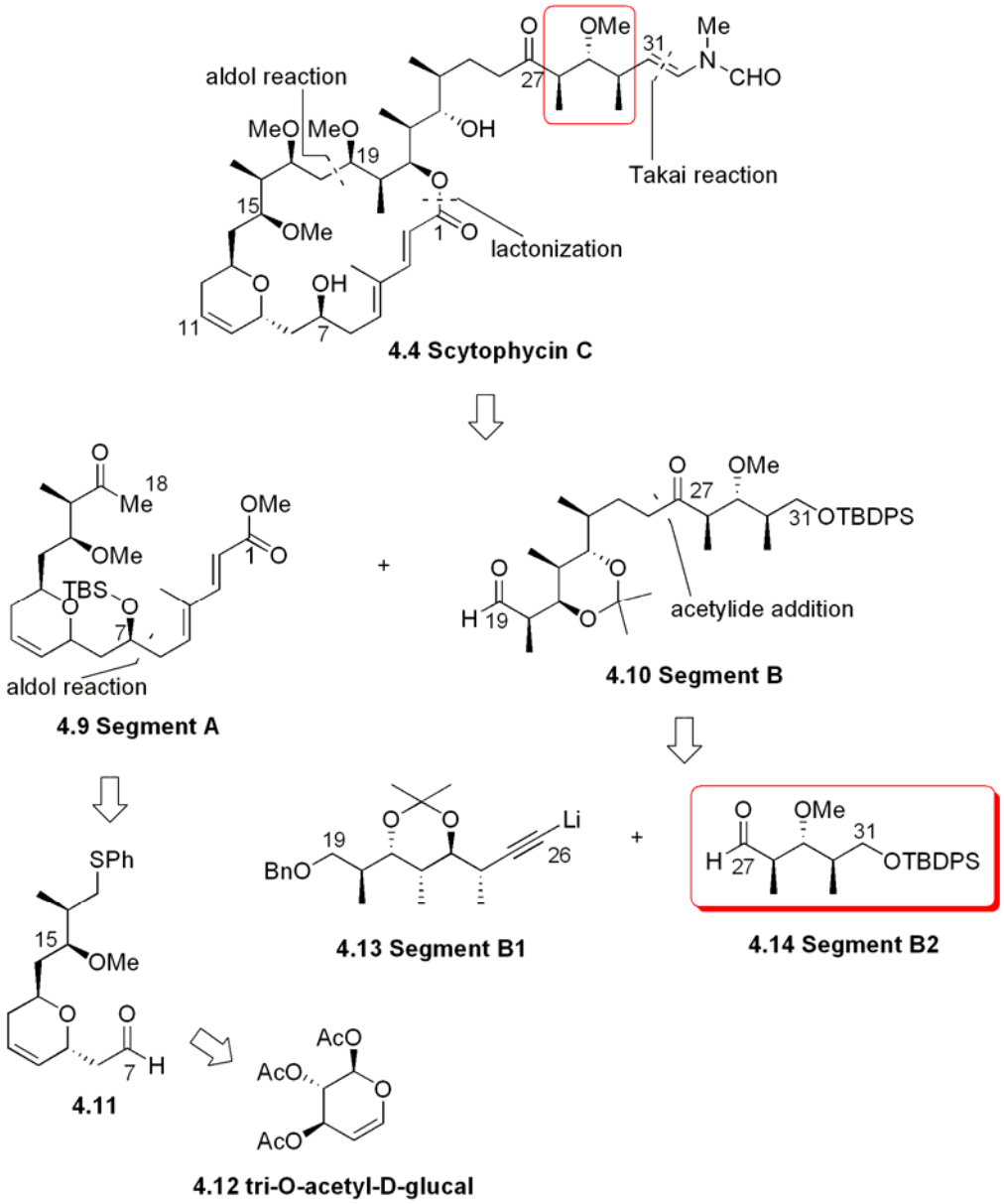


Figure 4-7 Structure of neamphamide A (**4.6**)

4.1.4 Miyashita's Total Synthesis of Scytophycin C (4.4)

In a retrosynthetic dissection of scytophycin C (**4.4** Scheme **4-1**),[104] the backbone of scytophycin C (**4.4**) was divided into the C(1)-C(18) segment (Segment **A**, **4.9**) and the C(19)-C(31) segment (Segemnt **B**, **4.10**). A designed aldol reaction could form the C18-C19 bond under Felkin-Anh control similarly to the Paterson's synthesis.[101] A Mukaiyama aldol reaction of aldehyde **4.11** with 2-methyl-1-trimethylsilyloxy-1,3-butadiene provided a 7:2 mixture of epimeric alcohols, the major component of which was further modified to segment **A** (**4.9**) in two steps. The dihydropyran ring bearing aldehyde **4.11** could be assembled from commercially available tri-*O*-acetyl-D-glucal **4.12**. On the other hand, an acetylide addition of the C(19)-C(26) acetylenic segment (Segment **B1**, **4.13**) and the C(27)-C(31) aldehyde segment (Segment **B2**, **4.14**) connected the C(26)-C(27) bond of segment **B** (**4.10**) containing eight asymmetric centers. A Takai reaction followed by a Buchwald amidation reaction introduced the acid-labile *N*-methyl-*N*-vinyl formamide moiety at the terminus. This introduction was designed to occur at the final stage of the synthesis due to the acid instability of scytophycin C (**4.4**). This total synthesis approach afforded scytophycin C (**4.4**) in 1.1% overall yield and with a longest linear sequence of 36 steps.

[104] (a) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*(20), 3579-3582. (b) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*(20), 3583-3586.

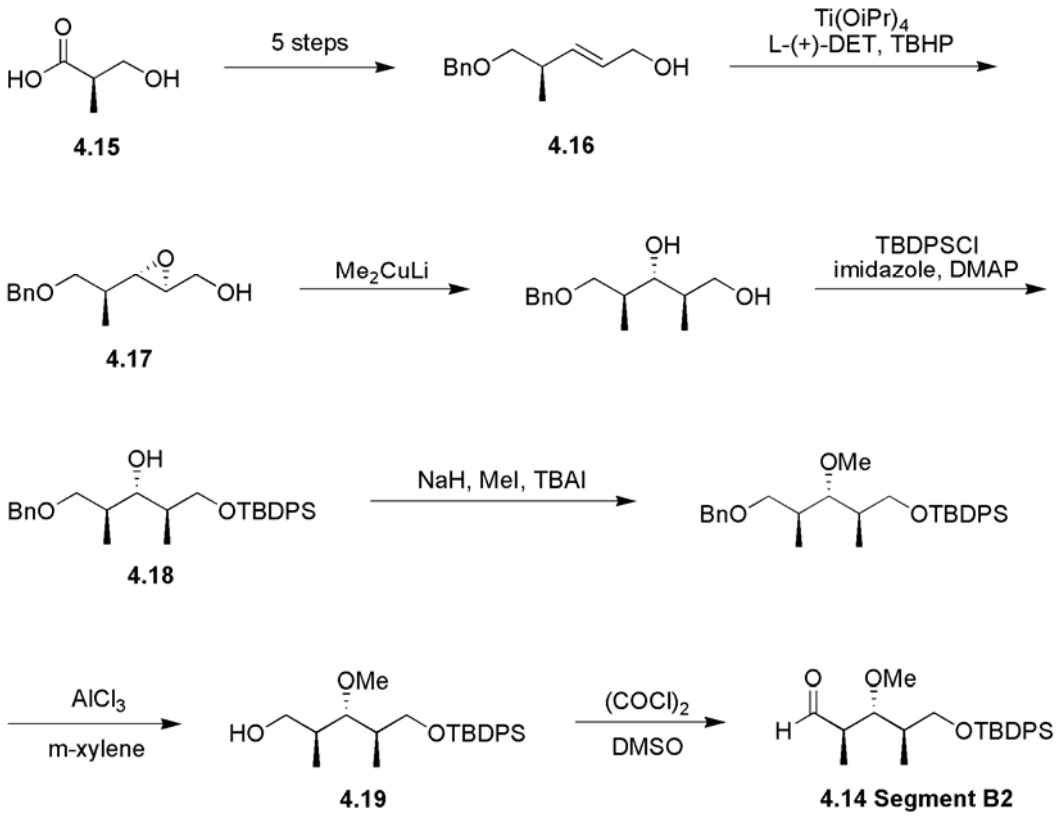


Scheme 4-1 Miyashita's total synthesis of scytophycin C (**4.4**)

4.1.4.1 Miyashita's Synthesis of Segment B2 (4.14)

The chiral allylic alcohol **4.15** was obtained from (*S*)-3-hydroxy-2- methylpropanoic acid **4.16** in 5 steps[105]. Then, it was subjected to the Katsuki–Sharpless asymmetric epoxidation with D-(-)-ethyl tartrate to give the β-epoxy alcohol **4.17**. After methyl cupration and protection, the β-epoxy alcohol **4.17** was converted to doubly protected triol **4.18**. A methylation followed by removal of the benzyl group provided terminal alcohol **4.19**. Finally, after Swern oxidation, the *anti*, *anti*-stereotriad segment B2 **4.14** was constructed in 32% yield for the 12 steps (Scheme **4-2**).

[105] Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873–3888.



Scheme 4-2 Miyashita's synthesis of segment B2 (**4.14**)

4.1.5 TMHEA (4.20)

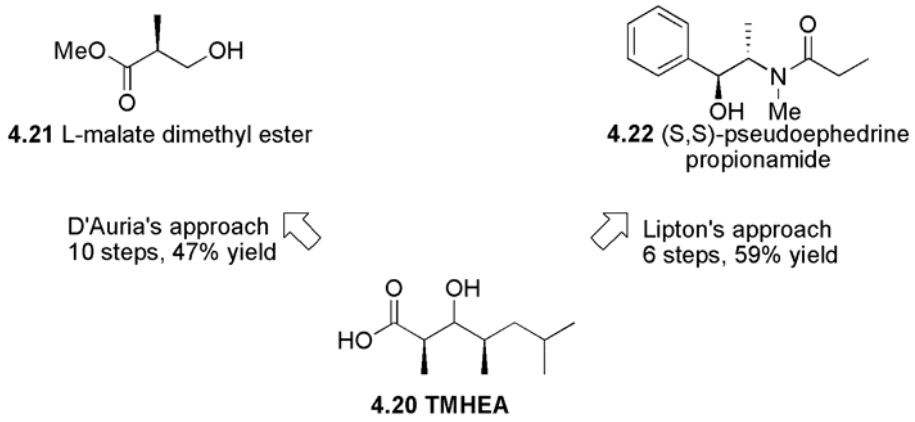
In the last decade, callipeltins have attracted significant interest among synthetic chemists due to their distinctive structural features and remarkable biological effects. However, synthetic efforts to prepare the intact natural products have not been achieved. Syntheses of structural subunits such as β-methoxytyrosine (βOMeTyr), (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxy-heptanoic acid (AGDHE), (3*S*,4*R*)-3,4-dimethyl-L-glutamine (diMeGln), and (2*R*,3*R*,4*R*)-3-hydroxy-2,4,6-trimethyl-heptanoic acid (TMHEA, **4.20**) have been described. These efforts provided essential building blocks for use in total synthesis of the parent peptide, and they also helped to unambiguously define the absolute stereochemistry of several key stereogenic centers.

The *anti*, *anti*-stereotriad containing subunit 3-hydroxy-2,4,6-trimethylheptanoic acid (TMHEA, **4.20**) has been synthesized by two groups: D'Auria's group and Lipton's group. In 2002, D'Auria's group synthesized TMHEA (**4.20**) from L-malate dimethyl ester (**4.21**) in 10 steps with 47 % yield[106]; in 2003 Lipton's group synthesized TMHEA (**4.20**) from (S,S)-pseudoephedrine propionamide (**4.22**) in 6 steps with 59% yield

[106] Zampella, A.; D'Auria, M. V. *Tetrahedron: Asym.* **2002**, *12*, 1237-1239.

(Scheme **4-3**).[107]

Each of these two syntheses of TMHEA (**4.20**) relied on an expensive chiral material as the source of chirality for construction of the building blocks. The high cost of starting material will hinder the application of these two synthetic strategies in large scale synthesis of callipeltins as drug candidates in the future. Efficient syntheses of appropriately protected TMHEA (use in total synthesis) in inexpensive materials are needed. The detailed synthesis strategies of TBS protected TMHEA (TBS-TMHEA, **4.23**) demonstrated by the Lipton group and the D'Auria group will be discussed in the following sections.



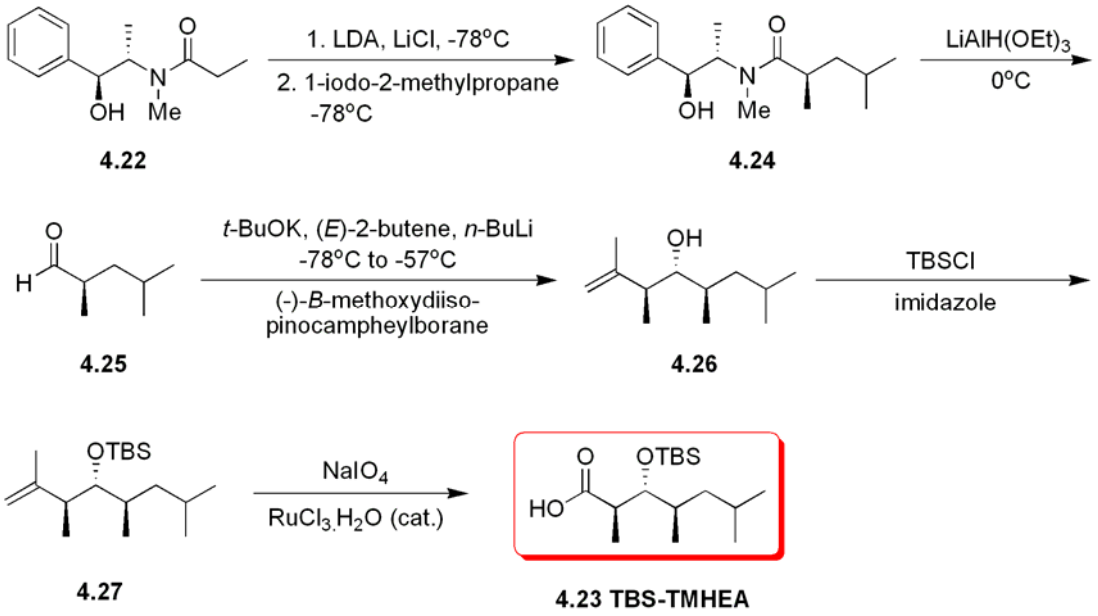
Scheme 4-3 Chirality source of previous syntheses of TMHEA (**4.20**)

4.1.5.1 Lipton Synthesis of TBS-TMHEA (4.23)

The Lipton group's synthesis of TBS-TMHEA (**4.23**) started with alkylation of (*S*,*S*)-pseudoephedrine propionamide (**4.22**) with 1-iodo-2 methylpropane using Myers conditions.[108] The resulting tertiary amide **4.24** was reduced to the aldehyde **4.25** with lithium triethoxyaluminium hydride. Then, treatment of the aldehyde **4.25** with the crotylborane derived from (-)-*B*-methoxydiisopinocampheylborane and *trans*-2-butene afforded alcohol **4.26**. Next, protection of alcohol **4.26** with benzyl-2,2,2-trichloroacetimidate (BTCA) and catalytic triflic acid provided benzyl ether **4.27**. Then, benzyl ether **4.27** was oxidized to TBS_TMHEA **4.23** by ruthenium chloride and sodium periodate. This synthetic approach afforded TBS-TMHEA (**4.23**) in 59% overall yield in 5 steps (Scheme **4-4**).

[107] Turk, J. A.; Visbal, G. S.; Lipton, M. A. *J. Org. Chem.* **2003**, *20*, 7841-7844.

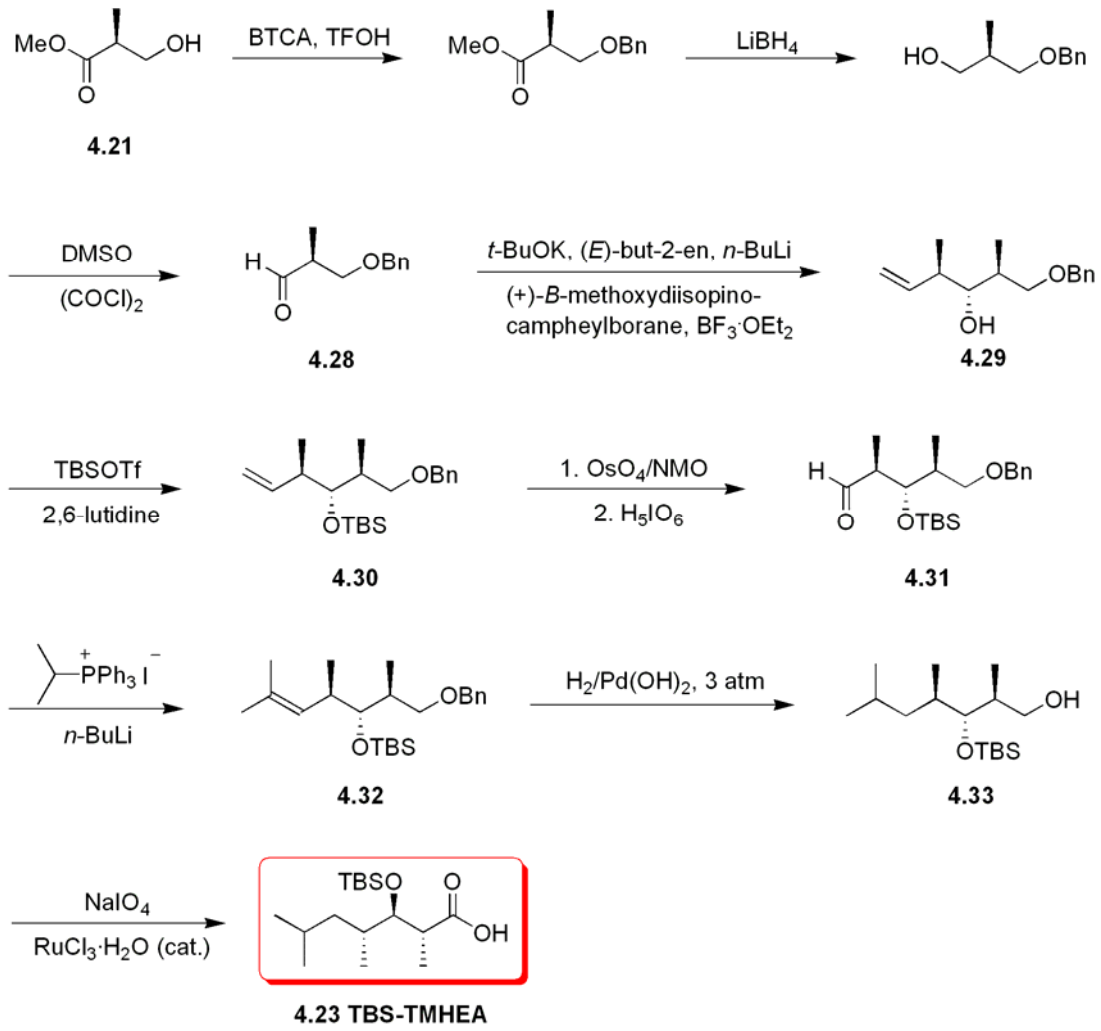
[108] Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* 1997, *119*, 6496-6511.



Scheme 4-4 Lipton synthesis of TBS-TMHEA (**4.23**)

4.1.5.2 D'Auria Synthesis of TBS-TMHEA (4.23)

In the D'Auria group's synthesis of TBS-TMHEA (**4.23**), aldehyde **4.28** was obtained from methyl (2*S*)-2-methyl-3-hydroxy propionate **4.21** by benzyl protection, lithium borohydride reduction and Swern oxidation sequentially. Then, aldehyde **4.28** reacted with the allylic borane derived from (-)-*B*-methoxydiisopinocampheylborane and (*E*)-2-butene to give alcohol **4.29** which was then converted into the TBS ether **4.30**. Next, the terminal double bond in TBS ether **4.30** was oxidatively cleaved by OsO_4, NMO, acetone-water and H_5IO_6 to yield aldehyde **4.31**. The Wittig olefination of the resulting aldehyde provided olefin **4.32**. Then, hydrogenation of **4.32** in the presence of Pearlman's catalyst resulted in alcohol **4.33**, which was oxidized to TBS-TMHEA (**4.23**) using $RuCl_3$-$NaIO_4$. Over all, TBS-TMHEA was synthesized in 10 steps with 46% yield (Scheme **4-5**).

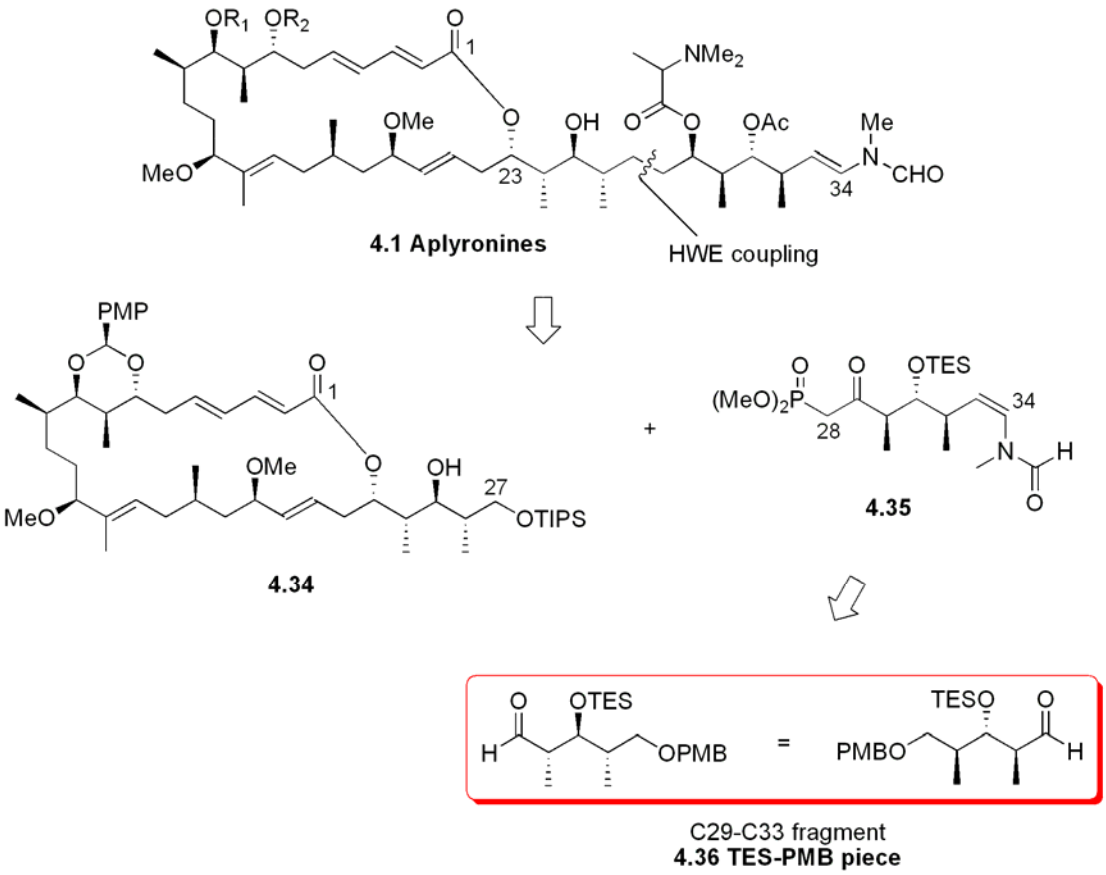


Scheme 4-5 D'Auria synthesis of TBS-TMHEA (**4.23**)

4.1.6 Paterson's Synthesis Approach of Aplyronines (4.1)[109]

In 2002, Paterson's group reported stereocontrolled synthesis of a C21–C34 subunit of the aplyronines, a study towards the total synthesis of aplyronines. The retrosynthetic strategy is shown in Scheme **4-6**. This synthesis approach relies upon a key Horner–Wadsworth–Emmons (HWE) coupling of a suitable C27 aldehyde, derived from the previously described macrolide **4.34** with the *β*-ketophosphonate **4.35** for elaboration of the side chain. The C28–C34 terminal *N*-methyl-*N*-vinyl formamide containing phosphonate subunit **4.35** was synthesized from TES and PMB protected intermediate **4.36** (TES-PMB piece), an *anti*, *anti*-stereotriad containing C29-C33 fragment.

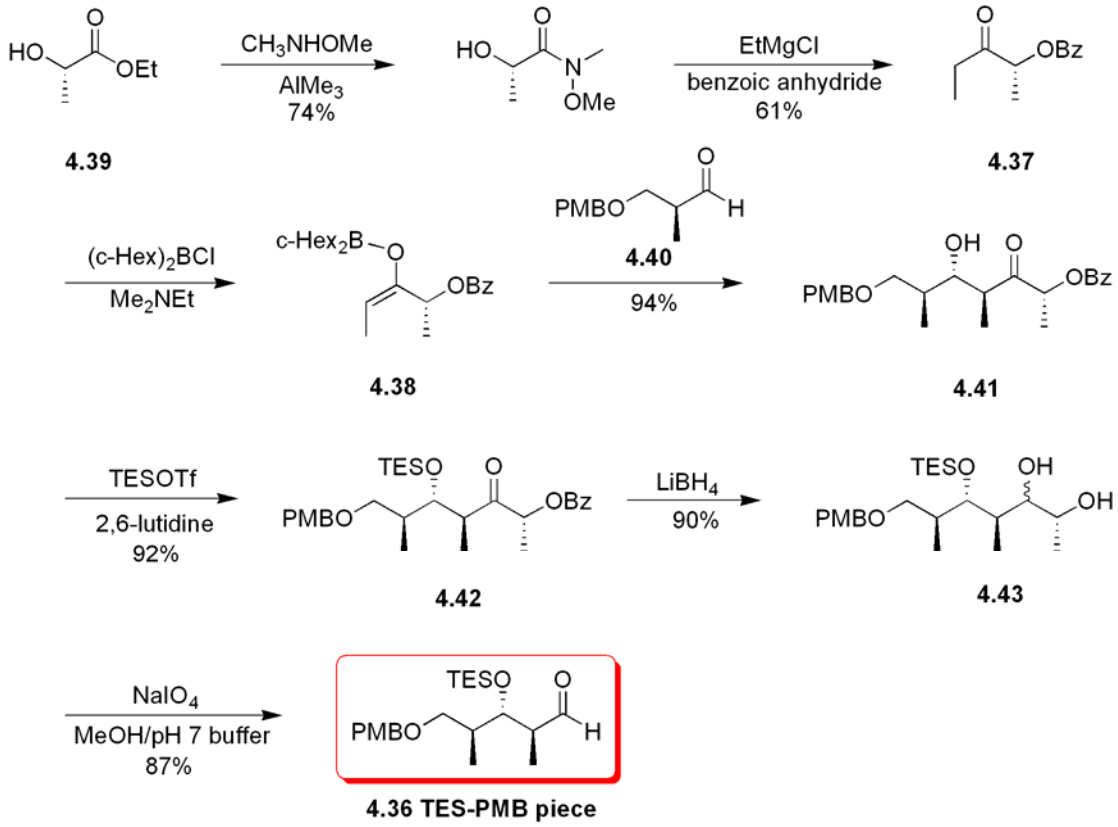
[109] Paterson, I; Blakey S.B.; Cowden, C. J.; *Tetrahedron Lett*. **2002**, *43*, 6005–6008



Scheme 4-6 Paterson's synthesis approach of aplyronies (4.1)

4.1.6.1 Paterson's Synthesis of TES-PMB Piece (4.36)

The Paterson group's synthesis started with enolisation of ketone **4.37** using $(c\text{-Hex})_2BCl/Me_2NEt$ to produce (*E*)-boron enolate **4.38**. The ketone **4.37** was constructed from ethyl lactate **4.39** in 2 steps with 45% yield. Reaction of freshly prepared aldehyde **4.40** with (*E*)-boron enolate **4.38** with an oxidative workup provided *anti*-aldol adduct **4.41** in 94% yield with >95% diastereoselectivity. TES protection using TESOTf and 2,6-lutidine gave TES ether **4.42** in 92% yield, which was then reduced to 1,2-diol **4.43** by $LiBH_4$. The resulting diol **4.43** was oxidatively cleaved with NaIO4 to give TES-PMB piece **4.36** with 87% yield. Overall, starting from ethyl lactate the TES-PMB piece **4.36** was synthesized in 7 steps with 31% yield (Scheme **4-7**).



Scheme 4-7 Paterson's synthesis of TES-PMB piece (4.36)

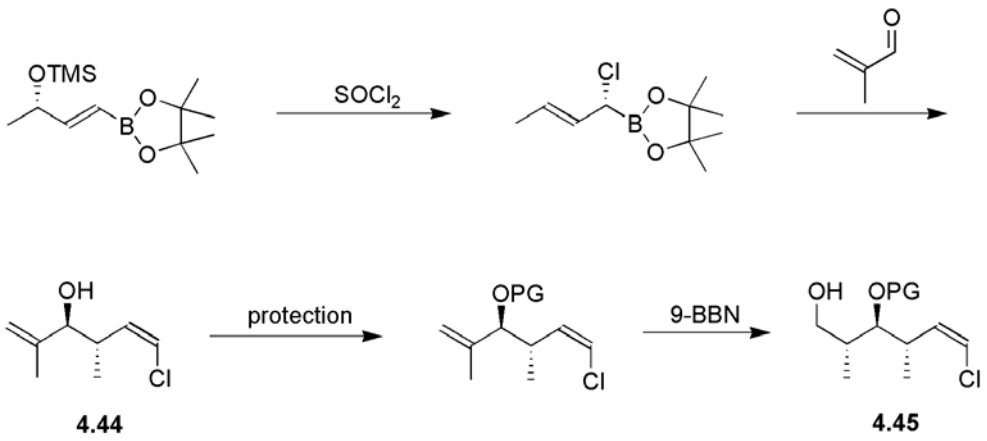
4.1.7 Previous Protocols for Construction of *Anti*, *Anti*-Stereotriads

The anti, anti-stereotriad has been the most challenging stereotriad in the course of polypropionate natural product synthesis. Many synthetic endeavors have contributed original approaches to this structural unit. However, most of these approaches depend critically on the level of asymmetric induction originating from the stating material. A successful protocol that starts from inexpensive, commercially available materials will be in high demand. Four typical routes are described in the following part.

4.1.7.1 Enantioselective Crotylboration/Hydroboration

Hoffman and coworkers [110] started with an enantioselective allyboration of methacrolein to give *anti*-allylic alcohol (**4.44**, diastereoselectivity = 90%) followed by protection and hydroboration of the 1,1-disubstituted double bond to provide building blocks (**4.45**) containing the *anti*, *anti*-stereotriad. Further oxidation of the "left end" will set the building block ready for immediate chain extension (Scheme **4-8**).

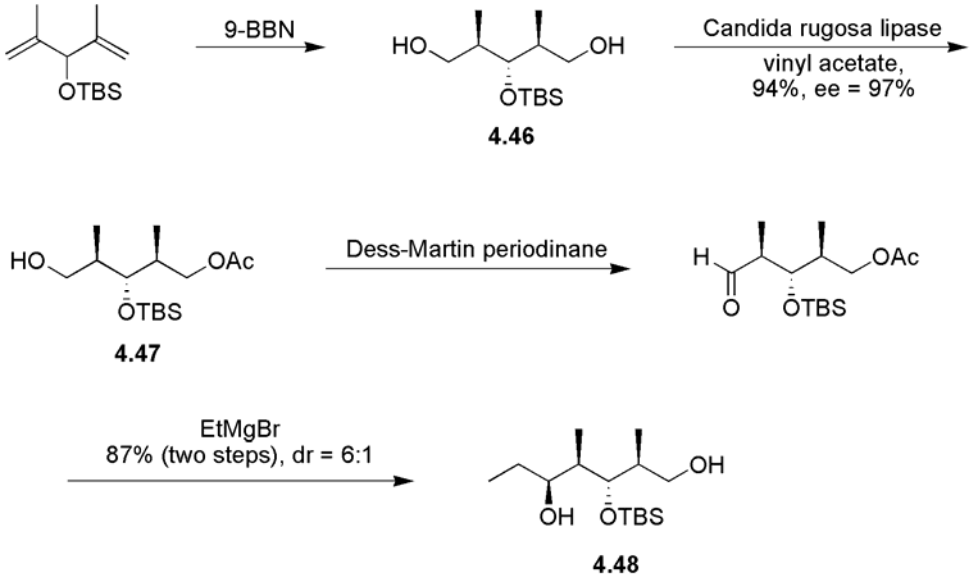
[110] Hoffmann, R. W.; Dahmann, G. *Tetrahedron Lett.* **1993**, *34*, 1115



Scheme 4-8 Enantioselective crotylboration/hydroboration

4.1.7.2 Chemoenzymatic Enantioselective Synthesis

Chenevert's group[111] reported a chemoenzymatic enantioselective synthesis of the polypropionate moiety in 2003. Hydroboration of methally alcohol with 9-BBN produced the symmetrical triol derivative **4.46** in high yield. Desymmetrization of this meso compound by stereoselective acylation in the presence of *Candida rugosa* lipase in hexane gave the corresponding (2*R*,3*R*,4*S*)-monoester **4.47**. High enantiomeric excess (97%) was achieved. Sequential chain extensions were performed by oxidation of the alcohol with Dess-Martin periodinane reagent and addition of ethylmagnesium bromide. The *syn*, *anti*, *anti*-diastereoisomer **4.48** was produced with dr = 6:1 (Scheme **4-9**).

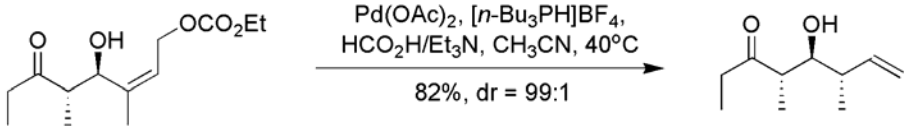


Scheme 4-9 Chemoenzymatic enantioselective synthesis

[111] Chenevert, R.; Courchesne, G.; Caron, D. *Tetrahedron Asy.* **2003**, *14*, 2567–2571

4.1.7.3 Diastereoselective Palladium-Catalyzed Formate Reduction of Allylic Carbonates

In 2005, Lautens and coworkers [112] reported that diastereoselective palladium-catalyzed formate reduction of allylic carbonates could provide entry into three of the four possible diastereomeric triads, namely *syn-syn*, *anti-syn*, and *anti-anti*. For example, reduction of the (*Z*)-carbonate (**4.49**) gave selectivity to favor formation of the *anti-anti* triad (**4.50**) in good yield with at least 99:1 diastereoselectivity by slow addition of the formate source over 6 h (Scheme **4-10**).



4.49 **4.50**

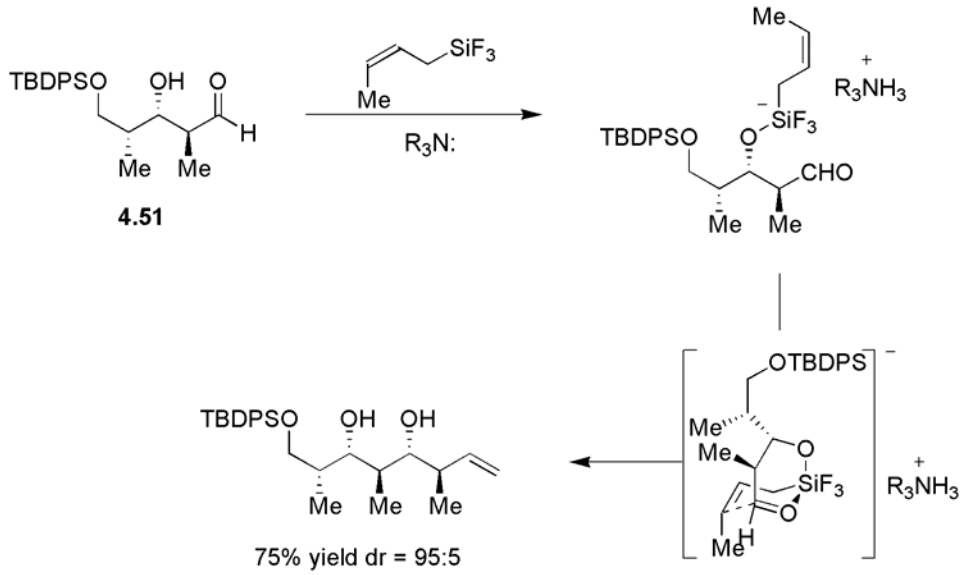
Scheme 4-10 Diastereoselective palladium-catalyzed formate reduction

4.1.7.4 Crotylation with Crotyltrifluorosilanes

Roush and coworkers[113] reported a method for the stereoselective synthesis of the *anti*, *anti*-stereotriad via the reaction of α-methyl-*β*-hydroxy aldehydes **4.51** with (*Z*)-crotyltrifluorosilane. These reactions were designed to occur through an internally chelated, bicyclic transition state. A covalent bound was formed between the silane reagent and the *β*-hydroxyl group of the aldehyde **4.51**. Then the crotyl group is transferred in an intramolecular allylation step. A diastereoslectivity of more than 95% was achieved. The researchers also noted that the *anti* stereochemistry of α-methyl group and *β*-hydroxy group of the aldehyde was required to react predominantly through conventional Zimmerman-Traxler transition states (**Scheme 4-11**).

[112] Chau, A.; Paquin, J.-F.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 1924-1933

[113] Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319-1333



Scheme 4-11 Crotylation with crotyltrifluorosilanes

4.2 RESULTS AND DISCUSSION

4.2.1 Synthesis of *Anti*, *Anti*-Stereotriads

4.2.1.1 Retrosynthetic Plan for *Anti*, *Anti*-Stereotriads

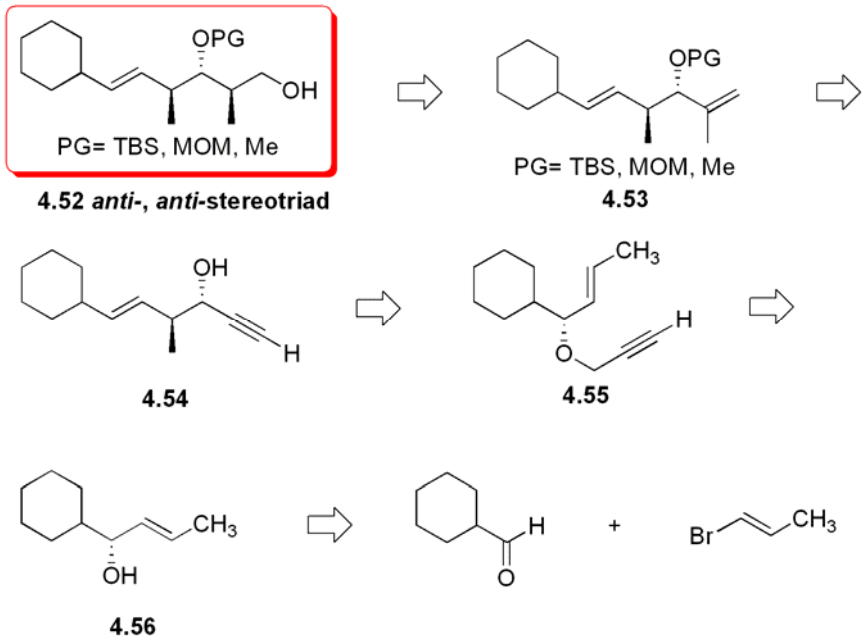
Our retrosynthetic strategy of *anti*, *anti*-stereotriads is shown in Scheme **4-12**. The *ant*-, *anti*-stereotriad **4.52** could be conveniently obtained from protected *anti*-allylic ether **4.53** by stereoselective hydroboration and oxidation of the terminal olefin group.[114] Then the *anti*-allylic ether **4.53** could be constructed by carbocupration of *anti*-propargyl alcohol **4.54** followed by protection.[115] It was reported that *anti*-propargyl alcohol **4.54** with two stereo centers could be constructed from (*S*)-propargyl allylic ether **4.55** with a bulky substituent group at the allylic position by a [2,3]-Wittig rearrangement in basic condition.[116] Simple alkylation of (*S*,*E*)-allylic alcohol **4.56** and 3-bromoprop-1-yne could produce (*S*)-propargyl allylic ether **4.55** handily. (+)-N- methylephedrine directed

[114] Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *8*, 2487-2489

[115] (a) Duboudin, J. G.; Jousseaume, B. *J. Organometallic Chem.* **1979**, *168*, 1-11; (b) Duboudin, J. G.; Jousseaume, B. J.; Bonakdar, A. *J. Organometallic Chem*. **1979**, *168*, 227-232

[116] Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem.* **1999,** *64,* 1459-1463

enantioselective addition of (*E*)-1-bromoprop-1-ene to cyclohexanecarbaldehyde could provide (*S*,*E*)-allylic alcohol **4.56** with correct chirality.[117] The *ant*-, *anti*-stereotriad **4.57** (enantiomer of *ant*-, *anti*-stereotriad **4.52**) could be synthesized by using (-)-N-methylephedrine in the enantioselective alkenylation step (Scheme **4-12**). The detailed results of this asymmetric synthetic approach will be discussed in the next section.

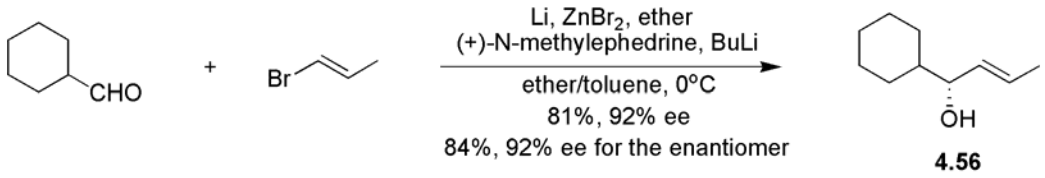


Scheme 4-12 Retrosynthetic plan for *anti*, *anti*-stereotriad **4.52**

4.2.1.2 Catalytic Asymmetric Synthesis of (*S*,*E*)-Allylic Alcohol 4.48

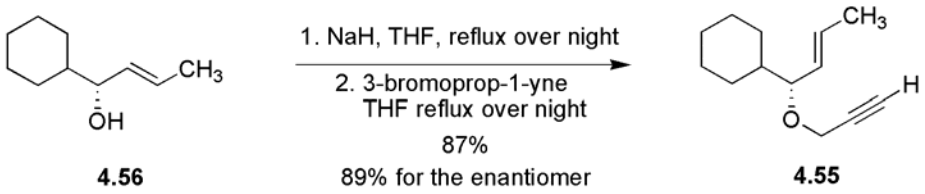
A methodology developed by Oppolzer and co-workers was adopted in our large scale synthesis of (*S*,*E*)-allylic alcohol **4.56**. A catalytic stereoselective addition of 1-propenyl zinc bromide with (+)-N-methylephedrine as ligand to the aldehyde could produce the chiral secondary alcohol with good yield and high ee. In this work, we used cyclohexanecarboxaldehyde-derived intermediates for convenience in handling. Also, for easy of handling in large-scale synthesis, the large amount of excess Li powder used in Oppolzer's procedure was reduced to one equivalent. (*S*,*E*)-allylic alcohol **4.56** was obtained in 84% yield and 92% ee (Scheme **4-13**). The chiral ligand (+)-N-methylephedrine was recovered quantitatively without lose of chirality. The mechanism of this reaction is discussed in section **3.2.1.1** of chapter **3**.

[117] Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.



Scheme 4-13 Catalytic asymmetric synthesis of (*S*,*E*)-allylic alcohol **4.56**

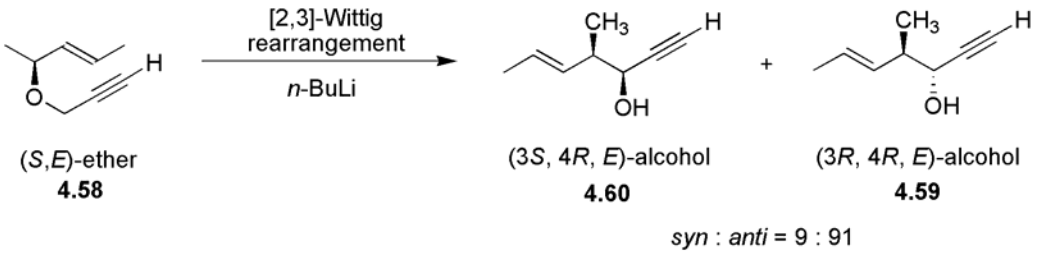
(*S*,*E*)-allylic alcohol **4.56** was converted to (*S*,*E*)-allylic propargyl ether **4.55** by etherification (alkylation) with 3-bromoprop-1-yne. The substrate of the [2,3]-Wittig rearrangement was afforded in 87% yield (Scheme **4-14**).



Scheme 4-14 Alkylation of (*S*,*E*)-allylic alcohol **4.56**

4.2.1.3 [2,3]-Wittig Rearrangment

In 1999, Tius's group reported a diastereoslective [2,3]-Wittig rearrangement to generate chiral alcohols with two stereocenters from propargyl allylic ethers. They reported that treatment of (*S*,*E*)-allylic propargyl ether **4.58** (R = H) with base resulted in *anti*-alcohol in good yield and excellent selectivity. The ratio between *anti* product **4.59** and *syn* product **4.60** was 91:9. (Scheme **4-15**.)

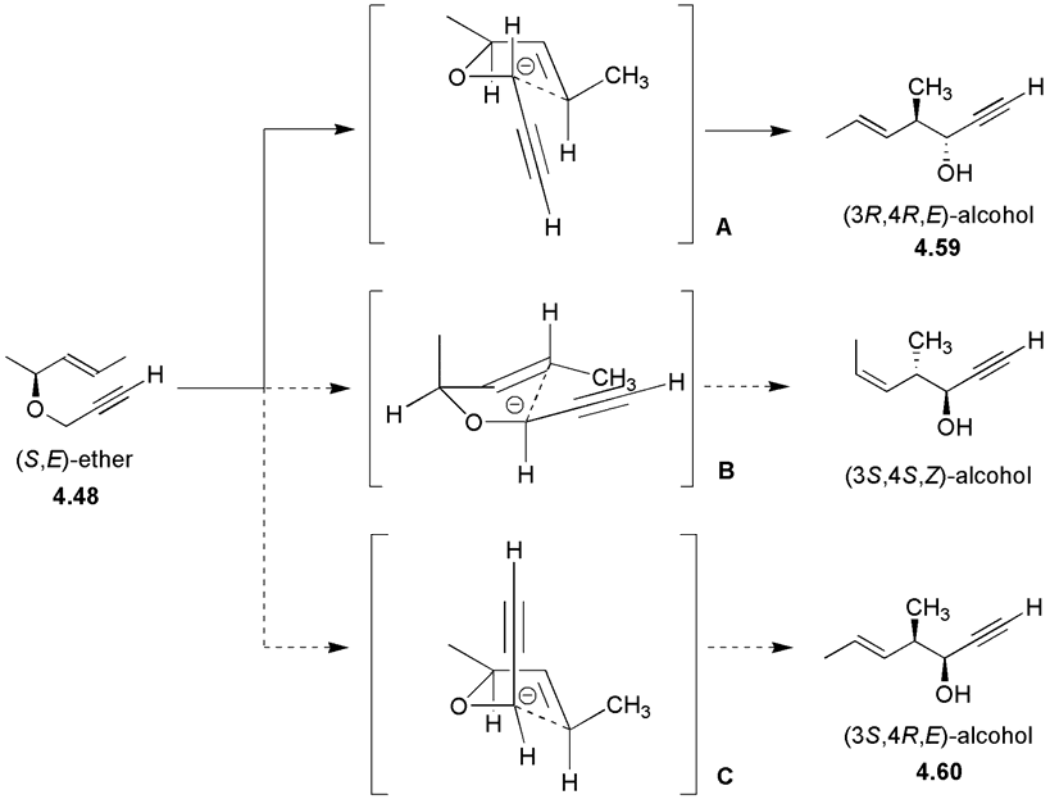


Scheme 4-15 [2,3]-Wittig rearrangement of (*S*,*E*)-allylic propargyl ether **4.58** (R = H)

In the 1980's, Nakai and Mikami proposed a five-membered cyclic transition state for the [2,3]-Wittig rearrangement[118]. According to the five-membered cyclic transition state theory, there could be transition states **A**, **B** and **C**. Transition state **A** will be favored

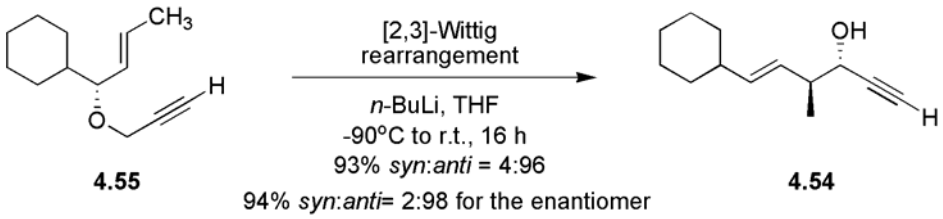
[118] (a) Mikami, K.; Azuma, K.-I.; Nakai, T. *Tetrahedron* **1984**, *40*, 2303-2308. (b) Mikami, K.; Azuma, K.; Nakai, T. *Chem. Lett.* **1983**, 1379-1382. (c) Sayo, N.; Kitahara, E.; Nakai, T. *Chem. Lett.* **1984**, 259-262.

over transition states **B** and **C** because both of the methyl groups and the acetylene group are at the less hindered equatorial positions. Transition state **A** will lead to the major product (3*R*, 4*R*, *E*) -alcohol **4.59** (Scheme **4-16**).



Scheme 4-16 Five-membered cyclic transition states theory

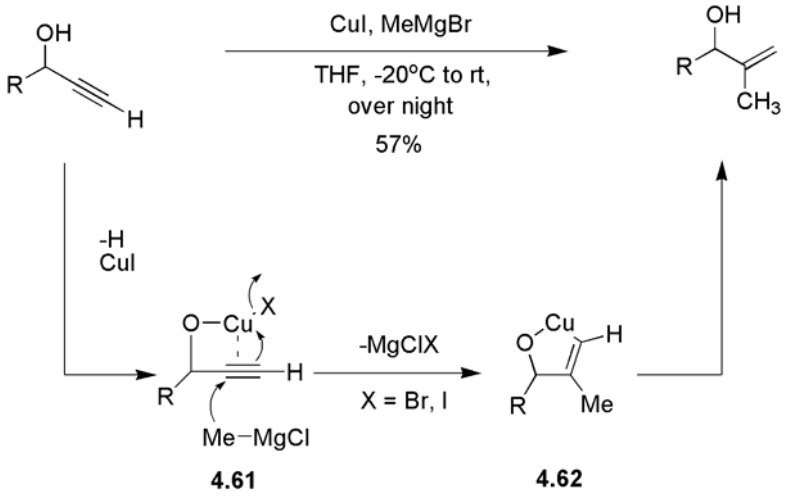
When standard [2,3]-Wittig rearrangement conditions were applied to (*S*,*E*)-allylic propargyl ether **4.55**, results similar to those of Tius were obtained. (3*S*,4*S*,*E*)-Propargylic halcohol **4.54** was the major product (93% yield). The ratio of the *anti*/*syn* diastereomers of this rearrangement product was, as judged by analysis of the ^{1}H NMR spectrum, 96:4. The bulkiness of the cyclohexyl substitutent could be the factor leads to improved selectivity (Scheme **4-17**).



Scheme 4-17 Synthesis of (3*S*,4*S*,*E*)-propargylic alcohol **4.54**

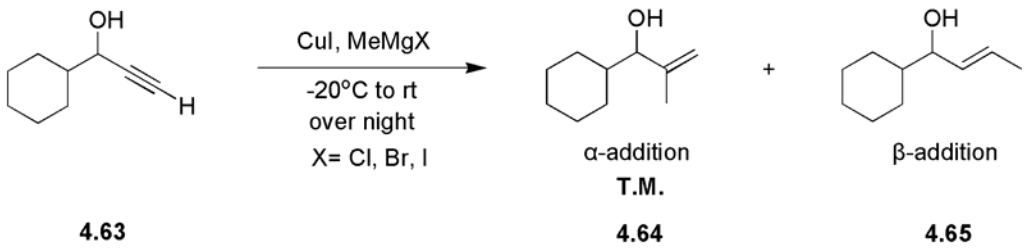
4.2.1.4 Regioselective Carbocupration and Protection

In 1979, Duboudin reported a cupper iodide directed carbocupration reaction of a methyl Grignard with propargyl alcohol to provide allylic alcohol in 57% yield (Scheme **4-18**). They proposed a five-membered cyclic intermediate to explain the regioselectivity. According to the five-membered intermediate theory, copper(I) cation would coordinate to the deprotonated hydroxyl group and the C-C triple bond to form intermediate **4.61**. Then, nucleophilic addition of methyl Grignard to the alkyne group would take place from the other side of the metal-alkyne bond and form a five-membered intermediate **4.62** which would transform to the desired α-addition product. This explains the selectivity of α-addition product over β-addition (would go through a four-membered cyclic intermediate) product.



Scheme 4-18 Regioselective carbocupration

With the reported condition (Table **4-1**, Entry **1**), the carbocupration of model propargyl alcohol **4.63** only yielded target molecule **4.64** (α-addition) with 24% yield. A 54% of starting material was recovered and a 22% of β-addition product **4.65** was also separated. In order to optimize this carbocupration step, a model study using different ratio of reagents and solvent was performed (Scheme **4-19**). The best result was provided (Entry **6**) with 4.0 eq of MeMgCl, 2.0 eq of CuI and THF as solvent. A 79% yield of α-addition product **4.64** was produced and only trace amount of β-addition product **4.65** was found in the crude mixture besides a 21 % of starting material.

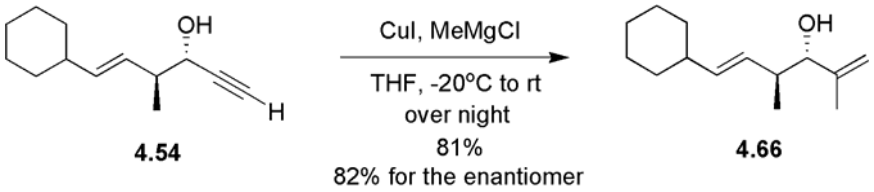


Scheme 4-19 Carbocupration of model propargyl alcohol **4.63**

Table 4-1 Carbocupration of model propargyl alcohol **4.63**

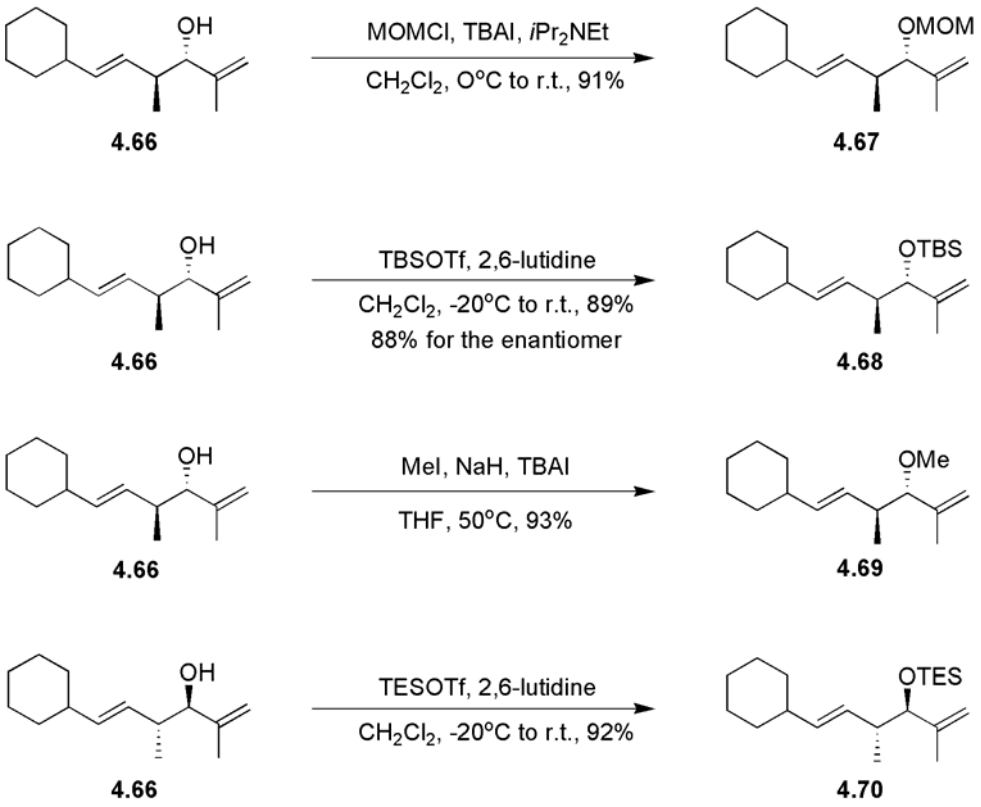
Entry	Gringard	CuI	Solvent	S.M.(%)	**4.65** Yield (%)	**4.64** Yield (%)
1	MeMgBr 2.5 eq	0.95 eq	THF	54	22	24
2	MeMgBr 4.0 eq	2.0 eq	THF	28	14	58
3	MeMgBr 4.0 eq	3.0 eq	THF	62	16	22
4	MeMgBr 4.0 eq	2.0 eq	Et_2O	65	31	4
5	MeMgBr 4.0 eq	2.0 eq	1,4-dioxane	100	0	0
6	MeMgCl 4.0 eq	2.0 eq	THF	21	trace	79
7	MeMgI 4.0 eq	2.0 eq	THF	87	trace	13

The optimized carbocupration condition was used in our *anti*, *anti*-stereotriad synthesis. The α-addition product, *anti*-allylic alcohol **4.66**, was successfully synthesized in 81% yield from anti-propargyl alcohol **4.54**. (Scheme **4-20**)



Scheme 4-20 Carbocupration of *anti*-propargyl alcohol **4.54**

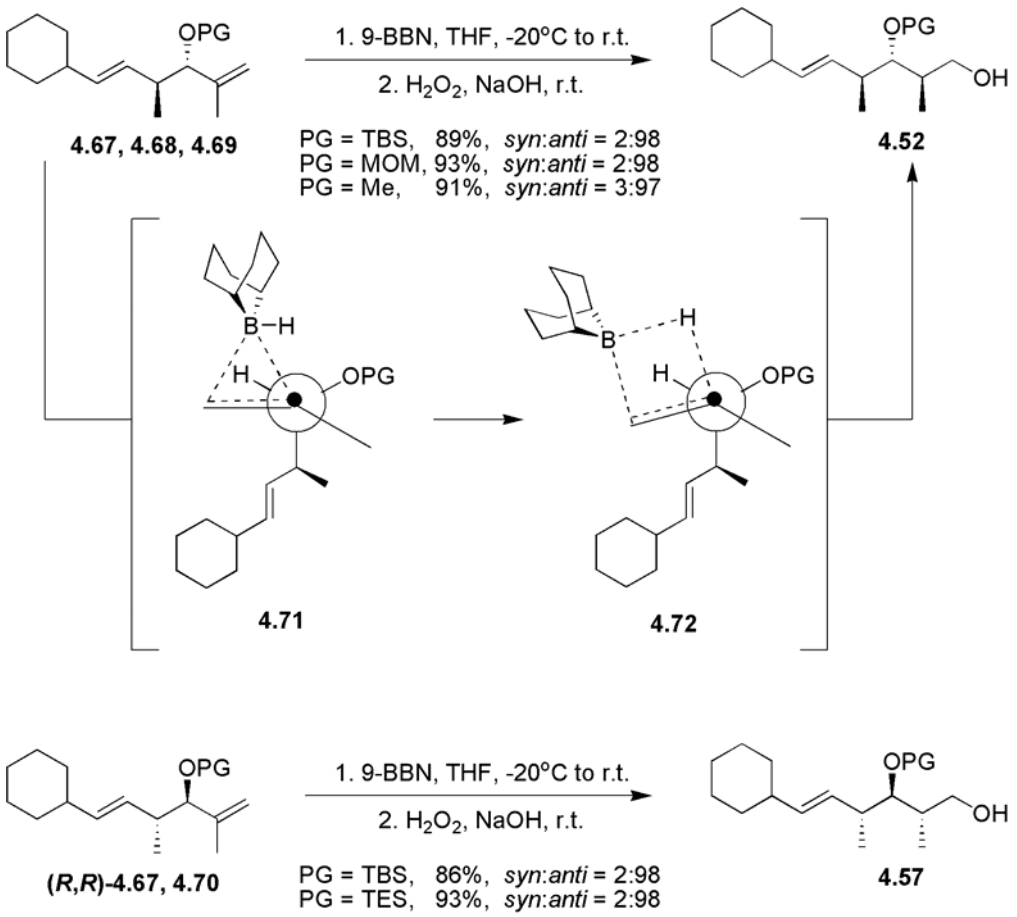
Next, the resulting *anti*-allylic alcohol **4.66** was protected with different protecting groups (MOM **4.67**, TBS **4.68**, TES **4.69**, Me **4.70**) to set up the stage for the stereoselective hydroboration with 9-BBN. The best condition for the protection steps are shown as follows (Scheme **4-21**).



Scheme 4-21 Protection of *anti*-allylic alcohol **4.66**

4.2.1.5 Stereoselective Hydroboration and Oxidation

With precursors in hand, diastereoselective hydroboration of the terminal olefin group in the *anti*-allylic ether **4.67-4.70** followed by oxidation generated terminal alcohol **4.52** (or **4.57**) containing the *anti*, *anti*-stereotriad in high yield and high diastereoselectivity (Scheme **4-22**, the diastereometric ratios were measured by careful integration of ^{1}H NMR spectra).

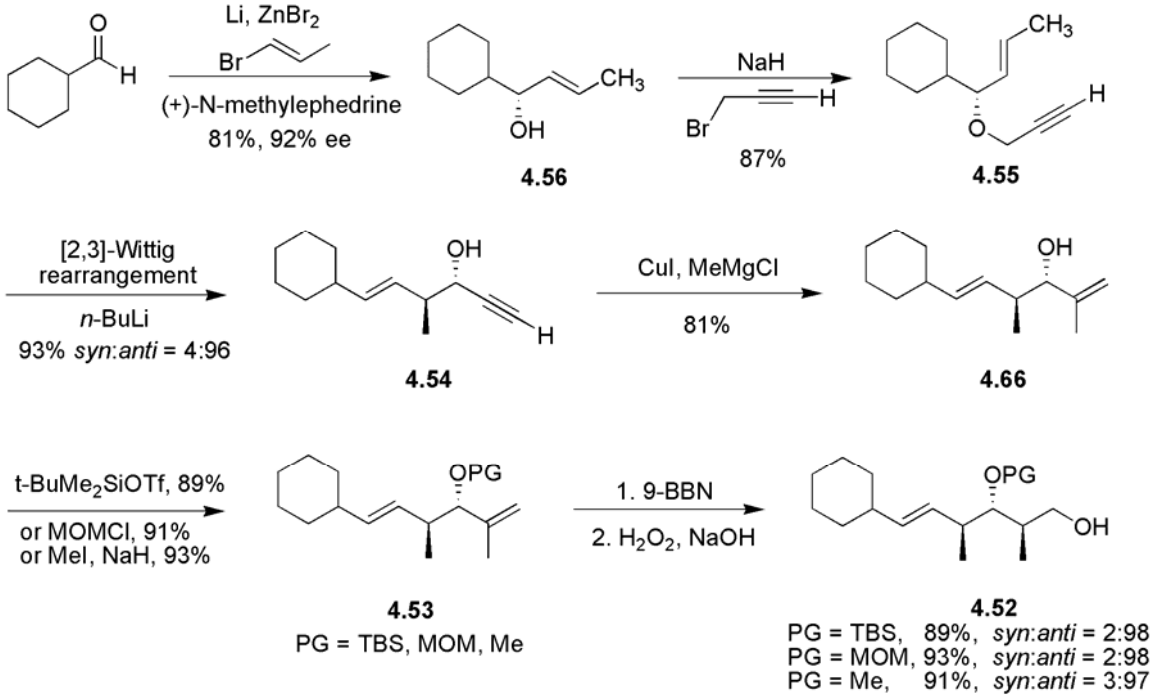


Scheme 4-22 Stereoselective hydroboration

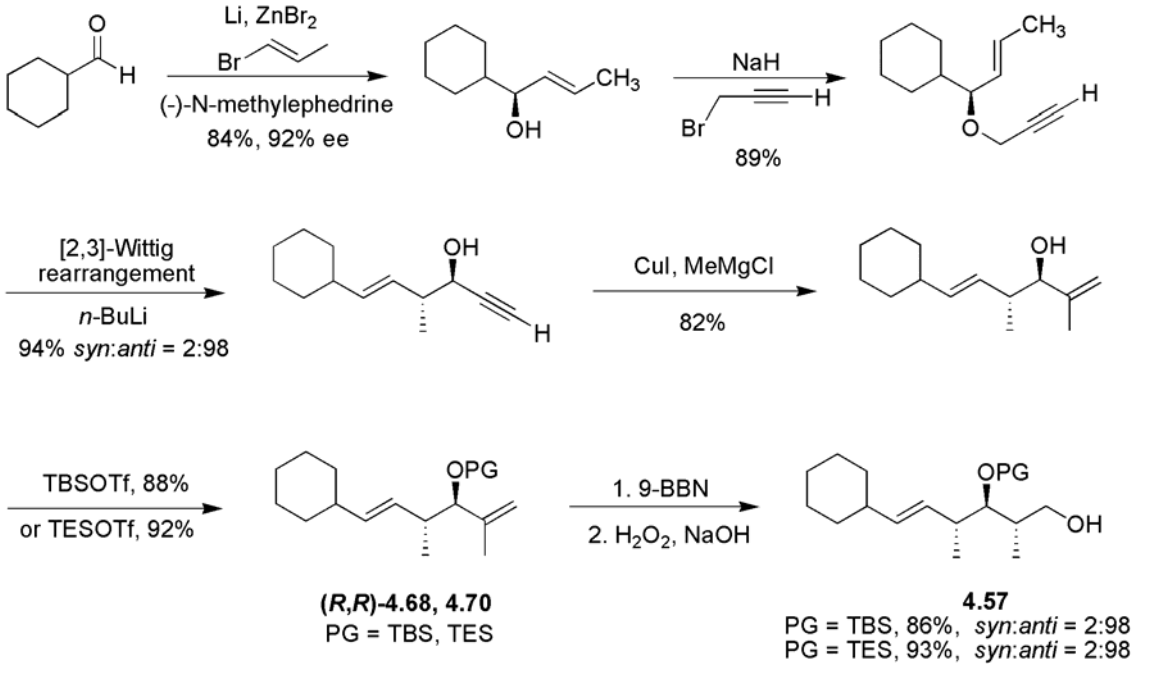
The stereoselectivity of this hydroboration reaction could be explained by a simple model (Scheme **4-22**). Among all the possible transition states, **4.71** or **4.72** would be the most likely one that the reaction would undergo because they have the smallest substituent (H) oriented over the face of the transition-state ring. The borane would approach from the less hindered side of olefinic π system and then the resulting less sterically encumbered transition state would lead to the selected *anti*- product.

4.2.1.6 Completion of the Synthesis of *Anti*, *Anti*-Stereotriads (4.52, 4.57)

In summary, anti, anti-stereotriad (**4.52**) was successfully synthesized in 6 steps and 42-45 % yield (PG = TBS, 42%; PG = MOM, 45%; PG = Me, 45%) from cyclohexanecarbaldehyde (Scheme **4-23**). The *ant*-, *anti*-stereotriad **4.57** (enantiomer of *ant*-, *anti*-stereotriad **4.52**) was synthesized in same steps and 44-49 % yield (PG = TBS, 44%; PG= TES, 49%) by using (-)-N- methylephedrine in the enantioselective alkenylation step (Scheme **4-24**).



Scheme 4-23 Synthesis of (2*S*,3*R*,4*R*)-*anti*, *anti*-stereotriad (**4.52**)

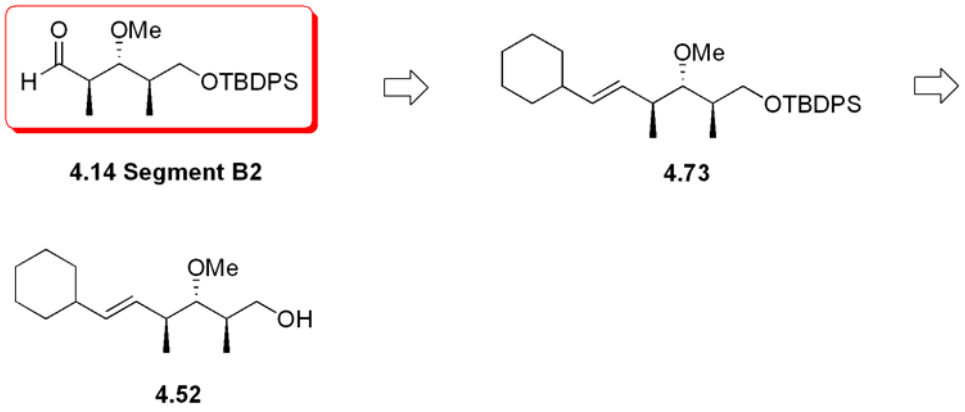


Scheme 4-24 Synthesis of (2*R*,3*S*,4*S*)-*anti*, *anti*-stereotriad (**4.57**)

4.2.2 Synthesis of Segment B2

4.2.2.1 Retrosynthetic Plan for Segment B2

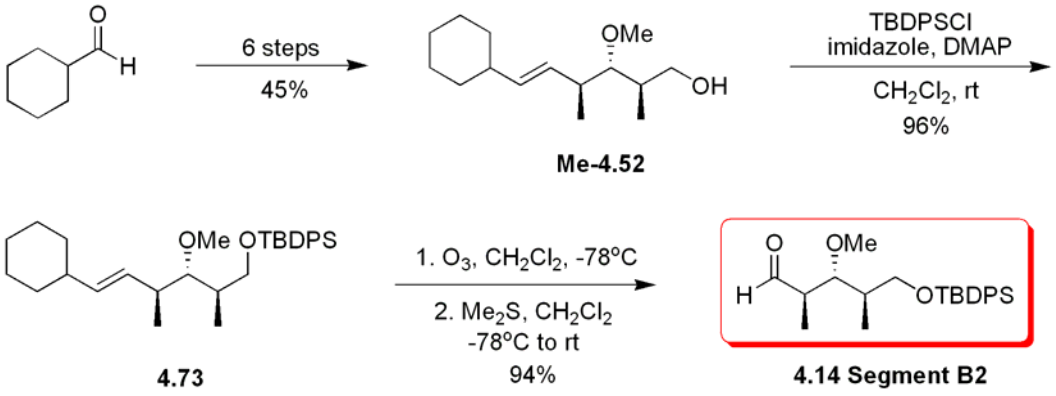
Our retrosynthesis of segment **B2** (**4.14**) of Miyashita's total synthesis of scytophycin C (**4.4**) is shown in Scheme **4-25**. Segment **B2** (**4.14**) could be conveniently obtained by ozonolysis of TBDPS ether **4.73**, which could be prepared from *anti*, *anti*-*β*-methoxy alcohol **4.52** handily. The detailed results will be discussed in the next section.



Scheme 4-25 Retrosynthetic plan for segment **B2** (**4.14**)

4.2.2.2 Completion of the Synthesis of Segment B2 (4.14)

With *anti*, *anti*-stereotriad containing β-methoxyl alcohol **Me-4.52** in hand, TBDPS protected ether **4.73** was conveniently obtained in 96% yield by treating β-methoxyl alcohol **4.52** with TBDPSCl, imidazole and a catalytic amount of DMAP in CH_2Cl_2. Then ozonolysis of TBDPS ether **4.73** afforded segment B2 in 94% yield (Scheme **4-26**). Over all, segment **B2** (**4.14**) was successfully synthesized in 8 steps and 41% yield from cyclohexanecarbaldehyde compared to 11 steps and 32% yield in Miyashita's synthesis.

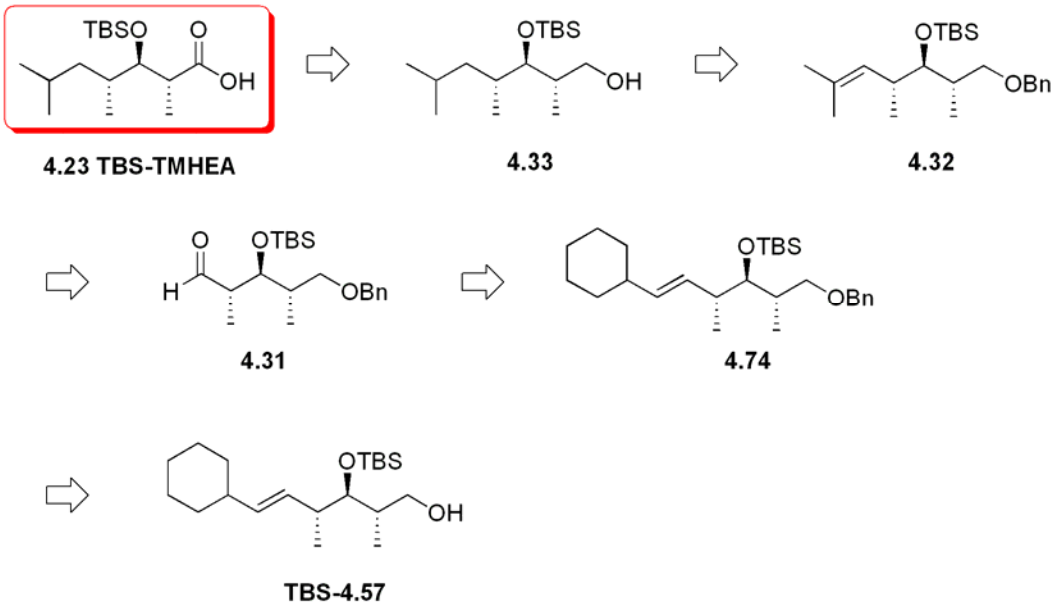


Scheme 4-26 Synthesis of segment **B2** (**4.14**)

4.2.3 Synthesis of TBS-TMHEA (4.23)

4.2.3.1 Retrosynthetic Plan for TBS-TMHEA (4.23)

Our retrosynthesis of TBS-TMHEA (**4.23**) is shown in Scheme **4-27**. The TBS-TMHEA (**4.23**) could be synthesized from aldehyde **4.33** by D'Auria's strategy (Wittig reaction, Hydrogen reduction and oxidation with $RuCl_3 \cdot H_2O/HIO_4$). The aldehyde **4.31** could be generated by ozonolysis of full protected olefin **4.74**, which could be obtained from benzyl protection of TBS protected *anti*, *anti*-stereotriad **4.57**. The detailed results of synthetic approach will be discussed in the following section.

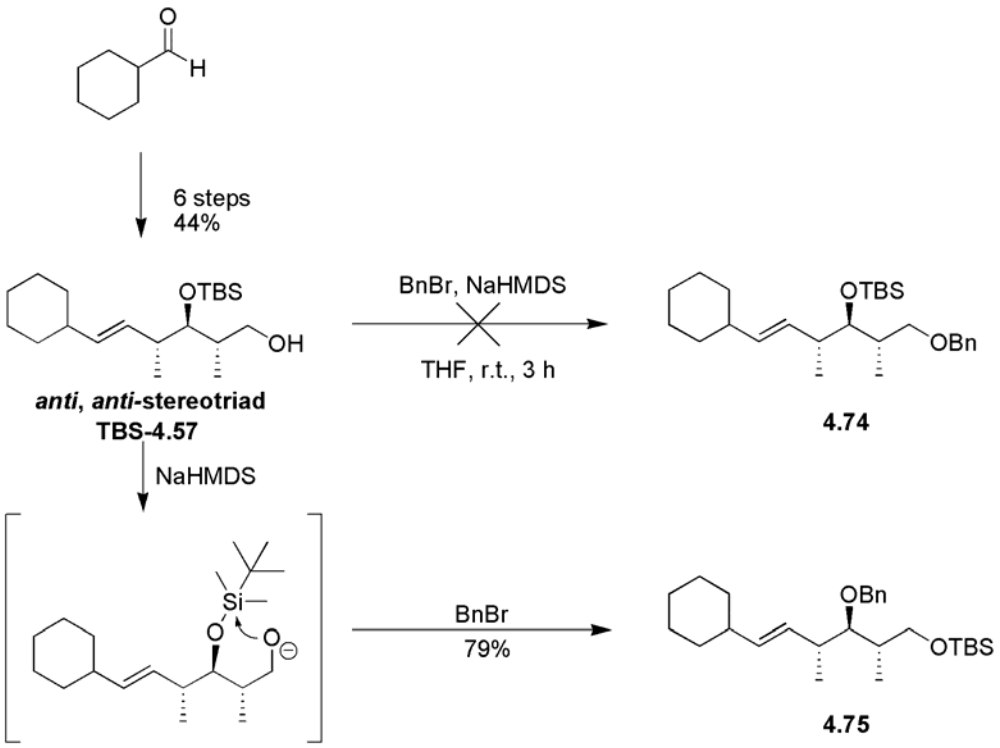


Scheme 4-27 Retrosynthetic strategy of TBS-TMHEA (**4.23**)

4.2.3.2 Benzyl Protection of the Primary Hydroxyl Group

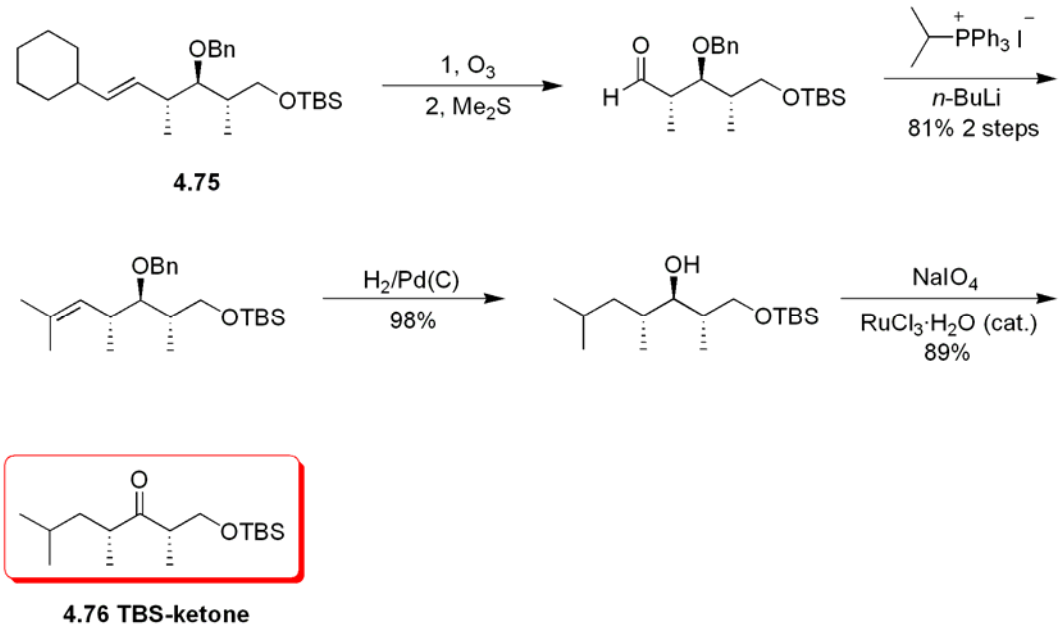
4.2.3.2.1 TBS Migration under Basic Condition

Initially, basic conditions were used to protect the terminal primary hydroxyl group in **TBS-4.57** with a benzyl group. After treatment with NaHMDS and benzyl bromide for three hours at room temperature, a migration product **4.75** was separated in 79 % yield. Only a trace of the desired product **4.74** was obtained. We proposed the TBS group is relatively unstable at the secondary hydroxyl position and has a tendency to migrate to the primary position. Right after the primary hydroxyl group is deprotonated, the resulting hydroxyl anion will attack the silyl group directly. After a SN2 like substitution with a six-membered ring transition state, the TBS group will migrated to the primary hydroxyl position. Then, the secondary hydroxyl anion will react with benzyl bromide to provid the migration product (Scheme **4-28**).



Scheme 4-28. TBS migration under basic condition

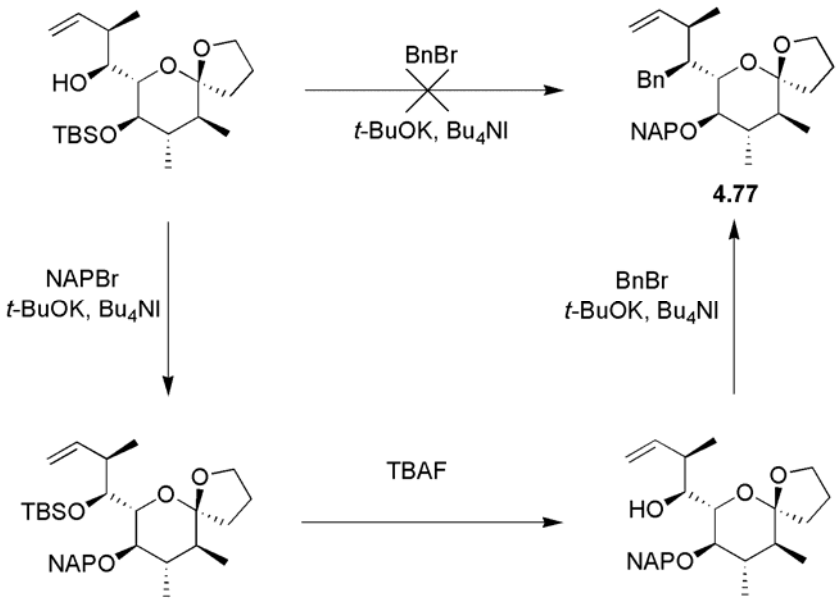
Unfortunately, the migration product has similar physical properties, NMR spectrum and IR spectrum with the desired product. That migration had occurred was not realized until four steps later in the sequence. A ketone **4.76** was obtained instead of a carboxylic acid. This clearly indicated the migration of the TBS group (Scheme **4-29**).



Scheme 4-29. Synthesis of TBS-ketone **4.76**

4.2.3.2.2 Previous Reported TBS Migration with Similar Substrate

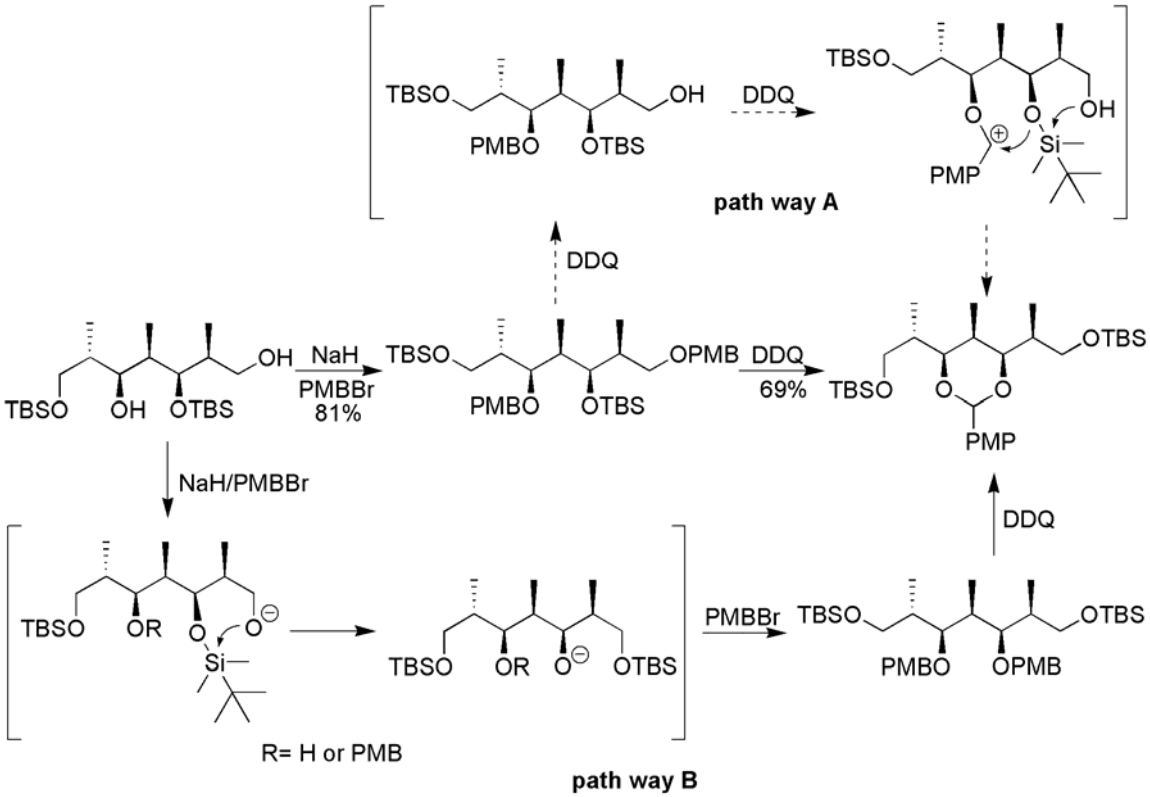
In 2005, Fujiwara's group reported a similar TBS migration under basic conditions in their synthesis of the C42 – C52 part of ciguatoxin CTX3C[119]. The strong basic conditions with potassium cation were found to accelerate and complete the migration. The researchers had to perform a three step protection/deprotection sequence to get the desired benzyl protected product **4.77** [(a) the TBS migration and (2-naphthyl)methyl (NAP) protection, (b) removal of the TBS group, and (c) Bn protection] (Scheme **4-30**).



Scheme 4-30. TBS migration reported by the Fujiwara group

In 2004, Ramachandran's group reported another example of TBS migration in their synthesis of C15-C21 subunits of (+)-discodermolide.[120] The researchers proposed that the TBS migration took place in the oxidative-cleavage of PMB group step. They also proposed a transition state mechanism (Scheme **4-31**, pathway A) for this migration during the oxidative-cleavage step. With our results of TBS migration under basic condition, it is more likely the TBS group already migrated during the PMB protection step in this Ramachandran group's sequence. The proposed mechanism is shown in Scheme **4-31** as pathway B.

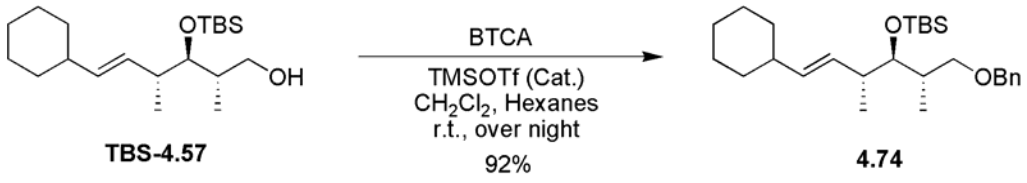
[119] Domon, D.; Fujiwara, K. et al. *Tetrahedron Lett.*, **2005**, *46*, 8279 – 8283
[120] Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* 2004, *69*, 6294-6304



Scheme 4-31. TBS migration reported by the Ramachandran group

4.2.3.2.3 Benzyl Protection under Acidic Condition

In order to protect the primary hydroxyl group without TBS migration, an acidic condition will be appropriate. An alternative procedure to use BTCA (benzyl 2,2,2-trichloroacetimidate) with catalytic amount of TMSOTf in a mix solvent of methylene chloride and hexanes proved to work smoothly. A 92 % of desired product **4.74** was obtained with the correct protecting pattern (Scheme **4-32**).

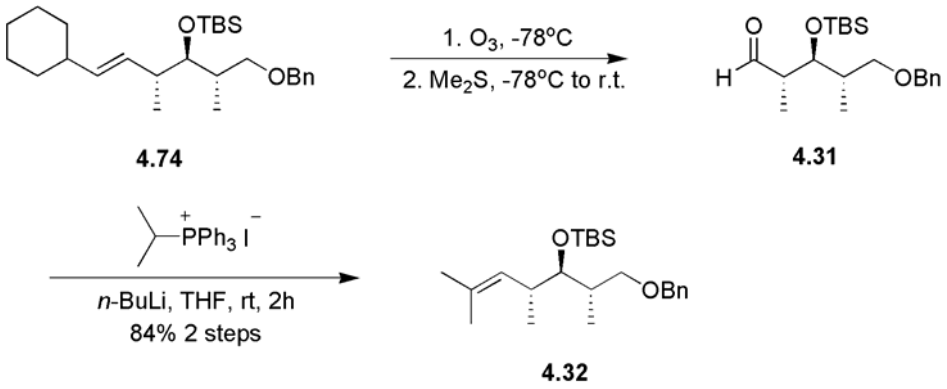


Scheme 4-32. Benzyl protection of **TBS-4.57**

4.2.3.3 Ozonolysis and Wittig Reaction

With fully protected olefin **4.74** in hand, aldehyde **4.31** was obtained by ozonolysis with dimethyl sulfide workup. The crude product was directly used in the next step without separation. An 84 % yield of desired trisubstituted olefin **4.32** was obtained by

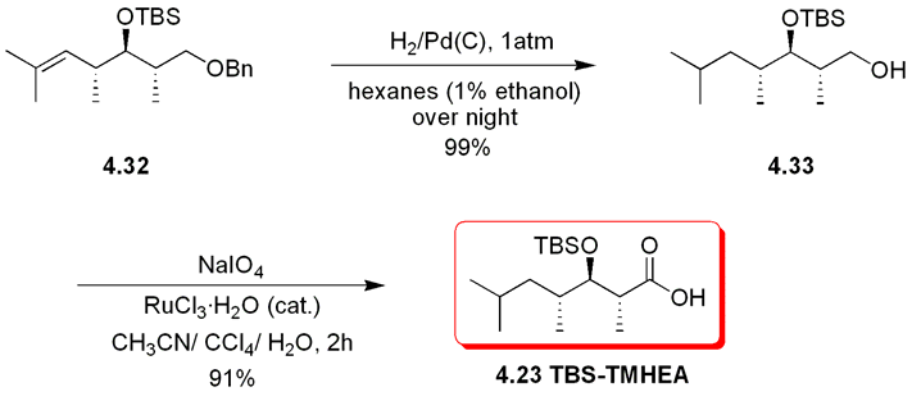
applied the standard Wittig reaction conditions with the crude aldehyde **4.31** (Scheme **4-33**). The resulting olefin has a similar polarity with triphenylphosphine, which was introduced into the raction mixture by starting material isopropyltriphenylphosphonium iodide. A washing procedure with hydrogen peroxide THF/H_2O solution for 15 min removed triphenylphosphine completely.



Scheme 4-33 Ozonolysis and Wittig reaction

4.2.3.4 Hydrogenation, Hydrogenolysis and Oxidation

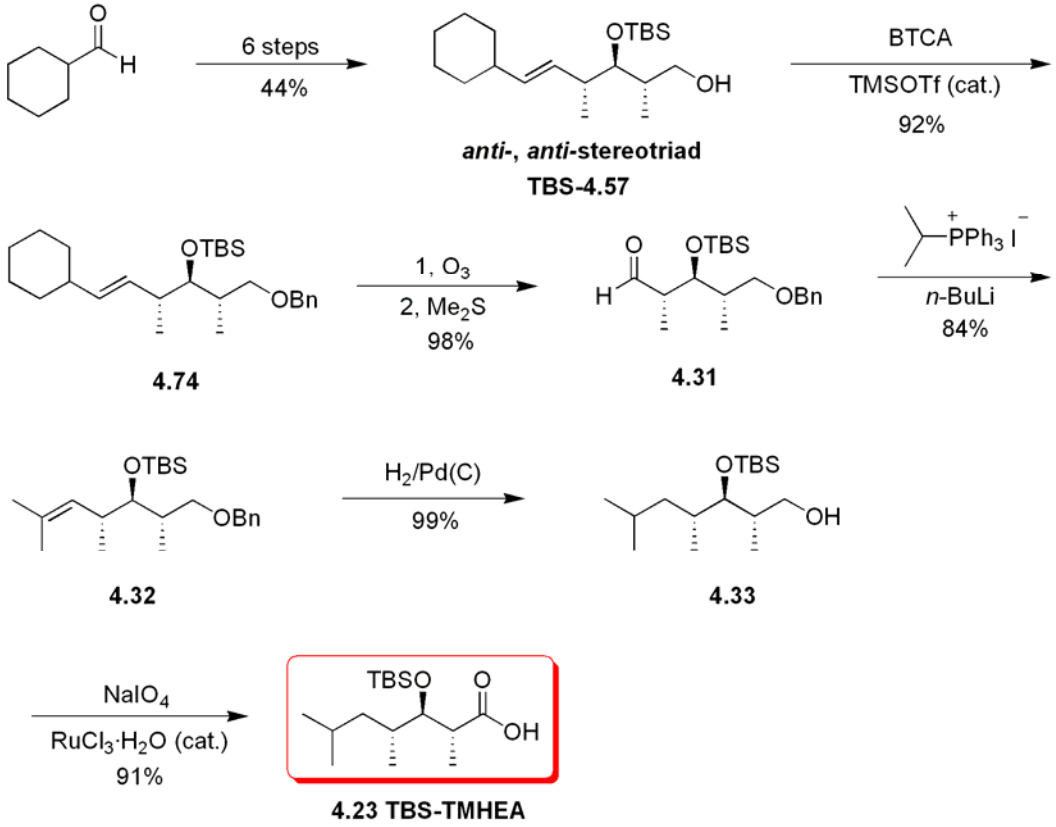
D'Auria's strategy was adopted to construct TBS-TMHEA (**4.32**) from trisubstituted olefin **4.33**. However, removal of the TBS protecting group was observed when we used Pearlman's catalyst to catalyze the hydrogenation/hydrogenolysis reaction of olefin **4.33** in ethanol. A modified procedure using palladium on active carbon as catalyst and hexanes (1% ethanol) as solvent proved to circumvent this problem. Clean reduction of the double bond and removal of the benzyl group with high yield (99%) was observed. Then, the resulting alcohol **4.33** was oxidized to TBS-TMHEA (**4.23**) using sodium periodate and catalytic amount of ruthenium trichloride with 91 % yield (Scheme **4-34**).



Scheme 4-34. Synthesis of TBS-TMHEA **4.23** from olefin **4.32**

4.2.3.5 Completion of the Synthesis of TBS-TMHEA (4.23)

TBS-TMHEA **4.23**, (2*R*,3*R*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethyl-heptanoic acid, was synthesized in 30% yield through an 11-step sequence overall. Benzylation of TBS protected (2*S*,3*R*,4*R*)-stereotriad **4.57** gave the fully protected olefin **4.74**. Ozonolysis provided aldehyde **4.31** which was subjected to Wittig reaction. Treatment of the trisubstituted olefin **4.32** with hydrogen in the presence of palladium on carbon effected both debenzylation and saturation of the double bond. Oxidation of the primary alcohol **4.33** then gave the target TBS-TMHEA (**4.23**, Scheme **4-35**).

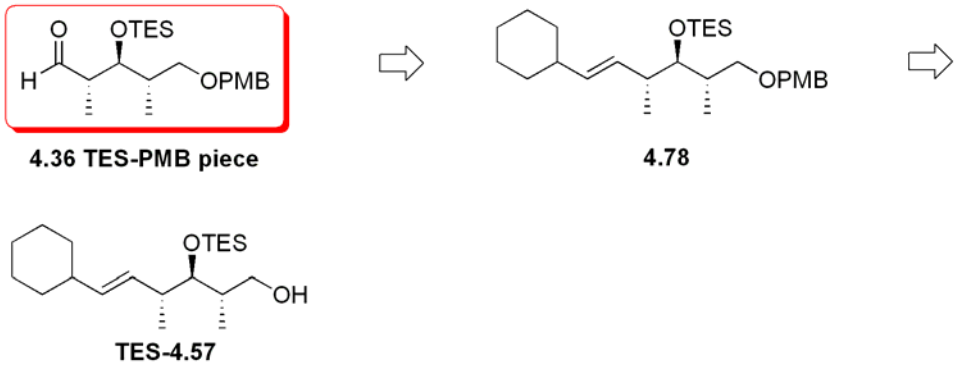


Scheme 4-35. Synthesis of TBS-TMHEA **4.23**

4.2.4 Synthesis of TES-PMB piece 4.36

4.2.4.1 Retrosynthetic Plan for TES-PMB piece 4.36

Our retrosynthesis of TES-PMB piece **4.36** of Paterson's synthesis approach of aplyronines is shown in Scheme **4-36**. TES-PMB piece **4.36** could be obtained by ozonolysis or periodate oxidation of full protected olefin **4.78**, which could be prepared from TES protected *anti*, *anti*-stereotriad 4.1 by PMB protection with standard acidic condition. The detailed results will be discussed in the next section.

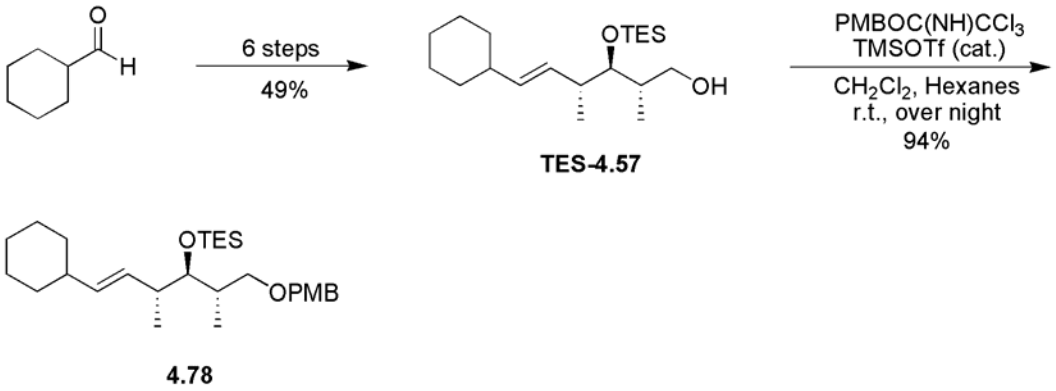


Scheme 4-36 Retrosynthetic strategy of TES-PMB piece **4.36**

4.2.4.2 Synthetic Approach towards TES-PMB piece

4.2.4.2.1 PMB protection

An acidic condition similar to what we used in benzyl protection of **TBS-4.57** to **4.74** in TBS-TMHEA **4.23** synthesis was applied to TES protected *anti*, *anti*-stereotriad **4.57**. The fullly protected olefin **4.78** with the correct pattern was obtained in 94% (Scheme **4-37**).



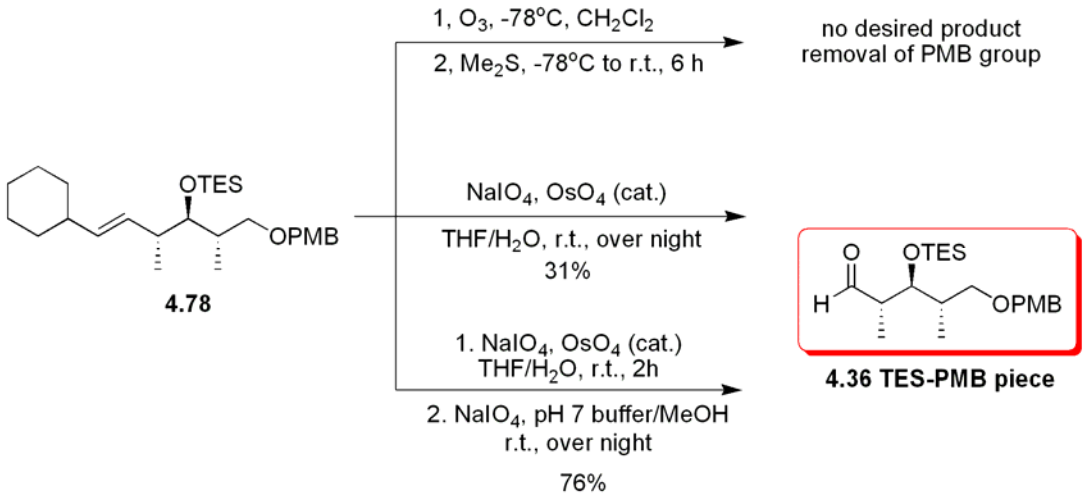
Scheme 4-37 PMB protection of **TES-4.57**

4.2.4.2.2 Oxidative-Cleavage Approach towards TBS-PMB piece 4.36

Our initial plan was to synthesis TBS-PMB piece **4.36** from olefin **4.78** by ozonolysis. Unfortunately, no desired product was obtained and ^{1}H NMR analysis of the reaction mixture indicated that the PMB group was removed (Scheme **4-38**).

In order to circumvent this problem, a one-pot oxidative-cleavage protocol using sodium periodate and osmium tetroxide was used next. The desired aldehyde TES-PMB piece **4.36** was obtained in 31% yield. No starting material was recovered and the major by-product was the related diol. Base on the results, we proposed that the oxidative-cleavage of diol is the slow step in this one-pot reaction. Then, a stepwise

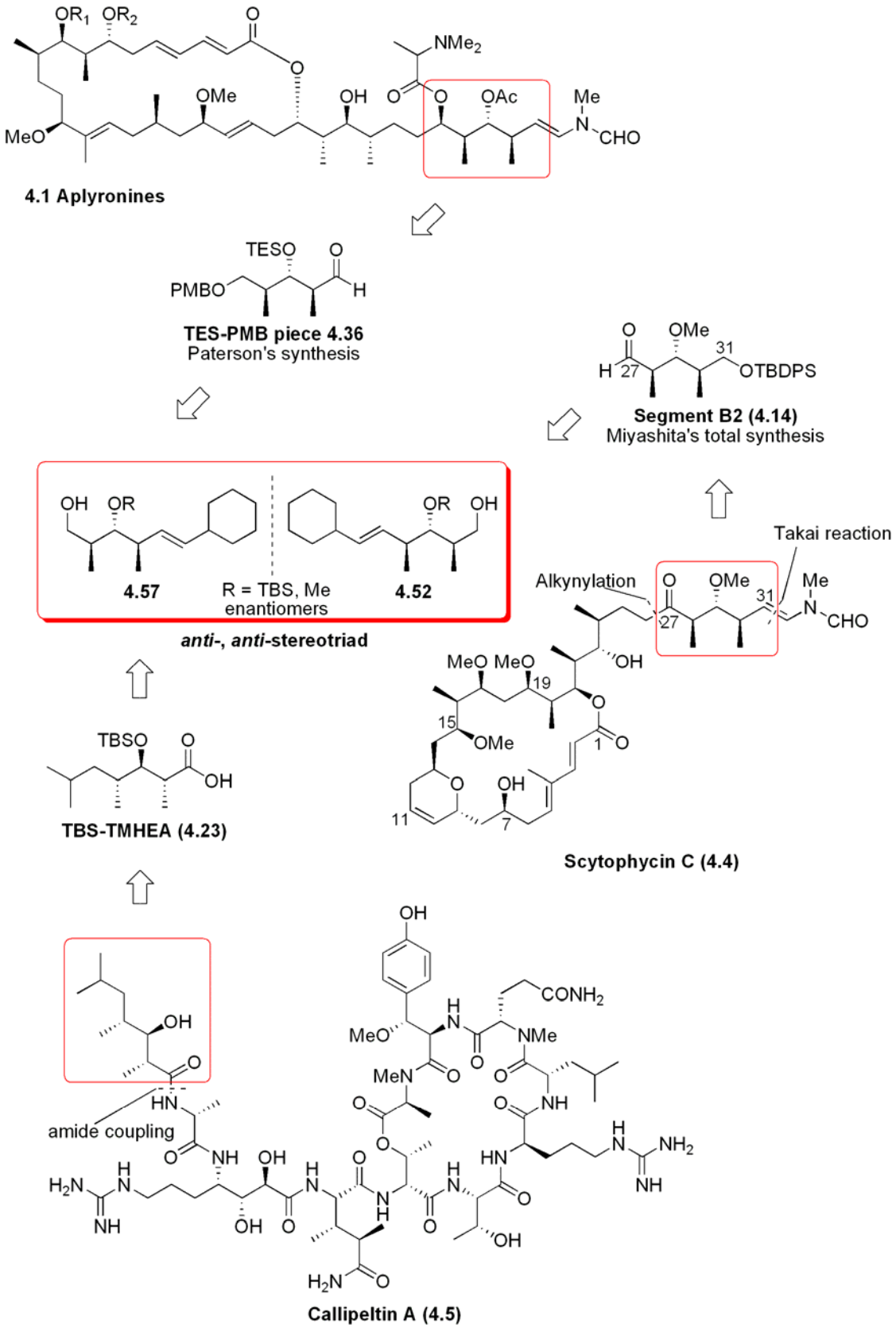
approach using pH=7 buffer and methanol mixed solvent produced TES-PMB piece **4.36** in 76% yield (Scheme **4-38**).



Scheme 4-38 Oxidative-cleavage approach towards TBS-PMB piece **4.36**

4.3 CONCLUSION

Starting from inexpensive, commercially available starting materials, a powerful protocol was developed to construct *anti*, *anti*-stereotriad building blocks for polypropionate natural products. Both enantiomers with various protecting groups (TBS, MOM and Me protecting groups for the (2*S*,3*S*,4*S*) series; TBS and PMB protecting groups for the (2*R*,3*R*,4*R*) series) were successfully synthesized in 6 steps with 42-49 % yield and high optical purity. Then segment B2 (**4.14**) of Miyashita's total synthesis of scytophycin C (**4.4**) was successfully synthesized from methyl protected (2*S*,3*S*,4*S*)-stereotriad building block in 2 steps and 90 % yield. Secondly, a key intermediate for callipeltin A (**4.5**) synthesis, TBS-TMHEA **4.23** was synthesized from TBS protected (2*R*,3*R*,4*R*)-stereotriad building block in 5 steps and 68% yield. At the same time, the C29-C33 fragment of aplyronines was also obtained from TES protected (2*R*,3*R*,4*R*)-stereotriad building block. Optimization of the periodate oxidative-cleavage step will be studied in the future. Overall, an asymmetric catalysis route to *anti*, *anti*-stereotriads was achieved and illustrated by applications (Scheme **4-39**).



Scheme 4-39 *Anti*, *anti*-stereotriads synthesis

4.4 EXPERIMENTAL SECTION

4.4.1 General Information

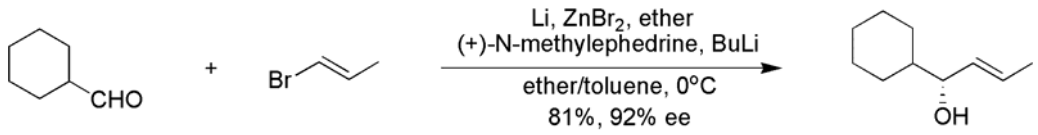
Reagents and solvents were purchased from Aldrich Chemical Company, Fisher Scientific, Lancaster, Alfa Aesar or Acros Organics. Liquid reagents were purified by distillation prior to use. Unless otherwise noted, solid reagents were used without further purification.

All air- and moisture sensitive reactions were performed under a positive pressure of dry argon in oven-dried or flame-dried glassware. All moisture sensitive solutions and anhydrous solvents were transferred via standard syringe and cannula techniques. Concentration of solutions was accomplished with a Buchi rotary evaporator evacuated by a water aspirator. In general, the residual solvent was removed on a vacuum line at 1-1.5 torr. Unless stated otherwise, commercially available reagents were used as supplied and solvents were dried over molecular sieves prior to use. HPLC grade hexane and HPLC grade ethyl acetate (EtOAc) were used in chromatography. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium-benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon gas. Diisopropylethylamine and triethylamine were distilled from sodium. The extracts were dried over Na_2SO_4 unless otherwise noted.

All experiments were monitored by thin layer chromatography (TLC) performed on EM Science precoated silica gel 60 F-254 glass supported plates with 0.25 mm thickness. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or to iodine vapor or by staining with a 10 % solution of phosphomolybdenic acid (PMA) in ethanol and then heating. Flash chromatography was carried out with Fisher brand silica gel (170-400 mesh).

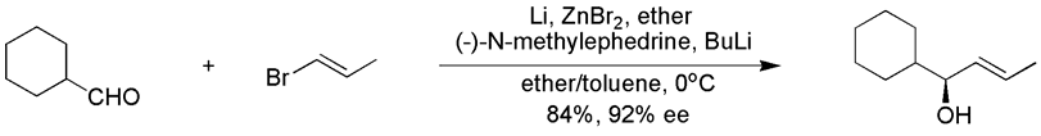
Infrared spectra were recorded with a Galaxy Series FT-IR 3000 infrared spectrophotometer. Samples were scanned as neat liquids on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded with a Varian Inova-600 (600 MHz for ^1H), Varian Inova-500 (500 MHz for ^1H), Varian Inova-400 (400 MHz for ^1H, 100 MHz for ^{13}C), or Gemini-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometer. Chemical shifts for proton NMR are reported in parts per million (ppm) relative to the singlet at 7.26 ppm for chloroform-*d*. Chemical shifts for carbon NMR are reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm. The following abbreviations are used in the experimental section for the description of ^1H-NMR spectra: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), doublet of quartets (dq), and broad singlet (bs). For complex multiplets, the chemical shift is given for the center of the multiplet. Coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectra were obtained with a Micromass 70-VSE spectrometer.

4.4.2 Experimental Procedures



4.56

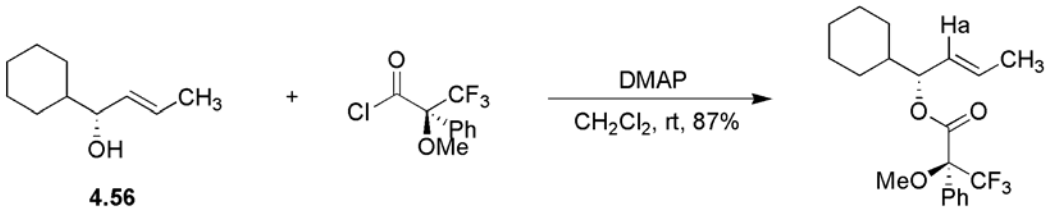
(*R*,*E*)-1-Cyclohexylbut-2-en-1-ol (4.56) To the lithium powder (233 mg, 33.2 mmol) under argon was added dry ether (20 mL) and the suspension was cooled to –35 ºC. With stirring, a solution of (E)-1-bromo-propene (1.96 g, 16.2 mmol) was added dropwise. The mixture was stirred at -35ºC for 2 h and treated dropwise with zinc bromide solution (1.6 M in ether, 11.1 mL, 17.8 mmol). The reaction mixture was stirred for an additional 1 h at 0 ºC and then a solution of lithium (-)-N-methylephedrate, prepared by the addition of n-butyllithium (1.6 M in hexanes, 10.6 mL, 17.0 mmol) to a solution of (+)-N-methylephedrine (3.05 g, 17.0 mmol) in toluene (20 mL) at 0 ºC, was added by cannula. The solution was stirred for 1 h at 0 ºC and cyclohexanecarboxaldehyde (1.45 g, 13.0 mmol) was added neat. After stirring for 1 h at 0 ºC, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether (3 x 30 mL). The organic phases were combined, washed with a second portion of the ammonium chloride solution, dried (MgSO4), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **4.56** (1.62 g, 81%, 92% ee. according to NMR study of Mosher ester) as clear liquid. (+)-N-methylephedrine was recovered quantitatively from the aqueous phases by basification to pH=12 with 2 N NaOH solution and extraction into ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.66 (dqd, *J*= 15.2, 6.4, 0.8 Hz, 1H), 5.51-5.44 (ddq, *J*= 15.2, 7.6, 1.6 Hz, 1H), 3.78-3.73 (td, *J*= 7.2, 2.8 Hz, 1H), 1.87-1.83 (m, 1H), 1.77-1.63 (m, 8H), 1.42-0.85 (m, 6H), IR (neat) ν_{max} 3391 (br), 2929, 2853, 1650, 1448, 1002, 967.



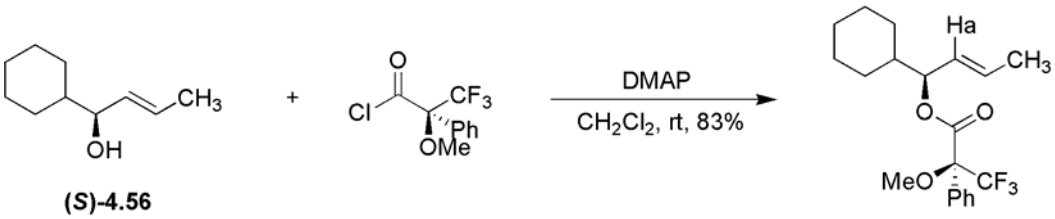
(*S*)-4.56

(*S*,*E*)-1-Cyclohexylbut-2-en-1-ol ((*S*)-4.56) To the lithium powder (1.19 g, 169.3 mmol) under argon was added dry ether (20 mL) and the suspension was cooled to –35 ºC. With stirring, a solution of (*E*)-1-bromo-propene (10.0 g, 82.6 mmol, in 40 mL ether) was added dropwise. The mixture was stirred at -35ºC for 2 h and treated dropwise with zinc bromide solution (19.5 g, 86.7 mmol). The reaction mixture was stirred for an additional 1 h at 0 ºC and then a solution of lithium (-)-N-methylephedrate, prepared by the addition of *n*-butyllithium (2.5 M in hexanes, 34.7 mL, 86.1 mmol) to a solution of (-)-N-methylephedrine (15.6 g, 86.7 mmol) in toluene (20 mL) at 0 ºC, was added by cannula. The solution was stirred for 1 h at 0 ºC and cyclohexanecarboxaldehyde (7.42 g,

66.1 mmol) was added neat. After stirring for 1 h at 0 ºC, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether (3 x 50 mL). The organic phases were combined, washed with a second portion of the ammonium chloride solution, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **(*S*)-4.56** (8.56 g, 84%, 92% ee. according to NMR study of Mosher ester) as clear liquid. (-)-N-methylephedrine was recovered quantitatively from the aqueous phases by basification to pH= 12 with 2 N NaOH solution and extraction into ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.66 (dqd, *J*= 15.2, 6.4, 0.8 Hz, 1H), 5.51-5.44 (ddq, *J*= 15.2, 7.6, 1.6 Hz, 1H), 3.78-3.73 (td, *J*= 7.2, 2.8 Hz, 1H), 1.87-1.83 (m, 1H), 1.77-1.63 (m, 8H), 1.42-0.85 (m, 6H), IR (neat) ν_{max} 3391 (br), 2929, 2853, 1650, 1448, 1002, 967.

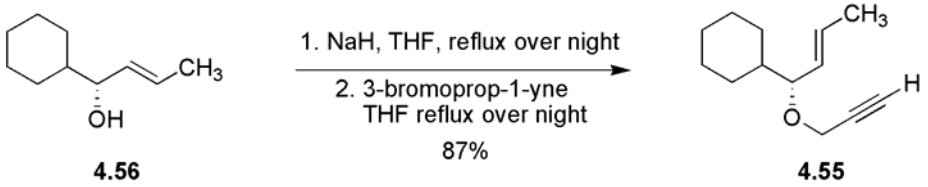


(*S*)-((*R*,*E*)-1-Cyclohexylbut-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate A sample of chiral allylic alcohol **4.56** (20 mg, 0.131 mmol) and DMAP (32 mg, 0.264 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (66 mg, 0.264 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 10: 1) through a silica gel column to give Mosher ester as a colorless oil (42 mg, 87%) for ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.42-7.35 (m, 3H), 5.88-5.79 (m, 0.95H, Ha), 5.77-5.73 (m, 0.05H, Ha), 5.48-5.42 (qd, *J*= 8.4, 1.6 Hz, 0.95H), 5.35-5.29 (qd, *J*= 8.4, 1.6 Hz, 0.05H), 5.24-5.20 (t, *J*=7.2, 1H), 3.55 (s, 3H), 1.74-1.54 (m, 9H), 1.26-1.11 (m, 4H), 0.92-0.89 (m, 2H).



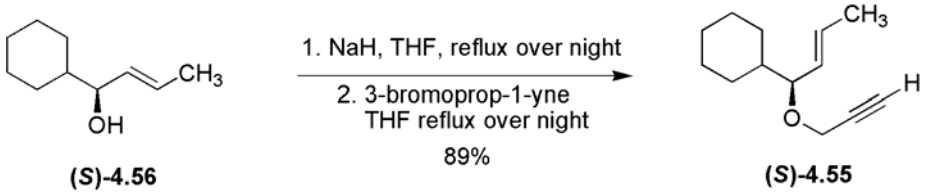
(*S*)-((*S*,*E*)-1-Cyclohexylbut-2-enyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate A sample of chiral allylic alcohol **(*S*)-4.56** (20 mg, 0.131 mmol) and DMAP (32 mg, 0.264 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (66 mg, 0.264 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was

washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 10: 1) through a silica gel column to give Mosher ester as a colorless oil (39 mg, 83%) for ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 2H), 7.42-7.35 (m, 3H), 5.88-5.79 (m, 0.03H, Ha), 5.77-5.73 (m, 0.97H, Ha), 5.48-5.42 (qd, *J*= 8.4, 1.6 Hz, 0.05H), 5.35-5.29 (qd, *J*= 8.4, 1.6 Hz, 0.95H), 5.24-5.20 (t, *J*= 7.2 Hz, 1H), 3.55 (s, 3H), 1.74-1.54 (m, 9H), 1.26-1.11 (m, 4H), 0.92-0.89 (m, 2H)..



4.56 **4.55**

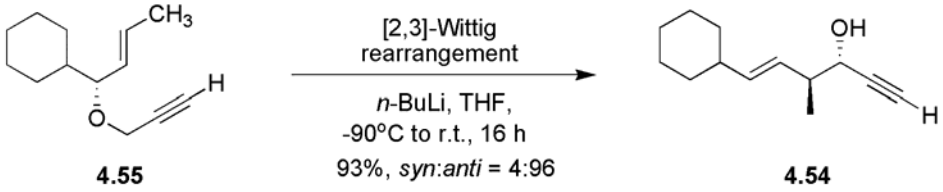
(*R*,*E*)-(1-(Prop-2-ynyloxy)but-2-enyl)cyclohexane (4.55) A 100-mL reaction flask was charged with 95% sodium hydride (1.31 g, 54.5 mmol) and 20 mL of dry THF. Then a sample of allylic alcohol **4.56** (1.20 g, 7.78 mmol) in 30 mL of THF was added dropwise. The mixture was refluxed over night. Then a sample of 3-bromoprop-1-yne (2.77 g, 23.3 mmol) was added slowly. The reaction mixture was refluxed overnight and cooled to room temperature. A 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL). The combined organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) produced ether **4.55** (1.32 g, 87%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.66-5.57 (dq, *J*= 15.2, 6.4 Hz, 1H), 5.27-5.19 (ddd, *J*= 15.2, 8.8, 1.6 Hz, 1H), 4.15-4.10 (dd, *J*= 15.6, 2.4 Hz, 1H), 3.98-3.93 (dd, *J*= 15.6, 2.4 Hz, 1H), 3.53-3.49 (t, *J*= 7.6 Hz, 1H), 2.34-2.32 (td, *J*= 4.8, 0.8 Hz, 1H), 1.92-1.88 (d, *J*= 12.8 Hz, 1H), 1.73-1.62 (m, 7H) , 1.46-1.37 (m, 1H) , 1.26-1.10 (m, 3H) , 1.00-0.85 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 130.27, 129.39, 84.21, 80.67, 73.21, 54.77, 42.22, 29.31, 28.93, 26.66, 26.15, 26.05, 17.75; IR (neat) ν_{max} 3308, 2925, 2853, 1650, 1449, 1073, 971, 734, 662, 625.



(*S*)-4.56 **(*S*)-4.55**

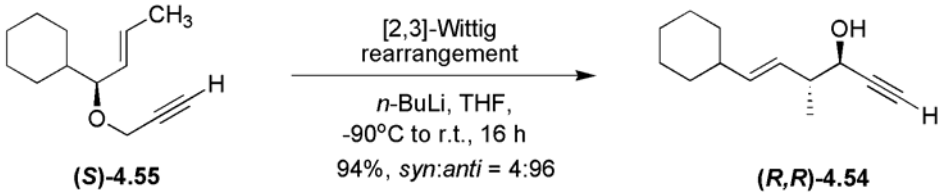
(*S*,*E*)-(1-(Prop-2-ynyloxy)but-2-enyl)cyclohexane ((*S*)-4.55) A 100-mL reaction flask was charged with 95% sodium hydride (1.31 g, 54.5 mmol) and 20 mL of dry THF. Then a sample of allylic alcohol **(*S*)-4.56** (1.20 g, 7.78 mmol) in 20 mL of THF was added dropwise. The mixture was refluxed over night. Then a sample of 3-bromoprop-1-yne (2.77 g, 23.3 mmol) was added slowly. The reaction mixture was refluxed overnight and cooled to room temperature. A 3 mL of water was added slowly to quench the excess sodium hydride. The mixture was poured into water and extracted with ether (3 x 30 mL).

The combined organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) produced ether **(*S*)-4.55** (1.32 g, 89%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66-5.57 (dq, *J*= 15.2, 6.4 Hz, 1H), 5.27-5.19 (ddd, *J*= 15.2, 8.8, 1.6 Hz, 1H), 4.15-4.10 (dd, *J*= 15.6, 2.4 Hz, 1H), 3.98-3.93 (dd, *J*= 15.6, 2.4 Hz, 1H), 3.53-3.49 (t, *J*= 7.6 Hz, 1H), 2.34-2.32 (td, *J*= 4.8, 0.8, 1H), 1.92-1.88 (d, *J*= 12.8, 1H), 1.73-1.62 (m, 7H) , 1.46-1.37 (m, 1H) , 1.26-1.10 (m, 3H) , 1.00-0.85 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 130.27, 129.39, 84.21, 80.67, 73.21, 54.77, 42.22, 29.31, 28.93, 26.66, 26.15, 26.05, 17.75; IR (neat) ν_{max} 3308, 2925, 2853, 1650, 1449, 1073, 971, 734, 662, 625.



4.55 **4.54**

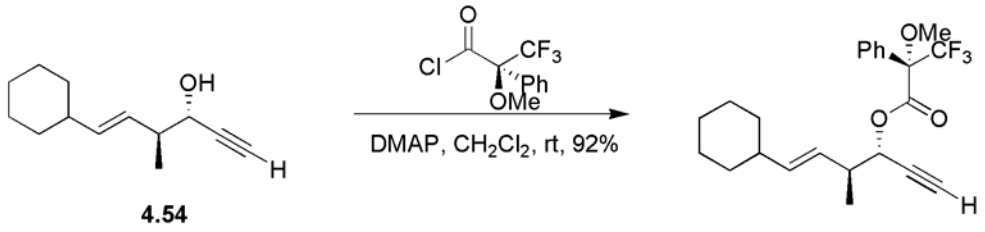
(3*S*,4*S*,*E*)-6-Cyclohexyl-4-methylhex-5-en-1-yn-3-ol (4.54) An aliquot of *n*-BuLi in hexane (1.6 M, 13.7 mL, 21.8 mmol) was evaporated in vacuo and the residue cooled to -90 °C. A solution of ether **4.55** (1.20 g, 6.24 mmol) in 20 mL of THF was slowly added. After the mixture was allowed to warm to room temperature overnight, the reaction was quenched with aqueous NH_4Cl. Extraction with Et_2O, drying, evaporation of the solvent, and purification of the residue on a silica gel column (HE: EA = 10:1) gave propargyl alcohol **4.54** (1.12 g, 93%, *syn*:*anti* = 4:96) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58-5.52 (dd, *J*= 15.6, 6.8 Hz, 1H), 5.34-5.28 (ddd, *J*= 15.6, 7.6, 1.2 Hz, 1H), 4.14-4.09 (m, 1H), 2.45-2.44 (d, *J*= 2.0 Hz, 1H), 2.40-2.37 (m, 1H), 1.96-1.92 (m, 2H), 1.72-1.60 (m, 7H) , 1.27-1.05 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.8, 127.56, 83.41, 73.49, 66.26, 43.46, 40.70, 33.06, 33.01, 26.11, 25.98, 15.81; IR (neat) ν_{max} 3380 (br), 3309, 2965, 2924, 2851, 1448, 1028, 971, 654, 628.



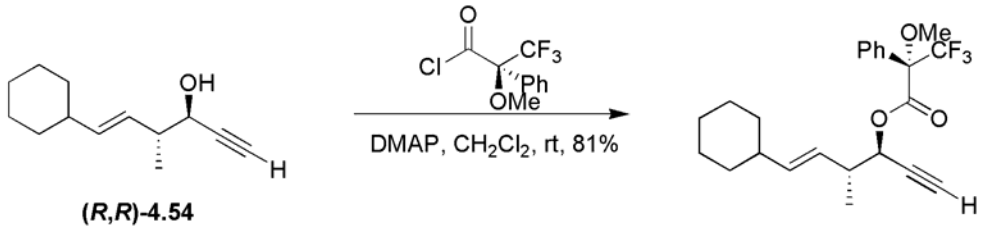
(*S*)-4.55 **(*R*,*R*)-4.54**

(3*R*,4*R*,*E*)-6-Cyclohexyl-4-methylhex-5-en-1-yn-3-ol ((*R*,*R*)-4.54) An aliquot of *n*-BuLi in hexane (2.5 M, 41.4 mL, 103.4 mmol) was evaporated in vacuo and the residue cooled to -90 °C. A solution of ether **(*S*)-4.55** (5.68 g, 29.5 mmol) in 20 mL of THF was slowly added. After the mixture was allowed to warm to room temperature overnight, the reaction was quenched with aqueous NH_4Cl. Extraction with Et_2O, drying, evaporation of the solvent, and purification of the residue on a silica gel column (HE: EA = 10:1) gave propargyl alcohol **(*R*,*R*)-4.46** (5.33 g, 94%, *syn*:*anti* = 2:98) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58-5.52 (dd, *J*= 15.6, 6.8 Hz, 1H), 5.34-5.28 (ddd, *J*= 15.6, 7.6, 1.2 Hz, 1H), 4.14-4.09 (m, 1H), 2.45-2.44 (d, *J*= 2.0 Hz, 1H), 2.40-2.37 (m, 1H),

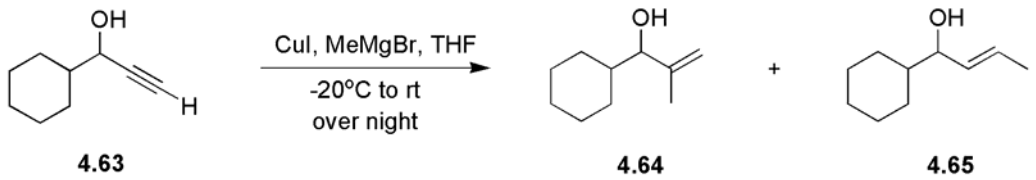
1.96-1.92 (m, 2H), 1.72-1.60 (m, 7H) , 1.27-1.05 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.8, 127.56, 83.41, 73.49, 66.26, 43.46, 40.70, 33.06, 33.01, 26.11, 25.98, 15.81; IR (neat) ν_{max} 3380 (br), 3309, 2965, 2924, 2851, 1448, 1028, 971, 654, 628.



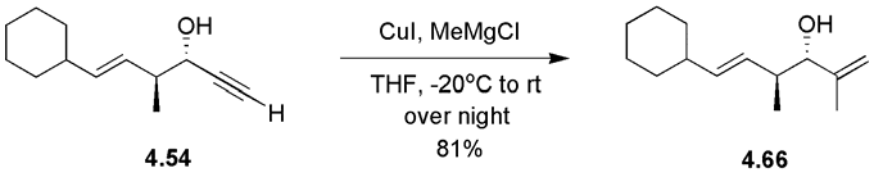
(*S*)-((3*S*,4*S*,*E*)-6-Cyclohexyl-4-methylhex-5-en-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate A sample of chiral propargyl alcohol **4.54** (20 mg, 0.104 mmol) and DMAP (25.4 mg, 0.208 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy- 2-phenylpropanoyl chloride (52.5 mg, 0.208 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 10: 1) through a silica gel column to give Mosher ester as a colorless oil (36.9 mg, 92%) for ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (bs, 0.89 H), 3.55 (bs, 0.11 H).



(*S*)-((3*R*,4*R*,*E*)-6-Cyclohexyl-4-methylhex-5-en-1-yn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate A sample of chiral propargyl alcohol **(*R*,*R*)-4.54** (20 mg, 0.104 mmol) and DMAP (25.4 mg, 0.208 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy- 2-phenylpropanoyl chloride (52.5 mg, 0.208 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 10: 1) through a silica gel column to give Mosher ester as a colorless oil (32.2 mg, 81%) for ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (bs, 0.13 H), 3.55 (bs, 0.87 H).

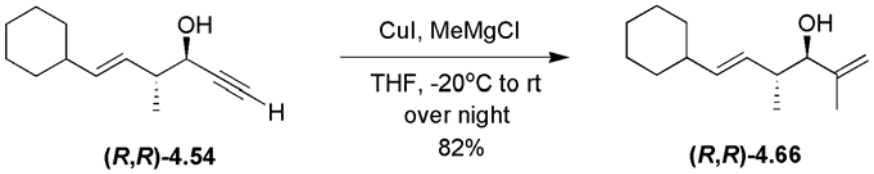


Carbocupration Approach with Model Compound 1-Cyclohexylprop-2-yn-1-ol (4.63) A 131 mg (0.689 mmol) of CuI was added to a dry round bottom flask under argon. Then 20 mL of dry THF was added. The mixture was cooled down to -20 ^{o}C. Then a sample of methylmagnesium bromide (0.531 ml, 3.0 M, 1.594 mmol) was added slowly over 5 min. The mixture was stirred for 20 mins at -20 ^{o}C. Then a sample of propargyl alcohol **4.63** (100 mg, 0.725 mmol) THF solution was added slowly. The reaction mixture was warmed up to room temperature in 1 h and stirred over night. The reaction was quenched with water and then extracted with ether (3 x 30 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Chromatography (HE: EA = 10:1) gave allylic alcohol **4.64** (27 mg, 24%), allylic alcohol **4.64** (23 mg, 21%) and starting material **4.63** (51.0 mg, 51%) as colorless oil. ^{1}H NMR of **4.64** (300 MHz, $CDCl_3$) δ 4.88-4.84 (m, 2H), 3.74-3.72 (d, *J*= 7.5 Hz, 1H), 1.95-1.90 (m, 1H), 1.80-1.38 (m, 7H), 1.30-1.10 (m, 5H), 1.03-0.88 (m, 2H); ^{1}H NMR of **4.65** (300 MHz, $CDCl_3$) δ 5.69-5.43 (m, 2H), 3.78-3.73 (dd, *J*= 6.9, 6.9 Hz, 1H), 1.88-1.82 (m, 1H), 1.78-1.62 (m, 7H), 1.42-1.09 (m, 5H), 1.03-0.88 (m, 2H).



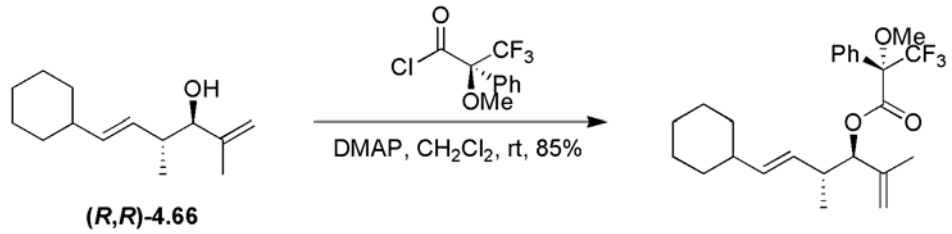
4.54 **4.66**

(3*S*,4*S*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-ol (4.66) A 2.00 g (10.52 mmol) of CuI was added to a dry round bottom flask under argon. Then 20 mL of dry THF was added. The mixture was cooled down to -20 ^{o}C. Then a sample of methylmagnesium chloride (7.01 ml, 3.0 M, 21.0 mmol) was added slowly over 5 min. The mixture was stirred for 20 mins at -20 ^{o}C. Then a sample of propargyl alcohol **4.54** (1.01 g, 5.26 mmol) THF solution was added slowly. The reaction mixture was warmed up to room temperature in 1 h and stirred over night. The reaction was quenched with water and then extracted with ether (3 x 30 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Chromatography (HE: EA = 10:1) gave allylic alcohol **4.66** (886 mg, 81%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.52 (dd, *J*= 15.6, 6.8 Hz, 1H), 5.26-5.20 (dd, *J*= 15.6, 7.6 Hz, 1H), 4.91-4.90 (d, *J*= 6.0 Hz, 2H), 3.67-3.64 (dd, *J*= 8.4, 2.3 Hz, 1H), 2.24-2.18 (m, 1H), 1.96-1.94 (m, 1H), 1.88-1.87 (d, *J*= 2.8 Hz, 1H), 1.71-1.62 (m, 8H), 1.30-0.85 (m, 8H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.02, 139.63, 129.08, 113.40, 79.51, 41.12, 40.78, 33.28, 33.19, 26.20, 26.08, 17.20, 17.04; IR (neat) ν_{max} 3420 (br), 3073, 2963, 2923, 2851, 1650, 1448, 1374, 1073, 1022, 977, 896.



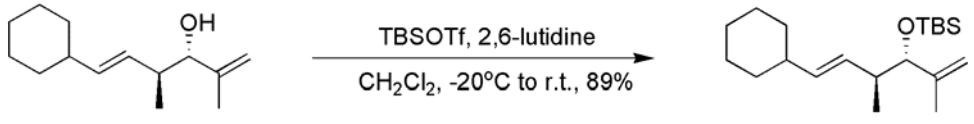
(*R*,*R*)-4.54 **(*R*,*R*)-4.66**

(3*R*,4*R*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-ol ((*R*,*R*)-4.66) A 9.01 g (47.3 mmol) of CuI was added to a dry round bottom flask under argon. Then 20 mL of dry THF was added. The mixture was cooled down to -20 ^{o}C. Then a sample of methylmagnesium chloride (31.6 ml, 3.0 M, 94.6 mmol) was added slowly over 5 min. The mixture was stirred for 20 mins at -20 ^{o}C. Then a sample of propargyl alcohol **(*R*,*R*)-4.54** (4.55 g, 23.7 mmol) THF solution was added slowly. The reaction mixture was warmed up to room temperature in 1 h and stirred over night. The reaction was quenched with water and then extracted with ether (3 x 30 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. Chromatography (HE: EA = 10:1) gave allylic alcohol **(*R*,*R*)-4.66** (4.04 g, 82%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.52 (dd, *J*= 15.6, 6.8 Hz, 1H), 5.26-5.20 (dd, *J*= 15.6, 7.6 Hz, 1H), 4.91-4.90 (d, *J*= 6.0 Hz, 2H), 3.67-3.64 (dd, *J*= 8.4, 2.3 Hz, 1H), 2.24-2.18 (m, 1H), 1.96-1.94 (m, 1H), 1.88-1.87 (d, *J*= 2.8 Hz, 1H), 1.71-1.62 (m, 8H), 1.30-0.85 (m, 8H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.02, 139.63, 129.08, 113.40, 79.51, 41.12, 40.78, 33.28, 33.19, 26.20, 26.08, 17.20, 17.04; IR (neat) ν_{max} 3420 (br), 3073, 2963, 2923, 2851, 1650, 1448, 1374, 1073, 1022, 977, 896.



(*R*,*R*)-4.66

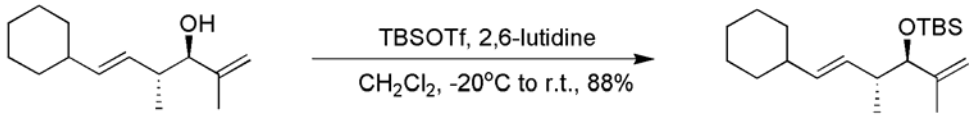
(*S*)-((3*R*,4*R*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate A sample of chiral allylic alcohol **(*R*,*R*)-4.66** (14 mg, 0.065 mmol) and DMAP (16 mg, 0.13 mmol) was dissolved in 2 mL of CH_2Cl_2 and (*R*)-3,3,3-trifluoro-2-methoxy- 2-phenylpropanoyl chloride (33 mg, 0.13 mmol) was added dropwise. After 2 h at room temperature, water (5 mL) and EtOAc (15 mL) were added. The organic phase was washed with saturated $NaHCO_3$ (2 x 5 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved and washed with solvent (HE: EA = 10: 1) through a silica gel column to give Mosher ester as a colorless oil (25 mg, 85%) for ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ. 3.545-3.542 (d, *J* = 1.2 Hz, 0.91 H), 3.510-3.507 (d, *J* = 1.2 Hz, 0.09 H).



4.66 4.68

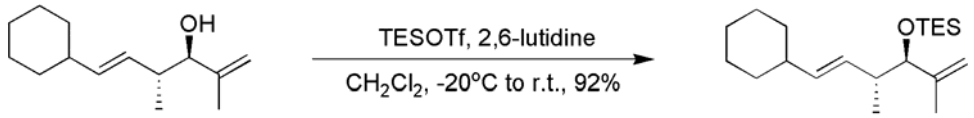
***tert*-Butyl((3*S*,4*S*,*E*)-6-cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yloxy)dimethylsilane (4.68)** A mixture of allylic alcohol **4.66** (500 mg, 2.40 mmol) and 2, 6-lutidine (1.54 g, 14.4 mmol) in 20 mL of CH_2Cl_2 was cooled to –20 ºC. Then a sample of *t*-$BuMe_2SiOTf$

(305 mg, 1.15 mmol) was added over 5 min. The mixture was stirred for 1 h at –20 ºC and 30 min at room temperature. The mixture was quenched with 20 mL saturated NH_4Cl aqueous solution and the aqueous phase was extracted with ether (3 x 30 mL). The combined organic solution was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine. The solution was then dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) gave TBS ether **4.68** as a colorless oil (687 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35-5.32 (m, 2H), 4.79-4.78 (m, 2H), 3.73-3.70 (d, *J*= 7.5 Hz, 1H), 2.19-2.17 (m, 1H), 1.93-1.84 (m, 1H), 1.73-1.62 (m, 8H), 1.32-0.84 (m, 17H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.9, 135.9, 130.7, 112.2, 81.8, 41.2, 41.1, 33.48, 33.47, 26.6, 26.5, 26.2, 18.6, 17.6, -4.3, -4.6; IR (neat) ν_{max} 2956, 2927, 2855, 1650, 1471, 1461, 1449, 1252, 1076, 898, 864, 836, 775.



(*R*,*R*)-4.66 **(*R*,*R*)-4.68**

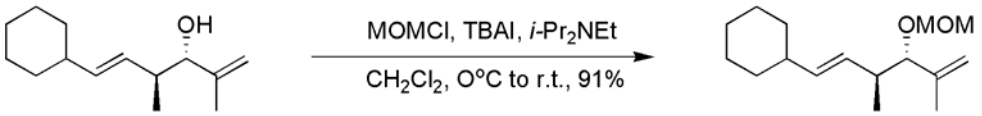
***tert*-Butyl((3*R*,4*R*,*E*)-6-cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yloxy)dimethylsilane ((*R*,*R*)-4.68)** A mixture of allylic alcohol **(*R*,*R*)-4.66** (2.40 g, 11.5 mmol) and 2, 6-lutidine (7.41 g, 69.1 mmol) in 20 mL of CH_2Cl_2 was cooled to –20 ºC. Then a sample of *t*-$BuMe_2SiOTf$ (12.2 g, 46.1 mmol) was added over 5 min. The mixture was stirred for 1 h at –20 ºC and 30 min at room temperature. The mixture was quenched with 20 mL saturated NH_4Cl aqueous solution and the aqueous phase was extracted with ether (3 x 30 mL). The combined organic solution was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine. The solution was then dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) gave TBS ether **(*R*,*R*)-4.68** as a colorless oil (3.26 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35-5.32 (m, 2H), 4.79-4.78 (m, 2H), 3.73-3.70 (d, *J*= 7.5 Hz, 1H), 2.19-2.17 (m, 1H), 1.93-1.84 (m, 1H), 1.73-1.62 (m, 8H), 1.32-0.84 (m, 17H), 0.02 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 146.9, 135.9, 130.7, 112.2, 81.8, 41.2, 41.1, 33.48, 33.47, 26.6, 26.5, 26.2, 18.6, 17.6, -4.3, -4.6; IR (neat) ν_{max} 2956, 2927, 2855, 1650, 1471, 1461, 1449, 1252, 1076, 898, 864, 836, 775.



4.66 **4.70**

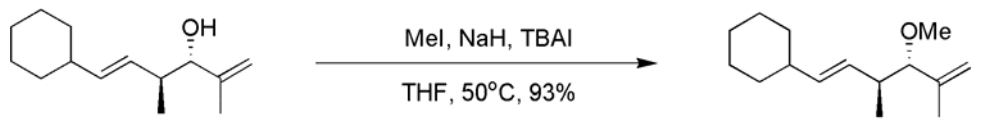
((3*S*,4*S*,*E*)-6-Cyclohexyl-2,4-dimethylhexa-1,5-dien-3-yloxy)triethylsilane (4.70) A mixture of allylic alcohol **4.66** (215 mg, 1.03 mmol) and 2, 6-lutidine (926 mg, 8.64 mmol) in 20 mL of CH_2Cl_2 was cooled to –20 ºC. Then a sample of TESOTf (1.52 g, 5.76 mmol) was added over 5 min. The mixture was stirred for 1 h at –20 ºC and 30 min at

room temperature. The mixture was quenched with 20 mL saturated NH_4Cl aqueous solution and the aqueous phase was extracted with ether (3 x 30 mL). The combined organic solution was washed with saturated NH_4Cl solution, saturated $NaHCO_3$ solution and brine. The solution was then dried over $MgSO_4$, filtered, and concentrated. Chromatography (HE: EA = 30: 1) gave TES ether **4.70** as a colorless oil (307 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42-5.28 (m, 2H), 4.81-4.77 (m, 2H), 3.75-3.72 (d, *J*= 10.0 Hz, 1H), 2.45-2.15 (m, 1H), 1.93-1.85 (m, 1H), 1.73-1.61 (m, 8H), 1.33-0.98 (m, 5H), 0.96-0.91 (t, *J*= 10.8 Hz, 9H), 0.85-0.83 (d, *J*= 9.2 Hz, 3H), 0.61-0.52 (q, *J*= 10.4 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 147.2, 136.0, 130.8, 112.3, 81.9, 41.1, 41.0, 33.5, 26.6, 26.5, 17.5, 17.4, 7.2, 5.2; IR (neat) ν_{max} 2955, 2924, 2876, 2852, 1449, 1073, 1014, 740.



4.66 **4.67**

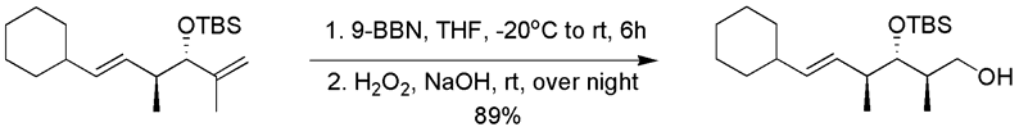
((3*S*,4*S*,*E*)-4-(Methoxymethoxy)-3,5-dimethylhexa-1,5-dienyl)cyclohexane (4.67) A sample of MOMCl (155 mg, 146 μL, 1.92 mmol) was added drop wise *via* syringe to a solution of allylic alcohol **4.66** (80 mg, 0.38 mmol) and Bu_4NI (14 mg, 0.039 mmol) in 8 mL of CH_2Cl_2 at 0 ºC, followed by addition of *i*-Pr_2NEt (248 mg, 335 μL, 1.92 mmol). The resulting mixture was stirred at 0 ºC for 2 h and then at ambient temperature for 16 h. A saturated solution of sodium carbonate (4 mL) was added to quench the reaction. The aqueous phase was extracted with ether (25 mL x 3) and the organic phases were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave MOM ether **4.67** as a colorless oil (88 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46-5.34 (m, 2H), 4.96 (br s, 1H), 4.88 (br s, 1H), 4.62-4.43 (AB, 2H), 3.69-3.66 (d, *J*= 8.8 Hz, 1H), 3.34 (s, 3H), 2.31-2.25 (m, 1H), 1.92-1.90 (m, 1H), 1.71-1.68 (m, 4H), 1.63 (s, 3H), 1.29-1.10 (m, 6H), 0.86-0.85 (d, *J*= 6.9 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 142.7, 136.2, 130.5, 115.4, 93.4, 84.4, 55.5, 40.7, 38.9, 31.1, 26.2, 26.1, 17.5, 16.8; IR (neat) ν_{max} 2956, 2927, 2855, 1650, 1471, 1461, 1449, 1252, 1076, 898, 864, 836, 775.



4.66 **4.69**

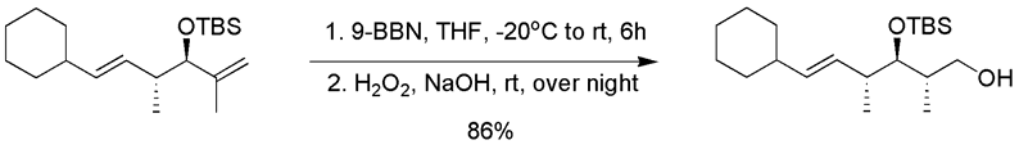
((3*S*,4*S*,*E*)-4-Methoxy-3,5-dimethylhexa-1,5-dienyl)cyclohexane (4.69) To a mixture of the allylic alcohol **4.66** (312 mg, 1.50 mmol) and sodium hydride (108 mg, 4.50 mmol) in dry THF (40 mL) were added methyl iodide (1.28 g, 9.00 mmol) followed by tetrabutylammonium iodide (33 mg, 0.09 mmol) at room temperature. After stirring for 16 h at 60 ^{o}C, the reaction was quenched with saturated NH_4Cl at 0 ^{o}C and the mixture

was separated. The organic layer was washed with brine and the aqueous layers were extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (HE: EA = 30:1) to give the methyl ether **4.69** (310 mg, 93%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39-5.34 (m, 2H), 4.95 (br s, 1H), 4.85 (br s, 1H), 3.18 (s, 3H), 3.16 (S, 3H), 2.26-2.21 (m, 1H), 1.92-1.89 (m, 1H), 1.71-1.58 (m, 6H), 1.30-1.01 (m, 7H), 0.85-0.84 (d, J= 7.2 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 143.3, 135.9, 130.4, 114.6, 90.6, 56.5, 40.8, 39.0, 33.4, 33.3, 26.4, 26.2, 17.4; IR (neat) ν_{max} 2963, 2926, 2852, 1650, 1449, 1260, 1095, 1020, 802.



4.68 **TBS-4.52**

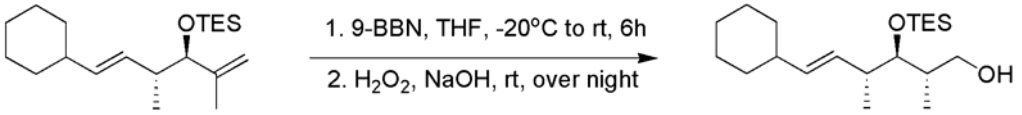
(2*R*,3*S*,4*S*,E)-3-(*tert*-Butyldimethylsilyloxy)-6-cyclohexyl-2,4-dimethylhex-5-en-1-ol (TBS-4.52) To the silyl ether **4.68** (672 mg, 2.09 mmol) in 20 mL of THF was added 9-BBN (0.5 M in THF, 12.5 mL, 6.26 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued for 6 h. TLC showed the completion of the reaction. Then 3 mL of 3 N NaOH (aq) was added and this was followed by 3 mL of 30wt% H_2O_2 (aq). The resulting mixture was stirred over night at room temperature and then poured into 40 mL of ether and 20 mL of saturated aqueous sodium chloride. The aqueous phase was extracted with ether and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **TBS-4.52** as a colorless oil (632 mg, 89%).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.23 (m, 2H), 3.52-3.51 (d, J= 5.6 Hz, 2H), 3.49-3.47 (dd, J= 5.6, 4.0 Hz, 1H), 2.72 (br s, 1H), 2.29-2.25 (m, 1H), 1.87-1.76 (m, 2H), 1.66-1.54 (m, 5H), 1.51-1.45 (m, 3H), 1.31-1.10 (m, 7H), 0.92 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (400 MHz, CDCl3) δ 136.01, 129.49, 80.69, 65.94, 41.92, 40.68, 37.66, 33.02, 32.97, 27.10, 25.96, 16.54, 15.88, -4.17, -4.26; IR (neat) ν_{max} 3420, 2955, 2927, 2854, 1693, 1462, 1449, 1253, 1083, 1029, 973, 836, 774.



(*R*,*R*)-4.68 **TBS-4.57**

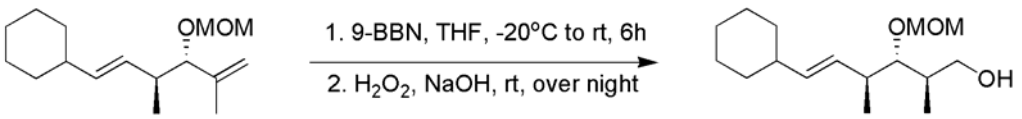
(2*S*,3*R*,4*R*,E)-3-(*tert*-Butyldimethylsilyloxy)-6-cyclohexyl-2,4-dimethylhex-5-en-1-ol (TBS-4.57) To the silyl ether **(*R*,*R*)-4.68** (3.20 g, 9.94 mmol) in 30 mL of THF was added 9-BBN (0.5 M in THF, 59.6 mL, 29.8 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued for 6 h. TLC showed the completion of the reaction. Then 12 mL of 3 N NaOH (aq) was added and this was

followed by 12 mL of 30 wt% H_2O_2 (aq). The resulting mixture was stirred for 12 hours at room temperature and then poured into 40 mL of ether and 20 mL of brine. The aqueous phase was extracted with ether and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **TBS-4.57** as a colorless oil (2.91 g, 86%).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34-5.23 (m, 2H), 3.52-3.51 (d, *J*= 5.6 Hz, 2H), 3.49-3.47 (dd, *J*= 5.6, 4.0 Hz, 1H), 2.72 (br s, 1H), 2.29-2.25 (m, 1H), 1.87-1.76 (m, 2H), 1.66-1.54 (m, 5H), 1.51-1.45 (m, 3H), 1.31-1.10 (m, 7H), 0.92 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (400 MHz, CDCl3) δ 136.01, 129.49, 80.69, 65.94, 41.92, 40.68, 37.66, 33.02, 32.97, 27.10, 25.96, 16.54, 15.88, -4.17, -4.26; IR (neat) ν_{max} 3420, 2955, 2927, 2854, 1693, 1462, 1449, 1253, 1083, 1029, 973, 836, 774.



4.70 **TES-4.57**

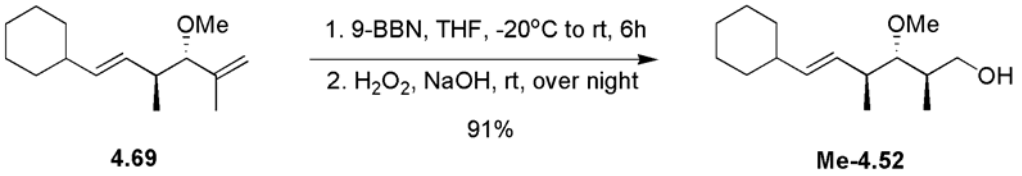
(2*S*,3*R*,4*R*,*E*)-6-Cyclohexyl-2,4-dimethyl-3-(triethylsilyloxy)hex-5-en-1-ol (TES-4.57) To the silyl ether **4.70** (283 mg, 0.879 mmol) in 10 mL of THF was added 9-BBN (0.5 M in THF, 5.28 mL, 2.64 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued for 6 h. TLC showed the completion of the reaction. Then 2 mL of 3 N NaOH (aq) was added and this was followed by 2 mL of 30 wt% H_2O_2 (aq). The resulting mixture was stirred over night at room temperature and then poured into 40 mL of ether and 20 mL of brine. The aqueous phase was extracted with ether (3 x 30 mL) and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave **TES-4.57** as a colorless oil (278 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39-5.23 (m, 2H), 3.64-3.48 (m, 3H), 2.66 (br s, 1H), 2.36-2.28 (m, 1H), 1.92-1.77 (m, 2H), 1.71-1.59 (m, 6H), 1.31-0.81 (m, 19H), 0.67-0.59 (q, *J*= 11.6 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 136.4, 129.7, 81.8, 66.2, 42.0, 40.7, 37.3, 33.1, 26.2, 26.0, 16.5, 15.8, 6.9, 5.2; IR (neat) ν_{max} 3354 (br), 2956, 2925, 2876, 1449, 1029, 1015, 973, 738.



4.67 **MOM-4.52**

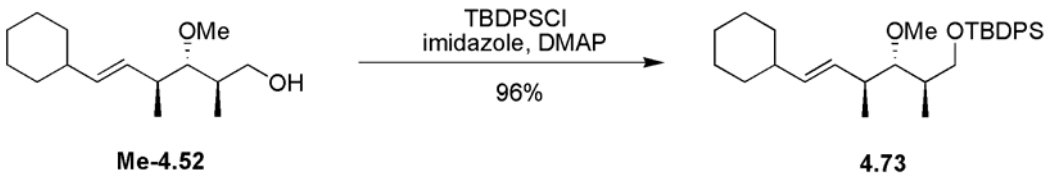
(2*R*,3*S*,4*S*,*E*)-6-Cyclohexyl-3-(methoxymethoxy)-2,4-dimethylhex-5-en-1-ol (MOM -4.52) To the MOM ether **4.67** (80 mg, 0.317 mmol) in 5 mL of THF was added 9-BBN (0.5 M in THF, 1.90 mL, 0.952 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued for 6 h. TLC showed the completion of the reaction. Then 3 mL of 3 N NaOH (aq) was added and this was followed by 3 mL of 30 wt% H_2O_2 (aq). The resulting mixture was stirred for 12 hours at

room temperature and then poured into 40 mL of ether and 20 mL of saturated aqueous sodium chloride. The aqueous phase was extracted with ether and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 10: 1) gave alcohol **MOM-4.52** as a colorless oil (79 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37-5.27 (m, 2H), 4.67-4.64 (t, *J*= 7.5 Hz, 2H), 3.81-3.78 (dd, *J*= 11.5, 2.0 Hz,1H), 3.48-3.45 (dd, *J*= 11.0, 3.0 Hz, 1H), 3.40 (s, 3H), 3.29-3.27 (dd, *J*= 8.0, 2.0 Hz, 1H), 2.69 (br s, 1H), 2.34-2.33 (m, 1H), 1.89-1.88 (m, 1H), 1.75 (br s, 1 H), 1.68-1.59 (m, 5H), 1.26-1.19 (q, *J*= 12.5 Hz, 2H), 1.15-1.10 (t, *J*= 12.5 Hz, 1H), 1.07-1.00 (m, 5H), 0.94-0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.1, 128.5, 98.8, 86.9, 65.2, 56.2, 40.7, 39.8, 37.6, 33.1, 26.1, 26.0, 18.2, 14.8; IR (neat) ν_{max} 3453 (br), 2961, 2925, 2851, 1449, 1144, 1094, 1033, 978, 920.



4.69 **Me-4.52**

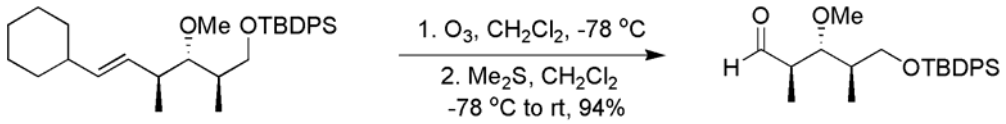
(2*R*,3*S*,4*S*,*E*)-6-Cyclohexyl-3-methoxy-2,4-dimethylhex-5-en-1-ol (Me-4.52) To the methyl ether **4.69** (314 mg, 1.41 mmol) in 5 mL of THF was added 9-BBN (0.5 M in THF, 8.48 mL, 4.24 mmol) at –20 ºC. After 10 min the reaction mixture was warmed to room temperature and stirring was continued for 6 h. TLC showed the completion of the reaction. Then 3 mL of 3 N NaOH (aq) was added and this was followed by 3 mL of 30 wt% H_2O_2 (aq). The resulting mixture was stirred for 12 hours at room temperature and then poured into 40 mL of ether and 20 mL of brine. The aqueous phase was extracted with ether and the organic solutions were combined, dried ($MgSO_4$), and concentrated. Chromatography (HE: EA = 5: 1) gave alcohol **Me-4.52** as a colorless oil (307 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41-5.31 (m, 2H), 3.65-3.60 (m, 2H), 3.46 (s, 3H), 2.95-2.92 (dd, *J*= 7.6, 4.4 Hz, 1H), 2.39-2.38 (m, 1H), 2.17-2.15, (m, 2H), 1.95-0.85 (m, 15H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.0, 129.2, 91.7, 66.8, 61.2, 41.0, 40.1, 37.8, 33.5, 27.7, 26.5, 26.4, 18.1; IR (neat) ν_{max} 3379 (br), 2924, 2925, 2853, 1449, 1094, 1056, 979.



Me-4.52 **4.73**

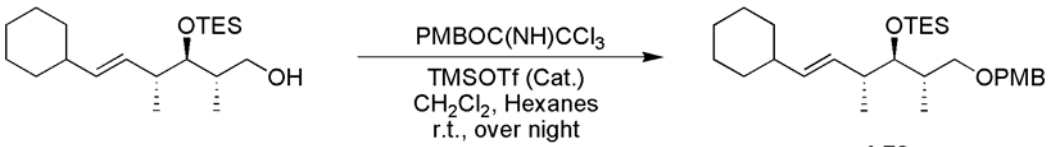
***tert*-Butyl((2*R*,3*S*,4*S*,*E*)-6-cyclohexyl-3-methoxy-2,4-dimethylhex-5-enyloxy)diphenyl silane (4.73)** To a mixture of **Me-4.52** (236 mg, 0.982 mmol), DMAP (12 mg, 0.098 mmol) and imidazole (201 mg, 2.95 mmol) in CH_2Cl_2 (15 mL) was added *tert*-butyldiphenylsilyl chloride (405 mg, 1.47 mmol) at room temperature. After stirring for 30 min, the reaction mixture was quenched with saturated $CuSO_4$ and separated. The

organic layer was washed with brine and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (HE: EA = 30:1) to give the silyl ether **4.73** as a colorless oil (454 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.43-7.34 (m, 6H), 5.32-5.30 (m, 2H), 3.77-3.64 (AB, 2H), 3.37 (s, 3H), 2.98-2.95 (dd, *J*= 8.0, 3.6 Hz, 1H), 2.33-2.27 (m, 1H), 1.91-1.85 (m, 1H), 1.77-1.60 (m, 6H), 1.28-0.95 (m, 17H), 0.94-2.92 (d, *J*= 7.2 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 136.6, 135.9, 135.8, 129.6, 129.6, 127.7, 87.4, 65.8, 61.2, 40.1, 39.7, 33.5, 27.3, 26.5, 26.4, 19.7, 19.0, 14.7; IR (neat) ν_{max} 2960, 2927, 2855, 1428, 1110, 701.



4.73 **4.14 Segment B2**

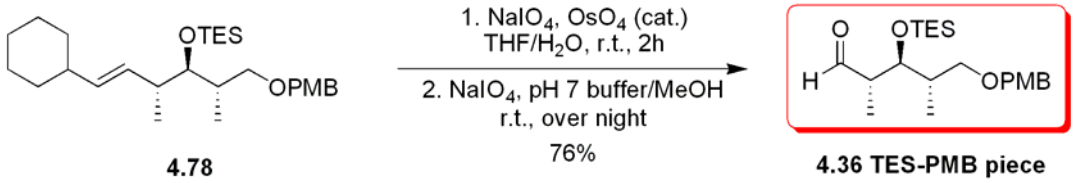
(2*R*,3*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methoxy-2,4-dimethylpentanal (4.14, Segment B2) A solution of alcohol **4.73** (134 mg, 0.280 mmol) in CH_2Cl_2 (6 mL) cooled to -78 oC was flushed with O_3. After its color turned to blue, the solution was flushed with argon for 10 min at –78 ºC. Then dimethyl sulfide (1.0 mL) was added. After 1 h at –78 ºC and 6 h at room temperature, the mixture was concentrated to give a colorless oil. The resulting oil was subjected to column chromatography (HE: EA = 10:1) to give aldehyde **4.14** as a clear liquid (105mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76-9.75 (d, *J*= 2.4 Hz, 1H), 7.69-7.63 (m, 4H), 7.45-7.36 (m, 6H), 3.77-3.66 (AB, 2H), 3.50-3.47 (dd, *J*= 6.8, 4.8 Hz, 1H), 3.37 (s, 3H), 2.71-2.64 (m, 1H), 2.00-1.94 (m, 1H), 1.13-1.11 (d, *J*= 7.2 Hz, 3H), 1.08 (s, 9H), 0.95-0.93 (d, *J*= 6.8 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 204.3, 135.55, 135.51, 133.59, 133.52, 129.5, 127.6, 84.1, 65.2, 59.6, 48.3, 38.3, 27.0, 19.4, 14.1, 11.2; IR (neat) ν_{max} 2961, 2932, 2892, 2958, 1725, 1428, 1111, 1089, 702.



TES-4.57 **4.78**

((2*R*,3*S*,4*S*,*E*)-6-Cyclohexyl-1-(4-methoxybenzyloxy)-2,4-dimethylhex-5-en-3-yloxy)triethylsilane (4.78) To a solution of **4.57** (180 mg, 0.529 mmol) and 4-methoxybenzyl trichloroacetimidate (299 mg, 1.06 mmol) in anhydrous CH_2Cl_2 (10 mL) and anhydrous hexane (5 mL) under Ar, was added TMSOTf (12 mg, 0.053 mmol) and the reaction was stirred over night. The mixture was quenched with a pH 7 buffer. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (HE: EA = 30:1) on silica gel gave **4.78** (212 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (d, *J*= 8.0 Hz, 2H), 6.89-6.87 (d, *J*= 8.0 Hz, 2H), 5.44-5.38 (dd, *J*= 15.6, 8.0 Hz,

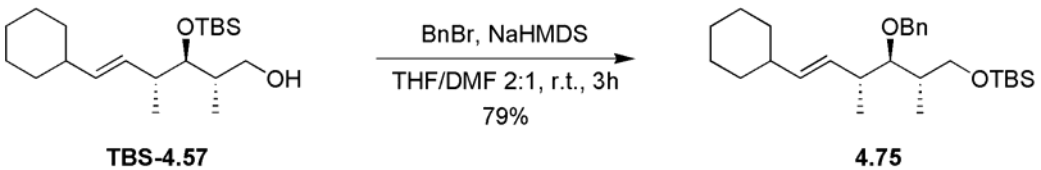
1H), 5.32-5.26 (dd, *J*= 15.6, 6.8 Hz, 1H), 4.45-4.38 (AB, 2H), 3.80 (S, 3H), 3.54-3.48 (m, 2H), 3.31-3.27 (dd, *J*= 8.4, 8.0 Hz, 1H), 2.29-2.23 (m, 1H), 1.92-1.87 (m, 1H), 1.71-1.62 (m, 6H), 1.31-0.87 (m, 19H), 0.63-0.57 (q, *J*= 8.0 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.1, 136.0, 131.1, 129.9, 129.3, 113.8, 78.8, 72.93, 72.87, 55.5, 41.05, 41.01, 38.2, 33.44, 33.40, 26.56, 26.41, 18.9, 15.3, 7.42, 5.81, 5.75; IR (neat) ν_{max} 2956, 2926, 2876, 2853, 1613, 1513, 1247, 1087, 1038, 1010, 736, 723.



4.78 **4.36 TES-PMB piece**

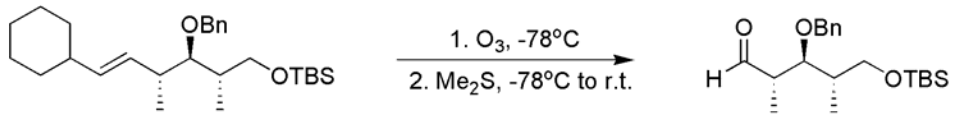
(2*S*,3*S*,4*S*)-5-(4-Methoxybenzyloxy)-2,4-dimethyl-3-(triethylsilyloxy)pentanal (4.36)
To a solution of alkene **4.78** (20 mg, 0.043 mmol) in a mixture of H_2O/THF (2 mL / 8 mL) was added OsO4 (4 % aqueous solution, 28 mg, 0.0043 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 min. To the reaction mixture was then added a solution of sodium periodate (100 mg, 0.467 mmol) over a 2 h interval. After that, a 20 ml of $Na_2S_2O_3$ (sat) was added to the mixture, and the aqueous layer was then extracted with Et_2O (3 x 30 ml). The organic layers were combined, washed with H_2O (30 ml), brine (30 ml, sat), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude diol

Then the crude diol was dissolved in a mixture of MeOH/pH 7 buffer (3 mL/2 mL). Then a 100 mg sodium periodate (0.467 mmol) was added in one portion. The reaction mixture was stirred at room temperature over night. After that, a 20 ml of $Na_2S_2O_3$ (sat) was added to the mixture, and the aqueous layer was then extracted with Et_2O (3 x 30 ml). The organic layers were combined, washed with H_2O (30 ml), brine (30 ml, sat), dried over $MgSO_4$ and concentrated under reduced pressure. The resulted oil was subjected to flash chromatography (HE: EA= 10:1) to give aldehyde **4.36** as a colorless oil (12.8 mg, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.762-9.755(d, *J*= 2.8 Hz, 1H), 7.25-7.23 (d, *J*= 8.8 Hz, 2H), 6.89-6.86 (d, *J*= 8.8 Hz, 2H), 4.45-4.37 (AB, 2H), 3.98-3.95 (dd, *J*= 5.6, 4.0 Hz, 1H), 3.81 (s, 3H), 3.48-3.31 (AB, 2H), 3.31-3.27 (dd, *J*= 8.4, 8.0 Hz, 1H), 2.57-2.53 (m, 1H), 2.06-2.00 (m, 1H), 1.11-1.09 (d, *J*= 7.2 Hz, 2H), 0.96-0.92 (m, 12H), 0.63-0.57 (q, *J*= 8.0 Hz, 6H); IR (neat) ν_{max} 2959, 2925, 1725, 1613, 1513, 1461, 1249, 1087, 1037, 807, 741.



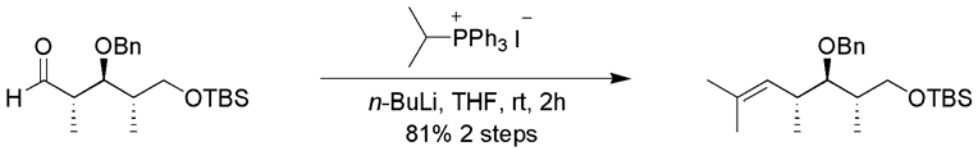
TBS-4.57 **4.75**

((2*S*,3*R*,4*R*,*E*)-3-(Benzyloxy)-6-cyclohexyl-2,4-dimethylhex-5-enyloxy)(*tert*-butyl)dimethylsilane (4.75) To a solution of **4.57** (873 mg, 2.57 mmol) and benzyl bromide (1.32 g, 7.71 mmol) in THF/DMF (2:1, 30 ml) cooled at 0 °C was added NaHMDS (2.0 M, 2.57 ml, 5.14 mmol). The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 3 h. The reaction was quenched with saturated NH_4Cl solution (30 ml) and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with brine (20 ml), dried, filtered and concentrated. Flash column chromatography on silica gel (HE: EA = 30:1) afforded **4.75** (872 mg, 79% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.44-5.32 (m, 2H), 4.59 (s, 2H), 3.72-3.60 (AB, 2H), 3.23-3.19 (dd, *J*= 10.8, 4.4 Hz, 1H), 2.41-2.37 (m, 1H), 1.98-1.84 (m, 1H), 1.70-1.67 (m, 1H), 1.27-1.19 (m, 8H), 1.09-1.07 (d, *J*= 9.2 Hz, 3H), 0.91-0.89 (d, *J*= 9.2 Hz, 3H), 0.91 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.5, 136.6, 129.7, 128.4, 127.7, 127.4, 85.4, 75.0, 65.2, 41.1, 40.0, 39.2, 33.6, 30.7, 30.0, 26.6, 19.3, 18.7, 14.8, -4.96, -5.05; IR (neat) ν_{max} 2959, 2927, 2856, 1451, 1252, 1090, 1050, 835, 775, 733, 697.



4.75 **4.75a**

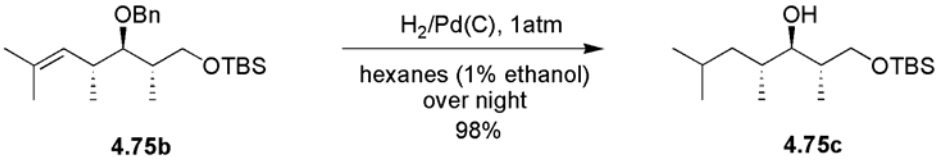
(2*S*,3*S*,4*S*)-3-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanal (4.75a) A solution of alcohol **4.75** (692 mg, 1.61 mmol) in CH_2Cl_2 (15 mL) cooled to -78 °C was flushed with O_3. After its color turned to blue, the solution was flushed with argon for 10 min at –78 ºC. Then dimethyl sulfide (2.0 mL) was added. After 1 h at – 78 ºC and 6 h at room temperature, the mixture was concentrated to give aldehyde **4.75a** as a colorless oil. The resulting oil was directly used in the next step.



4.75a **4.75b**

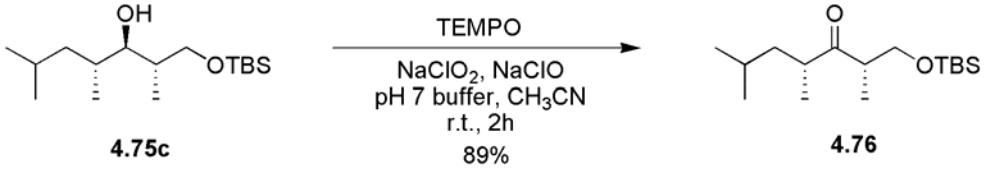
((2*S*,3*R*,4*R*)-3-(Benzyloxy)-2,4,6-trimethylhept-5-enyloxy)(*tert*-butyl)dimethylsilan (4.75b) A sample of *n*-BuLi (6.12 mL, 2.5 M in hexane, 15.3 mmol) was added dropwise to a suspension of isopropyltriphenylphosphonium iodide (6.96 g, 16.1 mmol) in dry THF (30 mL) at room temperature. The resulting red solution was stirred at room temperature for 30 min. A solution of the crude aldehyde **4.75a** in dry THF (10 mL) was introduced via cannula. After 2 h the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, dried and concentrated. The residue was subjected to column chromatography (HE: EA = 30:1) to afford **4.75b** (491 mg, 81% 2 steps). ^{1}H NMR (400

MHz, $CDCl_3$): δ 7.42-7.38 (m, 5H), 5.33-5.31 (d, *J*= 9.6 Hz, 1H), 4.70-4.64 (m, 2H), 3.80-3.67 (AB, 2H), 3.35-3.32 (dd, *J*= 8.4, 3.2 Hz, 1H), 2.76-2.70 (m, 1H), 1.86-1.79 (m, 1H), 1.75 (s, 3H), 1.67 (s, 3H), 1.12-1.11 (d, *J*= 6.8 Hz, 3H), 1.01 (s, 9H), 1.00-0.99 (d, *J*= 6.4 Hz, 3H), 0.14 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.2, 137.7, 133.5, 129.0, 128.2, 127.3, 85.3, 74.8, 64.9, 38.9, 35.1, 26.0, 25.9, 18.0, 16.2, 14.6, -5.2, -5.3; IR (neat) ν_{max} 2957, 2928, 2857, 1471, 1454, 1252, 1089, 1065, 835, 775, 733, 697.



4.75b **4.75c**

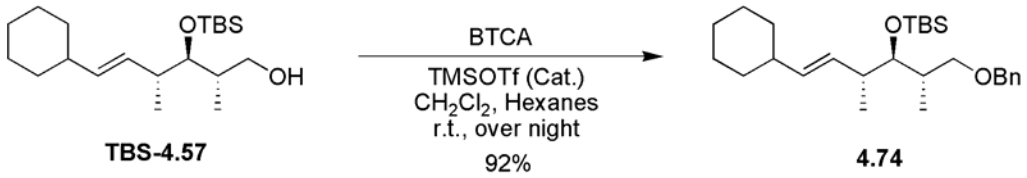
(2*S*,3*R*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptan-3-ol (4.75c) A solution of **4.75b** (80.0 mg, 0.213 mmol) in hexanes (1% ethanol) was hydrogenated in the presence of a Pd/C (425 mg, 5 wt%, 0.202 mmol) for 2 days in H_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (HE: EA = 10:1) gave **4.75c** as a colorless oil (59.6 mg, 98%); ^1H NMR (400 MHz, $CDCl_3$): δ 3.81-3.78 (dd, *J*= 10.0, 4.0 Hz, 1H), 3.69-3.68 (d, *J*= 3.6 Hz, 1H), 3.60-3.56 (dd, *J*= 10.0, 7.6 Hz, 1H), 3.32-3.29 (m, 1H), 1.85-1.82 (m, 1H), 1.68-1.62 (m, 1H), 1.29-1.15 (m, 3H), 0.95-0.93 (d, *J*= 7.2 Hz, 3H), 0.93-0.91 (d, *J*= 6.8 Hz, 3H), 0.90 (s, 9H), 0.85 (s, 3H), 0.83 (s, 3H), 0.08 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 81.8, 68.7, 39.0, 36.6, 33.5, 25.9, 25.3, 24.5, 21.3, 18.2, 17.0, 13.9, -5.51, -5.55; IR (neat) ν_{max} 3505, 2956, 2930, 2859, 1468, 1386, 1255, 1078, 837, 777.



4.75c **4.76**

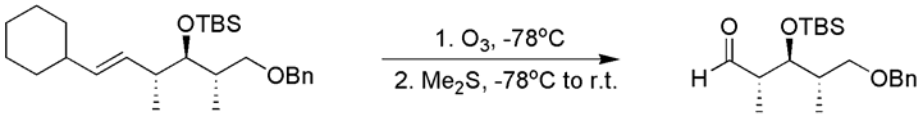
(2*S*,4*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptan-3-one (4.76) To a solution of **4.75** (10.0 mg, 0.0350 mmol) in acetonitrile (3.0 mL) and aqueous Na_2HPO_4/NaH_2PO_4 pH 7.0 buffer (2.0 mL) was added TEMPO (3 mg, 0.017 mmol). A water solution of sodium chlorite (16 mg, 0.175 mmol) and sodium hypochlorite (2.5 mg, 5 wt%, 0.07 mmol) was added simultaneously over 1 hour. Reaction stirred at room temperature for 2 h. The mixture was diluted with water (10ml). The reaction was quenched by pouring into 0 °C Na_2SO_3 solution. The aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to column chromatography (HE: EA = 10:1) to afford **4.76** (8.8 mg, 89%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.81-3.77 (dd, *J*= 9.6, 8.0 Hz, 1H), 3.53-3.50 (dd, *J*= 9.6, 5.6 Hz, 1H), 2.96-2.87 (qt, *J*= 7.2, 6.4 Hz, 1H), 2.74-2.66 (qt, *J*= 6.8, 6.4 Hz, 1H), 1.60-1.52 (m, 2H), 1.25-1.08 (m, 1H), 1.05-1.04 (d, *J*= 7.2 Hz, 3H), 1.02-1.00 (d, *J*= 7.2 Hz, 3H), 0.91-0.89

(d, *J*= 6.4 Hz, 3H), 0.87-0.86 (d, *J*= 6.0 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 217.2, 65.5, 47.4, 43.9, 41.4, 25.9, 23.3, 22.1, 18.2, 16.1, 13.8, -5.5, -5.6; IR (neat) ν_{max} 2958, 2930, 1713, 1465, 1258, 1097, 838, 778.



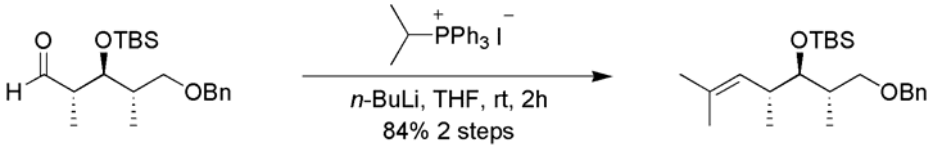
TBS-4.57 **4.74**

((2*S*,3*R*,4*R*,*E*)-1-(Benzyloxy)-6-cyclohexyl-2,4-dimethylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (4.74) To a solution of **4.57** (1 g, 2.94 mmol) and benzyl trichloroacetimidate (1.49 g, 5.88 mmol) in anhydrous CH_2Cl_2 (20 mL) and anhydrous hexane (10 mL) under Ar, was added TMSOTf (65 mg, 0.294 mmol) and the reaction was stirred over night. The mixture was quenched with a pH 7 buffer. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was dried over $MgSO_4$, and evaporated under reduced pressure. Purification by flash chromatography (HE: EA = 30:1) on silica gel gave **4.74** (1.16 g, 92 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.36 (m, 5H), 5.45-5.39 (ddd, *J*= 15.6, 8.0, 0.8 Hz, 1H), 5.30-5.25 (dd, *J*= 15.6, 6.4 Hz, 1H), 4.52-4.44 (AB, 2H), 3.56-3.50 (AB, 2H), 3.31-3.27 (dd, *J*= 9.2, 8.0 Hz, 1H), 2.31-2.26 (m, 1H), 1.98-1.84 (m, 1H), 1.73-1.62 (m, 6H), 1.28-1.13 (m, 5H), 0.99-0.97 (d, *J*= 7.2 Hz, 3H), 0.95-0.94 (d, *J*= 6.8 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.1, 135.8, 130.2, 128.4, 127.7, 127.5, 78.3, 13.3, 73.2, 41.2, 41.0, 38.3, 33.4, 26.6, 26.4, 18.9, 18.7, 15.3, -3.6, -3.8; IR (neat) ν_{max} 2957, 2926, 2854, 1471, 1452, 1362, 1253, 1088, 1048, 1031, 836, 773, 734, 697.



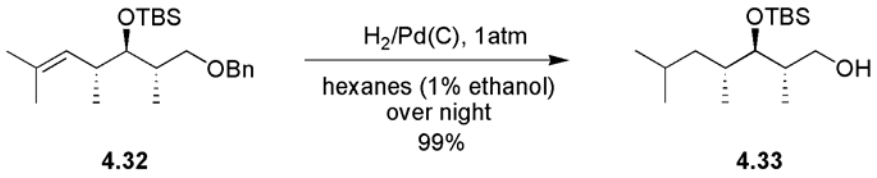
4.74 **4.31**

(2*S*,3*S*,4*S*)-5-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentanal (4.31) A solution of alcohol **4.74** (107 mg, 0.249 mmol) in CH_2Cl_2 (15 mL) cooled to -78 ^{o}C was flushed with O_3. After its color turned to blue, the solution was flushed with argon for 10 min at –78 ºC. Then dimethyl sulfide (1.0 mL) was added. After 1 h at – 78 ºC and 6 h at room temperature, the mixture was concentrated to give aldehyde **4.31** as a colorless oil. The resulting oil was directly used in the next step.



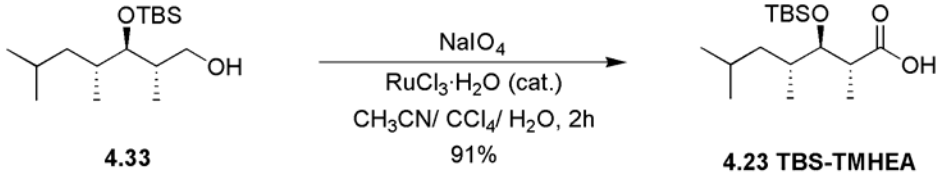
4.31 **4.32**

((2*S*,3*R*,4*R*)-1-(Benzyloxy)-2,4,6-trimethylhept-5-en-3-yloxy)(*tert*-butyl)dimethylsilan e (4.32) A sample of *n*-BuLi (0.948 mL, 2.5 M in hexane, 2.37 mmol) was added dropwise to a suspension of isopropyltriphenylphosphonium iodide (1.08 g, 2.49 mmol) in dry THF (10 mL) at room temperature. The resulting red solution was stirred at room temperature for 30 min. A solution of the crude aldehyde **4.31** in dry THF (10 mL) was introduced via cannula. After 2 h the reaction was diluted with ethyl acetate and washed with saturated $NaHCO_3$, water, dried and concentrated. The residue was subjected to column chromatography (HE: EA = 30:1) to afford **4.32** (78.7 mg, 84% 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 5.17-5.14 (d, *J*= 9.2, 1.2 Hz, 1H), 4.53-4.46 (m, 2H), 3.58-3.49 (AB, 2H), 3.30-3.26 (dd, *J*= 9.2, 1.2 Hz, 1H), 2.55-2.50 (m, 1H), 1.99-1.96 (m, 1H), 1.672-1.669 (d, *J*= 1.2 Hz, 3H), 1.564-1.561 (d, *J*= 1.2 Hz, 3H), 0.96-0.94 (d, *J*= 7.2 Hz, 3H), 0.94-0.92 (d, *J*= 7.2 Hz, 3H), 0.90 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.8, 135.7, 129.7, 128.2, 127.3, 125.4, 78.3, 73.0, 38.2, 36.3, 34.3, 30.4, 26.2, 26.0, 19.0, 18.5, 18.0, 15.1, -3.8, -3.9; IR (neat) ν_{max} 2958, 2929, 2856, 1456, 1252, 1088, 1029, 836, 773.



4.32 4.33

(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol (4.33) A solution of **4.32** (30.2 mg, 0.0798 mmol) in hexanes (1% ethanol) was hydrogenated in the presence of a Pd/C (5 wt%, 170 mg, 0.0798 mmol) over night in H_2 atmosphere. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (HE: EA = 10:1) gave **4.33** as a colorless oil (22.7 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.56 (AB, 2H), 3.51-3.49 (dd, *J*= 4.8, 4.8 Hz, 1H), 2.27 (br s, 1H), 1.92-1.85 (m, 1H), 1.79-1.71 (m, 1H), 1.66-1.58 (m, 1H), 1.23-1.14 (m, 1H), 1.09-1.02 (m, 1H), 0.98-0.96 (d, *J*= 6.8 Hz, 3H), 0.93-0.90 (m, 15H), 0.85-0.83 (d, *J*= 6.4 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 82.1, 66.5, 42.2, 36.6, 36.2, 26.1, 25.4, 24.1, 21.7, 18.3, 17.1, 15.3, -4.0, -4.2; IR (neat) ν_{max} 3379, 2956, 2930, 2857, 1565, 1384, 1366, 1255, 1067, 1031, 836, 773.



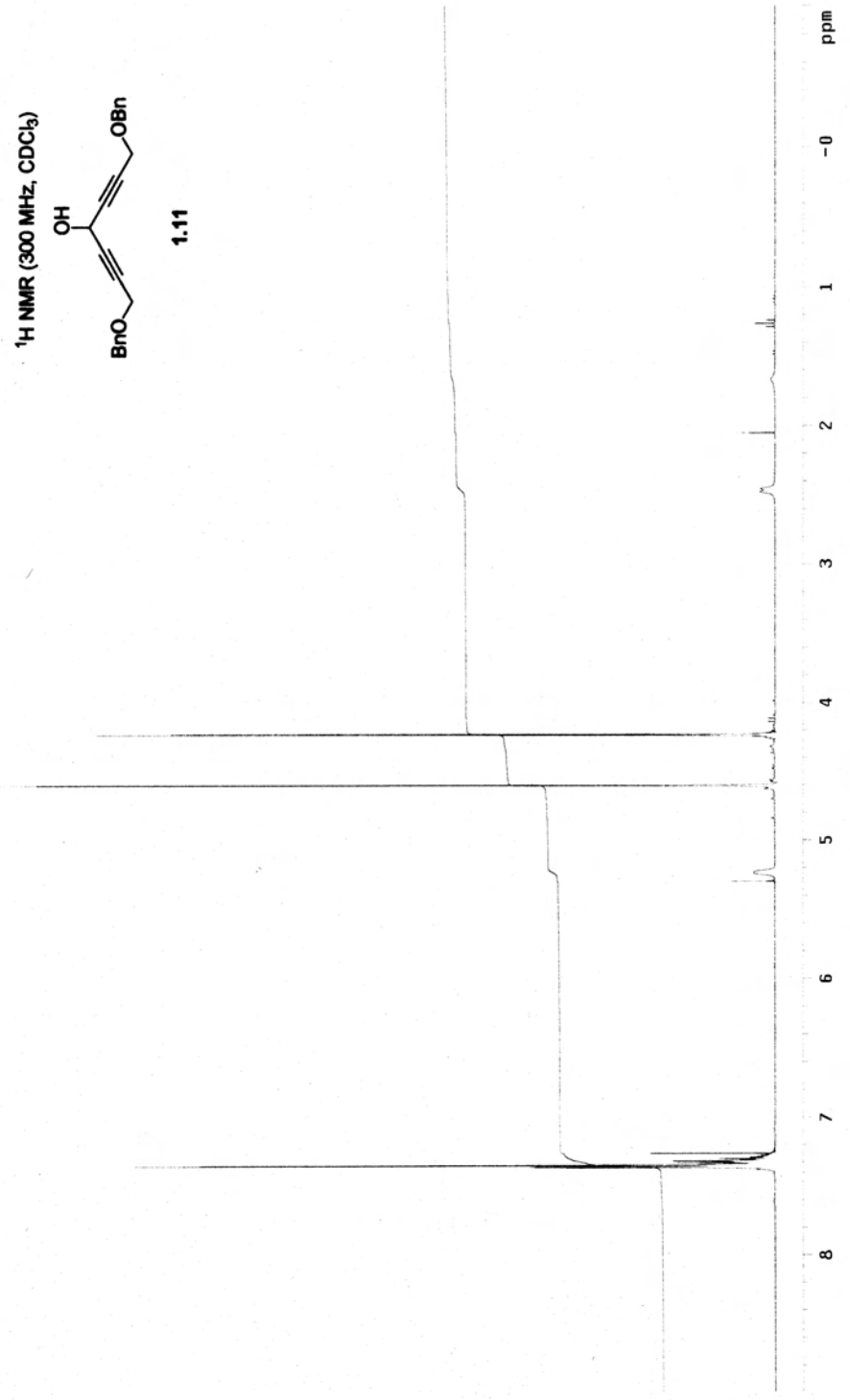
4.33 4.23 TBS-TMHEA

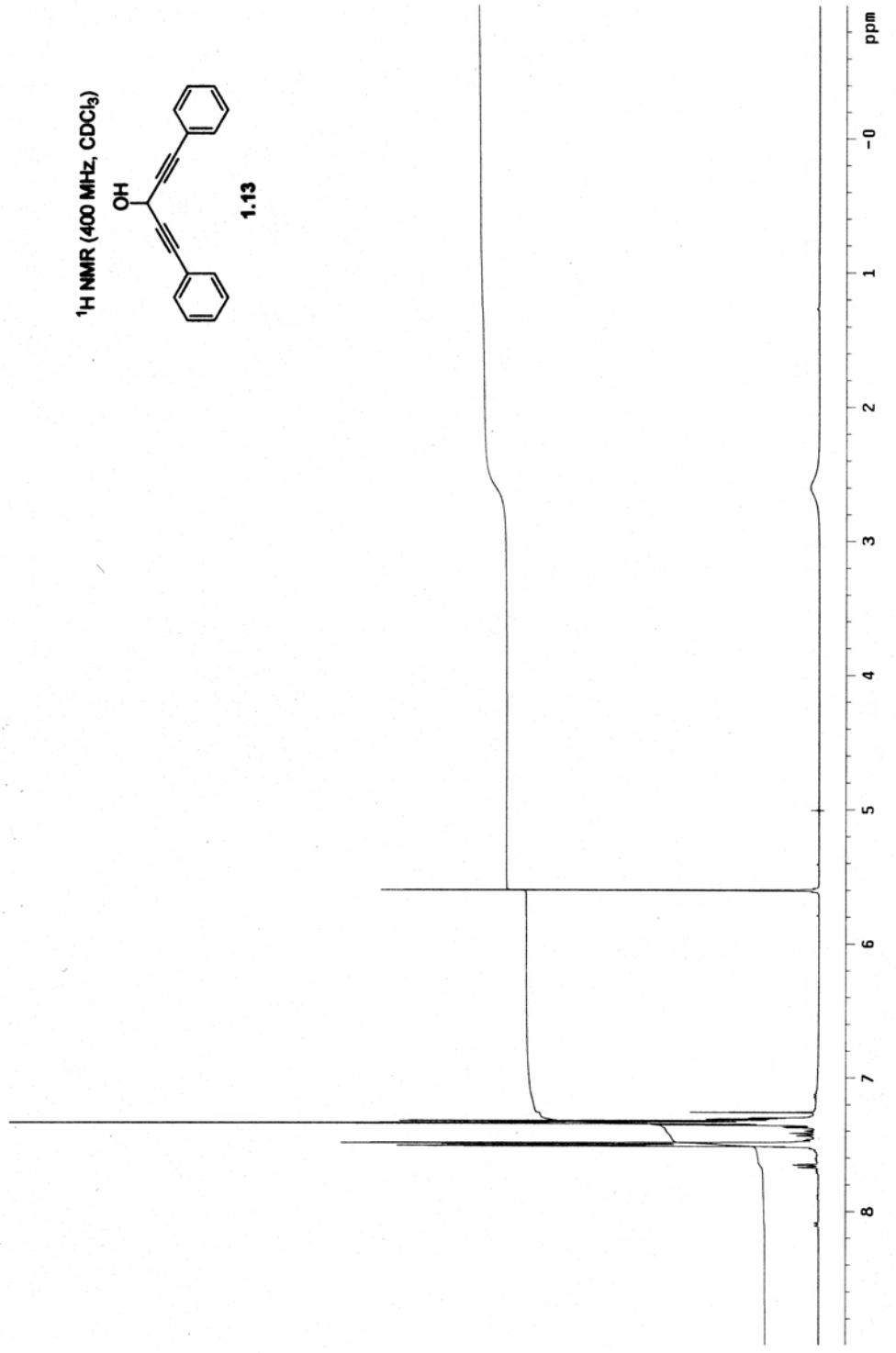
(2*R*,3*R*,4*R*)-3-(*tert*-Butyldimethylsilyloxy)-2,4,6-trimethylheptanoic acid (4.23) To a stirred solution of **4.33** (10.1 mg, 0.0353 mmol) in CCl_4 (1.0 mL), CH_3CN (1.0 mL) and

water (1.5 mL) were added sodium *meta*-periodate (37.0 g, 0.175 mmol) and $RuCl_3 \cdot H_2O$ (5.0 mg, 0.0180 mmol) sequentially. The mixture was stirred at 25°C for 2 h. A 20 mL of diethyl ether was added and the stirring was continued for 20 min to precipitate black RuO_2. The reaction mixture was dried and filtered through Celite and the solid residue was washed with ether. The combined organic phases were concentrated and chromatographed (HE: EA = 4:1) to give the carboxylic acid **4.23** (9.6 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.66 (dd, *J*= 4.0, 2.0 Hz, 1H), 2.64-2.62 (qd, *J*= 7.2, 2.0 Hz, 1H), 1.86-1.79 (m, 1H), 1.64-1.54 (m, 1H), 1.32-1.30 (d, *J*= 7.2 Hz, 3H), 1.18-1.04 (m, 1H), 0.96 (s, 9H), 0.93-0.92 (d, *J*= 3.6 Hz, 3H), 0.91-0.90 (d, *J*= 3.2 Hz, 3H), 0.85-0.84 (d, *J*= 6.4 Hz, 3H), 0.17 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.4, 79.9, 42.7, 40.4, 36.6, 25.8, 25.3, 23.7, 21.7, 18.1, 17.8, 14.2, -4.1, -4.6; IR (neat) ν_{max} 3080, 2955, 2929, 2858, 1710, 1463, 1254, 1074, 836, 775.

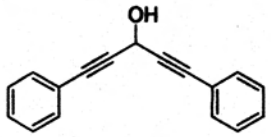
APPENDIX

Selected Spectra

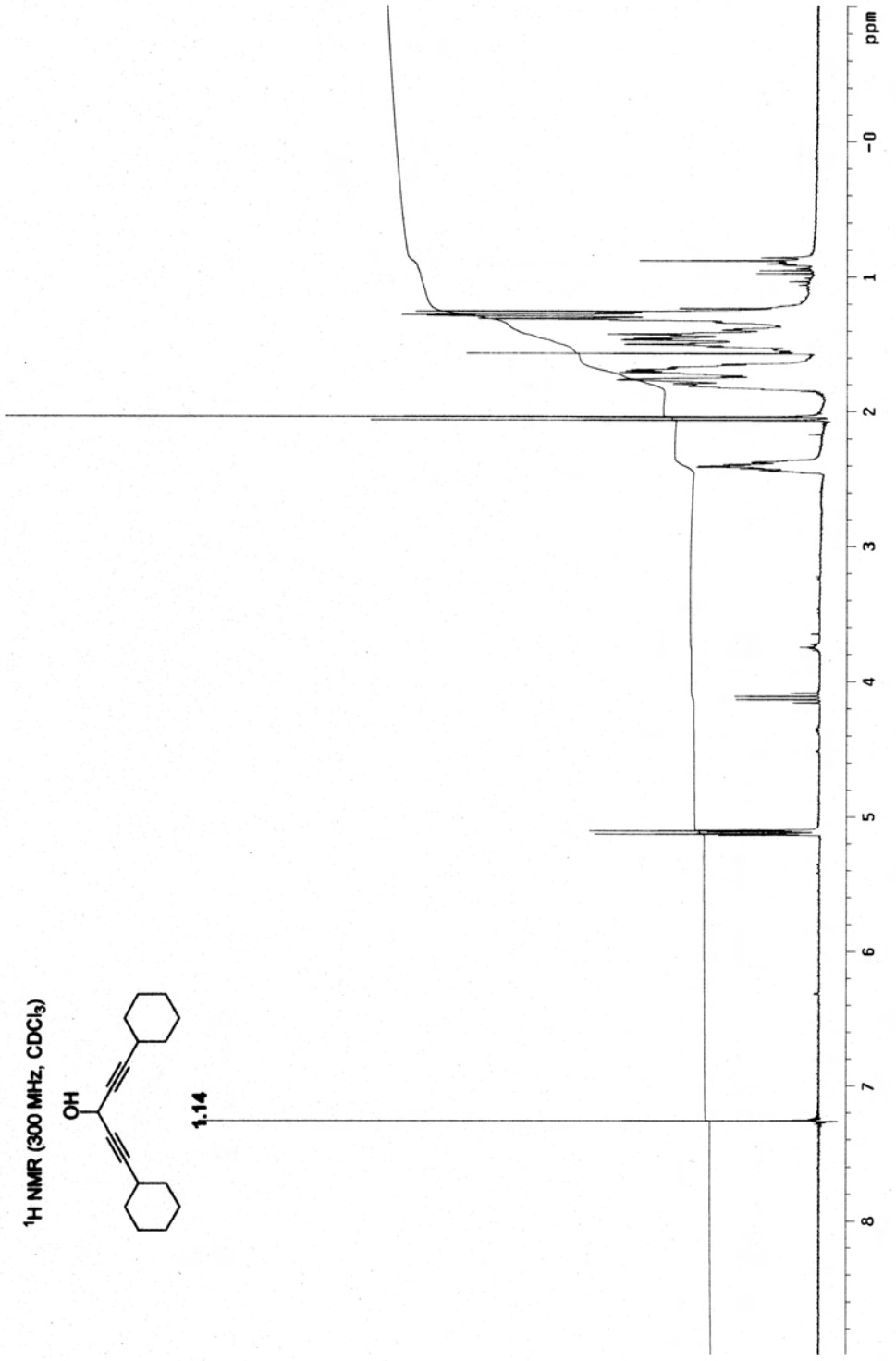

^{1}H NMR (300 MHz, $CDCl_3$)
OH
OBn
BnO
1.11
ppm
8
7
6
5
4
3
2
1
-0


^{1}H NMR (400 MHz, $CDCl_3$)
OH
1.13
ppm
8
7
6
5
4
3
2
1
-0

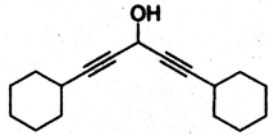
^{13}C NMR (400 MHz, $CDCl_3$)



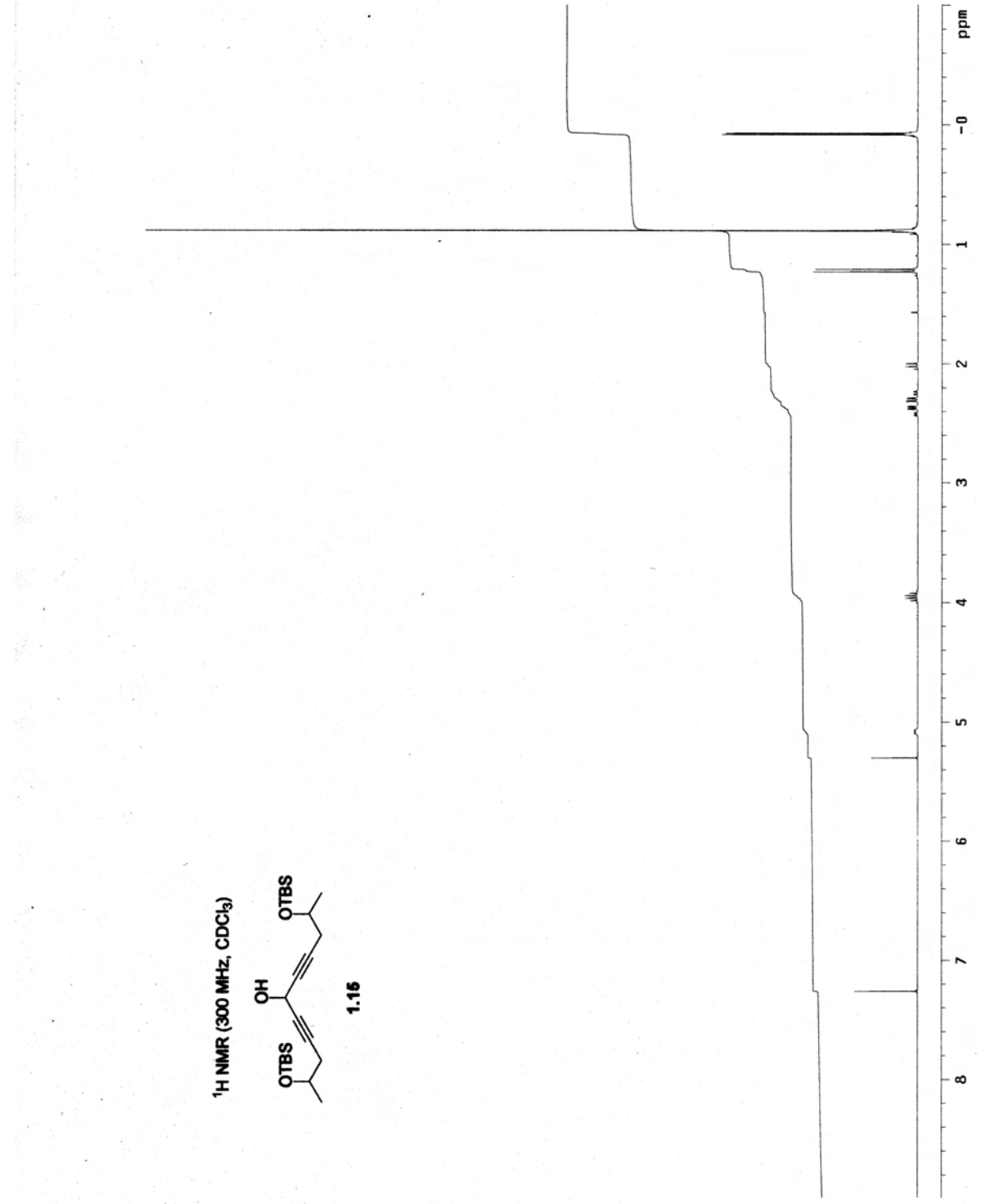
1.13


^{1}H NMR (300 MHz, $CDCl_3$)
OH
1.14
ppm

^{13}C NMR (400 MHz, $CDCl_3$)



1.14


^{1}H NMR (300 MHz, $CDCl_3$)
OTBS
OH
OTBS
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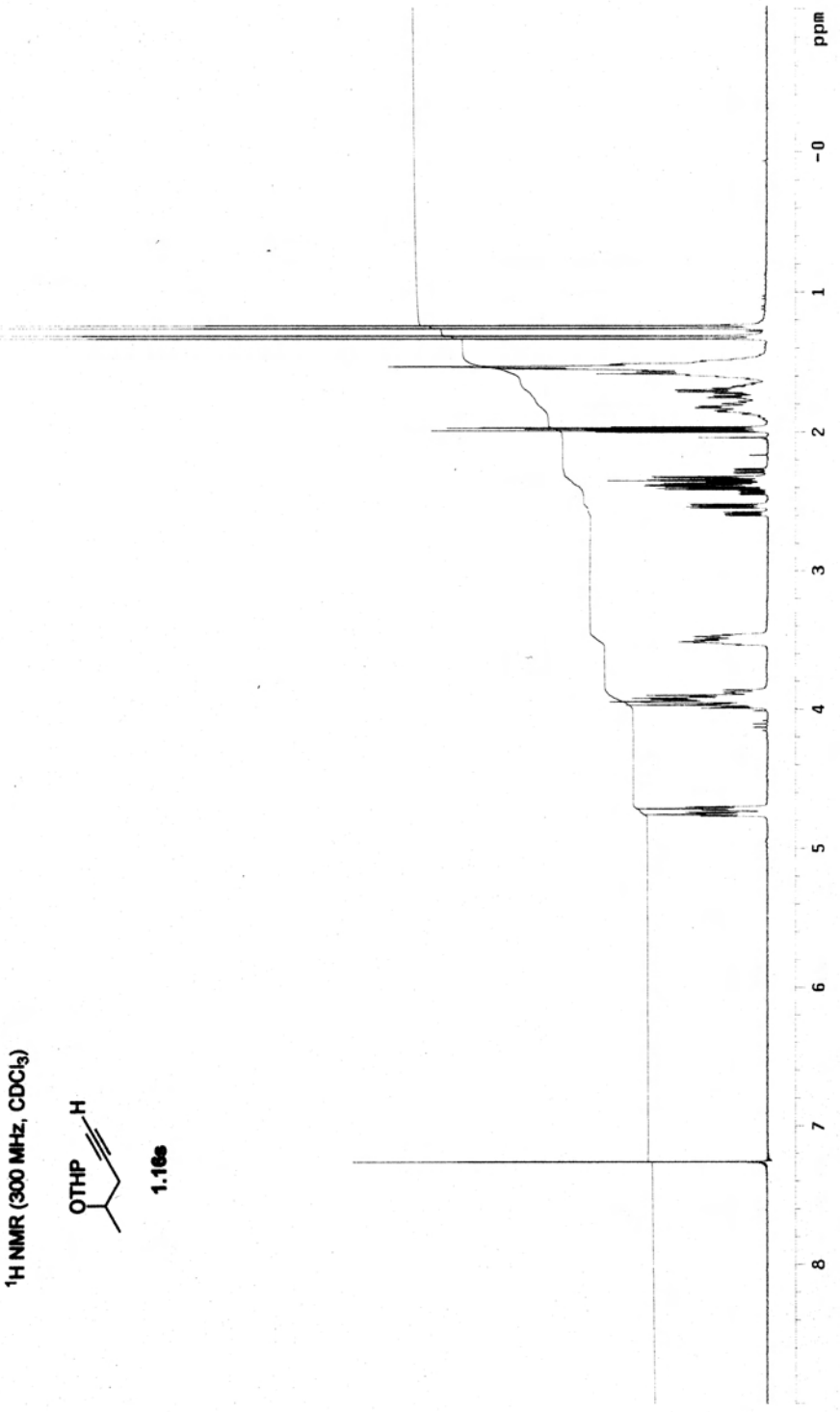
ppm
8
7
6
5
4
3
2
1
-0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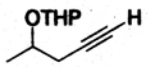
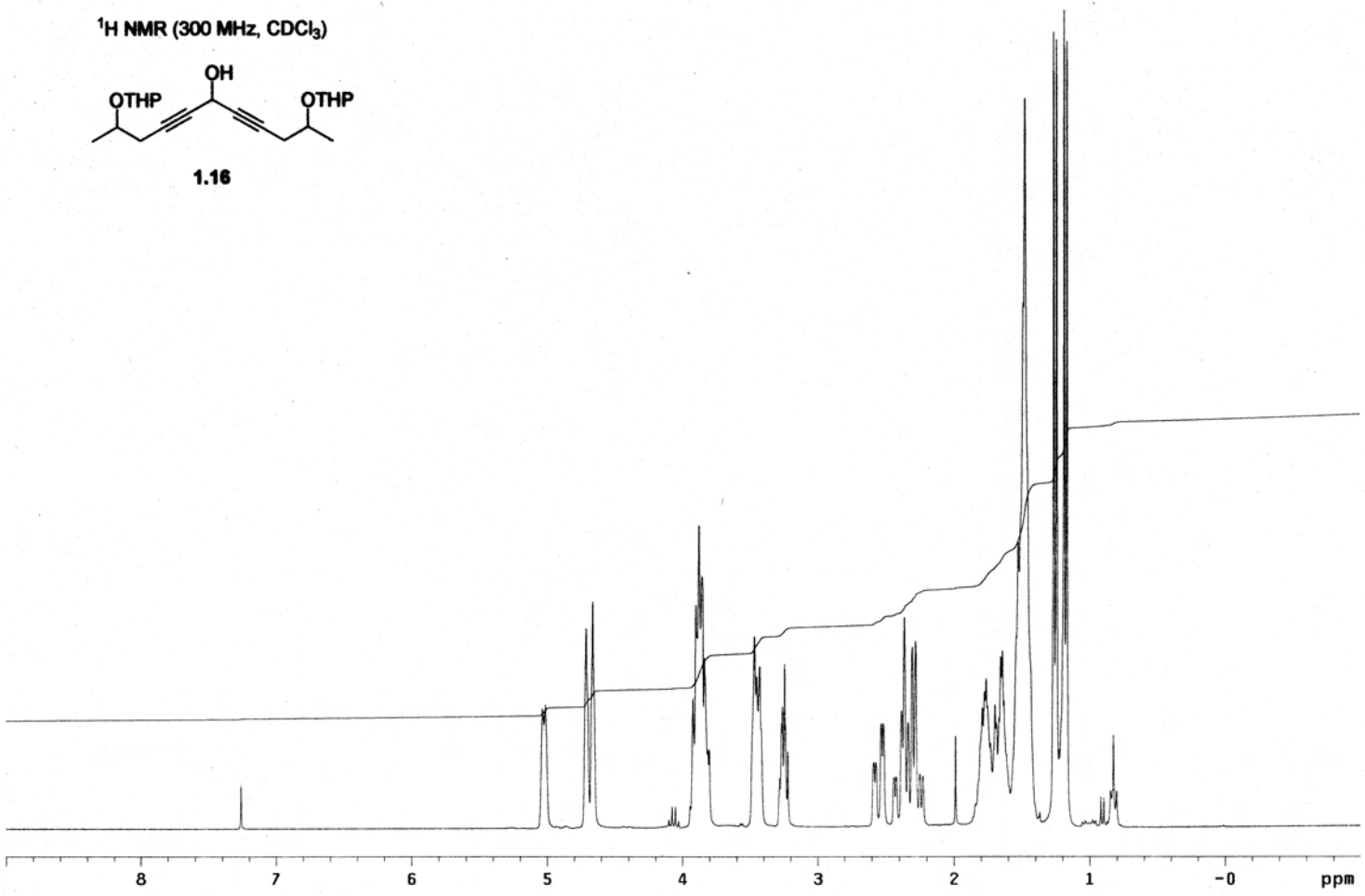
H
1.16s
ppm
8
7
6
5
4
3
2
1
0

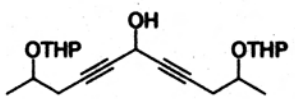
^{13}C NMR (300 MHz, $CDCl_3$)



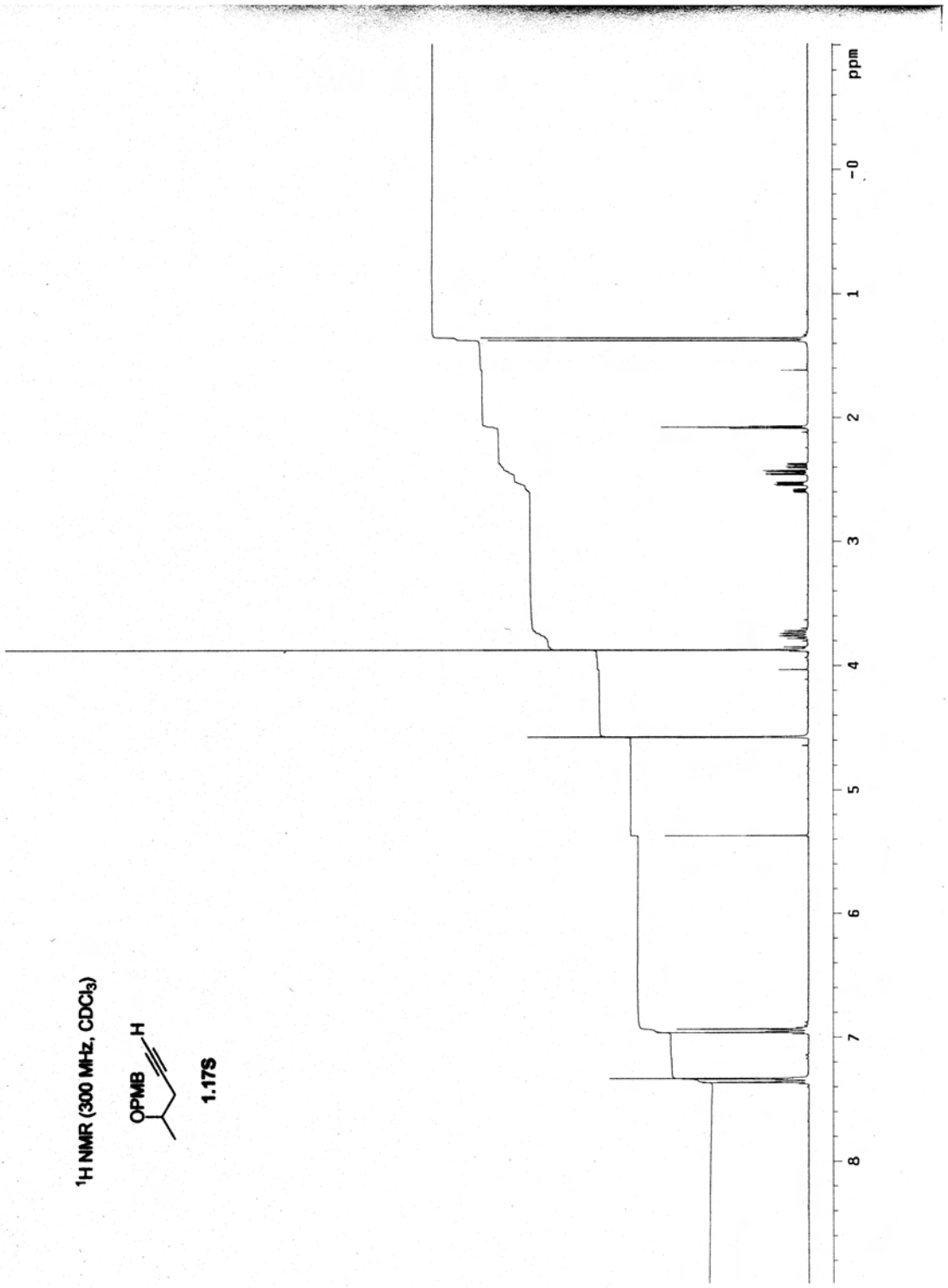
1.16s


^{1}H NMR (300 MHz, $CDCl_3$)
OH
OTHP
OTHP
1.16
8
7
6
5
4
3
2
1
-0
ppm

^{13}C NMR (300 MHz, $CDCl_3$)



1.16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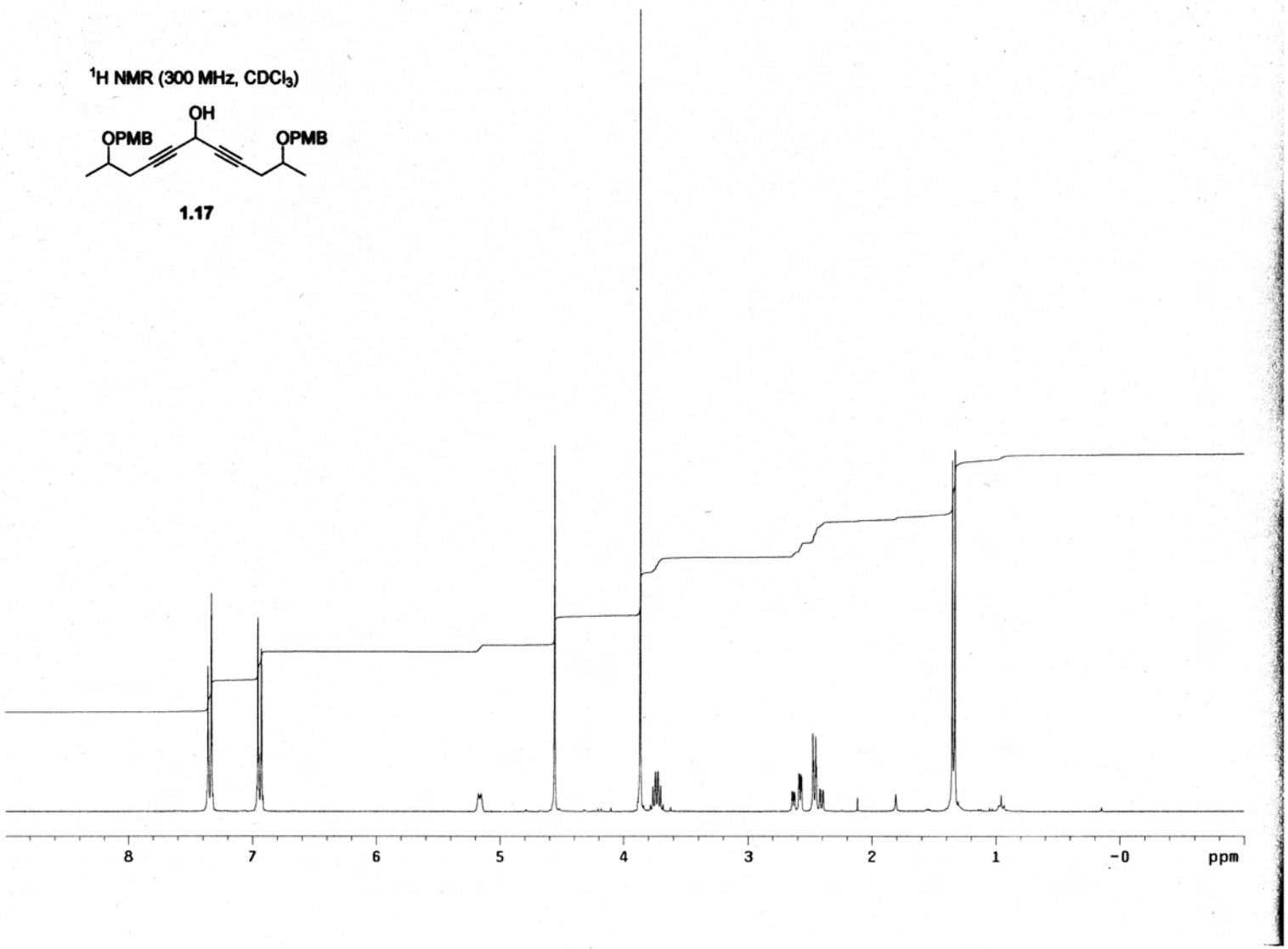
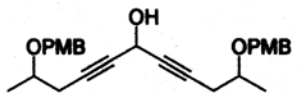
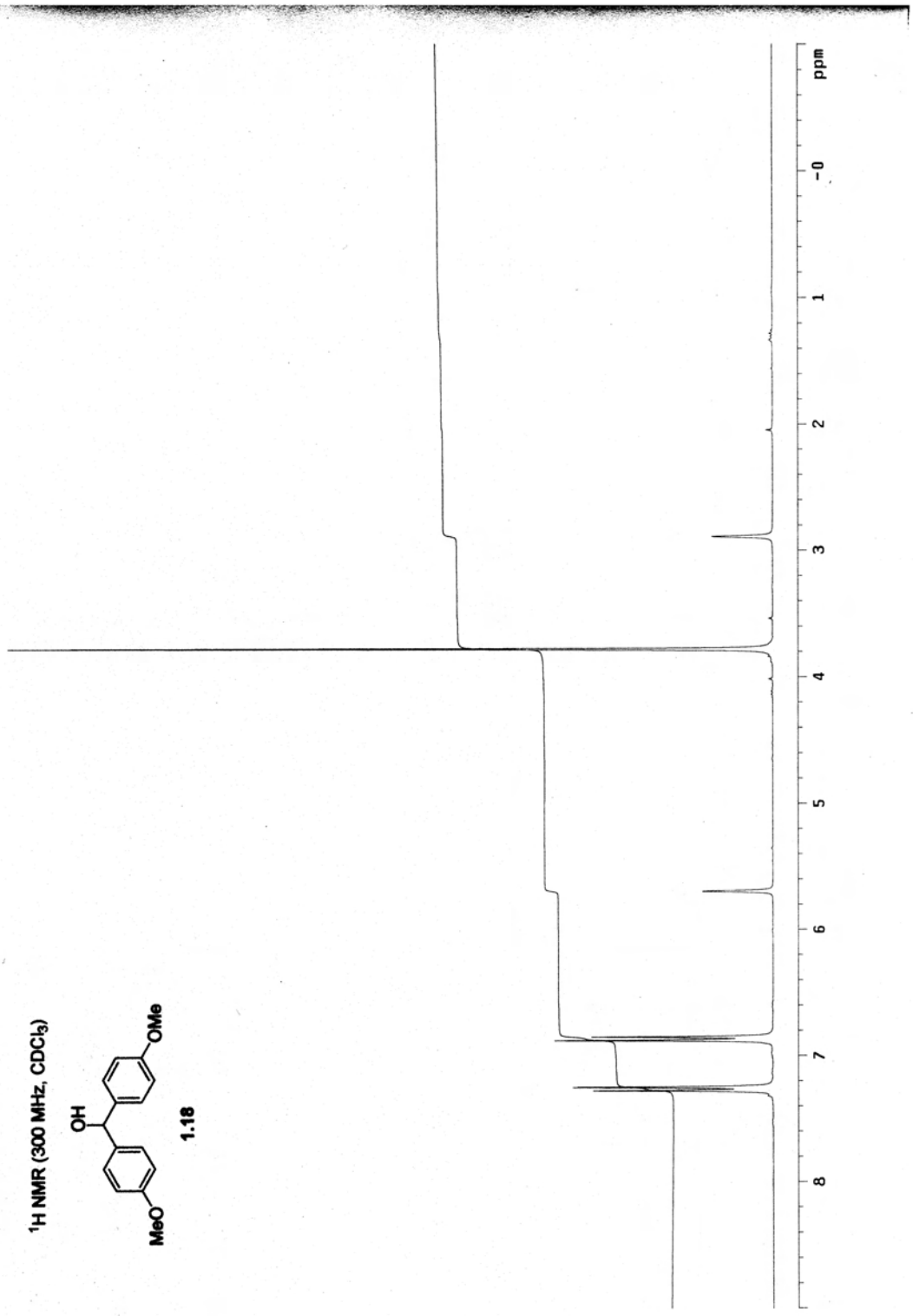
OPMB
H
1.17S
ppm


^{1}H NMR (300 MHz, $CDCl_3$)
OH
OPMB
OPMB
1.17
8
7
6
5
4
3
2
1
-0
ppm

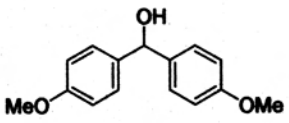
^{13}C NMR (300 MHz, $CDCl_3$)



1.17

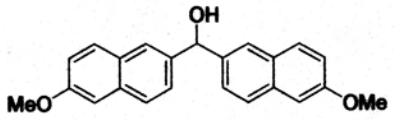

^{1}H NMR (300 MHz, $CDCl_3$)
OH
OMe
MeO
1.18
ppm

^{13}C NMR (300 MHz, $CDCl_3$)



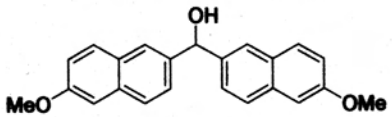
1.18

^{1}H NMR (300 MHz, $CDCl_3$)

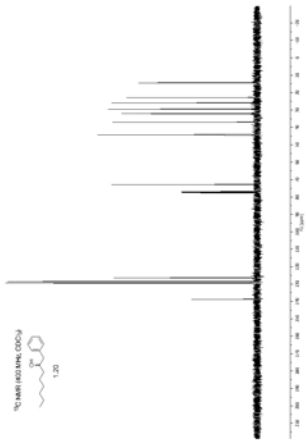


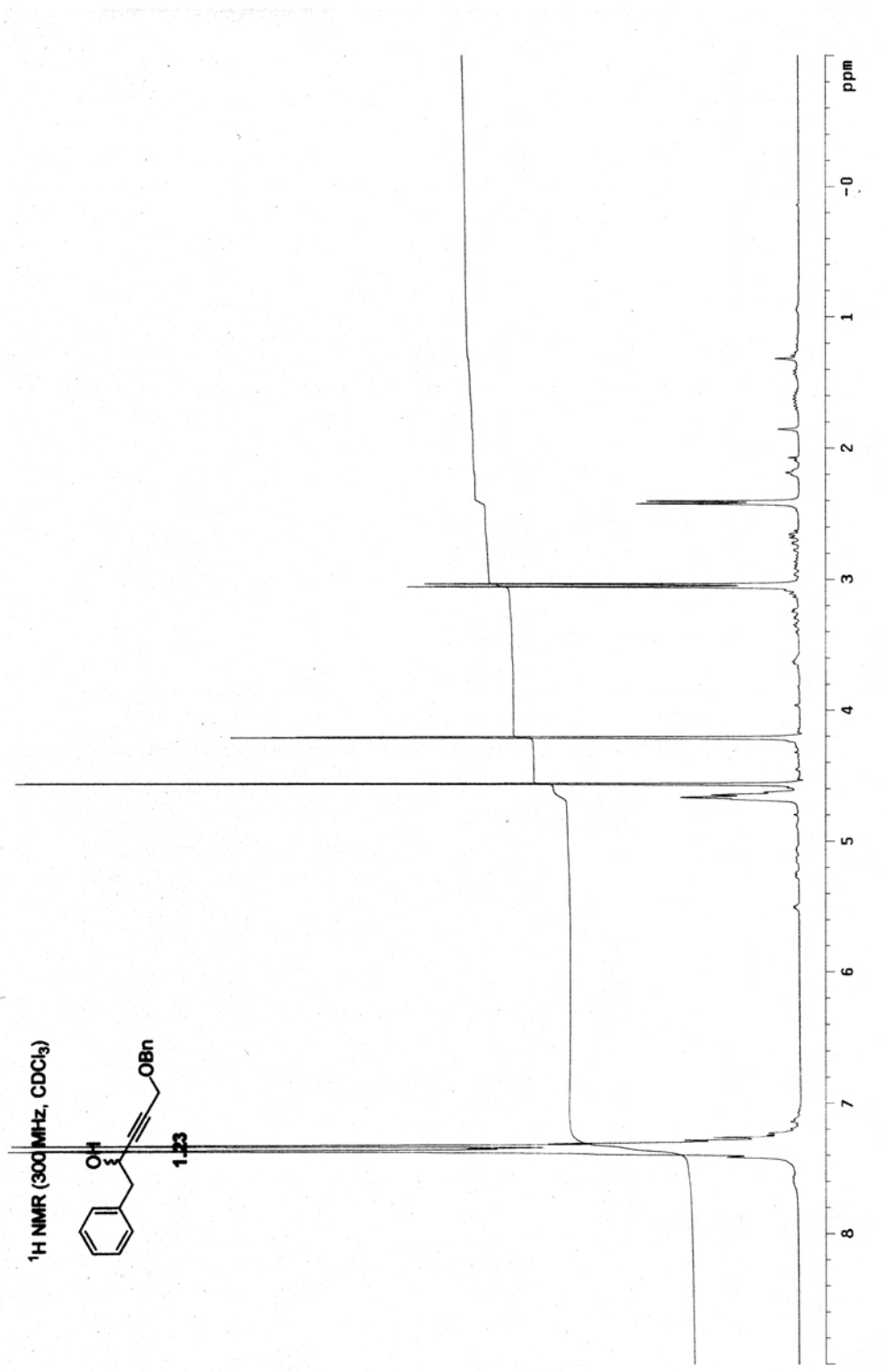
1.19

^{13}C NMR (300 MHz, $CDCl_3$)



1.19

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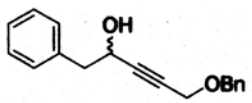
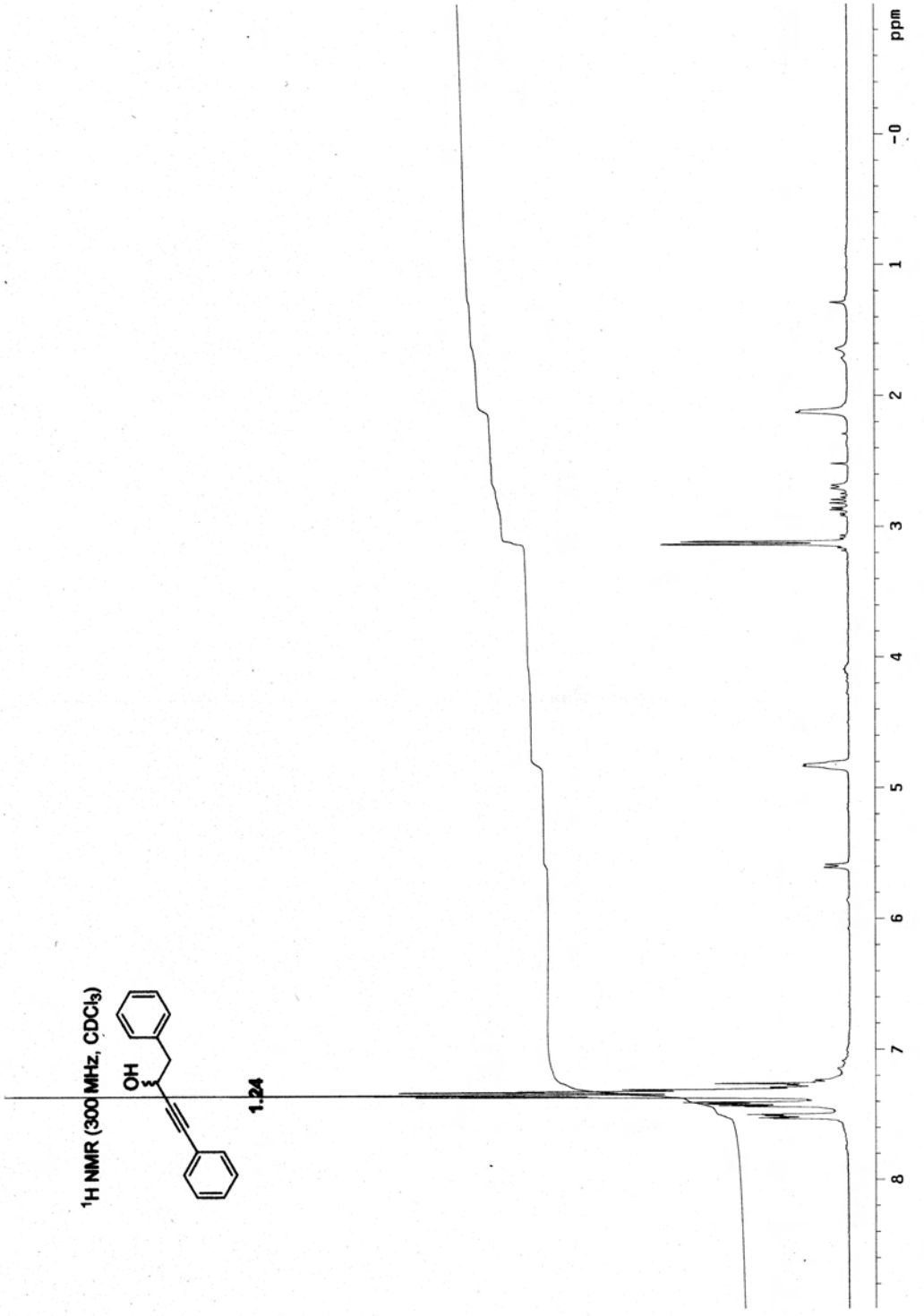
OH
OBn
1.23
ppm

^{13}C NMR (300 MHz, $CDCl_3$)



1.23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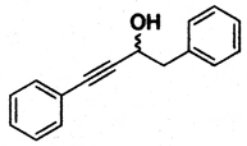
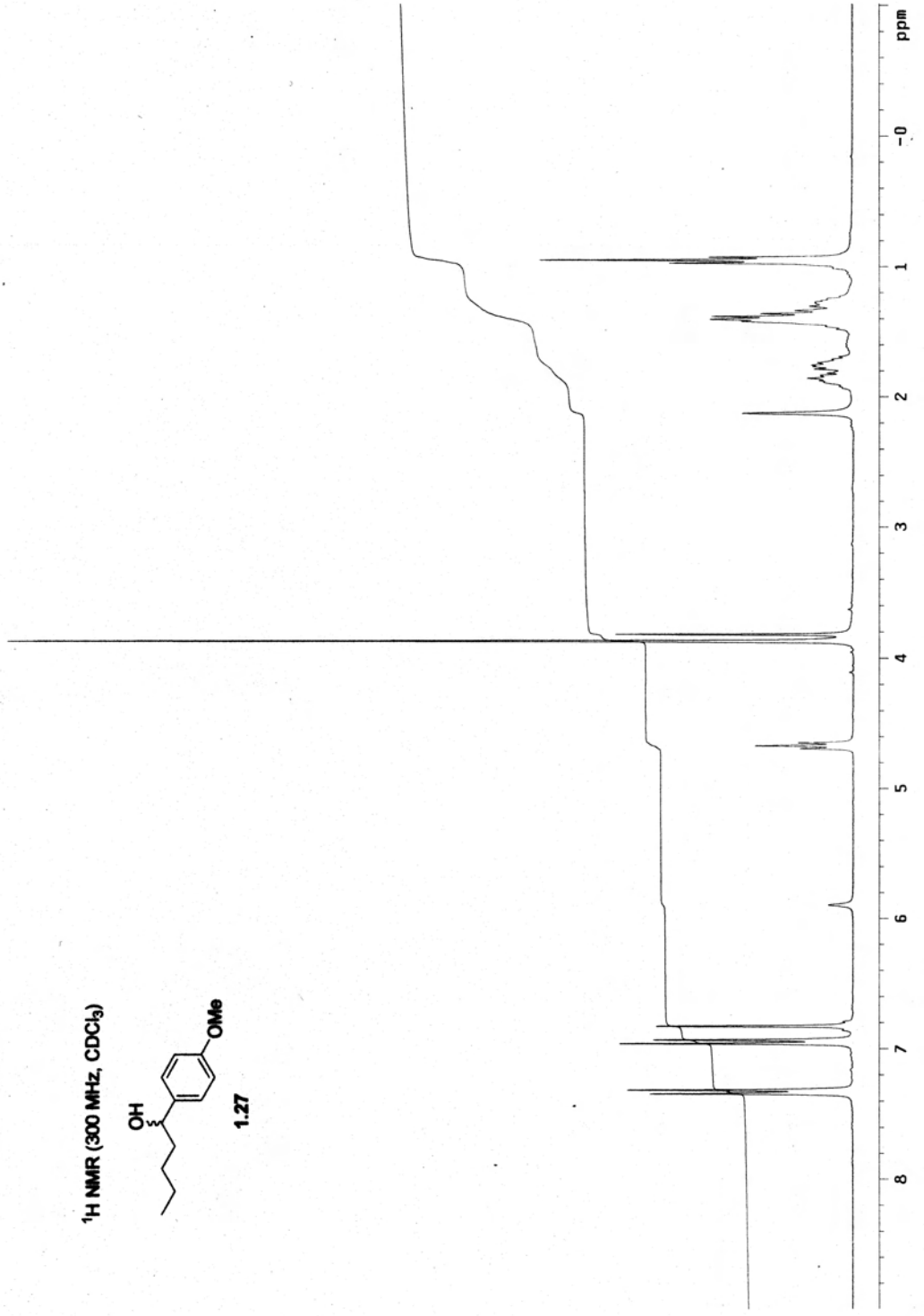
OH
1.24
ppm

^{13}C NMR (300 MHz, $CDCl_3$)



1.24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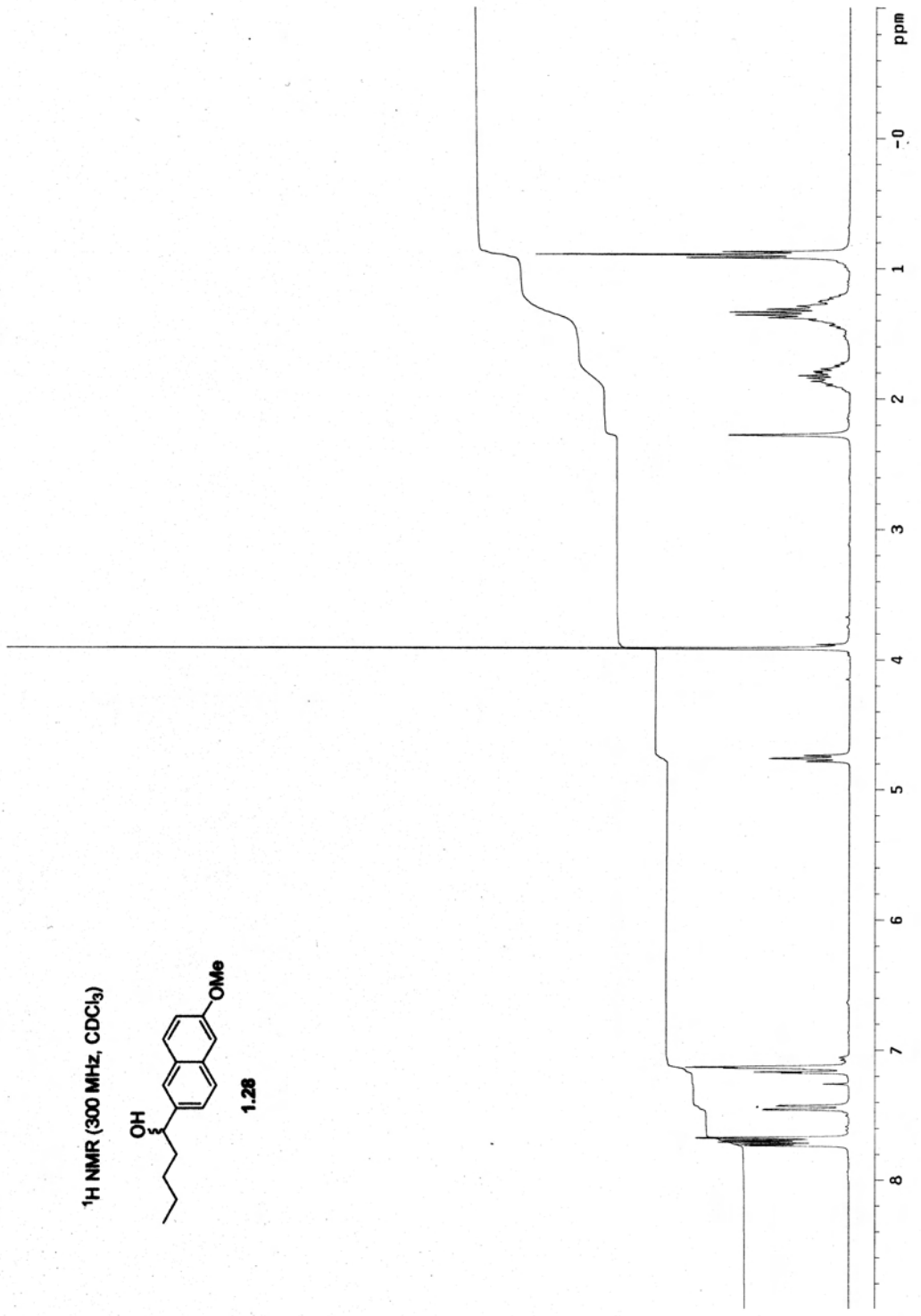
OH
OMe
1.27
ppm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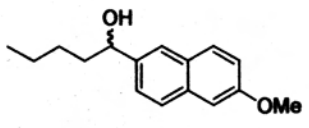
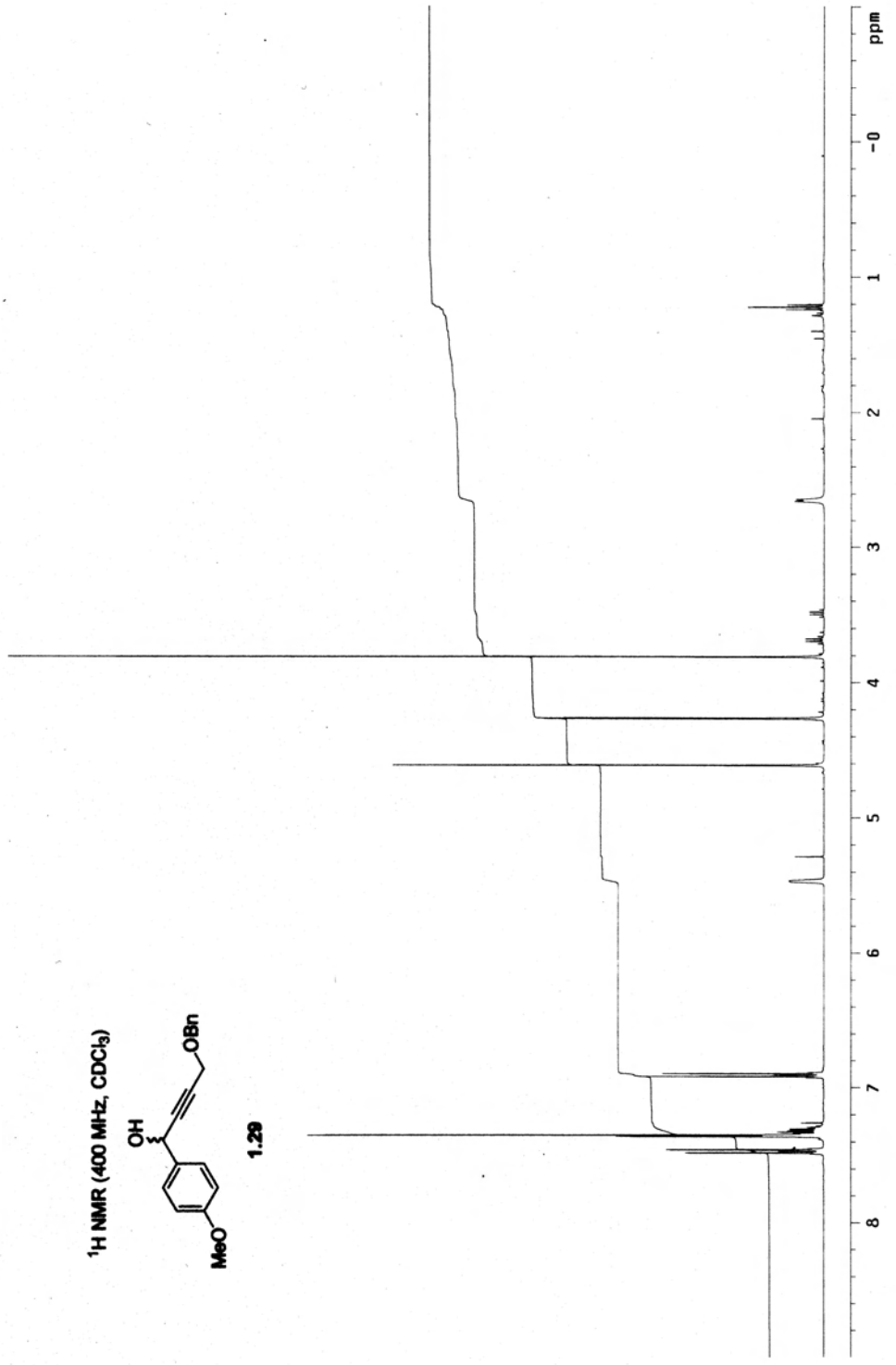
OH
OMe
1.28
ppm

^{13}C NMR (300 MHz, $CDCl_3$)



1.28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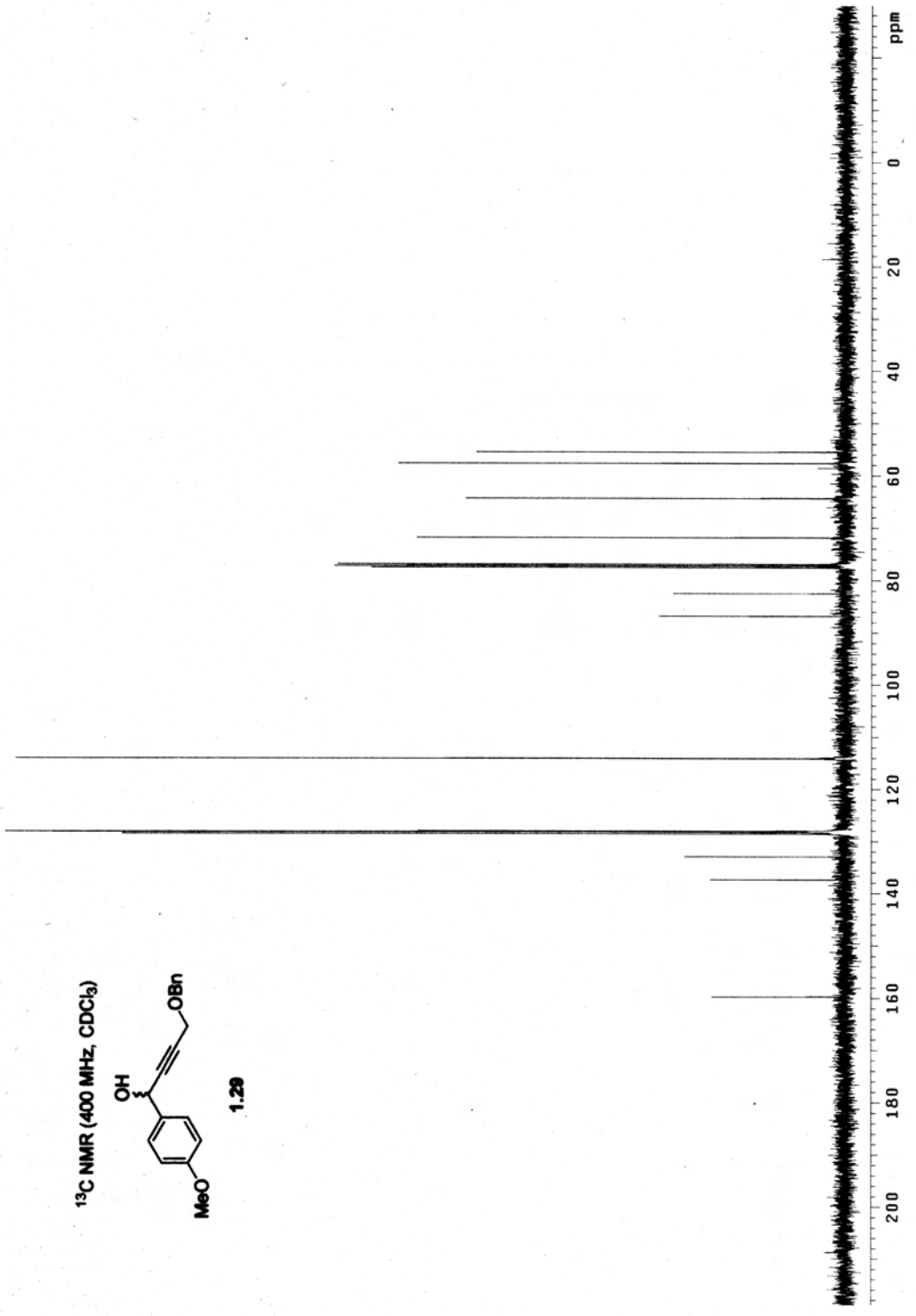
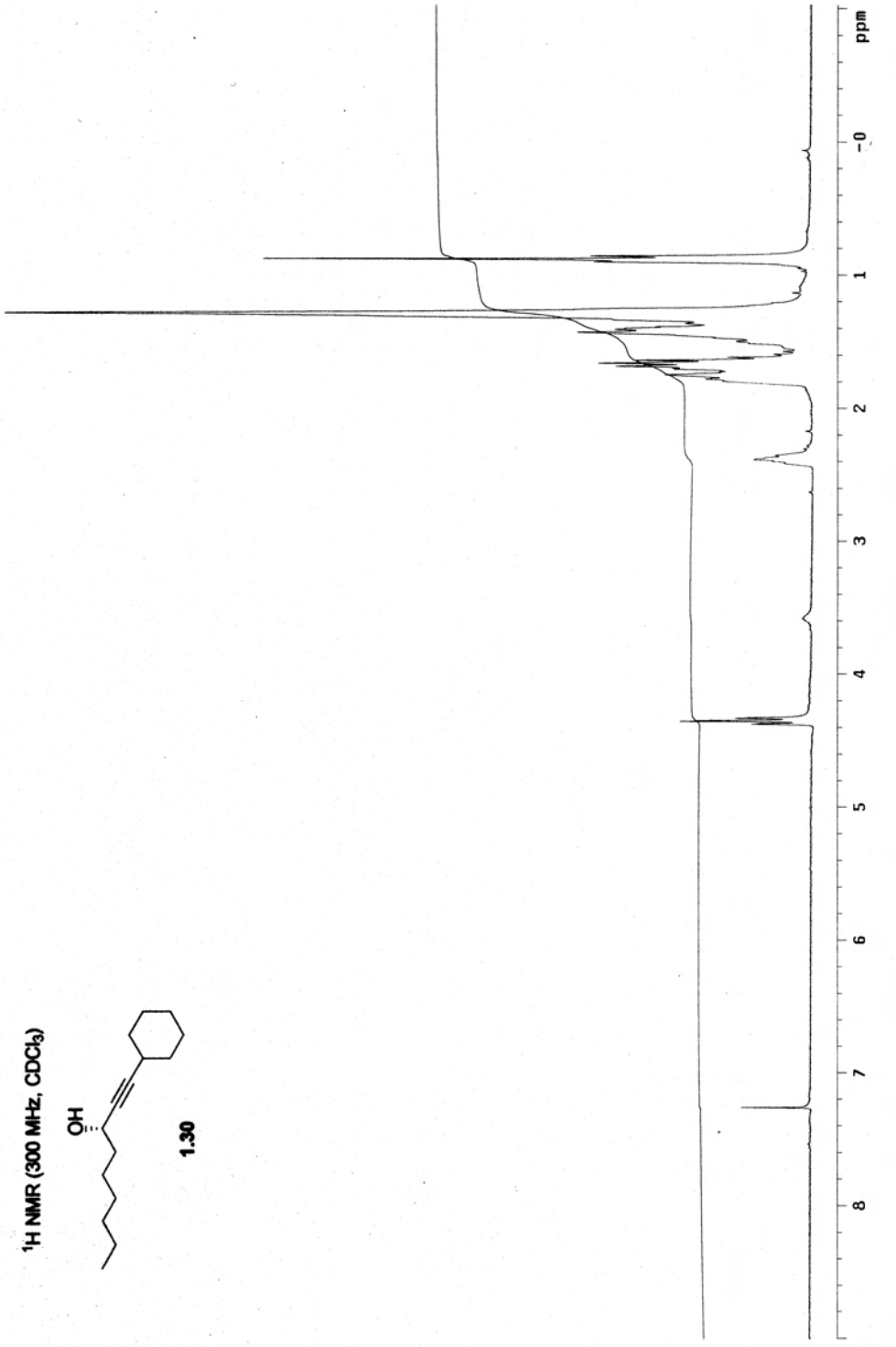
OBn
MeO
1.29
ppm


^{13}C NMR (400 MHz, CDCl$_3$)
OH
OBn
MeO
1.29
ppm
200
180
160
140
120
100
80
60
40
20
0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ppm
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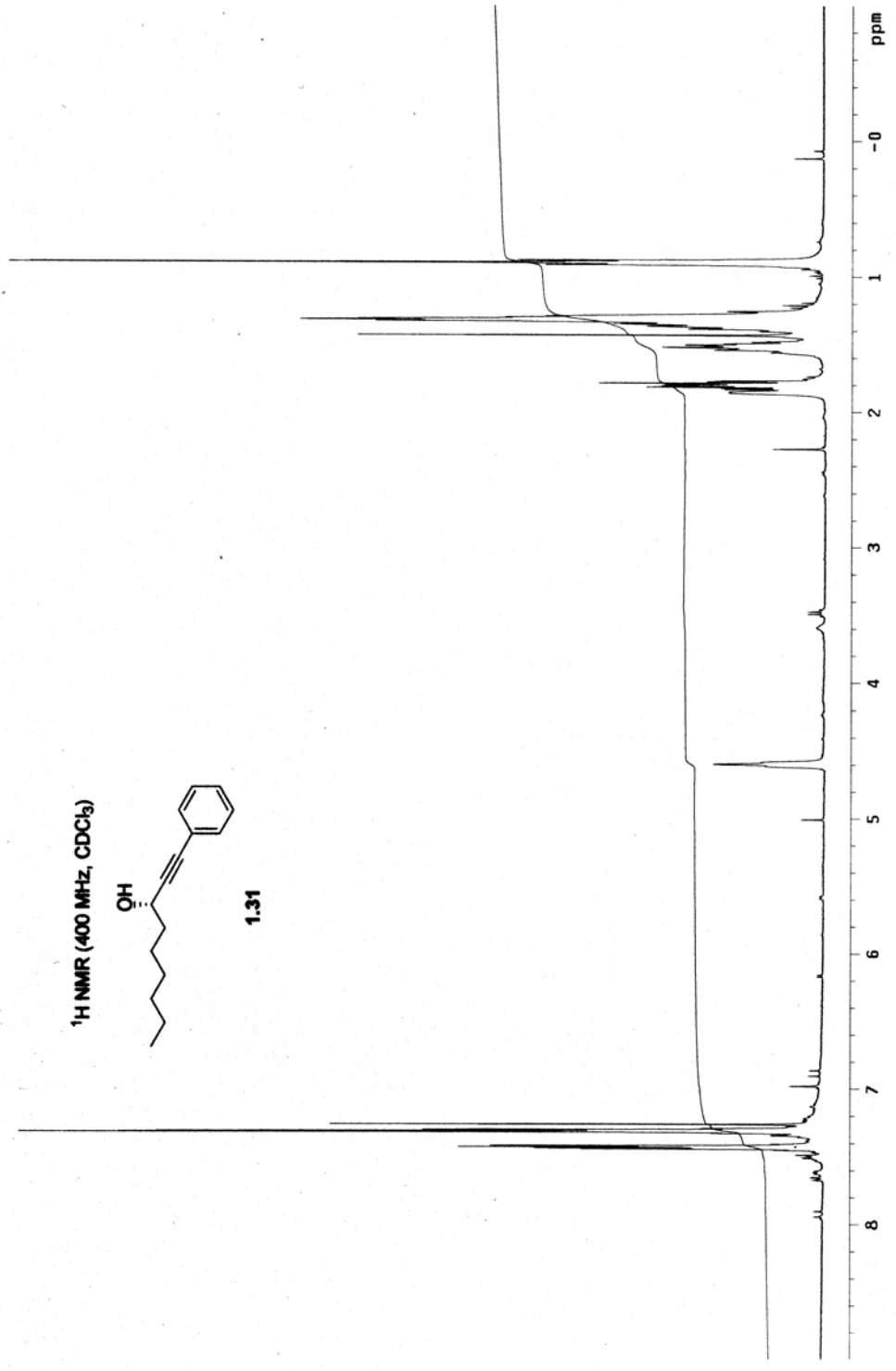
1
2
3
4
5
6
7
8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ppm
-0
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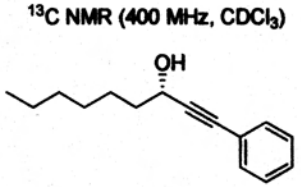
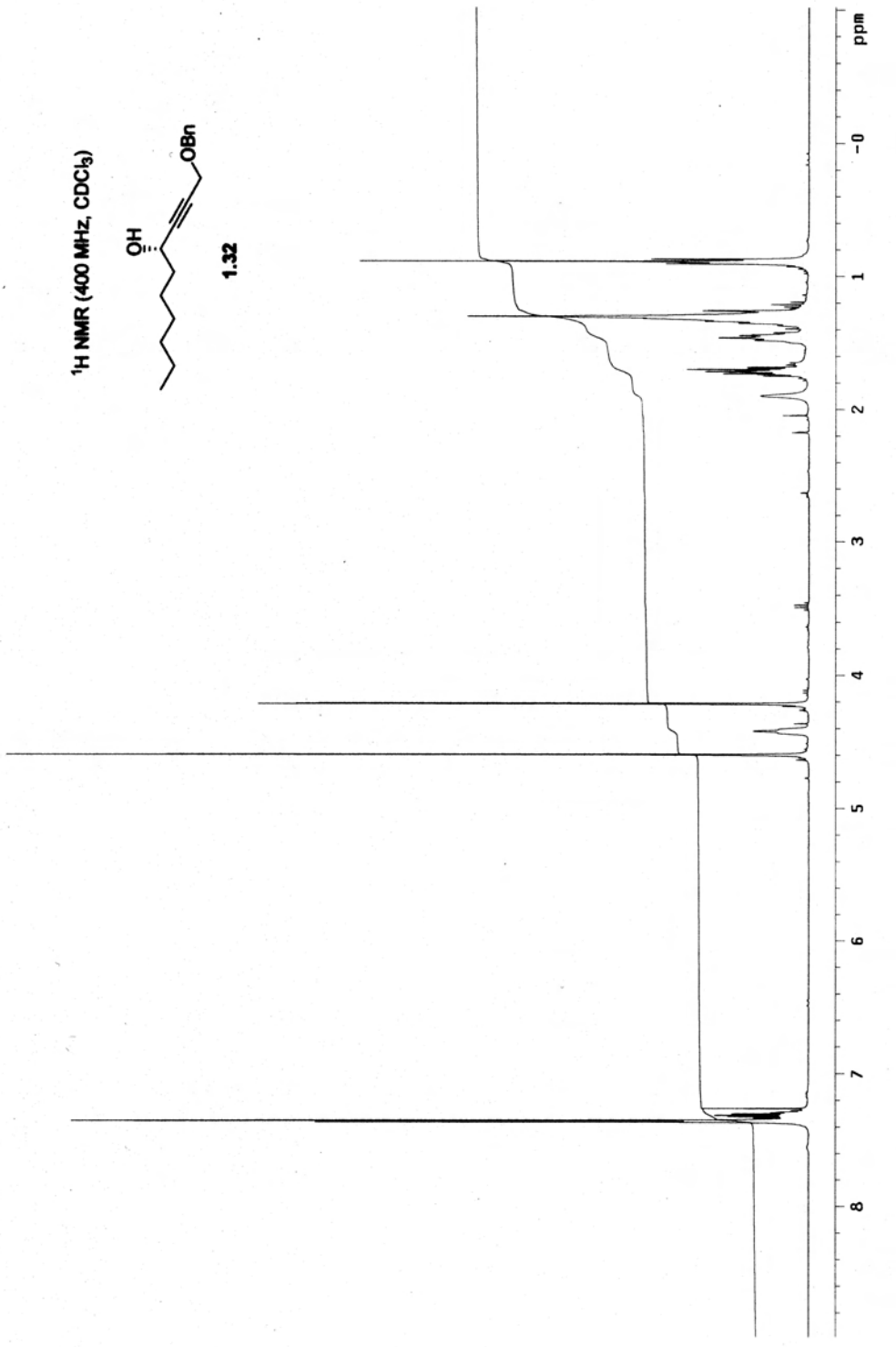
2
3
4
5
6
7
8

^{13}C NMR (400 MHz, $CDCl_3$)



1.31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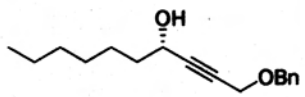
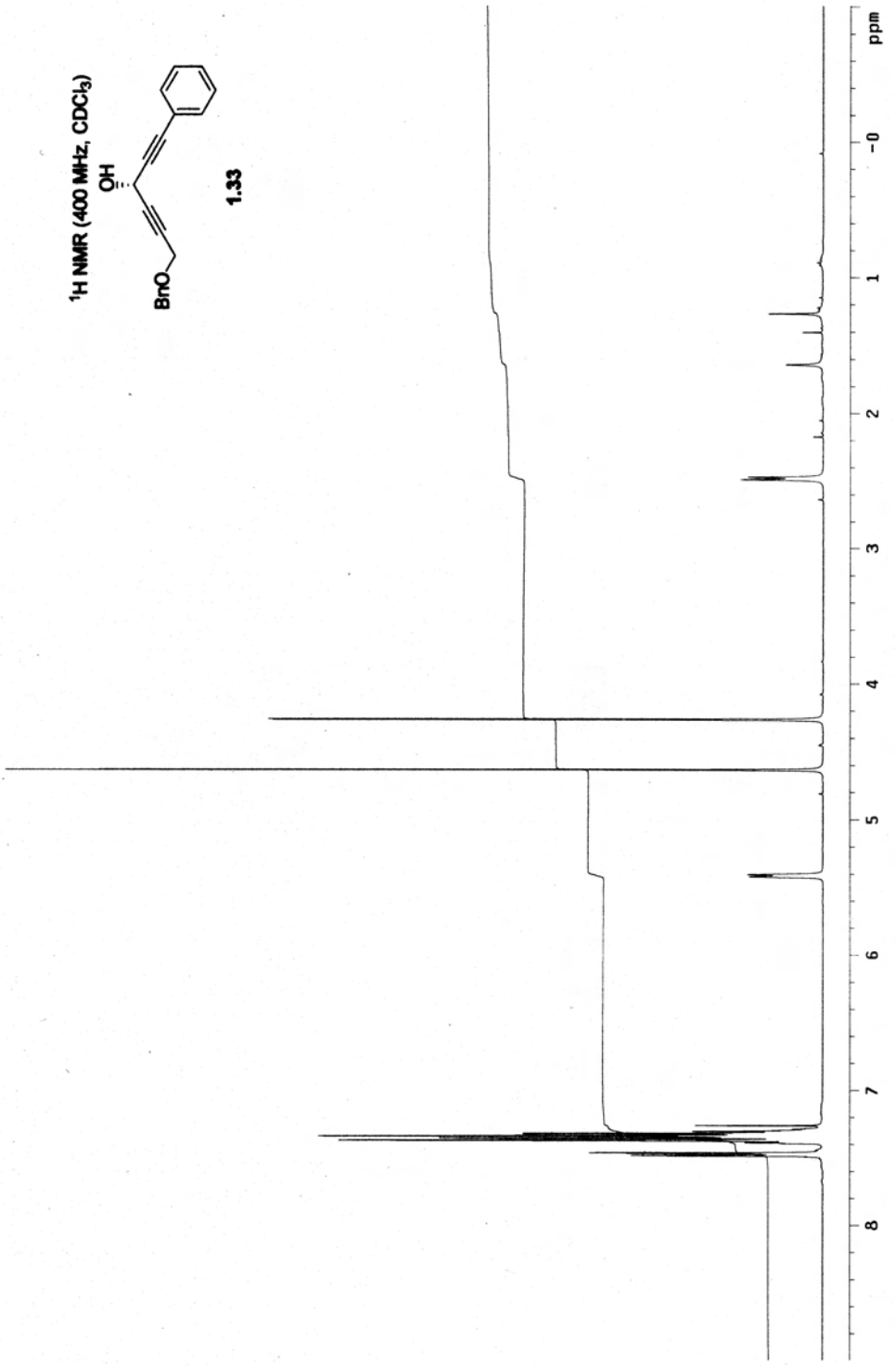
OH
OBn
1.32
ppm

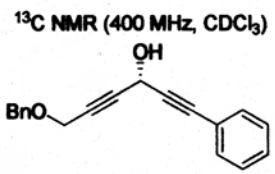
^{13}C NMR (400 MHz, $CDCl_3$)



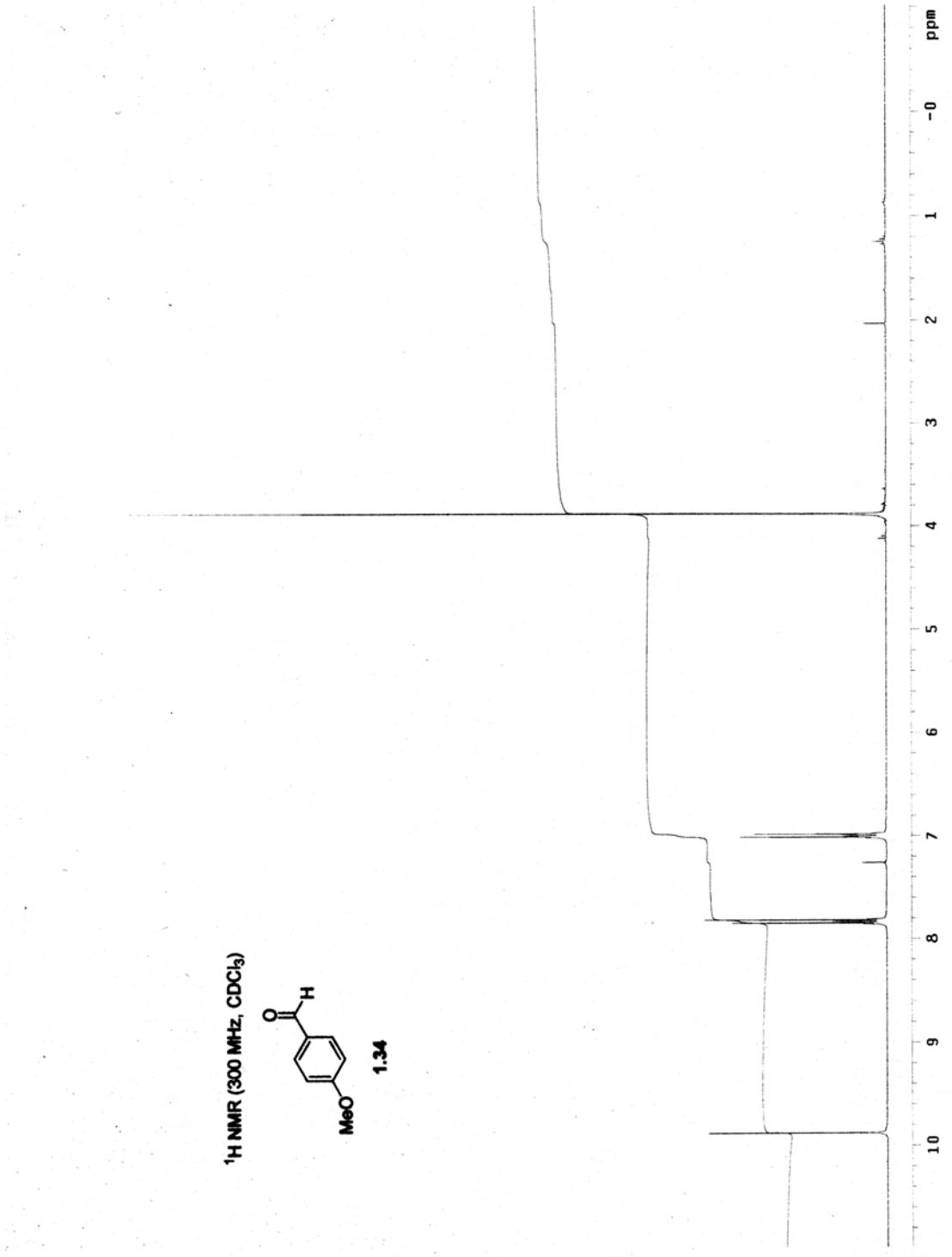
1.32

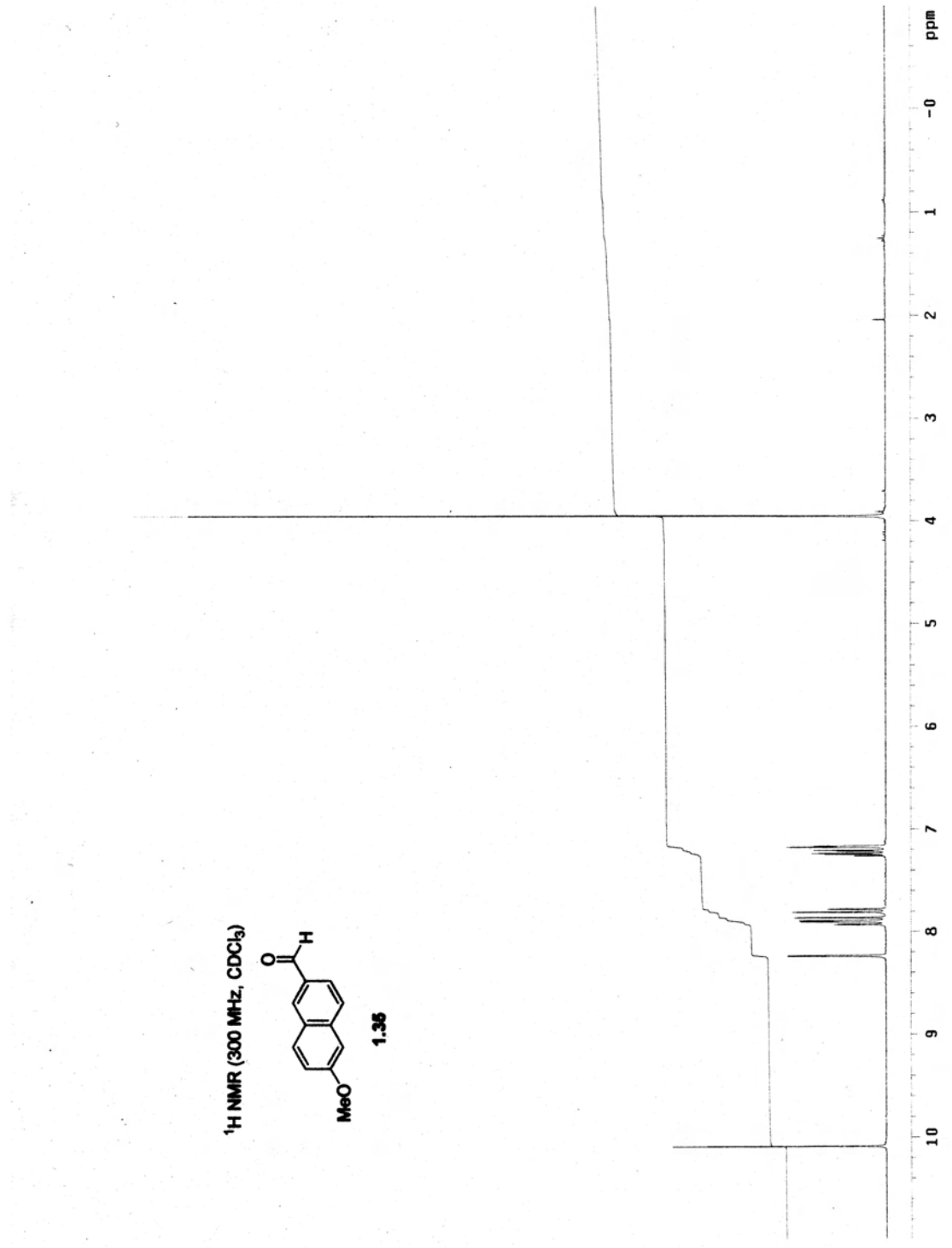

^{1}H NMR (400 MHz, CDCl$_3$)
OH
BnO
1.33
ppm

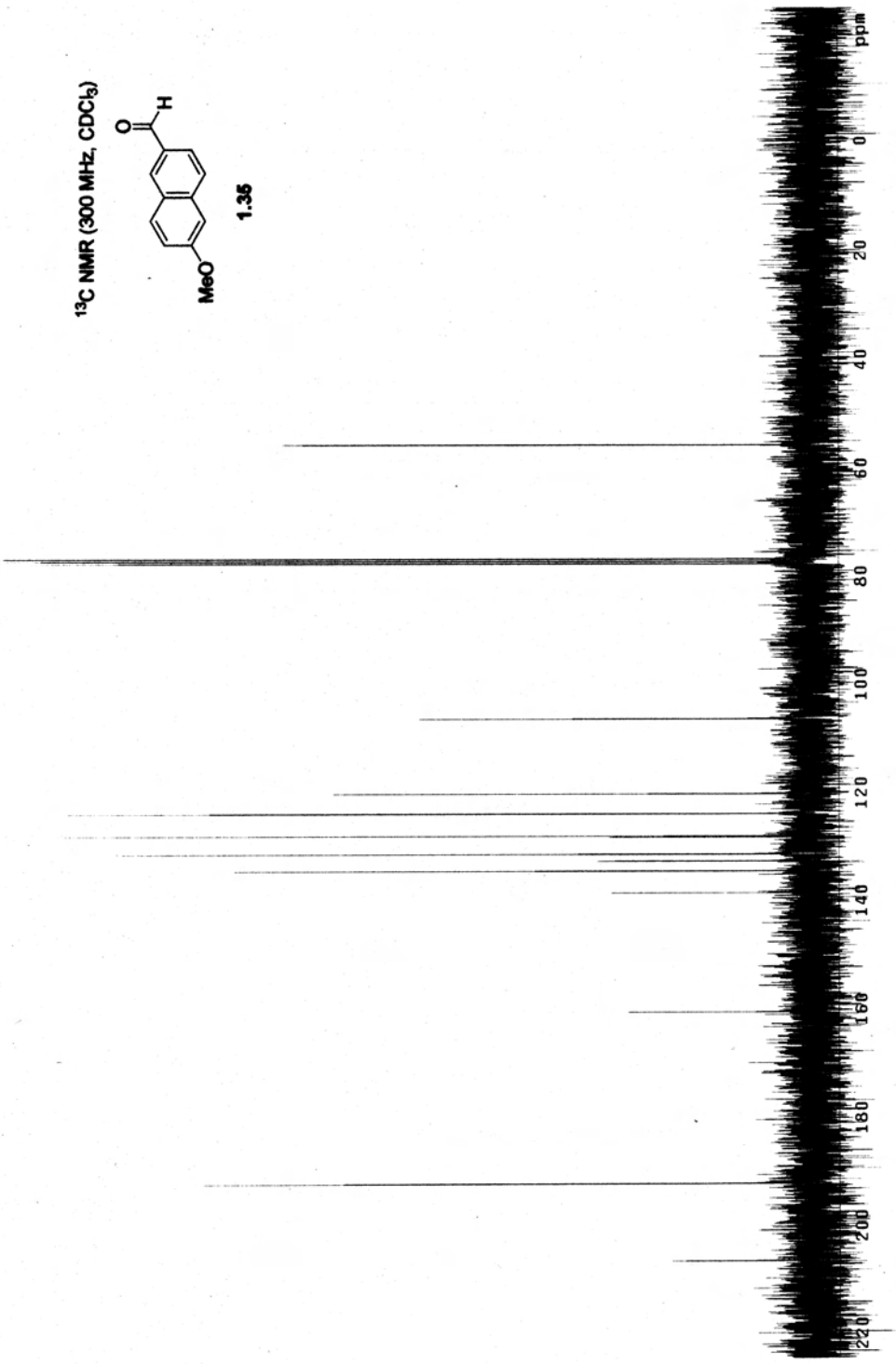
^{13}C NMR (400 MHz, $CDCl_3$)

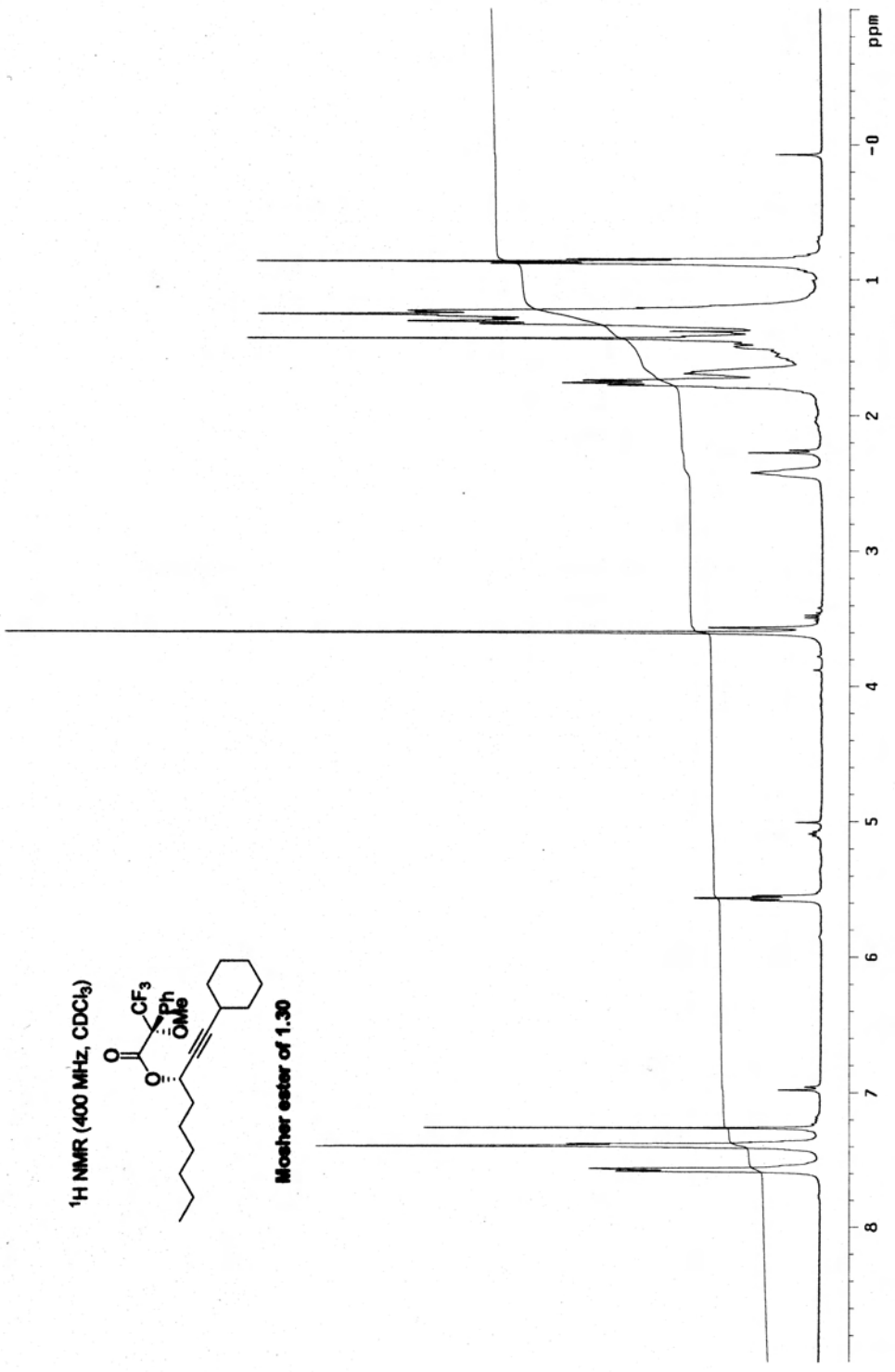


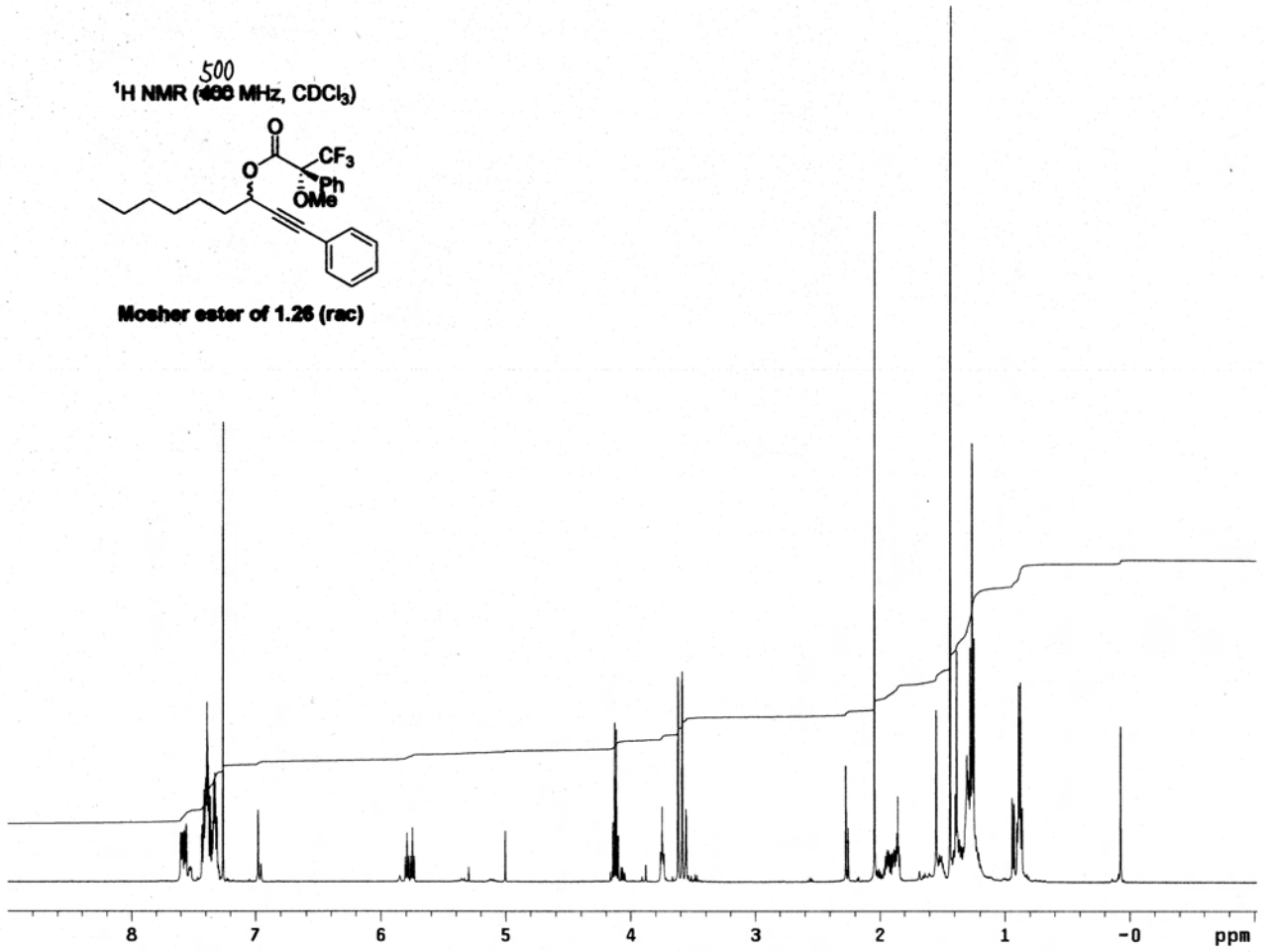
1.33

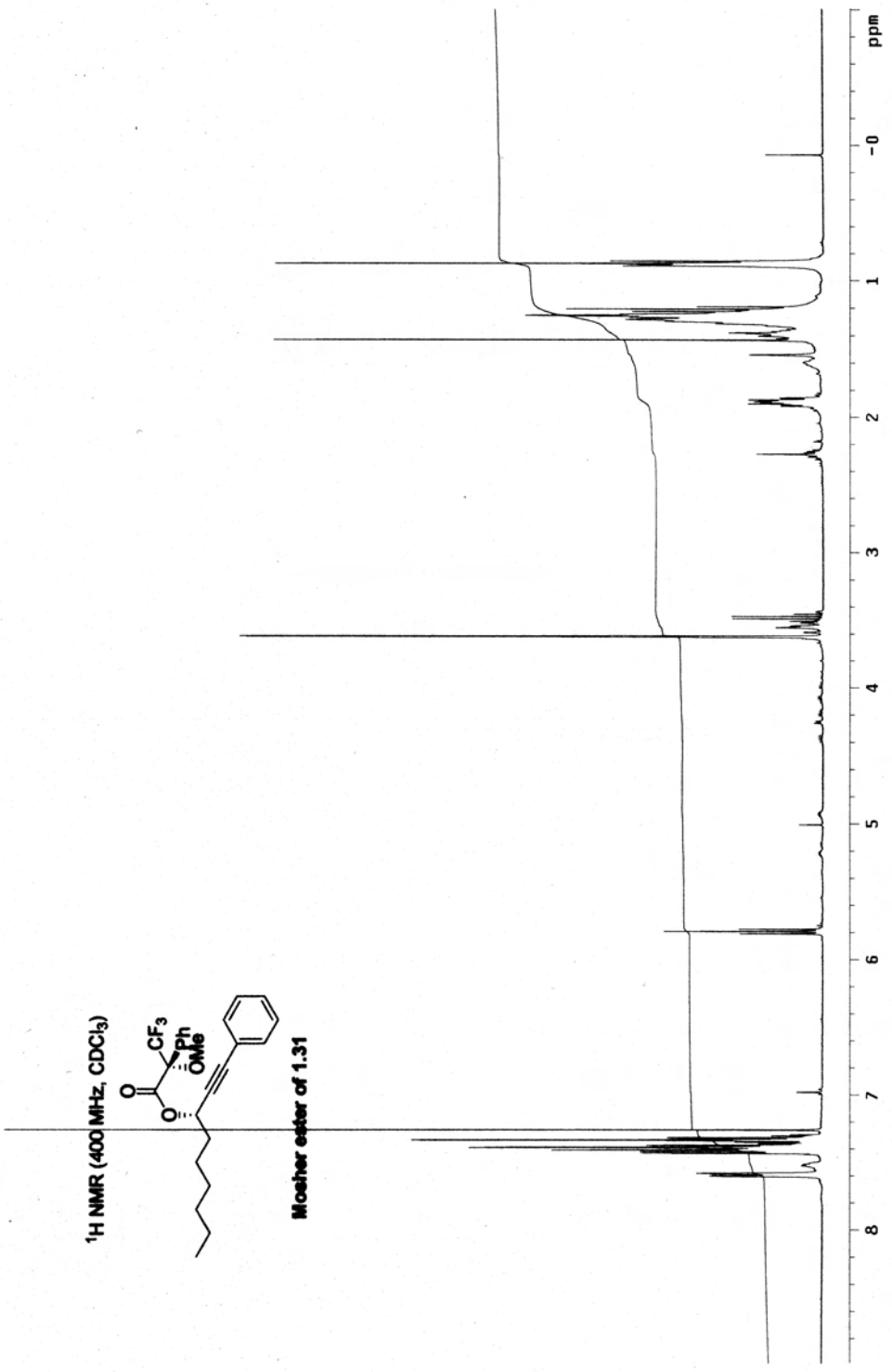

^{1}H NMR (300 MHz, CDCl$_3$)
O
H
MeO
1.34
ppm
10
9
8
7
6
5
4
3
2
1
-0

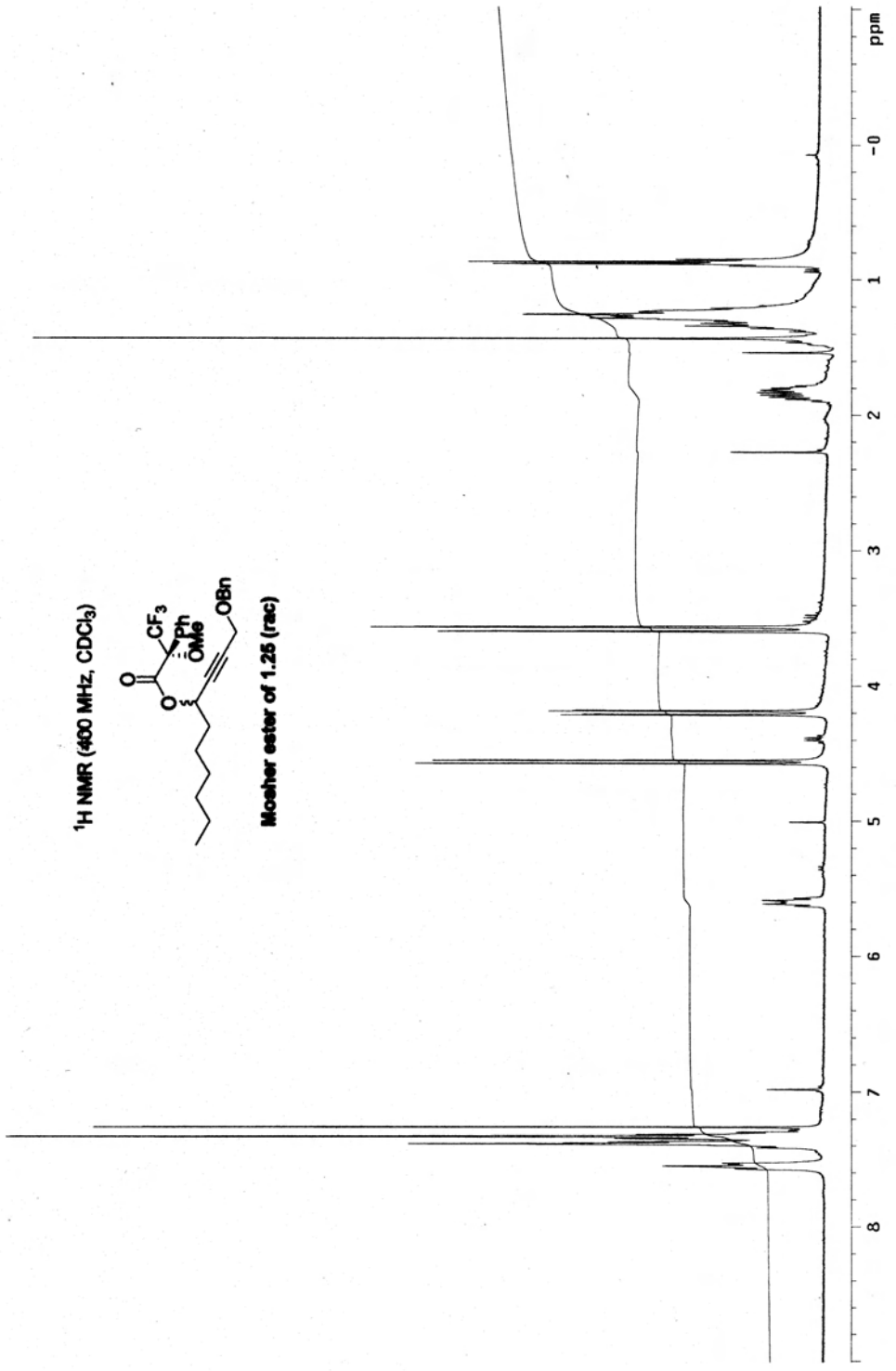

^{1}H NMR (300 MHz, CDCl$_3$)
O
H
MeO
1.35
ppm
10
9
8
7
6
5
4
3
2
1
0

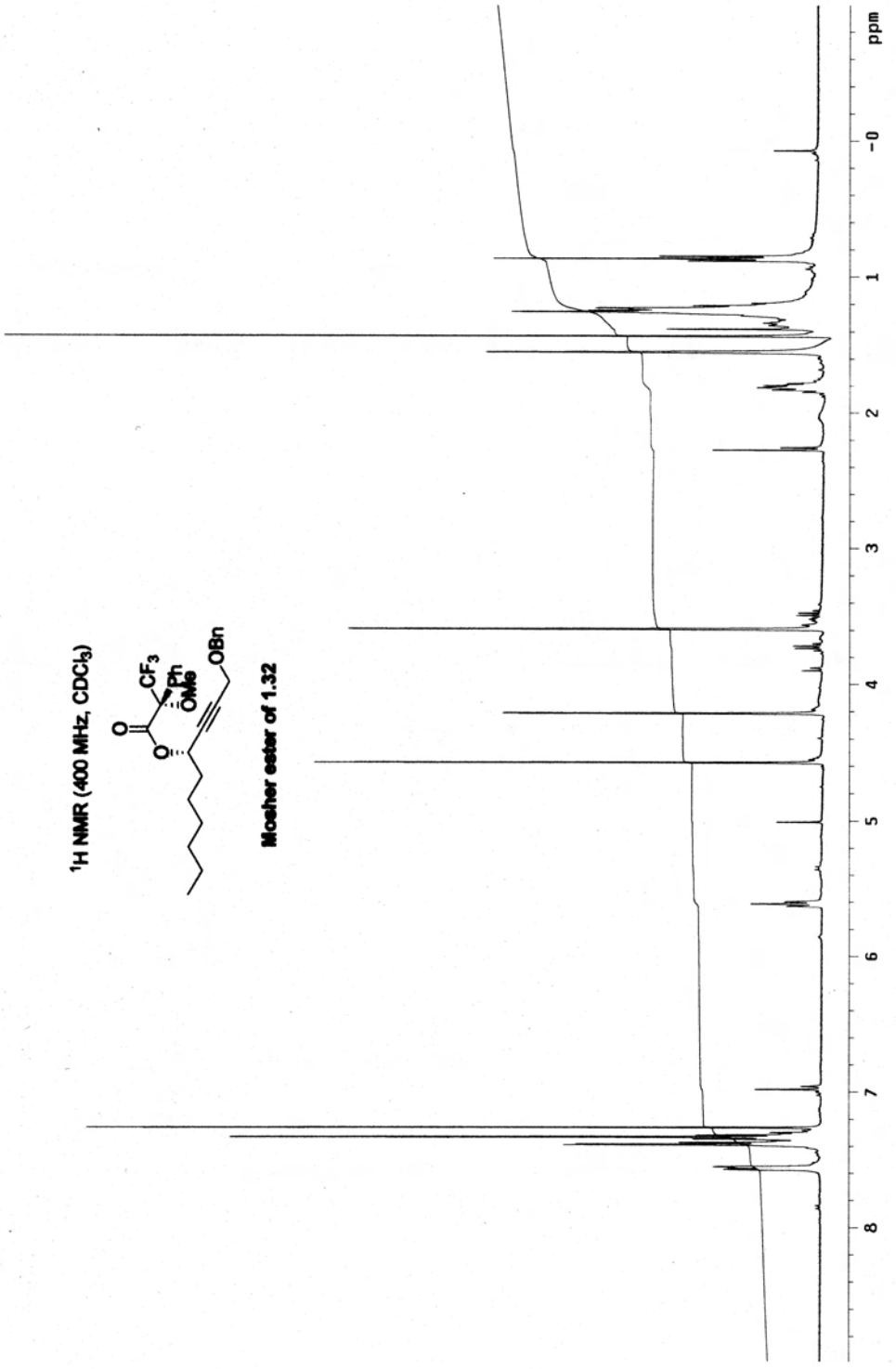

^{13}C NMR (300 MHz, CDCl$_3$)
O
H
MeO
1.35
ppm
0
20
40
60
80
100
120
140
160
180
200
220

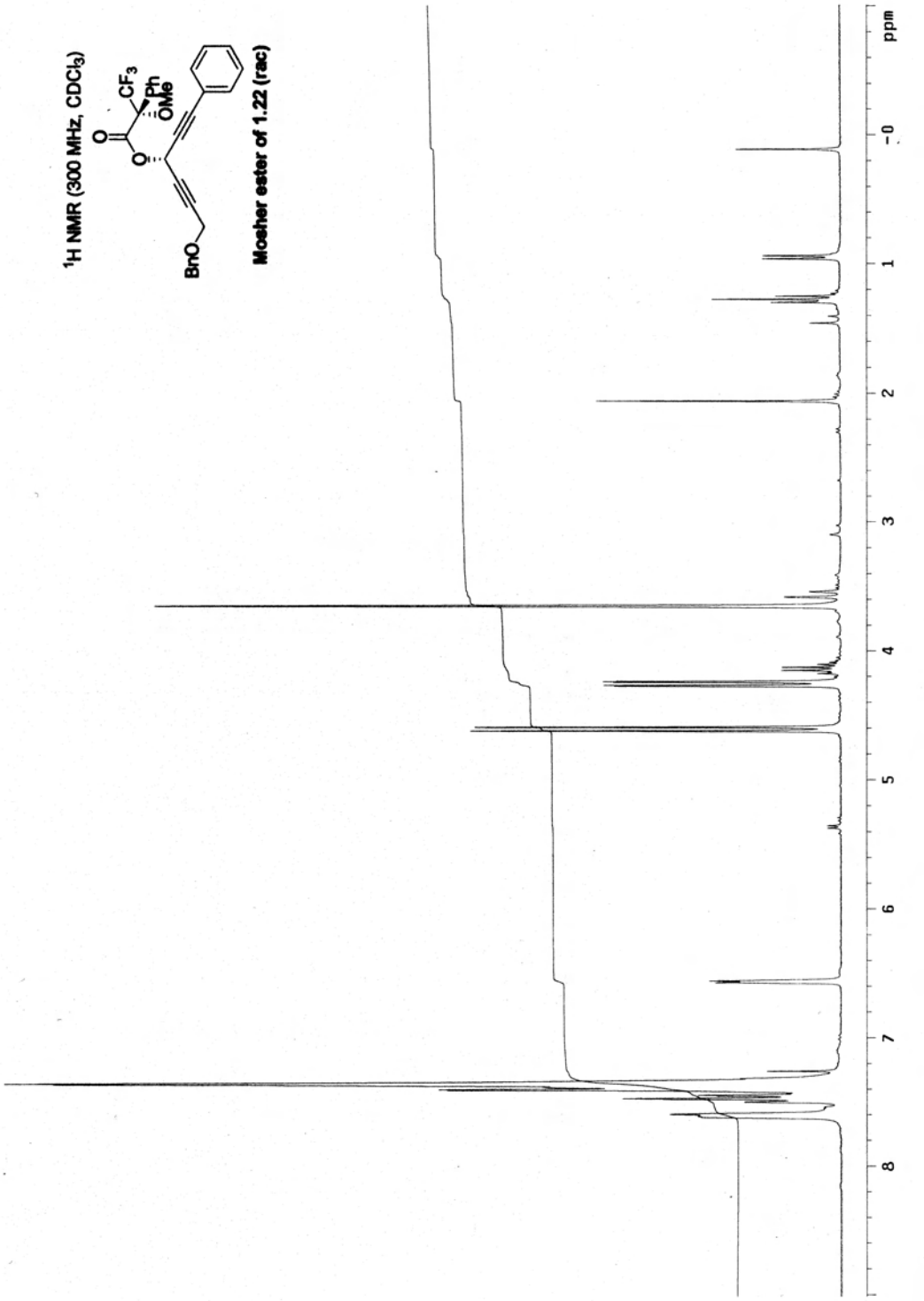

^{1}H NMR (400 MHz, CDCl$_3$)
Mosher ester of 1.30
ppm

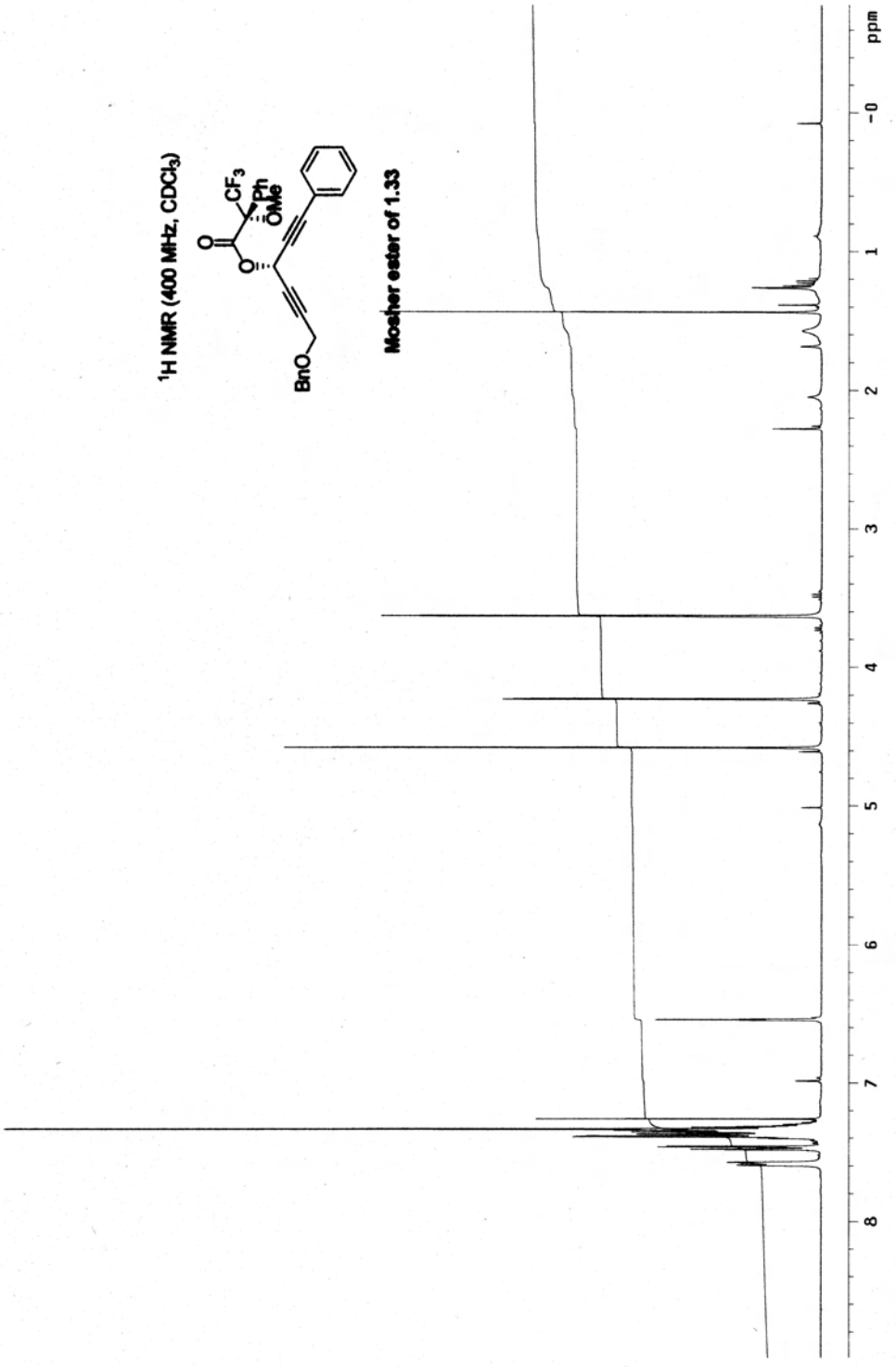

500
¹H NMR (400 MHz, CDCl3)
O
CF3
O
Ph
OMe
Mosher ester of 1.26 (rac)
8
7
6
5
4
3
2
1
-0
ppm

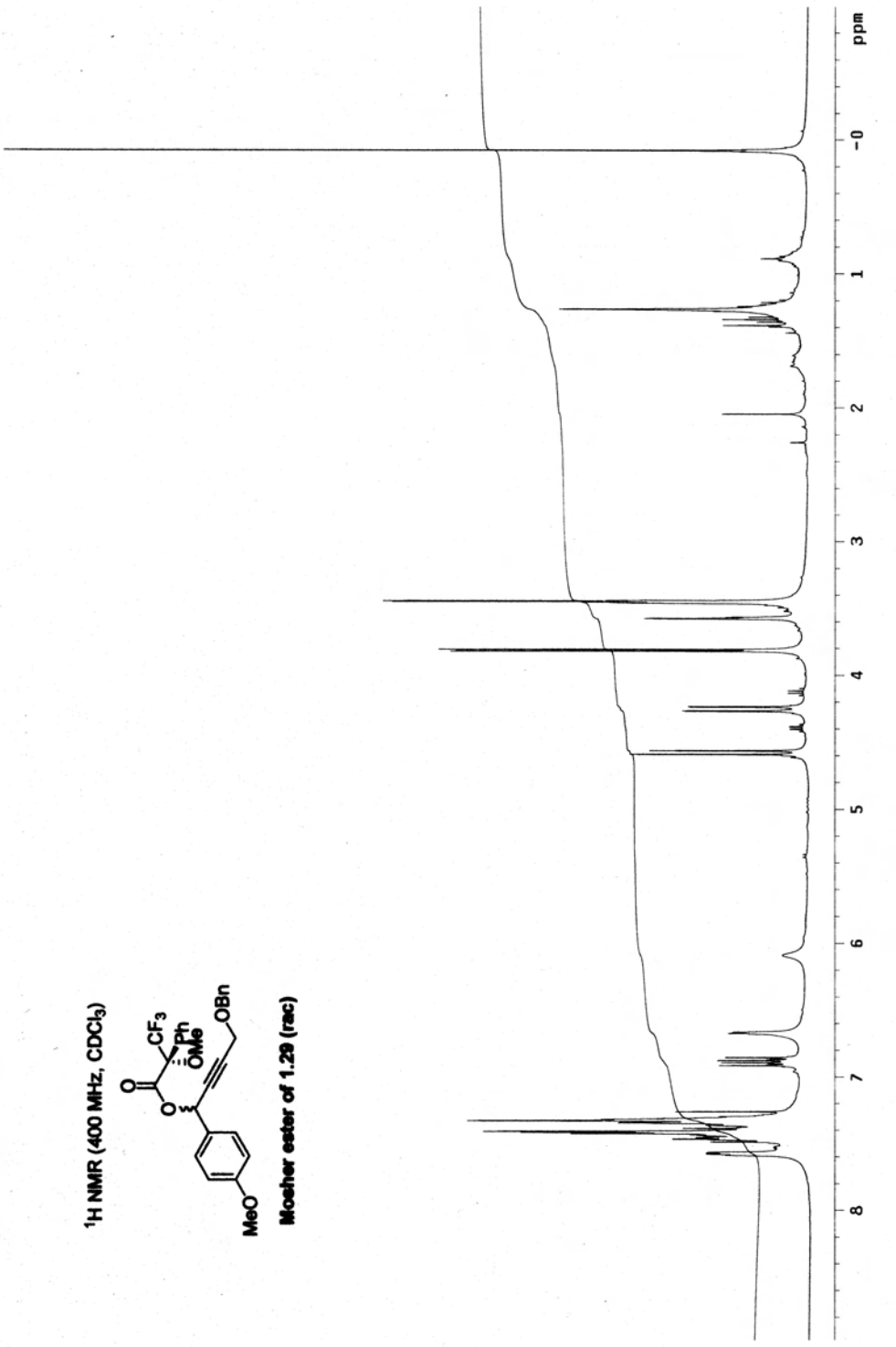

^{1}H NMR (400 MHz, CDCl$_3$)
CF$_3$
Ph
OMe
O
O
Mosher ester of 1.31
ppm
8
7
6
5
4
3
2
1
-0

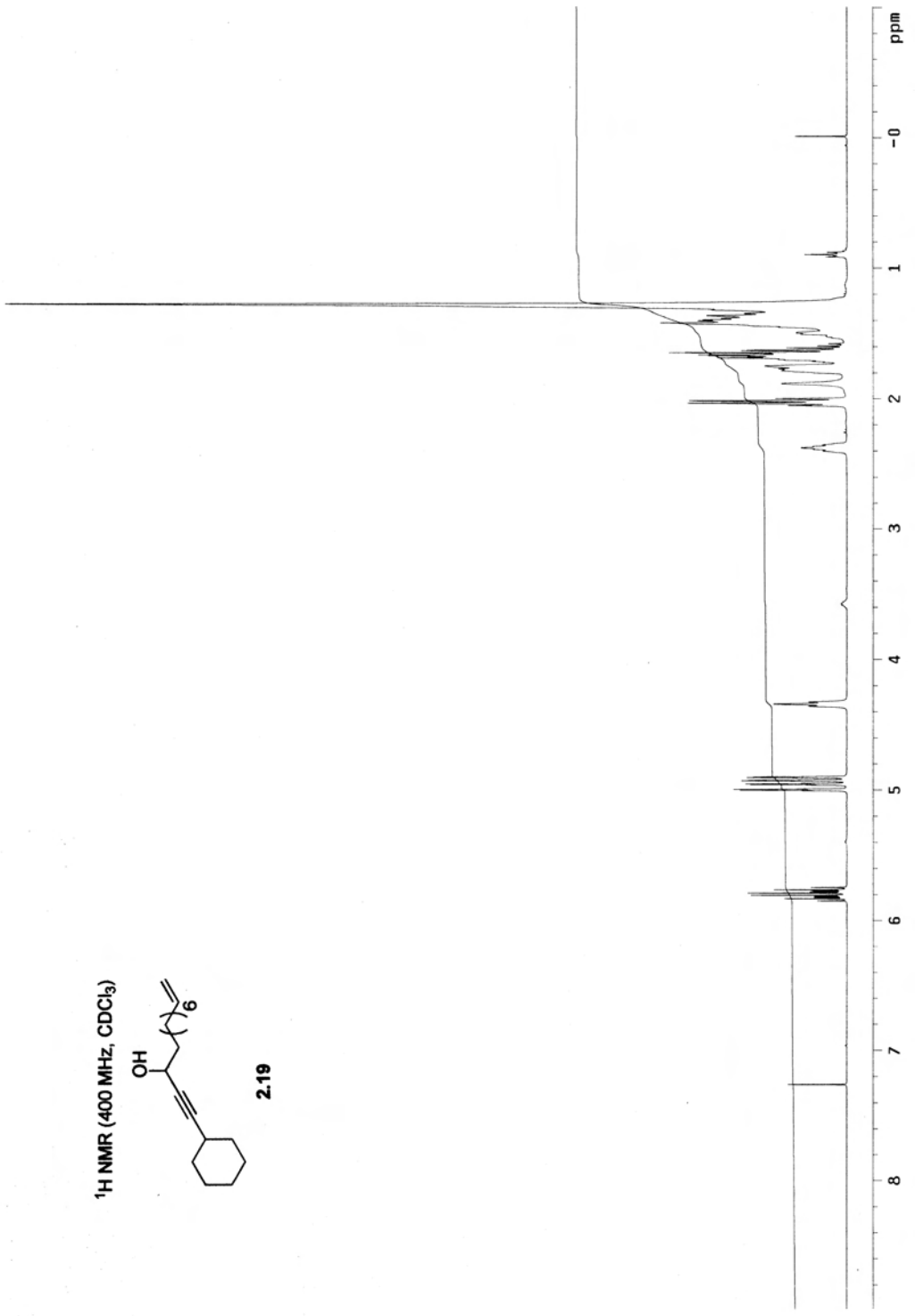

^{1}H NMR (400 MHz, CDCl$_3$)
CF$_3$
Ph
OMe
OBn
Mosher ester of 1.25 (rac)
ppm

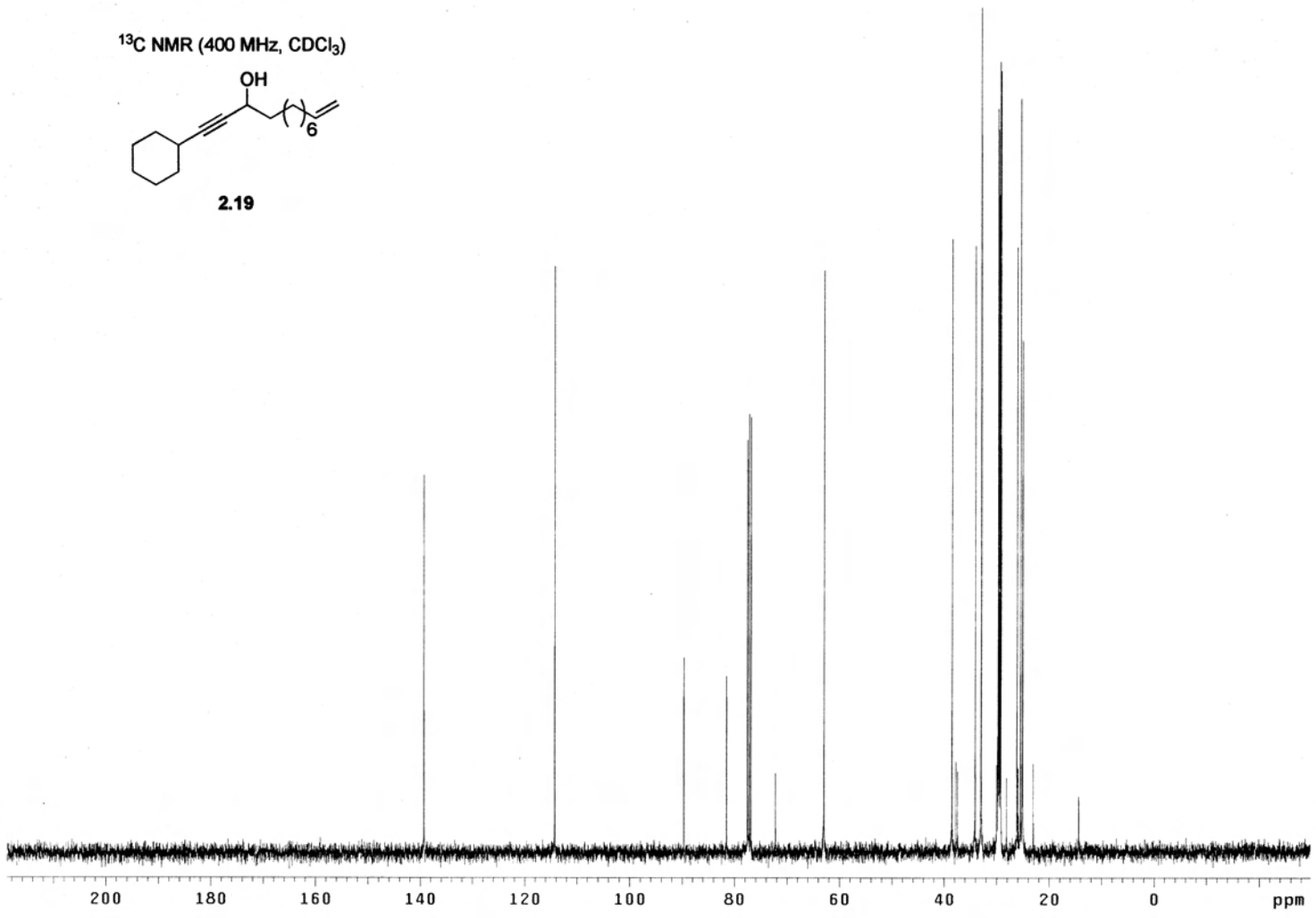

^{1}H NMR (400 MHz, CDCl$_3$)
Mosher ester of 1.32
CF$_3$
Ph
OMe
OBn
O
O
ppm
8
7
6
5
4
3
2
1
-0


^{1}H NMR (300 MHz, CDCl$_3$)
Mosher ester of 1.22 (rac)
BnO
CF$_3$
Ph
OMe
ppm

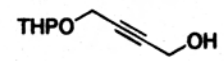

^{1}H NMR (400 MHz, CDCl$_3$)
Mosher ester of 1.33
BnO
OMe
Ph
CF$_3$
ppm


^{1}H NMR (400 MHz, CDCl$_3$)
CF$_3$
Ph
OMe
OBn
MeO
Mosher ester of 1.29 (rac)
ppm
8
7
6
5
4
3
2
1
0


^{1}H NMR (400 MHz, $CDCl_3$)
OH
6
2.19
ppm
-0
1
2
3
4
5
6
7
8

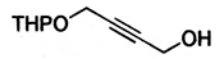

^{13}C NMR (400 MHz, $CDCl_3$)
OH
6
2.19
200
180
160
140
120
100
80
60
40
20
0
ppm

^{1}H NMR (300 MHz, $CDCl_3$)

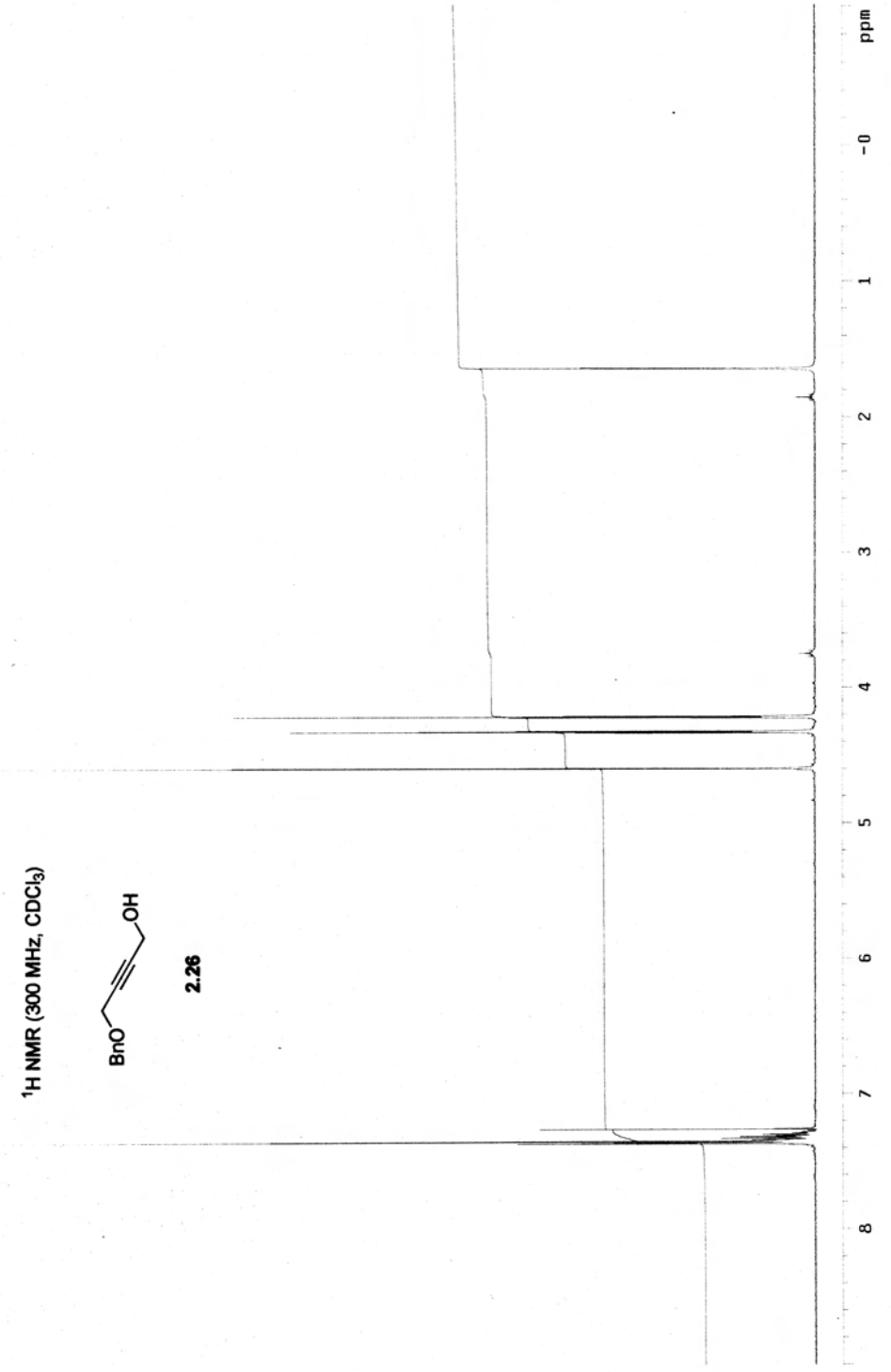


2.25

^{13}C NMR (300 MHz, $CDCl_3$)

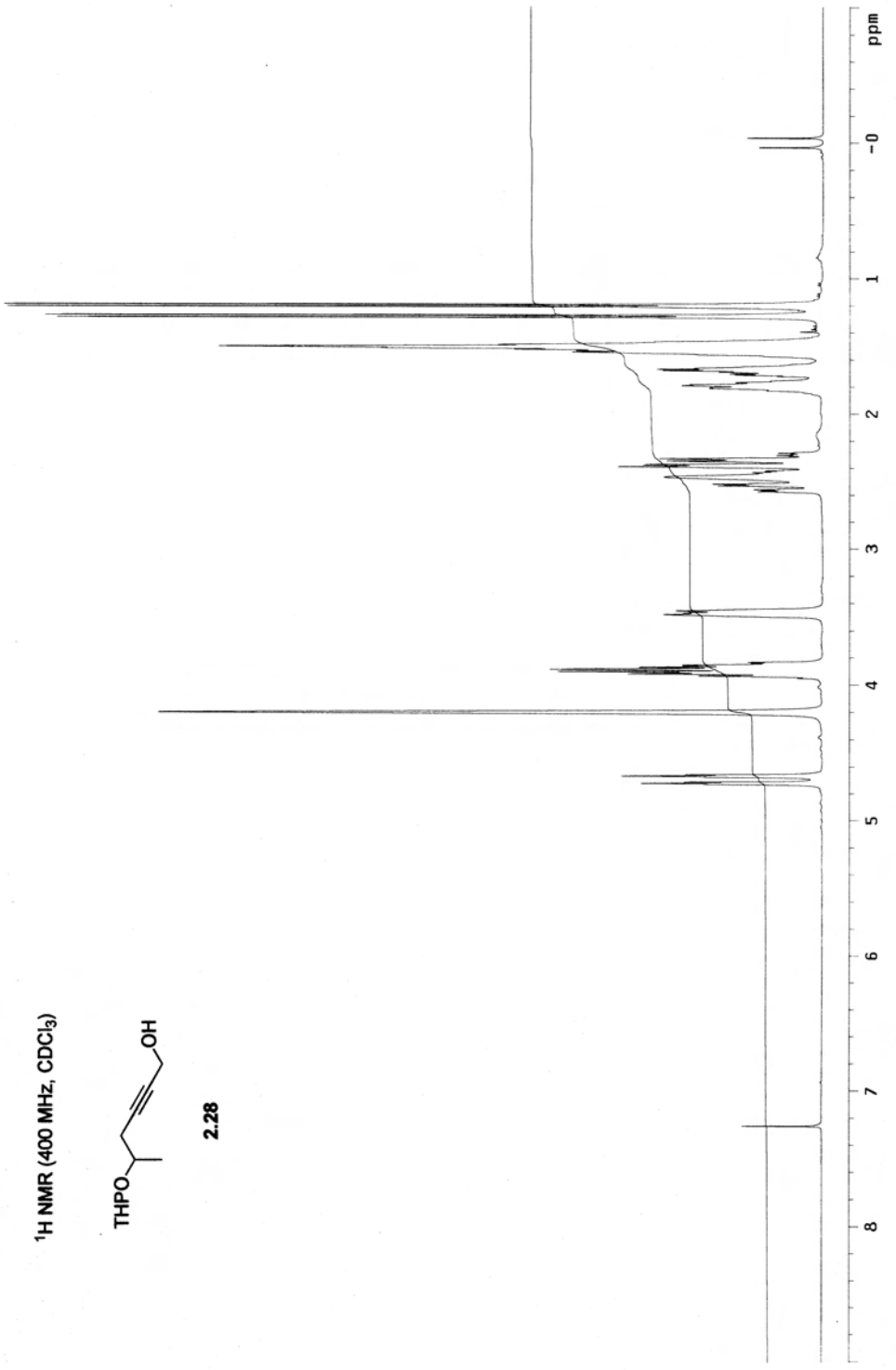


2.25

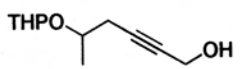

^{1}H NMR (300 MHz, $CDCl_3$)
BnO
OH
2.26
8
7
6
5
4
3
2
1
−0
ppm

^{1}H NMR (300 MHz, $CDCl_3$)

2.27

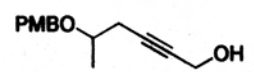

^{1}H NMR (400 MHz, $CDCl_3$)
THPO
OH
2.28
ppm
8
7
6
5
4
3
2
1
-0

^{13}C NMR (400 MHz, $CDCl_3$)



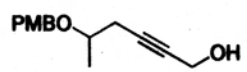
2.28

^{1}H NMR (300 MHz, $CDCl_3$)

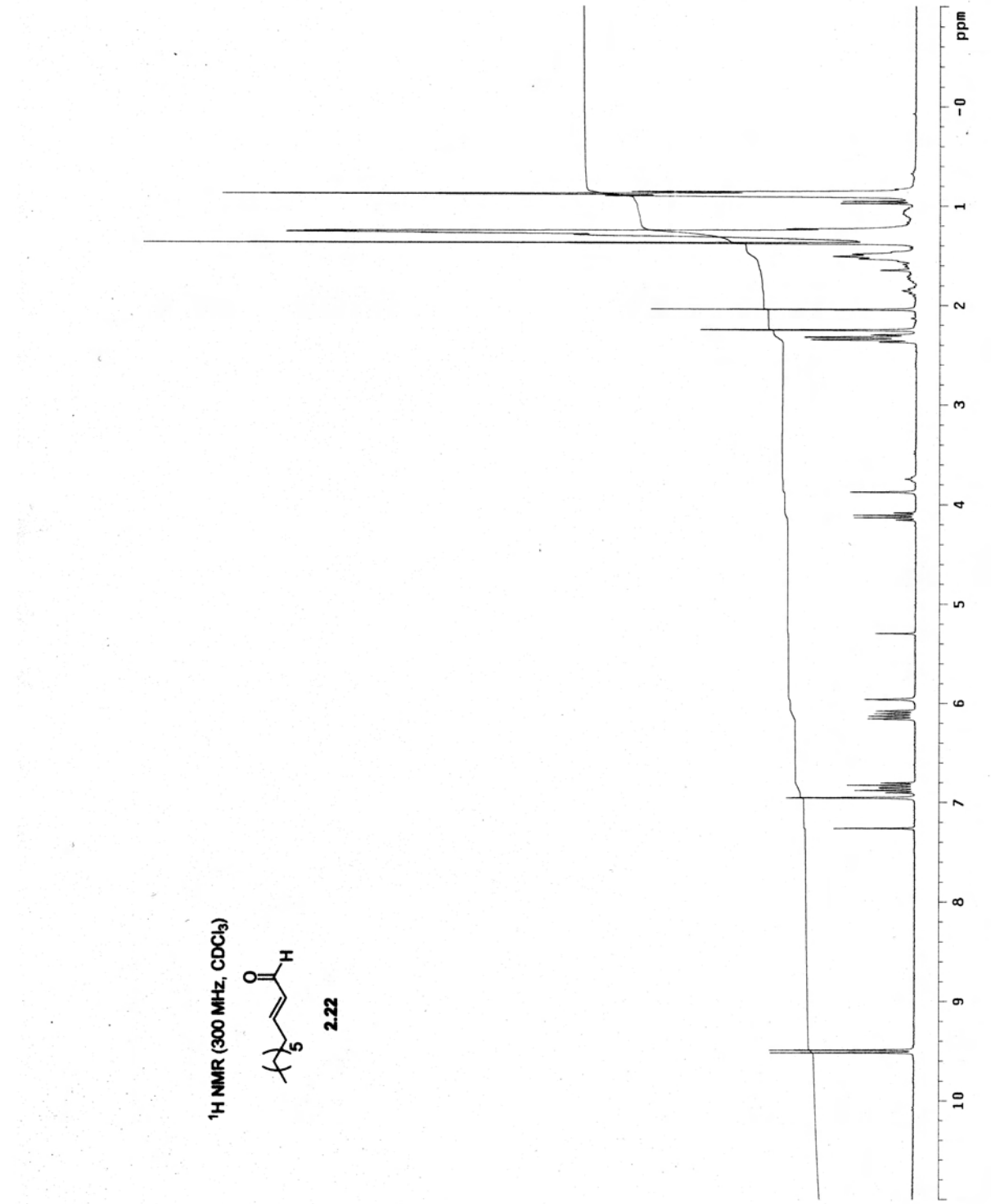


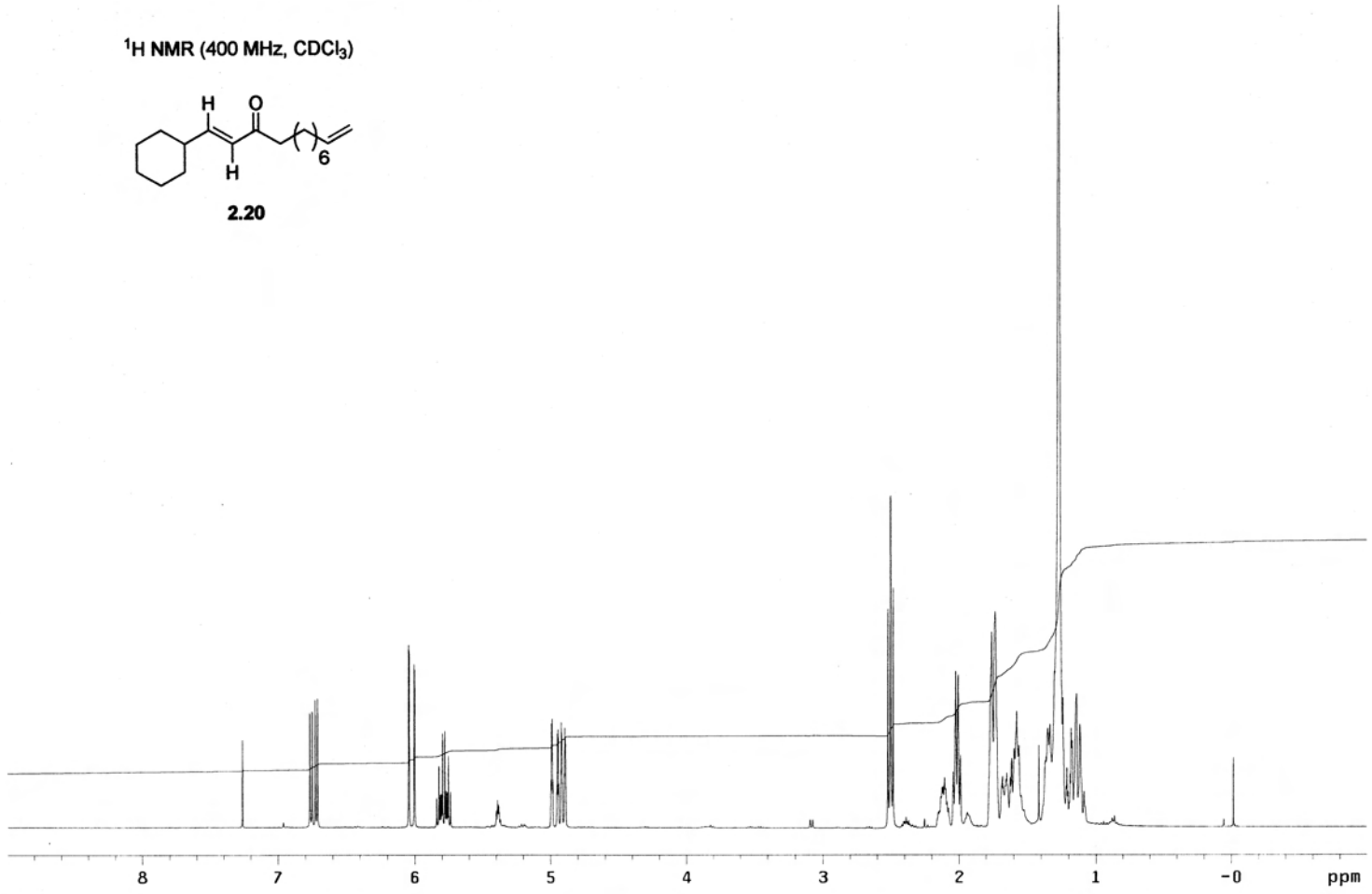
2.29

^{13}C NMR (300 MHz, $CDCl_3$)

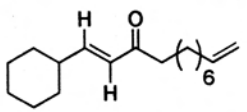


2.29

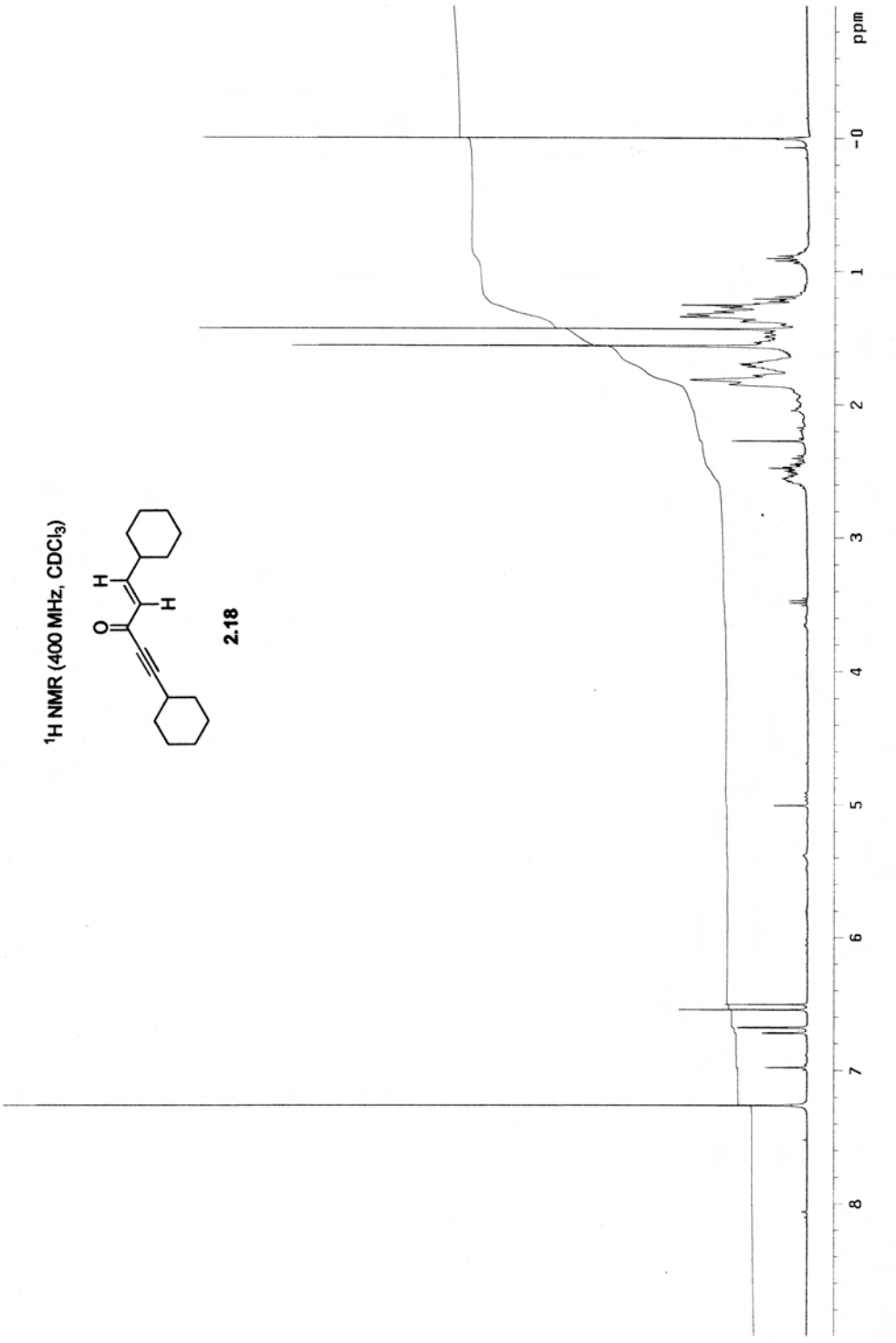

^{1}H NMR (300 MHz, CDCl$_3$)
O
H
5
2.22
ppm
10
9
8
7
6
5
4
3
2
1
0

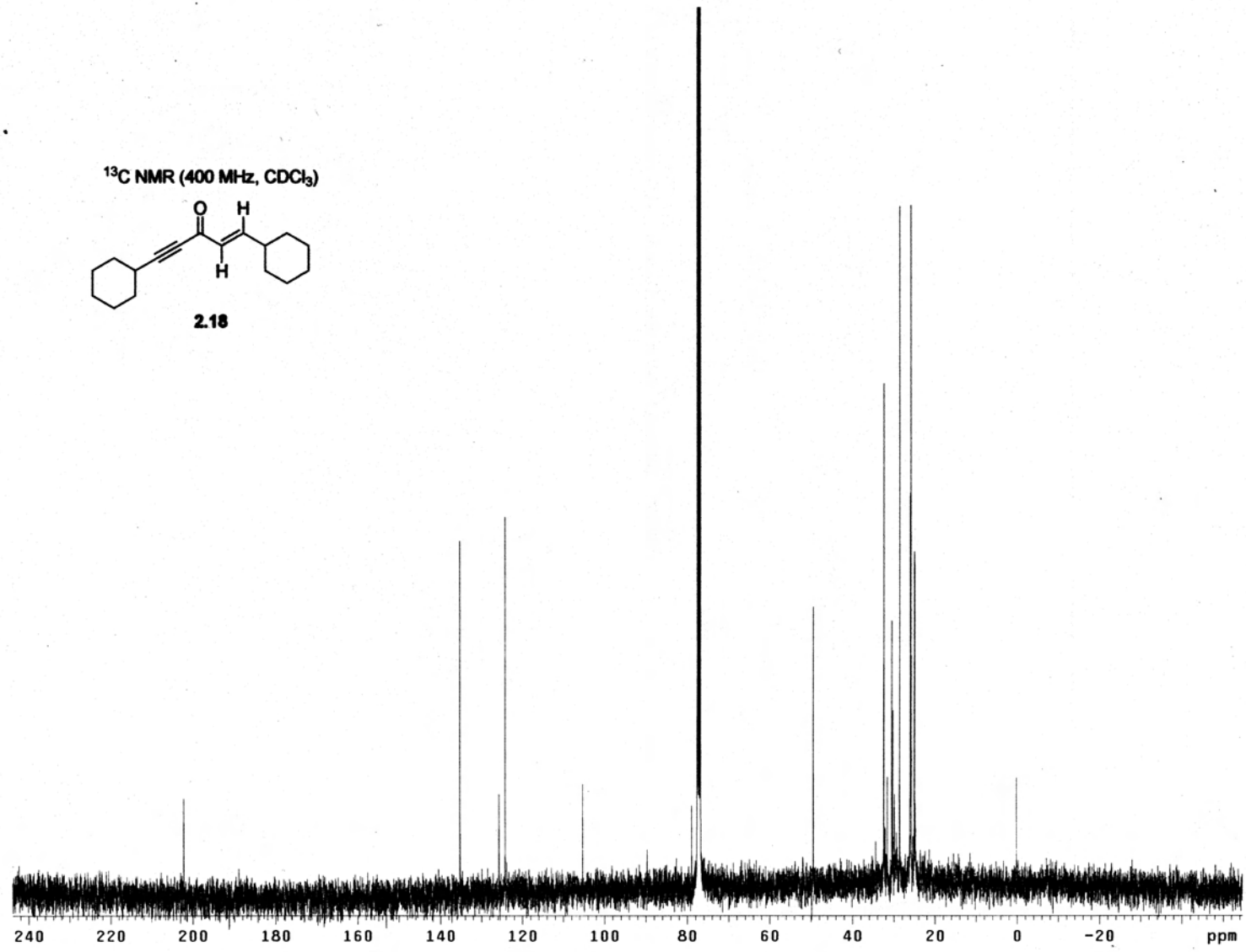

^{1}H NMR (400 MHz, $CDCl_3$)
H
O
6
H
2.20
8
7
6
5
4
3
2
1
-0
ppm

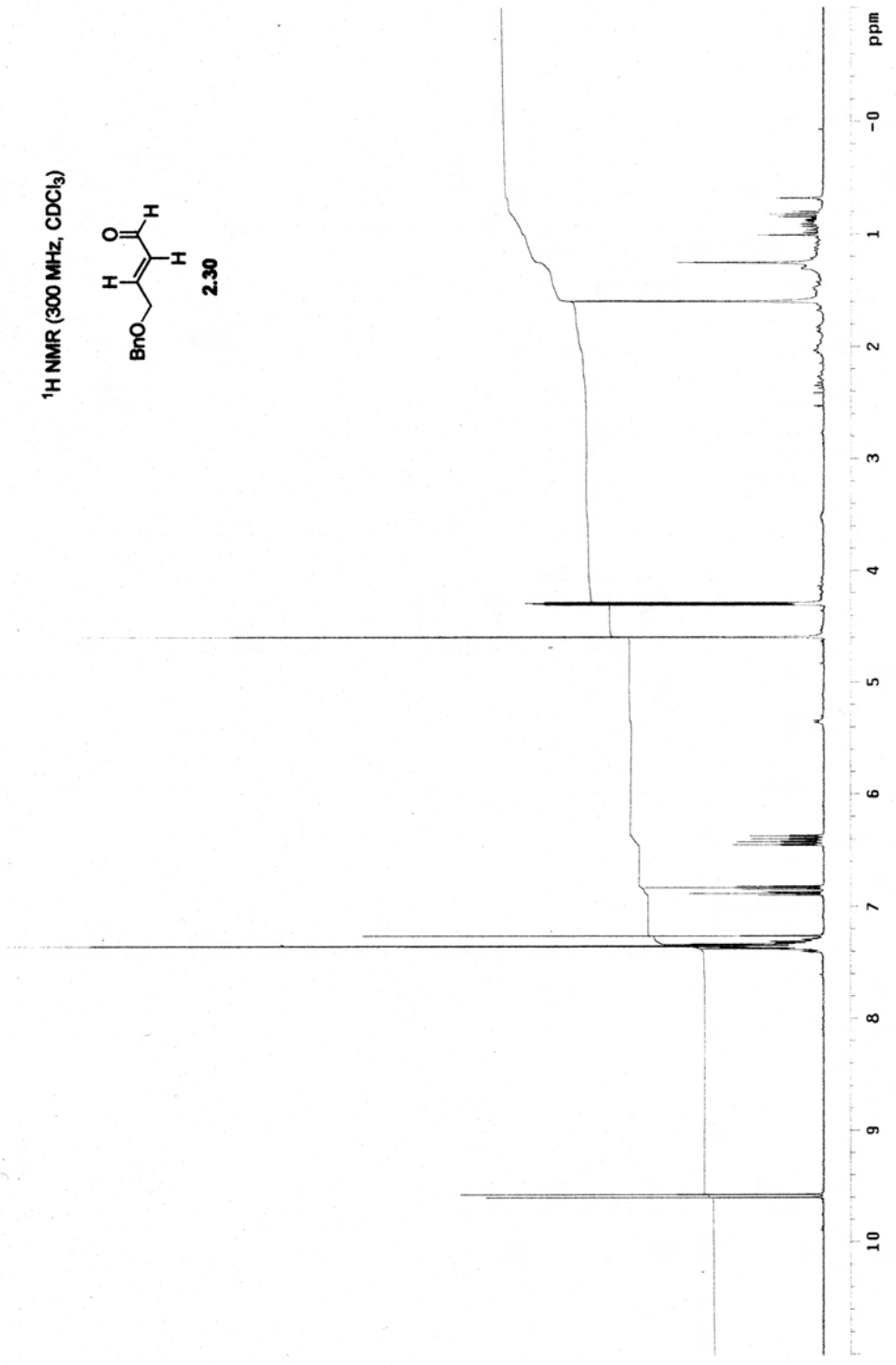
^{13}C NMR (400 MHz, $CDCl_3$)

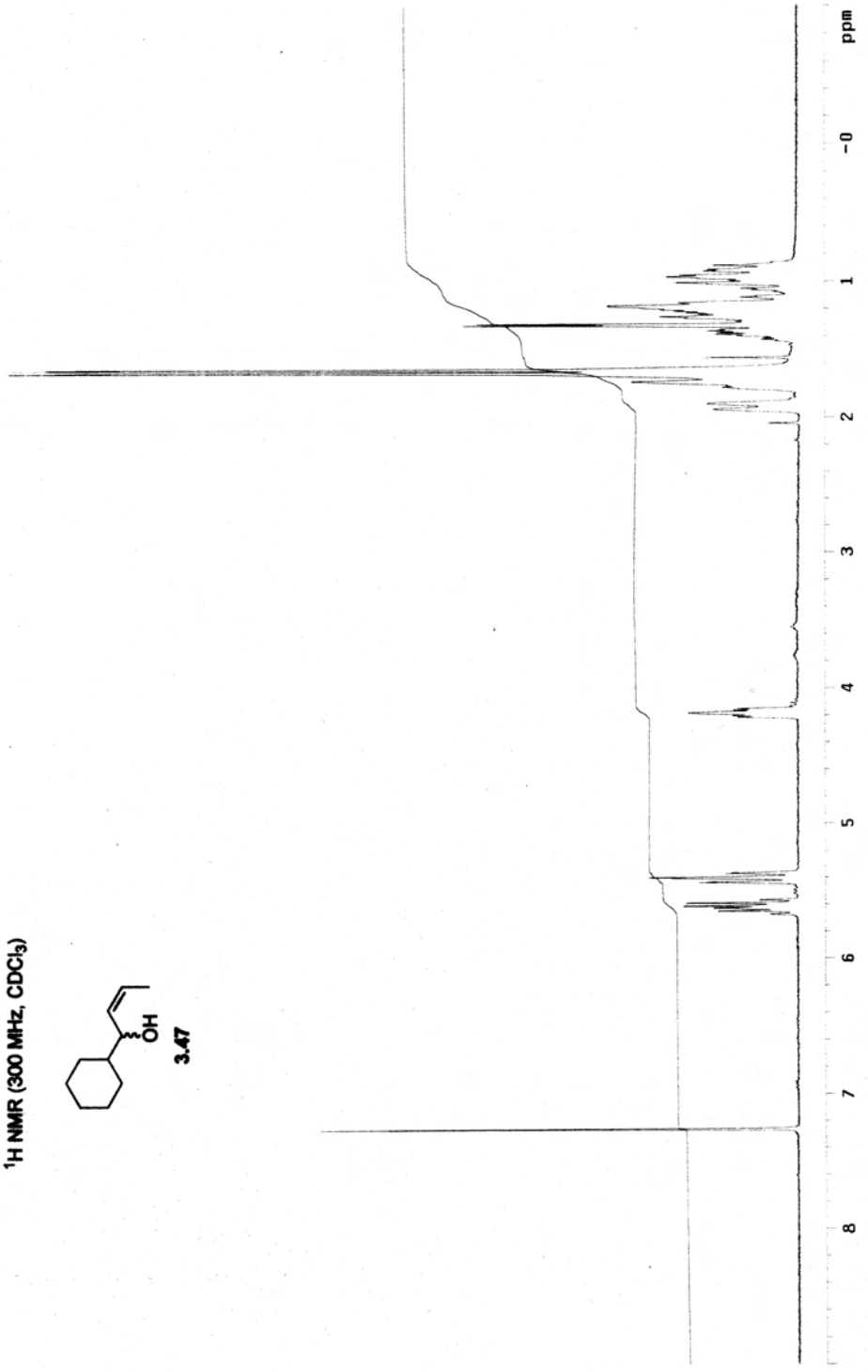


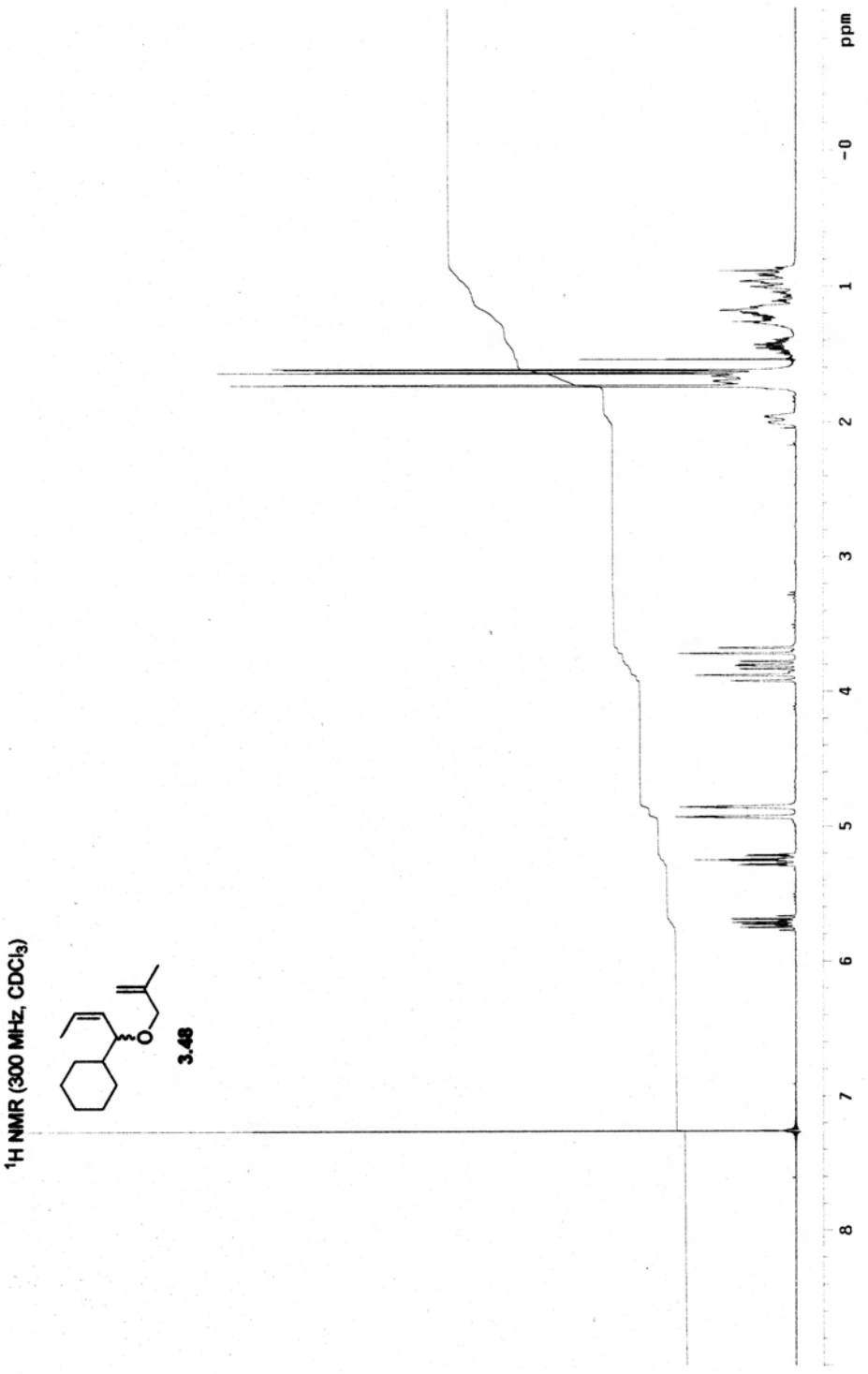
2.20

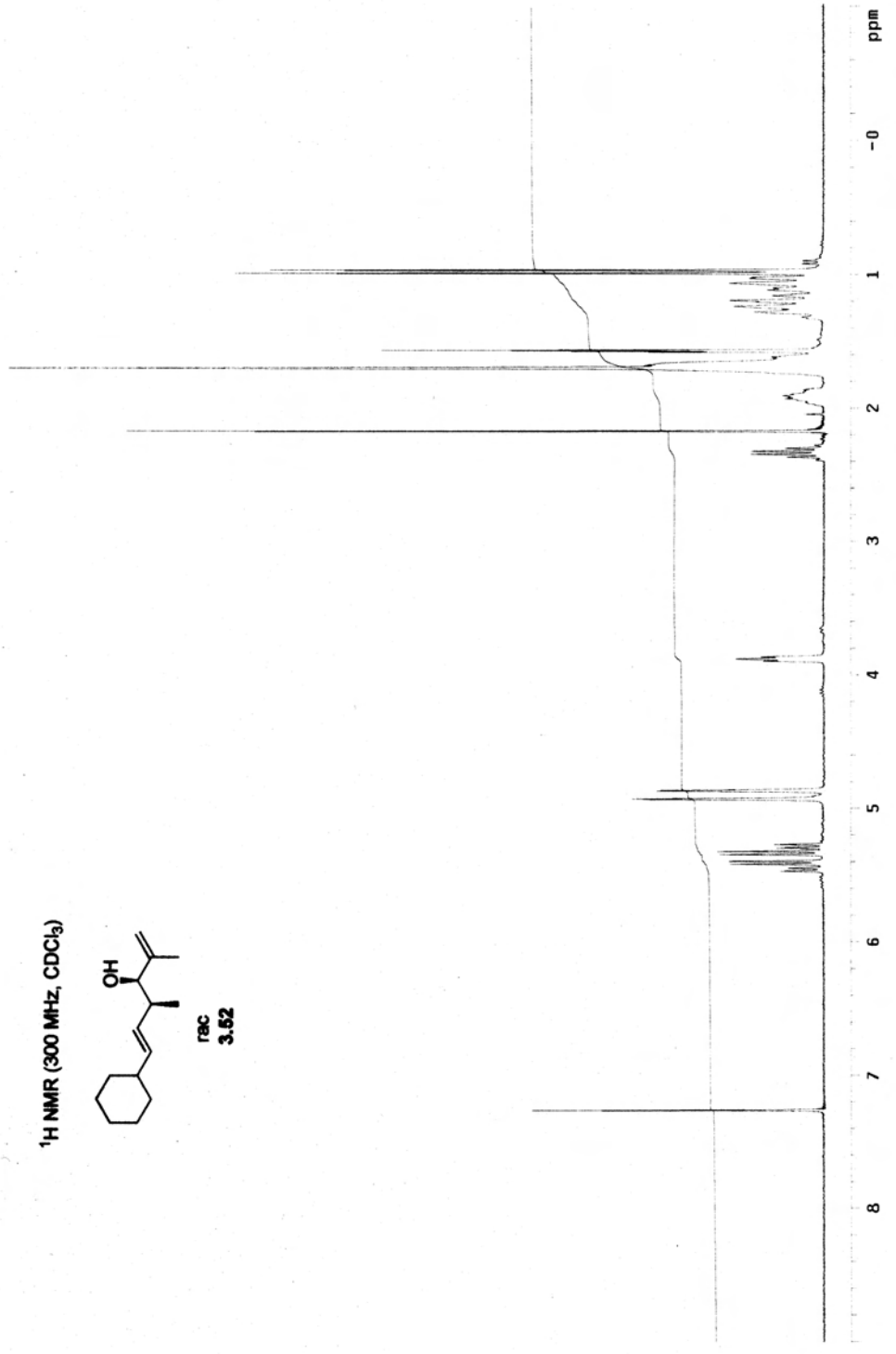

^{1}H NMR (400 MHz, CDCl$_3$)
H
O
H
2.18
ppm
8
7
6
5
4
3
2
1
0

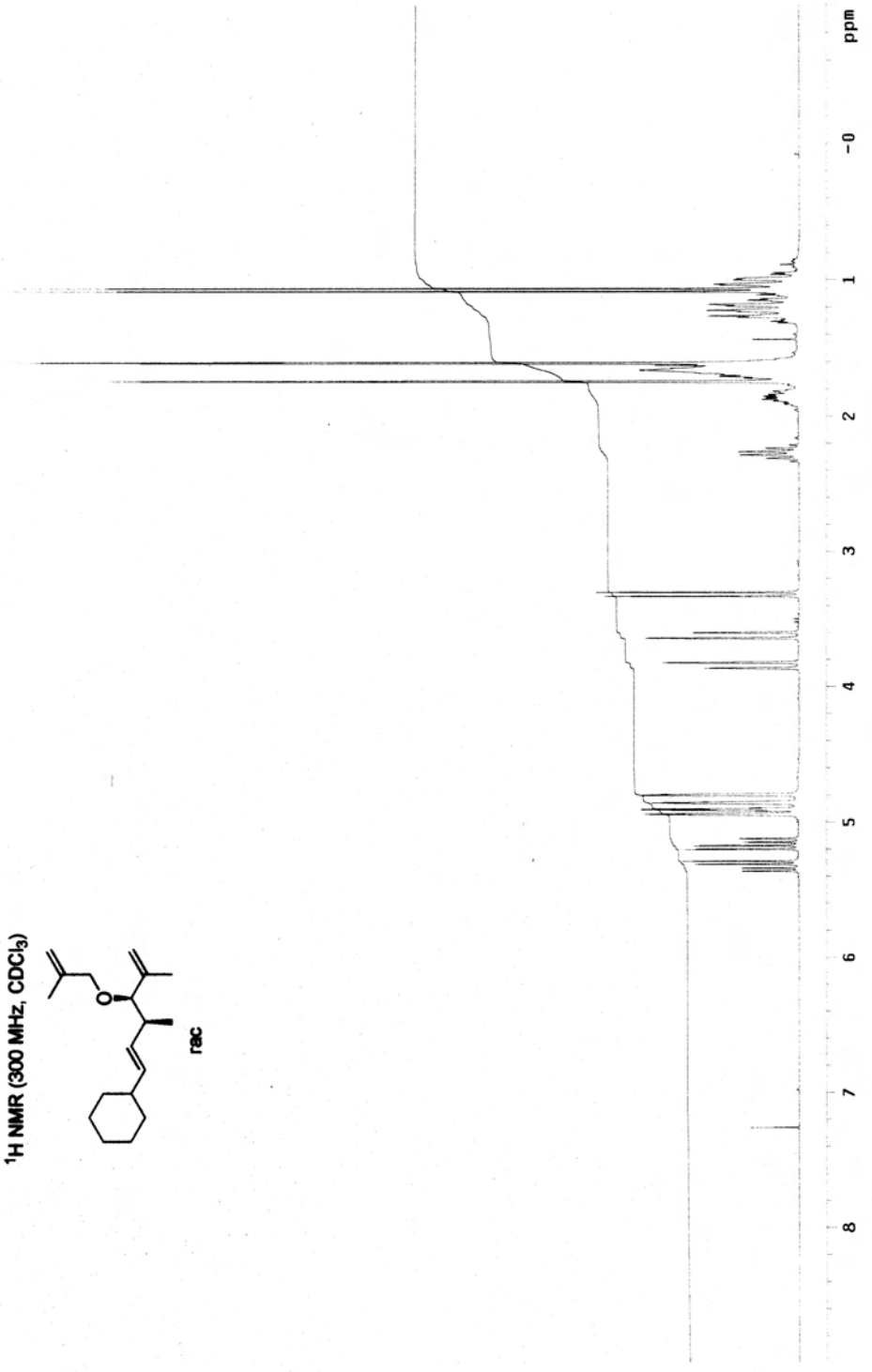

^{13}C NMR (400 MHz, $CDCl_3$)
O
H
H
2.18
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


^{1}H NMR (300 MHz, $CDCl_3$)
BnO
2.30
ppm

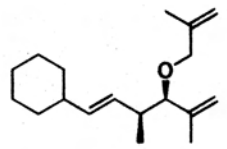

^{1}H NMR (300 MHz, $CDCl_3$)
OH
3.47
ppm
0
1
2
3
4
5
6
7
8


^{1}H NMR (300 MHz, CDCl$_3$)
3.48
8
7
6
5
4
3
2
1
−0
ppm

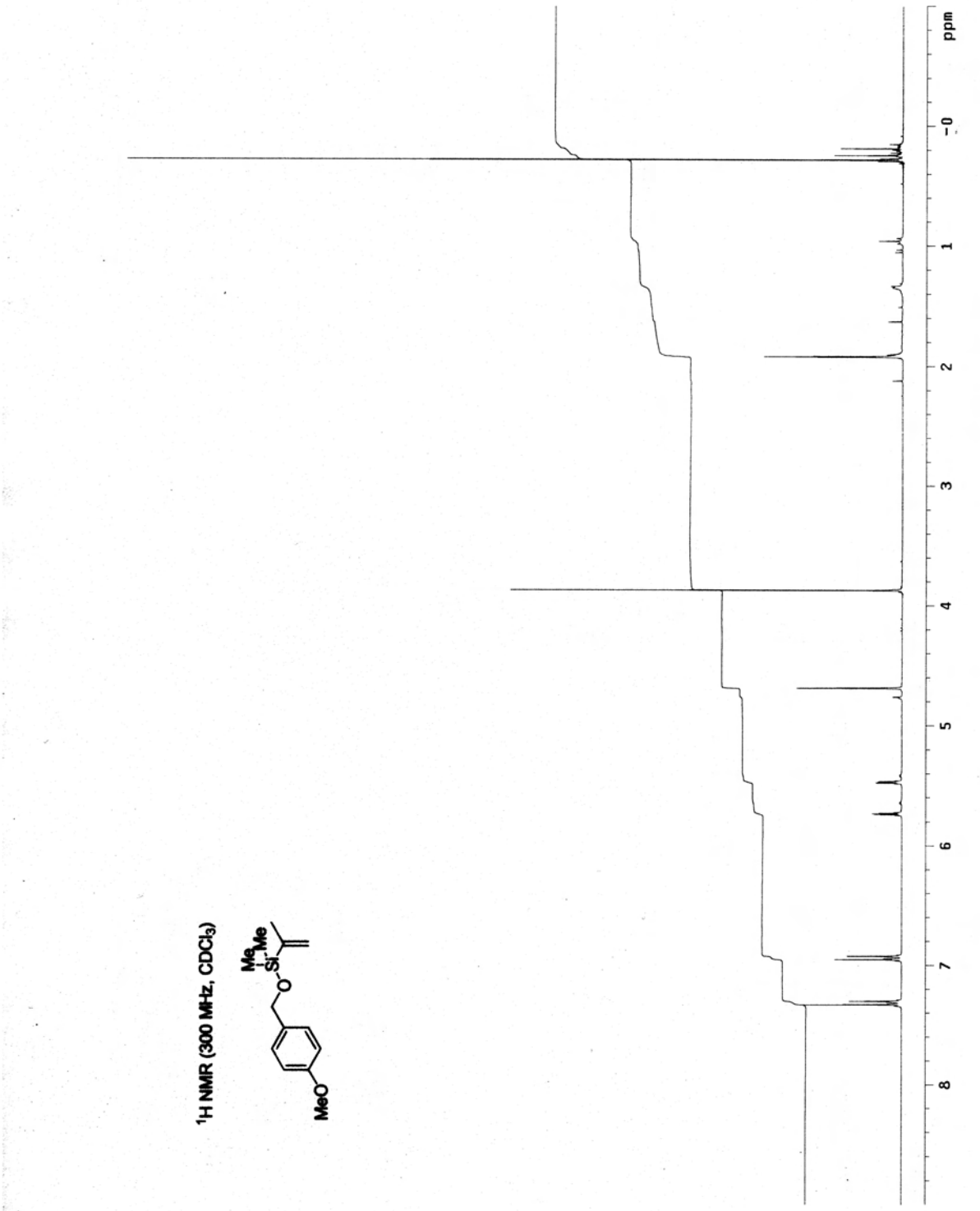

^{1}H NMR (300 MHz, $CDCl_3$)
OH
rac
3.52
8
7
6
5
4
3
2
1
-0
ppm

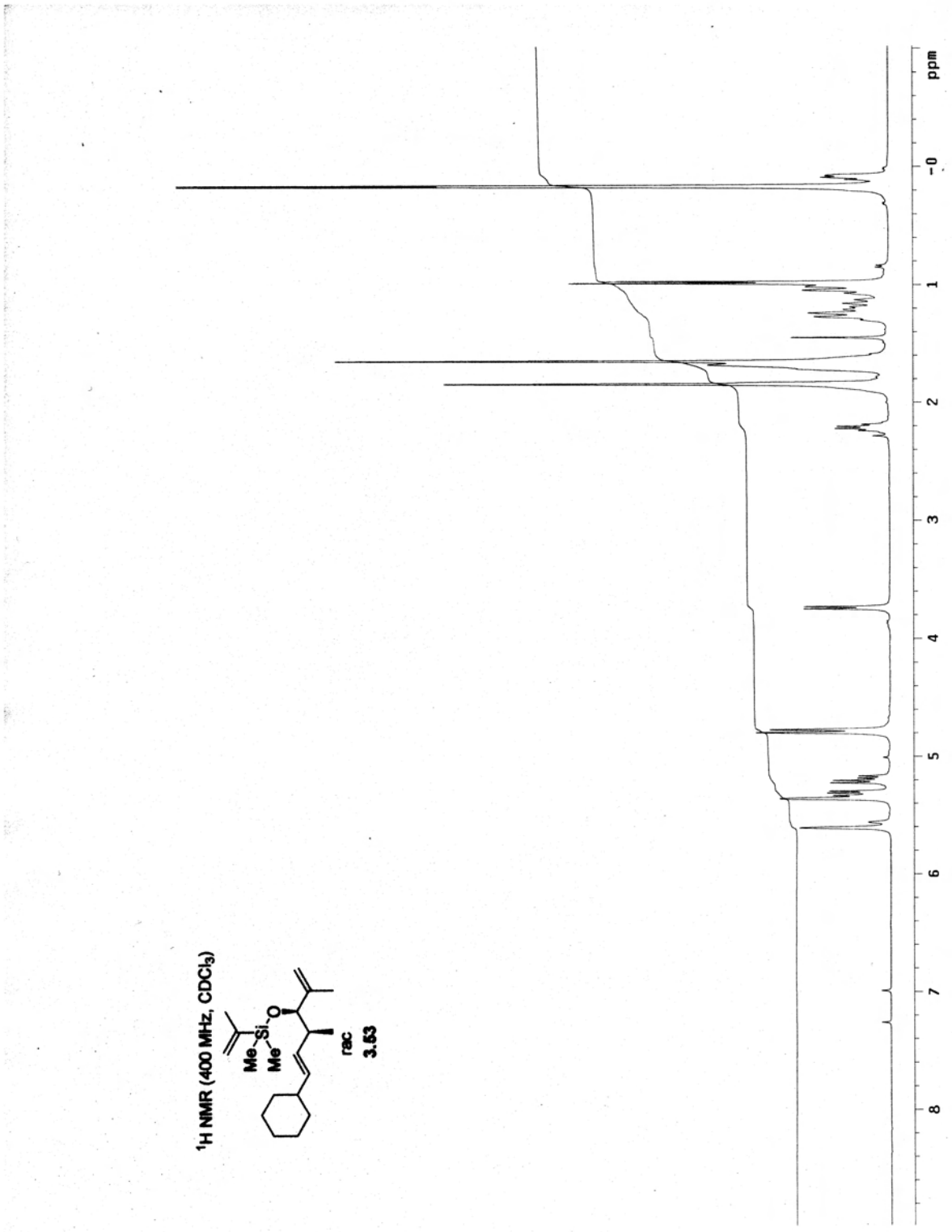

^{1}H NMR (300 MHz, $CDCl_3$)
rac
ppm
8
7
6
5
4
3
2
1
−0

^{13}C NMR (300 MHz, $CDCl_3$)

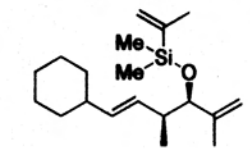


rac


^{1}H NMR (300 MHz, CDCl$_3$)
Me
Me
Si
O
MeO
8
7
6
5
4
3
2
1
0
ppm

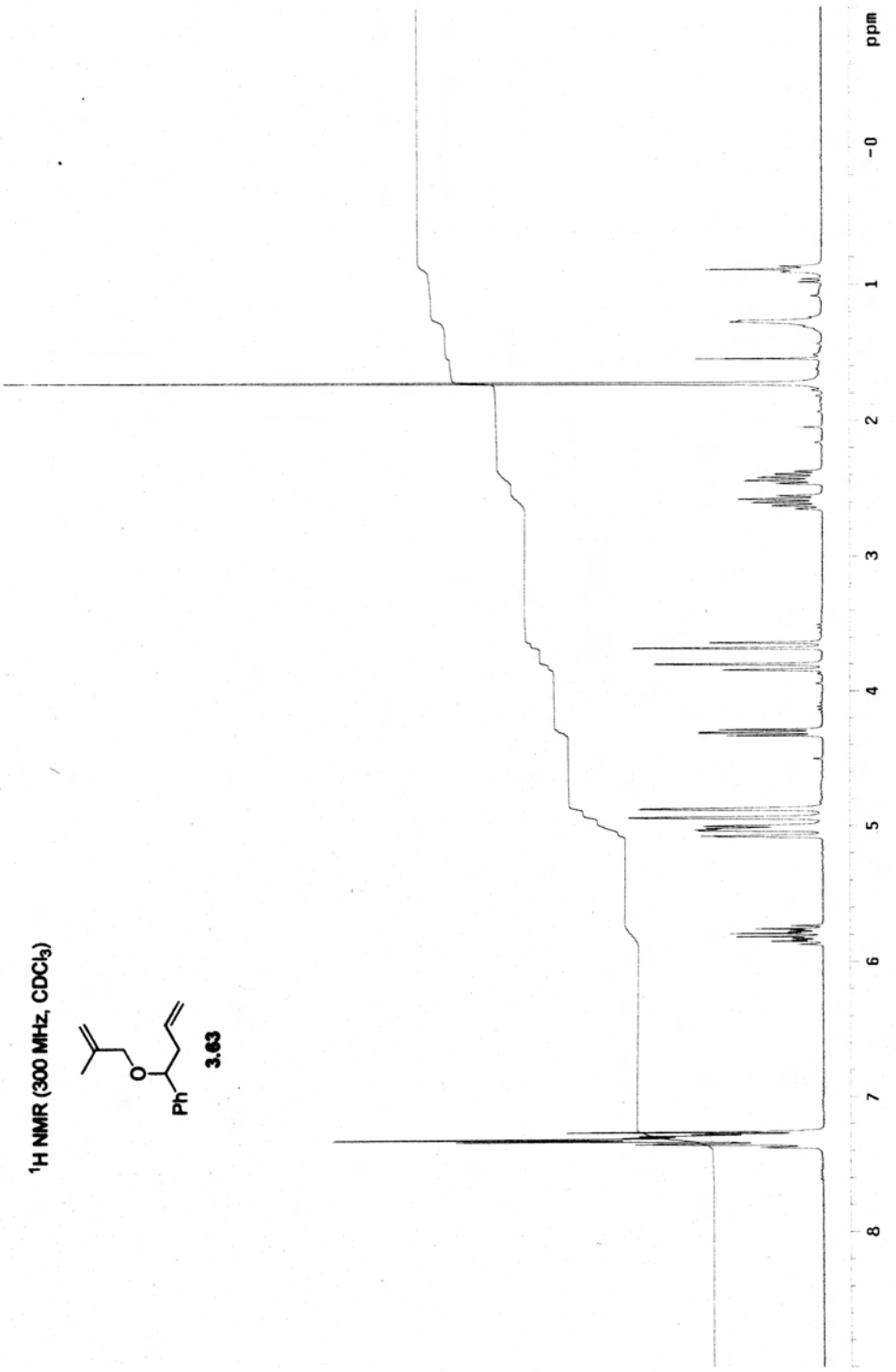

^{1}H NMR (400 MHz, CDCl$_3$)
Me
Si
Me
O
rac
3.53
ppm
8
7
6
5
4
3
2
1
0

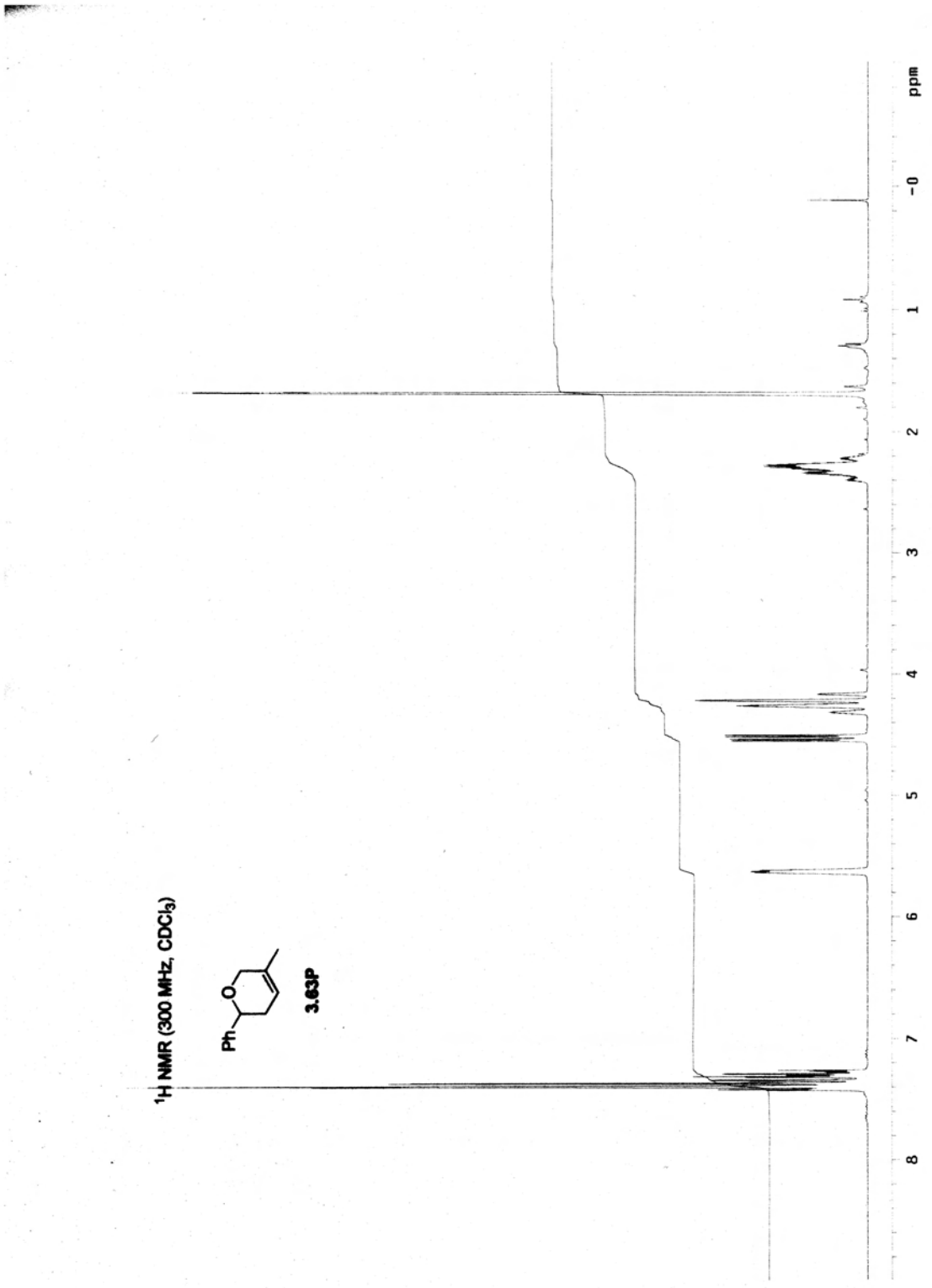
^{13}C NMR (400 MHz, $CDCl_3$)



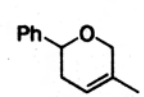
rac

3.53

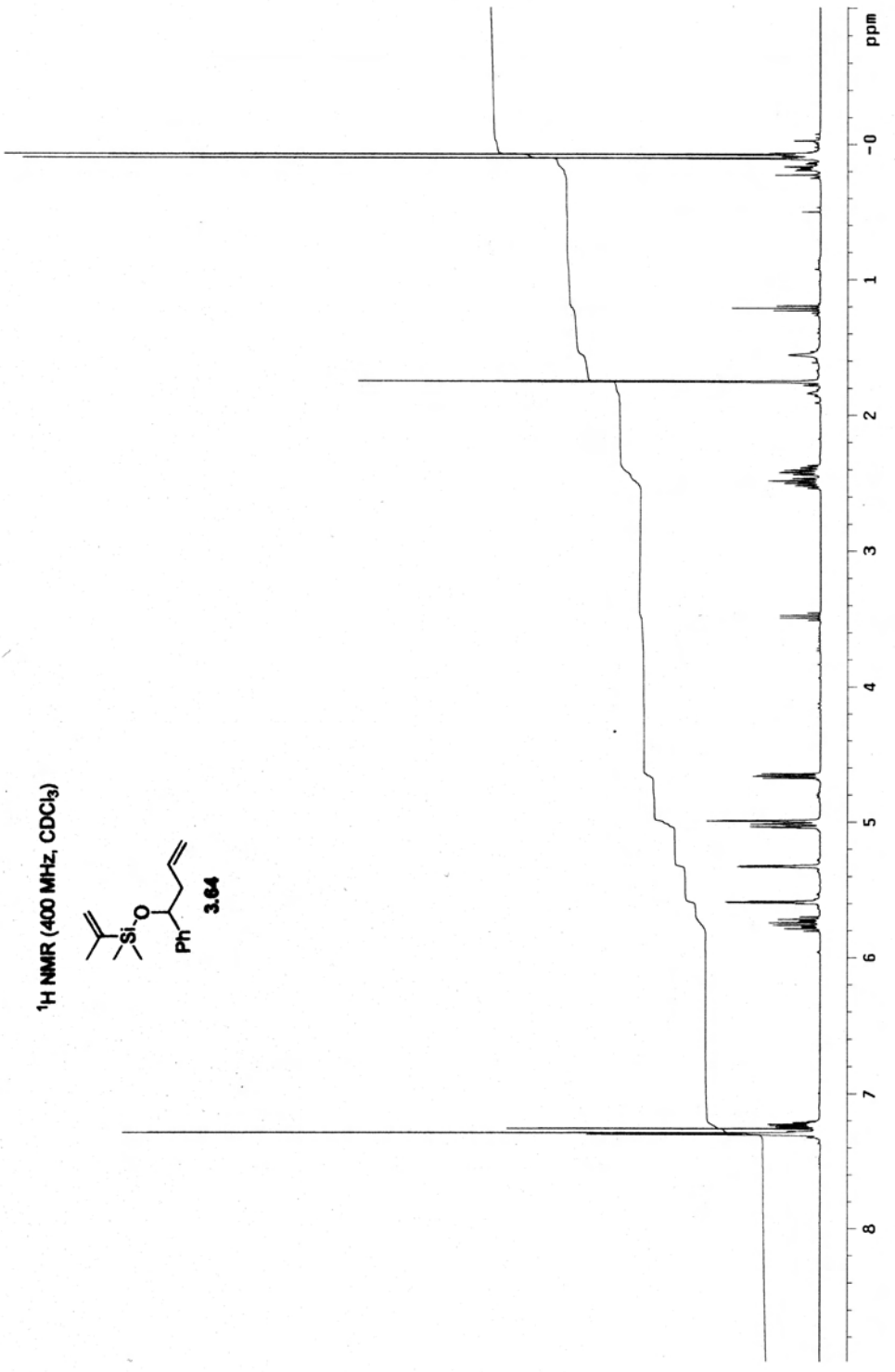

^{1}H NMR (300 MHz, CDCl$_3$)
O
Ph
3.63
8
7
6
5
4
3
2
1
-0
ppm

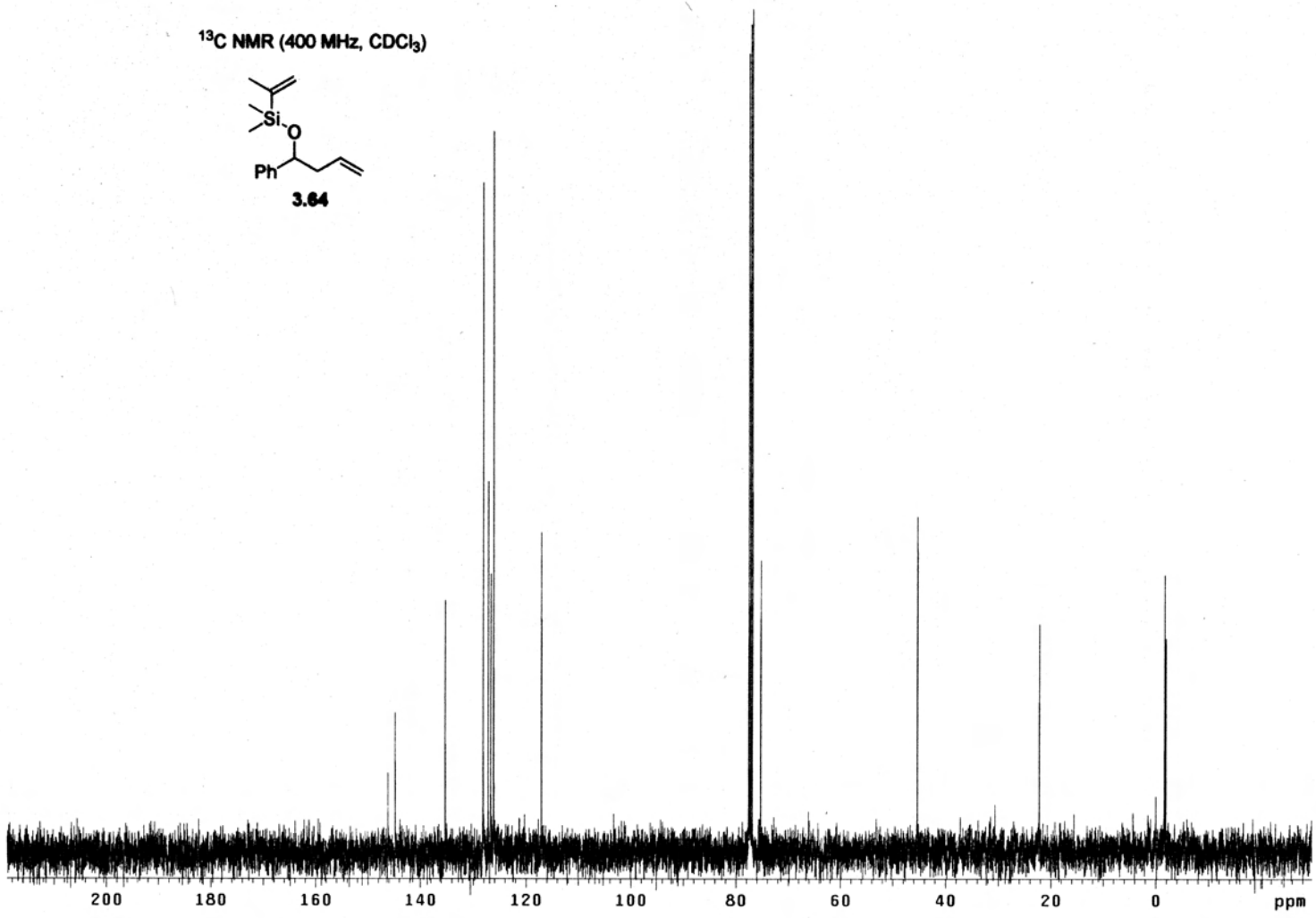

^{1}H NMR (300 MHz, $CDCl_3$)
Ph
O
3.63P
8
7
6
5
4
3
2
1
−0
ppm

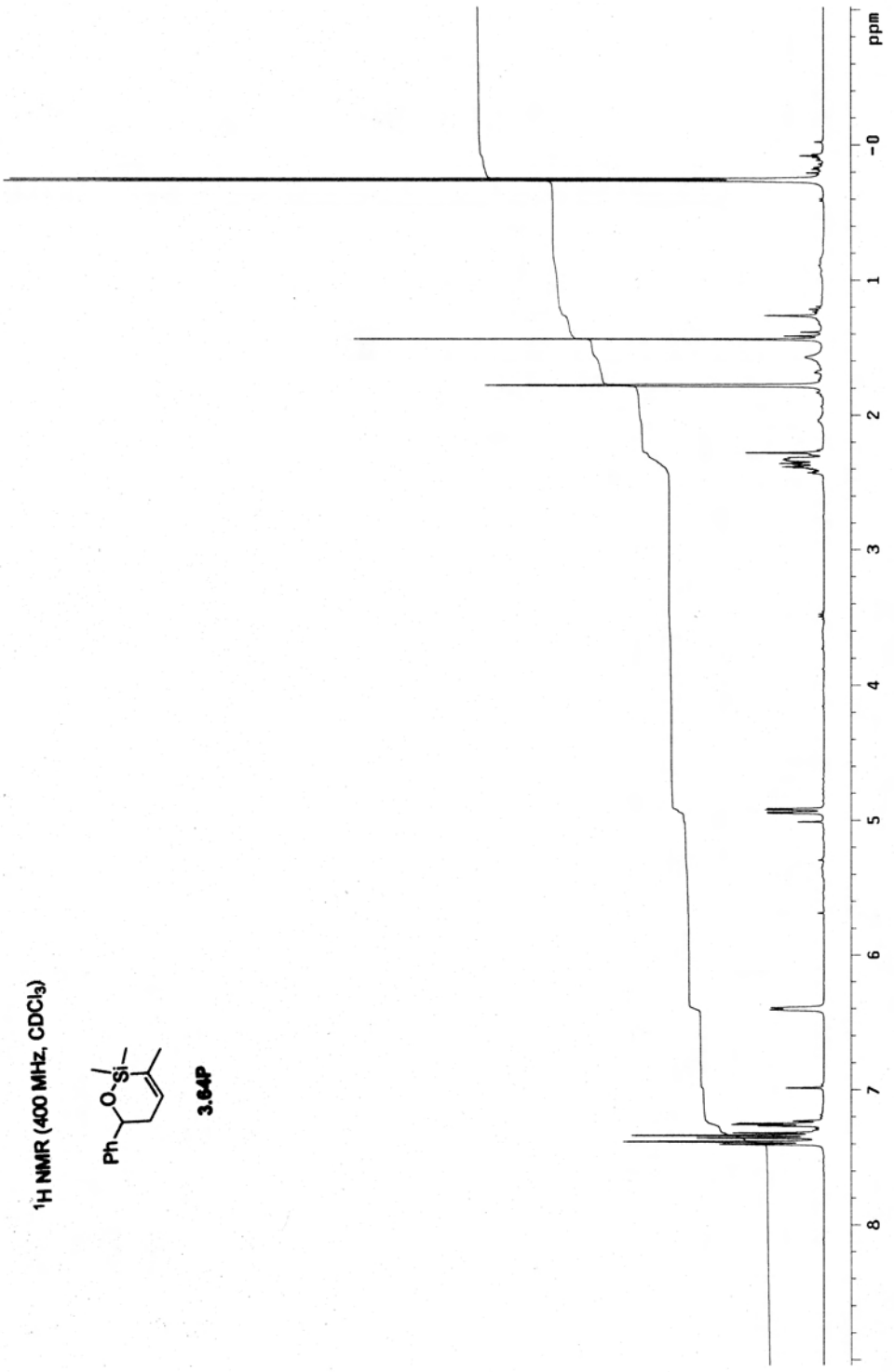
^{13}C NMR (300 MHz, $CDCl_3$)



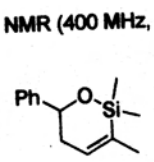
3.63P


^{1}H NMR (400 MHz, $CDCl_3$)
Si
O
Ph
3.64
ppm
8
7
6
5
4
3
2
1
0

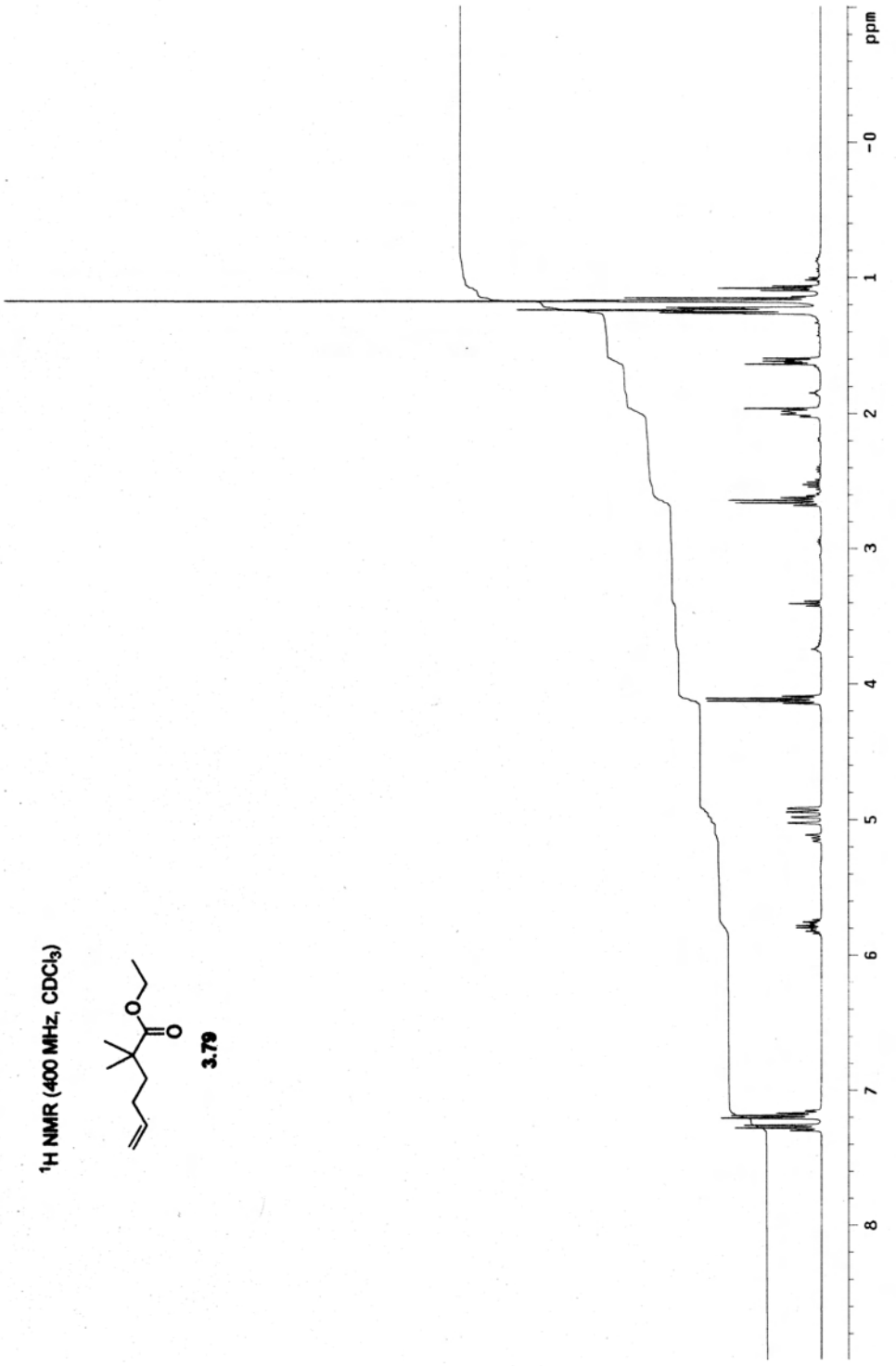

^{13}C NMR (400 MHz, $CDCl_3$)
Si
O
Ph
3.64
200
180
160
140
120
100
80
60
40
20
0
ppm


^{1}H NMR (400 MHz, $CDCl_3$)
Ph
O
Si
3.64P
ppm
8
7
6
5
4
3
2
1
-0

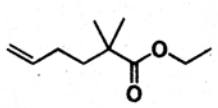
^{13}C NMR (400 MHz, $CDCl_3$)



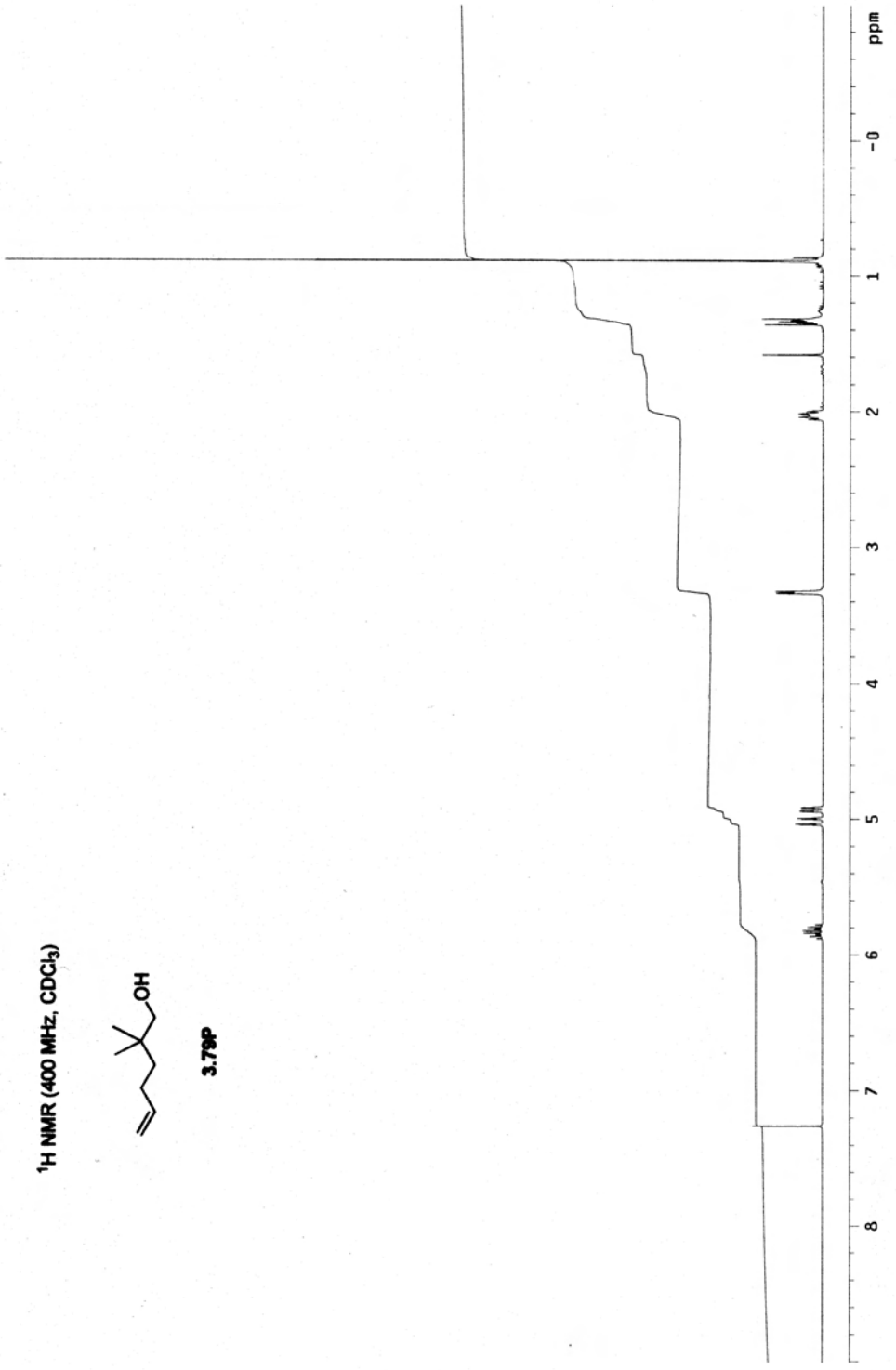
3.64P


^{1}H NMR (400 MHz, $CDCl_3$)
3.79
ppm
8
7
6
5
4
3
2
1
0

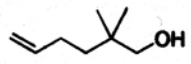
^{13}C NMR (400 MHz, $CDCl_3$)



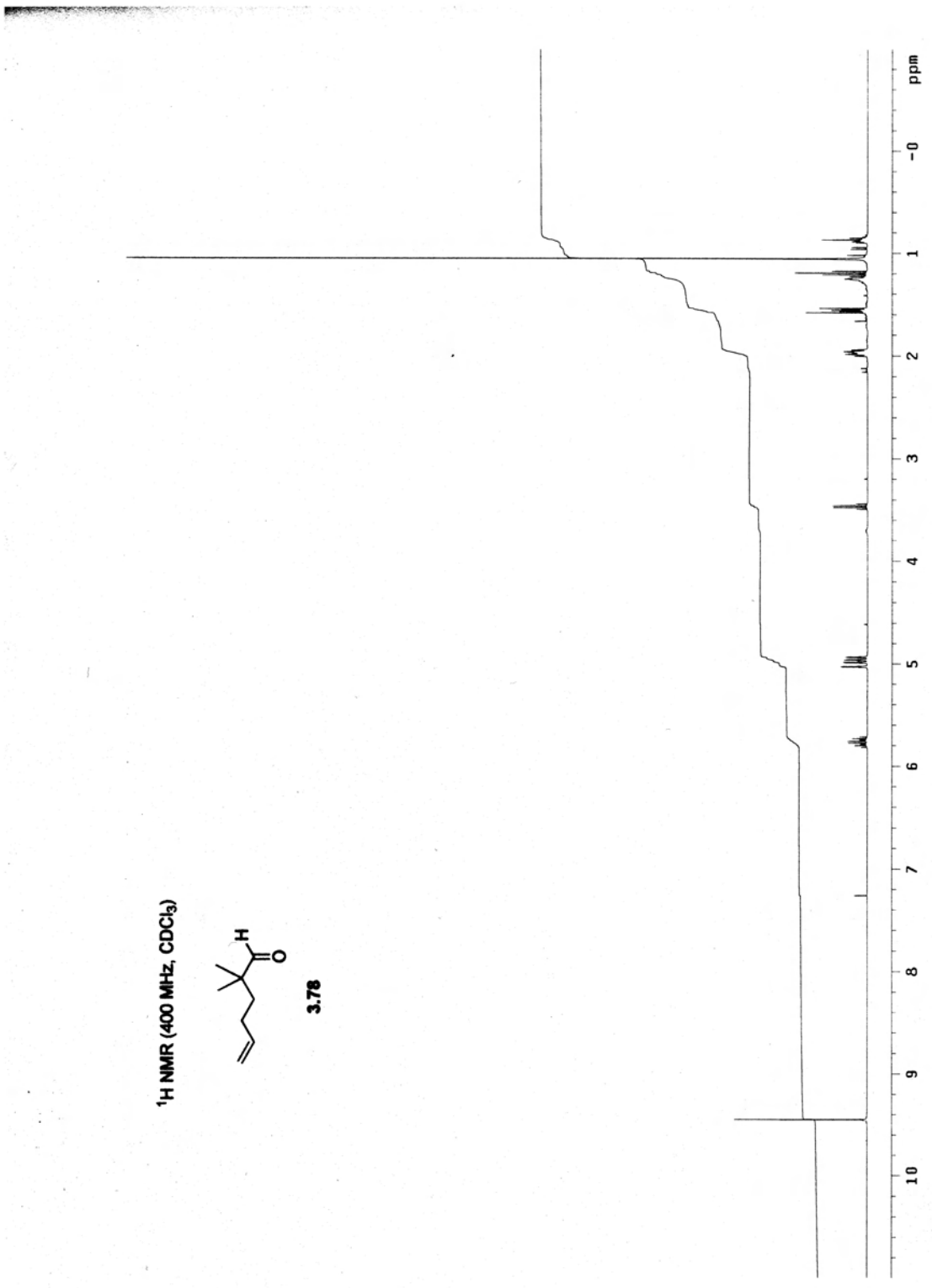
3.79


^{1}H NMR (400 MHz, $CDCl_3$)
OH
3.79P
ppm
8
7
6
5
4
3
2
1
-0

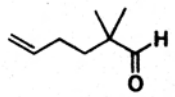
^{13}C NMR (400 MHz, $CDCl_3$)



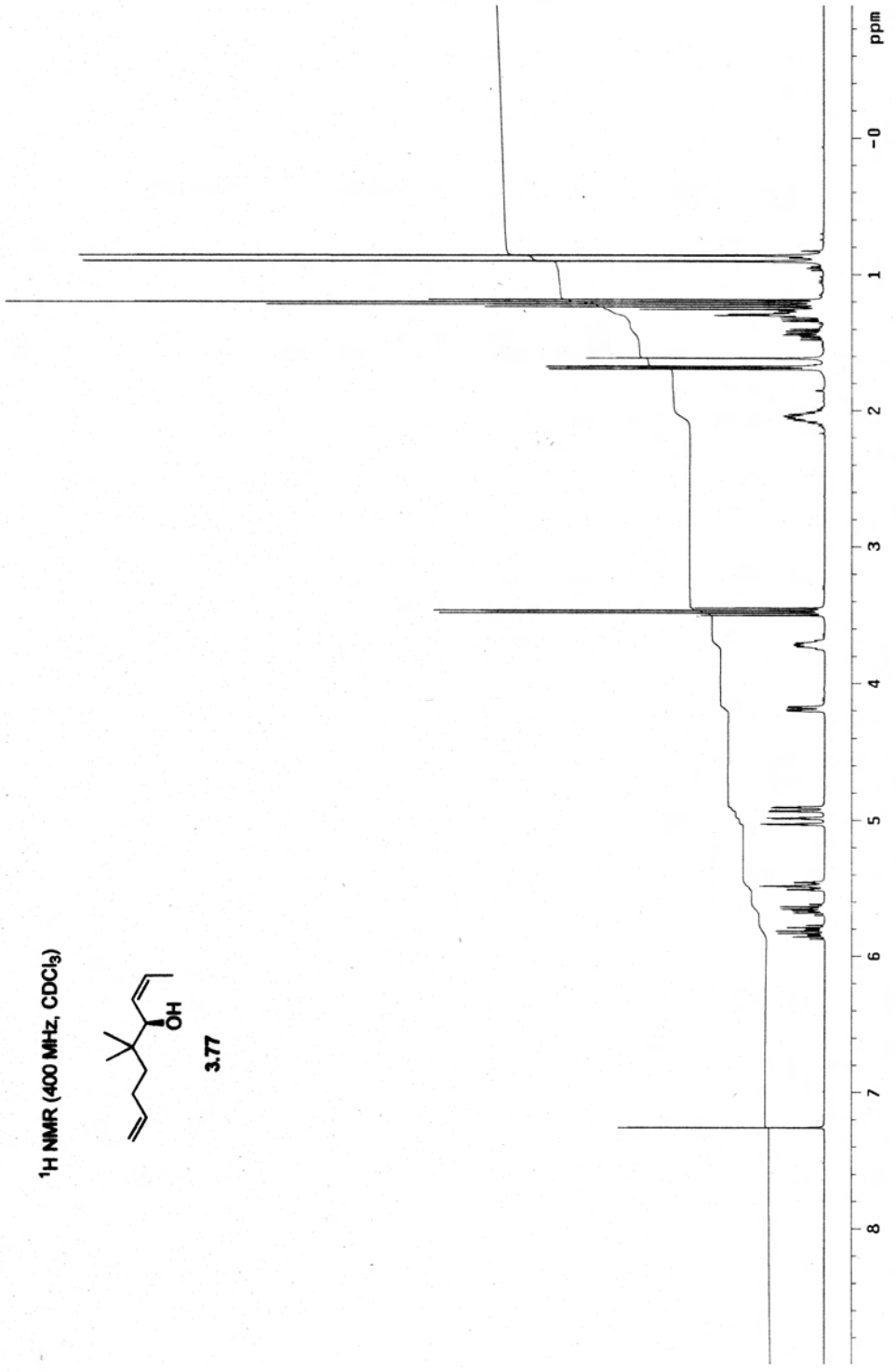
3.79P


^{1}H NMR (400 MHz, CDCl$_3$)
3.78
ppm

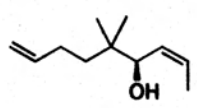
^{13}C NMR (400 MHz, $CDCl_3$)



3.78

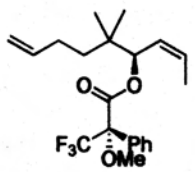

^{1}H NMR (400 MHz, $CDCl_3$)
OH
3.77
ppm
8
7
6
5
4
3
2
1
0

^{13}C NMR (400 MHz, $CDCl_3$)

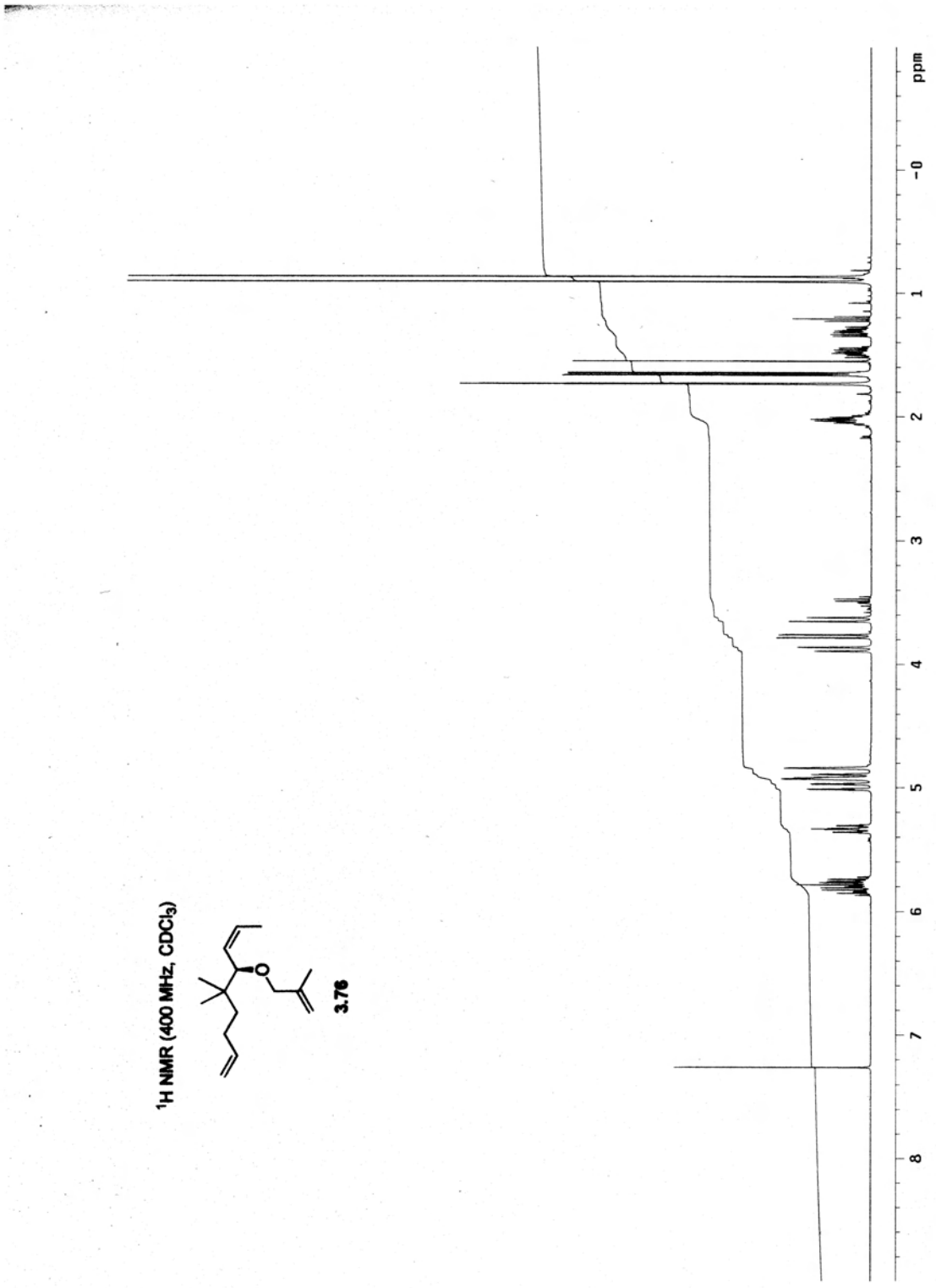


3.77

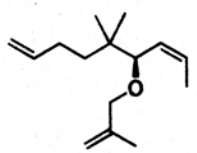
^{1}H NMR (400 MHz, $CDCl_3$)



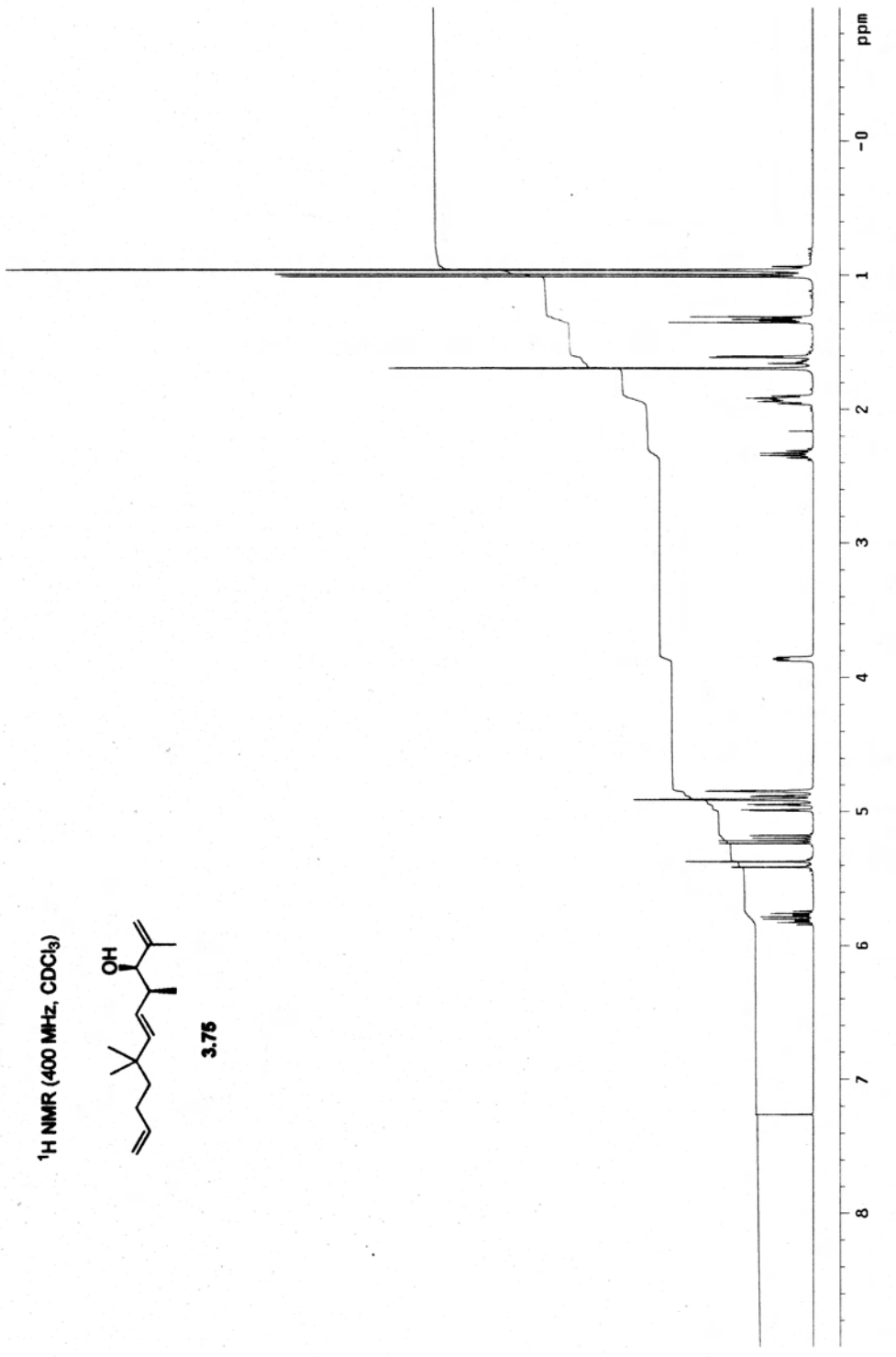
Mosher Ester of 3.77


^{1}H NMR (400 MHz, $CDCl_3$)
3.76
ppm
8
7
6
5
4
3
2
1
0

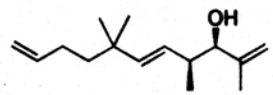
^{13}C NMR (400 MHz, $CDCl_3$)



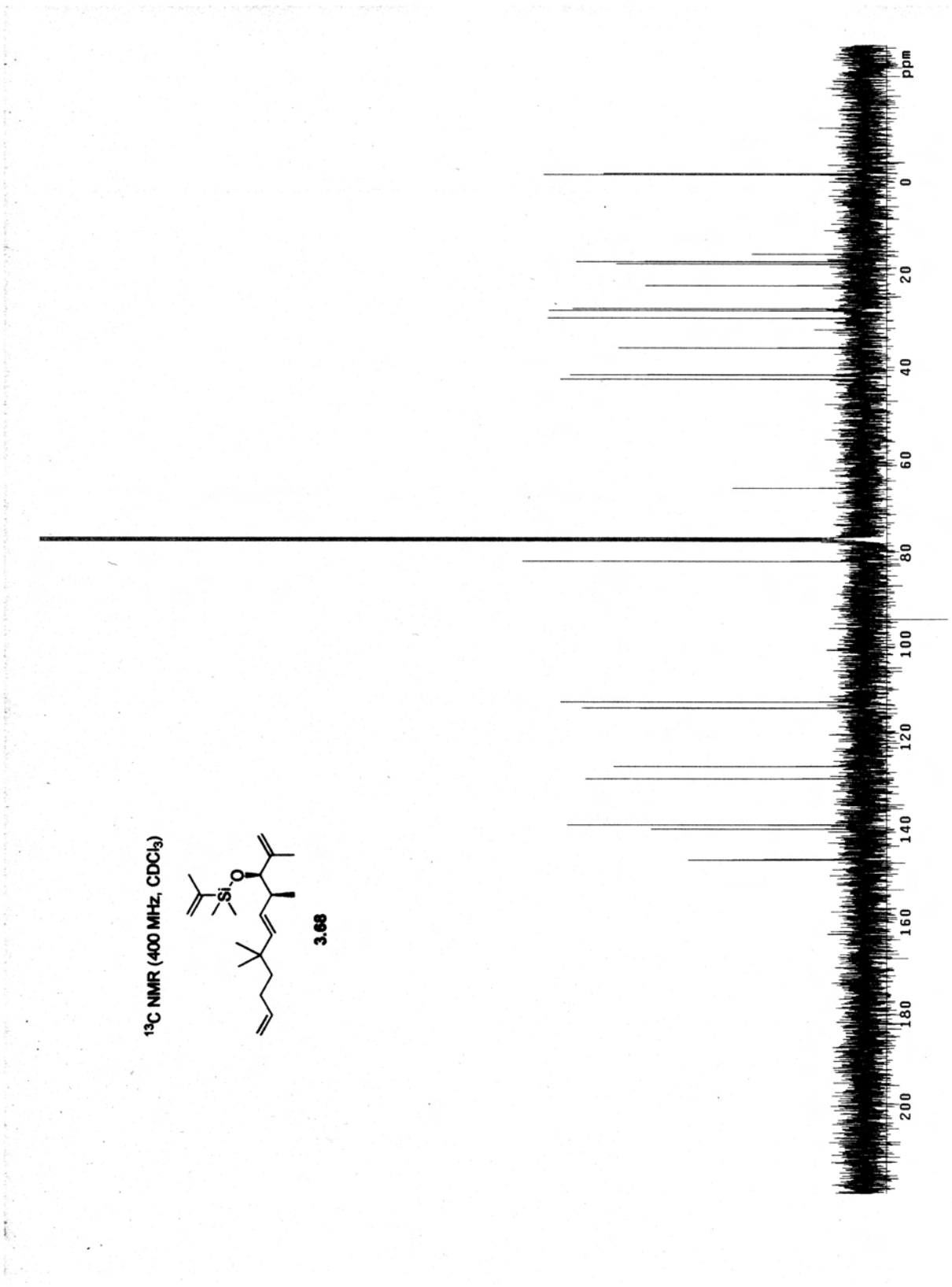
3.76

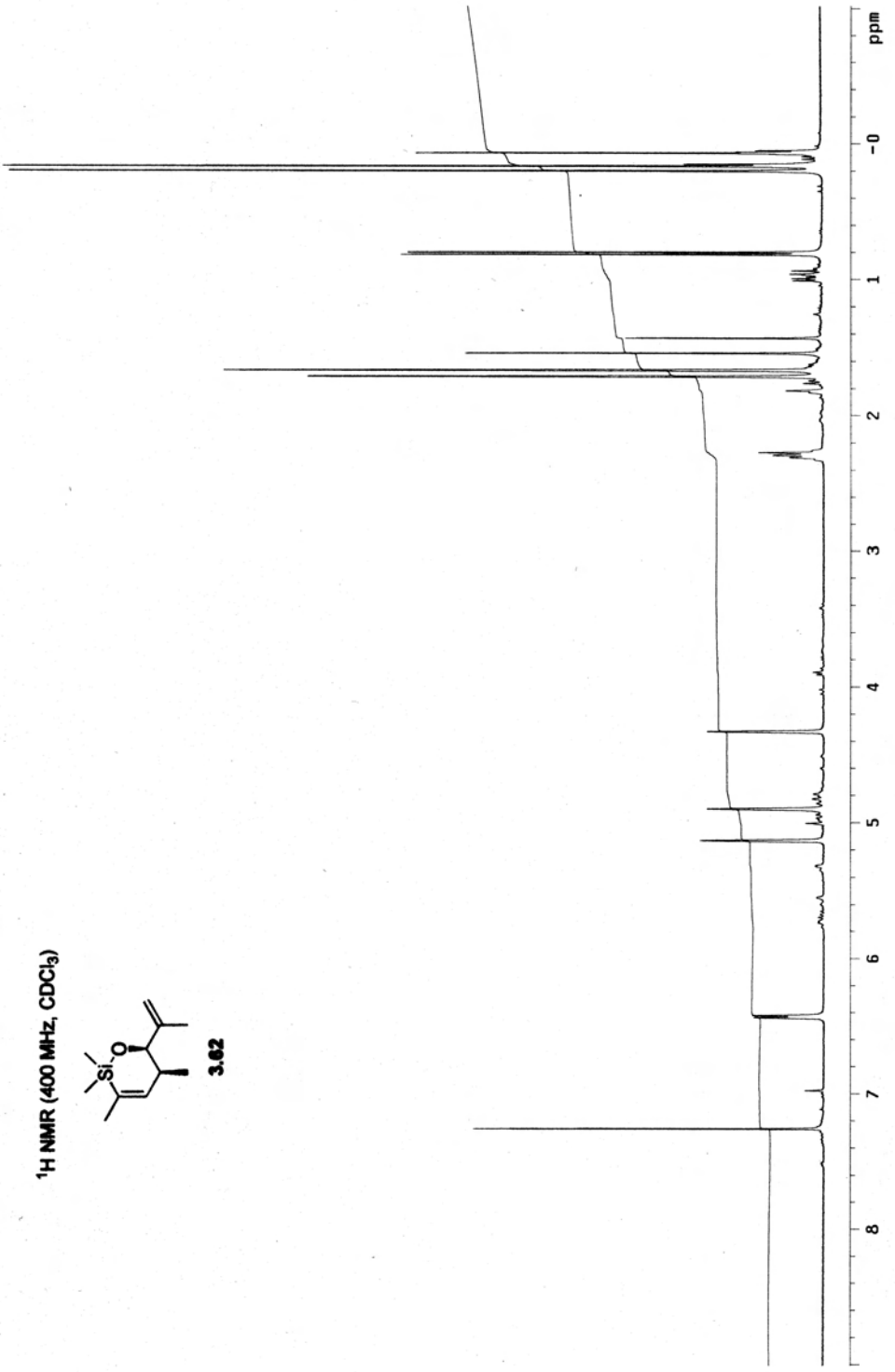

^{1}H NMR (400 MHz, $CDCl_3$)
OH
3.75
ppm
8
7
6
5
4
3
2
1
-0

^{13}C NMR (400 MHz, $CDCl_3$)



3.75

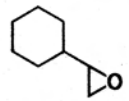

^{13}C NMR (400 MHz, $CDCl_3$)
3.68
Si
O
ppm
0
20
40
60
80
100
120
140
160
180
200


^{1}H NMR (400 MHz, CDCl$_3$)
3.62
ppm

^{13}C NMR (400 MHz, $CDCl_3$)

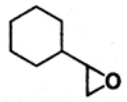
3.62

^{1}H NMR (300 MHz, $CDCl_3$)

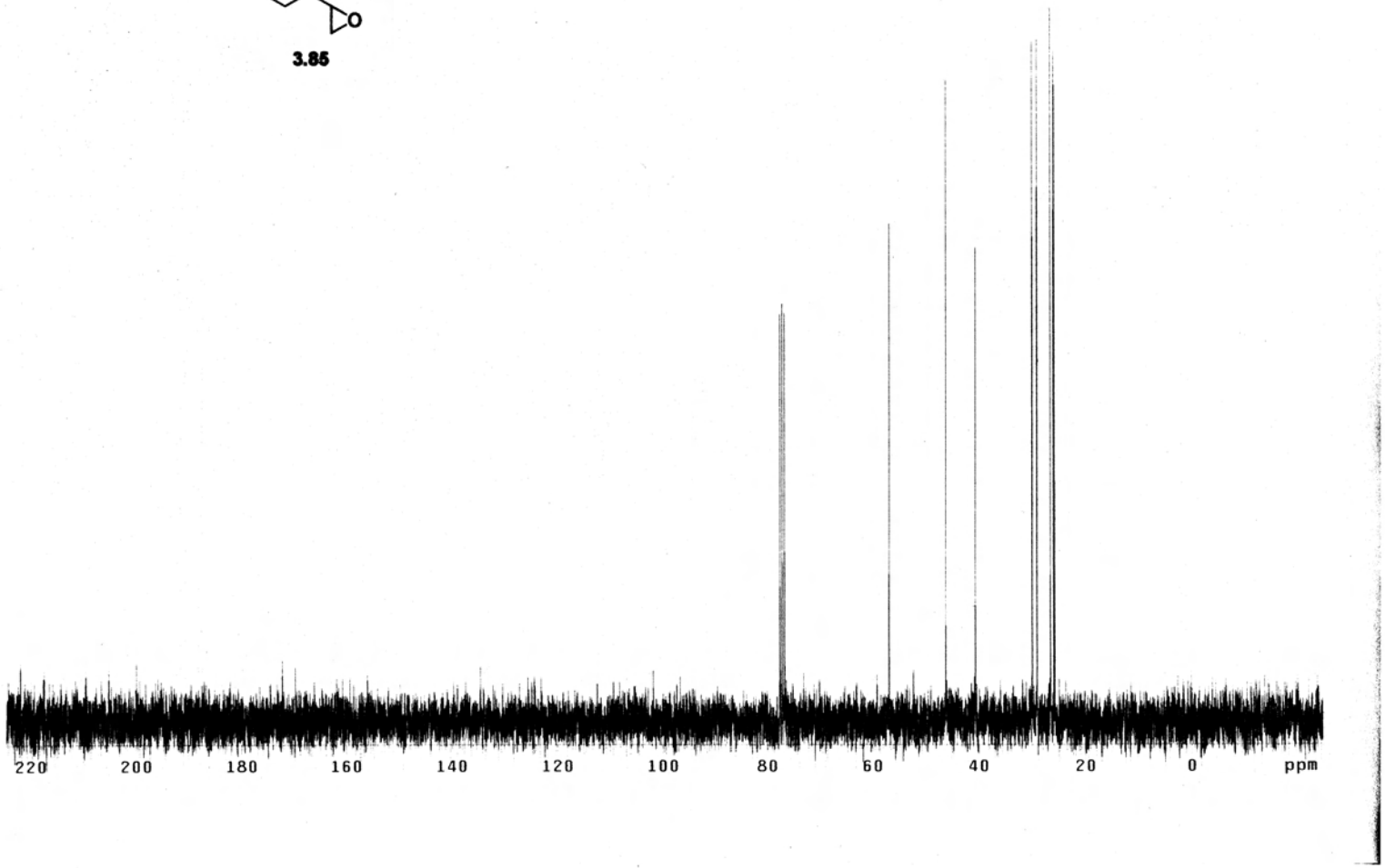


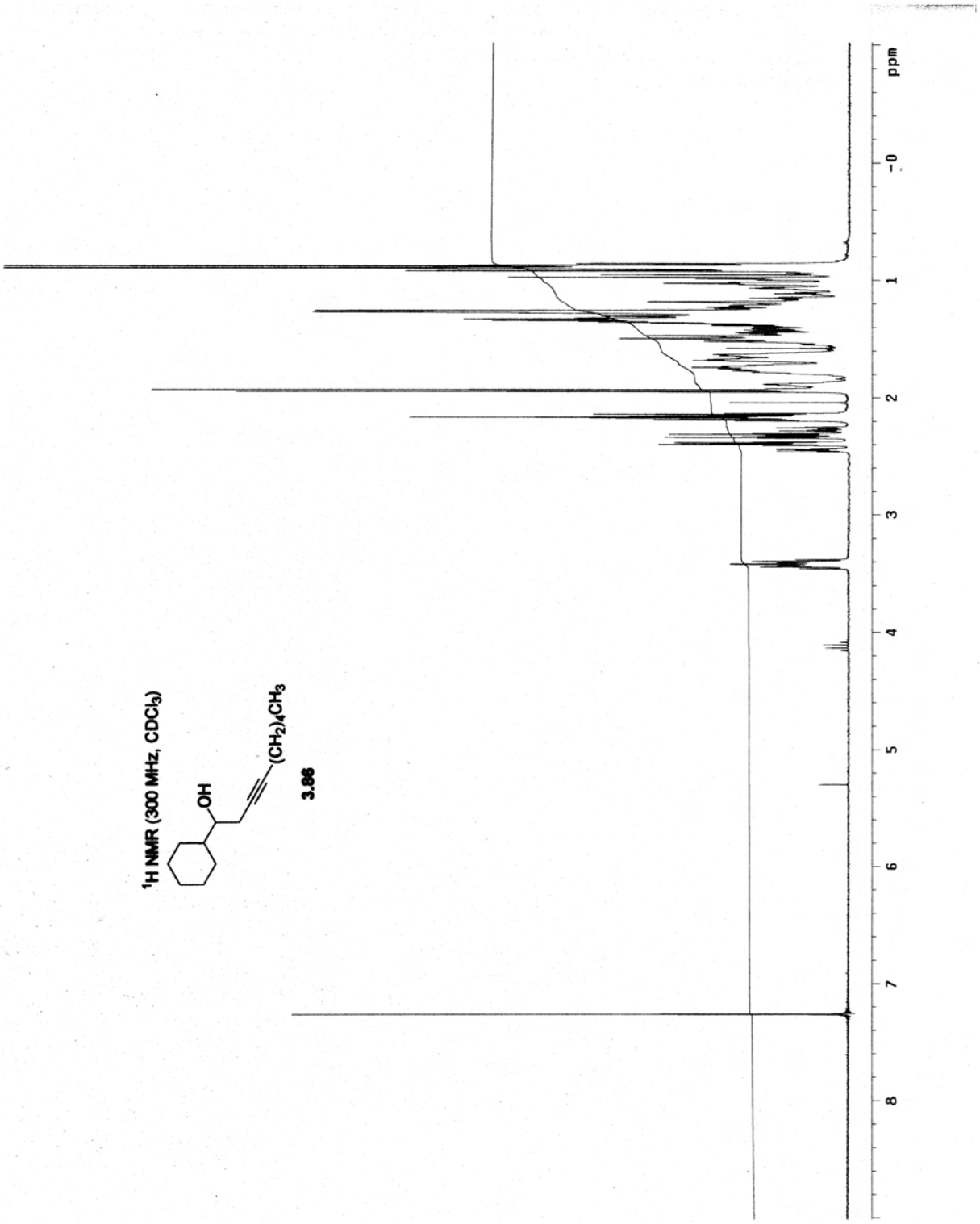
3.85

^{13}C NMR (300 MHz, $CDCl_3$)

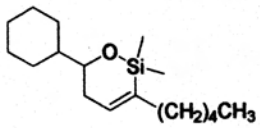


3.85



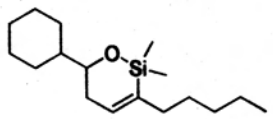

^{1}H NMR (300 MHz, CDCl$_3$)
OH
(CH$_2$)$_4$CH$_3$
3.86
ppm
0
1
2
3
4
5
6
7
8

^{1}H NMR (300 MHz, $CDCl_3$)

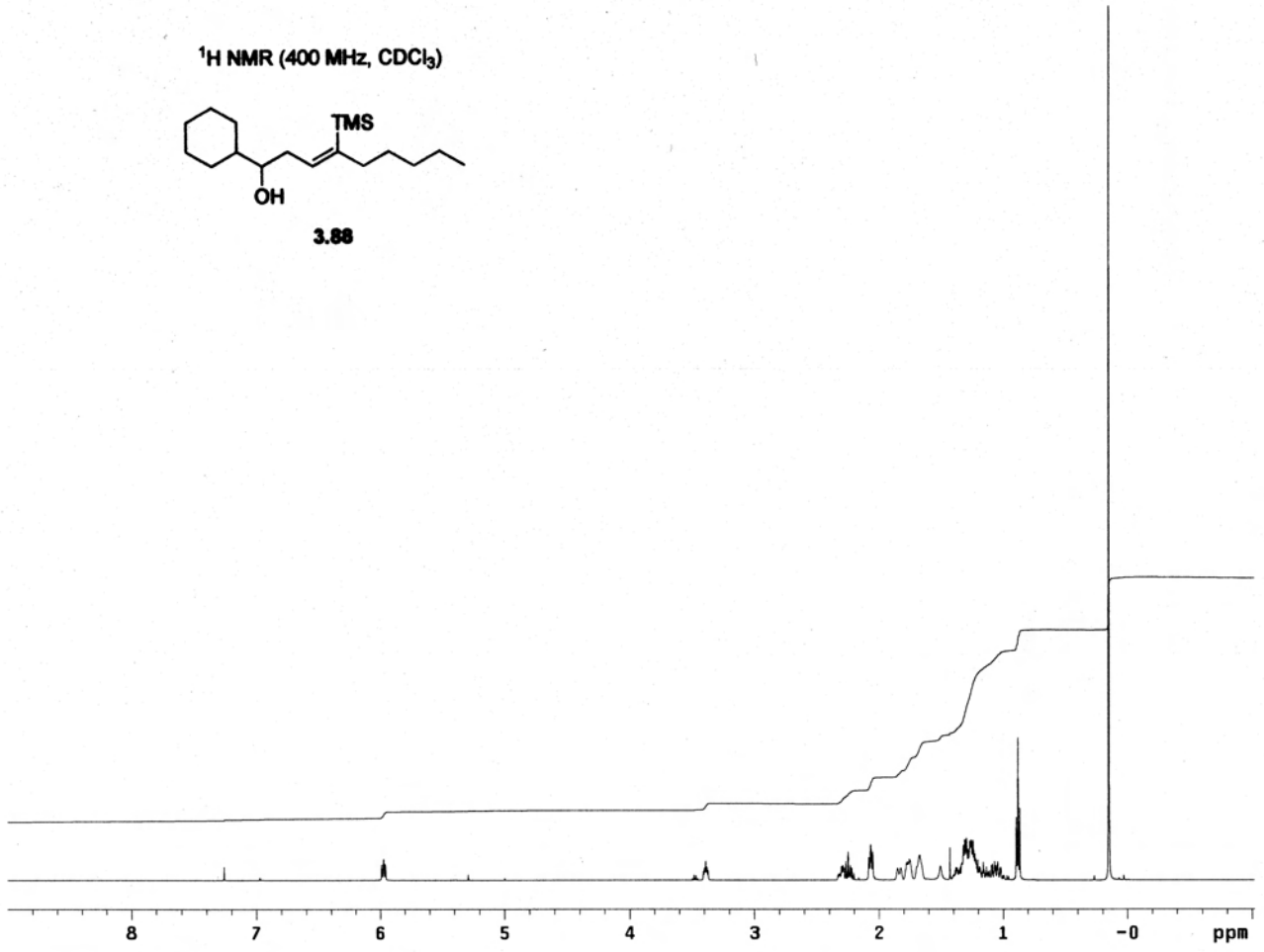


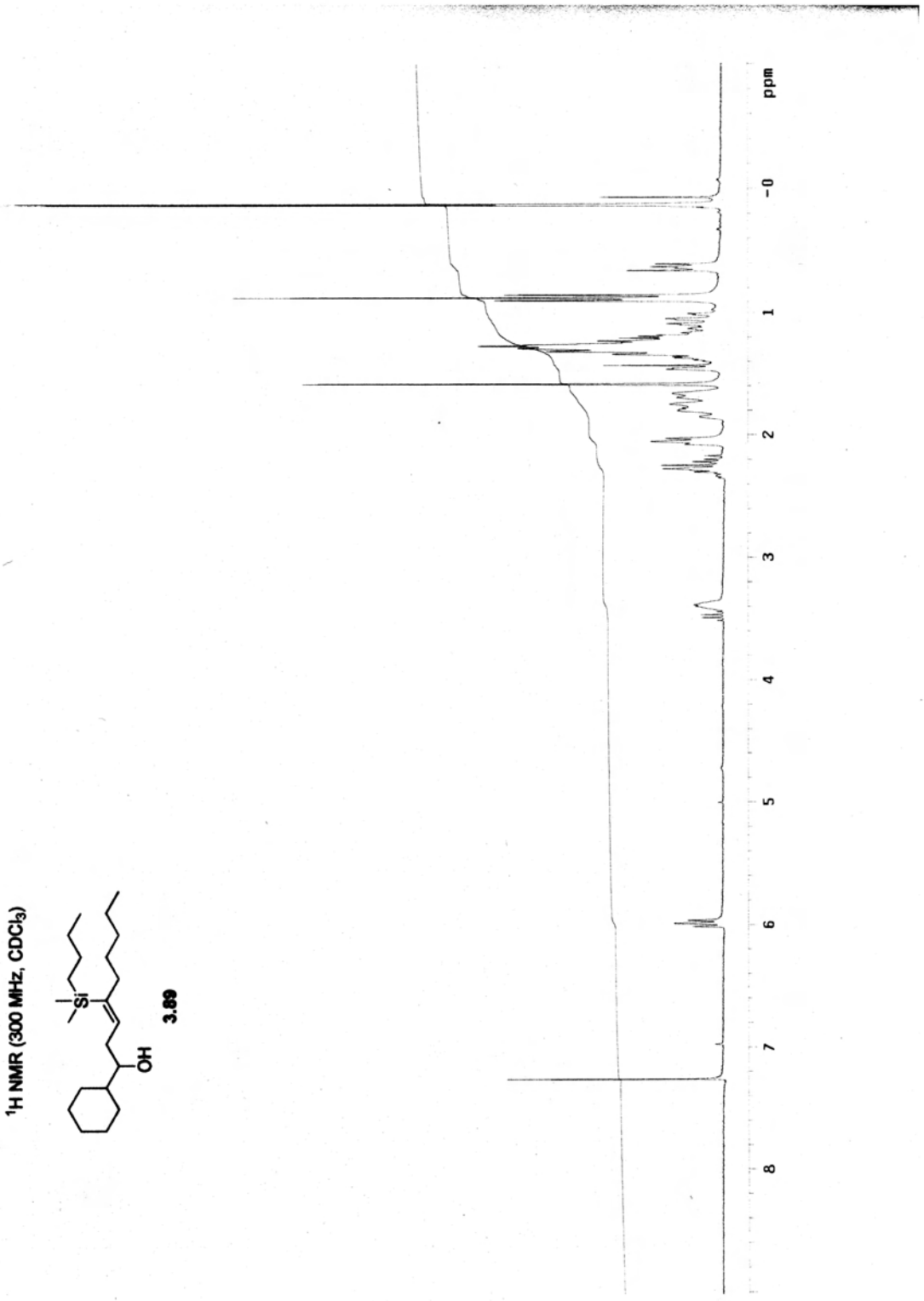
3.87

^{13}C NMR (300 MHz, $CDCl_3$)

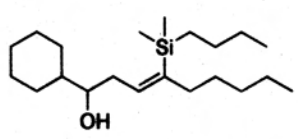


3.87

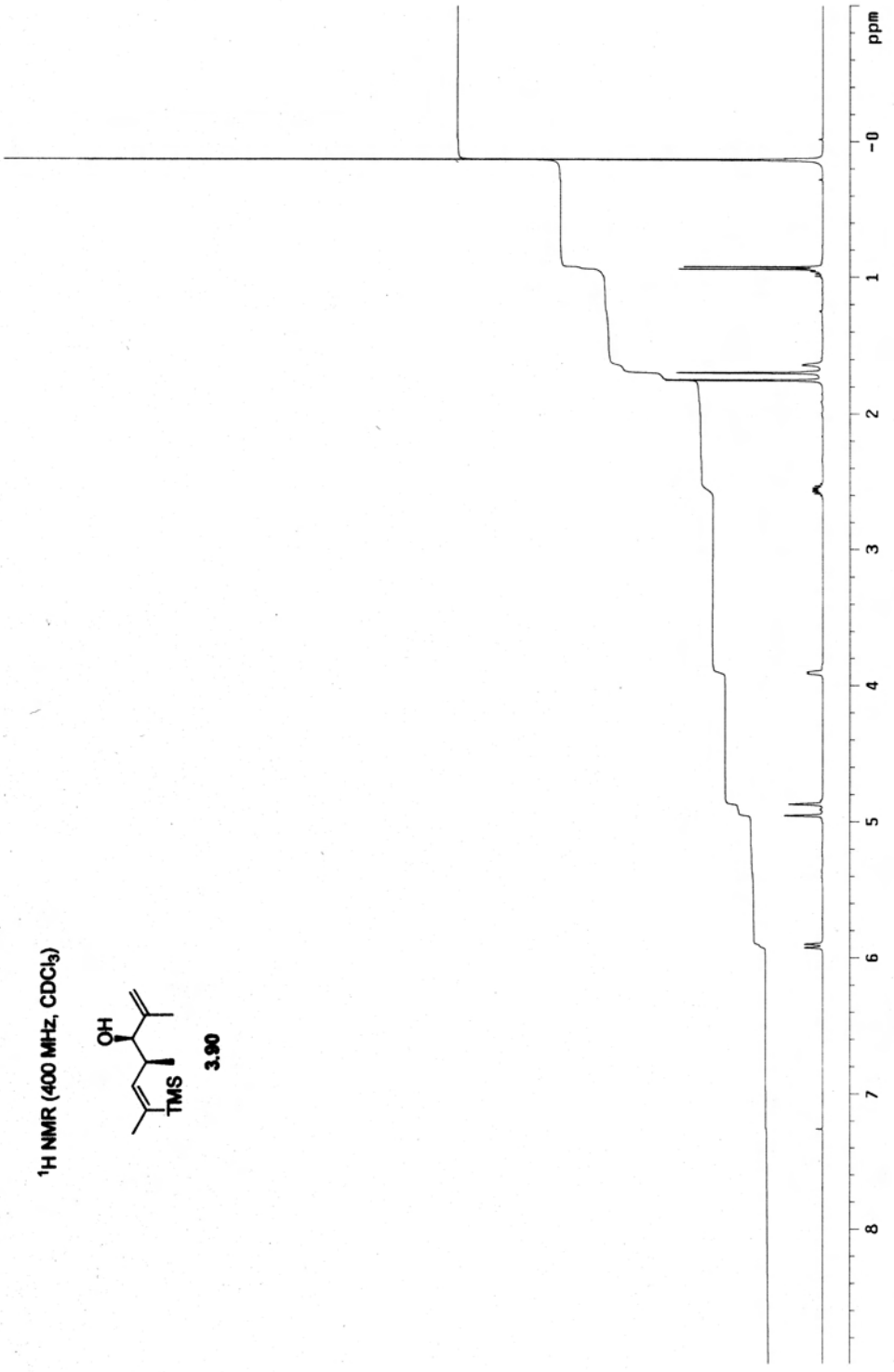

^{1}H NMR (400 MHz, $CDCl_3$)
TMS
OH
3.88
8
7
6
5
4
3
2
1
-0
ppm


^{1}H NMR (300 MHz, CDCl$_3$)
Si
OH
3.89
ppm
0
1
2
3
4
5
6
7
8

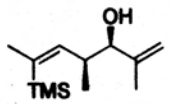
^{13}C NMR (300 MHz, $CDCl_3$)



3.89

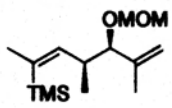

^{1}H NMR (400 MHz, $CDCl_3$)
OH
TMS
3.90
ppm
8
7
6
5
4
3
2
1
0

^{13}C NMR (400 MHz, $CDCl_3$)



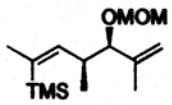
3.90

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

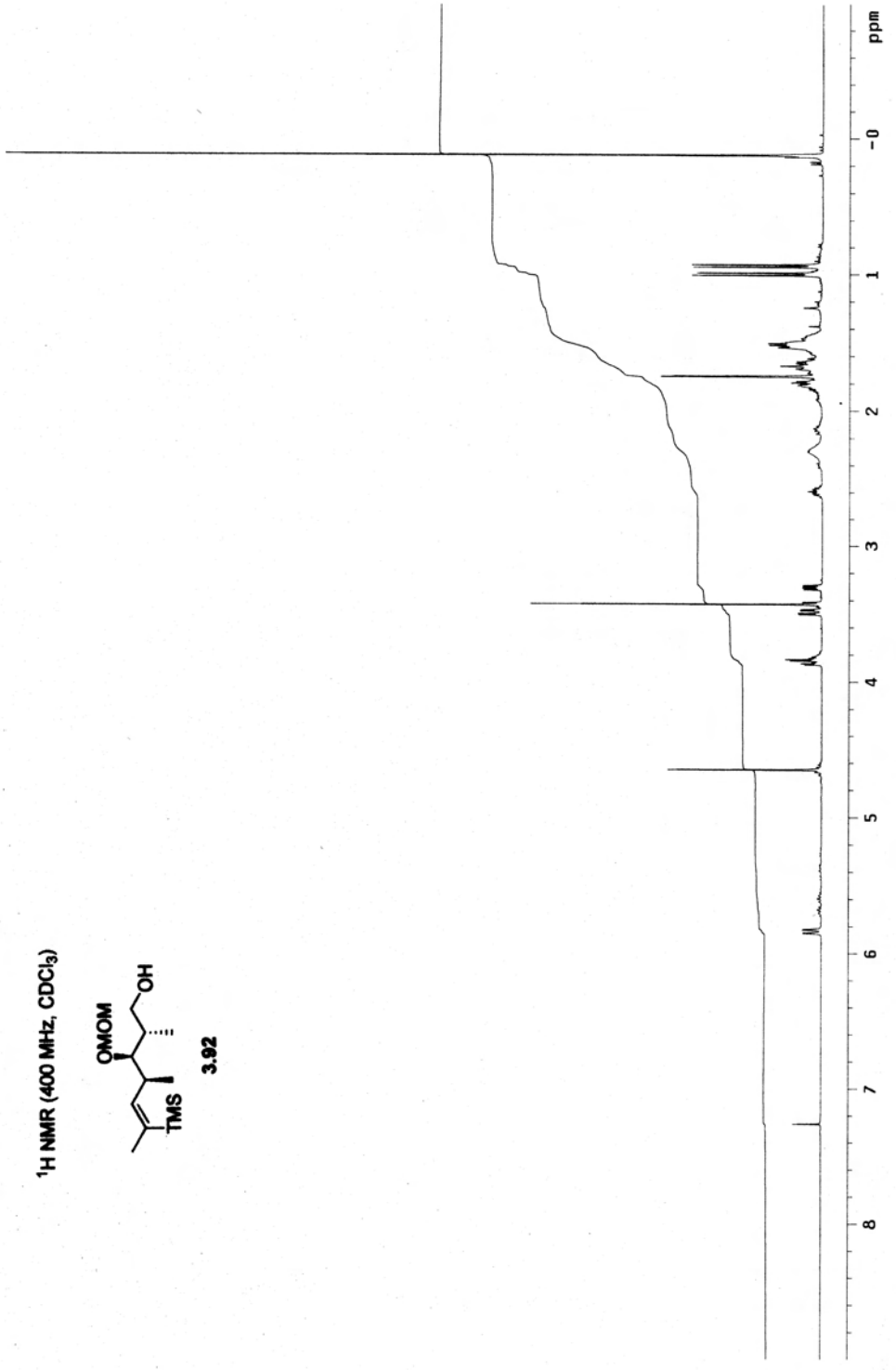


3.91

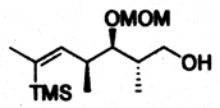
^{13}C NMR (400 MHz, $CDCl_3$)



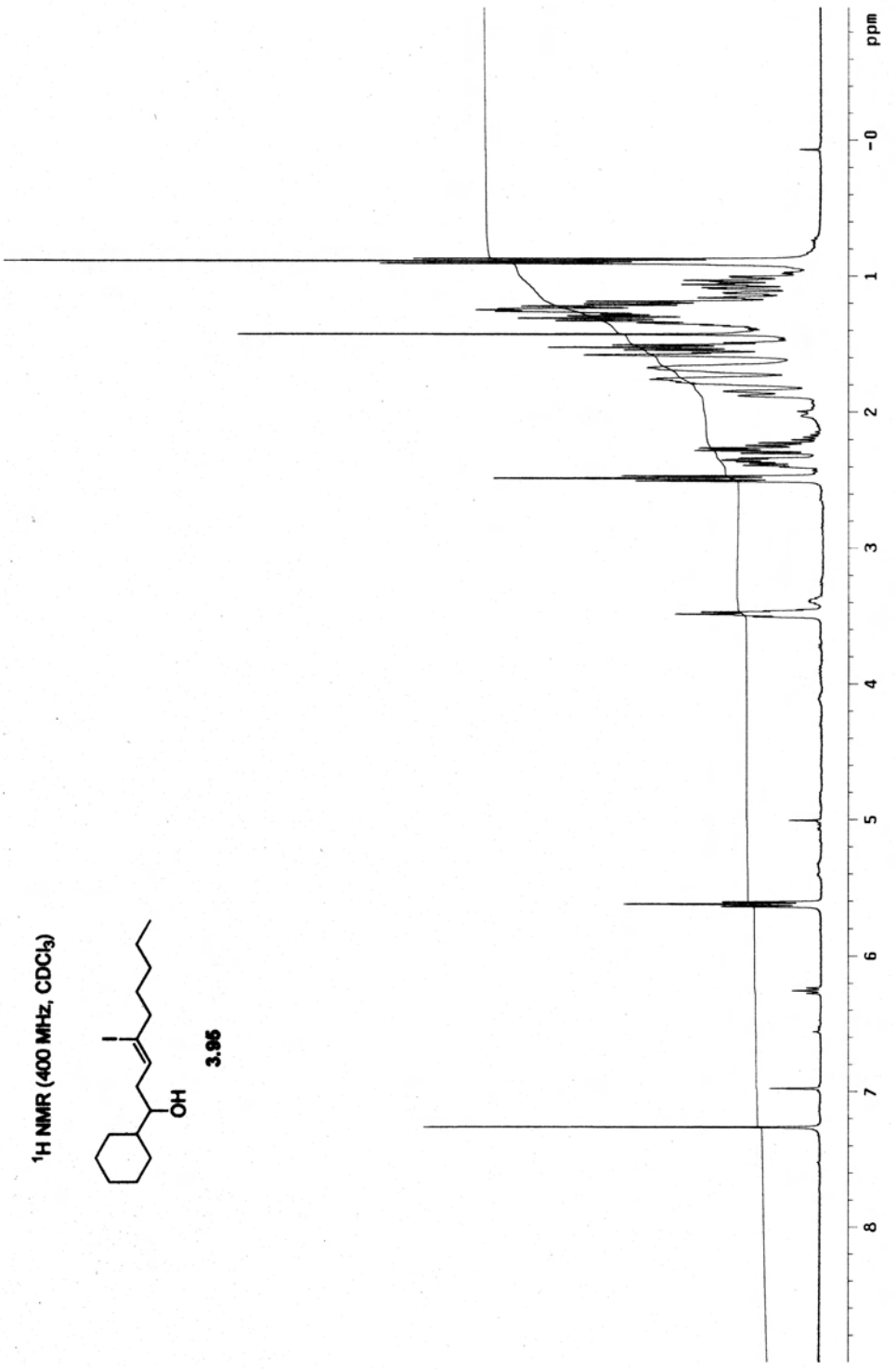
3.91


^{1}H NMR (400 MHz, CDCl$_3$)
OMOM
OH
TMS
3.92
ppm
8
7
6
5
4
3
2
1
-0

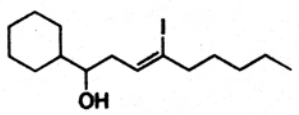
^{13}C NMR (400 MHz, $CDCl_3$)



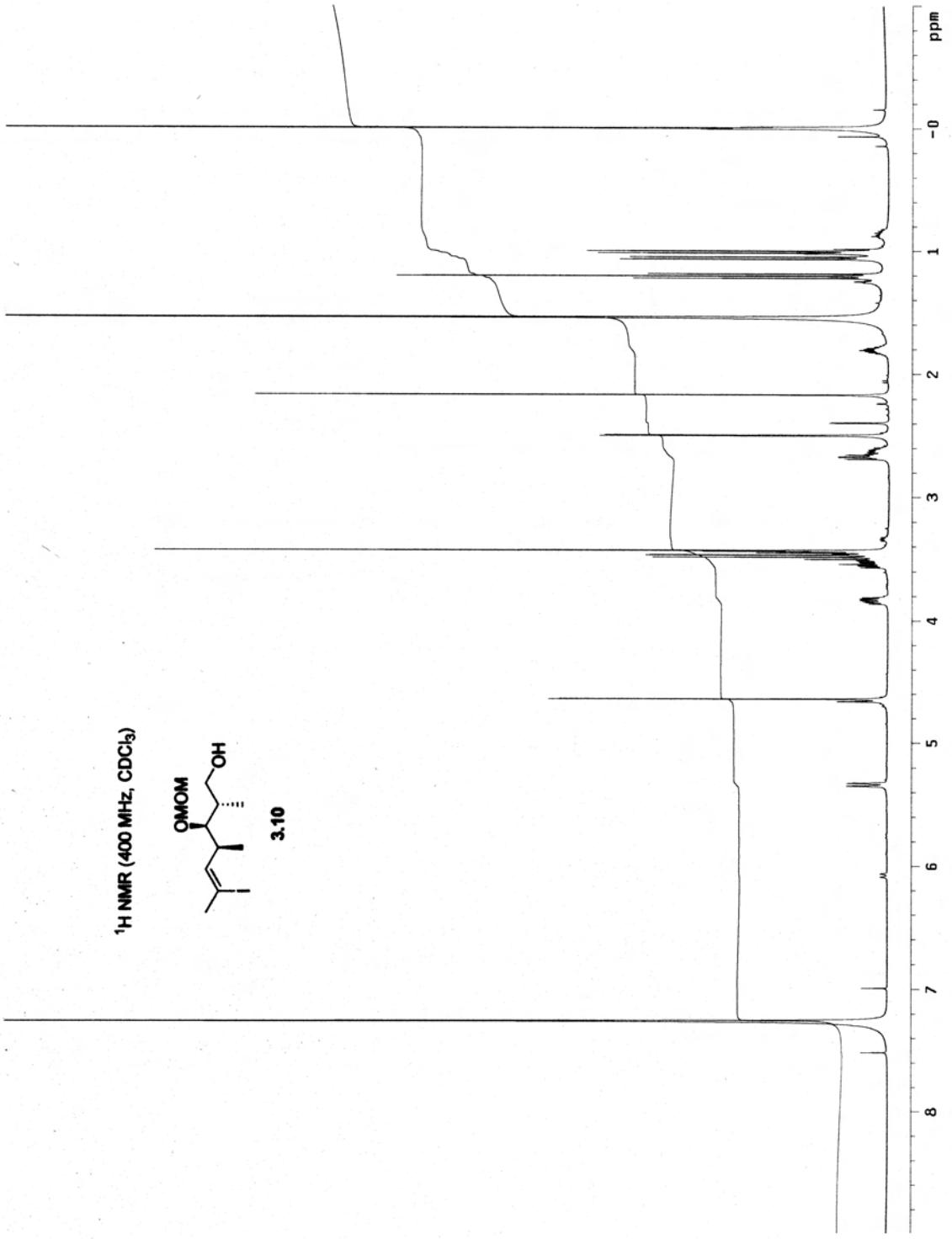
3.92

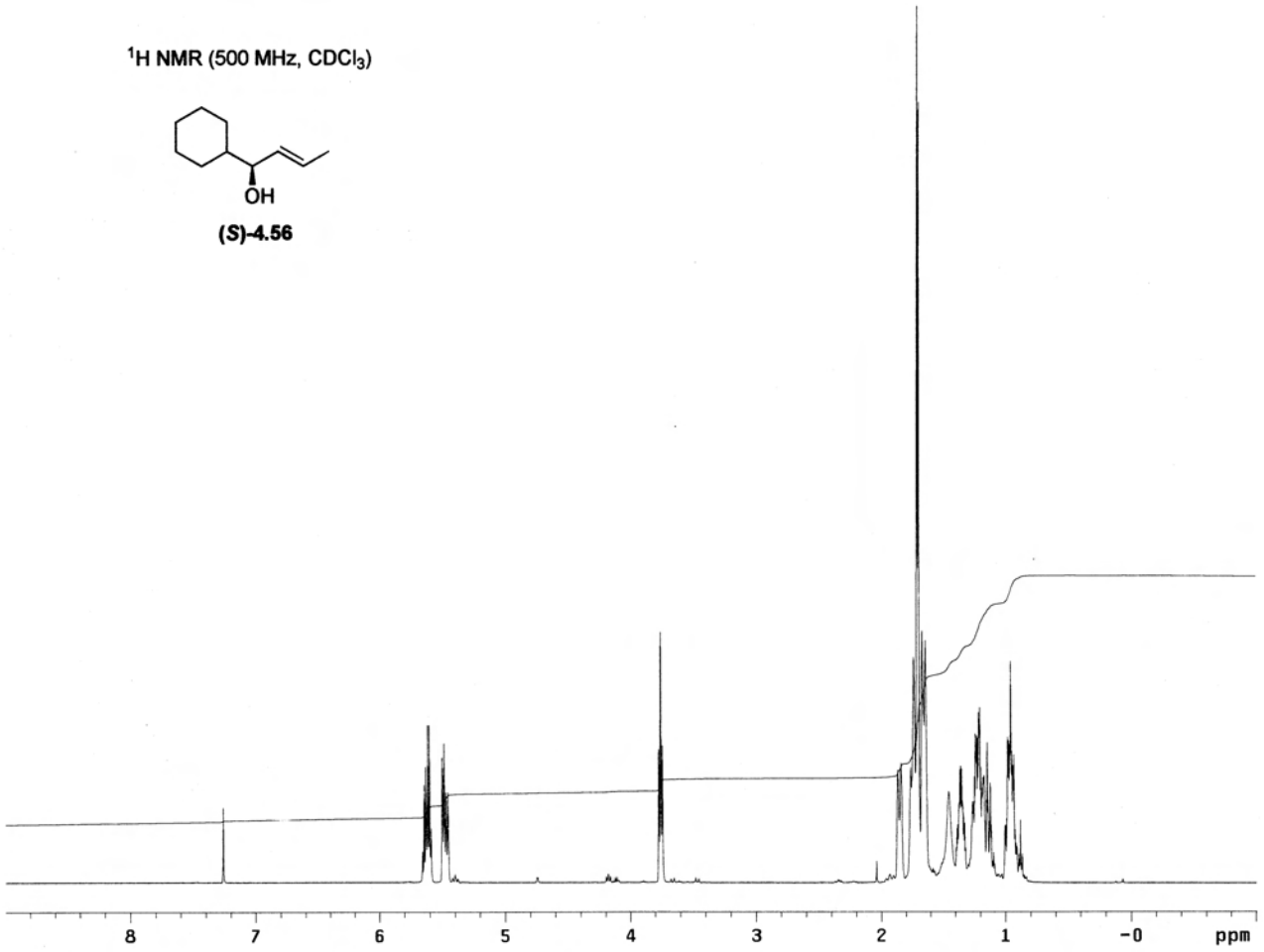

^{1}H NMR (400 MHz, $CDCl_3$)
OH
3.96
ppm
8
7
6
5
4
3
2
1
-0

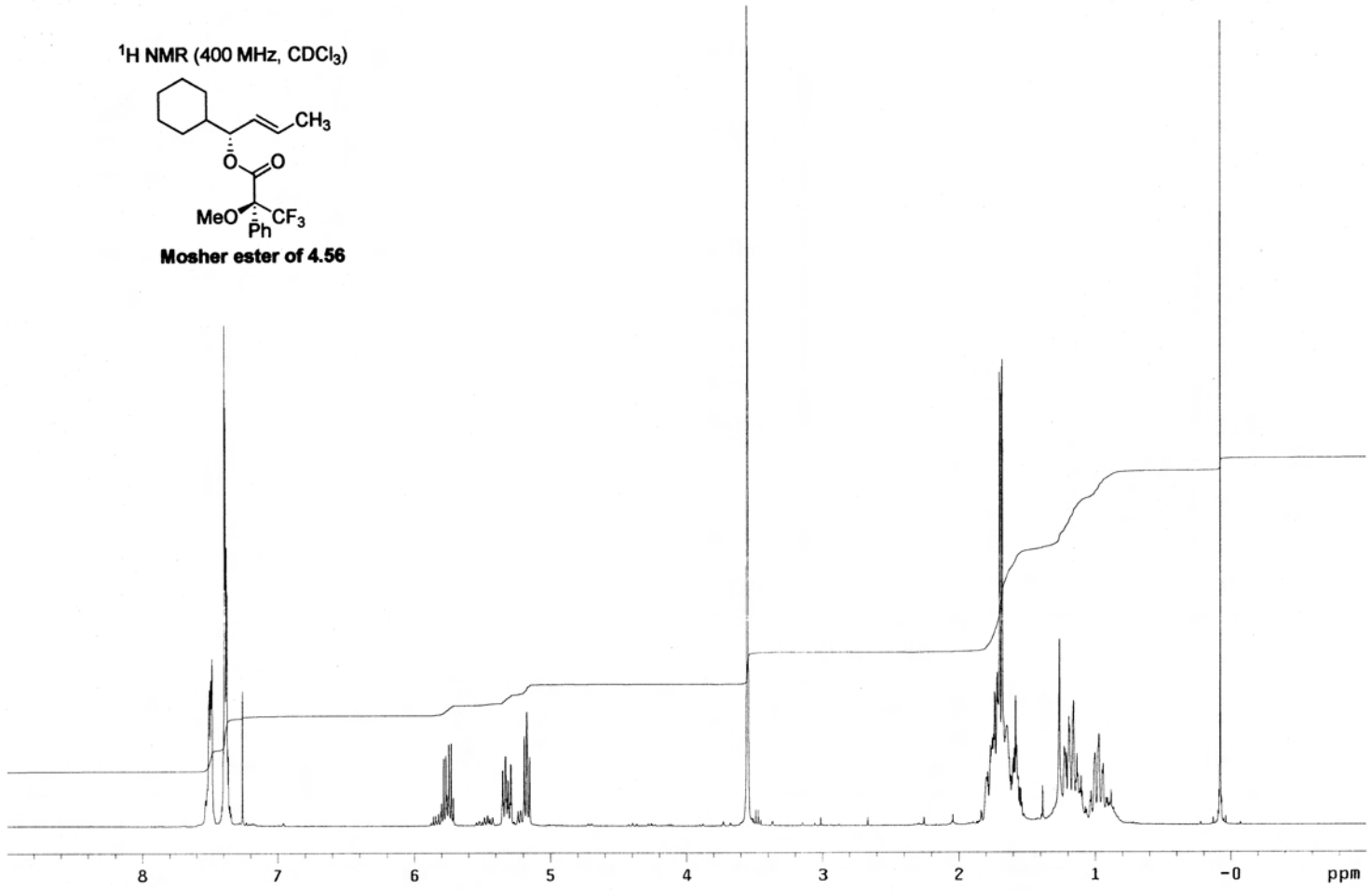
^{13}C NMR (400 MHz, $CDCl_3$)



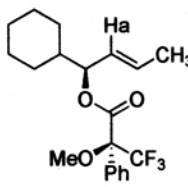
3.95


^{1}H NMR (400 MHz, $CDCl_3$)
OMOM
OH
3.10
8
7
6
5
4
3
2
1
−0
ppm

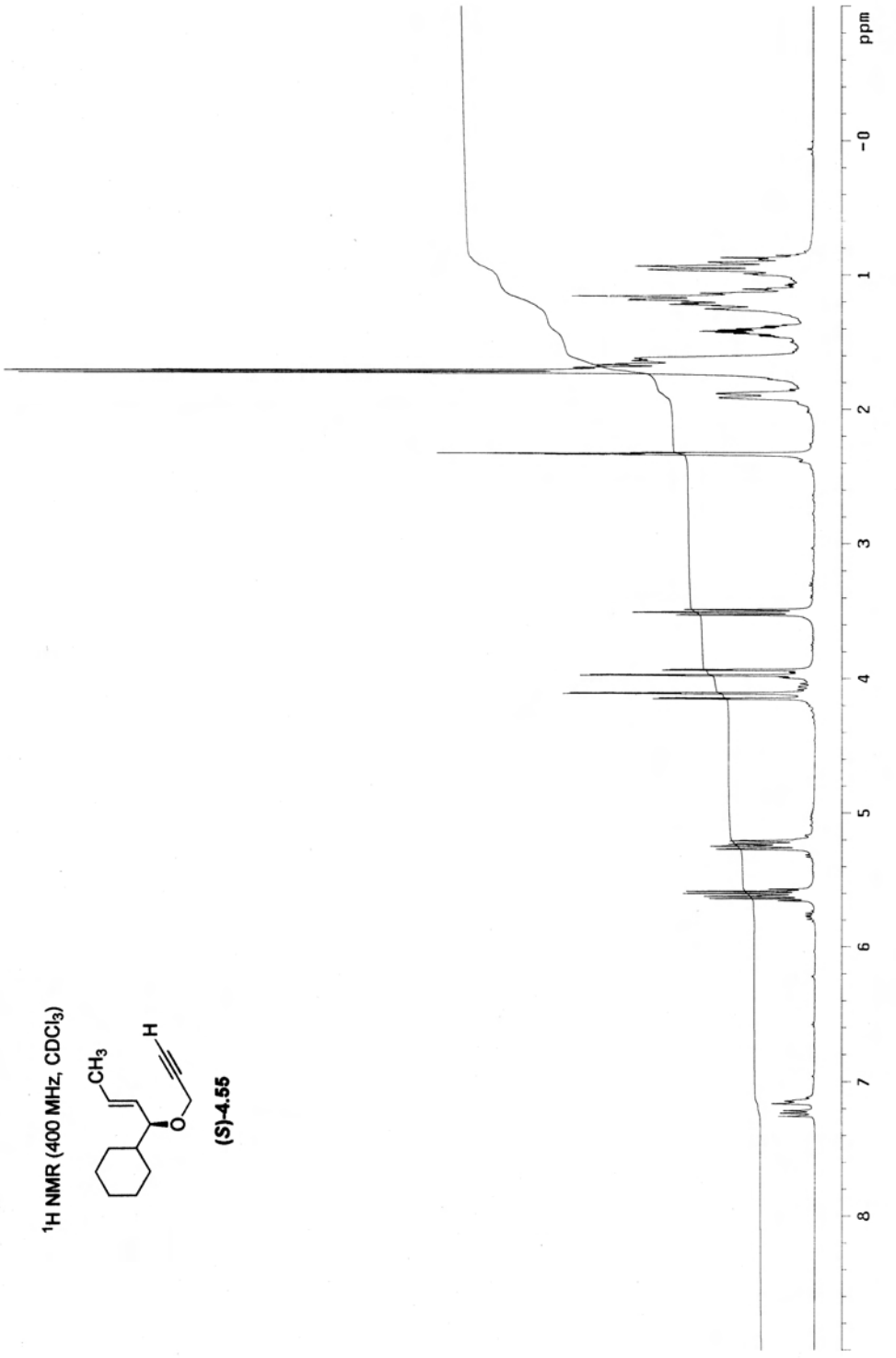

^{1}H NMR (500 MHz, $CDCl_3$)
OH
(S)-4.56
8
7
6
5
4
3
2
1
-0
ppm


^{1}H NMR (400 MHz, $CDCl_3$)
CH_3
O
O
MeO
CF_3
Ph
Mosher ester of 4.56
8
7
6
5
4
3
2
1
-0
ppm

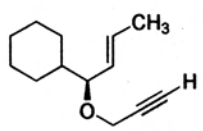
^{1}H NMR (500 MHz, $CDCl_3$)



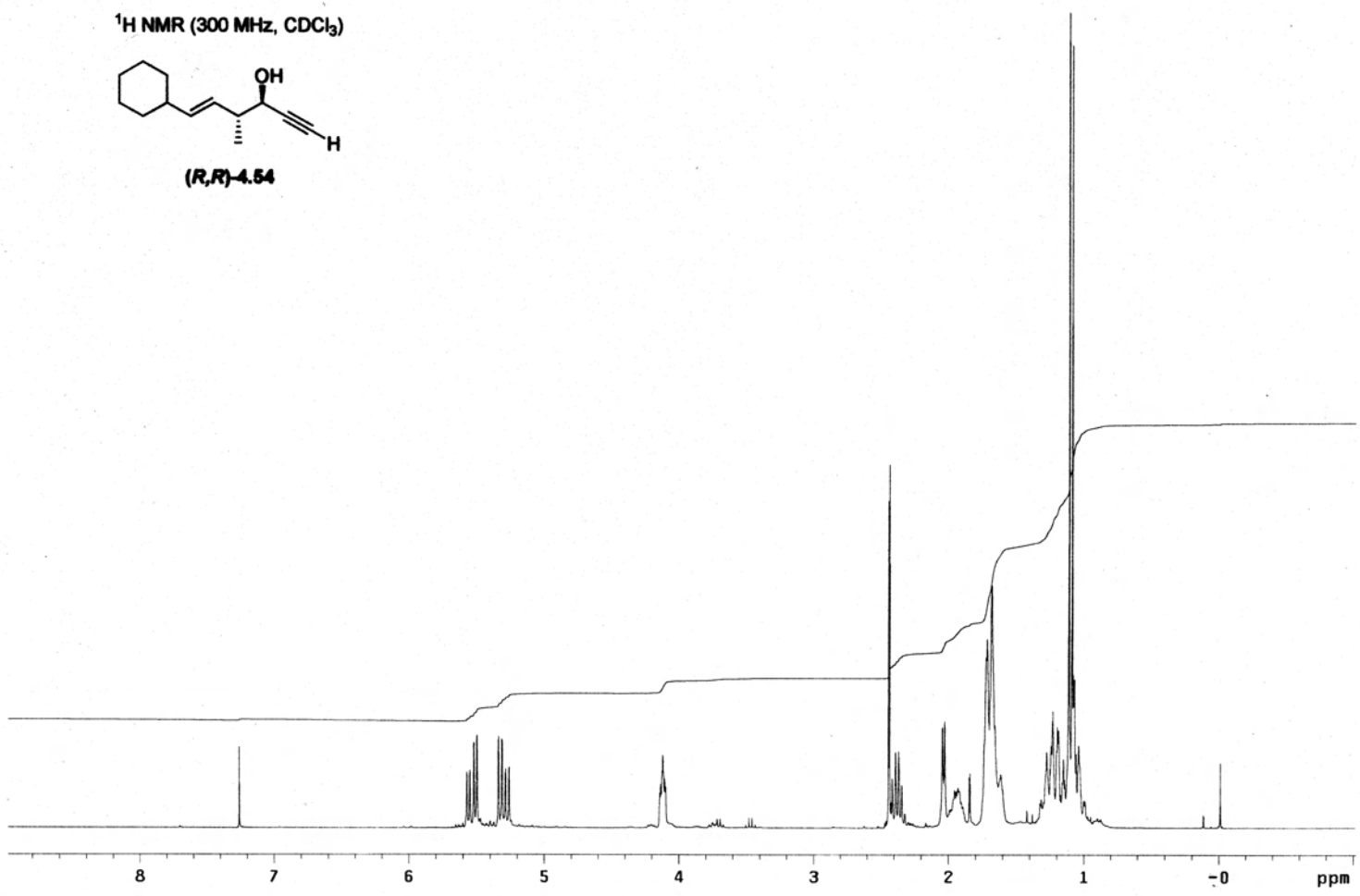
Mosher ester of (*S*)-4.56


^{1}H NMR (400 MHz, $CDCl_3$)
CH_3
H
O
(S)-4.55
ppm
8
7
6
5
4
3
2
1
0

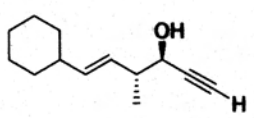
^{13}C NMR (400 MHz, $CDCl_3$)



(*S*)-4.55

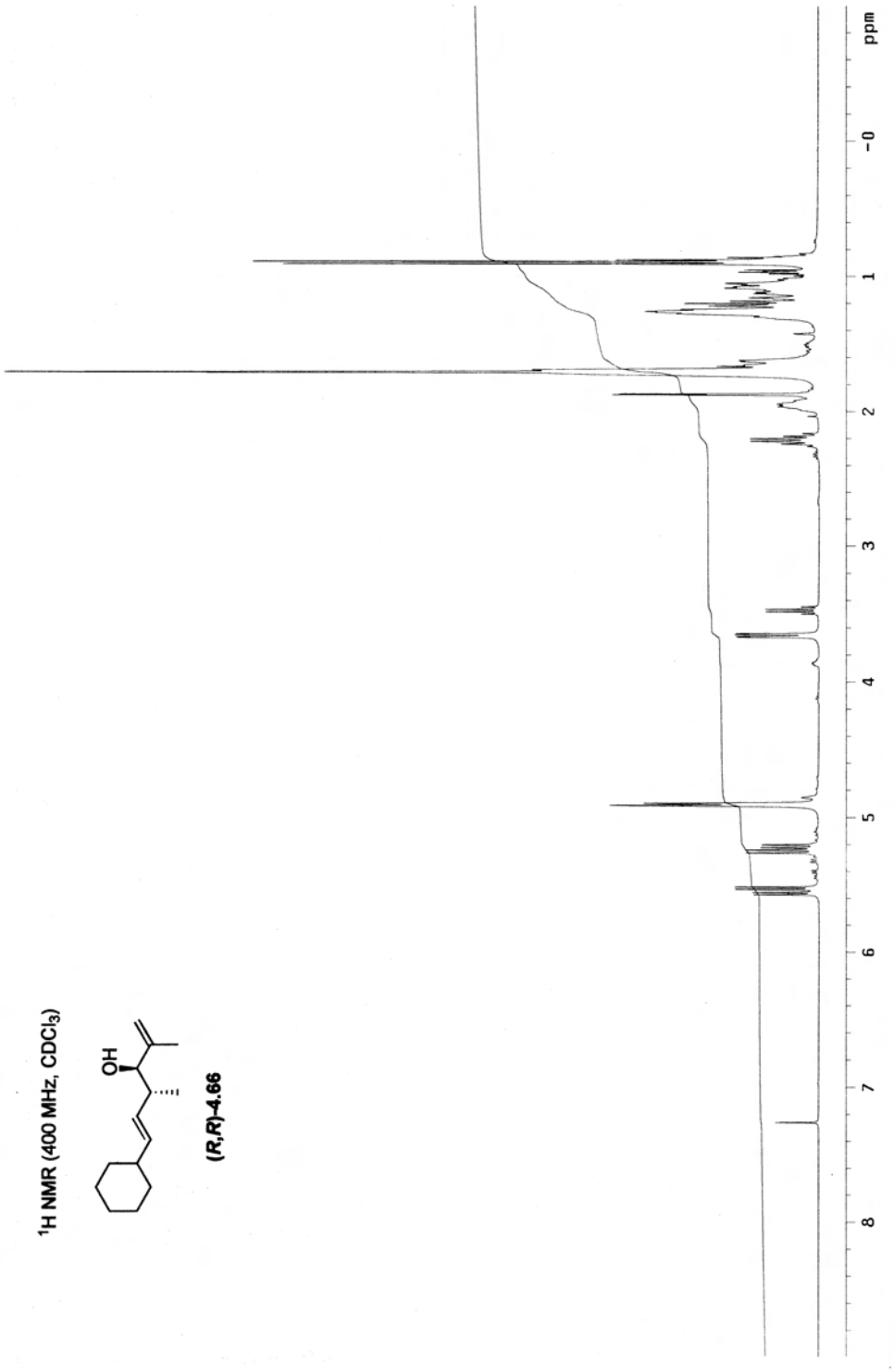

^{1}H NMR (300 MHz, $CDCl_3$)
OH
H
(*R*,*R*)-4.54
8
7
6
5
4
3
2
1
-0
ppm

^{13}C NMR (300 MHz, $CDCl_3$)

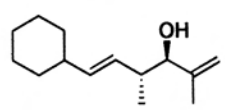


(*R,R*)-4.54

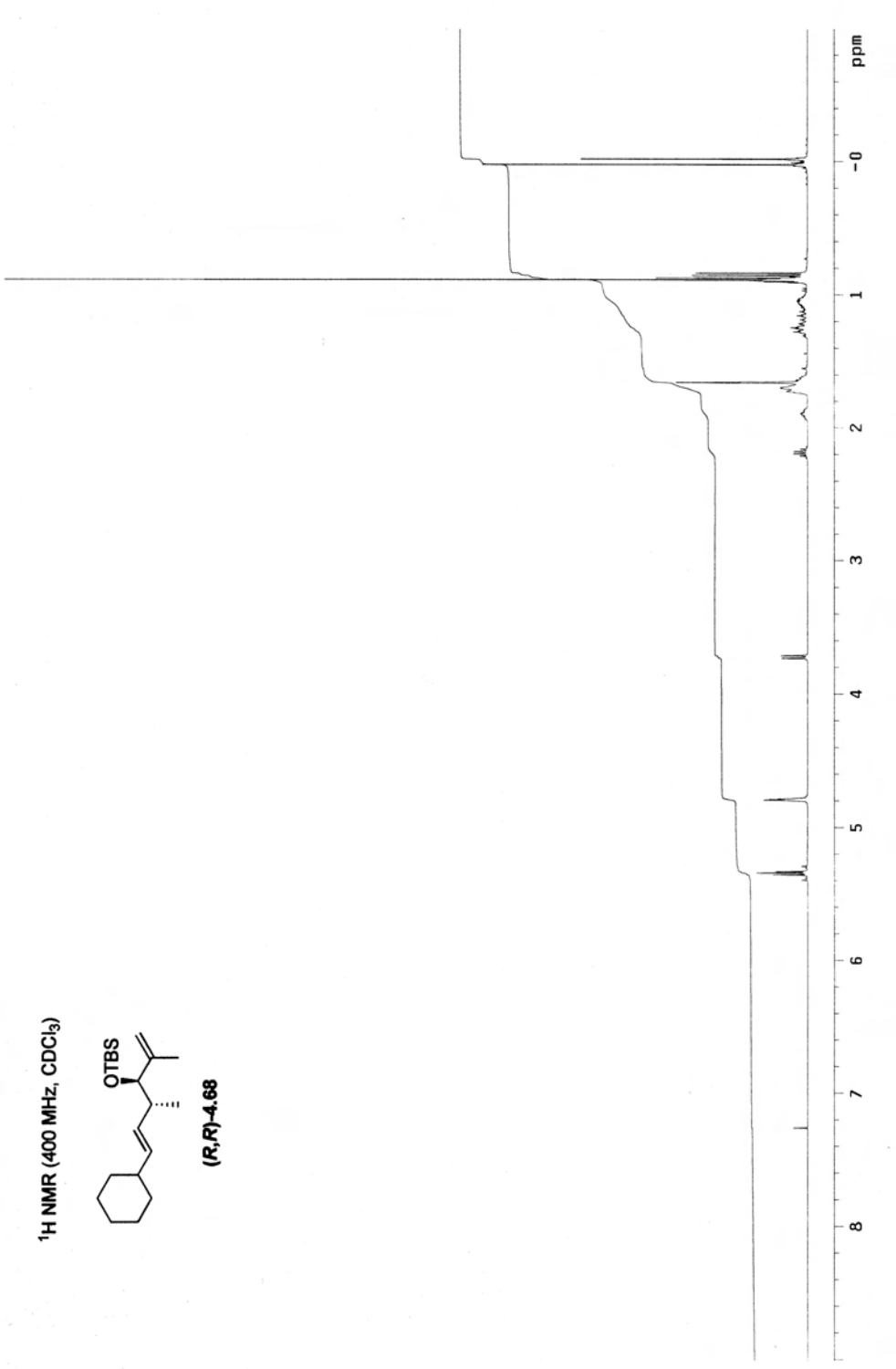
^{1}H NMR (400 MHz, CDCl$_3$)
Mukai's sator of 4.54


^{1}H NMR (400 MHz, $CDCl_3$)
OH
(R,R)-4.66
ppm
8
7
6
5
4
3
2
1
-0

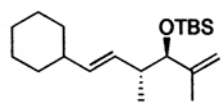
^{13}C NMR (400 MHz, $CDCl_3$)



(*R*,*R*)-4.66

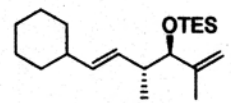

^{1}H NMR (400 MHz, $CDCl_3$)
OTBS
(R,R)-4.68
ppm
8
7
6
5
4
3
2
1
0

^{13}C NMR (400 MHz, $CDCl_3$)



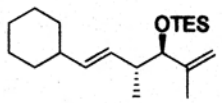
(*R*,*R*)-4.68

^{1}H NMR (300 MHz, $CDCl_3$)



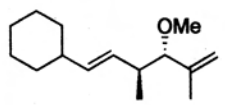
4.70

^{13}C NMR (300 MHz, $CDCl_3$)



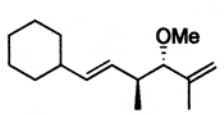
4.70

^{1}H NMR (400 MHz, $CDCl_3$)

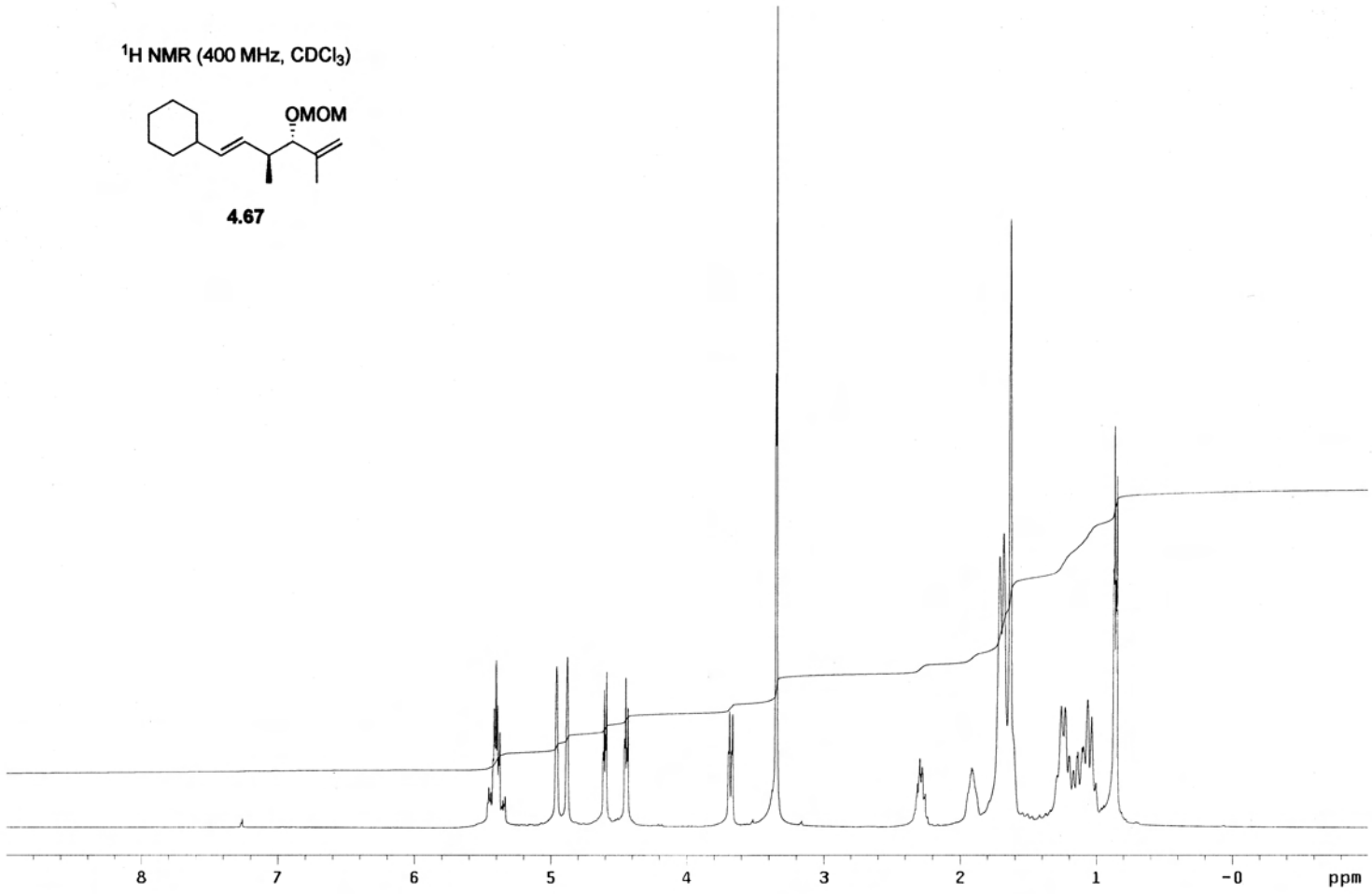


4.69

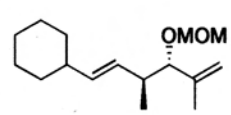
^{13}C NMR (400 MHz, $CDCl_3$)



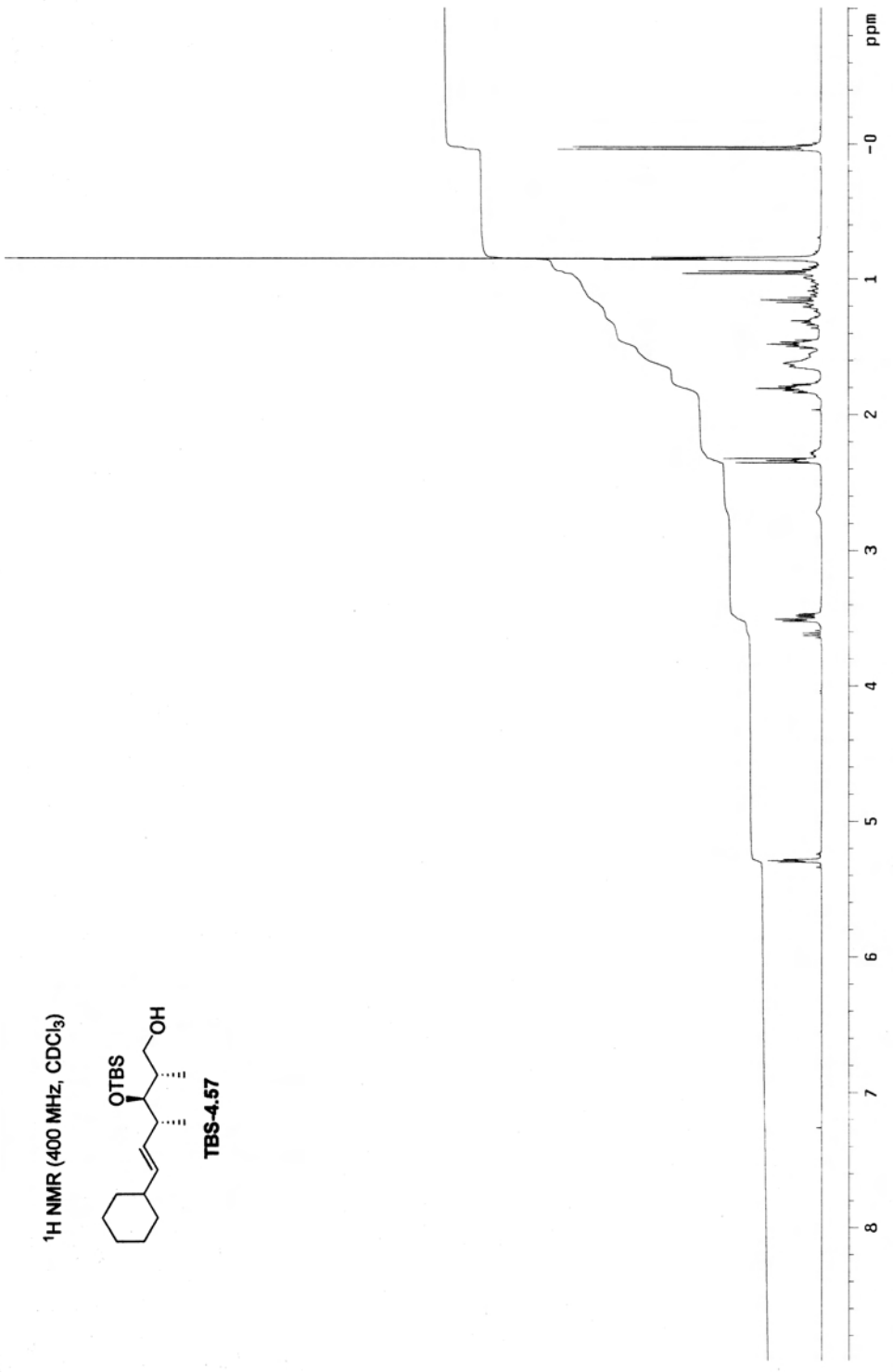
4.69


^{1}H NMR (400 MHz, $CDCl_3$)
OMOM
4.67
8
7
6
5
4
3
2
1
-0
ppm

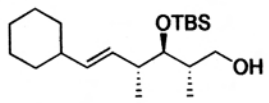
^{13}C NMR (400 MHz, $CDCl_3$)



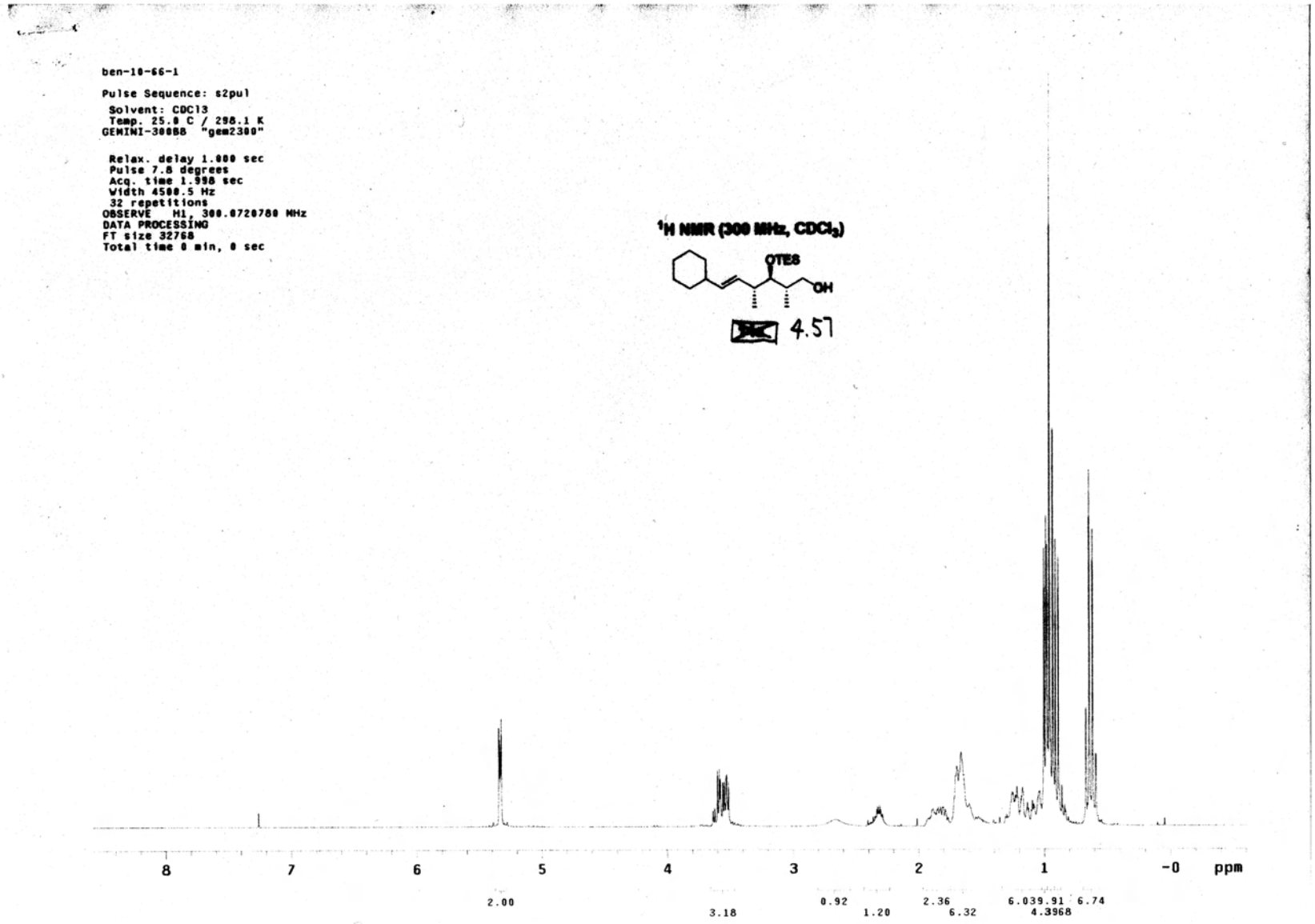
4.67


^{1}H NMR (400 MHz, $CDCl_3$)
OTBS
OH
TBS-4.57
ppm
8
7
6
5
4
3
2
1
−0

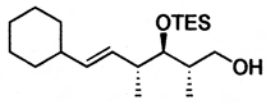
^{13}C NMR (400 MHz, $CDCl_3$)



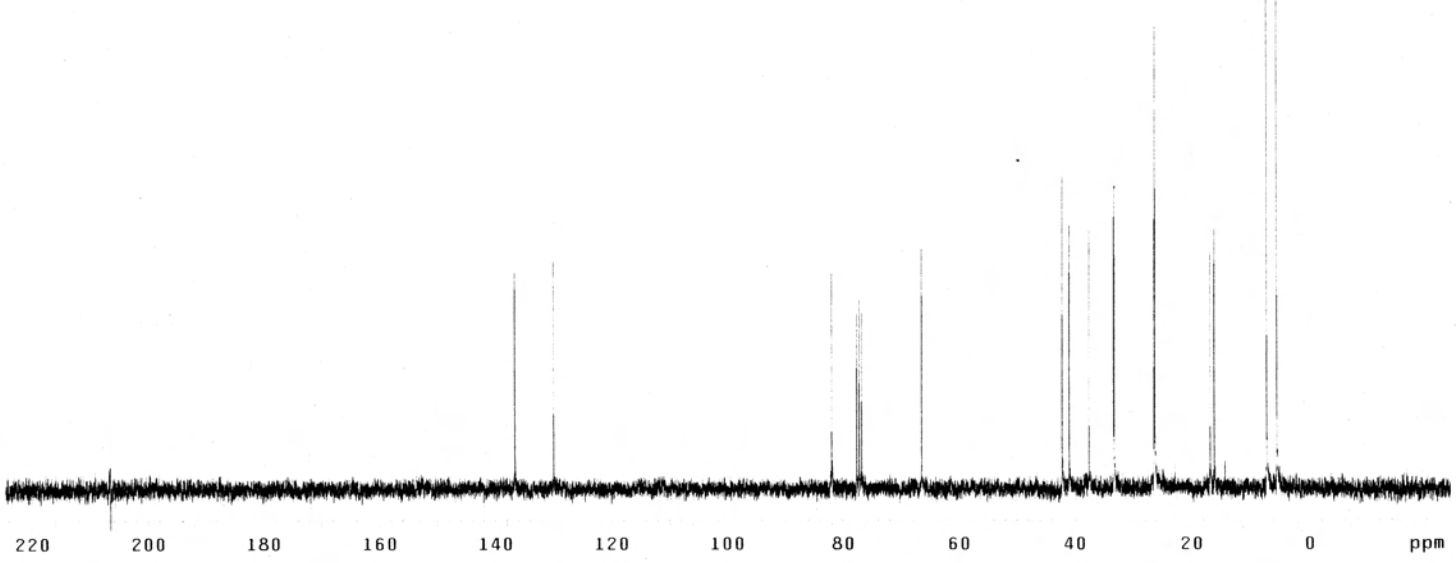
TBS-4.57

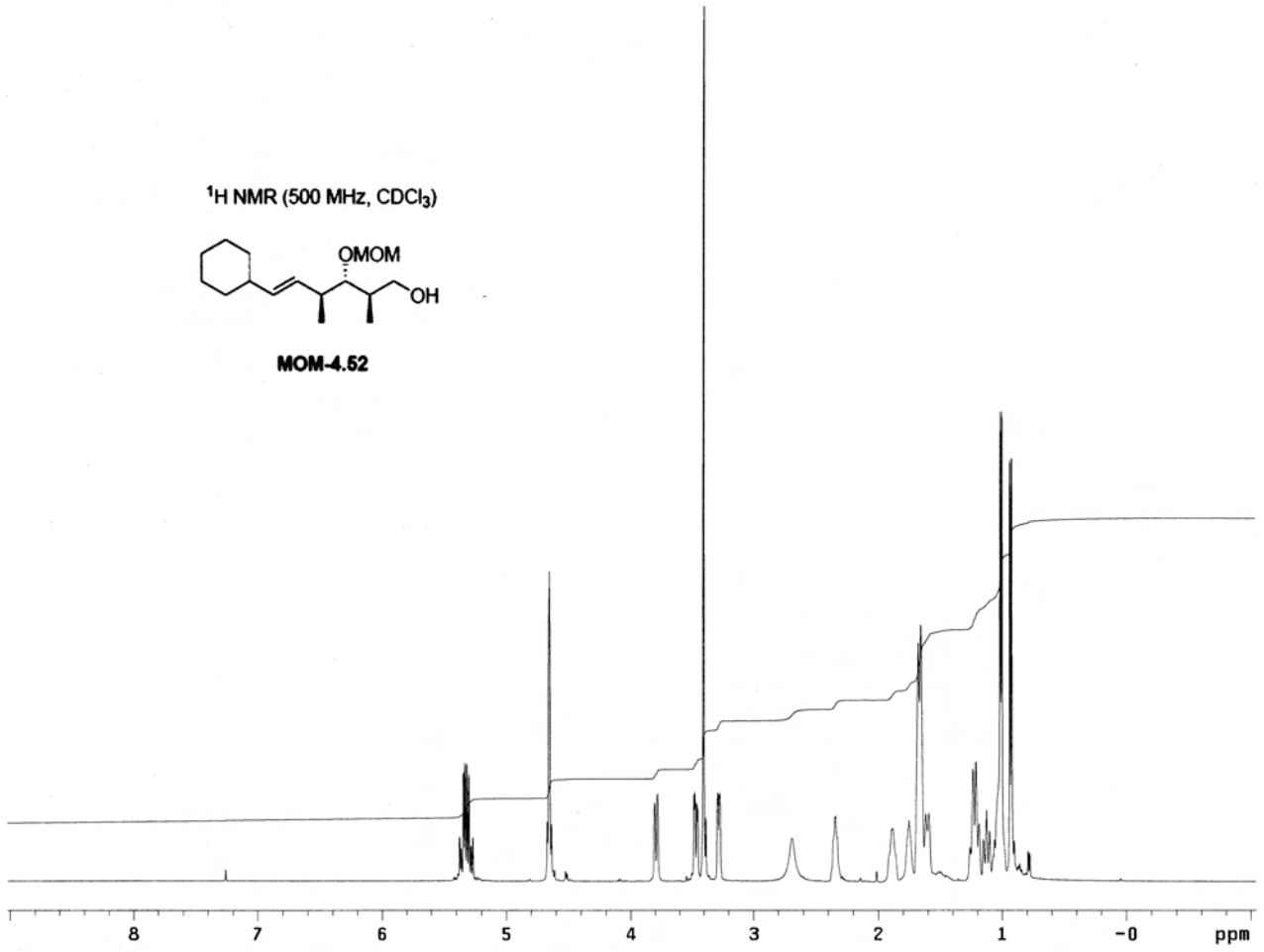

ben-10-66-1
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720780 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec
^{1}H NMR (300 MHz, CDCl$_3$)
OTES
OH
4.57
8
7
6
5
4
3
2
1
-0
ppm
2.00
3.18
0.92
1.20
2.36
6.32
6.039.91
4.3968
6.74

^{13}C NMR (400 MHz, $CDCl_3$)

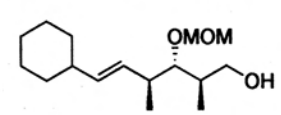


TES-4.57



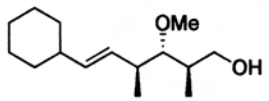

^{1}H NMR (500 MHz, $CDCl_3$)
OMOM
OH
MOM-4.52
8
7
6
5
4
3
2
1
-0
ppm

^{13}C NMR (400 MHz, $CDCl_3$)



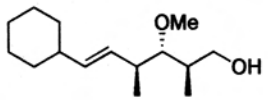
MOM-4.52

^{1}H NMR (400 MHz, $CDCl_3$)



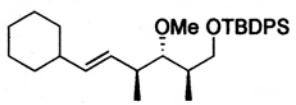
Me-4.52

^{13}C NMR (400 MHz, $CDCl_3$)



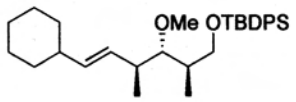
Me-4.52

^{1}H NMR (400 MHz, $CDCl_3$)

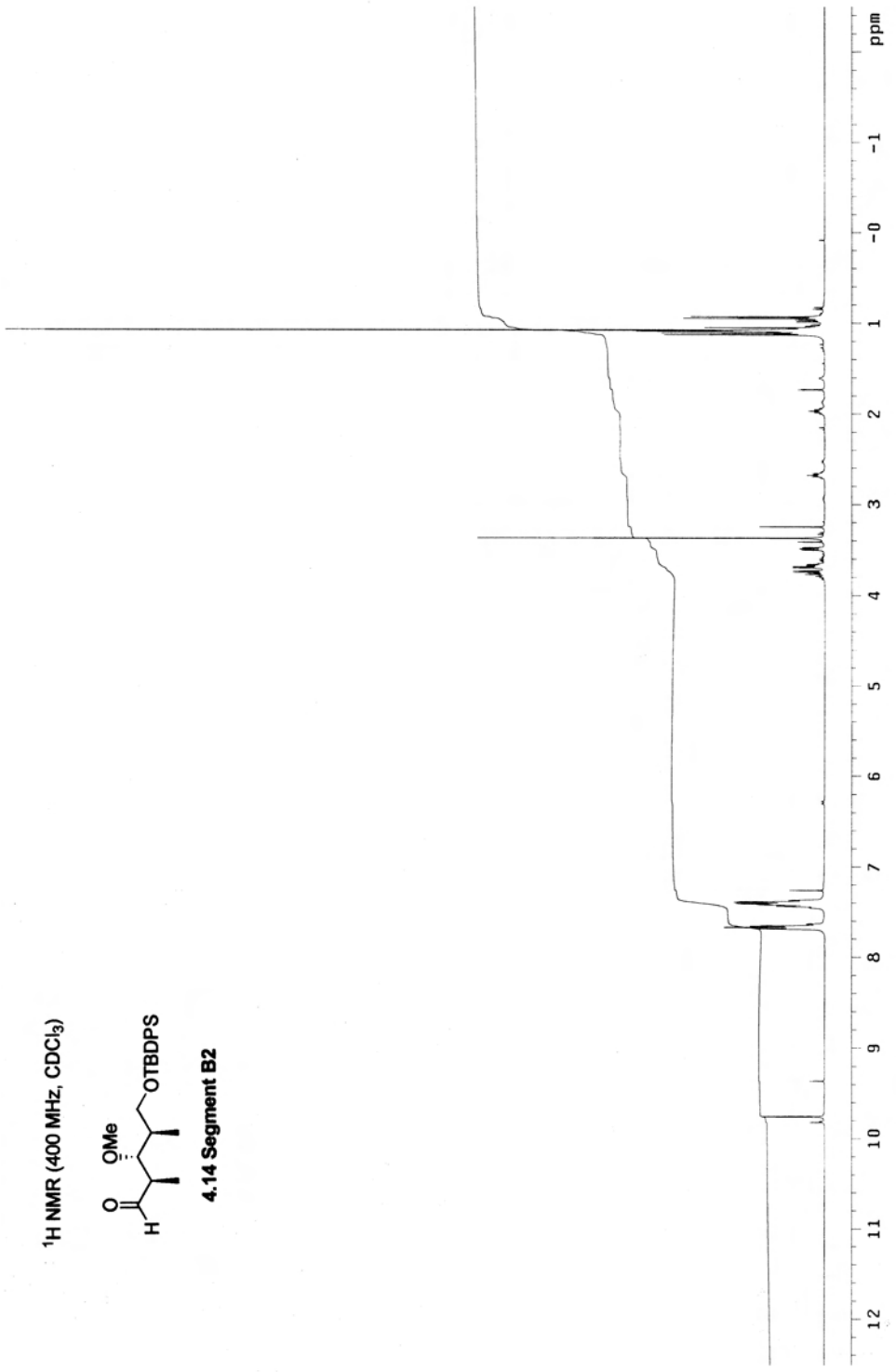


4.73

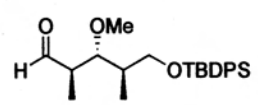
^{13}C NMR (400 MHz, $CDCl_3$)



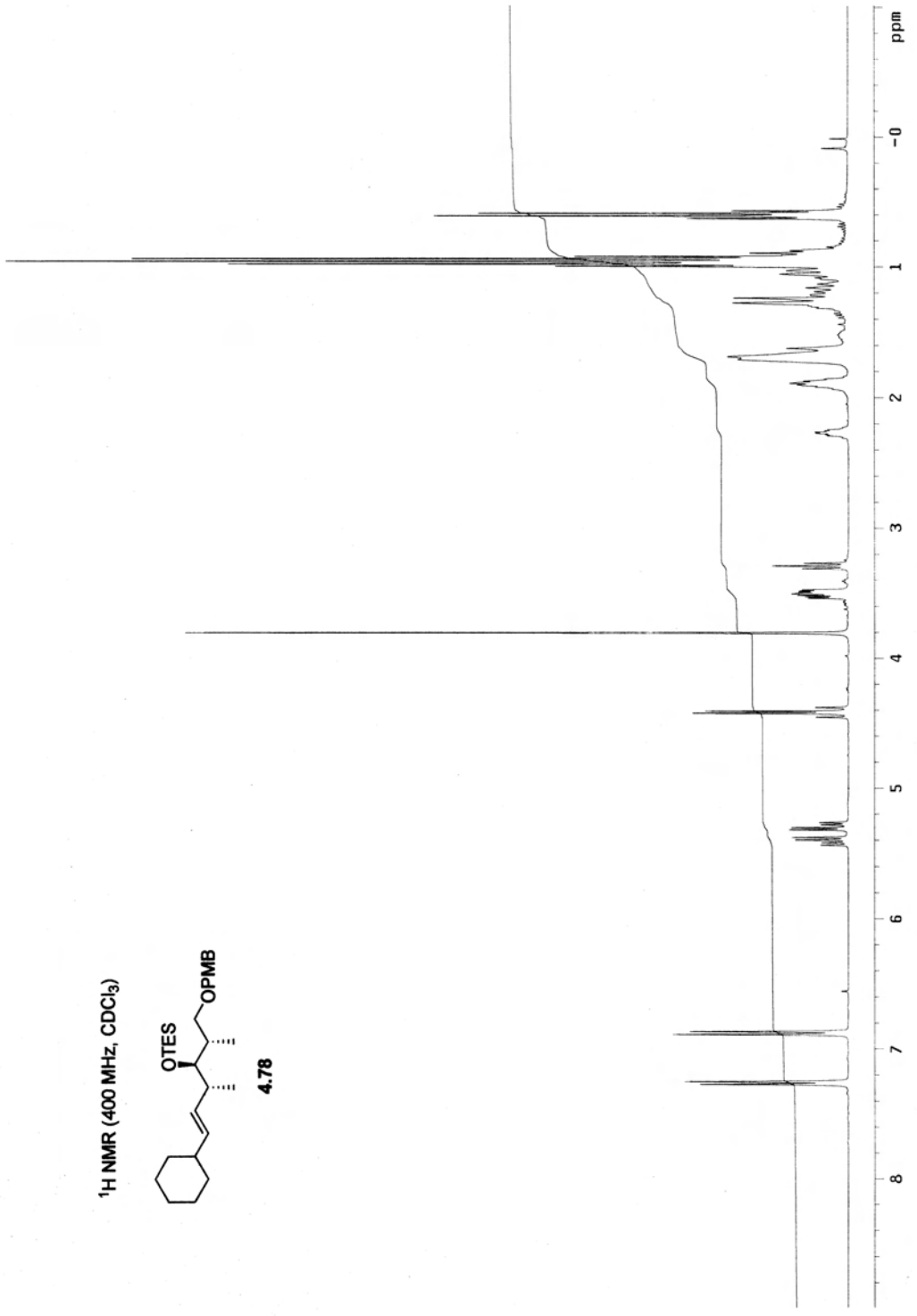
4.73


^{1}H NMR (400 MHz, $CDCl_3$)
OMe
O
H
OTBDPS
4.14 Segment B2
ppm
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1

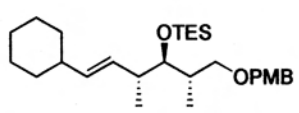
^{13}C NMR (400 MHz, $CDCl_3$)



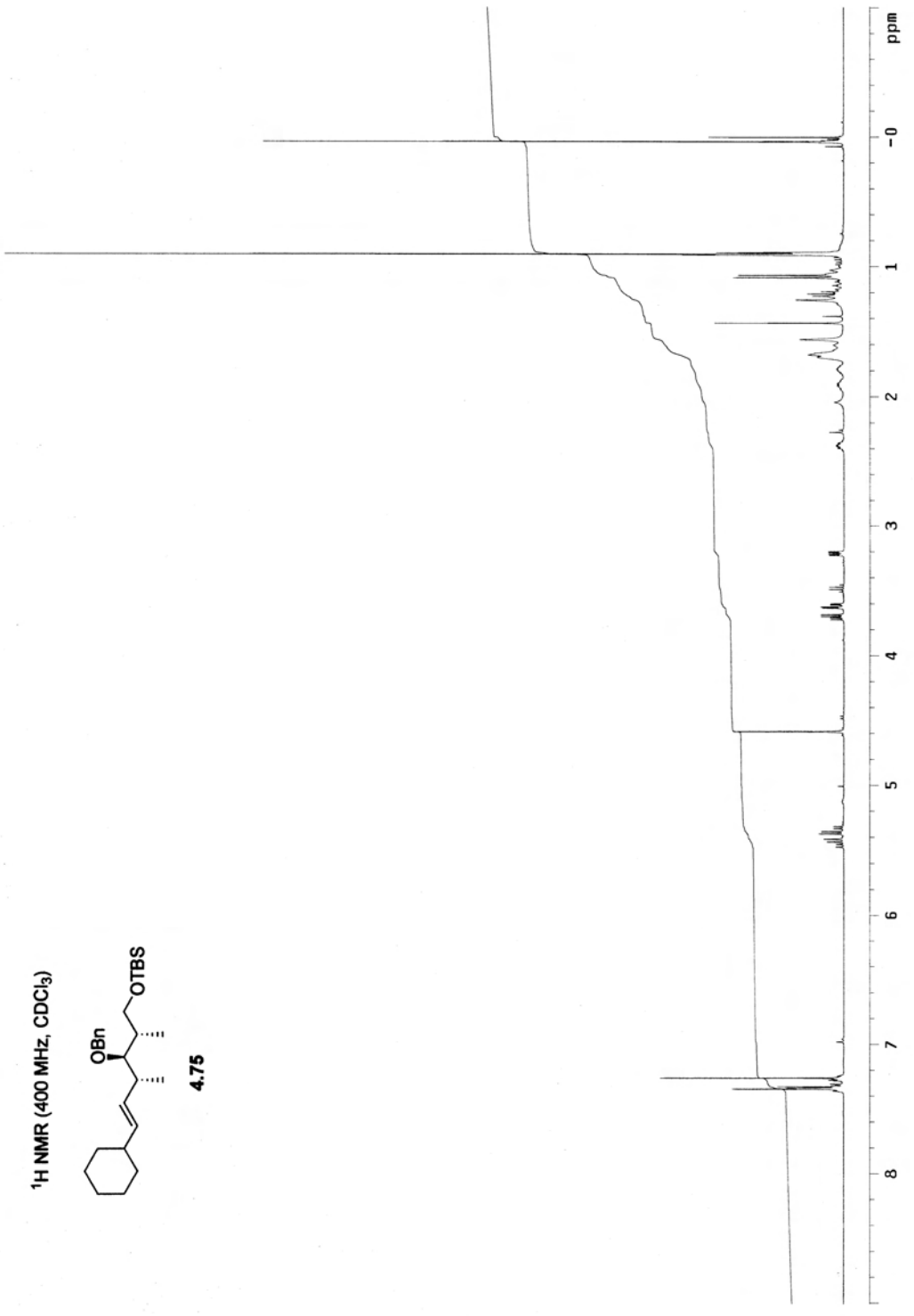
4.14 Segment B2


^{1}H NMR (400 MHz, $CDCl_3$)
OTES
OPMB
4.78
ppm
8
7
6
5
4
3
2
1
0

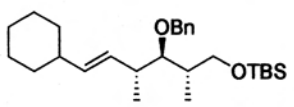
^{13}C NMR (400 MHz, $CDCl_3$)



4.78

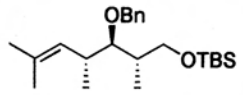

^{1}H NMR (400 MHz, $CDCl_3$)
OBn
OTBS
4.75
ppm
8
7
6
5
4
3
2
1
−0

^{13}C NMR (400 MHz, $CDCl_3$)



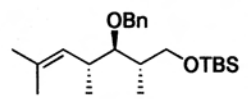
4.75

^{1}H NMR (400 MHz, $CDCl_3$)



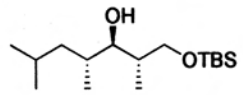
4.75b

^{13}C NMR (400 MHz, $CDCl_3$)



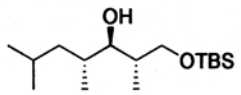
4.75b

^{1}H NMR (400 MHz, $CDCl_3$)



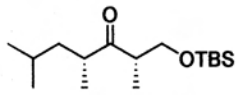
4.75c

^{13}C NMR (400 MHz, $CDCl_3$)



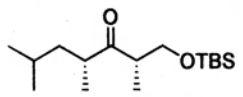
4.75c

^{1}H NMR (400 MHz, $CDCl_3$)



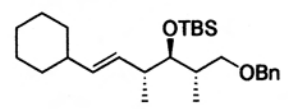
4.76 TBS-ketone

^{13}C NMR (400 MHz, $CDCl_3$)



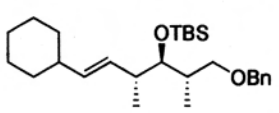
4.76 TBS-ketone

^{1}H NMR (400 MHz, $CDCl_3$)

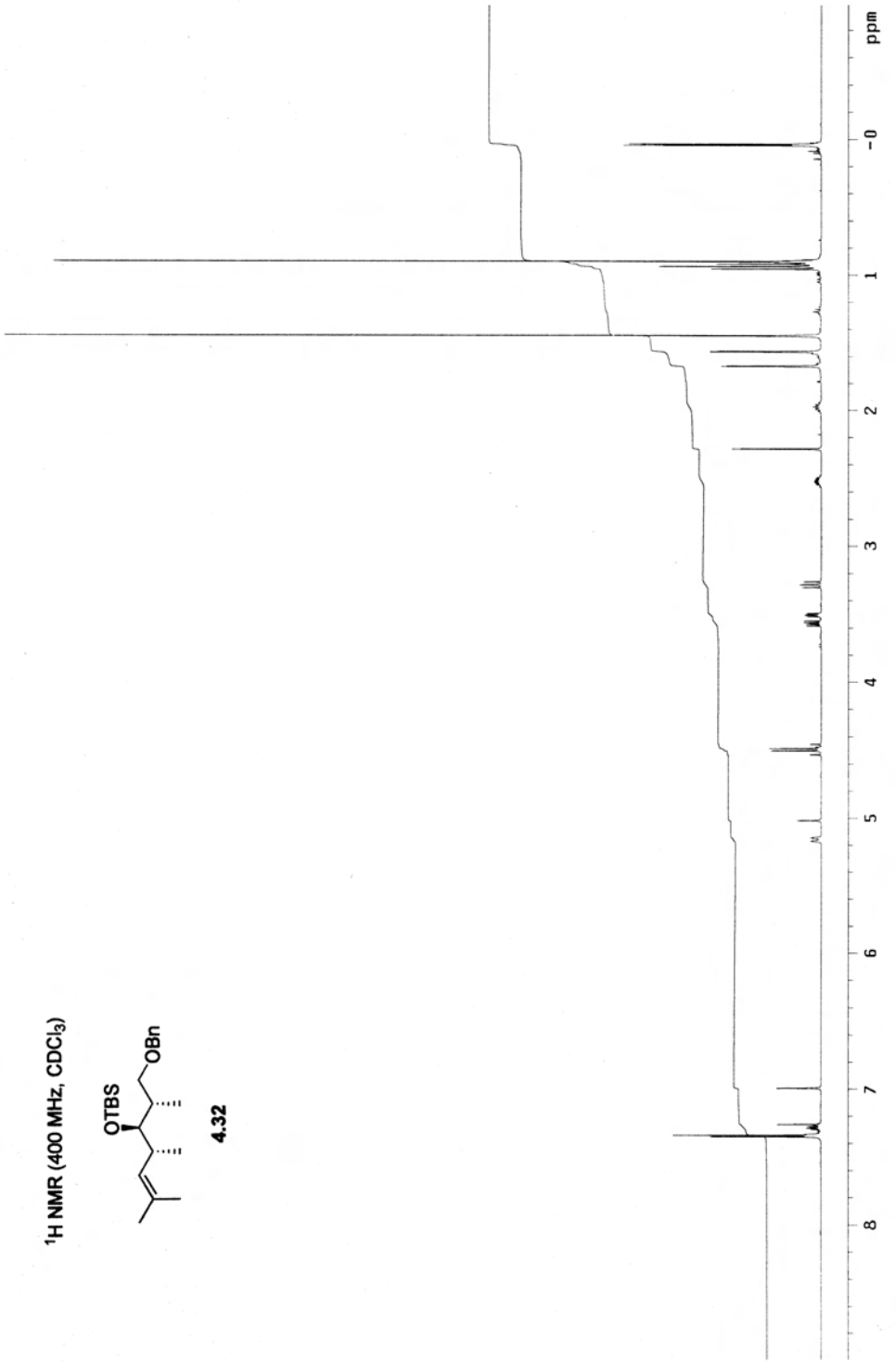


4.74

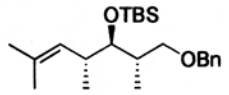
^{13}C NMR (400 MHz, $CDCl_3$)



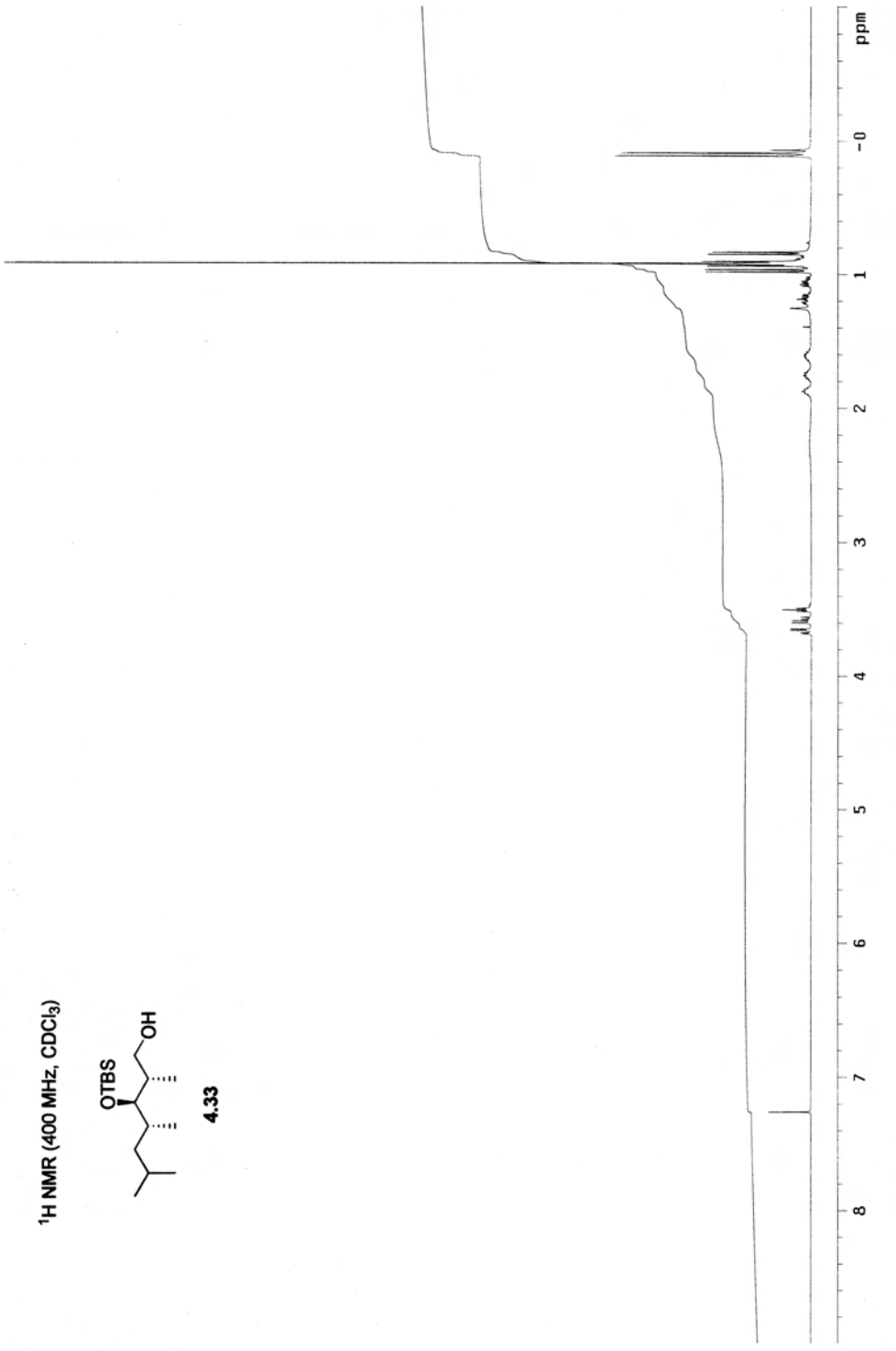
4.74


^{1}H NMR (400 MHz, $CDCl_3$)
OTBS
OBn
4.32
ppm
8
7
6
5
4
3
2
1
−0

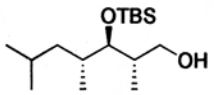
^{13}C NMR (400 MHz, $CDCl_3$)



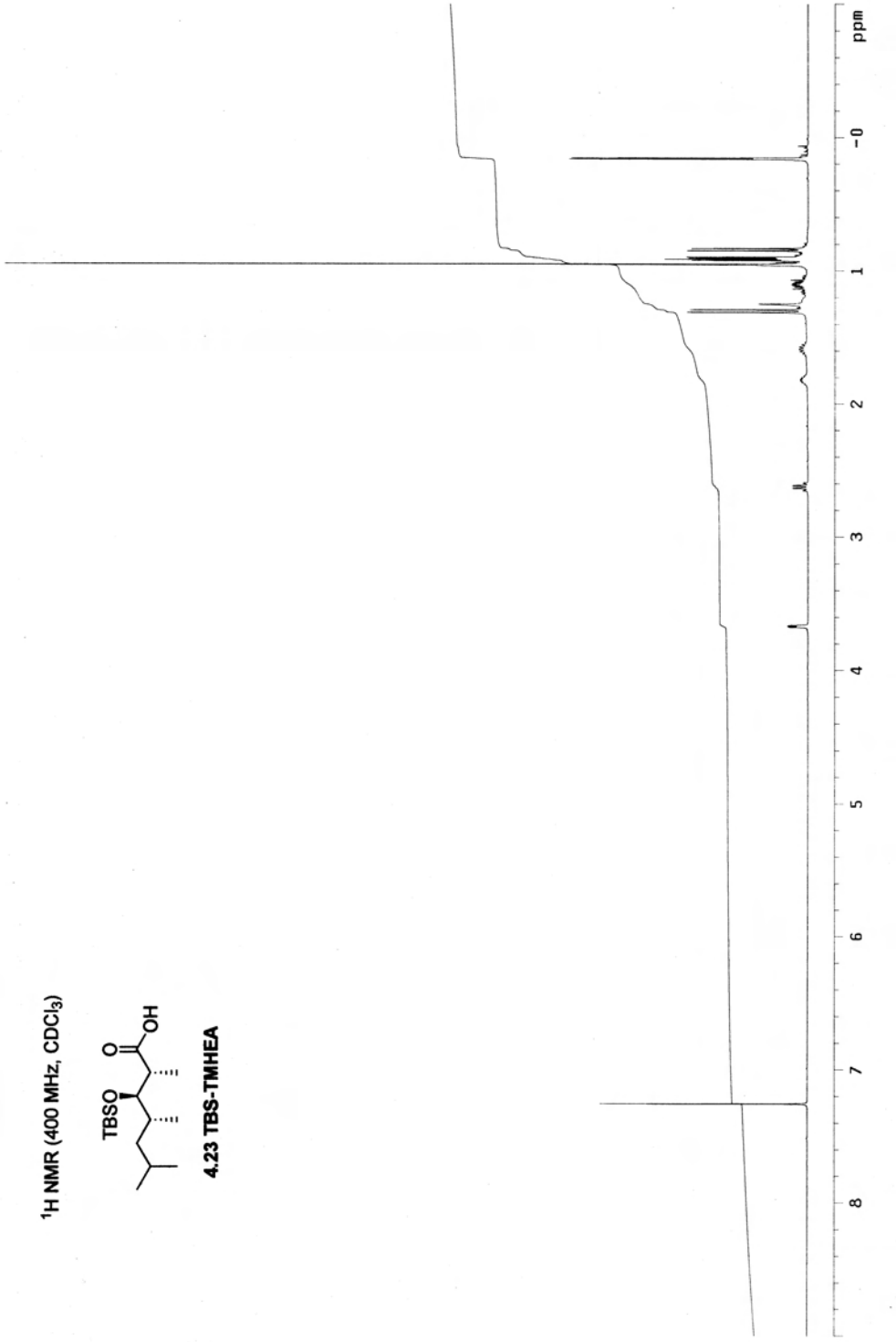
4.32


^{1}H NMR (400 MHz, $CDCl_3$)
OTBS
OH
4.33
ppm
8
7
6
5
4
3
2
1
0

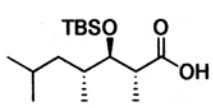
^{13}C NMR (400 MHz, $CDCl_3$)



4.33


^{1}H NMR (400 MHz, $CDCl_3$)
TBSO
O
OH
4.23 TBS-TMHEA
ppm
8
7
6
5
4
3
2
1
-0

^{13}C NMR (400 MHz, $CDCl_3$)



4.23 TBS-TMHEA