I. A Scalable Protocol for the Synthesis and Use of Neomenthyldiphenylphosphine.

II. Synthetically Versatile Templates for Epoxide-Opening Cascades.

by

Aaron R. Van Dyke

B.S., Chemistry with Honors
Seattle University, Seattle, 2004

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

May 2009

Signature of the Author _____
Department of Chemistry
May 14, 2009

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This doctoral thesis has been examined by a committee in the Department of Chemistry as follows:

Professor Mohammad Movassaghi _____
Chairman

Professor Timothy F. Jamison _____
Thesis Supervisor

Professor Gregory C. Fu _____

To my parents, Bob and Margaret.

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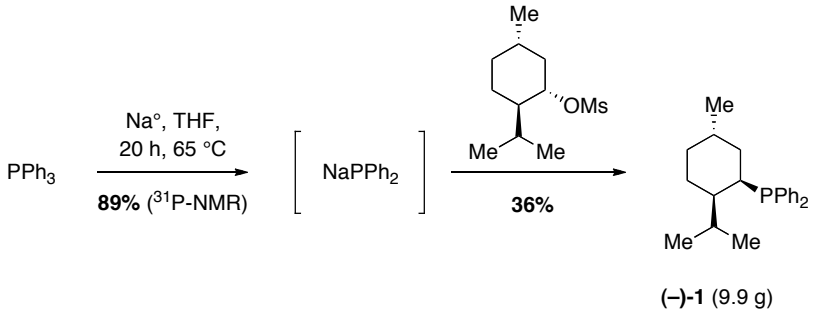
Doctor of Philosophy in Organic Chemistry

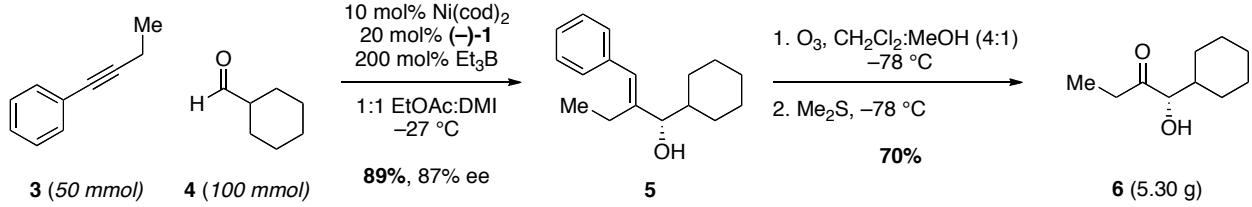
ABSTRACT

Chapter I.

A scalable and reproducible protocol has been developed for the preparation of (–)-neomenthyldiphenylphosphine (**(–)-1**) from inexpensive starting materials.



This ligand was then utilized in the nickel-catalyzed reductive coupling of alkyne **3** and aldehyde **4** to afford allylic alcohol **5** in high yield and enantiomeric excess. Several important modifications were made to the initially communicated procedure in order to effectively translate this methodology from the millimole to decimole scale. Allylic alcohol **5** was then ozonolyzed to afford β–hydroxy ketone **6** with complete preservation of enantiomeric purity.



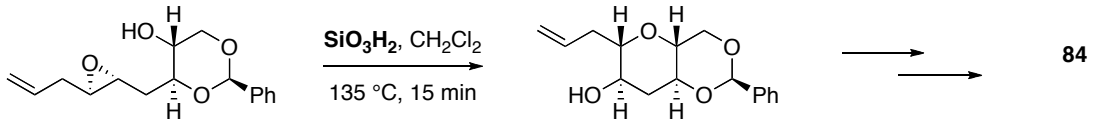
Chapter II.

The *endo*-selective cyclization of alcohols onto epoxides provides a direct route for constructing the oxygen heterocycles found in ladder polyether natural products. Additionally,

strategies to transform multiple epoxides into multiple new rings have appealing parallels to the proposed biogenesis of these compounds. A continuing challenge is to overcome the inherent preference for the undesired smaller ring product over the larger ring product, processes termed *exo* and *endo* cyclization, respectively. Additionally, any method to address this problem should yield products that are themselves synthetically relevant intermediates.

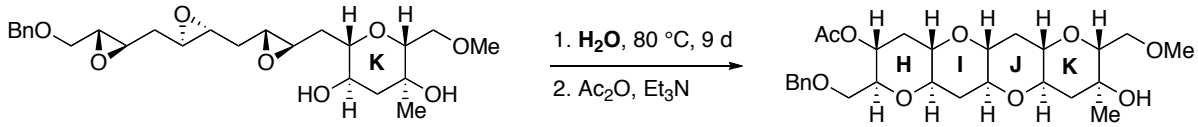
We discovered that a benzylidene acetal templated the cyclization of electronically unbiased epoxy alcohols, such as **75**, affording products with significant synthetic utility. Critical for high *endo*-selectivity was the use of silicon-dioxide based promoters. Highlighting the template's utility, the newly formed product (**76**) was then transformed into a highly decorated THP template (**84**), corresponding to ring *K* of gymnocin A. In water, **84** underwent a water-promoted cascade to construct three additional rings of gymnocin A.

benzylidene acetal template



75 **76**

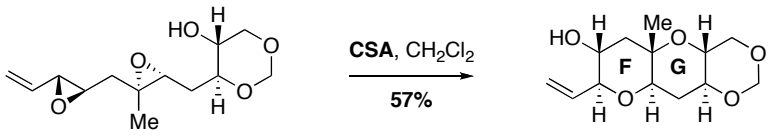
THP template *fragment of gymnocin A*



84 **83**

We have also achieved cascades of methylene acetal templates with electronically activated epoxides to construct the *FG* rings of gambierol.

methylene acetal template *fragment of gambierol*



100 **99**

Use of these functionalized templates and the products derived from them sets the stage for the convergent total synthesis of ladder polyether natural products.

Thesis Supervisor: Timothy F. Jamison
Title: Professor of Chemistry

Preface

Portions of this thesis have appeared in the following articles that were co-written by the author:

(*S*)-(+)-Neomenthyldiphenylphosphine in Nickel-Catalyzed Asymmetric Reductive Coupling of Alkynes and Aldehydes: Enantioselective Synthesis of Allylic Alcohols and α-Hydroxy Ketones.

Van Dyke, A. R.; Miller, K. M.; Jamison, T. F. *Org. Synth*. **2007**, *84*, 111–119.

Functionalized Templates for the Convergent Assembly of Polyethers: Synthesis of *HIJK* Rings of Gymnocin A.

Van Dyke, A. R.; Jamison, T. F. *Angew. Chem. Int. Ed*. **2009**, Article Early View, DOI: 10.1002/anie.200900924

Acknowledgements

Non solum autem, sed et gloriamur in tribuationibus scientes quod tribulatio patientiam operatur, patientia autem probationem, probation vero spem; spes autem non confundit.

This gathering of letters and punctuation cannot justly express my gratitude for those who have shaped me as an individual and scientist. Foremost deserving of credit is my advisor, Tim Jamison, who provided me tremendous freedom in my research. As is true of any substantial intellectual pursuit, there have been seasons of thrill and seasons of acedia; through it all, Tim reminded me to keep the larger picture in mind and to persevere.

Tim has also assembled a remarkable cohort of scientists who have made the past 5 years truly unforgettable. Dr. Betsy Colby was a kind and patient mentor, helping me with my first project in the group. I also thank Dr. Karen Miller-Moslin who was tremendously helpful in scaling up her reductive-coupling methodology for *Organic Syntheses*. I was extremely privileged to have worked with Dr. Graham Simpson, who introduced me to the ladder polyethers and also showed me that one can perform great research and still have a social life. My deskmate for 3 years, Dr. Ryan Moslin, confirmed for me that no matter how hopeless things may seem, life goes on. I thank Dr. Chudi Ndubaku for his tremendous kindness and encouragement, Dr. Neil Langille for his endless supply of quips, and Dr. Stefan Kaiser for many lunch time conversations.

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Thanks also to Dr. Victor Gehling and Kristin Schleicher for being fantastic labmates and roommates. It was also wonderful, whenever I needed straight talk or a homemade pastry, having Dr. Megan Foley in the lab. I find it apropos that I began working in the Jamison Group with a Colby and my final months have been spent collaborating with another. It was a privilege to

work (and trade recipes) with Dr. Denise Colby and I hope that her total synthesis is short and *endo*-selective. I also owe a debt, for daily interactions, to the rest of the Jamison group past and present who helped create such a lively work environment; Dr. Tim Heffron, Dr. Sze-Sze Ng, Azusa Kondoh, Dr. Hirohisa Ohmiya, Dr. Matt Bedore, Dr. Yutaka Ikeuchi, Dr. Adam Sniady, Dr. Alessandro Agosti, Dr. Ryosuke Matsubara, Ivan Vilotijevic, Brian Underwood, Jessica "Sunshine" Tanuwidjaja, Kurt Ambrust, Hyung Kyoo Kwon, Nikolas Huwyler, Brian Sparling and Ngan Nguyen. I also wish the best to my classmates Katrina Woodin, Andrew Lauer, Dustin Siegel, and Meiliana Tjandra.

It is often said that those who are educated by the Jesuits are "ruined for life," because of their holistic approach to education. In that tradition, there are communities and individuals outside of MIT that have been equally influential in shaping and sustaining me. First, completing this Ph.D. is a testament to the quality of professors, mentors, and peers at Seattle University from whom I continue to benefit. Thanks especially to my SU classmate Kevin Grove, CSC, for the opening Latin translation of scripture. I would also be remiss to not acknowledge my high school chemistry teacher, Dr. Beth Baranowski, who planted the idea, early in my mind, of pursuing an advanced degree in the field.

I am tremendously grateful for the Paulist Center of Boston, which provided a place for worship and fellowship. I am especially indebted to the members of my small group at the Paulist Center for sharing meals together, apple picking adventures, and summer trips to Canada. I will always consider each of you a close friend. During my time in Cambridge, I also had the great fortune of meeting Bill Polk who helped me overcome some considerable health challenges. As a result, he has literally transformed my life for the better. Finally, from preschool to Ph.D. my family has been wonderful for letting my intellectual curiosity take me where it will, supporting me every step of the way. I always look forward to spending time with my sisters Sarah and Leah and hope that someday we'll all live in the same time zone. My parents, Bob and Margaret, especially, have been pillars of strength during my time at MIT. It is because of their support and love that I have made it to this point and it is to them that I dedicate this work.

Aaron R. Van Dyke
Cambridge, Massachusetts

Table of Contents

Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
cod	cyclooctadiene
CAM	ceric ammonium molybdate
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
DET	diethyl tartrate
DIBALH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*'-dimethylformamide
DMI	dimethylimidizolidinone
DMM	dimethoxymethane
DMP	Dess-Martin periodinane
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron ionization
ESI	electron spray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide

HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Imid	imidazole
i-Pr	isopropyl
LA	Lewis acid
LAH	lithium aluminum hydride
Lut	2,6-lutidine
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
mol	mole
Ms	methanesulfonyl
MS	molecular sieves
n-Bu	*n*-butyl
n-Hex	*n*-hexyl
nm	nanometer
NMDPP	neomenthyldiphenylphosphine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nucler Overhauser effect spectroscopy
Nu	nucleophile
Ph	phenyl
PMA	phosphomolybdic acid
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PPTS	pyridine *para*-toluenesulfonate
Pr	propyl
psi	pounds per square inch
salen	*N*,*N*'-*bis*(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino
s-Bu	*sec*-butyl

TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
TBME	*tert*-butylmethylether
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TES	triethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl

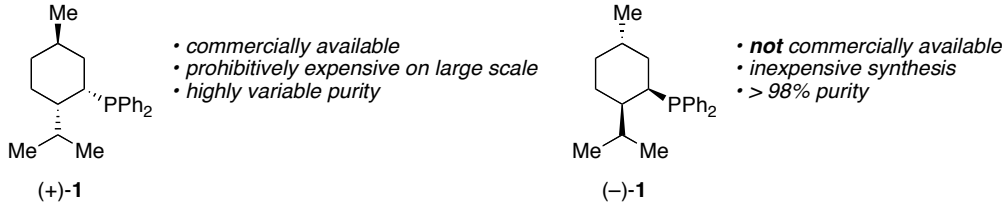
Chapter 1

A Scalable Protocol for the Synthesis and Use of Neomenthyldiphenylphosphine

Introduction

Originally prepared by Morrison[1] over 30 years ago, (+)-neomenthyldiphenylphosphine (NMDPP) (**(+)-1**)[2] is a commercially available monodentate ligand utilized for asymmetric hydrogenation,[3] carbomethoxylation,[4] and the resolution of organometallic complexes.[5] Currently it is also the only phosphine ligand that, in nickel-catalyzed reductive coupling reactions of alkynes and aldehydes, affords the allylic alcohol products in high enantiomeric excess.[6] We sought to demonstrate the utility of this transformation on large scale and thus required multigram quantities of **1**. Unfortunately, only the dextrorotatory (+) antipode of **1** is commercially available. Moreover, commercial sources of (+)-**1** can be prohibitively expensive, and some vendors did not disclose the purity of the phosphine ligand (Figure 1).[7] Consequently, we sought an inexpensive and reproducible synthesis of **1** that would afford multigram quantities of either enantiomer.

Figure 1

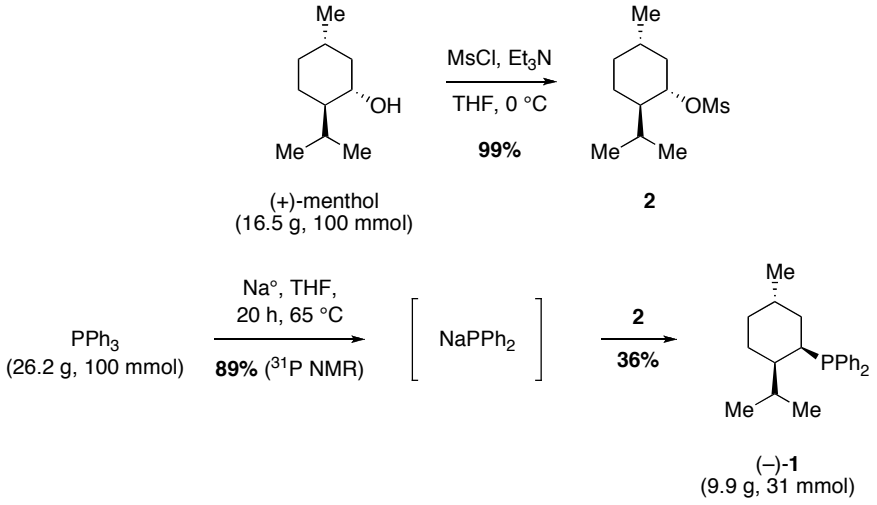


[1] Morrison, J. D.; Masler, W. F. *J. Org. Chem*. **1974**, *39*, 270–272.
[2] (+)-NMDPP is often referred to as "(*S*)-NMDPP".
[3] (a) Morrison, J.; Burnett, R.; Aguiar, A.; Morrow, C.; Phillips, C. *J. Am. Chem. Soc*. **1971**, *93*, 1301–1303. (b) Valentine, D. Jr.; Johnson, K. K.; Priester, W.; Sun, R. C.; Toth, K.; Saucy, G. *J. Org. Chem.* 1980, **45**, 3698–3703.
[4] Cometti, G.; Chiusoli, G. P. *J. Organomet. Chem*. **1982**, *236*, C31–C32.
[5] (a) Salvadori, P.; Pertici, P.; Marchetti, F.; Lazzaroni, R.; Vitulli, G. *J. Organomet. Chem*. **1989**, *370*, 155–171. (b) Howell, J.; Squibb, A. *Organometallics*. **1990**, *9*, 80–91.
[6] (a) Miller, K. M.; Huang, W. S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442–3443. (b) Colby, E. A.; Jamison, T. F. *J. Org. Chem.* **2003**, *68*, 156–166.
[7] As of May 2009, (+)-**1** was available from Strem ($118/gram, undisclosed purity), 3B Scientific ($184/gram, 98% pure), and Acros ($407/gram, undisclosed purity).

Results and Discussion

A survey of the literature at the beginning of this work revealed that NMDPP is frequently prepared by the nucleophilic displacement of a diphenylphosphide anion upon menthyl chloride or menthyl mesylate. The diphenylphosphide species is typically generated from either diphenylphosphine[1,8] or diphenylphosphinous chloride,[9] both of which are highly noxious and air-sensitive compounds. Alternatively, triphenylphosphine may be converted to diphenylphosphide, but the most efficient conditions in the literature employ undesirably forcing conditions: a sodium-potassium alloy under high hydrogen pressure (50 psi).[10,11] Furthermore, regardless of how the nucleophile is generated, protocols for the displacement reaction vary greatly, with no explanation for the differences between these procedures.

Scheme 1. Synthesis of (–)-**1** employed in this work.



[8] Honaker, M. T.; Sandefur, B. J.; Hargett, J. L.; McDaniel, A. L.; Salvatore, R. N. *Tetrahedron Lett*. **2003**, *44*, 8373–8377.

[9] Aguiar, A. M.; Morrow, C. J.; Morrison, J. D.; Burnett, R. E.; Masler, W. F.; Bhacca, N. S. *J. Org. Chem*. **1976**, *41*, 1545–1547.

[10] Beaumont, A. J.; Kiely, C.; Rooney, D. A. *J. Fluorine Chem*. **2001**, *108*, 47–50.

[11] (a) Layman, W. J.; Welsh, G. W. Production of high purity alkali metal diarylphosphide and cycloalkyldiarylphosphines. U.S. Patent 5,866,720. February 2, **1999**. (b) Senaratne, K. Synthesis of cycloalkyldiarylphosophines. U.S. Patent 5,710,340. January 20, **1998**. (c) Senaratne, K.: Malcolm, A.; Orihuela, F.; Elnagar, H. Synthesis of cycloalkyldiarylphosophines. U.S. Patent 5,654,486, August 5, **1997**.

We decided to employ a two-step sequence for the production of **(–)-1**, the antipode that is not commercially available (Scheme 1). The first step, preparation of menthol methanesulfonate (**2**), proceeded quantitatively from (+)-menthol under routine conditions. The second step, formation of diphenylphosphide and its displacement reaction with **2**, began with our study of the sodium metal reduction of triphenylphosphine. Triphenylphosphine was refluxed with elemental sodium (400 mol%) to afford sodium diphenylphosphide in 89% yield, on average, as determined by ^{31}P NMR.[12] Longer reaction times and/or increasing the amount of sodium did not substantially improve the yield of the phosphide. Menthyl mesylate **2** was then added to the sodium diphenylphosphide to afford the desired phosphine **(–)-1**. The yield for the displacement, when performed in refluxing THF, was variable and irreproducible ranging from 18 to 35% after recrystallization from MeOH (Table 1, entry 1). We suspected that refluxing temperatures were not required for the displacement and repeated the reaction at ambient

Table 1. Nucleophilic displacement of sodium diphenylphosphide on menthyl mesylate **2**.

entry	mmol PPh_3	yield $NaPPh_2$[a]	mmol **2**	T (°C)	yield **(–)-1**[b]
1	50	88%	50	66	18–35%[c]
2	50	89%	50	23	36–40%[d]
3	100	89%	100	23	36

(a) Generated by addition of 400 mol% Na° to PPh_3 in THF; yield determined by ^{31}P NMR. (b) Yield based on **2**. (c) Range observed over 4 trials. (d) Range observed over 3 trials.

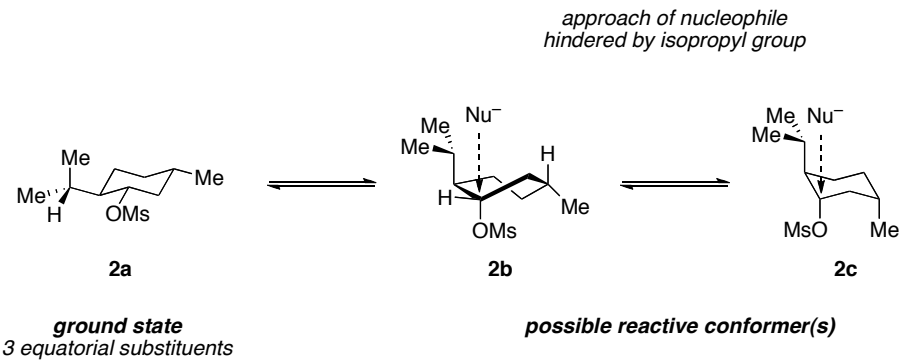
temperature, obtaining the title compound in 38% yield in a reproducible and scalable fashion (entries 2,3). The irreproducibility at higher temperatures may have been due to solvent

[12] A 600 μL aliquot of the crude reaction mixture was placed in an argon filled NMR tube and sealed with a rubber septum: ^{31}P NMR (300MHz, THF) δ: –22 ($NaPPh_2$), –4.9 (PPh_3). Batchelor, R.; Birchall, T. *J. Am. Chem. Soc.* **1982**, 104, 674.

decomposition.[13]

The mediocre yield in the displacement reaction is due to both incomplete conversion and competing E2 elimination. These phenomena can both be explained by the fact that efficient displacement would be expected to occur with the leaving group (mesylate (–OMs), in this case) in an axial or pseudo-axial orientation (Figure 2). In order to achieve this, the cyclohexane

Figure 2. Factors hindering the nucleophilic displacement of mesylate **2**.



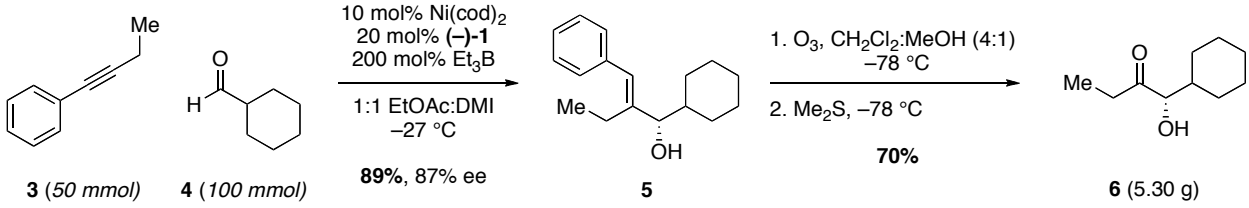
would be required to change from its ground state (**2a**) into a higher energy conformation. One such conformer is a chair (**2c**) in which all three substituents would be axially disposed and in which a 1,3-diaxial interaction between the mesylate and the methyl group is present. In order for **2a** to convert to **2c**, the cyclohexane ring must pass through a twist-boat conformer (**2b**). While the twist boat avoids the 1,3-diaxial interactions found in **2c**, a flagpole-type interaction is present between the isopropyl group and transannular hydrogen. In both of these possible reactive conformers, attack by the nucleophile is hindered by the isopropyl group. Nevertheless, despite its moderate yield, this preparation reproducibly yields multigram quantities of **(–)-1**, which is not commercially available, in >98% purity. It can also be used to prepare the

[13] Reduction of PPh_3 generates $NaPPh_2$ and NaPh either of which may be acting as a base, deprotonating THF and generating ethylene and acetaldehyde byproducts that can quench $NaPPh_2$.

commercially available enantiomer ((+)-NMDPP) from (–)-menthol at a fraction of the market price.

With an efficient, scalable, and reproducible method for the preparation of (–)-**1** and (+)-**1**, we turned our attention to the use of this ligand in the nickel-catalyzed asymmetric reductive coupling of alkynes and aldehydes, a method for the preparation of enantiomerically enriched (*E*)-trisubstituted allylic alcohols. Specifically, we investigated a large scaling coupling of alkyne **3** and aldehyde **4** to give allylic alcohol **5** (Scheme 2).[14] The catalyst for this reaction is derived from $Ni(cod)_2$ and **(–)-1**, in combination with Et_3B (the stoichiometric reductant).[6] In the initial report,[6a] reductive couplings were performed with 0.5 mmol alkyne and 1.0 mmol aldehyde. We

Scheme 2.



sought to scale up this reaction by two orders of magnitude. Consequently, we discovered several critical modifications to the original procedure when running this reaction on large scale. First, the physical state of the $Ni(cod)_2$ should be a yellow crystalline solid.[15] Second, the co-solvent dimethylimidizolidinone (DMI) is *extremely* hygroscopic and must be freshly distilled (from CaH_2) prior to use. Use of DMI that had been distilled a week prior, presumably containing trace water, gave 10% of the alkylative coupling product (transfer of an ethyl group from Et_3B) instead

[14] Van Dyke, A. R.; Miller, K. M.; Jamison, T. F. *Org. Synth*. **2007**, *84*, 111–119.
[15] Only commercial material from Strem was consistently reliable during the course of these investigations.

of reductive coupling.[16] Freshly distilled DMI consistently gave less than 2% of the alkylative coupling product. Finally, on smaller scale, after the reaction is quenched with acid the solution can be stirred open to the air to oxidize all nickel species to Ni(II) salts and to facilitate cleavage of the RO–BEt_2 bond, liberating the product. However, on a 50 mmol scale complete oxidation was not achieved, even after stirring for several hours. Having significantly increased the reaction volume on this scale, we realized that aeration cannot be achieved on this scale with simple stirring. This problem was overcome by vigorously bubbling air through the reaction for 30 min. Oxidation was accompanied by a characteristic orange to light yellow color change.[17] With these modifications, the desired allylic alcohol (**5**) can be reproducibly obtained in 89% yield and 87% ee, comparable to the values achieved when performed on smaller scale. While useful in their own right, these allylic alcohols can also be cleaved by ozonolysis to afford β–hydroxy ketones, another class of synthetically important building blocks. Specifically, ozonolysis of **5** proceeded uneventfully in 70% yield to afford **6** with complete preservation of enantiomeric purity. As an example of the utility of the product of this sequence, the TBS ether of **6** was developed by Masamune for use in asymmetric aldol reactions.[18]

Conclusion

In summary, a scalable and reproducible protocol has been developed for the preparation of (–)-neomenthyldiphenylphosphine (**(–)-1**) from inexpensive starting materials. This ligand was then utilized in the nickel-catalyzed reductive coupling of alkyne **3** and aldehyde **4** to afford

[16] The alkylative coupling product was inseparable from the product by chromatography but identified by its carbinol proton: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.35 (d, J = 9 Hz, 1H).

[17] Alternatively, slow addition of a basic hydrogen peroxide solution via syringe (50 mL 30% H_2O_2 in 200 mL 0.75M NaOH) also proved effective for oxidizing the nickel and alkoxyborane species.

[18] (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc*. **1981**, *103*, 1566–1568. (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc*. **1981**, *103*, 1568–1571.

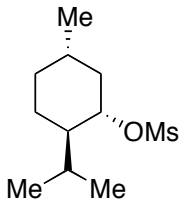
allylic alcohol **5** in high yield and enantiomeric excess. Several important modifications were made to the initially communicated procedure in order to effectively translate this methodology from the millimole to decimole scale. Allylic alcohol **5** was then ozonolyzed to afford β–hydroxy ketone **6** with completely preservation of enantiomeric purity.

Experimental Section

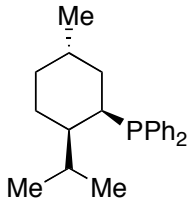
General Information. All reactions were performed under an oxygen-free atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. Tetrahydrofuran was distilled from a blue solution of benzophenone ketyl. Ethyl acetate was distilled from $MgSO_4$. DMI was distilled from CaH_2 and used immediately. Degassed solutions were prepared by sparging with argon for 20 min prior to use. Triphenylphosphine (99%) was purchased from Alfa Aesar and recrystallized from anhydrous EtOH (2.4 mL EtOH/gram PPh_3). Triethylamine, methanesulfonyl chloride, (*1S,2R,5S*)-(+)-Menthol, and lump sodium metal were purchased from Aldrich Chemical Co. and used as received.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$, unless otherwise noted, on a 300 MHz Varian Mercury spectrometer, Bruker Avance 400 MHz spectrometer, or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the

δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts in ^{31}P NMR spectra are reported on the δ scale from an internal standard of phosphoric acid (0.00 ppm). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. Elemental analysis was performed by Midwest Microlab Inc.



Menthyl Mesylate (2). A solution of (+)-menthol (15.59 g, 100 mmol), triethylamine (16.7 mL, 120 mmol) and tetrahydrofuran (50 mL) was cooled to 0 ˚C. Methanesulfonyl chloride (8.5 mL, 110 mmol) was added over 15 min via syringe pump, affording a beige slurry that was stirred 30 min at 0 ˚C and then quenched with ice water (50 mL). The organic layer was washed twice with brine (25 mL), dried over $MgSO_4$, and concentrated on a rotary evaporator affording **2** as a light yellow oil (23.05 g, 99%). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.83–0.99 (m, 11H), 1.25–1.33 (q, J = 11.2, 1H), 1.41–1.55 (m, 2H), 1.70–1.77 (m, 2H), 2.10–2.13 (m, 1H), 2.27–2.31 (m, 1H), 3.03 (s, 3H), 4.54–4.60 (td, J = 10.8, 4.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 16.0, 21.1, 22.2, 23.4, 26.0, 31.9, 34.1, 39.3, 42.5, 47.7, 83.4.



(–)-Neomenthyldiphenylphosphine ((–)–1, **(–)-NMDPP)**. A thoroughly dry flask equipped with a magnetic stirbar, reflux condenser, and argon inlet was charged with triphenylphosphine (26.22 g, 100 mmol) and THF (200 mL). Sodium metal (9.2 g, 400 mmol) was added quickly by temporary removal of the reflux condenser, and the vessel was heated to reflux for 20 hours. The reaction was cooled to ambient temperature, giving a deep red solution of sodium diphenylphosphide (87%). This solution was transferred via cannula to a three-necked flask equipped with a mechanical stirrer and argon inlet. The diphenylphosphide flask was washed with THF (60 mL) and the washings added via cannula to the three-neck flask. A solution of **2** in THF (20 mL) was added via syringe pump over 35 minutes and stirred at room temperature until the diphenylphosphide was consumed (approximately 4 hours by ^{31}P NMR), giving an orange solution. The reaction was quenched with degassed water (100 mL), extracted twice with degassed EtOAc (100 mL), and dried over Na_2SO_4. The dried solution was then transferred via cannula into a weighed, argon purged 1 L flask equipped with a magnetic stir bar (Figure 3). The solvent was removed via rotary evaporation (backfilling with argon) to give cream-colored crystals that were purified by quick attachment of a reflux condenser (following argon backfill) and recrystallizing from degassed refluxing methanol (50 mL), typically 3-4 times, until impurities observed by ^{31}P are removed.[19] In each recrystallization, the methanol solution was

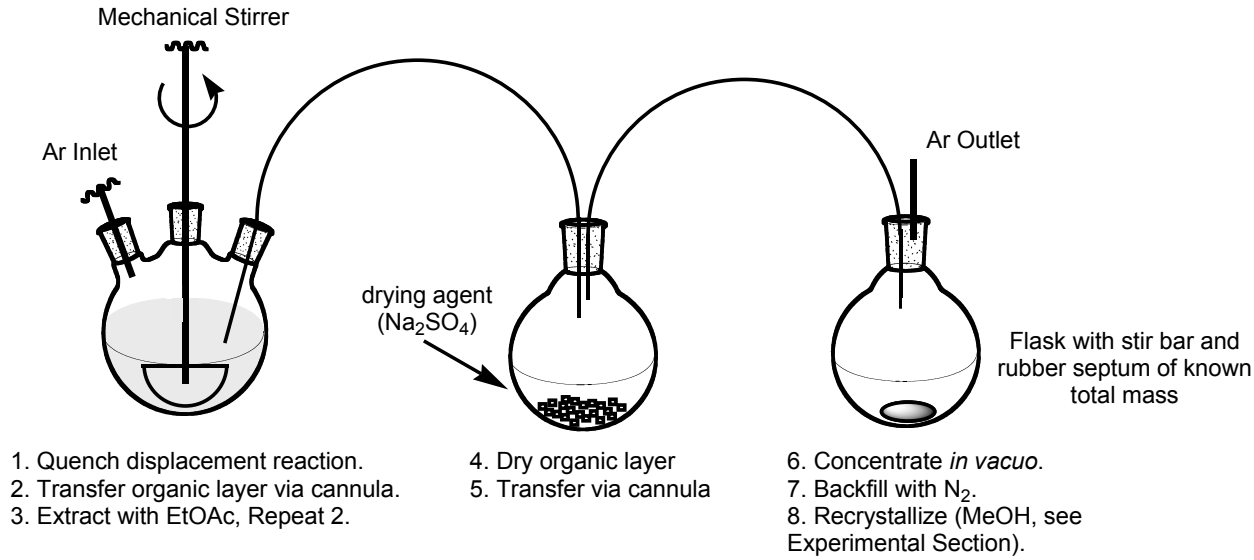
[19] NMDPP oxide is a tenacious impurity; air must be rigorously excluded during workup and recrystallization in order to avoid oxidation of NMDPP. The methanol mother liquors contained small amounts of diphenylphosphine, which has a very strong stench. Major impurities observed: ^{31}P NMR (300MHz, THF) δ: –41 ($HPPh_2$), 23

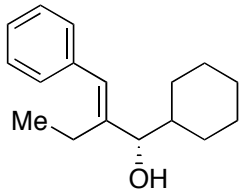
heated with stirring until the solid dissolved. The magnetic stirrer was then shut off, and the flask was removed from the oil bath and allowed to cool on a cork ring. After each recrystallization, the mother liquor was removed via cannula and the crystals washed with 30 mL of cold methanol. Trace methanol was removed under vacuum to yield 9.98 g (36%) of **(–)-1** as long white needles that were spectroscopically identical to literature reports.[20] ^{31}P NMR (300 MHz, $CDCl_3$) δ: –14.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.59 (d, *J* = 6.4, 3H), 0.72 (d, *J* = 6.4, 3H), 0.84 (d, *J* = 6.4, 3H), 0.88–0.93 (m, 1H), 1.21–1.44 (m, 3H), 1.52–1.59 (m, 1H), 1.76–1.81 (m, 4H), 3.12 (m, 1H), 7.29–7.37 (m, 6H), 7.61–7.66 (m, 2H), 7.74–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 22.6, 22.9, 26.5–26.4 (d, *J* = 9.2, 1C), 27.8–27.9 (d, *J* = 5.8, 1C), 30.2–30.3 (d, *J* = 9.3, 1C), 35.8–35.9 (d, *J* = 18.0, 1C), 36.3, 39.5, 50.1–50.2 (d, *J* = 15.4, 1C), 128.5–128.6 (d, *J* = 7.3 Hz, 1C), 128.5–128.6 (d, *J* = 7.0 Hz, 1C), 128.9, 129.1, 134.2–134.4 (d, *J* = 20.8 Hz, 1C), 135.4–135.6 (d, *J* = 22.2 Hz, 1C), 138.2–138.4 (d, *J* = 15.1 Hz, 1C), 139.4–139.5 (d, *J* = 13.1 Hz, 1C); Anal. Calcd for $C_{22}H_{29}P$: C, 81.44; H, 9.01; P, 9.55. Found: C, 81.36; H, 9.07; P, 9.65.

($OPHPh_2$), 33 (NMDPP oxide). *Phosphorus-31 NMR: Principles and Applications*, Gorenstein, D., Ed.; Academic Press Inc: Orlando, 1984; p. 554.

[20] Aguair, A. M.; Morrow, C. J.; Morrison, J. D.; Burnett, R. E.; Masler, W. F. *J. Org. Chem*. **1976**. 41, 1545.

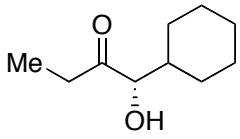
Figure 3: Air-free workup of **(–)-1**.





(*S*)-(*E*)-2-Benzylidiene-1-cyclohexyl-butan-1-ol (5).[6] In a glovebox, a flame-dried 500-mL round-bottomed flask was charged with $Ni(cod)_2$ (1.38 g, 5.00 mmol) and **(–)-1** (3.24 g, 10.0 mmol). The flask was sealed with a septum, removed from the glovebox, and transferred to a fume-hood. An argon inlet was then attached to the flask and degassed EtOAc (50 mL), freshly distilled, degassed DMI (50 mL), and triethylborane (14.5 mL, 100 mmol) were added sequentially via syringe. *Caution! Triethylborane is extremely pyrophoric*. The solution was allowed to stir 15 min at room temperature and then was placed in a –27 °C bath for 30 min. **3** (7.1 mL, 50 mmol) was added in one portion via syringe, followed by addition of **4** (9.1 mL, 75 mmol) via syringe pump over 9 h to the solution in a –27 °C bath. The reaction was stirred at –27

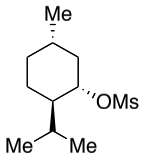
°C for 36 h, then quenched with saturated NH_4Cl (100 mL) and 1M HCl (40 mL) at –27 °C. The solution was allowed to warm to room temperature and then stirred 15 min at room temperature. Air was vigorously bubbled through the reaction using a Pasteur pipet for 30 min, which resulted in a light yellow emulsion. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed twice with saturated NH_4Cl (300 mL), once with brine (300 mL), dried over $MgSO_4$ (10 g), filtered and concentrated on a rotary evaporator (20 °C, 11 mmHg, then 3 mmHg) to remove trace EtOAc. The resulting yellow oil was purified by flash chromatography on silica gel with a hexanes to 9:1 hexanes:ethyl acetate gradient to yield 10.87 g (89%) of **5** as a colorless oil. The product was visualized with UV followed by PMA stain, R_f = 0.20 (5:1, hexanes : EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.99–1.30 (m, 8 H) 1.55–1.82 (m, 6 H), 2.00 (d, J = 12.5 Hz, 1 H), 2.21 (dq, J = 19, 7.5 Hz, 1 H), 2.36 (dq, J = 19, 7.5 Hz, 1 H), 3.93 (d, J =7 Hz, 1 H), 6.45 (s, 1 H), 7.22–7.36 (m, 5 H); ^{13}C NMR (100 MHz, CDCl3) δ: 14.0, 21.4, 26.1, 26.3, 26.5, 28.3, 30.1, 41.6, 81.4, 126.3, 126.4, 128.1, 128.6, 137.6, 145.5; IR (thin film NaCl): 3395, 3055, 3023, 2927, 2851, 1599, 1493, 1448, 1308, 1261, 1173. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.30; H, 9.81. Enantiomeric excess (87%) was established by chiral HPLC (Chiralcel OD, hexanes:2-propanol, 98:2, 1 mL/min): t_R[(*R*)-**1**] = 14.5 min, t_R[(*S*)-**1**] = 16.5 min.



(*S*)-1-Cyclohexyl-1-hydroxy-butan-2-one (6).[6] In a 1-L round-bottomed, one-necked flask with a magnetic stirbar, **1** (10.87 g, 44.5 mmol) was dissolved in methanol (60 mL) and

dichloromethane (240 mL). The vessel was cooled to -78 ° C and ozone was bubbled through the solution using a Pasteur pipet until a persistent blue color appeared (approximately two hours). Argon was then bubbled through the solution for 30 min, and dimethylsulfide (131 mL, 1780 mmol) was added. The reaction was warmed slowly to ambient temperature and stirred for 13 h. The solvent and excess dimethylsulfide were removed by rotary evaporation (20 °C, 11 mmHg). The crude oil was purified by flash chromatography on silica gel, eluting with 50:1 hexanes: ethyl acetate to yield 5.30 g (70%) of **6** as a colorless oil. Product was visualized with PMA stain, R_f = 0.25 (8:2, hexanes:ethyl acetate); 1H NMR (400 MHz, CDCl3) δ: 1.13–1.35 (m, 8 H), 1.48 (dq, J = 12.5, 4 Hz, 1 H), 1.64–1.83 (m, 5 H), 2.41–2.57 (overlapping dq, J = 19, 7.5 Hz, 2 H), 3.41 (d, J = 10 Hz, 1 H), 4.06 (br s, 1H); 13 C NMR (100 MHz, CDCl3) δ: 7.6, 25.1, 25.8, 26.0, 26.5, 30.1, 31.4, 41.4, 80.5, 213.0; IR (thin film NaCl): 3474, 2976, 2931, 2853, 1709, 1450, 1406, 1349, 1260, 1105; Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.35; H, 10.55. Enantiomeric excess 88%, established by chiral GC (Alltech B-PH, column = 95 °C, injector = 200 °C, flow (H_2) = 2 mL/min): t_R[(*R*)-**2**] = 30.7 min, t_R[(*S*)-**2**] = 31.5 min.

Chapter 1: Spectra



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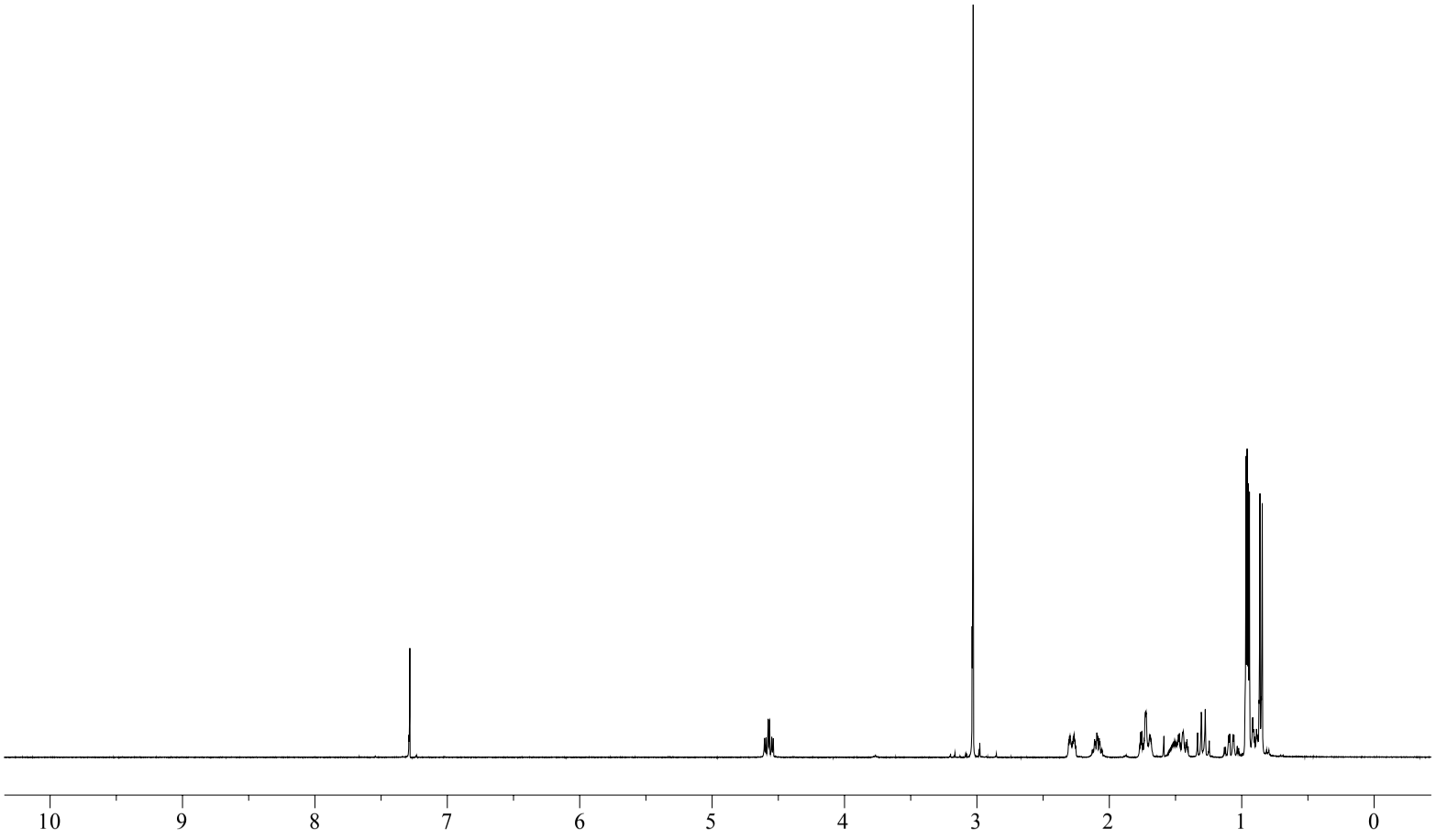

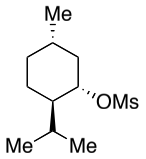

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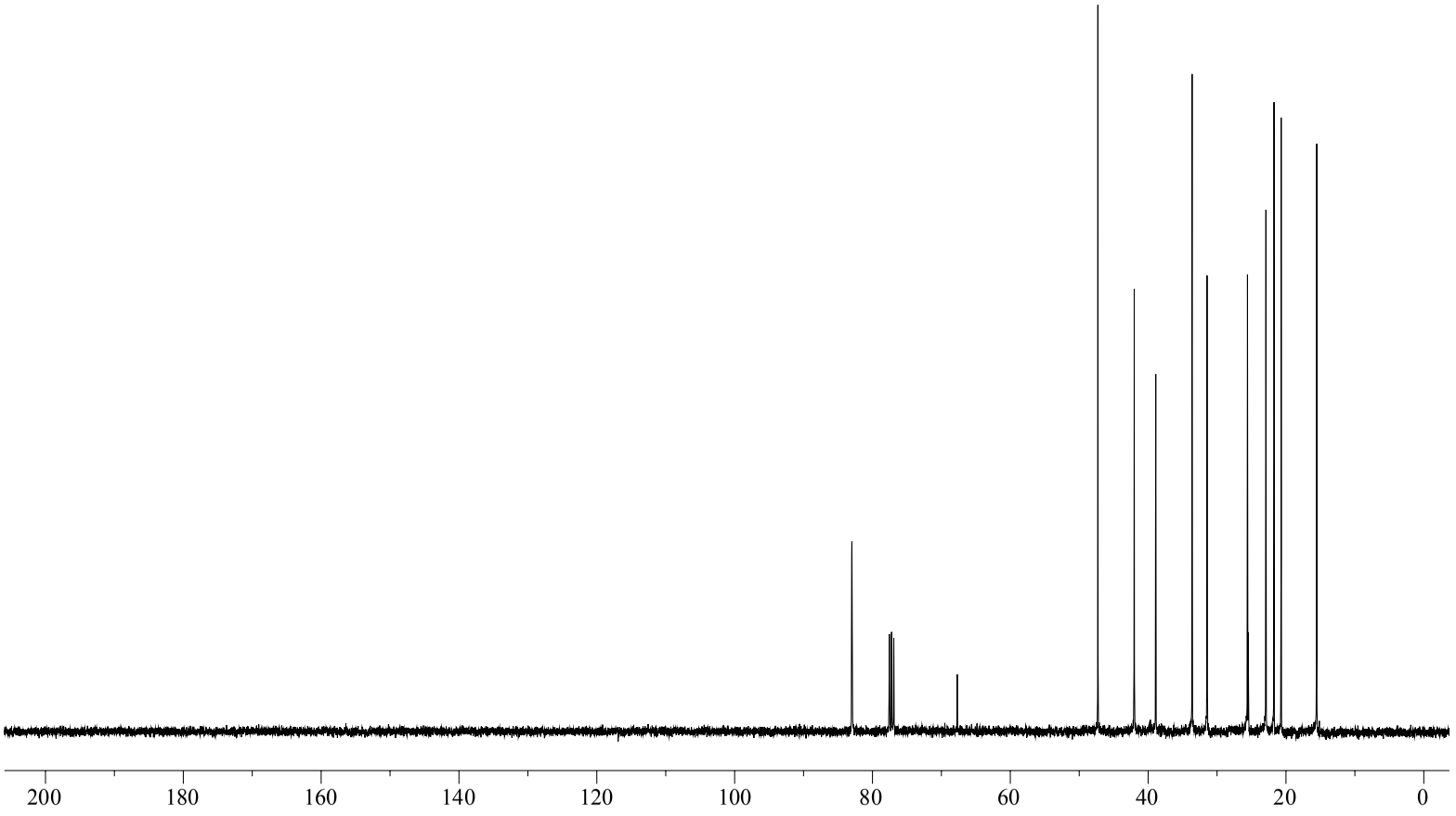
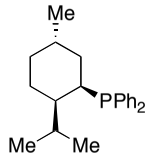
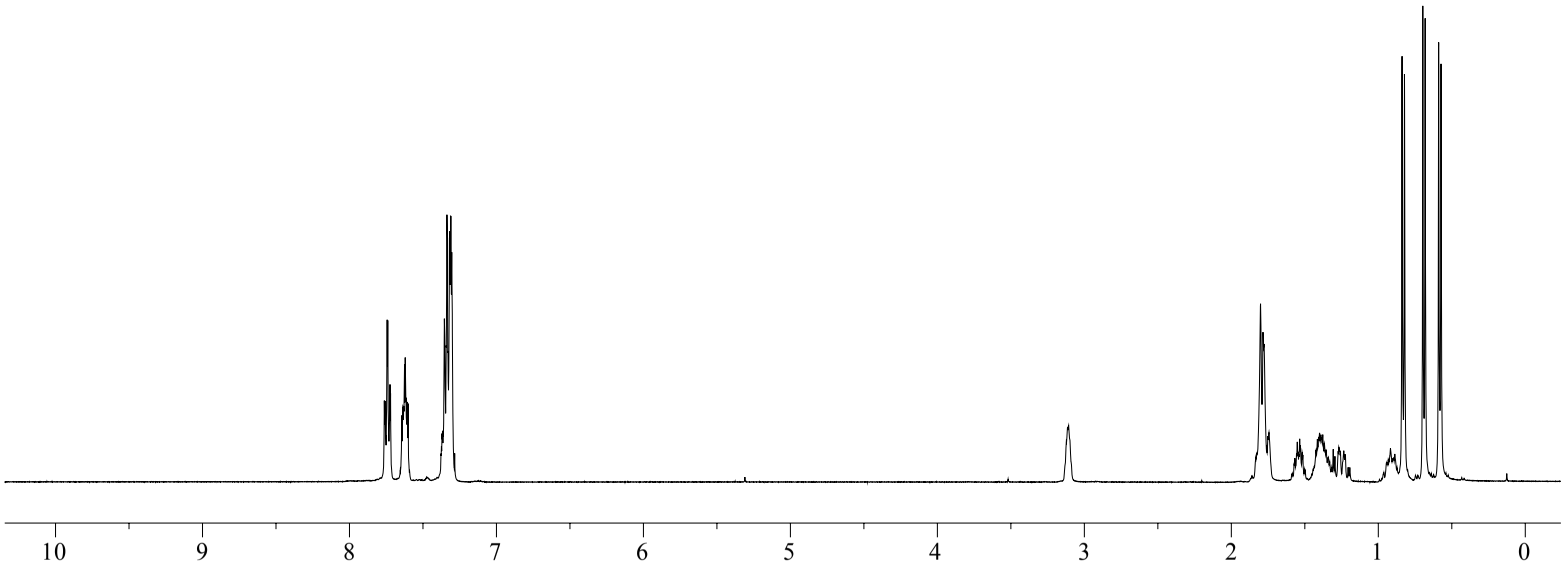
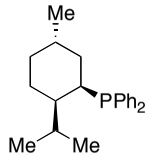




(–)-1





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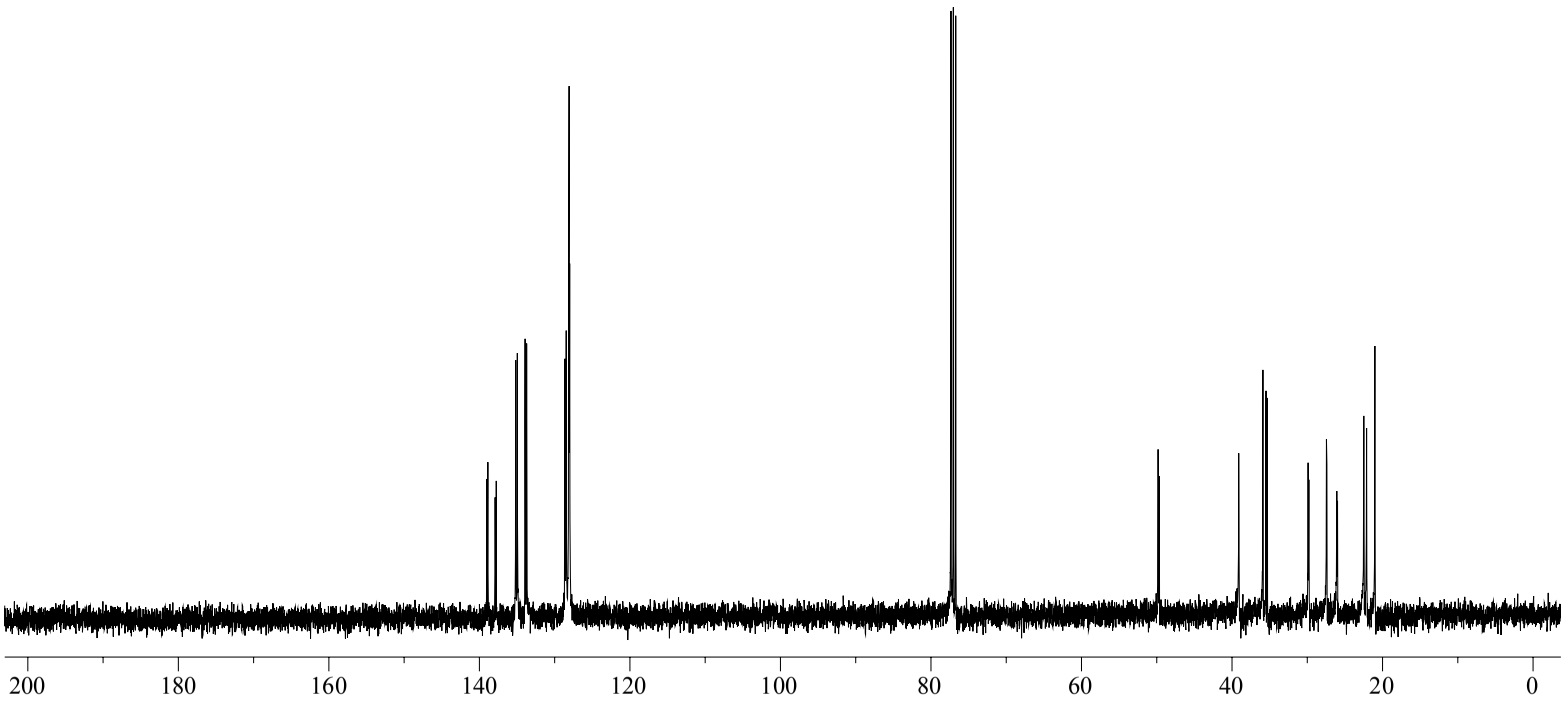
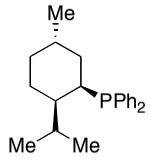


31P-NMR



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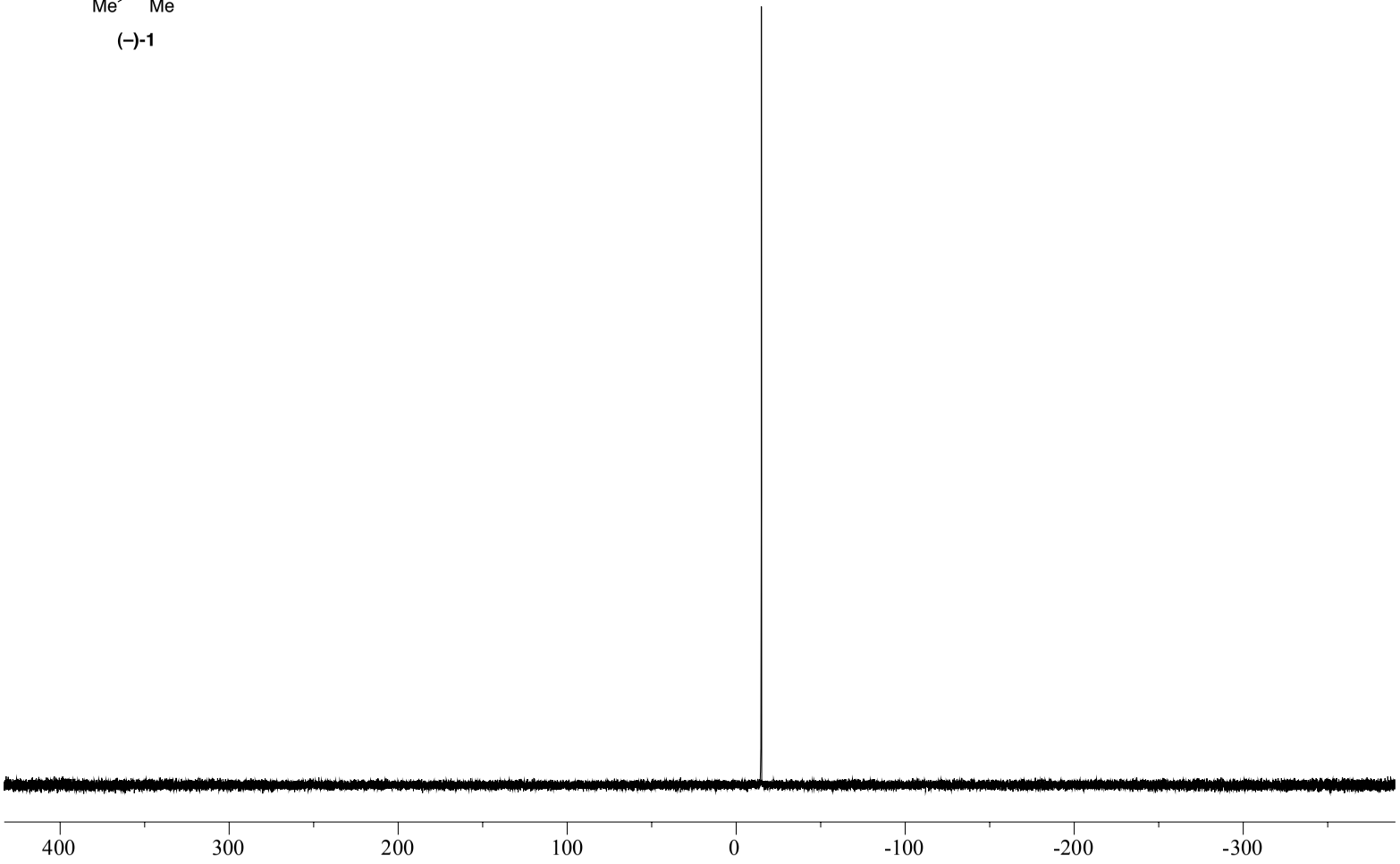

Chapter 2

Synthetically Versatile Templates for Epoxide-Opening Cascades

Introduction

A. Ladder Polyether Natural Products

The ladder polyether family of marine natural products has captivated synthetic organic chemists since the isolation of its first members nearly 30 years ago.[1] Produced by dinoflagellates during the course of harmful algal blooms, colloquially referred to as red tide events, ladder polyethers are potent biological agents with remarkable chemical architectures.[2] When ingested, many polyethers bind to and disrupt the normal function of voltage-gated ion channels in the body; brevetoxin B (**1**)[3] shows selectivity for sodium channels[4] while gambierol (**2**)[5] targets potassium channels (Figure 1).[6] Identification of the biological targets of yet other toxic polyethers, such as gymnocin A (**3**), remains an active area of research.

At first glance, the members of this natural product family appear to be distant cousins, with brevenal (**4**),[7] a potential candidate for the treatment of cystic fibrosis,[8] at one end and maitotoxin (**5**),[9] the largest and most toxic non-biopolymer natural product isolated to date, at the other (Figure 1). Largely responsible for their structural complexity is the array of oxygen

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[1] For reviews detailing synthetic approaches towards ladder-polyethers see: (a) Nicolaou, K. C.; Frederick, M. O.; Aversa, R. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7182–7225. (b) Inoue, M. *Chem. Rev*. **2005**, *105*, 4379–4405. (c) Alvarez, E.; Candenas, M. L.; Perez, R.; Ravelo, J. L.; Delgado Martin, J. *Chem Rev*. **1995**, *95*, 1953–1980.

[2] Kobayashi, J.; Ishibashi, M. Marine Natural Products and Marine Chemical Ecology. In *Comprehensive Natural Product Chemistry*; Baron, D., Nakanishi, K., Eds.; Elsevier: New York, 1999; 476–515.

[3] Isolation and structure determination for brevetoxin B see: Lin, Y.; Risk, M.; Ray, S.; Van Engen, D.; Clardy, J.; Golik, J.; James, J.; Nakanishi, K. *J. Am. Chem. Soc*. **1981**, *103*, 6773–6775. For early studies of the toxicity associated with these natural products see: Yasumoto, T.; Oshima, Y.; Yamaguchi, M. *Bull. Jpn. Soc. Sci. Fish*. **1978**, *44*, 1249–1255.

[4] Catterall, W. A.; Risk, M. *Mol. Pharmacol*. **1981**, *19*, 345–348.

[5] For isolation see: Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc*. **1993**, *115*, 361–362.

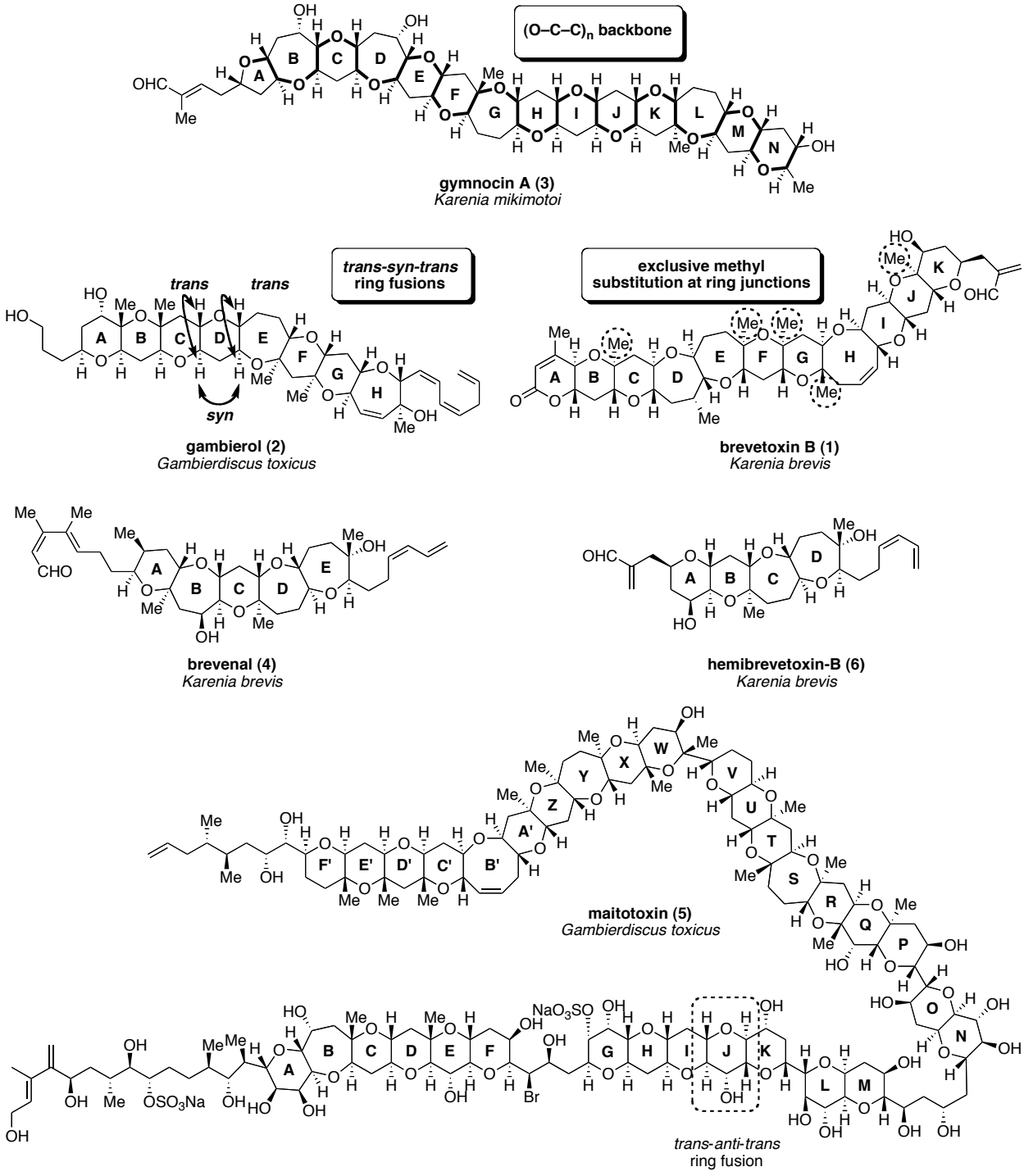
[6] Ghiaroni, V.; Sasaki, M.; Fuwa, H.; Rossini, G. P.; Scalera, G.; Yasumoto, T.; Pietra, P.; Bigiani, A. *Toxicol. Sci*. **2005**, *85*, 657–665.

[7] For isolation and initial structural assignment see: Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M.; Gaden, D. G. *J. Nat. Prod.* **2005**, *68*, 2–6. Total synthesis and revised structure see: Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 16989–16999.

[8] Abraham, W. M.; Bourdelais, A. J.; Sabater, J. R.; Ahmed, A.; Lee, T. A.; Serebriakov, I.; Baden, D. G. *Am. J. Respir. Crit. Care Med*. **2005**, *171*, 26–34.

[9] For isolation from dinoflagallates see: Yokoyama, A.; Murata, M.; Oshima, Y.; Iwashita, T.; Yasumoto, T. *J. Biochem*. **1988**, *104*, 184–187.

Figure 1. Representative structures and unifying elements of the ladder polyether family (producing organism in italics).



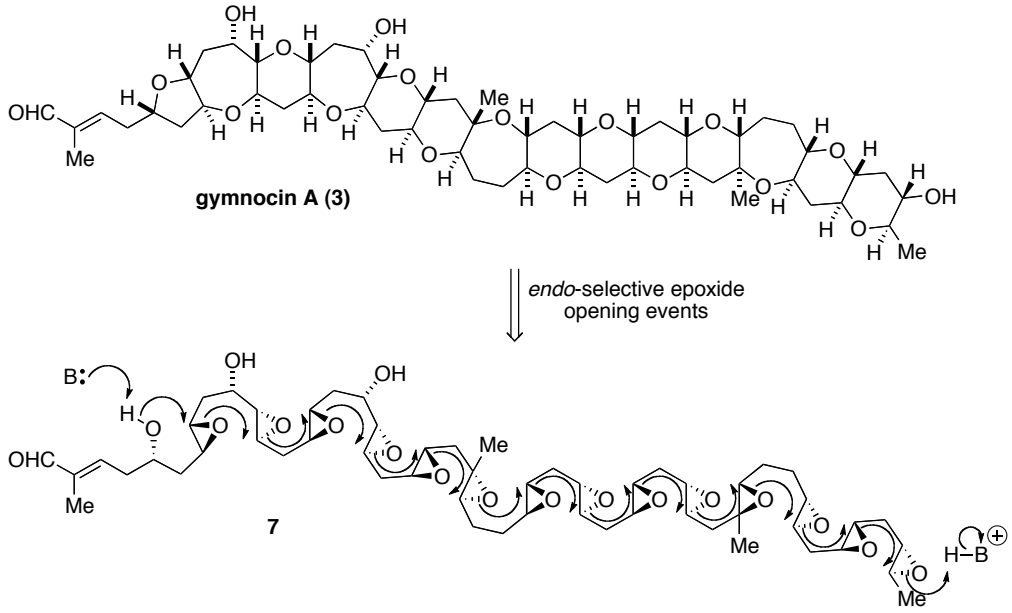
heterocycles found at their core; heterocycles that are not limited to a single ring size or frequency. Ring sizes range from five-membered tetrahydrofurans (THFs) to nine-membered

oxonanes, and one can see differences in the frequency at which various ring sizes appear by comparing hemibrevetoxin-B (**6**), and gymnocin A (**3**), with the first containing two tetrahydropyran (THP) rings and the latter nine THPs. Additionally, the medium to larger sized rings (i.e. oxepanes, oxocanes, and oxonanes) often possess a degree of unsaturation. The ladder array may also be relatively short in length, as in hemibrevetoxin-B (**6**), or truly colossal, as in maitotoxin (**5**). Despite these befuddling structural differences, closer inspection reveals several compelling similarities between the members of this family. First, in every polyether an uninterrupted -(O–C–C)-$_n$ backbone weaves its way from one end of the ladder to the other. This repeating subunit is independent of ring size, substitution, or ladder length (see **3** in Figure 1). Second, the ring fusions possess a *trans-sin-trans* stereochemistry that confers upon these molecules a ladder-type topography (see **2** in Figure 1). Consequently, this characteristic is also the inspiration for the family's name. The only known exception to this observation is a single ring fusion in maitotoxin which bears a *trans-anti-trans* relationship between the *J* and *K* rings (see **5** in Figure 1). Finally, while the ring junction position is most commonly occupied by hydrogen, methyl substitution is also observed at nearly 25% of these positions (see **1** in Figure 1). Interestingly, besides these two privileged substituents, hydrogen and methyl, no other group is ever found at a ring junction.

In order to account for these unifying character traits, specifically the -(O–C–C)-$_n$ backbone and the stereochemistry about the ring junctions, Nakanishi proposed a biosynthesis in which each oxygen heterocycle is formed by ring expansion of an epoxide.[10] In short, an appropriately decorated polyepoxide such as **7** could undergo a series of epoxide-opening events to afford a polyether such as gymnocin A (**3**) (Figure 2). One quickly recognizes that in such a reaction, the alcohol can cyclize to generate two regioisomeric products.

[10] Nakanishi, K. *Toxicon* **1985**, *23*, 473–479.

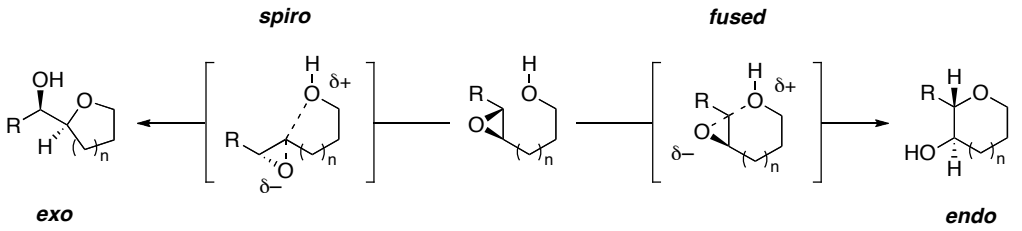
Figure 2. A proposed biosynthesis of gymnocin A (**3**) from a polyepoxide precursor (**7**).



Epoxy alcohol cyclizations that form a larger or a smaller ring are termed *endo* and *exo* cyclization respectively (Figure 3).[11] This epoxide opening terminology, first applied by Baldwin, is ingrained in the literature. However, in both of these cases the epoxide's C–O bond that is broken during the course of the reaction lies outside the newly formed ring. Therefore, by Baldwin's nomenclature, both modes of epoxide opening could be considered *exo* processes. A helpful distinction may be to consider the relationship between the epoxide and the newly forming ring in the transition state. For cyclizations affording the *endo* product the rings have a *fused* relationship while for the *exo* product the rings have a *spiro* relationship (Figure 3). However, because of their familiarity, the terms *endo* and *exo* will be used in the present discussion.

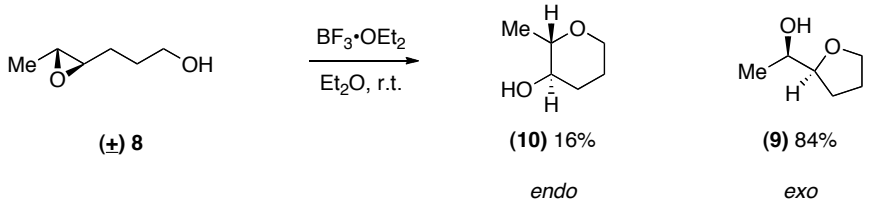
[11] See: Baldwin, J. E. *J. Chem. Soc*., *Chem. Commun.* **1976**, *18*, 734–736.

Figure 3.



Interestingly, in Nakanishi's proposed biosynthesis, all epoxides undergo the *endo*-mode of ring opening. To a first approximation, Coxon and coworkers have modeled this transformation with epoxy alcohol **8**. However, upon treatment with a Lewis acid, **8** cyclized to give predominately the undesired *exo* product (**9**) and only minor quantities of the *endo* product (**10**) (Scheme 1).[12] An outstanding challenge, then, in the chemical literature, is the development of methods that overcome this inherent selectivity and make possible the *endo*-selective cyclization of epoxy alcohols.

Scheme 1.



B. Existing Strategies for *Endo*-Selective Epoxide Opening

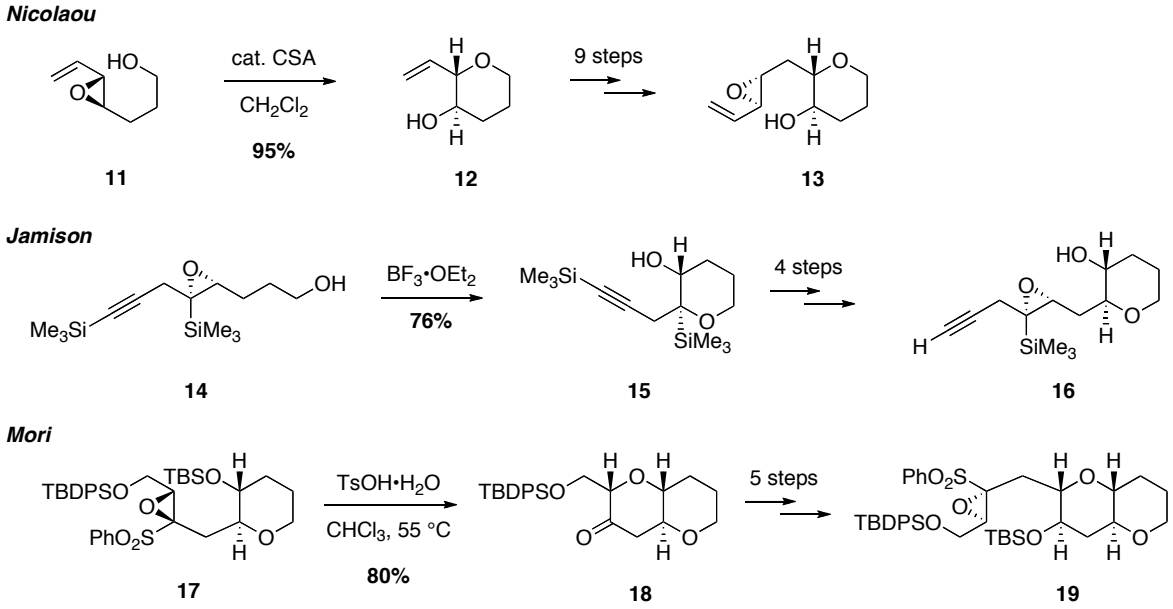
As the tetrahydropyran (THP) occurs more frequently than any other sized ring in the ladder polyethers, it is not surprising that a variety of methods have been developed to favor its formation from epoxy alcohols over the kinetically preferred tetrahydrofuran (THF) product. At

[12] Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem*. **1973**, *26*, 2521–2526.

this work's inception, however, all of the reported methods to achieve *endo*-selectivity relied on either electronically modifying the epoxide or on reagent control.

Under the category of electronically modified epoxides, Nicolaou has used vinyl substitution (**11**) to stabilize carbocation formation at the *endo* position. For example, under acidic conditions, epoxy alcohol **11** undergoes cyclization to afford the THP-containing product (**12**) in excellent yield and with clean inversion of stereochemistry (Scheme 2).[13] In nine steps, **12** could be elaborated into epoxy alcohol **13**, allowing for iterative construction of additional THP rings. Jamison has shown that trimethylsilyl (TMS) is also an effective directing group, with Lewis acid promoters, enabling the transformation of epoxysilane **14** into THP **15** in good yield (Scheme 2).[14] In four operations **14** could be homologated into epoxysilane **16**, which is poised for formation of a second THP ring. In a slightly different vein, instead of attempting to

Scheme 2. *Endo*-selective methods utilizing electronically modified epoxides (prior to 2007).

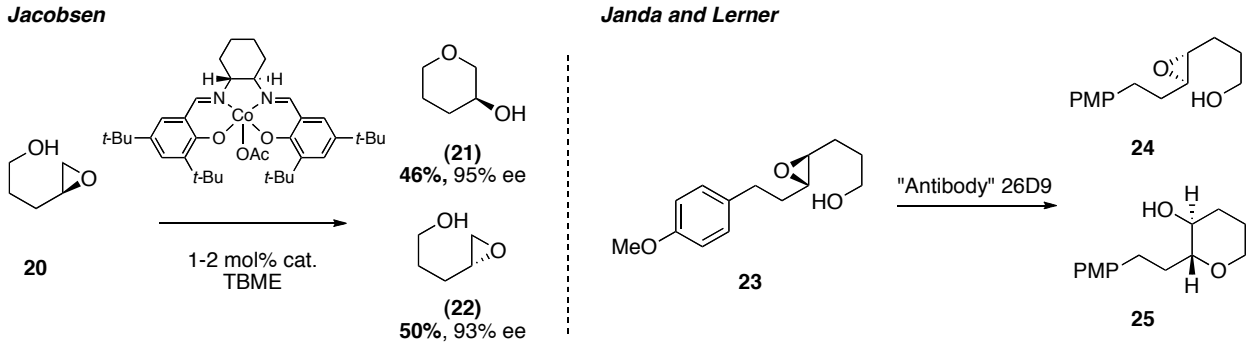


[13] Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc*. **1989**, *111*, 5330–5334.
[14] (a) Heffron, T. P.; Jamison, T. F. *Org. Lett*. **2003**, *5*, 2339–2342. (b) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc*. **2006**, *128*, 1056–1057.

activate the site of *endo* cyclization, Mori has placed an inductively deactivating sulfone at the *exo* position.[15] Thus, upon treatment with acid, epoxysulfone **17** cyclizes and then subsequently rearranges to extrude phenylsulfinic acid, affording ketone **18** (Scheme 2). Also amenable to iterative construction, **18** can be elaborated to epoxysulfone **19** in four steps. All of these methods have been employed for the construction of THP arrays found in polyether natural products.

While substitution on an epoxide can bias the regioselectivity of ring opening, regiochemical control can also be achieved with reagent control in systems that are not electronically biased. For example, Jacobsen has reported that treatment of racemic epoxide **20** with a Co^{III}(salen) catalyst leads to kinetic resolution and formation of THP **21** (Scheme 3).[16] Both the cyclized and uncyclized products are obtained in high enantiomeric excess. In a biologically inspired approach, Janda and Lerner identified antibody 26D9 as effective for the resolution and cyclization of epoxy alcohol **23**.[17] While promising, the potential of these reagent control strategies has yet to be realized in the synthesis of ladder polyethers.

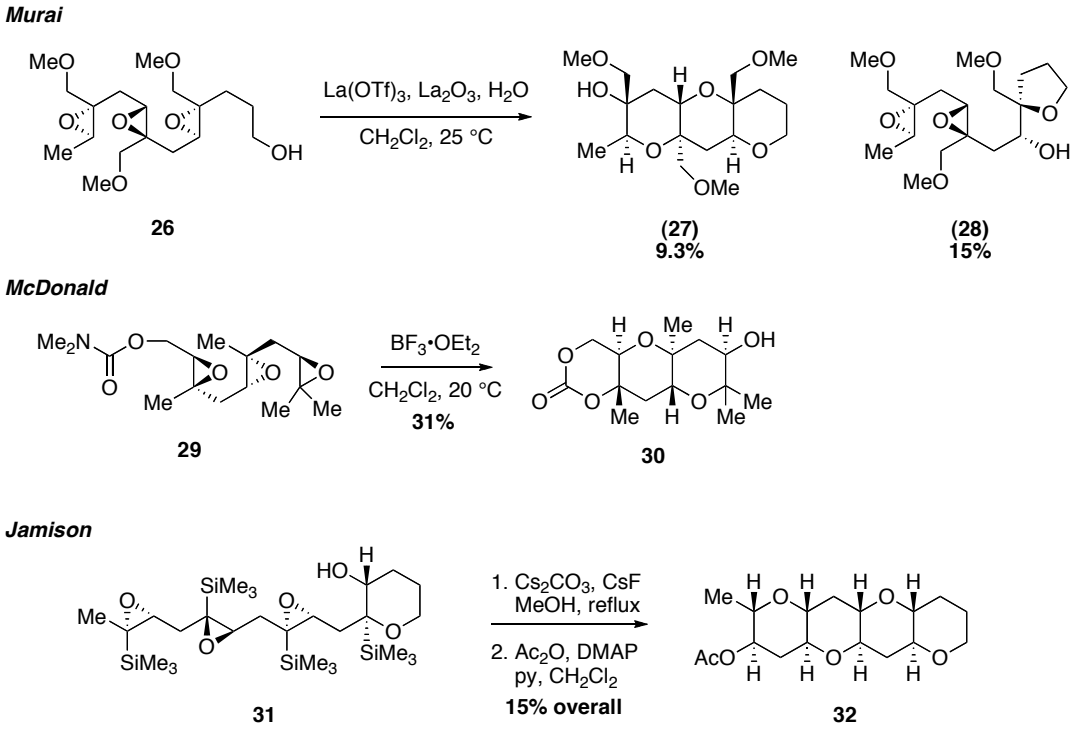
Scheme 3. Reagent control for the *endo*-selective cyclization and resolution of epoxy alcohols.



[15] Furuta, H.; Takase, T.; Hayashi, H.; Noyori, R.; Mori, Y. *Tetrahedron* **2003**, *59*, 9767–9777.
[16] Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **1999**, *38*, 2012–2014.
[17] Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490–493.

All of the aforementioned strategies utilize one epoxide to generate one new ring; in short, the synthesis of polycyclic systems is iterative. Alternatively, one could employ a cascade approach that, in a single operation emulating Nakanishi's hypothesis, transforms multiple epoxides into multiple new rings. Indeed, at the commencement of this work such cascades had been reported in the literature, all relying on electronically modified epoxides in order to achieve *endo*-selectivity. The first such example was reported by Murai and coworkers, who utilized a methoxymethyl substituted triepoxide (**26**) and lanthanum Lewis acids in order to construct three new THP rings in a single step to afford **27** (Scheme 4).[18] While the transformation was low yielding, it was a landmark achievement in the nascent field of epoxide-opening cascades.

Scheme 4. Cascade methodologies for the construction of THP subunits (prior to 2007).



[18] Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, *3*, 335–338.

Alternatively, McDonald has demonstrated that methyl is also an effective directing group, guiding attack of the nucleophile under acidic conditions to the more electrophilic tertiary carbon of each epoxide in **29** (Scheme 4).[19] The final epoxide is opened intramolecularly by the pendant carbamate which, after hydrolysis, affords cyclic carbonate **30**.

While the cascades developed by Murai and McDonald are successful in constructing the THP scaffold, the products are decorated in a manner that precludes or severely limits their application to the synthesis of ladder polyethers. No known ladder polyether contains methoxymethyl substitution at ring junctions, and while methyl is the only non-hydrogen substituent, it does not occur with the ubiquity necessary to retain *endo*-regioselectivity in Lewis acid-promoted cascades. As one solution to this problem, Jamison reported that cascades could be achieved utilizing "disappearing" trimethylsilyl directing groups (**31**) (Scheme 4).[20] After performing its function as a directing group, the trimethylsilyl is protiodesylated under the reaction conditions affording the all hydrogen-substituted THP tetrad (**32**), a signature subunit of the ladder polyethers. Because of the protiodesylation step, at present only hydrogen can be installed at the ring junction position, and from the perspective of atom economy, a significant loss of mass occurs in this transformation. Furthermore, while **32** represents a characteristic subunit of the ladder polyethers, it is not poised for further elaboration, limiting its utility in total synthesis. It was clear, then, that a strategy for the rapid and efficient construction of THP scaffolds, directly amenable to the total synthesis of ladder polyethers, would be of considerable value.

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[19] Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Do, B.; Hardcastle, K. I. *Org Lett*. **2003**, *5*, 2123–2126. This cascade strategy has also been successfully applied to the formation of polyoxepane systems. In such cases, a methyl directing group need only be present on the first and last epoxides of the polyepoxide precursor. For a review see: McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem*. **2007**, *79*, 281–291.

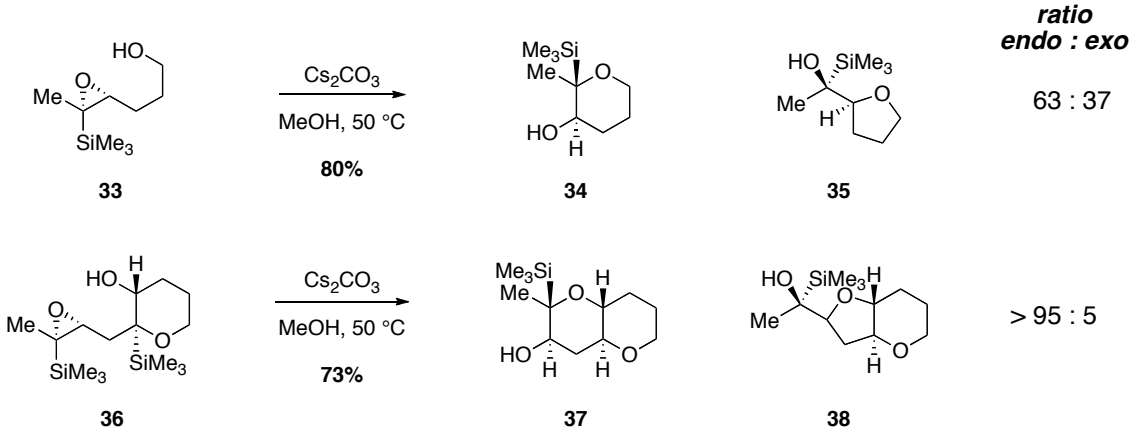
[20] Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc*. **2006**, *128*, 1056–1057.

Results and Discussion

A. Effect of Relative Stereochemistry on Epoxy Alcohol Cyclizations

In the course of studying epoxysilane directing groups, an interesting difference was noticed between epoxy alcohols **33** and **36**, with the latter showing improved selectivity for formation of the THP product (Scheme 5).[21] In the first case (**33**), the nucleophile is a primary alcohol, whereas in the other case (**36**) it is a secondary alcohol and attached to a stereogenic center on a ring. We were curious, then, to understand how the relative stereochemical relationship between the alcohol nucleophile and the epoxide electrophile would affect *endo* selectivity. In order to deconvolute this effect from that of silyl substitution on the epoxide

Scheme 5.

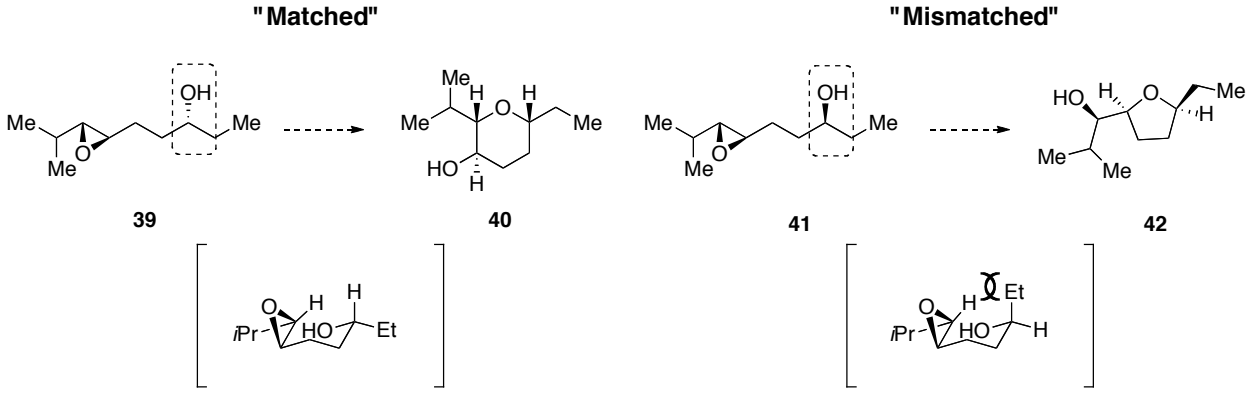


(which was previously explored in our laboratory),[21] we targeted *trans*-disubstituted epoxy alcohols **39** and **41** (Scheme 6). These diastereomeric epoxy alcohols differ in their stereochemistry at C7, and we hypothesized that, if the cyclization occurred through a chair-like transition state, then one might observe a measurably different matched and mismatched

[21] Heffron, T. P. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2005.

reactivity for the two substrates. For the matched case (**39**) all substituents would be expected to reside in pseudo-equatorial positions in the presumed chair-like transition state leading to *endo* cyclization (**40**) (Figure 4). Alternatively, the diastereomer (**41)** could represent a mismatched case where the ethyl substituent at C7 resides in the pseudo-axial position, disfavoring the chair-like transition state. Therefore, it may prefer to cyclize by way of a different conformer, leading to *exo* cyclization (**42**).

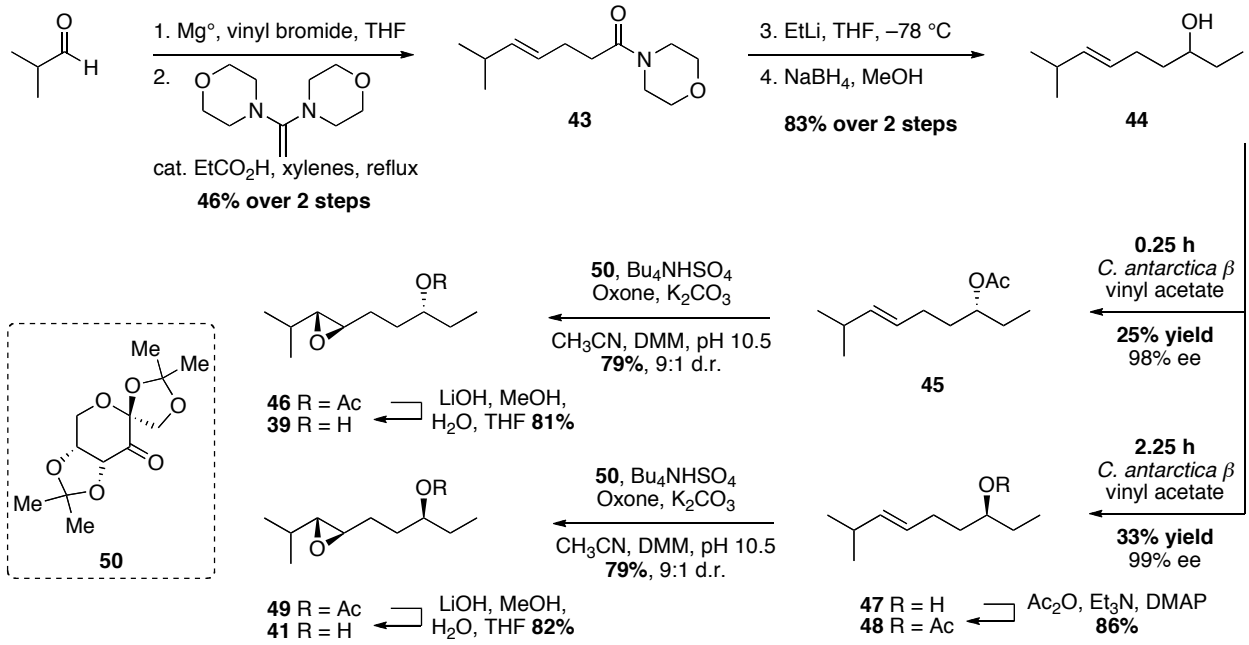
Figure 4. Possible reactive conformations of "matched" and "mismatched" substrates.



We envisioned a divergent synthesis in which both **39** and **41** could be accessed from common intermediate **44** through a lipase resolution (Scheme 6). This alcohol (**44**) was prepared in four steps beginning with addition of vinyl Grignard to isobutyraldehyde, followed by conversion to morpholine amide **43** using a modification of the Eschenmoser-Claisen rearrangement reported by Trauner.[22] Addition of ethyllithium afforded the ethyl ketone, which was then reduced to racemic alcohol **44**. By carefully controlling the reaction time, a lipase resolution of alcohol **44** with *Candida antarctica β* provided acetate **45** and alcohol **47** in high enantiomeric excess. Alcohol **47** was then converted to the acetate to prevent premature

[22] Gradl, S.; Kennedy-Smith, J. J.; Kim, J.; Trauner, D. *Synlett* **2002**, *3*, 411–414.

Scheme 6.

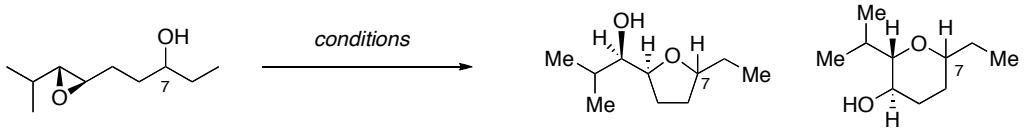


cyclization during the subsequent epoxidation. Asymmetric epoxidation, under the conditions reported by Shi,[23] proceeded in good yield and diastereomeric ratio and was followed by removal of the acetate.

With both the expected matched (**39**) and expected mismatched (**41**) epoxy alcohol substrates in hand, we investigated their cyclization in a variety of solvents (polar protic, polar aprotic, and nonpolar) and with a variety of promoters (Brønsted bases, Lewis and protic acids) but in all cases we observed exclusive formation of the undesired THF ring with no evidence of *endo* cyclization to form the larger THP ring (Table 1). Consequently we cannot definitely say if a matched and mismatched relationship exists for the two substrates. The fact that we do not observe even trace formation of the THP ring, as was observed in Coxon's system, may be a function of branching α to the epoxide.

[23] (a) Tu, Y.; Wang, Z-X.; Shi, Y. *J. Am. Chem. Soc*. **1996**, *118*, 9806–9807. (b) Wang, Z-X.; Tu, Y., Frohn, M.; Shi, Y. *J. Org. Chem*. **1997**, *62*, 2328–2329.

Table 1. Cyclization of "matched" (**39**) and "mismatched" (**41**) epoxy alcohols.



C7 (*R*): **39** "*matched*"
C7 (*S*): **41** "*mismatched*"

C7 (*R*): **51**
C7 (*S*): **42**

C7 (*R*): **40**
C7 (*S*): **52**

Entry	Solvent	Promoter (equiv)	T (°C)	Time	**51 : 40**	**42 : 52**
1	MeOH	Cs_2CO_3 (20) CsF (20)	60	12 h	> 95:5	> 95:5
2	MeOH	NaOH (7)	60	12 h	> 95:5	> 95:5
3	MeOH	K_2CO_3 (7)	60	12 h	> 95:5	> 95:5
4	THF	NaOH (7)	23	3 d	> 95:5[a]	> 95:5[a]
5	THF	K_2CO_3 (7)	23	3 d	> 95:5[a]	> 95:5[a]
6	H_2O	NaOH (7)	60	12 h	> 95:5	> 95:5
7	H_2O	K_2CO_3 (7)	60	12 h	> 95:5	> 95:5
8	DMSO	KCH_2SOCH_3 (2.5)	23	2 min	> 95:5	> 95:5
9	CF_3CH_2OH	NaOH (7)	60	12 h	> 95:5	> 95:5
10	CF_3CH_2OH	K_2CO_3 (7)	60	12 h	> 95:5	> 95:5
11	CH_2Cl_2	BF_3•OEt_2 (1)	0	1 h	> 95:5	> 95:5
12	CH_2Cl_2	CSA (0.5)	23	1 h	> 95:5	> 95:5

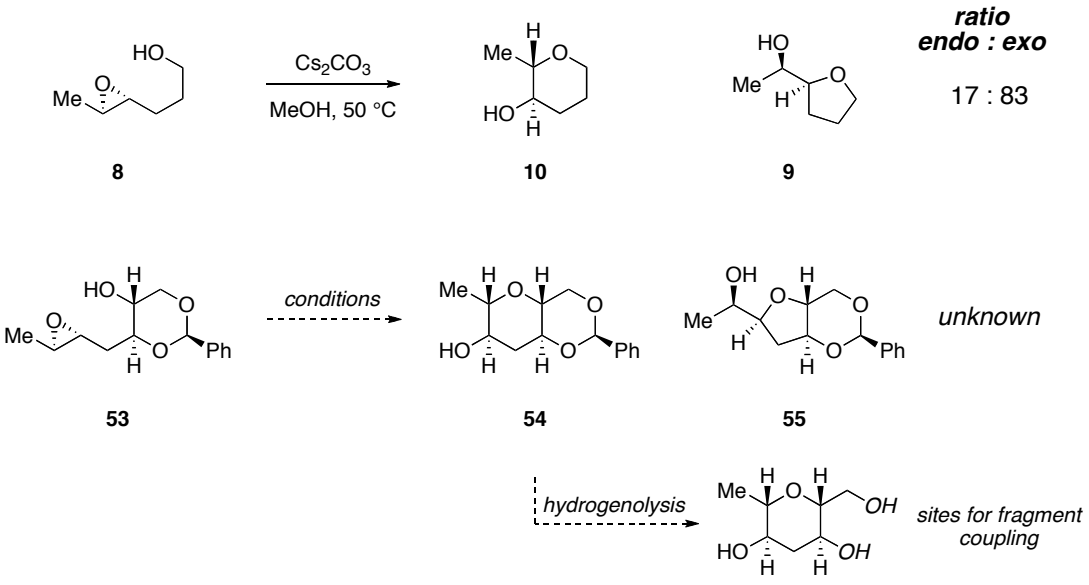
(a) Less than 15% conversion

Therefore, in this acyclic system the stereochemistry of the nucleophile does not appear to measurably affect the regioselectivity of the epoxide opening. Returning then to our analysis of the enhanced *endo* regioselectivity of the epoxide opening in **36** over **33**, we recognized that while the nucleophile is at a stereogenic center (as opposed to the acyclic case) in **36** it is also attached to an organized molecular scaffold, namely a THP ring. Consequently, we undertook an investigation to see if other 6-membered cyclic scaffolds could impart *endo*-selectivity with electronically unbiased epoxides.

B. Epoxy Alcohol Cyclizations Directed by 1,3-Dioxane Templates

The vast majority of acyclic epoxy alcohols in the form of **8** cyclize to give an undesired THF in a variety of promoter and solvent combinations.[21] Having observed improved selectivity for epoxysilanes in which the cyclizing nucleophile was attached to a preexisting THP ring, herein termed a *template*, we desired to know if *endo*-selective cyclizations of electronically unbiased *trans*-disubstituted epoxides could be achieved using a 1,3-dioxane template (Figure 5). In contrast to THP templates, 1,3-dioxane templates can be cleaved after cyclization, unveiling two new sites for subsequent functionalization. The potential for such elaboration is an indispensible criterion for any method to be effectively employed in the service of total synthesis.

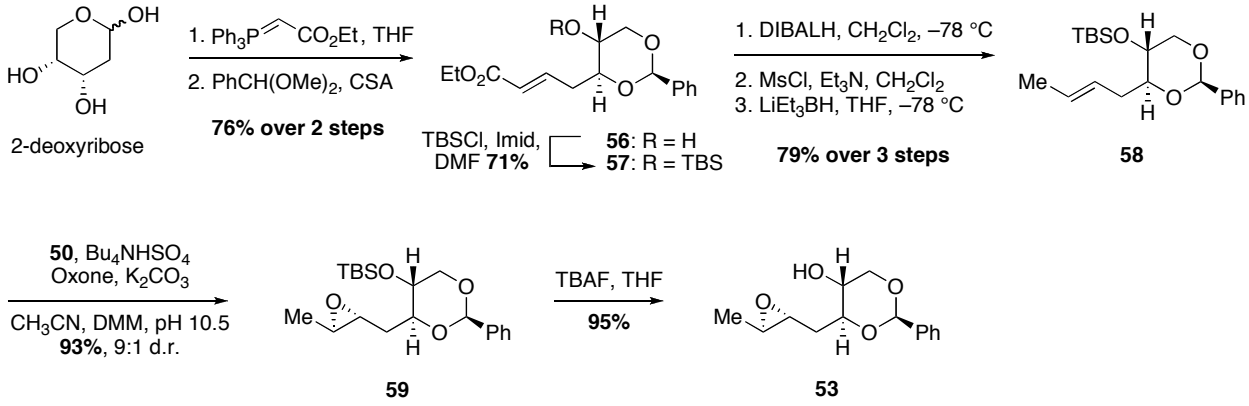
Figure 5.



Having never examined 1,3-dioxanes as templates for epoxide openings, we began with the synthesis and evaluation of benzylidene acetal **53** in this context. We recognized that two of

the stereocenter at the C5 and C6 positions of the template could be derived from inexpensive and commercially available 2-deoxyribose. This carbohydrate was subjected to a Wittig olefination followed by diastereoselective 1,3-protection of the resulting triol under thermodynamic conditions to set the final stereocenter on the template, giving 1,3-dioxane **56** in good yield and >15:1 dr.[24] Next, the alcohol was protected as a silyl ether under standard conditions to give a more than a hectogram of **57**, a synthetically versatile intermediate (vide infra). In order to arrive at the desired model system, we then needed to transform the ethyl ester moiety into a methyl group. This was accomplished by a three-step protocol beginning with reduction of the ester to the allylic alcohol, formation of the allylic mesylate and displacement with lithium triethylborohydride (SuperHydride®). No chromatography was required over these three steps, affording the desired olefin (**58**) in good yield. Shi epoxidation proceeded in excellent yield and diastereoselectivity, and finally, removal of the silyl group afforded epoxy alcohol **53** in eight steps and 38% overall yield from 2-deoxyribose.

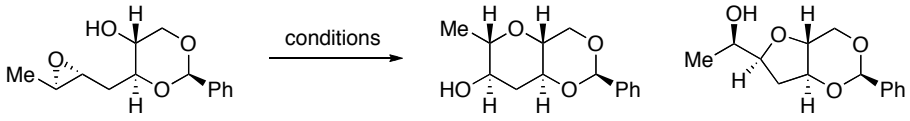
Scheme 7.



[24] For examples of Wittig olefinations on 2-deoxyribose see: (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, C.; Hwang, C. K. *Tetrahedron* **1990**, *46*, 4517–4552. (b) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019–3033. (c) Inoue, M.; Wang, J.; Wang, G-X.; Ogasawara, Y.; Hirama, M. *Tetrahedron* **2003**, *59*, 5645–5659.

With epoxy alcohol **53** in hand, we were eager to examine the regioselectivity of its cyclization relative to those of acyclic epoxy alcohol **8**. Previous work demonstrated that **8** produced a 17:83 mixture of *endo*:*exo* products in Cs_2CO_3 and MeOH. Gratifyingly, the benzylidene acetal template of **53** completely reversed this selectivity, affording an 84:16 mixture of *endo*:*exo* products, with THP **54** isolated in 60% yield (Table 2, entry 1). This result was the first example, to our knowledge, of an *endo*-selective cyclization of a templated alcohol onto an electronically unbiased epoxide. X-ray crystallographic analysis confirmed that the cyclization to form **54** occurred at the desired site of the epoxide and proceeded with clean inversion of stereochemistry (Figure 6). Other basic promoters, such as sodium hydroxide at ambient temperature, gave comparable selectivity and even higher yields (Table 2, entry 2). The use of stronger base at lower temperature was found to be preferable to Cs_2CO_3 in MeOH at 50

Table 2.



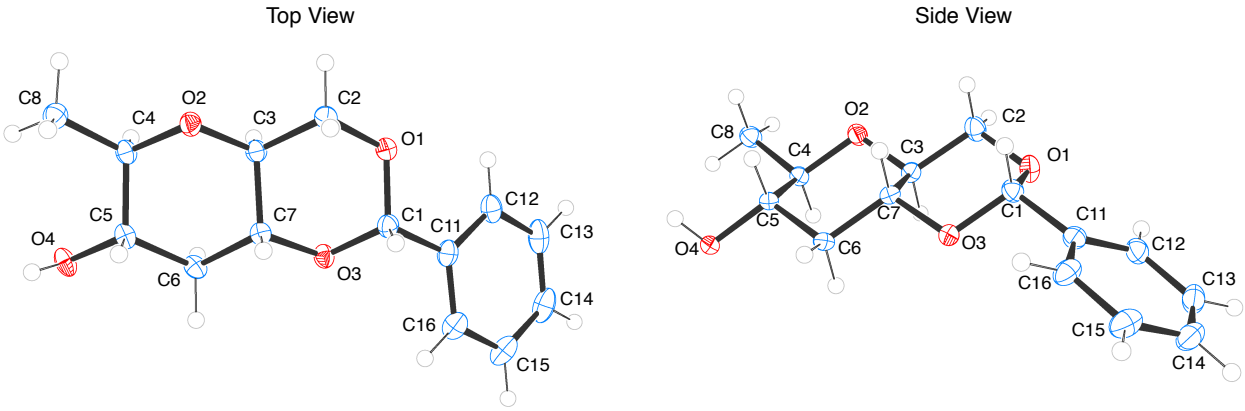
53 **54** **55**

entry	solvent	promoter (equiv)	*T* (°C)	*t*	**54** : **55**[a]	yield **54**
1	MeOH	Cs_2CO_3 (5)	50	12 h	84 : 16	60%
2	MeOH	Nach (5)	23	12 h	82 : 18	71%
3	MeOH	imidazole (5)	23	12 h	--[b]	--
4	MeOH	none	23	9 d	--[b]	--
5	C_6H_6	CSA (0.5)	23	1 h	65 : 35[c]	51%
6	CH_2Cl_2	none	40	2 d	--[b]	--
7	CH_2Cl_2	SiO_2 (35)[d]	40	2 d	> 90 : 10	72%
8	H_2O	none	23	13 d	--[b]	--
9	H_2O	none	60	3 d	--[c]	--

(a) Determined by ^{1}H NMR. (b) <5% cyclization of **53**. (c) 1,3-dioxane cleaved. (d) mg silica promoter/mg **53**.

°C, as elevated temperatures appear to encourage opening of the epoxide by solvent. Organic amine bases gave no appreciable cyclization, and methanol alone behaved similarly (Table 2, entries 3-4). Low selectivity was observed with protic acids such as CSA (Table 2, entry 5). Reflecting the highly strained nature of the 6,5-fused ring system present in *exo* product **55**, acetal cleavage also occurred under these acidic conditions, presumably due to trace water. Somewhat unexpectedly, the most selective of all the promoters examined was silica gel (Table 2, entry 7). Although one previous report in the literature employed silica gel to promote the cyclization of epoxysilanes,[25] to our knowledge it had never been used as a promoter for electronically unmodified epoxides. Consequently, we were interested in studying further the utility of silica-promoted epoxide-opening cyclizations (vide infra).

Figure 6. X-Ray crystal structure for **54** (thermal ellipsoids displayed at 50% probability).

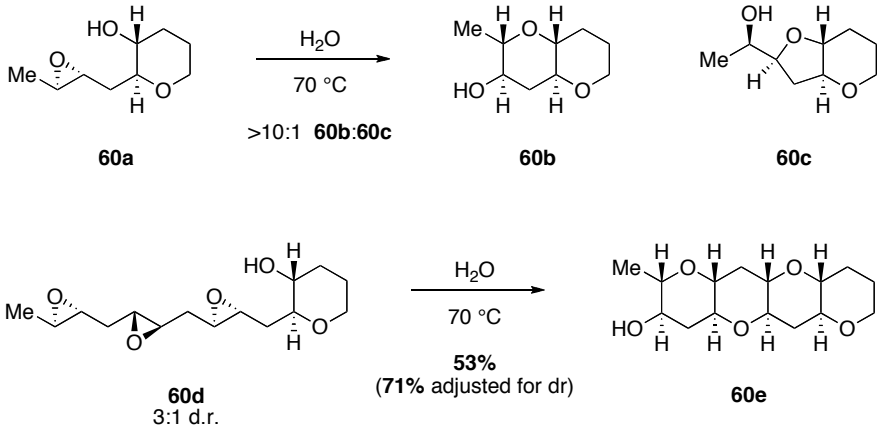


Shortly after these studies, our lab discovered that a closely related epoxy alcohol (**60a**), containing a THP template instead of a benzylidene acetal, exhibited even higher *endo*-selectivity (>10:1 *endo*:*exo*) when cyclized in water or aqueous buffers near neutral pH (Figure

[25] Adiwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Tetrahedron Lett*. **1995**, *36*, 8771–8774.

7).[26] Additionally, this could be extended to polyepoxide substrates that undergo a cascade of ring openings in water as in the reaction of triepoxide **60d** to afford THP tetrad **60e**.

Figure 7. *Endo*-selective cyclization and cascade of THP templates in water.



Interestingly, very different results were obtained when applying these aqueous conditions to the 1,3-dioxane template. Epoxy alcohol **53** was unreactive in water at ambient temperature; even after 13 days negligible cyclization was observed and only starting material was recovered (Table 1, entry 8). Heating the reaction to 60 °C lead to cleavage of the benzylidene acetal, resulting in a triol and a complex mixture of cyclization products (Table 1, entry 9). These results clearly demonstrate that changing the template from a THP to a benzylidene acetal is a significant perturbation. Indeed, it appears that the optimal solvent/promoter combination is intimately connected to the identity of the template. There are important differences between the THP and 1,3-dioxane that may account for the latter's tempered reactivity in aqueous media. A benzylidene acetal is conformationally more rigid than a THP template. It may be that the increased reactivity of THP templates in water is because the

[26] Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189–1192.

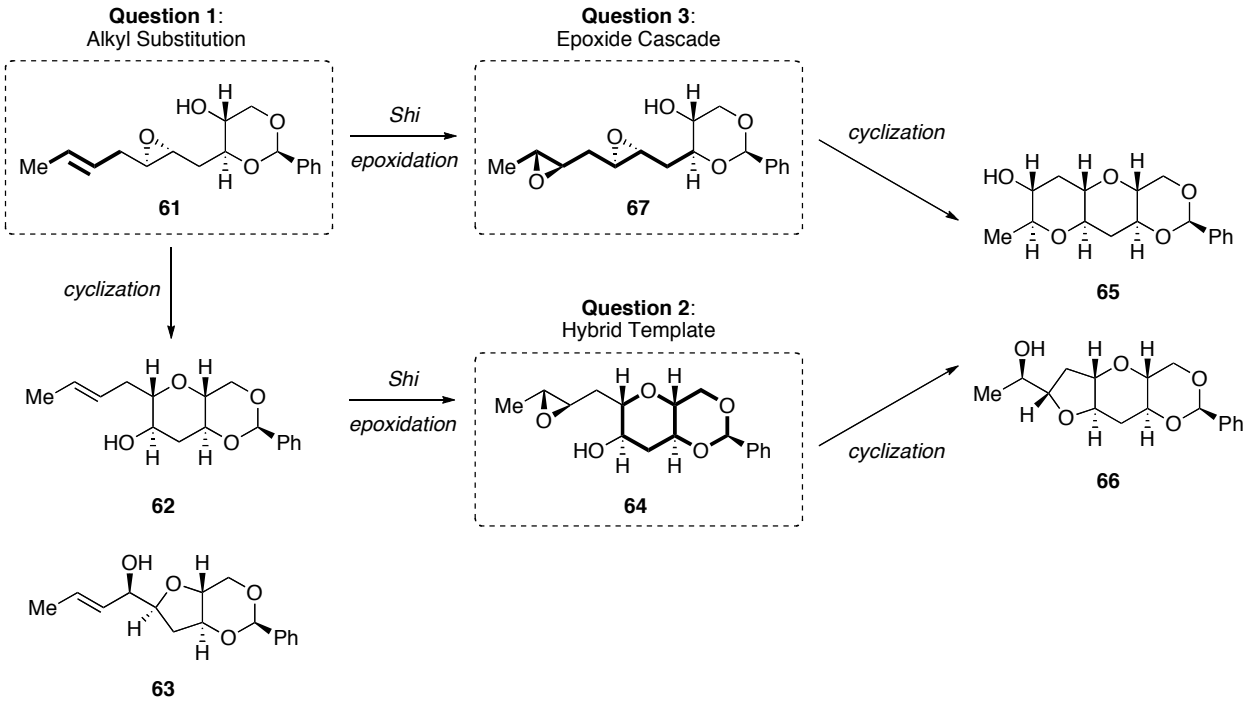
system can achieve a reactive conformer not accessible to the benzylidene acetal. Additionally, the 1,3-dioxane template contains an additional ring oxygen that may inductively lower the nucleophilicity of the alcohol resulting in a slower rate of cyclization.[27]

While studies with **53** were illuminating, three new questions arose which could not be answered by this system (Figure 8). These questions were as follows: (1) Would a larger alkyl substituent on the epoxide affect selectivity? System **53** possessed a methyl substituent, but could equally high *endo*-selectivity be achieved with a larger alkyl chain? Maintaining good regioselectivity with larger substituents is critical for epoxide-opening cascades, as in **60d**, where the first epoxide undergoing cyclization contains a long alkyl chain bearing one or more subsequent epoxides. (2) What would the selectivity be for a "hybrid" template containing a THP fused to a 1,3-dioxane? This question is again relevant for epoxide-opening cascades, in which an intermediate containing such a hybrid template should be formed after cyclization onto the first epoxide. (3) Can a 1,3-dioxane template an *endo*-selective cascade of two electronically unactivated *trans*-disubstituted epoxides to form two new THP rings?

To address these questions, three new model systems were required (Figure 8). By comparison with **53**, cyclization studies of **61** would address the effect of alkyl substitution on the first epoxide. The *endo*-cyclization product of this reaction (**62**) could be epoxidized to yield epoxy alcohol **64**, which could then be used to study the behavior of hybrid (i.e., THP/1,3-dioxane) templates. Finally, if olefin **61** were epoxidized prior to cyclization, diepoxide **67** could be generated, allowing one to investigate an epoxide opening cascade initiated by a 1,3-dioxane-templated alcohol.

[27] It has been observed that removing the oxygen in the THP template (i.e. using a cyclohexane-templated epoxy alcohol) results in a cyclization that is an order of magnitude faster than the THP template in pH = 7 buffer. Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, Article ASAP, DOI: 10.1021/ja9004909.

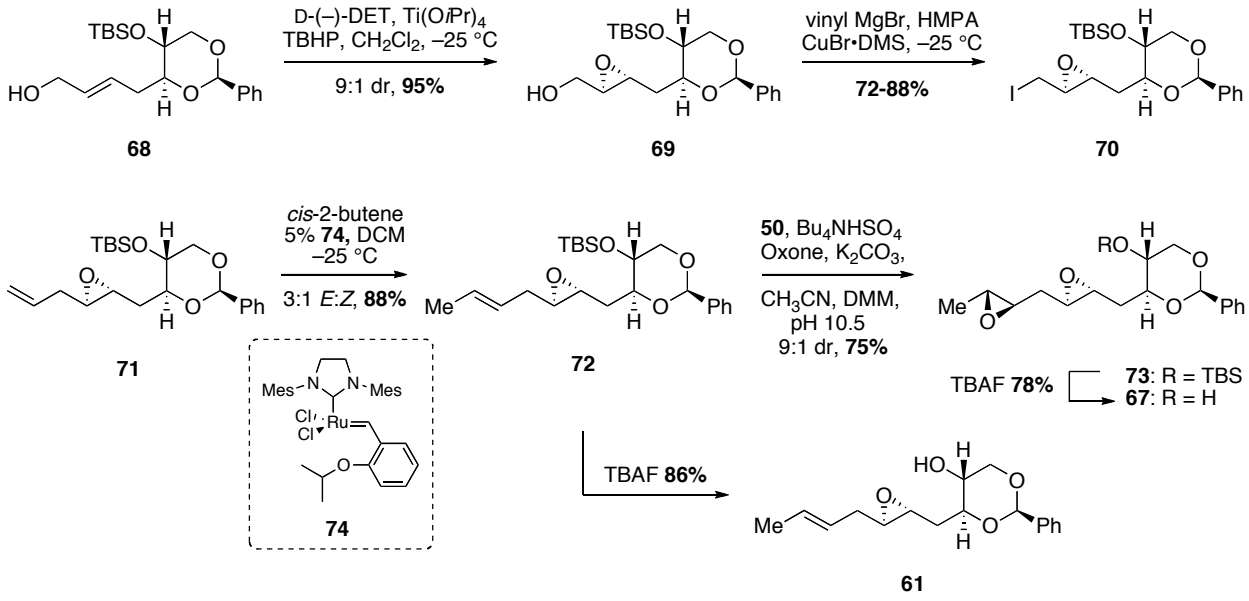
Figure 8.



Conveniently, all of these model systems could be accessed from common intermediate **61** which itself was prepared from allylic alcohol **68**, an intermediate from the synthesis of the previous model system (Scheme 8). Sharpless asymmetric epoxidation of **68** and conversion of the alcohol to the iodide set the stage for a copper-mediated displacement with vinyl Grignard.[28] The resulting terminal olefin was then subjected to cross-metathesis with *cis*-2-butene and the Hoveyda-Grubbs catalyst (**74**). The low 3:1 *E*:*Z* selectivity was improved to 10:1 after column chromatography with $AgNO_3$-impregnated silica. Removal of the silyl group proceeded uneventfully to afford epoxy alcohol **61**.

[28] Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett*. **1984**, *25*, 2069–2072.

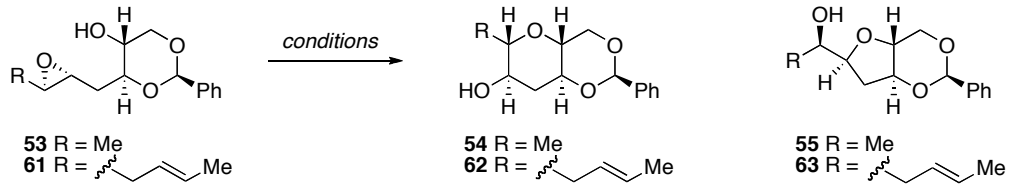
Scheme 8.



To address the question of epoxide substitution, we compared cyclizations of **61** to the original system bearing a methyl substituent (**53**) under representative acidic, basic, and aqueous conditions. With Cs_2CO_3 in MeOH, and when R = Me (**53**), good selectivity for the *endo* product was observed, but this eroded as the size of R increased to *trans*-crotyl (**61**) (Table 3, entry 1).[29] Conversely, under acidic conditions (CSA in CH_2Cl_2) selectivity was not significantly affected upon changing R from Me to *trans*-crotyl (Table 3, entry 2). It was clear from the low regioselectivity of epoxide opening that neither of these promoters would be effective for compounds like **61**, with 1,3-dioxane templates bearing long alkyl chains. Gratifyingly, silica gel still gave high *endo*-selectivity with epoxy alcohol **61**, albeit in low conversion (Table 3, entry 3). Not surprisingly, epoxy alcohol **61** was equally unreactive as **53** in deionized water at ambient temperature (Table 3, entry 4).

[29] Selectivity erodes further with additional methyl substitution at the endo position (i.e. *distal*-trisubstituted epoxide, see footnote 41.)

Table 3.



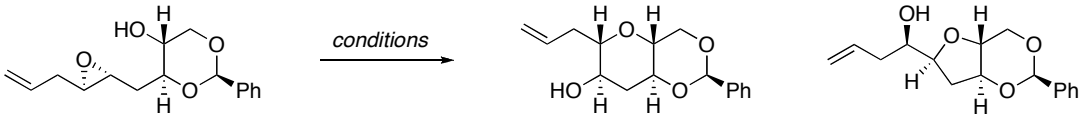
entry	solvent	promoter (equiv)	T (°C)	*t*	**54** : **55**	**62** : **63**
1	MeOH	Cs_2CO_3 (5)	50	12 h	84 :16	64 : 36
2	CH_2Cl_2	CSA (0.5)	23	12 h	65 : 35	62 : 38
3	CH_2Cl_2	SiO_2 (35)[a]	40	2 d	> 90 : 10	> 90 : 10[b]
4	H_2O	none	23	12 d	--[c]	--[c]

(a) mg silica promoter/mg epoxy alcohol. (b) 55% conversion. (c) Less than 5% cyclization.

While silica gel gave the highest *endo*-selectivity, the conversion needed to be improved in order to render the cyclization synthetically useful. We began by optimizing the reaction parameters with epoxy alcohol **75**. We found that increased promoter loadings led to increased conversion (Table 4, entries 1, 2, 5). After 2 days at 40 °C, only 16% conversion was observed with 5 mg SiO_2/mg **75**, while full conversion was observed with 90 mg SiO_2/mg **75**. Interestingly, maximum conversion was achieved after a reaction time of 2 days, shorter reaction times gave even lower conversion while longer reaction times gave negligible increases in conversion (Table 4, entries 2 and 3). Recalling that our studies of 1,3-dioxane templates in water showed these epoxy alcohols to be unreactive, we recognized that silica is hygroscopic and wondered if trace water was somehow impeding the conversion. However, this did not appear to be the case, as rigorous drying of the promoter did not affect selectivity or conversion (Table 4, entries 2 and 4). We also discovered that silicic acid, the monomeric building block of polymeric silica gel, promoted the reaction (Table 4, entry 6). Possibly due to the mildly acidic nature of silica gel as a promoter, only the major diastereomer of **75** cyclized at 40 °C, allowing for facile

removal of the unwanted stereoisomer which was previously inseparable by chromatography. Conveniently, microwave heating reduced the reaction time from days to minutes with no

Table 4.



75
9:1 d.r.

76

77

entry	solvent	promoter (mg/mg **75**)	T (°C)	t	conversion[a]	**76** : **77**	mass recovery
1	CH_2Cl_2	5 SiO_2	40	2 d	16%	> 90 : 10	96%
2	CH_2Cl_2	35 SiO_2	40	2 d	56%	> 90 : 10	97%
3	CH_2Cl_2	35 SiO_2	40	4 d	58%	> 90 : 10	96%
4	CH_2Cl_2	35 SiO_2[b]	40	2 d	58%	> 90 : 10	96%
5	CH_2Cl_2	90 SiO_2[b]	40	2 d	> 95%	> 90 : 10	93%
6	CH_2Cl_2	35 SiO_3H_2[b]	40	2 d	89%	> 90 : 10	99%
7	CH_2Cl_2[c]	35 SiO_3H_2[b]	125	15 min	90%	> 90 : 10	99%
8	CH_2Cl_2	none	40	2 d	< 5%	--	95%
9	CH_3CN	35 SiO_3H_2[b]	125	15 min	49%	87 : 13	98%
10	THF	35 SiO_3H_2[b]	125	15 min	31%	88 : 12	98%
11	EtOAc	35 SiO_3H_2[b]	125	15 min	< 5%	--	96%

(a) Based on major diastereomer. (b) Promoter dried at 140 °C for 12 h prior to use. (c) Identical results were obtained using 1,2-dichloroethane in place of dichloromethane.

appreciable drop in yield or selectivity (Table 4, entry 7). A control experiment, conducted in the absence of promoter, demonstrated that the cyclization does not proceed to an appreciable extent in dichloromethane (Table 4, entry 8). Therefore, we believe that, indeed, the silanol surface of the silicon dioxide is the promoting species.

In order to explore silica promoters in greater detail, we examined the effect of solvent on the cyclization and found that nonpolar solvents such as dichloromethane and 1,2-dichloroethane gave higher conversion than polar solvents such as acetonitrile, tetrahydrofuran, or ethyl acetate

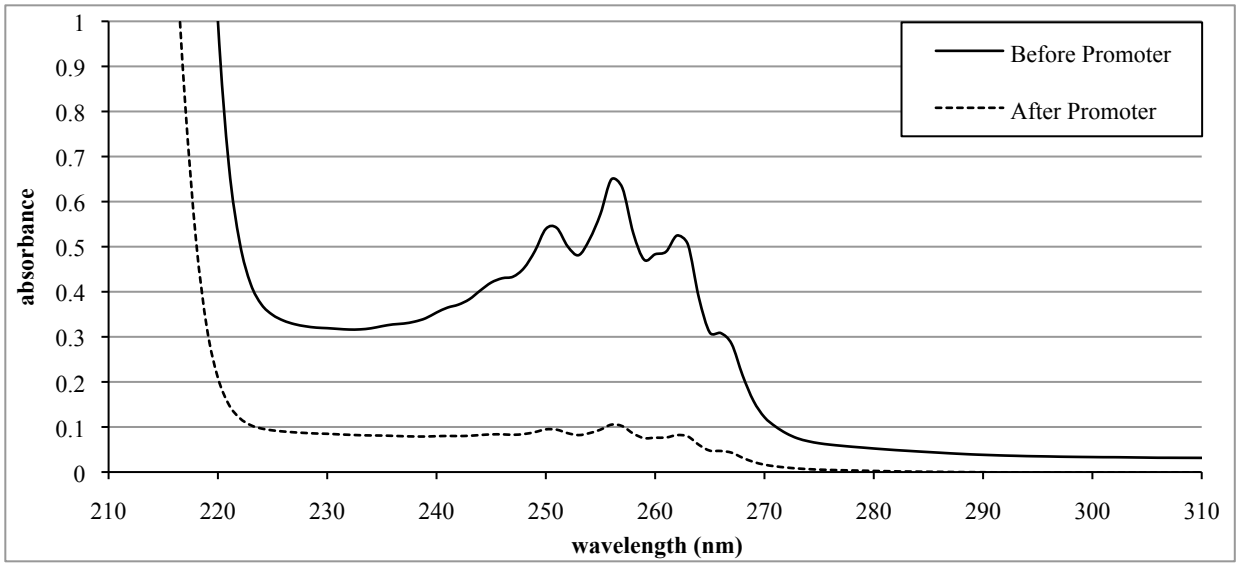
(Table 4, entries 9-11). In order for the cyclization to be promoted by silanol(s), it is plausible that the epoxy alcohol must adhere to the surface of the silica. Consequently, Lewis basic solvents such as THF and EtOAc may effectively outcompete the substrate for binding to the silanol, resulting in lower conversion. As EtOAc contains two Lewis basic sites, it is perhaps not surprising that it exhibits the lowest conversion. This hypothesis is supported by UV vis measurements of the concentration of **75** in solution both before and after the addition of promoter. In dichloromethane, the concentration of **75** in solution drops from 20 mM to 2 mM after the addition of SiO_3H_2, suggesting that the substrate has adsorbed onto the silica (Graph 1, a). High conversion is observed in this case. However, the solution concentration of **75** in solvents such as acetonitrile and tetrahydrofuran stays constant at 20 mM both before and after the addition of SiO_3H_2, suggesting that the substrate does not interact with the promoter as strongly, resulting in low conversion (Graph 1, b).

The fact that higher promoter loadings are required for complete conversion may be a consequence of the number of silanols on the silica with the proper geometry to promote the cyclization, perhaps like an enzyme active site. The lower promoter loadings (by mass) of silicic acid needed to promote the reaction, relative to silica gel, may reflect a different number of promoting silanols that are available to bind the substrate. Additionally, the plateau in conversion may be due to product binding to silica, in analogy to product inhibition as seen with some enzymes. There is an interesting possibility that our observation of solvent effects could be exploited to address this issue of product inhibition. We have observed that Lewis basic solvents such as EtOAc and Et_2O are effective at ejecting the product from the silica and into solution. Perhaps addition of a Lewis basic co-solvent or additive to reactions in dichloromethane could aid conversion by displacing the product and allowing another molecule of starting material to

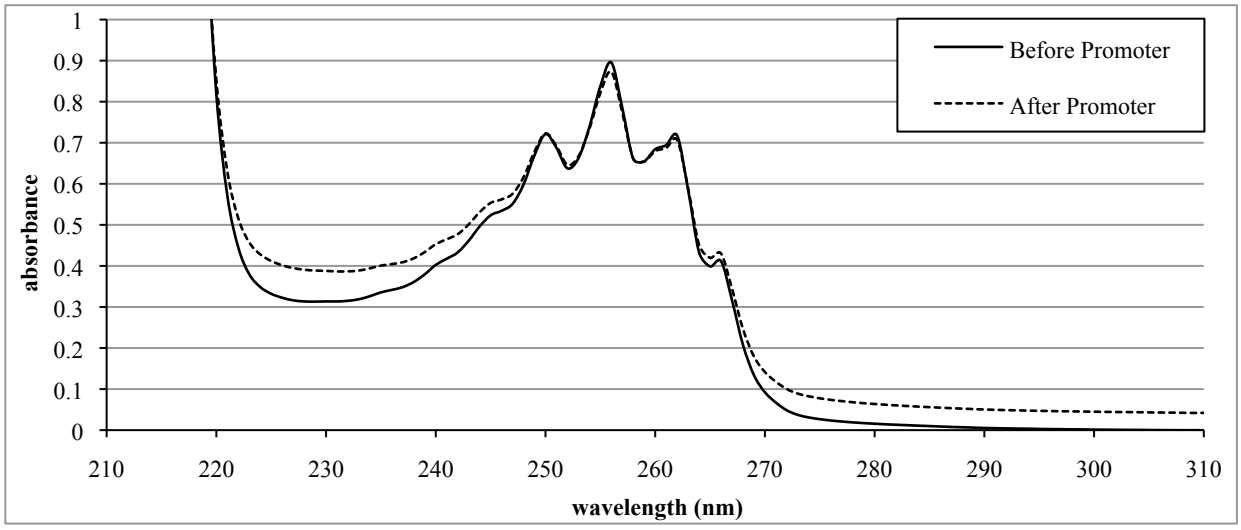
bind. One caveat, though, is that the epoxy alcohol must be bound to silica long enough to cyclize before being displaced by the Lewis-basic additive.

Graph 1. UV vis absorbance of **75** in (a) dichloromethane and (b) CH_3CN before and after addition of SiO_3H_2 promoter, λ_{max} = 254nm.

(a)

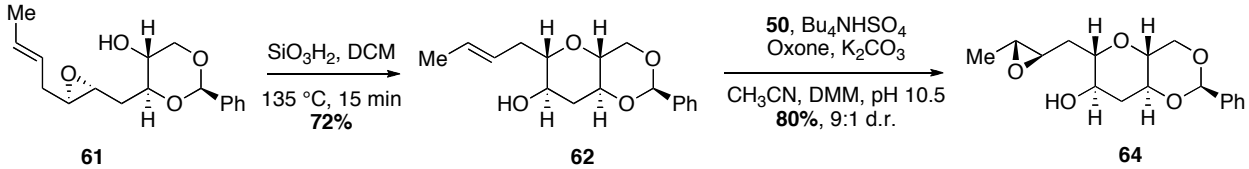


(b)



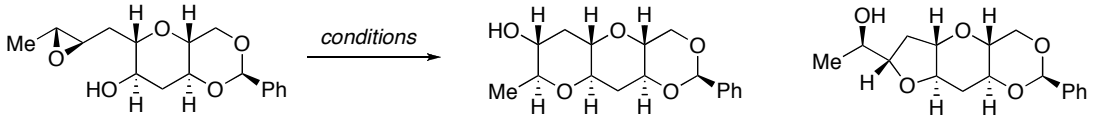
Having identified optimal conditions for cyclization of the benzylidene acetal template onto a single epoxide, we then investigated a hybrid template in which a THP ring is fused to a benzylidene acetal. Such a substrate is easily accessed by first cyclizing epoxy alcohol **61** with silicic acid, which proceeded in good yield to afford the fused template **62** (Scheme 9). Olefin **62** was then epoxidized according to the protocol of Shi to give epoxy alcohol **64**.

Scheme 9.



We had previously observed that the benzylidene acetal template (**61**) in a mixture of Cs_2CO_3 and MeOH exhibited low *endo*-selectivity (64:36). Interestingly, cyclization of the hybrid template (**64**) under identical conditions revealed a changeover in selectivity, with the *exo* product now predominating (Table 5, entry 1). This selectivity is of the same sense (i.e. *exo* predominates) as the cyclization of THP template **60a**, which gave a 27:73 mixture of *endo*:*exo* products in Cs_2CO_3 and MeOH. This is not perhaps surprising, as the nucleophile is directly attached to the THP ring of the bicycle and may be expected to behave more like a THP templated alcohol. Lower selectivity was also observed with CSA in dichloromethane, which gave a nearly equal mixture of *endo* and *exo* products (Table 5, entry 2). Silica gel showed a slight erosion in selectivity but still provided a synthetically useful 82:18 ratio of **65**:**66** (Table 5, entry 3). Perhaps the most convincing evidence that **64** behaves more like a THP than a 1,3-dioxane system is that **64** cyclizes in water at 60 °C with good *endo*-selectivity (Table 5, entry 4). The fact that extensive hydrolysis of the acetal does not occur for **64** may be due to the

Table 5.



64 **65** **66**

entry	solvent	promoter	T (°C)	t	conversion dioxane **61**	**62** : **63**	conversion hybrid **64**	**65** : **66**
1	MeOH	Cs_2CO_3	50	12 h	100%	64 : 36	100%	37 : 63
2	CH_2Cl_2	CSA	23	12 h	100%	62 : 38	100%	56 : 44
3	CH_2Cl_2	SiO_3H_2	40	48 h	95%	> 90 : 10	100%	82 : 18
4	H_2O	none	60	72 h	--	--[a]	100%	83 : 17
5	H_2O	pH = 2.0[b]	23	72 h	--	--[a]	--	--[a]
6	H_2O	pH = 4.0[b]	23	72 h	< 5%	--	44%	78 : 22
7	H_2O	pH = 6.0[b]	23	72 h	< 5%	--	27%	79 : 21
8	H_2O	pH = 7.0[b]	23	72 h	< 5%	--	23%	83 : 17
9	H_2O	pH = 8.0[b]	23	72 h	< 5%	--	22%	84 : 16
10	H_2O	pH = 10.0[b]	23	72 h	< 5%	--	32%	64 : 36

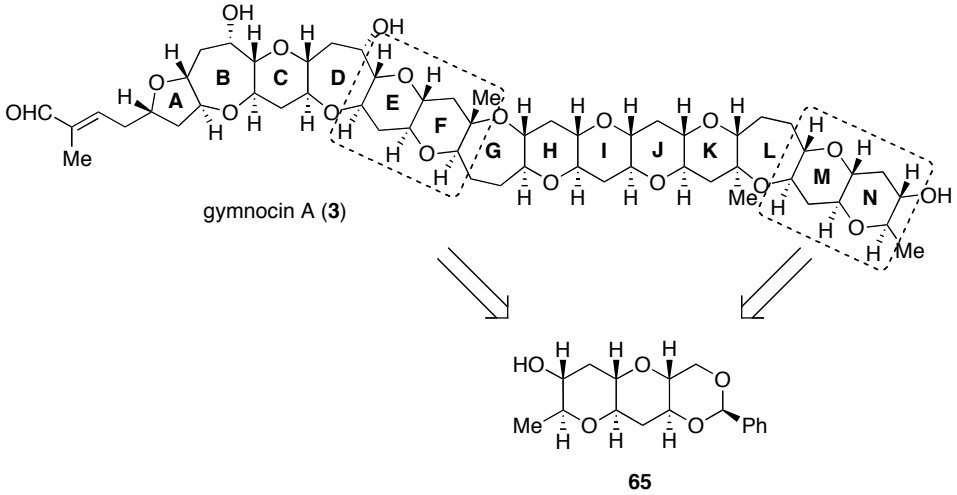
(a) Cleavage of benzylidene acetal resulted in a complex mixture. (b) 1.0 M potassium phosphate buffer.

entropic bias provided by the THP ring of the hybrid, which could promote intramolecular trapping of any hemiacetal that is formed during the course of the reaction. Also interesting is that the hybrid cyclized in aqueous buffers at ambient temperature (Table 5, entries 5-10), with maximum *endo* selectivity observed near neutral pH, in analogy to studies of **60a**. However, in contrast to the THP templated **60a**, complete conversion was not achieved after three days. It is also interesting to note that while one observes the highest conversion in highly acidic and basic regimes, these regimes also induce the lowest selectivity. Conversely, near a neutral pH regime, conversion is low but selectivity is higher.[30]

[30] Studies of THP **60a** in buffer reveal that the pH affording maximum selectivity is the same pH affording the lowest conversion. Byers, J. A.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, Article ASAP, DOI: 10.1021/ja9004909.

In summary, from these studies we found that silicon dioxide-based promoters were uniquely effective for the *endo*-selective opening of *trans*-disubstituted epoxides attached to 1,3-dioxane templates. This promoter works well for epoxides bearing both short and longer alkyl substituents. Additionally, synthetically useful selectivities were obtained with this promoter and hybrid template **64** in which a THP is fused to a benzylidene acetal. Interestingly, the behavior of **64** appears to be dominated by the THP template bearing the alcohol nucleophile and not the more remote benzylidene acetal. With an eye towards application to total synthesis, **65**, the product of the cyclization of **64** maps onto rings *EF* and *MN* of gymnocin A. Moreover, the benzylidene acetal is suitably disposed for installation of the axial methyl group on ring *F* via addition of an appropriate nucleophile (vide infra section D) or for reduction to afford the equatorial methyl group on ring *N* (Figure 9). With these encouraging results, we were eager to extend the 1,3-dioxane template to polyepoxide cascades.

Figure 9.



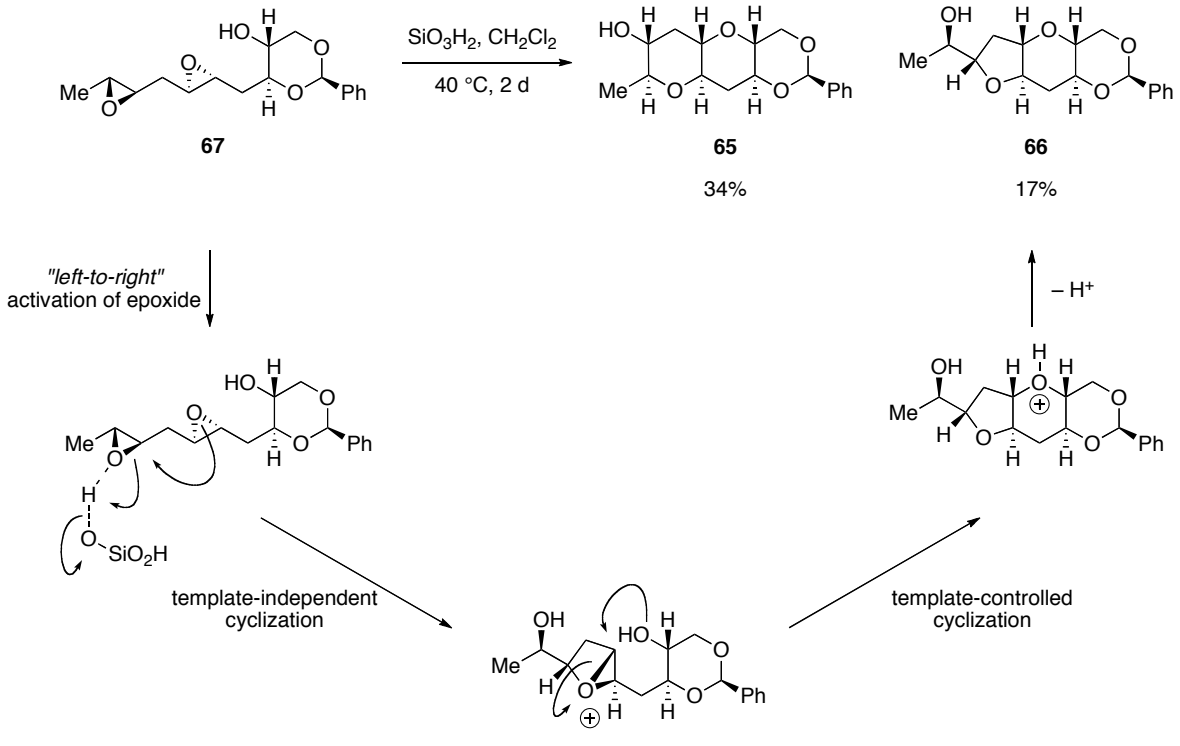
C. 1,3-Dioxane Templates in Epoxide Opening Cascades

The cyclization of epoxy alcohols **61** and **64** model, in an iterative fashion, the cascade of diepoxide **67** (Figure 8). We believed that if the cascade for **67** proceeded in the desired "right-to-left" fashion as drawn (i.e. beginning with attack of the alcohol nucleophile onto the first epoxide) it would exhibit selectivity in each step that was analogous to each of the iterative cyclizations. In other words, using SiO_3H_2 as a promoter the first ring should form with >90:10 *endo*:*exo* selectivity and the second with 82:18 *endo*:*exo* selectivity. Based on these selectivities, one might predict a theoretical yield of 73% for **65**.

Unfortunately, treatment of **67** with SiO_3H_2 in dichloromethane gave the desired triad (**65**) in only 34% yield, with an additional 17% of *exo*-product **66** isolated from the reaction. Because of this low yield, it is clear then that diepoxide **67** displays selectivity that is not a simple combination of the two iterative cyclizations. It was surprising that a significant amount of **66** was formed along with **65**. One possible explanation for this is that the cascade is not occurring exclusively in a "right-to-left" fashion. This manifold may be in competition with a "left-to-right" mechanism, one that begins with activation of the epoxide furthest from the template by silicic acid, which induces nucleophilic attack by the adjacent epoxide (Scheme 10). Because this cyclization is not necessarily template-controlled, one would not expect it to be *endo*-selective. Intramolecular trapping of the resulting epoxonium and loss of a proton would lead to **66**. Contributing to this competitive pathway may be the tempered nucleophilicy of the alcohol on the benzylidene template, which could slow down the desired "right-to-left" mode of cascade initiation. We also observed that while promoter loadings of 35mg SiO_3H_2/mg substrate gave complete conversion for systems containing one epoxide, only partial conversion was obtained for diepoxide **67**. Complete conversion was finally obtained by increasing the promoter

loading to 70 mg SiO_3H_2/mg substrate, again indicating that silica was not a catalytic promoter.

Scheme 10.

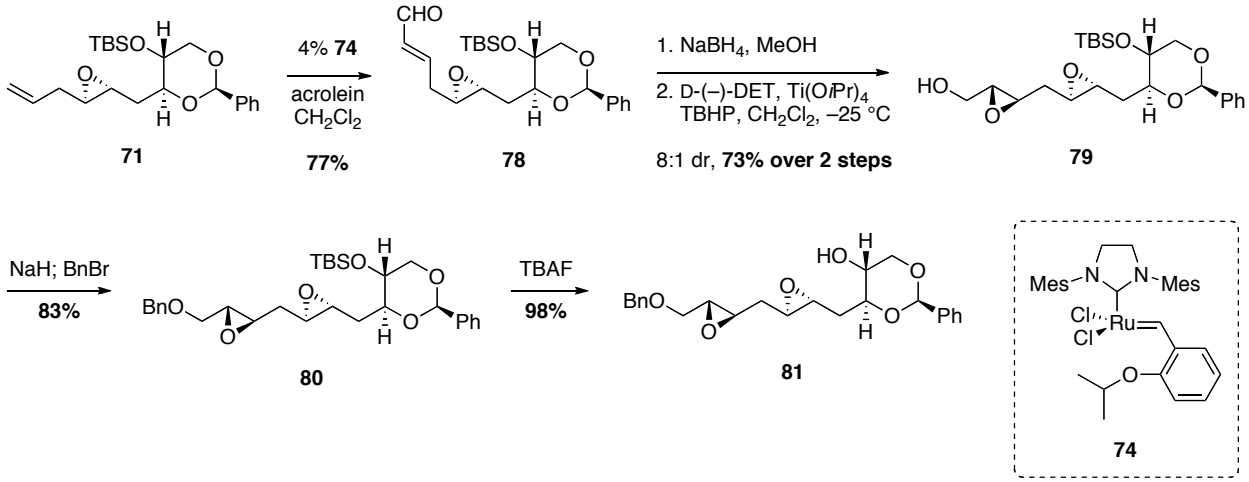


We also attempted a cascade with a slightly modified substrate (**81**) in which a benzyl ether has been appended to the terminating methyl group of **67**. This substrate was easily accessed from allylic epoxide **71** in five steps and 46% yield (Scheme 11). Treatment with silicic acid gave **82**, in which the first epoxide has undergone *exo* cyclization to form a THF and is followed by a second *exo* cyclization to give an oxetane.[31] While previous cascades have never afforded oxetanes, it is likely that the electronegative oxygen of the benzyl ether is inductively biasing *exo* opening of the epoxide under these mildly acidic conditions. We also tried a cascade of **81** in a pH neutral regime by heating to 50 °C in 1.0 M potassium phosphate buffer at pH = 7

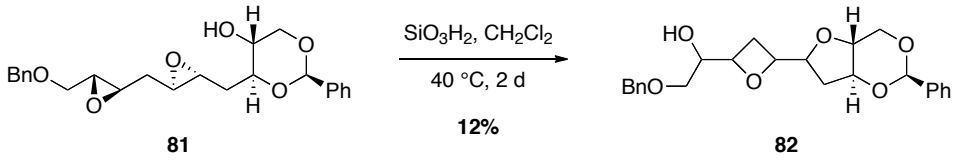
[31] Approximately 25% of the remaining mass balance was unreacted starting material and the rest appeared by ^{1}H-NMR to be a complex mixture of *exo*-cyclization and epoxide rearrangement products.

(Scheme 12).[32] Although, consistent with our previous observations of 1,3-dioxane templates, even after 7 days, no cyclization was observed. Quantitative recovery of starting material reinforces how unreactive the 1,3-dioxane template is in water.

Scheme 11.



Scheme 12.



We were not able to achieve *endo*-selective cascades with *trans*-disubstituted epoxides appended to a 1,3-dioxane template. These results highlight the complexity that arises when homologating a system with additional epoxides.[33] These studies also bring into focus a key difference between 1,3-dioxane templates and their THP analogues, namely the lethargic reactivity of 1,3-dioxane templates in aqueous media and the need to develop new promoters to

[32] The buffer pH was adjusted to 7.0 at 50 °C, using a pH meter calibrated at 50 °C.
[33] For additional studies of cascades involving trisubstituted epoxides see: Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc*. **2009**, *131*, Article ASAP, DOI: 10.1021/ja9025243.

affect this transformation. Our observations of silica promoted epoxy alcohol cyclizations represent an exciting new frontier for exploration. While a large swath of mechanistic territory remains to be charted for these promoters, one could envision silicon dioxide as a starting point for developing zeolite catalysts that promote *endo*-selective polyepoxide cascades. Because zeolites contains diverse and tunable functionalities including Lewis acidic metals and Lewis basic oxygens, they have the potential to be versatile reagents. Furthermore, because these catalysts are macromolecular one may, in principle, also tune the binding properties to preferentially activate a structural element such as a template but not an epoxide.

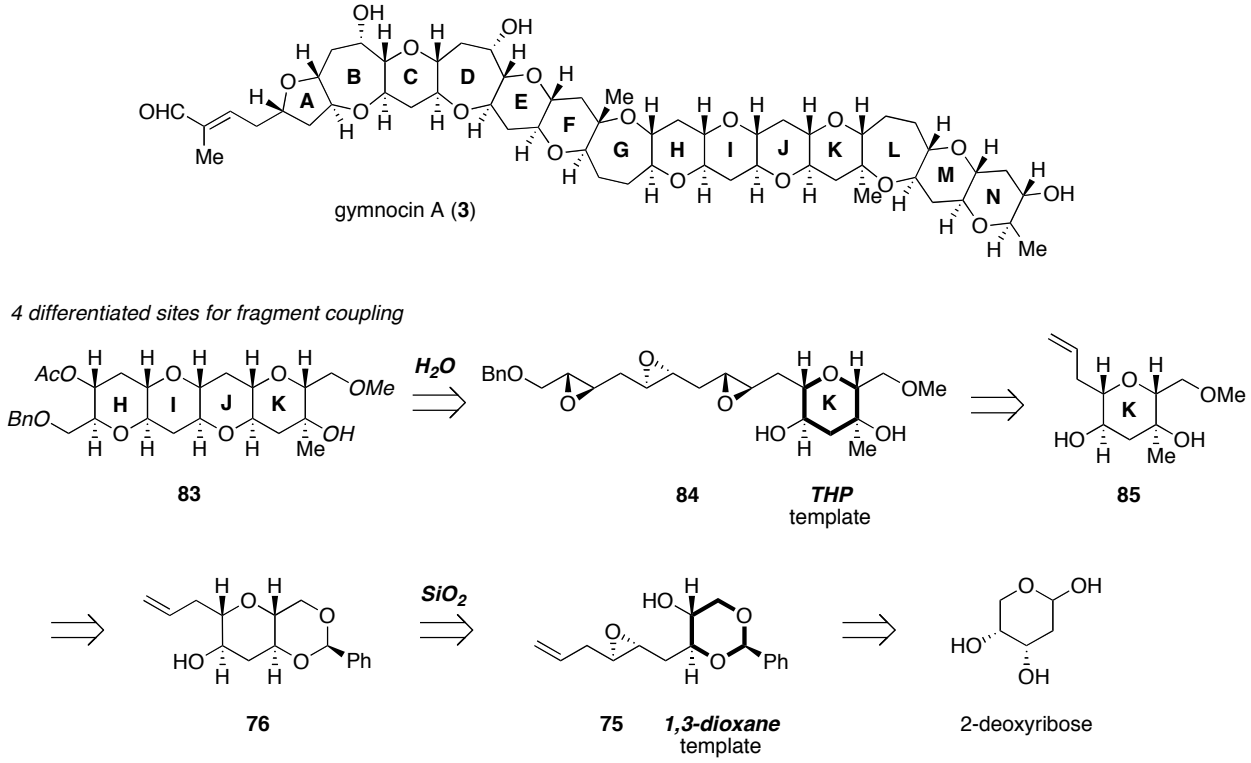
While an interesting avenue for future investigation, given the current technology available to us we perceived the best application of these functionalize templates would be to use a benzylidene acetal template for a single cyclization involving a single epoxide. The product, a versatile synthetic platform, could then be elaborated into a THP-type template and used for a water-promoted polyepoxide cascade for the construction of additional rings.

D. Application to Gymnocin A: Synthesis of *HIJK* Rings

Because a serious limitation of the products obtained from epoxide opening cascades in the past was their inapplicability to synthesis (due to irremovable directing groups and/or the difficulty of subsequent functionalization), we sought to showcase the utility of 1,3-dioxane templates by preparing a synthetically versatile fragment of the ladder polyether gymnocin A (**3**).[34] Specifically, we targeted THP tetrad **83** corresponding to the *HIJK* ring system of the natural product. This fragment bears two differentiated sites for fragment coupling at *each* terminus, allowing for bidirectional functionalization and extension of the ladder.

[34] One total synthesis of **3** has been reported to date: Tsukano, C.; Sasaki, M. *J. Am. Chem. Soc*. **2003**, *125*, 14294–14295.

Scheme 13.

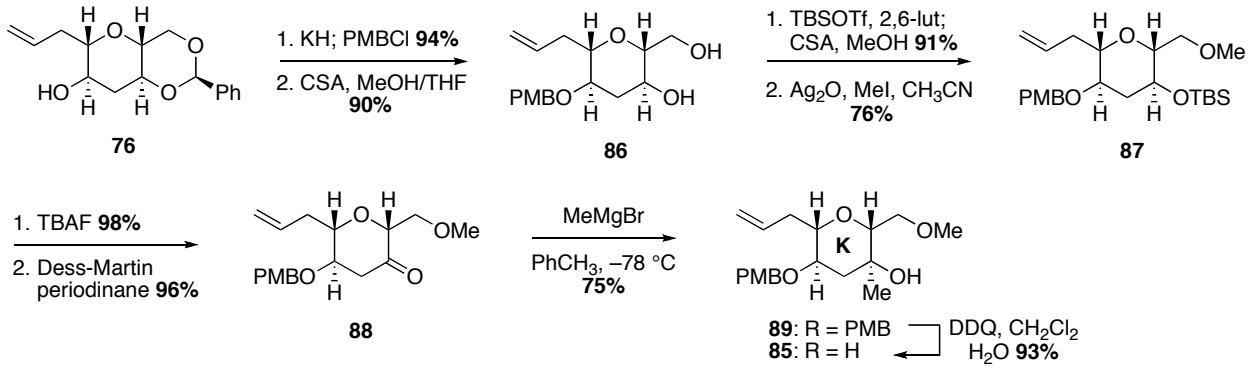


Retro synthetically, we envisioned the *HIJ* rings arising via a water promoted cascade of triepoxide **84**, templated by ring *K* of the natural product (Scheme 13). The ring *K* template (**85**) could itself be accessed from diad **76**, which had already been prepared via a silicon dioxide-promoted cyclization of 1,3-dioxane templated epoxy alcohol **75**.

In order to transform THP **76** into the ring *K* template, we needed to install an axial methyl group at the 3-position. This proved straightforward, given the synthetic flexibility of the benzylidene acetal. PMB protection of the secondary alcohol was followed by removal of the acetal under standard conditions, unveiling diol **86** (Scheme 14). Next, selective formation of the secondary silyl ether[35] and alkylation of the primary alcohol afforded methyl ether **87**. The methyl ether was chosen to serve as an orthogonal protected fragment coupling site following the

[35] Koch, G.; Loiseleur, O.; Altmann, K. H. *Synlett* **2004**, *4*, 693–697.

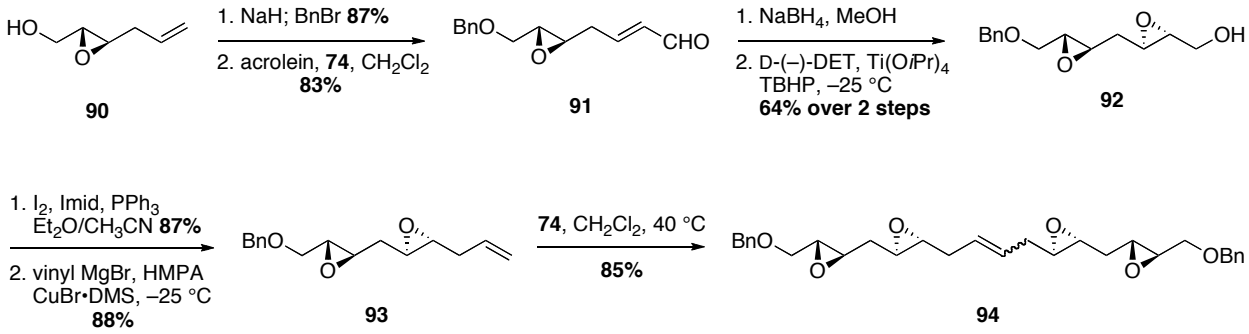
Scheme 14.



epoxide-opening cascade. Deprotection of the secondary alcohol and oxidation with Dess-Martin periodinane set the stage for a stereoselective addition of methyl Grignard[36] affording **89**, ring *K* of gymnocin A. This functionalized ring of the natural product and template for the subsequent cascade was accessed from **76** in seven steps and 38% overall yield.

With the template in hand, we then needed to append a triepoxide moiety that would be transformed into the *HIJ* rings of the natural product. We planned to use cross-metathesis to unite the template with epoxide-bearing olefin **93**, itself accessible in six steps and 35% yield from known epoxy alcohol **90** (Scheme 15).[37] Cognizant of the challenges inherent with

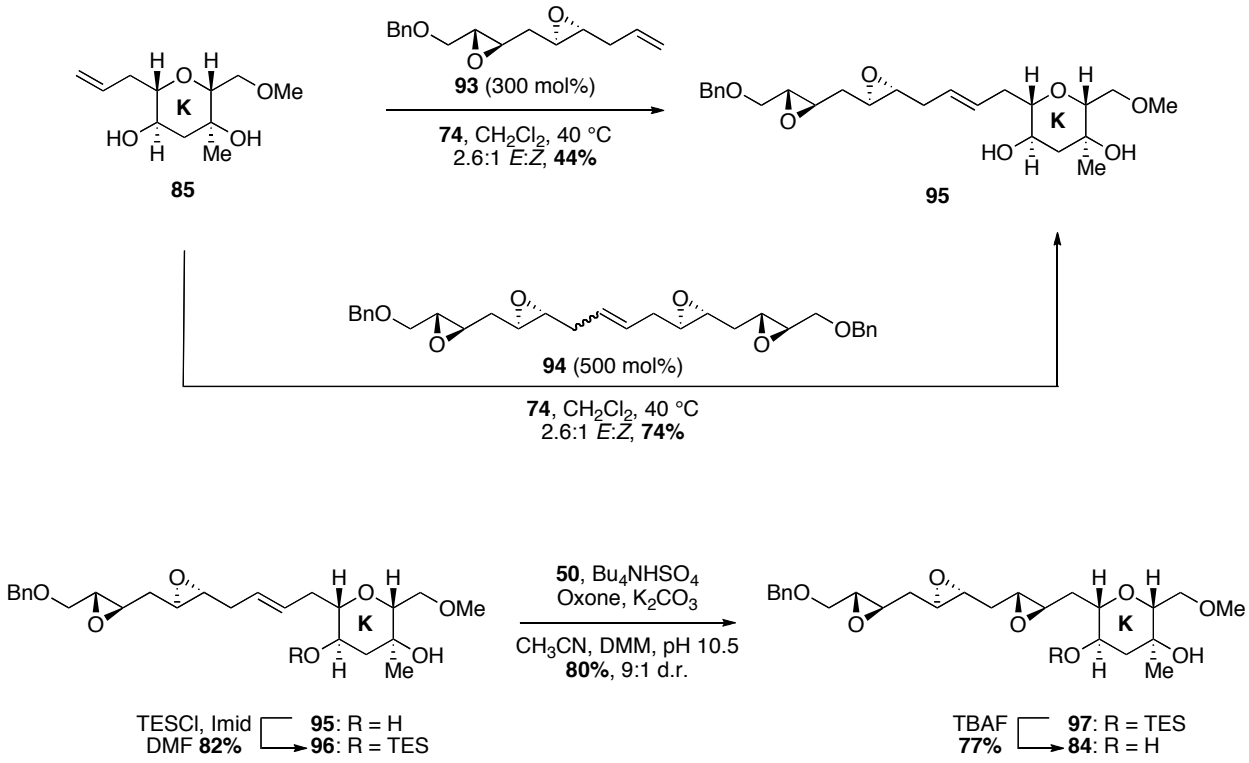
Scheme 15.



[36] Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019–3033.
[37] Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett*. **2005**, *46*, 6567–6570.

achieving the cross-metathesis product as opposed to the self-metathesis product of two similar olefins, we began with coupling olefins **89** and **93** in the presence of the 2nd generation Hoveyda-Grubbs catalyst (**74**) (Scheme 16). As expected, we observed significant quantities of olefin **94**, the self-metathesis product of olefin **93**, being formed but saw no evidence of the desired cross-metathesis product. Suspecting that the congested steric environment around the PMB ether of **89** was interfering with the desired reaction,[38] this group was removed. Under identical reaction conditions diol **85** underwent cross-metathesis with **93** to give **95** in moderate yield and *E*:*Z* selectivity (Scheme 16). The yield was improved significantly by replacing olefin **93** with an

Scheme 16.



[38] Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed*. **2003**, *42*, 1900–1923.

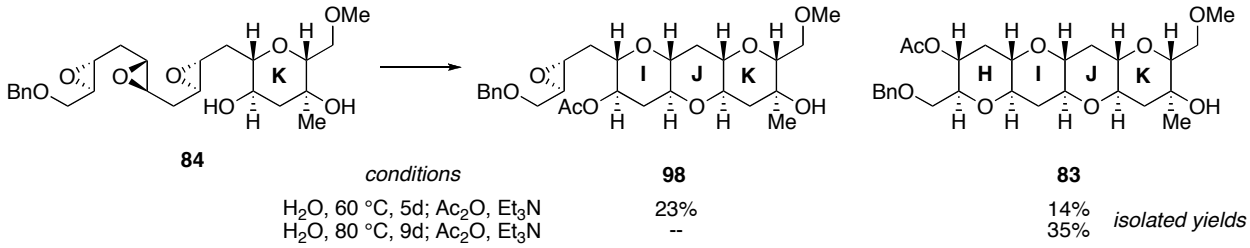
excess of its self-metathesis product **94** (Scheme 16).[39] More than 90% of unreacted **94** could be recovered and reused. While the cross-metathesis proceeded with moderate *E*:*Z* selectivity, the olefin isomers were separable. Additionally, because cross-metathesis is under thermodynamic control, the undesired *Z*-olefin could be recycled by isomerization to an equilibrium mixture (2.6:1 *E*:*Z*) favoring the *E*-olefin. With this protocol, several hundred milligrams of **95** could be prepared, even without resorting to recycling. Finally, protection of alcohol **95** prevented premature cyclization during the subsequent Shi epoxidation with ketone **50**. This epoxidation proceeded in good yield and dr and was followed by removal of the silyl group, affording epoxy alcohol **84** (Scheme 16).

Having convergently assembled triepoxy alcohol **84**, we were eager to explore its water-promoted cascade. Having already seen that changes to the template composition can radically affect *endo* selectivity, it was challenging to predict *a priori* whether ring *K*, which bears a methoxymethyl substituent at the 2-position as well as a tertiary alcohol and axial methyl group at the 3-position, would template the reaction in the desired fashion. Incubation of **84** in H_2O at 60 °C for 5 days followed by acetylation afforded a mixture of the desired tetrad (**83**) and a compound in which rings *IJ* had formed, but the final epoxide remained intact (Scheme 17). This triad (**98**) intrigued us for two reasons. In previous cascades in water, complete conversion was typically observed after 3 days at 60 °C. Second, we had not previously isolated an epoxide-containing intermediate *en route* to the final cascade product. The structure of triad (**98**) also suggests that the cascade is proceeding in the desired "right-to-left" direction. The attenuated reactivity of the remaining epoxide is likely due to the presence of the electron-withdrawing oxygen atom in the benzyl ether which could destabilize formation of positive charge at the site

[39] (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 58–71. (b) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett*. **1998**, *39*, 7427–7430.

of epoxide opening, a feature that may find use in future polyepoxide cascades. A higher temperature and longer reaction time (80 °C, 9 d) overcame this stalled cascade and, after acetylation, afforded **83**, the desired *HIJK* fragment of gymnocin A in 35% yield, corresponding to approximately 70% yield per newly formed ring.

Scheme 17.



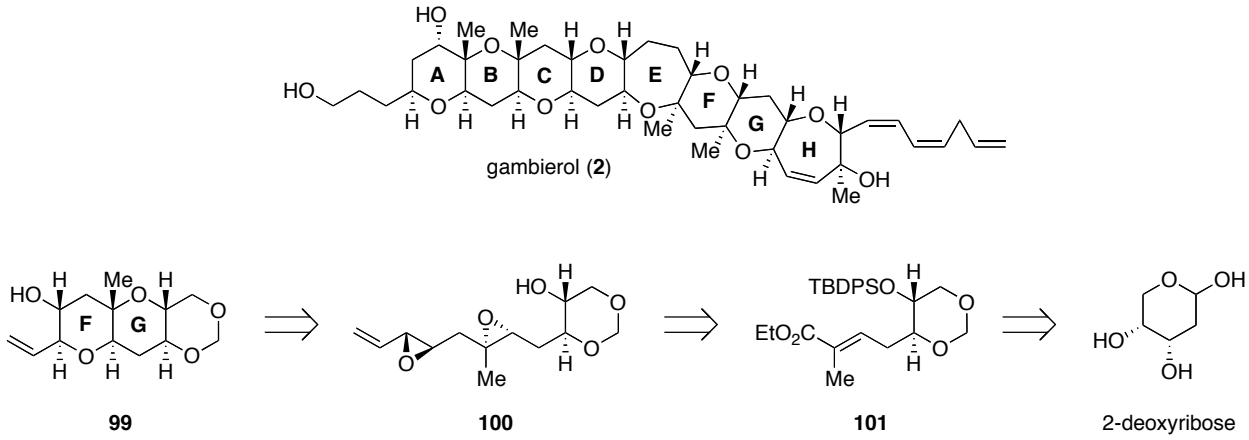
In summary, we have employed two different functionalized templates for the synthesis of the *HIJK* rings of gymnocin A. The *first* template (the 1,3-dioxane of **75**) provided high *endo*-selectivity in the presence of silicon dioxide-based promoters. The product of this cyclization (**76**), a synthetically versatile intermediate, was facilely elaborated into a *second* template (ring *K* of gymnocin A), enabling a water-promoted cascade of triepoxide **84** into tetrad **83**. Noteworthy is that polyether fragment **83** enjoys a total of 4 differentiated functional groups, 2 at each end, thus allowing for elaboration of both termini and significantly increasing the synthetic utility of products obtained from epoxide-opening cascades.

E. Application to Gambierol: Synthesis of *FG* Rings

Having yet to identify an effective promoter for cascades of 1,3-dioxanes bearing two simple *trans*-disubstituted epoxides (vide supra, Section C), we thought that *endo*-selectivity could be improved by utilizing appropriately activated epoxides. Epoxide openings employing

directing groups such as methyl (in the context of polyepoxide cascades)[19] and vinyl (in the context of cyclizations onto a single epoxide)[13] have been reported in the literature. With acidic promoters, these directing groups create a considerable electronic preference for opening of the epoxide at the carbon to which they are attached. While the relative paucity of methyl group substitution in the ladder polyether natural products precludes the use of such directing groups as a general solution for epoxide opening cascades, a judicious application can be advantageous. With this in mind, we sought to utilize a cascade of activated epoxides to assemble rapidly the *FG* ring system of gambierol (**2**).[40]

Scheme 18.



Retrosynthetically, we envisioned rings *FG* (**99**) arising from an acid-promoted cascade of diepoxide **100**, which features a distally[41] trisubstituted epoxide closest to the template

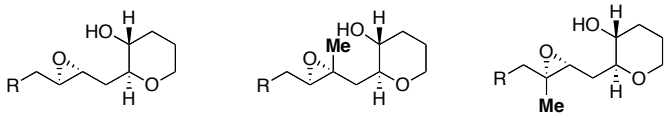
[40] Three total syntheses of **2** have been reported to date: (a) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 14983–14992. (b) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 11893–11899. (c) Johnson, H. W. B.; Majumder, U.; Rainier, J. D. *J. Am. Chem. Soc*. **2005**, *127*, 848–849 and references therein.

[41] The terms "proximally" and "distally" trisubstituted epoxides refers to the position of a substituent with respect to the template. For example, trisubstituted epoxides bearing a methyl at the carbon closest to the template are proximally trisubstituted, while those bearing a methyl at the carbon further from the template are distally

followed by a *trans*-disubstituted epoxide bearing an allyl substituent (Scheme 18). It is worth noting that while previous cascades employed a benzylidene acetal template, this cascade employs a methylene acetal. Being unable to predict the optimal acidic promoter for this cascade, we chose this template because it would be robust under a variety of conditions. In turn, diepoxide **100** could be accessed from **101**, which bears striking resemblance to a previously prepared intermediate (**57**) and could ultimately arise from 2-deoxyribose via an analogous sequence of transformations.

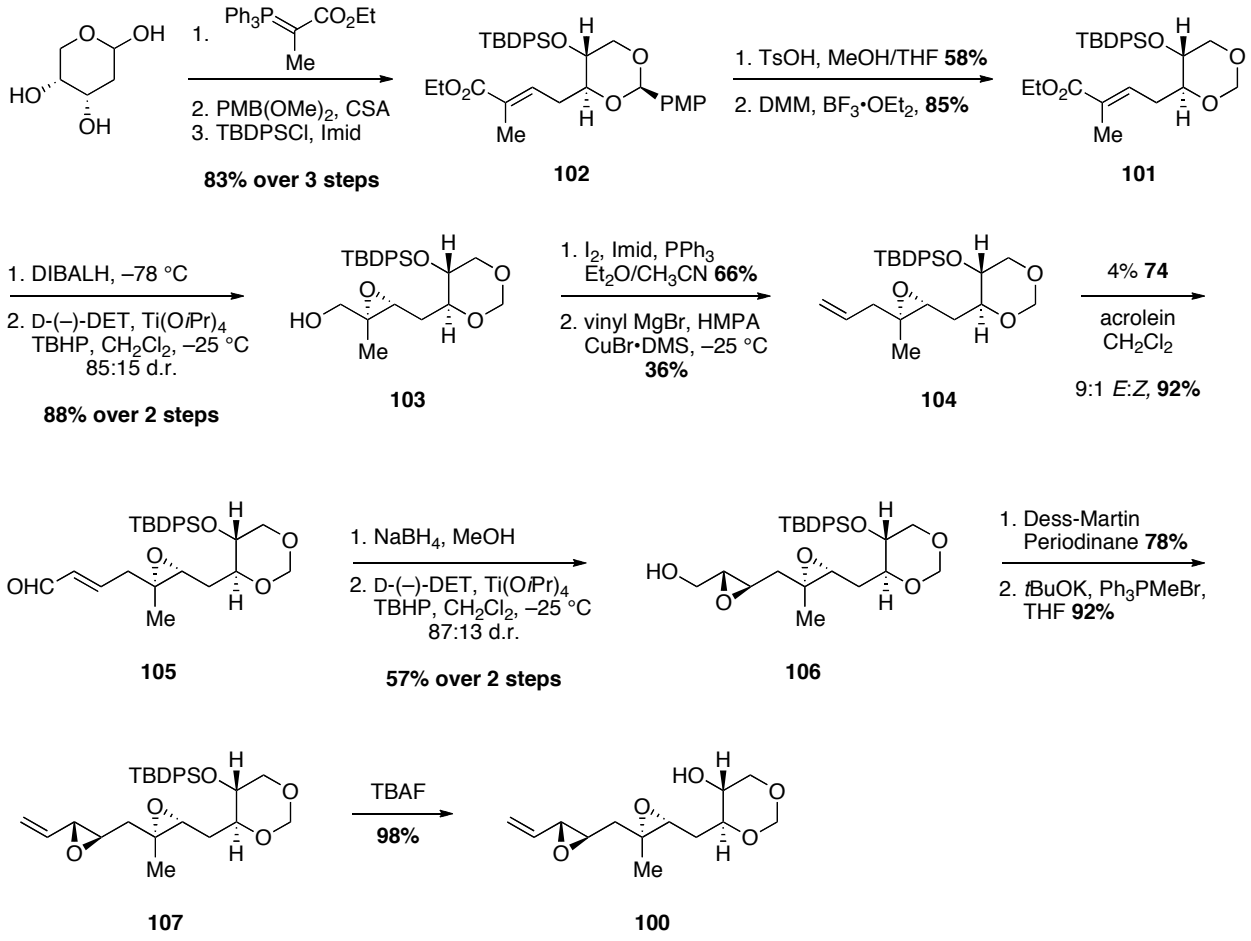
Treatment of 2-deoxyribose with the appropriate stabilized phosphor and protection of the triol under conditions to favor formation of the thermodynamically more stable 1,3-*para*-methoxybenzylidene acetal was followed by protection of the secondary alcohol as a silyl ether (Scheme 19). In a two-step protocol, the PMB acetal was converted to a methylene acetal.[42] Subsequent reduction of the ester and epoxidation of the resulting allylic alcohol proceeded in good yield and diastereoselectivity. Conversion of alcohol **103** to the iodide and displacement with an alkenyl cuprate reagent set the stage for homologation into the diepoxide. This was accomplished by a selective cross-metathesis of olefin **104** with acrolein, which proceeded in high yield and *E*:*Z* selectivity. In a straightforward fashion, this enal was elaborated into the desired vinyl epoxide followed by removal of the silyl group in good yield to afford **100**.

trisubstituted. Those without an additional substituent are referred to as *trans*-disubstituted. Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc*. **2009**, *131*, Article ASAP, DOI: 10.1021/ja9025243.



[42] It is also reasonable to assume that conversion of PMB acetal **102** to methylene acetal **101** could be accomplished in a single step with an acid catalyst. We chose a two-step protocol to better explore different conditions for installation of the methylene acetal via the diol intermediate.

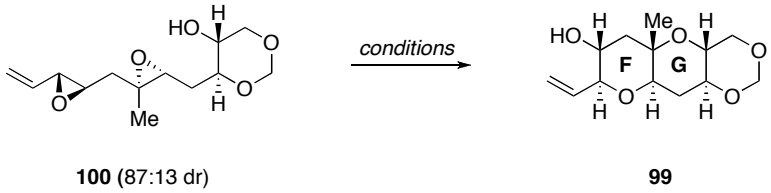
Scheme 19.



With the desired diepoxy alcohol **100** in hand, we began by promoting its cyclization with a Lewis acid (BF_3•OEt_2) at low temperature (Table 10, entry 1) which gave the desired product in 35% yield. Recognizing that because of the highly activated nature of these epoxides, Wagner-Meerwein rearrangement to the ketone could be a competing side reaction, we also investigated a milder Brønsted acid, CSA. Gratifyingly, the desired triad was obtained in 57% yield after 15 hours.[43] Stopping the reaction before this time, for example at 9 hours, showed

[43] Preliminary analysis indicates that the remaining mass balance is a mixture of products one of which appears to involve *exo* opening of the first epoxide followed by *endo* opening of the vinyl epoxide to afford two new THF rings. Additionally, there is ^{1}H-NMR evidence of *endo* cyclization of the first epoxide followed by rearrangement of the vinyl epoxide to an allylic ketone.

Table 10.

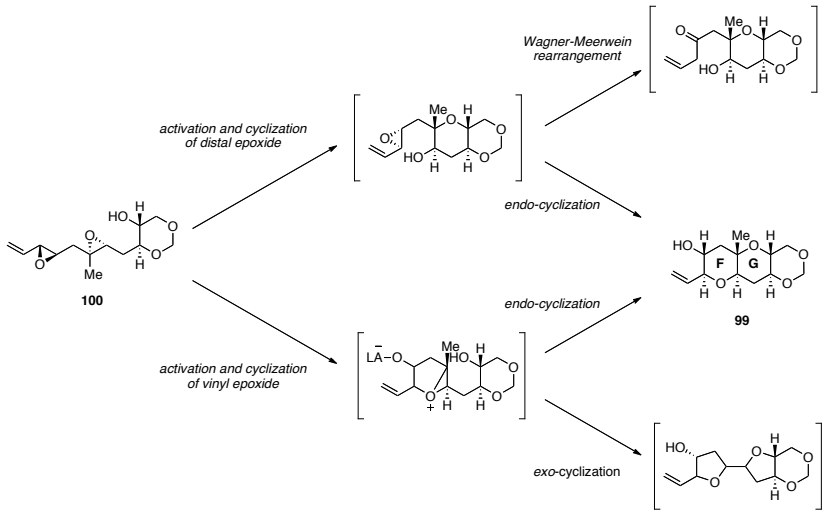


100 (87:13 dr) **99**

entry	solvent	promoter (equiv)	T (°C)	yield **99**
1	CH_2Cl_2	BF_3•OEt_2 (0.25)	-78	35% (40%)[a]
2	CH_2Cl_2	CSA (0.25)	23	57% (65%)[a]
3	H_2O	none	60	22% (25%)[a,b]

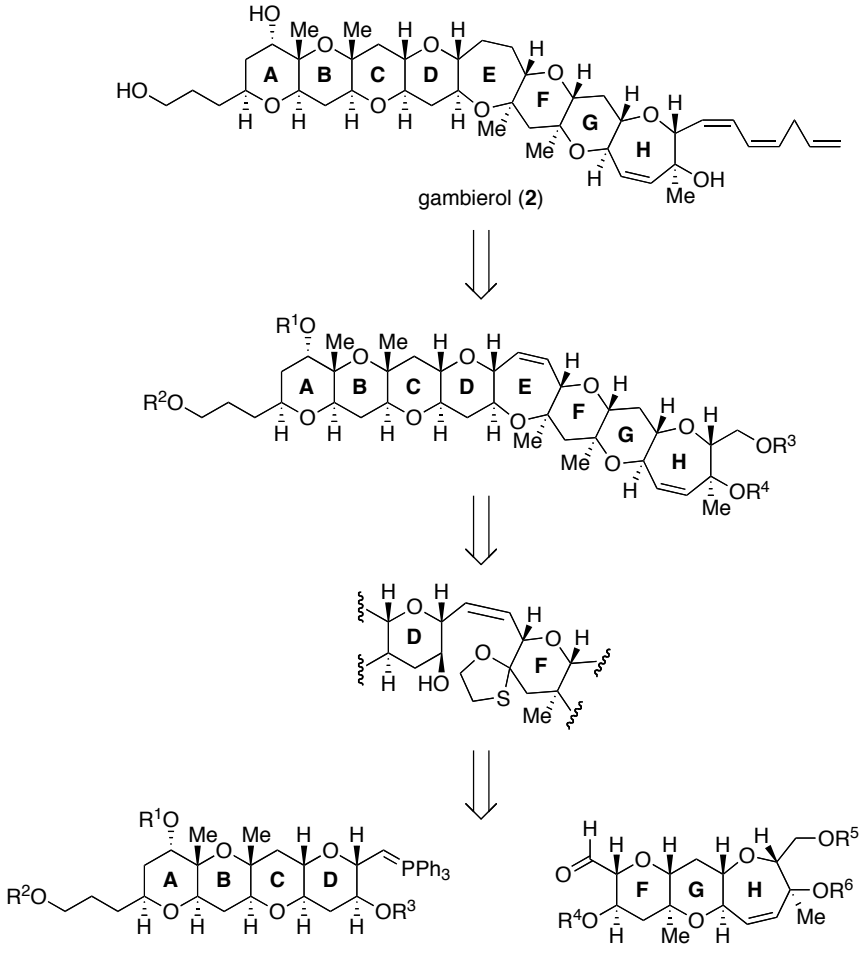
(a) Yield adjusted for dr of epoxide. (b) Yield based on NMR.

incomplete conversion. Deionized water was not an effective promoter for this cascade, affording the desired product in low yield. Notably, however, product formation is observed in water with this methylene acetal template, in contrast to studies with benzylidene acetal templates. We believe this is due to (1) the methylene acetal's increased stability towards hydrolysis and (2) the increased electrophilicity of the epoxides (arising from electronic activating groups) rendering attack by the relatively poorly nucleophilic 1,3-dioxane-templated alcohol feasible. We cannot rule out, however, that in water at elevated temperature some product may be formed via an acid-promoted mechanism. If acid activation is occurring, the



overall yield could be low because the desired intramolecular reaction is outcompeted by intermolecular opening of the epoxide by solvent.

Scheme 20. Proposed fragment coupling and methyl installation towards gambierol (**2**).



Having assembled the *FG* THP rings of gambierol, remaining is installation of the final methyl group on ring *F*. Late stage installation of this methyl group could be envisioned by first coupling rings *ABCD* and *FGH* via a Wittig olefination. Next, formation of a mixed thioketal on ring *F* and treatment with *m*-CPBA followed by trimethylaluminum would facilitate ring closure and installation of the axial methyl substituent (Scheme 20). Work towards the construction of

ring *H* as well as the *ABCD* ring system is ongoing in our laboratory.[44]

Conclusion

The *endo*-selective cyclization of alcohols onto electronically unbiased epoxides provides a direct route for constructing ladder polyether structures. Additionally, strategies to transform multiple epoxides into multiple new rings have appealing parallels to the proposed biogenesis of these natural products. Mindful that any method for constructing polyethers should yield products that are themselves synthetically relevant intermediates, we investigated 1,3-dioxanes and found that they templated the cyclization of an alcohol onto an unbiased epoxide. Critical for high *endo*-selectivity was the use of silicon-dioxide based promoters. Taking advantage of the synthetic handles offered by the benzylidene acetal template, the newly formed THP ring was then used to template a water promoted cascade, constructing the *HIJK* rings of gymnocin A. We have also achieved cascades of methylene acetal templates with electronically activated epoxides to construct the *FG* rings of gambierol. Use of these functionalized templates and the products derived from them sets the stage for the convergent total synthesis of ladder polyether natural products.

[44] A synthesis of the *ABCD* ring system and fragment coupling was proposed by NIH postdoctoral fellow Dr. Denise Colby.

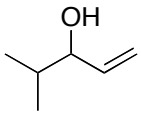
Experimental Section

General Information. Unless otherwise noted all reactions were performed under an oxygen-free atmosphere of argon with rigorous exclusion of moisture from reagents and glassware. Except where noted, dichloromethane was either distilled from calcium hydride or purified via an SG Water USA solvent column system. Tetrahydrofuran and Et_2O were either distilled from a blue solution of benzophenone ketyl or purified via an SG Water USA solvent column system. Triethylamine was purified via an SG Water USA solvent column system. Deionized water was used without any additional purification. Chiral ketone **50**, used in Shi asymmetric epoxidation was prepared by oxidation[1] of the corresponding alcohol. The alcohol was obtained through contract synthesis.

Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid (PMA), basic potassium permanganate ($KMnO_4$), or cerium ammonium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ^1H and ^{13}C spectra were recorded in $CDCl_3$, unless otherwise noted, on a Bruker Avance 400 MHz spectrometer, or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from the center peak of an internal standard of either residual chloroform (7.27 ppm), dichloromethane (5.32 ppm), methanol (4.78 and 3.31 ppm), or benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent, and br = broad),

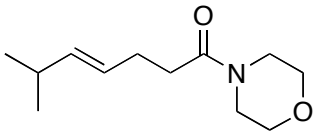
[1] Mio, Shigeru, Kumagawa, Y., Sugai, S. *Tetrahedron Lett*. **1990**, *47*, 2133–2144.

coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.23 ppm), dichloromethane (54.00 ppm), methanol (49.15 ppm), or benzene (128.39 ppm).



S1

4-methylpent-1-en-3-ol (S1): To a solution of isobutryaldehyde (15.2 mL, 167 mmol) in THF (130 mL) at –78 °C was added vinyl magnesium bromide (1M in THF, 200 mL, 200 mmol) dropwise. The reaction was stirred at 0 °C for 1 h then slowly quenched with 1M HCl (150 mL). The mixture was extracted with Et_2O (5 x 100 mL), the combined organic extracts were dried with $MgSO_4$, and concentrated *in vacuo*. The oil was purified by column chromatography (10% EtOAc in hexane) to afford **S1** as a colorless oil (14.1g, 84%) which was spectroscopically identical to the literature reported compound.[2]

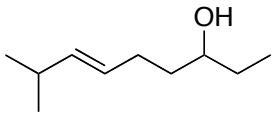


43

(*E*)-6-methyl-1-morpholinohept-4-en-1-one (43): Allylic alcohol **S1** (3.9 g, 39 mmol), 1,1-bismorpholinoethylene (8.4 g, 42 mmol), propanoic acid (100 µL, 1.3 mmol), and xylene (100

[2] Makosza, Mieczyslaw; Urbanska, Natalia; Chesnokov, Alexey A. *Tetrahedron Lett*. **2003**, *44*; 1473–1476.

mL) were combined in a sealed vessel and heated to 150 °C for 12 h. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (gradient: 20% to 40% EtOAc in hexanes) to afford **43** as a colorless oil (4.6 g, 56%). Product was visualized with $KMnO_4$ stain, R_f = 0.53 (40% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91–0.93 (d, *J* = 6.8 Hz, 6H), 2.15–2.24 (octet, *J* = 6.7 Hz, 1H), 2.25–2.36 (m, 4H), 3.42–3.45 (dd, *J* = 5.1, 4.6 Hz, 2H), 3.56–3.64 (m, 6H), 5.31–5.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 28.3, 31.0, 33.3, 41.9, 46.1, 66.7, 67.0, 125.5, 138.8, 171.4; IR (thin film NaCl): 2959, 2859, 1650, 1432, 1382, 1361, 1329, 1299, 1272, 1234, 1196, 1116, 1069, 1026, 971, 849 cm^{-1}; HR-MS (ESI) Calcd for $C_{12}H_{21}NO_2$ $(M+Na)^+$ 212.1645, found 212.1652.

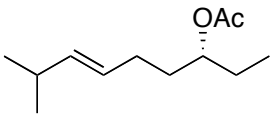


44

(*E*)-8-methylnon-6-en-3-ol (44): A solution of morpholine amide **43** (4g, 19 mmol) in THF (140 mL) was cooled to –78 °C. To this solution was added ethyl lithium (0.5M solution 9:1 benzene:cyclohexane, 57 mL, 29 mmol) slowly over 20 min. The reaction was warmed to ambient temperature and stirred for 1 h. The reaction was quenched at 0 °C with 100 mL aqueous sat. NH_4Cl. The aqueous layer was extracted with Et_2O (5 x 100 mL), the combined organic extracts were dried with $MgSO_4$, concentrated *in vacuo* and the resulting ketone was used without further purification due to its volatility.

The crude ketone was dissolved in MeOH (150 mL) and cooled to 0 °C. To this solution was added $NaBH_4$ (1.1g , 29 mmol) in portions and the reaction was stirred at ambient temperature for 30 min. The solvent was removed *in vacuo*, the crude material was redissolved in Et_2O (100 mL) and the reaction was quenched with 1M HCl (50 mL). The aqueous layer was

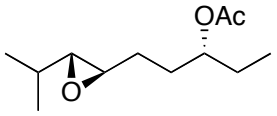
extracted with Et_2O (5 x 75 mL), the combined organic extracts dried with $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexanes) to afford **44** as a colorless oil (2.47 g, 83% over 2 steps). Product was visualized with $KMnO_4$ stain, R_f = 0.21 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–0.91 (t, *J* = 7.5 Hz, 3H), 0.91–0.95 (d, *J* = 6.8 Hz, 6H), 1.36–1.56 (m, 4H), 1.82 (s, 1H), 1.99–2.16 (m, 2H), 2.17–2.26 (octet, *J* = 6.7 Hz, 1H), 3.48–3.54 (dddd, *J* = 9.1, 7.5, 4.7, 4.4 Hz, 1H), 5.32–5.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.0, 22.7, 22.8, 29.1, 30.3, 31.1, 36.8, 73.1, 126.9, 138.3; IR (thin film NaCl): 3343, 2961, 2871, 1464, 1381, 1362, 1171, 1118, 1029, 968, 875 cm^{-1}; HR-MS (ESI) Calcd for $C_{10}H_{20}O$ $(M+Na)^+$ 179.1406, found 149.1051.



45

(*R*,*E*)-8-methylnon-6-en-3-yl acetate (45): To a solution of **44** (1.9g, 12 mmol) in hexane (12 mL) was added vinyl acetate (1.1 mL, 12 mmol), powdered 4Å molecular sieves (500 mg), and resin-immobilized *Candida antarctica* β lipase (1.2 g). The reaction was stirred at ambient temperature for 15 min and then filtered through Celite, which was subsequently washed with Et_2O. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc in hexanes) to afford acetate **45** (600 mg, 25%) as a colorless oil. Product was visualized with CAM stain, R_f = 0.54 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86–0.89 (t, *J* = 7.4 Hz, 3H), 0.94–0.96 (d, *J* = 6.8 Hz, 6H), 1.52–1.61 (m, 4H), 1.94–2.01 (m, 2H), 2.04 (s, 3H), 2.17–2.26 (octet, *J* = 6.6 Hz, 1H), 4.78–4.84 (dddd, *J* = 7.0, 7.0, 5.4, 5.4 Hz, 1H), 5.28–5.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 21.4, 22.8, 27.1, 28.6, 31.2,

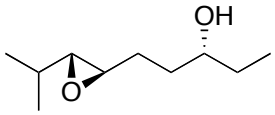
33.7, 75.2, 126.2, 138.4, 171.1; IR (thin film NaCl): 2964, 2870, 1740, 1464, 1372, 1244, 1109, 1084, 1019, 969 cm^{-1}; $[\alpha]_D^{23}$ = 6.5 (*c* = 0.065, $CHCl_3$); HR-MS (ESI) Calcd for $C_{12}H_{22}O_2$ $(M+Na)^+$ 221.1512, found 221.1522. Enantiomeric excess (98%) was established by chiral GC (β-Ph column, H_2 flow 1 mL/min, isothermal 95 °C) t_R[(*R*)-**45**] = 47.1 min, t_R[(*S*)-**48**] = 48.9 min.



46

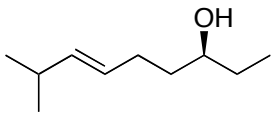
(*R*)-1-((2*R*,3*R*)-3-isopropyloxiran-2-yl)pentan-3-yl acetate (46): To a solution of olefin **45** (207 mg, 1.04 mmol) in 1:2 CH_3CN:DMM (43 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (28 mL), and *n*$BuNHSO_4$ (452 mg, 1.04 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (343 mg, 1.04 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (11.9 mL) and a solution of Oxone® (1.64 g, 2.08 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (13.3 mL) were added simultaneously over 20 min via syringe pump. The reaction was stirred at 0 °C for an additional 30 min then diluted with H_2O (50 mL). The aqueous layer was extracted with EtOAc (8 x 50 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes) to afford epoxide **46** (175 mg, 79%, 9:1 dr by ^{1}H-NMR) as a colorless oil. Product was visualized with CAM stain, R_f = 0.30 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84–0.88 (t, *J* = 7.4 Hz, 3H), 0.91–0.93 (d, *J* = 6.9 Hz, 3H), 0.97–0.99 (d, *J* = 6.7 Hz, 3H), 1.42–1.71 (m, 7H), 2.02 (s, 3H), 2.41–2.44 (dd, *J* = 7.0, 2.3 Hz, 1H), 2.67–2.70 (ddd, *J* = 6.2, 5.2, 2.3 Hz, 1H), 4.76–4.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 18.5, 19.2, 21.3, 27.1, 28.4, 30.2, 30.6, 57.5, 64.4, 75.1, 171.0; IR (thin film

NaCl): 2965, 2875, 1737, 1463, 1373, 1244, 1117, 1023, 952, 893 cm^{-1}; $[\alpha]_D^{23}$ = 22.6 (*c* = 0.018, $CHCl_3$); HR-MS (ESI) Calcd for $C_{12}H_{22}O_3$ $(M+Na)^+$ 237.1461, found 237.1456.



39

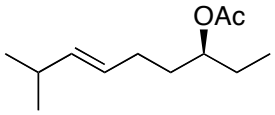
(*R*)-1-((2*R*,3*R*)-3-isopropyloxiran-2-yl)pentan-3-ol (39): To a solution of acetate **46** (100 mg, 0.46 mmol) in THF (4.2 mL), MeOH (1.8 mL), and H_2O (0.6 mL) at 0 °C was added lithium hydroxide (28 mg, 0.92 mmol). The reaction was stirred at 0 °C for 2 h and then the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 10% to 20% EtOAc in hexanes to afford **39** as a colorless oil (64 mg, 81%). Product was visualized with CAM stain, R_f = 0.25 (30% EtOAc in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ: 0.78–0.79 (d, *J* = 6.9 Hz, 3H), 0.90–0.94 (m, 6H), 1.31–1.55 (m, 6H), 1.60–1.66 (m, 1H), 2.28–2.30 (dd, *J* = 6.9, 2.2 Hz, 1H), 2.52–2.55 (ddd, *J* = 6.4, 4.8, 2.3 Hz, 1H), 3.39–3.45 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ: 10.7, 18.8, 19.5, 29.2, 31.0, 31.1, 34.3, 58.1, 64.3, 72.6; IR (thin film NaCl): 3427, 2962, 2874, 1463, 1384, 1366, 1281, 1249, 1198, 1123, 1028, 940, 892, 782, 731 cm^{-1}; $[\alpha]_D^{23}$ = 8.6 (*c* = 0.024, $CHCl_3$); HR-MS (ESI) Calcd for $C_{10}H_{20}O_2$ $(M+Na)^+$ 195.1356, found 195.1362.



47

(*S*,*E*)-8-methylnon-6-en-3-ol (47): To a solution of **44** (1.9 g, 12 mmol) in hexane (12 mL) was added vinyl acetate (1.1 mL, 12 mmol), powdered 4Å molecular sieves (500 mg), and resin

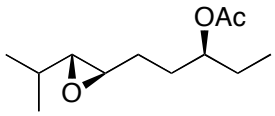
immobilized *Candida antarctica* β lipase (1.2 g). The reaction was stirred at ambient temperature for 135 min and then filtered through Celite, which was subsequently washed with Et_2O. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (20% EtOAc in hexanes to afford alcohol **47** (631 mg, 33%) as a colorless oil. Product was visualized with $KMnO_4$ stain, R_f = 0.21 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90–0.91 (t, *J* = 7.5 Hz, 3H), 0.91–0.95 (d, *J* = 6.8 Hz, 6H), 1.36–1.56 (m, 4H), 1.82 (s, 1H), 1.99–2.16 (m, 2H), 2.17–2.26 (octet, *J* = 6.7 Hz, 1H), 3.48–3.54 (dddd, *J* = 9.1, 7.5, 4.7, 4.4 Hz, 1H), 5.32–5.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.0, 22.7, 22.8, 29.1, 30.3, 31.1, 36.8, 73.1, 126.9, 138.3; IR (thin film NaCl): 3343, 2961, 2871, 1464, 1381, 1362, 1171, 1118, 1029, 968, 875 cm^{-1}; $[\alpha]_D^{23}$ = 9.4 (*c* = 0.030, $CHCl_3$); HR-MS (ESI) Calcd for $C_{10}H_{20}O$ $(M+Na)^+$ 179.1406, found 149.1045. Enantiomeric excess was measured of acetate derivative **48**.



48

(*S*,*E*)-8-methylnon-6-en-3-yl acetate (48): To a solution of alcohol **47** (416 mg, 2.66 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (1.48 mL, 10.6 mmol), acetic anhydride (0.50 mL, 5.32 mmol) and DMAP (33 mg, 0.26 mmol). The reaction was stirred at ambient temperature for 3 h, diluted with H_2O (3 mL) and extracted with EtOAc (3 x 8 mL). The solvent was removed *in vacuo* and the crude material was purified by column chromatography (10% EtOAc in hexanes) to afford **48** as a colorless oil (453 mg, 86%). Product was visualized with CAM stain, R_f = 0.54 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86–0.89 (t, *J* = 7.4 Hz, 3H), 0.94–0.96 (d, *J* = 6.8 Hz, 6H), 1.52–1.61 (m, 4H), 1.94–2.01 (m, 2H), 2.04 (s, 3H), 2.17–2.26 (octet, *J* = 6.6 Hz, 1H),

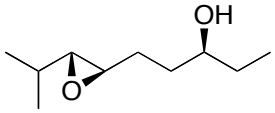
4.78–4.84 (dddd, J = 7.0, 7.0, 5.4, 5.4 Hz, 1H), 5.28–5.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 21.4, 22.8, 27.1, 28.6, 31.2, 33.7, 75.2, 126.2, 138.4, 171.1; IR (thin film NaCl): 2964, 2870, 1740, 1464, 1372, 1244, 1109, 1084, 1019, 969 cm^{-1}; $[\alpha]_D^{23}$ = –6.4 (c = 0.076, $CHCl_3$); HR-MS (ESI) Calcd for $C_{12}H_{22}O_2$ $(M+Na)^+$ 221.1512, found 221.1529. Enantiomeric excess (99%) was established by chiral GC (β-Ph column, H_2 flow 1 mL/min, isothermal 95 °C) t_R[(*R*)-**45**] = 47.1 min, t_R[(*S*)-**48**] = 48.9 min.



49

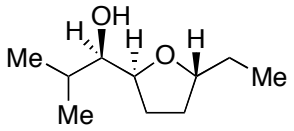
(*S*)-1-((2*R*,3*R*)-3-isopropyloxiran-2-yl)pentan-3-yl acetate (49): To a solution of olefin **45** (437 mg, 2.2 mmol) in 1:2 CH_3CN:DMM (71 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (47 mL), and *n*-$BuNHSO_4$ (747 mg, 2.2 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (568 mg, 2.2 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (20 mL) and a solution of Oxone® (2.70 g, 4.4 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (22 mL) were added simultaneously over 20 min via syringe pump. The reaction was stirred at 0 °C for an additional 30 min then diluted with H_2O (100 mL). The aqueous lyaer was extracted with EtOAc (8 x 75 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes to afford epoxide **49** (372 mg, 79%, 9:1 dr by ^{1}H-NMR) as a colorless oil. Product was visualized with CAM stain, R_f = 0.32 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84–0.88 (t, J = 7.5 Hz, 3H), 0.91–0.93 (d, J = 6.8 Hz, 3H), 0.96–0.98 (d, J = 6.7 Hz, 3H), 1.43–1.66 (m, 7H), 2.01 (s, 3H), 2.41–2.44 (dd, J = 7.0, 2.0

Hz, 1H), 2.68–2.71 (td, J = 5.6, 2.0 Hz, 1H), 4.80–4.86 (pentet, J = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.7, 18.5, 19.2, 21.3, 27.2, 28.1, 30.0, 30.6, 57.3, 64.4, 74.8, 171.0; IR (thin film NaCl): 2965, 2875, 1737, 1463, 1372, 1244, 1116, 1022, 952, 894, 779 cm^{-1}; $[\alpha]_D^{23}$ = 3.2 (c = 0.070, $CHCl_3$); HR-MS (ESI) Calcd for $C_{12}H_{22}O_3$ $(M+Na)^+$ 237.1461, found 237.1464.



41

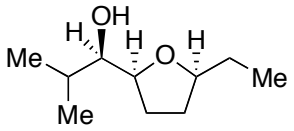
(*S*)-1-((2*R*,3*R*)-3-isopropyloxiran-2-yl)pentan-3-ol (41): To a solution of acetate **49** (311 mg, 1.45 mmol) in THF (30 mL), MeOH (13 mL), and H_2O (8.7 mL) at 0 °C was added lithium hydroxide (104 mg, 4.35 mmol). The reaction was stirred at 0 °C for 2 h and then the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 10% to 20% EtOAc in hexanes to afford **41** as a colorless oil (204 mg, 82%). Product was visualized with CAM stain, R_f = 0.23 (30% EtOAc in hexanes; ^{1}H NMR (400 MHz, C_6D_6) δ: 0.79–0.81 (d, J = 6.9 Hz, 3H), 0.90–0.92 (t, J = 7.5 Hz, 3H), 0.93–0.95 (d, J = 6.7 Hz, 3H), 1.32–1.40 (m, 3H), 1.41–1.47 (m, 2H), 1.53–1.58 (m, 2H), 2.29 (br s, 1H), 2.33–2.35 (dd, J = 6.9, 2.2 Hz, 1H), 2.57–2.60 (td, J = 5.6, 2.2 Hz, 1H), 3.37–3.40 (pentet, J = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ: 10.6, 18.8, 19.5, 29.4, 31.1, 31.2, 34.0, 57.9, 64.7, 72.9; IR (thin film NaCl): 3422, 2962, 1463, 1384, 1366, 1282, 1253, 1199, 1122, 1025, 935, 892 cm^{-1}; $[\alpha]_D^{23}$ = 37.8 (c = 0.043, $CHCl_3$); HR-MS (ESI) Calcd for $C_{10}H_{20}O_2$ $(M+Na)^+$ 195.1356, found 195.1364.



51

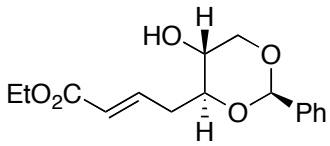
(*R*)-1-((2*S*,5*R*)-5-ethyltetrahydrofuran-2-yl)-2-methylpropan-1-ol (51):

Representative Procedure: To a mixture of epoxy alcohol **39** (10 mg, 0.058 mmol) in MeOH (0.50 mL) was added NaOH (16 mg, 0.41 mmol). The reaction was heated to 60 °C for 12 h, then cooled to ambient temperature. The reaction was diluted with Et_2O (5 mL) and washed with sat. NH_4Cl (3 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexanes to afford **51** (8.5 mg, 85%) as a colorless oil. Product was visualized with CAM stain, R_f = 0.31 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88–0.89 (d, *J* = 6.8 Hz, 3H), 0.90–0.94 (t, *J* = 7.4 Hz, 3H), 1.02–1.03 (d, *J* = 6.6 Hz, 3H), 1.41–1.55 (m, 2H), 1.57–1.69 (m, 2H), 1.82–1.94 (m, 2H), 2.00–2.09 (m, 2H), 3.44–3.47 (dd, *J* = 8.2, 3.6 Hz, 1H), 3.87–3.94 (dddd, *J* = 12.4, 8.5, 6.3, 6.3 Hz, 1H), 4.02–4.07 (ddd, *J* = 9.8, 6.3, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 19.0, 19.5, 25.1, 29.1, 30.7, 32.1, 77.2, 80.0, 81.5; IR (thin film NaCl): 3450, 2962, 2876, 1465, 1383, 1365, 1300, 1247, 1180, 1082, 1035, 981, 939, 880 cm^{-1}; $[\alpha]_D^{23}$ = –20.0 (*c* = 0.006, $CHCl_3$); HR-MS (ESI) Calcd for $C_{10}H_{20}O_2$ $(M+Na)^+$ 195.1356, found 195.1362.



42

(*R*)-1-((2*S*,5*S*)-5-ethyltetrahydrofuran-2-yl)-2-methylpropan-1-ol (42): Product was visualized with CAM stain, R_f = 0.32 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.82–0.84 (d, *J* = 6.8 Hz, 3H), 0.86–0.90 (t, *J* = 7.5 Hz, 3H), 0.96–0.98 (d, *J* = 6.6 Hz, 3H), 1.38–1.49 (m, 2H), 1.51–1.64 (m, 2H), 1.66–1.96 (m, 3H), 2.34 (br s, 1H), 3.37–3.40 (dd, *J* = 8.1, 3.6 Hz, 1H), 3.70–3.77 (dddd, *J* = 7.1, 6.5, 6.6, 6.5 Hz, 1H), 3.88–3.93 (td, *J* = 7.5, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.5, 18.8, 19.3, 23.9, 28.7, 30.7, 31.0, 76.7, 80.4, 80.8; IR (thin film NaCl): 3459, 2962, 2877, 1465, 1383, 1366, 1299, 1247, 1178, 1080, 1035, 948, 877 cm^{-1}; $[\alpha]_D^{23}$ = –10.4 (*c* = 0.018, $CHCl_3$); HR-MS (ESI) Calcd for $C_{10}H_{20}O_2$ $(M+Na)^+$ 195.1356, found 195.1353.

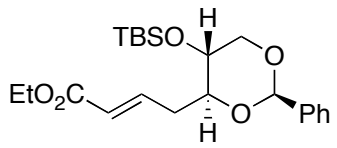


56

(*E*)-ethyl 4-((2*R*,4*S*,5*R*)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (56): To a slurry of 2-deoxyribose (92 g, 684 mmol) in THF (1.3 L) was added (carbethoxymethylene) triphenyphosphorane (262 g, 752 mmol). The mixture was refluxed for 3 h, cooled to room temperature, and concentrated *in vacuo*. The crude oil was used without purification.[3]

[3] If desired, the product can be purified by column chromatography (gradient: 3% to 10% MeOH in CH_2Cl_2) to afford the corresponding triol (27.3 g, 98%, 83:17 E:Z) as a colorless oil.

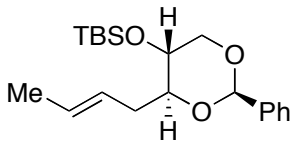
The oil was dissolved in CH_2Cl_2 (700 mL) followed by addition of camphorsulfonic acid (CSA) (48 g, 205 mmol), and benzaldehyde dimethyl acetal (185 mL, 1230 mmol). The reaction was stirred at ambient temperature for 12 h, then quenched by addition of Et_3N (29 mL). The reaction was concentrated *in vacuo* and the crude material was purified by column chromatography (gradient: 20 to 30% EtOAc in hexanes to afford alcohol **56** as a colorless oil (152 g, 76%); Product was visualized with CAM stain, R_f = 0.29 (50% EtOAc in hexanes; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.29–1.32 (t, *J* = 7.1 Hz, 3H), 2.53–2.58 (ddd, *J* = 15.2, 7.6, 7.6 1.3 Hz, 1H), 2.76–2.77 (d, *J* = 5.4 Hz, 1H), 2.78–2.83 (dddd, *J* = 15.2, 6.9, 3.3, 1.5 Hz, 1H), 3.55–3.63 (m, 2H), 3.67–3.70 (td, *J* = 8.6, 3.3 Hz, 1H), 4.18–4.24 (m, 3H), 5.48 (s, 1H), 5.95–5.98 (d, *J* = 15.7 Hz, 1H), 7.07–7.12 (dt, *J* = 15.7, 7.2 Hz, 1H), 7.35–7.40 (m, 3H), 7.48–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 34.7, 60.7, 65.3, 71.4, 80.6, 101.1, 123.9, 126.3, 128.4, 129.2, 137.6, 144.9, 166.9; IR (thin film NaCl): 3473, 3067, 3036, 2981, 2932, 2906, 2864, 1710, 1655, 1453, 1370, 1316, 1215, 1078, 979, 750, 698 cm^{-1}; $[\alpha]_D^{23}$ = –47.5 (*c* = 0.024, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_5$ $(M+Na)^+$ 315.1203, found 315.1203.



57

(*E*)-ethyl-4-((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)but-2-enoate (7): To a solution of alcohol **56** (152 g, 520 mmol) in DMF (520 mL) at 0 °C was added imidazole (62 g, 1040 mmol), and TBSCl (118 g, 780 mmol). The reaction was warmed to ambient temperature, stirred for 5 h and was then quenched by addition of sat. NH_4Cl (500 mL).

The aqueous layer was extracted with EtOAc (4 x 500 mL), the combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The oil was purified by column chromatography (gradient: 5% to 20% EtOAc in hexanes to afford silyl ether **57** as a colorless oil (151 g, 71%); Product was visualized with CAM stain, R_f = 0.15 (5% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.27–1.31 (t, *J* = 7.1 Hz, 3H), 2.43–2.51, (app dtd, *J* = 15.4, 8.5, 1.4 Hz, 1H), 2.73–2.80 (dddd, *J* = 15.2, 6.8, 2.8, 1.7 Hz, 1H), 3.56–3.64 (m, 2H), 3.67–3.72 (td, *J* = 8.3, 3.0 Hz, 1H), 4.17–4.22 (m, 3H), 5.49 (s, 1H), 5.93–5.98 (d, *J* = 15.7 Hz, 1H), 7.05–7.13 (dt, *J* = 15.7, 7.1 Hz, 1H), 7.33–7.39 (m, 3H), 7.47–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.0, 14.4, 18.0, 25.8, 34.6, 60.3, 66.4, 71.8, 81.1, 101.0, 123.8, 126.2, 128.3, 129.0, 137.8, 144.8, 166.5; IR (thin film NaCl): 3037, 2956, 2930, 2887, 2858, 1721, 1657, 1463, 1389, 1312, 1261, 1177, 1108, 1029, 838, 778, 698 cm^{-1}; $[\alpha]_D^{23}$ = –50.3 (*c* = 0.058, $CHCl_3$); HR-MS (ESI) Calcd for $C_{22}H_{34}O_5Si$ $(M+Na)^+$ 429.2068, found 429.2067.



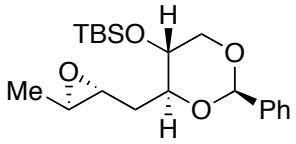
58

((2*R*,3*R*)-3-(((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl) oxiran-2-yl)methanol (58): Ester **57** (50 g, 123 mmol) was dissolved in CH_2Cl_2 (410 mL) and cooled to –78 °C. A solution of DIBALH (310 mL of 1M in CH_2Cl_2, 307 mmol) was added via addition funnel over 20 min and stirred at –78 °C an additional 30 min. The reaction was quenched at –78 °C by dropwise addition of MeOH (50 mL) and then poured into sat. Rochelle's salt (600 mL) at ambient temperature followed by vigorous stirring for 12 h. The aqueous layer

was extracted with CH_2Cl_2 (3 x 1L), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford allylic alcohol **68** which was used without further purification.

Allylic alcohol **68** (4.7 g, 13.0 mmol) was dissolved in CH_2Cl_2 (65 mL) and Et_3N (2.2 mL, 15.7 mmol) and cooled to 0 °C. To this solution was added methanesulfonyl chloride dropwise (1.1 mL, 14.4 mmol) and the reaction was stirred at 0 °C for 1h. The reaction was quenched by addition of H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 75 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was used without further purification.

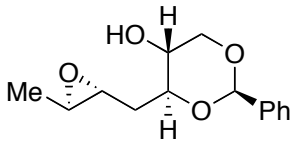
To a solution of the crude allylic mesylate (5.78 g, 13.0 mmol) in THF (130 mL) at 0 °C was added SuperHydride® (1M in THF, 26.1 mL, 26.1 mmol) dropwise. The reaction was stirred at 0 °C for 30 min then quenched slowly with H_2O (50 mL). The aqueous layer was extracted with EtOAc (5 x 75 mL), the combined organic extracts dried with $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes to afford **58** as a colorless oil (3.61 g, 79%). Product was visualized with CAM stain, R_f = 0.65 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.13 (s, 3H), 0.93 (s, 9H), 1.71–1.72 (d, J = 5.4 Hz, 3H), 2.22–2.32 (ddd, J = 13.5, 7.2, 5.9 Hz, 1H), 2.55–2.61 (ddd, J = 15.5, 6.0, 2.5 Hz, 1H), 3.56–3.66 (m, 3H), 4.18–4.21 (m, 1H), 5.50 (s, 1H), 5.55–5.65 (m, 2H), 7.33–7.41 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –3.9, 18.1, 18.2, 25.9, 34.9, 66.3, 71.9, 82.5, 100.9, 126.3, 126.9, 127.7, 128.4, 128.9, 138.3; IR (thin film NaCl): 3034, 2956, 2930, 2857, 2887, 1472, 1462, 1389, 1361, 1291, 1253, 1215, 1107, 1030, 972, 878, 858, 837, 777, 747 cm^{-1}; $[\alpha]_D^{23}$ = –38.0 (c = 0.076, $CHCl_3$); HR-MS (ESI) Calcd for $C_{20}H_{32}O_3Si$ $(M+Na)^+$ 371.2013, found 371.2025.



59

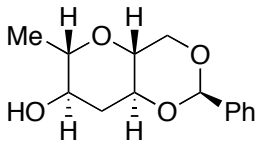
***tert*-butyldimethyl((2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)silane (59)**: To a solution of olefin **58** (500 mg, 1.43 mmol) in 1:2 CH_3CN:DMM (46 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (30 mL), and *n*-$BuNHSO_4$ (485 mg, 1.43 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (369 mg, 1.43 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (12.9 mL) and a solution of Oxone® (1.76 g, 4.4 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (14 mL) were added simultaneously over 20 min via syringe pump. The reaction was stirred at 0 °C an additional 30 min then diluted with H_2O (75 mL). The aqueous layer was extracted with EtOAc (8 x 75 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes to afford epoxide **59** (484 mg, 93%, 9:1 dr by ^{1}H-NMR) as a colorless oil. Product was visualized with CAM stain, R_f = 0.31 (10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.32–1.33 (d, *J* = 5.2 Hz, 3H), 1.95–1.98 (t, *J* = 5.2 Hz, 2H), 2.80–2.84 (qd, *J* = 5.2, 2.3 Hz, 1H), 2.93–2.96 (td, *J* = 5.6, 2.3 Hz, 1H), 3.55–3.60 (m, 1H), 3.66–3.71 (m, 2H), 4.18–4.22 (dd, *J* = 10.7, 4.4 Hz, 1H), 5.22 (s, 1H), 7.35–7.41 (m, 3H), 7.48–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.0, 17.9, 18.1, 25.9, 34.1, 54.3, 56.7, 66.2, 72.1, 80.4, 101.0, 126.2, 128.5, 129.1, 138.0; IR (thin film NaCl): 3067, 2956, 2929, 2886, 2857, 1472, 1462, 1383, 1361, 1295, 1253, 1216, 1105, 1029, 1006, 978, 939, 914, 880, 857, 838, 778,

751, 698 cm^{-1}; $[\alpha]_D^{23}$ = –45.3 (*c* = 0.013, $CHCl_3$). HR-MS (ESI) Calcd for $C_{20}H_{32}O_4Si$ $(M+Na)^+$ 387.1962, found 387.1967.



53

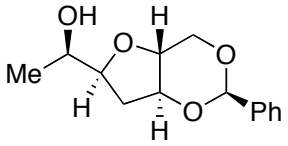
(2R,4S,5R)-4-(((2R,3R)-3-methyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-ol(53): Silyl ether **53** (438 mg, 1.20 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. A solution of TBAF (1.4 mL of 1M in THF, 1.40 mmol) was added dropwise and the reaction was stirred at 0 °C for 30 min. The reaction was quenched by addition of brine (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (gradient: 20% to 50% EtOAc in hexanes to afford epoxy alcohol **53** (285 mg, 95%) as a white solid; Product was visualized with CAM stain, R_f = 0.25 (50% EtOAc in hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.33–1.34 (d, *J* = 5.2 Hz, 3H), 1.85–1.92 (ddd, *J* = 15.2, 7.4, 5.1 Hz, 1H), 2.20–2.26 (dt, *J* = 15.2, 3.5 Hz, 1H), 2.87–2.93 (qd, *J* = 5.2, 2.5 Hz, 1H), 3.01–3.04 (dt, *J* = 7.5, 2.7 Hz, 1H), 3.12–3.13 (d, *J* = 5.0 Hz, 1H), 3.56–3.62 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.69–3.74 (ddd, *J* = 9.0, 5.0, 4.0 Hz, 1H), 3.80–3.86 (ddd, *J* = 10.0, 5.0, 4.6 Hz, 1H), 4.27–4.31 (dd, *J* = 10.7, 5.1 Hz, 1H), 5.50 (s, 1H), 7.35–7.41 (m, 3H), 7.49–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 34.2, 54.6, 56.6, 65.0, 71.3, 79.8, 101.3, 126.3, 128.5, 129.2, 137.8; IR (KBr pellet): 2428, 2968, 2925, 2857, 1454, 1383, 1294, 1216, 1075, 1027, 916, 856, 800, 754, 699 cm^{-1}; $[\alpha]_D^{23}$ = 4.1 (*c* = 0.036, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{18}O_4$ $(M+Na)^+$ 273.1097, found 273.1101.



54

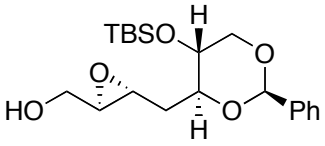
(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-methyl-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (54):

Representative Procedure: To a mixture of epoxy alcohol **54** (50 mg, 0.20 mmol) in MeOH (5 mL) was added Cs_2CO_3 (1.3 g, 4 mmol). The reaction was heated to 50 °C for 12 h, then cooled to ambient temperature. The reaction was diluted with Et_2O (50 mL) and washed with sat. NH_4Cl (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc in hexanes to afford **54** (30 mg, 60%) as a white solid. Product was visualized with CAM stain, R_f = 0.34 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.25–1.27 (d, *J* = 5.9 Hz, 3H), 1.55–1.64 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.99–2.00 (d, *J* = 5.5 Hz, 1H), 2.36–2.41 (dt, *J* = 11.3, 4.4 Hz, 1H), 3.25–3.36 (m, 3H), 3.49–3.56 (ddd, *J* = 11.6, 9.0, 4.2 Hz, 1H), 3.62–3.67 (dd, *J* = 10.3, 10.3 Hz, 1H), 4.24–4.27 (dd, *J* = 10.4, 4.9 Hz, 1H), 5.51 (s, 1H), 7.35–7.40 (m, 3H), 7.45–7.48 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 18.2, 38.7, 69.9, 71.8, 73.6, 77.3, 79.2, 102.0, 126.7, 128.7, 129.5, 138.4; IR (KBr pellet): 3403, 2909, 2876, 1457, 1382, 1331, 1294, 1235, 1168, 1099, 1065, 1029, 1016, 946, 959, 903, 753 cm^{-1}; $[\alpha]_D^{23}$ = –13.2 (*c* = 0.015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{18}O_4$ $(M+Na)^+$ 273.1097, found 273.1103.



55

Product was visualized with CAM stain, R_f = 0.24 (50% EtOAc in hexanes; ^{1}H NMR (400 MHz, CD_3OD) δ: 1.03–1.04 (d, *J* = 6.4 Hz, 3H), 1.90–1.98 (td, *J* = 11.2, 9.1 Hz, 1H), 2.14–2.20 (dt, *J* = 12.8, 6.4 Hz, 1H), 3.37–3.43 (ddd, *J* = 10.2, 9.0, 4.4 Hz, 1H), 3.62–3.69 (ddd, *J* = 11.3, 9.0, 6.5 Hz, 1H), 3.69–3.73 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.76–3.79 (m, 1H), 3.87–3.92 (ddd, *J* = 9.1, 6.4, 4.8 Hz, 1H), 4.28–4.31 (dd, *J* = 9.6, 4.4 Hz, 1H), 5.47 (s, 1H), 7.22–7.24 (m, 3H), 7.34–7.37 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ: 19.3, 31.1, 70.5, 72.7, 74.6, 82.4, 83.0, 103.5, 127.7, 129.3, 130.1, 139.2; IR (KBr pellet): 3405, 2914, 2880, 1726, 1465, 1459, 1395, 1355, 1235, 1169, 1123, 1066, 1029, 1020, 1184, 1070, 1045, 918, 660, 430 cm^{-1}; HR-MS (ESI) Calcd for $C_{14}H_{18}O_4$ $(M+Na)^+$ 273.1097, found 273.1108.



69

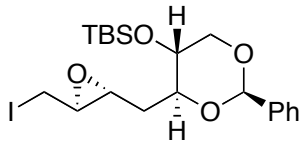
((2*R*,3*R*)-3-(((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl) oxiran-2-yl)methanol (69): Ester **7** (50 g, 123 mmol) was dissolved in CH_2Cl_2 (410 mL) and cooled to –78 °C. A solution of DIBALH (310 mL of 1M in CH_2Cl_2, 307 mmol) was added via addition funnel over 20 min and stirred at –78 °C an additional 30 min. The reaction was quenched at –78 °C by dropwise addition of MeOH (50 mL) and then poured into sat. Rochelle's

salt (600 mL) at ambient temperature followed by vigorous stirring for 12 h. The mixture was extracted with CH_2Cl_2 (3 x 1L), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford allylic alcohol **68** which was used in the subsequent epoxidation without purification.

In a 1L round bottom flask, 4Å molecular sieves (25 g) were flame dried *in vacuo* for 8 min then cooled to ambient temperature. A magnetic stir bar, CH_2Cl_2 (300 mL), and (–)-diethyl (D)-tartrate (3 g, 15 mmol) were then added and the slurry was cooled to –25 °C. Next, $Ti(O\textit{i}Pr)_4$ (3.7 mL, 12.3 mmol) was added followed by slow addition of a *t*-BuOOH solution (45 mL of 5.5M in decane, 246 mmol). The mixture was allowed to stir at –25 °C for 30 minutes followed by addition of a solution of the allylic alcohol (above) in CH_2Cl_2 (50 mL). The reaction was stirred at –25 °C for an additional 15 h and warmed to 0 °C. In a separate flask, iron(II) sulfate heptahydrate (41g), tartaric acid (12.3 g), and H_2O (430 mL) were cooled to 0 °C. The crude epoxidation reaction was slowly poured into the aqueous solution, stirred at ambient temperature for 15 min. The aqueous layer was extracted with Et_2O (4 x 600 mL). To the combined organic extracts was added 300 mL 30% NaOH in brine[4] and the mixture was stirred at ambient temperature for 1 h. The organic layer was separated, dried over $MgSO_4$, and purified by column chromatography (30% EtOAc in hexanes) affording epoxy alcohol **69** as a colorless oil (44 g, 95%); Product was visualized with CAM stain, R_f = 0.42 (30% EtOAc in hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.84–1.88 (dd, *J* = 7.2, 5.7 Hz, 1H), 1.97–2.08 (m, 2H), 2.97–3.00 (dt, *J* = 4.4, 2.3, 1H), 3.22–3.26 (td, *J* = 5.5, 2.3, 1H), 3.56–3.73 (m, 4H), 3.90–3.94 (ddd, *J* = 12.6, 5.7, 2.6 Hz, 1H), 4.20–4.23 (m, 1H), 5.52 (s, 1H), 7.34–7.40 (m, 3H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.0, 18.0, 25.9, 33.5, 53.1,

[3] 300 mL of 30% NaOH in brine was prepared by combining 15 g NaCl, 90 g NaOH, and 270 mL H_2O.

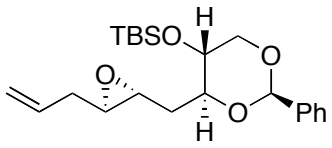
58.0, 61.9, 66.0, 72.0, 80.2, 101.0, 126.2, 128.5, 129.1, 137.9; IR (thin film NaCl): 3443, 2955, 2929, 2885, 2857, 1462, 1388, 1253, 1107, 1029, 857, 838, 778, 698 cm^{-1}; $[\alpha]_D^{23}$ = –38.6 (*c* = 0.03, $CHCl_3$); HR-MS (ESI) Calcd for $C_{20}H_{32}O_5Si$ $(M+Na)^+$ 403.1911, found 403.1908.



70

***tert*-butyl((2*R*,4*S*,5*R*)-4-(((2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)dimethylsilane (70)**: Triphenylphosphine (PPh_3) (18.2 g, 70 mmol) and imidazole (4.7 g, 70 mmol) were dissolved in Et_2O (180 mL) and CH_3CN (120 mL) and cooled to 0 °C. With vigorous stirring, iodine (17.6 g, 70 mmol) was added in portions over 10 min then the reaction was warmed to ambient temperature and stirred for 15 min. The slurry was then cooled to 0 °C and a solution of epoxy alcohol **69** (23 g, 60 mmol) in Et_2O (36 mL) was added dropwise over 10 min. The reaction was warmed to ambient temperature and stirred for 15 min. The reaction was quenched by addition of sat. $Na_2S_2O_3$ (400 mL) and extracted with Et_2O (3 x 400 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was dissolved in a minimal amount of CH_2Cl_2 and loaded onto silica gel for purification by column chromatography (5% EtOAc in hexanes) to afford iodide **70** as a yellow oil (24.6 g, 83%); Product was visualized with CAM stain, R_f = 0.61 (20% EtOAc in hexanes; ^1H NMR (600 MHz, $CDCl_3$) δ: 0.11 (s, 6H), 0.90 (s, 9H), 1.93–1.96 (ddd, *J* = 14.3, 6.1, 3.0 Hz, 1H), 2.01–2.06 (ddd, *J* = 14.3, 8.2, 5.1 Hz, 1H), 3.01–3.04 (dd, *J* = 9.8, 7.3 Hz, 1H), 3.08–3.13 (m, 2H), 3.29–3.32 (dd, *J* = 9.9, 5.5 Hz, 1H), 3.58–3.62 (app t, *J* = 10.6 Hz, 1H), 3.66–3.70 (td, *J* = 9.8, 4.9 Hz, 1H), 3.74–3.77 (td, *J* = 8.7, 3.1 Hz, 1H), 4.20–4.23 (dd, *J* = 10.6, 4.9 Hz, 1H), 5.54

(s, 1H), 7.35–7.41 (m, 3H), 7.52–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.1, 5.1, 18.0, 25.9, 33.8, 57.9, 59.6, 66.2, 71.9, 80.3, 101.0, 126.2, 128.4, 129.1, 137.8; IR (thin film NaCl): 2955, 2928, 2885, 2856, 1462, 1387, 1253, 1111, 1029, 838, 778, 698 cm^{-1}; $[\alpha]_D^{23}$ = –36.8 (*c* = 0.25, $CHCl_3$); HR-MS (ESI) Calcd for $C_{20}H_{31}O_4ISi$ $(M+Na)^+$ 513.0929, found 513.0916.

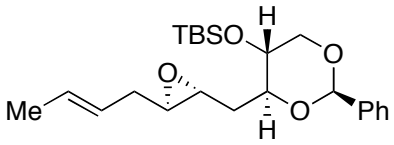


71

((2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-allyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)(*tert*-butyl) dimethylsilane (71): To a solution of iodide **70** (3.0 g, 6.1 mmol) in THF (30 mL) was added copper(I) bromide-dimethyl sulfide (430 mg, 2.1 mmol), and HMPA (4 mL, 25 mmol). The solution was immediately cooled to –25 °C and stirred for 5 min. Then a solution of vinyl magnesium bromide (15.3 mL of 1M in THF, 15.3 mmol) was added dropwise over 5 min with vigorous stirring. The reaction was stirred at –25 °C for 15 min, then quenched at –25 °C by addition of sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (5% EtOAc in hexanes to afford olefin **71** (1.79 g, 75%) as a colorless oil;[5] Product was visualized with CAM stain, R_f = 0.20 (5% EtOAc in hexanes; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.94–2.03 (m, 2H), 2.26–2.31 (m, 1H), 2.36–2.41 (m, 1H), 2.82–2.84 (td, *J* = 5.6, 2.2 Hz, 1H), 3.02–3.04 (td, *J*

[4] Attempts to scale this reaction beyond 6.1 mmol of iodide **70** led to a precipitous drop in yield.

= 5.6, 2.2 Hz, 1H), 3.57–3.61 (m, 1H), 3.67–3.73 (m, 2H), 4.19–4.22 (dd, *J* = 10.7, 4.5 Hz, 1H), 5.09–5.11 (dd, *J* = 10.3, 1.4 Hz, 1H), 5.15–5.18 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.51 (s, 1H), 5.81–5.88 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 1H), 7.35–7.40 (m, 3H), 7.49–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.1, 18.0, 25.9, 34.0, 36.4, 55.4, 57.2, 66.2, 72.0, 80.4, 101.0, 117.6, 126.2, 128.4, 129.1, 133.5, 138.0; IR (thin film NaCl): 3070, 2956, 2929, 2886, 2857, 1462, 1387, 1253, 1110, 1029, 857, 838, 778, 698 cm^{-1}; $[\alpha]_D^{23}$ = –43.0 (*c* = 0.1, $CHCl_3$); HR-MS (ESI) Calcd for $C_{22}H_{34}O_4Si$ $(M+Na)^+$ 413.2119, found 413.2116.

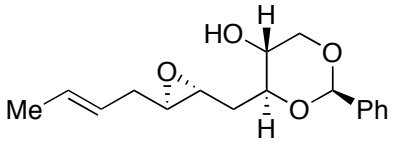


72

((2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-((*E*)-but-2-enyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)(*tert*-butyl)dimethylsilane (72): Approximately 4 mL of *cis*-2-butene (approx 1 mol) was condensed into a round bottom flask at –78 °C. In a separate flask olefin **71** (2.0 g, 5.12 mmol) was dissolved in CH_2Cl_2 (40 mL) and the solution was cooled to –78 °C. *Cis*-2-butene was added to the olefin solution via cannula transfer followed by addition of the 2nd generation Hoveyda-Grubbs catalyst **74** (160 mg, 0.25 mmol). The reaction was warmed to –20 °C and stirred at this temperature for 2 h. The reaction was quenched by stirring with ethyl vinyl ether (10 mL) at –20 °C for 10 min. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (5% EtOAc in hexanes) to afford **72** (1.81 g, 88%, *E*:*Z* 3:1 by ^{1}H-NMR). Up to 10:1 *E*:*Z* enrichment can be obtained by a second column with $AgNO_3$ impregnated silica.[6]

[6] Standard Procedure for $AgNO_3$ column: $AgNO_3$ (0.05g/g SiO_2) was dissolved in a minimal amount of H_2O. This

Product was visualized with CAM stain, R_f = 0.19 (5% EtOAc in hexanes; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.66–1.67 (d, *J* = 6.4 Hz, 3H), 1.94–2.02 (m, 2H), 2.18–2.22 (dt, *J* = 14.8, 8.1 Hz, 1H), 2.29–2.33 (dt, *J* = 14.8, 5.7 Hz, 1H), 2.78–2.80 (td, *J* = 5.6, 2.1 Hz, 1H), 2.99–3.01 (td, *J* = 5.6, 1.4 Hz, 1H), 3.56–3.60 (m, 1H), 3.68–3.70 (m, 2H), 4.19–4.22 (dd, *J* = 10.8, 3.7 Hz, 1H), 5.44–5.47 (dt, *J* = 13.6, 6.6 Hz, 1H), 5.51 (s, 1H), 5.54–5.59 (dq, *J* = 13.9, 6.4 Hz, 1H), 7.34–7.39 (m, 3H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.0, 18.1, 18.3, 25.9, 34.1, 35.4, 55.5, 57.8, 66.2, 72.1, 80.4, 101.0, 125.8, 126.2, 128.3, 128.5, 129.1, 138.0; IR (thin film NaCl): 3067, 2929, 2709, 1462, 1387, 1296, 1253, 1216, 1108, 1029, 969, 940, 838, 778, 697, 677 cm^{-1}; $[\alpha]_D^{23}$ = –49.4 (*c* = 0.063, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{36}O_4Si$ $(M+H)^+$ 427.2275, found 427.2283.

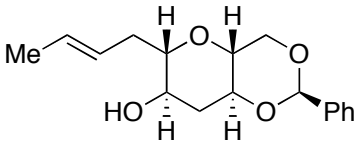


61

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-((*E*)-but-2-enyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-ol (61): Silyl ether **61** (787 mg, 1.94 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. A solution of TBAF (2.9 mL of 1M in THF, 2.9 mmol) was added dropwise and the reaction was stirred at ambient temperature for 30 min. The reaction was quenched by addition of brine (10 mL) then the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (gradient: 30% to 40% EtOAc in hexanes) to afford epoxy alcohol **61** (483 mg,

aqueous solution was added to a slurry of the SiO_2 in acetonitrile. The column was wet-loaded with the slurry and flushed with Et_2O, then hexanes, and finally the desired solvent system.

86%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.05 (20% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.67–1.69 (dd, *J* = 6.3, 1.3 Hz, 3H), 1.86–1.94 (ddd, *J* = 15.2, 7.5, 5.2 Hz, 1H), 2.24–2.29 (m, 3H), 2.73–2.74 (d, *J* = 5.0 Hz, 1H), 2.84–2.88 (td, *J* = 5.5, 2.4 Hz, 1H), 3.08–3.11 (dt, *J* = 7.5, 2.8 Hz, 1H), 3.59–3.64 (dd, *J* = 10.5, 10.5 Hz, 1H), 3.71–3.76 (ddd, *J* = 9.1, 5.0, 3.9 Hz, 1H), 3.87–3.94 (app septet, *J* = 4.9 Hz, 1H), 4.30–4.33 (dd, *J* = 10.7, 5.1 Hz, 1H), 5.40–5.47 (dt, *J* = 15.0, 6.6 Hz, 1H), 5.51 (s, 1H), 5.54–5.62 (dq, *J* = 15.3, 6.3 Hz, 1H), 7.36–7.41 (m, 3H), 7.49–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.3, 34.4, 35.2, 55.3, 57.9, 65.2, 71.3, 80.0, 101.4, 125.4, 126.3, 128.5, 128.6, 129.2, 137.9; IR (thin film NaCl): 3436, 2970, 2918, 2855, 1454, 1377, 1309, 1216, 1075, 1028, 970, 915, 753, 699 cm^{-1}; $[\alpha]_D^{23}$ = –17.5 (*c* = 0.021, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{22}O_4$ $(M+Na)^+$ 313.1410, found 313.1416.

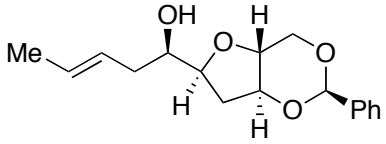


62

(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-((*E*)-but-2-enyl)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (62):

Representative Procedure: To a mixture of epoxy alcohol **61** (50 mg, 0.20 mmol) in MeOH (5 mL) was added Cs_2CO_3 (1.3 g, 4 mmol). The reaction was heated to 50 °C for 12 h, then cooled to ambient temperature. The reaction was diluted with Et_2O (50 mL) and washed with sat. NH_4Cl (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc in hexanes) to afford **62**

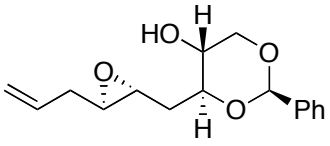
(28 mg, 56%) as a white solid. Product was visualized with CAM stain, R_f = 0.60 (50% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.63–1.70 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.70–1.72 (d, *J* = 5.0 Hz, 3H), 1.89–1.90 (d, *J* = 5.2 Hz, 1H), 2.24–2.31 (dt, *J* = 12.3, 5.5 Hz, 1H), 2.43–2.53 (m, 2H), 3.21–3.26 (ddd, *J* = 9.2, 6.8, 4.3 Hz, 1H), 3.32–3.38 (ddd, *J* = 10.1, 9.2, 4.9 Hz, 1H), 3.51–3.57 (m, 2H), 3.58–3.72 (dd, *J* = 10.3, 10.3 Hz, 1H), 4.31–4.35 (dd, *J* = 10.5, 4.9 Hz, 1H), 5.51–5.64 (m, 3H), 7.34–7.41 (m, 3H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.2, 35.5, 38.1, 69.5, 69.6, 73.2, 76.8, 82.0, 101.8, 126.3, 126.9, 128.1, 128.5, 129.3, 137.5; IR (KBr pellet): 3503, 2069, 3044, 3025, 2982, 2943, 2876, 1455, 1408, 1391, 1339, 1317, 1281, 1216, 1186, 1140, 1091, 1025, 1000, 964, 919, 887, 857, 765 cm^{-1}; $[\alpha]_D^{23}$ = –17.1 (*c* = 0.021, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{22}O_4$ $(M+Na)^+$ 313.1410, found 313.1410.



63

(*R*,*E*)-1-((2*R*,4a*R*,6*S*,7a*S*)-2-phenyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)pent-3-en-1-ol (63): Cyclization in Cs_2CO_3 and MeOH (vide supra) afforded **63** (11 mg, 22%). Product was visualized with CAM stain, R_f = 0.50 (50% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.70–1.72 (dd, *J* = 6.3, 1.1 Hz, 3H), 1.96 (br s, 1H), 2.11–2.31 (m, 4H), 3.58–3.64 (ddd, *J* = 10.0, 9.0, 4.3 Hz, 1H), 3.72–3.76 (ddd, *J* = 11.3, 9.0, 6.5 Hz, 1H), 3.82–3.87 (m, 2H), 4.10–4.15 (ddd, *J* = 9.2, 6.3, 4.6 Hz, 1H), 4.51–4.55 (dd, *J* = 9.6, 4.3 Hz, 1H), 5.41–5.49 (dt, *J* = 15.6, 7.5 Hz, 1H), 5.53 (s, 1H), 5.56–5.65 (dq, *J* = 15.4, 6.3 Hz, 1H), 7.36–7.41 (m, 3H), 7.49–7.53 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 18.3, 30.1, 36.8, 72.2, 73.2, 73.8, 80.6, 81.5, 102.6, 126.8, 127.1, 128.7, 129.4, 129.5, 138.2; IR (KBr pellet): 3422, 2984, 2894, 1371, 1342, 1292, 1247,

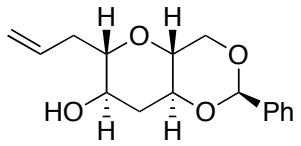
1222, 1182, 1131, 1084, 1046, 1029, 1007, 987, 969, 956, 921, 744 cm^{-1}; $[\alpha]_D^{23}$ = –11.3 (*c* = 0.006, $CHCl_3$). HR-MS (ESI) Calcd for $C_{17}H_{22}O_4$ $(M+Na)^+$ 313.1410, found 313.1396.



75

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-allyloxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-ol (75): Silyl ether **71** (14 g, 36 mmol) was dissolved in THF (180 mL) and cooled to 0 °C. A solution of TBAF (54 mL of 1M in THF, 54 mmol) was added dropwise and the reaction stirred at 0 °C for 30 min. The reaction was quenched by addition of brine (300 mL) and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (40% EtOAc in hexanes) to afford epoxy alcohol **75** (9.2 g, 93%) as a white solid; Product was visualized with CAM stain, R_f = 0.43 (50% EtOAc in hexanes; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.88–1.93 (ddd, *J* = 15.2, 7.6, 5.2 Hz, 1H), 2.26–2.29 (dt, *J* = 15.2, 3.5 Hz, 1H), 2.34–2.36 (app dd, *J* = 6.5, 5.7 Hz, 2H), 2.56–2.57 (d, *J* = 5.0 Hz, 1H), 2.89–2.91 (td, *J* = 5.5, 2.3 Hz, 1H), 3.10–3.12 (m, 1H), 3.61–3.64 (t, *J* = 10.7, 1H), 3.73–3.76 (m, *J* = 1H), 3.89–3.94 (app sp, *J* = 4.8 Hz, 1H), 4.31–4.34 (dd, *J* = 10.7, 4.8 Hz, 1H), 5.11–5.13 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.15–5.18 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.51 (s, 1H), 5.80–5.87 (ddt, *J* = 17.2, 10.3, 6.8 Hz, 1H), 7.36–7.40 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.3, 36.2, 55.2, 57.4, 65.1, 71.2, 78.0, 101.4, 117.9, 126.3, 128.5, 129.2, 133.1, 137.8; IR (KBr pellet): 3309, 2983, 2917, 1460, 1409, 1385, 1220, 1126,

1067, 1013, 975, 917, 766 cm^{-1}; $[\alpha]_D^{23}$ = –0.5 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1253.



76

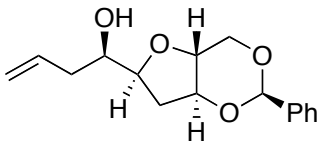
(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-allyl-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-7-ol (76):

Representative microwave procedure:[7,8] Silicic acid (5.25 g, 35 mg/mg **75**) was loaded into a 20 mL microwave vial with magnetic stir bar. The vial was heated in an oven to 140 °C for 12 h then cooled to ambient temperature *in vacuo* (5 torr). Epoxy alcohol **75** (150 mg, 0.54 mmol) was added and the vial was capped quickly with a septum. With the vial attached to an argon inlet, solvent was added (18 mL), the argon inlet was removed, and vial was shaken manually to achieve mixing. The vial was heated in a microwave reactor to 135 °C for 10 min. Once the vial had cooled to ambient temperature the septum was pierced with a needle to release any pressure. The silica promoter was removed by filtration through a glass frit. The silica promoter was then washed with 95:5 Et_2O:MeOH (100 mL). The combined organic solvent was concentrated *in vacuo* and purified by column chromatography (30% EtOAc in hexanes) to afford alcohol **76** (108 mg, 72%) as a white solid. Product was visualized with CAM stain, R_f = 0.53 (50% EtOAc in hexanes; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.66–1.72 (ddd, *J* = 11.4, 11.4, 11.4 Hz, 1H), 1.76 (s,

[7] For cyclizations conducted in a microwave reactor, adventitious moisture resulted in hydrolysis of the benzylidene acetal. Therefore, the silica promoter was dried prior to use. Due to the size of vials accommodated by the microwave, the maximum scale per cyclization was 150 mg (0.54 mmol) of epoxy alcohol **75**. Furthermore, 1,2-dichloroethane (DCE) was used in place of CH_2Cl_2 since high reaction pressures triggered an automatic shutdown of the microwave. Changing solvent to 1,2-DCE had no significant effect on selectivity or yield.

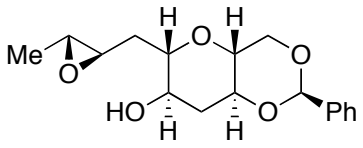
[8] For cyclizations not conducted in a microwave, the promoter was dried and cooled in an analogous fashion in a round bottom flask. The epoxy alcohol was added and a reflux condenser was attached. The reaction was heated to reflux for the desired time. After cooling, the silica was washed in analogy to the microwave conditions.

1H), 2.31–2.36 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.46–2.49 (dt, *J* = 11.4, 4.5 Hz, 1H), 2.57–2.61 (m, 1H), 3.28–3.32 (ddd, *J* = 9.2, 7.1, 4.0, 1H), 3.34–3.38 (td, *J* = 9.9, 4.9, 1H), 3.53–3.59 (m, 2H), 3.68–3.71 (dd, *J* = 10.2, 10.2, 1H), 4.31–4.34 (dd, *J* = 10.5, 4.9 Hz, 1H), 5.11–5.13 (d, *J* = 10.2 Hz, 1H), 5.16–5.19 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.53 (s, 1H), 5.90–5.97 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 7.37–7.39 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.4, 38.2, 69.3, 69.4, 73.1, 76.7, 81.6, 101.7, 117.4, 126.3, 128.5, 129.3, 134.6, 137.4; IR (thin film NaCl): 3419, 2983, 2952, 2872, 1644, 1452, 1366, 1120, 1097, 1008, 924 cm^{-1}; $[\alpha]_D^{23}$ = –19.5 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1261.



77

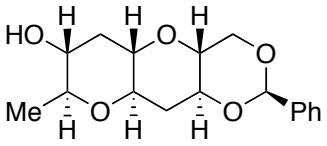
(*R*)-1-((2*R*,4a*R*,6*S*,7a*S*)-2-phenyltetrahydro-4*H*-furo[3,2-*d*][1,3]dioxin-6-yl)but-3-en-1-ol (77): Product was visualized with CAM stain, R_f = 0.51 (50% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.99–2.00 (d, *J* = 3.6 Hz, 1H), 2.18–2.24 (m, 2H), 2.28–2.32 (dt, *J* = 12.6, 6.3 Hz, 1H), 2.33–2.38 (m, 1H), 3.73–3.78 (ddd, *J* = 11.3, 9.0, 6.4 Hz, 1H), 3.83–3.86 (dd, *J* = 9.9, 9.9 Hz, 1H), 3.88–3.91 (m, 1H), 4.12–4.15 (ddd, *J* = 9.3, 4.6, 6.2 Hz, 1H), 4.52–4.54 (dd, *J* = 9.7, 4.4 Hz, 1H), 5.17–5.21 (m, 2H), 5.56 (s, 1H), 5.82–5.89 (ddt, *J* = 17.2, 10.2, 7.2 Hz, 1H), 7.35–7.41 (m, 3H), 7.51–7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.9, 37.6, 71.9, 72.4, 73.5, 80.2, 81.2, 102.5, 118.6, 126.5, 128.6, 129.4, 134.2, 137.3; IR (KBr pellet): 3423, 2979, 2930, 2891, 1451, 1411, 1369, 1340, 1220, 1137, 1105, 1095, 1045, 983, 751 cm^{-1}; $[\alpha]_D^{23}$ = –11.7 (*c* = 0.02, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_4$ $(M+Na)^+$ 299.1254, found 299.1255.



64

(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)-2-phenylhexahydropyrano [3,2-*d*][1,3]dioxin-7-ol (64): To a solution of olefin **62** (179 mg, 0.62 mmol) in 1:2 CH_3CN:DMM (19 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (13 mL), and *n*BuNHSO$_4$ (105 mg, 0.31 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (159 mg, 0.62 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (8.3 mL) and a solution of Oxone® (1.14 g, 1.85 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (8.3 mL) were added simultaneously over 20 min via syringe pump. The reaction was stirred at 0 °C an additional 30 min then diluted with H_2O (30 mL). The aqueous layer was extracted with EtOAc (8 x 30 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (50% EtOAc in hexanes) to afford epoxide **64** (151 mg, 80%, 9:1 dr by ^{1}H-NMR) as an amorphous solid. Product was visualized with CAM stain, R_f = 0.26 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33–1.34 (d, *J* = 5.1 Hz, 3H), 1.68–1.75 (m, 2H), 2.22–2.24 (d, *J* = 15.2 Hz, 1H), 2.47–2.51 (m, 2H), 2.84–2.85 (m, 1H), 2.92–2.93 (m, 1H), 3.37–3.42 (m, 2H), 3.57–3.61 (dt, *J* = 9.4, 4.1 Hz, 1H), 3.69–3.72 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.77–3.81 (ddd, *J* = 5.3, 4.3, 4.3 Hz, 1H), 4.31–4.34 (dd, *J* = 10.3, 4,7 Hz, 1H), 5.54 (s, 1H), 7.36–7.40 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 34.4, 37.7, 54.6, 56.5, 68.9, 69.5, 73.7, 77.4, 80.7, 101.9, 126.4, 128.6, 129.3, 137.6; IR (KBr pellet): 3438, 2927, 2871, 1453, 1382, 1334, 1314,

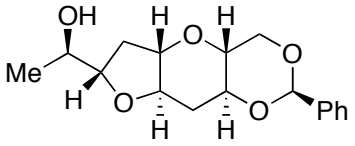
1284, 1101, 1009, 916, 857, 801 cm^{-1}; $[\alpha]_D^{23} = -5.8$ (c = 0.002, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{22}O_5$ $(M+Na)^+$ 329.1359, found 329.1360.



65

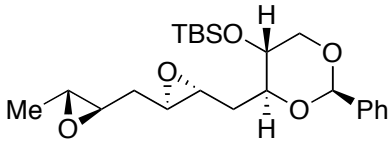
Tetrahydropyran (65):

Representative Procedure: To a mixture of epoxy alcohol **64** (50 mg, 0.20 mmol) in MeOH (5 mL) was added Cs_2CO_3 (1.3 g, 4 mmol). The reaction was heated to 50 °C for 12 h, then cooled to ambient temperature. The reaction was diluted with Et_2O (50 mL) and washed with sat. NH_4Cl (20 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc in hexanes) to afford **65** (15 mg, 30%) as a white solid. Product was visualized with CAM stain, R_f = 0.27 (50% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ: 1.31–1.33 (d, J = 6.1 Hz, 3H), 1.47–1.52 (ddd, J = 11.2, 11.2, 11.2 Hz, 1H), 1.63–1.64 (d, J = 5.4 Hz, 1H), 1.58–1.74 (ddd, J = 11.2, 11.2, 11.2 Hz, 1H), 2.39–2.42 (dt, J = 11.4, 4.0 Hz, 1H), 2.43–2.46 (dt, J = 11.5, 4.1 Hz, 1H), 3.15–3.27 (m, 3H), 3.38–3.45 (m, 2H), 3.59–3.64 (ddd, J = 11.9, 9.1, 4.2 Hz, 1H), 3.70–3.73 (dd, J = 10.3, 10.3 Hz, 1H), 4.32–4.34 (dd, J = 10.5, 4.8 Hz, 1H), 5.55 (s, 1H), 7.36–7.40 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 18.1, 35.4, 38.9, 69.7, 71.9, 94.1, 76.9, 77.5, 77.6, 79.0, 102.2, 126.7, 128.7, 129.5, 138.3; IR (KBr pellet): 3582, 2929, 2872, 1452, 1375, 1332, 1290, 1234, 1177, 1110, 1073, 1038, 1007, 991, 976, 947, 926, 760, 702 cm^{-1}; $[\alpha]_D^{23} = -9.1$ (c = 0.015, $CHCl_3$). HR-MS (ESI) Calcd for $C_{17}H_{22}O_5$ $(M+Na)^+$ 329.1359, found 329.1368.



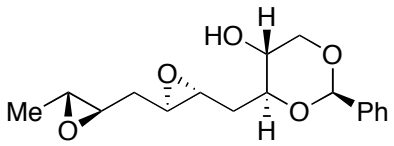
66

Tetrahydrofuran (66): Cyclization in Cs_2CO_3 and MeOH (vide supra) afforded **66** (27 mg, 54%). Product was visualized with CAM stain, R_f = 0.17 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, CD_2Cl_2) δ: 1.10–1.12 (d, *J* = 6.5 Hz, 3H), 1.25–1.28 (m, 1H), 1.66–1.74 (ddd, *J* = 10.8, 10.8, 10.8 Hz, 1H), 1.92–1.99 (td, *J* = 11.0, 9.5 Hz, 1H), 2.08–2.14 (dt, *J* = 11.0, 6.2 Hz, 1H), 2.51–2.56 (dt, *J* = 10.5, 3.8 Hz, 1H), 3.43–3.62 (m, 3H), 3.67–3.76 (dd, *J* = 10.2, 10.2 Hz, 1H), 3.94–4.00 (td, *J* = 6.5, 4.0 Hz, 1H), 4.05–4.12 (ddd, *J* = 9.5, 6.4, 3.9 Hz, 1H), 4.29–4.33 (dd, *J* = 10.5, 4.7 Hz, 1H), 5.49 (s, 1H), 7.35–7.38 (m, 3H), 7.45–7.47 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ: 18.4, 29.2, 35.7, 69.6, 69.8, 75.2, 77.8, 78.1, 82.0, 82.5, 102.5, 126.7, 128.7, 129.5, 138.2; IR (KBr pellet): 3433, 2974, 2873, 1455, 1389, 1372, 1332, 1313, 1293, 1240, 1211, 1178, 1109, 1073, 1030, 1004, 944, 920, 891, 858, 795, 751 cm^{-1}; $[\alpha]^{23}_D$ = –32.0 (*c* = 0.007, $CHCl_3$). HR-MS (ESI) Calcd for $C_{17}H_{22}O_5$ $(M+Na)^+$ 329.1359, found 329.1352.



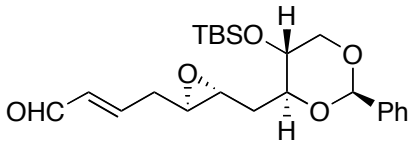
73

***tert*-butyldimethyl((2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-yloxy)silane (73)**: To a solution of olefin **72** (268 mg, 0.66 mmol) in 1:2 CH_3CN:DMM (21 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (14 mL), and *n*-$BuNHSO_4$ (224 mg, 0.66 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (170 mg, 0.66 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (6 mL) and a solution of Oxone® (811 mg, 1.32 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (6 mL) were added simultaneously over 20 min via syringe pump. The reaction was stirred at 0 °C an additional 30 min then diluted with H_2O (40 mL). The aqueous layer was extracted with EtOAc (8 x 25 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexanes) to afford diepoxide **73** (207 mg, 75%, 9:1 dr by ^{1}H-NMR) as a amorphous solid. Product was visualized with CAM stain, R_f = 0.30 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.28–1.30 (d, *J* = 4.9 Hz, 3H), 1.76–1.78 (dd, *J* = 7.1, 5.6 Hz, 2H), 1.97–2.00 (dd, *J* = 5.5, 5.0 Hz, 2H), 2.78–2.83 (m, 2H), 2.89–2.92 (ddd, *J* = 6.1, 6.0, 2.2 Hz, 1H), 3.00–3.04 (td, *J* = 6.0, 2.2 Hz, 1H), 3.55–3.61 (m, 1H), 3.66–3.74 (m, 2H), 4.18–4.22 (dd, *J* = 10.7, 4.5 Hz, 1H), 5.51 (s, 1H), 7.34–7.40 (m, 3H), 7.47–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.1, 17.7, 18.1, 25.9, 33.9, 35.2, 25.6, 55.2, 55.6, 56.7, 66.1, 72.0, 80.3, 101.0, 126.2, 128.5, 129.1, 137.9 ; IR (thin film NaCl): 3067, 3036, 2956, 2929, 2857, 1472, 1463, 1386, 1361, 1297, 1253, 1216, 1106, 1028, 979, 939, 879, 838, 778, 752, 723, 698 cm^{-1}; $[\alpha]_D^{23}$ = –25.1 (*c* = 0.036, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{36}O_5Si$ $(M+Na)^+$ 443.2224, found 443.2234.



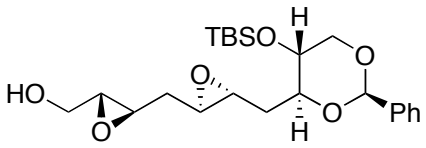
67

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-methyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-phenyl-1,3-dioxan-5-ol (67): Silyl ether **73** (103 mg, 0.245 mmol) was dissolved in THF (1.2 mL) and cooled to 0 °C. A solution of TBAF (0.49 mL of 1M in THF, 0.49 mmol) was added and the reaction was stirred at ambient temperature for 30 min. The reaction was quenched by addition of brine (1 mL) and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (60% EtOAc in hexanes) to afford epoxy alcohol **67** (59 mg, 78%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.35 (85% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29–1.32 (d, *J* = 5.0 Hz, 3H), 1.73–1.76 (ddd, *J* = 14.5, 6.7, 4.9 Hz, 1H), 1.81–1.83 (ddd, *J* = 14.5, 6.6, 4.2 Hz, 1H), 1.93–2.00 (ddd, *J* = 15.0, 7.0, 5.3 Hz, 1H), 2.18–2.24 (dt, *J* = 15.1, 4.0 Hz, 1H), 2.66–2.67 (d, *J* = 5.1 Hz, 1H), 2.81–2.85 (m, 2H), 2.96–2.99 (ddd, *J* = 6.8, 4.8, 2.3 Hz, 1H), 3.07–3.11 (ddd, *J* = 6.6, 3.8, 2.3 Hz, 1H), 3.59–3.64 (dd, *J* = 10.5, 1H), 3.73–3.75 (dt, *J* = 9.4, 5.0 Hz, 1H), 3.85–3.89 (ddd, *J* = 9.7, 5.1, 4.8 Hz, 1H), 4.29–4.34 (dd, *J* = 10.8, 5.1 Hz, 1H), 5.51 (s, 1H), 7.35–7.41 (m, 3H), 7.49–7.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.7, 34.6, 35.0, 54.8, 55.5, 55.6, 56.7, 65.3, 71.3, 79.8, 101.3, 126.3, 128.5, 129.2, 137.8; IR (thin film NaCl): 2438, 2983, 2924, 2857, 1454, 1382, 1307, 1216, 1076, 1027, 978, 855, 754, 700, 679 cm^{-1}; $[\alpha]_D^{23}$ = 32.5 (*c* = 0.019, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{22}O_5$ $(M+Na)^+$ 329.1359, found 329.1363.



78

(E)-4-((2R,3R)-3-(((2R,4S,5R)-5-(tert-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl) methyl)oxiran-2-yl)but-2-enal(78): To a solution of olefin **71** (5.2 g, 13.3 mmol) in CH_2Cl_2 (25 mL) was added acrolein (2.7 mL, 39.9 mmol) and the Hoveyda-Grubbs 2nd generation catalyst (333 mg, 0.5 mmol). A reflux condenser was attached and the reaction was heated to reflux for 16 h. The reaction was cooled to ambient temperature, ethyl vinyl ether was added (10 mL), the reaction was stirred at room temperature for 10 min and then concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (gradient: 10% to 20% EtOAc in hexanes) to afford aldehyde **78** (4.2 g, 77%). Product was visualized with CAM stain, R_f = 0.27 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.11 (s, 6H), 0.90 (s, 9H), 2.00–2.03 (t, *J* = 5.1 Hz, 2H), 2.52–2.66 (m, 2H), 2.90–2.93 (ddd, *J* = 5.9, 5.8, 2.2 Hz, 1H), 3.03–3.06 (ddd, *J* = 5.5, 5.5, 2.1 Hz, 1H), 3.55–3.60 (m, 1H), 3.69–3.71 (m, 2H), 4.18–4.22 (dd, *J* = 10.7, 4.4 Hz, 1H), 5.51 (s, 1H), 6.18–6.25 (ddt, *J* = 15.8, 7.8, 1.5 Hz, 1H), 6.77–6.85 (dt, *J* = 15.8, 6.7 Hz, 1H), 7.34–7.40 (m, 3H), 7.46–7.49 (m, 2H), 9.46–9.48 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.7, –4.1, 18.0, 25.8, 33.6, 35.1, 55.3, 55.2, 66.0, 71.9, 80.0, 101.0, 126.1, 128.4, 129.1, 134.8, 137.8, 152.4, 193.6; IR (thin film NaCl): 3036, 2929, 2857, 2738, 1695 ,1638, 1472, 1463, 1387, 1361 ,1297, 1253, 1216, 1112, 1029, 976, 938, 838, 778, 699, 678 cm^{-1}; $[\alpha]_D^{23}$ = –38.3 (*c* = 0.047, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{34}O_5Si$ $(M+Na)^+$ 441.2068, found 441.2086.

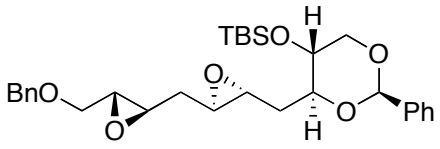


79

((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,4*S*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-2-phenyl-1,3-dioxan-4-yl)methyl)oxiran-2-yl)methyl)oxiran-2-yl)methanol (79): A solution of aldehyde **78** (4.1 g, 9.8 mmol) in MeOH (20 mL) was cooled to 0 °C and $NaBH_4$ (277 mg, 7.34 mmol) was added in portions, after which the reaction was stirred at 0 °C for 20 min, quenched with sat. NH_4Cl (30 mL) and extracted with EtOAc (5 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude allylic alcohol was used without further purification.

Powdered 4Å molecular sieves (2 g) were flame dried under vacuum for 8 minutes and then cooled to ambient temperature. To the sieves was added CH_2Cl_2 (25 mL), D–(-)-diethyl tartrate (241 mg, 1.17 mmol) and the mixture was cooled to –25 °C. Next, $Ti(OiPr)_4$ (290 μL, 0.98 mmol) was added in one portion followed by the dropwise addition of *t*-BuOOH (3.5 mL of 5.5M in decane, 19.6 mmol) and the reaction was stirred at –25 °C for 30 min. The allylic alcohol was added as a solution in CH_2Cl_2 (10 mL) and the reaction was stirred at –25 °C for 15 h. The reaction was quenched by slow addition to a solution of $Fe(II)SO_4 \bullet 7H_2O$ (3.2 g), tartaric acid (1 g), and H_2O (34 mL) at 0 °C. The mixture was stirred at room temperature for 15 min and extracted with Et_2O. The organic extracts were combined and to them was added 30mL 30% NaOH in brine. The mixture was stirred at room temperature for 1h. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (40% EtOAc in hexanes) to afford epoxide **79** (3.1 g, 73%). Product was visualized with CAM stain, R_f = 0.19 (40% EtOAc in hexanes); ^1H NMR (400

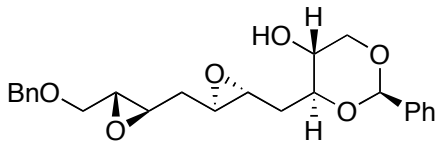
MHz, $CDCl_3$) δ: 0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.79–1.83 (m, 2H), 1.98–2.03 (m, 3H), 2.89–2.93 (m, 1H), 2.95–2.97 (ddd, *J* = 4.5, 2.4, 2.4 Hz, 1H), 3.01–3.04 (td, *J* = 5.6, 2.1 Hz, 1H), 3.10–3.14 (m, 1H), 3.54–3.60 (m, 2H), 3.66–3.72 (m, 2H), 3.81–3.86 (m, 1H), 4.18–4.22 (dd, *J* = 10.8, 4.5 Hz, 1H), 5.52 (s, 1H), 7.33–7.40 (m, 3H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.1, 18.0, 25.8, 33.8, 34.7, 53.0, 54.9, 55.6, 58.3, 61.5, 66.1, 72.0, 80.2, 101.0, 126.2, 128.4, 129.1, 137.9; IR (thin film NaCl): 3460, 2955, 2929, 2857, 1472, 1463, 1388, 1361, 1297, 1253, 1216, 1109, 1029, 980, 856, 838, 778, 698 cm^{-1}; $[\alpha]_D^{23}$ = –20.4 (*c* = 0.037, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{36}O_6Si$ $(M+Na)^+$ 459.2173, found 459.2179.



80

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl) methyl)-2-phenyl-1,3-dioxan-5-ol (80): Sodium hydride (418 mg of 60% NaH in oil, 10.4 mmol) was added to THF (15 mL) at 0 °C followed by a solution of alcohol **79** (3.04 g, 7.0 mmol) in THF (10 mL). The reaction was warmed to ambient temperature and stirred for 30 min. Benzyl bromide (1.24 mL, 10.4 mmol) was then added and the reaction was stirred an additional 2 h. The mixture was then cooled to 0 °C, quenched with sat. NH_4Cl and the aqueous lyaer was extracted with EtOAc (3 x 50mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (10% to 20% EtOAc in hexanes) to afford benzyl ether **80** (3.04 g, 83%). Product was visualized with CAM stain, R_f = 0.46 (30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.12 (s, 3H), 0.13 (s,

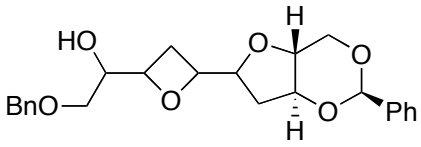
3H), 0.91 (s, 9H), 1.76–1.88 (m, 2H), 1.99–2.02 (m, 2H), 2.91–2.95 (m, 1H), 3.01–3.07 (m, 3H), 3.45–3.49 (dd, *J* = 11.5, 5.4 Hz, 1H), 3.56–3.61 (m, 1H), 3.68–3.76 (m, 3H), 4.20–4.23 (dd, *J* = 10.8, 4.5 Hz, 1H), 4.53–4.56 (d, *J* = 12.0 Hz, 1H), 4.58–4.61 (d, *J* = 12.0 Hz, 1H), 5.53 (s, 1H), 7.31–7.40 (m, 8H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.6, –4.1, 18.0, 25.8, 33.9, 34.9, 53.1, 54.9, 55.6, 56.8, 66.1, 70.1, 71.9, 73.4, 80.2, 100.9, 126.2, 127.8, 127.9, 128.4, 128.5, 129.0, 137.9, 138.0; IR (thin film NaCl): 3065, 3033, 2955, 2928, 2856, 1472, 1454, 1387, 1361, 1297, 1525, 1215, 1108, 1028, 978, 939, 881, 856, 838, 778, 749, 698 cm^{-1}; $[\alpha]_D^{23}$ = –20.8 (*c* = 0.045, $CHCl_3$); HR-MS (ESI) Calcd for $C_{30}H_{42}O_6Si$ $(M+Na)^+$ 549.2643, found 549.2643.



81

(2*R*,4*S*,5*R*)-4-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl) methyl)-2-phenyl-1,3-dioxan-5-ol (81): To a solution of silyl ether **80** (1.6 g, 3.0 mmol) in THF (15 mL) at 0 °C was added TBAF (4.5 mL of 1M solution in THF, 4.5 mmol) and the reaction was stirred at 0 °C for 30 min. The reaction was quenched with brine (20 mL). The aqueous lyaer was extracted with EtOAc (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The material was purified by column chromatography (50% to 80% EtOAc in hexanes) to afford alcohol **81 (**1.2 g, 98%). Product was visualized with CAM stain, R_f = 0.1 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74–1.81 (ddd, *J* = 14.5, 6.6, 4.9 Hz, 1H), 1.83–1.89 (ddd, *J* = 14.5, 6.6, 4.0 Hz, 1H), 1.94–2.00 (ddd, *J* = 15.0, 6.0, 6.0 Hz, 1H), 2.15–2.21 (ddd, *J* = 15.0, 4.1, 4.1 Hz, 1H), 2.96–2.99 (m, 2H), 3.02 (m, 2H), 3.09–3.12 (m, 1H), 3.48–3.52 (dd, *J* =

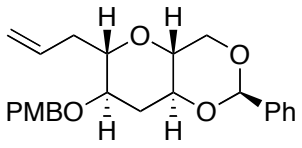
11.5, 5.4 Hz, 1H), 3.55–3.60 (dd, *J* = 10.5, 10.5 Hz, 1H), 3.69–3.83 (m, 3H), 4.24–4.28 (dd, *J* = 10.8, 5.1 Hz, 1H), 4.53–4.56 (d, *J* = 11.9 Hz, 1H), 4.58–4.61 (d, *J* = 11.9 Hz, 1H), 5.50 (s, 1H), 7.30–7.41 (m, 8H), 7.50–7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.3, 34.6, 53.1, 55.3, 55.5, 56.9, 65.0, 70.0, 71.3, 73.5, 79.6, 101.1, 126.2, 127.9, 128.0, 128.4, 128.6, 129.1, 137.7, 137.8; IR (thin film NaCl): 3443, 3064, 3032, 2985, 2919, 2857, 1454, 1397, 1368, 1215, 1075, 1028, 978, 915, 883, 751, 699 cm^{-1}; $[\alpha]_D^{23}$ = 19.0 (*c* = 0.042, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{28}O_6$ $(M+Na)^+$ 435.1778, found 435.1795.



82

2-(benzyloxy)-1-(4-((2R,4aR,7aS)-2-phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-6-yl) oxetan-2-yl)ethanol (82): Product was visualized with CAM stain, R_f = 0.24 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74–1.80 (ddd, *J* = 11.1, 11.0, 11.0 Hz, 1H), 2.00–2.05 (td, *J*= 11.3, 9.1 Hz, 1H), 2.22–2.27 (dt, *J*= 11.6, 6.4 Hz, 1H), 2.45–2.46 (d, *J* = 4.5 Hz, 1H), 2.58–2.61 (dt, *J* = 10.6, 3.9 Hz, 1H), 3.4–3.57 (m, 4H), 3.59–3.66 (m, 2H), 3.74–3.78 (dd, *J*= 10.4, 10.0 Hz, 1H), 3.93–3.97 (m, 1H), 4.18–4.22 (dt, *J* = 8.9, 6.5 Hz, 1H), 4.35–4.38 (dd, *J* = 10.5, 4.6 Hz, 1H), 4.54–4.56 (d, *J* = 11.8 Hz, 1H), 4.59–4.61 (d, *J*= 11.8 Hz, 1H), 5.52 (s, 1H), 7.32–7.40 (m, 8H), 7.50–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.7, 35.2, 69.5, 71.3, 72.8, 73.8, 74.8, 77.1, 77.8, 78.4, 81.6, 102.3, 126.4, 128.0, 128.1, 128.6, 128.7, 129.4, 137.4, 137.9; IR (thin film NaCl): 3459, 3033, 2872, 1496, 1454, 1371, 1334, 1313, 1292, 1234, 1176,

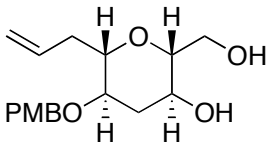
1113, 1028, 969, 848, 751, 699 cm^{-1}; $[\alpha]_D^{23}$ = –28.0 (*c* = 0.003, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{28}O_6$ $(M+Na)^+$ 435.1778, found 435.1793.



S2

(2*R*,4a*R*,6*S*,7*R*,8a*S*)-6-allyl-7-(4-methoxybenzyloxy)-2-phenylhexahydropyrano[3,2-*d*][1,3] dioxine (S2): Potassium hydride (3 g of 30% in oil by weight, 22.5 mmol) was loaded into a round bottom flask. A solution of alcohol **76** (4.1 g, 15.0 mmol) in THF (150 mL) was added and the reaction was heated to 50 °C for 40 min affording an orange/red solution. *para*-Methoxybenzyl chloride (2.6 mL, 19.4 mmol) was added dropwise and the reaction was stirred at 50 °C for an additional 40 min. The reaction was cooled to 0 °C, quenched by dropwise addition of MeOH (6 mL) followed by addition of brine (80 mL). The aqueous layer was extracted with EtOAc (3 x 130 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 5% to 10% to 30% EtOAc in hexanes) to afford PMB ether **S2** (5.2 g, 94%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.34 (in 30% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.63–1.72 (ddd, *J* = 11.6, 11.6, 11.6 Hz, 1H), 2.23–2.31 (dt, *J* = 14.9, 7.4 Hz, 1H), 2.61–2.69 (m, 2H), 3.31–3.53 (m, 4H), 3.66–3.71 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.83 (s, 3H), 4.31–4.34 (dd, *J* = 10.4, 4.9 Hz, 1H), 4.42–4.45 (d, *J* = 11.1 Hz, 1H), 4.58–4.61 (d, *J* = 11.1 Hz, 1H), 5.08–5.15 (m, 2H), 5.53 (s, 1H), 5.84–5.95 (dddd, *J* = 17.4, 10.2, 7.5, 6.4 Hz, 1H), 6.89–6.93 (d, *J* = 8.7 Hz, 2H), 7.26–7.29 (d, *J* = 8.7 Hz, 2H), 7.36–7.42 (m, 3H), 7.50–7.52

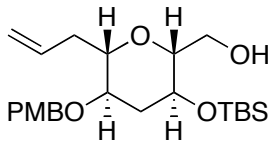
(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 36.2, 55.5, 69.6, 70.8, 73.2, 75.3, 76.9, 80.5, 101.8, 114.1, 117.2, 126.4, 128.5, 129.3, 129.7, 130.1, 134.9, 137.6, 159.5; IR (thin film NaCl): 3071, 3035, 2999, 2935, 2871, 1641, 1612, 1586, 1513, 1455, 1386, 1365, 1302, 1249, 1173, 1090, 1031, 1013, 966, 916, 820, 751, 698 cm^{-1}; $[\alpha]_D^{23}$ = –53.3 (*c* = 0.046, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{28}O_5$ $(M+Na)^+$ 419.1829, found 419.1835.



86

(2*R*,3*S*,5*R*,6*S*)-6-allyl-2-(hydroxymethyl)-5-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-3-ol (86): Ether **S2** (4.5 g, 12.2 mmol) was dissolved in MeOH (225 mL) and THF (75 mL) followed by addition of CSA (860 mg, 3.7 mmol). The reaction as stirred at ambient temperature for 90 min, quenched by addition of Et_3N (0.5 mL) and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 40% EtOAc in hexanes to 100% EtOAc) to afford diol **86** (3.3 g, 90%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.30 (in 80% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42–1.50 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 1H), 2.17–2.24 (m, 2H), 2.30–2.31 (d, *J* = 5.3 Hz, 1H), 2.54–2.65 (m, 2H), 3.17–3.23 (m, 2H), 3.28–3.33 (ddd, *J* = 9.1, 7.8, 3.1 Hz, 1H), 3.55–3.64 (m, 1H), 3.72–3.78 (ddd, *J* = 11.5, 5.4, 5.3, 1H), 3.82–3.87 (m, 4H), 4.39–4.42 (d, *J* = 11.1 Hz, 1H), 4.55–4.58 (d, *J* = 11.1 Hz, 1H), 5.05–5.11 (m, 2H), 5.81–5.88 (dddd, *J* = 17.3, 10.2, 7.4, 6.5 Hz, 1H), 6.88–6.90 (d, *J* = 8.7 Hz, 2H), 7.25–7.27 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 36.2, 38.4, 55.5, 63.4, 66.9, 70.9, 75.2, 79.8, 81.0, 114.1, 117.1, 129.7, 130.2, 135.0, 159.5; IR (thin film NaCl): 3430, 3037, 3005, 2936, 2880, 2855, 1646, 1614, 1515, 1465, 1401, 1339, 1305, 1253, 1183,

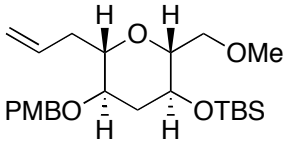
1127, 1101, 1043, 999, 918, 824, 771, 669 cm^{-1}; $[\alpha]_D^{23} = -31.3$ ($c = 0.006$, $CHCl_3$); HR-MS (ESI) Calcd for $C_{17}H_{24}O_5$ $(M+Na)^+$ 331.1516, found 331.1528.



S3

((2*R*,3*S*,5*R*,6*S*)-6-allyl-3-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)tetrahydro-2*H*-pyran-2-yl)methanol (S3): Diol **86** (3.3 g, 10.8 mmol) was dissolved in CH_2Cl_2 (108 mL), 2,6-lutidine (5 mL, 43.2 mmol) was added and the flask was cooled to 0 °C. *Tert*-butyldimethylsilyl trifluoromethanesulfonate (6.2 mL, 27 mmol) was added dropwise and the reaction was stirred at 0 °C for 30 min, then quenched by addition of MeOH (3 mL) and diluted with EtOAc (200 mL). The organic layer was washed with 1M HCl (100 mL), then sat. $NaHCO_3$ (100 mL) and finally brine (100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude residue was dissolved in MeOH (100 mL) and cooled to 0 °C followed by addition of CSA (1.5 g, 6.5 mmol). The reaction was stirred at 0 °C for 20 min. The reaction was quenched with Et_3N (0.9 mL), the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 10% to 20% EtOAc in hexanes) to afford silyl ether **S3** (4.1 g, 91% over 2 steps) as a colorless oil; Product was visualized with CAM stain, $R_f = 0.66$ (in 50% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.06 (s, 6H), 0.88 (s, 9H), 1.40–1.49 (ddd, J = 11.2, 11.2, 11.2 Hz, 1H), 2.00–2.03 (dd, J = 7.2, 5.7 Hz, 1H), 2.17–2.24 (dt, J = 15.2, 7.6 Hz, 1H), 2.34–2.39 (dt, J = 11.8, 4.5 Hz, 1H), 2.59–2.65 (dddd, J = 14.7, 4.6, 3.1, 1.5 Hz, 1H), 3.13–3.21 (m, 2H), 3.28–3.33 (ddd, J = 9.2, 7.7, 3.0 Hz, 1H), 3.45–3.51 (ddd, J = 11.0, 9.1, 4.6 Hz, 1H), 3.54–3.59 (dt, J = 11.6, 5.6 Hz, 1H), 3.79–3.84 (m, 4H), 4.41–4.43 (d, J = 11.1 Hz,

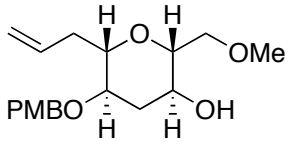
1H), 4.53–4.56 (d, J = 11.1 Hz, 1H), 5.04–5.12 (m, 2H), 5.81–5.92 (dddd, J = 17.6, 10.2, 7.5, 6.2 Hz, 1H), 6.88–6.91 (d, J = 8.7 Hz, 2H), 7.26–7.28 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.7, –4.0, 18.1, 25.9, 36.3, 39.2, 55.5, 63.0, 67.0, 71.0, 75.3, 79.7, 81.8, 114.1, 117.1, 129.7, 130.4, 135.0, 159.5; IR (thin film NaCl): 3480, 3075, 2953, 2929, 2857, 1641, 1612, 1514, 1463, 1360, 1302, 1250, 1173, 1095, 1004, 913, 861, 837, 777, 670 cm^{-1}; $[\alpha]_D^{23}$ = –0.30 (c = 0.011, $CHCl_3$); HR-MS (ESI) Calcd for $C_{23}H_{38}O_5Si$ $(M+Na)^+$ 445.2381, found 445.2384.



87

((2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)tetrahydro-2*H*-pyran-3-yloxy)(*tert*-butyl)dimethylsilane (87): Alcohol **S3** (3.2 g, 7.6 mmol) was dissolved in CH_3CN (75 mL) followed by addition of MeI (9.4 mL, 152 mmol) and silver(I) oxide (1.9 g, 8.4 mmol). The reaction was heated to 60 °C in the dark for 18 h then cooled to ambient temperature affording a white cloudy solution. The solution was filtered through Celite, the Celite was washed with Et_2O and the organic solvent was removed *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes) to afford methyl ether **87** (2.5 g, 76%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.52 (in 20% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.06 (s, 3H), 0.88 (s, 9H), 1.38–1.44 (ddd, J = 11.3, 11.3, 11.3 Hz, 1H), 2.24–2.29 (dt, J = 14.7, 7.3 Hz, 1H), 2.34–2.38 (dt, J = 11.8, 4.5 Hz, 1H), 2.58–2.62 (m, 1H), 3.16–3.21 (m, 2H), 3.24–3.27 (td, J = 9.2, 3.2 Hz, 1H), 2.26 (s, 3H), 3.49–3.51 (dd, J = 10.4, 4.6 Hz, 1H), 3.56–3.61 (m, 2H), 3.81 (s, 3H), 4.41–4.42 (d, J = 11.1 Hz, 1H), 4.52–4.54 (d, J = 11.1 Hz, 1H), 5.04–5.05 (d, J = 10.2 Hz, 1H), 5.08–5.11 (d, J = 17.2 Hz,

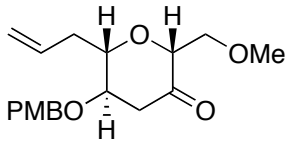
1H), 5.90–5.97 (dddd, J = 17.2, 10.2, 6.9, 6.9 Hz, 1H), 6.88–6.89 (d, J = 8.5 Hz, 2H), 7.26–7.27 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: –4.9, –4.2, 17.9, 25.8, 36.1, 39.4, 55.3, 59.4, 66.0, 70.8, 71.7, 75.2, 80.4, 81.7, 113.9, 116.5, 129.6, 130.4, 135.3, 159.4; IR (thin film NaCl): 3074, 2953, 2929, 2885, 2857, 1641, 1612, 1586, 1514, 1471, 1463, 1302, 1250, 1203, 1173, 1102, 1037, 1004, 912, 862, 837, 776, 669 cm^{-1}; $[\alpha]_D^{23}$ = 0.4 (c = 0.0026, $CHCl_3$); HR-MS (ESI) Calcd for $C_{24}H_{40}O_5Si$ $(M+Na)^+$ 459.2537, found 459.2543.



S4

(2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)tetrahydro-2*H*-pyran-3-ol (S4): Silyl ether **87** (3.0 g, 6.9 mmol) was dissolved in THF (70 mL) and cooled to 0 °C. A solution of TBAF (10.3 mL of 1M in THF, 10.3 mmol) was added, the reaction was allowed to warm to ambient temperature and stirred for 1.75 h before being dilluted with brine (100 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 40% to 60% EtOAc in hexanes then 100% EtOAc) to afford alcohol **S4** (2.1 g, 98%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.2 (in 60% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.39–1.47 (ddd, J = 11.3, 11.3, 11.3 Hz, 1H), 2.18–2.25 (dt, J = 14.7, 7.4 Hz, 1H), 2.52–2.62 (m, 2H), 3.19–3.29 (m, 4H), 3.39 (s, 3H), 3.53–3.57 (m, 2H), 3.64–3.67 (dd, J = 9.9, 4.7 Hz, 1H), 3.79 (s, 3H), 4.37–4.40 (d, J = 11.1 Hz, 1H), 4.54–4.57 (d, J = 11.1 Hz, 1H), 5.03–5.10 (m, 2H), 5.85–5.93 (dddd, J = 17.1, 10.2, 6.9, 6.9 Hz, 1H), 6.87–6.89 (d, J = 8.7 Hz, 2H), 7.24–7.26 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz,

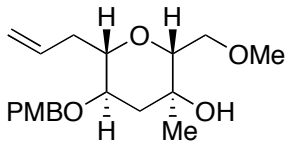
$CDCl_3$) δ: 36.0, 37.8, 55.3, 59.7, 68.3, 70.6, 74.1, 75.0, 79.1, 80.0, 113.9, 116.7, 129.6, 130.2, 135.1, 159.3; IR (thin film NaCl): 3431, 3074, 2869, 1641, 1612, 1586, 1514, 1456, 1347, 1302, 1249, 1201, 1173, 1100, 916, 820 cm^{-1}; $[\alpha]_D^{23}$ = –56.2 (*c* = 0.042, $CHCl_3$); HR-MS (ESI) Calcd for $C_{18}H_{26}O_5$ $(M+Na)^+$ 345.1672, found 345.1673.



88

(2*R*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)dihydro-2*H*-pyran-3(4*H*)-one (88): Alcohol **S4** (2.1 g, 6.7 mmol) was dissolved in CH_2Cl_2 (70 mL) to which was added Dess-Martin periodinane (6.0 g, 14.1 mmol). The reaction was stirred at ambient temperature for 90 min. The reaction was quenched by addition of sat. $NaHCO_3$ (100 mL) and then sat. $Na_2S_2O_3$ (100 mL). The aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc in hexanes) to afford ketone **88** (2.0 g, 96%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.38 (in 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.43–2.47 (t, *J* = 6.4 Hz, 2H), 2.58–2.63 (dd, *J* = 15.3, 4.5 Hz, 1H), 2.80–2.85 (dd, *J* = 15.3, 4.5 Hz, 1H), 3.36 (s, 3H), 3.63–3.67 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.71–3.76 (m, 2H), 3.79 (s, 3H), 3.83–3.86 (dd, *J* = 4.5, 4.5 Hz, 1H), 4.00–4.02 (dd, *J* = 5.3, 2.5 Hz, 1H), 4.31–4.34 (d, *J* = 11.3 Hz, 1H), 4.46–4.49 (d, *J* = 11.3 Hz, 1H), 5.09–5.13 (m, 2H), 5.81–5.92 (dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, 1H), 6.85–6.88 (d, *J* = 8.6 Hz, 2H), 7.19–7.21 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 37.9, 41.5, 55.4, 59.7, 70.4, 71.5, 76.0, 79.7, 82.0, 114.0, 118.0, 129.5, 129.6, 133.8, 159.5, 208.5; IR (thin film NaCl): 2908, 1737, 1612,

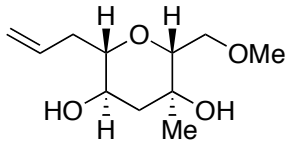
1586, 1513, 1467, 1303, 1249, 1174, 1099, 920, 821 cm^{-1}; $[\alpha]_D^{23}$ = 52.7 (*c* = 0.045, $CHCl_3$); HR-MS (ESI) Calcd for $C_{18}H_{24}O_5$ $(M+Na)^+$ 343.1516, found 343.1518.



89

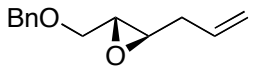
(2*R*,3*S*,5*R*,6*S*)-6-allyl-5-(4-methoxybenzyloxy)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3-ol (89): Ketone **88** (1.8 g, 5.7 mmol) was dissolved in toluene (60 mL) and cooled to –78 °C followed by addition of a solution of methyl magnesium bromide (4.7 mL of 3M in THF, 14.2 mmol). The reaction was stirred at –78 °C for 1 h then quenched at –78 °C by addition of sat. NH_4Cl (60 mL). The aqueous layer was extracted with EtOAc (3 x 80 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (40% EtOAc in hexanes) to afford alcohol **89** (1.4 g, 75%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.18 (in 40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 3H), 1.53–1.59 (m, 1H), 2.19–2.30 (m, 2H), 2.56–2.62 (dddd, *J* = 14.7, 4.8, 3.3, 1.6 Hz, 1H), 3.15–3.21 (ddd, *J* = 11.2, 9.2, 4.5 Hz, 1H), 3.28–3.32 (ddd, *J* = 9.2, 7.2, 3.3 Hz, 1H), 3.39 (s, 3H), 3.43–3.47 (dd, *J* = 7.6, 6.2 Hz, 1H), 3.50–3.58 (m, 2H), 3.81 (s, 3H), 4.36–4.38 (d, *J* = 11.0 Hz, 1H), 4.52–4.55 (d, *J* = 11.0 Hz, 1H), 5.03–5.10 (m, 2H), 5.81–5.92 (dddd, *J* = 17.5, 10.2, 7.5, 6.3 Hz, 1H), 6.87–6.90 (d, *J* = 8.7 Hz, 2H), 7.24–7.27 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 36.1, 44.2, 55.5, 59.7, 70.7, 71.0, 72.6, 74.6, 79.4, 80.4, 114.0, 117.0, 129.7, 130.3, 135.0, 159.4; IR (thin film NaCl): 3460, 3074, 2934, 1641, 1612, 1586, 1514, 1464, 1376, 1301, 1249, 1202, 1173, 1095, 1035,

915, 821, 759 cm^{-1}; $[\alpha]_D^{23}$ = –19.8 (*c* = 0.016, $CHCl_3$); HR-MS (ESI) Calcd for $C_{19}H_{28}O_5$ $(M+Na)^+$ 359.1829, found 359.1813.



85

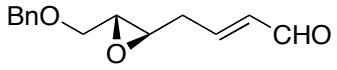
(2*R*,3*S*,5*R*,6*S*)-6-allyl-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (85): Ether **89** (1.3 g, 3.7 mmol) was dissolved in CH_2Cl_2 (36 mL), H_2O (1.8 mL) and cooled to 0 °C. 2,3-Dichloro-5,6-dicyano-1,4-benzo-quinone (DDQ) (1.7 g, 7.4 mmol) was added and the reaction was stirred at 0 °C for 1.5 h. The reaction was quenched with $NaHCO_3$ (80 mL) and then the aqueous lyaer was extracted with EtOAc (5 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo.* The crude residue was purified by column chromatography to afford diol **85** (750 mg, 93%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.05 (in 40% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ: 1.23 (s, 3H), 1.57–1.61 (t, *J* = 11.7 Hz, 1H), 1.63–1.64 (d, *J* = 5.4 Hz, 1H), 2.13–2.16 (dd, *J* = 11.7, 4.7 Hz, 1H), 2.28–2.33 (dt, *J* = 14.2, 7.2 Hz, 1H), 2.53–2.57 (m, 1H), 3.13 (s, 1H), 3.16–3.19 (ddd, *J* = 9.3, 6.9, 4.2 Hz, 1H), 3.40 (s, 3H), 3.41–3.47 (m, 2H), 3.51–3.58 (m, 2H), 5.07–5.09 (d, *J* = 10.2 Hz, 1H), 5.13–5.16 (d, *J* = 17.2 Hz, 1H), 5.88–5.95 (dddd, *J* = 17.2, 10.2, 7.0, 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.6, 36.3, 47.9, 59.6, 68.3, 70.9, 72.3, 80.1, 81.8, 117.1, 134.9; IR (thin film NaCl): 3383, 3076, 2978, 2933, 1642, 1463, 1377, 1285, 1202, 1099, 952, 916 cm^{-1}; $[\alpha]_D^{23}$ = –17.9 (*c* = 0.06, $CHCl_3$); HR-MS (ESI) Calcd for $C_{11}H_{20}O_4$ $(M+Na)^+$ 239.1254, found 239.1257.



S5

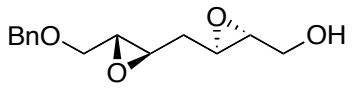
(2R,3R)-2-allyl-3-(benzyloxymethyl)oxirane(S5): Sodium hydride (1.14 g, 47.6 mmol) was added to THF (55 mL) at 0 °C followed by a solution of alcohol **90**[9] (3.62 g, 31.7 mmol) in THF (10 mL). The reaction was warmed to ambient temperature and stirred for 30 min. Benzyl bromide (5.66 mL, 47.6 mmol) was then added and the reaction was stirred an additional 3 h. The mixture was then cooled to 0 °C and quenched with sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 50mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (10% EtOAc in hexanes) to afford benzyl ether **S5** (5.64 g, 87%). Product was visualized with CAM stain, R_f = 0.47 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34–2.38 (2 dt, *J* = 5.4, 1.4 Hz, 2H), 2.93–2.96 (td, *J* = 5.4, 2.2 Hz, 1H), 2.99–3.02 (ddd, *J* = 5.6, 3.3, 2.2 Hz, 1H), 3.48–3.52 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.72–3.76 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.54–5.63 (2 d, *J* = 11.9 Hz, 2H), 5.10–5.14 (ddd, *J* = 10.3, 3.0, 1.2 Hz, 1H), 5.14–5.20 (ddd, *J* = 17.2, 3.0, 1.2 Hz, 1H), 5.78–5.88 (ddt, *J* = 17.2, 10.3, 6.7 Hz, 1H), 7.27–7.32 (m, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 35.9, 55.1, 56.6, 70.4, 73.4, 117.9, 127.9, 128.0, 128.6, 133.0, 138.1; IR (thin film NaCl): 3066, 3031, 2982, 2859, 1642, 1454, 1365, 1207, 1103, 1028, 997, 917, 738, 699 cm^{-1}; $[\alpha]_D^{23}$ = 9.0 (*c* = 0.13, $CHCl_3$); HR-MS (ESI) Calcd for $C_{13}H_{16}O_2$ $(M+Na)^+$ 227.1043, found 227.1044.

[9] Sabitha, G.; Sudhakar, K.; Reddy, N. M.; Rajkumar, M.; Yadav, J. S. *Tetrahedron Lett*. **2005**, *46*, 6567–6570.



91

(*E*)-4-((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)but-2-enal (91): To a solution of olefin **S5** (4.33 g, 21.2 mmol) in CH_2Cl_2 (35 mL) was added acrolein (4.3 mL, 63.3 mmol) and the Hoveyda-Grubbs 2nd generation catalyst (331 mg, 0.5 mmol). A reflux condenser was attached and the reaction was heated to reflux for 15 h. The reaction was cooled to ambient temperature and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (gradient: 10% to 30% EtOAc in hexanes) to afford aldehyde **91** (4.08g, 83%). Product was visualized with CAM stain, R_f = 0.47 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52–2.60 (dddd, *J* = 16.0, 7.4, 6.2, 1.5 Hz, 1H), 2.67–2.74 (dddd, *J* = 16.0, 6.2, 4.4, 1.5 Hz, 1H), 3.01–3.07 (m, 2H), 3.53–3.57 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.71–3.75 (dd, *J* = 11.5, 3.3 Hz, 1H), 4.54–4.62 (2d, *J* = 12 Hz, 2H), 6.20–6.27 (ddt, *J* = 15.8, 7.8, 1.5 Hz, 1H), 6.79–6.87 (dt, *J* = 15.8, 6.7 Hz, 1H), 7.27–7.39 (m, 5H), 9.54 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.6, 53.6, 56.7, 69.7, 73.6, 127.9, 128.0, 128.7, 135.0, 137.9, 152.0, 193.7; IR (thin film NaCl): 3063, 3031, 2993, 2859, 2744, 1689, 1454, 1366, 1102, 979, 911, 872, 740, 699 cm^{-1}; $[\alpha]_D^{23}$ = 9.2 (*c* = 0.31, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{16}O_3$ $(M + Na)^+$ 255.0992, found, 255.0998.



92

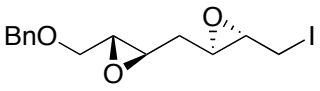
((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)methanol (92): A solution of aldehyde **91** (5.1 g, 22.0 mmol) in MeOH (45 mL) was cooled to 0 °C and $NaBH_4$

(625 mg, 16.5 mmol) was added in portions, after which the reaction was stirred at 0 °C for 20 min. The reaction was quenched with sat. NH_4Cl (80 mL) and the aqueous layer was extracted with EtOAc (5 x 80 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The allylic alcohol was used without further purification.

Powdered 4Å molecular sieves (2.5 g) were flame dried under vacuum for 8 minutes and then cooled to ambient temperature. To the sieves was added CH_2Cl_2 (44 mL), D–(-)-diethyl tartrate (542 mg, 2.63 mmol) and the mixture was cooled to –25 °C. Then $Ti(OiPr)_4$ (650 μL, 2.19 mmol) was added in one portion followed by the dropwise addition of *t*-BuOOH (8 mL of 5.5M in decane, 43.8 mmol) and the reaction was stirred at –25 °C for 30 min. The allylic alcohol was added as a solution in CH_2Cl_2 (10 mL) and the reaction was stirred at –25 °C for 15 h. The reaction was quenched at –25 °C by addition of a solution of anhydrous citric acid (410 mg) in Et_2O (77 mL).[10] The reaction was stirred for 30 min at ambient temperature, filtered through Celite and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (60% EtOAc in hexanes) to afford epoxide **92** (3.5 g, 64%). Product was visualized with CAM stain, R_f = 0.05 (60% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ: 1.76–1.81 (ddd, *J* = 14.5, 6.8, 4.7 Hz, 1H), 1.84–1.88 (ddd, *J* = 14.5, 6.8, 4.2 Hz, 1H), 2.06 (bs, 1H), 2.98–3.00 (dt, *J* = 4.4, 2.4 Hz, 1H), 3.01–3.05 (m, 2H), 3.13–3.16 (ddd, 6.8, 4.7, 2.2 Hz, 1H), 3.50–3.52 (dd, *J* = 11.4, 5.4 Hz, 1H), 3.65 (d, *J* = 9.9 Hz, 1H), 3.72–3.75 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.92 (d, *J* = 12.6 Hz, 1H), 4.54–4.61 (2 d, *J* = 11.9 Hz, 2H), 7.29–7.31 (m, 1H), 7.34–7.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.5, 52.9, 53.0, 57.0, 58.4, 61.5, 70.0, 73.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3438, 3030, 2923, 2854, 1496, 1454, 1366,

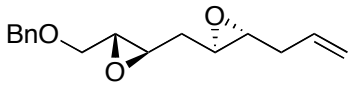
[10] Because anhydrous citric acid was slow to dissolve in Et_2O, the solution was prepared by stirring overnight.

1273, 1091, 844, 738, 699 cm^{-1}; $[\alpha]_D^{23}$ = 45.1 (*c* = 0.055 , $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{18}O_4$ $(M + Na)^+$ 273.1097, found 273.1086.



S6

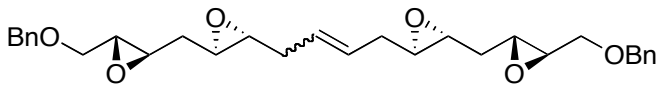
(2*R*,3*R*)-2-(benzyloxymethyl)-3-(((2*R*,3*S*)-3-(iodomethyl)oxiran-2-yl)methyl)oxirane (S6): To a mixture of PPh_3 (3.70 g, 14 mmol) and imidazole (0.95 g, 14 mmol) was added Et_2O (30 mL) and CH_3CN (10 mL). The solution was cooled to 0 °C and I_2 (3.55g, 14 mmol) was added in portions over 15 min with vigorous stirring followed by stirring at ambient temperature for 15 min. The solution was then cooled to 0 °C and a solution of alcohol **92** (3.05 g, 12.2 mmol) in Et_2O (6 mL) and CH_3CN (2 mL) was added. The reaction was stirred at ambient temperature for 30 min, quenched with sat. $Na_2S_2O_3$, then extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (30% EtOAc in hexanes) to afford iodide **S6** (3.80 g, 87%): Product was visualized with CAM stain, R_f = 0.27 (30% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ: 1.78–1.87 (m, 2 H), 2.99–3.10 (m, 5H), 3.23–3.27 (dd, *J* = 13.1, 8.8 Hz, 1H), 3.51–3.54 (dd, *J* = 11.4, 5.2 Hz, 1H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 1H), 4.55–4.62 (2 d, *J* = 12 Hz, 2H), 7.30–7.32 (m, 1H), 7.34–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.5, 34.6, 52.7, 56.9, 58.2, 59.4, 70.0, 73.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3495, 3062, 3029, 2989, 2858, 1454, 1366, 1246, 1207, 1175, 1096, 890, 739, 699, 608, 379 cm^{-1}; $[\alpha]_D^{23}$ = 14.8 (*c* = 0.025, $CHCl_3$); HR-MS (ESI) Calcd for $C_{14}H_{17}IO_3$ $(M+Na)^+$ 383.0115, found 383.0111.



93

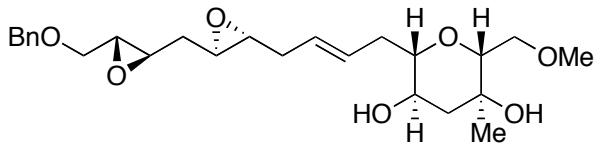
(2*R*,3*R*)-2-allyl-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxirane (93): Iodide **S6** (250 mg, 0.69 mmol) was dissolved in THF (3.5 mL) followed by addition of CuBr•DMS (57 mg, 0.28) and HMPA (0.29 mL, 2.8 mmol). The solution was immediately cooled to –25 °C and stirred for 5 min followed by dropwise addition of a solution of vinyl magnesium bromide (1 mL of 1M in THF, 1.0 mmol). The reaction was stirred at –25 °C for 20 min then quenched with sat NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, the solvent was removed *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexanes) to afford olefin **93** (150 mg, 84%) as a colorless oil.[11] Product was visualized with CAM stain, R_f = 0.31 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78–1.81 (m, 2H), 2.33–2.35 (m, 2H), 2.82–2.85 (td, *J* = 5.4, 2.1 Hz, 1H), 2.88–2.92 (m, 1H), 3.00–3.04 (m, 2H), 3.49–3.53 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.72–3.75 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.54–4.57 (d, *J* = 11.9 Hz, 1H), 4.59–4.62 (d, *J* = 11.0 Hz, 1H), 5.10–5.19 (m, 2H), 5.77–5.87 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1H), 7.28–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 36.1, 53.1, 55.1, 57.0, 57.5, 70.1, 73.5, 117.8, 127.9, 128.0, 128.6, 133.0, 138.0; IR (thin film NaCl): 3065, 3030, 2982, 2912, 2859, 1641, 1496, 1454, 1363, 1328, 1246, 1208, 1098, 1028, 996, 918, 738, 699 cm^{-1}; $[\alpha]_D^{23}$ = 42.4 (*c* = 0.029, $CHCl_3$); HR-MS (ESI) Calcd for $C_{16}H_{20}O_3$ $(M+Na)^+$ 283.1305, found 283.1305.

[11] Yields varied between 55-84% depending on reaction scale.



94

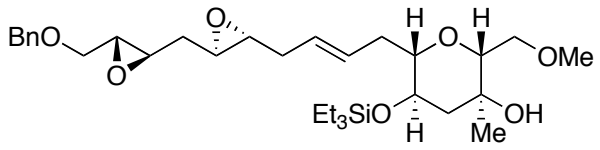
1,4-bis((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-ene (94): To a solution of olefin **93** (56 mg, 0.215 mmol) in CH_2Cl_2 (3 mL) was added 2nd generation Hoveyda-Grubbs catalyst (13 mg, 0.0215 mmol). A condenser was attached and the reaction was heated to 40 °C for 12 h, followed by removal of the solvent *in vacuo*. The residue was purified by column chromatography (gradient: 20% to 50% EtOAc in hexanes) to afford olefin **94** as a tan oil (45 mg, 85%). Product was visualized with CAM stain, R_f = 0.30 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.77–1.79 (t, *J* = 5.6 Hz, 4H), 2.26–2.36 (m, 4H), 2.79–2.82 (td, *J* = 5.6, 2.1 Hz, 2H), 2.87–2.90 (td, *J* = 5.6, 2.1 Hz, 2H), 2.99–3.04 (m, 4H), 3.48–3.52 (dd, *J* = 11.4, 5.4 Hz, 2H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 2H), 4.53–4.56 (d, *J* = 11.9 Hz, 2H), 4.59–4.62 (d, *J* = 11.9 Hz, 2H), 5.56–5.57 (m, 2H), 7.28–7.38 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.9, 35.0, 53.1, 55.1, 57.0, 57.7, 70.2, 73.5, 127.7, 127.9, 128.0, 128.6, 138.0; IR (thin film NaCl): 3089, 3062, 3030, 2992, 2895, 1721, 1689, 1497, 1471, 1453, 1422, 1367, 1329, 1272, 1244, 1210, 1112, 1028, 981, 939, 914, 892, 880, 858, 824, 734, 697, 620 cm^{-1}; $[\alpha]_D^{23}$ = 41.4 (*c* = 0.015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{30}H_{36}O_6$ $(M+Na)^+$ 515.2404, found 515.2396.



95

(2*R*,3*S*,5*R*,6*S*)-6-(4-((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-enyl)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (95): To a solution of olefin **85** (156 mg, 0.72 mmol) and olefin **94** (1.7 g, 3.60 mmol) in CH_2Cl_2 (4 mL) was added 2nd generation Hoveyda-Grubbs catalyst (68 mg, 0.11 mmol). A condenser was attached and the reaction was heated to 40 °C for 12 h, followed by removal of the solvent *in vacuo*. The residue was purified by column chromatography (gradient: 20% EtOAc to 50% EtOAc to 100% EtOAc to 5% MeOH in EtOAc to 10% MeOH in EtOAc) to afford olefin **95** as a tan oil (244 mg, 74%).[12] Product was visualized with CAM stain, R_f = 0.07 (70% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 3H), 1.46–1.52 (m, 1H), 1.59–1.66 (m, 1H), 1.75–1.81 (m, 1H), 2.02–2.05 (m, 2H), 2.17–2.24 (m, 3H), 2.35–2.47 (m, 1H), 2.71–2.74 (ddd, *J* = 5.4, 5.4, 2.2 Hz, 1H), 2.79–2.82 (m, 1H), 2.93–2.94 (m, 2H), 3.02–3.13 (m, 2H), 3.30–3.36 (m, 5H), 3.40–3.47 (m, 3H), 3.62–3.68 (dd, *J* = 11.4, 3.0 Hz, 1H), 4.46–4.49 (d, *J* = 11.9 Hz, 1H), 4.51–4.54 (d, *J* = 11.9 Hz, 1H), 5.42–5.49 (m, 1H), 5.54–5.63 (m, 1H), 7.22–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 34.8, 35.1, 35.5, 47.9, 53.2, 55.2, 57.0, 58.0, 59.6, 68.4, 70.1, 70.9, 72.5, 73.5, 79.7, 81.8, 126.8, 127.9, 128.0, 128.6, 129.6, 137.9; IR (thin film NaCl): 3431, 2978, 2928, 1455, 1364, 1272, 1202, 1098, 978 cm^{-1}; $[\alpha]_D^{23}$ = –80.0 (*c* = 0.01, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{36}O_7$ $(M+Na)^+$ 471.2353, found 471.2369.

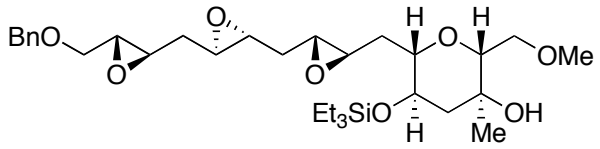
[12] Alternatively, the cross metathesis of olefin **85** with 300 mol% **93** afforded **95** in 44% yield as a 2.6:1 mixture of *E*:*Z* isomers.



96

(2*R*,3*S*,5*R*,6*S*)-6-((*E*)-4-((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl)oxiran-2-yl)but-2-enyl)-2-(methoxymethyl)-3-methyl-5-(triethylsilyloxy)tetrahydro-2*H*-pyran-3-ol (17): To a solution of alcohol **95** (576 mg, 1.28 mmol) in DMF (6.5 mL) was added imidazole (192 mg, 3.2 mmol) and TESCl (0.32 mL, 1.86 mmol). The reaction was stirred at ambient temperature for 1.5 h then quenched by addition of brine (5 mL). The aqueous layer was extracted with EtOAc (5 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude oil was purified by column chromatography (gradient: 40% to 60% EtOAc in hexanes) to afford silyl ether **96** as a colorless oil (591 mg, 82%). At this stage, the E:Z olefin isomers were separated by preparative HPLC (5μm silica column, hexanes:2-propanol, 97:3, 15 mL/min): t_R[(**96**)-*Z*] = 21.8 min, t_R[(**96**)-*E*] = 26.5 min. Product was visualized with CAM stain, R_f = 0.55 (80% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.56–0.62 (q, *J* = 7.9 Hz, 6H), 0.93–0.97 (t, *J* = 7.9 Hz, 9H), 1.21 (s, 3H), 1.59–1.65 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.71–1.84 (m, 2H), 2.02–2.11 (m, 2H), 2.27–2.30 (t, *J* = 5.8 Hz, 2H), 2.49–2.55 (dd, *J* = 14.6, 6.0 Hz, 1H), 2.76–2.79 (ddd, *J* = 5.3, 5.3, 2.1 Hz, 1H), 2.87–2.89 (m, 1H), 2.99–3.03 (m, 2H), 3.08–3.13 (ddd, *J* = 8.7, 8.7, 2.8 Hz, 1H), 3.15 (s, 1H), 3.31–3.38 (m, 4H), 3.40–3.44 (dd, *J* = 7.6, 6.3 Hz, 1H), 3.47–3.56 (m, 3H), 3.72–3.75 (dd, *J* = 11.4, 3.1 Hz, 1H), 4.53–4.56 (d, *J* = 11.9 Hz, 1H), 4.59–4.61 (d, *J* = 11.9 Hz, 1H), 5.43–5.51 (ddd, *J* = 14.1, 6.6, 6.6 Hz, 1H), 5.58–5.65 (ddd, *J* = 14.1, 6.9, 6.9 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.2, 7.0, 21.9, 34.9, 35.0, 35.2, 48.4, 53.2, 55.1, 57.0, 58.0, 59.6, 69.3, 70.2, 70.9, 72.7, 73.5, 79.4, 82.5, 126.4, 127.9, 128.0,

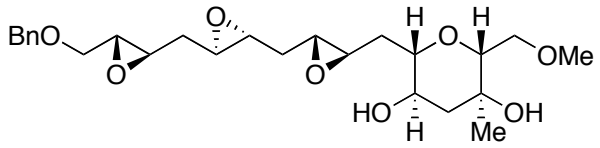
128.6, 123.0, 138.0; IR (thin film NaCl): 3462, 2876, 1496, 1456, 1414, 1378, 1274, 1240, 1202, 1097, 1006, 964, 844, 788, 743, 698 cm^{-1}; $[\alpha]_D^{23} = -11.8$ (c = 0.04, $CHCl_3$); HR-MS (ESI) Calcd for $C_{31}H_{50}O_7Si$ $(M+Na)^+$ 585.3218, found 585.3239.



97

(2*R*,3*S*,5*R*,6*S*)-6-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl) oxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-(methoxymethyl)-3-methyl-5-(triethylsilyloxy) tetrahydro-2*H*-pyran-3-ol (97): To a solution of olefin **96** (87 mg, 0.154 mmol) in 1:2 CH_3CN:DMM (5.0 mL) was added a solution of 0.05M $Na_2B_4O_7$•10 H_2O in 4.0 x 10^{-4} M Na_2(EDTA) (3.2 mL), and *n*-$BuNHSO_4$ (26 mg, 0.077 mmol). The solution was cooled to 0 °C with rapid stirring. Then chiral ketone **50** (80 mg, 0.308 mmol) was added and immediately, a 0.89 M solution of K_2CO_3 (2.6 mL) and a solution of Oxone® (756 mg, 1.23 mmol) in 4.0 x 10^{-4} M Na_2(EDTA) (2.7 mL) were added simultaneously over 15 min via syringe pump. The reaction was stirred at 0 °C an additional 30 min then 1 g of NaCl was added. The solution was extracted with EtOAc (8 x 25 mL), the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by column chromatography (gradient: 50% to 60% EtOAc in hexanes) to afford triepoxide **97** (73 mg, 82%) as a colorless oil. Diastereomeric ratio (93:7) was established by chiral HPLC (Chiralcel OD-H, hexanes:2-propanol, 96:4, 2 mL/min): t_R [(minor)-**97**] = 27.7 min, t_R [(major)-**97**] = 38.0 min. Product was visualized with CAM stain, R_f = 0.22 (60% EtOAc in hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ:

0.57–0.61 (q, *J* = 8.1 Hz, 6H), 0.93–0.95 (t, *J* = 8.1 Hz, 9H), 1.23 (s, 3H), 1.60–1.64 (dd, *J* = 11.7, 11.7 Hz, 1H), 1.69–1.81 (m, 5H), 1.95–1.97 (m, 1H), 2.05–2.08 (dd, *J* = 12.2, 4.5 Hz, 1H), 2.85–2.86 (m, 1H), 2.90–2.92 (m, 3H), 3.01–3.04 (m, 2H), 3.12 (s, 1H), 3.22–3.24 (m, 1H), 3.38–3.43 (m, 4H), 3.45–3.53 (m, 3H), 3.56–3.58 (dd, *J* = 9.1, 6.0 Hz, 1H), 3.73–3.75 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.54–4.56 (d, *J* = 11.9 Hz, 1H), 4.59–4.61 (d, *J* = 11.9 Hz, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 5.2, 7.0, 21.9, 34.1, 34.9, 35.3, 48.5, 53.1, 54.9, 55.4, 55.7, 56.2, 57.0, 59.7, 69.4, 70.2, 70.8, 72.6, 73.5, 79.5, 80.8, 128.0, 128.1, 128.6, 138.0; IR (thin film NaCl): 3465, 2954, 2876, 1456, 1414, 1376, 1275, 1240, 1202, 1097, 1006, 961, 844, 788, 743, 699 cm^{-1}; $[\alpha]_D^{23}$ = 3.0 (*c* = 0.01, $CHCl_3$); HR-MS (ESI) Calcd for $C_{31}H_{50}O_8Si$ $(M+Na)^+$ 601.3167, found 601.3181.



84

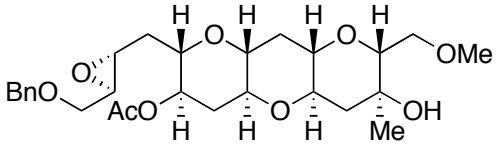
(2*R*,3*S*,5*R*,6*S*)-6-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(benzyloxymethyl)oxiran-2-yl)methyl) oxiran-2-yl)methyl)oxiran-2-yl)methyl)-2-(methoxymethyl)-3-methyltetrahydro-2*H*-pyran-3,5-diol (84): To a solution of silyl ether **97** (116 mg, 0.20 mmol) in THF (0.5 mL) at 0 °C was added a solution of TBAF (0.3 mL, 1M in THF). The reaction was stirred at 0 °C for 20 min and then loaded directly onto a silica column for purification. The solution was purified by column chromatography (gradient: 50% EtOAc in hexanes to 100% EtOAc) to afford triepoxide **84** (71 mg, 77%) as a colorless oil. Product was visualized with CAM stain, R_f = 0.08 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 3H), 1.54–1.60 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.68–1.78 (m,

4H), 1.80–1.88 (ddd, *J* = 14.2, 6.1, 3.8 Hz, 1H), 2.10–2.14 (dd, *J* = 11.6, 4.2 Hz, 2H), 2.63–2.64 (d, *J* = 5.1 Hz, 1H), 2.87–2.92 (m, 3H), 2.96–3.04 (m, 3H), 3.09 (s, 1H), 3.22–3.26 (ddd, *J* = 9.3, 5.6, 3.6 Hz, 1H), 3.37 (s, 3H), 3.42–3.57 (m, 5H), 3.70–3.74 (dd, *J* = 11.5, 3.0 Hz, 1H), 4.52–4.55 (d, *J* = 11.9 Hz, 1H), 4.57–4.60 (d, *J* = 11.9 Hz, 1H), 7.28–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 34.2, 34.8, 34.9, 47.8, 53.1, 55.2, 55.4, 55.5, 55.7, 57.0, 59.6, 68.0, 70.0, 70.8, 72.3, 73.5, 80.3, 80.5, 127.9, 128.0, 128.6, 137.9; IR (thin film NaCl): 3437, 2982, 2925, 2862, 1721, 1496, 1454, 1366, 1275, 1202, 1098, 981, 958, 933, 740, 700 cm^{-1}; $[\alpha]_D^{23}$ = 38.5 (*c* = 0.015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{36}O_8$ $(M+Na)^+$ 487.2302, found 487.2316.

Products of Water-Promoted Cascade (98 and 83):

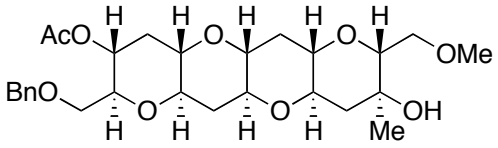
Representative Procedure: Triepoxide **84** (28mg, 0.06 mmol) was incubated in deionized H_2O (10 mL) at 60 °C for 5 days.[13] The water was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (6 mL) to which was added DMAP (3.5 mg, 0.03 mmol), Et_3N (0.17 mL, 1.21 mmol) and Ac_2O (0.11 mL, 1.21 mmol). The reaction was stirred at ambient temperature for 30 min. At which time SiO_2 was added and the solvent was removed *in vacuo*. The SiO_2 was then loaded onto a column and the product was purified by column chromatography (70% EtOAc in hexanes) to give a mixture of **98** and **83** which was purified further by preparative HPLC (5 μm SiO_2, hexanes:2-propanol, 92:8, 25 mL/min): t_R [**83**] = 13.7 min, t_R [**98**] = 15.2 min, to afford **98** (6.8 mg, 23%) and **83** (4.3 mg, 14%) as white solids.

[13] Treatment of **84** in H_2O at 80 °C for 9 days followed by analogous acetylation and purification afforded tetrad **83** (10.2 mg, 35%).



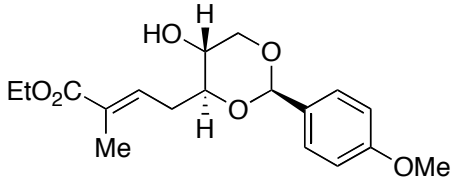
98

Triad 98: Product was visualized with CAM stain, R_f = 0.18 (70% EtOAc in hexanes)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.26 (s, 3H), 1.43–1.50 (dddd, *J* = 11.0, 11.0, 11.0, 11.0 Hz, 2H), 1.59–1.63 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.74–1.79 (ddd, *J* = 13.4, 7.3, 6.0 Hz, 1H), 1.84–1.88 (ddd, *J* = 14.8, 4.6, 3.3 Hz, 1H), 2.05 (s, 3H), 2.10–2.13 (dd, *J* = 11.8, 4.1 Hz, 1H), 2.33–2.35 (ddd, *J* = 11.4, 3.6, 3.6 Hz, 1H), 2.47–2.50 (ddd, *J* = 11.8, 4.2, 4.2 Hz, 1H), 2.94 (s, 1H), 2.97–2.99 (m, 1H), 3.00–3.03 (m, 1H), 3.04–3.12 (m, 4H), 3.41 (s, 3H), 3.44–3.50 (m, 3H), 3.53–3.59 (m, 2H), 3.70–3.72 (dd, *J* = 11.4, 3.4 Hz, 1H), 4.54–4.56 (d, *J* = 11.9 Hz, 1H), 4.59–4.61 (d, *J* = 11.9 Hz, 1H), 4.65–4.69 (ddd, *J* = 10.7, 10.7, 4.7 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 21.6, 22.9, 35.2, 36.7, 36.8, 46.9, 53.8, 57.7, 59.7, 71.0, 71.7, 72.1, 73.1, 74.1, 77.4, 77.8, 78.3, 78.4, 78.9, 85.4, 128.9, 129.1, 129.8, 140.3, 170.7; IR (thin film NaCl): 3462, 3062, 2922, 2853, 1739, 1456, 1374, 1236, 1099, 1030, 974, 957, 801, 738, 700 cm^{-1}; $[\alpha]_D^{23}$ = –10.2 (*c* = 0.0026, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{38}O_9$ $(M+Na)^+$ 529.2408, found 529.2405.



83

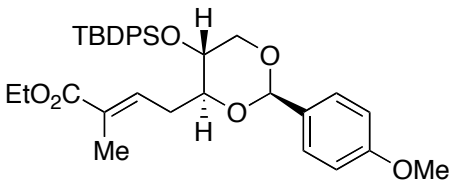
Tetrad 83: Product was visualized with CAM stain, R_f = 0.18 (70% EtOAc in hexanes)); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.27 (s, 3H), 1.44–1.50 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 2H), 1.54–1.58 (ddd, *J* = 11.0, 11.0, 11.0 Hz, 1H), 1.61–1.65 (dd, *J* = 11.8, 11.8 Hz, 1H), 1.91 (s, 3H), 2.12–2.15 (dd, *J* = 11.9, 4.1 Hz, 1H), 2.35–2.38 (ddd, *J* = 11.4, 3.9, 3.9 Hz, 1H), 2.39–2.42 (ddd, *J* = 11.6, 3.8, 3.8 Hz, 1H), 2.49–2.53 (ddd, *J* = 11.1, 4.4, 4.4 Hz, 1H), 2.91 (s, 1H), 3.04–3.18 (m, 6H), 3.40 (s, 3H), 3.48–3.59 (m, 6H), 4.48–4.50 (d, *J* = 12.3 Hz, 1H), 4.61–4.63 (d, *J* = 12.3 Hz, 1H), 4.82–4.86 (ddd, *J* = 11.2, 9.8, 4.9 Hz, 1H), 7.29–7.34 (m, 5H); ^{13}C NMR (125 MHz, CD_3CN) δ: 21.6, 22.4, 36.0, 36.2, 36.3, 46.2, 59.5, 68.1, 70.4, 71.0, 72.7, 74.2, 77.0, 77.4, 77.8, 77.9, 78.2, 78.4, 80.0, 84.5, 129.0, 129.3, 129.7, 139.8, 170.9; IR (thin film NaCl): 3495, 3030, 2935, 2875, 1740, 1496, 1455, 1370, 1338, 1237, 1205, 1153, 1100, 1067, 1042, 975, 954, 901, 735, 699 cm^{-1}; $[\alpha]_D^{23}$ = –16.5 (*c* = 0.0015, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{38}O_9$ $(M+Na)^+$ 529.2408, found 529.2416.



S7

(*E*)-ethyl 4-((2*R*,4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2-methylbut-2-enoate (S7): To a slurry of 2-deoxyribose (13.5 g, 101 mmol) in THF (200 mL) was added (carbethoxyethylidene)triphenylphosphorane (38.5 g, 106 mmol). The solution

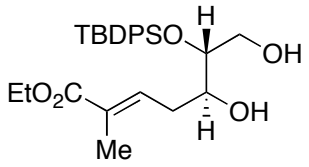
was heated to reflux for 3h, then the reaction was cooled to room temperature and the solvent was removed *in vacuo*. To this crude solid was added PMB dimethylacetal (32 mL, 181 mmol), CSA (4.6 g, 20 mmol) and CH_2Cl_2 (200 mL). The reaction was stirred at ambient temperature for 12 h. The reaction was quenched with Et_3N (2.8 mL, 20 mmol) and the solvent was removed *in vacuo*. The material was purified by column chromatography (20% to 50% EtOAc in hexanes) to afford alcohol **S7** (33 g, 99%). Product was visualized with CAM stain, R_f = 0.26 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28–1.32 (t, *J* = 7.1 Hz, 3H), 1.88 (s, 3H), 2.50–2.57 (dt, *J* = 15.0, 7.4 Hz, 1H), 2.67 (s, 1H), 2.73–2.79 (ddd, *J* = 15.6, 7.0, 2.0 Hz, 1H), 3.52–3.68 (m, 3H), 3.79 (s, 3H), 4.17–4.23 (m, 3H), 5.43 (s, 1H), 6.88–6.90 (d, *J* = 8.8 Hz, 2H), 6.91–6.96 (td, *J* = 7.3, 1.4 Hz, 1H), 7.39–7.42 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 14.4, 31.4, 55.4, 60.8, 65.6, 71.4, 81.0, 101.0, 113.7, 127.5, 130.0, 130.1, 137.8, 160.1, 168.4; IR (thin film NaCl): 3469, 2933, 2855, 1699, 1651, 1615, 1589, 1519, 1464, 1394, 1368, 1251, 1172, 1082, 997, 932, 871, 829, 785, 635 cm^{-1}; $[\alpha]_D^{23}$ = –36.1 (*c* = 0.095, $CHCl_3$); HR-MS (ESI) Calcd for $C_{18}H_{24}O_6(M+Na)^+$ 337.1646, found 337.1649.



102

(*E*)-ethyl 4-((2*R*,4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-2-methylbut-2-enoate (102): To a solution of alcohol **S7** (33 g, 101 mmol) and imidazole (16.5 g, 242 mmol), in DMF (67 mL) were added TBDPSCl (26 mL, 101 mmol) and the reaction was allowed to stir at ambient temperature overnight. The reaction was quenched by addition of sat. NH_4Cl (100 mL) and the aqueous layer was extracted with EtOAc (5 x 50 mL). The

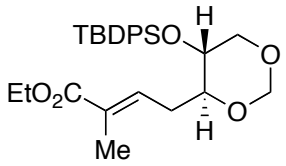
combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (5% to 20% EtOAc in hexanes) affording silyl ether **102** (47 g, 83%). Product was visualized with CAM stain, R_f = 0.38 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.14 (s, 9H), 1.31–1.35 (t, *J* = 7.1 Hz, 3H), 1.82 (s, 3H), 2.25–2.33 (dt, *J* = 15.9, 7.8 Hz, 1H), 2.78–2.84 (dd, *J* = 15.6, 6.7 Hz, 1H), 3.64–3.69 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.72–3.77 (td, *J* = 8.8, 4.6 Hz, 1H), 3.79–3.86 (m, 4H), 4.04–4.07 (dd, *J* = 10.2, 4.5 Hz, 1H), 4.21–4.26 (q, *J* = 7.1 Hz, 2H), 5.48 (s, 1H), 6.87–6.95 (m, 3H), 7.37–7.51 (m, 8H), 7.70–7.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 14.4, 19.4, 27.1, 31.2, 55.3, 60.5, 67.3, 71.5, 81.3, 100.7, 113.5, 127.3, 127.8, 127.9, 129.6, 130.1, 130.2, 132.9, 133.5, 134.9, 135.8, 135.9, 137.8, 159.9, 168.0; IR (thin film NaCl): 3049, 3071, 2932, 2858, 1708, 1652, 1616 1589, 1518, 1463, 1428, 1391, 1366, 1251, 1172, 1104, 1035, 979, 936, 823, 781, 741, 703, 652, 614 cm^{-1}; $[\alpha]_D^{23}$ = –17.3 (*c* = 0.038, $CHCl_3$); HR-MS (ESI) Calcd for $(M+Na)^+$ $C_{34}H_{42}O_6Si$ 575.2823, found 575.2811.



S8

(5*S*,6*R*,*E*)-ethyl 6-(*tert*-butyldiphenylsilyloxy)-5,7-dihydroxy-2-methylhept-2-enoate (S8): To a solution of PMP acetal **102** (23 g, 41 mmol) in MeOH (255 mL), THF (60 mL) and H_2O (20 mL) was added TsOH monohydrate (1.5 g, 8 mmol). The reaction was heated to 60 °C for 2 h, cooled to ambient temperature and quenched with Et_3N (1.1 mL). The solvent was removed *in vacuo* and the crude material was purified by column chromatography (gradient: 20% to 40% EtOAc in hexanes) to afford diol **S8** as a colorless oil (11 g, 58%). Product was visualized with

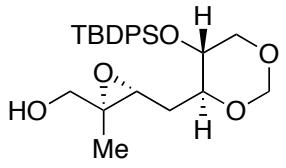
CAM stain, R_f = 0.32 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (s, 9H), 1.27–1.31 (t, *J* = 7.1 Hz, 3H), 1.76–1.77 (d, *J* = 1.4 Hz, 3H), 2.23–2.30 (m, 2H), 2.38–2.44 (ddd, *J* = 15.4, 6.4, 4.2 Hz, 1H), 2.74–2.75 (d, *J* = 4.5 Hz, 1H), 3.61–3.70 (m, 2H), 3.72–3.78 (m, 1H), 3.82–3.88 (sextet, *J* = 4.5 Hz, 1H), 4.15–4.20 (q, *J* = 7.1 Hz, 2H), 6.71–6.75 (td, *J* = 7.3, 1.4 Hz, 1H), 7.38–7.48 (m, 6H), 7.68–7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 14.5, 19.6, 27.2, 32.7, 60.7, 64.0, 73.5, 75.7, 128.0, 128.1, 130.1, 130.2, 130.3, 133.1, 133.7, 135.9, 136.0, 138.0, 168.1; IR (thin film NaCl): 3451, 3071, 3049, 2932, 2893, 2858, 1707, 1649, 1472, 1428, 1391, 1367, 1278, 1191, 1111, 916, 822, 741, 704 cm^{-1}; $[\alpha]_D^{23}$ = 15.4 (*c* = 0.075, $CHCl_3$); HR-MS (ESI) Calcd for $C_{26}H_{36}O_5Si$ $(M+Na)^+$ 479.2224, found 479.2212.



101

(*E*)-ethyl 4-((4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-1,3-dioxan-4-yl)-2-methylbut-2-enoate (101): To a solution of diol **S8** (8.6 g, 18.8 mmol) in CH_2Cl_2 (80 mL) was added dimethoxymethane (DMM) (2.5 mL, 30 mmol) and BF_3•OEt_2 (3.7 mL, 30 mmol). The reaction was stirred at ambient temperature for 1h and then quenched with aqueous sat. $NaHCO_3$ (30 mL). The aqueous layer was extracted with EtOAc (3 x 40 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (20% EtOAc in hexanes) to afford methylene acetal **101** (7.5 g, 85%) as a colorless oil. Product was visualized with CAM stain, R_f = 0.45 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (s, 9H), 1.29–1.32 (t, *J* = 7.5 Hz, 3H), 1.76–1.77 (d, *J* = 1.0 Hz,

3H), 2.10–2.18 (ddd, J = 16.0, 7.8, 7.8 Hz, 1H), 2.68–2.74 (dd, J = 16.3, 6.7 Hz, 1H), 3.35–3.40 (dd, J = 10.4, 9.7 Hz, 1H), 3.52–3.63 (m, 2H), 3.90–3.94 (dd, J = 10.5, 4.6 Hz, 1H), 4.18–4.23 (q, J = 7.1 Hz, 2H), 4.54–4.56 (d, J = 6.1 Hz, 1H), 4.90–4.92 (d, J = 6.1 Hz, 1H), 6.79–6.83 (td, J = 6.9, 1.4 Hz, 1H), 7.39–7.49 (m, 6H), 7.64–7.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.8, 14.5, 19.4, 27.1, 31.3, 60.6, 67.6, 71.5, 81.4, 93.4, 127.9, 128.0, 129.9, 130.3, 130.4, 132.9, 133.5, 135.9, 136.0, 137.6, 168.0; IR (thin film NaCl): 3072, 3050, 2932, 2896, 2857, 2772, 1709, 1652, 1472, 1428, 1391, 1365, 1280, 1257, 1219, 1173, 1106, 1034, 947, 837, 820, 741, 703 cm^{-1}; $[\alpha]_D^{23}$ = 15.1 (c = 0.075, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{36}O_5Si$ $(M+Na)^+$ 491.2224, found 491.2232.

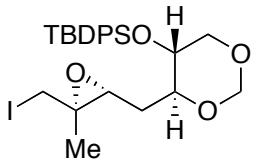


103

((2*R*,3*R*)-3-(((4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)methanol (103): Ester **101** (9 g, 19.2 mmol) was dissolved in CH_2Cl_2 (80mL) and cooled to –78 °C. A solution of DIBALH (48 mL of 1M in CH_2Cl_2, 48 mmol) was added dropwise over 20 min and the reaction was stirred at –78 °C an additional 30 min. The reaction was quenched at –78 °C by dropwise addition of MeOH (20 mL) and then poured into sat. Rochelle's salt (200 mL) at ambient temperature followed by vigorous stirring for 3 h. The mixture was extracted with CH_2Cl_2 (3 x 150 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford allylic the alcohol which was used in the subsequent epoxidation without purification.

In a round bottom flask, 4Å molecular sieves (5 g) were flame dried *in vacuo* for 8 min then cooled to ambient temperature. A magnetic stir bar, CH_2Cl_2 (65 mL), and (–)-diethyl (D)-tartrate (474 mg, 2.3 mmol) were then added and the slurry was cooled to –25 °C. Next, $Ti(O\textit{i}Pr)_4$ (0.57 mL, 1.9 mmol) was added followed by slow addition of a *t*-BuOOH solution (7 mL of 5.5M in decane, 38 mmol). The mixture was allowed to stir at –25 °C for 30 minutes followed by addition of a solution of the allylic alcohol (above) in CH_2Cl_2 (10 mL). The reaction was stirred at –25 °C for an additional 15 h and warmed to 0 °C. In a separate flask, Fe(II) sulfate heptahydrate (6.3 g), tartaric acid (1.9 g), and H_2O (67 mL) were cooled to 0 °C. The crude epoxidation reaction was slowly poured into the aqueous solution and stirred at ambient temperature for 15 min. The aqueous layer was extracted with Et_2O (4 x 100 mL). To the combined organic extracts was added 50 mL 30% NaOH in brine and the mixture was stirred at ambient temperature for 1 h. The organic layer was separated, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 40% to 50% EtOAc in hexanes) affording epoxy alcohol **103** as a colorless oil (7.4 g, 88% over 2 steps, 85:15 dr by ^{1}H-NMR); Product was visualized with CAM stain, R_f = 0.22 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (s, 9H), 1.24 (s, 3H), 1.59–1.66 (ddd, *J* = 14.8, 8.7, 6.2 Hz, 1H), 1.85–1.88 (dd, *J* = 8.2, 4.5 Hz, 1H), 2.04–2.10 (ddd, *J* = 14.7, 5.8, 2.6 Hz, 1H), 3.12–3.15 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.32–3.37 (dd, *J* = 10.6, 9.5 Hz, 1H), 3.53–3.69 (m, 4H), 3.86–3.89 (dd, *J* = 10.6, 3.9 Hz, 1H), 4.55–4.56 (d, *J* = 6.1 Hz, 1H), 4.92–4.93 (d, *J* = 6.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.62–7.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.4, 19.4, 27.1, 30.8, 57.3, 60.1, 65.4, 67.5, 71.5, 80.9, 93.3, 127.9, 128.1, 130.2, 130.3 132.8, 133.6, 135.9, 136.0; IR (thin film NaCl): 3451, 3071, 3050, 2931, 2858, 2765, 1473, 1427, 1391, 1362, 1293,

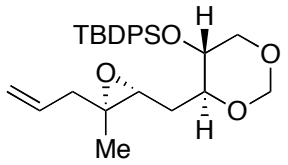
1265, 1173, 1112, 1035, 946, 888, 820, 740, 702 cm^{-1}; $[\alpha]_D^{23} = -1.7$ (c = 0.022, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{34}O_5Si$ $(M+Na)^+$ 465.2068, found 465.2074.



S9

***tert*-butyl((4*S*,5*R*)-4-(((2*R*,3*S*)-3-(iodomethyl)-3-methyloxiran-2-yl)methyl)-1,3-dioxan-5-yloxy)diphenylsilane (S9)**: Triphenylphosphine (PPh_3) (5.1 g, 19 mmol) and imidazole (1.3 g, 19 mmol) were dissolved in Et_2O (60 mL) and CH_3CN (20 mL) and cooled to 0 °C. With vigorous stirring, iodine (4.92 g, 19 mmol) was added in portions over 10 min then warmed to ambient temperature and stirred for 15 min. The slurry was then cooled to 0 °C and a solution of epoxy alcohol **103** (7.5 g, 16.9 mmol) in Et_2O (10 mL) was added dropwise over 10 min. The reaction was warmed to ambient temperature and stirred for 15 min. The reaction was then quenched by addition of sat. $Na_2S_2O_3$ (100 mL). The aqueous layer was extracted with Et_2O (3 x 75 mL), and the combined organic extracts were dried over $MgSO_4$. The solvent was removed *in vacuo* and the crude material was loaded onto silica gel using a minimal amount of CH_2Cl_2 for purification by column chromatography (5% EtOAc in hexanes) to afford iodide **S9** as a yellow oil (6.1 g, 66%); Product was visualized with CAM stain, R_f = 0.70 (40% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.43 (s, 3H), 1.62–1.69 (ddd, J = 14.4, 8.7, 5.7 Hz, 1H), 1.94–2.00 (ddd, J = 14.7, 6.7, 2.4 Hz, 1H), 2.97–3.00 (dd, J = 6.5, 6.5 Hz, 1H), 3.03–3.06 (d, J = 9.8 Hz, 1H), 3.20–3.22 (d, J = 9.8 Hz, 1H), 3.33–3.38 (dd, J = 10.6, 10.6 Hz, 1H), 3.55–3.58 (m, 2H), 3.85–3.89 (dd, J = 10.5, 3.6 Hz, 1H), 4.55–4.57 (d, J = 6.1 Hz, 1H), 4.92–4.93 (d, J = 6.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.60–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0,

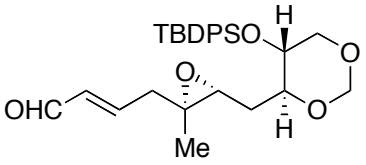
16.2, 19.4, 27.1, 31.5, 59.6, 63.6, 67.5, 71.6, 80.7, 93.4, 128.0, 128.1, 130.3, 130.4, 132.8, 133.6, 135.9, 136.0; IR (thin film NaCl): 3071, 2857, 2763, 1471, 1426, 1386, 1362, 1292, 1256, 1217, 1105, 998, 947, 895, 819, 740, 701 cm^{-1}; $[\alpha]_D^{23} = -8.5$ (c = 0.048, $CHCl_3$); HR-MS (ESI) Calcd for $C_{25}H_{33}IO_4Si$ $(M+Na)^+$ 575.1085, found 575.1076.



104

((4*S*,5*R*)-4-(((2*R*,3*R*)-3-allyl-3-methyloxiran-2-yl)methyl)-1,3-dioxan-5-yloxy)(*tert*-butyl) diphenylsilane (104): To a solution of iodide **S9** (1.8 g, 3.26 mmol) in THF (16 mL) was added copper(I) bromide-dimethyl sulfide (234 mg, 1.1 mmol), and HMPA (1.4 mL, 13.0 mmol). The solution was immediately cooled to –25 °C and stirred for 5 min. Then a solution of vinyl magnesium bromide (8.2 mL of 1M in THF, 8.2 mmol) was added dropwise over 5 min with vigorous stirring. The reaction was stirred at –25 °C for 15 min, then quenched at –25 °C by addition of sat. NH_4Cl. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by column chromatography (10% EtOAc in hexanes) to afford olefin **104** (531 mg, 36%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.22 (10% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01 (s, 9H), 1.19 (s, 3H), 1.55–1.63 (ddd, J = 14.6, 8.7, 6.0 Hz, 1H), 1.95–2.00 (ddd, J = 14.6, 6.3, 2.7 Hz, 1H), 2.12–2.17 (dd, J = 14.3, 6.8 Hz, 1H), 2.27–2.32 (dd, J = 14.2, 7.3 Hz, 1H), 2.83–2.86 (dd, J = 6.1, 6.1 Hz, 1H), 3.27–3.32 (dd, J = 10.5, 9.6 Hz, 1H), 3.70–3.57 (m, 2H), 3.79–3.83 (dd, J = 10.5, 4.1 Hz, 1H), 4.50–4.52 (d, J = 6.1 Hz, 1H), 4.88–4.89 (d, J = 6.2 Hz, 1H), 5.05–5.09 (m, 2H), 5.69–5.79 (m, 1H), 7.34–7.44 (m,

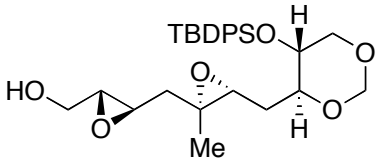
6H), 7.58–7.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.9, 19.5, 27.2, 31.4, 43.2, 59.6, 60.0, 67.6, 71.6, 81.1, 93.4, 118.0, 127.9, 128.1, 130.2, 130.4, 132.9, 133.7, 133.8, 135.9, 136.0; IR (thin film NaCl): 3072, 2931, 2857, 1472, 1427, 1390, 1361, 1292, 1172, 1112, 1036, 998, 947, 820, 741, 702, 672, 622 cm^{-1}; $[\alpha]_D^{23}$ = –7.1 (*c* = 0.012, $CHCl_3$); HR-MS (ESI) Calcd for $C_{27}H_{36}O_4Si(M+Na)^+$ 475.2275, found 475.2265.



105

(*E*)-4-((2*R*,3*R*)-3-(((4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)but-2-enal (105): To a solution of olefin **104** (1.77 g, 3.91 mmol) in CH_2Cl_2 (10 mL) was added acrolein (0.780 mL, 11.7 mmol) and the Hoveyda-Grubbs 2nd generation catalyst (134 mg, 0.21 mmol). A reflux condenser was attached and the reaction heated to reflux for 12 h. The reaction was cooled to ambient temperature and ethyl vinyl ether was added (5 mL). The reaction is stirred at room temperature for 10 min and then was concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography (gradient: 10% to 20% EtOAc in hexanes) to afford aldehyde **105** (1.7 g, 92%, 9:1 *E*:*Z* by ^{1}H-NMR); Product was visualized with CAM stain, R_f = 0.12 (20% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.25 (s, 3H), 1.64–1.71 (ddd, *J* = 14.3, 8.0, 6.0 Hz, 1H), 1.97–2.03 (ddd, *J* = 14.8, 6.2, 2.8 Hz, 1H), 2.48–2.59 (m, 2H), 2.84–2.87 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.32–3.37 (dd, *J* = 10.5, 9.5 Hz, 1H), 3.53–3.62 (m, 2H), 3.86–3.90 (dd, *J* = 10.4, 4.1 Hz, 1H), 4.55–4.56 (d, *J* = 6.1 Hz, 1H), 4.92–4.93 (d, *J* = 6.0 Hz, 1H), 6.15–6.21 (dd, *J* = 15.7, 7.9 Hz, 1H), 6.74–6.82 (ddd, *J* = 15.7, 7.0, 7.0 Hz, 1H), 7.38–7.48 (m, 6H), 7.62–7.68 (m, 4H), 9.52–9.54 (d, *J* = 7.9 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ: 17.3, 19.4, 27.1, 31.1, 41.5, 58.7, 59.9, 67.4, 71.6, 80.8, 93.4, 127.9, 128.1, 130.3, 130.4, 132.8, 133.5, 135.5, 135.9, 136.0, 152.7, 193.8; IR (thin film NaCl): 3071, 2961, 2931, 2857, 2763, 1693, 1638, 1472, 1428, 1389, 1361, 1293, 1234, 1173, 1112, 1035, 978, 947, 890, 820, 742, 703 cm^{-1}; $[\alpha]_D^{23}$ = 6.0 (*c* = 0.016, $CHCl_3$); HR-MS (ESI) Calcd for $C_{28}H_{36}O_5Si$ $(M+Na)^+$ 503.2224, found 503.2235.

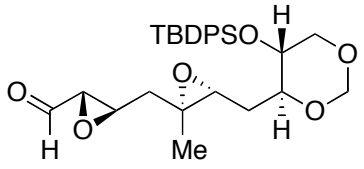


106

((2*R*,3*R*)-3-(((2*R*,3*R*)-3-(((4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)methyl)oxiran-2-yl)methanol (106): A solution of aldehyde **105** (1.73 g, 3.6 mmol) in MeOH (7 mL) was cooled to 0 °C and $NaBH_4$ (102 mg, 2.7 mmol) was added, after which the reaction was stirred at 0 °C for 20 min. The reaction was quenched with sat. NH_4Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude allylic alcohol was used without further purification.

Powdered 4Å molecular sieves (1 g) were flame dried under vacuum for 8 minutes and then cooled to ambient temperature. To the sieves was added CH_2Cl_2 (15 mL), D–(-)-diethyl tartrate (89 mg, 0.432 mmol) and the mixture was cooled to –25 °C. Next, $Ti(OiPr)_4$ (107 μL, 0.36 mmol) was added in one portion followed by the dropwise addition of *t*-BuOOH (1.3 mL of 5.5M in decane, 7.2 mmol) and the reaction was stirred at –25 °C for 30 min. The allylic alcohol was added as a solution in CH_2Cl_2 (3 mL) and the reaction was stirred at –25 °C for 15 h. The reaction was quenched by slow addition to a solution of $Fe(II)SO_4•7H_2O$ (1.2 g), tartaric acid

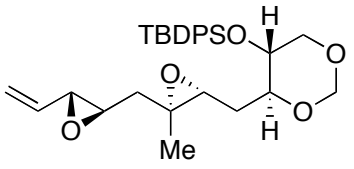
(360 mg), and H_2O (13 mL) at 0 °C. The reaction was stirred at room temperature for 15 min and the aqueous layer extracted with Et_2O. The organic extracts were combined and to them was added 30% NaOH in brine (10 mL) and the reaction was stirred at room temperature for 1h. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient: 30% to 40% EtOAc in hexanes) to afford epoxide **106** (983 mg, 57% over 2 steps); Product was visualized with CAM stain, R_f = 0.14 (40% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.32 (s, 3H), 1.66–1.71 (dd, *J* = 14.6, 6.7 Hz, 1H), 1.75–1.80 (dd, *J* = 14.3, 4.8 Hz, 1H), 1.91 (s, 1H), 1.98–2.04 (ddd, *J* = 14.9, 6.4, 2.5 Hz, 1H), 2.84–2.87 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.93–2.95 (ddd, *J* = 4.6, 2.5, 2.5 Hz, 1H), 3.07–3.10 (ddd, *J* = 6.9, 4.6, 2.3 Hz, 1H), 3.32–3.37 (dd, *J* = 10.5, 9.4 Hz, 1H), 3.54–3.67 (m, 3H), 3.85–3.92 (m, 2H), 4.55–4.56 (d, *J* = 6.1 Hz, 1H), 4.91–4.93 (d, *J* = 6.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.62–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 19.4, 27.1, 31.0, 41.0, 52.8, 58.0, 58.4, 60.5, 61.6, 67.4, 71.6, 80.8, 93.3, 127.9, 128.1, 130.2, 130.3, 132.8, 133.6, 135.9, 136.0; IR (thin film NaCl): 3453, 3071, 2931, 2858, 1472, 1428, 1389, 1361, 1293, 1232, 1172, 1111, 1034, 946, 820, 742, 703, 671 cm^{-1}; $[\alpha]_D^{23}$ = 11.7 (*c* = 0.019, $CHCl_3$); HR-MS (ESI) Calcd for $C_{28}H_{38}O_6Si$ $(M+Na)^+$ 521.2330, found 521.2323.



S10

(2*S*,3*R*)-3-(((2*R*,3*R*)-3-(((4*S*,5*R*)-5-(*tert*-butyldiphenylsilyloxy)-1,3-dioxan-4-yl)methyl)-2-methyloxiran-2-yl)methyl)oxirane-2-carbaldehyde (S10): Alcohol **106** (698 g, 1.4 mmol) was

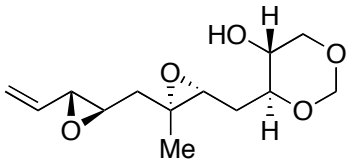
dissolved in CH_2Cl_2 (14 mL) to which was added solid $NaHCO_3$ (1.2 g, 14 mmol) and Dess-Martin periodinane (890 mg, 2.1 mmol). The reaction was stirred at ambient temperature for 1h. The reaction was quenched by addition of water (10 mL) followed by addition of sat. $Na_2S_2O_3$ (19 mL). The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (30% EtOAc in hexanes) to afford aldehyde **S10** (529g, 78%) as a colorless oil; Product was visualized with CAM stain, R_f = 0.62 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.33 (s, 3H), 1.64–1.74 (m, 2H), 1.85–1.90 (dd, *J* = 14.5, 4.1 Hz, 1H), 1.97–2.03 (ddd, *J* = 14.7, 6.4, 2.7 Hz, 1H), 2.83–2.86 (dd, *J* = 6.1, 6.1 Hz, 1H), 3.15–3.17 (dd, *J* = 6.2, 2.0 Hz, 1H), 3.33–3.38 (m, 2H), 3.53–3.63 (m, 2H), 3.86–3.89 (dd, *J* = 10.0, 3.8 Hz, 1H), 4.54–4.56 (d, *J* = 6.1 Hz, 1H), 4.91–4.93 (d, *J* = 6.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.62–7.69 (m, 4H), 9.03–9.04 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.2, 19.4, 27.1, 30.9, 40.7, 53.9, 58.1, 58.5, 60.6, 67.4, 71.6, 80.7, 93.4, 128.0, 128.1, 130.3, 130.4, 132.8, 133.6, 135.9, 136.0, 198.1; IR (thin film NaCl): 3071, 2931, 2857, 1729, 1472, 1428, 1389, 1362, 1292, 1232, 1172, 1112, 1034, 946, 890, 821, 741, 704, 671 cm^{-1}; $[\alpha]_D^{23}$ = –8.9 (*c* = 0.012, $CHCl_3$); HR-MS (ESI) Calcd for $C_{28}H_{36}O_6Si$ $(M+Na)^+$ 519.2173, found 519.2155.



107

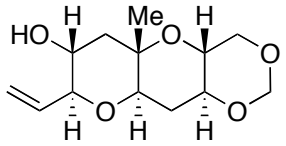
***tert*-butyl((4*S*,5*R*)-4-(((2*R*,3*R*)-3-methyl-3-(((2*R*,3*R*)-3-vinyloxiran-2-yl)methyl)oxiran-2-yl) methyl)-1,3-dioxan-5-yloxy)diphenylsilane (107)**: Methyltriphenylphosphonium bromide (446

mg, 1.25 mmol) and *t*BuOK (140 mg, 1.25 mmol) were loaded into a round bottom flask in a glovebox. The flask was removed from the box and a reflux condenser was attached. To the flask was added THF (10 mL) and the reaction was heated to 55 °C for 30 min, accompanied by formation of a yellow slurry. The reaction was cooled to ambient temperature and aldehyde **S10** was added as a solution in THF (3 mL). The reaction was stirred at ambient temperature for 15 min and was quenched with aqueous sat. NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (gradient 10% to 30% EtOAc in hexanes) to afford vinyl epoxide **107** (454 mg, 92%); Product was visualized with CAM stain, R_f = 0.48 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (s, 9H), 1.32 (s, 3H), 1.60–1.71 (m, 2H), 1.78–1.82 (dd, *J* = 14.2, 5.0 Hz, 1H), 1.99–2.05 (ddd, *J* = 14.7, 6.4, 2.6 Hz, 1H), 2.86–2.89 (dd, *J* = 6.1, 6.1 Hz, 1H), 2.94–2.98 (ddd, *J* = 6.8, 4.8, 2.1 Hz, 1H), 3.10–3.13 (dd, *J* = 7.1, 2.1 Hz, 1H), 3.32–3.37 (dd, *J* = 10.7, 9.6 Hz, 1H), 3.53–3.62 (m, 2H), 3.84–3.88 (dd, *J* = 10.5, 3.7 Hz, 1H), 4.55–4.56 (d, *J* = 6.1 Hz, 1H), 4.91–4.93 (d, *J* = 6.3 Hz, 1H), 5.28–5.31 (dd, *J* = 9.7, 2.0 Hz, 1H), 5.46–5.62 (m, 2H), 7.37–7.48 (m, 6H), 7.62–7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 19.4, 27.2, 31.1, 41.5, 57.3, 58.4, 58.4, 60.5, 67.5, 71.6, 80.7, 93.4, 119.8, 127.9, 128.1, 130.2, 130.3, 132.8, 133.6, 135.5, 135.9, 136.0; IR (thin film NaCl): 3072, 3050, 2931, 2857, 2764, 1472, 1428, 1403, 1389, 1361, 1292, 1255, 1232, 1172, 1111, 1035, 998, 946, 878, 820, 742, 703, 671 cm^{-1}; $[\alpha]_D^{23}$ = 7.1 (*c* = 0.011, $CHCl_3$); HR-MS (ESI) Calcd for $C_{29}H_{38}O_5Si$ $(M+Na)^+$ 517.2381, found 517.2369.



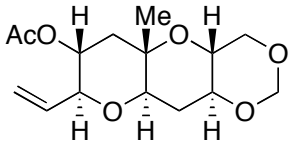
100

(4*S*,5*R*)-4-(((2*R*,3*R*)-3-methyl-3-(((2*R*,3*R*)-3-vinyloxiran-2-yl)methyl)oxiran-2-yl)methyl)-1,3-dioxan-5-ol (100): To a solution of silyl ether **107** (227 g, 0.46 mmol) in THF (0.50 mL) at 0 °C was added TBAF (0.690 mL of 1M solution in THF, 0.69 mmol) and the reaction was stirred at 0 °C for 30 min. The material was loaded directly onto a silica gel column and purified (gradient 10% to 50% EtOAc in hexanes) to afford **100** (116 mg, 98%); Product was visualized with CAM stain, R_f = 0.18 (50% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.41 (s, 3H), 1.65–1.69 (dd, *J* = 14.3, 7.3 Hz, 1H), 1.89–1.94 (m, 2H), 2.09–2.13 (ddd, *J* = 15.0, 4.1, 4.1 Hz, 1H), 2.33–2.34 (d, *J* = 5.4 Hz, 1H), 2.98–3.00 (ddd, *J* = 6.9, 4.4, 2.1 Hz, 1H), 3.08–3.10 (dd, *J* = 7.7, 4.2 Hz, 1H), 3.12–3.14 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.34–3.37 (dd, *J* = 10.4, 10.4 Hz, 1H), 3.52–3.55 (ddd, *J* = 9.5, 5.9, 3.9 Hz, 1H), 3.72–3.77 (m, 1H), 4.16–4.19 (dd, *J* = 10.8, 5.0 Hz, 1H), 4.60–4.61 (d, *J* = 6.1 Hz, 1H), 5.02–5.03 (d, *J* = 6.1 Hz, 1H), 5.30–5.31 (d, *J* = 10.1 Hz, 1H), 5.48–5.51 (d, *J* = 17.2 Hz, 1H), 5.55–5.61 (ddd, *J* = 17.4, 10.2, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 17.3, 31.1, 41.5, 57.3, 58.6, 59.1, 60.2, 65.5, 71.1, 80.3, 93.5, 120.0, 135.3; IR (thin film NaCl): 3443, 3088, 2992, 2923, 2855, 2772, 1457, 1407, 1387, 1285, 1226, 1171, 1129, 1073, 1027, 940, 878, 843, 677 cm^{-1}; $[\alpha]_D^{23}$ = 13.0 (*c* = 0.005, $CHCl_3$); HR-MS (ESI) Calcd for $C_{13}H_{20}O_5$ $(M+Na)^+$ 279.1203, found 279.1208.



99

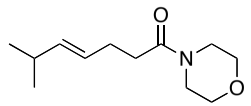
Triad (99): To a solution of diepoxide **100** (67 mg, 0.26 mmol) in CH_2Cl_2 (9 mL) was added CSA (15 mg, 0.065 mmol). The reaction was stirred at ambient temperature for 15 h and the solvent was removed *in vacuo*. The crude material was purified by column chromatography (50% EtOAc in hexanes) to afford **99** (39 mg, 57%) as a white solid. Product was visualized with CAM stain, R_f = 0.20 (50% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.51–1.55 (dd, *J* = 10.9, 10.9 Hz, 1H), 1.72 (br s, 1H), 1.74–1.80 (ddd, *J* = 11.8, 11.8, 11.8 Hz, 1H), 2.19–2.25 (m, 2H), 3.24–3.27 (dd, *J* = 12.2, 3.8 Hz, 1H), 3.28–3.33 (ddd, *J* = 11.5, 9.5, 4.4 Hz, 1H), 3.41–3.44 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.57–3.63 (m, 3H), 4.10–4.12 (dd, *J* = 10.3, 4.6 Hz, 1H), 4.62–4.63 (d, *J* = 6.2 Hz, 1H), 5.01–5.02 (d, *J* = 6.2 Hz, 1H), 5.35–5.37 (d, *J* = 10.6 Hz, 1H), 5.43–5.46 (d, *J* = 17.3 Hz, 1H), 5.85–5.90 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.1, 30.5, 45.4, 66.5, 68.8, 69.9, 74.1, 78.6, 78.9, 85.5, 94.1, 119.8, 135.5; IR (KBr pellet): 3452, 2988, 2941, 2860, 2777, 1460, 1381, 1289, 1267, 1229, 1201, 1169, 1099, 1065, 1029, 946, 926, 858, 735 cm^{-1}; $[\alpha]_D^{23}$ = 21.4 (*c* = 0.007, $CHCl_3$); HR-MS (ESI) Calcd for $C_{13}H_{20}O_5$ $(M+Na)^+$ 279.1203, found 279.1214.



S11

Acetylated triad (S11): To a solution of triad **99** (7 mg, 0.03 mmol) in CH_2Cl_2 (0.5 mL) was added Ac_2O (0.025 mL, 0.27 mmol) and Et_3N (0.063 mL, 0.45 mmol). The reaction was stirred at ambient temperature for 30 min. A small amount of SiO_2 was then added and the solvent was removed *in vacuo*. The material was then dry loaded onto a silica gel column and purified (20% EtOAc in hexanes) to afford **S11** (6 mg, 67%) as a white solid. Product was visualized with CAM stain, R_f = 0.45 (50% EtOAc in hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.36 (s, 3H), 1.53–1.57 (dd, *J* = 11.4, 11.4 Hz, 1H), 1.76–1.82 (ddd, *J* = 11.8, 11.8, 11.7 Hz, 1H), 2.02 (s, 3H), 2.19–2.23 (dt, *J* = 11.6, 4.2 Hz, 1H), 2.23–2.26 (dd, *J* = 11.6, 5.3 Hz, 1H), 3.27–3.32 (m, 2H), 3.39–3.42 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.58–3.62 (td, *J* = 9.7, 4.6 Hz, 1H), 3.77–3.80 (dd, *J* = 9.8, 6.9 Hz, 1H), 4.10–4.12 (dd, *J* = 10.3, 4.6 Hz, 1H), 4.62–4.63 (d, *J* = 6.2 Hz, 1H), 4.84–4.88 (ddd, *J* = 11.3, 9.8, 5.3 Hz, 1H), 5.02–5.03 (d, *J* = 6.2 Hz, 1H), 5.24–5.27 (ddd, *J* = 10.5, 1.5, 1.0 Hz, 1H), 5.34–5.37 (ddd, *J* = 17.2, 1.4, 1.0 Hz, 1H), 5.76–5.81 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.9, 21.3, 30.5, 42.9, 66.6, 69.9, 70.0, 73.9, 78.6, 79.2, 82.4, 94.2, 119.3, 134.8, 170.0; IR (thin film NaCl): 2955, 2858, 2777, 1743, 1461, 1432, 1376, 1280, 1236, 1202, 1170, 1098, 1067, 1029, 971, 978, 927, 911, 889, 863, 801, 736, 675; $[\alpha]_D^{23}$ = 1.4 (*c* = 0.003, $CHCl_3$). HR-MS (ESI) Calcd for $C_{15}H_{22}O_6$ $(M+Na)^+$ 321.1309, found 321.1309.

Chapter 2: Spectra



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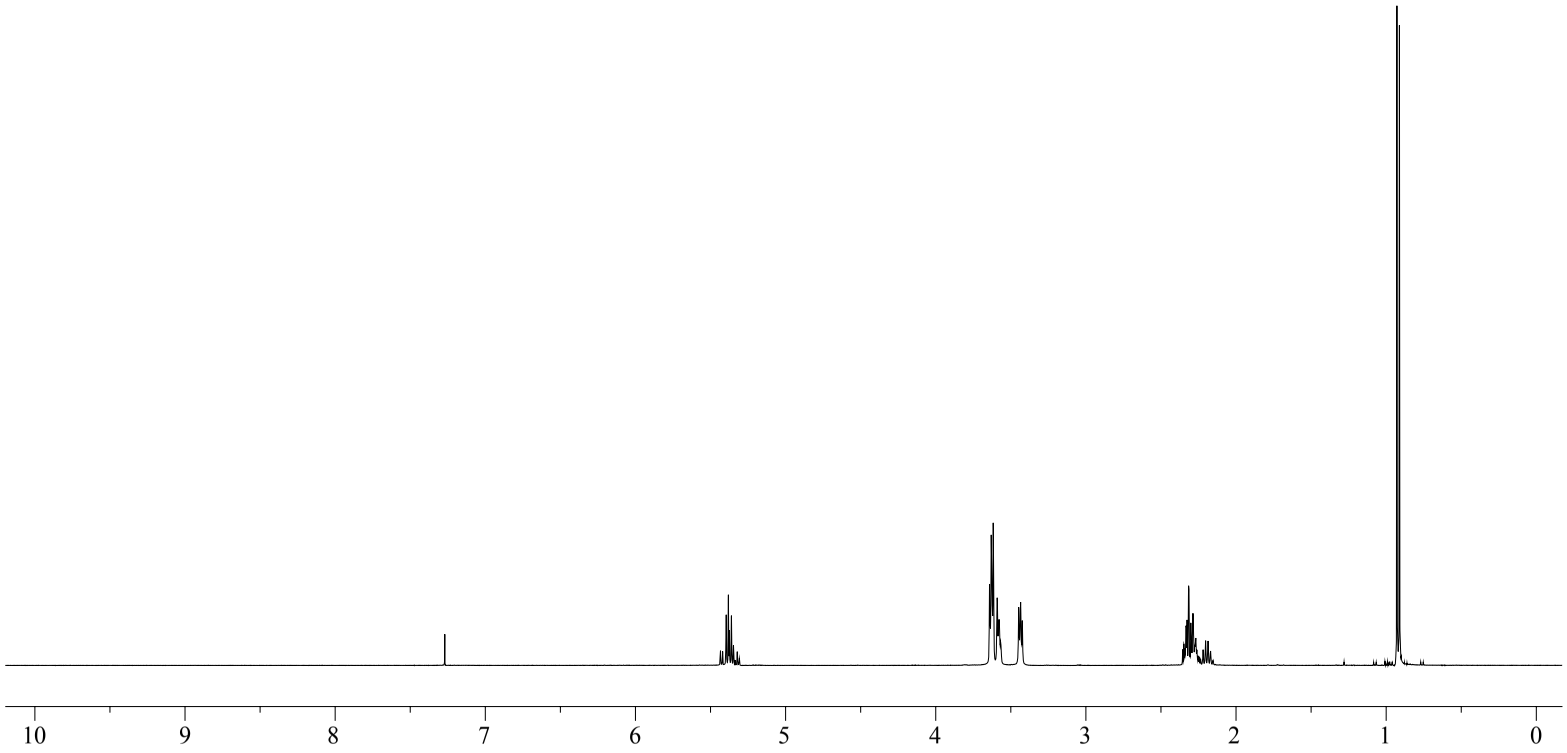

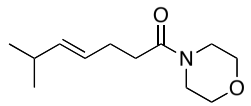

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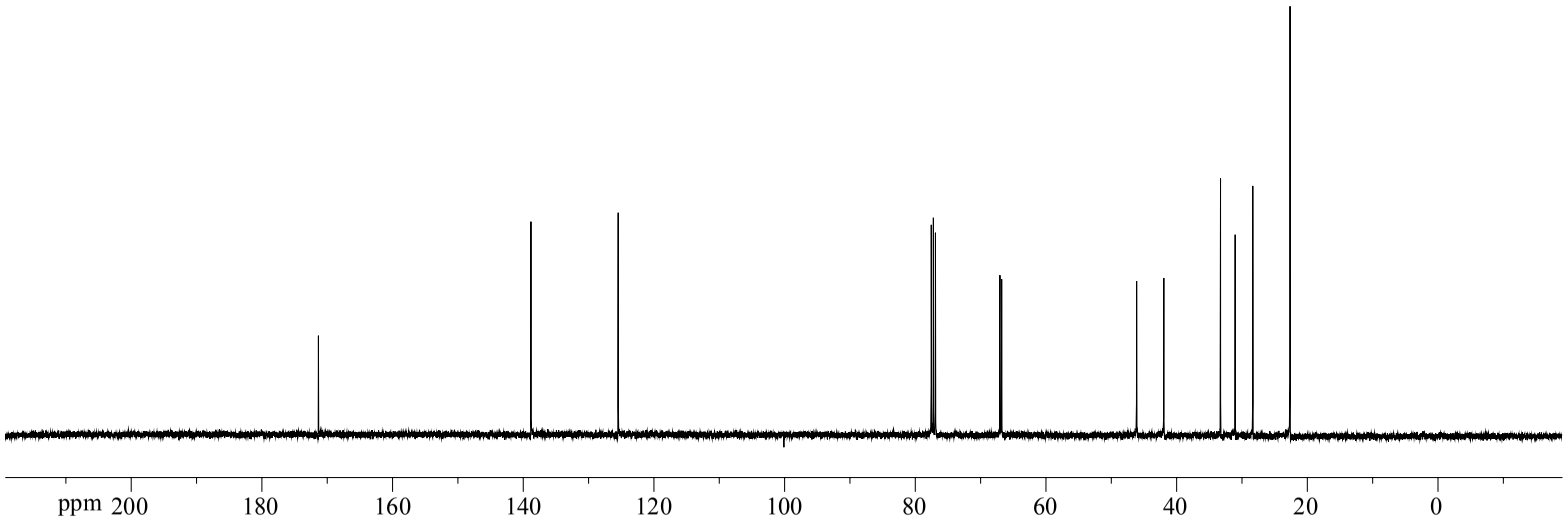

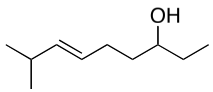

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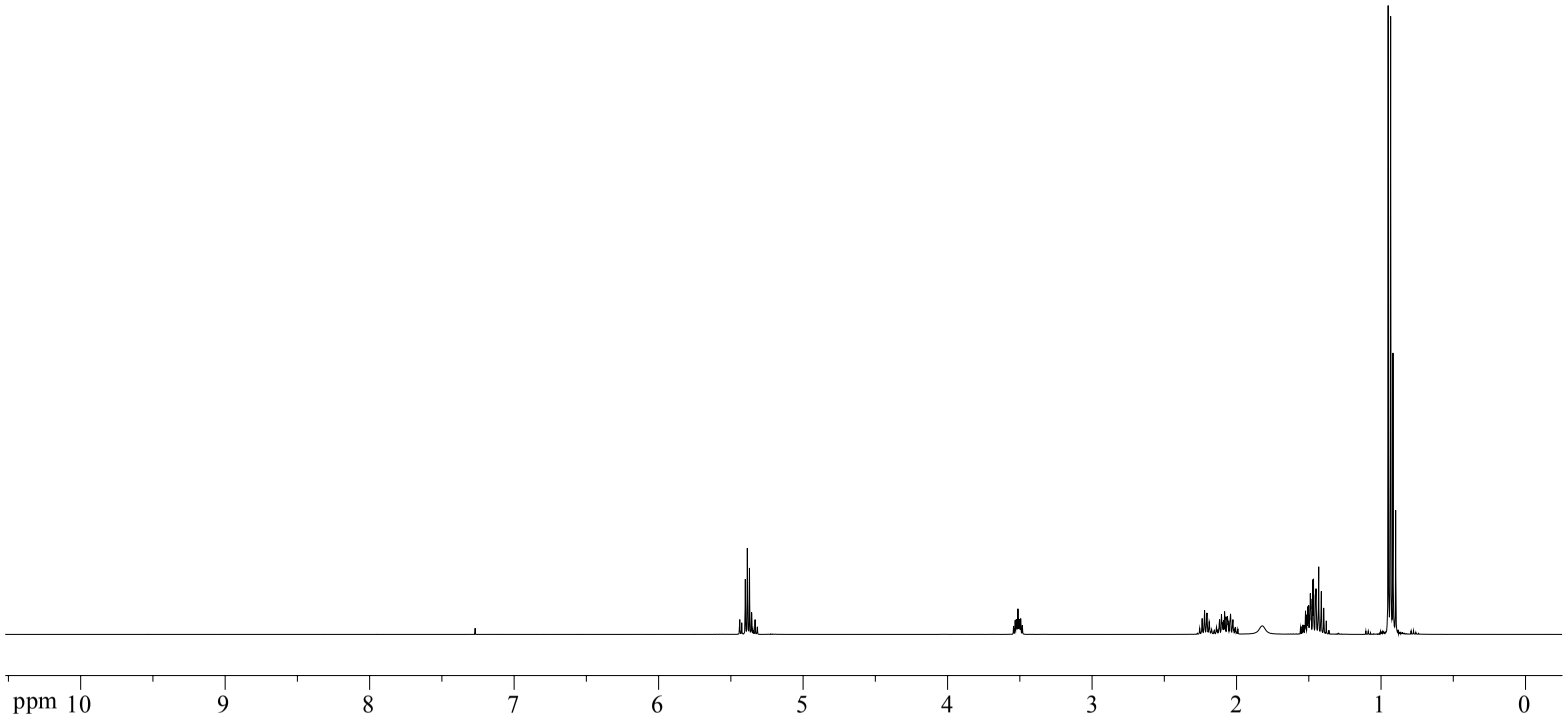

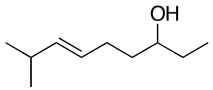

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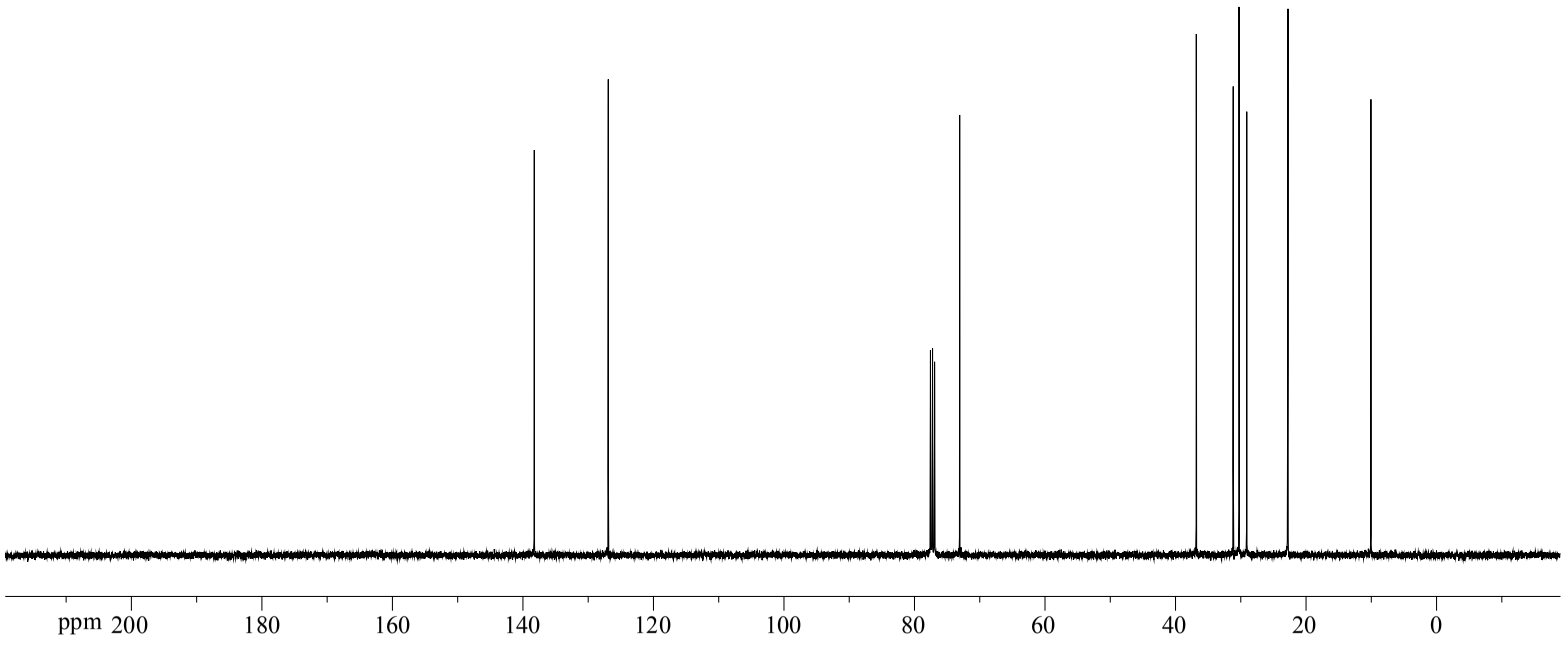

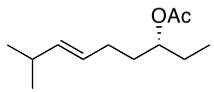

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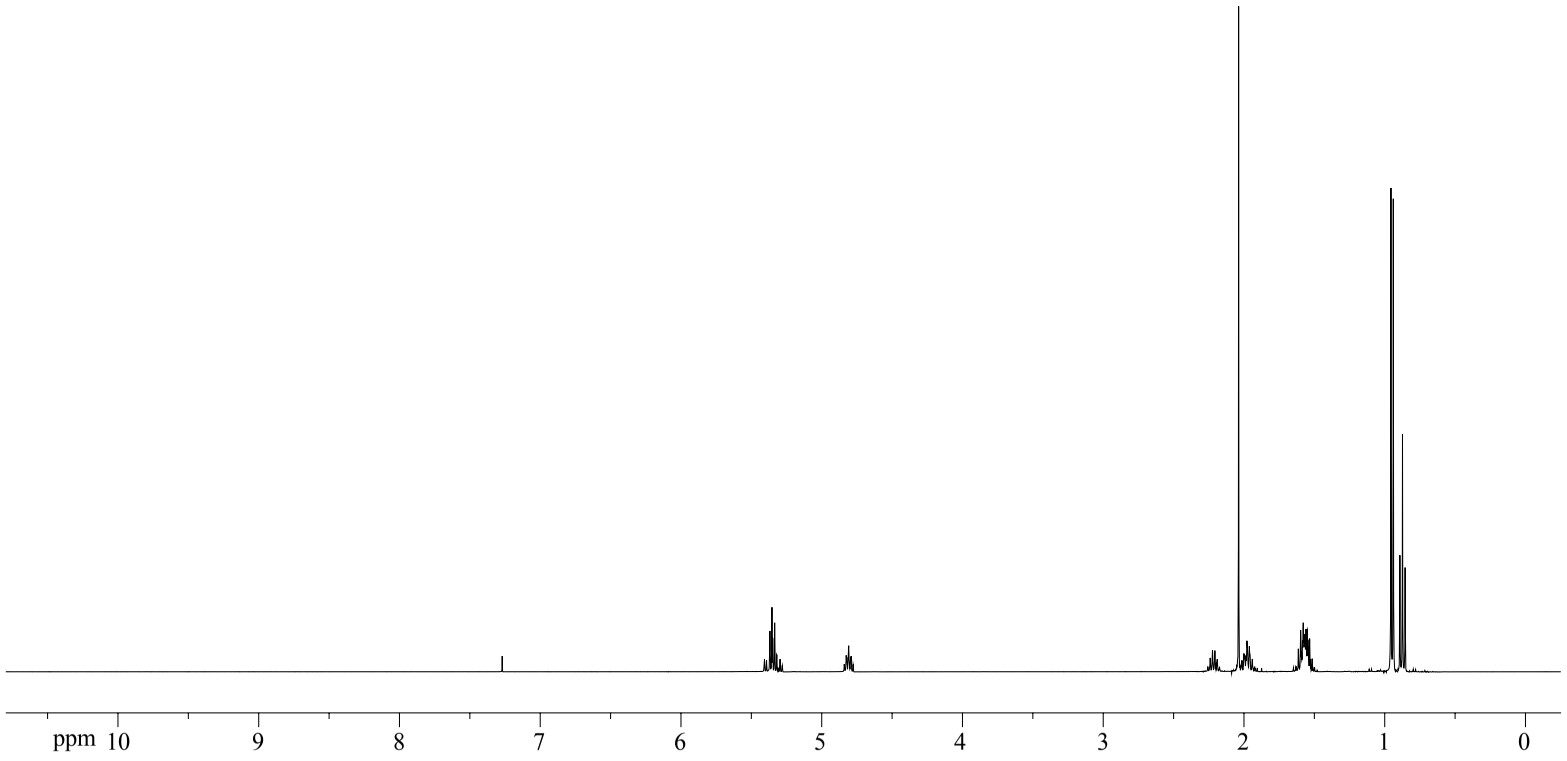

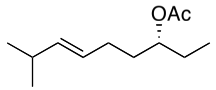

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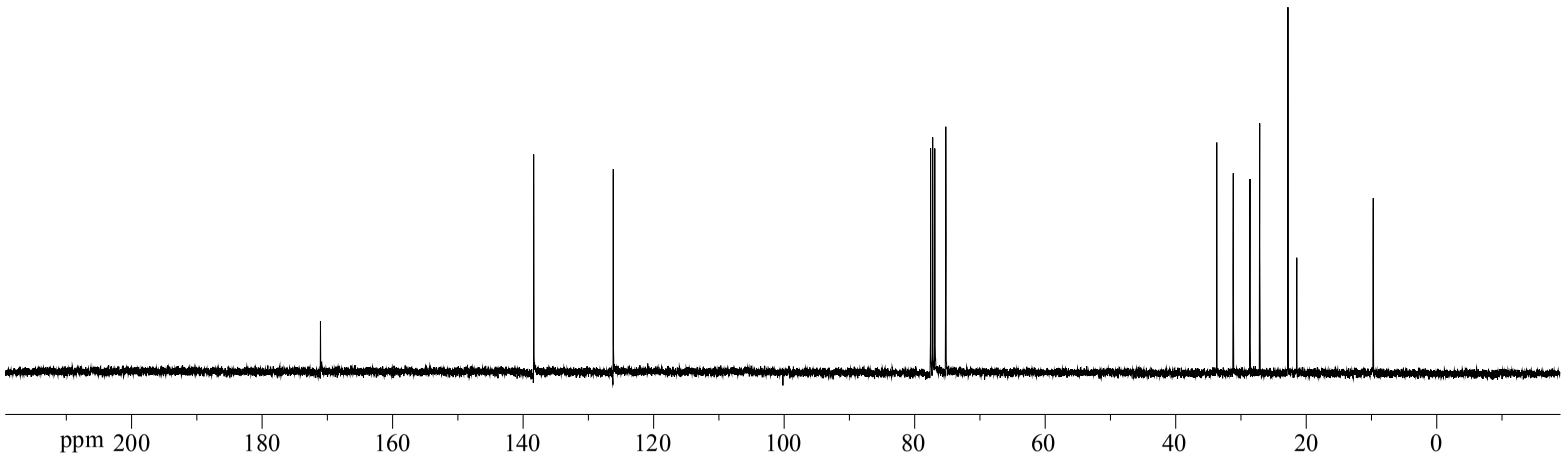

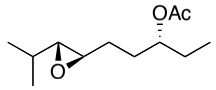

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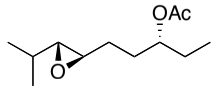

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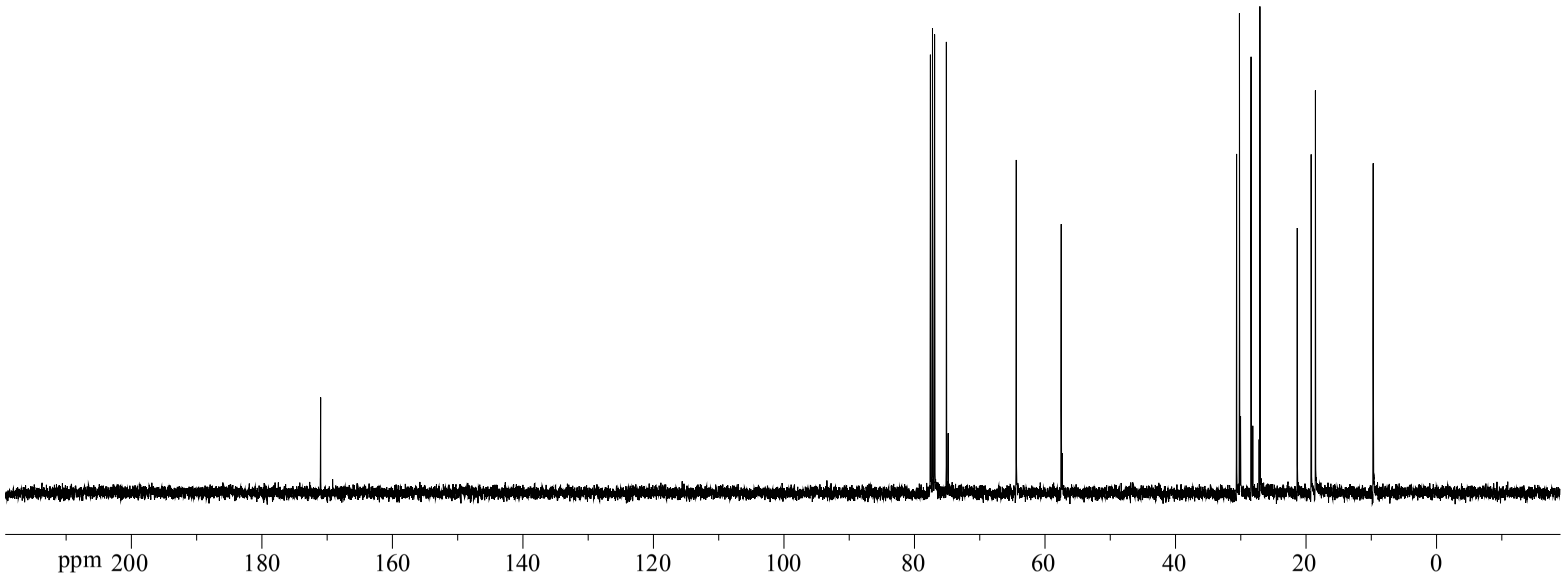

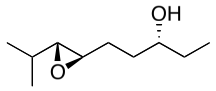

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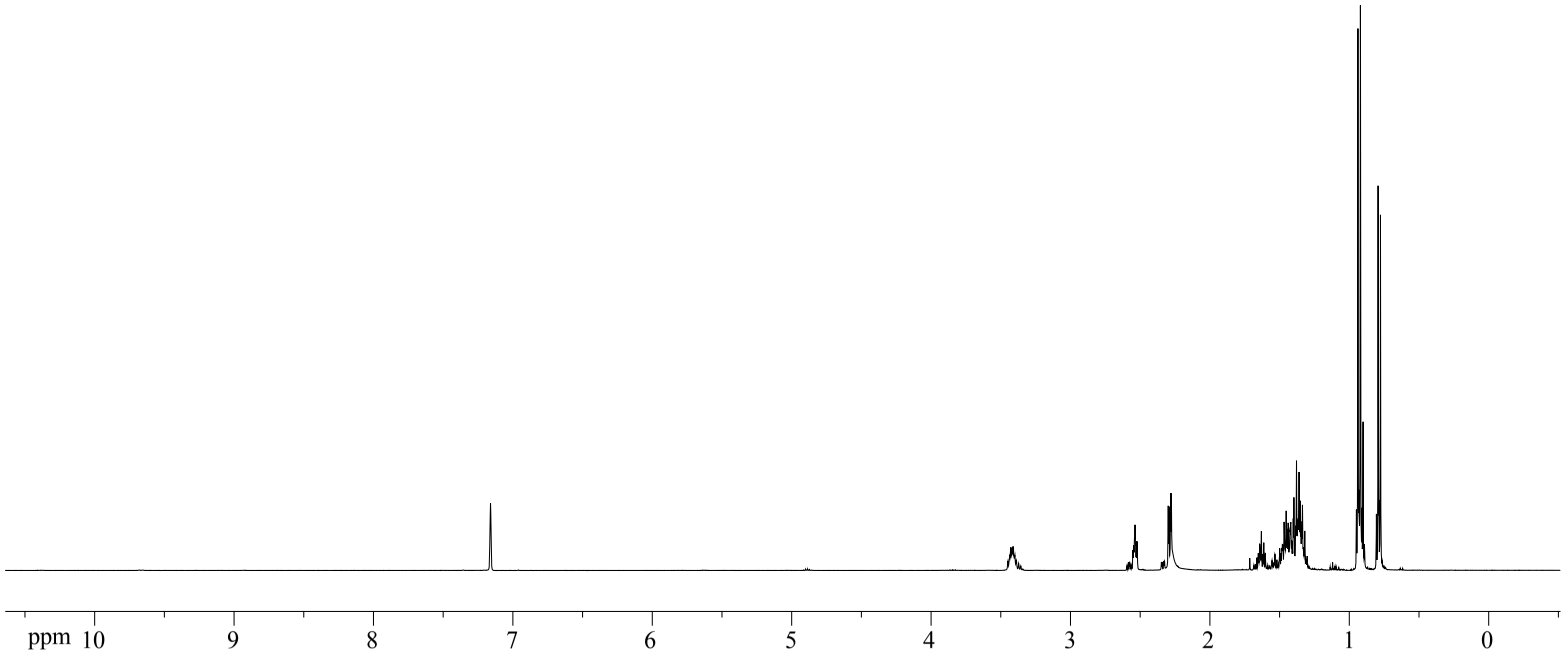

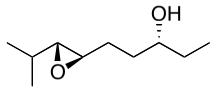

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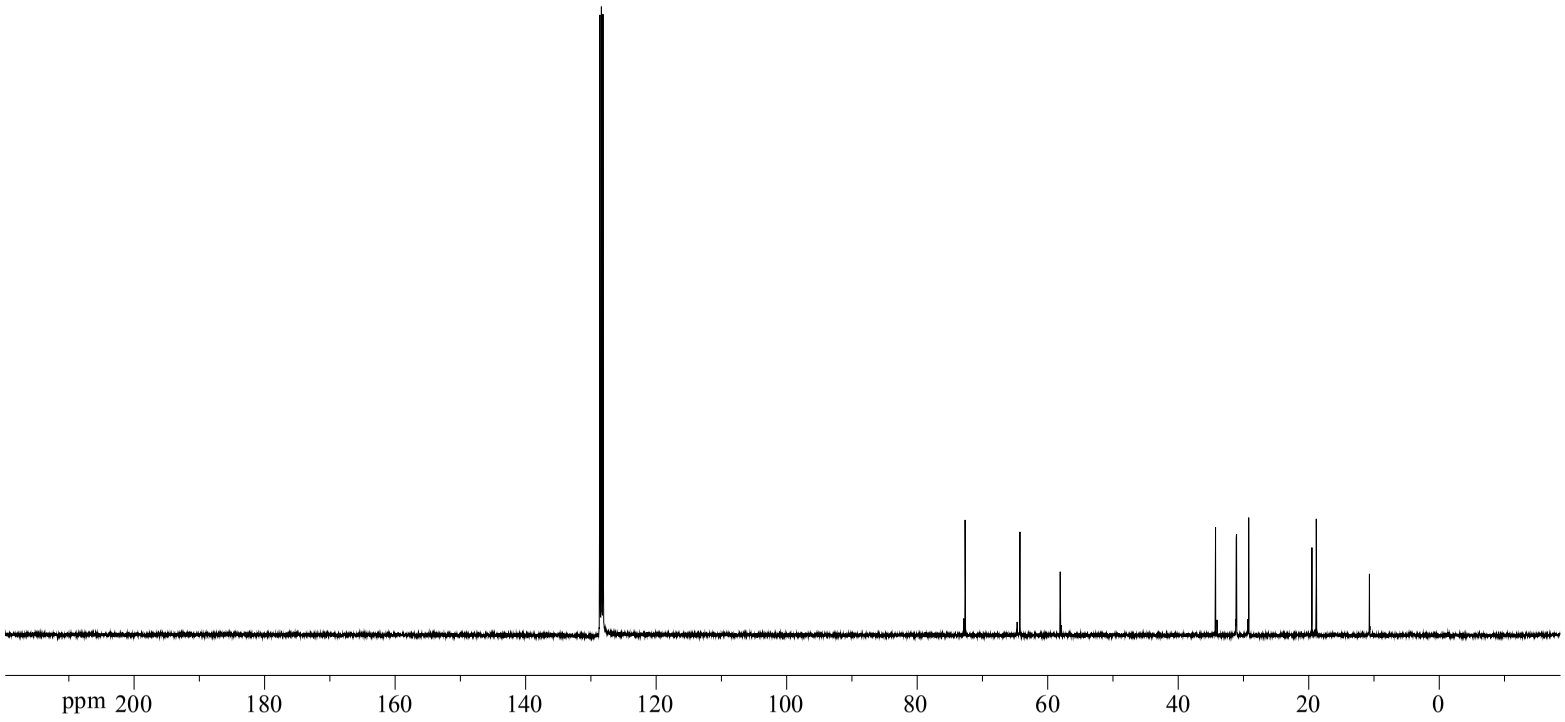

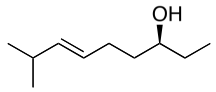

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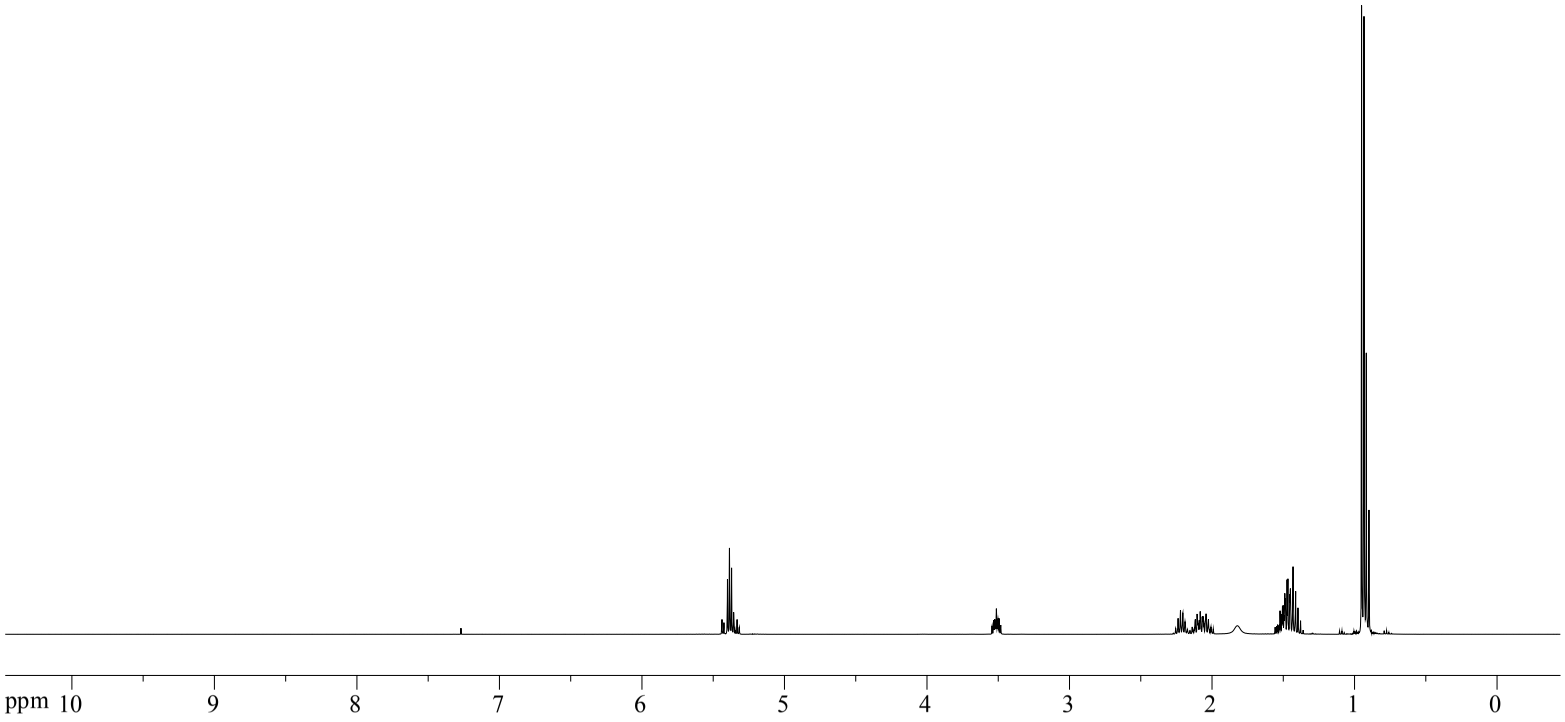

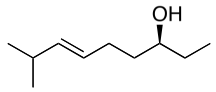

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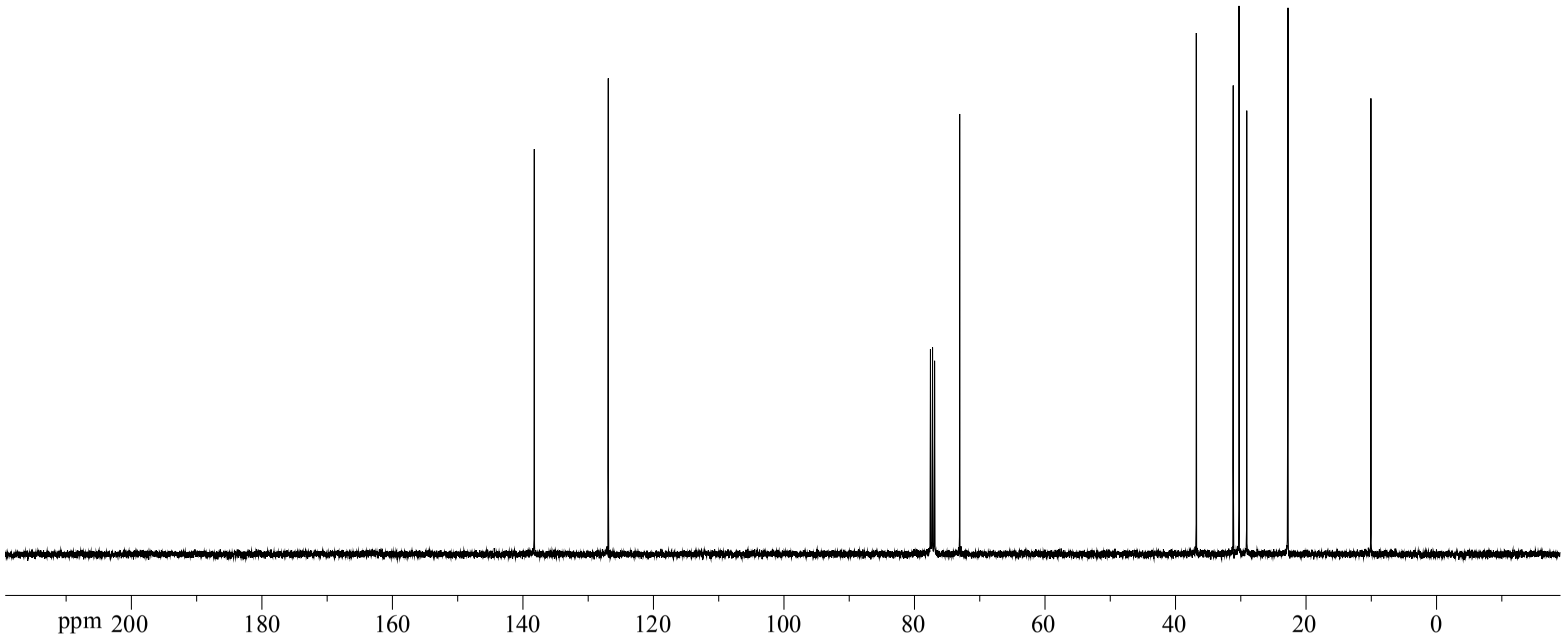

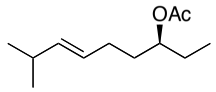

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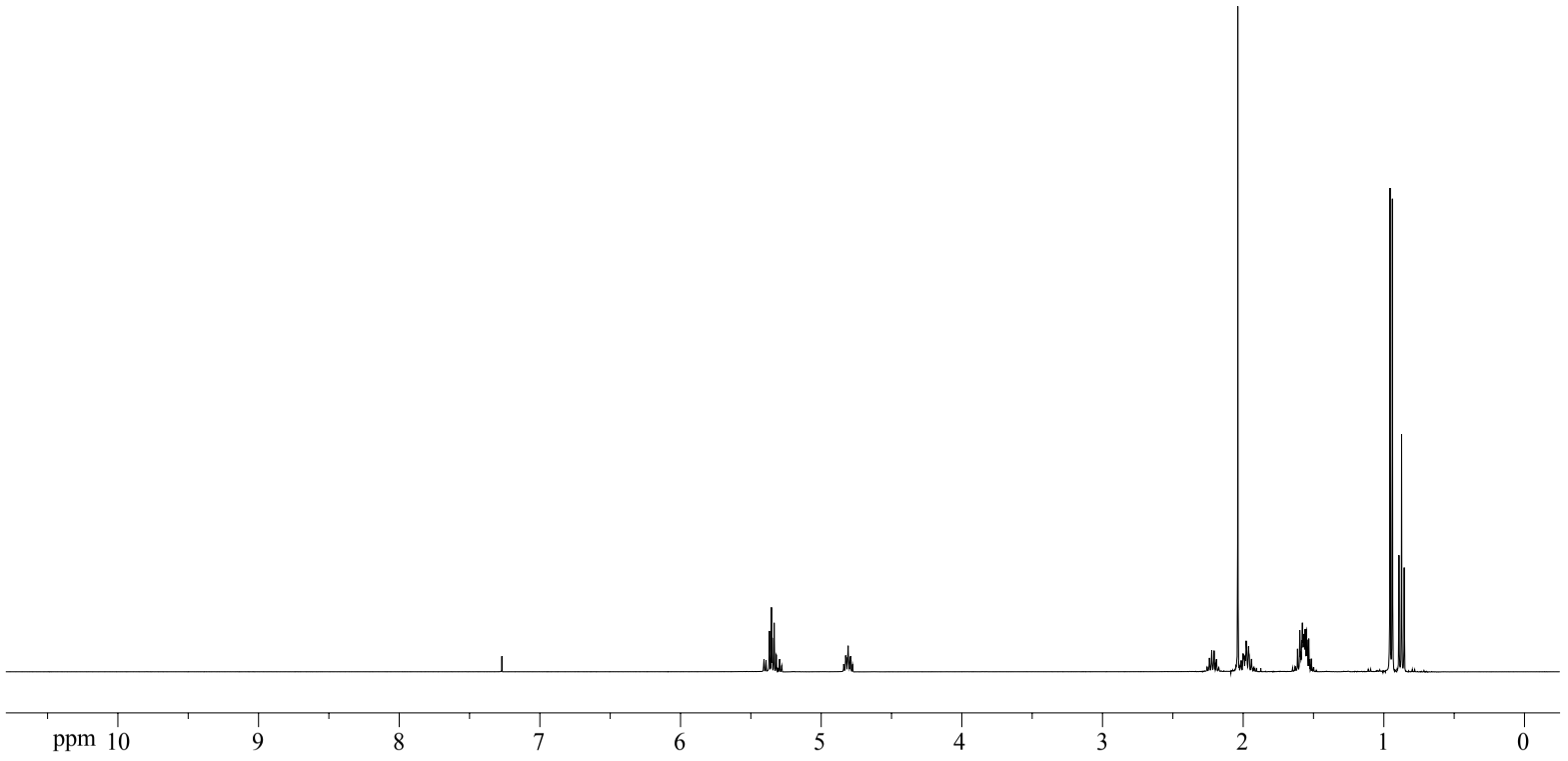

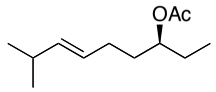

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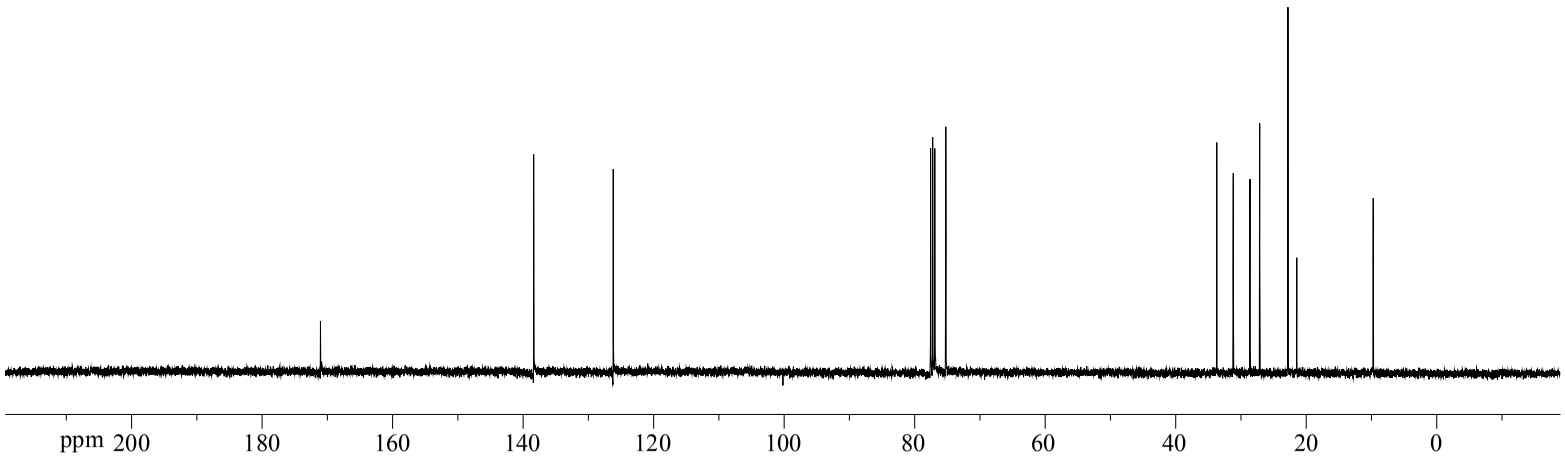

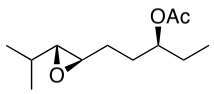

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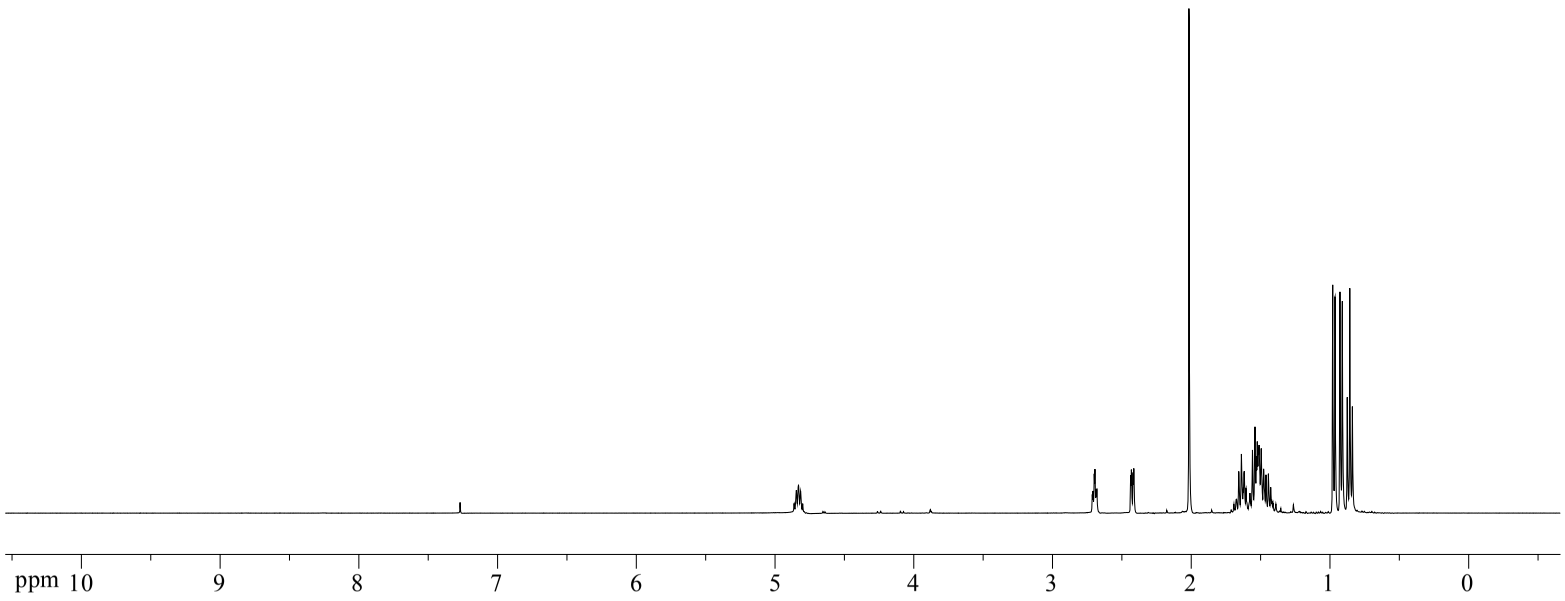

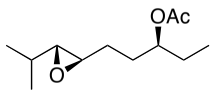

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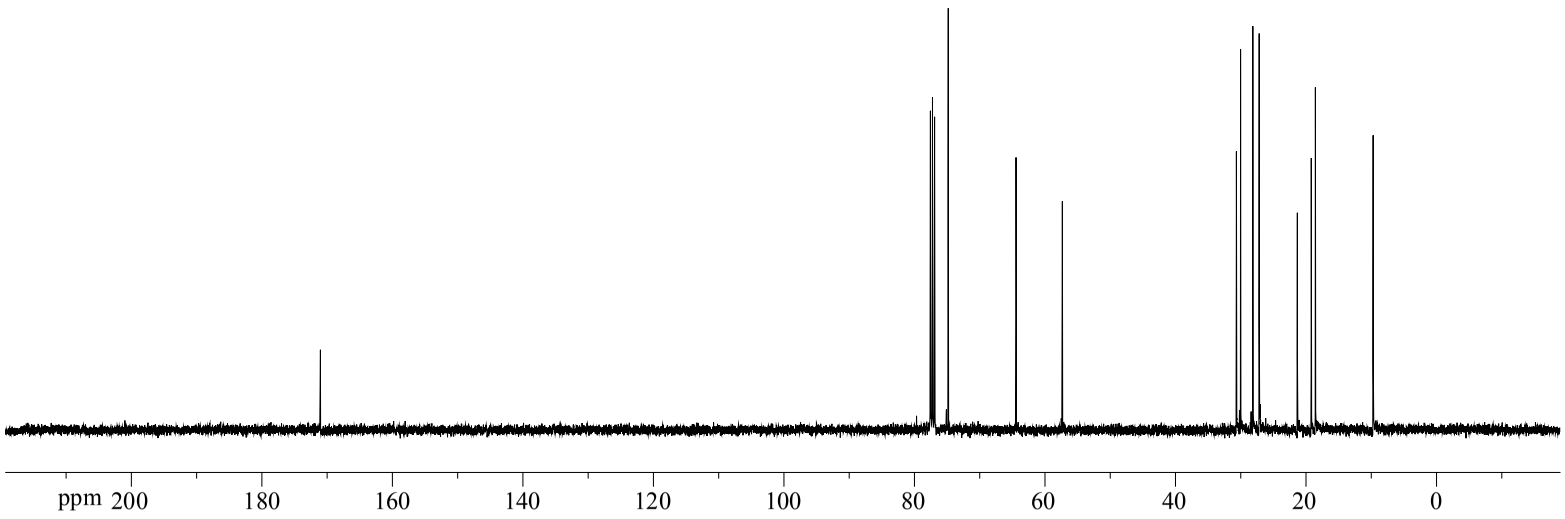

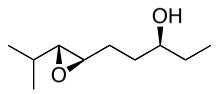

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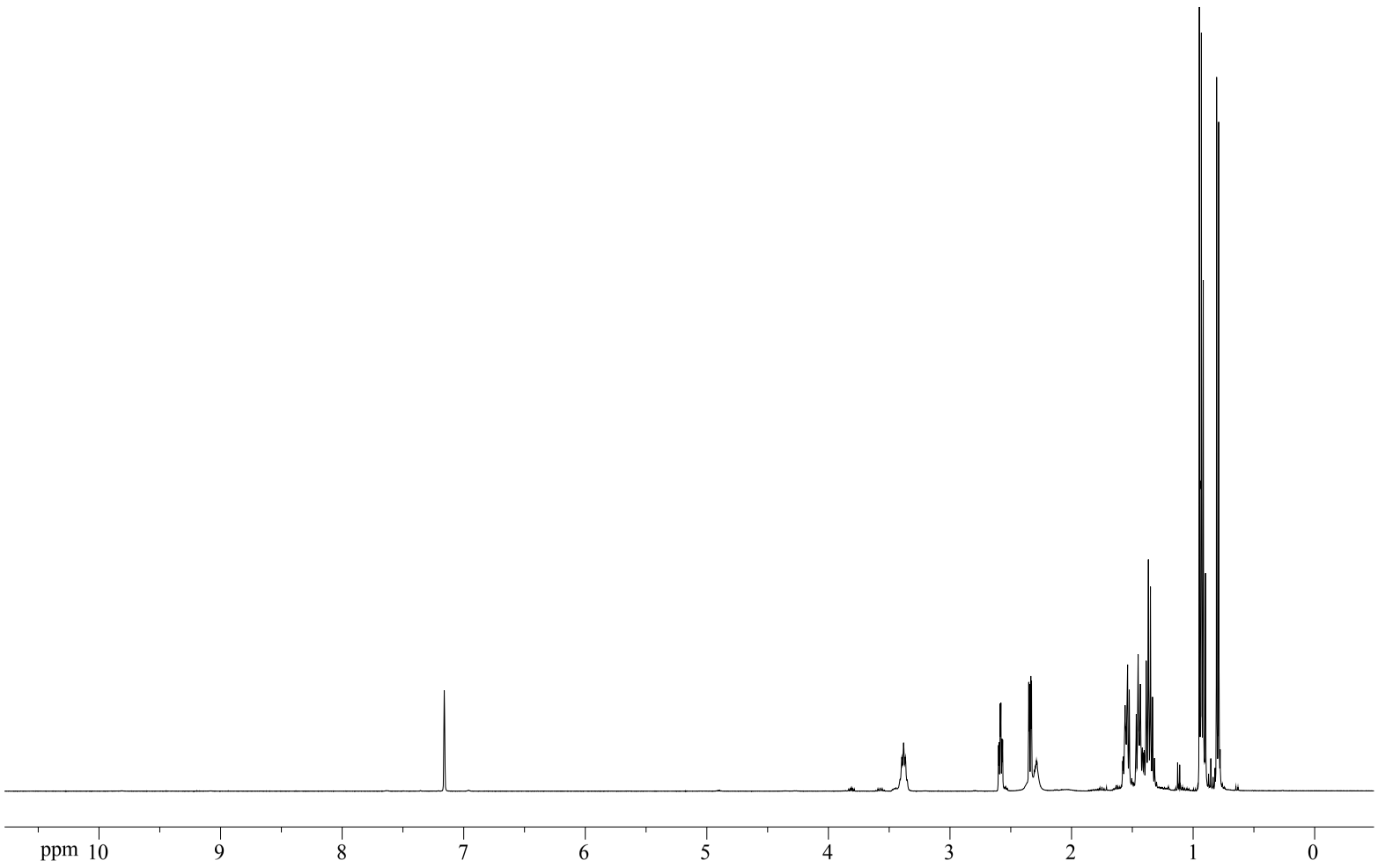

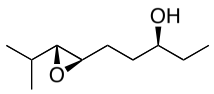

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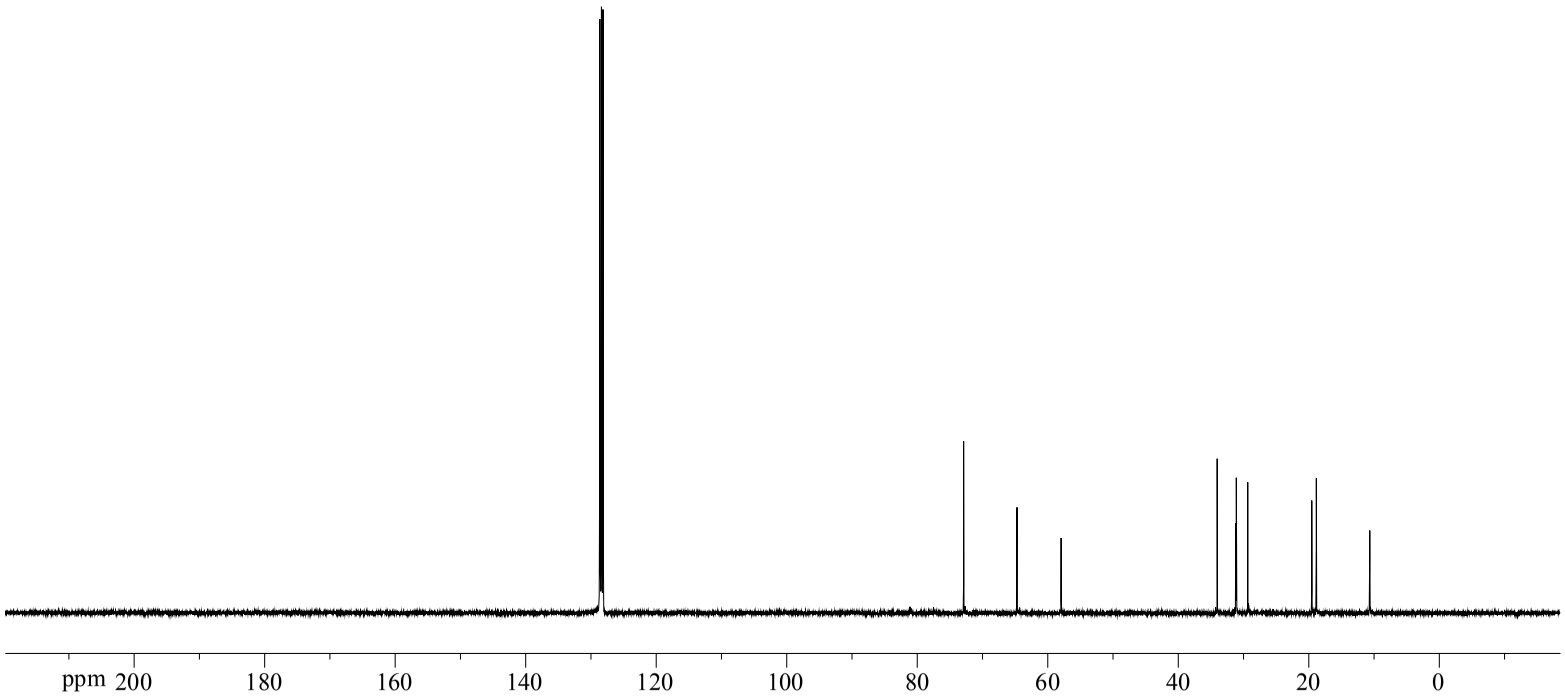

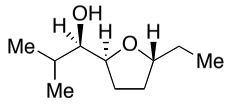

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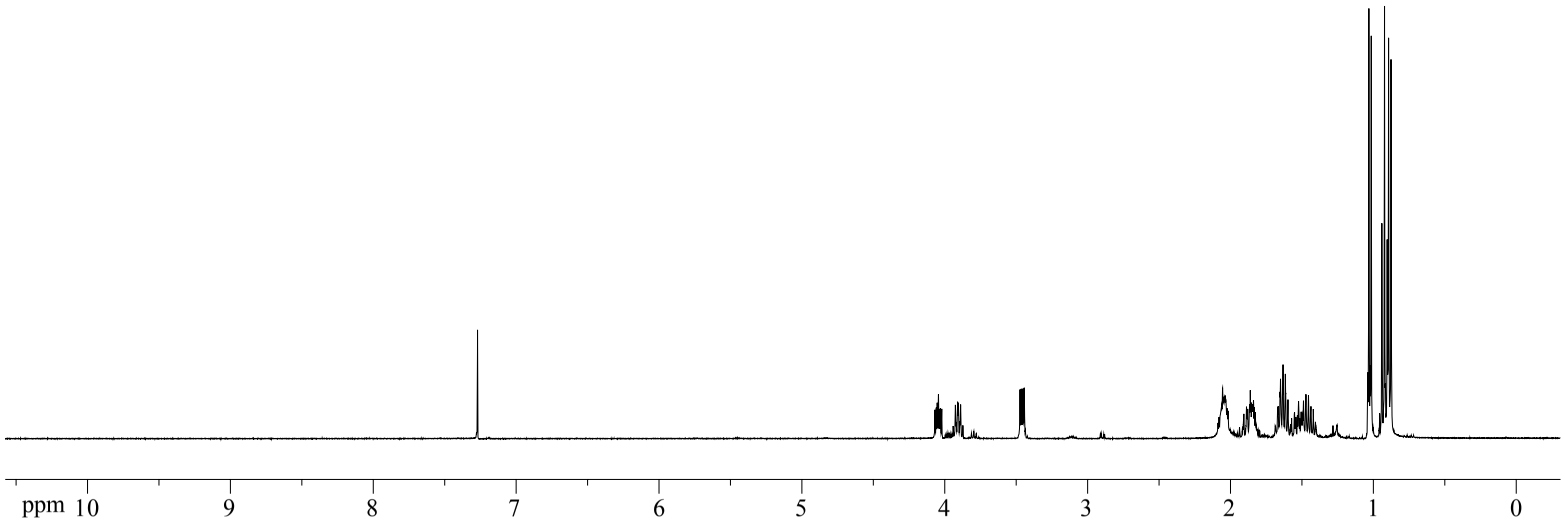

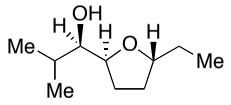

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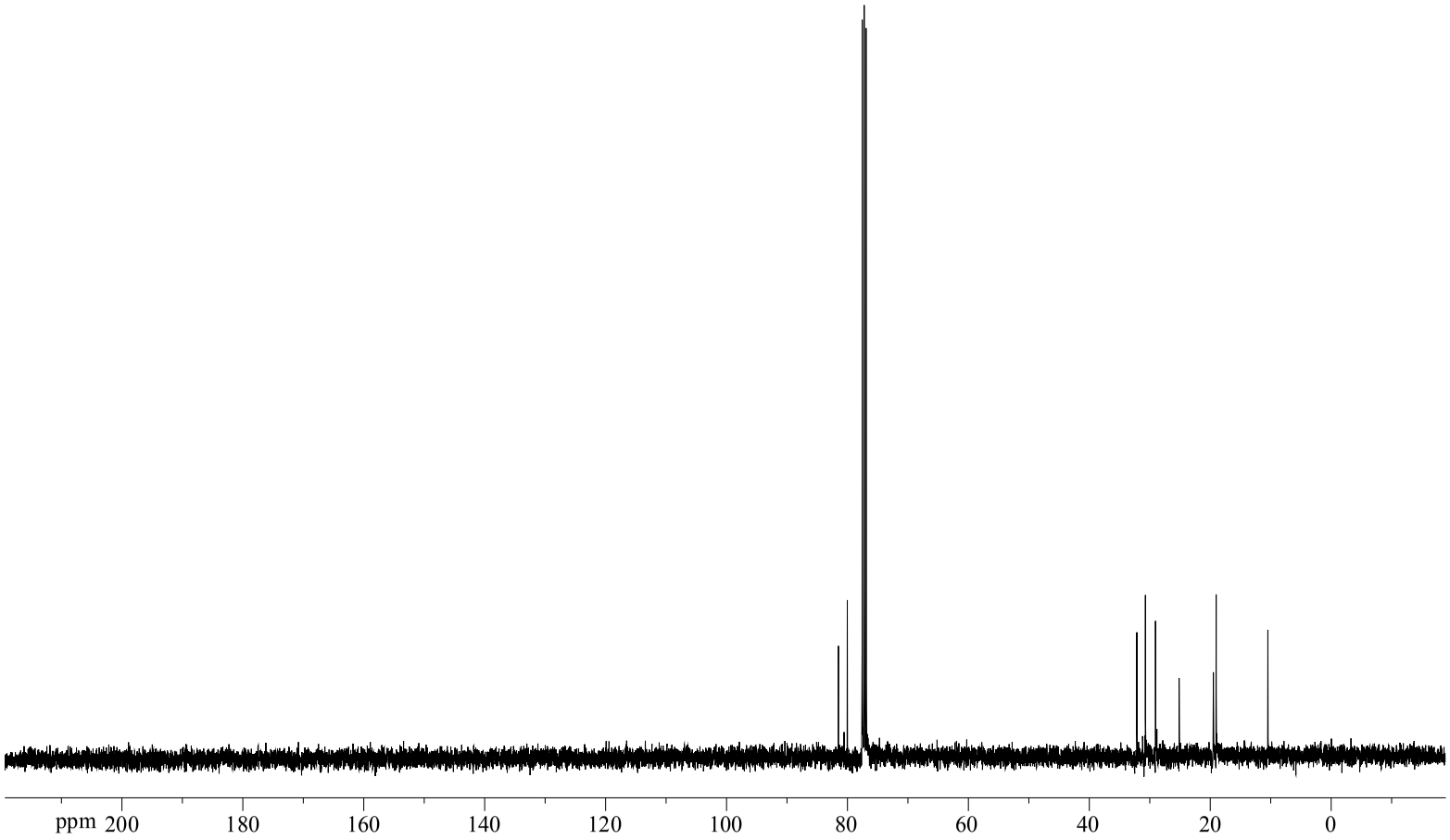

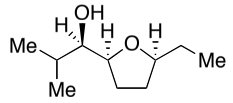

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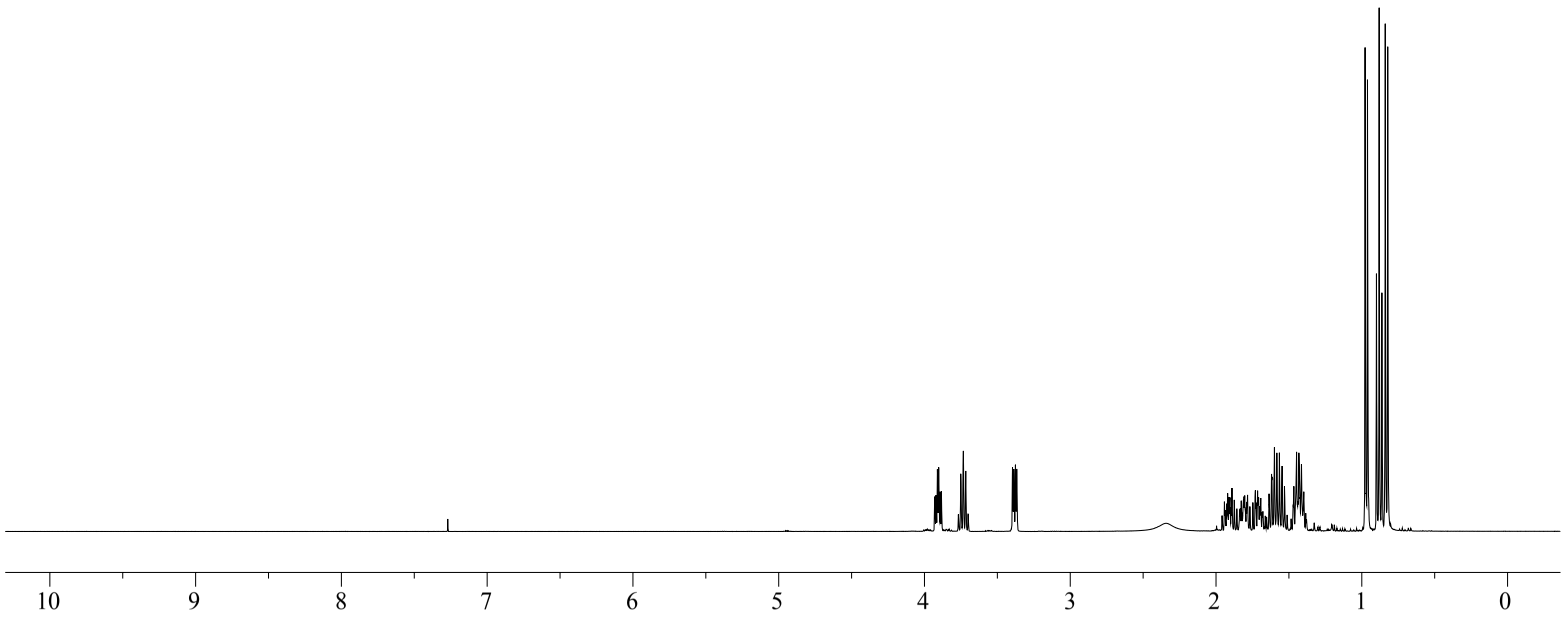

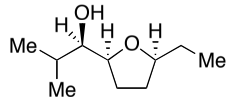

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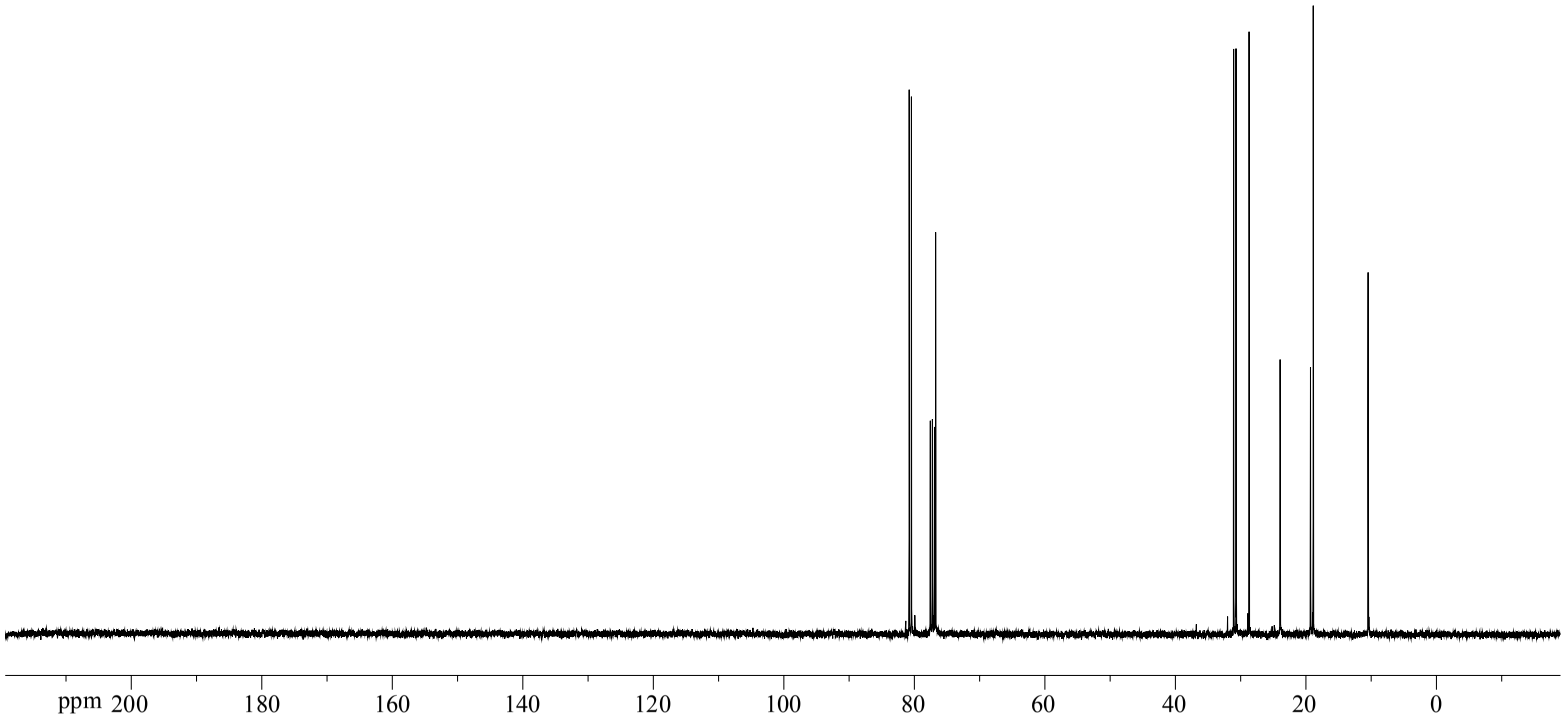

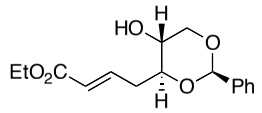

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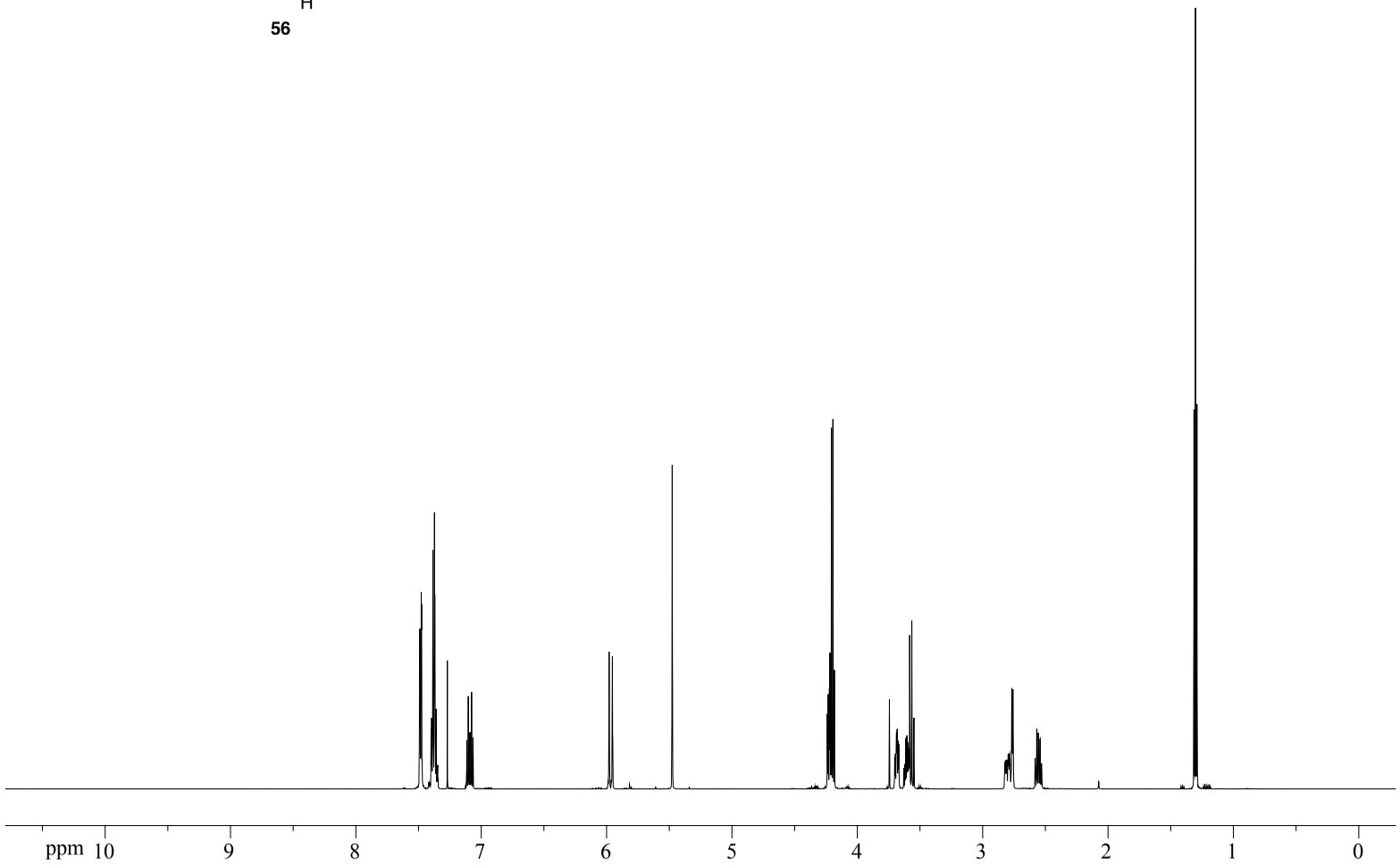

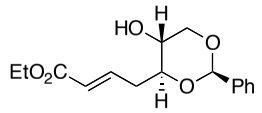

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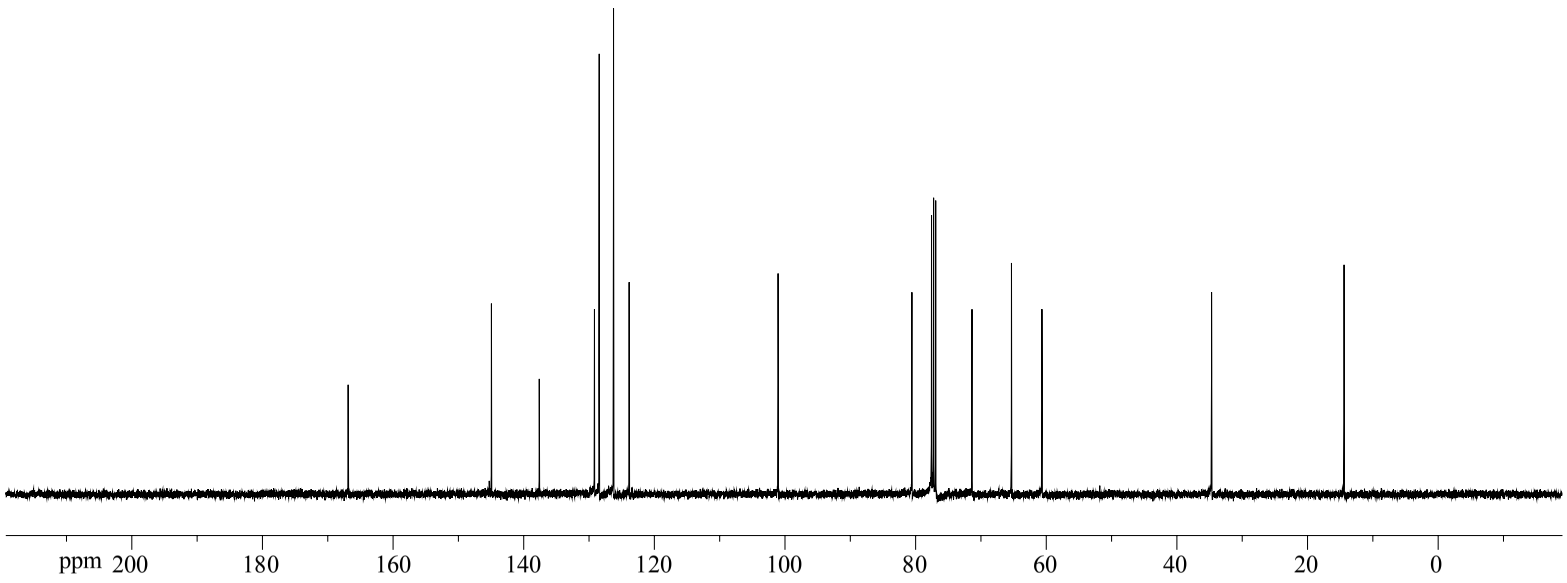

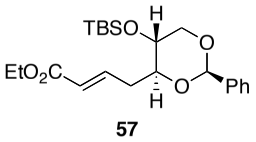

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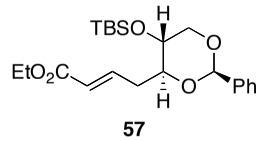

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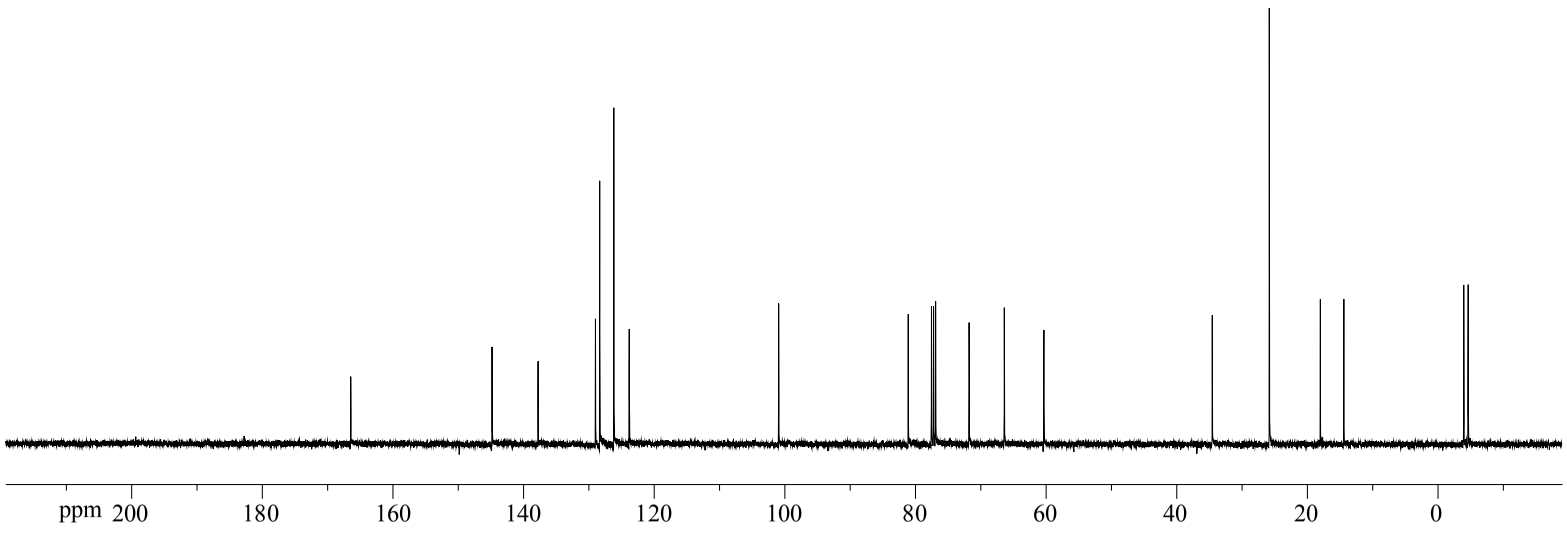

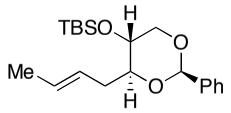

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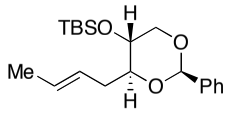

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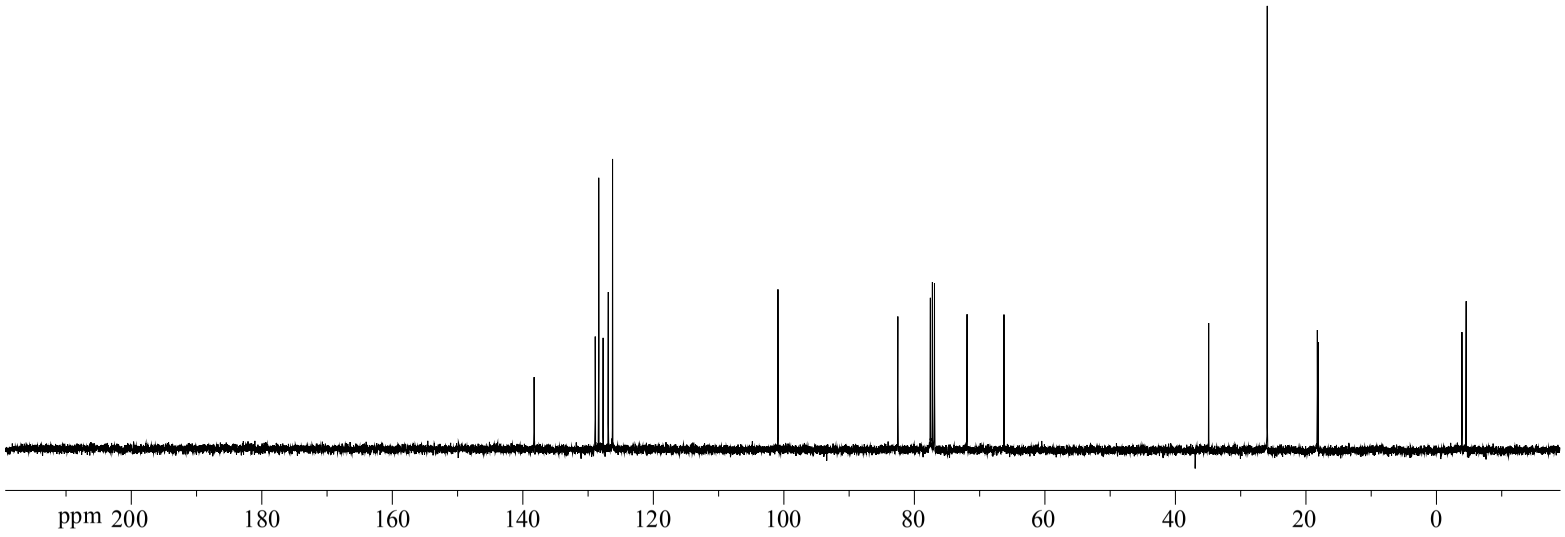

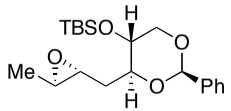

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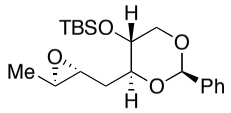

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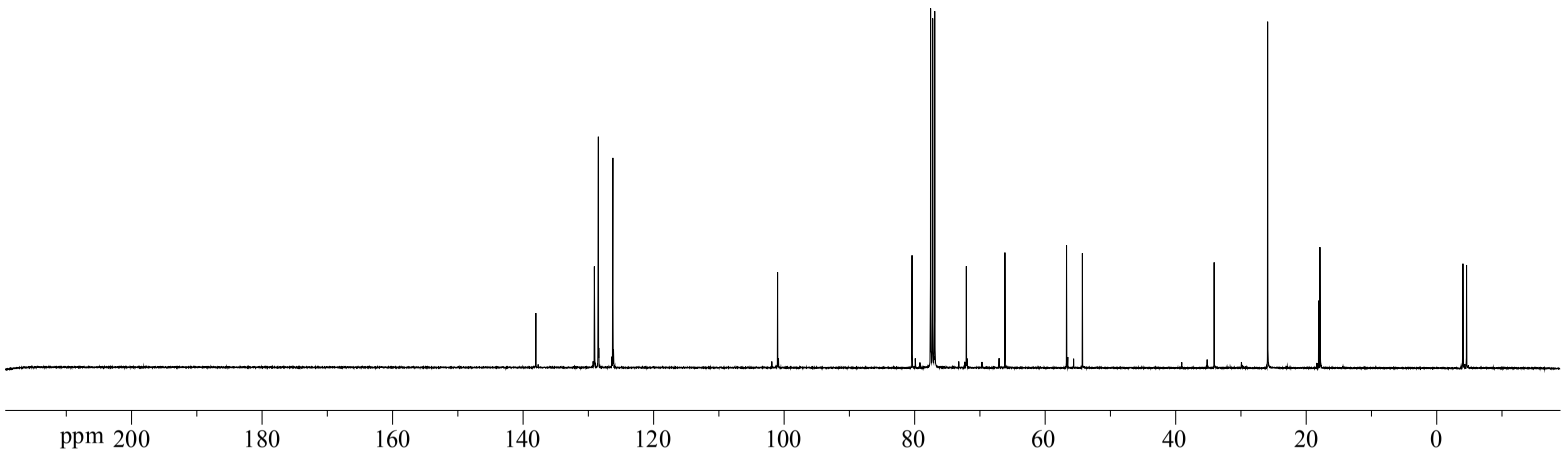

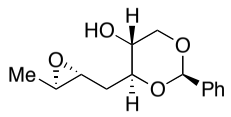

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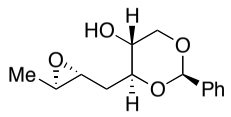

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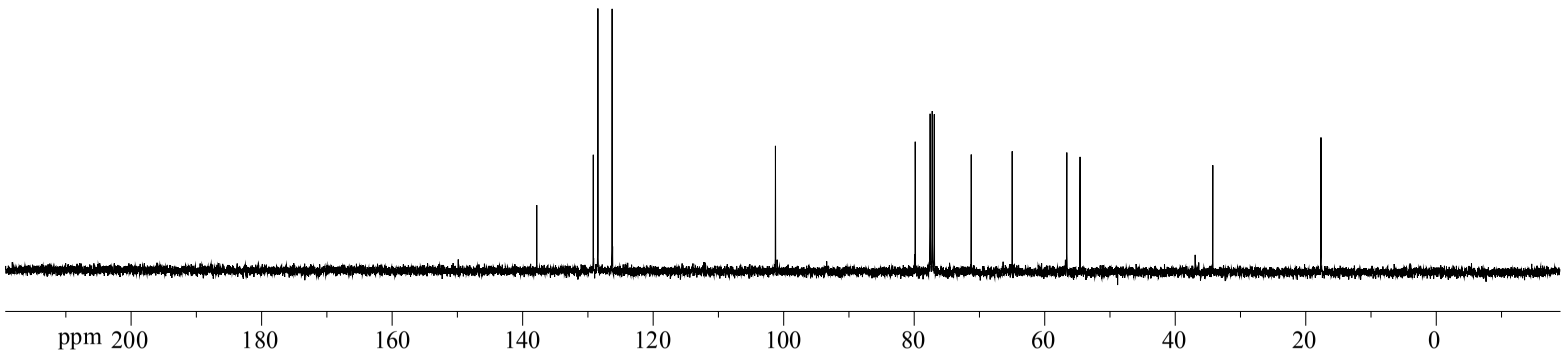

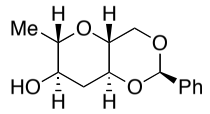

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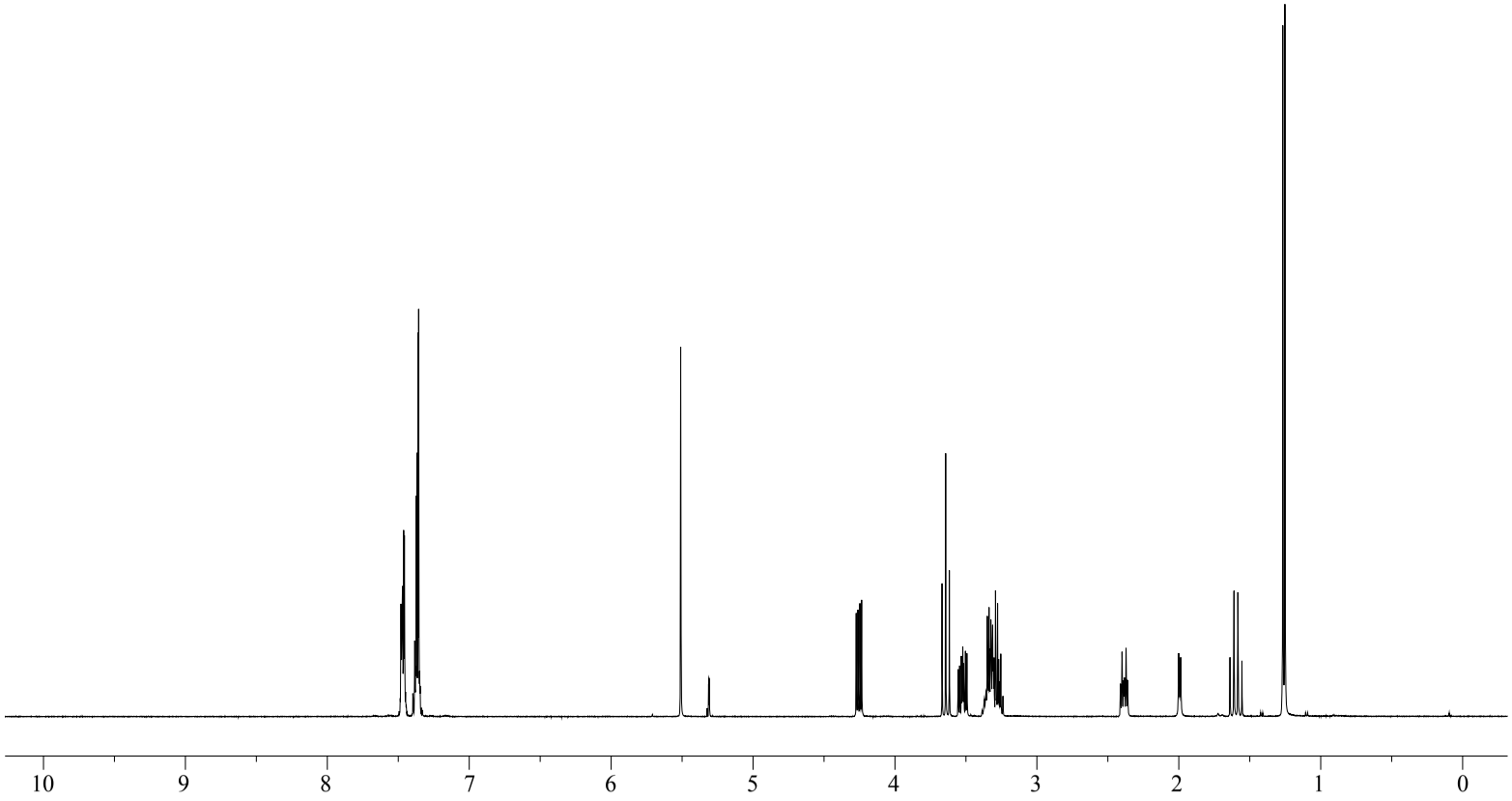

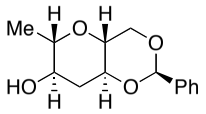

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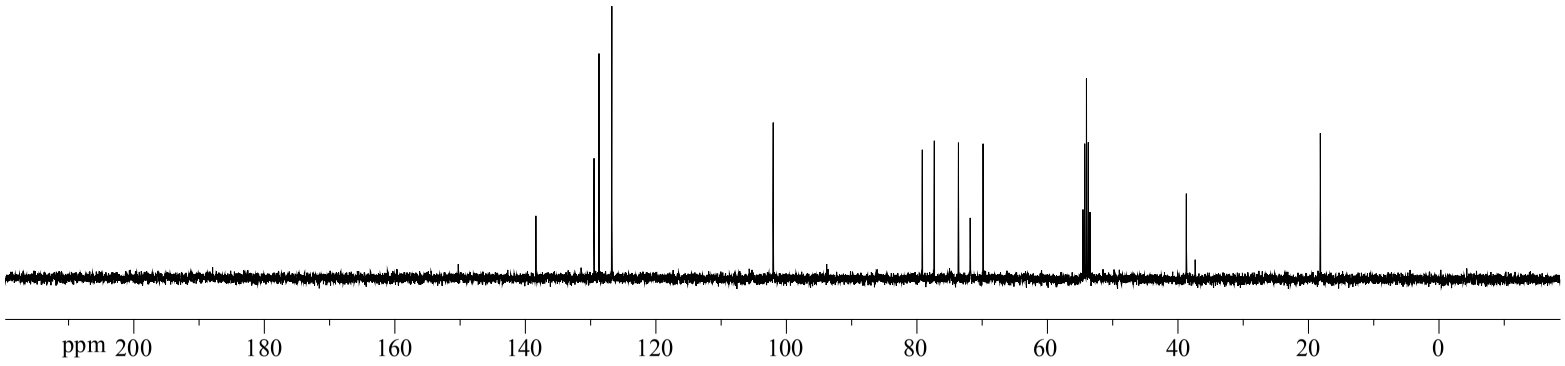

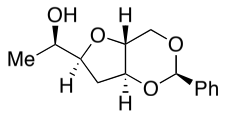

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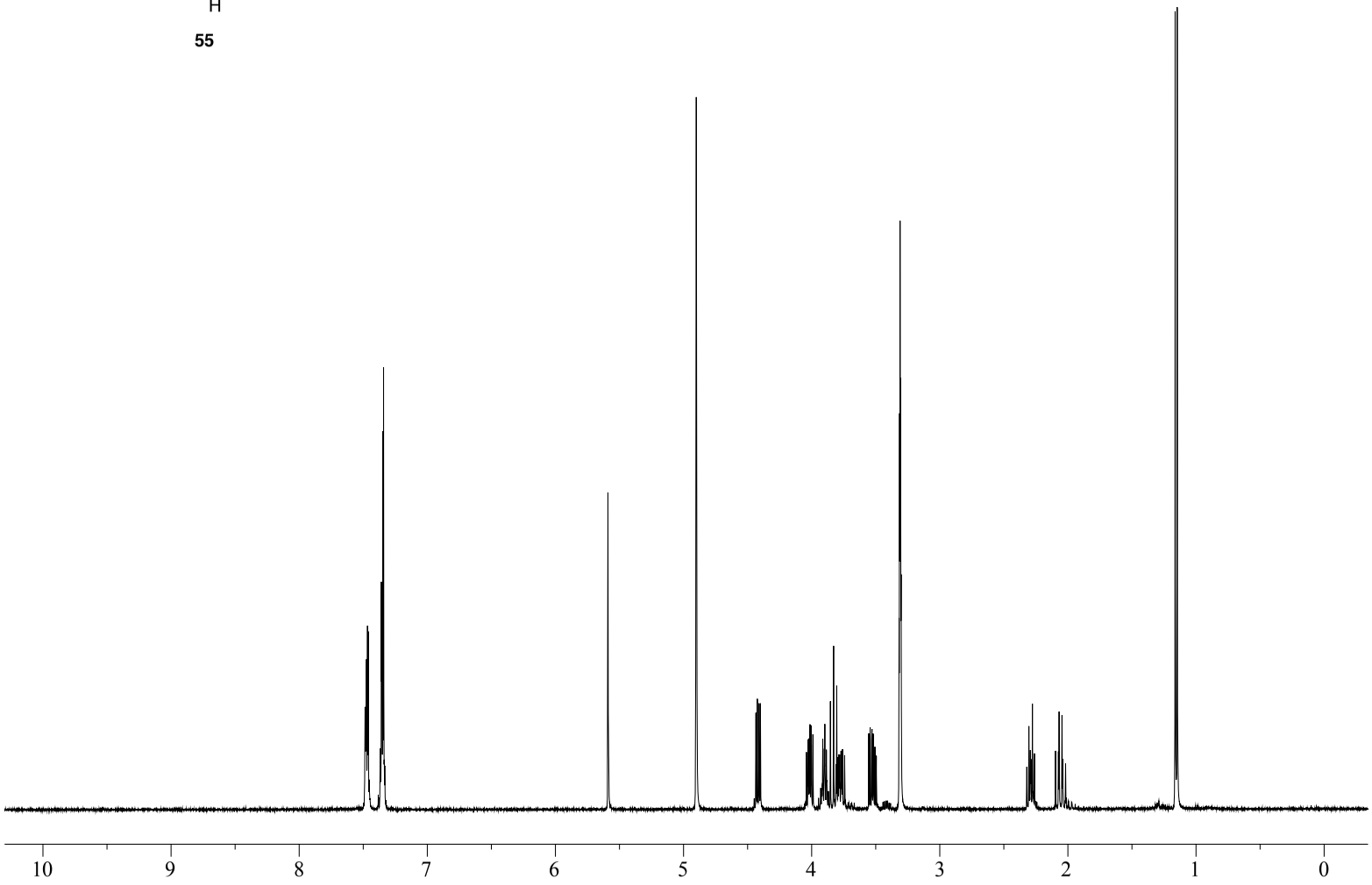

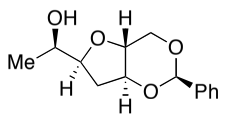

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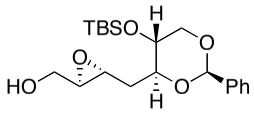

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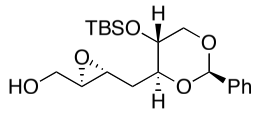

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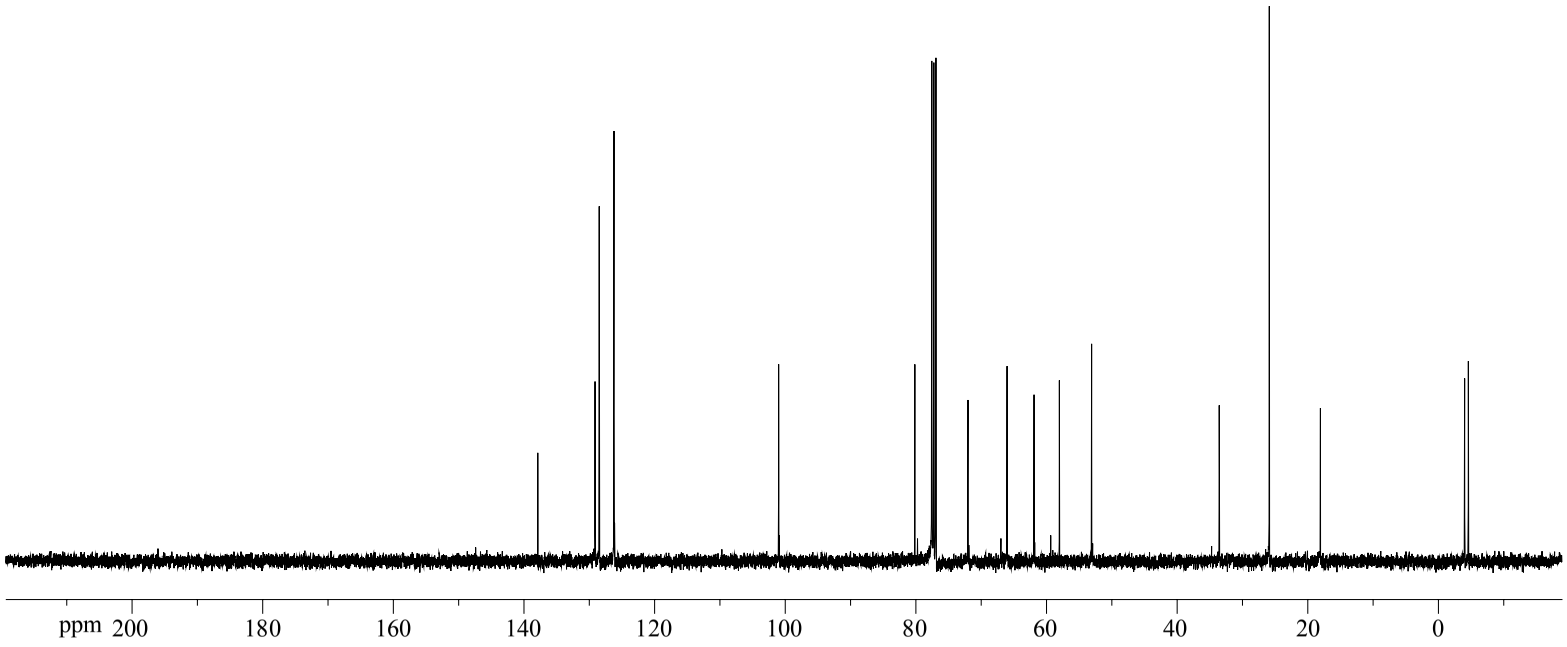

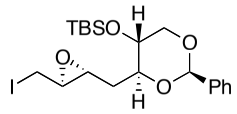

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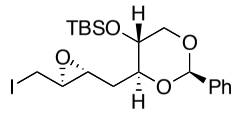

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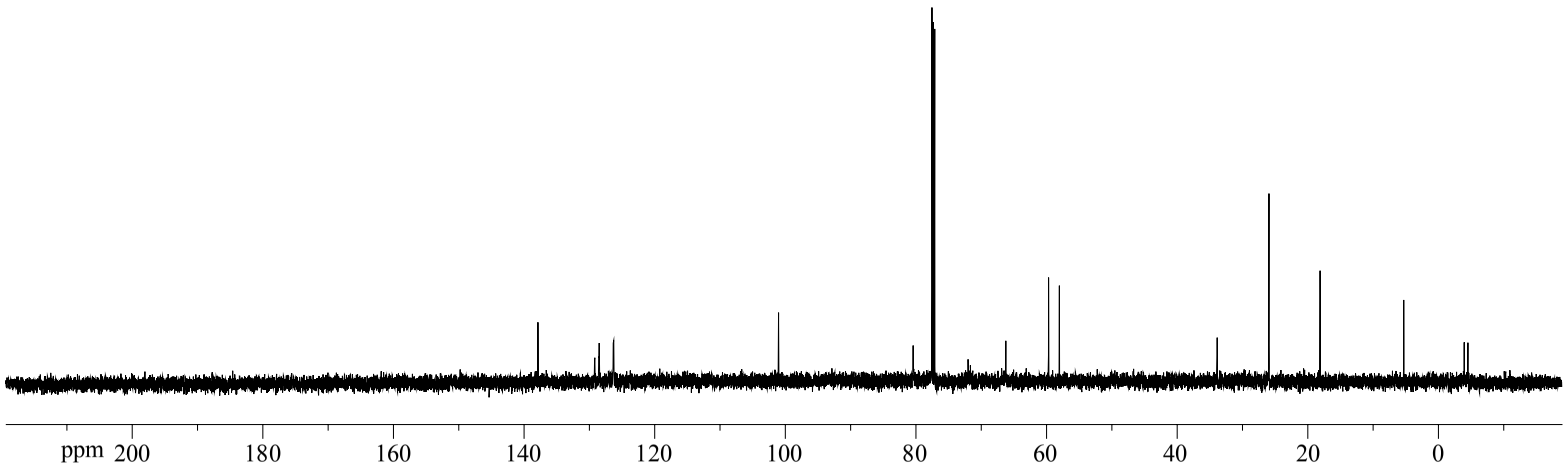

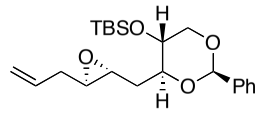

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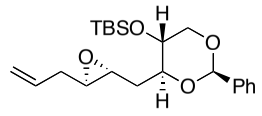

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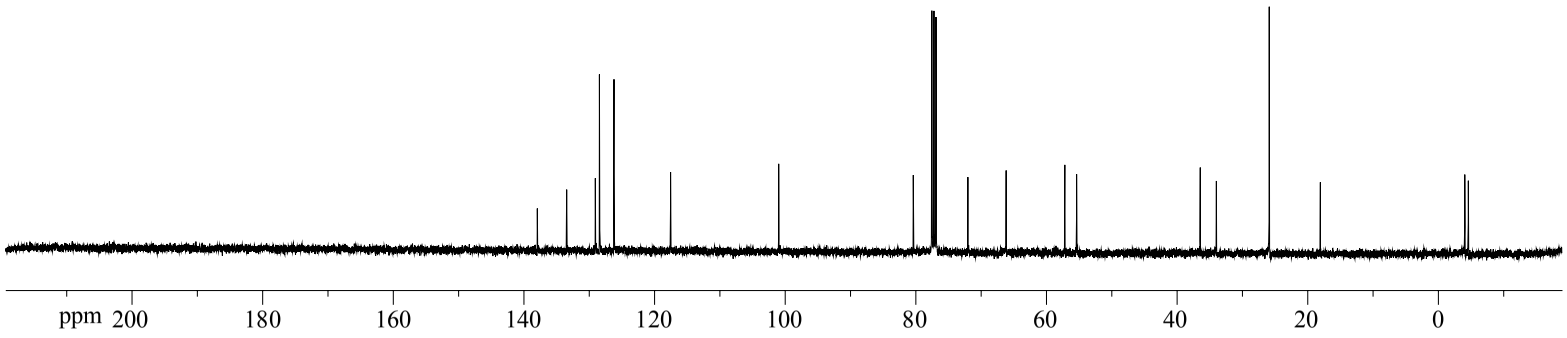

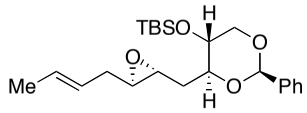

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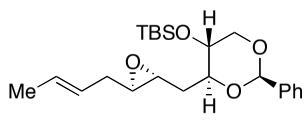

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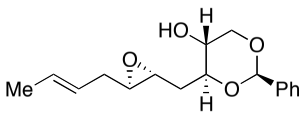

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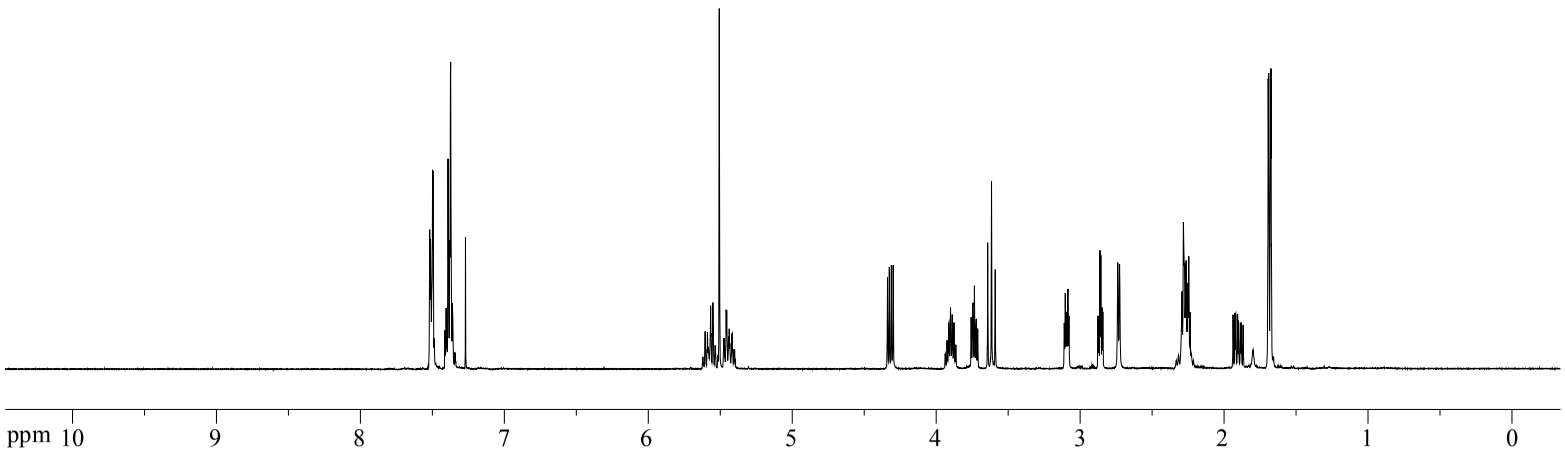

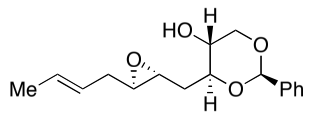

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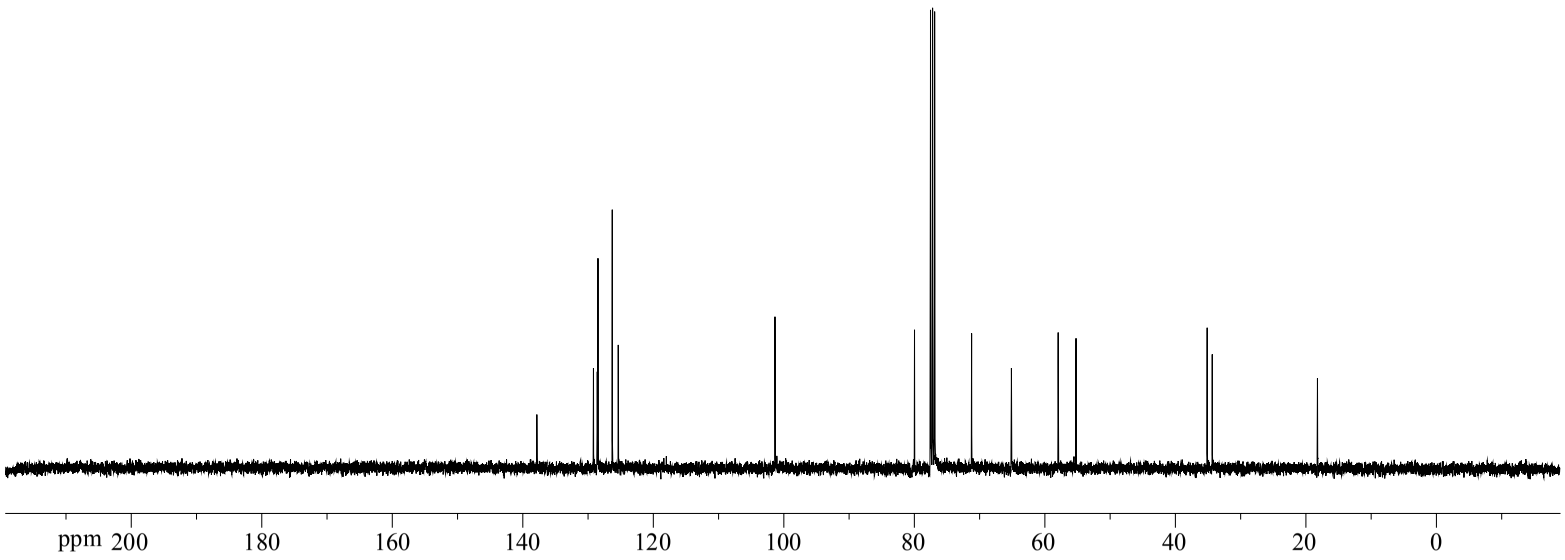

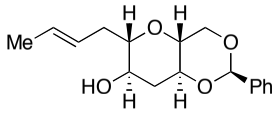

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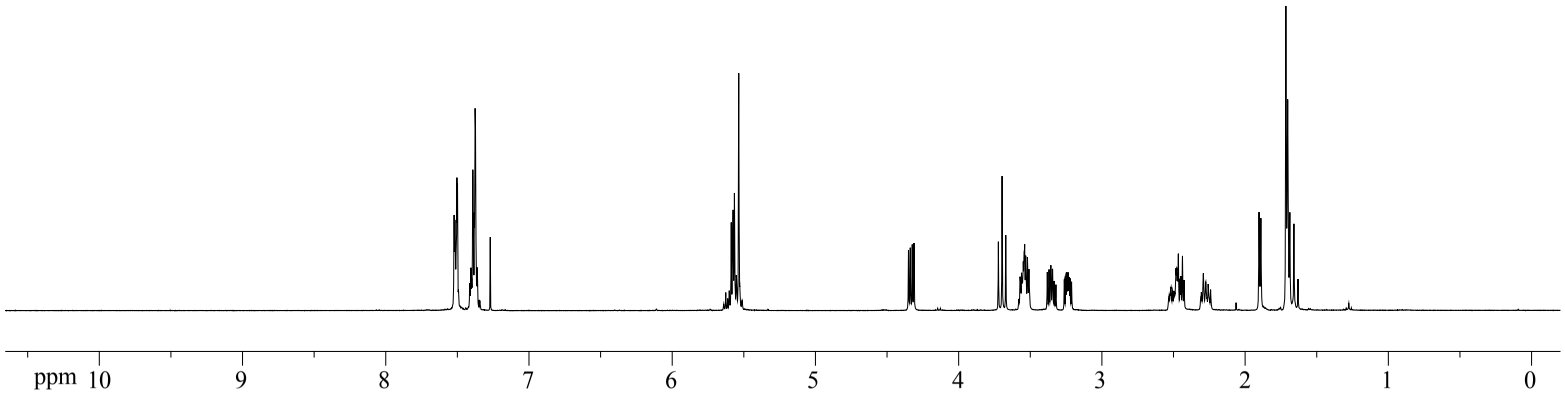

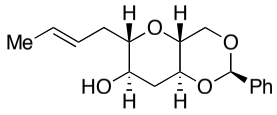

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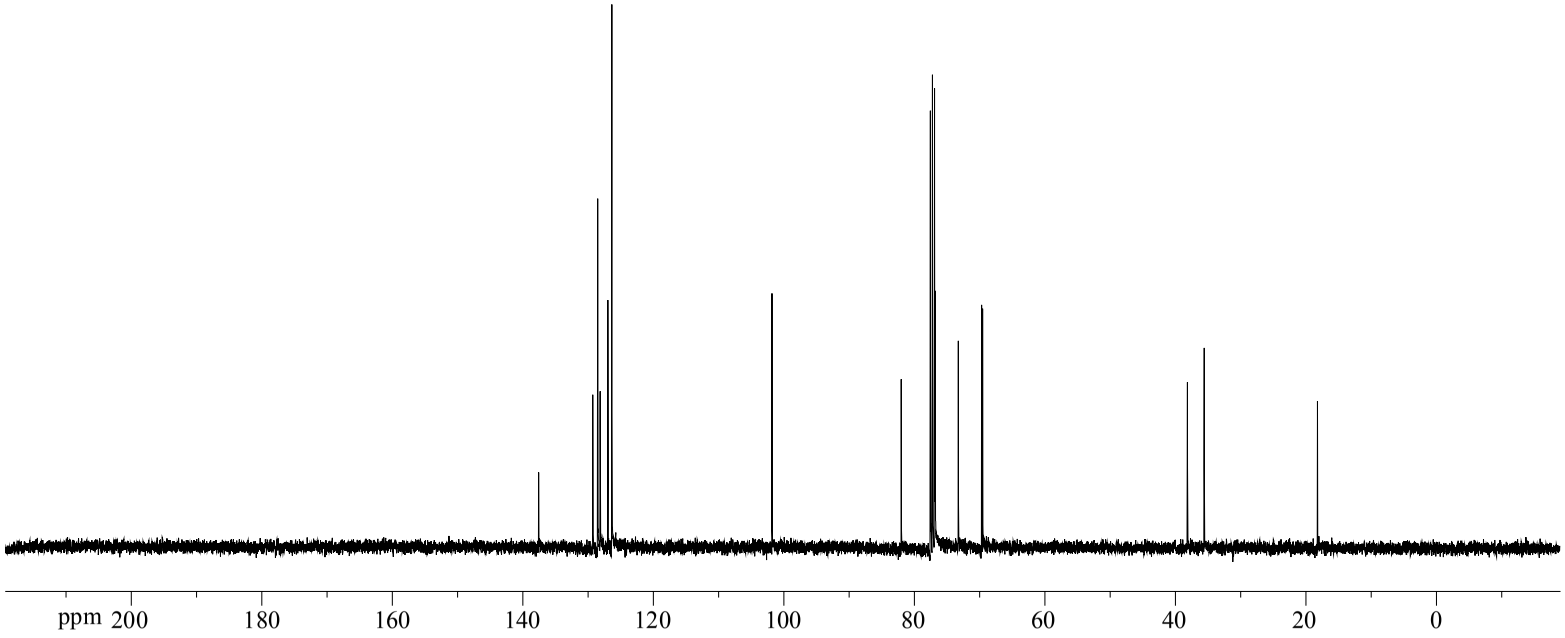

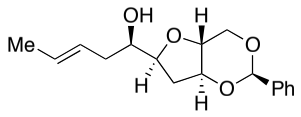

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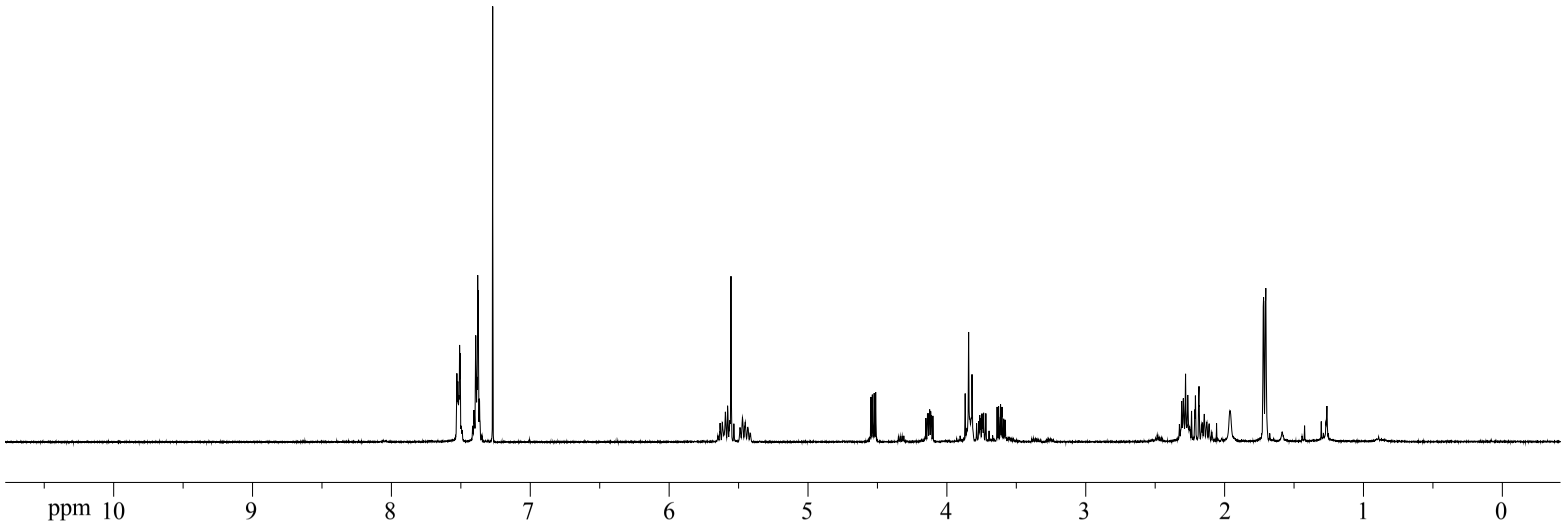

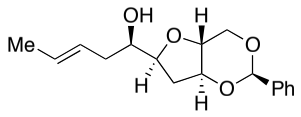

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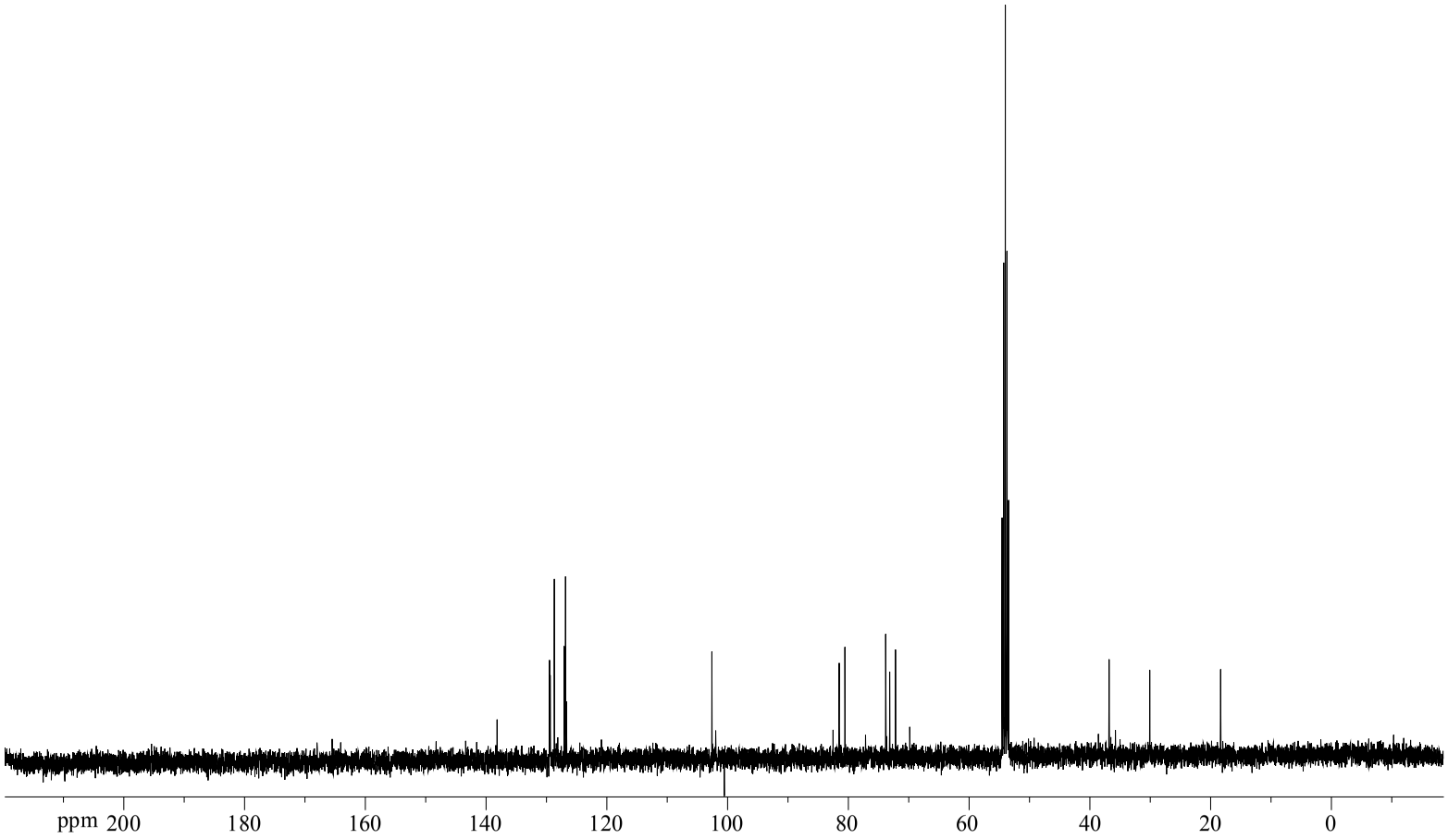

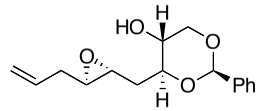

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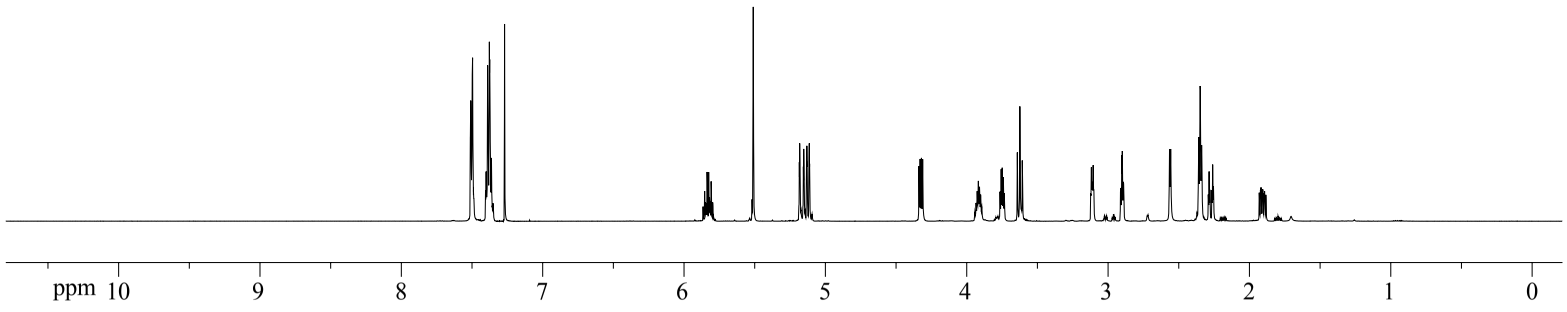

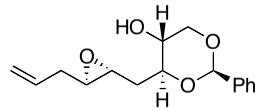

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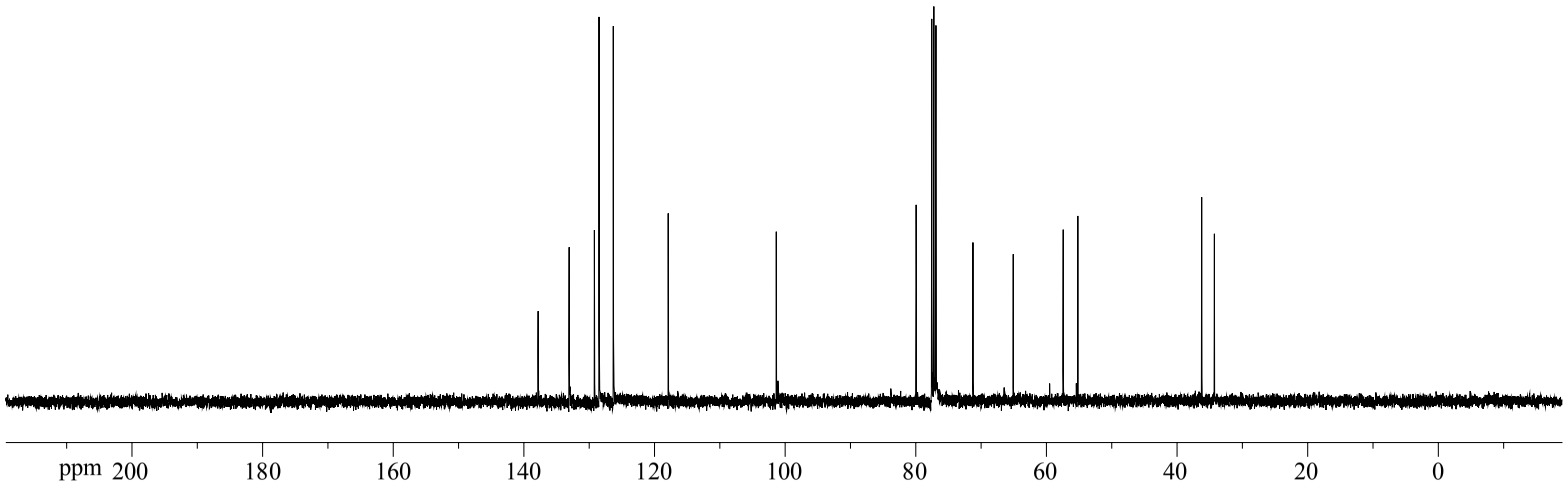

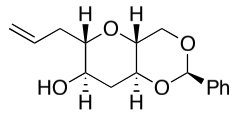

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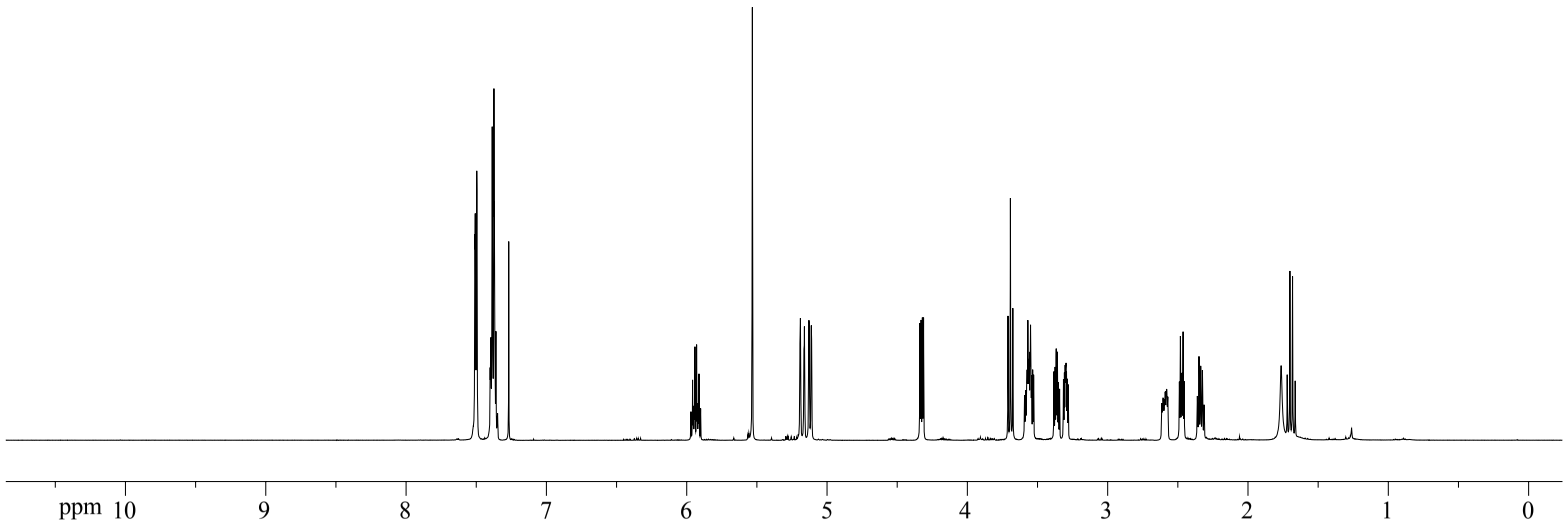

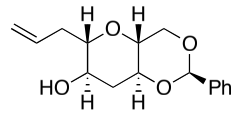

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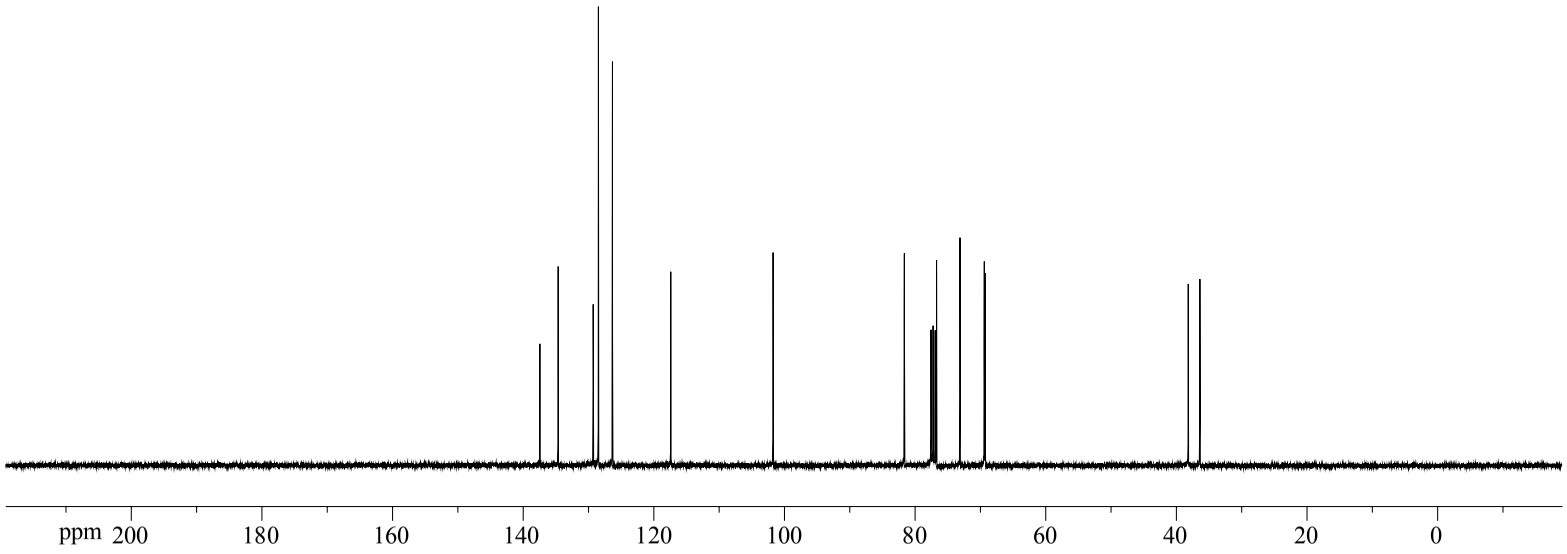

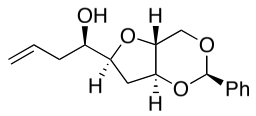

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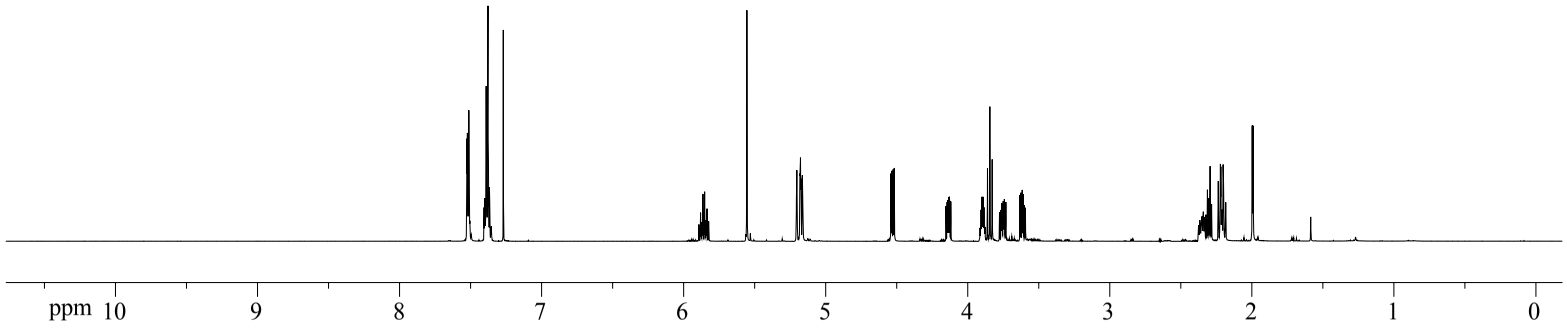

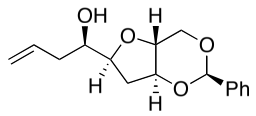

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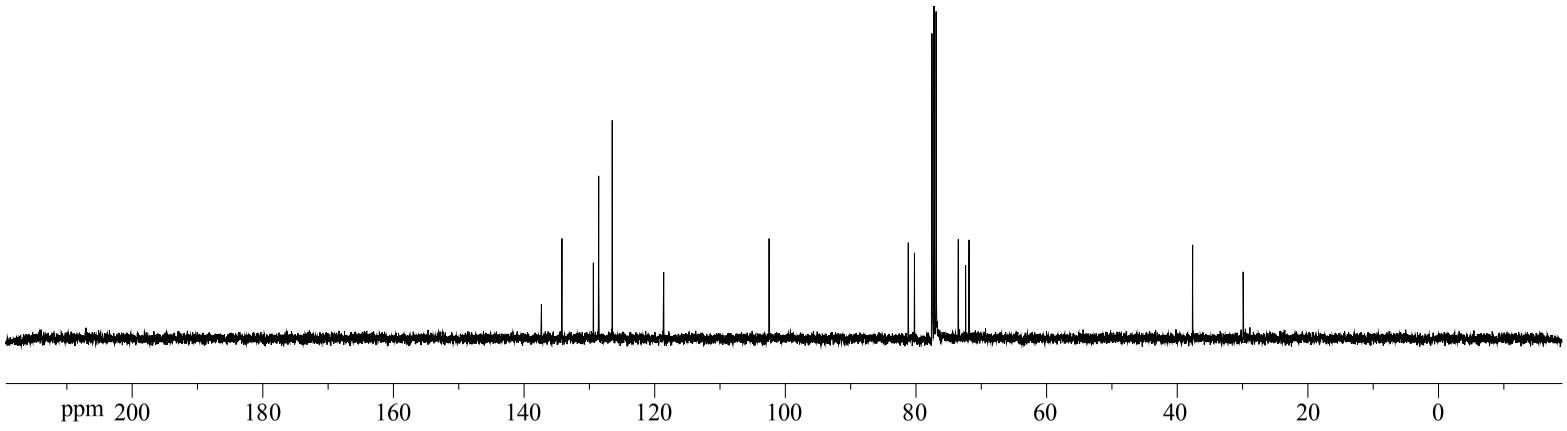

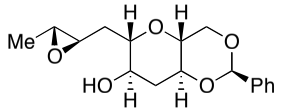

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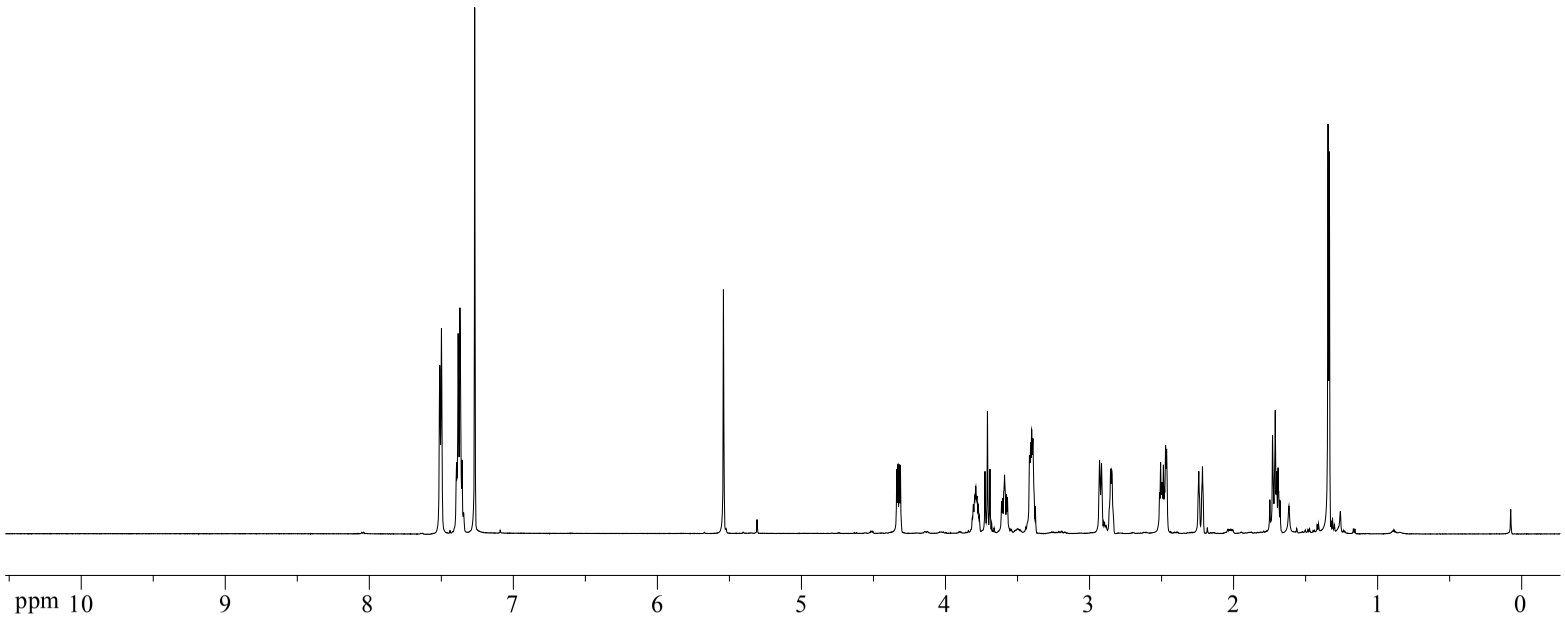

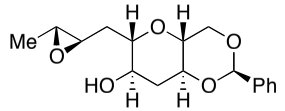

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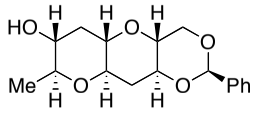

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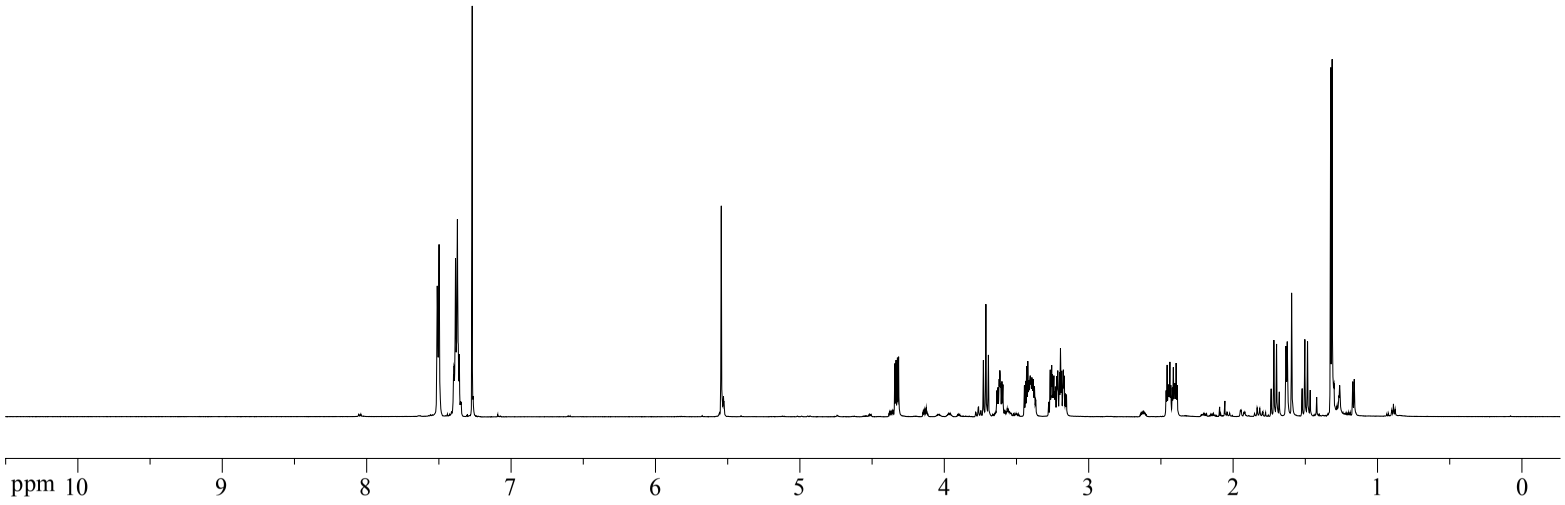

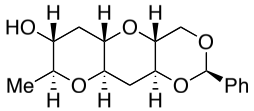

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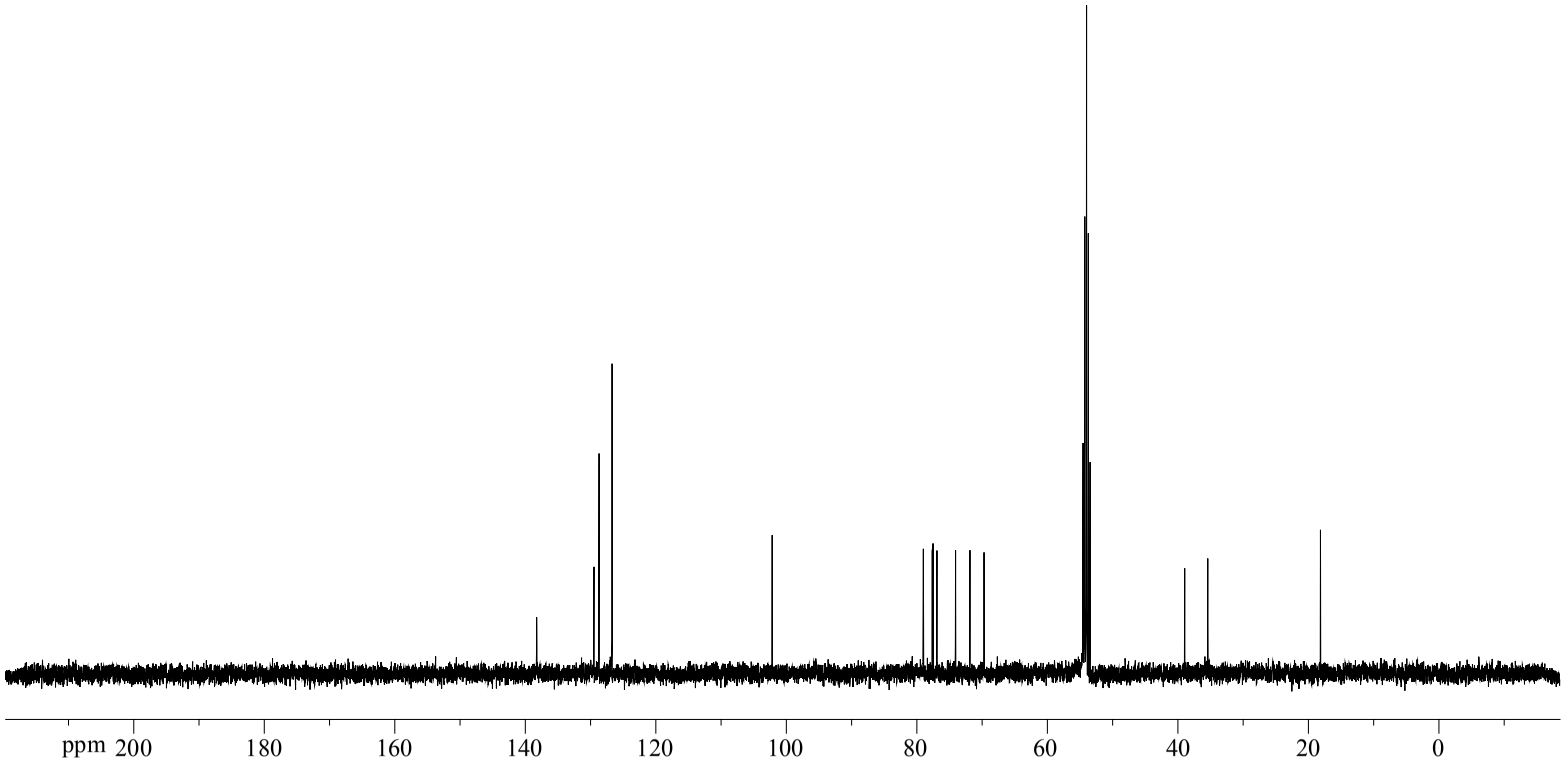

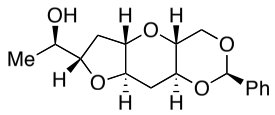

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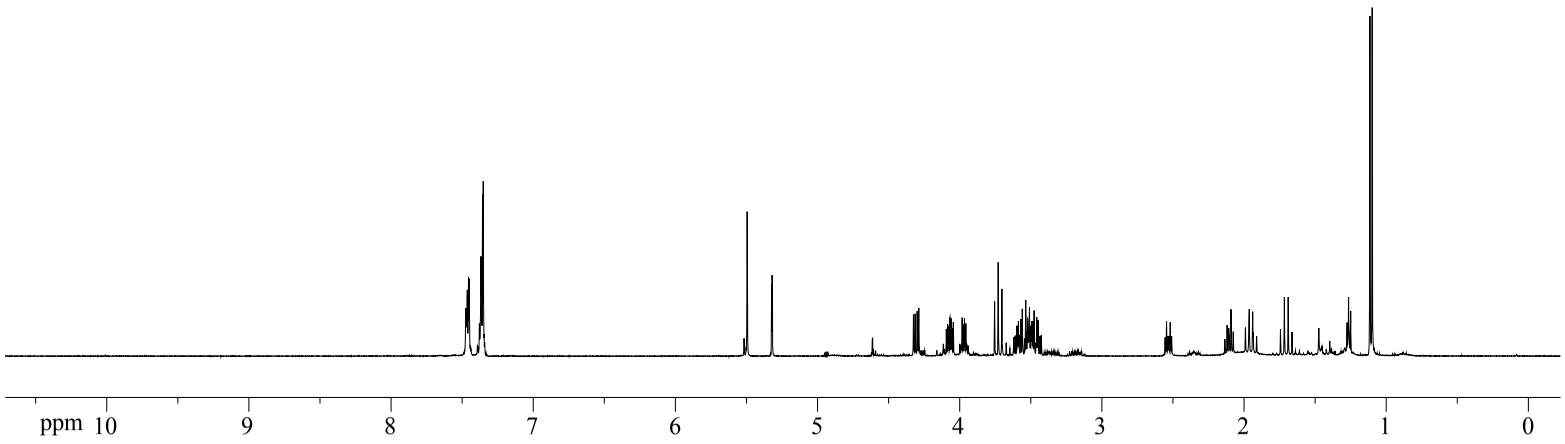

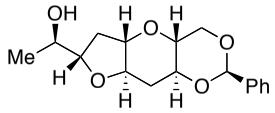

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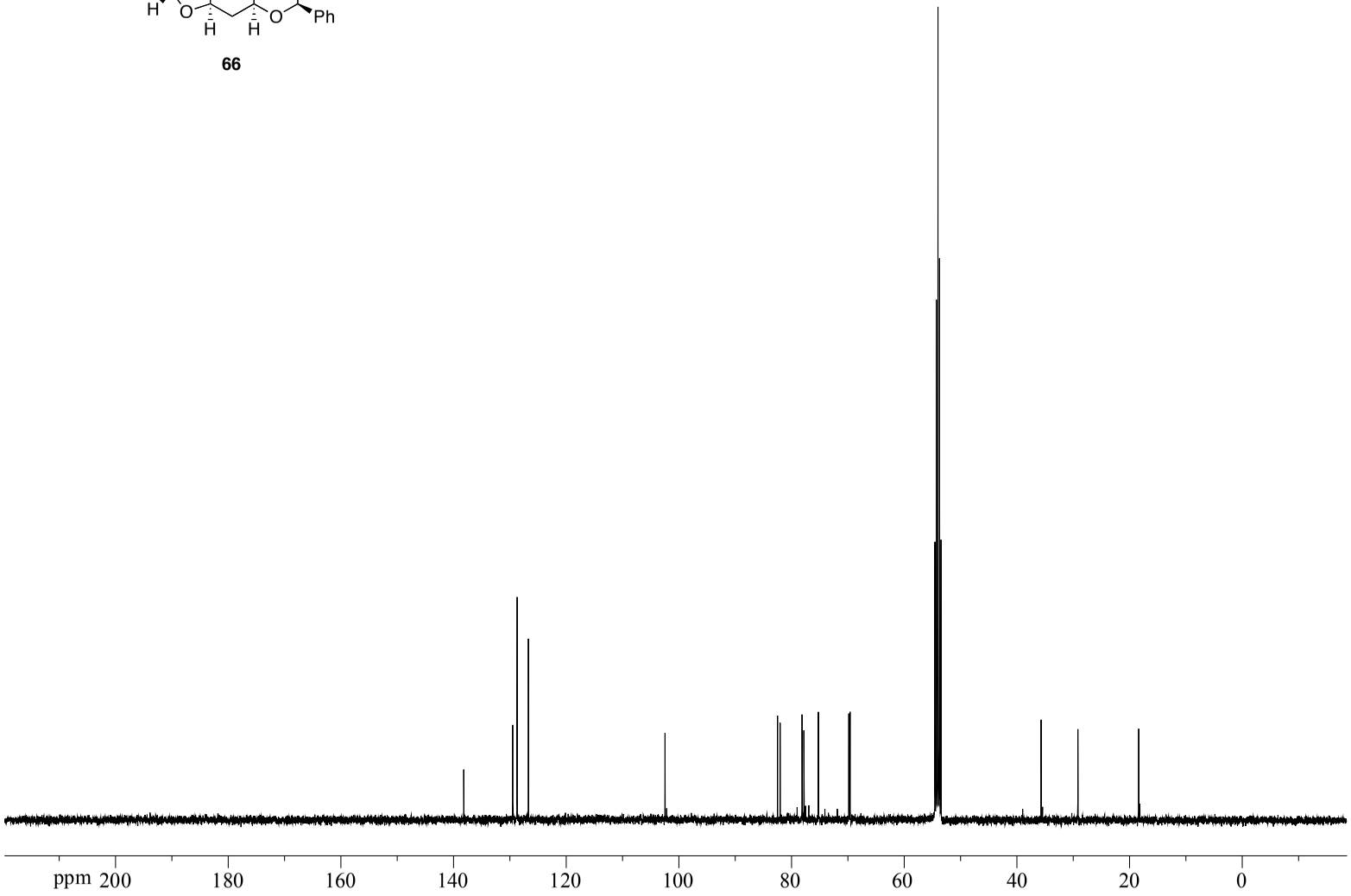

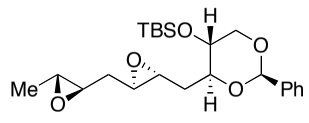

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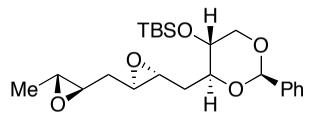

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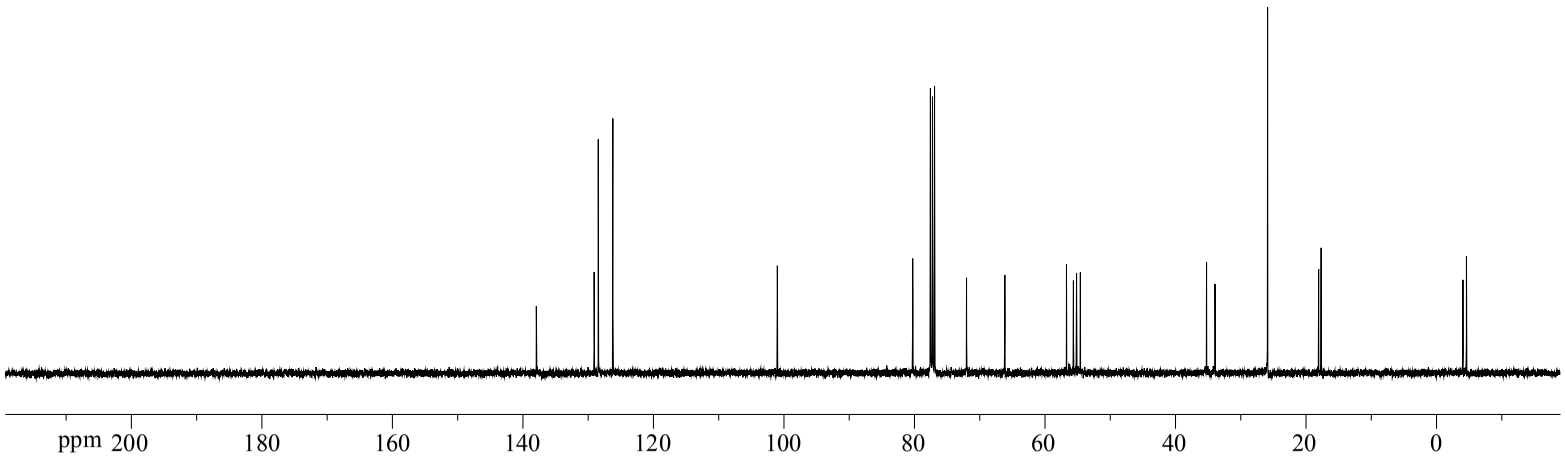

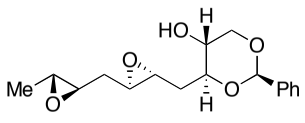

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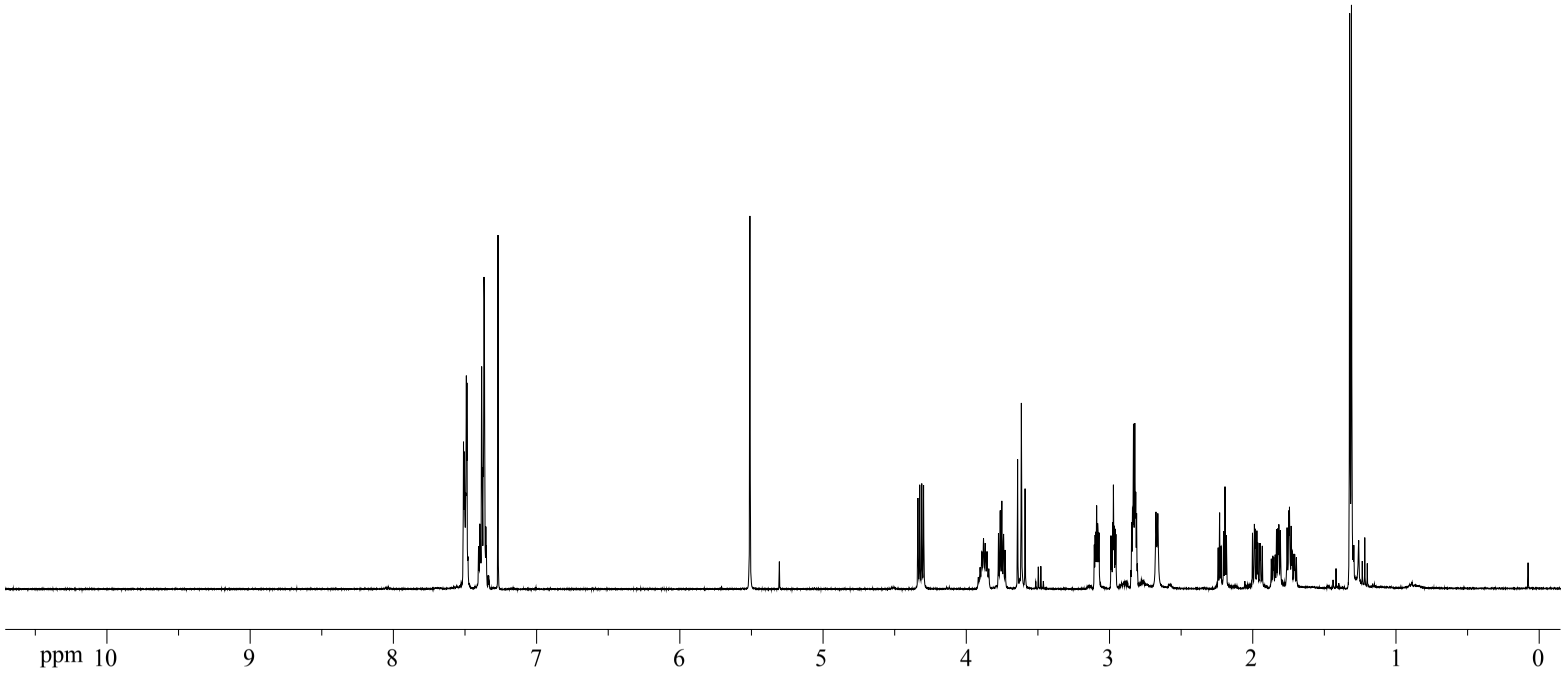

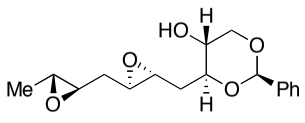

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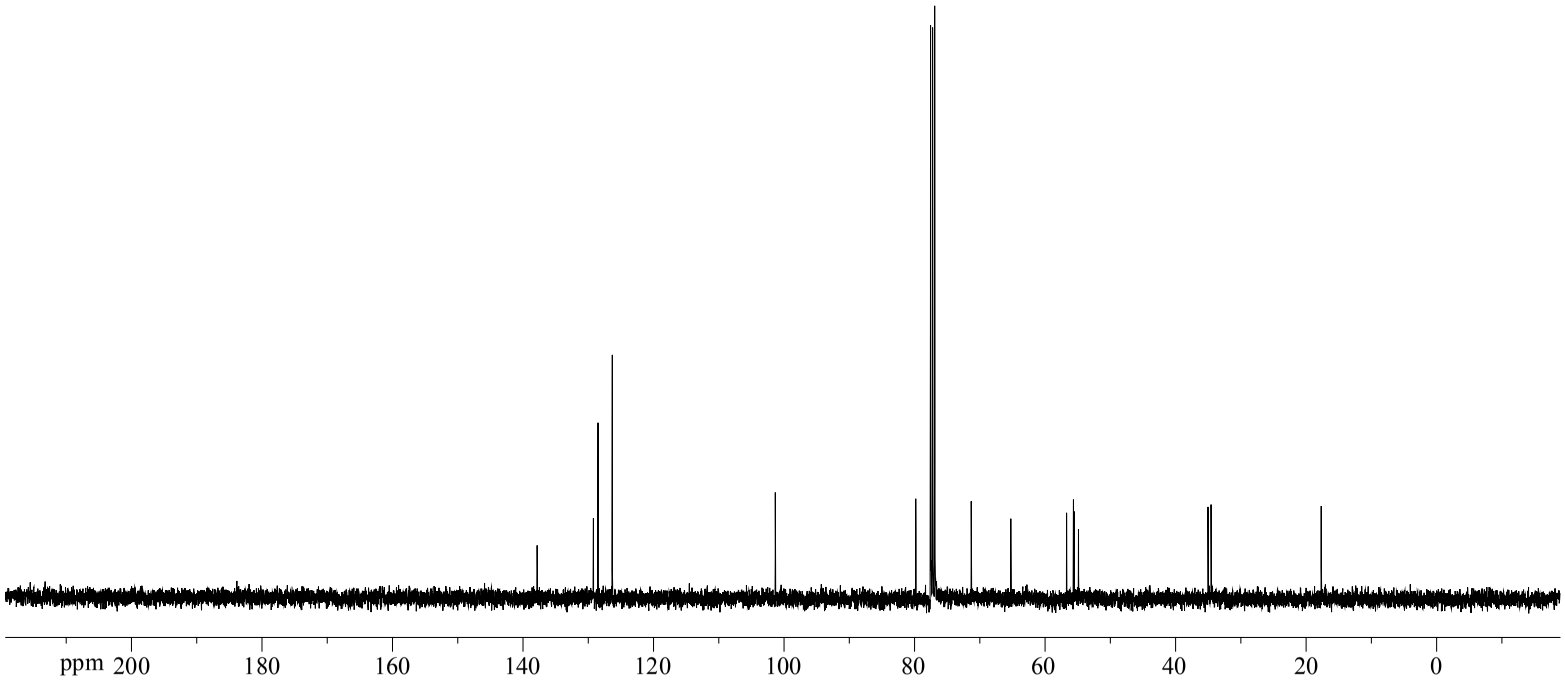

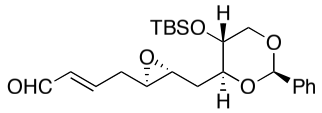

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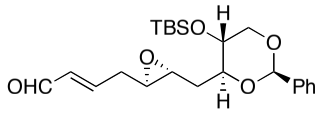

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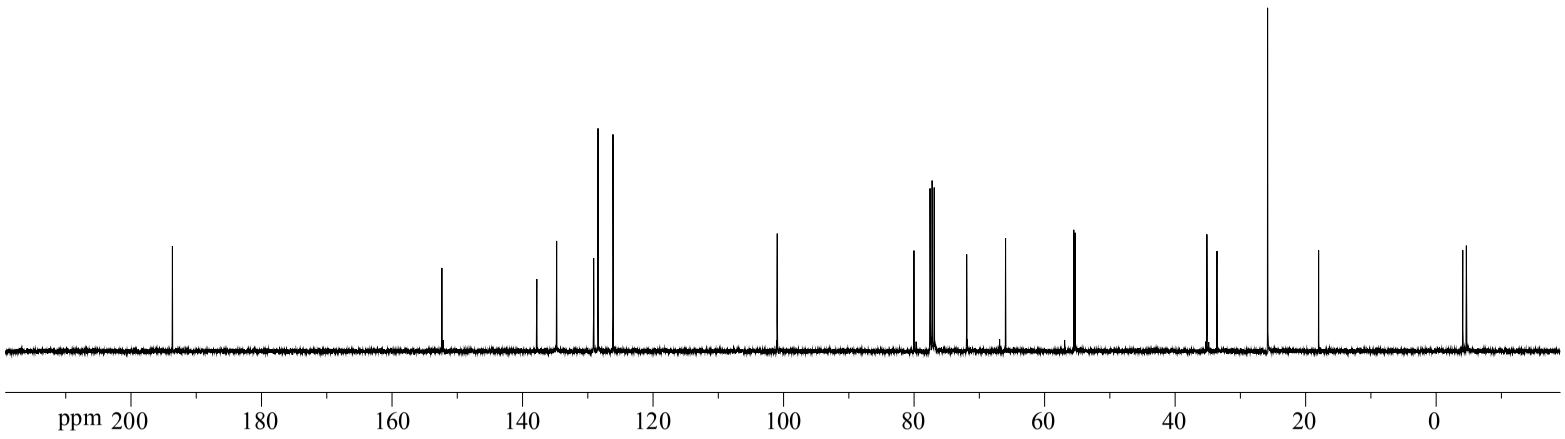

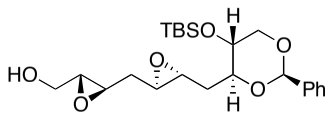

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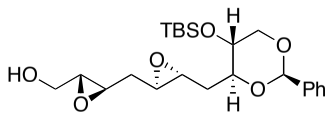

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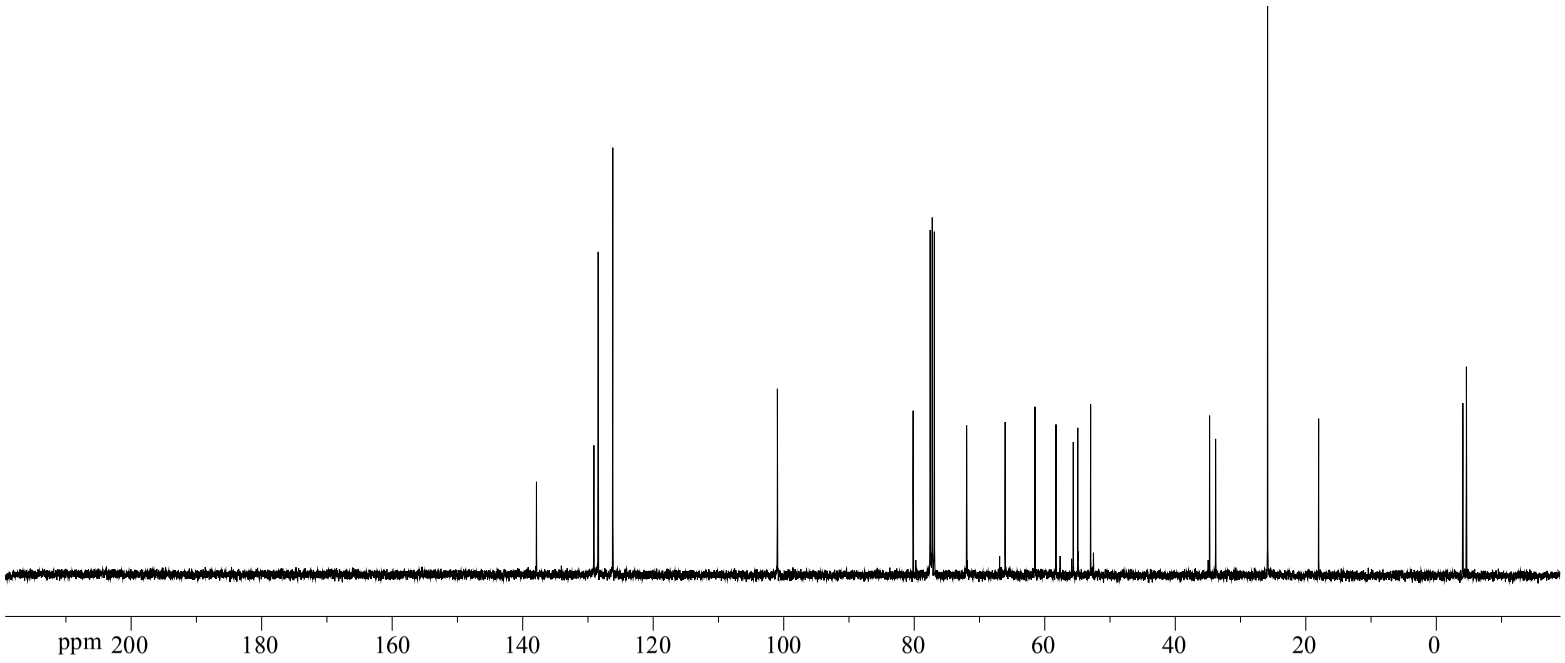

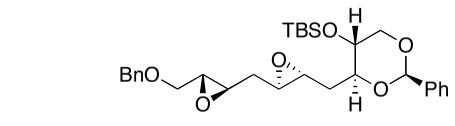

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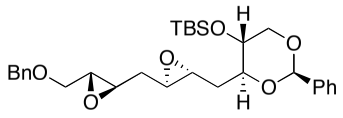

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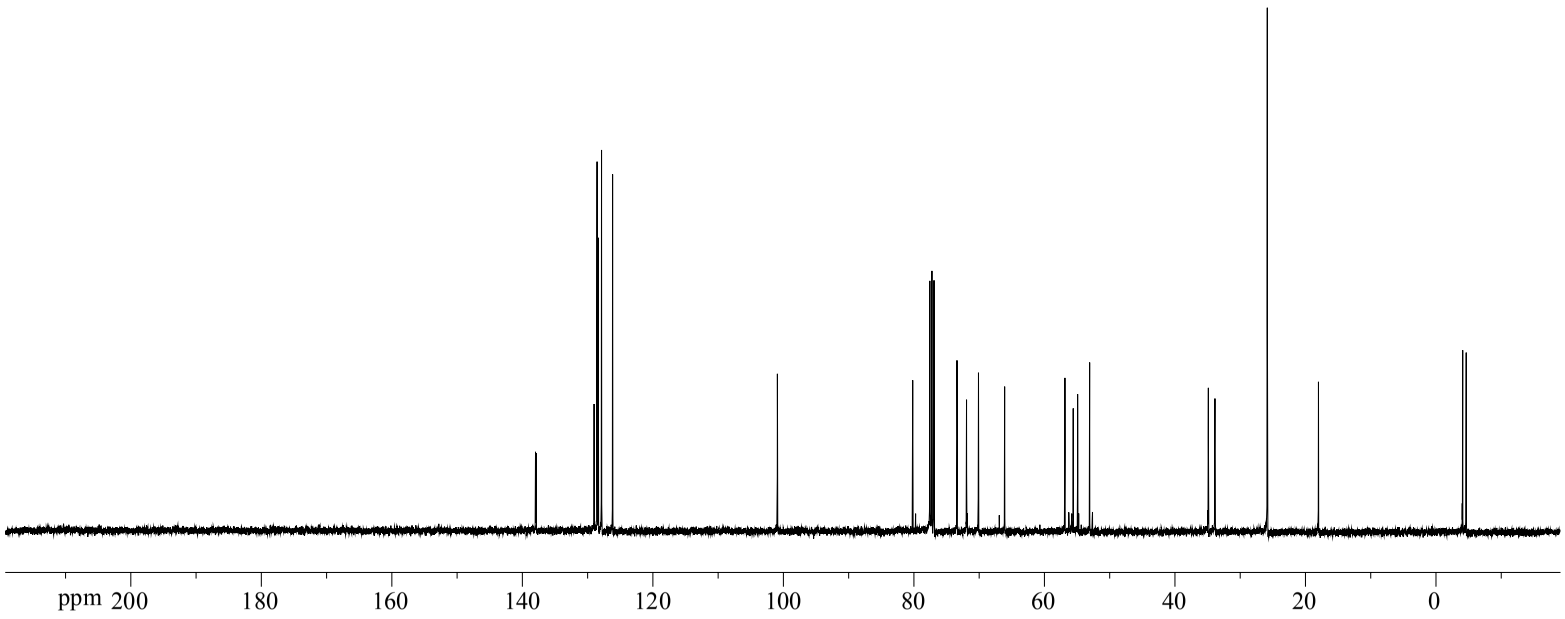

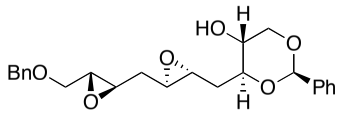

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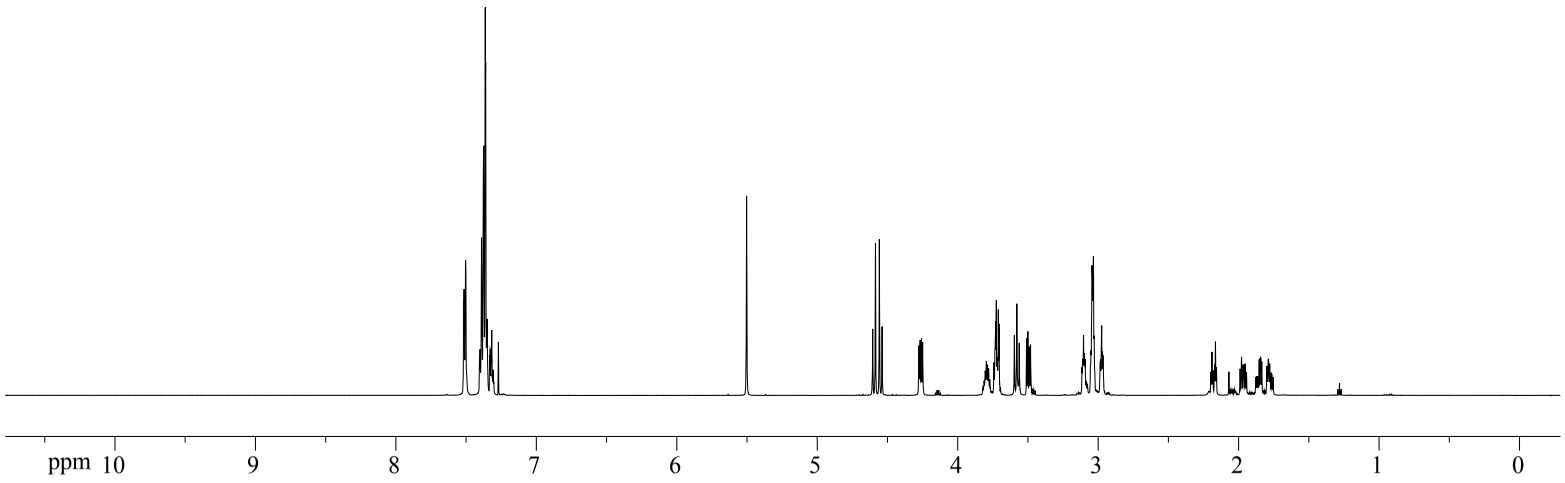

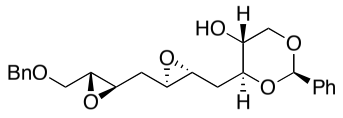

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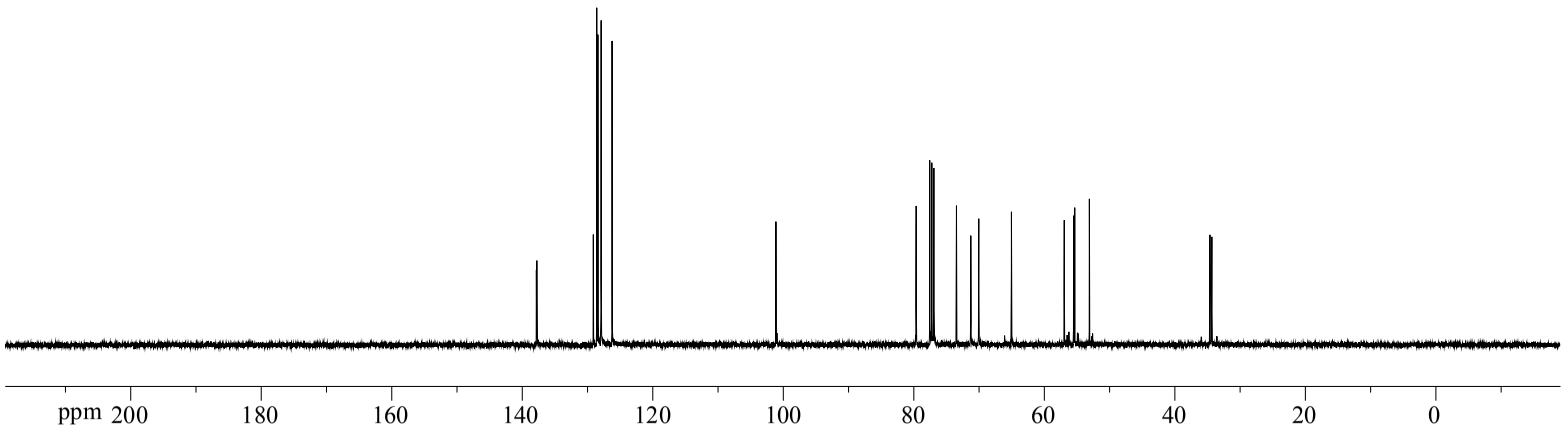

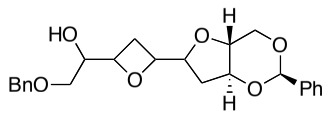

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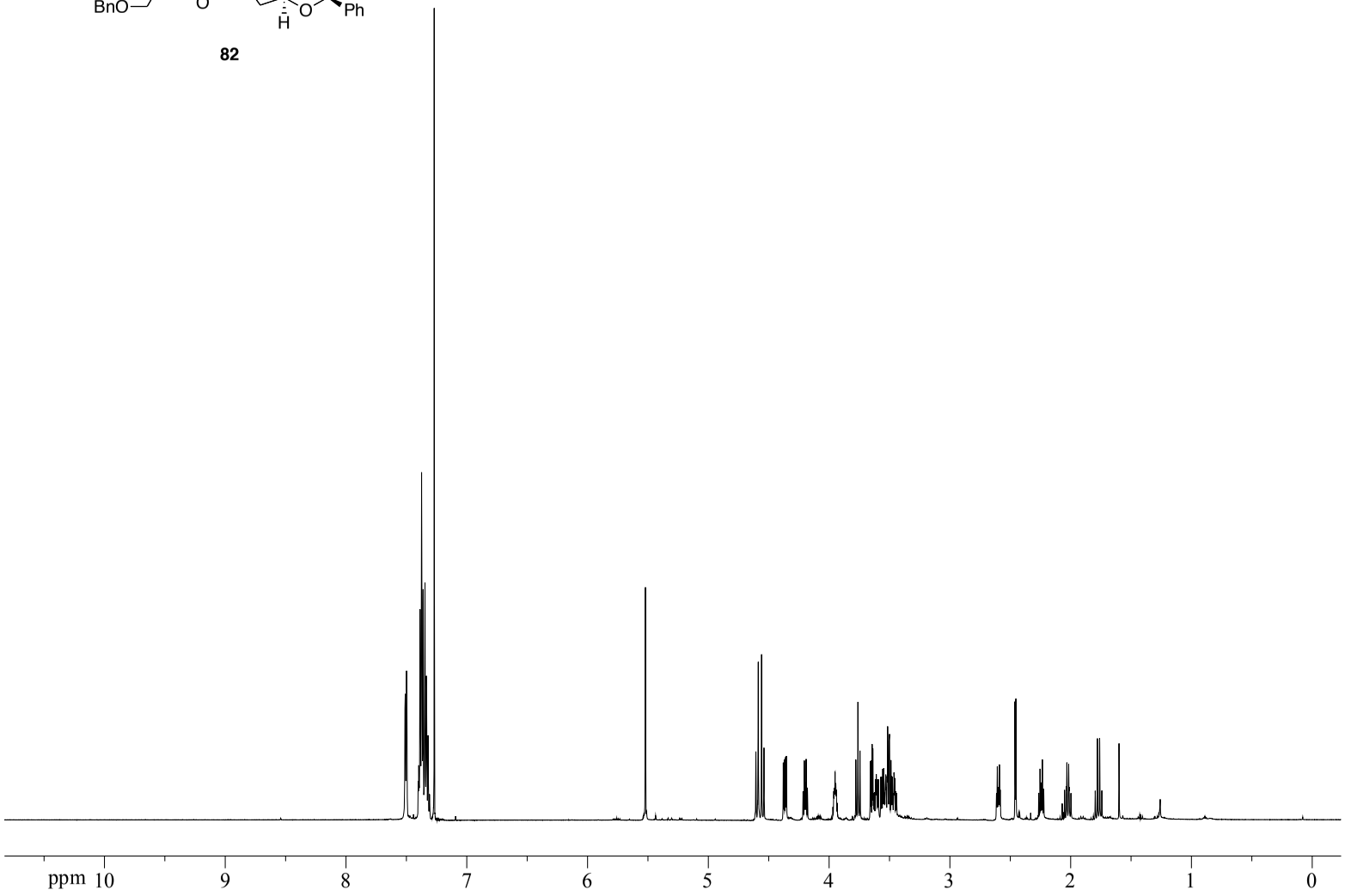

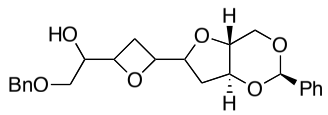

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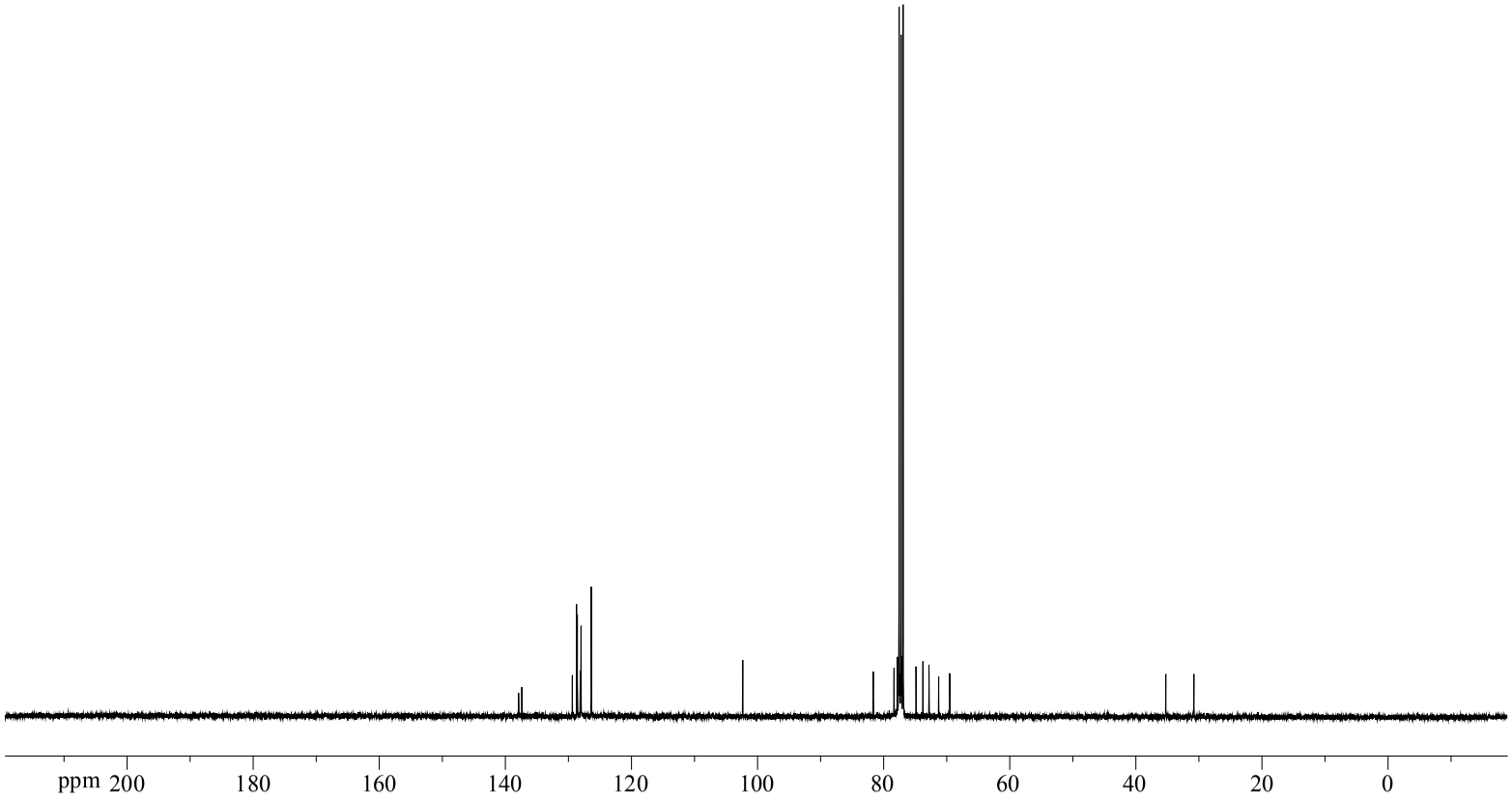

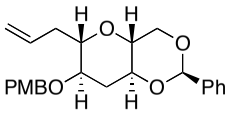

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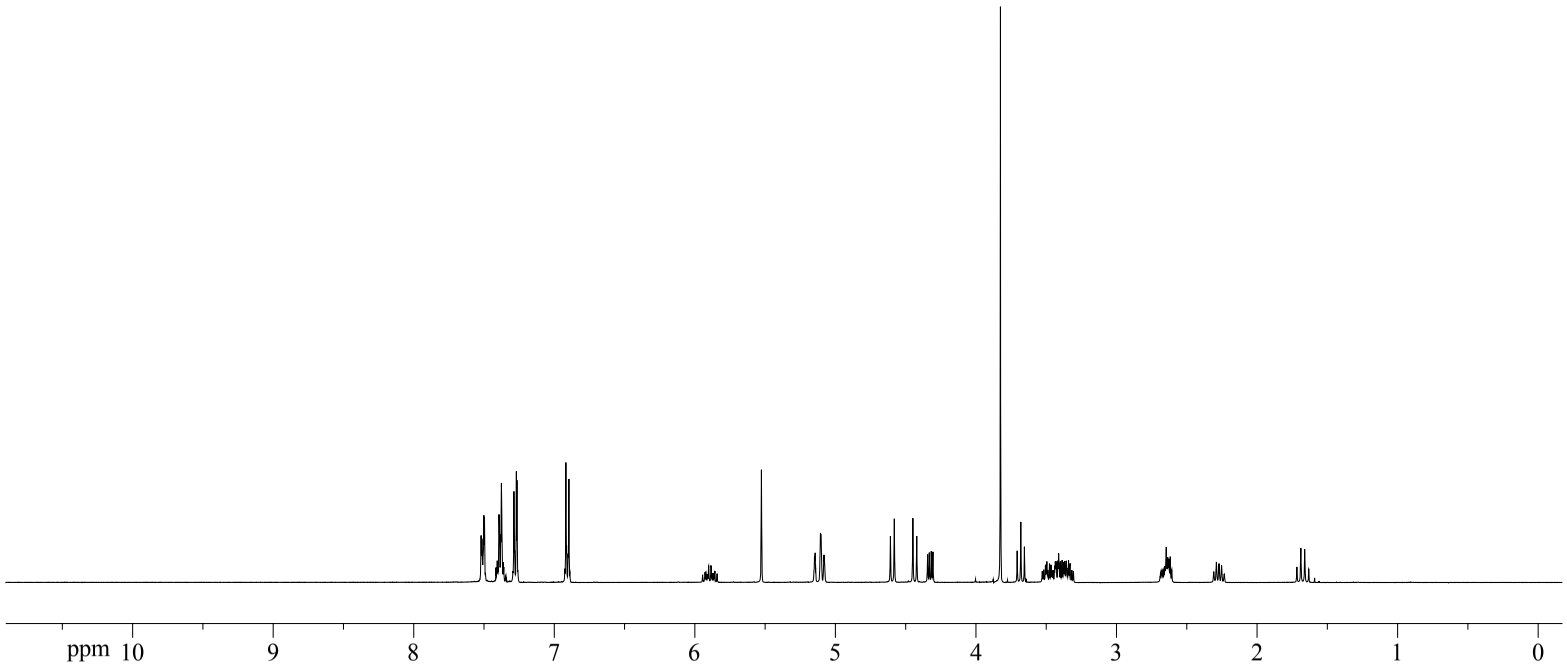

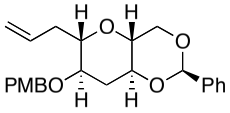

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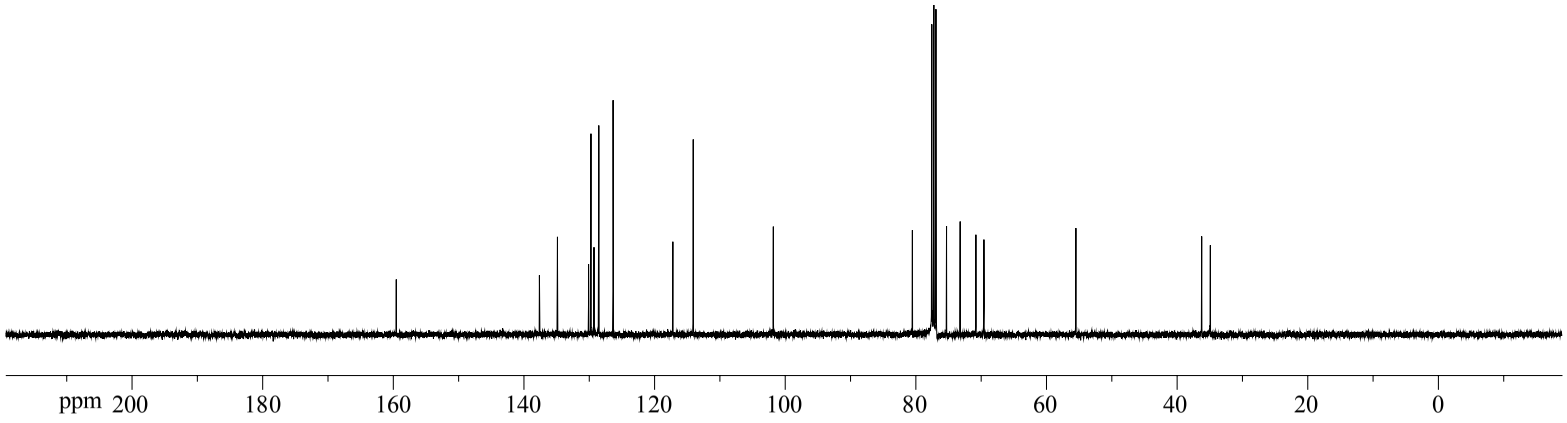

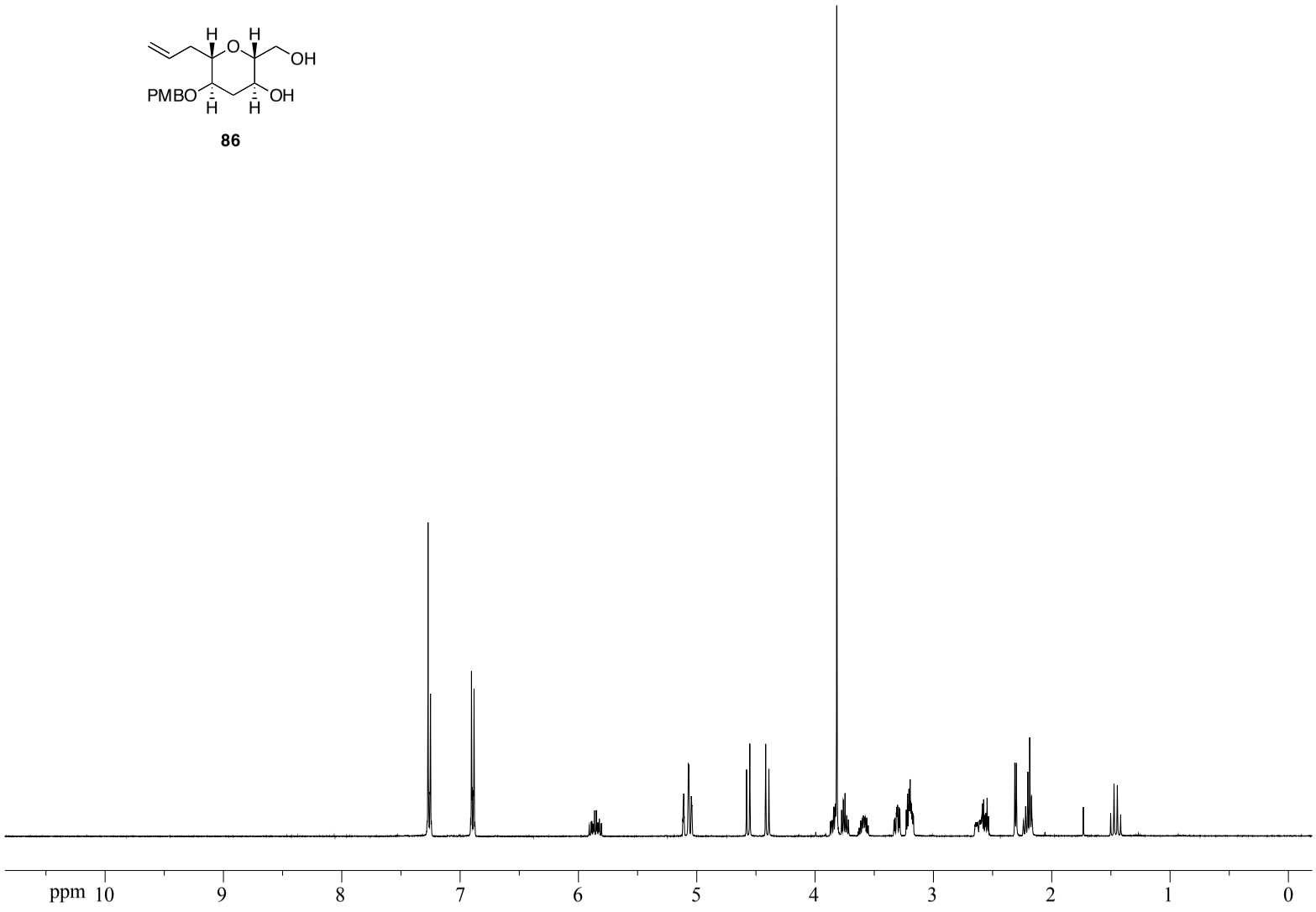

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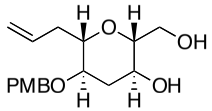

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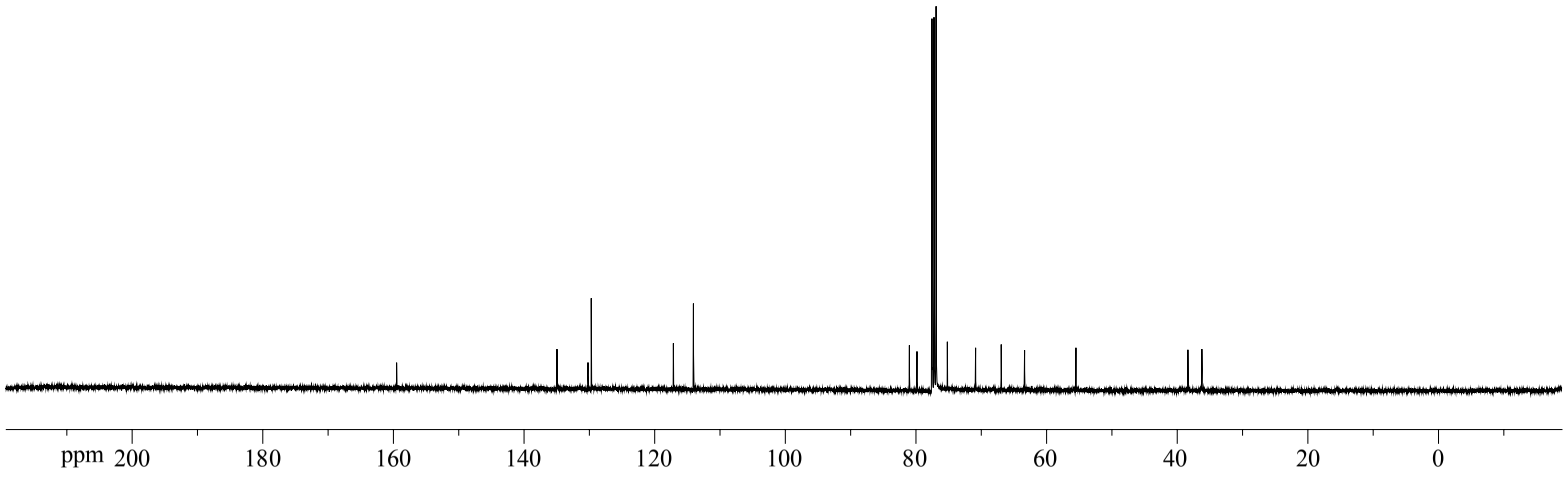

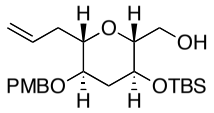

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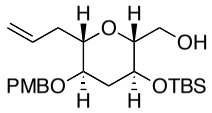

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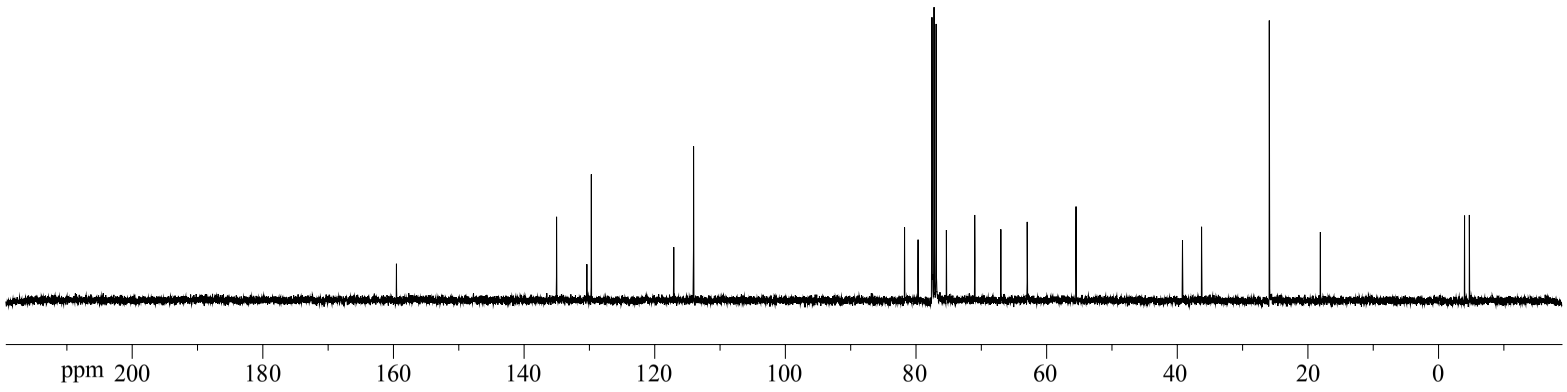

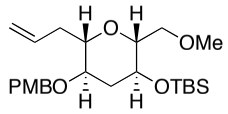

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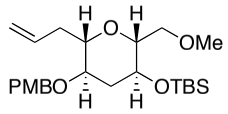

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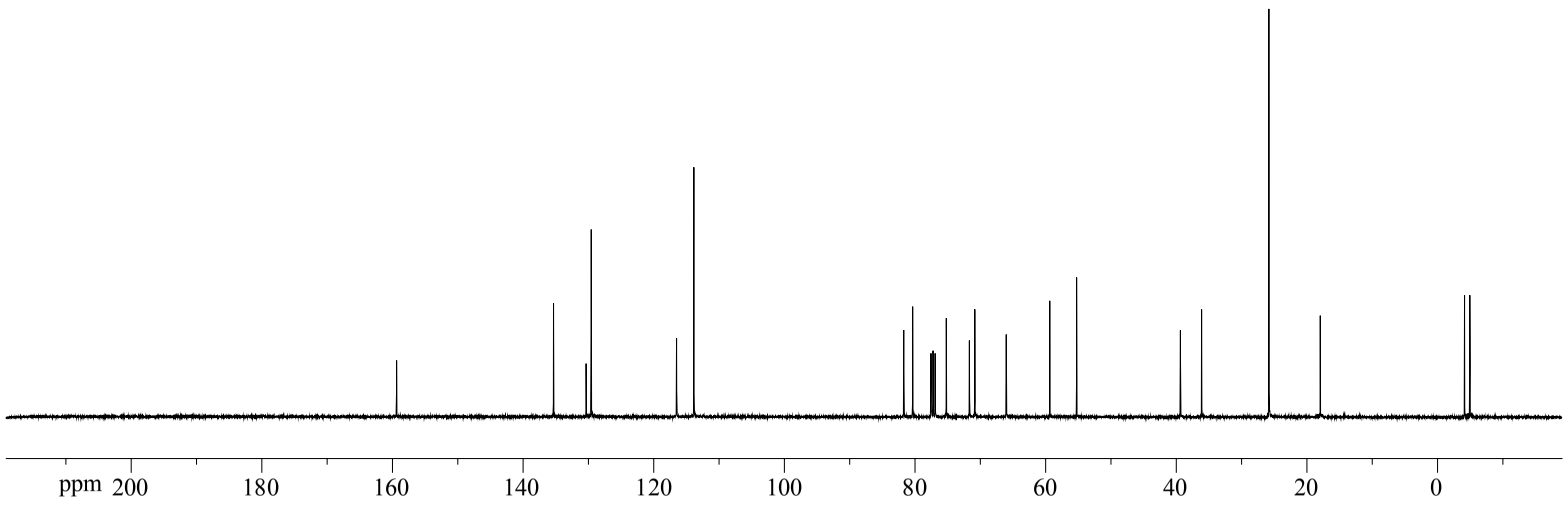

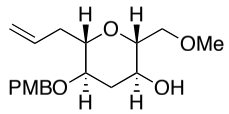

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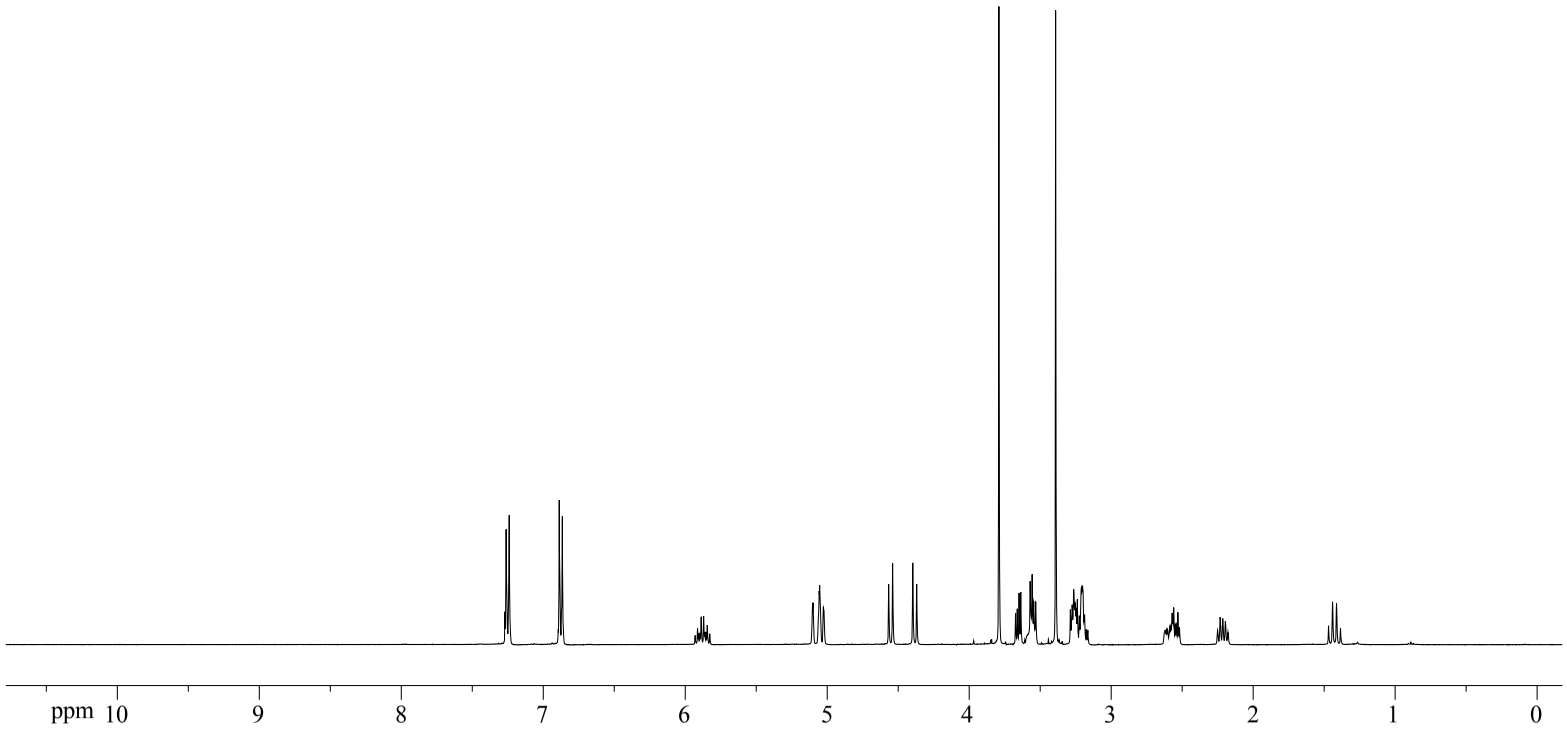

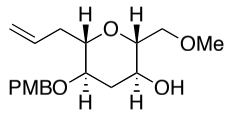

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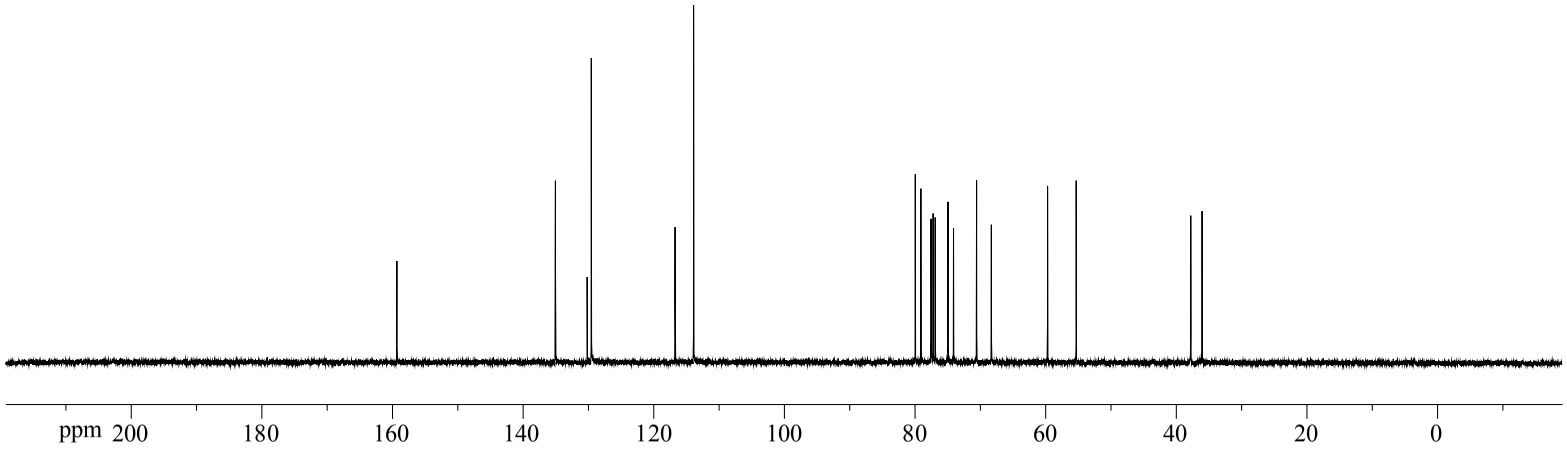

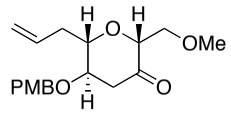

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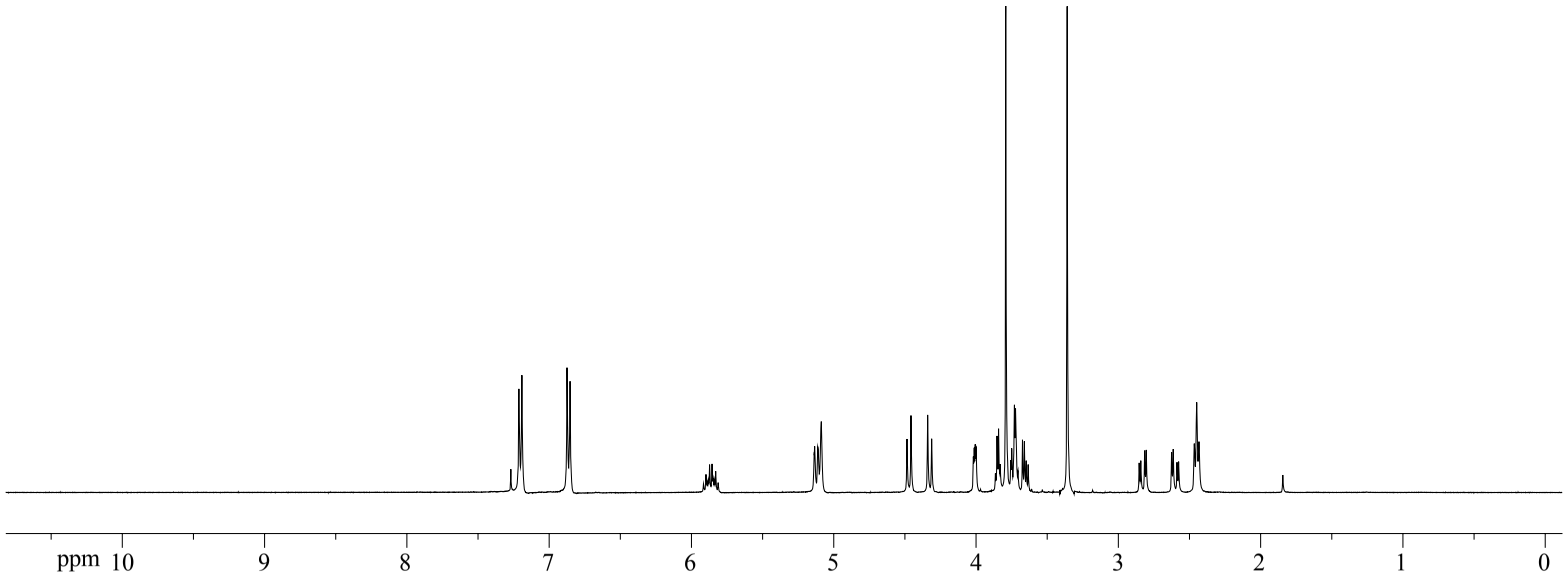

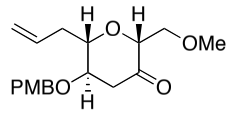

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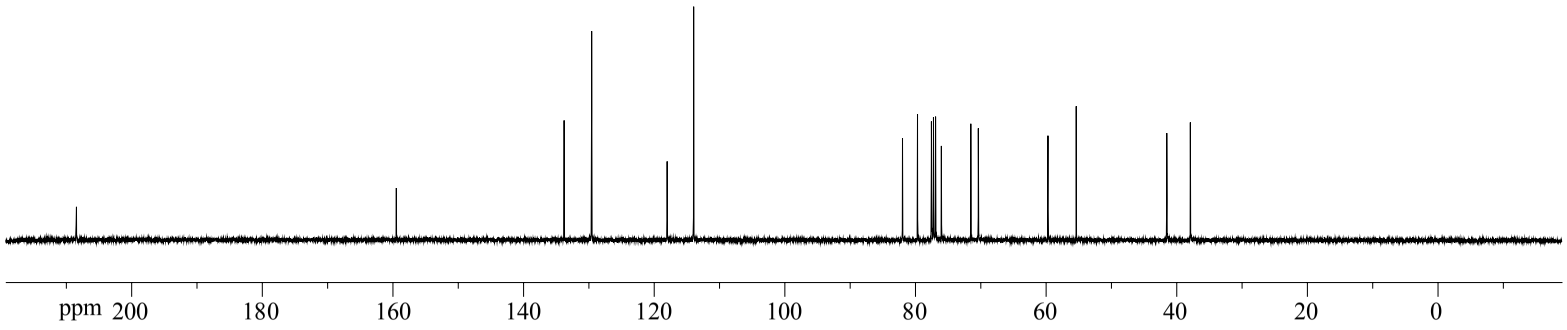

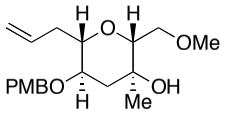

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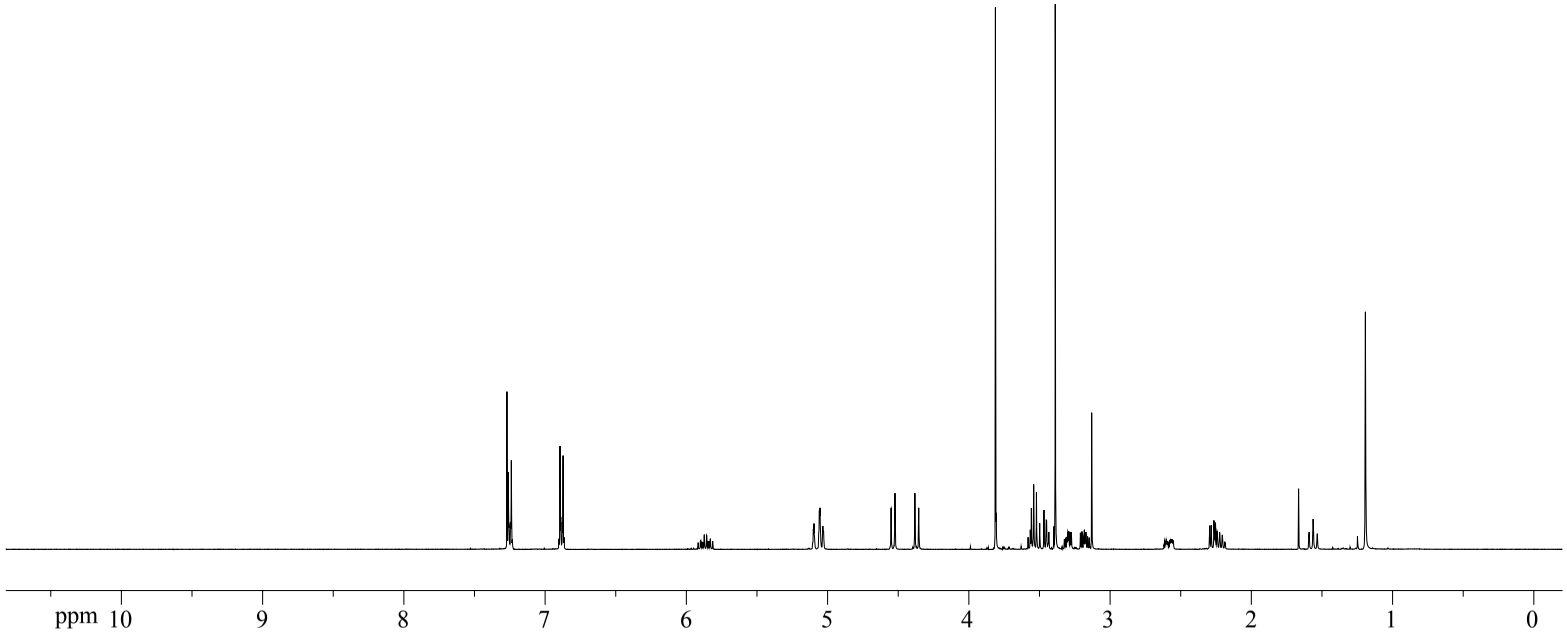

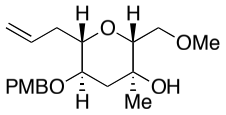

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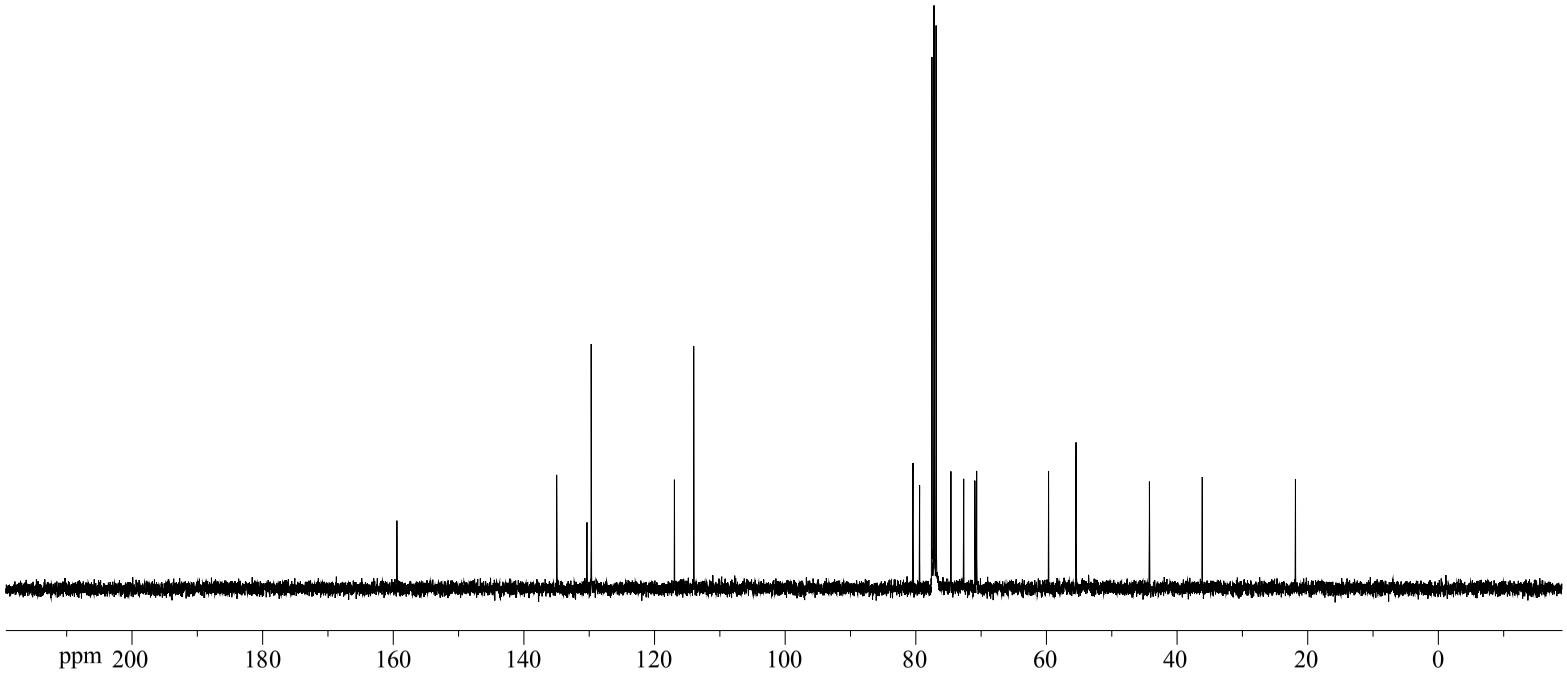

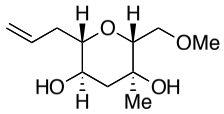

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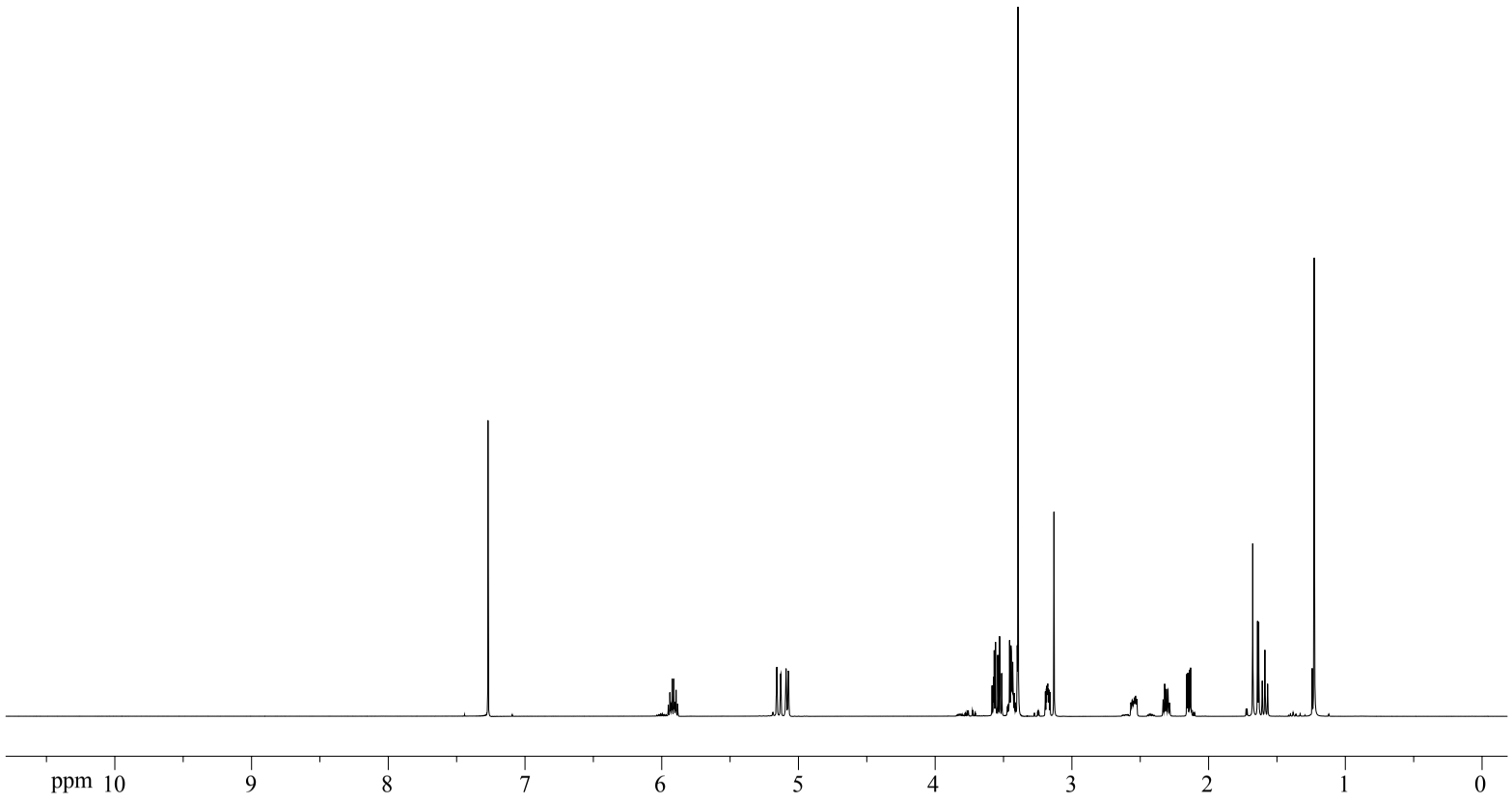

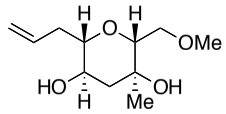

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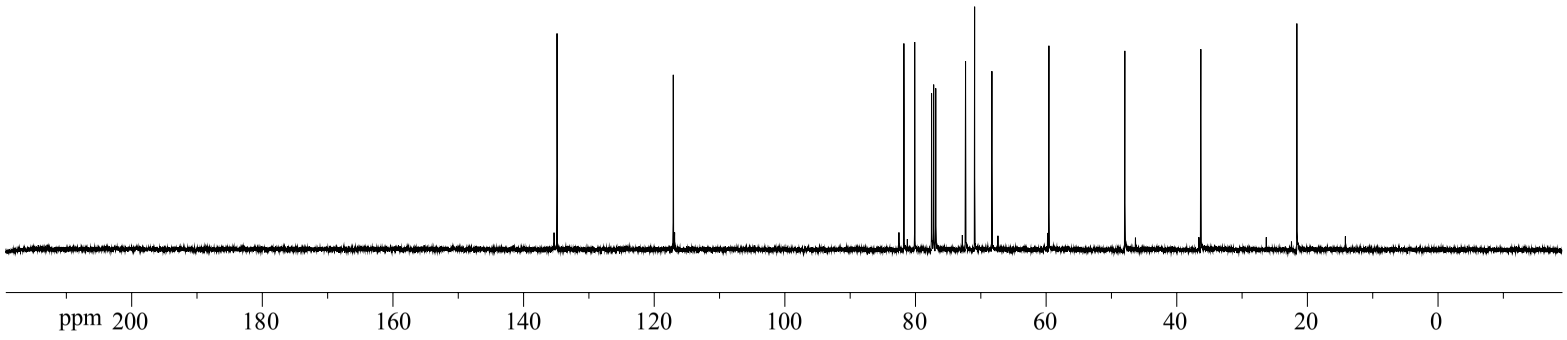

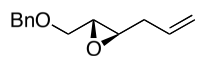

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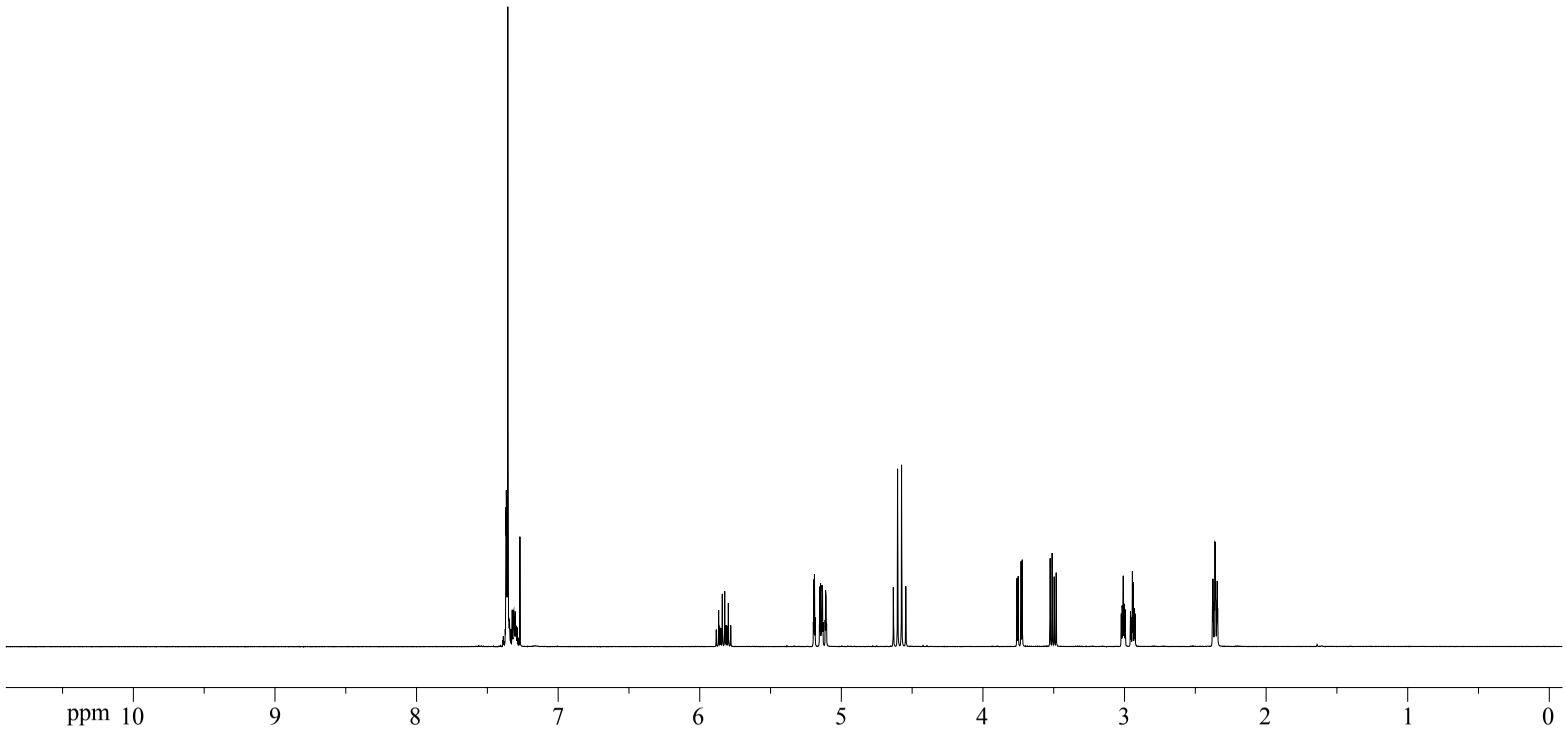

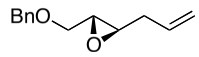

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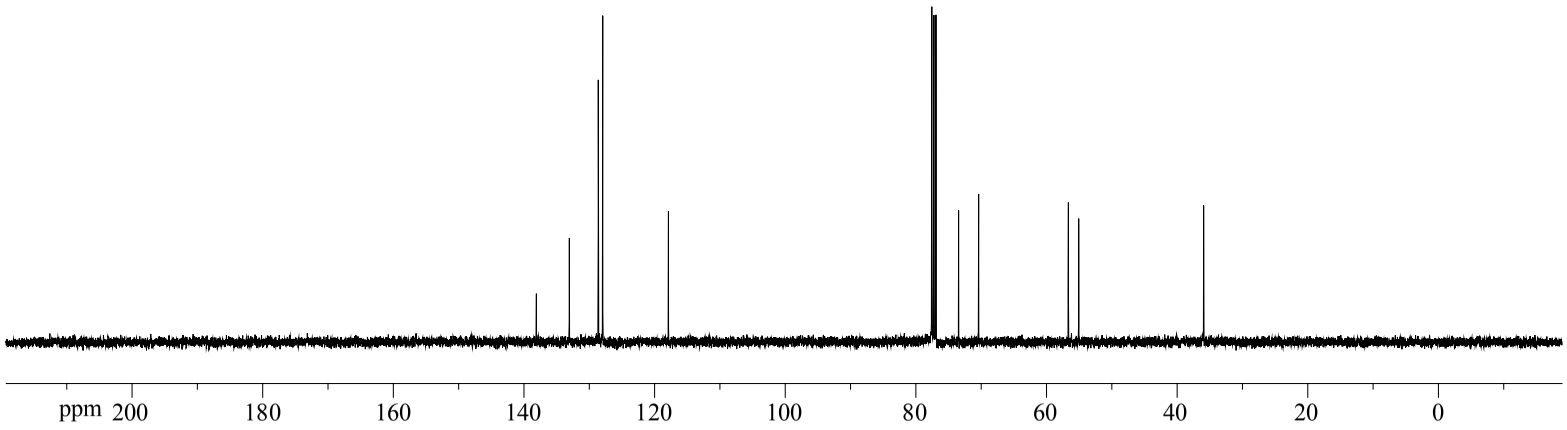

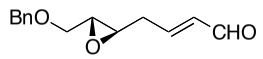

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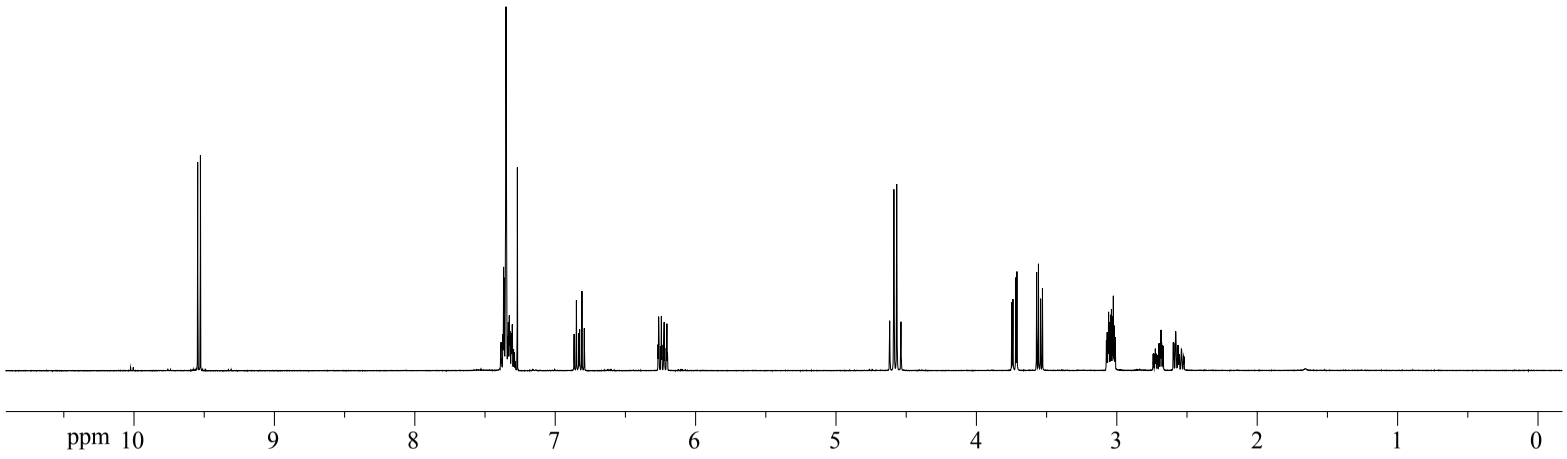

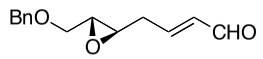

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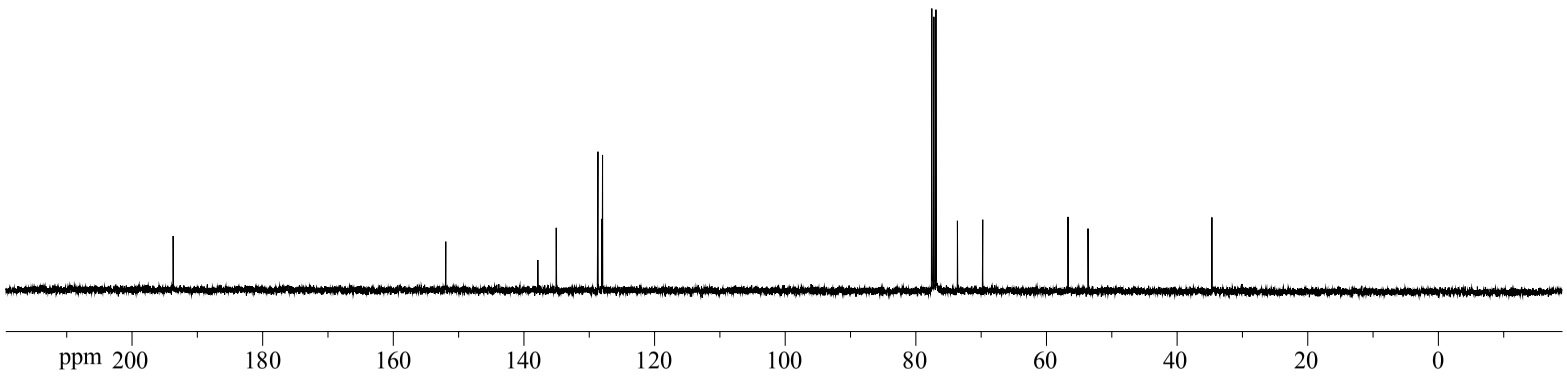

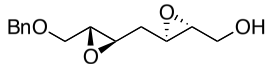

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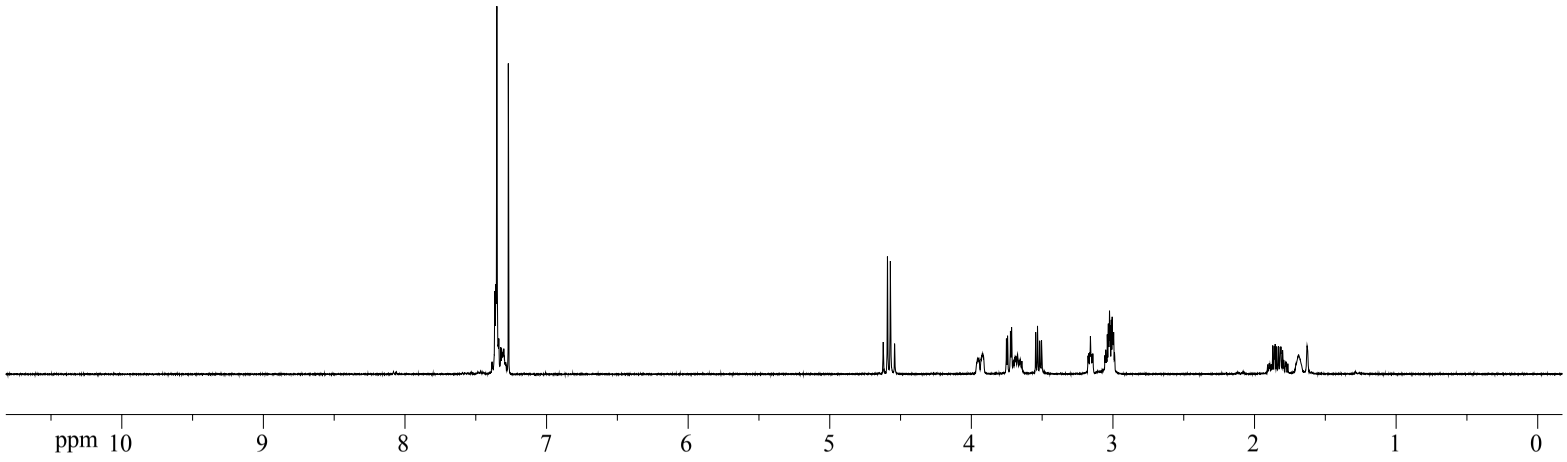

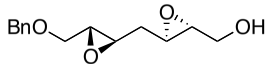

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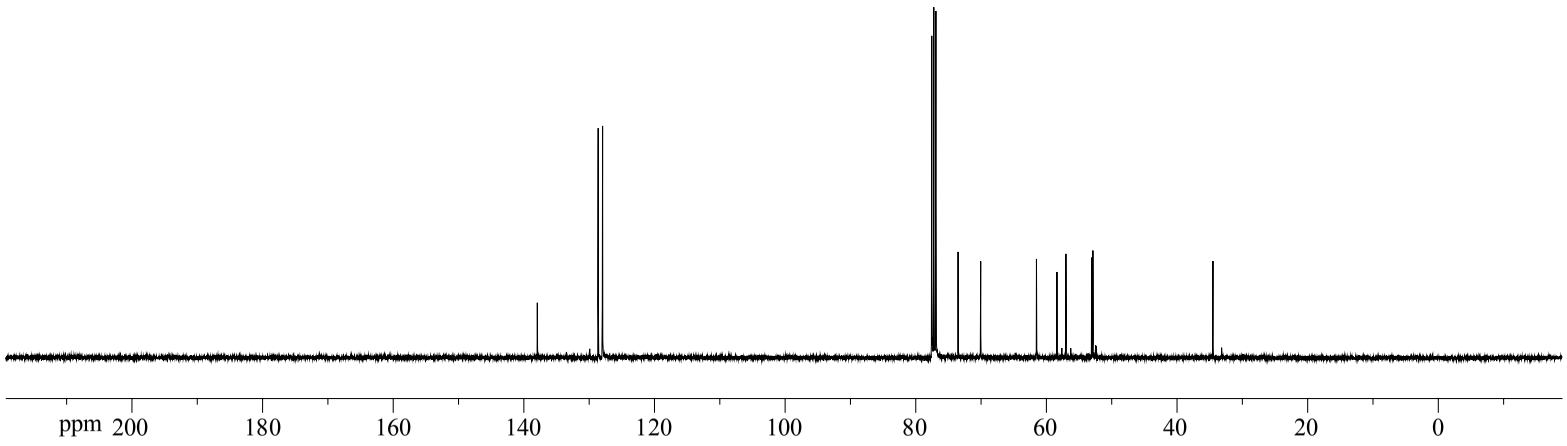
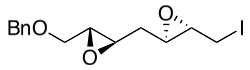
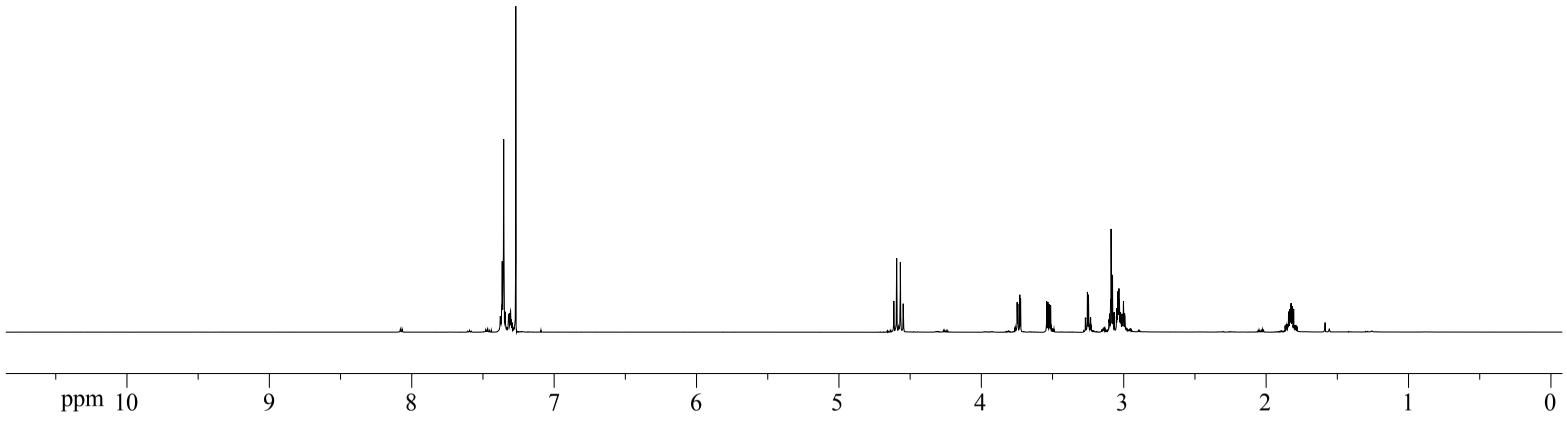
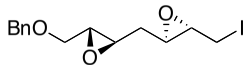




S6





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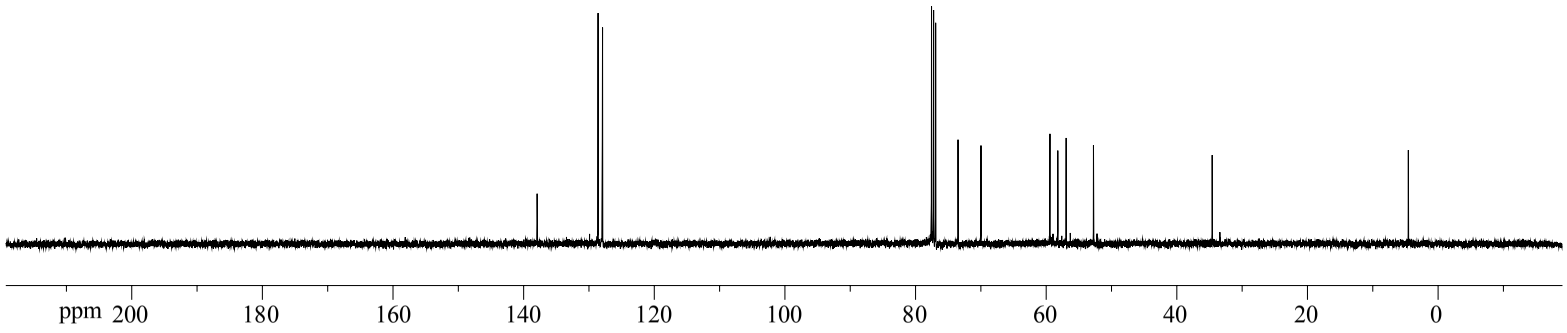

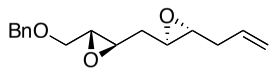

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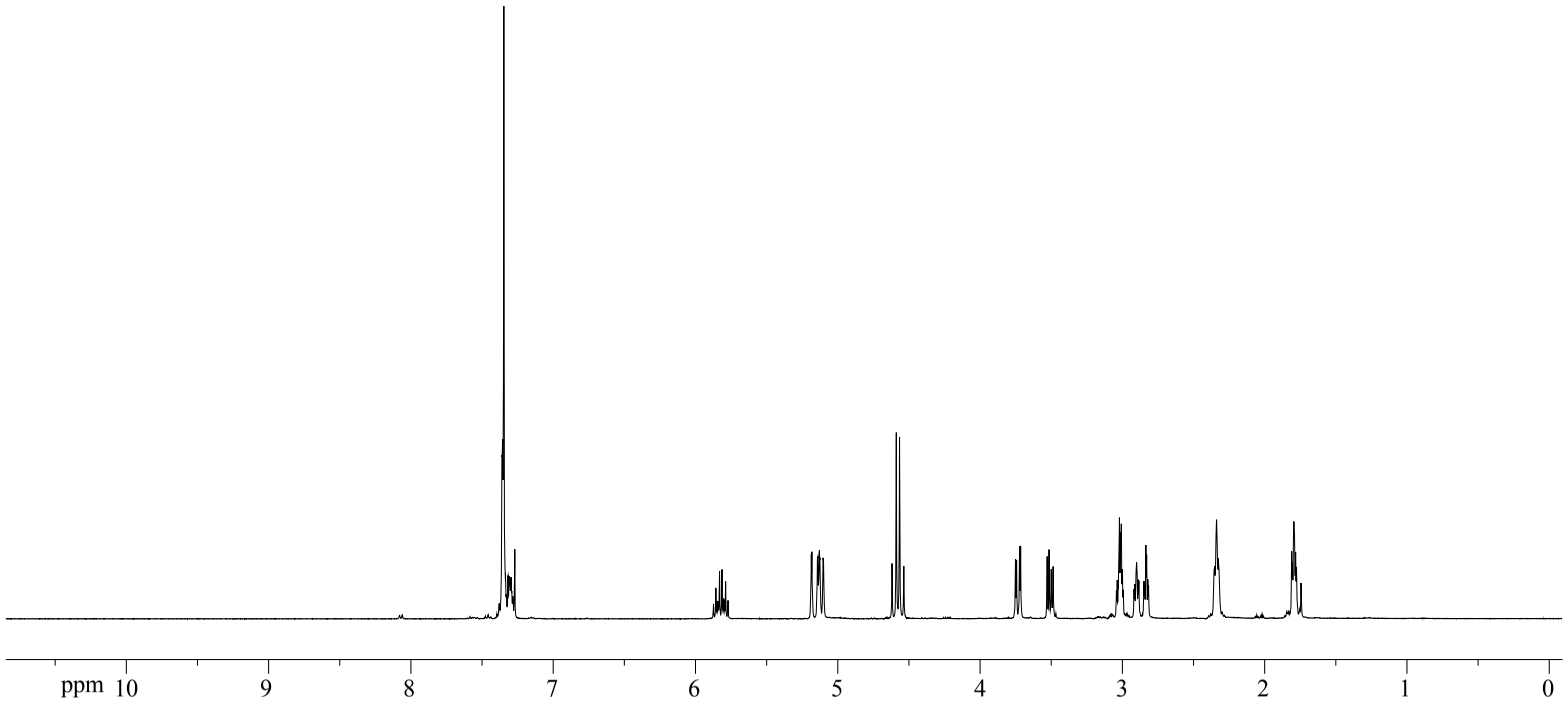

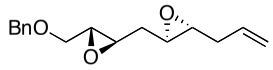

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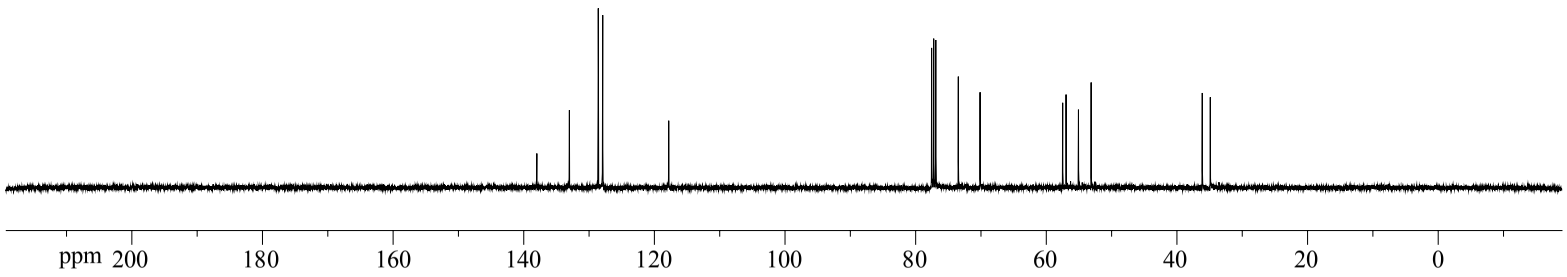

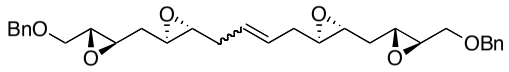

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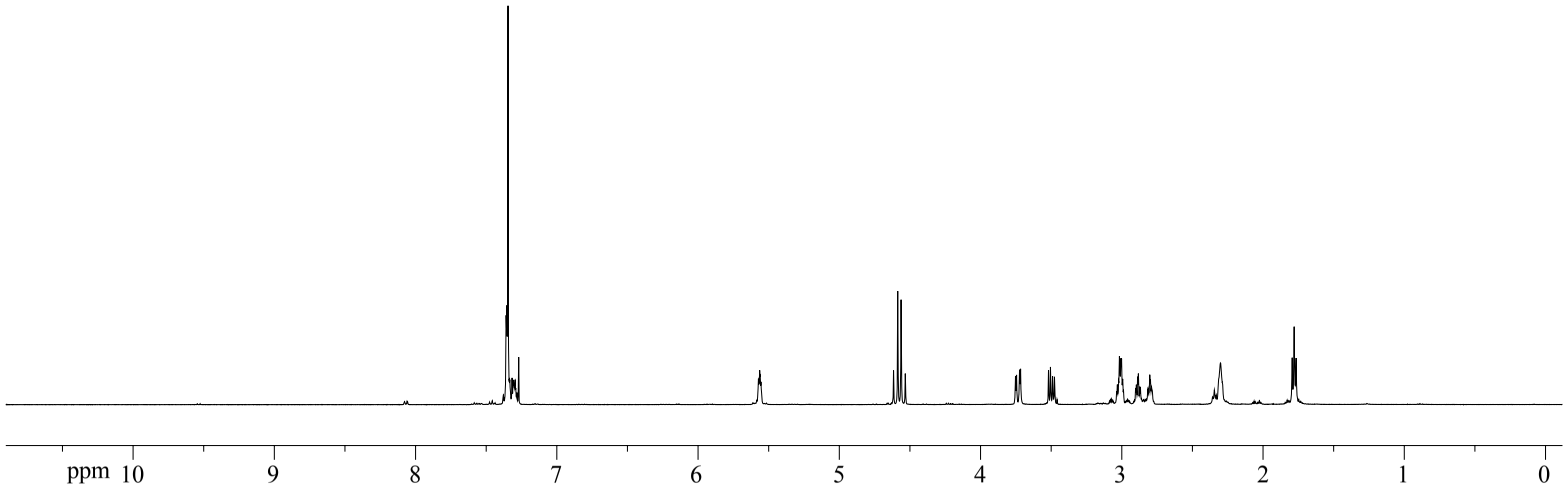

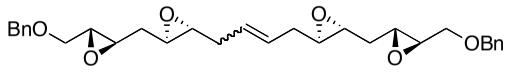

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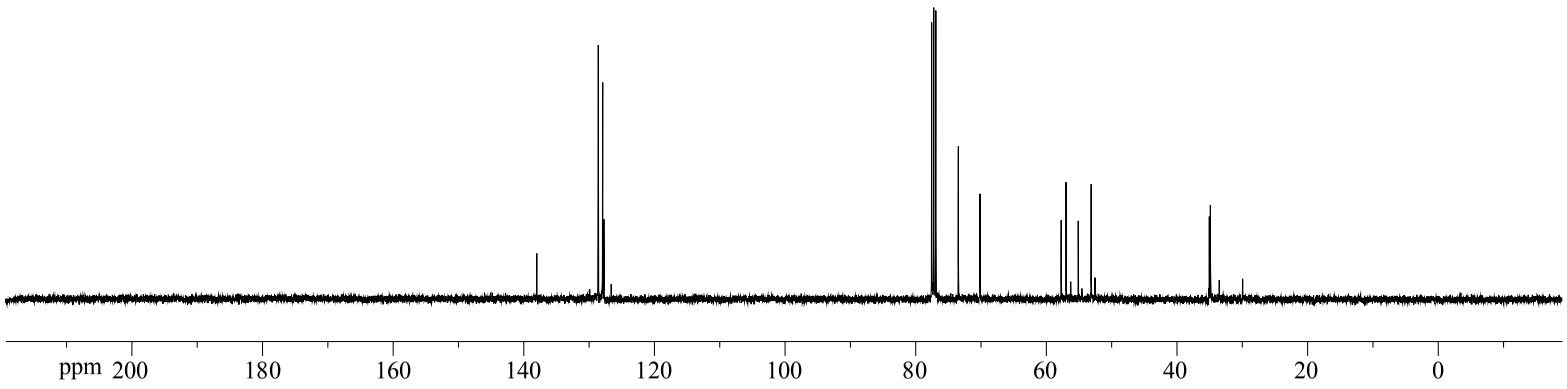

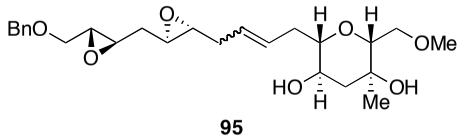

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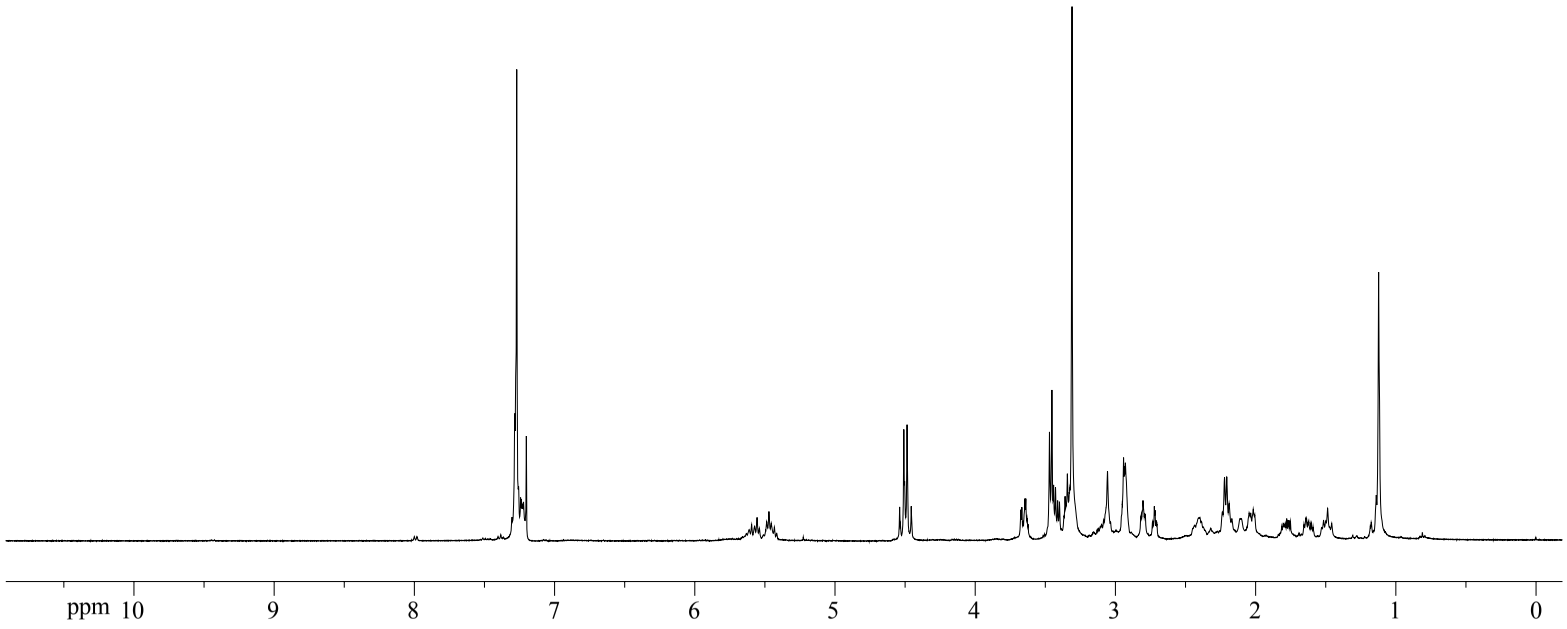

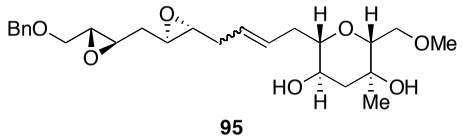

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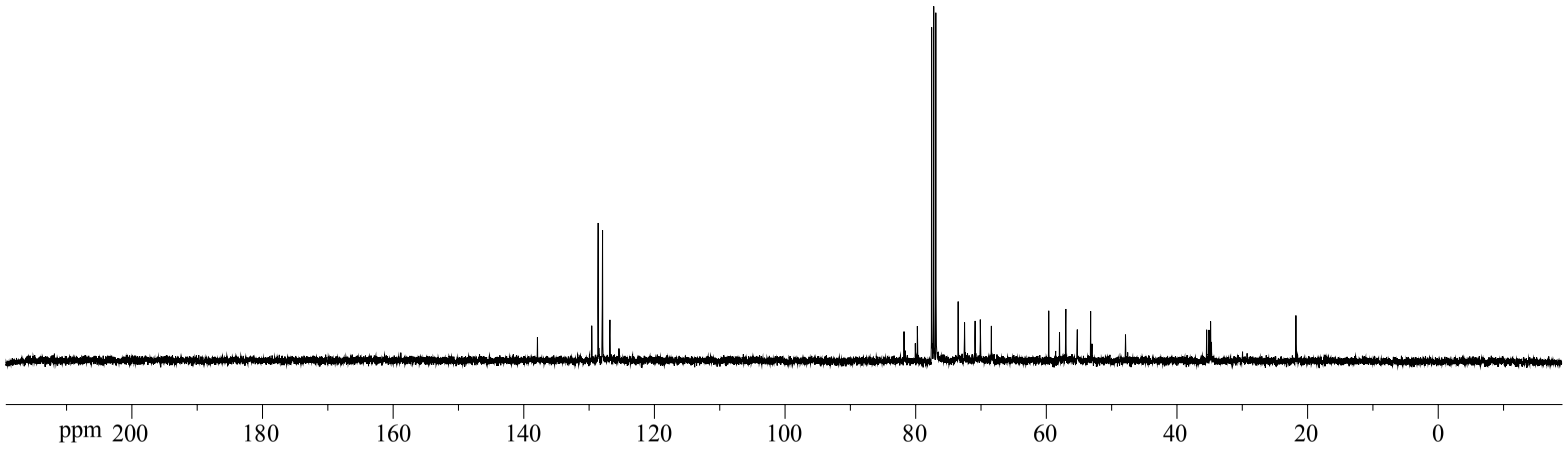

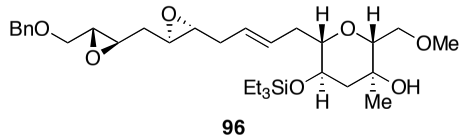

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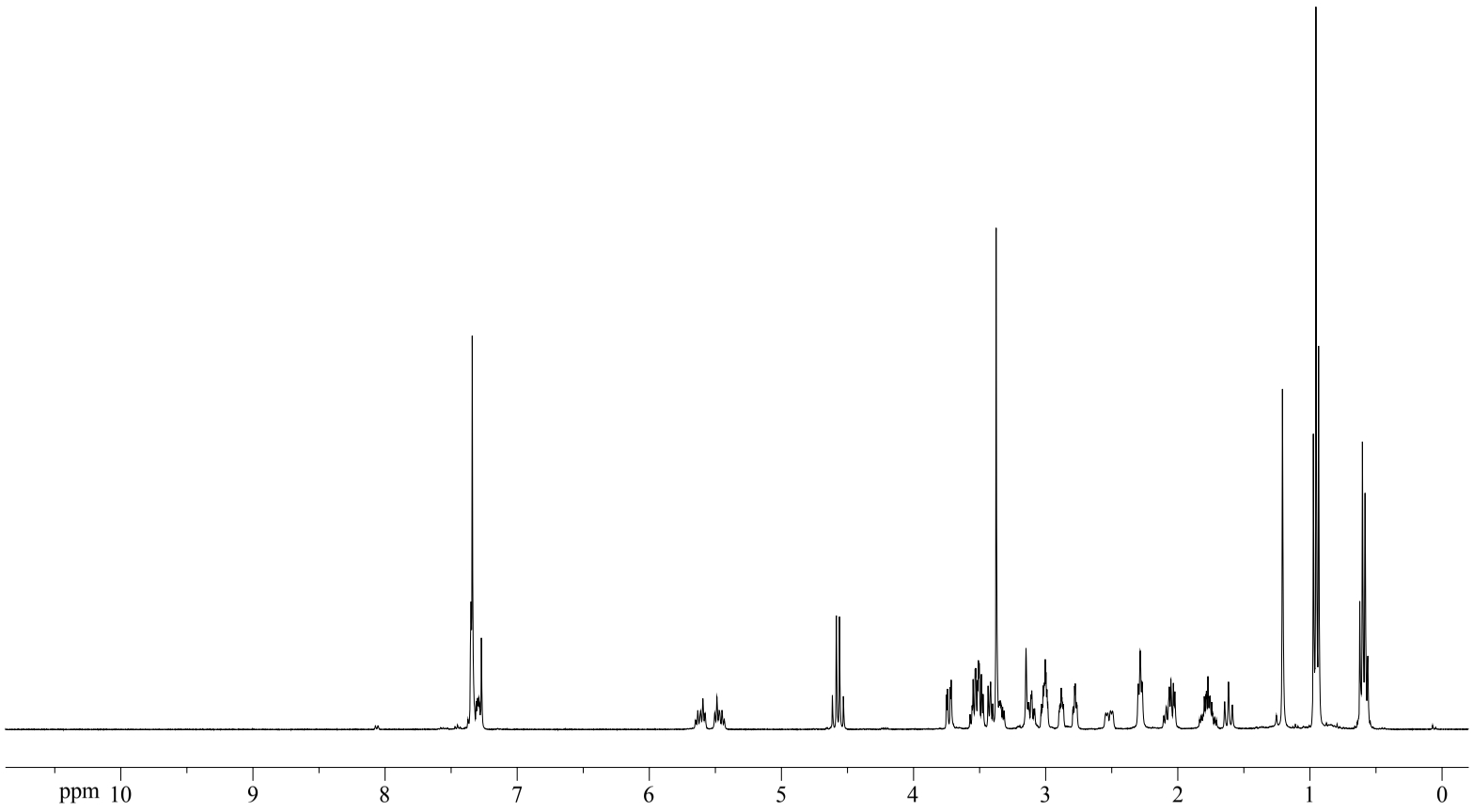

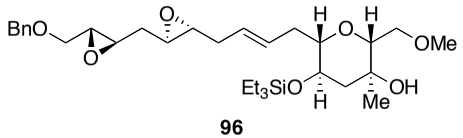
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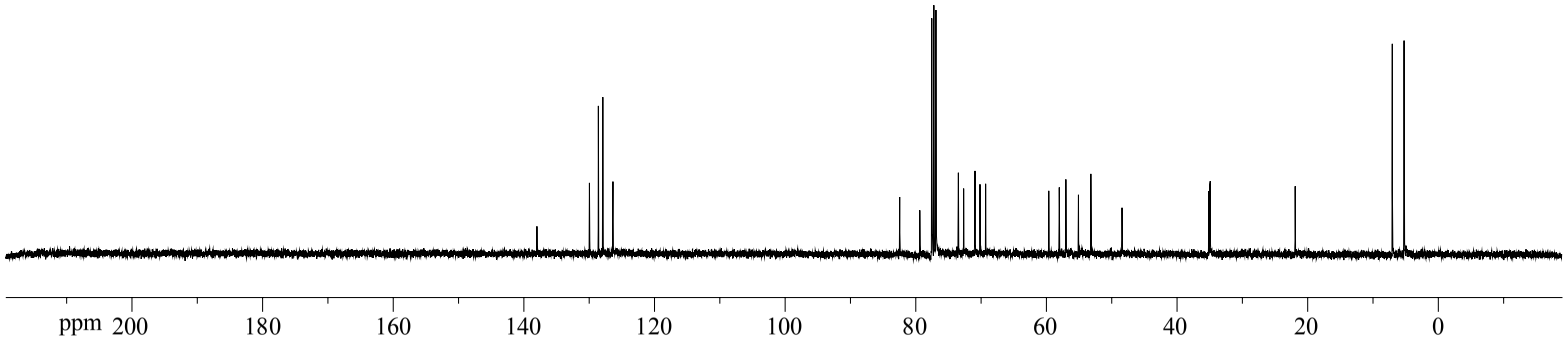
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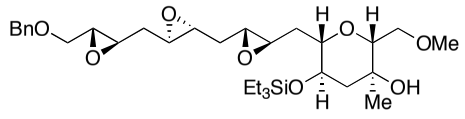

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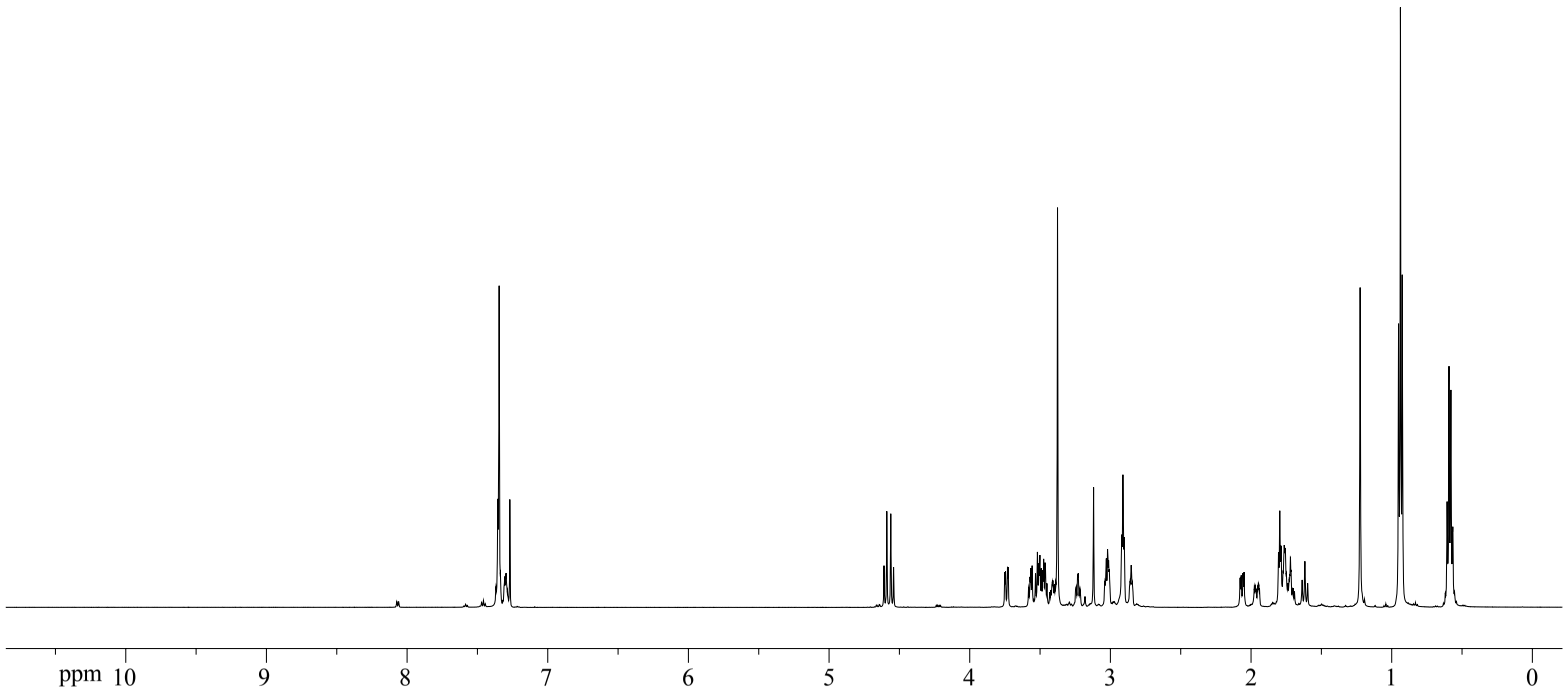

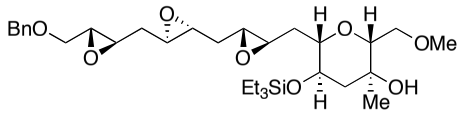
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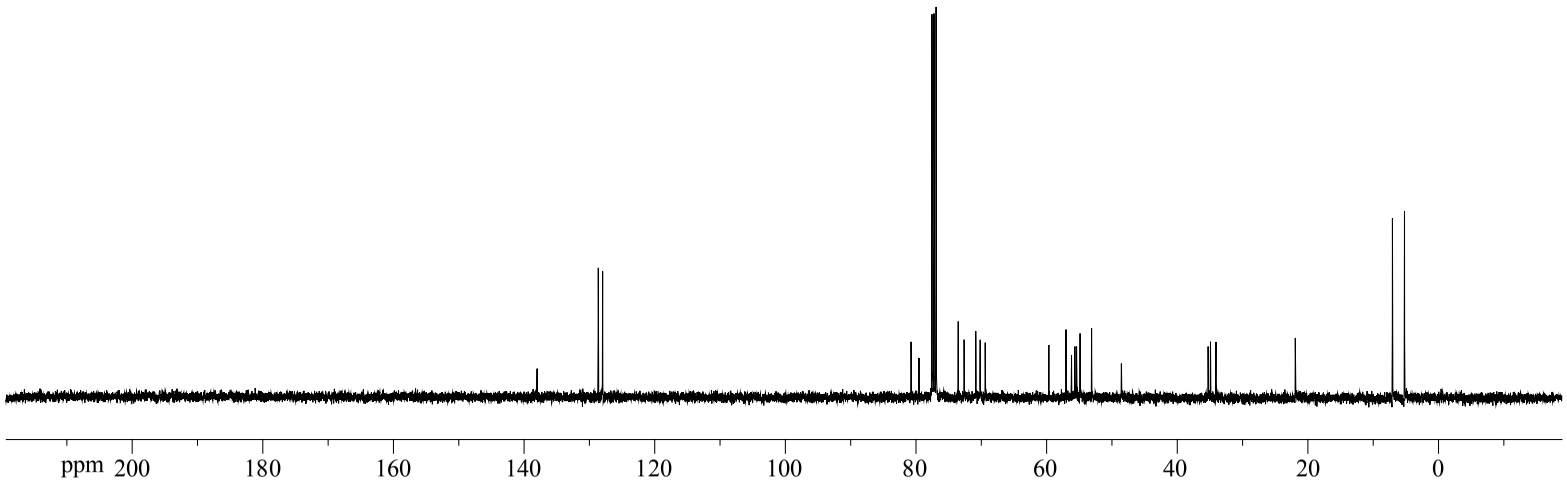
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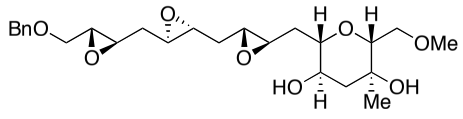

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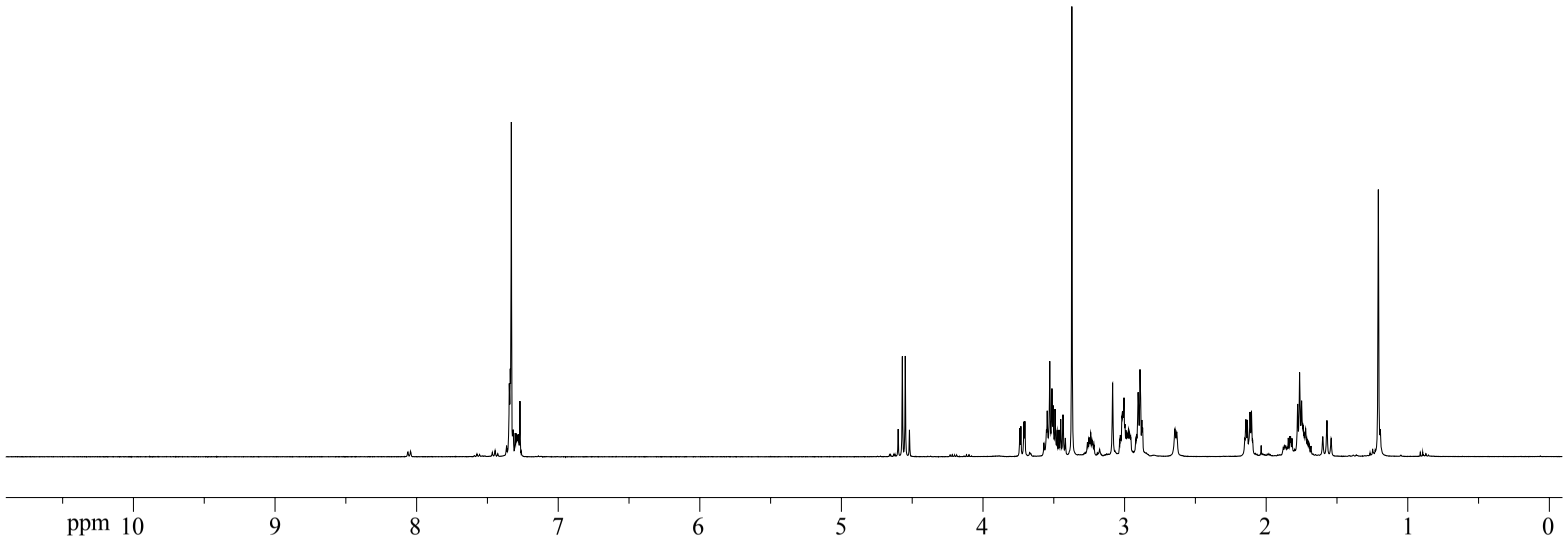

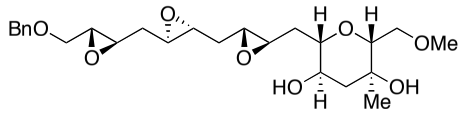

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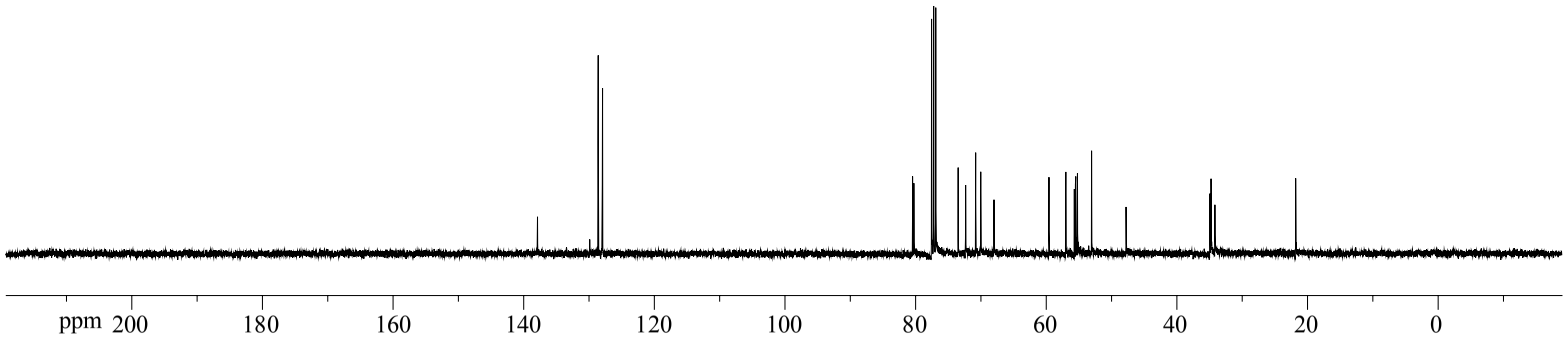

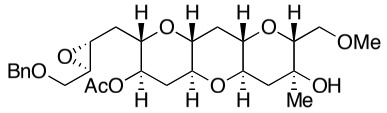

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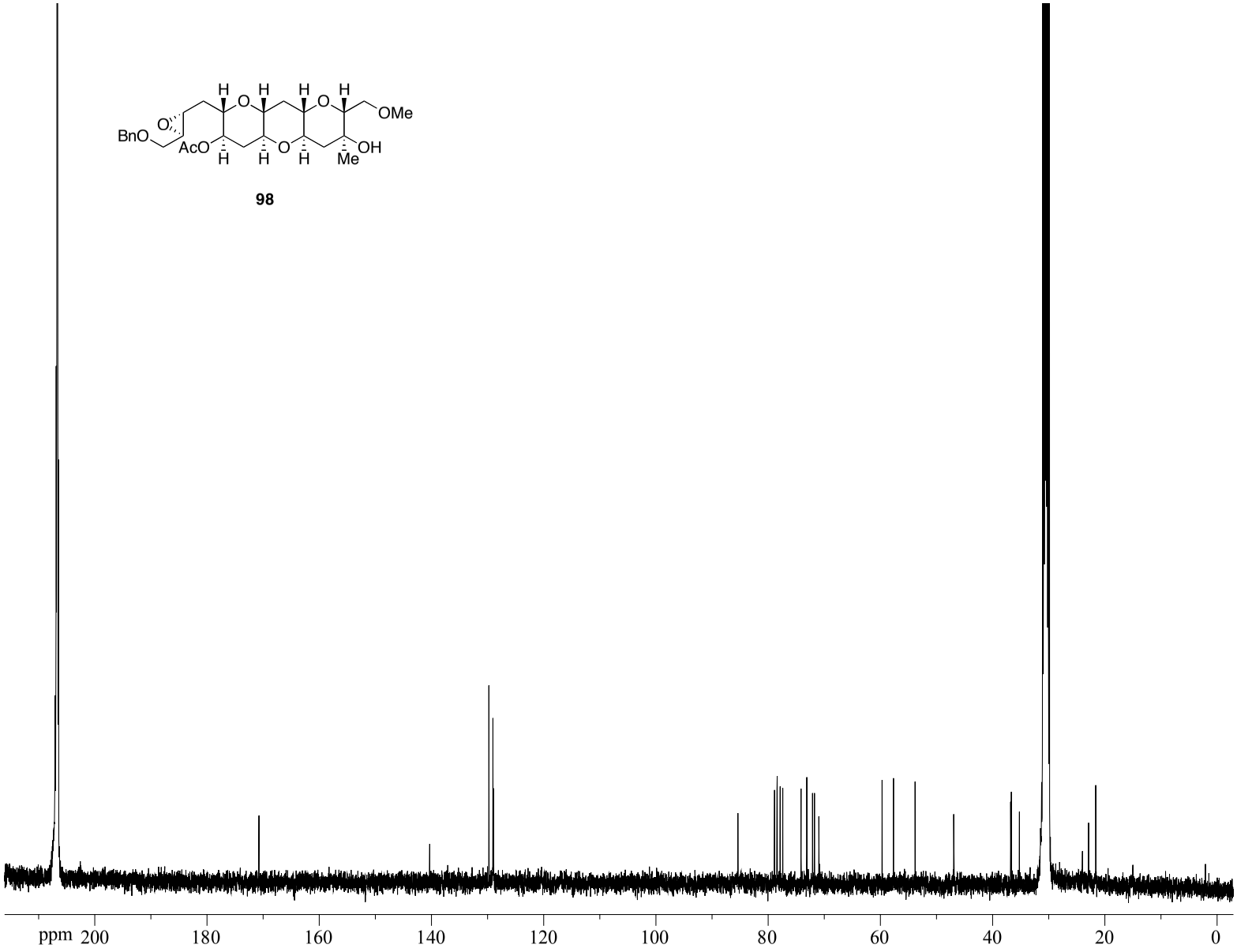
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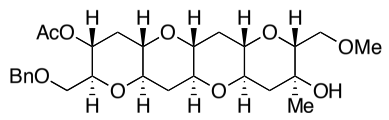

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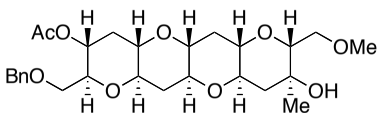

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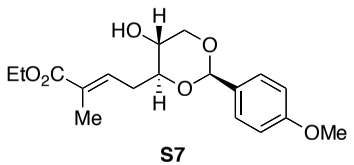

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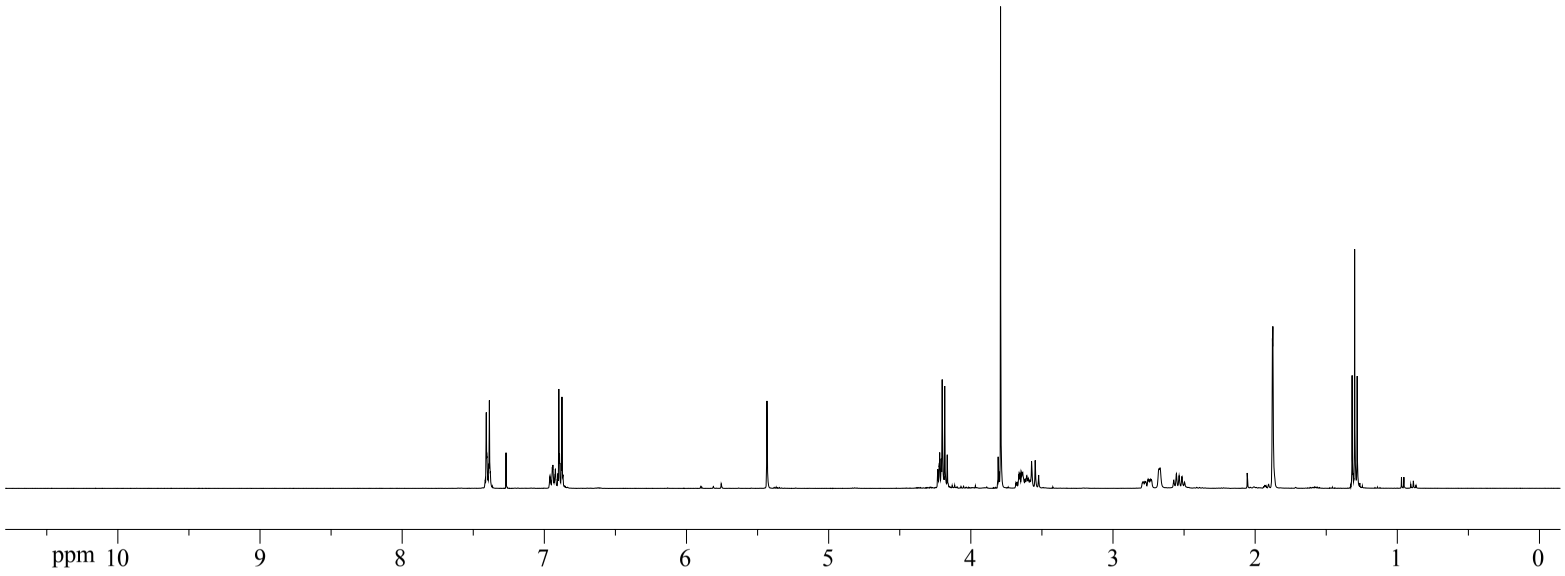

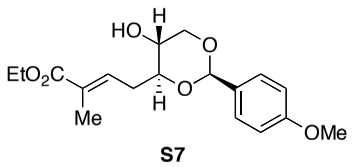

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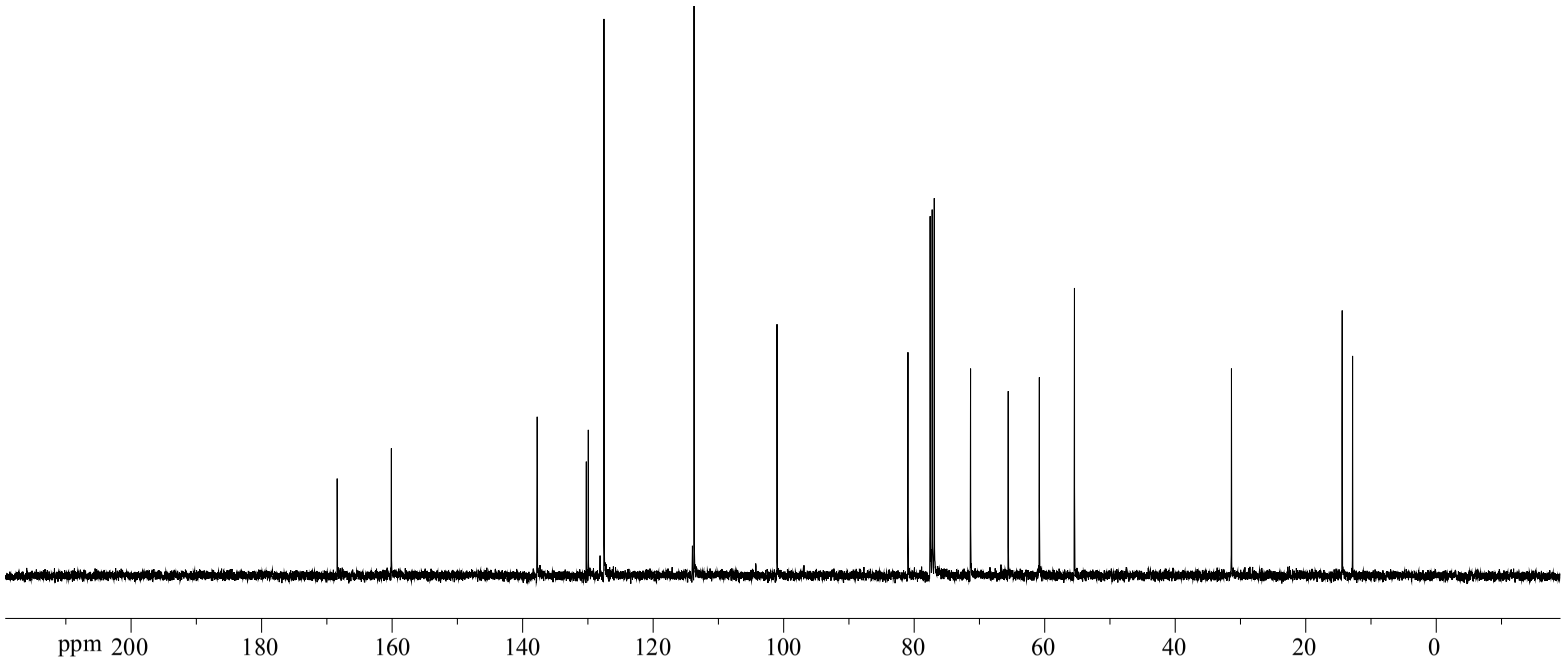

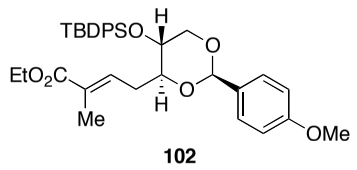

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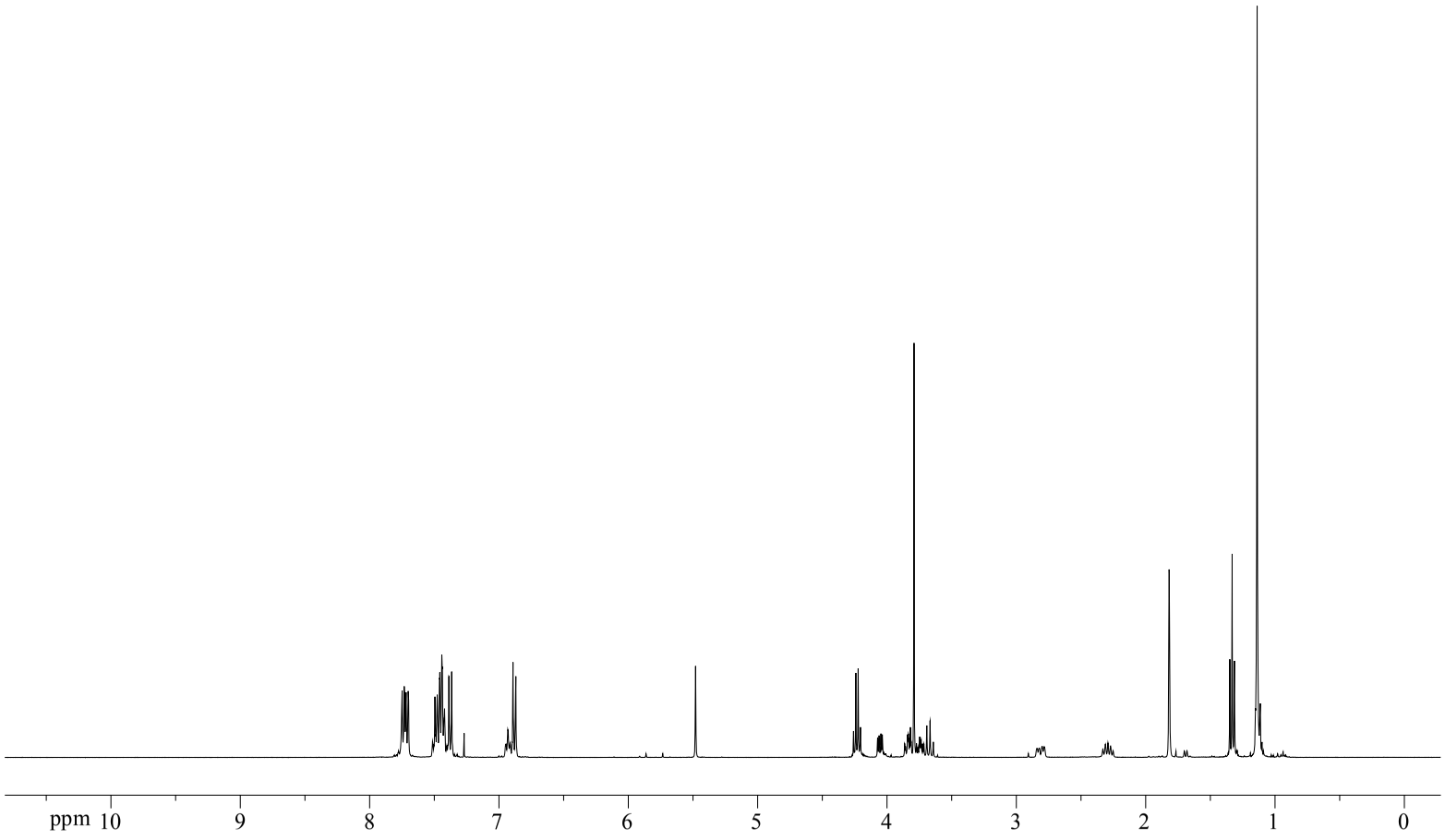

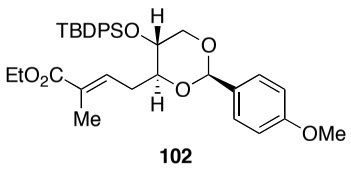
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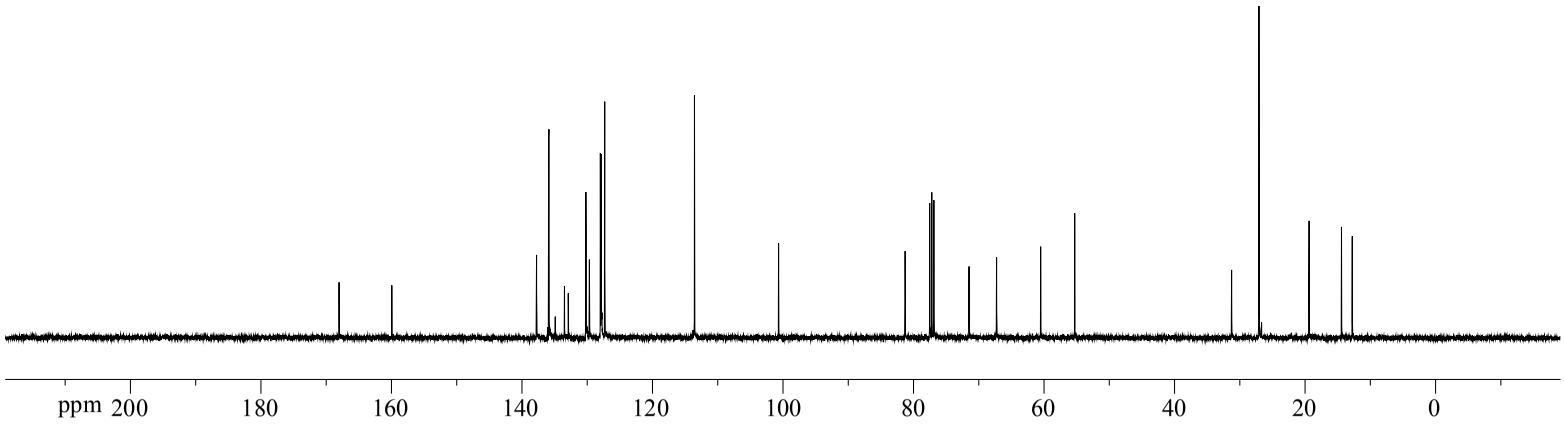
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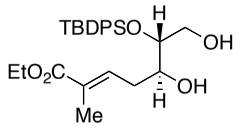

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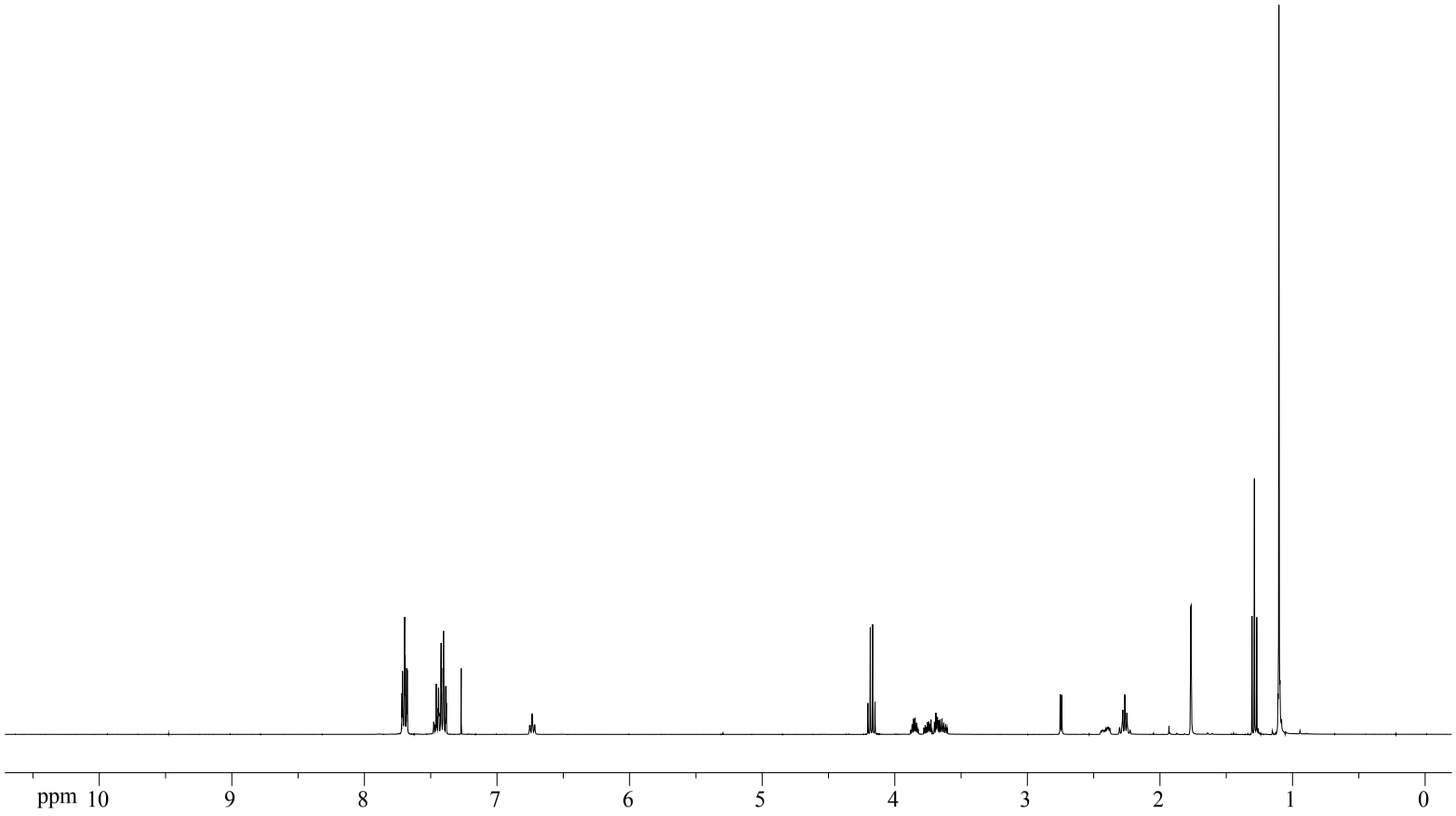

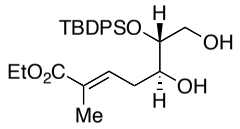

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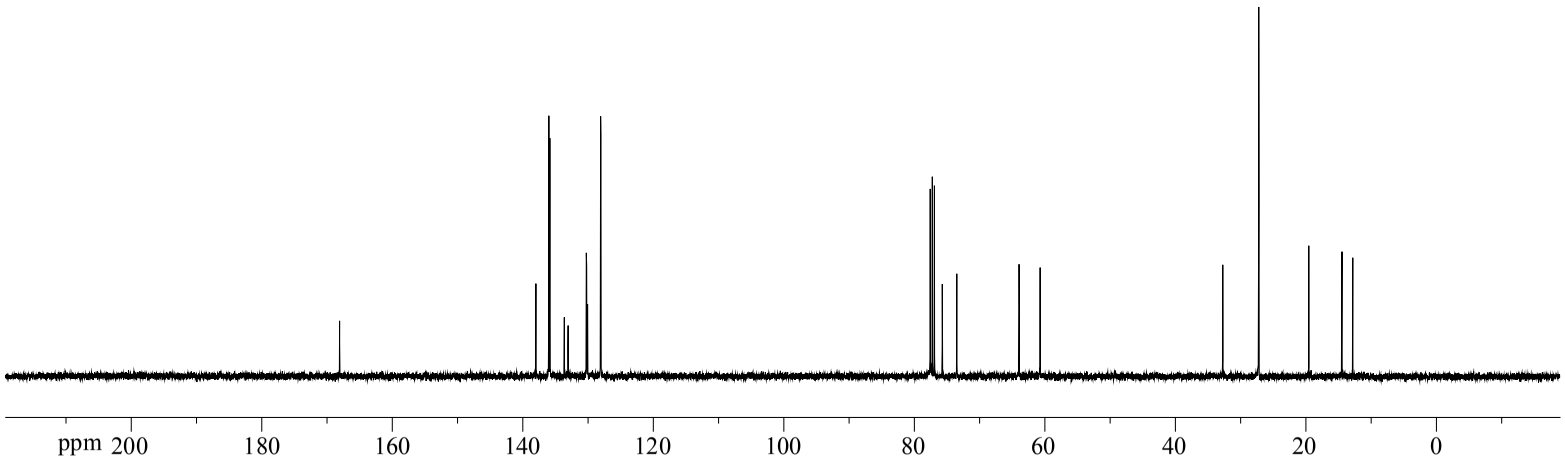

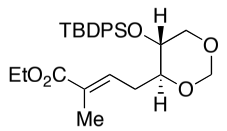

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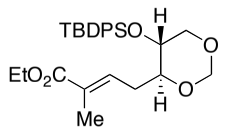

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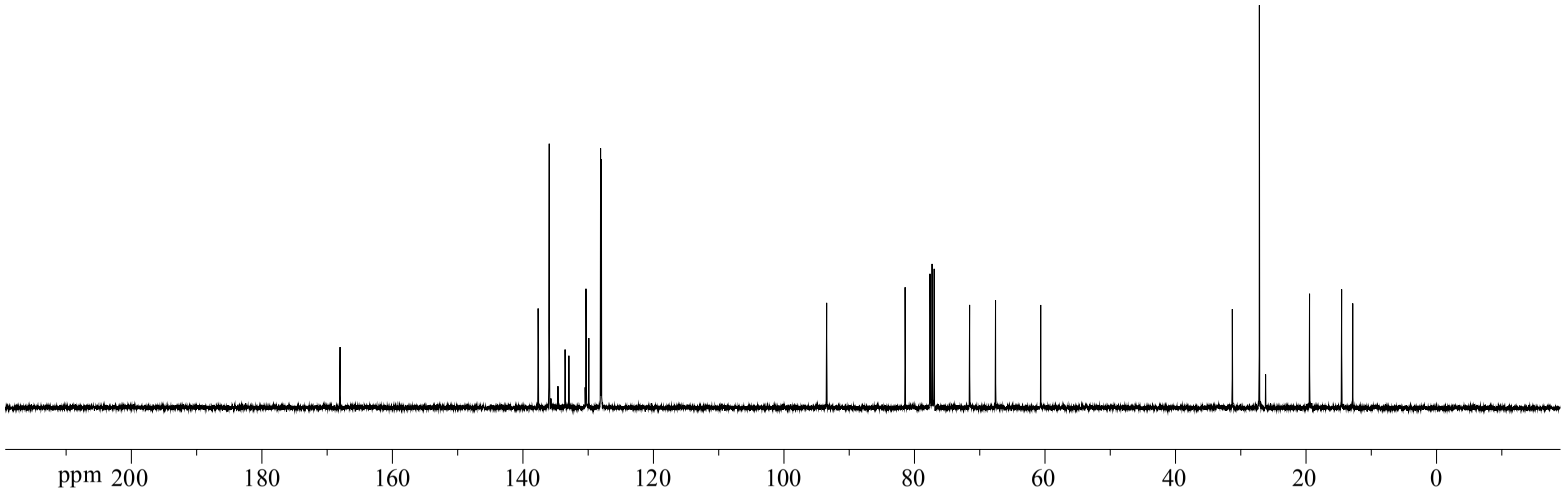

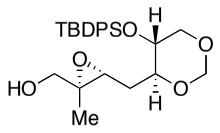

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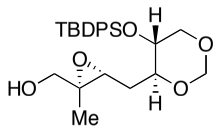

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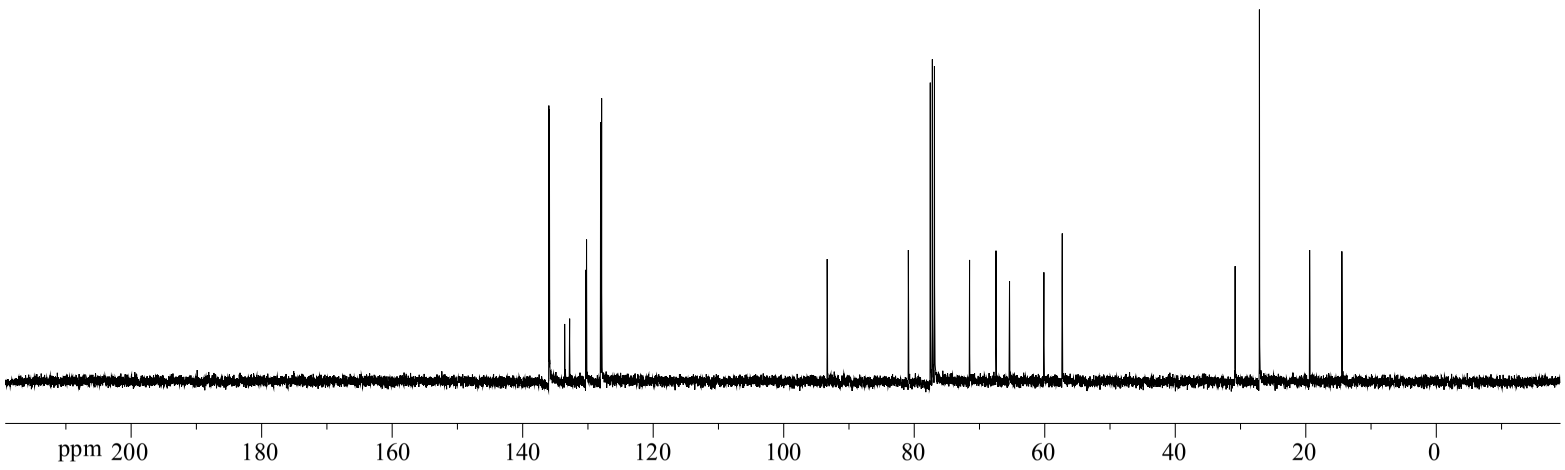
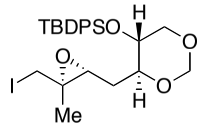
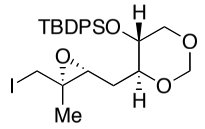




S9



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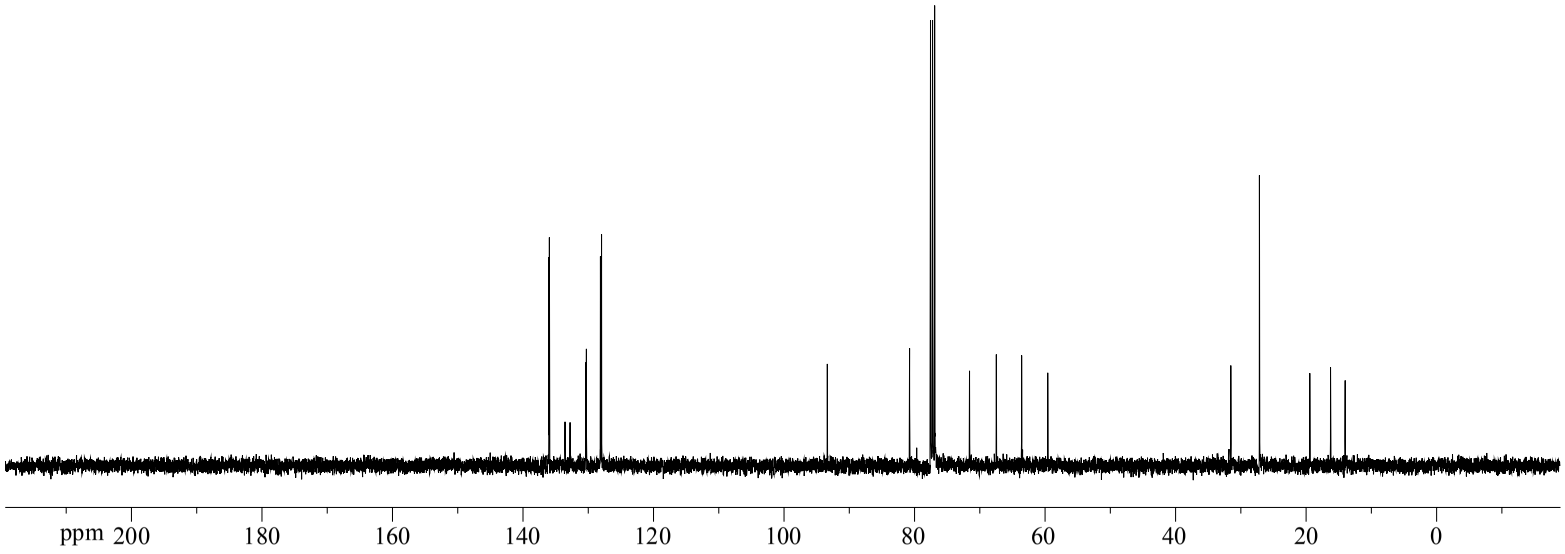

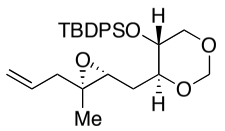

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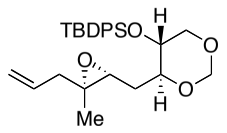

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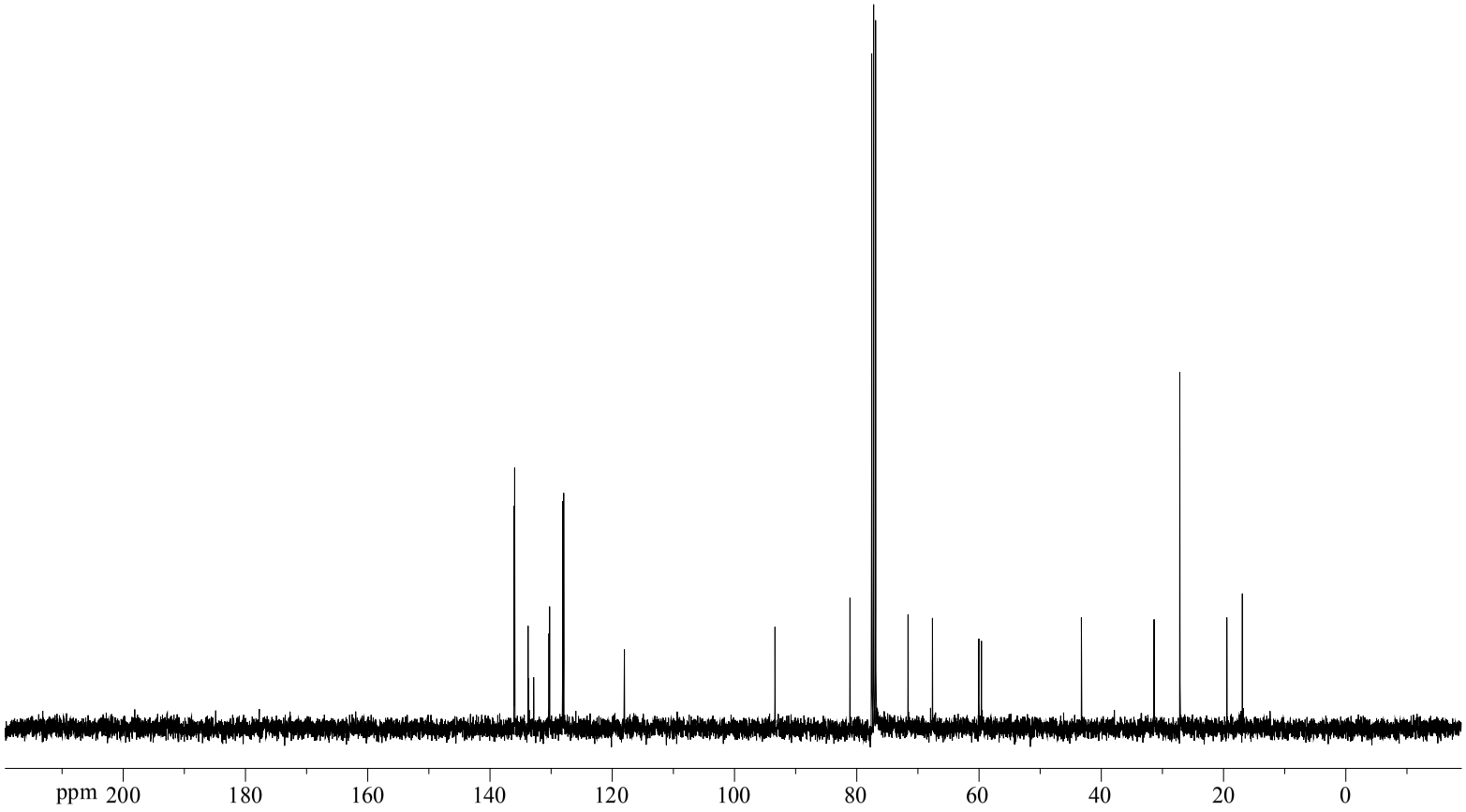

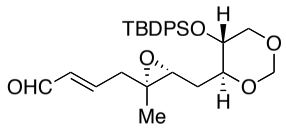

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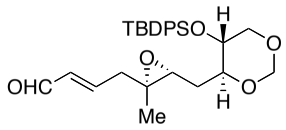

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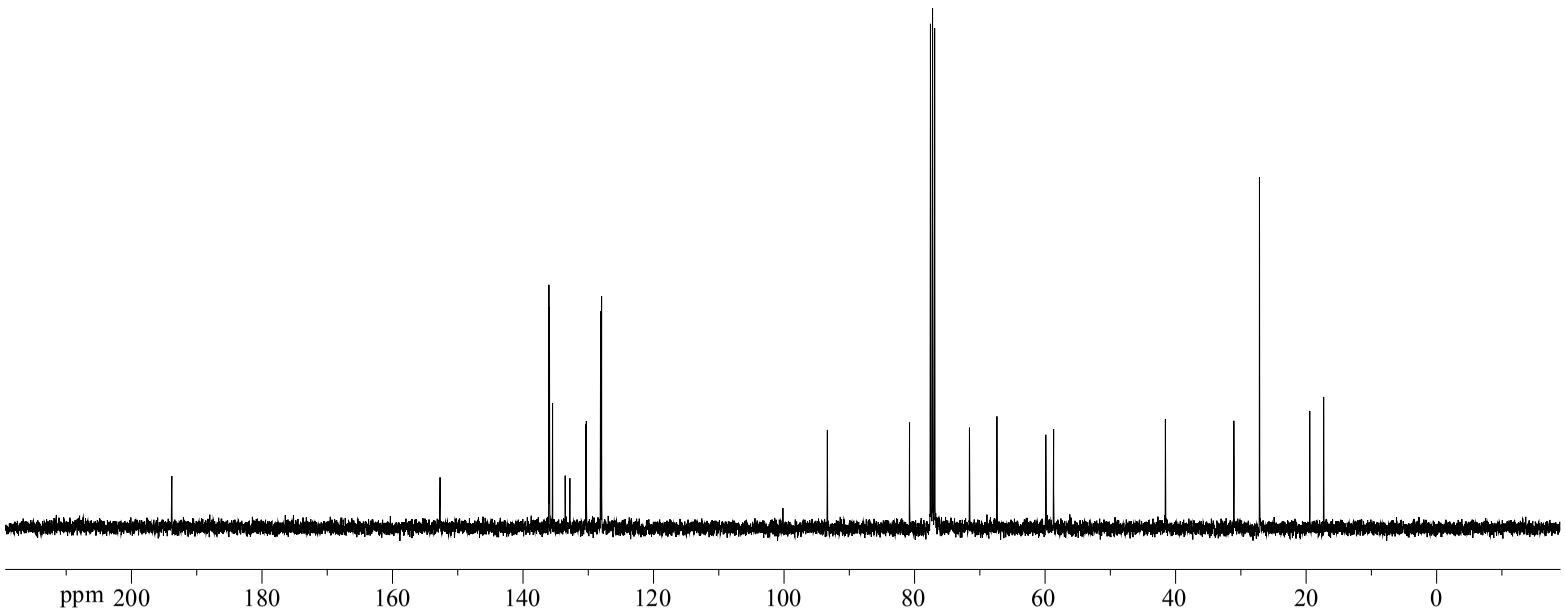

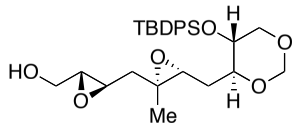

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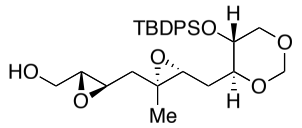

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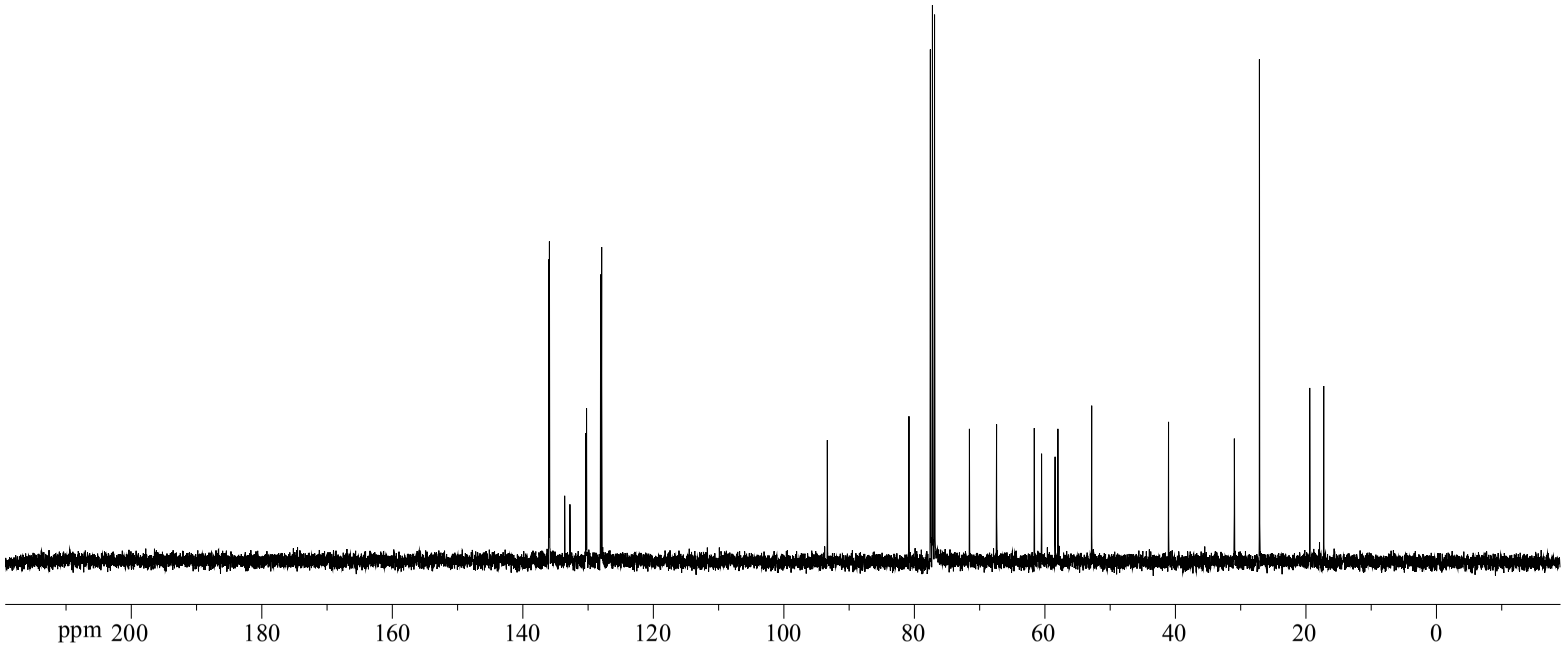

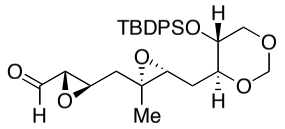

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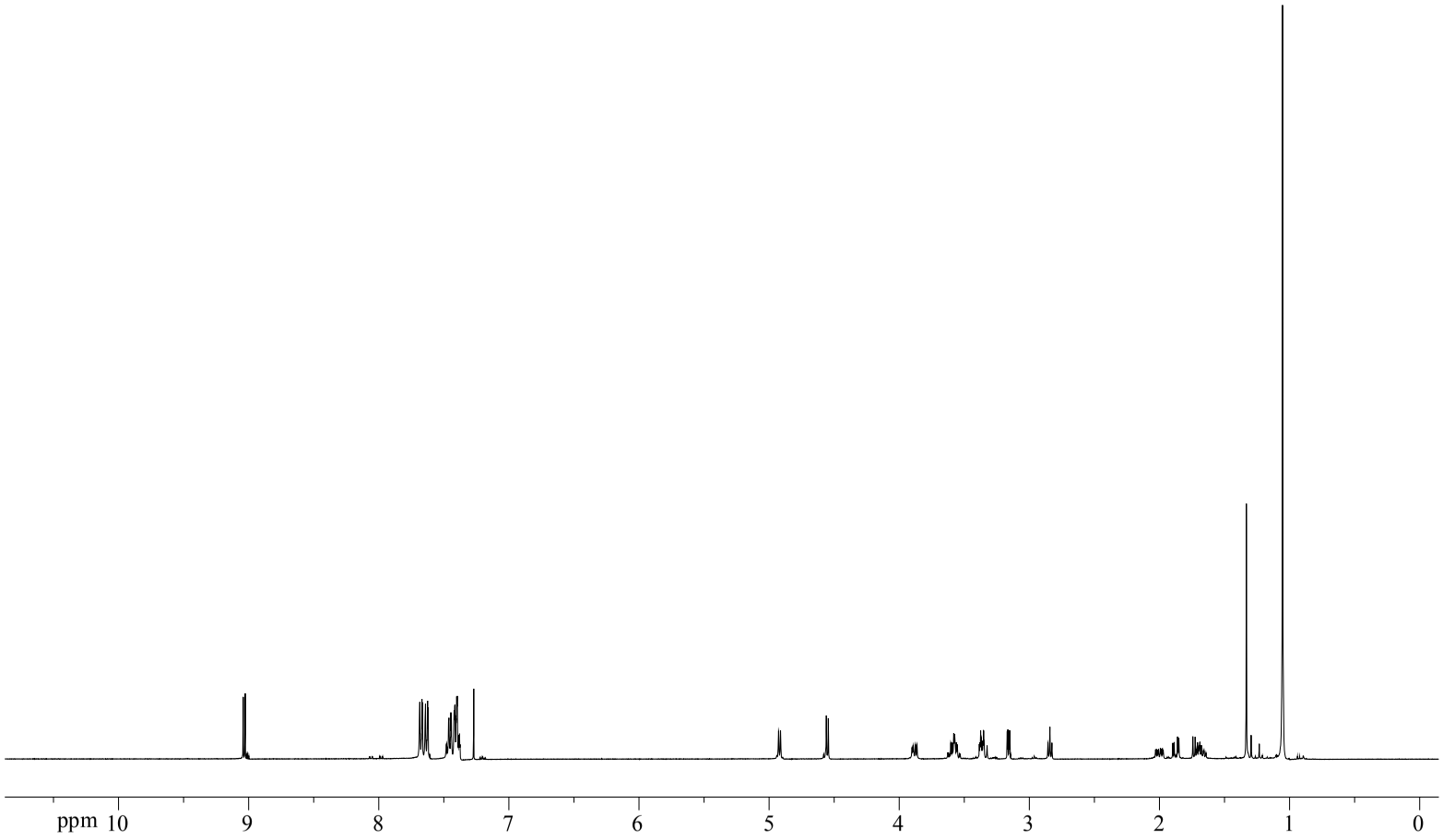

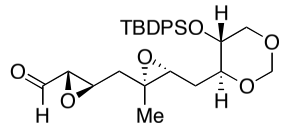

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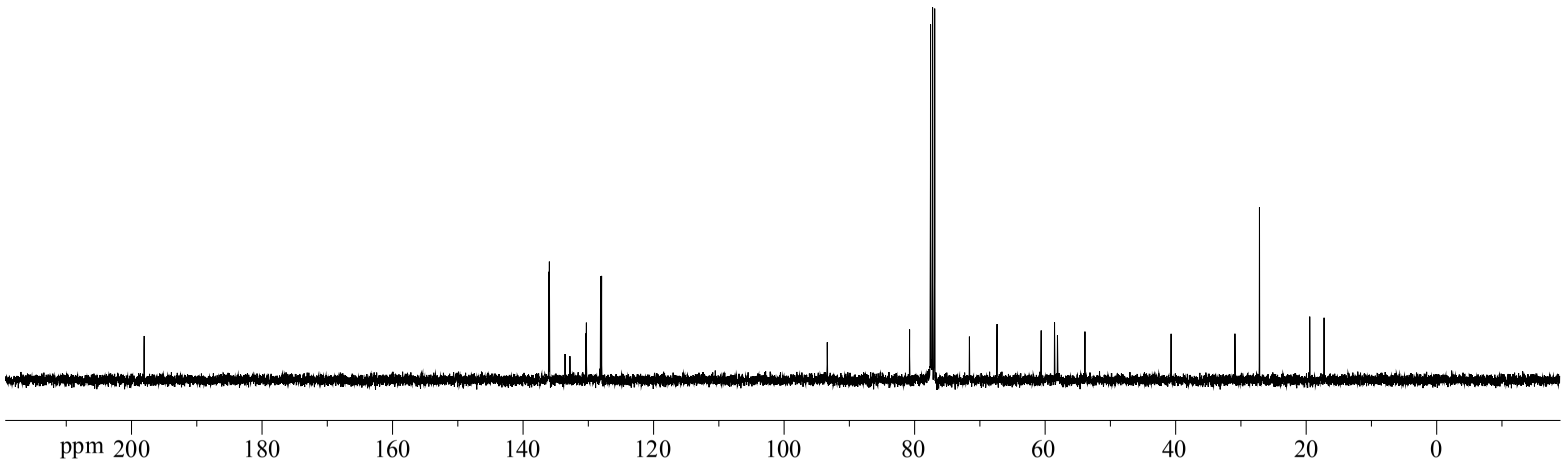

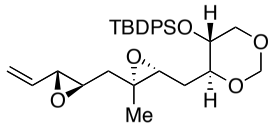

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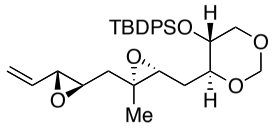

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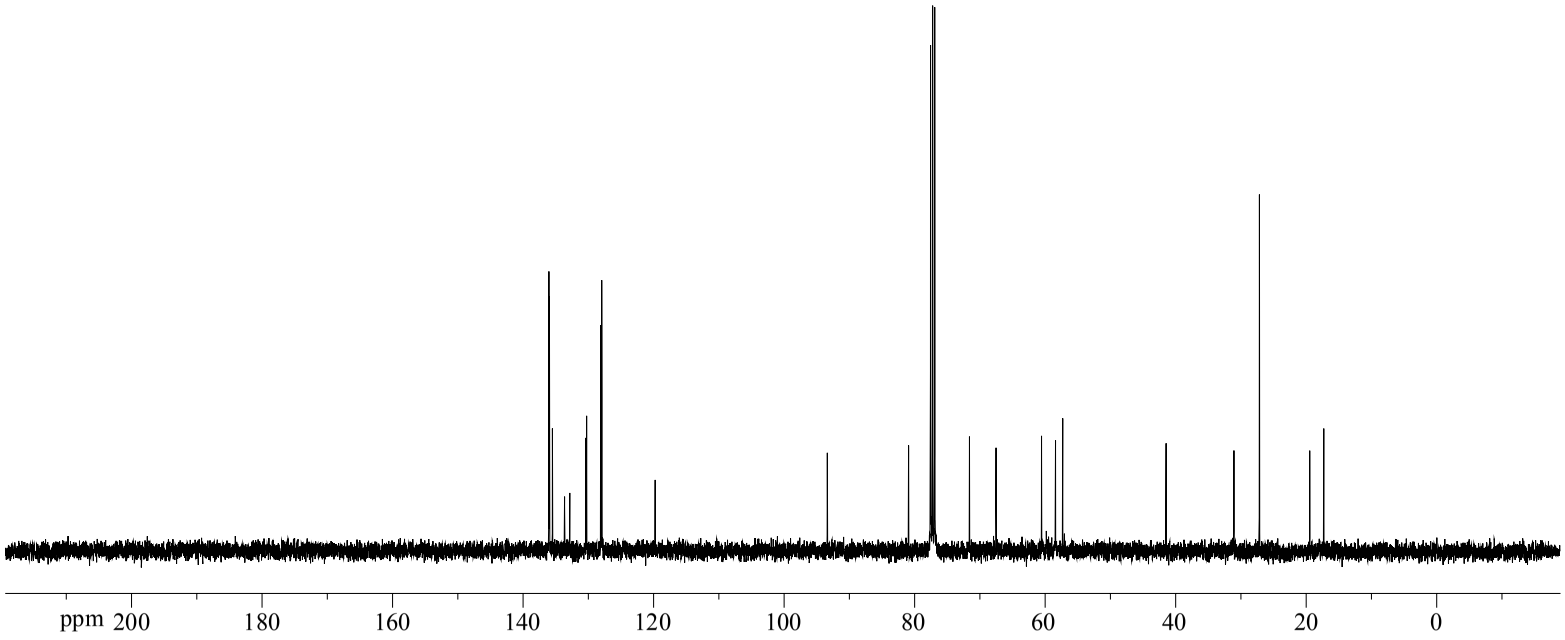

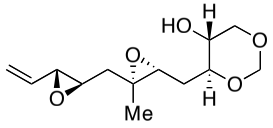

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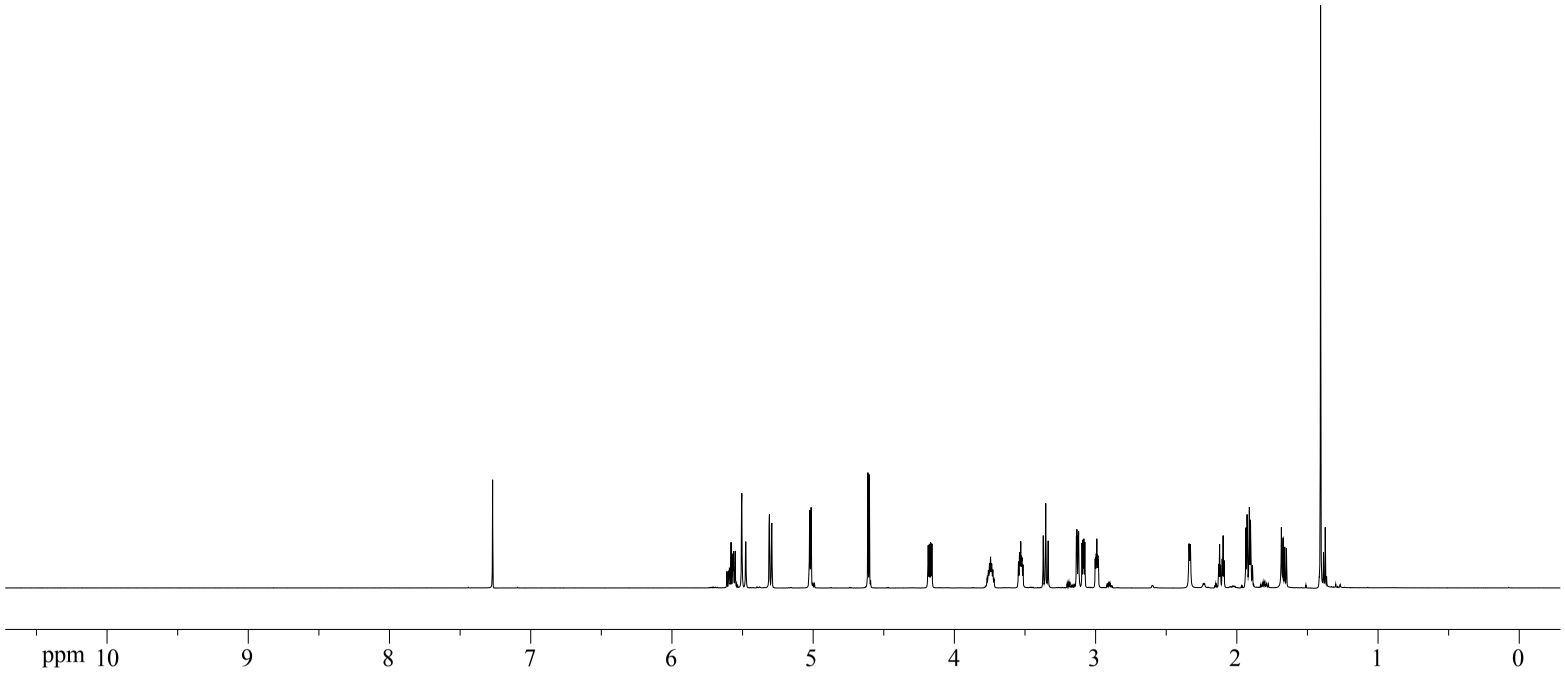

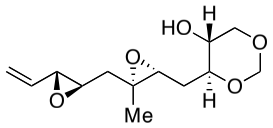

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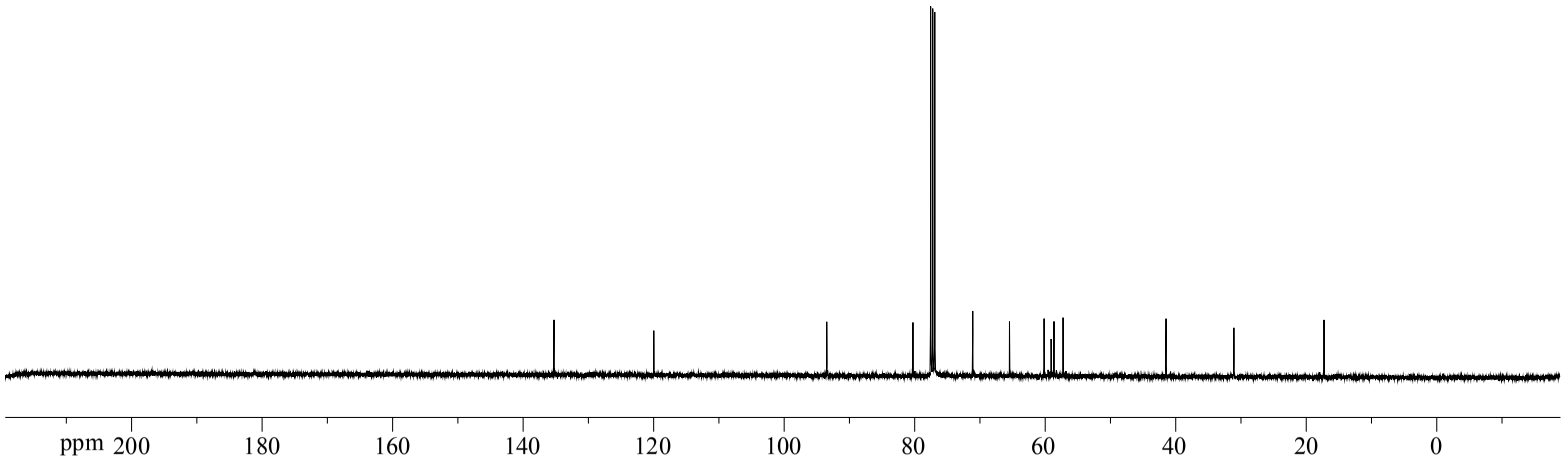

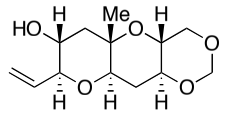

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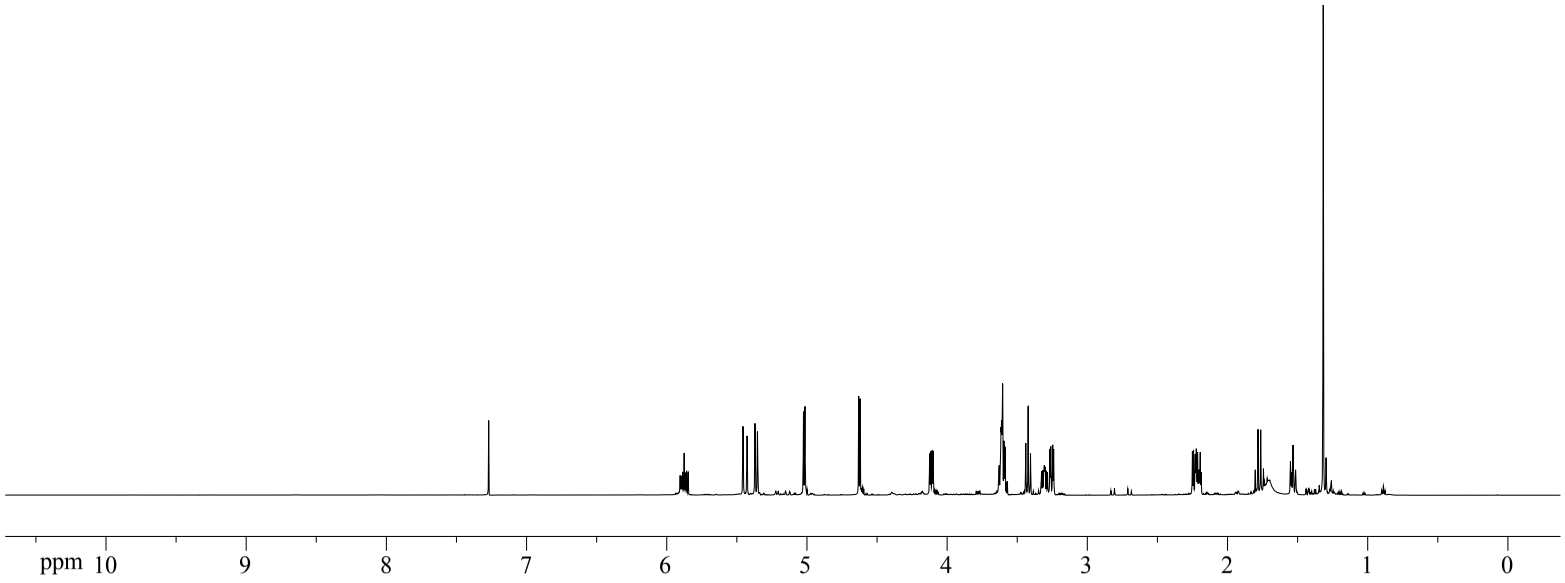

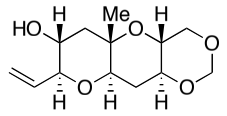

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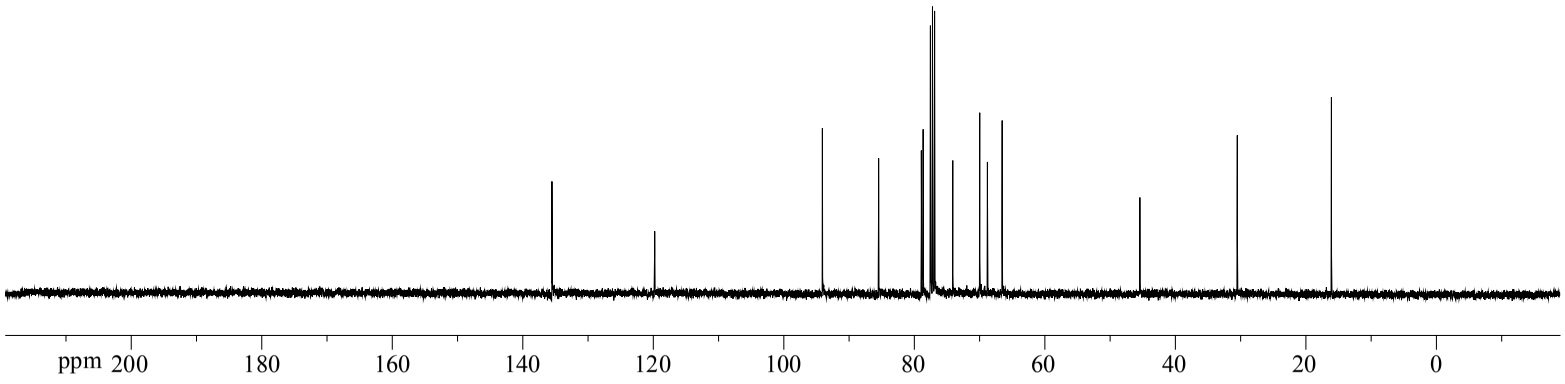
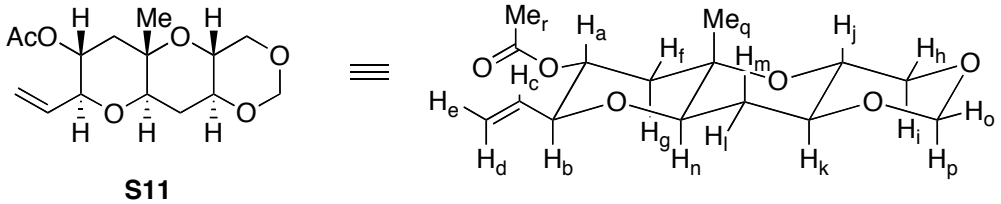


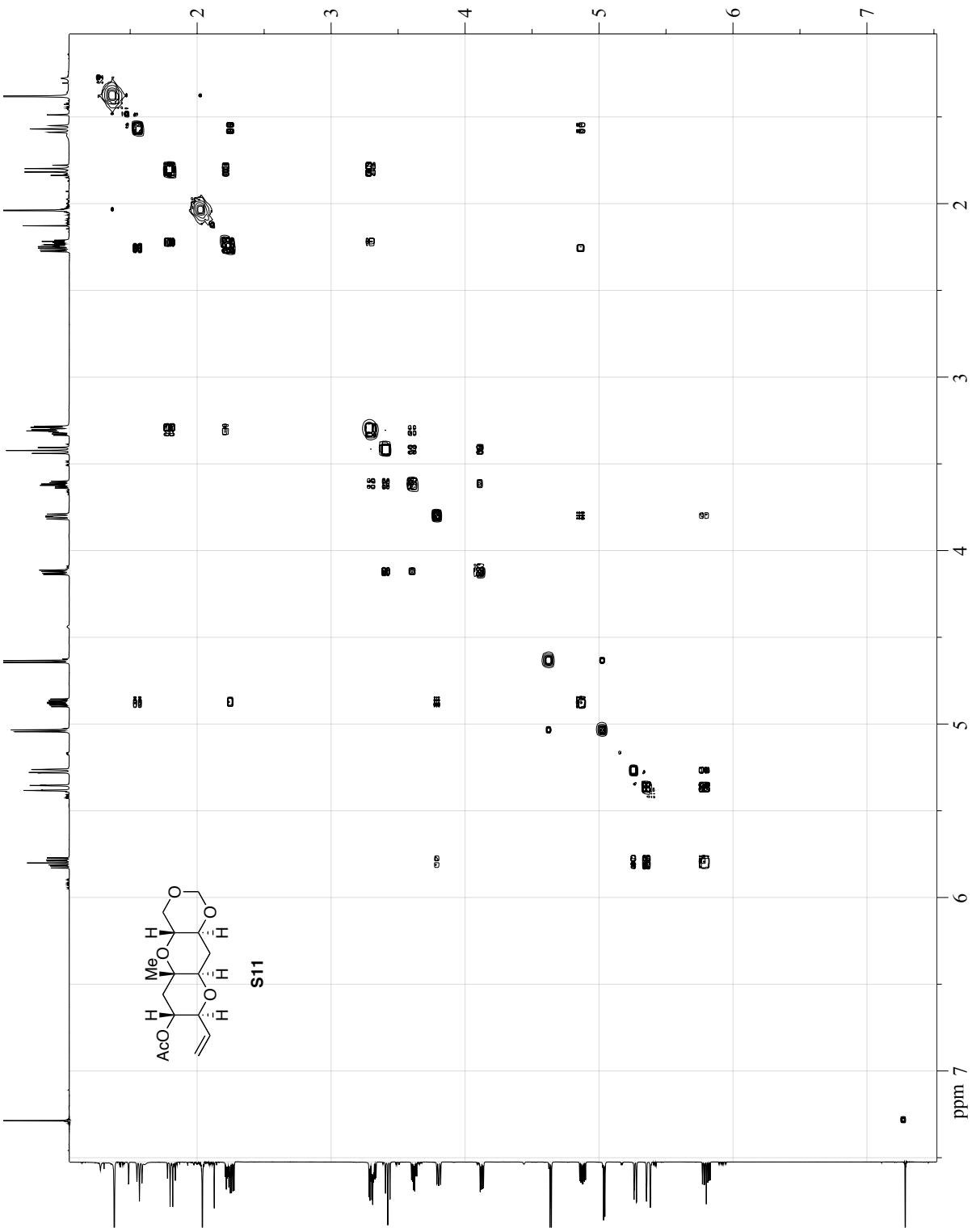
Assignment of S11 by ^{1}H-^{1}H gCOSY



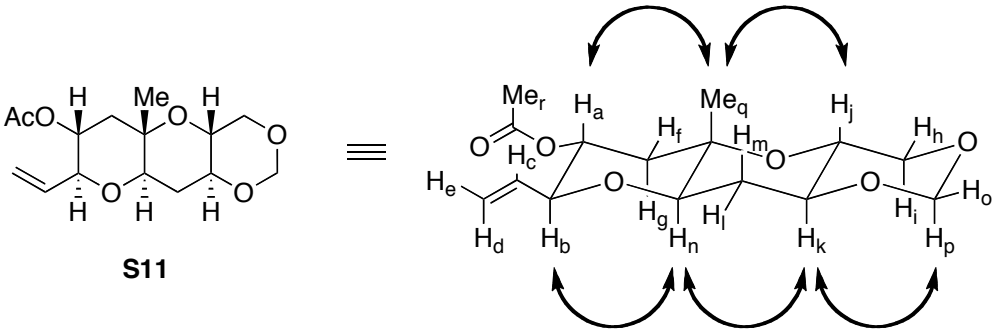
S11

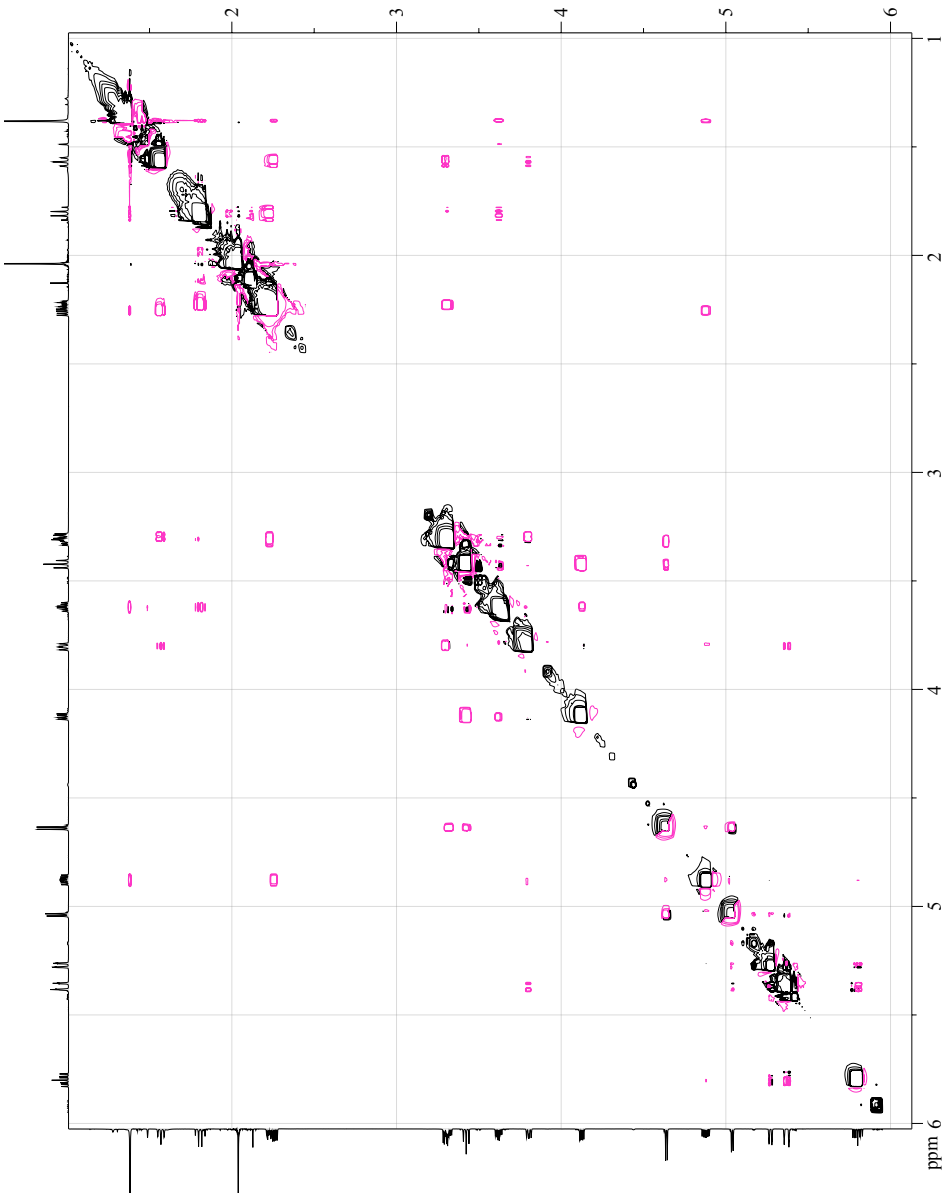
chemical shift (δ)	**^{1}H-^{1}H gCOSY assignment**
1.36 (s, 3H)	Me_q
1.53–1.57 (dd, *J* = 11.4, 11.4 Hz, 1H)	H_g
1.76–1.82 (ddd, *J* = 11.8, 11.8, 11.7 Hz, 1H)	H_m
2.02 (s, 3H)	Me_r
2.19–2.23 (dt, *J* = 11.6, 4.2 Hz, 1H)	H_l
2.23–2.26 (dd, *J* = 11.6, 5.3 Hz, 1H)	H_f
3.27–3.32 (m, 2H)	H_k and H_n
3.39–3.42 (dd, *J* = 10.1, 10.1 Hz, 1H)	H_i
3.58–3.62 (td, *J* = 9.7, 4.6 Hz, 1H)	H_j
3.77–3.80 (dd, *J* = 9.8, 6.9 Hz, 1H)	H_b
4.10–4.12 (dd, *J* = 10.3, 4.6 Hz, 1H)	H_h
4.62–4.63 (d, *J* = 6.2 Hz, 1H)	H_p
4.84–4.88 (ddd, *J* = 11.3, 9.8, 5.3 Hz, 1H)	H_a
5.02–5.03 (d, *J* = 6.2 Hz, 1H)	H_o
5.24–5.27 (ddd, *J* = 10.5, 1.5, 1.0 Hz, 1H)	H_e
5.34–5.37 (ddd, *J* = 17.2, 1.4, 1.0 Hz, 1H)	H_d
5.76–5.81 (ddd, *J* = 17.3, 10.5, 6.9 Hz, 1H)	H_c

gCOSY for compound S11



NOESY for compound S11





X-Ray Crystallographic Data for Compound 54

Top View **54** (Structure displayed as enantiomer of **54**)

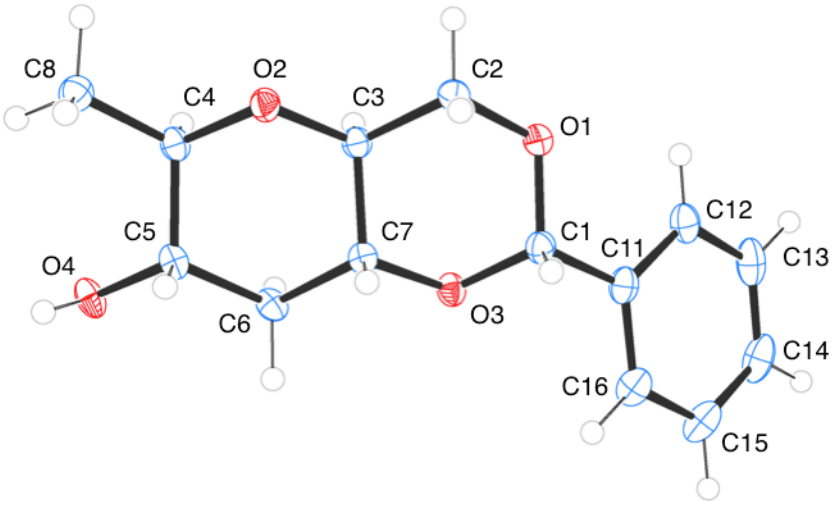


Table 1. Crystal data and structure refinement for 06149.

Identification code	06149	
Empirical formula	C14 H18 O4	
Formula weight	250.28	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 4.8624(3) Å	a= 90°.
	b = 11.8321(8) Å	b= 90°.
	c = 21.8581(14) Å	g = 90°.
Volume	1257.55(14) Å^3	
Z	4	
Density (calculated)	1.322 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	536	
Crystal size	0.25 x 0.10 x 0.10 mm^3	
Theta range for data collection	1.96 to 29.13°.	
Index ranges	-6<=h<=6, -16<=k<=16, -29<=l<=29	
Reflections collected	24532	
Independent reflections	1994 [R(int) = 0.0456]	

Completeness to theta = 29.13°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9905 and 0.8840
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1994 / 1 / 167
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0383, wR2 = 0.0864
R indices (all data)	R1 = 0.0472, wR2 = 0.0908
Absolute structure parameter	?
Largest diff. peak and hole	0.250 and -0.209 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 06149. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	787(4)	8105(2)	1834(1)	18(1)
C(11)	-1264(4)	7759(2)	2316(1)	20(1)
C(12)	-2592(5)	6715(2)	2307(1)	23(1)
C(13)	-4567(5)	6468(2)	2752(1)	29(1)
C(14)	-5194(5)	7247(2)	3202(1)	30(1)
C(15)	-3848(5)	8281(2)	3217(1)	28(1)
C(16)	-1885(4)	8533(2)	2776(1)	23(1)
O(1)	1055(3)	7244(1)	1390(1)	21(1)
C(2)	2961(5)	7550(2)	912(1)	22(1)
C(3)	1917(4)	8633(2)	620(1)	16(1)
O(2)	3805(3)	9010(1)	160(1)	19(1)
C(4)	2747(4)	9998(2)	-148(1)	17(1)
C(8)	4694(5)	10290(2)	-664(1)	21(1)
C(5)	2409(4)	10961(2)	315(1)	16(1)
O(4)	1296(3)	11942(1)	19(1)	20(1)
C(6)	554(4)	10621(2)	844(1)	18(1)
C(7)	1640(4)	9529(2)	1114(1)	16(1)
O(3)	-224(3)	9127(1)	1573(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for 06149.

C(1)-O(1)	1.414(2)
C(1)-O(3)	1.425(2)
C(1)-C(11)	1.506(3)
C(11)-C(16)	1.393(3)
C(11)-C(12)	1.395(3)
C(12)-C(13)	1.398(3)
C(13)-C(14)	1.381(3)
C(14)-C(15)	1.388(3)
C(15)-C(16)	1.389(3)
O(1)-C(2)	1.442(2)
C(2)-C(3)	1.519(3)
C(3)-O(2)	1.432(2)
C(3)-C(7)	1.519(3)
O(2)-C(4)	1.444(2)
C(4)-C(8)	1.512(3)
C(4)-C(5)	1.532(3)
C(5)-O(4)	1.435(2)
C(5)-C(6)	1.522(3)
C(6)-C(7)	1.516(3)
C(7)-O(3)	1.433(2)

O(1)-C(1)-O(3)	111.55(14)
O(1)-C(1)-C(11)	110.18(16)
O(3)-C(1)-C(11)	106.43(16)
C(16)-C(11)-C(12)	119.42(19)
C(16)-C(11)-C(1)	117.99(18)
C(12)-C(11)-C(1)	122.57(18)
C(11)-C(12)-C(13)	119.6(2)
C(14)-C(13)-C(12)	120.5(2)
C(13)-C(14)-C(15)	120.1(2)
C(14)-C(15)-C(16)	119.8(2)
C(15)-C(16)-C(11)	120.6(2)

C(1)-O(1)-C(2)	112.03(14)
O(1)-C(2)-C(3)	107.58(16)
O(2)-C(3)-C(7)	109.81(14)
O(2)-C(3)-C(2)	110.09(16)
C(7)-C(3)-C(2)	108.62(15)
C(3)-O(2)-C(4)	110.56(15)
O(2)-C(4)-C(8)	108.06(16)
O(2)-C(4)-C(5)	109.37(15)
C(8)-C(4)-C(5)	112.92(16)
O(4)-C(5)-C(6)	109.41(15)
O(4)-C(5)-C(4)	110.17(15)
C(6)-C(5)-C(4)	111.70(15)
C(7)-C(6)-C(5)	108.33(16)
O(3)-C(7)-C(6)	109.56(15)
O(3)-C(7)-C(3)	108.81(14)
C(6)-C(7)-C(3)	110.46(15)
C(1)-O(3)-C(7)	110.14(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 06149. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	18(1)	17(1)	2(1)	-2(1)	0(1)
C(11)	16(1)	24(1)	19(1)	5(1)	-4(1)	0(1)
C(12)	22(1)	23(1)	25(1)	7(1)	-5(1)	-2(1)
C(13)	22(1)	32(1)	33(1)	15(1)	-6(1)	-8(1)
C(14)	18(1)	48(1)	24(1)	13(1)	-1(1)	-4(1)
C(15)	21(1)	45(1)	18(1)	1(1)	0(1)	-2(1)
C(16)	18(1)	31(1)	21(1)	1(1)	-1(1)	-5(1)
O(1)	29(1)	16(1)	19(1)	1(1)	4(1)	-1(1)
C(2)	28(1)	17(1)	20(1)	1(1)	5(1)	4(1)
C(3)	16(1)	16(1)	17(1)	1(1)	0(1)	-1(1)
O(2)	21(1)	17(1)	19(1)	3(1)	3(1)	3(1)
C(4)	15(1)	16(1)	19(1)	3(1)	-2(1)	0(1)
C(8)	21(1)	22(1)	20(1)	2(1)	0(1)	3(1)
C(5)	12(1)	16(1)	22(1)	4(1)	-1(1)	0(1)
O(4)	14(1)	16(1)	32(1)	7(1)	0(1)	1(1)
C(6)	13(1)	16(1)	24(1)	1(1)	1(1)	2(1)
C(7)	12(1)	17(1)	18(1)	1(1)	0(1)	0(1)
O(3)	16(1)	17(1)	20(1)	3(1)	2(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 06149.

	x	y	z	U(eq)
H(1)	2612	8248	2030	22
H(12)	-2157	6174	2001	28
H(13)	-5484	5759	2745	35
H(14)	-6549	7075	3500	36
H(15)	-4267	8814	3528	33
H(16)	-958	9239	2788	28
H(2A)	3069	6941	603	26
H(2B)	4819	7670	1085	26
H(3)	79	8492	429	20
H(4)	905	9813	-325	20
H(8A)	6511	10468	-495	32
H(8B)	3987	10947	-887	32
H(8C)	4845	9645	-943	32
H(5)	4263	11157	482	20
H(4O)	2680(40)	12340(20)	-50(12)	24
H(6A)	547	11222	1160	21
H(6B)	-1354	10513	697	21
H(7)	3480	9669	1303	19

Table 6. Hydrogen bonds for 06149 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(4)-H(4O)...O(4)#1	0.835(16)	1.953(17)	2.7678(12)	165(3)

Symmetry transformations used to generate equivalent atoms:

#1 x+1/2,-y+5/2,-z

Aaron R. Van Dyke *Curriculum Vitae*

Education

2004-present

Massachusetts Institute of Technology, Cambridge, MA
Candidate for Doctor of Philosophy in Organic Chemistry
Research Advisor: Timothy F. Jamison
Degree Expected: May 2009

2000-2004

Seattle University, Seattle, WA
B.S. in Chemistry with University Honors, Minor in Philosophy,
Summa Cum Laude
Research Advisor: Greg T. Spyridis
Senior Thesis: "Solvatochromic behavior of azulene and its derivatives: Developing a solvent polarity scale."

Teaching Experience

2007 Teaching Assistant, 5.13 (Organic Chemistry II)

2006 Teaching Assistant, 5.46 (NMR Spectroscopy and Structure Determination)

2005 Head Teaching Assistant, 5.13 (Organic Chemistry II)

2005 Laboratory Assistant, 5.32 (Intermediate Chemical Experimentation)

2004 Teaching Assistant, 5.112 (Principles of Chemical Science)

Honors

2008 MIT Wyeth Scholar, Wyeth Research

2008 Vivian A. and E. Emerson Morse Travel Grant, MIT Department of Chemistry

2005 Excellence in Teaching Award, MIT Department of Chemistry

2004 John S. Ju Award, Seattle University (Awarded to the valedictorian of the School of Science and Engineering)

2004 Outstanding Chemistry Major, Seattle University

2003 Undergraduate Achievement Award, ACS Division of Analytical Chemistry

2003 Alpha Sigma Nu, National Jesuit Honor Society

2001 Outstanding Achievement in Freshman Chemistry, CRC Press

2000 Sullivan Scholar, Seattle University (4 years of tuition and board)

2000 Washington State Promise Scholar, Governor of Washington State

1996 Eagle Scout, Boy Scouts of America

Presentations

(5) "Template-directed *endo* cyclizations of epoxy alcohols: Synthesis of *HIJK* rings of gymnocin A." Aaron R. Van Dyke and Timothy F. Jamison. Invited Seminar Speaker. AstraZeneca. Waltham, MA. November 2008.

(4) "Template-directed *endo* cyclization of epoxy alcohols towards the *HIJK* rings of gymnocin A." Aaron R. Van Dyke and Timothy F. Jamison. Poster. Gordon Research Conference: Bioorganic Chemistry. June 2008.

(3) "Benzylidene-directed *endo* cyclization of epoxy alcohols." Aaron R. Van Dyke and Timothy F. Jamison. Oral Presentation. ORGN 49, 234th National Meeting of the American Chemical Society. Boston, MA. August 2007.

(2) "Red Tide in a flask: Methods for the synthesis of ladder polyethers." Aaron R. Van Dyke and Timothy F. Jamison. Invited Seminar Speaker. Seattle University. Seattle, WA. April 2007.

(1) "The solvatochromic properties of azulene and its derivatives: Developing a quantitative solvent polarity scale." Aaron R. Van Dyke and Greg T. Spyridis. Poster. CHED 804, 225th National Meeting of the American Chemical Society. New Orleans, LA. March 2003.

Publications

(4) Van Dyke, A. R.; Jamison, T. F. Functionalized templates for the convergent assembly of polyethers: Synthesis of *HIJK* rings of gymnocin A. *Angew. Chem. Int. Ed.* **2009**, *48*, Early View DOI: 10.1002/anie.200900924

(3) Van Dyke, A. R.; Jamison, T. F. [(1S,2S,5R)-5-Methyl-2-(1-methylethyl)cyclohexyl] diphenylphosphine. In *Encyclopedia of Reagents for Organic Synthesis, Second Edition*; Paquette, L. A., Crich, D., Fuchs, P. L., Molander, G., Eds.; Wiley: Hoboken, **2009**.

(2) Van Dyke, A. R.; Miller, K. M.; Jamison, T. F. (*S*)-(+)-Neomenthyldiphenylphosphine in nickel-catalyzed asymmetric reductive coupling of alkynes and aldehydes: Enantioselective synthesis of allylic alcohols and a-hydroxyketones. *Org. Synth*. **2007**, *84*, 111–119.

(1) Blice-Baum, A.; Van Dyke, A. R.; Sigmon, I.; Salter, A.; Wierzbicki, A.; Pocker, Y.; Spyridis, G. T. Computational and spectroscopic studies concerning the solvatochromic behavior of 1,3-disubstituted azulenes. *Int. J. Quant. Chem*. **2006**, *106*, 2331–2338.