2016

Catalytic enantioselective α,β,γ-trioxygenation and anti-1,2-diol from α-oxyaldehydes and its application in total synthesis of oxylipins isolated from Dracontium loretense

Gayan Aruna Abeykoon
Iowa State University

Catalytic enantioselective α,β,γ-trioxygenation and *anti*-1,2-diol from α-oxyaldehydes and its application in total synthesis of oxylipins isolated from *Dracontium loretense*

by

Gayan Aruna Abeykoon

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Jason S. Chen, Co-Major Professor
George A. Kraus, Co-Major Professor
L. Keith Woo
Edward Yu
Levi M. Stanley

Iowa State University

Ames, Iowa

2016

Dedicate to my family

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

Å	angstrom
Ac	acetyl
Ac_2O	acetic anhydride
AcOH	acetic acid
APCI	atmospheric-pressure chemical ionization
aq.	aqueous
Ar	aryl
BINOL	1,1'-bi-2-napthol
Bn	benzyl
Bu	butyl
˚C	degrees centigrade
Calcd	calculated
δ	NMR chemical shift in ppm downfield from tetramethylsilane
d	doublet
DCM	dichloromethane
dd	doublet of doublets
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
dd	doublet of doublet
ddd	doublet of doublet of doublet
dr	diastereomeric ratio

E	electrophile
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Et_3N	trimethylamine
EtOAc	ethyl acetate
EtOH	ethanol
h	hour
HRMS	high-resolution mass spectrometry
HPLC	high pressure liquid chromatography
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
L	liter
μ	micron
m	multiplet
Me	methyl
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute

mL	milliliter
mm	millimeter
mmol	millimole
m.p.	melting point
$NaBH_4$	sodium borohydride
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
PCy_3	tricyclohexylphosphine
ppm	parts per million
q	quartet
quant.	quantitative
R_f	retention factor
s	singlet
t	triplet
TBS	*tert*-butyldimethlsilyl
TES	triethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidinyl
TLC	thin-layer chromatography

ACKNOWLEDGMENTS

First and foremost, I would like to express my sincere gratitude to major advisor Professor Jason S. Chen for immense support during my graduate studies from 2011. My Ph.D. journey would not be successful without his gracious support, guidance, inspiration and motivation over the past five years. I feel very fortunate to have such an excellent advisor like him and I will always remember his dedication and passion for mentoring and teaching. This is the best time to express my sincere gratitude to my co-major advisor Professor George Kraus for taking me in to his research group in the later stage of my graduate studies. I would like to thank him for his guidance, motivation and fairness in leadership and most importantly being an inspirational mentor in my short stay in his group.

Also, I would like to thank my graduate committee members Professor Keith Woo, Professor Edward Yu and Professor Levi Stanley for their guidance, support and in my helpful suggestions in my research and career.

I very much appreciate the support from the Department of Chemistry and NSF for funding my research.

Also, I would like to thank the staff of Chemical instrumentation facility of Iowa State University, specially Dr. Sarah Cady, Dr. Shu Xu and Dr. Kamel Harrata. I appreciate their generous support in the training in instruments and troubleshooting instrumentation problems.

I would like to thank all the present and past Chen and Kraus group member for their support and wonderful memories, specially Shreyosree Chatterjee with whom I worked closely in synthesizing oxylipins.

This is the right moment to appreciate the help that got from my friends in Ames. Specially, Supipi, Rajeeva, Umayangani, Purnima and Chamara for being my family in Ames, Iowa. Without their enormous help my life in Ames would not be that smooth.

I am lucky to have a supporting wife like Sagarika Weerasekara. I would like to thank her for being an inspiration and supporting me in my ups and downs of the life. Also, I am deeply indebted to my parents, my sister Savithrie, my brother Mohan and my in-laws for their continuous support throughout my life and for their generous sacrifications to make my life better.

Last but not least, I would take this moment to thank and appreciate the kind help and the motivation I got from Mr. Cecil Samarasinghe throughout the time. I am deeply indebted to him for his support.

ABSTRACT

Mother nature creates structurally diverse interesting secondary metabolites often with unexpected biological activity, but in scarce quantities. Target-oriented total synthesis provides access to such natural products in sufficient amounts for further exploration of bioactivity. In target-oriented total synthesis, there is a never ending demand for the development of new reaction methodologies in order to address challenges in the synthesis and also to improve current synthetic protocols. Taking this idea to heart, we have worked on novel asymmetric method development and applied some of the methodologies that we developed to total synthesis. This thesis is composed of five chapters. Chapter 1 provides a general introduction to the research work discussed in Chapter 2, 3 and 4. Also, the introduction at the beginning of each chapter discusses the relevant background of the research so as to provide sufficient understanding about the significance of the work and the results. Moreover, some of the research in chapters 2 and 3 was published in *Org. Lett.* in 2014 and rest of the work is from the manuscript which is currently in preparation. Also, the work disclosed in chapter 4 is published in *Org. Lett.* in full in 2015.

Chapter 2 describes the development of a novel method for the synthesis of differentially protected chiral *anti* 1,2-diols via organomagnesium or organolithium addition to α-oxyaldehydes synthesized via organocatalytic oxidative incorporation of TEMPO. Excellent diastereoselectivity was observed in these reactions, regardless of the hybridization or presence or absence of branching of the incoming carbon nucleophile. Further attempts to access masked *syn* 1,2-diols using the same method via promoting

chelation control was unsuccessful. But, degradation of initial diastereoselectivity was often observed. Therefore, oxidation-reduction sequence was used to deliver *syn* 1,2-diols, despite of the low diastereoselectivity.

Chapter 3 describes the application of the methodology discussed in chapter 2, to a short synthesis of unnamed oxylipins isolated from *Dracontium loretense*. This chapter discuss our two successful approaches in synthesizing oxylipins. Our first generation synthesis describes a stereoflexible synthesis of all possible diastereomers, which led to the absolute stereochemical determination of natural oxylipins isolated from the *Dracontium loretense*. Moreover, a second generation synthesis provides the shortest route ever to immunostimulatory oxylipin with highest ever overall yield (33%).

Chapter 4 discusses the first ever α,β,γ-trifunctionalization of enals using organocatalysis. Subjecting an enal to catalytic enantioselective aldehyde α-oxygenation condition led to discovery of the first ever α,β,γ-trioxygenation. Moderate yields and enantioselectivity for trioxygenation of enals were observed when using tryptophan based chiral imidazolidinone catalyst in fluorinated aromatic solvents.

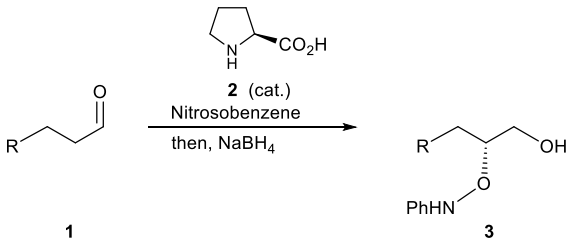
Chapter 5 is the conclusion of the thesis. Furthermore, it discusses future directions of the work is described in Chapter 4.

CHAPTER 1

INTRODUCTION

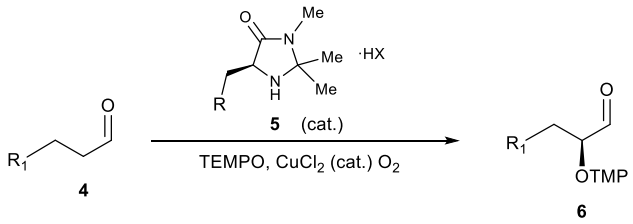
Chiral catalysis has become a powerful and efficient way of introducing chirality in natural products. Although, transition metal catalyzed asymmetric transformations have had a greater impact in synthetic organic chemistry, asymmetric transformations of aldehydes and enals using chiral amines as the catalysts has become popular in last decade and has become a hot field of research.[1] α-Functionalizations[2] of aldehydes and β-functionalizations[3] of enals are the most heavily studied organocatalytic transformations. In addition to that, some organocatalytic remote transformations of carbonyl compounds have been reported. [4]

Organocatalytic chiral oxygenations of aldehydes and enals are important, because of their potential broad applications in total synthesis of natural products. The most common variant of this class is chiral α-oxygenation of aldehydes. Moreover, these α-oxygenation reactions proceed via enamine catalysis. Nucleophilic enamine species generated by the reaction between aldehyde and the chiral secondary amine traps any electrophilic oxygen species at the α-position. Earlier examples of these chiral α-oxygenations, employed L-proline **2** as the catalyst and nitrosobenzene as the electrophilic oxygen source (Scheme 1).[5] Unfortunately, nitrobenzene incorporation led to unstable α-oxyaldehydes making these methods synthetically less useful. Also, the method to α-oxygenate aldehyde using radical oxygen was not synthetically appealing because of the poor enantioselectivity.[6]



Scheme 1. Proline catalyzed α-oxygenation of aldehydes

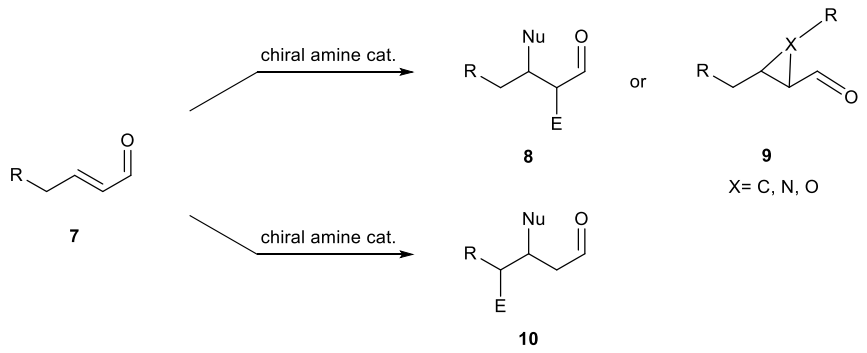
Further explorations of methods to improve chiral α-oxygenations led to the discovery of oxidative incorporation of TEMPO using chiral imidazolidinones **5** as the catalyst (Scheme 2).[7] Moreover, stability and high enantioselectivity of these α-oxyaldehydes is more appealing to total synthesis.



Scheme 2. α-Oxygenation of aldehydes catalyzed by chiral imidazolidinones

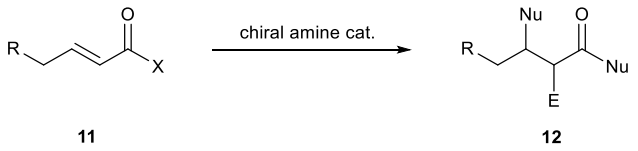
Conjugate addition of oxygen nucleophiles such as substituted hydroxylamine,[8] alcohols[9] or hydrogen peroxides[10] to iminium species formed between an enal and a chiral amine catalyst lead to β-oxygenation. Although, there are ample examples for β-oxygenation, the reversible nature of the addition of the oxygen nucleophiles makes these methods less synthetically useful.[11] Also, there is an example for nonenantioselective organocatalytic γ-oxygenation via oxidative incorporation of TEMPO.[12]

Asymmetric organocascade reactions enable the setup of multiple stereocenters in one-pot.[13] Difunctionalization organocascade reactions comprise α,β- and β,γ-difunctionalizations (Scheme 3). Conjugate addition of a nucleophile to an α,β-unsaturated iminium ion would trap a nucleophile at β-position and the resultant enamine which is nucleophilic at the α-position would trap an electrophile. Although, there are some examples for forming a three-membered ring when α and β carbons of enal can form bonds to the same atom of the incoming group,[14] the most common variants have two different reaction partners at α and β carbons . However, there is no such a literature precedent for α,β-dioxygenation cascade reactions, although α,β-difunctionalizations involving either α-[15] or β-monooxygenation[16,9c] is precedented.



Scheme 3. Organocatalytic difunctionalization cascades

β,γ-difunctionalizations using organocatalysis are known.[17] But, there is no precedent for a cascade α,β,γ-trifunctionalization (or trioxygenation) of enals under any conditions. But, Fu et. al., Smith et. al. and Romo et. al. have reported some cascade *ipso*,α,β-trifunctionalizations of activated carboxylic acid derivatives using organocatalysis (Scheme 4).[18]

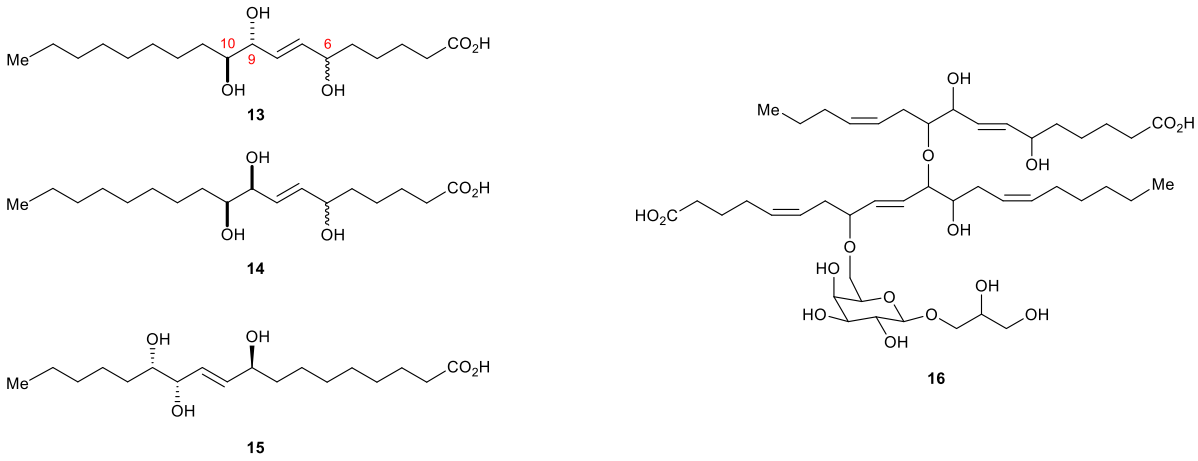


11 12

Scheme 4. *ipso*,α,β-trifunctionalization cascade of activated carboxylic derivatives

Chiral 1,2-diols are among commonly found functional groups in natural products. The Sharpless asymmetric dihydroxylation is the default choice to access such chiral *syn*-1,2-diols in high enantioselectivity from *trans* alkenes. One common disadvantage of the Sharpless asymmetric dihydroxylation is the poor enantiomeric ratio when *cis* alkenes are converted into corresponding *anti*-1,2-diols.[19] As an alternative to this fundamental limitation of the Sharpless asymmetric dihydroxylation in delivering chiral *anti*-1,2-diols, carbon–carbon bond formation reactions are used. The middle carbon–carbon bond between the two carbenol carbons of *anti*-1,2-diols could be formed by nucleophilic addition to an aldehyde constructing both stereocenters simultaneously. Enolates or enols derived from α-oxycarbonyl compounds[20-22] and functionalized allyl reagents[23,24] are suitable nucleophiles capable of such a transformation. Also, nucleophilic addition to a chiral α-oxyaldehyde with substrate-,[25,26] reagent-,[27] or catalyst-based[28] stereocontrol can deliver *anti*-1,2-diols too. Although, prior setting of the α-chiral center of the aldehyde required, the large substrate scope of this approach makes more appealing. Moreover, a method employing nucleophilic addition to an epoxyalcohol[29] to deliver *anti*-1,2-diols is more appealing, because these epoxy alcohols can be prepared with desired stereochemistry by kinetic resolution of a racemic allylic alcohol through the Sharpless asymmetric epoxidation.[30] Furthermore, *anti*-1,2-diols can be accessed by alkene epoxidation followed by epoxide opening,[31] allylic substitution reactions[32] and desymmetrization reactions.[33]

Nucleophilic addition to α-oxyaldehydes[25–28] is more appealing for diol synthesis for two reasons. One is the broad range of nucleophiles available for such a transformation. The other reason is the substrate-controlled stereoinduction that can be achieved, based on the masking group on the chiral α-hydroxyl group. For an example a α-TBS ether may promote polar Felkin-Anh control, whereas α-benzyl ether could facilitate chelation control.[25,26a] Previously, chiral α-oxyaldehydes required multiple steps to prepare because of the unavailability of direct α-oxygenations. But, now direct aldehyde α-oxygenation is available via organocatalysis and such α-oxyaldehydes could be accessed in one step from the starting aldehydes.[7]



Scheme 5. Natural oxylipins (**13**, **14** and **15**) and Nigricanoside A (**16**)

Glactolipid Nigricanoside A **16** (Scheme 5) is a scarce natural product isolated from the green algae *Avrainvillea nigricans* in 2001.[33] The isolation chemists reported an exceptional cytotoxicity via microtubule-stabilizing activity, which drew our attention as a synthetic target (But, in 2015, Nigricanoside A was found to be lacking reported bioactivity).[35] Unnamed oxylipins **13** and **14** (Scheme 5) were isolated from the Peruvian

plant *Dracontium loretense* in trace quantities.[36] Moreover, oxylipin **13** has shown immunostimulatory properties while oxylipin **14** is bio-inactive. However, the isolation chemists were only able to assign relative stereochemistry of C-9 and C-10 stereocenters of oxylipins **13** and **14**, while the stereochemistry of C-6 was undetermined. These fatty acid derivatives share the same stereochemically-unassigned trioxygenated motif (3-ene-1,2,5 triol moiety) found in the fatty acid domains of Nigricanoside A **16**, qualifying them to be an ideal model system for synthetic method development.

There are five total syntheses are reported for these oxylipins other than ours.[37] Sharma et. al.[37a] and Narsaiah et. al.[37b] each reported a synthesis single isomer oxylipin. Neither group interested in comparing their synthetic compounds with the spectroscopic data of natural oxylipins, which prevented them from making a stereochemical assignment. Barua et. al.[37c] reported a synthetic route to both diastereomers of natural oxylipins. This synthesis also didn't lead to a stereochemical assignment because, the reported NMR data of their synthetic oxylipins was in $CDCl_3$, which was different from what the isolation team used (CD_3OD). Moreover, in the synthesis which is reported by Reddy et. al.[37d] compared their NMR spectral data with a synthetic oxylipin instead of that of isolation chemists'.[37d] This ambiguity of the absolute stereochemistry urged us to devise a stereochemically flexible route to all four diastereomers of oxylipins in order to make an unambiguous absolute stereochemical determination. Moreover, pinellic acid **15** which has been a target for several syntheses,[38] is closely related in structure to these oxylipins. Only the synthesis[38a] by Ōmura was able to furnish all possible diastereomers of pinnelic acid, while Kuwahara synthesis[38b] is the shortest ever synthetic route with 7 linear steps.

References

1. (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc*. **2000**, *122*, 2395. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. **2000**, *122*, 4243.

2. (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471. (b) MacMillan, D. W. C.; Beeson, T. D. In Science of Synthesis, Asymmetric Organocatalysis; List, B., Maruoka, K., Eds.; Georg Thieme: Stuttgart, **2012**; Vol. *1*, pp 271−307. (c) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874.(d) Deng, Y.; Kumar, S.; Wang, H. *Chem. Commun*. **2014**, *50*, 4272.

3. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416.

4. (a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem*. **2012**, *2012*, 865. (b) Lear, M. J.; Hayashi, Y. *ChemCatChem* **2013**, *5*, 3499.

5. (a) Zhong, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247. (b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. **2003**, *125*, 10808. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293.
6. Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc*. **2004**, *126*, 8914.

7. (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc*. **2007**, *129*, 4124. (b) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. (c) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; Macmillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 10012. (d) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci*. **2012**, *3*, 58.

8. Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 1536.

9. (a) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*,8658. (b) Díez, D.; Núñez, M. G.; Benéitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, *2009*, 390. (c) McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett*. **2011**, *13*, 6460.

10. Hu, L.; Lu, X.; Deng, L. *J. Am. Chem. Soc*. **2015**, *137*, 8400.

11. Nising, C. F.; Bräse, S. *Chem. Soc. Rev*. **2012**, *41*, 988.

12. Ho, X.-H.; Jung, W.-J.; Shyam, P. K.; Jang, H.-Y. *Catal. Sci. Technol*. **2014**, *4*, 1914.

13. (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem*. **2010**, *2*, 167. (b) Pellissier, H. *Adv. Synth. Catal*. **2012**, *354*, 237. (c) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev*. **2014**, *114*, 2390.

14. (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2005**, *127*, 3240. (b) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 6964. (c) Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413. (d) Zhao, G.-L.; Ibrahem, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 1210. (e) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed*. **2007**, *46*, 778.

15. (a) Yoon, H.-S.; Ho, X.-H.; Jang, J.; Lee, H.-J.; Kim, S.-J.; Jang, H.-Y. *Org. Lett*. **2012**, *14*, 3272. (b) Kim, J.-H.; Park, E.-J.; Lee, H.-J.; Ho, X.-H.; Yoon, H.-S.; Kim, P.; Yun, H.; Jang, H.-Y. *Eur. J. Org. Chem*. **2013**, *2013*, 4337. (c) Shyam, P. K.; Jang, H.-Y. Eur. J. Org. Chem. **2014**, *2014*, 1817.

16. (a) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Li, H.; Wang, J.; ENunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun*. **2007**, 507. (c) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova,A. *Chem. - Eur. J*. **2007**, *13*, 574. (d) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett*. **2007**, *48*, 5701. (e) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed*. **2009**, *48*, 5701. (f) Lin, S.; Zhao, G.-L.; Deiana, L.; Sun, J.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Chem. - Eur. J.* **2010**, *16*, 13930. (g) Quintard, A.; Alexakis, A. *Chem. Commun*. **2011**, *47*, 7212. (h) McGarraugh, P. G.; Johnston, R. C.; Martínez-Muñoz, A.; Cheong, P. H.-Y.; Brenner-Moyer, S. E. *Chem. - Eur. J.* **2012**, *18*, 10742.

17. (a) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2012**, *134*, 2543. (b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem., Int. Ed*. **2012**, *51*, 4104. (c) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem*. **2012**, *77*, 8828.

18. (a) Bappert, E.; Müller, P.; Fu, G. C. *Chem. Commun*. **2006**, 2604. (b) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci*. **2013**, *4*, 2193. (c) Liu, G.; Shirley, M. E.; Van, K. N.; McFarlin, R. L.; Romo, D. *Nat. Chem*. **2013**, *5*, 1049. (d) Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 13688. (e) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc*. **2014**, *136*, 4492.

19. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

20. Selected methods featuring chiral auxiliaries: (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753(b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A.

S. *J. Org. Chem.* **1992**, *57*, 1961. (c) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591.

21. Selected methods featuring chiral small molecule catalysts: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556. (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., In t. Ed.* **2004**, *43*, 2152. (d) Denmark, S. E.; Chung, W.-j. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890.
22. Enzymatic method: Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed.* **1991**, *30*, 555.

23. Selected methods featuring chiral auxiliaries: (a) Barrett, A. G. M.; Malecha, J. W. *J. Org.Chem.* **1991**, *56*, 5243. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (c) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105. (e) Hunt, J. A.; Roush, W. R.*J. Org. Chem.* **1997**, *62*, 1112. (f) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. (g) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602.

24. Method featuring chiral catalyst: Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760.

25. (a) Cram, D. J.; Elhafez, F. A. A.; *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (c) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dâu, M.-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146.

26. (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784. (c) Iio, H.; Mizobuchi, T.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1986**, *27*, 6373. (d) Savall, B. M.; Powell, B. M.; Roush, W.

R. *Org. Lett.* **2001**, *3*, 3057. (e) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441.

27. (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017 – 3020. (b) Marshall, J. A., Eidam, P. *Org. Lett.* **2004**, *6*, 445 – 448.

28. Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937.

29. Selected recent examples: (a) O'Sullivan, T. P.; Vallin, K. S. A.; Shah, S. T. A.; Fakhry, J.; Maderna, P.; Scannell, M.; Sampaio, A. L. F.; Perretti, M.; Godson, C.; Guiry, P. J. *J. Med. Chem.* **2007**, *50*, 5894. (b) Garbe, L.-A.; Morgenthal, K.; Kuscher, K.; Tressl, R. *Helv. Chim. Acta* **2008**, *91*, 993. (c) Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758. (d) Show, K.; Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1212.

30. (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.

31. (a) Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763. (b) Albrecht, L. ; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188.

32. (a) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717. (b) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4203.

33. (a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (b) Arai, T.; Mizukami, T.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 1145. (c) Hartung, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3885.

34. Williams, D. E.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, 129, 5822.

35. Chen, J.; Koswatte, P.; DeBergh, J. B.; Fu, P.; MacMillan, J. B.; Ready, J. M. *Chem. Sci.* **2015**, *6*, 2932.

36. Benavides, A.; Napolitano, A.; Bassarello, C.; Carbone, V.; Gazzerro, P.; Malfitano, A. M.; Saggese, P.; Bifulco, M.; Piacente, S.; Pizza, C. *J. Nat. Prod.* **2009**, *72*, 813.

37. (a) Chatterjee, S.; Kanojia, S. V.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2011**, *22*, 367. (b) Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. *Tetrahedron Lett.* **2012**, *53*, 3955. (c) Saikia, B.; Devi, T. J.; Barua, N. C. *Tetrahedron* **2013**, 69, 2157. (d) Yadav, J. S.; Shankar, K. S.; Reddy, A. N. Helv. *Chim. Acta* **2014,** *97*, 546. (e) Reddy, N. S.; Das. B.; *Helv. Chim. Acta* **2015,** *98*, 78.

38. (a)Shirahata, T.; Sunazuka, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Nagai, T.; Kiyohara, H.; Yamada, H.; Kuwajima, I.; Ōmura, S. *Bioorg. Med. Chem.* **2003**, *13*, 937. (b) Miura, A.; Kuwahara, S. *Tetrahedron* **2009**, *65*, 3364. (c) Sabitha, G.; Reddy, E. V.; Bhikshapathi, M.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 313.

CHAPTER 2

CHIRAL *anti*-1,2-DIOLS FROM α-OXYALDEHYDES

Published in part in *Org. Lett.*[*]

Manuscript in preparation

Introduction

Chiral 1,2-diols are among the most common functional groups found in natural products. Although, the Sharpless asymmetric dihydroxylation provides a powerful mean to access *syn*-1,2-diols from *trans* alkenes, poor enantioselectivity was often observed when *cis* alkenes were converted to *anti*-1,2-diols.[1] To circumvent this fundamental limitation of the Sharpless dihydroxylation in *anti*-1,2-diols synthesis, C-C bond formation reactions are employed as outlined in Figure 1. *Anti*-1,2-diols **1** may be formed by nucleophilic addition of enolates and enols derived from α-oxycarbonyl compounds[2-4] and functionalized ally reagents[5-6] to aldehydes **2** (method **a**), constructing the central C-C bond while setting the both stereocenters at the same time. Nucleophilic addition to chiral α-oxyaldehydes **3** with substrate-,[7-8] reagent-[9] or catalyst-control[10] gives *anti*-1,2-diols forging a C-C bond next to the diol moiety (method **b**). Although prior setting up of one chiral center is necessary, a larger substrate scope makes this approach appealing. *Anti* diol synthesis can also be envisioned via nucleophilic addition to an epoxyalcohol **4** (method **c**).[11] The synthesis of epoxyalcohols **4** via kinetic resolution of racemic allylic alcohols followed by a Sharpless asymmetric epoxydation makes this method attractive.[12] Moreover *anti*-1,2-diols can be accessed by alkene epoxidation followed by epoxide opening,[13] allylic substitution reactions [14] and desymmetrization reactions.[15]

---

[*] *Org. Lett.* **2014**, *16*, 32

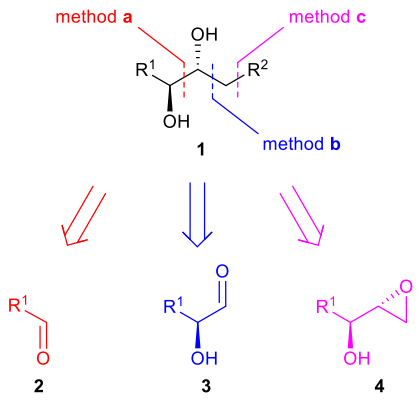


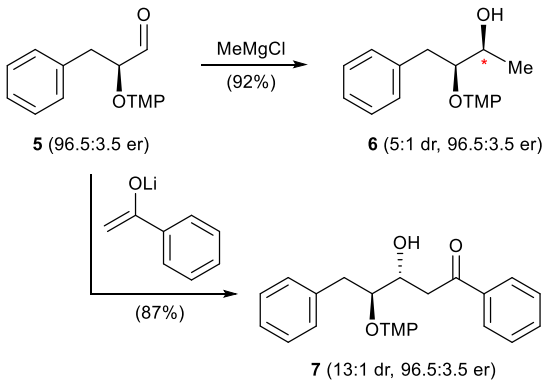
Figure 1. Strategies towards making *anti* 1,2-diols

Unstable α-oxyaldehyde products in organocatalytic nitrosobenzene incorporation[16] and poor stereoselectivity of singlet oxygen incorporation[17] led us to consider oxidative incorporation of TEMPO[18] in preparation of an α-oxyaldehyde for diol syntheses. Moreover, a 2,2,6,6-tetramethylpiperidinyl masking group at the α-oxygen can promote both polar Felkin-Ahn (due to steric congestion) and chelation control (through basic nitrogen or oxygen) pathway for nucleophilic addition depending on the choice of reaction conditions.

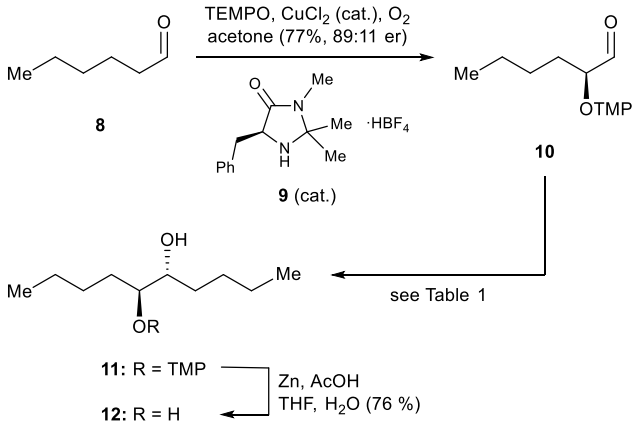
Result and discussion

In 2011, MacMillan showed that these α-oxyaldehydes can undergo a variety of transformations including Grignard additions, aldol reactions, Wittig reactions etc. without degrading the enantiomeric ratio.[18d] Furthermore, he reported a Grignard addition to these α-oxyaldehydes to give masked *syn*-1,2-diol **6**, whereas the related aldol

addition gave a masked *anti*-1,2-diol **7** (Scheme 1.). Also, Maruoka reported a Grignard addition to these α-oxyaldehydes to give a masked *anti*-1,2-diol.[18b] We were surprised by the stereochemical oddity of the outcomes of similar nucleophilic addition to α-oxyaldehydes. Therefore, we independently investigated the related Grignard addition to α-oxyaldehydes. Diol **12** was prepared by a Grignard addition to α-oxyaldehyde **8** followed by reductive cleavage (Zn, AcOH)[19] of the N-O bond of the -OTMP moiety (Scheme 2). NMR spectroscopic and the optical rotation comparison with known *syn*[20] and *anti* isomers[21] revealed that masked diol **11** to have *anti* stereochemical relationship. We confirmed the stereochemical outcome of the Grignard addition to the α-oxyaldehydes to be *anti*.[22] Therefore, polar Felkin-Anh control predominates in Grignard addition to such α-oxyaldehyde **8**.



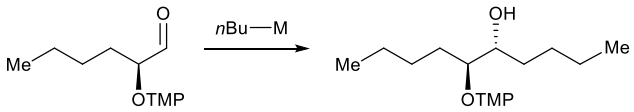
Scheme 1. Some published reactions of α-oxyaldehydes



Scheme 2. Determination of stereochemical outcome of the Grignard addition to α-oxyaldehydes

Our attempts to improve the selectivity and yield of the Grignard addition are summarized in Table 1. Modest yield and selectivity were observed when the addition of *n*-butylmagnesium chloride to aldehyde **10** was conducted in ether at 0 °C. The primary alcohol formed by the reduction of aldehyde **10** was a significant side product under these conditions. Both yield and selectivity were improved further when THF was used as the solvent for the *n*-butylmagnesium chloride addition. Aldehyde reduction to primary alcohol was observed to be suppressed in THF. But, poor yield and diastereoselectivity were observed when using more polar dioxanes as solvent. However, superior yields and selectivity were observed when lowering the temperature to -78 °C in THF. Despite the high yield, modest selectivity was observed when changing the nucleophile to *n*-butyllithium in THF. But the selectivity could be recovered when hexanes is used as a solvent for *n*-butyllithium addition at -78 °C.

Table 1. Tuning the Diastereoselectivity[a] of Grignard addition to α-oxyaldehydes



10 **11**

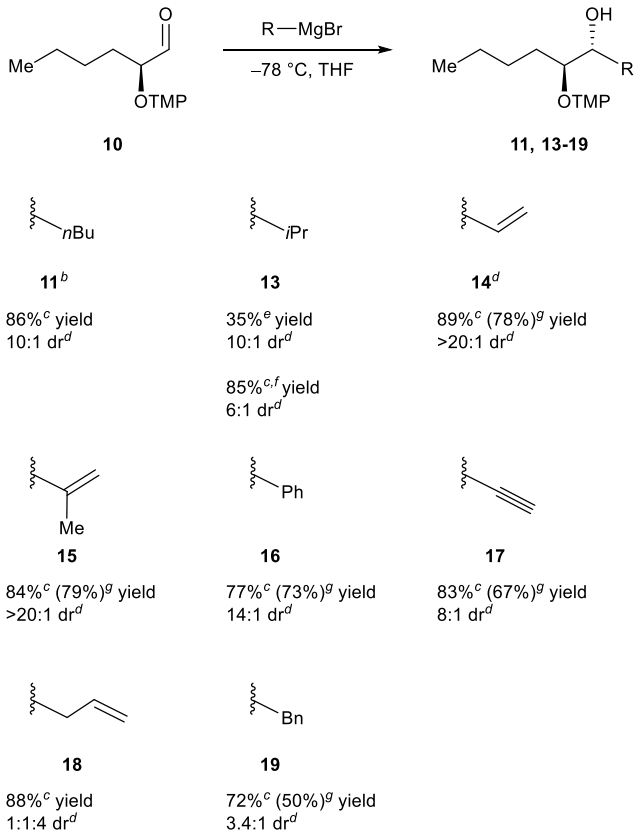
M	solvent	Temp (°C)	dr[b]	yield[c] (%)
MgCl	E_2O	0	4:1	60[d]
MgCl	THF	0	6:1	70
MgCl	Dioxanes	0	3:1	50[d]
MgCl	THF	-78	10:1	86
Li	THF	-78	6:1	81
Li	hexanes	-78	12:1	84

[a]0.8-1.0 mmol scale. [b]Determined by ^{1}H-NMR analysis of the crude mixture. [c]Isolated yield of a mixture of diastereomers. [d]Estimated by ^{1}H-NMR analysis of the crude mixture. Major byproduct was primary alcohol derived from aldehyde reduction.

Both functional group tolerance of the α-oxygenation and the Grignard addition to aldehydes were well investigated previously.[18d] Therefore, we were more interested in a study of the variation of the diastereoselectivity of the Grignard addition to α-oxyaldehydes with different classes of Grignard reagents considering the branched, unbranched, and hybridization of the Grignard reagent. Although, good selectivity was observed in the isopropylmagnesium bromide addition, the yield was modest due the significant reduction of aldehyde **10** to the corresponding primary alcohol. Reduction was found to be suppressed by premixing aldehyde **10** with $CeCl_3$ but little degradation of the diastereoselectivity was resulted due to chelation. Excellent selectivities were observed for sp^2 Hybridized Grignard reagents. However, the selectivity in ethynylmagnesium bromide addition was moderate, possibly due to low steric interactions.

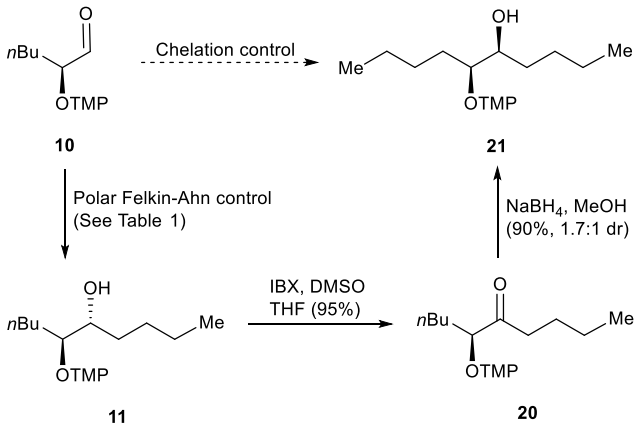
Surprisingly, allylmagnesium bromide addition to aldehyde **10** gave *syn*-1,2-diol as the major product with little selectivity for either diastereomer. The slight preference

for the *syn* 1,2-diol with allylmagnesium bromide addition may be explained by the chelation control or by a different stereoinduction model such as the Zimmerman-Traxler model. However, benzylmagnesium bromide addition follows polar Felkin-Ahn control, as observed with other Grignard reagents, to give the *anti*-1,2-diol despite the low diastereoselectivity.



[a]1 mmol scale. [b]Used *n*-butylmagnesium chloride. [c]Isolated yield of a mixture of diastereomers. [d]Determined by ^{1}H-NMR analysis of the crude mixture. [e]Estimated by ^{1}H-NMR analysis of the crude mixture. Major product was primary alcohol derived from aldehyde reduction. [f]1.5 equiv of $CeCl_3$ added. [g]Isolated yield of a single diastereomer.

Scheme 3. *anti*-1,2-diol synthesis varying the carbon nucleophile[a]



Scheme 4. *syn*-1,2-Diol synthesis via oxidation and reduction

Degradation of diastereoselectivity in 1,2-diol synthesis upon premixing with $CeCl_3$ with isopropylmagnesium bromide (Scheme 3, **13**) to suppress the reduction of aldehyde gave a hope in optimizing the diol synthesis towards *syn* selectivity via chelation control. In light of this observation, oxyphilic Lewis acids, solvents and temperature were screened to promote chelation control. Early transition metal salts (e.g. scandium and titanium salts), late transition metal salts (e.g. copper and zinc salts), main group complexes (e.g. boron, aluminum complexes) and lanthanide salts (e.g. cerium, samarium and lanthanum salts) were found to be ineffective in degrading initial diastereomeric ratio to favor *syn*-1,2-diols. Butylmagnesium chloride addition to aldehyde **10** in the presence of the above mentioned oxophillic salts in ethereal solvents always gave *anti*-1,2-diols as the major product. Only lithium triflate and lithium chloride in diglyme at RT was found to be effective in bringing the diastereoselectivity down to 2.2:1 and 2.5:1 respectively with good yields (80% and 85% crude NMR yields of both diastereomers, respectively). Since polar Felkin-Anh control is predominating always in this system, hydride addition to the corresponding ketone should also occur

from the least hindered site inverting the stereocenter of the free alcohol. Therefore, oxidation of the free alcohol moiety of the *anti*-1,2-diol to a ketone and reduction of the corresponding ketone is a viable route to *syn*-1,2-diols. As a result, an oxidation and reduction sequence was used as shown in Scheme 4 in *syn* 1,2-diol synthesis. IBX oxidation of alcohol **11** to ketone **20** followed by $NaBH_4$ gave an inseparable diastereomeric mixture of masked 1,2-diols favoring *syn* stereoisomer **21** in only a 1.7:1 diastereomeric ratio in 90% yield.

The ^{1}H NMR peak for the hydroxyl proton of both masked *anti*- and *syn*-1,2-diol unusually far apart (by 5 ppm). Moreover, the ^{1}H NMR peak for the hydroxy proton of compounds **11** and **13-19** consistently appeared at ca. 2 ppm for the major diastereomer (masked *anti*-1,2-diol) and at ca. 7 ppm for the minor diastereomer (masked *syn*-1,2-diol). The exact ^{1}H NMR chemical shifts of the hydroxy protons of the major and minor diastereomers of compounds **11** and **13-19** are summarized in Table 2 below. Using the built in stereochemical probe that we developed we established the stereochemistry of the Grignard product **6** (Scheme 1) to be *anti*, which was previously misassigned by MacMillan.[18d] Also, we confirmed the stereochemistry of the aldol product **17** (Scheme 1) to be *syn* using this built in stereochemical probe.

Table 2. [1]H NMR Chemical shifts of hydroxyl protons of major (*anti*) and minor (*syn*) masked 1,2-diols of **11** and **13-19**

Compound	Chemical shift of hydroxyl protone in $CDCl_3$	
	major diastereomer (*anti*)	minor diastereomer (*syn*)
11	2.03	7.31
13	1.94	7.05
14	2.50	7.53
15	2.15	7.46
16	2.41	c. a. 7[a]
17	2.45	7.56
18	2.26[b]	7.33[c]
19	2.05	c. a.7[a]

[a] Masked by the aromatic protons. [b]Minor diasteremor. [c]Major diastereomer.

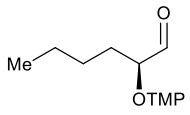
Conclusion

We developed a promising method to access differentially protected *anti*-1,2-diols with high diastereoselectivity via Grignard additions to α-oxyaldehydes. Moreover, high diastereomeric ratios were observed regardless of the branched/unbranched nature or hybridization of the Grignard reagent. Furthermore, this method can be used as an alternative to the Sharpless dihydroxylation, which has a fundamental limitation in delivering *anti*-1,2-diols with high enantioselectivity. Attempts to optimize the above diol technology to access *syn*-1,2 diols using chelation control, were not successful, although degradation of the initial diastereomeric ratio was often observed. Therefore, an oxidation-reduction sequence was used to access *syn*-1,2-diols from *anti*-1,2-diols utilizing the dominating Felkin-Ahn control.

Experimental

General procedures

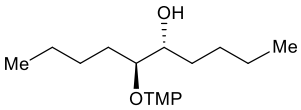
Unless otherwise noted, all reactions were performed with stirring under an argon atmosphere under anhydrous conditions. Organomagnesium and -lithium reagents were purchased from Aldrich. All other reagents were purchased at the most-economical grade. Dry tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), dichloromethane, and toluene were obtained by passing HPLC grade solvents through commercial solvent purification systems. All other chemicals were used as received, without purification. Flash column chromatography was performed using Grace Davison Davisil silica gel (60 Å, 35 – 70 μm). Unless otherwise noted, yields refer to chromatographically- and spectroscopically- (^{1}H NMR) homogeneous samples of single diastereomers. Thin-layer chromatography (TLC) was performed on Grace Davison Davisil silica TLC plates using UV light and common stains for visualization. NMR spectra were calibrated using residual undeuterated solvent as an internal reference. Apparent couplings were determined for multiplets that could be deconvoluted visually.



10

Aldehyde **10:** To a mixture of activated 4 Å molecular sieves (500 mg, powdered) and imidazolidinone catalyst **9** (1.22 g, 4 mmol, 0.2 equiv.) in 12 mL acetone was added $CuCl_2 \cdot 2H_2O$ (340 mg, 2 mmol, 0.1 equiv.). The green reaction mixture was stirred open to air for 5 minutes until the copper salt dissolved and the mixture turned dark orange. The reaction was cooled to 0 °C for 10 minutes, then hexanal (**8**; 2.50 mL, 20 mmol, 1.0 equiv.) was added dropwise over 2 minutes. The reaction was stirred at 0 °C for 10 minutes, then a solution of TEMPO (3.75

g, 24 mmol, 1.2 equiv.) in 6 mL of acetone was added dropwise over 3 minutes. The reaction mixture was capped with a rubber septum and an air inlet line was attached via an 18-gauge needle. The reaction was stirred at 0 °C for 24 hours, then partitioned between ether (50 mL) and saturated NH_4Cl (150 mL). The aqueous layer was extracted with ether (2 × 150 mL) and the combined organic layers were washed with brine (300 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give an orange oil. Flash column chromatography (3 % EtOAc / hexanes) gave α-oxyaldehyde **10** (3.91 g, 77 % yield) as a colorless oil. A sample was derivatized [1. $NaBH_4$, MeOH; 2. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 3. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 10 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 8.7 (major), 10.0 (minor) minutes] to have 89:11 er. **10:** R_f = 0.44 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −77.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 2933, 1732 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 9.77 (d, *J* = 4.4 Hz, 1H), 4.07 (dt, *J* = 8.9, 5.2 Hz, 1H), 1.74 (m, 1H), 1.66 (m, 1H), 1.48 – 1.10 (m, 22H), 0.90 (t, *J* = 6.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.74, 88.74, 40.26, 31.97, 30.14, 29.82, 29.48, 29.31, 24.40, 22.78, 17.29, 14.23 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{30}NO_2^+$ [M + H^+]: 256.2277, found: 256.2278.

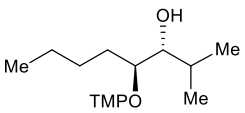


11

Alcohol **11**: To a solution of aldehyde **10** (200 mg, 0.78 mmol, 1.0 equiv.) in 780 μL of THF at –78 °C was added *n*BuMgCl (2.0 M in ether, 590 μL, 1.5 mmol, 1.5 equiv.) dropwise over 3 minutes. The resultant solution was stirred at –78 °C for 30 minutes, then warmed to ambient temperature. The reaction mixture was partitioned between saturated NH_4Cl (5

mL) and ether (20 mL). The organic phase was washed with water (2 × 20 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated to give a colorless oil. Flash column chromatography (4 % EtOAc / hexanes) gave alcohol **11** (210 mg, 86 % yield, 10:1 mixture of diastereomers) as a colorless oil. **11:** R_f = 0.27 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −8.3 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3583, 2933 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 3.88 (m, 2H), 2.03 (s, 1H), 1.82 (m, 1H), 1.61 – 1.24 (m, 18H), 1.23 – 1.08 (m, 11H), 0.91 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 84.94, 72.45, 40.79, 31.75, 29.09, 28.75, 23.42, 22.93, 17.37, 14.24 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{40}NO_2^+$ [M + H^+]: 314.3059, found: 314.3056.

Alcohol **13**: To a suspension of cerium(III) chloride in 0.2 mL of THF at –78 °C was added *i*PrMgBr (1.0 M in THF, 1.50 mL, 1.5 mmol, 1.5 equiv.). After 30 minutes at –78 °C, aldehyde **10** (255 mg, 1.0 mmol, 1.0 equiv.) in 1 mL of THF was added dropwise over 5 minutes. The resultant solution was stirred at –78 °C for 30 minutes, then warmed to ambient temperature. The reaction mixture was partitioned between saturated NH_4Cl (5 mL) and ether (20 mL). The organic phase was washed with water (2 × 20 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated to give a colorless oil. Flash column chromatography (5 % EtOAc / hexanes) gave alcohol **13** (85 % yield, 6:1 mixture of diastereomers) as a colorless oil. **13:** R_f = 0.42 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −8.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3584, 2932 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 3.95 (m, 1H), 3.66 (m, 1H), 1.94 (d, *J* = 3.92 Hz, 1H), 1.73 (m, 2H), 1.54 – 1.07 (m, 23H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.93 – 0.88 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ

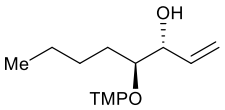


13

= 83.49, 77.20, 60.16, 40.86, 30.07, 29.32, 23.60,19.89, 19.36, 17.34, 14.23; HRMS (ESI-QTOF) calcd for $C_{17}H_{38}NO_2^+$ [M + H^+]: 300.2897, found: 300.2900.

Alcohols 11, 13–19 were prepared in the same manner as alcohol **11** using the appropriate solutions of organomagnesium bromide reagents dissolved in THF.

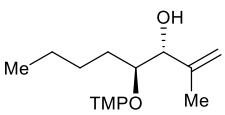
Alcohol **14**: Flashcolumn chromatography (4 % EtOAc / hexanes) gave pure alcohol **14**



14

(78 % yield) as a colorless oil as well as a mixture of diastereomers (11 % yield) as a colorless oil. **14:** R_f = 0.51 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = +10.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3580, 3052, 2934, 1467 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 5.94 (m, 1H), 5.29 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* =10.6 Hz, 1H), 4.44 (m, 1H) 3.99 (m, 1H), 2.50 (s, 1H), 1.80 (m, 1H), 1.64 – 1.06 (m, 23H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 137.44, 115.88, 84.36, 73.94, 60.38, 40.77, 28.84, 28.59, 23.27, 17.33, 14.20 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{34}NO_2^+$ [M + H^+]: 284.2584, found: 284.2587.

Alcohol **15**: Flash column chromatography (4 % EtOAc / hexanes) gave pure alcohol **15**

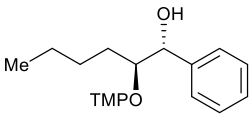


15

(79 % yield) as a colorless oil as well as a mixture of diastereomers (5 % yield) as a colorless oil. **15:** R_f = 0.42 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −8.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3497, 2929, 1461 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 5.06 (m, 1H), 4.91 (m, 1H), 4.51 (m, 1H), 3.96 (m, 1H) 2.15 (d, *J* = 4.0 Hz, 1H), 1.76 (s, 3H), 1.66 (m, 1H), 1.53 – 1.06 (m, 23H), 0,89 (t, *J* = 6.7 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.68, 111.37, 83.61,

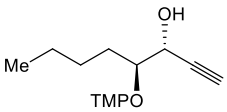
75.13, 74.87, 40.88, 29.28, 27.93, 23.39, 20.19, 17.33, 14.20 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{36}NO_2^+$ [M + H^+]: 298.2741, found: 298.2743.

Alcohol **16**: Flash column chromatography (4 % EtOAc / hexanes) gave pure alcohol **16** (73 % yield) as a colorless oil as well as a mixture of diastereomers (4 % yield) as a colorless oil. **16:** R_f = 0.34 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −7.9 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3484, 2930, 1464 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 5.22 (m, 1H), 4.06 (m, 1H), 2.41 (d, *J* = 4.2 Hz, 1H), 1.68 (m, 1H), 1.54 – 0.96 (m, 23H), 0.79 (t, *J* = 7.4 Hz, 3H)ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 128.11, 127.02, 126.52, 86.47, 73.62, 40.88, 29.07, 27.45, 23.24, 17.36, 14.09; HRMS (ESI-QTOF) calcd for $C_{21}H_{36}NO_2^+$ [M + H^+]: 334.2741, found: 334.2743.

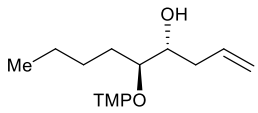


16

Alcohol **17:** Flash column chromatography (4 % EtOAc / hexanes) gave pure alcohol **17** (67 % yield) as a light yellow oil as well as a mixture of diastereomers (16 % yield) as a light yellow oil. **17:** R_f = 0.36 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −33.4 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3583, 3303, 2934, 2306, 1467 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 4.83 (s, 1H), 4.64 (s, 1H), 4.25 (m, 1H), 2.45 (s, 1H), 1.78 (m, 1H), 1.64 – 1.05 (m, 23H), 0.92 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): 83.11, 81.69, 74.58, 66.20, 61.36, 60.80, 40.95, 40.68, 35.01, 34.21, 30.08, 28.61, 23.15, 20.71, 17.26, 14.16 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{32}NO_2^+$ [M + H^+]: 282.2428, found: 282.2429.

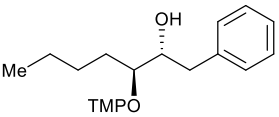


17



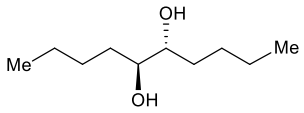
18

Alcohol **18**: Prepared by the above method. Flash Column Chromatography (5% EtOAc / hexanes) gave diol **18** as an inseperable mixture of diastereomers (262mg, 88% yield, 1.4:1 mixtures of diastereomers) as colorless oil. **18:** R_f = 0.33 (5% EtOAc / hexanes); $[\alpha]_D^{23}$ = –27.4 (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3429, 2928, 2871, 1640 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.33 (brs, 1H), 5.98–5.93 (m, 1H), 5.16–5.01 (m, 2H), 4.02–3.85 (m, 2H), 2.26 (m, 1H), 2.09 (m, 1H), 1.93–1.04 (m, 24H), 0.91 (t, *J*= 7.4 Hz, 3H) ppm ; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.2, 116.5, 82.9,74.8, 61.7, 60.2, 40.5, 37.0, 32.1, 28.9, 23.1, 20.7, 17.3, 14.1 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{36}NO_2^+$ [M + H^+]: 298.2746, found: 298.2742.



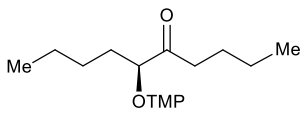
19

Alcohol **19**: Prepared by the above method. Flash Column Chromatography (3% EtOAc / hexanes) gave alcohol **19** (174 mg, 50% yield) as an colorless oil and mixture of diastereomers (76 mg, 22% yield, 3.4:1 mixture diastereomers). **19:** R_f = 0.30 (4 % EtOAc / hexanes); $[\alpha]_D^{23}$ = –10.8 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3480, 3028, 2928 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.6 Hz, 2H), 7.27 (m, 2H), 7.21 (tt, *J*= 7.3, 1.3 Hz, 1H), 4.23 (m, 1H), 3.95 (dt, *J* = 6.0, 2.3 Hz, 1H), 2.83–2.73 (m, 2H), 2.05 (d, *J* = 5.8 Hz, 1H), 1.90 (m, 1H), 1.64–1.28 (m, 11H), 1.20 (brs, 3H), 1.14 (brs, 6H), 1.09 (brs, 3H), 0.93 (t, *J*= 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.6, 129.4, 128.5, 126.3, 84.4, 73.3, 40.8, 39.1, 29.1, 28.8, 23.4, 17.4, 14.3 ppm; HRMS (ESI-QTOF) calcd for $C_{22}H_{38}NO_2^+$ [M + H^+]: 348.2903, found: 348.2900.



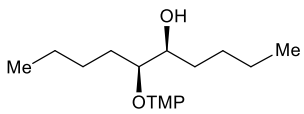
12

Diol **12:** To a solution of alcohol **11** (240 mg, 0.77 mmol, 1.0 equiv., 12:1 mixture of diastereomers) in 5 mL of a 3:1:1 solvent mixture (HOAc:H_2O:THF) was added zinc (500mg, 7.7 mmol, 10 equiv.). The reaction mixture was stirred at 70 °C for one hour. After cooling, the reaction mixture was filtered through Celite, concentrated, and azeotroped dried with toluene to give a white solid. Flash column chromatography (30 % EtOAc / hexanes) gave known diol **12**[21] (102 mg, 76 % yield, 18:1 mixture of diastereomers) as a white solid.



20

Ketone **20:** To a solution of alcohol **11** (266 mg, 0.85 mmol, 1.0 equiv.) in 3 mL of THF was added a solution of IBX (309 mg, 1.11 mmol, 1.3 equiv.) in 1 mL of DMSO. The reaction mixture was stirred for 1.5 hours, then diluted with 50 mL of ether and filtered. The organic phase was washed with water (3 × 50 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated to give a colorless oil. Flash chromatography (3% EtOAc / hexanes) gave ketone **20** (251 mg, 95% yield) as a colorless oil. **20**: R_f = 0.31 (3% EtOAc / hexanes); $[\alpha]_D^{23}$ = –16.6 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 2930, 1713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 4.14 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.66 (ddd, *J* = 18.0, 8.8, 6.3 Hz, 1H), 2.46 (ddd, *J* = 18.0, 8.5, 6.3 Hz, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 1.56 (m, 3H), 1.43 (m, 4H), 1.38–0.94 (m, 19H), 0.92 (t, *J*= 7.4 Hz, 3H) ppm, 0.87 (t, *J*= 7.3 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 212.6, 91.2, 40.5, 39.2, 31.5, 26.7, 25.2, 22.9, 22.6, 17.3, 14.08, 14.05ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{38}NO_2^+$ [M + H^+]: 312.2903, found: 312.2900.



21

Alcohol **21:** Ketone **20 (**230 mg, 0.74 mmol, 1.0 equiv.**)** in 4.0 mL Ethanol at 0 °C was added $NaBH_4$ (42 mg, 1.11 mmol, 1.5 equiv.). The reaction mixture was stirred for one hour, then diluted with ether (50 mL), washed with saturated NH_4Cl (50 mL), water (50 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give a colorless orange oil. Flash chromatography (5% EtOAc/ Hexanes) gave alcohol **21** as an inseperable mixture of diastereomers (208 mg, 90% yield, 1.7:1 mixtures of diastereomers). **21**: R_f = 0.27 (5% EtOAc / hexanes); $[\alpha]_D^{23}$ = 44.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3214, 2928, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.31 (brs, 1H), 3.92–3.82 (m, 2H), 1.66–1.07 (m, 30H), 0.92 (t, *J*= 7.0 Hz, 3H), 0.90 (t, *J*= 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 83.5, 75.1, 61..7, 60.2, 40.5, 40.0, 33.7, 32.2, 30.7, 28.7, 27.7, 27.1, 23.14, 23.07, 20.7, 17.3, 14.26, 14.19 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{40}NO_2^+$ [M + H^+]: 314.3059, found: 314.3059.

References

1. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

2. Selected methods featuring chiral auxiliaries: (a) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753(b) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961. (c) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591.

3. Selected methods featuring chiral small molecule catalysts: (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) Yoshikawa, N.; Suzuki, T.; Shibasaki, M. *J. Org. Chem.* **2002**, *67*, 2556. (c) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., In t. Ed.* **2004**, *43*, 2152. (d) Denmark, S. E.; Chung, W.-j. *Angew. Chem., Int. Ed.* **2008**, *47*, 1890.

4. Enzymatic method: Fessner, W.-D.; Sinerius, G.; Schneider, A.; Dreyer, M.; Schulz, G. E.; Badia, J.; Aguilar, J. *Angew. Chem., Int. Ed.* **1991**, *30*, 555.

5. Selected methods featuring chiral auxiliaries: (a) Barrett, A. G. M.; Malecha, J. W. *J. Org.Chem.* **1991**, *56*, 5243. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (c) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686. (d) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 105. (e) Hunt, J. A.; Roush, W. R.*J. Org. Chem.* **1997**, *62*, 1112. (f) Yamamoto, Y.; Miyairi, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem.* **1999**, *64*, 296. (g) Chen, M.; Handa, M.; Roush, W. R. *J. Am. Chem. Soc.* **2009**, *131*, 14602.

6. Method featuring chiral catalyst: Han, S. B.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1760 – 1761.

7. (a) Cram, D. J.; Elhafez, F. A. A.; *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *9*, 2199. (c) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Dâu, M.-E. T. H. *J. Am. Chem. Soc.* **1973**, *95*, 6146.

8. (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265. (b) Banfi, L.; Bernardi, A.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1984**, *49*, 3784. (c) Iio, H.; Mizobuchi, T.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1986**, *27*, 6373. (d) Savall, B. M.; Powell, B. M.; Roush, W. R. *Org. Lett.* **2001**, *3*, 3057. (e) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441.

9. (a) El-Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017 – 3020. (b) Marshall, J. A., Eidam, P. *Org. Lett.* **2004**, *6*, 445 – 448.

10. Luanphaisarnnont, T.; Ndubaku, C. O.; Jamison, T. F. *Org. Lett.* **2005**, *7*, 2937.

11. Selected recent examples: (a) O'Sullivan, T. P.; Vallin, K. S. A.; Shah, S. T. A.; Fakhry, J.; Maderna, P.; Scannell, M.; Sampaio, A. L. F.; Perretti, M.; Godson, C.; Guiry, P. J. *J. Med. Chem.* **2007**, *50*, 5894. (b) Garbe, L.-A.; Morgenthal, K.; Kuscher, K.; Tressl, R. *Helv. Chim. Acta* **2008**, *91*, 993. (c) Singh, S.; Guiry, P. J. *J. Org. Chem.* **2009**, *74*, 5758. (d) Show, K.; Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1212.

12. (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687.

13. (a) Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763. (b) Albrecht, L. ; Jiang, H.; Dickmeiss, G.; Gschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188.

14. (a) Park, J. K.; McQuade, D. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 2717. (b) Kim, D.; Lee, J. S.; Kong, S. B.; Han, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 4203.

15. (a) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (b) Arai, T.; Mizukami, T.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 1145. (c) Hartung, J.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3885.

16. a) Zhong, G. *Angew. Chem. Int. Ed*. **2003**, *42*, 4247 – 4250. b) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808 – 10809. c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tettrahedron Lett.* **2003**, *44*, 8293 – 8296.

17. Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914 – 8915.

18. a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124 – 4125. b) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 6638-6641. c) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 10012 – 10014. d) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 58 – 61.

19. Boger, D. L.; Garbaccio, R. M.; Jin, Q. J. *J. Org. Chem*. **1997**, *62*, 8875 – 8891.

20. Plietker, B. *Org. Lett.* **2004**, *6*, 289 – 291.

21. Rosatella, A. A.; Afonso, C. A. M. *Adv. Synth. Catal.* **2011**, *353*, 2920 – 2926.

22. Abeykoon, G. A.; Chatterjee, S.; Chen, J. S. *Org. Lett.* **2014**, *16*, 3248 – 3251.

CHAPTER 3

TOTAL OF SYNTHESIS OF OXYLIPINS ISOLATED FROM *Dracontium loretence*

Published in part in *Org. Lett.*[*]

Manuscript in preparation

Introduction

Oxylipins are a class of oxygenated secondary metabolites of fatty acids. These have wide range of distribution and functions in aerobic organisms.[1] Among the linear oxylipins isolated from the Peruvian plant *Dracontium loretense,* fatty acid **1** has shown immunostimulatory properties whereas fatty acid **2** is biologically inactive (Figure 1).[2]

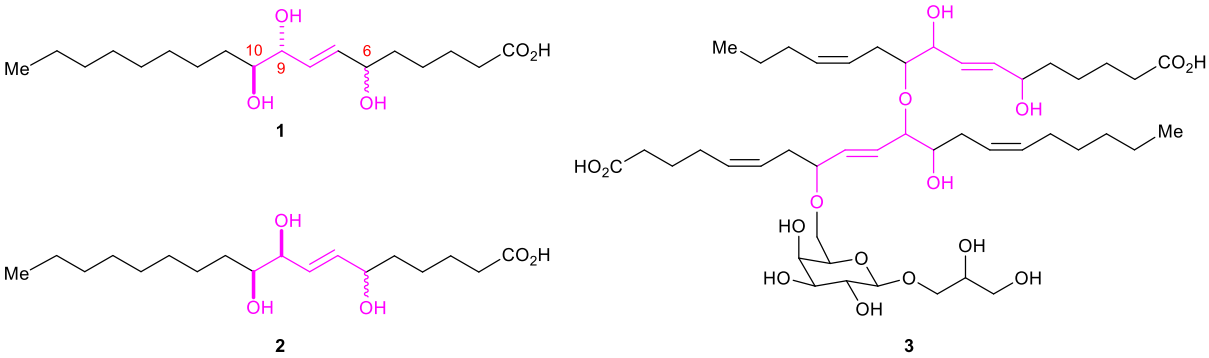


Figure 1. Linear oxylipins isolated from *Dracontium loretence* (**1** and **2**) and Nigricanoside A (**3**), which share the same 3-ene-1,2,5 triol moiety

Unique structure and impressive biological activity of Nigricanoside A **3** (Figure 1) drew our attention as a synthetic target.[3] Both Nigricanoside A and oxylipin **1** and **2** share the same 3-ene-1,2,5 triol moiety. Moreover, our synthetic methodology to access differentially protected *anti*-1,2-diols from α-oxyaldehydes could be very useful in the

[*]*Org. lett*. **2014**, *16*, 32.

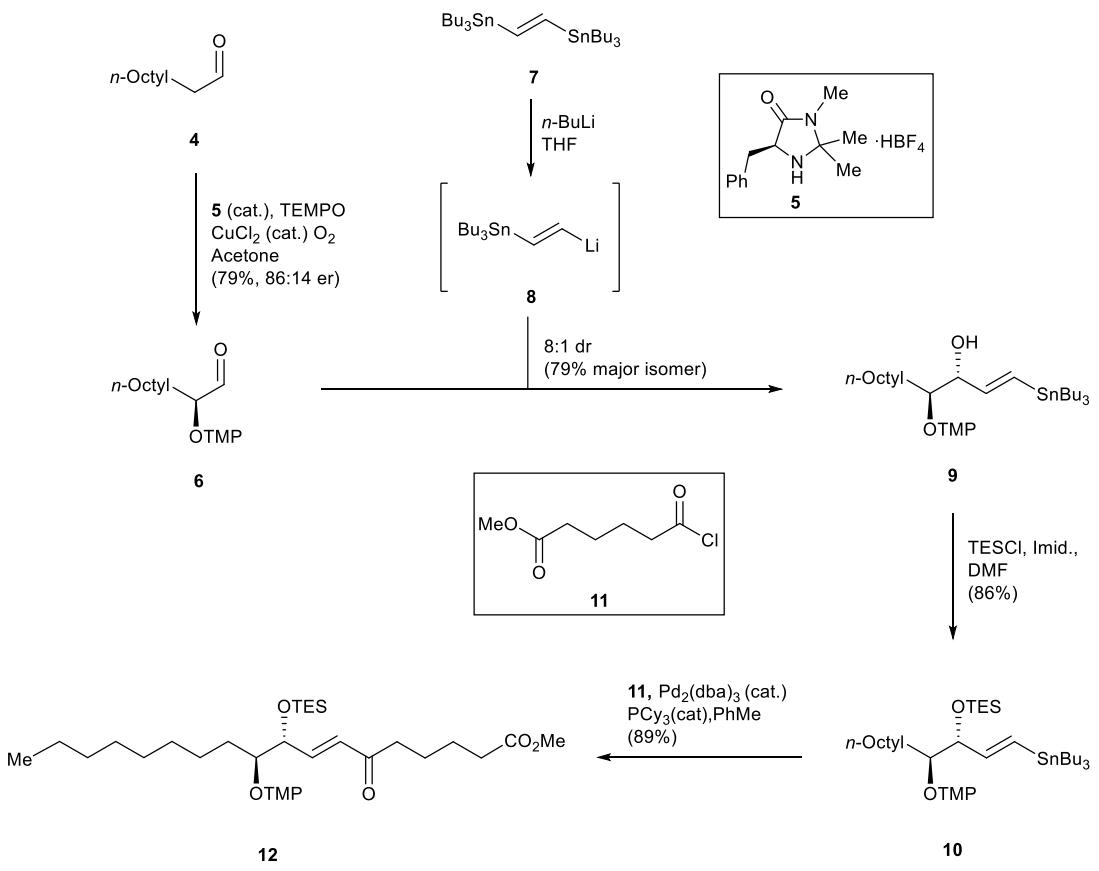
synthesis of ether linkages between the fatty acid chains in Nigricanoside A . Therefore, these oxylipins can be used as a model system for the total synthesis of Nigricanoside A. Furthermore, isolation chemists were only able to assign relative stereochemistry of the C-9 and C-10 chiral centers of oxylipins **1** and **2**. But the configuration of the chiral center at C-6 has not been determined.[2] Therefore, such a total synthesis to access all possible diastereomers of oxylipins could lead to the absolute stereochemical determination of oxylipins isolated from *Dracontium loretense*.

Lack of stereoflexibility is one of the common features of all five reported total syntheses of this natural product.[4] Since, the previous syntheses did not lead to an unambiguous stereochemical assignment of naturally occurring oxylipins, our goal was to develop a stereochemically flexible route to access all the diastereomers of oxylipins so as to assign the absolute stereochemistry unambiguously.

Results and Discussion

First generation synthesis

We envisioned the incorporation of our methodology in the synthesis of *anti*-1,2-diols from α-oxyaldehydes (chapter 2) in the total synthesis of oxylipins. α-Oxygenation of aldehydes via organocatalytic enantioselective oxidative incorporation of TEMPO[5] was used to set the first chiral center with the hope of setting the second chiral center employing a substrate-controlled Grignard addition (Scheme 1).



Scheme 1. Synthesis of enone **12**

We could have used the more sterically demanding, expensive tryptophan-based chiral imidazolidinone[5d] as the catalyst in the α-oxygenation of decanal **4** for superior enantioselectivity. But the lengthy synthesis of the tryptophan-based imidazolidinone and the subsequent enantio-enriching step (chiral enone reduction) in the synthesis justified our decision to choose phenylalanine-based imidazolidinones **5**, despite their moderate enantioselectivity in α-oxygenation . Under the oxidative co-catalytic influence of $CuCl_2$, imidazolidinone **5** catalyzed the enantioselective α-oxygenation of decanal **4** to give α-oxyaldehyde **6** in 79% yield with 84:14 er (20 mmol scale, 20 mol% loading of **5**). Lithiation of distanane **7** and addition of lithio intermediate **8** to aldehyde **6** gave an 8:1

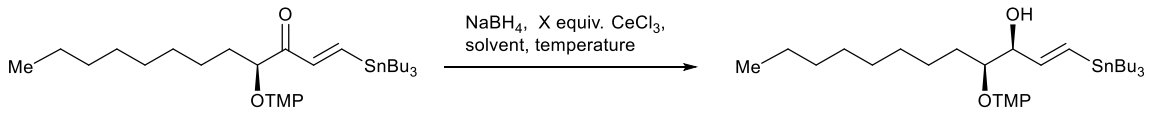
chromatographically separable mixture of diastereomers of masked 1,2-diol **9** in 89% yield. The major product, *anti* 1,2-diol **9** was isolated in 79% yield without degrading the initial enantioselectivity. Moreover, the scalability of this Grignard addition (15 mmol) was one of the advantages in the synthesis. Furthermore, careful deoxygenation of disatannane **7** was found out be critical for the generation of lithio species **8.** Silyl ether protection of alcohol **9** followed by Stille cross coupling[6] with acid chloride **11** gave enone **12** in 77% yield over two steps.

The 1,2-diol technology that we developed (chapter 2) could not generate *syn*-1,2-diols directly via chelation control. However, an oxidation-reduction sequence can be used to epimerize the free alcohol moiety of *anti*-1,2-diol **9**. Since polar Felkin-Ahn control predominates in this system, hydride addition to the corresponding ketone **13** should occur from the least hindered side resulting in *syn*-1,2-diol **14**. Upon oxidation, alcohol **9** afforded enone **13** in 96% yield.

Our design plan was to use the Luche reduction[7] to reliably deliver masked *syn* 1,2-diol **14**. At 0 °C in MeOH, use of stoichiometric $CeCl_3$ (1 equiv.) in the Luche reduction led to better diastereoselectivity and yield than when a catalytic amount of $CeCl_3$ (0.2 equiv.) is used (Table 1). However, the 1,4 reduction product was found to be the major side product of these reductions. Further, decreasing the temperature to -20 °C in MeOH improved the diastereomeric ratio while retaining the former yield. However, poor solubility of the enone **13** was observed in MeOH due to the nonpolar tributyltin moiety. To address the solubility issue of enone **13** EtOH was used as a solvent. Although, enone **13** was completely soluble in EtOH, surprisingly no selectivity was observed in the reduction at -20 °C (*syn*:*anti* 1.2:1),. Since MeOH is an essential

component for the retention of a high diastereoselectivity, mixed solvents containing MeOH were further screened. The Luche reduction in a MeOH:hexanes (3:1) solvent mixture gave a mixture of diastereomers of alcohol **14** in 60% yield, with high dr (13:1). However, the Luche reduction in MeOH:THF (3:1) at -20 °C gave alcohol **14** in 70% yield with 11:1 dr. Despite the improved yields of the desired product in mixed solvents, a major side product was the 1,4 reduced product of enone **13**. Due to the high yield, the MeOH:THF (3:1) solvent mixture was chosen as the solvent combination for the further optimization of the 1,2-reduction of enone. Moreover, to suppress the 1,4 reduction of enone **13**, $CeCl_3$ loading was raised to 2 equivalents. To our delight conjugate reduction of the enone was found to be further suppressed, and the yield of alcohol **14** (82%) was increased while improving the diastereoselectivity (18:1).

Table 1. Optimization of Luche reduction of enone **13**

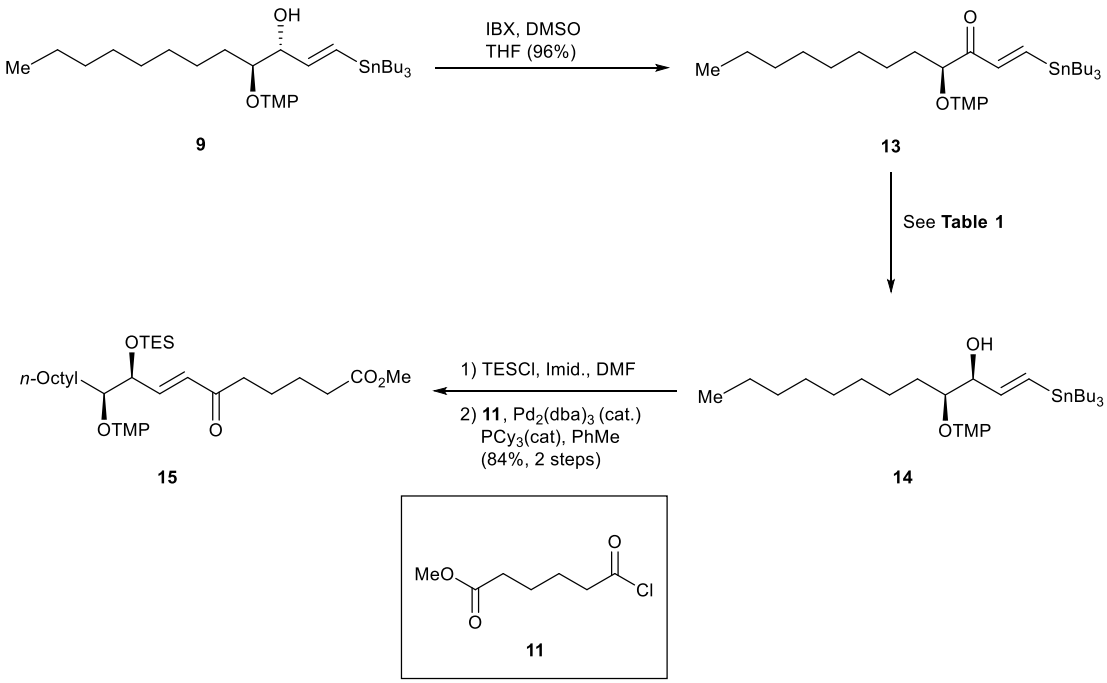


13 **14**

solvent	Temp (°C)	$CeCl_3$ (equiv.)	dr[a]	Yield[b] (%)
MeOH	0	0.2	6:1	40
MeOH	0	1	7:1	55
MeOH	-20	1	10:1	54
EtOH	-20	1	1.2:1	45
MeOH: hexanes (3:1)	-20	1	13:1	60(52)[c]
MeOH:THF (3:1)	-20	1	11:1	70(62)[c]
MeOH:THF (3:1)	-20	2	18:1	88(82)[c]

[a]Determined by analysis of crude ^{1}H NMR. [b]Combined yield of both diastereomers, determined by analysis of crude ^{1}H NMR in the presence of an internal standard. [c]Isolated yield of major diastereomer.

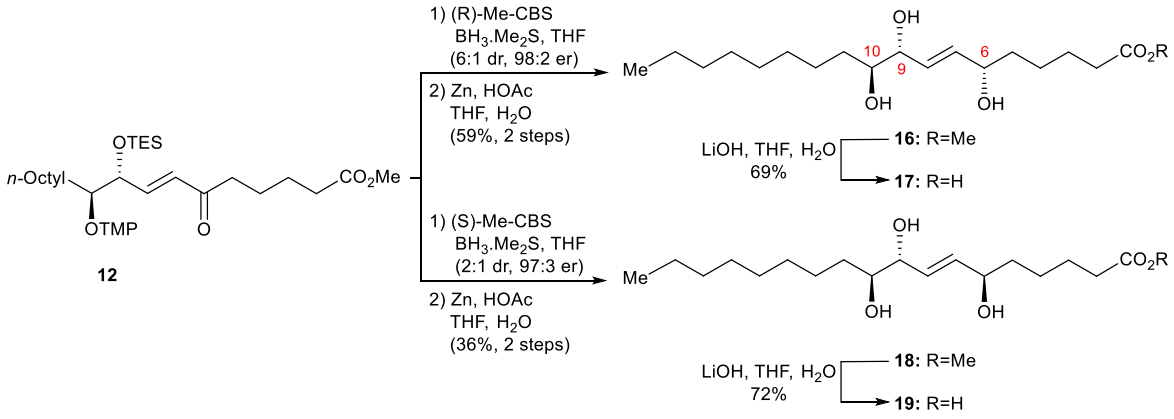
The silyl protection of alcohol **14** followed by Stille cross coupling with acid chloride **11** furnished enone **15** in 84% yield over two steps (Scheme 2).



Scheme 2. Synthesis enone **15**

Having furnished the carbon back bone, the final chiral center of the natural product was planned to be achieved by asymmetric ketone reduction, with the hope of further enantio-enrichment. Chiral Me-CBS-oxazoborolidinone ligand with borane-dimethyl sulfide complex was used in the diastereoselective reduction of enone **12**.[8] Although, better diastereoselectivity and also better isolated yields were observed for *R*-Me-CBS chiral ligand (6:1 dr), poor diastereoselectivity and yield were observed with the *S*-Me-CBS ligand (2:1 dr) due to unfortunate substrate bias (Scheme 3). Zn mediated reductive unmasking of the TMP group also deprotected the silyl protecting group in one

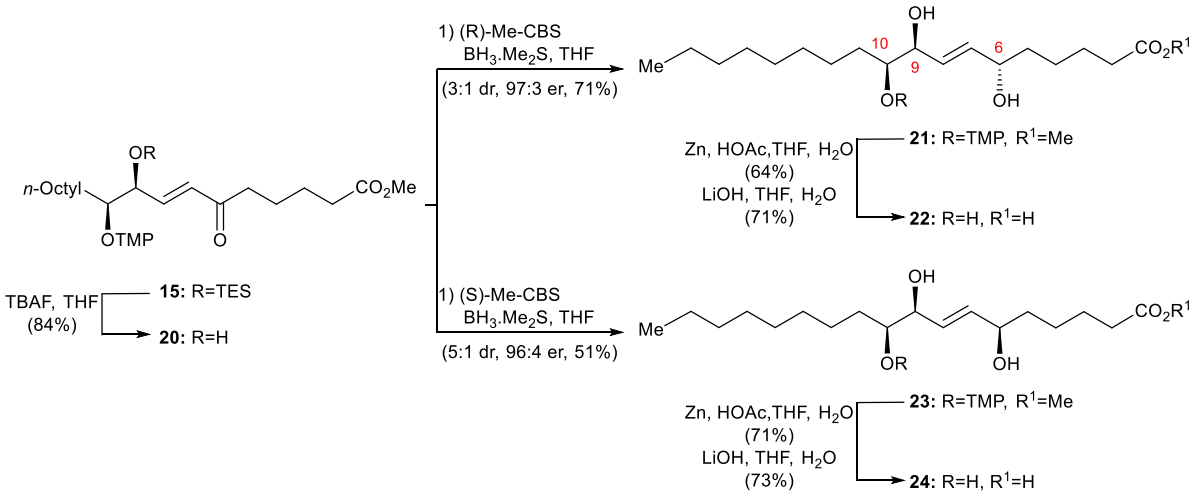
step to afford a single diastereomer of triol **16** in 59% yield over two steps with enriched enantioselectivity (98:2 er). Similarly, a single diastereomer of triol **18** was also obtained in 36% yield over two steps and 97:3 er. Basic hydrolysis of methyl esters gave the C-6 epimeric natural product **17** and **19**, which contain the *anti*-1,2-diol moiety (69% and 72% yield respectively). Although, our seven step is the shortest synthesis compared to the synthesis of related oxylipins containing the *anti*-1,2-diol moiety, it is tied with Kuwahara's pinellic acid (another class of oxylipin) synthesis[9] for the shortest synthesis of oxylipins containing the 3-ene-1,2,5-triol moiety.



Scheme 3. Synthesis of oxylipins with *anti* 1,2-diol moiety

For the enone **15,** optimum diastereoselectivity for the CBS reduction was observed when the silyl deprotected enone **20** was used (Scheme 4). Asymmetric reductions of enone **20** using *R*-Me-CBS and *S*-Me-CBS oxazaborilidinone yielded a 3:1 and 5:1 mixture of diastereomers which gave a single diastereomer of enol **21** (71% yield, 97:3 er) and **23** (51% yield, 96:4 er), respectively. Subsequent reductive cleavage

of the TMP masking group followed by ester hydrolysis furnished the C-6 epimeric natural products **22** and **24** with *syn* 1,2-diol moiety (45% and 52% yields over two steps respectively).



Scheme 4. Synthesis of oxylipins with *syn* 1,2-diol moiety

After furnishing all the possible diastereomers of oxylipins isolated from *Dracontium loretense*, the stage was set for the assignment of absolute stereochemistry of the naturally occurring oxylipins. Comparison of the NMR data taken in methanol and optical rotation of our synthetic oxylipins with what is reported by the isolation chemists led to the absolute stereochemical determination. The absolute stereochemistry of the immunostimulatory natural oxylipin **1** contain *anti*-1,2-diol moiety was found to be (6R,9S,10R) and it is the enantiomer of oxylipin **17**. Furthermore, the absolute stereochemistry of the bio-inactive oxylipins **2** with *syn*-1,2-diol moiety was found to be (6R,9S,10S)-**24.** Moreover, these naturally occurring oxylipins are C-10 epimers of each other.

Second generation synthesis

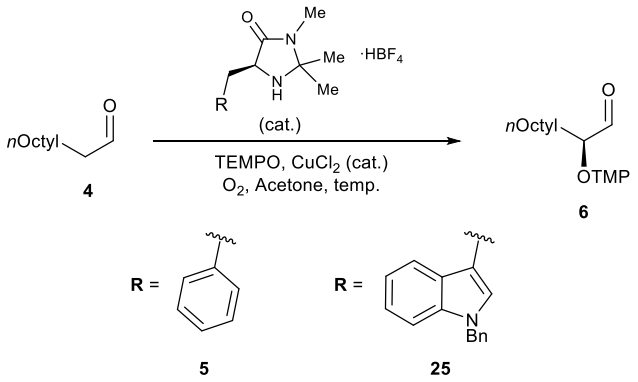
Our first generation total synthesis of oxylipins was designed with the hope of extending the synthetic methodology to access alkyl chains of the Nigricanoside A. The presence of alkene moieties in Nigricanoside A did not allow the incorporation of olefin metathesis into the model synthesis. Otherwise, our first generation total synthesis of oxylipins would have been even shorter. In 2015, Nigricanoside A was synthesized and found not to have the previously reported bioactivity. Since we are not interested in Nigricanoside A anymore, we redesigned the oxylipin synthesis to become even shorter and more efficient by incorporation of convergency via olefin metathesis and by removal of additional masking groups.

In our previous oxylipins synthesis we have used HBF_4 salt of phenylalanine based chiral imidazolidinone catalyst **5** in organocatalytic, enantioselective α-oxygenation of decanal **4**.[10] Subsequent chiral enhancing step from CBS reduction in the oxylipin synthesis and a laborious 5 step synthesis of the tryptophan based sterically demanding imidazolidinone **25** led us to use more accessible phenylalanine based chiral imidazolidinone **5** despite of the moderate enantioselectivity in the α-oxygenation. Our significantly shorter oxylipins synthesis and the demand for superior enantioselectivity in the α-oxygenation step, led us to consider a more sterically demanding chiral imidazolidinone catalyst **25** despite its multi-step synthesis.[5d] Salts of tryptophan-based chiral imidazolidinone **25** were our default choice because it is the optimum catalyst in MacMillan's aldehyde α-oxygenation.[5d] Also, recently our group has successfully employed this tryptophan-based chiral imidazolidinone **25** as the catalyst in the enantiomeric enrichment in catalytic, enantioselective α,β,γ-trioxygenation of enals.[11]

The HBF_4 salt of the tryptophan-based imidazolidinones **25** in acetone at -10 °C gave superior enantioselectivity and yield compared to phenylalanine-based imidazolidinone **5** (Table 2). Fast reaction rates (20 mol% of **25**, 6 hours), high yields, and the lengthy synthesis of catalyst **25** encouraged us to screen lower catalyst loadings. It was found that the catalyst loading can be lowered up to 5 mol% when using imidazolidinones **25** with no meaningful decrease in enantioselectivity (89:11 er) or yield. Screening lower temperature revealed that enantioselectivity at 5 mol% catalyst loading can be further improved when the temperature was lowered to -10 °C. At this catalyst loading, the yield suffered when the temperature was decreased further. Further decreasing the catalyst loading to 2 mol% at 0 °C decreased the yield significantly but highest turnover number (40.0) for the catalyst was observed while retaining the enantioselectivity. Further lowering of temperature to -10 °C at 2 mol% catalyst loading decreased the yield although the excellent enantioselectivity was retained.

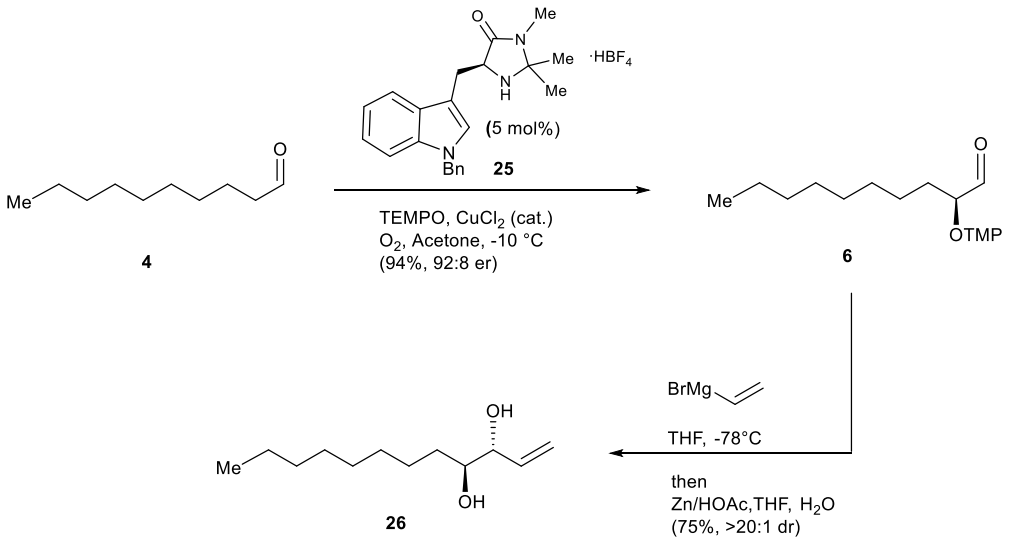
Diol **26** was synthesized in 75% yield with high diastereoselectivity[10] after vinyl Grignard addition to aldehyde **6** and reductive cleavage of the TMP masking group (Scheme 5).

Table 2: Optimization of α-oxygenation[a]



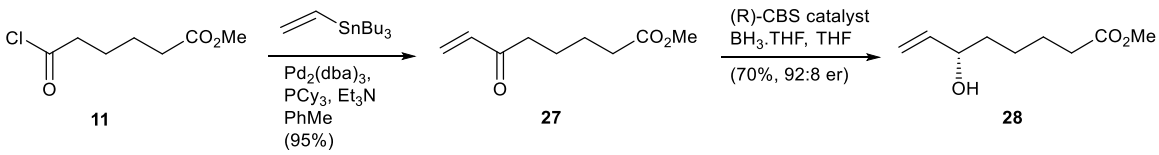
R	cat. loading	temp (°C)	yield[b] (%)	er[c]	turnover number
5	20	-10	90	88:12	4.5
25	20	0	96	92:8	4.8
25	10	0	94	88:12	9.4
25	5	0	92	89:11	18.4
25	5	-10	94	92:8	18.8
25	2	0	80	91:9	40.0
25	2	-10	66	92:8	33.0

[a]2 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC analysis.



Scheme 5. Two step synthesis of diol **27**

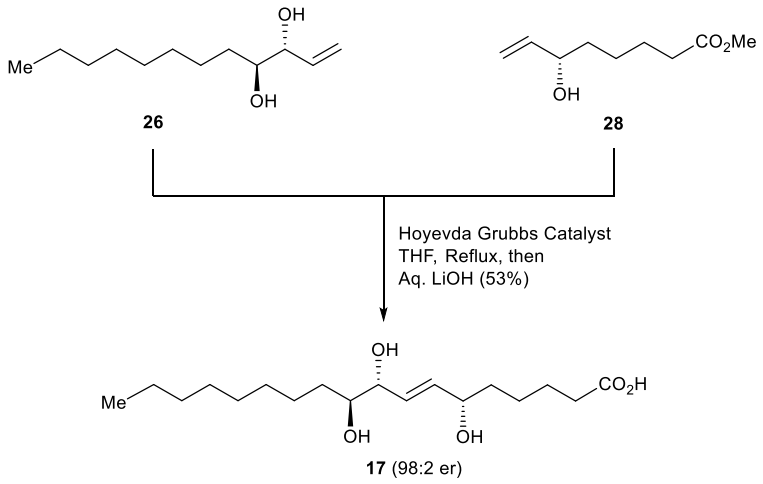
Among the methods[12-14] used to access allylic alcohol **28** in literature, we explored the enantioselective vinyl bromide addition to methyl-6-oxohexanoate mediated by chiral methylephedrines. Since the vinyl bromide additions did not lead to promising results, we chose enantioselective ketone reductions to furnish allylic alcohol **28**. A Stille cross coupling between tributylvinylstannane and acid chloride **11** followed by diastereoselective reduction of enone **27** using BH_3.THF and *R*-Me-CBS-oxazoborolidinone as the chiral ligand furnished allylic alcohol **28** in 92:8 er and 67% yield in two steps (Scheme 6). The 1,4 conjugate addition product of enone **28** was the major product in other enone chiral reduction including Noyori reduction[13] and chiral hydride reductions mediated by chelating BINOL ligands.[15]



Scheme 6. Two step synthesis of allylic alcohol 28

Having both alkene partners in hand, the stage was set for the olefin metathesis to construct the carbon back bone of the natural product. As secondary allylic alcohols both alkene partners **26** and **28** are expected behave as type II alkenes. The olefin metathesis was expected to be challenging because their homodimers are sparingly consumable.[16] Surprisingly, under olefin metathesis conditions allylic alcohol **28** was found to behave as a type I alkene, undergoing rapid homodimerization, though alkene **26** behaved as a type II alkene as expected. However, chromatographic purification of the desired adduct from

homodimers was a nightmare when allylic alcohol **28** was used in excess. Therefore, diol **26** which is made in high yields in catalytic steps was used in excess in the olefin metathesis to address the purification issue. Olefin metathesis between alkene **26** and **28** followed by in situ ester hydrolysis furnished a single diastereomer of oxylipins **17** in 53% yield (98:2 er) (Scheme 7). Our current three step synthesis is the shortest and most efficient (33% overall yield) route to any oxylipin with the 3-ene-1,2,5-triol moiety.



Scheme 7. Synthesis of oxylipin **17** via olefin metathesis

Conclusion

In conclusion, we further improved the Macmillan's existing protocol for enantioselective organocatalytic α-oxygenation of simple aldehydes by optimizing the reaction to utilize lower catalyst loadings. Our 5 mol % loading (i.e. one fourth of the organocatalyst loading compared to Macmillan's condition) of chiral imidazolidinones is the lowest ever reported loading in the oxidative incorporation of TEMPO in organocatalytic α-oxygenation with excellent yield and ee.

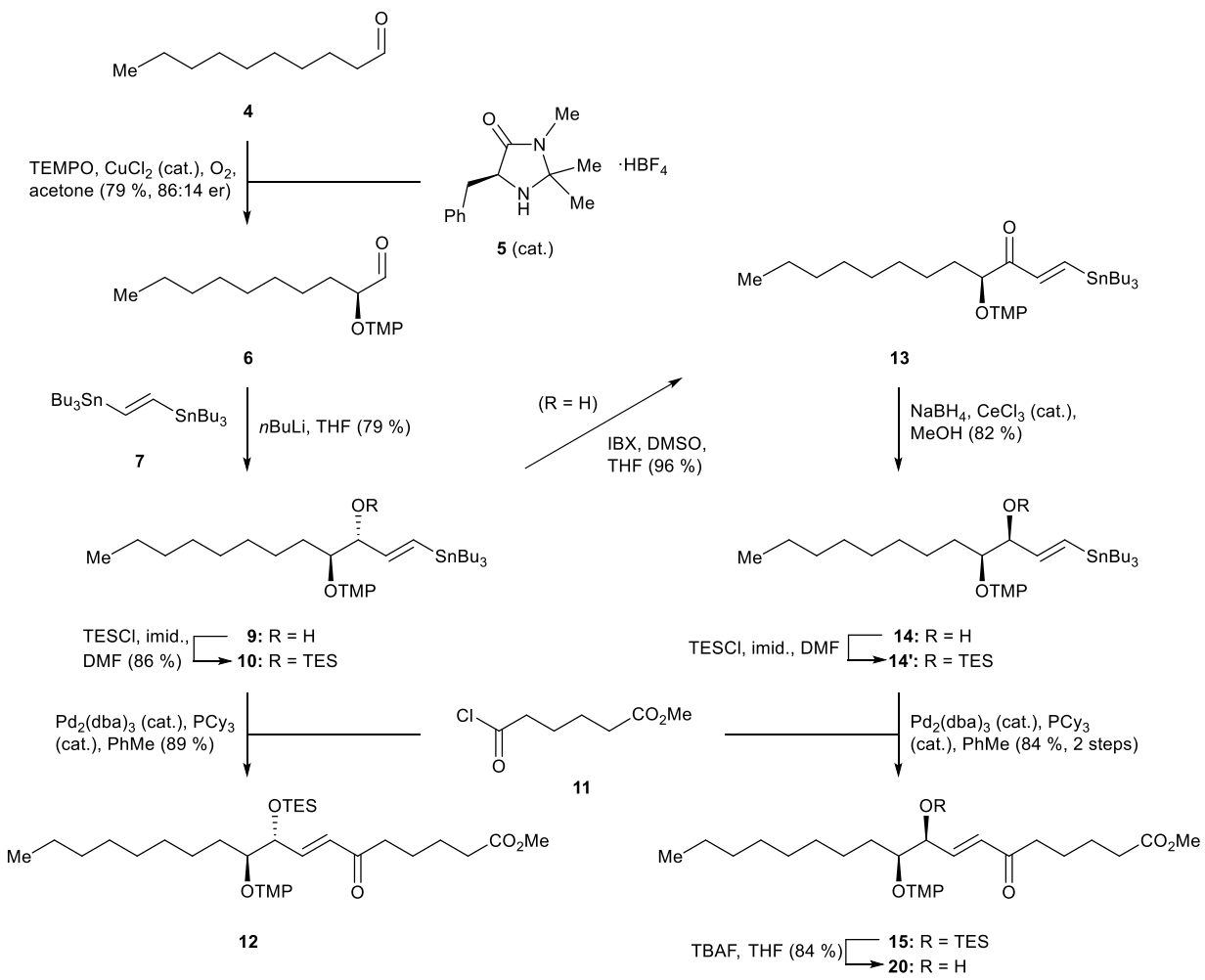
Utilizing our *anti*-1,2-diol technology, all possible diastereomers of oxylipins isolated from *Dracontium loretense* were synthesized in our first generation synthesis. Moreover, our total synthesis led to an unambiguous stereochemical assignment of the natural oxylipins. Incorporation of olefin cross metathesis in the convergent synthesis led to an efficient 3-step second generation synthesis, which is not only the shortest but also the synthesis with highest overall yield of oxylipins containing the 3-ene-1,2,5 triol moiety.

Experimental

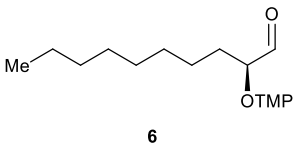
General procedures

Unless otherwise noted, all reactions were performed with stirring under an argon atmosphere under anhydrous conditions. Organomagnesium and -lithium reagents were purchased from Aldrich. All other reagents were purchased at the most-economical grade. Dry tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), dichloromethane, and toluene were obtained by passing HPLC grade solvents through commercial solvent purification systems. All other chemicals were used as received, without purification. Flash column chromatography was performed using Grace Davison Davisil silica gel (60 Å, 35 – 70 μm). Unless otherwise noted, yields refer to chromatographically- and spectroscopically- (^{1}H NMR) homogeneous samples of single diastereomers. Thin-layer chromatography (TLC) was performed on Grace Davison Davisil silica TLC plates using UV light and common stains for visualization. NMR spectra were calibrated using residual undeuterated solvent as an internal reference. Apparent couplings were determined for multiplets that could be deconvoluted visually.

Compounds of first generation synthesis



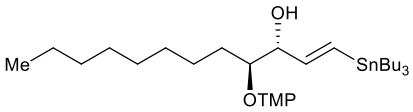
Scheme 8. Synthesis of eneone **12** and **20**



6

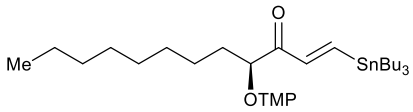
α-Oxyaldehyde 6: To a mixture of activated 4 Å molecular sieves (500 mg, powdered) and imidazolidinone catalyst **5** (1.22 g, 4 mmol, 0.2 equiv.) in 12 mL acetone was added $CuCl_2 \cdot 2H_2O$ (340 mg, 2 mmol, 0.1 equiv.). The green reaction mixture was stirred open to air for 5 minutes until the copper salt dissolved and the mixture turned dark orange.

The reaction was cooled to 0 °C for 10 minutes, then decanal (**4**; 3.92 mL, 20 mmol, 1.0 equiv.) was added dropwise over 2 minutes. The reaction was stirred at 0 °C for 10 minutes, then a solution of TEMPO (3.75 g, 24 mmol, 1.2 equiv.) in 6 mL of acetone was added dropwise over 3 minutes. The reaction mixture was capped with a rubber septum and an air inlet line was attached via an 18-gauge needle. The reaction was stirred at 0 °C for 24 hours, then partitioned between ether (50 mL) and saturated NH_4Cl (150 mL). The aqueous layer was extracted with ether (2 × 150 mL) and the combined organic layers were washed with brine (300 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give an orange oil. Flash column chromatography (3 % EtOAc / hexanes) gave α-oxyaldehyde **6** (4.83 g, 77 % yield) as a colorless oil. A sample was derivatized [1. $NaBH_4$, MeOH; 2. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 3. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 10 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 10.7 (major), 12.3 (minor) minutes] to have 86:14 er. Another sample was converted into (*S*)-1,2-decanediol (1. $NaBH_4$, MeOH; 2. Zn, AcOH, THF, H_2O) and its optical rotation was compared with that of the commercial substance in order to confirm the absolute configuration. **6:** R_f = 0.37 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −102.5 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 2931, 1727 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 9.77 (d, *J* = 4.5 Hz, 1H), 4.07 (dt, *J* = 9.8, 5.0 Hz, 1H), 1.73 (m, 1H), 1.65 (m, 1H), 1.48 – 1.41 (m, 4H), 1.37 – 1.22 (m, 14H), 1.20 – 1.10 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 204.8, 88.7, 60.7, 59.8, 40.3, 34.5, 33.9, 32.0, 30.1, 29.8, 29.5, 29.3, 24.4, 22.8, 20.5, 20.4, 17.3, 14.2 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{38}NO_2^+$ [M + H^+]: 312.2903, found: 312.2904.



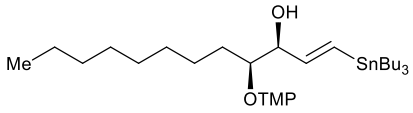
9

Vinylstannane 9: To a deoxygenated solution (3×freeze–pump–thaw) of *trans*-1,2-bis(tributylstannyl)ethene (**7**; 16.4 g, 27 mmol, 1.8 equiv.) in 50 mL of THF at 0 °C was added *n*BuLi (2.5 M in hexanes, 10.8 mL, 27 mmol, 1.8 equiv.) dropwise over 5 minutes. The resultant yellow solution was stirred at 0 °C for 30 minutes, cooled to –78 °C, then transferred by cannula to a deoxygenated solution (3 × freeze–pump–thaw) of aldehyde **9** (4.67 g, 15 mmol, 1.0 equiv.) in 15 mL of THF at –78 °C. The reaction was warmed to ambient temperature by removing the cooling bath, then partitioned between saturated NH_4Cl (50 mL) and EtOAc (50 mL). The organic phase was washed with water (2 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Flash column chromatography (2 % ether / hexanes) gave vinylstannane **9** (7.43 g, 79 % yield) as a colorless oil as well as epimeric vinylstannane **14** contaminated with a trace of vinylstannane **9** (752 mg, 8 % yield). A small sample was elaborated to oxylipin (6*R*,9*S*,10*S*)-**17** using a Luche reduction ($NaBH_4$, $CeCl_3$, MeOH) instead of a CBS reduction and determined to have 86:14 er. **9:** R_f = 0.35 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = +16.4 ° (*c* = 1.34, $CHCl_3$); IR (thin film): ν_{max} = 3683, 3019, 2928, 1465 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.19 (dd, *J* = 19.1, 1.0 Hz, 1H), 6.08 (dd, *J* = 19.2, 5.6, 1H), 4.39 (td, *J*= 5.0, 1.3 Hz, 1H), 3.98 (m, 1H), 2.47 (d, *J* = 6.9 Hz, 1H), 1.80 (m, 1H), 1.60 – 1.41 (m, 11H) 1.39 – 1.20 (m, 23H), 1.16 – 1.09 (m, 9H), 0.88 (m, 18H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.2, 129.2, 84.7, 76.3, 60.3, 40.8, 34.5, 32.0, 30.3, 29.7, 29.5, 29.3, 29.0, 27.5, 26.7, 22.8, 20.8, 20.6, 17.4, 14.3, 13.8, 9.6 ppm; HRMS (ESI-QTOF) calcd for $C_{33}H_{68}NO_2Sn^+$ [M + H^+]: 630.4272, found: 630.4308.



13

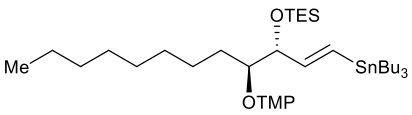
Enone 13: To a solution of vinylstannane **9** (654 mg, 1.04 mmol, 1.0 equiv.) in 3 mL of THF was added a solution of IBX (378 mg, 1.36 mmol, 1.3 equiv.) in 1 mL of DMSO. The reaction mixture was stirred for 1.5 hours, then diluted with 50 mL of ether and filtered. The organic phase was washed with water (3 × 50 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated to give enone **13** (627 mg, 96 %) as a yellow oil. **13**: R_f = 0.46 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = –88.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 2927, 1697, 1464 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 19.5 Hz, 1H), 6.99 (d, *J* = 19.5 Hz, 1H), 4.28 (dd, *J* = 9.9, 3.8 Hz, 1H), 1.89 (m, 1H), 1.74 (m, 1H), 1.59 – 1.06 (m, 39H), 1.04 – 0.91 (m, 9H), 0.87 (m, 12H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 198.8, 150.9, 142.2, 90.6, 59.8, 40.5, 34.0, 32.3, 32.0, 29.8, 29.5, 29.3, 29.2, 27.4, 24.5, 22.8, 20.4, 20.3, 17.3, 14.2, 13.8, 9.9 ppm; HRMS (ESI-QTOF) calcd for $C_{33}H_{66}NO_2Sn^+$ [M + H^+]: 628.4116, found: 628.4116.



14

Allylic alcohol 14. To a solution of enone **13** (700 mg, 1.11 mmol, 1.0 equiv.) in 2.7 mL of THF and 8.3 mL of MeOH was added $CeCl_3 \cdot 7H_2O$ (834 mg, 2.24 mmol, 2.0 equiv.). The reaction mixture was stirred for 15 minutes, then cooled to –20 °C. $NaBH_4$ (43 mg, 1.11 mmol, 1.0 equiv.) was added, and since TLC analysis showed remaining enone **13** additional $NaBH_4$ (22 mg, 0.56 mmol, 0.5 equiv.) was added. The reaction mixture was partitioned between ether (50 mL) and water (100 mL). The aqueous layer was extracted with ether (100 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to give a colorless oil.

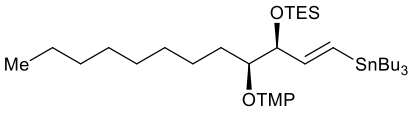
Flash column chromatography (2 % ether / hexanes) gave allylic alcohol **14** (573 mg, 82 % yield) as a colorless oil as well as epimeric allylic alcohol **9** (43 mg, 6 % yield). A small sample was elaborated to oxylipin (6*R*,9*S*,10*S*)-**24** using a Luche reduction ($NaBH_4$, $CeCl_3$, MeOH) instead of a CBS reduction and determined to have 86:14 er. **14:** R_f = 0.34 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = –20.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3576, 3018, 2925, 1465 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.48 (br s, 1H), 6.27 (d, *J* = 19.0 Hz, 1H), 5.87 (dd, *J* = 18.9, 6.4 Hz, 1H), 4.31 (t, *J* = 7.6 Hz, 1H), 3.87 (dt, *J* = 8.4, 2.5 Hz, 1H), 1.63 – 1.24 (m, 38H), 1.18 (br s, 3H), 1.13 (br s, 3H), 0.88 (t, *J* = 7.5 Hz, 18H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.5, 131.0, 82.8, 80.8, 61.8, 60.2, 40.5, 40.0, 34.6, 32.1, 32.0, 31.4, 30.0, 29.6, 29.4, 29.2, 27.4, 25.6, 22.8, 17.3, 14.2, 13.8, 9.6ppm; HRMS (ESI-QTOF) calcd for $C_{33}H_{68}NO_2Sn^+$ [M + H^+]: 630.4272, found: 630.4286.



10

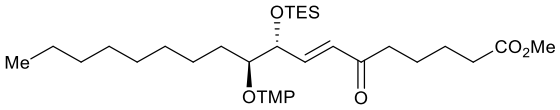
Silyl ether 10: To a solution of alcohol **9** (1.25 g, 2 mmol, 1.0 equiv.) and imidazole (204 mg, 3 mmol, 1.5 equiv.) in 8 mL of DMF was added TESCl (402 µL, 2.4 mmol, 1.2 equiv.) dropwise over 2 minutes. The reaction mixture was stirred for 45 minutes, then partitioned between water (50mL) and ether (100 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated to give a colorless oil**.** Flash column chromatography (1 % ether / hexanes) gave silyl ether **10** (1.48 g, 86 % yield) as a colorless oil. **10:** R_f = 0.56 (5 % EtOAc / hexanes); $[\alpha]_D^{23}$ = –17.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3054, 2957, 1421 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.10 (dd, *J* = 19.0, 6.8 Hz, 1H), 6.03 (d, *J* = 19.2 Hz,

1H), 4.20 (dd, *J* = 6.4, 2.7 Hz, 1H), 3.83 (m, 1H), 1.94 (m, 1H), 1.62 – 1.13 (m, 37H), 1.07 (m, 6H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.88 (t, *J* = 7.4 Hz , 18H), 0.59 (q, *J* = 7.8 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 149.4, 128.6, 86.3, 79.3, 60.9, 59.4, 40.6, 34.6, 32.1, 30.4, 30.1, 29.8, 29.5, 29.4, 27.5, 27.0, 22.9, 20.8, 17.5, 14.3, 13.9, 9.6, 7.1, 5.4 ppm; HRMS (ESI-QTOF) calcd for $C_{39}H_{82}NO_2SnSi^+$ [M + H^+]: 744.5137, found: 744.5185.



14'

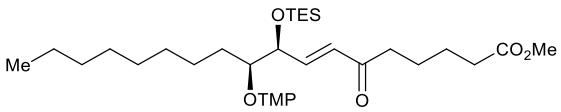
Silyl ether 14': was prepared in the same manner as TES ether **10**. Flash column chromatography (1 % EtOAc / hexanes) gave a colorless oil that was contaminated with TESOH.



12

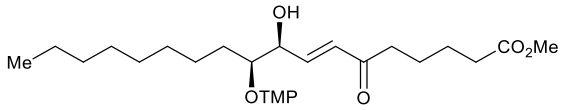
Enone 12: To a deoxygenated solution (3 × freeze–pump–thaw) of vinylstannane **10** (1.27 g, 1.7 mmol, 1.0 equiv.), $PCy_3{\cdot}HBF_4$ (31 mg, 85 μmol, 0.05 equiv.), *i*Pr_2NEt (15 μL, 85 μmol, 0.05 equiv.), and $Pd_2(dba)_3$ (38 mg, 43 μmol, 0.025 equiv.) in 34 mL of toluene was added acid chloride **11** (528 μL, 3.4 mmol, 2.0 equiv.) dropwise over 2 minutes. The reaction mixture was heated at 50 °C for 45 minutes, then cooled and diluted with 75 mL EtOAc. The organic phase was washed with 3 % aq. NH_4OH (85 mL), water (2 × 75 mL), and brine (75 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Flash column chromatography (8 % EtOAc / hexanes) gave enone **12** (914 mg, 89 % yield) as a colorless oil. **12:** R_f = 0.36 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = +21.0 ° (*c* = 1.10, $CHCl_3$); IR (thin film): ν_{max} = 3022, 2929,

1733, 1670 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.91 (dd, *J* = 16.1, 5.9 Hz, 1H), 6.20 (dd, *J* = 16.0, 1.4 Hz, 1H), 4.40 (ddd, 5.8, 2.6, 1.4 Hz, 1H), 3.91 (m, 1H), 3.67 (s, 3H), 2.59 (m, 2H), 2.33 (m, 2H), 2.03 (m, 1H), 1.70 – 1.62 (m, 4H), 1.51 – 1.37 (m, 4H), 1.35 – 1.23 (m, 15H), 1.19 (br s, 3H), 1.15 (br s, 3H), 1.05 (br s, 3H), 1.03 (br s, 3H), 0.96 (t, 8.0 Hz, 9H), 0.88 (t, 6.9 Hz, 3H), 0.60 (q, 7.9 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.3, 174.0, 147.3, 129.3, 86.3, 74.6, 61.0, 59.4, 51.6, 40.7, 40.4, 39.5, 34.6, 34.4, 34.0, 32.0, 30.21, 30.17, 29.7, 29.4, 27.0, 24.7, 23.8, 22.8, 20.8, 20.6, 17.4, 14.2, 7.0, 5.1 ppm; HRMS (ESI-QTOF) calcd for $C_{34}H_{66}NO_5Si^+$ [M + H^+]: 596.4705, found: 596.4704.



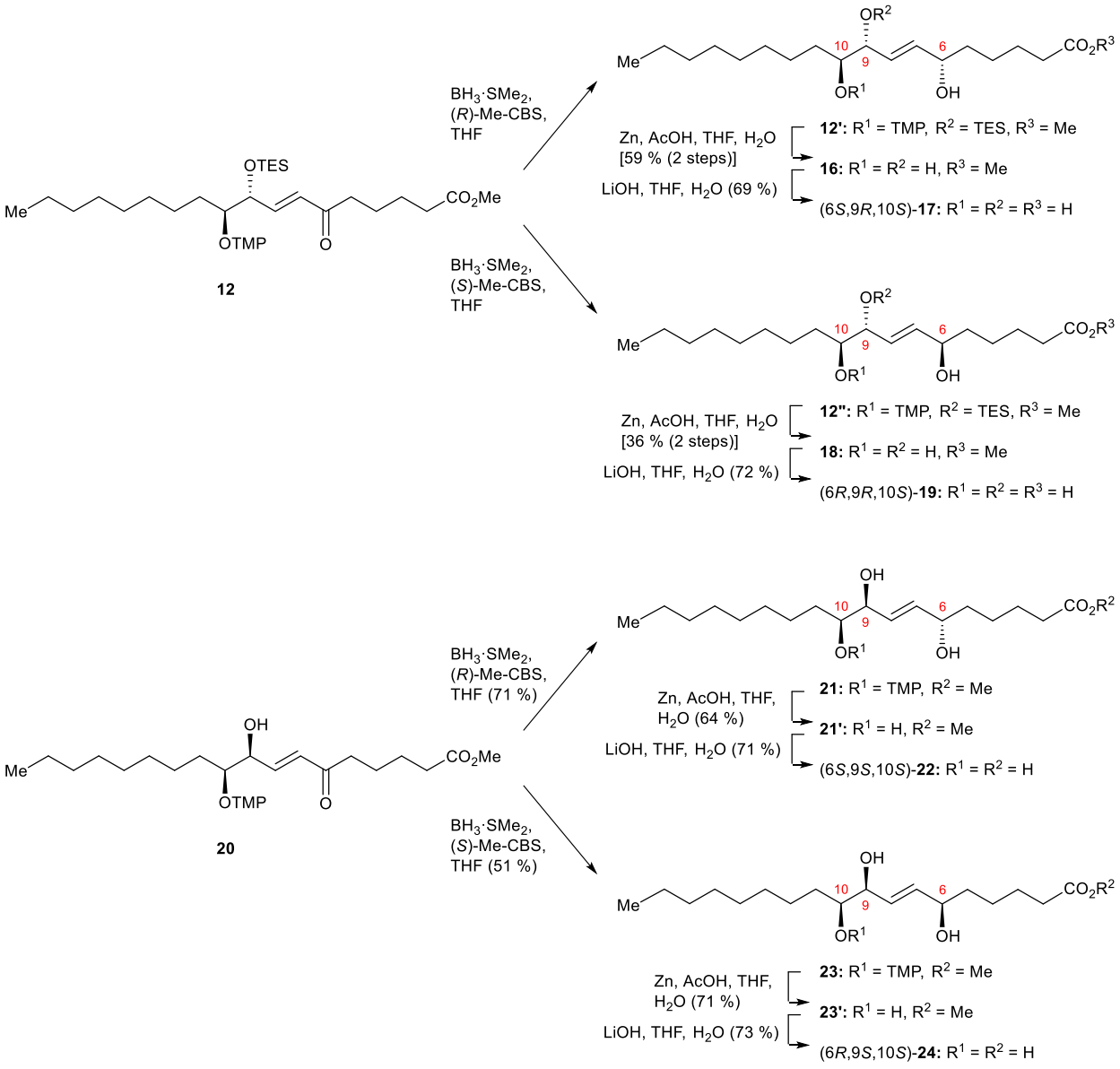
15

Enone 15 was prepared in the same manner as enone **12**. Flash column chromatography (8 % EtOAc / hexanes) gave enone **15** (84 % yield over two steps) as a colorless oil. **15:** R_f = 0.38 (10 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −60.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3022, 2955, 1737, 1695, 1678, 1458 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.02 (dd, *J* = 15.9, 3.6 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 4.70 (m, 1H), 3.86 (m, 1H), 3.67 (s, 3H), 2.60 (m, 2H), 2.34 (m, 2H), 1.66 (m, 5H), 1.58 – 1.18 (m, 19H), 1.12 (br s, 12H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.61 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.1, 174.0, 147.8, 129.1, 85.3, 72.3, 60.2, 51.6, 40.8, 39.8, 34.0, 32.0, 30.2, 29.7, 29.4, 26.9, 24.7, 23.8, 22.8, 20.6, 17.4, 14.2, 7.0, 5.0 ppm; HRMS (ESI-QTOF) calcd for $C_{34}H_{66}NO_5Si^+$ [M + H^+]: 596.4705, found: 596.4712.

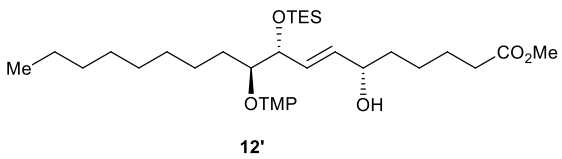


20

Alcohol 20: To a solution of silyl ether **15** (380 mg, 0.64 mmol, 1.0 eqiv.) in 2.5 mL of THF was added TBAF (1.0 M in THF, 1.92 mL, 1.92 mmol, 3.0 equiv) over 2 minutes. The reaction mixture was stirred for 10 minutes, then partitioned between water (20mL) and EtOAc (20 mL). The organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated to give a colorless oil. Flash column chromatography (13 % EtOAc / hexanes) gave alcohol **20** (256 mg, 84 % yield) as a colorless oil. **20:** R_f = 0.26 (20 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −24.0 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3674, 3054, 2929, 1695, 1677, 1633 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.86 (br s, 1H), 6.72 (dd, *J* = 15.7, 5.1 Hz, 1H), 6.45 (d, *J* = 15.8 Hz, 1H), 4.57 (m, 1H), 3.89 (m, 1H), 3.66 (s, 3H), 2.57 (m, 2H), 2.33 (m, 2H), 1.67 – 1.63 (m, 4H), 1.54 – 1.22 (m, 26H), 1.19 (br s, 3H), 1.14 (br s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H), ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 199.8, 173.9, 144.2, 129.7, 82.7, 76.2, 62.0, 60.4, 51.6, 40.8, 40.5, 40.0, 34.6, 34.0, 31.99, 31.95, 31.3, 29.9, 29.6, 29.4, 25.4, 24.6, 23.5, 22.8, 20.72, 20.66, 17.2, 14.2 ppm; HRMS (ESI-QTOF) calcd for $C_{28}H_{52}NO_5^+$ [M + H^+]: 482.3840, found: 482.3844.



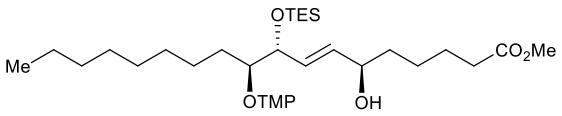
Scheme 9. Synthesis of oxylipins



Allylic alcohol 12': To a solution of enone **12** (200 mg, 0.34 mmol, 1.0 equiv.) in 150

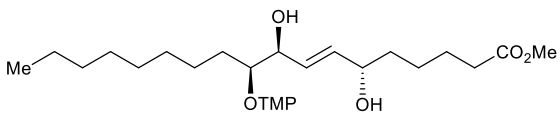
μL of THF at −78 °C was added a pre-mixed solution of (*R*)-Me-CBS (122 mg, 0.44 mmol, 1.3 equiv.) and $BH_3 \cdot SMe_2$ (2 M in THF, 220 μL, 0.44 mmol, 1.3 equiv.) dropwise over 1 minute. After 5 minutes the reaction mixture was warmed to 0 °C and quenched by adding 50 μL of methanol and 10 μL of 4 *N* HCl. After stirring at ambient temperature for 30 minutes, the reaction mixture was diluted with EtOAc (10mL). The organic layer was washed with water (2 × 10 mL), brine (10 mL), and saturated $NaHCO_3$ (10 mL), dried over Na_2SO_4, and concentrated to give a yellow oil as a 5.7:1 mixture of diastereomers. Flash column chromatography (40 % EtOAc / hexanes) gave allylic alcohol **12'** as a mixture of diastereomers that was a colorless oil. A sample was converted into methyl (*S*)-6,7-dihydroxyheptanoate (1. O_3, MeOH, THF; then Me_2S; 2. $NaBH_4$, EtOH) and its optical rotation was compared with that of the known substance in order to confirm the absolute configuration.

Allylic alcohols 12" – 26 were prepared in the same manner as allylic alcohol **12'**.



12"

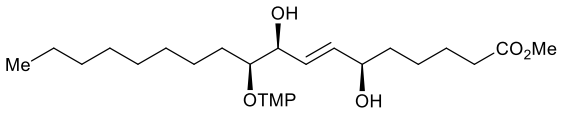
Allylic alcohol 12": Flash column chromatography (40 % EtOAc / hexanes) gave allylic alcohol **12"** (2.0:1 mixture of diastereomers) as a colorless oil.



21

Allylic alcohol 21: Flash column chromatography (40 % EtOAc / $CHCl_3$) gave allylic alcohol **21** in 68 % yield as a

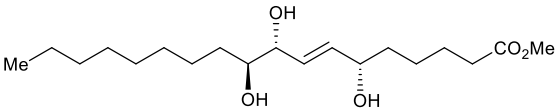
colorless oil and epimeric alcohol **23** in 13 % yield. A small sample of allylic alcohol **21** was purified for characterization. **21:** R_f = 0.38 (40 % EtOAc / $CHCl_3$); $[\alpha]_D^{23}$ = −40.4 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3457, 3014, 2924, 1729 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.66 (br s, 1H), 5.80 (dd, *J* = 15.4 Hz, 6.0 Hz, 1H), 5.59 (dd, *J* = 15.4 Hz, 6.7 Hz, 1H), 4.35 (t, *J* = 7.7 Hz, 1H), 4.13 (m, 1H), 3.86 (t, *J* = 8.2 Hz, 1H), 3.66 (s, 3H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.20 (m, 33H), 1.17 (s, 3H), 1.12 (s, 3H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.3, 135.6, 130.0, 82.9, 72.1, 61.9, 60.3, 51.6, 40.5, 40.0, 36.9, 34.6, 34.1, 32.1, 32.0, 31.4, 30.0, 29.7, 29.4, 25.6, 25.1, 25.0, 22.8, 20.74, 20.67, 17.3, 14.2 ppm; HRMS (ESI-QTOF) calcd for $C_{28}H_{54}NO_5^+$ [M + H^+]: 484.3997, found: 484.4002.



23

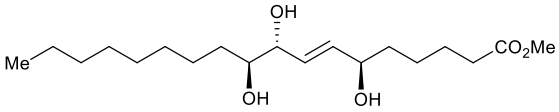
Allylic alcohol 23: Flash column chromatography (40 % EtOAc / $CHCl_3$) gave allylic alcohol **23** in 51 % yield as a colorless oil, epimeric alcohol **21** in 7 % yield, and a mixture of the two epimers in 7 % yield. **23:** R_f = 0.33 (40 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −20.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3357, 3924, 1739 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.70 (br s, 1H), 5.80 (dd, *J* = 15.6 Hz, 7.0 Hz, 1H), 5.58 (dd, *J* = 15.4 Hz, 6.8 Hz, 1H), 4.36 (t, *J* = 7.7 Hz, 1H), 4.11 (m, 1H), 3.88 (t, *J* = 8.2 Hz, 1H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.70 – 1.20 (m, 33H), 1.18 (s, 3H), 1.13 (s, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.2, 135.5, 130.5, 83.0, 72.5, 51.6, 40.5, 40.0, 36.9, 34.59, 34.56, 34.1, 32.0, 31.5, 30.0, 29.7, 29.4, 25.5, 25.2, 25.0, 22.8, 20.8, 20.7, 17.3, 14.2 ppm; HRMS (ESI-QTOF) calcd for $C_{28}H_{54}NO_5^+$ [M + H^+]: 484.3997, found: 484.4002.

Triols 16, 18, 21' and **23'** were prepared in the same manner as diol **12** of chapter 2.



16

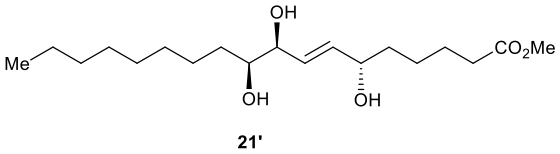
Triol 16: Flash column chromatography (85 % EtOAc / hexanes) gave triol **16** (59 % yield over two steps) as a white solid as well as epimeric triol **18** (11 % yield). A 98:2 er was established after saponification to oxylipin (6*S*,9*R*,10*S*)-**16**. **15:** R_f = 0.21 (80 % EtOAc / hexanes); $[\alpha]_D^{23}$ = +8.2 ° (*c* = 0.6, MeOH); IR (thin film): ν_{max} = 3332, 2920, 2844, 1732, cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ = 5.73 (dd, *J* = 15.6 Hz, 6.3 Hz, 1H), 5.67 (dd, *J* = 15.8 Hz, 6.4 Hz, 1H), 4.05 (q, *J* = 6.3 Hz, 1H), 3.92 (dd, *J* = 6.3 Hz, 4.7 Hz, 1H), 3.65 (s, 3H), 3.49 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.63 (m, 2H), 1.59 – 1.26 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 175.9, 136.4, 131.0, 76.5, 75.7, 73.0, 52.0, 38.0, 34.8, 33.8, 33.1, 30.9, 30.7, 30.4, 27.0, 26.1, 26.0, 23.7, 14.4 ppm; ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{36}O_5Na^+$ [M + Na^+]: 367.2460, found: 367.2455.



18

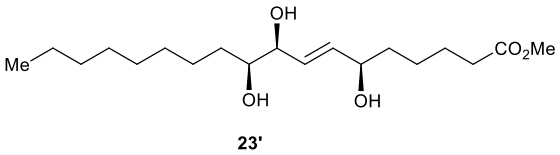
Triol 18: Flash column chromatography (85 % EtOAc / hexanes) gave triol **18** (36 % yield over two steps) as a white solid as well as epimeric triol **16** (23 % yield). **18:** R_f = 0.26 (80 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −6.8 ° (*c* = 0.25, MeOH); IR (thin film): ν_{max} = 3278, 2929, 2847, 1730 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ = 5.73 (dd, *J* = 15.7 Hz, 6.1 Hz, 1H), 5.69 (dd, *J* = 15.6 Hz, 5.9 Hz, 1H), 4.06 (q, *J* = 6.0 Hz, 1H), 3.92 (t, *J* = 5.4 Hz, 1H), 3.65 (s, 3H), 3.47 (m, 1H),

2.33 (t, *J* = 7.4 Hz, 2H), 1.63 (m, 2H), 1.57 – 1.20 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ =175.9, 136.4, 131.1, 76.5, 75.7, 72.9, 52.0, 37.9, 34.8, 33.6, 33.1, 30.9, 30.7, 30.5, 27.0, 26.1, 26.0, 23.7, 14.4 ppm; ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{36}O_5Na^+$ [M + Na^+]: 367.2460, found: 367.2464.



21'

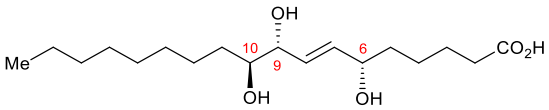
Triol 21': Flash column chromatography (85 % EtOAc / hexanes) gave triol **21'** (64 % yield) as a white solid. **21':** R_f = 0.36 (80 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −11.4° (*c* = 0.50, MeOH); IR (thin film): ν_{max} = 3357, 3313, 2924, 2841, 1739 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.70 (m, 2H), 4.05 (q, *J* = 6.1 Hz, 1H), 3.90 (t, *J* = 5.6 Hz, 1H), 3.65 (s, 3H), 3.41 (m, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.63 (m, 2H), 1.58 – 1.25 (m, 18H), 0.90 (t, *J* = 6.22, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 175.9, 136.4, 131.2, 76.5, 75.8, 72.8, 52.0, 38.0, 34.8, 33.6, 33.1, 30.9, 30.7, 30.5, 26.9, 26.1, 26.0, 23.7, 14.4 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{36}O_5Na^+$ [M + Na^+]: 367.2460, found: 367.2461.



23'

Triol 23': Flash column chromatography (85 % EtOAc / hexanes) gave triol **23'** (71 % yield) as a white solid. **23':** R_f = 0.29 (80 % EtOAc / hexanes); $[\alpha]_D^{23}$ = −36.3° (*c* = 0.30, MeOH); IR (thin film): ν_{max} = 3537, 3313, 2924, 2841, 1739 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.70 (dd, *J* = 15.6 Hz, 6.0 Hz, 1H), 5.65 (dd, *J* = 15.6 Hz, 6.2 Hz, 1H), 4.04 (q, *J* = 6.4 Hz, 1H), 3.88 (t, *J* = 6.1 Hz, 1H), 3.65 (s, 3H), 3.40 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.63 (m, 2H), 1.59 – 1.21

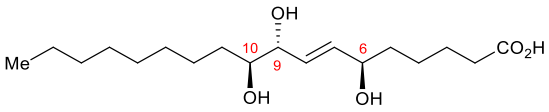
(m, 18H) 0.90 (t, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 175.9, 136.6, 131.4, 76.6, 75.7, 72.9, 52.0, 37.9, 34.8, 33.8, 33.1, 30.9, 30.7, 30.4, 26.8, 26.1, 26.0, 23.8, 14.5 ppm; HRMS (ESI-QTOF) calcd for $C_{19}H_{36}O_5Na^+$ [M + Na^+]: 367.2460, found: 367.2460.



(6*S*,9*R*,10*S*)-**17**

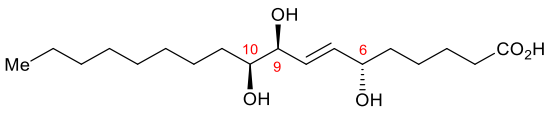
Oxylipin (6*S*,9*R*,10*S*)**-17:** To a solution of triol **16** (20 mg, 0.056 mmol, 1.0 equiv.) in THF (2.7 mL) was added 0.3 mL of an aqueous 1.0 M LiOH solution over one minute. The reaction mixture was stirred overnight, then partitioned between EtOAc (5 mL) and 1 *N* HCl (5 mL). The organic phase was washed with water (2 × 5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated to give a white solid. Flash column chromatography (0 – 10 % MeOH / EtOAc) gave oxylipin (6*S*,9*R*,10*S*)**-17** (13 mg, 69 % yield) as a white solid. A sample was derivatized (*p*-nitrobenzyl amine·HCl, BOP–BF_4, HOBt, *i*Pr_2NEt, DMF) and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 12 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 11.4 (major), 12.7 (minor) minutes] to have 98:2 er. (6*S*,9*R*,10*S*)**-17:** R_f = 0.29 (100 % EtOAc); $[\alpha]_D^{23}$ = +4.4 ° (*c* = 0.9, MeOH); IR (thin film): ν_{max} = 3386, 3019, 2941, 1712 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.73 (dd, J = 15.6 Hz, 6.4 Hz, 1H), 5.67 (dd, J = 15.6 Hz, 6.2 Hz, 1H), 4.06 (q, J = 6.2 Hz, 1H), 3.92 (t, J = 5.3 Hz, 1H), 3.49 (m, 1H), 2.29 (t, J = 7.2 Hz, 2H), 1.62 (m, 2H) 1.59 – 1.22 (m, 18H), 0.90 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 177.7, 136.5, 131.0, 76.5, 75.7, 73.1, 38.0, 35.1, 33.8, 33.1, 30.9, 30.7, 30.4, 27.0, 26.2, 26.1, 23.7, 14.4 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{34}O_5Na^+$ [M + Na^+]: 353.2304, found: 353.2301.

The other diastereomeric of oxylipins **19**, **22** and **24** were prepared in the same manner as oxylipin (6*S*,9*R*,10*S*)-**17**.



(6*R*,9*R*,10*S*)-**19**

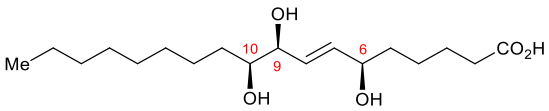
Oxylipin (6*R*,9*R*,10*S*)-**19:** Flash column chromatography (0 – 5 % MeOH / EtOAc) gave oxylipin (6*R*,9*R*,10*S*)-**19** (72 % yield) as a white solid. A sample was derivatized (*p*-nitrobenzyl amine·HCl, BOP–BF_4, HOBt, *i*Pr_2NEt, DMF) and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 12 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 12.9 (major), 10.9 (minor) minutes] to have 96:4 er. (6*R*,9*R*,10*S*)-**19:** R_f = 0.18 (5 % MeOH / $CHCl_3$); $[\alpha]_D^{23}$ = −14.6 ° (*c* = 0.15, MeOH); IR (thin film): ν_{max} = 3312, 2923, 1701 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.74 (dd, *J* = 15.6 Hz, 6.1 Hz, 1H), 5.69 (dd, *J* = 15.6 Hz, 6.0 Hz, 1H), 4.06 (q, 6.0 Hz, 1H), 3.92 (t, *J* = 6.0 Hz, 1H), 3.47 (ddd, *J* = 9.0, 4.9, 3.0 Hz, 1H),), 2.29 (t, *J* = 7.5 Hz, 2H), 1.62 (m, 2H), 1.59 – 1.23 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): 136.4, 131.1, 76.6, 75.7, 73.0, 38.0, 35.1, 33.6, 33.1, 30.9, 30.8, 30.5, 27.0, 26.2, 26.1, 23.7, 14.4.ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{34}O_5Na^+$ [M + Na^+]: 353.2304, found: 353.2304.



(6*S*,9*S*,10*S*)-**22**

Oxylipin (6*S*,9*S*,10*S*)-**22:** Flash column chromatography (0 – 5 % MeOH / EtOAc) gave oxylipin (6*S*,9*S*,10*S*)-**22** (71 % yield) as a white solid. A sample was derivatized (*p*-nitrobenzyl amine·HCl, BOP–BF_4, HOBt,

iPr_2NEt, DMF) and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 12 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 11.3 (major), 14.2 (minor) minutes] to have 98:2 er. (6*S*,9*S*,10*S*)-**22:** R_f = 0.23 (10% MeOH / $CHCl_3$); $[\alpha]_D^{23}$ = −21.2 ° (*c* = 0.25, MeOH); IR (thin film): ν_{max} = 3338, 2914, 1700 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.72 (dd, *J* = 15.6 Hz, 5.6 Hz, 1H), 5.68 (dd, *J* = 15.6 Hz, 5.9 Hz, 1H), 4.06 (q, *J* = 6.1 Hz, 1H), 3.91 (t, *J* = 5.6 Hz, 1H), 3.42 (m, 1H), 2.28 (t, *J* = 7.4 Hz, 2H), 1.62 (m, 2H), 1.58 – 1.22 (m, 18H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 136.3, 131.0, 76.4, 75.6, 72.7, 37.9, 35.3, 33.4, 32.9, 30.7, 30.6, 30.3, 26.8, 26.1, 26.0, 23.6, 14.3 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{34}O_5Na^+$ [M + Na^+]: 353.2304 found: 353.2302.

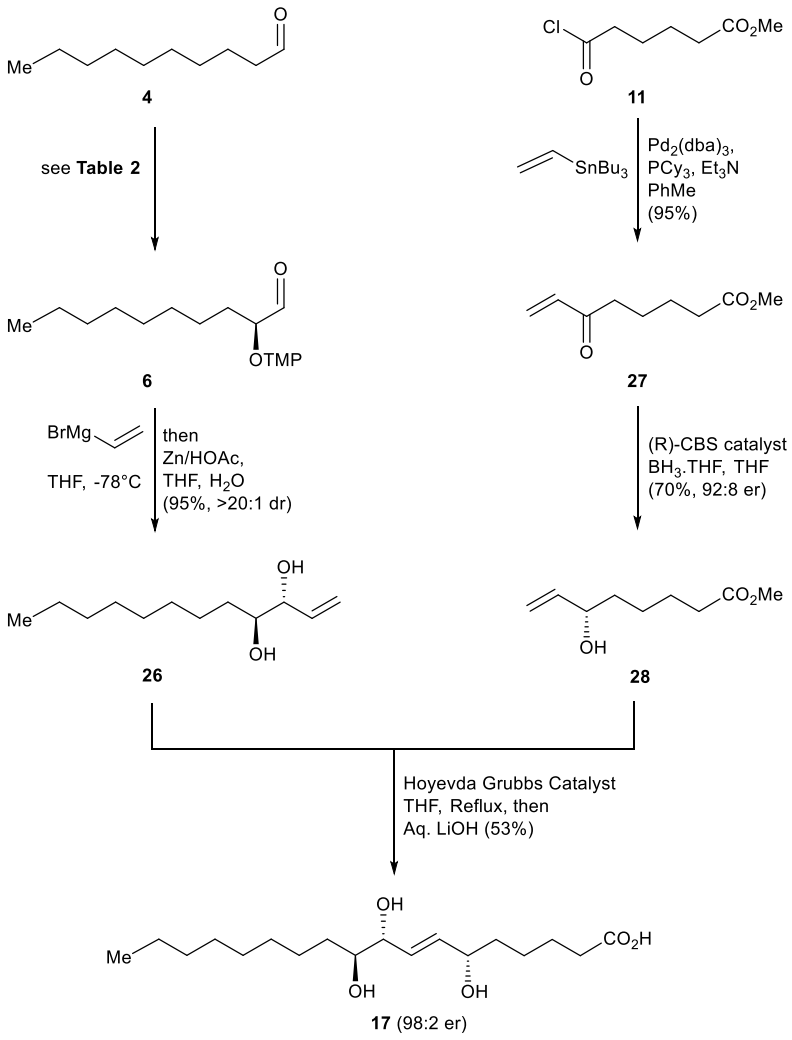


(6*R*,9*S*,10*S*)-**24**

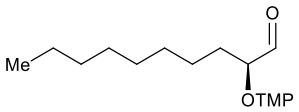
Oxylipin (6*R*,9*S*,10*S*)-**24:** Flash column chromatography (0 – 5 % MeOH / EtOAc) gave oxylipin (6*R*,9*S*,10*S*)-**16** (73 % yield) as a white solid. A sample was derivatized (*p*-nitrobenzyl amine·HCl, BOP–BF_4, HOBt, *i*Pr_2NEt, DMF) and determined by chiral HPLC [Chiraltech IC column, 2.1 × 100 mm, 3 μm; 12 % *i*PrOH / hexanes, 0.2 mL / min, 25 °C; 280 nm UV detection; R_t = 13.4 (major), 11.4 (minor) minutes] to have 96:4 er. (6*R*,9*S*,10*S*)-**24:** R_f = 0.19 (10 % MeOH / $CHCl_3$); $[\alpha]_D^{23}$ = −30.4 ° (*c* = 0.25, MeOH); IR (thin film): ν_{max} = 3395, 2917, 1686 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ = 5.71 (dd, *J* = 15.6 Hz, 6.1 Hz, 1H), 5.66 (dd, *J* = 15.6 Hz, 6.3 Hz, 1H), 4.05 (q, *J* = 6.3 Hz, 1H), 3.88 (t, *J* = 6.11, 1H), 3.40 (m, 1H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.62 (m, 2H), 1.59 – 1.21 (m, 18H), 0.90 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (150 MHz, CD_3OD): δ = 136.6, 131.4, 76.9, 75.6, 72.8, 38.2, 35.0, 33.8, 33.0,

30.9, 30.7, 30.4, 26.9, 26.2, 26.1, 23.7, 14.4 ppm; HRMS (ESI-QTOF) calcd for $C_{18}H_{34}O_5Na^+$ [M + Na^+]: 353.2304, found: 353.2303.

Second generation synthesis

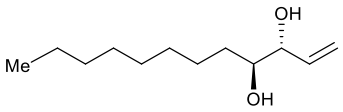


Scheme 10. Second generation synthesis of oxylipins



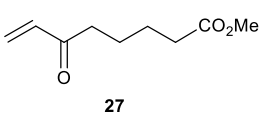
6

α-Oxyaldehyde 6: Prepared as first generation protocol for α-Oxyaldehyde **6** using 5 mol% of HBF_4 salt of imizazolidinone **25** at -10 °C.



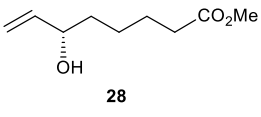
26

Diol 26: To a solution of aldehyde **6** (562 mg, 1.80 mmol, 1.0 equiv.) in 1.80 mL of THF at –78 °C was added vinylmagnesium bromide (1.0 M in THF, 2.33 mmol, 1.3 equiv.) dropwise over 3 minutes. The resultant solution was stirred at –78 °C for 30 minutes, then warmed to room temperature and was diluted with 20 mL of a 3:1:1 solvent mixture (HOAc:H_2O:THF). To the resulting solution was added zinc (1.18 g, 18.0 mmol, 10 equiv.) and refluxed at 70 °C for 6 hours. After cooling, the reaction mixture was filtered through Celite, concentrated, and azeotrope dried with toluene to give a white solid. Flash column chromatography (30 % EtOAc / hexanes) gave diol **27** (270 mg, 75 % yield, >20:1 mixture diastereomers) as a white solid. **27**: R_f = 0.29 (35% EtOAc / hexanes); $[\alpha]_D^{23}$ = –3.5 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3305, 3212, 2916, 2849 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 5.93 (ddd, *J* = 17.1, 10.6, 6.5 Hz, 1H), 5.34 (td, *J* = 17.3, 1.5 Hz, 1H), 5.28 (td, *J* = 10.5, 1.3 Hz, 1H), 4.10 (m, 1H), 3.69 (td, *J* = 8.7, 4.2 Hz, 1H), 1.79 (brs, 2H), 1.54 – 1.19 (m, 13H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 136.2, 117.9, 76.1, 74.2, 32.3, 32.0, 29.8, 29.7, 29.4, 26.0, 22.8, 14.3 ppm; HRMS (ESI-QTOF) calcd for $C_{12}H_{24}O_2^+$ [M^+]: 200.1776, found: 200.1776.



27

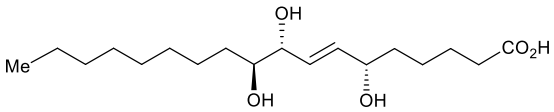
Enone 27: To a deoxygenated solution of tributyl(vinyl)tin (1.58 g, 5 mmol, 1.0 equiv.), $PCy_3 \cdot HBF_4$ (368 mg, 1 mmol, 0.2 equiv.), *i*-Pr_2NEt (170 µL, 1 mmol, 0.2equiv.), and $Pd_2(dba)_3$ (457 mg, 0.5 mmol, 0.1 equiv.) in 50 mL of toluene was added methyl adipoyl chloride **11** (1.6 mL, 10 mmol, 2.0 equiv.) dropwise over 2 minutes and stirred for one hour at room temperature. The reaction mixture was diluted with EtOAc (75 mL) organic phase was washed with 3% aq. NH_4OH (75 mL), water (2 × 75 mL), and brine (75 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Flash column chromatography (20% EtOAc / hexanes) gave enone **26** (770 mg, 90.6% yield) as yellow oil. **26:** R_f = 0.32 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 2953, 1732, 1699 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.34 (dd, *J* = 17.7, 10.6 Hz, 1H), 6.21 (d, *J* = 17.6 Hz, 1H), *5*.82 (d, *J*= 10.6 Hz, 1H), 3.66 (s, 3H), 2.61 (m, 2H), 2.34 (m, 2H) ppm, 1.65 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = ^{13}C NMR (151 MHz, Chloroform-*d*) δ 200.5, 174.0, 136.6, 128.2, 51.7, 39.3, 34.0, 24.6, 23.4ppm; HRMS (ESI-QTOF) calcd for $C_9H_{15}O_3^+$ [M + H^+]: 171.1000, found: 171.1017.



28

Allylic alcohol 28: To enone **26** (50 mg, 0.29 mmol, 1.0 equiv.) was added a solution of (R)-Me-CBS (163.35 mg, 0.59 mmol, 2.0 equiv.) in 300 µL THF and cooled to -78 °C. Then $BH_3 \cdot THF$ (1 M in THF, 0.3 mL, 0.3 mmol, 1.0 equiv.) was added dropwise over 1 minute. The reaction was quenched by adding 50 µL of methanol and 10 µL of 4 N HCl and warmed to room temperature. The reaction mixture was diluted with EtOAc (10 mL). The organic layer was washed with water (2 × 10 mL), brine (10 mL), and saturated $NaHCO_3$ (10 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Flash column chromatography (30% EtOAc /

hexanes) gave allylic alcohol **26** as a colorless oil (34 mg, 69.5% yield). **26:** R_f = 0.33 (30% EtOAc / hexanes); $[\alpha]_D^{23}$ = –90.5 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3433, 2936, 1735 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 17.3. 10.5, 6.2 Hz, 1H), 5.22 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.11 (dd, *J* = 10.4, 1.0 Hz,1H), 4.10 (m, 1H), 3.66 (s, 3H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.71–1.33 (m, 6H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.3, 141.2, 114.9, 73.1, 51.7, 36.7, 34.1, 25.0, 24.9 ppm; HRMS (ESI-QTOF) calcd for $C_9H_{17}O_3^+$ [M + H^+]: 173.1200, found: 173.1172.



17

Oxylipin 17: Allylic alcohol **28** (85 mg, 0.49 mmol, 1 equiv) and diol **27** (313 mg, 1.48 mmol, 3 equiv) were dissolved in 9 mL of THF and then Hoyveda Grubbs catalyst (21.1 mg, 0.026 mmol, 0.05 quiv) was added and heated to reflux for 24 hours. The reaction mixture was cooled to room temperature then LiOH (450 mg, 9.8 mmol, 20 equiv) dissolved in 1 mL water was added and stirred for another 24 hours. Reaction mixture was partitioned between EtOAc (20 mL) and 1N HCl (20 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4 and concentrated to give a white solid. Flash column chromatography (90 % EtOAc/hexanes) gave oxylipin **17** (86 mg, 53% yield) as a white solid.

References

1. Mosblech, A.; Feussner, I.; Heilmamm, I. *Plant Physiogy and Biochemistry* **2009**, *47*, 511.

2. Benavides, A.; Napolitano, A.; Bassarello, C.; Carbone, V.; Gazzerro, P.; Malfitano, A. M.; Saggese, P.; Bifulco, M.; Piacente, S.; Pizza, C. *J. Nat. Prod.* **2009**, *72*, 813.

3. Williams, D. E.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, 129, 5822.

4. (a) Chatterjee, S.; Kanojia, S. V.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2011**, *22*, 367. (b) Wadavrao, S. B.; Ghogare, R. S.; Narsaiah, A. V. *Tetrahedron Lett.* **2012**, *53*, 3955. (c) Saikia, B.; Devi, T. J.; Barua, N. C. *Tetrahedron* **2013**, 69, 2157. (d) Yadav, J. S.; Shankar, K. S.; Reddy, A. N. Helv. *Chim. Acta* **2014,** *97*, 546. (e) Reddy, N. S.; Das. B.; *Helv. Chim. Acta* **2015,** *98*, 78.

5. (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc*. **2007**, *129*, 4124. (b) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. (c) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; Macmillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 10012. (d) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci*. **2012**, *3*, 58.

6. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Milstein, D.; Stille, J. K. *J. Org. Chem.* **1979**, *44*, 1613.

7. Luche; J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

8. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

9. Miura, A.; Kuwahara, S. *Tetrahedron* **2009**, *65*, 3364.

10. Abeykoon, G. A.; Chatterjee, S.; Chen, J. S. *Org. Lett.* **2014**, *16*, 3248.

11. Chen, J. S.; Abeykoon, G. A. *Org. Lett.* **2015**, *17*, 6050.

12. (a) Covell, D. G.; White, M. C. *Angew. Chem. Intl. Ed.* **2008**, *47*, 6448. (b) Neufeld, K.; Henpen, B.; Pietruszka, J. *Angew. Chem. Intl. Ed.* **2008**, *48*, 13253.

13. Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605.

14. Matsumara, M.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

15. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

16. Chatterjee, A. K.; Choi, T-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

17. Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222 – 11231.

CHAPTER 4

CATALYTIC ENANTIOSELECTIVE α,β,γ-TRIOXYGENATION

Paper published in full in *Organic Letters*[*]

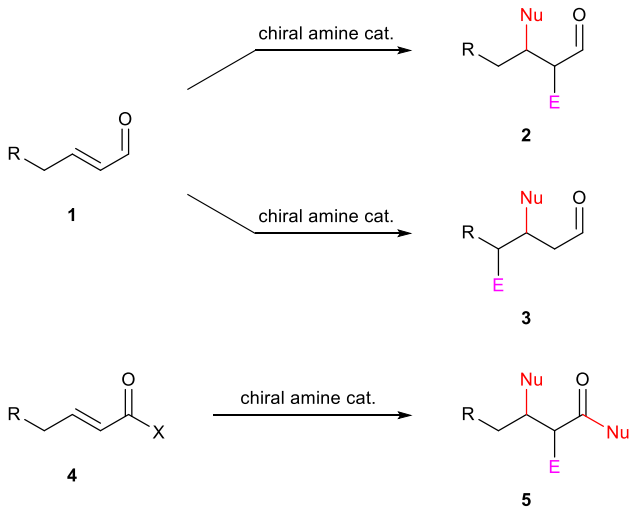
Introduction

Enantioselective transformations of aldehydes and enals promoted by chiral amine catalysts have been heavily studied since 2000.[1] The most common variants of these reactions are aldehyde α-functionalizations[2] and enal β-functionalizations,[3] but reactions at more-remote sites are also known.[4] α-Oxygenations have been developed using nitrosobenzene,[5] TEMPO radical,[6] or singlet oxygen[7] as the oxygen source. β-Oxygenations through conjugate addition of substituted hydroxylamines,[8] alcohols,[9] or hydrogen peroxide[10] have been described, but have found limited application due to their reversible nature.[11] A non-enantioselective γ-oxygenation using TEMPO radical has been reported.[12]

Organocatalytic cascade reactions[13] have also been popular. Conjugate addition to an α,β-unsaturated iminium ion (generated by condensation of an enal with an amine catalyst) forms an enamine whose further reaction with an electrophile leads to α,β-difunctionalization (**1**→**2**, Scheme 1). The α and β positions may form new bonds to the same atom, generating a three-membered ring.[14] More often, the enal is coupled to two different reaction partners. Organocatalytic α,β-difunctionalizations involving oxygenation at the α[15] or β[16,9c] position have been developed, but organocatalytic α,β-dioxygenation is unknown. Some examples of enal β,γ-difunctionalization (**1**→**3**) have

[*]Reprinted with permission from *Org. lett*. **2015**, *17*, 6050.

been reported,[17] but there is no precedent for enal α,β,γ-trifunctionalization (organocatalytic or otherwise). However, *ipso*,α,β-trifunctionalizations of activated carboxylic acid derivatives (**4**→**5**) have been described.[18]

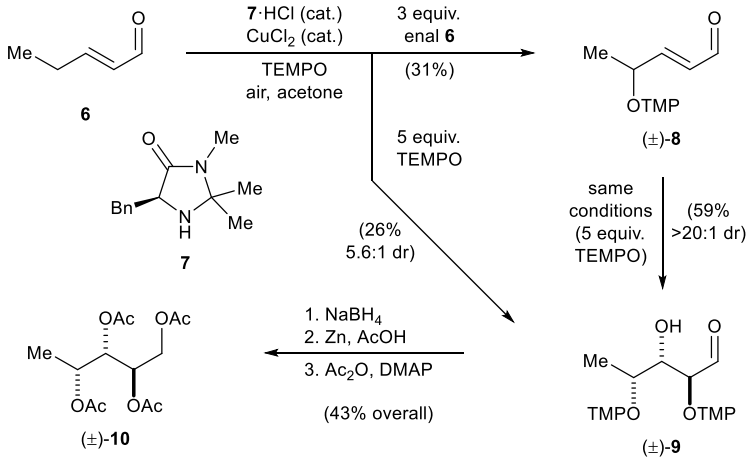


Scheme 1. Summary of related cascade reactions

We became interested in organocatalytic aldehyde α-oxygenation using stoichiometric TEMPO[6] as part of a strategy for preparing *anti*-1,2-diols from simple aldehydes.[19] The α-oxygenation proceeds through an enamine mechanism,[6c] but the optimal catalysts are imidazolidinone salts originally designed to promote enal reactions through the intermediacy of α,β-unsaturated iminium ions.[1b] This apparent mismatch led us to wonder what would happen if an enal were subjected to the α-oxygenation conditions. Would α-oxygenation proceed with transposition of the alkene? Would conjugate addition of a nucleophile occur? Or would γ-oxygenated be observed?

Results and Discussion

To distinguish these possibilities, we subjected enal **6** (Scheme 2) to the aldehyde α-oxygenation conditions. Enal **6** and TEMPO reacted under the influence of imidazolidinone salt **7**·HCl to give γ-oxyenal **8** and α,β,γ-trioxyaldehyde **9**, both in racemic form. Using an excess of enal **6** favored formation of γ-oxyenal **8**, and using an excess of TEMPO favored trioxyaldehyde **9**. Resubjecting γ-oxyenal **8** to the reaction conditions effected its conversion into trioxyaldehyde **9**, demonstrating that γ-oxyenal **8** likely is an intermediate in the cascade. The relative stereochemistry of trioxyaldehyde **9** was ascertained by comparing the NMR spectra of tetraacetate derivative **10** against the published spectra of all diastereomers of this compound.[20] Shortly after we commenced these experiments, Jang and coworkers reported the conversion of enal **6** into γ-oxyenal (±)-**8** under similar reaction conditions;[12] however, they apparently did not observe trioxyaldehyde **9** since they used TEMPO as the limiting reagent.



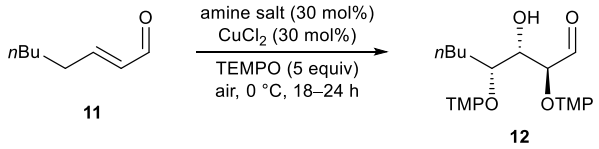
Scheme 2. Discovery of a trioxygenation cascade

C_5 enal **6** is difficult to observe by TLC analysis due to its moderate volatility, and so reaction optimization was conducted on C_8 enal **11** (Table 1). Some aldol and Michael reaction products were observed, and so enal **11** was added portionwise in order to suppress its self-dimerization. The reaction was sluggish, and thus it was run at high concentration (500 μL of solvent for a 1 mmol reaction) in order to increase the reaction rate. At this concentration, TEMPO became a significant contributor to reaction volume; to further enhance the initial rate, TEMPO was added in two portions. Under these conditions, imidazolidinone salt **7**·AcOH delivered trioxyaldehyde **12** in higher yield and with superior stereoselectivity as compared with the hydrochloride salt (Table 1, entries 1 and 2). A solvent screen revealed improved enantioselectivity in toluene, but at the expense of yield (Table 1, entries 3–6). Copper(II) chloride was poorly dissolved in toluene, and so we speculated that more polar fluorinated aromatic solvents may better dissolve the copper salt, and thus rescue the reaction yield while retaining the improved stereoselectivity (Table 1, entries 7–10). This proved to be the case; use of pentafluorobenzene delivered a higher yield of the major diastereomer than that obtained in acetone (albeit with a lower yield of the combined diatereomers) an enantiomeric ratio comparable to that achieved in toluene. The anion of the amine salt was then varied, but no improvements were forthcoming (Table 1, entries 11 and 12).

Believing that use of a sterically more demanding catalyst would improve enantioselectivity, we switched to tryptophan-derived catalyst **13**·AcOH (Figure 1 and Table 1, entries 13–15).[21] The desired trioxygenation did not proceed in acetone using the bulkier catalyst; only aldol and Michael addition products were observed. However, use of the bulkier catalyst improved the enantiomeric ratio to 85:15 when the reaction was

conducted in pentafluorobenzene. Unfortunately, this change also slowed the conversion of the intermediate γ-oxyenal into trioxyaldehyde **12**. The γ-oxyenal was present in 21% yield after 24 hours, but the yield of trioxyaldehyde **12** peaked at this time since the product slowly decomposed under the reaction conditions. Nonetheless, a 59% combined yield of two diastereomers of **12** was obtained. After aldehyde reduction to facilitate chromatographic separation, the major diastereomer was isolated in 51% overall yield (i.e., average of 80% yield per oxygenation)

Table 1. Trioxygenation cascade optimization



entry	amine salt	solvent	yield (%)[a]	dr[b]	er[c]
1	**7**·HCl	acetone	47	2.7:1	43:57
2	**7**·AcOH	acetone	78 (57)	4.1:1	61:39
3	**7**·AcOH	THF	39	9.0:1	66:34
4	**7**·AcOH	DMSO	0	ND	ND
5	**7**·AcOH	$CHCl_3$	0	ND	ND
6	**7**·AcOH	PhMe	42	5.5:1	73:27
7	**7**·AcOH	$PhCF_3$	69 (52)	5.0:1	71:29
8	**7**·AcOH	$C_6H_3F_3$[d]	54	6.8:1	72:28
9	**7**·AcOH	C_6HF_5	66 (59)	>20:1	70:30
10	**7**·AcOH	C_6F_6	48	3.5:1	75:25
11	**7**·TFA	C_6HF_5	67	6.2:1	68:32
12	**7**·HCl	C_6HF_5	58	5.7:1	71:29
13	**13**·AcOH	acetone	0	ND	ND
14	**13**·AcOH	$PhCF_3$	45 (36)	6.4:1	84:16
15	**13**·AcOH	C_6HF_5	59 (51)	8.9:1	85:15

[a]Combined yield of two major diastereomers, determined by crude NMR in the presence of an internal standard. Yields in parentheses refer to the isolated yield of the major diastereomer after $NaBH_4$-mediated reduction.Determined by crude NMR. [c] Determined by chiral HPLC for the major diastereomer. [d] 1,3,5-Trifluorobenzene. ND = not determined.

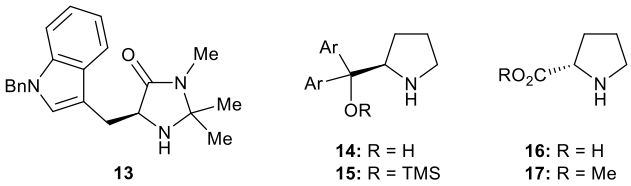
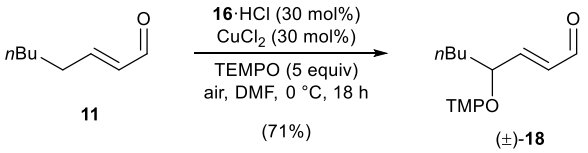


Figure 1. Other secondary amine catalysts screened

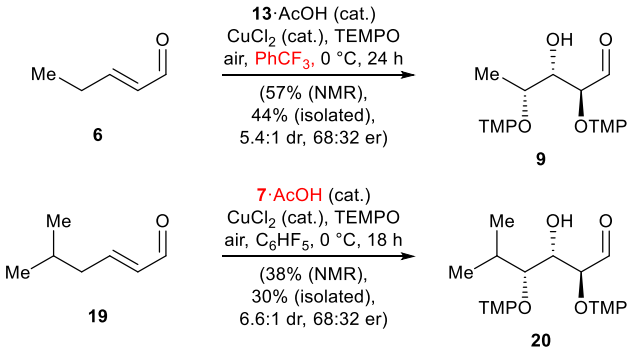
Amine salts of α,α-diarylprolinols (**14**) and related silyl ethers (**15**) also catalyzed the formation of trioxyaldehyde **12**. However, the reactions became even more sluggish when using these catalysts, and neither yield nor stereoselectivity was improved. Proline (**16**), proline methyl ester (**17**), and their salts did not catalyze the trioxygenation cascade. However, proline hydrochloride (**16**·HCl) proved to be a good catalyst for γ-oxygenation. The 71% isolated yield of γ-oxyenal **18** (Scheme 3) using enal **11** as the limiting reagent is comparable to the best γ-oxygenation yields reported by Jang and co-workers using TEMPO as the limiting reagent.[12]



Scheme 3. Proline-catalyzed γ-oxygenation

As shown in Scheme 4, the optimized reaction of C_5 enal **6** gave chiral trioxyaldehyde **9**, but with a worse enantiomeric ratio than that achieved in the reaction of C_8 enal **11**. The absolute configuration of trioxyaldehyde **9** (and, by extension, the

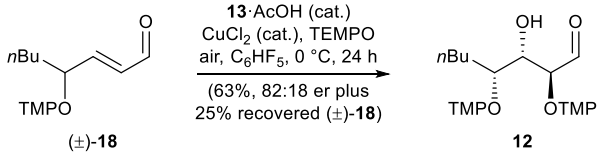
other trioxyaldehydes) was determined by comparing the optical rotation of optically-active tetraacetate **10** (Scheme 2) against that of the known carbohydrate-derived tetraacetate.[22] Since the functional group tolerance of the reaction condition has already been demonstrated in the context of α-oxygenation,[6] we investigated whether the cascade reaction tolerated branching on or near the enal. Substrates with branching at the α, β, or γ position did not undergo α,β,γ-trioxygenation or even γ-oxygenation. Cinnamaldehyde was similarly unreactive. δ-Branching was tolerated (see **19**→**20**), but with poor kinetics. Use of the less bulky catalyst **7**·AcOH delivered a 38% yield of the combined diastereomers, but the enantiomeric ratio suffered.



Scheme 4. Trioxygenation of other substrates

We probed the reaction mechanism of the transformation since such knowledge might assist design of improved enal α,β,γ-trifunctionalizations. As shown in Scheme 5, racemic γ-oxyenal **18** reacted under the optimized trioxygenation conditions to afford trioxyaldehyde **12** in 63% isolated yield (single diastereomer after aldehyde reduction) with 82:18 er and racemic recovered starting material ((±)-**18**) in 25% isolated yield. The

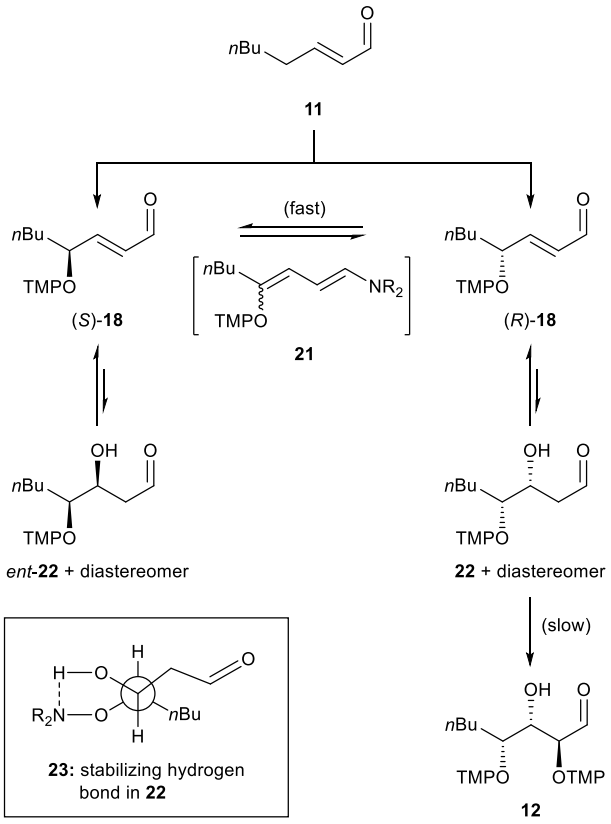
64% combined yield of compounds with the (*R*) configuration at the γ position (12% (*R*)-**18** + 52% major enantiomer of **12**) proves that the enantiomers of γ-oxyenal **18** interconvert under the reaction conditions to afford dynamic kinetic resolution.[16f,h]



Scheme 5. Evidence for dynamic kinetic resolution

The above data leads to a clear mechanistic overview of the cascade, outlined in Scheme 6 using enal **11** as a model substrate. The reaction proceeds through initial formation of γ-oxyenal **18**, a compound that undergoes rapid racemization through the intermediacy of dienamine **21**. β,γ-Dioxyaldehyde **22** is not detected, suggesting that consistent with the nonaqueous reaction conditions, conjugate addition of water is thermodynamically unfavorable.[11] Our recent computational study on 2,2,6,6-piperidinyl-masked vicinal diols[23] reveals a thermodynamic preference for the *syn* diastereomer of **22**, which adopts a six-membered ring hydrogen bond between the β-hydroxyl proton and the piperidinyl nitrogen of the masked γ-hydroxyl group (see **23**). The stability conferred by this hydrogen bond appears to be critical for achieving a sufficiently-high concentration of β,γ-dioxyaldehyde **22** for the subsequent α-oxygenation to proceed at a viable rate; recall that cinnamaldehyde is unreactive. Since water addition is reversible and the enantiomers of γ-oxyenal **18** equilibrate, α-oxygenation sets all three

stereocenters with double dynamic kinetic resolution. The configuration of the masked α-hydroxyl group is consistent with that observed in the α-oxygenation of simple aldehydes.[6]



Scheme 6. Proposed trioxygenation mechanism

Conclusion

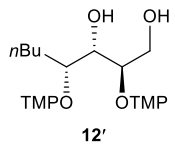
In conclusion, we discovered the first enal α,β,γ-trifunctionalization cascade. The reported trioxygenation is of limited synthetic utility due to moderate enantioselectivity, but the mechanistic insights gained are expected to be useful for the design of improved polyfunctionalization cascades. For example, using a tethered nucleophile or a nucleophile that adds irreversibly should enhance the overall reaction rate by improving

the thermodynamic driving force for the β-functionalization step. The latter change might also enhance enantioselectivity since the catalyst would be able to exert its influence at two steps (α- and β-functionalization). Efforts to translate these ideas into improved cascades are under way.

Experimental

General procedures.

Unless otherwise noted, all reactions were performed with stirring under an argon atmosphere under anhydrous conditions. Reagents were purchased at the most-economical grade. Dry tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and dichloromethane were obtained by passing HPLC grade solvents through commercial solvent purification systems. All other chemicals were used as received, without purification. Flash column chromatography was performed using Grace Davison Davisil silica gel (60 Å, 35–70 μm). Unless otherwise noted, yields refer to chromatographically- and spectroscopically- (^{1}H NMR) homogeneous samples of single diastereomers. Thin-layer chromatography (TLC) was performed on Grace Davison Davisil silica TLC plates using UV light and common stains for visualization. NMR spectra were calibrated using residual undeuterated solvent as an internal reference. Apparent couplings were determined for multiplets that could be deconvoluted visually.



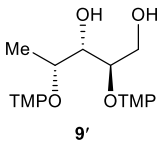
12′

Primary alcohol 12′. To an uncapped solution of imidazolidinone salt **13**·AcOH (104 mg, 0.30 mmol, 0.30 equiv) in pentafluorobenzene (500 μL) was added AcOH (18 μL, 0.30 mmol, 0.30 equiv), $CuCl_2 \cdot 2H_2O$ (51

mg, 0.30 mmol, 0.30 equiv), and dried powdered 4Å molecular sieves (30 mg). The green mixture was stirred for 5 minutes until the copper salt dissolved. The resultant dark brown reaction mixture was cooled to 0 °C and kept at this temperature for the remainder of the reaction. Addition of octenal **11** (52 μL, 0.33 mmol, 0.33 equiv) and TEMPO (315 mg, 2.00 mmol, 2.00 equiv) resulted in a dark orange color. At 45 and 90 minutes (all timings from the initial addition of TEMPO), another equal-sized aliquot of octenal **11** was added. At 135 minutes, additional TEMPO (473 mg, 3.00 mmol, 3.00 equiv) was added. At 24 hours, the reaction mixture was diluted with EtOAc (10 mL) and filtered through Celite. The filtrate was partitioned between EtOAc (30 mL) and saturated NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL), then the combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated to give crude aldehyde **12** as an orange oil.

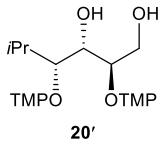
To crude aldehyde **12** in ethanol (5 mL) was added $NaBH_4$ (100 mg, excess). The reaction mixture was stirred for 10 minutes, then diluted with ether (50 mL) and washed with saturated NH_4Cl (50 mL), water (50 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated to give an orange oil. Flash column chromatography (7% EtOAc / $CHCl_3$) gave a single diastereomer of primary alcohol **12′** (233 mg, 51% yield) as a white solid. A sample was derivatized [1. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 2. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IA column, 2.1 × 100 mm, 3 μm; 2% *i*PrOH / hexanes, 0.2 mL / min; 25 °C; 280 nM UV detection; R_t = 7.3 (major), 4.9 (minor) minutes] to have 85:15 er. **12′**: R_f = 0.23 (10% EtOAc / hexanes); $[\alpha]_D^{23}$ = −11.1 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3320, 2930, 1373 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 6.73 (br s, 1H), 5.27 (br s, 1H),

4.16 (dd, *J* = 12.2, 7.8 Hz, 1H), 4.10 – 3.96 (m, 3H), 3.87 (br d, *J* = 10.8 Hz, 1H), 1.63 – 1.42 (m, 13H), 1.41 – 1.27 (m, 14H), 1.25 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.13 (s, 6H), 0.91 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 81.7, 80.8, 76.6, 64.5, 61.4, 61.3, 60.5, 60.2, 40.6, 40.5, 40.3, 40.1, 34.41, 34.35, 33.2, 32.3, 30.3, 27.9, 23.1, 20.74, 20.70, 20.67, 20.64, 17.27, 17.25, 14.3 ppm; HRMS (ESI-QTOF) calcd for $C_{26}H_{53}N_2O_4^+$ [M + H^+]: 457.4005, found: 457.4000.



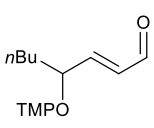
9′

Primary alcohol 9′. Primary alcohol **9′** was prepared in the same manner as primary alcohol **12′**, using α,α,α-trifluorotoluene instead of pentafluorobenzene. Flash column chromatography (7% EtOAc / $CHCl_3$) gave a single diastereomer of primary alcohol **9′** (44% yield) as a white solid. A sample was derivatized [1. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 2. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IA column, 2.1 × 100 mm, 3 μm; 2% *i*PrOH / hexanes, 0.2 mL / min; 25 °C; 280 nM UV detection; R_t = 10.8 (major), 7.3 (minor) minutes] to have 68:32 er. **9′**: R_f = 0.29 (15% EtOAc / hexanes); $[\alpha]_D^{23}$ = +1.9 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3318, 2932, 1373 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 5.94 (br s, 1H), 5.31 (d, *J* = 8.9 Hz, 1H), 4.21 – 4.11 (m, 2H), 4.07 (m, 1H), 3.91 – 3.83 (m, 2H), 1.67 – 1.42 (m, 10H), 1.39 – 1.26 (m, 11H), 1.23 (s, 3H), 1.20 – 1.16 (m, 6H), 1.13 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 81.8, 77.9, 77.5, 77.0, 64.5, 61.4, 60.9, 60.5, 60.2, 40.6, 40.4, 40.3, 40.2, 34.5, 34.4, 33.1, 32.7, 20.73, 20.70, 20.6, 17.28, 17.27, 16.6 ppm; HRMS (ESI-QTOF) calcd for $C_{23}H_{47}N_2O_4^+$ [M + H^+]: 415.3536, found: 415.3532.



20′

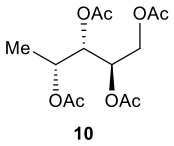
Primary alcohol 20′. Primary alcohol **20′** was prepared in the same manner as primary alcohol **12′**, using imidazolidinone salt **7**·AcOH instead of imidazolidinone salt **13**·AcOH and with a reaction time of 18 hours instead of 24 hours for the trioxygenation step. Flash column chromatography (7% EtOAc / $CHCl_3$) gave a single diastereomer of primary alcohol **20′** (30% yield) as a white solid. A sample was derivatized [1. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 2. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IA column, 2.1 × 100 mm, 3 μm; 2% *i*PrOH / hexanes, 0.2 mL / min; 25 °C; 280 nM UV detection; R_t = 9.7 (major), 5.2 (minor) minutes] to have 68:32 er. **20′**: R_f = 0.31 (10% EtOAc / hexanes); $[\alpha]_D^{23}$ = +16.2 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 3470, 3456, 2926, 1360 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 5.17 (d, *J* = 8.6 Hz, 1H), 4.30 (dd, *J* = 9.2, 3.4 Hz, 1H), 4.21 (dd, *J* = 12.3, 7.7 Hz, 1H), 4.04 (dt, *J* = 7.6, 3.1 Hz, 1H), 3.93 (dd, *J* = 9.2, 1.9 Hz, 1H), 3.82 (ddd, *J* = 12.3, 9.0, 3.0 Hz, 1H), 2.01 (doublet of septets, *J* = 6.9, 1.8 Hz, 1H), 1.64 – 1.55 (m, 2H), 1.54 – 1.41 (m, 8H), 1.38 – 1.31 (m, 8H), 1.290 (s, 3H), 1.286 (s, 3H), 1.19 (s, 3H), 1.16 (s, 3H), 1.15 (s, 6H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 84.8, 81.8, 75.8, 64.1, 62.2, 61.1, 60.8, 60.3, 40.7, 40.6, 40.4, 40.1, 34.7, 34.5, 33.2, 31.8, 29.7, 21.4, 20.73, 20.69, 20.65, 17.3, 17.2, 15.2 ppm; HRMS (ESI-QTOF) calcd for $C_{25}H_{51}N_2O_4^+$ [M + H^+]: 443.3849, found: 443.3847.



18

γ-Oxyenal 18. γ-Oxyenal **18** was prepared following the above protocol for the synthesis of aldehyde **12**, using proline salt **16**·HCl instead of

imidazolidinone salt **13**·AcOH, using DMF instead of pentafluorobenzene, and with a reaction time of 18 hours. Flash column chromatography (4% EtOAc / hexanes) gave γ-oxyenal **18** (71% yield) as a light yellow oil. A sample was derivatized [1. NaBH, EtOH 2. *m*-nitrobenzoyl chloride, Et_3N, DMAP (cat.), CH_2Cl_2; 3. Zn, AcOH, THF, H_2O] and determined by chiral HPLC [Chiraltech IB column, 2.1 × 100 mm, 3 μm; 0.5% *i*PrOH / hexanes, 0.2 mL / min; 25 °C; 280 nM UV detection; R_t = 17.8, 19.1 minutes] to be racemic. **18**: R_f = 0.40 (5 % Et_2O / hexanes); IR (thin film): ν_{max} = 2931, 1694, 1132 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 9.57 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 15.9, 8.0 Hz, 1H), 6.12 (ddd, *J* = 15.8, 8.0, 0.7 Hz, 1H), 4.43 (dt, *J* = 5.4, 7.7 Hz, 1H), 1.79 (m, 1H), 1.58 (m, 1H), 1.50 – 1.23 (m, 10H), 1.18 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 193.7, 159.3, 131.7, 83.1, 60.1, 59.3, 40.0, 34.5, 33.8, 33.4, 26.9, 22.5, 20.2, 20.1, 16.9, 13.8 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{32}NO_2^+$ [M + H^+]: 282.2433, found: 282.2428.



10

Tetraacetate 10: To a solution of alcohol **9′** (128 mg, 0.31 mmol, 1.0 equiv.) in 5 mL of 3:1:1 solvent mixture (HOAc:H_2O:THF) was added zinc (201 mg, 3.1 mmol, 10 equiv.). The reaction mixture was stirred at 70 °C for one hour. After cooling, the reaction mixture was diluted with dichloromethane (20 mL), filtered through Celite, concentrated, and azeotropically dried with toluene to give a white solid. To this solid was added pyridine (3.0 mL, excess), Ac_2O (3.0 mL, excess), and DMAP (1.9 mg, 0.015 mmol, 0.05 equiv.). The reaction mixture was stirred for 16 hours, then partitioned with EtOAc (30 mL) and 0.5 *N* HCl (30 mL). The organic phase was washed with water (2 × 30 mL) and brine (20 mL), dried over Na_2SO_4, and

concentrated to give a white solid. Flash column chromatography (20% EtOAc / hexanes) gave tetraacetate **10** (41 mg, 43% yield) as a white solid. **10**: R_f = 0.31 (30% EtOAc / hexanes); $[\alpha]_D^{23}$ = +11.6 ° (*c* = 1.00, $CHCl_3$); IR (thin film): ν_{max} = 2927, 1738, 1373, 1212 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 5.23 (dd, *J* = 8.4, 3.0 Hz, 1H), 5.20 – 5.15 (m, 2H), 4.24 (dd, *J* = 12.4, 2.5 Hz, 1H), 4.15 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.14 (s, 3H), 2.053 (s, 3H), 2.050 (s, 3H), 2.04 (s, 3H), 1.18 (d, *J* = 6.5 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.8, 170.4, 170.1, 170.0, 71.6, 68.7, 67.5, 62.1, 21.1, 20.9, 20.84, 20.77, 16.4 ppm; HRMS (ESI-QTOF) calcd for $C_{13}H_{21}O_8^+$ [M + H^+]: 305.1236, found: 305.1237.

References

1. (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc*. **2000**, *122*, 2395. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. **2000**, *122*, 4243.

2. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*.**2007**, *107*, 5471. (b) MacMillan, D. W. C.; Beeson, T. D. In Science of Synthesis, Asymmetric Organocatalysis; List, B., Maruoka, K., Eds.; Georg Thieme: Stuttgart, **2012**; Vol. *1*, pp 271−307. (c) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874.(d) Deng, Y.; Kumar, S.; Wang, H. *Chem. Commun*. **2014**, *50*, 4272.

3. Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416.
4. (a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem*. **2012**, *2012*, 865. (b) Lear, M. J.; Hayashi, Y. *ChemCatChem* **2013**, *5*, 3499.

5. (a) Zhong, G. *Angew. Chem., Int. Ed*. **2003**, *42*, 4247. (b) Brown, S. P.;

Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. J. Am. Chem. Soc. **2003**, *125*, 10808. (c) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett*. **2003**, *44*, 8293.

6. (a) Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc*. **2007**, *129*, 4124. (b) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6638. (c) Van Humbeck, J. F.; Simonovich, S. P.; Knowles, R. R.; Macmillan, D. W. C. *J. Am. Chem. Soc*. **2010**, *132*, 10012. (d) Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci*. **2012**, *3*, 58.

7. Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc*. **2004**, *126*, 8914.

8. Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2007**, *129*, 1536.

9. (a) Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* **2007**, *63*,8658. (b) Díez, D.; Núñez, M. G.; Benéitez, A.; Moro, R. F.; Marcos, I. S.; Basabe, P.; Broughton, H. B.; Urones, J. G. *Synlett* **2009**, *2009*, 390. (c) McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett*. **2011**, *13*, 6460.

10. Hu, L.; Lu, X.; Deng, L. *J. Am. Chem. Soc*. **2015**, *137*, 8400.

11. Nising, C. F.; Bräse, S. *Chem. Soc. Rev*. **2012**, *41*, 988.

12. Ho, X.-H.; Jung, W.-J.; Shyam, P. K.; Jang, H.-Y. *Catal. Sci. Technol*. **2014**, *4*, 1914.

13. (a) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem*. **2010**, *2*, 167. (b) Pellissier, H. *Adv. Synth. Catal*. **2012**, *354*, 237. (c) Volla, C. M. R.; Atodiresei, I.;

Rueping, M. *Chem. Rev.* **2014**, *114*, 2390.

14. (a) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2005**, *127*, 3240. (b) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 6964. (c) Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413. (d) Zhao, G.-L.; Ibrahem, I.; Sundén, H.; Córdova, A. *Adv. Synth. Catal*. **2007**, *349*, 1210. (e) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778.

15. (a) Yoon, H.-S.; Ho, X.-H.; Jang, J.; Lee, H.-J.; Kim, S.-J.; Jang, H.-Y. *Org. Lett*. **2012**, *14*, 3272. (b) Kim, J.-H.; Park, E.-J.; Lee, H.-J.; Ho, X.-H.; Yoon, H.-S.; Kim, P.; Yun, H.; Jang, H.-Y. *Eur. J. Org. Chem*. **2013**, *2013*, 4337. (c) Shyam, P. K.; Jang, H.-Y. Eur. J. Org. Chem. **2014**, *2014*, 1817.

16. (a) Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (b) Li, H.; Wang, J.; ENunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun*. **2007**, 507. (c) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova,A. *Chem. - Eur. J*. **2007**, *13*, 574. (d) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett*. **2007**, *48*, 5701. (e) Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem., Int. Ed*. **2009**, *48*, 5701. (f) Lin, S.; Zhao, G.-L.; Deiana, L.; Sun, J.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Chem. - Eur. J.* **2010**, *16*, 13930. (g) Quintard, A.; Alexakis, A. *Chem. Commun*. **2011**, *47*, 7212. (h) McGarraugh, P. G.; Johnston, R. C.; Martínez-Muñoz, A.; Cheong, P. H.-Y.; Brenner-Moyer, S. E. *Chem. - Eur. J.* **2012**, *18*, 10742.

17. (a) Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2012**, *134*, 2543. (b) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem., Int. Ed*. **2012**, *51*, 4104.

(c) Appayee, C.; Fraboni, A. J.; Brenner-Moyer, S. E. *J. Org. Chem*. **2012**, *77*, 8828.

18. (a) Bappert, E.; Müller, P.; Fu, G. C. *Chem. Commun*. **2006**, 2604. (b) Robinson, E. R. T.; Fallan, C.; Simal, C.; Slawin, A. M. Z.; Smith, A. D. *Chem. Sci*. **2013**, *4*, 2193. (c) Liu, G.; Shirley, M. E.; Van, K. N.; McFarlin, R. L.; Romo, D. *Nat. Chem*. **2013**, *5*, 1049. (d) Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 13688. (e) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc*. **2014**, *136*, 4492.

19. Abeykoon, G. A.; Chatterjee, S.; Chen, J. S. *Org. Lett*. **2014**, *16*, 3248.

20. Takai, K.; Heathcock, C. H. *J. Org. Chem*. **1985**, *50*, 3247.

21. Peifer, M.; Berger, R.; Shurtleff, V. W.; Conrad, J. C.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2014**, *136*, 5900.

22. Sowden, J. C.; Strobach, D. R. *J. Am. Chem. Soc*. **1960**, *82*, 3707.

CHAPTER 5

CONCLUSION

The new methodology to access differentially protected *anti*-1,2-diols from organomagnesium or organolithium addition to α-oxyaldehydes is described in the second chapter. *Anti*-1,2-diols can be synthesized with high diastereoselectivity applying the method developed, regardless of the hybridization or the nature of branching of the incoming carbon nucleophile. However, the attempts to optimize of the protocol towards complete *syn* selectivity, using chelating metal salts was not successful suggesting that the TMP masking group on the α-hydroxyl group is too bulky to be coordinated. However, initial diastereoselectivity was often degraded when the chelating agents were introduced. As a solution, oxidation of *anti*-1,2-diols followed by reduction of the corresponding ketones was used to deliver masked *syn*-1,2-diols.

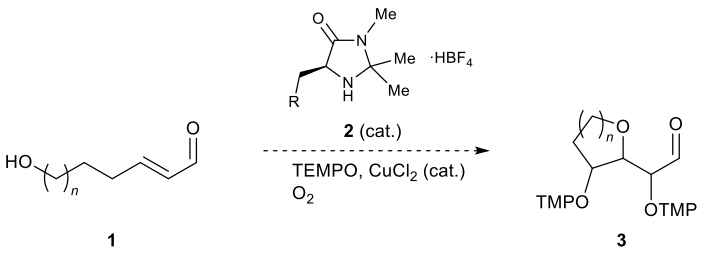
The third chapter showcases the application of the 1,2-diol synthesis discussed in chapter two in a short synthesis of unnamed oxylipins isolated from the Peruvian plant *Dracontium loretense*. In the first generation, we synthesized all possible diastereomers of oxylipins and compared the NMR spectroscopic data and polarimetry data of the synthetic oxylipins with what was reported by isolation chemists, which led to the unambiguous absolute stereochemical determination of natural oxylipins isolated from *Dracontium loretense*. Furthermore, the absolute configuration of the natural immunostimulant is 6*R*, 9*S*, 10*R*, whereas the natural oxylipin with *syn* 1,2-diol moiety is 6*R*, 9*S*, 10*S*. Our seven step long first generation synthesis is tied for the shortest synthesis of oxylipins containing the 3-ene-1,2,5-triol moiety. However, our synthesis is the shortest route to access oxylipins with *anti*-1,2-diol moiety. Furthermore,

incorporation of olefin metathesis and minimalizing masking group transformations in our second generation synthesis led to development of shortest ever oxylipin synthesis with three steps. This synthesis is not only the shortest, but also it is the most efficient synthesis with highest overall yield (33%). Also, optimization of the organocatalytic enantioselective α-oxygenation via oxidative incorporation of TEMPO to explore low organocatalyst loadings is one of the outcome of the our second generation oxylipin synthesis. Furthermore, our 5 mol % loading of chiral imdazolidinone salts is the lowest ever reported catalyst loading for any reported organocatalytic, enantioselective α-oxygenation of aldehydes via oxidative incorporation of TEMPO.

Subjecting an enal to the enantioselective organocatalytic enantioselective α-oxygenation, led to the discovery of the first ever α,β,γ-trifunctionalization cascade of enals, which is detailed in chapter 4. Moderate yields and enantioselectivities were observed in trioxygenation when tryptophan based chiral imidazolidinones were used as the catalyst in fluorinated aromatic solvents. Moreover, the trioxygenation reaction cascade proceeds via initial γ-incorporation of TEMPO to the enal, which undergoes rapid racemization. Next, the reversible conjugate addition of water followed by final α-incorporation of TEMPO sets all three chiral centers with double dynamic kinetic resolution.

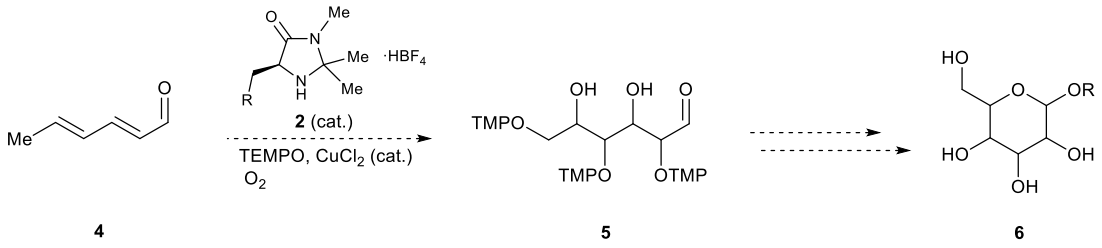
Future work in this α,β,γ-trifunctionalization cascade of enals includes further optimization of enantioselectivity. However, one of the problems of optimization of the enantioselectivity of the α,β,γ-trioxygenation is the reversible conjugate addition of water to enal. Therefore, incorporation of a tethered oxygen nucleophile such as a hydroxyl

group, which can make a thermodynamically favorable ring at β position, could overcome the thermodynamically unfavorable nature of the conjugate addition of oxygen nucleophile (Scheme 1). Hence, enantioselectivity may be improved. Moreover, use of different nucleophiles such as the anion of diethyl malonate, nitrile could introduce different functionalities at the β position of the enal.



Scheme 1: Cyclic ether synthesis

Another potential direction is the extension of this α,β,γ-trioxygenation technology to polyoxygenation of extended enals **4**. The resultant masked polyoxygenated aldehyde may deliver a protected hexose **6** upon cyclization (Scheme 2).



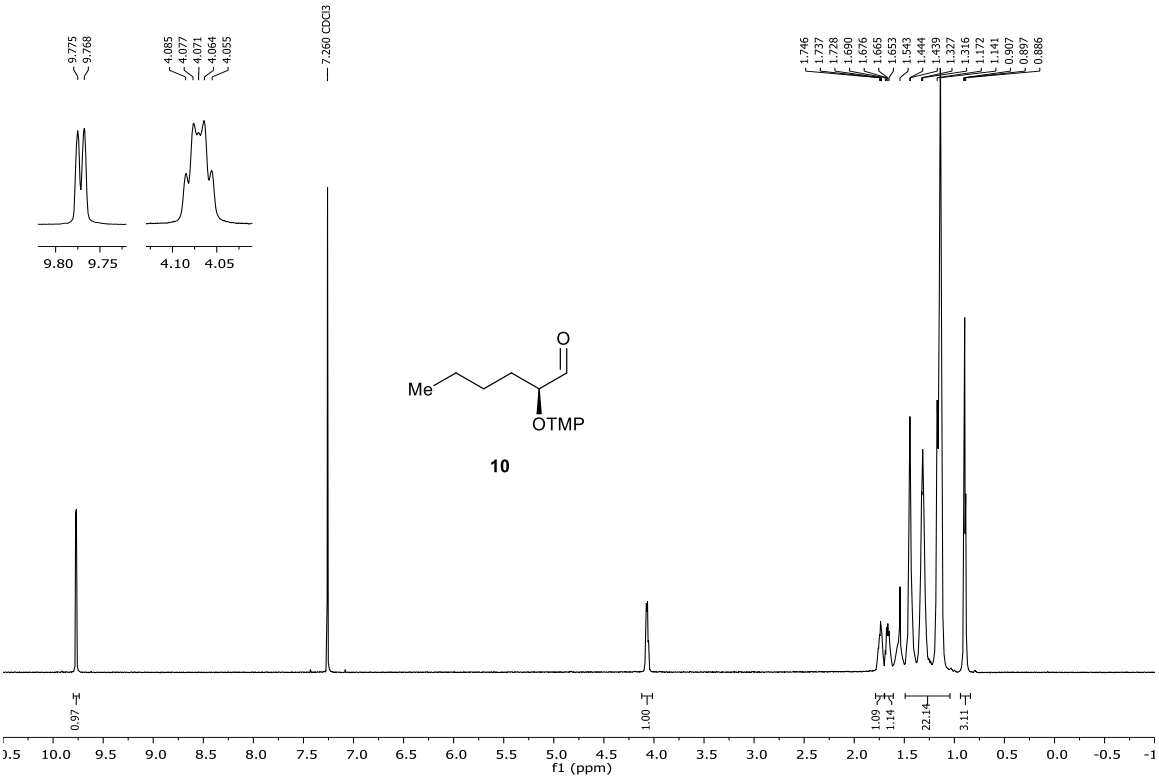
Scheme 2: Extended polyoxygenation towards hexoses synthesis.

APPENDIX A

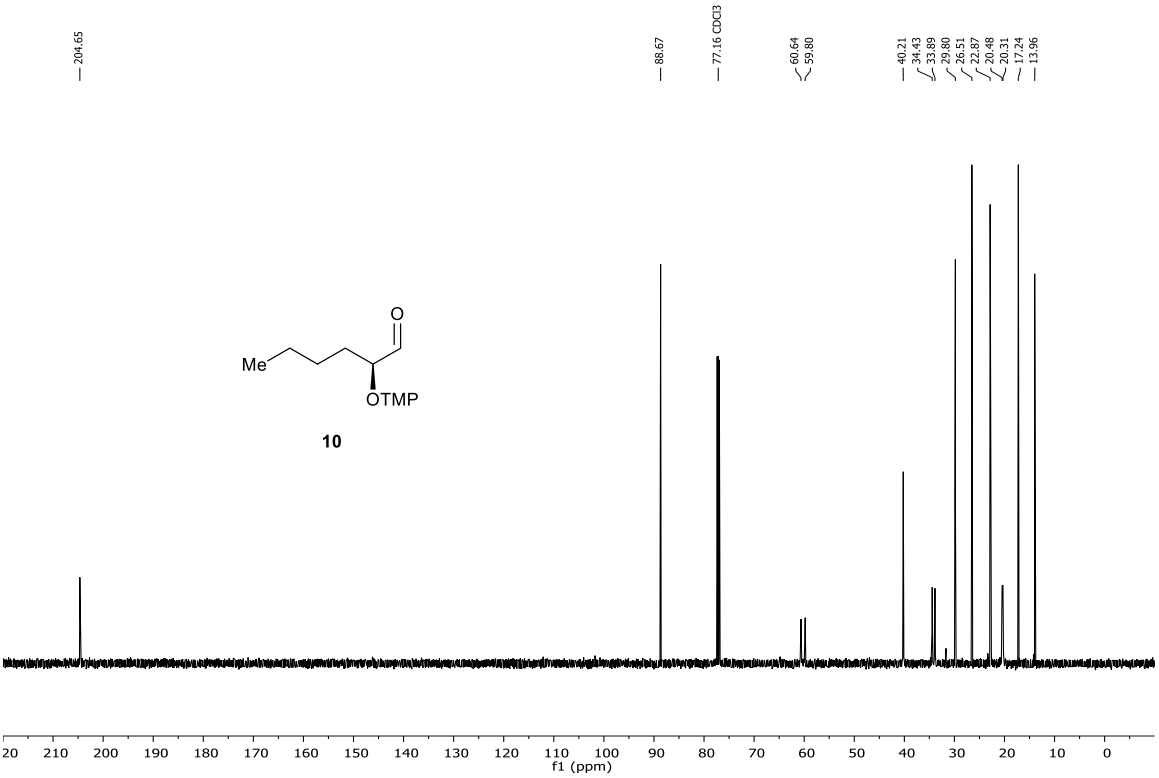
CHAPTER 1: *ANTI* 1,2-DIOLS FROM α-OXYALDEHYDES

NMR SPECTRA

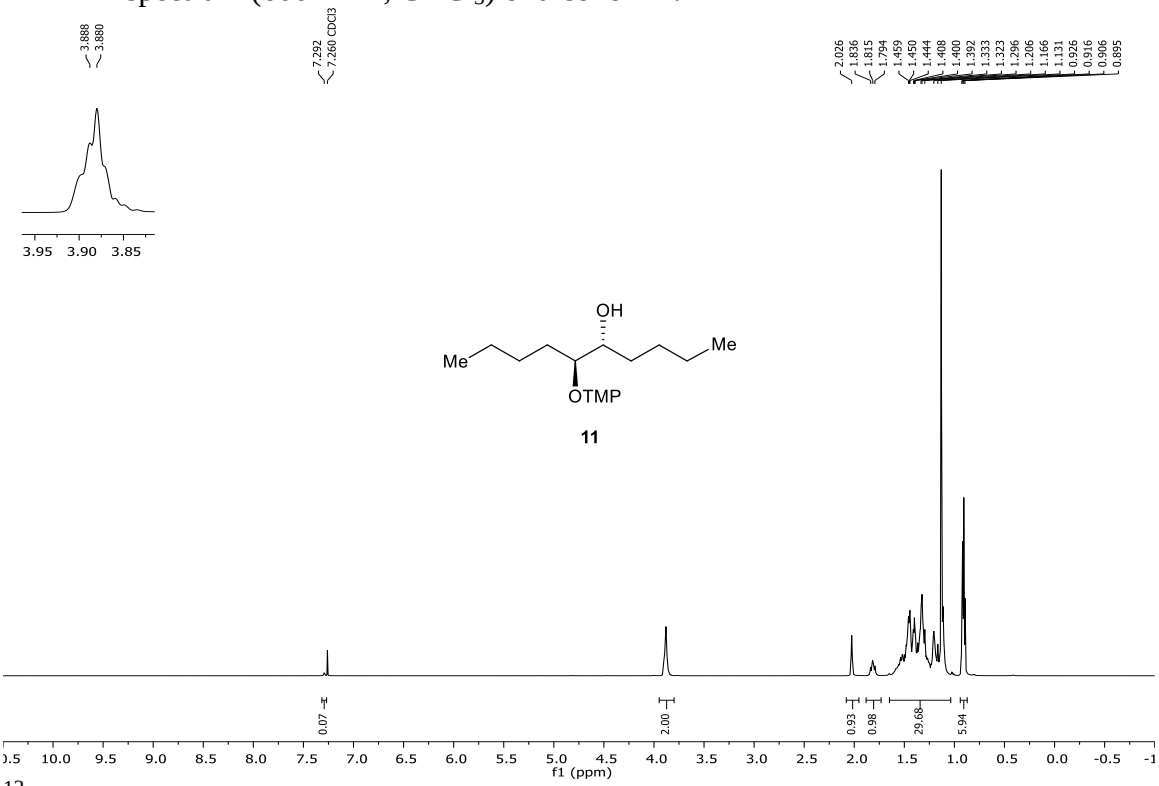
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of aldehyde **10:**



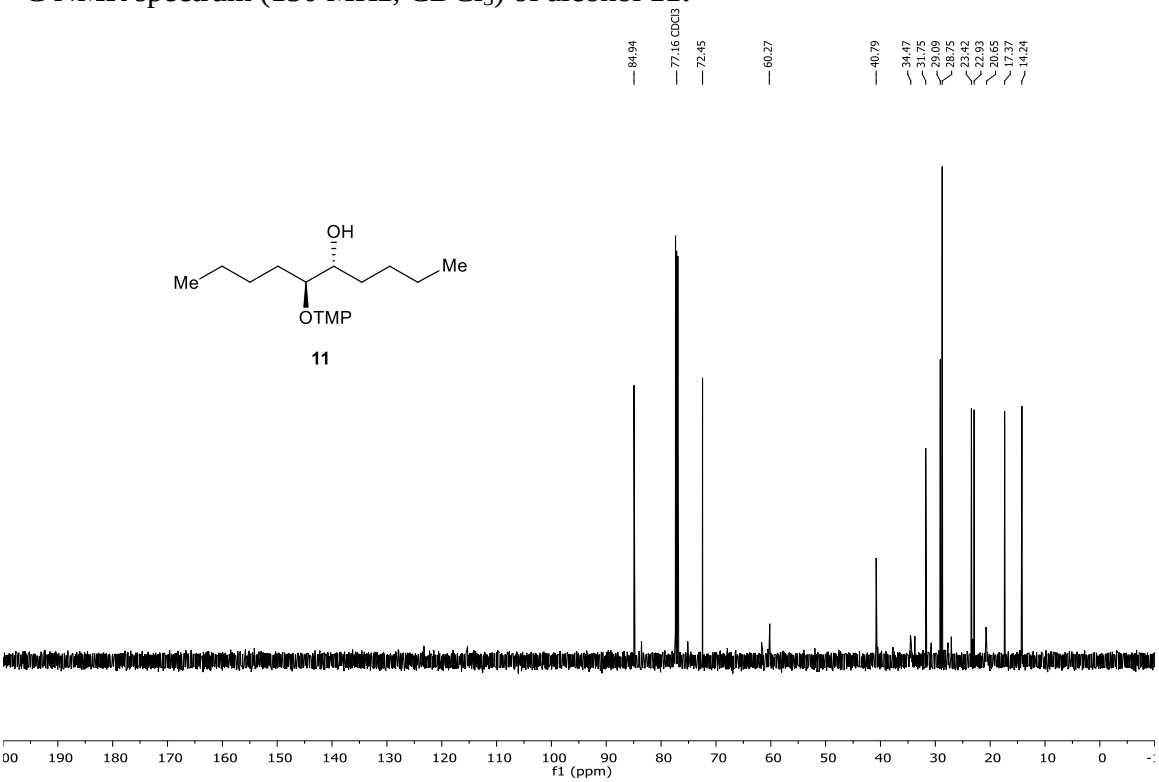
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of aldehyde **10:**



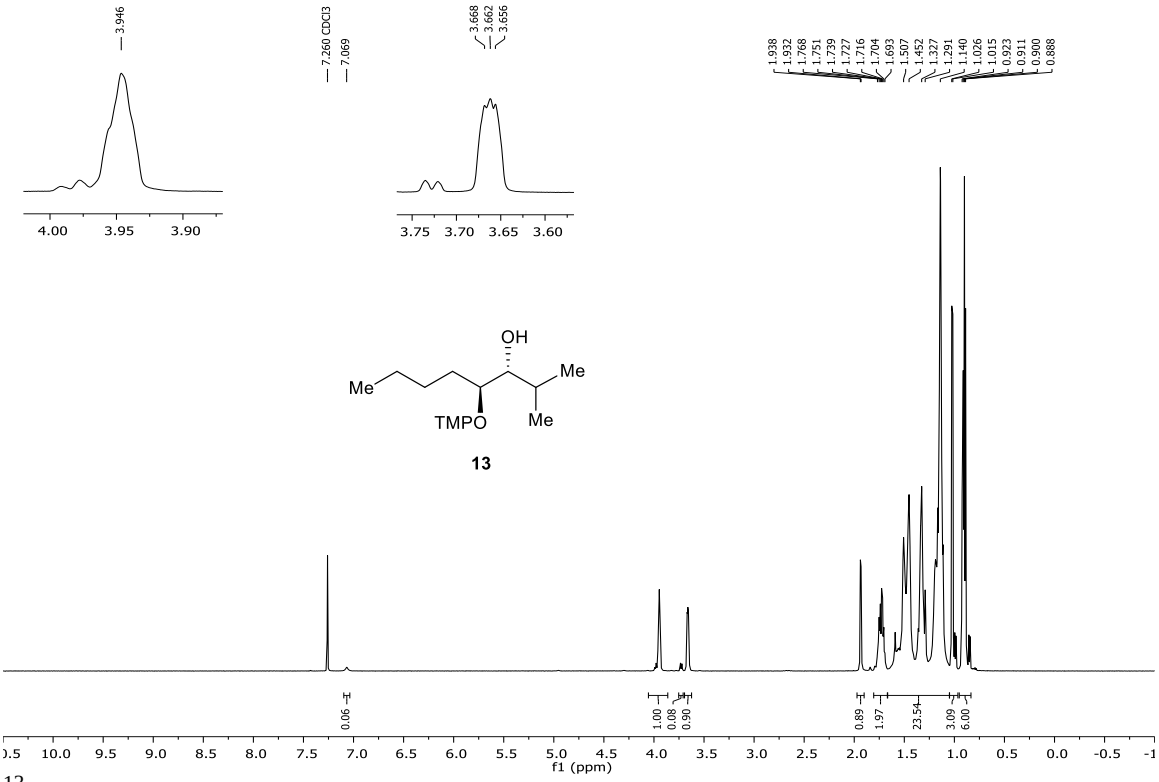
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **11:**



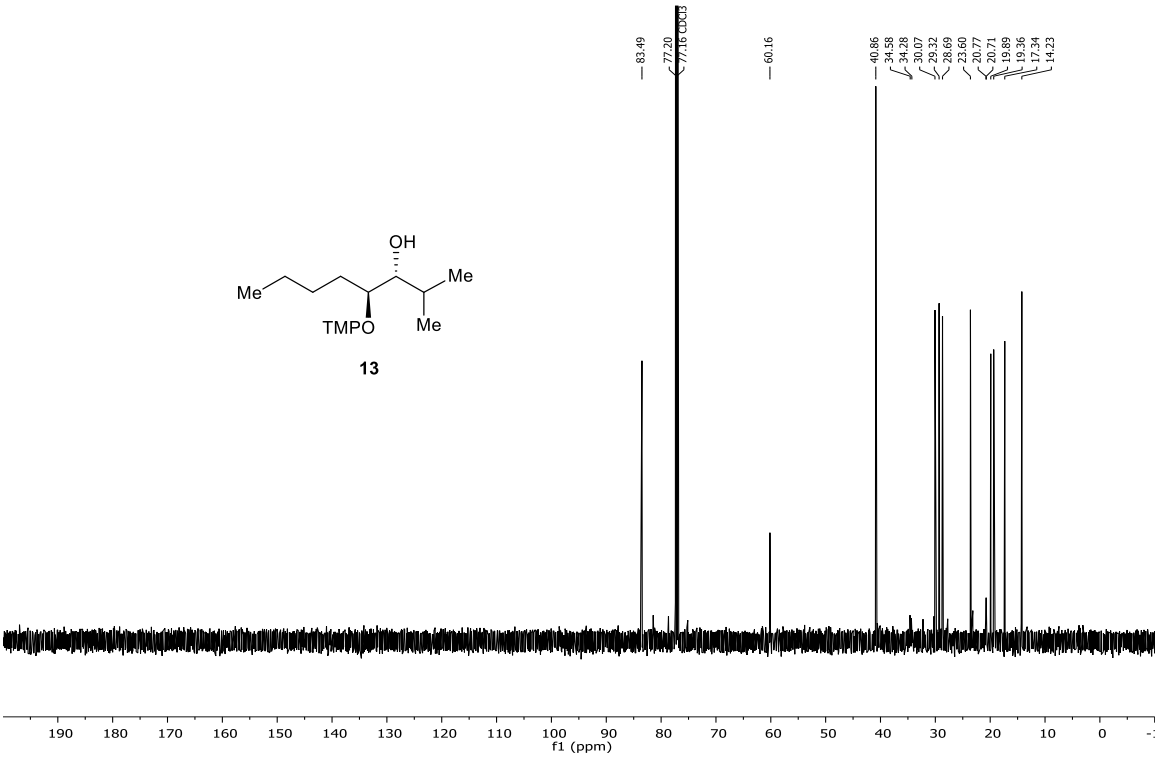
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **11:**



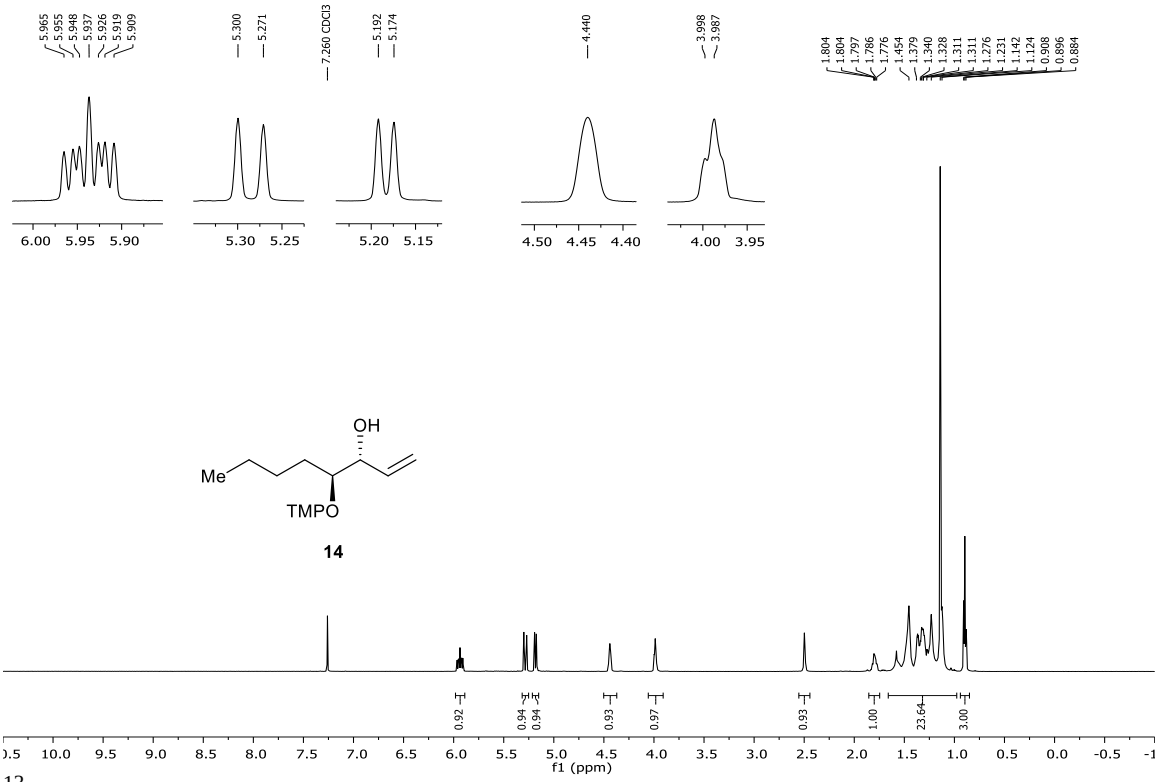
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **13:**



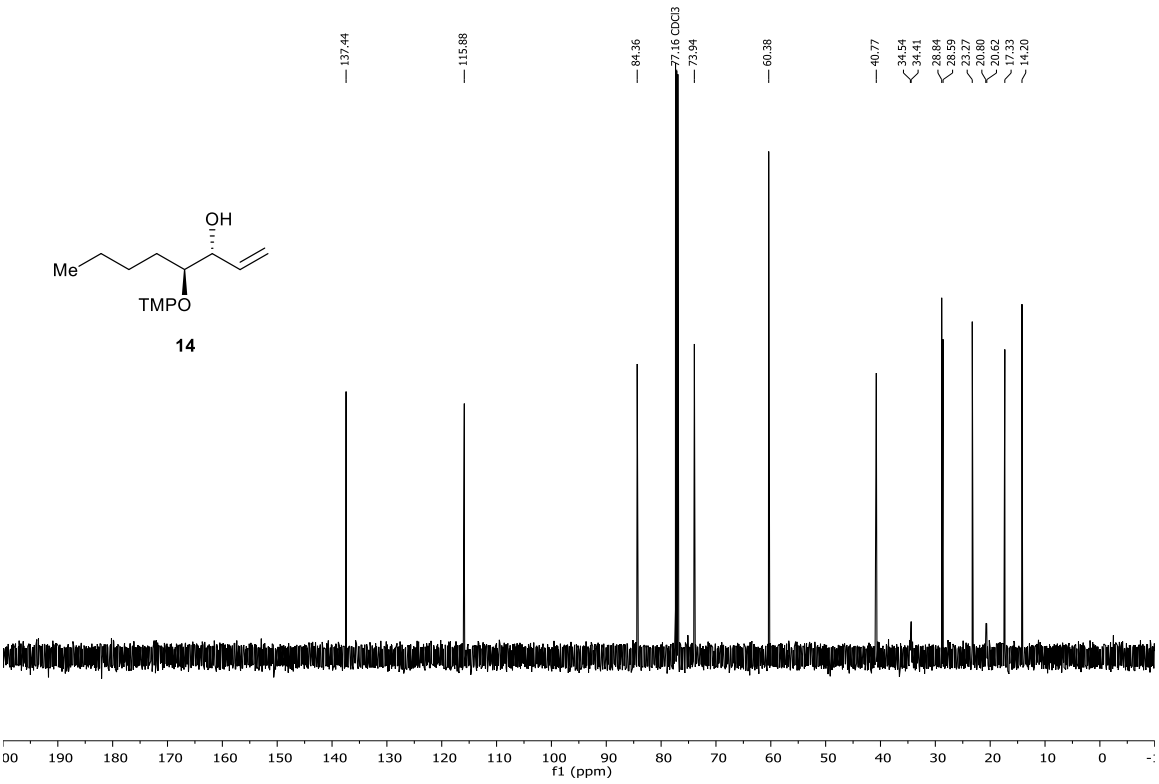
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **13:**



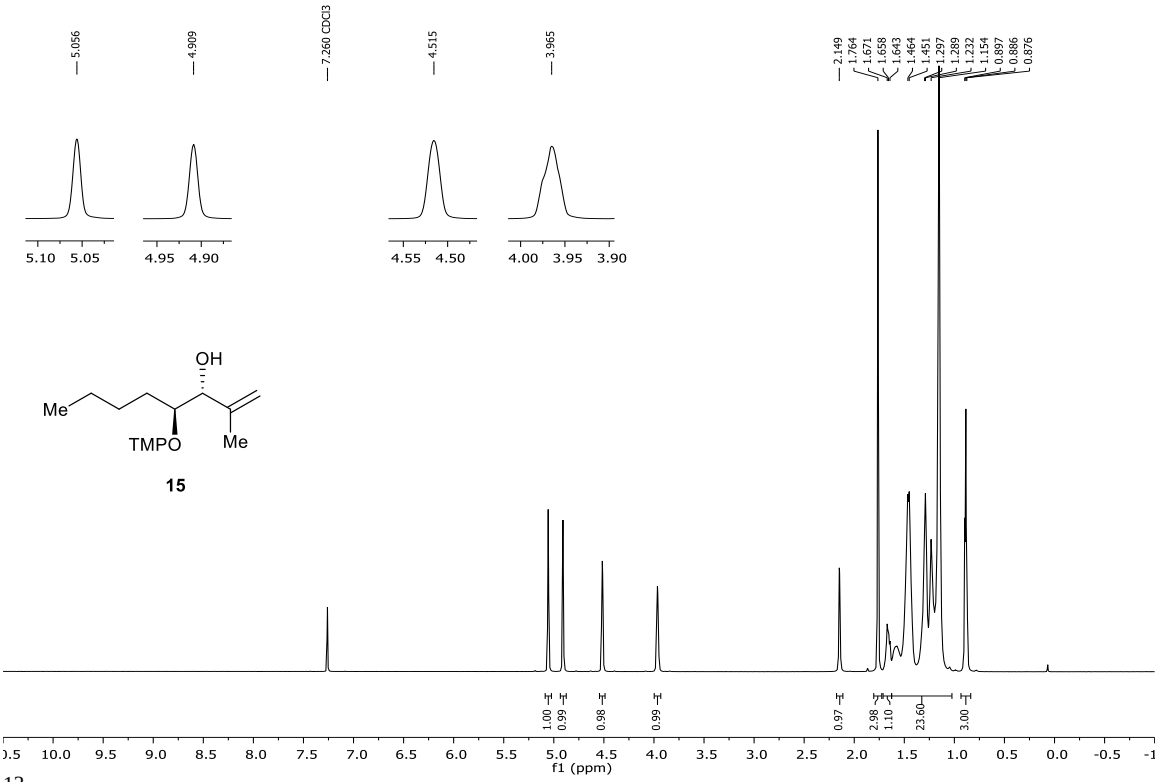
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **14**



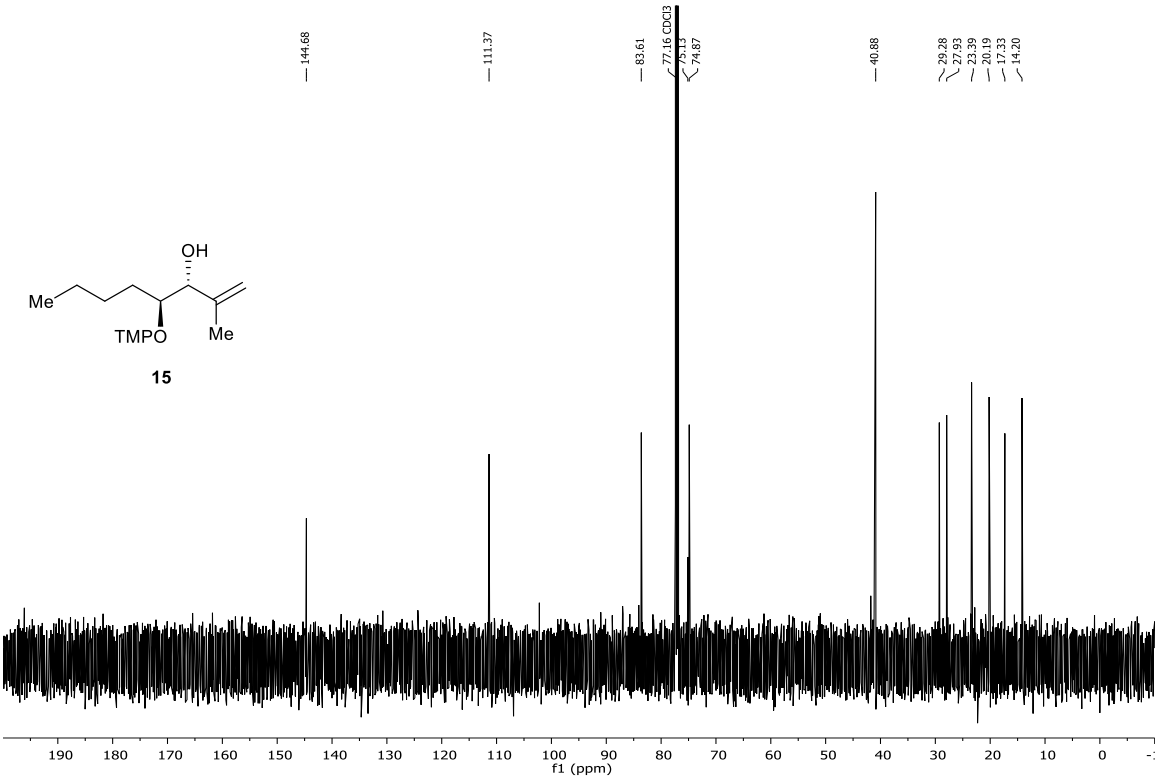
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **14:**



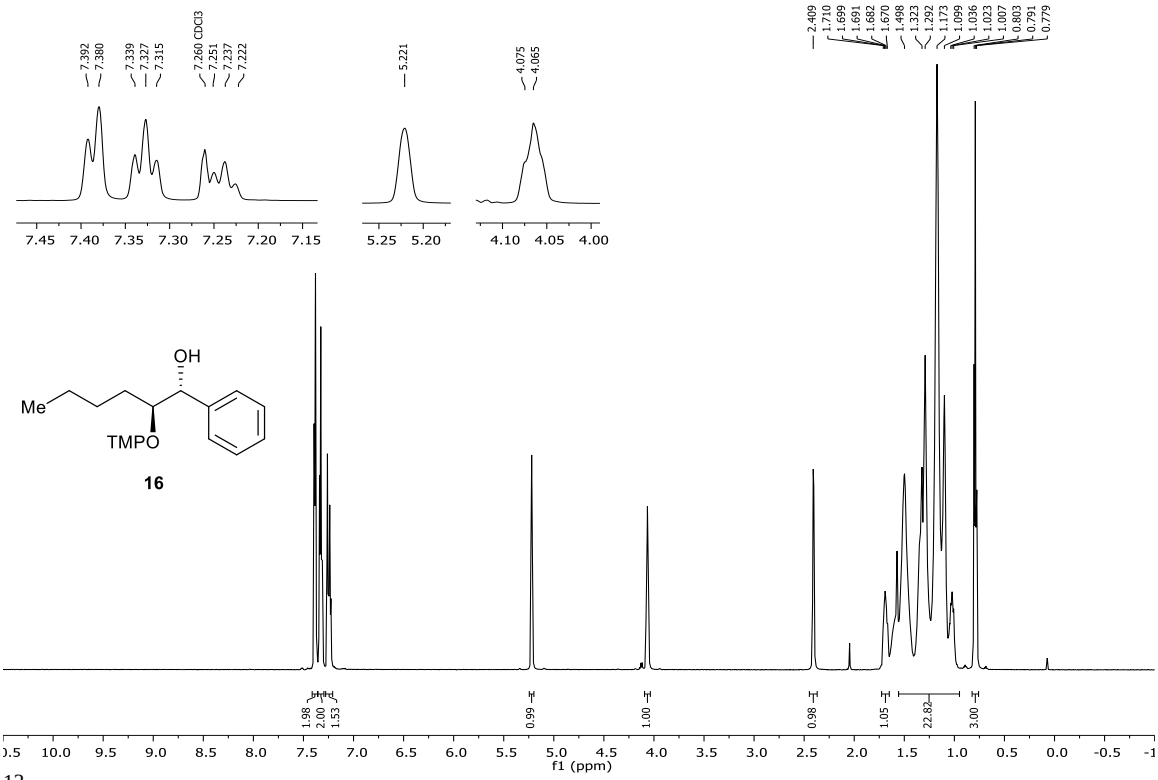
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **15:**



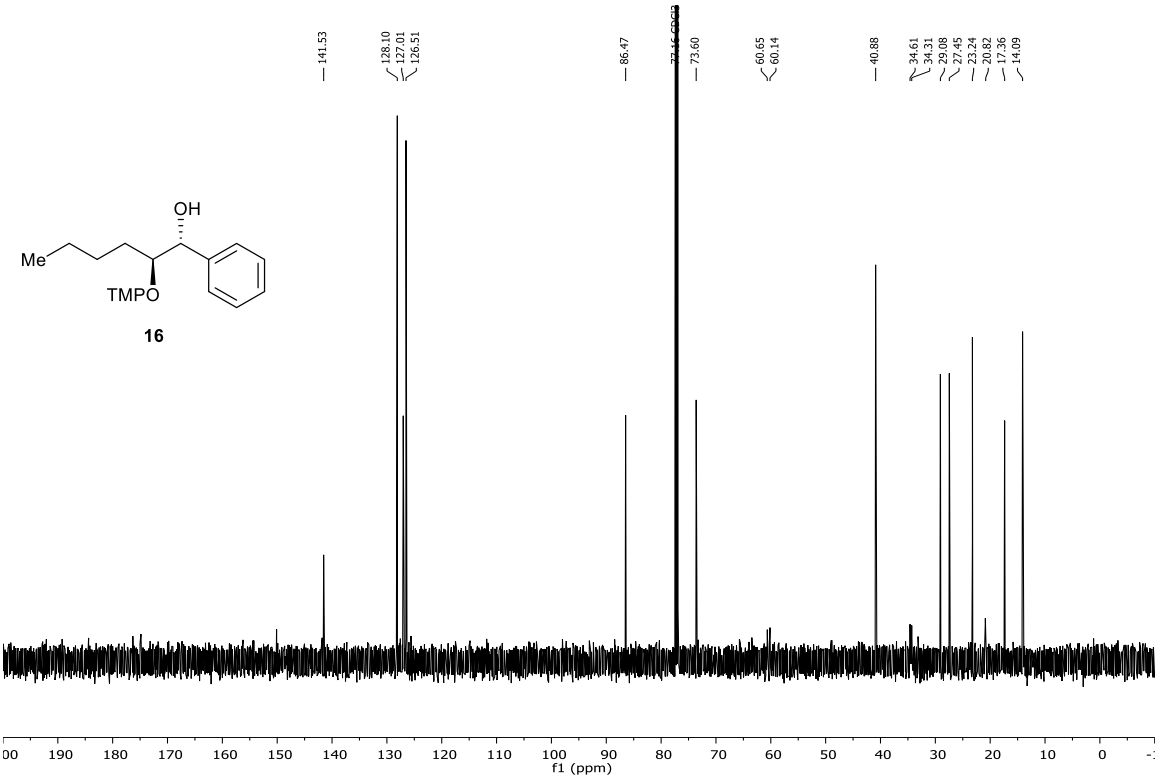
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **15:**



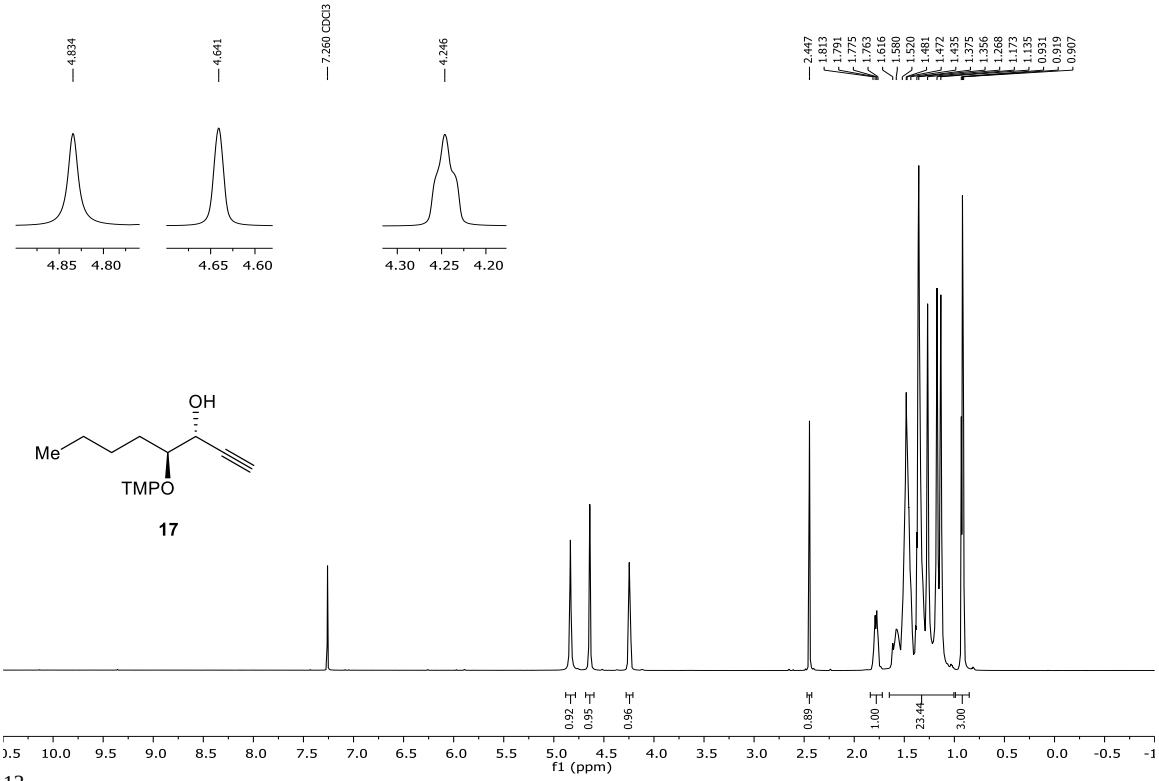
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **16:**



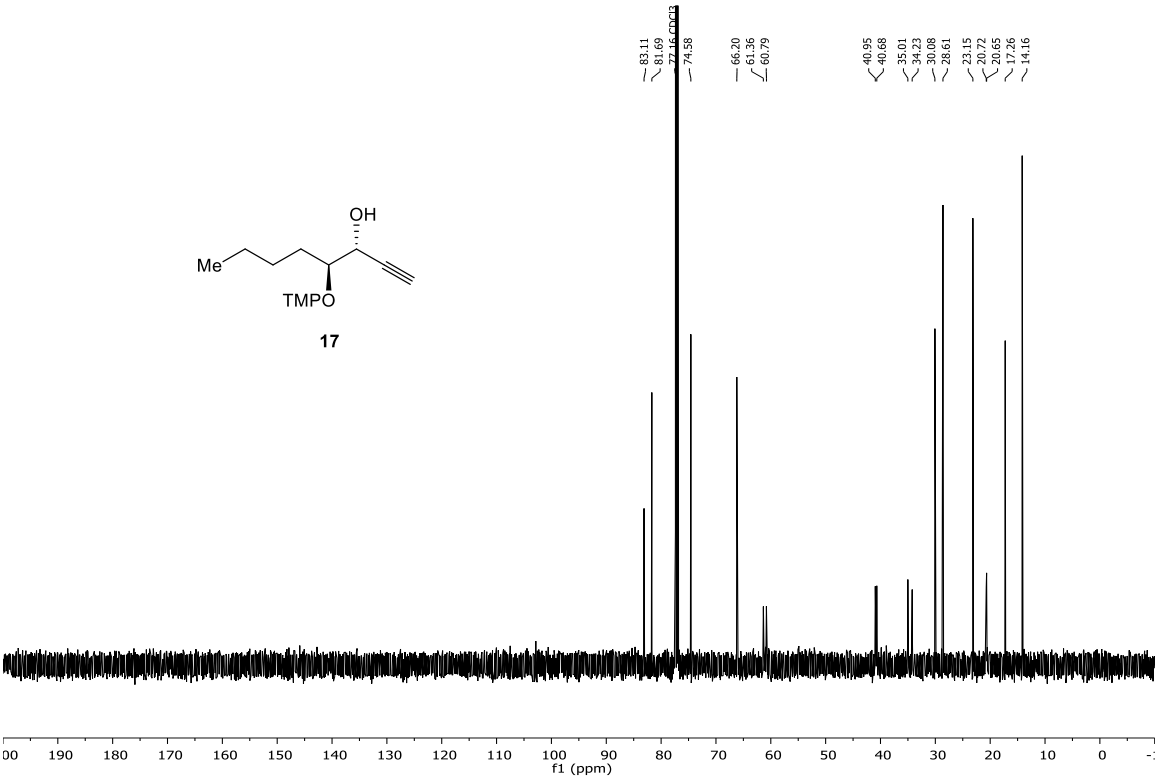
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **16:**



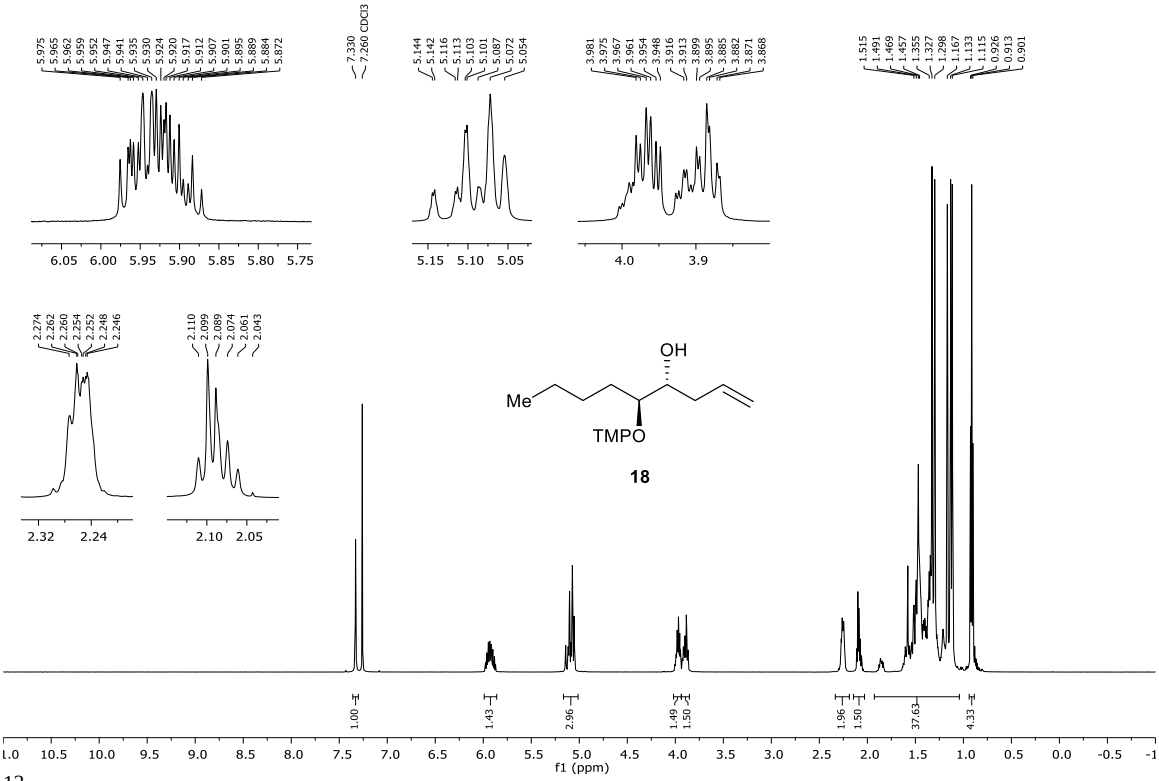
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **17:**



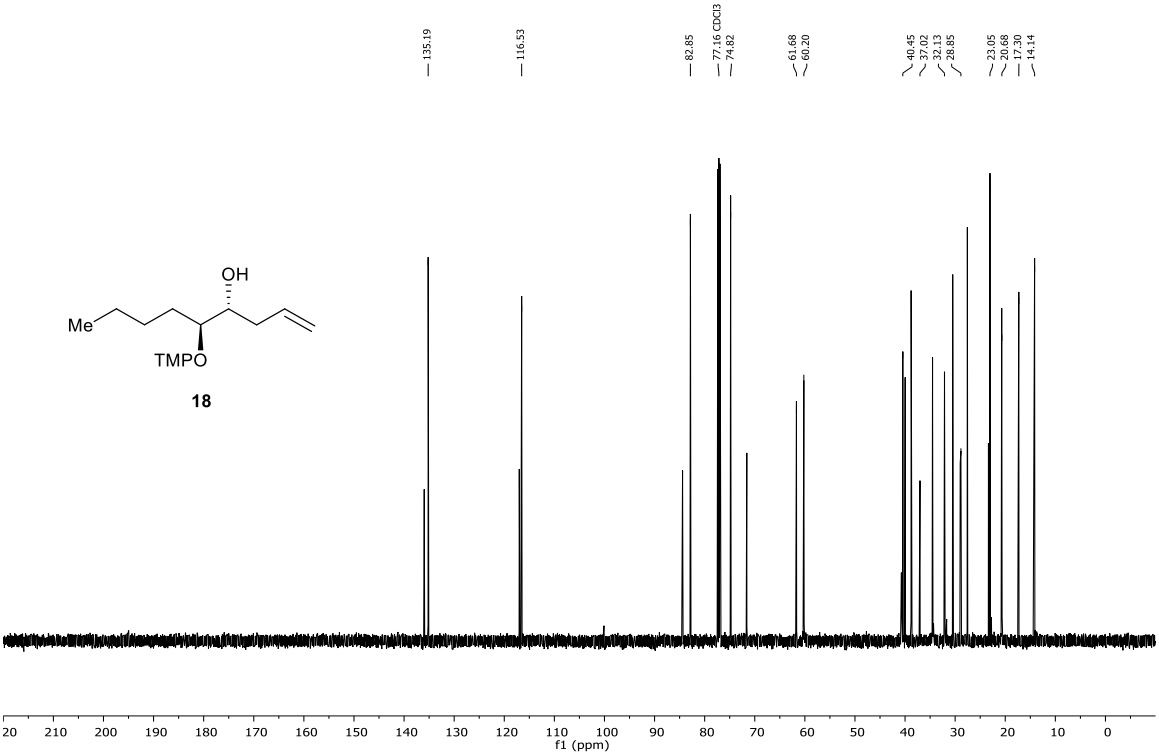
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **17:**



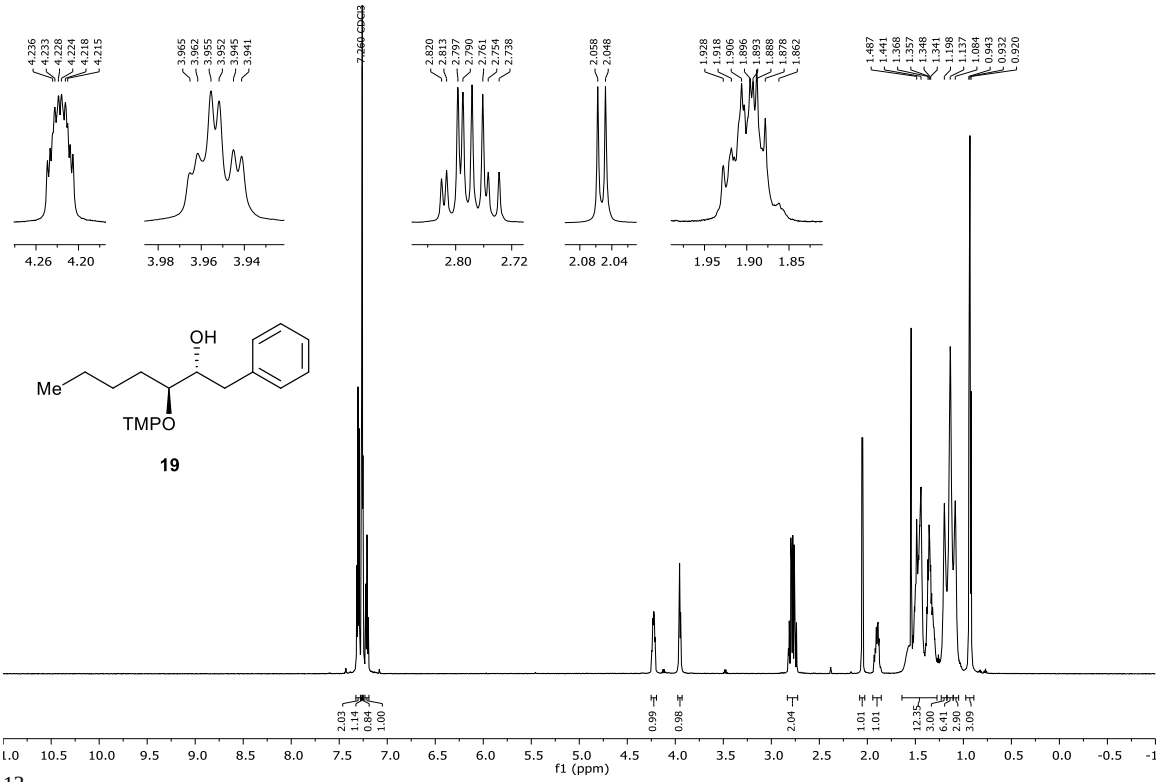
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **18:**



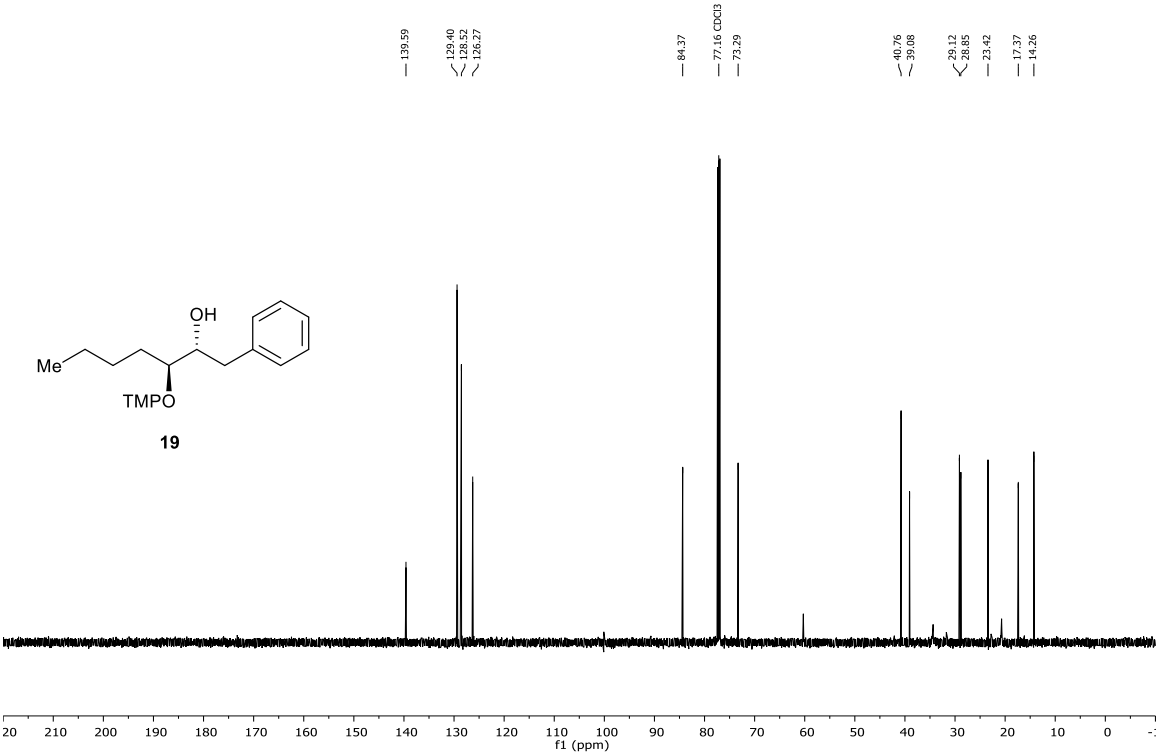
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of of alcohol **18:**



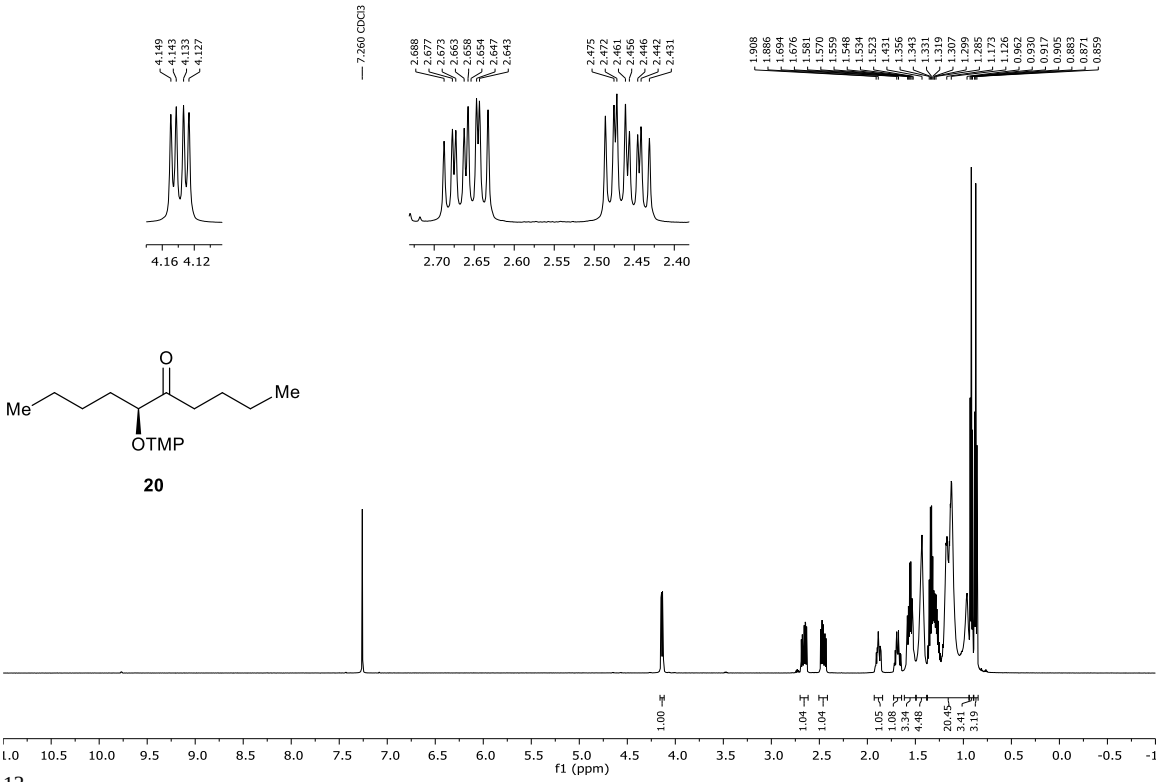
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **19:**



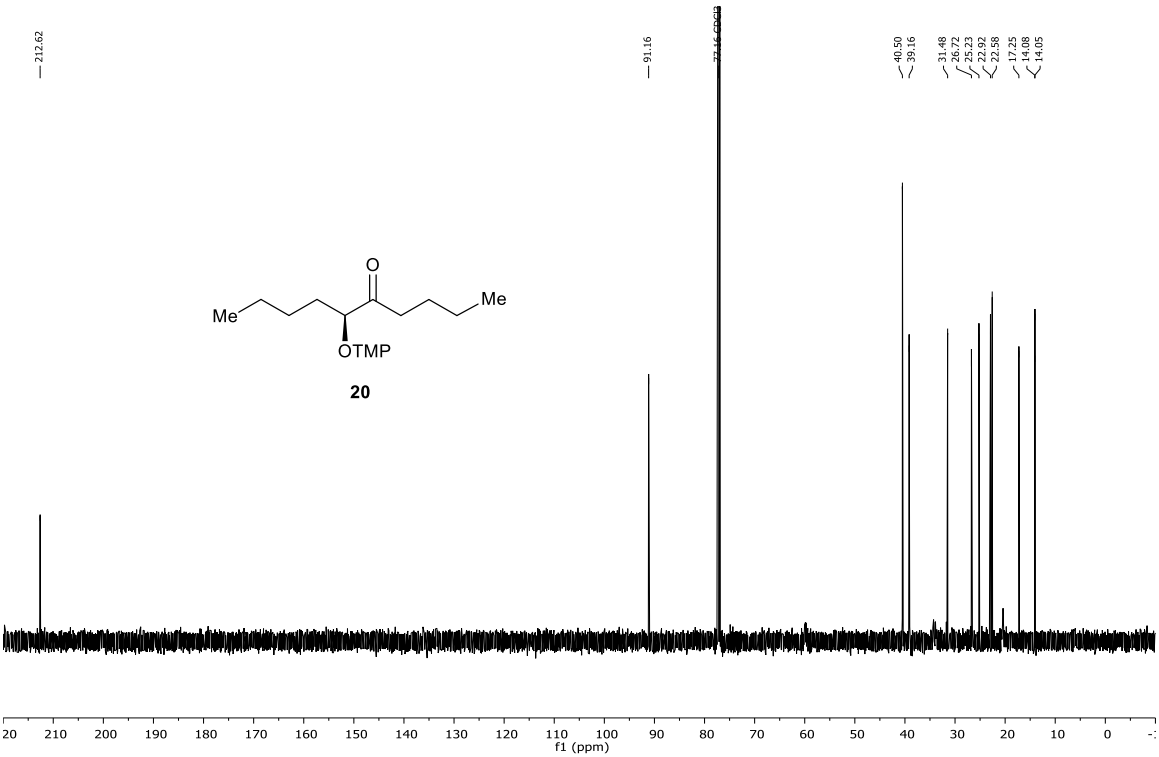
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **19:**



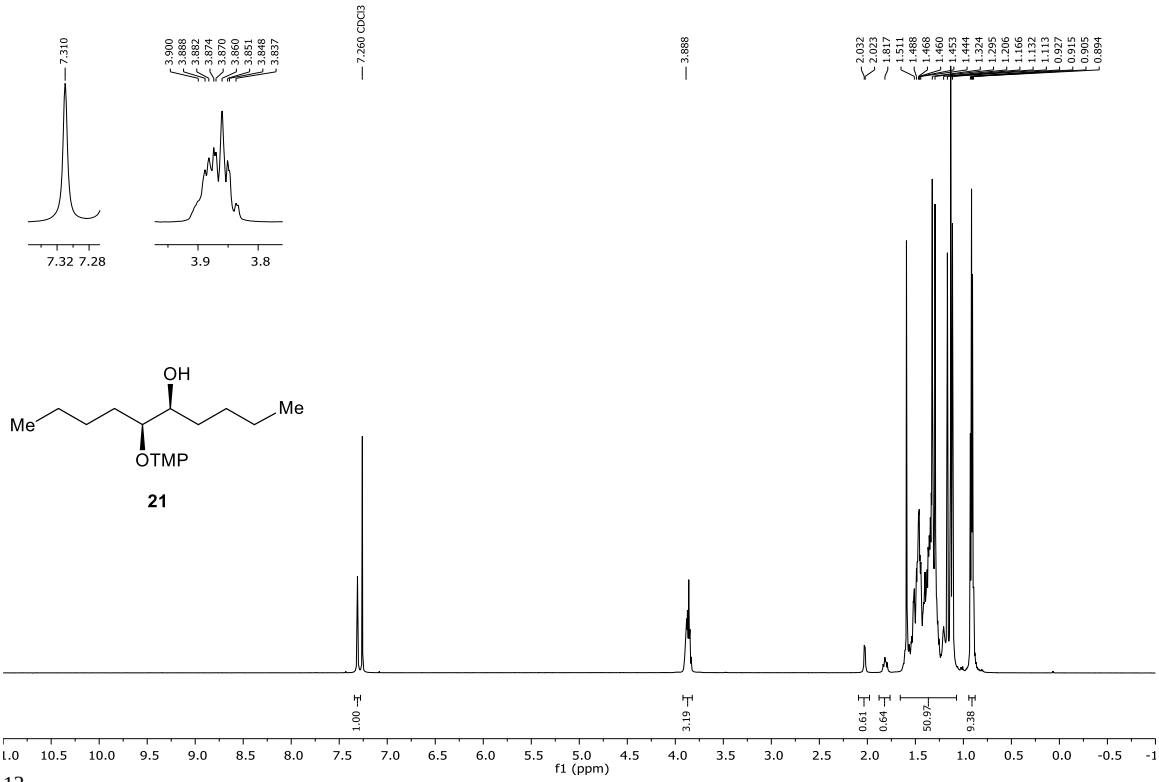
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of ketone **20:**



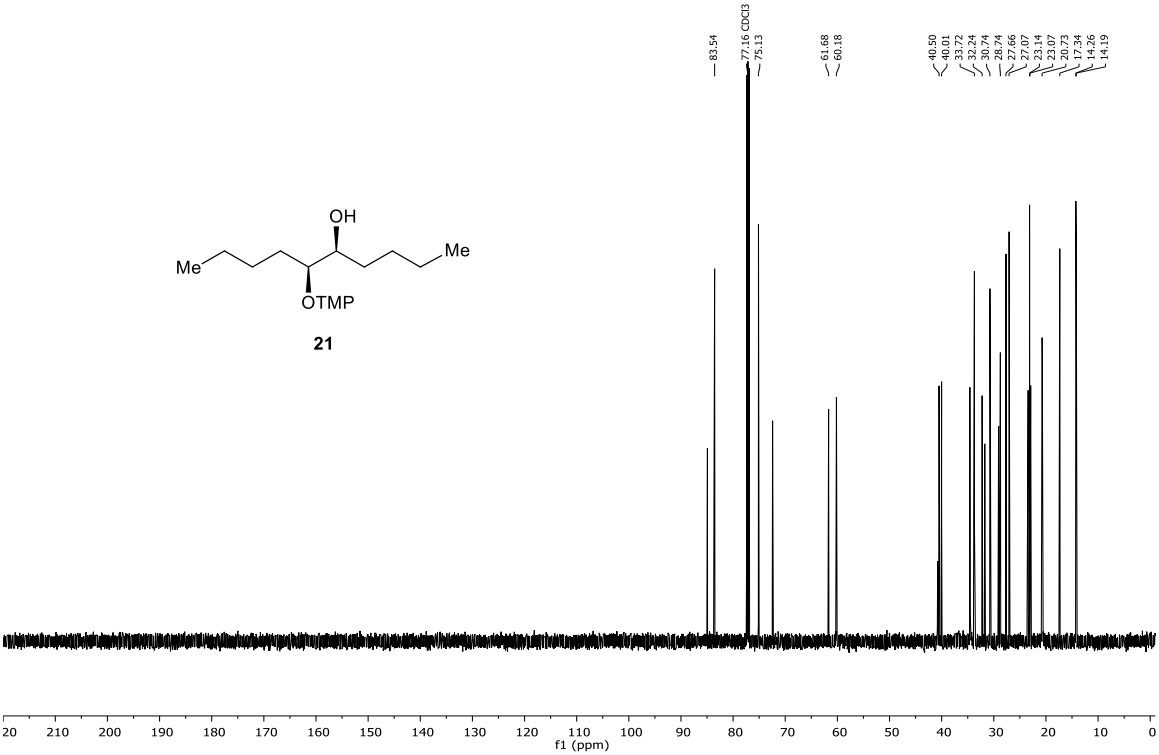
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of ketone **20:**



^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **21:**



^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **21:**

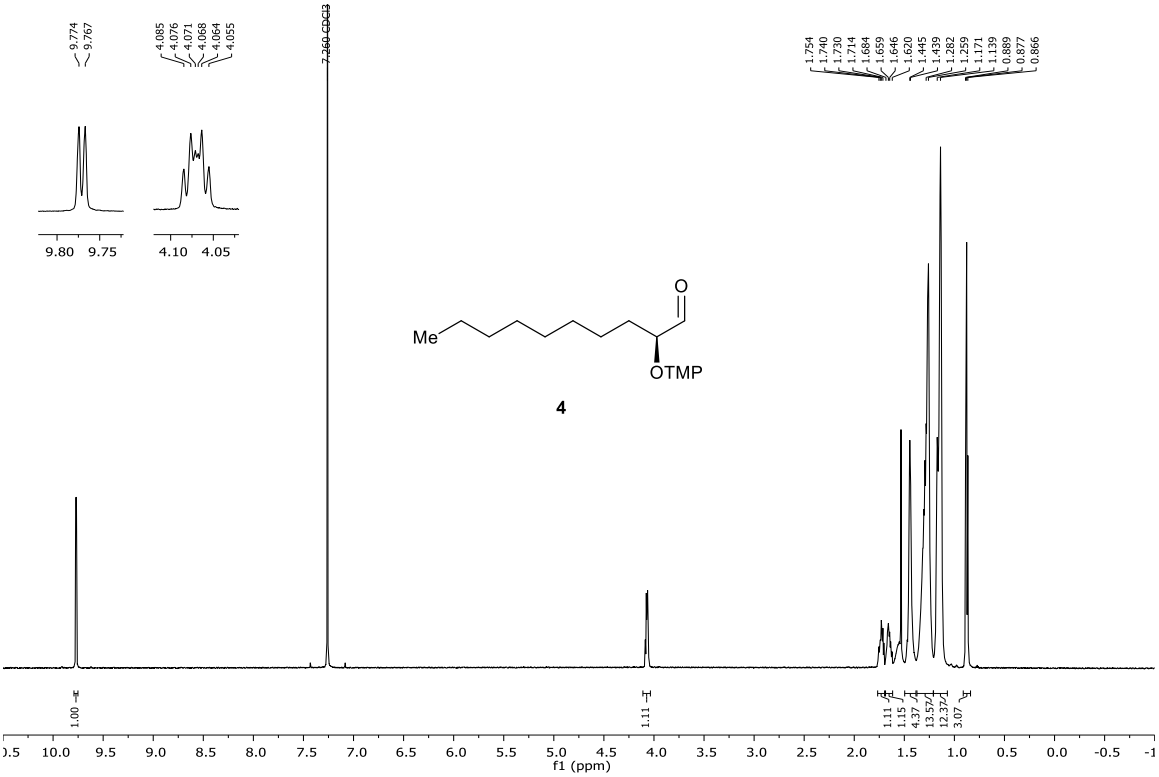


APPENDIX B

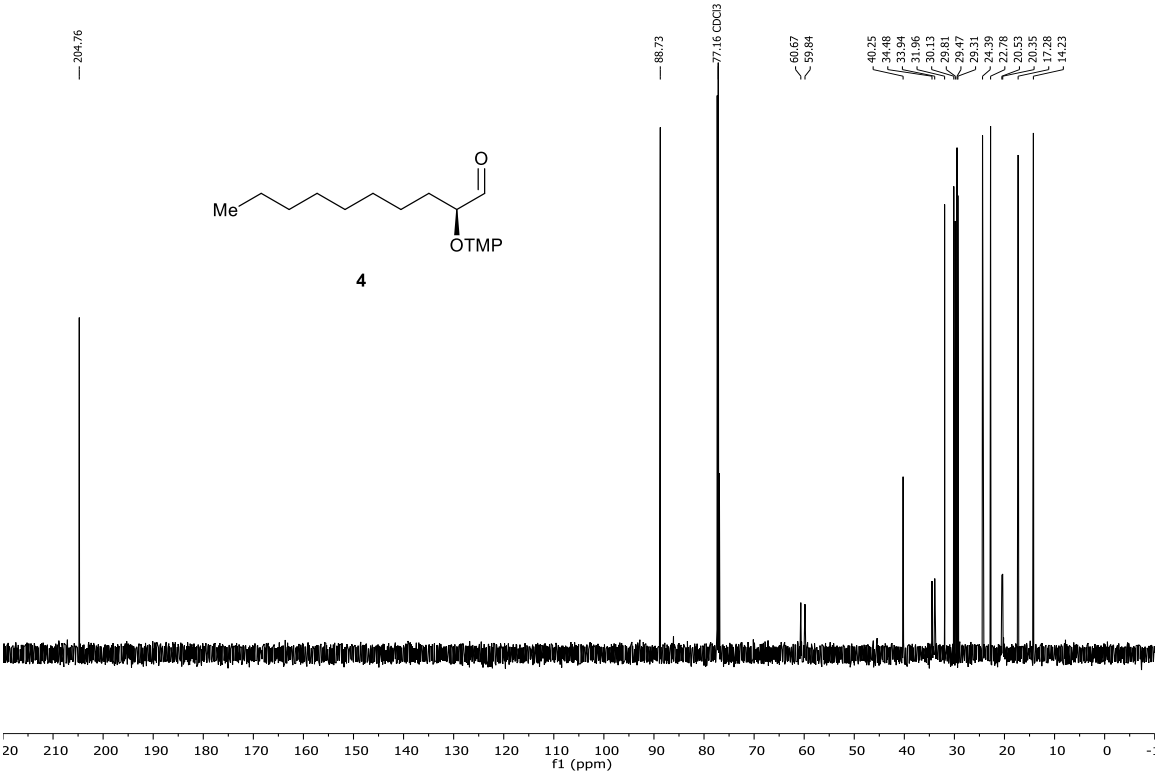
Chapter 2: TOTAL SYNTHESIS OF OXYLIPINS ISOLATED FROM *Dracontium loretense*

NMR SPECTRA

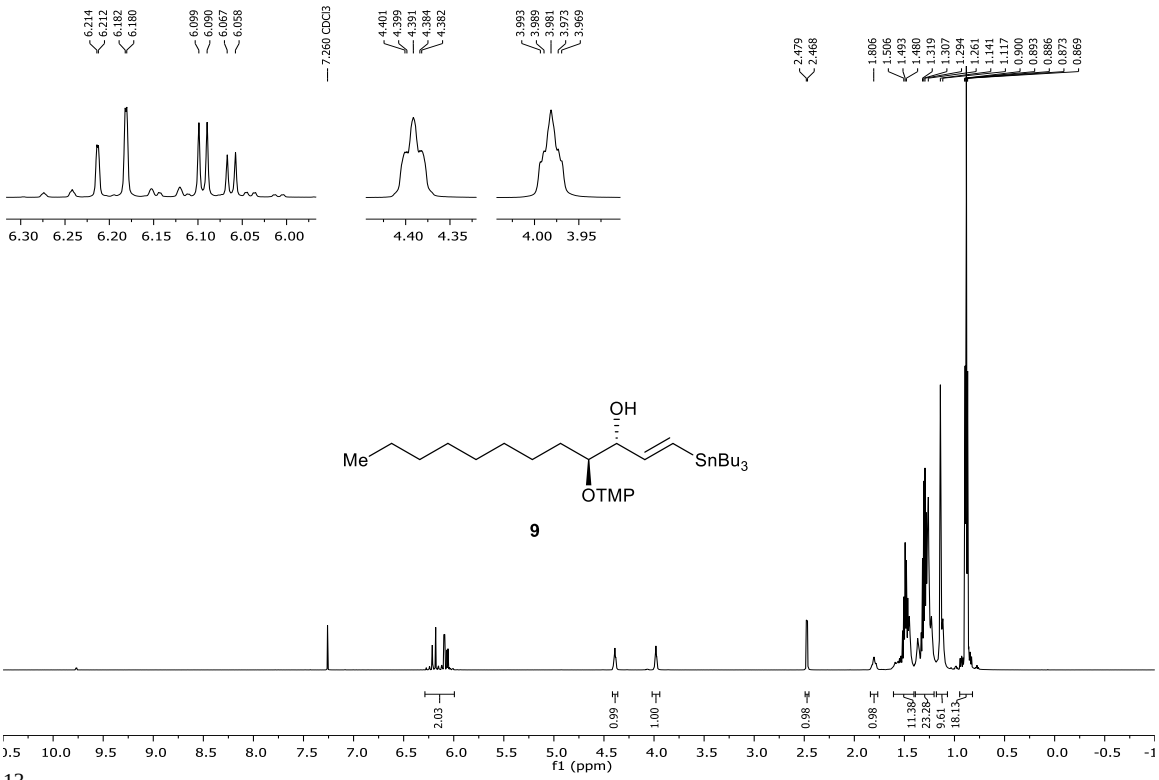
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of α-oxyaldehyde **4:**



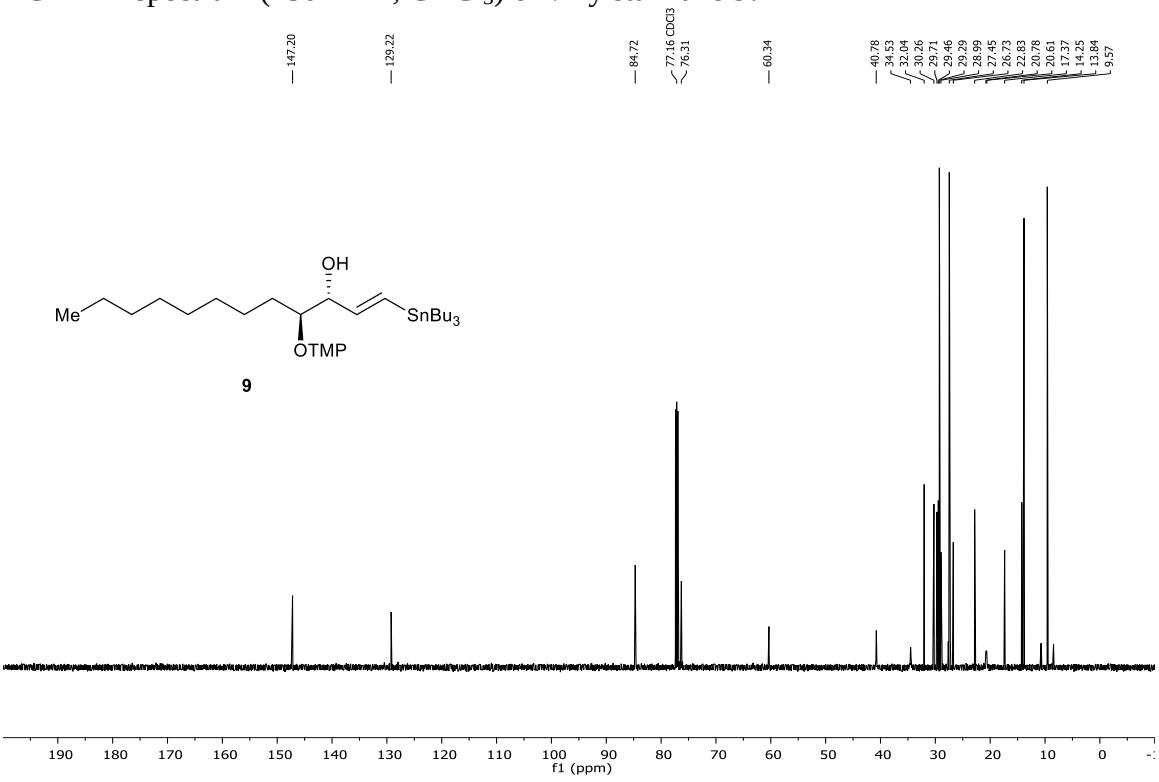
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of α-oxyaldehyde **4:**



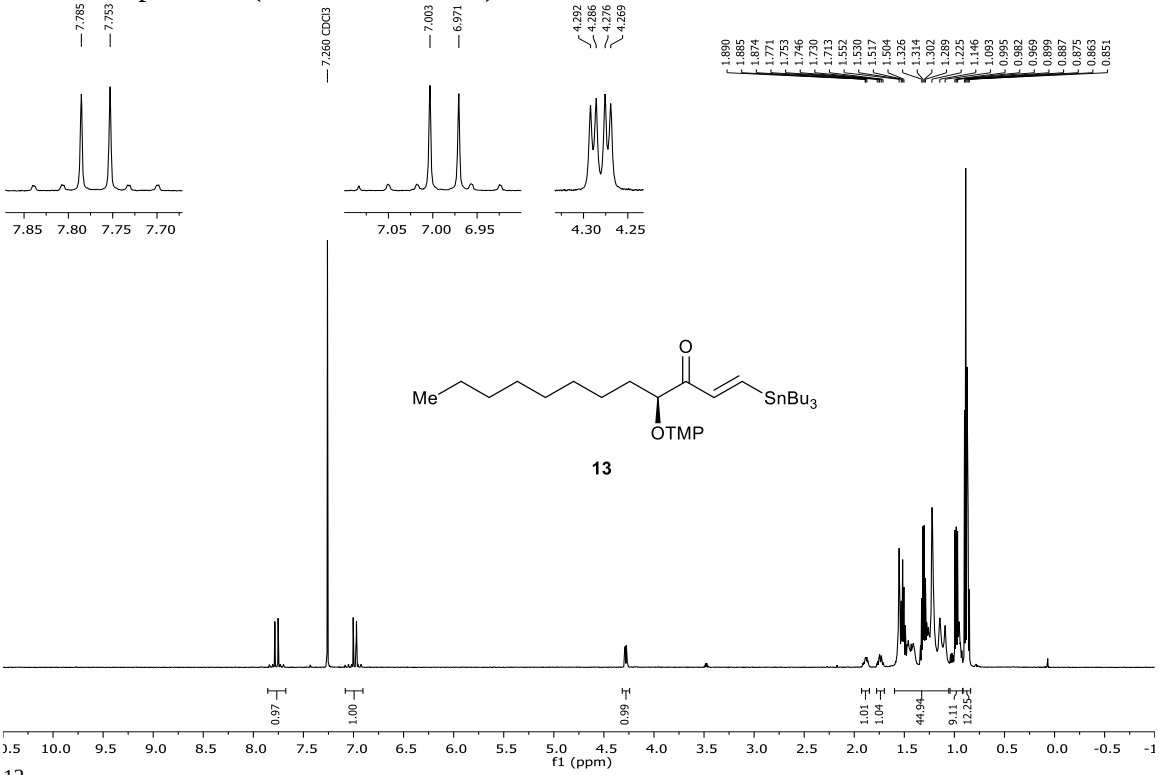
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of vinylstannane **9:**



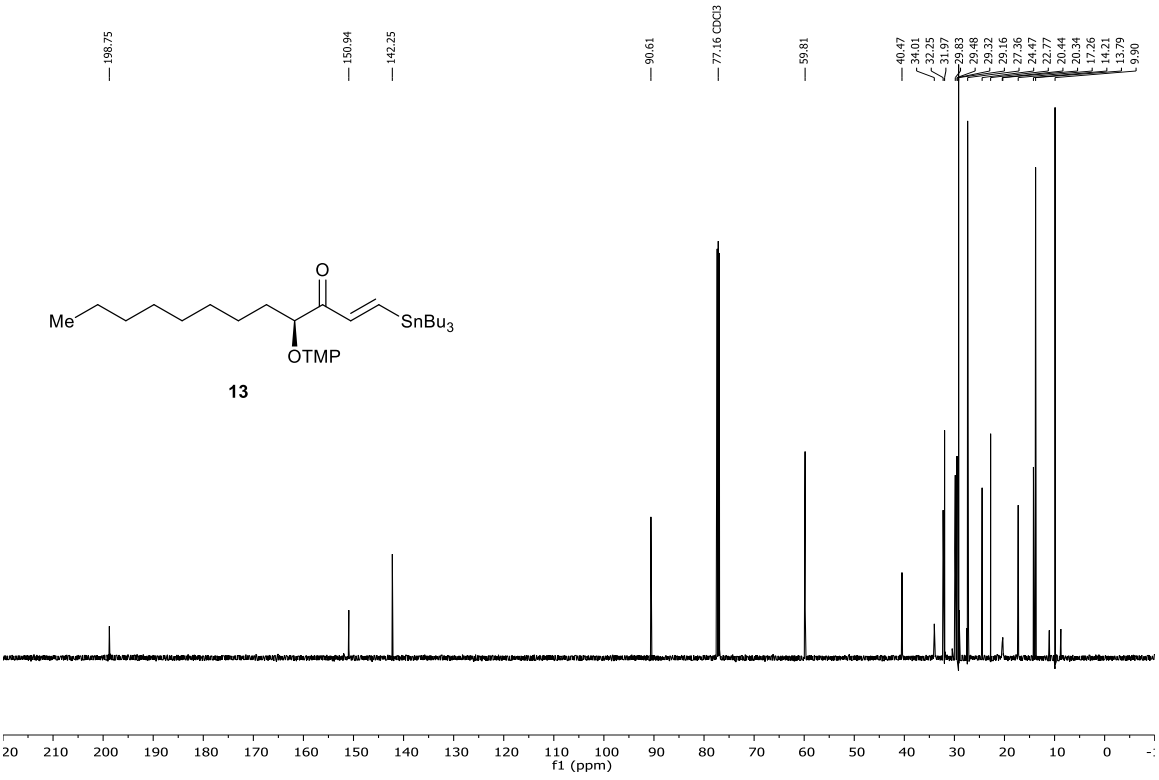
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of vinylstannane **9:**



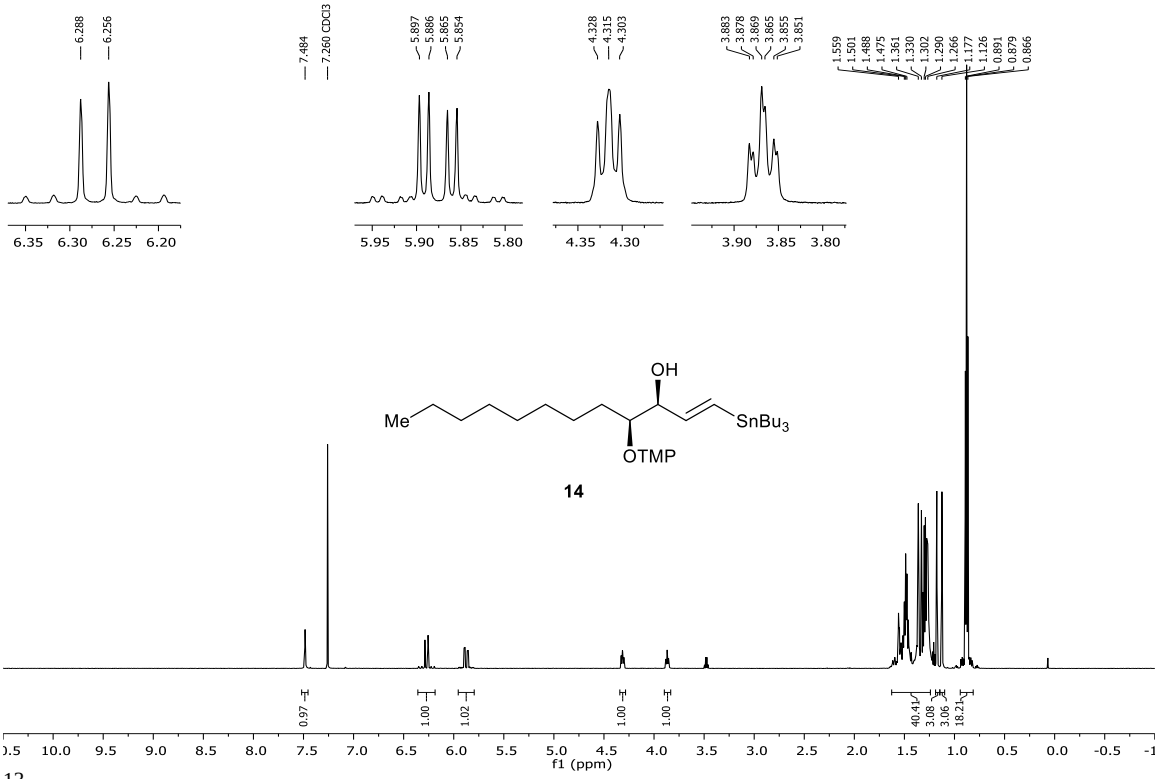
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of enone **13:**



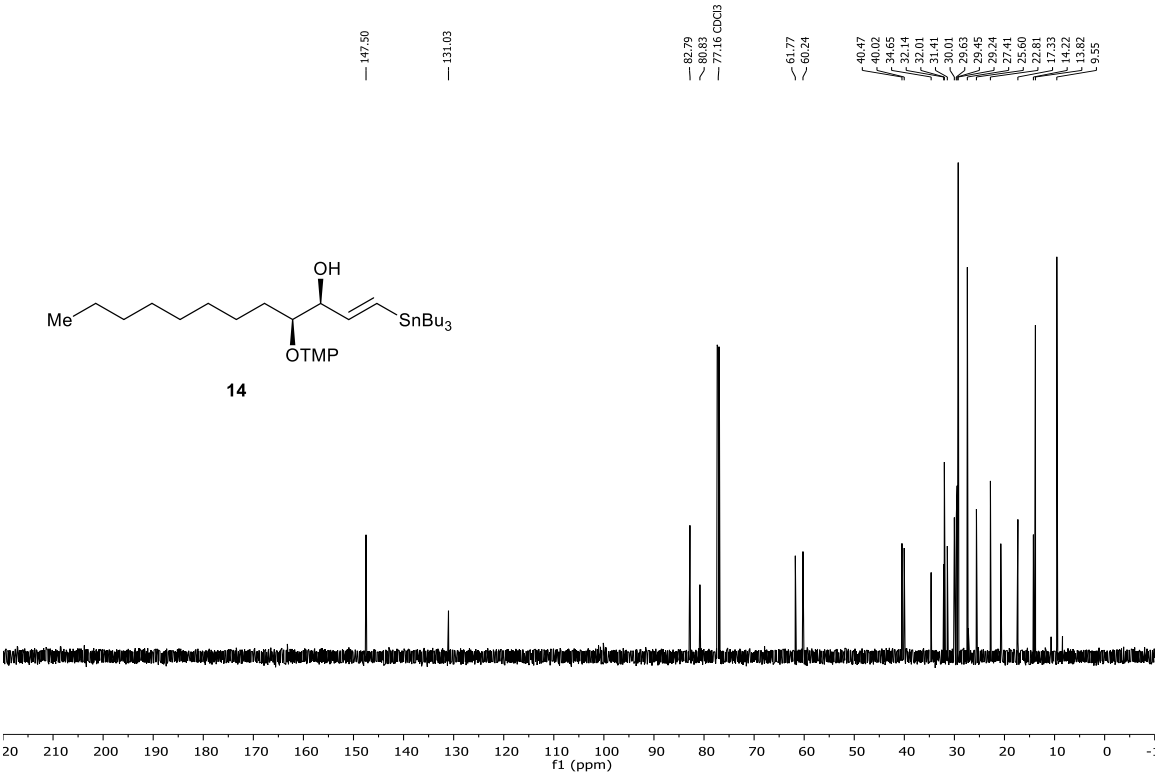
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of enone **13:**



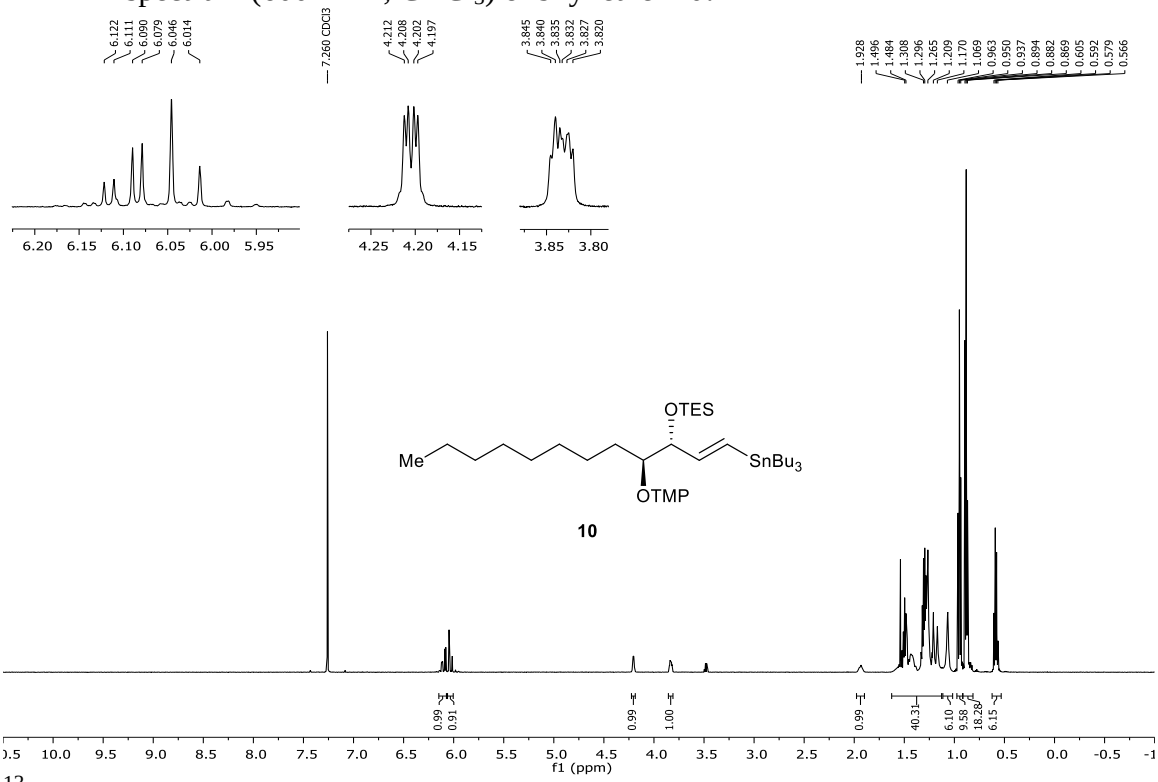
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of allylic alcohol **14:**



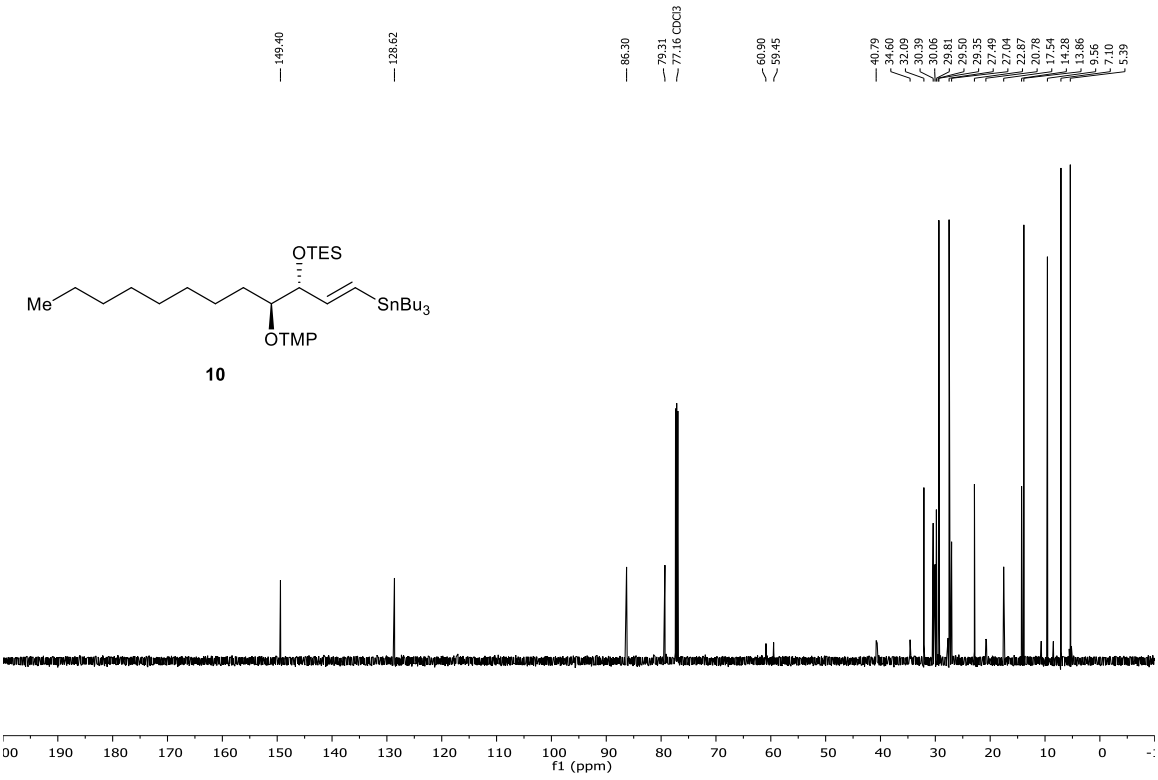
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of allylic alcohol **14:**



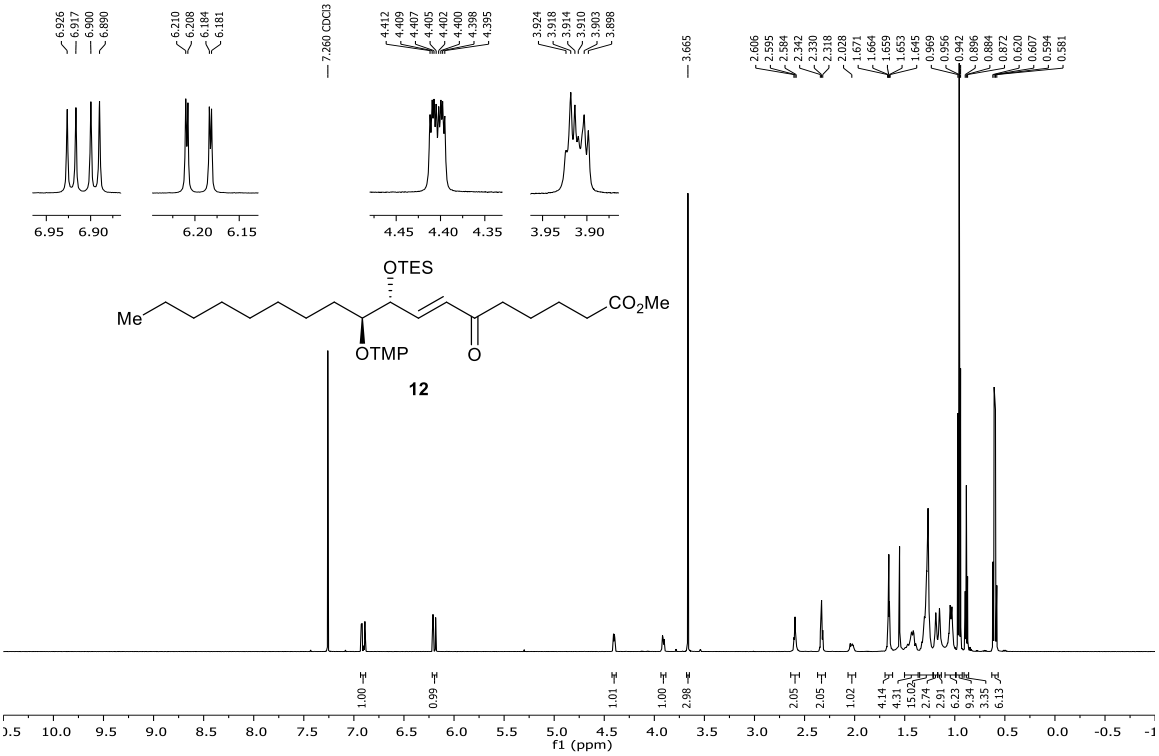
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of silyl ether **10:**



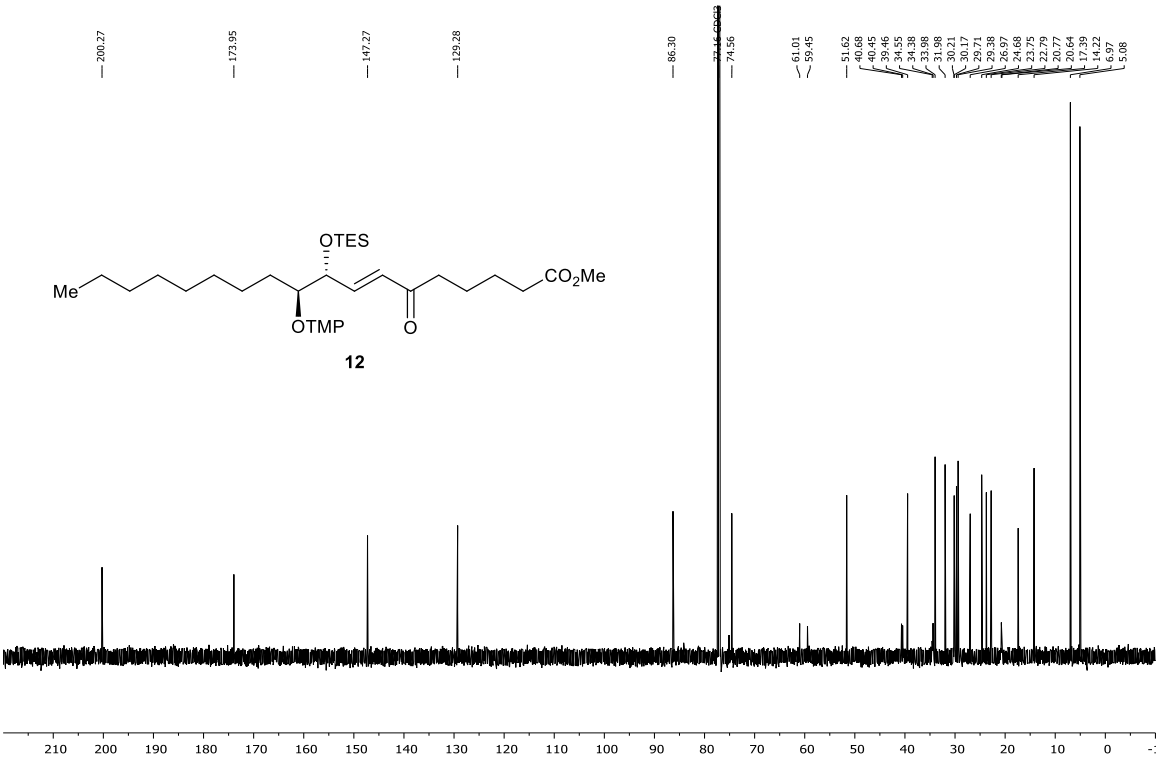
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of silyl ether **10:**



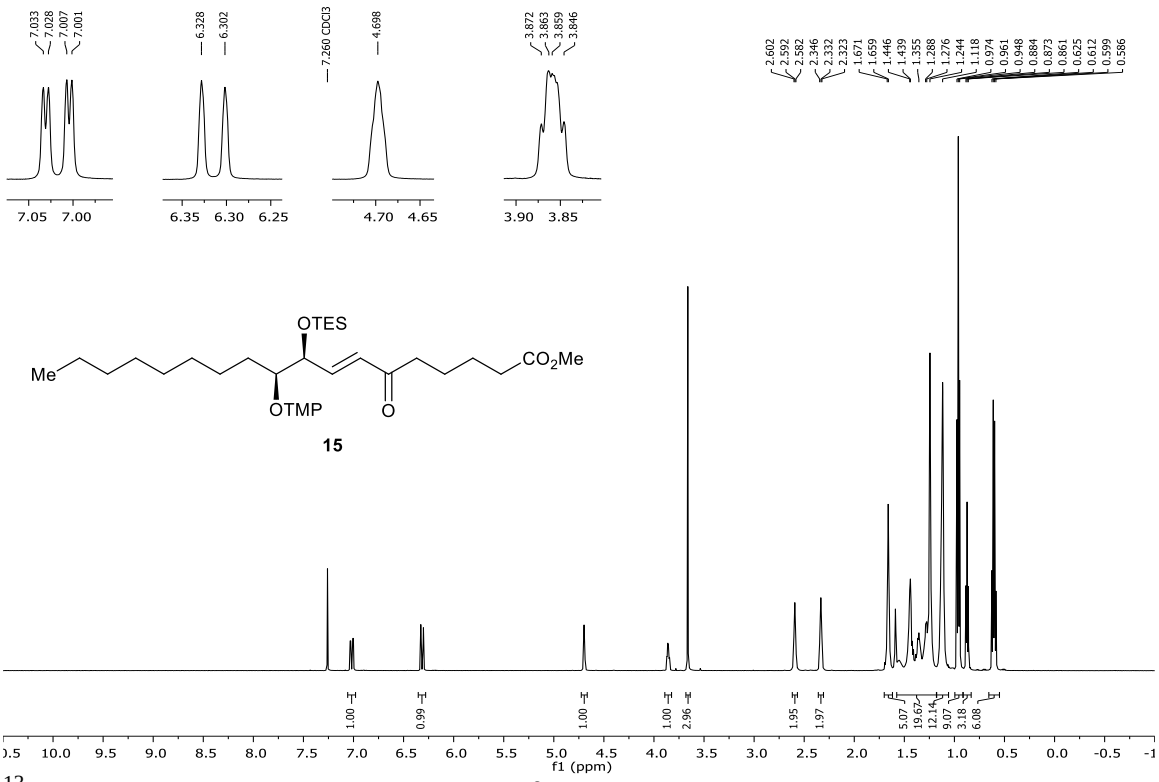
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of enone **12:**



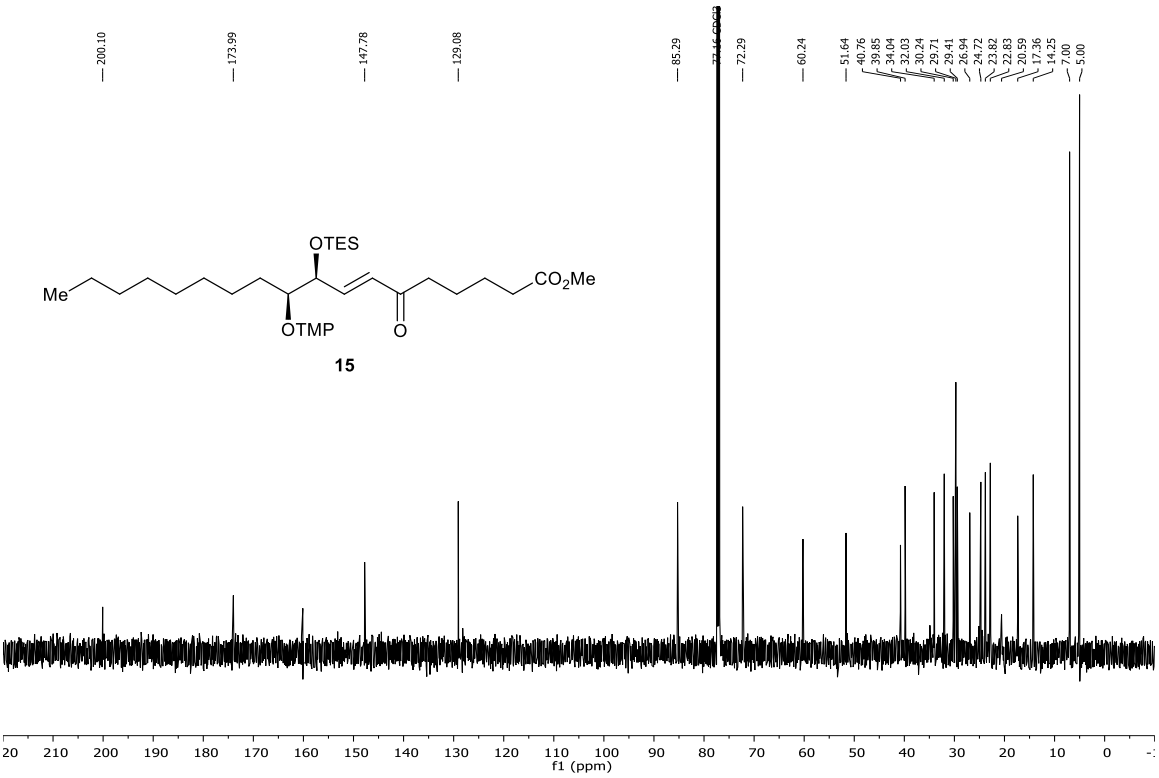
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of enone **12:**



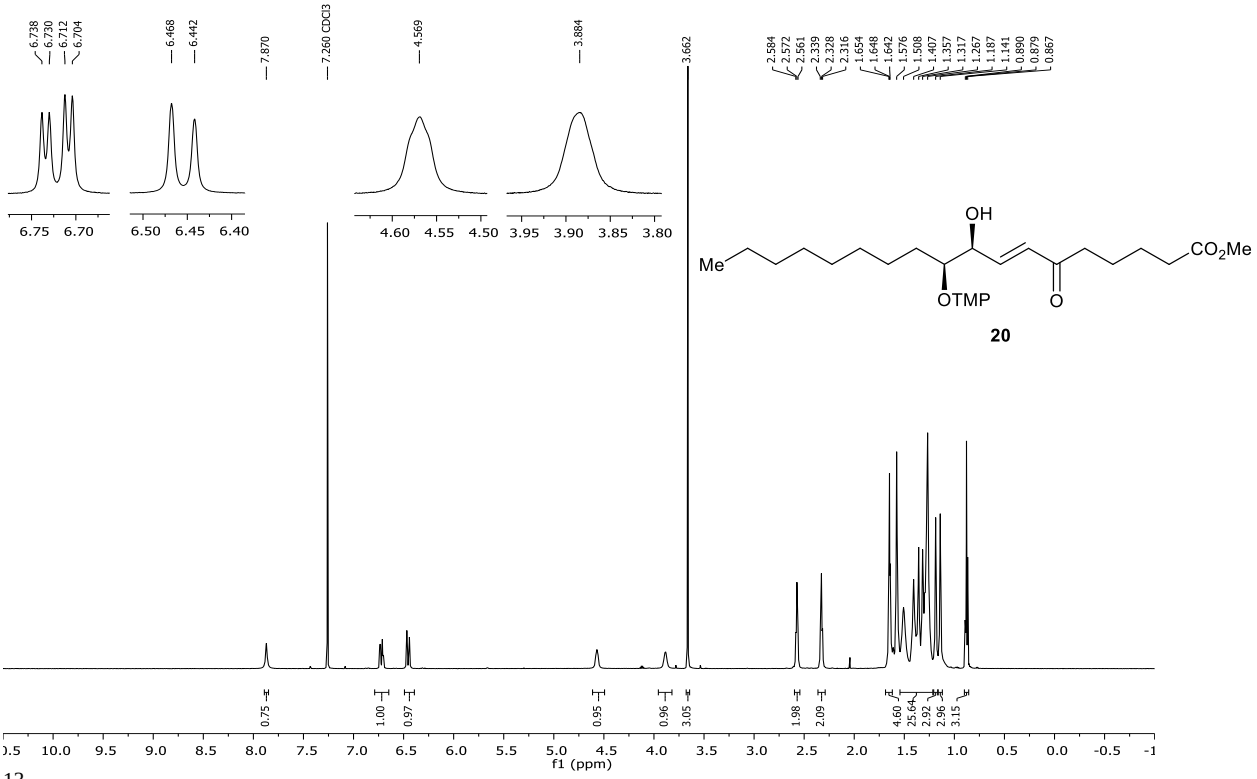
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of enone **15:**



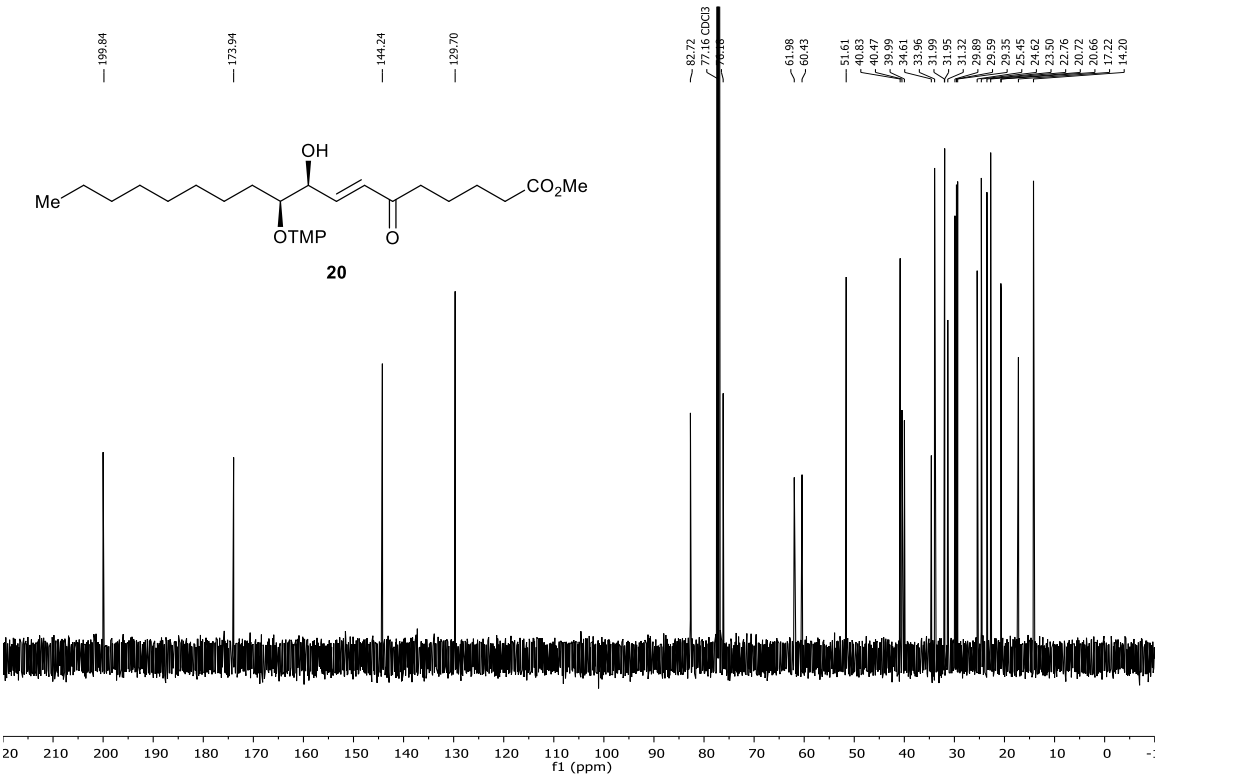
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of enone **15:**



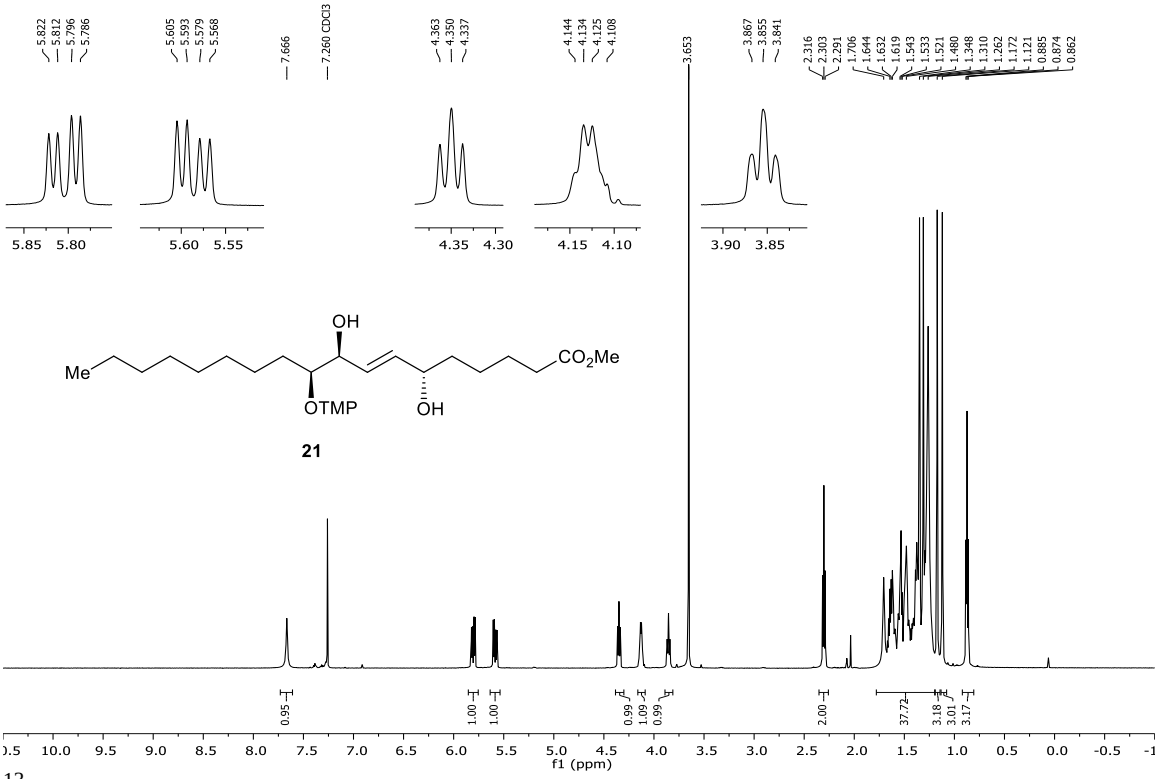
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of alcohol **20:**



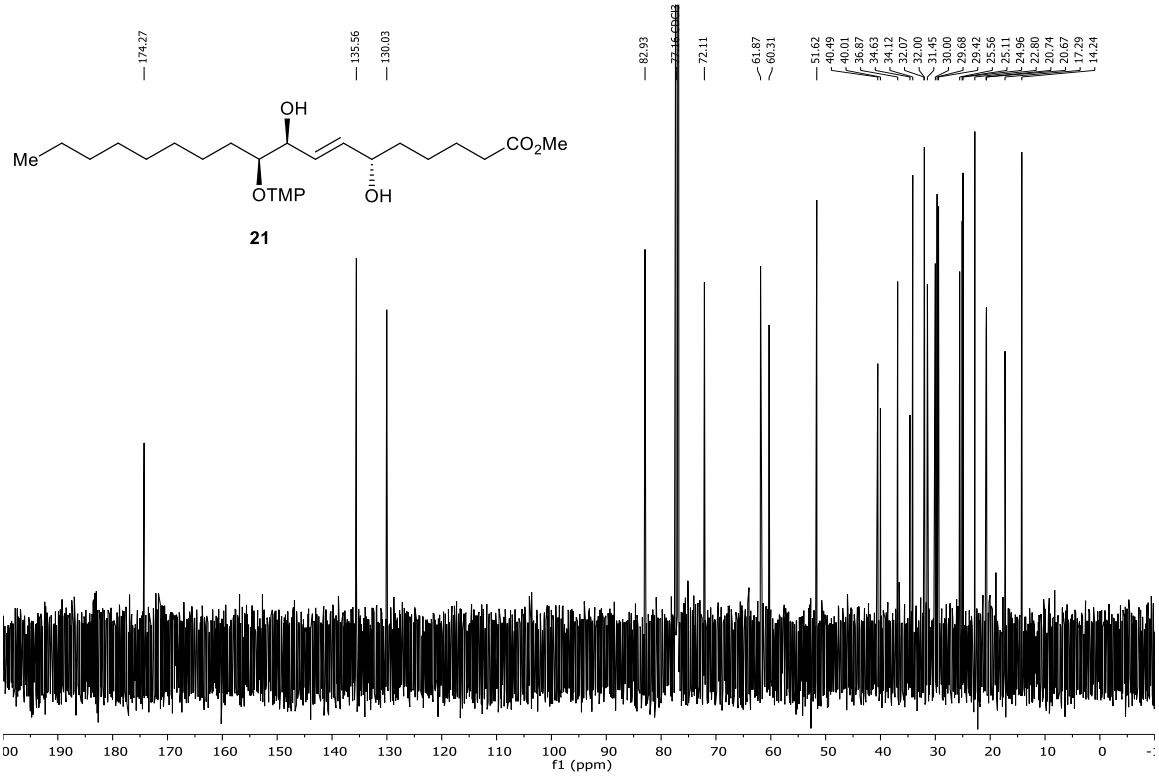
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of alcohol **20:**



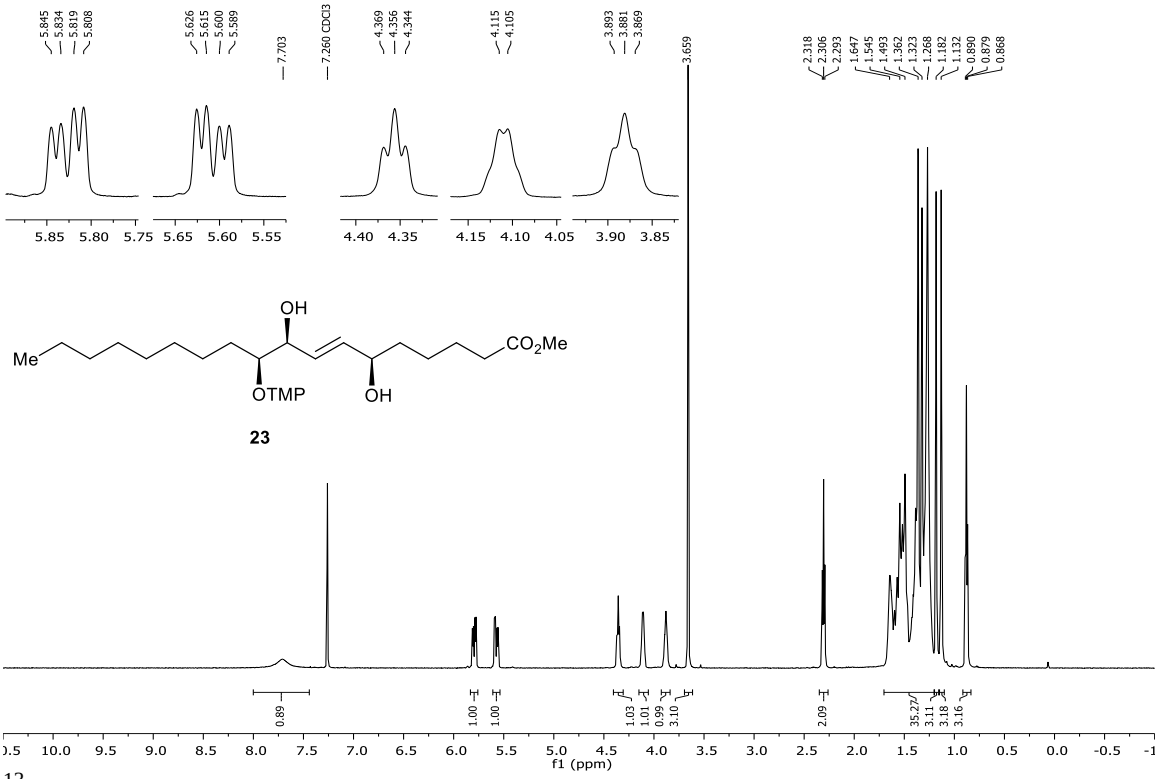
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of allylic alcohol **21:**



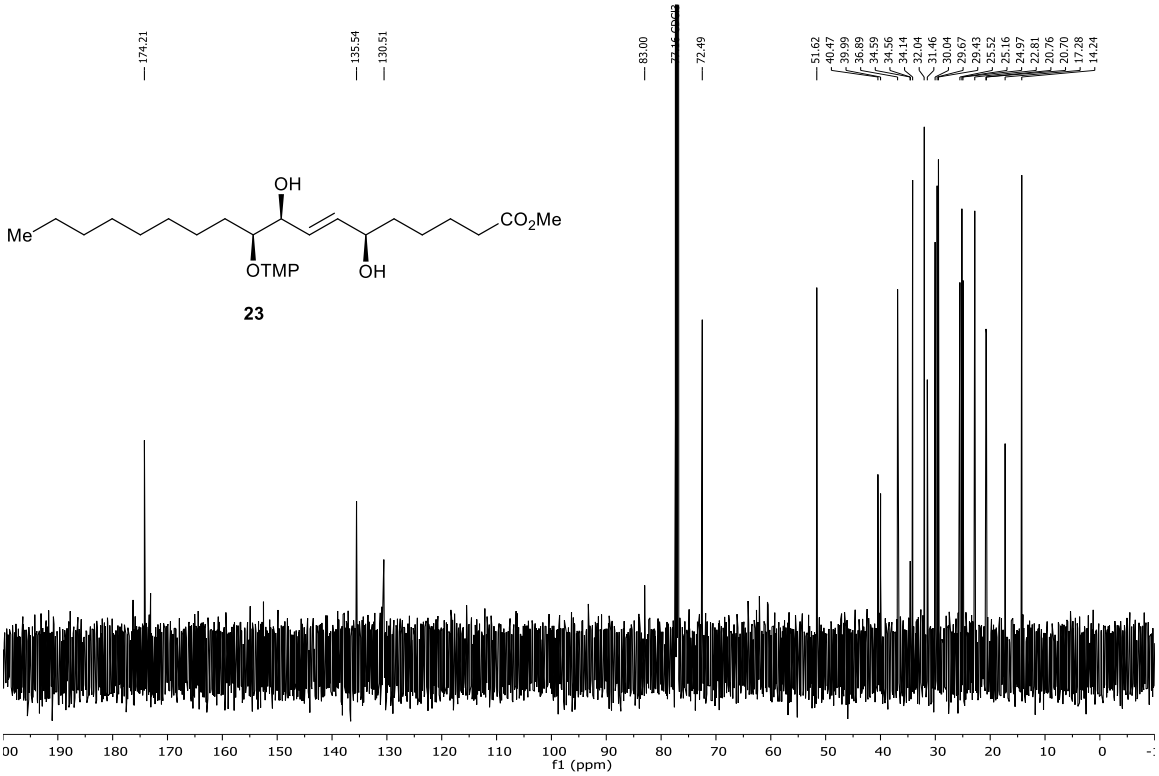
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of allylic alcohol **21:**



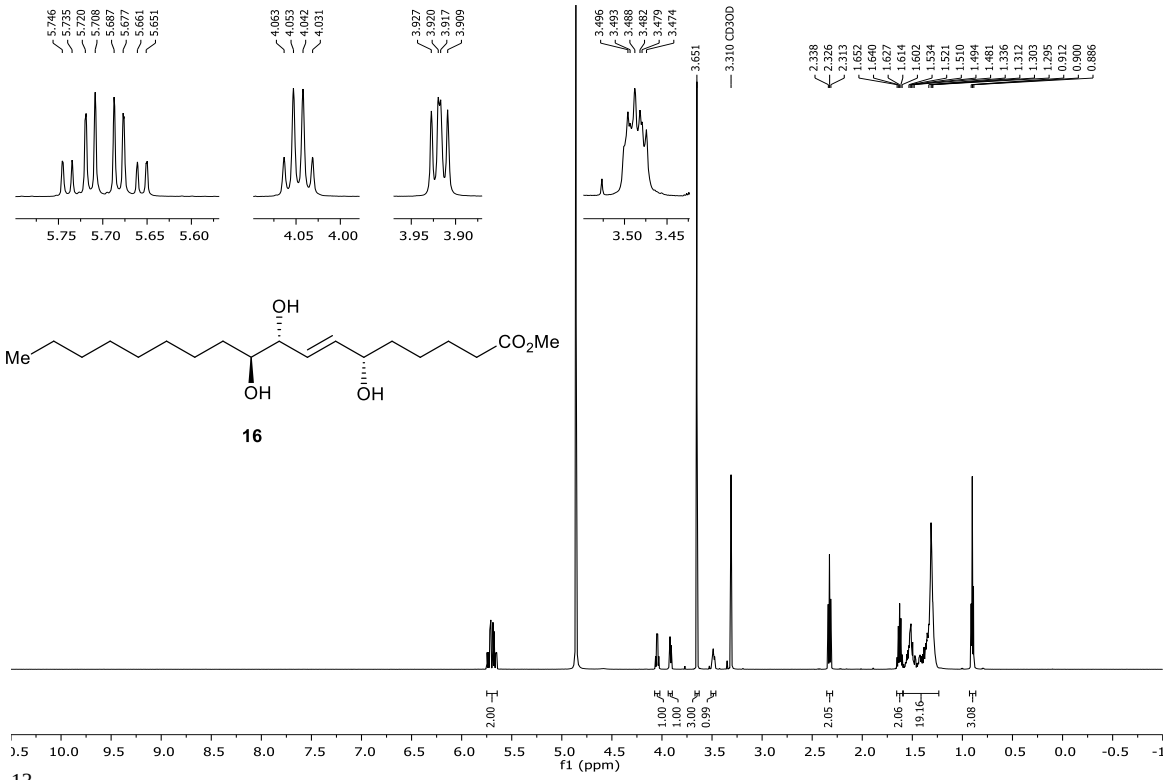
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of allylic alcohol **23:**



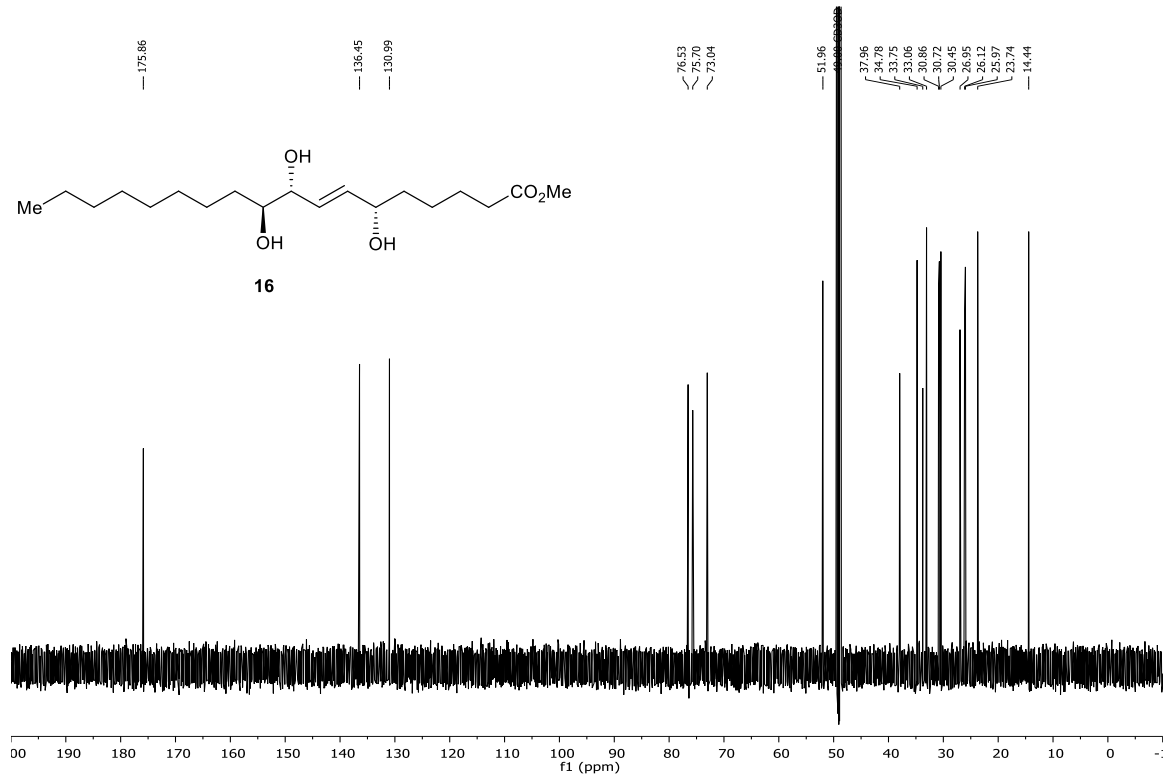
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of allylic alcohol **23:**



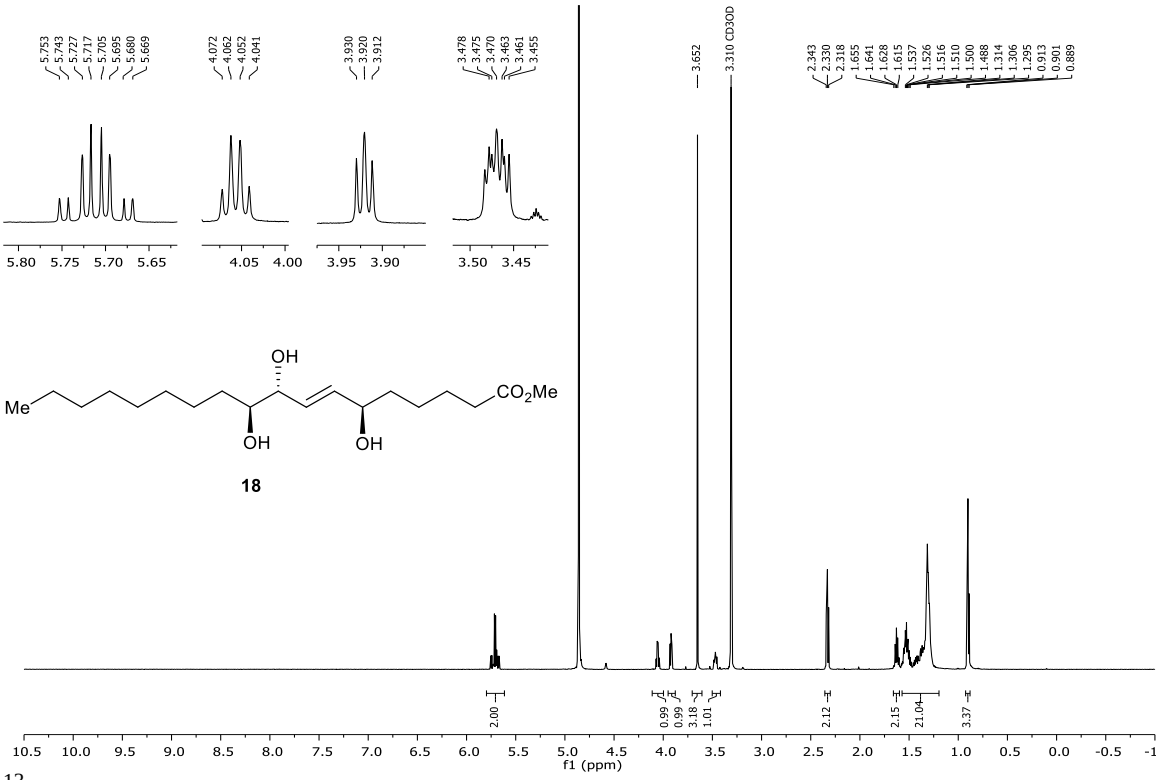
^{1}H NMR spectrum (600 MHz, CD_3OD) of triol **16:**



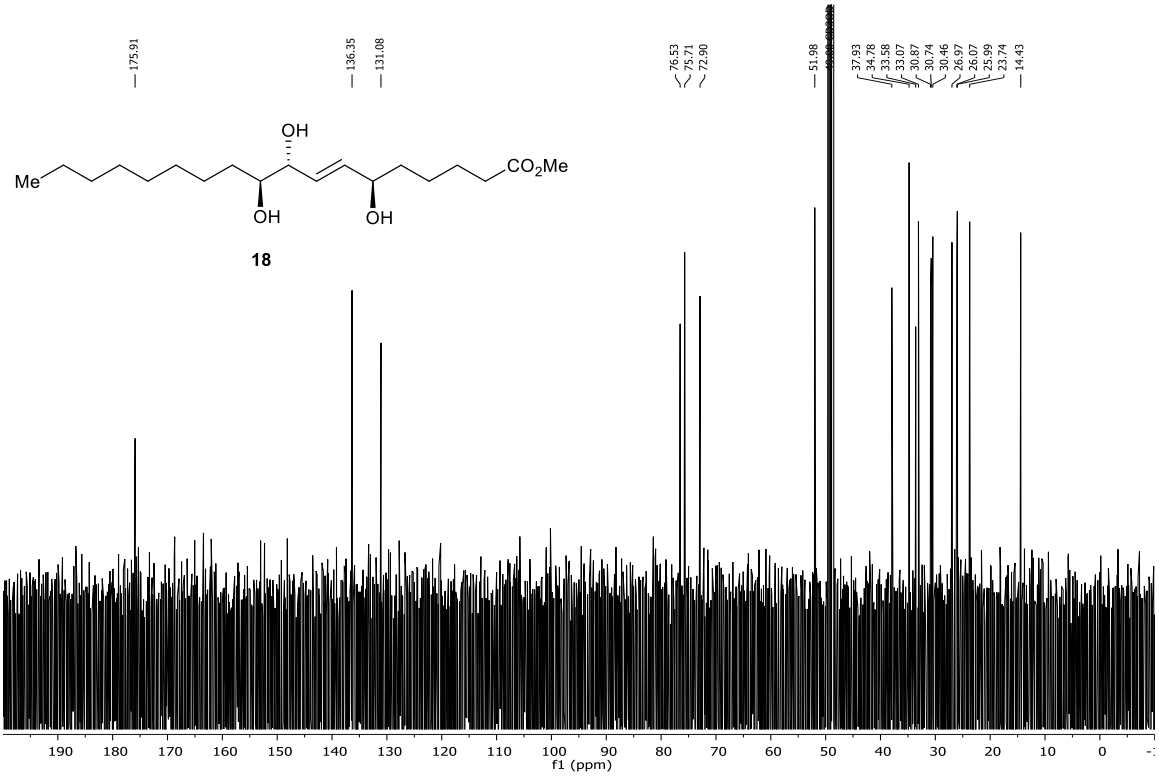
^{13}C NMR spectrum (150 MHz, CD_3OD) of triol **16:**



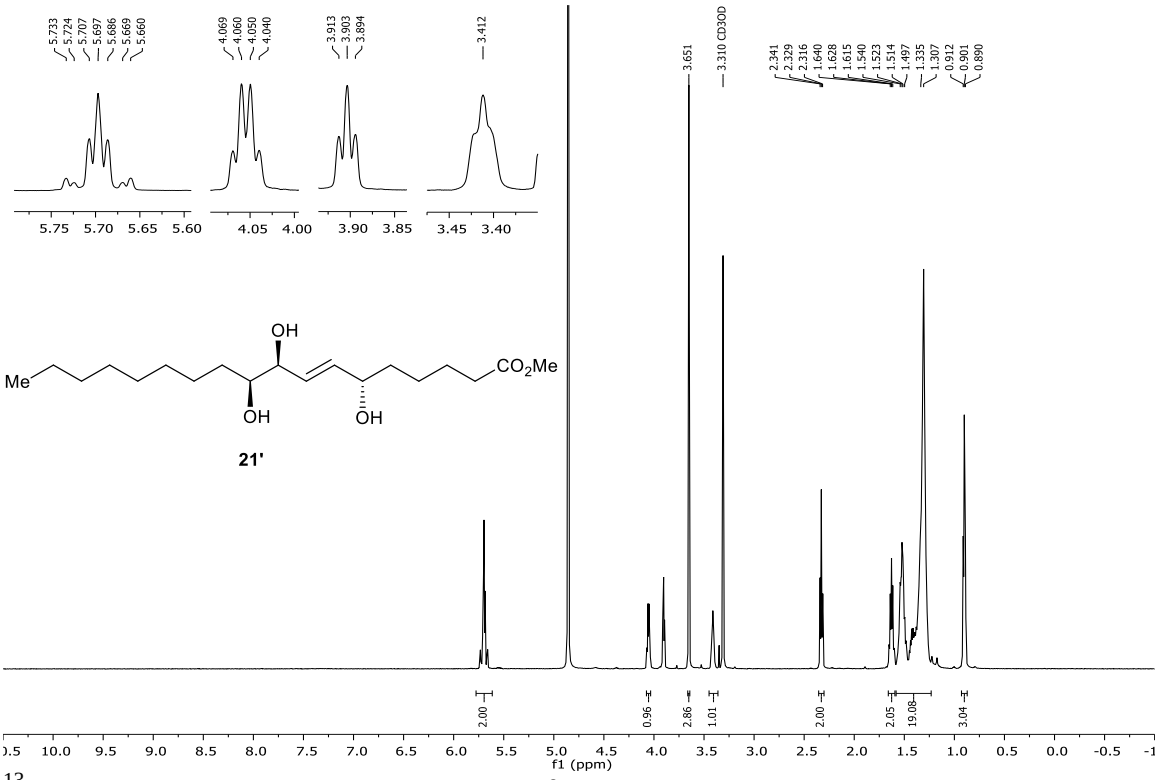
^{1}H NMR spectrum (600 MHz, CD_3OD) of triol **18:**



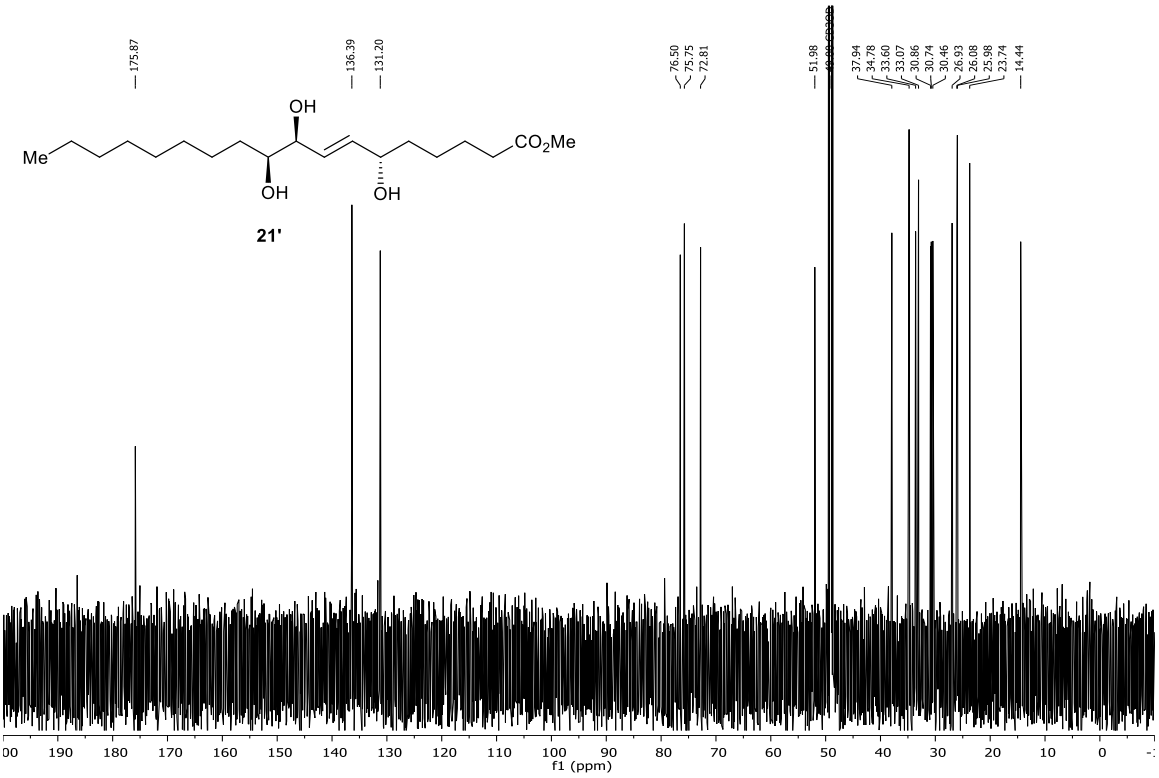
^{13}C NMR spectrum (150 MHz, CD_3OD) of triol **18:**



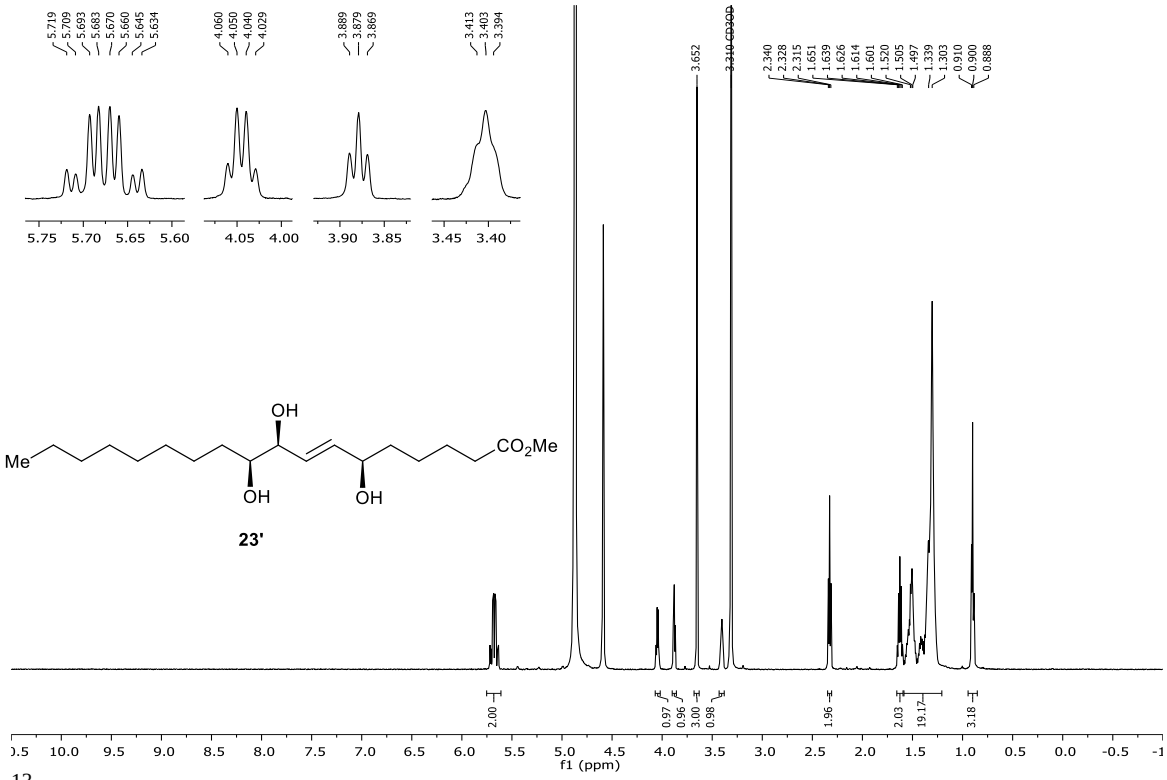
^{1}H NMR spectrum (600 MHz, CD_3OD) of triol **21':**



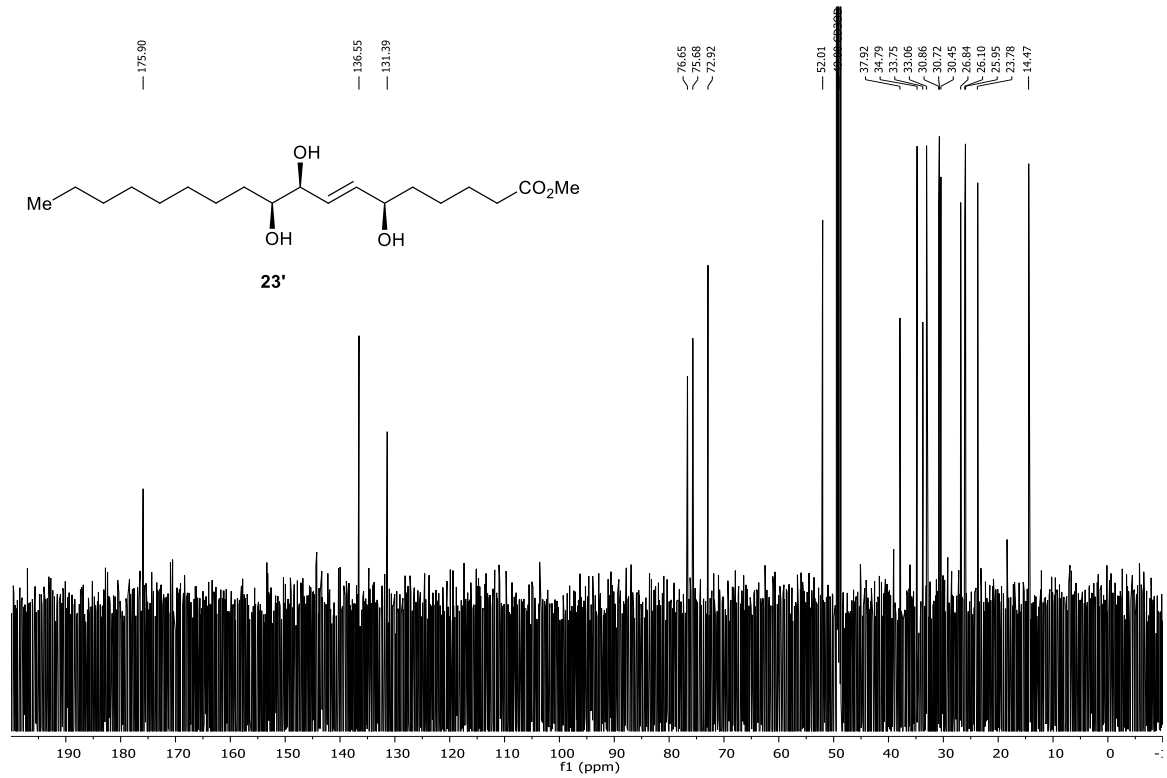
^{13}C NMR spectrum (150 MHz, CD_3OD) of triol **21':**



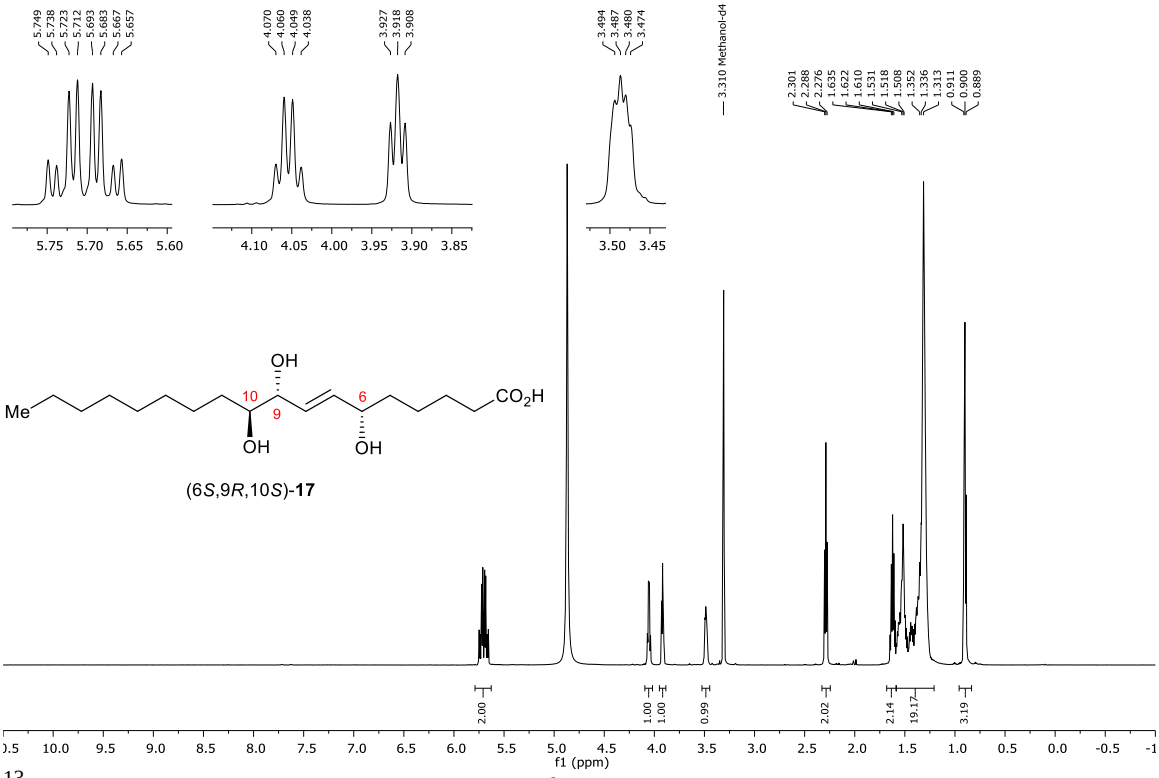
^{1}H NMR spectrum (600 MHz, CD_3OD) of triol **23':**



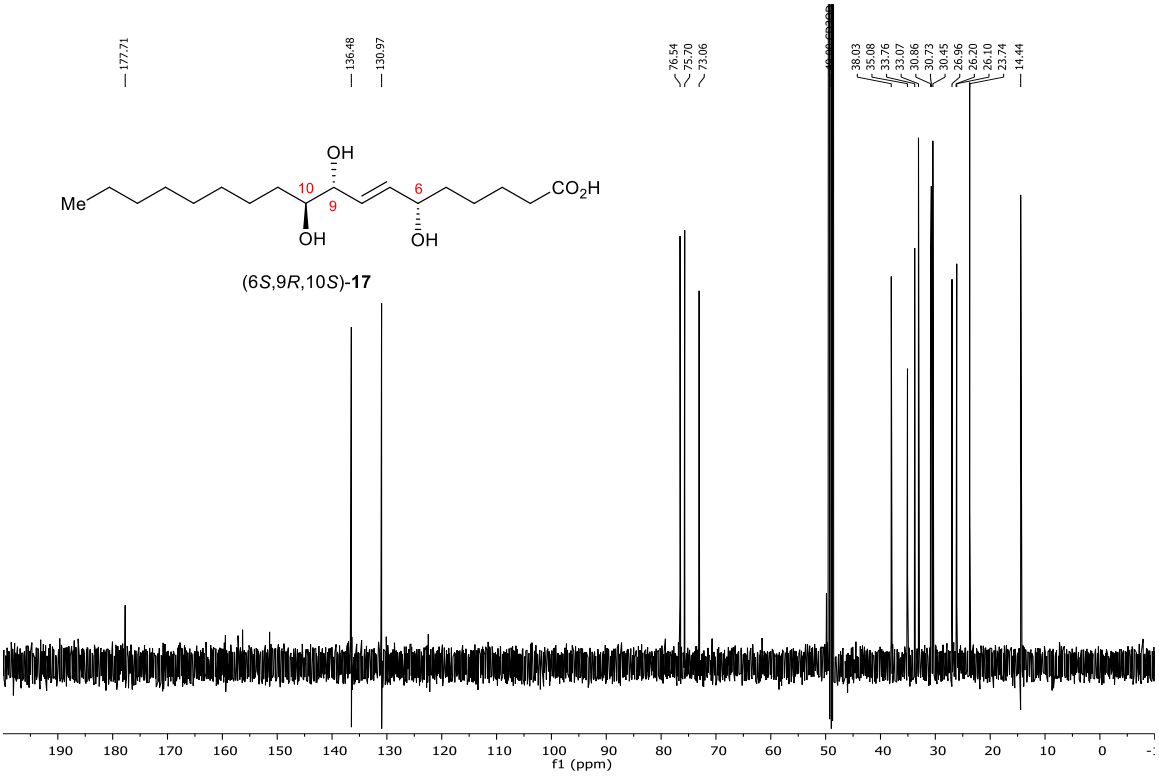
^{13}C NMR spectrum (150 MHz, CD_3OD) of triol **23':**



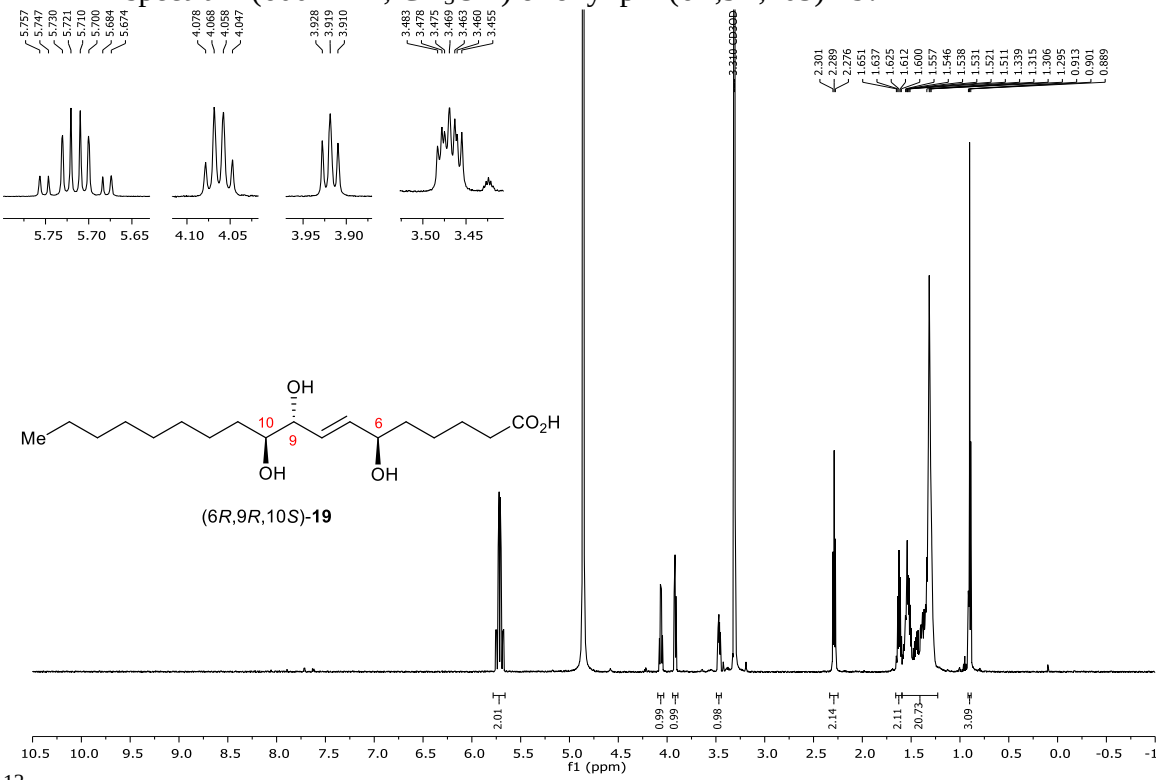
^{1}H NMR spectrum (600 MHz, CD_3OD) of oxylipin (6*S*,9*R*,10*S*)-**17:**



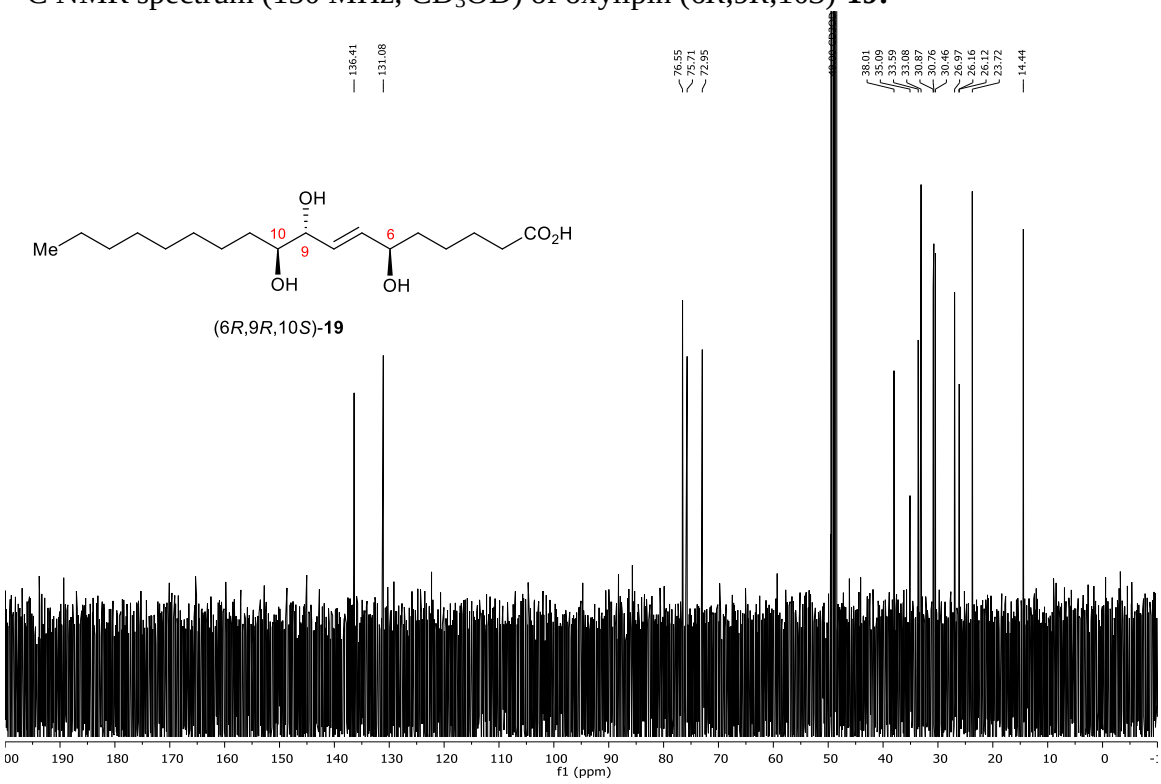
^{13}C NMR spectrum (150 MHz, CD_3OD) of oxylipin (6*S*,9*R*,10*S*)-**17:**



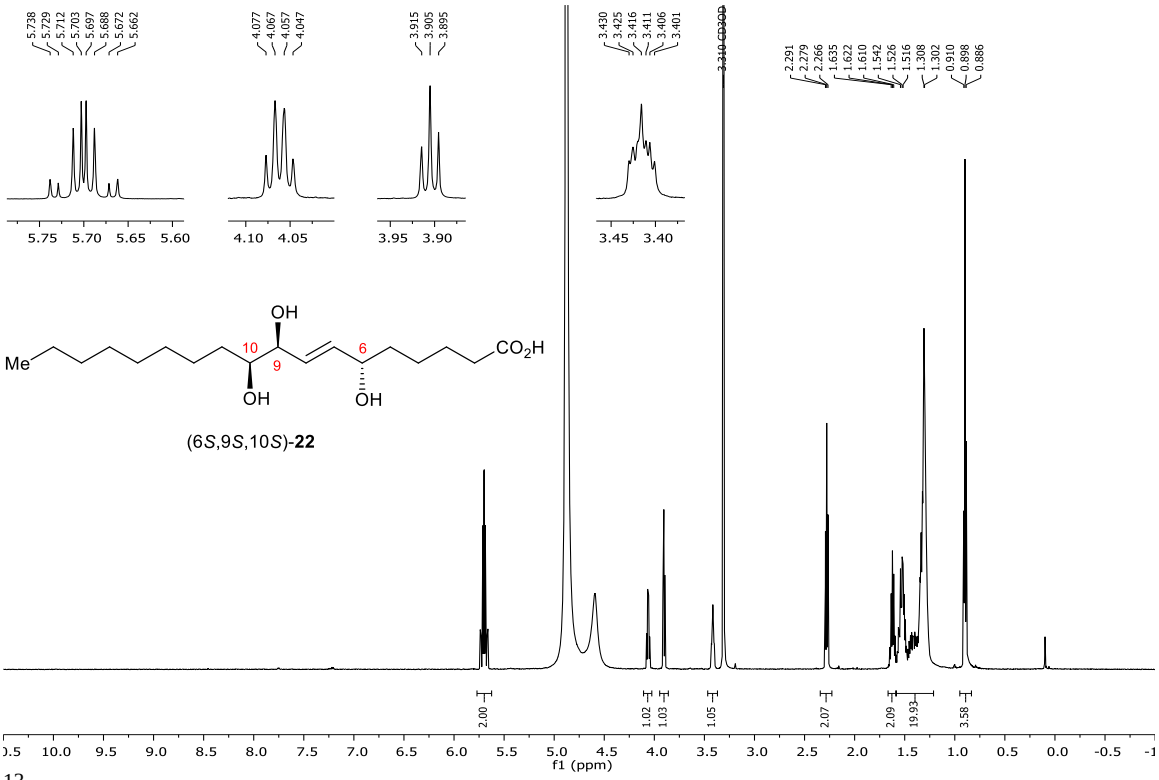
^{1}H NMR spectrum (600 MHz, CD_3OD) of oxylipin (6*R*,9*R*,10*S*)-**19:**



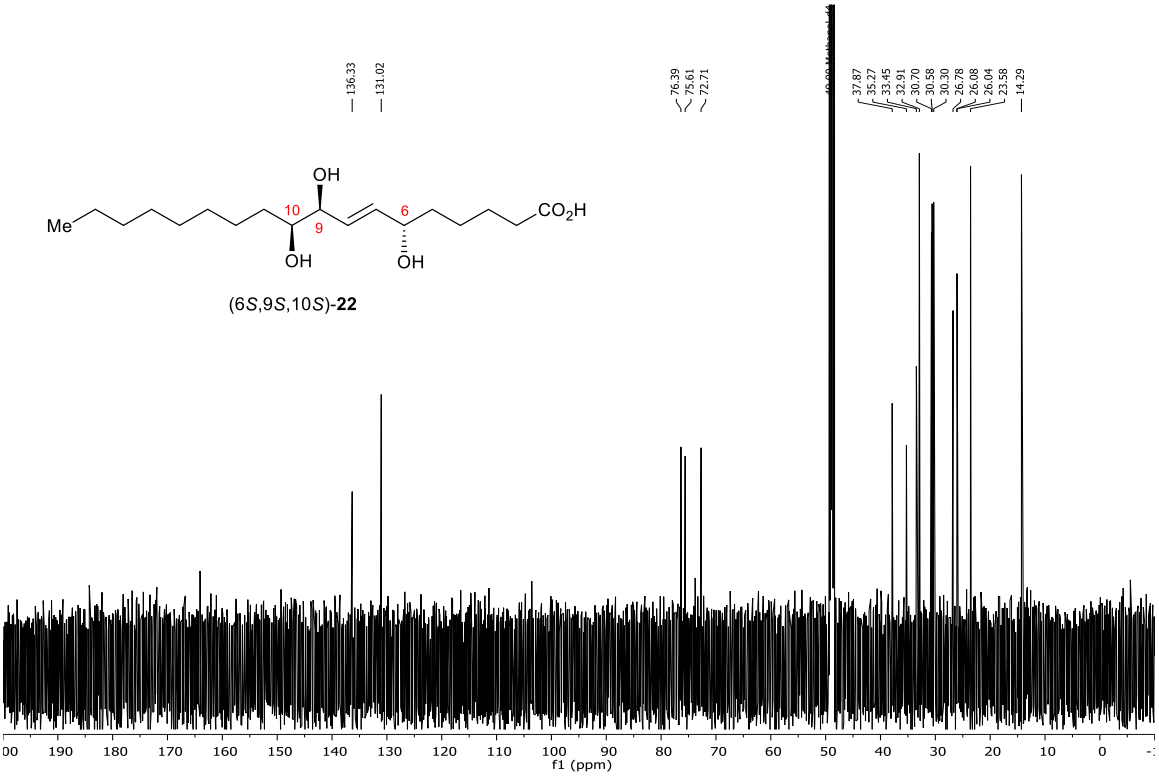
^{13}C NMR spectrum (150 MHz, CD_3OD) of oxylipin (6*R*,9*R*,10*S*)-**19:**



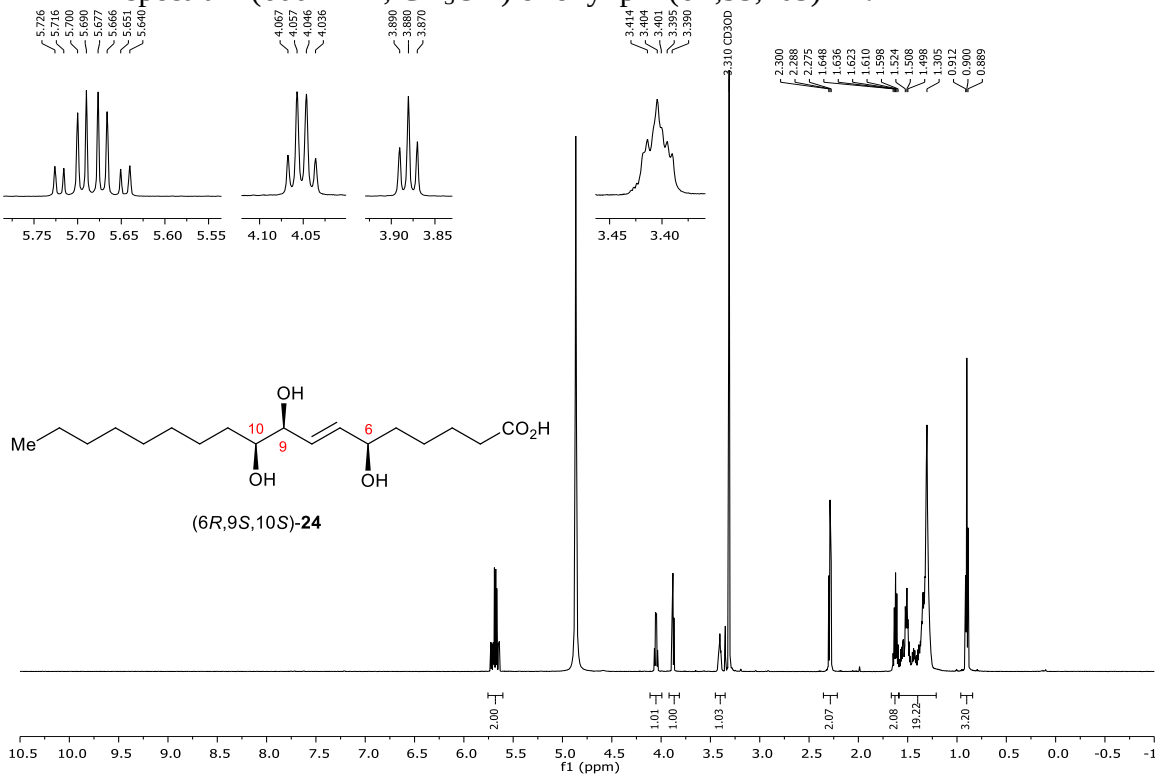
^{1}H NMR spectrum (600 MHz, CD_3OD) of oxylipin (6*S*,9*S*,10*S*)-**22:**



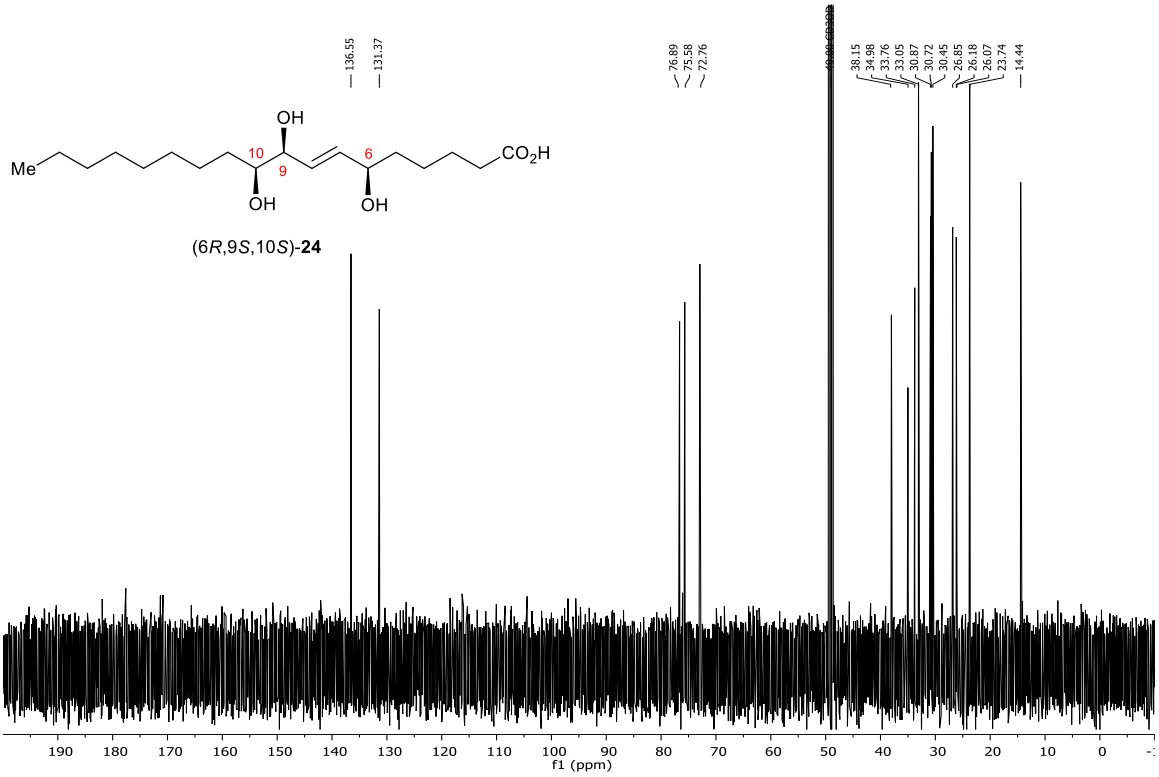
^{13}C NMR spectrum (150 MHz, CD_3OD) of oxylipin (6*S*,9*S*,10*S*)-**22:**



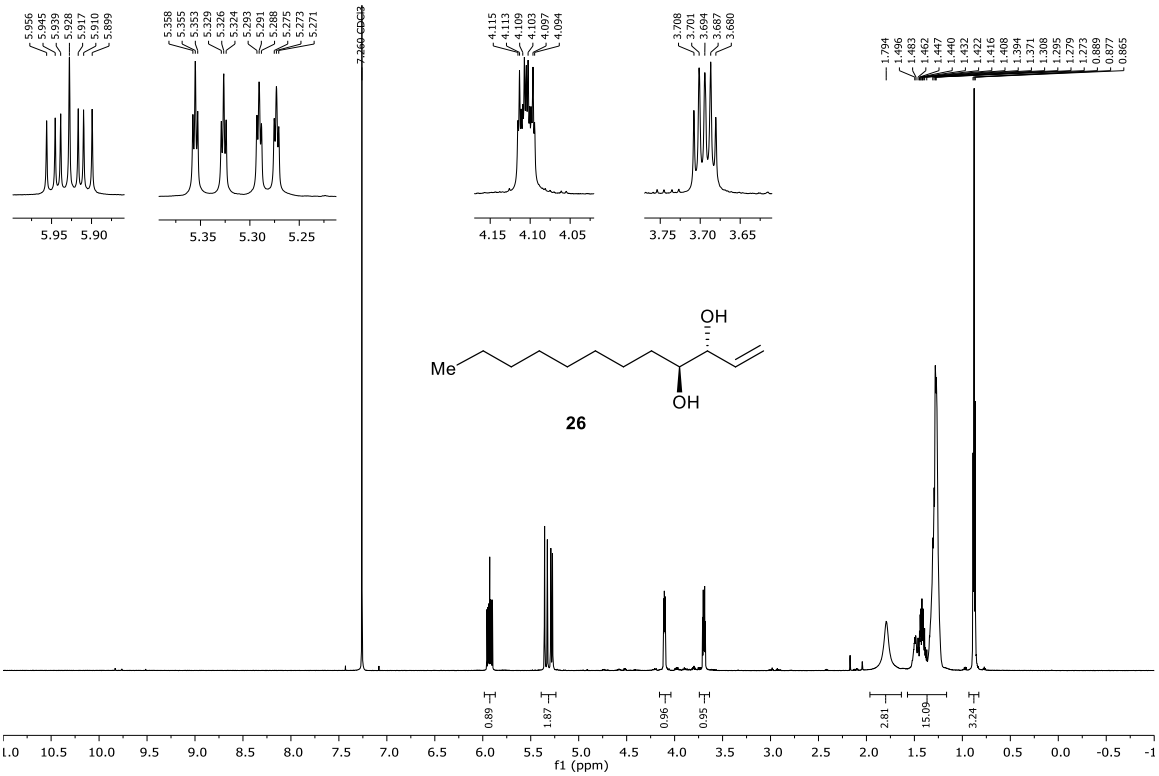
^{1}H NMR spectrum (600 MHz, CD_3OD) of oxylipin (6*R*,9*S*,10*S*)-**24:**



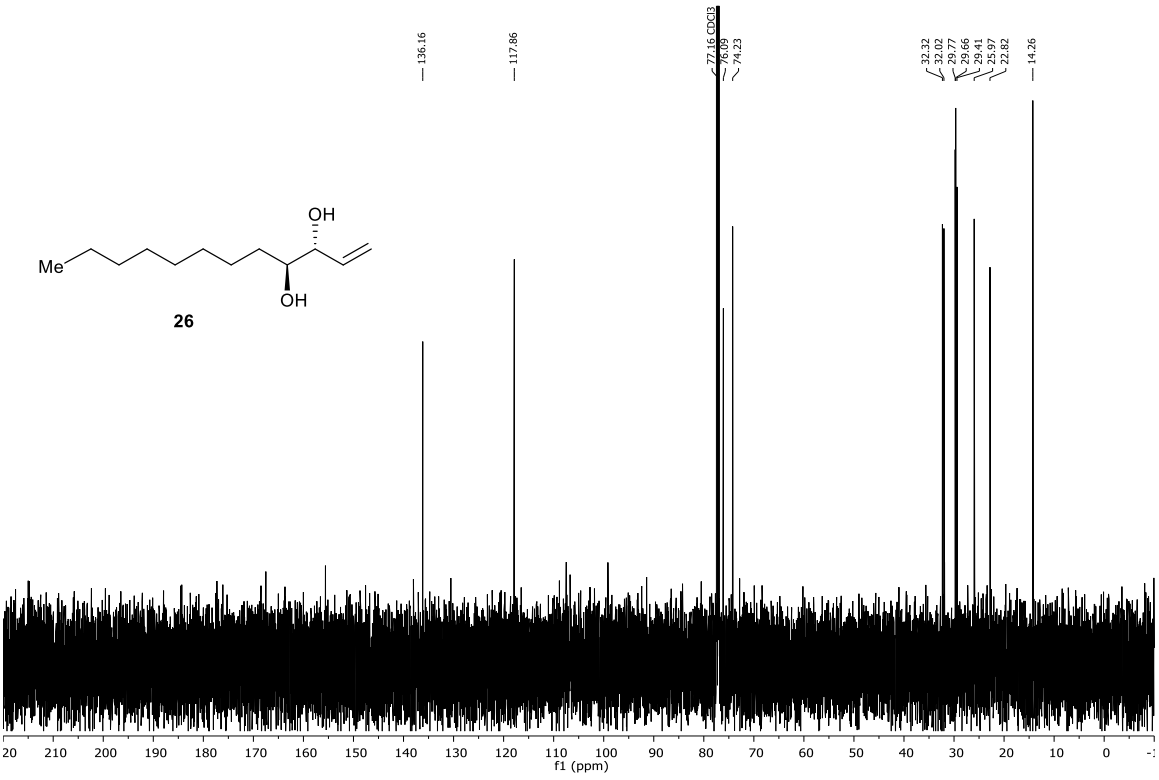
^{13}C NMR spectrum (150 MHz, CD_3OD) of oxylipin (6*R*,9*S*,10*S*)-**24:**



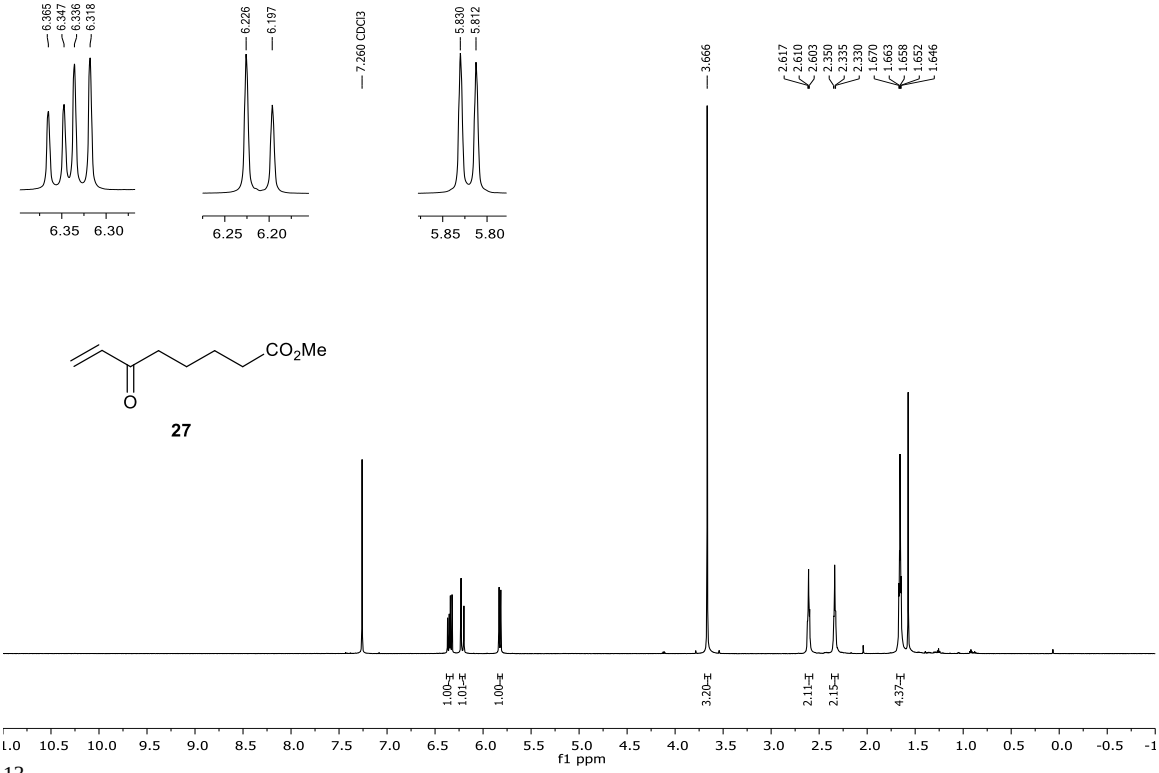
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of diol **26:**



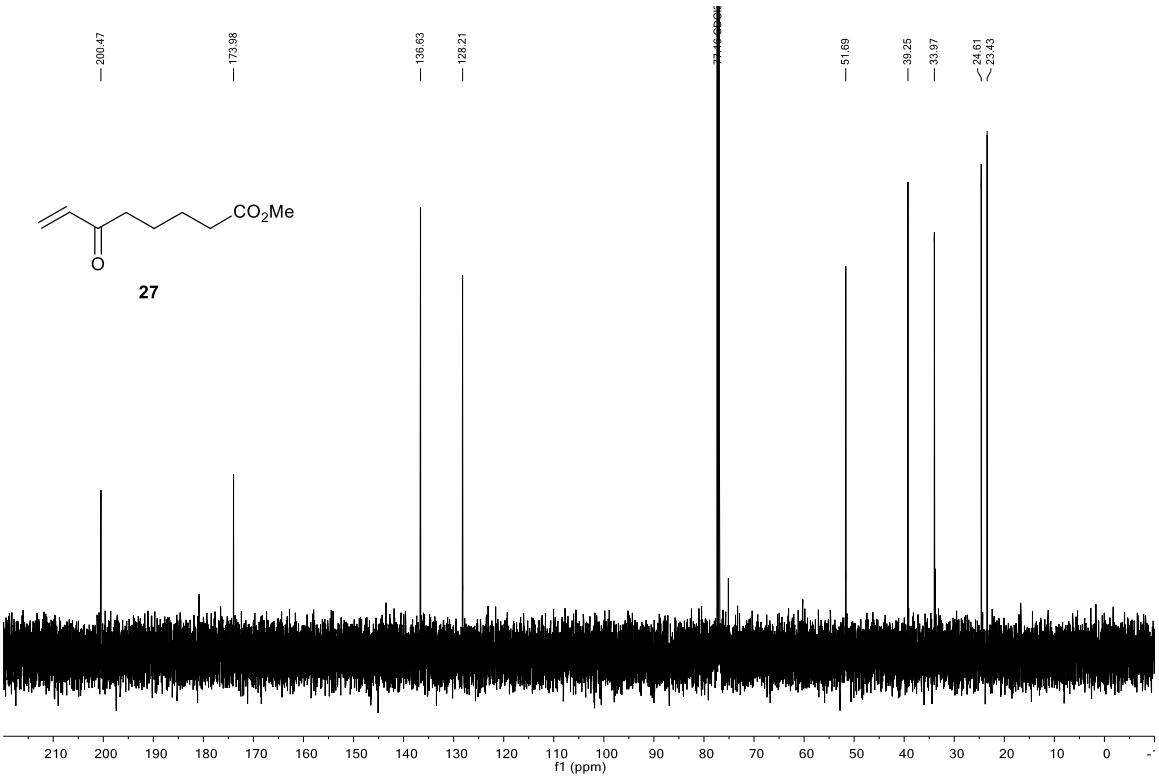
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of diol **26:**



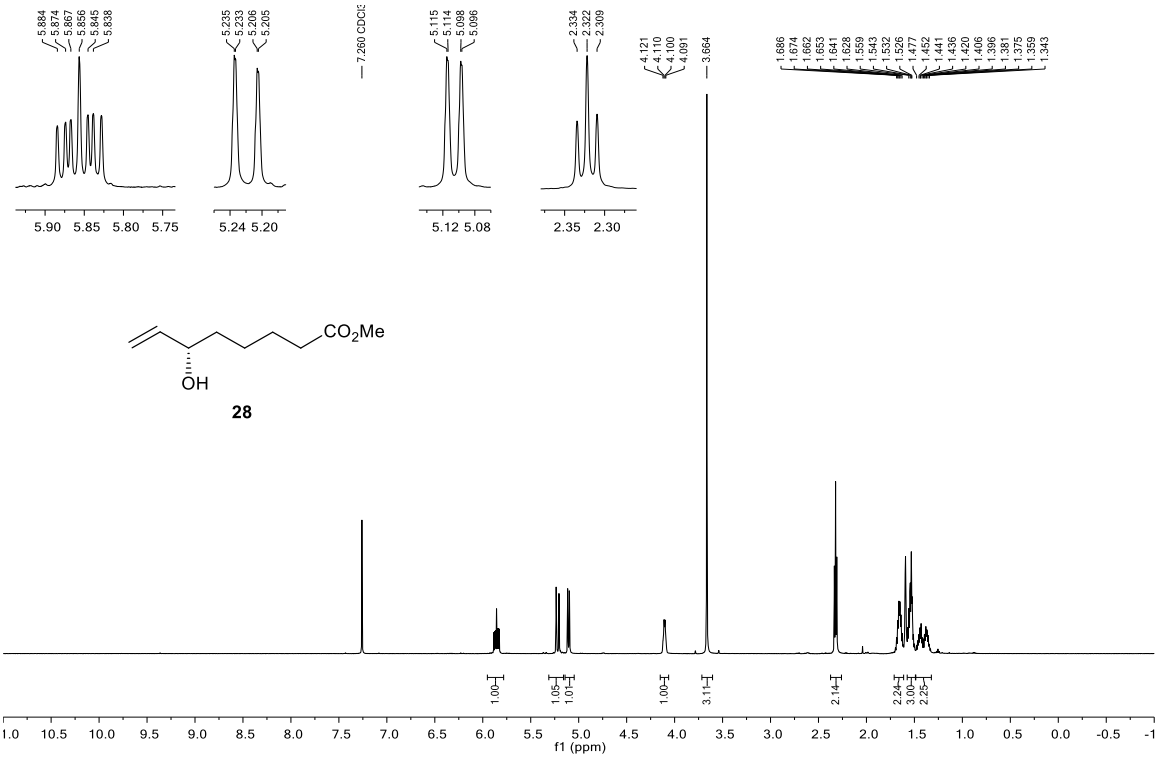
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of enone **27:**



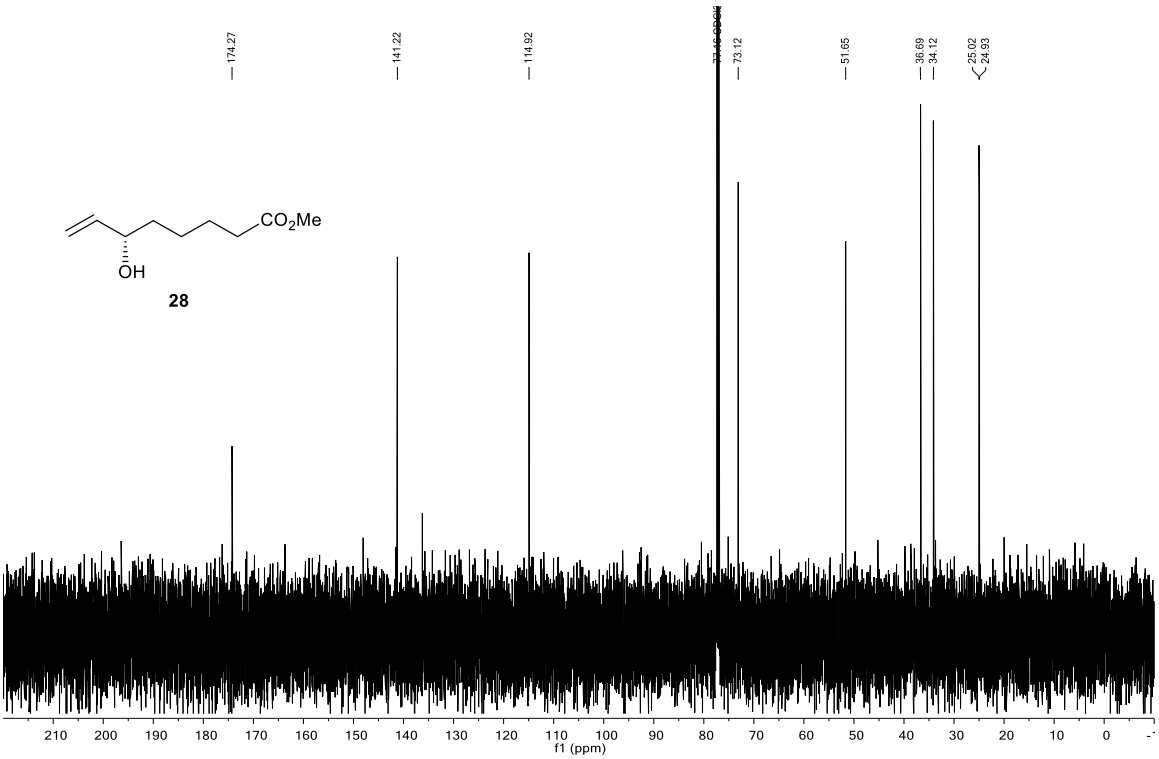
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of enone **27:**



^{1}H NMR spectrum (600 MHz, $CDCl_3$) of allylic alcohol **28:**



^{13}C NMR spectrum (150 MHz, $CDCl_3$) of allylic alcohol **28:**



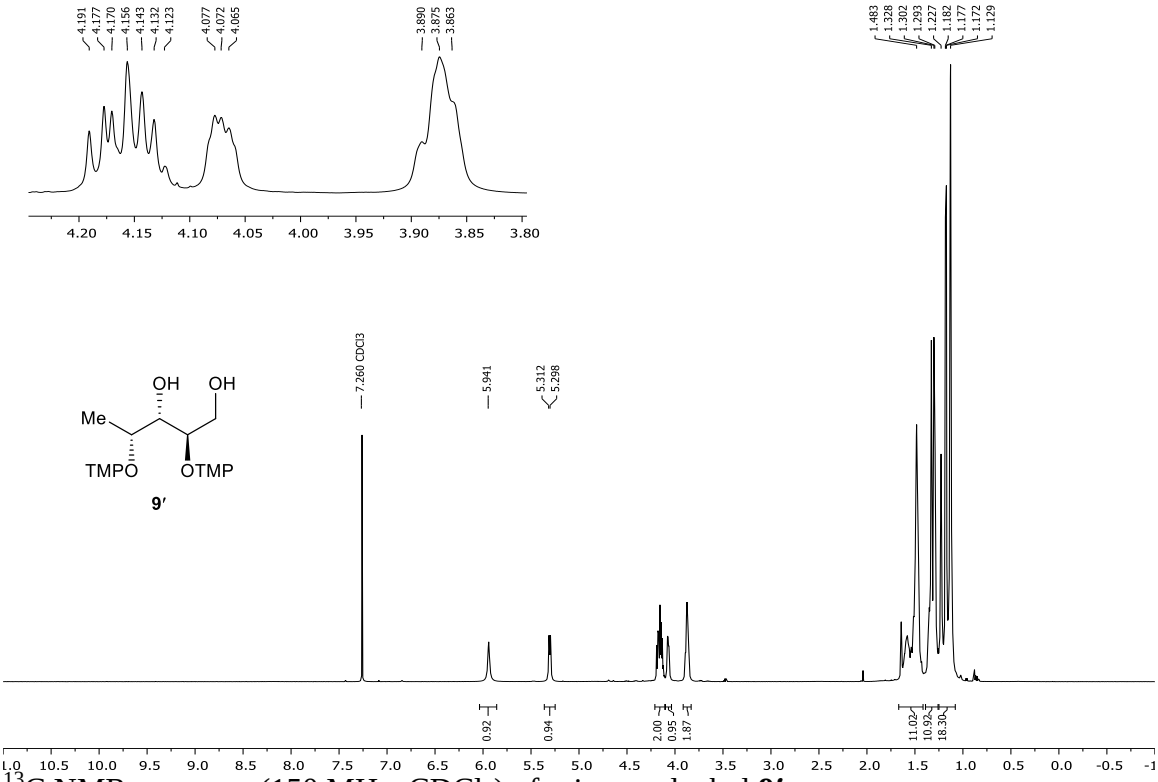
APPENDIX C

CHAPTER 3 : CATATYLTIC ENANTIOSELECTIVE

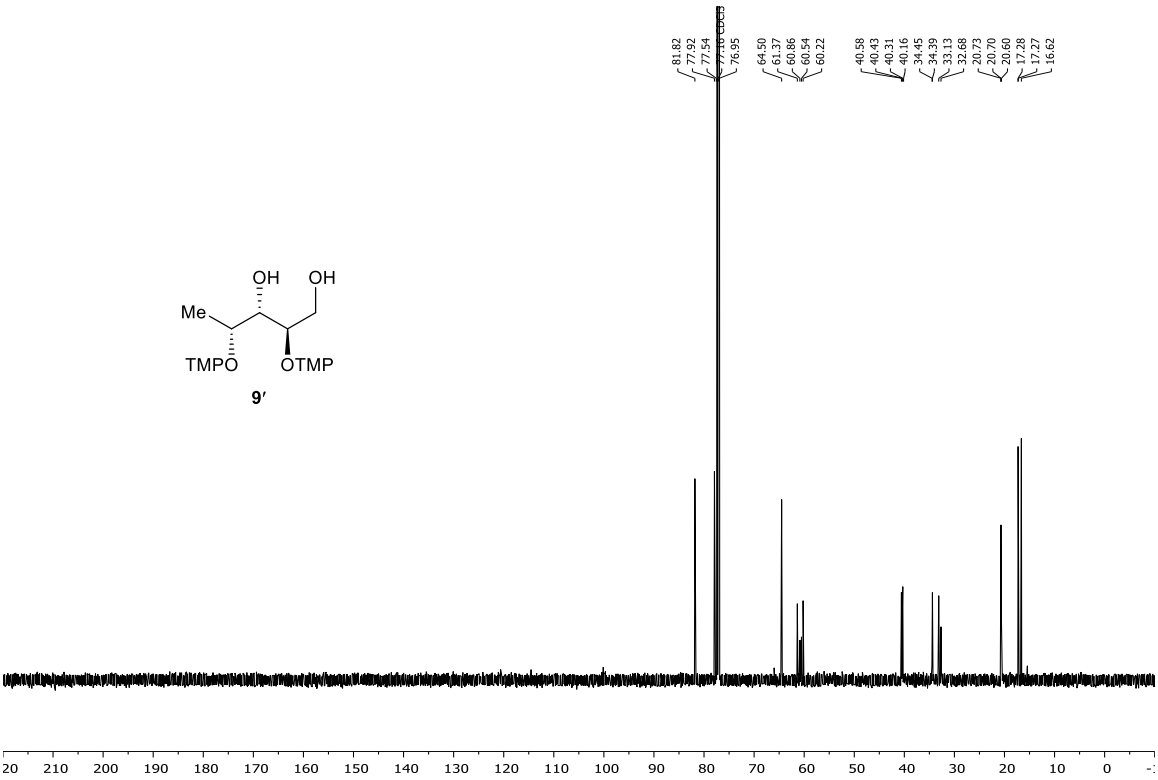
α,β,γ- TRIOXYGENATION

NMR SPECTRA AND HPLC TRACES

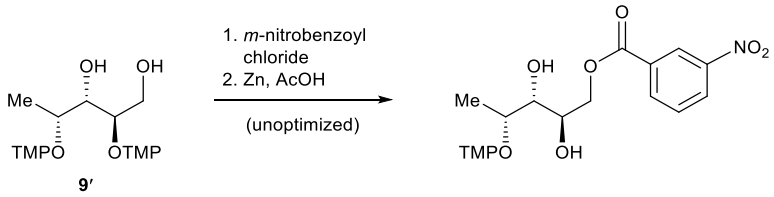
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of primary alcohol **9′:**

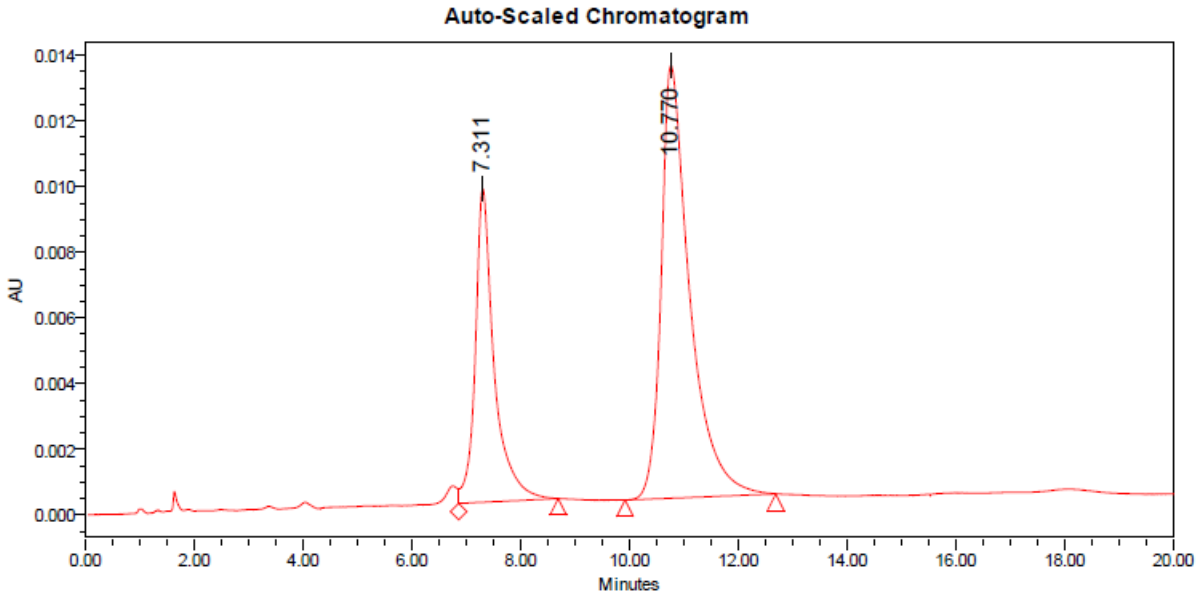


^{13}C NMR spectrum (150 MHz, $CDCl_3$) of primary alcohol **9′:**



HPLC trace of a derivative of primary alcohol **9′:**

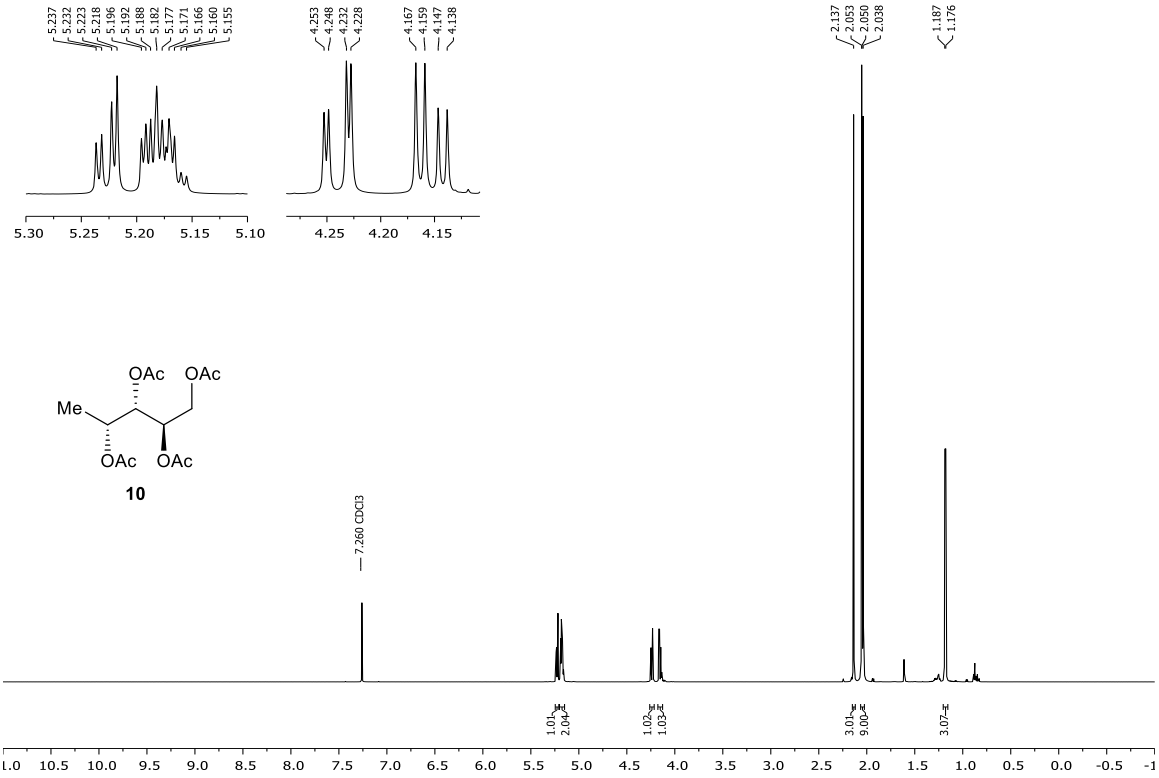




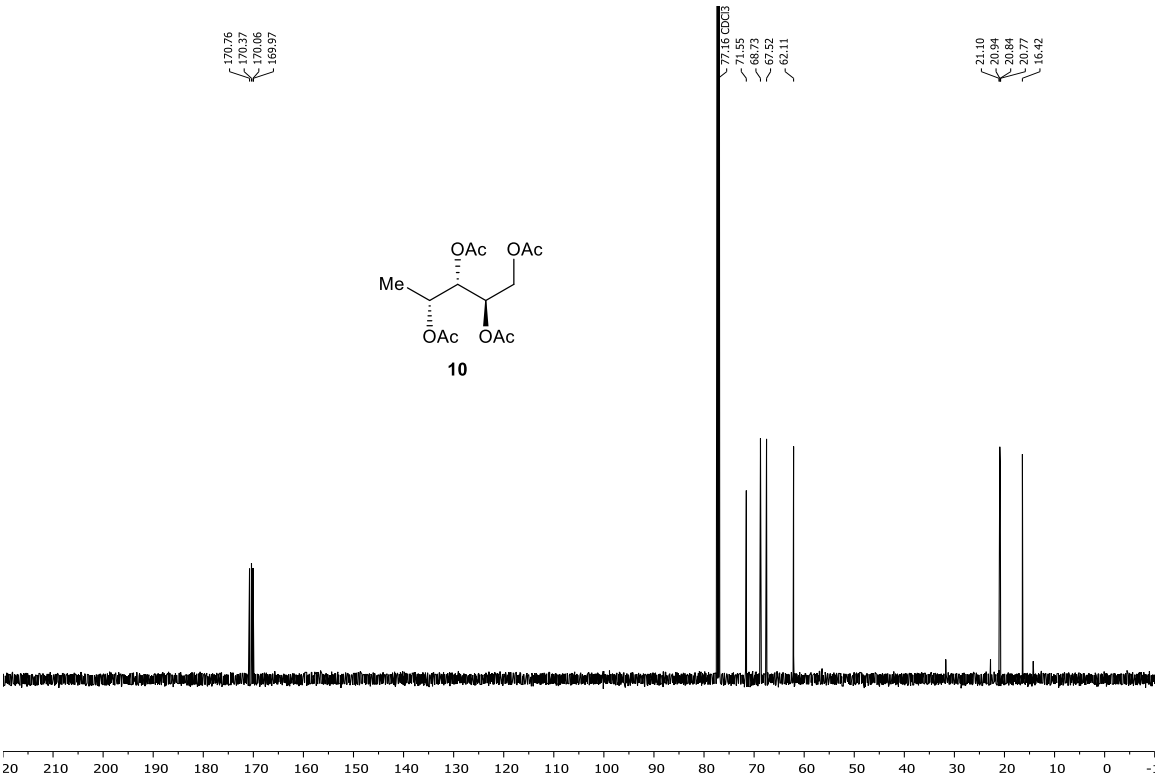
Chiraltech IA column, 2.1 × 100 mm, 3 μm
2% *i*PrOH / hexanes, 0.2 mL / min, 25 °C
280 mm UV detection

retention time / min	absolute area	relative area (%)
7.3	230573	32.31
10.8	482961	67.69

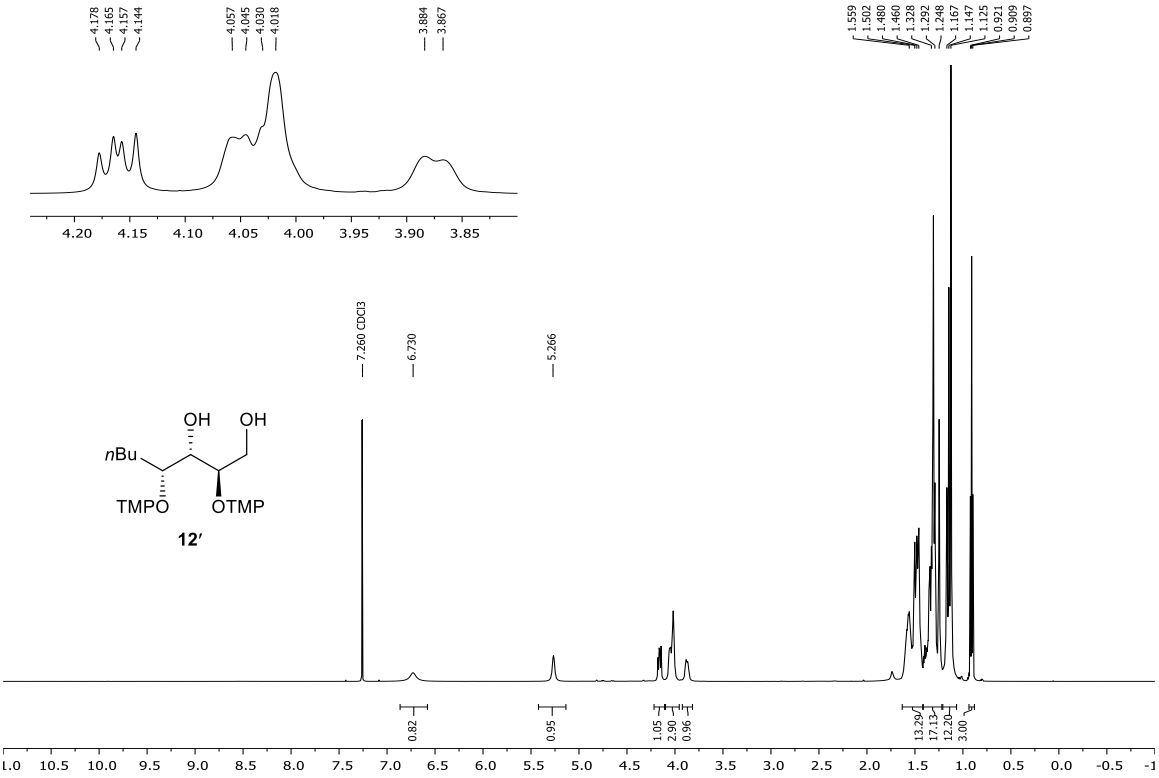
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of tetraacetate **10:**



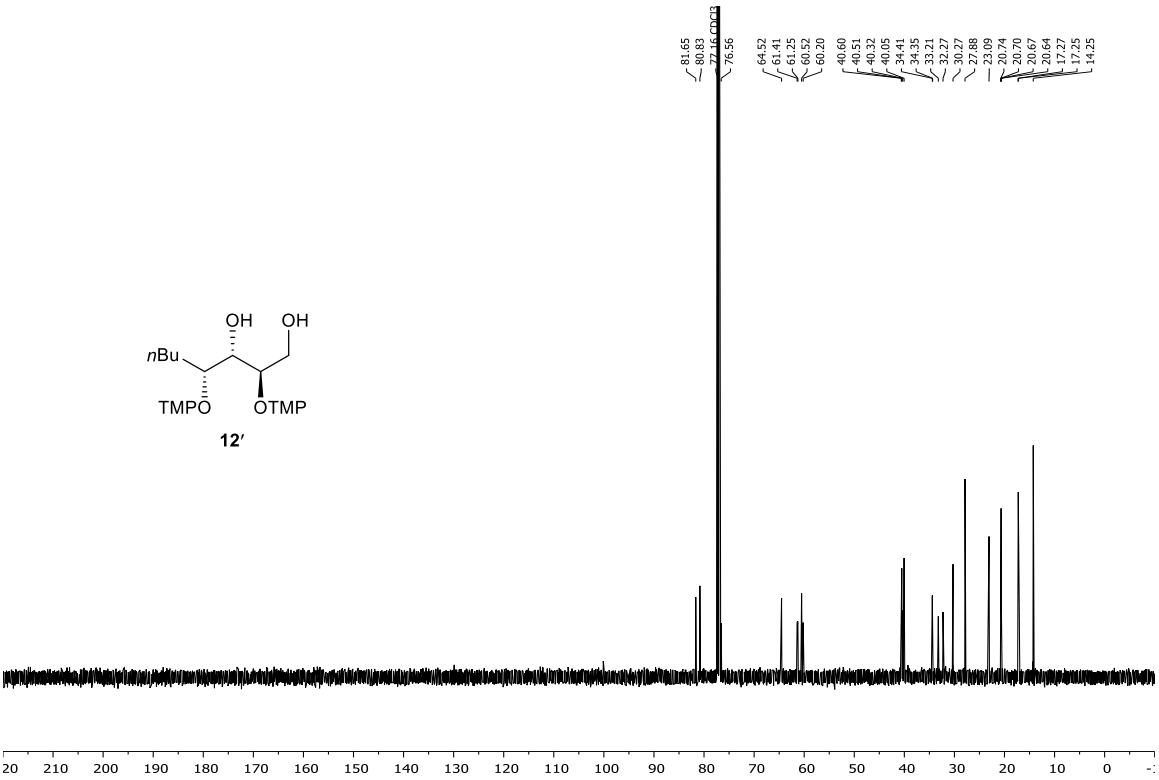
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of tetraacetate **10:**



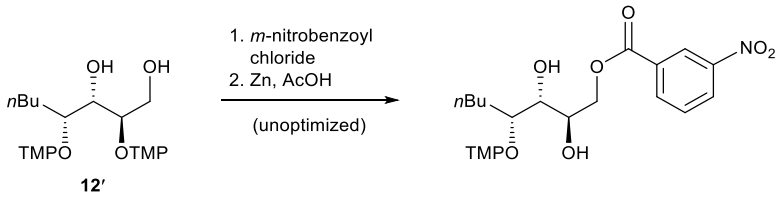
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of primary alcohol **12′:**

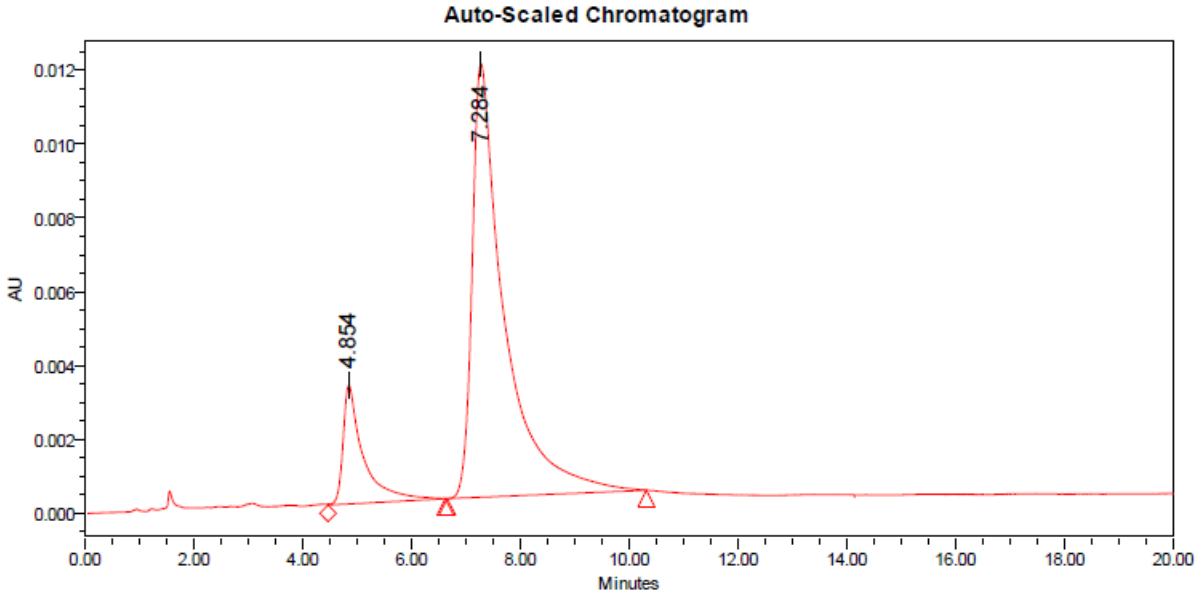


^{13}C NMR spectrum (150 MHz, $CDCl_3$) of primary alcohol **12′:**



HPLC trace of a derivative of primary alcohol **12′:**

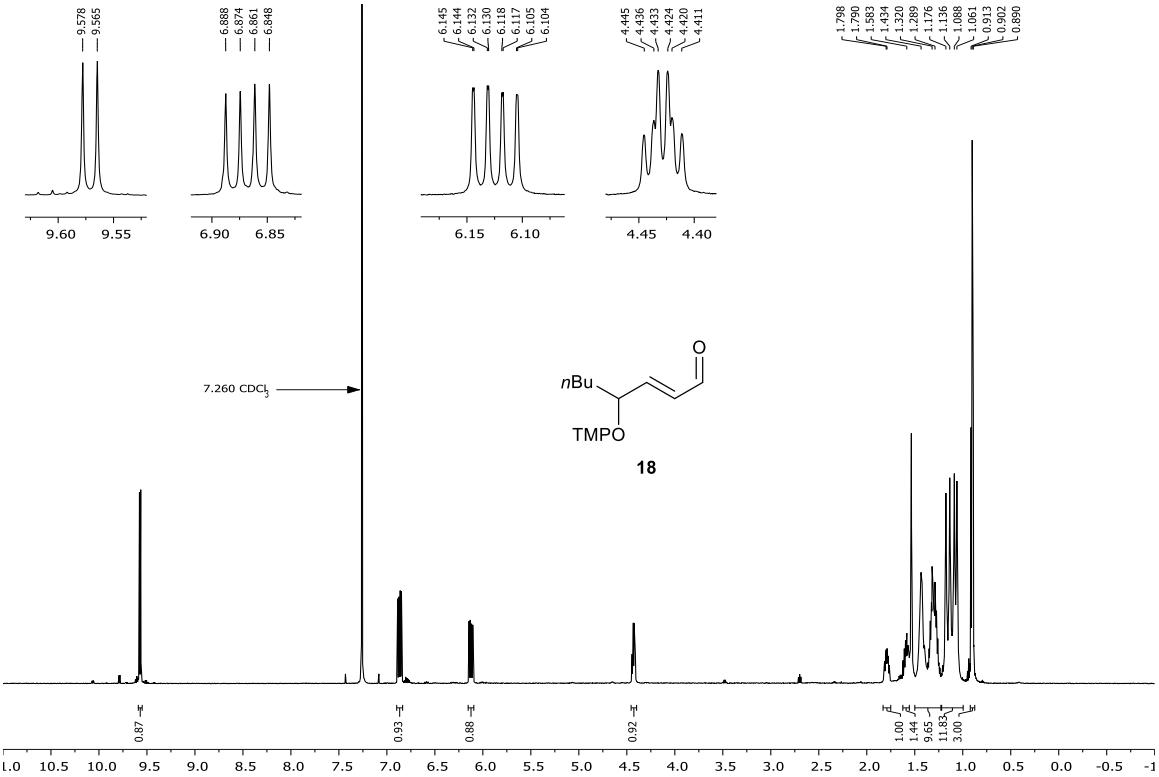




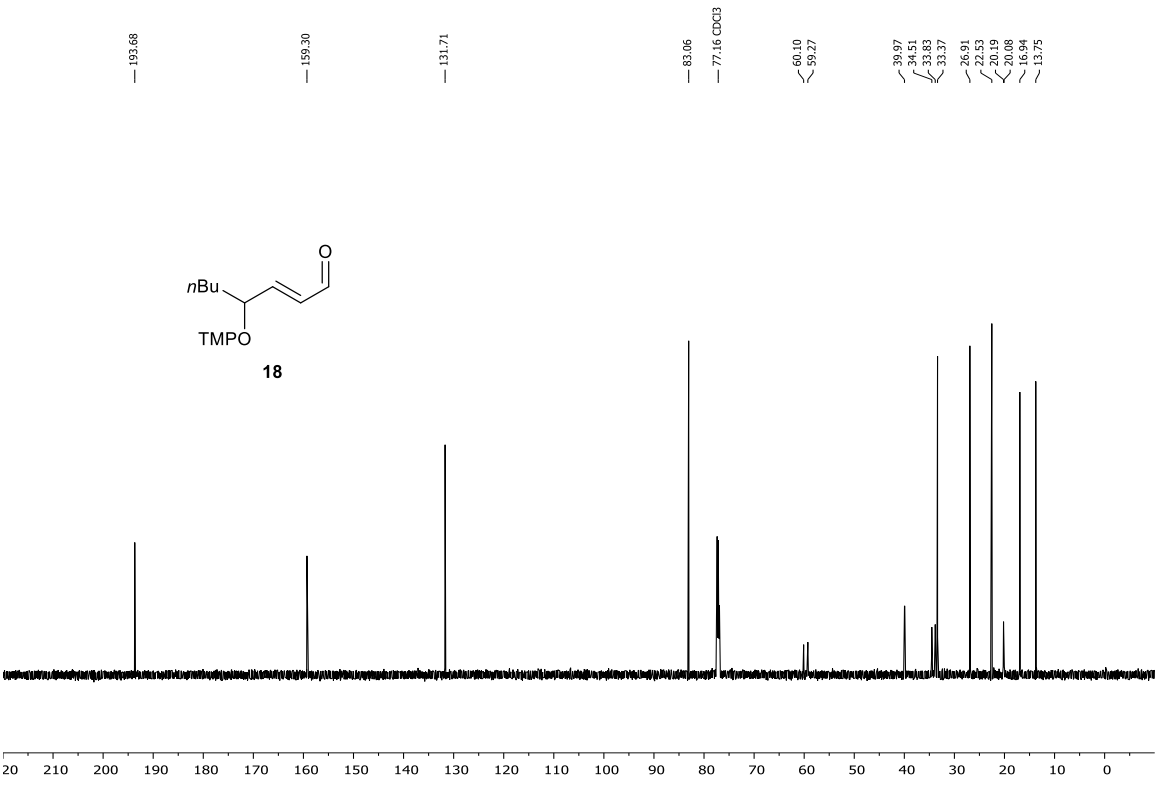
Chiraltech IA column, 2.1 × 100 mm, 3 μm
2% *i*PrOH / hexanes, 0.2 mL / min, 25 °C
280 mm UV detection

retention time / min	absolute area	relative area (%)
4.9	83302	14.72
7.3	482529	85.28

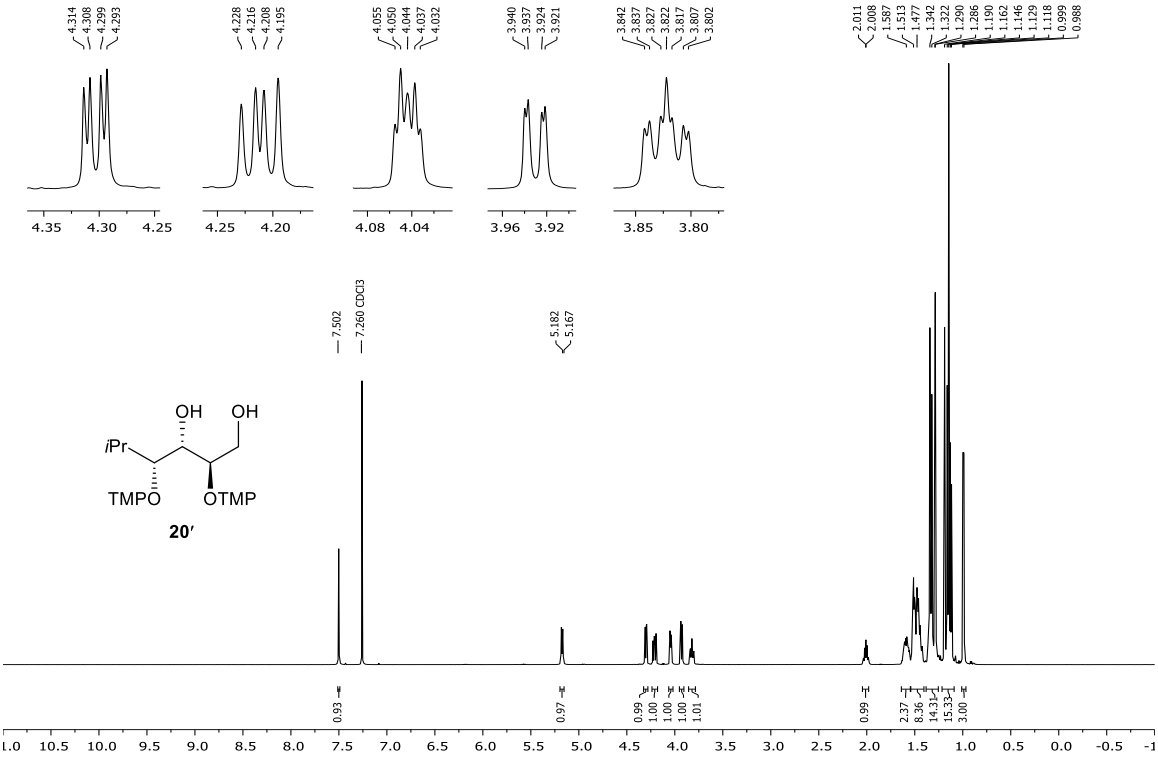
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of γ-oxyenal **18:**



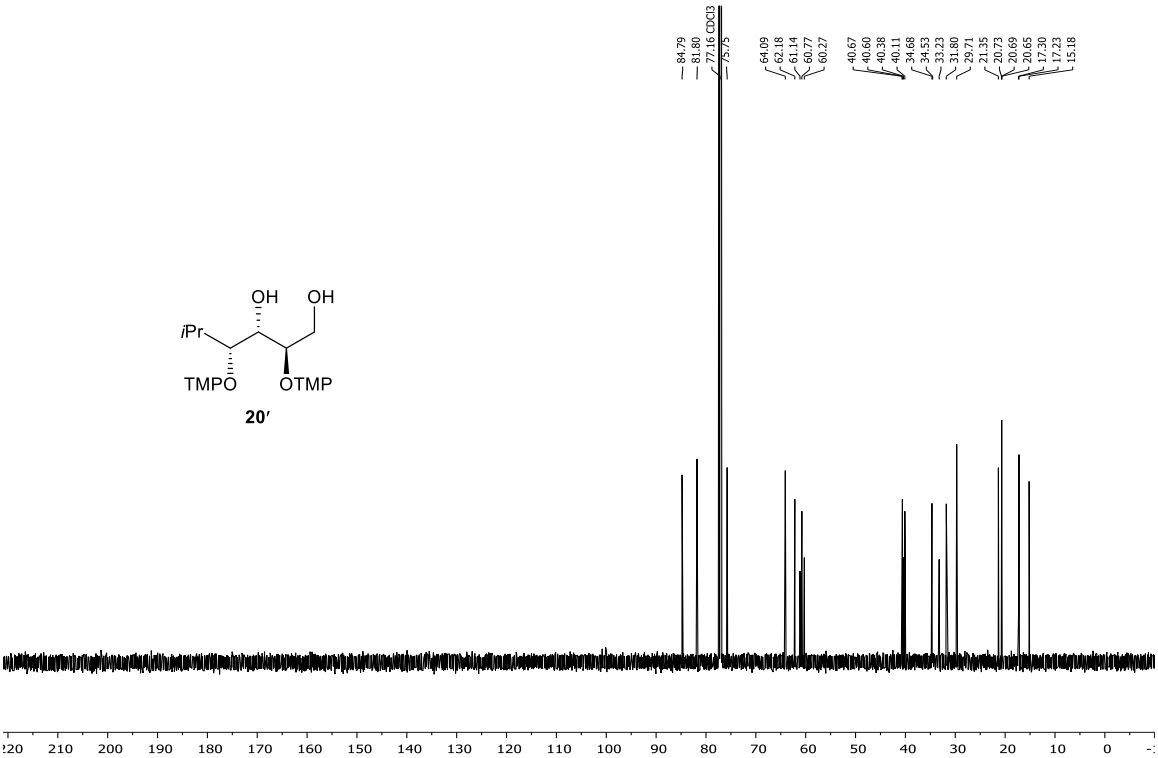
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of γ-oxyenal **18:**



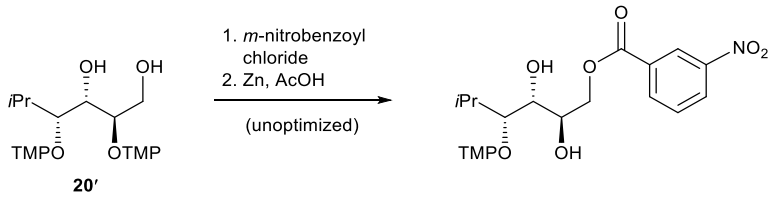
^{1}H NMR spectrum (600 MHz, $CDCl_3$) of primary alcohol **20′:**

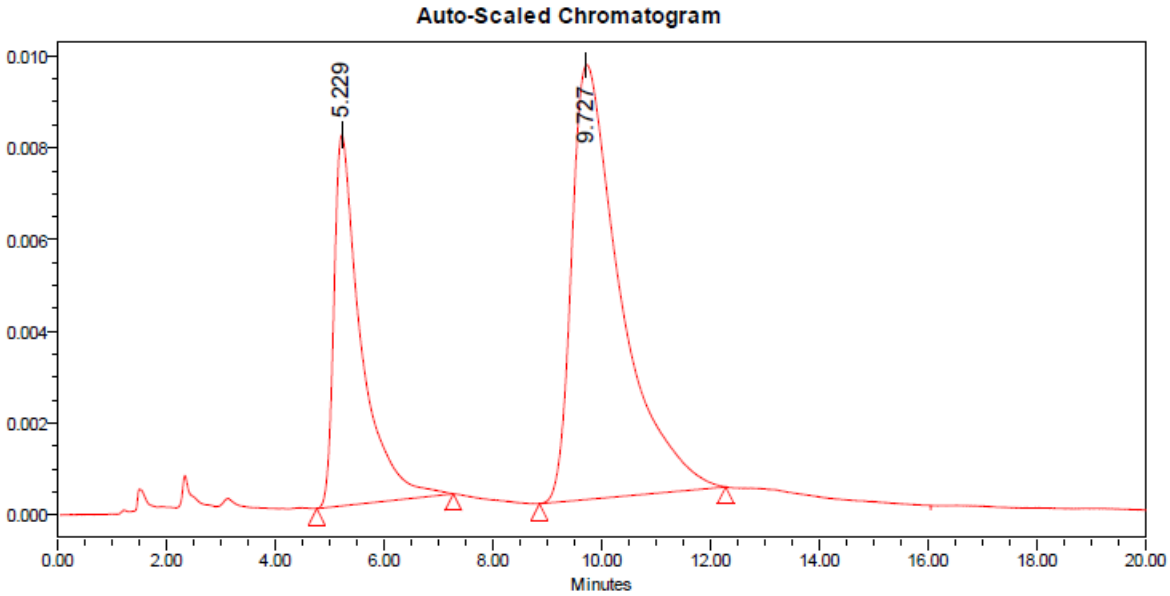


^{13}C NMR spectrum (150 MHz, $CDCl_3$) of primary alcohol **20′:**



HPLC trace of a derivative of primary alcohol **20′**:





Chiraltech IA column, 2.1 × 100 mm, 3 μm
2% *i*PrOH / hexanes, 0.2 mL / min, 25 °C
280 mm UV detection

retention time / min	absolute area	relative area (%)
5.2	280247	32.18
9.7	590595	67.82