Synthetic Efforts Toward a Total Synthesis of (+)-Peloruside A

A THESIS

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By

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Abstract

This thesis has been divided into six chapters that describe synthetic efforts toward the cytotoxic marine macrolide (+)-peloruside A, isolated by Northcote and coworkers from the New Zealand marine sponge *Mycale hentscheli*. Chapter 1 discusses the background of peloruside A and published literature studies relating to its biological activity.

Chapter 2 conveys a detailed report of the synthetic efforts by others that have resulted in three total syntheses and multiple efforts toward the total synthesis of peloruside A.

Chapter 3 describes the previous synthetic efforts by Hoye group members toward peloruside A. Two different strategies for synthesizing the C13-C20 fragment of (+)-peloruside A have been established using ring-closing metathesis. Synthesis of the C1-C9 fragment of (+)-peloruside A was accomplished using a kinetic lactonization strategy.

Chapter 4 reports on my efforts at scaling-up and optimizing the synthesis of the C1-C9 fragment of (+)-peloruside A and modifications to the previous route.

Chapter 5 describes the new progress toward synthesizing (+)-peloruside A that was achieved. These efforts culminated in the synthesis of a C1-C11 fragment of (+)-peloruside A along with studies investigating the coupling of late stage segments via a 1,5-*anti* boron-mediated aldol.

Chapter 6 highlights the key features of my synthetic efforts toward (+)-peloruside A.

Table of Contents

List of Abbreviations

Ac	Acetyl
Anal.	Analysis
aq.	aqueous
Ar	Aryl
9-BBN	9-Borabycyclo[3.3.1]nonane
Bn	Benzyl ($C_6H_5CH_2$-)
n-Bu or ^{n}Bu	normal-Butyl
t-Bu or ^{t}Bu	tertiary-Butyl
Calcd	Calculated
ºC	degrees Celsius
CH_2Cl_2	Dichloromethane
CI	Chemical Ionization
CM	Cross Metathesis
COSY	Correlated spectroscopy
CSA	(+/-)-10-Camphorsulphonic acid
d	Chemical shift, in NMR spectroscopy
d	Doublet, in NMR spectroscopy
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	Distortionless Enhancement Polarization Transfer
DIBAL-H	Diisobutylaluminum hydride
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimthylformamide
DMP	Dimethoxypropane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EI	Electron impact

ESI	Electrospray Ionization
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
equiv	Equivalent
er	Enantiomeric ratio
FAB	Fast atom bombardment
g	Gram(s)
GOESY	Gradient nuclear Overhauser effect spectroscopy
GC-MS or GCMS	Capillary gas chromatography-mass spectrometry
h	Hour
n-Hex or ^{n}Hex	normal-Hexyl
HMBC	Hetero-nuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correhence
HOMO2DJ	Homonuclear multiple bond correlation
HSQC	Heteronuclear spin quantum correlation
HMPA	Hexamethylphosphoric triamide
HRMS	High resolution mass spectrometry
Hz	Hertz (cycles per second)
IC_{50}	50% of the concentration for complete inhibition of cellular viability
IR	Infrared
J	Coupling constant (NMR)
KO*t*-Bu	potassium *tert*-butoxide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LRMS	low-resolution mass spectrum
m	Multiplet, in NMR spectroscopy
Me	Methyl
Meerwien's Salt	trimethyloxonium fluoroborate ($Me_3O^+BF_4^-$)

MHz	Megahertz
mol	Mole(s)
mmol	milliMole
MOM	Methoxymethyl
Mp	Melting point
MPLC	Medium pressure liquid chromatography
4Å MS	4-angstrom molecular sieves
MTPA	α-Methoxytrifluoromethylphenylacetyl
NBS	*N*-bromosuccinimide
ND	not determined
NMO	4-Methylmorpholine-N-Oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect/Enhancement
NR	no reaction
p	pentet (NMR)
PCC	Pyridinium chlorochromate
Ph	Phenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonic acid
PTSA	*p*-Toluenesulfonic acid monohydrate
i-Pr or ^{i}Pr	Isopropyl
q	Quartet, in NMR spectroscopy
R	Rectus (configurational)
RCM	Ring-closing metathesis
R_f	Ratio to front
ROMP	Ring-opening metathesis
ROESY	Rotational frame NOE
RT or rt	Room temperature
S	Sinister (configurational)
s	Singlet, in NMR spectroscopy

t	Triplet, in NMR spectroscopy
TBAF	Tetrabutylammonium fluoride
TBDPS	*tertiary*-Butyldiphenylsilyl
TBDPSCl	*tertiary*-Butyldiphenylsilyl chloride
TBS	*tertiary*-Butyldimethylsilyl
TBSCl	*tertiary*-Butyldimethylsilyl chloride
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	tri*iso*propylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
TOCSY	Total correlated spectroscopy
TOF	Time of flight
t_R	Retention time
Ts	*para*-Toluenesulfonyl

List of Figures

List of Tables

I. Introduction and Background

A. (+)-Peloruside A Isolation

(+)-Peloruside A **1** (**Figure 1**) was isolated from the New Zealand marine sponge *Mycale hentscheli* in 2000 by Northcote and coworkers.[1] Specimens were collected from the Pelorus Sound on the north coast of the south island. A single specimen (170 g, wet weight) yielded 3.0 mg of (+)-peloruside A **1** after crude extract separation and final purification with reverse phase high-perfomance liquid chromatography (RP-HPLC). It is interesting to note that only specimens collected at the deeper depth of the sponge population contained detectable amounts of peloruside A **1**. The previously known antiviral and antitumor agents mycalamide A **2** and pateamine **3** were isolated from the same crude extracts.[2] The structure and relative stereochemistry of peloruside **1** was determined using extensive nuclear magnetic resonance (NMR) studies: ^{1}H NMR, ^{13}C NMR, DEPT, COSY, ROESY, HSQC, HMBC, 1D TOCSY, and GOESY. The synthesis of ***ent*-1** by De Brabander at UT Southwestern Medical Center later verified the proposed structure and determined the absolute configuration as (+)-peloruside A **1**.[3]

The interesting structural features of (+)-peloruside A **1** include: 10 stereogenic centers, a pyranose ring-containing 16 membered macrolide, high degree of oxygenation, sterically hindered C8-C11 segment containing *gem*-dimethyl moiety, and a *Z*-trisubstituted olefin.

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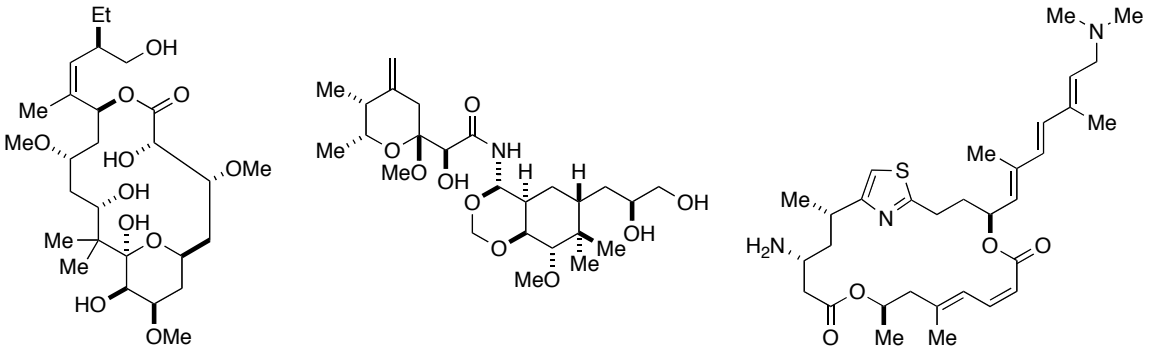
[1] "Peloruside A: A potent cytotoxic macrolide isolated from the New Zealand marine sponge Mycale sp." West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445-449.

[2] (a) "Mycalamide A, an antiviral compound from a New Zealand sponge of the genus Mycale." Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Pannell, L. K. *J. Am. Chem. Soc.* **1988**, *110*, 4850-4851. (b) "Antiviral and antitumor agents from a New Zealand sponge, Mycale sp. 2. Structures and solution conformations of mycalamides A and B." Perry, N.; Blunt, J.; Munro, M.; Thompson, A. *J. Org. Chem.* **1990**, *55*, 223-227. (c) "Pateamine: A potent cytotoxin from the New Zealand marine sponge, Mycale sp." Northcote, P. T.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett.* **1991**, *32*, 6411-6414.

[3] "Total synthesis and absolute configuration of the novel microtubule-stabilizing agent peloruside A." Liao, X.; Wu, Y.; De Brabander, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1648-1652.

Figure 1

Natural Products Isolated from the Marine Sponge Mycale Hentscheli



(+)-peloruside A ***1*** mycalamide A ***2*** pateamine ***3***

B. (+)-Peloruside A Biological Activity

Peloruside A **1** was subjected to an initial screening of biological assays in the report by Northcote et al. and was found to be cytotoxic to P388 murine leukemia cells with an IC_{50} value of 10 ng/mL (18 nM).[1] It is also intriguing that although mycalamide A **2** and pateamine **3** were isolated from the same species of sponge and share similar structural features, they exhibit little, if any, of the same biological activity.[4]

In 2001, further testing of peloruside A **1** showed it to be a potent inhibitor of cell proliferation and capable of inducing apoptosis in a dose-dependent manner in murine (32D) and human (HL-60) myeloid cell lines.[5] Further studies revealed IC_{50} values of 4-15 nM when various cell lines were treated with peloruside A **1**.

In the same study, Hood et al. were interested in determining if peloruside A **1** and bryostatin 1 **4** had a similar mechanism of action in regard to protein kinase C (PKC) activity because both compounds contain similar structural features and bryostatin 1 **4** is known to be a PKC activator (proposed pharmacophores of bryostatin 1 **4** are highlighted by boxes in **Figure 2**). However, competitive binding tests to PKC in HL-60 cells revealed peloruside A **1** did not bind and therefore must have a mechanism of action different from that of bryostatin 1 **4**.

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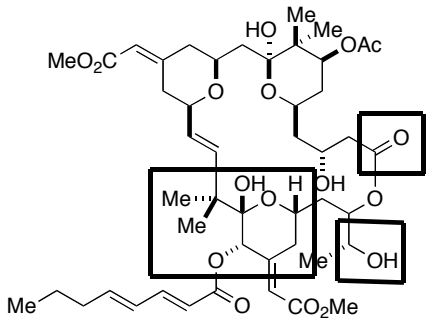
[4] "Induction of apoptosis by the marine sponge (Mycale) metabolites, mycalamide A and pateamine." Hood, K. A.; West, L. M.; Northcote, P. T.; Berridge, M. B.; Miller, J. H. *Apoptosis* **2001**, *6*, 207-219.

[5] "The novel cytotoxic sponge metabolite peloruside A, structurally similar to bryostatin-1, has unique bioactivity independent of protein kinase C." Hood, K. A.; Bäckström, B. T.; West, L. M.; Northcote, P. T. *Anti-Cancer Drug Design* **2001**, *16*, 155-166.

Figure 2

Proposed Pharmacophores of Bryostatin 1



bryostatin 1 ***4***

Additional biological studies by Miller and coworkers in 2002 identified (+)-peloruside A **1** as having microtubule stabilizing activity similar to paclitaxel (Taxol® **5**) and taxotere (Docetaxel **6**) (**Figure 3**). It was shown that peloruside A **1** arrests cells in the G_2-M phase of the cell cycle, which results in apoptosis.[6]

Subsequent investigations in 2004 into the binding of peloruside A **1** revealed that it remains cytotoxic in multidrug resistance (MDR)-overexpressing cells that are resistant to paclitaxel **5**.[7] Mutations at the taxoid binding site of β-tubulin were shown not to affect peloruside's activity and thus, additional evidence for a different binding sight than that of paclitaxel **5**. Competition experiments showed that peloruside A **1** and laulimalide **10** (**Figure 3**) compete for the same or overlapping binding sites.

Peloruside A **1** has been shown to preferentially target oncogene-transformed cells towards undergoing apoptosis over non-transformed cells.[8] Evidence reported in 2006 revealed the synergistic effects of peloruside A **1** with various taxoid binding site agents (paclitaxel **5**, epothilone A **9**, discodermolide **12**, dictyostatin **11**, eleutherobin **7**,

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[6] "Peloruside A, a novel antimitotic agent with paclitaxel-like microtubule-stabilizing activity." Hood, K. A.; West, L. M.; Rouwe, B.; Northcote, P. T. *Cancer Research* **2002**, *62*, 3356-3360.

[7] "Peloruside A does not bind to the taxoid site on β-tubulin and retains its activity in multidrug-resistant cell-lines." Teesdale-Spittle, P.; Andreu, J. M.; Miller, J. H. *Cancer Research* **2004**, *64*, 5063-5067.

[8] "Peloruside A enhances apoptosis in H-*ras*-transformed cells and is cytotoxic to proliferating T cells." Miller, J. H.; Rouwé, B.; Gaitanos, T. N.; Hood, K. A.; Crume, K. P.; Bäckström, B. T.; La Flamme, A. C.; Berridge, M. V.; Northcote, P. T. *Apoptosis* **2004**, *9*, 785-796.

et al., **Figure 3**) on tubulin assembly.[9] This synergy was also found to be present with respect to the cytotoxic effects of peloruside A **1** with both epothilone A **1** and paclitaxel **5** on two cancer cell lines.[10] Additional biological tests revealed peloruside A **1** is able to induce cell death without having the proinflammatory side effects that are present with paclitaxel **5**.[11]

To date there are two publications reporting on the binding site of (+)-peloruside A **1** to microtubules. The first report, published in 2006, proposed that the bioactive conformation of peloruside A **1** binds to the α-tubulin monomer, different from paclitaxol **5** and its binding to the β-tubulin monomer.[12] In 2008 a second proposal was made for peloruside A **1** binding to the exterior of β-tubulin.[13] There is definitely a need for reevaluation of the proposed binding sites before an agreement between α vs. β-tubulin binding can be made.

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[9] "Synergistic effects of peloruside A and laulimalide with taxoid site drugs, but not with each other, on tubulin assembly." Hamel, E.; Day, B.; Miller, J.; Jung, M.; Northcote, P.; Ghosh, A.; Curran, D.; Cushman, M.; Nicolaou, K.; Paterson, I.; Sorensen, E. *Mol. Pharmacology* **2006**, *70*, 1555-1564.

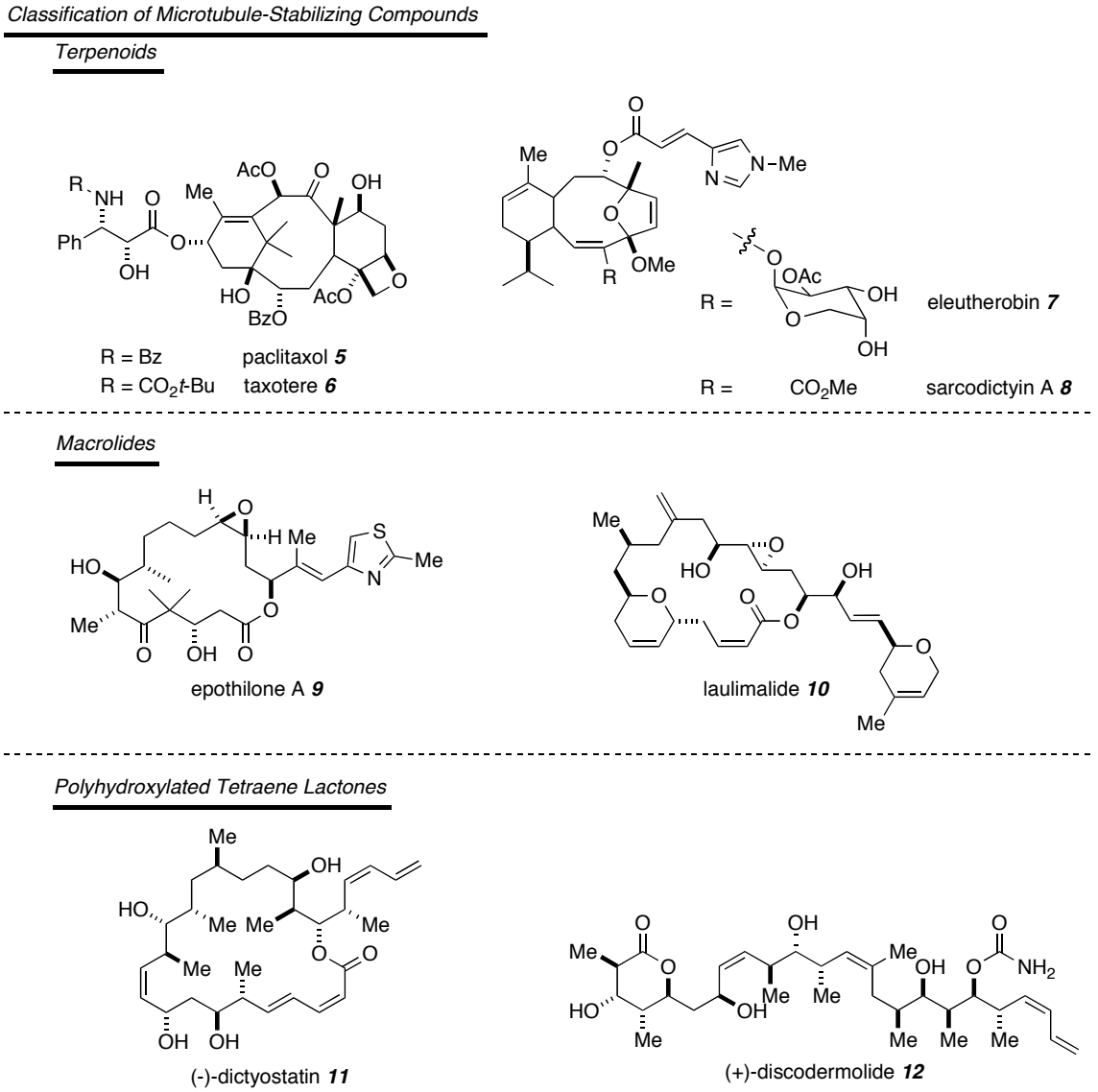
[10] "Peloruside A synergizes with other microtubule stabilizing agents in cultured cancer cell lines." Wilmes, A.; Bargh, K.; Kelly, C.; Northcote, P. T. *Mol. Pharmaceutics* **2007**, *4*, 269-280.

[11] "Peloruside A, antimitotic agent, specifically decreases tumor necrosis factor-a production by lipopolysaccharide-stimulated murine macrophages." Crume, K. P.; Miller, J. H.; La Flamme, A. C. *Experimental Biology and Medicine* **2007**, *232*, 607-613.

[12] "NMR determination of the bioactive conformation of peloruside A bound to microtubules." Jimenez-Barbero, J.; Canales, A.; Northcote, P. T. *J. Am. Chem. Soc.* **2006**, *128*, 8757-8765.

[13] "A unique mode of microtubule stabilization induced by peloruside A." Huzil, J. T.; Chik, J. K.; Slysz, G. W.; Freedman, H.; Tuszynski, J.; Taylor, R. E.; Sackett, D. L.; Schriemer, D. C. *J. Mol. Biol.* **2008**, *378*, 1016-1030.

Figure 3



C. (+)-Peloruside A Via Aquaculture

Page and coworkers, in 2005, reported aquaculture trials for the production of (+)-peloruside A **1**, mycalamide A **2** and pateamine **3** from the New Zealancd sponge *Mycale hentscheli*.[14] Their results showed that in-sea aquaculture is a viable process for a short- to medium-term supply of these compounds for drug development. Peloruside A **1** was

[14] "Aquaculture trials for the production of biologically active metabolites in the New Zealand sponge Mycale hentscheli (Demospongiae Poecilosclerida)." Page, M. J.; Northcote, P. T.; Webb, V. L.; Mackey, S.; Handley, S. J. *Aquaculture* **2005**, *250*, 256-269.

found to be present in a small portion of wild sponges and only explants from these sponges, cultured in their native environment produced quantifiable amounts.

II. Synthetic Strategies Toward Peloruside A

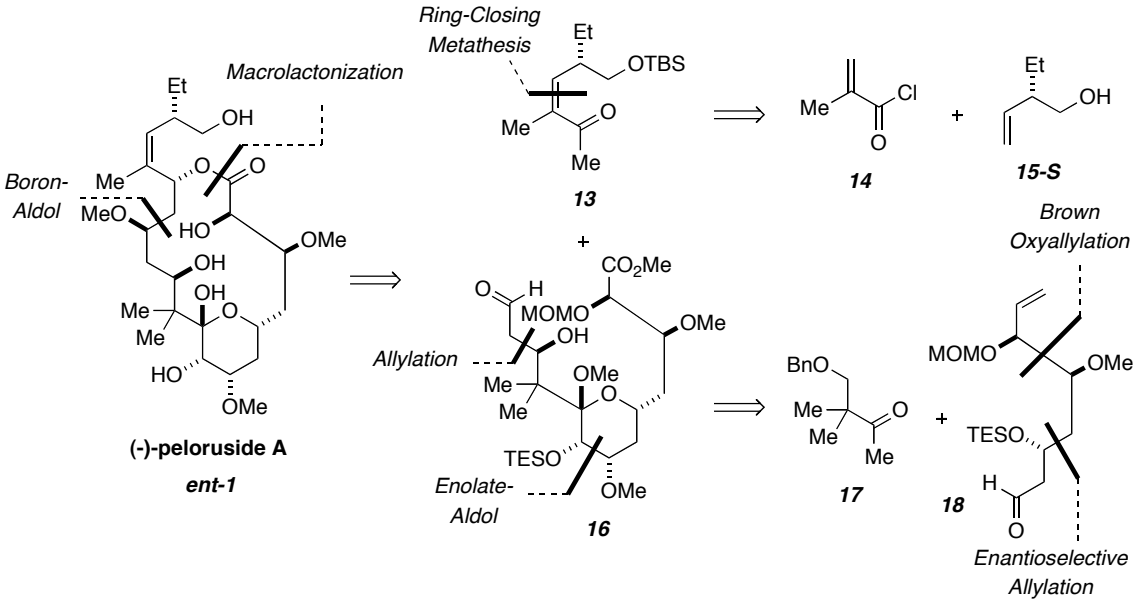
A. Total Syntheses of Peloruside A

1. J. De Brabander's Total Synthesis of (-)-Peloruside A

The first total synthesis of peloruside A **1** was reported in 2003 by the research group of Jeff De Brabander at UT Southwestern Medical Center.[3] Their synthetic efforts provided the unnatural enantiomer (-)-peloruside A ***ent*-1** and established the absolute configuration of the natural product. The retrosynthetic analysis of the molecule included a late stage aldol coupling between ketone **13** and aldehyde **16 (Scheme 1)**. Variability in either acylative or invertive macrocyclization was believed to enhance the possibility of success in the ring closure event. The employment of late stage aldol reactions to couple complex intermediates and macrocyclizations will turn out to be a reccurring theme in many synthetic efforts toward peloruside A **1**. Ketone **13** could be derived from methacryloyl chloride **14** and the known homoallylic alchohol **15**. It was anticipated that sequential asymmetric allylations, aldol, and functional group manipulations would provide aldehyde **16**.

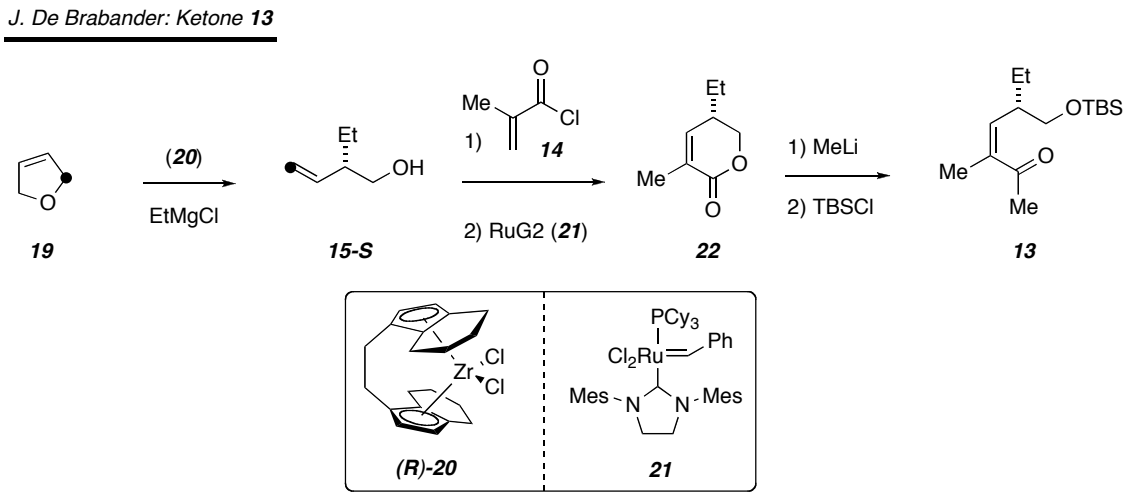
Scheme 1

J. Debrabander (2003): Retrosynthesis of (-)-peloruside A



The De Brabander synthesis began with the formation of the homoallylic alcohol **15-*S*** from 2,5-dihydrofuran **19** using asymmetric zirconium catalyst **20**, as previously described by Hoveyda (**Scheme 2**).[15] Subsequent acylation of the alcohol **15-*S*** with methacryloyl chloride **14** and ring-closing metathesis (RCM) with Grubbs second generation catalyst (**Ru^{G2}**) **21** produced the lactone **22**, which contained the desired *Z*-trisubstituted olefin. Treatment of lactone **22** with methyl lithium and silylation of the resulting primary alcohol completed the synthesis of ketone **13**.

Scheme 2



Synthesis of the highly functionalized aldehyde **16** began with TES protection of alcohol **23** (**Scheme 3**). Dihydroxylation[16] of the olefin followed by oxidative glycol cleavage afforded the aldehyde that was then subjected to Brown asymmetric oxyallylation.[17] Methylation under standard conditions provided alkene **24**. Deprotection

[15] "Applications of Zr-catalyzed carbomagnesation and Mo-catalyzed macrocyclic ring closing metathesis in asymmetric synthesis. Enantioselective total synthesis of Sch 38516 (Fluvirucin B1)." Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302-10316.

[16] (a) "Improved catalytic OsO_4 oxidation of olefins to *cis*-1,2-glycols using tertiary amine oxides as oxidant." Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973-1976. (b) "An efficient protocol for Sharpless-style racemic dihydroxylation." Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. In *J. Chem. Soc. Perk. Trans. 1* **1999**, 1095-1103.

[17] "Chiral synthesis via organoboranes. 13. A highly diastereoselective and enantioselective addition of [(Z)-.gamma.-alkoxyallyl]diisopinocampheylboranes to aldehydes." Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535-1538.

of the PMB-ether and Parikh-Doering oxidation[18] provided the aldehyde that was exposed to the lithium enolate of methyl ketone **17**. Subsequent Dess-Martin oxidation[19] of the aldol addition product provided β-diketone **25**. Exposure of **25** to *p*-toluenesulfonic acid (PTSA) affected removal of the secondary TES-ether with concomitant cyclization to a dihydropyranone. Stereoselective Luche reduction[20] of the dihydropyranone formed the requisite stereocenter for a hydroxy-directed epoxidation followed by methanolysis of the epoxide to produce a single glycoside. Sequential regioselective methylation and silylation of the equatorial and axial hydroxyl groups, respectively, provided alkene **26**. The terminal olefin of **26** was converted into a methyl ester in a four-step sequence: dihydroxylation, Pb^{IV}-mediated oxidative cleavage to the aldehyde, Pinnick oxidation[21] to the carboxylic acid, and esterification with diazomethane. The benzyl group of ester **27** was removed by hydrogenation and oxidation of the resulting primary alcohol provided an intermediate aldehyde that was subjected to a diastereoselective allylation using allyldiethylborane. The terminal olefin from the allylation event was converted into aldehyde **16** via two-step dihydroxylation and glycol cleavage.

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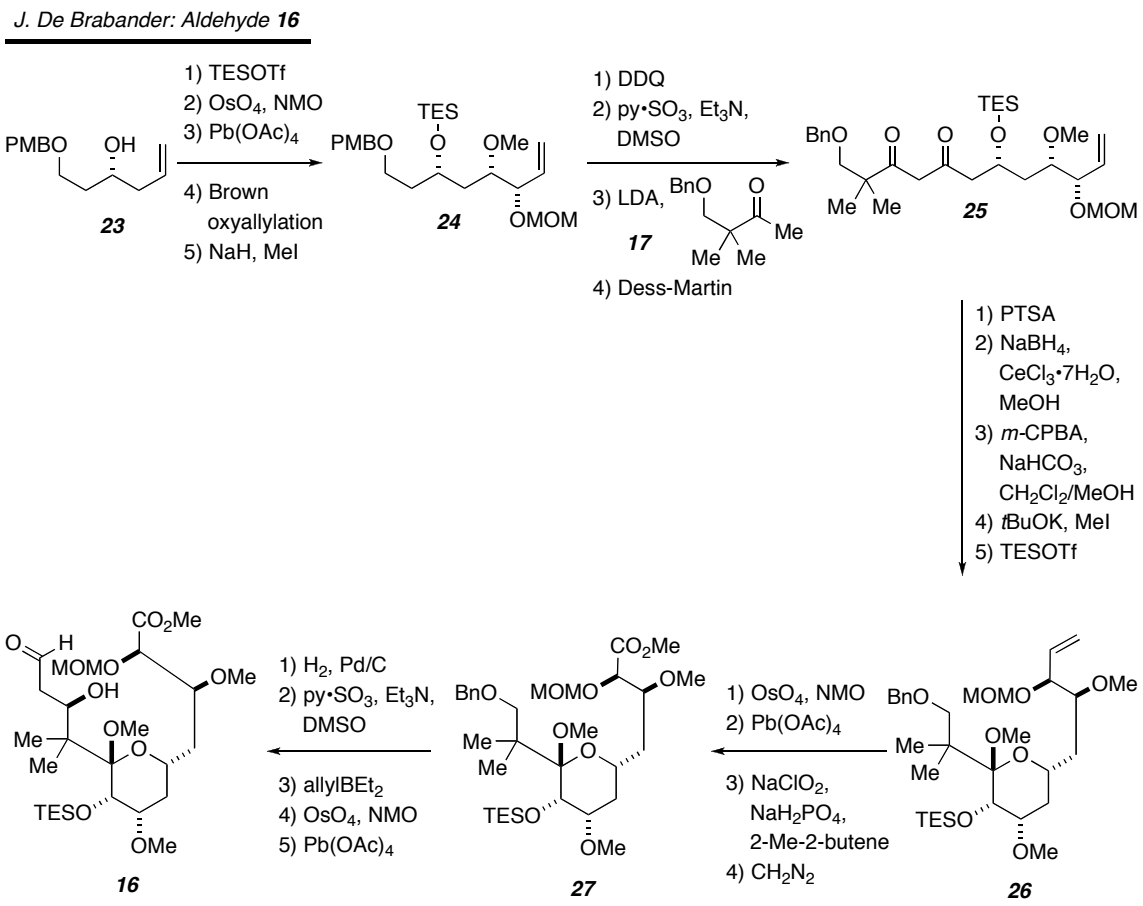
[18] "Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide." Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

[19] "A useful 12-I-5 triacetoxyperiodinane (the Dess-Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species." Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

[20] "Lanthanides in organic chemistry. 1. Selective 1,2 reductions of conjugated ketones." Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

[21] "Oxidation of α,β-unsaturated aldehydes." Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096.

Scheme 3



The end game coupling was accomplished by subjecting the enolboronate derived from ketone **13** to aldehyde **16** (**Scheme 4**). This provided a separable 2:1 mixture of diastereomers that were individually carried through the final steps of the synthesis. Regioselective methylation using Meerwein's salt (trimethyloxonium tetrafluoroborate, Me_3OBF_4) and 2,6-di-*t*butyl-4-methylpyridine provided enone **28**. Completion of the synthesis involved CBS [(*R*)- or (*S*)-*B*-Me-CBS-oxazaborolidine and borane dimethylsulfide] reduction of the enone,[22] methyl ester saponification, Mitsunobu lactonization[23] of the *seco*-acid with retention of configuration at C15, and global deprotection under acidic conditions to provide (-)-peloruside A ***ent*-1**.

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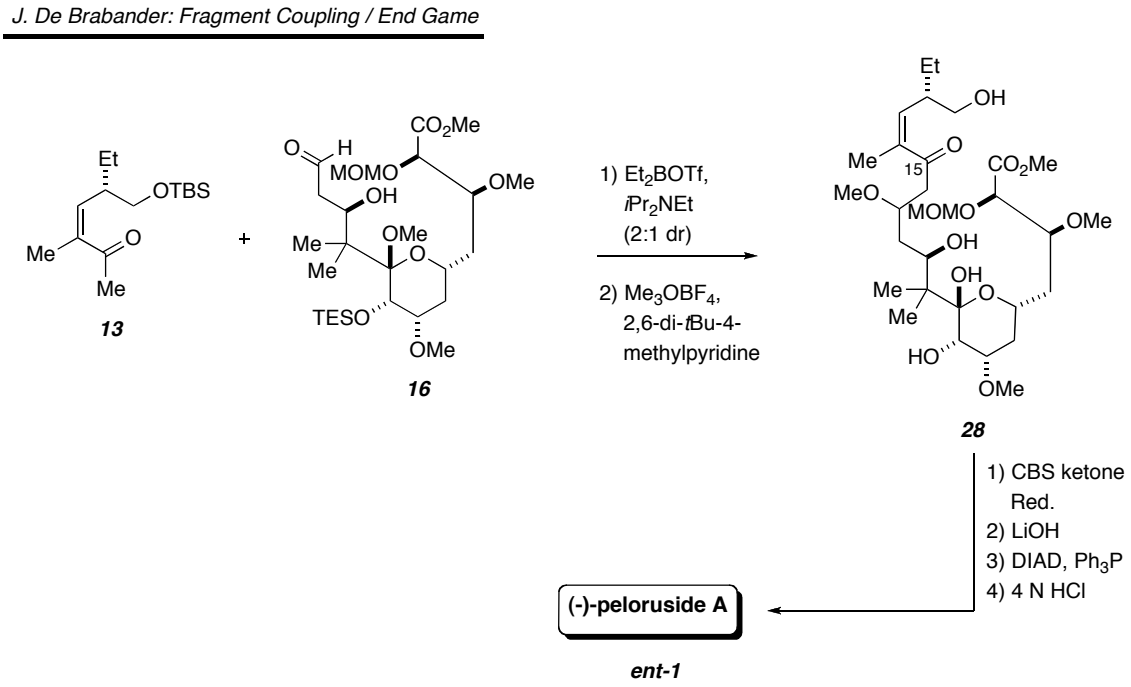
[22] "An efficient and catalytically enantioselective route to (*S*)-(-)-phenyloxirane." Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861-2863.

[23] "The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products." Mitsunobu, O. *Synthesis* **1981**, 1-28.

Scheme 4



2. R. Taylor's Total Synthesis of (+)-Peloruside A

Taylor and Jin published their initial work regarding the synthesis of the C8-C20 region of (+)-peloruside A **1** around the same time as the De Brabander group reported their total synthesis of (-)-peloruside A ***ent*-1**.[24] This preliminary report later resulted in the first total total synthesis of (+)-peloruside A **1**.[25] The retrosynthetic analysis of Taylor's route involved a late stage aldol coupling between ketone **29** and aldehyde **30** and then a Yamaguchi macrocylclization[26] (**Scheme 5**), a similar strategy to the one used by De Brabander in **Scheme 1**.

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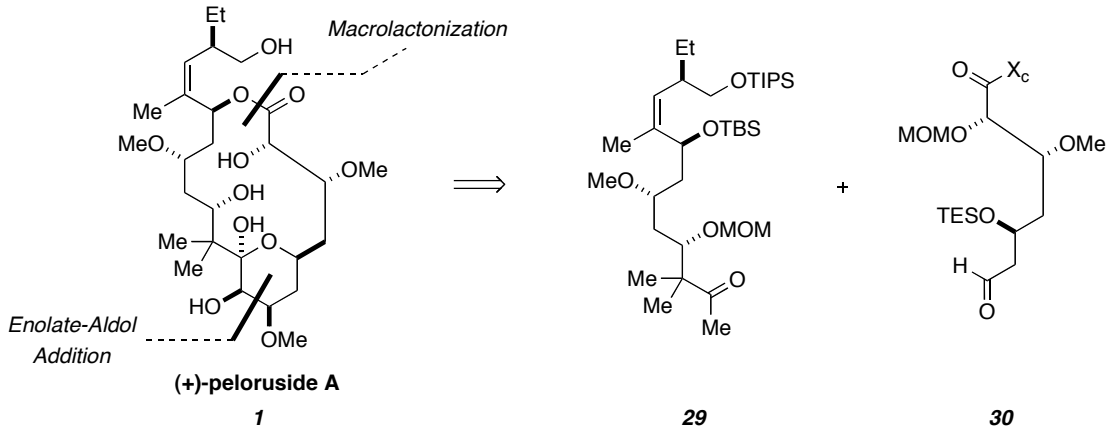
[24] "Toward a total synthesis of peloruside A: Enantioselective preparation of the C8-C19 region." Taylor, R. E.; Jin, M. *Org. Lett.* **2003**, *5*, 4959-4961.

[25] "Total synthesis of (+)-peloruside A." Jin, M.; Taylor, R. E. *Org. Lett.* **2005**, *7*, 1303-1305.

[26] "Rapid esterification by means of mixed anhydride and its application to large-ring lactonization." Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *B. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

Scheme 5

R. Taylor (2005): Retrosynthesis of (+)-peloruside A



The Taylor synthesis of the C8-C20 ketone **29** began with the preparation of enatiopure alcohol **32** by stereoselectively alkylating oxazolidinone **31-*R*** with benzyloxymethyl chloride (BOMCl) and titanium tetrachloride (**Scheme 6**).[27] Protecting group exchange and reductive removal of the chiral auxiliary with lithium borohydride ($LiBH_4$) provided primary alcohol **32**. Dess-Martin oxidation of **32** followed by Still-Gennari olefination[28] provided the desired *Z*-trisubstituted alkene **33**. Formation of the enal occurred through a two-step reduction/oxidation sequence using DIBAL-H and Dess-Martin periodinane. A Grignard allylation proceeded to give a 1:1 mixture of diastereomers **34**. The desired (*S*)-C15 diastereomer **34** could be moved forward while the (*R*)-C15 **34** epimer required inversion under Mitsunobu conditions. Installation of the C13 hydroxyl group was accomplished via iodine-induced carbonate cyclization using *N*-iodosuccinimide.[29] Exposure of iodide **35** to a basic methanolic solution removed the carbonate, which resulted in closure to an epoxide, thereby freeing the allylic hydroxyl for *tert*-butyldimethylsilyl (TBS) protection to provide epoxide **36**. Treatment of the epoxide **36** with the lithium anion of 1,3-dithiane opened the epoxide, allowing for

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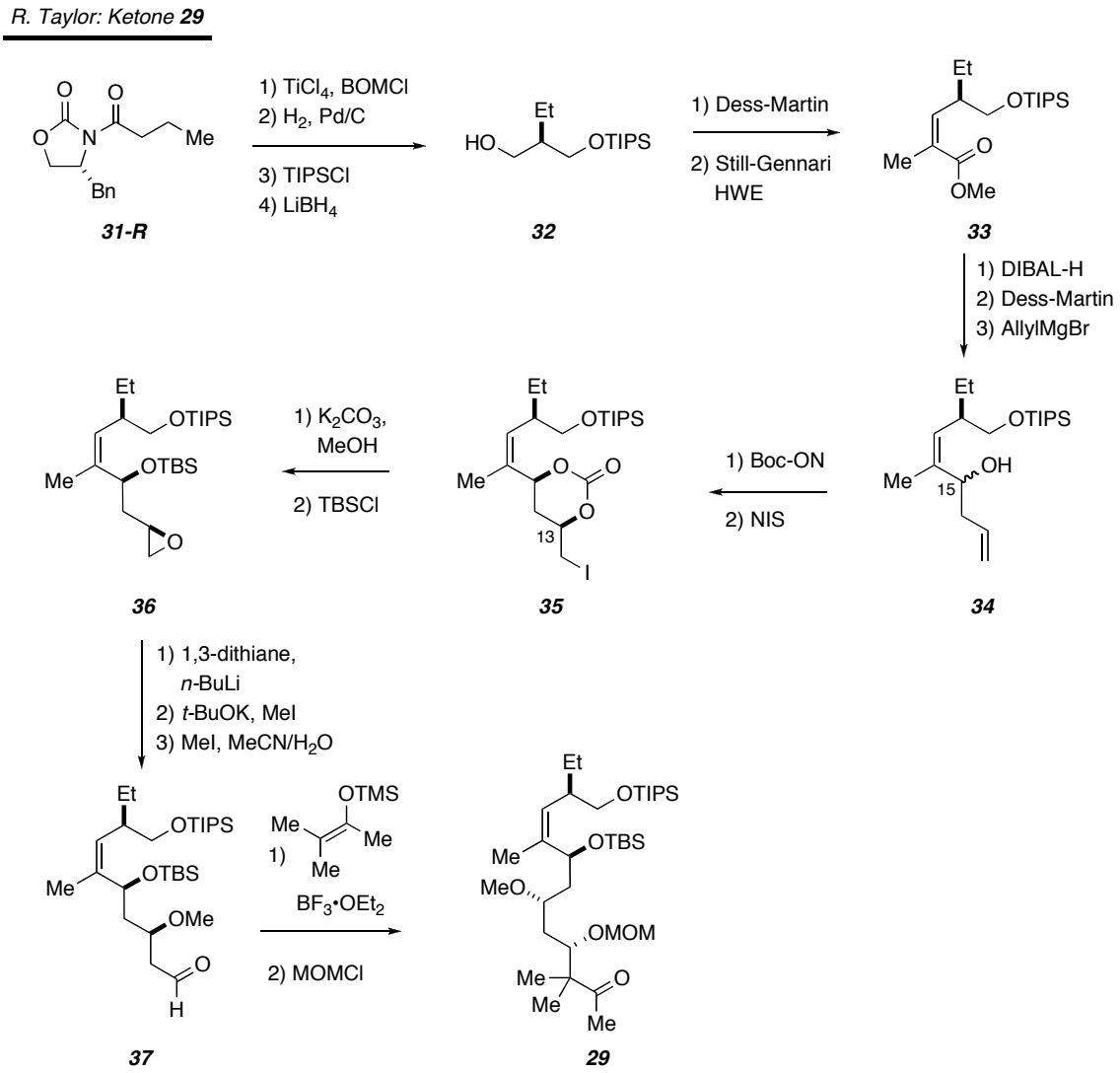
[27] "Synthesis of six-membered compounds by environmentally friendly cyclization using indirect electrolysis." Ihara, M.; Katsumata, A.; Setsu, F.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 677-684.

[28] "Direct synthesis of *Z*-unsaturated esters - A useful modification of the Horner-Emmons olefination." Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

[29] "Iodine monobromide (IBr) at low-temperature - enhanced diastereoselectivity in electrophilic cyclizations of homoallylic carbonates." Duan, J. J. W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703-3711.

methylation of the resulting hydroxyl. Hydrolysis of the dithiane revealed aldehyde **37**, which would later undergo a Mukaiyama aldol reaction[30] with the appropriate silylketene acetal to give the desired 1,3-*anti* stereochemistry. Protection of the resulting hydroxyl as its MOM-ether finished the synthesis of fully functionalized ketone **29**.

Scheme 6

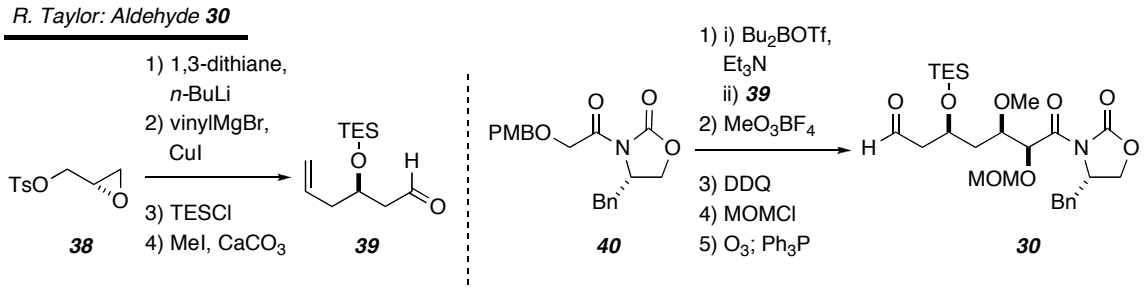


Synthesis of the aldehyde **30** began by treating commercially available (*S*)-glycidyl tosylate **38** with lithiated 1,3-dithiane, followed by a copper catalyzed Grignard addition to install the terminal alkene (**Scheme 7**). Protection of the secondary alcohol as its TES ether and dithiane removal provided aldehyde **39**. The crude aldehyde was

[30] "Explorations into new reaction chemistry." Mukaiyama, T. *Angew. Chem. Int. Ed.* **2004**, *43*, 5590-5614.

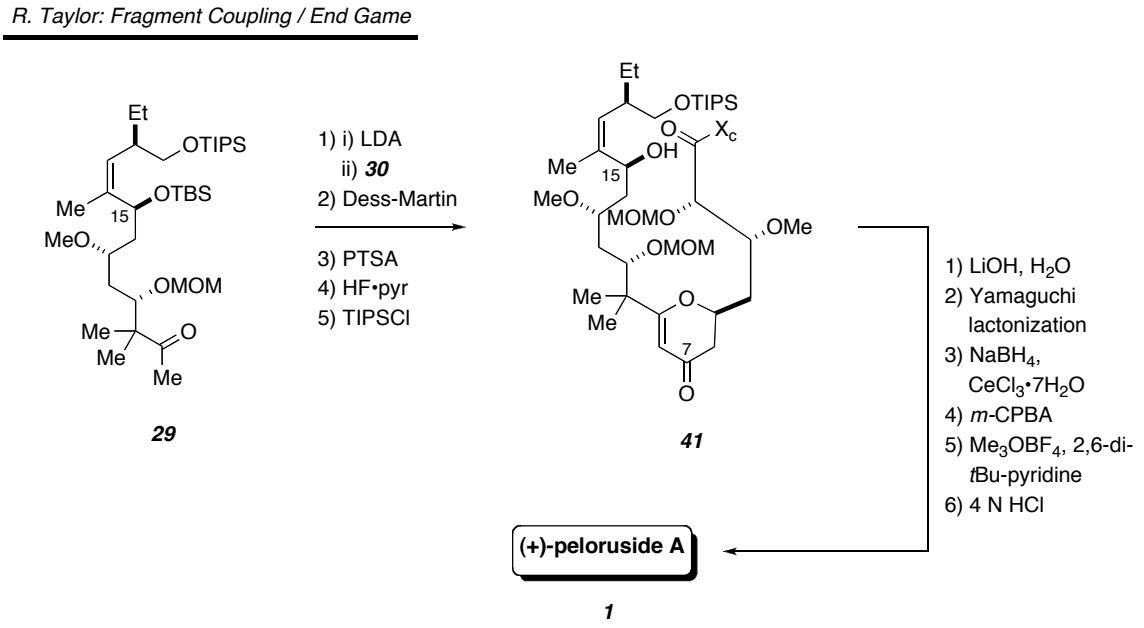
subjected to an Evans enolboronate aldol reaction with oxazolidinone **40**. The aldol product was methylated followed by protecting group exchange and ozonolytic cleavage of the alkene to give aldehyde **30**.

Scheme 7



With construction of both fragments complete, the lithium enolate of ketone **29** was reacted with aldehyde **30** (**Scheme 8**). The resulting mixture of diastereomers was oxidized with Dess-Martin periodinane and treated with PTSA to remove the secondary TES-ether and form the pyranone ring. Removal of both silyl protecting groups with HF•pyridine was followed by selective protection of the primary hydroxyl as its triisopropysilyl (TIPS)-ether to give dihydropyranone **41**. The oxazolidinone functionality was hydrolyzed to give the *seco*-acid, which underwent lactonization with the C15 hydroxyl using Yamaguchi's protocol.[23] Reduction of the ketone under Luche conditions provided an allylic alcohol that was subjected to *m*-CPBA in methylene chloride to install the final oxygenation of the macrolide through an interesting MOM group participating epoxide ring fragmentation. The synthesis of (+)-peloruside A **1** was completed by selective methylation of the less hindered equatorial C7 hydroxyl (similar to De Brabander's approach) and global deprotection by exposure to hydrochloric acid.

Scheme 8



3. A. Ghosh's Total Synthesis of (+)-Peloruside A

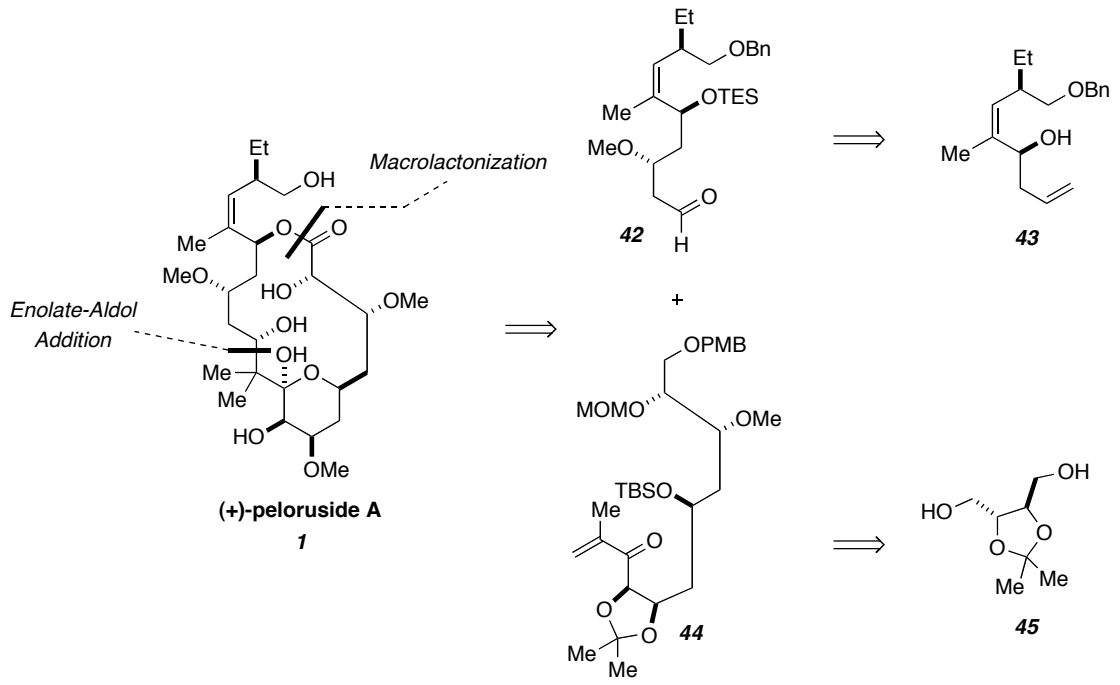
Ghosh and coworkers published two fragment syntheses of peloruside A **1** in 2003.[31] They later published a total synthesis in 2008[32] using some of the same key disconnections employed by Taylor and De Brabander. Their coupling strategy for the two late stage intermediates involved a reductive enolization of enone **44** followed by the addition of aldehyde **42**, thereby avoiding the difficulties associated with the direct aldol reaction of a *gem*-dimethyl ketone (**Scheme 9**). A Yamaguchi lactonization was again planned for closure of the macrocyclic ring.

[31] (a) "An enantioselective synthesis of the C1-C9 segment of antitumor macrolide peloruside A." Ghosh, A. K.; Kim, J. H. *Tetrahedron Lett.* **2003**, *44*, 3967-3969. (b) "Synthetic studies of microtubule stabilizing agent peloruside A: An asymmetric synthesis of C10-C24 segment." Ghosh, A. K.; Kim, J. H. *Tetrahedron Lett.* **2003**, *44*, 7659-7661.

[32] "Enantioselective total synthesis of peloruside A: A potent microtubule stabilizer." Ghosh, A. K.; Xu, X.; Kim, J. H.; Xu, C. X. *Org. Lett.* **2008**, *10*, 1001-1004.

Scheme 9

A. Ghosh (2008): Retrosynthesis of (+)-peloruside A

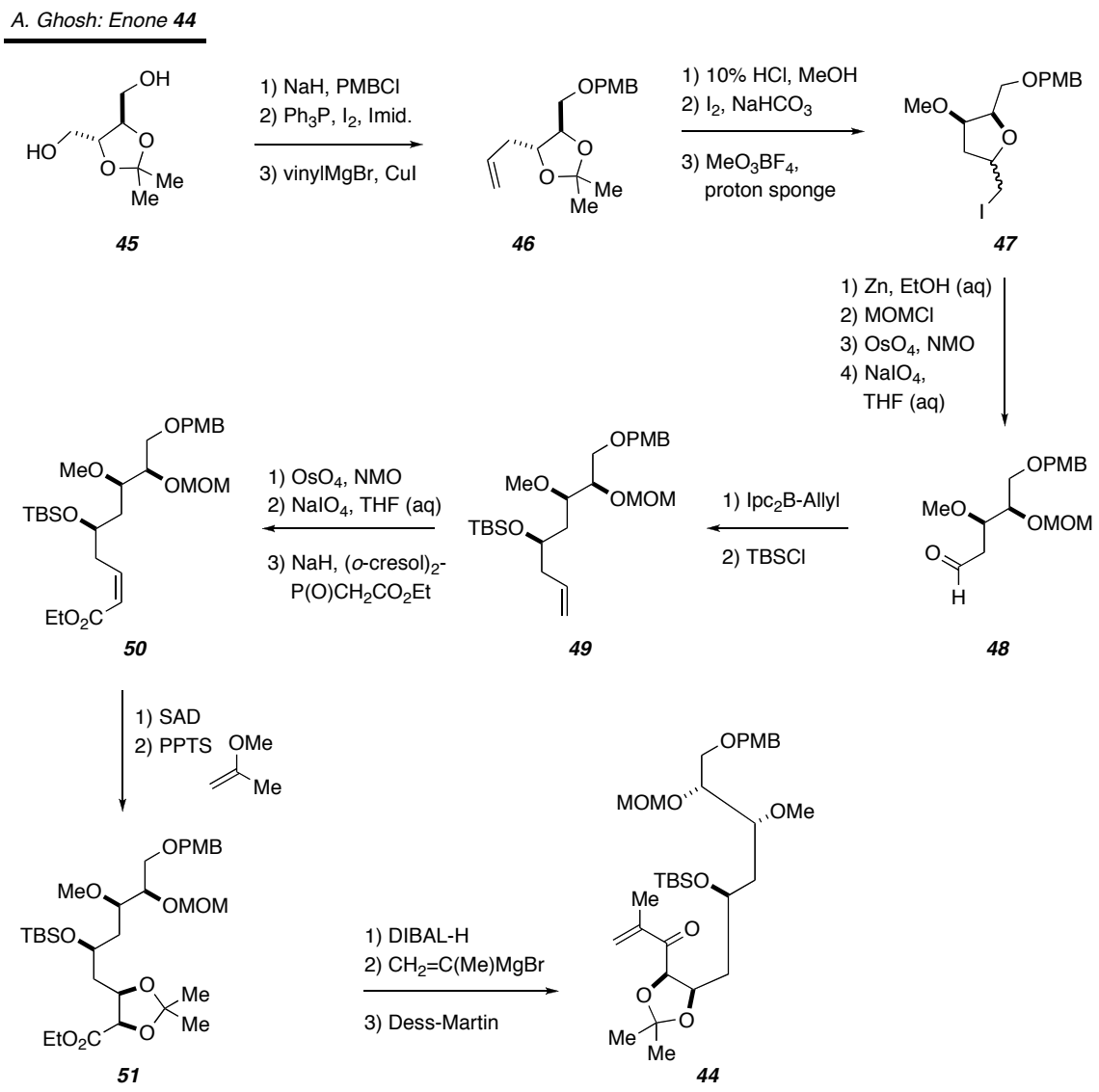


Ghosh's synthesis commenced with monobenzylation of commercially available (-)-2,3-*O*-isopropylidene-D-threitol **45** with *p*-methoxybenzyl chloride (PMBCl) to provide the primary alcohol that was converted into an iodide (**Scheme 10**). Subjecting the newly formed iodide to vinyl magnesium bromide in the presence of a catalytic amount of copper iodide provided the alkene **46**. Acid-catalyzed removal of the acetonide and iodoetherification provided a free hydroxyl that was methylated with Meerwein's salt to give iodide **47**. Reductive cleavage of the iodoether with zinc dust produced an alcohol that was protected with methoxymethyl chloride (MOMCl). Dihydroxylation and oxidative cleavage of the olefin produced aldehyde **48**. Asymmetric allylation and subsequent TBS-ether formation was again followed by converting the olefin into an aldehyde by a dihydroxylation/oxidative cleavage process. The aldehyde was subjected to a Horner-Wadsworth-Emmons (HWE) olefination using Ando's protocol[33] to give the desired *Z*-olefin **50**. The diol that resulted from Sharpless

[33] "*Z*-selective Horner-Wadsworth-Emmons reaction of α-substituted ethyl (diarylphosphono)acetates with aldehydes." Ando, K. *J. Org. Chem.* **1998**, *63*, 8411-8416.

asymmetric dihydroxylation (SAD)[34] of the *Z*-olefin **50** was treated with 2-methoxypropene under acidic conditions to give acetonide **51**. Subjecting acetonide **51** to a three-step process consisting of DIBAL-H reduction, Grignard addition, and Dess-Martin oxidation provided the desired enone **44**.

Scheme 10

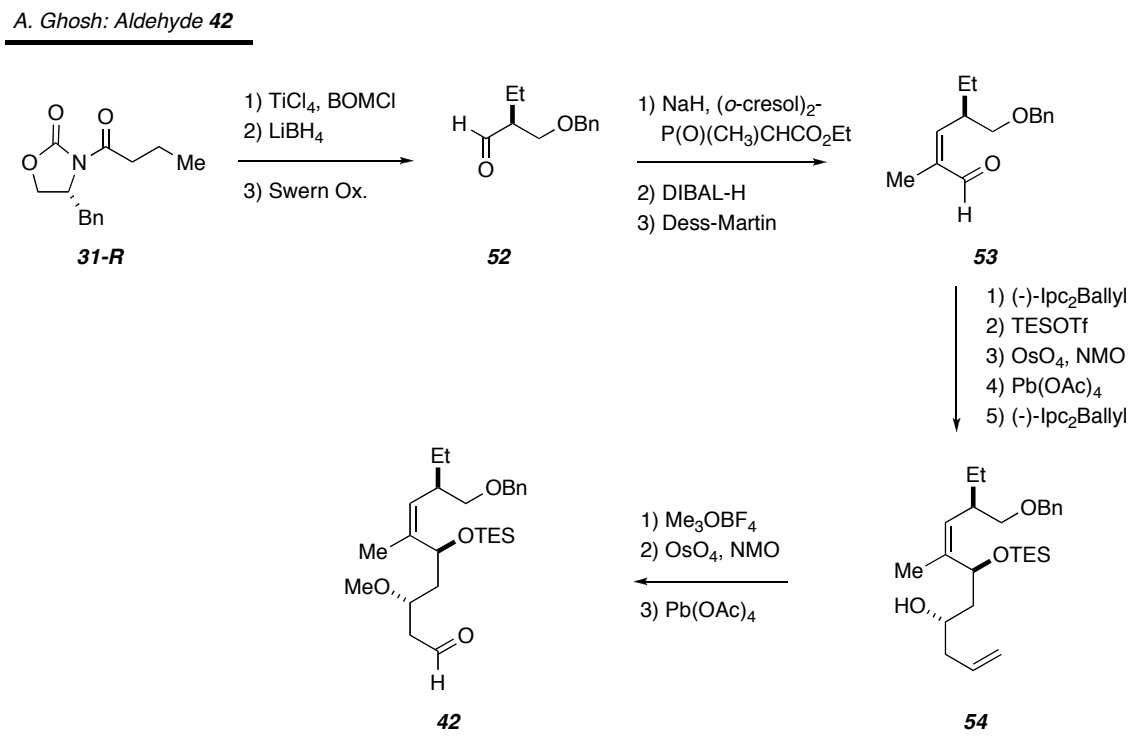


Asymmetric alkylation of the oxazolidinone **31-*R*** with benzyloxymethyl chloride (BOMCl) using Evans' protocol was followed by reductive removal of the chiral

[34] "Catalytic asymmetric dihydroxylation." Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, *94*, 2483-2547.

auxiallary and oxidation of the resulting alcohol to provide aldehyde **52** (**Scheme 11**). Olefination of the aldehyde as described by Ando[33] furnished the desired trisubstituted *Z*-olefin. The ester was reduced to the alcohol and oxidized to provide enal **53**. The allylic alcohol that resulted from Brown asymmetric allylation[35] was protected as a TES-ether. Dihydroxylation of the terminal alkene and oxidative cleavage of the resulting diol provided another aldehyde that was exposed to another round of asymmetric allylation conditions to provide homoallylic alcohol **54**. The alcohol was methylated and the olefin oxidatively cleaved to provide aldehyde **42**.

Scheme 11

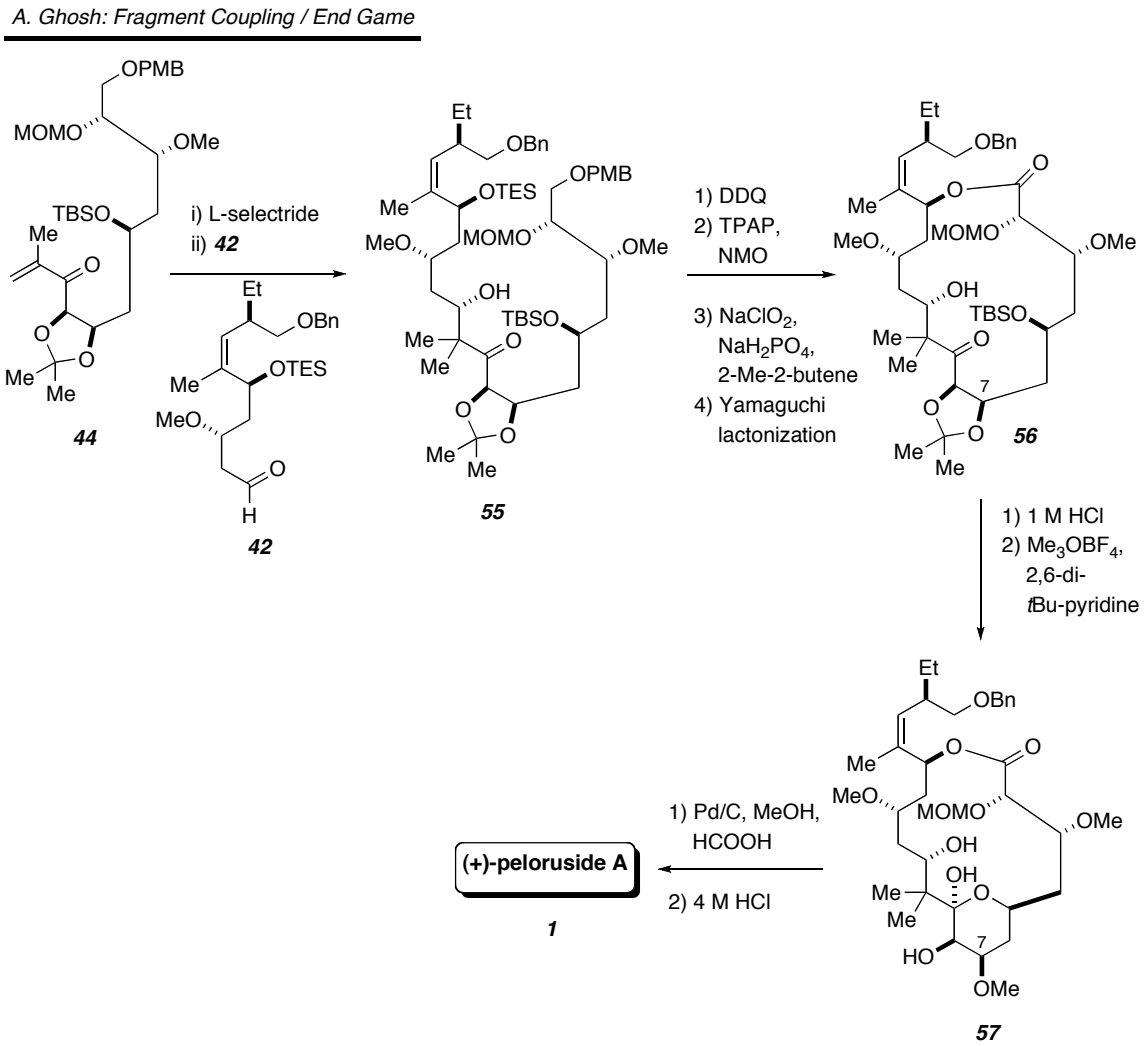


With the synthesis of enone **44** and aldehyde **42** complete, the enone **44** was treated with L-selectride at -78 ºC to form the necessary enolate followed by reaction with aldehyde **42** to form the desired aldol product **55** (**Scheme 12**). Exposure of ketone **55** to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in loss of the secondary TES group and primary PMB-ether. The primary alcohol was selectively oxidized with

[35] "Chiral synthesis via orbanoboranes. 5. Asymmetric allylboration via chiral allyldialkylboranes. Synthesis of homoallylic alcohols with exceptionally high enantiomeric excess." Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432-439.

tetrapropylammonium perruthenate (TPAP) to an aldehyde, which was subsequently oxidized to the carboxylic acid with sodium chlorite. Closure of the macrolactone **56** was accomplished by utilizing the Yamaguchi lactonization protocol. Treatment of the macrolactone **56** with 1 M HCl removed the TBS and isoprolylidene groups. The synthesis of (+)-peloruside A **1** was finished by selective methylation of the less hindered equatorial C7 hydroxyl (similar to Taylor's and De Brabander's approaches), hydrogenation to remove the primary benzyl group, and exposure to 4 M HCl to remove the MOM group.

Scheme 12



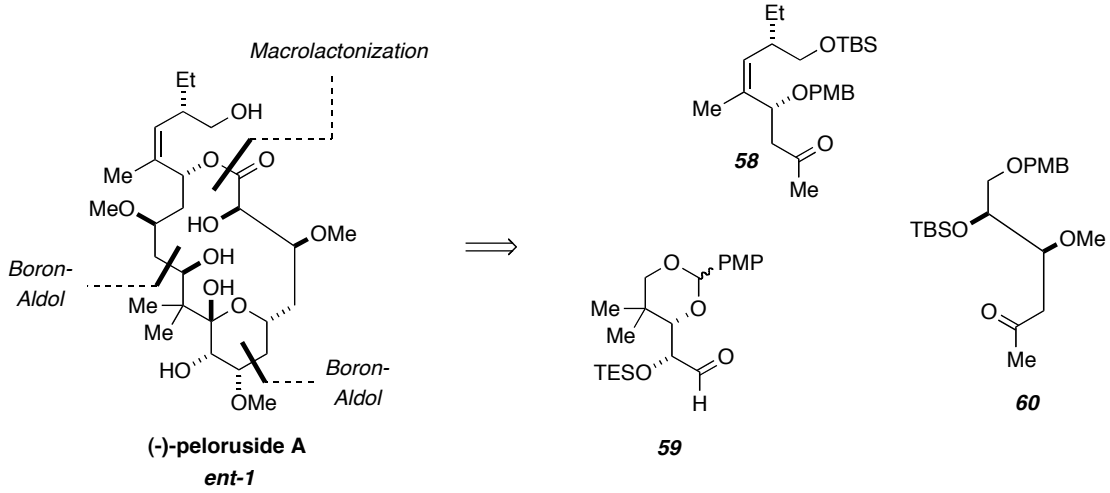
B. Synthetic Efforts Toward Peloruside A

1. I. Paterson's Synthetic Efforts Toward (-)-Peloruside A

Ian Paterson and coworkers were among a number of groups to publish their progress toward the synthesis of peloruside A **1** in 2003.[36] Relying on methodology developed by their research group, Paterson et al. envisioned the convergent construction of peloruside A **1** via stereoselective boron-mediated aldols between the advanced intermediates: ketone **58**, aldehyde **59**, and ketone **60** (**Scheme 13**). The end game strategy involved a selective macrolactonization similar to the one achieved by Ghosh.

Scheme 13

I. Paterson (2003): Retrosynthesis of (-)-peloruside A



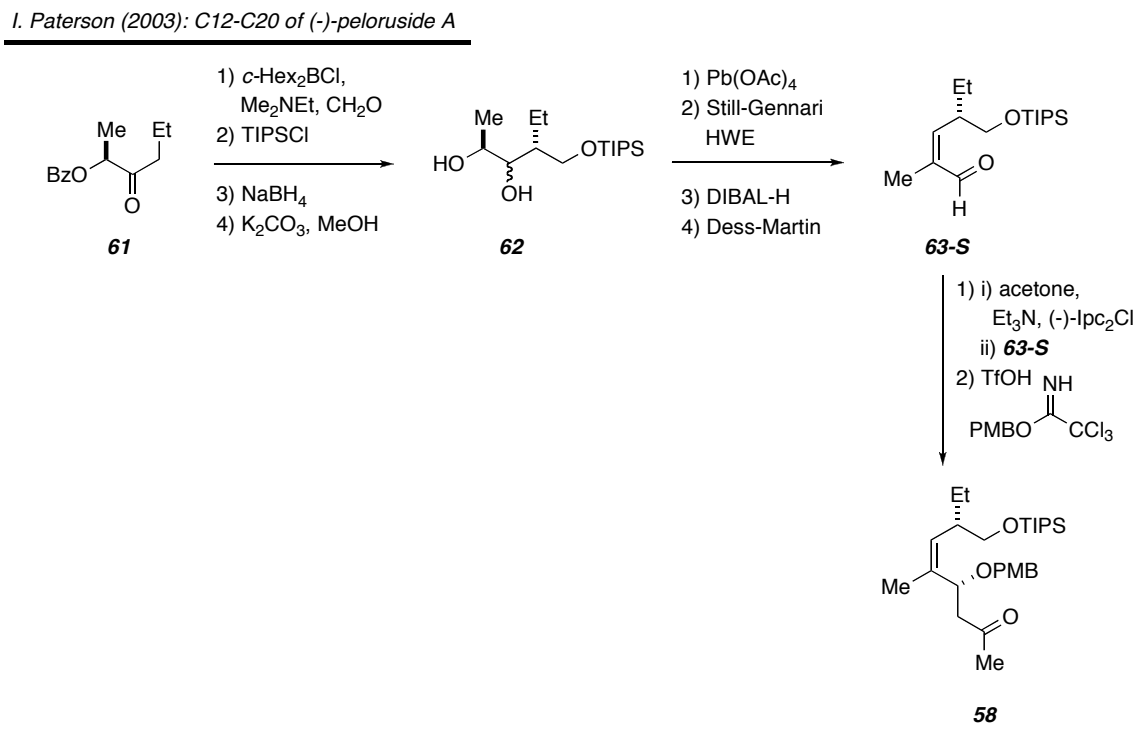
The ketone **58** was prepared by application of Paterson's asymmetric boron aldol methodology[37] that makes use of the (*S*)-lactate-derived-ketone **61**, which is available from (*S*)-lactate in three-steps (**Scheme 14**). An aldol reaction of ketone **61** with formaldehyde using dicyclohexylchloroborane (*c*-Hex_2BCl) provided a primary alcohol that was TIPS protected. Reduction of the ketone was followed by benzoate hydrolysis to give diol **62**, which was subjected to glycol cleavage to produce an aldehyde. This

[36] "Toward the synthesis of peloruside a: Fragment synthesis and coupling studies." Paterson, I.; Di Francesco, M. E.; Kuhn, T. *Org. Lett.* **2003**, *5*, 599-602.

[37] (a) "Studies in polypropionate synthesis - high π-face selectivity in *syn* and *anti* aldol reactions of chiral boron enolates of lactate-derived ketones." Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083-9086. (b) "Polyketide synthesis using the boron-mediated, *anti*-aldol reactions of lactate-derived ketones: Total synthesis of (-)-ACRL, toxin IIIB." Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639-652.

aldehyde was homologated to the *Z*-enoate using the Still-Gennari HWE variant.[28] Reduction/oxidation chemistry produced the aldehyde **63-*S*** that was subjected to a reagent-controlled aldol using diisopinocampheylchloroborane [(-)-Ipc_2Cl] and acetone. The resulting carbinol from the aldol reaction was protected as a PMB-ether under acidic conditions to provide the C12-C20 segment.

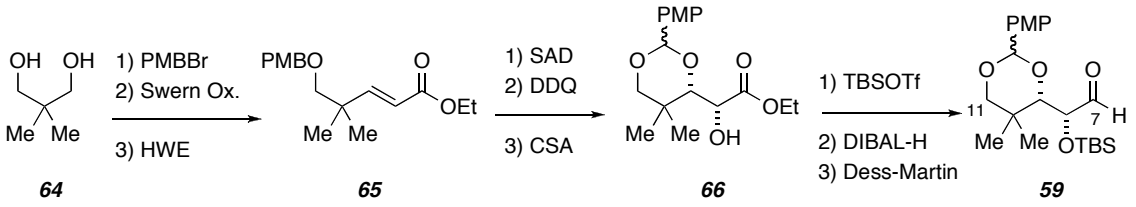
Scheme 14



Preparation of the C7-C11 subunit began with selective mono-PMB protection of the neopentylglycol **64** (**Scheme 15**). The remaining hydroxyl was oxidized to the aldehyde and subjected to HWE homologation to give the enoate **65**. Installation of the 1,2-*syn* diol was achieved using catalytic SAD (96% *ee*). Oxidative cyclization of the PMB protected diol resulted in a mixture of PMP acetals that could be equilibrated in the presence of camphorsulphonic acid (CSA) to the thermodynamically more stable six-membered cyclic acetal. Silylation of the free hydroxyl with TBSOTf, ester reduction, and primary alcohol oxidation completed the synthesis of aldehyde **59**.

Scheme 15

I. Paterson (2003): C7-C11 of (-)-peloruside A

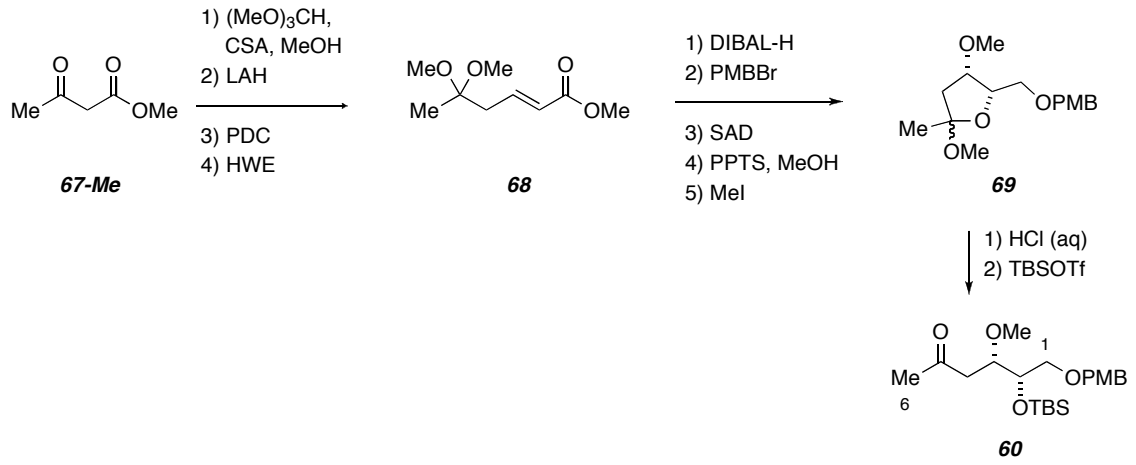


64 ***65*** ***66*** ***59***

The synthesis of the final subunit, C1-C6, began by protecting the ketone of methyl acetoacetate (**67-Me**) as a methyl ketal (**Scheme 16**). A standard three-step homologation sequence (reduction, oxidation, and HWE olefination) was used to produce enoate **68**. Reduction of the ester was followed by PMB protection of the resulting primary alcohol. Sharpless asymmetric dihydroxylation (SAD) conditions were screened in an effort to raise the *ee* of the diol to 92%. Treating the diol with PPTS in MeOH differentiated the two hydroxyls by engaging one of them as a ketal, while the other remained available for methylation to form **69**. Careful hydrolysis of ketal **69** was followed by TBS protection to finish the synthesis of the second ketone **60**.

Scheme 16

I. Paterson (2003): C1-C6 of (-)-peloruside A



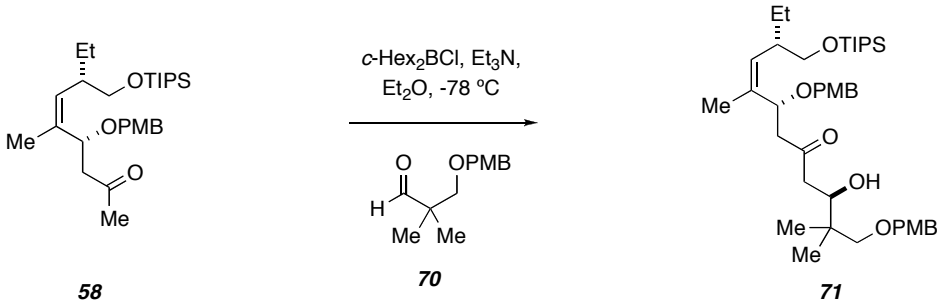
67-Me ***68*** ***69*** ***60***

With all three building blocks in hand, it was time to investigate the key aldol couplings required to create the carbon skeleton of peloruside A **1**. Coupling of ketone **58** with the simple *gem*-dimethyl aldehyde **70** using *c*-Hex_2BCl/NEt_3 proceeded, as

anticipated, to give a high level of remote 1,5-*anti* induction (>95:5 dr) in favor of β-hydroxy ketone **71** (**Scheme 17**).[38]

Scheme 17

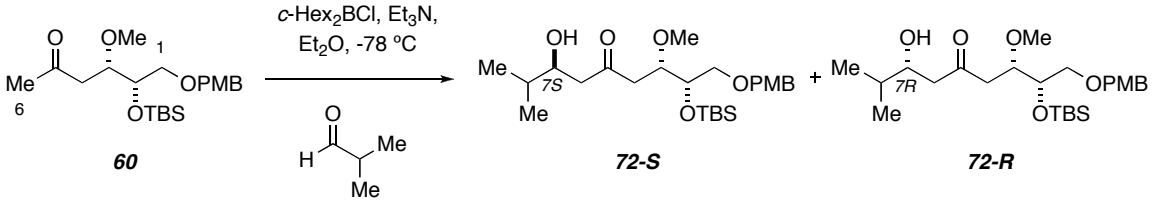
I. Paterson (2003): C12-C20 Aldol 1 - Enolate Stereoinduction



The next series of aldol reactions would explore the influences of the stereogenic centers within ketone **60** and aldehyde **59**. The first aldol reaction between β-methoxy ketone **60** and isobutyraldehyde using *c*-Hex_2BCl/NEt_3 again resulted in the desired 1,5-*anti* induction, although in a modest 75:25 *dr* (**Scheme 18**). The decrease in stereoinduction was postulated to be a result of the bulky TBS-ether.[39]

Scheme 18

I. Paterson (2003): C1-C6 Aldol 3 - Enolate Stereoinduction



The π-facial selectivity of aldehyde **59** was evaluated with acetone under a variety of reaction conditions. The undesired all *syn*-diastereomer was preferred under a majority of the conditions employed. Fortunately, the desired (7*S*)-configuration in **73**

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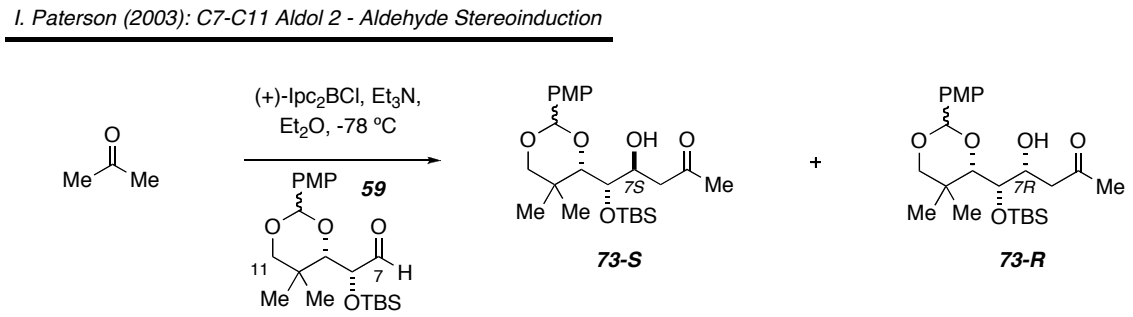
[38] (a) "Remote, 1,5-*anti* stereoinduction in the boron-mediated aldol reactions of *β*-oxygenated methyl ketones." Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585-8588. (b) "Remote, 1,5-stereoinduction in boron aldol reactions of methyl ketones: Application to the convergent assembly of the 1, 3-polyol sequence of (+)-roxaticin." Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187-1191.

[39] "Stereocontrolled total synthesis of (+)-altohyrtin A/spongistatin 1." Paterson, I.; Chen, D. Y. K.; Coster, M. J.; Acena, J. L.; Bach, J.; Gibson, K. R.; Keown, L. E.; Oballa, R. M.; Trieselmann, T.; Wallace, D. J.; Hodgson, A. P.; Norcross, R. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 4055-4059.

could be achieved using (+)-Ipc_2BCl (**Scheme 19**). The work from Paterson's group has confirmed the viability of their route and justified their ongoing studies toward completing the total synthesis of peloruside A **1**.

Scheme 19



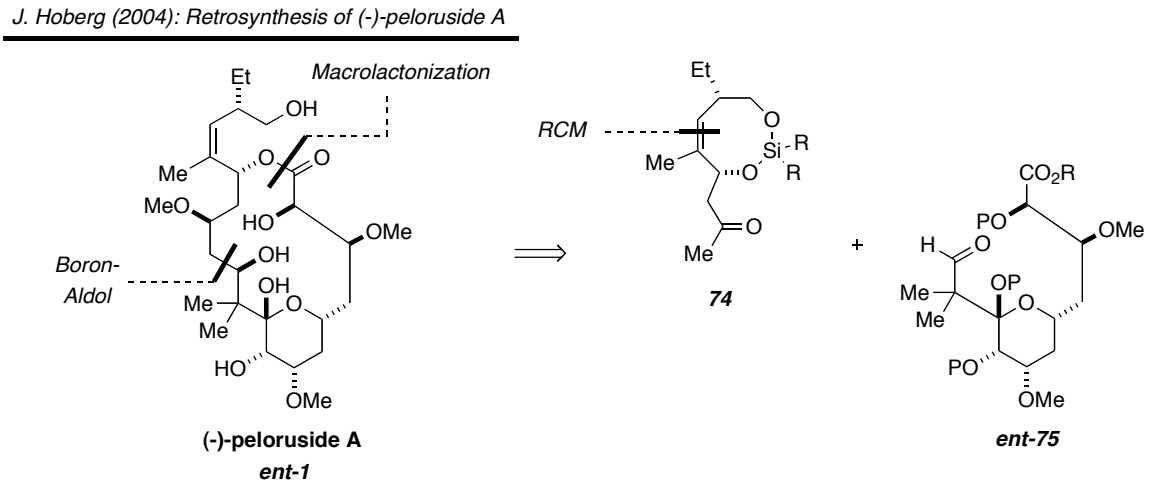
2. J. Hoberg's Synthetic Efforts Toward (-)-Peloruside A

In 2004 Hoberg and coworkers reported studies on the origin of 1,5-*anti* induction in boron-mediated aldol reactions, which was a result of their initial studies toward the synthesis of a C12-C22 fragment of (-)-peloruside A ***ent*-1**.[40] The keys to their synthetic strategy was a late stage boron-mediated aldol and macrolactonization, like those mentioned before (**Scheme 20**). The 1,5-*anti* induction would be controlled by a silyl-protected β-alkoxy substituent that would come from a silicon-tethered metathesis.[41]

[40] "Studies on the origin of 1,5-*anti* induction in boron-mediated aldol reactions." Stocker, B. L.; Teesdale-Spittle, P.; Hoberg, J. O. *Eur. J. Org. Chem.* **2004**, 330-336.

[41] (a) "Silicon tethered ring-closing metathesis reactions for self- and cross-coupling of alkenols." Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429-1432. (b) "Temporary silicon-tethered ring-closing metathesis approach to C_2-symmetrical 1,4-diols: Asymmetric synthesis of D-Altritol." Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768-6769.

Scheme 20

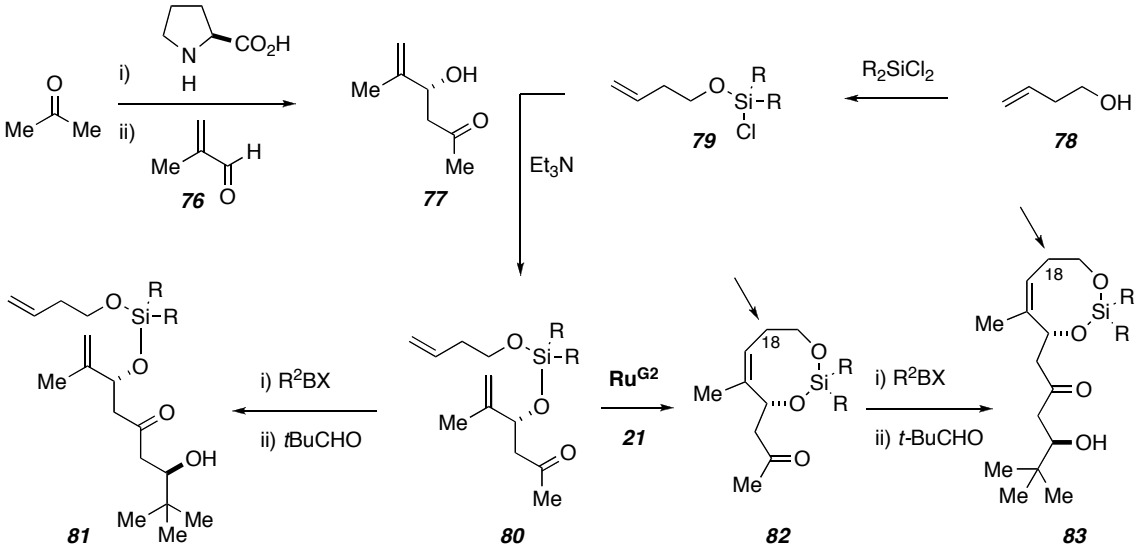


The mixed silaketals **80** were prepared by reacting the primary alcohol **78** with different dichlorosilanes followed by addition of the β-hydroxy ketone **77** [prepared by List's direct aldol procedure[42] between acetone and methacrolein (**76**) (**Scheme 21**)]. Exposure of silaketal **80** to Grubbs second generation catalyst (**Ru^{G2}**, **21**) resulted in formation of the trisubstituted *Z*-olefin of **82**. Boron-mediated aldol reactions involving the diphenylsilyl-ethers of ketone **80** and ketone **82** with pivaldehyde showed excellent diastereoselectivities, whereas the diisopropyl protecting group provided only modest selectivites. These experiments show promise in applying this approach to construct peloruside A **1**; however, there is some concern regarding the lack of the C18 stereocenter and how this may affect the enolate geometry that is proposed to influence the 1,5-*anti* stereoinduction.

[42] (a) "Amino acid catalyzed direct asymmetric aldol reactions: A bioorganic approach to catalytic asymmetric carbon-carbon bond-forming reactions." Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267. (b) "Proline-catalyzed direct asymmetric aldol reactions." List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396. (c) "Efficient proline-catalyzed Michael additions of unmodified ketones to nitro olefins." List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423-2425.

Scheme 21

J. Hoberg (2004): C12-C22 Fragment of (-)-peloruside A

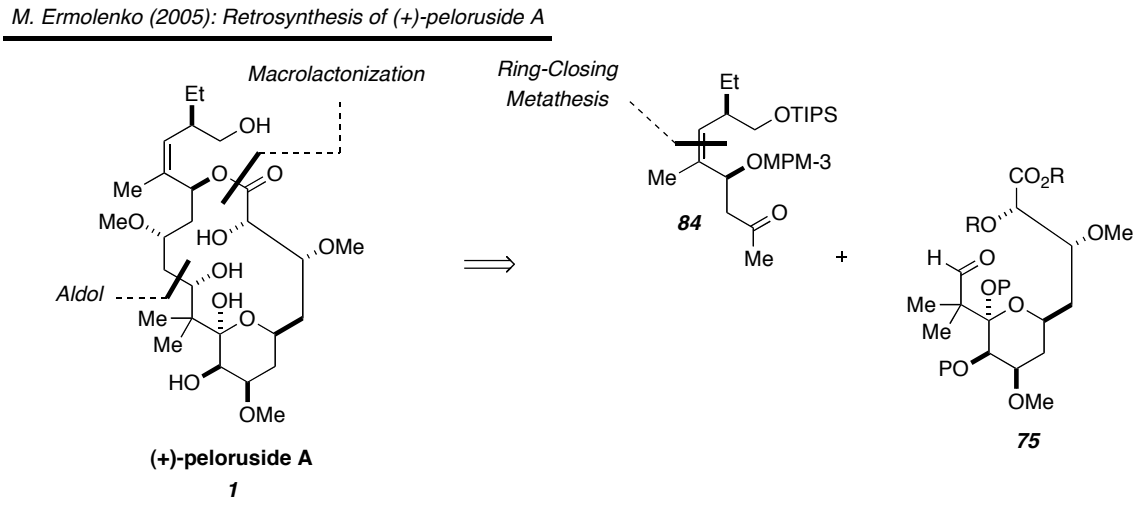


3. M. Ermolenko's Synthetic Efforts Toward (+)-Peloruside A

Another strategy exemplifying the utility of metathesis in constructing the C12-C20 fragment of (+)-peloruside A **1** was reported in 2005 by Ermolenko and coworkers.[43] In an effort to construct ketone **84** for later use in an aldol reaction with aldehyde **75**, they were delighted to find an unexpected diastereomer-discriminating RCM reaction (**Scheme 22**).

[43] "Synthesis of the C12-C19 fragment of (+)-peloruside A through a diastereomer-discriminating RCM reaction." Roulland, E.; Ermolenko, M. S. *Org. Lett.* **2005**, *7*, 2225-2228.

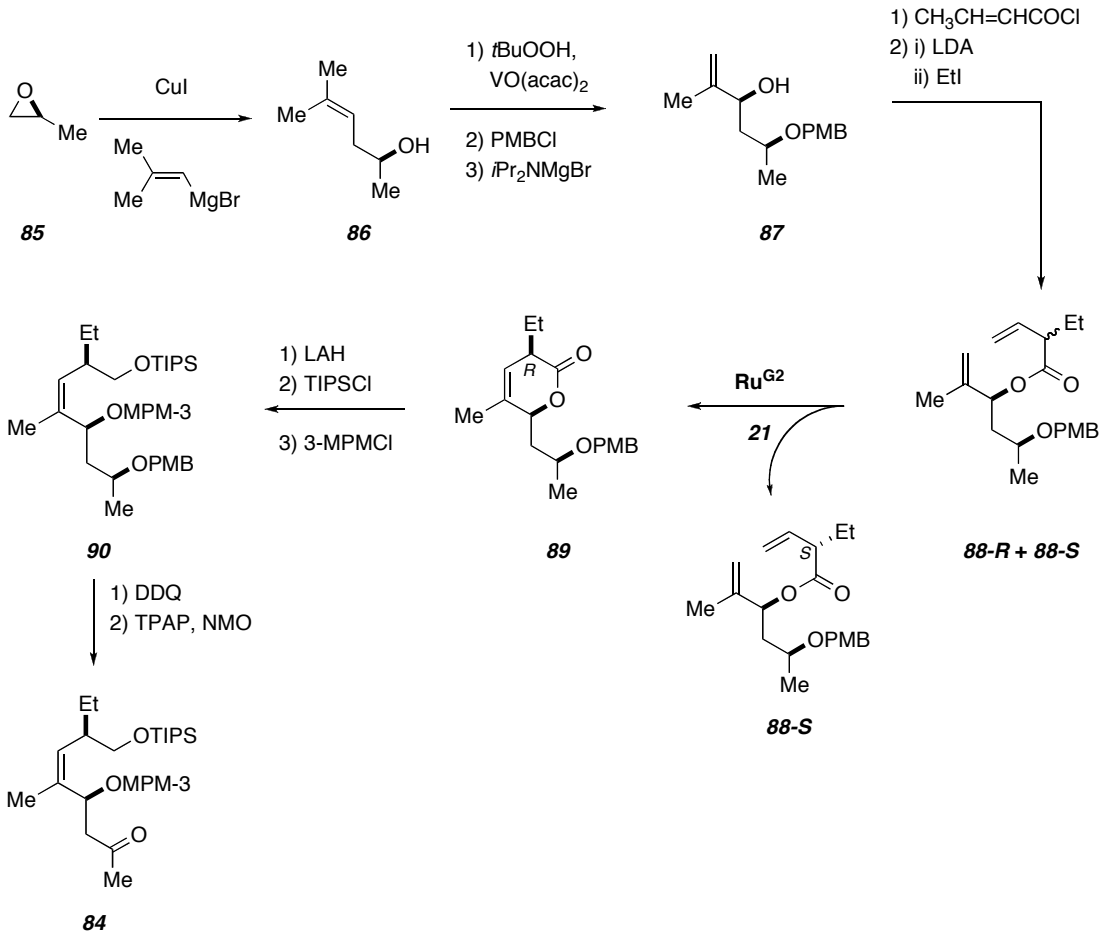
Scheme 22



(*S*)-Propylene oxide **85**, prepared by Jacobsen hydrolytic kinetic resolution of the racemate, was regioselectively opened with 2-methyl-propenylmagnesium bromide to furnish the homoallylic alcohol **86** (**Scheme 23**). The alcohol that resulted from a vanadium catalyzed epoxidation was protected as a PMB-ether. Deprotonation of a methyl proton adjacent to the epoxide formed the terminal olefin and allylic alcohol of **87** in one-step. Acylation of alcohol **87** with crotonoyl chloride was followed by alkylation with ethyl iodide to give a mixture of diastereomers **88-*R*** and **88-*S***. Exposing this mixture to the second generation Grubbs initiator (**Ru**^{G2}, **21**) promoted the diastereoselctive RCM, allowing formation of lactone **89** and recovery of the unreacted diene **88-*S***. Reduction of lactone **89** produced a diol that was regioselectively protected as its primary TIPS ether. The remaining secondary hydroxyl was protected with *meta*-methoxybenzyl chloride to give **90**. Selective oxidative cleavage of the PMB-ether was followed by oxidation with TPAP, leading to the target ketone **84** and completion of the C12-C20 segment of (+)-peloruside A **1**.

Scheme 23

M. Ermolenko (2005): C12-C20 Fragment of (+)-peloruside A

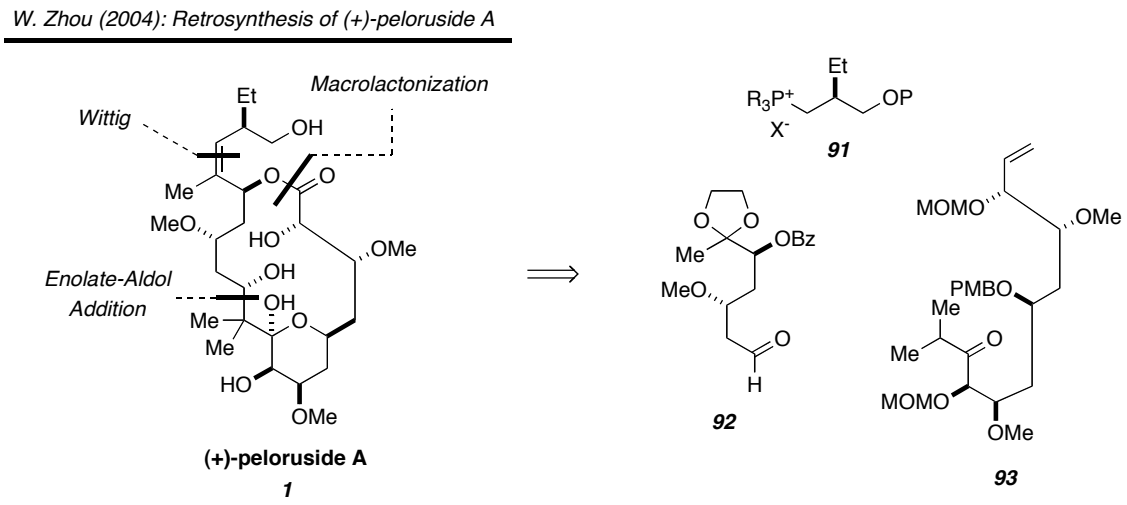


4. W. Zhou's Synthetic Efforts Toward (+)-Peloruside A

The Zhou group reported in 2004 the preparation of the C1-C16 backbone of (+)-peloruside A **1**.[44] Their retrosynthetic analysis involved the typical disconnections made by others, consisting of late stage aldol and macrolactonization events (**Scheme 24**). Their strategy was distinct in the fact that they planned to install the *Z*-trisubstituted olefin after the aldol coupling of segments **92** and **93**.

[44] "Toward the total synthesis of natural peloruside A: Stereoselective synthesis of the backbone of the core." Liu, B.; Zhou, W. S. *Org. Lett.* **2004**, *6*, 71-74.

Scheme 24

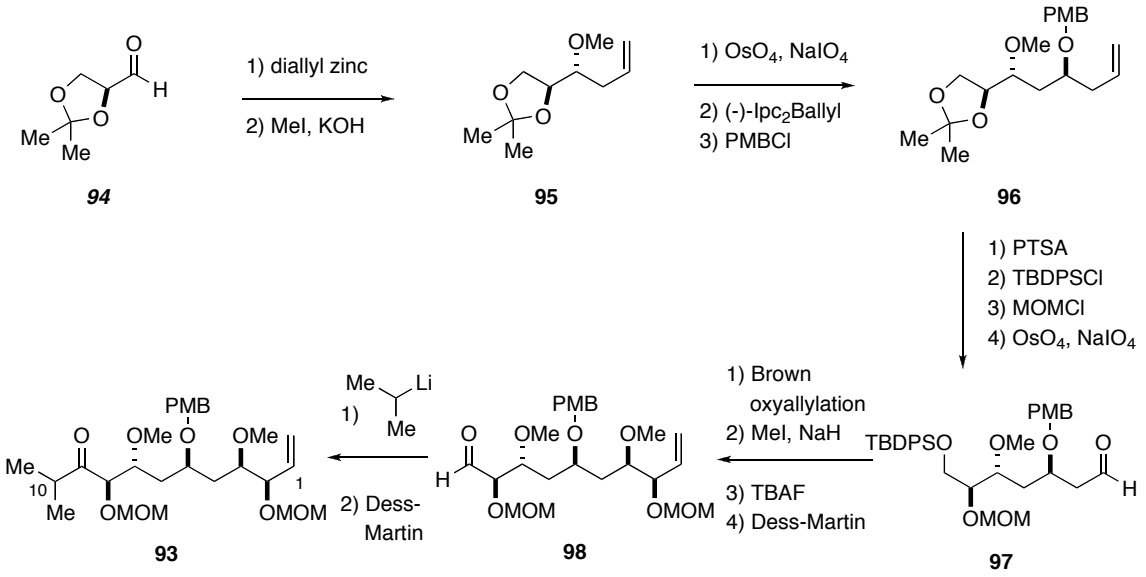


L-glyceraldehyde acetonide **94** served as the starting material for both fragment syntheses (**Scheme 25**). A substrate controlled stereoselective allylation furnished the homoallyl alcohol (85:15 *dr*) that was subsequently methylated. Johnson-Lemeieux oxidation[45] of alkene **95** gave the aldehyde needed for Brown asymmetric allylation. The resulting carbinol was protected as a PMB-ether to produce alkene **96**. A series of protecting group manipulations began by treating alkene **96** with PTSA to remove the acetonide, selective protection of the primary hydroxyl as a TBDPS-ether, and finally MOM-ether formation at the remaining hydroxyl group. Another Johnson-Lemieux oxidation converted the alkene into aldehyde **97**. Brown asymmetric oxyallylation introduced the final stereocenter, which was subsequently methylated with sodium hydride and methyl iodide. Removal of the TBDPS-ether and Dess-Martin oxidation yielded aldehyde **98**. The addition of isopropyllithium and oxidation finished the synthesis of C1-C10 subunit **93**.

[45] "Notes-osmium tetroxide-catalyzed periodate oxidation of olefinic bonds." Pappo, R.; Allen, D. Jr; Lemieux, R.; Johnson, W. *J. Org. Chem.* **1956**, *21*, 478-479.

Scheme 25

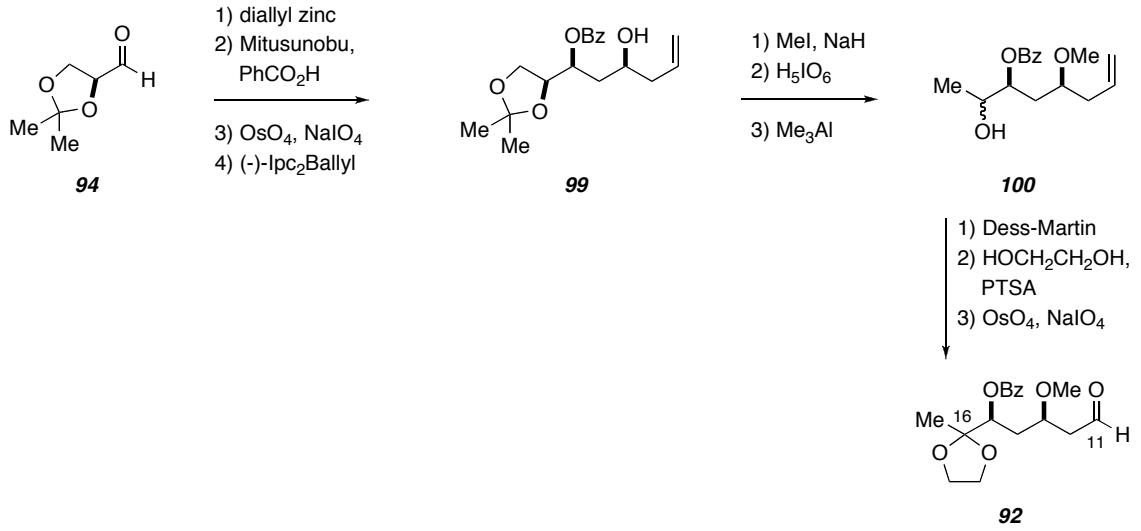
W. Zhou (2004): C1-C10 Fragment of (+)-peloruside A



The synthesis of aldehyde **92** began with the previously mentioned substrate-control stereoselective allylation of aldehyde **94** (**Scheme 26**). This time, the resulting major diastereomer was subjected to Mitsunobu inversion to achieve the desired stereochemistry. The alkene was cleaved to the aldehyde and subjected to Brown asymmetric allylation to provide alcohol **99** followed by methyl ether formation. Oxidative cleavage of the acetonide was followed by chemoselective addition of trimethyl aluminum to the aldehyde in the presence of the benzoyl protecting group to give **100**. Oxidation to the ketone and protection with ethylene glycol in the presence of PTSA was followed by another cleavage of the alkene using Johnson-Lemieux conditions to supply aldehyde **92**.

Scheme 26

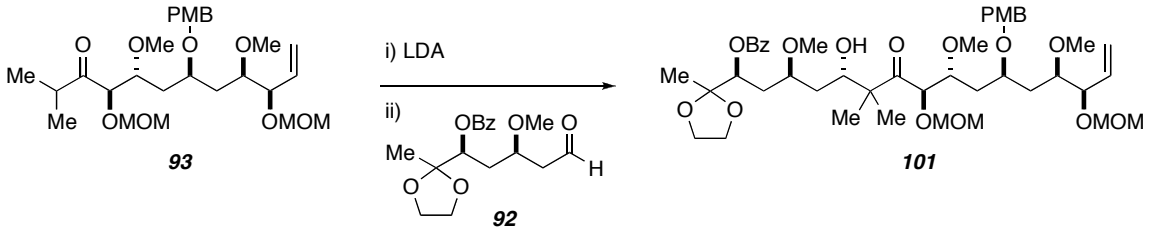
W. Zhou (2004): C11-C16 Fragment of (+)-peloruside A



After screening a number of aldol conditions to couple fragments **92** and **93**, the optimal conditions were found to be the lithium enolate addition of **93** to aldehyde **92** to provide β-hydroxy ketone **101** in a modest 60% yield (74:26 *dr*) (**Scheme 27**).

Scheme 27

W. Zhou (2004): C1-C10 to C11-C16 Fragment Coupling of (+)-peloruside A



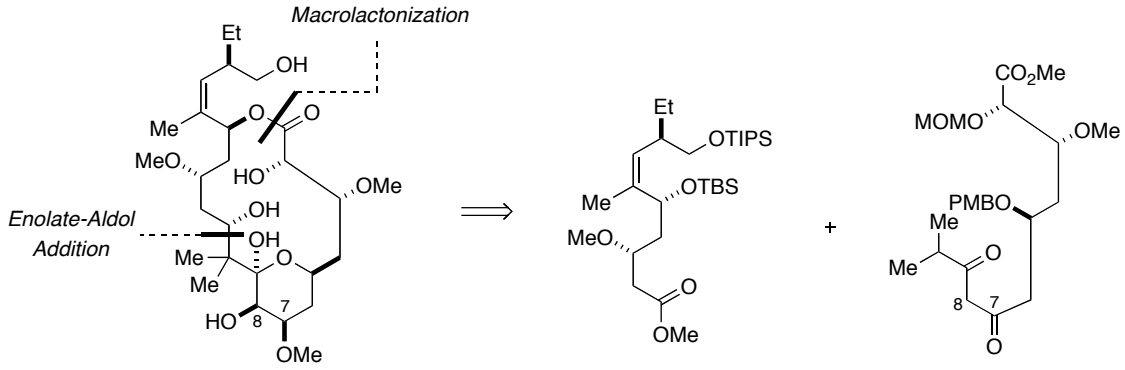
With the synthesis of the C1-C16 backbone of the core in hand, it would be reasonable to assume that we would eventually see a total synthesis of peloruside **1** coming from the Zhou group in the not too distant future. Only two years later, in 2006, they did publish another paper relating to peloruside A **1**. However, it was not a total synthesis, but rather a stereoselective route to the C11-C20 fragment.[46] It turns out that

[46] "A stereoselective synthesis of the C11-C19 fragment of (+)-peloruside A." Chen, Z.; Zhou, W. *Tetrahedron Lett.* **2006**, *47*, 5289-5292.

they happened to run into some roadblocks along the way in completing their original synthesis. Since installation of the *Z*-trisubstituted olefin was found to be problematic they planned to install the alkene earlier in the route (**Scheme 28**). It still appears as if they plan to couple using an aldol reaction between an aldehyde derived from **102** and isopropyl ketone **103**, but have decided to install the C7 and C8 stereocenters after fragment coupling.

Scheme 28

W. Zhou (2006): Revised Retrosynthesis of (+)-peloruside A

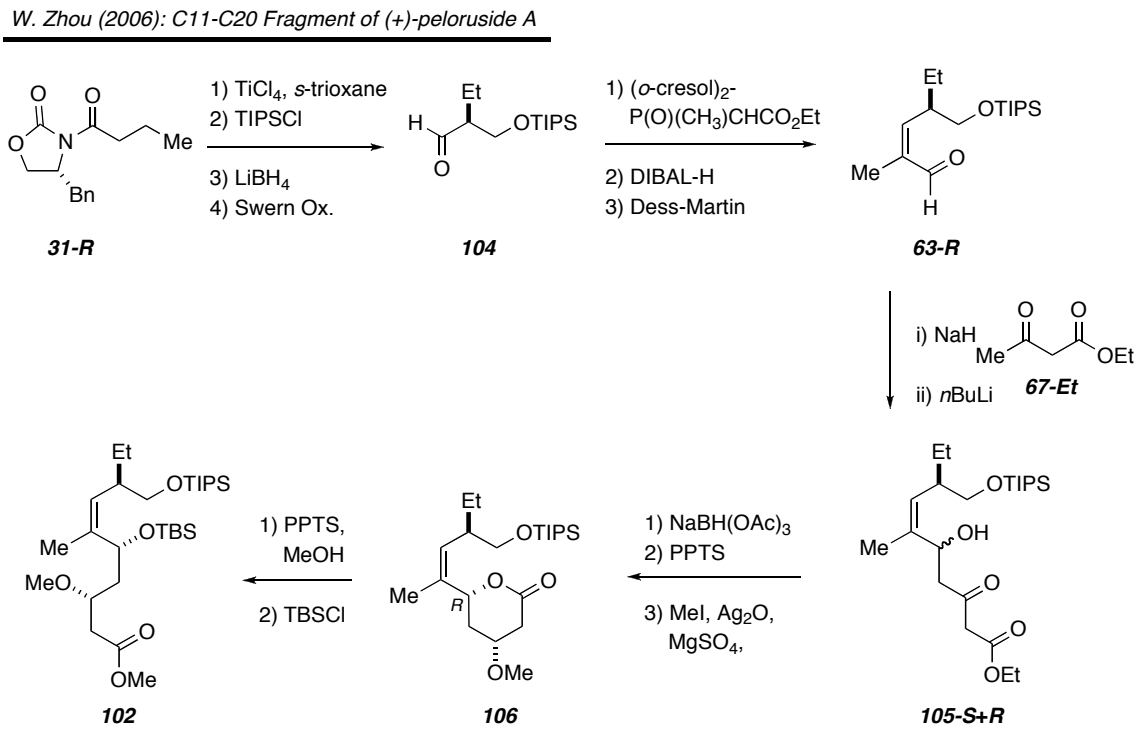


The synthesis of the C11-C20 segment began, like others, with oxazolidone **31-*R*** derived from Evans' chiral auxiliary (**Scheme 29**). Installation of the primary hydroxyl was accomplished by an aldol followed by protection with TIPSCl. Removal of the auxiliary was followed by oxidation to give aldehyde **104**. Formation of the *Z*-trisubstituted olefin using Ando's procedure[33] gave the α,β-unsaturated ester that was reduced and oxidized to furnish enal **63-*R***. The aldehyde **63-*R*** was reacted with the Weiler dianion[47] of ethyl acetoacetate **67-Et** to give **105-*S*** and **105-*R*** as a 1:1 mixture of separable diastereomers in 69% combined yield. Reduction of the β-hydroxy ketone **105-*R*** to the 1,3-*anti* diol was followed by cyclization to the corresponding lactone with PPTS, allowing methylation of the remaining alcohol. Methanolysis of **106** to the

[47] "Alkylation of dianions of .beta.-keto esters." Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082-1087.

hydroxy ester and silylation of the free alcohol completed the C11-C20 subunit **102** that could later be converted into the corresponding aldehyde for completion of the synthesis.

Scheme 29

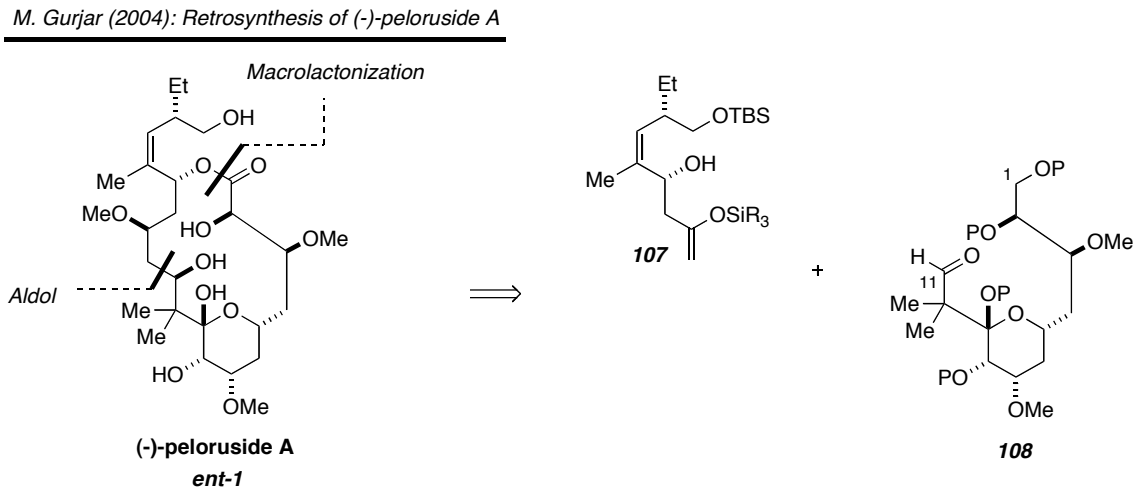


5. M. Gurjar's Synthetic Efforts Toward (-)-Peloruside A

The Gurjar group, in 2004, published a chiral pool approach to the synthesis of the C1-C11 subunit of (-)-peloruside A ***ent*-1**.[48] The main disconnections, like others, consisted of separating the molecule into two segments that were to be joined via a Mukaiyama aldol reaction and macrocyclization (**Scheme 30**).

[48] "Toward a synthesis of the antitumor macrolide peloruside A: A chiral pool approach for the C1–C11 segment." Gurjar, M. K.; Pedduri, Y.; Ramana, C. V.; Puranik, V. G. *Tetrahedron Lett.* **2004**, *45*, 387-390.

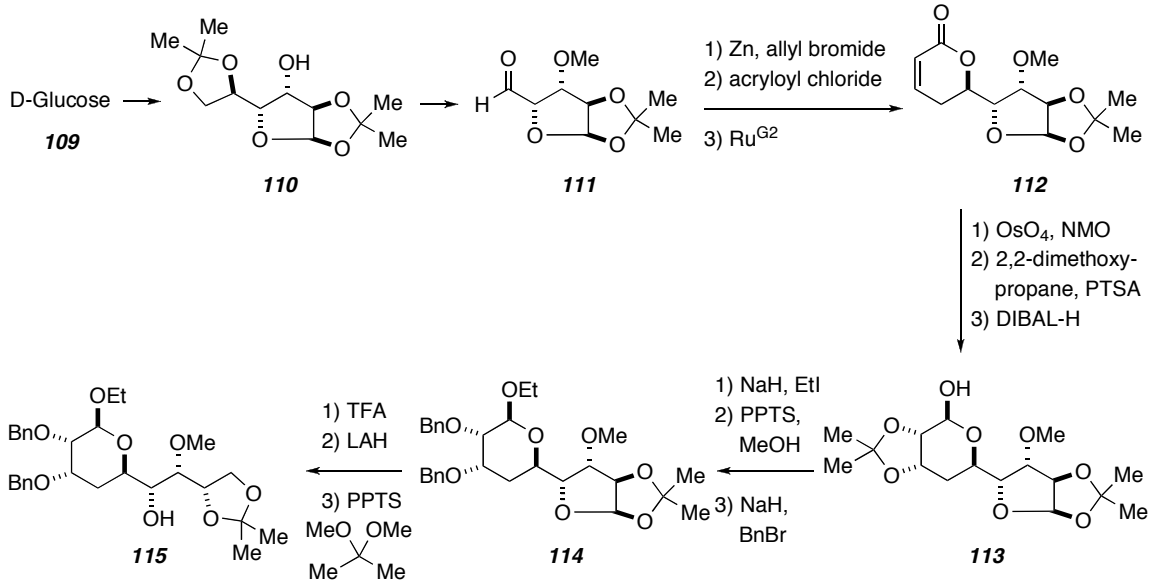
Scheme 30



Commercially available bis acetonide **110**, easily prepared from D-glucose **109**, was converted to aldehyde **111** following a precedented literature procedure (**Scheme 31**). The product resulting from a highly stereoselective addition of allylbromide to **111** under Barbier conditions was acylated with acryloyl chloride. Ring-closing metathesis with **[Ru]**^{G2} (**21**) provided the α,β-unsaturated δ-valerolactone **112**. A highly diastereoselective dihydroxylation of the alkene in **112** was followed by formation of its acetonide and DIBAL-H reduction to the corresponding lactol **113**. Anomeric *O*-ethylation was followed by regioselective removal of one of the acetonides and reprotection of the hydroxyls as benzyl-ethers to give compound **114**. Acid catalyzed hydrolysis of the furanoside, reduction of the resulting acetal with LAH, and selective formation of the 1,2-acetonide formed alcohol **115**, freeing the hydroxyl that needs to be removed from the carbon backbone.

Scheme 31

M. Gurjar (2004): C1-C11 Fragment of (-)-peloruside A

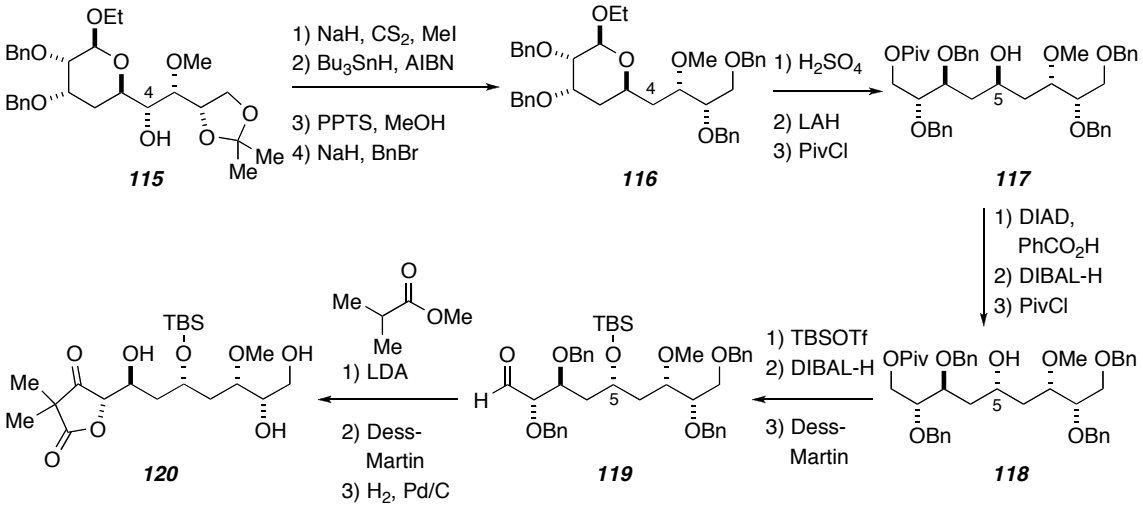


A Barton McCombie deoxygenation[49] was applied to compound **115** to remove the C4 hydroxyl, followed by removal of the acetonide and reprotection with benzyl bromide to give tetrasubstituted benzyl ether **116** (**Scheme 32**). Subsequent treatment of **116** with H_2SO_4 produced the cyclic acetal, which was reduced with LAH to give a diol. The primary hydroxyl was selectively protected as the pivaloyl ester to give compound **117**, leaving the C5 stereocenter susceptible to Mitsunobu inversion. Inversion of the C5 carbinol using diisopropyl azodicarboxylate (DIAD) and benzoic acid gave the inverted benzoate ester. Treatment of the diester with DIBAL-H furnished a diol in which the primary alcohol was reprotected as the pivaloate ester, giving product **118**. The C5 stereocenter was protected as the TBS-ether, followed by removal of the pivaloate and periodinane oxidiation to give aldehyde **119**. The carbinol product that resulted from the lithium enolate of 2-methylpropionate reacting with aldehyde **119** was oxidized to its corresponding ketone. Hydrogenation removed the benzyl ethers to give an intermediate tetraol that cyclized to ketolactone **120**, completing the C1-C11 fragment of (-)-peloruside A ***ent*-1**.

[49] "A new method for the deoxygenation of secondary alcohols." Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Perk. Trans. 1* **1975**, 1574-1585.

Scheme 32

M. Gurjar (2004): C1-C11 Fragment of (-)-peloruside A

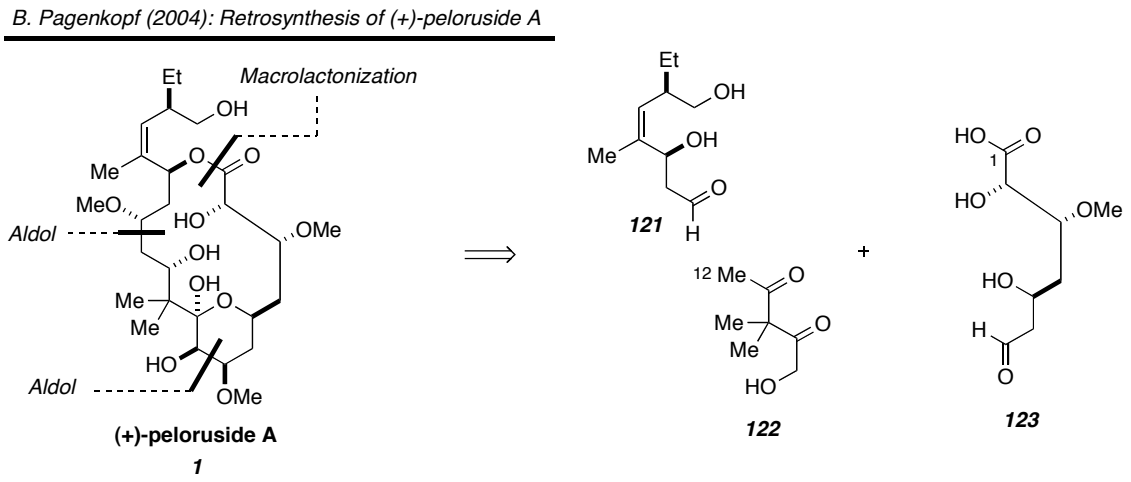


6. B. Pagenkopf's Synthetic Efforts Toward (+)-Peloruside A

In 2004, Pagenkopf and coworkers reported their synthesis of the C1-C12 segment of peloruside A **1**.[50] Their retrosynthetic strategy is shown in **Scheme 33**. The instrumental bond forming events are two aldol reactions, from aldehydes **121** and **123** and diketone **122**. A Yamaguchi lactonization is again required to complete their synthesis. This route allowed for expansion of α-hydroxy ketone aldol methodology, particularly regarding the effects of a α-*gem* dimethyl group.

[50] "Synthesis of the C1-C12 segment of peloruside A by an α-benzyloxymethyl ketone aldol strategy." Engers, D. W.; Bassindale, M. J.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 663-666.

Scheme 33

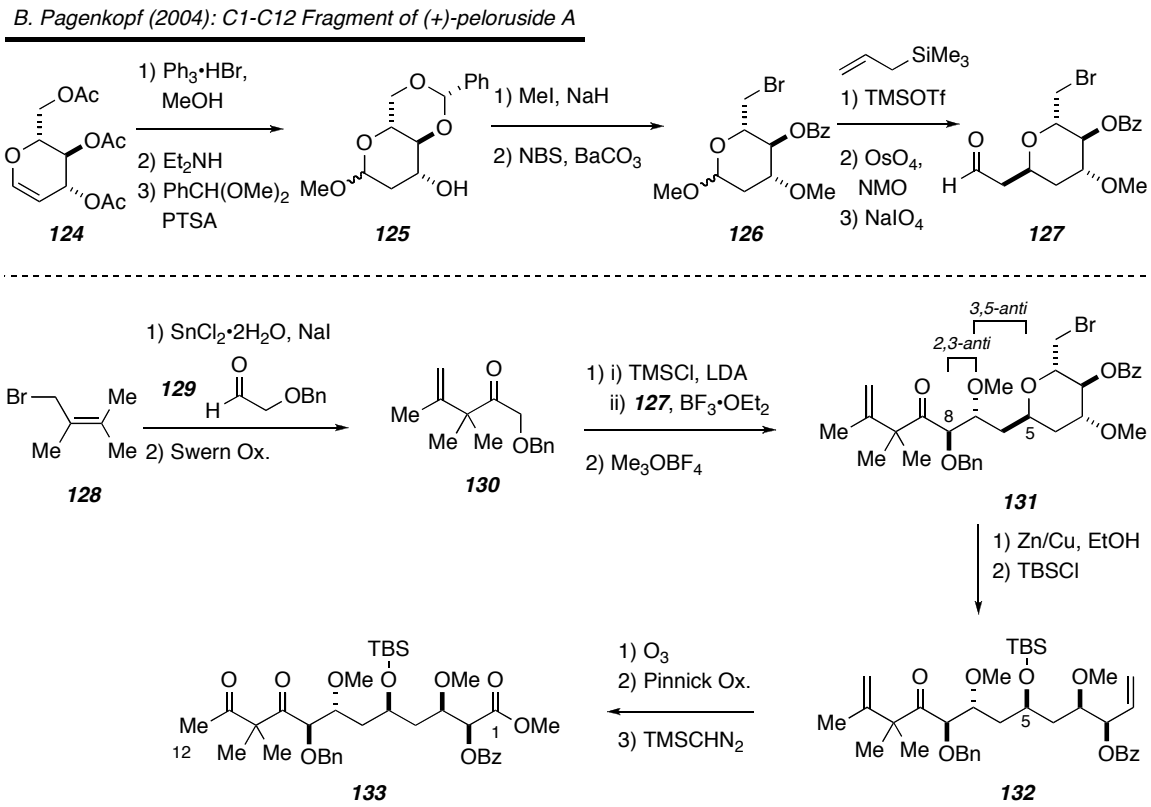


Synthesis of the C1-C12 segment began by treating commercially available triacetyl D-glucal **124** with methanol and catalytic Ph_3P•HBr to provide a net addition of methanol across the olefin of glucal **124** (**Scheme 34**). Acetate cleavage and selective 1,3-benzylidene acetal formation provided alcohol **125**. Following routine methylation of **125**, selective cleavage of the primary benzylidene ether under Hanessian-Huller radical bromination conditions (NBS, $BaCO_3$, CCl_4, reflux) furnished the known pyranoside **126**. Allylation of **126** was performed using trimethylsilyl triflate (TMSOTf) and allyltrimethylsilane to give exclusively one diastereomer. A stepwise dihydroxylation and glycol cleavage under Johnson-Lemieux conditions supplied aldehyde **127** in 46% overall yield from triacetyl D-glucal **124**.

With the desired aldehyde in hand, the ketone **130** was formed by addition of an allylic stannane, prepared *in situ*, to benzyloxy aldehyde **129** followed by Swern oxidation (**Scheme 34**). Extensive studies resulted in a Mukaiyama aldol reaction promoted by BF_3•OEt_2 to provide the desired 2,3-*anti*-3,5-*anti*-aldol product with acceptable diastereoselectivity (ca. 3.5:1). The hydroxyl resulting from the aldol addition was methylated using Meerwein's salt to give **131**. Utilization of the known Vasella ring cleavage to provide the C5 hydroxyl and terminal olefin was followed by TBS-ether formation. The newly formed silyl ether **132**, when treated with ozone, converted the two olefins into their corresponding carbonyl derivatives. Standard oxidation of the

aldehyde and esterification of the resulting acid provided methyl ester **133**, completing the C1-C12 segment of (+)-peloruside A **1**.

Scheme 34

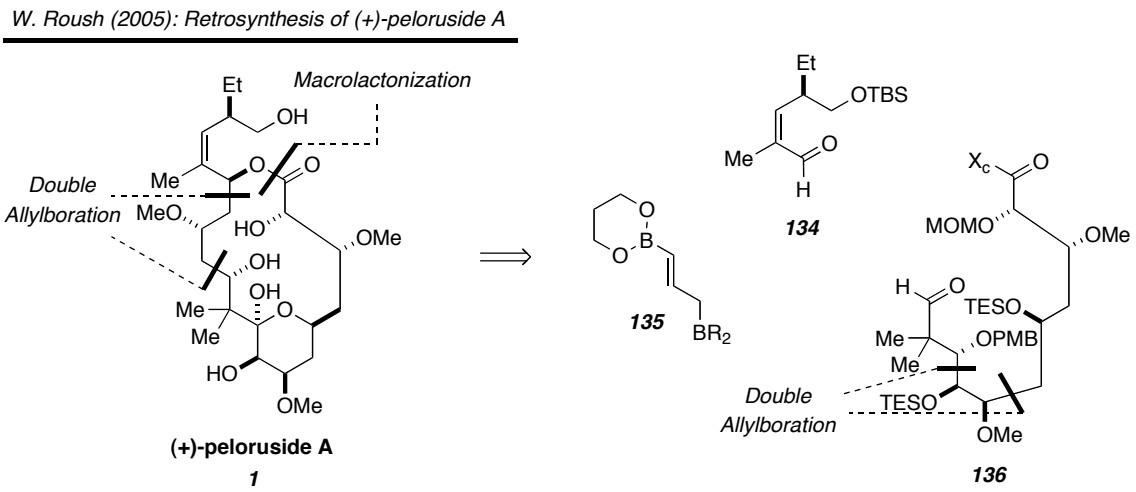


7. W. Roush's Synthetic Efforts Toward (+)-Peloruside A

Roush and coworkers published their progress toward (+)-peloruside A **1** in 2005.[51] They envisioned applying their recently reported double allylboration methodology wherein aldehyde **136** would be made first via double allylboration, while the second time it would be used to combine segments **134** and **136** (**Scheme 35**).

[51] "Stereoselective synthesis of the C1-C11 fragment of peloruside A." Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941-3944.

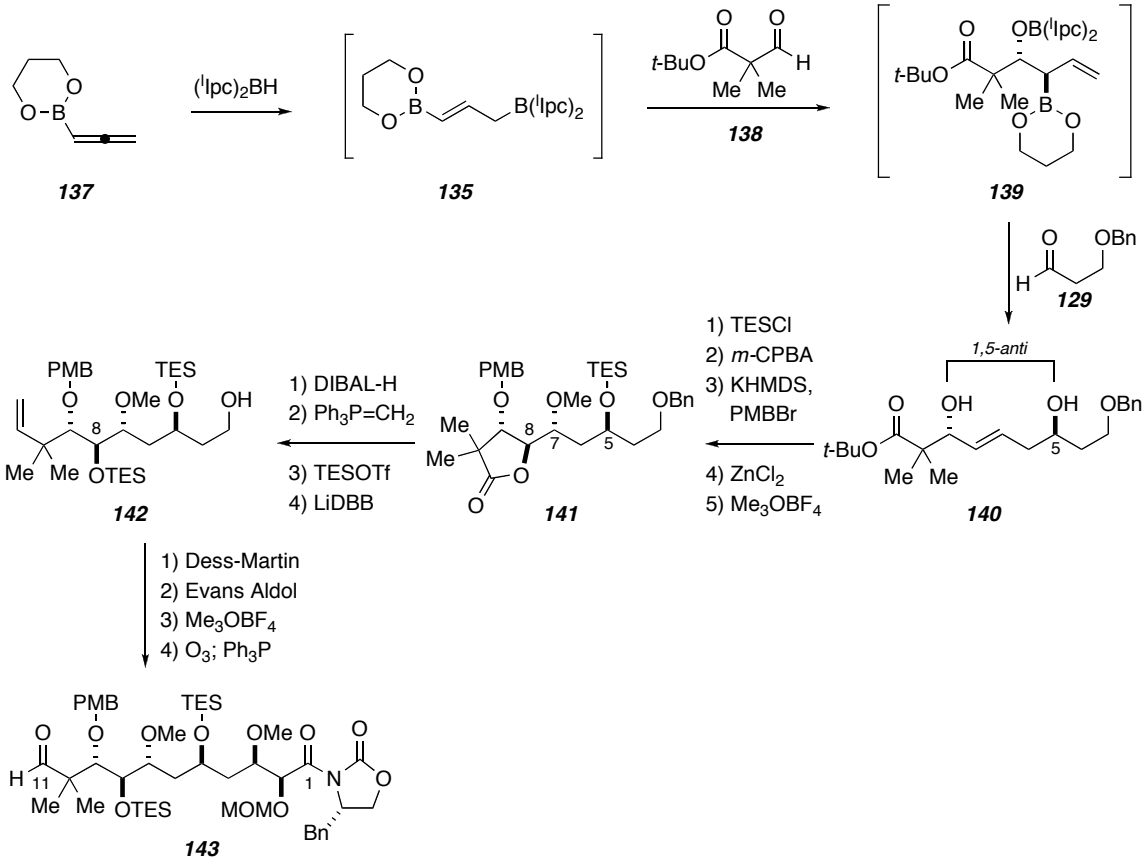
Scheme 35



The ^{l}Ipc-derived γ-boryl-substituted allylborane **135** was prepared *in situ* by the hydroboration of allene **137** with $(^{l}Ipc)_2BH$. Sequential addition of aldehyde **138** to form the intermediate boronate **139** and addition of the second aldehyde **129** provided the 1,5-*anti* diol **140** as a single diastereomer in 77% yield and 85% *ee* (**Scheme 36**). Selective protection of the C5 hydroxyl as a TES-ether was followed by *m*-CPBA epoxidation and protection of the remaing alcohol with *p*-methoxybenzyl bromide. Intramolecular opening of the epoxide with zinc chloride ($ZnCl_2$) to give the γ-lactone allowed for the subsequent methylation of the C7 hydroxyl with Meerwein's salt to give compound **141**. Partial reduction of the lactone with DIBAL-H and Wittig olefination isolated the C8 hydroxyl for TES-ether formation. Selective removal of the benzyl group with lithium 4,4´-di-*tert*-butylbiphenyl (LiDBB) provided primary alcohol **142**. Oxidation of the primary alcohol to an aldehyde and reaction with the appropriate *N*-acyl oxazolidinone provided the desired alcohol, which was then methylated. Ozonolysis of the terminal alkene provided aldehyde **143** and completed the C1-C11 fragment of (+)-peloruside A **1**.

Scheme 36

W. Roush (2005): C1-C11 Fragment of (+)-peloruside A



III. Previous Hoye Group Efforts Toward (+)-Peloruside A

A. M. Tennakoon's Synthetic Efforts Toward (+)-Peloruside

The synthetic efforts in the Hoye group toward (+)-peloruside A **1** began shortly after the publication of the isolation paper by Northcote et al. A graduate student, M. Tennakoon, performed the initial studies that laid the foundation for future work in this area by other Hoye group members.

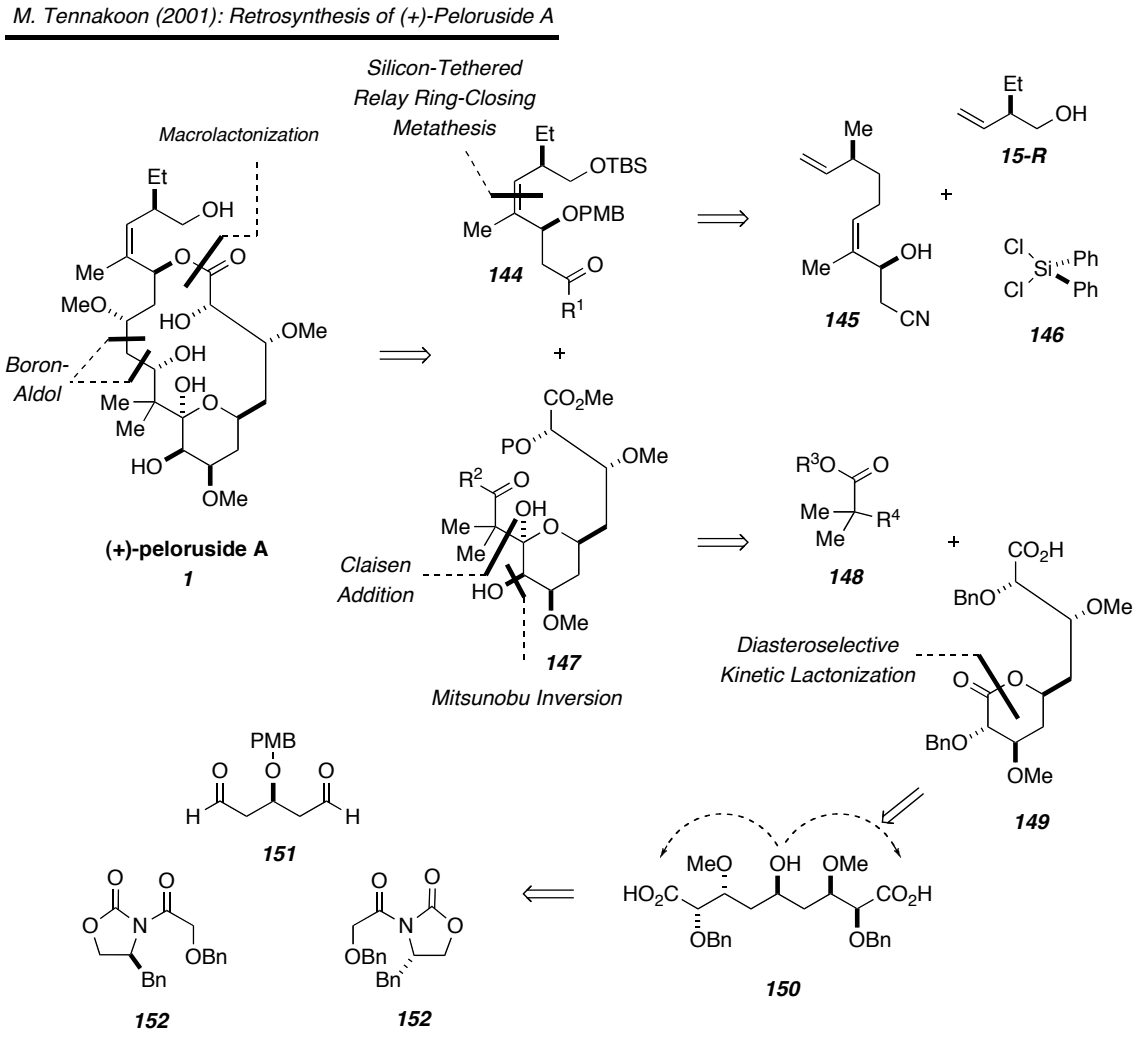
The initial retrosynthetic analysis proposed by Hoye and Tennakoon is shown in **Scheme 37**. Yamaguchi lactonization would be used to close the macrolide and a boron-mediated aldol reaction would combine fragments **144** and **147**, either of which could be converted into the corresponding ketone or aldehyde.[52] The *Z*-trisubstituted olefin in **144** could be constructed from the relay ring-closing metathesis of temporarily silicon-tethered carbinols **145** and **15-*R***.[40,53] Claisen addition of a substrate similar to ester **148** into lactone **149** could form the requisite C9-C10 bond. Kinetic lactonization of carbinol **150** to give lactone **149** was proposed based on earlier precedent from the Hoye group. Bidirectional addition of chiral auxiliary **152** to a bis-aldehyde like **151** could be used in the synthesis of the lactonization precursor **150**.

---

[52] Tennakoon, M. A., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2001**.

[53] (a) "Relay ring-closing metathesis (RRCM): A strategy for directing metal movement throughout olefin metathesis sequences." Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126,* 10210-10211. (b) Zhao, H., Ph.D. Thesis, University of Minnesota, Minneapolis, Minnesota, **2000**. (c) Danielson, M. E., Ph.D. Thesis, University of Minnesota, Minneapolis, Minnesota, **2003**. (d) Hoye, T. R.; Wang, J. Abstracts of Papers, 226th National Meeting of the American Chemical Society, Sept 7-11, **2003**, New York; American Chemical Society: Washington, DC, 2003; ORGN-670.

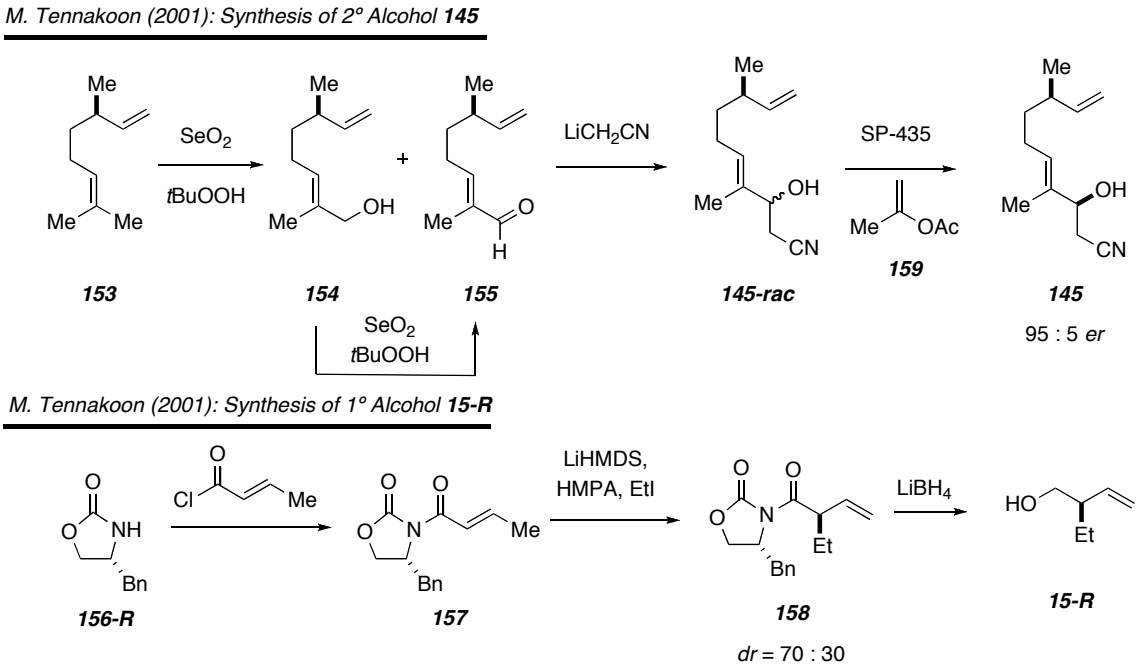
Scheme 37



A large portion of Tennakoon's work was directed toward the synthesis of the C13-C20 segment of peloruside A **1**. The viability of this route would depend on the synthesis of allylic alcohol **145** and homoallylic alcohol **15-*R***, as well as their silicon tethering. The synthesis of allylic alcohol **145** began with the regioselective allylic oxidation of commercially available (*R*)-citronellene **153** to produce a mixture of the primary allylic alcohol **154** and enal **155** (**Scheme 38**). Resubjection of the mixture to the reaction conditions (or simply addition of more oxidizing reagent) converted the mixture to the desired enal **155**. The lithium enolate of acetonitrile was added into enal **155** to provide the racemic secondary allylic alcohol **145-*rac***. The enzymatic resolution

of **145-*rac*** in the presence of isopropenyl acetate yielded the enantioenriched secondary alcohol for use in silicon tethering.

Scheme 38

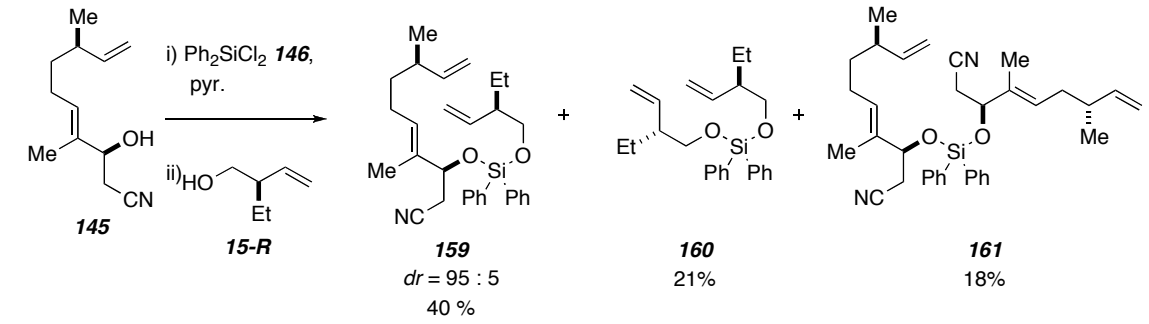


The synthesis of the homoallylic alcohol **15-*R*** began with acylation of the chiral auxiliary, oxazolidinone **156-*R***, with *trans*-crotonyl chloride to form **157** (**Scheme 38**). Deprotonation of the allylic position with lithium hexamethyldisilazide (LiHMDS) followed by treatment with ethyl iodide provided **158** in modest diastereoselectivity (70:30 *dr*). Separation of the mixture of diastereomers proved to be somewhat difficult, but was later accomplished by employing medium pressure liquid chromatography (MPLC). The auxiliary was reductively removed with lithium borohydride ($LiBH_4$) to give homoallylic alcohol **15-*R***. While this route to **15-*R*** is relatively short and straightforward, the low diastereoselectivity during the alkylation and difficulty in separating the products led to only a small amount of material being prepared.

Silicon tethering of the two alcohols, **145** and **15-*R***, allowed for the preparation of mixed silaketal **159** in a modest 40% yield (**Scheme 39**). A significant problem was the formation of homodimers **160** and **161** formed from the starting alcohols. Even with the difficulties encountered, Tennakoon was still able to prepare enough material to study the RRCM.

Scheme 39

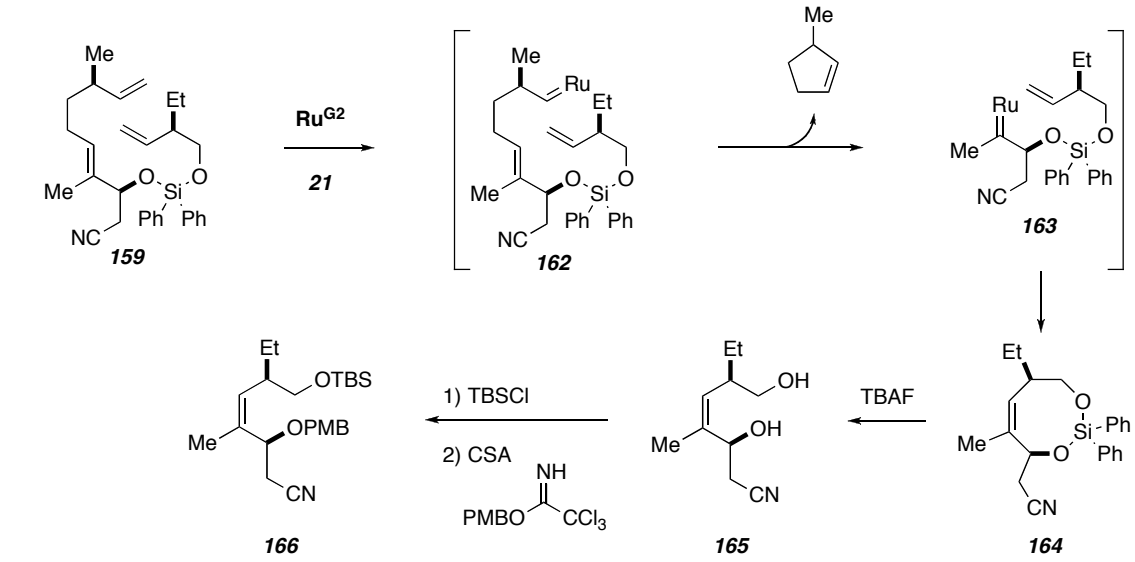
*M. Tennakoon (2001): Synthesis of Unsymmetrical Silaketal **159***



Exposure of the mixed silaketal **159** to Grubbs second generation initiator (**Ru**^{G2}, **21**) began the RRCM process.[40,53] The RRCM process generally proceeds with the catalyst loading onto the most activated and/or sterically accessible alkene, in this case to form the ruthenium alkylidene intermediate **162** (**Scheme 40**). From this point, two productive pathways are possible. The first pathway involves association of the active alkylidene to the distal alkene, forming a 13-membered macrocyclic alkene. The second pathway, leading to the desired product **164**, occurs when the alkylidene associates with the proximal alkene and ejects methylcyclopentene, forming the truncated 1,1´-disubstituted ruthenium alkylidene **163**. This alkylidene can then continue on in a productive fashion to produce the trisubstituted alkene **164**. Removal of the temporary silicon tether gave diol **165** and the primary hydroxyl was selectively protected as its TBS-ether. PMB-ether formation of the remaining hydroxyl under acidic conditions with a PMB trichloroacetimidate gave nitrile **166**, thereby alleviating the problem of β-elimination. At this point Tennakoon was able to construct the C13-C20 segment of (+)-peloruside A **1** while exemplifying the utility of silicon-tethered RRCM.

Scheme 40

M. Tennakoon (2001): C13-C20 Fragment of (+)-peloruside A

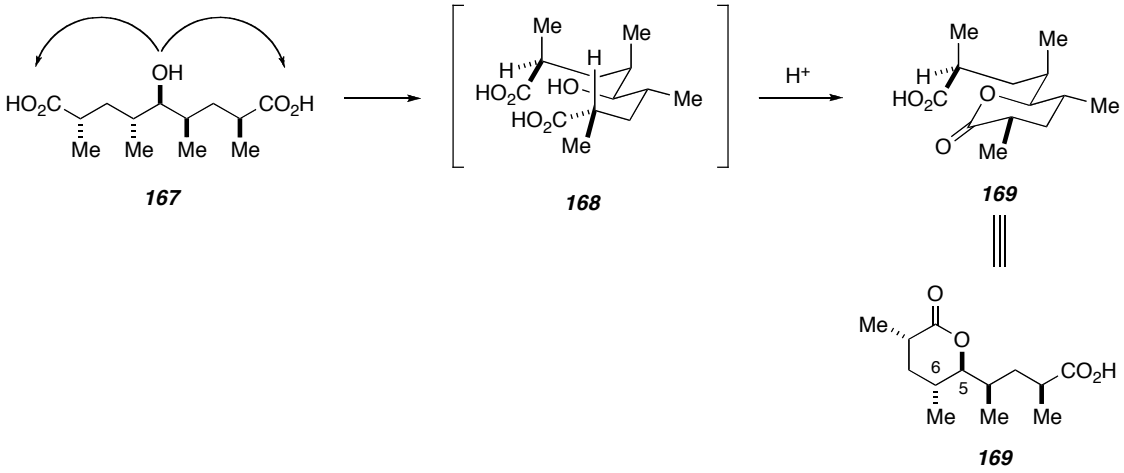


Having devised a route to the C13-C20 framework of peloruside A **1**, Tennakoon next started working toward construction the C1-C9 lactone **149**, coming from a diastereoselective kinetic lactonization of **150**. Earlier work in the Hoye lab supplied the precedence for this highly diastereocelective transformation. When the tetramethyl derivative **167** was treated with acid, a ≥350:1 ratio (GC-MS analysis) favoring the 5,6-*trans* lactone **169** was formed (**Scheme 41**).[54] While the structures of the two lactones **169** and **149** are different, it was logical to expect that a high level of diastereoselectivity could be attained in the lactonization of **150**.

[54] "Kinetic lactonization of 4,6-dimethyl-5-hydroxyazelaic and 2,4,6,8-tetramethyl-5-hydroxyazelaic acids: Ground-state conformational control." Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738-2739.

Scheme 41

T. Hoye, D. Peck, & T. Swanson Kinetic Lactonization



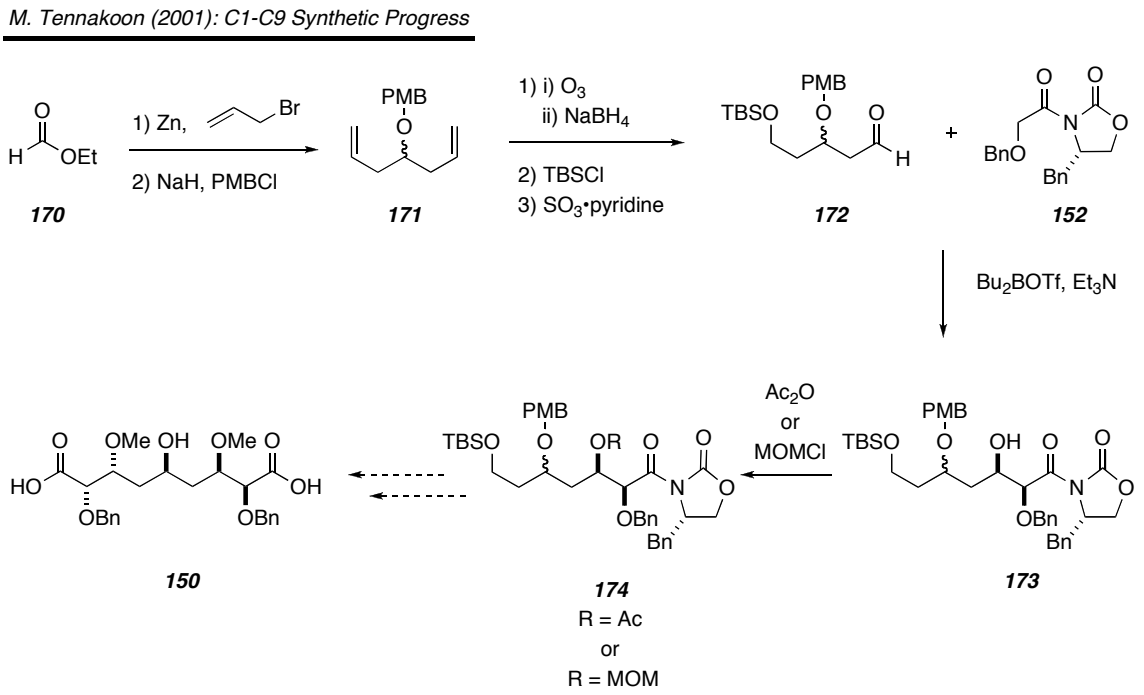
167 ***168*** ***169*** ***169***

In an effort to test the kinetic lactonization hypothesis and apply it toward the synthesis of peloruside A **1**, Tennakoon set out to construct the carbinol bis-acid **150**. Only the synthesis of the most advanced intermediate obtained will be discussed here. One is referred to Tennakoon's thesis for a more detailed report about the attempted strategies.[52]

All attempts to perform a one-pot double addition into bis-aldehyde **151** were unsuccessful in providing any desired product. Therefore, a stepwise approach was determined to be the logical solution. The sequence of steps began with the double allylation of ethyl formate (**170**) using allyl bromide and zinc metal (**Scheme 42**). Protection of the resulting alcohol as a PMB-ether provided symmetric diene **171**. Ozonolysis of **171**, employing a reductive workup with sodium borohydride ($NaBH_4$) afforded the corresponding diol. Mono protection of the diol afforded the TBS-ether, allowing for oxidation of the remaining alcohol to form racemic aldehyde **172**. Addition of the known enol boronate of *N*-acyl oxazolidinone **152** to aldehyde **172** produced a 1:1 mixture of diastereomers **173**, resulting from the use of racemic aldehyde **172**. All attempts by Tennakoon to methylate the newly formed carbinol under a variety of conditions were unsuccessful. Acetylation and MOM-ether formation to give **174** (R = Ac or MOM) were the only successful transformations. At this stage the project was

passed from the leaving graduate student, M. Tennakoon, to the new graduate student T. Ryba.

Scheme 42



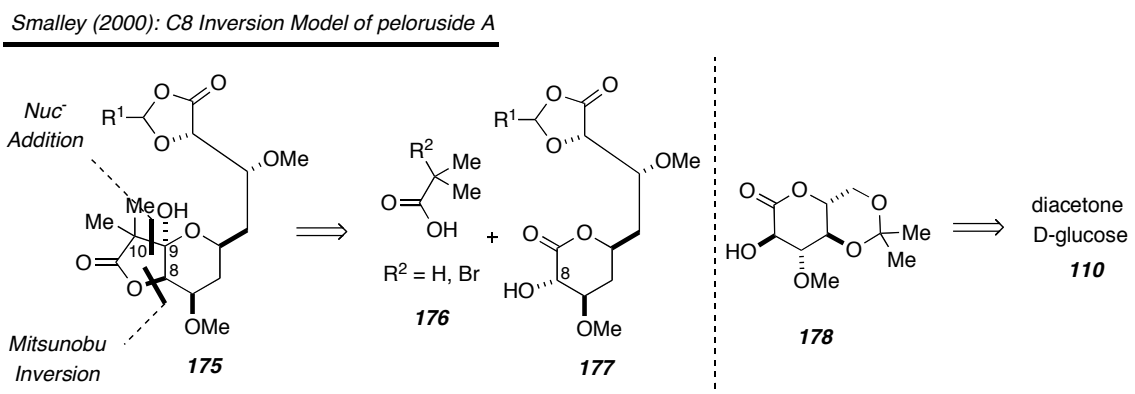
B. M. Smalley's Peloruside A Model System Inversion

Early on in Tennakoon's work toward synthesizing (+)-peloruside A **1**, she was mentoring an undergraduate student, M. Smalley, who was investigating possible strategies for inversion of the C8 stereocenter of peloruside **1**.[55] Two methods were proposed to accomplish this task. The first of which involved using the appropriate acid under standard Mitsunobu conditions (**Scheme 43**). The resulting product could then be used in an intramolecular Claisen-like addition to form the C9-C10 bond to give **175**. The second strategy involved reversing the sequence of the Mitsunobu and Claisen reactions. An intermolecular Claisen-like addition would form the new carbon-carbon bond followed by an intramolecular Mitsunobu reaction to invert the C8 stereocenter, providing the same intermediate **175** as before. Model lactone **178**, derived from

[55] "Model substrate for the Mitsunobu inversion reaction relevant to a projected synthesis of peloruside A." Smalley, M. K.; Hoye, T. R.; Tennakoon, M. *Abstr. Pap. Am. Chem. Soc.* **2001**, *221*, U139-U140.

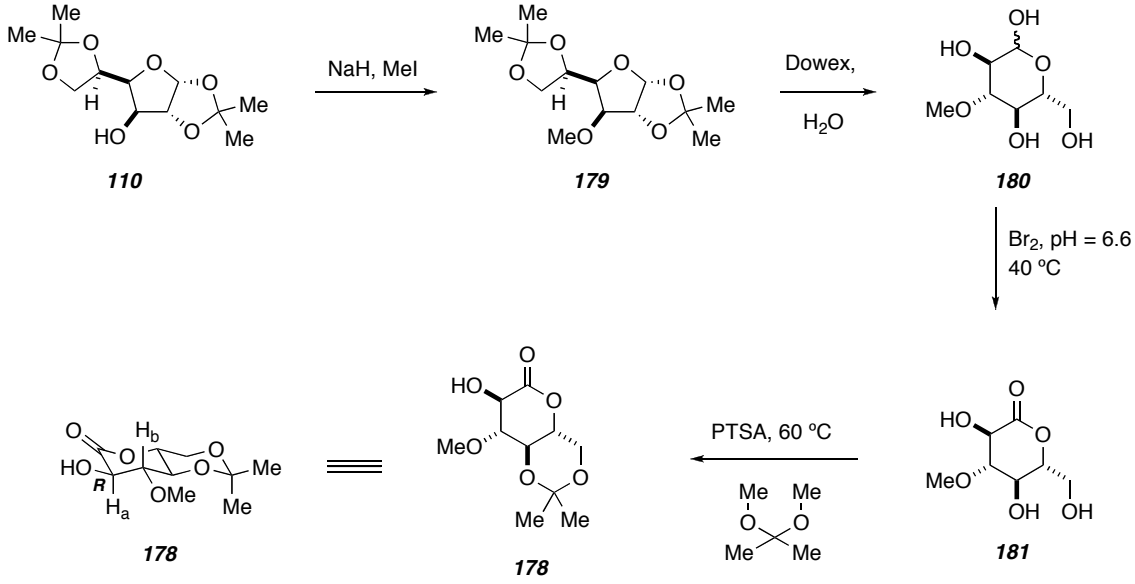
diacetone D-glucose (**110**), was proposed as a relevant and easily accessible model system to investigate this strategy.

Scheme 43



The synthesis of model lactone **178** began with methylation of diacetone D-glucose (**110**) (**Scheme 44**). The acetonides were then removed under acidic conditions using Dowex resin to give hemiacetal **180**. Oxidation to the lactone was accomplished with bromine. The 1,3-diol of **181** was selectively protected as an acetonide to give α-hydroxy lactone **178**.

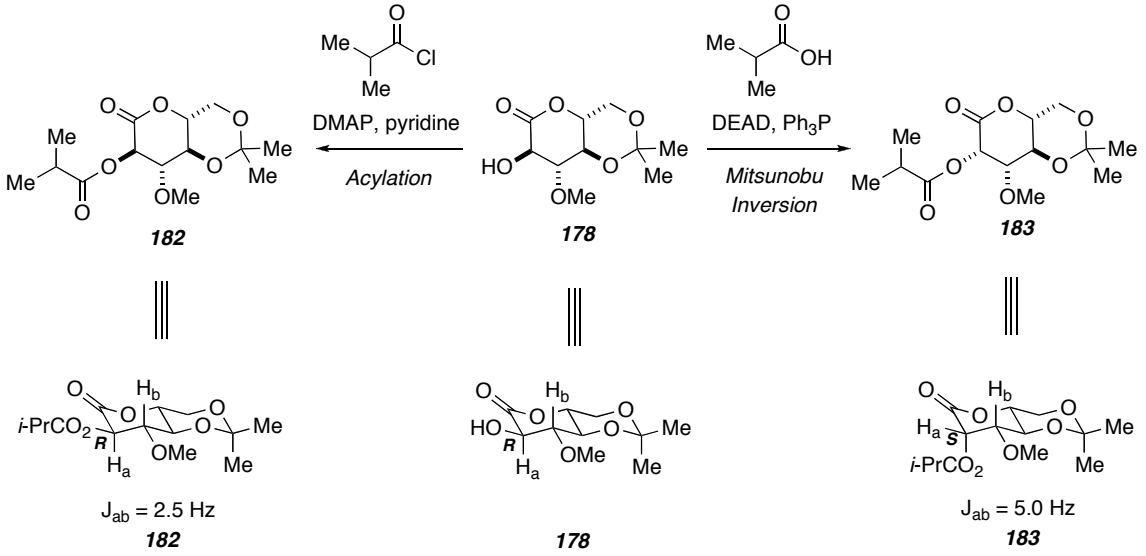
Scheme 44



Smalley began her investigation by synthesizing a retention standard. This was done by acylating α-hydroxy lactone **178** with isobutyryl chloride to provide **182** (**Scheme 45**). The next step was to subject α-hydroxy lactone **178** to standard Mitsunobu conditions (DEAD, Ph_3P) using isobutyric acid.[23] It was determined that the α-stereocenter was inverted by comparing the spectrum of the isolated product **183** from the Mitsunobu inversion reaction to that of the acylated product **182**. The results obtained by Smalley in the model system helped support the likelihood of this strategy working when applying it to the inversion of the C8 stereocenter of a peloruside substrate.

Scheme 45

*Smalley (2000): Inversion of Glucose Model Lactone **178** with Isobutyric Acid*



C. T. Ryba's Synthetic Efforts Toward (+)-Peloruside A

As was mentioned earlier, T. Ryba picked up where Tennakoon had left off in her effort to synthesize (+)-peloruside A **1**. Ryba had accomplished and learned a number of things during his time on the project. Therefore, only the major highlights will be discussed here. The reader is referred elsewhere for a more in depth report of the research Ryba performed.[56]

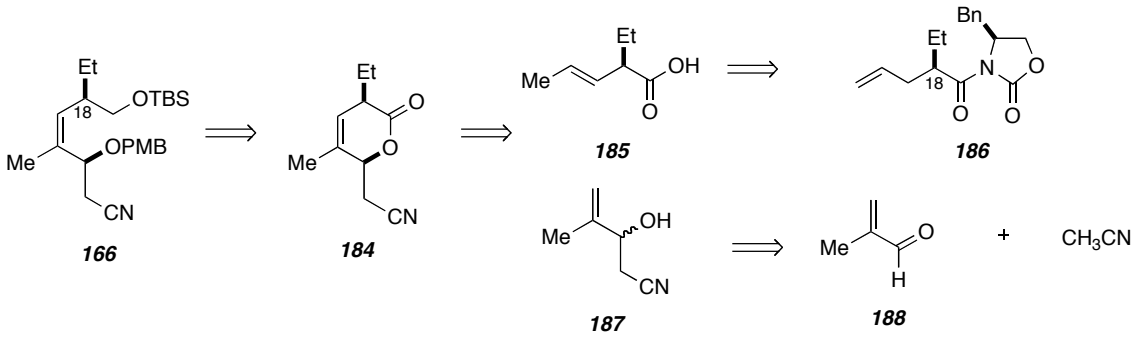
One of the problems associated with the synthesis of the C13-C20 fragment of peloruside A **1** by Tennakoon was the difficulty in obtaining large amounts of material

[56] Ryba, T. D., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**.

needed for later steps in the synthesis. One of Ryba's objectives was to solve this problem. He devised a new retrosynthetic strategy to arrive at the same desired nitrile **166** (**Scheme 46**). Nitrile **166** could be derived from lactone **184** upon oxidation state and protecting group manipulations. Ring-closing metathesis would be used to form the *Z*-trisubstituted olefin in lactone **184** using acid **185** and a α-hydroxy nitrile **187**. The desired C18 stereocenter of acid **185** would be installed, similar to other groups, using an Evans oxazolidinone aldol followed by rhodium-catalyzed isomerization of the terminal alkene.

Scheme 46

T. Ryba (2005): C13-C20 Retrosynthesis of (+)-peloruside A



The synthetic work began by acylation of the commercially available (*S*)-Evans oxazolidinone **156-*S*** with butyryl chloride to form the known imide **31-*S***. Allylation of the imide **31-*S*** with allyl bromide following a Paquette protocol furnished the known alkene **186** (**Scheme 47**).[57] With the terminal alkene in hand, it was necessary to isomerize it to an internal position without transposing the olefin into conjugation and forming the undesired α,β-unsaturated carbonyl compound. This was realized by exposing alkene **186** to a heated ethanol solution of $RhCl_3 \bullet 3H_2O$ to produce a mixture of *E* and *Z* disubstituted olefins **189**.[58] The hydrolysis of the imide **189** with lithium hydroxide produced acid **185**. A one-pot procedure converted the acid **185** to an acid

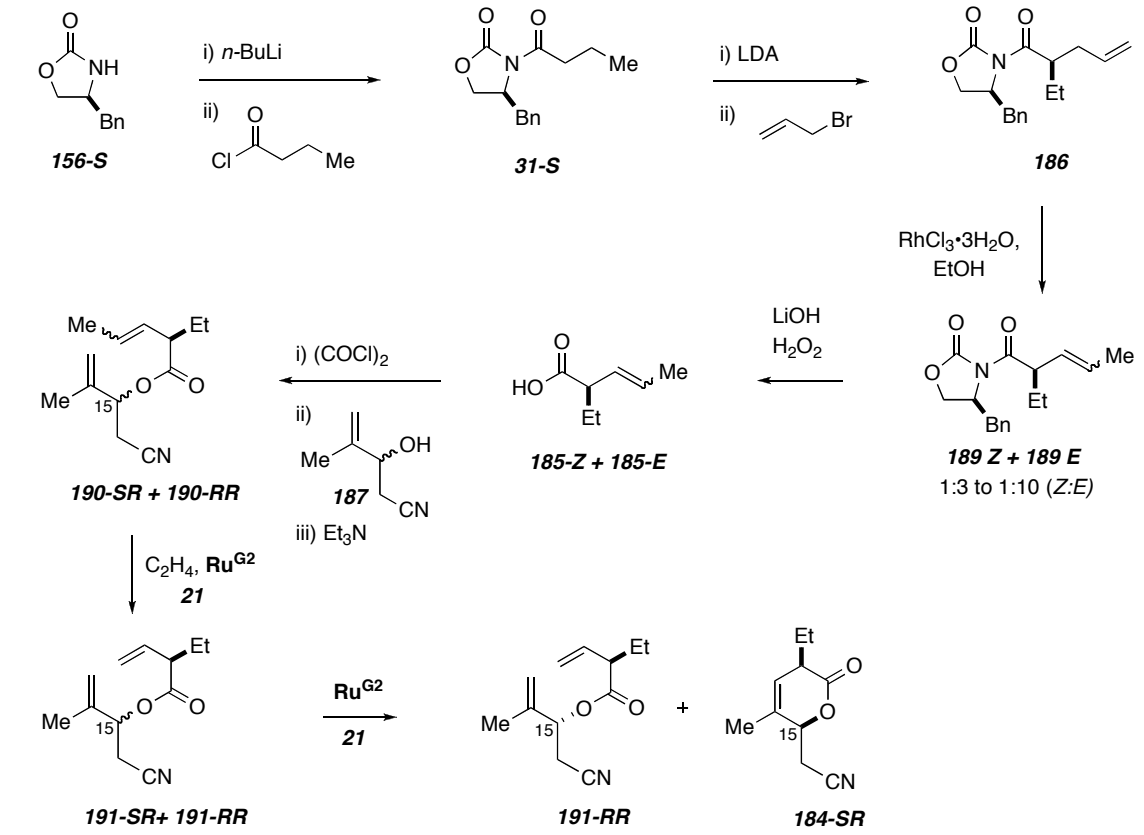
[57] "Convergent enantioselective synthesis of vinigrol, an architecturally novel diterpenoid with potent platelet aggregation inhibitory and antihypertensive properties. 1. Application of anionic sigmatropy to construction of the octalin substructure." Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096-6107.

[58] "Efficient hydride-assisted isomerization of alkenes via rhodium catalysis." Morrill, T. C.; D'Souza, C. A. *Organometallics* **2003**, *22*, 1626-1629.

chloride and treatment with the β-hydroxy nitrile **187** formed the mixture of C15 epimeric esters **190-*SR*** and **190-*RR***. Exposure of this mixture to one atmosphere of ethylene and **Ru**^{G2} (**21**) provided the newly formed terminal alkenes **191-*SR*** and **191-*RR***. Exposure of dienes **191-*SR*** and **191-*RR*** to **Ru**^{G2} in refluxing benzene provided the desired ring closed product **184-*SR*** and unreacted diene **191-*RR*** in good overall yield (based on recovered **191-*RR***). This result suggested that a diastereoselective RCM, similar to the one reported by Ermolenko, had taken place.[43] With a newly devised route to access large quantities of lactone **184-*SR***, Ryba ended his work on the C13-C20 segment of peloruside **1** to focus on chemistry elsewhere.

Scheme 47

T. Ryba (2005): Synthesis of C13-C20 Fragment of (+)-peloruside A

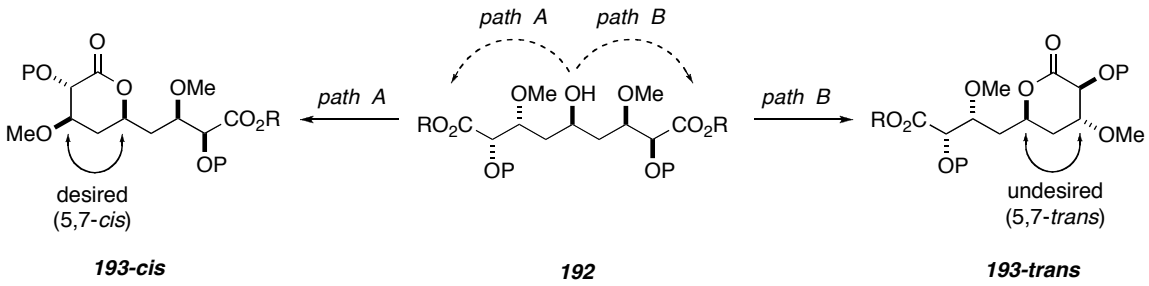


Early in T. Ryba's graduate career, the synthesis of the azelaic ester **192** was proceeding slower than anticipated (**Scheme 48**). A variety of routes to **192** all ended with limited success for one particular reason or another. These strategies and reasons will not be discussed here, but are made clear in T. Ryba's Ph.D. thesis.[56] In Ryba's own

words, "For quite some time I had acquired tunnel vision trying to synthesize the azelaic ester." He later came to the understanding that peloruside A **1** was simply a manifold for broadening the scope of different methodologies developed in the Hoye labs, one of these being the diastereoselective lactonization of azelaic ester **192**. With this new insight, he wondered about what experiences he could gain with the diastereoselective kinetic lactonization. Recall that in the lactonization process, substrate **192** has two possible modes of closure: path A) which produces lactone **193-*cis*** with the desired 5,7-*cis* stereochemical relationship or path B) which produces lactone **193-*trans*** having a 3,5-*trans* stereochemical relationship (**Scheme 48**).

Scheme 48

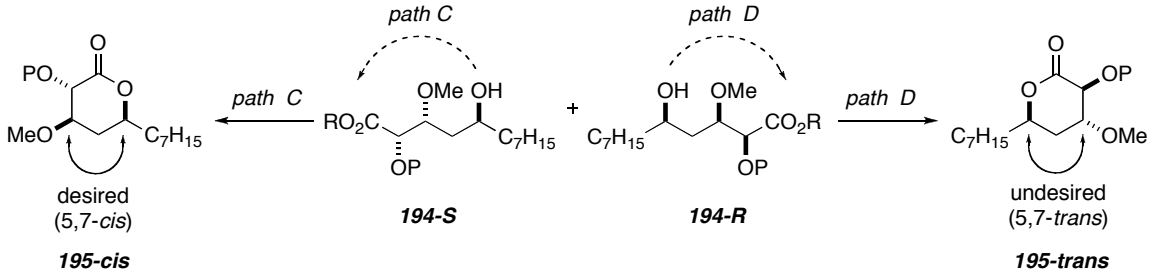
T. Ryba (2005): (+)-peloruside A Lactonization Synthon



So the main question to be answered was, "Which mode of closure was faster and by how much?" With this goal in mind, Ryba wondered if it was possible to obtain any meaningful information about the relative rates of the lactonization in a simpler system. He eventually decided on "half-model" esters **194-*R*** and **194-*S*** (**Scheme 49**). The hypothesis was that exposure of an equal amount of **194-*R*** and **194-*S*** to the same lactonization conditions would provide information about their intramolecular rates of lactonization affording both **195-*cis*** and **195-*trans*** (i.e. via path C and path D) and that this information would be applicable to the lactonization of **192**. The knowledge gained about the lactonization conditions in the model systems would not come from the final product ratio in the reaction, but from the relative lactonization rates determined by monitoring the ratios of **195-*cis*** and **195-*trans*** at early conversion.

Scheme 49

T. Ryba (2005): (+)-peloruside A Half-Model Lactonization Synthons



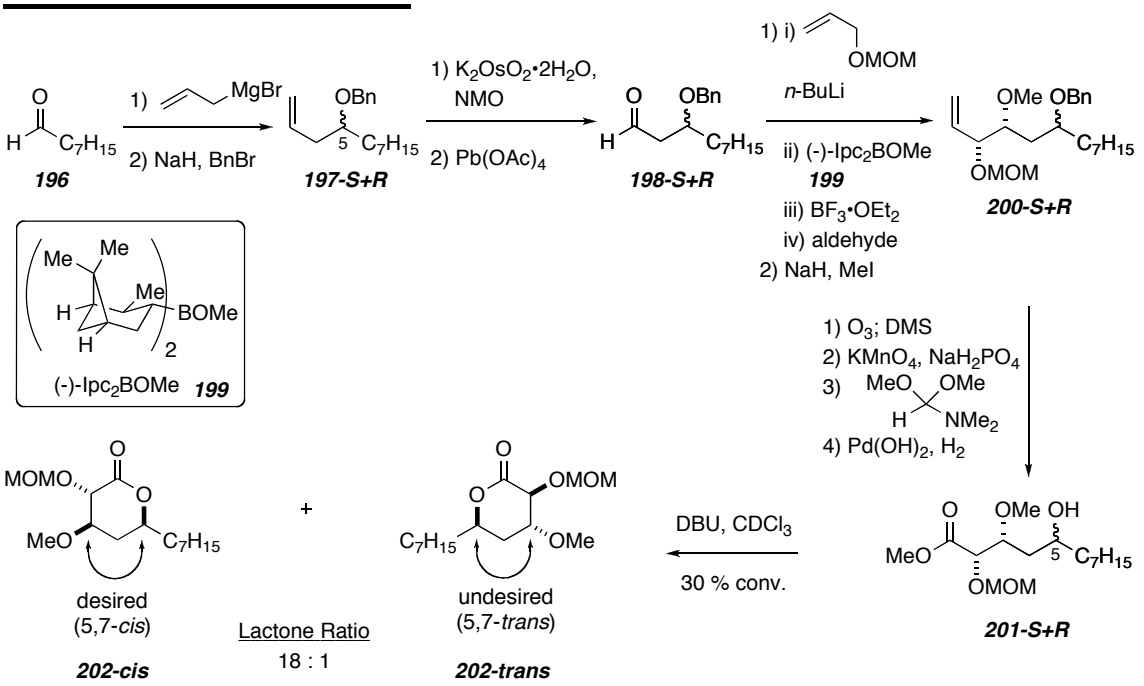
The synthesis of the half-models began with Grignard addition of allylmagnesium bromide to octyl aldehyde **196** and then benzyl-ether formation at the resulting homoallylic alcohols to provide **197-*S+R*** (**Scheme 50**).[59] Dihydroxylation of the terminal alkene was followed by oxidative cleavage using Creigee conditions to provide aldehyde **198-*S+R***. Asymmetric oxyallylation of the aldehyde **198-*S+R*** was performed using commercially available borinate **199** following a modified literature protocol.[17,60] The newly formed carbinol was then methylated with methyl iodide and sodium hydride to furnish alkene **200-*S+R***. A three-step sequence of ozonolysis, mild oxidation of the aldehyde to the acid using Masamune's protocol[61] and methyl ester formation with dimethylformamide dimethylacetal (DMF-DMA) converted the terminal alkene to a methyl ester. Removal of the benzyl group with palladium hydroxide and hydrogen provided the esters **201-*S*** and **201-*R***. After screening various reaction conditions, 30 mol% DBU was found to catalyze the lactonization of **201-*S*** much faster than it did for **201-*R***, in a ratio of 18:1 (**202-*cis*** and **202-*trans***) at 60% conversion.

[59] The *R* and *S* nomenclature refer to the stereogenicity at their point of difference C5, using peloruside numbering.

[60] "Chiral synthesis via organoboranes. 27. Remarkably rapid and exceptionally enantioselective (approaching 100% ee) allylboration of representative aldehydes at -100 ºC under new, salt-free conditions." Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

[61] "Potassium permanganate revisited: Oxidation of aldehydes to carboxylic acids in the *tert*-butyl alcohol-aqueous NaH_2PO_4 system." Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537-4540.

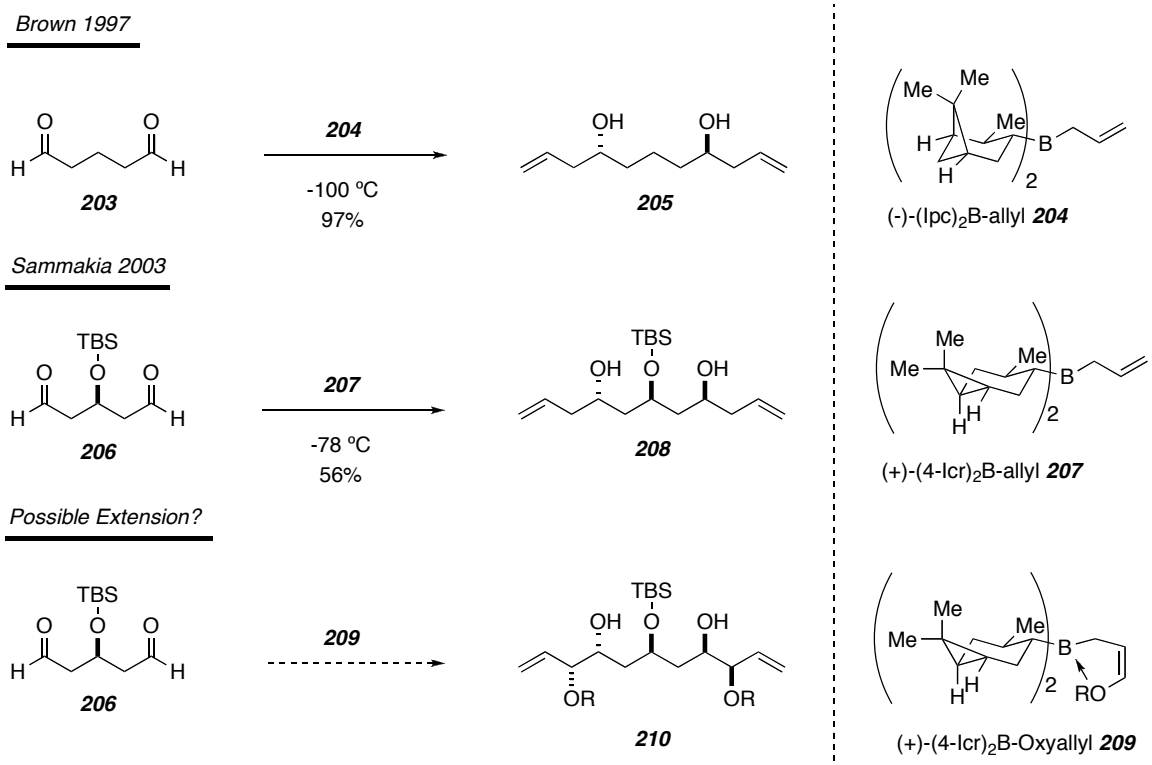
Scheme 50



Having succeeded in performing the oxyallylation of a simple aldeyde, Ryba was now encouraged to resume work on the peloruside A-relevant substrate. Another reason for this is that it had recently come to his attention that Brown had reported the high yielding $(Ipc)_2$B-allyl **204** mediated double allylation of glutaraldehyde **203** to form diol **205** in both high diastereomeric and enantiomeric excess.[62] (**Scheme 51**) Also, in 2003, while Tom Hoye was visiting the University of Colorado at Boulder, the Sammakia group was investigating the $(4\text{-Icr})_2$B-allyl **207** mediated double allylation of 3-oxy-substituted glutaraldehyde derivative **206** to form diol **208**. Upon becoming aware of this information, Hoye and Ryba immediately wondered if these methodologies could be expanded to include the 4-(Icr)_2-oxyallyl **209** mediated oxyallylation of 3-oxy-substituted glutataldehyde derivatives.

[62] "Efficient synthesis of enantiomerically pure *C2*-symmetric diols via the allylboration of appropriate dialdehydes." Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417-2420.

Scheme 51

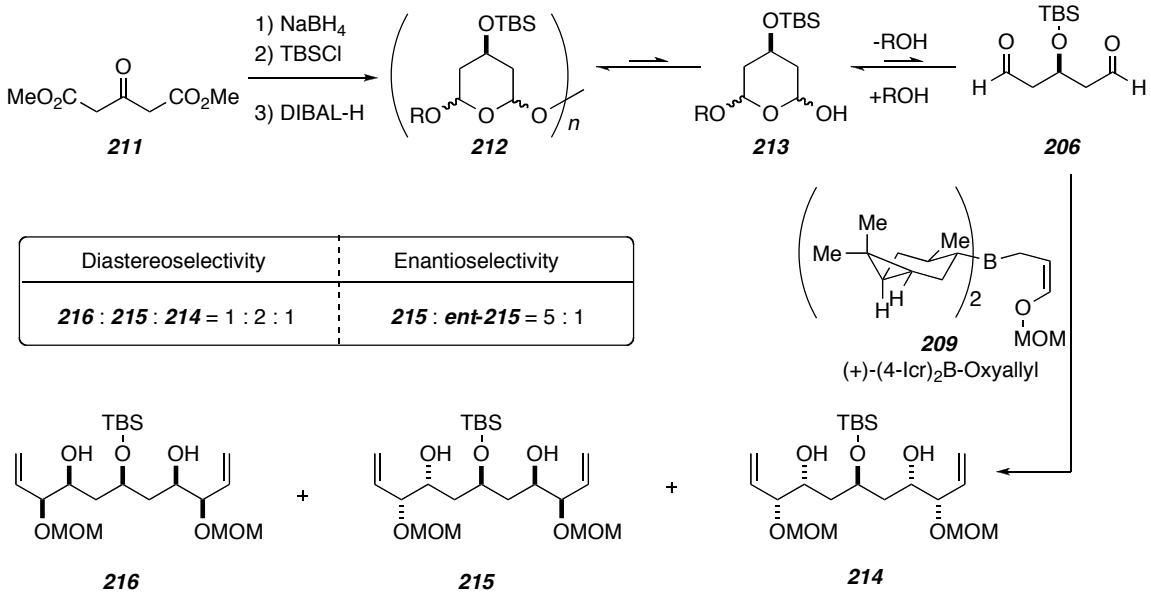


Before the oxyallylation could be attempted, dialdehyde **206** needed to be prepared. The Sammakia group was kind enough to provide a protocol for its preparation. The commercially available dimethylacetone dicarboxylate (**211**) was reduced with sodium borohydride ($NaBH_4$) and the resulting carbinol was protected as the TBS-ether (**Scheme 52**). Double reduction of the esters to the corresponding aldehydes occurred uneventfully to give dialdehyde **206** and hemiacetals **213**. Upon standing, dialdehyde **206** was converted into what was believed to be **213** or polymer **212**. Fortunately, upon heating the viscous oil under vacuum, dialdehyde **206** was reformed. Adding freshly prepared dial **206** to 2.2 equivalents of borinate **209** at -78 ºC produced the double oxyallylated products in good yield (70-85%) and modest diastereoselectivity. A 1:2:1 ratio of diastereomers **216**:**215**:**214** were routinely obtained regardless of reaction conditions. However, these diastereomers were easily separated by flash chromatography, allowing for Mosher ester analysis of the desired product **215**. Unfortunately, analysis of the data revealed a modest 5:1 ratio of enantiomers. Without the possibility of increasing the *ee* by crystallization, the oxyallylation route would not be

useful for an enantioselective synthesis of (+)-peloruside A **1**, therefore another route needed to be explored.

Scheme 52

T. Ryba (2005): Double Oxyallylatiion



Before devising another strategy for the synthesis of azelaic ester **192**, Ryba optimized and pushed material through the low-yielding double oxyallylation in an effort to investigate the lactonization on a peloruside-relevant substrate. The synthesis of the lactonization precursor **192** continued with the double methylation of diol **215** (**Scheme 53**). This was followed by the conversion of both alkenes to their corresponding methyl esters in one-step using a procedure developed by Marshall.[63] Removal of the TBS-ether with hydrogen fluoride (HF) in acetonitrile occurred uneventfully to provide pseudosymmetric azelaic ester **218**.

Ryba next surveyed a variety of catalysts in three different solvents (C_6D_6, $CDCl_3$, and THF-*d8*) to promote the diastereoselective lactonization.[56,64] After inspection of the data, there seemed to be no correlation between the solvent polarity and

[63] (a) "Oxidative cleavage of mono-, di-, and trisubstituted olefins to methyl esters through ozonolysis in methanolic sodium hydroxide." Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675-3680. (b) "The direct conversion of olefins into esters through ozonolysis." Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett.* **1992**, 643-645.

[64] "Divergent kinetic control of classical versus ozonolytic lactonization: Mechanism-based diastereoselection." Hoye, T. R.; Ryba, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 8256-8257.

diastereoselectivity. Although C_6D_6 produced the largest ratio of **219-*cis*** to **219-*trans***, it was a negligible difference. The three catalysts that were the most efficient in promoting the diastereoselective lactonization were DBU, DBN, and TMG (**Scheme 53**, **Figure 4**, **Table 1**). All three catalysts provided high diastereoselectivity, but the rates were considerably different. DBU was significantly faster at promoting the lactonization; however, the desired product would decompose if it remained subjected to the reaction conditions for an extended period of time. No decomposition by-products were ever isolated, but it was speculated that these compounds were the result of epimerization and/or elimination. Both TMG and DBN were less destructive to the product lactones and proceeded with little or no decomposition. The reactions were eventually optimized and reported to routinely provide ~90% yield of the desired **219-*cis*** lactone.

Scheme 53

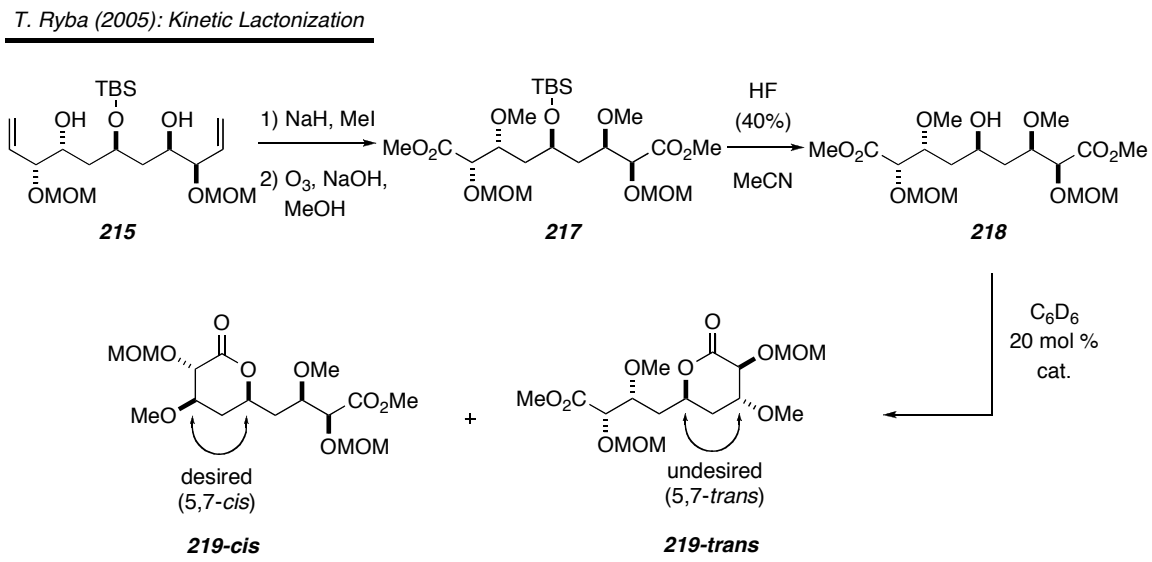


Figure 4

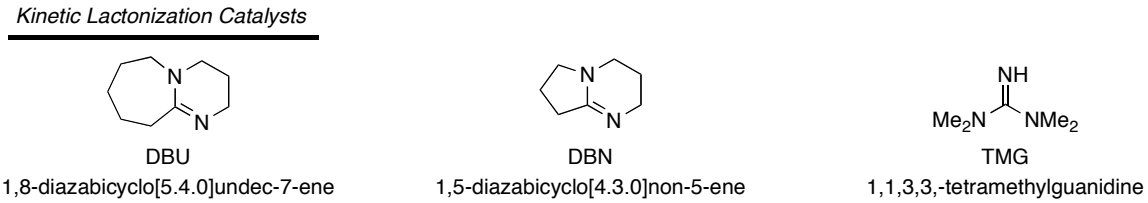


Table 1

T. Ryba (2005): Kinetic Lactonization Ratios (Methyl)

Catalyst	Time (h)	Lactone Ratio (***219-cis*:*219-trans***)
DBU	15	10 : 1
TMG	40	13 : 1
DBN	40	10 : 1

For a detailed rationalization of the resulting diastereomeric ratios, one is again referred to T. Ryba's Ph.D. thesis,[56] as well as Hoye's and Ryba's 2005 *J. Am. Chem. Soc.* article.

After gaining knowledge from performing the kinetic lactonization on a peloruside A relevant substrate, Ryba again focused his efforts toward designing a new route to the synthesis of bis-ester **192**. He eventually arrived at a bidirectional assembly of a bis-α,β-unsaturated ester via a modification of a Takacs protocol.[65,66] The ketal **220** was cooled to -78 ºC and DIBAL-H was added, forming the bis-tetrahedral intermediate **221** (**Scheme 54**). A THF solution of the sodium salt of triethylphosphonoacetate **222** was added to the ethereal solution of **221** and warmed slowly to ambient temperature. Upon workup and purification the ketal diene **223** was formed in excellent yield.

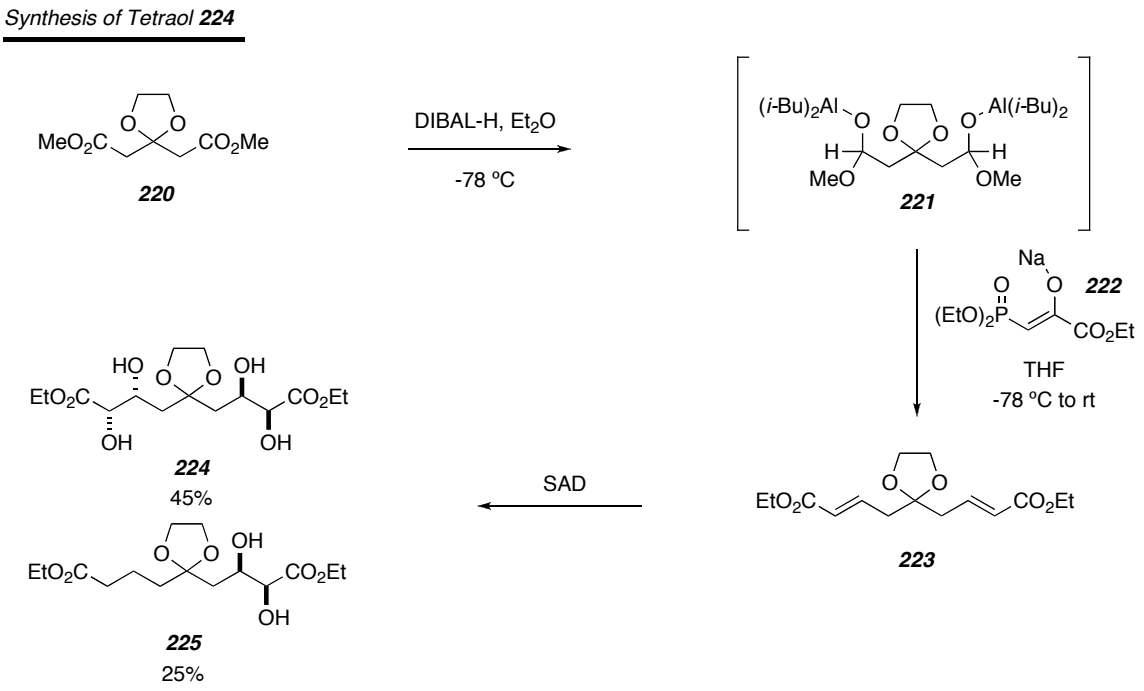
[In an effort to expand on this methodology, I joined T. Ryba on this project to investigate producing various unstable dial substrates *in situ* and capturing them with various nucleophiles. This research has been published in *Synthesis* and will be discussed in Appendix A.]

The diene **223** was next subjected to double Sharpless asymmetric dihydroxylation, only to produce poor yields of tetraol **224 (**45%) and diol **225** (25%).[34] After thinking more in depth about the mechanism and reviewing the literature, Ryba had come to the conclusion that the water solubility of diol **225** resulted in its low conversion

[65] "An improved procedure for the two carbon homologation of esters to α,β-unsaturated esters." Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257-1260.
[66] "In situ generation and nucleophilic capture of 1,n-dial equivalents from 1,n-dioates (α,ω-diesters)." Hoye, T. R.; Kopel, L. C.; Ryba, T. D. *Synthesis* **2006**, 1572-1574.

into tetraol **224**.[67] His solution was to change the solubility of the diene, making it more hydrophobic by switching the carbon chain length on the esters.

Scheme 54

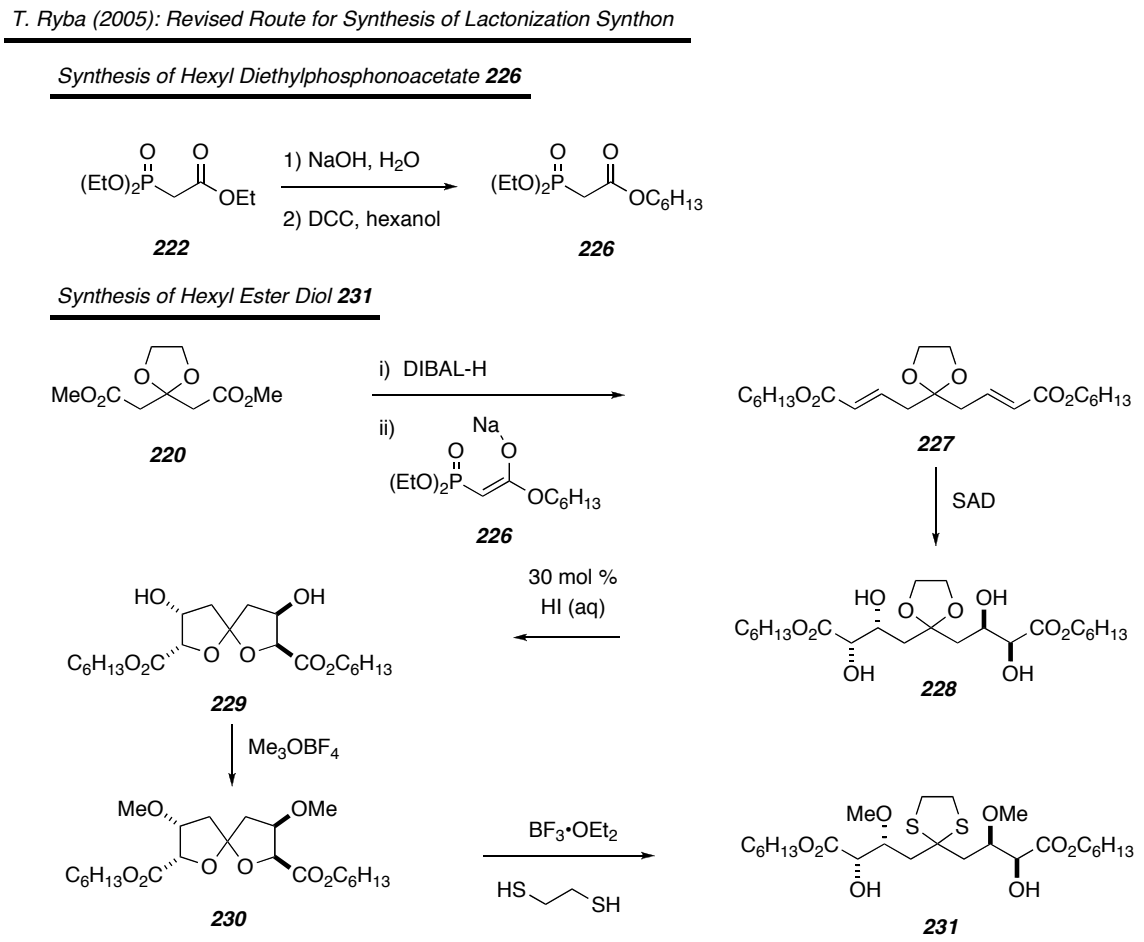


To do this, he first hydrolyzed **222** to its acid with aqueous sodium hydroxide. The acid was then subjected to N,N-dicyclohexylcarbodiimide (DCC) coupling with hexanol to provide hexyl diethylphosphonoacetate **226** (**Scheme 55**).[68] Performing the double one-pot DIBAL-H mediated reduction/HWE olefination of ketal **220** with phosphonoacetate **226** gave the desired diene **227**. The SAD on the less polar bis-hexyl ester **227** proceeded as expected to afford tetraol **228**. Spirocyclization of tetraol **228** was achieved using an aqueous hydroiodic acid (HI) solution to furnish spirocycle **229** as thin white crystals. This was the first time an intermediate showed any signs of crystallinity. The hydroxyl groups on the spirocycle were then methylated using Meerwein's salt

[67] "Total asymmetric synthesis of ethyl D-ido-4-heptulosuronate derivatives starting from diethyl 4-oxopimelate." Lemaire-Audoire, S.; Vogel, P. *Tetrahedron: Asymmetry*. **1999**, *10*, 1283-1293.
[68] "Synthesis of verrucarin J." Roush, W. R.; Blizzard, T. A. *J. Org. Chem*. **1983**, *48*, 758-759.

(Me_3OBF_4) to provide **230**. Transketalization of spirocycle **230** was performed using BF_3•OEt_2 in neat 1,2-ethanedithiol to provide dithiane **231**.[69]

Scheme 55



Due to the simple fact that Ryba had performed his lactonization studies with MOM protected α-hydroxyls, he protected the hydroxyls of dithiane **231** as MOM-ethers (**Scheme 56**).[70] This protection was also a preventative measure against cyclizing back to **230**. Deprotection of the dithiane occurred using buffered iodine in acetone-water to

[69] "Macrolide total synthesis. The synthesis of spiro ketal intermediates and their cleavage into open-chain derivatives." Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303-1312.

[70] "A new preparation of chloromethyl methyl ether free of bis(chloromethyl) ether." Amato, J. S.; Karady, S.; Sletzinger, M.; Weinstock, L. M. *Synthesis* **1979**, 970-971.

yield ketone **233**.[71] Exposing ketone **233** to Raney-Nickel under 40 atm of hydrogen provided carbinol **234**.

Like before, a variety of catalysts and solvents were screened to study the diastereoselectivity of the lactonization. The nonpolar solvent C_6D_6 provided the best diastereoselectivity and the overall trends in catalyst behavior were similar to those observed previously. DBN proved to be the best catalyst (1:0 ; **235-*cis***:**235-*trans*** at 70% conversion), only because DBU (10:1 ; **235-*cis*** : **235-*trans*)** often promoted major side-product formation (**Scheme 56**, **Table 2**). The absolute reaction rate turned out to be much slower in the hexyl series than it was with the methyl ester series. Interestingly, the lactonization using DBN seemed to slow down after approximately 75% conversion. At this point in time, it was unclear what the exact reason for the difference in reactivity between the hexyl and methyl series was, but T. Ryba's work on this project had come to an end along with his stay in the Hoye group. It was at this point where I picked up where he had left off.

[71] "Total synthesis of brevetoxin A: Part 1: First generation strategy and construction of BCD ring system." Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S. H.; Somers, P. K.; Wallace, P. A.; Chu, X. J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. A Eur. Jour.* **1999**, *5*, 599-617.

Scheme 56

T. Ryba (2005): Revised Route for Synthesis of Lactonization Synthon

*Synthesis of Hexyl Ester Lactone **235-cis***

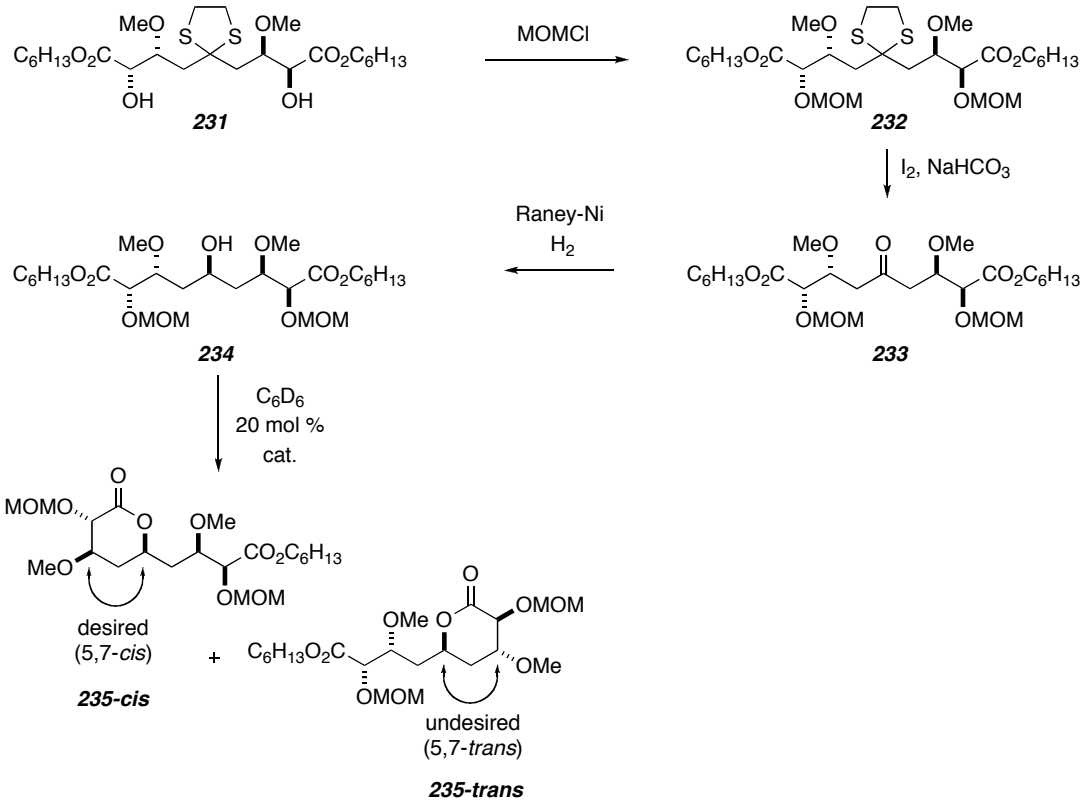


Table 2

T. Ryba (2005): Kinetic Lactonization Ratios (Hexyl)

Catalyst	% Conv.	Time	Lactone Ratio (***235-cis***:***235-trans***)
DBU	100	3 days	10 : 1
TMG	<10	3 days	ND
DBN	70	3 days	1 : 0

IV. Scale-Up and Optimization of T. Ryba's Synthetic Route to the C1-C9 Fragment of (+)-Peloruside A

A. Synthesis of C1-C9 Hexyl Ester Lactone

My endeavor on the synthesis of the C1-C9 segment (+)-peloruside A **1** started shortly before T. Ryba left the Hoye group. The speed with which I was able to come up to pace was definitely helped by his expertise and knowledge. I began by performing the same reactions he had done before. I synthesized the hexyl diethylphosphonoacetate **226** in the same manner, by saponification with sodium hydroxide and DCC coupling with hexanol. Fortunately, I learned from Ryba's experiences and was extra cautious not to have the same reaction to DCC, as he broke out in a serious rash. This was one of the reasons I wanted to revisit the synthesis of the hexyl diethylphosphonoacetate **226**. The difficulty experienced in removing excess DCC and the urea by-product when performing large scale workup procedures were additional reasons. One common way of making various phosphonoacetates is through an Arbuzov reaction, in which an alkyl bromoacetate is reacted with trialkylphosphite with heating.[72] In order to try this reaction, I needed to synthesize the noncommercially available hexyl bromoacetate **238**. Subjecting commercially available methyl bromoacetate **236** to hexanol and Otera catalyst **237** in refluxing toluene produced the desired hexyl bromoacetate **238** in 92% yield (**Scheme 57**).[73]

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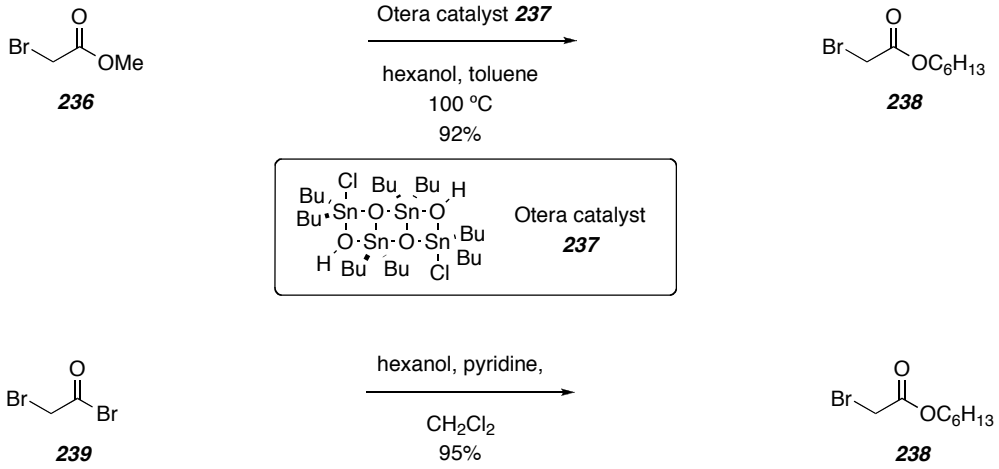
[72] "Michaelis-Arbuzov rearrangement." Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415-430.

[73] (a) "Mild and practical acylation of alcohols with esters or acetic anhydride under distannoxane catalysis." Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899-2910. (b) "Novel effects of distannoxane catalysts in highly efficient transesterification and esterification." Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56,* 5307-5311.

Scheme 57

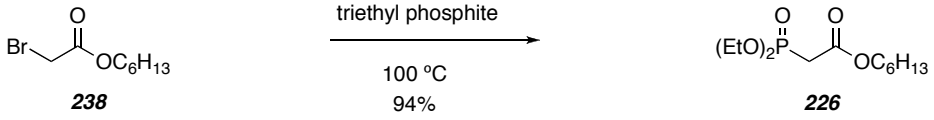
*Synthesis of Hexyl Bromomacetate **238** (LCK)*



A simple acylation of hexanol with bromoacetyl bromide (**239)** also provided hexyl bromoacetate **238** in high yield (95%) (**Scheme 57**). Hundreds of grams of hexyl bromoacetate **238** could be made via this acylation route and used in the following reaction without any purification. Hexyl bromoacetate **238** was slowly added to a neat solution of triethylphosphite at 100 ºC (not a closed system) to provide pure hexyl diethylphosphonoacete **226** after distillative removal of the triethylphosphate by-product (**Scheme 58**). There was a red color to the hexyl diethylphosphonoacetate **226** that could be removed by filtration through silica gel, but this proved to be unnecessary.

Scheme 58

*Synthesis of Hexyl Diethylphosphonoacetate **226** (LCK)*

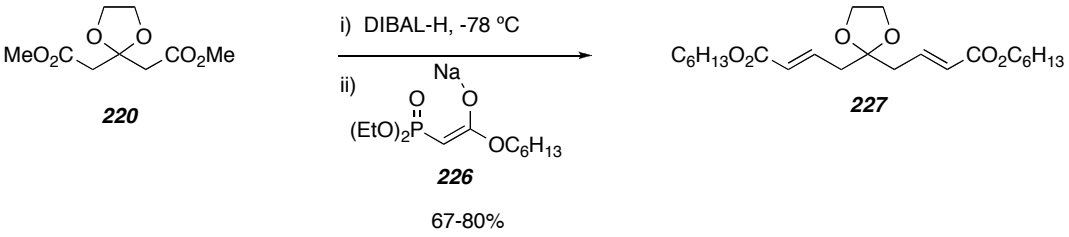


Having completed the Arbuzov reaction to form phosphonacetate **226**, it was then used in the one-pot double reduction/HWE olefination to form diene **227** without any problems (**Scheme 59**). The same modified Takacs protocol that Ryba had initially used was followed.[65,66] Unfortunately, attempts to use more than 10 grams of ketal **220** in the reaction resulted in lower isolated yields of diene **227**. Optimally, 10 grams of ketal **220**

(45.8 mmol), DIBAL-H (100.8 mmol) 38.5 grams of hexyl diethylphosphonoacetate **226** (137.4 mmol), and 3.08 grams of sodioum hydride (NaH) (2.8 mmol) were used. These reaction conditions typically led to yields ranging from 67-80% with manageable reaction times. It was imperative that titration of the DIBAL-H occur prior to use or the mono-homologated product would be isolated in substantial quantities.[74]

Scheme 59

*Synthesis of Diene **227** (LCK)*

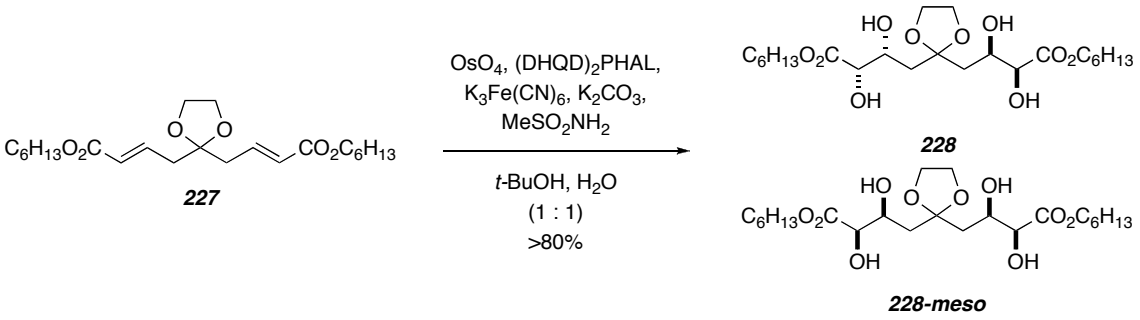


The next process that needed to be scaled-up was the SAD of dienoate **227** (**Scheme 60**).[34] Only slight variations were made to the procedure implemented by Ryba. Osmium tetroxide was used (carefully-highly toxic) instead of the potassium osmate (VI) dihydrate. The percent osmium was reduced from 2 mol% to 1 mol% in an effort to minimize the cost associated with osmium. The $(DHQD)_2PHAL$ ligand was also reduced from 2.6 mol% to 2 mol%. The reduction in osmium resulted in a longer reaction time, usually reaching full conversion after 72 hours. Unlike Ryba's SAD, the *meso* tetraol **228** was observed in varying quantities by crude ^1H NMR. It was unnecessary to separate *meso* tetraol **228-*meso*** and the desired tetraol **228**, since purification could be achieved through recrystallization after the spirocyclization.

[74] "Reaction titration: A convenient method for tittering reactive hydride agents (Red-Al, $LiAlH_4$, DIBALH, L-Selectride, NaH, and KH) by No-D NMR Spectroscopy." Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D. *Org. Lett.* **2005**, *7*, 2205-2208.

Scheme 60

*Synthesis of Tetraol **228** (LCK)*



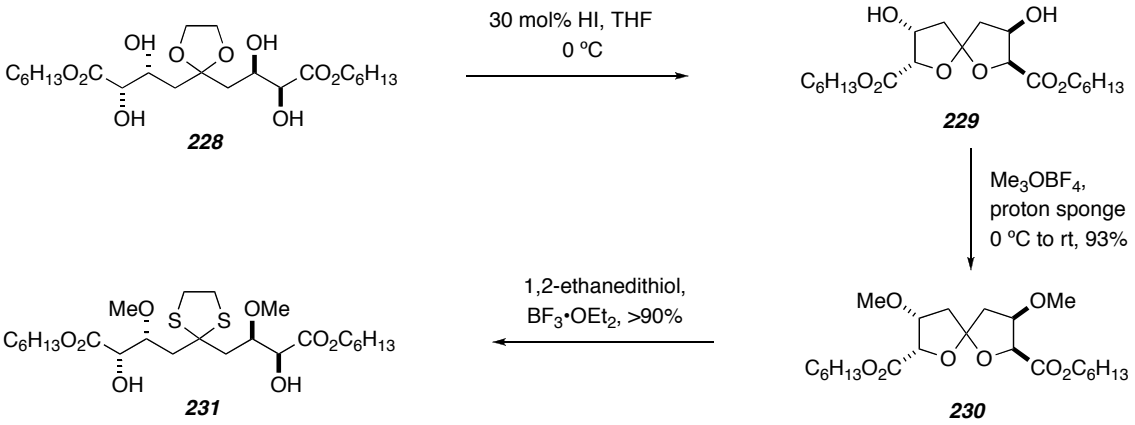
With the mixture of tetraols **228** and **228-*meso*** in hand, spirocyclization was performed following Ryba's procedure using an HI solution in THF (**Scheme 61**). No problems were observed during multi-gram scale reactions. The resulting spirocycle **229** was recrystallized following Ryba's protocol, layering a warm ethyl acetate solution of **229** with hexanes. Diethyl ether could be substituted for ethyl acetate, producing similar results.

The hydroxyl groups of spirocycle **229** were methylated using Meerwein's salt as before (**Scheme 61**). However, the molar equivalents were increased from 3 to 4 to provide bis-methyl ether **230** in 93% yield. The reaction was warmed to room temperature to reach complete conversion instead of keeping the reaction at 0 ºC. It was necessary to purify the crude material immediately after workup or decomposition would occur.

Treatment of spirocycle **230** with BF_3•OEt_2 in 1,2-ethanedithiol produced diol **231** in reproducible yields of >90% (**Scheme 61**). The same procedure laid out by Ryba was followed; however, a significant amount of 1,2-ethanedithiol remained after workup. It was initially removed by vacuum distillation using a water aspirator. Eventually, a decision was made to remove it with a high vacuum rotovap equipped with a sequence of two dry ice traps (a rotovap was set up in a fume hood to minimize exposure to the stench from the 1,2-ethandithiol; this is highly recommended). The opening of the spirocycle **230** was run on multi-gram scale with no reduction in yield and the resulting diol **231** was capable of being carried forward without purification.

Scheme 61

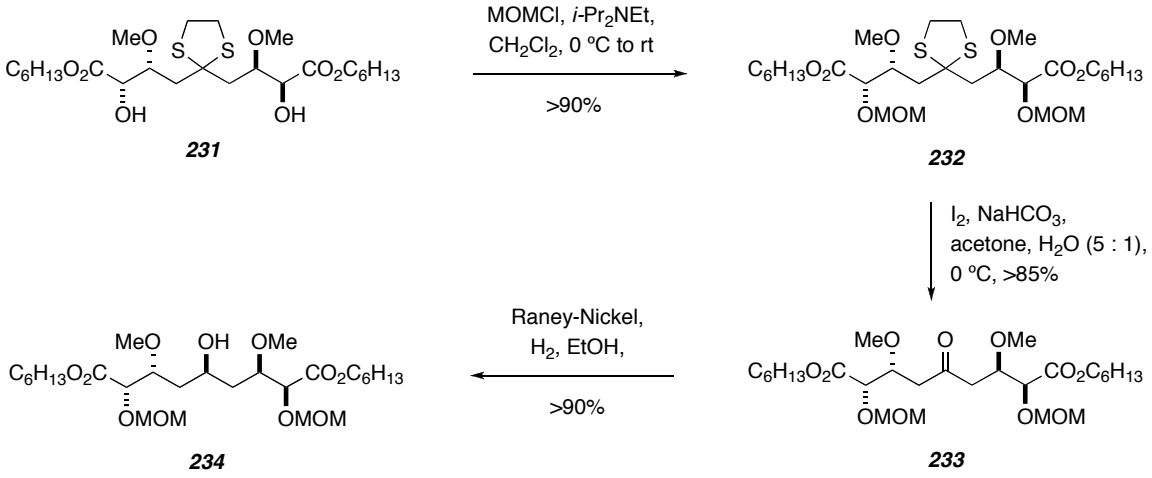
*Synthesis of Dithiane-Diol **231** (LCK)*



The resulting diol **231** was subjected to the same three-step sequence of reactions to produce pseudosymmetric ester **234** as before: MOM-ether formation, oxidative removal of the dithiane, and reduction of the resulting ketone with an ethanolic solution of Raney-Nickel under a H_2 atmosphere (**Scheme 62**). The only difference between what Ryba had reported and what I did was sometimes I added additional equivalents of reagents if the reaction was proceeding too slowly.

Scheme 62

*Synthesis of Pseudosymmetric Hexyl Ester **234** (LCK)*

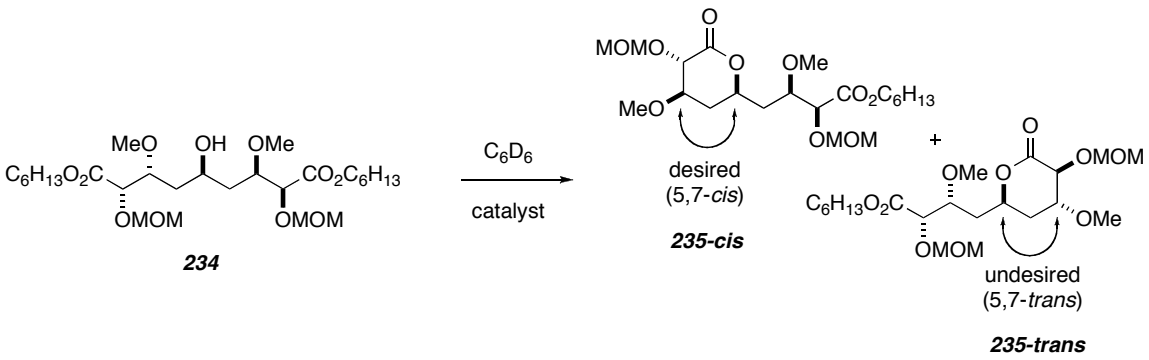


After synthesizing a suitable quantity of carbinol **234**, it was now time to reinvestigate the kinetic lactonization and answer some of the questions that remained

from Ryba's initial screenings. Ryba's initial results pointed towards using DBN as the catalyst and deuterated benzene (C_6D_6) as the solvent. So when I began to perform my initial screening of conditions for the kinetic lactonization of carbinol **234**, I chose to use DBN (30 mol%, same as Ryba) as the catalyst in deuterated benzene (C_6D_6) and change the concentrations: 0.1 M, 0.025 M, and 0.005 M (**Scheme 63**). It is important to note that these initial reactions were conducted in nuclear magnetic resonance (NMR) tubes and monitored by ^{1}H NMR.

Scheme 63

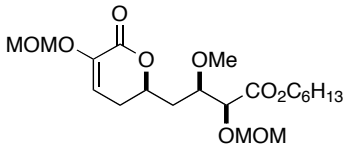
*Revisit Kinetic Lactonization Conditions for Hexyl Ester **234** (LCK)*



The more dilute conditions resulted in better diastereoselectivity and cleaner reactions. However, I experienced the same problems that Ryba encountered as the reaction progressed. The lactonization appeared to stop around 70% conversion and the spectrum would become complex, as what was believed to be by-products from epimerization and elimination would grow in. At this point in time I was not concerned about reaction yields, I only wanted to determine if the two lactones **235-*cis*** and **235-*trans*** were separable. I was fortunate enough to separate both lactones **235-*cis*** and **235-*trans***, along with the by-product α,β-unsaturated lactone **240** using MPLC (**Figure 5**). At the time, the isolation of **240** still led me to believe that the complexity of the spectrum was a result of the formation of unwanted by-products. Due to the difficulty in separating the starting carbinol **234** from the products **235-*cis*** and **235-*trans***, the problem with the lactonization reaching 100% conversion needed to be solved.

Figure 5

*Isolated By-Product from Hexyl Ester **234** Kinetic Lactonization (LCK)*



240

In an attempt to reach full conversion, the kinetic lactonization was performed at 0.005 M and 0.0025 using C_6D_6, while varying the molar ratio of DBN used as the catalyst.

Table 3

Kinetic Lactonization of 234 Using DBN at 0.005 M in C_6D_6

mol % DBN	2 h	4 h	7 h	18 h	19 h	32 h
60	-	8% conv	-	17% conv	-	25% conv
100	-	12% conv	-	22% conv	-	33% conv
200	-	15% conv	-	29% conv	-	50% conv
400	24% conv	-	50% conv	-	70% conv	-
800	33% conv	-	59% conv	-	90% conv	-
1000	39% conv	-	64% conv	-	90% conv	-
1500	37% conv	-	71% conv	-	90% conv	-

Table 4

Kinetic Lactonization of 234 Using DBN at 0.0025 M in C_6D_6

mol % DBN	2 h	4 h	7 h	18 h	19 h	32 h
50	-	4% conv	-	10% conv	-	17% conv
100	-	11% conv	-	16% conv	-	23% conv
200	-	12% conv	-	23% conv	-	34% conv
500	-	18% conv	-	34% conv	-	52% conv
1000	30% conv	-	50% conv	-	70% conv	-
1500	33% conv	-	59% conv	-	90% conv	-
2000	34% conv	-	66% conv	-	90% conv	-

As you can see in **Table 3** and **Table 4**, increasing the molar equivalents of DBN did increase the rate of the reaction, however full conversion was never achieved under these conditions. Could the percent conversion problem that I am having come strictly from the sterics associated with changing from the methyl ester carbinol **218** to the hexyl

ester carbinol **234**? It was after performing the previous sets of experiments and thinking about this question, that I started to piece things together. While interpreting the spectra from the DBN molar ratio experiments, I observed that as the ratio of DBN increased, so too did the peaks that I initially assigned as being associated with by-products. Upon purification of the crude mixture from the lactoniztion experiments, I did not observe an appropriate mass balance ratio between products and by-products when compared to what was observed by ^{1}H NMR. With this analysis of the information, the hypothesis was made that the DBN was reacting with the lactone products to form a non-isolable complex and consuming the DBN. This would account for the failure of the reaction to reach 100% conversion when <100 mol% of catalyst was used. In order to test this, some control experiments needed to be run.

Shortly after screening for an optimal molar equivalent of DBN, I conducted another round of experiments, the results of which can be seen in **Table 5**. The idea was to obtain the largest percent conversion possible (with the best diastereoselectivity), then treat with trifluoroacetic acid (TFA). In all of the previous lactonizations with TFA, there was never a problem reaching complete conversion to product, only low diastereoselctivity for the desired lactone **235-*cis***. I reverted back to using 30 mol% DBU in C_6D_6 at three different molarities, following conditions outlined by Ryba to obtain 100% conversion when starting with hexyl ester **234**. According to his data, lactonization of hexyl ester **234** with 30 mol% DBN in C_6D_6 (0.1 M) reached 100% conversion after 3 days. Unfortunately, all three reactions I ran had not yet reached full conversion after 7 days, with the closest being the 0.1 M solution at 95% conversion. On day seven, 60 mol% of TFA was added to the reaction mixture. After 3 hours, the ^{1}H NMR spectra were taken and it was determined that all three reactions had reached 100% conversion to produce lactones **235-*cis*** and **235-*trans*** in varying degrees of diastereoselectivity. I made an interesting obsevation when looking at the spectra, the complexity present in the spectra before the addition of TFA (initially believed to be due to by-product formation) was gone. This gave some additional evidence to support my previous hypothesis that the amine catalyst was reacting with the lactone products and in

the process stopping percent conversion. Upon treatment with TFA, the amine-product complex then broke down to reform the desired lactone products.

Table 5

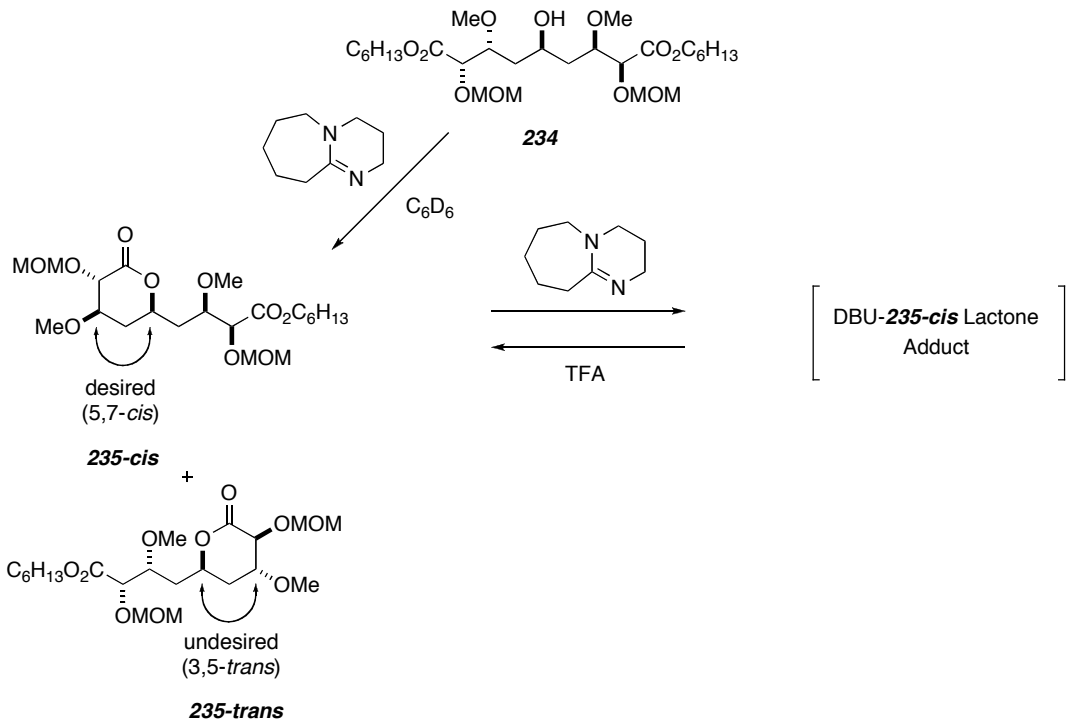
Kinetic Lactonization of 234 Using 30 mol% DBU in C_6D_6

Molarity	28 h	7 days	3 h after 60 mol% TFA added on day 7
0.1	25% conv	95% conv	100% conv (4:1 *cis*:*trans*)
0.025	21% conv	29% conv	100% conv (6:1 *cis*:*trans*)
0.005	15% conv	20% conv	100% conv (9:1 *cis*:*trans*)

With all of the evidence before me, I needed to subject the pure lactones **235-*cis*** and **235-*trans*** to the amine catalyst (DBU was chosen because of its rate of reaction). As expected, treatment of **235-*cis*** with 1 equivalent of DBU in C_6D_6 (after 3 hours) produced the same complex mixture of peaks seen in previous ^{1}H NMR spectra. Treatment of this sample with 1 equivalent of TFA, removed the undesired peaks from the spectrum and converted all of the sample back to **235-*cis***. While subjecting **235-*trans*** to the same 1 equivalent of DBU in C_6D_6 (after 3 hours), resulted in no change. So what does this mean? I believe this information supports the idea that the additional peaks (peaks not correlated to product) are in fact coming from an amine-product complex (likely involving only **235-*cis***) and upon treatment with TFA, this adduct collapses to regenerate the desired lactone product (**Scheme 64**).

Scheme 64

DBU-5,7-cis Lactone Adduct Formation (LCK)



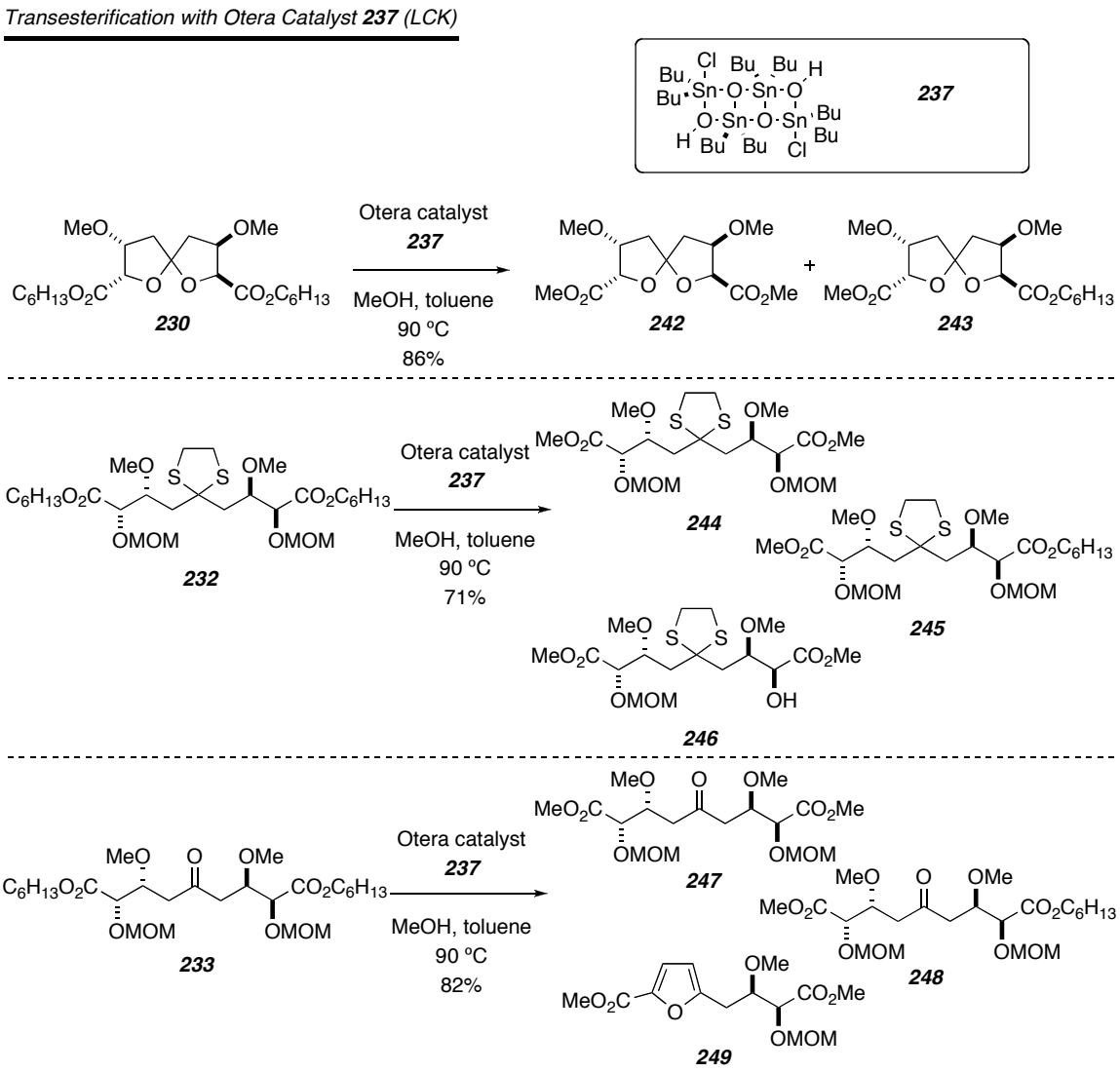
With the apparent selectivity of DBU towards adduct formation with the **235-*cis*** lactone, one should be able to take advantage of this. The problem is, without reaching full conversion during the lactonization, I won't be able to obtain the high levels of diastereoselctivity that I could otherwise achieve. This includes using the two-step process i) DBU or DBN ii) TFA. The two-step sequence leaves too much room for error and variability in the selectivity ratios. To solve this dilemma, I was going to revisit the diastereoselective lactonization of methyl ester **218**, first studied by Ryba during his first round of lactonization studies.

B. Synthesis of C1-C9 Methyl Ester Lactone

Before I could revisit the lactonization the methyl ester carbinol **218**, I needed to convert the hexyl esters to methyl esters at some stage of the sequence after the SAD and before the ketone reduction. Due to the mild nature of the reaction conditions and Ryba's recommendation for performing transesterifications, I chose to use Otera catalyst **237**.[56,73] Transesterification of methyl-ether **230**, dithiane **232**, and ketone **233** to their respective bis-methyl esters occurred in decent yields along with ~10% of the mono-methyl esters

(**Scheme 65**). A trace amount of the alcohol **246** and furan **249** were isolated as a result of MOM-ether deprotection during the reaction. The methyl esters were shown that they could be formed with any of these compounds, but the properties that each has and how they would behave during spirocycle opening, MOM protection, and dithiane removal still remained to be seen.

Scheme 65

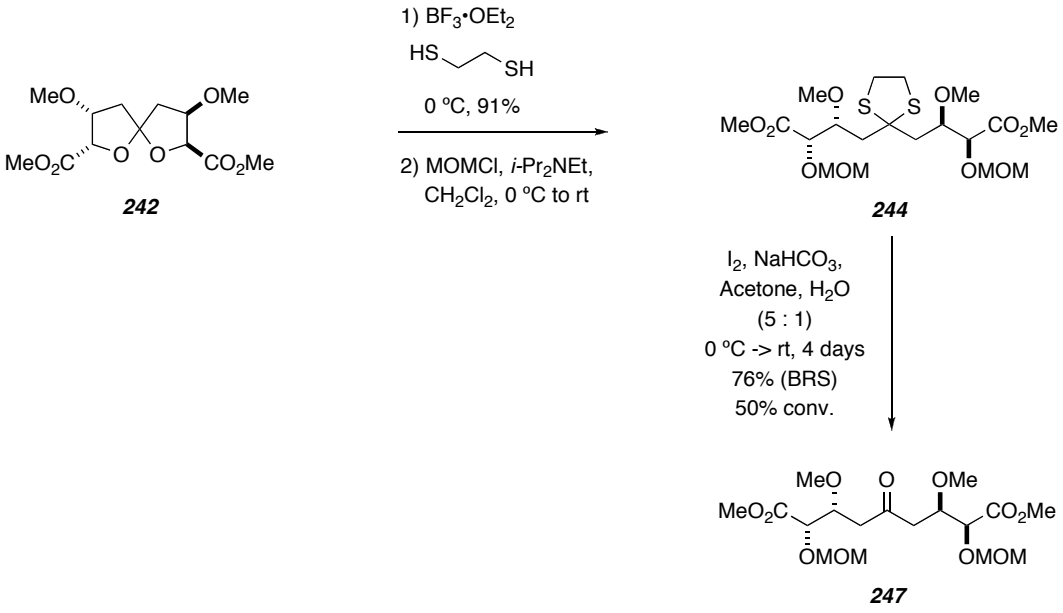


Before the transesterification reaction was performed on large scale, a three-step sequence of converting spirocycle **242** to ketone **247** was conducted (**Scheme 66**). Treating spirocycle **242** with BF_3•OEt_2 in 1,2-ethane dithiol afforded the diol without any problems. The hydroxyls were converted to MOM-ethers to provide dithiane **244**.

Attempting to remove the dithiane from methyl ester **244** under the previous conditions [I_2, $NaHCO_3$, Acetone:H_2O (5:1) at 0 ºC], only produced ketone **247** in 76% yield (BRS, 50% conversion) after 4 days at ambient temperature. The low yield was suspected to be due to a solubility problem, but instead of screening various solvents or deprotection conditions, the decision was made to perform the methyl ester transesterification with ketone **233**.

Scheme 66

Methyl Ester Spiro-Opening / MOM Prot. / Dithiane Deprot.

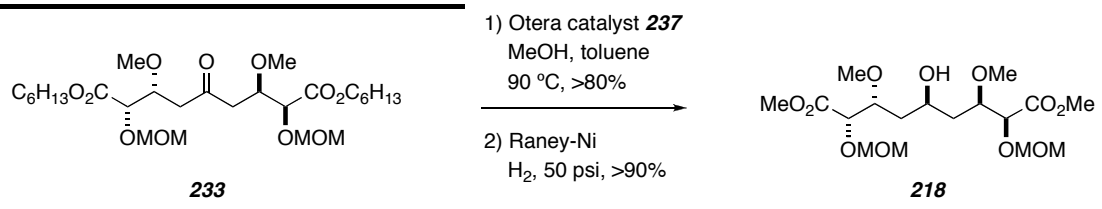


242 ***244*** ***247***

Performing the transesterification of hexyl ester **233** to methyl ester **247** on gram scale resulted in >80% isolated yield (**Scheme 67**). Reduction of the ketone **247** with Raney-Nickel and H_2, routinely produced the pseudosymmetric carbinol **218** in >90% yield. Now I was able to revisit Ryba's procedures and scale-up the kinetic lactonization of methyl ester carbinol **218**.

Scheme 67

Methyl Transesterification / Ketone Reduction (LCK)

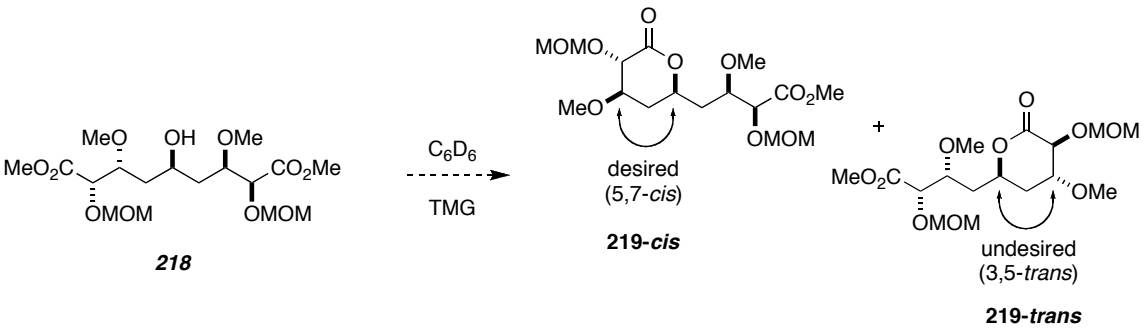


233 ***218***

After looking at the conditions Ryba had screened, it was decided to use 1,1,3,3-tetramethylguanidine (TMG) as the catalyst in C_6D_6 because of its high selectivity for forming the desired product **219-*cis*** (13:1, *cis*:*trans*) (**Scheme 68**).[56,64] TMG was also reported not to have the problems associated with decomposition of product. However, it is now believed that this so-called decompostion was mainly due to an amine-product adduct. Although the rate of the lactonization was reported to be slow when using TMG, it was believed that this problem could be solved using a greater amount of catalyst.

Scheme 68

*Revisit Kinetic Lactonization Conditions for Methyl Ester **219** (LCK)*



The intitial reaction conditions screened can be seen in **Table 6**. Both reactions appeared not to reach full conversion when monitoring by ^{1}H NMR, stalling out at around 80-90 % conversion. However, it was intriguing to find no starting material observable in the crude ^{1}H NMR, after aqueous workup. This led me to believe that the minor amount of remaining carbinol **218** was lactonizing during the workup procedure. I was still able to obtain a modest diastereomeric ratio of ~4:1 favoring **219-*cis***. Considering this, I believed I could obtain a respectable diastereomeric ratio, even if the reaction had not reached full conversion. I then set out to further optimize the lactonization with TMG.

Table 6

Kinetic Lactonization of Methyl Ester 218 with TMG in C_6D_6

eq. TMG / M	1.5 h	3 h	4.5 h	15 h	crude *cis* : *trans* ratio
3.3 eq / 0.076 M	74% conv	8% conv	82% conv	74% conv	83 : 17
6.5 eq / 0.044 M	73% conv	12% conv	88% conv	74% conv	80 : 20

The results from the next set of reactions can be seen in **Table 7**. Previous experience with these lactonization reactions revealed higher ratios in favor of **219-*cis*** vs. **219-*trans*** when using dilute conditions. Therefore, the molarity was reduced to 0.015 M, down from the previous 0.044 M. None of the reactions reached full conversion when monitored by ^{1}H NMR, but after workup high diastereoselectivities and full conversion were obtained. Taking into consideration reaction times and product ratios, the reaction conditions chosen for scale-up were: 1 equiv. carbinol **218**, 2 equiv. TMG, 0.015 M in C_6H_6 and 24 hours reaction time.

Table 7

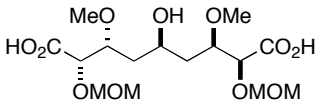
Kinetic Lactonization of Methyl Ester 218 with TMG at 0.015 M in C_6D_6

eq. TMG	5 min	6 h	9 h	23 h	30 h	48 h	crude *cis* : *trans* ratio
0.5	3% conv	35% conv	47% conv	74% conv	78% conv	82% conv	97 : 3
1.0	5% conv	58% conv	71% conv	80% conv	80% conv	80% conv	94 : 6
2.0	6% conv	62% conv	73% conv	88% conv	88% conv	-	95 : 5
3.0	10% conv	74% conv	83% conv	84% conv	84% conv	-	94 : 6
5.0	14% conv	81% conv	85% conv	85% conv	85% conv	-	91 : 9

At this point in time I believed I knew exactly what conditions I needed to provide gram quantities of lactone **219-*cis***. I was mistaken. For a couple of lactoniztion reactions I received lower than expected yields ~50-60%. I should have known better, but this was rather puzzling to me. The cause was eventually traced back to the order of addition of reagents during the workup. If the reaction was diluted with H_2O first, low percent yields were be obtained. While if CH_2Cl_2 was added first, respectable yields of 70-80% were seen. In one of the procedures in which H_2O was added first during workup, I acidified and azeotroped away the water to determine if the product was in the aqueous phase. Subjecting the residue to LC-MS provided evidence for the presence of bis-acid carbinol **250** (**Figure 6**). I will admit that the bis-acid **250** is probably coming during the azeotropic removal of H_2O, but a hypothesis is that the initial solubility problem is from the collapse of the amine-product adduct to form a highly water soluble acid derivative.

Figure 6

By-Product from Lactonization Workup



250

Modifying the workup procedure solved the problem with variations in yield. After 24 hours of reaction time, 1 equiv. of TFA was added and stirred for 3-5 minutes. Then a normal basic workup with aqueous sodium bicarbonate and extraction with CH_2Cl_2 afforded diastereosectivities >9:1 (**219-*cis***:**219-*trans***) and >90 %yields. Large amounts of lactone **219-*cis*** were now able to be formed and could be used to investigate the inversion of the C8 stereocenter and formation of the sterically crowded C9-C10 bond.

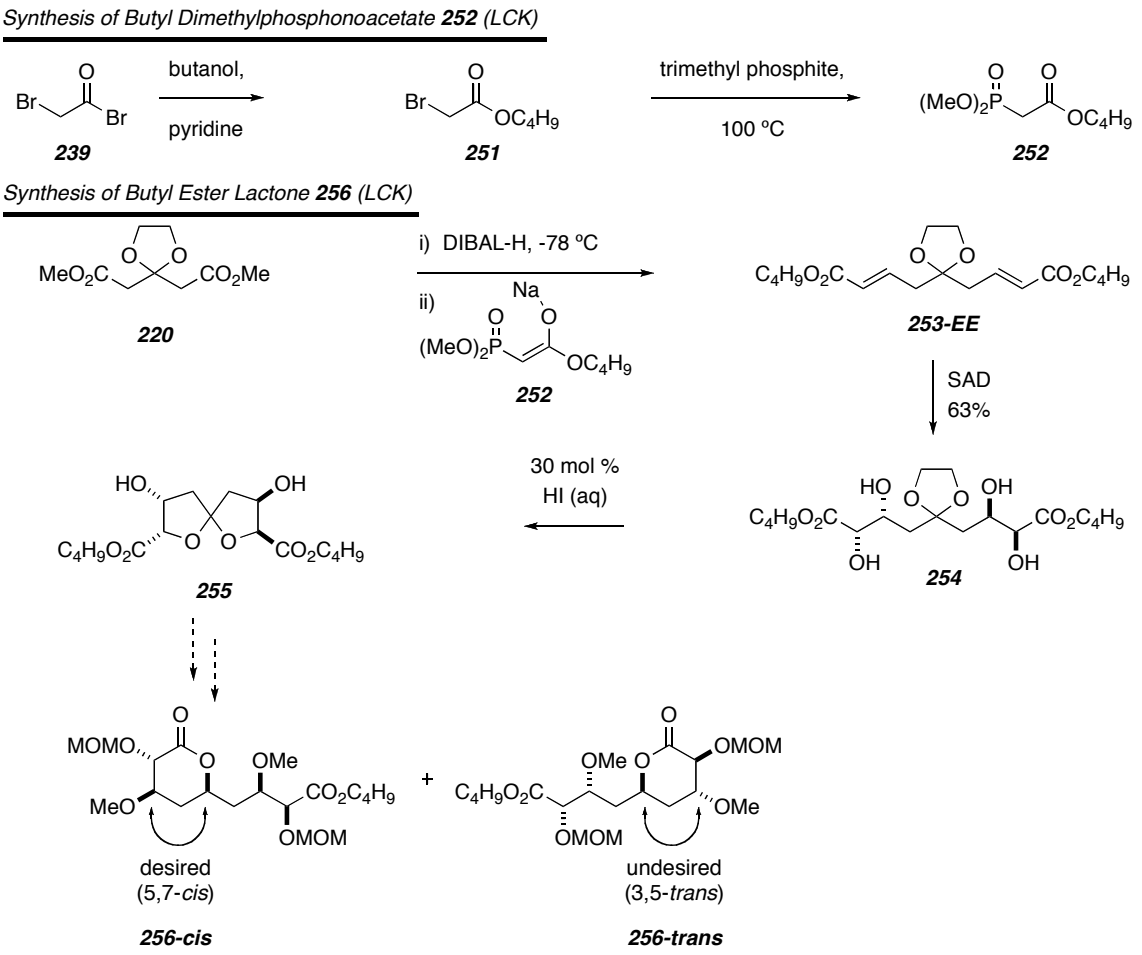
C. Synthetic Efforts Toward C1-C9 Butyl Ester Lactone

Looking at the data of the hexyl ester and methyl ester lactonizations, I began to think that there must be a happy medium between the ester chain length necessary for full conversion during the lactonization and for solubility in the SAD. To answer this question, the butyl series of compounds were chosen as a potential candidate.

The same route to the hexyl compounds was used to create the butyl series. Bromoacetyl bromide **239** was reacted with butanol to afford butyl ester **251** (**Scheme 69**). An Arbuzov reaction with trimethyl phosphite was used to synthesize phosphonoacetate **252**.[72] The bi-directional reduction/HWE olefination with phosphonoacetate **252** produced the desired *E,E*-dienoate **253-*EE*** along with isomeric *E,Z*-dienoate and *Z,Z*-dienoate. It is interesting to note that this is the first time performing this reaction in which the *Z,Z* isomer was ever isolated, even if it was a very minor component. Subjection of dienoate **253-*EE*** to SAD resulted in good mass recovery for the crude tetraol **254**, however only a modest 63% yield was obtained after purification by MPLC. This reaction was only tried once so I am still not yet convinced the low yield was due to the solubility of the tetraol **254** or its diol intermediate. The tetraol **254** was subjected to the HI spirocyclization conditions to provide diol **255**. The

spirocycle **255** was not carried forward, since I had started to focus more of my attention on progress I had made elsewhere.

Scheme 69



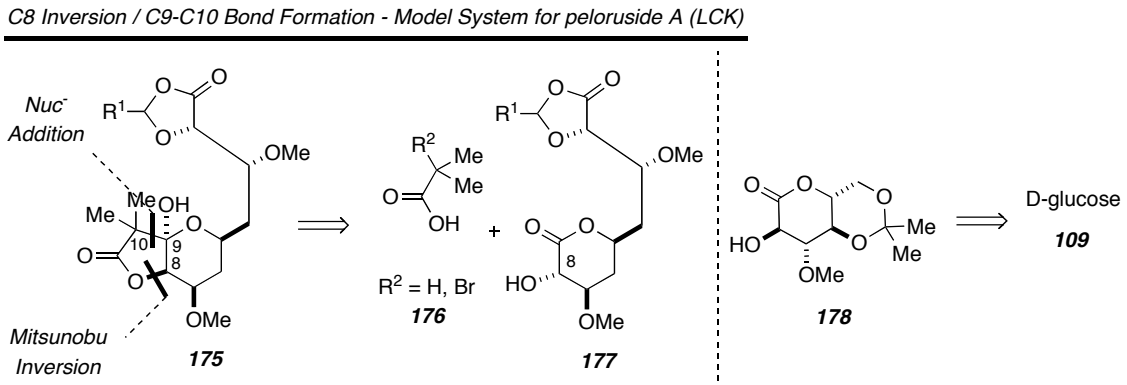
V. New Progress Toward (+)-Peloruside A

A. C8 Inversion Model Studies

1. D-Glucose Derived Lactone Model System

One of my projects in the Hoye group, while working towards the ultimate goal of synthesizing (+)-peloruside A **1**, was to investigate the inversion of the C8 stereocenter and look into the C9-C10 bond formation for application towards a peloruside substrate. The initially proposed synthesis of (+)-peloruside A **1** by Hoye had two potential routes to invert the C8 stereocenter and form the C9-C10 bond (**Scheme 70**). The first one included inversion of the isolated C8 stereocenter using standard Mitsunobu conditions and the appropriate acid followed by an intramolecular Claisen-like addition to form the C9-C10 bond. The other proposed idea was to reverse the order of events and perform an intermolecular Claisen-like addition followed by intramolecular Mitsunobu reaction. Lactone **178**, derived from D-glucose **109**, was believed to be an effective model system to probe these reactions. M. Smalley, an undergraduate working in the Hoye group under the tutelage of graduate student M. Tennakoon, started the initial investigations into this area **(See Chapter 3. A. II.)**. She was able to synthesize lactone **178** and perform the Mitsunobu inversion of the C8-relevant stereocenter using isobutyric acid (**176-H**) and diethylazodicarboxylate (DEAD). I hoped to expand on the knowledge already learned inverting the α-hydroxy stereocenter and screen conditions for forming the C9-C10 bond.

Scheme 70

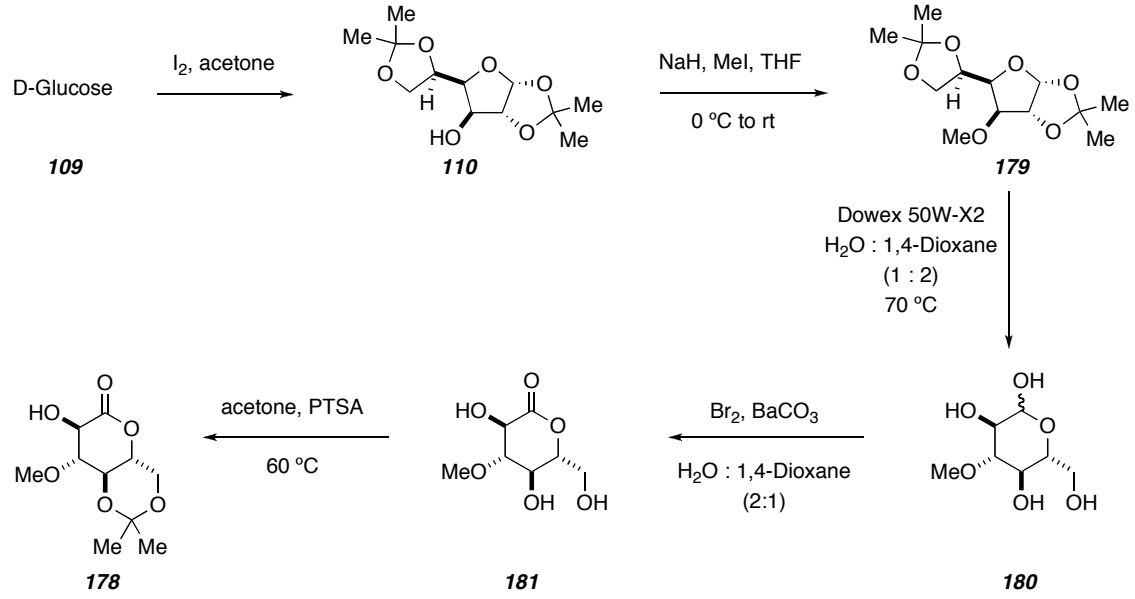


The model lactone **178** needed to be synthesized before a single Mitsunobu reaction could be run. The same general sequence of reactions performed by Smalley

was followed, but with modified conditions (**Scheme 71**). With no commercially available diacetone D-glucose (**110**) readily at hand, D-glucose (**109**) was subjected to iodine in acetone to produce **110** in suitable quantities for what was initially needed.[75] Eventually a commercial source was obtained and used instead. Diacetone D-glucose **110** was methylated with NaH and methyl iodide to produce methyl-ether **179**. Treatent of methyl-ether **179** with strongly acidic Dowex resin in H_2O:dioxane (1:2) removed both acetonides to form hemiacetal **180**. The lactone **181** was produced by the oxidation of hemiacetal **180** with bromine (Br_2).[76] Hemiacetal **180** and lactone **181** were both highly water soluble, therefore no chromatography was performed after their preparation. Protection of the 1,3-diol of **181** as the acetonide was accomplished by treating with PTSA in acetone and heating to 60 ºC. This produced lactone **178**, needed for investigation of the Mitsunobu and Claisen-like addition reactions.

Scheme 71

*Synthesis of Glucose Model Lactone **178** (LCK)*



Smalley previously used isobutyric acid (**176-H**) to perform the α-hydroxy stereocenter inversion of model lactone **178**. In an effort to expand on the work she had

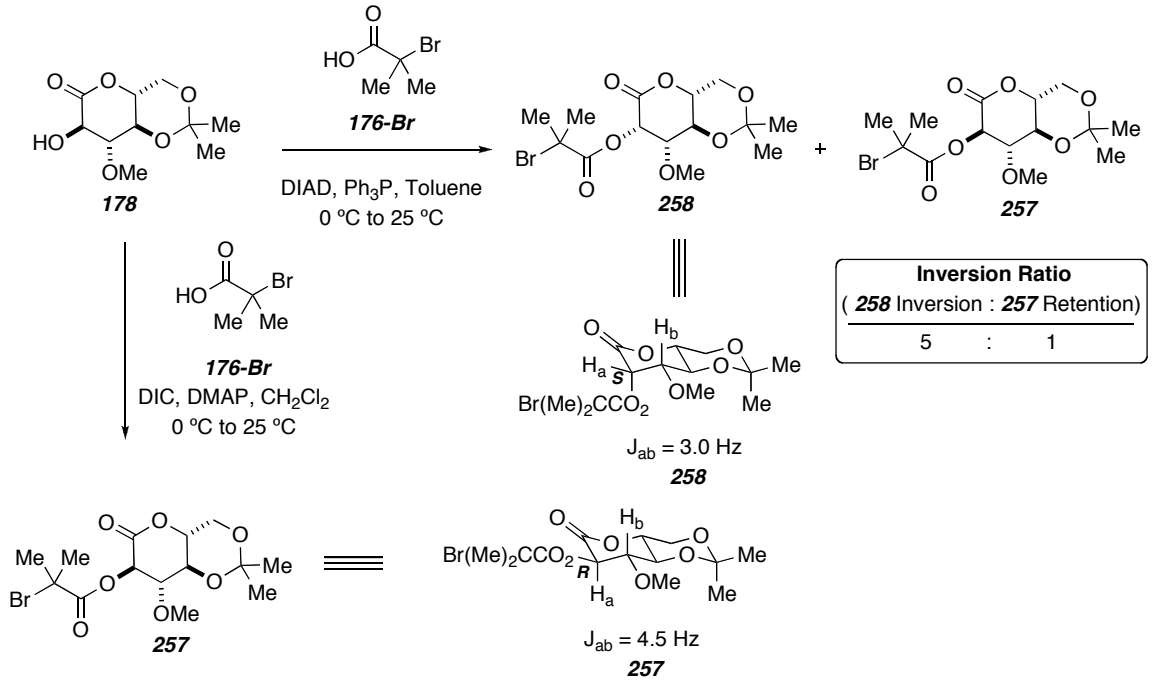
[75] "Iodine, a novel catalyst in carbohydrate reactions. I. O-isopropylidination of carbohydrates." Kartha, K. P. R. *Tetrahdron Lett*. **1986**, *27*, 3415-3416.

[76] "Iodomethyl group as a hydroxymethyl synthetic equivalent: Application to the syntheses of d-*manno*-hept-2-ulose and l-fructose derivatives." Bessires, B.; Morin, C. *J. Org. Chem*. **2003**, *68*, 4100-4103.

done 2-bromoisobutyric acid (**176-Br**) was chosen as the carboxylic acid for the Mitsunobu reaction (**Scheme 72**). After performing the Mitsunobu inversion, the bromine atom would allow for more procedural flexibility in forming the C9-C10 bond. The acylated reference compound needed to be prepared before the inversion reaction could be run. The coupling of model lactone **178** and 2-bromoisobutyric acid (**176-Br**) was performed using a standard 1,3-diisopropylcarbodiimide (DIC) protocol to produce lactone **257**. Availability and ease of transferring a liquid were the only reasons for using DIC instead of the commonly used DCC. After performing the Mitsunobu reaction, the crude ^{1}H NMR revealed a 5:1 ratio in favor of the desired inversion product **258**. Comparing the coupling constants J_{ab} for lactones **257** (retention) and **258** (inversion) with those of compounds **182** (retention) and **183** (inversion) obtained by Smalley revealed inconsistencies with the coupling constant data (**Scheme 72**, **Figure 7**).

Scheme 72

*Inversion of Glucose Model Lactone **178** with 2-Bromoisobutyric Acid (**176-Br**) (LCK)*

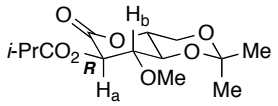


The coupling constant J_{ab} = 4.5 Hz for lactone **257** (retention) does not match the magnitude of coupling constant J_{ab} = 2.5 Hz for lactone **182** (retention). Also, the coupling constant J_{ab} = 3.0 Hz for lactone **258** (inversion) does not match the magnitude

of coupling constant J_{ab} = 5.0 Hz for lactone **183** (inversion). One would typically expect the largest coupling constant for J_{ab} of the retention products **182** and **257** with H_a and H_b both being axial in an idealized chair conformation, while the coupling constants between equatorial H_a and axial H_b for **183** and **258** would be smaller. This indeed turns out to be the case for **257** and **258** but is not for **182** and **183**. The acylation experiment to provide lactone **182** was repeated, only to see the same coupling constant data reported by Smalley. I was, however, never able to reproduce the inversion product **183**. The retention product **182** was consistantly isolated under a variety of Mitsunobu conditions.

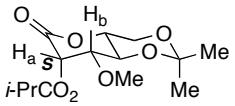
Figure 7

M. Smalley's Inversion Structures



J_{ab} = 2.5 Hz

182



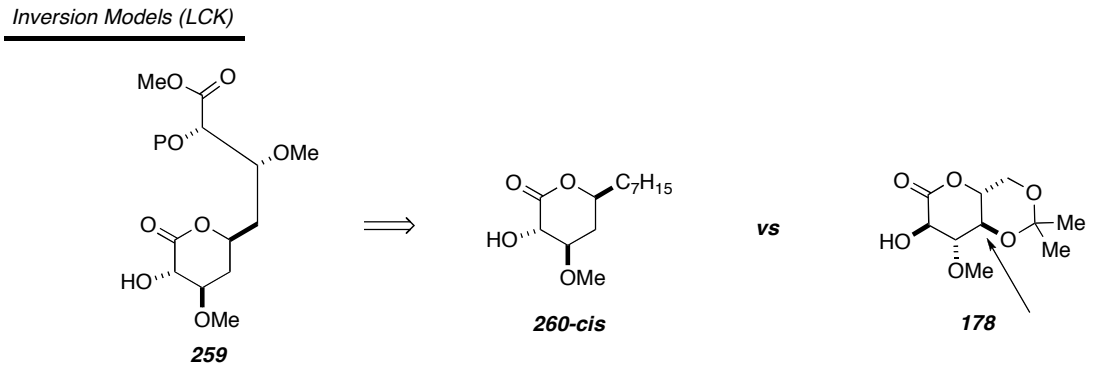
J_{ab} = 5.0 Hz

183

2. Revised Lactone Model System

At this point in time we had to go back and determine if this model system **178** was even a good model system at all. One concern that we started to think was a larger factor than we previously had believed was the bicyclic nature of lactone **178** (**Scheme 73**). This is believed to be what is attributing to the strange coupling constant data. This is when Ryba had suggested using the half-model lactones **260-*cis*** and **260-*trans***, which could easily be produced from the lactone products of his half-model kinetic lactonization studies. This would be a quick entry into a more realistic system and the chemical transformations to provide lactone **260-*cis*** have been proven to work reliably.

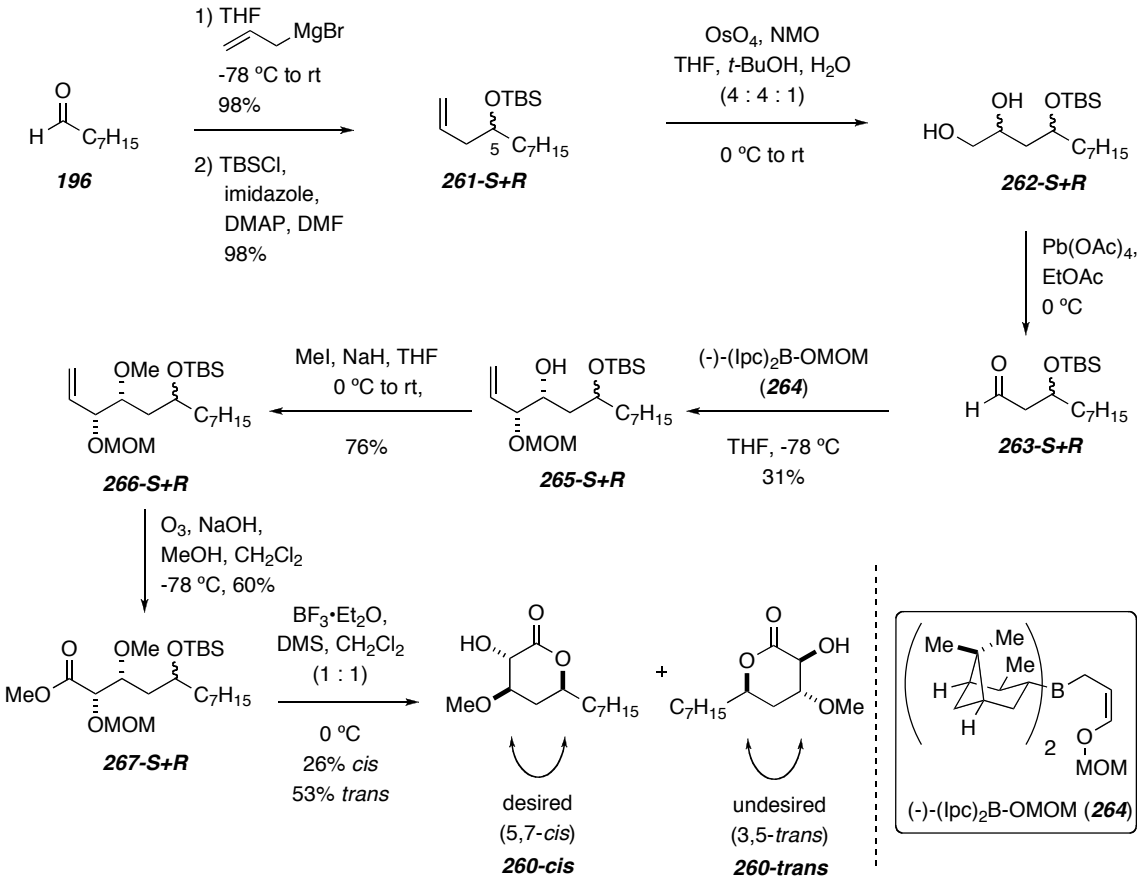
Scheme 73



The synthesis began the same way Ryba's had before, addition of allyl magnesium bromide into octyl aldehyde (**196**) (**Scheme 74**).[56] Instead of benzyl protecting the resulting alcohol as Ryba had done previously the TBS-ether was formed to provide alkene **261-*S+R***.[59] Using the TBS-ether would allow for a simultaneous deprotection of the MOM and TBS-ethers and cyclization to the desired lactones **260-*cis*** and **260-*trans***. Alkene **261-*S+R*** was transformed into the aldehyde **263-*S+R*** by dihydoxylation and oxidative cleavage under Creigee conditions. Oxyallylation with borane **264** of the newly formed aldehyde **263-*S+R*** provided a mixture of ~2:1 diastereomeric mixture of alcohols **265-*S+R***.[17,60] Not obtaining a 1:1 diastereomeric ratio was an interesting result. It is speculated that one of the epimers of aldehyde **263-*S+R*** reacts at a faster rate with borane **264** than the other and as a result the ratio is reflected in the product alcohols **265-*S+R***. Not a whole lot of time was spent becoming proficient with this oxyallylation reaction and this can be seen in the low yields that were obtained. The hydroxyl of **265-*S+R*** was methylated and the alkene was converted to a methyl ester using Ryba's modifications of the Marshall protocol to afford methyl ester **267-*S+R***.[63] Teatment of methyl ester **267-*S+R*** with BF_3•OEt_2 in a solution of DMS:CH_2Cl_2 (1:1) provided a separable mixture of **260-*cis***:**260-*trans*** (1:2 *dr*). Deprotection of the MOM and TBS protecting groups was accompanied by cyclization to form the lactone. It is interesting to note that the MOM protected lactones **202-*cis*** and **202-*trans*** were reported to be inseparable by Ryba. Unfortunately, the minor product from this sequence of reactions was lactone **260-*cis***, which most resembles the peloruside relevant-substrate **259**.

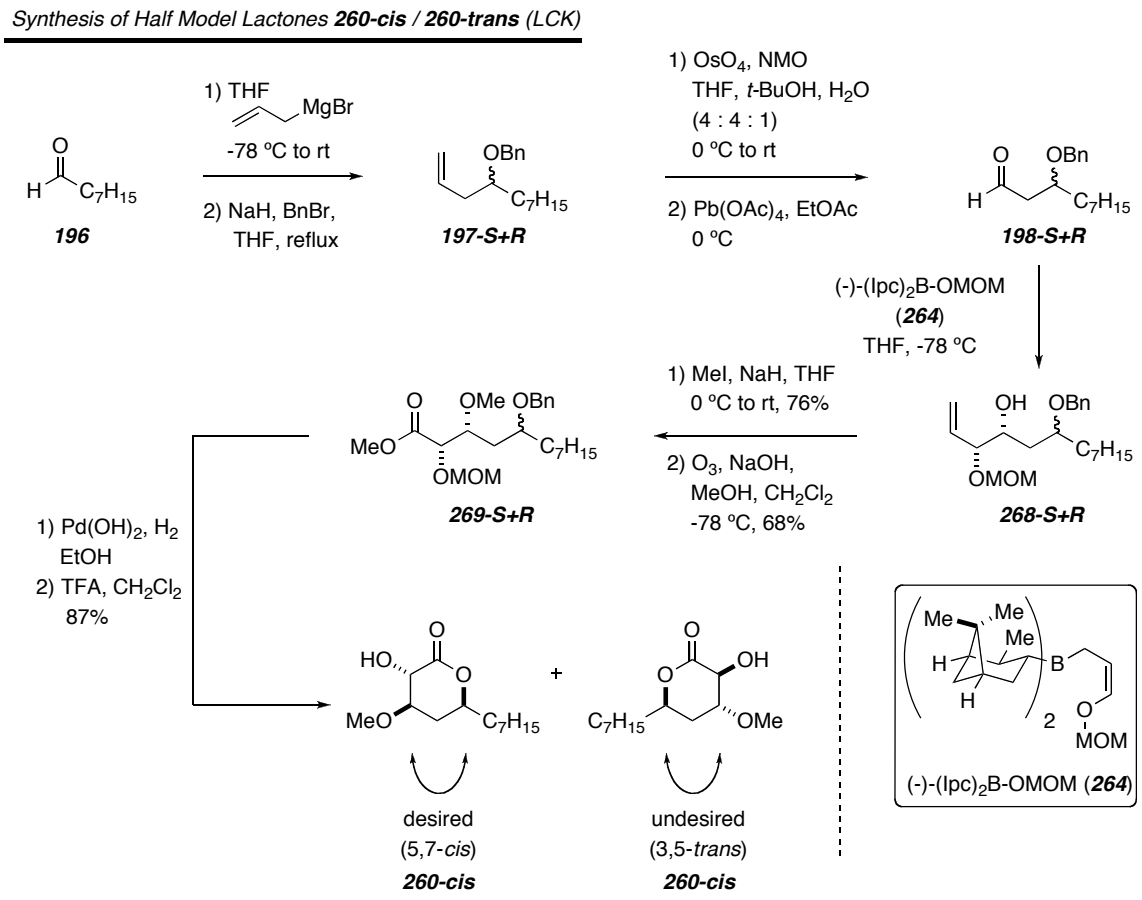
Scheme 74

*Synthesis of Half Model Lactones **260-cis** / **260-trans** (LCK)*



In an effort to obtain more of lactone **260-*cis***, the decision was made to prepare it via the benzyl protection route that Ryba used for synthesizing compounds for his half-model lactonization studies.[56] All of the reactions in the sequence went forward with no problems. The only modification came after formation of methyl ester **269**. Ester **269** was subjected to reducing conditions to remove the benzyl protecting group (**Scheme 75**). The reaction mixture was filtered and exposed to TFA in order to remove the MOM-ether and cyclize to the desired lactones **260-*cis*** and **260-*trans*** (1:1; *cis*:*trans*).

Scheme 75

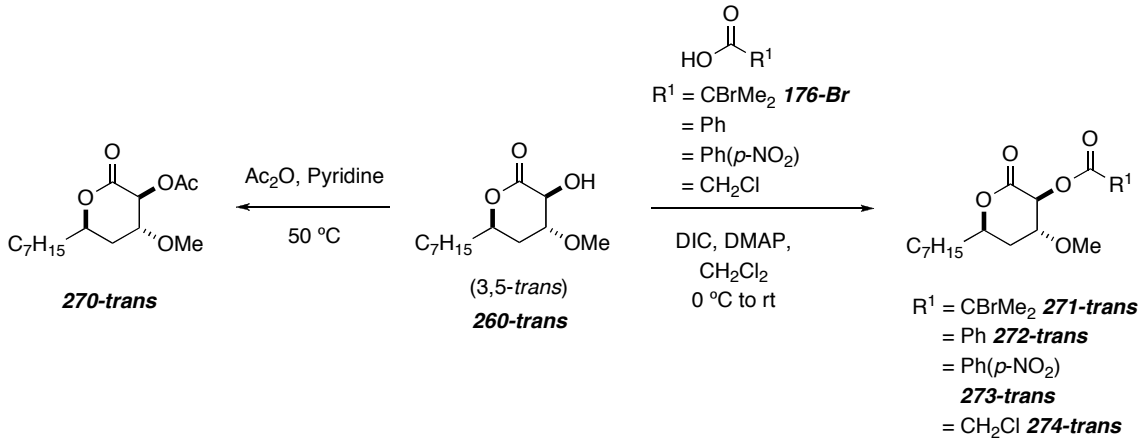


After a manageable amount of lactones **260-*cis*** and **260-*trans*** were synthesized, it was time to investigate the inversion of the α-hydroxy lactone stereocenter. Retention standards were made first, as was done before with the glucose derivatives. The **260-*trans*** lactone was initially used for my studies for the mere fact that there was a larger quantity of it compared to the **260-*cis***. Acylation with acetic anhydride and pyridine produced the acetylated lactone **270-*trans*** (**Scheme 76**). The other acylation products of **260-*trans*** needed to be prepared via DIC coupling. Acids, 2-bromoisobutyric acid (**176-Br**), benzoic acid, *p*-nitrobenzoic acid, and monochloroacetic acid were used in the acylation of **260-*trans*** to provide their respective products **271-*trans***, **272-*trans***, **273-*trans***, and **274-*trans***. Attempts at inverting the hydroxyl of **260-*trans*** with all of the various acids and under a variety of Mitsunobu conditions resulted in retention of

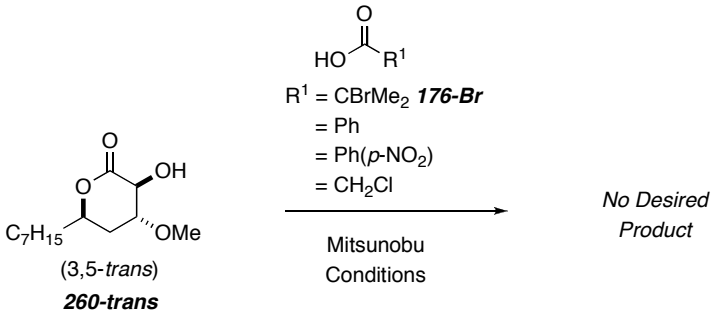
configuration in my hands.[23,77] A trace amount of inverted product was seen for some of the reactions, but later attributed to epimerization of the α-stereocenter. Obtaining retention of configuration is not a totally uncommon occurrence in Mitsunobu reactions.[78]

Scheme 76

Synthesis of 3,5-trans Half-Model Standards (LCK)



Mitsunobu Inversion: 3,5-trans Half-Model (LCK)



Unable to invert the hydroxyl stereocenter of **260-*trans***, it was time to switch over and use **260-*cis*** in the Mitsunobu reactions. Synthesis of the retention standards occurred the same as before (**Scheme 77**). Treatment of lactone **260-*cis*** with acetic anhydride and

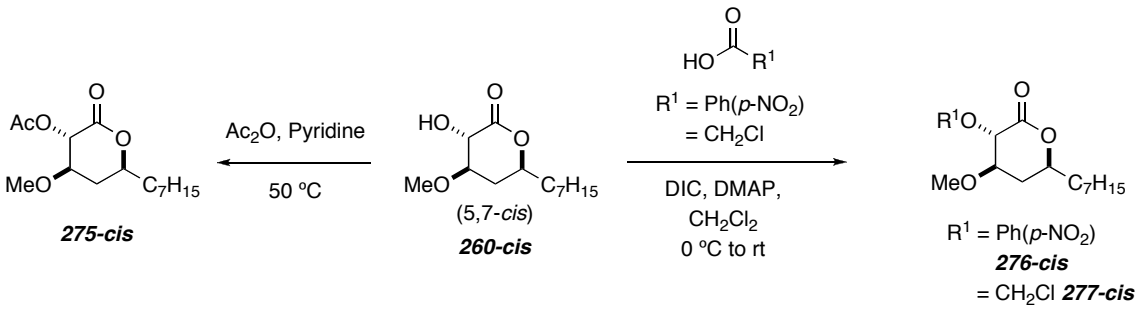
[77] (a) "A low-temperature Mitsunobu reaction for the inversion of sterically hindered secondary alcohols." Coleman, R. S.; Grant, E. B. *Tetrahedron Lett.* **1994**, *35*, 8341-8344. (b) "The use of chloroacetic acid in the Mitsunobu reaction." Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317-4320. (c) "Dimethylmalonyltrialkylphosphoranes: New general reagents for esterification reactions allowing controlled inversion or retention of configuration on chiral alcohols." McNulty, J.; Capretta, A.; Laritchev, V.; Dyck, J.; Robertson, A. J. *J. Org. Chem.* **2003**, *68*, 1597-1600.

[78] (a) "Mechanistic study of the Mitsunobu reaction." Ahn, C.; Correia, R.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 1751-1753. (b) "Total syntheses of (+)-zampanolide and (+)-dactylolide exploiting a unified strategy." Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102-11113.

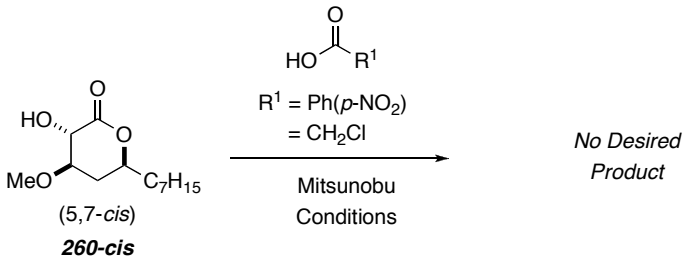
pyridine provided lactone **275-*cis***. Only the acylations with *p*-nitrobenzoic acid, and monochloroacetic acid were performed to provide lactones **276** and **277**. The reason for this is that both attempts using *p*-nitrobenzoic acid and monochloroacetic acid failed under a variety of Mitsunobu conditions. Again, only a trace amount of inverted product was seen and this was again attributed to epimerization after the acylation had occurred.

Scheme 77

Synthesis of 5,7-cis Half-Model Standards (LCK)



Mitsunobu Inversion: 5,7-cis Half-Model (LCK)



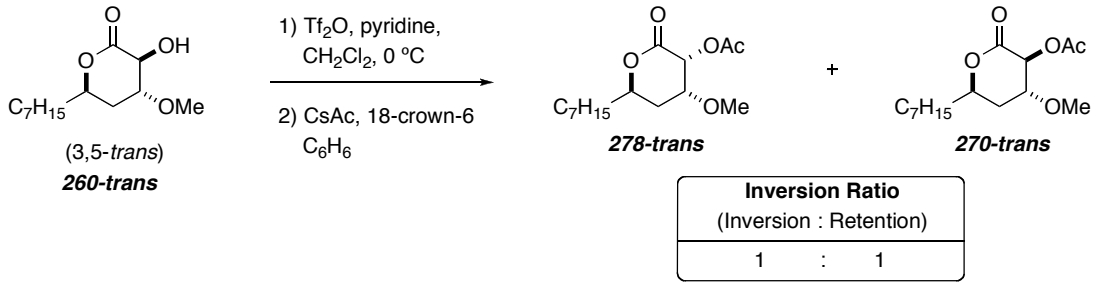
After not experiencing any success with the Mitsunobu conditions, an alternative method for performing the inversion of the α-hydroxy stereocenter needed to be found. Therefore, instead of using the one-pot two-step process associated with the Mitsunobu inversion (i. activation, ii. inversion), activation via triflate formation and inversion with a cesium carboxylate process was pursued.

Lactone **260-*trans*** was again used for the initial trials. Lactone **260-*trans*** was treated with triflic anhydride (Tf_2O) to activate the hydroxyl for inversion (**Scheme 78**). Subsequent displacement with commercially available cesium acetate and 18-crown-6 in

benzene provided a 1:1 mixture of inversion and retention products **278-*trans*** and **270-*trans***.[79]

Scheme 78

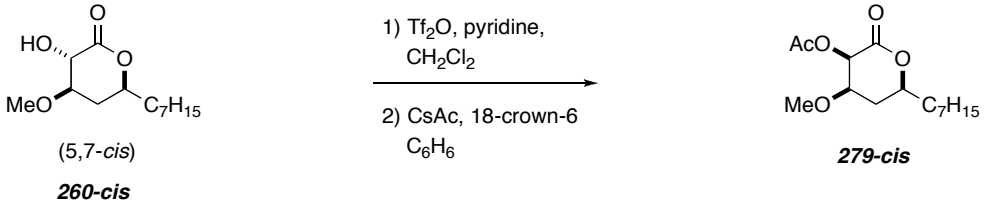
Tf / CsAc Inversion of 3,5-trans Half-Model (LCK)



After obtaining some promising results displacing a triflate with cesium acetate on lactone **260-*trans***, these reaction conditions were next attempted with lactone **260-*cis*** (**Scheme 79**). The inversion product lactone **279-*cis*** was the only product isolated during purification.

Scheme 79

Tf / CsAc Inversion of 5,7-cis Half-Model (LCK)



Expansion on the inversion of lactones **260-*cis*** and **260-*trans*** with different cesium carboxylate salts was next on the agenda to be explored. Cesium isobutyrate **280** was formed by treating acid **176-H** with cesium carbonate in methanol and removal of the residual solvent (**Scheme 80**). This afforded a white solid that was mildly susceptible to moisture.

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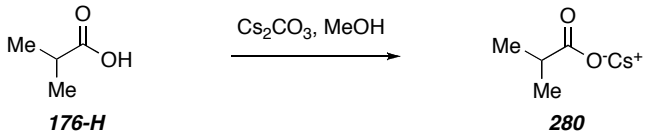
[79] (a) "Efficient method for inversion of secondary alcohols by reaction of chloromethanesulfonates with cesium acetate." Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145-6148. (b) "Efficient hydroxyl inversion in propionates via cesium carboxylates." Arbelo, D. O.; Castro-Rosario, L.; Prieto, J. A. *Syn. Commun.* **2003**, *33*, 3211-3223. (c) "Cesium trifluoroacetate displacement of triflates in the inversion of alcohols." Bell, A. A.; Pickering, L.; Finn, M.; Fuente, C. de la; Krülle, T. M.; Davis, B. G.; Fleet, G. W. J. *Synlett* **1997**, 1077-1078.

Scheme 80

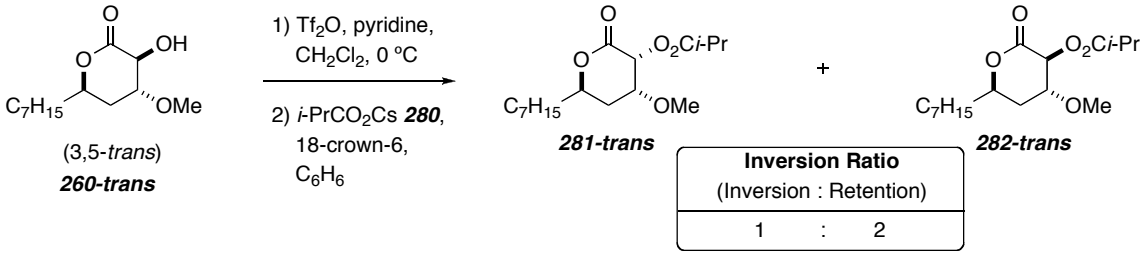
*Synthesis of Cesium Isobutyrate **280** (LCK)*



The triflate of lactone **260-*trans*** was reacted with newly prepared cesium isobutyrate **280** and 18-crown-6 in benzene to afford another mixture of inversion and retention products **281-*trans*** and **282-*trans*** (1:2, inversion:retention) (**Scheme 81**). The expected ratio of inverted to retention products with cesium isobutyrate **280** was lower than that of cesium acetate. This is probably a result of the extra bulk from the isopropyl group that leads to an increase in retention product.

Scheme 81

*Tf / Cs Isobutyrate **280** Inversion of 3,5-trans Half-Model (LCK)*

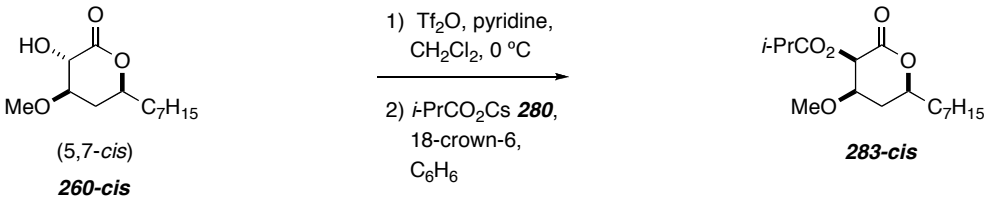


Inversion Ratio (Inversion : Retention)
1 : 2

It was now time to apply what was learned on the inversion of **260-*trans*** with cesium isobutyrate **280** to the inversion of the more peloruside-relevant lactone **260-*cis*** (**Scheme 82**). Preparation of the triflate from lactone **260-*cis*** occurred with no problem. This triflate was then subjected to the same reaction conditions as before to furnish the desired inverted product **283-*cis***.

Scheme 82

*Tf / Cs Isobutyrate **280** Inversion of 5,7-cis Half-Model (LCK)*

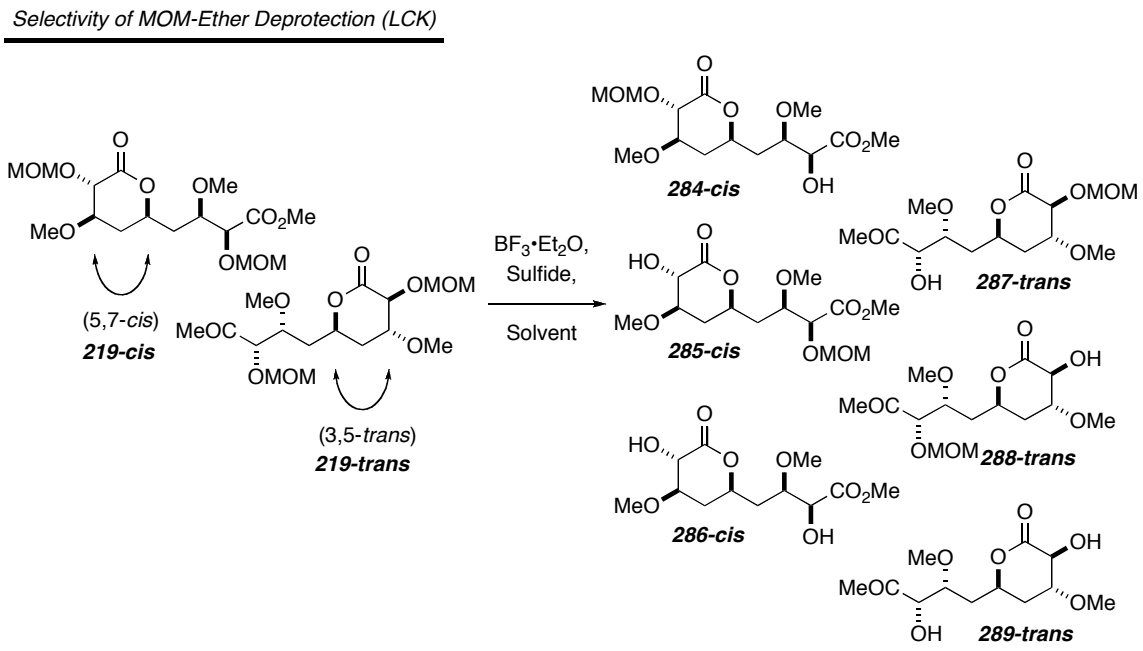


B. Application of Activation/Displacement Strategy Toward Inversion of the C8 Stereocenter of a Peloruside A Intermediate

To recap, I have now been able to scale-up the preparation of lactone **219-*cis*** and have devised a way to invert the α-hydroxy stereocenter on a relevant model system **260-*cis***. The next step in the process is to apply the inversion reaction on a (+)-peloruside A **1** intermediate. Before this can be done, the hydroxyls α to the ester and lactone need to be differentiated. The quickest way to solve the problem is to try and selectively remove one of them. After all, they are in different chemical environments and therefore should have a different rate of deprotection. The question is, "Is the difference in rate large enough for us to take advantage of?"

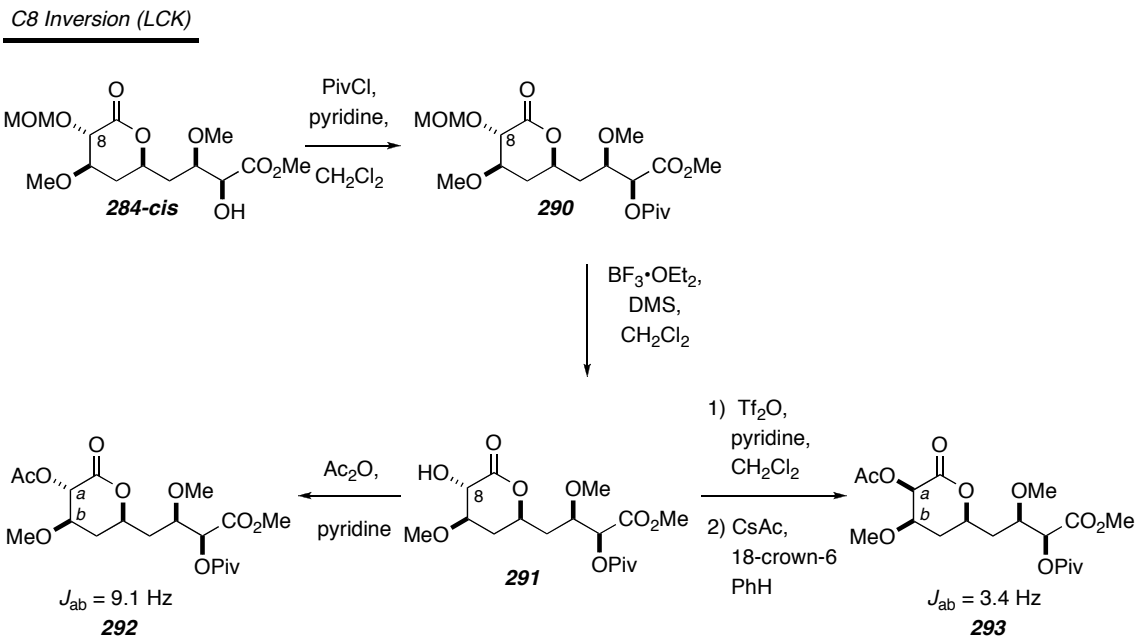
A significant amount of time was spent screening different reaction conditions for the selective deprotection of the MOM-ethers using BF_3•OEt_2 (**Scheme 83**). Performing the reaction in CH_2Cl_2 was too fast and led to the production of diols **286** and **289**. THF-*d8* as the solvent reduced the rate enough that the reaction could be monitored by ^1H NMR. A variety of sulfides were screened for the deprotection: methyl isopropyl sulfide, *sec*-butyl methyl sulfide, 2-butyl-phenyl sulfide, benzyl methyl sulfide, and dimethyl sulfide (DMS). All of the sulfides, when used in THF-*d8*, produced approximately the same ratio of products at 50% conversion: **284-*cis***:**285-*cis***:**286-*cis*** ; (4:2:1) with varying trace amounts of *trans*-lactones **287-*trans***, **288-*trans***, and **289-*trans***. The percent conversion of the reaction could not be pushed any further without forming more of the diol lactones **286-*cis*** and **289-*trans***. Through careful MPLC chromatography using CH_2Cl_2:MeOH (95:5) all of the products were able to be separated and fully characterized. Unfortunately, some mixed fractions were unavoidable. All of the products were eventually shown to be separable using a reverse-phase column on the Hoye group's LC-MS. However, the same separation characteristics were never obtained when using our reverse-phase prep-HPLC. The diffuculty encountered in separating the various products stopped the scale-up of this reaction. A scalable alternative would have to be devised.

Scheme 83



Before moving on to find a new strategy for inverting the C8 stereocenter, the triflate displacement process was applied to the peloruside intermediate **284-*cis*** (**Scheme 84**). Protection of the free acyclic hydroxyl of **284-*cis*** with pivaloyl chloride produced the lactone **290**. Removal of the MOM-ether of **290** was performed under standard BF_3•OEt_2 conditions to provide α-hydroxy lactone **291**. An inversion standard was prepared by treating **291** with acetic anhydride to give the acetylated lactone **292**. The coupling constant between the *a* and *b* protons of lactone **292** was J_{ab} = 9.1 Hz. The α-hydroxy lactone **291** was next treated with triflic anhydride to activate the hydroxyl for displacement. The triflate of lactone **291** was treated with cesium acetate and 18-crown-6 in benzene to invert the C8 stereocenter providing lactone **293**.[79] The coupling constant between the *a* and *b* protons of lactone **293** was J_{ab} = 3.4 Hz. The coupling constant values for the retention and inversion products, **292** and **293**, were consistent with those reported for the half-models **275-*cis*** and **279-*cis*** and provided evidence for inversion of the C8 stereocenter. Having succeeded at inverting the C8 stereocenter using this method, this route was set aside with some apprehension.

Scheme 84

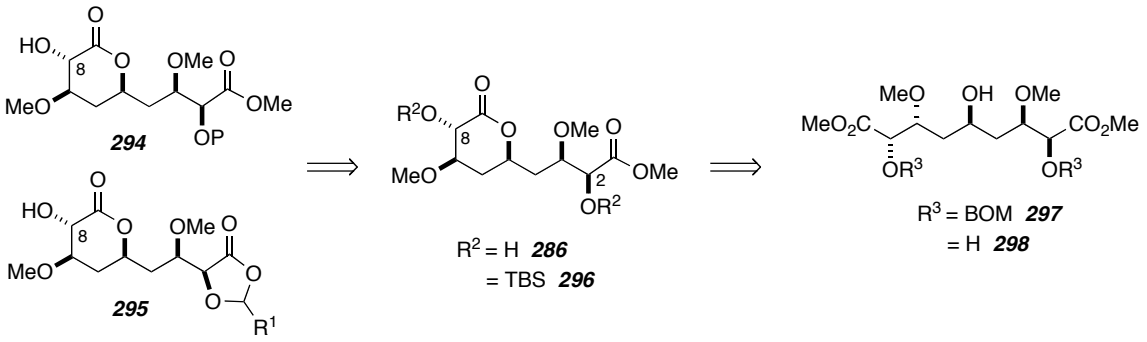


C. Protecting Group Manipulation Strategies for Isolation of C8 Stereocenter

After reacquainting myself with some of the originally proposed ideas, I decided to attempt to isolate the C8 hydroxyl by one of three different ways. The first method, and quickest, was to selectively protect either the C2 or C8 hydroxyl of diol **286** (**Scheme 85**). The second method would involve forming a hemi-ketal of a α-hydroxy carboxylic acid to make compound **295**. The final idea was to attempt to selectively remove a different protecting group, for example, a TBS-ether. Inversion of any triflate intermediate with cesium carboxylate would produce the desired C8 inversion. Initial attempts to form diol **286** from the double deprotection of the MOM-ethers routinely resulted in low yields (~50%). It was speculated that the BF_3•OEt_2 was opening the lactone ring and allowing formation a highly water-soluble by-product. The diol **286** was also shown to be particularly water soluble, more so than its hexyl ester derivative. In order to solve the low isolated yields from the MOM-ether removal, the hydroxyls were protected as BOM-ethers, which could be reductively removed with no aqueous workup. This would also allow for investigation into the kinetic lactonization of the pseudosymmetric triol **298**. Triol **298** could easily be prepared using the same Raney-Nickel reduction conditions as before.

Scheme 85

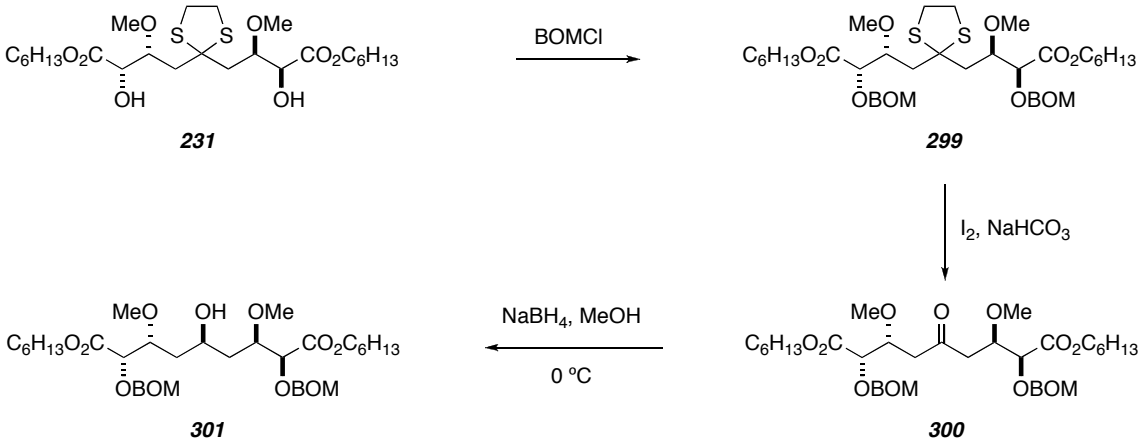
Protection Strategy for C8 Inversion Strategy (LCK)



Introduction of the BOM-ethers was performed on diol **231** (**Scheme 86**). The dithiane removal allowed for reduction of the resulting ketone with sodium borohydride to provide carbinol **301**. Even though my intentions were to use the BOM protected methyl ester carbinol **297**, the lactonization of the hexyl ester carbinol **294** was investigated in order to compare it to the previous lactonizations.

Scheme 86

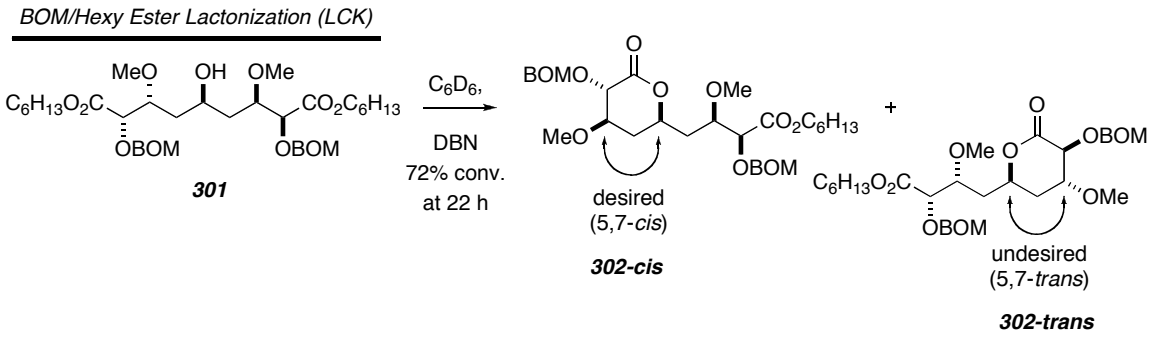
*Synthesis of BOM/Hexyl Carbinol **301** (LCK)*



Carbinol **301** was treated with 40 mol% DBN in C_6D_6 to provide lactone **302-*cis*** (**Scheme 87**). This lactonization like other hexyl series, suffered from low converion (72% at 22 h). The starting carbinol **301** and lactone **302-*cis*** were moderately separable by MPLC, with no evidence for the undersired lactone **302-*trans***. This evidence suggests that the extra sterics from the BOM-ethers are negligible in affecting the lactonization

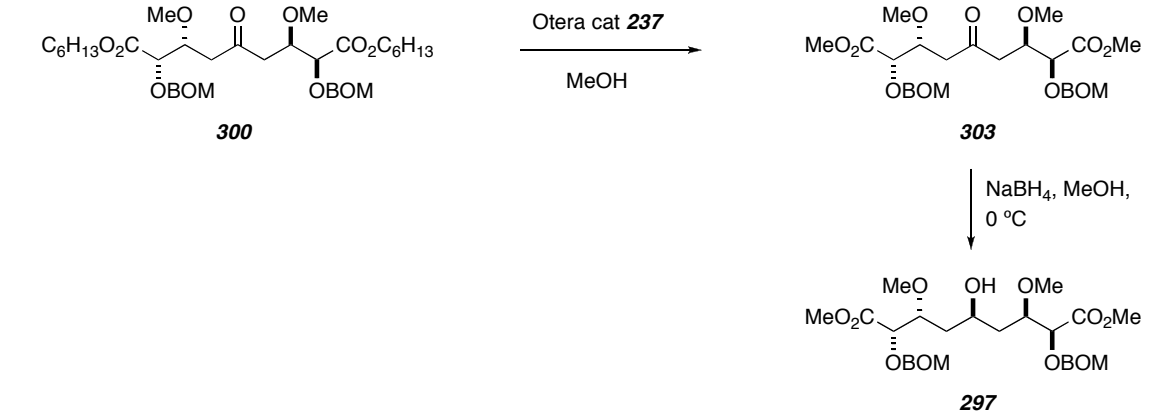
rate, when one compares them to the MOM-ether series of reactions. The major contributing factor is the ester functionality.

Scheme 87



The hexyl ester ketone **300** was heated in the presence of MeOH and Otera catalyst **237** to transesterify to the methyl ester (**Scheme 88**). Reduction of the ketone with sodium borohydride at 0 ºC provided the carbinol **297**.

Scheme 88



The newly formed carbinol **297** was treated with 2 equiv. TMG in C_6H_6, using the revised TFA workup procedure, to afford the desired lactones **304-*cis***:**304-*trans*** (11:1 dr) (**Scheme 89**). Only one attempt was made at hydrolyzing the methyl ester of lactone **304-*cis*** to the carboxylic acid. Treatment with a methanolic solution of lithium hydroxide only produced the bis-carboxylic acid **305** when analyzed by LC-MS (**Figure 8**).

Scheme 89

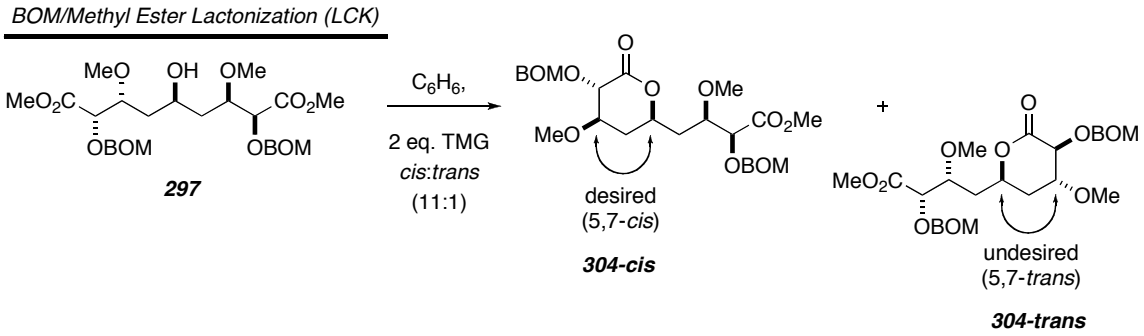
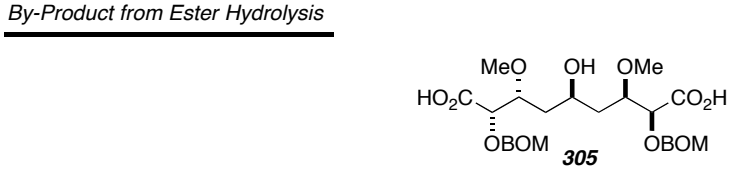


Figure 8

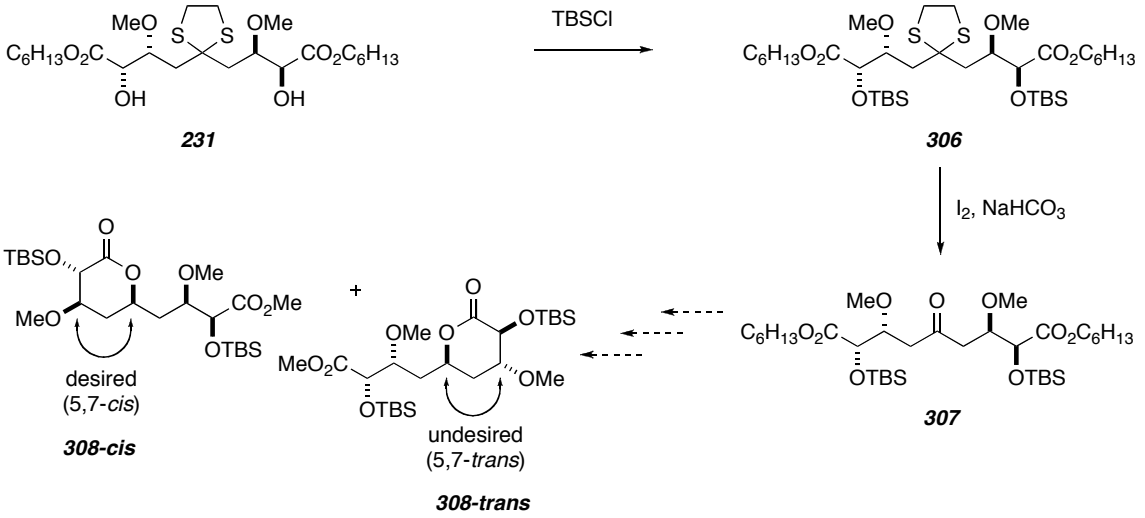


Exposure of lactone **304-*cis*** to reductive conditions should result in the formation of diol **286**. However, I never pursued this route any further because I was able to make progress elsewhere.

At approximately the same time as I was preparing lactone **304-*cis*** for C8 inversion studies, I was attempting to synthesize the TBS protected version in order to investigate the selective removal of one of the TBS-ethers (**Scheme 90**). Treatment of the diol **231** with TBSCl provided bis-TBS-ether **306**. The dithiane of **306** was removed using the previously discussed methods to arrive at ketone **307**. Ketone **307** was never moved forward to the desired lactone **308-*cis*** in order to study the selective removal of a single TBS-ether. The reason for ending my progress on this route was the same as before. I felt that progress had been made via another route and I wanted it to have my full attention.

Scheme 90

*Synthesis of TBS/Methyl Lactone **308-cis** (LCK)*



I do still believe that selective protection, selective deprotection, and the hemi-ketal routes are worthwhile to explore. Unfortunately, the quickest way to advance in the synthesis of (+)-peloruside A **1** was to push forward elsewhere. At this point in time I do believe that one of these three methods for differentiating the C8 stereocenter, in particular the hemi-ketal, show promise in significantly reducing the number of steps towards the total synthesis of (+)-peloruside A **1**.

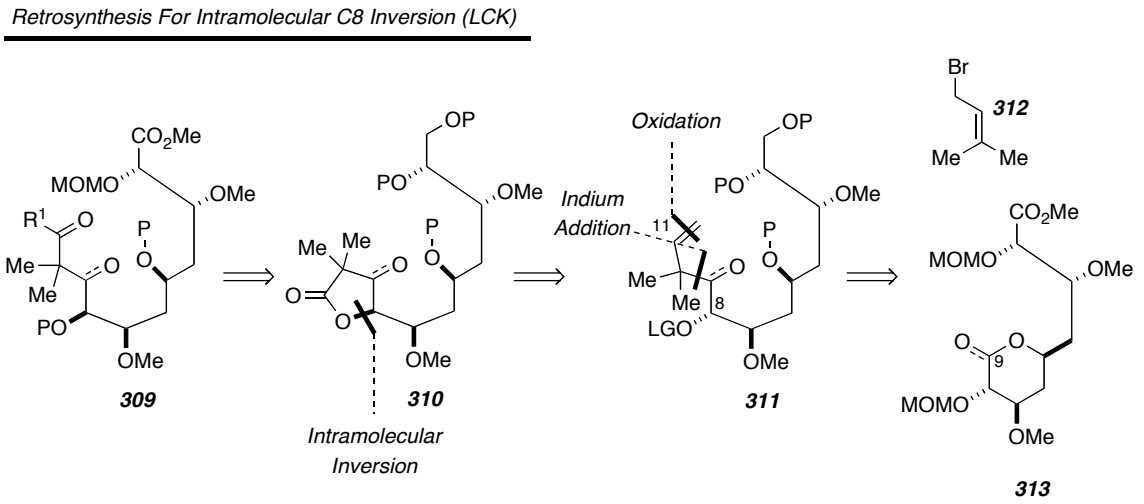
D. Intramolecular C8 Stereocenter Inversion Strategy

1. Indium Addition

So far hints of success with various routes toward inverting the C8 stereocenter have presented themselves, however a different method is still needed. A number of the potential options relied on selectivity and differences in rates between the C2 and C8 functionalities. I began to believe that I could potentially spend my graduate years attempting a variety of conditions in order to perform a selective differentiation of the two stereocenters and not even accomplish this goal, unless I got *lucky*. After reviewing some of the peloruside literature, a new strategy of performing an intramolecular inversion had been devised. Having the C11 position as a carboxylic acid and conversion of the C8 hydroxyl into an activated leaving group, when treated with base, should allow for ring closure to the γ-lactone and inversion of the C8 stereocenter to arrive at an

intermediate like **310** (**Scheme 91**). Opening of the lactone and protection of the C8 alcohol will allow for formation of compound **309**. The C9-C10 carbon bond could be installed via an indium-mediated alkylation with prenyl bromide **312**.[80] Addition into the lactone or aldehyde/hemiacetal **313** would be tried, with the more likely approach being the latter. If the prenyl species was able to add into the lactone, the breakdown of the tetrahedral intermediate should provide a ketone next to a *gem*-dimethyl group that should reduce the reactivity towards a second addition. This would keep the oxidation state at the C9 position that is necessary for (+)-peloruside A **1**.

Scheme 91



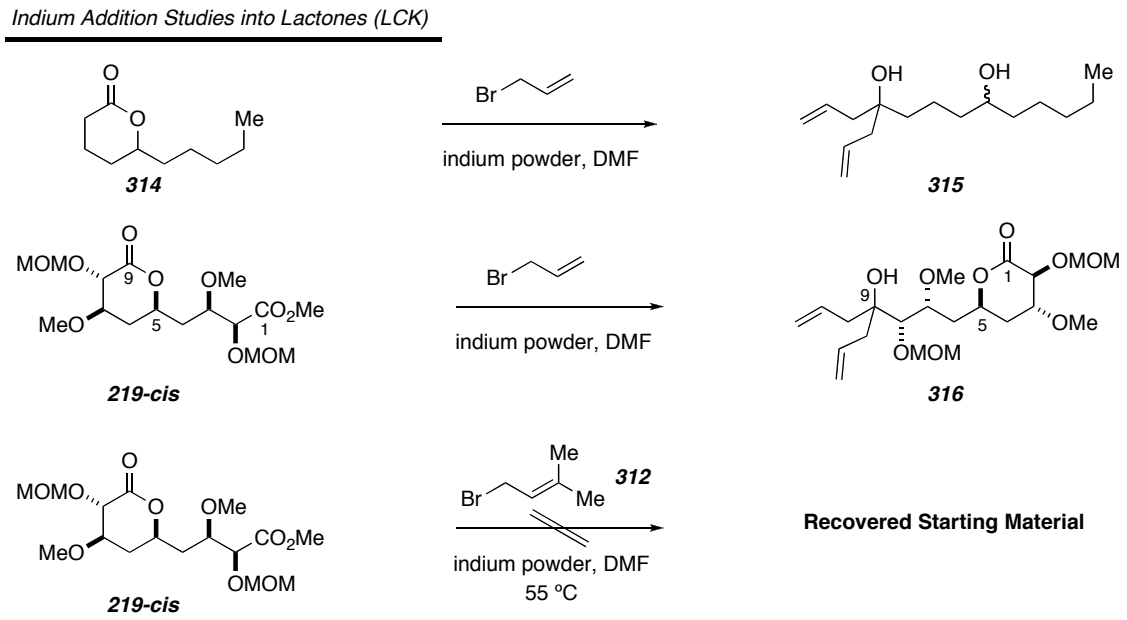
The addition of indium allyl species into lactones was initially studied. A suspicion that sterics may affect the alkylation with prenyl bromide **312** was the reason for using the allyl indium species. To my knowledge there were no examples in the literature about addition of allyl indium reagents into lactones. Indium species are known to react with aldehydes, ketones, imines etc., but not esters. Therefore, the selective alkylation that is needed between the lactone and ester functionalities should be achieved. Prenyl indium is known for its selectivity for carbon bond formation at the more hindered sight when compared to other prenyl species.

---

[80] (a) "Aqueous Barbier-Grignard type reaction: Scope, mechanism, and synthetic applications." Li, C. J. *Tetrahedron* **1996**, *52*, 5643-5668. (b) "Indium in organic synthesis." Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633-655. (c) "Indium in organic-synthesis: Indium-mediated allylation of carbonyl-compounds." Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831-1833.

The addition of an *in-situ* prepared allyl indium species into δ-decalactone **314** occurred with the expected double alkylation to provide tertiary alcohol **315** (**Scheme 92**). Having showed the ability of an allyl indium species to react with a simple lactone, lactone **219-*cis*** was subjected to the allyl indium alkylation. Exposure of lactone **219-*cis*** to allyl bromide and indium powder in DMF afforded the desired tertiary alcohol **316**. The double allylation of the C9 position was accompanied by lactone formation between a proposed C5 indium alkoxide intermediate and the C1 methyl ester. The alkylation of lactone **219-*cis*** with a prenyl indium reagent was attempted next, but was unsuccessful at producing the desired product, even with some moderate heating. Only starting material was recovered after workup.

Scheme 92

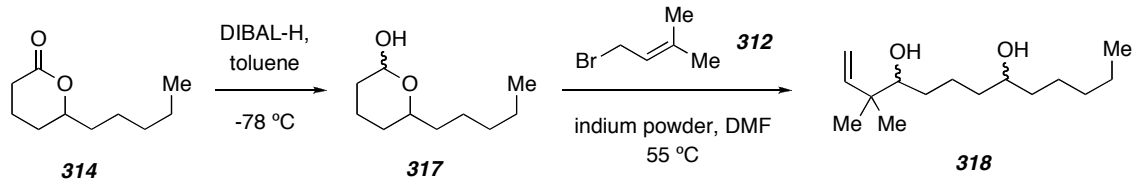


Unable to form the C9-C10 bond via addition of a prenyl indium reagent into a lactone, the decision was made to investigate the addition into the aldehyde/hemiacetal. Not having the C9 position at the ketone oxidation state would remove any epimerization liabilities associated with it. Reduction of δ-decalactone **314** with DIBAL-H provided hemiacetal **317** (**Scheme 93**). Hemiacetal **317** was reacted with prenyl bromide **312** and indium powder in DMF at 55 ºC to provide diol **318**. The previous reactions adding allyl indium into lactones were capable of being run at room temperature, while it was

necessary to react prenyl indium with the aldehyde/hemiacetal at 55 ºC. The heating of the reaction is believed to be necessary to alter the equilibrium between the closed hemiacetal **317** and the open straight chain aldehyde.

Scheme 93

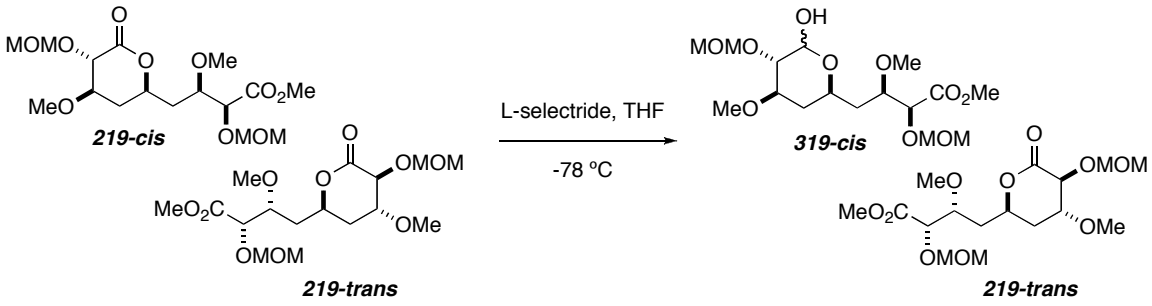
Indium-Prenyl Bromide Addition to Model Aldehyde (Hemiacetal) (LCK)



In order to apply the indium addition to the aldehyde of a peloruside-relevant compound, it was necessary to selectively reduce the lactone in the presence of the methyl ester. There are examples of this transformation being performed with DIBAL-H at low temperature in the literature. I was unable to achieve the same selectivity as others had reported with the problem being reduction at the methyl ester. Another example reported by the S. Schreiber group was found where they selectively reduce a lactone in the presence of a methyl ester with L-selectride in THF at -78 ºC.[81] Treatment of a >9:1 mixture of **219-*cis*** and **219-*trans*** with L-selectride under the conditions reported by Schreiber provided the desired hemiacetal **319-*cis*** and recovered lactone **219-*trans***, which were separable by flash chromatography (**Scheme 94**).

Scheme 94

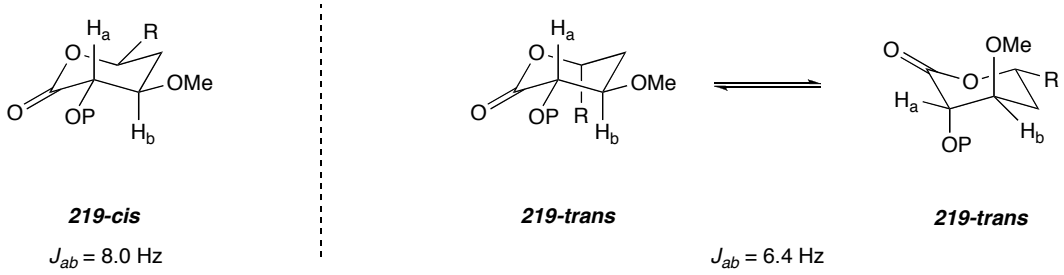
Diasterioselective/Chemoselective Lactone Reduction (LCK)



[81] "Total synthesis of FK506 and an FKBP probe reagent, [C(8),C(9)-13C2]-FK506." Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583-5601.

An explanation for the diastereoselective reduction of the **219-*cis*** over **219-*trans*** begins with the conformations that the lactones reside in as a result of the substituents on the ring (**Scheme 95**). All three of the substituents on **219-*cis*** reside in equatorial positions, allowing for easier approach from the L-selectride while the substituents on **219-*trans*** more than likely reside in pseudo-axial positions hindering the trajectory of the reducing agent. The conformational analysis is supported by the coupling constants between H_a and H_b of both lactones. The large coupling, J_{ab} = 8.0 Hz, for **219-*cis*** gives evidence for the axial relationship between the protons and the other substituents being equatorial. The medium coupling, J_{ab} = 6.4 Hz, for **219-*trans*** provides evidence for a time average of both chair conformers in which there is a pseudo-equatorial relationship between the protons and the other substituents are pseudo-axial.

Scheme 95



Hemiacetal **319-*cis*** was treated with the prenyl indium reagent in DMF at 55 ºC to afford carbinol **320** as the only isolable isomer (**Scheme 96**). It became necessary to monitor the reaction closely and not allow for the temperature to rise too high, or the eliminated by-product **321** would begin to appear (**Figure 9**).

Scheme 96

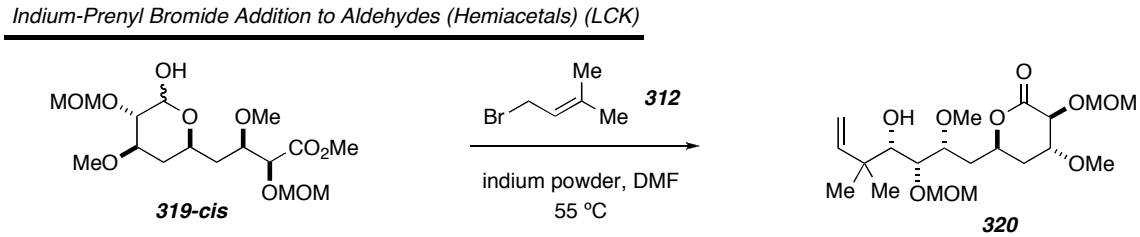
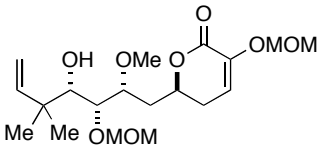


Figure 9

By-Product from Prenyl Indium Addition

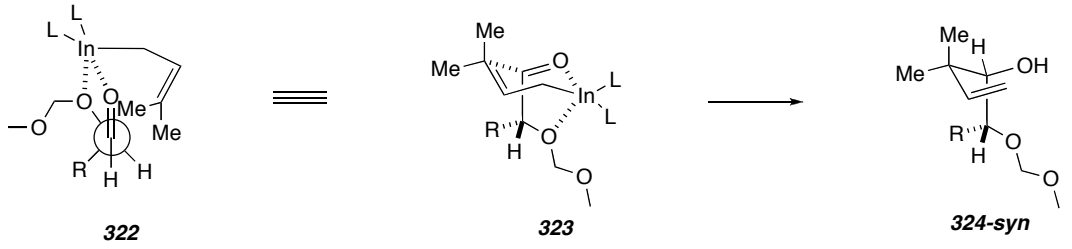


321

At this time the stereochemical outcome of the product **320** was assumed to be *R* on the association with diastereoselective studies performed by Paquette and Mitzel in which they studied the effect of α/β-oxygenation on the indium-mediated allylation of aldehydes.[82] They conclude that the asymmetric induction that is seen in the α-series and responsible for producing the *syn* isomer can be explained by the Cram model shown in **322** (**Scheme 97**). The allyl group is transferred from the less hindered π-face after complexation of the indium species. The chelation pathway also allows for a chair conformation **323** that leads to the *syn* allylation product **324-*syn***.

Scheme 97

L. Paquette (1996) : Stereochemical Model For Indium-Mediated Allylations to α–Oxygenated Aldehydes



322 ***323*** ***324-syn***

Modified Reproduced from *J. Am. Chem. Soc.***1996**, *118*, 1931-1937.

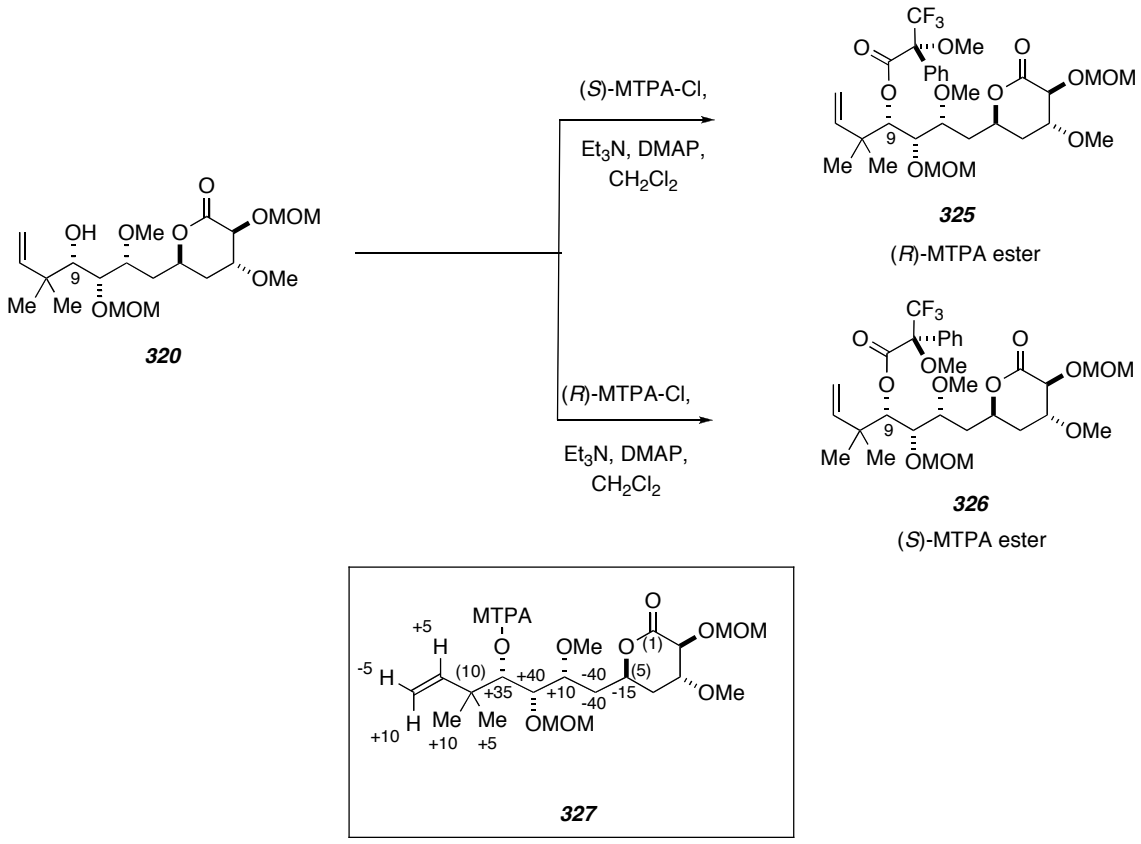
Although I was confident in assigning the newly formed *syn* relationship of **320**, and the fact that eventual oxidation of the C9 hydroxyl would remove any stereogenicity, I still decided to do a Mosher ester analysis. The (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid [(*R*)-MTPA] was converted into its corresponding (*S*)-MTPA-Cl according to the procedure reported by D. Ward and reacted with **320** to

[82] "Addition of allylindium reagents to aldehydes substituted at Cα or Cβ with heteroatomic functional groups. Analysis of the modulation in diasteroselectivity attainable in aqueous, organic, and mixed solvent systems." Paquette, L.; Mitzel, T. *J. Am. Chem. Soc.* **1996**, *118*, 1931-1937.

produce the (*R*)-MTPA ester **325**.[83] The (*S*)-MTPA was converted into its corresponding (*R*)-MTPA-Cl using the same procudure and reacted with **320** to produce the (*S*)-MTPA ester **326**. Interpretation of the data resulted in the $\Delta\delta^{SR}$ values shown in **Scheme 98** and **Table 8**. Unfortunately the resulting $\Delta\delta^{SR}$ values are not consistent on both sides of the MTPA-ester. This is believed to be a result of the *gem*-dimethyl substituent changing the conformation of the MTPA-esters and as a result this alters the $\Delta\delta^{SR}$ values. Therefore, no conclusions were made regarding the C9 configuration using Mosher ester analysis.

Scheme 98

Determination of C9 Stereocenter Configuration (Mosher Analysis) (LCK)



[83] (a) "A simple method for the microscale preparation of Mosher's acid chloride." Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166. (b) "Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons." Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451-2458.

Table 8

Determination of C9 Stereocenter Configuration via Mosher Analysis

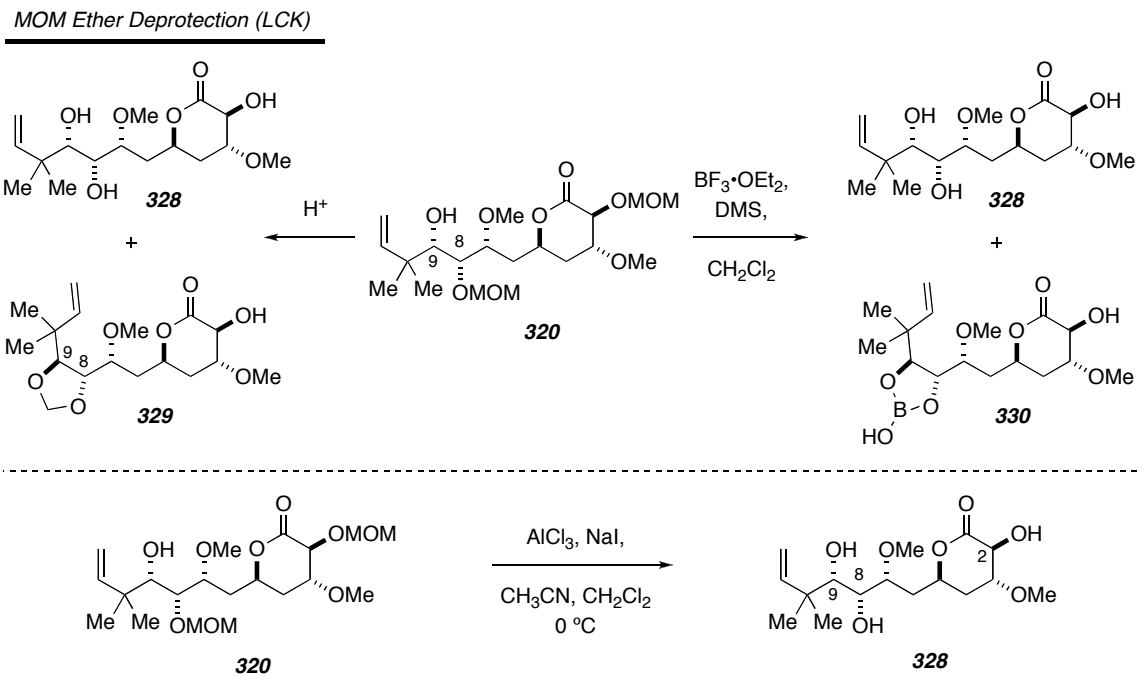
	δ *S*-Ester (***326S***) (ppm)	δ *R*-Ester (***325R***) (ppm)	$\Delta\delta^{SR}$ (= δ_S - δ_R) ppm	Hz (500 MHz
H_{12}	5.07	5.07	- .01	- 5
$H_{12'}$	5.07	5.05	+ .02	+ 10
H_{11}	5.85	5.84	+ .01	+ 5
Me	1.04	1.02	+ .02	+ 10
Me	1.02	1.01	+ .01	+ 5
H_9	5.22	5.15	+ .07	+ 35
H_8	3.90	3.82	+ .08	+ 40
H_7	3.60	3.58	+ .02	+ 10
H_6	1.67	1.75	- .08	- 40
$H_{6'}$	1.44	1.52	- .08	- 40
H_5	4.60	4.63	- .03	- 15

2. MOM-Ether Deprotection

In order to differentiate the hydroxyls for C8 inversion, it was necessary to prepare triol **328**. Attempts at using strong acid conditions to remove the MOM-ethers resulted in varying ratios of triol **328** and dioxolane **329** (**Scheme 99**). The two compounds could be separated via careful MPLC, but the deprotection could not consistently be run in a way to reduce the presence of dioxolane **329**. The formation of dioxolane **329** comes from the trapping of the oxonium intermediate, formed during the MOM-ether deprotection, by the adjacent C9 hydroxyl. It is speculated that the trapping of the oxonium intermediate is assisted by the buttressing affect of the *gem*-dimethyl substituent. Attempts at using BF_3•OEt_2 and DMS to remove the MOM-ethers proceeded to give triol **328** and surprisingly borate **330** in varying ratios. Both compounds were separable by MPLC. The ^{1}H NMR data for borate **330** was similar to triol **328**. It wasn't until the HRMS data was interpreted that the exact structure of **330** was determined. Taking the HRMS in MeOH exchanged the hydroxyl on boron for a methoxide and allowed for the determination of borate **330**. Experiencing trouble with the current deprotection methods, the trapping nucleophile of the oxonium intermediate during the deprotection needed to be altered so that it would out compete the C9 hydroxyl. I finally settled on the aluminum trichloride ($AlCl_3$) and sodium iodide (NaI) conditions reported

by Grieco.[84] Even if the dioxolane **329** were to form, it should be readily converted into triol **328** under these conditions. Treatment of carbinol **320** with $AlCl_3$ and NaI in CH_3CN/CH_2Cl_2 at 0 ºC provided the triol **328** in good yield. The 1,2-diol of triol **328** needed to be protected in order to isolate the C2 hydroxyl for reprotection.

Scheme 99

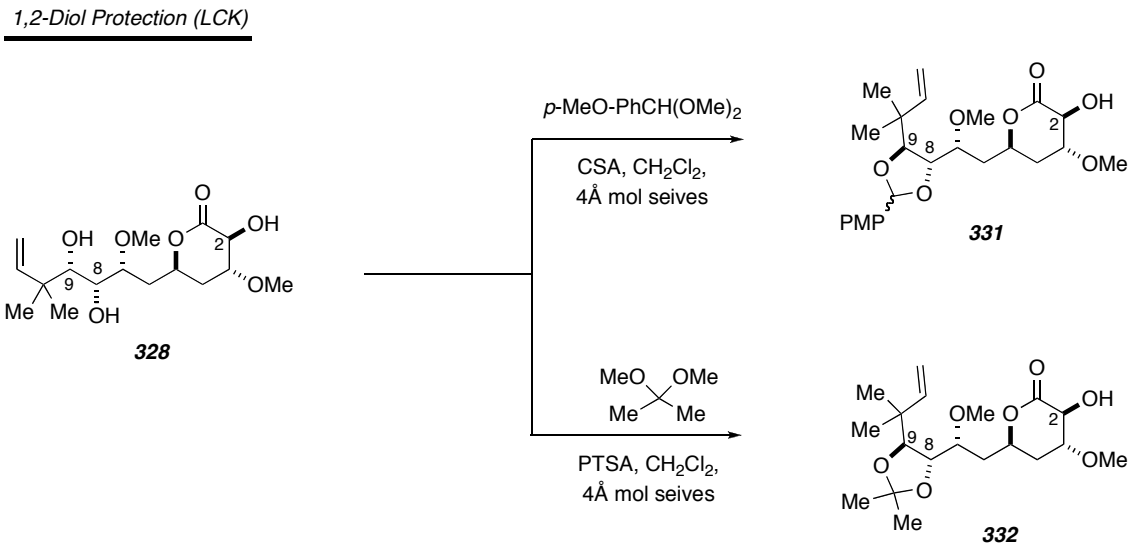


3. C8 Inversion of TBS Protected Bis-Mesylate

In an effort to differentiate the C2 hydroxyl of **328** from the C8 and C9, triol **328** was treated with *para*-anisaldehyde dimethyl acetal and CSA to afford the mixture of PMP acetals **331** (**Scheme 100**). Acetonide **332** was also formed by exposing triol **320** to 2,2-dimethyoxypropane and PTSA in CH_2Cl_2. The formation of acetonide **332** allowed for a cleaner spectrum to interpret, unlike the mixture of PMP acetals for **331**. The decision was made to carry the PMP acetal **331** forward in the synthesis because it would be easier to remove in the presence of the acid sensitive MOM-ether at a later stage.

[84] "C19 Quassinoids: Total synthesis of *dl*-samaderin B." Grieco, P. A.; Piñeiro-Nuñez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606-7615.

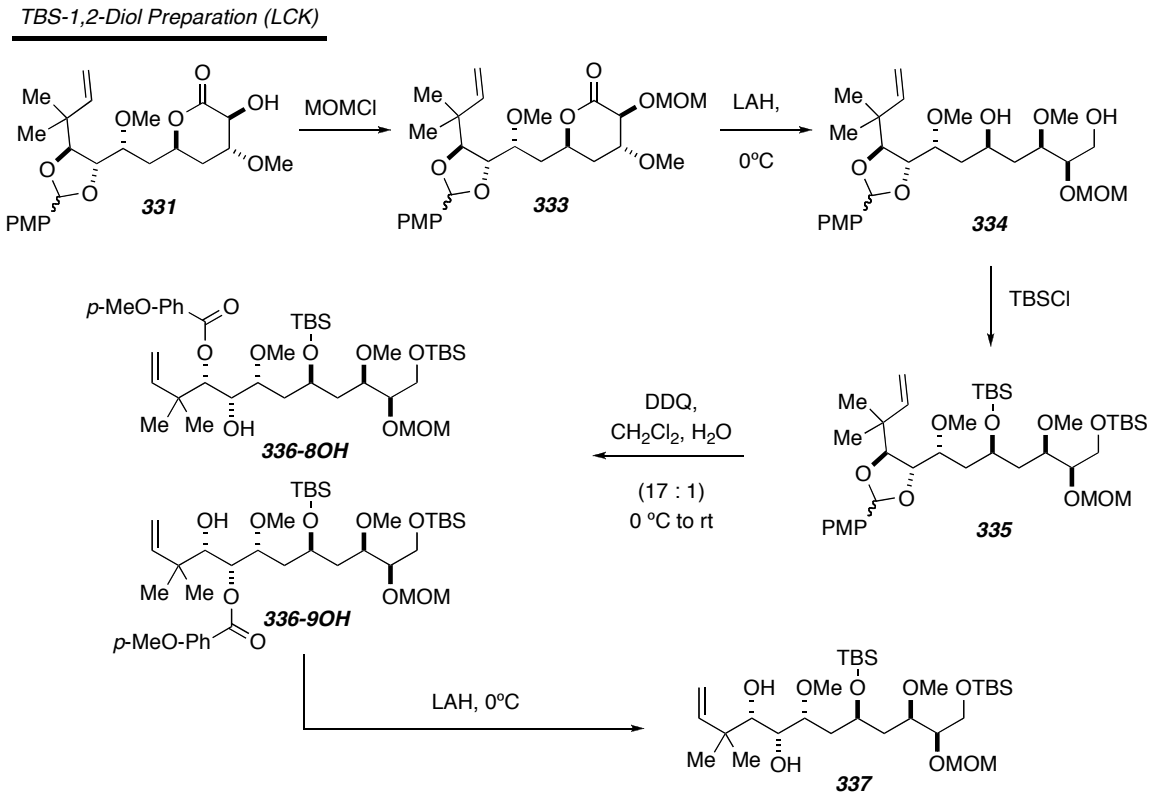
Scheme 100



The alcohol of **331** was protected with MOMCl to give lactone **333** (**Scheme 101**). The complete reduction of lactone **333** to diol **334** was done with LAH in THF at 0 ºC. A trace amount of the hemiacetal was observed as a result of incomplete reduction. The primary and secondary hydroxyls of diol **334** were protected as their TBS-ethers. A two-step procedure was used for the formation of diol **337**. The PMP acetal was oxidatively cleaved to give an inseparable mixture of C8 and C9 alcohols (1:3) **336-8OH** and **336-9OH**.[85] This mixture of alcohols was then treated with LAH at 0 ºC to produce the diol **337**. With TBS protected diol **337** in hand, the appropriate leaving group to perform the intramolecular inversion was ready to be installed.

[85] "Protection of hydroxy groups by intramolecular oxidative formation of methoxybenzylidene acetals with DDQ." Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889-892.

Scheme 101

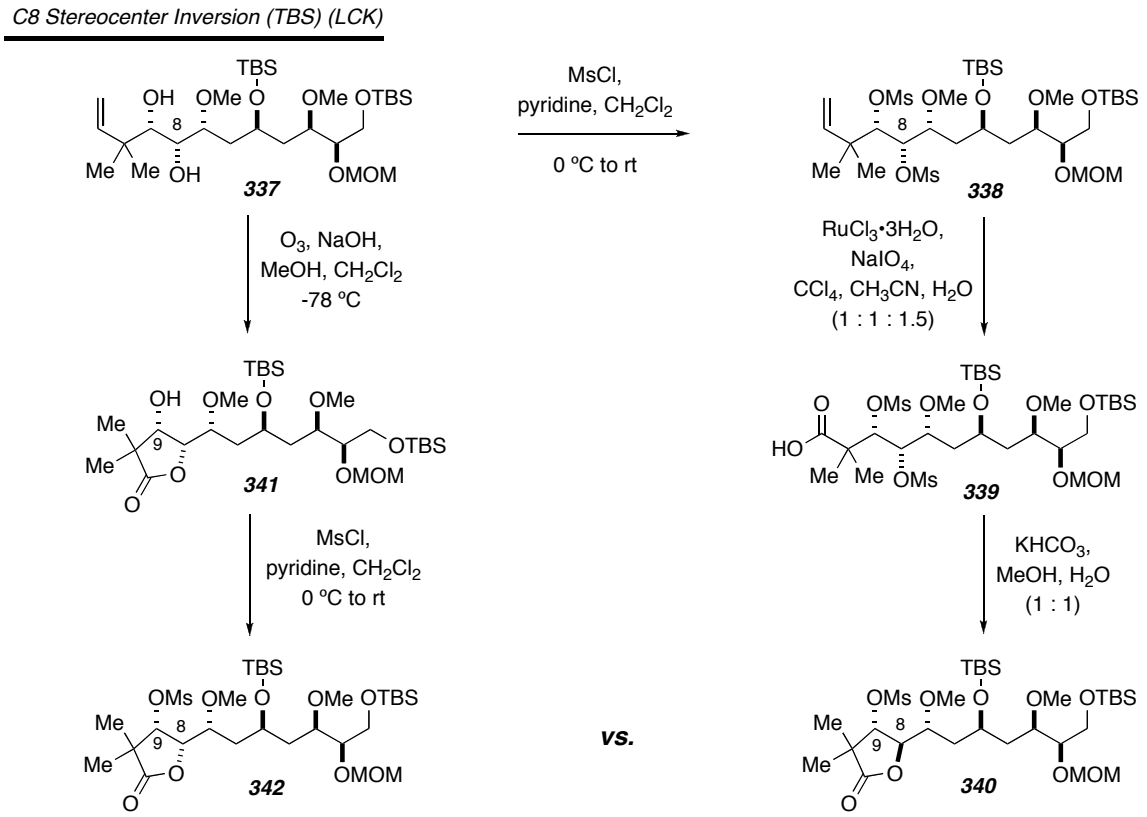


In order to confirm the inversion of the C8 stereocenter both of the C8 epimers needed to be synthesized. This began by bis-mesylation of diol **337** to afford alkene **338** (**Scheme 102**). The alkene of **338** was converted in one-step to the carboxylic acid with ruthenium trichloride ($RuCl_3$) and sodium periodate ($NaIO_4$).[86] The crude carboxylic acid **339** was treated with potassium bicarbonate ($KHCO_3$) in MeOH:H_2O to provide the cyclized lactone **340**, with inversion at the C8 stereocenter.[87] In order to further verify the inversion had occurred, diol **337** was subjected to the oxidative Marshall conditions for converting alkenes directly into esters.[63] The conversion into the ester was followed by cyclization to give γ-lactone **341**. The mesylation of the C9 alcohol provided the lactone **342**, a C8 epimer of **340**. Comparison of the ^1H NMR spectra confirmed that the desired stereochemistry at C8 had been achieved. The C1-C11 fragment of (+)-

[86] "A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds." Carlsen, P. H. J.; Katsuki, T.; Marin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936-3938.
[87] "Preparation of macrodiolides via a common chiral building block. Total synthesis of (-)-pyrenophorin and (-)-pyrenophorol." Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841-844.

peloruside A **1** had now been synthesized with all of the desired stereochemistry and oxygenation in place. Even though I was not fully satisfied with the number of steps required to perform the inversion, I believed I could at least move forward using this route if needed.

Scheme 102



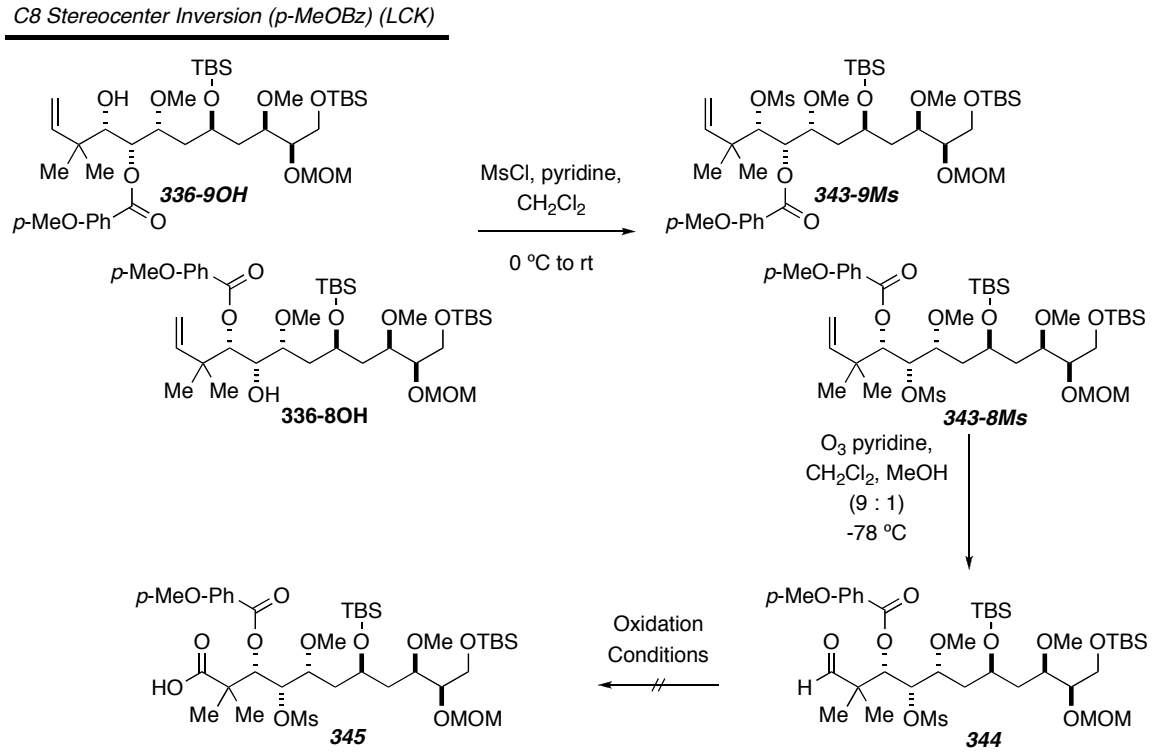
4. Attempted C8 Inversion of TBS Protected Mono-Mesylate

One way in which I believed I could reduce a couple of steps in the current route was by taking advantage of the regioselective opening of the PMP acetal to provide **336-8OH** as the major isomer (3:1). This would keep me from having to perform a protecting group swap after the inversion (OMs to OP at C9) or perhaps the benzoyl protecting group at C9 might be removed under the inversion conditions leaving the hydroxyl free to protect or oxidize.

The mixture of PMP acetals **336-8OH** and **336-9OH** were mesylated under the same conditions as before to afford the separable regioisomers **343-9Ms** and **343-8Ms** (**Scheme 103**). The alkene of **343-8Ms** was unable to be directly converted into a

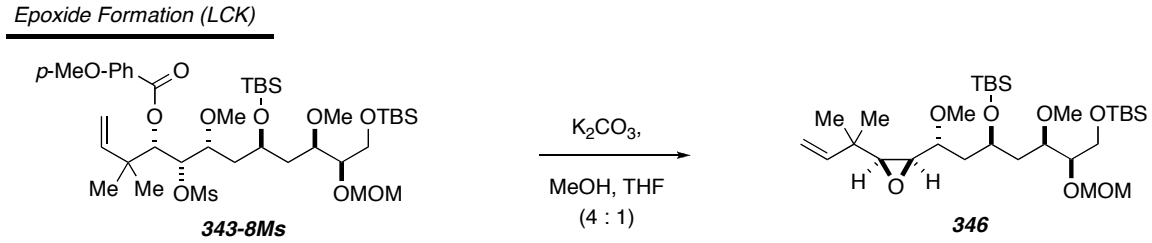
carboxylic acid under the previously used conditions. In order to solve this problem alkene **343-8Ms** was converted into the aldehyde **344** using ozonolytic conditions. However, the carboxylic acid **345** was still unable to be formed using a variety of oxidation procedures. The failure to produce acid **345** was attributed to the lability of the *p*-methoxybenzoyl group and the TBS-ethers. Exchanging the TBS-ethers for TBDPS-ethers was expected to be a solution to this problem.

Scheme 103



Before moving on, attempts were made to remove the *p*-methoxybenzoyl group from **343-8Ms** in an effort to exchange protecting groups without affecting the nearby mesylate (**Scheme 104**). After treating **343-8Ms** with potassium carbonate in MeOH:THF, the *cis*-epoxide **346** was isolated, obviously affecting the mesylate. The coupling constant data for **346** was consistent with formation of a *cis*-epoxide and therefore was indirect evidence for the *syn* stereochemistry resulting from the prenyl indium alkylation of aldehyde/hemiacetal **319-*cis*** (**Scheme 96**).

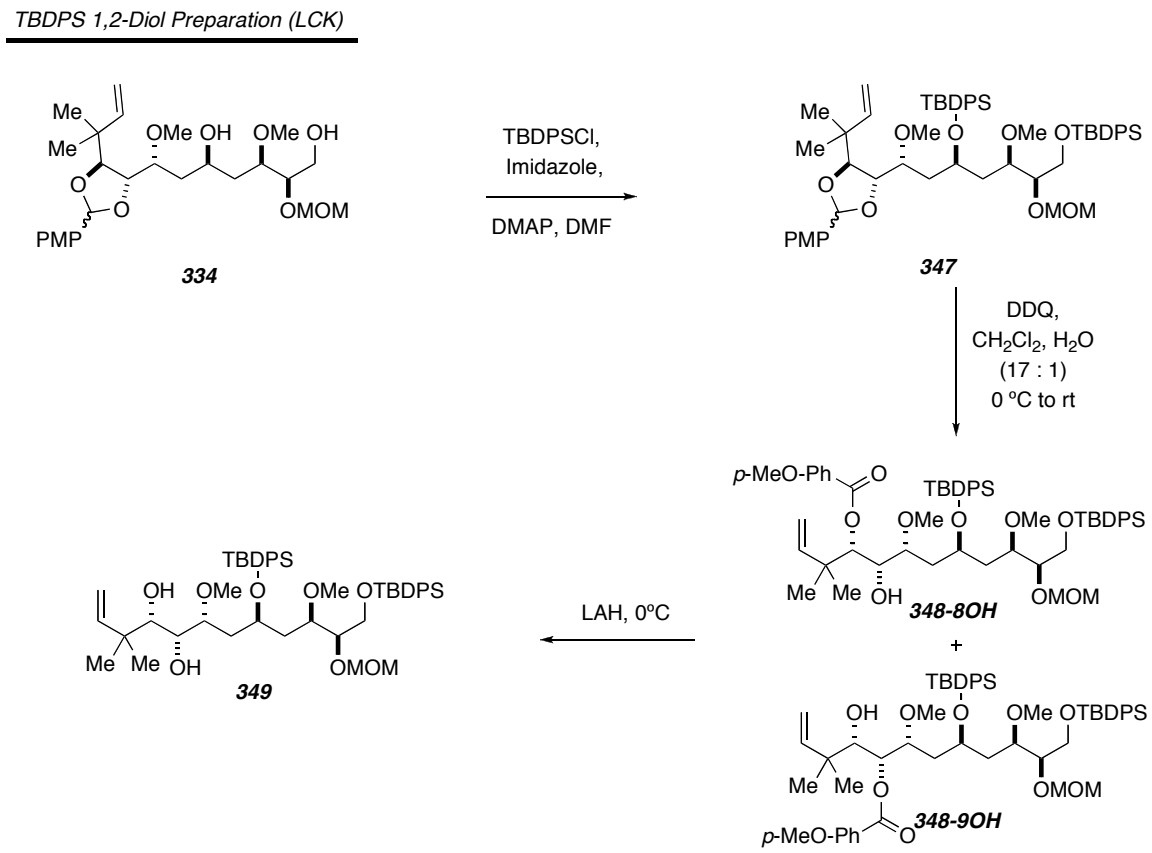
Scheme 104



5. C8 Inversion of TBDPS Protected Bis-Mesylate

In an effort to improve protecting group stability for later reactions, diol **334** was reacted with TBDPSCl in DMF to provide the PMP acetal **347** (**Scheme 105**). Oxidative cleavage of the PMP acetal **347** provided an inseparable regioisomeric mixture of alcohols **348-8OH** and **348-9OH** (1:4) as before. The C8 stereocenter was only inverted two times using the TBS bis-mesylate **339**. In an effort to reconfirm the likeliness of the inversion working, I chose to make the TBDPS bis-mesylate **350** before attempting to invert any mono-mesylated compound. To accomplish this, the mixture of alcohols **348-8OH** and **348-9OH** were exposed to LAH at 0 ºC to produce the desired 1,2-diol **349**.

Scheme 105

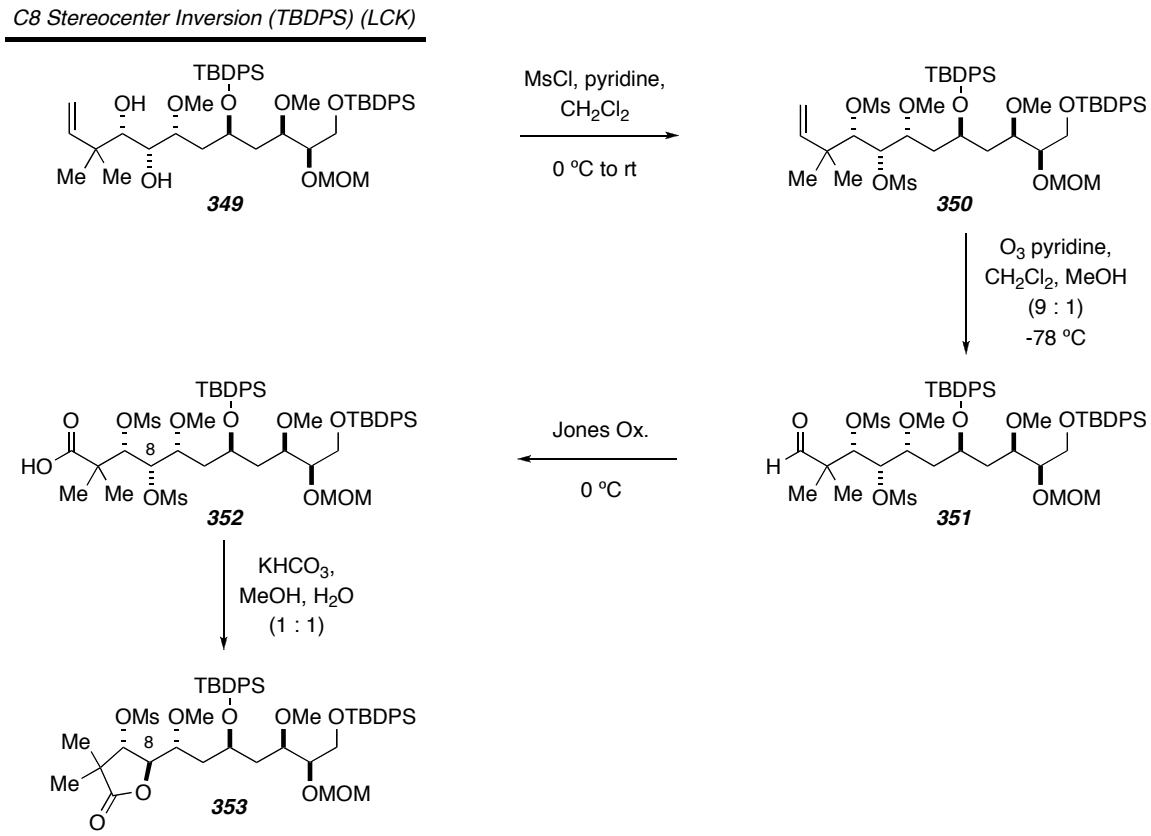


The diol **349** was mesylated using the previous reaction conditions to furnish alkene **350** (**Scheme 106**). Instead of using the one-step $RuCl_3$ procedure to form the carboxylic acid, I was convinced by another Hoye group member, A. Burns, to use a 2-step process instead. The aldehyde **351** was produced under ozonolytic conditions followed by a carefully monitored Jones oxidation[88] of the aldehyde to carboxylic acid **352**. A Jones oxidation on a late stage intermediate like aldehyde **351** would not be a person's first choice of conditions for performing this type of transformation. However, changing to more acid stable TBDPS-ethers and the ease of running the reaction required me to at least try the reaction conditions. The oxidation provided the carboxylic acid **352** in good enough purity that it could be used crude in the next reaction. The inversion of

[88] (a) "13. Researches on acetylenic compounds. Part I. The preparation of acetylenic ketones by oxidation of acetylenic carbinols and glycols." Bowden K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39-45. (b) "129. Researches on acetylenic compounds. Part XV. The oxidation of primary acetylenic carbinols and glycols." Heilbron, S. I.; Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 604-607.

the C8 stereocenter occurred, as before, by treating acid **352** with $KHCO_3$ in MeOH:H_2O to afford the γ-lactone **353**. Success with the TBDPS series of compounds gave me more confidence in performing these types of reactions and an eagerness to find an alternative to the bis-mesylation approach. This would release me from having to use sodium/mercury amalgum to remove the remaining mesylate and reprotecting.

Scheme 106



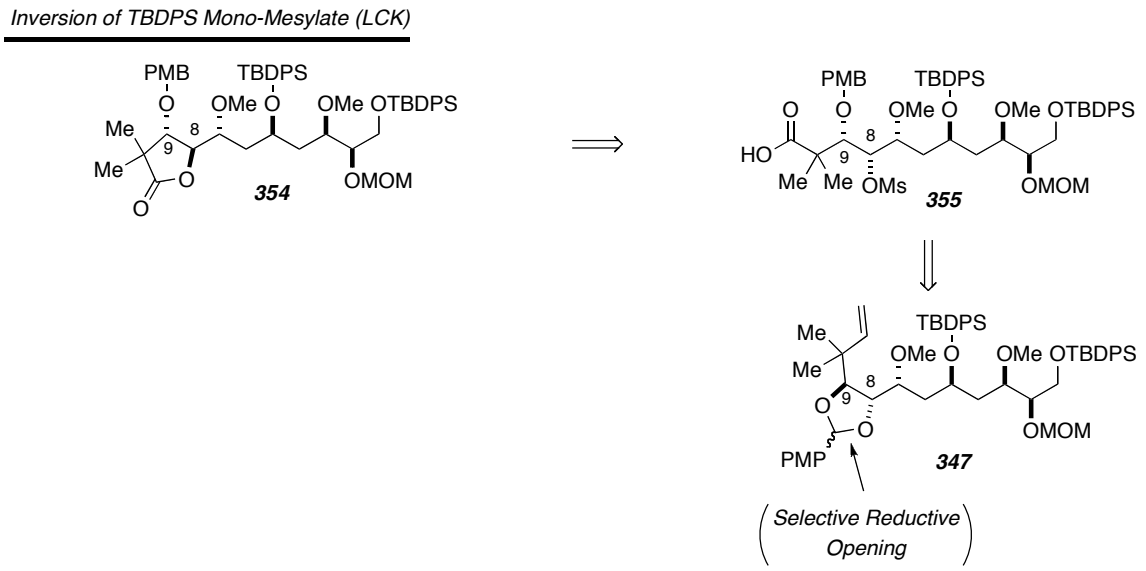
6. C8 Inversion of TBDPS Protected Mono-Mesylate

In the back of my mind I had a specific reason for choosing to protect triol **328** with *p*-anisaldehyde dimethyl acetal. There was literature precedence for the opening of PMP acetals to provide a primary alcohol and a secondary PMB-ether.[81,89] I first became aware of this when a labmate of mine, A. May, used this strategy for some of his model study work. I wondered if I could apply this strategy to the opening of PMP acetal **347** (**Scheme 107**). It was suspected that the *gem*-dimethyl substituent along with the

[89] "A facile cleavage of benzylidene acetals with diisobutylaluminum hydride." Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593-1596.

oxygenation near the C8 stereocenter would allow for selective cleavage between the C8 oxygen and the benzylic carbon of the PMP acetal. The reductive opening could provide the desired regiochemistry needed for elaboration into carboxylic acid **355**. The inversion of the C8 sterecenter would produce γ-lactone **354**, in which no protecting group manipulation would need to occur at the C9 position. Only one previously relevant example was found in which a PMP acetal opening occurred in which both oxygens of the acetal were secondary hydroxyls.[90] Only a modest selectivity was shown and was attributed to the delivery of the reducing agent by a nearby oxygen containing stereocenter in a contrasteric sense.

Scheme 107

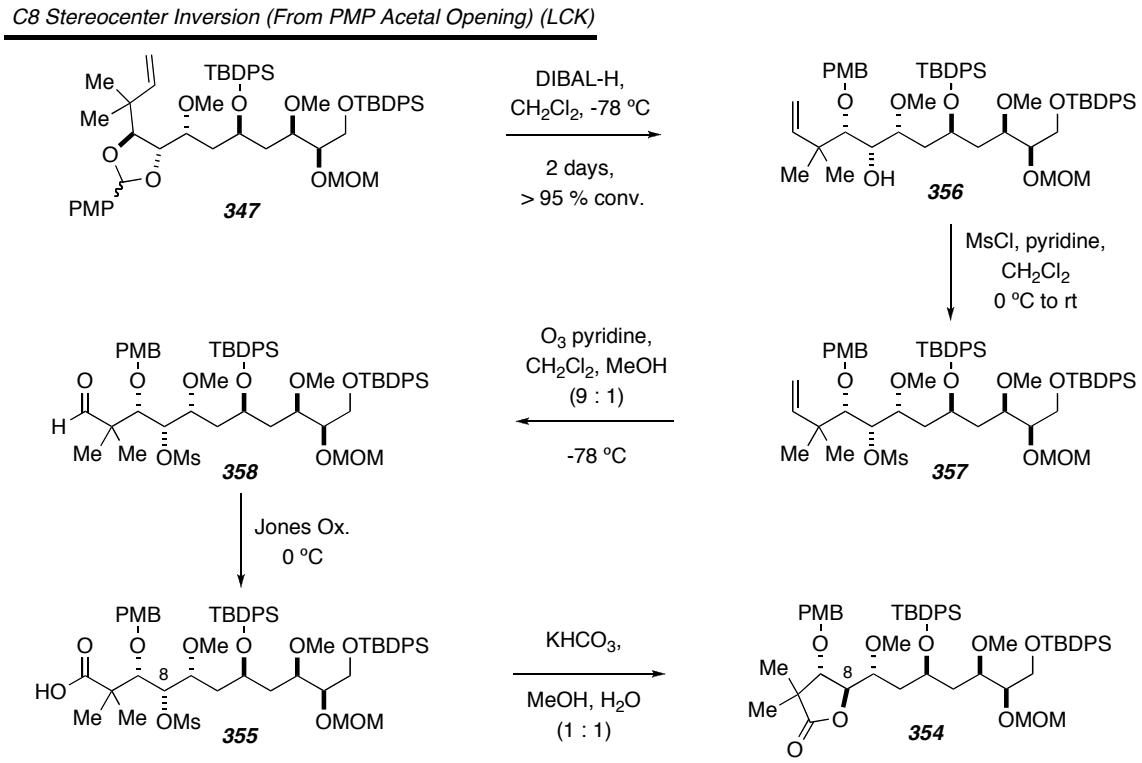


PMP acetal **347** was treated with an excess of DIBAL-H in CH_2Cl_2 at -78 ºC for 2 days to produce the alcohol **356** as the sole product after purification (**Scheme 108**). The reaction rarely went to full conversion under the reaction conditions used, but the remaining starting material **347** could easily be separated from the product **356**. Mesylation of the hydroxyl in **356** was followed by ozonolysis to convert alkene **357** into aldehyde **358**. The ozonlysis had to be stopped at the first sign of blue color, or risk the possibility of oxidizing the benzylic positions of the PMB-ether. A carefully monitored

[90] "Total synthesis of the macrolide antibiotic cytovaricin." Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112,* 7001-7031.

oxidation of aldehyde **358** with Jones reagent provided the carboxylic acid **355**. Like the ozonlysis, if the oxidation were allowed to proceed for too long, a by-product would begin to form. This by-product was never fully characterized, but the crude ^{1}H NMR supported the formation of a *p*-methoxybenzoyl ester. The cylcization of acid **355** with $KHCO_3$ formed the γ-lactone **354** while inverting the C8 stereocenter.

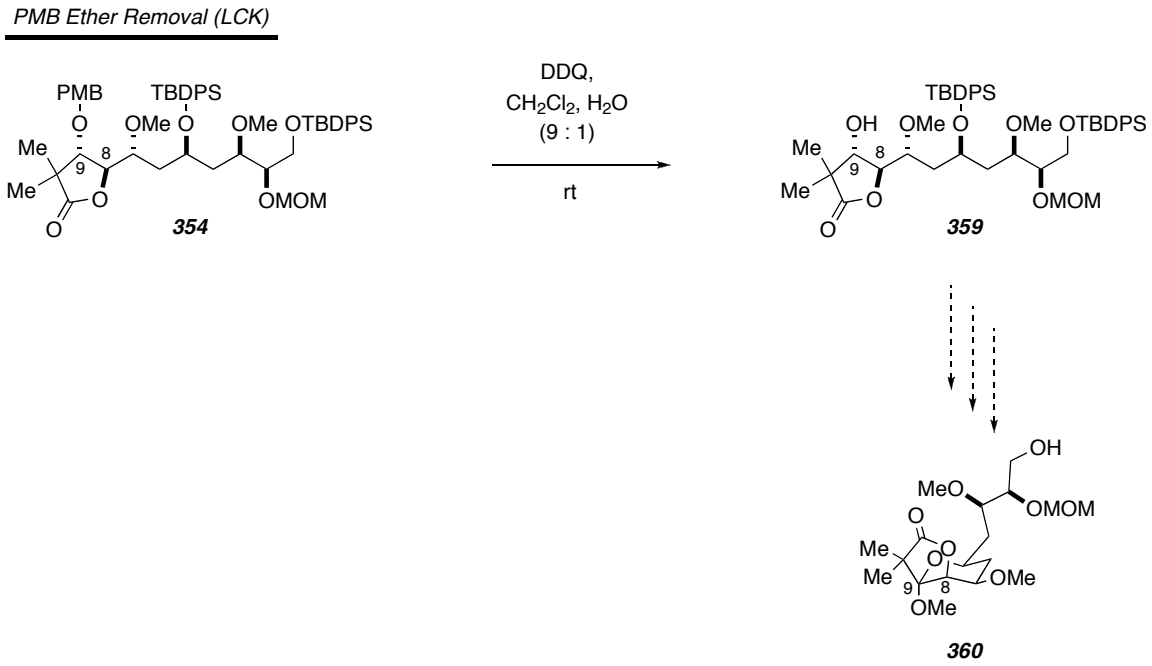
Scheme 108



Removal of the PMB-ether from **354** was investigated at this stage. Treatment of lactone **354** with DDQ in CH_2Cl_2:H_2O (9:1) cleanly removed the PMB-ether to provide alcohol **359** (**Scheme 109**).[91] The C9 hydroxyl could be oxidized at this stage for cyclization to a ketal if needed. However, the decision was made not to perform this operation here due to the possibility of epimerization at the C8 stereocenter during the ketal formation.

[91] "On the selectivity of deprotection of benzyl, MPM (4-methoxybenzyl) and DMPM (3,4-dimethoxybenzyl) protecting groups for hydroxy functions." Horita, K.; Yoshjoka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42,* 3021-3028.

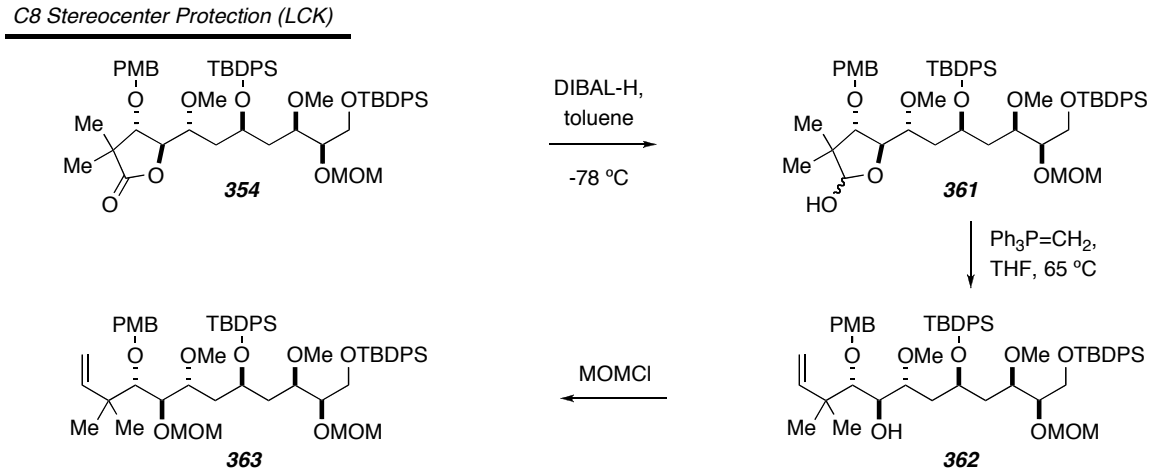
Scheme 109



E. Completion of the C1-C11 Aldehyde Synthesis

The newly formed γ-lactone **354** resembles an intermediate similar to that reported by Roush et al. (compound **141**) in their synthesis of a C1-C11 fragment of (+)-peloruside A **1**.[51] In an effort to reveal the C8 hydroxyl for reprotection, a procedure similar to the one they report was used. Reduction of the γ-lactone **354** with DIBAL-H at -78 ºC produced a 2:1 mixture of anomers of the hemiacetal **361** (**Scheme 110**). A Wittig reaction on this mixture of **361** provided the alkene **362**. Roush reports that in order for the Wittig reaction to proceed at any reasonable rate, it is necessary to heat the reaction. This is due to the equilibrium between the aldehyde and hemiacetal strongly favoring the hemiacetal. This equilibrium was verified by the absence of any aldehyde peak in the ^{1}H NMR of hemiacetal **361**. The free hydroxyl of **362** was then protected as a MOM-ether to provide the bis-MOM-ether **363**.

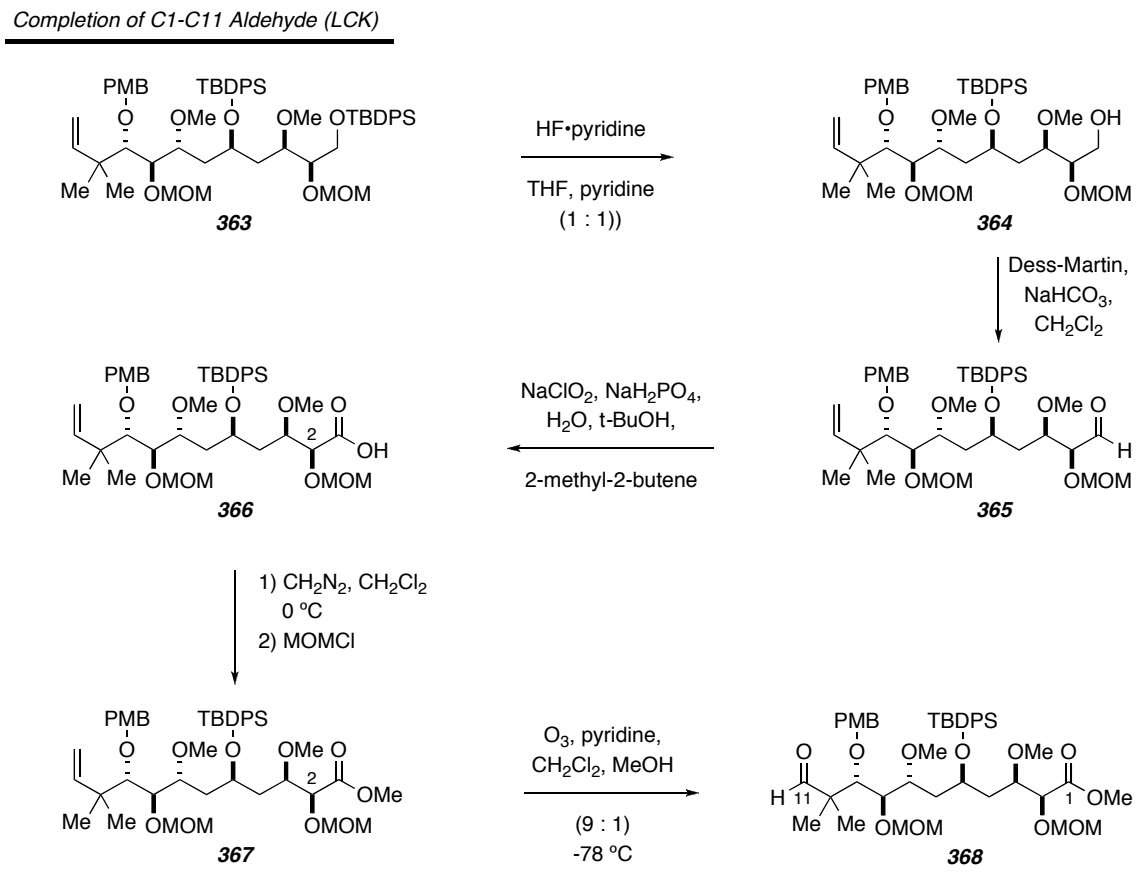
Scheme 110



In order to complete the C1-C11 fragment synthesis, an oxidation state change at C1 and conversion of the terminal alkene into an aldehyde needed to be done (**Scheme 111**). The primary TBDPS-ether needed to be removed in the presence of the secondary. With literature precedence as a guide, treatment of the bis-TBDPS-ether **363** with HF•pyridine in THF/pyridine formed the primary alcohol **364** without affecting the secondary TBDPS.[92] The hydroxyl was converted into a methyl ester under a commonly used three-step protocol. The primary alcohol **364** was converted into aldehyde **365** with Dess-Martin periodinane. The aldehyde was oxidized with sodium chlorite ($NaClO_2$) to provide the carboxylic acid **366**. Esterification of acid **366** with diazomethane produced the desired methyl ester **367**, along with varying amounts of the C2 hydroxyl of ester **367**, resulting from deprotection of the MOM-ether. The removal of the MOM-ether is suspected to be a result of residual acid from the workup during the aldehyde oxidation being added to the CH_2Cl_2 used in the methylation. No MOM deprotection was ever seen in the crude NMR of acid **366** if there was no exposure to a halogenated solvent. It was also later shown that changing the solvent during the methylation to Et_2O eliminated any problems associated with the C2 MOM. Conversion of alkene **367** into aldehyde **368** using ozonolytic conditions completed the C1-C11 fragment of (+)-peloruside A **1**. This aldehyde was now ready to be used in the boron-mediated aldol reaction to bring the two segments of peloruside **1** together.

[92] "Selective monodeprotection of bis-silyl ethers." Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833-5871.

Scheme 111



F. Model Fragment Coupling Strategies

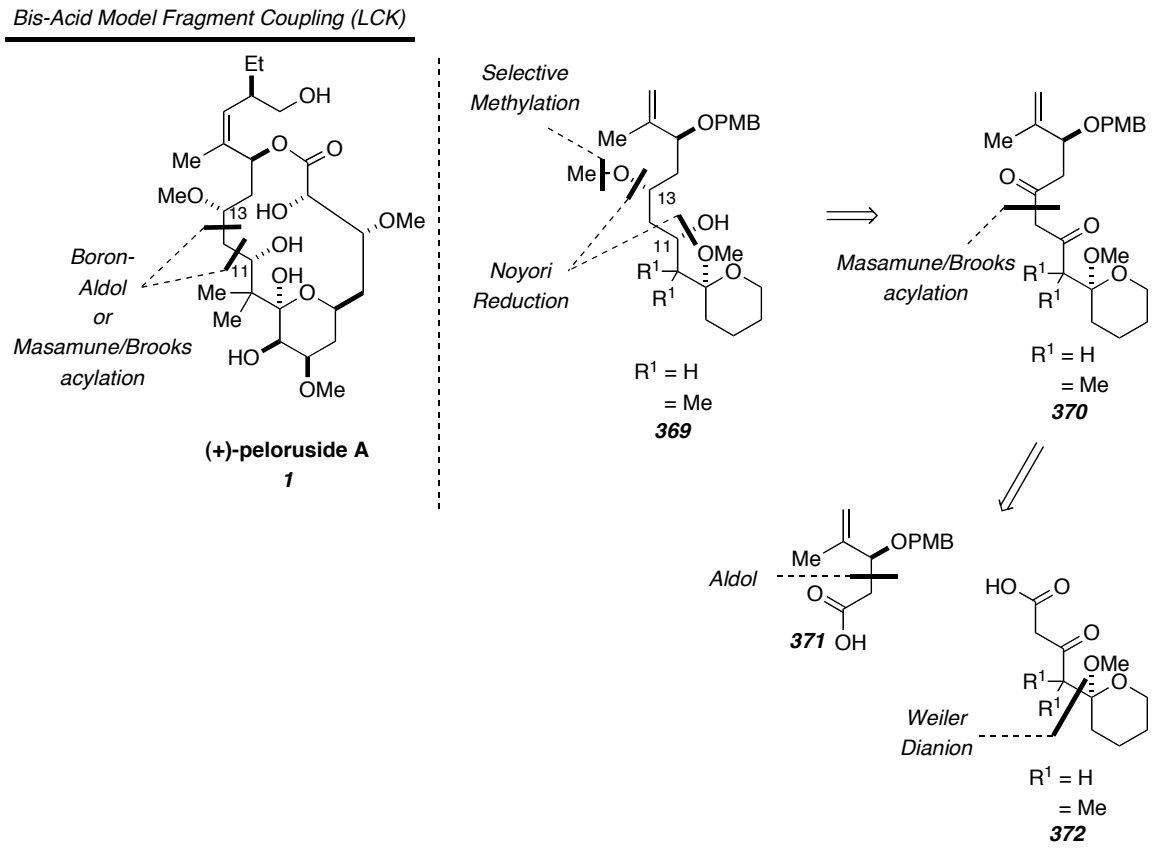
1. 1,3-Diketone Formation

In order to bring the two segments of pelorside A **1** together, our retrosynthetic analysis was initially going to rely on the1,5-induction of a boron-mediated aldol reaction to set the C11 stereocenter, which in turn would be used to set the C13 center (**Scheme 37**). Along the way of working on the synthesis of (+)-peloriside A **1** we became aware of the mild Masamune/Brook acylation to provide 1,3-diketones from a carboxylic acid and β-keto acid (**Scheme 112**).[93] We believed that this reaction could be shown to be useful in a complex natural product setting. The 1,3-diketones could then be reduced

[93] (a) "Use of β-ketocarboxylic acids for syntheses of 6-substituted 4-hydroxy-2-pyrones and acyclic β-diketones." Ohta, S.; Tsujimura, A.; Okamoto, M. *Chem. Pharm. Bull.* **1981**, *29*, 2762-2768. (b) "Synthesis of both the enantiomers of the heterocyclic pheromones isolated from the male swift moth hepialus hecta l." Mori, K.; Kisida, H. *Tetrahedron*, **1986**, *42,* 5281-5290. (c) "C-Acylation under virtually neutral conditions." Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem, Int. Ed.* **1979**, *18*, 72-74.

using Noyori's conditions to provide the desired 1,3-*anti* stereochemistry at C11 and C13. Before committing material to this sequence of reactions attempts were made to apply these conditions to a simple model system in order to learn how to perform the chemistry and see if there were any major problems using this chemistry with our particular type of substrates. The β-keto acid **372** would be formed via a Weiler dianion addition into a lactone. The acid **371** can come from the lithium enolate addition into methacrolein (**76**) followed by protecting group manipulations. The Masamune/Brook acylation would then provide 1,3-diketone **370**, ready for Noyori reduction and selective methylation.

Scheme 112

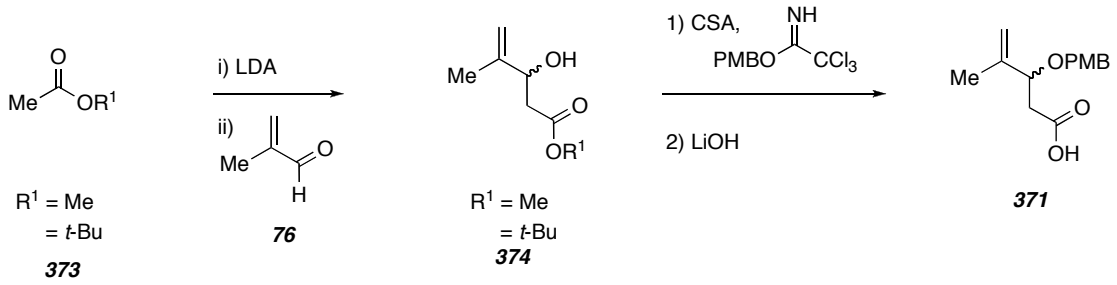


Unaware whether methyl or *t*-butyl acetate **373** would be more appropriate to use, both were initially added into methacrolein (**76**) using their respective lithium enolates (**Scheme 113**). The resulting β-hydroxy methyl and *t*-butyl esters **374** were protected under acidic conditions with PMB trichloroacetimidate. At this stage, only methyl ester

374 was able to be converted into the corresponding acid **371** using lithium hydroxide. All attempts to remove the *t*-butyl ester under acidic conditions led to a complex mixture, resulting from loss of the PMB protecting group. With acid **371** in hand, it was now time to synthesize the β-keto acid.

Scheme 113

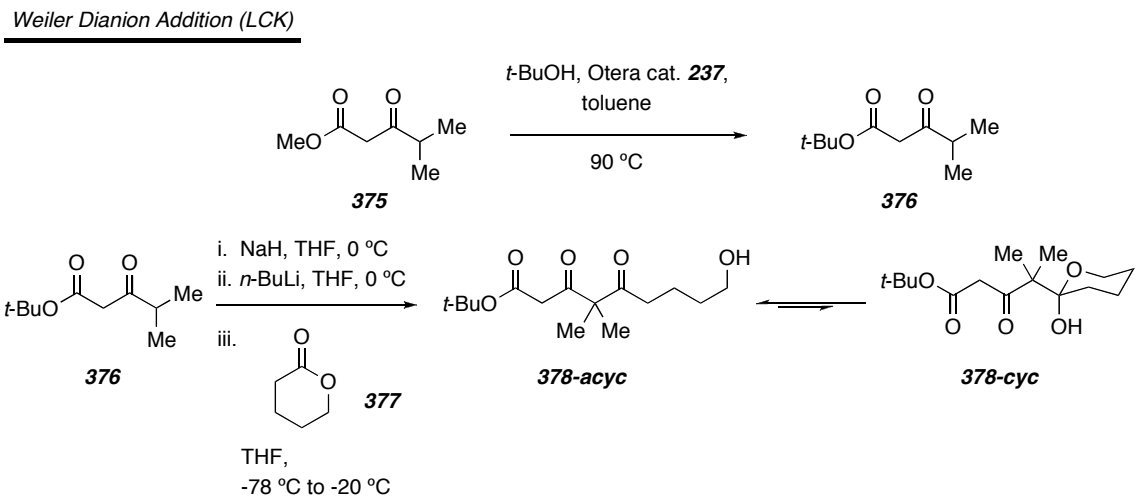
*Synthesis of Acid Fragment **371** (LCK)*



The methyl ester **375** was transesterified with *t*-BuOH and Otera catalyst **237** in toluene to provide the *t*-butyl ester **376** (**Scheme 114**). The Weiler dianion of β-keto ester **376** was formed by sequential treatment with sodium hydride (NaH) and *n*-butyl lithium (*n*-BuLi).[47] A THF solution of δ-valerolactone **377** was added to the dianion solution at -78 ºC and slowly allowed to warm. Purification revealed an equilibrium mixture of acyclic **378-acyc** and cyclic **378-cyc** β-keto esters. The *t*-butyl ester containing the *gem*-dimethyl substituent was not carried forward because the dianion addition of **376** required the use of NaH and *n*-BuLi to form the Weiler dianion. Since there was no readily available access to a glovebox within our group, the quality of the NaH would be compromised with every use if weighed open to the air. This would lead to fluctuations in reproducibility of the reaction. At no time was the reaction successfully reproduced using 2 equiv. of LDA. Therefore, the commercially available *t*-buty acetoacetate (**379**) was used instead because the dianion could easily be prepared with 2 equiv. of LDA. I could at least be confident in the concentration of the LDA as long as the *n*-BuLi was titered.[94]

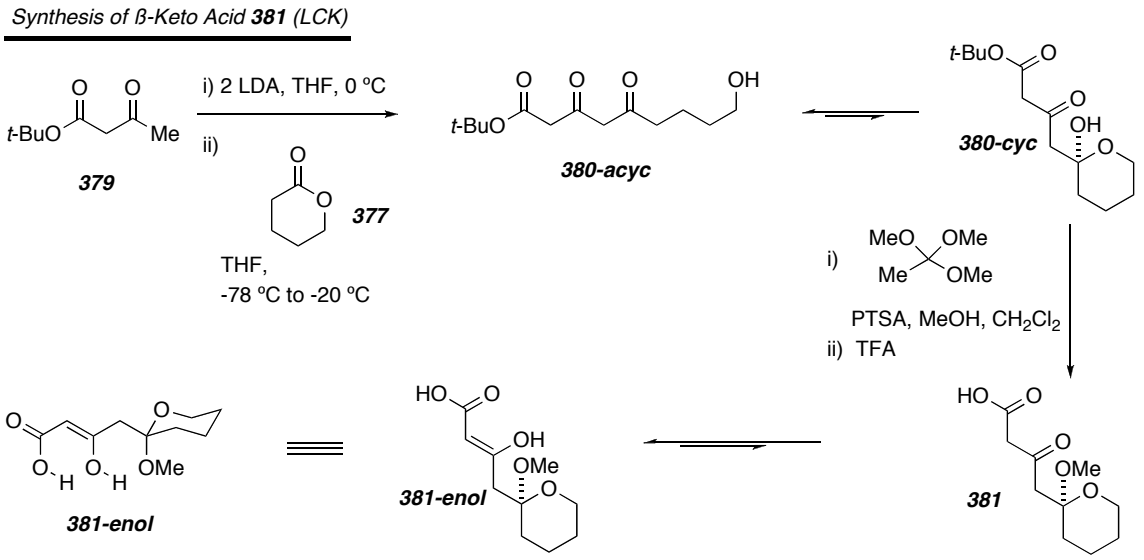
[94] "No-D NMR Spectroscopy as a convenient method for tittering organolithium (RLi), RMgX, and LDA solutions." Hoye, T. R.; Eklov, B. M.; Voloshin, M. *Org. Lett.* **2004**, *6*, 2567-2570.

Scheme 114



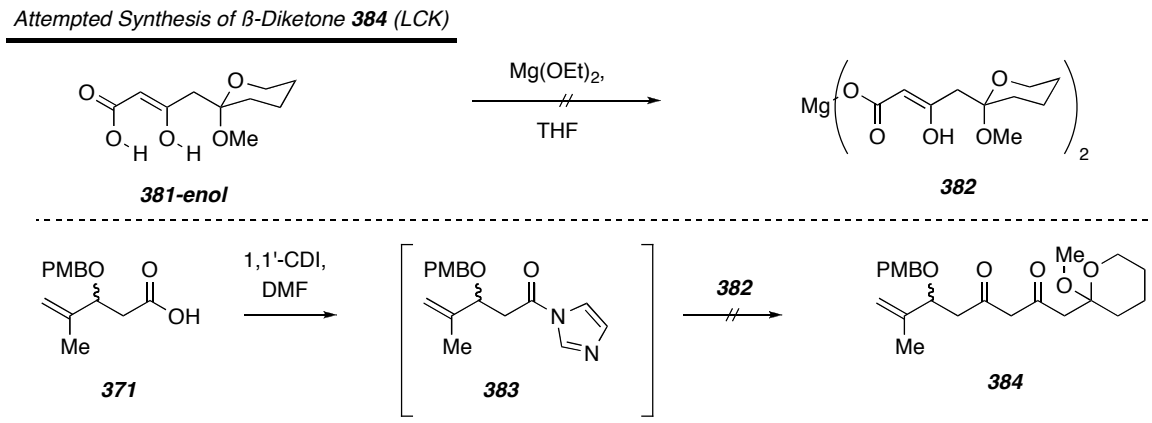
A THF solution of δ-valerolactone **377** was added to the Weiler dianion of *t*-buty acetoacetate (**379**), prepared with 2 equiv. LDA, to produce the equilibrium mixture of **380-*acyc*** and **380-*cyc*** (**Scheme 115**). The β-keto acid **381** was prepared in a one-pot two-step process. The β-keto ester **380** was first subjected to trimethyl orthoformate and PTSA in MeOH:CH_2Cl_2 to produce the methyl ketal. Once TLC showed complete consumpion of the starting material, treatment of this same reaction mixture with TFA afforded the β-keto acid **381**. It is important to state that the acid **381** was shown to reside completely in the enol conformation **381-*enol*** by ^{1}H NMR analysis. The high enol content is believed to be an artifact of the increased stability that results from the hydrogen bonding.

Scheme 115



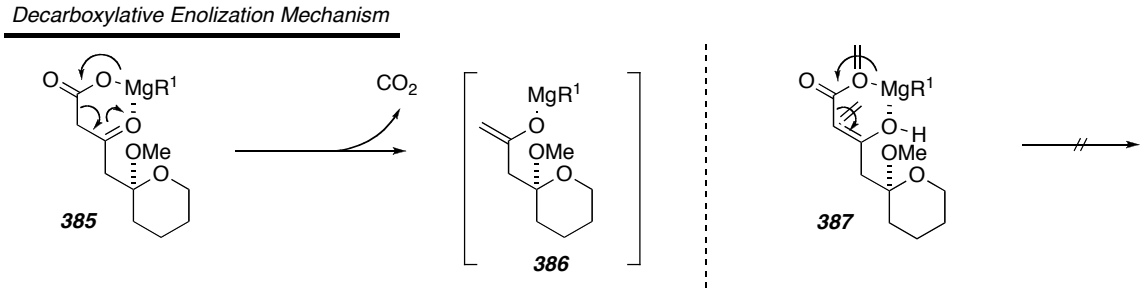
I was now in a position to try the Masamune/Brooks acylation reaction between acid **371** and β-keto acid **381-*enol***. The β-keto acid **381-*enol*** was treated with commercially available magnesium ethoxide to produce what was assumed to be magnesium salt **382** (**Scheme 116**). The acid **371** was reacted with 1,1'-carbonyldiimidazole (1,1'-CDI) in DMF to produce an intermediate imidazolide **383**. The previously prepared magnesium salt **382** was added to the reaction. Upon workup, none of the desired 1,3-diketone **384** was formed. Only the starting materials were recovered after purification.

Scheme 116



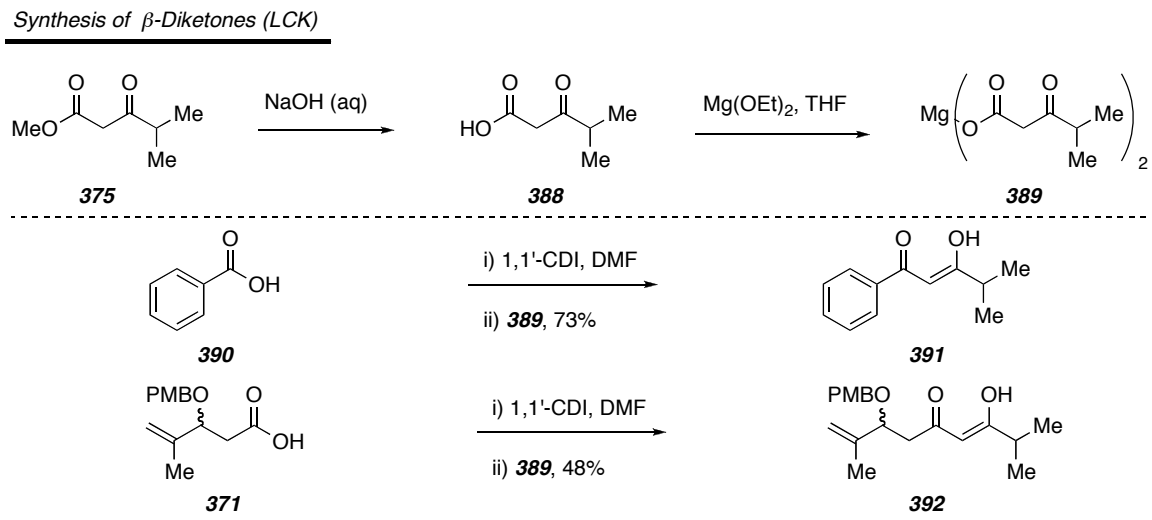
I now had to determine where the reaction was going wrong. There was no way of determining whether magnesium salt **382** was pure or if it was even being formed. After thinking about the mechanism of the enolization event, the trouble was believed to be coming from the magnesium salt **382**, or rather the β-keto acid **381-*enol*** that is transformed into it. In **Scheme 117** one can see that the decarboxylative enolization to form **386** requires the β-keto ester form **385** and not the enol form **387**. With the β-keto acid **381-*enol*** residing only in the enol form, and if this translates over to the magnesium salt **387**, the coupling between the two species will not occur. This exclusivity in the enol content may even be responsible for not forming the magnesium salt **382**.

Scheme 117



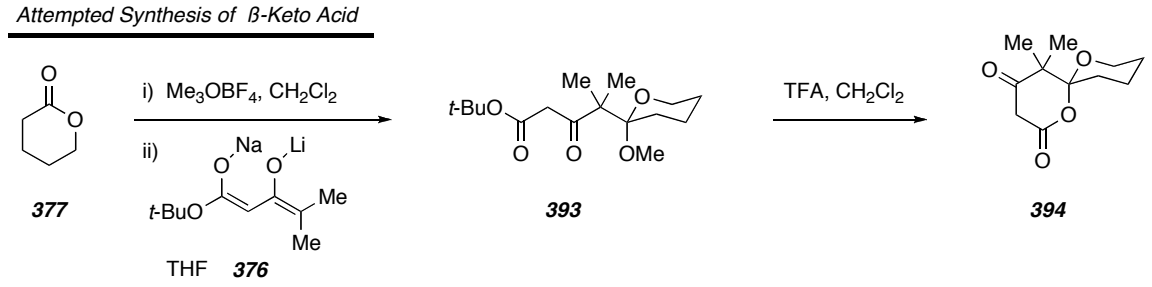
Starting to suspect that the problems with the Masamune/Brooks acylation involved the enol content of β-keto acid **381**, the decision was made to change the acids. Hydrolysis of the commercially available β-keto ester **375** with sodium hydroxide afforded the β-keto acid **388** (**Scheme 118**). Treatment of acid **388** with magnesium ethoxide in THF followed by removal of the solvent provided the magnesium salt **389**. Commercially available benzoic acid (**390**) was initially reacted with 1,1'-CDI followed by addition of the magnesium salt **389** to furnish the 1,3-diketone **391** in a moderate 73% yield. Having succeeded in performing the Masamune/Brooks acylation, acid **371** was subjected to the same reaction conditions as before. After purification by MPLC, the 1,3-diketone **392** was produced in a modest 48% yield. This allowed for some confidence in the likelihood of the Masamune/Brooks acylation producing the desired product when applied to an acyclic peloruside fragment coupling.

Scheme 118



After setting this model system aside for some time I came back to it after having listened to a lecture by Horacio Olivo from the University of Iowa. I attempted to apply some of his reaction conditions in an effort to have a simple one-pot access to β-keto ester **393**.[95] Pretreatment of δ-valerolactone (**377**) with Meerwein's salt followed by addition of Weiler dianion **376** provided a minimal amount of β-keto ester **393** (**Scheme 119**). In an attempt at removing the *t*-butyl group, **393** was treated with TFA like before. The only product isolated from the reaction was the bicyclic system **394**. Production of the cyclization product under these reaction conditions is likely a result of the buttressing affect of the *gem*-dimethyl substituents. This provided more evidence for the Masamune/Brooks acylation not working on a ketal system like **393**.

Scheme 119



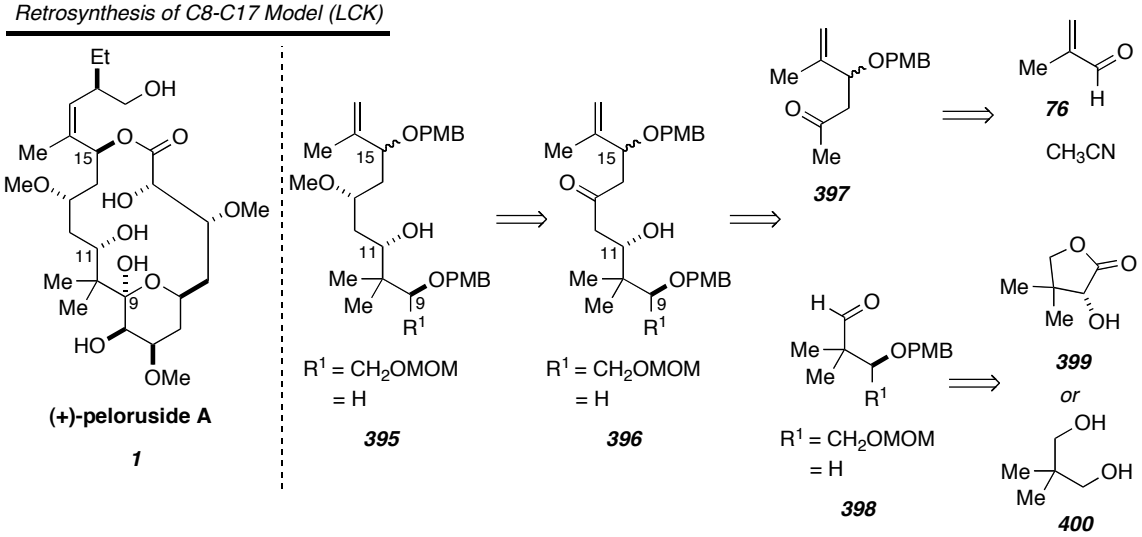
[95] "Synthesis of bicyclic γ-ylidenetetronates." Velázquez, F.; Olivo, H. F. *Org. Lett.* **2002**, *4*, 3175-3178.

Even after achieving some success with the simple acyclic model systems, I was apprehensive in carrying forward with this route. Obtaining low to moderate yields and lack of literature precedence pushed my efforts more towards using the well-established boron-mediated aldol reaction to combine the two fragments of (+)-pelorusdie A **1**.

2. 1,5-*anti* Boron-Mediated Aldol

Our retrosynthetic analysis of (+)-peloruside A **1** relies on two potential reactions for bringing late stage intermediates together. With limited success in the previously discussed Masamune/Brooks acylation, the boron-mediated adol reaction was beginning to look like a more reliable way to go. In an effort to learn about handling the air sensitive boron reagents, their use in aldol reactions, and saving valuable material while investigating other needed chemistry, the synthesis of alcohol **395** was undertaken (**Scheme 120**). The intermediate **395** can come from a 1,3-*anti* reduction of ketone **396** followed by a selective methylation. The β-hydroxy ketone **396** could come from the aldol reaction between ketone **397** and aldehyde **398**. Addition of the lithium anion of acetonitrile into methacrolein (**76**) and subsequent manipulations will arrive at ketone **397**. The aldehyde used in the aldol reaction can come from either (*R*)-pantolactone (**399**) or 2,2-dimethyl-1,3-propane diol (**400**).

Scheme 120

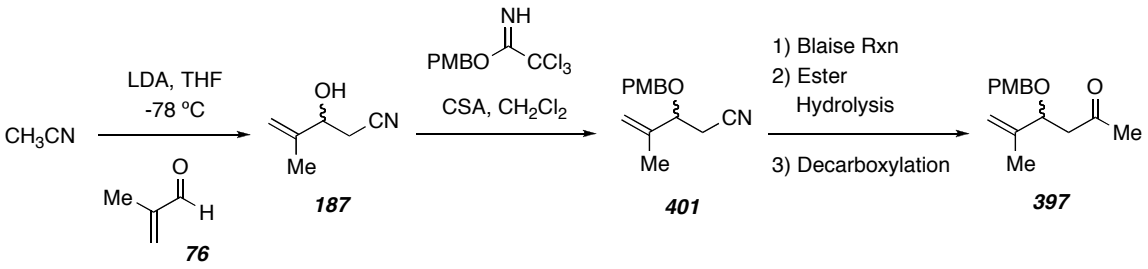


The synthesis of ketone **397** began with the addition of the lithium enolate of acetonitrile into methacrolein (**76**) (**Scheme 121**). Protection of the resulting hydroxyl as

the PMB-ether was conducted with the *p*-methoxybenzyl trichloroacetimidate and CSA to afford nitrile **401**. Conversion of nitrile **401** into ketone **397** was performed by graduate student Junha Jeon who joined me on the project of completing the synthesis of (+)-peloruside A **1**.[96] A three-step sequence was eventually used to produce ketone **397** due to the lability of the protected hydroxyl at the β-position. A Blaise reaction[97] to form the β-keto ester was followed by hydrolysis and finally decarboxylation[98] of the β-keto acid provided ketone **397**.

Scheme 121

*Synthesis of Model Ketone **397** (LCK)*



My initial attempt at the synthesis of a model aldehyde began with reduction of (*R*)-pantolactone **399** followed by 1,3-PMP acetal formation using modified literature procedures (**Scheme 122**).[99] The remaining primary alcohol was protected with MOMCl. Treatment of PMP acetal **402** with DIBAL-H at -78 ºC in CH_2Cl_2 was prematurely believed to give the primary alcohol **403**. It was not until the product alcohol **404** from the reductive opening was oxidized under Swern conditions that the regiochemistry from acetal claeavage had been definitively assigned. The ^{1}H NMR of the product from the Swern oxidation showed no signs of an aldehyde peak and loss of all stereogenicity, helping to confirm the product as ketone **405**. This evidence helped to conclude that the

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[96] Junha, J. D., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2008**.

[97] "One-pot preparation of β-hydroxy esters catalysed by a bis (cyclopentadienyl) titanium (IV) dichloride-zinc system." Ding, Y.; Zhao, G. *J. Chem. Soc., Chem. Commun.* **1992**, 941-942.

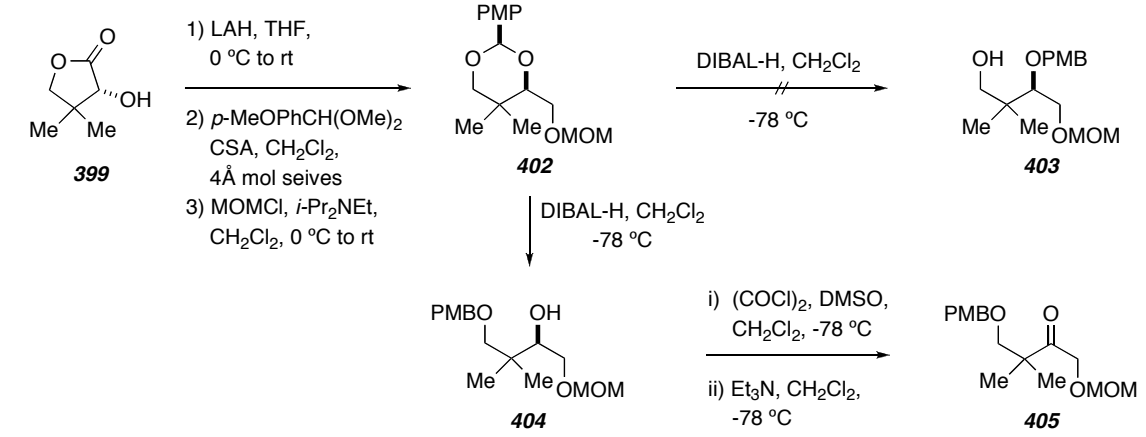
[98] "Development of beta-keto ester and malonate chemsitry: Palladium-catalyzed new reactions of their allylic esters." Tsuji, J. *Proc. Japan. Acad.* **2004**, *80(B)*, 349-358.

[99] (a) "An effective method for the preparation of chiral polyoxy 8-membered ring enone corresponding to the B ring of taxol." Shiina, I.; Shibata, J.; Ibuka, R.; Imai, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 113-122. (b) "The synthesis of deoxyfusapyrone. 1. An approach to the pyrone moiety." Organ, M. G.; Wang, J. *J. Org. Chem.* **2002**, *67*, 7847-7851. (c) "Total synthesis of polycavernoside A, a lethal toxin of the red alga *polycavernosa tsudai*." Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449-5460.

reductive cleavage of the PMP acetal had gone in the complete opposite direction from what literature examples would have predicted. It is not uncommon to obtain mixtures of products during these reactions, but for it to go selectively in the opposite direction is unusual. This result could be attributed to some sort of delivery by the MOM-ether to produce the secondary alcohol **404**.[90]

Scheme 122

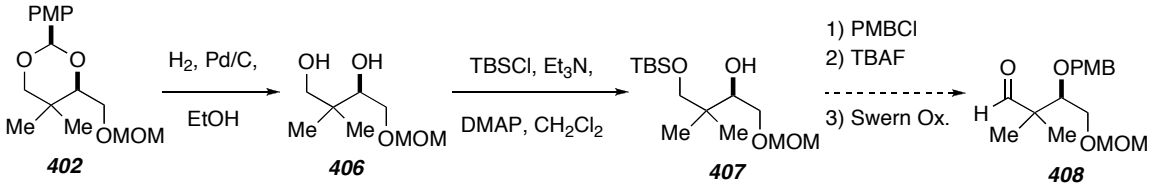
*Attempted Synthesis of Model Aldehyde **405** (LCK)*



In an effort to bypass the regioisomer problem from the acetal opening, PMP acetal **402** was subjected to protecting group manipulations (**Scheme 123**). Hydrogenation provided the diol **406** followed by selective TBS protection of the primary hydroxyl to afford the alcohol **407**. Only three-steps remained to convert **407** into aldehyde **408**: PMB-ether formation, TBS deprotection, and Swern oxidation. However, the decision was made not to pursue this path any further since the number of steps had become too high for what aldehyde **408** was intended for.

Scheme 123

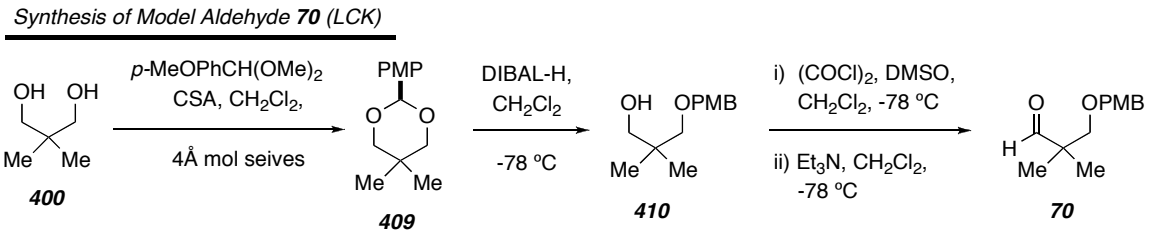
*Alternative Synthesis of Model Aldehyde **408** (LCK)*



The aldehyde Paterson and coworkers used in one of their aldol reactions was used instead (**Scheme 124**).[36] The 1,3-diol **400** was protected as a PMP acetal followed

by reductive cleavage with DIBAL-H to provide alcohol **410**. A final Swern oxidation gave the aldehyde **70** for use in the boron-mediated aldol reaction.

Scheme 124



With both aldehyde **70** and ketone **397-*rac*** in hand it was now time to use the 1,5-*anti* aldol methodology developed by Paterson to combine the two pieces.[36,100] A solution of ketone **397-*rac*** was added to a Et_2O solution containing dicyclohexylchloroborane (*c*-Hex_2BCl) and Et_3N to form the boron enolate (**Scheme 125**). The aldehyde **70** in Et_2O was then added to the preformed boron enolate to provide, after workup, β-hydroxy ketone **411-*rac*** in modest yields. The ^1H NMR spectrum revealed one major diastereomer with an occasional trace amount of the minor isomer in the baseline. The β-hydroxy ketone **411-*rac*** was treated with recently prepared tetramethylammonium triacetoxyborohydride [$Me_4NBH(OAc)_3$] to afford the 1,3-*anti* diol **412-*rac*** in 85% yield.[101] Subjecting diol **412-*rac*** to 2,2'-dimethoxypropane and PPTS provided acetonide **413-*rac*** for ^{13}C NMR analysis according to Rychnovsky's protocol. The data supported the 1,3-*anti* relationship between the hydroxyls in diol **412-*rac***.

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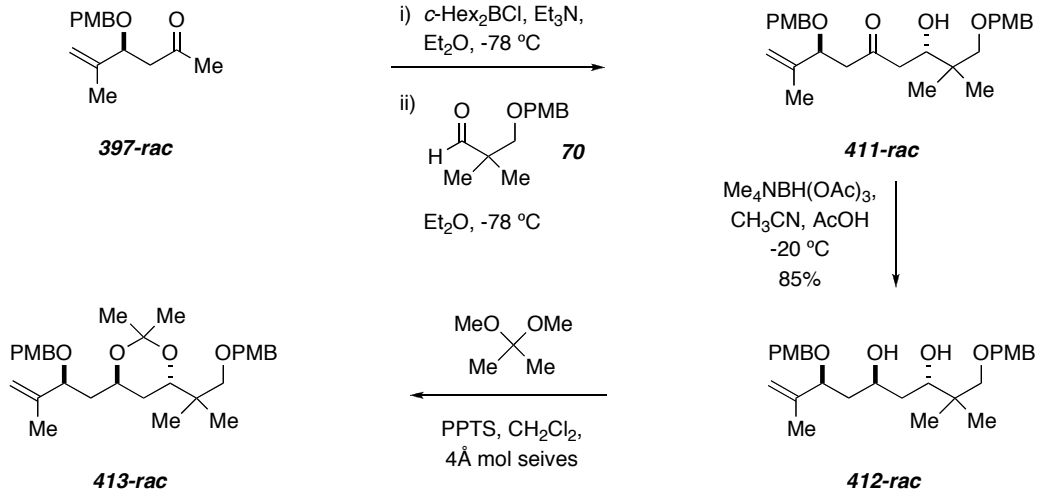
[100] (a) "The stereocontrolled total synthesis of altohyrtin A/spongistatin 1: The AB-spiroacetal segment." Paterson, I.; Coster, M. J.; Chen, D. Y. K.; Oballa, R. M. *Org. Biomol. Chem.* **2005**, *3*, 2399-2409. (b) "The stereocontrolled total synthesis of altohyrtin A/spongistatin 1: The southern hemisphere EF segment." Paterson, I.; Coster, M. J.; Chen, D. Y. K.; Aceña, J. L.; Bach, J. Keown, L. E.; Trieselmann, T. *Org. Biomol. Chem.* **2005**, *3*, 2420-2430. (c) "The stereocontrolled total synthesis of altohyrtin A/spongistatin 1: Fragment couplings, completion of the synthesis, analogue generation and biological evaluation." Paterson, I.; Chen, D. Y. K.; Coster, M. J.; Aceña, J. L.; Bach, J.; Wallace, D. J. *Org. Biomol. Chem.* **2005**, *3*, 2431-2440.

[101] "Directed reduction of β-hydroxy ketones employing tetramethylammonium triacetoxyborohydride," Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578.

Scheme 125

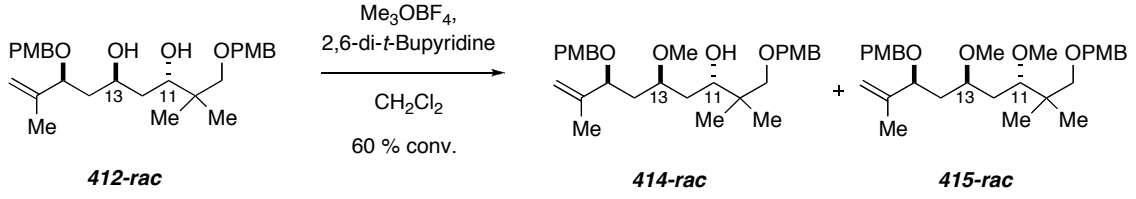
*Synthesis of 1,3-anti Diol **413** Model (LCK)*



In an attempt to learn as much on this model system as possible before moving on to the peloruside intermedieates, the selective methylation of the C13 hydroxyl was investigated (**Scheme 126**). The optimal reaction conditions for selective methylation required treating diol **412-*rac*** with an excess of Meerwein's salt and 2,6-di-*t*-butyl-pyridine and stopping at early conversion, usually between 50% and 60%. The desired methyl ether **414-*rac*** was isolated along with, the sometimes present, bis-methyl ether **415-*rac***. This helped to support using the more direct $Me_4NBH(OAc)_3$ approach instead of the Evans-Tischenko method.[102] Having accomplished as much as possible with this model system, it was now time to apply these transformations to the real system.

Scheme 126

Regioselective Methylation (LCK)



[102] "Samarium-catalyzed intramolecular Tishcheko reduction of β-hydroxy ketones. A stereoselective approach to the synthesis of differentiated *anti*-1,3-diol monoesters." Evans, D. A.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **1990**, *112*, 6447-6449.

G. Boron-Mediated Aldols of Peloruside A Intermediates

I was now in position to use the knowledge I acquired while working with the model system and apply it to the coupling of the highly functionalized ketone **416** (graciously provided by Junha Jeon) and aldehyde **368** (**Scheme 127**).[96] Addition of ketone **416** to an ethereal solution *c*-Hex_2BCl and Et_3N formed the boron enolate. Evidence for the boron enolate formation came from the precipitation of the triethylammonium chloride salt. The aldehyde **368** was next added via an ether solution and allowed to react with the preformed boron enolate. Unfortunately, workup and purification only resulted in recovery of the starting ketone **416** and hemiacetal **417**. No desired aldol product was evident in the crude ^1H NMR. The hemiacetal **417** is believed to arise from a kind of double activation resulting from the complexation of the boron. The lewis acid association of the boron with the aldehyde activates the aldehyde for alkylation during the aldol event, but it in turn activates the MOM-ether for deprotection as well (**Figure 10**). The rates of these two processes must be such that the removal of the MOM-ether is faster and therefore traps the aldehyde as the hemiacetal, stopping any possible chance at constructing the new carbon-carbon bond. It is likely that the *gem*-dimethyl functionality places the conformation of the aldehyde in close proximity to the MOM-ether oxygen, and this allows for this double activation process.

Scheme 127

*C11-Aldehyde **368** / C13 Ketone **416** Aldol Coupling (LCK)*

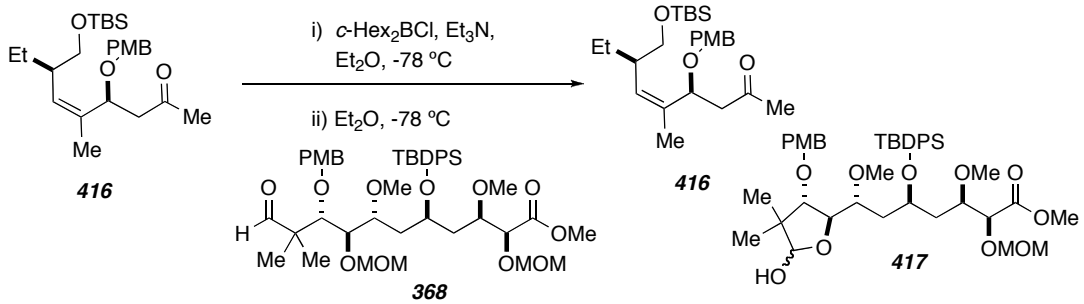
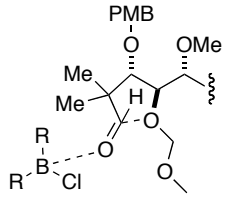


Figure 10

Proposed Double Activation for MOM-Ether Deprotection

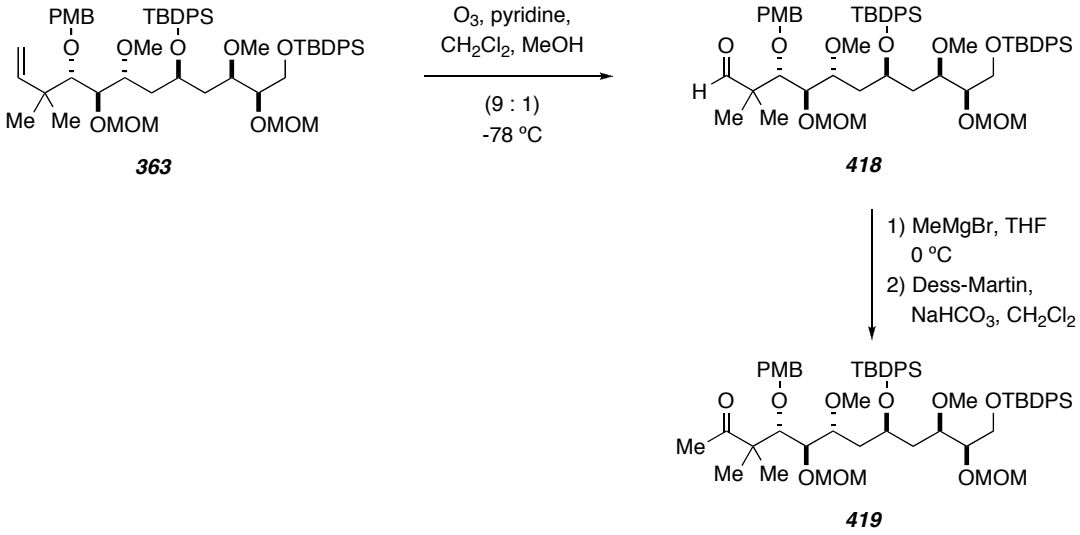


This result called for a modification of the substrate. The logical idea is to replace the MOM-ether with some other type of protecting group and this is what I was intending on doing with material that was coming through the proverbial pipeline. However, a significant amount of bis-MOM protected intermediates were in hand. While scaling-up, the C1-C11 aldehyde fragment was converted into a C1-C12 ketone fragment. One of the reasons for attempting this was that production of ketone **416** required an additional three-steps and resulted in moderate yields,[96] while formation of the C13 aldehyde would require only one through the reduction of the nitrile. This would also allow us to learn more about the coupling of these two late stage intermediates. For instance, would a similar problem with hemiketal formation occur during the production of the boron enolate? An added benefit to this approach is that the stereochemistry of the C9 PMB-ether allows for using Paterson's same 1,5-*anti* aldol methodology to set the C13 stereocenter instead of having to use a chiral reagent based approach.

In order to move forward alkene **363** was converted into the methyl ketone **419** by a simple three-step process (**Scheme 128**). Ozonolysis of alkene **363** provided the aldehyde **418**. This was followed by methyl Grignard addition to produce a mixture of diastereomeric alcohols that were oxidized with Dess-Martin periodinane to produce the methyl ketone **419**.

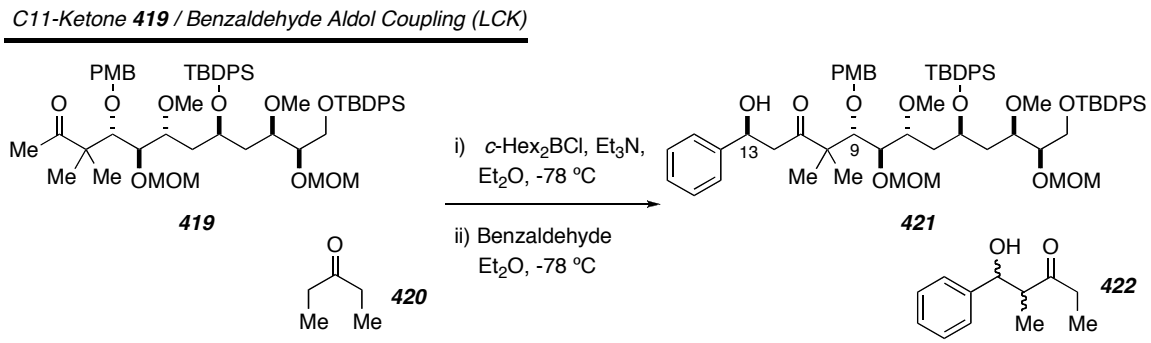
Scheme 128

*Synthesis of C11-Ketone **419** (LCK)*



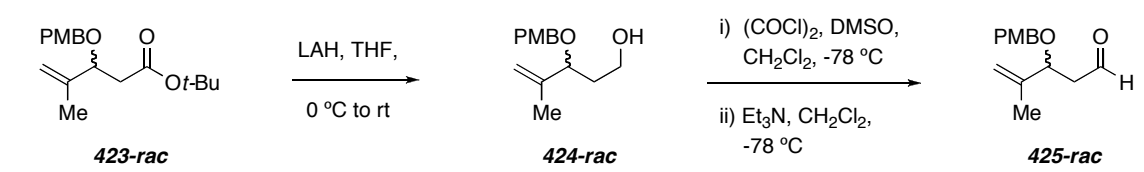
With methyl ketone **419** now in hand, it was time to attempt the boron-mediated aldol. Before trying to couple the valuable peloruside ketone **419** and aldehyde **430**, ketone **419** was reacted with benzaldehyde in an effort to remove any liabilities that may be due to the complex aldehyde **430**. So if any problems presented themselves, they would be because of the ketone **419** and not the aldehyde. Instead of running the aldol reaction with only ketone **419**, a small quantity of ketone **419** was added to 3-pentanone (**420**) and this mixture was subjected to the boron-mediated aldol reaction with benzaldehyde. This *doping* process, allows for a greater quantity of *c*-Hex_2BCl to be used and as a result eliminates quenching a large amount of the reagent by adventitious water. Reaction of ketones **419** and **420** (1 equiv. total) with 2 equiv. benzaldehyde under the same reaction conditions as previously mentioned provided the two separable β-hydroxy ketones **421** and **422** (**Scheme 129**). Interpretation of the ^1H NMR spectrum of **421** revealed only one diastereomer and it was assumed to contain the 1,5-*anti* relationship between the C9 and C13 stereocenters. Even with some positive results using the C11 ketone in the aldol reaction, another aldol needed to be performed with a more representive aldehyde.

Scheme 129



The known aldehyde **425-*rac*** was chosen as a more relevant aldol partner. I was fortunate enough to have already prepared an ample quantity of *t*-butyl ester **423-*rac*** (**Scheme 130**). Complete reduction of ester **423-*rac*** to the primary alcohol **424-*rac*** with LAH was followed by a Swern oxidation to provide known aldehyde **425-*rac***.

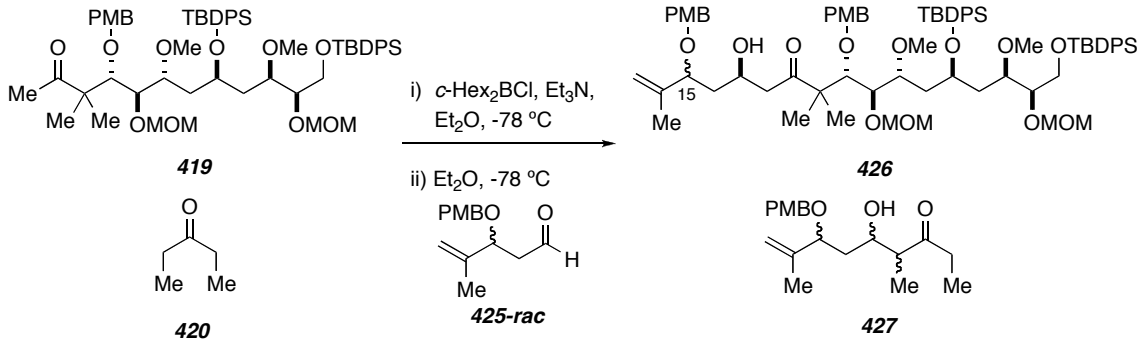
Scheme 130



The newly prepared aldehyde **425-*rac*** (2 equiv.) was subjected to a mixture of the boron enolates derived from ketones **419** and **420** (1 equiv. total), while following the same *doping* procedure previously described to afford β-hydroxy ketones **426** and **427** (**Scheme 131**). The outcome was both exciting and intriguing because only one major diastereomer of β-hydroxy ketone **426** was isolated. Having used the racemic aldehyde **425-*rac***, a ~1:1 ratio of diastereomers that differed at the C15 stereocenter was expected to be obtained. There are two possible explanations that could account for this. I could have just completely missed the other diastereomer during the isolation or perhaps the boron enolate of ketone **419** was biased toward reacting with only one of the enantiomers of aldehyde **425-*rac***. The latter is possible, although somewhat unlikely, since a large excess of aldehyde **425-*rac*** was used compared to ketone **419**.

Scheme 131

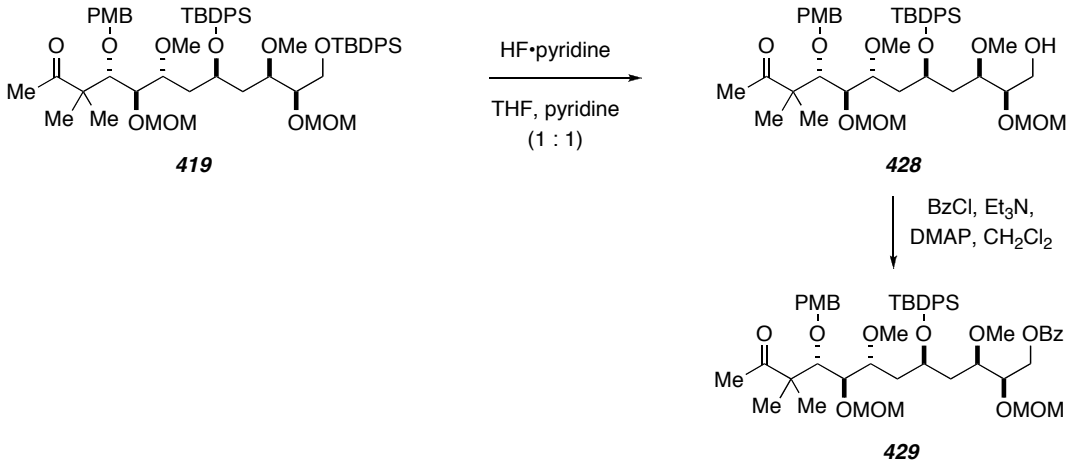
*C11-Ketone **419** / C13 Model Aldehyde **425-rac** Aldol Coupling (LCK)*



After determining that the C11 ketone was a viable coupling partner in the aldol reaction, it was now time to apply it to the real system. Before this could be done some protecting group transformations needed to be performed. The primary TBDPS-ether at C1 of ketone **419** would need to be changed to something else since there is already a primary TBS-ether on the other portion of the peloruside fragment and there is still a need to perform some oxidation chemistry at the C1 position. If one tried to remove the primary TBDPS-ether after the aldol reaction, the primary TBS-ether would more than likely be removed under the same conditions and therefore end any forward progress. To solve this problem, the primary TBDPS-ether was converted to a benzoyl protecting group (**Scheme 132**). Treatment of ketone **419** with HF•pyridine selectively removed the primary TBDPS-ether to give the primary alcohol **428**. Reaction of alcohol **428** with benzoyl chloride provided ketone **429** for the aldol reaction.

Scheme 132

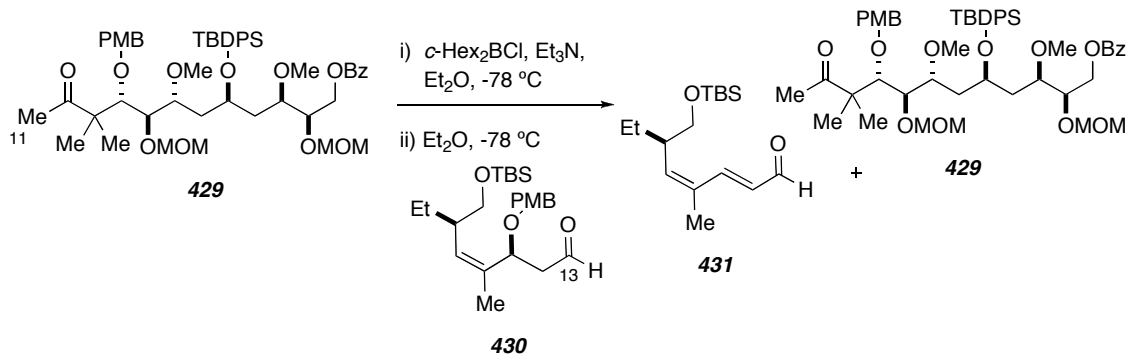
*C11 Ketone **419** Protecting Group Manipulation (LCK)*



After performing the appropriate change of protecting groups, the aldol between C11 ketone **429** and C13 aldehyde **430** could be performed. The C13 aldehyde **430** was prepared by J. Jeon and one is directed toward his Ph.D. thesis for more information about its preparation.[96] Unlike the previous reactions involving the C11 ketone, only 1:1 ketone:aldehyde ratio was used due to the limited quantity of available **430**. This was a result of the difficulty in preparing aldehyde **430**. Treatment of ketone **429** with *c*-Hex_2BCl and Et_3N in Et_2O formed the reactive boron enolate and was followed by the addition of aldehyde **430** in Et_2O (**Scheme 133**). After workup, the crude ^1H NMR spectrum was taken to reveal that no desired aldol product was formed. The only compounds in the spectrum were determined to be recovered ketone **429**, dienal **431**, and *p*-methoxybenzyl alcohol. The latter two are a result of the elimination of the PMB-ether at the β-position under the reaction conditions. It was speculated early on that this elimination process was going to be a potential problem if this route was taken. This line of thinking was supported by Ryba's previous experience with handling aldehyde **198-*S+R*** during the prepration of his lactonization model.

Scheme 133

*C11-Ketone **429** / C13 Aldehyde **430** Aldol Coupling (LCK)*



After discussing the results from using ketone **429** and aldehyde **430**, we reevaluated the likelihood of success using these two fragments and came to the conclusion that the aldehyde **430** was just too unstable to be used in the aldol reaction. The difficulty in preparing aldehyde **430** only compounded matters. I then stopped performing any aldol reactions so I could bring material through as quickly as possible. The next strategy to couple the two fragments of peloruside was to revisit the old route and go back to using the C11 aldehyde and C13 ketone for the aldol. The only difference this time is that the C8 hydroxyl would not be protected as a MOM-ether, but as a TBS-ether. This change in protecting group should eliminate the deprotection and hemiacetal formation previously responsible for stopping the aldol reaction.

H. Revised C1-C11 Aldehyde Synthesis

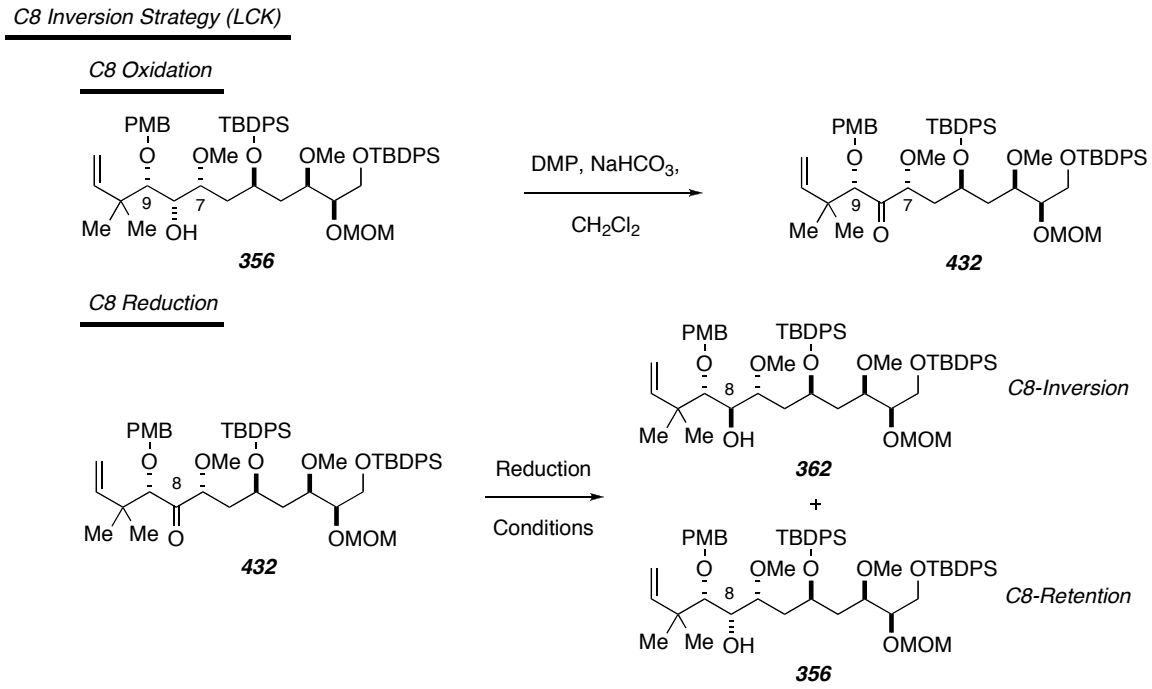
1. New C8 Inversion Strategy (Oxidation/Reduction)

The C8 stereocenter of alcohol **356** was previously inverted by a lengthy intramolecular inversion strategy: mesylation, ozonolysis, oxidation to the acid, cyclization to invert, DIBAL-H reduction, and Wittig to reveal the inverted C8 hydroxyl. Even though all the steps are high yielding, there are still a large number of reactions to perform. One of the ideas I wanted to try the next time I had alcohol **356** in hand was to try a simple oxidation/reduction to invert the C8 stereocenter. Having obtained pure samples of both C8 epimers **356** and **362** via the previous route, the two samples were compared side by side using TLC. It was then concluded that the R_f values of each would allow for easy separataion by MPLC if the reduction was not 100% selective for

the (*R*)-isomer. A recycling process could then take place to prepare more material. There were two reasons for not attempting this before. First of all, the two epimers may not have been separable by normal chromatographic methods. Second, epimerization at the adjacent C7 and C9 stereocenters was thought to be a potential problem. With one of those concerns addressed, the only way to know about the other is to perform the oxidation and reduction reactions.

The oxidation was performed with Dess-Martin periodinane because of its ability to oxidize sensitive substrates (**Scheme 134**). Treatment of alcohol **356** with a slight excess of periodinane provided ketone **432** after workup. No epimerization of the adjacent stereocenters was apparent at this point. The next task was to screen reducing conditions to find the one that gave the best ratio of products.

Scheme 134



The range of conditions screened can be seen in **Table 9**. The chelation controlled reducing agents like zinc borohydride [$Zn(BH_4)_2$] were believed to be the best option for obtaining the *anti*-relationship needed in the product.[103] There seemed to be no

[103] "Stereoselective reduction of α-hydroxy ketones." Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653-2656.

apparent trend between the various conditions. Some notable conditions to point out are the reductions with DIBAL-H and $CeCl_3$•$NaBH_4$ because both of them resulted in 100% retention of the C8 configuration. There did appear to be a small solvent effect changing from Et_2O to CH_2Cl_2 when $Zn(BH_4)_2$ was used. A slight increase in the ratio of the desired C8 inverted product **362** was a result of this. The decision was eventually made to reduce ketone **432** using $Zn(BH_4)_2$ in CH_2Cl_2 at 0 ºC. It was a quick and simple process that resulted in yields of 50-60% (over two-steps) and ~15-20% of non-inverted alcohol **356**. The oxidation/reduction process eliminated four-steps from the previous route.

Table 9

C8 Inversion Strategy (Reduction Conditions)

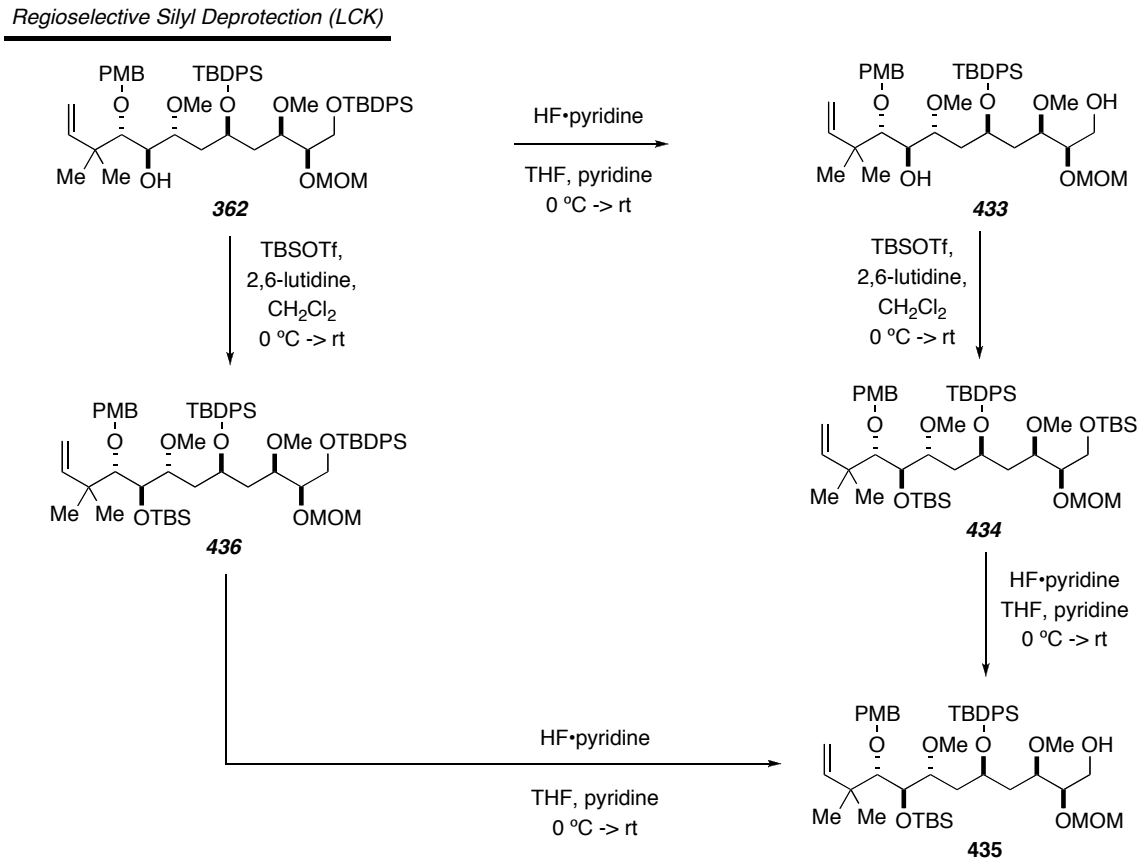
Reducing Agent	Solvent	Temp. ºC	Molarity M	Stereochemistry *C8-Inversion **362** : C8-Retention **356***
$Zn(BH_4)_2$	Et_2O	0	.005	1.3 : 1
$Zn(BH_4)_2$	Et_2O	- 20	.005	1.3 : 1
DIBAL-H	CH_2Cl_2	- 78	.005	0 : 1
L-selectride	THF	- 78	.005	0 : trace < 5 % conv.
$LiBH_4$	Et_2O	0	.005	1.2 : 1
$HLiAl(O\textit{t}\text{-}Bu)_3$	Et_2O	0 -> rt	.005	1 : 2.5
$LiBH_4$	Et_2O	0	.005	1.5 : 1
$CeCl_3$•$NaBH_4$	EtOH	-78 -> rt	.005	0 : 1
Red-Al	toluene	-78 -> 0	.005	1 : 3.8
$LiBH_4$	Et_2O	0	.014	1 : 2.9
$Zn(BH_4)_2$	Et_2O	0	.015	1.2 : 1
** $Zn(BH_4)_2$	CH_2Cl_2	0	.02	2 : 1

2. Completion of C5-TBDPS Protected C1-C11 Aldehyde

With all of the stereocenters for (+)-peloruside A **1** now set, it was time to install the new protecting group at the C8 hydroxyl. A TBS-ether seemed to be a logical choice because of its compatibility with other groups and robustness towards the transformations that still needed to be performed. The dilemma was, if the C8 hydroxyl of **362** was protected as a TBS-ether, the primary TBDPS-ether needed to be removed in the presence of the newly formed secondary TBS-ether. There was not good literature precedence for this taking place. One way around this was to deprotect the primary TBDPS-ether of **362** with HF•pyridine under the same conditions as before to provide

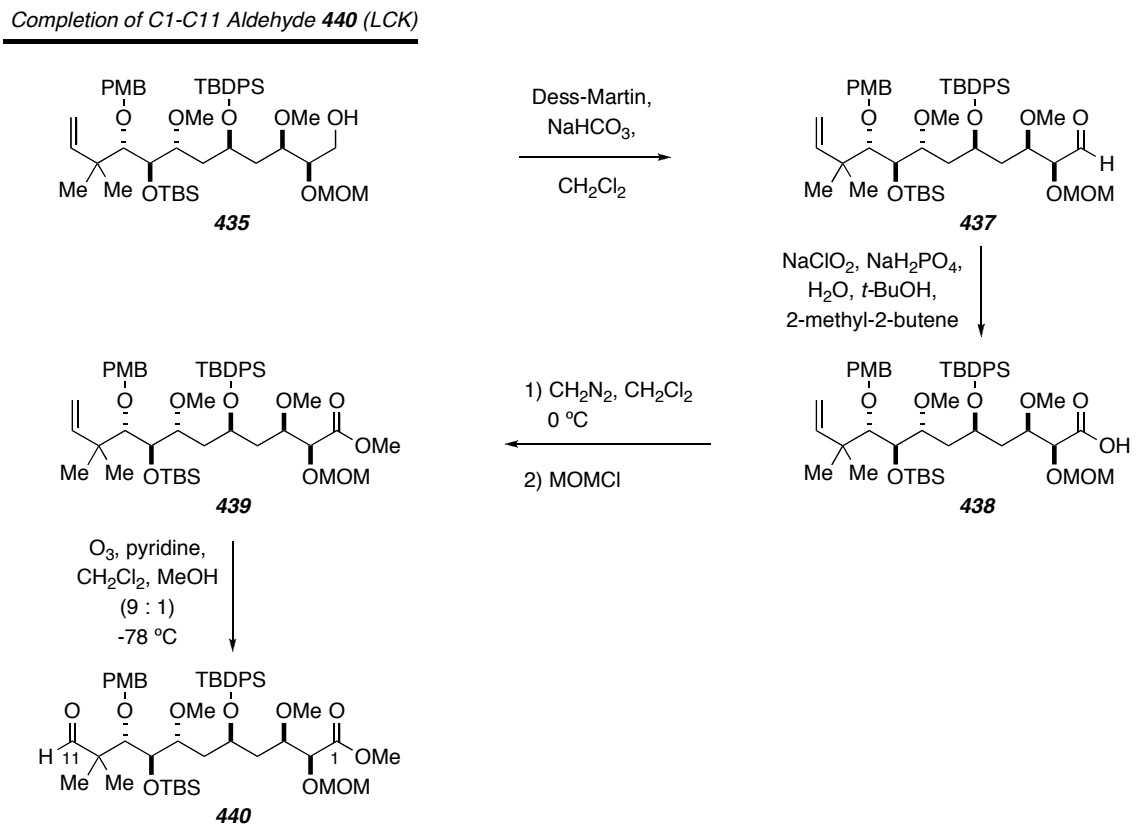
diol **433** (**Scheme 135**). This diol was then bis-protected with TBSOTf to give **434**. There is much more precedence in the literature for deprotecting a primary TBS in the presence of a secondary TBS. The bis-TBS-ether **434** was treated with HF•pyridine at 0 ºC. Due to the slow nature of the deprotection, the reaction was warmed to room temperature. After TLC showed complete consumption of the starting material, the reaction was worked up to provide alcohol **435**. Taking into consideration the amount of time the reaction was at room temperature, it was concluded that the rates of the primary TBDPS and secondary TBS deprotections were different enough under the HF•pyridine conditions that at least an attempt at removing the primary TBDPS in the presence of the secondary TBS was warranted. Protection of alcohol **362** with TBSOTf provided the TBS-ether **436**. The silyl ether **436** was treated with HF•pyridine under the same reaction conditions as previously described to induce loss of the primary TBDPS and provide the primary alcohol **435** after workup. The selectivity in the primary TBDPS removal can be attributed to the congested environment that the secondary TBS-ether resides in.

Scheme 135



The alcohol **435** was now in a position to perform some oxidation chemistry on and finish the C1-C11 fragment. Aldehyde **437** was formed from the oxidation of alcohol **435** with Dess-Martin periodinane (**Scheme 136**). A Pinnick oxidation was then used to convert aldehyde **437** into the carboxylic acid **438**. Diazomethane allowed for formation of the methyl ester from acid **438**. The crude methyl ester was contaminated with a minor amount of the C2 hydroxyl. Subjecting this mixture of crude material to MOMCl produced the methyl ester **439**. Over 1.0 gram of **439** was produced via this route. Careful ozonolysis of the alkene in **439** provided the aldehyde **440** and finished the synthesis of the C1-C11 fragment of (+)-peloruside A **1**.

Scheme 136



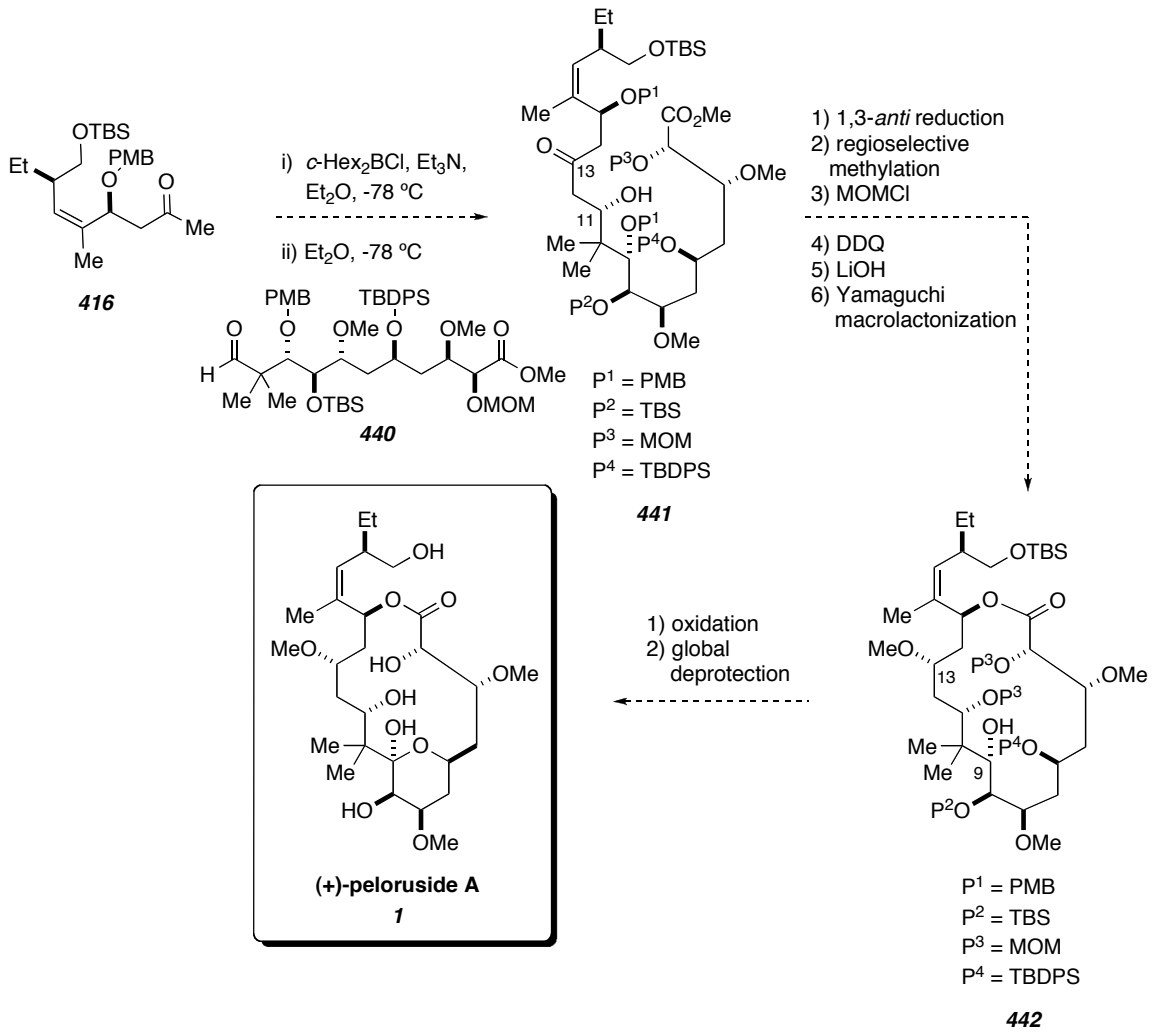
I. Projected Completion of (+)-Peloruside A

Instead of continuing on with conducting aldol experiments and carrying on towards finishing the synthesis of (+)-peloruside A **1**, I handed the advanced intermediate **440** over to my fellow capable coworker and graduate student Junha Jeon, whenever it was needed, so he could move this project forward and eventually to completion. At this point only nine-steps remained to complete the synthesis of peloruside A **1** (**Scheme 137**). The 1,5-*anti* aldol methodology should be able to combine ketone **416** and aldehyde **440** to form β-hydroxy ketone **441** and set the C11 stereochemistry. The 1,3-*anti* reduction of **441** with $Me_4NBH(OAc)_3$ should provide the desired 1,3-*anti* diol. This would be followed by selective methylation of the C13 hydroxyl. Both the reduction process and selective methylation have already been shown to work in a simple model system. The remaining C11 hydroxyl can be protected as a MOM-ether. Treatment with DDQ should remove both of the PMB-ethers. The methyl ester can be hydrolyzed to provide the corresponding acid. This acid can then be subjected to selective Yamaguchi

lactonization to close the macrolactone ring and form macrolide **442**. Oxidation of the remaining free C9 hydroxyl should produce the ketone and a final global deprotection would provide (+)-peloruside A **1**.

Scheme 137

Projected Completion of (+)-Peloruside A (LCK)



J. Synthesis of C5-TBS Protected C1-C11 Aldehyde

During Junha Jeon's work at advancing toward pelourside A **1**, he became increasing concerned about the harsh conditions that it may take to remove the secondary TBDPS-ether. Through discussion with him, a decision was made to advance some material forward that I had left behind at an earlier stage. This material was strategically stored in case removing the TBDPS was a problem.

The PMP acetal **335** was treated with DIBAL-H at -78 ºC to selectively form the alcohol **443** (**Scheme 138**). The oxidation/reduction process was investigated to determine the optimal conditions for producing the C8 inverted product. Treatment of alcohol **443** with Dess-Martin periodinane furnished the ketone **444**. Only a few reduction conditions were tried, but eventually I went back to the same $Zn(BH_4)_2$ conditions that were used before (**Table 10**). Similar yields and selectivities were seen with the TBS protected ketone **444** as was seen with the TBDPS ketone **432**.

Scheme 138

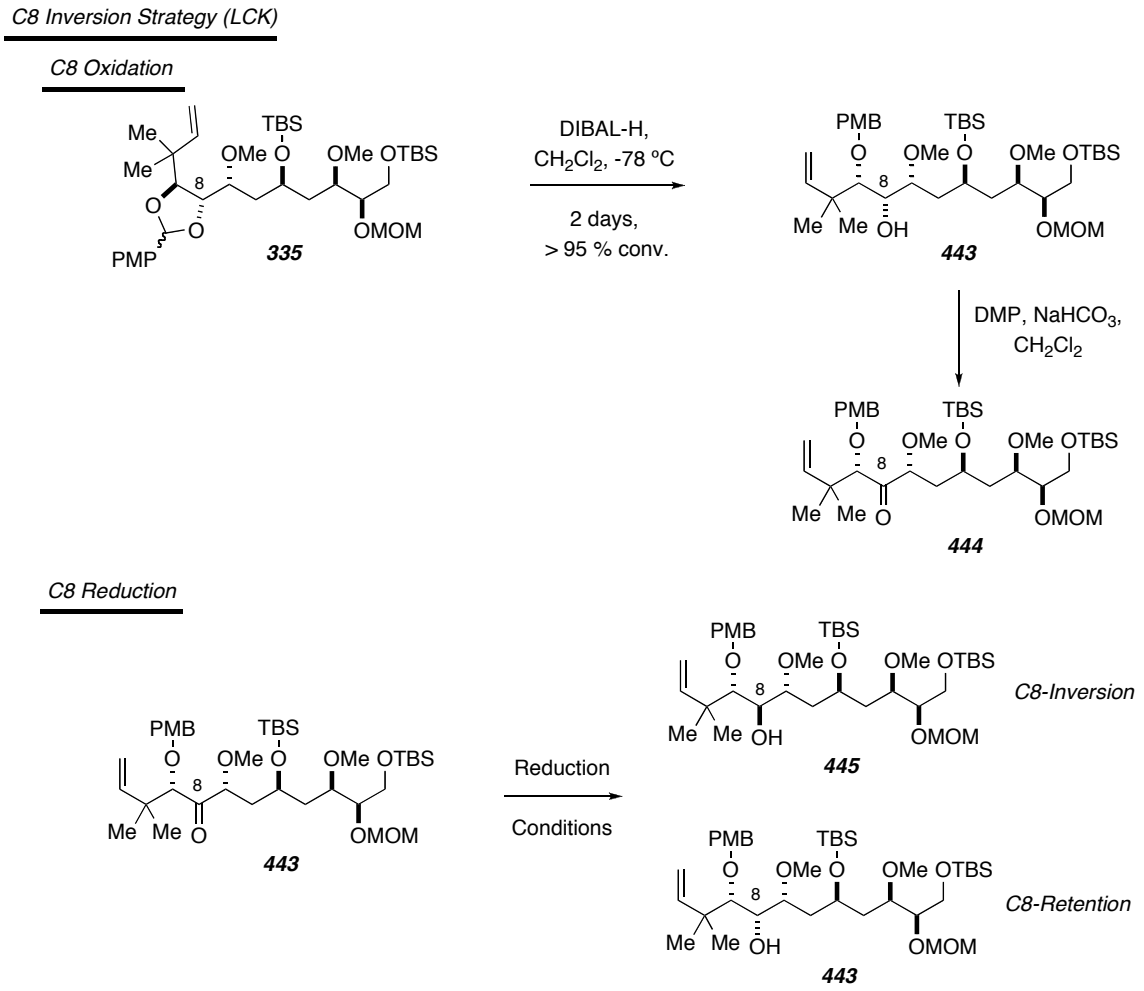


Table 10

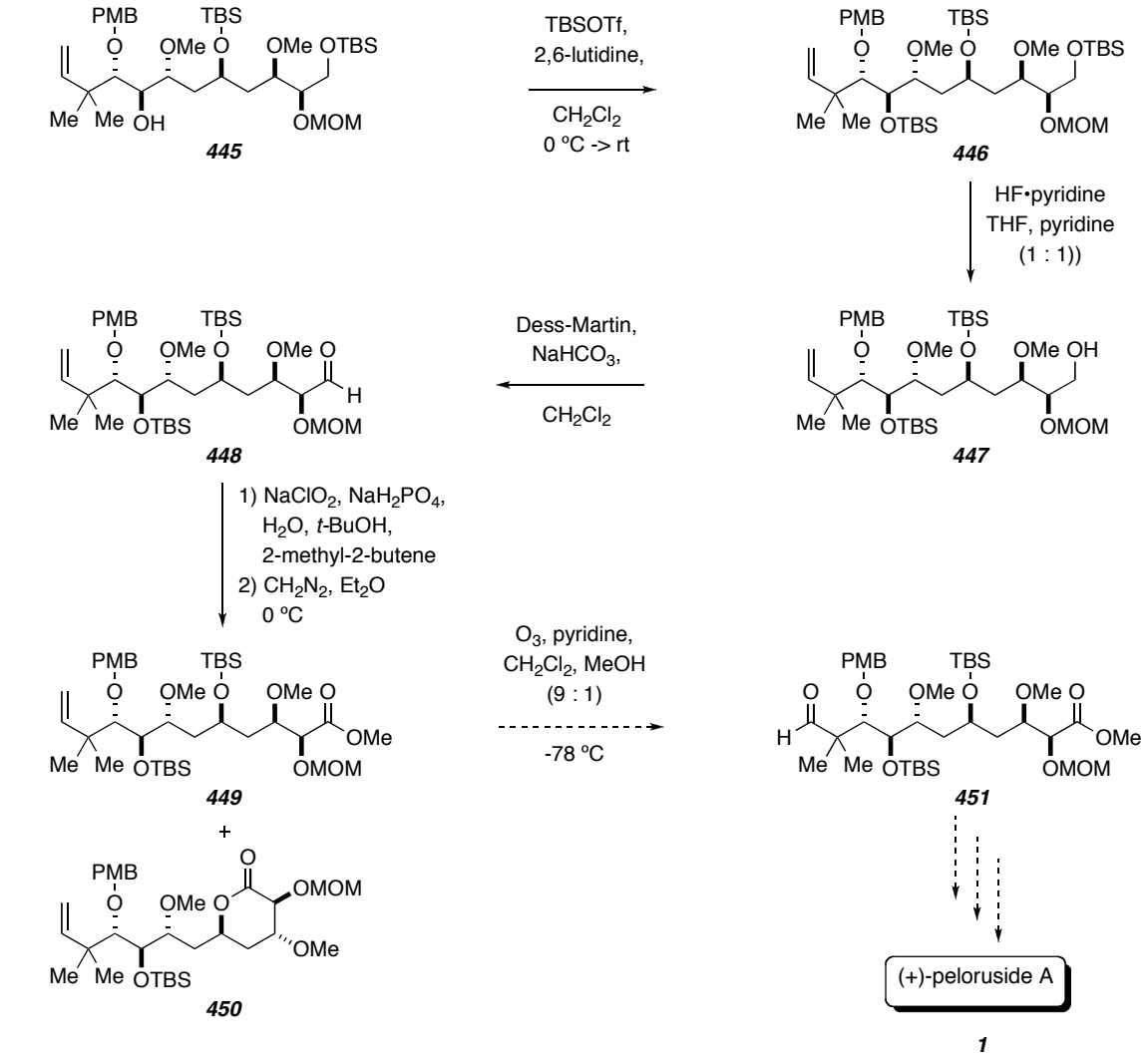
C8 Inversion Strategy (Reduction Conditions)

Reducing Agent	Solvent	Temp. °C	Molarity	Stereochemistry *C8-Inversion **445** : C8-Retention **443***
$LiBH_4$	Et_2O	0	.014	1 : 2.9
$Zn(BH_4)_2$	Et_2O	0	.015	1.2 : 1
** $Zn(BH_4)_2$	CH_2Cl_2	0	.020	2 : 1

The alcohol **445** was reacted with TBSOTf to produce the tri-TBS-ether **446** (**Scheme 139**). The primary TBS of **446** was removed using the same HF•pyridine conditions as before to produce the primary alcohol **447**. Dess-Martin oxidation of **447** resulted in the formation of aldehyde **448**. The aldehyde **448** was converted into its corresponding acid followed by esterification with diazomethane to provide the desired methyl ester **449** and lactone **450**. The lactone **450** is a result of TBS deprotection at C5 and cyclization onto the C1 methyl ester. The cyclization more than likely occurred as the crude acid was stored in the freezer overnight. If necessary, the lactone **450** can be converted into methyl ester **449** using the same chemistry that has previously been discussed. Over 350 mg of alkene **449** were isolated from the reaction and can be converted into the corresponding aldehyde **451** using the same ozonolytic conditions as before. The same reactions as those shown in **Scheme 137** can be used to produce (+)-peloruside A **1** from aldehyde **451**. I again stopped my efforts on this project and turned over the alkene **449** to Jeon so that he could use it if it was found necessary.

Scheme 139

*Completion of C1-C11 Aldehyde **451** (LCK)*



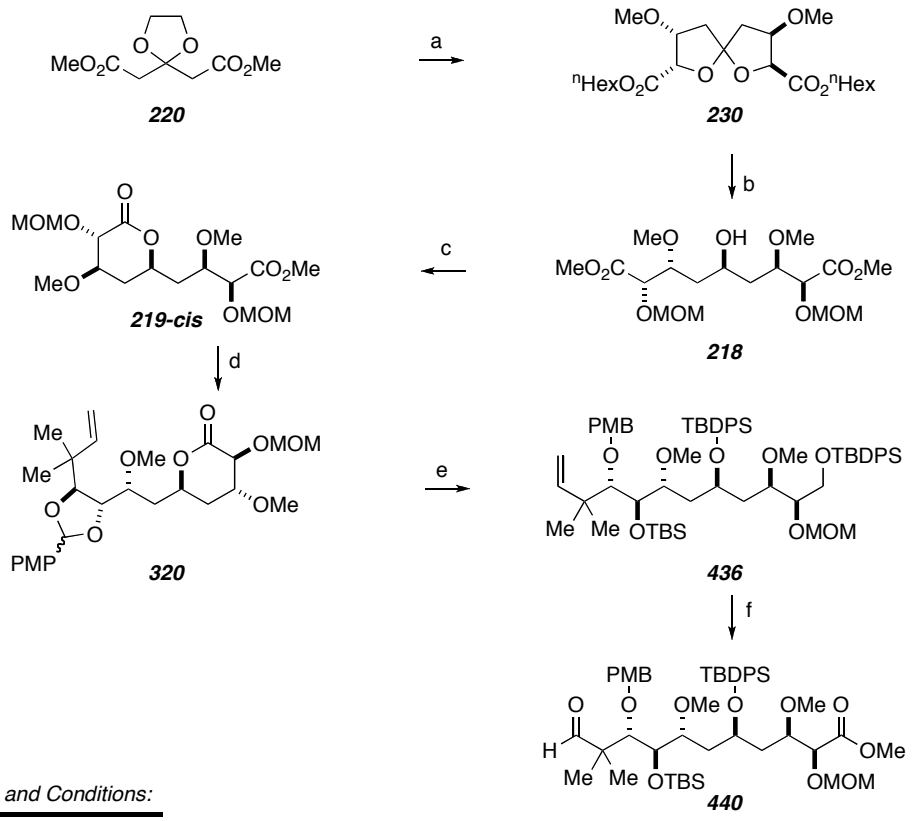
VI. Conclusions

The synthesis of a C1-C11 fragment of (+)-peloruside A was accomplished in 27 linear steps from commercially available dimethyl acetonedicarboxylate (**Scheme 140**). Highlights of the C1-C11 fragment synthesis include: 1) a one-pot two-step bi-directional reduction/HWE olefination, 2) a scaleable diastereoselective kinetic lactonization (12:1), 3) a chemoselective and diastereoselective reduction with L-selectride of a mixture of lactones, 4) a highly diastereoselective indium-mediated allylation with prenyl bromide, 5) a highly regioselective PMP acetal cleavage of two protected secondary alcohols, 6) an intramolecular carboxylate displacement of a mesylate for inversion of the C8 stereocenter, 7) an oxidation/reduction sequence with Dess-Martin periodinane and $Zn(BH_4)_2$ to invert the C8 stereocenter, and 8) the selective deprotection of a primary TBDPS in the presence of a secondary TBS.

Some other notable accomplishments during this research include: 1) inversion of the C8 stereocenter of a α-hydroxy lactone intermediate via cesium carboxylate displacement of a triflate, 2) one of the first examples of allyl indium reagents adding into lactones, 3) synthesis of a C1-C11 ketone that allows for setting the desired C13 stereocenter with Paterson's 1,5-*anti* aldol methodology, 4) the application of Patterson's 1,5-*anti* aldol methodology in a model system of peloruside to costruct of the C12-C11 bond and set the C11 stereocenter, 5) the 1,3-*anti* reduction of a C9-C17 model system of peloruside to set the C13 stereocenter, and 6) the selective methylation of the C13 hydroxyl of a C9-C17 model system of peloruside.

Scheme 140

Final Synthetic Route to C1-C11 Aldehyde for the Synthesis of (+)-Peloruside A



Reagents and Conditions:

(a) (i) DIBAL-H,$(EtO)_2P(O)CH(Na)CO_2{}^nHex$, >80%. (ii) SAD, 0 ºC, 88%. (iii) 30 mol% HI, THF, 0 ºC, 83%. (iv) Me_3OBF_4, proton sponge, 0 ºC to rt, 84%. (b) (i) 1,2-ethanedithiol, BF_3•OEt_2, 0 ºC. (ii) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 90% 2-steps. (iii) I_2, $NaHCO_3$, Acetone, H_2O, 0 ºC, 91%. (iv) Otera catalyst **237**, MeOH, toluene, 90 ºC, 77%. (v) Raney-Nickel, H_2, EtOH, 91%. (c) TMG, C_6H_6, 98%. (d) (i) L-selectride, THF, -78 ºC, 87%. (ii) prenyl bromide, indium powder, DMF, 55 ºC, 80%. (iii) $AlCl_3$, NaI, CH_3CN, CH_2Cl_2, 0 ºC, 92%. (iv) *(p*-MeO)-$PhCH(OMe)_2$, CSA, CH_2Cl_2, 4Å mol seives, 87%. (v) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 99%. (e) (i) LAH, THF, 0 ºC, 96%. (ii) TBDPSCl, Imid, DMAP, DMF, 92%. (iii) DIBAL-H, CH_2Cl_2, -78 ºC, 95%. (iv) DMP, $NaHCO_3$, CH_2Cl_2. (v) $Zn(BH_4)_2$, CH_2Cl_2, 0 ºC (2:1), 78% brs 2-steps. (vi) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%. (f) (i) HF•pyridine, THF, pyridine 91%. (ii) DMP, $NaHCO_3$, CH_2Cl_2. (iii) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, Me_2C=CHMe. (iv) CH_2N_2, 87% 3-steps. (v) O_3, pyridine, CH_2Cl_2, MeOH, 75%.

Experimental Section

General Methods

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in either oven or flame dried glassware. Anhydrous THF, diethyl ether, toluene, and methylene chloride were passed through a column of activated alumina. Triethylamine, diisopropylamine, and pyridine were distilled from KOH. DMF and DMSO were stored over 4 Å molecular sieves. Benzene and MeOH were stored over 3 Å molecular sieves. BF_3•OEt_2 was distilled from CaH_2.

DIBAL-H and anionic solutions (e.g., *n*-BuLi, Grignards) were tittered by published No-D spectroscopic methods.

MPLC refers to medium pressure liquid chromatography (25-200 psi) using hand-packed columns of Silasorb silica gel (18-32 μm, 60 Å pore size), a Waters HPLC pump, a Waters R401 differential refractive index detector. Flash chromatography was performed using E. Merk silica gel(230-400 mesh).

NMR spectra were recorded on Varian Inova 500 (500 Mhz), Varian Inova 300 (300 Mhz), and Varian VXR 300 (300 Mhz) spectrometers. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (0.00 ppm), in PhH-d_6 to 7.16 ppm. ^{13}C NMR chemical shifts in $CDCl_3$ are referenced to chloroform (77.23 ppm). The following format was used to report peaks in the NMR spectra: chmical shift in ppm (multiplicity, coupling constant(s) in Hz, integal, assignment). ^{1}H NMR assignments are indicated by number, i.e., H-3a, or structural characteristic, i.e., CH_aH$_b$. The number refers to the corresponding atom belonging to the longes segment of numbered carbons in the CAS name. Complex structures are numbered in their structures in order to simplify proton assignment numbering and naming

High resolution mass spectra were recorded on AEI MS-30, VG 7070E-HF, or Finnigan MAT 95 instruments, or Bruker Biotof II instruments.

Tandem gas chromatography/low resolution mass spectroscopy (GC/MS) using electron impact ionization (EI) was performed at 70 eV on a Hewlett-Packard 5890 series II gas chromatograph equipped with a Hewlett Packard 5971 A mass selective detector or

an Agilent Technologies 6890N gas chromatograph equipped with an Agilent Technologies 5975 inert XL mass selective detector.

Optical rotation data was recorded on a JASCO DIP-370 digital polarimeter using a 3.5 i.d. x 50 mm or 100 mm length cell

Some known compounds reported in my thesis have already been reported in the literature and therefore have not been duplicated here. There are also some compounds that have been reported that I am including in this section. The reason for this is that a more detailed interpretation could be concluded from the spectra than had previously been published.

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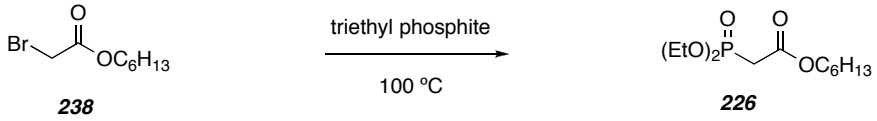
hexyl 2-(diethoxyphosphoryl)ethanoate **226**

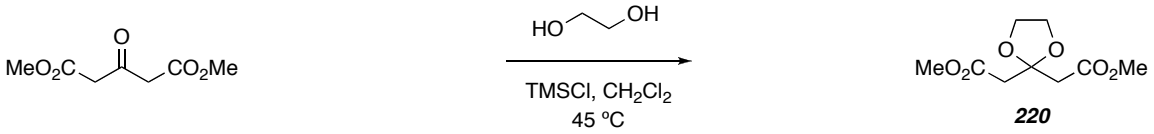


238 ***226***

Triethyl phosphite (200 mL, 1.15 mol) was added to a 3-neck 1L flask equipped with a reflux condensor and additional funnel. The third neck was loosely capped for venting of formed vapors. The solution was heated to ~95-100 ºC. Hexyl-2-bromoacetate (182 g, 0.821 mol) was added slowly via an addition funnel and then stirred for 3 hours with continued heating. The solution was cooled to room termperature and transferred to a new round bottom flask. The excess triethyl phosphite and triethyl phosphate by-products were removed by vacuum distillation to provide phosphonate **226**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.19 (dq, $J_{H\text{-}H}$ = 7.3 Hz, $J_{H\text{-}P}$ = 7.3 Hz, 4H, CH_3CH_2OP), 4.14 (t, J = 6.8 Hz, 2H, CO_2CH_2), 2.97 (d, $J_{H\text{-}P}$ = 21.2 Hz, 2H, $PCH_2CO_2C_6H_{13}$), 165 (p, J = 7.7 Hz, 2H, $CO_2CH_2CH_2$), 1.35 (t, J = 7.2 Hz, 6H, CH_3CH_2OP), 1.31 (m, 5H, Alk-H), and 0.89 (t, J = 6.4 Hz, 3H, Alk-*Me*).

Dimethyl 3-(1,3-dioxolane)-glutarate **220**



220

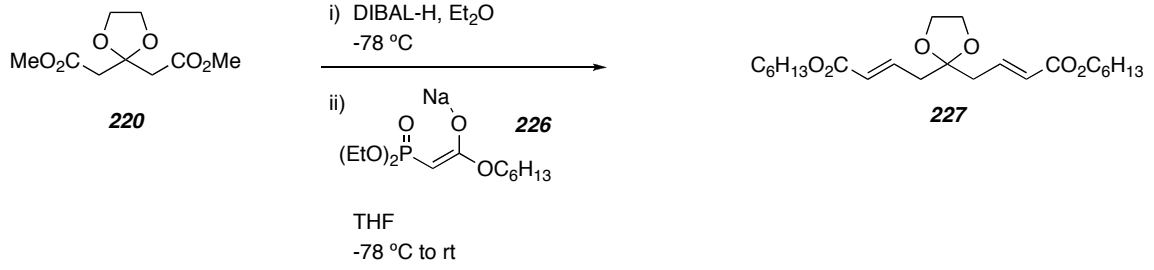
Dimethyl acetonedicarboxylate (100 g, 574 mmol) was dissolved in CH_2Cl_2 (1.5 L, 0.38M) and ethylene glycol (71 mL, 1.27 mol) was then added followed by TMSCl (164 mL, 1.26 mol) at room temperature. The reaction was stirred under reflux until all starting material had been consumed. Saturated aqueous $NaHCO_3$ (200 mL) was carefully added to quench the reaction and the layers were separated. The aqueous layer was diluted with water (200 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Distillation of the crude oil (140 °C pot temp) under reduced pressure (2 mm Hg) provided pure **220** as a light yellow oil.[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.02 (s, 4H, OCH_2CH_2O), 3.70 (s, 6H, CO_2Me), and 2.96 (s, 4H, CH_2CO_2Me).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 106.7, 65.2, 51.8, and 41.9.

HR ESI-MS: Calcd for $C_9H_{14}O_6Na$ $(M+Na)^+$: 241.0668 Found: 241.0676.

(2*E*,7*E*)-Dihexyl 5-(1,3-dioxolane)-nona-2,7-dienedioate **227**



220 ***226*** ***227***

Ketal **220** (10.0 g, 45.9 mmol) was added to a 1L, 3-neck flask, dissolved in Et_2O (182

mL, 0.25M) and cooled to -78 ºC (the use of an internal temperature probe for reactions of this type is absolutely imperative). Recently titrated DIBAL-H (82 mL, 101 mmol, 1.23 M in toluene) was cannulated into a dry graduated addition funnel. This colorless DIBAL-H solution was added dropwise to the colorless ethereal solution with constant stirring and under a N_2 atmosphere at -78 ºC. During the dropwise DIBAL-H addition, the THF solution of sodium hexyl phosphonoacetate (**226**) was prepared according to the following protocol (**226**: 38.5 g, 137 mmol; NaH: 3.07 g, 128 mmol; THF: 240 mL, 0.5M). **[**To NaH (3.07 g, 128 mmol) in an oven dried round bottom flask under N_2, equipped with a stir bar and vent line, was added dry THF (240 mL, 0.5M) and cooled to 0 ºC. With vigorous stirring, hexyl phosphonoacetate **226** (38.5 g, 137 mmol) was added dropwise. The red heterogeneous solution evolved gas and eventually became a homogeneous red color. (The red color comes from a minor impurity in the hexyl phosphonoacetate.) Anion titration can be performed according to the protocol previously established in the Hoye group.**]** Upon the generation of a homogenous red solution (**226** THF solution), it was transferred by cannula dropwise to the DIBAL-H solution, taking great care that the rate of addition did not warm the temperature beyond -70 ºC. Once all of the phosphonoacetate anion was added, the reaction was removed from the dry-ice bath and allowed to stir at room temperature for 1-2 hours. At room temperature, the red orange solution was then transferred to a 2L Erlenmeyer flask equipped with a stir bar and a gallon bucket with ice water was kept handy to address exotherm issues. Small portions of saturated aqueous Rochelle's salt (Na,K-Tartrate) were added and the reaction was monitored very closely for exotherm and cooled if necessary. Upon this addition, the reaction will go from homogeneous to a gelatinous solution, and upon addition of more sat. aq. Rochelle's salt, back to homogeneous. Addition of more Et_2O might be necessary if the reaction got too warm and boiled some off. The reaction was then usually allowed to stir for an additional 18 hours. The reaction is done when both the aqueous and the organic layers are homogeneous and clear. The layers were separated and the aqueous layer was exhaustively extracted with EtOAc (3 x 300 mL). The organic layer was separated, washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide a redish-orange oil. This oil, which contains the excess phosphonoacetate and the

desired product, was purified by flash chromatography (6:1 hexanes:ethyl acetate) to provide the bis enone ketal **227** (≥ 80%) as a light yellow colored oil.[56]

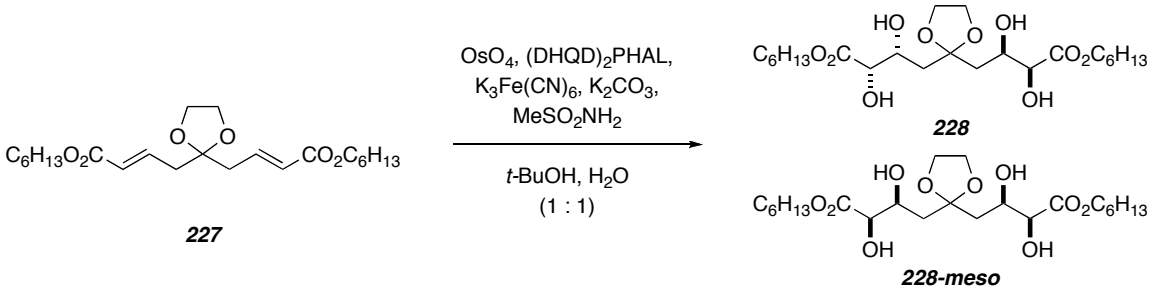
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (dt, *J* = 15.3 and 7.4 Hz, 2H, HC=C*H*CH_2), 5.90 (dt, *J* = 15.6 and 1.6 Hz, 2H, *H*C=CHCH_2), 4.12 (t, *J* = 6.8 Hz, 4H, CO_2CH_2), 3.97 (s, 4H, OCH_2CH_2O), 2.53 (dd, *J* = 7.4 and 1.2 Hz, 4H, HC=CHCH_2), 1.64 (m, 4H, CH_2), 1.32 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 7.1 Hz, 6H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 142.5, 125.1, 109.5, 65.6, 64.7, 40.9, 31.5, 28.7, 25.7, 22.7, and 14.3.

HR ESI-MS: Calcd for $C_{23}H_{38}O_6Na$ $(M+Na)^+$: 433.2566 Found: 433.2597.

TLC: R_f = 0.59; 3:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-(1,3-dioxolane)-2,3,7,8-tetrahydroxynonanedioate **228**



$K_3Fe(CN)_6$ (31.2 g, 94.8 mmol) and K_2CO_3 (13.1 g, 94.8 mmol) were added to a dry round bottom flask equipped with a stir bar. $(DHQD)_2PHAL$ (246 mg, 0.316 mmol) and OsO_4 (40 mg, 0.16 mmol) were next added to the dry mixture and this mixture was stirred until it appeared well mixed (ca. 15 minutes, but it is doubtful that this actually helps). A 1:1 mixture of a *t*-BuOH:H_2O solution (158 mL total volume, 0.1M) was next added and the heterogeneous, biphasic solution was stirred for 10 minutes before cooling to 0 ºC (measured by internal probe). Bis enone **227** (6.5 g, 15.8 mmol) was next added to this cooled heterogeneous solution using a minimal amount of *t*-BuOH, followed by the addition of $MeSO_2NH_2$ (3.76 g, 39.5 mmol). This orange mixture was allowed to stir at 0

ºC until all the starting material had been consumed by TLC (approximately 72 hrs).

Solid Na_2SO_3 was added at 0 ºC until the yellow solution turned brown. The reaction was diluted with water (200 mL) and extracted with EtOAc (3 x 200 mL). The organic layer was then washed with 0.1N KOH (if this layer becomes intensely yellow, then some of the desired bisester has been saponified) washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide **228** (88%) as white foam.[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.23 (ddd, *J* = 7.0, 7.0, and 3.6 Hz, 2H, H_βCOH), 4.23 (m, 4H, CO_2CH_2), 4.07 (s, 4H, OCH_2CH_2O), 4.03 (d, *J* = 6.9 Hz, 2H, H_αCOH), 3.22 (d, *J* = 4.1 Hz, 1H, O*H*), 3.14 (s, 1H, O*H*), 3.08 (d, *J* = 7.0 Hz, 1H, O*H*), 2.23 (dd, *J* = 15.0 and 9.9 Hz, 2H, CH_aH_b), 1.96 (dd, *J* = 15.2 and 2.8 Hz, 2H, CH_aH_b), 1.69 (p, *J* = 6.9 Hz, 4H, $CO_2CH_2CH_2$), 1.33 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.9 Hz, 6H, Alk-*Me*).

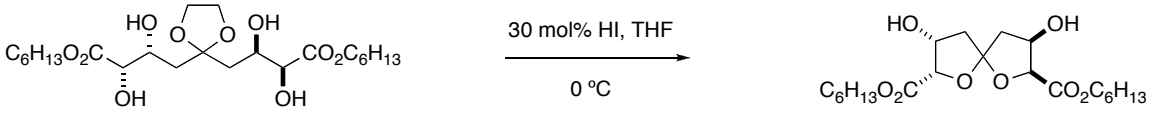
^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 111.1, 74.2, 69.0, 66.2, 64.9, 39.7, 31.5, 28.6, 25.5, 22.6, and 14.1.

HR ESI-MS: Calcd for $C_{23}H_{42}O_{10}Na$ $(M+Na)^+$: 501.2676 Found: 501.2747.

TLC: R_f = 0.40; 1:3 hexanes:ethyl acetate.

(2*S*,3*R*,7*S*,8*R*)-2,7-(Dihexyl dicarboxylic acid)-3,8-dihydroxy-1,6-dioxaspiro[4.4]nonane

229



228 ***229***

To tetrol **228** (1.24 g, 2.9 mmol) was added THF (5.8 mL, 0.5M) and this solution was cooled to 0 ºC. Brown, aqueous HI (65 μL, 870 μmol;) was added dropwise and the solution was stirred at 0 ºC until the reaction was deemed complete by careful TLC analysis (approximately 3 hours). Saturated aqueous $NaHCO_3$ (5 mL) was added dropwise followed by saturated aqueous Na_2SO_3 until the yellow color disappears. This

solution was then diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to provide spirocycle **229** (83%), The spirocycle **229** was recrystalized using either Et_2O / hexanes or EtOAc / hexanes to produce white needles.[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.78 (dddd, *J* = 6.7, 5.1, 5.1, and 3.7 Hz, 2H, *H*COH), 4.63 (d, *J* = 5.9 Hz, 2H, *H*CCO_2), 4.21 (dt, *J* = 6.6 and 2.8 Hz, 4H, CO_2CH_2), 2.76 (dd, *J* = 14.4 and 6.7 Hz, 2H, CH_aH_b), 2.27 (dd, *J* = 14.0 and 3.4 Hz, 2H, CH_aH_b), 2.20 (d, *J* = 5.6 Hz, 2H, O*H*), 1.67 (p, *J* = 6.8 Hz, 4H, $CO_2CH_2CH_2$), 1.31 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.2 Hz, 6H, Alk-*Me*).

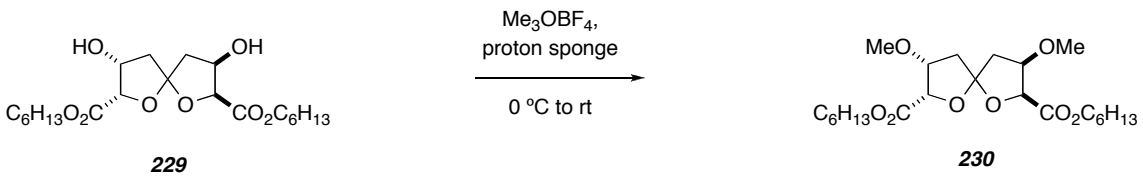
^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 114.7, 81.1, 72.6, 65.7, 44.6, 31.5, 28.6, 25.6, 22.7, and 14.2.

HR ESI-MS: Calcd for $C_{21}H_{36}O_8Na$ $(M+Na)^+$: 439.2308 Found: 439.2334.

TLC: R_f = 0.50; 1:3 hexanes:ethyl acetate.

M.p. = 101 – 105 ºC.

(2*S*,3*R*,7*S*,8*R*)-2,7-(Dihexyl dicarboxylic acid)-3,8-dimethoxy-1,6-dioxaspiro[4.4]nonane **230**



229 ***230***

Spirocycle **229** (9.30 g, 22.3 mmol) was dissolved in CH_2Cl_2 (223 mL, 0.1M) and the reaction was cooled to 0 ºC. Proton Sponge (21.5 g, 89.3 mmol) was next added followed by Meerwein salt (13.2 g, 89.3 mmol) and the reaction was stirred for 18 hours at room temperature. Upon complete conversion by TLC, the reaction was diluted with water (75 mL), and quenched with saturated aqueous NH_4Cl (100 mL). The aqueous

layer was extracted with EtOAc (3 x 250 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. To prevent decomposition, immediate flash chromatography (2:1 hexanes / ethyl acetate) was required to remove the residual Proton Sponge and provide bis methyl-ether **230** (8.33 g, 84%) as a colorless oil.[56]

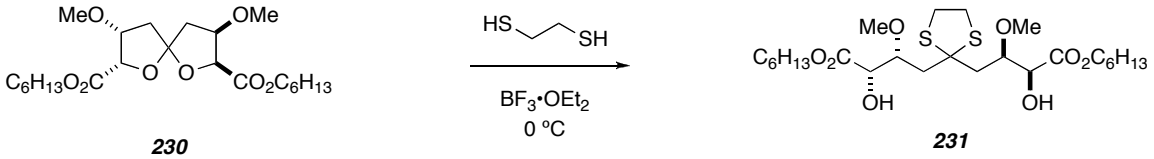
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.68 (d, *J* = 6.0 Hz, 2H, *H*CCO_2), 4.35 (ddd, *J* = 6.2, 6.2, and 5.3 Hz, 2H, *H*COMe), 4.17 (dt, *J* = 6.4 and 6.4 Hz, 4H, CO_2CH_2), 3.31 (s, 6H, O*Me*), 2.64 (dd, *J* = 13.7 and 6.2 Hz, 2H, CH_aH_b), 2.29 (dd, *J* = 13.7 and 5.2 Hz, 2H, CH_aH_b), 1.64 (p, *J* = 6.9 Hz, 4H, $CO_2CH_2CH_2$), 1.32 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.2 Hz, 6H, Alk-*Me*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 115.1, 81.3, 79.8, 65.3, 57.9, 41.2, 31.6, 28.7, 25.7, 22.7, and 14.2.

HR ESI-MS: Calcd for $C_{23}H_{40}O_8Na$ $(M+Na)^+$: 467.2621 Found: 467.2618.

TLC: R_f = 0.52; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-(1,3-dithiolane)-2,8-dihydroxy-3,7-dimethoxynonanedioate **231**



Bis methyl-ether **230** (14.7 g, 33.1 mmol) was dissolved in 1,2-ethanedithiol (285 mL, 0.116M) and cooled to 0 ºC. BF_3•OEt_2 (42.0 mL, 331 mmol) was added against the side of the round bottom in order to pre-cool it. The reaction was stirred for 3.5 hours at 0 ºC, the reaction was quenched by the dropwise addition of saturated aqueous $NaHCO_3$ (150 mL), dilution with water (50 mL) and extraction with Et_2O (3 x 400 mL). The combined organic layers were washed with 15% aq. NaOH (1 x 100 mL) in order to remove some of the excess sulfur reagent. The organic layer was dried over Na_2SO_4 and

concentrated *in vacuo* to provide crude diol **231** contaminated with a signifigant amount of 1,2-ethanedithiol. 1,2-ethanedithiol was removed using a high vacuum rotovap to reveal crude diol **231** as a colorless oil. Diol **231** was used in the next reaction without purification. (NOTE: It is important to wash all equipment and waste with bleach so that the 1,2-ethanedithiol does not diffuse into the lab.[56]

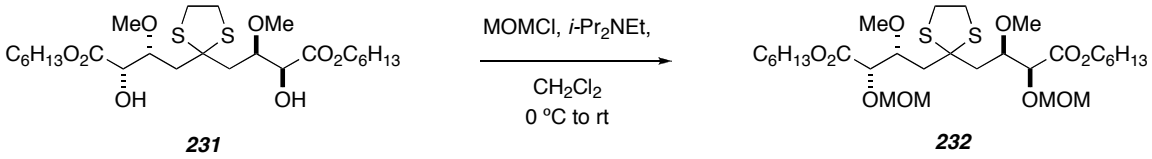
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.44 (dd, *J* = 8.1 and 1.9 Hz, 2H, *H*COH), 4.22 (dt, *J* = 6.8 and 4.1 Hz, CO_2CH_2), 3.93 (ddd, *J* = 6.3, 4.5, and 2.1 Hz, 2H, *H*COMe), 3.34 (s, 10H, O*Me* and SCH_2CH_2S), 2.90 (d, *J* = 8.9 Hz, 1H, O*H*), 2.53 (dd, *J* = 15.3 and 6.0 Hz, 2H, CH_aH_b), 2.20 (dd, J = 15.4 and 4.5 Hz, 2H, CH_aH_b), 1.73-1.63 (m, 4H, $CO_2CH_2CH_2$), 1.35 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 7.4 Hz, 6H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 80.4, 73.4, 67.9, 65.9, 57.7, 43.7, 40.2, 31.5, 28.7, 25.7, 22.7, and 14.1.

HR ESI-MS: Calcd for $C_{25}H_{46}O_8S_2Na$ $(M+Na)^+$: 561.2532 Found: 561.2567.

TLC: R_f = 0.31; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-(1,3-dithiolane)-(3,7-dimethoxy-2,8-bis(methoxymethoxy)nonanedioate **232**



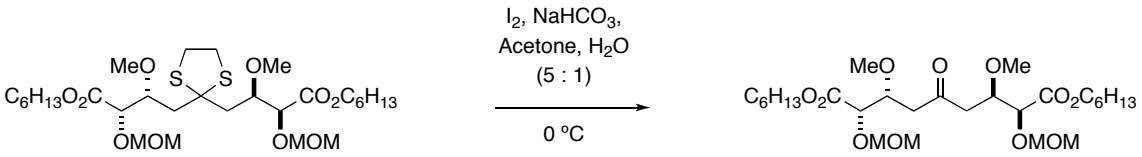
231 ***232***

To 500 mL round bottom equipped with a stir bar, under N_2, containing crude diol **231** (33.1 mmol) was added CH_2Cl_2 (110 mL, 0.3M) and *i*Pr_2NEt (95.9 mL, 497 mmol). Upon cooling the solution to 0 ºC, MOMCl (56.0 mL, 331 mmol; from a prepared solution containing 45% MOMCl : 55% methyl acetate and dimethoxymethane) was added dropwise and the reaction was warmed to room temperature and stirred until no additional diol was observed by TLC. After recooling to 0 ºC, saturated aqueous $NaHCO_3$

(100 mL) was then added followed by dilution with H_2O (100 mL). The reaction was warmed to room temperature and stirred for 15 minutes. The aqueous layer was extracted with EtOAc (3 x 400 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided **232** as a colorless oil in excellent yield over 2-steps (18.7 g, 90%).[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.76 (d, *J* = 7.0 Hz, 2H, OC*H*$_a$H$_b$OMe), 4.74 (d, *J* = 7.0 Hz, 2H, OCH$_a$*H*$_b$OMe), 4.45 (d, *J* = 3.7 Hz, 2H, *H*COMOM), 4.17 (dd, *J* = 6.9 and 1.5 Hz, 2H, *H*COMe), 3.43 (s, 6H, O*Me*), 3.39 (s, 6H, O*Me*), 3.32 (s, 4H, SC*H*$_2$C*H*$_2$S), 2.47 (dd, *J* = 15.6 and 4.5 Hz, 2H, C*H*$_a$H$_b$), 2.17 (dd, *J* = 15.4 and 5.5 Hz, 2H, CH$_a$*H*$_b$), 1.66 (p, J = 7.4 Hz, 4H, $CO_2CH_2CH_2$), 1.33 (m, 12H, Alk-*H*), 0.89 (t, *J* = 7.1 Hz, 6H, Alk-*Me*).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 96.9, 80.1, 77.9, 68.6, 65.4, 57.9, 56.6, 44.0, 40.0, 31.6, 28.8, 25.8, 22.7, and 14.2.
HR ESI-MS: Calcd for $C_{29}H_{54}O_{10}S_2Na$ $(M+Na)^+$: 649.3056 Found: 649.3056.
TLC: R_f = 0.50; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 3,7-Dimethoxy-2,8-bis(methoxymethoxy)-5-oxononanedioate **233**



232 ***233***

To dithiane **232** (12.0 g, 19.1 mmol) was added a 5:1 mixture of acetone:water (159 mL total volume, 0.12M). $NaHCO_3$ powder (12.8 g, 153 mmol) was added and the heterogeneous solution was cooled to 0 ºC. Crystalline I_2 (16.5 g, 64.9 mmol) was added and the solution turned a deep purple/black color. The reaction was stirred at 0 ºC for 3 hours. At this time, an additional portions of $NaHCO_3$ powder (6.42 g, 77.0 mmol) and I_2

(8.2 g, 32.5 mmol) were added to the solution. Stirring continued until TLC indicated that all starting material had been consumed. Saturated aqueous $NaHCO_3$ (50 mL) was then added followed by saturated aqueous Na_2SO_3 until the orange/yellow color disappeared. This was followed by dilution with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 250 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (2:1 hexanes / ethyl acetate) provided ketone **233** (9.57 g, 91%) as a colorless oil.[56]

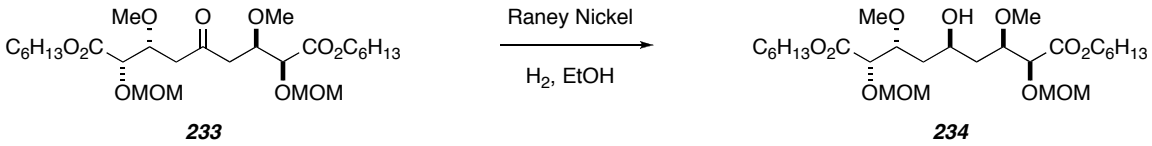
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.71 (d, *J* = 7.0 Hz, 2H, OC*H*$_a$H$_b$OMe), 4.68 (d, *J* = 6.9 Hz, 2H, OCH$_a$*H*$_b$OMe), 4.28 (d, *J* = 4.2 Hz, 2H, *H*COMOM), 4.17 (m, 6H, *H*COMe and CO_2CH_2), 3.39 (s, 6H, O*Me*), 3.37 (s, 6H, O*Me*), 2.82 (dd, *J* = 18.0 and 8.1 Hz, 2H, C*H*$_a$H$_b$), 2.78 (dd, *J* = 17.6 and 5.6 Hz, 2H, CH$_a$*H*$_b$), 1.66 (p, *J* = 7.0 Hz, 4H, $CO_2CH_2CH_2$), 1.34 (m, 12H, Alk-*H*), 0.89 (t, *J* = 6.8 Hz, 6H, Alk-*Me*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5, 170.6, 96.8, 76.3, 65.5, 58.9, 56.5, 44.2, 31.6, 28.7, 25.7, 22.7, and 14.2.

HR ESI-MS: Calcd for $C_{29}H_{54}O_{10}S_2Na$ $(M+Na)^+$: 573.3251 Found: 573.3259.

TLC: R_f = 0.28; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-Hydroxy-3,7-dimethoxy-2,8-bis(methoxymethoxy)nonanedioate **234**



To ketone **233** (478 mg, 0.868 mmol) was added EtOH (8.68 mL, 0.1 M) and black Raney Nickel (1 mL of an aqueous heterogeneous solution; commercially available reagent, used as received) in a Fischer-Porter tube equipped with the largest possible stir bar. The tube was flushed 3 times with H_2 and then filled with 50 psi of H_2. The

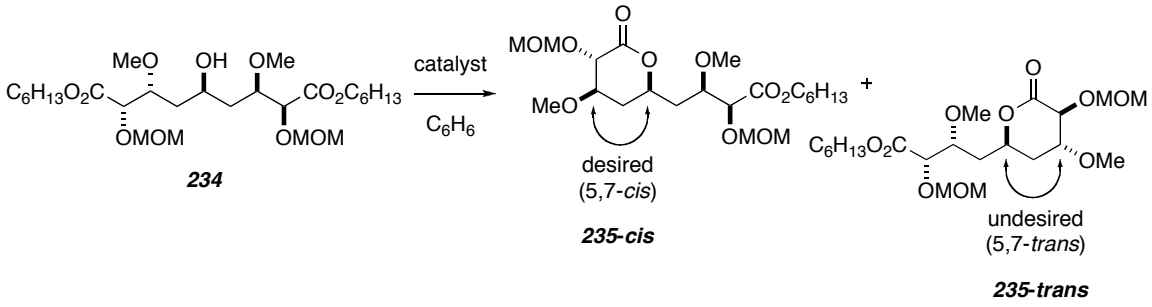
heterogeneous solution was vigorously stirred until it was determined by TLC that the ketone had been fully converted into the alcohol. The reaction residue was filtered through a pad of celite using ethyl acetate and the filtrate was concentrated *in vacuo* to give the crude carbinol **234** as a colorless oil.[56]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.74 (d, *J* = 6.9 Hz, 1H, OCH_aH_bOMe), 4.73 (d, *J* = 6.9 Hz, 1H, OCH_aH_bOMe), 4.71 (d, *J* = 6.9 Hz, 1H, OCH_aH_bOMe), 4.70 (d, *J* = 6.9 Hz, 1H, OCH_aH_bOMe), 4.26 (d, *J* = 4.2 Hz, 1H, *H*COMOM), 4.22 (d, *J* = 3.9 Hz, 1H, *H*COMOM), 4.17 (nfom, 4H, CO_2CH_2), 4.00 (m, 1H, *H*COH), 3.95 (ddd, *J* = 9.5, 3.6, and 3.6 Hz, 1H, *H*COMe), 3.87 (ddd, *J* = 7.1, 7.1, and 4.2 Hz, 1H, *H*COMe), 3.48 (s, 2H, O*Me*), 3.46 (s, 2H, O*Me*), 3.41 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 1.76 (m, 2H, $CO_2CH_2CH_2$), 1.66 (p, *J* = 6.7 Hz, 2H, $CO_2CH_2CH_2$), 1.33 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.7 Hz, 6H, Alk-*Me*).

(2*S*,3*R*)-Hexyl 3-Methoxy-4-((2*R*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxo-tetrahydro-2*H*-pyran-2-yl)-2-(methoxymethoxy)butanoate **235-*cis***

and

(2*S*,3*R*)-Hexyl 3-Methoxy-4-((2*S*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxo-tetrahydro-2*H*-pyran-2-yl)-2-(methoxymethoxy)butanoate **235-*trans***



A survey of lactonization conditions for carbinol **234** were performed in a similar fashion to those previously reported by Ryba. See **Table 3**, **Table 4**, and **Table 5**. To a NMR tube containing varying amounts of **234** (1 to 46 mg; the desired amount to obtain a

certain Molarity) was added C_6D_6 (the desired amount necessary to obtain a certain Molarity) followed by varing amounts of catalyst (DBU, DBN, TMG, and TFA). The conversion to product was monitered by ^{1}H NMR (varying degrees of percent conversion were reached depending on the reaction conditions). The reaction was quenched by dilution with water and CH_2Cl_2. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford **235-*cis*** and **235-*trans***. No one condition screened proved to be optimal for carrying material forward in the sequence toward (+)-peloruside A. Difficulties in separating the two lactones were encountered, however, useful amounts of both lactones were obtained by careful MPLC purification (1:1 hexanes / ethyl acetate).

Characterization Data for 235-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 6.5 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.75 (d, *J* = 6.5 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.66 (d, *J* = 6.9 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.54 (d, *J* = 6.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.33 (d, *J* = 4.3 Hz, 1H, *H*COMOM), 4.22 (dddd, *J* = 9.6, 6.5, 5.8, and 2.8 Hz, 1H, *H*COC=O), 4.17 (d, *J* = 8.3 Hz, 1H, *H*COMOM), 4.07 (nfom, 2H, CO_2CH_2), 3.89 (dd, *J* = 6.3, 6.3 Hz, 1H, *H*COMe), 3.35 (s, 3H, O*Me*), 3.24 (m, 1H, *H*COMe), 3.20 (s, 3H, O*Me*), 3.16 (s, 3H, O*Me*), 3.02 (s, 3H, O*Me*), 2.00 (ddd, *J* = 6.1, 6.1, and 3.5 Hz, 2H, CH_2), 1.87 (ddd, *J* = 13.7, 5.0, and 2.8 Hz, 1H, CH_aH$_b$), 1.45 (nfom, 2H, $CO_2CH_2CH_2$), 1.31 (ddd, *J* = 13.8, 11.6, and 10.6 Hz, 1H, CH$_a$$H_b$), 1.15 (m, 6H, Alk-*H*), and 0.85 (t, *J* = 7.3 Hz, 3H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.3, 97.0, 96.8, 77.8, 76.3, 75.3, 73.7, 65.6, 58.2, 57.6, 56.5, 56.3, 35.9, 34.3, 31.5, 28.7, 25.8, 22.6, and 14.1.

HR ESI-MS: Calcd for $C_{21}H_{38}O_{10}Na$ $(M+Na)^+$: 473.2363 Found: 473.2351.

TLC: R_f = 0.44; 1:1 hexanes:ethyl acetate.

Characterization Data for 235-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 6.8 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.68 (d, *J* = 6.5 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.67 (d, *J* = 7.1 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.67 (m, 1H, *H*COC=O), 4.54 (d, *J* = 6.8 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.42 (d, *J* = 6.2 Hz, 1H, *H*COMOM), 4.33 (d, *J* = 5.0 Hz, 1H, *H*COMOM), 4.09 (t, *J* = 6.9 Hz, 2H, CO_2CH_2),

4.04 (ddd, *J* = 10.5, 5.1, and 2.0 Hz, 1H, *H*COMe), 3.30 (m, 1H, *H*COMe), 3.29 (s, 3H, O*Me*), 3.25 (s, 3H, O*Me*), 3.24 (s, 3H, O*Me*), 2.95 (s, 3H, O*Me*), 2.07 (ddd, *J* = 14.6, 10.1, and 2.5 Hz, 1H, CH_{a1}CH$_{b1}$), 1.87 (ddd, *J* = 14.4, 10.7, and 3.0 Hz, 1H, CH$_{a1}$CH_{b1}), 1.48 (m, 1H, CH_{a2}CH$_{b2}$), 1.41 (ddd, *J* = 15.1, 11.6, and 6.5 Hz, CH$_{a2}$CH_{b2}), 1.17 (m, 8H, Alk-*H*), 0.86 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

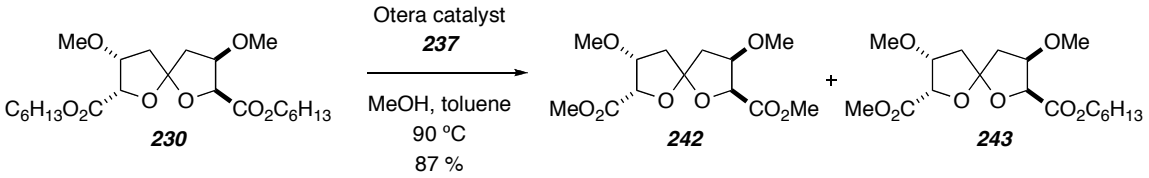
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.5, 96.6, 96.2, 77.6, 77.3, 76.2, 73.9, 71.9, 65.5, 59.4, 57.3, 56.5, 56.2, 37.1, 34.8, 31.5, 38.7, 25.7, 22.7, and 14.2.

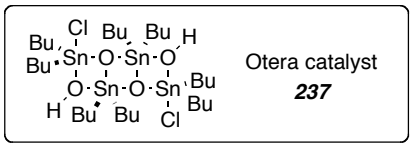
HR ESI-MS: Calcd for $C_{21}H_{38}O_{10}Na$ $(M+Na)^+$: 473.2363 Found: 473.2358.

TLC: R_f = 0.52; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*S*,8*R*)-Dimethyl 3,8-Dimethoxy-1,6-dioxaspiro[4.4]nonane-2,7-dicarboxylate

242





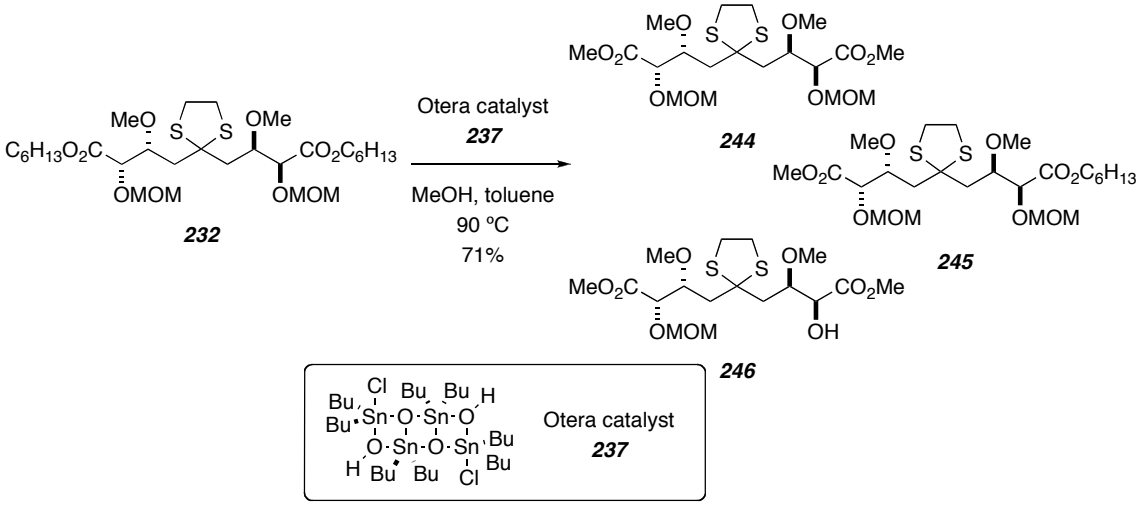
To a nitrogen-flushed culture tube containing hexyl ester spirocycle **230** (1.00 g, 2.25 mmol) was added toluene (7.5 mL, 0.3 M), MeOH (5.4 mL, 135 mmol; shaken with solid anhydrous K_2CO_3 immediately before use), and Otera catalyst **237** (1.20 g, 1.13 mmol). The septum on the culture tube was replaced by a screw cap with a Teflon liner and the mixture was stirred at 90 ºC for 3 days. The solution was transferred to a round bottom flask using $CHCl_3$ and concentrated *in vacuo*. Flash chromatography (1:1 hexanes / ethyl acetate) provided bis-methyl ester spirocycle **242** (593 mg, 87%) and mono-methyl-hexyl ester spirocycle **243** (98 mg) as colorless oils.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.70 (d, *J* = 5.8 Hz, 2H, *H*CCO_2), 4.36 (ddd, *J* = 6.2, 6.2, and 5.0 Hz, 2H, *H*COMe), 3.78 (s, 6H, CO_2*Me*), 3.32 (s, 6H, O*Me*) 2.65 (dd, *J* = 13.8 and 6.4 Hz, 2H, C$H_a$$H_b$), and 2.29 (dd, *J* = 13.8 and 5.0 Hz, 2H, C$H_a$$H_b$).

HR ESI-MS: Calcd for $C_{13}H_{20}O_8Na$ $(M+Na)^+$: 327.1050 Found: 327.1081.

TLC: R_f = 0.39; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dimethyl 5-(1,3-dithiolane)-(3,7-dimethoxy-2,8-bis(methoxymethoxy)nonanedioate **244**



To a nitrogen-flushed culture tube containing hexyl ester dithiane **232** (55 mg, 0.124 mmol) was added toluene (0.60 mL, 0.21 M), MeOH (0.60 mL, 14.8 mmol; shaken with solid anhydrous K_2CO_3 immediately before use), and Otera catalyst **237** (30 mg, 0.028 mmol). The septum on the culture tube was replaced by a screw cap with a Teflon liner and the mixture was stirred at 90 ºC for 3 days. The solution was transferred to a round bottom flask using $CHCl_3$ and concentrated *in vacuo*. Gradient flash chromatography (2:1 -> 1:1 -> 1:2 hexanes / ethyl acetate) provided bis-methyl ester dithiane **244** (30 mg, 71%) and mono-methyl-hexyl ester dithiane **245** (7 mg) as colorless oils along with trace amounts of bis-methyl ester alcohol **246**.

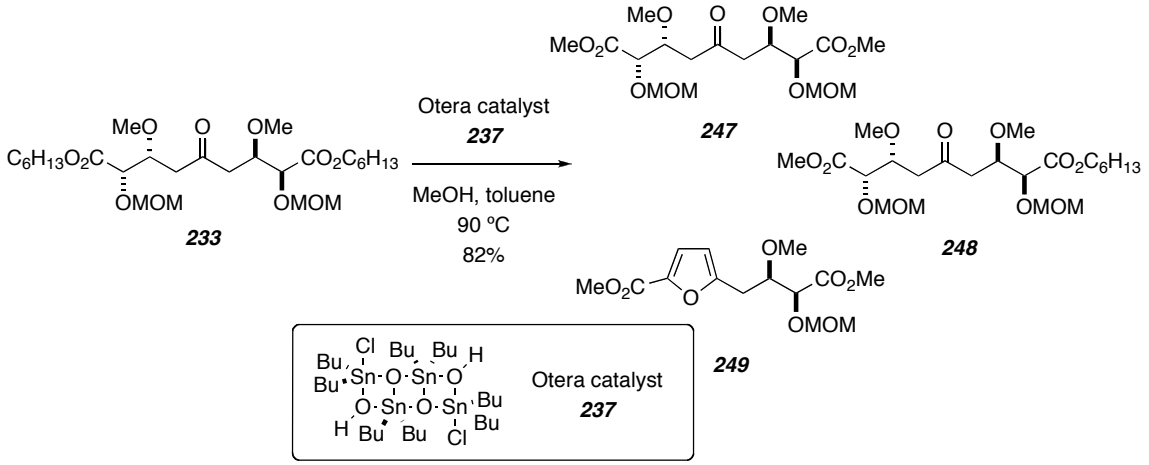
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (s, 4H, OC*H*$_2$OMe), 4.44 (d, 3.8 Hz, 2H, *H*COMOM), 3.94 (ddd, *J* = 5.7, 4.0, and 4.0 Hz, 2H, *H*COMe), 3.78 (s, 6H, CO_2*Me*), 3.44 (s, 6H, O*Me*), 3.40 (s, 6H, O*Me*), 3.36-3.30 (m, 4H, SC*H*$_2$C*H*$_2$S), 2.45 (dd, *J* = 15.5 and 4.3 Hz, 2H, C*H*$_a$H$_b$), and 2.17 (dd, *J* = 15.5 and 5.7 Hz, 2H, CH$_a$*H*$_b$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 97.0, 80.0, 77.8, 68.6, 58.0, 56.6, 52.2, 43.9, and 39.8.

HR ESI-MS: Calcd for $C_{19}H_{34}O_{10}S_2Na$ $(M+Na)^+$: 509.1486 Found: 509.1438.

TLC: R_f = 0.33; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dimethyl 3,7-Dimethoxy-2,8-bis(methoxymethoxy)-5-oxononanedioate **247**



To a large nitrogen-flushed culture tube containing hexyl ester ketone **233** (1.50 g, 2.72 mmol) was added toluene (9.1 mL, 0.3 M), MeOH (6.6 mL, 163 mmol; shaken with solid anhydrous K_2CO_3 immediately before use), and Otera catalyst **237** (1.45 g, 1.36 mmol). The septum on the culture tube was replaced by a screw cap with a Teflon liner and the mixture was stirred at 90 ºC for 3 days. The solution was transferred to a round bottom flask using $CHCl_3$ and concentrated *in vacuo*. Gradient flash chromatography (2:1 -> 1:1 -> 1:2 hexanes / ethyl acetate) provided the methyl ester ketone **247** (860 mg, 77%) as a colorless oil.

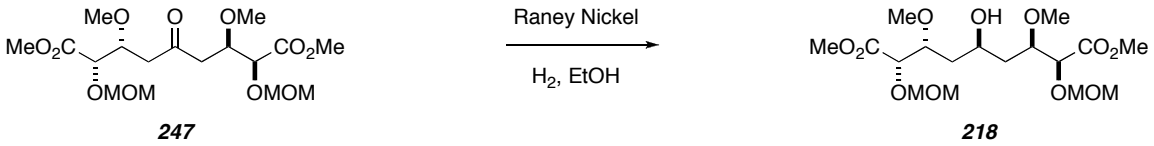
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.71 (d, *J* = 7.0 Hz, 2H, OC$H_a$$H_b$OMe), 4.68 (d, *J* = 6.9 Hz, 2H, OC$H_a$$H_b$OMe), 4.29 (d, *J* = 4.0 Hz, 2H, *H*COMOM), 4.19 (ddd, *J* = 7.2, 5.1, and 4.0 Hz, 2H, *H*COMe), 3.78 (s, 6H, CO_2*Me*), 3.39 (s, 6H, O*Me*), 3.38 (s, 6H, O*Me*), 2.85 (dd, *J* = 17.5 and 7.4 Hz, 2H, C$H_a$$H_b$), and 2.78 (dd, *J* = 17.5 and 5.1 Hz, 2H, C$H_a$$H_b$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.2, 170.9, 96.8, 76.9, 76.3, 58.9, 56.4, 52.2, and 44.1.

HR ESI-MS: Calcd for $C_{17}H_{30}O_{11}Na$ $(M+Na)^+$: 433.1680 Found: 433.1685.

TLC: R_f = 0.26; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dimethyl 5-Hydroxy-3,7-dimethoxy-2,8-bis(methoxymethoxy)nonanedioate **218**



247 ***218***

To ketone **247** (1.02 g, 2.49 mmol) was added EtOH (25.0 mL, 0.1 M) and black Raney Nickel (4 mL of an aqueous heterogeneous solution; commercially available reagent, used as received) in a Fischer-Porter tube equipped with the largest possible stir bar. The tube was flushed 3 times with H_2 and then filled with 50 psi of H_2. The heterogeneous solution was vigorously stirred until it was determined by TLC that the ketone had been fully converted into the alcohol. The reaction residue was filtered through a pad of celite using ethyl acetate and the filtrate was concentrated *in vacuo* to give the carbinol **218** as a colorless oil (935 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.73 (d, *J* = 7.0 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.72 (d, *J* = 7.0 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.71 (d, *J* = 7.0 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.70 (d, *J* = 7.0 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.27 (d, *J* = 4.2 Hz, 1H, *H*COMOM), 4.24 (d, *J* = 4.0 Hz, 1H,

*H*COMOM), 4.03-3.97 (m, 1H, *H*COH), 3.93 (ddd, *J* = 9.2, 3.7, and 3.7 Hz, 1H, *H*COMe), 3.86 (ddd, *J* = 7.4, 7.3, and 4.3 Hz, 1H, *H*COMe), 3.78 (s, 3H, CO_2*Me*), 3.77 (s, 3H, CO_2*Me*), 3.48 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), and 1.75-1.61 (m, 4H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$).

^{13}C NMR (125 MHz, C_6D_6): δ = 171.5, 171.2, 97.2, 97.1, 82.0, 79.1, 78.7, 77.6, 67.5, 59.2, 58.2, 56.3, 56.2, 51.7, 51.6, 39.7, and 38.9.

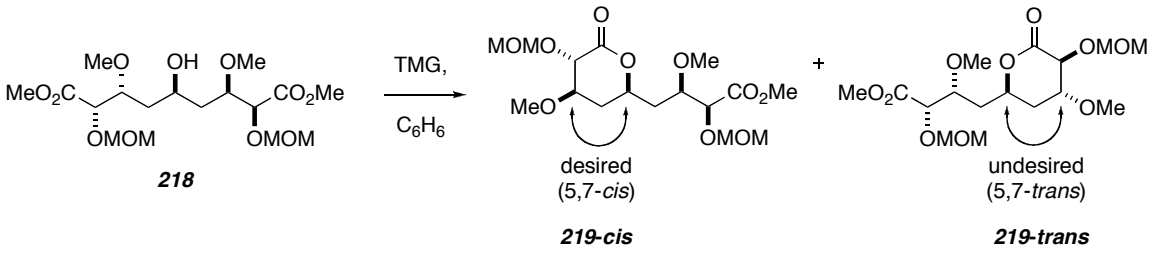
HR ESI-MS: Calcd for $C_{17}H_{32}O_{11}Na$ $(M+Na)^+$: 435.1837 Found: 435.1829.

TLC: R_f = 0.33; 1:3 hexanes:ethyl acetate.

(2*S*,3*R*)-Methyl 3-Methoxy-4-((2*R*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)-2-(methoxymethoxy)butanoate **219-*cis***

and

(2*S*,3*R*)-Methyl 3-Methoxy-4-((2*S*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)-2-(methoxymethoxy)butanoate **219-*trans***



Benzene (150 mL, 0.015 M) was added to a 500 mL round bottom flask containing alcohol **218** (930 mg, 2.26 mmol). 1,1,3,3-Tetramethylguanidine (0.57 mL, 4.51 mmol) was added dropwise and the reaction was stirred for 24 hours. Trifluoroacetic acid (0.174 mL, 2.25 mmol) was added dropwise and the reaction mixture was stirred for 3-5 minutes and partitioned into CH_2Cl_2 and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 200 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to afford **219-*cis*** and **219-*trans*** (842 mg, 98%) as a colorless oil. (**219-*cis***:**219-*trans*** 12:1) The crude mixture of lactones **219-*cis*** and **219-*trans*** were used in the next reaction without purification.

Characterization Data for 219-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.02 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.80 (d, *J* = 6.8 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.73 (d, *J* = 8.0 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.72 (d, *J* = 7.0 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.54-4.46 (m, 1H, *H*COC=O), 4.28 (d, *J* = 3.6 Hz, 1H, *H*COMOM), 4.16 (d, *J* = 8.0 Hz, 1H, *H*COMOM), 3.91 (ddd, *J* = 6.6, 6.6, and 3.3 Hz, 1H, *H*COMe), 3.78 (s, 3H, CO_2*Me*), 3.65 (ddd, *J* = 10.2, 8.0, and 5.0 Hz, 1H, *H*COMe), 3.47 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 3.38 (s, 3H, O*Me*), 2.38 (ddd, *J* = 13.9, 5.0, and 2.9 Hz, 1H, C$H_{a1}$$H_{b1}$), 2.09 (ddd, *J* = 14.4, 7.7, and 6.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.98 (ddd, *J* = 14.4, 6.7, and 5.0 Hz, 1H, C$H_{a2}$$H_{b2}$), and 1.72 (ddd, *J* = 13.9, 11.5, and 10.1 Hz, 1H, C$H_{a2}$$H_{b2}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.7, 97.1, 96.9, 77.8, 76.3, 75.2, 73.7, 66.1, 58.3, 57.6, 56.6, 56.4, 52.4, 35.9, and 34.3.

HR ESI-MS: Calcd for $C_{16}H_{28}O_{10}Na$ $(M+Na)^+$: 403.1580 Found: 403.1585.

TLC: R_f = 0.25; 1:1 hexanes:ethyl acetate.

Characterization Data for 219-*trans* [sample obtained from the experiment that follows in which the L-selectride reduction proceeds much faster for **219-*cis*** (to give **319**) than for **219-*trans***]

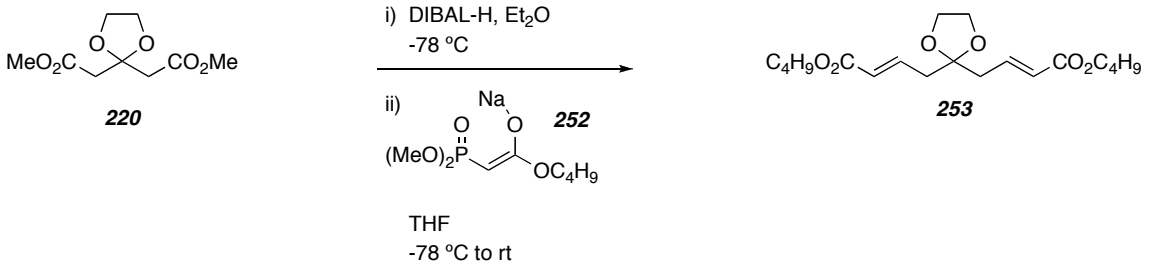
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.94 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.77 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.76-4.66 (m, 1H, *H*COC=O), 4.72 (d, *J* = 7.0 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.69 (d, *J* = 7.0 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.38 (d, *J* = 6.4 Hz, 1H, *H*COMOM), 4.23 (d, *J* = 4.0 Hz, 1H, *H*COMOM), 3.95 (ddd, *J* = 9.3, 8.0, and 4.0 Hz, 1H, *H*COMe), 3.78 (s, 3H, CO_2*Me*), 3.65 (ddd, *J* = 6.4, 6.4, and 1.9 Hz, 1H, *H*COMe), 3.46 (s, 3H, O*Me*), 3.45 (s, 3H, O*Me*), 3.42 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), and 2.03 (ddd, *J* = 15.1, 2.4, and 2.4 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.94 (ddd, *J* = 15.1, 11.2, and 6.4 Hz, 1H, C$H_{a1}$$H_{b1}$), and 1.87-1.82 (m, 2H, C$H_{a2}$$H_{b2}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 170.3, 96.5, 95.9, 77.3, 77.1, 76.0, 73.7, 71.7, 59.2, 57.1, 56.2, 55.9, 52.0, 37.0, and 34.5.

HR ESI-MS: Calcd for $C_{16}H_{28}O_{10}Na$ $(M+Na)^+$: 403.1580 Found: 403.1598.

TLC: R_f = 0.30; 1:1 hexanes:ethyl acetate.

(2*E*,7*E*)-Dibutyl 5-(1,3-dioxolane)-nona-2,7-dienoate **253**



The same experimental procedure to make **227** was followed to provide **253**. Ketal **220** (2.0 g, 9.17 mmol), Et_2O (36.7 mL, 0.25M), titrated DIBAL-H (14.6 mL, 20.2 mmol, 1.38 M in toluene); **252** (6.16 g, 27.5 mmol), NaH (1.03 g, 25.7 mmol, 60% in mineral oil), THF (55 mL, 0.5M). The crude mixture was purified by flash chromatography (6:1 hexanes:ethyl acetate) to provide the bis enone ketal **253** (≥ 80%) as a light yellow colored oil.

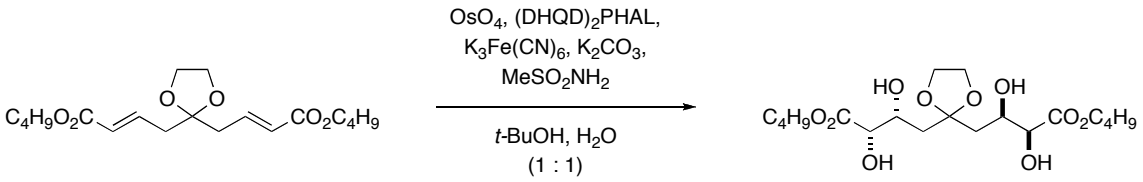
Characterization Data for trans-trans-Diene 253-*EE*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.91 (dt, *J* = 15.3 and 7.2 Hz, 2H, HC=C*H*CH_2), 5.90 (d, *J* = 15.6, 2H, *H*C=CHCH_2), 4.13 (t, *J* = 6.9 Hz, 4H, CO_2CH_2), 3.97 (s, 4H, OCH_2CH_2O), 2.53 (dd, *J* = 12.5 and 1.2 Hz, 4H, HC=CHCH_2), 1.62 (p, *J* = 7.2 Hz, 4H, $CO_2CH_2CH_2$), 1.45-1.30 (m, 4H, CH_2Me), and 0.94 (t, *J* = 7.2 Hz, 3H, *Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 142.6, 125.2, 109.6, 65.7, 64.4, 65.6, 64.4, 41.0, 30.9, 19.4, and 13.9.

TLC: R_f = 0.19; 6:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dibutyl 5-(1,3-dioxolane)-2,3,7,8-tetrahydroxynonanedioate **254**



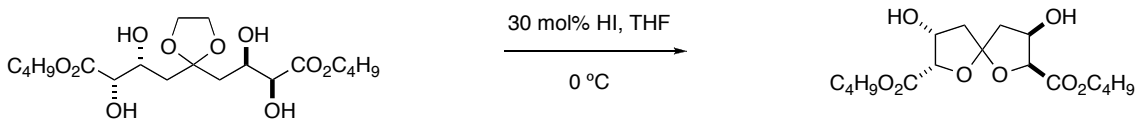
253 ***254***

The same experimental procedure to make **228** was followed to provide **254**. $K_3Fe(CN)_6$ (2.79 g, 8.46 mmol), K_2CO_3 (1.17 g, 8.46 mmol), $(DHQD)_2PHAL$ (44 mg, 0.056 mmol), OsO_4 (7 mg, 0.028 mmol), 1:1 mixture of a *t*-BuOH:H_2O solution (28.2 mL total volume, 0.05M), bis enone **253** (0.50 g, 1.41 mmol), and $MeSO_2NH_2$ (0.34 g, 3.53 mmol). The crude mixture was purified via MPLC (1:2 hexanes / ethyl acetate) to provide tetraol **254** (378 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.30-4.20 (m, 6H, H_βCOH and CO_2CH_2), 4.07 (s, 4H, OCH_2CH_2O), 4.03 (d, *J* = 1.9 Hz, 2H, H_αCOH), 3.12 (s, 1H, O*H*), 3.05 (d, *J* = 7.3 Hz, 1H, O*H*), 2.23 (dd, *J* = 15.0 and 9.9 Hz, 2H, CH_aH_b), 1.96 (dd, *J* = 15.0 and 2.4 Hz, 2H, CH_aH_b), 1.68 (p, *J* = 6.8 Hz, 4H, $CO_2CH_2CH_2$), 1.45-1.36 (m, 4H, CH_2Me), and 0.95 (t, *J* = 7.4 Hz, 6H, *Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.1, 111.1, 74.2, 69.0, 65.9, 64.9, 39.8, 30.7, 19.2, and 13.8.

(2*S*,3*R*,7*S*,8*R*)-2,7-(Dibutyl dicarboxylic acid)-3,8-dihydroxy-1,6-dioxaspiro[4.4]nonane **255**



254 ***255***

The same experimental procedure to make **229** was followed to provide **255**. Tetrol **254** (0.378 g, 0.892 mmol), THF (1.80 mL, 0.5M), and aqueous HI (0.020 mL, 0.267 mmol). The crude mixture was purified via MPLC (1:3 hexanes / ethyl acetate) to provide spirocycle **255**.

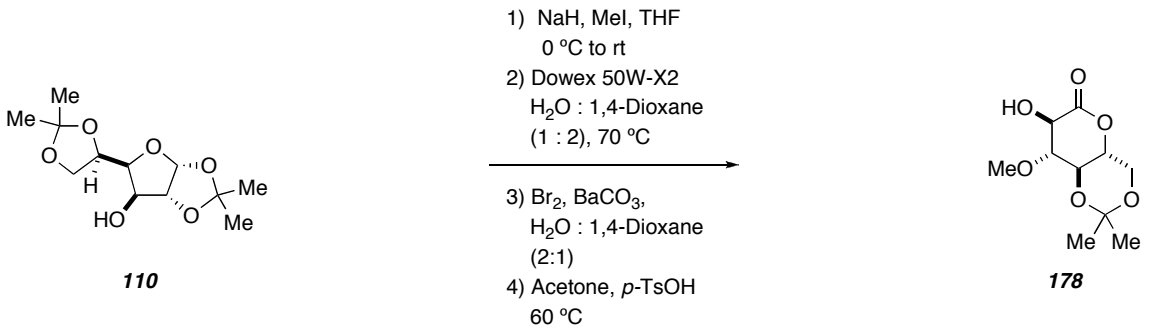
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.80-4.75 (m 2H, *H*COH), 4.63 (d, *J* = 5.0 Hz, 2H, *H*CCO_2), 4.27-4.17 (m, 4H, CO_2CH_2), 2.76 (dd, *J* = 14.4 and 6.6 Hz, 2H, CH_aH_b), 2.27 (dd, *J* = 14.4 and 3.7 Hz, 2H, CH_aH_b), 2.17 (d, *J* = 5.5 Hz, 2H, O*H*), 1.66 (p, *J* = 6.9 Hz, 4H, $CO_2CH_2CH_2$), 1.43-1.35 (m, 4H, CH_2Me), and 0.94 (t, *J* = 7.4 Hz, 6H, CH_2*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 114.8, 81.1, 72.6, 65.4, 44.6, 30.7, 19.2, and 13.8.

HR ESI-MS: Calcd for $C_{17}H_{28}O_8Na$ $(M+Na)^+$: 383.1676 Found: 383.1652.

TLC: R_f = 0.41; 1:3 hexanes:ethyl acetate.

(4a*R*,7*R*,8*R*,8a*R*)-7-Hydroxy-8-methoxy-2,2-dimethyltetrahydropyrano[3,2-*d*][1,3]dioxin-6(7*H*)-one **178**



110 ***178***

Methylation

To a 25 mL round bottom flask containing alchohol **110** (1.00 g, 3.84 mmol) was added THF (7.4 mL, 0.52 M) followed by cooling the solution to 0 ºC. Sodium hydride (221 mg, 9.20 mmol) was added in three incremental portions and the reaction was stirred until the evolution of gas ceased. Methyl iodide (0.720 mL, 11.5 mmol) was then added.

The solution was warmed to room temperature and stirred for 3 hours. Methanol was added to the reaction mixture to quench any excess sodium hydride. The solution was then diluted with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude methyl-ether **179** (989 mg, 94%). The crude product was then carried on to the next step without purification.

Acetonide Removal

To a 250 mL round bottom flask containing crude acetonide **179** (10.0 g, 36.5 mmol) was added 1,4-dioxane:H_2O (2:1, 40 mL:15 mL). The strongly acidic Dowex 50W-X2 (~7 g) was added to the reaction mixture followed by stirring for 24 hours. The Dowex resin was removed via filtration with a Buchner funnel and washed with MeOH. The filtrate was concentrated *in vacuo* and azeotropic removal of the H_2O was done with with either toluene or benzene to provide the crude lactol **180**. The crude product was then carried on to the next step without purification.

Bromine Oxidation

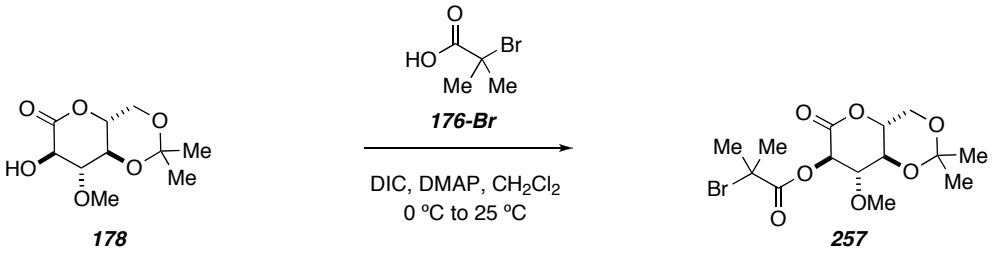
To a 100 mL round bottom flask, bromine (0.450 mL, 1.75 mmol) was added dropwise to a mixture of crude lactol **180** (1.36 g, 7.02 mmol) and barium carbonate (1.66 g, 8.42) in H_2O (14 mL) and 1,4-dioxane (7 mL). The reaction was covered in aluminum foil and stirred in the dark for 18 hous. Saturated aqueous Na_2SO_3 was added to quench the excess bromine. Azeotropic removal of the H_2O was done with either toluene or benzene. The remaining residue was taken up in MeOH and filtered through a pad of celite and the organic layer was concentrated *in vacuo* to provide the crude lactone **181**. The crude product was then carried on to the next step without purification.

Acetonide Formation

To a 25 mL round bottom flask containing the crude lactone **181** (1.01 g) was added acetone (6.0 mL) and PTSA (15 mg, 0.079). The mixture was stirred at 60 ºC for 18 hours. The solution was cooled to room temperature and the insoluble material was filtered through a pad of celite with acetone. The filtrate was washed with H_2O and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified via MPLC (1:1 hexanes / ethyl acetate) to provide lactone **178**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.69 (dd, *J* = 6.1 and 6.1 Hz, *H*COMe$_2$), 4.40 (ddd, *J* = 6.2, 6.2, and 6.2 Hz, 1H, *H*COC=O), 4.38 (d, *J* = 4.1 Hz, 1H, *H*COH), 4.09 (dd, *J* = 8.8 and 6.4 Hz, 1H, C*H*$_a$H$_b$), 4.06 (dd, *J* = 5.7 and 4.3 Hz, 1H, *H*COMe), 3.95 (dd, *J* = 8.8 and 5.8 Hz, 1H, CH$_a$*H*$_b$), 3.50 (s, 3H, O*Me*), 1.45 (s, 3H, C*Me*), and 1.38 (s, 3H, C*Me*).

(4a*R*,7*R*,8*S*,8a*R*)-8-Methoxy-2,2-dimethyl-6-oxohexahydropyrano[3,2-*d*][1,3]dioxin-7-yl 2-bromo-2-methylpropanoate **257**



To a culture tube containing lactone **178** (15 mg, 0.065 mmol) in CH_2Cl_2 (0.650 mL, 0.1 M) at 0 ºC was added 2-bromoisobutyric acid **176-Br** (27 mg, 0.16 mmol), DMAP (24 mg, 0.20 mmol), and 1,3-diisopropylcarbodiimide (0.05 mL, 0.3 mmol). The reaction mixture was warmed to room temperature and stirred for 24 hours. The solvent was removed and the residue was purified by MPLC (6:1 hexanes / ethyl acetate) to provide lactone **257** (12 mg, 48%).

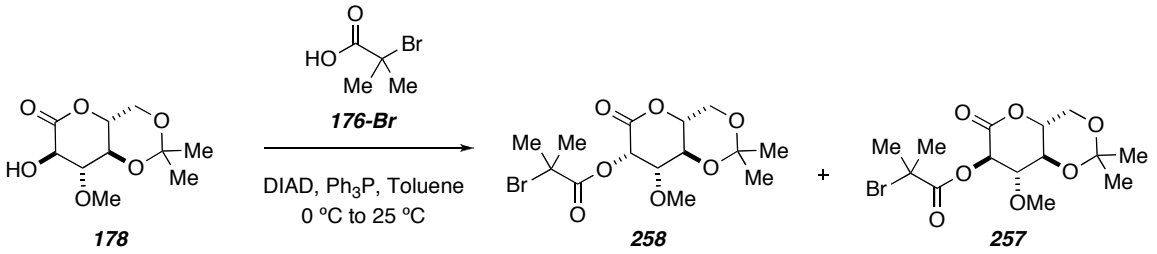
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.49 (d, *J* = 4.7 Hz, 1H, *H*COC=OCMe$_2$Br), 4.42 (ddd, *J* = 8.1, 6.0 and 4.2 Hz, 1H, *H*COC=O), 4.33 (dd, *J* = 8.1 and 3.0 Hz, 1H, *H*COCMe$_2$), 4.30 (dd, *J* = 4.6 and 3.0 Hz, 1H, *H*COMe), 4.15 (dd, *J* = 9.1 and 6.0 Hz, 1H, C*H*$_a$H$_b$), 4.07 (dd, *J* = 9.2 and 4.2 Hz, CH$_a$*H*$_b$), 3.59 (s, 3H, O*Me*), 2.05 (s, 3H, C*Me*MeBr), 2.01 (s, 3H, C*Me*MeBr), 1.45 (s, 3H, C*Me*), and 1.38 (s, 3H, C*Me*).

(4a*R*,7*S*,8*S*,8a*R*)-8-Methoxy-2,2-dimethyl-6-oxohexahydropyrano[3,2-*d*][1,3]dioxin-7-yl

2-bromo-2-methylpropanoate **258**

and

(4a*R*,7*R*,8*S*,8a*R*)-8-Methoxy-2,2-dimethyl-6-oxohexahydropyrano[3,2-*d*][1,3]dioxin-7-yl 2-bromo-2-methylpropanoate **257**



To a 25 mL round bottom flask containing lactone **178** (153 mg, 0.659 mmol) in toluene (13 mL, 0.05 M) at 0 ºC was added 2-bromoisobutyric acid (275 mg, 1.65 mmol), triphenylphosphine (519 mg, 1.98 mmol), and diisopropyl azodicarboxylate (0.390 mL, 1.98 mmol). The solution was warmed to room temperature and stirred for 18 hours. The solvent was removed and the residue was purified by MPLC (6:1 hexanes / ethyl acetate) to provide lactone **258** (133 mg, 53%) and lactone **257** (23 mg, 9%).

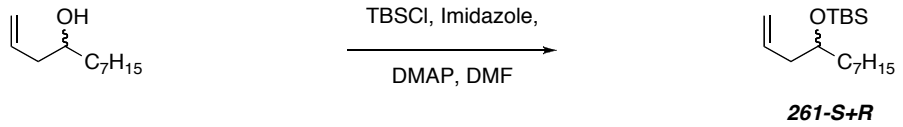
Characterization Data for 258 (Inversion)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.24 (d, *J* = 2.6 Hz, 1H, *H*COC=OCMe$_2$Br), 4.70 (dd, *J* = 6.6 and 5.2 Hz, 1H, *H*COCMe$_2$), 4.45 (ddd, *J* = 6.0, 6.0 and 6.0 Hz, 1H, *H*COC=O), 4.11 (dd, *J* = 8.9 and 6.3 Hz, 1H, C*H*$_a$H$_b$), 4.09 (dd, *J* = 5.1 and 2.6 Hz, 1H, *H*COMe), 4.02 (dd, *J* = 8.9 and 5.3 Hz, CH$_a$*H*$_b$), 3.52 (s, 3H, O*Me*), 1.98 (s, 3H, C*Me*MeBr), 1.97 (s, 3H, C*Me*MeBr), 1.45 (s, 3H, C*Me*), and 1.38 (s, 3H, C*Me*).

Characterization Data for 257 (Retention)

(previously reported in experimental section)

4-(*tert*-Butyldimethylsilyloxy)undec-1-ene **261-*S*+*R***



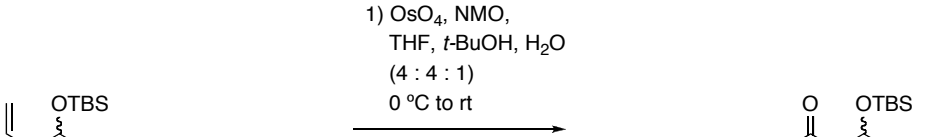
261-S+R

To a 500 mL round bottom flask containing the crude alcohol (12.2 g, 71.9 mmol) was added DMF (360 mL, 0.2 M), imidazole (9.79 g, 144 mmol), DMAP (878 mg, 0.66 mmol), and TBSCl (16.3, 108 mmol). The reaction was stirred for 18 hours, at which time TLC showed no remaining alcohol. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ was then added to the solution followed by dilution with H_2O and Et_2O. The reaction mixture was warmed to room temperature and stirred for 15-30 minutes. The aqueous layer was extracted with Et_2O (3 x 250 mL) and the combined organic layers were washed with H_2O (2 x 150 mL), saturated aqueous NaCl (1 x 150 mL), and then dried over Na_2SO_4, and concentrated *in vacuo* to provide the crude TBS-ether **261-*S+R*** (20.2 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (dddd, *J* = 17.4, 10.4, 7.2, and 7.2 Hz, 1H, CH_2=C*H*), 5.07-5.00 (m, 2H, CH_2=CH), 3.68 (p, *J* = 5.8 Hz, 1H, *H*COTBS), 2.26-2.14 (m, 2H, CH_2=CHCH_2), 1.68-1.16 (m, 12H, Alk-*H*), 0.89 (s, 9H, SiCMe_3), 0.88 (t, *J* = 7.4 Hz, 3H, Alk-*Me*), and 0.05 (s, 6H, SiMe_2).

TLC: R_f = 0.84; 19:1 hexanes:ethyl acetate.

3-(*tert*-Butyldimethylsilyloxy)decanal **263-*S+R***



261-S+R ***263-S+R***

Diol Formation

To a 100 mL round bottom flask containing crude alkene **261-*S+R*** (1.00 g, 3.51

mmol) in a THF:*t*-BuOH:H_2O [(4:4:1), (15.6 mL:15.6 mL:3.9 mL)] solution at 0 ºC was added NMO (0.872 mL, 4.21 mmol, 50 wt% solution in H_2O), and K_2OsO_4•H_2O (233 mg, 0.702 mmol). The solution was stirred at 0 ºC for 1 hour and then warmed to room temperature and stirred for 18 hours, at which time no starting material was observed by TLC. The soution was cooled to 0 ºC and saturated aqueous $Na_2S_2O_3$ was added to the reaction mixture. The solution was diluted with H_2O and Et_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (1 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude diol. The crude product was then carried on to the next step without purification.

Aldehyde Formation

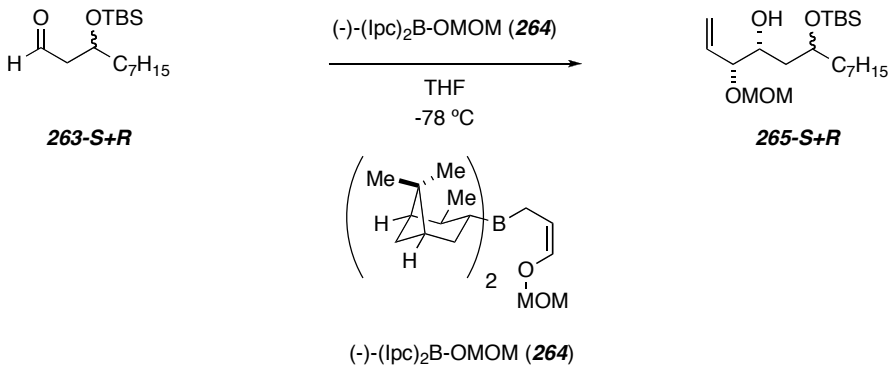
To a 100 mL round bottom flask containing crude diol (~1.11 g, ~3.51 mmol) in ethyl acetate (35 mL, 0.1 M) at 0 ºC was added $Pb(OAc)_4$ (1.87 g, 4.21 mmol) and the solution was stirred until no remaining starting material was observed by TLC. The reaction mixture was then filtered through silica gel using ethyl acetate. The resulting filtrate was concentrated *in vacuo* to provide the crude aldehyde **263-*S+R***. The crude product was then carried on to the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.81 (t, *J* = 2.5 Hz, 1H, *H*C=O), 4.23-4.02 (m, 1H, *H*COTBS), 2.59-2.52 (m, 2H, CH_aH_b), 1.64-1.18 (m, 12H, Alk-*H*), 0.90 (s, 9H, SiCMe_3), 0.87 (s, 9H, SiCMe_3), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

TLC: R_f = 0.38; 19:1 hexanes:ethyl acetate.

(3*R*,4*R*)-6-(*tert*-Butyldimethylsilyloxy)-3-(methoxy)tridec-1-en-4-ol

265-*S+R*



To a 100 mL round bottom flask containing allyl MOM-ether (0.950 mL, 8.38 mmol) in THF (3.5 mL) at -40 ºC (monitored by internal temperature probe) was added *n*-BuLi (3.25 mL, 6.98 mmol, 2.15 M in hexanes) dropwise down the side of the flask (to precool the solution) while keeping the temperature below -20 ºC. The color of the solution was monitored for the appearance of a dark/intense orange color as a sign of anion formation. Once the desired color was observed the solution's temperatrure was adjusted to -78 ºC followed by the addition of a solution of (-)-$(Ipc)_2$BOMe (2.21 g, 6.98 mmol) in THF (7.0 mL) down the side of the flask (to precool the solution) making sure the temperature never rose above -70 ºC. The solution was stirred at -78 ºC for 30 minutes. Recently distilled BF_3•OEt_2 (1.12 mL, 9.07 mmol) was added dropwise to the solution, making sure the temperature never rose above -70 ºC. Upon recooling to -78 ºC, the freshly prepared aldehyde **263-*S+R*** (2.00 g, 6.98 mmol) in a THF (3.5 mL) solution was added to the reaction mixture. The reaction was stirred at -78 ºC for 3 hours and then the solution was warmed to 0 ºC. The solution was then transferred to a 500 mL round bottom equipped with a stir bar followed by the addition of 30% aqueous H_2O_2 and 3 M NaOH, slowly at first followed by the addition of more H_2O_2 and NaOH. (Caution: This leads to an exotherm). The reaction mixture was stirred at room temperature overnight. The aqueous layer was extracted with Et_2O (4 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (9:1 hexanes:EtOAc) provided alcohol **265-*S+R*** (846 mg, 31%).

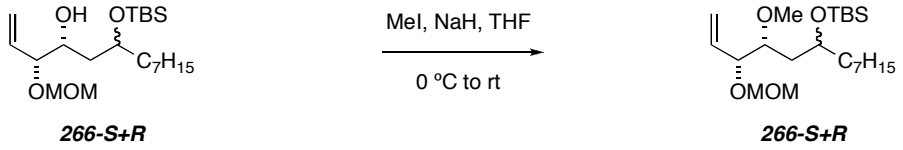
Characterization Data for Mixture of Diastereomers 265-*S+R* (1:2 ; *S*:*R*)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.80-5.67 (m, 1H, CH_2=C*H*), 5.80-5.67 (m, 1H, CH_2=C*H*), 5.36-5.28 (m, 2H, CH_2=CH), 5.36-5.28 (m, 2H, CH_2=CH), 4.74 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.73 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.60 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 4.60 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 4.11-3.69 (m, 3H, *H*COMOM, *H*COH, and *H*COTBS), 4.11-3.69 (m, 3H, *H*COMOM, *H*COH, and *H*COTBS), 3.39 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 1.72-1.16 (m, 14H, C$H_a$$H_b$ and Alk-*H*), 0.89 (s, 9H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.88 (t, *J* = 7.1 Hz, 3H, Alk-*Me*), 0.88 (t, *J* = 7.1 Hz, 3H, Alk-*Me*), 0.13 (s, 3H, Si*Me*), 0.12 (s, 3H, Si*Me*), 0.09 (s, 3H, Si*Me*), and 0.08 (s, 3H, Si*Me*).

TLC: R_f = 0.36; 9:1 hexanes:ethyl acetate.

(3*R*,4*R*)-6-(*tert*-Butyldimethylsilyloxy)-4-methoxy-3-(methoxymethoxy)tridec-1-ene

266-*S+R*



266-S+R ***266-S+R***

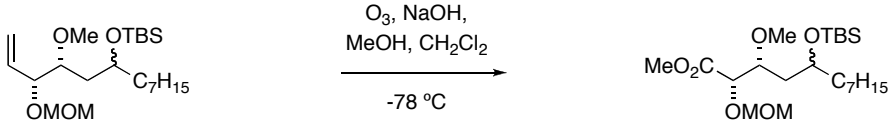
To a 50 mL round bottom flask containing alchohol **265-*S+R*** (864 mg, 2.18 mmol) was added THF (7.3 mL, 0.3 M) followed by cooling the solution to 0 ºC. Sodium hydride (130 mg, 4.36 mmol) was added and the reaction was stirred until the evolution of gas ceased. Methyl iodide (0.340 mL, 11.5 mmol) was then added. The solution was warmed to room temperature and stirred for 18 hours. Methanol was added to the reaction mixture to quench any excess sodium hydride. The solution was then diluted with ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (9:1 hexanes:EtOAc) provided methyl-ether **266-*S+R*** (669 mg, 76%.

Characterization Data for Mixture of Diastereomers 266-*S+R* (1:2 ; *S*:*R*)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (ddd, *J* = 17.7, 10.1, and 7.6 Hz, 1H, CH_2=C*H*), 5.83-5.74 (m, 1H, CH_2=C*H*), 5.32-5.26 (m, 2H, CH_2=CH), 5.32-5.26 (m, 2H, CH_2=CH), 4.71 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.70 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.59 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.58 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.17 (dd, *J* = 7.1 and 5.1 Hz, 1H, *H*COMOM), 4.08 (dd, *J* = 7.6 and 4.3 Hz, 1H, *H*COMOM), 3.87 (dddd, *J* = 9.3, 6.6, 5.0, and 2.9 Hz, 1H, *H*COTBS), 3.81 (p, *J* = 6.0 Hz, 1H, *H*COTBS), 3.48 (ddd, *J* = 9.8, 5.0, and 2.4 Hz, 1H, *H*COMe), 3.47 (s, 3H, O*Me*), 3.42 (s, 3H, O*Me*), 3.390 (s, 3H, O*Me*), 3.386 (s, 3H, O*Me*), 3.36 (ddd, *J* = 7.4, 5.2, and 4.3 Hz, 1H, *H*COMe), 1.76-1.21 (m, 15H, CH_aH_b and Alk-*H*), 1.76-1.21 (m, 15H, CH_aH_b and Alk-*H*), 0.90 (s, 9H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.89 (t, *J* = 7.0 Hz, 3H, Alk-*Me*), 0.89 (t, *J* = 7.0 Hz, 3H, Alk-*Me*), 0.08 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), 0.06 (s, 3H, Si*Me*), and 0.05 (s, 3H, Si*Me*).

TLC: R_f = 0.37; 19:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*R*)- and (2*S*,3*R*,5*S*)-Methyl 5-(*tert*-Butyldimethylsilyloxy)-3-methoxy-2-(methoxymethoxy)dodecanoate **267-*S+R***



266-S+R ***267-S+R***

To a 100 mL round bottom flask containing alkene **266-*S+R*** (256 mg, 0.636 mmol) was added CH_2Cl_2 (21.2 mL, 0.03 M) followed by cooling the solution to -78 ºC. A solution of methanolic NaOH (2.6 mL, 6.36 mmol, from a 2.5 M stock solution of NaOH/MeOH) was added. Ozone was sparged through the system using a pipette tip. Once sparging began, a characteristic yellow color developed. Ozone was sparged into the solution until TLC showed complete consumption of the starting material. Oxygen was then sparged through the solution. Et_2O (30 mL) and H_2O (15 mL) were added and

the solution was warmed to room temperature. The solution was adjusted to a neutral pH with 10% aqueous HCl and then diluted with Et_2O and H_2O followed by extraction of the aqueous layer with Et_2O (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (9:1 hexanes:ethyl acetate) provided methyl ester **267-*S+R*** (204 mg, 74%).

Characterization Data for Mixture of Diastereomers 267-*S+R* (1:2 ; *S*:*R*)

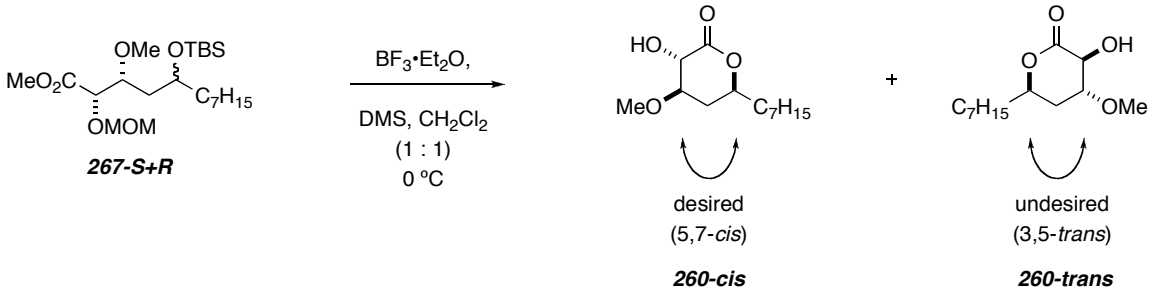
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.75 (d, *J* = 7.1 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.73 (d, *J* = 7.1 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.70 (d, *J* = 6.9 Hz, 1H, OCH$_a$*H*$_b$OMe), 4.70 (d, *J* = 7.1 Hz, 1H, OCH$_a$*H*$_b$OMe), 4.22 (d, *J* = 3.9 Hz, 1H, *H*COMOM), 4.20 (d, *J* = 3.1 Hz, 1H, *H*COMOM), 3.91-3.70 (m, 2H, *H*COMe and *H*COTBS), 3.91-3.70 (m, 2H, *H*COMe and *H*COTBS), 3.77 (s, 3H, CO_2*Me*), 3.77 (s, 3H, CO_2*Me*), 3.42 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 3.35 (s, 3H, O*Me*), 1.85-1.19 (m, 15H, C*H*$_a$*H*$_b$ and Alk-*H*), 1.85-1.19 (m, 15H, C*H*$_a$*H*$_b$ and Alk-*H*), 0.90 (s, 9H, SiC*Me*$_3$), 0.90 (s, 9H, SiC*Me*$_3$), 0.88 (t, *J* = 7.0 Hz, 3H, Alk-*Me*), 0.88 (t, *J* = 7.0 Hz, 3H, Alk-*Me*), 0.08 (s, 3H, Si*Me*), 0.072 (s, 3H, Si*Me*), 0.072 (s, 3H, Si*Me*), and 0.068 (s, 3H, Si*Me*).

TLC: R_f = 0.32; 9:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-Heptyl-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **260-*cis***

and

(3*S*,4*R*,6*R*)-6-Heptyl-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **260-*trans***



To a 50 mL round bottom flask containing ester **267-*S+R*** (405 mg, 0.932 mmol)

in a solution of CH_2Cl_2 (9.0 mL) and DMS (9.0 mL) at 0 ºC was added BF_3•OEt_2 (2.40 mL, 18.6 mmol). The reaction was stirred at 0 ºC until no remaining starting material was observed by TLC. Saturated aqueous $NaHCO_3$ was added to the reaction mixture at 0 ºC followed by warming the solution to room temperature and diluting the solution with ethyl acetate and H_2O. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (1 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification via MPLC (3:1 hexanes:ethyl acetate) provided lactone **260-*cis*** (60 mg, 26%) and **260-*trans*** (120 mg, 53%).

Characterization Data for 260-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 428 (dddd, *J* = 11.9, 7.3, 5.3, and 3.0 Hz, 1H, *H*COC=O), 4.07 (d, *J* = 9.4 Hz, 1H, *H*COH), 3.60 (ddd, *J* = 11.4, 9.4, and 4.2 Hz, 1H, *H*COMe), 3.53 (s, 3H, O*Me*), 2.32 (ddd, *J* = 13.9, 4.3, and 3.0 Hz, 1H, CH_aH$_b$), 1.79-1.58 (m, 2H, CH_2-Alk), 1.68 (ddd, *J* = 13.8, 11.4, and 11.4 Hz, 1H, CH$_a$$H_b$), 1.53-1.20 (m, 10H, Alk-*H*), and 0.88 (t, *J* = 7.0 Hz, 3H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 78.3, 78.0, 73.6, 57.9, 35.8, 33.8, 31.8, 29.4, 29.2, 24.9, 22.7, and 14.2.

TLC: R_f = 0.17; 3:1 hexanes:ethyl acetate.

Characterization Data for 260-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.54-4.47 (m, *H*COC=O), 4.32 (d, *J* = 6.1 Hz, 1H, *H*COH), 3.57 (ddd, *J* = 6.5, 6.5, and 2.4 Hz, 1H, *H*COMe), 3.49 (s, 3H, O*Me*), 2.01-1.89 (m, 2H, C$H_a$$H_b$), 1.77-1.67 (m, 1H, C$H_aH_b$-Alk), 1.61-1.52 (m, 1H, CH$_a$$H_b$-Alk), 1.50-1.20 (m, 10H, Alk-*H*), and 0.88 (t, *J* = 6.9 Hz, 3H, Alk-*Me*).

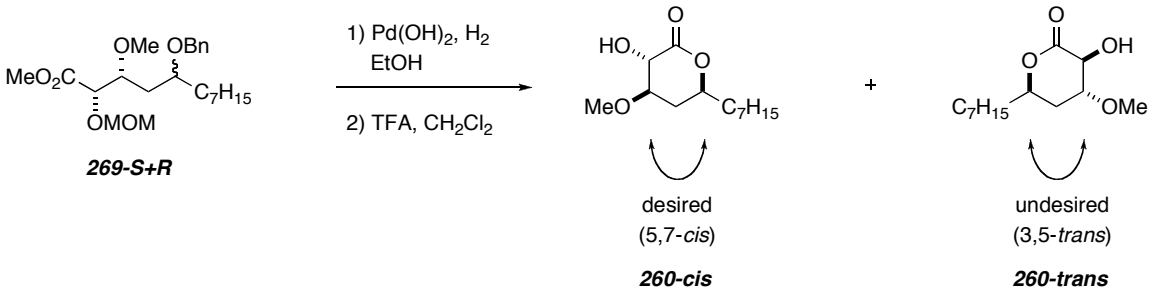
^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 78.9, 76.1, 72.6, 57.5, 35.7, 35.0, 31.9, 29.4, 29.3, 25.1, 22.8, and 14.3.

TLC: R_f = 0.23; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-Heptyl-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **260-*cis***

and

(3*S*,4*R*,6*R*)-6-Heptyl-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **260-*trans***



The ester **269-*S+R*** (100 mg, 0.244 mmol) was dissolved in ethanol (1.5 mL, 0.2 M) at room temperature in a Fischer-Porter tube. Pearlman's catalyst [$Pd(OH)_2$] (~30 mg) was added and the heterogeneous solution was placed under 50 psi H_2. The reaction was stirred under a H_2 atmosphere until TLC showed complete removal of the PMB-ether. The reaction mixture was filtered through celite with ethyl acetate and the filtrate was concentrated *in vacuo* to provide the crude mixture of alcohols. This mixture was then suspended in a solution of CH_2Cl_2 (2 mL) and TFA (0.280 mL, 3.66 mmol) was added to the reaction mixture. This solution was stirred until TLC showed complete conversion to the lactone products had occurred. The solution was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (15 mL) was added followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (3:1 hexanes:EtOAc) provided lactones **260-*cis*** (21 mg, 35%) and **260-*trans*** (20 mg, 33%).

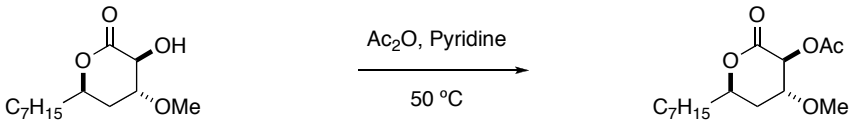
Characterization Data for 260-*cis*

(previously reported in experimental section)

Characterization Data for 260-*trans*

(previously reported in experimental section)

(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl ethanoate **270-*trans***



260-trans ***270-trans***

To a small vial containing lactone **260-*trans*** (~2 mg) was added pyridine (~0.02 mL) and acetic anhydride (~0.15 mL). The solution was gently heated with a heat gun for ~10 minutes. The excess reagents were then removed at room temperature under vacuum to provide the crude lactone **270-*trans*** (~2 mg).

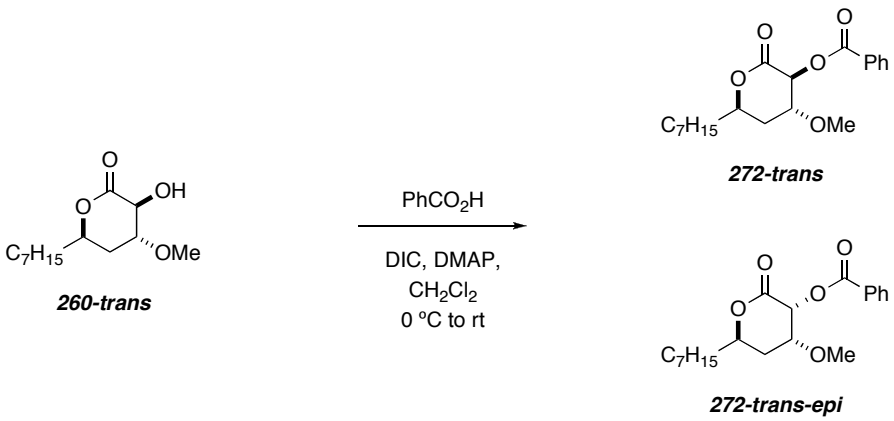
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.38 (d, *J* = 6.7 Hz, 1H, *H*COAc), 4.61-4.49 (m, 1H, *H*COC=O), 3.76 (ddd, *J* = 6.8, 6.8, and 2.0 Hz, 1H, *H*COMe), 3.39 (s, 3H, O*Me*), 2.22 (s, 3H, OC=O*Me*), 2.10-1.88 m, 2H, CH_aH_b), 1.78-1.22 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 7.0 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.45; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl benzoate **272-*trans***

and

(3*R*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl benzoate **272-*trans-epi***



260-trans ***272-trans*** ***272-trans-epi***

To a small vial containing lactone **260-*trans*** (2 mg, 0.008 mmol) in CH_2Cl_2 (0.200 mL, 0.04 M) at 0 ºC was added benzoic acid (2 mg, 0.12 mmol), DMAP (3 mg,

0.024 mmol), and 1,3-diisopropylcarbodiimide (0.006 mL, 0.04 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed and the residue was purified by MPLC (3:1 hexanes / ethyl acetate) to provide an inseparable 4:1 mixture of acylation and acylation/epimerization lactones **272-*trans*** and **272-*trans-epi*** (1 mg, 30%).

Characterization Data for Mixture of 272-*trans* and 272-*trans-epi* (4:1 ratio)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.18 (m, 2H, PhH_a), 8.18 (m, 2H, PhH_a), 7.63-7.58 (m, 1H, PhH_b), 7.63-7.58 (m, 1H, PhH_b), 7.50-7.44 (m, 2H, PhH_c), 7.50-7.44 (m, 2H, PhH_c), 5.63 (d, *J* = 6.5 Hz, 1H, *H*COC=OPh), 5.61 (d, *J* = 3.0 Hz, 1H, *H*COC=OPh), 4.05 (ddd, *J* = 4.7, 3.1, and 1.7 Hz, 1H, *H*COMe), 3.94 (ddd, *J* = 6.7, 6.7, and 2.4 Hz, 1H, *H*COMe), 3.54 (s, 3H, O*Me*), 3.42 (s, 3H, O*Me*), 2.36-1.21 (m, 14H, CH_aH_b and Alk-*H*), 2.36-1.21 (m, 14H, CH_aH_b and Alk-*H*), 0.89 (t, *J* = 6.8 Hz, 3H, Alk-*Me*), and 0.89 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.63; 3:1 hexanes:ethyl acetate.

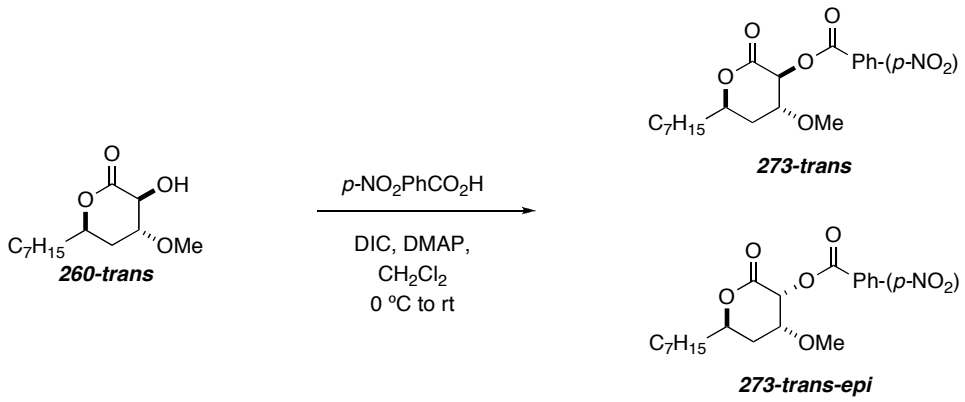
(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 4-nitrobenzoate

273-*trans*

and

(3*R*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 4-nitrobenzoate

273-*trans-epi*



To a small vial containing lactone **260-*trans*** (10 mg, 0.041 mmol) in CH_2Cl_2 (0.300 mL, 0.14 M) at 0 ºC was added *p*-nitrobenzoic acid (10 mg, 0.61 mmol), DMAP (15 mg, 0.123 mmol), and 1,3-diisopropylcarbodiimide (0.031 mL, 0.20 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed and the residue was purified by MPLC (3:1 hexanes / ethyl acetate) to provide the separable acylation lactone **273-*trans*** (8 mg, 50%) and acylation/epimerization lactone **273-*trans-epi*** (1 mg, 6%).

Characterization Data for 273-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.9 Hz, 2H, (*p*-NO_2)PhH_a), 8.29 (d, *J* = 8.5 Hz, 2H, (*p*-NO_2)PhH_b), 5.64 (d, *J* = 6.6 Hz, 1H, *H*COC=OPh(*p*-NO_2)), 4.64 (dddd, *J* = 10.8, 7.5, 4.9, and 2.7 Hz, 1H, *H*COC=O), 3.95 (ddd, *J* = 6.9, 6.9, and 1.9 Hz, 1H, *H*COMe), 3.42 (s, 3H, O*Me*), 2.14 (ddd, *J* = 15.1, 2.4, and 2.4 Hz, 1H, C$H_a$$H_b$), 2.06 (ddd, *J* = 15.1, 10.9, and 6.9 Hz, 1H, C$H_a$$H_b$), 1.77 (dddd, *J* = 12.8, 9.8, 7.5 and 4.7 Hz, 1H, C$H_a$$H_b$-Alk), 1.67-1.58 (m, 1H, C$H_a$$H_b$-Alk), 1.58-1.23 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 6.9 Hz, 3H, Alk-*Me*).

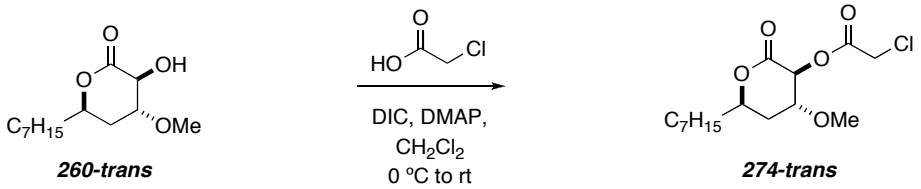
TLC: R_f = 0.53; 3:1 hexanes:ethyl acetate.

Characterization Data for 273-*trans-epi*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 9.5 Hz, 2H, (*p*-NO_2)PhH_a), 8.31 (d, *J* = 9.3 Hz, 2H, (*p*-NO_2)PhH_b), 5.60 (d, *J* = 3.1 Hz, 1H, *H*COC=OPh(*p*-NO_2)), 4.69 (dddd, *J* = 11.8, 7.3, 5.0, and 3.2 Hz, 1H, *H*COC=O), 4.08 (ddd, *J* = 4.7, 3.1, and 1.7 Hz, 1H, *H*COMe), 3.53 (s, 3H, O*Me*), 2.37 (ddd, *J* = 14.7, 4.8, and 3.8 Hz, 1H, C$H_a$$H_b$), 1.91 (ddd, *J* = 14.7, 11.8, and 1.8 Hz, 1H, C$H_a$$H_b$), 1.78 (dddd, *J* = 14.0, 10.2, 7.5 and 4.9 Hz, 1H, C$H_a$$H_b$-Alk), 1.69-1.60 (m, 1H, C$H_a$$H_b$-Alk), 1.58-1.19 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 6.9 Hz, 3H, Alk-*Me*).

(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 2-chloroethanoate

274-*trans*

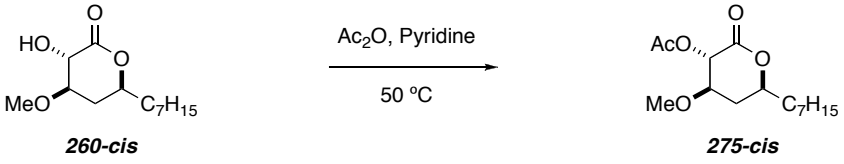


To a small vial containing lactone **260-*trans*** (2 mg, 0.008 mmol) in CH_2Cl_2 (0.200 mL, 0.04 M) at 0 ºC was added monochloroacetic acid (2 mg, 0.12 mmol), DMAP (3 mg, 0.024 mmol), and 1,3-diisopropylcarbodiimide (0.006 mL, 0.04 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed and the residue was purified by MPLC (3:1 hexanes / ethyl acetate) to provide lactone **274-*trans*** (1 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.41 (d, *J* = 6.6 Hz, 1H, *H*COC=OCH_2Cl), 4.56 (dddd, *J* = 10.6, 7.4, 4.5, and 2.4 Hz, 1H, *H*COC=O), 4.23 (s, 2H, COC=OC*H*$_2$Cl), 3.80 (ddd, *J* = 6.9, 6.9, and 1.9 Hz, 1H, *H*COMe), 3.40 (s, 3H, O*Me*), 2.07 (ddd, *J* = 15.1, 2.3, and 2.3 Hz, 1H, C*H*$_a$H$_b$), 1.99 (ddd, *J* = 15.1, 10.9, and 7.0 Hz, 1H, CH$_a$*H*$_b$), 1.73 (dddd, *J* = 13.8, 10.3, 8.0, and 4.9 Hz, 1H, C*H*$_a$H$_b$-Alk), 1.62-1.54 (m, 1H, CH$_a$*H*$_b$-Alk), 1.54-1.21 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 6.9 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.53; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl ethanoate **275-*cis***

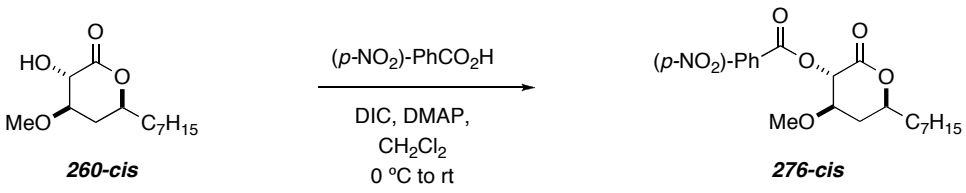


To a small vial containing lactone **260-*cis*** (~2 mg) was added pyridine (~0.02 mL) and acetic anhydride (~0.15 mL). The solution was gently heated with a heat gun for ~10 minutes. The excess reagents were then removed at room temperature under vacuum to provide the crude lactone **275-*cis*** (~2 mg).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.02 (d, *J* = 9.3 Hz, 1H, *H*COAc), 4.32 (dddd, *J* = 11.8, 7.4, 5.1, and 2.5 Hz, 1H, *H*COC=O), 3.79 (ddd, *J* = 11.4, 9.2, and 4.4 Hz, 1H, *H*COMe), 3.42 (s, 3H, O*Me*), 2.37 (ddd, *J* = 13.9, 4.5, and 2.6 Hz, 1H, CH_aH$_b$), 2.20 (s, 3H, OC=O*Me*), 1.83-1.53 (m, 3H, CH$_a$$H_b$ and C$H_a$$H_b$-Alk), 1.53-1.24 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 7.0 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.40; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 4-nitrobenzoate **276-*cis***



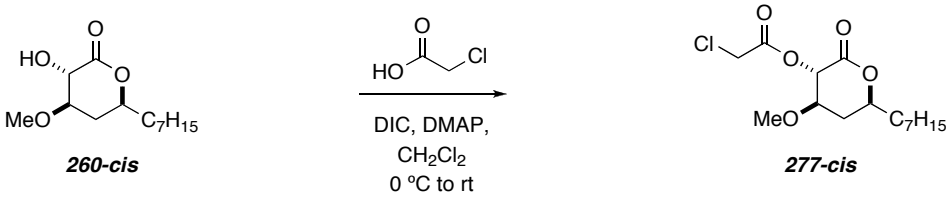
To a small vial containing lactone **260-*cis*** (2 mg, 0.008 mmol) in CH_2Cl_2 (0.200 mL, 0.04 M) at 0 ºC was added *p*-nitrobenzoic acid (2 mg, 0.12 mmol), DMAP (3 mg, 0.024 mmol), and 1,3-diisopropylcarbodiimide (0.006 mL, 0.04 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed and the residue was purified by MPLC (3:1 hexanes / ethyl acetate) to provide lactone **276-*cis*** (1 mg, 30%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.9 Hz, 2H, (*p*-NO_2)PhH_a), 8.28 (d, *J* = 8.8 Hz, 2H, (*p*-NO_2)PhH_b), 5.33 (d, *J* = 9.4 Hz, 1H, *H*COC=OPh(*p*-NO_2)), 4.41 (dddd, *J* = 12.0, 7.5, 5.2, and 2.8 Hz, 1H, *H*COC=O), 3.95 (ddd, *J* = 11.6, 9.5, and 4.6 Hz, 1H, *H*COMe), 3.43 (s, 3H, O*Me*), 2.46 (ddd, *J* = 13.9, 4.5, and 2.6 Hz, 1H, CH_aH$_b$), 1.86-1.78 (m, 1H, CH_aH$_b$-Alk), 1.79 (ddd, *J* = 14.0, 11.6, and 11.6 Hz, 1H, CH$_a$$H_b$), 1.73-1.64 (m, 1H, CH$_a$$H_b$-Alk), 1.60-1.21 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.47; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 2-chloroethanoate

277-*cis*



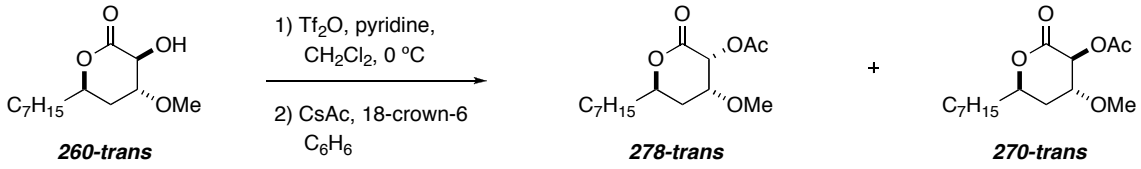
To a small vial containing lactone **260-*cis*** (2 mg, 0.008 mmol) in CH_2Cl_2 (0.200 mL, 0.04 M) at 0 ºC was added monochloroacetic acid (2 mg, 0.1 mmol), DMAP (3 mg, 0.02 mmol), and 1,3-diisopropylcarbodiimide (0.006 mL, 0.04 mmol). The reaction mixture was warmed to room temperature and stirred for 18 hours. The solvent was removed to provide crude lactone **277-*cis***.

TLC: R_f = 0.37; 3:1 hexanes:ethyl acetate.

(3*R*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl ethanoate **278-*trans***

and

(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl ethanoate **270-*trans***



Triflate Formation

To a small vial containing lactone **260-*trans*** (10 mg, 0.041 mmol) in CH_2Cl_2 (0.600 mL, 0.07 M) at 0 ºC was added pyridine (0.012 mL, 0.15 mmol) and trifluoromethanesulfonic anhydride (0.024 mL, 0.14 mmol). The reaction mixture was warmed to room temperature and stirred until TLC showed no remaining starting

material. The reaction mixture was diluted with CH_2Cl_2 and the solution was filtered through a pad of celite. The resulting filtrate was concentrated *in vacuo* and the crude triflate was then carried on to the next step without any further purification.

Characterization Data for Triflate

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.21 (d, *J* = 7.2 Hz, 1H, *H*COTf), 4.60-4.46 (m, 1H, *H*COC=O), 3.83 (ddd, *J* = 7.1, 7.1, and 2.9 Hz, 1H, *H*COMe), 3.45 (s, 3H, O*Me*), 2.17-1.98 (m, 2H, CH_aH_b), 1.83-1.17 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.6 Hz, 3H, Alk-*Me*).

HR ESI-MS: Calcd for $C_{14}H_{23}F_3O_6SNa$ $(M+Na)^+$: 399.1060 Found: 399.1102.

TLC: R_f = 0.82; 3:1 hexanes:ethyl acetate.

Triflate Displacement

To a small vial containing the crude triflate (~10 mg, 0.041 mmol) in benzene (0.300 mL, 0.14 M) at room temperature was added 18-crown-6 (6 mg, 0.021 mmol) and cesium acetate (24 mg, 0.123 mmol). The reaction mixture was stirred at room temperature until TLC showed no remaining starting material. The solution was then diluted with ethyl acetate and filtered through a pad of celite using ethyl acetate. The resulting filtrate was concentrated *in vacuo* to provide the crude residue. Purification via MPLC (3:1 hexanes / ethyl acetate) provided the separable inverted lactone **278-*trans*** (~2 mg) and acylation lactone **270-*trans*** (~2 mg).

Characterization Data for Inverted 278-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.33 (d, *J* = 3.0 Hz, 1H, *H*COAc), 4.36-4.29 (m, 1H, *H*COC=O), 3.26 (ddd, *J* = 4.6, 3.1, and 1.7 Hz, 1H, *H*COMe), 3.03 (s, 3H, O*Me*), 1.81 (s, 3H, OC=O*Me*), 1.48 (ddd, *J* = 14.5, 4.6, and 3.6 Hz, 1H, CH_aH_b), 1.39-1.01 (m, 13H, Alk-*H* and CH_aH_b), and 0.92 (t, *J* = 7.1 Hz, 3H, Alk-*Me*).

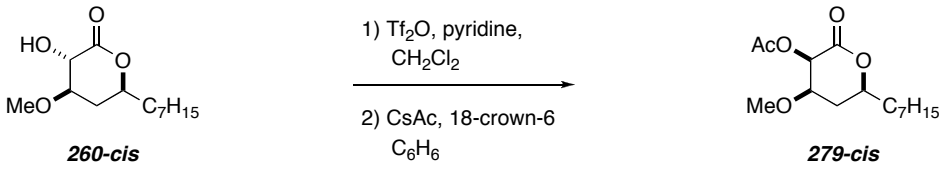
HR ESI-MS: Calcd for $C_{15}H_{26}O_5Na$ $(M+Na)^+$: 309.1672 Found: 309.1687.

TLC: R_f = 0.29; 3:1 hexanes:ethyl acetate.

Characterization Data for Acylation 270-*trans*

(previously reported in experimental section)

(3*R*,4*R*,6*S*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl ethanoate **279-*cis***



260-cis ***279-cis***

Triflate Formation

To a small vial containing lactone **260-*cis*** (10 mg, 0.041 mmol) in CH_2Cl_2 (0.600 mL, 0.07 M) at 0 ºC was added pyridine (0.024 mL, 0.297 mmol) and trifluoromethanesulfonic anhydride (0.048 mL, 0.285 mmol). The reaction mixture was warmed to room temperature and stirred until TLC showed no remaining starting material. The reaction mixture was diluted with CH_2Cl_2 and the solution was filtered through a pad of celite. The resulting filtrate was concentrated *in vacuo* and the crude triflate was then carried on to the next step without any further purification.

Characterization Data for Triflate

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.98 (d, *J* = 9.9 Hz, 1H, *H*COTf), 4.28 (dddd, *J* = 12.1, 7.6, 5.3, and 2.7 Hz, 1H, *H*COC=O), 3.83 (ddd, *J* = 7.1, 7.1, and 2.9 Hz, 1H, *H*COMe), 3.49 (s, 3H, O*Me*), 2.48 (ddd, *J* = 14.1, 4.4, and 2.9 Hz, 1H CH_aH$_b$), 1.83-1.70 (m, 1H, CH_aH$_b$-Alk), 1.74 (ddd, *J* = 14.0, 11.8, and 11.8 Hz, 1H, CH$_a$$H_b$), 1.69-1.61 (m, 1H, CH$_a$$H_b$-Alk), 1.53-1.18 (m, 10H, Alk-*H*), and 0.89 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 110.0, 82.6, 78.2, 76.0, 57.8, 35.6, 34.0, 31.9, 29.4, 29.2, 24.9, 22.8, and 14.3.

HR ESI-MS: Calcd for $C_{14}H_{23}F_3O_6SNa$ $(M+Na)^+$: 399.1060 Found: 399.1017.

TLC: R_f = 0.73; 3:1 hexanes:ethyl acetate.

Triflate Displacement

To a small vial containing the crude triflate (~10 mg, 0.041 mmol) in benzene (0.300 mL, 0.14 M) at room temperature was added 18-crown-6 (6 mg, 0.021 mmol) and cesium acetate (24 mg, 0.123 mmol). The reaction mixture was stirred at room temperature until TLC showed no remaining starting material. The solution was then diluted with ethyl acetate and filtered through a pad of celite using ethyl acetate. The resulting filtrate was concentrated *in vacuo* to provide the crude residue. Purification via MPLC (3:1 hexanes / ethyl acetate) provided inverted lactone **279-*cis*** (~6 mg).

Characterization Data for Inverted 279-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26 (d, *J* = 3.5 Hz, 1H, *H*COAc), 3.97-3.88 (m, 1H, *H*COC=O), 3.62 (ddd, *J* = 7.8, 3.6, and 2.1 Hz, 1H, *H*COMe), 3.23 (s, 3H, O*Me*), 2.05 (s, 3H, OC=O*Me*), 1.84 (ddd, *J* = 14.8, 7.8, and 4.9 Hz, 1H CH_aH$_b$), 1.61 (ddd, *J* = 14.9, 11.3, and 2.2 Hz, 1H CH$_a$$H_b$), 1.60-1.50 (m, 1H, C$H_aH_b$-Alk and Alk-*H*), and 0.90 (t, *J* = 6.9 Hz, 3H, Alk-*Me*).

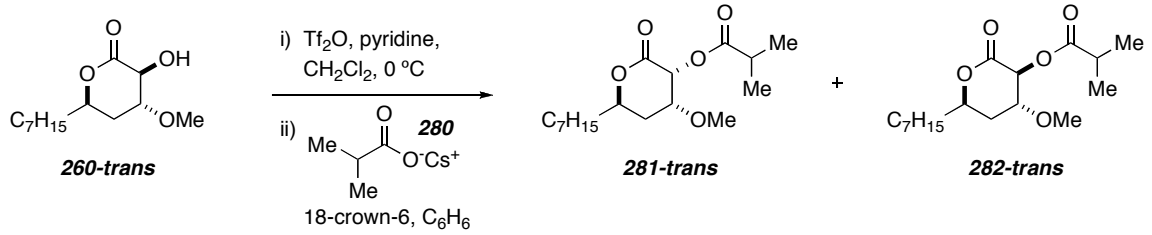
(3*R*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 2-methylpropanoate

281-trans

and

(3*S*,4*R*,6*R*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 2-methylpropanoate

282-*trans*



260-trans ***281-trans*** ***282-trans***

Triflate Formation

The same experimental procedure previously described to make the triflate of

260-*trans*, used in the production of **278-*trans***, was followed here as well. Lactone **260-*trans*** (5 mg, 0.020 mmol), CH_2Cl_2 (0.500 mL, 0.04 M), pyridine (0.012 mL, 0.148 mmol), trifluoromethanesulfonic anhydride (0.024 mL, 0.143 mmol). The crude triflate was then used in the next step without any further purification.

Characterization Data for Triflate

(previously reported in experimental section)

Triflate Displacement

The same experimental procedure previously described to produce **278-*trans*** and **270-*trans*** via displacement of a triflate by cesium acetate was used here in the production of **281-*trans*** and **282-*trans***. Crude triflate (2 mg, 0.056 mmol), benzene (0.300 mL, 0.19 M), 18-crown-6 (6 mg, 0.021 mmol), cesium isobutyrate **280** (24 mg, 0.123 mmol). Purification via MPLC (3:1 hexanes / ethyl acetate) provided the separable inverted lactone **281-*trans*** (~0.5 mg) and acylation lactone **282-*trans*** (~0.5 mg).

Characterization Data for Inverted 281-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.36 (d, *J* = 3.0 Hz, 1H, *H*COC=OCHMe$_2$), 4.66-4.58 (m, 1H, *H*COC=O), 3.26 (ddd, *J* = 4.7, 3.0, and 1.7 Hz, 1H, *H*COMe), 3.49 (s, 3H, O*Me*), 2.74 (sept., *J* = 7.3 Hz, 1H, HCOC=OC*H*Me$_2$), 2.27 (ddd, *J* = 14.6, 4.6, and 3.6 Hz, 1H, C*H$_a$*H$_b$), 1.83 (ddd, *J* = 14.2, 11.9, and 1.7 Hz, 1H, CH$_a$*H$_b$*), 1.77-1.23 (m, 12H, Alk-*H*), 1.27 (d, *J* = 7.0 Hz, 6H, HCOC=OCH*Me*$_2$), 1.25 (d, *J* = 7.0 Hz, 6H, HCOC=OCH*Me*$_2$), and 0.88 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.60; 3:1 hexanes:ethyl acetate

Characterization Data for Acylation 282-*trans*

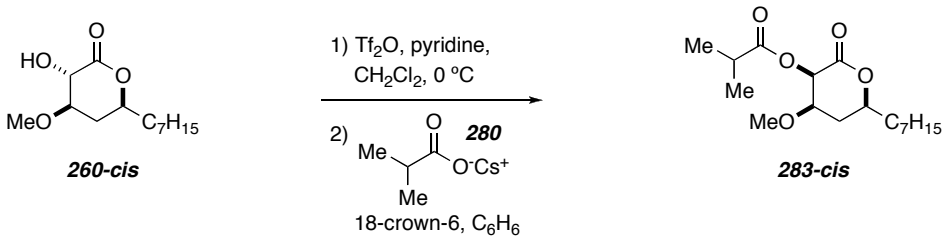
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.36 (d, *J* = 6.5 Hz, 1H, *H*COC=OCHMe$_2$), 4.61-4.51 (m, 1H, *H*COC=O), 3.79-3.73 (m, 1H, *H*COMe), 3.38 (s, 3H, O*Me*), 2.71 (sept., *J* = 7.2 Hz, 1H, HCOC=OC*H*Me$_2$), 2.01-1.93 (m, 2H, C*H$_a$H$_b$*), 1.78-1.22 (m, 12H, Alk-*H*), 1.27

(d, J = 7.0 Hz, 6H, HCOC=OCHMe_2), 1.24 (d, J = 7.0 Hz, 6H, HCOC=OCHMe_2), and 0.88 (t, J = 7.0 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.68; 3:1 hexanes:ethyl acetate

(3*R*,4*R*,6*S*)-6-Heptyl-4-methoxy-2-oxotetrahydro-2*H*-pyran-3-yl 2-methylpropanoate

283-*cis*



Triflate Formation

The same experimental procedure previously described to make the triflate of **260-*cis***, used in the production of **279-*cis***, was followed here as well. Lactone **260-*cis*** (32 mg, 0.13 mmol), CH_2Cl_2 (2.4 mL, 0.05 M), pyridine (0.110 mL, 1.36 mmol), trifluoromethanesulfonic anhydride (0.206 mL, 1.22 mmol). The crude triflate was then used in the next step without any further purification.

Characterization Data for Triflate

(previously reported in experimental section)

Triflate Displacement

The same experimental procedure previously described to produce **279-*cis*** via displacement of a triflate by cesium acetate was used here in the production of **283-*cis***. Crude triflate (~42 mg, 0.118 mmol), benzene (1.5 mL, 0.08 M), 18-crown-6 (16 mg, 0.059 mmol), cesium isobutyrate **280** (78 mg, 0.350 mmol). Purification via MPLC (3:1 hexanes / ethyl acetate) provided inverted lactone **283-*cis*** (29 mg, 71% over 2-steps).

Characterization Data for Inverted 283-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 (d, *J* = 3.5 Hz, 1H, *H*COC=OCHMe$_2$), 4.35 (dddd, *J* = 11.3, 7.7, 4.9, and 4.9 Hz, 1H, *H*COC=O), 3.96 (ddd, *J* = 7.8, 3.6, and 2.2 Hz, 1H, *H*COMe), 3.44 (s, 3H, O*Me*), 2.76 (sept., *J* = 7.0 Hz, 1H, HCOC=OC*H*Me$_2$), 2.35 (ddd, *J* = 14.9, 7.8, and 4.9 Hz, 1H, C*H*$_a$H$_b$), 1.88 (ddd, *J* = 14.9, 11.2, and 2.2 Hz, 1H, CH$_a$*H*$_b$), 1.76 (dddd, *J* = 13.8, 9.8, 7.7, and 4.8 Hz, 1H, C*H*$_a$H$_b$-Alk), 1.63-1.55 (m, 1H, CH$_a$*H*$_b$-Alk), 1.55-1.21 (m, 10H, Alk-*H*), 1.27 (d, *J* = 7.0 Hz, 3H, HCOC=OCH*Me*$_a$Me$_b$), 1.25 (d, *J* = 7.0 Hz, 3H, HCOC=OCHMe$_a$*Me*$_b$), and 0.88 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 167.5, 75.3, 74.8, 70.7, 58.6, 35.7, 35.1, 34.0, 31.9, 29.4, 29.3, 25.2, 22.8, 19.10, 19.08, and 14.3.

TLC: R_f = 0.75; 3:1 hexanes:ethyl acetate.

(2*S*,3*R*)-Methyl 2-Hydroxy-3-methoxy-4-((2*S*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)butanoate **284-*cis***

and

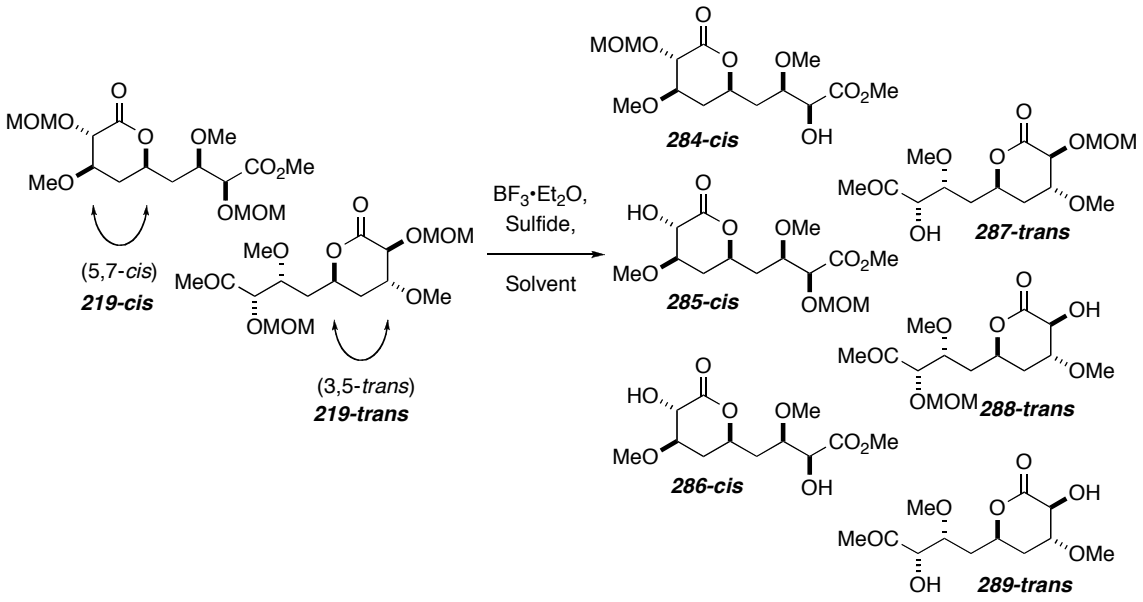
(2*S*,3*R*)-Methyl 4-((2*R*,4*R*,5*S*)-5-Hydroxy-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxy-2-(methoxymethoxy)butanoate **285-*cis***

and

(2*S*,3*R*)-Methyl 2-Hydroxy-4-((2*R*,4*R*,5*S*)-5-hydroxy-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **286-*cis***

and

(3*S*,4*R*,6*R*)-3-Hydroxy-6-((2*R*,3*S*)-3-hydroxy-2-methoxy-4-oxopentyl)-4-methoxytetrahydro-2*H*-pyran-2-one **289-*trans***



Selective deprotection conditions were screened as follows. To a crude lactone mixture of **219-*cis*** and **219-*trans*** in a NMR tube was added THF-*d8* (550 mL, 0.018M), followed by the corresponding sulfide, in varying amounts, that was going to be screened (methyl isopropyl sulfide, *sec butyl* methyl sulfide, 2-butyl-phenyl sulfide, benzyl methyl sulfide, thiophenol, 2-methyl-2-propanethiol, and dimethyl sulfide). The desired amount of BF_3•OEt_2 was then added at room temperature. The conversion to product was monitored by ^{1}H NMR and stopped at approximately 50% conversion by quenching with saturated sodium bicarbonate. Extraction of the aqueous layer with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (95:5 CH_2Cl_2:MeOH) provided varying amounts of starting lactone **219-*cis*** and **219-*trans***, as well as products **284-*cis***, **285-*cis***, **286-*cis***, and **289-*trans***. All sulfides gave similar ratios of products at 50% conversion, most importantly **284-*cis***:**285-*cis***:**286-*cis*** in a 2:1:1 ratio.

Characterization Data for Mono-Acyclic Alcohol 284-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.02 (d, *J* = 6.7 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.79 (d, *J* = 6.7 Hz, 1H, OCH$_a$*H*$_b$OMe), 4.44 (dddd, *J* = 11.9, 9.2, 3.5, and 3.5 Hz, 1H, *H*COC=O), 4.22 (dd, *J* = 7.4 and 2.2 Hz, 1H, *H*COH), 4.16 (d, *J* = 8.0 Hz, 1H, *H*COMOM), 3.90 (ddd, *J* = 8.0, 5.2, and 2.2 Hz, 1H, *H*COMe), 3.83 (s, 3H, CO_2*Me*), 3.66 (ddd, *J* = 10.1, 7.9, and 5.0

Hz, 1H, *H*COMe), 3.47 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.32 (s, 3H, O*Me*), 2.94 (bd, 1H, O*H*), 2.42 (ddd, *J* = 14.0, 5.0, and 2.9 Hz, 1H, CH_{a1}H$_{b1}$), 2.12-1.97 (m, 2H, C$H_{a2}H_{b2}$), and 1.70 (ddd, *J* = 14.0, 10.7, and 10.7 Hz, 1H, CH$_{a1}H_{b1}$).

HR ESI-MS: Calcd for $C_{14}H_{24}O_9Na$ $(M+Na)^+$: 359.1313 Found: 359.1338.

TLC: R_f = 0.31; 95:5 dichloromethane:methanol.

Characterization Data for Mono-Lactone Alcohol 285-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.73 (d, *J* = 7.0 Hz, 1H, OCH_aH$_b$OMe), 4.71 (d, *J* = 7.1 Hz, 1H, OCH$_a$$H_b$OMe), 4.50-4.44 (m, 1H, *H*COC=O), 4.29 (d, *J* = 3.7 Hz, 1H, *H*COMOM), 4.10 (d, *J* = 9.3 Hz, 1H, *H*COH), 3.89 (ddd, *J* = 6.6, 6.6, and 3.6 Hz, 1H, *H*COMe), 3.79 (s, 3H, CO_2*Me*), 3.62 (ddd, *J* = 11.1, 9.2, and 4.2 Hz, 1H, *H*COMe), 3.54 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 3.24 (bs, 1H, O*H*), 2.36 (ddd, *J* = 13.9, 3.6, and 3.6 Hz, 1H, CH_{a1}H$_{b1}$), 2.15-1.97 (m, 2H, C$H_{a2}H_{b2}$), and 1.77 (ddd, *J* = 14.0, 11.4, and 11.4 Hz, 1H, CH$_{a1}H_{b1}$).

HR ESI-MS: Calcd for $C_{14}H_{24}O_9Na$ $(M+Na)^+$: 359.1313 Found: 359.1318.

TLC: R_f = 0.29; 95:5 dichloromethane:methanol.

Characterization Data for Diol 286-*cis*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.41 (dddd, *J* = 12.0, 9.1, 3.5, and 3.5, 1H, *H*COC=O), 4.22 (bs, 1H, *H*COH), 4.11 (d, *J* = 9.4 Hz, 1H, *H*COH), 3.89 (ddd, *J* = 8.5, 5.3, and 2.2 Hz, 1H, *H*COMe), 3.84 (s, 3H, CO_2*Me*), 3.62 (ddd, *J* = 11.3, 9.4, and 4.2 Hz, 1H, *H*COMe), 3.53 (s, 3H, O*Me*), 3.32 (s, 3H, O*Me*), 2.41 (ddd, *J* = 13.9, 4.2, and 2.9 Hz, 1H, CH_{a1}H$_{b1}$), 2.11 (ddd, *J* = 14.4, 9.1, and 5.4 Hz, 1H, CH_{a2}H$_{b2}$), 2.04 (ddd, *J* = 14.3, 8.6, and 3.9 Hz, 1H, CH$_{a2}H_{b2}$), and 1.76 (ddd, *J* = 13.9, 11.5, and 11.5 Hz, 1H, CH$_{a1}H_{b1}$).

HR ESI-MS: Calcd for $C_{12}H_{20}O_8Na$ $(M+Na)^+$: 315.1050 Found: 315.1049.

TLC: R_f = 0.24; 95:5 dichloromethane:methanol.

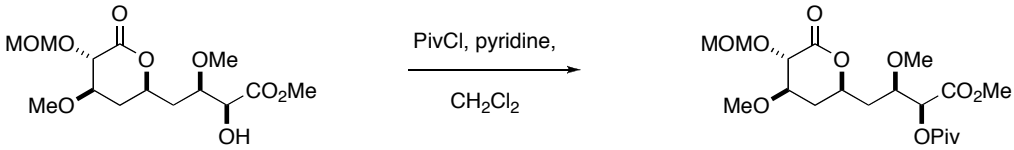
Characterization Data for Diol 289-*trans*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.77-4.71 (m, 1H, *H*COC=O), 4.36 (d, *J* = 6.0 Hz, 1H, *H*COH), 4.06 (bs, 1H, *H*COH), 3.96 (ddd, *J* = 10.4, 2.8, and 2.8 Hz, 1H, *H*COMe), 3.84 (s, 3H, CO_2*Me*), 3.62-3.58 (m, 1H, *H*COMe), 3.49 (s, 3H, O*Me*), 3.35 (s, 3H, O*Me*), 2.88

(bd, 1H, O*H*), 2.06-1.96 (m, 3H, C$H_{a1}H_{b1}$ and CH_{a2}H$_{b2}$), and 1.80 (ddd, *J* = 14.6, 10.3, and 2.9 Hz, 1H, CH$_{a2}H_{b2}$).

TLC: R_f = 0.28; 95:5 dichloromethane:methanol.

(2*S*,3*R*)-Methyl 2-(2,2-Dimethylpropanoyloxy)-3-methoxy-4-((2*R*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)butanoate **290**



284-cis ***290***

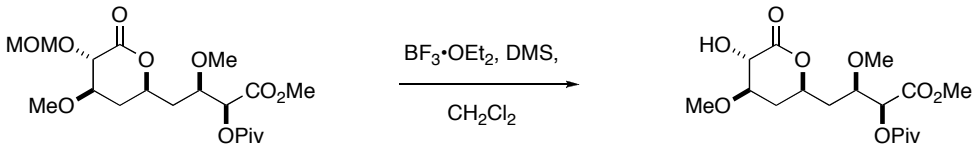
To a vial containing alcohol **284-*cis*** (4 mg, 0.012 mmol) in CH_2Cl_2 (0.45 mL, 0.027M) at 0 ºC was added pyridine (0.015 mL, 0.188 mmol) and trimethyl acetyl chloride (0.012 mL, 0.094 mmol). The reaction mixture was warmed to room temperature and stirred until TLC showed complete consumption of the starting material. The solution was recooled to 0 ºC, diluted with CH_2Cl_2, followed by the addition of saturated aqueos $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (1:1 hexanes / ethyl acetate) provided lactone **290** (4 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 3.3 Hz, 1H, *H*COPiv), 5.01 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.79 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.43-4.35 (m, 1H, *H*COC=O), 4.16 (d, *J* = 7.8 Hz, 1H, *H*COMOM), 4.03 (ddd, *J* = 6.8, 6.8, and 3.4 Hz, 1H, *H*COMe), 3.78 (s, 3H, CO_2*Me*), 3.65 (ddd, *J* = 9.9, 7.7, and 5.1 Hz, 1H, *H*COMe), 3.47 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 2.32 (ddd, *J* = 14.0, 5.2, and 3.0 Hz, 1H, CH_{a1}H$_{b1}$), 2.13-2.06 (m, 1H, CH_{a2}H$_{b2}$), 1.81 (ddd, *J* = 14.5, 7.0, and 4.9 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.69 (ddd, *J* = 14.0, 11.4, and 10.0 Hz, 1H, CH$_{a1}$$H_{b1}$), and 1.28 (s, 9H, COC=OCMe_3).

HR ESI-MS: Calcd for $C_{19}H_{32}O_{10}Na$ $(M+Na)^+$: 443.1888 Found: 443.1894.

TLC: R_f = 0.59; 1:2 hexanes:ethyl acetate.

(2*S*,3*R*)-Methyl 2-(2,2-Dimethylpropanoyloxy)-4-((2*R*,4*R*,5*S*)-5-hydroxy-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **291**



290 ***291***

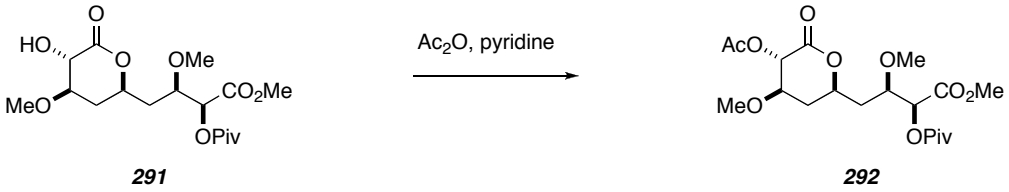
To a vial containing lactone **290** (3 mg, 0.007 mmol) in CH_2Cl_2 : DMS (2 : 1, 0.450 mL, 0.016M) at 0 ºC was added BF_3•OEt_2 (0.009 mL, 0.07 mmol). The reaction mixture was stirred at 0 ºC until TLC showed complete consumption of the starting material, approximately 10 minutes. To the solution at 0 ºC, was added saturated aqueos $NaHCO_3$ (10 mL) followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude alcohol **291** (~2 mg, 67%) that was used in the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.19 (d, *J* = 3.4 Hz, 1H, *H*COPiv), 4.39-4.33 (m, 1H, *H*COC=O), 4.10 (dd, *J* = 9.2 and 1.3 Hz, 1H, *H*COH), 4.02 (ddd, *J* = 6.8, 6.8, and 3.4 Hz, 1H, *H*COMe), 3.79 (s, 3H, CO_2*Me*), 3.61 (ddd, *J* = 11.1, 9.2, and 4.2 Hz, 1H, *H*COMe), 3.54 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.24 (d, *J* = 1.2 Hz, 1H, O*H*), 2.31 (ddd, *J* = 13.9, 4.2, and 3.1 Hz, 1H, C$H_{a1}$$H_{b1}$), 2.15-2.09 (m, 1H, C$H_{a2}$$H_{b2}$), 1.85 (ddd, *J* = 14.6, 6.9, and 5.1 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.75 (ddd, *J* = 13.9, 11.3, and 11.3 Hz, 1H, C$H_{a1}$$H_{b1}$), and 1.28 (s, 9H, COC=OCMe_3).

HR ESI-MS: Calcd for $C_{17}H_{28}O_9Na$ $(M+Na)^+$: 399.1626 Found: 399.1626.

TLC: R_f = 0.35; 1:2 hexanes:ethyl acetate.

(2*S*,3*R*)-Methyl 2-(2,2-Dimethylpropanoyloxy)-4-((2*R*,4*R*,5*S*)-5-(ethanoyloxy)-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **292**

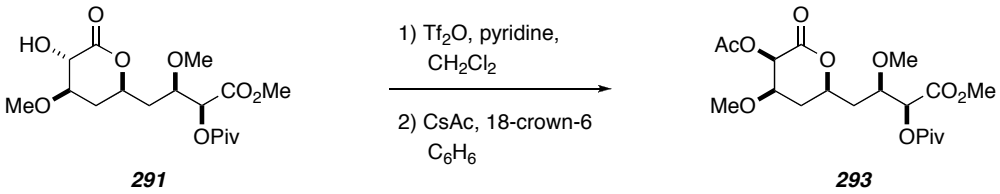


291 ***292***

To a vial containing crude alcohol **291** (2 mg, 0.005 mmol) in CH_2Cl_2 (0.300 mL, 0.017M) was added pyridine (0.018 mL, 0.224 mmol) and acetic anhydride (0.01 mL, 0.106 mmol) The reaction mixture was stirred at room temperature for 18 hours until TLC showed complete consumption of the starting material. To the solution at 0 ºC, was added saturated aqueos $NaHCO_3$ (10 mL) followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude lactone **292** (~1.5 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.18 (d, *J* = 3.4 Hz, 1H, *H*COPiv), 5.05 (d, *J* = 9.1 Hz, 1H, *H*COAc), 4.44-4.37 (m, 1H, *H*COC=O), 4.03 (ddd, *J* = 6.7, 6.7, and 3.4 Hz, 1H, *H*COMe), 3.81 (m, 1H, *H*COMe), 3.78 (s, 3H, CO_2Me), 3.43 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 2.36 (ddd, *J* = 13.6, 4.6, and 2.6 Hz, 1H, $CH_{a1}H_{b1}$), 2.20 (s, 3H, OC=O*Me*), 2.16-2.08 (m, 1H, $CH_{a2}H_{b2}$), 1.85 (ddd, *J* = 14.6, 6.7 and 5.1 Hz, 1H, $CH_{a2}H_{b2}$), 1.76 (ddd, *J* = 13.9, 11.5, and 11.5 Hz, 1H, $CH_{a1}H_{b1}$), and 1.28 (s, 9H, COC=OCMe_3).

(2*S*,3*R*)-Methyl 2-(2,2-Dimethylpropanoyloxy)-4-((2*R*,4*R*,5*R*)-5-(ethanoyloxy)-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **293**



291 ***293***

Triflate Formation

The same experimental procedure previously described to make the triflate of **260-*cis***, used in the production of **279-*cis***, was followed here as well. Lactone **291** (2 mg, 0.005 mmol), CH_2Cl_2 (0.600 mL, 0.008 M), pyridine (0.008 mL, 0.10 mmol), trifluoromethanesulfonic anhydride (0.018 mL, 0.10 mmol). The crude triflate of **291** was used in the next step without any further purification.

Characterization Data for Triflate

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 3.5 Hz, 1H, *H*COPiv), 5.01 (d, *J* = 9.9 Hz, 1H, *H*COTf), 4.47-4.39 (m, 1H, *H*COC=O), 4.00 (ddd, *J* = 6.6, 6.6, and 3.5 Hz, 1H, *H*COMe), 3.87-3.79 (m, 1H, *H*COMe), 3.79 (s, 3H, CO_2*Me*), 3.50 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 2.48 (ddd, *J* = 14.1, 4.4, and 2.8 Hz, 1H, CH_{a1}H$_{b1}$), 2.15-2.08 (m, 1H, CH_{a2}H$_{b2}$), 1.88 (ddd, *J* = 14.7, 6.4, and 5.2 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.84 (ddd, *J* = 14.1, 11.7, and 11.7 Hz, 1H, CH$_{a1}$$H_{b1}$), and 1.28 (s, 9H, COC=OCMe_3).

HR ESI-MS: Calcd for $C_{18}H_{27}F_3O_{11}SNa$ $(M+Na)^+$: 531.1118 Found: 531.1132.

TLC: R_f = 0.85; 1:2 hexanes:ethyl acetate.

Triflate Displacement

The same experimental procedure previously described to produce **279-*cis*** via displacement of a triflate by cesium acetate was used here in the production of **293**. Crude triflate (~2 mg, 0.005 mmol), benzene (0.300 mL, 0.017 M), 18-crown-6 (1 mg, 0.0025 mmol), cesium acetate (13 mg, 0.059 mmol). Purification via MPLC (1:2 hexanes / ethyl acetate) provided inverted lactone **293** (1 mg, 50% over 2-steps).

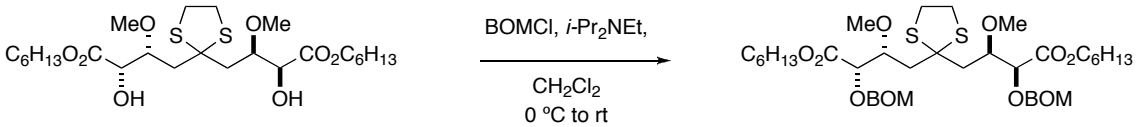
Characterization Data for Inverted 293

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.46 (d, *J* = 3.4 Hz, 1H, *H*COAc), 5.18 (d, *J* = 3.3 Hz, 1H, *H*COPiv), 4.53-4.45 (m, 1H, *H*COC=O), 4.01 (ddd, *J* = 6.9, 6.9, and 3.4 Hz, 1H, *H*COMe), 3.99 (ddd, *J* = 7.6, 3.5, and 2.0 Hz, 1H, *H*COMe), 3.78 (s, 3H, CO_2*Me*), 3.44 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 2.34 (ddd, *J* = 14.8, 7.6, and 5.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 2.25 (s, 3H, OC=O*Me*), 2.21-2.12 (m, 1H, C$H_{a2}$$H_{b2}$), 1.98 (ddd, *J* = 14.9, 10.9, and 2.1 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.79 (ddd, *J* = 14.5, 7.2, and 4.9 Hz, 1H, $CH_{a2}$$H_{b2}$), and 1.27 (s, 9H, COC=OCMe_3).

HR ESI-MS: Calcd for $C_{19}H_{30}O_{10}Na$ $(M+Na)^+$: 441.1731 Found: 441.1733.

TLC: R_f = 0.48; 1:2 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-(1,3-dithiolane)-(3,7-dimethoxy-2,8-bis(benzyloxymethoxy)nonanedioate **299**



231 ***299***

To a 50 mL round bottom flask containing alcohol **231** (1.0 g, 1.86 mmol) was added CH_2Cl_2 (6.2 mL, 0.3 M) and *i*Pr_2NEt (9.70 mL, 55.7 mmol). Upon cooling the solution to 0 ºC, BOMCl (5.16 mL, 37.1 mmol; commercially available 60% BOMCl solution) was added dropwise and the reaction was warmed to room temperature and stirred for 48 hours. The reaction mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (25 mL) was then added. The reaction was warmed to room temperature and stirred for 15 minutes followed by dilution with H_2O (15 mL). The aqueous layer was extracted with EtOAc (3 x 125 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided dithiane **299** (1.24 g, 86%).

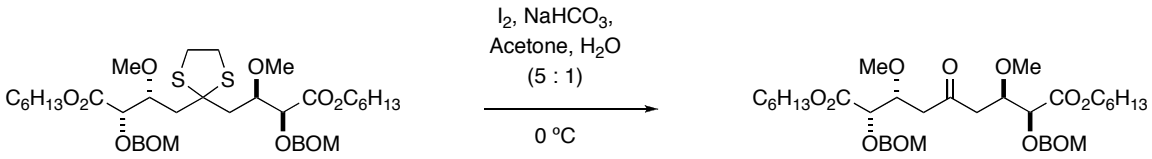
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37-7.30 (m, 10H, Ph*H*), 4.89 (d, *J* = 7.2 Hz, 2H, OC*H*$_a$H$_b$OBn), 4.86 (d, *J* = 7.4 Hz, 2H, OCH$_a$*H*$_b$OBn), 4.69 (m, 4H, PhC*H*$_2$), 4.53 (d, *J* = 3.5 Hz, 2H, *H*COBOM), 4.12 (t, *J* = 6.9 Hz, 4H, CO_2C*H*$_2$), 3.96 (ddd, *J* = 4.8, 4.8, and 4.8 Hz, 2H, *H*COMe), 3.37 (s, 6H, O*Me*), 3.27 (s, 4H, SC*H*$_2$C*H*$_2$S), 2.49 (dd, *J* = 15.5 and 4.5 Hz, 2H, C*H*$_a$H$_b$), 2.18 (dd, *J* = 15.5 and 5.4 Hz, 2H, CH$_a$*H*$_b$), 1.63 (p, *J* = 6.9 Hz, 4H, CO_2CH_2C*H*$_2$), 1.40-1.21 (m, 12H, Alk-*H*), and 0.88 (t, *J* = 6.6 Hz, 6H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 137.7, 128.6, 128.0, 127.9, 113.2, 95.0, 80.0, 78.0, 70.5, 68.6, 65.3, 57.9, 44.0, 40.0, 31.6, 28.7, 25.8, 22.7, and 14.2.

HR ESI-MS: Calcd for $C_{41}H_{62}O_{10}Na$ $(M+Na)^+$: 801.3677 Found: 801.3707.

TLC: R_f = 0.68; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 3,7-Dimethoxy-2,8-bis(benzyloxymethoxy)-5-oxononanedioate **300**



299 ***300***

To a 50 mL round bottom flask containing dithiane **299** (1.23 g, 1.58 mmol) was added a 5:1 mixture of acetone:water (13.2 mL total volume, 0.12M). $NaHCO_3$ powder (1.06 g, 12.6 mmol) was added and the heterogeneous solution was cooled to 0 ºC. Crystalline I_2 (1.36 g, 5.37 mmol) was added and the solution turned a deep purple/black color. The reaction was stirred at 0 ºC for 5 hours. At this time, additional portions of $NaHCO_3$ powder (0.53 g, 6.31 mmol) and I_2 (0.55 g, 2.17 mmol) were added to the solution. Stirring continued until TLC indicated that all starting material had been consumed. Saturated aqueous $NaHCO_3$ (20 mL) was then added followed by saturated aqueous Na_2SO_3 until the orange/yellow color disappeared. This was followed by dilution with water (50 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL) and the

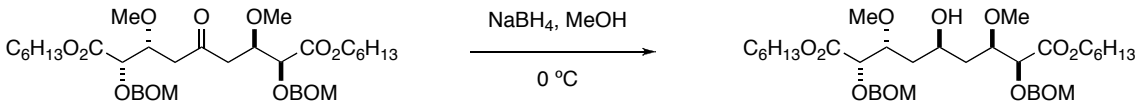
combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided ketone **300** (984 mg, 89%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.24 (m, 10H, Ph*H*), 4.82 (s, 4H, OCH_2OBn), 4.66 (d, *J* = 11.9 Hz, 2H, PhCH_aH$_b$), 4.62 (d, *J* = 11.9 Hz, 2H, PhCH$_a$$H_b$), 4.35 (d, *J* = 4.0 Hz, 2H, *H*COBOM), 4.20-4.07 (m, 6H, *H*COMe and CO_2CH_2), 3.33 (s, 6H, O*Me*), 2.82 (dd, *J* = 17.5 and 7.3 Hz, 2H, CH_aH$_b$), 2.75 (dd, *J* = 17.6 and 5.1 Hz, 2H, CH$_a$$H_b$), 1.62 (p, *J* = 6.8, 4H, CO_2CH_2CH_2), 1.38-1.22 (m, 12H, Alk-*H*), and 0.88 (t, *J* = 6.5 Hz, 6H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.4, 170.5, 137.6, 128.6, 127.99, 127.97, 113.0, 94.9, 77.0, 76.6, 70.5, 65.5, 58.8, 44.2, 31.5, 28.7, 25.7, 22.7, and 14.2.

TLC: R_f = 0.31; 3:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-Hydroxy-3,7-dimethoxy-2,8-bis(benzyloxymethoxy)nonanedioate **301**



300 ***301***

To a vial containing ketone **300** (43 mg, 0.061 mmol) was added MeOH (0.320 mL, 0.19 M), followed by cooling the reaction mixture to 0 ºC and addition of $NaBH_4$ (0.004 g, 0.089 mmol). The reaction was stirred at 0 ºC for 18 minutes, at which time TLC showed no remaining starting material. The reaction was quenched by the addition of a few drops of 0.1 M HCl until no gas evolution was seen, followed immediately by addition of saturated aqueous $NaHCO_3$. The resulting solution was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL), dried over Na_2SO_4, and

concentrated *in vacuo* to provide crude carbinol **301** (30 mg, 71%) that was used without any further purification.

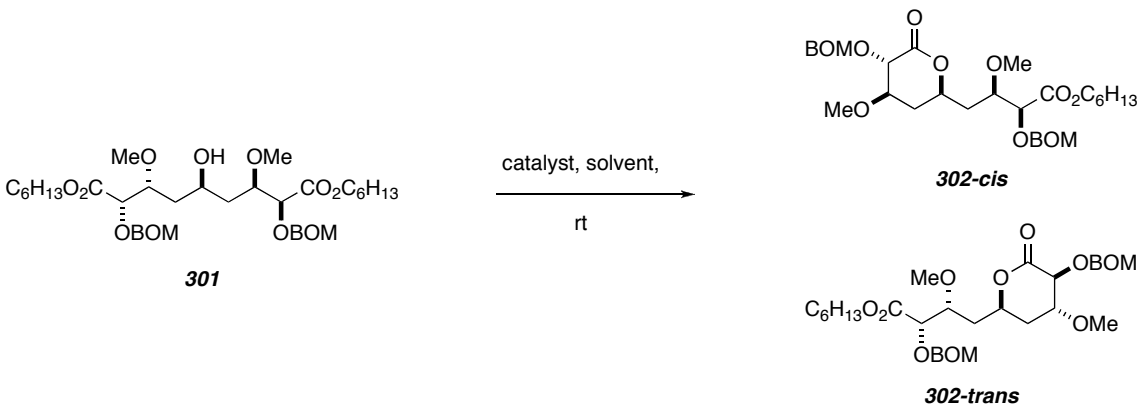
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37-7.23 (m, 10H, Ph*H*), 4.88-4.82 (m, 4H, OCH_2OBn), 4.69-4.60 (m, 4H, PhCH_2), 4.31 (d, *J* = 4.3 Hz, 1H, *H*COBOM), 4.30 (d, *J* = 3.9 Hz, 1H, *H*COBOM), 4.17-4.07 (m, 4H, CO_2CH_2), 4.04-3.96 (m, 1H, *H*COH), 3.93 (ddd, *J* = 9.2, 3.7, and 3.7 Hz, 1H, *H*COMe), 3.84-3.79 (m, 1H, *H*COMe), 3.46 (s, 3H, O*Me*), 3.45 (s, 3H, O*Me*), 3.21 (bs, 1H, O*H*), 1.79-1.57 (m, 4H, $CO_2CH_2CH_2$), 1.38-1.21 (m, 12H, Alk-*H*), and 0.88 (t, *J* = 6.6 Hz, 6H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 170.7, 137.7, 137.6, 128.7, 128.6, 128.04, 128.00, 127.9, 94.9, 81.9, 78.7, 77.7, 76.6, 70.6, 70.3, 67.5, 65.5, 65.4, 59.4, 58.6, 39.2, 38.1, 31.6, 31.5, 28.71, 28.66, 25.71, 25.68, 22.7, and 14.2.

HR ESI-MS: Calcd for $C_{39}H_{60}O_{11}Na$ $(M+Na)^+$: 727.4028 Found: 727.4067.

TLC: R_f = 0.57; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*)-hexyl 2-(benzyloxymethoxy)-4-((2*R*,4*R*,5*S*)-5-(benzyloxymethoxy)-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **302-*cis***



To a NMR tube containing carbinol **301** (15 mg, 0.021 mmol) was added C_6D_6 (0.700 mL, 0.03 M) and DBN (0.001 mL, 0.008 mmol). The reaction was monitored by

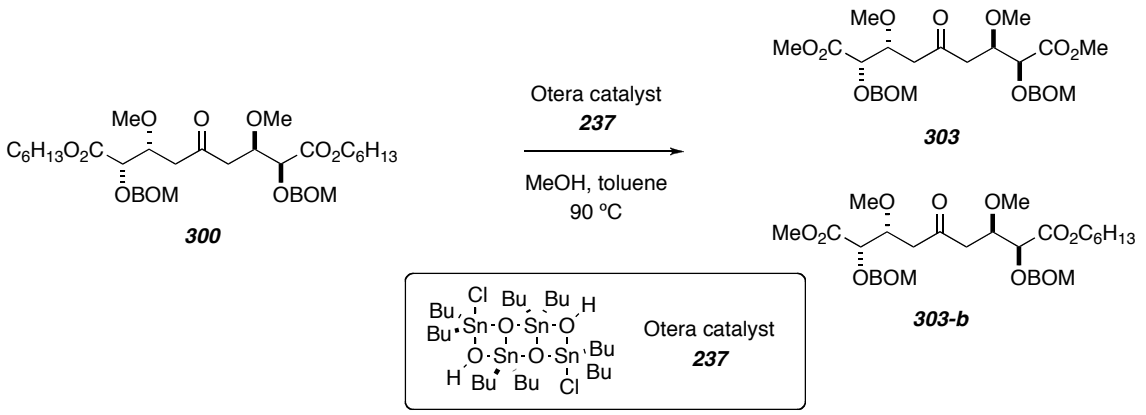
^{1}H NMR and stopped when the reaction appeared to quit at 80% conversion. At which time the reaction was diluted with CH_2Cl_2 and H_2O. The aqeous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (98:2 CH_2Cl_2 / MeOH) provided enough clean material for characterization of **302-*cis***.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41-7.27 (m, 10H, Ph*H*), 5.11 (d, *J* = 6.8 Hz, 1H, OC*H*$_{a1}$H$_{b1}$OBn), 4.93 (d, *J* = 6.8 Hz, 1H, OCH$_{a1}$*H*$_{b1}$OBn), 4.90 (d, *J* = 7.2 Hz, 1H, OC*H*$_{a2}$H$_{b2}$OBn), 4.86 (d, *J* = 7.2 Hz, 1H, OCH$_{a2}$*H*$_{b2}$OBn), 4.76 (d, *J* = 11.3 Hz, 1H, PhC*H*$_{a1}$H$_{b1}$), 4.68 (d, *J* = 12.0 Hz, 1H, PhC*H*$_{a2}$H$_{b2}$), 4.68 (d, *J* = 11.3 Hz, 1H, PhCH$_{a1}$*H*$_{b1}$), 4.63 (d, *J* = 12.0 Hz, 1H, PhCH$_{a2}$*H*$_{b2}$), 4.47-4.40 (m, 1H, *H*COC=O), 4.35 (d, *J* = 3.6 Hz, 1H, *H*COBOM), 4.20 (d, *J* = 8.2 Hz, 1H, *H*COBOM), 4.19-4.08 (m, 2H, CO_2CH_2), 3.91 (ddd, *J* = 6.8, 6.8, and 3.5 Hz, 1H, *H*COMe), 3.49 (ddd, *J* = 10.5, 8.4, and 5.0 Hz, 1H, *H*COMe), 3.37 (s, 3H, O*Me*), 3.36 (s, 3H, O*Me*), 2.25 (ddd, *J* = 13.9, 4.9, and 2.9 Hz, 1H, C*H*$_{a1}$H$_{b1}$), 2.07 (ddd, *J* = 14.3, 7.9, and 6.5 Hz, 1H, C*H*$_{a2}$H$_{b2}$), 1.99 (ddd, *J* = 14.5, 7.2, and 5.0 Hz, 1H, CH$_{a2}$*H*$_{b2}$), 1.70-1.60 (m, 3H, CH$_{a1}$*H*$_{b1}$ and $CO_2CH_2CH_2$), 1.43-1.22 (m, 6H, Alk-*H*), and 0.88 (t, *J* = 6.7 Hz, 3H, Alk-*Me*).

HR ESI-MS: Calcd for $C_{33}H_{46}O_{10}Na$ $(M+Na)^+$: 625.2983 Found: 625.3011.

TLC: R_f = 0.76; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dimethyl 3,7-Dimethoxy-2,8-bis(benzyloxymethoxy)-5-oxononanedioate **303**



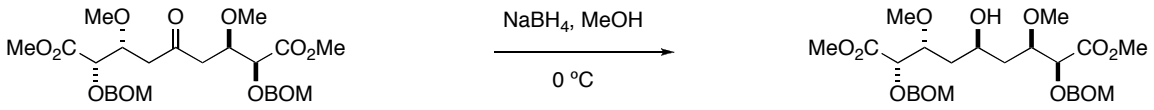
To a nitrogen-flushed culture tube containing hexyl ester ketone **300** (0.984 g, 1.40 mmol) was added toluene (4.7 mL, 0.3 M), MeOH (3.4 mL, 84.0 mmol; shaken with solid anhydrous K_2CO_3 immediately before use), and Otera catalyst **237** (0.748 g, 0.70 mmol). The septum on the culture tube was replaced by a screw cap with a Teflon liner and the mixture was stirred at 90 ºC for 3 days. The solution was transferred to a round bottom flask using $CHCl_3$ and concentrated *in vacuo*. Gradient flash chromatography (2:1 -> 1:1 -> 1:2 hexanes / ethyl acetate) provided methyl ester ketone **303**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 10H, Ph*H*), 4.82 (s, 4H, OCH_2OBn), 4.66 (d, *J* = 11.8 Hz, 2H, PhCH_aH$_b$), 4.60 (d, *J* = 11.9 Hz, 2H, PhCH$_a$$H_b$), 4.35 (d, *J* = 3.8 Hz, 2H, *H*COBOM), 4.19-4.12 (m, 2H, *H*COMe), 3.73 (s, 6H, CO_2*Me*), 3.34 (s, 6H, O*Me*), 2.80 (dd, *J* = 17.6 and 7.5 Hz, 2H, CH_aH$_b$), and 2.75 (dd, *J* = 17.2 and 5.0 Hz, 2H, CH$_a$$H_b$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 206.3, 171.0, 137.6, 128.7, 128.02, 127.97, 95.0, 77.0, 76.6, 70.5, 58.9, 52.2, and 44.2.

TLC: R_f = 0.27; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dimethyl 5-Hydroxy-3,7-dimethoxy-2,8-bis(benzyloxymethoxy)nonanedioate **297**



303 ***297***

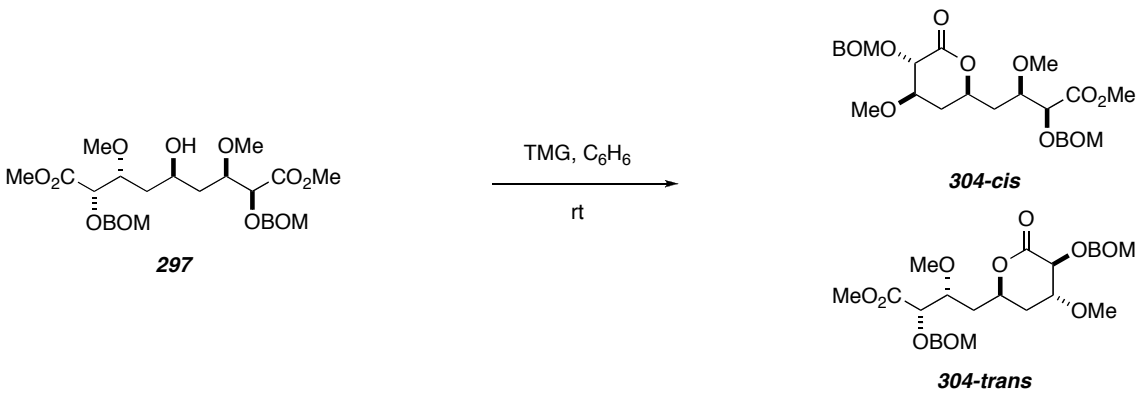
To a vial containing ketone **303** (58 mg, 0.103 mmol) was added MeOH (0.500 mL, 0.20 M), followed by cooling the reaction mixture to 0 ºC and addition of $NaBH_4$ (0.004 g, 0.089 mmol). The reaction was stirred at 0 ºC for 30 minutes, at which time TLC showed no remaining starting material. The reaction was quenched by the addition of a few drops of 0.1 M HCl until no gas evolution was seen, followed immediately by addition of saturated aqueous $NaHCO_3$. The resulting solution was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide crude carbinol **297** (35 mg, 60%) that was used without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38-7.25 (m, 10H, Ph*H*), 4.86 (s, 2H, OCH_2OBn), 4.84 (s, 2H, OCH_2OBn), 4.70-4.60 (m, 4H, PhCH_2), 4.32 (d, *J* = 4.3 Hz, 1H, *H*COBOM), 4.31 (d, *J* = 4.0 Hz, 1H, *H*COBOM), 4.03-3.96 (m, 1H, *H*COH), 3.92 (ddd, *J* = 8.9, 3.9, and 3.9 Hz, 1H, *H*COMe), 3.80 (ddd, *J* = 8.1, 4.6, and 4.6, 1H, *H*COMe), 3.72 (s, 6H, CO_2Me), 3.46 (s, 3H, O*Me*), 3.45 (s, 3H, O*Me*), 3.20 (bd, *J* = 1.8 Hz, 1H, O*H*), and 1.78-1.60 (m, 4H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 171.1, 137.7, 137.5, 128.7, 128.6, 128.05, 128.03, 127.99, 127.95, 95.0, 81.9, 78.7, 77.8, 76.8, 70.6, 70.4, 67.5, 59.4, 58.7, 52.3, 52.1, 39.1, and 38.0.

TLC: R_f = 0.47; 1:3 hexanes:ethyl acetate.

(2*S*,3*R*)-methyl 2-(benzyloxymethoxy)-4-((2*R*,4*R*,5*S*)-5-(benzyloxymethoxy)-4-methoxy-6-oxotetrahydro-2*H*-pyran-2-yl)-3-methoxybutanoate **304-*cis***



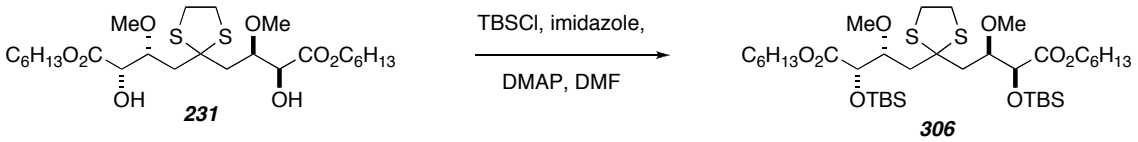
Benzene (4.13 mL, 0.015 M) was added to a culture tube containing alcohol **218** (35 mg, 0.062 mmol). 1,1,3,3-Tetramethylguanidine (0.016 mL, 0.124 mmol) was added dropwise and the reaction was stirred for 24 hours. Trifluoroacetic acid (0.005 mL, 0.002 mmol) was added and the reaction mixture was stirred for 3-5 minutes and partitioned into CH_2Cl_2 and saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo* to afford **304-*cis*** and **304-*trans*** (28 mg, 85%) as a colorless oil. (**304-*cis***:**304-*trans***; 10:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.22 (m, 10H, Ph*H*), 5.11 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OBn), 4.93 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}H_{b1}$OBn), 4.90 (d, *J* = 7.2 Hz, 1H, OC$H_{a2}$$H_{b2}$OBn), 4.86 (d, *J* = 7.2 Hz, 1H, OC$H_{a2}H_{b2}$OBn), 4.76 (d, *J* = 11.4 Hz, 1H, PhC$H_{a1}$$H_{b1}$), 4.68 (d, *J* = 12.2 Hz, 1H, PhC$H_{a2}$$H_{b2}$), 4.68 (d, *J* = 11.8 Hz, 1H, PhC$H_{a1}H_{b1}$), 4.63 (d, *J* = 12.1 Hz, 1H, PhC$H_{a2}H_{b2}$), 4.47-4.39 (m, 1H, *H*COC=O), 4.36 (d, *J* = 3.5 Hz, 1H, *H*COBOM), 4.21 (d, *J* = 8.2 Hz, 1H, *H*COBOM), 3.91 (ddd, *J* = 6.8, 6.8, and 3.5 Hz, 1H, *H*COMe), 3.75 (s, 3H, CO_2Me), 3.53-3.44 (m, 1H, *H*COMe), 3.373 (s, 3H, O*Me*), 3.365 (s, 3H, O*Me*), 2.25 (ddd, *J* = 14.0, 4.9, and 3.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 2.06 (ddd, *J* = 14.4, 7.9, and 6.4 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.98 (ddd, *J* = 14.5, 7.1, and 4.8 Hz, 1H, C$H_{a2}H_{b2}$), and 1.65 (ddd, *J* = 13.9, 10.8, and 10.8 Hz, 1H, C$H_{a1}H_{b1}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.3, 137.7, 137.6, 128.7, 128.6, 128.5, 128.4, 128.04, 127.98, 127.5, 113.0, 95.05, 94.95, 77.7, 77.4, 76.4, 75.4, 73.7, 70.5, 70.2, 67.7, 58.3, 57.5, 52.3, 36.0, and 34.3.

HR ESI-MS: Calcd for $C_{28}H_{36}O_{10}Na$ $(M+Na)^+$: 555.2201 Found: 555.2206.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 5-(1,3-dithiolane)-(3,7-dimethoxy-2,8-bis(*tert*-butyldimethylsilyloxy)nonanedioate **306**



To a culture tube containing crude diol **231** (50 mg, 0.93 mmol) was added DMF (0.500 mL, 0.19 M), imidazole (25 mg, 0.37 mmol), DMAP (1 mg, 0.009 mmol), and TBSCl (42 mg, 0.278 mmol). The reaction was stirred for 18 hours, at which time TLC showed no remaining diol **331**. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ was then added to the solution followed by dilution with H_2O and Et_2O. The reaction mixture was warmed to room temperature and stirred for 15-30 minutes. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Residual DMF was sometimes removed via a high vacuum rotovap. Purification via MPLC (2:1 hexanes / ethyl acetate) provided bis-TBS ether **306** (52 mg, 73%).

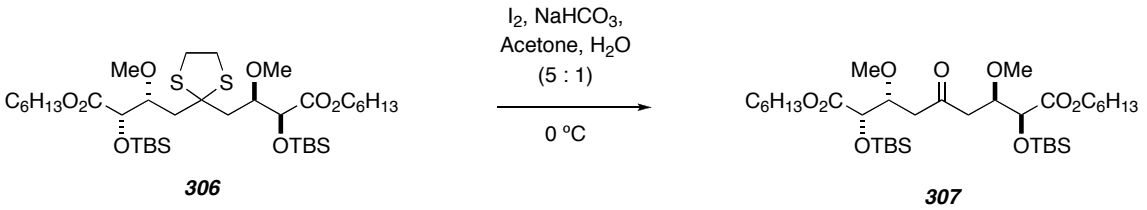
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.43 (d, *J* = 4.6 Hz, 2H, *H*COTBS), 4.12 (t, *J* = 6.8 Hz, 4H, CO_2CH_2), 3.78 (ddd, *J* = 7.1, 4.7, and 3.1 Hz, 2H, *H*COMe), 3.41 (s, 6H, O*Me*), 3.28 (s, 4H, SCH_2CH_2S), 2.44 (dd, *J* = 15.7 and 3.2 Hz, 2H, CH_aH_b), 2.03 (dd, *J* = 15.6 and 6.5 Hz, 2H, CH_aH_b), 1.65 (p, *J* = 7.0 Hz, 4H, $CO_2CH_2CH_2$), 1.42-1.24 (m, 12H, Alk-*H*), 0.92 (s, 18H, $SiCMe_3$), 0.89 (t, *J* = 6.9 Hz, 6H, Alk-*Me*), 0.10 (s, 6H, Si*Me*), and 0.09 (s, 6H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 113.3, 81.0, 74.2, 69.6, 65.1, 57.9, 43.4, 39.4, 31.6, 28.8, 26.0, 25.8, 22.8, and 18.5.

HR ESI-MS: Calcd for $C_{37}H_{74}O_8S_2Si_2Na$ $(M+Na)^+$: 789.4256 Found: 789.4255.

TLC: R_f = 0.48; 9:1 hexanes:ethyl acetate.

(2*S*,3*R*,7*R*,8*S*)-Dihexyl 3,7-Dimethoxy-2,8-bis(*tert*-butyldimethylsilyloxy)-5-oxononanedioate **307**



306 ***307***

To a vial containing dithiane **306** (10 mg, 0.13 mmol) was added a 5:1 mixture of acetone:water (0.110 mL total volume, 0.12M). $NaHCO_3$ powder (8 mg, 0.09 mmol) was added and the heterogeneous solution was cooled to 0 ºC. Crystalline I_2 (11 mg, 0.044 mmol) was added and the solution turned a deep purple/black color. The reaction was stirred at 0 ºC for 3 hours. At this time, additional portions of $NaHCO_3$ powder (8 mg, 0.09 mmol) and I_2 (11 mg, 0.044 mmol) were added to the solution. Stirring continued until TLC indicated that all starting material had been consumed. Saturated aqueous $NaHCO_3$ (5 mL) was then added followed by saturated aqueous Na_2SO_3 until the orange/yellow color disappeared. This was followed by dilution with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via MPLC (6:1 hexanes / ethyl acetate) provided ketone **307**.

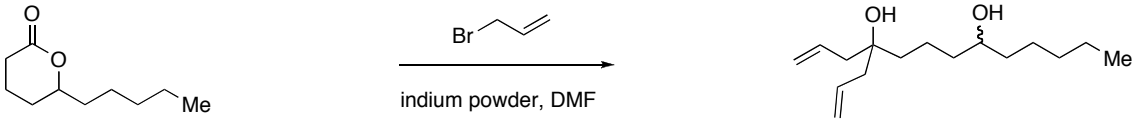
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.37 (d, *J* = 4.4 Hz, 2H, *H*COTBS), 4.14 (t, *J* = 6.8 Hz, 4H, CO_2CH_2), 4.04 (ddd, *J* = 7.3, 4.6, and 4.6 Hz, 2H, *H*COMe), 3.37 (s, 6H, O*Me*), 2.80 (dd, *J* = 17.6 and 4.9 Hz, 2H, CH_aH_b), 2.73 (dd, *J* = 17.5 and 7.4 Hz, 2H, CH_aH_b), 1.65 (p, *J* = 6.9 Hz, 4H, $CO_2CH_2CH_2$), 1.41-1.24 (m, 12H, Alk-*H*), 0.90 (s, 18H, SiCMe_3), 0.89 (t, *J* = 7.0 Hz, 6H, Alk-*Me*), 0.09 (s, 6H, Si*Me*), and 0.04 (s, 6H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.1, 113.3, 81.0, 74.2, 69.6, 65.1, 57.9, 43.4, 39.4, 31.6, 28.8, 26.0, 25.8, 22.8, and 18.5.

HR ESI-MS: Calcd for $C_{37}H_{74}O_8S_2Si_2Na$ $(M+Na)^+$: 789.4256 Found: 789.4255.

TLC: R_f = 0.48; 9:1 hexanes:ethyl acetate.

4-Allyltridec-1-ene-4,8-diol **315**



314 ***315***

To a culture tube containing δ-decanolactone **314** (0.031 mL, 0.179 mmol) was added DMF (1.2 mL, 0.15 M), allyl bromide (0.060 mL, 0.71 mmol), and indium powder (82 mg, 0.071 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction was transferred to a 50 mL Erlenmeyer flask using ethyl acetate, and saturated aqueous $NaHCO_3$ (20 mL) was slowly added to quench the reaction. The solution was diluted with H_2O, the aqueous layer was extracted with EtOAc (4 x 50 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (2:1 hexanes / ethyl acetate) provided diol **315** (14 mg, 31%) as a colorless oil.

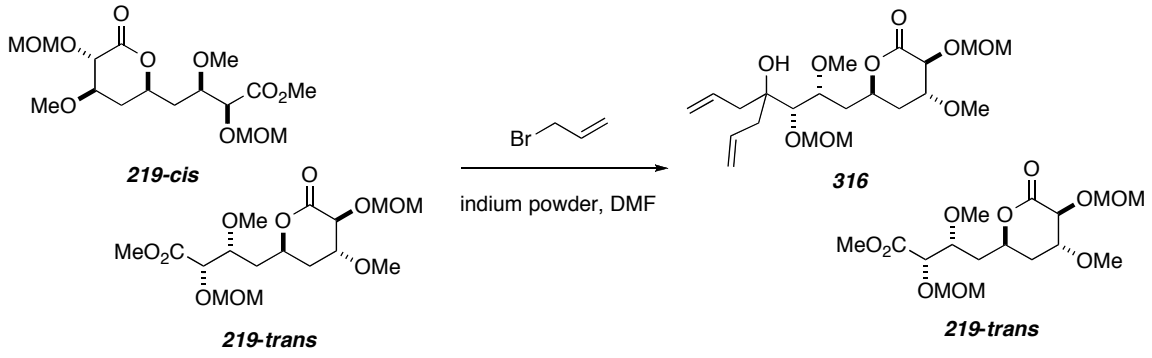
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.85 (dddd, *J* = 17.6, 10.3, 7.4, and 7.4 Hz, 2H, CH_2=C*H*), 5.18-5.09 (m, 4H, CH_2=CH), 4.28 (dddd, *J* = 10.5, 7.5, 5.0, and 2.8 Hz, 1H, *H*COH, 3.61 (bs, 1H, O*H*), 3.57 (bs, 1H, O*H*), 2.57 (ddd, *J* = 7.1, 5.0, and 1.3 Hz, 1H, CH_aH$_b$), 2.45 (ddd, *J* = 17.7, 8.8, and 7.1 Hz, 1H, CH$_a$$H_b$), 2.26 (dd, *J* = 13.8 and 7.3 Hz, 2H, CH_2=CHCH_aH$_b$), 2.22 (dd, *J* = 13.8 and 7.3 Hz, 2H, CH_2=CHCH$_a$$H_b$), 1.97-1.20 (m, 12H, Alk-*H*), and 0.89 (t, *J* = 6.8 Hz, 3H, Alk-*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 133.96, 133.93, 118.93, 118.91, 73.8, 72.0, 44.0, 43.9, 39.2, 37.9, 37.7, 32.1, 25.6, 22.9, 19.6, and 14.3.

HR ESI-MS: Calcd for $C_{16}H_{30}O_2Na$ $(M+Na)^+$: 277.2138 Found: 277.2169.

TLC: $\mathbf{R_f}$ = 0.52; 2:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*R*)-6-((2*R*,3*S*)-4-Allyl-4-hydroxy-2-methoxy-3-(methoxymethoxy)hept-6-enyl)-4-methoxy-3-(methoxymethoxy)tetrahydro-2*H*-pyran-2-one **316**



To a culture tube containing a 2:1 mixture of lactones **219-*cis*** and **219-*trans*** (68 mg, 0.179 mmol) was added DMF (1.2 mL, 0.15 M), allyl bromide (0.060 mL, 0.71 mmol), and indium powder (82 mg, 0.071 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was transferred to a 50 mL Erlenmeyer flask using ethyl acetate, and saturated aqueous $NaHCO_3$ (20 mL) was slowly added to quench the reaction. The solution was diluted with H_2O, the aqueous layer was extracted with EtOAc (4 x 50 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (1:1 hexanes / ethyl acetate) provided alcohol **316** (22 mg, 29%) and recovered starting material **219-*trans*** (17 mg, 22%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.99-5.86 (m, 2H, CH_2=C*H*), 5.18-5.08 (m, 4H, CH_2=CH), 4.94 (d, *J* = 6.8 Hz, 1H, $OCH_{a1}H_{b1}OMe$), 4.78 (d, *J* = 6.9 Hz, 1H, $OCH_{a2}H_{b2}OMe$), 4.77 (d, *J* = 6.9 Hz, 1H, $OCH_{a1}H_{b1}OMe$), 4.74 (d, *J* = 6.9 Hz, 1H, $OCH_{a2}H_{b2}OMe$), 4.72-4.63 (m, 1H, *H*COC=O), 4.36 (d, *J* = 6.3 Hz, 1H, *H*COMOM), 3.79 (ddd, *J* = 8.2, 4.7, and 3.3 Hz, 1H, *H*COMe), 3.65 (ddd, *J* = 6.4, 6.4, and 2.0 Hz, 1H, *H*COMe), 3.49 (d, *J* = 3.2 Hz, 1H, *H*COMOM), 3.463 (s, 6H, O*Me*), 3.457 (s, 3H, O*Me*),

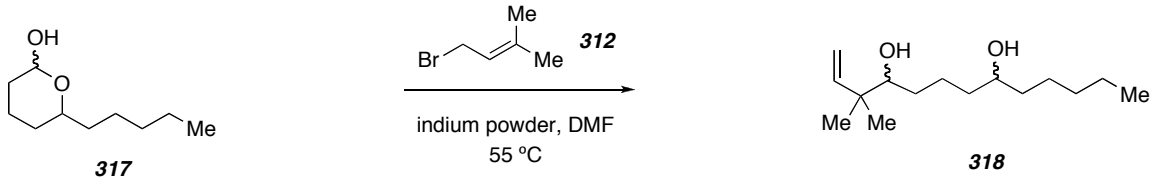
3.43 (s, 3H, O*Me*), 3.07 (s, 1H, O*H*), 2.52 (dd, *J* = 14.4 and 6.7 Hz, 1H, CH_2=CHC$H_{a1}H_{b1}$), 2.43 (dd, *J* = 14.3 and 7.1 Hz, 1H, CH_2=CHC$H_{a2}H_{b2}$), 2.36-2.29 (m, 2H, CH_2=CHC$H_{a1}H_{b1}$ and CH_2=CHC$H_{a2}H_{b2}$), 2.04 (ddd, *J* = 15.0, 2.4, and 2.4 Hz, 1H, C$H_{a1}H_{b1}$), and 2.00-1.89 (m, 3H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 134.1, 134.0, 118.62, 118.55, 99.4, 96.2, 83.6, 77.58, 77.52, 75.8, 74.0, 72.5, 59.1, 57.4, 56.8, 56.2, 41.6, 40.8, 38.3, and 34.9.

HR ESI-MS: Calcd for $C_{21}H_{36}O_9Na$ $(M+Na)^+$: 455.2252 Found: 455.2257.

TLC: R_f = 0.46; 1:2 hexanes:ethyl acetate.

3,3-Dimethyltridec-1-ene-4,8-diol **318**

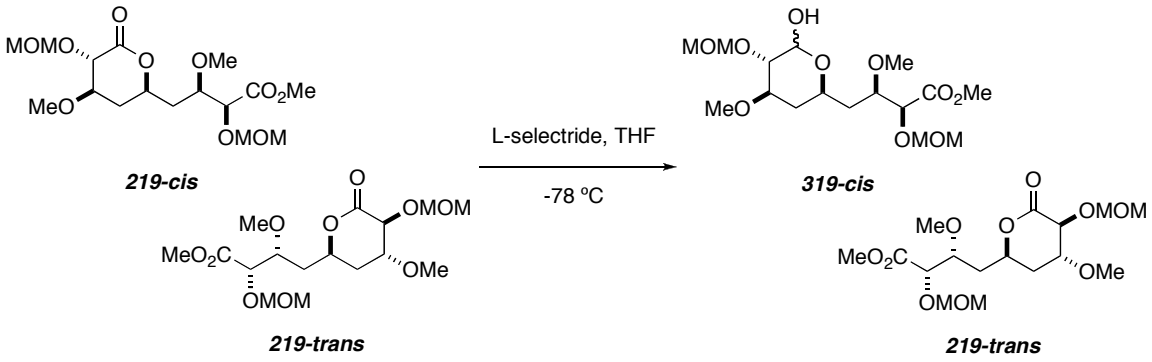


To a culture tube containing lactol **317** (10 mg, 0.058 mmol) was added DMF (0.300 mL, 0.19 M), 1-bromo-3-methyl-2-butene **312** (0.021 mL, 0.182 mmol), and indium powder (17 mg, 0.148 mmol). The reaction mixture was stirred at room temperature for 72 hours. The reaction mixture was transferred to a 50 mL Erlenmeyer flask using ethyl acetate, and saturated aqueous $NaHCO_3$ (20 mL) was slowly added to quench the reaction. The solution was diluted with H_2O, the aqueous layer was extracted with EtOAc (4 x 50 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (2:1 hexanes / ethyl acetate) provided diol **318** (5 mg, 33%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.81 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.09 (d, *J* = 10.7 Hz, 1H, CH_aH_b=CH), 5.05 (d, *J* = 17.6 Hz, 1H, CH_aH_b=CH), 3.65-3.56 (m, 1H, *H*COH), 3.25 (d, *J* = 10.4 Hz, *H*COH), 1.77-1.19 (m, 14H, Alk-*H*), 1.00 (s, 6H, CMe_2), and 0.89 (t, *J* = 6.7 Hz, 3H, Alk-*Me*).

TLC: R_f = 0.30; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*)-Methyl 4-((2*R*,4*R*,5*S*)-6-Hydroxy-4-methoxy-5-(methoxymethoxy)tetrahydro-2*H*-pyran-2-yl)-3-methoxy-2-(methoxymethoxy)butanoate **319-*cis***



To a 100 mL round bottom flask containing the mixture of lactones **219-*cis*** and **219-*trans*** (0.845 g, 2.22 mmol) was added THF (22.3 mL, 0.1M). This solution was cooled to -78 ºC, L-selectride (2.44 mL, 2.44 mmol, 1.0M in THF) was added dropwise, and the reaction mixture was stirred for 1 hour at -78 ºC. Saturated aqueous $NaHCO_3$ (30 mL) was added at -78 ºC and the resulting mixture was warmed to room temperature. H_2O (15 mL) was added and the mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude mixture that was purified via MPLC (100% ethyl acetate) to provide **219-*trans*** and a ~2:1 mixture of **319-*cis*,** major (*ax*-C2-OH) and minor (*eq*-C2-OH) anomers (722 mg, 87%) as a colorless oil.

Characterization Data for Mixture of 319-*maj* and 319-*min* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.34 (dd, *J* = 3.2 and 3.2 Hz 1H, *H*$COH_{(maj)}$), 4.87, (d, *J* = 6.2 Hz, 1H, OC*H*HOMe), 4.85 (d, 6.4 Hz, 1H, OC*H*HOMe), 4.80 (d, *J* = 6.4 Hz, 1H, OC*H*HOMe), 4.76 (d, *J* = 7.1 Hz, 1H, OC*H*HOMe), 4.76 (d, *J* = 6.6 Hz, 1H, OC*H*HOMe), 4.75 (d, *J* = 7.2 Hz, 1H, OC*H*HOMe), 4.72 (d, *J* = 7.0 Hz, 1H, OC*H*HOMe), 4.72 (d, *J* = 7.1 Hz, 1H, OC*H*HOMe), 4.54 (dd, *J* = 7.6 and 4.3 Hz, 1H,

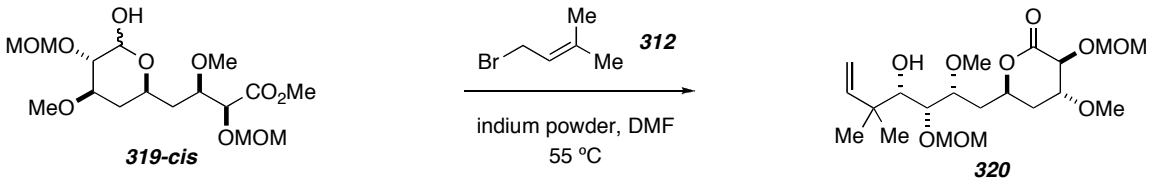
*H*COH$_{(min)}$), 4.28 (d, *J* = 3.4 Hz, 1H, *H*COMOM$_{(maj)}$), 4.26 (d, *J* = 3.4 Hz, 1H, *H*COMOM$_{(min)}$), 4.16-4.09 (m, 1H, *H*COCOH$_{(maj)}$), 3.90 (ddd, *J* = 7.4, 6.2, and 3.5 Hz, 1H, *H*COMe$_{(min)}$), 3.85 (ddd, *J* = 7.5, 5.8, and 3.3 Hz, 1H, *H*COMe$_{(maj)}$), 3.782 (s, 3H, CO_2*Me*$_{(maj)}$), 3.780 (s, 3H, CO_2*Me*$_{(min)}$), 3.63 (ddd, *J* = 11.3, 9.6, and 5.0 Hz, 1H, *H*COMe$_{(maj)}$), 3.61-3.53 (m, 1H, *H*COCOH$_{(min)}$), 3.52 (dd, *J* = 9.3, and 3.6 Hz, 1H, *H*COMOM$_{(maj)}$), 3.47 (s 3H, O*Me*), 3.43 (s 3H, O*Me*), 3.42 (s 3H, O*Me*), 3.41 (s 3H, O*Me*), 3.37 (s 3H, O*Me*), 3.36 (s 3H, O*Me*), 3.35-3.28 (m, 1H, *H*COMe$_{(min)}$), 3.19 (dd, *J* = dd, *J* = 9.0 and 7.6 Hz, 1H, *H*COMOM$_{(min)}$), 2.16-2.08 (m, 1H, C*H*$_{a1}$H$_{b1(maj)}$), 2.14-2.07 (m, 1H, C*H*$_{a1}$H$_{b1(min)}$), 2.07-1.97 (m, 1H, C*H*$_{a2}$H$_{b2(min)}$), 1.94-1.80 (m, 2H, C*H*$_{a2}$*H*$_{b2(maj)}$), 1.90-1.81 (m, 1H, CH$_{a2}$*H*$_{b2(min)}$), and 1.44-1.31 (m, 1H, CH$_{a1}$*H*$_{b1(min)}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 171.4, 98.1, 97.3, 96.81, 96.77, 96.73, 92.7, 82.9, 79.6, 79.1, 78.4, 78.1, 76.54, 76.49, 76.0, 68.5, 64.1, 58.11, 58.07, 57.4, 56.51, 56.48, 55.9, 55.7, 52.2, 36.6, 36.1, 35.1, and 34.9.

HR ESI-MS: Calcd for $C_{16}H_{30}O_{10}Na$ $(M+Na)^+$: 405.1731 Found: 405.1751.

TLC: R_f = 0.29; 1:3 hexanes:ethyl acetate.

(3*S*,4*R*,6*R*)-6-((2*R*,3*R*,4*S*)-4-Hydroxy-2-methoxy-3-(methoxymethoxy)-5,5-dimethylhept-6-enyl)-4-methoxy-3-(methoxymethoxy)tetrahydro-2*H*-pyran-2-one **320**



To a large culture tube containing lactol **319-*cis*** (1.46 g, 3.81 mmol) was added DMF (19.0 mL, 0.2 M), 1-bromo-3-methyl-2-butene **312** (1.76 mL, 15.2 mmol), and indium powder (1.75g, 15.2 mmol). The reaction mixture was stirred at 55 ºC for 18 hours. The reaction was cooled to room temperature, transferred to a 250 mL Erlenmeyer flask using ethyl acetate, and saturated aqueous $NaHCO_3$ (100 mL) was slowly added to quench the reaction. The solution was diluted with H_2O, the aqueous layer extracted with

EtOAc (4 x 200 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide **320** (1.28 g, 80%) as a colorless oil. The crude product **320** was consistently used in the next reaction without purification.

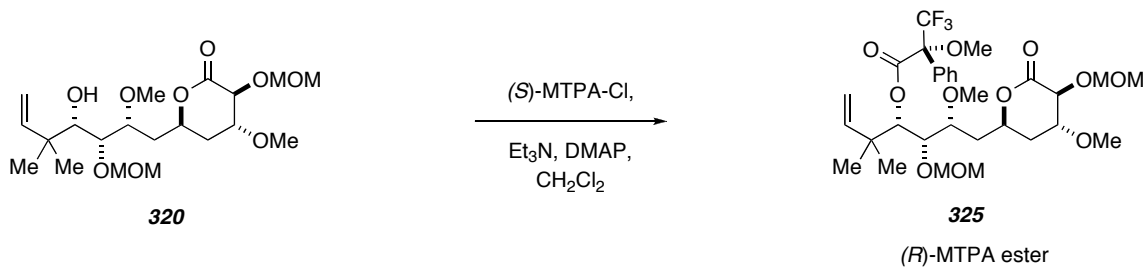
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83 (dd, *J* = 17.4 and 10.9 Hz, 1H, CH_2=C*H*), 5.06 (d, *J* = 10.7 Hz, 1H, C$H_a$$H_b$=CH), 5.04 (d, *J* = 17.7 Hz, 1H, $CH_a$$H_b$=CH), 4.94 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.77 (d, *J* = 6.8 Hz, 1H, $OCH_{a1}$$H_{b1}$OMe), 4.73 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.72-4.63 (m, 1H, *H*COC=O), 4.65 (d, *J* = 6.8 Hz, 1H, $OCH_{a2}$$H_{b2}$OMe), 4.37 (d, *J* = 6.5 Hz, 1H, *H*COMOM), 3.76 (d, *J* = 4.3 Hz, 1H, *H*COMOM), 3.66 (ddd, *J* = 11.3, 4.3, and 1.8 Hz, 1H, *H*COMe), 3.63 (ddd, *J* = 6.5, 6.5, and 2.1 Hz, 1H, *H*COMe), 3.46 (s, 3H, O*Me*), 3.43 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.38 (s, 3H, O*Me*), 2.61 (d, *J* = 9.9 Hz, 1H, O*H*), 2.02 (ddd, *J* = 15.1, 2.4, and 2.4 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.94 (ddd, *J* = 15.0, 10.3, and 1.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.92 (ddd, *J* = 15.1, 11.2, and 6.5 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.74 (ddd, *J* = 14.9, 11.3, and 2.1 Hz, 1H, $CH_{a1}$$H_{b1}$), and 1.03 (s, 6H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 144.9, 112.9, 97.9, 96.2, 77.7, 77.3, 74.1 73.7, 73.2, 72.3, 58.4, 57.3, 56.9, 56.2, 42.1, 35.8, 34.9, 24.5, and 21.9.

HR ESI-MS: Calcd for $C_{20}H_{36}O_9Na$ $(M+Na)^+$: 443.2252 Found: 443.2259.

TLC: R_f = 0.67; 1:3 hexanes:ethyl acetate.

(*R*)-((4*S*,5*S*,6*R*)-6-Methoxy-7-((2*R*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)-5-(methoxymethoxy)-3,3-dimethylhept-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **325**



320

325

(R)-MTPA ester

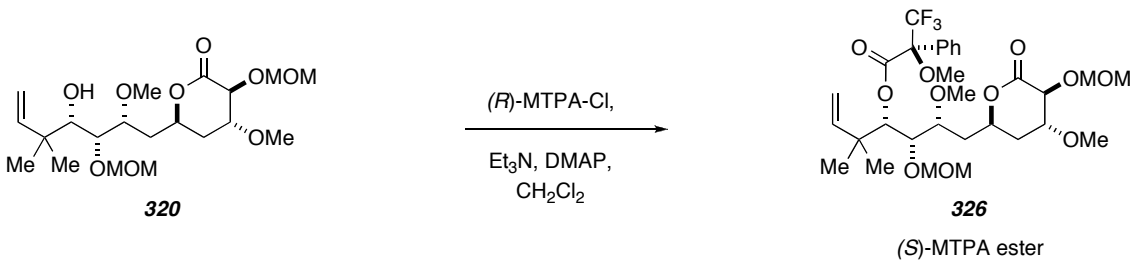
To a conical vial containing alcohol **320** (7 mg, 0.017 mmol) was added CH_2Cl_2 (0.200 mL, 0.09 M), Et_3N (0.021 mL, 0.203 mmol), and DMAP (2 mg, 0.016 mmol). Crude (*S*)-MTPA-Cl[83] (0.094 mmol) was added to the reaction mixture by rinsing with CH_2Cl_2 (0.200 mL). The reaction was stirred at room temperature for 24 hours. The reaction mixture was diluted with CH_2Cl_2 and quenched by slow addition of saturated aqueous $NaHCO_3$. The solution was diluted with H_2O and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (1:1 hexanes / ethyl acetate) provided (*R*)-MTPA-ester **325**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67-7.61 (m, 2H, Ph*H*), 7.46-7.38 (m, 3H, Ph*H*), 5.84 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.15 (d, *J* = 2.6 Hz, 1H, *H*CO-(*R*)-MTPA), 5.07 (dd, 10.8 and 1.0 Hz, 1H, C$H_a$$H_b$=CH), 5.05 (dd, *J* = 17.5 and 1.1 Hz, 1H, CH$_a$$H_b$=CH), 4.93 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.76 (d, *J* = 6.8 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.63 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.66-4.59 (m, 1H, *H*COC=O), 4.48 (d, *J* = 6.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.35 (d, *J* = 6.5 Hz, 1H, *H*COMOM), 3.82 (dd, *J* = 4.7 and 2.6 Hz, 1H, *H*COMOM), 3.63-3.55 (m, 2H, *H*COMe), 3.54 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.38 (s, 3H, O*Me*), 3.34 (s, 3H, O*Me*), 1,93 (ddd, *J* = 15.1, 2.2, and 2.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.77 (ddd, *J* = 15.1, 11.4, and 6.6 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.74 (ddd, *J* = 14.5, 10.2, and 1.9 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.52 (ddd, *J* = 14.5, 10.2, and 1.9 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.02 (s, 3H, C*Me*), and 1.01 (s, 3H, C*Me*).

HR ESI-MS: Calcd for $C_{30}H_{43}F_3O_{11}Na$ $(M+Na)^+$: 659.2650 Found: 659.2646.

TLC: R_f = 0.50; 1:1 hexanes:ethyl acetate.

(*S*)-((4*S*,5*S*,6*R*)-6-Methoxy-7-((2*R*,4*R*,5*S*)-4-methoxy-5-(methoxymethoxy)-6-oxotetrahydro-2*H*-pyran-2-yl)-5-(methoxymethoxy)-3,3-dimethylhept-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate **326**



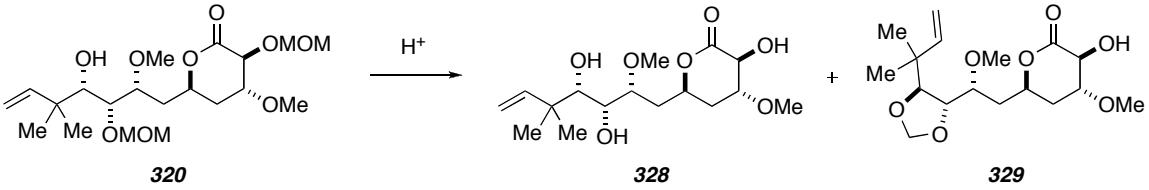
To a conical vial containing alcohol **320** (5 mg, 0.013 mmol) was added CH_2Cl_2 (0.100 mL, 0.13 M), Et_3N (0.012 mL, 0.117 mmol), and DMAP (1 mg, 0.0082 mmol). Crude (*R*)-MTPA-Cl[83] (0.047 mmol) was added to the reaction mixture by rinsing with CH_2Cl_2 (0.200 mL). The reaction was stirred at room temperature for 48 hours. The reaction mixture was diluted with CH_2Cl_2 and quenched by slow addition of saturated aqueous $NaHCO_3$. The solution was diluted with H_2O and the aqueous layer extracted with CH_2Cl_2 (3 x 25 mL), the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (1:1 hexanes / ethyl acetate) provided (*S*)-MTPA-ester **326** and recovered starting material **320**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.79-7.71 (m, 2H, Ph*H*), 7.43-7.36 (m, 3H, Ph*H*), 5.84 (dd, *J* = 17.9 and 10.4 Hz, 1H, CH_2=C*H*), 5.21 (d, *J* = 1.9 Hz, 1H, *H*CO-(*S*)-MTPA), 5.07 (dd, 11.7 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 5.06 (dd, *J* = 16.5 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 4.92 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.76 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.72 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.59 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.64-4.55 (m, 1H, *H*COC=O), 4.32 (d, *J* = 6.5 Hz, 1H, *H*COMOM), 3.90 (dd, *J* = 4.5 and 1.9 Hz, 1H, *H*COMOM), 3.65 (s, 3H, O*Me*), 3.59 (ddd, *J* = 11.3, 4.7, and 1.8 Hz, 1H, *H*COMe), 3.54 (ddd, *J* = 6.6, 6.6, and 1.8 Hz, 1H, *H*COMe), 3.45 (s, 3H, O*Me*), 3.41 (s, 3H, O*Me*), 3.38 (s, 3H, O*Me*), 3.36 (m, 3H, O*Me*), 1.81 (ddd, *J* = 14.6, 10.5, and 1.8 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.67 (ddd, *J* = 14.6, 10.5, and 1.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.59 (ddd, *J* = 15.2, 11.3, and 6.7 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.44 (ddd, *J* = 13.7, 11.3, and 2.2 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.03 (s, 3H, C*Me*), and 1.02 (s, 3H, C*Me*).

HR ESI-MS: Calcd for $C_{30}H_{43}F_3O_{11}Na$ $(M+Na)^+$: 659.2650 Found: 659.2681.

TLC: R_f = 0.63; 1:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-3-Hydroxy-4-methoxy-6-((*R*)-2-methoxy-2-((4*S*,5*S*)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)ethyl)tetrahydro-2*H*-pyran-2-one **329**



320 ***328*** ***329***

A couple of standard acid mediated conditions for deprotection of MOM-ethers were tried (TFA, CH_2Cl_2 and HCl,THF:H_2O) and resulted in varying ratios of products **328** and **329**. Elimination of the undesired product **329** could not be achieved under the reaction conditions tried.

Characterization Data for 328

(reported later in experimental section)

Characterization Data for 329

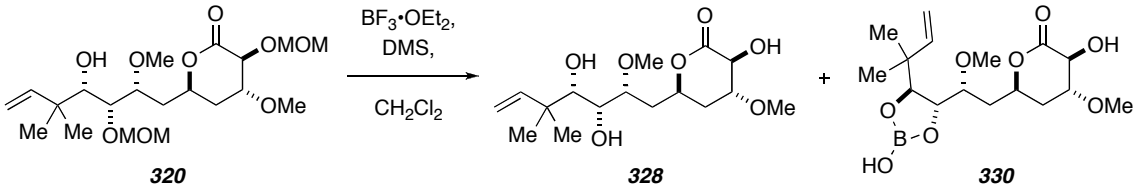
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (dd, *J* = 17.5 and 10.9 Hz, 1H, CH_2=C*H*), 5.09 (dd, 10.8 and 1.1 Hz, 1H, C$H_a$$H_b$=CH), 5.07 (dd, *J* = 17.5 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 5.05 (d, *J* = 0.8 Hz, 1H, OC$H_a$$H_b$O), 5.01 (d, *J* = 0.9 Hz, 1H, OC$H_a$$H_b$O), 4.77 (dddd, *J* = 10.1, 10.1, 2.9, and 2.9 Hz, 1H, *H*COC=O, 4.36 (dd, *J* = 6.0 and 2.7 Hz, 1H, *H*COH), 3.82 (dd, *J* = 4.8 and 3.7 Hz, 1H, *H*COCH_2O), 3.78 (d, *J* = 4.8 Hz, 1H, *H*COCH_2O), 3.59 (ddd, *J* = 6.5, 6.5, and 2.2 Hz, 1H, *H*COMe), 3.51 (ddd, *J* = 10.2, 3.0, and 3.0 Hz, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.47 (s, 3H, O*Me*), 3.34 (d, *J* = 2.7 Hz, 1H, O*H*), 2.05-1.93 (m, 2H, C$H_{a1}$$H_{b1}$), 1.86 (ddd, *J* = 14.6, 10.2, and 2.7 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.76 (ddd, *J* = 14.7, 10.0, and 3.0 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.08 (s, 3H, C*Me*), and 1.06 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 143.7, 113.7, 95.5, 83.8, 79.0, 78.8, 77.6, 72.9, 72.6, 60.5, 57.5, 40.3, 37.7, 36.0, 24.0, and 22.7.

HR ESI-MS: Calcd for $C_{17}H_{28}O_7Na$ $(M+Na)^+$: 367.1727 Found: 367.1713.

TLC: R_f = 0.63; 1:3 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-3-Hydroxy-6-((*R*)-2-((4*R*,5*S*)-2-hydroxy-5-(2-methylbut-3-en-2-yl)-1,3,2-dioxaborolan-4-yl)-2-methoxyethyl)-4-methoxytetrahydro-2*H*-pyran-2-one **330**



To a vial containing alcohol **320** (6 mg, 0.014 mmol) in CH_2Cl_2 : DMS (2:1, 0.420 mL, 0.033M) at 0 ºC was added BF_3•OEt_2 (0.011 mL, 0.085 mmol). The reaction mixture was stirred at 0 ºC until TLC showed complete consumption of the starting material. To the solution at 0 ºC, was added saturated aqueos $NaHCO_3$ (5 mL) followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture of **328** and **330** in a ~1:2 ratio. Purification via MPLC (95:5 CH_2Cl_2 / MeOH) provided **328** and **330**.

Characterization Data for 328

(reported later in experimental section)

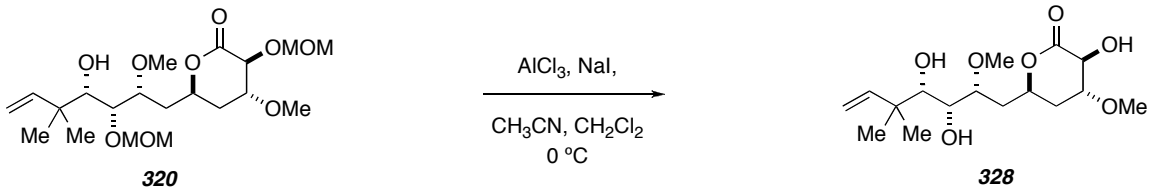
Characterization Data for 330

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (dd, *J* = 17.5 and 10.9 Hz, 1H, CH_2=C*H*), 5.13 (dd, *J* = 10.8 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 5.10 (dd, *J* = 17.5 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 4.76 (dddd, *J* = 10.2, 10.2, 2.3, and 2.3 Hz, 1H, *H*COC=O), 4.35 (dd, *J* = 6.0 and 2.0 Hz, 1H, *H*COH), 4.09 (dd, *J* = 3.7 and 3.7 Hz, 1H, *H*COBOH), 3.94 (d, *J* = 4.1 Hz, 1H, *H*COBOH), 3.59 (ddd, *J* = 6.5, 6.5, and 2.3 Hz, *H*COMe, 3.49-3.42 (m, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.33 (d, *J* = 2.7 Hz, 1H, O*H*), 2.09-1.92 (m, 2H, C$H_{a1}$$H_{b1}$), 1.82 (ddd, *J* = 14.6, 9.7, and 3.1 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.76 (ddd, *J* = 14.5, 9.3, and 3.3 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.04 (s, 3H, O*Me*), and 1.03 (s, 3H, O*Me*).

LR ESI-MS: Calcd for $C_{16}H_{27}BO_8Na$ $(M-H+Me+Na)^+$: 395.1853 Found: 395.1826.

TLC: R_f = 0.40; 95:5 dichloromethane:methanol.

(3*S*,4*R*,6*R*)-6-((2*R*,3*R*,4*S*)-3,4-Dihydroxy-2-methoxy-5,5-dimethylhept-6-enyl)-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **328**



320 ***328***

To a 500 mL round bottom flask was added $AlCl_3$ (3.56 g, 26.7 mmol) and acetonitrile (84.8 mL, 0.021 M). The solution was cooled to 0 ºC, followed by the addition of NaI (4.00 g, 26.7 mmol). After 5 minutes, lactone **320** (677 mg, 1.78 mmol) was added as a solution in CH_2Cl_2 (30 mL). The reaction was stirred for 8 minutes at 0 ºC. Saturated aqueous $NaHCO_3$ (100 mL) was added to the reaction, followed by saturated aqueous Na_2SO_3 until all yellow color disappeared. The solution was diluted with H_2O and the aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide triol **328** (546 mg, 92%) as a colorless oil. The crude triol **328** was consistently used in the next reaction without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.88 (dd, *J* = 17.4 and 10.9 Hz, 1H, CH_2=C*H*), 5.11 (dd, *J* = 10.9 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 5.09 (dd, *J* = 17.4 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.80-4.69 (m, 1H, *H*COC=O), 4.35 (dd, *J* = 6.0 and 2.7 Hz, 1H, H_{lact}COH), 3.72 (dd, *J* = 6.6 and 4.7 Hz, 1H, H_{acyc}COH), 3.58 (ddd, *J* = 8.9, 6.3, and 2.3 Hz, 1H, *H*COMe), 3.51 (ddd, *J* = 9.7, 4.5, and 2.9 Hz, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.45 (s, 3H, O*Me*), 3.38-3.33 (m, 2H, *H*COH, O*H*), 2.03-1.94 (m, *2*H, C$H_{a1}$$H_{b1}$), 1.88 (ddd, *J* = 14.7, 9.3, and 3.1 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.77 (ddd, *J* = 14.8, 9.6, and 3.4 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.08 (s, 3H, C*Me*), and 1.07 (s, 3H, C*Me*).

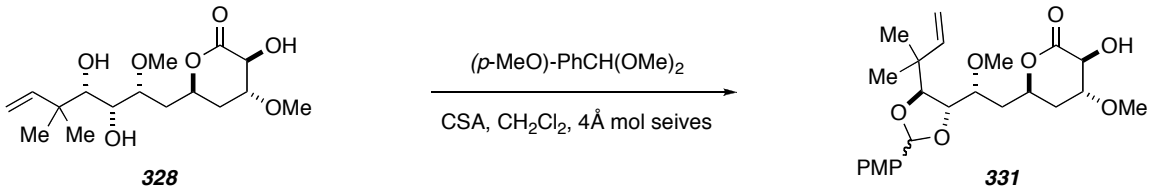
^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 145.2, 113.7, 80.1, 78.8, 76.0, 73.0, 72.6, 69.1,

59.5, 57.5, 41.7, 36.8, 36.1, 23.8, and 22.7.

HR ESI-MS: Calcd for $C_{16}H_{28}O_7Na$ $(M+Na)^+$: 355.1727 Found: 355.1698.

TLC: $\mathbf{R_f}$ = 0.36; 1:3 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-3-Hydroxy-4-methoxy-6-((2*R*)-2-methoxy-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)ethyl)tetrahydro-2*H*-pyran-2-one **331**



To a 100 mL round bottom flask containing triol **328** (520 mg, 1.56 mmol) was added CH_2Cl_2 (31.2 mL, 0.05 M) and 4 Å molecular sieves (100 mg). After 10 minutes *p*-anisaldehyde dimethylacetal (0.43 mL, 2.5 mmol) was added to the flask. The reaction was treated with CSA (22 mg, 0.078 mmol) and stirred at room temperature for 9 minutes, at which time TLC showed no signs of the starting triol **328**. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (30 mL). Dilution with EtOAc and H_2O followed by decanting away a majority of the molecular sieves allowed for extraction of the aqueous layer with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to afford a crude mixture that was purified via MPLC (1:1 hexanes / ethyl acetate) to provide alcohol **331** (609 mg, 87%).

Characterization Data for Mixture of 331 (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 7.41 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.90 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.89 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.95 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.92 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.92 (s, 1H, MeOPhC*H*), 5.85 (s, 1H, MeOPhC*H*), 5.15 (dd, *J* = 10.2 and 1.3 Hz, 1H, C$H_{a1}H_{b1}$=CH), 5.13 (dd, *J* = 10.2 and 1.2 Hz, 1H, C$H_{a2}H_{b2}$=CH), 5.11 (dd, *J* = 17.5 and 1.3 Hz, 1H, $CH_{a1}H_{b1}$=CH), 5.11 (dd, *J* = 17.5 and 1.3 Hz, 1H,

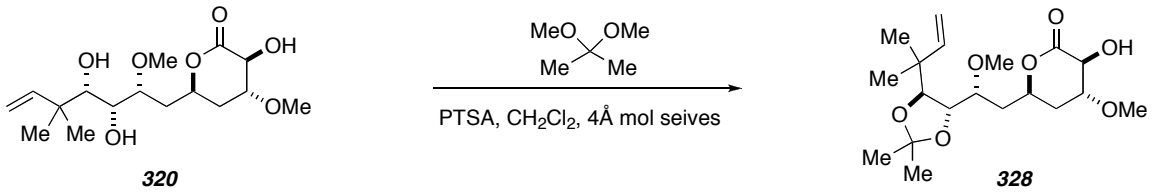
$CH_{a2}H_{b2}$=CH), 4.83-4.73 (m, 1H, *H*COC=O), 4.83-4.73 (m, 1H, *H*COC=O), 4.36 (dd, *J* = 6.0 and 2.8 Hz, 1H, *H*CO(CH)PMP), 4.33 (dd, *J* = 6.0 and 2.7 Hz, 1H, *H*CO(CH)PMP), 4.06 (dd, *J* = 5.8 and 3.3 Hz, 1H, *H*COMe), 3.98 (d, *J* = 5.7 Hz, 1H, *H*COH), 3.98 (d, *J* = 5.8 Hz, 1H, *H*COH), 3.85 (dd, *J* = 5.7 and 2.8 Hz, 1H, *H*COMe), 3.81 (s, 3H, PhO*Me*), 3.80 (s, 3H, PhO*Me*), 3.63-3.33 (m, 3H, *H*CO(CH)PMP, *H*COMe, and O*H*), 3.63-3.33 (m, 3H, *H*CO(CH)PMP, *H*COMe, and O*H*), 3.54 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.46 (s, 6H, O*Me*), 2.05-1.77 (m, 4H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$), 2.05-1.77 (m, 4H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$), 1.18 (s, 3H, C*Me*), 1.15 (s, 3H, C*Me*), 1.12 (s, 3H, C*Me*), and 1.10 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.22, 174.17, 160.7, 160.6, 143.8, 130.3, 129.7, 128.6, 128.4, 114.1, 113.93, 113.90, 113.8, 104.7, 104.4, 84.4, 84.2, 80.7, 79.6, 78.7, 76.9, 73.0, 72.9, 72.6, 61.1, 57.4, 55.5, 41.1, 39.8, 38.6, 37.5, 35.9, 24.3, 24.1, 23.5, and 22.9.

HR ESI-MS: Calcd for $C_{20}H_{36}O_9Na$ $(M+Na)^+$: 473.2146 Found: 473.2146.

TLC: R_f = 0.30; 1:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-((*R*)-2-((4*S*,5*S*)-2,2-Dimethyl-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)-2-methoxyethyl)-3-hydroxy-4-methoxytetrahydro-2*H*-pyran-2-one **332**



To a vial containing triol **320** (6 mg, 0.018 mmol) was added CH_2Cl_2 (0.400 mL, 0.45 M), 4 Å molecular sieves, 2,2-dimethoxy propane (0.01 mL, 0.072 mmol), and PTSA (2 mg, 0.0036 mmol) and allowed to stir for 18 hours. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ (5 mL) was then added followed by dilution with H_2O and EtOAc. The aqueous layer was extracted with EtOAc (3 x 25 mL), the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Flash

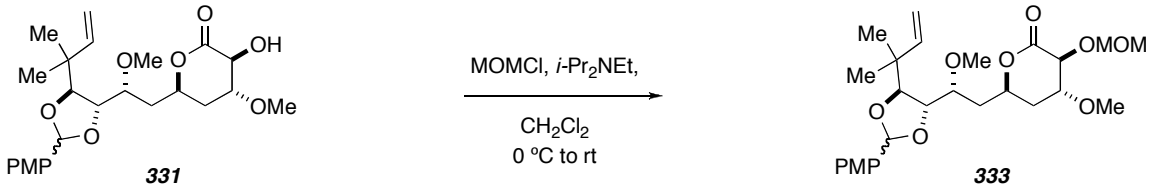
chromatography (1:1 hexanes / ethyl acetate) provided alcohol **328**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.09 (dd, 10.8 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 5.06 (dd, *J* = 17.6 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 4.77 (dddd, *J* = 10.5, 10.5, 2.6, and 2.6 Hz, 1H, *H*COC=O, 4.35 (dd, *J* = 6.0 and 2.8 Hz, 1H, *H*COH), 3.87 (d, *J* = 7.6 Hz, 1H, *H*COCMe$_2$), 3.68 (dd, *J* = 6.0 and 2.8 Hz, 1H, *H*COCMe$_2$), 3.58 (ddd, *J* = 7.0, 7.0, and 1.9 Hz, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.47 (s, 3H, O*Me*), 3.45 (ddd, *J* = 10.9, 3.2, and 3.2 Hz, 1H, *H*COMe), 2.05-1.90 (m, 3H, C$H_{a1}$$H_{b1}$ and C$H_{a2}$$H_{b2}$), 1.77 (ddd, *J* = 14.7, 10.1, and 2.9 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.40 (s, 3H, C*Me*), 1.39 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), and 1.08 (s, 3H, C*Me*).

HR ESI-MS: Calcd for $C_{19}H_{32}O_7Na$ $(M+Na)^+$: 395.2040 Found: 395.2044.

TLC: R_f = 0.64; 1:3 hexanes:ethyl acetate.

(3*S*,4*R*,6*R*)-4-Methoxy-6-((2*R*)-2-methoxy-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)ethyl)-3-(methoxymethoxy)tetrahydro-2*H*-pyran-2-one **333**



To a 50 mL round bottom flask containing alcohol **331** (609 mg, 1.35 mmol) was added CH_2Cl_2 (4.5 mL, 0.3 M) and *i*Pr_2NEt (6.60 mL, 40.5 mmol). Upon cooling the solution to 0 ºC, MOMCl (4.56 mL, 27.0 mmol; from a prepared solution containing 45% MOMCl : 55% methyl acetate and dimethoxymethane) was added dropwise and the reaction was warmed to room temperature and stirred until no starting alcohol **331** was observed by TLC. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ (15 mL) was then added followed by dilution with H_2O (15 mL). The reaction was warmed to room temperature and stirred for 15 minutes. The aqueous layer was extracted

with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (1:1 hexanes / ethyl acetate) provided lactone **333** in excellent yield (661 mg, 99%).

Characterization Data for 333-*major* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.90 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.95 (dd, *J* = 17.4 and 10.9 Hz, 1H, CH_2=C*H*), 5.92 (s, 1H, MeOPhC*H*), 5.17-5.07 (m, 2H, CH_2=CH), 4.95 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.77 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.76-4.72 (m, 1H, *H*COC=O), 4.38 (d, *J* = 6.2 Hz, 1H, *H*COMOM) 3.98 (d, *J* = 5.7 Hz, 1H, *H*CO(CH)PMP), 3.85 (dd, *J* = 5.7 and 2.7 Hz, 1H, *H*CO(CH)PMP), 3.81 (s, 3H, PhO*Me*), 3.65 (ddd, *J* = 6.3, 6.3, and 1.5 Hz, 1H, *H*COMe), 3.57 (s, 3H, O*Me*), 3.52 (ddd, *J* = 10.5, 2.7, and 2.7 Hz, 1H, *H*COMe), 3.47 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 2.08-1.75 (m, 4H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$), 1.15 (s, 3H, C*Me*), and 1.12 (s, 3H, C*Me*).

Characterization Data for 333-*minor* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.89 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.92 (dd, *J* = 16.8 and 10.7 Hz, 1H, CH_2=C*H*), 5.85 (s, 1H, MeOPhC*H*), 5.17-5.07 (m, 2H, CH_2=CH), 4.94 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.77 (d, *J* = 6.9 Hz, 1H, OCH$_a$$H_b$OMe), 4.72-4.70 (m, 1H, *H*COC=O), 4.37 (d, *J* = 6.2 Hz, 1H, *H*COMOM) 4.04 (dd, *J* = 5.8 and 3.2 Hz, 1H, *H*CO(CH)PMP), 3.98 (d, *J* = 5.8 Hz, 1H, *H*CO(CH)PMP), 3.80 (s, 3H, PhO*Me*), 3.65 (ddd, *J* = 6.3, 6.3, and 1.5 Hz, 1H, *H*COMe), 3.60 (ddd, *J* = 10.4, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.49 (s, 3H, O*Me*), 3.46 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 2.08-1.75 (m, 4H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$), 1.18 (s, 3H, C*Me*), and 1.10 (s, 3H, C*Me*).

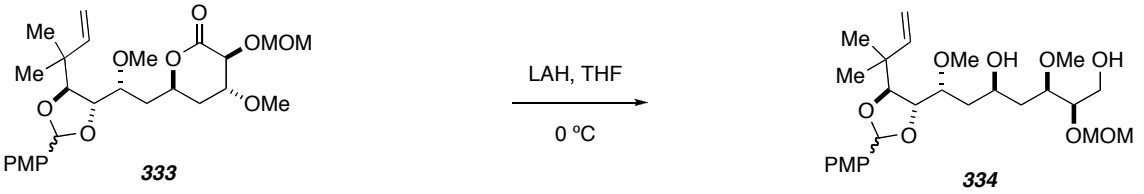
Characterization Data for mixture of 333-*major* and 333-*minor* (2:1)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.5, 160.6, 143.7, 130.3, 129.7, 128.6, 128.4, 114.0, 113.9, 113.8, 104.6, 104.3, 96.1, 84.4, 84.1, 80.8, 79.8, 78.7, 77.62, 77.58, 76.9, 74.0, 73.9, 72.3, 72.2, 61.3, 60.3, 57.3, 56.2, 55.4, 41.1, 39.7, 38.9, 37.8.

HR ESI-MS: Calcd for $C_{26}H_{38}O_9Na$ $(M+Na)^+$: 517.2408 Found: 517.2440.

TLC: R_f = 0.48; 1:1 hexanes:ethyl acetate.

(2*R*,3*R*,5*S*,7*R*)-3,7-Dimethoxy-2-(methoxymethoxy)-7-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)heptane-1,5-diol **334**



To a 100 mL round bottom flask was added LAH powder (153 mg, 4.02 mmol). THF (20.1 mL, 0.2 M) was added then the solution was cooled to 0 ºC. Lactone **333** (660 mg, 1.34 mmol) was slowly added as a solution in THF (13.4 mL) and the reaction was stirred for 1 hour, at which time no starting lactone **333** was visible by TLC. H_2O (0.157 mL), aqueous 15% NaOH (0.157 mL), and H_2O (0.471 mL) were added to the solution at 0 ºC and stirred for 30 minutes upon warming to room temperature. The reaction was filtered through a pad of celite using ethyl acetate and concentrated *in vacuo* to give the crude diol **334**. Purification via flash chromatography, although usually not necessary for the following reactions, provided **334** (642 mg, 96%).

Characterization Data for 334-*major* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.8 Hz, 2H, MeOPhH_a), 6.89 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.97 (dd, *J* = 17.5 and 10.9 Hz, 1H, CH_2=C*H*), 5.94 (s, 1H, MeOPhC*H*), 5.10 (dd, *J* = 11.0 and 1.5 Hz, 1H, C$H_a$$H_b$=CH), 5.09 (dd, *J* = 17.5 and 1.4 Hz, 1H, $CH_a$$H_b$=CH), 4.74 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$OMe), 4.70 (d, *J* = 6.9 Hz, 1H, $OCH_a$$H_b$OMe), 4.08-3.96 (m, 1H, *H*COH), 3.99 (d, *J* = 5.7 Hz, 1H, *H*CO(CH)PMP), 3.90 (dd, *J* = 5.7 and 2.8 Hz, 1H, *H*CO(CH)PMP), 3.80 (s, 3H, PhO*Me*), 3.78-3.71 (m, 2H, *H*COMOM and C$H_a$$H_b$OH), 3.67-3.56 (m, 2H, *H*COMe and $CH_a$$H_b$OH), 3.59 (s, 3H, O*Me*), 3.53-3.44 (m, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.42 (s, 3H, O*Me*), 3.34 (d, *J* = 2.0 Hz, 1H, CHO*H*), 2.91 (dd, *J* = 7.9 and 3.4 Hz, 1H, CH_2O*H*), 1.84-1.71 (m, 2H,

CH_{a1}H$_{b1}$ and CH_{a2}H$_{b2}$), 1.70-1.62 (m, 1H, CH$_{a1}$$H_{b1}$), 1.60-1.51 (m, 1H, CH$_{a2}$$H_{b2}$), 1.14 (s, 3H, C*Me*), and 1.12 (s, 3H, C*Me*).

Characterization Data for 334-*minor* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.88 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.93 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.84 (s, 1H, MeOPhC*H*), 5.13 (dd, *J* = 10.8 and 1.2 Hz, 1H, CH_aH$_b$=CH), 5.09 (dd, *J* = 17.5 and 1.3 Hz, 1H, CH$_a$$H_b$=CH), 4.74 (d, *J* = 6.9 Hz, 1H, OCH_aH$_b$OMe), 4.69 (d, *J* = 6.9 Hz, 1H, OCH$_a$$H_b$OMe), 4.08-3.96 (m, 1H, *H*COH), 4.06 (dd, *J* = 6.1 and 3.0 Hz, 1H, *H*CO(CH)PMP), 3.99 (d, *J* = 6.1 Hz, 1H, *H*CO(CH)PMP), 3.80 (s, 3H, PhO*Me*), 3.78-3.71 (m, 2H, *H*COMOM and CH_aH$_b$OH), 3.67-3.56 (m, 2H, *H*COMe and CH$_a$$H_b$OH), 3.50 (s, 3H, O*Me*), 3.53-3.44 (m, 1H, *H*OMe), 3.46 (s, 3H, O*Me*), 3.42 (s, 3H, O*Me*), 3.34 (d, *J* = 1.7 Hz, 1H, O*H*), 1.84-1.71 (m, 2H, CH_{a1}H$_{b1}$ and CH_{a2}H$_{b2}$), 1.70-1.62 (m, 1H, CH$_{a1}$$H_{b1}$), 1.60-1.51 (m, 1H, CH$_{a2}$$H_{b2}$), 1.17 (s, 3H, C*Me*), and 1.10 (s, 3H, C*Me*).

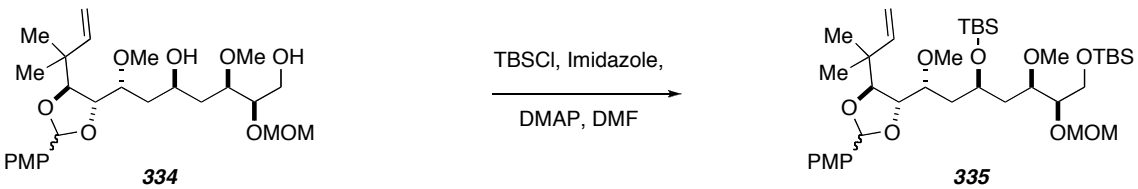
Characterization Data for mixture of 334-*major* and 334-*minor* (2:1)

^{13}C NMR (125 MHz, $CDCl_3$): δ =160.59, 160.55, 144.05, 144.00, 130.6, 130.0, 128.6, 128.5, 113.86, 113.82, 113.5, 112.4, 104.6, 104.2, 97.7, 84.7, 84.3, 82.4, 82.3, 81.1, 80.9, 80.4, 79.6, 77.8, 68.2, 68.1, 67.1, 62.4, 62.3, 60.5, 59.8, 58.34, 58.30, 56.1, 55.5, 41.1, 40.6, 39.8, 39.7, 37.19, 37.16, 24.2, 24.0, 23.6, and 23.0.

HR ESI-MS: Calcd for $C_{26}H_{42}O_9Na$ $(M+Na)^+$: 521.2721 Found: 521.2724.

TLC: R_f = 0.32; 100% ethyl acetate.

(5*S*,7*R*,8*R*)-7-Methoxy-5-((2*R*)-2-methoxy-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)ethyl)-8-(methoxymethoxy)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane **335**



334 ***335***

To a 100 mL round bottom flask containing crude diol **334** (~3.32 mmol) was added DMF (16.6 mL, 0.2 M), imidazole (791 mg, 11.6 mmol), DMAP (81 mg, 0.66 mmol), and TBSCl (1.50 g, 9.96 mmol). The reaction was stirred for 18 hours, at which time TLC showed no remaining diol **334**. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ was then added to the solution followed by dilution with H_2O and Et_2O. The reaction mixture was warmed to room temperature and stirred for 15-30 minutes. The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Residual DMF was sometimes removed via a high vacuum rotovap. Flash chromatography (6:1 hexanes / ethyl acetate) provided bis-TBS-ether **335** in excellent yield (1.88 g, 78%, 3-steps).

Characterization Data for 335-*major* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.89 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.95 (dd, *J* = 18.0 and 10.4 Hz, 1H, CH_2=C*H*), 5.92 (s, 1H, MeOPhC*H*), 5.15-5.04 (m, 2H, CH_2=CH), 4.78 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.64 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.09-4.01 (m, 1H, *H*COTBS), 3.97 (d, *J* = 5.4 Hz, 1H, *H*CO(CH)PMP), 3.90 (dd, *J* = 5.4 and 3.6 Hz, 1H, *H*CO(CH)PMP), 3.81 (s, 3H, PhO*Me*), 3.76 (dd, *J* = 10.1 and 5.3 Hz, 1H, CH_aH$_b$OTBDPS), 3.66 (dd, *J* = 10.2 and 3.2 Hz, 1H, CH$_a$$H_b$OTBDPS), 3.64-3.59 (m, 1H, *H*COMe), 3.52 (s, 3H, O*Me*), 3.51-3.47 (m, 2H, *H*COMe and *H*COMOM), 3.42 (s, 3H, O*Me*), 3.37 (s, 3H, O*Me*), 1.91 (ddd, *J* = 14.3, 8.3, and 3.7 Hz, 1H, CH_{a1}H$_{b1}$), 1.76 (ddd, *J* = 13.8, 9.1, and 4.3 Hz, 1H, CH_{a2}H$_{b2}$), 1.68 (ddd, *J* = 14.5, 8.2, and 3.9 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.66 (ddd, *J* = 14.1, 7.7, and 3.1 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.12 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.11 (s, 3H, Si*Me*), 0.09 (s, 3H, Si*Me*), 0.06 (s, 3H, Si*Me*), and 0.05 (s, 3H, Si*Me*).

Characterization Data for 335-*minor* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.9 Hz, 2H, MeOPhH_a), 6.87 (d, *J* = 8.8 Hz, 2H, MeOPhH_b), 5.93 (dd, *J* = 17.6 and 10.7 Hz, 1H, CH_2=C*H*), 5.84 (s, 1H, MeOPhC*H*), 5.15-5.04 (m, 2H, CH_2=CH), 4.77 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe),

4.64 (d, J = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.09-4.02 (m, 2H, HCOTBS and HCO(CH)PMP), 4.00 (d, J = 5.8 Hz, 1H, HCO(CH)PMP), 3.80 (s, 3H, PhOMe), 3.75 (dd, J = 10.4 and 5.3 Hz, 1H, CH_aH$_b$OTBDPS), 3.68 (dd, J = 9.8 and 3.1 Hz, 1H, CH$_a$$H_b$OTBDPS), 3.65-3.59 (m, 1H, HCOMOM), 3.56 (ddd, J = 9.3, 3.1, and 3.1 Hz, 1H, HCOMe), 3.51-3.47 (m, 1H, HCOMe), 3.42 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.36 (s, 3H, OMe), 1.94-1.86 (m, 1H, CH_{a1}H$_{b1}$), 1.80-1.73 (m, 1H, CH_{a2}H$_{b2}$), 1.71-1.60 (m, 2H, CH$_{a1}$$H_{b1}$ and CH$_{a2}$$H_{b2}$), 1.17 (s, 3H, C$Me$), 1.09 (s, 3H, C$Me$), 0.89 (s, 9H, SiC$Me_3$), 0.88 (s, 9H, SiC$Me_3$), 0.081 (s, 3H, Si$Me$), 0.078 (s, 3H, Si$Me$), 0.052 (s, 3H, Si$Me$), and 0.047 (s, 3H, Si$Me$).

Characterization Data for mixture of 335-*major* and 335-*minor* (2:1)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5, 160.4, 144.2, 144.1, 130.2, 128.5,128.4, 114.0, 113.4, 103.9, 97.1, 84.5, 84.2, 80.9, 79.3, 78.9, 68.7, 67.3, 62.7, 59.3, 58.9, 58.0, 55.9, 55.5, 41.1, 39.9, 39.8, 39.4, 39.1, 38.9, 26.21, 26.19, 26.12, 26.11, 24.3, 24.2, 22.8, 18.5, 18.3, -3.5, -3.6, -4.2, -4.3, -5.17, and -5.24.

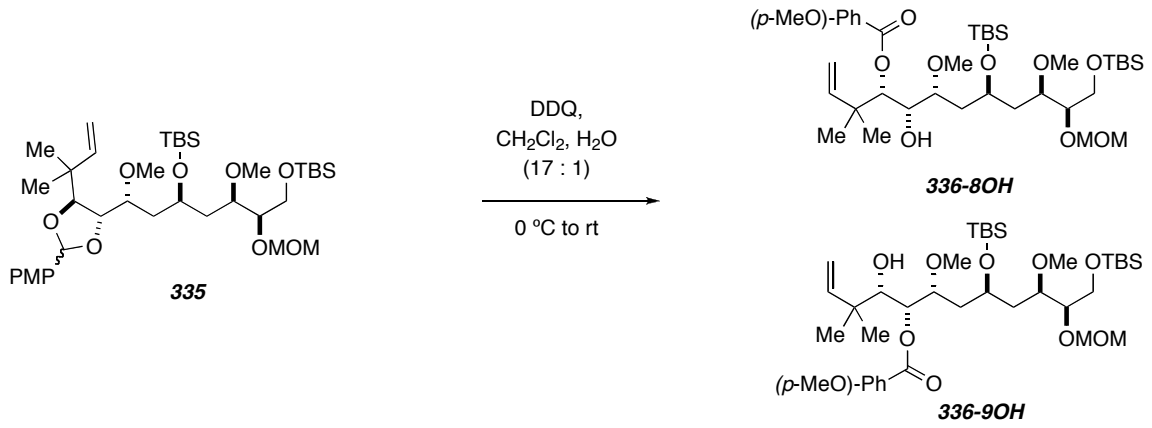
HR ESI-MS: Calcd for $C_{38}H_{70}O_9Si_2Na$ $(M+Na)^+$: 749.4451 Found: 749.4471.

TLC: R_f = 0.37; 6:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-5-hydroxy-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-4-yl 4-methoxybenzoate **336-8OH**

and

(4*S*,5*R*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-yl 4-methoxybenzoate **336-9OH**



To a 50 mL round bottom flask containing PMP acetal **335** (455 mg, 0.626 mmol) in CH_2Cl_2:H_2O (11.8 mL:0.7 mL) at 0 ºC was added DDQ (213 mg, 0.939 mmol). The solution was warmed to room temperature and stirred until there was no evidence of starting material by TLC. Saturated aqueous $NaHCO_3$ was added to the reaction mixture followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided the inseparable mixture of alcohols **336-8OH** and **336-9OH** (427 mg, 92%).

Characterization Data for Mixture of 336-8OH and 336-9OH (3:1 ; 8OH:9OH)

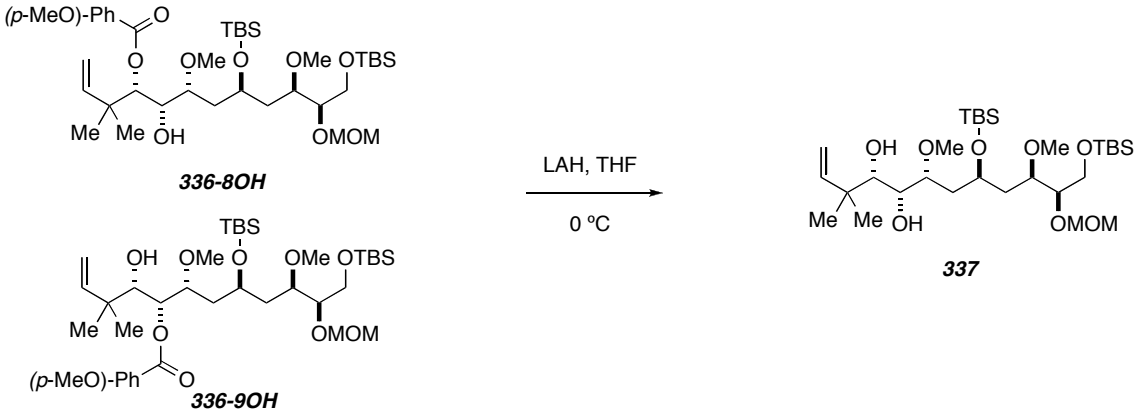
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.9 Hz, 2H, MeOPhH_a), 7.97 (d, *J* = 9.0 Hz, 2H, MeOPhH_a), 6.93 (d, *J* = 8.8 Hz, 2H, MeOPhH_b), 6.92 (d, *J* = 8.9 Hz, 2H, MeOPhH_a), 6.00 (dd, *J* = 17.6 and 11.3 Hz, 1H, CH_2=C*H*), 5.81 (dd, *J* = 17.6 and 10.7 Hz, 1H, CH_2=C*H*), 5.39 (d, *J* = 4.5 Hz, 1H, *H*COBz(*p*-MeO)), 5.10 (s, 1H, *H*COBz(*p*-MeO)), 5.10 (d, *J* = 17.2 Hz, 1H, C$H_a$$H_b$=CH), 5.08 (d, *J* = 10.9 Hz, 1H, $CH_a$$H_b$=CH), 5.00 (d, *J* = 17.4 Hz, 1H, C$H_a$$H_b$=CH), 4.93 (d, *J* = 10.9 Hz, 1H, $CH_a$$H_b$=CH), 4.77 (d, *J* = 6.9 hz, 1H, OC$H_a$$H_b$OMe), 4.76 (d, *J* = 7.4 hz, 1H, OC$H_a$$H_b$OMe), 4.64 (d, *J* = 6.8 hz, 1H, OC$H_a$$H_b$OMe), 4.63 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$OMe), 4.02-3.91 (m, 1H, *H*COTBS), 4.02-3.91 (m, 1H, *H*COTBS), 3.87 (s, 3H, PhO*Me*), 3.87 (s, 3H, PhO*Me*), 3.75 (dd, *J* = 9.7 and 4.9 Hz, 1H, C$H_a$$H_b$OTBS), 3.78 (m, 1H, C$H_a$$H_b$OTBS), 3.70-3.57 (m, 4H, *H*COMe, *H*COMOM, *H*COH, and C$H_a$$H_b$OTBS), 3.70-3.57 (m, 4H, *H*COMe, *H*COMOM, *H*COH, and C$H_a$$H_b$OTBS), 3.49-3.41 (m, 1H, *H*COMe), 3.49-3.41 (m, 1H,

*H*COMe), 3.45 (s, 3H, O*Me*), 3.40 (s, 3H, O*Me*), 3.382 (s, 3H, O*Me*), 3.378 (s, 3H, O*Me*), 3.36 (s, 3H, O*Me*), 3.28 (s, 3H, O*Me*), 2.53 (d, *J* = 7.9 Hz, 1H, O*H*), 2.39 (d, *J* = 8.7 Hz, 1H, O*H*), 1.85-1.61 (m, 4H, CH_2), 1.85-1.61 (m, 4H, CH_2), 1.18 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 1.07 (s, 3H, C*Me*), 1.03 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.84 (s, 9H, SiCMe_3), 0.77 (s, 9H, SiCMe_3), 0.063 (s, 3H, Si*Me*), 0.058 (s, 3H, Si*Me*), 0.052 (s, 3H, Si*Me*), 0.046 (s, 3H, Si*Me*), 0.03 (s, 3H, Si*Me*), and 0.02 (s, Si*Me*).

HR ESI-MS: Calcd for $C_{38}H_{70}O_{10}Si_2Na$ $(M+Na)^+$: 765.4400 Found: 765.4403.

TLC: R_f = 0.46; 3:1 hexanes:ethyl acetate.

(4*S*,5*R*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-ene-4,5-diol **337**



To a 50 mL round bottom flask was added LAH powder (121 mg, 3.18 mmol). THF (15.9 mL, 0.2 M) was added then the solution was cooled to 0 ºC. The mixture of alcohols **336-8OH** and **336-9OH** (787 mg, 1.06 mmol) were slowly added as a solution in THF (10.6 mL) and the reaction was stirred for 1 hour, at which time no starting alcohols were visible by TLC. H_2O (0.121 mL), aqueous 15% NaOH (0.121 mL), and H_2O (0.363 mL) were added to the solution at 0 ºC and stirred for 30 minutes upon warming to room temperature. The reaction was filtered through a pad of celite using ethyl acetate and concentrated *in vacuo* to give the crude diol **337**. Purification via flash

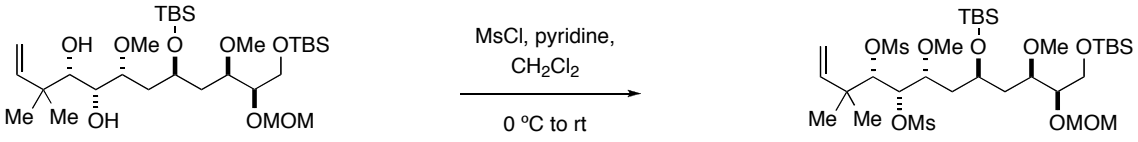
chromatography (2:1 hexanes / ethyl acetate) provided diol **337** (510 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.90 (dd, *J* = 18.0 and 10.4 Hz, 1H, CH_2=C*H*), 5.06 (dd, *J* = 12.1 and 1.5 Hz, 1H, C$H_a$$H_b$=CH), 5.06 (dd, *J* = 17.4 and 1.5 Hz, 1H, $CH_a$$H_b$=CH), 4.78 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.66 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.02-3.96 (m, 1H, *H*COTBS), 3.77 (dd, *J* = 10.3 and 5.4 Hz, 1H, C$H_a$$H_b$OTBS), 3.69 (dd, *J* = 10.2 and 6.5 Hz, 1H, $CH_a$$H_b$OTBS), 3.66-3.59 (m, 2H, *H*COH and *H*COMOM), 3.51 (ddd, *J* = 8.1, 4.1, and 4.1 Hz, 1H, *H*COMe), 3.44-3.36 (m, 1H, *H*COMe), 3.419 (s, 3H, O*Me*), 3.417 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 3.33 (d, *J* = 5.9 Hz, 1H, *H*COH), 2.85 (d, *J* = 5.9 Hz, 1H, O*H*), 2.66 (d, *J* = 5.7 Hz, 1H, O*H*), 1.80-1.63 (m, 4H, C$H_{a1}$$H_{b1}$ and C$H_{a2}$$H_{b2}$), 1.070 (s, 3H, C*Me*), 1.066 (s, 3H, C*Me*), 0.90 (s, 18H, SiCMe_3), 0.11 (s, 3H, Si*Me*), 0.09 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.0, 97.2, 81.3, 79.5, 77.2, 76.7, 69.6, 67.7, 67.6, 62.7, 58.7, 57.7, 55.9, 41.6, 38.8, 38.3, 26.2, 26.1, 24.2, 22.5, 18.5, 18.2, -3.8, -4.1, -5.17 and -5.25.

TLC: R_f = 0.88; 1:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-ene-4,5-diyl dimethanesulfonate **338**



337 ***338***

To a culture tube containing diol **337** (65 mg, 0.11 mmol) in CH_2Cl_2 (0.600 mL, 0.18 M) at 0 ºC was added pyridine (0.104 mL, 1.28 mmol) and methane sulfonylchloride (0.066 mL, 0.85 mmol). The reaction mixture was warmed to room temperature and stirred for 48 hours. The solution was recooled to 0 ºC followed by the addition of

saturated aqueous $NaHCO_3$ (10 mL). The mixture was then warmed to room temperature and stirred for 1 hour. The solution was again diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided the bis-mesylate **338** (72 mg, 88%).

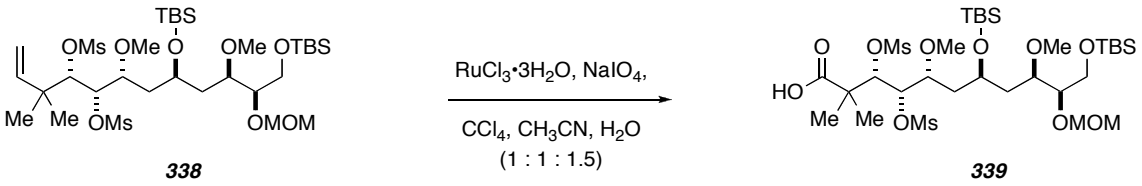
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (dd, *J* = 17.7 and 11.1 Hz, 1H, CH_2=C*H*), 5.22 (d, *J* = 10.7 Hz, 1H, C$H_a$$H_b$=CH), 5.21 (d, *J* = 17.5 Hz, 1H, $CH_a$$H_b$=CH), 4.78 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.69 (dd, *J* = 4.8 and 3.2 Hz, 1H, *H*COMs), 4.65 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.64 (d, *J* = 4.8 Hz, 1H, *H*COMs), 4.11-4.04 (m, 1H, *H*COTBS), 3.77 (dd, *J* = 13.3 and 7.9 Hz, 1H, C$H_a$$H_b$OTBS), 3.70-3.64 (m, 2H, *H*COMOM and $CH_a$$H_b$OTBS), 3.62 (ddd, *J* = 9.0, 3.1, and 3.1, 1H, *H*COMe), 3.53-3.47 (m, 1H, *H*COMe), 3.50 (s, 3H, *Me*), 3.42 (s, 3H, *Me*), 3.39 (s, 3H, *Me*), 3.16 (s, 3H, *Me*), 3.09 (s, 3H, *Me*), 1.96 (ddd, *J* = 14.4, 9.2, and 3.3 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.76 (ddd, *J* = 13.9, 9.7, and 3.6 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.69-1.59 (m, 2H, $CH_{a1}$$H_{b1}$ and $CH_{a2}$$H_{b2}$), 1.19 (s, 6H, C*Me*), 0.90 (s, 6H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.10 (s, 6H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.2, 116.0, 97.1, 82.7, 79.3, 78.9, 78.3, 77.2, 66.7, 62.8, 59.4, 58.8, 55.9, 41.7, 39.7, 39.3, 38.9, 38.8, 26.2, 26.1, 25.0, 21.7, 18.5, 18.2, -3.5, -4.1, -5.2, and -5.3.

HR ESI-MS: Calcd for $C_{32}H_{68}O_{12}S_2Si_2Na$ $(M+Na)^+$: 787.3583 Found: 787.3584.

TLC: R_f = 0.29; 3:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldimethylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-3,4-bis(methylsulfonyloxy)undecanoic acid **339**



338 ***339***

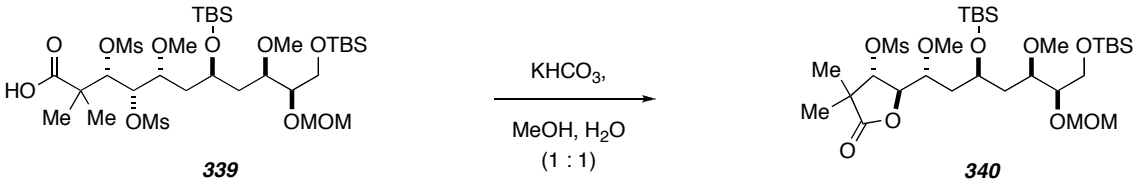
To a vial containing alkene **338** (10 mg, 0.013 mmol) in CCl_4:CH_3CN:H_2O (1:1:1.5; 0.364 mL, 0.036 M) was added $NaIO_4$ (0.027 g, 0.126 mmol) and $RuCl_3$•$3H_2O$ (2 mg, 0.0076 mmol). The reaction mixture was stirred until TLC showed complete consumption of the starting material. The solution was diluted with CH_2Cl_2 and filtered through a pad of celite using CH_2Cl_2 as the eluent. The solvent was removed *in vacuo* and purification by flash chromatography (1:1 hexanes / ethyl acetate) provided the acid **339** (1 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.08 (d, *J* = 5.0 Hz, 1H, *H*COMs), 4.85 (d, *J* = 6.5 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.74 (d, *J* = 6.7 Hz, 1H, OCH$_a$*H*$_b$OMe), 4.65 (dd, *J* = 5.2 and 2.3 Hz, 1H, *H*COMs), 4.03-3.94 (m, 1H, *H*COTBS), 3.85 (dd, *J* = 10.5 and 7.5 Hz, 1H, C*H*$_a$H$_b$OTBS), 3.80 (dd, *J* = 10.7 and 5.4 Hz, 1H, CH$_a$*H*$_b$OTBS), 3.72-3.62 (m, 2H, *H*COMe and *H*COMOM), 3.58 (m, 1H, *H*COMe), 3.46 (s, 3H, *Me*), 3.44 (s, 3H, *Me*), 3.39 (s, 3H, *Me*), 3.20 (s, 3H, *Me*), 3.12 (s, 3H, *Me*), 1.98-1.85 (m, 2H, C*H*$_{a1}$*H*$_{b1}$), 1.76-1.61 (m, 2H, C*H*$_{a2}$*H*$_{b2}$), 1.41 (s, 3H, C*Me*), 1.30 (s, 3H, C*Me*), 0.900 (s, 9H, SiC*Me*$_3$), 0.885 (s, 9H, SiC*Me*$_3$), 0.11 (s, 3H, Si*Me*), 0.090 (s, 3H, Si*Me*), and 0.086 (s, 6H, Si*Me*).

HR ESI-MS: Calcd for $C_{31}H_{66}O_{14}S_2Si_2Na$ $(M+Na)^+$: 805.3325 Found: 805.3324.

TLC: R_f = 0.61; 1:1 hexanes:ethyl acetate.

(2*R*,3*S*)-2-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4,4-dimethyl-5-oxotetrahydrofuran-3-yl methanesulfonate **340**



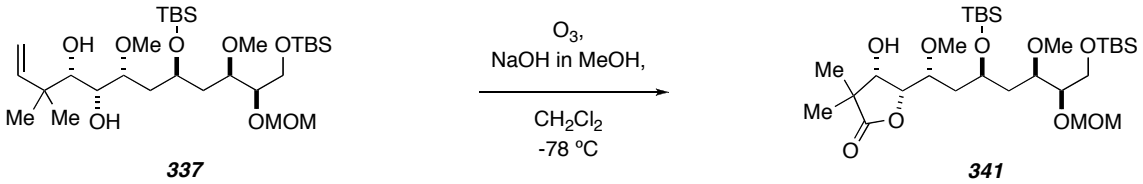
To a small vial containing acid **339** (10 mg, 0.013 mmol) was added MeOH (0.250 mL) followed by the slow addition of H_2O (0.250 mL) with vigorous stirring. Solid $KHCO_3$ (25 mg, 0.25 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes / ethyl acetate) provided lactone **340** (6 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.18 (d, *J* = 5.7 Hz, 1H, *H*COMs), 4.78 (d, *J* = 6.7 Hz, 1H, OC*H*$_a$H$_b$OMe), 4.65 (d, *J* = 6.7 Hz, 1H, OCH$_a$*H*$_b$OMe), 4.39 (dd, *J* = 5.8 and 2.6 Hz, 1H, *H*COC=O), 4.10-4.02 (m, 1H, *H*COTBS), 3.78 (ddd, *J* = 8.6, 3.2, and 3.2 Hz, 1H, *H*COMe), 3.78-3.72 (m, 1H, C*H*$_a$H$_b$OTBS), 3.70-3.61 (m, 2H, *H*COMOM and CH$_a$*H*$_b$OTBS), 3.49-3.43 (m, 1H, *H*COMe), 3.46 (s, 3H, *Me*), 3.42 (s, 3H, *Me*), 3.39 (s, 3H, *Me*), 3.09 (s, 3H, *Me*), 1.86-1.72 (m, 2H, C*H*$_{a1}$H$_{b1}$ and C*H*$_{a2}$H$_{b2}$), 1.67 (ddd, *J* = 14.1, 8.3, and 3.2 Hz, 1H, CH$_{a1}$*H*$_{b1}$), 1.58-1.48 (m, 1H, CH$_{a2}$*H*$_{b2}$), 1.42 (s, 3H, C*Me*), 1.31 (s, 3H, C*Me*), 0.901 (s, 9H, SiC*Me*$_3$), 0.898 (s, 9H, SiC*Me*$_3$), 0.11 (s, 3H, Si*Me*), 0.10 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

HR ESI-MS: Calcd for $C_{30}H_{62}O_{11}SSi_2Na$ $(M+Na)^+$: 725.3183 Found: 725.3200.

TLC: R_f = 0.64; 2:1 hexanes:ethyl acetate.

(4*S*,5*R*)-5-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3*H*)-one **341**



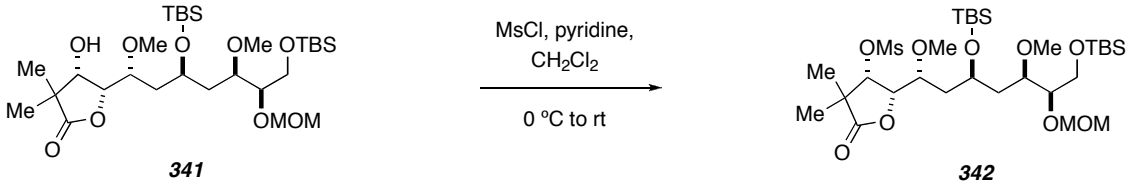
To a culture tube containing alkene **337** (12 mg, 0.0197 mmol) was added CH_2Cl_2 (0.660 mL, 0.03 M) followed by cooling the solution to -78 ºC. A solution of methanolic NaOH (0.079 mL, 0.197 mmol, from a 2.5 M stock solution of NaOH/MeOH) was added. Ozone was sparged through the system using a pipette tip. Once sparging began, a characteristic yellow color developed. Ozone was sparged into the solution until TLC showed complete consumption of the starting material. Oxygen was then sparged through the solution. Et_2O (10 mL) and H_2O (5 mL) were added and the solution was warmed to room temperature. The solution was adjusted to a neutral pH with 10% aqueous HCl and then diluted with Et_2O and H_2O followed by extraction of the aqueous layer with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided lactone **341** (4 mg, 33%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.78 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.66 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.37 (dd, *J* = 7.6 and 3.4 Hz, 1H, *H*COC=O), 4.12 (dddd, *J* = 9.4, 9.4, 3.0, and 3.0 Hz, 1H, *H*COTBS), 4.01 (dd, *J* = 3.3 and 3.3 Hz, 1H, *H*COH), 3.78 (ddd, *J* = 7.6, 7.6, and 2.6 Hz, 1H, *H*COMe), 3.76 (dd, *J* = 10.5 and 5.1 Hz, 1H, CH_aH$_b$OTBS), 3.67 (dd, *J* = 10.5 and 6.6 Hz, 1H, CH$_a$$H_b$OTBS), 3.62 (ddd, *J* = 6.0, 4.7, and 3.6 Hz, 1H, *H*COMOM), 3.54 (s, 3H, O*Me*), 3.46 (ddd, *J* = 10.1, 3.2, and 3.2 Hz, 1H, *H*COMe), 3.44 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 3.03 (d, *J* = 3.2 Hz, 1H, O*H*), 1.87-1.77 (m, 2H, CH_{a1}H$_{b1}$ and CH_{a2}H$_{b2}$), 1.71-1.61 (m, 2H, CH$_{a1}$$H_{b1}$ and CH$_{a2}$$H_{b2}$), 1.27 (s, 3H, C*Me*), 1.23 (s, 3H, C*Me*), 0.90 (s, 18H, SiCMe_3), 0.14 (s, 3H, Si*Me*), 0.13 (s, 3H, Si*Me*), 0.071 (s, 3H, Si*Me*), and 0.065 (s, 3H, Si*Me*).

HR ESI-MS: Calcd for $C_{29}H_{60}O_9Si_2Na$ $(M+Na)^+$: 631.3668 Found: 631.3670.

TLC: $\mathbf{R_f}$ = 0.26; 3:1 hexanes:ethyl acetate.

(2*S*,3*S*)-2-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldimethylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4,4-dimethyl-5-oxotetrahydrofuran-3-yl methanesulfonate **342**



To a small vial containing alcohol **341** (2 mg, 0.003 mmol) in CH_2Cl_2 (0.100 mL, 0.03 M) at 0 ºC was added pyridine (0.006 mL, 0.08 mmol) and methane sulfonylchloride (0.004 mL, 0.06 mmol). The reaction mixture was warmed to room temperature and stirred for 24 hours. The solution was recooled to 0 ºC followed by the addition of saturated aqueous $NaHCO_3$ (2 mL). The mixture was then warmed to room temperature and stirred for 30 minutes. The solution was again diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes / ethyl acetate) provided mesylate **342** (1 mg, 50%).

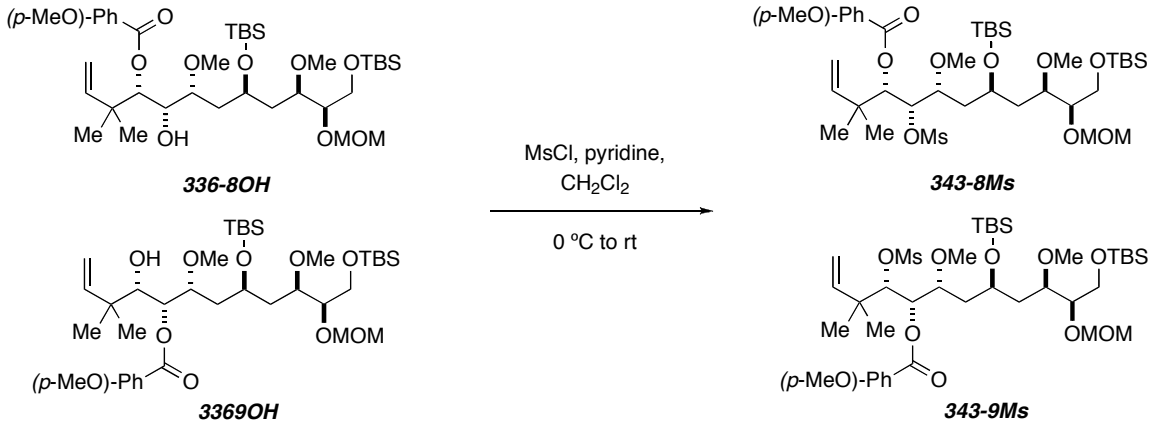
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 4.0 Hz, 1H, *H*COMs), 4.78 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.67 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.51 (dd, *J* = 7.7 and 4.0 Hz, 1H, *H*COC=O), 4.26-4.18 (m, 1H, *H*COTBS), 3.80-3.72 (m, 2H, CH_aH$_b$OTBS and *H*COMe), 3.70-3.60 (m, 2H, CH$_a$$H_b$OTBS and *H*COMOM), 3.57 (s, 3H, *Me*), 3.49-3.39 (m, 1H, *H*COMe), 3.43 (s, 3H, *Me*), 3.39 (s, 3H, *Me*), 3.20 (s, 3H, *Me*), 1.81 (ddd, *J* = 13.8, 10.0, and 3.4 Hz, 1H, CH_{a1}H$_{b1}$), 1.74-1.61 (m, 3H, CH_{a1}H$_{b1}$ and C$H_{a2}$$H_{b2}$), 1.38 (s, 3H, C*Me*), 1.34 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.13 (s, 3H, Si*Me*), 0.12 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

TLC: $\mathbf{R_f}$ = 0.46; 2:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyl-5-(methylsulfonyloxy)dodec-1-en-4-yl 4-methoxybenzoate **343-8Ms**

and

(4S,5S,6R,8S,10R,11R)-8,12-Bis(tert-butyldimethylsilyloxy)-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyl-4-(methylsulfonyloxy)dodec-1-en-4-yl 5-methoxybenzoate **343-9Ms**



To a culture tube containing the mixture of alcohols **336-8OH** and **336-9OH** (322 mg, 0.433 mmol) in CH_2Cl_2 (2.1 mL, 0.2 M) at 0 ºC was added pyridine (0.420 mL, 5.20 mmol) and methane sulfonylchloride (0.269 mL, 3.46 mmol). The reaction mixture was warmed to room temperature and stirred for 48 hours. The solution was recooled to 0 ºC followed by the addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was then warmed to room temperature and stirred for 1 hour. The solution was again diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (3:1 hexanes / ethyl acetate) provided the separable mesylates **343-8Ms** (262 mg, 74%) and **343-9OMs** (48 mg, 13%).

Characterization Data for 343-8Ms

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.8 Hz, 2H, MeOPhH_a), 6.93 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.88 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.32 (dd, *J* = 3.8 and 3.8 Hz, 1H, *H*COMs), 5.13 (d, *J* = 17.5 Hz, 1H, C$H_a$$H_b$=CH), 5.08 (d, *J* = 10.7 Hz, 1H, $CH_a$$H_b$=CH), 4.81 (d, *J* = 3.4 Hz, 1H, *H*COBz(*p*-MeO)), 4.75 (d, *J* = 6.7 Hz, 1H, C$H_a$$H_b$OMe), 4.64 (d, *J* = 6.7 Hz, 1H, $CH_a$$H_b$OMe), 4.06-3.97 (m, 1H, *H*COTBS), 3.87 (s, 3H, PhO*Me*), 3.75 (dd, *J* = 9.4 and 2.4 Hz, 1H, C$H_a$$H_b$OTBS), 3.70-3.59 (m, 3H, *H*COMe, *H*COMOM, $CH_a$$H_b$OTBS), 3.49 (ddd, *J* = 8.8, 3.2, and 3.2 Hz, 1H, *H*COMe), 3.44 (s, 3H, *Me*), 3.38 (s, 3H, *Me*), 3.33 (s, 3H, *Me*), 3.11 (s, 3H, *Me*), 1.84 (ddd, *J* = 13.6, 8.8, and 4.5 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.70 (ddd, *J* = 13.9, 8.8, and 4.1 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.65 (ddd, *J* = 10.9, 7.8, and 4.1 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.61 (ddd, *J* = 9.9, 8.2, and 4.7 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.18 (s, 3H, C*Me*), 1.14 (s, 3H, C*Me*), 0.88 (s, 9H, SiCMe_3), 0.83 (s, 9H, SiCMe_3), 0.052 (s, 3H, Si*Me*), 0.047 (s, 3H, Si*Me*), 0.03 (s, 3H, Si*Me*), and 0.00 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 163.8, 143.2, 132.1, 122.4, 114.4, 114.0, 97.1, 85.1, 79.0, 77.9, 76.9, 71.3, 66.8, 62.7, 58.69, 58.65, 55.8, 55.6, 41.7, 39.4, 38.43, 38.39, 26.2, 25.1, 22.2, 18.5, 18.1, -3.8, -4.3, -5.2, and -5.3.

TLC: R_f = 0.42; 3:1 hexanes:ethyl acetate.

Characterization Data for 343-9Ms

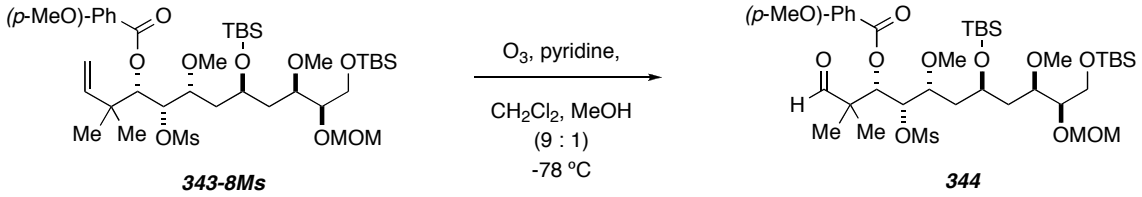
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.94 (d, *J* = 8.8 Hz, 2H, MeOPhH_b), 5.96 (dd, *J* = 17.4 and 10.7 Hz, 1H, CH_2=C*H*), 5.38 (d, *J* = 1.5 Hz, 1H, *H*COMs), 5.17 (d, *J* = 17.6 Hz, 1H, C$H_a$$H_b$=CH), 5.14 (d, *J* = 10.7 Hz, 1H, $CH_a$$H_b$=CH), 5.11 (dd, *J* = 4.7 and 1.3 Hz, 1H, *H*COBz(*p*-MeO)), 4.65 (d, *J* = 6.7 Hz, 1H, C$H_a$$H_b$OMe), 4.52 (d, *J* = 6.7 Hz, 1H, $CH_a$$H_b$OMe), 4.02-3.95 (m, 1H, *H*COTBS), 3.87 (s, 3H, PhO*Me*), 3.74 (dd, *J* = 9.6 and 4.7 Hz, 1H, *H*COMe), 3.67 (dd, *J* = 10.4 and 4.7 Hz, 1H, C$H_a$$H_b$OTBS), 3.62 (dd, *J* = 10.3 and 7.0 Hz, 1H, $CH_a$$H_b$OTBS), 3.51 (ddd, *J* = 7.5, 4.2, and 4.2 Hz, 1H, *H*COMOM), 3.42 (s, 3H, *Me*), 3.33 (s, 3H, *Me*), 3.32 (s, 3H, *Me*), 3.20 (ddd, *J* = 9.9, 3.4, and 3.4 Hz, 1H, *H*COMe), 3.07 (s, 3H, *Me*), 1.70 (ddd, *J* = 13.8, 9.7, and 3.7 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.64 (ddd, *J* = 14.4, 10.8, and 3.3 Hz, 1H, C$H_{a2}$$H_{b2}$),

1.55-1.42 (m, 2H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$), 1.20 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 0.89 (s, 9H, SiCMe_3), 0.83 (s, 9H, SiCMe_3), 0.05 (s, 9H, Si*Me*), and 0.04 (s, 3H, Si*Me*).

HR ESI-MS: Calcd for $C_{39}H_{72}O_{12}SSi_2Na$ $(M+Na)^+$: 843.4175 Found: 843.4204.

TLC: R_f = 0.54; 3:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldimethylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-4-(methylsulfonyloxy)-1-oxoundecan-3-yl 4-methoxybenzoate **344**

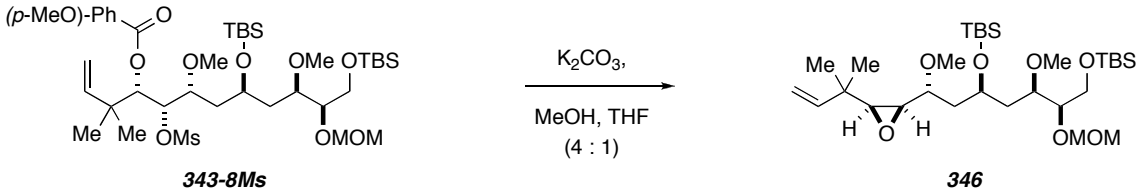


A 9:1 mixture of CH_2Cl_2:MeOH (0.67 mL, 0.02 M) was added to a culture tube containing alkene **343-8Ms** (11 mg, 0.013 mmol). This solution was cooled to -78 ºC and pyridine (0.012 mL, 0.133 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the reaction mixture, observed by the change of the solution from a light blue color to colorless. Dimethyl sulfide (1 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6 hours. The solution was concentrated under reduced pressure to provide the crude aldehyde **344** (7 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.54 (s, 1H, *H*C=O), 8.03 (d, *J* = 9.0 Hz, 2H, *p*-MeO-PhH_a), 6.94 (d, *J* = 8.9 Hz, 2H, *p*-MeO-PhH_b), 5.37 (dd, *J* = 4.8 and 4.8 Hz, 1H, *H*COMs), 5.26 (d, *J* = 5.0 Hz, 1H, *H*COBz(*p*-MeO)), 4.75 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.64 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.05-3.97 (m, 1H, *H*COTBS), 3.87 (s, 3H, PhO*Me*), 3.76 (dd, *J* = 9.6 and 4.4 Hz, 1H, C$H_a$$H_b$OTBS), 3.74-3.60 (m, 3H,

*H*COMOM, *H*COMe, and CH_aH_bOTBS), 3.53-3.45 (m, 1H, *H*COMe), 3.39 (s, 3H, *Me*), 3.37 (s, 3H, *Me*), 3.33 (s, 3H, *Me*), 3.03 (s, 3H, *Me*), 1.88 (ddd, *J* = 14.3, 8.7, and 4.1 Hz, 1H, $CH_{a1}H_{b1}$), 1.77-1.57 (m, 3H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$), 1.23 (s, 3H, C*Me*), 1.22 (s, 3H, C*Me*), 0.88 (s, 9H, SiCMe_3), 0.83 (s, 9H, SiCMe_3), 0.052 (s, 3H, Si*Me*), .045 (s, 3H, Si*Me*), 0.03 (s, 3H, Si*Me*), 0.01 (s, 3H, Si*Me*).

(5*S*,7*R*,8*R*)-7-Methoxy-5-((*R*)-2-methoxy-2-((2*R*,3*S*)-3-(2-methylbut-3-en-2-yl)oxiran-2-yl)ethyl)-8-(methoxymethoxy)-2,2,3,3,11,11,12,12-octamethyl-4,10-dioxa-3,11-disilatridecane **346**



To a culture tube containing mesylate **343-8Ms** (10 mg, 0.012 mmol) was added a MeOH:THF (4:1) solution (0.97 mL: 0.24 mL). Solid K_2CO_3 (82 mg, 0.59 mmol) was added to the reaction mixture and stirred for 24 hours. The mixture was diluted with H_2O and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by MPLC (6:1 hexanes / ethyl acetate) provided the epoxide **346** (5 mg, 69%).

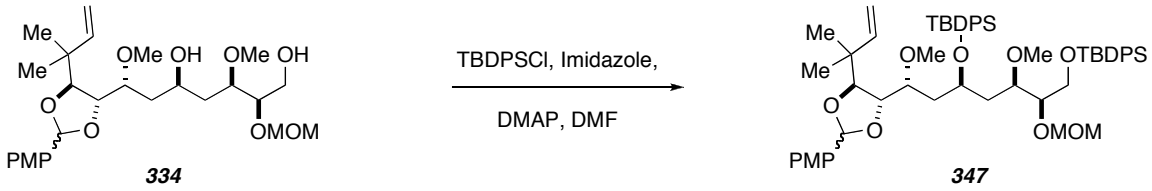
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.89 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.08 (dd, *J* = 17.6 and 1.0 Hz, 1H, CH_aH_b=CH), 5.04 (dd, *J* = 10.8 and 1.0 Hz, 1H, CH_aH_b=CH), 4.78 (d, *J* = 6.8 Hz, 1H, OCH_aH_bOMe), 4.65 (d, *J* = 6.8 Hz, 1H, OCH_aH_bOMe), 4.16 (dddd, *J* = 10.6, 8.1, 2.9 and 2.9 Hz, 1H, *H*COTBS), 3.76 (dd, *J* = 10.4 and 3.8 Hz, 1H, CH_aH_bOTBS), 3.66 (dd, *J* = 10.4 and 6.4 Hz, 1H, CH_aH_bOTBS), 3.62 (ddd, *J* = 10.6, 2.4, and 2.4 Hz, 1H, *H*COMe), 3.61-3.58 (m, 1H, *H*COMOM), 3.51 (s, 3H, O*Me*), 3.49 (ddd, *J* = 9.6, 3.3, and 3.3 Hz, 1H, *H*COMe), 3.42 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 2.87 (dd, *J* = 8.3 and 4.5 Hz, 1H, *H*C(O)CH), 2.70 (d, *J* = 4.5 Hz, 1H,

HC(O)C*H*), 1.75-1.56 (m, 4H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$), 1.15 (s, 3H, C*Me*), 1.11 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.08 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 6H, Si*Me*).

HR ESI-MS: Calcd for $C_{30}H_{62}O_7Si_2Na$ $(M+Na)^+$: 629.3666 Found: 629.3703.

TLC: R_f = 0.32; 6:1 hexanes:ethyl acetate.

(5*S*,7*R*,8*R*)-7-Methoxy-5-((2*R*)-2-methoxy-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-(2-methylbut-3-en-2-yl)-1,3-dioxolan-4-yl)ethyl)-8-(methoxymethoxy)-2,2,12,12-tetramethyl-3,3,11,11-tetraphenyl-4,10-dioxa-3,11-disilatridecane **347**



334 ***347***

To a 100 mL round bottom flask containing crude diol **334** (~6.27 mmol) was added DMF (20.9 mL, 0.3 M), imidazole (1.92 g, 28.2 mmol), DMAP (77 mg, 0.63 mmol), and TBDPSCl (6.5 mL, 25.1 mmol). The reaction was stirred for 24 hours, at which time TLC showed no remaining diol **334**. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ was then added to the solution followed by dilution with H_2O and Et_2O. The reaction mixture was warmed to room temperature and stirred for 15-30 minutes. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Residual DMF was sometimes removed via a high vacuum rotovap. Flash chromatography (6:1 hexanes / ethyl acetate) provided bis-TBDPS-ether **347** in excellent yield (5.06 g, 92%, 3-steps).

Characterization Data for 347-*major* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.59 (m, 8H, Ph*H*), 7.46-7.20 (m, 14H, Ph*H* and MeOPhH_a), 6.88 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.86 (dd, *J* = 17.9 and 10.5 Hz, 1H,

CH_2=C*H*), 5.77 (s, 1H, MeOPhC*H*), 5.00 (dd, *J* = 10.9 and 1.5 Hz, 1H, C$H_a$$H_b$=CH), 4.99 (dd, *J* = 17.0 and 1.5 Hz, 1H, $CH_a$$H_b$=CH), 4.68 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.54 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.15-4.08 (m, 1H, *H*COTBDPS), 3.84 (d, *J* = 5.3 Hz, 1H, *H*CO(CH)PMP), 3.80 (s, 3H, PhO*Me*), 3.74 (dd, *J* = 5.3 and 3.7 Hz, 1H, *H*CO(CH)PMP), 3.68-3.56 (m, 3H, *H*COMOM and CH_2OTBDPS), 3.45 (ddd, *J* = 9.4, 2.5, and 2.5 Hz, 1H, *H*COMe), 3.31 (ddd, *J* = 8.6, 3.7, and 3.7 Hz, 1H, *H*COMe), 3.24 (s, 3H, O*Me*), 3.18 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 1.92 (ddd, *J* = 14.7, 8.8, and 3.8 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.75-1.66 (m, 2H, $CH_{a1}$$H_{b1}$ and C$H_{a2}$$H_{b2}$), 1.63 (ddd, *J* = 14.2, 8.9, and 2.8 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.05 (s, 3H, C*Me*), 1.04 (s, 9H, SiCMe_3), 1.02 (s, 3H, C*Me*), and 1.01 (s, 9H, SiCMe_3).

Characterization Data for 347-*minor* (2:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.59 (m, 8H, Ph*H*), 7.46-7.20 (m, 14H, Ph*H* and MeOPhH_a), 6.84 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.86 (dd, *J* = 17.9 and 10.5 Hz, 1H, CH_2=C*H*), 5.78 (s, 1H, MeOPhC*H*), 5.04 (dd, *J* = 10.9 and 1.7 Hz, 1H, C$H_a$$H_b$=CH), 5.01 (dd, *J* = 17.5 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 4.66 (d, *J* = 6.6 Hz, 1H, OC$H_a$$H_b$OMe), 4.52 (d, *J* = 6.5 Hz, 1H, $OCH_a$$H_b$OMe), 4.15-4.08 (m, 1H, *H*COTBDPS), 3.92-3.89 (m, 2H, *H*CO(CH)PMP and *H*CO(CH)PMP), 3.80 (s, 3H, PhO*Me*), 3.68-3.56 (m, 3H, *H*COMOM and CH_2OTBDPS), 3.48-3.40 (m, 1H, *H*COMe), 3.42 (ddd, *J* = 9.1, 2.7, and 2.7 Hz, 1H, *H*COMe), 3.23 (s, 3H, O*Me*), 3.15 (s, 3H, O*Me*), 3.03 (s, 3H, O*Me*), 1.96-1.86 (m, 1H, C$H_{a1}$$H_{b1}$), 1.75-1.66 (m, 2H, $CH_{a1}$$H_{b1}$ and C$H_{a2}$$H_{b2}$), 1.66-1.58 (m, 1H, $CH_{a2}$$H_{b2}$), 1.04 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), 1.02 (s, 3H, C*Me*), and 1.01 (s, 9H, SiCMe_3).

Characterization Data for mixture of 347-*major* and 347-*minor* (2:1)

^{13}C NMR (125 MHz, $CDCl_3$): δ =160.5, 160.4, 144.2, 144.1, 136.24, 136.18, 135.8, 135.7, 134.5, 134.1, 133.6, 130.2, 129.78, 129.75, 129.66, 128.6, 128.5, 127.88, 127.86, 127.79, 127.72, 127.63, 127.55, 113.77, 113.73, 113.3, 104.5, 103.7, 97.0, 84.4, 84.1, 80.9, 79.1, 77.3, 69.0, 68.9, 68.2, 63.6, 63.5, 59.3, 58.6, 58.2, 55.9, 55.5, 41.0, 39.81, 39.79, 39.4, 39.1, 38.9, 27.3, 27.0, 24.2, 24.0, 23.5, 22.8, 19.56, 19.53, 19.32, and 19.30.

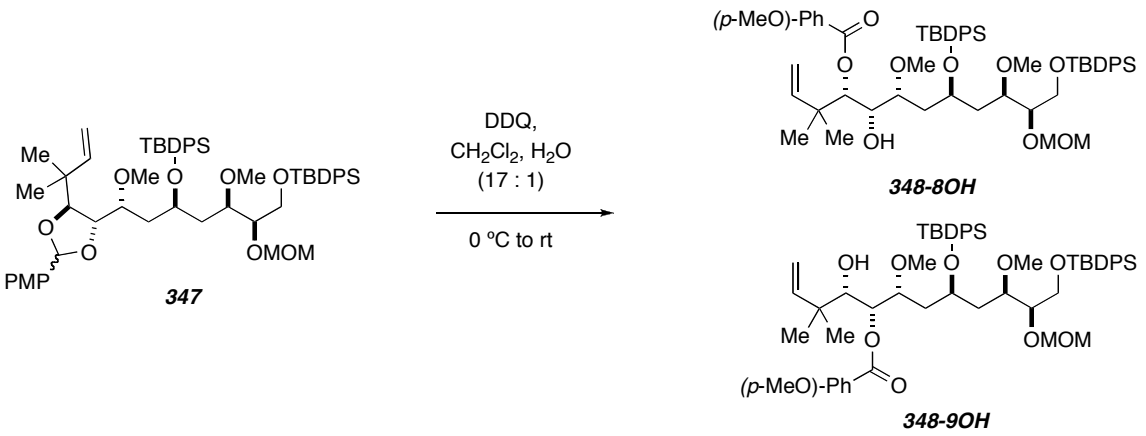
HR ESI-MS: Calcd for $C_{58}H_{78}O_9Si_2Na$ $(M+Na)^+$: 997.5077 Found: 997.5110.

TLC: R_f = 0.47; 6:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-5-hydroxy-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-4-yl 4-methoxybenzoate **348-8OH**

and

(4*S*,5*R*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-4-hydroxy-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-yl 4-methoxybenzoate **348-9OH**



To a culture tube containing PMP acetal **347** (153 mg, 0.157 mmol) in CH_2Cl_2:H_2O (3.0 mL:0.2 mL) at 0 ºC was added DDQ (54 mg, 0.235 mmol). The solution was warmed to room temperature and stirred for 5 hours. Saturated aqueous $NaHCO_3$ was added to the reaction mixture followed by dilution with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided the inseparable mixture of alcohols **348-8OH** and **348-9OH** (154 mg, 99%).

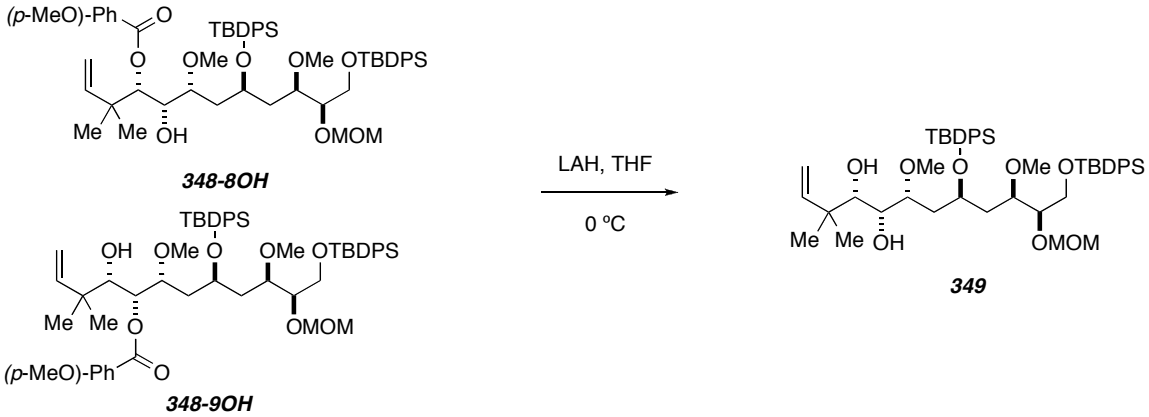
Characterization Data for Mixture of 348-8OH and 348-9OH (4:1 ratio)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.9 Hz, 2H, MeOPhH_a), 7.94 (d, *J* = 8.9 Hz, 2H, MeOPhH_a), 7.73-7.13 (m, 20H, Ph*H*), 6.91 (d, *J* = 9.0 Hz, 2H, MeOPhH_b), 6.91 (d, *J* = 9.0 Hz, 2H, MeOPhH_b), 5.93 (dd, *J* = 17.5 and 10.7 Hz, 1H, CH_2=C*H*), 5.76 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.32 (d, *J* = 4.5 Hz, 1H, *H*COBz(*p*-MeO)), 5.03 (d, *J*

= 17.6 Hz, 1H, CH_aH$_b$=CH), 5.02 (s, 1H, *H*COBz(*p*-MeO)), 5.01 (d, *J* = 11.0 Hz, 1H, CH$_a$$H_b$=CH), 4.97 (dd, *J* = 17.5 and 1.1 Hz, 1H, CH_aH$_b$=CH), 4.89 (dd, *J* = 10.8 and 1.1 Hz, 1H, CH$_a$$H_b$=CH), 4.67 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.65 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.53 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.51 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.10-3.96 (m, 1H, *H*COTBDPS), 4.10-3.96 (m, 1H, *H*COTBDPS), 3.87 (s, 3H, PhO*Me*), 3.86 (s, 3H, PhO*Me*), 3.64 (dd, *J* = 10.4 and 4.8 Hz, 1H, CH_aH$_b$OTBDPS), 3.68-3.61 (m, 1H, CH_aH$_b$OTBDPS), 3.61-3.47 (m, 4H, *H*COMe, *H*COMOM, *H*COH, and CH$_a$$H_b$OTBDPS), 3.61-3.47 (m, 4H, *H*COMe, *H*COMOM, *H*COH, and CH$_a$$H_b$OTBDPS), 3.38-3.30 (m, 1H, *H*COMe), 3.36 (ddd, *J* = 9.6, 2.6, and 2.6 Hz, *H*COMe), 3.26 (s, 3H, O*Me*), 3.21 (s, 3H, O*Me*), 3.13 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 3.01 (s, 3H, O*Me*), 2.99 (s, 3H, O*Me*), 2.41 (d, *J* = 8.0 Hz, 1H, O*H*), 2.26 (d, *J* = 8.4 Hz, 1H, O*H*), 1.86-1.77 (m, 2H, CH_2), 1.86-1.77 (m, 2H, CH_2), 1.78-1.69 (m, 1H, CH_aH$_b$), 1.74 (ddd, *J* = 13.7, 9.9, and 3.4 Hz, 1H, CH_aH$_b$), 1.66-1.55 (m, 1H, CH$_a$$H_b$), 1.61 (ddd, *J* = 13.9, 9.2, and 2.7 Hz, 1H, CH$_a$$H_b$), 1.11 (s, 3H, C*Me*), 1.05 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), 1.02 (s, 9H, SiCMe_3), 1.016 (s, 3H, C*Me*), 0.99 (s, 3H,C*Me*), 0.97 (s, 9H, SiCMe_3), and 0.923 (s, 9H, SiCMe_3).

TLC: R_f = 0.54; 3:1 hexanes:ethyl acetate.

(4*S*,5*R*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-11-(methoxymethoxy)-3,3-dimethyldodec-1-ene-4,5-diol **349**



To a culture tube was added LAH powder (80 mg, 1.56 mmol). THF (4.0 mL, 0.4 M) was added then the solution was cooled to 0 ºC. The mixture of alcohols **348-8OH** and **348-9OH** (155 mg, 0.156 mmol) was slowly added as a solution in THF (2.0 mL) and the reaction was stirred for 1 hour, at which time no starting alcohols were visible by TLC. H_2O (0.08 mL), aqueous 15% NaOH (0.08 mL), and H_2O (0.240 mL) were added to the solution at 0 ºC and stirred for 30 minutes upon warming to room temperature. The reaction was filtered through a pad of celite using ethyl acetate and concentrated *in vacuo* to give the crude diol **349**. Purification via flash chromatography (2:1 hexanes / ethyl acetate) provided diol **349** (123 mg, 92%).

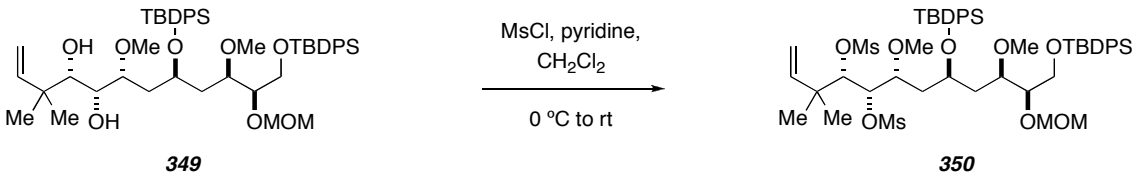
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.60 (m, 8H, Ph*H*), 7.47-7.28 (m, 12H, Ph*H*), 5.84 (dd, *J* = 17.9 and 10.4 Hz, 1H, CH_2=C*H*), 5.02 (dd, *J* = 18.0 and 1.5 Hz, 1H, C$H_a$$H_b$=C*H*), 5.02 (dd, *J* = 10.4 and 1.5 Hz, 1H, CH_aH_b=C*H*), 4.69 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.54 (d, *J* = 6.7 Hz, 1H, OCH_aH_bOMe), 4.10-4.03 (m, 1H, *H*COTBDPS), 3.66 (dd, *J* = 12.8 and 7.6 Hz, 1H, C$H_a$$H_b$OTBDPS), 3.63-3.57 (m, 2H, *H*COMOM and CH_aH_bOTBDPS), 3.50 (dd, *J* = 5.3 and 5.3 Hz, 1H, *H*COH), 3.45 (ddd, *J* = 9.3, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.29 (ddd, *J* = 7,2, 4.5, and 4.5 Hz, 1H, *H*COMe), 3.27 (s, 3H, O*Me*), 3.22 (d, *J* = 5.7 Hz, 1H, *H*COH), 3.16 (s, 3H, O*Me*), 3.05 (s, 3H, O*Me*), 2.76 (d, *J* = 5.6 Hz, 1H, O*H*), 2.41 (d, *J* = 5.9 Hz, 1H, O*H*), 1.80-1.67 (m, 3H, C$H_{a1}$$H_{b1}$ and C$H_{a2}H_{b2}$), 1.64 (ddd, *J* = 14.0, 8.6, and 3.3 Hz, 1H, $CH_{a1}H_{b1}$), 1.04 (s, 9H, SiCMe_3), 1.014 (s, 3H, C*Me*), and 1.010 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.6, 136.2, 136.1, 135.8, 135.7, 134.6, 134.1, 133.57, 133.55, 129.84, 129.8, 129.7, 127.9, 127.8, 127.7, 127.6, 112.9, 97.1, 81.2, 79.2, 77.4, 76.7, 69.6, 69.1, 63.6, 58.3, 57.8, 55.8, 41.6, 38.8, 38.4, 27.3, 27.0, 24.1, 22.5, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{50}H_{72}O_8Si_2Na$ $(M+Na)^+$: 879.4658 Found: 879.4658.

TLC: R_f = 0.65; 2:1 hexanes:ethyl acetate.

(methoxymethoxy)-3,3-dimethyldodec-1-ene-4,5-diyl dimethanesulfonate **350**



349 ***350***

To a culture tube containing diol **349** (123 mg, 0.143 mmol) in CH_2Cl_2 (1.43 mL, 0.1 M) at 0 ºC was added pyridine (0.185 mL, 2.29 mmol) and methane sulfonylchloride (0.133 mL, 1.72 mmol). The reaction mixture was warmed to room temperature and stirred for 48 hours. The solution was recooled to 0 ºC followed by the addition of saturated aqueous $NaHCO_3$ (10 mL). The mixture was then warmed to room temperature and stirred for 1 hour. The solution was again diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided bis-mesylate **350** (127 mg, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70-7.54 (m, 8H, Ph*H*), 7.49-7.17 (m, 12H, Ph*H*), 5.74 (dd, *J* = 17.4 and 10.7 Hz, 1H, CH_2=C*H*), 5.15 (d, *J* = 17.9 Hz, 1H, CH_aH$_b$=C*H*), 5.15 (d, *J* = 10.4 Hz, 1H, CH$_a$$H_b$=C*H*), 4.69 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.61 (dd, *J* = 5.1 and 3.0 Hz, 1H, *H*COMs), 4.54 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 4.53 (d, *J* = 5.0 Hz, 1H, *H*COMs), 4.15-4.08 (m, 1H, *H*COTBDPS), 3.64-3.60 (m, 1H, *H*COMOM), 3.58 (ddd, *J* = 9.7, 2.5, and 2.5 Hz, 1H, *H*COMe), 3.56 (dd, *J* = 10.7 and 4.0 Hz, 1H, CH_aH$_b$OTBDPS), 3.46 (dd, *J* = 10.7 and 7.4 Hz, 1H, CH$_a$$H_b$OTBDPS), 3.31 (ddd, *J* = 10.4, 2.6, and 2.6 Hz, 1H, *H*COMe), 3.26 (s, 3H, *Me*), 3.14 (s, 3H, *Me*), 3.10 (s, 3H, *Me*), 3.09 (s, 3H, *Me*), 3.01 (s, 3H, *Me*), 1.97 (ddd, *J* = 14.5, 9.8, and 2.4 Hz, 1H, CH_{a1}H$_{b1}$), 1.69-1.62 (m, 2H, CH$_{a1}$$H_{b1}$ and CH_{a2}H$_{b2}$), 1.56 (ddd, *J* = 13.9, 9.7, and 2.7 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.13 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 1.023 (s, 9H, SiCMe_3), and 1.016 (s, 9H, SiCMe_3).

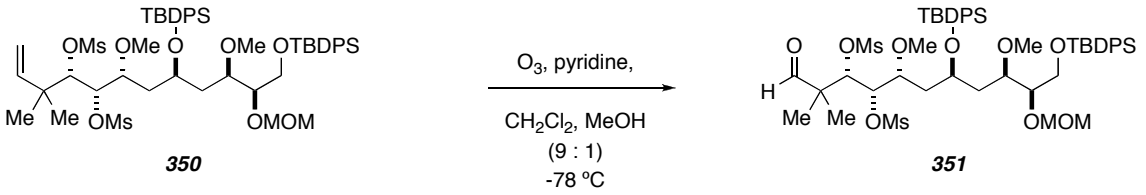
^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.9, 136.1, 136.0, 135.8, 135.7, 134.5, 133.7, 133.6, 129.9, 129.8, 127.84, 127.83, 127.80, 127.6, 116.1, 97.1, 82.6, 79.8, 78.6, 78.5, 77.4,

68.3, 63.6, 59.8, 58.3, 55.8, 41.5, 39.54, 39.50, 39.1, 39.0, 27.2, 27.0, 24.7, 21.8, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{52}H_{76}O_{12}S_2Si_2Na$ $(M+Na)^+$: 1035.4209 Found: 1035.4229.

TLC: $\mathbf{R_f}$ = 0.31; 3:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldiphenylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-1-oxoundecane-3,4-diyl dimethanesulfonate **351**



A 9:1 mixture of CH_2Cl_2:MeOH (3.2 mL, 0.02 M) was added to a culture tube containing alkene **350** (65 mg, 0.064 mmol). This solution was cooled to -78 ºC and pyridine (0.052 mL, 0.64 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the reaction mixture, observed by the change of the solution from a light blue color to colorless. Dimethyl sulfide (5 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6 hours. The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (2:1 hexanes / ethyl acetate) to provide aldehyde **351** (53 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.43 (s, 1H, *H*C=O), 7.71-7.56 (m, 8H, Ph*H*), 7.49-7.19 (m, 12H, Ph*H*), 5.05 (d, *J* = 4.3 Hz, 1H, *H*COMs), 4.81 (dd, *J* = 5.0 and 5.0 Hz, 1H, *H*COMs), 4.69 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.54 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.18-4.10 (m, 1H, *H*COTBDPS), 3.79 (ddd, *J* = 9.0, 5.2 and 2.7 Hz, 1H, *H*COMe), 3.66-3.57 (m, 2H, *H*COMOM and CH_aH$_b$OTBDPS), 3.55-3.48 (m, 1H,

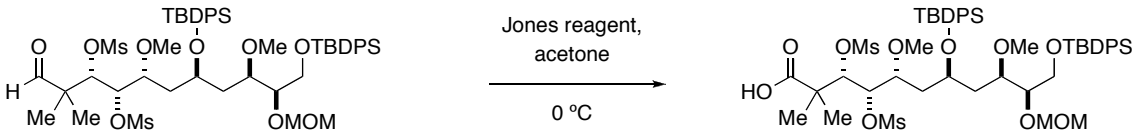
CH_aH_bOTBDPS), 3.43 (ddd, *J* = 10.1, 3.0, and 3.0 Hz, 1H, *H*COMe), 3.26 (s, 3H, *Me*), 3.14 (s, 3H, *Me*), 3.08 (s, 3H, *Me*), 3.05 (s, 3H, *Me*), 3.02 (s, 3H, *Me*), 1.98 (ddd, *J* = 14.5, 9.2, and 3.2 Hz, 1H, $CH_{a1}H_{b1}$), 1.78 (ddd, *J* = 14.6, 8.8, and 2.8 Hz, 1H, $CH_{a1}H_{b1}$), 1.67 (ddd, *J* = 14.0, 10.1, and 3.3 Hz, 1H, $CH_{a2}H_{b2}$), 1.61 (ddd, *J* = 14.1, 9.2, and 3.0 Hz, 1H, $CH_{a2}H_{b2}$), 1.20 (s, 3H, C*Me*), 1.16 (s, 3H, C*Me*), 1.033 (s, 9H, SiCMe_3), and 1.030 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 136.2, 136.1, 135.79, 135.75, 134.4, 133.8, 133.61, 133.59, 129.87, 129.85, 129.83, 129.81, 127.87, 127.85, 127.81, 127.6, 97.1, 79.8, 78.8, 78.5, 77.4, 77.3, 77.2, 68.1, 63.6, 58.3, 58.2, 55.9, 50.2, 39.4, 39.3, 38.7, 37.6, 27.3, 27.0, 19.5, 19.3, 19.2, and 19.1.

HR ESI-MS: Calcd for $C_{51}H_{74}O_{13}S_2Si_2Na$ $(M+Na)^+$: 1037.4002 Found: 1037.4016.

TLC: R_f = 0.41; 2:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldiphenylsilyloxy)-5,9-dimethoxy-10-(methoxymethoxy)-2,2-dimethyl-3,4-bis(methylsulfonyloxy)undecanoic acid **352**



351 ***352***

To a culture tube containing aldehyde **351** (53 mg, 0.052 mmol) in acetone (2.6 mL, 0.02 M) at 0 ºC. Jones reagent (0.042 mL, 0.104 mmol, ~2.5 M solution) was added to the reaction mixture followed by stirring for 30 minutes, at which time no starting aldehyde **351** was observed by TLC. Isopropanol was added at 0 ºC to quench the excess Jones reagent followed by warming to room temperature. The reaction mixture was filtered through celite with CH_2Cl_2 followed by ethyl acetate and the resulting solution was concentrated *in vacuo*. The crude product **352** was carried on to the next step without purification.

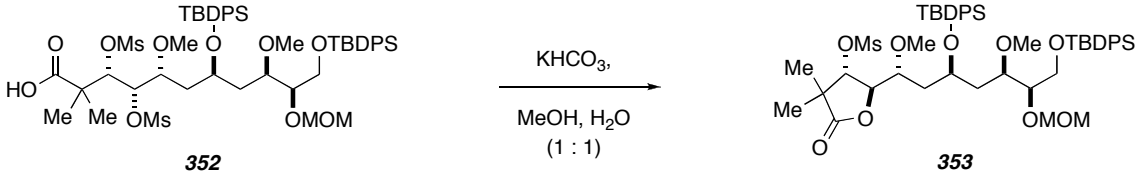
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71-7.60 (m, 8H, Ph*H*), 7.48-7.26 (m, 12H, Ph*H*), 5.05 (d, *J* = 5.3 Hz, 1H, *H*COMs), 4.83 (d, *J* = 6.6 Hz, 1H, OC$H_a$$H_b$OMe), 4.63 (d, *J* = 6.6 Hz, 1H, OC$H_a$$H_b$OMe), 4.57 (dd, *J* = 5.3 and 2.8 Hz, 1H, *H*COMs), 4.12-4.05 (m, 1H, *H*COTBDPS), 3.72 (ddd, *J* = 7.2, 5.1, and 2.8 Hz, 1H, *H*COMOM), 3.69-3.63 (m, 2H, CH_2OTBDPS), 3.59 (ddd, *J* = 5.9, 5.9, and 3.0 Hz, 1H, *H*COMe), 3.36 (s, 3H, *Me*), 3.33 (ddd, *J* = 9.0, 3.2, and 3.2 Hz, 1H, *H*COMe), 3.30 (s, 3H, *Me*), 3.17 (s, 3H, *Me*), 3.06 (s, 3H, *Me*), 2.93 (s, 3H, *Me*), 2.00 (ddd, *J* = 14.6, 6.4, and 5.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.84 (ddd, *J* = 14.8, 5.4, and 5.4 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.68 (ddd, *J* = 14.6, 9.2, and 4.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.62 (ddd, *J* = 14.2, 8.9, and 3.5 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.40 (s, 3H, C*Me*), 1.28 (s, 3H, C*Me*), and 1.03 (s, 18H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.0, 136.2, 136.1, 135.8, 134.2, 134.0, 133.4, 129.9, 127.9, 127.8, 127.7, 114.6, 105.0, 97.1, 80.8, 79.6, 79.2, 78.0, 68.3, 64.0, 60.6, 58.9, 58.4, 55.9, 46.9, 39.3, 39.1, 38.2, 37.6, 27.3, 27.0, 24.0, 21.3, 19.6, 19.5, 19.3, and 14.4.

HR ESI-MS: Calcd for $C_{51}H_{74}O_{14}S_2Si_2Na$ $(M+Na)^+$: 1053.3951 Found: 1053.3944.

TLC: R_f = 0.47; 1:3 hexanes:ethyl acetate.

(2*R*,3*S*)-2-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldiphenylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4,4-dimethyl-5-oxotetrahydrofuran-3-yl methanesulfonate **353**



To a culture tube containing acid **352** (53 mg, 0.052 mmol) was added MeOH (1.3 mL) followed by the slow addition of H_2O (1.3 mL) with vigorous stirring. Solid $KHCO_3$ (104 mg, 1.04 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (2:1

hexanes / ethyl acetate) provided lactone **353** (47 mg, 96%, 2-steps).

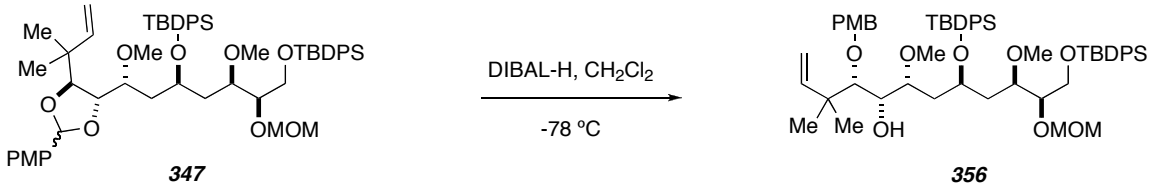
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72-7.59 (m, 8H, Ph*H*), 7.48-7.23 (m, 12H, Ph*H*), 5.04 (d, *J* = 5.7 Hz, 1H, *H*COMs), 4.73 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.59 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.14-4.07 (m, 1H, *H*COTBDPS), 4.11 (dd, *J* = 5.6 and 3.0 Hz, 1H, *H*COC=O), 3.70-3.55 (m, 4H, *H*COMe, *H*COMOM, and CH_2OTBDPS), 3.38 (ddd, *J* = 9.0, 3.4, and 3.4 Hz, 1H, *H*COMe), 3.30 (s, 3H, *Me*), 3.16 (s, 3H, *Me*), 3.00 (s, 3H, *Me*), 2.94 (s, 3H, *Me*), 1.77 (ddd, *J* = 14.4, 9.2, and 2.7 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.71 (ddd, *J* = 13.9, 8.7, and 3.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.67 (ddd, *J* = 13.9, 8.2, and 3.4 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.56 (ddd, *J* = 14.4, 8.7, and 2.8 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.34 (s, 3H, C*Me*), 1.26 (s, 3H, C*Me*), 1.034 (s, 9H, SiCMe_3), and 1.030 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4, 136.2, 136.1, 135.80, 135.76, 134.2, 133.8, 133.58, 133.56, 129.99, 129.91, 129.90, 127.90, 127.87, 127.7, 97.1, 82.7, 80.9, 78.9, 77.4, 77.0, 68.7, 63.8, 59.7, 58.4, 55.9, 43.6, 39.1, 39.0, 38.7, 27.2, 27.0, 23.1, 20.5, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{50}H_{70}O_{11}SSi_2Na$ $(M+Na)^+$: 973.3809 Found: 973.3822.

TLC: R_f = 0.47; 2:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **356**



Note: (2 reactions were run simultaneously with equal amounts of the reagents and combined for workup procedures.) To a large culture tube containing bis-TBDPS-ether **347** (700 mg, 0.718 mmol) was added CH_2Cl_2 (6.5 mL, 0.11 M). The reaction mixture was cooled to -78 ºC followed by the addition of DIBAL-H (6.5 mL, 7.15 mmol,

1.1 M in toluene). The reaction solution was kept at -78 ºC for 48 hours. Keeping both of the reactions at -78 ºC, ethyl acetate (6.5 mL) was added dropwise down the side of each culture tube to quench the excess DIBAL-H. Both of the reaction mixtures were then transferred to a 250 mL Erlenmeyer flask equipped with a stir bar using ethyl acetate and warmed to room temperature. Small portions of saturated aqueous Rochelle's salt (Na,K-Tartrate) were added and the reaction was monitored closely for exotherm and cooled if necessary. Upon this addition, the reaction will go from homogeneous to a gelatinous solution, and upon addition of more saturated aqueous Rochelle's salt, back to homogeneous. The two-phase solution in the Erlynmeyer flask was then usually allowed to stir for an additional 18 hours. The reaction is done when both the aqueous and the organic layers are homogeneous and clear. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided the alcohol **356** (1.33 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75-7.60 (m, 8H, Ph*H*), 7.46-7.20 (m, 14H, Ph*H* and MeOPhH_a), 6.86 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 5.77 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 4.96 (dd, *J* = 17.5 and 1.2 Hz, 1H, CH_aH$_b$=CH), 4.95 (dd, *J* = 10.8 and 1.3 Hz, 1H, CH$_a$$H_b$=CH), 4.69 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.55 (d, *J* = 10.4 Hz, 1H, MeOPhCH_aH$_b$), 4.54 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.43 (d, *J* = 10.4 Hz, 1H, MeOPhCH$_a$$H_b$), 4.17-4.08 (m, 1H, *H*COTBDPS), 3.81 (s, 3H, PhO*Me*), 3.69-3.56 (m, 3H, *H*COMOM, CH_2OTBDPS), 3.48 (ddd, *J* = 9.8, 2.9, and 2.9 Hz, 1H, *H*COMe), 3.46 (ddd, *J* = 6.7, 4.5, and 2.1 Hz, 1H, *H*COH), 3.25 (s, 3H, O*Me*), 3.22 (ddd, *J* = 6.0, 6.0, and 4.3 Hz, 1H, *H*COMe), 3.17 (s, 3H, O*Me*), 3.15 (s, 3H, O*Me*), 3.12 (d, *J* = 1.9 Hz, *H*COPMB), 2.84 (d, *J* = 7.0 Hz, 1H, O*H*), 1.78 (appt. t, *J* = 5.9 Hz, 2H, C$H_{a1}H_{b1}$), 1.70 (ddd, *J* = 13.8, 9.3, and 3.7 Hz, 1H, CH_{a2}H$_{b2}$), 1.63 (ddd, *J* = 14.2, 8.5, and 3.2 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.032 (s, 9H, SiC$Me_3$), 1.030 (s, 9H, SiC$Me_3$), 1.02 (s, 3H, C*Me*), and 0.99 (s, 3H, C*Me*).

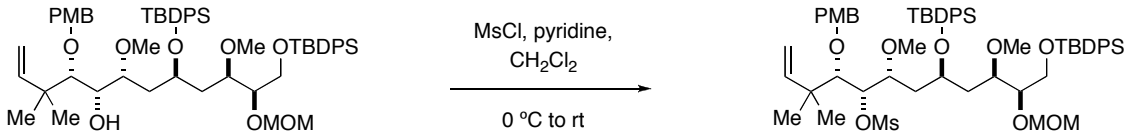
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 145.3, 136.3, 136.1, 135.79, 135.74, 134.7, 134.1, 133.6, 133.58, 130.5, 129.9, 129.8, 129.70, 129.69, 129.4, 127.88, 127.87, 127.7,

127.6, 113.9, 112.9, 97.0, 83.5, 80.5, 79.0, 77.3, 74.5, 70.2, 69.2, 63.7, 58.4, 58.1, 55.8, 55.5, 42.7, 38.7, 37.9, 27.3, 27.0, 24.6, 21.5, 19.6, and 19.3.

HR ESI-MS: Calcd for $C_{58}H_{80}O_9Si_2Na$ $(M+Na)^+$: 999.5233 Found: 999.5252.

TLC: $\mathbf{R_f}$ = 0.52; 3:1 hexanes:ethyl acetate.

(4*S*,5*S*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-yl methanesulfonate **357**



356 ***357***

To a 100 mL round bottom flask containing alcohol **356** (1.28 g, 1.30 mmol) in CH_2Cl_2 (18.6 mL, 0.07 M) at 0 ºC was added pyridine (2.95 mL, 36.5 mmol) and methane sulfonylchloride (2.43 mL, 31.3 mmol). The reaction mixture was warmed to room temperature and stirred for 48 hours. The solution was recooled to 0 ºC followed by the addition of saturated aqueous $NaHCO_3$ (40 mL). The mixture was then warmed to room temperature and stirred for 1 hour. The solution was again diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 125 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided mesylate **357** (1.29 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70-7.55 (m, 8H, Ph*H*), 7.47-7.15 (m, 14H, Ph*H* and MeOPhH_a), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.81 (dd, *J* = 17.5 and 10.7 Hz, 1H, CH_2=C*H*), 5.05 (d, *J* = 17.6 Hz, 1H, CH_aH$_b$=C*H*), 5.03 (d, *J* = 10.8 Hz, 1H, CH$_a$$H_b$=C*H*), 4.71 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.67 (d, *J* = 10.8 Hz, 1H, MeOPhCH_aH$_b$), 4.56 (dd, *J* = 6.2 and 2.6 Hz, 1H, *H*COMs), 4.53 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.39 (d, *J* = 10.9 Hz, 1H, MeOPhCH$_a$$H_b$), 4.15 (dddd, *J* = 9.4, 9.4, 2.6, and 2.6 Hz, 1H,

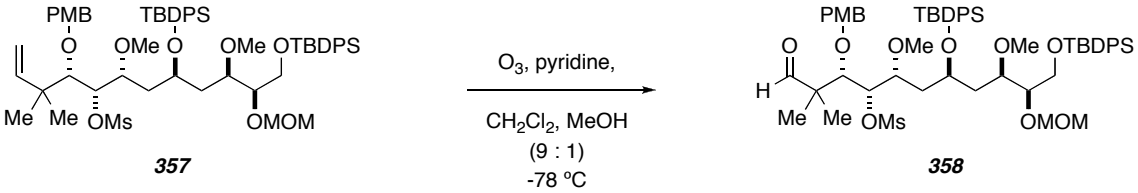
*H*COTBDPS), 3.80 (s, 3H, PhO*Me*), 3.65 (ddd, *J* = 10.1, 2.5, and 2.5 Hz, 1H, *H*COMe), 3.64-3.60 (m, 1H, *H*COMOM), 3.53 (dd, *J* = 10.8 and 3.9 Hz, 1H, C$H_a$$H_b$OTBDPS), 3.43 (dd, *J* = 10.8 and 7.7 Hz, 1H, C$H_a$$H_b$OTBDPS), 3.37 (d, *J* = 6.2 Hz, 1H, *H*COPMB), 3.29 (ddd, *J* = 9.8, 2.9, and 2.9 Hz, 1H, *H*COMe), 3.27 (s, 3H, O*Me*), 3.22 (s, 3H, O*Me*), 3.10 (s, 3H, O*Me*), 2.81 (s, 3H, SO_2*Me*), 2.04 (ddd, *J* = 14.6, 10.0, and 2.3 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.68 (ddd, *J* = 14.5, 9.7, and 2.3 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.61 (ddd, *J* = 13.9, 10.2, and 3.4 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.55 (ddd, *J* = 13.7, 9.4, and 2.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.07 (s, 3H, C*Me*), 1.04 (s, 3H, C*Me*), 1.019 (s, 9H, SiCMe_3), and 1.016 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 144.1, 136.2, 136.1, 135.80, 135.77, 134.7, 133.9, 133.7, 130.5, 129.78, 129.75, 129.7, 129.6, 127.8, 127.7, 127.5, 114.0, 113.8, 97.2, 84.4, 81.5, 78.6, 77.9, 77.6, 74.1, 68.6, 63.7, 59.3, 58.3, 55.9, 55.4, 41.9, 39.8, 39.1, 27.3, 27.0, 25.1, 22.0, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{59}H_{82}O_{11}SSi_2Na$ $(M+Na)^+$: 1077.5075 Found: 1077.5075.

TLC: R_f = 0.48; 3:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldiphenylsilyloxy)-5,9-dimethoxy-3-(4-methoxybenzyloxy)-10-(methoxymethoxy)-2,2-dimethyl-1-oxoundecan-4-yl methanesulfonate **358**



A 9:1 mixture of CH_2Cl_2:MeOH (30.7 mL, 0.02 M) was added to a 100 mL round bottom flask containing alkene **357** (647 mg, 0.613 mmol). This solution was cooled to -78 ºC and pyridine (0.496 mL, 6.13 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the

reaction mixture, observed by the change of the solution from a light blue color to colorless. Dimethyl sulfide (8 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6-8 hours. The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (2:1 hexanes / ethyl acetate) to provide aldehyde **358** (564 mg, 87%).

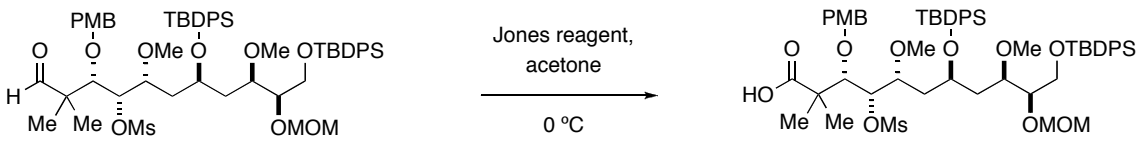
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.44 (s, 1H, *H*C=O), 7.74-7.56 (m, 8H, Ph*H*), 7.48-7.15 (m, 14H, Ph*H* and MeOPhH_a), 6.84 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.70 (dd, *J* = 4.9 and 4.9 Hz, 1H, *H*COMs), 4.68 (d, *J* = 6.9 Hz, 1H, OCH_aH$_b$OMe), 4.61 (d, *J* = 10.9 Hz, 1H, MeOPhCH_aH$_b$), 4.53 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.38 (d, *J* = 10.9 Hz, 1H, MeOPhCH$_a$$H_b$), 4.14 (dddd, *J* = 9.3, 9.3, 3.6, and 3.6 Hz, 1H, *H*COTBDPS), 3.81 (d, *J* = 5.4 Hz, 1H, *H*COPMB), 3.79 (s, 3H, PhO*Me*), 3.69 (ddd, *J* = 9.7, 4.3, and 2.2 Hz, 1H, *H*COMe), 3.63-3.48 (m, 3H, *H*COMOM, and CH_2OTBDPS), 3.37 (ddd, *J* = 9.9, 3.0, and 3.0 Hz, 1H, *H*COMe), 3.26 (s, 3H, O*Me*), 3.12 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 2.86 (s, 3H, SO_2*Me*), 1.96 (ddd, *J* = 14.5, 9.7, and 2.9 Hz, 1H, CH_{a1}H$_{b1}$), 1.82 (ddd, *J* = 14.6, 8.9, and 2.2 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.68 (ddd, *J* = 13.8, 9.9, and 3.5 Hz, 1H, CH_{a2}H$_{b2}$), 1.61 (ddd, *J* = 13.9, 9.2, and 3.2 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.15 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), 1.01 (s, 9H, SiCMe_3), and 0.99 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.3, 159.4, 136.2, 136.1, 135.8, 135.7, 134.4, 133.9, 133.61, 133.59, 129.83, 129.81, 129.80, 129.78, 129.5, 127.9, 127.85 127.77, 127.6, 113.9, 97.1, 82.2, 79.1, 78.8, 77.4, 77.3, 74.4, 68.6, 63.6, 58.5, 58.2, 55.8, 55.4, 50.4, 39.2, 39.0, 38.95, 27.3, 27.0, 19.7, 19.5, 19.3, and 18.4.

HR ESI-MS: Calcd for $C_{58}H_{80}O_{12}SSi_2Na$ $(M+Na)^+$: 1079.4801 Found: 1079.4935.

TLC: R_f = 0.59; 2:1 hexanes:ethyl acetate.

(3*S*,4*S*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldiphenylsilyloxy)-5,9-dimethoxy-3-(4-methoxybenzyloxy)-10-(methoxymethoxy)-2,2-dimethyl-4-(methylsulfonyloxy)undecanoic acid **355**



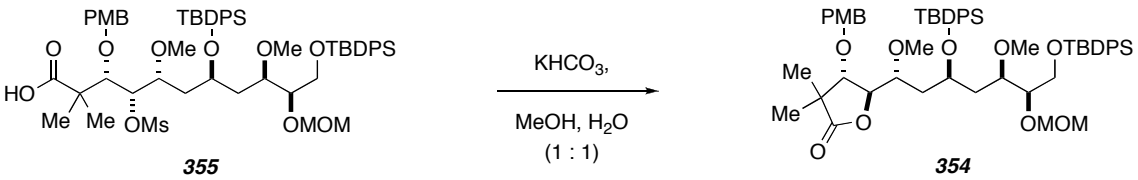
358 ***355***

To a 100 mL round bottom flask containing aldehyde **358** (683 mg, 0.646 mmol) in acetone (32.5 mL, 0.02 M) at 0 ºC. Jones reagent (0.775 mL, 1.94 mmol, ~2.5 M solution) was added to the reaction mixture followed by stirring for 33 minutes, at which time no starting aldehyde **358** was observed by TLC. Isopropanol was added at 0 ºC to quench the excess Jones reagent followed by warming to room temperature. The reaction mixture was filtered through celite with CH_2Cl_2 followed by ethyl acetate and the resulting solution was concentrated *in vacuo*. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71-7.60 (m, 8H, Ph*H*), 7.49-7.20 (m, 14H, Ph*H* and MeOPhH_a), 6.86 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 4.77 (d, *J* = 10.6 Hz, 1H, MeOPhCH_aH$_b$), 4.73 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OMe), 4.71 (dd, *J* = 4.5 and 4.5 Hz, 1H, *H*COMs), 4.56 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 4.46 (d, *J* = 10.6 Hz, 1H, MeOPhCH$_a$$H_b$), 4.16-4.10 (m, 1H, *H*COTBDPS), 3.83 (d, *J* = 4.8 Hz, 1H, *H*COPMB), 3.79 (s, 3H, PhO*Me*), 3.72 (ddd, *J* = 7.8, 3.5, and 3.5 Hz, 1H, *H*COMe), 3.65-3.54 (m, 3H, *H*COMOM and CH_2OTBDPS), 3.38 (ddd, *J* = 9.1, 3.7, and 3.7 Hz, 1H, *H*COMe), 3.29 (s, 3H, O*Me*), 3.23 (s, 3H, O*Me*), 3.09 (s, 3H, O*Me*), 2.84 (s, 3H, SO_2*Me*), 2.02 (ddd, *J* = 14.2, 8.2, and 4.1 Hz, 1H, CH_{a1}H$_{b1}$), 1.93 (ddd, *J* = 14.8, 7.5, and 3.6 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.74-1.54 (m, 2H, C$H_{a2}$$H_{b2}$), 1.25 (s, 3H, C*Me*), 1.23 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 1.02 (s, 9H, SiCMe_3).

TLC: R_f = 0.28; 3:1 hexanes:ethyl acetate.

(4*S*,5*R*)-5-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldiphenylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4-(4-methoxybenzyloxy)-3,3-dimethyldihydrofuran-2(3*H*)-one **354**



To a 100 mL round bottom flask containing crude acid **355** (~.646 mmol) was added MeOH (16.5 mL) followed by the slow addition of H_2O (16.5 mL) with vigorous stirring. Solid $KHCO_3$ (1.29 g, 12.9 mmol) was added and the reaction mixture was stirred at room temperature for 24 hours. The mixture was diluted with $CHCl_3$ and H_2O. The aqueous layer was extracted with $CHCl_3$ (3 x 75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided lactone **354** (591 mg, 94%, 2-steps).

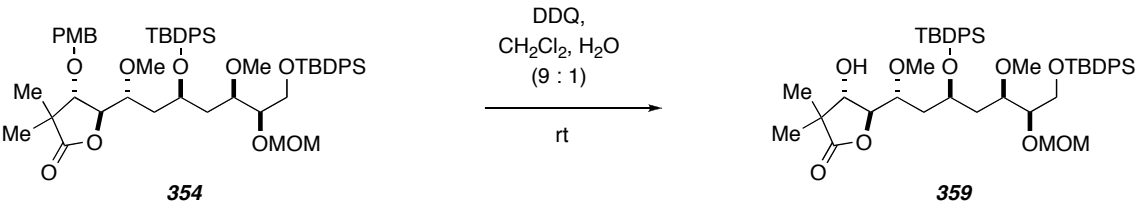
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74-7.57 (m, 8H, Ph*H*), 7.48-7.21 (m, 12H, Ph*H*), 7.17 (d, *J* = 8.4 Hz, 2H, MeOPhH_a), 6.86 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 4.69 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.54 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.39 (d, *J* = 10.8 Hz, 1H, MeOPhCH_aH$_b$), 4.34 (d, *J* = 10.8 Hz, 1H, MeOPhCH$_a$$H_b$), 4.15-4.09 (m, 1H, *H*COTBDPS), 4.08 (dd, *J* = 7.1 and 2.2 Hz, 1H, *H*COC=O), 3.91 (d, *J* = 7.0 Hz, 1H *H*COPMB), 3.80 (s, 3H, PhO*Me*), 3.68-3.56 (m, 4H, *H*COMe, *H*COMOM, and CH_2-OTBDPS), 3.39 (ddd, *J* = 9.7, 2.0, and 2.0 Hz, 1H, *H*COMe), 3.25 (s, 3H, O*Me*), 3.14 (s, 3H, O*Me*), 2.99 (s, 3H, O*Me*), 1.78 (ddd, *J* = 13.7, 9.8, and 3.4 Hz, 1H, CH_{a1}H$_{b1}$), 1.74-1.59 (m, 3H, CH$_{a1}$$H_{b1}$ and C$H_{a2}$$H_{b2}$), 1.25 (s, 3H, C*Me*), 1.21 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.2, 159.6, 136.2, 136.1, 135.8, 135.7, 134.3, 133.9, 133.6, 133.5, 129.88, 129.85, 129.81, 129.7, 129.5, 127.89, 127.87, 127.83, 127.6, 114.1, 97.0, 83.2, 82.3, 79.1, 73.0, 69.0, 63.6, 59.2, 58.6, 55.8, 55.5, 43.9, 39.5, 38.9, 27.2, 27.0, 24.6, 19.7, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{57}H_{76}O_{10}Si_2Na$ $(M+Na)^+$: 999.4869 Found: 999.4925.

TLC: R_f = 0.48; 3:1 hexanes:ethyl acetate.

(4*S*,5*S*)-5-((1*R*,3*S*,5*R*,6*R*)-3,7-Bis(*tert*-butyldiphenylsilyloxy)-1,5-dimethoxy-6-(methoxymethoxy)heptyl)-4-hydroxy-3,3-dimethyldihydrofuran-2(3*H*)-one **359**



354 ***359***

To a culture tube containing lactone **354** (4 mg, 0.0041 mmol) in CH_2Cl_2:H_2O (0.270 mL:0.020 mL) at 0 ºC was added DDQ (4 mg, 0.018 mmol). The solution was warmed to room temperature and stirred for 1.5 hours. Saturated aqueous $NaHCO_3$ was added to the reaction mixture followed by dilution with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided alcohol **359** (3 mg, 75%).

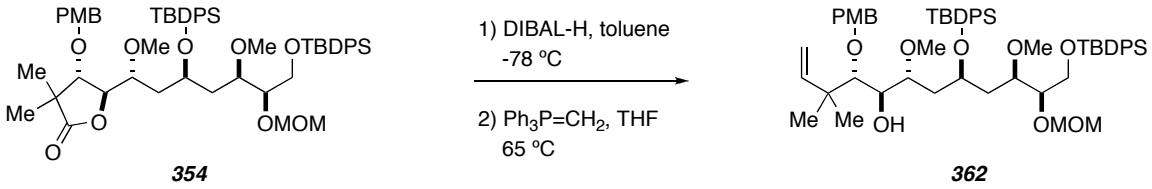
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75-7.61 (m, 8H, Ph*H*), 7.49-7.24 (m, 12H, Ph*H*), 4.71 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.60 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.15-4.06 (m, 1H, *H*COTBDPS), 3.96 (dd, *J* = 7.7 and 4.9 Hz, 1H, *H*COC=O), 3.83 (dd, *J* = 7.7 and 3.6 Hz, 1H *H*COH), 3.73-3.60 (m, 3H, *H*COMOM and CH_2OTBDPS), 3.53 (ddd, *J* = 7.6, 3.6, and 3.6 Hz, 1H, *H*COMe), 3.47-3.60 (m, 1H, *H*COMe), 3.30 (s, 3H, O*Me*), 3.16 (s, 3H, O*Me*), 3.05 (s, 3H, O*Me*), 1.84 (ddd, *J* = 14.5, 8.9, and 3.6 Hz, 1H, CH_{a1}H$_{b1}$), 1.77-1.71 (m, 2H, C$H_{a2}H_{b2}$), 1.62 (ddd, *J* = 14.4, 7.9, and 3.6 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.21 (s, 3H, C*Me*), 1.12 (s, 3H, C*Me*), 1.042 (s, 9H, SiCMe_3), and 1.036 (s, 9H, SiCMe_3).

HR ESI-MS: Calcd for $C_{49}H_{68}O_9Si_2Na$ $(M+Na)^+$: 879.4294 Found: 879.4309.

TLC: R_f = 0.27; 3:1 hexanes:ethyl acetate.

(4*S*,5*R*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-

methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **362**



354 ***362***

Lactol Formation

To a large culture tube containing lactone **354** (591 mg, 0.605 mmol) in toluene (6.1 mL, 0.1M) at -78 ºC was added DIBAL-H (0.825 mL, 0.907 mmol, 1.1 M in toluene) slowly down the side of the culture tube. The solution was stirred at -78 ºC for 15 minutes. Ethyl acetate (1 mL) was slowly added down the side of the tube to quench any excess DIBAL-H. The reaction mixture were then transferred to a 125 mL Erlenmeyer flask equipped with a stir bar using ethyl acetate and warmed to room temperature. Small portions of saturated aqueous Rochelle's salt (Na,K-Tartrate) were added and the reaction was monitored closely for exotherm and cooled if necessary. Upon this addition, the reaction will go from homogeneous to a gelatinous solution, and upon addition of more saturated aqueous Rochelle's salt, back to homogeneous. The two-phase solution in the Erlynmeyer flask was then usually allowed to stir for an additional 18 hours. The reaction is done when both the aqueous and the organic layers are homogeneous and clear. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes / ethyl acetate) provided the lactol **361** (491 mg, 83%).

Wittig Olefination

To a large culture tube containing methyltriphenylphosphonium bromide (896 mg, 2.51 mmol) suspended in THF (2.8 mL, 0.9 M) at 0 ºC was added *n*-BuLi (1.2 mL, 2.56 mmol, 2.13 M in hexanes) dropwise to the reaction mixture. The solution was warmed to room termperature and stirred for 1 hour. A solution of the lactol **361** (491 mg, 0.501 mmol) in THF (7 mL) was added to the ylide solution. The yellow suspension was heated to 65 ºC for 18 hours, cooled to room temperature and quenched with saturated aqueous NH_4Cl. The mixture was diluted with Et_2O and the aqueous layer was

extracted with Et_2O (3 x 75 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to provide the crude alkene **362**. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70-7.58 (m, 8H, Ph*H*), 7.46-7.16 (m, 14H, Ph*H* and MeOPhH_a), 6.81 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.05 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.03 (dd, *J* = 17.6 and 1.3 Hz, 1H, CH_aH$_b$=CH), 4.98 (dd, *J* = 10.8 and 1.3 Hz, 1H, CH$_a$$H_b$=CH), 4.64 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.64 (d, *J* = 10.9 Hz, 1H, MeOPhCH_aH$_b$), 4.50 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.40 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.28-4.21 (m, 1H, *H*COTBDPS), 3.98 (ddd, *J* = 7.1, 2.4, and 2.4 Hz, 1H, *H*COH), 3.77 (s, 3H, PhO*Me*), 3.70 (ddd, *J* = 10.6, 2.4, and 2.4 Hz, 1H, *H*COMe), 3.60 (dd, *J* = 12.9 and 7.5 Hz, 1H, CH_aH$_b$OTBDPS), 3.56-3.51 (m, 2H, CH$_a$$H_b$OTBDPS and *H*COMOM), 3.35 (ddd, *J* = 9.6, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.22 (s, 3H, O*Me*), 3.15 (d, *J* = 7.2 Hz, 1H, *H*COPMB), 3.10 (s, 3H, O*Me*), 3.06 (s, 3H, O*Me*), 2.00 (d, *J* = 2.4 Hz, 1H, O*H*), 1.95 (ddd, *J* = 14.2, 10.6, and 3.0 Hz, 1H, CH_{a1}H$_{b1}$), 1.79 (ddd, *J* = 14.7, 9.0, and 2.4 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.70 (ddd, *J* = 13.7, 9.5, and 3.6 Hz, 1H, CH_{a2}H$_{b2}$), 1.59 (ddd, *J* = 13.8, 9.4, and 3.2 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.12 (s, 3H, C*Me*), 1.11 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 0.97 (s, 9H, SiCMe_3).

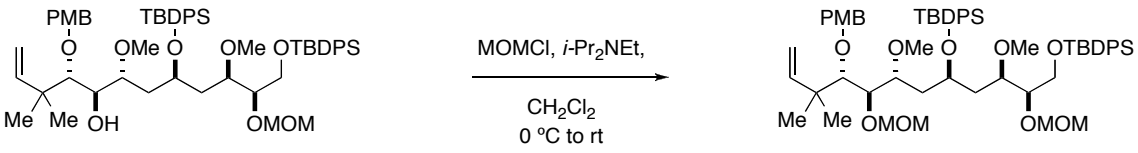
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 146.5, 136.2, 136.1, 135.8, 135.7, 134.9, 134.3, 133.63, 133.57, 131.0, 129.8, 129.60, 129.56, 128.7, 127.8, 127,6, 127.5, 113.7, 111.5, 97.1, 85.7, 79.6, 78.5, 77.5, 74.6, 71.6, 68.9, 63.7, 58.4, 56.5, 55.8, 55.4, 42.4, 39.9, 36.4, 27.3, 27.0, 25.5, 22.9, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{58}H_{80}O_9Si_2Na$ $(M+Na)^+$: 999.5233 Found: 999.5227.

TLC: R_f = 0.23; 6:1 hexanes:ethyl acetate (eluted 2 x).

[α]^{RT} = +18.5 (c = 0.55, $CDCl_3$).

(5*R*,6*R*,8*S*,10*R*,11*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6,10-dimethoxy-5-((*S*)-1-(4-methoxybenzyloxy)-2,2-dimethylbut-3-enyl)-11-(methoxymethoxy)-15,15-dimethyl-14,14-diphenyl-2,4,13-trioxa-14-silahexadecane **363**



362 ***363***

To 25 mL round bottom containing crude alcohol **362** (0.501 mmol) was added CH_2Cl_2 (2.5 mL, 0.2 M) and *i*Pr_2NEt (2.45 mL, 15.0 mmol). Upon cooling the solution to 0 ºC, MOMCl (1.69 mL, 10.0 mmol; from a prepared solution containing 45% MOMCl : 55% methyl acetate and dimethoxymethane) was added dropwise and the reaction was warmed to room temperature and stirred until no starting alcohol was observed by TLC. After recooling to 0 ºC, saturated aqueous $NaHCO_3$ (15 mL) was then added followed by dilution with H_2O (10 mL). The reaction was warmed to room temperature and stirred for 15 minutes. The aqueous layer was extracted with EtOAc (3 x 75 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided MOM-ether **363** (468 mg, 91%, 2-steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71-7.54 (m, 8H, Ph*H*), 7.46- 7.16 (m, 14H, Ph*H* and MeOPhH_a), 6.82 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.02 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.01 (dd, *J* = 17.6 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 4.98 (dd, *J* = 10.8 and 1.4 Hz, 1H, $CH_a$$H_b$=CH), 4.76 (d, *J* = 10.9 Hz, 1H, MeOPhC$H_a$$H_b$), 4.68 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.60 (d, *J* = 6.4 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.56 (d, *J* = 6.8 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.44 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.40 (d, *J* = 10.9 Hz, 1H, MeOPhC$H_a$$H_b$), 4.27 (dddd, *J* = 9.8, 9.8, 2.8, and 2.8 Hz, 1H, *H*COTBDPS), 4.02 (dd, *J* = 1.5 and 1.5 Hz, 1H, *H*COMOM), 3.82 (ddd, *J* = 9.6, 1.7, and 1.7 Hz, 1H, *H*COMe), 3.77 (s, 3H, PhO*Me*), 3.57 (dd, *J* = 9.3 and 4.1 Hz, 1H, C$H_a$$H_b$OTBDPS), 3.51-3.4 (m, 2H, *H*COMe and C$H_a$$H_b$OTBDPS),), 3.36 (s, 3H, O*Me*), 3.32 (d, *J* = 2.3 Hz, 1H, *H*COPMB),

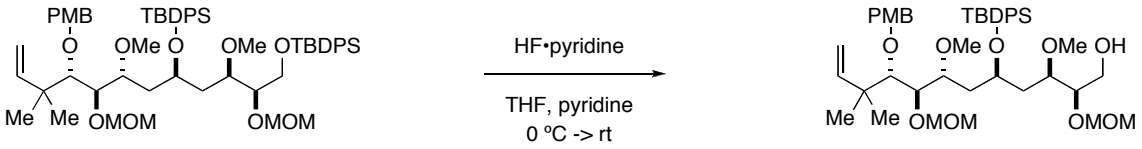
3.30 (ddd, *J* = 10.4, 2.4, and 2.4 Hz, 1H, *H*COMe), 3.17 (s, 3H, O*Me*), 3.10 (s, 3H, O*Me*), 3.03 (s, 3H, O*Me*), 1.97 (ddd, *J* = 14.7, 10.5, and 2.5 Hz, 1H, $CH_{a1}H_{b1}$), 1.90 (ddd, *J* = 14.4, 9.4, and 2.5 Hz, 1H, $CH_{a1}H_{b1}$), 1.66 (ddd, *J* = 13.5, 10.0, and 3.3 Hz, 1H, $CH_{a2}H_{b2}$), 1.42 (ddd, *J* = 13.2, 10.1, and 2.4 Hz, 1H, $CH_{a2}H_{b2}$), 1.11 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3), and 0.99 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 145.6, 136.24, 136.16, 135.8, 135.7, 135.4, 133.68, 133.65, 131.2, 129.82, 129.8,129.5, 129.4, 129.3, 127,9, 127.8, 127.5, 127.3, 113.7, 111.9, 97.1, 96.7, 88.6, 79.6, 78.8, 77.5, 77.1, 75.1, 68.8, 63.4, 58.7, 56.6, 55.8, 55.7, 55.4, 42.1, 40.5, 37.9, 27.3, 27.1, 25.4, 24.2, 19.5, and 19.3.

HR ESI-MS: Calcd for $C_{60}H_{84}O_{10}Si_2Na$ $(M+Na)^+$: 1043.5495 Found: 1043.5455.

TLC: R_f = 0.41; 3:1 hexanes:ethyl acetate.

(2*R*,3*R*,5*S*,7*R*,8*R*,9*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyldodec-11-en-1-ol **364**



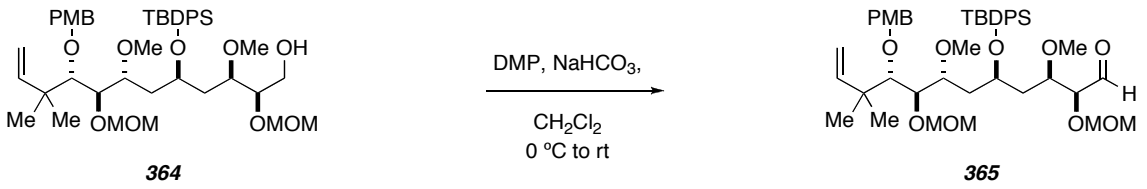
363 ***364***

Note: (2 reactions were run simultaneously with equal amounts of the reagents and combined for workup procedures.) To a plastic culture tube containing **363** (168 mg, 0.164 mmol) was added THF (5.1 mL, 0.032M) and pyridine (5.1 mL, 0.032M). The reaction was cooled to 0 ºC and HF•pyridine (1.0 mL of a 70% HF / 30% pyridine solution) was added dropwise. The reaction was stirred at room temperature for 5.5 hours at which time TLC showed completion of both reactions. Both of the reaction mixtures were diluted with EtOAc (~150 mL total) and transferred to a 500 mL Erlenmeyer flask. Saturated aqueous $NaHCO_3$ (~180 mL) was slowly added to the mixture until no evolution of gas was observed. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with H_2O (1 x 100 mL), saturated $CuSO_4$

(2 x 100 mL), and saturated NaCl (1 x 100 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (1:2 hexanes / ethyl acetate) to provide the primary alcohol **364** (231 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.3 Hz, 2H, Ph*H*), 7.65 (d, *J* = 7.3 Hz, 2H, Ph*H*), 7.42-7.26 (m, 8H, Ph*H* and MeOPhH_a), 6.84 (d, *J* = 8.4 Hz, 2H, MeOPhH_b), 6.01 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.01 (dd, *J* = 17.6 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 4.98 (dd, *J* = 10.8 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.68 (d, *J* = 10.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.67 (d, *J* = 6.6 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.63 (d, *J* = 6.4 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.52 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.40 (d, *J* = 10.8 Hz, 1H, MeOPhC$H_a$$H_b$), 4.39 (d, *J* = 6.8 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.17 (dddd, *J* = 8.2, 8.2, 4.0, and 4.0 Hz, 1H, *H*COTBDPS), 3.79 (s, 3H, PhO*Me*), 3.99 (dd, *J* = 2.9 and 1.2 Hz, 1H, *H*COMOM), 3.82-3.75 (m, 1H, *H*COMe), 3.43-3.33 (m, 2H, CH_2OH), 3.39 (s, 3H, O*Me*), 3.32 (s, 3H, O*Me*), 3.29 (d, *J* = 2.8 Hz, 1H, *H*COPMB), 3.21 (ddd, *J* = 7.1, 3.7, and 3.7 Hz, 1H, *H*COMOM), 3.19-3.14 (m, 1H, *H*COMe), 3.16 (s, 3H, O*Me*), 3.04 (s, 3H, O*Me*), 2.90 (dd, *J* = 8.4 and 3.9 Hz, 1H, O*H*), 1.98-1.83 (m, 2H, C$H_{a1}$$H_{b1}$), 1.66 (ddd, *J* = 13.6, 8.5, and 4.6 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.48 (ddd, *J* = 13.3, 8.3, and 4.3 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.11 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), and 1.01 (s, 9H, SiCMe_3).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 145.6, 136.3, 136.2, 135.1, 134.4, 131.2, 129.63, 129.58, 129.1, 127.63, 127.55, 113.7, 111.8, 97.6, 96.8, 88.3, 82.1, 79.1, 78.9, 77.3, 75.0, 68.8, 63.2, 58.1, 56.6, 55.95, 55.91, 55.4, 42.1, 39.2, 38.2, 27.3, 25.3, 24.2, and 19.6.
TLC: R_f = 0.38; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*R*,7*R*,8*R*,9*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyldodec-11-enal **365**



364 ***365***

To a 25 mL round bottom flask containing alcohol **364** (229 mg, 0.292 mmol) was added CH_2Cl_2 (5.9 mL, 0.05 M). The solution was cooled to 0 ºC followed by the addition of $NaHCO_3$ (148 mg, 1.76 mmol) and Dess-Martin periodinane (187 mg, 0.441 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred until monitoring by TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (5 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the desired aldehyde **365**. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.44 (d, *J* = 1.1 Hz, 1H, *H*C=O), 7.70 (d, *J* = 7.2 Hz, 2H, Ph*H*), 7.66 (d, *J* = 7.3 Hz, 2H, Ph*H*), 7.42-7.24 (m, 8H, Ph*H* and MeOPhH_a), 6.85 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 6.00 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.2 and 1.4 Hz, 1H, C$H_a$$H_b$=CH), 4.97 (dd, *J* = 10.8 and 1.4 Hz, 1H, $CH_a$$H_b$=CH), 4.67 (d, *J* = 6.4 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.63 (d, *J* = 10.6 Hz, 1H, MeOPhC$H_a$$H_b$), 4.62 (d, *J* = 6.8 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.51 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.39 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.36 (d, *J* = 6.9 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.14 (dddd, *J* = 8.4, 8.4, 4.1, and 4.1 Hz, 1H, *H*COTBDPS), 3.98 (dd, *J* = 2.9 and 1.2 Hz, *H*COMOM), 3.79 (s, 3H, PhO*Me*), 3.74 (ddd, *J* = 10.1, 1.9, and 1.9 Hz, 1H, *H*COMe), 3.56 (ddd, *J* = 8.2, 5.5, and 3.0 Hz, 1H, *H*COMe), 3.40 (dd, *J* = 3.0 and 1.2 Hz, *H*COMOM), 3.38 (s, 3H, O*Me*), 3.28 (s, 3H, O*Me*), 3.27 (d, *J* = 2.8 Hz, 1H, *H*COPMB), 3.16 (s, 3H, O*Me*), 3.00 (s, 3H, O*Me*), 1.98 (ddd, *J* = 14.6, 8.3, and 2.3 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.89 (ddd, *J* = 14.2, 10.3, and 3.4 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.84 (ddd, *J* = 13.1, 7.7, and 5.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.54

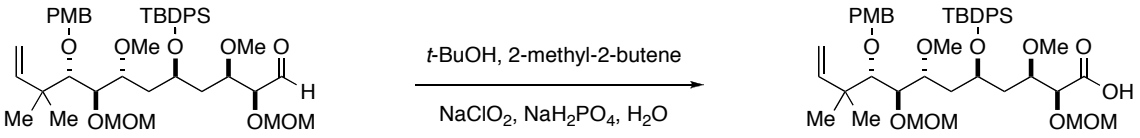
(ddd, J = 13.5, 7.4, and 5.5 Hz, 1H, $CH_{a2}H_{b2}$), 1.11 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.0, 159.1, 145.6, 136.29, 136.25, 134.8, 134.3, 131.1, 129.72, 129.68, 129.1, 127.71, 127.67, 113.7, 111.8, 97.5, 96.8, 88.2, 83.9, 78.9, 78.4 77.0, 75.0, 68.7, 58.2, 56.5, 56.3, 56.0, 55.4, 42.1, 39.4 38.4, 27.3, 25.3, 24.3, and 19.6.

HR ESI-MS: Calcd for $C_{44}H_{64}O_{10}SiNa$ $(M+Na)^+$: 803.4161 Found: 803.4195.

TLC: R_f = 0.61; 1:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*R*,7*R*,8*R*,9*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyldodec-11-enoic acid **366**



365 ***366***

To a 100 mL round bottom flask containing the crude aldehyde **365** (~0.292 mmol) was added *t*-BuOH (17.0 mL, 0.017 M) and 2-methyl-2-butene (5.6 mL, 0.052 M). To a vial equipped with a stir bar was added NaH_2PO_4 (264 mg, 2.92 mmol), $NaClO_2$ (201 mg, 1.46 mmol), and H_2O (7.7 mL, 0.19 M in $NaClO_2$). Once the mixture in the vial became homogeneous, the aqueous solution was added to the reaction flask. The reaction mixture was stirred at room temperature for 1 hour. The solution was then cooled to 0 ºC, and a newly prepared saturated solution of $NaHSO_3$ (6 mL) was added. The reaction was diluted with H_20 (40 mL) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the desired carboxylic acid **366**. The crude product was immediately carried on to the next step without purification.

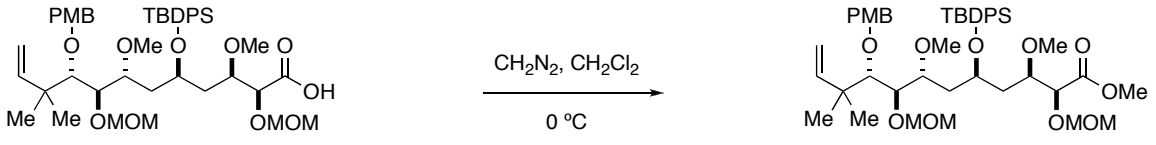
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.9 Hz, 2H, Ph*H*), 7.64 (d, J = 7.3 Hz, 2H,

Ph*H*), 7.43-7.25 (m, 8H, Ph*H* and MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.00 (dd, *J* = 17.5 and 10.7 Hz, 1H, CH_2=C*H*), 5.01 (dd, *J* = 17.0 and 1.4 Hz, 1H, C$H_a$$H_b$=CH), 4.98 (dd, *J* = 10.8 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.66 (d, *J* = 6.3 Hz, 1H, OC$H_{a1}$$H_{b1}$OMe), 4.65 (d, *J* = 10.2 Hz, 1H, MeOPhC$H_a$$H_b$), 4.62 (d, *J* = 6.4 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.55 (d, *J* = 6.7 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.41 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.37 (d, *J* = 6.7 Hz, 1H, OC$H_{a2}$$H_{b2}$OMe), 4.20-4.13 (m, 1H, *H*COTBDPS), 3.98 (d, *J* = 2.2 Hz, 1H, *H*COMOM), 3.80 (d, *J* = 3.1 Hz, 1H, *H*COMOM), 3.79 (s, 3H, PhO*Me*), 3.75 (dd, *J* = 9.4 and 2.1 Hz, 1H, *H*COMe), 3.58 (ddd, *J* = 8.9, 3.8, and 3.8 Hz, 1H, *H*COMe), 3.38 (s, 3H, O*Me*), 3.28 (d, *J* = 2.8 Hz, 1H, *H*COPMB), 3.27 (s, 3H, O*Me*), 3.12 (s, 3H, O*Me*), 3.10 (s, 3H, O*Me*), 1.96 (ddd, *J* = 14.5, 7.9, and 2.6 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.90 (ddd, *J* = 14.4, 9.9, and 3.7 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.79 (ddd, *J* = 13.8, 8.8, and 4.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.56-1.46 (m, 1H, $CH_{a2}$$H_{b2}$), 1.11 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 145.6, 136.3, 136.3, 136.2, 134.8, 134.2, 131.1, 129.68, 129.64, 129.2, 127.7, 127.6, 113.8, 111.9, 97.2, 96.8, 88.4, 78.9, 78.7, 75.1, 68.6, 58.7, 56.6, 56.5, 55.9, 55.4, 42.1, 39.9, 38.2, 27.3,25.3, 24.3, and 19.5.

HR ESI-MS: Calcd for $C_{44}H_{64}O_{11}SiNa$ $(M+Na)^+$: 819.4110 Found: 819.4170.

(2*S*,3*R*,5*R*,7*R*,8*R*,9*S*)-Methyl 5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyldodec-11-enoate **367**



366 ***367***

To a 50 mL Erlenmeyer flask equipped with a stir bar and containing the crude carboxylic acid **366** (~0.292 mmol) was added CH_2Cl_2 (30 mL, 0.01 M) followed by cooling the solution to 0 ºC. Diazald (400 mg, 1.87 mmol) and ethanol (7 mL) were added to a 50 mL side-arm Erlenmeyer flask equipped with a stir bar. The top of the 150

mL side-arm Erlenmeyer flask was covered with a new 24/40 septum that had a piece of teflon tubing punctured through the septum, having one end placed into the ethanol solution while the other end was connected to a N_2 line under positive pressure. A new 14/20 septa with another piece of teflon tubing punctured through it was placed on the side-arm and the opposite end of the teflon tubing was placed into the solution of CH_2Cl_2 containing **366** in the 50 mL Erlenmeyer flask. The N_2 flow was then regulated so that constant N_2 sparging was observed in both Erlenmeyer flasks. This is important because the flow of N_2 is what is going to carry the diazomethane as it is formed, to the 50 mL Erlenmeyer flask containing the carboxylic acid **366**. A sodium hydroxide solution (1 M) is added at a constant rate to the 50 mL side-arm Erlenmeyer flask while stirring, until all the yellow color in the 50 mL side-arm Erlenmeyer flask disappears. The esterification reaction is complete when the CH_2Cl_2 in the 50 mL Erlenmeyer flask turns yellow as the result of excess diazomethane accumulating in the solution. The teflon tubing is removed from the CH_2Cl_2 and a few drops of acetic acid is added until the CH_2Cl_2 solution turns colorless. Saturated aqueous $NaHCO_3$ (10 mL) was added to quench any excess acetic acid. The reaction was diluted with CH_2Cl_2 (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a mixture of the desired product **367** and the alcohol resulting from deprotection of the C2 MOM ether. **NOTE:** (It is believed that the MOM ether deprotection occurs during the addition of the CH_2Cl_2 to the crude carboxylic acid. This was later prevented by replacing CH_2Cl_2 with Et_2O as the solvent while keeping everything else remaining the same.) The MOM ether could easily be re-installed by taking this crude reaction mixture and subjecting it to the previously described procedure for MOM ether formation. Column chromatography was performed (2:1 hexanes / ethyl acetate) to provide methyl ester **367** (198 mg, 84%, 3-steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.2 Hz, 2H, Ph*H*), 7.64 (d, *J* = 7.3 Hz, 2H, Ph*H*), 7.40-7.25 (m, 8H, Ph*H* and MeOPhH_a), 6.84 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 6.00 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.01 (dd, *J* = 17.6 and 1.5 Hz, 1H, CH_aH$_b$=CH), 4.97 (dd, *J* = 10.8 and 1.4 Hz, 1H, CH$_a$$H_b$=CH), 4.70 (d, *J* = 11.1 Hz, 1H,

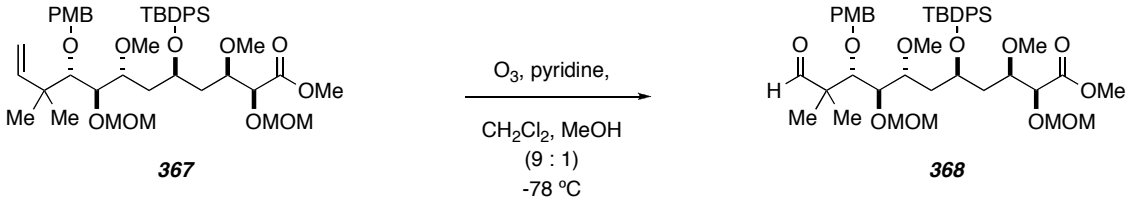
MeOPhCH_aH$_b$), 4.67 (d, J = 6.4 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.62 (d, J = 6.4 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.51 (d, J = 7.0 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.44 (d, J = 6.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.40 (d, J = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.24-4.18 (m, 1H, *H*COTBDPS), 3.99 (dd, J = 2.5 and 1.1 Hz, 1H, *H*COMOM), 3.78 (s, 3H, PhO*Me*), 3.81-3.73 (m, 2H, *H*OMe and *H*COMOM), 3.64 (s, 3H, CO$_2$*Me*), 3.59 (ddd, J = 8.9, 3.7, and 3.7 Hz, 1H, *H*COMe), 3.38 (s, 3H, O*Me*), 3.29 (d, J = 2.6 Hz, 1H, *H*COPMB), 3.21 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 3.03 (s, 3H, O*Me*), 1.96-1.86 (m, 3H, C$H_{a1}$$H_{b1}$ and CH_{a2}H$_{b2}$), 1.44 (ddd, J = 13.9, 8.7, and 3.9 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.4, 159.0, 145.6, 136.3, 136.2, 135.0, 134.2, 131.1, 129.5, 129.1, 127.6, 127.5, 113.7, 111.8, 96.8, 96.7, 88.4, 78.9, 78.8, 77.9, 77.1, 75.0, 68.7, 58.4, 56.5, 56.3, 55.9, 55.4, 51,9, 42.1, 40.1, 38.2, 27.3, 25.3, 24.2, and 19.5.

HR ESI-MS: Calcd for $C_{45}H_{66}O_{11}SiNa$ $(M+Na)^+$: 833.4267 Found: 833.4279.

TLC: R_f = 0.45; 2:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*R*,7*R*,8*R*,9*S*)-Methyl 5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyl-11-oxoundecanoate **368**



A 9:1 mixture of CH_2Cl_2:MeOH (6.9 mL, 0.02 M) was added to a 50 mL round bottom flask containing alkene **367** (110 mg, 0.138 mmol). This solution was cooled to -78 ºC and pyridine (0.22 mL, 2.73 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the reaction mixture, observed by the change of the solution from a light blue color to

colorless. Dimethyl sulfide (5 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6 hours. The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (1:1 hexanes / ethyl acetate) to provide aldehyde **368** (97 mg, 97%).

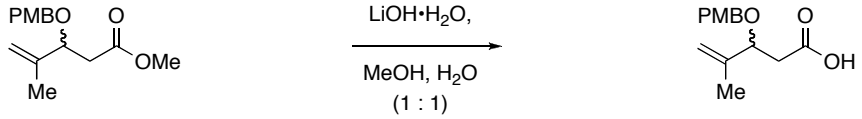
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.30 (s, 1H, *H*C=O), 7.73 (d, *J* = 7.3 Hz, 2H, Ph*H*), 7.68 (d, *J* = 7.4 Hz, 2H, Ph*H*), 7.44-7.25 (m, 6H, Ph*H*), 7.13 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.84 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.62 (d, *J* = 6.4 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.54 (d, *J* = 6.8 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.48 (d, *J* = 6.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.44 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.40 (d, *J* = 6.4 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.28 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.18-4.10 (m, 1H, *H*COTBDPS), 3.90 (d, *J* = 3.2 Hz, 1H, *H*COMOM), 3.80 (s, 3H, PhO*Me*), 3.75 (ddd, *J* = 8.1, 5.0, and 3.3 Hz, 1H, *H*COMe), 3.69 (s, 3H, CO_2*Me*), 3.64 (d, *J* = 8.7 Hz, 1H, *H*COMOM), 3.48 (ddd, *J* = 9.4 and 3.5 Hz, 1H, *H*COMe), 3.39 (d, *J* = 8.4 Hz, 1H, *H*COPMB), 3.29 (s, 3H, O*Me*), 3.24 (s, 3H, O*Me*), 3.19 (s, 3H, O*Me*), 3.14 (s, 3H, O*Me*), 1.98 (ddd, *J* = 13.8, 7.9, and 5.3 Hz, 1H, CH_{a1}H$_{b1}$), 1.87-1.76 (m, 2H, C$H_{a2}$$H_{b2}$), 1.69 (ddd, *J* = 14.2, 7.2, and 5.0 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.064 (s, 3H, C*Me*), 1.056 (s, 3H, C*Me*), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.7, 171.4, 159.2, 136.2, 136.1, 134.4, 134.2, 130.2, 129.8, 128.5, 127.75, 127.74, 113.8, 97.3, 96.8, 81.8, 79.3, 78.8, 77.6, 77.4, 74.7, 69.3, 58.3, 57.2, 57.1, 56.3, 55.4, 52.0, 50.5, 39.0, 38.6, 27.2, 21.3, 19.5, and 15.7.

HR ESI-MS: Calcd for $C_{44}H_{64}O_{12}SiNa$ $(M+Na)^+$: 835.4059 Found: 835.4078.

TLC: R_f = 0.62; 1:1 hexanes:ethyl acetate.

3-(4-Methoxybenzyloxy)-4-methylpent-4-enoic acid **371**



371

To a 250 mL round bottom flask containing PMB protected methyl ester (1.50 g, 5.68 mmol) was added MeOH:H_2O (1:1; 112 mL, 0.05 M). The reaction mixture was cooled to 0 ºC, LiOH•H_2O (0.476 g, 11.4 mmol) was added and the reaction mixture was stirred for 20 hours while gradually warming to room temperature. The solution was recooled to 0 ºC and acidified to a ~pH=2 using 0.5 M HCl. The aqeous layer was extracted with ethyl acetate (3 x 150 mL). The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (3:1 hexanes / ethyl acetate) to provide acid **371** (1.12 g, 79%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2H, PhH_a), 6.87 (d, *J* = 8.5 Hz, 2H, PhH_b), 5.07 (s, 1H, C$H_a$$H_b$=C(Me)), 5.06 (s, 1H, C$H_a$$H_b$=C(Me)), 4.49 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.27 (d, *J* = 11.2 Hz, 1H, MeOPhC$H_a$$H_b$), 4.24 (dd, *J* = 9.3 and 4.1 Hz, 1H, *H*COPMB), 3.80 (s, 3H, PhO*Me*), 2.73 (dd, *J* = 15.5 and 9.4 Hz, 1H, C$H_a$$H_b$), 2.52 (dd, *J* = 15.5 and 4.2 Hz, 1H, C$H_a$$H_b$), and 1.75 (s, 3H, CH_2=C(*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.9, 159.4, 143.0, 130.1, 129.7, 115.1, 114.0, 79.1, 70.2, 55.4, 39.8, and 16.9.

TLC: R_f = 0.36; 3:1 hexanes:ethyl acetate.

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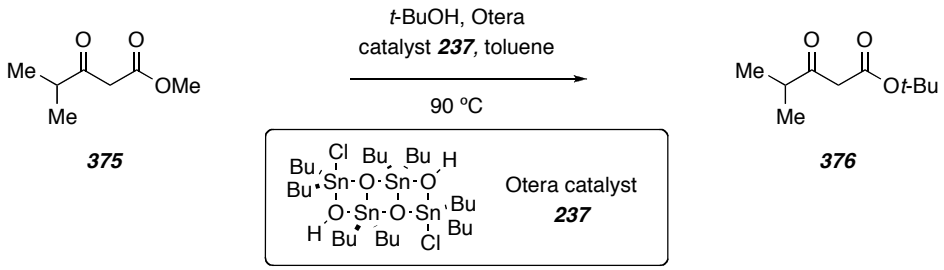
tert-Butyl 4-Methyl-3-oxopentanoate **376**



To a 500 mL round bottom flask containing methyl-4-methyl-3-oxovalerate (**375**) (5.0 mL, 35.1 mmol) was added toluene (117 mL, 0.3 M), *t*-BuOH (67.3 mL, 702 mmol) and Otera catalyst **237** (3.75 g, 3.51 mmol). The round bottom flask was then equipped

with a modified Soxlet extractor containing 4 Å molecular sieves and contected to a reflux condensor. The mixture was stirred at 90 ºC for 3 days. The solution was transferred to a round bottom flask using $CHCl_3$ and concentrated *in vacuo*. Purification via flash chromatography (95:5 hexanes / ethyl acetate) provided *t*-Butyl ester **376** (3.46 g, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.89 (s, C*H*=COH, enol), 3.40 (s, 2H, CH_2), 2.72 (sept., *J* = 6.9 Hz, 1H, C*H*Me_2), 1.49 (s, $CO_2C\mathit{Me}_3$, enol), 1.47 (s, 9H, $CO_2C\mathit{Me}_3$), and 1.13 (d, *J* = 6.9 Hz, 6H, $CH\mathit{Me}_2$).

TLC: R_f = 0.48; 9:1 hexanes:ethyl acetate.

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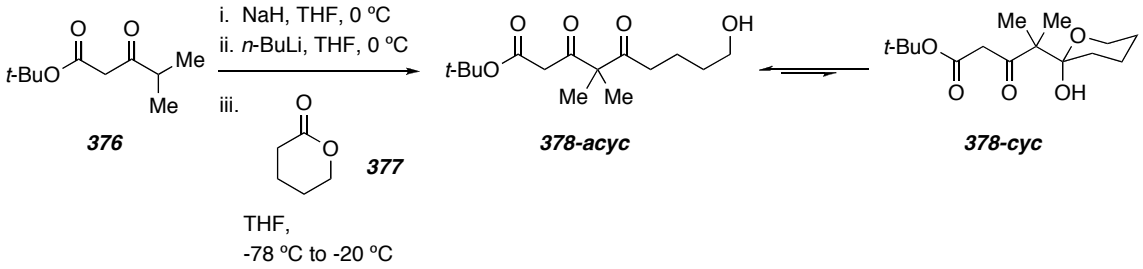
tert-Butyl 9-Hydroxy-4,4-dimethyl-3,5-dioxononanoate **378-*acyc***



To a 50 mL round bottom flask containing NaH (0.130 g, 3.23 mmol; 60% in mineral oil) was added THF (16.0 mL, 0.18 M). The reaction mixture was cooled to 0 ºC, a solution of *t*-butyl ester **376** (0.547 g, 2.94 mmol) in THF (1.0 mL, 3 M) was added dropwise and the reaction mixture was stirred for 15 minutes at 0 ºC. A solution of *n*-BuLi in hexanes (1.45 mL, 3.09 mmol, 2.13 M) was added down the side of the flask and the reaction mixture was stirred for 15 minutes at 0 ºC. Cooling the solution to -78 ºC was followed by the addtion of δ-valerolactone (**377**) (0.300 mL, 3.23 mmol) in THF (2.0 mL, 1.5 M), precooled by adding down the side of the flask. The mixture was stirred at -78 ºC for 1 hour, gradually warmed to -20 ºC over 1 hour, and finally the reaction was quenched at -20 ºC by the addition of saturated aqueous NH_4Cl (10 mL), followed by

warming to room temperature. The mixture was diluted with H_2O (10 mL) and EtOAc (25 mL), the aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via column chromatography (1:1 hexanes / ethyl acetate) provided an equlibrium mixture of **378-*acyc*** and **378-*cyc*** (195 mg, 21%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (s, 1H, C*H*=COH), 3.62 (t, *J* = 6.0 Hz, 2H, CH_2OH), 3.38 (s, 2H, C=OCH_2CO$_2$), 2.52 (t, *J* = 7.0 Hz, 2H, CH_2C=O), 1.74-1.42 (m, 4H, CH_2CH_2CH$_2$OH), 1.46 (s, 9H, CMe_3), and 1.37 (s, 6H, CMe_2).

HR ESI-MS: Calcd for $C_{15}H_{26}O_5Na$ $(M+Na)^+$: 309.1672 Found: 309.1680.

TLC: R_f = 0.35; 1:1 hexanes:ethyl acetate.

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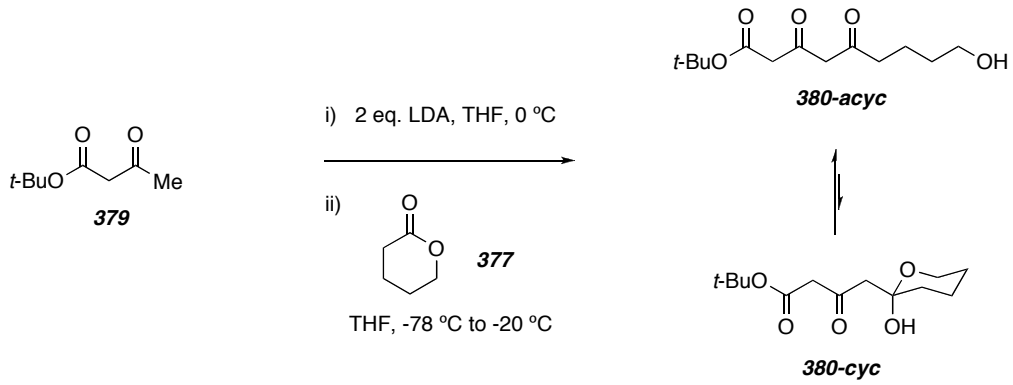
tert-Butyl 9-Hydroxy-3,5-dioxononanoate **380-*acyc***



To a 250 mL round bottom flask containing *i*-Pr_2NH (4.15 mL, 29.5 mmol) was added THF (70.0 mL, 0.4 M). The reaction mixture was cooled to 0 ºC, a solution of *n*-BuLi in hexanes (14.4 mL, 30.24 mmol, 2.1 M) was added dropwise and the reaction mixture was stirred for 40 minutes at 0 ºC allowing for the preparation of the LDA solution. The reaction mixture was cooled to -78 ºC and *t*-butyl acetoacetate (**379**) (2.39 mL, 14.4 mmol) in THF (4.8 mL, 3.0 M) was added down the side of the flask. The reaction mixture was warmed to 0 ºC and allowed to stir for 1 hour. The solution was

then recooled to -78 ºC and δ-valerolactone (**377**) (1.0 mL, 10.8 mmol) in THF (11.0 mL, 1 M) was added down the side of the flask. The reaction mixture was stirred at -78 ºC for 1.5 hours and a saturated aqueous solution of NH_4Cl (50 mL) was added to quench the reaction, followed by warming to room temperature. The mixture was diluted with H_2O (50 mL) and EtOAc (100 mL), the aqueous layer was extracted with EtOAc (3 x 125 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via column chromatography (1:1 hexanes / ethyl acetate) provided an equlibrium mixture of **380-*acyc*** and **380-*cyc*** (1.52 g, 55%).

***t*-Butyl Ester Isomers 380-*acyc* (3:1 ; *acyc*:*cyc*)**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.61 (s, 1H, C=OC*H*=COH), 3.66 (t, *J* = 6.3 Hz, 2H, CH_2OH), 3.25 (s, 2H, CH_2CO_2), 2.36 (t, *J* = 7.3 Hz, 2H, C=OCH=C(OH)CH_2), 1.94-1.44 (m, 4H, cyc. Alk-*H*), and 1.47 (s, 9H, CO_2CMe_3).

***t*-Butyl Ester Isomers 380-*cyc* (3:1 ; *acyc*:*cyc*)**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99-3.91 (m, 1H, CH_aH$_b$O), 3.61-3.53 (m, 1H, CH$_a$$H_b$O), 3.45 (d, *J* = 15.6 Hz, 1H, CH_aH$_b$CO$_2$), 3.39 (d, *J* = 15.6 Hz, 1H, CH$_a$$H_bCO_2$), 2.99 (d, *J* = 15.8 Hz, 1H, CH_aH$_b$C=O), 2.62 (d, *J* = 15.7 Hz, 1H, CH$_a$$H_b$C=O), 1.94-1.49 (m, 6H, cyc. Alk-*H*), and 1.47 (s, 9H, CO_2CMe_3).

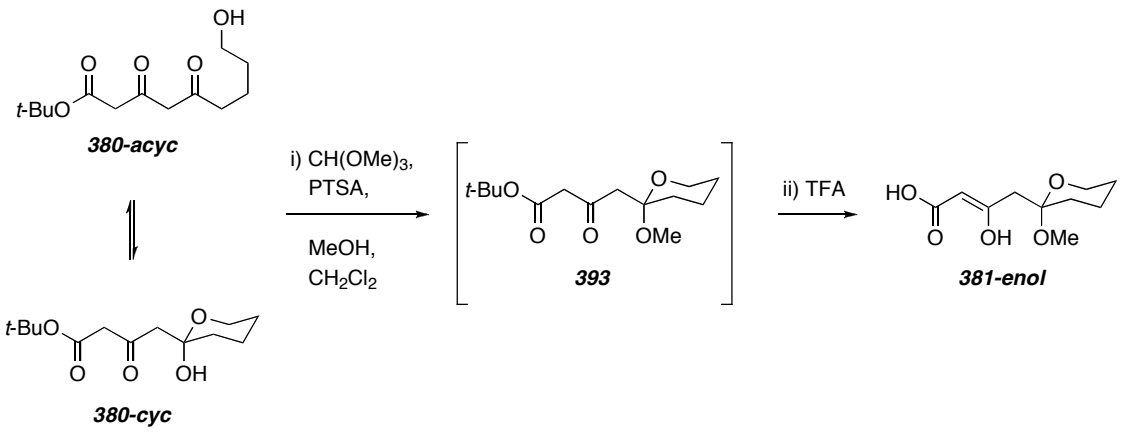
Characterization Data for *t*-Butyl Ester Isomers 380-*acyc* and 380-*cyc*

^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.1, 166.7, 88.1, 81.8, 48.5, 41.1, 31.7, 28.4, 28.0, 22.7, 19.8, 18.0, and 14.2.

HR ESI-MS: Calcd for $C_{13}H_{22}O_5Na$ $(M+Na)^+$: 281.1359 Found: 281.1374.

TLC: R_f = 0.31; 1:1 hexanes:ethyl acetate.

(*S*,*Z*)-3-Hydroxy-4-(2-methoxytetrahydro-2*H*-pyran-2-yl)but-2-enoic acid **381-*enol***



To a culture tube containing **380** (0.500 g, 1.95 mmol) in CH_2Cl_2 (3.9 mL, 0.5 M) was added trimethyl orthoformate (0.385 mL, 3.52 mmol), MeOH (0.200 mL, 4.88 mmol), and PTSA (20 mg, 0.10 mmol). The reaction mixture was stirred for 20 hours. The solution was then cooled to 0 ºC followed by the addition of TFA (0.252 mL, 2.92 mmol) and stirred until TLC showed no remaining **393**. The solvents were removed and the remaining crude residue was purified via MPLC (2:1 hexanes / ethyl acetate) to provide acid **381-*eonol*** (251 mg, 60%).

Characterization Data for *t*-Butyl Ester 393 (15% enol content)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67-3.60 (m, 2Hz, CH_aH_bO), 3.48 (d, *J* = 1.9 Hz, 2H, CH_2CO_2), 3.26 (s, 3H, O*Me*), 2.95 (d, *J* = 13.4 Hz, 1H, CCH_aH$_b$C=O), 2.64 (d, *J* = 13.4 Hz, 1H, CCH$_a$$H_b$C=O), 1.89-1.50 (m, 6H, cyc. Alk-*H*), and 1.47 (s, 9H, CO_2CMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.3, 166.9, 97.8, 81.9, 61.8, 51.7, 49.8, 48.1, 33.1, 28.2, 24.9, and 18.6.

TLC: R_f = 0.79; 2:1 hexanes:ethyl acetate.

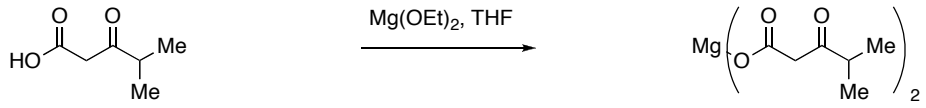
Characterization Data for Acid 381-*enol*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 1.7 Hz, 1H, C*H*=COH), 3.97 (ddd, *J* = 11.4, 11.4, and 4.7 Hz, CH_aH$_b$O), 3.74 (s, 3H, O*Me*), 3.73-3.63 (m, 1H, CH$_a$$H_b$O), 2.68 (dd, *J* = 17.3 and 1.7 Hz, 1H, CH_aH$_b$), 2.46 (d, *J* = 17.3 Hz, CH$_a$$H_b$), 2.15-1.95 (m, 2H, cyc. Alk-*H*), and 1.73-1.57 (m, 4H, cyc. Alk-*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 100.2, 89.6, 80.8, 62.7, 56.1, 39.1, 34.6, 24.6, and 18.1.

TLC: R_f = 0.72; 1:1 hexanes:ethyl acetate.

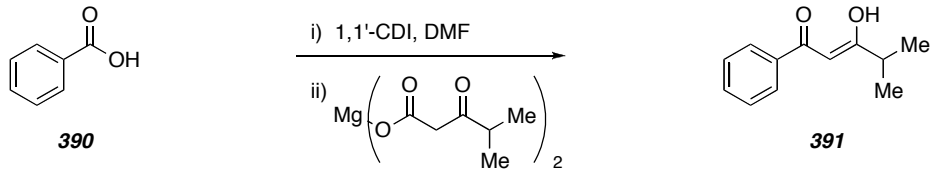
Magnesium 4-Methyl-3-oxopentanoate **389**



388 ***389***

β-Keto acid **388** (1.5 g, 0.90 mmol), THF (1.8 mL, 0.5 M), and $Mg(OEt)_2$ (0.660 g, 5.77 mmol) were added to a 50 mL round bottom flask and the reaction mixture was allowed to sir for 22 hours. The solvent was removed and toluene was used to azeotrope away residual H_2O and EtOH. The resulting crude magnesium salt **389** was placed under vacuum, stored under N_2 and later used in following reactions without any further purification.

(*Z*)-3-Hydroxy-4-methyl-1-phenylpent-2-en-1-one **391**



390 ***389*** ***391***

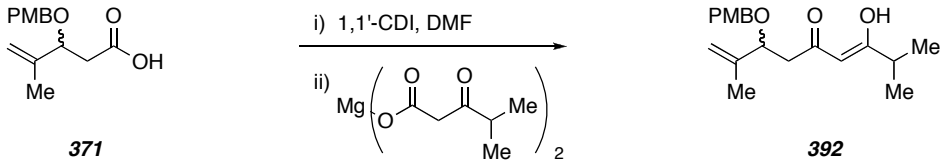
1,1'-Carbonyldiimidazole (0.146 g, 0.90 mmol), DMF (1.8 mL, 0.5 M), and benzoic acid (**390**) (100 mg, 0.819 mmol) were added to a culture tube and the solution was allowed to sir for 1 hour. Magnesium salt **389** (1.04 g, 3.69 mmol) was added in 3 portions over 18 hours. A saturated aqueous solution of NH_4Cl (10 mL) was added to quench the reaction, followed by diluting the mixture with H_2O (10 mL) and EtOAc (20

mL), the aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (9:1 hexanes / ethyl acetate) provided **391** (114 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.3 Hz, 2H, PhH_a), 7.52 (t, *J* = 7.4 Hz, 1H, PhH_b), 7.45 (t, *J* = 7.8 Hz, 2H, PhH_c), 6.19 (s, 1H, C*H*=COH), 2.63 (sept., *J* = 6.9 Hz, 1H, C*H*Me_2), and 1.23 (d, *J* = 7.0 Hz, 6H, CHMe_2).

TLC: R_f = 0.51; 9:1 hexanes:ethyl acetate.

(*Z*)-7-Hydroxy-3-(4-methoxybenzyloxy)-2,8-dimethylnona-1,6-dien-5-one **392**



1,1'-Carbonyldiimidazole (14 mg, 0.088 mmol), DMF (0.100 mL, 0.88 M), and acid **371** (20 mg, 0.080 mmol) in DMF (0.100 mL, 0.8 M) were added to a vial and the solution was allowed to sir for 1 hour. Magnesium salt **389** (24 mg, 0.086 mmol) was added and the reaction mixture was stirred for and additional 18 hours. A saturated aqueous solution of NH_4Cl (2 mL) was added to quench the reaction, followed by diluting the mixture with H_2O (5 mL) and EtOAc (20 mL), the aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via MPLC (9:1 hexanes / ethyl acetate) provided **392** (12 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8.4 Hz, 2H, MeOPhH_a), 6.84 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.53 (s, 1H, C*H*=COH), 5.02 (s, 1H, C$H_a$$H_b$=C(Me)), 5.00 (s, 1H, CH$_a$$H_b$=C(Me)), 4.44 (d, *J* = 11.3 Hz, 1H, MeOPhC$H_a$$H_b$), 4.21 (d, *J* = 11.4 Hz, 1H, MeOPhCH$_a$$H_b$), 4.20 (dd, *J* = 9.2 and 4.7 Hz, 1H, *H*COPMB), 3.80 (s, 3H, PhO*Me*), 2.63

(dd, J = 14.4 and 9.0 Hz, 1H, CH_aH$_b$), 2.45 (sept., J = 6.9 Hz, 1H, CHMe$_2$), 2.42 (dd, J = 14.4 and 4.5 Hz, 1H, CH$_a$$H_b$), 1.74 (s, 3H, CH$_2$=C(*Me*)), and 1.14 (d, J = 6.9 Hz, 6H, CH*Me*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.9, 191.8, 159.3, 143.7, 130.5, 129.6, 114.4, 113.9, 98.7, 79.8, 70.2, 55.5, 43.8, 36.9, 19.5 and 17.1.

TLC: R_f = 0.29; 9:1 hexanes:ethyl acetate.

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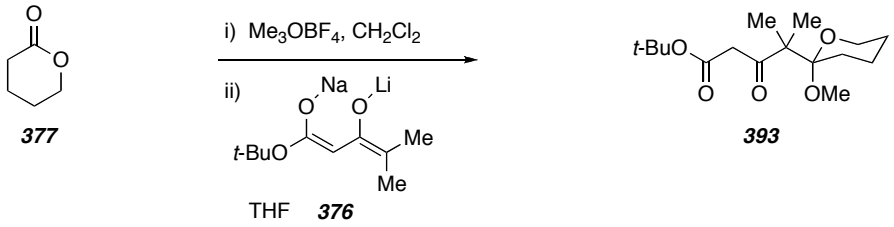
tert-Butyl 4-(2-Methoxytetrahydro-2*H*-pyran-2-yl)-4-methyl-3-oxopentanoate **393**



To a 100 mL round bottom flask containing Me_3OBF_4 (0.952 g, 6.44 mmol) in CH_2Cl_2 (12.9 mL, 0.5 M) at 0 ºC was added δ-valerolactone (**377**) (0.200 mL, 2.16 mmol). The reaction mixture was warmed to room temperature and stirred for 20 hours. The solution in the 100 mL round bottom was then cooled to -78 ºC. **[**To separate 50 mL round bottom flask containing NaH (0.121 g, 3.024 mmol; 60% in mineral oil) was added THF (21.6 mL, 0.13 M). The reaction mixture was cooled to 0 ºC, a solution of *t*-butyl ester **376** (0.523 g, 2.81 mmol) in THF (2.0 mL, 1.4 M) was added dropwise and the reaction mixture was stirred for 30 minutes at 0 ºC. A solution of *n*-BuLi in hexanes (1.21 mL, 2.96 mmol, 2.42 M) was added down the side of the flask and the reaction mixture was stirred for 40 minutes at 0 ºC. The dianion solution of **376** in the 50 mL round bottom flask was then cooled to -78 ºC.**]** The dianion solution of **376** was then transferred via cannula into the other flask containing Me_3OBF_4 and δ-valerolactone (**377**). The reaction mixture was then stirred at -78 ºC for 1 hour. A saturated aqueous solution of $NaHCO_3$ (25 mL) was added at -78 ºC to quench the reaction, the resulting solution was then warmed to room temperature, followed by diluting with H_2O (15 mL) and CH_2Cl_2

(25 mL), the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification required initial flash chromatography (9:1 hexanes / ethyl acetate), followed by MPLC (9:1 hexanes / ethyl acetate) to provide minimal quantities of **393**.

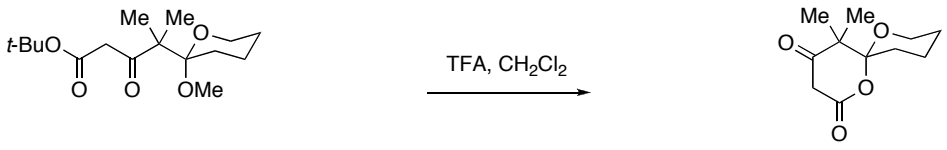
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.81-3.75 (m, 1H, CH_aH$_b$O), 3.78 (d, *J* = 16.3 Hz, 1H, CH_aH$_b$), 3.62 (d, *J* = 16.8, 1H, CH$_a$$H_b$), 3.60 (ddd, *J* = 15.2, 11.2, and 3.6 Hz, 1H, CH$_a$$H_b$O), 3.33 (s, 3H, O*Me*), 1.79-1.37 (m, 6H, cyc. Alk-*H*), 1.46 (s, 9H, CO_2C*Me*$_3$), 1.23 (s, 3H, C*Me*), and 1.17 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.9, 168.1, 100.7, 81.2, 62.8, 57.4, 50.7, 48.5, 29.7, 28.2, 24.9, 21.2, 20.4, and 19.2.

HR ESI-MS: Calcd for $C_{16}H_{28}O_5Na$ $(M+Na)^+$: 323.1829 Found: 323.1834.

TLC: R_f = 0.34; 9:1 hexanes:ethyl acetate.

5,5-Dimethyl-1,7-dioxaspiro[5.5]undecane-2,4-dione **394**



393 ***394***

To a vial containing β-keto ester **393** (6 mg, 0.02 mmol) in CH_2Cl_2 (0.200 mL, 0.1 M) at 0 ºC was added TFA (0.003 mL, 0.039 mmol). The solution was stirred for 15 minutes at 0 ºC, warmed to room temperature, and stirred for 30 minutes before additional TFA (0.003 mL, 0.039 mmol) was added. The solvents were removed and the remaining crude residue was purified via MPLC (3:1 hexanes / ethyl acetate) to provide the undesired bicycle **394** (2 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.89-3.75 (m, 2H, CH_2O), 3.56 (d, *J* = 20.5 Hz, 1H, CH_aH$_b$), 3.35 (d, *J* = 20.5 Hz, 1H, CH$_a$$H_b$), 2.09-1.92 (m, 2H, cyc. Alk-*H*), 1.82-1.59 (m, 3H, cyc. Alk-*H*), 1.26 (s, 3H, C*Me*), and 1.11 (s, 3H, C*Me*).

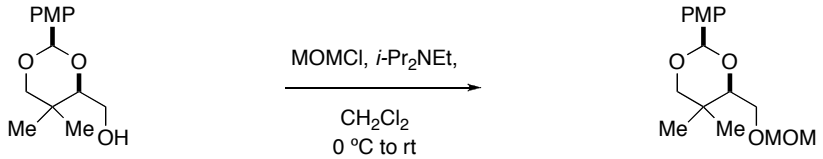
^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.5, 167.7, 106.6, 63.3, 51.5, 43.3, 26.7, 24.2, 19.9, 18.1, and 17.6.

HR ESI-MS: Calcd for $C_{11}H_{16}O_4Na$ $(M+Na)^+$: 235.0941 Found: 235.0946

TLC: R_f = 0.41; 3:1 hexanes:ethyl acetate.

(2*R*,4*R*)-4-((Methoxymethoxy)methyl)-2-(4-methoxyphenyl)-5,5-dimethyl-1,3-dioxane

402



399-2 ***402***

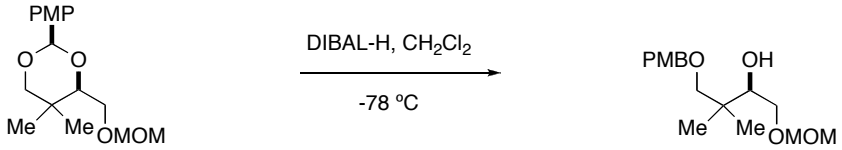
To 250 mL round bottom containing crude alcohol **399-*2*** (7.38 g, 29.3 mmol) was added CH_2Cl_2 (45.0 mL, 0.65 M) and *i*Pr_2NEt (29.3 mL, 180 mmol). Upon cooling the solution to 0 ºC, MOMCl (24.7 mL, 146 mmol; from a prepared solution containing 45% MOMCl : 55% methyl acetate and dimethoxymethane) was added dropwise and the reaction was warmed to room temperature and stirred until no starting alcohol was observed by TLC. After recooling to 0 ºC, saturated aqueous $NaHCO_3$ (75 mL) was then added followed by dilution with H_2O (25 mL). The reaction was warmed to room temperature and stirred for 15 minutes. The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided MOM ether **402** (7.21 g, 83%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.8 Hz, 2H, MeOPhH_a), 6.88 (d, *J* = 8.8

Hz, 2H, MeOPhH_b), 5.48 (s, 1H, MeOPhC*H*), 4.67 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OMe), 4.65 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 3.80 (s, 3H, PhO*Me*), 3.80 (dd, *J* = 8.0 and 2.3 Hz, 1H, CH_aH$_b$OMOM), 3.73 (dd, *J* = 10.9 and 2.3 Hz, 1H, CH$_a$$H_b$OMOM), 3.67 (d, *J* = 11.1 Hz, 1H, CH_aH$_b$), 3.62 (d, *J* = 11.2 Hz, 1H, CH$_a$$H_b$), 3.58 (dd, *J* = 10.9 and 8.0 Hz, 1H, *H*COCHPMP), 3.37 (s, 3H, O*Me*), 1.14 (s, 3H, C*Me*), and 0.87 (s, 3H, C*Me*).

TLC: R_f = 0.32; 6:1 hexanes:ethyl acetate.

(*R*)-4-(4-Methoxybenzyloxy)-1-(methoxymethoxy)-3,3-dimethylbutan-2-ol **404**



402 ***404***

To a large culture tube containing PMP-acetal **402** (616 mg, 2.08 mmol) was added CH_2Cl_2 (9.45 mL, 0.22 M). The reaction mixture was cooled to -78 ºC followed by the addition of DIBAL-H (9.45 mL, 10.4 mmol, 1.1 M in toluene). The reaction solution was kept at -78 ºC for 24 hours. Keeping the reaction mixture at -78 ºC, ethyl acetate (9.0 mL) was added dropwise down the side of the culture tube to quench the excess DIBAL-H. The reaction mixture was then transferred to a 250 mL Erlenmeyer flask equipped with a stir bar using ethyl acetate and warmed to room temperature. Small portions of saturated aqueous Rochelle's salt (Na,K-Tartrate) were added and the reaction was monitored closely for exotherm and cooled if necessary. Upon this addition, the reaction will go from homogeneous to a gelatinous solution, and upon addition of more saturated aqueous Rochelle's salt, back to homogeneous. The two-phase solution in the Erlynmeyer flask was then usually allowed to stir for an additional 18 hours. The reaction is done when both the aqueous and the organic layers are homogeneous and clear. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (2:1 hexanes / ethyl acetate) provided the alcohol

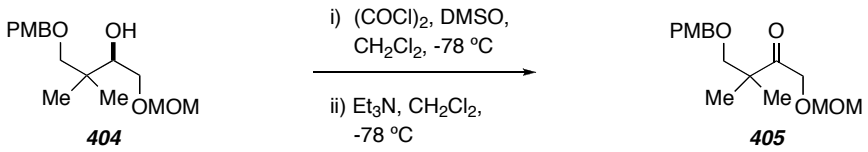
443 (565 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.87 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 4.67 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OMe), 4.66 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 4.44 (s, 2H, MeOPhCH_2), 3.81 (s, 3H, PhO*Me*), 3.73-3.68 (m, 2H, *H*COH and CH_aH$_b$OMOM), 3.47 (dd, *J* = 10.6 and 9.0 Hz, 1H, CH$_a$$H_b$OMOM), 3.38 (s, 3H, O*Me*), 3.33 (d, *J* = 8.9 Hz, 1H, CH_aH$_b$OPMB), 3.24 (d, *J* = 8.9 Hz, 1H, CH$_a$$H_b$OPMB), 3.17 (d, *J* = 3.3 Hz, 1H, O*H*), 0.95 (s, 3H, C*Me*), and 0.94 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 130.4, 129.3, 114.5, 113.9, 97.0, 78.3, 76.3, 73.2, 69.7, 55.5, 55.4, 37.6, 22.6, and 20.5.

TLC: R_f = 0.38; 2:1 hexanes:ethyl acetate.

4-(4-Methoxybenzyloxy)-1-(methoxymethoxy)-3,3-dimethylbutan-2-one **405**



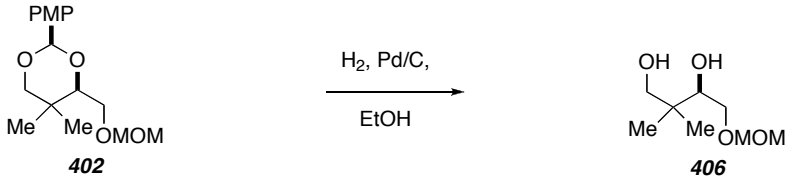
To a 100 mL round bottom flask containing oxalyl chloride (0.94 mL, 1.07 mmol) in CH_2Cl_2 (8.0 mL, 0.13 M) at -78 ºC was added a solution of DMSO (0.124 mL, 1.74 mmol) in CH_2Cl_2 (9.7 mL, 0.18 M). The reaction mixture was stirred for 30 minutes at -78 ºC and then a solution of alcohol **404** (80 mg, 0.268 mmol) in CH_2Cl_2 (8.9 mL, 0.03 M) was added. After the solution was stirred for 30 minutes, Et_3N (0.617 mL, 4.42 mmol) was added and the reaction mixture was allowed to warm to room temperature. Saturated aqueous $NHCl_4$ (30 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (2:1 hexanes / ethyl acetate) provided ketone **405** (62 mg, 78%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.87 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.67 (s, 2H, OCH_2OMe), 4.43 (s, 2H, MeOPhCH_2), 4.42 (s, 2H, CH_2OMOM), 3.81 (s, 3H, PhO*Me*), 3.39 (s, 2H, CH_2OPMB), 3.37 (s, 3H, O*Me*), and 1.16 (s, 6H, CMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.0, 159.1, 129.9, 129.1, 113.7, 96.3, 76.5, 73.0, 69.2, 55.5, 55.2, 45.8, and 21.7.

TLC: R_f = 0.46; 2:1 hexanes:ethyl acetate.

(*R*)-4-(Methoxymethoxy)-2,2-dimethylbutane-1,3-diol **406**



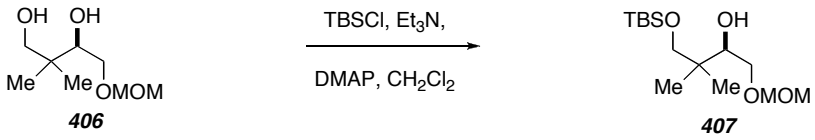
402 ***406***

To PMP acetal **402** (200 mg, 0.675 mmol) was added EtOH (3.38 mL, 0.2 M) and 5% Pd/C (70 mg) in a Fischer-Porter tube. The tube was flushed 2 times with H_2 and then filled with 50 psi of H_2. The heterogeneous solution was vigorously stirred until it was determined by TLC that the starting material had been consumed. The reaction residue was filtered through a pad of silica gel using ethyl acetate and the filtrate was concentrated *in vacuo* to give the crude residue. Flash chromatography (1:3 hexanes / ethyl acetate) provided diol **406** (96 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.69 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OMe), 4.67 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 3.77 (dd, *J* = 10.1 and 2.6 Hz, 1H, CH_aH$_b$OMOM), 3.72 (ddd, *J* = 8.7, 2.5, and 2.5 Hz, 1H, *H*COH), 3.52-3.46 (m, 3H, CH_2OH and CH$_a$$H_b$OMOM), 3.40 (s, 3H, O*Me*), 3.08 (d, *J* = 2.4 Hz, 1H, O*H*), 2.90 (dd, *J* = 5.7 Hz, 1H, O*H*), 0.94 (s, 3H, C*Me*), and 0.93 (s, 3H, C*Me*).

TLC: R_f = 0.36; 1:3 hexanes:ethyl acetate.

(*R*)-7,7,10,10,11,11-Hexamethyl-2,4,9-trioxa-10-siladodecan-6-ol **407**



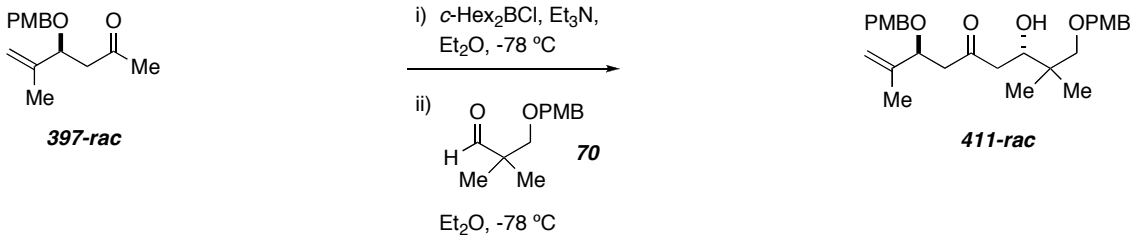
To a 50 mL round bottom flask containing diol **406** (936 mg, 5.25 mmol) was added CH_2Cl_2 (10.5 mL, 0.5 M), Et_3N (0.805 mL, 5.77 mmol), DMAP (26 mg, 0.21 mmol), and TBSCl (0.871 g, 5.78 mmol). The reaction was stirred for 20 hours, at which time TLC showed no remaining diol **406**. After cooling the reaction mixture to 0 ºC, saturated aqueous $NaHCO_3$ was then added to the solution followed by dilution with H_2O and EtOAc. The reaction mixture was warmed to room temperature and stirred for 15-30 minutes. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (9:1 hexanes / ethyl acetate) provided TBS ether **407** (1.33 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.69 (d, *J* = 6.6 Hz, 1H, OCH_aH$_b$OMe), 4.67 (d, *J* = 6.6 Hz, 1H, OCH$_a$$H_b$OMe), 3.74-3.69 (m, 2H, *H*COH and CH_aH$_b$OMOM), 3.49 (dd, *J* = 10.7 and 9.1 Hz, 1H, CH$_a$$H_b$OMOM), 3.47 (d, *J* = 9.7 Hz, 1H, CH_aH$_b$OTBS), 3.43 (d, *J* = 9.6 Hz, 1H, CH$_a$$H_b$OTBS), 3.43 (d, *J* = 3.0 Hz, 1H, O*H*), 3.39 (s, 3H, O*Me*), 0.92 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.89 (s, 3H, C*Me*), and 0.06 (s, 6H, SiMe_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 97.1, 76.7, 72.0, 69.9, 55.5, 37.9, 27.01, 22.1, 19.1, 18.3, -5.47, and -5.49.

TLC: R_f = 0.39; 6:1 hexanes:ethyl acetate.

(3*S*,7*S*)-7-Hydroxy-3,9-bis(4-methoxybenzyloxy)-2,8,8-trimethylnon-1-en-5-one **411-*rac***



To a culture tube containing dicyclohexylboron chloride (0.147 mL, 0.669 mmol) in Et_2O (6.7 mL, 0.1 M) at -78 ºC was added Et_3N (0.106 mL, 0.758 mmol). Ketone **397-*rac*** (0.111 g, 0.446 mmol) in Et_2O (1.5 mL) was added via syringe. The reaction was warmed to 0 ºC and stirred for 1 hr before recooling to -78 ºC. A solution of crude aldehyde **70** (~0.124 g, 0.558 mmol) in Et_2O (1.5 mL) was added via syringe and stirred for 3 hr at -78 ºC before transferring the reaction to a freezer (-20 ºC, 16 hr). To the rection mixture at 0 ºC was added a solution of pH 7 buffer (1.8 mL) and MeOH (5.4 mL) with vigorous stirring. A solution of pH 7 buffer (4.8 mL) and 30% aqueous H_2O_2 (2.4 mL) was added and the mixture was stirred at 0 ºC for 3 hr. The reaction mixture was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic layers were washed with saturated aqeous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via MPLC (3:1 hexanes / ethyl acetate) provided aldol product **411-*rac*** (157 mg, 75%).

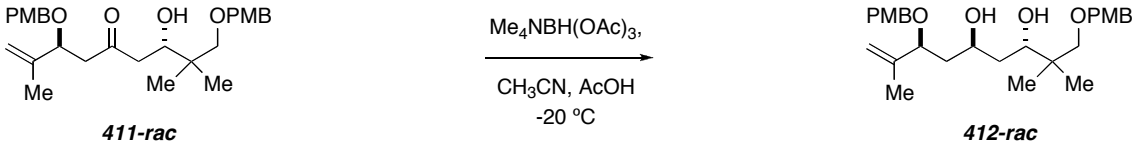
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 7.20 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.87 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.84 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.02 (bs, 1H, CH_aH$_b$=C(Me)), 4.98 (appt p, *J* = 1.6 Hz, 1H, CH$_a$$H_b$=C), 4.42 (d, *J* = 11.8 Hz, 1H, MeOPhCH_{a1}H$_{b1}$), 4.39 (d, *J* = 11.8 Hz, 1H, MeOPhCH$_{a1}$$H_{b1}$), 4.38 (d, *J* = 11.0 Hz, 1H, MeOPhCH_{a2}H$_{b2}$), 4.28 (dd, *J* = 9.4 and 3.6 Hz, 1H, *H*COPMB), 4.20 (d, *J* = 11.0 Hz, 1H, MeOPhCH$_{a2}$$H_{b2}$), 4.01 (ddd, *J* = 7.9, 4.7, and 3.6 Hz, 1H, *H*COH), 3.80 (s, 3H, PhO*Me*), 3.78 (s, 3H, PhO*Me*), 3.39 (d, *J* = 3.6 Hz, 1H, O*H*), 3.29 (d, *J* = 8.9 Hz, 1H, CH_aH$_b$OPMB), 3.24 (d, *J* = 8.9 Hz, 1H, CH$_a$$H_b$OPMB), 2.86 (dd, *J* = 15.6 and 9.4 Hz, 1H, CH_{a1}H$_{b1}$), 2.51 (d, *J* = 4.7 Hz, 1H, CH_{a2}H$_{b2}$), 2.51 (d, *J* = 7.7 Hz, 1H, CH$_{a2}$$H_{b2}$), 2.46 (dd, *J* = 15.6 and 3.7 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.72 (s, 3H, CH$_2$=C(*Me*)), 0.88 (s, 3H, C*Me*), and 0.84 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.6, 159.3, 143.7, 130.43, 130.36, 129.7, 129.3, 114.11, 113.92, 113.88, 79.1, 78.3, 73.5, 73.2, 70.3, 55.4, 48.5, 46.3, 38.2 22.3, 20.0, and 17.2.

HR ESI-MS: Calcd for $C_{28}H_{38}O_6Na$ $(M+Na)^+$: 493.2561 Found: 493.2479.

TLC: R_f = 0.37; 3:1 hexanes:ethyl acetate.

(3*S*,5*S*,7*S*)-1,7-Bis(4-methoxybenzyloxy)-2,2,8-trimethylnon-8-ene-3,5-diol **412-*rac***



411-rac ***412-rac***

To a culture tube containing $Me_4NBH(OAc)_3$ (0.407 g, 1.55 mmol) in CH_3CN (1.7 mL) and AcOH (1.7 mL) at -20 ºC was added hydroxy ketone **411-*rac*** (0.091 g, 0.193 mmol) in CH_3CN (1.5 mL) and AcOH (1.5 mL). The reaction was stirred at -20 ºC until TLC showed no trace of remaining starting material, at which time it was quenched by the addition of a 0.5 M solution of aqueous sodium potassium tartrate (6 mL) and stirred for 30 minutes at 0 ºC. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous layer was back extracted with CH_2Cl_2 (3 x) and the combined organic layers were again washed with saturated aqueous $NaHCO_3$. The aqueous layer was again back extracted with CH_2Cl_2 (3 x) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. The crude product **412-*rac*** (89 mg, 98%) was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 7.22 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.87 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.86 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 4.98 (s, 1H, C$H_a$$H_b$=C(Me)), 4.98 (s, 1H, C$H_a$$H_b$=C(Me)), 4.44 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_{a1}$$H_{b1}$), 4.44 (d, *J* = 11.7 Hz, 1H, MeOPhC$H_{a2}$$H_{b2}$), 4.40 (d, *J* = 11.7 Hz, 1H, MeOPhC$H_{a2}$$H_{b2}$), 4.20 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_{a1}$$H_{b1}$), 4.12-4.06 (m, 1H,

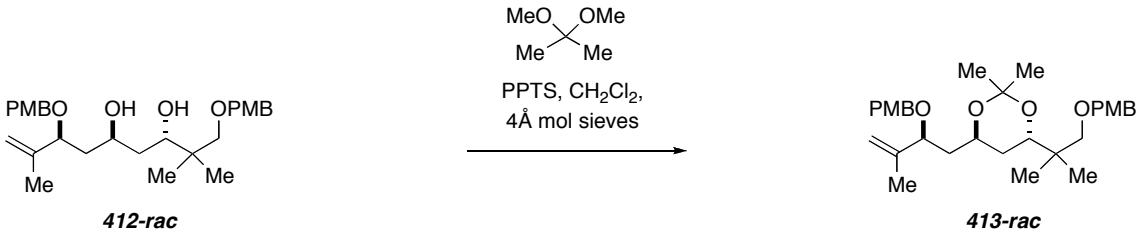
*H*COH), 4.05 (dd, *J* = 9.9 and 3.6 Hz, 1H, *H*COPMB), 3.92 (d, *J* = 1.7 Hz, 1H, O*H*), 3.82 (m, 1H, *H*COH), 3.80 (s, 3H, PhO*Me*), 3.79 (s, 3H, PhO*Me*), 3.64 (d, *J* = 3.4 Hz, 1H, O*H*), 3.32 (d, *J* = 8.8 Hz, 1H, C$H_a$$H_b$OPMB), 3.27 (d, *J* = 8.8 Hz, 1H, C$H_a$$H_b$OPMB), 2.92 (ddd, *J* = 14.4, 9.9 and 9.9 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.73 (s, 3H, CH_2=C(*Me*)), 1.58 (ddd, *J* = 14.4, 3.7 and 2.1 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.50 (ddd, *J* = 13.9, 7.8 and 2.3 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.43 (ddd, *J* = 13.8, 10.4 and 3.4 Hz, 1H, C$H_{a2}$$H_{b2}$), 0.88 (s, 3H, C*Me*), and 0.85 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.42, 159.37, 144.3, 130.24, 130.19, 129.7, 129.3, 114.1, 114.0, 84.1, 79.8, 74.8, 73.4, 69.9, 69.2, 55.5, 41.3, 38.7, 38.2, 22.7, 19.6, and 16.9.

HR ESI-MS: Calcd for $C_{28}H_{40}O_6Na$ $(M+Na)^+$: 495.2727 Found: 495.2738.

TLC: R_f = 0.33; 2:1 hexanes:ethyl acetate.

(4*S*,6*R*)-4-(1-(4-Methoxybenzyloxy)-2-methylpropan-2-yl)-6-((*S*)-2-(4-methoxybenzyloxy)-3-methylbut-3-enyl)-2,2-dimethyl-1,3-dioxane **413-*rac***



To a vial containing diol **412-*rac*** (16 mg, 0.034 mmol) in CH_2Cl_2 (0.500 mL, 0.068 mL) with 4Å molecular sieves was added 2,2-dimethoxypropane (0.042 mL, 0.339 mmol) and PPTS (3 mg, 0.009 mmol). The reaction was stirred until TLC showed no trace of remaining starting material. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, the aqueous layer was extracted with EtOAc (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (6:1 hexanes / ethyl acetate) provided acetonide **413-*rac*** (13 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.4 Hz, 4H, MeOPhH_a), 6.86 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.86 (d, *J* = 8.3 Hz, 2H, MeOPhH_b), 5.02 (s, 1H, CH_aH$_b$=C(Me)), 4.96 (s, 1H, CH$_a$$H_b$=C(Me)), 4.42 (d, *J* = 11.7 Hz, 1H, MeOPhCH_{a1}H$_{b1}$), 4.39 (d, *J* = 9.3 Hz, 1H, MeOPhCH_{a2}H$_{b2}$), 4.36 (d, *J* = 9.3 Hz, 1H, MeOPhCH$_{a2}$$H_{b2}$), 4.16 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_{a1}$$H_{b1}$), 3.90 (dd, *J* = 7.1 and 7.1 Hz, 1H, *H*COPMB), 3.80 (s, 3H, PhO*Me*), 3.79 (s, 3H, PhO*Me*), 3.75 (dd, *J* = 10.1 and 6.4 Hz, 1H, *H*COCMe$_2$), 3.66 (dddd, *J* = 9.9, 9.9, 5.4, and 5.4 Hz, 1H, *H*COMe$_2$), 3.23 (d, *J* = 8.6 Hz, 1H, CH_aH$_b$OPMB), 3.10 (d, *J* = 8.6 Hz, 1H, CH$_a$$H_b$OPMB), 1.92 (ddd, *J* = 14.1, 8.5 and 6.6 Hz, 1H, CH_{a1}H$_{b1}$), 1.64 (ddd, *J* = 12.5, 10.1 and 5.9 Hz, 1H, CH_{a2}H$_{b2}$), 1.59 (ddd, *J* = 8.4, 8.4 and 5.0 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.32 (ddd, *J* = 12.5, 9.9 and 6.5 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.28 (s, 3H, C*Me*), 1.24 (s, 3H, C*Me*), 0.86 (s, 3H, C*Me*), and 0.80 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 159.1, 144.1, 131.3, 130.9, 129.7, 129.1, 115.1, 113.9, 113.8, 100.4, 79.9, 76.5, 73.1, 69.7, 69.5, 64.2, 55.5, 39.8, 37.8, 33.2, 25.1, 24.4, 20.7, 20.0, and 16.3.

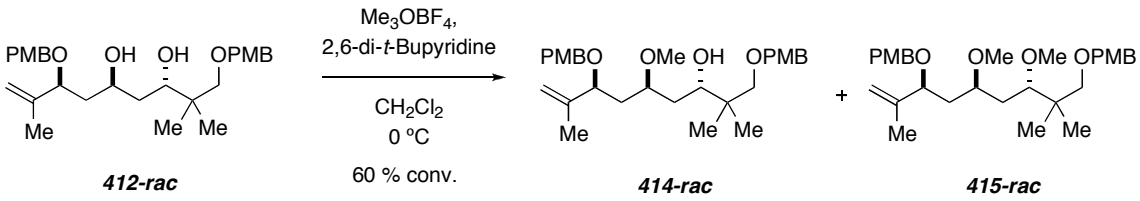
HR ESI-MS: Calcd for $C_{31}H_{44}O_6Na$ $(M+Na)^+$: 535.3030 Found: 535.3037.

TLC: R_f = 0.39; 6:1 hexanes:ethyl acetate.

(3*S*,5*S*,7*S*)-5-Methoxy-1,7-bis(4-methoxybenzyloxy)-2,2,8-trimethylnon-8-en-3-ol **414-*rac***

and

4,4'-((3*S*,5*R*,7*S*)-3,5-Dimethoxy-2,2,8-trimethylnon-8-ene-1,7-diyl)bis(oxy)bis(methylene)bis(methoxybenzene) **415-*rac***



412-rac ***414-rac*** ***415-rac***

To a culture tube containing crude diol **412-*rac*** (30 mg, 0.064 mmol) in CH_2Cl_2

(1.0 mL, 0.064 M) at 0 ºC was added 2,6-di-*t*-butylpyridine (0.215 mL, 0.953 mmol) and Me_3OBF_4 (0.094 g, 0.64 mmol). The reaction was warmed to room temperature and stirred until ~50-60% conversion, as determined by TLC or when the appearance of the bis methylated **415-*rac*** was seen by TLC. The reaction was cooled to 0 ºC and saturated aqueous $NaHCO_3$ was added, diluted with EtOAc and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (3:1 hexanes / ethyl acetate) provided mono-methylated **414-*rac*** (14 mg, 45%) and a trace amount of bis-methylated **415-*rac***.

Characterization Data for Mono-Methylation 414-*rac*

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 7.22 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.85 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 4.98 (s, 1H, CH_aH$_b$=C(Me)), 4.95 (s, 1H, CH$_a$$H_b$=C(Me)), 4.43 (d, *J* = 12.0 Hz, 1H, MeOPhCH_{a1}H$_{b1}$), 4.40 (d, *J* = 12.1 Hz, 1H, MeOPhCH_{a2}H$_{b2}$), 4.40 (d, *J* = 11.9 Hz, 1H, MeOPhCH$_{a1}$$H_{b1}$), 4.16 (d, *J* = 11.3 Hz, 1H, MeOPhCH$_{a2}$$H_{b2}$), 3.86 (dd, *J* = 7.9 and 5.4 Hz, 1H, *H*COPMB), 3.794 (s, 3H, PhO*Me*), 3.787 (s, 3H, PhO*Me*), 3.71-3.64 (m, 1H, *H*COH), 3.60 (appt. t, *J* = 6.0 Hz, 1H, *H*COMe), 3.36 (d, *J* = 4.0 Hz, 1H, O*H*), 3.33 (s, 3H, O*Me*), 3.31 (d, *J* = 8.9 Hz, 1H, CH_aH$_b$OPMB), 3.22 (d, *J* = 8.9 Hz, 1H, CH$_a$$H_b$OPMB), 2.02 (ddd, *J* = 14.1, 7.9 and 5.9 Hz, 1H, CH_{a1}H$_{b1}$), 1.72 (s, 3H, CH$_2$=C(*Me*)), 1.64 (ddd, *J* = 14.2, 5.9 and 5.9 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.53-1.47 (m, 2H, C$H_{a2}$$H_{b2}$), 0.86 (s, 3H, C*Me*), and 0.85 (s, 3H, C*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 159.2, 144.9, 130.9, 130.5, 129.7, 129.3, 114.1, 113.9, 80.1, 78.9, 76.4, 74.5, 73.3, 69.8, 57.1, 55.4, 38.5, 38.0, 35.4, 22.7, 20.1, and 16.8.

HR ESI-MS: Calcd for $C_{29}H_{42}O_6Na$ $(M+Na)^+$: 509.2874 Found: 509.2881.

TLC: R_f = 0.32; 3:1 hexanes:ethyl acetate.

Characterization Data for Bis-Methylation 415-*rac*

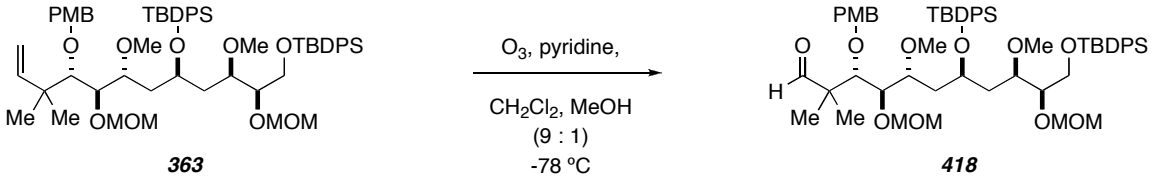
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.5 Hz, 4H, MeOPhH_a), 6.87 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.85 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 4.96 (s, 1H, CH_aH$_b$=C(Me)), 4.95 (s, 1H, CH$_a$$H_b$=C(Me)), 4.44 (d, *J* = 11.8 Hz, 1H, MeOPhCH_{a1}H$_{b1}$), 4.39 (d, *J* = 11.5 Hz, 1H, MeOPhCH$_{a1}$$H_{b1}$), 4.39 (d, *J* = 11.5 Hz, 1H, MeOPhCH_{a2}H$_{b2}$), 4.17 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_{a2}$$H_{b2}$), 3.84 (dd, *J* = 8.4 and 4.7 Hz, 1H, *H*COPMB), 3.80 (s, 3H,

PhO*Me*), 3.79 (s, 3H, PhO*Me*), 3.57-3.49 (m, 1H, *H*COMe), 3.43 (s, 3H, O*Me*), 3.34 (dd, *J* = 10.3 and 2.1 Hz, 1H, *H*COMe), 3.30 (s, 3H, O*Me*), 3.30 (d, *J* = 8.8 Hz, 1H, C$H_a$$H_b$OPMB), 3.10 (d, *J* = 8.7 Hz, 1H, C$H_a$$H_b$OPMB), 2.01 (ddd, *J* = 13.9, 8.3, and 4.9 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.72 (s, 3H, CH_2=C(*Me*)), 1.58 (ddd, *J* = 11.9, 9.4 and 2.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.54 (ddd, *J* = 11.8, 6.9 and 4.8 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.48 (ddd, *J* = 14.4, 10.1 and 2.9 Hz, 1H, C$H_{a1}$$H_{b1}$), 0.87 (s, 3H, C*Me*), and 0.85 (s, 3H, C*Me*).

HR ESI-MS: Calcd for $C_{30}H_{44}O_6Na$ $(M+Na)^+$: 523.3030 Found: 523.3011.

TLC: R_f = 0.50; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,5*R*,7*S*,9*R*,10*R*)-7,11-Bis(*tert*-butyldiphenylsilyloxy)-5,9-dimethoxy-3-(4-methoxybenzyloxy)-4,10-bis(methoxymethoxy)-2,2-dimethylundecanal **418**



A 9:1 mixture of CH_2Cl_2:MeOH (5.90 mL, 0.02M) was added to a 25 mL round bottom flask containing alkene **363** (122 mg, 0.119 mmol). This solution was cooled to -78 ºC and pyridine (0.095 mL, 1.18 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the reaction mixture, observed by the change of the solution from a light blue color to colorless. Dimethyl sulfide (6.0 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6 hours. The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (2:1 hexanes / ethyl acetate) to provide aldehyde **418** (116 mg, 97%) as a colorless oil.

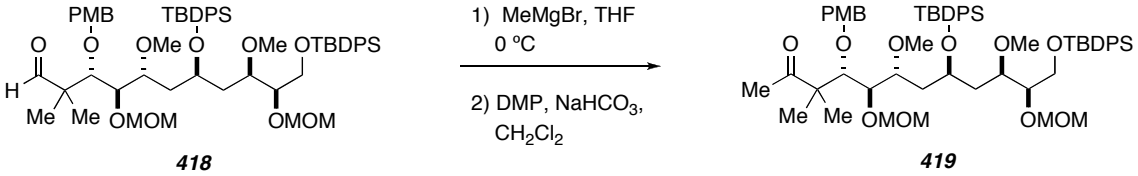
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.33 (s, 1H, *H*C=O), 7.71-7.59 (m, 8H, Ph*H*), 7.49-

7.17 (m, 12H, Ph*H*), 7.11 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.82 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.65 (d, *J* = 6.3 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.65 (d, *J* = 6.7 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.55 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.51 (d, *J* = 6.7 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.39 (d, *J* = 6.4 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.30 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.28-4.21 (m, 1H, *H*COTBDPS), 3.78 (s, 3H, PhO*Me*), 3.72 (dd, *J* = 8.5 and 1.3 Hz, 1H, *H*COMOM), 3.65-3.52 (m, 4H, *H*COMOM, *H*COMe, and CH_2OTBDPS), 3.47 (d, *J* = 8.5 Hz, 1H, *H*COPMB), 3.39 (ddd, *J* = 9.4, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.27 (s, 3H, O*Me*), 3.23 (s, 3H, O*Me*),), 3.13 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 1.88 (ddd, *J* = 14.5, 10.0, and 3.8 Hz, 1H, CH_{a1}H$_{b1}$), 1.79-1.70 (m, 2H, CH$_{a1}$$H_{b1}$ and CH_{a2}H$_{b2}$), 1.63 (ddd, *J* = 13.8, 8.7, and 3.3 Hz, CH$_{a2}$$H_{b2}$), 1.08 (s, 3H, C*Me*), 1.06 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 0.97 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.9, 159.2, 136.2, 136.1, 135.8, 135.7, 134.7, 134.3, 133.62, 133.57, 130.3, 129.85, 129.82, 129.7, 128.6, 127.86, 127.84, 127.7, 127.6, 113.8, 97.22, 97.17, 82.0, 79.5, 79.2, 77.6, 77.4, 77.1, 74.7, 69.1, 63.7, 58.5, 57.2, 57.0, 55.8, 55.4, 50.5, 39.3, 38.0, 27.3, 27.0, 21.4, 19.6, 19.3, and 15.8.

TLC: R_f = 0.64; 2:1 hexanes:ethyl acetate.

(4*S*,5*R*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-5,11-bis(methoxymethoxy)-3,3-dimethyldodecan-2-one **419**



418 ***419***

Grignard Addition

To a 25 mL round bottom flask containing aldehyde **418** (0.343 g, 0.335 mmol) in THF (5.6 mL, 0.06 M) at 0 ºC was added MeMgBr (1.05 mL, 2.63 mmol, ~2.5 M in THF) and the reaction mixture was stirred for 30 minutes at 0 ºC. Saturated aqueous NH_4Cl was added to quench the reaction at 0 ºC. The solution was diluted with H_2O and

EtOAc. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude alcohol resulting from Gignard addition was carried on to the next step without purification.

Characterization Data for Alcohol 418-1

TLC: R_f = 0.23; 2:1 hexanes:ethyl acetate.

Oxidation to Ketone

To a 50 mL round bottom flask containing crude alcohol **418-1** (~0.335 mmol) was added CH_2Cl_2 (7.2 mL, 0.046 M). The reaction was cooled to 0 ºC followed by the addition of $NaHCO_3$ (88 mg, 1.04 mmol), and Dess-Martin periodinane (185 mg, 0.435 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 1.5 hours. The mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (10 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (2:1 hexanes / ethyl acetate) provided ketone **419** (299 mg, 86% over 2-steps).

Characterization Data for Ketone 419

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.60 (m, 8H, Ph*H*), 7.46-7.16 (m, 12H, Ph*H*), 7.10 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.82 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.65 (d, *J* = 6.7 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.58 (d, *J* = 6.0 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.50 (d, *J* = 6.7 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.44 (d, *J* = 11.3 Hz, 1H, MeOPhCH_aH$_b$), 4.42 (d, *J* = 5.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.30 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_a$$H_b$), 4.26 (dddd, *J* = 7.9, 7.9, 3.7, and 3.7 Hz, 1H, *H*COTBDPS), 3.79 (s, 3H, PhO*Me*), 3.69-3.49 (m, 6H, *H*COPMB, *H*COMOM, *H*COMOM, *H*COMe, and CH_2OTBDPS), 3.39 (dd, *J* = 9.2 and 3.1 Hz, 1H, *H*COMe), 3.27 (s, 3H, O*Me*), 3.22 (s, 3H, O*Me*),), 3.15 (s, 3H, O*Me*), 3.09 (s, 3H, O*Me*), 2.03 (s, 3H, *Me*C=O), 1.88 (ddd, *J* = 14.3, 10.1, and 3.3 Hz, 1H, CH_{a1}H$_{b1}$), 1.78-1.70 (m,

2H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$), 1.65 (ddd, J = 13.9, 8.7, and 3.6 Hz, $CH_{a2}H_{b2}$), 1.11 (s, 6H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 0.97 (s, 9H, SiCMe_3).

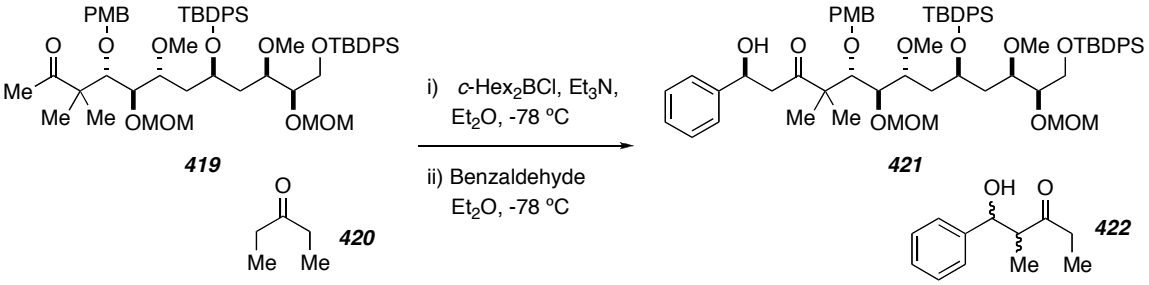
^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.3, 159.1, 136.2, 136.1, 135.8, 135.7, 134.5, 134.4, 133.63, 133.61, 130.6, 129.84, 129.81, 129.68, 129.65, 129.4, 127.8, 127.6, 113.8, 97.6, 97.3, 82.4, 79.6, 79.55, 77.6, 77.4, 74.7, 69.1, 63.8, 58.5, 57.2, 56.8, 55.8, 55.4, 52.2, 39.4, 37.8, 27.3, 27.1, 25.9, 24.6, 19.6, 19.3, and 17.2.

HR ESI-MS: Calcd for $C_{60}H_{84}O_{11}Si_2Na$ $(M+Na)^+$: 1059.5444 Found: 1059.5495.

TLC: R_f = 0.61; 2:1 hexanes:ethyl acetate.

[α]^{RT} = +3.16 (c = 0.19, $CDCl_3$).

(1*S*,5*S*,6*R*,7*R*,9*S*,11*R*,12*R*)-9,13-Bis(*tert*-butyldiphenylsilyloxy)-1-hydroxy-7,11-dimethoxy-5-(4-methoxybenzyloxy)-6,12-bis(methoxymethoxy)-4,4-dimethyl-1-phenyltridecan-3-one **421**



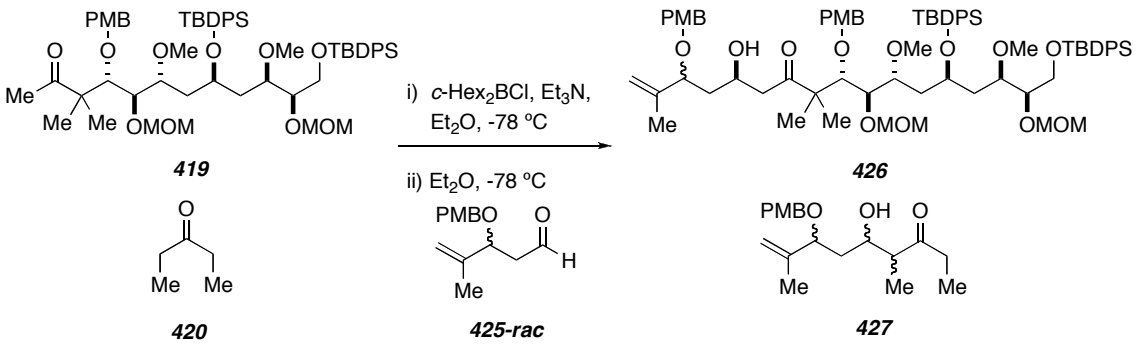
To a culture tube containing dicyclohexylboron chloride (0.100 mL, 0.456 mmol) in Et_2O (3.0 mL, 0.15 M) at -78 ºC was added Et_3N (0.072 mL, 0.517 mmol). Ketone **419** (39 mg, 0.038 mmol) and 3-pentanone (**420**) (0.028 mL, 0.266 mmol) in Et_2O (1.5 mL) was added via syringe. The reaction was warmed to 0 ºC and stirred for 1 hr before recooling to -78 ºC. A solution of benzaldehyde (0.062 mL, 0.608 mmol) in Et_2O (1.0 mL) was added via syringe and stirred for 3 hr at -78 ºC before transferring the reaction to a freezer (-20 ºC, 16 hr). To the rection mixture at 0 ºC was added a solution of pH 7 buffer (1.2 mL) and MeOH (3.6 mL) with vigorous stirring. A solution of pH 7 buffer (3.2 mL) and 30% aqueous H_2O_2 (1.6 mL) was added and the mixture was stirred at 0 ºC

for 3 hr. The reaction mixture was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O (3 x 30 mL), the combined organic layers were washed with saturated aqeous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via MPLC (3:1 hexanes / ethyl acetate) provided aldol product **421** (20 mg, 47%) and an inseparable mixture of **422**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72-7.59 (m, 8H, Ph*H*), 7.48-7.23 (m, 15H, Ph*H*), 7.18 (t, *J* = 7.5 Hz, 2H, Ph*H*), 7.07 (d, *J* = 8.5 Hz, 2H, MeOPhH_a), 6.80 (d, *J* = 8.5 Hz, 2H, MeOPhH_b), 5.08 (ddd, *J* = 8.5, 3.1, and 3.1 Hz, 1H, *H*COH), 4.66 (d, *J* = 6.9 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.64 (d, *J* = 5.7 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.50 (d, *J* = 6.7 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.48 (d, *J* = 5.8 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.40 (d, *J* = 11.2 Hz, 1H, MeOPhCH_aH$_b$), 4.24 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.23 -4.17 (m, 1H, *H*COTBDPS), 3.91 (d, *J* = 2.3 Hz, 1H, *H*COPMB), 3.78 (s, 3H, PhO*Me*), 3.72 (d, *J* = 9.0 Hz, *H*CO-X), 3.64-3.59 (m, 3H, *H*CO-X, *H*CO-X, *H*CO-X), 3.56 (dd, *J* = 11.4 and 8.4 Hz, , *H*CO-X), 3.49 (dd, *J* = 10.1 and 2.0 Hz, 1H, , *H*CO-X), 3.37 (ddd, *J* = 9.3, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.34 (s, 3H, O*Me*), 3.23 (s, 3H, O*Me*), 3.13 (s, 3H, O*Me*), 3.08 (s, 3H, O*Me*), 2.87-2.75 (m, 2H, HCOHCH_2C=O), 1.86 (ddd, *J* = 14.4, 10.1, and 3.5 Hz, 1H, CH_{a1}H$_{b1}$), 1.78-1.70 (m, 2H, CH_{a2}H$_{b2}$ and CH$_{a2}$$H_{b2}$), 1.66 (ddd, *J* = 13.6, 8.6, and 3.5 Hz, CH$_{a1}$$H_{b1}$), 1.12 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3) and 0.97 (s, 9H, SiCMe_3). [X represents unassigned functional group. The COSY necessary to fully assign the methine protons was not performed.]

TLC: R_f = 0.23; 3:1 hexanes:ethyl acetate.

(5*R*,9*S*,10*R*,11*R*,13*S*,15*R*,16*R*)-13,17-Bis(*tert*-butyldiphenylsilyloxy)-5-hydroxy-11,15-dimethoxy-3,9-bis(4-methoxybenzyloxy)-10,16-bis(methoxymethoxy)-2,8,8-trimethylheptadec-1-en-7-one **426**



To a culture tube containing dicyclohexylboron chloride (0.100 mL, 0.456 mmol) in Et_2O (3.0 mL, 0.15 M) at -78 ºC was added Et_3N (0.072 mL, 0.517 mmol). Ketone **419** (30 mg, 0.029 mmol) and 3-pentanone (**420**) (0.029 mL, 0.275 mmol) in Et_2O (2.0 mL) was added via syringe. The reaction was warmed to 0 ºC and stirred for 1 hr before recooling to -78 ºC. A solution of aldehyde **425-*rac*** (0.147 g, 0.608 mmol) in Et_2O (2.0 mL) was added via syringe and stirred for 3 hr at -78 ºC before transferring the reaction to a freezer (-20 ºC, 16 hr). To the rection mixture at 0 ºC was added a solution of pH 7 buffer (1.2 mL) and MeOH (3.6 mL) with vigorous stirring. A solution of pH 7 buffer (3.2 mL) and 30% aqueous H_2O_2 (1.6 mL) was added and the mixture was stirred at 0 ºC for 3 hr. The reaction mixture was diluted with H_2O and Et_2O. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organic layers were washed with saturated aqeous $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. Purification via MPLC (3:1 hexanes / ethyl acetate) provided aldol product **426** (22 mg, 60%) and a complex inseparable mixture of **427**.

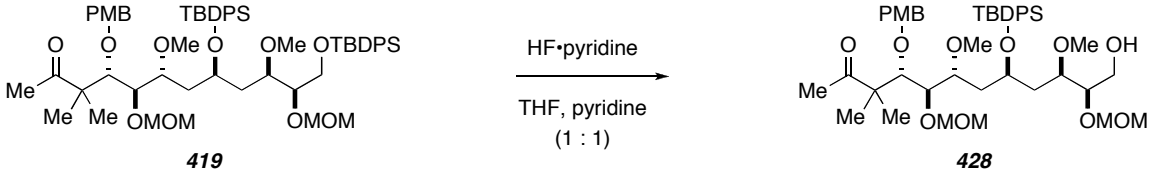
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73-7.15 (m, 12H, Ph*H*, MeOPhH_{a1}), 7.08 (d, *J* = 8.5 Hz, 2H, MeOPhH_{a2}), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_{b1}), 6.81 (d, *J* = 8.6 Hz, 2H, MeOPhH_{b2}), 5.02 (bs, 1H, CH_aH$_b$=C(Me)), 5.01 (bs, 1H, CH$_a$$H_b$=C(Me)), 4.65 (d, *J* = 6.7 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.57 (d, *J* = 5.9 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.50 (d, *J* = 6.7 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.43 (d, *J* = 11.2 Hz, 1H, MeOPhCH_{a1}H$_{b1}$), 4.41 (d, *J* = 5.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.40 (d, *J* = 11.3 Hz, 1H, MeOPhCH_{a2}H$_{b2}$), 4.23 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_{a2}$$H_{b2}$), 4.21 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_{a1}$$H_{b1}$), 4.26-4.15 (m, 1H, *H*CO-X), 4.14-4.07 (m, 1H, *H*CO-X), 4.08 (dd, *J* = 8.1 and 5.6 Hz, 1H, *H*CO-X), 3.79 (s, 3H,

PhO*Me*), 3.78 (s, 3H, PhO*Me*), 3.73-3.66 (m, 2H, *H*CO-X, *H*CO-X), 3.65-3.52 (m, 4H, *H*CO-X, *H*CO-X, *H*CO-X, *H*CO-X), 3.47 (dd, *J* = 10.0 and 2.1 Hz, 1H, *H*CO-X), 3.38-3.33 (m, 1H, *H*CO-X) 3.25 (s, 3H, O*Me*), 3.24 (d, *J* = 2.3 Hz, 1H, *H*COPMB), 3.22 (s, 3H, O*Me*), 3.15-3.12 (m, 1H, *H*CO-X), 3.13 (s, 3H, O*Me*), 3.05 (s, 3H, O*Me*), 2.70 (dd, *J* = 17.6 and 7.5 Hz, 1H, HC(OH)C$H_a$$H_b$C=O), 2.45 (dd, *J* = 17.6 and 4.3 Hz, 1H, HC(OH)C$H_a$$H_b$C=O), 1.94-1.49 (m, 6H, CH_2, CH_2, CH_2), 1.71 (s, 3H, $CH_a$$H_b$=C(*Me*)), 1.09 (s, 6H, CMe_2), 1.02 (s, 9H, SiCMe_3) and 0.96 (s, 9H, SiCMe_3). [X represents unassigned functional group. The COSY necessary to fully assign the methine protons was not performed.]

HR ESI-MS: Calcd for $C_{74}H_{102}O_{14}Si_2Na$ $(M+Na)^+$: 1293.6700 Found: 1293.6716.

TLC: R_f = 0.22; 3:1 hexanes:ethyl acetate.

(4*S*,5*R*,6*R*,8*S*,10*R*,11*R*)-8-(*tert*-Butyldiphenylsilyloxy)-12-hydroxy-6,10-dimethoxy-4-(4-methoxybenzyloxy)-5,11-bis(methoxymethoxy)-3,3-dimethyldodecan-2-one **428**



To a plastic culture tube containing ketone **419** (227 mg, 0.219 mmol) was added THF (13.5 mL, 0.016 M) and pyridine (13.5 mL, 0.016 M). The reaction was cooled to 0 ºC and HF•pyridine (1.35 mL of a 70% HF / 30% pyridine solution) was added dropwise. The reaction was stirred at room temperature for 3 hours at which time TLC showed remaining starting material. More HF•pyridine (1.6 mL of a 70% HF / 30% pyridine solution) was added dropwise and stirred for 4.5 hours. The reaction mixture was diluted with EtOAc and transferred to 250 mL Erlenmeyer flask. Saturated aqueous $NaHCO_3$ (~150 mL) was slowly added to the mixture until no evolution of gas was observed. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers

were washed with H_2O (2 x 150 mL), saturated $CuSO_4$ (2 x 100 mL), and saturated NaCl (1 x 100 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (1:3 hexanes / ethyl acetate) to provide alcohol **428** (162 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78-7.67 (m, 4H, Ph*H*), 7.45-7.30 (m, 6H, Ph*H*), 7.11 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.83 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 4.56 (d, *J* = 6.0 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.48 (d, *J* = 6.9 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.45 (d, *J* = 6.0 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.36 (d, *J* = 6.9 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.33 (d, *J* = 11.5 Hz, 1H, MeOPhCH_aH$_b$), 4.30 (d, *J* = 11.4 Hz, 1H, MeOPhCH$_a$$H_b$), 4.11-4.04 (m, 1H, *H*COTBDPS), 3.79 (s, 3H, PhO*Me*), 3.63 (d, *J* = 9.1 Hz, 1H, *H*COMOM or *H*COPMB), 3.58 (d, *J* = 9.1 Hz, 1H, *H*COMOM or *H*COPMB), 3.48-3.41 (m, 3H, *H*COMe and CH_2OH), 3.37-3.28 (m, 2H, *H*COMe and *H*COMOM), 3.32 (s, 3H, O*Me*), 3.31 (s, 3H, O*Me*), 3.20 (s, 3H, O*Me*), 3.17 (s, 3H, O*Me*), 3.03 (dd, *J* = 7.6 and 4.9 Hz, O*H*), 2.01 (s, 3H, *Me*C=O), 1.84 (ddd, *J* = 14.7, 9.5, and 4.8 Hz, 1H, CH_{a1}H$_{b1}$), 1.84-1.74 (m, 2H, CH$_{a1}$$H_{b1}$ and CH_{a2}H$_{b2}$), 1.70 (ddd, *J* = 13.9, 7.0, and 5.0 Hz, CH$_{a2}$$H_{b2}$), 1.12 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), and 1.03 (s, 9H, SiCMe_3).

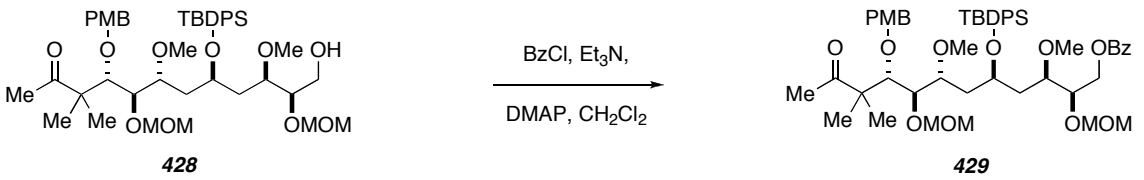
^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.2, 159.0, 136.13, 136.06, 134.17, 134.16, 130.4, 129.8, 129.7, 128.0, 127.7, 127.6, 113.7, 97.6, 97.5, 82.1, 81.9, 79.7, 78.9, 74.5, 69.3, 63.2, 58.0, 57.02, 57.00, 55.8, 55.3, 52.1, 38.4, 38.2, 27.1, 25.8, 24.5, 19.5, and 17.1.

HR ESI-MS: Calcd for $C_{44}H_{66}O_{11}SiNa$ $(M+Na)^+$: 821.4267 Found: 821.4263.

TLC: R_f = 0.48; 2:1 hexanes:ethyl acetate.

(2*R*,3*R*,5*S*,7*R*,8*R*,9*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2,8-bis(methoxymethoxy)-10,10-dimethyl-11-oxododecyl benzoate

429



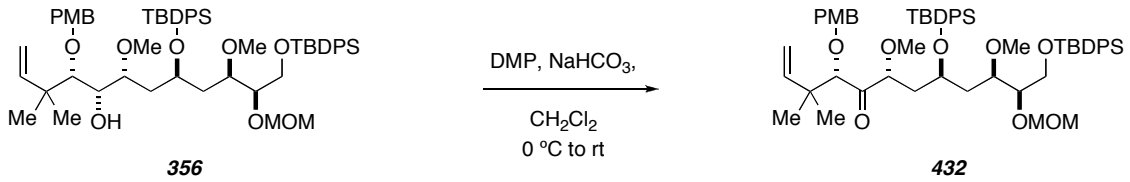
428 ***429***

To a culture tube containing alcohol **428** (160 mg, 0.200 mmol) was added CH_2Cl_2 (4.0 mL, 0.05 M). The reaction mixture was cooled to 0 ºC followed by the addition of Et_3N (0.126 mL, 0.901 mmol), DMAP (2 mg, 0.02 mmol), and benzoyl chloride (0.083 mL, 0.721 mmol). The solution was warmed to room temperature and stirred for 20 hours. The mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (20 mL) was added, followed by dilution with H_2O (10 mL) and EtOAc (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification via column chromatography (2:1 hexanes / ethyl acetate) provided alcohol **429** (165 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13-7.27 (m, 15H, SiPh*H* and O_2CPh*H*), 7.11 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.82 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 4.58 (d, *J* = 6.8 Hz, 1H, OCH_{a1}H$_{b1}$OMe), 4.56 (d, *J* = 6.0 Hz, 1H, OCH_{a2}H$_{b2}$OMe), 4.50 (d, *J* = 6.8 Hz, 1H, OCH$_{a1}$$H_{b1}$OMe), 4.43 (d, *J* = 6.0 Hz, 1H, OCH$_{a2}$$H_{b2}$OMe), 4.36 (d, *J* = 11.2 Hz, 1H, MeOPhCH_aH$_b$), 4.30 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_a$$H_b$), 4.28-4.18 (m, 3H, C$H_2$OBz and *H*OTBDPS), 3.77 (s, 3H, PhO*Me*), 3.72 (ddd, *J* = 6.6, 4.0, and 4.0 Hz, 1H, *H*COMOM), 3.65 (d, *J* = 9.1 Hz, 1H, *H*COPMB or *H*COMOM), 3.60 (d, *J* = 9.1 Hz, 1H, *H*COMOM or *H*COPMB), 3.48 (dd, *J* = 10.2 and 2.3 Hz, 1H, *H*COMe), 3.40 (ddd, *J* = 8.1, 4.2, and 4.2 Hz, 1H, *H*COMe), 3.28 (s, 3H, O*Me*), 3.25 (s, 6H, O*Me*), 3.14 (s, 3H, O*Me*), 2.02 (s, 3H, *Me*C=O), 1.92-1.83 (m, 2H, CH_{a1}H$_{b1}$ and CH_{a2}H$_{b2}$), 1.82-1.74 (m, 2H, CH$_{a1}$$H_{b1}$ and CH$_{a2}$$H_{b2}$), 1.11 (s, 3H, C*Me*), 1.10 (s, 3H, C*Me*), and 0.99 (s, 9H, SiCMe_3).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.4, 166.5, 159.1, 136.2, 136.1, 134.3, 133.8, 133.2, 130.5, 139.34, 139.28, 129.9, 129.8, 128.65, 128.57, 128.3, 127.82, 127.75, 113.8, 97.6, 97.1, 82.2, 79.7, 77.9, 77.4, 76.6, 74.6, 69.3, 65.0, 58.4, 57.1, 57.0, 55.9, 55.4, 52.2, 38.8, 38.4, 27.2, 25.9, 24.6, 19.6, and 17.2.
HR ESI-MS: Calcd for $C_{51}H_{70}O_{12}SiNa$ $(M+Na)^+$: 925.4529 Found: 925.4530.

TLC: R_f = 0.41; 2:1 hexanes:ethyl acetate.

(4*S*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-one **432**



356 ***432***

To a 100 mL round bottom flask containing alcohol **356** (1.15 g, 1.18 mmol) was added CH_2Cl_2 (25.6 mL, 0.046 M). The reaction was cooled to 0 ºC followed by the addition of $NaHCO_3$ (445 mg, 5.30 mmol), and Dess-Martin periodinane (619 mg, 1.46 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 18 hours. The mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous $Na_2S_2O_3$ (20 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (20 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude ketone **432** in >90%. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69-7.57 (m, 8H, Ph*H*), 7.45-7.18 (m, 14H, Ph*H* and MeOPhH_a), 6.83 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.99 (dd, *J* = 17.4 and 10.9 Hz, 1H, CH_2=C*H*), 4.99 (dd, *J* = 10.9 and 1.3 Hz, 1H, CH_aH$_b$=CH), 4.97 (dd, *J* = 17.4 and 1.3 Hz, 1H, CH$_a$$H_b$=CH), 4.65 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.51 (d, *J* = 11.0 Hz, 1H, MeOPhCH_aH$_b$), 4.49 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.35 (dd, *J* = 10.1 and 2.4 Hz, 1H, *H*COMe), 4.29 (d, *J* = 11.0 Hz, 1H, MeOPhCH$_a$$H_b$), 4.24 (dddd, *J* = 9.6, 9.6, 2.7, and 2.7 Hz, 1H, *H*COTBDPS), 3.77 (s, 3H, PhO*Me*), 3.74 (s, 1H, *H*COPMB), 3.61-3.54 (m, 1H, CH_aH$_b$OTBDPS), 3.54-3.47 (m, 2H, CH$_a$$H_b$OTBDPS and *H*COMOM), 3.25 (ddd, *J* =

10.3, 2.7, and 2.7 Hz, 1H, *H*COMe), 3.22 (s, 3H, O*Me*), 3.05 (s, 3H, O*Me*), 3.02 (s, 3H, O*Me*), 1.88 (ddd, *J* = 14.1, 9.4, and 2.5 Hz, 1H, CH_{a1}H$_{b1}$), 1.71-1.60 (m, 2H, CH$_{a1}$$H_{b1}$ and CH_{a2}H$_{b2}$), 1.48 (ddd, *J* = 13.9, 9.8, and 2.4 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.08 (s, 3H, C*Me*), 1.03 (s, 9H, SiCMe_3), and 1.02 (s, 9H, SiCMe_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.6, 159.4, 144.0, 136.2, 136.1, 135.8, 135.7, 134.7, 134.0, 133.6, 133.5, 129.9, 129.8, 129.7, 129.6, 127.9, 127.7, 127.5, 113.9, 113.1, 97.1, 89.3, 80.8, 79.3, 77.4, 74.1, 67.9, 63.7, 58.6, 57.4, 55.8, 55.4, 41.8, 39.7, 38.5, 27.3, 27.0, 23.84, 23.79, 19.6, and 19.3.

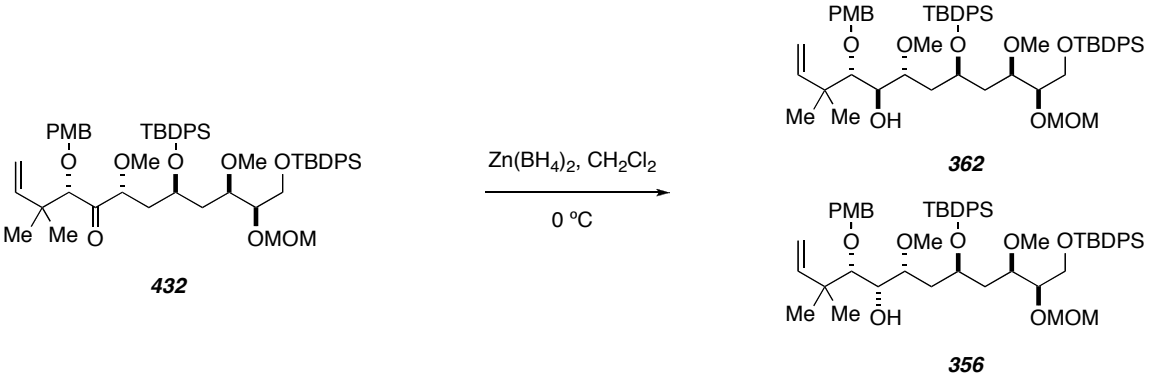
HR ESI-MS: Calcd for $C_{58}H_{78}O_9Si_2Na$ $(M+Na)^+$: 999.5077 Found: 997.5086.

TLC: R_f = 0.48; 6:1 hexanes:ethyl acetate (eluted 2 x).

(4*S*,5*R*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **362**

and

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldiphenylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **356**



432

362

356

To a 250 mL round bottom flask containing crude ketone **432** (~1.18 mmol) was added CH_2Cl_2 (58.8 mL, 0.02 M) and cyclohexene (1.17 mL, 11.6 mmol). The reaction was cooled to 0 ºC and $Zn(BH_4)_2$ (11.8 mL, 5.89 mmol, 0.5 M in Et_2O) was added. The solution was stirred for 50 minutes at 0 ºC until TLC showed complete consumption of

the starting material. Saturated aqueous NH_4Cl (30 mL) was added at 0 ºC to quench the reaction. The mixture was diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via MPLC (3:1 hexanes / ethyl acetate) to provide **362** (710 mg, 62%, 2-steps) and epimer **356** (242 mg, 21%).

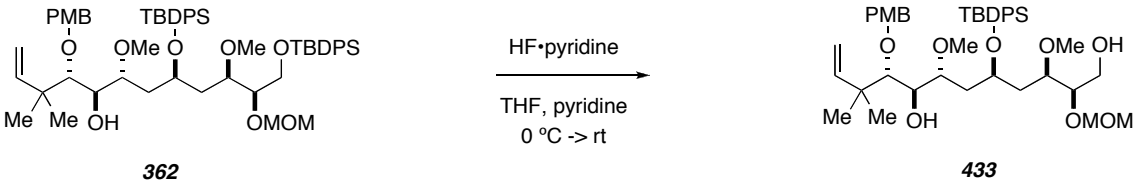
Characterization Data for 362

(previously reported in experimental section)

Characterization Data for 356

(previously reported in experimental section)

(2*R*,3*R*,5*R*,7*R*,8*R*,9*S*)-5-(*tert*-Butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-ene-1,8-diol **433**



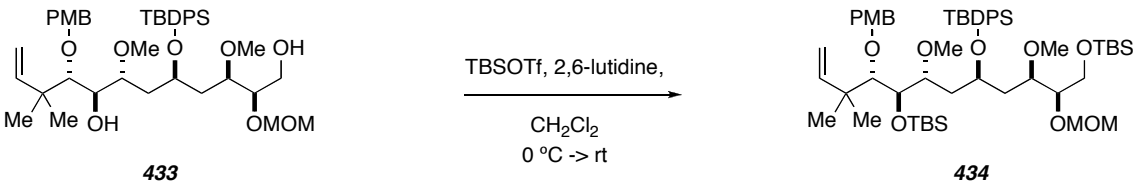
362 ***433***

To a plastic culture tube containing alcohol **362** (117 mg, 0.120 mmol) was added THF (3.7 mL, 0.032 M) and pyridine (3.7 mL, 0.032 M). The reaction was cooled to 0 ºC and HF•pyridine (0.73 mL of a 70% HF / 30% pyridine solution) was added dropwise. The reaction was stirred at room temperature for 3.5 hours at which time TLC showed no remaining starting material. The reaction mixture was diluted with EtOAc and transferred to 125 mL Erlenmeyer flask. Saturated aqueous $NaHCO_3$ (~60 mL) was slowly added to the mixture until no evolution of gas was observed. The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with H_2O (1 x 60 mL), saturated $CuSO_4$ (2 x 40 mL), and saturated NaCl (1 x 60 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified

via column chromatography (1:3 hexanes / ethyl acetate) to provide the diol **433** (58 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72-7.63 (m, 4H, Ph*H*), 7.43-7.29 (m, 6H, Ph*H*), 7.17 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.82 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.04 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.04 (dd, *J* = 17.6 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 5.00 (dd, *J* = 10.8 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.55 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.50 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.41 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$OMe), 4.36 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.13 (dddd, *J* = 12.4, 7.6, 4.8, and 4.8 Hz, 1H, *H*COTBDPS), 3.95 (ddd, *J* = 7.3, 2.4, and 2.4 Hz, 1H, *H*COH), 3.79 (s, 3H, PhO*Me*), 3.59 (ddd, *J* = 9.5, 2.9, and 2.9 Hz, 1H, *H*COMe), 3.48-3.37 (m, 2H, CH_2OH), 3.33 (s, 3H, O*Me*), 3.30-3.22 (m, 2H, *H*COMe and *H*COMOM), 3.14 (s, 6H, O*Me*), 3.09 (d, *J* = 7.3 Hz, 1H, *H*COPMB), 2.95 (dd, *J* = 8.3 and 4.2 Hz, 1H, O*H*), 1.99 (d, *J* = 2.6 Hz, 1H, O*H*), 1.88 (ddd, *J* = 14.5, 9.4, and 4.5 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.83 (ddd, *J* = 14.7, 8.0, and 3.2 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.73 (ddd, *J* = 13.9, 8.0, and 5.1 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.65 (ddd, *J* = 13.8, 7.6, and 4.6 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.12 (s, 3H, C*Me*), 1.11 (s, 3H, C*Me*), and 1.01 (s, 9H, SiCMe_3).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 146.4, 136.3, 136.2, 134.6, 134.4, 131.0, 129.8,129.7, 128.5, 127.7, 127.6, 113.7, 111.6, 97.6, 85.8, 81.8, 79.0, 78.9, 74.5, 71.9, 69.0, 63.2, 58.1, 56.6, 55.9, 55.4, 42.3, 38.7, 37.1, 27.2, 25.5, 22.8, and 19.5.
HR ESI-MS: Calcd for $C_{42}H_{62}O_9SiNa$ $(M+Na)^+$: 761.4055 Found: 761.4018.
TLC: R_f = 0.72; 100% ethyl acetate.

(5*R*,6*R*,8*S*,10*R*,11*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6,10-dimethoxy-5-((*S*)-1-(4-methoxybenzyloxy)-2,2-dimethylbut-3-enyl)-11-(methoxymethoxy)-2,2,3,3,14,14,15,15-octamethyl-4,13-dioxa-3,14-disilahexadecane **434**



433 ***434***

To a 25 mL round bottom flask containing alcohol **433** (171 mg, 0.235 mmol), was added CH_2Cl_2 (4.8 mL, 0.05 M). The solution was cooled to 0 ºC followed by the addition of 2,6-lutidine (0.167 mL, 1.45 mmol) and TBSOTf (0.249 mL, 1.08 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 2 hours until TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was diluted with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (9:1 hexanes / ethyl acetate) to provide **434** (159 mg, 60%).

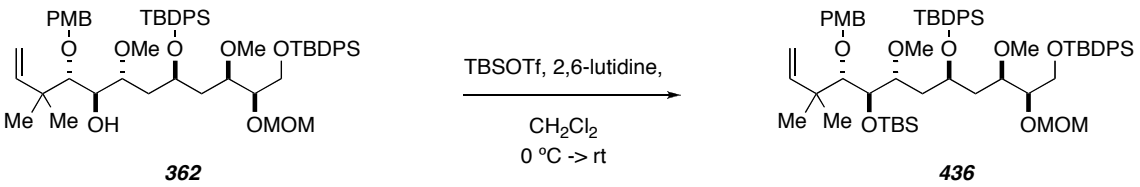
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.0 and 1.3 Hz, 2H, Ph*H*), 7.61 (dd, *J* = 7.9 and 1.3 Hz, 2H, Ph*H*), 7.40-7.25 (m, 8H, Ph*H* and MeOPhH_a), 6.84 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.00 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.6 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 4.98 (dd, *J* = 10.8 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.85 (d, *J* = 10.9 Hz, 1H, MeOPhC$H_a$$H_b$), 4.57 (d, *J* = 6.7 Hz, 1H, OC$H_a$$H_b$OMe), 4.40 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.40 (d, *J* = 10.0 Hz, 1H, MeOPh$CH_a$$H_b$), 4.33-4.26 (m, 1H, *H*COTBDPS), 4.12 (dd, *J* = 1.1 and 1.1 Hz, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.81-3.76 (m, 1H, *H*COMe), 3.44 (dd, *J* = 10.2 and 4.4 Hz, 1H, C$H_a$$H_b$OTBDPS), 3.39 (ddd, *J* = 7.2, 4.3, and 3.3 Hz, 1H, *H*COMOM), 3.31-3.25 (m, 2H, $CH_a$$H_b$OTBDPS and *H*COPMB), 3.22 (s, 3H, O*Me*), 3.14 (ddd, *J* = 10.3, 2.6, and 2.6 Hz, 1H, *H*COMe), 3.12 (s, 3H, O*Me*), 3.09 (s, 3H, O*Me*), 1.95-1.85 (m, 2H, C$H_{a1}$$H_{b1}$), 1.62 (ddd, *J* = 13.7, 10.4, and 3.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.36 (ddd, *J* = 13.2, 10.4, and 2.5 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.09 (s, 3H, C*Me*), 1.08 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3), 0.92 (s, 9H, SiCMe_3), 0.85 (s, 9H, SiCMe_3), 0.06 (s, 3H, Si*Me*), 0.04 (s, 3H, Si*Me*), -0.015 (s, 3H, Si*Me*), and -0.018 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 145.9, 136.24, 136.20, 135.9, 134.8, 131.5, 129.5, 129.4, 129.3, 127.5, 127.3, 113.7, 111.9, 97.1, 91.8, 79.6, 79.0, 77.9, 75.7, 73.7, 68.8, 63.1, 58.9, 56.6, 55.6, 55.4, 42.0, 40.4, 37.6, 27.4, 26.3, 26.2, 25.9, 24.1, 19.6, 18.5, 18.4, -3.8, -4.8, -5.2, and -5.3.

HR ESI-MS: Calcd for $C_{54}H_{90}O_9Si_3Na$ $(M+Na)^+$: 989.5785 Found: 989.5803.

TLC: R_f = 0.43; 9:1 hexanes:ethyl acetate.

(5*R*,6*R*,8*S*,10*R*,11*R*)-8-(*tert*-Butyldiphenylsilyloxy)-6,10-dimethoxy-5-((*S*)-1-(4-methoxybenzyloxy)-2,2-dimethylbut-3-enyl)-11-(methoxymethoxy)-2,2,3,3,15,15-hexamethyl-14,14-diphenyl-4,13-dioxa-3,14-disilahexadecane **436**



To a 50 mL round bottom flask containing alcohol **362** (651 mg, 0.666 mmol), was added CH_2Cl_2 (13.3 mL, 0.05 M). The solution was cooled to 0 ºC followed by the addition of 2,6-lutidine (0.470 mL, 4.00 mmol) and TBSOTf (0.69 mL, 3.00 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 2 hours until TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and quenched with saturated aqueous $NaHCO_3$ (20 mL). The mixture was diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (9:1 hexanes / ethyl acetate) to provide **436** (649 mg, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66-7.11 (m, 22H, Ph*H* and MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.99 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.7 and 1.4 Hz, 1H, C$H_a$$H_b$=CH), 4.97 (dd, *J* = 10.7 and 1.2 Hz, 1H, $CH_a$$H_b$=CH), 4.86 (d, *J*

= 11.0 Hz, 1H, MeOPhCH_aH$_b$), 4.67 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.46 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.39 (d, *J* = 11.0 Hz, 1H, MeOPhCH$_a$$H_b$), 4.27-4.20 (m, 1H, *H*COTBDPS), 4.11 (s, 1H, *H*COTBS), 3.78 (s, 3H, PhO*Me*), 3.81-3.75 (m, 1H, *H*COMe), 3.54 (ddd, *J* = 7.3, 3.6, and 3.6 Hz, 1H, *H*COMOM), 3.48 (dd, *J* = 10.8 and 3.8 Hz, 1H, CH_aH$_b$OTBDPS), 3.39 (dd, *J* = 10.8 and 7.7 Hz, 1H, CH$_a$$H_b$OTBDPS), 3.29 (s, 1H, *H*COPMB), 3.18 (s, 3H, O*Me*), 3.11 (ddd, *J* = 10.5, 2.8, and 2.8 Hz, 1H, *H*COMe), 3.07 (s, 3H, O*Me*), 3.01 (s, 3H, O*Me*), 1.93-1.84 (m, 2H, C$H_{a1}$$H_{b1}$), 1.52 (ddd, *J* = 13.6, 10.4, and 3.2 Hz, 1H, CH_{a2}H$_{b2}$), 1.38 (ddd, *J* = 13.3, 10.4, and 2.3 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.082 (s, 3H, C*Me*), 1.075 (s, 3H, C*Me*), 1.00 (s, 9H, SiCMe_3), 0.98 (s, 9H, SiCMe_3), 0.90 (s, 9H, SiCMe_3), 0.05 (s, 3H, Si*Me*), and 0.02 (s, 3H, Si*Me*).

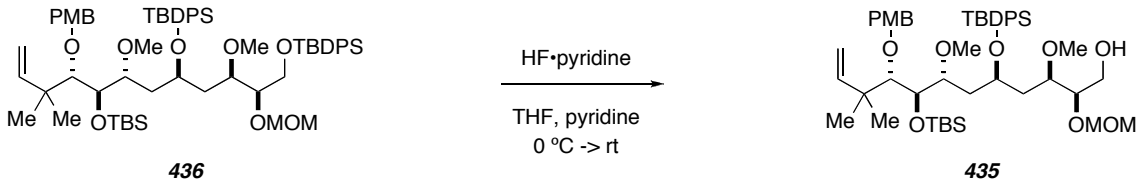
^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 145.8, 136.2, 136.1, 135.9, 135.8, 135.6, 134.5, 133.55, 133.52, 131.3, 129.60, 129.55, 129.3, 129.2, 129.1, 127.6, 127.3, 127.1, 113.5, 111.7, 97.0, 91.7, 79.2, 78.8, 75.6, 73.6, 68.6, 64.0, 58.5, 56.4, 55.5, 55.2, 41.9, 40.1, 37.4, 27.2, 26.9, 26.1, 25.7, 23.9, 19.4, 19.1, 18.2, -4.0, and -4.9.

HR ESI-MS: Calcd for $C_{64}H_{94}O_9Si_3Na$ $(M+Na)^+$: 1113.6098 Found: 1113.6147.

TLC: R_f = 0.38; 9:1 hexanes:ethyl acetate.

[α]^{RT} = +23.4 (c = 0.35, $CDCl_3$).

(2*R*,3*R*,5*S*,7*R*,8*R*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-en-1-ol **435**



Note: (2 reactions were run simultaneously with equal amounts of the reagents and combined for workup procedures.) To a plastic culture tube containing **436** (324 mg, 0.297 mmol) was added THF (9.2 mL, 0.032M) and pyridine (9.2 mL, 0.032M). The

reaction was cooled to 0 ºC and HF•pyridine (1.78 mL of a 70% HF / 30% pyridine solution) was added dropwise. The reaction was stirred at room temperature for 6 hours at which time TLC showed completion of both reactions. Both of the reaction mixtures were diluted with EtOAc (~150 mL total) and transferred to a 500 mL Erlenmeyer flask. Saturated aqueous $NaHCO_3$ (~250 mL) was slowly added to the mixture until no evolution of gas was observed. The aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with H_2O (1 x 100 mL), saturated $CuSO_4$ (2 x 100 mL), and saturated NaCl (1 x 100 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (3:1 hexanes / ethyl acetate) to provide the primary alcohol **435** (459 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (dd, *J* = 8.0 and 1.5 Hz, 2H, Ph*H*), 7.64 (dd, *J* = 8.0 and 1.4 Hz, 2H, Ph*H*), 7.41-7.27 (m, 8H, Ph*H* and MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.00 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.7 and 1.4 Hz, 1H, CH_aH$_b$=CH), 4.98 (dd, *J* = 10.8 and 1.4 Hz, 1H, CH$_a$$H_b$=CH), 4.79 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.51 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.40 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.37 (d, *J* = 6.9 Hz, 1H, OCH$_a$$H_b$OMe), 4.20-4.13 (m, 1H, *H*COTBDPS), 4.12 (s, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.74 (dd, *J* = 10.4 and 2.4 Hz, 1H, *H*COMe), 3.37-3.29 (m, 2H, CH_2OH), 3.30 (s, 3H, O*Me*), 3.28 (d, *J* = 1.2 Hz, 1H, *H*COPMB), 3.20 (ddd, *J* = 7.8, 3.9, and 3.9 Hz, 1H, *H*COMOM), 3.12 (s, 3H, O*Me*), 3.10 (ddd, *J* = 8.0, 3.8, and 3.8 Hz, 1H, *H*COMe), 3.03 (s, 3H, O*Me*), 2.83 (dd, *J* = 8.2 and 4.1 Hz, 1H, O*H*), 1.94 (ddd, *J* = 14.5, 8.8, and 2.2 Hz, 1H, CH_{a1}H$_{b1}$), 1.87 (ddd, *J* = 14.2, 10.4, and 2.9 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.62 (ddd, *J* = 13.4, 8.7, and 4.6 Hz, 1H, CH_{a2}H$_{b2}$), 1.43 (ddd, *J* = 13.6, 8.9, and 4.2 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.08 (s, 3H, C*Me*), 1.01 (s, 9H, SiCMe_3), 0.93 (s, 9H, SiCMe_3), 0.07 (s, 3H, Si*Me*), and 0.04 (s, 3H, Si*Me*).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 145.8, 136.2, 135.4, 134.5, 131.5, 129.6, 129.5, 129.3, 127.6, 127.5, 114.1, 113.69, 113.66, 111.9, 97.5, 91.8, 81.7, 79.3, 79.0, 75.7, 73.5, 68.8, 68.7, 63.1, 58.2, 56.5, 55.9, 55.4, 41.9, 39.6, 38.0, 27.3, 26.2, 25.8, 24.4, 19.5, 18.4, -4.0, and -4.6.

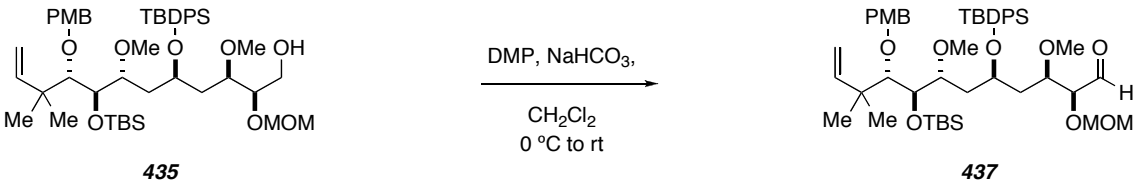
HR ESI-MS: Calcd for $C_{48}H_{76}O_9Si_2Na$ $(M+Na)^+$: 875.4920 Found: 875.4926.

TLC: $\mathbf{R_f}$ = 0.27; 3:1 hexanes:ethyl acetate.

$\mathbf{[\alpha]^{RT}}$ = +37.7 (c = 0.35, $CDCl_3$).

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-enal

437



435 ***437***

To a 50 mL round bottom flask containing alcohol **435** (459 mg, 0.538 mmol) was added CH_2Cl_2 (11.6 mL, 0.046 M). The solution was cooled to 0 ºC followed by the addition of $NaHCO_3$ (181 mg, 2.15 mmol) and Dess-Martin periodinane (285 mg, 0.672 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred until monitoring by TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (5 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the desired aldehyde **437**. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.40 (d, *J* = 1.0 Hz , 1H, *H*C=O), 7.70 (dd, *J* = 7.9 and 1.4 Hz, 2H, Ph*H*), 7.66 (dd, *J* = 8.0 and 1.3 Hz, 2H, Ph*H*), 7.41-7.25 (m, 8H, Ph*H* and MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.97 (dd, *J* = 17.7 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.4 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 4.97 (dd, *J* = 10.6 and 1.2 Hz,

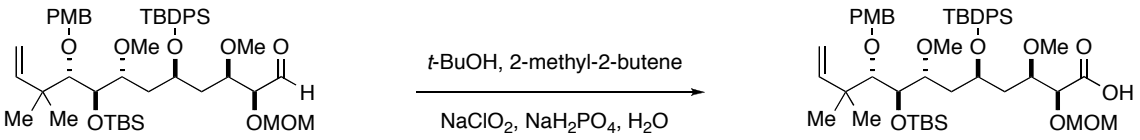
1H, CH_aH_b=CH), 4.72 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.50 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.40 (d, *J* = 11.4 Hz, 1H, MeOPhC$H_a$$H_b$), 4.32 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$OMe), 4.16-4.09 (m, 1H, *H*COTBDPS), 4.11 (s, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.69 (d, *J* = 9.9 Hz, 1H, *H*COMe), 3.52-3.47 (m, 1H, *H*COMe), 3.38 (d, *J* = 2.9 Hz, 1H, *H*COMOM), 3.28-3.26 (m, 1H, *H*COPMB), 3.26 (s, 3H, O*Me*), 3.11 (s, 3H, O*Me*), 2.98 (s, 3H, O*Me*), 1.99 (ddd, *J* = 15.0, 8.7, and 1.6 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.86 (ddd, *J* = 14.4, 10.7, and 3.5 Hz, 1H, $CH_{a1}H_{b1}$), 1.79 (ddd, *J* = 13.5, 7.6, and 5.3 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.50 (ddd, *J* = 13.3, 7.5, and 5.1 Hz, 1H, $CH_{a2}H_{b2}$), 1.08 (s, 3H, C*Me*), 1.06 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3), 0.93 (s, 9H, SiCMe_3), 0.07 (s, 3H, Si*Me*), and 0.05 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.7, 159.1, 145.8, 136.3, 134.4, 131.5, 129.7, 129.6, 129.3, 127.7, 127.6, 113.7, 111.9, 97.4, 91.7, 83.7, 79.0, 78.5, 75.7, 73.4, 68.8, 68.66, 68.65, 58.4, 56.4, 56.3, 55.4, 41.9, 39.9, 38.3, 27.3, 26.2, 25,8, 24.5, 19.6, 18.4, -4.0, and -4.6.

HR ESI-MS: Calcd for $C_{48}H_{74}O_9Si_2Na$ $(M+Na)^+$: 873.4764 Found: 873.4750.

TLC: R_f = 0.38; 6:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-8-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-enoic acid **438**



437 ***438***

To a 250 mL round bottom flask containing the crude aldehyde **437** (~0.538 mmol) was added *t*-BuOH (31.7 mL, 0.017 M) and 2-methyl-2-butene (10.4 mL, 0.052 M). To a vial equipped with a stir bar was added NaH_2PO_4 (487 mg, 5.38 mmol), $NaClO_2$ (371 mg, 2.69 mmol), and H_2O (14.2 mL, 0.19 M in $NaClO_2$). Once the mixture in the

vial became homogeneous, the aqueous solution was added to the reaction flask. The reaction mixture was stirred at room temperature for 1 hour. The solution was then cooled to 0 ºC, and a newly prepared saturated solution of $NaHSO_3$ (8 mL) was added. The reaction was diluted with H_20 (75 mL) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the desired carboxylic acid **438**. The crude product was immediately carried on to the next step without purification.

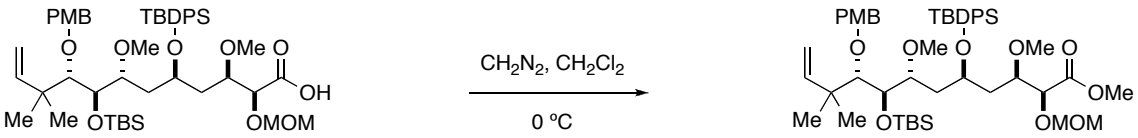
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 8.0 and 1.5 Hz, 2H, Ph*H*), 7.64 (dd, *J* = 8.0 and 1.5 Hz, 2H, Ph*H*), 7.41-7.28 (m, 8H, Ph*H* and MeOPhH_a), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.97 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.4 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 4.97 (dd, *J* = 10.5 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.72 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.56 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.41 (d, *J* = 11.1 Hz, 1H, MeOPhC$H_a$$H_b$), 4.36 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.19-4.09 (m, 1H, *H*COTBDPS), 4.10 (s, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.78 (d, *J* = 2.8 Hz, 1H, *H*COMOM), 3.69 (dd, *J* = 10.4 and 2.1 Hz, 1H, *H*COMe), 3.50 (ddd, *J* = 9.0, 3.5, and 3.5 Hz, 1H, *H*COMe), 3.28 (d, *J* = 1.1 Hz, 1H, *H*COPMB), 3.25 (s, 3H, O*Me*), 3.10 (s, 3H, O*Me*), 3.08 (s, 3H, O*Me*), 1.97 (ddd, *J* = 13.8, 9.1, and 4.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.88 (ddd, *J* = 14.6, 10.3, and 2.8 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.76 (ddd, *J* = 13.8, 9.8, and 4.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.48 (ddd, *J* = 13.8, 8.9, and 3.8 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.08 (s, 3H, C*Me*), 1.07 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3), 0.92 (s, 9H, SiCMe_3), 0.06 (s, 3H, Si*Me*), and 0.03 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.8, 159.0, 145.8, 136.3, 136.2, 135.0, 134.3, 131.5, 129.6, 129.5, 129.3, 127.6, 127.5, 113.7, 111.9, 97.0, 91.8, 79.0, 78.8, 76.9, 75.7, 73.4, 68.6, 58.8, 56.5, 56.4, 55.4, 42.0, 40.5, 38.0, 27.3, 26.2, 25.8, 24.4, 19.5, 18.4, -4.0, and -4.6.

HR ESI-MS: Calcd for $C_{48}H_{74}O_{10}Si_2Na$ $(M+Na)^+$: 889.4713 Found: 889.4744.

TLC: R_f = 0.51; 100% ethyl acetate.

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-Methyl 8-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-enoate **439**



438 ***439***

To a 125 mL Erlenmeyer flask equipped with a stir bar and containing the crude carboxylic acid **438** (~0.538 mmol) was added CH_2Cl_2 (38 mL, 0.014 M) followed by cooling the solution to 0 ºC. Diazald (1.10 g, 5.13 mmol) and ethanol (18 mL) were added to a 150 mL side-arm Erlenmeyer flask equipped with a stir bar. The top of the 150 mL side-arm Erlenmeyer flask was covered with a new 24/40 septum that had a piece of teflon tubing punctured through the septum, having one end placed into the ethanol solution while the other end was connected to a N_2 line under positive pressure. A new 14/20 septa with another piece of teflon tubing punctured through it was placed on the side-arm and the opposite end of the teflon tubing was placed into the solution of CH_2Cl_2 containing **438** in the 125 mL Erlenmeyer flask. The N_2 flow was then regulated so that constant N_2 sparging was observed in both Erlenmeyer flasks. This is important because the flow of N_2 is what is going to carry the diazomethane as it is formed, to the 125 mL Erlenmeyer flask containing the carboxylic acid **438**. A sodium hydroxide solution (1 M) is added at a constant rate to the 125 mL side-arm Erlenmeyer flask while stirring, until all the yellow color in the 125 mL side-arm Erlenmeyer flask disappears. The esterification reaction is complete when the CH_2Cl_2 in the 125 mL Erlenmeyer flask turns yellow as the result of excess diazomethane accumulating in the solution. The teflon tubing is removed from the CH_2Cl_2 and a few drops of acetic acid is added until the CH_2Cl_2 solution turns colorless. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench any excess acetic acid. The reaction was diluted with CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a mixture of the desired product **439** and the C2 hydroxyl resulting from the deprotection of the MOM ether.

NOTE: (It is believed that the MOM ether deprotection occurs during the addition of the CH_2Cl_2 to the crude carboxylic acid. This was later prevented by replacing CH_2Cl_2 with Et_2O as the solvent while keeping everything else remaining the same.) The MOM ether could easily be re-installed by taking this crude reaction mixture and subjecting it to the previously described procedure for MOM ether formation. Column chromatography was performed (4:1 hexanes / ethyl acetate) to provide methyl ester **439** (414 mg, 87%, 3-steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.0 and 1.5 Hz, 2H, Ph*H*), 7.62 (dd, *J* = 8.0 and 1.4 Hz, 2H, Ph*H*), 7.39-7.23 (m, 8H, Ph*H* and MeOPhH_a), 6.86 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 5.98 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.00 (dd, *J* = 17.2 and 1.5 Hz, 1H, CH_aH$_b$=CH), 4.97 (dd, *J* = 10.8 and 1.8 Hz, 1H, CH$_a$$H_b$=CH), 4.82 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.52 (d, *J* = 7.0 Hz, 1H, OCH_aH$_b$OMe), 4.42 (d, *J* = 7.0 Hz, 1H, OCH$_a$$H_b$OMe), 4.41 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_a$$H_b$), 4.19 (dddd, *J* = 9.3, 7.8, 3.7, and 3.7 Hz, 1H, *H*COTBDPS), 4.10 (s, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.79 (d, *J* = 3.0 Hz, 1H, *H*COMOM), 3.71 (dd, *J* = 9.3 and 3.3 Hz, 1H, *H*COMe), 3.62 (s, 3H, CO_2*Me*), 3.52 (ddd, *J* = 9.1, 3.1, and 3.1 Hz, 1H, *H*COMe), 3.28 (d, *J* = 1.1 Hz, 1H, *H*COPMB), 3.19 (s, 3H, O*Me*), 3.05 (s, 3H, O*Me*), 3.01 (s, 3H, O*Me*), 1.97-1.85 (m, 3H, C$H_{a1}H_{b1}$ and CH_{a2}H$_{b2}$), 1.40 (ddd, *J* = 14.6, 9.3, and 3.1 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.08 (s, 3H, C*Me*), 1.07 (s, 3H, C*Me*), 1.02 (s, 9H, SiCMe_3), 0.93 (s, 9H, SiCMe_3), 0.06 (s, 3H, Si*Me*), and 0.04 (s, 3H, Si*Me*).

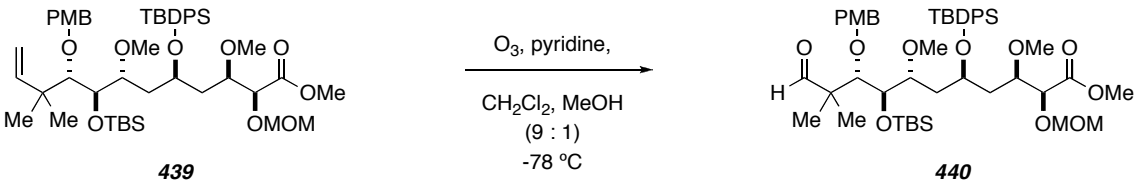
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 158.8, 145.7, 136.1, 136.0, 135.2, 134.1, 131.3, 129.3, 129.2, 129.1, 127.4, 127.2, 113.5, 111.7, 96.3, 91.7, 78.9, 78.8, 77.5, 75.5, 73.4, 68.6, 58.5, 56.3, 56.1, 55.2, 51.6, 41.8, 40.9, 37.8, 27.1, 26.1, 25.6, 24.1, 19.3, 18.2, -4.2, and -4.8.

HR ESI-MS: Calcd for $C_{49}H_{76}O_{10}Si_2Na$ $(M+Na)^+$: 903.4869 Found: 903.4868.

TLC: R_f = 0.52; 3:1 hexanes:ethyl acetate.

$[\alpha]^{RT}$ = +13.1 (c = 0.45, $CDCl_3$).

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-Methyl 8-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyl-11-oxoundecanoate **440**



439 ***440***

A 9:1 mixture of CH_2Cl_2:MeOH (13.7 mL, 0.02M) was added to a 50 mL round bottom flask containing alkene **439** (241 mg, 0.273 mmol). This solution was cooled to -78 ºC and pyridine (0.22 mL, 2.73 mmol) was added. Ozone was sparged through the system using a pipette tip until the first sign of a light blue color. At this point the pipette was removed and the reaction showed complete consumption of the starting material by TLC. Oxygen was then sparged through the system to remove any residual ozone in the reaction mixture, observed by the change of the solution from a light blue color to colorless. Dimethyl sulfide (6.0 mL) was added and the reaction mixture was warmed to room temperature and stirred for 6 hours. The solution was concentrated under reduced pressure and the resulting oil was purified via column chromatography (3:1 hexanes / ethyl acetate) to provide aldehyde **440** (181 mg, 75%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.41 (s, 1H, *H*C=O), 7.73 (dd, *J* = 8.0 and 1.6 Hz, 2H, Ph*H*), 7.66 (dd, *J* = 8.0 and 1.4 Hz, 2H, Ph*H*), 7.43-7.28 (m, 6H, Ph*H*), 7.18 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.85 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 4.54 (d, *J* = 6.9 Hz, 1H, OCH_aH$_b$OMe), 4.53 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.46 (d, *J* = 6.9 Hz, 1H, OCH$_a$$H_b$OMe), 4.28 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.15-4.09 (m, 1H, *H*COTBDPS), 3.91 (d, *J* = 3.2 Hz, 1H, *H*COMOM), 3.87 (dd, *J* = 4.8 and 1.9 Hz, 1H, *H*COTBS), 3.80 (s, 3H, PhO*Me*), 3.67 (s, 3H, CO_2*Me*), 3.72-3.62 (m, 1H, *H*COMe), 3.44 (d, *J* = 4.8 Hz, 1H, *H*COPMB), 3.40 (ddd, *J* = 6.7, 4.8, and 1.9 Hz, 1H, *H*COMe), 3.23 (s, 3H, O*Me*), 3.14 (s, 3H, O*Me*), 3.07 (s, 3H, O*Me*), 1.95 (ddd, *J* = 13.8, 8.4, and 4.9 Hz, 1H, CH_{a1}H$_{b1}$), 1.90-1.81 (m, 2H, C$H_{a2}$$H_{b2}$), 1.62 (ddd, *J* = 13.9, 8.0, and 4.4 Hz, 1H,

$CH_{a1}H_{b1}$), 1.09(s, 3H, C*Me*), 1.07 (s, 3H, C*Me*), 1.01 (s, 9H, SiCMe_3), 0.90 (s, 9H, SiCMe_3), 0.08 (s, 3H, Si*Me*), and 0.04 (s, 3H, Si*Me*).

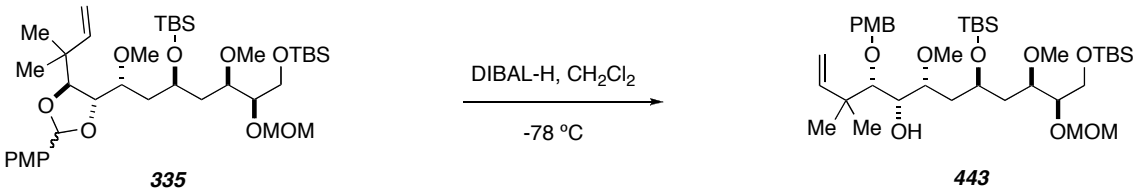
^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.2, 171.3, 159.2, 136.3, 136.2, 134.7, 134.1, 130.5, 129.72, 129.67, 129.0, 127.8, 127.6, 113.8, 96.7, 85.8, 79.6, 78.9, 77.5, 74.9, 74.1, 69.2, 58.5, 57.0, 56.3, 55.4, 51.9, 50.2, 40.0, 38.5, 27.2, 26.4, 20.8, 19.5, 19.0, 18.5, -3.4, and -4.3.

HR ESI-MS: Calcd for $C_{48}H_{74}O_{11}Si_2Na$ $(M+Na)^+$: 905.4662 Found: 905.4677.

TLC: R_f = 0.52; 3:1 hexanes:ethyl acetate.

[α]^{RT} = -4.33 (c = 0.30, $CDCl_3$).

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **443**



335 ***443***

Note: (2 reactions were run simultaneously with equal amounts of the reagents and combined for workup procedures.) To a large culture tube containing bis-TBS-ether **335** (937 mg, 1.29 mmol) was added CH_2Cl_2 (8.5 mL, 0.15 M). The reaction mixture was cooled to -78 ºC followed by the addition of DIBAL-H (9.91 mL, 12.9 mmol, 1.3 M in toluene). The reaction solution was kept at -78 ºC for 48 hours. Keeping both of the reactions at -78 ºC, ethyl acetate (8.0 mL) was added dropwise down the side of each culture tube to quench the excess DIBAL-H. Both of the reaction mixtures were then transferred to a 250 mL Erlenmeyer flask equipped with a stir bar using ethyl acetate and warmed to room temperature. Small portions of saturated aqueous Rochelle's salt (Na,K-Tartrate) were added and the reaction was monitored closely for exotherm and cooled if necessary. Upon this addition, the reaction will go from homogeneous to a gelatinous solution, and upon addition of more saturated aqueous Rochelle's salt, back to

homogeneous. The two-phase solution in the Erlynmeyer flask was then usually allowed to stir for an additional 18 hours. The reaction is done when both the aqueous and the organic layers are homogeneous and clear. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (3:1 hexanes / ethyl acetate) provided the alcohol **443** (1.48 g, 79%).

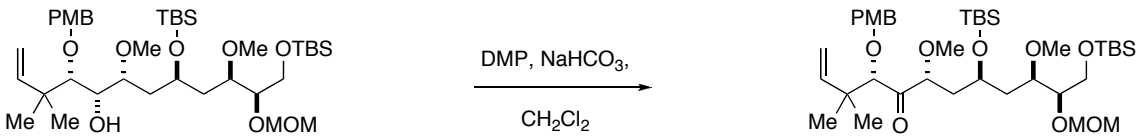
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.5 Hz, 2H, MeOPhH_a), 6.88 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 5.86 (dd, *J* = 17.8 and 10.5 Hz, 1H, CH_2=C*H*), 5.05 (dd, *J* = 18.1 and 1.4 Hz, 1H, CH_aH$_b$=CH), 5.04 (dd, *J* = 11.5 and 1.4 Hz, 1H, CH$_a$$H_b$=CH), 4.78 (d, *J* = 6.7 Hz, 1H, OCH_aH$_b$OMe), 4.69 (d, *J* = 10.4 Hz, 1H, MeOPhCH_aH$_b$), 4.65 (d, *J* = 6.7 Hz, 1H, OCH$_a$$H_b$OMe), 4.54 (d, *J* = 10.3 Hz, 1H, MeOPhCH$_a$$H_b$), 4.06-3.99 (m, 1H, *H*COTBS), 3.81 (s, 3H, PhO*Me*), 3.77 (dd, *J* = 10.1 and 5.4 Hz, 1H, CH_aH$_b$OTBS), 3.69 (dd, *J* = 10.1 and 6.6 Hz, 1H, CH$_a$$H_b$OTBS), 3.66-3.60 (m, 2H, *H*COH and *H*COMOM), 3.52 (ddd, *J* = 8.8, 3.8, and 3.8 Hz, 1H, *H*COMe), 3.48 (s, 3H, O*Me*), 3.42 (s, 6H, O*Me*), 3.22 (ddd, *J* = 7.3, 4.6, and 4.6 Hz, 1H, *H*COMe), 3.24 (d, *J* = 1.8 Hz, 1H, O*H*), 3.00 (d, *J* = 7.1 Hz, 1H, *H*COPMB), 1.81-1.66 (m, 4H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$), 1.08 (s, 3H, C*Me*), 1.06 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.89 (s, 9H, SiCMe_3), 0.11 (s, 3H, Si*Me*), 0.09 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), and 0.06 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.4, 145.3, 130.5, 129.5, 113.9, 113.0, 97.1, 83.5, 80.5, 79.4, 77.1, 74.7, 70.5, 68.56, 68.54, 67.4, 62.7, 58.8, 58.2, 55.9, 55.5, 42.8, 39.0, 38.1, 26.2, 26.1, 24.7, 21.7, 18.5, 18.3, -3.8, -4.1, -5.17, and -5.24.

HR ESI-MS: Calcd for $C_{38}H_{72}O_9Si_2Na$ $(M+Na)^+$: 751.4607 Found: 751.4616.

TLC: R_f = 0.61; 3:1 hexanes:ethyl acetate.

(4*S*,6*R*,8*S*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-one **444**



443 ***444***

To a 100 mL round bottom flask containing alcohol **443** (1.48 g, 2.04 mmol) was added CH_2Cl_2 (44.2 mL, 0.046 M). The reaction was cooled to 0 ºC followed by the addition of $NaHCO_3$ (445 mg, 5.30 mmol), and Dess-Martin periodinane (619 mg, 1.46 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 18 hours. The mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous $Na_2S_2O_3$ (30 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (20 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude ketone **444** in >90%. The crude product was carried on to the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.02 (dd, *J* = 17.5 and 10.8 Hz, 1H, CH_2=C*H*), 5.03 (dd, *J* = 10.9 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 5.00 (dd, *J* = 17.3 and 1.1 Hz, 1H, $CH_a$$H_b$=CH), 4.76 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.62 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.60 (d, *J* = 11.0 Hz, 1H, MeOPhC$H_a$$H_b$), 4.33 (dd, *J* = 9.7 and 2.2 Hz, 1H, *H*COMe), 4.33 (d, *J* = 11.4 Hz, 1H, MeOPh$CH_a$$H_b$), 4.13-4.06 (m, 1H, *H*COTBS), 3.81 (s, 3H, PhO*Me*), 3.75 (s, 1H, *H*COPMB), 3.74 (dd, *J* = 10.4 and 5.1 Hz, 1H, C$H_a$$H_b$OTBS), 3.65 (dd, *J* = 10.3 and 6.6 Hz, 1H, $CH_a$$H_b$OTBS), 3.59 (ddd, *J* = 6.5, 4.9, and 3.5 Hz, 1H, *H*COMOM), 3.40 (ddd, *J* = 9.8, 3.1, and 3.1 Hz, 1H, *H*COMe) 3.361 (s, 3H, O*Me*), 3.356 (s, 3H, O*Me*), 3.28 (s, 3H, O*Me*), 1.81 (ddd, *J* = 14.0, 9.5, and 2.6 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.71 (ddd, *J* = 13.8, 9.8, and 3.5 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.65 (ddd, *J* = 13.9, 10.0, and 2.4 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.59 (ddd, *J* = 14.1, 8.4, and 2.9 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.09 (s, 6H, Si*Me*), 0.051 (s, 3H, Si*Me*), and 0.045 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.5, 159.4, 144.0, 129.9, 129.5, 113.9, 113.1, 97.1, 89.7, 80.7, 79.3, 77.2, 74.1, 66.1, 62.7, 59.0, 57.3, 55.8, 55.4, 41.7, 39.6, 38.6, 30.5, 26.13, 26.10, 23.89, 23.85, 18.5, 18.2, 15.5, -3.8, -4.5, -5.20, and -5.25.

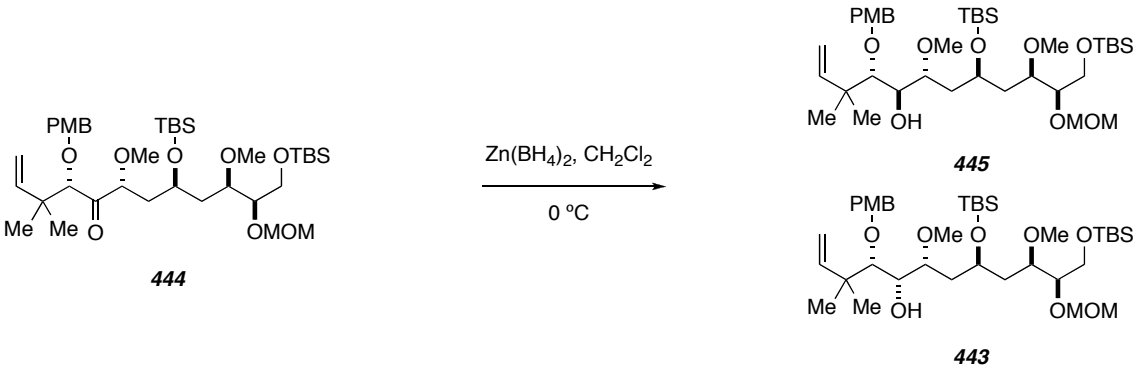
HR ESI-MS: Calcd for $C_{38}H_{70}O_9Si_2Na$ $(M+Na)^+$: 749.4451 Found: 749.4478.

TLC: R_f = 0.65; 6:1 hexanes:ethyl acetate (eluted 2 x).

(4*S*,5*R*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **445**

and

(4*S*,5*S*,6*R*,8*R*,10*R*,11*R*)-8,12-Bis(*tert*-butyldimethylsilyloxy)-6,10-dimethoxy-4-(4-methoxybenzyloxy)-11-(methoxymethoxy)-3,3-dimethyldodec-1-en-5-ol **443**



To a 250 mL round bottom flask containing crude ketone **444** (~2.04 mmol) was added CH_2Cl_2 (101.7 mL, 0.02 M) and cyclohexene (2.04 mL, 20.1 mmol). The reaction was cooled to 0 ºC and $Zn(BH_4)_2$ (20.4 mL, 10.2 mmol, 0.5 M in Et_2O) was added. The solution was stirred for 40 minutes at 0 ºC until TLC showed complete consumption of the starting material. Saturated aqueous NH_4Cl (50 mL) was added at 0 ºC to quench the reaction. The mixture was diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via MPLC (3:1 hexanes / ethyl acetate) to provide (801 mg, 54%, 2-steps).

Characterization Data for 445

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.08 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.05 (dd, *J* = 18.9 and 1.3 Hz, 1H, C$H_a$$H_b$=CH), 5.01 (dd, *J* = 10.8 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.78 (d, *J* = 6.9 Hz, 1H, OC$H_a$$H_b$OMe), 4.76 (d, *J* = 10.5 Hz, 1H, MeOPhC$H_a$$H_b$), 4.65 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.46 (d, *J* = 10.9 Hz, 1H, MeOPh$CH_a$$H_b$), 4.16-4.10 (m, 1H, *H*COTBS), 4.07 (ddd, *J* = 7.6, 2.3, and 2.3 Hz, 1H, *H*COH), 3.80 (s, 3H, PhO*Me*), 3.76 (dd, *J* = 10.3 and 5.3 Hz, 1H, C$H_a$$H_b$OTBS), 3.70 (ddd, *J* = 10.4, 2.2, and 2.2 Hz, 1H, *H*COMe), 3.68 (dd, *J* = 10.3 and 6.6 Hz, 1H, $CH_a$$H_b$OTBS), 3.60 (ddd, *J* = 6.5, 5.2, and 3.3 Hz, 1H, *H*COMOM), 3.46 (ddd, *J* = 9.9, 2.9, and 2.9 Hz, 1H, *H*COMe), 3.41 (s, 3H, O*Me*), 3.377 (s, 3H, O*Me*), 3.375 (s, 3H, O*Me*), 3.22 (d, *J* = 7.6 Hz, 1H, *H*COPMB), 2.06 (d, *J* = 2.5 Hz, 1H, O*H*), 1.89 (ddd, *J* = 14.0, 10.6, and 2.3 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.79 (ddd, *J* = 13.7, 9.9, and 3.3 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.74 (ddd, *J* = 14.5, 9.5, and 1.9 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.66 (ddd, *J* = 14.0, 8.9, and 3.0 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.14 (s, 3H, C*Me*), 1.13 (s, 3H, C*Me*), 0.90 (s, 9H, SiCMe_3), 0.82 (s, 9H, SiCMe_3), 0.074 (s, 3H, Si*Me*), 0.067 (s, 3H, Si*Me*), 0.060 (s, 3H, Si*Me*), and 0.02 (s, 3H, Si*Me*).

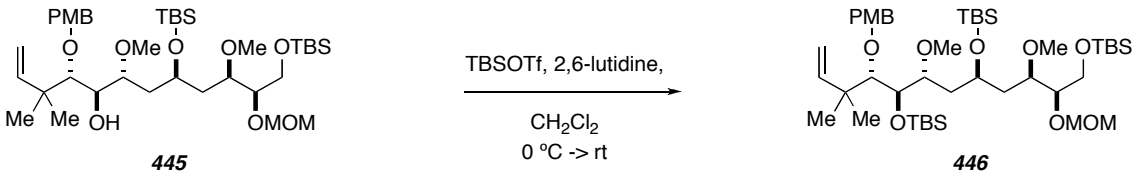
^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.0, 146.6, 131.1, 128.8, 113.7, 111.5, 97.2, 85.7, 79.9, 78.5, 77.5, 74.7, 71.4, 66.9, 62.8, 59.2, 56.7, 55.9, 55.4, 42.4, 40.3, 36.4, 26.2, 26.1, 25.7, 22.7, 18.5, 18.2, -3.9, -4.2, -5.19, and -5.25.

TLC: R_f = 0.28; 6:1 hexanes:ethyl acetate (eluted 2 x).

Characterization Data for 443

(previously reported in experimental section)

(5*R*,6*R*,8*S*,10*R*,11*R*)-8-(*tert*-Butyldimethylsilyloxy)-6,10-dimethoxy-5-((*S*)-1-(4-methoxybenzyloxy)-2,2-dimethylbut-3-enyl)-11-(methoxymethoxy)-2,2,3,3,14,14,15,15-octamethyl-4,13-dioxa-3,14-disilahexadecane **446**



To a 100 mL round bottom flask containing alcohol **445** (761 mg, 1.04 mmol), was added CH_2Cl_2 (20.9 mL, 0.05 M). The solution was cooled to 0 ºC followed by the addition of 2,6-lutidine (0.730 mL, 6.26 mmol) and TBSOTf (1.08 mL, 4.70 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred for 2 hours 15 minutes until TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and quenched with saturated aqueous $NaHCO_3$ (40 mL). The mixture was diluted with CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (9:1 hexanes / ethyl acetate) to provide **446** (810 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.7 Hz, 2H, MeOPhH_a), 6.84 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.02 (dd, *J* = 17.9 and 10.5 Hz, 1H, CH_2=C*H*), 5.01 (dd, *J* = 17.8 and 1.3 Hz, 1H, CH_aH$_b$=CH), 5.01 (dd, *J* = 10.6 and 1.3 Hz, 1H, CH$_a$$H_b$=CH), 4.93 (d, *J* = 11.1 Hz, 1H, MeOPhCH_aH$_b$), 4.74 (d, *J* = 6.8 Hz, 1H, OCH_aH$_b$OMe), 4.60 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.38 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_a$$H_b$), 4.14 (dd, *J* = 1.2 and 1.2 Hz, 1H, *H*COTBS), 4.05 (dddd, *J* = 9.0, 9.0, 3.7, and 2.5 Hz, 1H, *H*COTBS), 3.80 (s, 3H, PhO*Me*), 3.74 (dd, *J* = 10.3 and 5.4 Hz, 1H, CH_aH$_b$OTBS), 3.69 (ddd, *J* = 10.1, 2.3, and 0.90 Hz, 1H, *H*COMe), 3.65 (dd, *J* = 10.3 and 6.7 Hz, 1H, CH$_a$$H_b$OTBS), 3.56 (ddd, *J* = 6.7, 5.3, and 3.2 Hz, 1H, *H*COMOM), 3.36-3.31 (m, 1H, *H*COMe), 3.35 (s, 3H, O*Me*), 3.32 (s, 3H, O*Me*), 3.29 (d, *J* = 1.4 Hz, 1H, *H*COPMB), 3.26 (s, 3H, O*Me*), 1.85 (ddd, *J* = 14.5, 10.0, and 2.3 Hz, 1H, CH_{a1}H$_{b1}$), 1.79 (ddd, *J* = 14.5, 9.4, and 2.4 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.75 (ddd, *J* = 13.8, 9.9, and 3.8 Hz, 1H, CH_{a2}H$_{b2}$), 1.49 (ddd, *J* = 13.9, 9.1, and

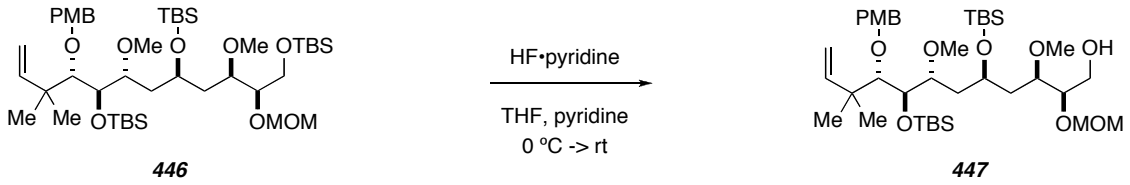
3.0 Hz, 1H, $CH_{a2}H_{b2}$), 1.09 (s, 3H, C*Me*), 1.08 (s, 3H, C*Me*), 0.93 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.87 (s, 9H, SiCMe_3), 0.073 (s, 3H, Si*Me*), 0.068 (s, 3H, Si*Me*), 0.064 (s, 3H, Si*Me*), 0.050 (s, 3H, Si*Me*), 0.047 (s, 3H, Si*Me*), and 0.042 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 145.9, 131.6, 129.0, 113.6, 111.8, 97.1, 91.8, 79.7, 79.0, 77.7, 75.7, 73.4, 66.9, 62.9, 59.3, 56.6, 55.8, 55.4, 41.9, 40.8, 37.7, 26.27, 26.23, 26.17, 25.9, 24.4, 18.5, 18.4, 18.2, -2.7, -3.6, -3.8, -4.1, -4.7, -5.17, and -5.24.

HR ESI-MS: Calcd for $C_{44}H_{86}O_9Si_3Na$ $(M+Na)^+$: 865.5472 Found: 865.5479.

TLC: R_f = 0.35; 9:1 hexanes:ethyl acetate.

(2*R*,3*R*,5*S*,7*R*,8*R*,9*S*)-5,8-Bis(*tert*-butyldimethylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-en-1-ol **447**



446 ***447***

Note: (2 reactions were run simultaneously with equal amounts of the reagents and combined for workup procedures.) To a plastic culture tube containing **446** (405 mg, 0.297 mmol) was added THF (15.0 mL, 0.032M) and pyridine (15.0 mL, 0.032M). The reaction mixture was cooled to 0 ºC and HF•pyridine (2.88 mL of a 70% HF / 30% pyridine solution) was added dropwise. The reaction was stirred at room temperature for 5 hours 15 minutes at which time TLC showed completion of both reactions. Both of the reaction mixtures were diluted with EtOAc (~150 mL total) and transferred to a 500 mL Erlenmeyer flask. Saturated aqueous $NaHCO_3$ (~250 mL) was slowly added to the mixture until no evolution of gas was observed. The aqueous layer was extracted with EtOAc (2 x 250 mL). The combined organic layers were washed with H_2O (1 x 100 mL), saturated $CuSO_4$ (2 x 100 mL), and saturated NaCl (1 x 100 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to provide a crude mixture that was purified via column chromatography (3:1 hexanes / ethyl acetate) to provide the primary alcohol

447 (540 mg, 77%).

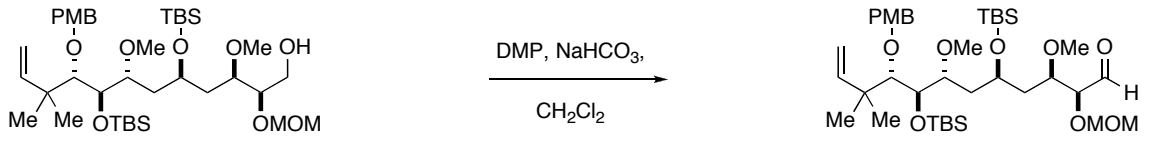
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.85 (d, *J* = 8.7 Hz, 2H, MeOPhH_b), 6.03 (dd, *J* = 17.9 and 10.5 Hz, 1H, CH_2=C*H*), 5.02 (dd, *J* = 10.4 and 1.5 Hz, 1H, C$H_a$$H_b$=CH), 5.01 (dd, *J* = 18.0 and 1.5 Hz, 1H, $CH_a$$H_b$=CH), 4.93 (d, *J* = 11.2 Hz, 1H, MeOPhC$H_a$$H_b$), 4.69 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.61 (d, *J* = 6.8 Hz, 1H, $OCH_a$$H_b$OMe), 4.41 (d, *J* = 11.2 Hz, 1H, MeOPh$CH_a$$H_b$), 4.14 (s, 1H, *H*COTBS), 4.05-3.98 (m, 1H, *H*COTBS), 3.80 (s, 3H, PhO*Me*), 3.71-3.64 (m, 2H, *H*COMe and C$H_a$$H_b$OH), 3.64-3.58 (m, 1H, $CH_a$$H_b$OH), 3.58-3.52 (m, 1H, *H*COMOM), 3.38 (s, 3H, O*Me*), 3.30-3.27 (m, 2H, *H*COPMB and *H*COMe), 3.30 (s, 3H, O*Me*), 3.25 (s, 3H, O*Me*), 2.04 (dd, *J* = 8.5 and 3.7 Hz, 1H, O*H*), 1.84-1.78 (m, 2H, C$H_{a1}$$H_{b1}$), 1.66 (ddd, *J* = 14.1, 8.7, and 4.2 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.59-1.53 (m, 1H, $CH_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), 0.93 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.08 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), 0.05 (s, 3H, Si*Me*), and 0.04 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.9, 145.7, 131.6, 128.8, 113.6, 111.8, 97.6, 91.9, 81.9, 79.2, 78.9, 75.7, 73.2, 66.9, 63.1, 58.5, 56.5, 55.9, 55.3, 41.8, 39.8, 37.8, 26.17, 26.14, 25.8, 24.6, 18.5, 18.1, -3.8, -4.1, -4.2, and -4.6.

HR ESI-MS: Calcd for $C_{38}H_{72}O_9Si_2Na$ $(M+Na)^+$: 751.4607 Found: 751.4616.

TLC: R_f = 0.30; 3:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-5,8-Bis(*tert*-butyldimethylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-enal **448**



447 ***448***

To a 50 mL round bottom flask containing alcohol **447** (540 mg, 0.741 mmol) was added CH_2Cl_2 (16.1 mL, 0.046 M). The solution was cooled to 0 ºC followed by the

addition of $NaHCO_3$ (248 mg, 2.96 mmol) and Dess-Martin periodinane (408 mg, 0.963 mmol) to the reaction mixture. The solution was warmed to room temperature and stirred until monitoring by TLC showed complete consumption of the starting material. The reaction mixture was cooled to 0 ºC and saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL) were added. The two-phase mixture was warmed to room temperature and stirred till both layers were clear. The mixture was diluted with H_2O (5 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the desired aldehyde **448**. The crude product was carried on to the next step without purification.

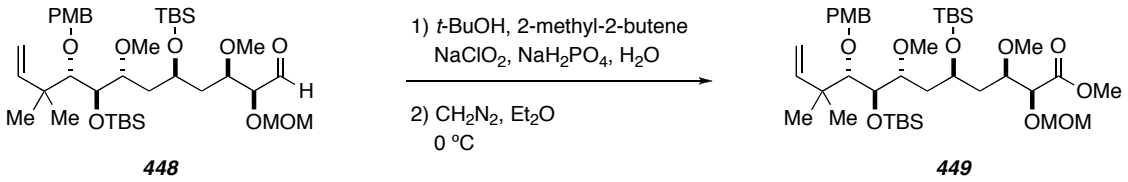
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.71 (s, 1H, *H*C=O), 7.29 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.03 (dd, *J* = 17.9 and 10.5 Hz, 1H, CH_2=C*H*), 5.02 (dd, *J* = 18.2 and 1.6 Hz, 1H, CH_aH$_b$=CH), 5.02 (dd, *J* = 10.4 and 1.6 Hz, 1H, CH$_a$$H_b$=CH), 4.93 (d, *J* = 11.2 Hz, 1H, MeOPhCH_aH$_b$), 4.73 (d, *J* = 6.9 Hz, 1H, OCH_aH$_b$OMe), 4.65 (d, *J* = 6.8 Hz, 1H, OCH$_a$$H_b$OMe), 4.42 (d, *J* = 11.2 Hz, 1H, MeOPhCH$_a$$H_b$), 4.14 (s, 1H, *H*COTBS), 4.02-3.95 (m, 1H, *H*COTBS), 3.88 (dd, *J* = 3.3 and 1.4 Hz, *H*COMOM), 3.80 (s, 3H, PhO*Me*), 3.67-3.62 (m, 2H, *H*COMe), 3.39 (s, 3H, O*Me*), 3.30 (d, *J* = 1.5 Hz, 1H, *H*COPMB), 3.26 (s, 3H, O*Me*), 3.25 (s, 3H, O*Me*), 1.89-1.75 (m, 3H, C$H_{a1}H_{b1}$ and CH_{a2}H$_{b2}$), 1.63 (ddd, *J* = 14.2, 7.7, and 4.6 Hz, 1H, CH$_{a2}$$H_{b2}$), 1.10 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), 0.93 (s, 9H, SiCMe_3), 0.87 (s, 9H, SiCMe_3), 0.08 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), 0.05 (s, 3H, Si*Me*), and 0.04 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.1, 158.9, 145.7, 131.5, 128.9, 113.6, 111.8, 97.4, 91.9, 83.5, 79.0, 78.8, 75.8, 73.1, 66.9, 58.7, 56.5, 56.3, 55.4, 41.9, 40.2, 37.9, 30.5, 26.2, 26.1, 25.7, 24.7, 18.4, 18.1, -3.81, -4.08, -4.15, and -4.54.

HR ESI-MS: Calcd for $C_{38}H_{70}O_9Si_2Na$ $(M+Na)^+$: 749.4451 Found: 749.4455.

TLC: R_f = 0.71; 3:1 hexanes:ethyl acetate.

(2*S*,3*R*,5*S*,7*R*,8*R*,9*S*)-Methyl 5,8-Bis(*tert*-butyldimethylsilyloxy)-3,7-dimethoxy-9-(4-methoxybenzyloxy)-2-(methoxymethoxy)-10,10-dimethyldodec-11-enoate **449**



448 ***449***

Carboxylic Acid Formation

To a 250 mL round bottom flask containing the crude aldehyde **448** (~0.741 mmol) was added *t*-BuOH (43.6 mL, 0.017 M) and 2-methyl-2-butene (14.3 mL, 0.052 M). To a vial equipped with a stir bar was added NaH_2PO_4 (670 mg, 7.41 mmol), $NaClO_2$ (511 mg, 3.70 mmol), and H_2O (19.5 mL, 0.19 M in $NaClO_2$). Once the mixture in the vial became homogeneous, the aqueous solution was added to the reaction flask. The reaction mixture was stirred at room temperature for 1 hour. The solution was then cooled to 0 ºC, and a newly prepared saturated solution of $NaHSO_3$ (8 mL) was added. The reaction was diluted with H_20 (75 mL) and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude carboxylic acid. The crude product was carried on to the next step without purification.

Methyl Ester Formation

To a 125 mL Erlenmeyer flask equipped with a stir bar and containing the crude carboxylic acid (~0.741 mmol) was added Et_2O (57 mL, 0.016 M) followed by cooling the solution to 0 ºC. Diazald (1.62 g, 7.56 mmol) and ethanol (27 mL) were added to a 150 mL side-arm Erlenmeyer flask equipped with a stir bar. The top of the 150 mL side-arm Erlenmeyer flask was covered with a new 24/40 septum that had a piece of teflon tubing punctured through the septum, having one end placed into the ethanol solution while the other end was connected to a N_2 line under positive pressure. A new 14/20 septa with another piece of teflon tubing punctured through it was placed on the side-arm and the opposite end of the teflon tubing was placed into the solution of Et_2O containing the crude carboxylic acid in the 125 mL Erlenmeyer flask. The N_2 flow was then regulated so that constant N_2 sparging was observed in both Erlenmeyer flasks. This is

important because the flow of N_2 is what is going to carry the diazomethane as it is formed, to the 125 mL Erlenmeyer flask containing the crude carboxylic acid. A sodium hydroxide solution (1 M) is added at a constant rate to the 125 mL side-arm Erlenmeyer flask while stirring, until all the yellow color in the 125 mL side-arm Erlenmeyer flask disappears. The esterification reaction is complete when the Et_2O in the 125 mL Erlenmeyer flask turns yellow as the result of excess diazomethane accumulating in the solution. The teflon tubing is removed from the Et_2O and a few drops of acetic acid is added until the Et_2O solution turns colorless. Saturated aqueous $NaHCO_3$ (20 mL) was added to quench any excess acetic acid. The reaction was diluted with Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to provide a mixture of the desired product **449** and lactone **450**. Column chromatography was performed (3:1 hexanes / ethyl acetate) to provide methyl ester **449** (350 mg, 52%, 3-steps). **NOTE:** Lactone **450** resulted from the deprotection of the secondary TBS ether after the oxidation step. The crude mixture of the carboxylic acid was left in the freezer overnight and this is where the deprotection likely occurred.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.6 Hz, 2H, MeOPhH_a), 6.85 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.02 (dd, *J* = 18.0 and 10.6 Hz, 1H, CH_2=C*H*), 5.05-4.99 (m, 2H, CH_2=CH), 4.94 (d, *J* = 11.2 Hz, 1H, MeOPhCH_aH$_b$), 4.70 (d, *J* = 7.0 Hz, 1H, OCH_aH$_b$OMe), 4.65 (d, *J* = 7.1 Hz, 1H, OCH$_a$$H_b$OMe), 4.41 (d, *J* = 11.1 Hz, 1H, MeOPhCH$_a$$H_b$), 4.15 (s, 1H, *H*COTBS), 4.07 (d, *J* = 3.2, *H*COMOM), 4.07-4.01 (m, 1H, *H*COTBS), 3.79 (s, 3H, PhO*Me*), 3.72 (s, 3H, CO_2*Me*), 3.70-3.63 (m, 2H, *H*COMe), 3.35 (s, 3H, O*Me*), 3.31-3.28 (m, 1H, *H*COPMB), 3.29 (s, 3H, O*Me*), 3.25 (s, 3H, O*Me*), 1.89 (ddd, *J* = 13.7, 9.2, and 4.2 Hz, 1H, CH_{a1}H$_{b1}$), 1.89-1.75 (m, 2H, C$H_{a2}$$H_{b2}$), 1.47 (ddd, *J* = 14.0, 8.4, and 3.4 Hz, 1H, CH$_{a1}$$H_{b1}$), 1.10 (s, 3H, C*Me*), 1.09 (s, 3H, C*Me*), 0.94 (s, 9H, SiCMe_3), 0.88 (s, 9H, SiCMe_3), 0.08 (s, 3H, Si*Me*), 0.07 (s, 3H, Si*Me*), 0.06 (s, 3H, Si*Me*), and 0.05 (s, 3H, Si*Me*).

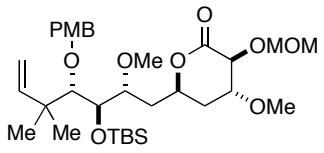
^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.42, 158.9, 145.7, 131.6, 128.9, 113.6, 111.8, 96.6, 91.9, 79.2, 78.8, 77.6, 75.7, 73.2, 66.7, 59.0, 56.5, 56.3, 55.3, 51.9, 41.9, 41.1, 37.9, 26.2,

26.1, 25.8, 24.5, 18.4, 18.1, -3.8, -4.1, -4.2, and -4.5.

HR ESI-MS: Calcd for $C_{39}H_{72}O_{10}Si_2Na$ $(M+Na)^+$: 779.4556 Found: 779.4571.

TLC: $\mathbf{R_f}$ = 0.77; 3:1 hexanes:ethyl acetate.

(3*S*,4*R*,6*S*)-6-((2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methoxy-4-(4-methoxybenzyloxy)-5,5-dimethylhept-6-enyl)-4-methoxy-3-(methoxymethoxy)tetrahydro-2*H*-pyran-2-one **450**



450

Lactone **450** (122 mg, 0.200 mmol) was isolated as a by-product during the formation of methyl ester **449**, resulting from the deprotection of the secondary TBS-ether after the oxidation step.

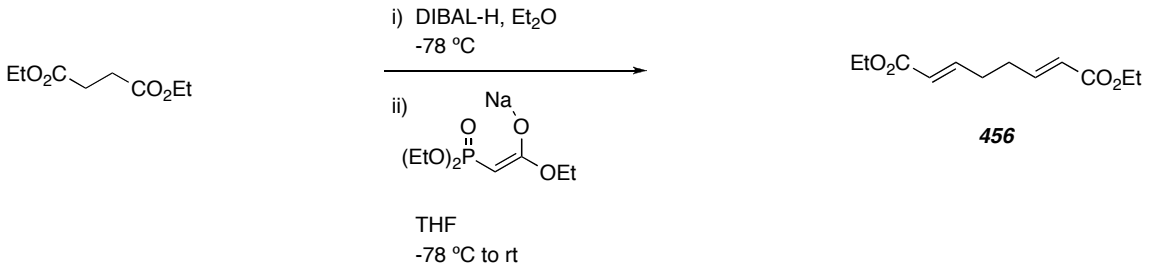
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2H, MeOPhH_a), 6.86 (d, *J* = 8.6 Hz, 2H, MeOPhH_b), 6.03 (dd, *J* = 17.6 and 10.8 Hz, 1H, CH_2=C*H*), 5.06 (dd, *J* = 10.8 and 1.2 Hz, 1H, C$H_a$$H_b$=CH), 5.03 (dd, *J* = 17.6 and 1.3 Hz, 1H, $CH_a$$H_b$=CH), 4.92 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.84 (d, *J* = 10.8 Hz, 1H, MeOPhC$H_a$$H_b$), 4.76 (d, *J* = 6.8 Hz, 1H, OC$H_a$$H_b$OMe), 4.62 (dddd, *J* = 11.5, 9.2, 3.9, and 2.5 Hz, 1H, *H*COC=O), 4.46 (d, *J* = 10.9 Hz, 1H, MeOPhC$H_a$$H_b$), 4.30 (d, *J* = 3.2, *H*COMOM), 4.15-4.10 (m, 1H, *H*COTBS), 3.80 (s, 3H, PhO*Me*), 3.67 (dd, *J* = 10.2 and 2.4 Hz, 1H, *H*COMe), 3.54 (ddd, *J* = 7.0, 7.0, and 1.9 Hz, 1H, *H*COMe), 3.46 (s, 3H, O*Me*), 3.39 (s, 3H, O*Me*), 3.30 (d, *J* = 1.7 Hz, 1H, *H*COPMB), 3.25 (s, 3H, O*Me*), 2.13 (ddd, *J* = 14.8, 9.3, and 2.2 Hz, 1H, C$H_{a1}$$H_{b1}$), 1.91 (ddd, *J* = 15.1, 2.3, and 2.3 Hz, 1H, C$H_{a2}$$H_{b2}$), 1.73 (ddd, *J* = 15.2, 11.2, and 7.0 Hz, 1H, $CH_{a2}$$H_{b2}$), 1.71 (ddd, *J* = 13.7, 10.1, and 3.9 Hz, 1H, $CH_{a1}$$H_{b1}$), 1.111 (s, 3H, C*Me*), 1.106 (s, 3H, C*Me*), 0.93 (s, 9H, SiCMe_3), 0.09 (s, 3H, Si*Me*), and 0.07 (s, 3H, Si*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8, 159.0, 145.3, 131.1, 129.0, 113.7, 112.1, 96.0, 91.3, 78.2, 77.7, 75.9, 74.2, 73.06, 73.05, 57.3, 57.1, 56.0, 55.3, 41.7, 35.9, 35.1, 26.1, 25.3, 24.9, 18.3, -4.2, and -4.7.

HR ESI-MS: Calcd for $C_{32}H_{54}O_9SiNa$ $(M+Na)^+$: 633.3429 Found: 633.3417.

TLC: R_f = 0.43; 3:1 hexanes:ethyl acetate.

(2*E*,6*E*)-Diethyl octa-2,6-dienedioate **456**



See (2*E*,7*E*)-diethyl nona-2-7-dienedioate **458** for a representative procedure.

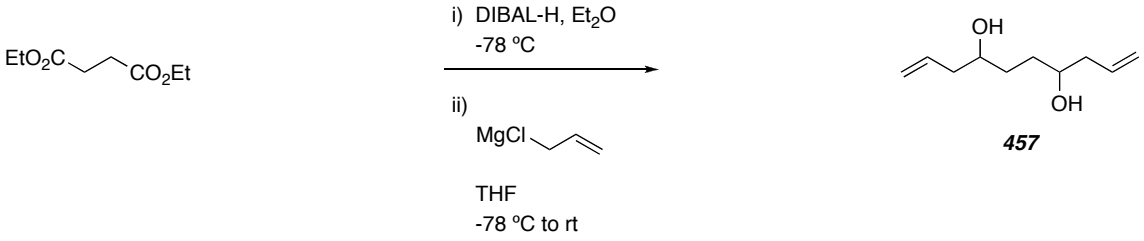
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.01-6.87 (br dt, *J* = 16.0 and 6.0 Hz, 2H, CH_β=CHCO$_2$), 5.86 (d, *J* = 15.0 Hz, 2H, CH=CH_αCO$_2$), 4.19 (q, *J* = 7.0 Hz, 4H, OCH_2Me), 2.46-2.33 (m, 4H, CH_2), and 1.29 (t, *J* = 7.5 Hz, 6H, OCH$_2$*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 147.0, 122.5, 60.4, 30.6, and 14.4.

HR ESI-MS: Calcd for $C_{12}H_{18}O_4Na$ $(M+Na)^+$: 249.1103 Found: 249.1103.

TLC: R_f = 0.60; 3:1 hexanes:ethyl acetate.

Deca-1,9-diene-4,7-diol **457**



See undeca-1,10-diene-4,8-diol **459** for a representative procedure.

Mixture of Diastereomers

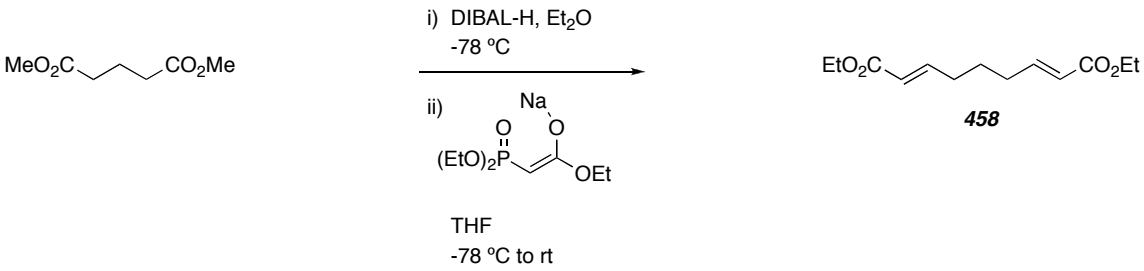
^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.90-5.68 (two overlapping dddd, *J* = 17.0, 10.0, 8.0, and 7.0 Hz, 2H, CH_2=C*H*), 5.19-5.11 (m, 4H, CH_2=CH), 3.76-3.64 (br s ($W_{1/2h}$ = 19 Hz, 2H, *H*COH), 2.38 (br s, 1H, O*H*), 2.30 (two overlapped br ddd, *J* = 13.0, 6.0, and 6.0 Hz, CH_2=CHC$H_{a1}H_{b1}$ and CH_2=CHC$H_{a2}H_{b2}$), 2.20 (two overlapped app dddd, *J* = 14.0, 8.0, 8.0, and 1.0 Hz, CH_2=CHC$H_{a1}H_{b1}$ and CH_2=CHC$H_{a2}H_{b2}$), 2.13 (br s, 1H, O*H*), 1.75-1.64 (m, 2H, C$H_{a1}H_{b1}$ and C$H_{a2}H_{b2}$), and 1.62-1.50 (m, 2H, $CH_{a1}H_{b1}$ and $CH_{a2}H_{b2}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.3, 118.2, 71.5*, 71.0**, 42.6*, 42.3**, 33.8*, and 32.9**. (* one diastereomer, ** the other diastereomer).

HR ESI-MS: Calcd for $C_{10}H_{18}O_2Na$ $(M+Na)^+$: 193.1205 Found: 193.1191.

TLC: R_f = 0.60; 1:1 hexanes:ethyl acetate.

(2*E*,7*E*)-Diethyl nona-2-7-dienedioate **458**



Representative procedure for *In Situ* Generation and Nucleophilic Capture by a Triethyl Phosphonoacetate Sodium Salt of 1,n-Dial Equivalents from 1,n-Dioates. A solution of DIBAL-H in toluene (10.0 mL, 15 mmol) was slowly added (over ca. 15 min) to a solution of dimethyl glutarate (1.0 mL, 6.8 mmol) in diethyl ether (27 mL) at -78 ºC under N_2. The internal temperature was maintained below -70 ºC (internal temperature probe). The mixture was stirred for 30 min at -78 ºC. A solution of the phosphonoacetate anion (20 mmol, preparation below) was added via cannula at -78 ºC. The reaction mixture was then warmed to room temperature and stirred for 2 h. Water (~30 mL) and a saturated solution of Rochelle's salt (~30 mL) were added and the resulting mixture was stirred until the two layers were homogeneous. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo, and the resulting material was purified via flash chromatography (25% ethyl acetate: 75% hexanes) to provide 1.48 g (6.16 mmol, 91%) of the dienoate product **458**.

Representative Procedure for Formation of Triethyl Phosphonoacetate Sodium Salt. Triethyl phosphonoacetate (4.1 mL, 20 mmol) was added to a suspension of NaH (0.46 g, 19 mmol) in THF (40 mL) at 0 ºC. The mixture was stirred until the evolution of H_2 gas ceased (≤10 min). At this time the solution had become homogeneous. No-D ^{1}H NMR analysis confirmed that a small amount of starting, non-deprotonated triethyl phosphonoacetate remained. In the case of entry 5, excess sodium hydride remaining after sodiophosphonoacetate generation will lead to decomposition of the desired product. It therefore was necessary to use a slight excess (0.05 equiv) of phosphonoacetate relative to sodium hydride.

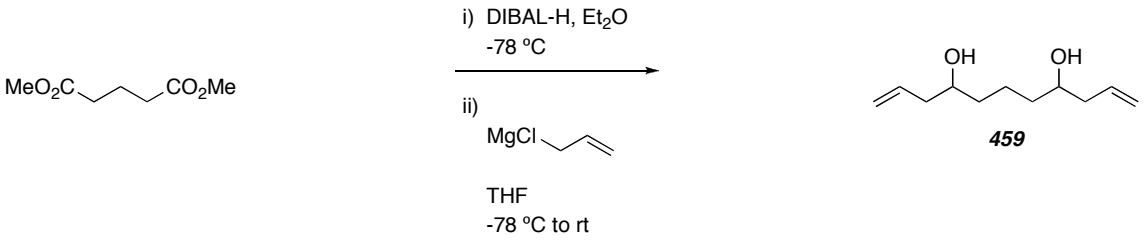
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.93 (dt, *J* = 15.5 and 6.3 Hz, 2H, CH_β=CHCO$_2$), 5.83 (d, *J* = 16.0 Hz, 2H, CH=CH_αCO$_2$), 4.19 (q, *J* = 7.0 Hz, 4H, OCH_2Me), 2.24 (dt, *J* = 7.0 and 7.0 Hz, 4H, CH=CHCH_2), 1.64 (p, *J* = 7.0 Hz, 2H, CH$_2$CH_2CH$_2$), and 1.29 (t, *J* = 7.5 Hz, 6H, OCH$_2$*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 148.2, 122.1, 60.4, 31.6, 26.5, and 14.4.

HR ESI-MS: Calcd for $C_{13}H_{20}O_4Na$ $(M+Na)^+$: 263.1259 Found: 263.1263.

TLC: $\mathbf{R_f}$ = 0.70; 3:1 hexanes:ethyl acetate.

Undeca-1,10-diene-4,8-diol **459**



Representative procedure for *In Situ* Generation and Nucleophilic Capture by Allylmagnesium Chloride of 1,n-Dial Equivalents from 1,n-Dioates. A solution of DIBAL-H in toluene (5.0 mL, 7.5 mmol) was slowly added (over ca. 7 min) to a solution of dimethyl glutarate (0.50 mL, 3.4 mmol) in diethyl ether (13.6 mL) at -78 ºC under N_2. The internal temperature was maintined below -70 ºC. The mixture was stirred for 30 min at -78 ºC. A solution of allylmagnesium chloride in diethyl ether (3.7 mL, 7.5 mmol) was added -78 ºC. The reaction mixture was then warmed to room temperature and stirred for 2 h. The mixture was quenched with saturated ammonium chloride solution at 0 ºC. A saturated solution of Rochelle's salt was added at room temperature, and the two-phase mixture was stirred for approximately 8 h. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried with Na_2SO_4. The solvent was removed in vacuo, and the resulting material was purified via flash chromatography (50% ethyl acetate: 50% hexanes) to provide 0.44 g (2.4 mmol, 71%) of the desired product **459**.

Mixture of Diastereomers

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83 (dddd, *J* = 17.0, 10.0, 8.0, and 7.0 Hz, 2H, CH_2=C*H*), 5.17-5.12 (m, 4H, CH_2=CH), 3.70-3.64 (m, 2H, *H*COH), 2.31 (br dt, *J* = 13.0 and 6.0 Hz, 2H, CH_2=CHC$H_{a1}H_{b1}$ and CH_2=CHC$H_{a2}H_{b2}$), 2.15 (ddd, *J* = 14.5, 7.5, and 7.5

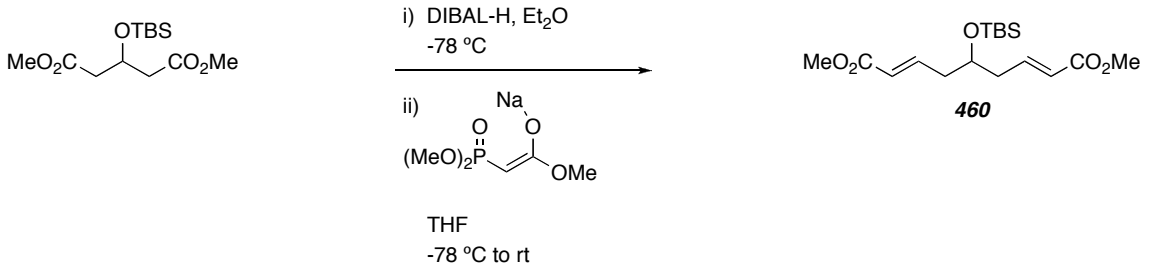
Hz, 2H, CH_2=CHC$H_{a1}H_{b1}$ and CH_2=CHC$H_{a2}H_{b2}$), and 1.77-1.45 (m, 8H, CH_2CH_2CH_2 and O*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.1, 135.1, 117.9, 117.8, 70.7, 70.6, 42.2, 42.0, 36.7, 36.5, 21.8, and 21.7.

HR ESI-MS: Calcd for $C_{11}H_{20}O_2Na$ $(M+Na)^+$: 207.1361 Found: 207.1370.

TLC: R_f = 0.30; 1:1 hexanes:ethyl acetate.

(2*E*,7*E*)-Dimethyl 5-(triethylsilyloxy)nona-2-7-dienedioate **460**



See (2*E*,7*E*)-diethyl nona-2-7-dienedioate **458** for a representative procedure.

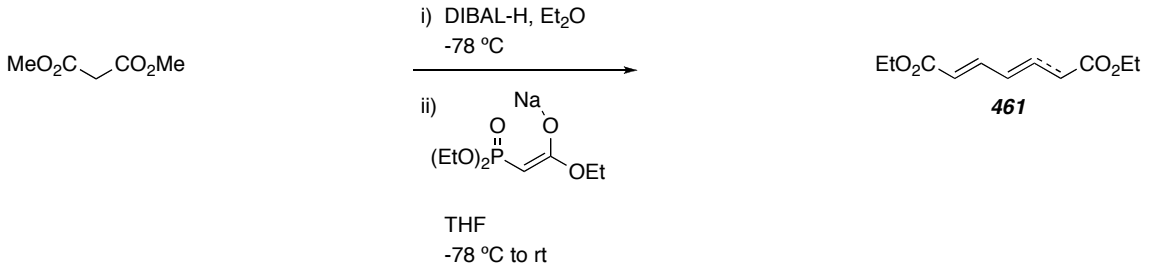
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.94 (dt, *J* = 15.3 and 7.5 Hz, 2H, CH_{β}=CHCO$_2$), 5.86 (dt, *J* = 15.6 and 1.5 Hz, 2H, CH=CH_{α}CO$_2$), 3.93 (tt, *J* = 11.4 and 5.7 Hz, 1H, *H*COTBS), 3.73 (s, 6H, CO$_2$*Me*), 2.36 (nfom, 4H, CH_2), 0.95 (t, *J* = 7.8 Hz, 9H, Si(CH$_2$CH_3)$_3$), and 0.59 (q, *J* = 7.8 Hz, 6H, Si(CH_2CH$_3$)$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 145.0, 123.5, 70.1, 51.5, 40.1, 6.9, and 4.9.

HR ESI-MS: Calcd for $C_{17}H_{30}O_5Na$ $(M+Na)^+$: 365.1760 Found: 365.1793.

TLC: R_f = 0.25; 9:1 hexanes:ethyl acetate.

(2*E*,4*E*)-Diethyl hepta-2-4-dienedioate **461**



461

See (2*E*,7*E*)-diethyl nona-2-7-dienedioate **458** for a representative procedure.

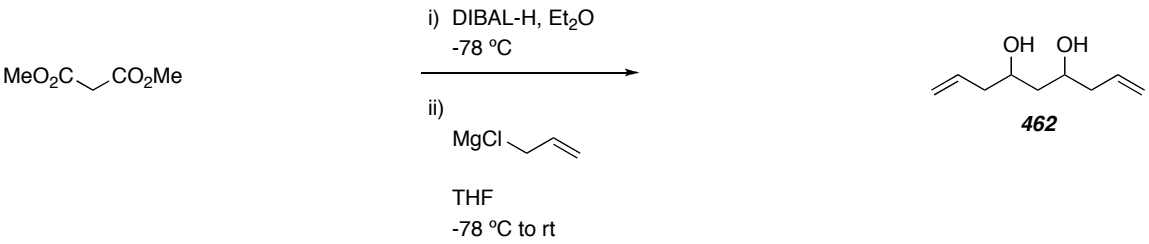
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27 (dd, *J* = 15.0 and 10.0 Hz, 1H, C*H*$_\square$=CHCO$_2$), 6.27 (dd, *J* = 15.0 and 10.0 Hz, 1H, CH=C*H*$_\gamma$-CH=CHCO$_2$), 6.19 (dt, *J* = 14.0 and 7.0 Hz, 1H, C*H*$_\delta$=CH-CH=CHCO$_2$), 5.85 (d, *J* = 15.0 Hz, 1H, CH=C*H*$_\alpha$CO$_2$), 4.20 (q, *J* = 7.5 Hz, 2H, CO$_2$C*H*$_2$Me, 4.16 (q, *J* = 7.0 Hz, 2H, CO$_2$C*H*$_2$Me), 3.20 (d, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.30 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$*Me*), and 1.27 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$*Me*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 167.0, 143.8, 134.3, 131.5, 121.4, 61.1, 60.4, 38.3, 14.4, and 14.3.

HR ESI-MS: Calcd for $C_{11}H_{16}O_4Na$ $(M+Na)^+$: 235.0946 Found: 235.0958.

TLC: R_f = 0.70; 3:1 hexanes:ethyl acetate.

Undeca-1,10-diene-4,8-diol **462**



462

See undeca-1,10-diene-4,8-diol **459** for a representative procedure.

Mixture of Diastereomers

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.82 (dddd, *J* = 17.0, 10.0, 7.0, and 7.0 Hz, 2H, CH_2=C*H*), 5.15 (br d, *J* = 16 Hz, 2H, C$H_{a1}$$H_{b1}$=CH and C$H_{a2}$$H_{b2}$=CH), 5.14 (br d, *J* = 11.0 Hz, 2H, $CH_{a1}H_{b1}$=CH and $CH_{a2}H_{b2}$=CH), 4.01 (app p, *J* = 6.0 Hz, 2H, *H*COH), 2.36 (br s, 1H, O*H*), 2.28 (ddddd, *J* = 14.0, 7.0, 7.0, 1.0, and 1.0 Hz, 2H, CH_2=CHC$H_{a1}$$H_{b1}$ and CH_2=CHC$H_{a2}$$H_{b2}$), 2.27 (ddddd, *J* = 14.0, 7.0, 7.0, 1.0, and 1.0 Hz, 2H, CH_2=CH$CH_{a1}H_{b1}$ and CH_2=CH$CH_{a2}H_{b2}$), and 1.66 (t, *J* = 6.0 Hz, 2H, COHCH_2COH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.9*, 134.5**, 118.1**, 118.0*, 71.9**, 68.2*, 42.6**, 42.1*, 41.8**, and 41.6*. (* *anti* and ** *syn* diastereomer)

HR ESI-MS: Calcd for $C_9H_{16}O_2Na$ $(M+Na)^+$: 179.1048 Found: 179.1050.

TLC: R_f = 0.50; 1:1 hexanes:ethyl acetate.

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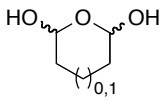
Appendix A

In situ Generation and Nucleophilic Capture of 1,n-Dial Equivalents From 1,n-Dioates

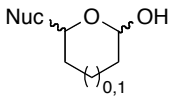
During T. Ryba's efforts toward synthesizing (+)-peloruside A **1** it became necessary to chain extend various 3-oxygenated glutaraldehydes via a Horner Wadsworth Evans (HWE) olefination. Even though he had experience working with these substrates, he was unable to produce the necessary glutaraldehyde needed to perform the HWE olefination via DIBAL-H reduction of the corresponding glurate ester. These dialdehydes of the glutaric and succinic families are well known for their tendencies to react intramolecularly with one another. This event then disrupts the reactivity of the second aldehyde, shutting down the ability to symmetrically chain elongate. Examples of this include internal hydrate formation and attack by an external nucleophile (Nuc) to one free aldehyde and subsequent intramolecular adduct formation with the other (**Figure 11**).

Figure 11

By-Products of Dialdehydes



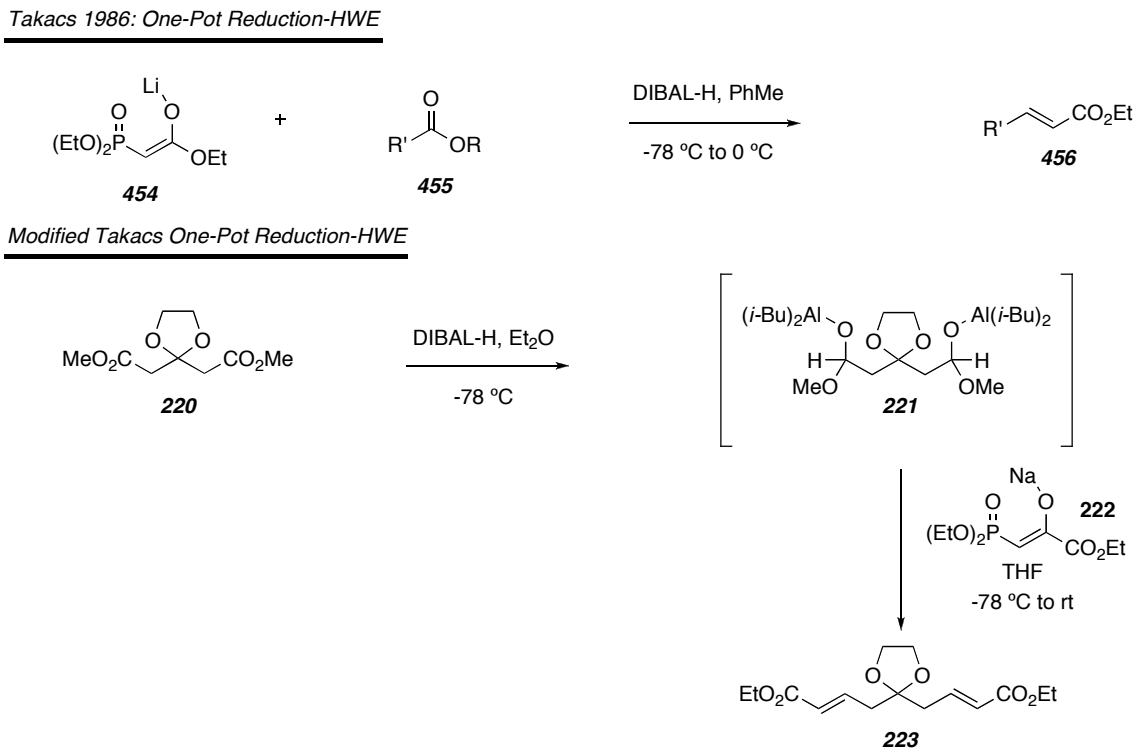
452



453

While in discussions with a fellow lab member, Ryba was directed toward a literature protocol by Takacs.[65] In the protocol, triethylphosphonoacetate **222** is treated *n*-BuLi to prepare the lithium salt **454** followed by addition of ester **455** as a solution (**Scheme 140**). DIBAL-H is then added to the reaction mixture at -78 ºC followed by warming to 0 ºC to cleanly provide the homologated α,β-unsaturated ester **456**.

Scheme 140



Ryba believed that he could apply similar methodology to his system in an effort to solve the problem with production of the glutaraldehyde species, by never directly forming it. It was envisioned, that the pair of tetrahedral intermediates of **221** would sequentially collapse upon warming to provide the corresponding aldehydes at different times. If a suitable nucleophile was present during the formation of each aldehyde, then the typical problems encountered using these unstable glutaraldehyde species would be avoided and advantageous. In Ryba's modified procedure, ketal **220** was cooled to -78 ºC followed by addition of 2 equiv. of DIBAL-H to provide the bis-tetrahedral intermediate **221**. A THF solution of the pregenerated sodium salt of triethylphosphonoacetate (**222**) was added to the ethereal solution containing intermediate **221** and this combined solution was gradually warmed to room temperature. Upon workup the newly formed diene **223** was isolated in high yield.[56]

After Ryba laid the groundwork and showed the utility of this methodology, I joined him on this project to investigate both the scope of substrates and trapping nucleophiles. For the study we chose to investigate double Horner-Emmons and double

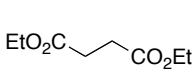
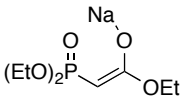
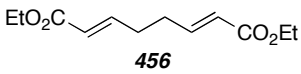
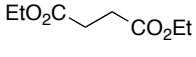
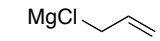
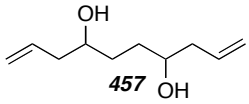
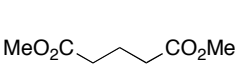
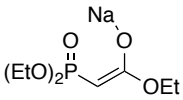
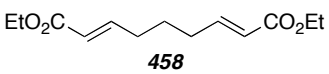
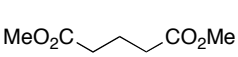
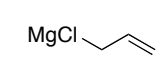
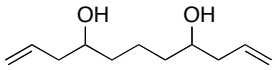
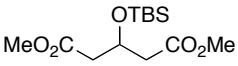
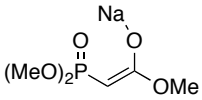
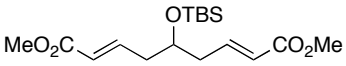
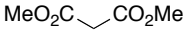
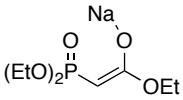
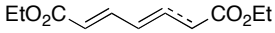
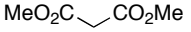
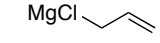
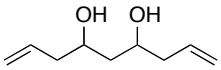
Grignard additions using phosphonoacetates and allylmagnesium chloride as representative trapping nucleophiles.[66]

The results of this study are shown in **Table 11**. The succinate (entries 1 and 2) and glutarate (entries 3-5) esters provided the dienoate esters or 1,n diols in good to excellent yields. Even the 3-triethylsilyloxyglutarate ester shown in entry 5 was tolerated and showed no signs of complication from elimination when an excess of the neutral phosphonoacetate was used. The reaction was even applicable to malonate esters (entries 6 and 7) for quick entry into 1,3-dienes and -diols. However, there were other competing events (see **Table 11**, note b) that affected the overall efficiency of the transformation, but no attempts were made to optimize the dimethyl malonate reactions.

This study has resulted in a convenient way to symmetrically elongate various 1,n-dial equivalents via sequential reduction of the corresponding 1,n-dioates and addition of an appropriate nucleophile.

Table 11

Results of Sequential Reaction of Starting Diesters with i) DIBAL-H and ii) Either Phosphonate Anion or Allylmagnesium Chloride

Entry	Starting Diester	Nucleophile	Product	Yield (%)[a]	Comments
1			 ***456***	75	94:6 (*E,E*:*E,Z*)
2			 ***457***	73	dr ca. 1:1 (^{13}C NMR)
3			 ***458***	91	95:5 (*E,E*:*E,Z*)
4			 ***459***	71	dr ca. 1:1 (^{13}C NMR)
5			 ***460***	87	98:2 (*E,E*:*E,Z*)
6[b]			 ***461***	18	–
7			 ***462***	41	dr ca. 1:1 (^{13}C NMR)

[a] Isolated following purification by silica gel chromatography.

[b] Varying ratios of deconjugated (1,4-) and conjugated (1,3-) dienes were obtained; isomerization to the latter, more stable isomer generally occurred upon handling and storage.