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Studies Directed Towards the Total Synthesis of (+)-Peloruside A

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Studies Directed Towards the Total Synthesis of (+)-Peloruside A

by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

May 2006

To my parents, who have given me endless love and support.

This would not have been possible without you.

Acknowledgements

I would like to thank my advisor Dr. Brian L. Pagenkopf for his guidance and support. He provided me the freedom to grow and develop as a synthetic chemist and for that I am grateful.

I would like to thank the entire Pagenkopf group, especially Dr. Julie Le and Jeffrey Gorman for many insightful discussions in lab. I also would like to thank Dr. Martin Bassindale, a former post-doc, for his early contributions in this project and Hongda Zhao for his helpful suggestions for the expoxide ring opening procedure.

I would like to acknowledge the Willson research group for the use of the infrared spectroscopy; the Martin group, for the use of the HPLC; Dr. Vince Lynch for his assistance in gathering crystallography data for this dissertation; research associates Steven Sorey and Jim Wallin for their help in the NMR analysis.

Finally, I would like to express my gratitude toward my parents who believed in me and have always been there for me. I am grateful for the support and encouragement of my brother David, and his beloved family, Amy, Sam and J-Ro. This would not have been possible without all of you.

Studies Directed Towards the Total Synthesis of (+)-Peloruside A

Publication No._____

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The University of Texas at Austin, 2006

Supervisor: Brian L. Pagenkopf

Peloruside A, isolated from marine sponge *Mycale hentscheli*, has shown potent cytotoxicity toward P388 murine leukemia cells (10 ng/mL, 18 nM), and functions like Taxol® by inducing apoptosis in the G2-M phase of the cell cycle through microtubule-stabilization. To date, there have been two total synthesis of peloruside A. The goal of our research was to have the most efficient and practical synthesis of peloruside A.

In this study, the application of a variety of aldol methodologies towards the convergent synthesis of peloruside A will be discussed. In our initial approach, the key synthetic strategy for peloruside A is the Mukaiyama aldol reaction between a glucose-derived aldehyde and an α-benzyloxymethyl ketone. Alternatively, a similar segment of peloruside A can be constructed with a complex methyl ketone using a Walsh multicomponent coupling reaction and a Carreira enantioselective dienolate addition. The study is concluded with a concise synthesis of an advanced intermediate of peloruside A.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ac	Acyl
Atm	Atmosphere
Bn	Benzyl
n-Bu	*normal*-Butyl
t-Bu	*tert*-Butyl
°C	Degrees Celsius
CAM	Cerium ammonium molybdate
CH_2Cl_2	Dichloromethane
COSY	Correlated spectroscopy
δ	Chemical shift, in NMR spectroscopy
d	Doublet, in NMR spectroscopy
m-CPBA	*meta*-Chloroperoxybenzoic acid
Cy	Cyclohexane
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-*N,N*-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
g	Gram(s)

ee	Enantiomeric excess
Et	Ethyl
FID	Flame ionization detector
FT-IR	Fourier Transform-infrared
GOESY	Gradient nuclear Overhauser effect spectroscopy
HPLC	High pressure (or performance) liquid chromatography
HRMS	High resolution mass spectrometry
$(Ipc)_2BOTf$	Diisopinocampheylboron triflate
i-Pr	*iso*-Propyl
J	Coupling constant (NMR)
IC_{50}	50% of the concentration for complete inhibition of
IR	Infrared
KO^tBu	Potassium *tert*-butoxide
LA	Lewis acid
LDA	Lithium diisopropyl amine
m	Multiplet, in NMR spectroscopy
Me	Methyl
Meerwein's salt	Trimethyloxonium flouroborane ($Me_3O^+BF_4^-$)
mmol	Millimole
MOMCl	Methoxymethane chloride
NBS	*N*-bromosuccinimide
NMO	4-Methylmorpholine-N-Oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser effect
OMe	Methoxy

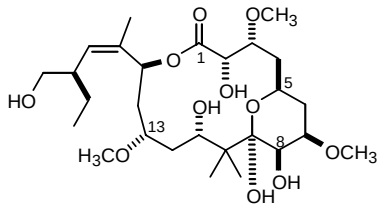
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
Oxone	Potassium peroxymonosulfate
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMB	*para*-Methoxybenzyloxy
PPTS	Pyridinium *p*-toluenesulfonate
R_f	Ratio to front
ROESY	Rotational nuclear Overhauser effect spectroscopy
rt	Room temperature
s	Singlet, in NMR spectroscopy
t	Triplet, in NMR spectroscopy
Tf	Triflate or Trifluoromethylsulfonyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
THF	Tetrahydrofuran
TMEDA	*N, N, N', N'*-Tetramethylethylenediamine
TLC	Thin layer chromatography
TMS	Trimethyl
TMSCl	Trimethylsilyl chloride
TOCSY	Total correlated spectroscopy
p-TolBINAP	2,2'-Bis(di-*p*-tolyl-phosphino)-1,1'-binaphthalenyl
t_R	Retention time

Chapter 1: Introduction

1.1 Introduction: Isolation and Biological Activity of Peloruside A

Macrolide peloruside A (Figure 1.1, **1.1**) was isolated from the *Mycale* sponge from Pelorus Sound in 2000 by the Northcote research group.[1] Evidence from ^{1}H and ^{13}C NMR spectroscopic analysis confirmed the presence of three methoxy groups, a trisubstituted olefin and a saturated ester, possibly a lactone. The relative configuration and connectivity were assigned through COSY, TOCSY, ROESY and NOE NMR experiments.

Figure 1.1 Peloruside A



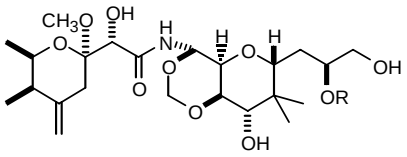
(+)-peloruside A **1.1**

The absolute configuration remained unsolved until the first total synthesis of unnatural *ent*-peloruside A by De Brabander in 2003.[2] The absolute configuration was assigned as 2*S*, 3*R*, 5*R*, 7*R*, 8*R*, 9*R*, 11*S*, 13*S*, 15*S*, 18*R*.

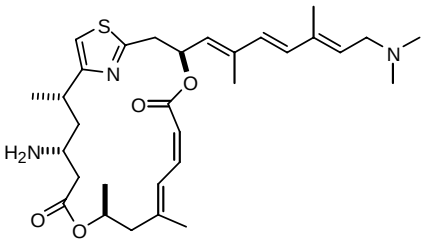
Page et al.[3] studied the biosynthesis of peloruside A through the aquaculture of wild *Mycale* sponges. Interestingly, only 50% of the sponges contained detectable concentrations of peloruside A, and only those sponges grown in their native environment continued to biosynthesize peloruside A. Due to insufficient quantities from natural sources, peloruside A is an ideal target for total synthesis. An efficient synthesis should provide enough material for pre-clinical analysis.

Other diverse structures have been found from sponges of the genus *Mycale* included antiviral and antitumor agents mycalamide A (Figure 1.2**, 1.2**),[4] mycalamide B (**1.3**)[5] and cytotoxic macrolide pateamine (**1.4**).[6] These natural products have garnered considerable attention with several elegant total synthesis of mycalamide A,[7] mycalamide B[8] and pateamine[9] reported.

Figure 1.2 Other bioactive secondary metabolites from the *Mycale* sponge



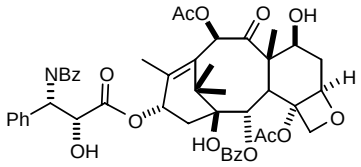
R=H mycalamide A **1.2**
R=Me mycalamide B **1.3**



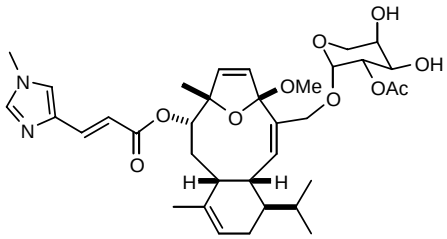
pateamine **1.4**

Peloruside A has shown potent cytotoxicity at nanomolar concentrations toward multiple cell lines and is thought to function like Taxol by inducing apoptosis in the G2-M phase of the cell cycle through microtubule stabilization.[10,11] Drugs like Taxol **1.5** (Figure 1.3) target tubulin and shift the equilibrium to the polymerized form, thus stabilizing microtubules, and have proven to be effective cancer therapeutics. Other natural products that are classified as micro-tubulin stabilizing agents are eleutherobin **1.6,** epothilones **1.7**, discodermalide **1.8** and laulimalide **1.9**. Interestingly, Villarrasa et al.[12] compared laulidalide **1.9** and peloruside A **1.1** to the microtubule-stabilizing drug Taxol **1.5** by different computational methods. While peloruside A does have a favorable interaction to the β tubulin binding site, the α docking site is preferred. For this reason, peloruside A might be a superior anticancer agent remaining active to Taxol resistant cells.

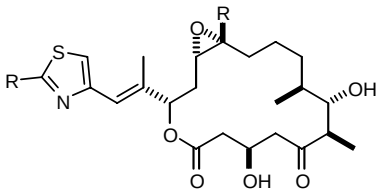
Figure 1.3 Other microtubule-stabilizing Agents



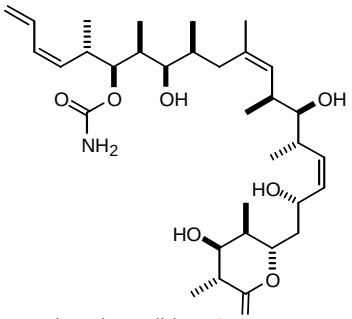
Taxol **1.5**



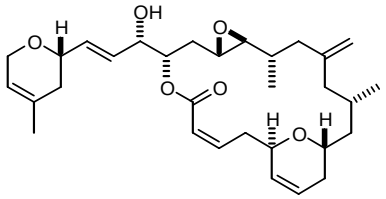
Eleutherobin **1.6**



Epithilones **1.7**



Discodermalide **1.8**



Laulimalide **1.9**

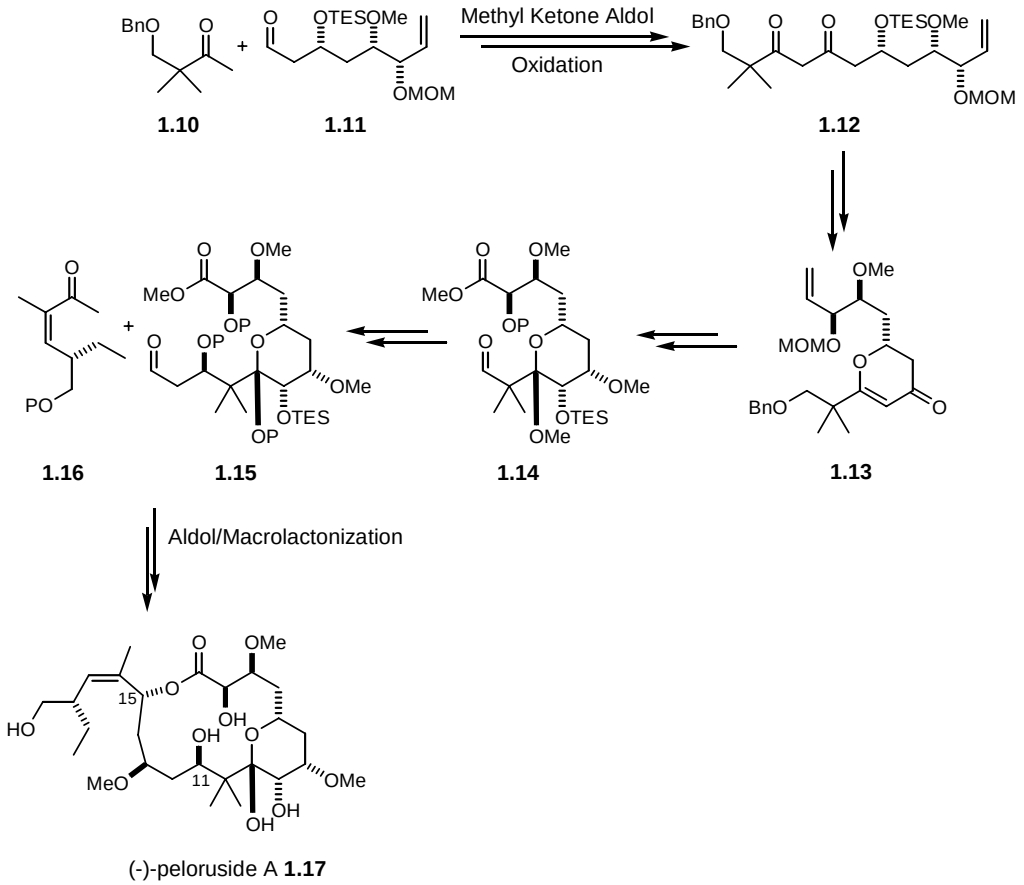
1.2 REPORTED TOTAL SYNTHESIS OF PELORUSIDE A

There have been two total syntheses of peloruside A by De Brabander[2] and Taylor[13] and several reported synthetic efforts.[14] In the following section, we will discuss the two total syntheses of peloruside A.

1.2.1 Total Synthesis by De Brabander

De Brabander et al.[2] in 2003 reported the first total synthesis of peloruside A (Scheme 1.1). At the onset of their synthesis, the absolute configuration had not been established, so they targeted the (–)-peloruside A as proposed by Northcote.

Scheme 1.1 De Brabander Synthesis



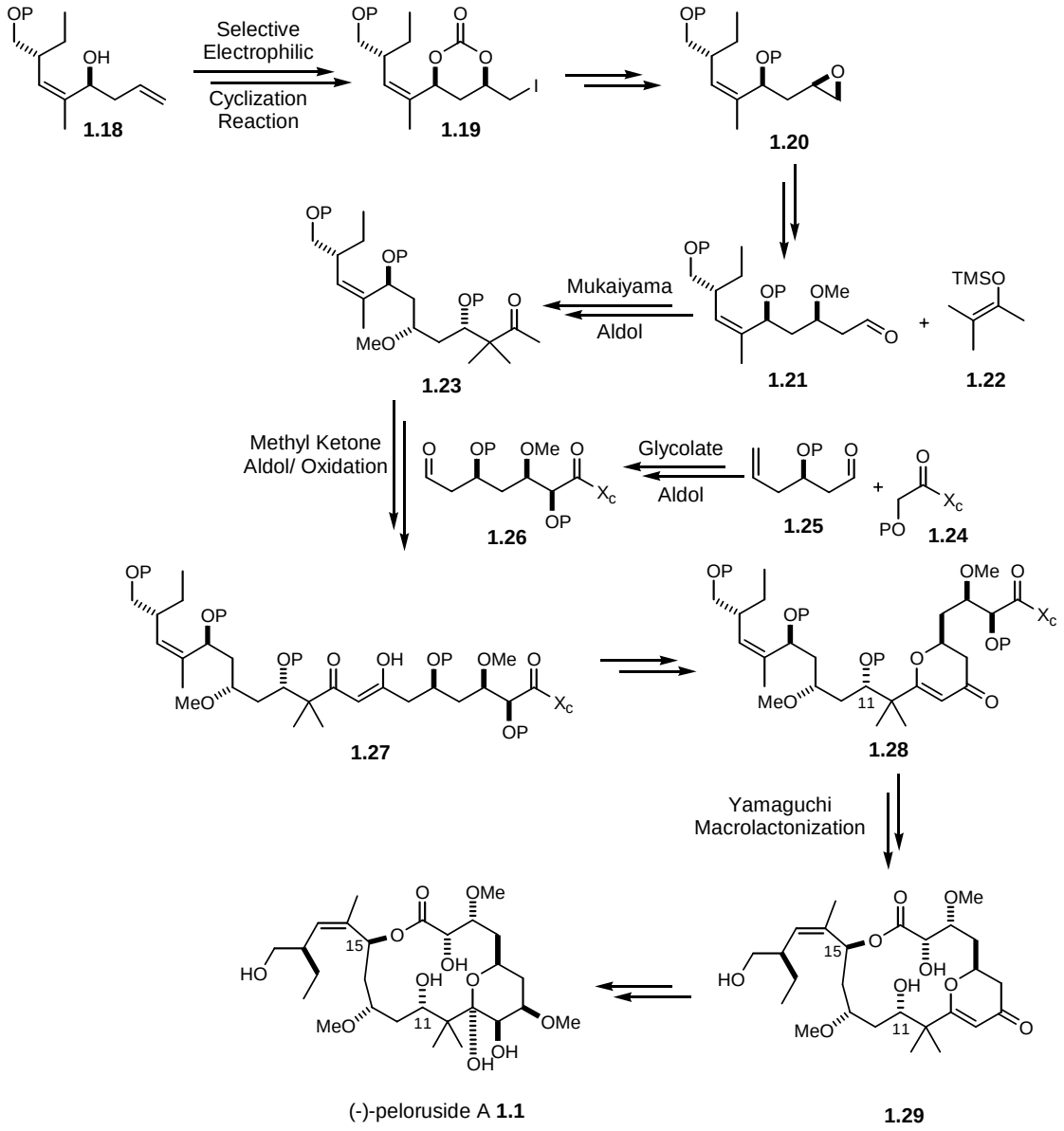
The synthesis began with an aldol reaction between methyl ketone **1.10** and aldehyde **1.11** and subsequent oxidation of the resulting *β*-hydroxy ketone yielded *β*-diketone **1.12**. After formation of the dihydropyranone **1.13** under acidic dehydrating conditions, an efficient sequence of synthetic steps built the densely functionalized pyran **1.14**. Asymmetric allylation and subsequent oxidative cleavage provided aldehyde **1.15** that was subjected to an aldol coupling with methyl ketone **1.16**. Macrolactonization of the resulting allylic alcohol gave (–)-peloruside A **1.17**. This was the first total synthesis and more importantly documented the absolute configuration of naturally occurring (+)-peloruside A.

1.2.2 Total Synthesis by Taylor

In 2005, Taylor et al.[13] reported the total synthesis of (+)-peloruside A (Scheme 1.2). The synthesis of homoallylic alcohol **1.18** was highlighted by a Still-Gennari olefination and a Brown asymmetric allylation. A selective electrophilic cyclization reaction provided carbonate **1.19** (92% yield). After revealing the 1,3-*syn* diol and subsequent epoxide formation, an anionic dithiane strategy afforded aldehyde **1.21**.

The Mukayiama aldol between aldehyde **1.21** and trimethyl silyl enol ether **1.22** provided the methyl ketone **1.23** (91% yield) with good *anti*/*syn* selectivity (8:1). After another aldol forming the C_7-C_8 bond and Dess-Martin oxidation, the dihydropyranone **1.28** was obtained. A Yamaguchi lactonization provided macrolactone **1.29** (51% yield) and elaboration of the functionalized pyranoside completed the synthesis of (+)-peloruside A **1.1**.

Scheme 1.2 Taylor Synthesis

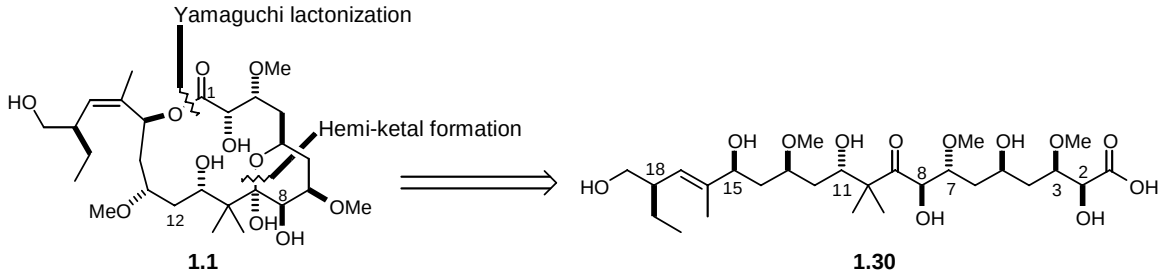


1.3 OUR INITIAL RETROSYNTHESIS OF PELORUSIDE A

In designing the retrosynthesis of peloruside A we focused on two criteria: synthetic convergence and systematic placement of the methyl ethers without the

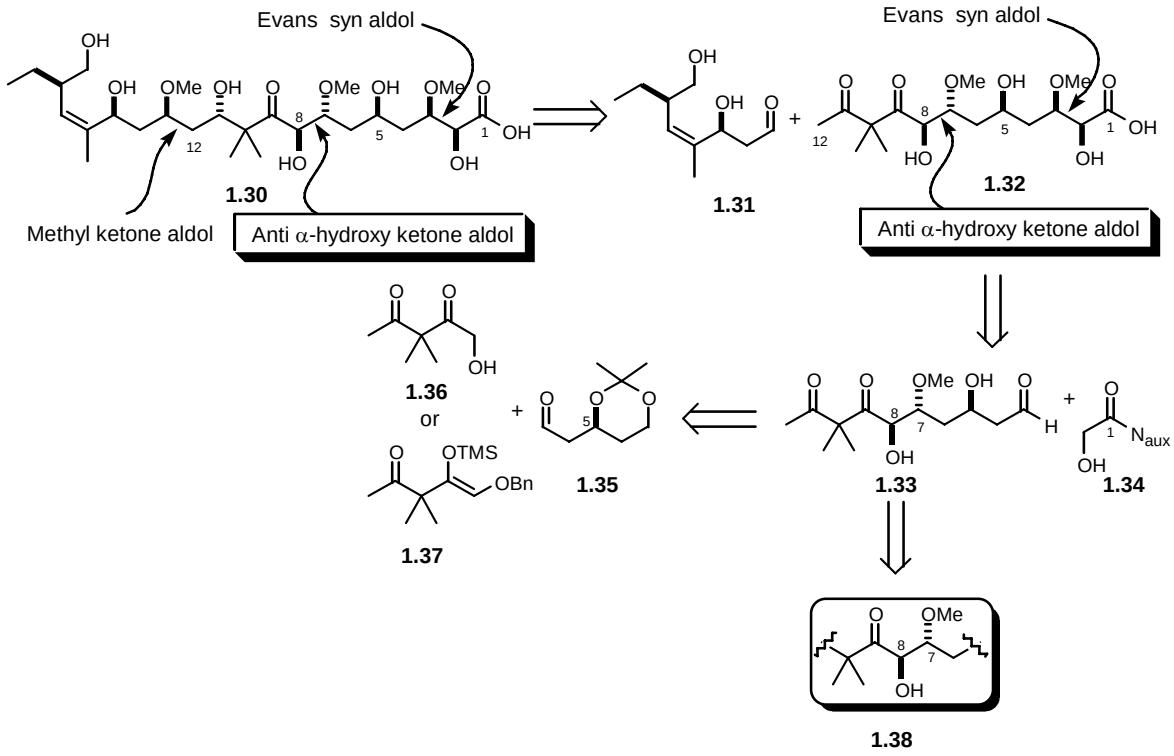
painstaking protection and deprotection of diols. The plan to synthesize peloruside A involves a Yamaguchi lactonization[15] and a hemi-ketal cyclization to form the linear polyoxygenated structure **1.30** (Scheme 1.3). After forming the acyclic compound **1.30**, the strategic disconnections were identified to be C_7-C_8.

Scheme 1.3 Retrosynthesis I



After identifying these crucial bond disconnections, we envisioned the disconnection of C_{12}-C_{13} would allow access to two linear molecules of similar length and complexity (Scheme 1.4). Aldehyde **1.31**[16] will be connected to compound **1.32** by a methyl ketone aldol using an asymmetric boron reagent, such as (+)-chlorodiisopinocampheylborane.[17] A further disconnection of **1.32** by a boron-mediated *syn*-aldol using Evans auxiliary **1.34** will set the stereochemistry at C_2 and C_3.[18]

Scheme 1.4 Retrosynthesis I (cont'd)



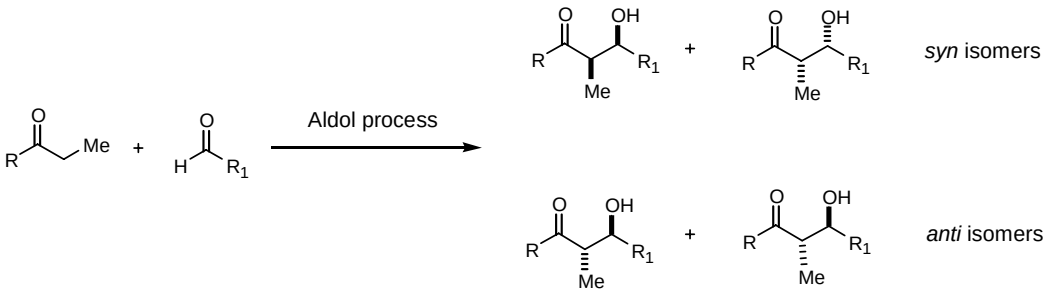
Compound **1.33** contains a α′,α′-dimethyl-*anti*-α-hydroxy-β-methoxyketone fragment **1.38**, and no efficient procedures for the synthesis of this substructure were identified from the Beilstien or Scifinder databases. In a polyoxygentated molecule like **1.33**, when β-methoxy and α-hydroxy functionalities are present, a possible disconnection is an aldol reaction. It would be beneficial for the resulting product to have a lone free hydroxyl group, so that selective methylation can immediately follow as required for the natural product. By employing a protected α-hydroxy ketone enolate in the peloruside A synthesis, each free β-hydroxyl can be methylated as it is formed. Our goals in this project were to efficiently synthesize the natural product and develop a general *anti*-aldol methodology for preparing α-hydroxy-β-alkoxy ketones. Addressing the asymmetric C_7-C_8 bond formation was the focus of our initial research (Chapter 2).

Chapter 2: Aldol Methodologies Directed Towards the C_7-C_8 Bond Formation of Peloruside A

2.1 BACKGROUND. ALDOL REACTIONS

Aldol reactions are well-known carbon-carbon bond forming processes. There are several different types of aldol reactions and two of the most predominate are the boron-mediated[19] and the Mukaiyama type aldols. In the reaction of ethyl ketones and an aldehyde, the formation of the α-methyl-β-hydroxy ketone is a powerful synthetic reaction because of the creation of two new stereocenters. With aldol reactions, there are four possible products, which can be subdivided into *syn* and *anti* stereoisomers (Scheme 2.1). Selectively synthesizing one of the four possible diastereomers has been at the cusp of modern aldol methodology. Product selectivity is possible by manipulation of the enolate geometry and the facial discrimination of the enolate.

Scheme 2.1 Formation of four stereoisomers

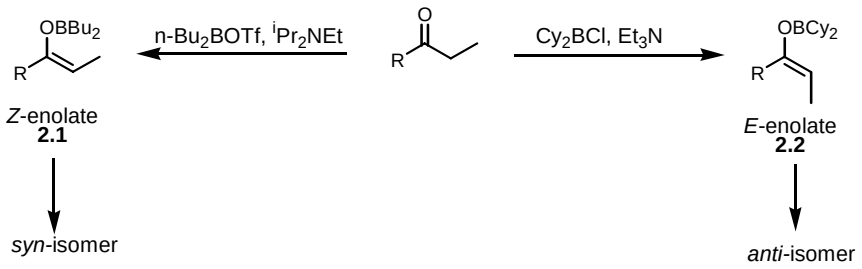


2.1.1 Boron-mediated Aldols

In boron-mediated aldol reactions, the selective formation of either *E* or *Z* enolate isomer is critical to good stereocontrol (Scheme 2.2). Good *syn*-stereoselectivity in boron-mediated aldols hinges on the selective formation of the *Z*-enolate **2.1**, whereas good *anti*-relative stereochemistry relies on the formation of the *E*-enolate **2.2**. The *Z*-enolate of a ketone or ester derivative is formed efficiently from dibutylboron triflate and

a bulky amine base (Hunig's base). The *E*-enolate of a ketone or ester derivative is formed efficiently from dicyclohexylboron chloride and a relatively small amine base (Et_3N).[20] Theories have been proposed that explain the stereoselectivity of enolate formation, and they usually point to steric hindrance of the boron reagent as the main driving force for the selective *E*-enolate geometry.[21] With the ability to prepare either enolate stereoisomer, it is often possible to control the syn and anti product stereochemistry.

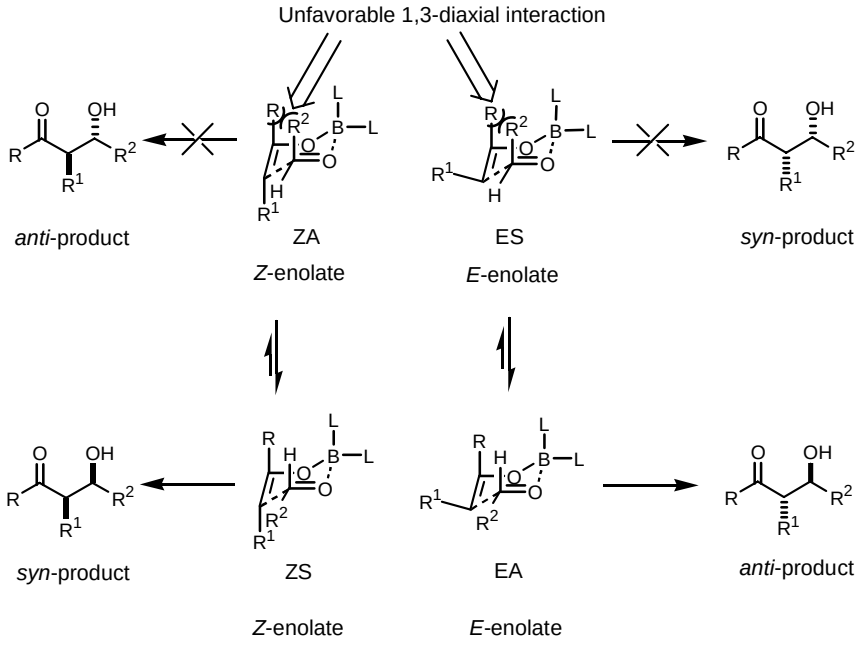
Scheme 2.2 Selective boron-enolate formation



Zimmerman and Traxler developed a transition state model to rationalize the product stereochemistry observed in boron mediated aldol reactions (Figure 2.1).[22] In the transition state an ate-complex is formed when the aldehyde coordinates to the enolate boron atom. The actual carbon-carbon bond forming interaction between the aldehyde and the enolate occurs by a closed six-membered transition state. In the lower energy transition state, the larger groups are placed in equatorial positions to avoid 1,3-diaxial interactions, which are indicated in transition states ZA and ES. By placing R^2 in the equatorial position, transition states ZS and EA illustrate the appropriate relative stereoselectivity of the aldol products. The Zimmerman-Traxler model holds true in the prediction and rationalization of aldol relative stereochemistry, but absolute stereochemistry depends on π-facial selectivity. Facial selectivity can be achieved

through the application of chiral boron reagents, chiral auxiliaries, or by chiral substrate directed selectivity.

Figure 2.1 Zimmerman-Traxler closed transition state model

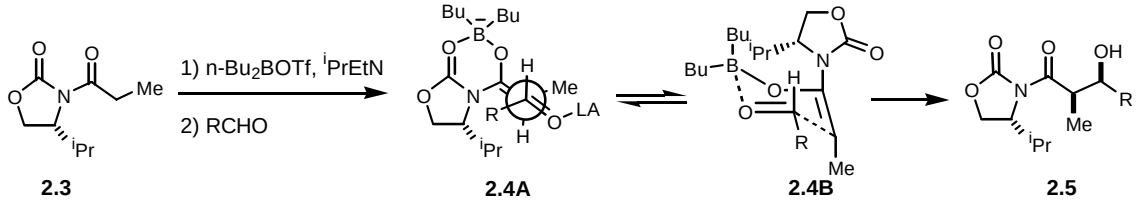


2.1.1.1 Syn boron-mediated aldol

Evans introduced a reliable boron-mediated methodology for the preparation of optically active *syn*-propionate aldols. The reactions using chiral oxazolidone auxiliaries, which are derived from (*S*)-valinol and (1*S*,2*R*)-norephedrine, gave good absolute stereoselectivity (Scheme 2.3).[8a] When stoichiometric Bu_2BOTf was used to form the enolate, the aldol follows a closed transition state **2.4B** and gave the *syn*-aldol product **2.5**, and π-facial discrimination was influenced by the oxazolidone chiral center (i.e. **2.4B**). In the reaction, the aldehyde will approach the less hindered face of the enolate, leading to high diastereoselectivity at C(2). Once again, relative stereochemistry can be explained by invoking the Zimmerman-Traxler model for closed transition states. The Evans aldol methodology has been used extensively throughout natural product synthesis

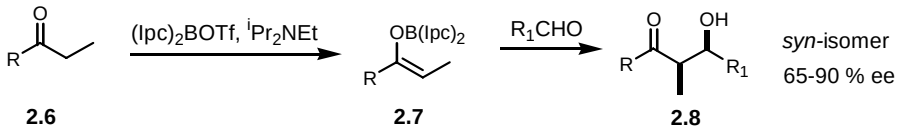
because of its generality, high enantioselectivity and efficiency. Later, Heathcock showed that the stoichiometry of the boron reagent can dramatically affect the stereochemistry of the reaction. With excess boron reagent or other Lewis acids, *anti*-aldol products were obtained. It is postulated that the reaction proceeds through an open transition state, and these will be discussed later.

Scheme 2.3 Propionate syn-aldol using oxazolidone



In aldol reactions of achiral n-alkyl ethyl ketones mediated by Bu_2BOTf, the *syn*-product is similarly obtained in high yield. In order to control absolute stereochemistry, one must use a chiral reagent or invoke chiral induction from the substrate. With a chiral boron reagent like (+) or (−) diisopinocampheylboron triflate (Ipc_2BOTf), Paterson demonstrated the efficient asymmetric synthesis of *syn*-α-methyl-β-hydroxy ketones (**2.8**) from achiral ethyl ketones (Scheme 2.4).[23] While this method does not provide consistently spectacular enantioselectivity (65-90% ee), it is a widely accepted method for the synthesis of the optically active *syn*-diastereomer from achiral ketones.

Scheme 2.4 Effective chiral boron reagent

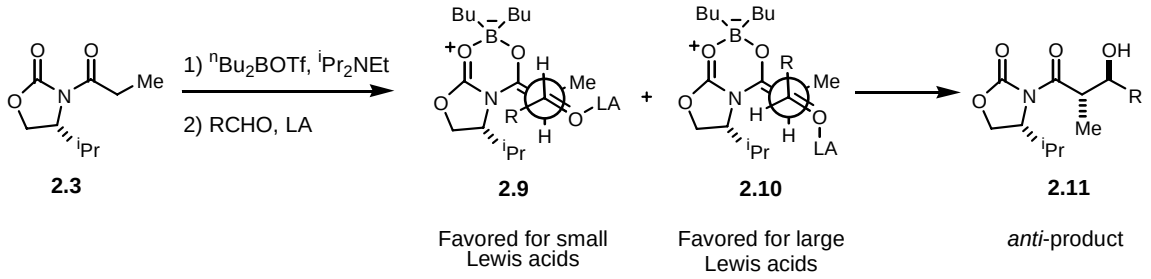


2.1.1.2 Anti boron-mediated aldol

Asymmetric methods have been developed for accessing aldol products possessing *anti*-stereochemistry from the same chiral oxazolidone auxiliaries (Scheme

2.5).[24] As mentioned above, the use of excess Lewis acid reverses the usual preference for syn stereochemistry, and the *anti*-products **2.11** are obtained as the predominate diastereomer.[25] Lewis acids ($SnCl_4$, $TiCl_4$, and Et_2AlCl), coordinated to the aldehyde, were introduced to an enolate and the various product stereochemistry was studied. The relative size of the Lewis acid, which is attributed to the metal-oxygen bond distance, correlates with the *anti*-selectivity. With Et_2AlCl, the oxygen-aluminum bond distance is less than the titanium-oxygen and the tin-oxygen bond. In summary, the *anti*-aldol with excess Lewis acid goes through an open transition state, where Heathcock noted the slight change in reaction conditions dramatically changes the stereoselectivities.

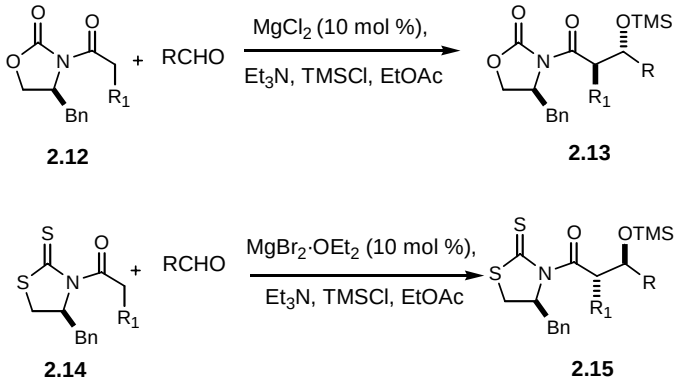
Scheme 2.5 Propionate anti-aldol using oxazolidone



Although these stoichiometric boron-mediated *syn*-aldols are well established and highly diastereoselective, it is worth-noting that Evans recently advanced the utility of oxazolidinones to prepare *anti*-aldols by employing a mild magnesium halide catalyst (

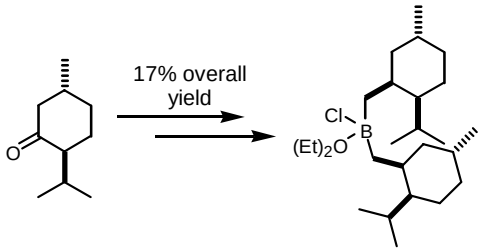
Scheme **2.6**).[26] The ability to access both *anti*-aldols in yields greater than 90% and diastereomeric ratios of greater than 25:1 by simply changing the nature of the magnesium salt is superior to the aforementioned boron-mediated oxazolidinone *anti*-aldol methodologies. With Evans' recent work, all four possible diastereomers of propionate derivatives are obtainable by either boron-mediated *syn* aldols or catalytic magnesium aldols.

Scheme 2.6 Magnesium halide-catalyzed anti-aldol

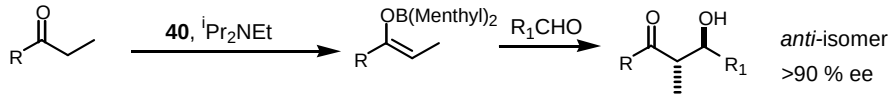


In contrast to the stereochemical control possible with oxazolidinone derivatives, very few reports have demonstrated even moderate levels of stereoselectivity in the boron mediated *anti*-aldol reactions with achiral ketones. Gennari and Paterson designed and subsequently synthesized chiral dimenthylboron chloride etherate **2.17**, prepared from (–) -menthone **2.16** (Scheme 2.7).[27] This chiral reagent showed the first highly enantioselective anti aldol reactions of ethyl ketone. [3:1-10:1 (*re*:*si*)]. However, the preparation of this stoichiometric reagent is tedious and inefficient (17% overall). The poor selectivity sometimes observed with this reagent coupled with the fact that **2.17** is painstakingly difficult to synthesize underscores the need for general methods for preparing these kinds of aldol products. Chiral boron reagents for preparing optically active *anti*-aldols is an undeveloped field in *anti*-aldol methodology, scarcely being used in natural product synthesis because of the reagent's difficult synthesis or ineffective diastereomeric control.[28]

Scheme 2.7 Chiral boron reagents for anti-aldols



2.16 **2.17**

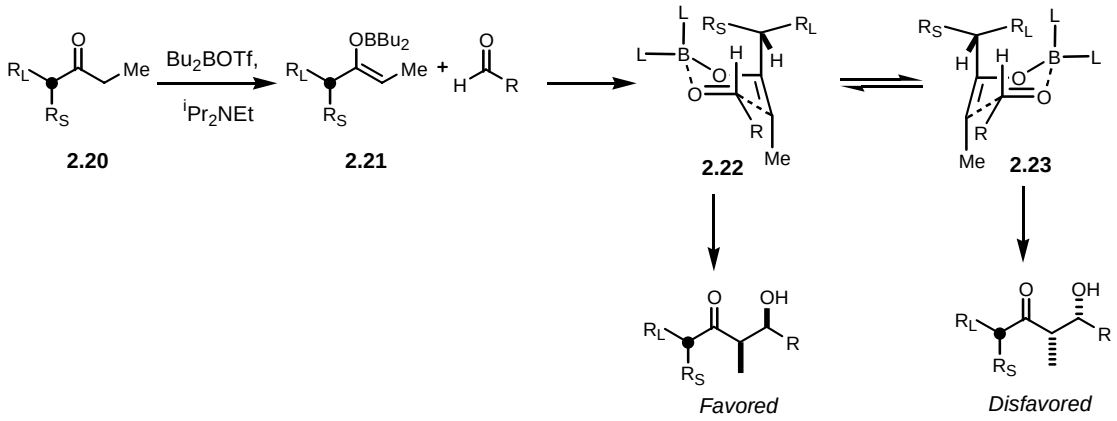


2.6 **2.18** **2.19**

2.1.2 Substrate π-facial Control

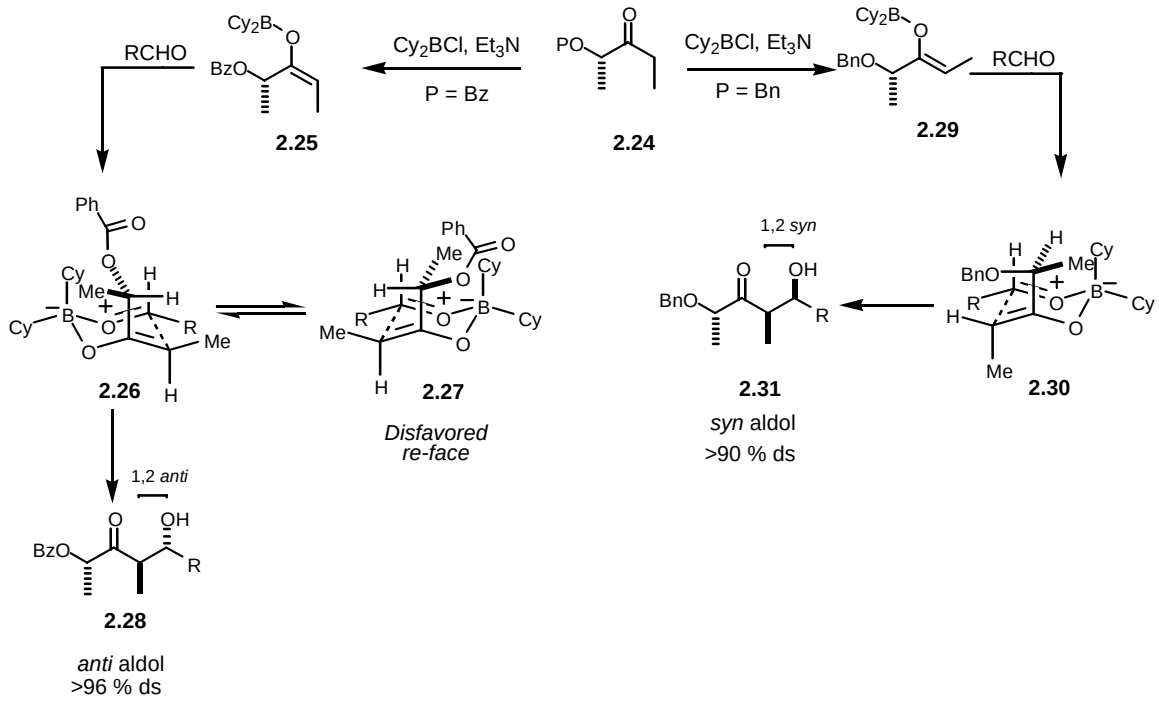
Substrate control of stereochemistry is frequently a superior method for controlling π-facial selectivity in ketone aldols. By employing a pre-existing stereocenter on the substrate to control facial selectivity, often highly stereoselective reactions are possible (Scheme 2.8). The minimization of allylic strain is thought to be the origin of stereocontrol by the α′-stereocenter on the enolate. In the favored transition state conformation, the α′-hydrogen occupies a position *cis* to the enolate π-bond, which orients R_S or R_L towards the boron ligand (**2.22** vs. **2.23**). Evans postulated that the interaction of the R_S or R_L with the ligand of the boron reagent imposes significant facial selectivity.[29] Others have seen the importance of the α′-stereocenter in aldol reactions.[30]

Scheme 2.8 Chiral stereocenters directing facial selectivity



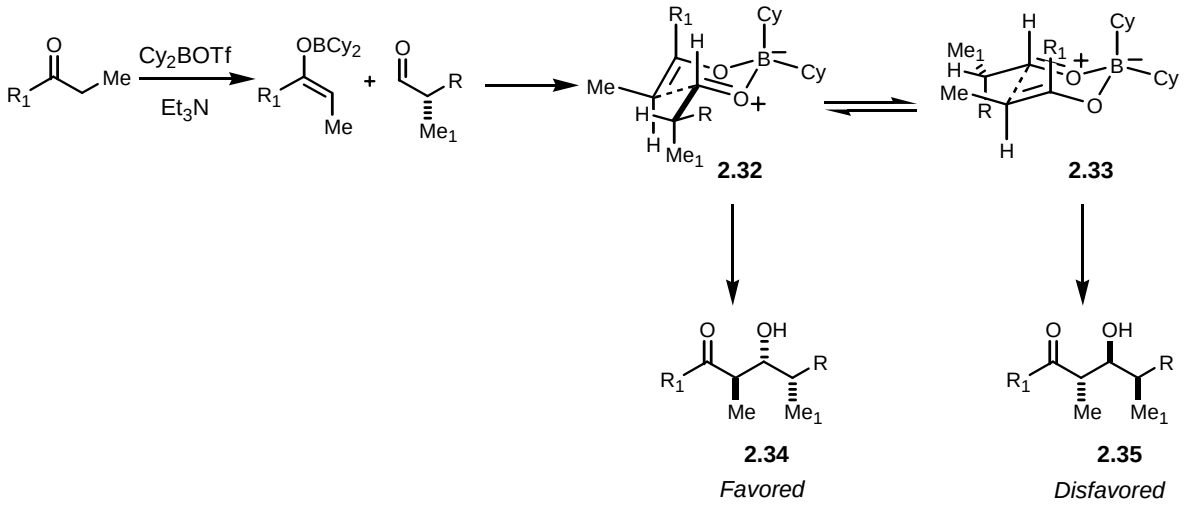
In the synthesis of *anti*-aldols, chiral ketones have worked effectively for controlling facial selectivity. Aldol reactions with lactate-derived ketones **2.24** have shown diastereoselectivities greater than 90% (Scheme 2.9).[31] Paterson has shown manipulation of the protecting group can greatly influence the stereochemistry. For example, when the α-hydroxyl was protected with a benzoyl group, the *anti*-product **2.28** was formed with high facial selectivity. The origin of the excellent facial discrimination in these reactions is illustrated in transition states **2.26** and **2.30**. In the low energy conformations **2.26** and **2.30**, the α′-hydrogen is positioned over the π-face of the enolate to minimize 1,3-allylic strain. The difference between **2.26** and **2.27** is electrostatic in nature. A lone pair repulsion of the benzoate oxygen and the enolate leads to instability in **2.27**. Interestingly enough, when the α-hydroxyl group is protected with a benzyl group, high *syn*-diastereoselectivity (**2.31**) was produced. *Syn*-selectivity can be attributed to the *Z*-enolate formation **2.29**.

Scheme 2.9 Facial selectivity from chiral ketones



While aldehydes with α-chiral stereocenters can provide high facial selectivity and superb *syn*-diastereomeric ratios, facial selectivity in the corresponding *anti*-aldols is more difficult to control. High facial selectivity in *anti*-aldol reactions of aldehydes with α-chiral stereocenters has only been observed when R is much larger than Me_1 (Scheme 2.10) because differential *syn*-pentane interactions lead to the most stable transition state **2.32**. While the α-stereocenter does not induce consistent facial selectivity, it does work synergistically alongside another directing method (i.e. chiral boron reagent) to provide a "matched" aldol resulting in a higher enantioselectivity.[32] The "matched" induction has been elegantly used throughout natural product synthesis.

Scheme 2.10 Facial selectivity from chiral aldehydes

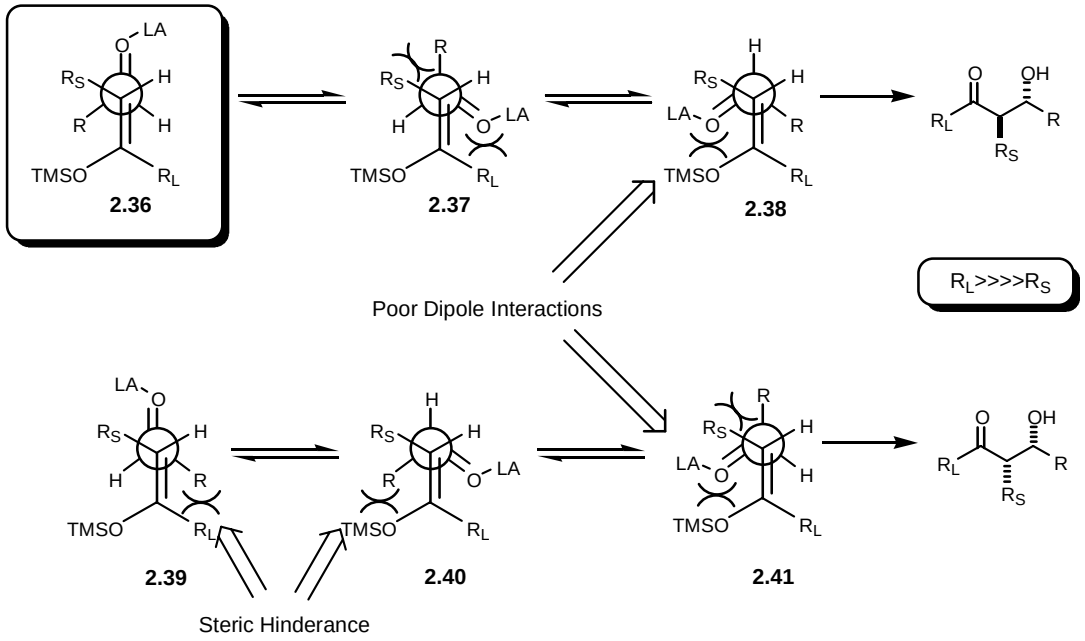


2.1.3 Mukaiyama Aldol

Another possible route to fragment **1.38** involves a Mukaiyama aldol of trimethyl silyl enol ether **1.37** and β-alkoxy aldehyde **1.35** (Scheme 1.4). The stereochemistry observed in Mukaiyama aldols cannot be explained by the Zimmerman-Traxler closed transition state model (Figure 2.1), but rather an open transition state has been proposed (Figure 2.2).[33] When R_L is sterically bulky and R_S is small, *anti* selectivity can be rationalized by a transition state that minimizes unfavorable dipole and steric interactions. Transition state **2.37** has a plethora of unfavorable nonbonding interactions, while **2.38** and **2.41** suffer from unfavorable dipole-dipole interactions. Transition state **2.39** is destabilized by steric crowding from $R_L \leftrightarrow R$ interaction as the Lewis acid-coordinated aldehyde approaches the enolate. In the same way, transition state **2.40** is unfavorable because of the R ↔ oxygen interaction. Only transition state **2.36** allows a bond to be formed without unfavorable dipole or steric interactions. The model presented in Figure 2.2 is applicable to the formation of **1.33** because of the structural similarities to α′,α′-

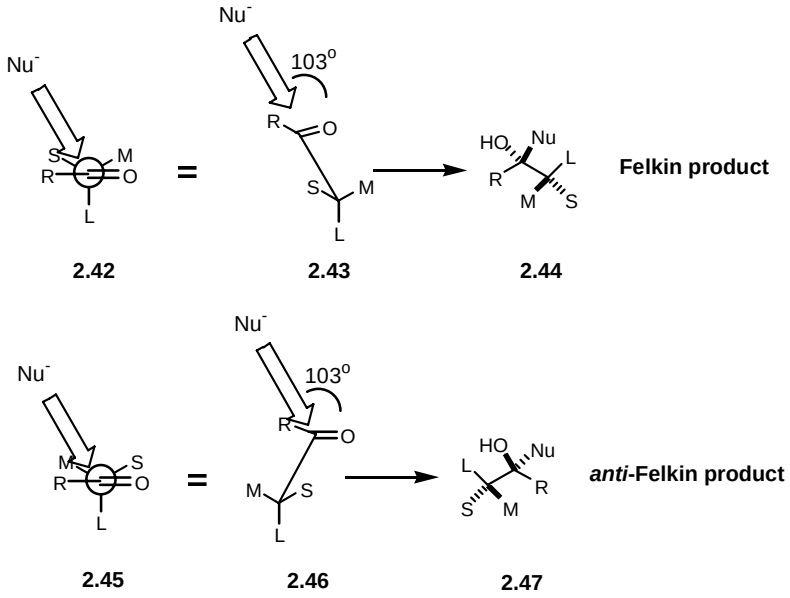
dimethyl-α-methyl silyl enol ether **1.37** substituents (Scheme 1.4, α′ position = R_L, Hydrogen = R_S).

Figure 2.2 Open transition state model for Mukaiyama aldol



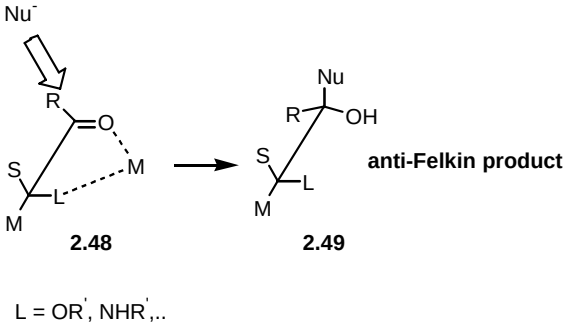
The aforementioned open transition state model can be used to predict relative stereochemistry, but π-facial selectivity has yet to be addressed. The Cram and Felkin-Ahn models for nucleophilic additions to α-chiral aldehydes can be applied to the Mukaiyama aldol (Figure 2.3).[34] When the large group (L) is positioned perpendicular to the carbonyl group it avoids steric interactions with the approaching nucleophile. Facial selectivity will be influenced by steric interaction between the approaching nucleophile and the substituents M and S (**2.43** vs. **2.46**). The alignment of L perpendicular to the carbonyl can have an important electronic effect when L is electronegative. The conformation with L perpendicular to the carbonyl allows electron delocalization of the carbonyl π-electron density into the σ* orbital of the L group. Sterics and electronics play an important role in the Felkin-Anh model.

Figure 2.3 Felkin-Anh model



In the Cram-chelate model, a Lewis acid coordinates to a α-heteroatom and the carbonyl, thus stabilizing the five-membered chelate **2.48** (Figure 2.4). The nucleophile attacks the carbonyl on the least hindered face, and in these situations good relative stereoselectivity has been observed. Facial selectivity is enhanced when M and S are significantly differentiated. It can be generalized that heteroatoms in the α-position do not behave the same as alkyl groups and result in different π-facial selectivity.

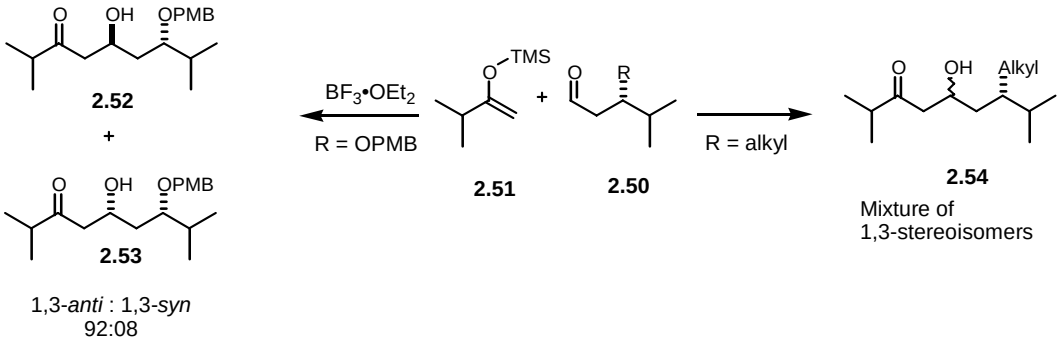
Figure 2.4 Cram's chelate model



The above models allow for the prediction of product facial selectivity in the Mukaiyama aldol. Unfortunately, aldehyde **1.35** (Scheme 1.4) does not have a α-chiral

center. A β-stereocenter of the aldehyde usually plays a minor role on product selectivity in the general Mukaiyama aldol. However, in the nucleophilic addition to β-heteroaldehydes, Evans noted that when a bulky substituent (e.g. ^{t}Bu or ^{i}Pr) was present at the α' position on the silyl enol ether, remarkably selective 1,3-*anti*-stereochemistry could be obtained (Scheme 2.11).[35] A correlation was made between the Lewis acid and the preference for 1,3-*anti*-stereochemistry. While $TiCl_4$ gave very little selectivity (3:2, *anti*:*syn*), BF_3•OEt_2 showed a clear improvement (92:08). These observations suggest that a bidentate chelation between the aldehyde **2.50** and silyl enol ether **2.51** was not influential in control of facial selectivity and a bidentate chelation with $TiCl_4$ between the β-heteroatom and the aldehyde differs in the origin of stereoselectivity than the BF_3•OEt_2 aldol. When R was an alkyl substituent, no selectivity was observed.

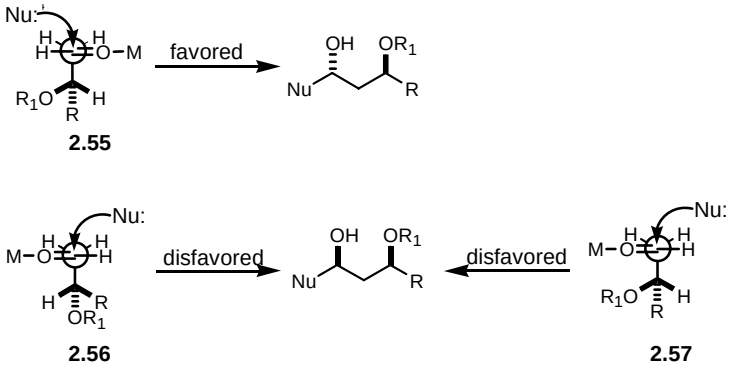
Scheme 2.11 Examples of 1,3-stereoinduction



In the nucleophilic addition to β-heteroaldehydes, Evans postulated that the selectivity arose from a conformation that minimized dipole interactions (Figure 2.5). Conformation **2.55** was proposed as the most important pre-transition state conformer because conflicting dipole moments and R ↔ C=O steric interactions were minimized. Transition states **2.56** and **2.57** are disfavored because of the R ↔ C=O gauche or dipole-dipole interactions. The Evans modified Felkin-Ahn model places the β-heteroatom in a

position relative to the carbonyl that minimizes the dipole-dipole and R ↔ C=O gauche interactions.

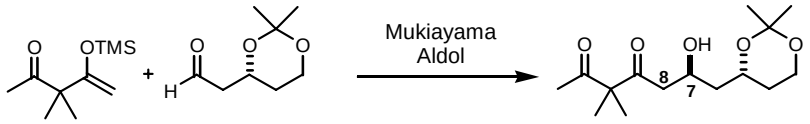
Figure 2.5 Induction of facial selectivity



2.55 **2.56** **2.57**

The Evans model provides insight into the origin of the good selectivity of the Mukaiyama aldol with β-heteroaldehydes, and this strategy can be applied to the reaction of **2.58** and **2.59** to make a key peloruside A substructure (**2.60**) (Scheme 2.12). Based on the Evans model for chirality transfer, we anticipate that the substituent at C_5 can direct the relative stereochemistry of the new C_7-C_8 bond.

Scheme 2.12 Evans chirality transfer application



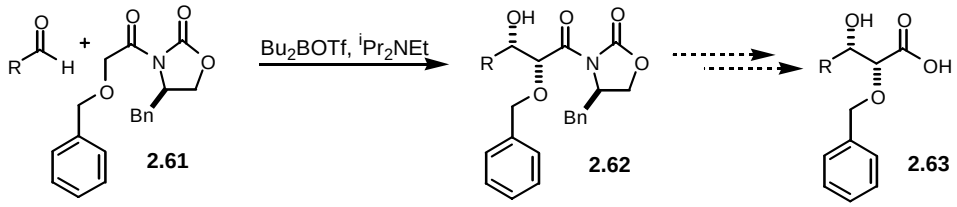
2.58 **2.59** **2.60**

2.1.4 Aldols of α-oxygenated substrates

While a considerable number of methods have been developed for *syn* and *anti* ethyl ketone aldols, much less is known about aldols for α-oxygenated ketones, yet these aldols are required for the synthesis of peloruside A. Boron-mediated aldols of glycolate oxazolidone auxiliaries (**2.61**) have shown high yields and stereoselectivities in *syn*-aldols,[36] which is why we plan on setting C(2) and C(3) by this method (Scheme 2.13).

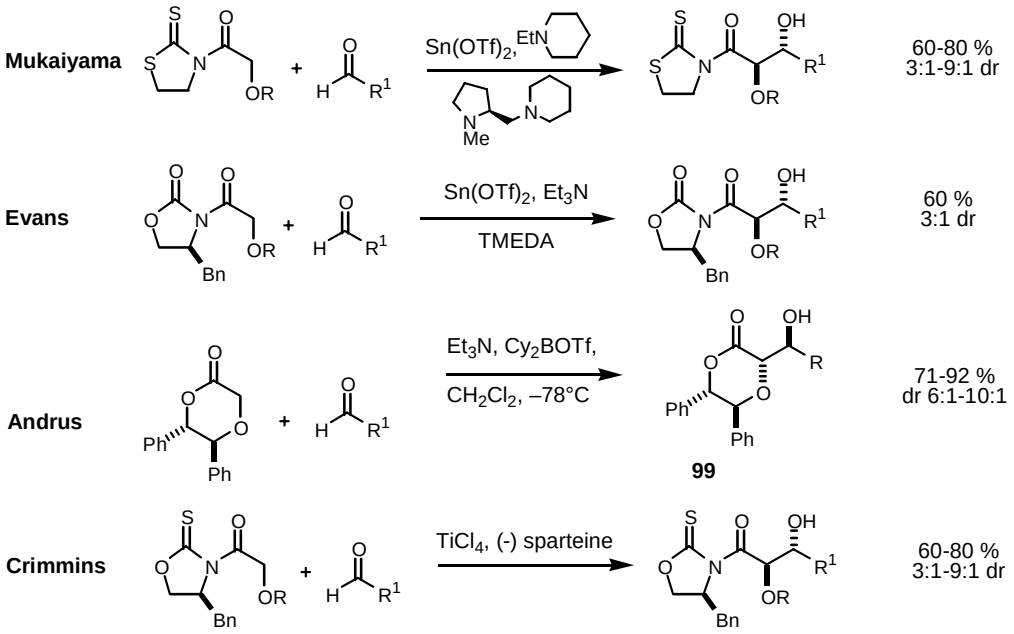
The method provides an excellent medium for inputting two crucial stereocenters, while incorporating the correct carboxylic acid oxidation state at C(1) for the Yamaguchi lactonization.

Scheme 2.13 Syn glycolate aldol



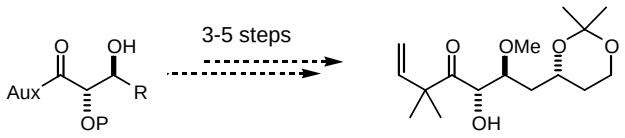
Glycolate aldols have not been well established for *anti* aldol reactions. This fact was emphasized by Andrus, who noted "recent aldol methods provide high *anti*-selectivity in propionate versions, yet their application to the *anti* glycolate reaction has not been established." In this regard, the pioneering work by Mukaiyama et al.[37] revealed that the addition of TMEDA to the tin(II) enolate of a benzyloxy acetate derivative provided the *anti*-aldol product with modest selectivity and good yield (Scheme 2.14). Evans et al.[38] reported similar yields and stereoselectivities employing a tin(II) enolate of chiral glycolate imides. Cyclic derivatives have been used in the Cy_2BOTf-mediated *anti*-aldol,[39] resulting in high yield and selectivity. More recently, Crimmins et al.[40] reported the first general method for anti-selective glycolate aldols mediated by thiazolidinethione auxiliary resulting in the highest selectivity and yields to date.

Scheme 2.14 Published anti-glycolate aldol



The difficulty that the glycolate aldol presents, as well as the propionate aldol, is the conversion to the desired α′,α′-dimethyl ketone (i.e. **2.65**). This process will take a minimum of 3-5 steps (Scheme 2.15). The elaborate scheme to input good stereoselectivity and then go through five more steps to get the desired ketone seemed inefficient, so this method was not implemented for the synthesis of peloruside A.

Scheme 2.15 Anti glycolate aldol inefficiency

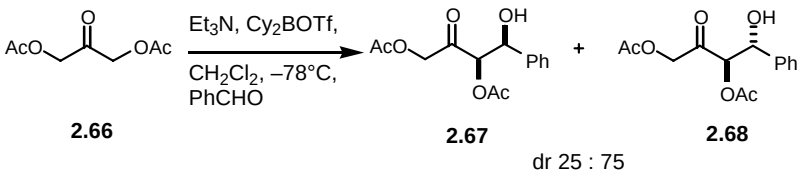


2.64 **2.65**

Efficient boron-mediated *anti*-aldols very rarely involve an enolate component consisting of an α-protected hydroxy ketone. A recent report has shown 90% diastereoselectivity for α-oxygenated ketone *syn*-aldols, but the methodology appears to be very substrate dependant in that only reactions with dihydroxy acetone are reported

(Scheme 2.16).[41] However, *anti* aldols **2.68** were obtained with only moderate 3:1 selectivity. While these results are encouraging, the problem of general *anti*-aldol methodologies with α-oxygenated ketones remains unsolved.

Scheme 2.16 Anti oxygenated ketone aldol



2.66 **2.67** **2.68**

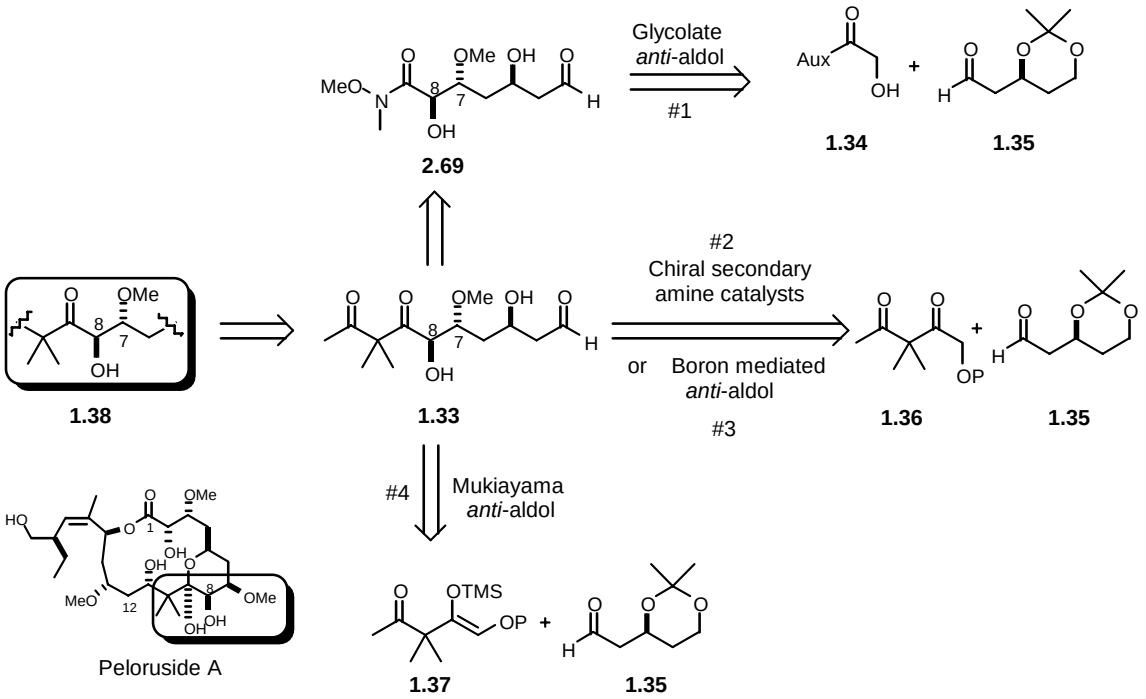
dr 25 : 75

For aldol reactions, ethyl and α-protected hydroxy ketones cannot be compared to one another as the above background on boron-mediated aldols has illustrated. However, the α-protected hydroxy ketone aldols are not well studied and the origin of their unique stereoselective properties is unknown. Ethyl and α-protected hydroxy ketone behave very differently, depending on α-protecting groups, existing chiral centers, auxiliaries, and boron reagents. The Zimmerman-Traxler and open transition state models can be successfully applied for the prediction of α-protected hydroxy and ethyl ketone aldol stereochemistry, but discrepancies of selective enolization, chelation, and reactivity are still unclear. We have attempted to illustrate a lack of progress by the synthetic community towards α-hydroxy ketone aldols, even though they are early synthons for natural product synthesis and could significantly alter retrosynthetic analysis with the pre-existing knowledge that such a key carbon-carbon bond formation has been exerted successfully. To the best of our knowledge, there is no literature precedent for *anti*-aldols between a β-chiral aldehyde and an achiral α-hydroxy ketone that would provide good levels of facial selectivity.

2.2 RESULTS AND DISCUSSION: ALDOL REACTIONS.

Several aldol methodologies towards **1.33** were considered from the outset of the project (Scheme 2.17). As stated above (Scheme 2.14), reports of the glycolate anti-aldol reaction provide moderate selectivity and yield, but an inefficient transformation to the corresponding ketone would be 5-6 additional steps. Chiral secondary amine catalyzed aldols (Scheme 2.17, entry #2), boron mediated *anti*-aldols (entry #3) and Mukaiyama *anti*-aldols (entry #4) are all attractive methods and were considered in designing a concise route towards the synthesis of fragment **1.38**. Namely, the ability to establish the 2,3-*anti* stereochemistry, π-facial selectivity and overall synthetic efficiency were paramount issues in studying this transformation. A more thorough discussion of each aldol will be discussed below.

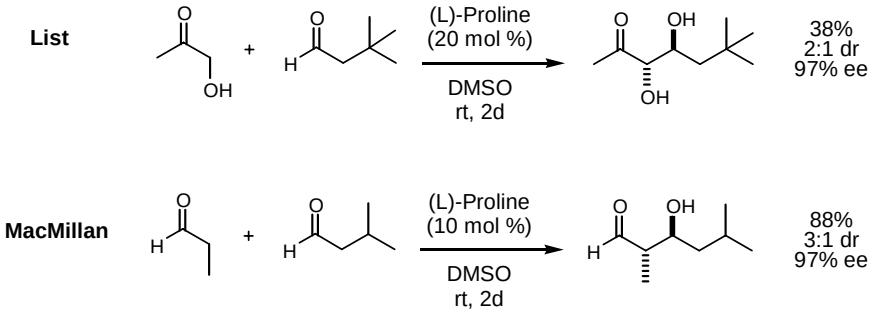
Scheme 2.17 Aldol Methodologies



2.2.1 Chiral Secondary Amine Catalysts

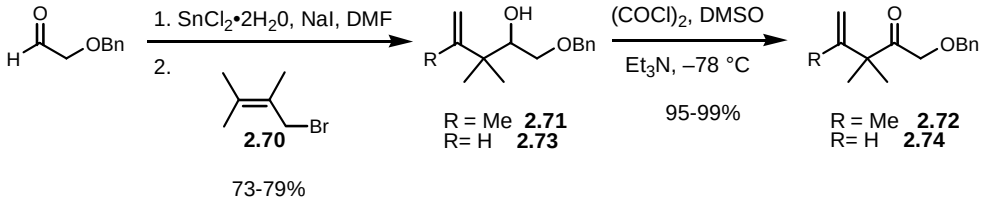
Recently, chiral secondary amines, specifically (L)-proline, have been reported to catalyze aldol reactions providing *anti*-selective aldols (Scheme 2.18). List[42] reported acetol in proline catalyzed direct aldol reactions provided excellent diastereoselectivity and enantioselectivity, albeit in moderate yields. Likewise, the pioneering work by MacMillan[43] implemented (L)-proline in a cross-aldol reaction resulting in high yield and enantioselectivity. The direct aldol reaction utilizing a secondary amine catalyst would be an attractive route towards the synthesis of fragment **1.38**.

Scheme 2.18 Reports of aldols catalyzed with (L)-proline



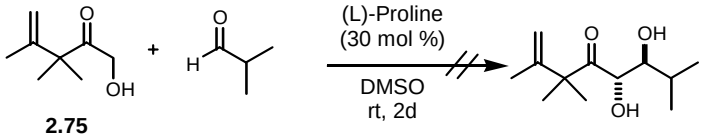
Before conducting the aldol reaction, a suitable α-hydroxy ketone with α',α'-dimethyl groups was synthesized (Scheme 2.19). Alcohol **2.70** was prepared by a S_E2' addition of the allylic stannane, generated in situ from Barbier-type reaction of allylic bromide **2.70**[44] with $SnCl_2 \bullet 2H_2O$, and benzyloxy acetaldehyde (73% yield).[45] Similarly, alcohol **2.72** also was synthesized from 3-chloro-bromobut-2-ene and benzyloxy acetaldehyde in 79% yield. The secondary alcohols were successfully oxidized under Swern conditions affording ketones **2.72** and **2.74** (95-99% yield).

Scheme 2.19 The synthesis of ketones **2.72** and **2.74**



Unfortunately, the direct aldol catalyzed by proline with ketone **2.75** resulted in no product and only recovery of starting material (Scheme 2.20). Mechanistically, the aldol proceeds through an enamine intermediate before the new carbon-carbon bond is formed. Thus, due to the steric hindrance of the ketone **2.75**, specifically the geminal methyl groups, the enamine never was created. Although chiral secondary amines are an attractive branch of aldol chemistry, an *anti*-aldol derived from a ketone with the steric hindrance of geminal methyl groups is not feasible.

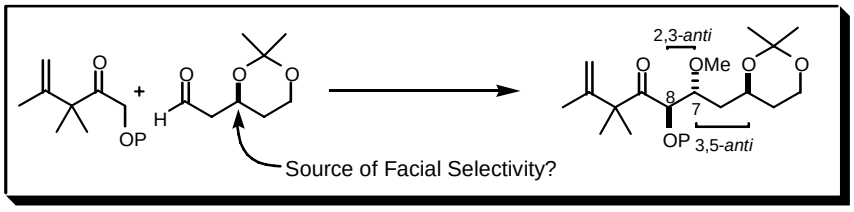
Scheme 2.20 (L)-proline catalyzed aldol results



2.2.2 Boron-mediated Aldol Reaction

The second aldol approach that can be used to synthesize the 2,3-*anti*-3,5-*anti* fragment **1.38** is a boron mediated aldol (Scheme 2.17 , entry #3). It is widely accepted that the use of dicyclohexyl boron chloride will provide the 2,3-*anti*-stereochemistry, but how would the π-facial selectivity be obtained (Scheme 2.21)? Based on the previously mentioned Evans model for chirality transfer,[35] we anticipated that the substituent at C_5 can direct the relative stereochemistry of the new C_7-C_8 bond.

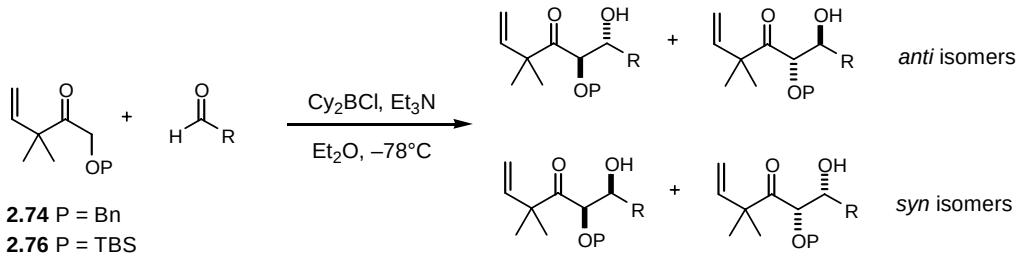
Scheme 2.21 Scientific question

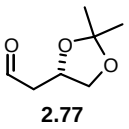
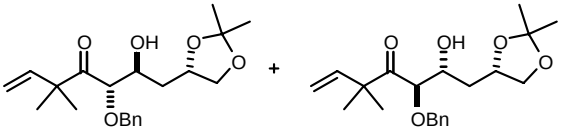
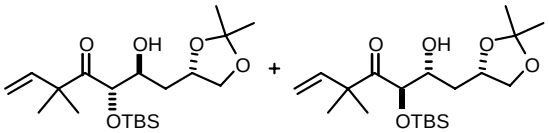
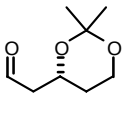
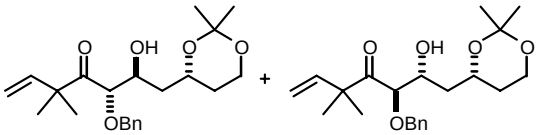


The preliminary boron-mediated aldol with *α*-hydroxy ketone protected with a benzyl group **2.74** and previously synthesized aldehydes **2.77** and **2.59** provided aldol products **2.78**/**2.79** (95%, 1:5 dr, Table 2.1, entry 1) and **2.82**/**2.83** (93%, 1:4.5 dr, entry 3). Not surprisingly, the *anti*-diastereomers were the only evident products, as was determined by comparison of the *α*-hydrogen coupling constant (J = 4.7-5.5 Hz) and literature precedence with *tert*-butyl ethyl ketones,[46,33a] but the 3,5-relative stereochemistry was yet to be determined. Interestingly, lower π-facial selectivity was observed with *α*-silyloxy ketone **2.76** (Table 2.1, entry 2). Additionally, other protecting groups, such as a more bulky trityl group, *tert*-butyl diphenyl silyl (TBDPS), and

acetates, failed to successfully form the boron enolate, probably due to the increase in steric bulk, so those ketones were discarded.

Table 2.1 Summary of anti-aldols with cyclic *β*-substituted aldehydes

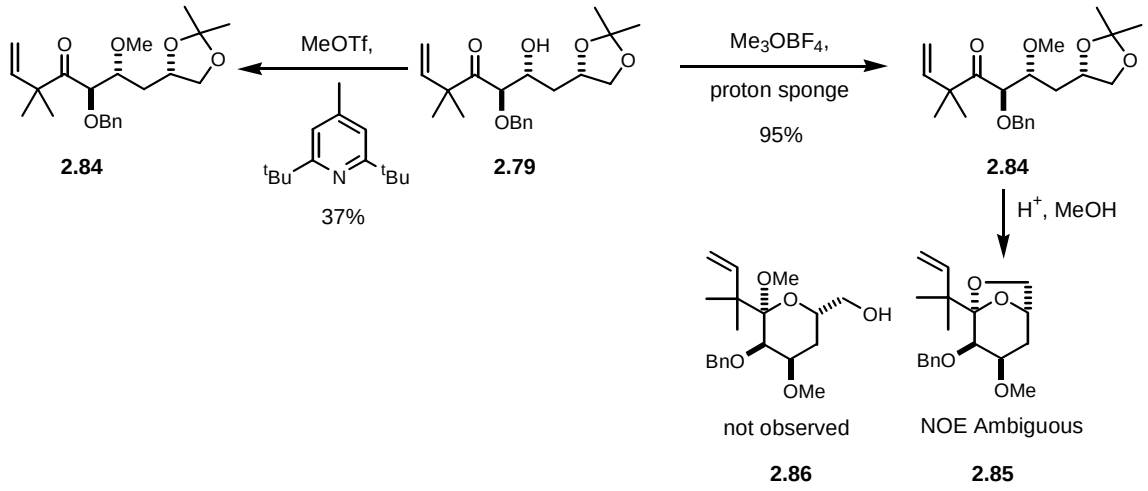


Entry	Aldehyde	Products	Yield (%)	Ratio
1	 **2.77**	 **2.78** **2.79**	95	1:5
2	**2.77**	 **2.80** **2.81**	72	1:2
3	 **2.59**	 **2.82** **2.83**	93	1:4.5

After the promising aldol results, the 3,5-relative stereochemistry needed to be determined. The most suitable procedure would be to follow the peloruside A synthetic route through to the methyl ketal and use ^{1}H NMR experiments to assign the relative stereochemistry. Aldol products are prone to retro-aldol and epimerization at the *α*-stereocenter can occur, so mild conditions for methylating *β*-hydroxy ketones were necessary. Evans[47] reported that the methylation of lonomycin A intermediates with

Meerwein's salt and proton sponge gave superior yields in some cases to that of methyl triflate (MeOTf) and 2,6-di-*tert*-butyl-4-methyl-pyridine. Our initial efforts to methylate the aldol product (MeOTf, 2,6-di-tert-butyl-4-methyl-pyridine) provided the *β*-methoxy ketone **2.84** (37% yield, Scheme 2.22). However, when the methylation was carried out using Meerwein salt, the desired product **2.84** was obtained in more than 95% yield. Unfortunately, under various acidic conditions, the undesired bicyclic ketal **2.85** was obtained in 95% yield. Bicyclic ketal **2.85** could still provide the relative stereochemistry created from the boron-mediated aldol, but the NOE data was inconclusive at the time.[48] Although attempts to determine the 3,5-relative stereochemistry were unsuccessful, the boron-mediated aldol reaction did provide good π-facial selectivity and by utilizing a different aldehyde that had differentially protected alcohols, the methyl ketal formation could be achieved.

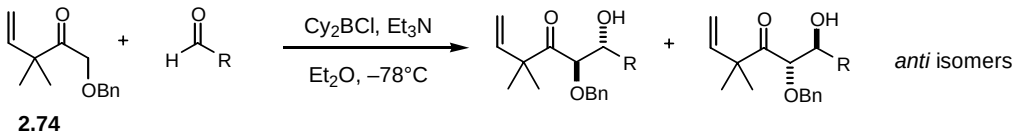
Scheme 2.22 Methylation of aldol products



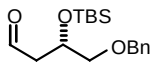
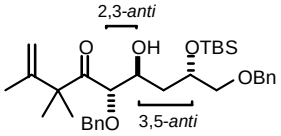
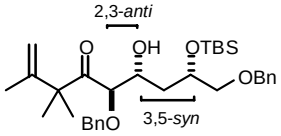
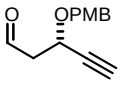
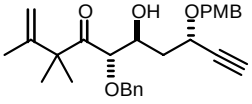
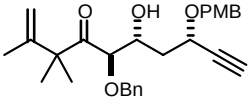
An aldol product originating from aldehyde **2.87** or **2.90** with differentially protected or "masked" diols would allow selective deprotection, thus overcoming the bicyclic ketal formation (Table 2.2). However, under the boron-mediated aldol conditions, these aldehydes only provided an inseparable mixture of *anti*-diastereomers.

Additionally, the aldol of the acyclic aldehydes afforded no π-facial selectivity. Disappointed by these results, the structural components of the aldehyde needed to be analyzed.

Table 2.2 Summary of anti-aldols with acyclic *β*-substituted aldehydes



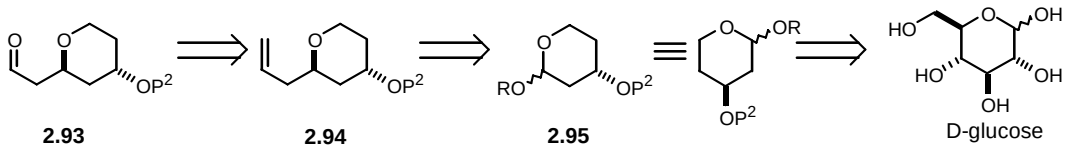
2.74

Entry	Aldehyde	Products	Yield (%)	Ratio
1	 **2.87**	 **2.88**  **2.89**	73	1:1
2	 **2.90**	 **2.91**  **2.92**	87	1:1

The requirements of the aldehyde gained from the previous boron-mediated aldols (Table 2.1 and Table 2.2) highlights the acetonide aldehydes **2.59** and **2.77** provided good π-facial selectivity, but formed the unwanted bicyclic ketal. Conversely, the differentially protected acyclic aldehydes **2.87** and **2.90** gave no π-facial selectivity. Therefore, an aldehyde with differentially protected diols that consisted of a *β*-substituted heterocycle was needed, similar to compound **2.93** and its initial retrosynthetic analysis is depicted in Scheme 2.23. Aldehyde **2.93** was anticipated to be prepared from olefin **2.94** by an oxidative cleavage. Olefin **2.94** could be formed from a kinetically-controlled axial allylation on the acetal **2.95**. The functionalized acetal could be derived from D-glucose,

a substrate that had never been used in studies towards the synthesis of peloruside A at the time.

Scheme 2.23 Retrosynthetic analysis of aldehyde **2.93**



2.93 **2.94** **2.95**

Prior to the preparation of the appropriate aldehyde for the use in the synthesis of peloruside A, two model aldehydes were synthesized to support the hypothesis that a *β*-heterocylic aldehyde was a critical component in the boron-mediated aldol. The direct acid-catalyzed addition of MeOH to D-glucal with Ph_3P•HBr provided acetal **2.96** (91% yield, Scheme 2.24).[49] Olefin **2.97** was prepared from a kinetically-controlled axial attack with allyl trimethylsilane on the intermediate oxonium ion providing a single trans-substituted tetrahydropyran (70% yield).[50] The trans-relationship was unambiguously confirmed by NOE difference experiments. Oxidative cleavage of olefin **2.97** by ozonolysis provided aldehyde **2.98** (75 % yield).

Gratifyingly, the boron-mediated aldols with aldehydes **2.99** and **2.98** gave good π-facial selectivity (18:1-4:1), though the yield was only moderate (38-53% yield,

Table **2.3**). These unoptimized results did confirm the importance of a *β*-substituted heterocycle in the aldol reaction. The preparation of a suitable aldehyde for the synthesis of peloruside A was needed.

Scheme 2.24 Preparation of aldehyde **2.98** from D-Glucal

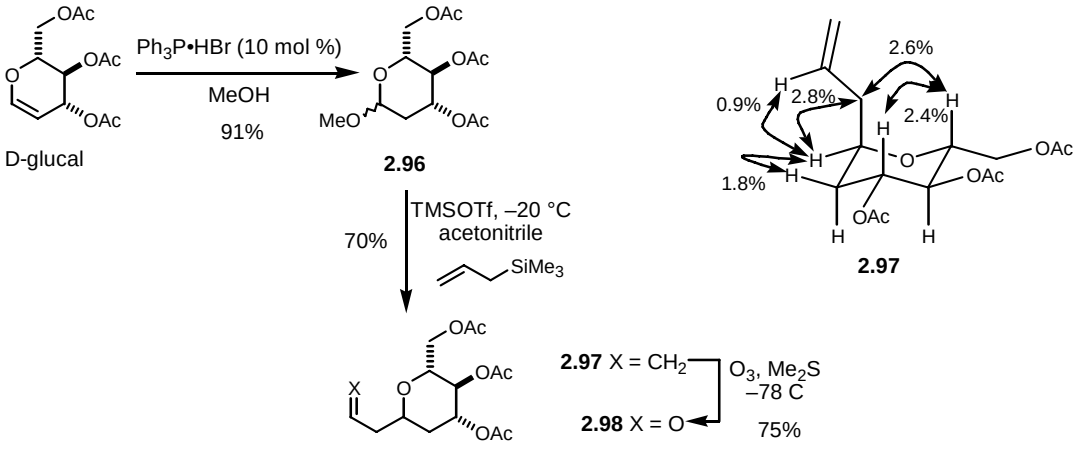
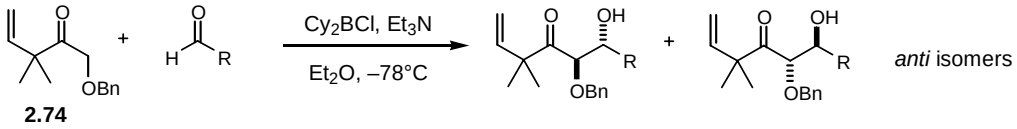
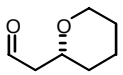
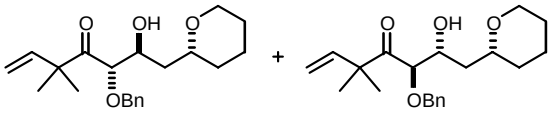
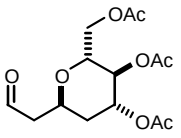
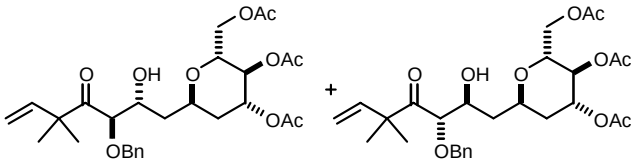


Table 2.3 Boron mediated aldols with *β*-heterocyclic aldehydes

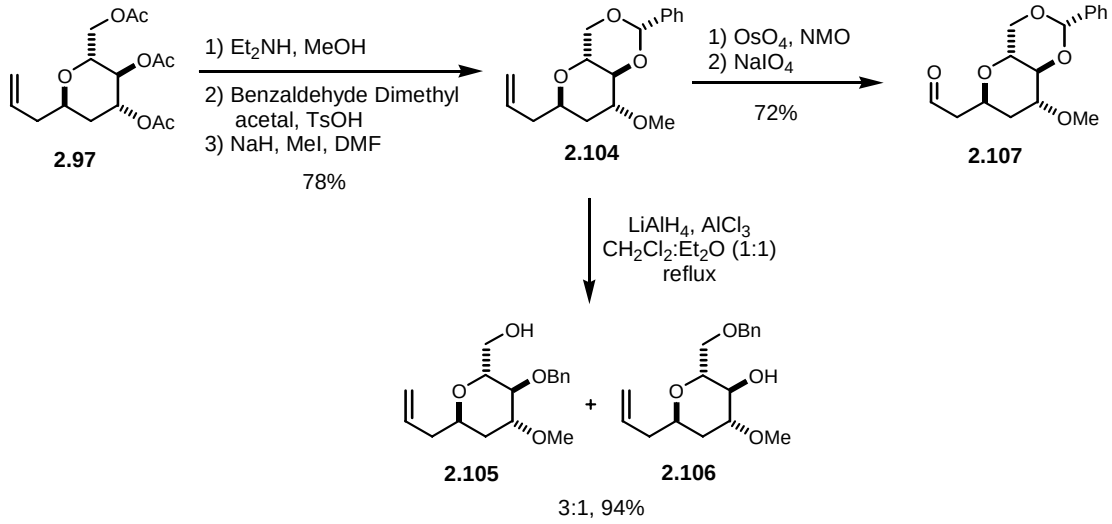


Entry	Aldehyde	Products	Yield (%)	Ratio
1	 **2.99**	 **2.100** **2.101**	38	1:18
2	 **2.98**	 **2.102** **2.103**	53	1:4

In the preparation of the aldehyde for the synthesis of peloruside A, the systematic methylation of C(5) and the ability to expose the carboxylic acid at C(1) later in the

synthesis had to be considered. Olefin **2.97** was globally deprotected with diethyl amine (Et_2NH) and the 4,6-benzylideneactal was selectively formed (Scheme 2.25). The free hydroxyl group was then methylated providing **2.104** (78% yield over three steps). A regioselective reduction of the acetal **2.104** with $LiAlH_4$ and $AlCl_3$ gave the primary alcohol **2.105** as the major product (3:1 ratio, 94%). However, the regioisomers were difficult to separate, thus it would be an impractical route on larger scale. After a two-step oxidative cleavage of olefin **2.104** with osmium tetraoxide followed by $NaIO_4$, aldehyde **2.107** was obtained (72% yield).

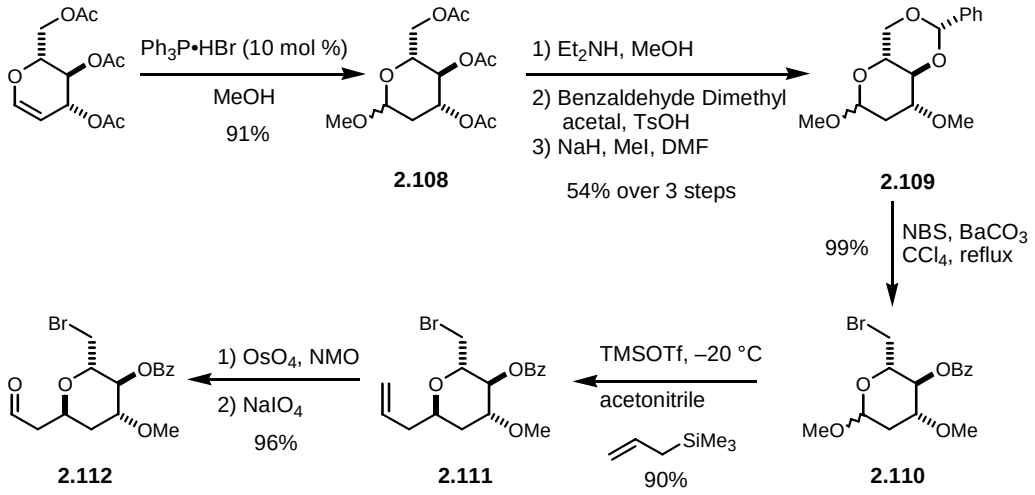
Scheme 2.25 Synthesis of aldehyde **2.107**



An alternative synthetic approach towards the synthesis of a suitable functionalized aldehyde **2.112** was based on a work by Danishefsky et al.[51] Acetal formation with triphenylphosphine hydrobromide provided pyranoside **2.108** (91% yield, Scheme **2.26**). After a global deprotection (Et_2NH, MeOH) and selective 4,6-benzylideneacetal formation, the resulting free alcohol was methylated under Williamson-ether conditions in good yield (54% over three steps). The selective cleavage of the primary benzylidene ether under Hanessian-Hullar[52] radical bromination

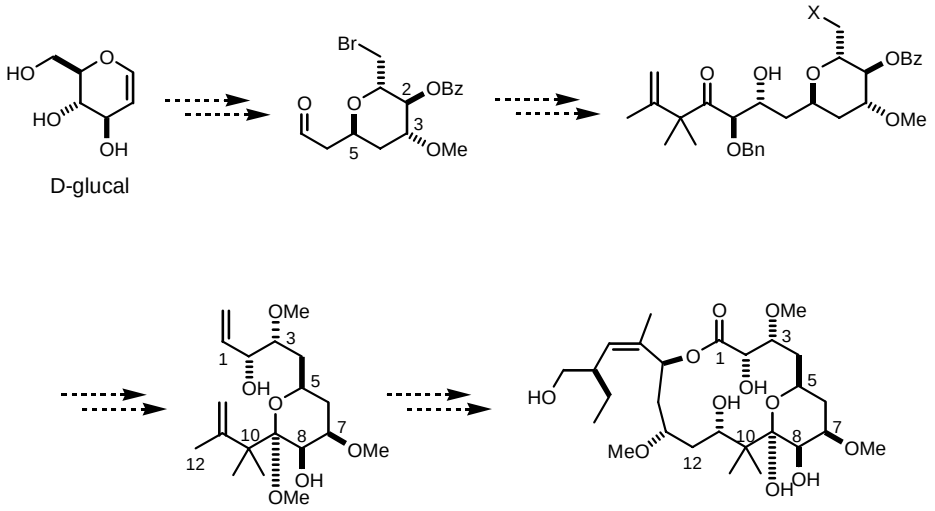
conditions gave the known pyranoside **2.110** (99% yield).[51] Allylation of **2.110** (Me_3SiOTf and allyl trimethylsilane, 95% yield) afforded exclusively diastereomer **2.111**. It was convenient to stockpile the material at this stage and prepare the aldehyde as needed. Stepwise dihydroxylation and glycal cleavage consistently delivered aldehyde **2.112** in excellent yield (96% yield). The entire optimized route was repeated with 50 g of triacetyl D-glucal and provided approximately ~31 g of aldehyde **2.112** (46% yield overall yield).

Scheme 2.26 Preparation of aldehyde **2.112**



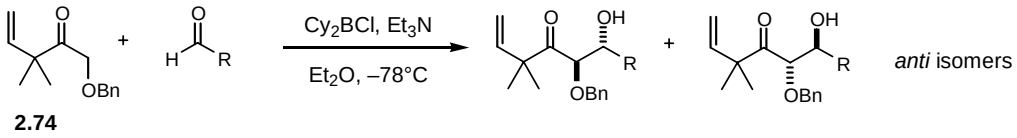
The aldehyde **2.112** derived from D-glucal contains atoms C(1)-C(7) of peloruside A with the correct stereochemistry at C(2), C(3) and C(5) (Scheme 2.27). The C(3) methyl alcohol was systematically installed in the synthesis and the primary bromide can be manipulated to achieve the C(1) carboxylic acid. Assuming the aldol can provide the correct stereoisomer, the aldol product can be again systematically methylated at C(7). After ring-opening of the pyran, the methyl ketal can be synthesized under acidic conditions, thus after three steps from the aldol product, a considerable portion of peloruside A, C(1)-C(12) segment, will have been completed. The significance of the D-glucal derived aldehyde **2.112** cannot be understated.

Scheme 2.27 Significance of aldehyde **2.112** derived from D-glucal



The boron-mediated aldol of aldehyde **2.112** provided 2,3-*anti*-stereoisomers (Table 2.4, entry 1, 54% yield, 1:4 dr) and (entry 2, 69% yield, 1:5 dr) that were confirmed by ^{1}H NMR coupling constants and literature precedence with *tert*-butyl ethyl ketones.[53] Interestingly, the bicyclic aldehyde **2.107** produced a similar yield, but failed to generate any π-facial selectivity. Gratifyingly, a crystal of 2,3-*anti*-3,5-*anti*-aldol product **2.117** was suitable for X-ray analysis (Figure 2.6) and provided further support of the 2,3-*anti*-stereochemistry.

Table 2.4 Boron mediated aldol with aldehyde **2.112** and **2.107**



2.74

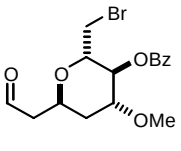
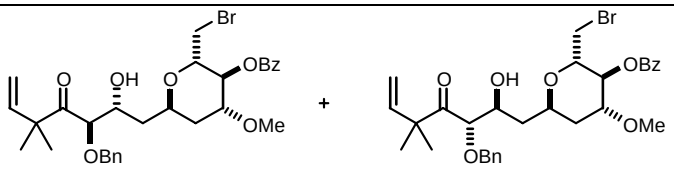
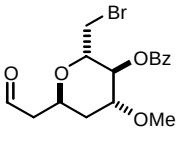
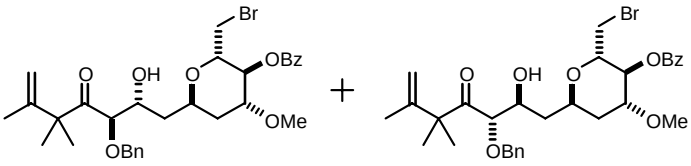
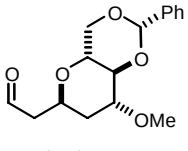
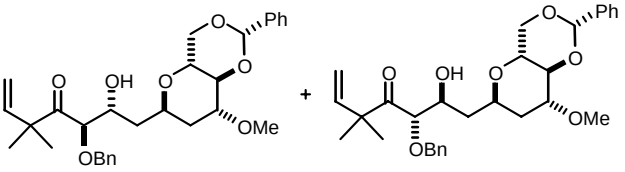
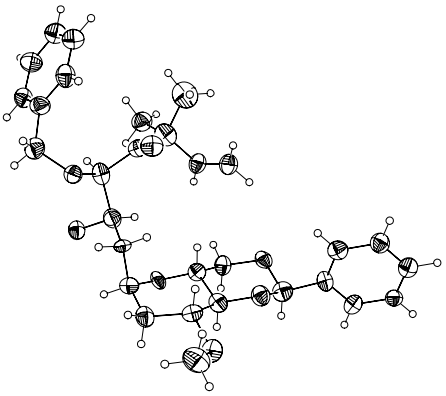
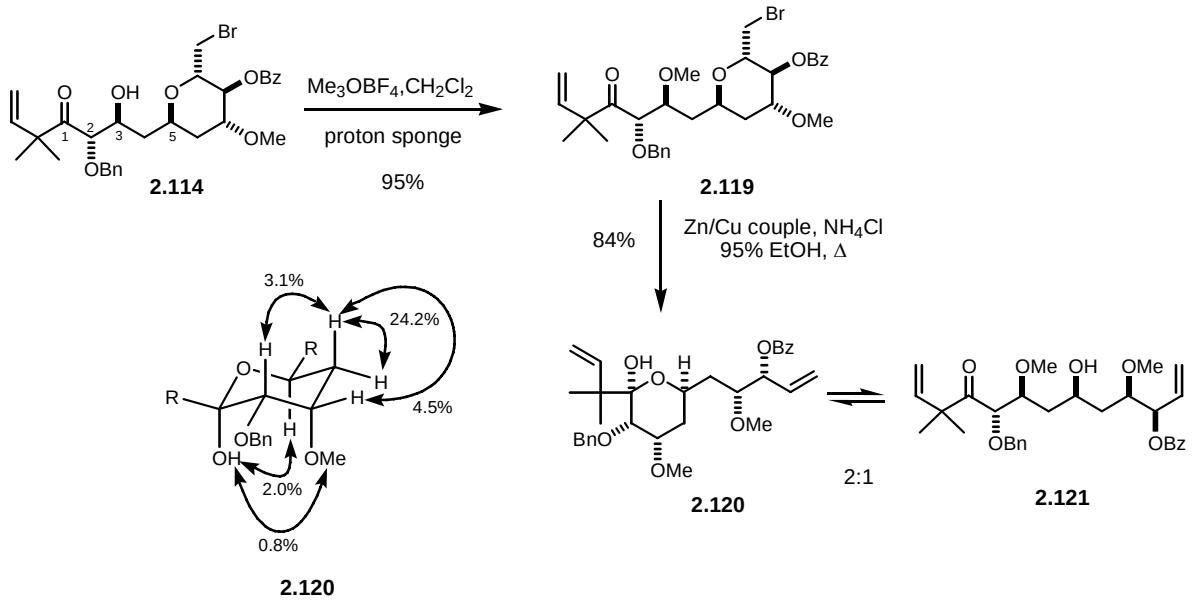
Entry	Aldehyde	Products	Yield (%)	Ratio
1	 **2.112**	 **2.113** + **2.114**	54	1:4
2	 **2.112**	 **2.115** + **2.116**	69	1:5
3	 **2.107**	 **2.117** + **2.118**	49	1:1

Figure 2.6 ORTEP diagram of aldol **2.117**



The major aldol product **2.114** was subjected to Meerwein Salt and proton sponge providing *β*-methoxyketone **2.119** (95% yield, Scheme 2.28). Next, in order to ascertain the relative stereochemistry of the C(3) and C(5), a Vasella reduction[54] of bromide **2.119** (Zn/Cu couple, EtOH, reflux) was expected to provide a cyclic hemiketal **2.120** in which the relative stereochemistry may be obtained using NOESY experiments. It was anticipated that the Vasella reduction would concurrently install a terminal olefin, which after further manipulation can be unmasked as the C(1) carboxylic acid of peloruside A. Therefore, the methylated aldol product **2.119** under Vasella conditions (Zn/Cu couple, 95% EtOH, reflux) gave two compounds (**2.120** and **2.121**). It was found that hemiketal **21** and acyclic hydroxyketone **2.121** were slowly interconverting in a 2:1 ratio. Interestingly, hemiketal **2.120** could be isolated and if dissolved in D6-DMSO, isomerization was slow enough to allow a structural elucidation using a NOESY experiment which confirmed the major aldol product was the 2,3-*anti*-3,5-*syn*-stereoisomer.

Scheme 2.28 Formation of hemiacetal **2.120** and structural elucidation



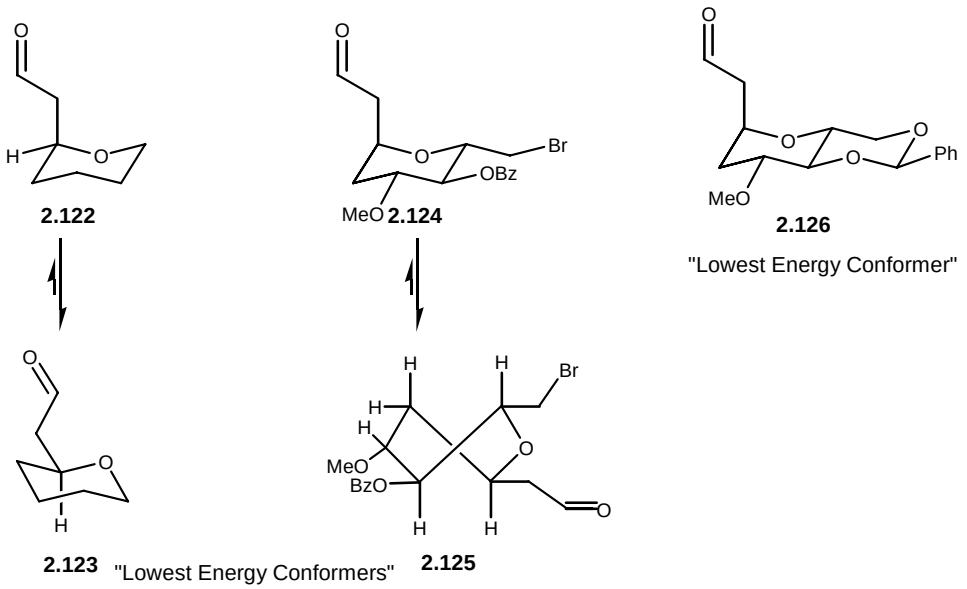
While the boron-mediated aldol method has provided rather disappointing results, some conclusions and observations can be made about its application with *β*-heterocyclic aldehydes. With acyclic or bicyclic aldehydes such as (**2.87** and **2.90**, Table 2.2 and **2.107**, Table 2.4), no π-facial selectivity was observed, while a monsubstituted tetrahydropyran (**2.99**,

Table **2.3**) gave excellent facial selectivity (18:1 dr). Aldehydes derived from D-glucal (**2.98** and **2.112**,

Table **2.3** and Table 2.4) and the acetonide aldehydes (**2.59** and **2.77**, Table 2.1) gave good π-facial selectivity (4:1-5:1 dr). A trend for estimating the level of π-facial selectivity can be drawn from the lowest energy conformation of these aldehydes (Figure 2.7). When the methyl carbaldehyde group is in an equatorial position of a chair conformation, as in aldehyde **2.123**, the best diastereoselectivity was obtained. However, in the rigid bicyclic aldehyde **2.126**, when the methyl carbaldehyde group is in an axial conformation, no selectivity was observed. Aldehydes, derived from D-glucal consist in

the transition state as a twist boat because of preferred pseudo-equatorial conformations, provided moderate levels of selectivity. An estimation of the diastereoselectivity can be achieved for a β-heterocyclic aldehyde used in a boron-mediated aldol.

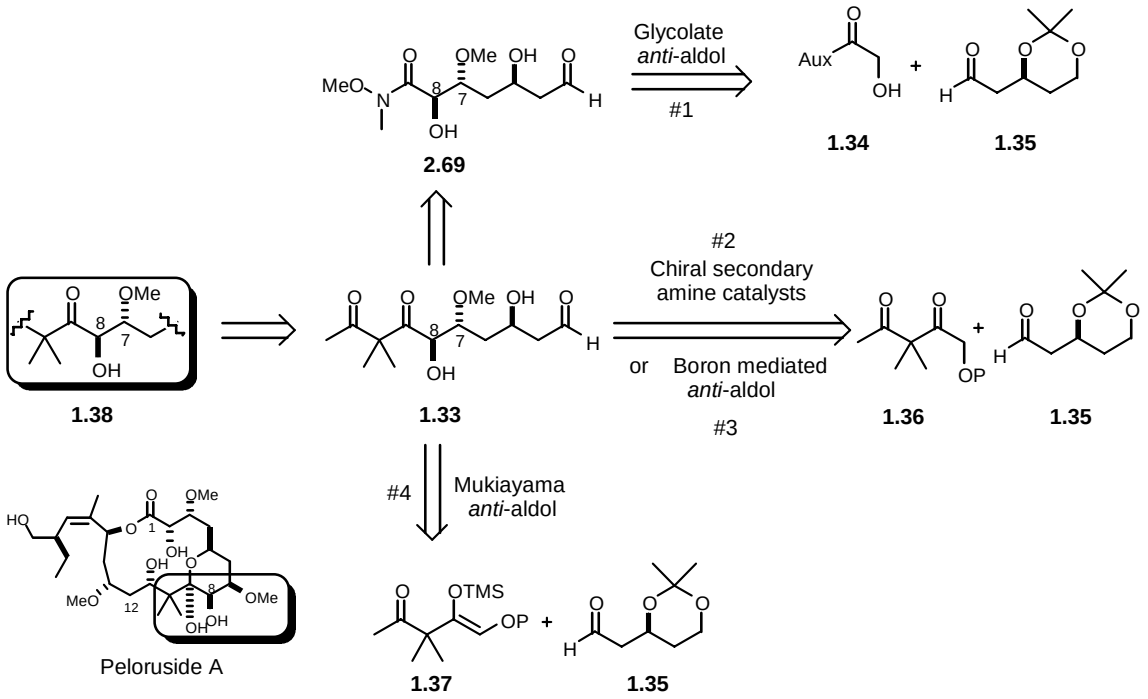
Figure 2.7 Trends of β-heterocyclic aldehydes in boron-mediated aldols



2.2.3 Mukaiyama Aldol Results

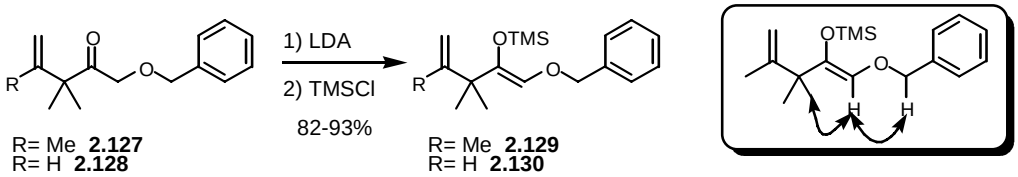
The final route, the Mukaiyama *anti*-aldol reaction, could possibly be used to construct the 2,3-*anti*-3,5-*anti* fragment **1.38** (Scheme 2.17, route #4). Selectively synthesizing the *Z*-trimethylsilyl enol ether and applying the previously mentioned Evans model for chirality transfer, we anticipated that the substituent at C(5) can direct the relative stereochemistry of the new C(7)-C(8) bond (Scheme 2.21). Although this assumption proved incorrect for the boron-mediated aldol, Evans model was based on the Mukaiyama aldol.

Scheme 2.17 Aldol Methodologies



The *Z*-trimethylsilyl enol ethers **2.127** and **2.128** were prepared at –78°C with LDA and TMSCl (82-93% yield, Scheme 2.29). The geometrical configuration was confirmed using a NOE experiment.

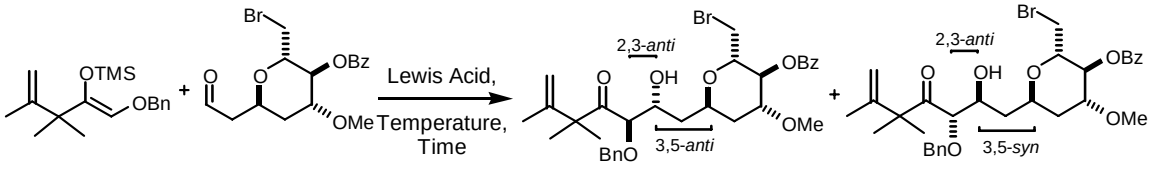
Scheme 2.29 Z-trimethylsilyl enol ether synthesis



In screening reaction conditions for the Mukaiyama aldol reaction, silyl enol ether **2.129** and aldehyde **2.112** were chosen because of their relevance towards the synthesis of peloruside A. Initially, standard Mukaiyama conditions (BF_3•OEt_2 at –78°C) resulted in no reaction conversion. However, the 2,3-*anti*-aldol products were formed at –20°C

and surprisingly the π-facial selectivity seemed to be opposite of the boron-mediated aldol resulting in the 2,3-*anti*-3,5-*anti*-stereoisomer **2.115** as the major product (74% yield, 3:1 dr). The optimal conditions were to add the reagents at –20°C and then slowly warm the reaction temperature to 0°C (Table 2.5). While this resulted in the same diastereoselectivity, the overall yield significantly improved.

Table 2.5 Mukaiyama aldol condition optimization



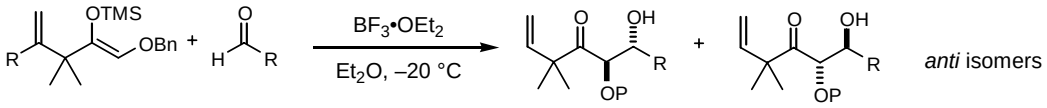
2.129 **2.112** **2.115** **2.116**

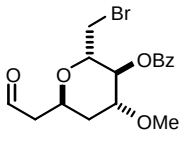
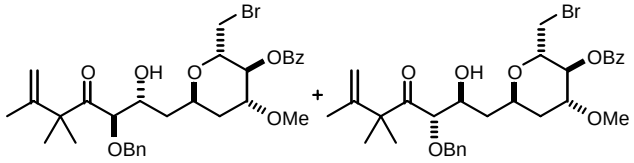
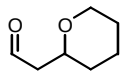
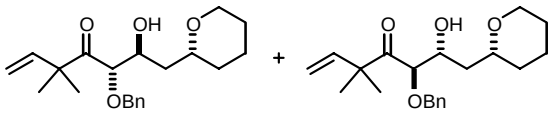
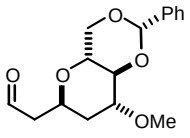
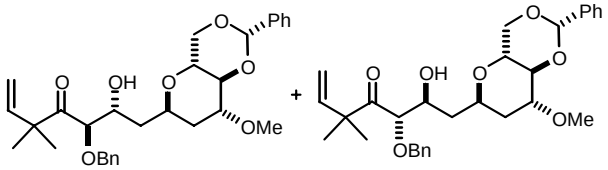
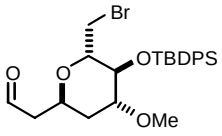
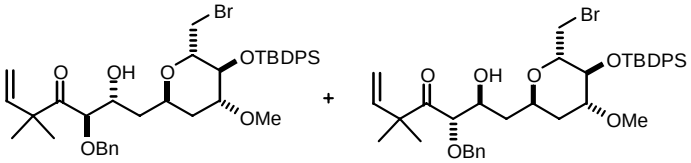
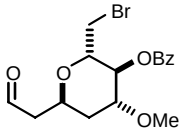
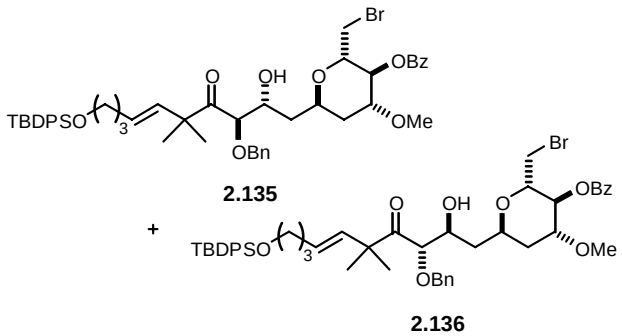
Lewis Acid	Temp (°C)	Time (h)	dr	Yield (%)
BF_3•OEt_2	–78	24	n/a	No reaction
BF_3•OEt_2	–20	8	3:1	74%
BF_3•OEt_2	–20 to 0	2	3.5:1	85%

Other Lewis acids, such as Et_2AlCl, BF_3•Me_2S, $TiCl_4$, $SnCl_4$, and $MgBr_2$•OEt_2, gave inferior yields and/ or facial selectivity, so it was clear that BF_3•OEt_2 was the optimal Lewis acid. The silyl enol ether **2.129** bearing geminal methyl groups gave products with the correct 2,3-*anti*-3,5-*anti*-stereochemistry under Mukaiyama aldol conditions.

This aldol method was also applied with various aldehydes (Table 2.6). Aldehydes **2.99** and **2.112** resulted in moderate selectivity (3.5:2 and 3.5:1, respectively).

Table 2.6 Results of Mukaiyama aldol reactions



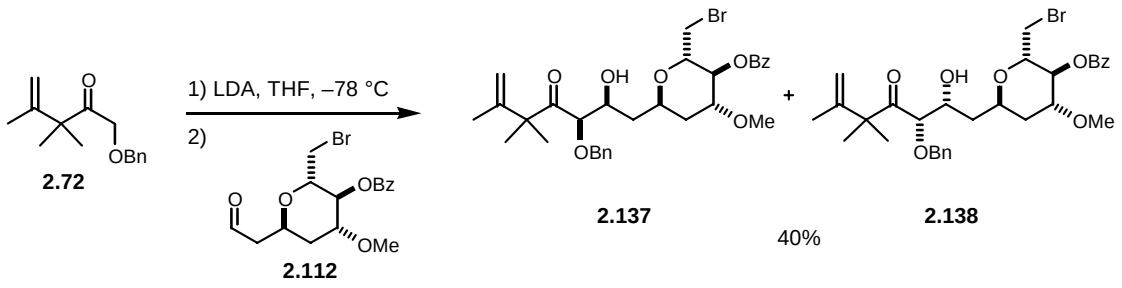
Entry	Aldehyde	Products	Yield (%)	Ratio
1	 **2.112**	 **2.115** + **2.116**	85	3.5:1
2	 **2.99**	 **2.100** + **2.101**	55	3.5:2
3	 **2.107**	 **2.117** + **2.118**	53	1:1
4	 **2.131**	 **2.132** + **2.133**	77	3:1
5	 **2.112**	 **2.135** + **2.136**	55	4:1

The rigid bicyclic aldehyde **2.107** maintains the methyl carbaldehyde in the axial position and loses all selectivity. In order to understand if any of the pyran's appendages affected the selectivity, whether by steric or electronic interactions in the transition state, the benzoate was replaced by a larger TBDPS group (Table 2.6, entry 4).

The Mukaiyama aldol reaction with aldehyde **2.131** provided similar results to aldehyde **2.112** (77% yield, 3:1 dr). Also, a more functionalized silyl enol ether from ketone **2.134** (entry 5) was subjected to the Mukaiyama conditions and provided good selectivity (4:1 dr), albeit in moderate yield (55% yield).

The relative stereochemistry of 2,3-*anti*-3,5-*anti*-stereoisomer **2.115** was confirmed by two separate experiments. First, all four possible stereoisomers were synthesized, and their coupling constants were compared (Scheme 2.30). It was found that the coupling constants of the α-hydrogens of 2,3-*syn*-stereoisomers **2.137** and **2.138** (3.3 ± 0.16 Hz and 3.4 ± 0.17 Hz, respectively) and 2,3-*anti*-stereoisomers **2.115** and **2.116** (4.2 ± 0.13 Hz and 3.9 ± 0.13 Hz, respectively) unambiguously confirmed that the 2,3-*anti*-stereoisomers were the products of the boron-mediated and Mukaiyama aldol reaction, but the relative 3,5-stereochemistry remained unsolved which lead us to the second experiment.

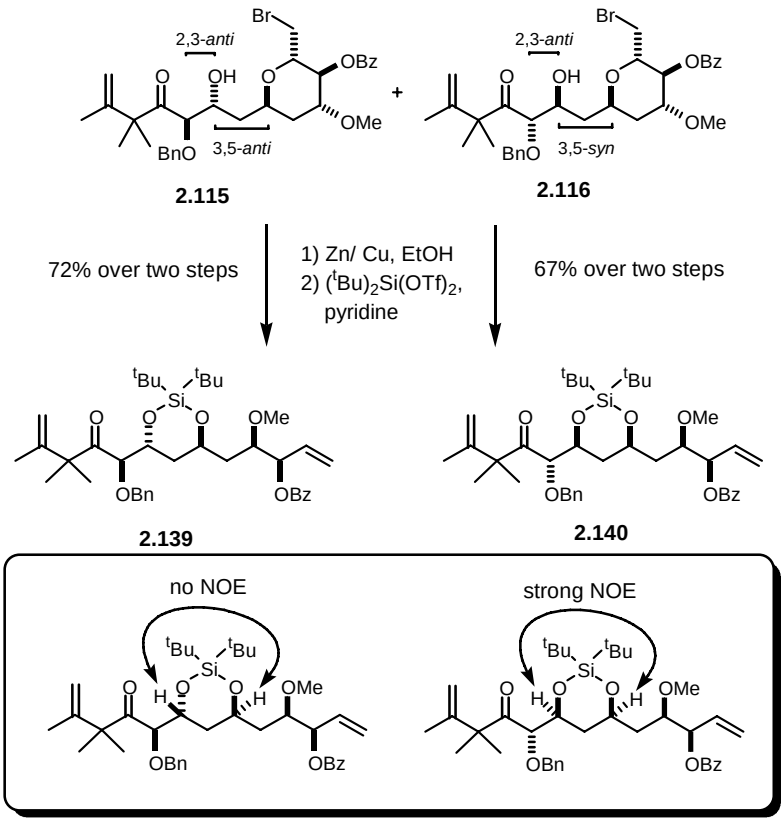
Scheme 2.30 Synthesis of the 2,3-syn-stereoisomers



The 3,5-relative stereochemistry was confirmed from the NOE experiments of the silylidene acetal **2.139** and **2.140** (Scheme 2.31).[55] After ring opening of the pyran under

Vasella reaction conditions, the di-*tert*-butyl silylidene acetal **2.139** (72% over two steps) and **2.140** (67% over two steps) was formed. The NOE data unmistakably confirmed the 3,5-relative stereochemistry.

Scheme 2.31 The 3,5-relative stereochemistry elucidation



2.3 CONCLUSION

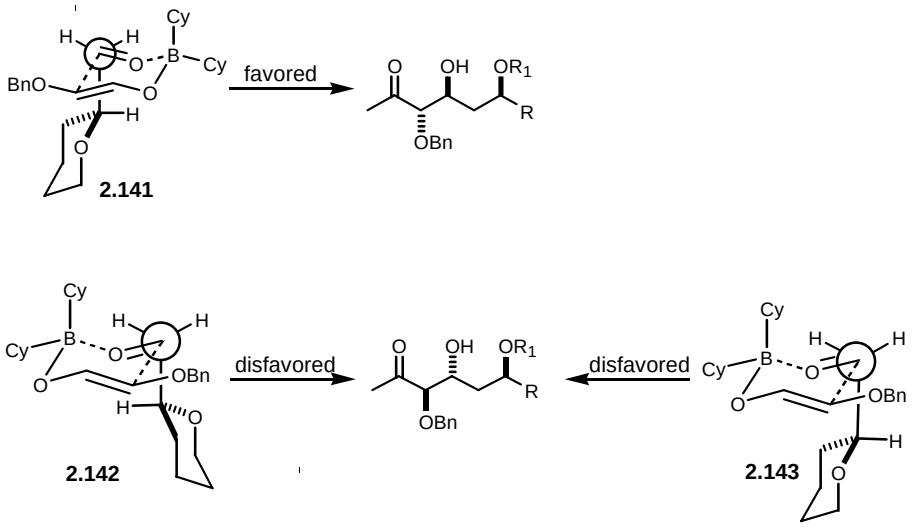
The formation of the C_7-C_8 bond of peloruside A was accomplished with a Mukaiyama aldol reaction between a silyl enol ether **2.129** and a *β*-heterocyclic aldehyde **2.112**. The major diastereomer gave the 2,3-*anti*-3,5-*anti*-stereoisomer (85% yield, 3.5:1 dr) and the absolute stereochemistry for all stereoisomers was established by ^{1}H NMR experiments and comparison of the coupling constants. While the boron-mediated aldol reaction failed to provide the correct 2,3-*anti*-3,5-*anti*-stereoisomer necessary for the

synthesis of peloruside A, remarkably, the 2,3-*anti*-3,5-*syn*-stereoisomer was obtained (69% yield, 1:5 dr).

Evans chirality transfer model explains the relative stereochemistry from the Mukaiyama aldol reaction. The chirality transfer of a *β*-substituted aldehyde can also be used to rationalize the stereochemistry for boron-mediated aldols. Aldehyde **2.99** with a *β*-monopyran provided good selectivity (1:18 dr,

Table **2.3**) and in the lowest energy conformer, the methyl carbaldehyde is in the equatorial position. We proposed the moderate selectivity for *β*-heterocyclic aldehydes is derived by the minimization of dipole and gauche interactions (Figure 2.8). Conformation **2.141** is postulated as the most important pre-transition state conformer because conflicting dipole moments and pyran ↔ C=O steric interactions were minimized. Zimmerman-Traxler transition state models **2.142** and **2.143** are disfavored because of the pyran ↔ C=O gauche or dipole-dipole interactions.

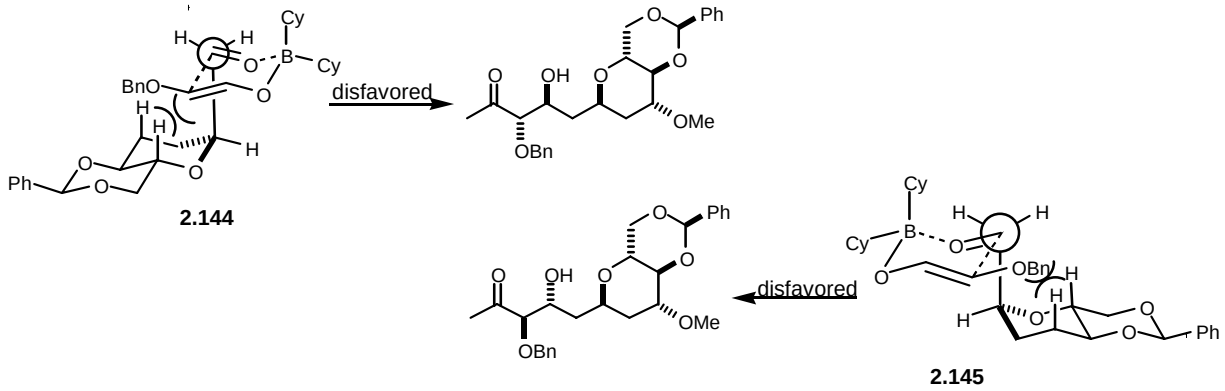
Figure 2.8 Chiral transfer model for boron-mediated aldol I



Bicyclic aldehyde **2.107** did not provide any π-facial selectivity (1:1 dr, Table 2.4). We suggested that an axial methyl carbaldehyde group in the lowest energy

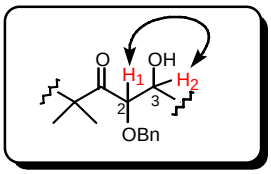
conformation, minimizing gauche and dipole-dipole interactions, positions the rigid bicyclic group perpendicular to the six-membered transition state (Figure 2.9). The unfavorable steric interaction in **2.144** and **2.145** between the boron enol ether and the bicyclic pyranoside does not differentiate between the two lowest energy conformers, thus providing no diastereoselectivity. However, a novel Mukaiyama aldol reaction has been achieved allowing the continuation of the peloruside A synthesis.

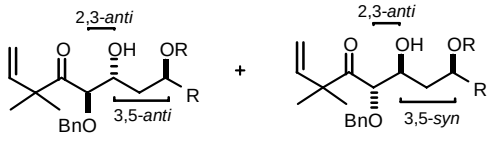
Figure 2.9 Chiral transfer model for boron-mediated aldol II



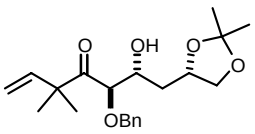
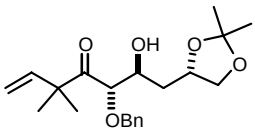
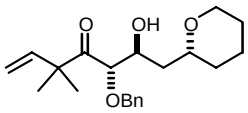
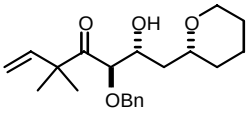
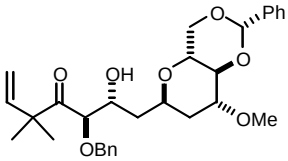
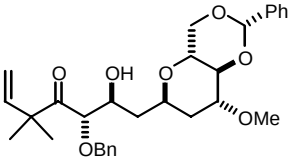
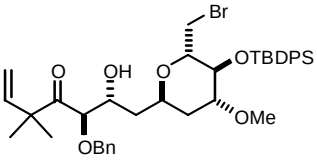
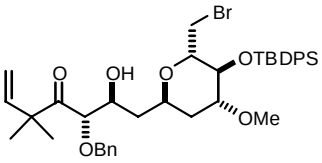
Several aldol products have been characterized with Heteronuclear Single Quantum Correlation (HSQC) and the data is summarized below along with the C2-C3 ^{1}H NMR coupling constant (Table 2.7). The ^{1}H NMR coupling constant between the C2-C3 ranges between 4.5-5.5 Hz, well within the excepted range for *anti*-aldols. Interestingly, the ^{13}C NMR data of the C3 varies depending on the relative 3,5-stereochemistry. When the aldol product is 2,3-*anti*-3,5-*anti*-diastereomer, the C3 is below 70 ppm, where the 2,3-*anti*-3,5-*syn*-diastereomer has the C3 above 70 ppm.

Table 2.7 Summary of NMR Data for Aldol Products





2,3-*anti*-diastereomers

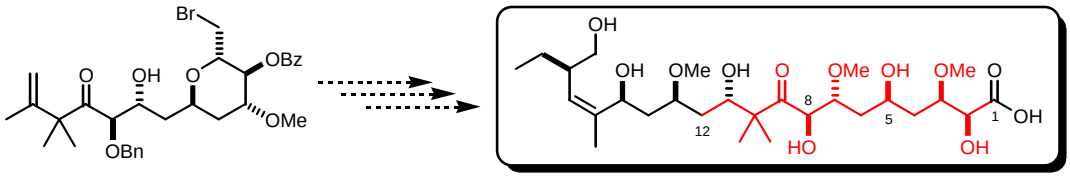
Product	J H_{C2-C3} (Hz)	C2	C3	C5
 **2.78**	5.5	81.8	71.7	75.6
 **2.79**	4.7	82.1	68.9	73.3
 **2.100**	5.5	81.4	69.3	75.5
 **2.101**	5.5	81.8	73.3	79.3
 **2.117**	4.5	82.8	68.0	70.0
 **2.118**	4.5	82.1	71.9	73.6
 **2.132**	4.5	82.5	68.2	63.4
 **2.133**	5.0	82.1	72.9	67.2

Chapter 3: Studies Toward the Synthesis of the C(1)-C(20) segment of Peloruside A

3.1 Studies toward the Synthesis of the Methyl Ketal of peloruside A

The synthesis of the C(1)-C(12) segment of peloruside A, utilizing the new Mukaiyama aldol reaction, was nearly completed (Scheme 3.1). The aldol product **2.115** contained the appropriate stereocenters at C(2), C(3), C(5), C(7) and C(8) corresponding to peloruside A. We envisioned the next step in the synthesis would be the installation of the methyl ether at C(7) followed by a Vasella ring-opening, which can be transformed to the methyl ketal under acidic conditions.

Scheme 3.1 Synthetic significance of aldol product **2.115** to C(1)-C(12) segment

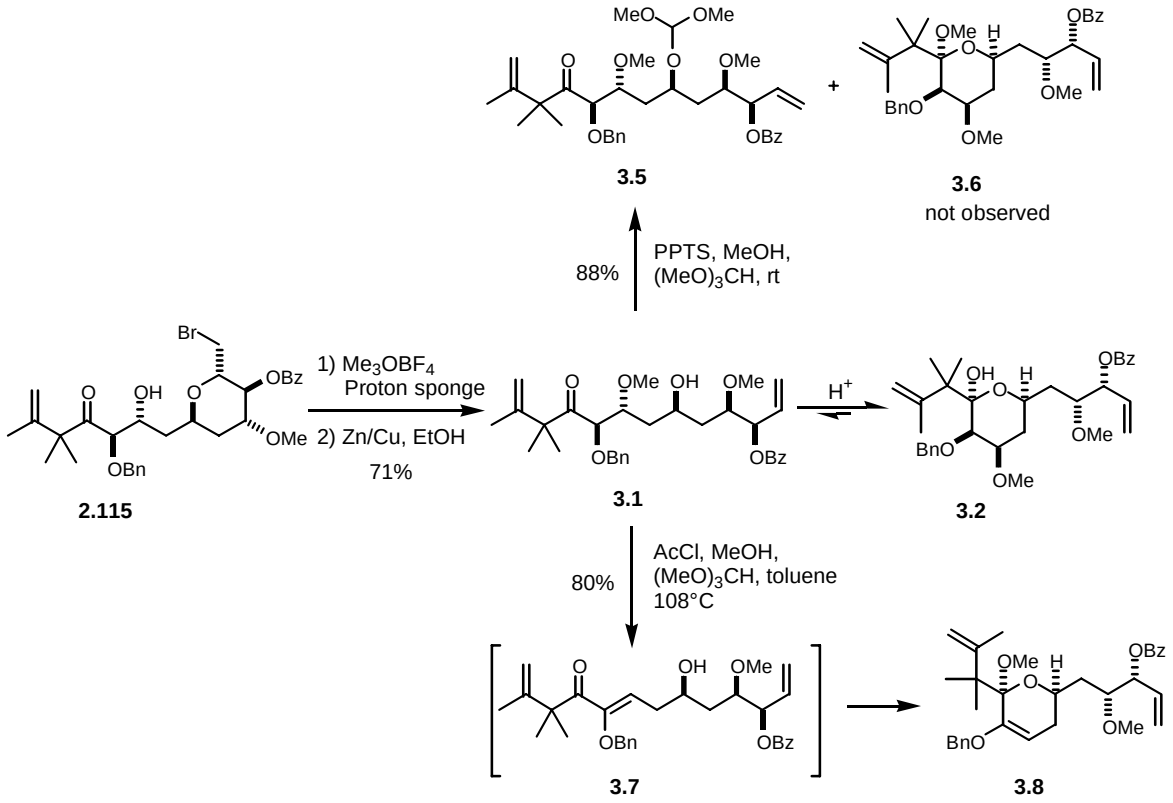


2.115

The methylation of the 2,3-*anti*-3,5-*anti*-stereoisomer **2.115** was performed with Meerwein's salt and proton sponge providing the desired product (99% yield, Scheme 3.2). Under Vasella's conditions,[54] the ring cleavage of 2,3-*anti*-3,5-*anti*-stereoisomer **2.115** afforded alcohol **3.1** in 75% yield but no hemiketal **3.2** was observed. Interestingly, applying the same conditions to the reaction of the 2,3-*anti*-3,5-*syn*-stereoisomer, the Vasella ring-opening gave alcohol **3.3** along with a small amount of hemiketal **3.4** (~13%). To improve the result by enhancing the position of the equilibrium, several acidic conditions were screened. It was found that under mildly acidic conditions, such as PPTS, in trimethyl orthoformate and methanol at room temperature, only ortho ester **3.5** was obtained (88% yield). The structure of **3.5** was

confirmed by ^{13}C NMR spectroscopy data showing the presence of a carbonyl peak at 209.3 ppm and an ortho ester peak at 117.5 ppm.

Scheme 3.2 Attempted synthesis of methyl ketal **3.6**



Another approach to form compound **3.6** also failed when the starting material **3.1** was treated with more forceful conditions, such as elevated reaction temperatures. Under acidic conditions such as anhydrous hydrogen chloride generated from AcCl in methanol, the reaction was heated to 108°C to allow lower boiling reagents to be removed by distillation and drive the equilibrium in favor of the product. However, the desired methyl ketal **3.6** was not found, but rather the methyl ketal **3.8** derived from the *β*-elimination aldol product **3.7** (80% yield) was isolated.

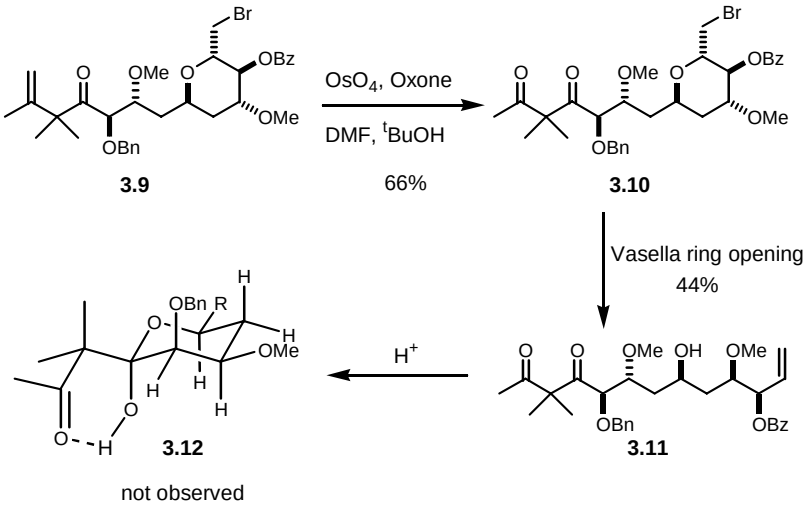
We also tested a variety of Lewis and Brønsted acids such as: Amberlyst 15,[56] $Sc(OTf)_3$, $SnCl_2•H_2O$, $B(OMe)_3$, silica gel , TESOTf and $HClO_4$ in the presence of acetic

anhydride or trimethyl orthoformate, but were unable to find conditions that afforded the desired product **3.6**. In addition, identification of the product from a crude reaction mixture using ^{1}H NMR spectroscopic analysis with various solvents such as $CDCl_3$, CD_3OD, d-DMSO and C_6D_6 proved to be unsuccessful and the desired product remained elusive.

Given the difficulties we encountered with the preparation of compound **3.6**, our attention turned to understanding the conformations of hemiketals derived from the 2,3-*anti*-3,5-*anti*-aldol product and its isomer, the 2,3-*anti*-3,5-*syn*-aldol product. Both hemiketals were bearing one common feature, i.e. an axial ether, methyl ether in **2.120** and benzyl ether in **3.2**, Therefore, it seemed that an important factor that might explain why one isomer could result into a minute amount of the desired hemiketal while the other did not is the 1,5-syn pentane interaction. This steric interaction is induced between the benzyloxy group and the geminal methyl groups. One other possibility that could contribute to the disappointing results is the inability to form the oxonium ion during the transition state under such significant strain. We decided to abandon the direct methyl ketal formation because of these (Scheme 3.2).

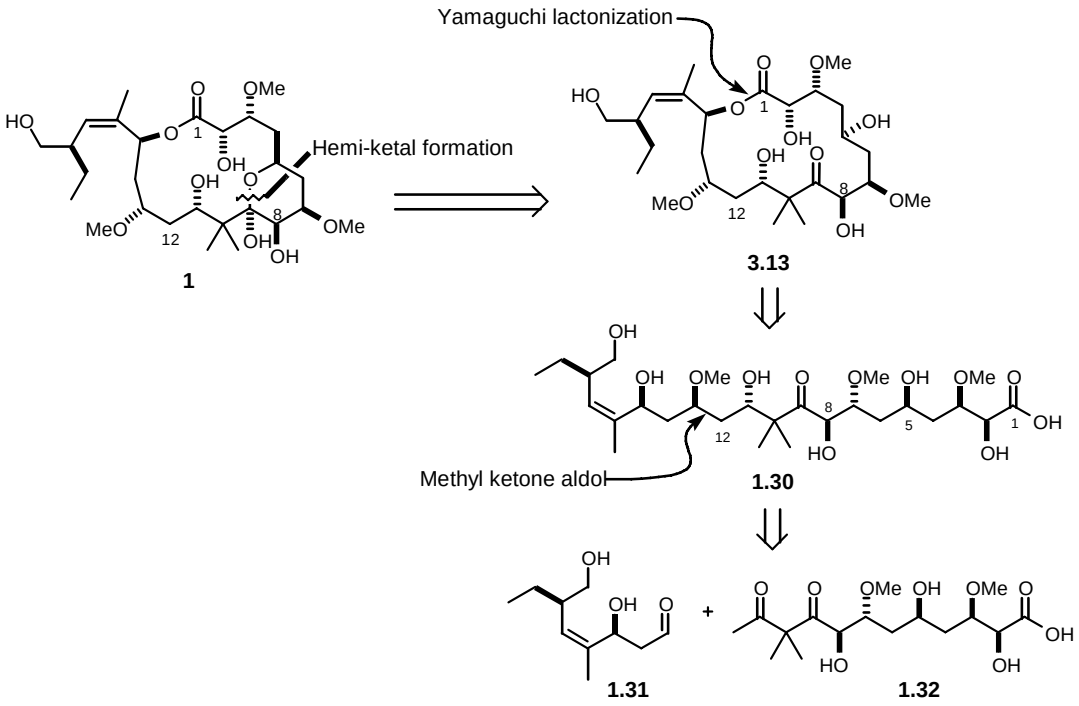
We envisioned that a newly exposed ketone might be able to stabilize the hemiketal **3.12** by hydrogen bonding (Scheme 3.3). In preparing the appropriate substrate, olefin **3.9** was subjected to Borhan's oxidative cleavage conditions which employed an organometallic ozonolysis.[57] In this procedure, the osmate ester was initially formed and under the treatment with Oxone, oxidized to Os(VIII), which was subsequently hydrolyzed to provide 1,3-diketone **3.10** (66% yield without optimization). Unfortunately, attempts to convert 1,3-diketone **3.10** to hemiketal **3.12** using Vasella ring cleavage followed by treatment with acid proved to be unsuccessful.

Scheme 3.3 Attempted synthesis of hemiketal **3.12**



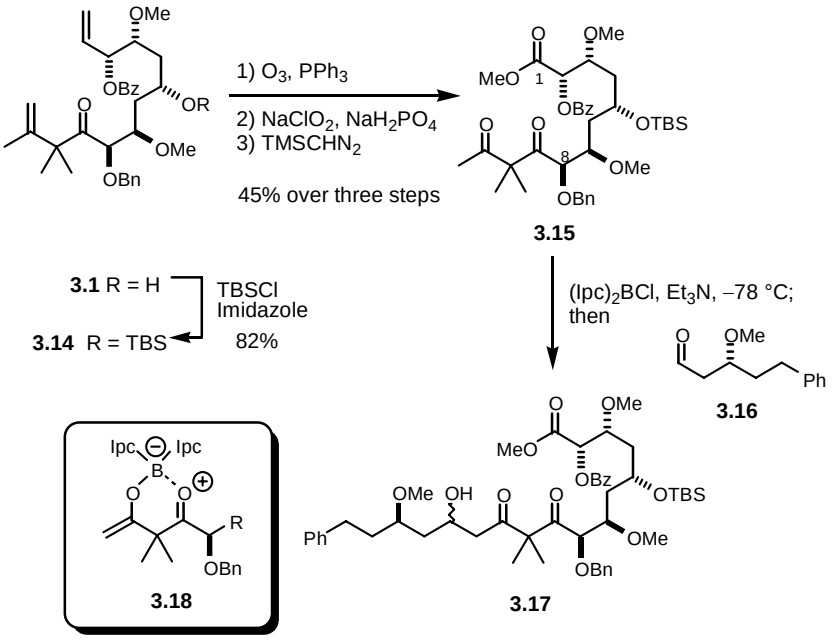
At this point, we were not able to develop conditions that would allow us to synthesize methyl ketal **3.6**. By modifying our retrosynthesis of peloruside A (Scheme 3.4), we envisioned that the formation of hemiketal could be done in the last step of the total synthesis along with a Yamaguchi macrolactonization of the acyclic polyol. In addition, we thought that the useful building block **3.1** bearing two olefin functional groups (as shown in Scheme 3.2) could be converted to methyl ketone **1.32** which in turn would undergo an aldol reaction with aldehyde **1.31** to construct a C(12)-C(13) bond.

Scheme 3.4 Retrosynthetic analysis of peloruside A



In an attempt to synthesize the highly functionalized methyl ketone **3.15**, the secondary alcohol **3.1** was protected as the silyl ether **3.14** (82% yield, Scheme 3.5). Oxidative cleavage by ozonolysis followed by an immediate oxidation with sodium chlorite in the presence of 2-methyl-2-butene as an acid trap provided the desired carboxylic acid, which was carried on to the next step. Esterification with trimethylsilane diazomethane afforded the desired methyl ester **3.15** (45% yield for the three steps).

Scheme 3.5 Preparation of methyl ester **3.15**



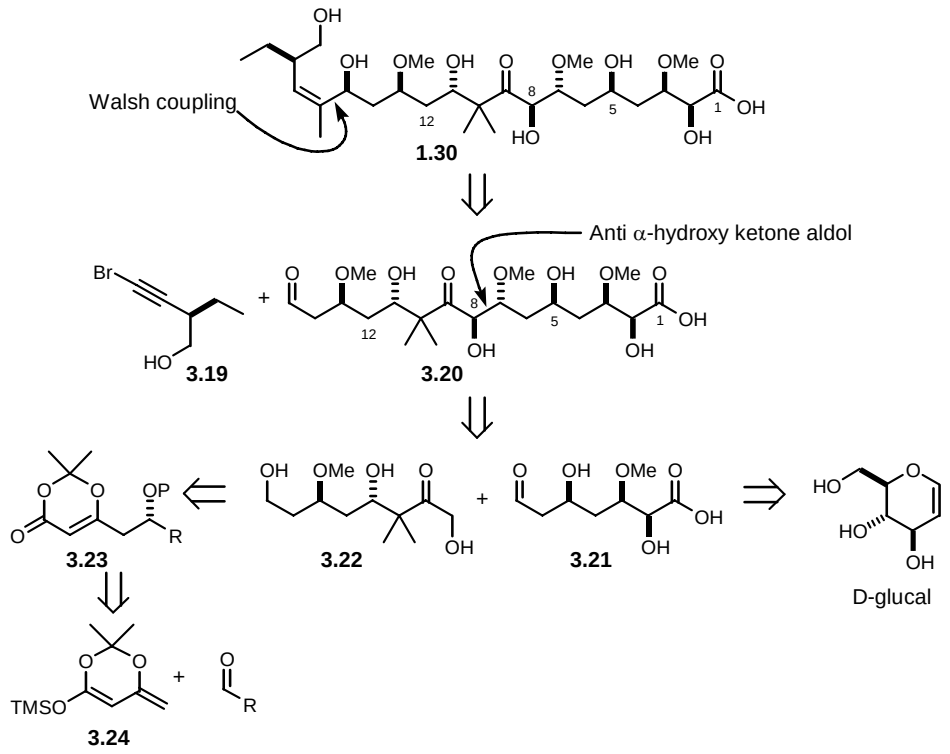
To explore the stereoselective aldol reaction, a *β*-methoxy model aldehyde **3.16** was added to a pre-formed boron enolate of methyl ketone **3.15**. However, no desired product was observed, even though the formation of the boron enolate was confirmed by the ^{1}H NMR spectroscopy analysis. Therefore, one possible explanation for the unsuccessful reaction was that the formation of a stable six-member intramolecular boron ate-complex **3.18** prevented the construction of the desired aldol product.

In conclusion, despite the significant effort that had been invested for the formation of methyl ketal **3.6** and selective aldol reactions, this was not a viable route to the synthesis of peloruside A as we had originally planned. We sought for an alternative route, which will be discussed in the next section.

3.2 STUDIES TOWARD THE SYNTHESIS OF ACYCLIC C(1)-C(20) SEGMENT

In a modified retrosynthesis, we envisioned a disconnection into two highly functionalized segments, bromoalkyne **3.19** and aldehyde **3.20**, which will be joined by a multicomponent coupling reaction (Scheme 3.6). We were intrigued by a recent report from Walsh in which he selectively synthesized (*Z*)-trisubstituted allylic alcohols from bromoalkynes.[58] This ingenious methodology could be applied to the synthesis of C(1)-C(20) segment. The highly functionalized aldehyde **3.20** can be disconnected at the C_7-C_8 with a late stage Mukaiyama aldol reaction. While aldehyde **3.21** would be synthesized from D-glucal, the α-hydroxy ketone **3.22** with the C(11) stereocenter is ideally arranged for assembly by a Carreria asymmetric dienolate aldol reaction.[59]

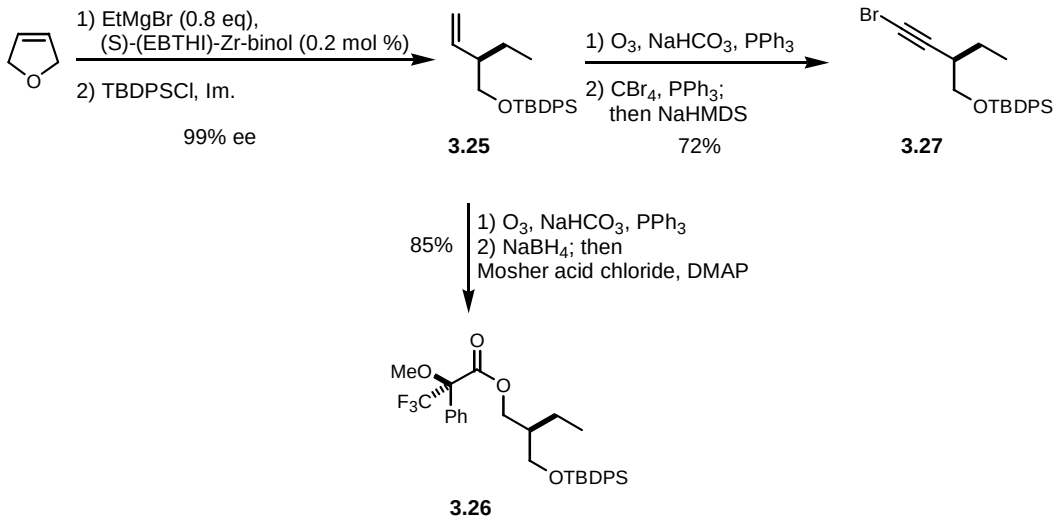
Scheme 3.6 Retrosynthesis of the C(1)-C(20) segment



3.2.1 Walsh Multicomponent Coupling Reaction

Before exploring the suitability of the Walsh coupling reaction for application here, a suitable bromoalkyne **3.27** for the synthesis of peloruside A was prepared (Scheme 3.7). The synthesis began with Hoveyda's zirconium-catalyzed asymmetric carbomagnesation[60] provided the primary alcohol that was immediately protected as the TBDPS ether **3.25**. Ether **3.25** was transformed into the chiral ester **3.26** using Mosher's acyl chloride and the ^{19}F NMR spectrum showed a single peak with the chemical shift at –72.0 ppm, confirming the enantiomeric excess (i.e. 99%).[60] The synthesis of the bromoalkyne **3.27** was concluded with a two step procedure, formation of the dibromoalkene and subsequent elimination to the desired product **3.27** (72% yield from olefin **3.25**).

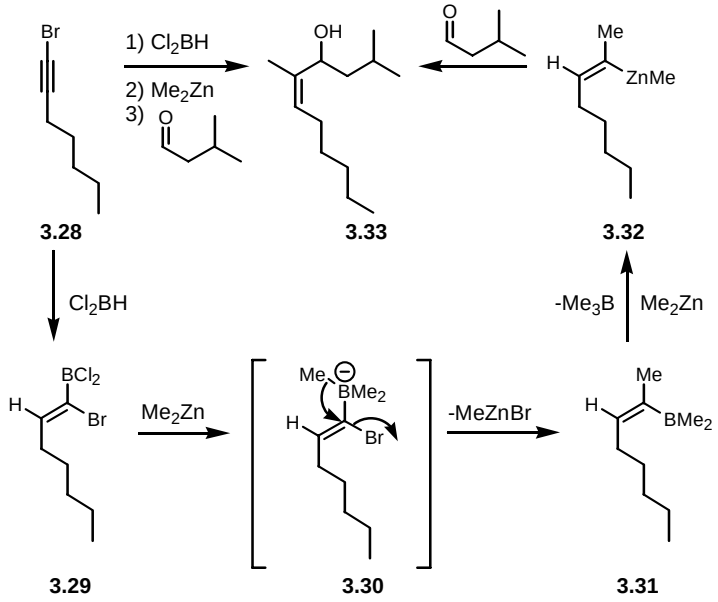
Scheme 3.7 Preparation of bromoalkyne **3.27**



With bromoalkyne **3.27** in hand, our attention focused on the Walsh's coupling reaction. This modern method is an alternative to the classic Still-Gennari[61] modification of the Horner-Wadsworth-Emmons olefination, which is a two carbon homologation and impractical for the direct coupling of larger fragments. In the Walsh's coupling reaction

(Scheme 3.8), dichloroborane reacts with bromoalkyne **3.28** resulting in dihalovinylborane **3.29**. With the addition of excess Me_2Zn, a boron-halogen exchange occurs to produce intermediate **3.30**, which undergoes inversion to form a (*Z*)-trisubstituted vinyldimethylborane **3.31**. Further reaction of vinyl dimethylborane with Me_2Zn induces transmetallation to form the intermediate vinylzinc **3.32** that can then be intercepted with an aldehyde to give an allylic secondary alcohol in 70-92% yield.[58]

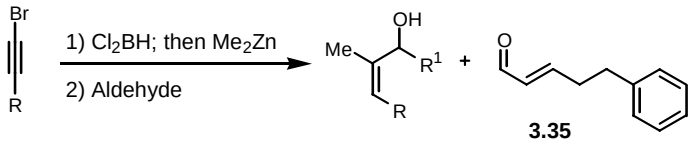
Scheme 3.8 An example of Walsh multicomponent coupling reaction

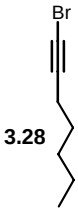
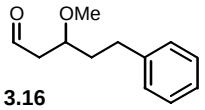
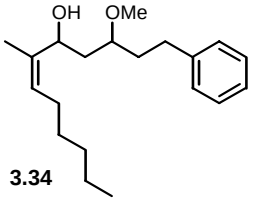
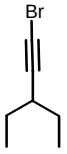
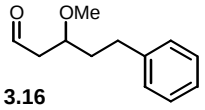
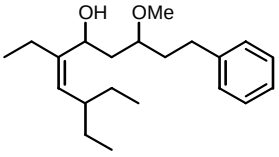
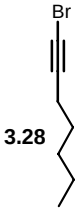
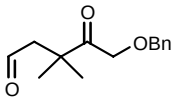
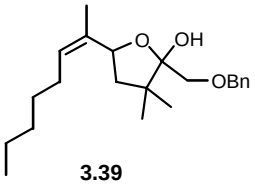


Model studies were carried out to investigate the diastereomeric ratio of Walsh's chelation controlled addition. Reaction of the bromoalkyne **3.28** under the reported Walsh conditions followed by coupling with *β*-methoxy aldehyde **3.16** gave a 1:1 mixture of the desired allylic alcohol **3.34** and unwanted *α*,*β*-unsaturated aldehyde **3.35** resulting from *β*-elimination (Table 3.1, entry 1). It was found that by decreasing the reaction concentration from 1.0M to 0.30M, the yield of the desired allylic alcohol **3.34** improved (43%, 2:1 dr). While the results were modest, this procedure had provided a direct route to the *Z*-trisubstituted allylic alcohol that is more concise than reported alternatives.

Applying the same conditions to the more relevant branched bromoalkyne **3.36** (entry 2), the allylic alcohol **3.37** was obtained in 50% yield and 2:1 ratio for the anti/syn diastereomers. Reaction with aldehyde **3.38** containing a sterically hindered ketone (entry 3) was tested. It was found that such a sterically hindered ketone does not interfere with the coupling to the aldehyde and a comparable yield was obtained (46% yield).

Table 3.1 Results of Walsh multicomponent coupling reaction



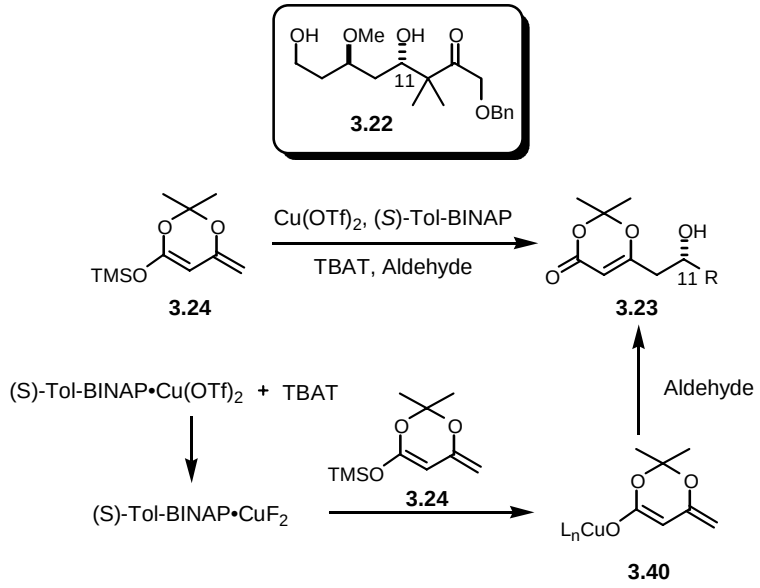
Entry	Alkyne	Aldehyde	Product	Yield (%)	Dr
1	 **3.28**	 **3.16**	 **3.34**	43	2:1
2	 **3.36**	 **3.16**	 **3.37**	50	2:1
3	 **3.28**	 **3.38**	 **3.39**	46	2.5:1 (α:β)

The overall yield for the Walsh multicomponent coupling reaction was quite low, but the methodology will provide the most direct synthesis of the desired (*Z*)-trisubstituted allylic alcohol, a significant component of peloruside A.

3.2.2 Carreira Enantioselective Aldol Reaction

After establishing the viability of the Walsh coupling reaction, we next focused on the synthesis of the highly functionalized α-benzyloxy ketone **3.22** using a Carreria enantioselective aldol (Scheme 3.9).[59] This idea was based on previous results disclosed by Carreria et al., in which the addition of a chiral copper dienolate **3.40** derived from dioxinyloxy trimethylsilane **3.24** to an α',α'-dimethyl aldehyde afforded desired product **3.23** in excellent enantioselectivities and yield.

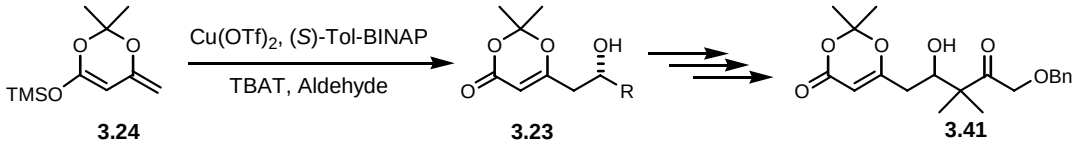
Scheme 3.9 Carreira enantioselective aldol reaction



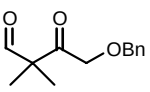
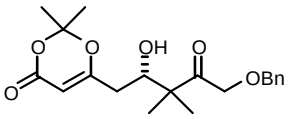
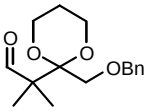
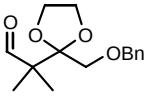
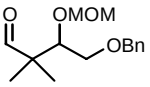
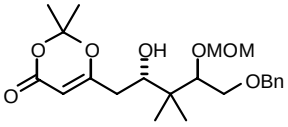
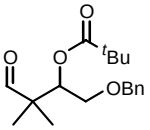
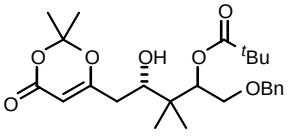
Addition of dienosilane **3.24** to aldehyde **3.42** under the Carreira aldol conditions gave only a small amount of the desired product (Table 3.2, entry 1). The ^{1}H NMR spectroscopy analysis of the crude reaction mixture appeared to show the formation of mixed aldols. In order to avoid the formation of the mix aldol products, the ketone was

protected as an acetal **3.43** and **3.44** (entries 2 and 3). These substrates were subjected to the same reaction conditions; however, they failed to react, possibly due to the increased steric bulk from the acetal.

Table 3.2 Preliminary results of Carreira's enantioselective aldol



3.24 **3.23** **3.41**

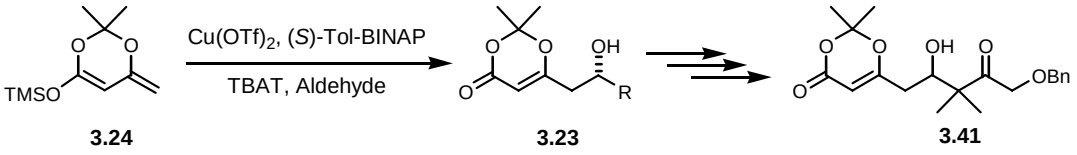
Entry	Aldehyde	Product	Yield (%)	ee (%)
1	 **3.42**	 **3.41**	20	n/a
2	 **3.43**	No reaction	--	--
3	 **3.44**	No reaction	--	--
4	 **3.45**	 **3.46**	49	n/a
5	 **3.47**	 **3.48**	51	n/a

As we sought for another solution, we envisioned that to reduce the steric bulk from the protecting group, ketone **3.42** could be masked as protected secondary alcohols **3.45** and

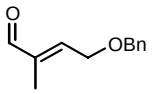
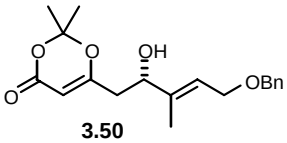
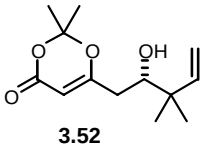
3.47 (entries 4 and 5). As anticipated, the use of MOM ether **3.45** and Pivolate ester **3.47** did provide the desired aldol products **3.46** (49% yield, entry 4) and **3.48** (51% yield, entry 5).

In an attempt to improve the results in the previous table, we decided to examine the aldehydes that had been employed in the published and unpublished works by Carreria et al.[62] It was concluded that only the aldol reactions of the α,β-unsaturated aldehydes resulted in high enantioselectivity and yield. This could possibly be explained by an advantageous π-stacking interaction between the aldehyde and the chiral ligand, (*S*)-Tol-BINAP., Aldehydes **3.49**[63] and **3.51** were screened using the same Carreria's aldol conditions and provided aldol products **3.50** (73% yield, 88% ee, Table 3.3, entry 1) and **3.52** (78% yield, 76% ee, entry 2). The optical purity of aldol product **3.52** could be improved to 99% by a single recrystallization.

Table 3.3 Additional results of Carreira's enantioselective aldol

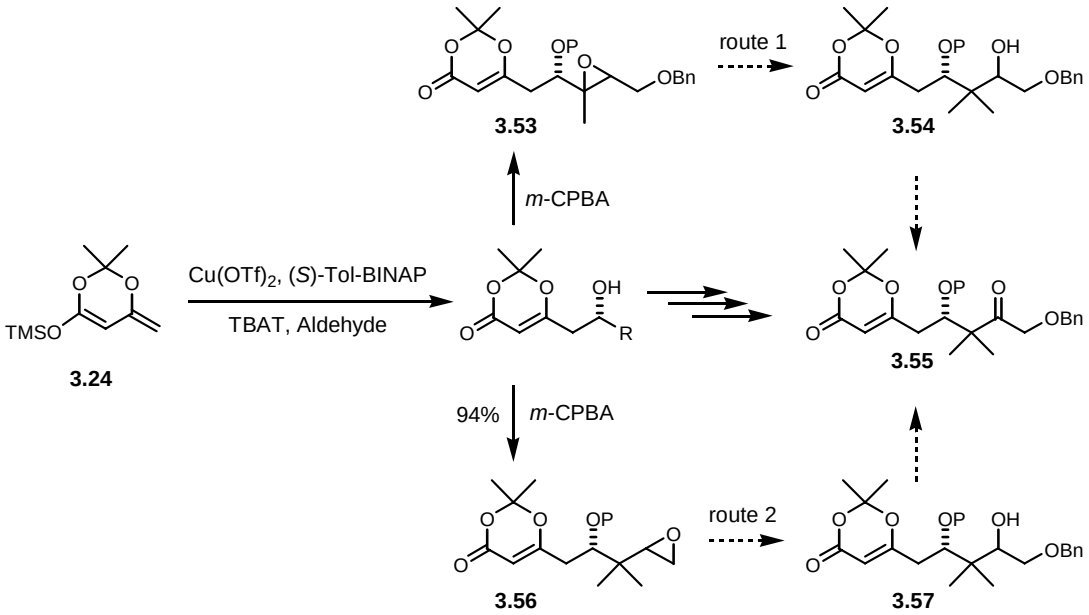


3.24 **3.23** **3.41**

Entry	Aldehyde	Product	Yield (%)	ee (%)
1	 **3.49**	 **3.50**	73	88
2	 **3.51**	 **3.52**	78	76 (99)

With these aldol products in hand, we planned for the conversion to the desired α-benzyloxy ketone **3.55** by two routes (Scheme 3.10). In route 1, we envisioned that after the epoxidation of the aldol product **3.50** (Table 3.3, entry 1), the Zhao-Pagenkopf[64] ring-opening of the corresponding epoxide would provide the free alcohol **3.54**. Subsequent oxidation would afford the α-benzyloxy ketone **3.55**. Unfortunately, the conditions for the alkynylation at the more hindered carbon of trisubstituted epoxides did not work with tetramethylaluminates, thus the route was abandoned.

Scheme 3.10 Attempts to prepare the α-benzyloxy ketone **3.55**

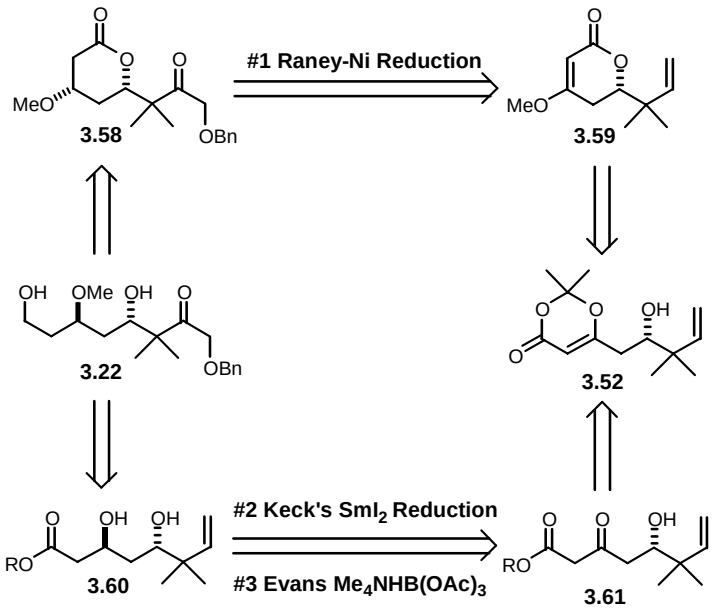


In route 2, we envisioned epoxidation of olefin **3.52** could provide the α-benzyloxy ketone **3.55** by a more traditional approach (Scheme 3.10). However, applying the titanium(IV)benzyloxide-mediated[65] ring-opening of the epoxide **3.56** and other more conventional benzyloxide reagents were ineffective. Due to the difficulties associated with the synthetic route for the preparation of α-benzyloxy ketone **3.55** directly from the aldol product **3.50**/ **3.52**, we decided to shift our focus to the construction of the acyclic 1,3-anti diols.

3.2.3 Synthesis of 1,3-anti Diols

Three possible routes toward a 1,3-anti diol were investigated in the course of this project (Scheme 3.11). In the first route, the synthesis of ketone **3.22** featured a catalytic diastereoselective hydrogenation with Raney-Nickel[66] and concurrent protection of the hydroxy adjacent to the geminal methyl groups. The ketone **3.22** could also be derived from the selective *anti*-reduction of *β*-keto ester **3.61** by either a samarium diiodide reduction[67] or the Evans directed reduction with tetramethylammonium triacetoxyborohydride.[68] These routes will be discussed in more detail in the following sections.

Scheme 3.11 Retrosynthesis of acyclic *α*-benzyloxy ketone **3.22**

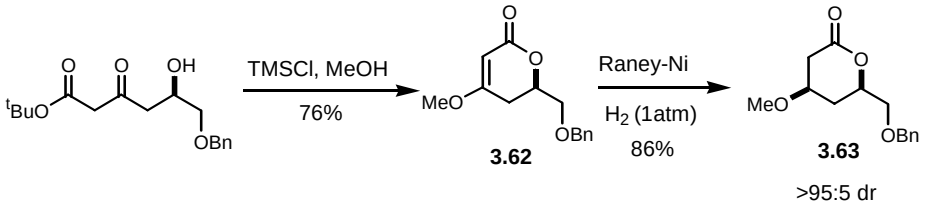


3.2.3.1 Catalytic Raney-Nickel Hydrogenation

A diastereoselective hydrogenation with catalytic Raney-Nickel has been reported by Evans et al.[66] to provide *β*-methoxy lactone **3.63** (Scheme 3.12). A *β*-ketoester was converted into the methyl enol ether **3.62** under acidic conditions in MeOH. A

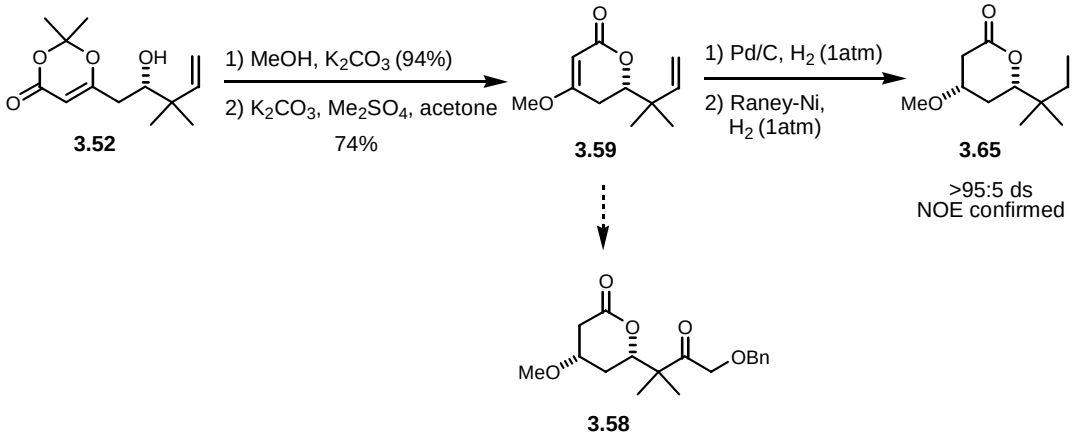
hydrogenation with catalytic Raney-Nickel resulted in the *β*-methoxy lactone **3.63** with high diastereoselectivity. We envisioned this sequence estabilishing the necessary 1,3-*anti*-selectivity and also systematically installing the methyl ether that corresponds to the C(13) of peloruside A.

Scheme 3.12 Evans' Raney-Nickel reduction



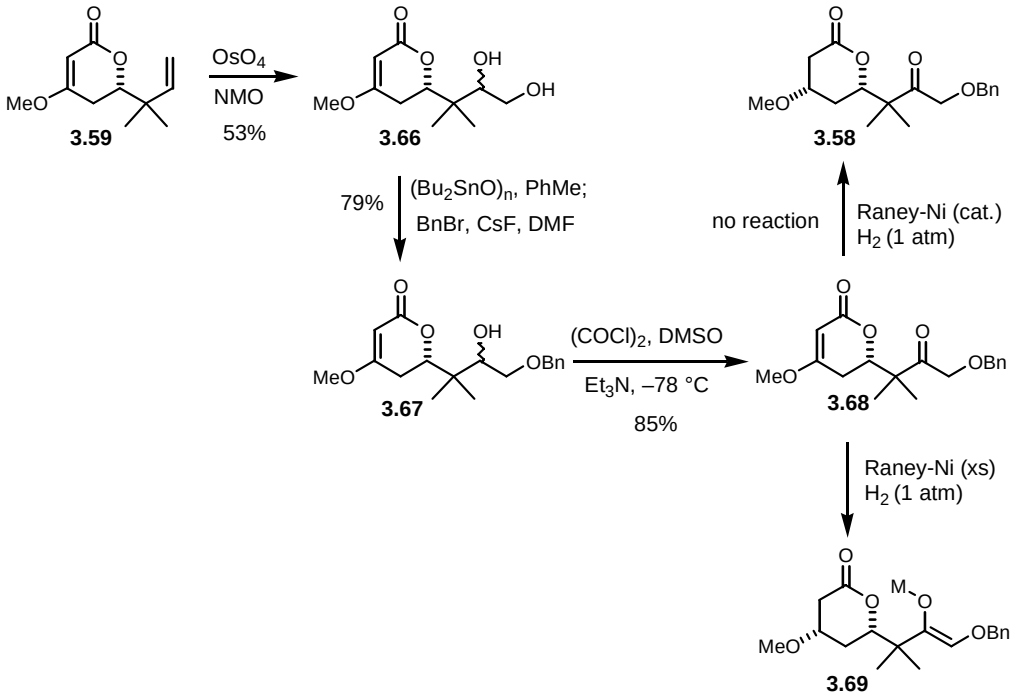
With the presence of the *gem*-methyl on **3.52**, a study was necessary to determine the diastereoselectivity of the Raney-Nickel reduction. Cyclization of *β*-ketolactone **3.64** (MeOH, K_2CO_3) followed by methyl enol ether formation provided **3.59** (74% yield, Scheme 3.13).[69] After hydrogenation of the olefin, the diastereoselective reduction with catalytic Raney-Nickel provided one single diastereomer **3.65** that was confirmed by NOE analysis. With the diastereoselectivity having been established, the remaining challenge was to transform the terminal olefin into the *α*-benzyloxy ketone **3.58** while applying the catalytic Raney-Nickel reduction.

Scheme 3.13 Confirmation of the stereoselective Raney-Nickel reduction



We envisioned that the conversion of the terminal olefin into the α-benzyloxy ketone or a suitable intermediate would be necessary prior to the catalytic hydrogenation (Scheme 3.14). Serendipitously, the dihydroxylation of **3.59** only provided diol **3.66** in a moderate 53% yield. A selective monobenzylation of unsymmetric diols was accomplished with Ohno's conditions which involved the ring-opening of the stannylene acetal with a fluoride anion and subsequent alkylation.[70] Swern oxidation of the free alcohol **3.67** afforded the ketone **3.68** in good yield (85% yield). Various catalytic Raney-Nickel hydrogenation conditions were tested, but no conversion to the desired product was observed. We speculated it was possible that the α-benzyloxy ketone **3.68** could form the enolate **3.69** thereby preventing the metal from participating in the reductive catalytic cycle. Although when excess metal hydride was employed, the reaction resulted in multiple products which were unable to be identified. We decided to abandon this route due to the poor regioselectivity and low yield in the dihydroxylation and Raney-Nickel reduction.

Scheme 3.14 Attempted synthesis of α-benzyloxy ketone **3.58**

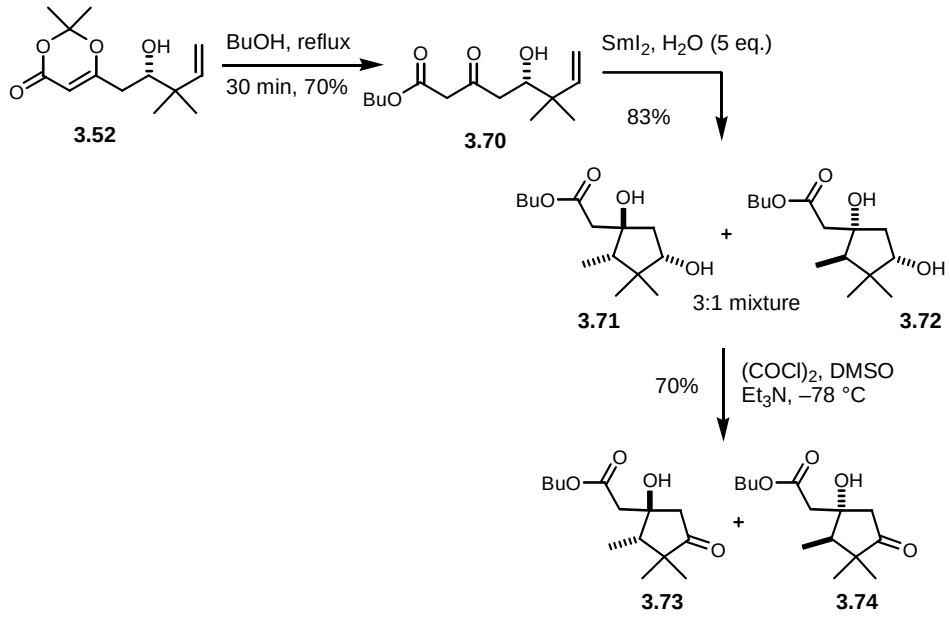


3.2.3.2 Keck Samarium Diiodide (SmI_2) Reduction

Another route towards α-benzyloxy ketone **3.22** was the diastereoselective reduction of the β-ketoester **3.70** with samarium diiodide (Scheme 3.15).[67] The Keck reduction is based on sequential one-electron transfer as opposed to the more conventional hydride transfer. The method is an attractive one because of its ease of implementation and experimental simplicity, which involves merely the addition of samarium diiodide and a proton source, either MeOH or water. It was found that the β-ketoester **3.70** and samarium diiodide with MeOH (10 equivalents) did not undergo any reaction at 0°C. At room temperature, a 3:1 mixture of diastereomers was obtained; however, the terminal olefin was no longer evident by the ^{1}H NMR spectroscopic analysis. Interestingly, the products were confirmed as unanticipated cyclopentanes **3.71** and **3.72**. One possible explanation for the formation of these cyclopentanes was that the

carbinol radical might react with the olefin before a second rapid electron transfer giving a samarium carbanion can occur. The facility of this radical cyclization is further enhanced by the *gem*-disubstituent effect,[71] and Molander reported a similar reductive cyclization of unactivated olefinic ketones using samarium diiodide.[72] The inseparable mixture of diastereomers **3.71** and **3.72** was structurally verified by oxidation to the enantiomeric ketones **3.73** and **3.74** (70% yield), which provided identical ^{1}H NMR spectra.

Scheme 3.15 Keck's reduction to 1,3-diols with samarium diiodide

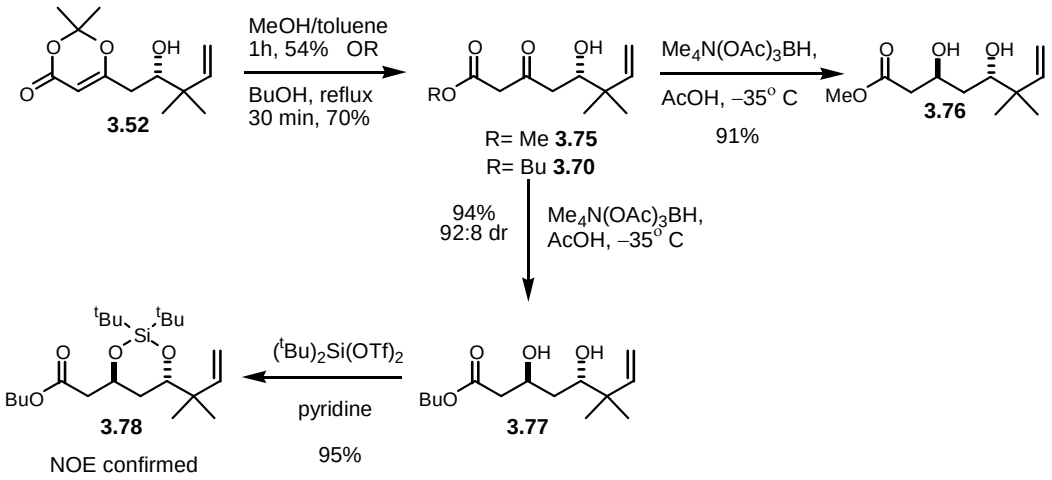


3.2.3.3 Evans Directed Reduction with Tetramethylammonium Triacetoxyborohydride

The final route to the α-benzyloxy ketone **3.22** was a directed reduction with tetramethylammonium triacetoxyborohydride (Scheme 3.16).[68] After formation of the β-ketoester **3.70** or **3.75**,[73] the methyl ester **3.75** was reduced to the diol **3.76** (91% yield) and the butyl ester **3.70** was reduced to the diol **3.77** (94% yield, 92:8 dr). The relative

stereochemistry was verified by NOE analysis of the silylidene acetal **3.78**. The Evans reduction had shown a remarkable level of diastereoselectivity and provided excellent yield for the desired 1,3-*anti*-diol **3.77**, even though the Evans reduction was not a catalytic method.

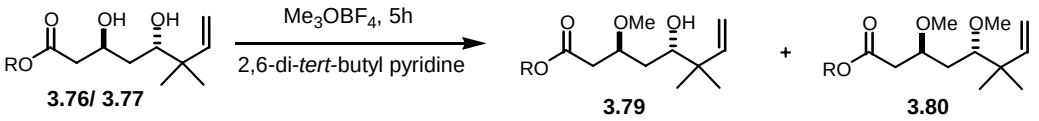
Scheme 3.16 Tetramethylammonium triacetoxyborohydride reduction

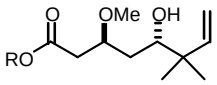
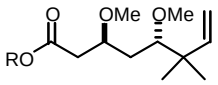


Once we had diol **3.77** at hand, the next challenge to overcome was the regioselective methylation. Having experienced interference from the *gem*-methyl in past successful and unsuccessful chemical reactions, we felt confident that methylation with Meerwein's salt and a bulky base, 2,6-di-*tert*-butyl pyridine, would regioselectively methylate the less hindered secondary alcohol in diol **3.77**. When diol **3.77** was treated with two equivalents of Meerwein's salt and 2,6-di-*tert*-butyl pyridine for 5 h (Table 3.4, entry A), the desired *β*-methoxyester **3.80A** was obtained in only 34% yield along with the bis-methyl ether **3.80A** in 54% yield. To improve the selectivity, diol **3.77** was subjected to the same reagents, but with only 1.1 equivalents of Meerwein's salt (entry B), the desired product **3.79B** was obtained in 86% yield based on recovered starting material. The bis-methyl ether **3.80B** was also isolated, but in minute amounts (~10%).

The unreacted starting material was recovered and could be resubjected to the methylation protocol.

Table 3.4 Synthesis of *β*-methoxy ester **3.79A** and **3.79B**



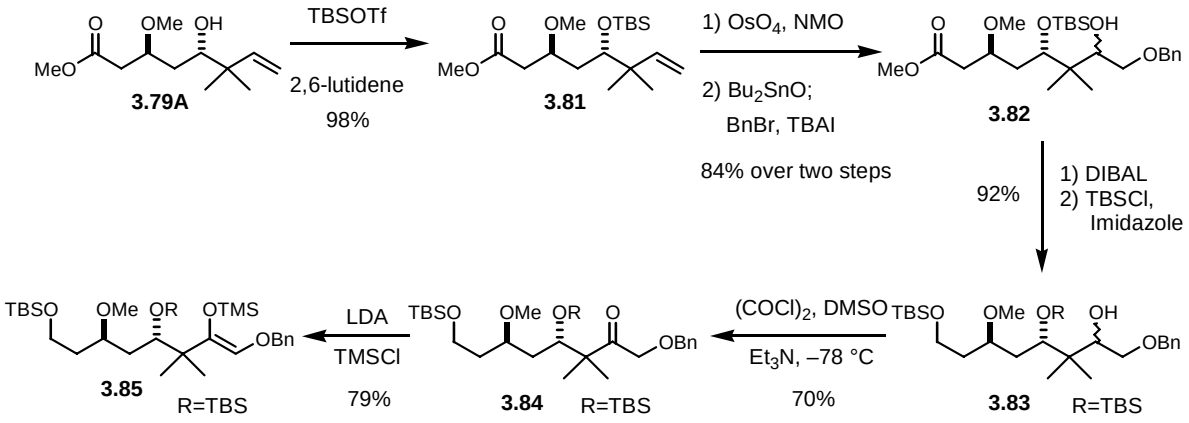
Entry	R group	Meerwein's salt (# of equivalents)	Yield (%)	
			 3.79	 3.80
A	Me	2.0	34	54
B	*n*-Bu	1.1	86 (brms)	10

3.2.4 Synthesis of Trimethylsilyl Enol Ether 3.85

With the *β*-methoxy ester **3.79B** at hand, the remaining tasks in the synthesis involved straightforward synthetic steps to the *α*-benzyloxy ketone **3.84** (Scheme 3.17). First, the free alcohol in **3.79A** was protected as the silyl ether (TBSOTf, 2,6-lutidene, 98% yield). It is worth noting that protection of the hindered free alcohol with TBSCl and TBDPSCl resulted in little to no product because of the steric environment around the hydroxyl group, while the heightened reactivity of the silyl triflate could overcome this. Dihydroxylation of the terminal olefin **3.81** followed by the regioselective monobenzylation with Ohno's stannylene acetal method gave an inconsequential mixture of diastereomers **3.82** in high yield (84% over two steps). Reduction of the methyl ester **3.82** followed by the reaction of the resulting primary alcohol with *tert*-butyl

dimethylsilyl chloride provided **3.83** as a mixture of diastereomers. The desired α-benzyloxy ketone **3.84** was obtained from the oxidation of the alcohol **3.83** which was then converted into the trimethylsilyl enol ether **3.85** in 79% yield.

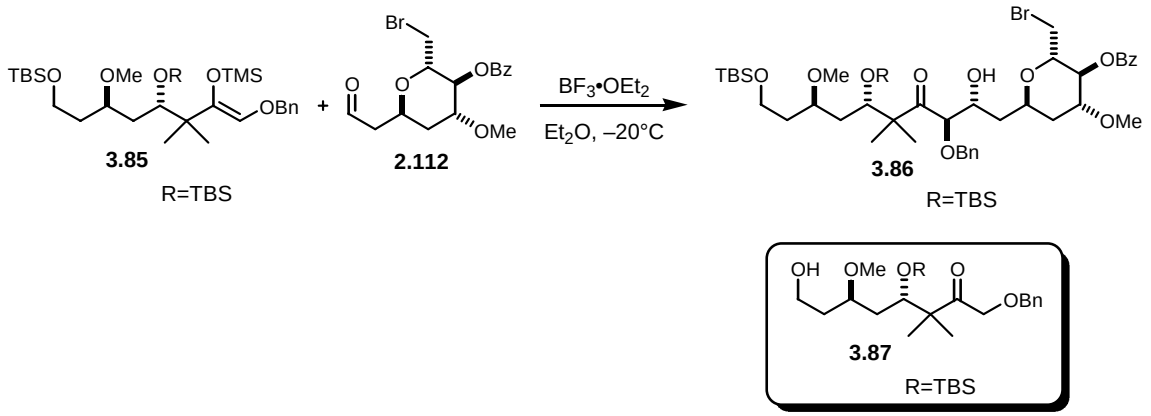
Scheme 3.17 Synthesis of trimethylsilyl enol ether **3.85**



3.2.5 Aldol Reaction between Silyl Enol Ether 3.85 and Aldehyde 2.112

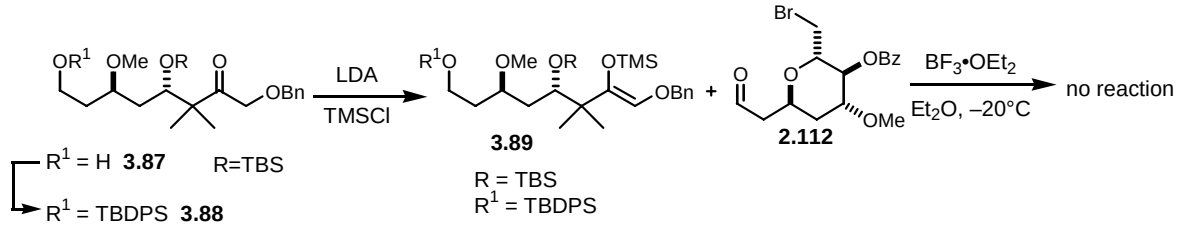
We envisioned the Mukaiyama aldol reaction between trimethylsilyl enol ether **3.85** and aldehyde **2.112** would provide the C(1)-C(15) segment with 7 stereocenters and two of the three methyl ethers protected accordingly (Scheme 3.18). However, when enol ether **3.85** and aldehyde **2.112** were treated with BF_3•OEt_2 in diethyl ether at –20°C, no product conversion was detected by thin-layer chromatography. However at 0°C, deprotection of the primary *tert*-butyl-di-methylsilyl ether resulting in ketone **3.87** was observed. While there were reports that BF_3•OEt_2 would remove silyl ethers,[74] we were optimistic that the Mukaiyama aldol reaction would take precedence over deprotection.

Scheme 3.18 Attempted Mukaiyama aldol reaction of aldehyde **2.112**



Ketone **3.88** with a more robust silyl ether such as TBDPS, after forming the trimethylsilyl enol ether **3.89**, was subjected to the same aldol reaction conditions. After 3 h at 0°C, the reaction was abandoned because of decomposition of the starting materials. It seems that BF_3•OEt_2 were too harsh of conditions for the α-benzyloxyketone **3.88**.

Scheme 3.19 Attempted Mukaiyama aldol reaction II



3.3 CONCLUSION

While testing the Walsh coupling reaction for the application in this study was successful, we were unable to complete the synthesis of the complex polyol **1.30** using the Mukaiyama aldol**.** It was found that although the protecting groups were too acid labile, the lack of silyl enol ether reactivity at 0°C was the major unanticipated failure in this method. It is possible that poor reactivity is due to the new stereocenter (C11), sp^3-

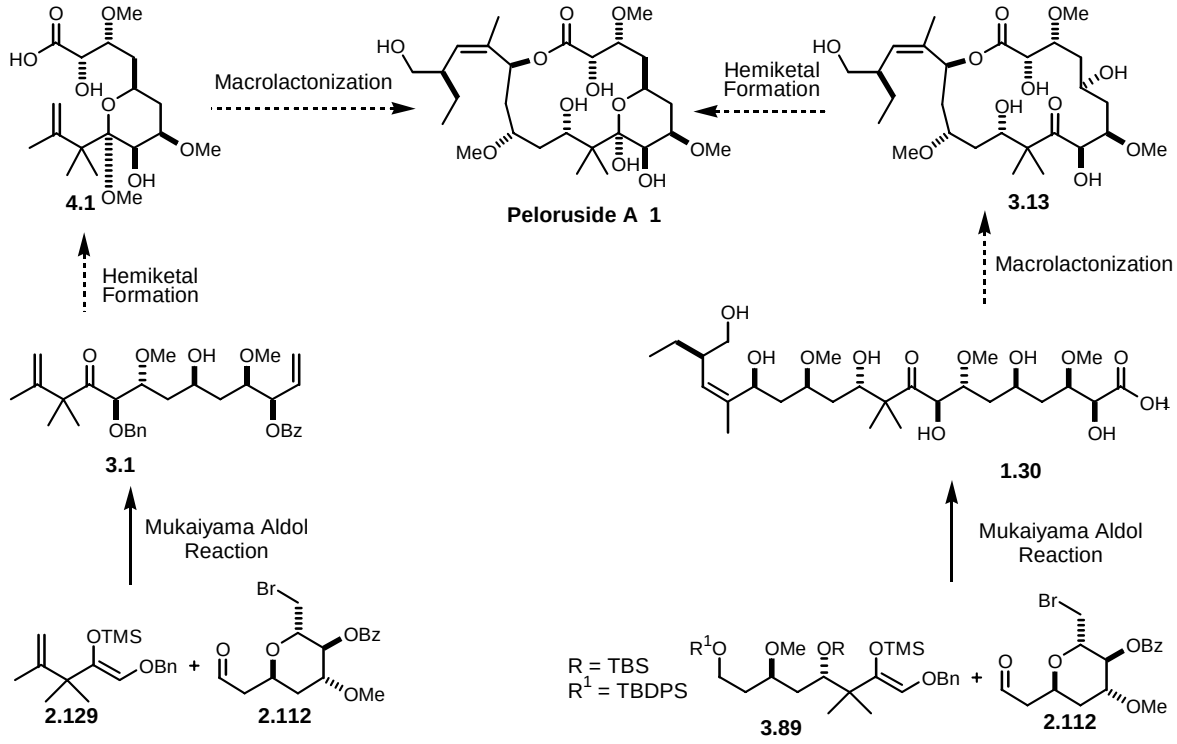
hydridized which has more steric hindrance than the sp^2-hybridized trimethyl silyl enol ether **2.129** which previously resulted in good yield and facial selectivity. Although the results in this study are rather disappointing, we were pleased to obtain an efficient synthesis of two major segments which would be extremely useful in another approach towards the synthesis of peloruside A, which will be discussed in Chapter 4.

Chapter 4: New Approach to the Synthesis of peloruside A

4.1 INTRODUCTION

At this point in the project, the complete synthesis of peloruside A remained elusive since the two approaches toward the synthesis of either cyclic intermediate hemiketal **4.1** or macrolactone **3.13** were unsuccessful (Scheme 4.1). The application of the novel Mukaiyama aldol conditions to the reaction of silyl enol ether **2.129** and aldehyde **2.112** were highly successful and gave polyol **3.1** (85% yield, 3.5 dr), but unfortunately failed to construct the methyl ketal **4.1** that was necessary to continue the synthesis towards peloruside A.

Scheme 4.1 Previous approaches towards the synthesis of peloruside A

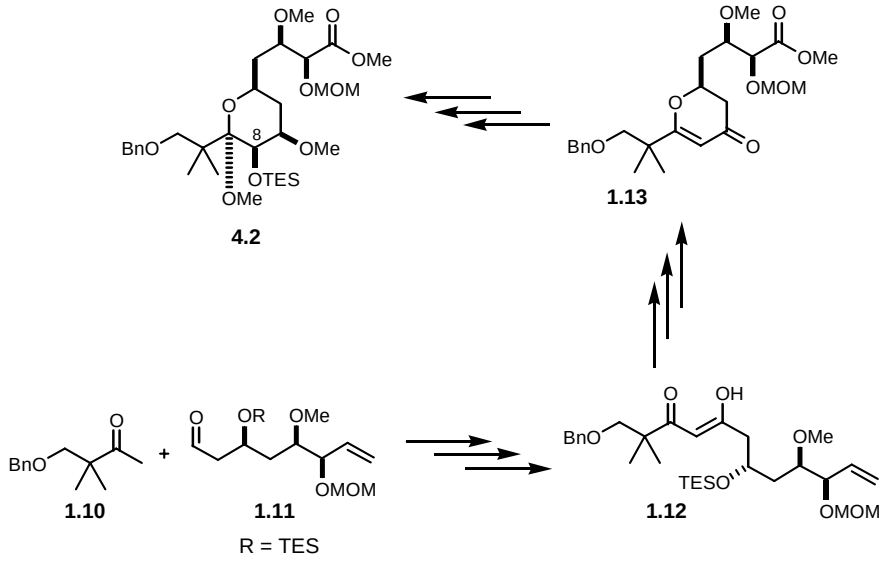


We envisioned that we could overcome the inability of the methyl ketal **4.1** formation with an alternative approach by synthesizing the complete acyclic carbon framework of peloruside A **1.30** and subsequently cyclization to the macrocycle **3.13**. Macrolactonizations of 16-membered ring systems have been well-documented,[75] but it was unclear whether enthalpic factors from strain energy would play a significant role. If the lactone **3.13** could be prepared, the hemiketal would be suitably positioned to cyclize. Unfortunately, our attempts to apply the Mukaiyama aldol condition to form the longer carbon segment **1.30** of peloruside A failed due to the lack of reactivity of the trimethylsilyl enol ether **3.89** (Scheme 3.19). In the following section, we will examine some of the published approaches to the synthesis of methyl ketal fragment of peloruside A or other macrocycles that exhibit similar 1,5-*syn*-pentane interactions between geminal methyls and an axial stereocenter on a pyran ring. By doing so, we hoped that our new approach would be more efficient and less problematic.

4.2 STRUCTURAL COMPARISONS OF PELORUSIDE A PYRANOSIDE AND BRYOSTATINS PYRANOSIDE

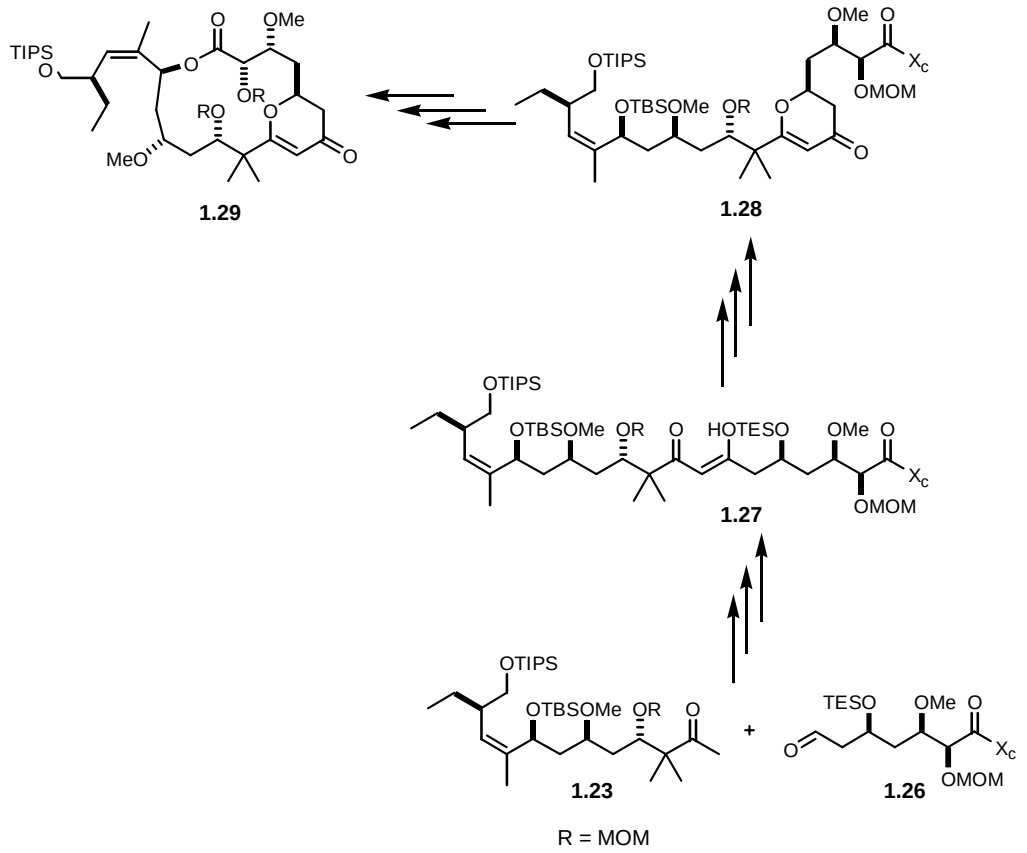
The first synthesis of *ent*-peloruside A reported by De Brabander et. al was achieved in an elegantly devised and efficient manner (Scheme 4.2). The synthesis of the densely functionalized tetrahydropyranyl fragment **4.2** began with the aldol reaction of the corresponding methyl ketone **1.10** and aldehyde **1.11** followed by the oxidation to form enolic diketone **1.12**. After formation of the dihydropyranone **1.13** under acidic conditions, the appropriate functionality of the tetrahydopyranyl fragment could be installed including the problematic C(8) triethylsilyloxy ether.

Scheme 4.2 De Brabander's synthesis of methyl ketal **4.2**



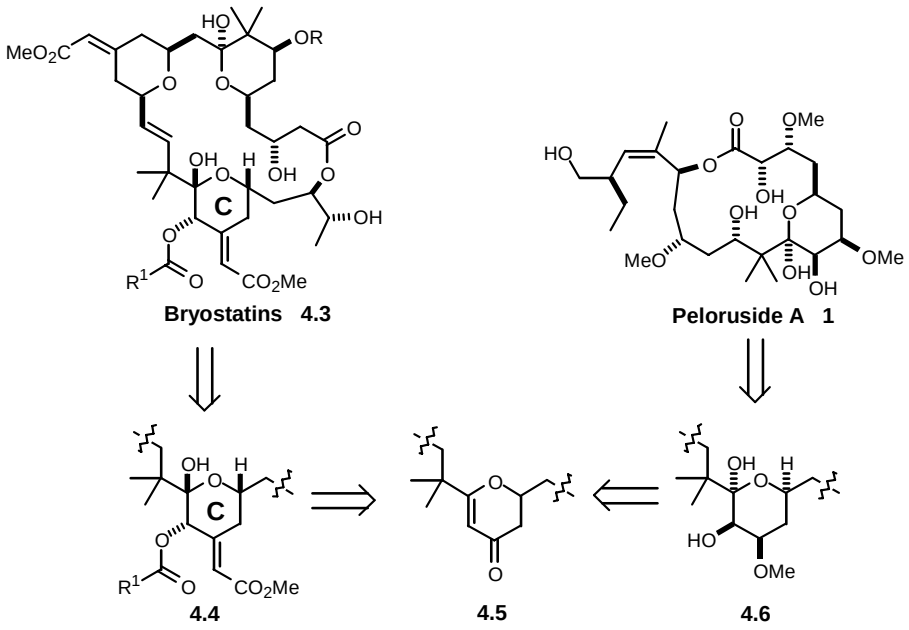
The Taylor total synthesis[13] (Scheme 4.3 Taylor's synthesis of pyranone) of peloruside A started with an aldol reaction between the methyl ketone **1.23**, containing the complete C(8)-C(19) carbon framework, and aldehyde **1.26** (i.e. the remaining C(1)-C(8) segment). After the oxidation, the *β*-diketone **1.27** was cyclized to the dihydropyranone **1.28** under mild acidic conditions. The densely functionalized tetrahydropyranyl segment was exposed after macrolactone **1.29** had been synthesized. The Taylor and De Brabander syntheses had demonstrated that the synthesis of the pyranoside could be completed through the pyranone intermediates **1.13** (in De Brabander's approach) and **1.28** (in Taylor's approach). However, to the best of our knowledge, there is no report on the synthesis of methyl ketal **4.1** with similar 1,5-*syn*-pentane interaction as in peloruside A.

Scheme 4.3 Taylor's synthesis of pyranone **1.28**



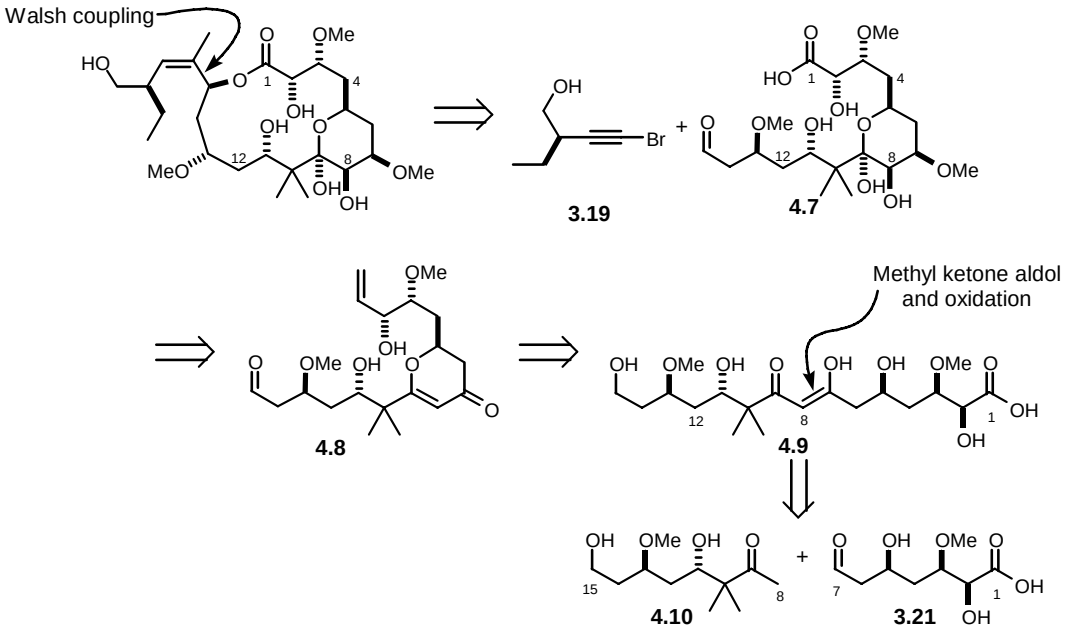
The bryostatin class of natural products offer a valid structural comparison to peloruside A because its C-ring which contains a similar 1,5-*syn*-pentane interaction (Scheme 4.4). In reviewing the bryostatin synthetic routes of Masamune,[76] Evans,[77] Wender[78] and Hale,[79] the functionalized pyranoside **4.4** arose from either the dihydropyran or the hydropyranone **4.5**. With the aforementioned 1,5-*syn* pentane structural similarities, it was not unexpected that the synthesis of the C-ring **4.4** in bryostatin or the pyranoside **4.6** in peloruside A have a similar synthetic intermediate **4.5**.

Scheme 4.4 Bryostatin structural similarities



On the basis of these considerations, a new retrosynthetic analysis for the synthesis of peloruside A via hydropyranone intermediate **4.8** is shown in Scheme 4.5. We envisioned that macrolactonization followed by the Walsh multicomponent coupling reaction with a bromoalkyne **3.19** would provide the aldehyde **4.7**. The densely functionalized pyranoside **4.7** could be derived from the hydropyranone **4.8**, which could be obtained from the *β*-diketone **4.9** under acidic dehydration conditions. The *β*-diketone **4.9** could be prepared from the methyl ketone **4.10** and the D-glucal derived aldehyde **3.21**.

Scheme 4.5 Retrosynthesis for peloruside A III

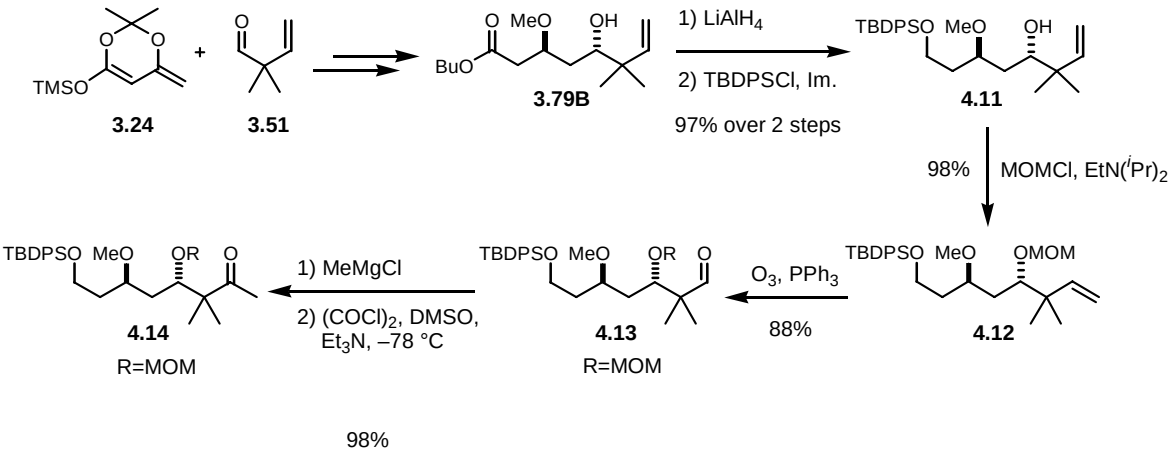


4.3 SYNTHESIS OF METHYL KETONE 4.14

Methyl ketone **4.14** could be obtained from a previously described reaction of **3.24** and **3.51** using the Carreira enantioselective aldol methodology (Table 3.3, entry 2). The synthesis of methyl ketone **4.14** is outlined in Scheme 4.6. The aldol product underwent *n*-butyl ester formation and subsequent regioselective methylation providing the *β*-methoxy ester **3.79B**. Reduction of **3.79B** with lithium aluminum hydride afforded the crude diol which was then regioselectively protected at the primary position with *tert*-butyl-di-phenyl chloride providing compound **4.11** (97% yield over two steps). The sterically hindered alcohol **4.11** was protected as a methoxymethoxy ether **4.12** (98% yield) and the terminal olefin was oxidatively cleaved by ozonolysis to afford aldehyde **4.13** in good yield (88%). In a two-step procedure, aldehyde **4.13** was converted to the methyl ketone **4.14** by methyl Grignard addition to aldehyde **4.13** followed by Swern oxidation of the inconsequential 1:1 mixture of diastereomers (98% yield over two

steps).[80] Overall, the methyl ketone **4.14** was prepared on multi-gram scale from trimethylsilyl dienolate in 10 steps and 23% yield.

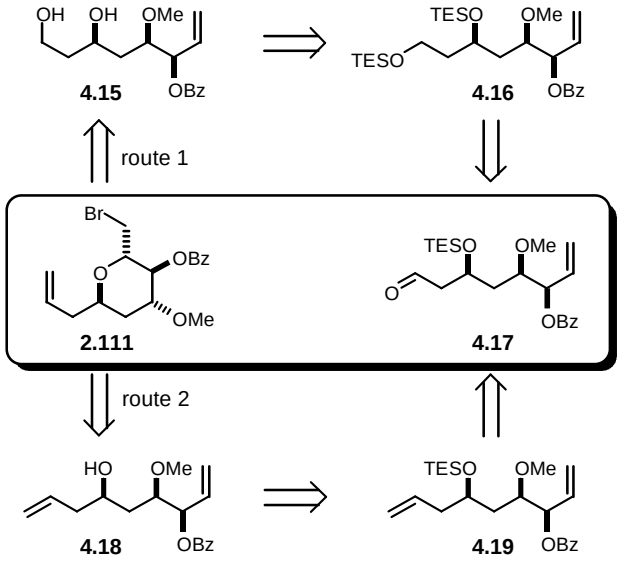
Scheme 4.6 Synthesis of methyl ketone **4.14**



4.4 SYNTHESIS OF ACYCLIC *B*-TRIETHYLSILOXY ALDEHYDE 4.17

With the methyl ketone **4.14** at hand, we envisioned that aldehyde **4.17** could be prepared from the olefin **2.11** by at least two possible routes (Scheme 4.7): (route 1) Selective oxidation of the terminal triethylsiloxy ether under Swern conditions or (route 2) Regioselective dihydroxylation of diene **4.19** followed by oxidative cleavage. We initially decided to pursue the selective oxidation route (route 1) mainly because of literature precedence.[81] For the dihydroxylation of diene **4.19** (route 2), the two terminal olefins differentiate somewhat electronicly (unsubstituted vs allylic deactivated), but the regioselectivity of the dihydroxylation of diene **4.19** had not been reported**.** Both routes will be discussed in more detail below.

Scheme 4.7 Retrosynthetic analysis of aldehyde **4.17**

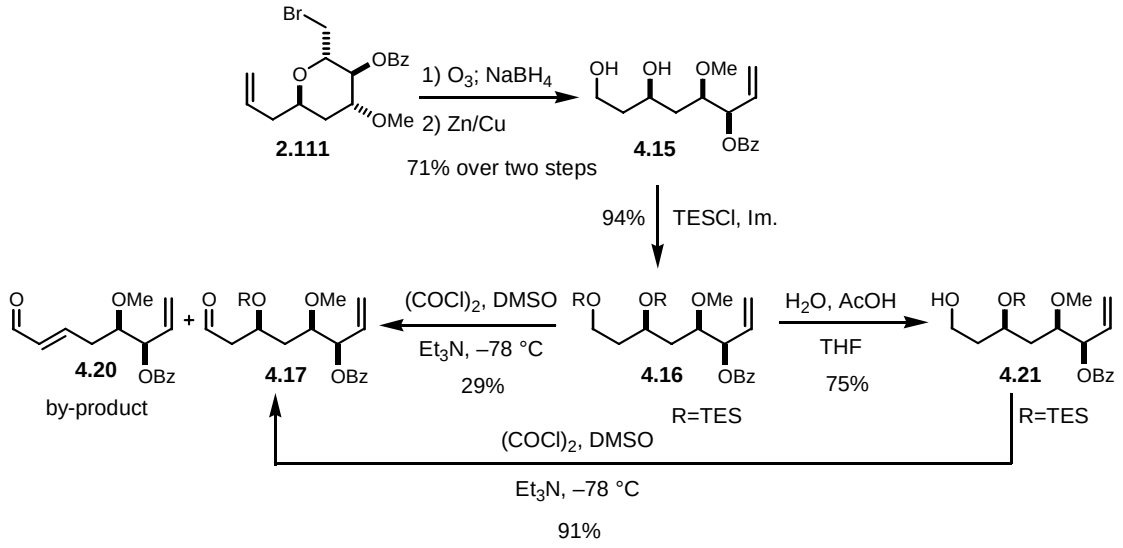


4.4.1 Aldehyde 4.17 Synthesis by Selective Oxidation of Primary Silylether 4.16

The synthesis of aldehyde **4.17** began with the oxidative cleavage of the terminal olefin **2.111** by ozonolysis followed by *in situ* reduction with $NaBH_4$ (Scheme 4.8).[82] The crude mixture from the reaction was subjected to Vasella ring-opening conditions affording diol **4.15** (71% overall yield over two steps). Protection of both hydroxyl groups as triethylsilyl ethers (TES) and a regioselective oxidation of the primary silyl ether under Swern conditions[81] gave the desired aldehyde **4.17** (29% yield) along with the α,β-unsaturated aldehyde **4.20** as the major by-product. It was found that extended reaction time and/or temperature changes did not improve the yield of aldehyde **4.17.** We therefore decided to settle for a two-step procedure. Under acidic conditions (H_2O:AcOH:THF) the bis-triethylsilyl ether **4.16** was regioselectively deprotected[83] to form the alcohol **4.21** which could be converted to aldehyde **4.17** by Swern oxidation. However, we thought this might not be an efficient route since the overall sequence required 5 steps from the advanced intermediate **2.11** and was accomplished in only 45%

yield. We decided to investigate the next route (Scheme 4.7, route 2) in the hope for a short and efficient synthesis toward the aldehyde **4.17**.

Scheme 4.8 Synthesis of aldehyde **4.17**

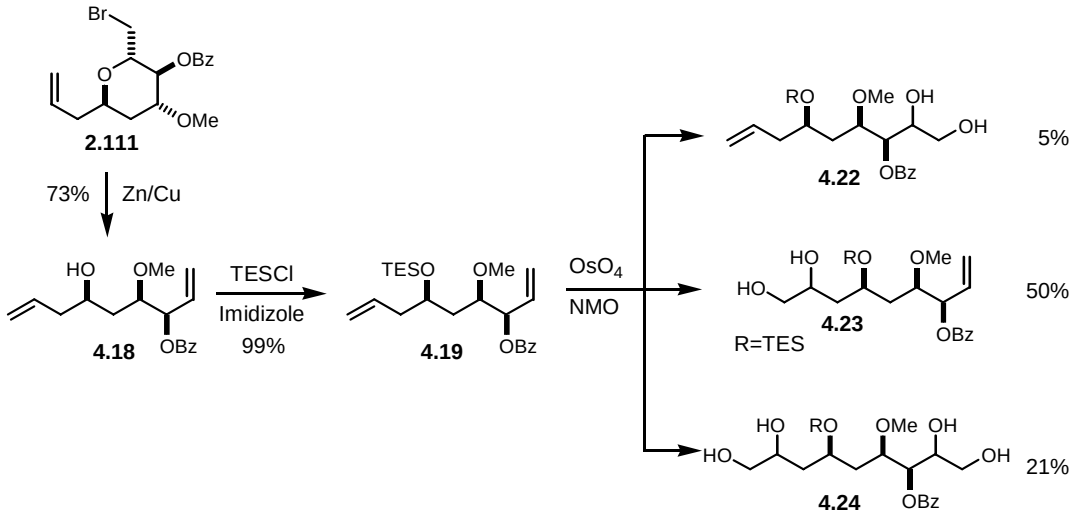


4.4.2 Aldehyde 4.17 Synthesis by Regioselective Dihydroxylation

Next, we studied the dihydroxylation reaction of **4.19** that should favor the most electron-rich olefin with the least surrounding steric environment (Scheme 4.9). The Vasella ring-opening of olefin **2.11** was converted into alcohol **4.18** (73% yield). After the alcohol was protected as the triethylsilyl ether, diene **4.19** was subjected to standard dihydroxylation conditions with osmium tetraoxide resulting in three regioisomeric products (**4.22**, **4.23** and **4.24**). The products **4.22** and **4.23**, both mixtures of diastereomers, were differentiated from one another by the ^{1}H NMR spectroscopy analysis. The global dihydroxylation product **4.24** was easily identified due to its considerably more polar R_f value on thin layer chromatography. While disappointed by the yield of the desired product **4.23** (50% yield), we were pleased to find that treatment of substrate **4.19** under dihydroxylation conditions did demonstrate regioselectivity in the

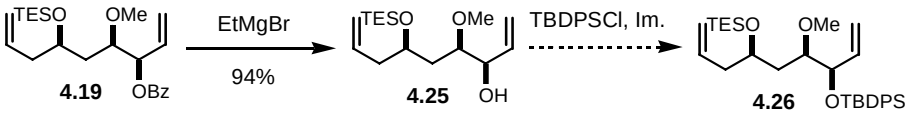
dihydroxylation. We therefore suggested that the regioselectivity could be substantially improved if the benzoate was replaced with a more sterically intrusive protecting group.

Scheme 4.9 Regioselective dihydroxylation of diene **4.19**



We initially envisioned that the appropriately protected diene **4.26** could be derived directly from the diene **4.19** (Scheme 4.10)**.** Selective benzoate deprotection of **4.19** using ethyl Grignard reagent[84] followed by the *tert*-butyl-di-phenysiloxy ether formation would provide the desired product **4.26**. However, it was found that although the deprotection of the benzoate provided alcohol **4.25** in 94% yield, the ether formation was complicated by substantial silyl migration. Therefore, we anticipated the installation of the bulky protecting group should be done at an earlier point in the synthesis.

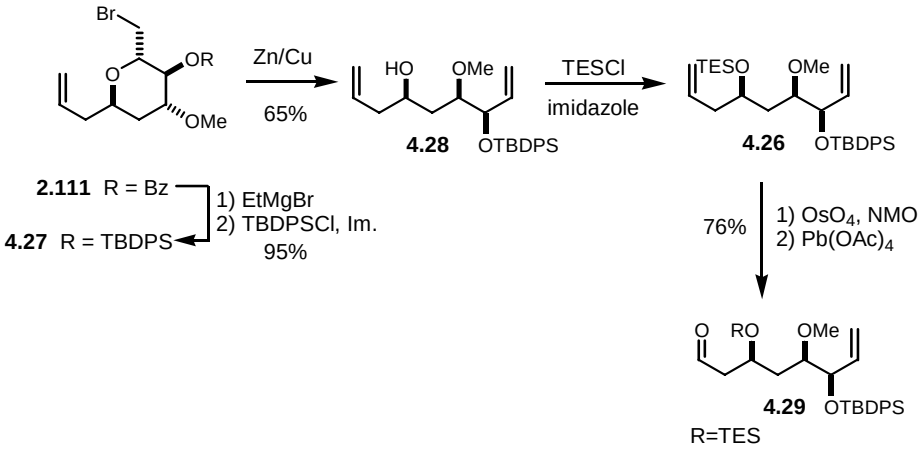
Scheme 4.10 Attempted synthesis of substrate **4.26**



The synthesis of diene **4.26** from olefin **2.111** began with the removal of the benzoate with ethyl Grignard reagent and subsequent *tert*-butyl-diphenylsilyloxy ether formation gave diene **4.27** (95% yield over two steps, Scheme 4.11). After the Vasella

ring-opening with zinc-copper couple (65% yield), triethylsilyloxy ether formation provided the fully protected diene **4.26**. The dihydroxylation reaction of diene **4.26** provided only one regioisomer as an inconsequential mixture of diastereomers, which was oxidatively cleaved with lead tetraacetate to obtain aldehyde **4.29** (76% overall yield from diene **4.26**).

Scheme 4.11 Preparation of aldehyde **4.29**



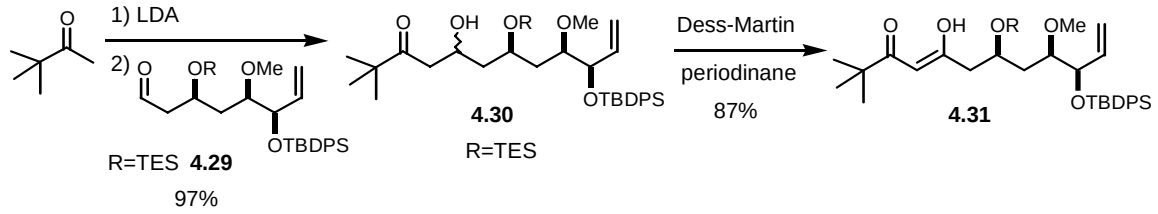
It is noteworthy to mention that the dihydroxylation/ oxidative cleavage protocol of diene **4.26** with sodium periodate resulted in low yield of aldehyde **4.29**. This was due to a significant silyl deprotection which has been observed by others.[85] We had access to aldehyde **4.29** in 6 steps and 47% overall yield from olefin **2.111**. Although the total steps and overall yields are similar, synthetic route two (Scheme 4.11) was better than one (Scheme 4.8) because the benzoate ester had been replaced by a TBDPS ether, which will prove beneficial later in the synthesis.

4.5 A SYNTHESIS OF THE MODEL PYRANOSIDE 4.34

Once the aldehyde **4.29** had been prepared (Scheme 4.11), to insure the applicability the pyranone strategy, we turned our attention to the synthesis of the model pyranoside **4.34** (Scheme 4.13). The synthesis began with an aldol reaction of aldehyde

4.29 and pinacolone, a good mimic of ketone **4.14**, to afford the *β*-hydroxyketone **4.30** (97% yield).

Scheme 4.12 Synthesis of *β*-diketone **4.31**

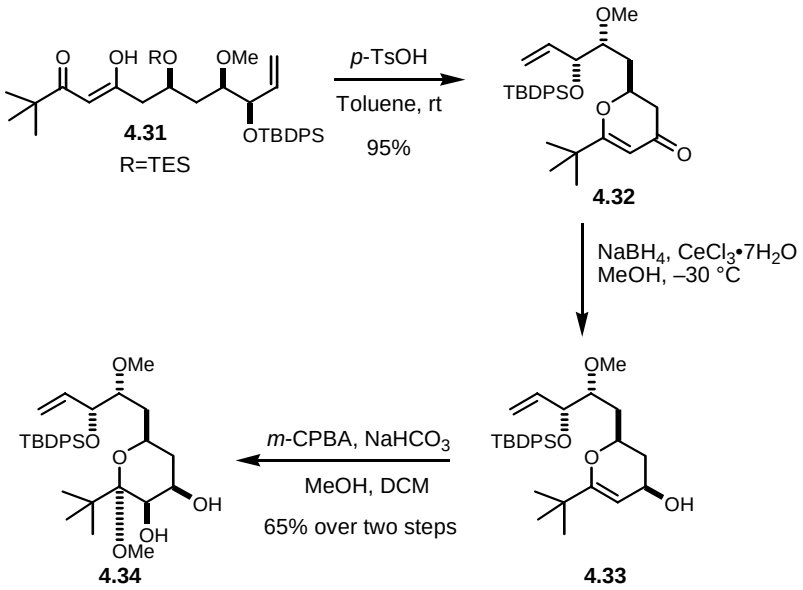


Several methods for the oxidation of the *β*-hydroxy ketone **4.30** to diketone **4.31** were investigated in the course of this project. Oxidation with PCC cleanly gave one product (TLC), but only in 38% isolated yield. It was found that oxidation of the *β*-hydroxy ketone **4.30** with Swern conditions provide diketone **4.31** in irreproducibly moderate yields (~50% yield), but optimal results were obtained with standard Dess-Martin conditions (85% yield over two steps).[86] However, reproducing the reaction efficiently became problematic at (5 mmol) and isolated yields dropped to only 33% yield. Heathcock[87] reported the oxidation of a *β*-hydroxy ketone in the synthesis of spongistatins, where he noted that oxidation with Swern, PCC, PDC, TPAP and standard Dess-Martin conditions give inferior yields to an optimized Dess-Martin procedure containing water (1.5 equivalents of each). He describes the appearance of a white precipitate, possibly an iodine (III) species, coincided with higher product yields. The iodine (III) species, if it was to remain in solution, would oxidize the *β*-diketone **4.31** in a deleterious manner, which has been reported.[88] In accord with Heathcock's observations, his protocol reproducibly gave enolic diketone **4.31** (80-87% yield). It was suggested that during small scale Dess-Martin oxidations inadvertent amounts of water resulted in the precipitation of the iodine (III) species, but with gram scale oxidations, not nearly

enough water was present for the iodine (III) species to precipitate out of solution, thus the need for water as an additive.

Continuing with the synthesis of pyranoside **4.34**, dehydration of the enolic diketone **4.31** under acidic conditions provided hydropyranone **4.32** in 95% yield (Scheme 4.13). A two-step transformation to diol **4.34** began with a diastereoselective Luche reduction,[89] which De Brabander reported must be done at –30 °C to prevent product decomposition. The crude allylic alcohol **4.33** was isolated and immediately subjected to hydroxy-directed epoxidation with pure *m*-CPBA[90] followed by methanolysis of the glycal-epoxide intermediate to form methyl ketal **4.34** (65 % yield from **4.32**).

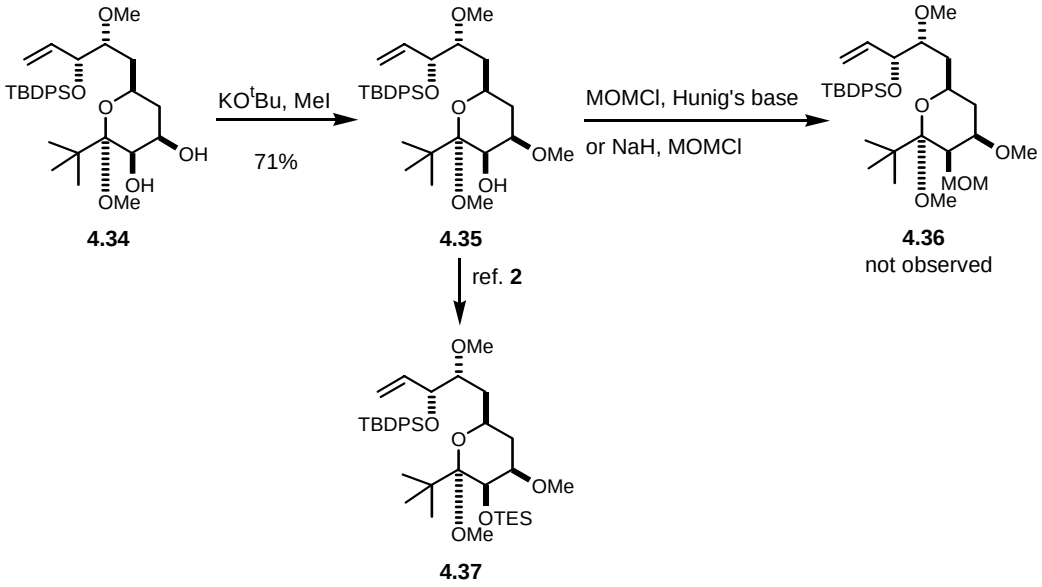
Scheme 4.13 Synthesis of model pyranoside **4.34**



With the pyranoside connectivity established, sequential methylation and protection of the corresponding alcohol needed to be addressed (Scheme 4.14). The methylation of the equatorial hydroxyl group attempted with Meerwein's salt and 2,6-di-*tert*-butyl-4-methylpyridine provided compound **4.35**, but the superior method for

methylation (KO^{t}Bu, MeI) afforded methyl ether **4.35** in 71% yield based on recovered starting material. After experiencing the difficulty of protecting the alcohol next to the geminal methyls, we felt that the protecting group could not be massive in size and had to be acid labile for the final global deprotection. Therefore, we selected a MOM protecting group, but the sterically hindered axial alcohol was unreactive with MOMCl and Hunig's base, and under forcing conditions (MOMCl, NaH), decomposition of starting material resulted. With these difficulties, TESOTf and pyridine was expected to provide the triethyl silyl ether **4.37** as had been reported by De Brabander et al.[2]

Scheme 4.14 Selective methylation and global protection of diol **4.34**

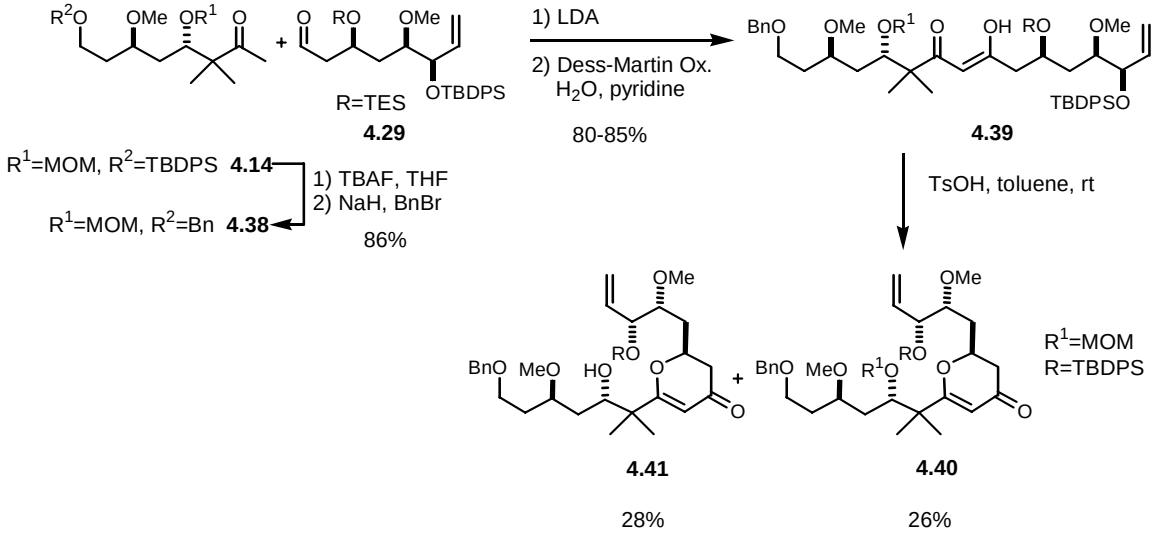


4.6 SYNTHESIS OF THE PELORUSIDE A PYRANONE

In our synthesis of peloruside A, ketone **4.14** and aldehyde **4.29** were applied to the formation of the dihydropyranone **4.40** (Scheme 4.15). Prior to the aldol reaction, the TBDPS ether was removed and the alcohol was protected as benzyl ether (86% over two steps). Aldol reaction between aldehyde **4.29** and methyl ketone **4.14** provided an

inconsequential 1:1 mixture of β-hydroxy ketone diastereomers that were oxidized with the Heathcock modified Dess-Martin oxidation affording the β-diketone **4.39** (85% yield from **4.38**). Treatment of the β-diketone **4.39** with p-TsOH did not proceed smoothly to the desired pyranone **4.40**, but gave a mixture of products, two of which where the desired product **4.40** (26% yield) and the deprotected MOM ether product **4.41** (28% yield). Taylor reported that heating the dehydration product to 45 °C for 2.5 hours resulted in 60% yield,[13] but in our hands the pyranones **4.41** and **4.40** were obtained in a 4:1 mixture favoring the deprotected product **4.41** (48% yield).

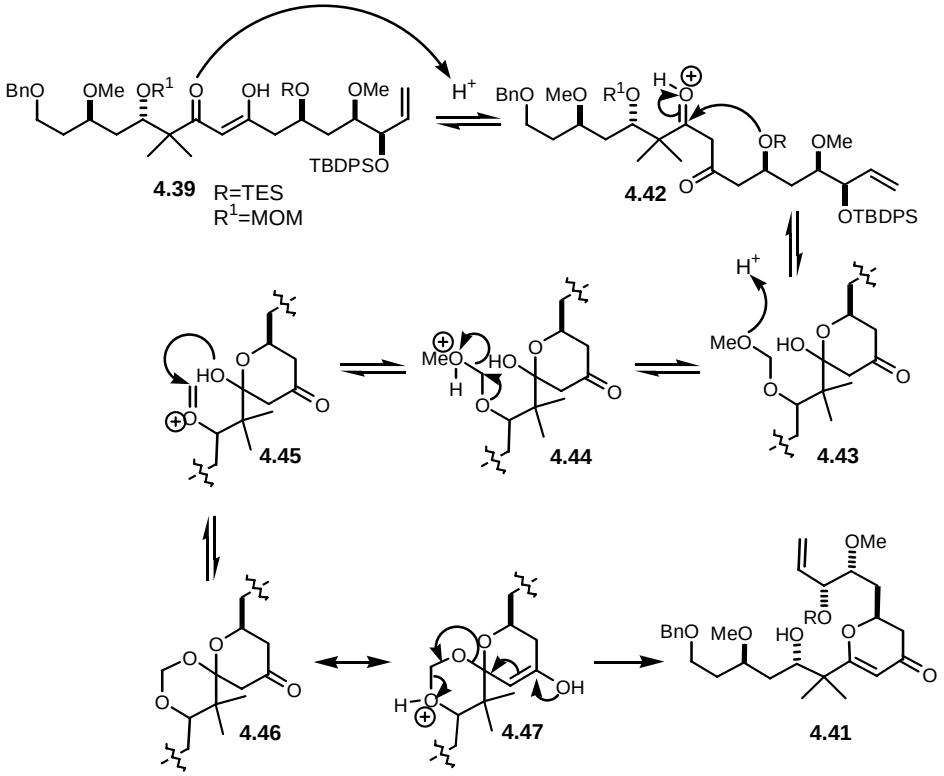
Scheme 4.15 Synthesis of pyranone **4.40**



We did not anticipate the intramolecular promoted deprotection of the MOM ether, but it is certainly feasible (Scheme 4.16). After protonation of the carbonyl group, the hemiketal **4.43** is obtained and the methoxy group can be protonated as in intermediate **4.44**. An intramolecular assisted elimination of methanol affords the oxonium ion **4.45** that is trapped with the hydroxyl group of the hemiketal. After tautamerization to form the enol **4.47**, a cascade elimination of the ketal provides the pyranone **4.41** with the free

alcohol. Due to this unanticipated transformation reevaluation of the protecting group strategy in the synthesis of peloruside A is necessary.

Scheme 4.16 Mechanism of intramolecular deprotection product **4.41**

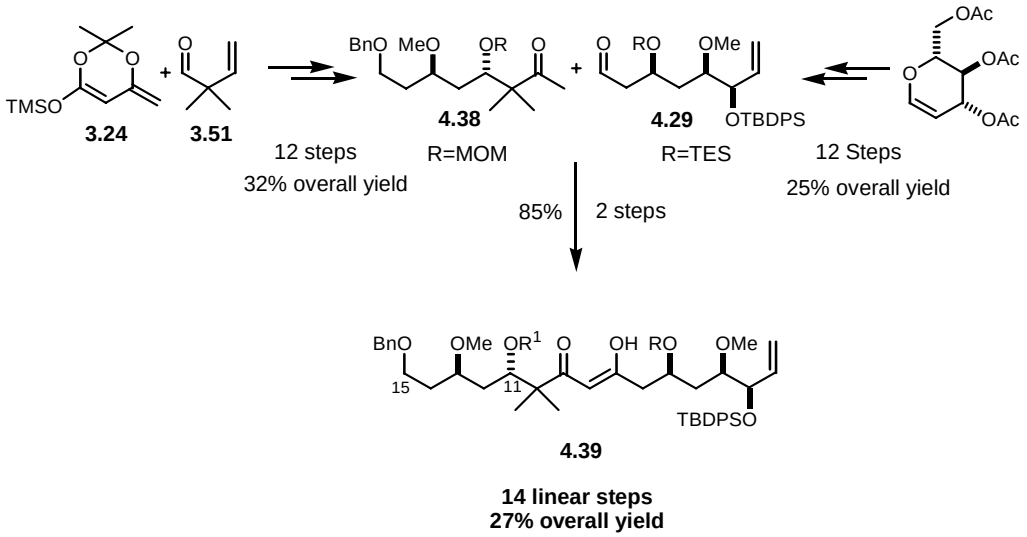


4.7 CONCLUSIONS

Although the total synthesis of peloruside A was unable to be completed at this point, these efforts have contributed to the syntheses of several useful building blocks (Scheme 4.17). As a result, the convergent synthesis to the *β*-diketone **4.39** has been achieved in an efficient 27% yield from aldehyde **4.29** and methyl ketone **4.38**. Aldehyde **4.29** was prepared from D-glucal in 12 linear steps (25% overall yield) and is conducive to large scale preparation. Methyl ketone **4.38** has been synthesized in 12 linear steps (32% overall yield) using as the key step, the Carreira enantioselective chiral copper enolate addition to aldehyde **3.51**. After an aldol coupling reaction of fragment

4.38 and **4.29**, and subsequent Heathcock modified Dess-Martin oxidation, *β*-diketone **4.39** has been obtained in a concise diastereoselective sequence.

Scheme 4.17 A summary of synthetic approaches



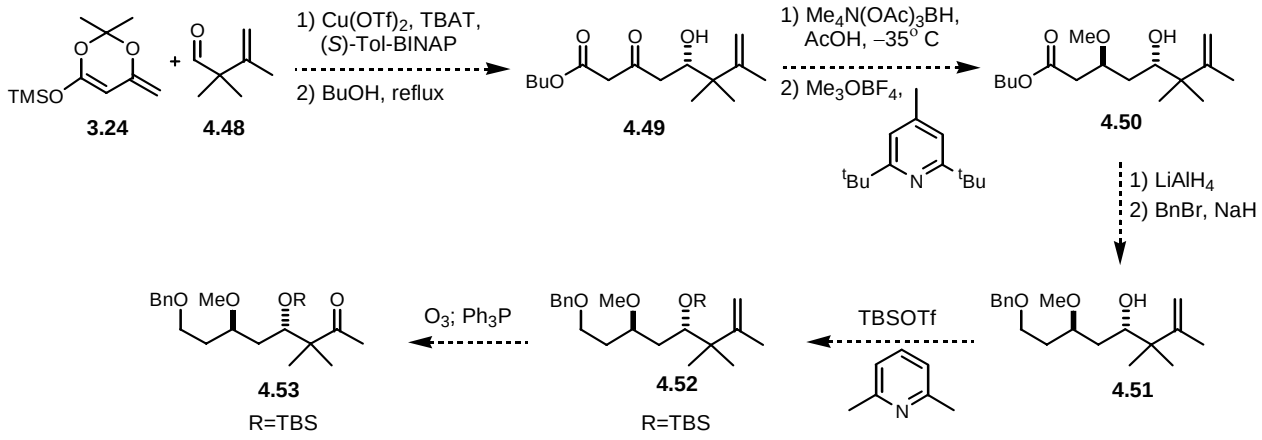
4.8 PROPOSED FUTURE SYNTHESIS

4.8.1 The Synthesis of Methyl Ketone 4.53

Although the synthesis of methyl ketone **4.38** (Scheme 4.15) was efficient, it could be prepared in fewer steps using aldehyde **4.48** (Scheme 4.18). Implementation of the disubstituted olefin **4.48** could help to eliminate the three step conversion of a terminal olefin **4.12** to the methyl ketone **4.14** in the previous synthesis (Scheme 4.6). After formation of the butyl ester **4.49**, reduction ($Me_4N(OAc)_3BH$, AcOH) and regioselective methylation would provide *β*-methoxy ester **4.50**. After reduction of the ester and benzylation of the primary alcohol, the remaining free alcohol can be protected (TBSOTf, 2,6-lutidene). It is worth mentioning the selection of this protecting group has a profound impact on the pyranone formation, as a migratory prone protecting group (Scheme 4.15, MOM ether) resulted in low yields. The TBS ether should not participate

in the intramolecular migration and can be globally deprotected in the final step of the synthesis. The methyl ketone **4.53** can be obtained from ozonolytic cleavage of the olefin. These minor adjustments will provide not only a shorter synthetic route of methyl ketone **4.53** (from 12 steps to 8 steps) but also address the protecting group difficulties in the pyranone formation.

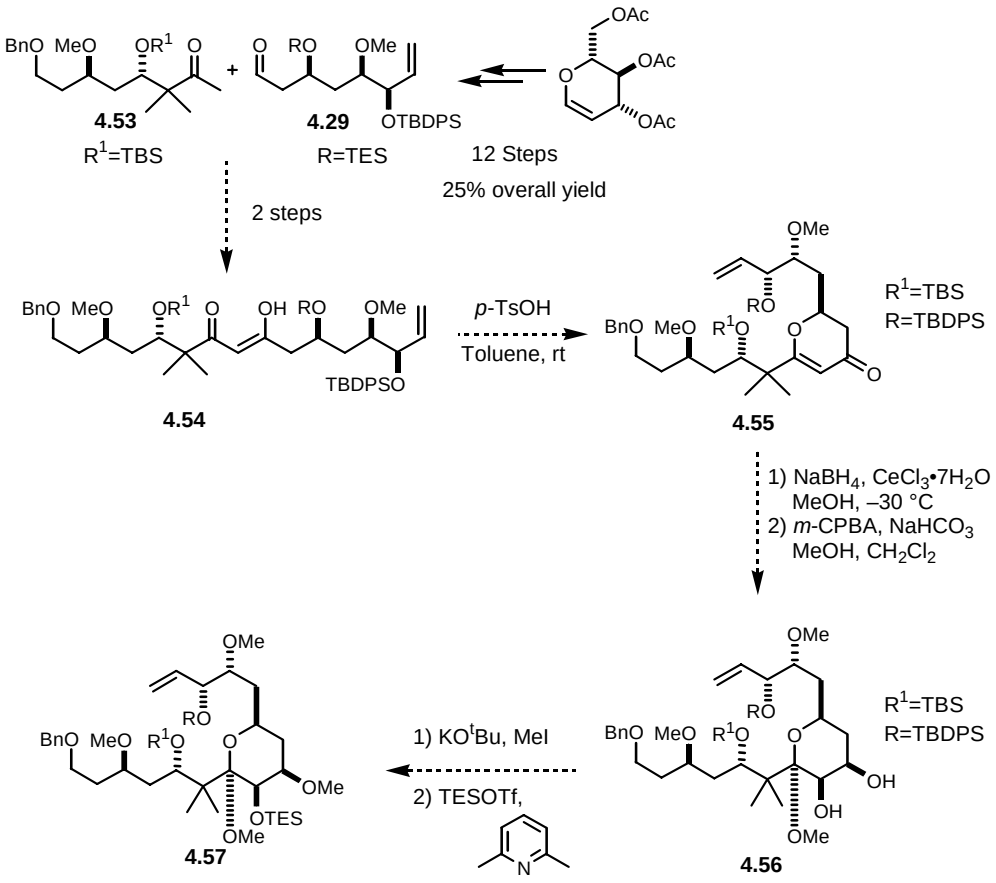
Scheme 4.18 Synthesis of methyl ketone **4.53**



4.8.2 Synthesis of the Pyranoside 4.57

With the methyl ketone **4.53** and aldehyde **4.29** derived from D-glucal at hand, the synthetic sequence similar to the model synthesis (Scheme 4.13) can be used to obtain the densely functionalized pyranoside **4.57** (Scheme 4.19). After the methyl ketone aldol and the enolic ketone **4.54** with the Heathcock modified Dess Martin,[87] the pyranone **4.55** can be obtained by dehydration conditions (*p*-TsOH, toluene, rt). Luche reduction[89] of the pyranone **4.55** and subsequent epoxidation and methyl ketal formation will afford **4.56**. Regioselective methylation of the diol and formation of the TES ether provides the fully protected C(1)-C(15) carbon segment **4.57** in 19 linear steps from D-glucal.

Scheme 4.19 Synthesis of pyranoside **4.57**

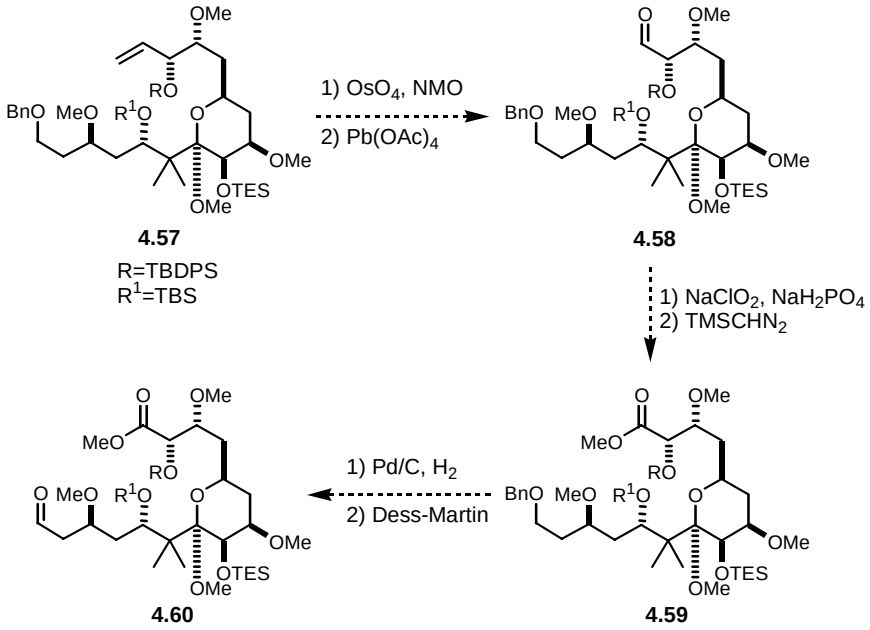


4.8.3 Synthesis of Methyl Ester 4.60

After the conversion of the benzyl ether and the terminal olefin to an aldehyde and a methyl ester (Scheme 4.20), respectively, the Walsh coupling reaction will provide the complete carbon framework. The synthesis of the methyl ester **4.60** would begin with dihydroxylation (OsO_4, NMO) of olefin **4.57** and subsequent oxidative cleavage ($Pb(OAc)_4$) to provide aldehyde **4.58**. The aldehyde can be oxidized to the carboxylic acid ($NaClO_2$, NaH_2PO_4) and immediate formation of the methyl ester **4.59**. After deprotection of the benzyl ether under hydrogenation conditions, the aldehyde **4.60** can be obtained by Dess-Martin oxidation. After 25 linear steps, a fully protected aldehyde is

obtained that is suitable for coupling with the vinyl zinc reagent formed by the Walsh coupling method.

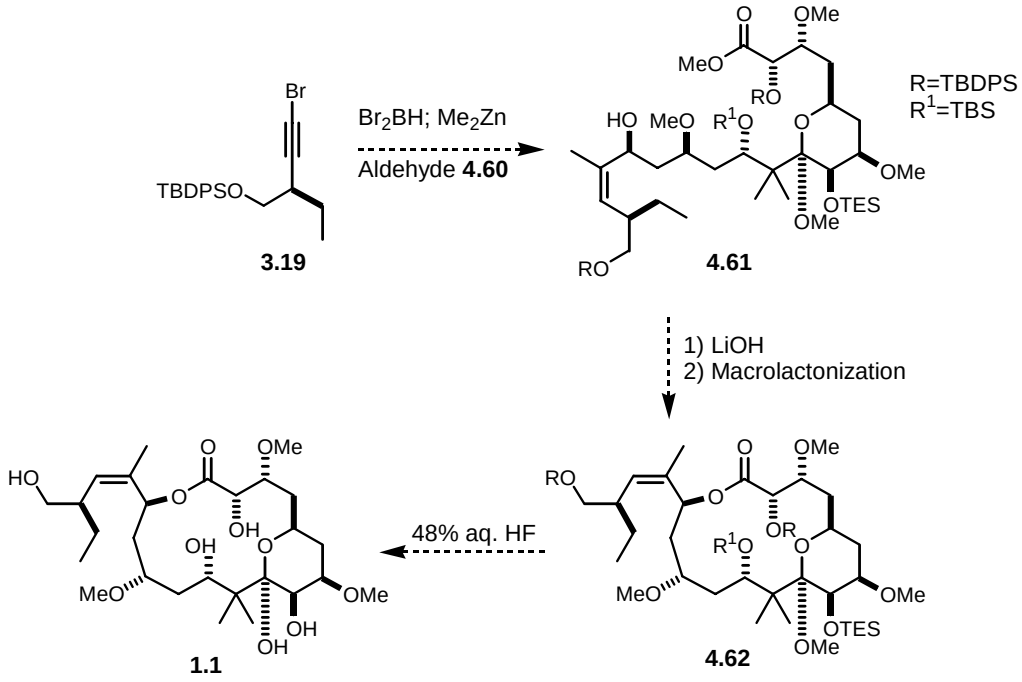
Scheme 4.20 Synthesis of methyl ester **4.60**



4.8.4 Completion of Peloruside A

The Walsh coupling reaction with bromoalkyne **3.19** and aldehyde **4.60** will provide allylic alcohol **4.61** (Scheme 4.21). After methyl ester hydrolysis, macrolactone synthesis can be achieved by either a Yamaguchi protocol or a Mitsunobu-type method affording desired macrolactone **4.62**. Global deprotection with HF (48% aq. solution) should provide sufficient quantities of peloruside A **1.1** in 29 linear steps.

Scheme 4.21 Total synthesis of peloruside A



Chapter 5: Experimental Procedures

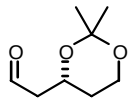
5.1 General Procedures

All reactions were conducted under argon atmosphere unless otherwise indicated. Flasks were oven or flame-dried and allowed to cool in a dessicator prior to use. Solvents and reagents were purified by standard methods.[91] Toluene, benzene, $CHCl_3$, CH_2Cl_2, CH_3NO_2 and CH_3CN were purified by distillation from CaH_2 under argon atmosphere prior to use. THF and Et_2O were purified by distillation from Na metal with benzophenone indicator. Analytical thin-layered chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The plates were visualized by staining with $KMnO_4$ or CAM.[92] Liquid chromatography was performed by using forced flow (flash chromatography) on EM Reagents silica gel 60 (230-400 mesh). Organolithium reagents (i.e. *n*-butyllithium) were titrated by the Suffert method.[93]

HRMS (CI) were determined with a VG analytical ZAB2-E instrument. ^1H and ^{13}C were recorded on Bruker AM-250, Varian Unity Plus 300, Varian INOVA 400 or 500 spectrometer at ambient temperature. NOE differences were determined using a double pulsed field gradient spin echo sequence (mixing time = 800 msec) and values are reported adjacent to the enhanced hydrogen(s). Infrared spectra were obtained on a Nicolet AVATAR 360 FTIR. Where appropriate, descriptions of signals include broad (br), apparent (app) and multiplet (m). Enantiomeric excess was determined by chiral HPLC with (*S,S*)-Poly Whelk-01 column, Chiralpak AD, and Chiralcel OD columns (particle size: 5.0 μm; column dimensions: 250 × 4.6 mm).

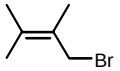
LDA•THF complex was prepared by dropwise addition of *n*-BuLi solution (22 mL, 2.25 M in hexanes, 50 mmol) to a solution of *N*, *N*-diisopropylamine (7.7 mL, 55 mmol) in THF (50 mL) at –5 °C. The solution was stirred for 15 min and allowed to

warm to 0 °C. The complex was prepared and used immediately. Note that titration of *n*-BuLi was accomplished using the method of Suffert.[93]



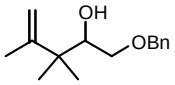
2.59

[(4*R*)-2,2-Dimethyl-1,3-dioxan-4-yl]acetaldehyde (2.59). The title compound was prepared according to the literature procedure: R_f 0.35 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.5 Hz, 1H), 4.40 (dddd, *J* = 11.4, 5.3, 3.0 Hz, 1H), 3.98 (ddd, *J* = 12.1, 12.1, 3.0 Hz, 1H), 3.81 (ddd, *J* = 12.0, 5.4, 1.5 Hz, 1H), 2.60 (ddd, *J* = 16.7, 7.1, 2.2 Hz, 1H), 2.44 (ddd, *J* = 16.7, 5.1, 1.2 Hz, 1H), 1.63 (dddd, *J* = 12.7, 12.7, 12.7, 5.4 Hz, 1H), 1.52-1.49 (m, 1H), 1.44 (s, 3H), 1.33 (s, 3H).[94]



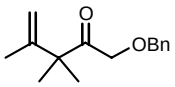
2.70

1-Bromo-2,3-dimethyl-2-butene (2.70). To a 500-mL round bottom flask fitted with a reflux condenser was added *N*-bromosuccinimide (42.4 g, 238 mmol), 2,3-dimethyl-2-butene (35.2 mL, 293 mmol) and CCl_4 (185 mL) at rt. Benzoyl peroxide initiator (213 mg, 0.88 mmol) was added and the reaction heated to reflux. After 4 h, the orange reaction mixture was cooled to rt, filtered through Celite to remove insoluble succinimide and concentrated *in vacuo*. The residue was cooled (–78 °C) and purified by vacuum transfer (0.5 mmHg) to a –78°C receiving flask. The resulting oil was further purified by distillation (26 mmHg, 55-57°C) to provide a clear oil (24.0 g, 50%): ^{1}H NMR (250 MHz, $CDCl_3$) δ3.99 (s, 2H), 1.77 (br s, 6H), 1.71 (s, 3H).[95]



2.71

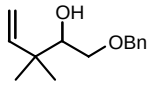
1-(Benzyloxy)-3,3,4-trimethylpent-4-en-2-ol (2.71). To a stirred suspension of $SnCl_2$•$2H_2O$ (26.2 g, 116 mmol), 1-bromo-2,3-dimethyl-2-butene **2.70** (13.9 g, 85 mmol) and 2-benzyloxyacetaldehyde (11.6 g, 78 mmol) in DMF (155 mL) at 0°C was added sodium iodide (17.4 g, 116 mmol). After 10 min, the cold bath was removed and after 16 h, an aqueous ammonium bifluoride solution (30%, 750 mL) was added. After 30 min the solution was extracted with Et_2O (3 × 50 mL) and the combined organic fractions were washed with brine (30 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (7:1 hexanes/EtOAc) provided alcohol **2.71** as a pale yellow oil (13.41 g, 73%): R_f 0.59 (50% EtOAc/hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 4.83 (app p, *J* = 1.3 Hz, 1H), 4.81-4.79 (m, 1H), 4.54 (s, 2H), 3.83 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.54 (dd, *J* = 9.5, 2.4 Hz, 1H), 3.35 (dd, *J* = 9.5, 8.8 Hz, 1H), 2.30 (br s, 1H, O*H*), 1.76 (s, 3H), 1.09 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.4, 138.0, 128.4, 127.6, 127.5, 111.2, 74.4, 73.3, 71.6, 41.8, 23.3, 21.9, 19.8; IR (thin film) ν 3468 (br), 3082-2862, 1080 cm^{-1}; HRMS *m/z* 235.1698 (calcd for $C_{15}H_{22}O_2$ $[M+H]^+$, 235.1698).



2.72

1-(Benzyloxy)-3,3,4-trimethylpent-4-en-2-one (2.72). A 500-mL flame dried three-necked flask, fitted with a low temperature thermometer and an addition funnel, was charged with DMSO (8.0 mL, 112 mmol) dissolved in CH_2Cl_2 (150 mL). The solution was cooled to –78°C and then oxalyl chloride (6.0 mL, 68.6 mmol) in CH_2Cl_2 (75 mL) was added dropwise over 1 h. After the addition was completed, alcohol **2.71** (10.7 g,

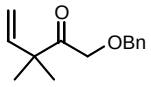
45.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. After 1 h at –78°C, Et_3N (25.5 mL, 183 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the cold bath was removed. After 3 h, the reaction mixture was added to deionized H_2O (300 mL). After extracting the mixture with CH_2Cl_2 (3 × 75 mL), the combined organic layers were washed with H_2O (2 × 50 mL), brine (50 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (elution gradient: 4%–10%EtOAc/hexanes) provided ketone **2.72** as a pale yellow oil (10.15 g, 95%): R_f 0.65 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30-7.32 (m, 5H), 4.90 (d, J = 4.2 Hz, 2H), 4.53 (s, 2H), 4.22 (s, 2H), 1.63 (s, 3H), 1.21 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 209.4, 147.0, 137.3, 128.3, 127.8, 127.7, 112.2, 72.9, 70.1, 51.9, 23.2, 20.0; IR (thin film) ν 3096-2875, 1722, 1131, 1038 cm^{-1}; HRMS *m/z* 233.1531 (calcd for $C_{15}H_{20}O_2$ $[M+H]^+$, 233.1542).



2.73

1-(Benzyloxy)-3,3-dimethylpent-4-en-2-ol (2.73). To a stirred suspension of $SnCl_2$•$2H_2O$ (9.8 g, 43.7 mmol), 1-chloro-3-methyl-2-butene (3.61 g, 32.1 mmol) and 2-benzyloxyacetaldehyde (4.37 g, 29.1 mmol) in DMF (60 mL) at 0°C was added sodium iodide (6.6 g, 43.7 mmol). After 10 min, the cold bath was removed. After 16 h, a 30% aqueous ammonium bifluoride solution (100 mL) was added followed by the addition of diethyl ether (200 mL). After 30 min, the organic layer was separated and the aqueous solution was extracted with Et_2O (3 × 50 mL) and the combined organic fractions were washed with brine (100 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (10% hexanes/EtOAc) provided alcohol **2.73** as a pale yellow oil (5.05 g, 79%): R_f 0.40 (33% EtOAc/hexanes).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 5.85 (dd, *J* = 16.7, 11.5 Hz, 1H), 5.02 (s, 1H), 4.96 (d, *J* = 7.0 Hz, 1H), 4.51 (s, 2H), 3.57 (d, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 9.8 Hz, 1H), 2.41 (d, *J* = 2.3 Hz, 1H), 1.01 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.6, 137.9, 128.3, 127.6, 127.5, 112.4, 73.2, 71.4, 39.6, 23.3, 22.6; IR (thin film) ν 3480 (br), 3089-2864, 1458, 1112, 999, 913, 742 cm^{-1}; HRMS *m/z* 221.1541 (calcd for $C_{14}H_{21}O_2$ $[M+H]^+$, 221.1542).



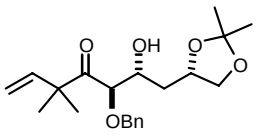
2.74

1-(Benzyloxy)-3,3-dimethylpent-4-en-2-one (2.74). A 500-mL flame dried three-necked flask, fitted with a low temperature thermometer and an addition funnel, was charged with DMSO (3.7 mL, 52.1 mmol) dissolved in CH_2Cl_2 (50 mL). The solution was cooled to –78°C and then a solution of oxalyl chloride (2.72 mL, 31.2 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 1 h. After the addition was completed, alcohol **2.73** (4.58 g, 20.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise over 30 min. After 1 h at –78°C, Et_3N (15.7 mL, 113 mmol) in CH_2Cl_2 (50 mL) was added dropwise and after an additional 30 min, the cold bath was removed. After 2 h, the reaction mixture was added to deionized H_2O (100 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL) and the combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 12% EtOAc/hexanes as elution provided ketone **2.74** as a pale yellow oil (4.50 g, 99%): R_f 0.42 (33% EtOAc/hexanes). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33-7.23 (m, 5H), 5.85 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 4.53 (s, 2H), 4.25 (s,

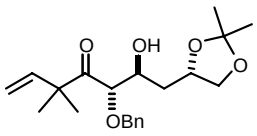
2H), 1.20 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 208.9, 141.5, 137.3, 128.3, 127.8, 127.7, 114.8, 72.9, 70.9, 49.2, 23.3.

5.1.1 General procedure for Boron Mediated Aldol

To a flame dried 25 mL round bottom flask charged with ketone **2.73** (1.0 mmol) in anhydrous Et_2O (4 mL) and fitted with a reflux condenser, was added dropwise Et_3N (1.5 mmol) followed by Cy_2BCl (1.2 mmol). After the solution was heated at reflux for 1.5 h, it was cooled to –78°C and a solution of aldehyde (1.5 mmol) in Et_2O (1 mL) was added. After 1.5 h, a solution of MeOH:30% H_2O_2:pH 7 buffer (5:1:1, v/v) was added and the cold bath was removed. After 1 h, deionized H_2O (3 mL) was added and the solution extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (2 × 5 mL) and dried (Na_2SO_4). Filtration through Celite and concentration *in vacuo* supplied the crude products as a pale yellow oil which purified by flash chromatography on silica gel with EtOAc/hexanes as elution gave the desired product.



2.78

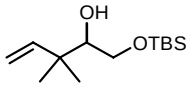


2.79

(5*R*, 6*R*)-5-Benzyloxy-7-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.78) and (5*S*, 6*S*)-5-Benzyloxy-7-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.79). The title compound was prepared according to the general procedure described above. Purification by flash chromatography on silica gel with EtOAc/hexanes for elution gave the desired product provided β-alcohol **2.78** (292 mg, 79%) and diastereoisomer **2.79** (49 mg, 16%) as colorless oils.

2.78: R_f 0.50 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.22 (m, 5H), 5.95 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.16 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.14 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.35 (d, *J* = 5.5 Hz, 1H), 4.19 (dddd, *J* = 13.0, 9.5, 6.0, 3.5 Hz, 1H), 4.06 (dddd, *J* = 5.0, 5.0, 3.0, 3.0 Hz, 1H), 4.02 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.50 (dd, *J* = 8.0, 7.0 Hz, 1H), 3.27 (d, *J* = 3.0 Hz, 1H), 1.85 (ddd, *J* = 14.5, 6.0, 2.0 Hz, 1H), 1.71 (ddd, *J* = 14.5, 9.5, 9.5 Hz, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 141.7, 137.5, 128.2, 127.7 (2C), 114.7, 109.2, 81.8, 75.6, 72.3, 71.7, 69.5, 50.5, 35.5, 26.7, 25.6, 23.5, 23.3; IR (thin film) ν 3508 3031, 2984, 2934, 1712, 1455, 1371, 1215, 1069, 920, 738, 699 cm^{-1}.

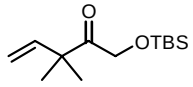
2.79: R_f 0.45 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 5.91 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 5.17 (d, *J* = 17.7 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.42 (d, *J* = 4.7 Hz, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 4.31-4.10 (m, 2H), 4.00 (dd, *J* = 6.0, 8.0 Hz, 1H), 3.48 (ddd, *J* = 10.6, 7.8, 7.8 Hz, 1H), 2.64 (d, *J* = 8.0 Hz, 1H), 1.78-1.57 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.1, 141.4, 137.3, 128.4, 128.0, 115.3, 108.8, 82.1, 73.3, 72.1, 69.4, 68.9, 50.5, 35.5, 26.9, 25.6, 23.8, 23.3.



2.76A

1-(*tert*-Butyl-dimethylsilanyloxy)-4,4-dimethylhex-5-en-3-ol (2.76A). Prenyl chloride (0.1 mL, 0.89 mmol) was added to a suspension of Mg turnings (2.00 g, 82.4 mmol) in THF (20 mL) containing one crystal of I_2. Upon initiation and decolorization of the solution, the flask was cooled to –40°C and the remaining prenyl chloride (3.0 ml, 26.6 mmol) in THF (20 mL) was added dropwise over 2 h. After that time, the mixture was

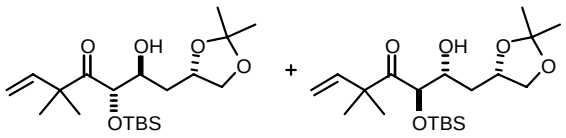
warmed to 22°C for a further 1 h. A solution of *tert*-butyl-dimethyl silyloxy acetaldehyde (4.00 g, 22.9 mmol) in THF (20 mL) was added over 5 min. An exotherm was noted as the addition took place. The mixture was stirred for 2 h before the reaction was quenched by addition of saturated solution NH_4Cl (20 mL). The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic fractions were washed with H_2O (10 mL), brine (10 mL) and then dried ($MgSO_4$). Filtration through Celite and concentration *in vacuo* supplied the crude products as a yellow oil. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes as elution provided a pale yellow oil (3.14 g, 56%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 18.4, 10.0 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 4.96 (d, *J* = 18.4 Hz, 1H), 3.66-3.62 (m, 1H), 3.45-3.37 (m, 2H), 1.02 (s, 6H), 0.87 (s, 1H), 0.04 (s, 6H), No ROH found; ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.9, 112.2, 77.7, 63.7, 39.6, 25.8, 23.6, 22.7, -5.4.



2.76

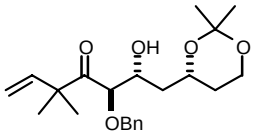
1-(*tert*-Butyl-dimethylsilanyloxy)-4,4-dimethylhex-5-en-3-one (2.76). To a solution of oxalyl chloride (2.2 mL, 25.5 mmol) in CH_2Cl_2 (40 mL) at –78°C was added dropwise a solution of DMSO (3.0 mL, 41.7 mmol) in CH_2Cl_2 (20 mL). After 30 min, a solution of alcohol **2.76A** (4.16 g, 17 mmol) in CH_2Cl_2 (15 mL) was added dropwise to the reaction mixture. After 1 h, a solution of Et_3N (9.5 ml, 68 mmol) in CH_2Cl_2 (10 mL) was added dropwise and after 10 min, the cold bath was removed. After 30 min at rt, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic fractions were washed with $NaHCO_3$ (50 mL), brine (50 mL) and then dried ($MgSO_4$). Filtration through Celite and concentration *in vacuo* supplied the crude products as a pale yellow oil. Purification by flash chromatography on silica gel with

10% EtOAc/hexanes gave the desired product which was then stirred in the presence of 10 mol% benzenethiol for 16 h to remove remaining silyl alcohol. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided **2.76** as a colorless oil (3.38 g, 82%): R_f 0.50 (20% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.15 (d, *J* = 17.5 Hz, 1H), 5.13 (d, *J* = 10.6 Hz, 1H), 4.43 (s, 2H), 1.23 (s, 6H), 0.87 (s, 9H), 0.05 (s, 6H).



2.80 **2.81**

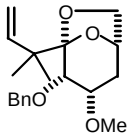
(5*R*, 6*R*)-5-(*tert*-Butyldimethylsilanyloxy)-7-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.80) and (5*S*, 6*S*)-5-(*tert*-Butyldimethylsilanyloxy)-7-((*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.81). The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 15% EtOAc/hexanes as elution gave β-alcohol **2.80** and diastereoisomer **2.81** as an inseparable mixture (277 mg, 1:2 dr, 72%).



2.83

(5*R*,6*R*)-5-Benzyloxy-7-((*R*)-2,2-dimethyl-[1,3]dioxan-4-yl)-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.83). The title compound was prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 15–25% EtOAc/hexanes as elution provided *β*-alcohol

2.83 (285 mg, 76%) and impure diastereoisomer **2.82** (65 mg, 17%) as colorless oils**:** R_f 0.50 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ7.32-7.30 (m, 5H), 5.98 (dd, *J* = 16.5, 10.7, 1H), 5.21 (s, 1H), 5.15 (d, *J* = 8.1 Hz, 1H), 4.47 (q, *J* = 8.7 Hz, 2H), 4.34 (d, *J* = 0.6 Hz, 1H), 4.12 (m, 1H), 3.95 (m, 1H), 3.81 (m, 1H), 3.55 (m, 1H), 2.38 (s, 1H), 1.87-1.83 (m, 2H), 1.77-1.67 (m, 2H), 1.46 (s, 3H), 1.37 (s, 3H), 1.25 (d, *J* = 5.6 Hz, 6H).

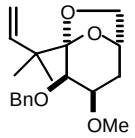


2.85A

(1*S*,3*S*,4*S*,5*R*)-4-Benzyloxy-5-(1,1-dimethylallyl)-3-methoxy-6,8-dioxabicyclo[3.2.1]octane (2.85A). To a solution of β-hydroxyketone **2.79** (168 mg, 0.45 mmol) in CH_2Cl_2 (4 mL) at rt was added proton sponge™ (289 mg, 1.35 mmol) and MeO_3BF_4 (200 mg, 1.35 mmol). After 6 h, the reaction mixture was poured into a saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). Tthe combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$), filtered through Celite and concentrated *under vacuo.* The ^{1}NMR of the crude reaction mixture showed a mixture of desired *β*-methoxy ketone and anhydrosugar **2.85A**, so the mixture was immediately subjected to the anhydro-sugar formation.

To a solution of the above mixture in MeOH (2 mL) was added acetyl chloride (~3 drops). After 30 min, Et_3N (0.20 mL) was added and the reaction mixture was poured into a saturated solution of $NaHCO_3$ (5 mL) and EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($NaSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 12 %

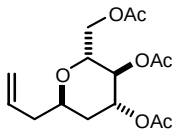
EtOAc/hexanes for elution gave the desired product provided anhydro-sugar **2.85A** (136 mg, 95%): R_f 0.25 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.41 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.18 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.08 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.43 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.13 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.04 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 3.99 (dd, *J* = 6.5, 1.0 Hz, 1H), 3.96 (ddd, *J* = 5.0, 5.0, 1.0 Hz, 1H), 3.64 (d, *J* = 5.0 Hz, 1H), 3.52 (ddd, *J* = 7.0, 5.0, 1.5 Hz, 1H), 3.34 (app q, *J* = 5.0 Hz, 1H), 3.01 (s, 3H), 1.60 (dddd, *J* = 14.0, 5.0, 5.0, 1.5 Hz, 1H), 1.47 (ddd, *J* = 14.5, 3.0, 1.5 Hz, 1H), 1.46 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 144.9, 137.8, 128.2, 127.9, 127.3, 110.8, 109.7, 78.2, 74.4, 72.9, 70.3, 69.5, 57.5, 43.4, 31.2, 22.8, 22.4; IR (thin film) ν 3081, 3032, 2979, 2933, 2880, 1459, 1371, 1095, 1011, 915 cm^{-1}; HRMS *m/z* 319.1896 (calcd for $C_{19}H_{27}O_4$ $[M+H]^+$, 319.1909).



2.85

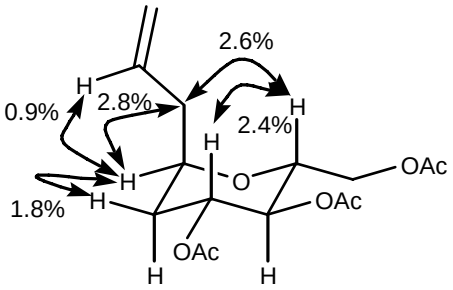
(1*S*,3*R*,4*R*,5*R*)-4-Benzyloxy-5-(1,1-dimethylallyl)-3-methoxy-6,8-dioxabicyclo[3.2.1]octane (2.85). The title compound was prepared according to the procedure described above: R_f 0.25 (33% EtOAc/hexanes). Purification by flash chromatography on silica gel with 12 % EtOAc/hexanes as elution gave the desired product provided **2.85** (23 mg, 90%); ^{1}H NMR (500 MHz, C_6D_6) δ 7.37-7.34 (m, 2H), 7.28 (dddd, *J* = 7.0, 7.0, 1.5, 1.5 Hz, 2H), 7.22 (dddd, *J* = 7.5, 7.5, 1.5, 1.5 Hz, 1H), 6.12 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.02 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.94 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.80 (dd, *J* = 10.5 Hz, 1H), 4.59-4.57 (m, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.92 (d, *J* = 3.0 Hz, 1H), 3.72 (d, *J* = 7.0 Hz, 1H), 3.65 (ddd, *J* = 9.0, 5.5, 3.5 Hz, 1H), 3.59 (ddd, *J*

= 6.0, 4.0, 1.5 Hz, 1H), 3.38 (s, 1H), 2.04 (dddd, *J* = 15.0, 12.0, 3.5, 2.0 Hz, 1H), 1.84 (dddd, *J* = 9.0, 3.0, 2.0, 1.0 Hz, 1H), 1.12 (s, 3H), 1.115 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 138.7, 128.0, 127.97, 127.1, 110.8, 110.4, 76.4, 74.9, 73.5, 73.2, 67.9, 56.6, 43.2, 31.3, 22.3, 22.2.

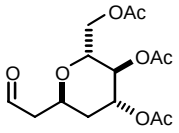


2.97

Acetic acid (2*R*,3*S*,4*R*,6*R*)-4-acetoxy-2-acetoxymethyl-6-allyltetrahydropyran-3-yl ester (2.97). To a solution of acetal **2.96** (2.0 g, 6.5 mmol) and allyl trimethyl silane (2.1 mL, 13.2 mmol) in acetonitrile (66 mL) at 0°C was added dropwise TMSOTf (4.75 mL, 26.3 mmol). After 3 h at rt, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL) and dried ($MgSO_4$). Filtered through Celite, concentrated under vacuo and purified by flash chromatography on silica gel with 20% EtOAc/hexanes provided a pale yellow oil (1.45 g, 70%): R_f 0.50 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (dddd, *J* = 17.2, 10.0, 6.0, 6.0 Hz, 1H), 5.12-5.02 (m, 3H), 4.85 (ddd, *J* = 7.2, 7.2, 2.4 Hz, 1H), 4.34 (ddd, *J* = 11.6, 11.6, 6.4 Hz, 1H), 4.05-4.00 (m, 1H), 3.87 (ddd, *J* = 6.4, 6.4, 3.6 Hz, 1H), 2.26 (ddd, *J* = 14.4, 6.8, 6.8 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.96 (ddd, *J* = 13.6, 4.7, 4.7 Hz, 1H), 1.82 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 170.6, 169.9, 169.6, 133.6, 117.4, 70.5, 69.7, 68.5, 68.5, 61.9, 36.5, 31.9, 20.9, 20.6, 20.4; IR (thin film) ν 3060, 2979, 2955, 1736, 1639, 1437, 1363, 1227, 1227, 1095, 1041, 998, 920 cm^{-1}; HRMS *m/z* 315.1440, (calcd for $C_{15}H_{23}O_7$ $[M+H]^+$, 315.1444).

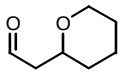


2.97



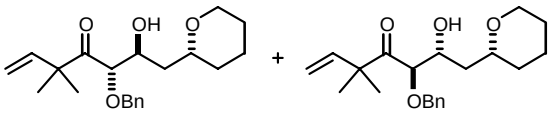
2.98

Acetic acid (2*R*,3*S*,4*R*,6*R*)-4-acetoxy-2-acetoxymethyl-6-(2-oxoethyl)-tetrahydropyran-3-yl ester (2.98). To a solution of pyran 2.97 (0.16 g, 0.5 mmol) and $NaHCO_3$ (4.2 g, 5.0 mmol) in a CH_2Cl_2:MeOH (3:1, v/v) at –78°C was purged with ozone until a blue solution was observed. After purging the reaction mixture with Ar, Me_2S (0.37 mL, 5.0 mmol) was added and the cold bath was removed. After 6 h, the reaction mixture was filtered through Celite and concentrated under *vacuo*. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and washed with brine (3 × 10 mL). Purification by flash chromatography on silica gel with 50% EtOAc/hexanes as elution provided the desired product as colorless oil (0.12 g, 75%): R_f 0.10 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.64 (s, 1H), 4.97 (ddd, *J* = 10.8, 6.3 Hz, 1H), 4.72 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.54-4.50 (m, 1H), 4.45 (dd, *J* = 11.9, 7.1 Hz, 1H), 4.03-3.92 (m, 2H), 3.90-3.92 (m, 1H), 2.70 (ddd, *J* = 16.5, 8.7, 2.9 Hz, 1H), 2.48 (dd, *J* = 16.4, 4.9 Hz, 1H), 1.98 (s, 9H), 1.85 (ddd, *J* = 14.3, 7.3, 2.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 198.4, 170.5, 169.5, 169.4, 71.8, 67.6, 67.3, 63.9, 61.0, 46.7, 31.8, 20.8, 20.6, 20.5; HRMS *m/z* 317.1232, (calcd for $C_{14}H_{21}O_8$ $[M+H]^+$, 317.1236).



2.99

Tetrahydro-2*H*-pyran-2-yl acetaldehyde (2.99). A stream of ozone was passed through a heterogeneous mixture of olefin (2.1 g, 16.7 mmol) and $NaHCO_3$ (7.0 g, 84 mmol) in CH_2Cl_2 (25 mL) at –78°C until a persistent blue color was observed. After purging the reaction mixture with Ar, Me_2S (12.3 mL, 167 mmol) was added and the cold bath was removed. After 16 h, the solvent was removed under vacuo and the resulting residue was purified with flash chromatography on silica gel (25% EtOAc/hexanes) provided the desired product as colorless oil (1.56 g, 73%): R_f 0.40 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.2 Hz, 1H), 3.93 (dd, *J* = 13.2, 3.1 Hz, 1H), 3.78 (ddd, *J* = 10.7, 8.2, 8.2, 2.9 Hz, 1H), 3.47 (dd, *J* = 6.7, 6.7 Hz, 1H), 3.40 (dd, *J* = 7.0, 2.4 Hz, 1H), 2.55 (ddd, *J* = 16.2, 7.7, 2.6 Hz, 1H), 2.41 (ddd, *J* = 16.4, 4.8, 2.0 Hz, 1H), 1.83-1.14 (m, 6H); ^{13}C NMR (63MHz, $CDCl_3$) δ 201.5, 73.0, 68.5, 50.1, 31.7, 25.6, 23.2; HRMS *m/z* 129.0921 (calcd for $C_7H_{13}O_2$ $[M+H]^+$, 129.0916).



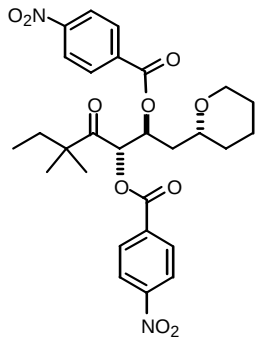
2.100 2.101

(5*S*,6*S*)-5-Benzyloxy-6-hydroxy-3,3-dimethyl-7-(*R*)-tetrahydropyran-2-ylhept-1-en-4-one (2.100) and **(5*R*,6*R*)-5-Benzyloxy-6-hydroxy-3,3-dimethyl-7-(*R*)-tetrahydropyran-2-ylhept-1-en-4-one (2.101).** The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution provided *β*-alcohol **2.100** (7 mg, 2%) and diastereoisomer **2.101** (124 mg, 36%) as colorless oils.

The title compounds were also prepared according to the General Procedure of Mukaiyama Aldol described below providing **2.100** (121 mg, 35%), **2.101** (70 mg, 20%) as colorless oils.

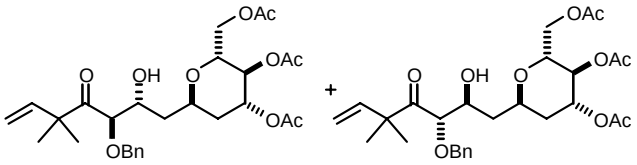
2.100: R_f 0.50 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 5.95 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 10.5, 1.0 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 5.5 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.18-4.12 (m, 1H), 3.90-3.87 (m, 1H), 3.48 (dddd, *J* = 11.0, 5.5, 3.0, 3.0 Hz, 1H), 3.31 (ddd, *J* = 11.5, 2.5, 2.5 Hz, 1H), 3.30 (s, 1H), 1.78-1.75 (m, 1H), 1.67 (ddd, *J* = 15.0, 8.0, 3.0 Hz, 1H), 1.60 (ddd, *J* = 15.0, 8.5, 2.5 Hz, 1H), 1.51-1.30 (m, 3H), 1.24 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 141.9, 137.6, 128.3, 127.9, 127.8, 114.7, 81.4, 75.5, 71.9, 69.3, 68.3, 50.5, 37.6, 31.5, 25.8, 23.7, 23.28, 23.25; HRMS *m/z* 347.2223 (calcd for $C_{21}H_{31}O_4$ $[M+H]^+$, 347.2222).

2.101: R_f 0.45 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 5.97 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.15 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.12 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.30 (d, *J* = 5.5 Hz, 1H), 4.07 (dddd, *J* = 10.0, 5.0, 1.5, 1.5 Hz, 1H), 3.97 (d, *J* = 1.5 Hz, 1H), 3.94-3.91 (m, 1H), 3.48 (dddd, *J* = 10.5, 10.5, 2.5, 2.5 Hz, 1H), 3.40 (ddd, *J* = 11.5, 11.5, 2.5 Hz, 1H), 1.78-1.74 (m, 1H), 1.74 (ddd, *J* = 14.5, 2.5, 2.5 Hz, 1H), 1.66 (ddd, *J* = 14.5, 10.0, 10.0 Hz, 1H), 1.55-1.40 (m, 4H), 1.30 (ddd, *J* = 11.0, 3.0, 3.0 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 142.1, 137.8, 128.3, 127.8, 127.6, 114.5, 81.8, 79.3, 73.3, 72.4, 68.3, 50.6, 38.1, 32.2, 25.7, 23.6, 23.4, 23.1; HRMS *m/z* 347.2231 (calcd for $C_{21}H_{31}O_4$ $[M+H]^+$, 347.2222).

2.100A 

(2S,3S)-5,5-dimethyl-4-oxo-1-((R)-tetrahydro-2H-pyran-2-yl)heptane-2,3-diyl bis(4-nitrobenzoate) (2.100A). To a solution of aldol adduct **2.100** (50 mg, 0.14 mmol) in EtOAc (10 mL) at rt was added Pd/C (~10 mg). After introducing the reaction mixture to a H_2 atmosphere, the reaction mixture was heated to 40°C. After 16 h, the reaction mixture was filtered through Celite and concentrated. The crude oil was dissolved in CH_2Cl_2 (2 mL) at 0°C and to this was added 2,6-lutidene (0.49 mL, 0.42 mmol) and DMAP (~10 mg, cat.). After the dropwise addition of *p*-nitrobenzoyl chloride (55 mg, 0.29 mmol), the cold bath was removed. After 6h, the reaction mixture was added to a saturated solution of $NaHCO_3$ (20 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution provided the desired product **2.100A** (64 mg, 83% over two steps). Recrystallization in CH_2Cl_2/hexanes (2:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 9.6, 2.4 Hz, 2H), 8.26 (dd, *J* = 8.8, 1.6 Hz, 2H), 8.20 (dd, *J* = 9.2, 2.0 Hz, 2H), 8.16 (dd, *J* = 9.2, 2.4 Hz, 2H), 6.15 (d, *J* = 2.0 Hz, 1H), 5.91 (dt, *J* = 10.8, 2.0 Hz, 1H), 3.88-3.84 (m, 1H), 331-3.20 (m, 1H), 2.11 (dddd, *J* = 15.2, 11.2, 2.4, 2.4 Hz, 1H), 1.83-1.76 (m, 2H), 1.73 (dd, *J* = 7.6, 4.0 Hz, 1H), 1.69 (d, *J* = 8.0, 4.0 Hz, 1H), 1.60-1.41 (m, 4H), 1.34 (s, 3H), 1.30 (s, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.0, 164.3, 163.7, 150.8,

150.7, 134.9, 134.7, 130.8, 123.7 (2C), 73.1, 69.9, 68.3, 47.9, 34.9, 32.4, 32.4, 32.2, 25.8, 23.8, 23.7, 23.4, 8.8; HRMS *m/z* 557.2134, (calcd for $C_{28}H_{33}N_2O_{10}$ $[M+H]^+$, 557.2135).



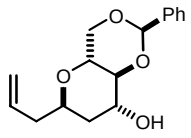
2.102 **2.103**

Acetic acid (2*R*,3*S*,4*R*,6*S*)-3-acetoxy-2-acetoxymethyl-6-((2*R*,3*R*)-3-benzyloxy-2-hydroxy-5,5-dimethyl-4-oxohept-6-enyl)-tetrahydropyran-4-yl-ester (2.102) and Acetic acid (2*R*,3*S*,4*R*,6*S*)-3-acetoxy-2-acetoxymethyl-6-((2*S*,3*S*)-3-benzyloxy-2-hydroxy-5,5-dimethyl-4-oxohept-6-enyl)-tetrahydropyran-4-yl-ester (2.103). The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 10-15% EtOAc/hexanes for elution provided *β*-alcohol **2.102** (70 mg, 13%) and diastereoisomer **2.103** (210 mg, 40%) as colorless oils.

2.102: R_f 0.25 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31-7.23 (m, 5H), 6.00-5.87 (m, 1H), 5.17 (d, *J* = 11.0 Hz, 1H), 5.15 (d, *J* = 17.2 Hz, 1H), 4.99 (q, *J* = 4.2 Hz, 1H), 4.72 (q, *J* = 4.7 Hz, 1H), 4.54-4.47 (m, 2H), 4.41 (s, 1H), 4.39-4.31 (m, 2H), 4.21-3.85 (m, 4H), 2.05-2.03 (m, 9H), 2.02-2.00 (m, 4H) 1.40-1.23 (m, 6H); HRMS *m/z* 535.2540, (calcd for $C_{28}H_{39}O_{10}$ $[M+H]^+$, 535.2543).

2.103: R_f 0.31 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26-7.19 (m, 5H), 5.90 (dd, *J* = 17.0, 10.3 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 5.10 (d, *J* = 17.0 Hz, 1H), 4.95 (q, *J* = 6.4 Hz, 1H), 4.67 (t, *J* = 5.4 Hz, 1H), 4.47-4.37 (m, 3H), 4.32-4.29 (m, 1H), 4.13-3.92 (m, 6H), 3.25 (d, *J* = 3.1 Hz, 1H), 2.00-1.98 (br s, 6H), 1.95 (s, 3H), 1.89-1.64

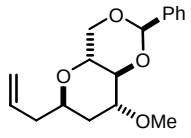
(m, 4H), 1.20-1.14 (m, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.5, 170.4, 169.5, 169.4, 141.6, 137.4, 128.2, 127.7, 114.7, 81.7, 72.3, 72.2, 71.6, 69.3, 67.7, 67.5, 61.1, 60.2, 50.4, 34.6, 32.2, 23.4, 23.2, 20.8, 20.6, 20.5, 14.0; HRMS *m/z* 535.2537, (calcd for $C_{28}H_{39}O_{10}$ $[M+H]^+$, 535.2543).



2.104A

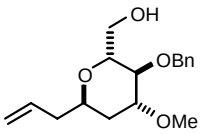
(2*R*,4a*R*,6*R*,8*R*,8a*S*)-6-Allyl-2-phenylhexadydropyrano[3,2-*d*][1,3]dioxin-8-ol (2.104A). To a solution of olefin **2.97** (5.6 g, 17.8 mmol) in MeOH (150 mL) was added Et_2NH (5.9 mL, 57.1 mmol). After the reaction was completed (monitored by TLC), the solvent was removed under *vacuo*. The crude mixture was dissolved in CH_2Cl_2 (100 mL) and benzaldehyde dimethylacetal (1.35 g, 8.9 mmol) and *p*-TsOH (100 mg) were added. After 16 h, a saturated solution of $NaHCO_3$ (75 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under *vacuo*. Purification by flash chromatography on silica gel with 30% EtOAc/hexanes provided a white solid (4.0 g, 81%): R_f 0.15 (30% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49-7.45 (m, 2H), 7.37-7.32 (m, 3H), 5.82 (dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.54 (s, 1H), 5.10 (d, *J* = 8.1 Hz, 1H), 5.08 (d, *J* = 9.2 Hz, 1H), 4.22 (dd, *J* = 8.9, 3.4 Hz, 1H), 4.17-4.01 (m, 2H), 3.65 (ddd, *J* = 9.8, 9.8, 9.8 Hz, 1H), 3.59 (ddd, *J* = 9.7, 9.7, 4.4 Hz, 1H), 3.47 (t, *J* = 9.0 Hz, 1H), 2.64 (ddd, *J* = 14.6, 7.4, 7.4 Hz, 1H), 2.36 (ddd, *J* = 14.1, 7.1, 7.1 Hz, 1H), 2.07 (dd, *J* = 13.3, 5.3 Hz, 1H), 1.93-1.80 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 137.3, 134.2, 129.2, 128.4, 126.2, 117.5, 102.0, 84.6, 73.4, 69.4, 66.2, 64.0, 36.0, 35.0 ; IR (thin film) ν 3321 (br), 3069, 3034, 2978, 2942, 2892, 1645, 1494, 1451, 1409, 1383, 1289,

1262, 1213, 1135, 1104, 1012, 925, 764 cm^{-1}; HRMS *m/z* 277.1445, (calcd for $C_{16}H_{21}O_4$ $[M+H]^+$, 277.1440).



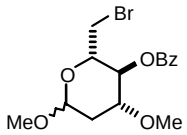
2.104

(2*R*,4a*R*,6*R*,8*R*,8a*S*)-6-Allyl-8-methoxy-2-phenylhexadydropyrano[3,2-*d*][1,3]dioxin (2.104). To a heterogeneous mixture of NaH (0.18 g, 7.4 mmol) in DMF (25 mL) at 0°C was added acetal **2.104A** (1.37 g, 4.96 mmol). The cold bath was removed and after 45 min at rt, MeI (0.93 mL, 14.9 mmol) was added. After 16 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (25 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). Filtered through Celite and concentrated under *vacuo*. Purification by flash chromatography on silica gel with 30% EtOAc/hexanes provided a white solid (1.38 g, 96%): R_f 0.50 (50% EtOAc/hexanes); ^1H NMR (250 MHz, $CDCl_3$) δ 7.51-7.41 (m, 2H), 7.37-7.31 (m, 3H), 5.84 (dddd, *J* = 17.1, 10.1, 7.0, 7.0 Hz, 1H), 5.57 (s, 1H), 5.11 (d, *J* = 17.8 Hz, 1H), 5.10 (d, *J* = 9.7 Hz, 1H), 4.23 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.14-4.05 (m, 1H), 3.73-3.59 (m, 4H), 3.50 (s, 3H), 2.65 (ddd, *J* = 14.5, 7.2, 7.2 Hz, 1H), 2.36 (ddd, *J* = 14.1, 6.9, 6.9 Hz, 1H), 2.11 (ddd, *J* = 11.9, 3.0, 1.5 Hz, 1H), 1.83 (ddd, *J* = 13.4, 10.3, 6.1 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 137.5, 134.2, 128.8, 128.1, 126.0, 117.4, 101.4, 84.3, 74.7, 73.1, 69.4, 64.2, 58.3, 36.0, 33.4; HRMS *m/z* 291.1590, (calcd for $C_{17}H_{23}O_4$ $[M+H]^+$, 291.1596).



2.105

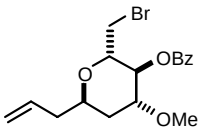
[(2*R*,3*S*,4*R*,6*R*)-6-Allyl-3-benzyloxy-4-methoxytetradydropyran-2-yl]-methanol (2.105). To a solution of **2.104** (32 mg, 0.11 mmol), CH_2Cl_2 (1 mL) and diethyl ether (1 mL) was added $LiAlH_4$ (5 mg, 0.13 mmol). After the reaction mixture was heated to reflux, a solution of $AlCl_3$ (16 mg, 0.12 mmol) in Et_2O (0.200 mL) was added dropwise over 10 min. After 16 h, the reaction mixture was slowly added to EtOAc and diluted with water (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 50% EtOAc/hexanes as elution yielded a clear oil (3:1 mixture of regioisomers, 30 mg, 94%): R_f 0.25 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 5.82 (dddd, *J* = 17.4, 10.6, 7.1, 7.1 Hz, 1H), 5.09 (d, *J* = 6.7 Hz, 1H), 5.03 (s, 1H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.62 (d, *J* = 11.3 Hz, 1H), 4.05-3.95 (m, 1H), 3.76-3.64 (m, 2H), 3.61-3.55 (m, 2H), 3.38 (s, 3H), 3.33 (dd, *J* = 7.7 Hz, 1H), 2.51 (ddd, *J* = 15.0, 8.1, 8.1 Hz, 1H), 2.26 (ddd, *J* = 14.0, 8.1, 6.9 Hz, 1H), 2.03 (ddd, *J* = 13.5, 7.2, 4.0 Hz, 1H), 1.90 (bs, 1H), 1.69 (ddd, *J* = 14.7, 6.9, 5.2 Hz, 1H).



2.110

Benzoic acid (2*R*,3*R*,4*R*) 2-bromomethyl-4,6-dimethoxytetrahydropyran-3-yl ester (2.110). R_f 0.52 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05-8.01 (m, 2H), 7.59-7.52 (m, 1H), 7.46-7.40 (m, 2H), 5.06 (t, *J* = 9.5 Hz, 1H), 4.89 (d, *J* = 2.7 Hz,

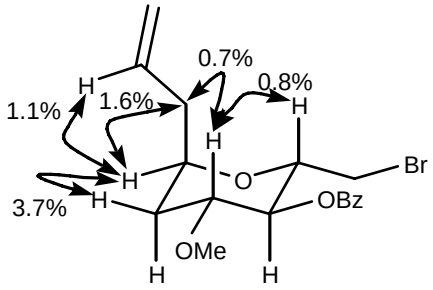
1H), 4.02 (ddd, *J* = 10.1, 7.8, 2.6 HZ, 1H), 3.84 (ddd, *J* = 11.5, 9.0, 5.1 Hz, 1H), 3.50 (dd, *J* = 11.1, 2.6 Hz, 1H), 3.42 (dd, *J* = 11.1, 7.9 Hz, 1H), 3.40 (s, 3H), 3.28 (s, 3H), 2.33 (ddd, *J* = 13.2, 6.4, 1.3 Hz, 1H), 1.76 (ddd, *J* = 13.2, 11.5, 3.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.6, 133.3, 129.8, 129.5, 128.5, 98.3, 75.8, 74.1, 69.9, 57.4, 55.0, 34.7, 32.2; IR (thin film) ν 3100-2800, 1728, 1270, 1118, 1049, 711 cm^{-1}.[51]



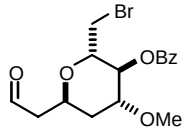
2.111

Benzoic acid (2*R*,3*R*,4*R*,6*R*)-6-allyl-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (2.111). To a solution of **2.110** (4.7 g, 13.2 mmol), acetonitrile (130 mL), and allyltrimethylsilane (6.3 mL, 39.5 mmol) at –20°C was added trimethylsilyl triflate (4.75 mL, 26.3 mmol) dropwise over 20 min. After 20 min the reaction was added to saturated aqueous $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 10-30% EtOAc/hexanes provided allylic pyran **2.111** (4.6 g, 95%) as a yellow oil: R_f 0.55 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.56 (dddd, *J* = 7.0, 7.0, 1.5, 1.5 Hz, 1H), 7.44 (dd, *J* = 8.0, 2.0 Hz, 2H), 5.86 (dddd, *J* = 17.0, 10.0, 7.0, 7.0 Hz, 1H), 5.21 (dd, *J* = 4.0, 4.0 Hz, 1H), 5.12 (dddd, *J* = 17.5, 1.5, 1.5, 1.5 Hz, 1H), 5.08 (dddd, *J* = 10.5, 1.0, 1.0, 1.0 Hz, 1H), 4.13 (ddd, *J* = 7.0, 7.0, 3.0 Hz, 1H), 3.96 (dddd, *J* = 13.0, 7.0, 3.2, 3.2 Hz, 1H), 3.73 (d, *J* = 7.0 Hz, 2H), 3.65 (ddd, *J* = 4.5 Hz, 1H), 3.43 (s, 3H), 2.45-2.39 (m, 1H), 2.28-2.22 (m, 1H) 1.86 (ddd, *J* = 14.0, 9.0, 3.5 Hz, 1H), 1.79 (ddd, *J* = 14.1, 4.0, 4.0 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.4, 134.1, 133.2, 129.6, 129.5, 128.3, 117.1, 74.9, 74.7, 67.9, 66.3, 57.3, 39.0, 31.2, 30.5; IR

(thin film) ν 3072-2834, 1725, 1323, 1274, 1100, 720 cm^{-1}; HRMS *m/z* 369.0693 (calcd for $C_{17}H_{21}BrO_4$ $[M+H]^+$, 369.0701).



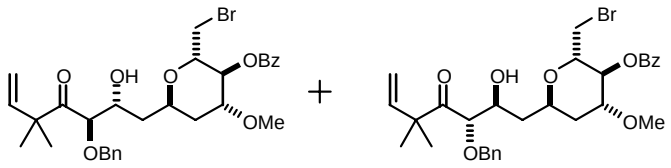
2.111



2.112

Benzoic acid (2*R*,3*R*,4*R*,6*S*)-2-bromomethyl-4-methoxy-6-(2-oxoethyl)-tetrahydropyran-3-yl ester (2.112). To a solution of *tert*-butanol:H_2O (1:1 v/v, 120 mL) and allylic pyranoside **2.111** (4.3 g, 11.8 mmol) was added OsO_4 (~50 mg, 0.2 mmol). After 15 min, 4-methylmorpholine *N*-oxide (2.8 g, 23.5 mmol) was added. After 12 h, the solution was transferred to a mixture of EtOAc (100 mL) and saturated aqueous Na_2SO_3 (50 mL). After extracting with EtOAc (2 × 75 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under *vacuo*. The residue was dissolved in THF:H_2O (5:1 v/v, 75 mL) and subjected to $NaIO_4$ (3.02 g, 14.1 mmol). When the diol was completely consumed (monitored by TLC, ~6 h), the reaction mixture was added to saturated aqueous $NaHCO_3$ (75 mL). After extracting with EtOAc (3 × 50 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 25% EtOAc/hexanes provided a pale yellow oil (4.17 g, 96%): R_f 0.45 (50%

EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.83 (dd, *J* = 2.6, 1.7 Hz, 1H), 8.04-8.00 (m, 2H), 7.60-7.53 (m, 1H), 7.46-7.39 (m, 2H), 5.20 (dd, *J* = 3.7, 2.2 Hz, 1H), 4.45 (ddd, *J* = 13.1, 8.4, 4.8 Hz, 1H), 4.14 (dd, *J* = 7.3, 7.3 Hz, 1H), 3.85 (dd, *J* = 10.7, 8.6 Hz, 1H), 3.72 (dd, *J* = 10.8, 6.3 Hz, 1H), 3.66 (ddd, *J* = 3.4, 3.4, 3.4 Hz, 1H), 3.45 (s, 3H), 2.73 (ddd, *J* = 16.5, 11.1, 2.8 Hz, 1H), 2.54 (ddd, *J* = 16.4, 6.1, 1.6 Hz, 1H) 1.92-1.81 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.6, 165.4, 133.4, 129.7, 129.5, 128.5, 75.4, 74.4, 66.8, 61.5, 57.5, 48.6, 31.3, 29.9; IR (thin film) ν 3071-2831, 1720, 1266, 1095, 1068, 711 cm^{-1}; HRMS *m/z* 371.0502 (calcd for $C_{16}H_{18}BrO_5$ $[M+H]^+$, 371.0494).



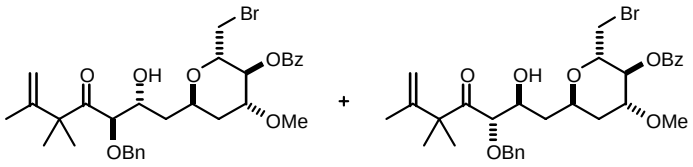
2.113 **2.114**

Benzoic acid (2*S*,3*S*,4*R*,6*R*)-6-((2*R*,3*R*)-3-benzyloxy-2-hydroxy-5,5-dimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl-ester (2.113) and **Benzoic acid (2*S*,3*S*,4*R*,6*R*)-6-((2*S*,3*S*)-3-benzyloxy-2-hydroxy-5,5-dimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl-ester (2.114).** The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 20% EtOAc/hexanes for elution provided 2,3-*anti*-3,5-*anti* **2.113** (20 mg, 11%) and 2,3-*anti*-3,5-*syn* **2.114** (76 mg, 43%) as colorless oils.

2.113: R_f 0.45 (33% EtOAc/hexanes); ^{1}H NMR (250 MHz, C_6D_6) δ 8.10 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.32 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.19-7.00 (m, 7H), 5.95 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.07 (dd, *J* = 2.9, 2.8 Hz, 1H), 5.00 (d, *J* = 17.5 Hz, 1H), 4.99 (d, *J* = 10.6 Hz, 1H), 4.61-4.58 (m, 1H), 4.51 (d, *J* = 4.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.32 (d, *J* = 11.4

Hz, 1H), 4.23-4.15 (m, 1H), 4.05-4.00 (m, 1H), 3.77 (dd, *J* = 10.7, 9.5 Hz, 1H), 3.30-3.24 (m, 1H), 2.93 (s, 3H), 2.81 (br s, 1H), 1.92 (ddd, *J* = 14.6, 9.2, 2.5 Hz, 1H), 1.75 (ddd, *J* = 14.4, 9.5, 2.8 Hz, 3H), 1.59 (ddd, *J* = 13.8, 10.4, 3.3 Hz, 3H), 1.41-1.33 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (63 MHz, C_6D_6) δ 210.4, 165.2, 142.3, 138.5, 133.2, 130.4, 130.0 (2C), 128.6, 128.2, 127.8, 114.7, 83.4, 75.5, 74.8, 72.3, 68.6, 68.0, 63.0, 56.9, 50.7, 37.5, 31.7, 31.0, 23.9, 23.5.

2.114: R_f 0.55 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.51 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.37 (dd, *J* = 7.7, 7.2 Hz, 2H), 7.25-7.17 (m, 5 H), 5.88 (dd, *J* = 16.8, 11.1 Hz, 1H), 5.09 (d, *J* = 11.1 Hz, 1H), 5.08 (d, *J* = 16.8 Hz, 1H), 5.04-5.02 (m, 1H), 4.47-4.45 (m, 2H), 4.34 (d, *J* = 4.3 Hz, 1H), 4.12-4.08 (m, 2H), 3.98-3.91 (m, 1H), 3.87 (dd, *J* = 10.8, 10.1 Hz, 1H), 3.56-3.50 (m, 2H), 3.34 (s, 3H), 1.83-1.65 (m, 4H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.5, 165.4, 141.4, 137.8, 133.5, 129.8, 129.4, 128.5, 128.3, 127.8, 127.7, 114.9, 81.9, 75.1, 74.3, 72.7, 72.5, 67.0, **67.0,** 57.4, 50.6, 36.7, 35.5, 32.0, 30.2, 23.6, 23.4; IR (thin film) ν 3512 (br), 2968-2825, 1722, 1451, 1273, 1099, 1063, 917, 718 cm^{-1}; HRMS *m/z* 589.1801 (calcd for $C_{30}H_{38}BrO_7$ $[M+H]^+$, 589.1801).



2.115 **2.116**

Benzoic acid (2*R*,3*R*,4*R*,6*S*) 6-((2*R*,3R) 3-benzyloxy-2-hydroxy-5,5,6-trimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (2.115) and **Benzoic acid (2R,3R,4R,6S)-6-((2S,3S)-3-benzyloxy-2-hydroxy-5,5,6-trimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (2.116).**

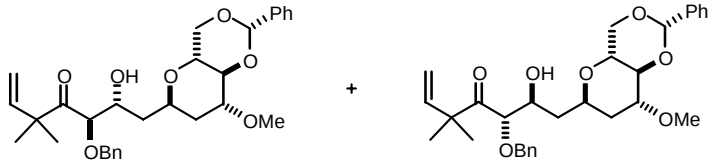
The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 20% EtOAc/hexanes as elution provided 2,3-*anti*-3,5-*anti* **2.115** (0.21 g, 11%) and 2,3-*anti*-3,5-*syn* **2.116** (1.08 g, 58%) as colorless oils.

The title compounds were also prepared according to the General Procedure of Mukaiyama Aldol described above providing **2.115** (1.99 g, 66%), **2.116** (0.56 g, 19%) as colorless oils.

2.115: R_f 0.29 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.4, 1.5 Hz, 2H), 7.57 (dddd, *J* = 7.2, 7.2, 1.5, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.33-7.26 (m, 5H), 5.10 (dd, *J* = 3.6, 3.0 Hz, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 4.2 Hz, 1H), 4.40 (d, *J* = 11.1 Hz, 1H), 4.34-4.28 (m, 1H), 4.20 (dddd, *J* = 9.3, 9.3, 3.3, 3.3 Hz, 1H), 4.06 (ddd, *J* = 8.1, 5.7, 3.3 Hz, 1H), 3.84 (dd, *J* = 10.8, 9.3 Hz, 1H), 3.61 (dd, *J* = 8.4, 5.1 Hz, 1H), 3.64-3.58 (m, 1H), 3.39 (s, 3H), 2.70 (d, *J* = 7.2 Hz, 1H), 1.85 (ddd, *J* = 13.8, 9.6, 3.3 Hz, 1H), 1.77-1.66 (m, 3H), 1.68 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 165.4, 146.3, 137.6, 133.4, 129.7, 129.5, 128.4, 128.3, 127.9, 127.8, 113.3, 81.7, 74.8, 74.7, 72.1, 68.1, 63.0, 57.3, 53.5, 36.4, 31.8, 30.9, 23.5, 23.2, 20.4; IR (thin film) ν 3497 (br), 2969-2332, 1720, 1272, 1107 cm^{-1}; HRMS *m/z* 603.1935 (calcd for $C_{31}H_{39}BrO_7$ $[M+H]^+$, 603.1957).

2.116: R_f 0.33 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.58 (dddd, *J* = 7.5, 7.5, 1.5, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.35-7.25 (m, 5 H), 5.10 (dd, *J* = 2.4, 2.4 Hz, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 3.9 Hz, 1H), 4.19-4.15 (m, 2H), 4.11-4.02 (m, 1H), 3.96 (dd, *J* = 10.8, 10.2 Hz, 1H), 3.64-3.58 (m, 2H), 3.41 (s, 3H), 1.91-1.70 (m, 4H), 1.65 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 165.4, 146.4, 137.9, 133.4, 129.7, 129.4, 128.5, 128.2, 127.8, 127.6, 113.1, 80.9,

75.1, 74.3, 72.9, 72.7, 67.2, 67.0, 57.4, 53.5, 36.4, 32.0, 30.2, 23.4, 23.0, 20.3; IR (thin film) ν 3511 (br), 2968-2887, 1708, 1269, 1095, 916 cm^{-1}; HRMS *m/z* 603.1949 (calcd for $C_{31}H_{39}BrO_7$ $[M+H]^+$, 603.1957).



2.117 **2.118**

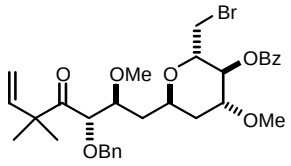
(5*R*,6*R*)-5-Benzyloxy-6-hydroxy-7-((2*S*,4a*R*,6*R*,8*R*,8a*S*)-8-methoxy-2-phenylhexahydropyrano-[3,2-*d*][1,3]dioxin-6-yl)-3,3-dimethylhept-1-en-4-one (2.117) and **(5*S*,6S)-5-Benzyloxy-6-hydroxy-7-((2*S*,4a*R*,6*R*,8*R*,8a*S*)-8-methoxy-2-phenylhexahydropyrano-[3,2-*d*][1,3]dioxin-6-yl)-3,3-dimethylhept-1-en-4-one (2.118).** The title compounds were prepared according to the General Procedure of Boron Mediated Aldol described above. Purification by flash chromatography on silica gel with 20-35% EtOAc/hexanes as elution provided 2,3-*anti*-3,5-*anti* **2.117** (88 mg, 22%) and 2,3-*anti*-3,5-*syn* **2.118** (108 mg, 27%) as white solids. Recrystallization through slow evaporative mixing of a benzene solution of **2.117** with DCM/heptane provided a crystal suitable for X-ray analysis.

The title compounds were prepared according to the General Procedure of Mukaiyama Aldol described above. Purification by flash chromatography on silica gel with 20-35% EtOAc/hexanes for elution provided **2.117** (68 mg, 27%) and **2.118** (66 mg, 26%) as solids.

2.117: R_f 0.10 (50% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.36-7.28 (m, 8H), 5.93 (dd, *J* = 17.5, 10.5 Hz, 1H), 5.54 (s, 1H), 5.24 (dd, *J* = 10.5, 0.5 Hz, 1H), 5.21 (dd, *J* = 17.5, 0.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J*

= 4.5 Hz, 1H), 4.33 (d, *J* = 11.0 Hz, 1H), 4.33-4.30 (m, 1H), 4.12 (dd, *J* = 10.5, 5.0 Hz, 1H), 4.06-4.04 (m, 1H), 3.67 (t, *J* = 10.0 Hz, 1H), 3.56-3.53 (m, 2H), 3.46 (s, 3H), 3.40 (ddd, *J* = 9.5, 9.5, 5.0 Hz, 1H), 2.23 (d, *J* = 8.5 Hz, 1H), 2.04-1.94 (m, 2H), 1.83 (dddd, *J* = 8.0, 6.5, 6.5, 6.5 Hz, 1H), 1.46 (ddd, *J* = 15.0, 11.0, 3.5 Hz, 1H), 1.26 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9, 141.3, 137.5, 137.2, 128.9, 128.6, 128.2, 128.1 (2C), 126.2, 115.6, 101.6, 84.3, 82.8, 74.8, 72.3, 70.0, 69.4, 68.0, 64.3, 58.3, 50.5, 34.8, 32.7, 23.8, 23.4; IR (thin film) ν 3465, 3064, 2968, 2931, 2875, 1711, 1454, 1379, 1208, 1103, 1007, 919, 750, 699 cm^{-1}; HRMS *m/z* 511.2696, (calcd for $C_{30}H_{39}O_7$ $[M+H]^+$, 511.2694).

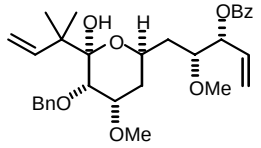
2.118: R_f 0.15 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.36-7.28 (m, 8H), 5.94 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.55 (s, 1H), 5.20 (dd, *J* = 10.5, 0.5 Hz, 1H), 5.18 (dd, *J* = 17.5, 0.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 4.5 Hz, 1H), 4.24-4.21 (m, 1H), 4.16 (ddd, *J* = 3.5, 3.5, 1.5 Hz, 1H), 4.04-4.02 (m, 1H), 3.69 (d, *J* = 11.0 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.60-3.56 (m, 2H), 3.46 (s, 3H), 2.85 (d, *J* = 4.0 Hz, 1H), 2.07 (ddd, *J* = 14.5, 10.5, 10.5 Hz, 1H), 1.98 (ddd, *J* = 14.0, 5.0, 2.5 Hz, 1H), 1.80 (dddd, *J* = 14.0, 6.0, 6.0, 6.0 Hz, 1H), 1.67 (ddd, *J* = 15.0, 4.5, 4.5 Hz, 1H), 1.243 (s, 3H), 1.240 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3, 141.6, 137.42, 137.40, 128.9, 128.5, 128.2, 128.0, 127.97, 126.11, 115.2, 101.5, 84.0, 82.1, 74.7, 73.6, 72.5, 71.9, 69.2, 64.5, 60.4, 58.3, 50.6, 34.6, 33.1, 23.7, 23.4; IR (thin film) ν 3481, 3033, 2928, 2866, 1711, 1454, 1379, 1210, 1103, 1101, 918, 750, 699 cm^{-1}; HRMS *m/z* 511.2696, (calcd for $C_{30}H_{39}O_7$ $[M+H]^+$, 511.2693).



2.119

Benzoic acid (2*S*,3*S*,4*R*,6S)-6-((2*S*,3*S*)-3-benzyloxy-2-methoxy-5,5-dimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl-ester (2.119). To a solution of β-hydroxyketone **2.114** (208 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at rt was added proton sponge™ (222 mg, 1.03 mmol) and MeO_3BF_4 (153 mg, 1.03 mmol). After 6 h, the mixture was poured into aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic fractions were washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (12% EtOAc/hexanes) provided **2.119** as a colorless oil (181 mg, 86%): R_f 0.52 (50% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.55 (app d, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.30-7.23 (m, 5H), 5.19 (t, *J* = 4.2 Hz, 1H), 4.98 (app d, *J* = 12.8 Hz, 2H), 4.56-4.49 (m, 2H), 4.15-4.05 (m, 2H), 3.68 (app d, *J* = 7.1 Hz, 2H), 3.65-3.60 (m, 2H), 3.40 (s, 3H), 3.38-3.34 (m, 1H), 3.29 (s, 3H), 2.05-1.73 (m, 4H), 1.65 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{1}H NMR (250 MHz, C_6D_6) δ 8.13 (dd, *J* = 8.5, 1.6 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.20-7.00 (m, 6H), 5.26 (app t, *J* = 3.4 Hz, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 5.4 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.21-4.14 (m, 2H), 3.92 (ddd, *J* = 10.4, 5.3, 0.0 Hz, 1H), 3.72 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.46 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.43 (ddd, *J* = 7.6, 3.8, 0.0 Hz, 1H), 3.15 (s, 3H), 3.01 (s, 3H), 2.14 (ddd, *J* = 14.9, 7.4, 5.5 Hz, 1H), 2.01 (ddd, *J* = 14.6, 4.9, 4.9 Hz, 1H), 1.71-1.57 (m, 2H), 1.63 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 211.8, 165.5, 142.0, 137.7, 133.3, 129.8, 129.7, 128.5, 128.3, 127.9, 127.8, 114.8, 79.3 (2C), 75.1, 74.5, 72.3, 68.4,

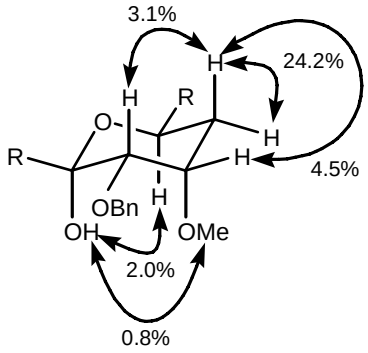
64.8, 57.5, 57.4, 50.7, 34.8, 32.1, 31.1, 23.7, 23.5; IR (thin film) ν 2964-2833, 1723, 1267, 1107, 1065, 719 cm^{-1}; HRMS *m/z* 603.1953 (calcd for $C_{31}H_{40}BrO_7$ $[M+H]^+$, 603.1957).



2.120

Benzoic acid (*R*)-1-{(*R*)-2-[(2*S*,4*S*,5*S*,6*R*)-5-benzyloxy-6-(1,1-dimethylallyl)-6-hydroxy-4-methoxytetrahydropyran-2-yl]-1-methoxyethyl}allyl ester (2.120). A solution mixture of methyl ether **2.119** (112 mg, 0.19 mmol), Zn/Cu couple (3.12 g, 4.8 mmol) and NH_4Cl (50 mg, 0.95 mmol) in 95% EtOH/H_2O (9:1, 20 mL) was heated at reflux for 16 h. The reaction was cooled, filtered through Celite, diluted with H_2O (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic fractions were washed with aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried ($MgSO_4$). After filtration through Celite and concentration *in vacuo*, a ^1H NMR of the crude residue confirmed a 2:1 mixture of hemi-ketal **2.120** and acyclic hydroxyl ketone **2.121**, so the residue was dissolved in CH_2Cl_2 (2 mL) and PPTS (~10 mg) was added. After 30 min, the reaction mixture was added to $NaHCO_3$ (4 mL). After extraction with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 12-25% EtOAc/hexanes as elution provided the hemi-ketal (68 mg, 68%): R_f 0.30 (33% EtOAc/hexanes); ^1H NMR (500 MHz, *d*-DMSO) δ 8.00 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.65 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.54 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.34-7.25 (m, 5H), 6.12 (dd, *J* = 17.7, 10.8 Hz, 1H), 5.99 (ddd, *J* = 16.9, 10.6, 5.6 Hz, 1H), 5.59 (t, *J* = 5.2 Hz, 1H), 5.32 (s, 1H), 5.30 (dd, *J* = 17.5, 1.5 Hz, 1H), 5.27 (d, *J* = 10.5 Hz, 1H), 4.89 (dd, *J* = 17.5, 2.0 Hz, 1H), 4.82 (d, *J* =

10.5, 2.0 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.02-3.95 (m, 2H), 3.57 (ddd, *J* = 5.8, 5.8, 0.0 Hz, 1H), 3.46 (d, *J* = 3.0 Hz, 1H), 3.35 (s, 3H), 3.32 (s, 3H), 3.30 (s, 1H), 1.97 (d, *J* = 14.0, 3.5 Hz, 1H), 1.70-1.61 (m, 2H), 1.34 (dd, *J* = 14.1, 2.4 Hz, 1H), 1.02 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (63 MHz, *d*-DMSO) δ 164.8, 146.0, 138.1, 133.6, 133.5, 129.6, 129.2, 128.8, 128.1, 127.9, 127.5, 117.5, 110.1, 100.2, 78.2, 75.6, 75.0, 74.7, 69.4, 60.3, 57.8, 57.5, 44.9, 35.2, 33.3, 22.6, 22.4; HRMS *m/z* 525.2860 (calcd for $C_{31}H_{41}O_7$ $[M+H]^+$, 525.2852).

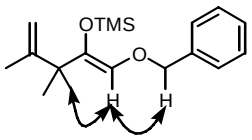


2.120

5.1.2 General Procedure for Mukaiyama Aldol

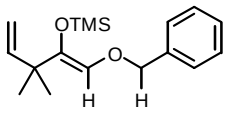
To a solution of aldehyde (1.0 mmol) in CH_2Cl_2 (0.1 M) at –20°C was added freshly distilled BF_3•OEt_2 (1.3 mmol). After 5 min, a solution of silyl enol ether (1.5 mmol) in CH_2Cl_2 (2 mL) was added and the cold bath was replaced by an ice bath (0°C). When the reaction was completed (monitored by TLC, ~2 h), saturated aqueous $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were washed with H_2O (10 mL), brine (10 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash

chromatography on silica gel with EtOAc/hexanes as elution provided the desired products.



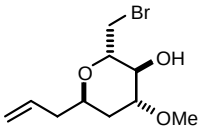
2.129

{1-[1-Benzyloxymeth-(*E*)-ylidene]-2,2,3-trimethylbut-3-enyloxy}trimethylsilane (2.129). A solution of n-BuLi in hexanes (2.0 M, 12.95 mL, 25.9 mmol) was added dropwise to a solution of diisopropylamine (3.94 mL, 28.1 mmol) in THF (0.1 M) at 0°C. After 15 min the solution was cooled to –78°C and a solution of benzyloxyketone **2.127** (5.00g, 21.6 mmol) was added. The cold bath was removed and the solution was allowed to warm to 0°C, then cooled to – 78°C before Me_3SiCl (8.31 mL, 64.8 mmol) was added. After 10 min the cold bath was removed and the rt solution was transferred to pentanes (500 mL) and the resulting solids were filtered. The filtrate was concentrated *in vacuo* and purification by flash chromatography on silica gel (elution gradient: hexanes to 1% Et_2O/hexanes) provided **2.129** as a colorless oil (5.77 g, 88%): R_f 0.85 (1% Et_2O /hexanes); ^1H NMR (250 MHz, $CDCl_3$) δ7.32-7.27 (m, 5H), 5.60 (s, 1H) 4.77 (s, 2H), 4.67 (s, 2H), 1.64 (s, 3H), 1.09 (s, 6H), 0.12 (s, 9H); ^1H NMR (250 MHz, C_6D_6) δ7.22-7.05 (m, 5H), 5.59 (s, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.39 (s, 2H), 1.74 (s, 3H), 1.19, (s, 6H), 0.27 (s, 9H); ^{13}C NMR (63 MHz, C_6D_6) δ 150.3, 141.7, 138.0, 129.4, 128.5, 127.3, 110.7, 73.8, 43.8, 25.5, 20.1, 1.1; IR (thin film) ν 3094-2870, 1252, 1181, 849 cm^{-1}; HRMS *m/z* 304.1855 (calcd for $C_{18}H_{28}O_2Si$ $[M+H]^+$, 304.1859).



2.130

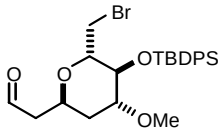
{1-[1-Benzyloxymeth-(*E*)-ylidene]-2,2-dimethylbut-3-enyloxy}trimethylsilane (2.130). The title compound was prepared in a similar manner to the procedure described above for the preparation of **2.129**. Purification by flash chromatography on silica gel with 1% EtOAc/hexanes as elution gave the desired product as a colorless oil (2.46 g, 82%): R_f 0.60 (10% Et_2O /hexanes); ^1H NMR (300 MHz, C_6D_6) δ7.33-7.24 (m, 5H), 5.81 (dd, *J* = 17.4, 10.5 Hz, 1H), 5.63 (s, 1H), 5.05 (dd, *J* = 17.4, 1.2 Hz, 1H), 4.95 (dd, *J* = 17.4, 1.2 Hz, 1H), 4.36 (s, 2H), 1.09 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 145.8, 142.0, 137.9, 128.6, 128.3, 128.2, 126.9, 111.6, 73.8, 40.7, 25.3, 0.99.



2.131A

(2*S*,3*S*,4*R*,6*R*)-6-Allyl-2-bromomethyl-4-methoxytetrahydropyran-3-ol (2.131A). To a solution of glycoside **2.111** (6.5 g, 17.7 mmol) in MeOH (50 mL) was added a solution of NaOMe (1.4 g, 26.0 mmol) in MeOH (50 mL). After 12 h, the brown solution was added to a solution of 10% HCl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (70 mL), dried ($MgSO_4$), filtered through Celite and concentrated under *vacuo*. Purification by flash chromatography on silica gel with 40% EtOAc/hexanes provided a pale yellow oil (4.33 g, 93%): R_f 0.30 (50% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 17.1, 14.1, 10.5, 7.5 Hz, 1H), 5.13-5.06 (m, 3H), 4.13-4.06 (m, 1H), 3.72-3.58 (m, 1H), 3.49 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.43 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.37 (s, 3H), 2.56 (s, 1H), 2.51 (ddd, *J* = 14.4, 8.1, 6.6 Hz, 1H), 2.25 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 2.03 (ddd, *J* = 13.2, 4.5, 3.3

Hz, 1H), 1.62 (ddd, J = 13.2, 9.9, 5.4 Hz, 1H; ^{13}C NMR (63 MHz, $CDCl_3$) δ 134.2, 117.3, 78.3, 72.7, 71.7, 71.5, 56.4, 36.3, 33.7, 30.8; IR (thin film) ν 3434, 2976, 2933, 2829, 1444, 1418, 1383, 1254, 1223, 1141, 1095, 984, 916 cm^{-1}; HRMS *m/z* 265.0437 (calcd for $C_{10}H_{18}BrO_3$ $[M+H]^+$, 265.0439).

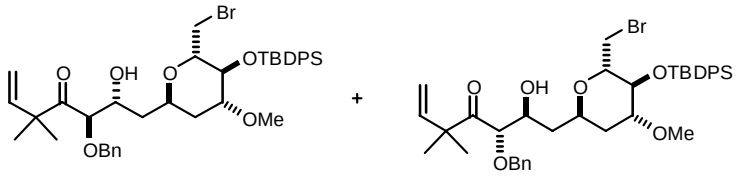


2.131

[(2*S*,4*R*,5*S*,6*S*)-6-Bromomethyl-5-(*tert*-butyldiphenylsilanyloxy)-4-methoxytetrahydropyran-2-yl]acetaldehyde (2.131). To a solution mixture of pyranoside **2.131A** (4.33 g, 16.4 mmol), DMAP (100 mg), and imidazole (2.33 g, 32.8 mmol) in DMF (10 mL) at 0°C was added ^{t}Bu(Ph)$_2$SiCl (6.45 mL, 24.6 mmol). After the addition was completed, the cold bath was removed. After 24 h, the reaction mixture was poured into a saturated solution of NH_4Cl (100 mL) and extracted with EtOAc (3 × 100 mL). The combined extracts were washed with H_2O (2 × 75 mL), brine (75 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography with 5% EtOAc/hexanes provided impure desired silyl ether: R_f 0.75 (40% EtOAc/hexanes); which was taken through to the next step.

To a solution of silyl ether (3.5 g, 6.96 mmol) in a mixture of *t*-BuOH:acetone:H_2O (1:1:1, v/v, 70 mL) was added OsO_4 (~10 mg) followed by 4-methylmorpholine *N*-oxide (1.77 g, 15.1 mmol). After 16 h, an inconsequential mixture of diastereomer was added a saturated solution of $NaHCO_3$ (100 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue was dissolved in a mixture of 5:1, v/v, THF:H_2O (50 mL) and $NaIO_4$

(1.25 g, 5.7 mmol) was added. After 16 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (75 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography with 20% EtOAc/hexanes as elution provided the desired product (2.0 g, 57% over 3 steps) as a pale yellow oil: R_f 0.40 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.67-7.63 (m, 4H), 7.45-7.35 (m, 6H), 4.30 (dddd, *J* = 12.4, 4.0, 2.4, 2.4 1H), 3.94 (appt, *J* = 7.2 Hz, 1H), 3.82 (dd, *J* = 3.6, 2.4 Hz, 1H), 3.63 (dd, *J* = 10.4, 8.0 Hz, 1H), 3.48 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.26 (dd, *J* = 7.2, 3.4 Hz, 1H), 2.67 (ddd, *J* = 16.4, 8.8, 2.8 Hz, 1H), 2.46 (ddd, *J* = 16.4, 4.4, 1.6 Hz, 1H), 1.97 (ddd, *J* = 14.0, 10.9, 3.2 Hz, 1H), 1.61 (ddd, *J* = 14.0, 3.2, 3.2 Hz, 1H) 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 135.8, 135.7, 133.4, 133.1, 129.90, 129.89, 127.7, 127.7, 77.7, 76.9, 66.2, 61.7, 56.5, 48.7, 30.7, 30.5, 27.0, 19.3; IR (thin film) ν 3070, 3049, 2931, 2893, 1857, 1727, 1472, 1427, 1105, 824, 741, 702 cm^{-1}; HRMS *m/z* 503.1255, (calcd for $C_{25}H_{32}BrO_4Si$ $[M-H]^+$, 503.1253).



2.132 **2.133**

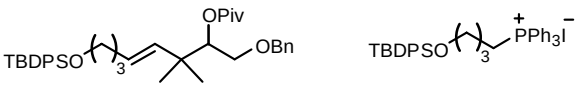
(5*R*,6*R*)-5-Benzyloxy-7-[(2*R*,4*R*,5*S*,6*S*)-6-bromomethyl-5-(di-*tert*-butylphenylsilanyloxy)-4-methoxytetrahydropyrano-2-yl]-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.132) and **(5*S*,6*S*)-5-Benzyloxy-7-[(2*R*,4*R*,5*S*,6*S*)-6-bromomethyl-5-(di-*tert*-butylphenylsilanyloxy)-4-methoxytetrahydropyrano-2-yl]-6-hydroxy-3,3-dimethylhept-1-en-4-one (2.133)** The title compounds were prepared according to the General Procedure of Mukaiyama Aldol described above. Purification

by flash chromatography on silica gel with 10% EtOAc/hexanes for elution provided *β*-alcohol **2.132** (203 mg, 58% based on recovered starting material) and *β*-alcohol **2.133** (67 mg, 19% based on recovered starting material) as colorless oils.

2.132: R_f 0.20 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.63 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.43-7.26 (m, 11H), 6.00 (dd, *J* = 17.5, 11.5 Hz, 1H), 5.21 (s, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 4.5 Hz, 1H), 4.36 (d, *J* = 11.5 Hz, 1H), 4.34-4.30 (m, 1H), 4.05 (dddd, *J* = 10.0, 10.0, 3.0, 3.0 Hz, 1H), 3.84 (dddd, *J* = 6.0, 6.0, 2.5, 2.5 Hz, 1H), 3.72 (app t, *J* = 3.0 Hz, 1H), 3.59 (dd, *J* = 10.5, 8.5 Hz, 1H), 3.40 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.27 (q, *J* = 4.0 Hz, 1H), 2.92 (s, 3H), 2.84-2.80 (m, 1H), 1.93 (ddd, *J* = 13.5, 10.0, 3.0 Hz, 1H), 1.73 (ddd, *J* = 14.5, 9.5, 2.5 Hz, 1H), 1.64 (ddd, *J* = 14.0, 9.0, 2.5 Hz, 1H), 1.49 (ddd, *J* = 14.0, 3.0, 3.0 Hz, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 141.7, 137.5, 135.8, 135.7, 133.5, 133.3, 129.8, 129.8, 128.4, 128.0, 127.9, 127.7, 127.7, 115.0, 82.5, 77.2, 77.2, 72.0, 68.2, 67.5, 63.4, 56.3, 50.5, 36.5, 31.6, 30.7, 26.9, 23.6, 23.4, 19.3.

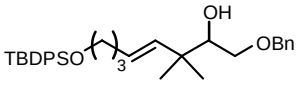
2.133: R_f 0.25 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.64 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.43 (dddd, *J* = 7.5, 7.5, 2.5, 2.5 Hz, 1H), 7.39-7.25 (m, 10H), 5.98 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.17 (dd, *J* = 11.0, 1.0 Hz, 2H), 5.15 (dd, *J* = 18.0, 0.5 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 5.0 Hz, 1H), 4.13 (dddd, *J* = 10.0, 4.5, 1.5 Hz, 1H), 3.97-3.89 (m, 2H), 3.72 (dd, *J* = 3.0, 2.5 Hz, 1H), 3.68 (dd, *J* = 11.0, 9.0 Hz, 1H), 3.35 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.23 (ddd, *J* = 3.0, 3.0, 3.0 Hz, 1H), 2.92 (s, 3H), 1.96 (ddd, *J* = 14.0, 10.5, 3.0 Hz, 1H), 1.86 (ddd, *J* = 14.5, 10.0, 10.0 Hz, 1H), 1.75 (ddd, *J* = 14.5, 2.0, 2.0 Hz, 1H), 1.54 (ddd, *J* = 14.0, 3.0, 3.0 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 141.9, 137.8, 135.74, 135.7, 133.3, 133.1, 129.91, 129.90, 128.3, 127.9, 127.72, 127.7, 114.7, 82.1, 77.6, 76.8, 72.9, 72.5, 67.2, 66.8, 56.5, 50.6, 36.7, 31.2, 30.9,

26.9, 23.6, 23.4, 19.2; HRMS *m/z* 723.2719, (calcd for $C_{39}H_{52}BrO_6Si$ $[M+H]^+$, 723.2717).



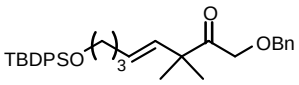
2.134A **2.134B**

2,2-Dimethylpropionic acid (*E*)-1-benzyloxymethyl-7-(*tert*-butyldiphenylsilanyloxy)-2,2-dimethylhept-3-enyl ester (2.134A). To a solution of Wittig salt **2.134B**[96] (6.35 g, 7.0 mmol) in THF (100 mL) at 0°C was added dropwise a solution of n-BuLi in hexanes (2.12 M, 3.30 mL). After 30 min, the reaction mixture was cooled to –78°C and a solution of aldehyde **3.47** (2.04 g, 6.7 mmol) in THF (30 mL) was added. After 15 min, the cold bath was removed. After 16 h, the reaction mixture was poured into a saturated solution of NH_4Cl (50 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided the desired product (3.49 g, 83%) as a colorless oil: R_f 0.60 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.0, 1.6 Hz, 4H), 7.44-7.25 (m, 11H), 5.27-5.25 (m, 2H), 5.16 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.53 (d, *J* = 12.4 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.67 (t, *J* = 6.4 Hz, 1H), 3.66 (dd, *J* = 11.6, 2.4 Hz, 1H), 3.50 (dd, *J* = 10.8, 8.8 Hz, 1H), 2.29-2.26 (m, 2H), 1.61 (dddd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 2H), 1.21 (s, 9H), 1.12 (s, 3H), 1.10 (s, 3H), 1.05 (s, 9H).



2.134C

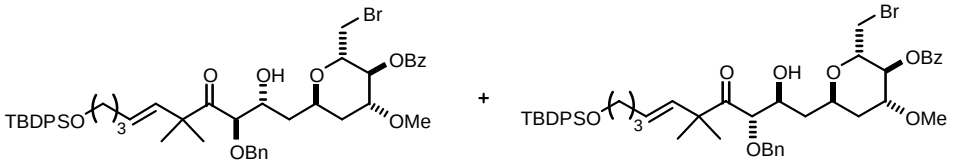
(*E*)-1-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxy)-3,3-dimethyloct-4-en-2-ol (2.134C). To a solution of **2.134A** (above) (2.4 g, 4.0 mmol) in a mixture of CH_2Cl_2:toluene (3:1, v/v, 60 mL) at –78°C was added a solution of DIBAL-H in toluene (1.5 M, 6.65 mL). After the addition was completed, the cold bath was replaced by an ice bath and the reaction was monitored by TLC. Upon the consumption of the starting material, EtOAc (20 mL) was added dropwise followed a saturated solution of Rochelle salt (20 mL). After 30 min, the organic layer separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided the desired product (3.49 g, 83%) as a colorless oil: R_f 0.40 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.5, 1.8 Hz, 4H), 7.43-7.26 (m, 11H), 5.28-5.25 (m, 2H), 4.52 (s, 2H), 3.65 (t, *J* = 6.6 Hz, 1H), 3.67-3.62 (m, 1H), 3.61 (dd, *J* = 9.6, 2.7 Hz, 1H), 3.37 (t, *J* = 9.0 Hz, 1H), 2.40 (d, *J* = 2.1 Hz, 1H), 2.24 (ddd, *J* = 8.1, 8.1, 5.4 Hz, 2H), 1.58 (dddd, *J* = 6.3, 6.3, 6.3, 6.3 Hz, 1H), 1.12 (s, 3H), 1.10 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 135.6, 135.4, 134.0, 130.7, 129.5, 128.4, 127.7, 127.65, 127.6, 77.2, 73.3, 71.6, 63.5, 39.5, 33.1, 26.8, 25.3, 25.2, 24.4, 19.2; IR (thin film) ν 3479 (br), 3068, 2958, 2933, 2864, 1476, 1428, 1111, 824 cm^{-1}; HRMS *m/z* 517.3145, (calcd for $C_{33}H_{45}O_3Si$ $[M+H]^+$, 517.3138).



2.134

(*E*)-1-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxy)-3,3-dimethyloct-4-en-2-one (2.134). To a solution of oxalyl chloride (0.45 mL, 5.22 mmol) in CH_2Cl_2 (20 mL) at –78°C was

added dropwise a solution of DMSO (0.62 mL, 8.75 mmol) in CH_2Cl_2 (5 mL). After 30 min, a solution of alcohol **2.134B** (1.5 g, 2.90 mmol) in CH_2Cl_2 (5 mL) was added dropwise. After 1 h, to the reaction mixture was added a solution of Hunig's base (2.43 mL, 14 mmol) in CH_2Cl_2 (5 mL). After 15 min, the cold bath was removed. After 5 h, the reaction mixture was poured into deionized H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided the desired product (1.40 g, 93%) as a colorless oil: R_f 0.65 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.6, 2.0 Hz, 4H), 7.42-7.25 (m, 11H), 5.40 (ddd, *J* = 11.2, 1.6, 1.6 Hz, 1H), 5.33 (ddd, *J* = 11.2, 7.2, 7.2 Hz, 1H), 4.53 (s, 2H), 4.26 (s, 2H), 3.58 (t, *J* = 6.8 Hz, 1H), 1.93 (dddd, *J* = 7.2, 7.2, 7.2, 7.2 Hz, 2H), 1.55-1.48 (m, 2H), 1.22 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 137.5, 135.5, 133.9, 133.6, 133.4, 129.5, 128.4, 127.9, 127.8, 127.6, 73.1, 70.9, 63.3, 47.3, 32.2, 26.8, 26.3, 24.9, 19.2; IR (thin film) ν 3068, 2964, 2926, 2854, 1718, 1470, 1425, 1394, 1356, 1107 cm^{-1}; HRMS *m/z* 515.2966, (calcd for $C_{33}H_{43}O_3Si$ $[M+H]^+$, 515.2966).



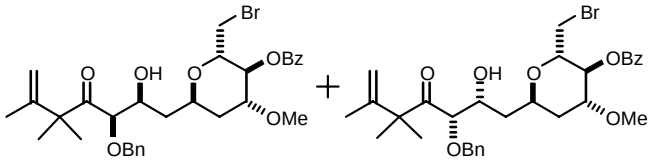
2.135 **2.136**

Benzoic acid (2*S*,3*S*,4*R*,6*R*)-6-[(E)-(2*R*,3*R*)-3-benzyloxy-10-(di-*tert*-butylphenylsilanyloxy)-2-hydroxy-5,5-dimethyl-4-oxodec-6-enyl]-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (2.135) and **Benzoic acid (2*S*,3*S*,4*R*,6*R*)-6-[(E)-(2*S*,3*S*)-3-benzyloxy-10-(di-*tert*-butylphenylsilanyloxy)-2-hydroxy-5,5-dimethyl-4-oxodec-6-enyl]-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (2.136)** The

title compounds were prepared according to the General Procedure of Mukaiyama Aldol described above. Purification by flash chromatography on silica gel with 20% EtOAc/hexanes for elution provided 2,3-*anti*-3,5-*anti* **2.135** (234 mg, 44%) and 2,3-*anti*-3,5-*syn* **2.136** (58 mg, 11%) as pale yellow oils.

2.135: R_f 0.35 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 6.9 Hz, 2H), 7.65-7.54 (m, 5H), 7.45-7.24 (m, 13H), 5.45-5.39 (m, 2H), 5.11 (dd, *J* = 3.9, 3.0 Hz, 1H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.42-4.36 (m, 1H), 4.32 (d, *J* = 3.9 Hz, 1H), 4.28-4.19 (m, 1H), 4.06 (ddd, *J* = 8.7, 5.4, 3.0 Hz, 1H), 3.81 (dd, *J* = 10.5, 9.0 Hz, 1H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.64-3.58 (m, 2H), 3.39 (s, 3H), 2.72 (d, *J* = 6.6 Hz, 1H), 2.07-2.02 (m, 2H), 1.85 (ddd, *J* = 17.4, 9.0, 3.3 Hz, 1H), 1.77-1.70 (m, 1H), 1.72 (dd, *J* = 6.3, 6.0 Hz, 2H), 1.56 (ddd, *J* = 13.5, 6.0, 6.0 Hz, 2H), 1.32 (s, 3H), 1.28 (s, 3H), 1.02 (s, 9H); HRMS *m/z* 883.3197, (calcd for $C_{49}H_{60}BrO_8Si$ $[M-H]^+$, 883.3241).

2.136: R_f 0.40 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.65-7.56 (m, 5H), 7.47-7.27 (m, 13H), 5.43 (d, *J* = 11.4 Hz, 1H), 5.35 (dd, *J* = 11.1, 7.0 Hz, 1H), 5.09 (s, 1H), 4.78 (d, *J* = 11.1 Hz, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 9.3 Hz, 1H), 4.31 (d, *J* = 3.0 Hz, 1H), 4.19-4.05 (m, 1H), 3.96 (t, *J* = 10.8 Hz, 1H), 3.65 (t, *J* = 10.5 Hz, 2H), 3.60 (d, *J* = 6.3 Hz, 2H), 3.39 (s, 3H), 2.03-1.54 (m, 9H), 1.30 (s, 3H), 1.26 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 165.4, 138.2, 135.5 (2C), 133.9, 133.44, 133.40, 132.4, 129.8, 129.5, 129.4, 128.5, 128.2, 127.63, 127.60 (2C), 127.4, 107.7, 84.3, 75.1, 74.3, 73.6, 73.5, 67.3, 67.0, 63.3, 57.4, 48.7, 36.2, 32.5, 31.9, 30.2, 26.8, 26.1, 25.8, 24.9, 19.1; HRMS *m/z* 885.3411, (calcd for $C_{49}H_{62}BrO_8Si$ $[M+H]^+$, 885.3397).

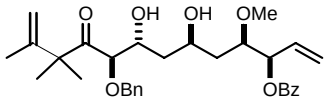


2.137 **2.138**

Acetic acid (2*S*,3*S*,4*R*,6*R*)-6-((3*S*,4*R*)-4-benzyloxy-3-hydroxy-6,6,7-trimethyl-5-oxooct-7-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (Syn-major isomer): To a solution of LDA (0.65 mmol) in THF (2 mL) at –78°C was added a solution of ketone **2.72** (0.15 g, 0.65 mmol) in THF (2 mL) followed by a solution of aldehyde **2.112** (0.2 g, 0.54 mmol) in THF (2 mL). After 1.5 h, the reaction mixture was poured into a saturated solution of NH_4Cl (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 15% EtOAc/hexanes as elution provided the desired syn diastereoisomers (120 mg, 40%): R_f 0.33 (33% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.58 (dddd, *J* = 7.5, 7.5, 1.3, 1.3 Hz, 1H), 7.45 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 2H), 7.32-7.26 (m, 5 H), 5.14 (dd, *J* = 3.5, 3.5 Hz, 1H), 5.02 (dd, *J* = 1.5, 1.0 Hz, 1H), 4.96 (s, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 3.3 Hz, 1H), 4.25-4.20 (m, 1H), 4.16-4.11 (m, 1H), 4.08 (ddd, *J* = 8.6, 5.7, 3.3 Hz, 1H), 3.81 (dd, *J* = 10.9, 8.9 Hz, 1H), 3.66 (dd, *J* = 10.9, 5.7 Hz, 1H), 3.62 (dd, *J* = 8.1, 4.2 Hz, 1H) 3.41 (s, 3H), 2.46 (d, *J* = 7.9 Hz, 1H), 1.84 (ddd, *J* = 14.0, 9.8, 3.4 Hz, 1H), 1.77 (ddd, *J* = 14.0, 3.7, 3.7 Hz, 1H), 1.74-1.67 (m, 2H), 1.70 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 165.5, 146.7, 137.7, 133.4, 129.8, 129.7, 128.5, 128.4, 128.0, 127.9, 112.9, 81.6, 75.0, 74.9, 72.4, 68.6, 68.1, 63.2, 57.3, 53.1, 39.3, 32.1, 30.9, 24.1, 23.4, 20.4; IR (thin film) ν 3501 (br), 3089-2828,

1725, 1277, 1109, 1070, 714 cm^{-1}; HRMS *m/z* 603.1951 (calcd for $C_{31}H_{39}BrO_7$ $[M+H]^+$, 603.1957).

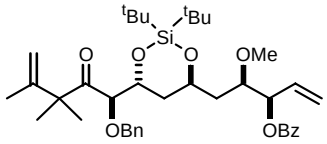
Syn minor isomer: R_f 0.29 (33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.58 (dddd, *J* = 7.5, 7.5, 1.4, 1.4 Hz, 1H), 7.45 (dd, *J* = 7.9, 7.5 Hz, 2H), 7.34-7.26 (m, 5H), 5.13 (dd, *J* = 3.4, 3.1 Hz, 1H), 5.02 (s, 1H), 4.97 (s, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.35 (d, *J* = 3.4 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.20-4.15 (m, 1H), 4.14-4.09 (m, 1H), 3.96 (dddd, *J* = 9.6, 9.6, 3.4, 3.4 Hz, 1H), 3.79 (dd, *J* = 10.6, 8.9 Hz, 1H), 3.61 (dd, *J* = 10.9, 5.8 Hz, 1H), 3.64-3.59 (m, 1H), 3.42 (s, 3H), 3.04 (d, *J* = 4.8 Hz, 1H), 1.94 (ddd, *J* = 14.4, 8.9, 8.9 Hz, 1H), 1.83 (ddd, *J* = 13.0, 9.6, 3.4 Hz, 1H), 1.74 (ddd, *J* = 13.3, 3.4, 3.4 Hz, 1H), 1.70-1.67 (m, 1H), 1.70 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 165.4, 146.9, 137.6, 133.4, 129.8, 129.5, 128.4, 128.1, 127.9, 127.9, 112.9, 79.8, 74.9, 74.6, 72.4, 70.8, 67.6, 66.0, 57.4, 53.4, 37.8, 31.9, 30.4, 23.8, 23.4, 20.4; IR (thin film) ν 3522 (br), 3085-2900, 1722, 1270, 1070 cm^{-1}; HRMS *m/z* 603.1946 (calcd for $C_{31}H_{39}BrO_7$ $[M+H]^+$, 603.1957).



2.139A

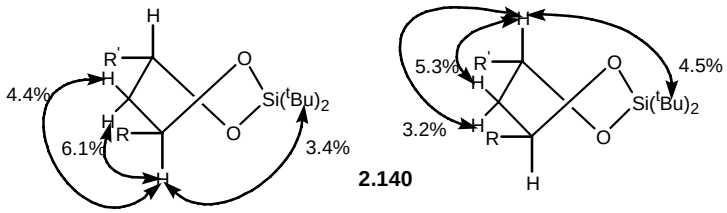
Benzoic acid (1*R*,2*R*,4*R*,7*R*,8*R*)-8-benzyloxy-4,7-dihydroxy-2-methoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (2.139A). Reaction procedure was run as in **2.140A** to yield a colorless oil (100 mg, 77%). **2.140A**: R_f 0.23 (50% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.57 (dddd, *J* = 7.5, 7.5, 1.2, 1.2 Hz, 1H), 7.44 (ddd, *J* = 7.5, 7.5, 1.8 Hz, 2H), 7.31-7.23 (m, 5H), 5.91 (ddd, *J* = 15.9, 10.5, 5.4 Hz, 1H), 5.71 (dd, *J* = 5.4, 5.1 Hz, 1H), 5.36 (dd, *J* = 17.4, 1.2, 1.2 Hz, 1H), 5.30 (d, *J* = 10.8, 1.2, 1.2 Hz, 1H), 5.03 (s, 1H), 5.00 (s, 1H), 4.50 (d, *J* = 11.1 Hz,

1H), 4.42 (d, *J* = 4.8 Hz, 1H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.28-4.20 (m, 1H), 4.14-4.05 (m, 1H), 3.67 (ddd, *J* = 10.2, 4.8, 4.8 Hz, 1H), 3.61 (br s, 1H), 3.52 (s, 3H), 3.23 (br s, 1H), 1.77-1.52 (m, 4H), 1.66 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 165.3, 146.4, 137.7, 133.3, 131.8, 129.8, 129.6, 128.5, 128.3, 127.9, 127.8, 118.3, 113.3, 82.4, 81.3, 73.6, 72.1, 68.9, 68.8, 58.4, 53.5, 38.3, 36.5, 23.4, 23.2, 20.5; IR (thin film) ν 3487 (br), 3094-2830, 1720, 1277, 1113, 1073, 720 cm^{-1}; HRMS *m/z* 525.2856 (calcd for $C_{31}H_{41}O_7$ $[M+H]^+$, 525.2852).

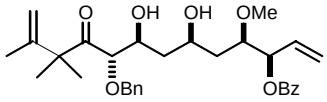


2.139

Benzoic acid (*R*)-1-{(*R*)-2-[(4*R*,7*R*)-7-((*R*)-1-benzyloxy-3,3,4-trimethyl-2-oxopent-4-enyl)-2,2-di-*tert*-butyl[1,3,2]dioxasilepan-4-yl]-1-methoxyethyl}allyl ester (2.139). Reaction procedure was run as in **2.140** to yield a colorless oil (118 mg, 93%): R_f 0.61 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ 8.20 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.23 (d, *J* = 6.9 Hz, 2H), 7.12-7.04 (m, 6H), 6.06-5.94 (m, 2H), 5.37 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.08 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.89 (s, 1H), 4.88 (s, 1H), 4.78 (ddd, *J* = 9.0, 6.3, 2.1 Hz, 1H), 4.66-4.60 (m, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 6.3 Hz, 1H), 3.70 (ddd, *J* = 6.3, 6.3, 4.2 Hz, 1H), 3.22 (s, 3H), 2.22-2.10 (m, 2H), 1.93-1.83 (m, 2H), 1.60 (s, 3H), 1.26 (s, 6H), 1.12 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, C_6D_6) δ 208.5, 165.4, 147.0, 138.4, 133.6, 132.9, 130.9, 130.1, 128.6, 128.5, 127.8, 117.5, 112.9, 81.8, 79.2, 74.7, 72.6, 70.0, 68.7, 58.0, 53.6, 38.0, 35.0, 27.4, 27.3, 23.8, 23.2, 21.7, 20.9, 20.5; IR (thin film) ν 3096-2857, 1722, 1273, 1117 cm^{-1}; HRMS *m/z* 665.3866 (calcd for $C_{39}H_{57}O_7Si$ $[M+H]^+$, 665.3874).



2.140

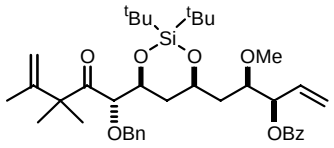


2.140A

Benzoic acid (1*R*,2*R*,4*R*,7*S*,8*S*)-8-benzyloxy-4,7-dihydroxy-2-methoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (2.140A). A 25-mL round bottom flask fitted with a reflux condenser was charged with hydroxyketone **2.116** (92 mg, 0.15 mmol), Zn/Cu couple (244 mg, 3.8 mmol), NH_4Cl (40 mg, 0.75 mmol) and 95% EtOH/H_2O (9:1, 14 mL). The suspension was heated at reflux for 16 h. The cooled suspension was filtered through Celite, H_2O (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (elution gradient: 15-35% EtOAc/hexanes) provided diol **2.140A** (60 mg, 74%).

2.140A: R_f 0.25 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.57 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.49 (dd, *J* = 8.1, 7.2 Hz, 2H), 7.34-7.27 (m, 5H), 5.91 (ddd, *J* = 17.1, 10.5, 5.7 Hz, 1H), 5.72 (dd, *J* = 5.7, 5.1 Hz, 1H), 5.37 (d, *J* = 17.4 Hz, 1H), 5.31 (d, *J* = 10.8 Hz, 1H), 4.99 (s, 1H), 4.95 (s, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 3.9 Hz, 1H), 4.13-4.09 (m, 1H), 4.07-3.98 (m, 1H), 3.89 (br s, 2H), 3.72 (ddd, *J* = 8.1, 5.1, 5.1 Hz, 1H), 3.53 (s, 3H), 1.77-1.58 (m, 4H), 1.63 (s, 3H), 1.26 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.7, 165.4,

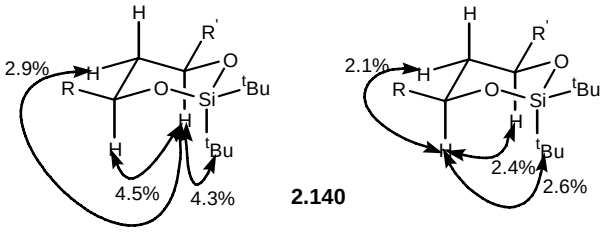
146.4, 137.9, 133.3, 131.9, 129.8, 129.6, 128.5, 128.3, 127.8, 127.7, 118.4, 113.1, 82.1, 81.2, 73.7, 73.0, 72.8, 72.2, 58.5, 53.5, 38.1, 37.2, 23.5, 23.0, 20.4; IR (thin film) ν 3477 (br), 3089-2827, 1725, 1267, 1103, 1033, 715 cm^{-1}; HRMS *m/z* 525.2866 (calcd for $C_{31}H_{41}O_7$ $[M+H]^+$, 525.2852).



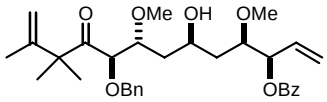
2.140

Benzoic acid (*R*)-1-{(*R*)-2-[(4*R*,7*S*)-7-((*S*)-1-benzyloxy-3,3,4-trimethyl-2-oxopent-4-enyl)-2,2-di-*tert*-butyl[1,3,2]dioxasilepan-4-yl]-1-methoxyethyl}allyl ester (2.140). To a solution of diol **2.140A** (60 mg, 0.11 mmol), pyridine (40 μL, 0.45 mmol) and dimethylformamide (3 mL) at –35 °C was added $(^tBu)_2Si(OTf)_2$ (80 μL, 0.22 mmol) dropwise over 5 min. After 30 min, the reaction mixture was added to aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentration *in vacuo*. Purification by flash chromatography on silica gel (15% EtOAc/hexanes) provided **2.140** (69 mg, 91%): R_f 0.62 (50% EtOAc/hexanes); ^1H NMR (300 MHz, C_6D_6) δ 8.17 (dd, *J* = 6.9, 1.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.15-7.00 (m, 6H), 6.10-5.98 (m, 2H), 5.42 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.09 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.91 (s, 1H), 4.90 (d, *J* = 1.2 Hz, 1H), 4.71 (ddd, *J* = 9.9, 6.6, 1.2 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.42-4.32 (m, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.23 (d, *J* = 6.6 Hz, 1H), 3.67 (ddd, *J* = 10.5, 5.4, 0.0 Hz, 1H), 3.22 (s, 3H), 1.97-1.67 (m, 4H), 1.61 (s, 3H), 1.28 (s, 6H), 1.10 (s, 18H); ^{13}C NMR (75 MHz, C_6D_6) δ 208.7, 165.4, 147.0, 138.5, 133.9, 132.9, 130.9, 130.0, 128.6, 127.9, 117.4, 112.9, 81.6, 79.2, 75.1, 74.5, 72.7, 71.7, 57.8, 53.7, 39.4, 37.9, 27.7, 27.4, 23.8, 23.1, 22.9, 20.5, 19.8;

IR (thin film) ν 3099-2865, 1720, 1262, 1113 cm^{-1}; HRMS *m/z* 665.3876 (calcd for $C_{39}H_{57}O_7Si$ $[M+H]^+$, 665.3874).



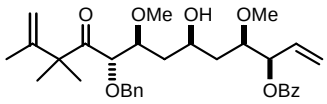
2.140



3.1

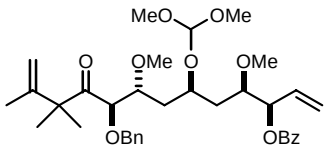
Benzoic acid (1*R*,2*R*,4*R*,7*R*,8*R*)-8-benzyloxy-4-hydroxy-2,7-dimethoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (3.1). A solution mixture of methyl ether **3.9** (83 mg, 0.13 mmol), Zn/Cu couple (879 mg, 13.4 mmol), NH_4Cl (35 mg, 0.65 mmol) in 95% EtOH/H_2O (9:1, 20 mL) was heated at reflux. After 16 h, the reaction mixture was cooled, filtered (Celite), and diluted with H_2O. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic fractions were washed with aqueous $NaHCO_3$ (30 mL), brine and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (elution gradient: 12% EtOAc/hexanes to 25% EtOAc/hexanes) provided hydroxyketone **3.1** (54 mg, 75%): R_f 0.29 (33% EtOAc/hexanes); ^1H NMR (400 MHz, DMSO) δ 7.98 (d, *J* = 8.2, 1.4 Hz, 2H), 7.65 (dddd, *J* = 7.5, 7.5, 1.4, 1.4 Hz, 1H), 7.52 (ddd, *J* = 7.5, 7.5, 1.7 Hz, 2H), 7.31-7.21 (m, 5H), 5.98 (ddd, *J* = 16.4, 10.6, 5.5 Hz, 1H), 5.58 (dd, *J* = 5.5, 4.8 Hz, 1H), 5.27 (dd, *J* = 16.4, 1.4 Hz, 1H), 5.23 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.98 (app t, *J* = 1.4 Hz, 1H), 4.95 (s, 1H), 4.54 (s, 1H), 4.53 (d, *J* = 3.4 Hz, 1H), 4.37 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.6

Hz, 1H), 3.73-3.66 (m, 2H), 3.53 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.31 (s, 3H), 3.20 (s, 3H), 1.59 (s, 3H), 1.57-1.52 (m, 3H), 1.39-1.33 (m, 1H), 1.18 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 210.0, 165.0, 146.5, 138.3, 134.0, 133.7, 129.8, 129.4, 129.1, 128.4, 127.7, 127.6, 117.5, 113.3, 79.0, 78.7, 77.9, 75.1, 71.5, 63.5, 57.7, 57.6, 53.0, 38.8, 38.0, 23.6, 23.3, 20.5; IR (thin film) ν 3507 (br), 3018-2834, 1714, 1636, 1602, 1270, 1113, 1027 cm^{-1}; HRMS *m/z* 539.3007 (calcd for $C_{32}H_{43}O_7$ $[M+H]^+$, 539.3009).



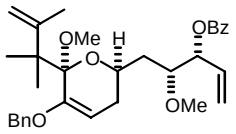
3.1A

Benzoic acid (1*R*,2*R*,4*R*,7*R*,8*S*)-8-benzyloxy-4-hydroxy-2,7-dimethoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (3.1A). Reaction procedure was run as in **3.1** to yield a colorless oil (273 mg, 73%): R_f 0.30 (33% EtOAc/hexanes); ^{1}H NMR (250 MHz,) δ 8.05 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.55 (dddd, *J* = 7.3, 7.3, 2.0, 2.0 Hz, 1H), 7.42 (app t, *J* = 7.7 Hz, 2H), 7.29-7.19 (m, 5H), 5.95 (ddd, *J* = 17.0, 10.7, 5.7 Hz, 1H), 5.69 (dd, *J* = 5.6, 4.6 Hz, 1H), 5.36 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.28 (d, *J* = 10.3 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.517 (d, *J* = 3.6 Hz, 1H), 4.515 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.96-3.90 (m, 1H), 3.71-3.59 (m, 1H), 3.46 (s, 3H), 3.26 (s, 3H), 1.90-1.64 (m, 4H), 1.60 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.3, 165.5, 146.7, 137.6, 133.1, 132.7, 130.0, 129.6, 128.4, 128.3, 127.9, 127.7, 118.0, 113.0, 81.6, 80.5, 78.4, 74.5, 72.5, 68.4, 58.3, 57.2, 53.4, 37.3, 36.6, 23.8, 23.2, 20.4; IR (thin film) ν 3518 (br), 3083, 3068, 3037, 2971, 2932, 2827, 1724, 1639, 1604, 1380, 1309, 1266, 1111, 1028, 985, 721 cm^{-1}; HRMS *m/z* 539.2997 (calcd for $C_{32}H_{43}O_7$ $[M+H]^+$, 539.3009).



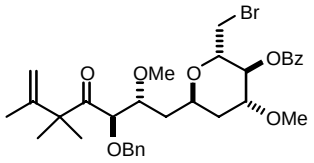
3.5

Benzoic acid (1*R*,2*R*,4*R*,7*R*,8*R*)-8-benzyloxy-4-dimethoxymethoxy-2,7-dimethoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (3.5). To a solution of alcohol **3.1** (30 mg, 0.06 mmol) in trimethyl orthoformate (2 mL) at rt was added PPTS (~10 mg, cat.). After 20 min, no starting material was evident by TLC and Et_3N (0.2 mL) was added. After concentration *under vacuo*, purification by flash chromatography on silica gel with 10% EtOAc/hexanes as elution provided acetal **3.5** (30 mg, 88%): R_f 0.55 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, DMSO) δ 8.18 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.34 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.07-7.04 (m, 6H), 5.91 (ddd, *J* = 7.0, 3.5, 3.5 Hz, 1H), 5.88 (ddd, *J* = 16.0, 10.5, 5.5 Hz, 1H), 5.33 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.14 (s, 1H), 5.06 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.87 (s, 2H), 4.63 (d, *J* = 3.0 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.32 (dddd, *J* = 12.0, 4.5, 4.5, 3.0 Hz, 1H), 4.10 (ddd, *J* = 10.0, 3.0, 2.0 Hz, 1H), 3.66 (ddd, *J* = 8.5, 4.0, 4.0 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 3.17 (s, 3H), 3.12 (s, 3H), 2.22 (ddd, *J* = 15.0, 10.2, 3.0 Hz, 1H), 2.08 (ddd, *J* = 14.5, 10.5, 2.0 Hz, 1H), 2.01 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 1H), 1.94 (ddd, *J* = 14.5, 8.0, 4.0 Hz, 1H), 1.62 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (63 MHz, C_7D_8) δ 209.3, 165.2, 147.7, 138.9, 133.7, 132.8, 131.1, 130.1 (3C), 128.9, 128.5 (2C), 117.5, 114.3, 112.6, 79.4, 78.8, 75.0, 72.3, 70.8, 60.1, 58.1, 57.2, 53.5, 50.6 (2C), 36.7, 36.3, 24.3, 23.6, 14.3; IR (thin film) ν 2975, 2927, 2824, 1717, 1698, 1629, 1552, 1456, 1265, 1104, 1019 cm^{-1}; HRMS *m/z* 613.3371 (calcd for $C_{35}H_{49}O_9$ $[M+H]^+$, 613.3377).



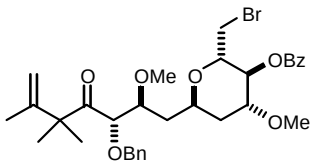
3.8

Cyclohexanecarboxylic acid (R)-1-{(R)-2-[(2R,6R)-5-benzyloxy-6-methoxy-6-(1,1,2-trimethylallyl)-3,6-dihydro-2*H*-pyran-2-yl]-1-methoxyethyl}allyl ester (3.8). In a 10 mL round bottom flask attached to a vigereux condenser and short path distillation apparatus, a solution of ketone **3.1** (68 mg, 0.15 mmol), acetyl chloride (14 mL, 0.20 mmol), trimethyl orthoformate (0.5 mL) and MeOH (0.016 mL, 0.40 mmol) in toluene (5 mL) was heated to 108°C. After the lower boiling solvent had been distilled off, the reaction mixture was removed from the heat and MeOH (2 mL) was added at rt followed by Et_3N (2 mL). The reaction mixture was added to brine (10 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 10-15% EtOAc/hexanes as elution provided methyl ketal **3.8** (54 mg, 80%): R_f 0.53 (25% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 7.1, 1.2 Hz, 2H), 7.56 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.43 (app t, *J* = 7.2 Hz, 2H), 7.39-7.26 (m, 5H), 6.03 (ddd, *J* = 17.0, 10.6, 6.0 Hz, 1H), 5.71 (dd, *J* = 5.7, 4.5 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.29 (d, *J* = 10.6 Hz, 1H), 5.08 (dd, *J* = 5.5, 3.8 Hz, 1H), 4.75 (d, *J* = 7.8 Hz, 2H), 4.68 (s, 1H), 3.75-3.65 (m, 1H), 3.44 (s, 3H), 3.32 (s, 3H), 2.10-1.93 (m, 2H), 1.90-1.69 (m, 2H), 1.81 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 165.7, 151.1, 137.1, 133.4, 133.1, 130.2, 129.7, 128.4 (2C), 128.37, 127.6, 127.2, 117.8, 111.5, 101.9, 98.6, 79.1, 74.9, 69.2, 68.9, 58.1, 52.2, 48.5, 35.8, 29.8, 24.0, 23.6, 22.6 ; HRMS *m/z* 521.2885 (calcd for $C_{32}H_{49}O_6$ $[M+H]^+$, 521.2903).



3.9

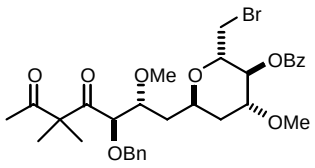
Benzoic acid (2*S*,3*S*,4*R*,6*S*)-6-((2*R*, 3*R*)-3-benzyloxy-2-methoxy-5,5,6-trimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (3.9). To a solution of *β*-hydroxyketone **2.115** (80 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) at rt was added proton sponge™ (86 mg, 0.40 mmol) and MeO_3BF_4 (59 mg, 0.40 mmol). After 6 h, the mixture was transferred to saturated aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (12% EtOAc/hexanes) provided **3.9** as a colorless oil (83 mg, 99%): R_f 0.45 (33% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.2, 1.4 Hz, 2H), 7.58 (dddd, *J* = 7.5, 7.5, 1.3, 1.3 Hz, 1H), 7.45 (dd, *J* = 7.7, 7.1 Hz, 2H), 7.32-7.25 (m, 5H), 5.06 (dd, *J* = 4.6, 4.4 Hz, 1H), 5.00 (s, 1H), 4.97 (s, 1H), 4.66 (d, *J* = 2.4 Hz, 1H), 4.59 (d, *J* =11.9 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.14-4.08 (m, 1H), 4.01-3.96 (m, 1H), 3.83 (ddd, *J* = 10.6, 2.0, 2.0 Hz, 1H), 3.76 (dd, *J* = 10.8, 10.7 Hz, 1H), 3.63-3.55 (m, 1H), 3.58 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 1.87-1.66 (m, 4H), 1.65 (s, 3H), 1.27 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.2, 165.6, 146.6, 137.8, 133.3, 129.8, 129.6, 128.5, 128.3, 127.9, 127.7, 113.3, 77.6, 77.5, 75.2, 74.1, 72.1, 69.7, 63.6, 57.9, 57.3, 53.5, 34.2, 32.3, 31.4, 23.6, 23.4, 20.6; IR (thin film) ν 3051-2251, 1717, 1265, 901 cm^{-1}; HRMS *m/z* 617.2113 (calcd for $C_{32}H_{41}BrO_7$ $[M+H]^+$, 617.2114).



3.9A

Benzoic acid (2*S*,3*S*,4*R*,6*S*)-6-((2*S*,3*S*) 3-benzyloxy-2-methoxy-5,5,6-trimethyl-4-oxohept-6-enyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (3.9A). To a solution mixture of β-hydroxyketone **2.116** (208 mg, 0.34 mmol) in CH_2Cl_2 (10 mL) at rt was added proton sponge™ (222 mg, 1.03 mmol) and MeO_3BF_4 (153 mg, 1.03 mmol). The mixture was stirred for 6 h before being added to aqueous NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel (12% EtOAc/hexanes) provided **3.9A** as a colorless oil (181 mg, 86%): R_f 0.48 (33% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.55 (app. d, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 2H), 7.30-7.23 (m, 5H), 5.19 (t, *J* = 4.2 Hz, 1H), 4.98 (app. d, *J* = 12.8 Hz, 2H), 4.56-4.49 (m, 2H), 4.15-4.05 (m, 2H), 3.68 (app. d, *J* = 7.1 Hz, 2H), 3.65-3.60 (m, 2H), 3.40 (s, 3H), 3.38-3.34 (m, 1H), 3.29 (s, 3H), 2.05-1.73 (m, 4H), 1.65 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{1}H NMR (250 MHz, C_6D_6) δ 8.13 (dd, *J* = 8.5, 1.6 Hz, 2H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.20-7.00 (m, 6H), 5.26 (app t, *J* = 3.4 Hz, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 5.4 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.21-4.14 (m, 2H), 3.92 (ddd, *J* = 10.4, 5.3, 0.0 Hz, 1H), 3.72 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.46 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.43 (ddd, *J* = 7.6, 3.8, 0.0 Hz, 1H), 3.15 (s, 3H), 3.01 (s, 3H), 2.14 (ddd, *J* = 14.9, 7.4, 5.5 Hz, 1H), 2.01 (ddd, *J* = 14.6, 4.9, 4.9 Hz, 1H), 1.71-1.57 (m, 2H), 1.63 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.6, 165.4, 146.6, 137.9, 133.3, 129.74, 129.7, 128.4, 128.2, 127.8, 127.6,

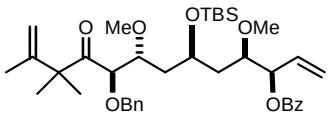
113.1, 79.5, 78.2, 75.0, 74.4, 72.3, 68.4, 65.0, 57.6, 57.3, 53.5, 34.7, 32.0, 31.0, 23.6, 23.1, 20.4; IR (thin film) ν 2983-2832, 1712, 1261, 1111 cm^{-1}; HRMS *m/z* 617.2112 (calcd for $C_{32}H_{42}BrO_7$ $[M+H]^+$, 617.2114).



3.10

Benzoic acid (2*S*,3*S*,4*R*,6*S*)-6-((2*R*,3*R*)-3-benzyloxy-2-methoxy-5,5-dimethyl-4,6-dioxoheptyl)-2-bromomethyl-4-methoxytetrahydropyran-3-yl ester (3.10). To a solution of olefin **3.9** (0.10 g, 0.16 mmol) in DMF (2 mL) was added at rt a solution of OsO_4 (a crystal) in *t*-BuOH (0.2 mL). After 5 min, Oxone (0.40 g, 0.65 mmol) was added and stirred until the solution became colorless. Na_2SO_3 (0.12 g, 0.95 mmol) was added and after 1h, EtOAc (10 mL) and a 1% HCl aqueous solution (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (15 mL), dried (Na_2SO_4), filtered through Celite and concentrated. Purification by flash chromatography on silica gel (12% EtOAc/hexanes) provided **3.10** as a colorless oil (65 mg, 66%): R_f 0.45 (33% EtOAc/hexanes); ^{1}H NMR (250 MHz, C_6D_6) δ 8.10 (dd, *J* = 7.0, 1.6 Hz, 2H), 7.33 (d, *J* = 7.0 Hz, 2H), 7.17-6.97 (m, 6H), 5.22 (dd, *J* = 3.6, 3.6 Hz, 1H), 4.77 (d, *J* = 10.7 Hz, 1H), 4.40-4.15 (m, 4H), 4.30 (d, *J* = 10.7 Hz, 1H), 3.75 (dd, *J* = 10.6, 8.8 Hz, 1H), 3.49 (dd, *J* = 10.6, 5.3 Hz, 1H), 3.42 (dd, *J* = 8.0, 4.2 Hz, 1H), 3.31 (s, 3H), 2.99 (s, 3H), 2.02 (ddd, *J* = 14.5, 10.5, 2.9 Hz, 1H), 1.82 (ddd, *J* = 14.0, 10.3, 1.6 Hz, 1H), 1.71-1.61 (m, 1H), 1.66 (s, 3H), 1.54 (ddd, *J* = 13.7, 3.8, 3.8 Hz, 1H), 1.14 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (63 MHz, C_6D_6) δ 208.5, 207.1, 165.4, 138.3, 133.2, 130.4, 130.1 (2C), 128.6 (2C), 127.8,

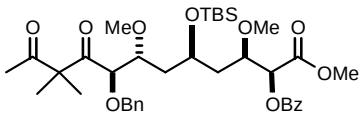
83.4, 79.4, 75.2 (2C), 74.0, 68.9, 63.2, 59.7, 58.2, 56.9, 36.8, 32.7, 31.3, 25.6, 22.4, 21.3; HRMS *m/z* 618.1899 (calcd for $C_{31}H_{40}BrO_8$ $[M+H]^+$, 619.1907).



3.14

Benzoic acid (1*R*,2*R*,4*R*,7*R*,8*S*)-8-benzyloxy-4-(*tert*-butyldimethylsilanoxy)-2,7-dimethoxy-10,10,11-trimethyl-9-oxo-1-vinyldodec-11-enyl ester (3.14). To a solution of **3.1** (140 mg, 0.26 mmol), imidazole (39 mg, 0.57 mmol) and DMF (2 mL) was added *t*-Bu(Me)$_2$SiCl (79 mg, 0.52 mmol). After 12 h the reaction mixture was added to saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentration *in vacuo*. Purification by flash chromatography on silica gel (10% EtOAc/hexanes) provided **3.14** (140 mg, 82%): R_f 0.59 (25% EtOAc/hexanes); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.54 (dddd, *J* = 7.4, 7.4, 2.4, 2.4 Hz, 1H), 7.42 (ddd, *J* = 7.6, 7.2, 1.2 Hz, 2H), 7.30-7.24 (m, 5H), 5.92 (ddd, *J* = 16.9, 10.6, 5.9 Hz, 1H), 5.58 (dd, *J* = 5.5, 5.4 Hz, 1H), 5.39 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.30 (dd, *J* = 10.6, 0.9 Hz, 1H), 4.96 (s, 1H), 4.90 (s, 1H), 4.56 (d, *J* = 3.0 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.11-4.03 (m, 1H), 3.72 (ddd, *J* = 10.4, 2.0, 2.0 Hz, 1H), 3.52 (ddd, *J* = 7.9, 4.9, 3.4 Hz, 1H), 3.45 (s, 3H), 3.25 (s, 3H), 1.95-1.52 (m, 4H), 1.62 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 210.1, 165.5, 146.9, 138.0, 133.0, 130.1, 129.7, 128.3 (2C), 128.1, 127.7, 127.5, 117.9, 112.8, 78.8, 78.3, 78.2, 75.5, 71.9, 66.3, 58.8, 57.0, 53.3, 39.5, 37.2, 25.9, 23.9, 23.3, 20.5, 17.9, -4.0, -4.5; IR (thin film) ν 3085, 3035, 2957, 2932, 2857,

2825, 1728, 1636, 1597, 1359, 1312, 1266, 1173, 1109, 1067, 1028, 714 cm^{-1}; HRMS *m/z* 653.3864 (calcd for $C_{38}H_{57}O_7Si$ $[M+H]^+$, 653.3874).



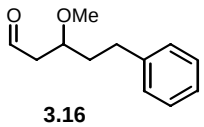
3.15

Benzoic acid (1*S*,2*R*,4*R*,7*R*,8*R*)-8-benzyloxy-4-(*tert*-butyldimethylsilanyloxy)-2,7-dimethoxy-1-methoxycarbonyl-10,10-dimethyl-9,11-dioxododecyl ester (3.15). A solution mixture of compound **3.14** (101 mg, 0.15 mmol) and $NaHCO_3$ (126 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) at –78°C was subjected to a stream of ozone until a faint blue solution persisted, then triphenyl phosphine (79 mg, 0.30 mmol) was added. After 30 min the cold bath was removed and the reaction mixture at rt was added to H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentration *in vacuo*. The residue was passed through a short column of silica gel (0.2" x 0.1") to remove the excess PPh_3 or $P(O)PH_3$ (EtOAc for elution).

After solvent was removed, the residue was added to a solution of *t*-BuOH/H_2O (1:1, v/v 2mL), 2-methyl-2-butene (1 mL), NaH_2PO_4•H_2O (196 mg, 1.42 mmol) and $NaClO_2$ (90 mg, 1.00 mmol) at 0°C. After 1 h, the mixture was added to aqueous $Na_2S_2O_3$ (1 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with 10% aqueous HCl (5 mL), H_2O (5 mL), and dried ($MgSO_4$). After filtering the mixture through a pad of Celite, the residue was concentrated *in vacuo*.

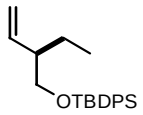
To a solution of the aforementioned acid in benzene (2 mL) and methanol (0.2 mL) was added Me_3SiCHN_2 (2.0 M in hexanes) until the yellow color persisted momentarily.

After 30 min the solution was concentrated and purification by flash chromatography on silica gel (20% EtOAc/hexanes) provided **3.15** (46 mg over 3 steps, 45%): R_f 0.51 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.58 (dddd, *J* = 7.6, 7.6, 1.2, 1.2 Hz, 1H), 7.44 (ddd, *J* = 8.0, 8.0, 2.0 Hz, 2H), 7.33-7.28 (m, 5H), 5.34 (d, *J* = 3.2 Hz, 1H), 4.80 (d, *J* = 10.4 Hz, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.31 (d, *J* = 2.0 Hz, 1H), 4.05-3.99 (m, 2H), 3.92 (ddd, *J* = 10.0, 2.0, 2.0 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 3H), 3.29 (s, 3H), 2.00-1.79 (m, 3H), 1.86 (s, 3H), 1.44 (ddd, *J* = 14.8, 9.6, 2.0, 1H), 1.29 (s, 3H), 1.18 (s, 3H), 0.91 (s, 9H), 0.091 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 208.5, 168.9, 166.0, 137.6, 133.4, 130.0, 129.3, 128.4, 128.3, 128.1, 127.9, 81.7, 80.6, 77.5, 74.1, 73.8, 66.9, 59.4, 58.5, 57.1, 52.4, 38.9, 38.9, 25.9, 22.5, 21.5, 18.0, 14.1, -4.1, -4.5; IR (thin film) ν 2955, 2927, 2855, 1771, 1726, 1698, 1300, 1259, 1214, 1108, 1071, 1027, 712 cm^{-1}; HRMS *m/z* 687.3550 (calcd for $C_{37}H_{55}O_{10}Si$ $[M+H]^+$, 687.3565).



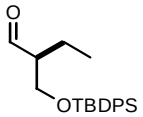
3.16

3-Methoxy-5-phenylpentanal (3.16). R_f 0.45 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (app t, *J* = 7.2 Hz, 1H), 7.29-7.16 (m, 5H), 3.72 (dddd, *J* = 6.4, 6.4, 4.2, 4.2 Hz, 1H), 3.35 (s, 3H), 2.66 (dddd, *J* = 6.3, 6.3, 4.5, 4.5 Hz, 2H), 2.62 (dd, *J* = 5.1, 2.1 Hz, 1H), 2.56 (dd, *J* = 5.1, 2.1 Hz, 1H), 1.96-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.9, 141.3, 128.1, 128.0, 125.6, 75.1, 56.3, 47.4, 35.3, 30.9.



3.25

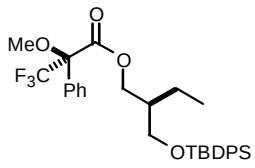
***tert*-Butyl(2-ethylbut-3-enyloxy)diphenylsilane (3.25).** To a solution of (S)-2-Ethyl-3-buten-1-ol[97] (0.60 g, 6.0 mmol) in DMF (5 mL) at 0°C was added sequentially imidazole (0.68 g, 10.0 mmol), DMAP (cat.) and $^{t}Bu(Me)_2SiCl$ (1.5 g, 6.0 mmol). After 16 h, the reaction mixture was added to a saturated solution of NH_4Cl (50 mL) and EtOAc (40 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The collected organic layers were washed with H_2O (2 × 25 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 1% EtOAc/hexanes provided the desired oil (1.70 g, 84%): R_f 0.60 (2% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.5, 3.0 Hz, 2H), 7.65 (dd, *J* = 7.5, 2.4 Hz, 2H), 7.44-7.25 (m, 6H), 5.65 (ddd, *J* = 16.5, 11.1, 8.1 Hz, 1H), 5.02 (dd, *J* = 17.7, 2.1 Hz, 1H), 5.00 (dd, *J* = 10.5, 2.1 Hz, 1H), 3.58 (d, *J* = 6.3 Hz, 1H), 2.16-2.08 (m, 1H), 1.64-1.57 (m, 1H), 1.28 (dddd, *J* = 10.5, 7.5, 7.5, 7.5 Hz, 1H), 1.04 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 135.6, 134.0, 129.5, 127.6, 115.5, 67.0, 48.2, 26.8, 23.6, 19.3, 11.5; HRMS *m/z* 339.2151 (calcd for $C_{22}H_{31}OSi$ $[M+H]^+$, 339.2144).



3.25A

2-(*tert*-Butylphenylsilanyloxymethyl)butyraldehyde (3.25A). A stream of ozone was passed through a mixture of olefin **3.25** (1.70 g, 5.03 mmol) and $NaHCO_3$ (2.11 g, 25.2 mmol) in CH_2Cl_2 (50 mL) at –78°C until a persistent blue color was observed. After purging the reaction mixture with Ar, Ph_3P (1.98 g, 7.6 mmol) was added and the cold

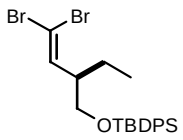
bath was removed. After 12 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (35 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuo. Purification with flash chromatography on silica gel with 10-15% EtOAc/hexanes as elutant provided the desired product with traces of Ph_3P that was taken to the next step: R_f 0.35 (33% EtOAc/hexanes).



3.26

(R)-3,3,3,-Trifluoro-2-methoxy-2-phenylpropionic acid 2-(*tert*-butyldiphenylsilanyloxymethyl)butyl ester (3.26). To a solution of aldehyde **3.25A** (20 mg, 0.06 mmol) in EtOH (1 mL) at 0°C was added $NaBH_4$ (10 mg, 0.26 mmol) and the cold bath was removed. After 30 min, the reaction mixture was poured slowly into a saturated solution of NH_4Cl (5 mL). After the addition of EtOAc (10 mL), the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under vacuo. The crude alcohol was dissolved in CH_2Cl_2 (0.2 mL) and DMAP (20 mg) was added. After cooling to 0°C, (R)-Mosher acid chloride was added and the reaction was monitored by TLC. The reaction mixture was poured into a saturated solution of $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 5% EtOAc/hexanes provided a pale yellow oil (~28 mg, 85%): R_f 0.33 (10%

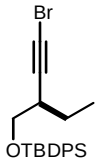
EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 1.8 Hz, 4H), 7.48 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.40-7.30 (m, 9H), 4.46 (dd, *J* = 11.1, 5.1 Hz, 1H), 4.38 (dd, *J* = 10.8, 6.3 Hz, 1H), 3.58 (dd, *J* = 10.2, 5.1 Hz, 1H), 3.52 (dd, *J* = 10.2, 6.0 Hz, 1H), 3.46 (s, 3H), 1.77 (ddd, *J* = 11.4, 5.4, 5.4 Hz, 1H), 1.33 (dddd, *J* = 10.8, 7.5, 7.5, 7.5 Hz, 2H), 1.02 (s, 9H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –72.0.



3.27A

***tert*-Butyl-(4,4-dibromo-2-ethylbut-3-enyloxy)diphenylsilane (3.27A).** To a solution of CBr_4 (1.84 g, 5.53 mmol) in CH_2Cl_2 (15 mL) at 0°C was added Ph_3P (3.03 g, 11.6 mmol). After 15 min, the cold bath was removed. After 1 h, a solution of impure aldehyde **3.25A** (5.0 mmol) in CH_2Cl_2 (15 mL) was added. After 16 h, the reaction mixture was poured into H_2O (25 mL) and extracted with EtOAc (3 × 30 mL). The collected organic fractions were washed with brine (15 mL), dried ($MgSO_4$), filtered through Celite and concentrated *under vacuo*. Purification on flash chromatography on silica gel with 2-5% EtOAc/hexanes provided viscous oil (2.11 g, 85% over 2 steps): R_f 0.45 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.5, 1.8 Hz, 4H), 7.49-7.42 (m, 6H), 6.28 (d, *J* = 9.6 Hz, 1H), 3.65 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.59 (dd, *J* = 10.2, 5.7 Hz, 1H), 2.55 (dddd, *J* = 11.4, 11.4, 11.4, 6.0 Hz, 1H), 1.62 (dddd, *J* = 13.8, 7.8, 7.8, 7.8 Hz, 1H), 1.40 (dddd, *J* = 16.0, 7.8, 7.8, 7.8 Hz, 1H), 1.08 (s, 9H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 135.64, 135.6, 133.53, 133.5, 129.7, 129.6, 127.7 (2C), 89.2, 65.2, 48.0, 26.8, 23.4, 19.3, 11.5; IR (thin film) ν 2954, 2928,

2852, 1455, 1425, 1111, 700 cm^{-1}; HRMS *m/z* 493.0197 (calcd for $C_{22}H_{27}OSiBr_2$ $[M–H]^+$, 493.0198).



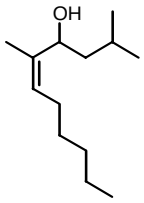
3.27

(4-Bromo-2-ethylbut-3-ynyloxy)*tert*-butyldiphenylsilane (3.27). To a solution of dibromoolefin **3.27A** (2.1 g, 4.23 mmol) in THF (30 mL) at –78°C was added dropwise a solution of NaHMDS (1.67 M in THF, 2.78 mL, 4.64 mol). After 2 h, the reaction mixture was poured into a satureated solution of NH_4Cl (30 mL) and extracted with EtOAc (3 × 50 mL). The collected organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered through Celite and concentrated. Purification on flash chromatography on silica gel with 1% EtOAc/hexanes provided viscous oil (1.47 g, 84%): R_f 0.60 (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 6.9, 1.5 Hz, 4H), 7.50-7.41 (m, 6H), 3.78 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.67 (dd, *J* = 9.9, 7.2 Hz, 1H), 2.64-2.55 (m, 1H), 1.75 (dddd, *J* = 12.6, 7.8, 7.8, 7.8 Hz, 1H), 1.55 (dddd, *J* = 15.3, 7.5, 7.5, 7.5 Hz, 1H), 1.13 (s, 9H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 133.5, 129.6, 127.7, 81.3, 65.6, 39.8, 37.5, 26.8, 23.9, 19.3, 11.4; IR (thin film) ν 3067, 3050, 2964, 2932, 2850, 1469, 1436, 1109, 1003, 821, 745, 702, 615 cm^{-1}; HRMS *m/z* 415.1081 (calcd for $C_{22}H_{28}OSiBr$ $[M+H]^+$, 415.1093).

5.1.3 General Procedure for Walsh Multicomponent Reaction[98]

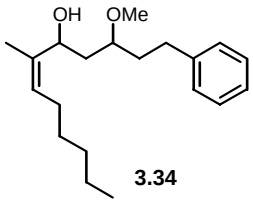
In a glove bag purged with Ar, to a solution of bromoalkyne (1.5 mmol) and toluene (1.5 mL) at rt in a 10 mL Schlenk flask with a rubber septum was added dropwise Cl_2BH

(0.172 mL, 1.5 mmol). After 1h at 70°C, the reaction mixture was cooled to –78°C and Me_2Zn or Et_2Zn (3.0 mL, 6.0 mmol, 2.0 M in toluene) was added dropwise. After 30 min, the cold bath was replaced by an ice bath and the rubber septum was replaced by a glass stopper coated with silicon grease. After the removal of the volatile reagents under high vacuum, the vinylzinc reagent was dissolved in toluene (1 mL) and the aldehyde (1.0 mmol) was added dropwise at 0°C. After 15 min, the cold bath was removed. After 16 h, a saturated solution of NH_4Cl (1 mL) was added dropwise followed by the addition of a solution of 10% HCl (2.0 mL) and EtOAc (5.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with $NaHCO_3$ (10 mL), brine (10 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *under vacuo* and purification by flash chromatography on silica gel with EtOAc/hexanes as elution provided the desired products.



3.33

(5*Z*)-2,5-dimethylundec-5-en-4-ol (3.33).[98] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (t, *J* = 7.6 Hz, 1H), 4.63 (dd, *J* = 8.0, 6.4 Hz, 1H), 2.07-1.95 (m, 2H), 1.66 (d, *J* = 1.2 Hz, 3H), 1.64-1.49 (m, 2H), 1.35-1.22 (m, 7H), 0.92 (d, *J* = 4.0 Hz, 1H), 0.90 (d, *J* = 4.0 Hz, 1H), 0.87 (t, *J* = 6.8 Hz, 3H).



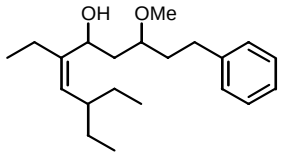
3.34

(*Z*)-3-Methoxy-6-methyl-1-phenyltridec-6-en-5-ol (3.34). The title compound was prepared according to the General Procedure of Walsh Multicomponent Reaction described above. Purification by flash chromatography on silica gel with 5-10% EtOAc/hexanes for elution provided a diastereomeric mixture of allylic alcohol **3.34** (131 mg, 43%, 2:1 dr) as pale yellow oils: R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR major Diastereomer (400 MHz, $CDCl_3$) δ 7.29-7.24 (m, 2H), 7.19-7.16 (m, 3H), 5.21 (t, *J* = 7.6 Hz, 1H), 4.74 (dd, *J* = 9.2, 3.6 Hz, 1H), 3.46-3.40 (m, 1H), 3.35 (s, 3H), 2.70-2.55 (m, 2H), 2.09-1.76 (m, 5H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.53 (ddd, *J* = 14.8, 3.6, 3.6 Hz, 1H), 1.36-1.21 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 136.5, 128.4, 128.3, 127.6, 125.8, 50.5, 69.1, 56.0, 37.8, 34.6, 31.6, 30.8, 29.7, 27.2, 22.6, 17.1, 14.1.

3.36

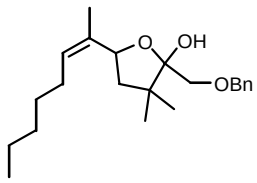
1-Bromo-3-ethylpent-1-yne (3.36). To a solution of dibromoolefin (9.0 g, 35.7 mmol) in THF (40 mL) at −78°C was added dropwise a solution NaHMDS (2.0 M in THF, 21.1 mL, 42.2 mmol). After 2 h, the reaction mixture was poured into a solution of aqueous NH_4Cl (50 mL) and was extracted with Et_2O (3 × 75 mL). The combined extracts were washed with brine (50 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed *under vacuo*, and the liquid was purified by distillation (b.p. 75-78°C at 65 mm

Hg) to provide a colorless oil (5.50 g, 88%): R_f 0.75 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22-2.16 (m, 1H), 1.45 (dddd, *J* = 15.2, 7.6, 7.6, 7.6 Hz, 4H), 0.96 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.6, 38.5, 36.3, 27.4, 11.8; HRMS *m/z* 172.9964 (calcd for $C_7H_{10}Br$ $[M-H]^+$, 172.9966).



3.37

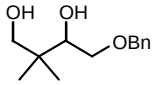
(*Z*)-6,8-Diethyl-3-methoxy-1-phenyldec-6-en-5-ol (3.37). The title compound was prepared according to the General Procedure of Walsh Multicomponent Reaction described above. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution provided an inseparable mixture of diastereomers **3.37** (152 mg, 50%, 2:1 dr) as pale yellow oils: R_f 0.55 (33% EtOAc/hexanes); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 141.8, 130.1, 128.3, 128.2, 125.7, 80.8, 70.1, 55.8, 40.2, 39.4, 34.5, 30.7, 28.3, 28.2, 22.9, 13.6, 11.9, 11.7; HRMS *m/z* 319.2627 (calcd for $C_{21}H_{35}O_2$ $[M+H]^+$, 319.2637).



3.39

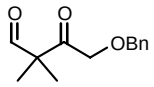
2-Benzylomethyl-3,3-dimethyl-5-((*Z*)-1-methylhept-1-enyl)tetrahydrofuran-2-ol (3.39). The title compound was prepared according to the General Procedure of Walsh Multicomponent Reaction described above. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution provided an inseparable mixture of isomers **3.39** (159 mg, 46%, 2.5:1 ratio of isomers) as pale yellow oils; ^{1}H NMR major

Diastereomer (mixture of α:β, 2.5:1) (400 MHz, C_6D_6) δ 7.24-7.21 (m, 2H), 7.12-7.04 (m, 3H), 5.38-5.27 (m, 1H), 5.17 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.46 (d, *J* = 12.4 Hz, 1H), 4.34 (d, *J* = 12.0 Hz, 1H), 3.61 (s, 1H), 3.46 (s, 2H), 2.22-1.98 (m, 2H), 2.00 (d, *J* = 1.2 Hz, 3H), 1.50 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.35-1.18 (m, 7H), 1.15 (s, 3H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.6, 136.4, 128.6, 128.0, 127.9, 127.5, 105.5, 75.8, 73.8, 72.4, 45.0. 43.7, 31.8, 30.2, 26.7, 25.8, 22.6, 22.5, 18.9, 14.2



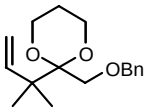
3.42A

4-Benzyloxy-2,2-dimethylbutane-1,3-diol (3.42A). A stream of ozone was passed through a solution of alcohol **2.73** (2.20 g, 10 mmol) and 4-methylbenzyl methylether (0.27 g, 2.0 mmol) in EtOH:CH_2Cl_2 (9:1, 20 mL) at –78°C. The reaction progress was followed (monitored by TLC) and after completion, the Ozone was stopped. After purging the reaction mixture with Ar, $NaBH_4$ (0.76 g, 20 mmol) was added and the cold bath was removed. After 12 h, to the reaction mixture at 0°C was added dropwise a 10% H_2SO_4 solution (5 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *under vacuo*. Purification with flash chromatography on silica gel with 15% EtOAc/hexanes as elutant provided the desired product as clear oil (1.78 g, 79%): R_f 0.33 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.35-7.27 (m, 5H), 4.55 (s, 2H), 3.73 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.60 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.47 (dd, *J* = 9.3, 8.7 Hz, 1H), 3.47 (s, 2H), 2.96 (bs, 1H), 2.85 (bs, 1H), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 128.5, 127.9, 127.7, 77.2, 73.5, 71.8, 71.1, 37.3, 22.5, 19.4 ; IR (thin film) ν 3413 (br), 2965, 2920, 2865, 1481, 1457, 1371, 1118, 1043, 914, 740 cm^{-1}; HRMS *m/z* 225.1493 (calcd for $C_{13}H_{21}O_3$ $[M+H]^+$, 225.1491).



3.42

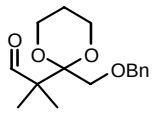
4-Benzyloxy-2,2-dimethyl-3-oxobutyraldehyde (3.42). To a solution of oxalyl chloride (2.33 mL, 26.8 mmol) in CH_2Cl_2 (40 mL) at –78°C was added dropwise a solution of DMSO (3.16 mL, 44.6 mmol) in CH_2Cl_2 (40 mL). After 30 min, a solution of diol **3.42A** (1.78 g, 7.95 mmol) in CH_2Cl_2 (40 mL) was added dropwise. After 1 h, to the reaction mixture was added dropwise a solution of Et_3N (9.90 mL, 71.2 mmol) in CH_2Cl_2 (40 mL). After 15 min, the cold bath was removed. After 5 h, the reaction mixture was poured into deionized H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 15-20% EtOAc/hexanes provided the desired product (1.23 g, 75%) as a colorless oil: R_f 0.25 (25% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.34-7.29 (m, 5H), 4.52 (s, 2H), 4.14 (s, 2H), 1.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.4, 200.0, 136.6, 128.5, 128.1, 128.0, 73.5, 72.6, 58.5, 19.2; HRMS *m/z* 221.1181 (calcd for $C_{13}H_{17}O_3$ $[M+H]^+$, 221.1178).



3.43A

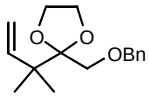
2-Benzyloxymethyl-2-(1,1-dimethylallyl) [1,3]dioxane (3.43A). A solution of ketone **2.74** (4.62 g, 20.64 mmol), 1,3-propanediol (3.72 mL, 51.6 mmol) and p-TsOH (~100 mg) in toluene (80 mL) was heated to reflux using a dean-stark apparatus. After 48 h, the reaction mixture was removed from the oil bath and Et_3N (1 mL) was added at rt. After removing the solvent *under vacuo*, purification by flash chromatography on silica gel

with 5% EtOAc/hexanes provided the desired product (3.72 g, 78% based on recovered starting material) as a clear oil: R_f 0.15 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.36-7.26 (m, 5H), 6.08 (dd, *J* = 17.7, 11.1 Hz, 1H), 4.96 (dd, *J* = 17.7, 1.8 Hz, 1H), 4.93 (dd, *J* = 10.5, 1.8 Hz, 1H), 4.51 (s, 2H), 3.98 (ddd, *J* = 12.0, 12.0, 3.0 Hz, 2H), 3.84 (ddd, *J* = 12.0, 5.1, 1.5 Hz, 2H), 3.68 (s, 2H), 1.97 (dddd, *J* = 12.0, 7.0, 5.1, 5.1 Hz, 1H), 1.35-1.29 (m, 1H), 1.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 138.0, 128.3, 127.9, 127.6, 111.5, 99.6, 73.3, 65.2, 60.7, 45.7, 25.0, 21.6; IR (thin film) ν 3078, 2971, 2872, 1476, 1455, 1412, 1380, 1271, 1266, 1248, 1138, 1099, 1081, 1035, 1010, 988, 917, 807, 743 cm^{-1}; HRMS *m/z* 277.1803 (calcd for $C_{17}H_{25}O_3$ $[M+H]^+$, 277.1804).



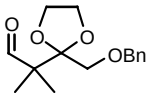
3.43

2-(2-Benzyloxymethyl-[1,3]dioxin-2-yl)-2-methylpropionaldehyde (3.43). A stream of ozone was passed through a solution of olefin **3.43A** (3.72 g, 13.48 mmol) and $NaHCO_3$ (5.7 g, 67.4 mmol) in CH_2Cl_2 (50 mL) at –78°C until a persistent blue color was observed. After purging the reaction mixture with Ar, Ph_3P (7.1 g, 27.0 mmol) was added and the cold bath was removed. After 12 h, the reaction mixture was poured into a H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuo. Purification with flash chromatography on silica gel with 20% EtOAc/hexanes as elutant provided the desired product as colorless oil (3.53 g, 94%): R_f 0.40 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 9.76 (s, 1H), 7.36-7.26 (m, 5H), 4.49 (s, 2H), 3.96-3.83 (m, 4H), 3.73 (s, 2H), 2.02 (dddd, *J* = 18.0, 12.3, 12.3, 6.6 Hz, 1H), 1.36 (ddd, *J* = 13.5, 2.1, 2.1 Hz, 1H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 137.5, 128.4, 127.9, 127.8, 99.8, 73.4, 63.3, 60.4, 53.2, 25.1, 17.1.



3.44A

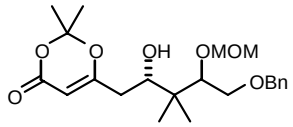
2-Benzyloxymethyl-2-(1,1-dimethylallyl) [1,3]dioxolane (3.44A). A solution of ketone **2.74** (1.0 g, 4.6 mmol), ethylene gycol (0.50 mL, 9.2 mmol) and p-TsOH (~15 mg) in benzene (40 mL) was heated to reflux. After 16 h, the reaction mixture was removed from the oil bath and Et_3N (1 mL) was added at rt. After removing the solvent *under vacuo*, purification by flash chromatography on silica gel with 5% EtOAc/hexanes provided the desired product (1.11 g, 93%) as a clear oil: R_f 0.28 (10% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.32-7.25 (m, 5H), 6.04 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.02 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.97 (s, 1H), 4.53 (s, 2H), 4.17-4.08 (m, 2H), 4.02-3.93 (m, 2H), 3.60 (s, 2H), 1.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 138.6, 128.2, 128.3, 127.3, 127.27, 112.5, 112.4, 73.6, 72.3, 66.7, 44.6, 22.1; IR (thin film) ν 3086, 3020, 2973, 2885, 1641, 1483, 1447, 1414, 1227, 1216, 1157, 1072, 1047, 1025, 962, 911, 882, 742 cm^{-1}.



3.44

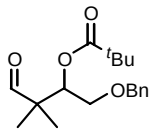
2-(2-Benzyloxymethyl-[1,3]dioxolan-2-yl)-2-methylpropionaldehyde (3.44) A stream of ozone was passed through a solution of olefin **3.44A** (0.54 g, 2.1 mmol) and $NaHCO_3$ (~100 mg) in CH_2Cl_2 (10 mL) at –78°C until a persistent blue color was observed. After purging the reaction mixture with Ar, Ph_3P (1.10 g, 4.2 mmol) was added and the cold bath was removed. After 12 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuo. Purification with

flash chromatography on silica gel with 20% EtOAc/hexanes as elutant provided the desired product as colorless oil (0.45 g, 83%): R_f 0.25 (33% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 9.72 (s, 1H), 7.35-7.25 (m, 5H), 4.48 (s, 2H), 4.03 (ddd, *J* = 6.5, 2.9, 1.2 Hz, 1H), 3.99 (ddd, *J* = 6.2, 2.7, 1.3 Hz, 1H), 3.39 (s, 2H), 1.06 (s, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.6, 137.4, 128.3, 127.8 (2C), 110.9, 73.6, 69.9, 65.8, 52.9, 17.5; IR (thin film) ν 3064, 3028, 2977, 2934, 2890, 1716, 1449, 1387, 1203, 1149, 1131, 1102, 1062, 1026, 737, 701 cm^{-1}; HRMS *m/z* 263.1280 (calcd for $C_{15}H_{19}O_4$ $[M-H]^+$, 263.1283).



3.46

6-((S)-5-Benzyloxy-2-hydroxy-4-methoxymethoxy-3,3-dimethylpentyl)-2,2-dimethyl[1,3]dioxin-4-one (3.46). The title compound was prepared according to the general procedure described above for the preparation of **3.52**. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution gave the desired product as a pale yellow oil (100 mg, 49%): R_f 0.17 (75% Et_2O/hexanes); ^{1}H NMR major Diastereomer (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5H), 5.27 (s, 1H), 4.78 (d, *J* = 6.9 Hz, 1H), 4.62 (d, *J* = 6.6 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 3.83 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.73-3.66 (m, 1H), 3. 61-3.54 (m, 1H), 3.37 (s, 3H), 2.39 (dd, *J* = 14.7, 1.5 Hz, 1H), 2.25 (dd, *J* = 14.4, 10.8 Hz, 1H), 1.68 (s, 3H), 1.64 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 161.3, 137.0, 128.6, 128.1, 127.8, 106.4, 92.2, 94.9, 82.0, 73.7, 72.4, 69.9, 56.1, 41.8, 36.0, 26.7, 24.2, 20.9, 18.6; HRMS *m/z* 409.2211 (calcd for $C_{22}H_{33}O_7$ $[M+H]^+$, 409.2226).

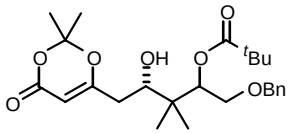


3.47

1-[(Benzyloxy)methyl]-2,2-dimethyl-3-oxopropyl 2,2-dimethylpropaneperoxoate (3.47). To a solution of alcohol **2.73** (11.0 g, 50 mmol), pyridine (8.9 mL, 110 mL) and DMAP (~20 mg, cat.) in CH_2Cl_2 (100 mL) at 0°C was added dropwise pivolyl chloride (6.77 mL, 55 mmol). After 30 min, the cold bath was removed. After 12 h, the reaction mixture was added to a saturated solution of $NaHCO_3$ (150 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL) and the combined organic fractions were washed with brine (125 mL), dried ($MgSO_4$), filtered and concentrated. The crude residue was taken through to the next step without purification.

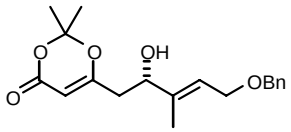
To a solution of the above ester in THF:H_2O (1:1 v/v, 100 mL) was added OsO_4 (~10 mg.) followed by the addition of 4-methylmorpholine *N*-oxide (13.5 g, 100 mL). After 12 h, the solution was transferred to a mixture of EtOAc (100 mL) and saturated aqueous Na_2SO_3 (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 70 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated. The solution of the residue in THF:H_2O (5:1 v/v, 100 mL) was subjected to $NaIO_4$ (11.8 g, 55.0 mmol) and, when the loss of the diol was completed (TLC, 6 h), the reaction mixture was added to saturated aqueous $NaHCO_3$ (75 mL). After extracting with EtOAc (3 × 50 mL), the combined organic layers were washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 20-30% EtOAc/hexanes provided a pale yellow oil (4.17 g, 96%): R_f 0.65 (100% Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.31-7.22 (m, 5H), 5.16 (t, J = 4.8 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.42 (d, J

= 12.0 Hz, 1H), 3.55 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.51 (dd, *J* = 10.4, 4.4 Hz, 1H), 1.18 (s, 9H), 1.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 177.2, 137.4, 128.1, 127.5, 127.3, 74.7, 73.0, 68.0, 48.3, 38.8, 26.9, 18.5, 18.4.



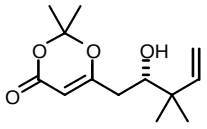
3.48

2,2-Dimethylpropionic acid (S)-1-Benzyloxymethyl-4-(2,2-dimethyl-6-oxo-*6H*-[1,3]dioxin-4-yl)-3-hydroxy-2,2-dimethylbutyl ester (3.48). The title compound was prepared according to the general procedure described above for the preparation of **3.52**. Purification by flash chromatography on silica gel with 10% EtOAc/hexanes for elution gave the desired product as a pale yellow oil (230 mg, 51%): R_f 0.33 (100% Et_2O); ^{1}H NMR major Diastereomer (300 MHz, $CDCl_3$) δ 7.36-7.15 (m, 5H), 5.23 (s, 1H), 4.95 (dd, *J* = 6.0, 3.9 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 3.81 (dd, *J* = 10.5, 2.4 Hz, 1H), 3.69 (dd, *J* = 10.5, 6.6 Hz, 1H), 3.49 (dd, *J* = 10.2, 3.6 Hz, 1H), 2.41 (d, *J* = 12.3 Hz, 1H), 2.21 (dd, *J* = 14.4, 10.8 Hz, 1H), 1.63 (s, 3H), 1.55 (s, 3H), 1.20 (s, 9H), 0.93 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 170.3, 161.1, 136.8, 128.6, 127.8, 106.5, 95.1, 75.6, 73.7, 71.9, 68.4, 41.5, 39.0, 36.0, 27.1, 25.6, 24.2, 20.2, 19.5; IR (thin film) ν 3500 (bs), 2978, 2931, 2865, 2842, 1734, 1714, 1631, 1393, 1373, 1284, 1208, 1162, 1010 cm^{-1}; HRMS *m/z* 449.2555 (calcd for $C_{25}H_{37}O_7$ $[M+H]^+$, 449.2539).



3.50

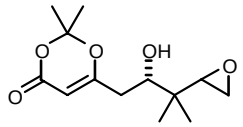
6-((E)-(S)-Benzyloxy-2-hydroxy-3,3-dimethylpent-4-enyl)-2,2-dimethyl[1,3]dioxin-4-one (3.50). The title compound was prepared according to the general procedure described below for the preparation of **3.52**. Purification by flash chromatography on silica gel with 20% EtOAc/hexanes for elution gave the desired product as a pale yellow oil (121 mg, 73%, 88% ee): R_f 0.18 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.70 (t, *J* = 6.3 Hz, 1H), 5.32 (s, 1H), 4.52 (s, 2H), 4.21 (dd, *J* = 6.6, 6.6 Hz, 1H), 4.07 (d, *J* = 6.3 Hz, 2H), 2.44 (d, *J* = 6.6 Hz, 2H), 2.35 (bs, 1H), 1.68 (s, 6H), 1.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 161.2, 139.7, 138.0, 128.3, 127.7, 127.6, 123.4, 106.6, 95.0, 73.4, 72.4, 66.1, 39.4, 25.3, 24.6, 12.0; Chiral HPLC (Daicel Chiralpak AD) hexanes:*i*-PrOH = 95:5; flow rate: 1.0 mL/min; λ_{max} = 245 nm; τ_{minor} = 16.057 min, τ_{major} = 18.059 min.



3.52

6-((S)-2-Hydroxy-3,3-dimethylpent-4-enyl)-2,2-dimethyl[1,3]dioxin-4-one (3.52). To a solution of $Cu(OTf)_2$ (0.271 g, 0.750 mmol) in THF (20.0 mL) was added a solution of (*S*)-p-tolyl-BINAP (0.610 g, 0.899 mmol) in THF (20 mL). After 15 min at rt, a solution of TBAT (0.814 g, 1.51 mmol) in THF (10.0 mL) was added. The reaction mixture was cooled to −78°C. A solution of silyl dienolate **3.24** (3.95 g, 18.46 mmol) was added followed by the addition of a solution of aldehyde **3.51** (1.507 g, 15.38 mmol) in THF (10 mL). After 8 hr, the cold bath was removed and the reaction was allowed to warm to rt.

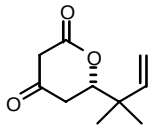
The reaction was monitored by ^{1}H NMR. After the reaction was completed, it was cooled to −78°C and trifluoroacetic acid (TFA, 3.00 mL, 39.0 mmol) was added dropwise. After 5 min, the cold bath was removed and H_2O (2.00 mL was added). Silyl ether deprotection was monitored by thin layer chromatography (TLC). The reaction was diluted with Et_2O (30 mL) and neutralized with 0.5 M NaOH (50 mL). The organic layer was separated and washed with brine (20 mL), dried ($MgSO_4$), and filtered through Celite. Solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product as a yellow oil (2.9 g, 78%, 76% ee)which was recrystallized using 3:1 Et_2O:hexanes to increase the enantioselectivity (99% ee). A white powder was obtained: R_f 0.21 (3:1 Et_2O/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.30 (s, 1H), 5.13 (dd, *J* = 10.5, 0.9 Hz, 1H), 5.07 (dd, *J* = 17.7, 1.2 Hz, 1H), 3.58 (d, *J* = 10.2 Hz, 1H), 2.42 (dd, *J* = 14.7, 2.1 Hz, 1H), 2.13 (dd, *J* = 15.0, 10.8 Hz, 1H), 1.81 (bs, 1H), 1.67 (s, 6H), 1.02 (s, 6H); ^{13}C NMR (79 MHz, $CDCl_3$) δ 170.2, 161.2, 144.0, 114.4, 106.6, 95.0, 74.8, 41.5, 36.5, 25.5, 24.5, 22.5, 22.3; Chiral HPLC (Daicel Chiralpak AD) hexanes:*i*-PrOH = 95:5; flow rate: 1.0 mL/min; λ_{max} = 245 nm; τ_{minor} = 12.289 min, τ_{major} = 14.549 min.



3.56

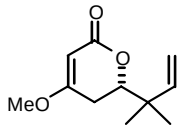
6-((*S*)-2-Hydroxy-3-dimethyl-3-oxiranyl-butyl)-2,2-dimethyl-[1,3]dioxin-4-one (3.56). To a solution of aldol adduct **3.52** (50 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) at 0°C was added Na_2HPO_4 (0.085 g, 0.60 mmol) and *m*-CPBA (75%, 0.130 g, 0.75 mmol). After 16 h at rt, the reaction mixture was added to saturated aqueous $NaHCO_3$ (10 mL).

The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered through a Celite pad and concentrated on a rotary evaporator under vacuum. The resulting yellow oil was purified by flash chromatography on silica gel with 10% EtOAc/hexanes for elution to give the desired product as pale yellow oil (50 mg, 94%): R_f 0.50 (10% EtOAc/hexanes); ^{1}H NMR major Diastereomer (300 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.73 (ddd, *J* = 10.8, 10.8, 2.4 Hz, 1H), 2.93 (dd, *J* = 3.9, 3.0 Hz, 1H), 2.71 (dd, *J* = 6.3, 4.5 Hz, 1H), 2.58 (dd, *J* = 4.5, 3.0 Hz, 1H), 2.50 (dd, *J* = 14.7, 1.8 Hz, 1H), 2.34 (dd, *J* = 14.7, 10.5 Hz, 1H), 1.67 (s, 6H), 0.97 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 161.3, 106.6, 95.0, 75.1, 56.3, 42.7, 37.8, 37.6, 25.3, 20.7, 17.3.



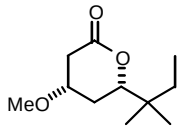
3.59A

(*S*)-6-(1,1-Dimethylbut-3-enyl)dihydropyran-2,4-dione (3.59A). A solution of aldol product **3.52** (0.500 g, 2.08 mmol) in methanol (20 mL) and K_2CO_3 (0.43 g, 3.13 mmol) was stirred at rt for until all starting material was consumed. The reaction solvent was removed under *vacuo*. A solution of 10% HCl/Et_2O (1:1 v/v) was added until pH = acidic. After the solvent was removed under *vacuo*, a yellow oil was obtained. Purification by flash chromatography on silica gel with 60% EtOAc/hexanes for elution gave the desired product as a pale yellow solid (0.353 g, 94%): R_f 0.20 (75% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.15 (dd, *J* = 10.8, 0.8 Hz, 1H), 5.11 (dd, *J* = 17.6, 0.8 Hz, 1H), 4.32 (dd, *J* = 14.2, 2.4 Hz, 1H), 3.38 (d, *J* = 18.8 Hz, 1H), 2.63 (dd, *J* = 18.4, 2.4 Hz, 1H), 2.42 (dd, *J* = 18.4, 12.4 Hz, 1H).



3.59

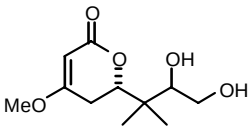
(*S*)-6-(1,1-Dimethylbut-3-enyl)-4-methoxy-5,6-dihydropyran-2-one (3.59). To a solution of lactone **3.59A** (1.29 g, 7.13 mmol) and dimethyl sulfate (0.88 mL, 9.27 mmol) in acetone (15 mL) was added K_2CO_3 (1.67 g, 12.1 mmol). After 16 h, H_2O (5 mL) was added and the reaction mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered through Celite and concentrated. Purification by flash chromatography on silica gel with 20-30% EtOAc/hexanes for elution gave the desired product as a white solid (1.03 g, 74%): R_f 0.50 (70% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.4, 11.1 Hz, 1H), 5.07 (dd, *J* = 10.5, 0.9 Hz, 1H), 5.05 (dd, *J* = 17.4, 0.9 Hz, 1H), 4.07 (dd, *J* = 13.2, 3.6 Hz, 1H), 3.69 (s, 1H), 2.47 (ddd, *J* = 17.1, 13.5, 1.8 Hz, 1H), 2.17 (dd, *J* = 17.1, 3.6 Hz, 1H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 167.5, 142.8, 113.9, 90.0, 82.1, 56.0, 39.8, 28.7, 23.1, 22.5; IR (thin film) ν 3080, 2971, 2939, 2874, 1713, 1626, 1460, 1441, 1410, 1383, 1336, 1296, 1220, 1091, 1033, 994 cm^{-1}; HRMS *m/z* 197.1180 (calcd for $C_{11}H_{17}O_3$ $[M+H]^+$, 197.1178).



3.65

(*S*)-6-(1,1-Dimethylbut)-4-methoxytetrahydropyran-2-one (3.65). To a solution of lactone **3.59** (20 mg, 0.10 mmol) in EtOAc (3 mL) at rt was added Pd/C (~10 mg) and a H_2 balloon was attached. After 16 h, the reaction mixture was filtered through Celite and concentrated. The crude residue was dissolved in ^{i}PrOH (3 mL). After Raney Nickel

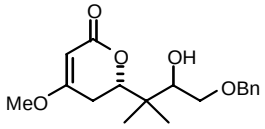
(50% slurry in H_2O, 3 drops) was added at rt, a H_2 balloon was introduced. After 16 h, the reaction mixture was filtered through Celite and concentrated. Purification by flash chromatography on silica gel with 30% EtOAc/hexanes for elution gave the desired product as a white solid (18 mg, 90%): R_f 0.42 (66% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.70 (dddd, *J* = 11.5, 7.5, 6.0, 6.0 Hz, 1H), 3.35 (s, 3H), 2.85 (ddd, *J* = 17.0, 6.0, 1.5 Hz, 1H), 2.45 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.22 (dddd, *J* = 13.5, 5.5, 3.0, 1.0 Hz, 1H), 1.50 (ddd, *J* = 13.5, 12.0, 9.0 Hz, 1H), 1.44 (dddd, *J* = 14.0, 8.0, 8.0, 8.0 Hz, 1H), 1.31 (dddd, *J* = 13.5, 7.5, 7.5, 7.5 Hz, 1H), 0.92 (s, 3H), 0.88 (s, 3H), 0.83 (t, *J* = 7.5 Hz, 3H).



3.66

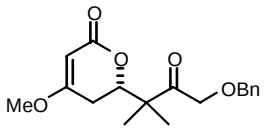
(*S*)-6-(3,4-Dihydroxy-1,1-dimethylbutyl)-4-methoxy-5,6-dihydropyran-2-one (3.66). To a heterogeneous mixture of olefin **3.59** (200 mg, 1.00 mmol) and $NaHCO_3$ (420 mg, 5.0 mmol) in a mixture of *t*-BuOH: H_2O (9:1, v/v, 15 mL) was added OsO_4 (~10 mg) followed by 4-methylmorpholine *N*-oxide (585 mg, 5.0 mmol). After 16 h, the reaction mixture was added to H_2O (20 mL) and EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography on silica gel with 1-5% MeOH/CH_2Cl_2 for elution gave the desired product as a pale yellow oil (122 mg, 53%): R_f 0.10 (10% MeOH/CH_2Cl_2); ^{1}H NMR major diastereoisomer (400 MHz, $CDCl_3$) δ 5.09 (t, *J* = 1.6 Hz, 1H), 4.37 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 3.71 (s, 3H), 3.63-3.51 (m, 3H), 3.45 (bs, 1H), 2.55 (dd, *J* = 13.6, 2.0 Hz, 1H), 2.32 (dd, *J* = 17.2, 3.2

Hz, 1H), 1.01 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 168.0, 89.8, 80.2, 76.0, 62.8, 56.0, 39.4, 28.3, 19.9, 18.4; HRMS *m/z* 231.1231 (calcd for $C_{15}H_{19}O_5$ $[M+H]^+$, 231.1232).



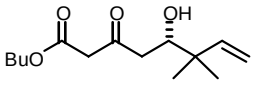
3.67

(*S*)-6-(4-Benzyloxy-3-hydroxy-1,1-dimethylbutyl)-4-methoxy-5,6-dihydropyran-2-one (3.67). A solution of diol **3.66** (100 mg, 0.43 mmol) and Bu_2SnO (110 mg, 0.43 mmol) in MeOH (4 mL) was heated to reflux. After 1 h, the solvent was removed under vacuo. To the stannylene acetal of the diol was added CsF (94 mg, 0.62 mmol) and the mixture was further dried on high vacuum. After 1 h on high vacuum, to the reaction mixture was added toluene (5 mL) and benzyl bromide (77 μL, 0.62 mmol) and the reaction was heated to 80°C. After 16h, the solvent was removed under vacuo and purification by flash chromatography on silica gel with 50% EtOAc/hexanes provided an inconsequential mixture of diastereomers (109 mg, 79%): R_f 0.60 (10% MeOH/CH_2Cl_2); ^{1}H NMR major diastereoisomer (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.12 (dd, *J* = 2.4, 2.0 Hz, 1H), 4.56 (s, 2H), 4.39 (dd, *J* = 13.2, 3.6 Hz, 1H), 4.02 (ddd, *J* = 8.8, 3.2, 3.2 Hz, 2H), 3.73 (s, 3H), 3.64 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.51 (dd, *J* = 9.2, 8.8 Hz, 1H), 2.61 (ddd, *J* = 16.8, 13.6, 2.0 Hz, 1H), 2.56 (bs, 1H), 2.24 (dd, *J* = 17.2, 3.6 Hz, 1H), 0.96 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 167.2, 137.6, 127.9, 127.2, 127.1, 89.5, 78.7, 72.7, 71.9, 70.8, 55.6, 39.1, 27.5, 18.1, 17.5 ; HRMS *m/z* 321.1697 (calcd for $C_{18}H_{25}O_5$ $[M+H]^+$, 321.1670).



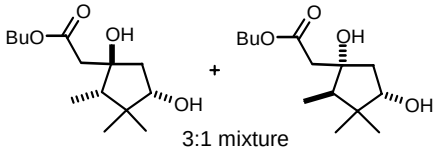
3.68

(*S*)-6-(4-Benzyloxy-1,1-dimethyl-3-oxobutyl)-4-methoxy-5,6-dihydropyran-2-one (3.68). To a solution of oxalyl chloride (0.040 mL, 0.47 mmol) in CH_2Cl_2 (4 mL) at –78°C was added dropwise a solution of DMSO (0.051 mL, 0.78 mmol) in CH_2Cl_2 (2 mL). After 30 min, a solution of alcohol **3.67** (89 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 1 h, to the reaction mixture was added a solution of Et_3N (0.175 mL, 1.25 mmol) in CH_2Cl_2 (2 mL). After 15 min, the cold bath was removed. After 5 h, the reaction mixture was poured into deionized H_2O (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided the desired product (76 mg, 85%) as a colorless oil: R_f 0.40 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.10 (d, *J* = 1.8 Hz, 1H), 4.57 (s, 2H), 4.54 (dd, *J* = 13.2, 3.6 Hz, 1H), 4.38 (s, 2H), 3.72 (s, 3H), 2.53 (ddd, *J* = 16.5, 12.9, 1.5 Hz, 1H), 2.23 (dd, *J* = 16.8, 3.6 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 172.9, 166.3, 137.1, 128.4, 128.0, 127.9, 90.0, 79.9, 73.2, 72.6, 56.1, 48.8, 28.1, 20.3, 20.0; HRMS *m/z* 319.1550 (calcd for $C_{18}H_{22}O_5$ $[M+H]^+$, 319.1550).



3.70

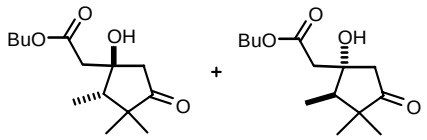
(*S*)-5-Hydroxy-6,6-dimethyl-3-oxooct-7-enoic butyl ester (3.70). A solution of aldol adduct **3.52** (5.8 g, 24.2 mmol) in *n*-BuOH (150 mL) was heated at reflux for 35 min. The reaction mixture was then cooled to rt and solvent was removed under *vacuo*. Purification by flash chromatography on silica gel with 25% EtOAc/hexanes for elution gave the desired product as a colorless oil (4.2 g, 68%): R_f 0.48 (100% Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.6, 10.0 Hz, 1H), 5.06 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.03 (dd, *J* = 17.6, 1.6 Hz, 1H), 4.12 (t, *J* = 6.8 Hz, 2H), 3.84 (dd, *J* = 10.0, 3.6, 2.0 Hz, 1H), 3.50 (d, *J* = 15.6 Hz, 1H), 3.56 (d, *J* = 15.6 Hz, 1H), 2.69 (dd, *J* = 17.2, 2.0 Hz, 1H), 2.60 (s, 1H), 2.55 (dd, *J* = 17.2, 10.0 Hz, 1H), 1.60 (dddd, *J* = 14.8, 14.8, 6.8, 6.8 Hz, 2H), 1.36 (dddd, *J* = 14.8, 7.6, 7.6, 7.6 Hz, 2H), 1.01 (s, 6H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 167.0, 144.4, 113.2, 73.6, 65.2, 49.9, 45.0, 40.7, 30.4, 22.9, 22.0, 18.9, 13.5; IR (thin film) ν 3529, 3083, 2963, 2935, 1875, 1741, 1715, 1638, 1466, 1413, 1381, 1319, 1150, 1066, 1027, 916 cm^{-1}; HRMS *m/z* 257.1744 (calcd for $C_{14}H_{25}O_4$ $[M+H]^+$, 257.1753).



3.71 **3.72**

((1*R*,2*S*,4*S*)-1,4-Dihydroxy-2,3,3-trimethylcyclopenyl)acetic acid benzyl ester (3.71) and **((1*S*,2*R*,4*S*)-1,4-Dihydroxy-2,3,3-trimethylcyclopenyl)acetic acid benzyl ester (3.72)**. To a solution of *β*-hydroxy ketone **3.70** (0.12 g, 0.47 mmol) and H_2O (18 μL, 1.0 mmol) in THF (6 mL) at 0°C was added dropwise a solution of SmI_2 (14.1 mL, 0.10 M in THF).[99] The cold bath was removed and after 1 h, the septum was removed. After the

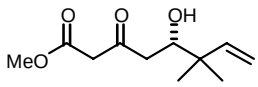
reaction mixture's color changed from blue to yellow, Et_2O (10 mL) was added followed by a 1% HCl solution (5 mL). After 10 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with a saturated solution of $Na_2S_2O_3$ (5 mL), dried (Na_2SO_4), filtered through Celite and concentrated. Purification on flash chromatography on silica gel with 25-40% EtOAc/hexanes provided the desired product as a pale yellow oil (100 mg, 83%) and diols **3.71** (9 mg, 7%) and **3.72** (10 mg, 8%): R_f 0.18 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (s, 1H), 4.11 (t, *J* = 6.8 Hz, 2H), 3.63(bs, 1H), 2.50 (d, *J* = 16.0 Hz, 1H), 2.35 (d, *J* = 16.0 Hz, 1H), 2.06 (q, *J* = 7.2 Hz, 1H), 2.00 (dd, *J* = 14.8, 4.8 Hz, 1H), 1.90 (d, *J* = 14.4 Hz, 1H), 1.62 (dddd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 1H), 1.35 (dddd, *J* = 15.7, 7.6, 7.6, 7.6 Hz, 1H), 1.07 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.6 Hz, 3H), 0.71 (s, 3H).



3.73 **3.74**

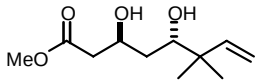
((1*R*,2*S*)-1-Hydroxy-2,3,3-trimethyl-4-oxocyclopenyl)acetic acid benzyl ester (3.73) and **((1*S*,2*R*)-1-Hydroxy-2,3,3-trimethyl-4-oxocyclopenyl)acetic acid benzyl ester (3.74)**. To a solution of oxalyl chloride (52 μl, 0.60 mmol) in CH_2Cl_2 (2 mL) at –78°C was added dropwise a solution of DMSO (66 μL, 1.00 mmol) in CH_2Cl_2 (2 mL). After 30 min, a solution of diols **3.71** and **3.72** (0.10 g, 0.39 mmol) in CH_2Cl_2 (2 mL) were added dropwise to the reaction mixture. After 1 h, a solution of Et_3N (0.25 ml, 1.56 mmol) in CH_2Cl_2 (2 mL) was added dropwise and after 10 min, the cold bath was removed. After 15 min at rt, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5

mL) and the combined organic fractions were washed with $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Filtration through Celite and concentration *in vacuo* supplied the crude products. Purification on flash chromatography on silica gel with 20% EtOAc/hexanes provided the desired product as a pale yellow oil (70 mg, 70%): R_f 0.20 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (bs, 1H), 4.12 (ddd, *J* = 6.8, 1.5, 1.5 Hz, 1H), 2.65 (d, *J* = 16.2 Hz, 1H), 2.57 (d, *J* = 18.0 Hz, 1H), 2.48 (d, *J* = 16.2 Hz, 1H), 2.47 (d, *J* = 18.0 Hz, 1H), 2.24 (q, *J* = 7.2 Hz, 1H), 1.66-1.56 (m, 2H), 1.42-1.30 (m, 2H), 1.19 (s, 3H), 0.96-0.90 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.6, 173.3, 75.8, 65.1, 51.3, 50.4, 48.6, 40.3, 30.5, 27.4, 20.8, 19.1, 13.6, 10.6; IR (thin film) ν 3501 (br), 2963, 2932, 2974, 1739, 1703, 1468, 1386, 1339, 1188, 1126, 1080, 1021 cm^{-1}; HRMS *m/z* 256.1673 (calcd for $C_{14}H_{24}O_4$ $[M]^+$, 256.1673).



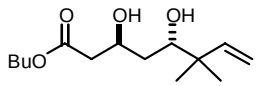
3.75

(*S*)-5-Hydroxy-6,6-dimethyl-3-oxooct-7-enoic acid methyl ester (3.75). A solution mixture of aldol adduct **3.52** (1.3 g, 5.42 mmol) in MeOH:toluene (5:1, v/v, 12 mL) was heated at reflux for 1.0 h. The reaction mixture was then cooled to rt and solvent was removed under *vacuo*. Purification by flash chromatography on silica gel with 25% EtOAc/hexanes for elution gave the desired product as a colorless oil (0.63 g, 54%): R_f 0.45 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.08–5.01 (m, 2H), 3.82 (ddd, *J* = 10.4, 4.0, 2.4 Hz, 1H), 3.72 (s, 3H), 3.48 (s, 2H), 2.66 (s, 1H), 2.49 (d, *J* = 3.6 Hz, 2H), 1.01 (s, 6H).



3.76

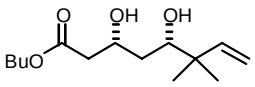
(3*S*,5*S*)-3,5-Dihydroxy-6,6-dimethyloct-7-enoic acid methyl ester (3.76). To a solution of $Me_4N(OAc)_3BH$ (716 mg, 2.72 mmol) in acetonitrile (1.5 mL) at rt was added acetic acid (1.5 mL). After 30 min, the resulting mixture was cooled to –40°C and a solution of *β*-keto ester **3.75** (73 mg, 0.34 mmol) in acetonitrile (0.5 mL) was added. After 15 h, the reaction mixture was poured into an aqueous solution of 0.5 N Rochelle salt. The cold bath was removed. Extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with $NaHCO_3$ (5 mL, sat'd) and brine (5 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product as a pale yellow oil (67 mg, 91%): R_f 0.35 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.09–5.00 (m, 2H), 4.32-4.25 (m, 1H), 3.69 (s, 3H), 3.63 (ddd, *J* = 10.8, 4.0, 2.0 Hz, 1H), 3.31 (d, *J* = 4.4 Hz, 1H), 2.51 (d, *J* = 6.0 Hz, 1H), 2.15 (d, *J* = 4.0 Hz, 1H), 1.61 (ddd, *J* = 14.0, 8.0, 2.0 Hz, 1H), 1.45 (ddd, *J* = 14.0, 10.4, 3.2 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 145.0, 113.5, 74.1, 65.8, 51.7, 41.3, 41.1, 36.9, 22.9, 22.0; HRMS *m/z* 217.1439 (calcd for $C_{11}H_{21}O_4$ $[M+H]^+$, 217.1440).



3.77

(3*S*,5*S*)-3,5-Dihydroxy-6,6-dimethyloct-7-enoic acid butyl ester (3.77). To a solution of $Me_4N(OAc)_3BH$ (22.0 g, 83.65 mmol) in acetonitrile (140 mL) at rt was added acetic

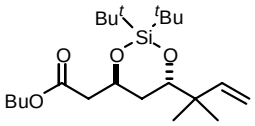
acid (60 mL). After 30 min, the resulting mixture was cooled to –40°C and a solution of *β*-keto ester **3.70** (3.6 g, 14.1 mmol) in acetonitrile (20 mL) was added. After 15 h, the reaction mixture was poured into an aqueous solution of 0.5 N Rochelle salt (20 mL). The cold bath was removed. The reaction mixture was stirred for 5 min and extracted with CH_2Cl_2 (3 × 150 mL). The combined extracts were washed with $NaHCO_3$ (150 mL, sat'd) and brine (100 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give a dr 92:8 of the desired product **3.77** (3.40, , 94%) as a pale yellow oil and diastereomer **3.77A** (0.19 g, 5%): R_f 0.20 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.06 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.02 (dd, *J* = 17.6, 1.6 Hz, 1H), 4.28 (dddd, *J* = 8.0, 6.4, 6.4, 4.2 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.62 (dd, *J* = 10.8, 2.0 Hz, 1H), 2.49 (appd, *J* = 6.0 Hz, 2H), 1.63-1.55 (m, 3H), 2.45 (ddd, *J* = 14.0, 10.8, 3.6 Hz, 1H), 1.35 (dddd, *J* = 14.4, 7.2, 7.2, 7.2 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.90 (t, *J* = 7.6 Hz, 3H); HRMS *m/z* 259.1901 (calcd for $C_{14}H_{27}O_4$ $[M+H]^+$, 217.1909).



3.77A

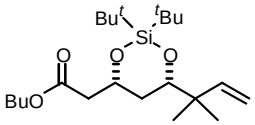
(3*R*,5*S*)-3,5-Dihydroxy-6,6-dimethyloct-7-enoic acid butyl ester (3.77A). R_f 0.22 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.05 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.01 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.21 (dddd, *J* = 12.4, 5.2, 2.4 Hz, 1H), 4.08 (t, *J* = 6.4 Hz, 2H), 3.87 (bs, 1H), 3.55 (dd, *J* = 16.4, 7.6 Hz, 1H), 3.09 (bs, 1H), 2.49 (dd, *J* = 16.4, 7.6 Hz, 1H), 2.44 (dd, *J* = 12.4, 1.2 Hz, 1H), 1.64-1.56 (m, 3H), 1.49-1.30 (m, 3H), 0.99 (s, 6H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 172.8, 145.4, 113.5, 78.9, 69.6, 64.8, 42.0, 41.6, 36.9, 30.8, 22.7, 22.6, 19.3, 13.9.



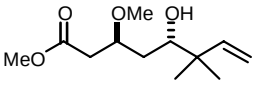
3.78

[(4*S*,6*S*)-2,2-Di-*tert*-butyl-6-(1,1-dimethylallyl)-[1,3,2]dioxasilinan-4-yl] acetic acid butyl ester (3.78). To a solution of diol **3.77** (15 mg, 0.06 mmol), pyridine (19 μL, 0.24 mmol) and dimethylformamide (2 mL) at –35 °C was added $(^tBu)_2Si(OTf)_2$ (62 μL, 0.12 mmol) dropwise over 5 min. After 30 min, the reaction mixture was added to a saturated solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentration *in vacuo*. Purification by flash chromatography on silica gel (10% EtOAc/hexanes) provided **3.78** (21 mg, 90%).: R_f 0.80 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 17.4, 11.1 Hz, 1H), 4.99 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.94 (dd, *J* = 9.9, 1.2 Hz, 1H), 4.64 (dddd, *J* = 6.6, 6.6, 6.6 Hz, 1H), 4.11 (ddd, *J* = 10.8, 6.6, 6.6 Hz, 1H), 4.04 (ddd, *J* = 10.8, 6.6, 6.6 Hz, 1H), 3.75 (dd, *J* = 10.8, 1.5 Hz, 1H), 2.71 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.41 (dd, *J* = 14.4, 6.3 Hz, 1H), 1.92 (ddd, *J* = 17.1, 11.1, 6.3 Hz, 1H), 1.63-1.48 (m, 3H), 1.36 (dddd, *J* = 15.0, 7.2, 7.2, 7.2 Hz, 2H), 1.00 (s, 3H), 0.99 (s, 3H), 0.974 (s, 9H), 0.970 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 144.9, 112.3, 75.0, 69.0, 64.2, 42.4, 41.6, 33.4, 30.7, 27.2, 27.0, 23.8, 21.7, 21.5, 20.8, 19.1, 13.7; IR (thin film) ν 2962, 2934, 2829, 1939, 1475, 1386, 1307, 1259, 1173, 1112, 1002, 917, 825, 649 cm^{-1}; HRMS *m/z* 399.2931 (calcd for $C_{21}H_{43}O_4Si$ $[M+H]^+$, 399.2927).



3.78A

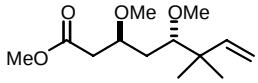
[(4*R*,6*S*)-2,2-Di-*tert*-butyl-6-(1,1-dimethylallyl)-[1,3,2]dioxasilinan-4-yl]acetic acid butyl ester (3.78A). Reaction procedure was run as in **3.78** to yield the desired product (22 mg, 93%): R_f 0.82 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 17.5, 10.5 Hz, 1H), 4.98 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.95 (dd, *J* = 12.0, 1.5 Hz, 1H), 4.45 (dddd, *J* = 13.5, 8.0, 5.5, 2.5 Hz, 1H), 4.11 (ddd, *J* = 11.0, 6.5, 6.5 Hz, 1H), 4.04 (ddd, *J* = 11.0, 6.5, 6.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 1.5 Hz, 1H), 2.49 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.36 (dd, *J* = 14.5, 5.0 Hz, 1H), 1.63 (ddd, *J* = 13.5, 2.5, 2.5 Hz, 1H), 1.60-1.55 (m, 3H), 1.41-1.33 (m, 3H), 1.00 (s, 3H), 0.99 (s, 3H), 0.98 (s, 9H), 0.95 (s, 9H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 145.0, 112.1, 80.4, 71.5, 64.2, 44.2, 41.8, 36.0, 30.7, 27.5, 27.1, 23.7, 22.9, 21.7, 19.8, 19.1, 13.7; IR (KBr) ν 2962, 2933, 2859, 1739, 1473, 1380, 1365, 1271, 1173, 1149, 1119, 1000, 956, 915, 826, 651 cm^{-1}; HRMS *m/z* 399.2930 (calcd for $C_{21}H_{43}O_4Si$ $[M+H]^+$, 399.2931).



3.79A

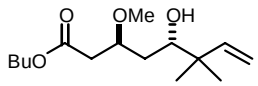
(3*S*,5*S*)-5-Hydroxy-3-methoxy-6,6-dimethyloct-7-enoic acid methyl ester (3.79A). To a solution of diol **3.76** (170 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) 2,6-di-tertbutyl-4-methyl pyridine (405 mg, 1.97 mmol) was added Meerwein salt (234 mg, 1.60 mmol). After 5 h at rt, the reaction mixture was poured into a solution of $NaHCO_3$ (10 mL, aq'd) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed under *vacuo*, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to

give the desired product as a pale yellow oil (62 mg, 34%): R_f 0.55 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.97–5.00 (m, 2H), 3.91 (dddd, *J* = 6.8, 6.8, 6.5, 3.6 Hz, 1H), 3.67 (s, 3H), 3.54 (ddd, *J* = 12.0, 4.0, 2.0 Hz, 1H), 3.37 (s, 3H), 2.66 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.48 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.30 (d, *J* = 4.0 Hz, 1H), 1.65 (ddd, *J* = 14.4, 6.8, 2.0 Hz, 1H), 1.53 (ddd, *J* = 14.4, 10.8, 4.0 Hz, 1H), 1.00 (s, 3H), 0.98 (s, 3H).



3.80A

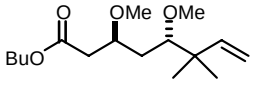
(3*S*,5*S*)-3,5-Dimethoxy-6,6-dimethyloct-7-enoic acid methyl ester (3.80A). The title compound was prepared according to the procedure above. Purification by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product as a yellow oil (110 mg, 54%): R_f 0.72 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dd, *J* = 16.8, 11.2 Hz, 1H), 4.98 (s, 1H), 4.94 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.78 (dddd, *J* = 9.2, 6.4, 6.4, 3.2 Hz, 1H), 3.67 (s, 3H), 3.46 (s, 3H), 3.43 (s, 3H), 3.08 (dd, *J* = 10.0, 1.6 Hz, 1H), 2.57 (dd, *J* = 14.8, 6.4 Hz, 1H), 2.42 (dd, *J* = 14.8, 6.0 Hz, 1H), 1.64 (ddd, *J* = 14.0, 9.6, 6.0 Hz, 1H), 1.40 (ddd, *J* = 14.0, 10.4, 2.8 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H).



3.79B

(3*S*,5*S*)-5-Hydroxy-3-methoxy-6,6-dimethyloct-7-enoic acid butyl ester (3.79B). To a solution of diol **3.77** (3.6 g, 14.1 mmol) in CH_2Cl_2 (150 mL) and 2,6-di-tert-butyl-4-methyl pyridine (4.36, 21.15 mmol) was added Meerwein salt (2.5 g, 16.9 mmol). After 5 h at rt, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (50 mL)

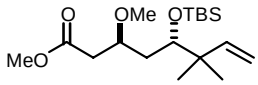
and extracted with EtOAc (3 × 50 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed under *vacuo*, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product **3.79B** as a pale yellow oil (2.5 g, 86% based on recovered starting material) and the dimethyl ether **3.80B** (0.29 g, 10%) as a minor by-product: R_f 0.45 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.05 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.01 (dd, *J* = 17.4, 1.5 Hz, 1H), 4.07 (t, *J* = 6.9 Hz, 2H), 3.91 (dddd, *J* = 6.6, 6.6, 6.6, 4.2 Hz, 1H), 3.54 (ddd, *J* = 10.2, 3.9, 2.4 Hz, 1H), 2.65 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.46 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.34 (d, *J* = 3.9 Hz, 1H), 1.69-1.49 (m, 4H), 1.36 (dddd, *J* = 14.7, 6.9, 6.9, 6.9 Hz, 2H), 1.00 (s, 3H), 0.98 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 145.1, 113.1, 76.1, 74.4, 64.4, 57.1, 41.2, 39.0, 35.2, 30.6, 22.7, 22.4, 19.1, 13.9; IR (thin film) ν 3502, 2961, 2932, 2875, 1734, 1465, 1380, 1312, 1160, 1075, 913, 734 cm^{-1}; HRMS *m/z* 273.2065 (calcd for $C_{15}H_{29}O_4$ $[M+H]^+$, 273.2066).



3.80B

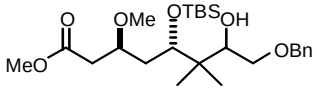
(3*S*,5*S*)-3,5-Dimethoxy-6,6-dimethyloct-7-enoic acid butyl ester (3.80B). R_f 0.60 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (dd, *J* = 16.8, 11.2 Hz, 1H), 4.97 (s, 1H), 4.93 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.06 (ddd, *J* = 6.4, 6.4, 1.2 Hz, 2H), 3.77 (dddd, *J* = 9.2, 6.0, 6.0, 3.2 Hz, 1H), 3.45 (s, 3H), 3.34 (s, 3H), 3.07 (dd, *J* = 10.0, 2.0 Hz, 1H), 1.64 (dd, *J* = 10.0, 2.0 Hz, 1H), 1.62-1.55 (m, 2H), 1.42 (dd, *J* = 10.8, 3.2 Hz, 1H), 1.40-1.31 (m, 2H), 0.98 (s, 3H), 0.97 (s, 3H), 0.90 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 145.6, 111.9, 85.1, 75.0, 64.4, 61.5, 56.3, 42.0, 39.5, 37.0, 30.6, 24.0, 22.5, 19.1,

13.7; IR (thin film) ν 2961, 2933, 2876, 2828, 1736, 1465, 1379, 1309, 1247, 1163, 1109, 1065, 912 cm^{-1}.



3.81

(3*S*,5*S*)-5-(*tert*-Butyl-dimethylsilanyloxy)-3-methoxy-6,6-dimethyloct-7-enoic acid methyl ester (3.81) To a solution mixture of **3.79A** (250 mg, 1.09 mmol) and 2,6-lutidene (0.252 mL, 2.2 mmol) in CH_2Cl_2 (15 mL) at 0°C was added dropwise TBSOTf (0.376 mL, 1.64 mmol). After the reaction was completed, the reaction mixture was poured into $NaHCO_3$ (10 mL, sat'd) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$) and filtered through Celite. Solvents were removed in *vacuo*, and the residue was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product as a pale yellow oil (368 mg, 98%): R_f 0.65 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 18.0, 10.4 Hz, 1H), 4.97-4.92 (m, 2H), 3.80 (dddd, *J* = 8.8, 6.4, 6.4, 2.8 Hz, 1H), 3.64 (s, 3H), 3.56 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.30 (s, 3H), 2.60 (dd, *J* = 14.8, 6.0 Hz, 1H), 2.29 (dd, *J* = 14.4, 6.4 Hz, 1H), 1.71 (ddd, *J* = 14.4, 10.4, 1.6 Hz, 1H), 1.32 (ddd, *J* = 14.4, 8.0, 6.8, 2.4 Hz, 1H), 6 Hz, 1H), 0.94 (s, 6H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 146.1, 111.7, 75.8, 74.2, 55.7, 51.6, 42.1, 39.6, 39.2, 30.1, 26.2, 24.8, 22.0, 18.4, –3.6, –3.5.

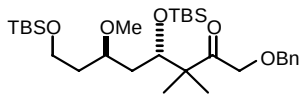


3.82

(3*S*,5*S*)-8-Benzyloxy-5-(*tert*-Butyl-dimethylsilanyloxy)-7-hydroxy-3-methoxy-6,6-dimethyloctanoic acid methyl (3.82). To a solution of olefin **3.81** (0.31 g, 0.90 mmol) in *t*-BuOH:H_2O (1:1 v/v, 10 mL) was added OsO_4 (~20 mg, 0.1 mmol). After 15 min, 4-methylmorpholine *N*-oxide (0.21 g, 1.8 mmol) was added. After 12 h, the solution was transferred to a mixture of EtOAc (30 mL) and saturated aqueous Na_2SO_3 (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 30% EtOAc/hexanes provided an inconsequential mixture of diastereomers (0.33 g, 97%): R_f 0.20 (50% EtOAc/hexanes).

A solution of the above diol (52 mg, 0.13 mmol) and Bu_2SnO (38 mg, 0.15 mmol) in MeOH was heated to reflux. After 1 h, the solvent was removed under vacuo. To the stannylene acetal of the diol was added Bu_4NBr (80 mg, 0.21 mmol) and the mixture was further dried on high vacuum. After 1 h on high vacuum, to the reaction mixture was added toluene (5 mL) and benzyl bromide (25 μL, 0.21 mmol) and the reaction was heated to 80°C. After 16h, the solvent was removed under vacuo and purification by flash chromatography on silica gel with 10-15% EtOAc/hexanes provided an inconsequential mixture of diastereomers (53 mg, 87%): R_f 0.66 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 4.59 (d, *J* = 12.3 Hz, 1H), 4.51 (d, *J* = 12.3 Hz, 1H), 3.95 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.84-3.58 (m, 2H), 3.65 (s, 3H), 3.53 (dd, *J* = 9.3, 1.7 Hz, 1H), 3.42 (dd, *J* = 9.3, 8.4 Hz, 1H), 3.35 (s, 3H), 2.65 (dddd, *J* = 14.7, 5.1, 2.7 Hz, 1H), 2.32 (dd, *J* = 15.0, 6.6 Hz, 1H), 1.97-1.82 (m, 1H), 1.59 (ddd, *J* = 15.0, 8.4, 1.4 Hz, 1H), 0.87 (s, 9H), 0.85 (3H), 0.76 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 171.5, 138.3, 128.4, 127.7, 127.6, 76.5, 74.6, 74.4, 73.4, 72.0, 56.4, 51.7, 41.5, 39.1, 39.0, 26.1, 22.2, 19.7, 18.2, –4.0, –3.5.



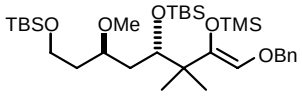
3.84

(4*S*,6*R*)-1-Benzyloxy-4,8-bis-(*tert*-Butyldimethylsilanyloxy)-6-methoxy-3,3-dimethyloctan-2-one (3.84). To a solution of methyl ester **3.82** (53 mg, 0.11 mmol) in CH_2Cl_2 (15 mL) at –78°C was added dropwise DIBAL-H (1.5 M, 0.3 mL). After 3h, EtOAc (3 mL) was added dropwise and the cold bath was removed. A saturated solution of Rochelle salt (8 mL) was added to the reaction mixture at rt and after 16 h, the organics were extracted with EtOAc (3 × 10 mL). The collected organic fractions were dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 20% EtOAc/hexanes provided an inconsequential mixture of diastereomers (45 mg, 92%): R_f 0.50 (50% EtOAc/hexanes).

To a solution of the above diol (40 mg, 0.09 mmol), imidazole (18 mg, 0.27 mmol) and DMF (2 mL) was added *t*-Bu$(Me)_2$SiCl (20 mg, 0.14 mmol) at 0°C. After 12 h, the reaction mixture was added to saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentration *in vacuo*. Purification by flash chromatography on silica gel (10% EtOAc/hexanes) provided a mixture of diastereomeric alcohols (48 mg, 96%): R_f 0.50 (25% EtOAc/hexanes).

To a solution of oxalyl chloride (40 μl, 0.47 mmol) in CH_2Cl_2 (3 mL) at –78°C was added dropwise a solution of DMSO (51 μL, 0.78 mmol) in CH_2Cl_2 (2 mL). After 30 min, a solution of the above alcohol **3.83** (0.17 g, 0.31 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture. After 1 h, a solution of Et_3N (0.17 ml, 1.24

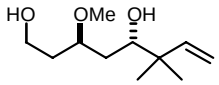
mmol) in CH_2Cl_2 (2 mL) was added dropwise and after 10 min, the cold bath was removed. After 15 min at rt, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic fractions were washed with $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification on flash chromatography on silica gel with 20% EtOAc/hexanes provided the desired product as a pale yellow oil (120 mg, 70%): R_f 0.60 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5H), 4.56 (s, 2H), 4.35 (d, *J* = 18.0 Hz, 1H), 4.27 (d, *J* = 17.6 Hz, 1H), 4.02 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.60 (dddd, *J* = 13.2, 10.0, 6.4, 6.4 Hz, 2H), 3.47 (dddd, *J* = 12.2, 4.8, 4.8, 2.4 Hz, 1H), 3.26 (s, 3H), 1.73 (dddd, *J* = 14.0, 14.0, 6.4, 6.4 Hz, 1H), 1.31 (ddd, *J* = 14.8, 8.0, 2.4 Hz, 1H), 1.07 (s, 3H), 1.04 (s, 3H), 0.87 (s, 9H), 0.83 (s, 9H), 0.07 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 137.6, 128.4, 127.9, 127.8, 74.3, 74.1, 73.1, 72.4, 59.3, 55.5, 52.0, 39.8, 36.6, 26.1, 25.9, 21.4, 20.6, 18.3, 18.2, –5.4, –3.9; HRMS *m/z* 551.3585 (calcd for $C_{30}H_{56}O_5Si_2$ [M–H], 551.3588).



3.85

[(*Z*)-(4*S*,6*R*)-4,8-bis-(*tert*-Butyldimethylsilanyloxy)-6-methoxy-3,3-dimethyl-2-trimethylsilanyloxyoct-1-enyloxymethyl]benzene (3.85). A solution of *n*-BuLi in hexanes (2.38 M, 0.16 mL, 0.37 mmol) was added dropwise to a solution of diisopropylamine (0.06 mL, 0.39 mmol) in THF (0.1 M) at 0°C. After 15 min the solution was cooled to –78°C and a solution of benzyloxyketone **3.84** (171 mg, 0.31 mmol) was added. The cold bath was removed and the solution was allowed to warm to 0 °C, then cooled to – 78°C before Me_3SiCl (0.06 mL, 0.47 mmol) was added. After 10 min the cold bath was removed and the rt solution was transferred to pentanes (5 mL) and

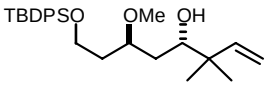
the resulting solids were filtered. The filtrate was concentrated *in vacuo* and purification by flash chromatography on silica gel (elution gradient: hexanes to 1-5% EtOAc/hexanes) provided **3.85** as a colorless oil (153 mg, 79%): R_f 0.3 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.05 (m, 5H), 5.60 (s, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.26 (dd, *J* = 8.4, 1.2 Hz, 1H), 3.78-3.67 (m, 3H), 3.25 (s, 3H), 1.93 (ddd, *J* = 14.4, 12.0, 1.2 Hz, 1H), 1.84 (dddd, *J* = 12.0, 6.0, 6.0, 6.0 Hz, 1H), 1.67 (dddd, *J* = 12.8, 6.8, 6.8, 6.8 Hz, 1H), 1.48 (ddd, *J* = 14.4, 8.4, 2.8 Hz, 1H), 1.20 (s, 3H), 1.06 (s, 9H), 1.04 (s, 3H), 1.00 (s, 9H), 0.31 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H),0.09 (s, 6H).



4.11A

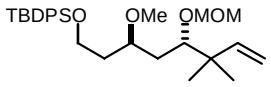
(3*R*,5*S*)-3-Methoxy-6,6-dimethyloct-7-ene-1,5-diol (4.11A). To a solution of β-methoxy ester **3.79B** (2.5 g, 9.2 mmol) in THF (20 mL) at rt was added a solution $LiAlH_4$ (76% w/w, 0.250 g, 5.0 mmol). After 5 min, another portion of $LiAlH_4$ (76% w/w, 0.250 g, 5.0 mmol) was added. After 1 h, a solution of 1.0 M NaOH (aq.) was added until all $LiAlH_4$ was quenched. The reaction mixture was filtered through Celite and the filter cake was rinsed with EtOAc (3 × 50 mL). Solvents were removed under *vacuo* and afforded a pale yellow oil which was carried on to the next step. R_f 0.10 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.07-4.99 (m, 2H), 3.78-3.63 (m, 3H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.37 (s, 3H), 2.56 (bs, 2H), 1.88-1.71 (m, 3H), 1.60 (ddd, *J* = 14.2, 7.2, 2.4 Hz, 1H), 1.52 (ddd, *J* = 14.4, 10.8, 3.6 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 113.2, 78.3,

74.7, 60.2, 57.1, 41.3, 35.6, 34.1, 22.7, 22.2; IR (thin film) ν 3384, 2957, 1456, 1418, 1072, 912 cm^{-1}; HRMS *m/z* 203.1650. (calcd for $C_{11}H_{23}O_3$ $[M+H]^+$, 203.1647).



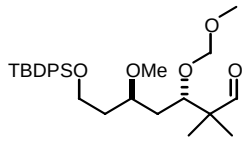
4.11

(4*S*,6*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-6-methoxy-3,3-dimethyloct-1-en-4-ol (4.11). To a solution of crude diol **4.11A** in DMF (40 mL) at 0°C was added sequentially imidazole (0.94 g, 13.8 mmol), DMAP (cat.) and $^tBu(Me)_2SiCl$ (2.89 mL, 11.04 mmol). After 16 h, the reaction mixture was added to a saturated solution of NH_4Cl (50 mL) and diethyl ether (40 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The collected organic layers were washed with H_2O (2 × 25 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 20% EtOAc/hexanes provided the desired oil (3.94 g, 97%): R_f 0.45 (33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 4H), 7.43-7.32 (m, 6H), 5.81 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.03 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.01 (dd, *J* = 17.6, 1.6 Hz, 1H), 3.77-3.67 (m, 3H), 3.58-3.54 (m, 1H), 3.31 (s, 3H), 2.69 (d, *J* = 2.8 Hz, 1H) 1.91 (dddd, *J* = 14.0, 6.4, 6.4, 6.4 Hz, 1H), 1.70 (dddd, *J* = 14.0, 6.8, 6.8, 6.8 Hz, 1H), 1.59 (ddd, *J* = 14.0, 10.8, 3.6 Hz, 1H), 1.50 (ddd, *J* = 14.8, 6.8, 2.0 Hz, 1H), 1.05 (s, 9H), 1.001 (s, 3H), 1.000 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 135.5, 133.7, 129.6, 127.6, 112.7, 76.5, 74.6, 60.5, 57.0, 41.2, 36.0, 34.1, 26.8, 22.64, 22.61, 19.2; IR (thin film) ν 3425 (br), 3071-2857, 1472, 1472, 1427, 1112 cm^{-1}; HRMS *m/z* 441.2823 (calcd for $C_{27}H_{41}O_3Si$ $[M+H]^+$, 441.2825).



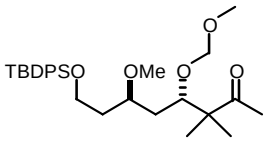
4.12

***tert*-Butyl-((3*R*,5*S*)-3-methoxy-5-methoxymethoxy-6,6-dimethyloct-7-enyloxy)diphenylsilane (4.12).** To a solution of alcohol **4.11** (3.25 g, 7.4 mmol) in CH_2Cl_2 (10 mmol) at 0°C was added successively Hunig's Base (2.6 mL, 14.8 mmol) and MOMCl (0.85 mL, 11.1 mmol). The cold bath was removed and the reaction was monitored for completion by TLC. After the reaction was complete, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under *vacuo*. Purification with flash chromatography on silica gel with 10% EtOAc/hexanes as elutant provided the desired product as colorless oil (3.51 g, 98%) : R_f 0.48 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.44-7.35 (m, 6H), 5.85 (dd, *J* = 18.0, 10.4 Hz, 1H), 4.99 (dd, *J* = 3.2, 1.6 Hz, 1H), 4.95 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.66 (s, 2H), 3.72 (ddd, *J* = 6.4, 3.2 Hz, 2H), 3.56 (dddd, *J* = 12.0, 7.2, 5.2, 2.8 Hz, 1H), 3.43 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.36 (s, 3H), 3.28 (s, 3H), 1.84 (dddd, *J* = 11.6, 6.4, 6.4, 6.4 Hz, 1H), 1.66 (dddd, *J* = 13.2, 6.8, 6.8, 6.8 Hz, 1H), 1.58 (ddd, *J* = 15.2, 10.8, 2.0 Hz, 1H), 1.44 (ddd, *J* = 14.8, 9.6, 2.4 Hz, 1H) 1.05 (s, 9H), 1.001 (s, 3H), 1.000 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 135.6, 133.8, 129.5, 127.6, 111.9, 98.7, 83.7, 74.6, 60.5, 55.9, 55.8, 41.6, 37.2, 36.4, 26.8, 24.0, 22.6, 19.1; IR (thin film) ν 3071-2821, 1472, 1428, 1379, 1111 cm^{-1}; HRMS *m/z* 485.3087 (calcd for $C_{29}H_{45}O_4Si$ $[M+H]^+$, 485.3087).



4.13

(3*S*,5*R*)-7-(*tert*-Butyldiphenylsilanyloxy)-5-methoxy-3-methoxymethoxy-2,2-dimethylheptanal (4.13): A stream of ozone was passed through a solution of olefin **4.12** (2.91 g, 6.0 mmol) and in CH_2Cl_2 (50 mL) at –78°C until a persistent blue color was observed. After purging the reaction mixture with Ar, Ph_3P (1.97 g, 7.5 mmol) was added and the cold bath was removed. After 12 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under vacuo. Purification with flash chromatography on silica gel with 25% EtOAc/hexanes as elutant provided the desired product as colorless oil (2.57 g, 88%): R_f 0.38 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (t, *J* = 5.6 Hz, 1H), 7.68-7.64 (m, 4H), 7.43-7.35 (m, 6H), 4.68 (d, *J* = 6.4 Hz, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 3.91 (dd, *J* = 8.4, 3.2 Hz, 1H), 3.74-3.68 (m, 2H), 3.60-3.54 (m, 1H), 3.28 (s, 3H), 3.275 (s, 3H), 1.89 (dddd, *J* = 10.8, 6.8, 4.8, 4.8 Hz, 1H), 1.64 (dddd, *J* = 12.8, 6.0, 6.0, 6.0 Hz, 1H), 1.57-1.52 (m, 2H), 1.05 (s, 3H), 1.04 (s, 9H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 135.5, 133.6, 129.6, 127.6, 98.2, 79.7, 74.3, 60.3, 55.9, 55.7, 50.5, 36.4, 36.0, 26.8, 19.3, 19.1, 16.6; IR (thin film) ν 3071-2823, 1732, 1471, 1428, 1373, 1240, 1104, 919, 823, 703, 614 cm^{-1}; HRMS *m/z* 487.2882 (calcd for $C_{28}H_{43}O_5Si$ $[M+H]^+$, 487.2880).

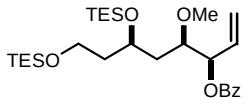


4.14

(4*S*,6*R*)-8-(*tert*-Butyldiphenylsilanyloxy)-6-methoxy-4-methoxymethoxy-3,3-dimethyloctan-2-one (4.14): To a solution of aldehyde **4.13** (3.9 g, 8.0 mmol) in THF (80 mL) at −78°C was added dropwise a solution of MeMgCl (3.55 mL, 22 % wt in THF). After 15 min, a saturated solution of NH_4Cl (50 mL) was added slowly and the cold bath was removed. After 30 min at rt, the reaction mixture was poured into EtOAc (50 mL) and the layers were separated. The aqueous fraction was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered through Celite and concentrated. The crude alcohol was immediately oxidized.

To a solution of oxalyl chloride (1.04 mL, 12.0 mmol) in CH_2Cl_2 (50 mL) at −78°C was added dropwise a solution of DMSO (1.42 mL, 20.0 mmol) in CH_2Cl_2 (20 mL). After 30 min, a solution of the crude alcohol in CH_2Cl_2 (20 mL) was added dropwise. After 1 h, to the reaction mixture was added a solution of Et_3N (4.5 mL, 32.0 mmol) in CH_2Cl_2 (20 mL). After 15 min, the cold bath was removed. After 5 h, the reaction mixture was poured into deionized H_2O (30 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 10% EtOAc/hexanes provided the desired product (3.92 g, 98%) as a colorless oil: R_f 0.39 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.64 (m, 4H), 7.40-7.34 (m, 6H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 1H), 3.94 (dd, *J* = 9.2, 1.6 Hz, 1H), 3.75-3.65 (m, 2H), 3.56 (dddd, *J* = 12.0, 7.6, 4.4, 2.0 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.16

(s, 3H), 1.85 (dddd, J = 11.2, 6.4, 4.8, 4.8 Hz, 1H), 1.61 (dddd, J = 12.8, 6.4, 6.4, 6.4 Hz, 1H), 1.50 (ddd, J = 14.4, 9.6, 2.4 Hz, 1H), 1.38 (ddd, J = 14.4, 10.0, 1.6 Hz, 1H), 1.12 (s, 3H), 1.03 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 135.6, 133.7, 129.6, 127.6, 98.4, 81.0, 74.5, 60.4, 55.9 (2C), 52.6, 37.4, 36.2, 26.8, 26.3, 20.7, 20.66, 19.1; IR (thin film) ν 3071-2858, 1705, 1472, 1418, 1150, 1111, 1035, 703 cm^{-1}; HRMS *m/z* 499.2881 (calcd for $C_{29}H_{44}O_5Si$ $[M-H]^+$, 499.2880).

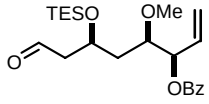


4.16

Benzoic acid (1*R*,2*R*,4*R*)-2-methoxy-4,6-bis-triethylsilanyloxy-1-vinylhexyl ester (4.16). To a solution of olefin **2.111** (5.14 g, 13.97 mmol) in a EtOH:CH_2Cl_2 (3:1 v/v, 120 mL) at −78°C was bubbled in a stream of ozone. After a light blue color persisted, the reaction mixture was purged with Ar. After 15 min, $NaBH_4$ (1.06 g, 27.93 mmol) was added in one portion and the cold bath was removed in 30 min. After 30 min at rt, the reaction mixture was slowly added to a saturated solution of NH_4Cl (100 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 75 mL) and the collected organic layers were dried (Na_2SO_4), filtered through Celite and concentrated. The crude alcohol was redisolved in 95% EtOH/H_2O (9:1, 200 mL). After the addition of Zn/Cu couple (22.7 g, 349.3 mmol), NH_4Cl (3.7 g, 70.0 mmol), the reaction mixture was brought to reflux. After 12 h, the suspension was cooled, filtered through Celite, diluted with H_2O was extracted with EtOAc (3 × 70 mL). The combined organic fractions were washed with brine (50 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with

75% EtOAc/hexanes as elutant provided diol **4.15** (2.91 g, 71%): R_f 0.27 (80% EtOAc/hexanes).

To a solution of diol **4.15** (1.70 g, 5.78 mmol) and imidazole (1.20 g, 16.0 mmol) in DMF (6 mL) at 0°C was added TESCl (2.4 mL, 14.3 mmol). The cold bath was removed. After 16 h, the reaction mixture was added to a saturated solution of NH_4Cl (30 mL) and diethyl ether (30 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The collected organic layers were washed with H_2O (2 × 25 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 2% EtOAc/hexanes provided a pale yellow oil (2.84 g, 94%): R_f 0.75 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 2H), 7.54 (app t, *J* = 7.2 Hz, 1H), 7.42 (app t, *J* = 7.2 Hz, 2H), 5.95 (ddd, *J* = 17.2, 11.2, 6.0 Hz, 1H), 5.64 (t, *J* = 5.6 Hz, 1H), 5.36 (d, *J* = 17.6 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.02 (dddd, *J* = 6.4, 6.4, 6.4, 6.4 Hz, 1H), 3.65 (t, *J* = 6.8 Hz, 2H), 3.52 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.45 (s, 3H), 1.76-1.62 (m, 4H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.53 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 133.0, 132.8, 130.1, 129.6, 128.3, 117.9, 78.8, 74.8, 66.4, 59.4, 58.5, 40.0, 38.3, 6.8, 6.7, 4.9, 4.3.



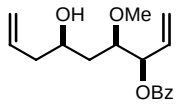
4.17

Benzoic acid (1*R*,2*R*,4*S*)-2-methoxy-6-oxo-4-triethylsilanyloxy-1-vinylhexyl ester (4.17). Method A: To a solution of oxalyl chloride (0.33 ml, 3.82 mmol) in CH_2Cl_2 (4 mL) at –78°C was added dropwise a solution of DMSO (0.54 mL, 7.68 mmol) in CH_2Cl_2 (2 mL). After 30 min, a solution of bis-triethylsilyl ether **4.16** (0.50 g, 0.96 mmol) in CH_2Cl_2 (3 mL) was added dropwise to the reaction mixture. After 1 h, a solution of Et_3N

(2.0 ml, 14.4 mmol) in CH_2Cl_2 (2 mL) was added dropwise and after 10 min, the cold bath was removed. After 15 min at rt, H_2O (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic fractions were washed with $NaHCO_3$ (20 mL), brine (20 mL) and then dried ($MgSO_4$). Filtration through Celite and concentration *in vacuo* supplied the crude products as a pale yellow oil. Purification on flash chromatography on silica gel with 5-10% EtOAc/hexanes provided the desired product as a pale yellow oil (0.11 g, 29%).

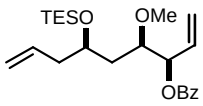
Method B: To a solution of oxalyl chloride (0.04 ml, 0.41 mmol) in CH_2Cl_2 (3 mL) at –78°C was added dropwise a solution of DMSO (0.05 mL, 0.68 mmol) in CH_2Cl_2 (2 mL). After 30 min, a solution of alcohol **4.21** (0.11 g, 0.27 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the reaction mixture. After 1 h, a solution of Et_3N (0.15 ml, 1.1 mmol) in CH_2Cl_2 (2 mL) was added dropwise and after 10 min, the cold bath was removed. After 15 min at rt, H_2O (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic fractions were washed with $NaHCO_3$ (10 mL), brine (10 mL) and then dried ($MgSO_4$). Filtration through Celite and concentration *in vacuo* supplied the crude products as a pale yellow oil. Purification on flash chromatography on silica gel with 5-10% EtOAc/hexanes provided the desired product as a pale yellow oil (0.10 g, 91%): R_f 0.50 (10% EtOAc/hexanes) : R_f 0.35 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (app t, *J* = 2.4 Hz, 1H), 8.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.56 (dddd, *J* = 7.6, 7.6, 1.2, 1.2 Hz, 1H), 7.43 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 2H), 5.93 (ddd, *J* = 17.6, 11.2, 6.0 Hz, 1H), 5.69 (dddd, *J* = 6.0, 6.0, 1.2, 1.2 Hz, 1H), 5.38 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.30 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 1H), 4.41 (ddd, *J* = 11.6, 6.4, 5.6 Hz, 1H), 3.58 (ddd, *J* = 7.2, 4.8, 4.8 Hz, 1H), 3.46 (s, 3H), 2.62 (ddd, *J* = 16.0, 5.6, 2.4 Hz, 1H), 2.55 (ddd, *J* = 16.0, 6.8, 2.6 Hz, 1H), 1.78 (d, *J* = 6.0 Hz, 1H), 1.77 (dd, *J* = 4.8, 2.0 Hz, 1H), 0.88 (t, *J* = 8.0 Hz, 9H), 0.54 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 201.9, 165.5, 133.2, 132.3, 129.6, 128.4, 118.1, 78.0, 74.1, 65.1, 58.1, 50.6, 37.4, 6.7, 4.8; IR (thin film) ν 2955, 2912, 2877, 2829, 1724, 1452, 1268, 1097, 1070, 1026, 1007, 712 cm^{-1}; HRMS *m/z* 405.2104 (calcd for $C_{22}H_{35}O_5Si$ $[M-H]^+$, 405.2104).



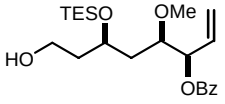
4.18

Benzoic acid (1*R*,2*R*,4*R*)-4-hydroxy-2-methoxy-1-vinylhep-6-enyl ester (4.18). To a solution of olefin **2.111** (4.50 g, 12.2 mmol) in 95% EtOH/H_2O (9:1, 200 mL) was added Zn/Cu couple (24.0 g, 370 mmol) followed by NH_4Cl (3.5 g, 66.0 mmol) and the reaction mixture was brought to reflux. After 12 h, the suspension was cooled, filtered through Celite, diluted with H_2O was extracted with EtOAc (3 × 100 mL). The combined organic fractions were washed with brine (100 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 20% EtOAc/hexanes as elution provided alcohol **4.18** (2.6 g, 73%): R_f 0.42 (50% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.57 (ddd, *J* = 8.8, 8.8, 1.6, 1.6 Hz, 1H), 7.46-7.42 (m, 2H), 5.94 (ddd, *J* = 16.4, 10.8, 5.6 Hz, 1H), 5.81 (dddd, *J* = 16.8, 10.0, 7.2, 7.2 Hz, 1H), 5.71 (dddd, *J* = 5.6, 5.6, 1.2, 1.2 Hz, 1H), 5.38 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1H), 5.31 (ddd, *J* = 10.8, 1.2, 1.2 Hz, 1H), 5.11-5.05 (m, 2H), 3.86 (dddd, *J* = 8.8, 6.4, 6.4, 3.2 Hz, 1H), 3.68 (ddd, *J* = 9.2, 3.6, 3.6 Hz, 1H), 3.54 (s, 3H), 3.10 (br s, 1H), 2.22 (dd, *J* = 6.8, 6.8 Hz, 2H), 1.75 (ddd, *J* = 14.8, 3.2, 3.2 Hz, 1H), 1.64 (ddd, *J* = 14.8, 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 134.6, 133.2, 132.2, 129.8, 129.6, 128.5, 118.2, 117.6, 82.0, 74.1, 70.2, 58.5, 42.0, 36.2.



4.19

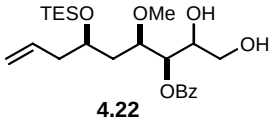
Benzoic acid (1*R*,2*R*,4*R*)-2-methoxy-4-triethylsilanyloxy-1-vinylhept-6-enyl ester (4.19). To a stirred solution of alcohol **4.18** (2.6 g, 8.97 mmol), imidazole (1.22 g, 17.94 mmol) and DMAP (~50 mg) in DMF (10 mL) at 0°C was added TESCl (1.97 mL, 11.7 mmol). The cold bath was removed and after 12 h, the reaction mixture was added to a saturated solution of NH_4Cl (50 mL) and diethyl ether (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The collected organic layers were washed with H_2O (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 10% EtOAc/hexanes provided a pale yellow oil (3.60 g, 99%): R_f 0.75 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.55 (ddd, *J* = 7.2, 7.2, 1.6, 1.6 Hz, 1H), 7.42 (dd, *J* = 7.2, 1.2 Hz, 2H), 5.96 (ddd, *J* = 17.2, 10.8, 6.0 Hz, 1H), 5.78 (dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.65 (dddd, *J* = 5.6, 2.8, 1.2, 1.2 Hz, 1H), 5.28 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1H), 5.00-4.92 (m, 2H), 3.89 (dddd, *J* = 5.6, 5.6, 5.6, 5.6 Hz, 1H), 3.53 (ddd, *J* = 8.4, 4.8, 4.8 Hz, 1H), 3.45 (s, 3H), 2.78 (br s, 1H), 2.19 (ddd, *J* = 14.0, 5.6, 5.6 Hz, 1H), 1.75 (ddd, *J* = 14.8, 7.2, 4.8 Hz, 1H), 1.68 (ddd, *J* = 14.0, 7.6, 5.2 Hz, 1H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 8.0 Hz, 6H).



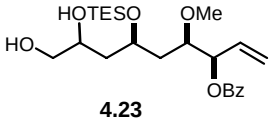
4.21

Benzoic acid (1*R*,2*R*,4*R*)-6-hydroxy-2-methoxy-4-triethylsilanyloxy-1-vinylhexyl ester (4.21). A solution of bis-triethylsilyl ether **4.16** (0.25 g, 0.48 mmol) in a solvent mixture of H_2O:AcOH:THF (1:3:10, 5 mL) was monitored by TLC. After 3h, the reaction mixture was cooled to 0°C and a saturated solution of $NaHCO_3$ (25 mL) was added. The cold bath was removed and EtOAc (25 mL) was added. After 30 min, the

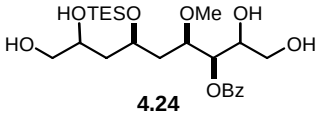
organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated under *vacuo*. Purification on flash chromatography on silica gel with 20% EtOAc/hexanes as elution provided a clear oil (0.147 g, 75%): R_f 0.20 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.56 (app t, *J* = 7.2 Hz, 1H), 7.44 (app t, *J* = 8.0 Hz, 2H), 5.95 (ddd, *J* = 17.2, 10.8, 5.6 Hz, 1H), 5.68 (app t, *J* = 6.0 Hz, 1H), 5.38 (d, *J* = 17.6 Hz, 1H), 5.30 (d, *J* = 11.2 Hz, 1H), 4.13 (dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 3.76 (ddd, *J* = 10.8, 8.0, 4.0 Hz, 1H), 3.50 (ddd, *J* = 7.6, 4.8, 4.8 Hz, 1H), 3.46 (s, 3H), 1.88-1.64 (m, 4H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H).



4.22



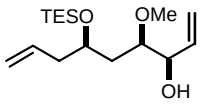
4.23



4.24

Benzoic acid (1*R*,2*R*,4*R*)-1-(1,2-dihydroxyethyl)-2-methoxy-4-triethylsilanyloxyhept-6-enyl ester (4.22) and **Benzoic acid (1*R*,2*R*,4*R*)-6,7-dihydroxy-2-methoxy-4-triethylsilanyloxy-1-vinylheptyl ester (4.23)** and **Benzoic acid (1*R*,2*R*,4*R*)-1-(1,2-dihydroxyethyl)-6,7-dihydroxy-2-methoxy-4-triethylsilanyloxyheptyl ester (4.24).** To a solution of triethylsilyl ether **4.19** (0.48 g, 1.23 mmol) in *tert*-butanol:H_2O (1:1 v/v, 10 mL) was added OsO_4 (~50 mg, 0.2 mmol). After 15 min, 4-methylmorpholine *N*-oxide (0.173 g, 1.5 mmol) was added. After 12 h, the solution was transferred to a mixture of EtOAc (20 mL) and saturated aqueous Na_2SO_3 (10 mL). After extracting with EtOAc (3 × 10 mL), the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on a pre-buffered (3:12:85, Et_3N:EtOAc:hexanes) silica gel with 20-65% EtOAc/hexanes provided three

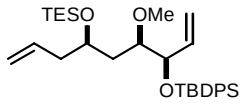
regioisomeric products **4.23** (0.26 g, 50%), **4.22** (0.02 g, 4%) and **4.24** (0.11 g, 21%): R_f 0.42 (50% EtOAc/hexanes), R_f 0.45 (50% EtOAc/hexanes), R_f 0.05 (50% EtOAc/hexanes); X1 major isomer ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 133.2, 132.3, 129.9, 129.6, 128.4, 118.2, 78.5, 74.4, 68.8, 68.0, 67.1, 58.4, 38.3, 36.9, 6.7, 4.7; HRMS *m/z* 439.2521 (calcd for $C_{23}H_{39}O_6Si$ $[M+H]^+$, 439.2516).



4.25

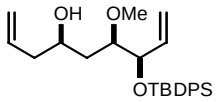
(3*R*,4*R*,6*R*)-4-Methoxy-6-triethylsilanyloxynona-1,8-dien-3-ol (4.25). To a solution of triethylsilyl ether **4.19** (3.60 g, 8.89 mmol) in Et_2O (100 mL) at 0°C was added dropwise ethyl grignard reagent (8.5 mL, 3.14 M). After 15 min, the cold bath was removed and the reaction was monitored (TLC). After 4h, the reaction mixture was cooled to 0°C and a saturated solution of NH_4Cl (10 mL) was slowly added. After 15 min, the reaction mixture was slowly added to a saturated solution of NH_4Cl:EtOAc (1:1, 100 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the collected organic layers were dried (Na_2SO_4), filtered through Celite and concentrated. Purification on flash chromatography on silica gel with 1-6% EtOAc/hexanes as elution provided a clear oil (2.50 g, 94%): R_f 0.2 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 17.2, 10.8, 6.0 Hz, 1H), 5.78 (dddd, *J* = 17.6, 10.4, 7.2, 7.2 Hz, 1H), 5.32 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.19 (ddd, *J* = 10.8, 1.6 Hz, 1H), 5.07-5.03 (m, 2H), 4.05 (t, *J* = 5.2 Hz, 1H), 3.84 (dddd, *J* = 6.9, 6.4, 5.2, 5.2 Hz, 1H), 3.37 (s, 3H), 3.27 (ddd, *J* = 6.8, 5.2, 5.2 Hz, 1H), 2.78 (br s, 1H), 2.31-2.20 (m, 2H), 1.74 (ddd, *J* = 14.8, 6.8, 5.2 Hz, 1H), 1.65 (ddd, *J* = 14.8, 6.4, 5.2 Hz, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 134.5, 117.3, 116.5, 80.7, 73.9, 69.1, 57.7, 41.8, 36.8, 6.9, 5.0; IR (thin film) ν

3440 (br), 2954-2877, 1641, 1458, 1415, 1239, 1097, 1004, 916, 743 cm^{-1}; HRMS *m/z* 301.2200 (calcd for $C_{16}H_{33}O_3Si$ $[M+H]^+$, 301.2199).



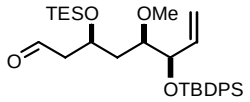
4.26

(5R,6R,8R)-8-allyl-10,10-diethyl-6-methoxy-2,2-dimethyl-3,3-diphenyl-5-vinyl-4,9-dioxa-3,10-disiladodecane (4.26). To a stirred solution of alcohol **4.28** (3.12 g, 7.36 mmol), imidazole (0.75 g, 11.04 mmol) and DMAP (~50 mg) in DMF (10 mL) at 0°C was added TESCl (1.61 mL, 9.57 mmol). The cold bath was removed and after 12 h, the reaction mixture was added to a saturated solution of NH_4Cl (50 mL) and diethyl ether (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The collected organic layers were washed with H_2O (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on silica gel with 3% EtOAc/hexanes provided a pale yellow oil (3.3 g, 83%): R_f 0.50 (10% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 6.8 Hz, 2H), 7.71 (d, *J* = 6.8 Hz, 2H), 7.48-7.37 (m, 6H), 5.90 (dd, *J* = 17.2, 5.6 Hz, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 5.06 (d, *J* = 6.4 Hz, 1H), 5.03 (s, 1H), 4.42 (dd, *J* = 4.4, 4.4 Hz, 1H), 3.81 (dddd, *J* = 8.8, 6.8, 6.8, 4.4 Hz, 1H), 3.02 (s, 3H), 2.96 (ddd, *J* = 10.4, 4.4, 2.8 Hz, 1H), 2.23 (ddd, *J* = 13.6, 5.3, 5.2 Hz, 1H), 2.13 (ddd, *J* = 13.6, 6.8, 6.8 Hz, 1H), 1.85 (ddd, *J* = 14.0, 9.2, 2.4 Hz, 1H), 1.55 (ddd, *J* = 14.0, 10.4, 4.4 Hz, 1H), 1.14 (s, 9H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 136.0, 135.9, 135.9, 135.6, 134.0, 133.6, 129.8, 129.6, 127.6, 127.4, 116.4, 115.9, 80.8, 72.5, 69.6, 57.4, 41.3, 37.0, 27.1, 19.3, 6.9, 4.9; HRMS *m/z* 539.3377 (calcd for $C_{32}H_{51}O_3Si_2$ $[M+H]^+$, 539.3381).



4.28

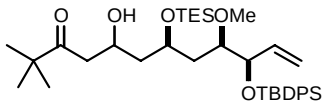
(4*R*,6*R*,7*R*)-7-(*tert*-Butyldiphenylsilanyloxy)-6-methoxynona-1,3-diene-4-ol (4.28). To a solution of olefin **4.27** (5.73 g, 11.4 mmol) in 95% EtOH/H_2O (9:1, 120 mL) was added Zn/Cu couple (18.5 g, 285 mmol) followed by NH_4Cl (3.0 g, 57.0 mmol) and the reaction mixture was brought to reflux. After 12 h, the suspension was cooled, filtered through Celite, diluted with H_2O was extracted with EtOAc (3 × 75 mL). The combined organic fractions were washed with brine (70 mL) and dried ($MgSO_4$). Filtration through Celite, concentration *in vacuo* and purification by flash chromatography on silica gel with 10-20% EtOAc/hexanes as elutant provided alcohol **4.28** (3.12 g, 65%): R_f 0.45 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.63 (m, 4H), 7.46-7.41 (m, 2H), 7.39-7.34 (m, 4H), 5.91-5.77 (m, 2H), 5.31 (ddd, *J* = 16.8, , 2.0, 2.0 Hz, 1H), 5.21 (ddd, *J* = 10.4, 2.0, 2.0 Hz, 1H), 5.13-5.07 (m, 2H), 4.41 (dddd, *J* = 4.4, 4.4, 1.6, 1.6 Hz, 1H), 3.69 (dddd, *J* = 8.8, 6.0, 6.0, 2.4 Hz, 1H), 3.29 (br s, 1H), 3.05 (ddd, *J* = 10.0, 4.0, 2.0 Hz, 1H), 2.96 (s, 3H), 2.27-2.11 (m, 2H), 1.88 (ddd, *J* = 15.2, 2.4, 2.4 Hz, 1H), 1.37 (ddd, *J* = 15.2, 10.0, 10.0 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (2C), 135.5, 134.9, 133.8, 133.1, 129.9, 129.7, 127.7, 127.5, 117.1, 116.1, 84.1, 71.4, 71.3, 56.9, 41.9, 34.4, 26.9, 19.2; IR (thin film) ν 3513 (br), 3072-2827, 1740, 1473, 1428, 1241, 1112, 920, 822, 703 cm^{-1}; HRMS *m/z* 425.2508 (calcd for $C_{26}H_{37}O_3Si$ $[M+H]^+$, 425.2512).



4.29

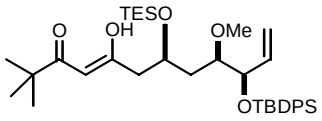
(3*S*,5*R*,6*R*)-6-(*tert*-Butyldiphenylsilanyloxy)-5-methoxy-3-triethylsilanyloxyoct-7-enal (4.29). To a solution of triethylsilyl ether **4.26** (2.70 g, 5.00 mmol) in *t*-BuOH:H_2O (1:1 v/v, 50 mL) was added OsO_4 (~50 mg, 0.2 mmol). After 15 min, 4-methylmorpholine *N*-oxide (0.74 g, 5.5 mmol) was added. After 12 h, the solution was transferred to a mixture of EtOAc (100 mL) and saturated aqueous Na_2SO_3 (50 mL). After extracting with EtOAc (2 × 50 mL), the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The solution of the residue in CH_2Cl_2 (50 mL) was subjected to pyridine (1.22 mL, 15.0 mmol) and $Pb(OAc)_4$ (2.77 g, 6.25 mmol) at 0°C. After 2h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (75 mL) and filtered through Celite. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification on flash chromatography on a pre-buffered (3:2:95, Et_3N:EtOAc:hexanes) silica gel with 3% EtOAc/hexanes provided a clear oil (2.06 g, 76%): R_f 0.50 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J* = 2.4 Hz, 1H) 7.67 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.44-7.39 (m, 2H), 7.37-7.33 (m, 4H), 5.84 (ddd, *J* = 17.2, 10.8, 4.8 Hz, 1H), 5.27 (ddd, *J* = 17.2, 2.0 Hz, 1H), 5.18 (ddd, *J* = 10.8, 2.0 Hz, 1H), 4.39 (dddd, *J* = 4.8, 4.8, 2.0, 2.0 Hz, 1H), 4.24 (dddd, *J* = 11.6, 5.6, 4.0, 4.0 Hz, 1H), 2.91 (s, 3H), 2.79 (ddd, *J* = 10.4, 4.4, 2.0 Hz, 1H), 2.35 (m, 2H), 1.80 (ddd, *J* = 14.0, 9.6, 2.0 Hz, 1H), 1.58 (ddd, *J* = 14.0, 10.8, 3.6 Hz, 1H), 1.07 (s, 9H), 0.90 (t, *J* = 7.6 Hz, 9H), 0.54 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 135.91, 135.88, 133.9, 133.4, 130.0, 129.8, 127.7, 127.5, 116.2, 80.1, 71.6, 65.7, 57.3, 50.1, 37.3, 27.1, 19.3, 6.8, 4.; IR

(thin film) ν 2956-2824, 1726, 1471, 1428, 1284, 1105 cm^{-1}; HRMS *m/z* 539.3009 (calcd for $C_{31}H_{48}O_4Si_2$ $[M-H]^+$, 539.3013).



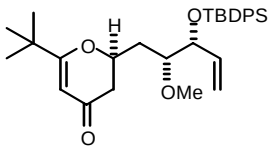
4.30

(7*R*,9*R*,10*R*)-10-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxy-9-methoxy-2,2-dimethyl-7-triethylsianyloxydodec-11-en-3-one (4.30). To a solution of LDA (3.77 mmol) in THF (20 mL) at –78°C was added a solution of pinacolone (0.43 mL, 3.45 mmol) and THF (5 mL) dropwise. After 1h, the cold bath was removed and replaced with an ice bath (0°C). After 2 min, the ice bath was removed and the reaction was cooled to –78°C. A solution of aldehyde **4.29** (1.7 g, 3.14 mmol) and THF (5 mL) was added dropwise and after 15 min, a saturated solution of NH_4Cl (30 mL) was added, followed by diethyl ether (30 mL) and the cold bath was removed. After 30 min, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The collected organic phases were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography on silica gel with 5% EtOAc/hexanes gave an inconsequential 4:1 mixture of diastereomers (1.95 g, 97%). : R_f 0.22 (10% EtOAc/hexanes); ^{1}H NMR major isomer (400 MHz, $CDCl_3$) δ 7.70-7.62 (m, 4H), 7.43-7.33 (m, 6H), 5.83 (ddd, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.19 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1H), 5.12 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 1H), 4.35 (dd, *J* = 5.2, 4.2 Hz, 1H), 4.25-4.21 (m, 1H), 4.09-4.03 (m, 1H), 3.55 (d, *J* = 3.2 Hz, 1H), 2.97 (s, 3H), 2.95 (ddd, *J* = 10.8, 4.0, 1.6 Hz, 1H), 2.5902.57 (m, 2H), 1.78 (ddd, *J* = 14.0, 10.0, 2.0 Hz, 1H), 1.60-1.50 (m, 2H), 1.38 (ddd, *J* = 14.4, 8.4, 2.4 Hz, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.58 (t, *J* = 8.0 Hz, 6H).



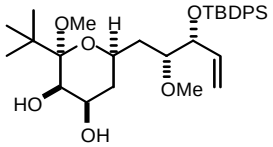
4.31

(*Z*)-(7*R*,9*R*,10*R*)-10-(*tert*-Butyldiphenylsilanyloxy)-5-hydroxy-9-methoxy-2,2-dimethyl-7-triethylsianyloxydodeca-4,11-dien-3-one (4.31). To a solution of the mixture of diastereomers **4.30** (0.2 g, 0.31 mmol), pyridine (0.16 mL, 1.86 mmol), H_2O (14 μL, 0.78 mmol) in THF/CH_2Cl_2 (1:1, 10 mL) at 0°C was added Dess-Martin Periodinane (2.8 mL, 0.28 M in CH_2CL_2) dropwise. After 5h, a solution of saturated $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 15 mL) was added and the cold bath was removed. After 10 min, the organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 X 15 mL). The collected organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography on a pre-buffered (3:2:95 Et_3N:EtOAc:hexanes) silica gel with 2-5% EtOAc/hexanes to give the product as a pale yellow oil (0.19 g, 87%): R_f 0.70 (10% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.43-7.32 (m, 6H), 5.82 (ddd, *J* = 16.0, 10.8, 5.2 Hz, 1H), 5.61 (s, 1H), 5.22 (ddd, *J* = 17.6, 1.6, 1.6 Hz, 1H), 5.13 (ddd, *J* = 10.8, 1.6, 1.6 Hz, 1H), 4.35 (app t, *J* = 4.8 Hz, 1H), 4.16 (dddd, *J* = 9.2, 9.2, 3.2, 3.2 Hz, 1H), 2.96 (s, 3H), 2.84 (ddd, *J* = 10.8, 4.8, 2.0 Hz, 1H), 2.32 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.21 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.76 (ddd, *J* = 14.0, 9.6, 2.0 Hz, 1H), 1.52 (ddd, *J* = 14.0, 10.4, 3.2 Hz, 1H), 1.14 (s, 9H), 1.07 (s, 9H), 0.86 (t, *J* = 8.0 Hz, 9H), 0.48 (q, *J* = 8.0 Hz, 6H).



4.32

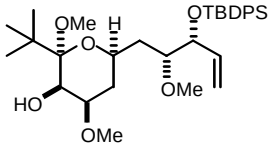
(*S*)-6-*tert*-Butyl-2-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-2-methoxypent-4-enyl]-2,3-dihydropyran-4-one (4.32). To a solution of *β*-diketone **4.31** (0.34 g, 0.53 mmol) in toluene (5 mL) at rt was added p-TsOH (~20 mg). After 16 h, the reaction mixture was immediately purified by flash column chromatography on a pre-buffered (3:5:92 Et_3N:EtOAc:hexanes) silica gel with 10% EtOAc/hexanes to give the desired product **4.32** (0.25 g, 95%) as a pale yellow oil: R_f 0.50 (25% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.62 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.45-7.33 (m, 6H), 5.89 (ddd, *J* = 17.2, 10.8, 4.8 Hz, 1H), 5.37 (s, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.42 (app t, *J* = 4.4 Hz, 1H), 4.29 (dddd, *J* = 8.8, 4.8, 4.8, 4.8 Hz, 1H), 2.94-2.89 (m, 1H), 2.91 (s, 3H), 2.30 (dd, *J* = 16.4, 13.2 Hz, 1H), 2.23 (dd, *J* = 16.8, 4.0 Hz, 1H), 2.01 (ddd, *J* = 14.4, 7.6, 2.4 Hz, 1H), 1.80 (ddd, *J* = 14.8, 10.4, 4.8 Hz, 1H), 1.09 (s, 9H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 177.5, 135.9 (2C), 135.85, 135.80, 133.9, 133.4, 129.9, 129.8, 127.7, 127.5, 116.4, 80.5, 71.9, 68.5, 57.0, 48.1, 38.6, 33.4, 30.1, 27.0, 19.3; HRMS *m/z* 507.2931 (calcd for $C_{31}H_{43}O_4Si$ $[M-H]^+$, 507.2931).



4.34

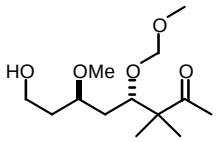
(2*R*,3*R*,4*R*,6*R*)-2-*tert*-Butyl-6-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-2-methoxypent-4-enyl]-2-methoxytetrahydropyran-3,4-diol (4.34). To a solution of

pyranone **4.32** (0.22 g, 0.43 mmol) in MeOH (10 mL) at rt was added $CeCl_3$•7 H_2O (0.16 g, 0.43 mmol). After 15 min, the reaction mixture was cooled to –30°C and $NaBH_4$ (22 mg, 0.57 mmol) was added in one portion. After 30 min, the reaction mixture was poured into a solvent mixture of brine:EtOAc (1:1, 50 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to provide the crude allylic alcohol **4.33** (R_f 0.37 (25% EtOAc/hexanes) that was used in the next step without purification due to the reported instability.[2] To a solution of the crude alcohol in a mixture of CH_2Cl_2: MeOH (2:1, 15 mL) at 0°C was added $NaHCO_3$ (0.30 g, 3.5 mmol) followed by the addition of purified m-CPBA (82 mg, 0.48 mmol). After 30 min, Et_3N (3 mL) was added and after an additional 20 min, Et_2O (20 mL) was added. After 15 min, the reaction mixture was filtered through Celite and concentrated. Purification by flash column chromatography on pre-buffered (3:7:90, Et_3N:EtOAc:hexanes) silica gel with 10-18% EtOAc/hexanes gave the desired diol **4.34** (0.18 g, 75 %) as a white foam: R_f 0.23 (25% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.64 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.43-7.39 (m, 2H), 7.37-7.32 (m, 4H), 5.90 (ddd, *J* = 16.8, 10.4, 4.8 Hz, 1H), 5.22 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 4.37 (t, *J* = 4.8 Hz, 1H), 3.90 (ddd, *J* = 12.0, 4.8, 3.2 Hz, 1H), 3.75 (d, *J* = 3.2 Hz, 1H), 3.52-3.46 (m, 1H), 3.19 (s, 3H), 3.07-3.03 (m, 1H), 2.99 (s, 3H), 1.93 (br s, 2H), 1.83 (ddd, *J* = 14.4, 7.2, 3.2 Hz, 1H), 1.62-1.56 (m, 1H), 1.55 (ddd, *J* = 12.0, 4.4, 2.8 Hz, 1H), 1.37 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.08 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 135.9 (2C), 133.9, 133.5, 129.8, 129.7, 127.6, 127.5, 116.2, 103.8, 80.5, 72.6, 70.5, 68.1, 67.1, 57.3, 51.7, 40.9, 34.9, 33.0, 27.1, 26.9, 19.3; IR (thin film) ν 3410 (br), 3065-2860, 1467, 1421, 1109, 1063, 1036, 924, 705 cm^{-1}; HRMS *m/z* 555.3157 (calcd for $C_{32}H_{48}O_6Si$ $[M-H]^+$, 555.3142).



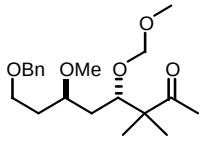
4.35

(2*R*,3*R*,4*R*,6*R*)-2-*tert*-Butyl-6-[(2*R*,3*R*)-3-(*tert*-Butyldiphenylsilanyloxy)-2-methoxypent-4-enyl]-2,4-dimethoxytetrahydropyran-3-ol (4.35). To a solution of diol **4.34** (85 mg, 0.15 mmol) in THF (2 mL) at 0°C was added *t*-BuOK (21 mg, 0.18 mmol) resulting in an orange solution and after 15 min, a solution of MeI (0.02 mL, 0.30 mmol) in THF (2 mL) was added dropwise. After 30 min, Et_3N (0.20 mL) was added and the reaction mixture was poured into a mixture of brine:EtOAc (1:1, 10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under *vacuo*. Purification by flash column chromatography on a pre-buffered (3:7:90 Et_3N:EtOAc:hexanes) silica gel with 10-20% EtOAc/hexanes provided the desired product as a pale yellow oil (53 mg, 71% based on recovered starting material): R_f 0.75 (50% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.66 (m, 4H), 7.47-7.35 (m, 6H), 5.94 (ddd, *J* = 16.2, 10.5, 5.7 Hz, 1H), 5.26-5.16 (m, 2H), 4.40 (app t, *J* = 4.5 Hz, 1H), 3.91 (m, 1H), 3.56-3.43 (m, 2H), 3.40 (s, 3H), 3.22 (s, 3H), 3.13 (ddd, *J* = 8.4, 3.0, 3.0 Hz, 1H), 3.06 (s, 3H), 2.08 (d, *J* = 1.8 Hz, 1H), 1.90 (ddd, *J* = 14.4, 6.9, 3.0 Hz, 1H), 1.64 (ddd, *J* = 14.4, 8.7, 5.4 Hz, 1H), 1.57-1.51 (m, 2H), 1.12 (s, 9H), 1.09 (s, 3H), 1.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 136.0 (2C), 134.8, 133.7, 129.6, 127.7, 127.6, 127.4, 116.2, 103.9, 80.6, 72.8, 68.2, 67.2, 55.5, 51.4, 41.2, 35.0, 29.6, 27.1, 26.7, 26.5, 19.4; IR (thin film) ν 3462 (br), 3006-2846, 1467, 1428, 1109, 1069, 1043, 930, 698 cm^{-1}.



4.38A

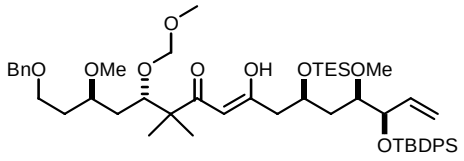
(4*S*,6*R*)-8-Hydroxy-6-methoxy-4-methoxymethoxy-3,3-dimethyloctan-2-one (4.38A): To a solution of silyl ether **4.14** (4.0g, 8.0 mmol) in THF (40 mL) at 0°C was added TBAF (9mL, 1M). After 15 min, the cold bath was removed and the reaction was monitored by TLC. After the starting material was consumed, brine (40 mL) was added and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the collected organic phases were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel with 10% MeOH/CH_2Cl_2 to give the desired product as a pale yellow oil (2.06 g, 99%): R_f 0.50 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 2H), 3.89 (dd, *J* = 9.2. 2.0 Hz, 1H), 3.76 (ddd, *J* = 11.2, 6.8, 5.6 Hz, 1H), 3.66 (ddd, *J* = 6.8 Hz, 1H), 3.61-3.56 (m, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 2.25 (bs, 1H), 2.15 (s, 3H), 1.83-1.69 (m, 2H), 1.53 (ddd, *J* = 14.4, 9.2, 2.0 Hz, 1H), 1.44 (ddd, *J* = 14.8, 9.2, 3.2 Hz, 1H), 1.12 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.0, 98.5, 81.6, 76.1, 59.8, 56.2, 55.9, 38.2, 36.7, 35.1, 26.4, 20.8, 20.7.



4.38

(4*S*,6*R*)-8-Benzyloxy-6-methoxy-4-methoxymethoxy-3,3-dimethyloctan-2-one (4.38). To a heterogeneous mixture of NaH (0.48 g, 8.8 mmol) in DMF (15 mL) at 0°C was added a solution of alcohol **4.38A** (2.06 g, 8.00 mmol) and DMF (10 mL) dropwise. After 20 min, benzyl bromide (1.91 mL, 16 mmol) was added and the cold bath was

removed. After 2h, a saturated solution of NH_4Cl (30 mL) was added and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the collected organic phases were washed with H_2O (2 × 30 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography on silica gel with 20% EtOAc/hexanes to give the desired product as a pale yellow oil (2.43 g, 86%): R_f 0.10 (20% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.25 (m, 5H), 4.63 (t, *J* = 7.2 Hz, 2H), 4.47 (s, 2H), 3.91 (dd, *J* = 9.2, 2.4 Hz, 1H), 3.56-3.47 (m, 3H), 3.32 (s, 3H), 3.31 (s, 3H), 2.15 (s, 3H), 1.91 (s, 1H), 1.70 (s, 1H), 1.48 (ddd, *J* = 14.4, 9.2, 2.4 Hz, 1H), 1.40 (ddd, *J* = 14.4, 10.0, 2.4 Hz, 1H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 212.9, 138.4, 128.3, 127.55, 127.50, 98.4, 81.1, 74.7, 73.0, 66.7, 56.1, 55.9, 52.6, 37.4, 33.5, 26.4, 20.8, 20.6; HRMS *m/z* 375.2147 (calcd for $C_{20}H_{32}O_5Na$ $[M+Na]^+$, 375.2147).



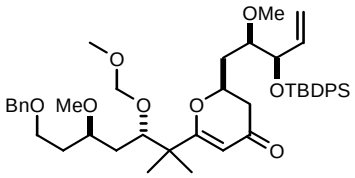
4.39

(*Z*)-(3*R*,5*S*,11*S*,13*R*,14*R*)-1-Benzyloxy-11-(*tert*-Butyldimethylsilanyloxy)-14-(*tert*-butyldiphenylsilanyloxy)-9-hydroxy-3,13-dimethoxy-5-methoxymethoxy-6,6-dimethylhexadeca-8,15-dien-7-one (4.39). To a solution of LDA (2.4 mmol) in THF (5 mL) at –78°C was added a solution of methyl ketone **4.38** (0.78 g, 2.20 mmol) and THF (5 mL) dropwise. After 1 h, the cold bath was removed and replaced with an ice bath (0°C). After 2 min, the ice bath was removed and the reaction was cooled to –78°C. A solution of aldehyde **4.29** (1.1 g, 2.03 mmol) and THF (5 mL) was added dropwise and after 15 min, a saturated solution of NH_4Cl (30 mL) was added, followed by Et_2O (30

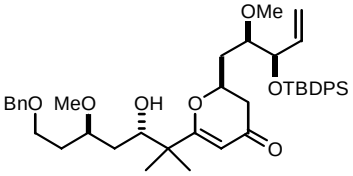
mL) and the cold bath was removed. After 15 min, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The collected organic phases were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography on a pre-buffered (3:7:90, Et_3N:EtOAc:hexanes)silica gel with 20% EtOAc/hexanes to give an inconsequential 1:1 mixture of diastereomers as a pale yellow oil (1.74 g, 96%): R_f 0.20 (20% EtOAc/hexanes).

To a solution of the mixture of diastereomers (0.9 g, 1.00 mmol), pyridine (0.43 mL, 5.0 mmol), H_2O (27 μL, 1.5 mmol) in THF/CH_2Cl_2 (1:1, 25 mL) at 0°C was added Dess-Martin Periodinane (5.36 mL, 0.28 M in CH_2CL_2) dropwise. After 5h or complete consumption of starting material via TLC, a solution of saturated $Na_2S_2O_3$ and $NaHCO_3$ (1:1, 30 mL) was added and the cold bath was removed. After 10 min, the organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 X 20 mL). The collected organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash column chromatography on a pre-buffered (3:3:94 Et_3N:EtOAc:hexanes) silica gel with 10% EtOAc/hexanes to give the product as a pale yellow oil (0.58 g, 91% based on recovered starting material): R_f 0.60 (33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.43-7.25 (m, 11H), 5.83 (ddd, *J* = 15.6, 10.4, 4.8 Hz, 1H), 5.66 (s, 1H), 5.22 (ddd, *J* = 17.2, 2.0, 2.0 Hz, 1H), 5.14 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1H), 4.65 (d, *J* = 6.4 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.49 (s, 2H), 4.36 (ddd, *J* = 4.8, 2.0, 2.0 Hz, 1H), 4.21-4.15 (m, 1H), 3.95 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.60-3.48 (m, 3H), 3.33 (s, 6H), 2.97 (s, 3H), 2.87 (ddd, *J* = 10.4, 4.4, 2.0 Hz, 1H), 2.33 (dd, *J* = 14.0, 3.6 Hz, 1H), 2.23 (dd, *J* = 14.0, 8.8 Hz, 1H), 1.93 (dddd, *J* = 12.0, 6.4, 6.4, 6.4 Hz, 1H), 1.80-1.67 (m, 2H), 1.56-1.48 (m, 3H), 1.16 (s, 3H), 1.08 (s, 9H), 1.07 (s, 3H), 0.87 (t, *J* = 8.0 Hz, 9H), 0.51 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 192.8, 138.4, 136.0, 135.9, 135.88,

133.9, 133.5, 129.9, 129.7, 128.3, 127.6, 127.5, 127.47 (2C), 116.0, 98.7, 98.6, 81.2, 80.4, 74.4, 73.0, 72.2, 67.4, 66.9, 57.5, 55.9, 55.7, 47.5, 46.3, 37.8, 37.1, 33.7, 27.0, 21.8, 20.8, 19.3; IR (thin film) ν 3072-2827, 1740, 1590, 1463, 1428, 1372, 1241, 922, 741, 702 cm^{-1}; HRMS *m/z* 891.5263 (calcd for $C_{51}H_{79}O_9Si_2$ $[M-H]^+$, 891.5271).



4.40



4.41

(*S*)-6-((2*R*,4*R*)-6-Benzyloxy-4-methoxy-2-methoxymethoxy-1,1-dimethylhexyl)-2-[(2*R*,3*R*)-3-(tert-butyldimethylsilanyloxy)-2-methoxypent-4-enyl]-2,3-dihydropyran-4-one (4.40) and **(*S*)-6-((2*S*,4*R*)-6-Benzyloxy-2-hydroxy-4-methoxy-1,1-dimethylhexyl)-2-[(2*R*,3*R*)-3-(tert-butyldiphenylsilanyloxy)-2-methoxypent-4-enyl]-2,3-dihydropyran-4-one (4.41)**. To a solution of *β*-diketone **4.39** (0.50 g, 0.56 mmol) in toluene (5 mL) was added p-TsOH (~20 mg) at rt. After 16 h, the reaction mixture was immediately purified by flash column chromatography on a pre-buffered (3:9:88 Et_3N:EtOAc:hexanes) silica gel with 15% EtOAc/hexanes to give the desired product **4.40** (0.111 g, 26%) as a pale yellow oil and the deprotected MOM analog **4.41** (120 mg, 28%).

4.40: R_f 0.30 (33% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.8 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.44-7.27 (m, 11H), 5.91 (ddd, *J* = 16.8, 10.8, 4.8 Hz, 1H), 5.44 (s, 1H), 5.32 (d, *J* = 16.8 Hz, 1H), 5.24 (d, *J* = 10.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 7.2 Hz, 1H), 4.49 (s, 2H), 4.45-4.40 (m, 1H), 4.34 (dddd, *J* = 12.0, 10.0, 6.0, 6.0 Hz, 1H), 3.84 (dd, *J* = 6.0, 6.0 Hz, 1H), 3.55-3.48 (m, 3H), 3.30 (s, 3H), 2.94 (s, 3H), 2.92-2.90 (m, 1H), 2.32-2.22 (m, 2H), 2.04-1.80 (m, 3H), 1.72 (ddd, *J* = 13.2, 13.2, 6.4 Hz, 1H), 1.53-1.45 (m, 2H), 1.09 (s, 12H), 1.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 193.5, 182.5, 138.4, 135.84, 135.82, 135.6, 133.7, 133.3, 130.1, 129.8, 128.3, 127.8, 127.6, 127.54, 127.50, 116.5, 103.1, 98.7, 81.2, 79.7, 77.3, 74.5, 73.0, 71.6, 66.8, 57.4, 55.9, 55.8, 45.0, 40.5, 37.0, 34.0, 33.6, 27.0, 21.9, 20.9, 19.3; IR (thin film) ν 3078-2820, 1666, 1595, 1474, 1427, 1335, 1103, 1036, 702 cm^{-1}; HRMS *m/z* 759.4294 (calcd for $C_{45}H_{63}O_8Si$ $[M+H]^+$, 759.4292).

4.41. R_f 0.20 (33% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.61 (m, 4H), 7.42-7.30 (m, 11H), 5.87 (ddd, *J* = 15.6, 11.2, 4.8 Hz, 1H), 5.40 (s, 1H), 5.32 (d, *J* = 16.8 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 4.50-4.44 (m, 1H), 4.46 (s, 2H), 3.82-3.79 (m, 1H), 3.64-3.48 (m, 3H), 3.31 (s, 3H), 2.98-2.85 (m, 2H), 2.90 (s, 3H), 2.32-2.20 (m, 2H), 1.92-1.65 (m, 5H), 1.51-1.40 (m, 2H), 1.07 (s, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.3, 182.5, 138.2, 135.8 (2C), 135.4, 133.7, 133.2, 130.2, 129.9, 128.4, 127.9, 127.65, 127.61 (2C), 116.6, 103.4, 80.2, 77.9, 73.1, 73.0, 71.3, 66.7, 57.3, 57.2, 44.5, 41.0, 35.2, 34.0, 33.4, 27.0, 21.8, 21.3, 19.3; IR (thin film) ν 3467 (br), 3065-2813, 1664, 1591, 1471, 1427, 1389, 1329, 1111, 1028, 702 cm^{-1}; HRMS *m/z* 715.4030 (calcd for $C_{43}H_{59}O_7Si$ $[M+H]^+$, 715.4030).

5.2 X-RAY CRYSTALLOGRAPHY

X-ray Experimental for $2C_{28}H_{32}N_2O_{10} - ½\ C_6H_{14}$ (2.100A)

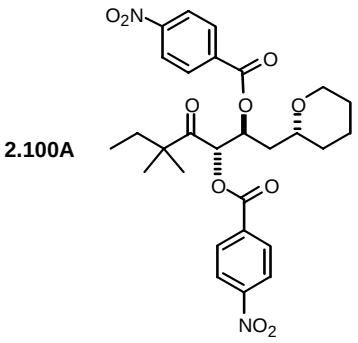
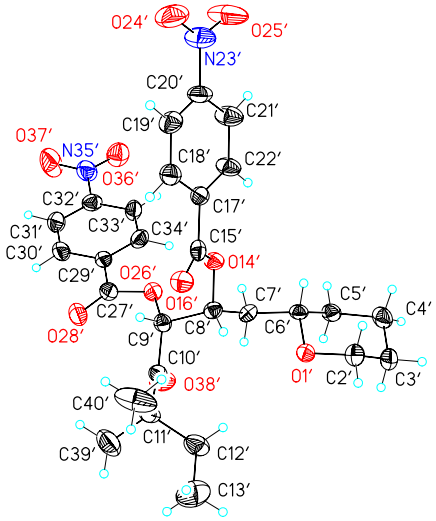


Figure 5.1 View of **2.100A** showing the atom labeling scheme.



Crystals grew as thin, colorless plates by slow evaporation from n-hexane. The data crystal was cut from a cluster and had approximate dimensions; 0.36 x 0.28 x 0.06 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 629 frames of data were collected using ω-scans with a scan range of 0.8° and a counting time of 119

seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in

Table **5.1**. Data reduction was performed using DENZO-SMN.[100] The structure was solved by direct methods using SIR97[101] and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using SHELXL-97.[102] The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms).

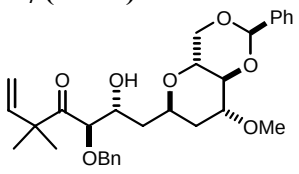
There are two crystallographically unique molecules per asymmetric unit. The molecules have slight conformation differences (Figure 3). In addition, there was what appeared to be a molecule of n-hexane that was found to be disordered about a crystallographic inversion center at 0, 0, 0. The disordered solvent was difficult to model properly. Therefore, the contribution to the scattering by the solvent was removed by the utility, SQUEEZE, in PLATON98.[103] PLATON98 was used as incorporated in WinGX.[104]

The function, $\Sigma w(|F_o|^2 - |F_c|^2)^2$, was minimized, where $w = 1/[(\sigma(F_o))^2 + (0.044*P)^2]$ and $P = (|F_o|^2 + 2|F_c|^2)/3$. $R_w(F^2)$ refined to 0.163, with R(F) equal to 0.0729 and a goodness of fit, S, = 1.05. Definitions used for calculating R(F), $R_w(F^2)$ and the goodness of fit, S, are given below. The data were corrected for secondary extinction effects. The correction takes the form: $F_{corr} = kF_c/[1 + (2.6(5)x10^{-6})* F_c^2 \lambda^3/(\sin 2\theta)]^{0.25}$ where k is the overall scale factor. Neutral atom scattering factors and values used to calculate the linear absorption coefficient are from the International Tables for X-ray Crystallography (1992). All figures were generated using SHELXTL/PC.

Table 5.1 Crystal data and structure refinement for **2.100A**

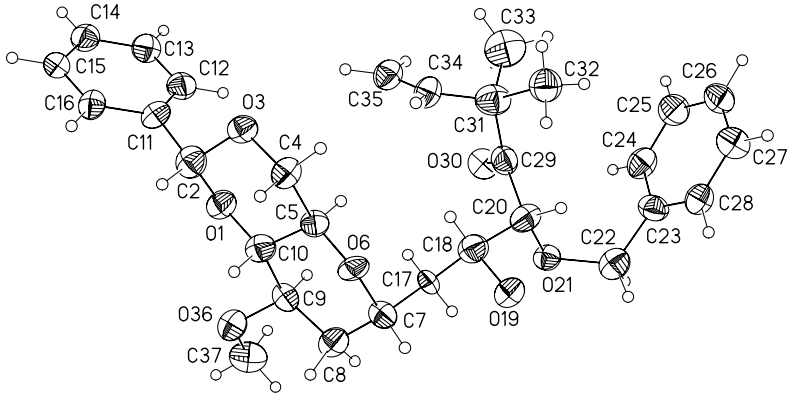
Empirical formula	C59 H71 N4 O20	
Formula weight	1156.20	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.7896(3) Å	□= 94.595(2)°
	b = 10.0226(4) Å	□= 91.099(2)°
	c = 33.0567(16) Å	□ = 112.472(2)°
Volume	2983.1(2) $Å^3$	
Z	2	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	1226	
Crystal size	0.36 x 0.28 x 0.06 mm	
Theta range for data collection	3.02 to 25.04°.	
Index ranges	-11<=h<=11, -11<=k<=11, -38<=l<=36	
Reflections collected	14333	
Independent reflections	9547 [R(int) = 0.0478]	
Completeness to theta = 25.04°	90.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9547 / 0 / 722	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0729, wR2 = 0.1416	
R indices (all data)	R1 = 0.2091, wR2 = 0.1630	
Extinction coefficient	$2.6(5)x10^{-6}$	
Largest diff. peak and hole	0.359 and -0.245 $e.Å^{-3}$	

X-ray Experimental for $C_{30}H_{38}O_7$ (2.117)



2.117

Figure 5.2 View of **2.117** showing the atom labeling scheme.



Crystals grew as clusters of very thin, colorless needles by slow evaporation from *n*-hexane. The data crystal was a needle that had approximate dimensions; 0.20x0.02x0.02 mm. The data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation (λ = 0.71073Å). A total of 321 frames of data were collected using ω-scans with a scan range of 1° and a counting time of 163 seconds per frame. The data were collected at 153 K using an Oxford Cryostream low temperature device. Details of crystal data, data collection and structure refinement are listed in Table 5.2. Data reduction were performed using DENZO-SMN.[100] The structure was solved by direct methods using SIR92 and refined by full-matrix least-squares on F^2 with anisotropic displacement parameters for the non-H atoms using

SHELXL-97. The hydrogen atoms on carbon were calculated in ideal positions with isotropic displacement parameters set to 1.2xUeq of the attached atom (1.5xUeq for methyl hydrogen atoms). The hydrogen atom on the hydroxyl oxygen atom, O19, was not located in a ΔF map and was not included in the refinement model.

Table 5.2 Crystal data and structure refinement for **2.117**

Empirical formula	C30 H38 O7	
Formula weight	510.60	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 15.451(3) Å	□= 90°.
	b = 5.628(1) Å	□= 113.420(1)°.
	c = 16.487(3) Å	□ = 90°.
Volume	1315.6(4) $Å^3$	
Z	2	
Density (calculated)	1.289 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	548	
Crystal size	.2 x .02 x .02 mm	
Theta range for data collection	2.87 to 22.49°.	
Index ranges	-16<=h<=16, -6<=k<=0, -17<=l<=17	
Reflections collected	3301	
Independent reflections	1889 [R(int) = 0.3435]	
Completeness to theta = 22.49°	97.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1889 / 229 / 310	
Goodness-of-fit on F^2	1.311	

Final R indices [I>2sigma(I)]	R1 = 0.1259, wR2 = 0.2364
R indices (all data)	R1 = 0.3382, wR2 = 0.2996
Absolute structure parameter	4(8)
Largest diff. peak and hole	0.393 and -0.283 e.Å^{-3}

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