Catalytic Asymmetric Synthesis of Complex Polypropionates:

A Synthesis of Erythronolide B

by

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Catalytic Asymmetric Synthesis of Complex Polypropionates: A Synthesis of Erythronolide B

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Studies towards the total synthesis of the polypropionate macrolide agycone Erythronolide B have been presented. Catalytic asymmetric AAC methodology has been applied to efficiently generate the C_{10}-C_{13} and the C_4-C_5 stereocenters in the polypropionate fragments **105** and **209** through β-lactones **76**, **80**, and **86** respectively. An efficient installation of the C_2 and C_3-stereocenters in **193** was realized through a Lewis-base catalyzed Mukaiyama aldol reaction. Finally, a highly stereoselective aldol coupling of fragments **105** and **209** was used to join the fragments together.

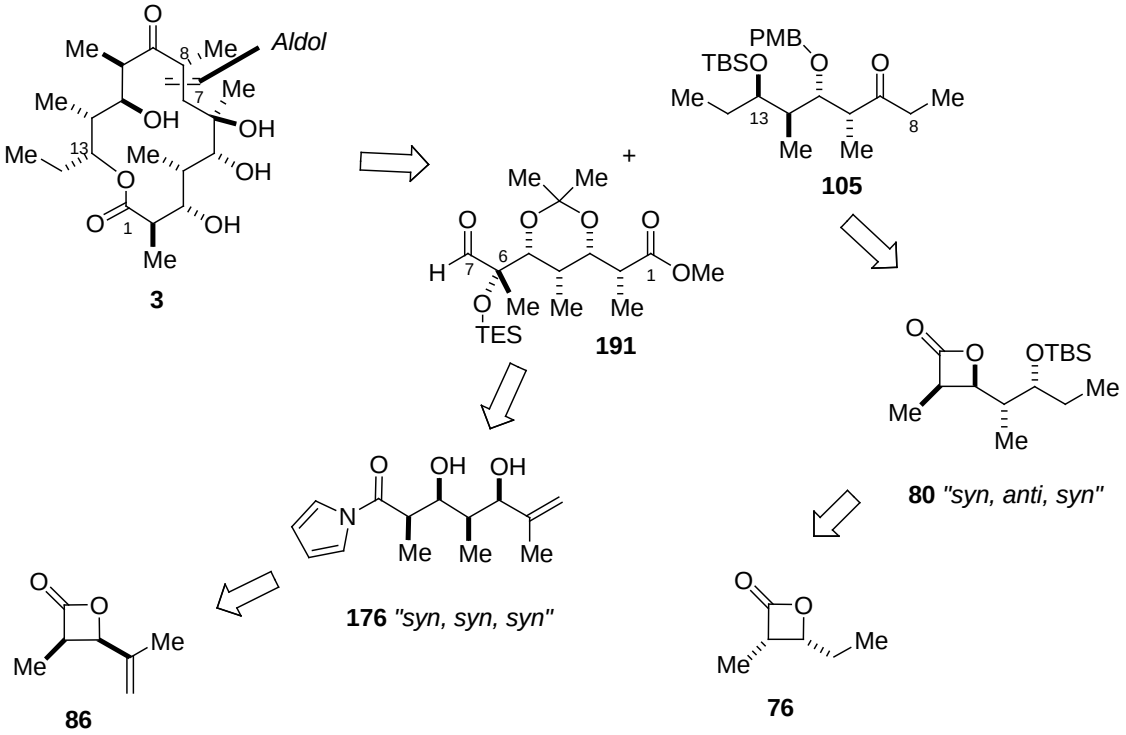


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

AAC	Acyl halide-aldehyde cyclocondensation
AD	Asymmtric dihydroxylation
AIBN	Azobisisobutyronitrile
Bn	Benzyl
COSY	Correlation spectroscopy
CSA	Camphor sulfonic acid
d.r.	Diastereomeric ratio
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DIBAL-H	Diisobutyl aluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMPU	*N*,*N*′-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoric triamide
HMQC	Heteronuclear multiple quantum coherence
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide

LHMDS	Lithium bis(trimethyl)amide
MOM	Methoxymethyl
NIS	*N*-Iodosuccinimide
NMR	Nuclear magnetic resonance
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
PPTS	Pyridinium *p*-toluenesulfonate
ROESY	Rotating-frame Overhauser effect spectroscopy
SAD	Sharpless asymmetric dihydroxylation
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
TESOTf	Triethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin-layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMS*Qd*	Trimethylsilylquinidine
TMS*Qn*	Trimethylsilylquinine
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl

PREFACE

First of all I am heartily thankful to my supervisor Prof. Scott Nelson for providing me the opportunity to work on this very challenging research project. This thesis would not have been possible without his incessant help and support. His encouragement and guidance from the initial to the final level along with the rich learning environment that he constantly fostered in our group, has enabled me to develop an in-depth understanding of the subject.

I would like to thank my committee members, Professors Craig S. Wilcox, Tara Meyer and Alexander Doemling for their invaluable suggestions and guidance during my time at the University of Pittsburgh. I would also like to thank Prof. Dennis Curran for mentoring my proposal.

Among my co-workers, I would specially like to thank Dezhi Fu whose work has directly enabled the successful completion of Erythronolide B. I would also like to thank all the members of the Nelson group, past and present, whose company, help and cooperation have made my stay here a memorable and enjoyable one.

The road to Erythronolide B was never an easy one and words surely cannot express my gratefulness to my husband and co-worker, Nihar Sarkar for helping me make it to the end. I am eternally indebted to him for being a constant source of comfort and support in all the difficult times. Finally I would like to thank my family for “everything”. Without your love and support nothing would have been possible.

1.0 INTRODUCTION

1.1 POLYPROPIONATE NATURAL PRODUCTS

Polyketide-derived natural products represent a large class of biologically active compounds that have found many applications. The polyketides possess very diverse structures which can be divided into subgroups: fatty acids, polypropionates and aromatic polyketides. Polypropionates can be further classified into three groups: polyether antibiotics, macrolides and spiroketals (Figure 1). Some of the most biologically active compounds are the polypropionates and as a result, their study has been a very active area of research.

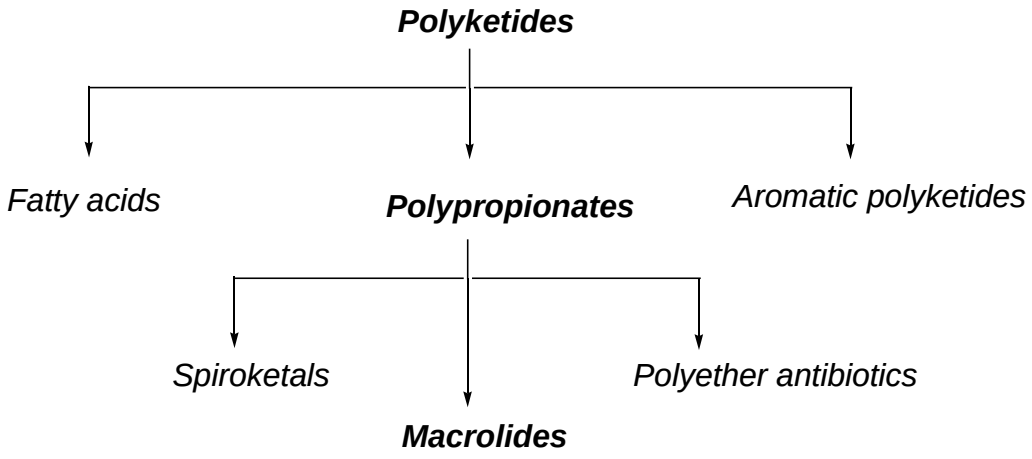
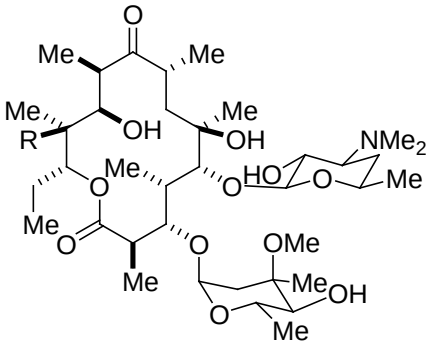


Figure 1. Classification of polyketides.

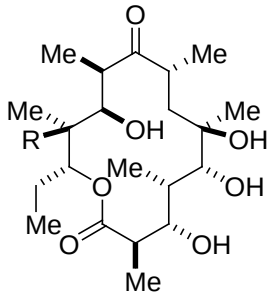
1.2 THE ERYTHROMYCINS

1.2.1 Occurrence, Biological Activity and Biosynthesis

Erythromycins A (**1**) and B (**2**) are the best known members of the clinically important family of the 14-membered macrolide polyketides which are produced by a strain of the fungus *Saccharopolyspera erythraeus* formerly known as *Streptomyces erythraeus*.[1] The aglycones of erythromycins A and B are called erythronolides A and B (**3**), respectively. The erythromycins were first isolated and discovered in 1952 from soil samples containing the fungus strain. The erythromycins are used for the treatment of infectious diseases caused by gram-positive bacteria.[1] The potent antibiotic activity of erythromycins is due to their efficient inhibition of ribosomal-dependent protein biosynthesis in gram positive bacteria.[1]



R = OH **1** Erythromycin A
R = H **2** Erythromycin B



R = OH Erythronolide A
R = H **3** Erythronolide B

The biosynthetic pathway of erythromycins was proposed by Martin *et al.*[2] Like other polyketides, they are synthesised in *Streptomyces* and related bacteria by the repetitive and

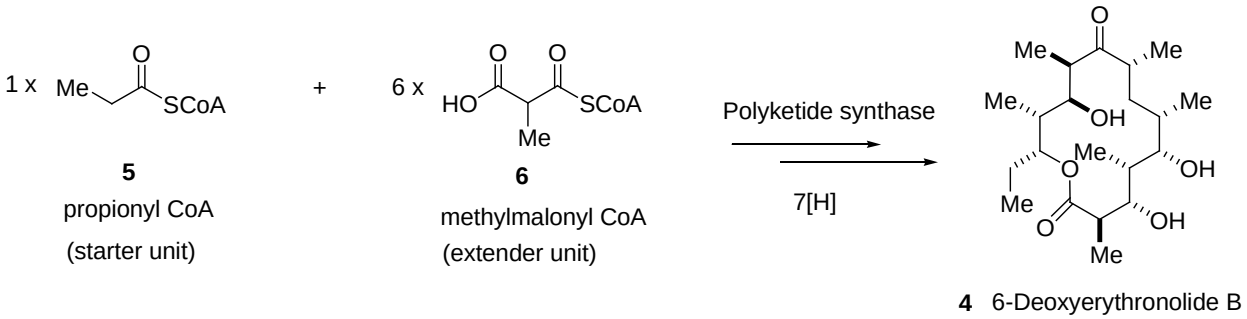
[1] (a) McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.;Smith, J. W. *Antibiot. Chemother*. (Washington, D. C.) **1952,** *2,* 281 (b) *Macrolide Antibiotics;* Omura, S., Ed.; Academic Press: Orlando, FL, 1984.
[2] Martin, J. R.; Rosenbrook, W. *Biochemistry* **1967**, *6*, 435-440.

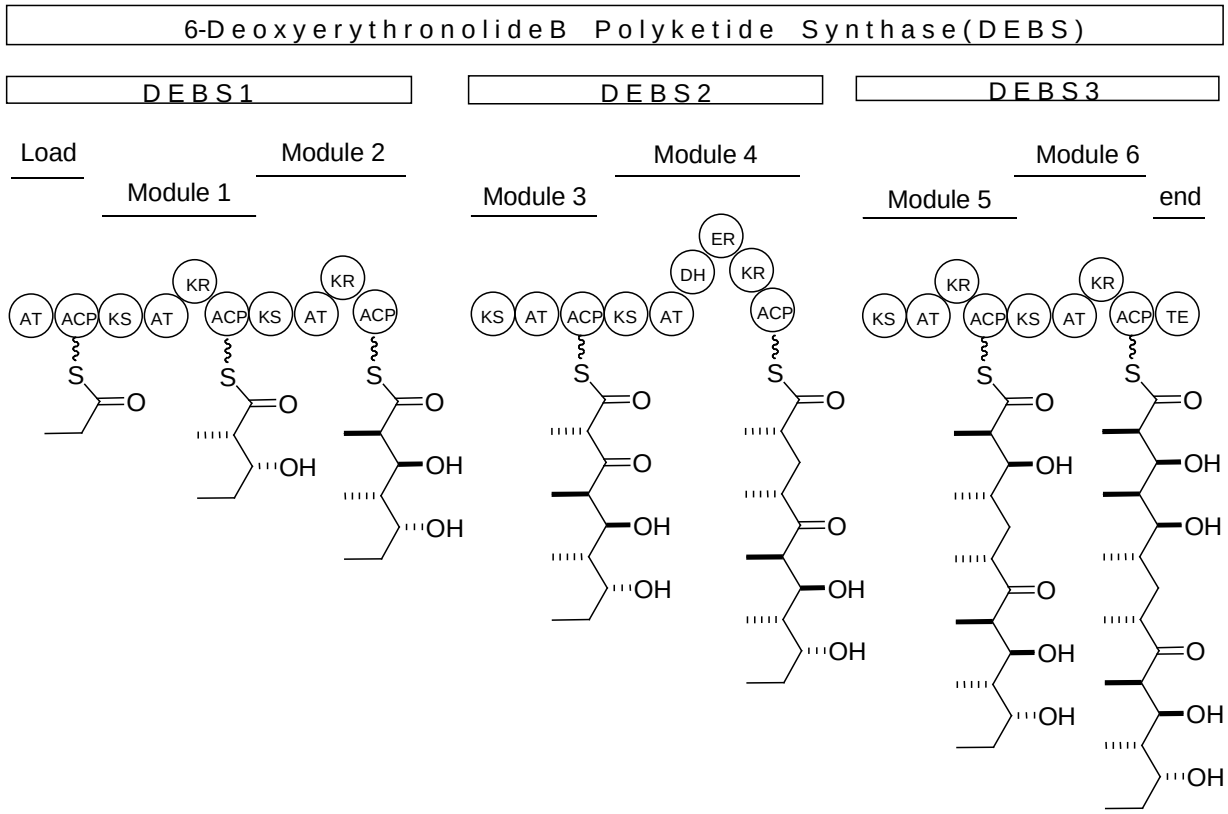
stepwise condensation of acyl thioesters.[3] The biosynthesis is initiated by a group of chain-forming enzymes known as polyketide synthases (PKS) that sequentially adds units to a growing chain of a polyketide. In the first phase of erythromycin biosynthesis, 6-deoxyerythronolide B (**4)** is biosynthesized in an iterative fashion, from one molecule of propionyl CoA **5** and six molecules of methylmalonyl CoA **6** (Scheme 1). The PKS possesses six modules and each module contains the three domains required to catalyze one cycle of chain extension [ketosynthase (KS), acyltransferase (AT) and acyl carrier protein ACP)] as well as a variable set of domains [ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER)] associated with keto group modification (depicted as a loop above the line of essential domains). DEBS 1 is preceded by a loading domain (AT and ACP) which accepts the starter unit propionate from propionyl-CoA, while DEBS 3 terminates with a thioesterase (TE) activity which is thought to catalyse the off-loading and cyclization of the fully-formed heptaketide intermediate to give 6-deoxyerythronolide B (**4)**. Throughout the entire biosynthetic sequence, the polyketide chains remain bound to the PKS. The three essential domains, KS, AT and ACP, co-operate to catalyze carbon–carbon bond formation by Claisen condensation, which results in a β-keto ester intermediate. The variable set of domains between the AT and ACP then carry out reductive modification of the keto group before the next round of chain extension. Module 3 has no reductive domains and so the keto group (at C_9) survives intact. In contrast, modules 1, 2, 5 and 6 each contain a KR domain, which catalyze reduction of the keto group to a hydroxy group (the

[3] Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, *18*, 380-416.

hydroxyl groups at C_{13}, C_{11}, C_5 and C_3 respectively). In module 4, there is a full set of reductive domains (DH, ER and KR) and so complete reduction occurs to produce a methylene (at C_7).

Scheme 1: Synthesis of 6-Deoxyerythronolide B





AT: acyltransferase; **ACP**: acyl carrier protein; **KS**: keto synthase; **KR**: keto reductase; **DH**: dehydratase; **ER**: enoylreductase; **TE**: thioesterase.

The first step of chain elongation in the catalytic cycle involves decarboxylative condensation of ACP bound methyl malonic acid **7** with KS bound propionate **8** (Figure 2). Subsequent acyl transfer of the newly formed ACP bound polypropionate (**9**→ **10** + **11**) and preparation of the second ACP bound methyl malonic acid (**11** + **6**→**7**) sets the stage for a second iteration in as few as two steps. Reiteration of this process with the growing KS bound polypropionates **10** and intervening functional group manipulations produces 6-deoxyerythronolide B in only 6 carbon-carbon bond forming reactions. 6-Deoxyerythronolide B is the first and common enzyme-free intermediate for all members of the erythromycin family (erythromycins A-F). In the second phase of erythromycin biosynthesis, as shown in Figure 3, 6-deoxyerythronolide B is elaborated by several post-PKS steps (such as introduction of the sugar units, O-methylation and C_{12}-hydroxylation), finally yielding the active erythromycin antibiotics.

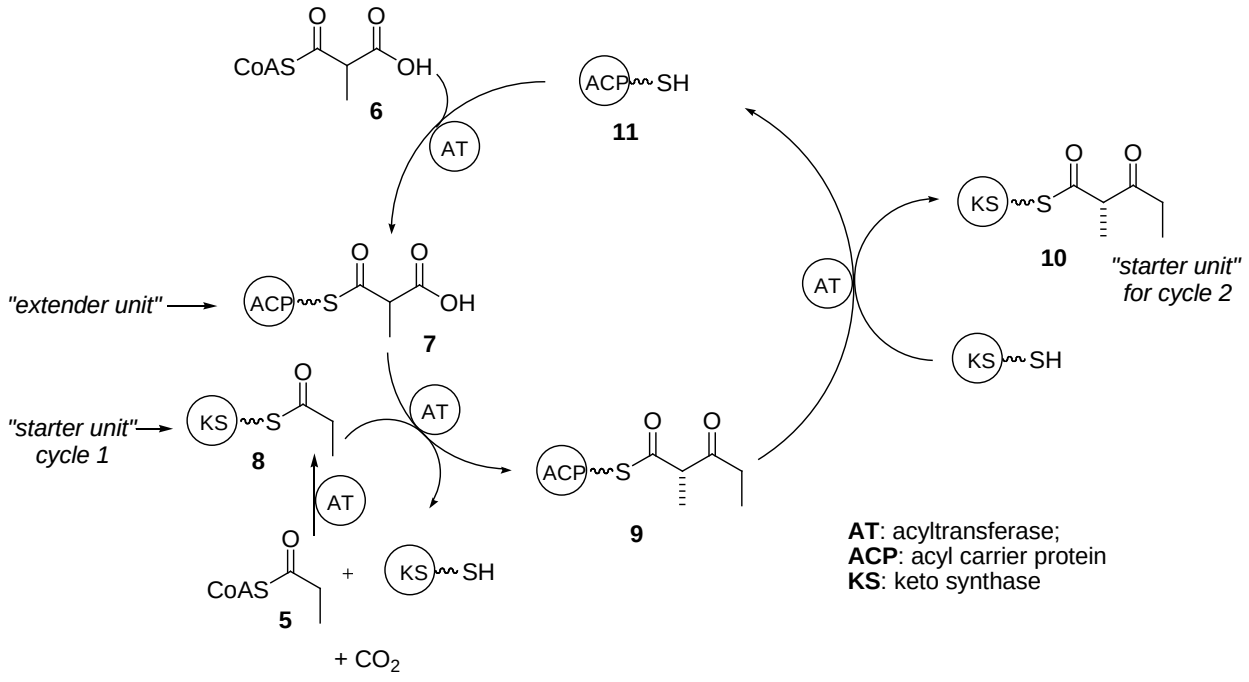


Figure 2. The catalytic cycle of chain elongation

This mechanism of iterative chain extension is the same for the biosynthesis of all aliphatic polyketides including the macrocyclic polyketides of the erythromycin family. The huge structural diversity found among natural polyketides arises from the selection of acetate or propionate as "starter" or "extender" units and from the differing ways of processing of the β-keto group observed after each condensation. The stereochemical outcome of these processing steps is also specified for each cycle of chain extension.

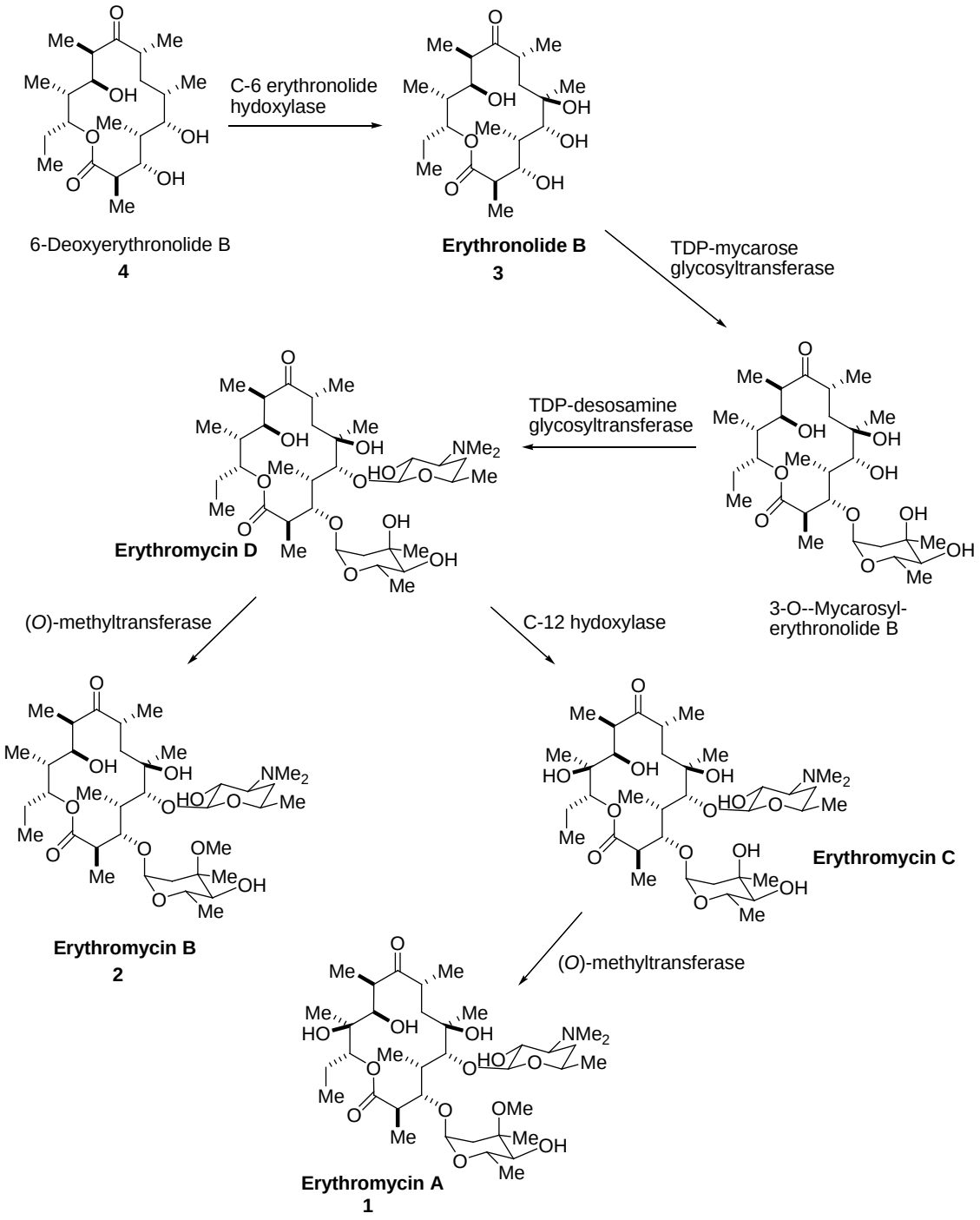


Figure 3. Second phase in the biosynthetic pathway of erythromycins

1.2.2 Previous Syntheses of Erythronolide B

The combination of therapeutic value and the densely functionalized complex architecture of their backbone have made the erythromycins an attractive target for synthesis and a popular platform for the invention and testing of numerous methodologies for polypropionate synthesis. Over the last few decades, many syntheses have been reported for the erythromycins themselves as well as a number of their aglycon derivatives including erythronolide A[4] and B (**3**)[5], 6-deoxyerythronolide B (**4**)[6], and (9S)-dihydroerythronolide A.[7] However, despite the numerous synthetic approaches used for the synthesis of these complex polypropionates, very few have been applied in an iterative fashion that attempts to mimic the elegant approach displayed in Nature.

So far, three total syntheses of erythronolide B have been reported, the first of which was completed by Corey in 1978.[5a] Later, Kochetkov (1987)[5b] and Mulzer (1991)[5c] also completed the synthesis of erythronolide B. All of the above syntheses were convergent and relied on C-C bond forming reaction between the two halves in the key step. Corey utilized the *cis*-fused bicycle **13** for the synthesis of the intermediate **14**. The three stereocenters at C_2, C_4 and C_5 of **14** were set by three consecutive iodolactonizations of enone **12** (Scheme 2). Selective

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[4] (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. B.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 131. (b) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron* **1989**, *45*, 5109. (c) Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4036-4038.

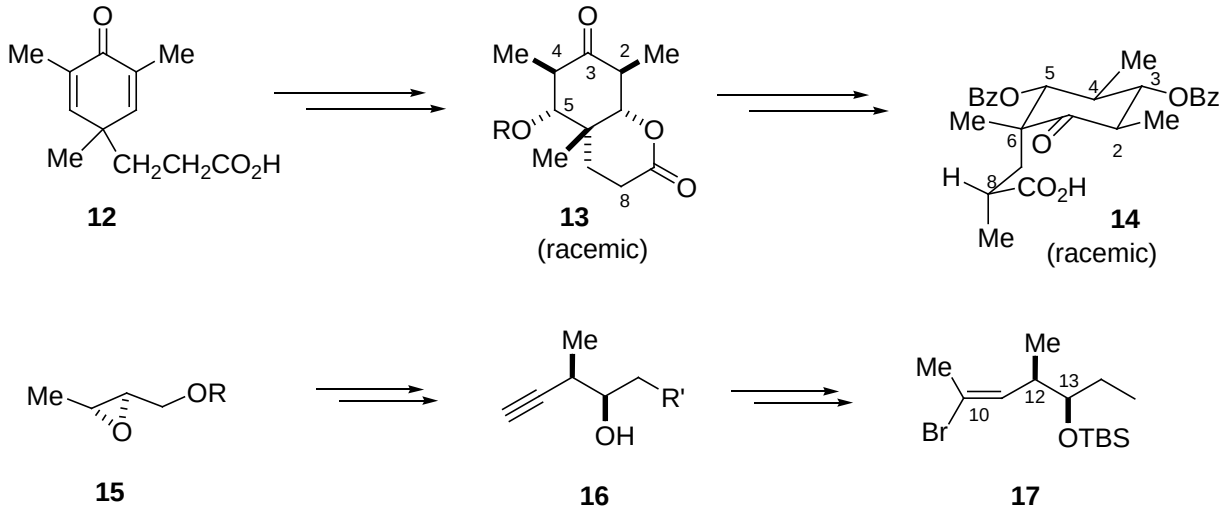
[5] (a) Corey, E. J.; Trybulski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrest, J. R.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.;Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, 100, 4618-4620. (b) Kochetkov, N. K.; Sviridov, A. F.; Ermolenko, M. S.; Yashunsky, D. V.; Borodkin, V. S. *Tetrahedron Lett.* **1987**, *28*, 3835-3839. (c) Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.;Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910-923. (d) Martin, S. F.; Lee, W-C.; Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674–4688.

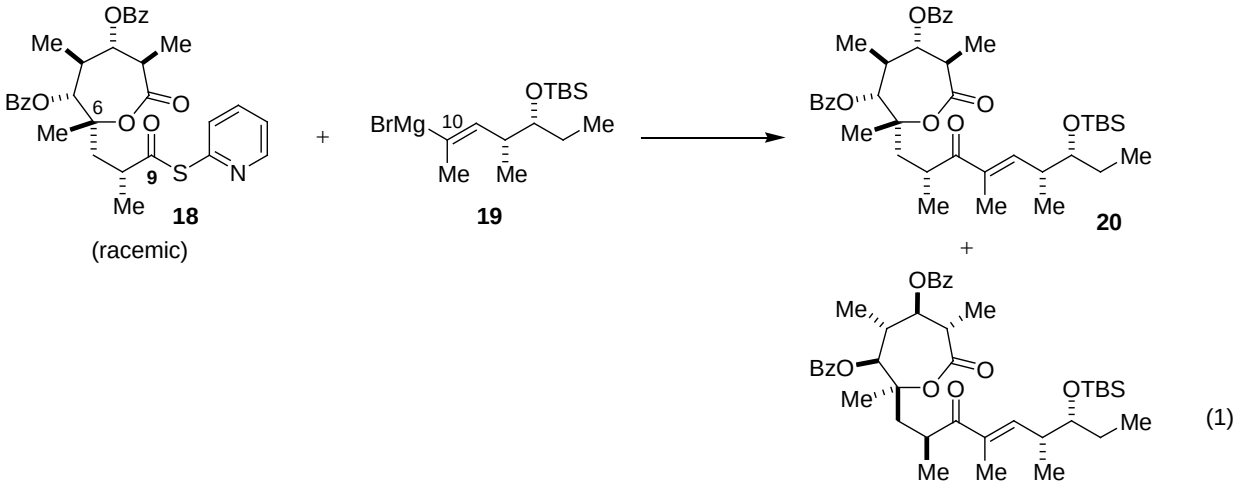
[6] (a) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103.* 1568. (b) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998,** *120*, 5921-5942. (c) Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191-2194.

[7] (a) Paterson, I.; Rawson, D. J. *Tetrahedron Lett.* **1989**, *30*, 7463-7466 (b) Peng, Z,-H.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 6018-6019.

hydrogenation of the carbonyl in **13** provided the alcohol at C_3. The desired C_8 center in **14** was installed by methylation which provided the thermodynamically more stable product. Bayer-Villiger oxidation of **14** inserted a hydroxyl group at C_6 of the C_1-C_9 intermediate (**18**) with retention of stereochemistry. The C_{10} to C_{15} fragment (**19**) was prepared by regioselective opening of epoxide **15** followed by hydrozirconation of a derivative of **16** to provide the vinyl bromide **17**. Corey coupled his fragments at the C_9-C_{10} bond by adding the optically active Grignard reagent **19** to the racemic thioester **18** derived from **17** and **14** respectively (eq 1). The resulting mixture of two diastereomers was separated and only one of them, diastereomer **20**, was carried forward.

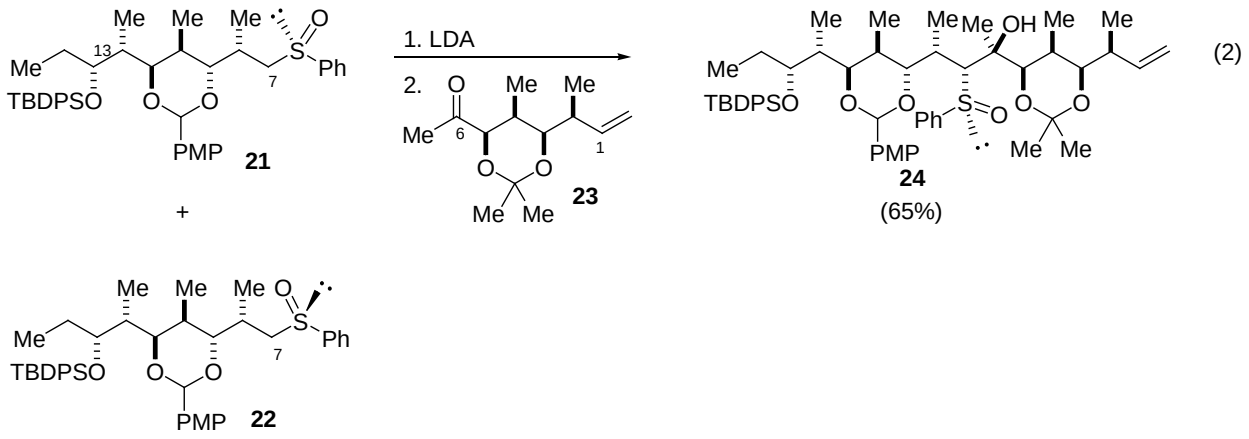
Scheme 2: Corey's synthesis of fragments



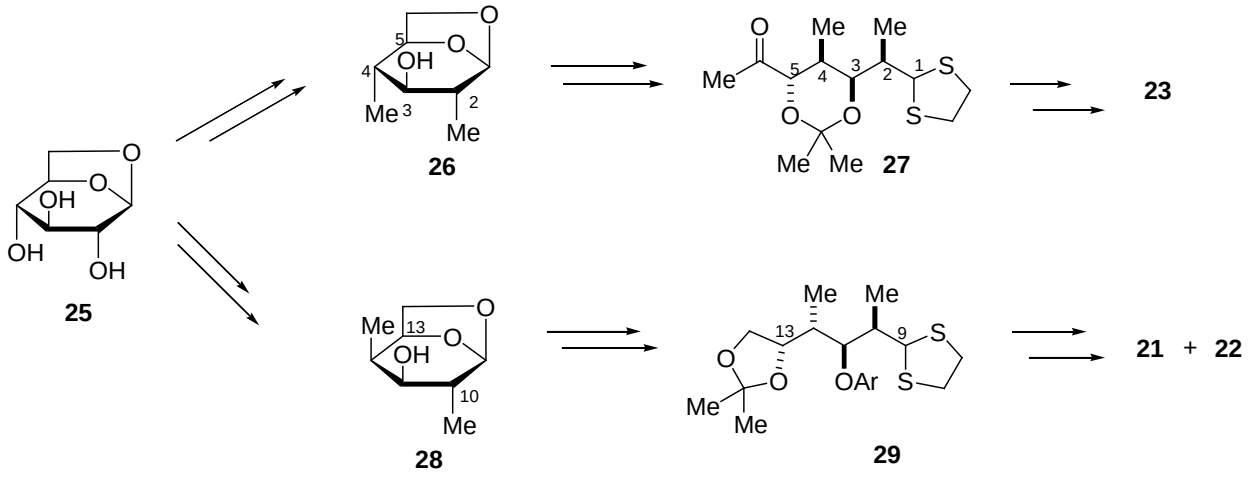


(1)

Kochetkov applied the addition of sulfoxide **21**/**22** to ketone **23** to form the tertiary alcohol center at C_6 in **24** (eq 2). Of the two sulfoxide diastereomers only **21** (the minor diastereomer) was reactive and **22** (the major diastereomer) had to be epimerized and recycled. As shown in Scheme 3, the C_1-C_6 and C_7-C_{15} segments **23** and **21**/**22**, respectively were both synthesized from a common carbohydrate, levoglucosan (1, 6-anhydro-β-D-glucose) **25**. The bicyclic nature of levoglucosan was exploited to introduce the methyl groups at C_2 and C_{10} with high regio and stereooselectivity. However introduction of the other methyl group at C_4 via a Barton deoxygenation of the corresponding *tert*-alcohol was not selective and gave a 1:1 mixture of diastereomers **26** and **28**. After separation, each acetal was converted into the open chain dithiane derivatives **27** and **29** respectively. The epimerization at C_5 of **27** and elaboration of **29** to a mixture of sulfoxide diastereomers **21** and **22** in a ratio of 22:74 completed the synthesis of the two key fragments.



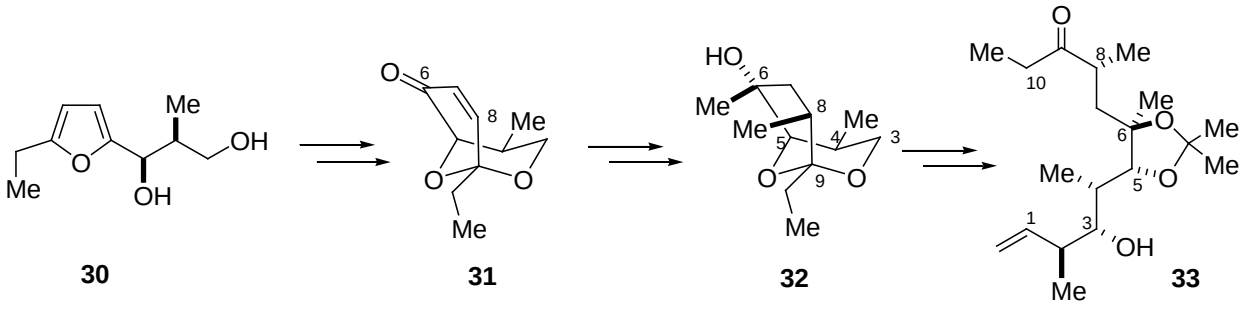
Scheme 3. Kochetkov's synthesis of key fragments



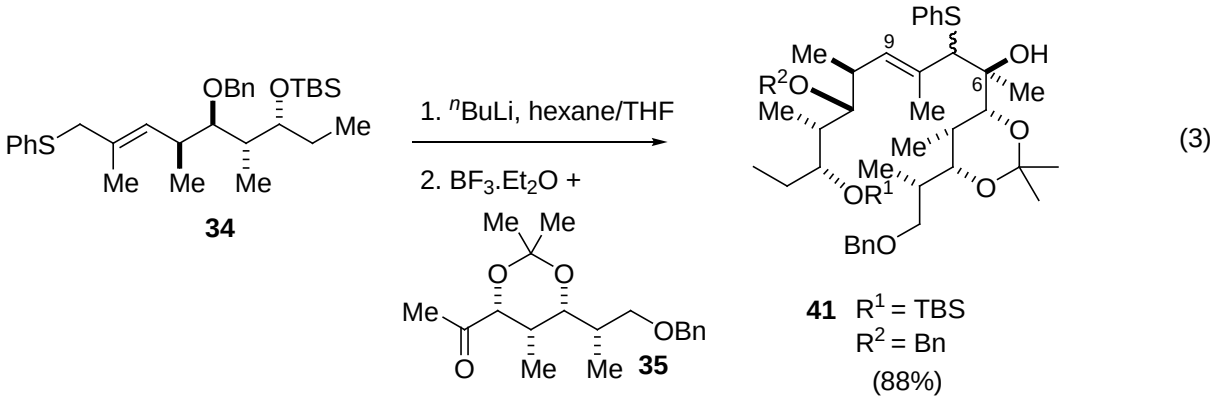
In Martin's synthesis[5d] of the C_1-C_{10} fragment of the erythronolide B seco-acid, the furan **30** prepared by an Evans aldol condensation was treated with bromine in aqueous acetonitrile to provide an intermediate that underwent acid-catalyzed cyclization to the ketal **31** (Scheme 4). The two methyl groups at C_8 and C_6 were added to **31** from the less hindered face of the bicycle to afford **32** which was then opened up to its acyclic form and subjected to a Lewis acid catalyzed crotylation reaction to introduce the C_2 and C_3 centers, finally providing the key ketone fragment **33** in 4:1 diastereoselectivity. The seco acid was formed in an aldol coupling reaction

of **33** with an aldehyde constituting the C_{11}-C_{14} segment (which was prepared by an Evans aldol reaction with propionaldehyde).

Scheme 4: Martin's synthesis of C_1-C_{10} fragment of the erythronolide B seco-acid

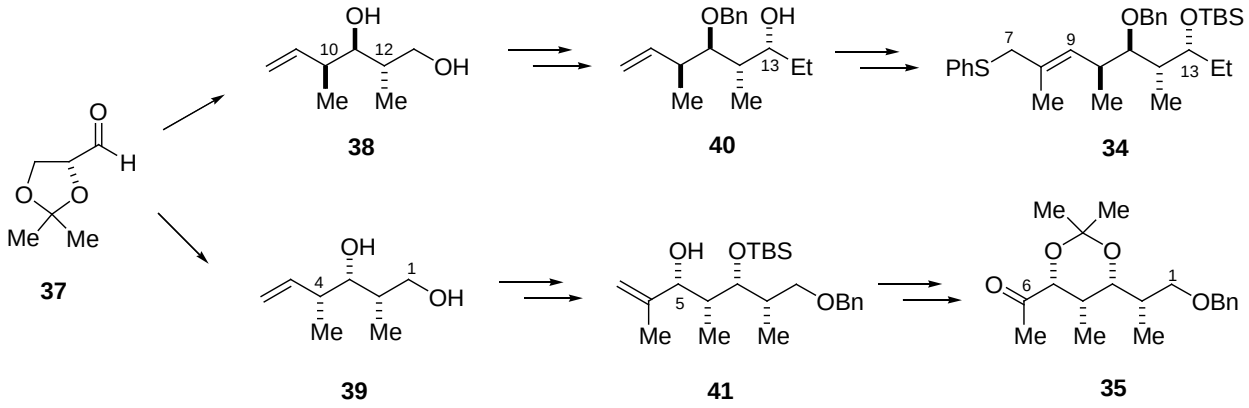


In Mulzer's synthesis[5c] the molecule was disconnected at the C_6-C_7 bond and involved the addition of the conjugated anion of **34** to the ketone **35** (eq 3). The fragments were prepared from a common chiral building block **37** via the stereotriads **38** and **39** in which the C_{11}/C_{12} and C_2/C_3 centers were set by stereo and regioselective opening of an epoxide derived from **37** (Scheme 5). Conversion to aldehyde followed by stereoselective addition of Grignard reagents installed the desired C_{13} and C_5 chiral centers in **40** and **41** respectively. A trans-selective Wittig resulted in sulfide fragment **34**, which was coupled with the C_1-C_6 ketone fragment **35**. The C_8 and C_9 centers in the aglycone seco-acid **36** were later set via hydroboration oxidation.



(3)

Scheme 5: Mulzer's synthesis of fragments



Woodward's landmark synthesis of erythronolide A illustrated some of the inherent problems associated with macrocyclization strategies for this family of macrolides and demonstrated that the conformational flexibility of the seco-acid backbone should be reduced in order to achieve successful lactonization.[8] In his pioneering studies he identified a number of structural features that must be incorporated in the seco-acid precursor for successful lactonization; (1) *S* configuration at C_9 and (2) dioxolane protecting groups at C_3/C_5 and C_9/C_{11}-hydroxyl groups are required for efficient lactonization. Only the seco-acid intermediate **42** possessing a (9*S*)-configuration and containing two dioxolane protecting groups masking C_3/C5-OHs and C_9/C_{11}-OHs successfully underwent macrocyclization to give **43** in 70% yield. Various other lactonization precursors **44**, **45** and **46** either possessing the epimeric (*R*)-configuration at C_9, or lacking the dioxolane protecting groups failed to undergo macrocyclization (Figure 4). Accordingly, the most common strategy for rigidification has been the incorporation of six-membered cyclic acetal groups on the C_3/C_5 hydroxyls as well as on the C_9/C_{11} hydroxyls.[4c, 5b, 6b,

[8] Woodward, R. B.; Logusch, E.; Nambiar, K. B.; Sakan, K.; Ward, D. E.; Au-Yeung, D. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênvert, R. B.; Fliri, A.; Frobel, K.; Gais, H. J.; Garrat, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.;Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; *J. Am. Chem. Soc.* **1981**, *103,* 3213-3215.

[7b] Another method of rigidification that has been used is the insertion of double bonds in the framework as in Mulzer's synthesis.[5c]

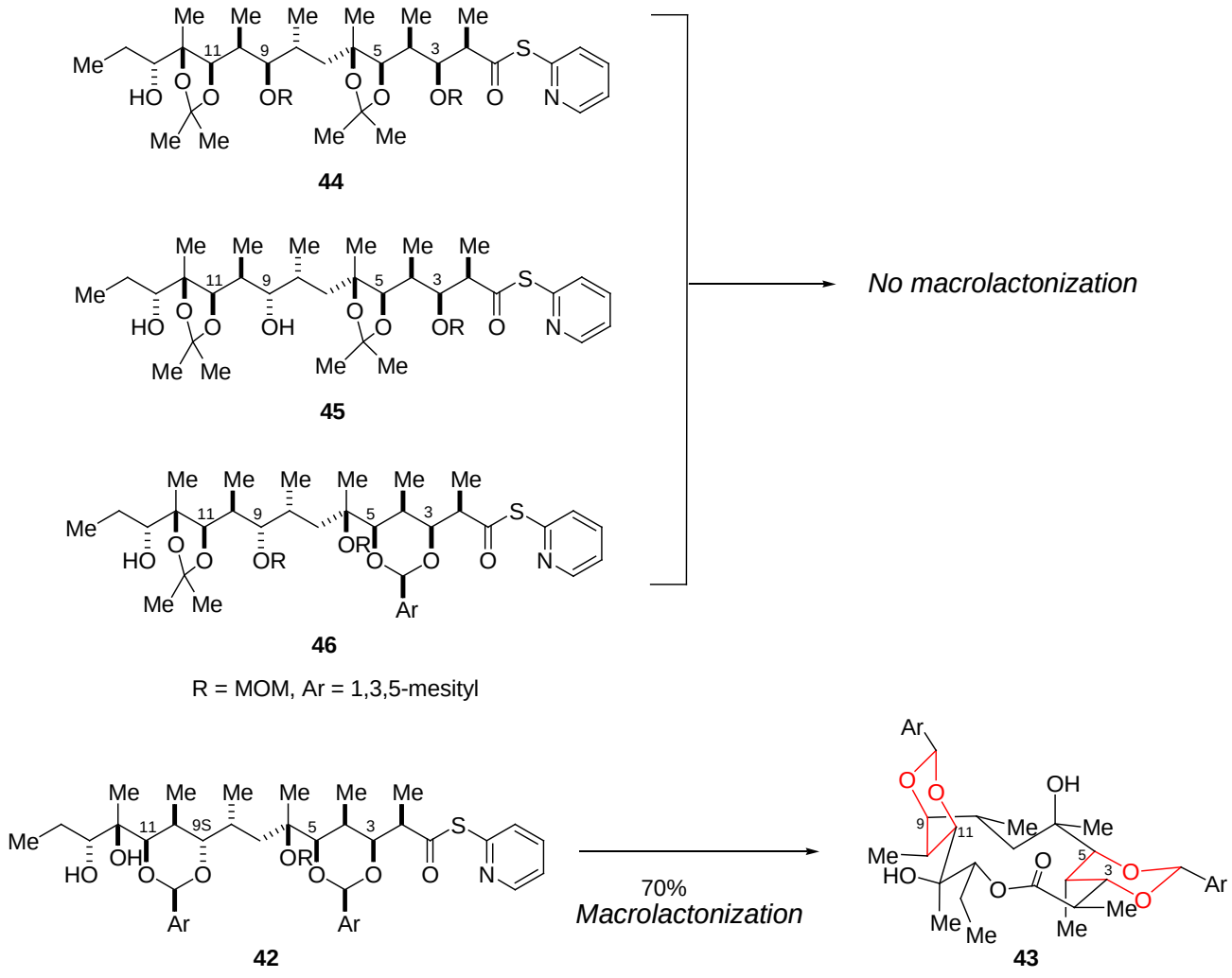


Figure 4. Macrolactonization studies by Woodward

1.3 SYNTHESIS OF POLYPROPIONATE UNITS

Due to their fascinating biological activities and low natural abundance, the total synthesis of polyketides has been of immense importance to the synthetic community. Nevertheless, it is the complexity of their molecular architecture that has attracted organic chemists the most and no doubt, polyketides have become one of the most extensively investigated groups of natural products. Polypropionate natural products are characterized by structure with alternating methyl groups and oxygen functionalities (alcohol, ketone and/or carboxyl) along a contiguous carbon chain (Figure 5). Among the approximately 5000-10000 known polypropionates, only 1% possess biological activity. Despite this rather low value, it surprisingly represents five times the average for natural products.[9]

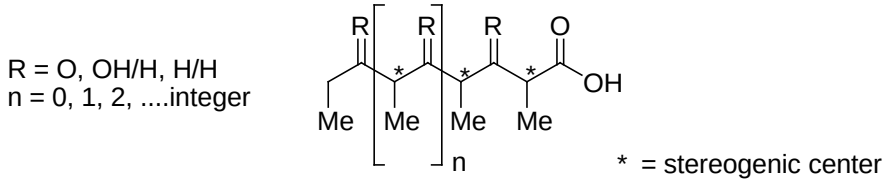


Figure 5. General structure of polypropionate natural products

During the past three decades, synthetic chemists have made significant contributions to the development and advancement of asymmetric synthetic methodologies.[10] The inherent challenge for the synthesis of polypropionates derives from the long sequence of stereocenters. For example, a dipropionate can have up to four different stereoisomers, a tripropionate (16), a

[9] Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677-690.
[10] Paterson, I.; Cowden, C. J.; Wallace, D. J. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 249-297. (b) Hoffmann, R. W. *Angew. Chem. Int., Ed. Engl.* **1987**, 26, 489-503.

tetrapropionate (64), a pentapropionate (256), a hexapropionate (1024) and a heptapropionate (4096) (Figure 6). While the alternating incorporation of acetate or propionate in their biosynthesis has been paralleled by aldol or aldol-type reactions in the syntheses of these compounds, the formation of the *different and specific* stereochemical arrays of these subunits at will, still poses a significant challenge for the synthetic chemist.

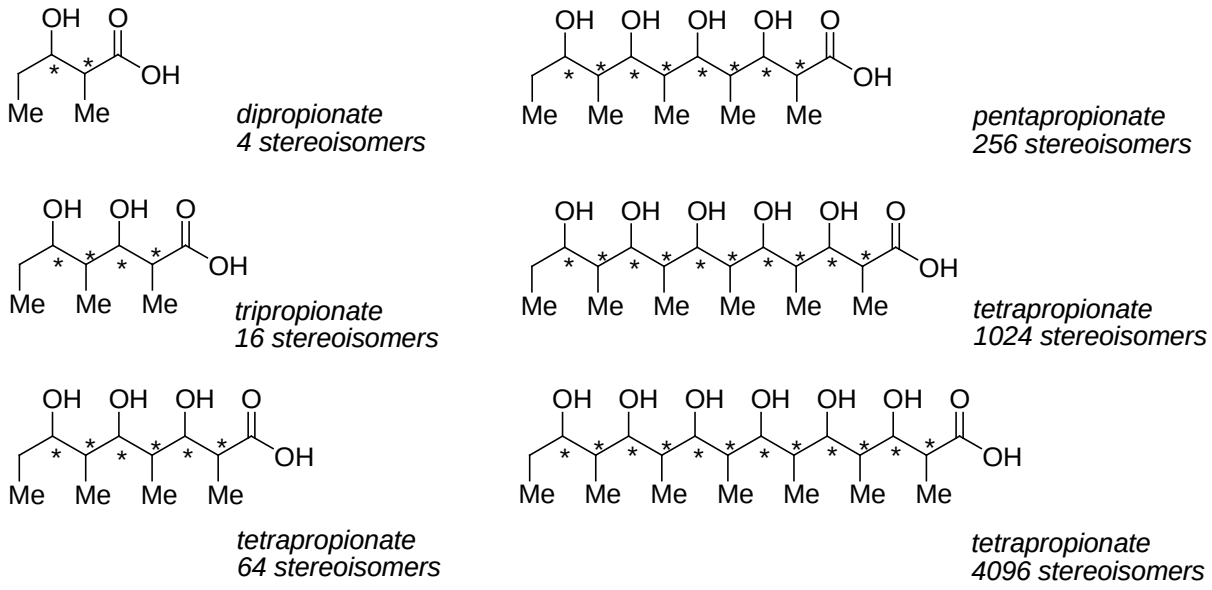


Figure 6. Possible number of stereoisomers for polypropionates

In polyketides, the stereotetrad is a common substructure which consists of four stereogenic centers, next to each other, resulting in eight possible diastereomeric combinations: *anti*, *anti*, *anti* (**47a**); *anti*, *anti*, *syn* (**47b**); *anti*, *syn*, *anti* (**47c**); *syn*, *anti*, *anti* (**47d**); *syn*, *syn*, *anti* (**47e**); *syn*, *anti*, *syn* (**47f**); *anti*, *syn*, *syn* (**47g**) and *syn*, *syn*, *syn* (**47h**) (Figure 7). The coupling of chiral stereotetrad fragments in a stereocontrolled fashion allows the construction of more elaborate polypropionate structures. However, this union can be complicated by double stereodifferentation and introduces a major obstacle to be overcome in any total synthesis. As a

result, numerous reactions have been developed for the synthesis of polypropionate structures. For example, aldol,[11] crotylation,[12] Diels-Alder,[13] Wittig,[14] alkylation,[15] and allylstannation[16] reactions are only a few of the numerous methods that have been applied for the synthesis of polypropionates. Despite the plethora of approaches available, the asymmetric synthesis of polypropionate compounds continues to be a synthetic challenge because very few methods can be generally applied for the iterative preparation of the numerous polypropionate motifs found in various natural products.

[11] (a) Yeung, K.–S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237-4313. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506-7525.
[12] (a) Hoffmann, K. W.; Dresely, S.; Hildebrandt, B. *Chem. Ber.* **1988**, *121*, 2225-2230. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919-5923. (c) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190. (d) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339-6348.
[13] (a) Myles, D. C.; Danishefsky, S. J. *J. Org. Chem.* **1990**, 55, 1636-1648. (b) Arjona, O.; Menchaca, R.; Plumet, J. *J. Org. Chem.* **2001**, *66*, 2400-2413. (c) Vogel, P.; Sevin, A.-F.; Kernen, P.; Bialecki, M. *Pure & Appl. Chem.* **1996**, *68*, 719-722.
[14] Hanessian, S.; Wang, W.; Gai, Y.; Eric, O. *J. Am. Chem. Soc.* **1997**, *119*, 10034-10041.
[15] (a) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603-5606. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739. (c) Mulzer, J.; Schollhorn, B. *Angew. Chem., Int. Ed.* **1990**, *29*, 1476-1478.
[16] Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31-47.

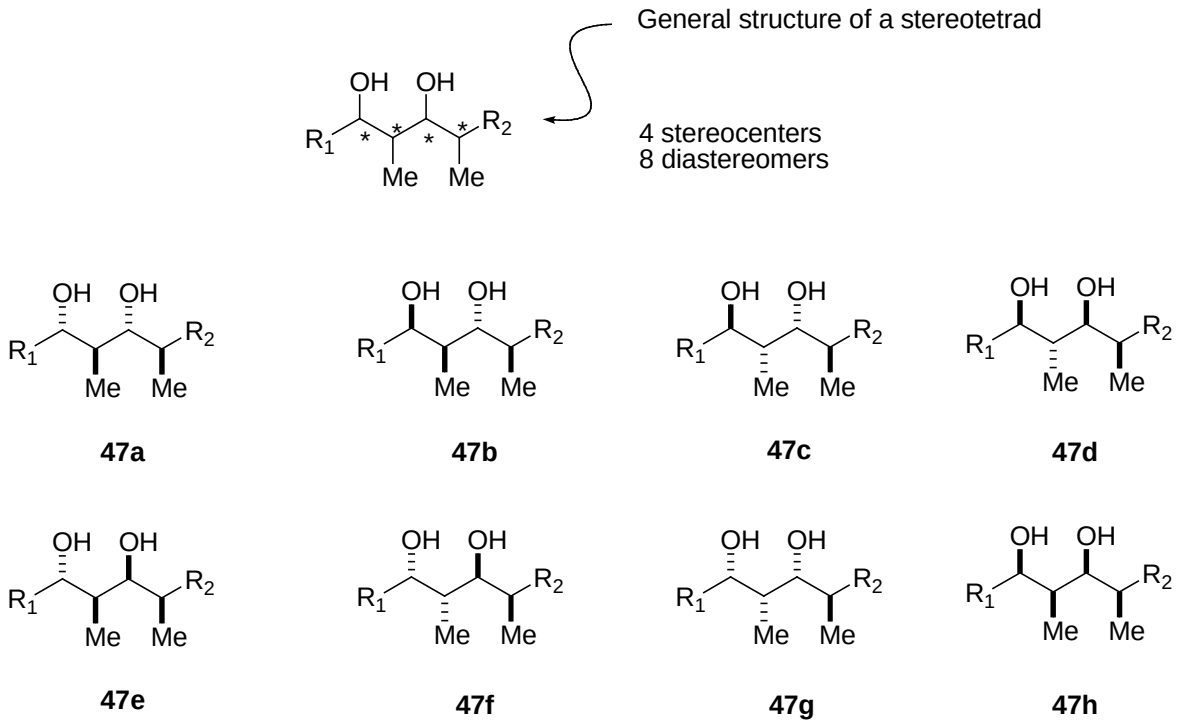


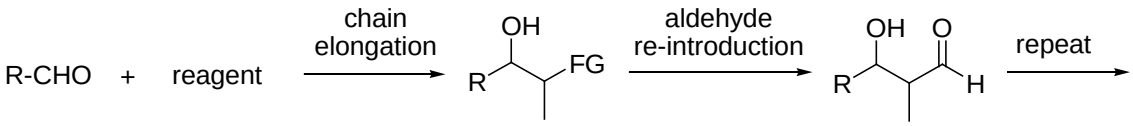
Figure 7. Stereotetrads

1.3.1 Iterative Strategies for Polypropionate Synthesis

Many of the iterative strategies for polypropionate synthesis developed to date involve the reaction of chiral (non-racemic) or achiral aldehydes with chiral (non-racemic) or achiral reagents generating one to two new stereocenters for each step. For an iterative strategy, the aldehyde must be prepared from the product resulting from the preceding chain elongating step (Scheme 6). There are two major obstacles for an iterative strategy: 1) the number of synthetic manipulations required for re-introduction of aldehyde and, 2) the enantio- and diastereoselectivities of the chain elongation steps. In Nature, as few as two steps are performed for each iteration and the enantio- and diastereoselectivities are controlled by enzymes. As was discussed earlier (Figure 6), the number of possible stereoisomers increases exponentially with

the number of stereogenic centers. Often, the major challenge faced by synthetic chemists involves establishing the desired configurations of the polypropionate compound. Over the past three decades, several iterative strategies for polypropionate synthesis have emerged and have found various applications for the synthesis of polypropionate compounds. The following examples are presented to provide a representation of iterative approaches. All of the examples have shown the capacity to control the stereochemical outcome of different reactions by exploiting substrate- and/or reagent-control.

Scheme 6. An iterative strategy



In 1990, Danishefsky and co-workers disclosed a Lewis acid catalyzed diene aldehyde cyclocondensation (LACDAC) reaction that was applied in an iterative fashion for the synthesis of racemic 6-deoxyerythronolide B (Figure 8).[13a] The strategy exploited substrate-controlled Diels-Alder reactions of diene **48** with various aldehydes in the presence of different Lewis acids (e.g. $ZnCl_2$ or $BF_3 \cdot OEt_2$) to produce dihydropyrones. Processing the dihydropyrones into their corresponding aldehydes (6 steps) permitted iteration of the sequence. Although the approach was iterative, a major limitation was the 6 steps (*ca.* 35-41% yields) required before the next iteration.

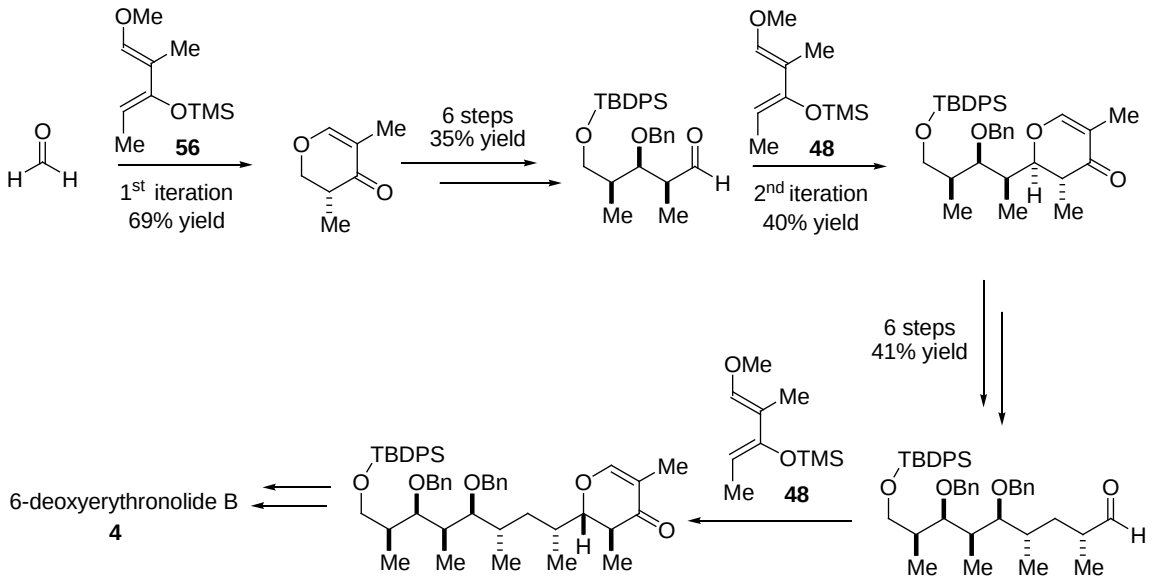


Figure 8. Iterative Lewis acid catalyzed Diene aldehyde cyclocondensation sequence for the synthesis of 6-deoxyerythronolide B

In a related synthesis, Roush and co-workers presented an impressive asymmetric synthesis of the C_{19}-C_{29} polyketide segment **49** of Rifamycin S (Figure 9).[17] The strategy employed four reagent-controlled crotylboration/allylboration reactions utilizing chiral tartarate ester-derived crotyl/allyl boronates **50**, **51** and **52** with chiral aldehydes, where after the first iteration, only 2 steps were required to prepare the aldehyde for iterative chain elongation. Similar strategies developed by Panek[18] and Marshall[19] employing chiral crotylsilanes and chiral allenylmetal reagents were used in the syntheses of polypropionates oleandolide and discodermolide, respectively.

[17] Roush, W. R.; Palkowitz , A. D. *J. Am. Chem. Soc.* **1987**, *109,* 953-955.
[18] Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475-12475. For a recent example of this strategy in total synthesis, see: Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999,** *121*, 9229-9230.
[19] Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556-5559. For a recent example of this strategy in total synthesis, see: Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998,** *63,* 7885-7892.

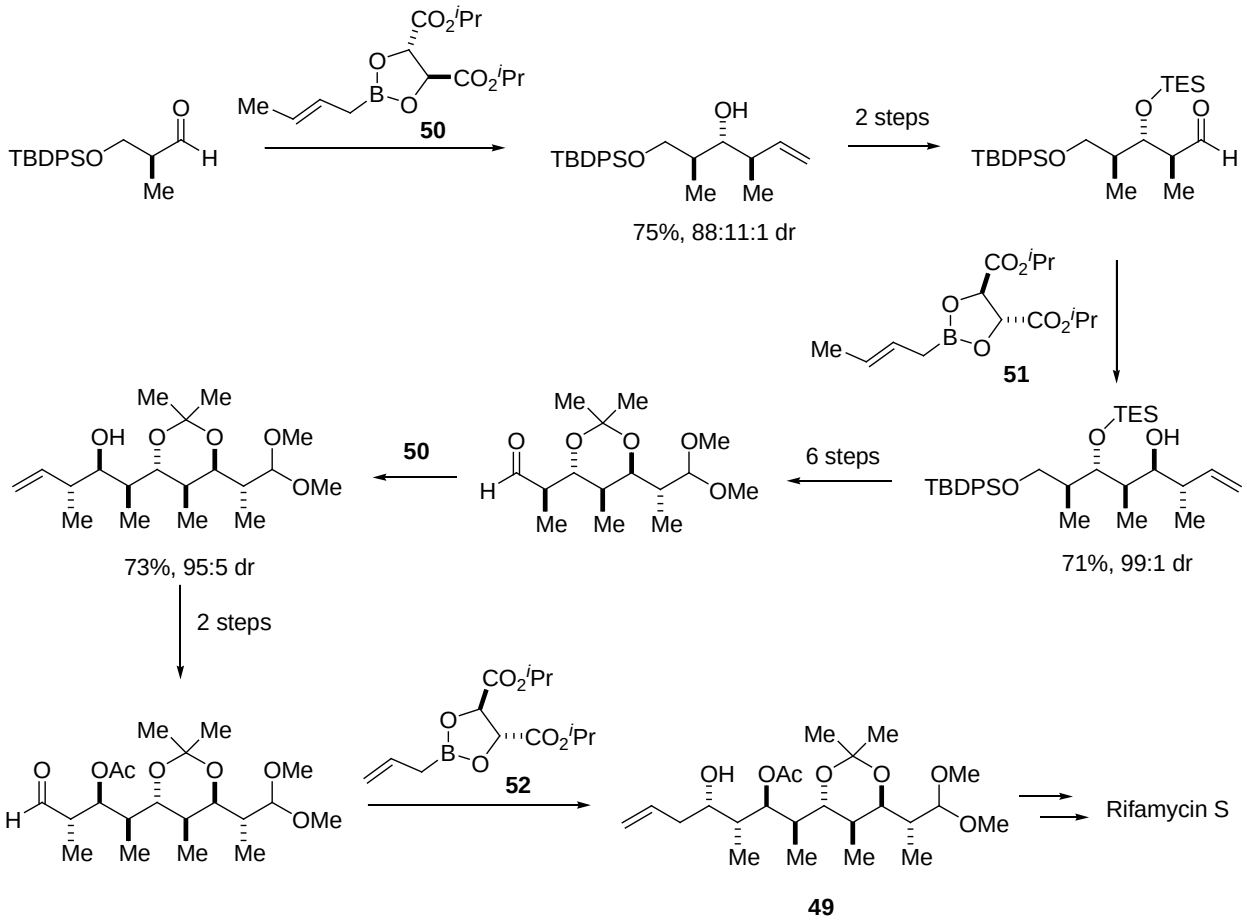


Figure 9. Iterative crotyboration (Roush).

Hanessian and co-workers utilized a Wittig methodology for building the same segment of Rifamycin S. The approach involved substrate-controlled methyl cuprate additions to protected chiral γ-alkoxy-α,β-unsaturated esters followed by a Davis α-hydroxylation to complete the installation of a propionate fragment (Figure 10).[20] Iteration was achieved by a three step sequence that provided the next aldehyde to be used for chain elongation. Unlike the

[20] Hanessian, S.; Wang, W.; Gai, Y.; Eric, O. *J. Am. Chem. Soc.* **1997**, *119*, 10034-10041.

previous examples, this approach sequentially installed the desired stereocenters after chain elongation.

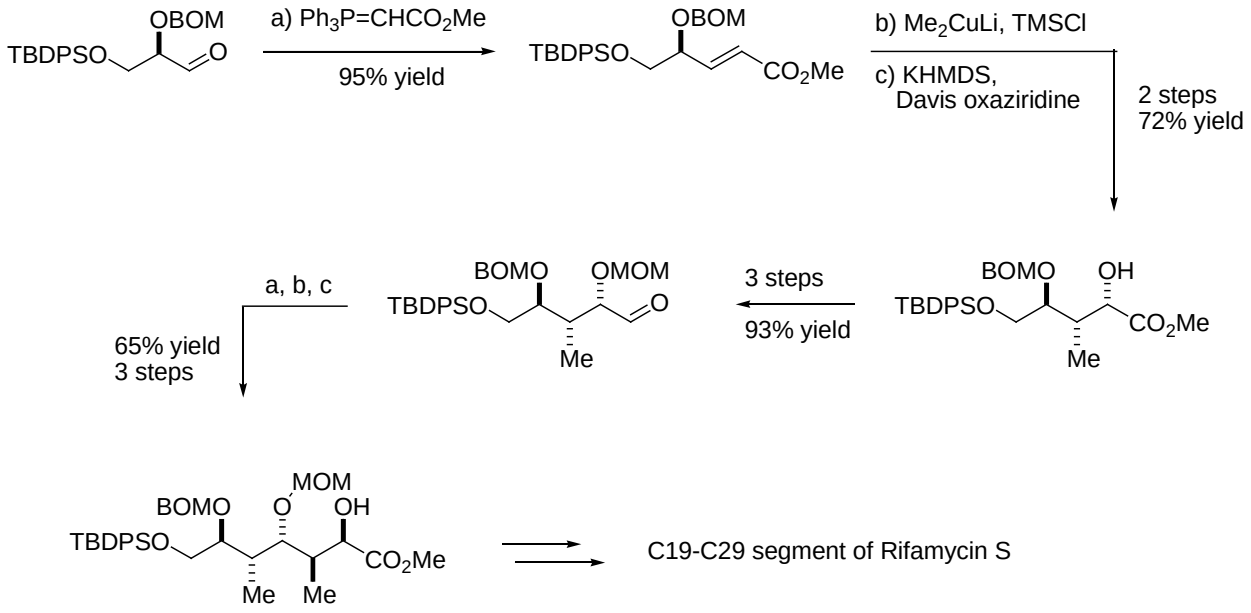
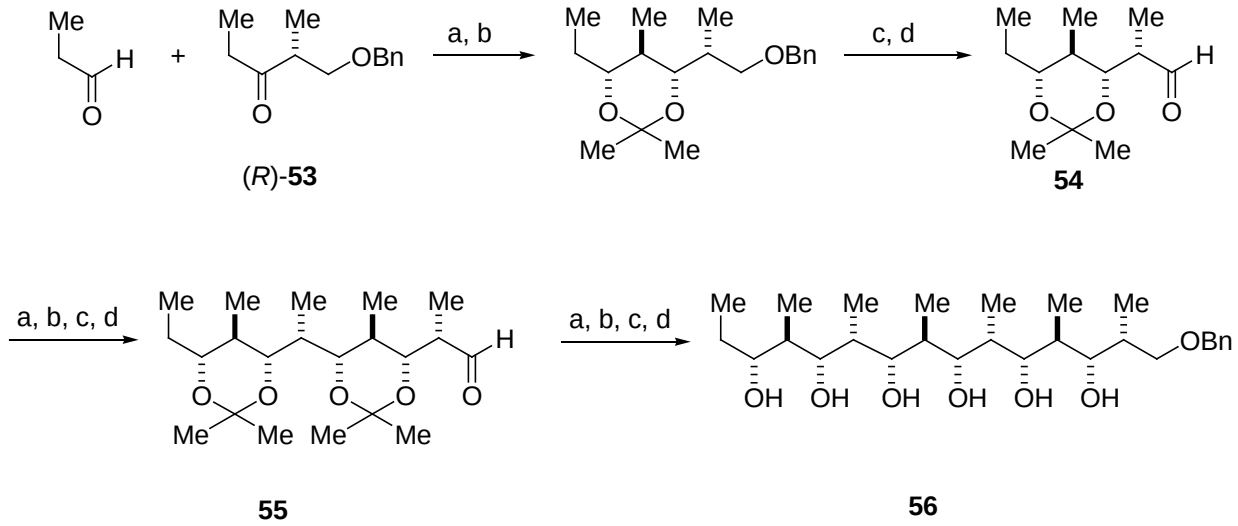


Figure 10. Iterative Wittig methodology

Although Diels-Alder, crotylation, Wittig reactions and many others have impacted the synthesis of polypropionates to a large extent, the aldol reaction presents the most important and general method for the stereocontrolled formation of polypropionates by directly mimicking the biosynthetic pathway. Under the iterative aldol-based strategies Paterson's chiral ketone methodology and the auxiliary based approaches are the most popular.

Paterson reported a boron-mediated aldol reaction strategy for the synthesis of polypropionate compounds. The strategy exploited substrate-controlled aldol reactions of

preformed chiral (*E*)-enol borinate (*R*)-**53** [or (*S*)-**53**] with various aldehydes.[21] The sequence was made iterable by a 4 step protocol that provided the desired aldehydes for subsequent iterations. The idea for this methodology was based on the polyketide biosynthesis where each chain extension unit introduced was correctly functionalized prior to the addition of the next. Aldol reaction of propionaldehyde and (*R*)-**53** provided the *anti* aldol adduct from which the aldehyde **54** was afforded in 4 steps. Repetition of this procedure followed by hydrolysis afforded **55** (97% ds) and **56** (97% ds). Thus, the introduction of twelve contiguous stereocenters in an eleven step protocol was accomplished in 41% yield with >88% diastereoselectivity.



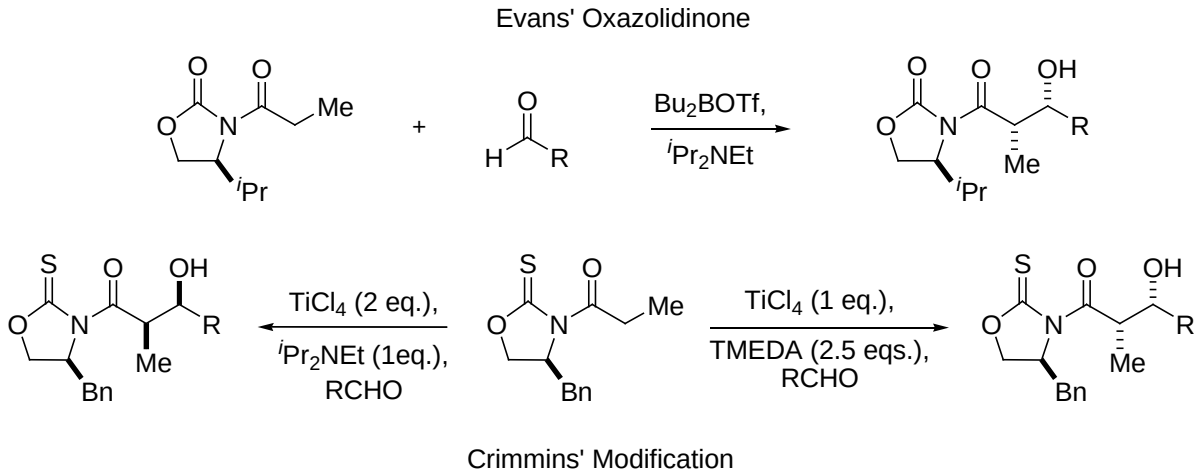
(a) (R)-**12**c-Hex$_2$BCl, Et$_3$N; LiBH$_4$; H$_2$O$_2$; (b) (MeO)$_2$CMe$_2$, PPTS; (c) Pd(OH)$_2$/C, H$_2$; (d) Swern; (e) Dowex-50

Figure 11. Iterative aldol condensation with Paterson's chiral ketone (*R*)-**12**

[21] (a) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7445-7448. (b) Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7441-7444. (c) Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999-15016.

Frequently, auxiliary-controlled aldol reactions have proven to be a reliable method to install repeating polypropionate units (Scheme 7). While additional steps in a synthetic sequence are needed for the installation and removal of the chiral auxiliary, this drawback is outweighed by the benefit gained from the high diastereoselective reliability of these auxiliary-based aldol

Scheme 7: Auxiliary-mediated aldol reactions



reactions. Evans[22] and Crimmins[23] have both used their respective chiral auxiliaries for the formal synthesis of 6-deoxyerythronolide B. While Evans' synthesis was based on a more convergent approach, Crimmins utilized a linear approach where the sequence was iterated five times during a 23 step synthesis. This was an excellent example where a chiral auxiliary was used for an iterative approach to a polypropionate natural product (Figure 12).

[22] Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921-5942.
[23] Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191-2194.

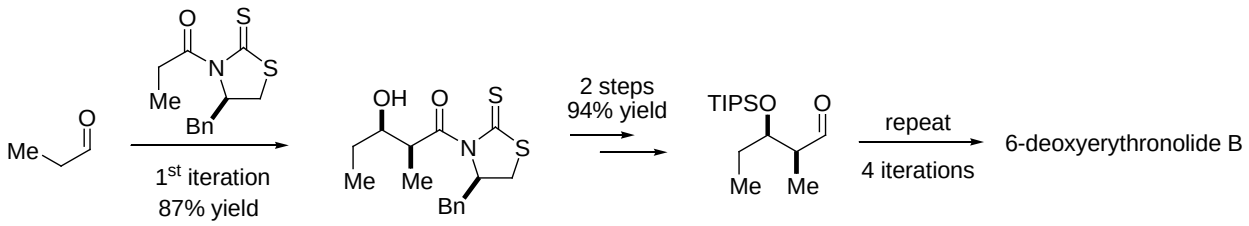


Figure 12. Iterative auxiliary based aldol sequence in Crimmins' synthesis of 6-deoxyerythronolide B

Although the aforementioned approaches presented very interesting and unique features that were exploited for the synthesis of various polypropionate compounds, many strategies required access to expensive chiral starting materials and/or reagents. As a result, there is a continuous demand for effective protocols that are both highly efficient and cost-effective with controllable access to chiral polypropionate compounds. The catalytic aldol reaction has always been the goal of many researchers, including our group. Even though many catalytic asymmetric aldol reactions have been successfully developed to form a single propionate unit,[24] too few examples have been used to set repeating networks of acetate or propionates.

1.3.2 The Cinchona Alkaloid-Catalyzed AAC Reaction for the Efficient Formation of Polypropionate Units

In 2004, our research group developed an alternative method for the production of propionate units by employing substoichiometric amounts of cinchona alkaloids in the acyl halide-aldehyde

[24] (a) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, *19*, 129-132. (*b*) Kobayashi, S.; Mukaiyama, T. In *Stereocontrolled Organic Synthesis*, Trost, B. M., Ed; Blackwell, Cambridge, 1994, pp. 37–65. (c) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989-1999 and references therein. (d) Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res.* **2004**, *37*, 580-591. (e) Northrup, A. B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799.

cyclocondensation (AAC) reaction (Figure 13).[25] The transformation of the enantioriched β-lactone product of the reaction to aldehyde allows the iterative use of the reaction for polypropionate synthesis.

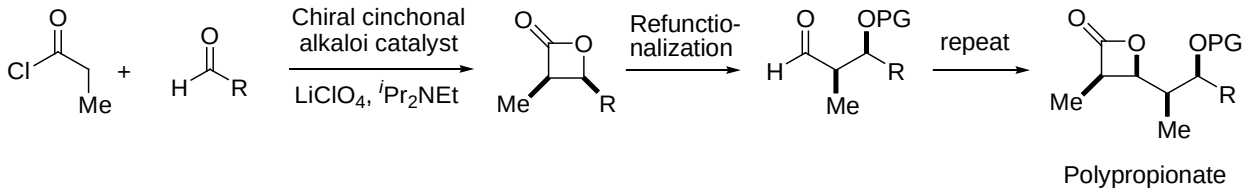
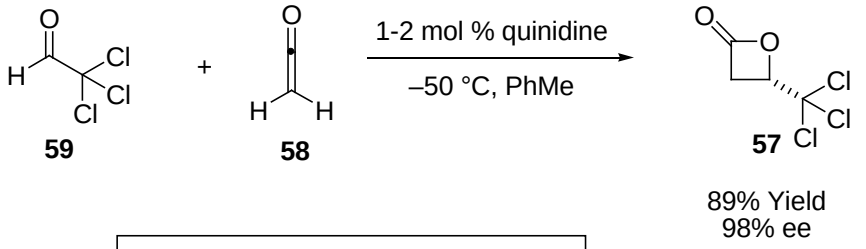


Figure 13. Iterative application of AAC reaction.

In 1982, Wynberg reported the formation of β-lactones via nucleophilic catalysis by alkaloid bases. β-Lactone **57** was obtained in excellent yield and optical purity by the [2+2] cycloaddition of ketene (**58**) with chloral (**59**) promoted by 1-2 mol% quinidine (eq 4).[26] This was the first time that an asymmetric and catalytic synthesis of optically pure β-lactones was demonstrated. Either enantiomer of the lactone could be obtained by the judicious choice of the alkaloid catalyst-quinidine (**60**) or quinine (**61**). The reaction was thought to proceed via an aldol-lactonization pathway involving an acyl-ammonium enolate intermediate **62** (Figure 14). Later, Wynberg investigated other carbonyl compounds but found that only highly activated aldehydes or ketenes participate in this reaction, severely limiting the scope of the methodology.[27]

[25] Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352-5353.
[26] Wynberg, H.; Staring, E. G. J. *J. Am.Chem. Soc.* **1982**, *104*, 166-168.
[27] Wynberg, H.; Staring, E. G. J. *J. Org. Chem.* **1985**, *50*, 1977-1979.



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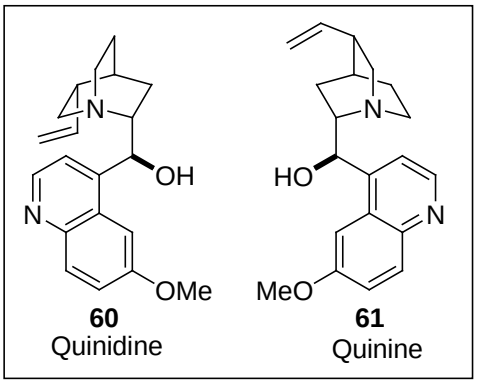


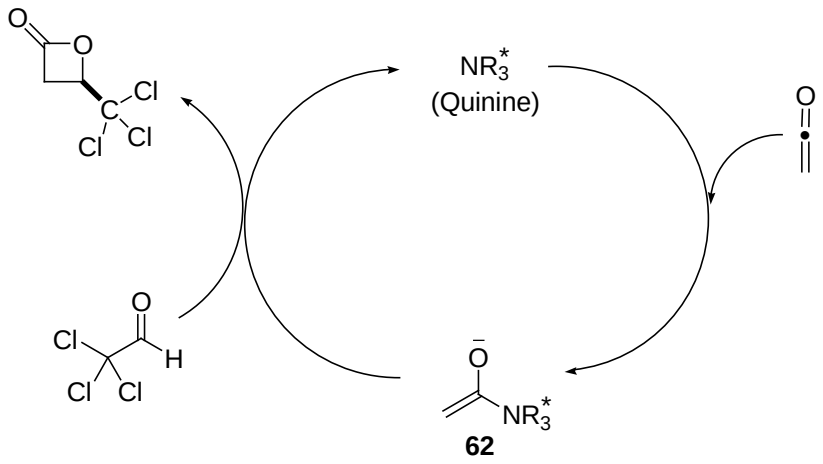
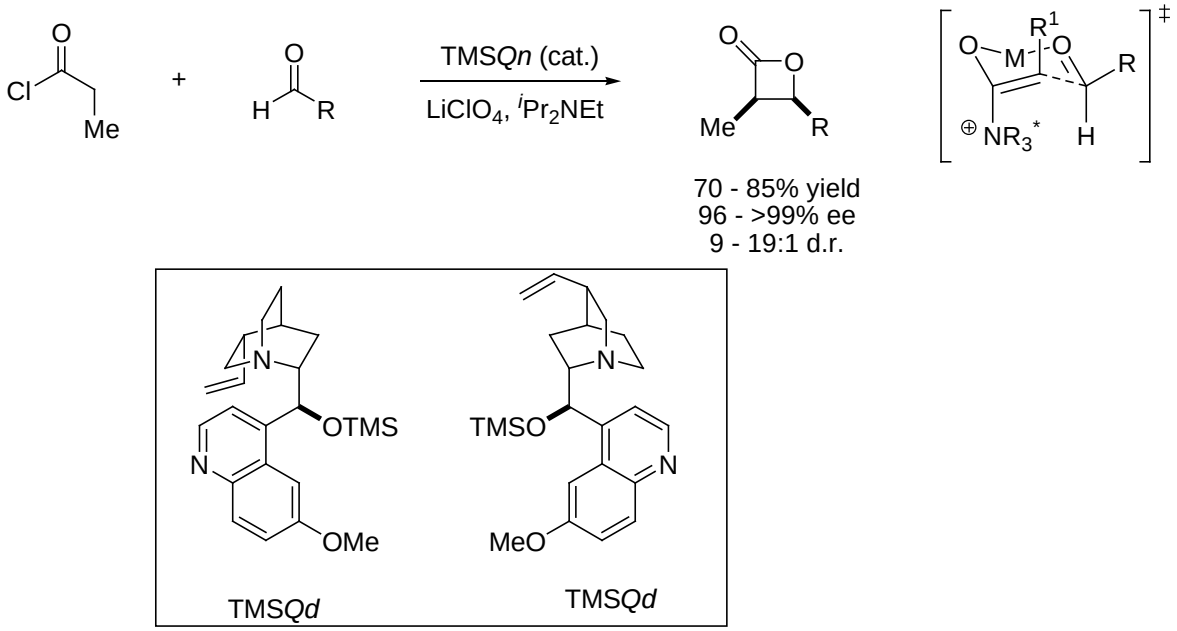


Figure 14. Mechanism proposed by Wynberg.

Subsequent developments of Wynberg's ketene-chloral addition led to reports of asymmetric alkaloid-catalyzed ketene-amine cycloadditions (Leckta),[28] ketene dimerizations (Calter)[29] and intramolecular ketene-aldehyde cycloadditions (Romo).[30] But intermolecular cross aldol type cycloadditions were limited to only highly activated aldehydes, suggesting that the acylammonium enolate intermediate **62** had limited nucleophilicity. In 2004, our research group developed the chiral cinchona alkaloid catalyzed acyl halide-aldehyde cyclocondensation (AAC) reaction (Scheme 8)[24] where both a Lewis acid and a Lewis base were incorporated within the reaction manifold, providing a dually activated system. While Lewis base catalysis (as with the Wynberg system) allowed for formation of a specific enantiomer of the optically active 2-oxetanone, the Lewis acid provided aldehyde activation, successfully extending the scope of the Wynberg ketene-aldehyde cycloaddition.

[28] (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc*. **2000**, *122*, 7831-7832. (b) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626-6635.
[29] Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007.
[30] Cortez, G. S.; Tennyson, C. L.; Romo, D. *J. Am. Chem. Soc.* **2001**, *123*, 7945-7946.

Scheme 8. Acyl halide-aldehyde cyclocondensation reaction



The mechanism postulated for the transformation is shown in Figure 15.[24] In this Lewis-base catalyzed AAC reaction, propionyl chloride undergoes a dehydrohalogenation reaction in the presence of Hünig's base to generate methyl ketene *in situ*. Methyl ketene is then intercepted by a catalytic amount of either TMS-quinine or the pseudoenantiomeric TMS-quinidine to produce exclusively a chiral (*Z*)-enolate. Subsequently, this chiral nucleophile reacts with an aldehyde via Zimmerman-Traxler chair transition state to yield a *syn*-disubstituted β-lactone product in good yield and in essentially enantio- and diastereomerically pure form. Thus, in addition to activating the aldehyde, the metallic Lewis acid also serves the dual role of stabilzing the ammonium-enolate **63** to afford the metalloenolate **64**. The metalloenolate then, adds to the aldehyde via a 6-membered closed transition state **65**, which is reminiscent of traditional aldol reactions. The cyclization of the resulting ammonium aldolate then produces the β-lactone,

releasing both the alkaloid and Lewis acid catalysts, completing the reaction cycle.

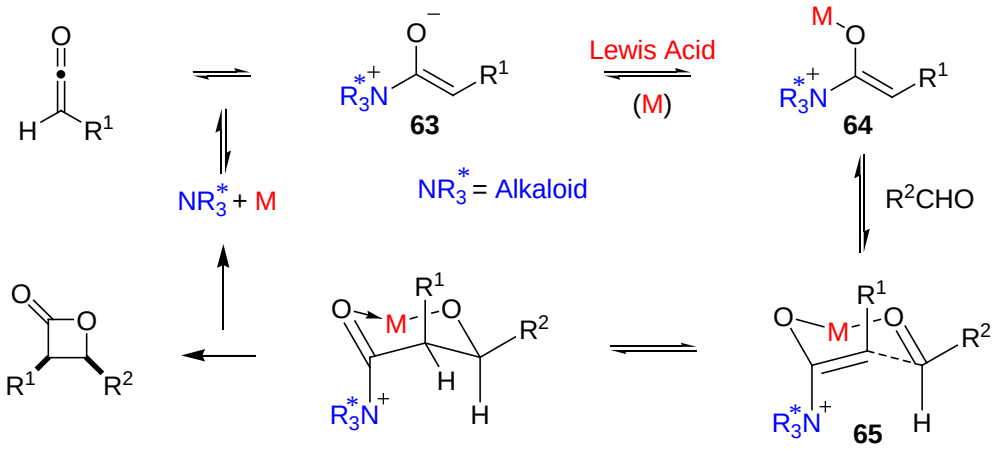


Figure 15. Postulated mechanism for the alkaloid catalyzed AAC reactions

Due to the highly efficient nature of this transformation, our research group began exploring the further potentials of this cinchona alkaloid-catalyzed AAC reaction. More specifically, we became interested in the effect double diastereoselection would have on the AAC reaction when α- and/or β-substituted enantioenriched aldehydes were used (Figure 16). If the cinchona alkaloid-catalyzed AAC reaction were amenable to these more elaborate aldehydes it would provide us with an avenue to form polypropionate units in an efficient and iterative fashion.

Figure 16. Formation of polypropionate units via cinchona alkaloid-catalyzed AAC

Cyclocondensation reactions with chiral aldehydes were thus investigated and the diastereoselectivities were interpreted using the well-known models that accurately predict and rationalize the stereochemical outcome of analogous aldol additions. The *syn*, *anti*, *syn* lactone **66** was formed from aldehyde **67** in the *O*-trimethylsilylquinidine (TMS*Qd*) (**68a**) catalyzed AAC whereas the quinine-derived catalyst **69b** yielded the *anti*, *anti*, *syn* lactone **70** (Figure 17),[31] providing a convenient and efficient iterative method for polypropionate assembly.

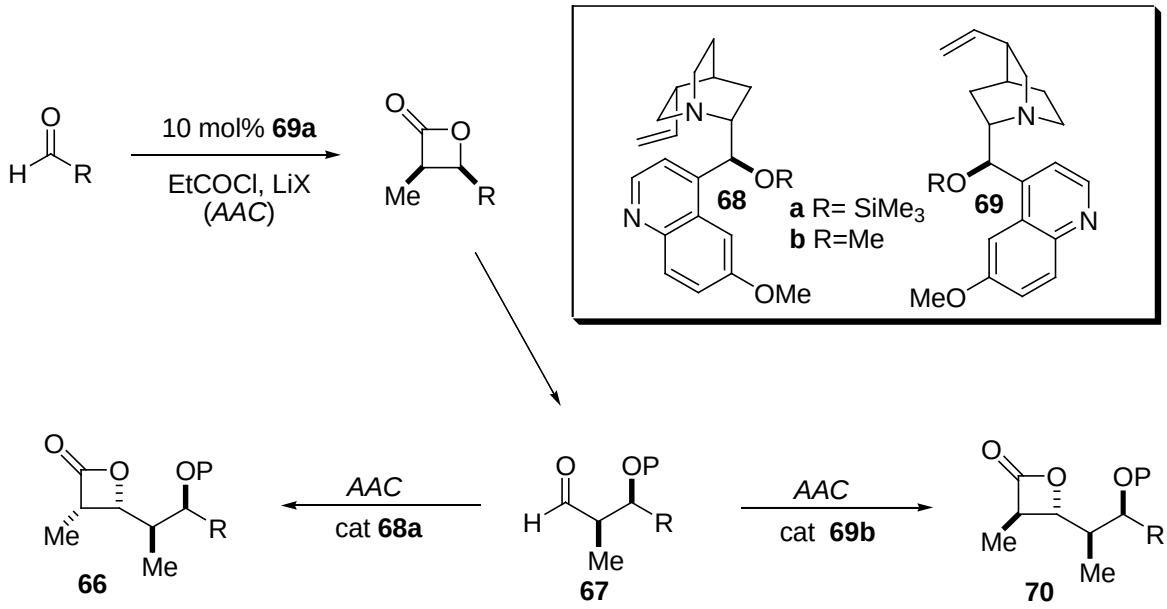


Figure 17. Iterative applications of AAC

Of the two possible chair transition states for the TMS*Qd* catalyzed reaction leading to **66**, the Felkin transition state **71** was disfavored by the *syn*-pentane interaction (Figure 18). Therefore to avoid this interaction the aldehyde underwent *anti*-Felkin type addition via transition state **72**. Also since the enolate face reacting in **72** was the favored enolate face for

[31] Shen, X.; Wasmuth, A. S.; Zhao, J.; Zhu, C.; Nelson, S. G. *J. Am. Chem. Soc*. **2006**, *128*, 7438-7439.

quinidine (*Re* face), the quinidine catalyzed AAC with aldehyde **67** constituted the matched case providing the *syn, anti, syn* lactone **66**. For the quinine catalyzed reaction, to accommodate the aldehyde's *anti*-Felkin preference, the reaction proceeded through a boat transition state **73** affording the *anti, anti, syn* lactone **70**.

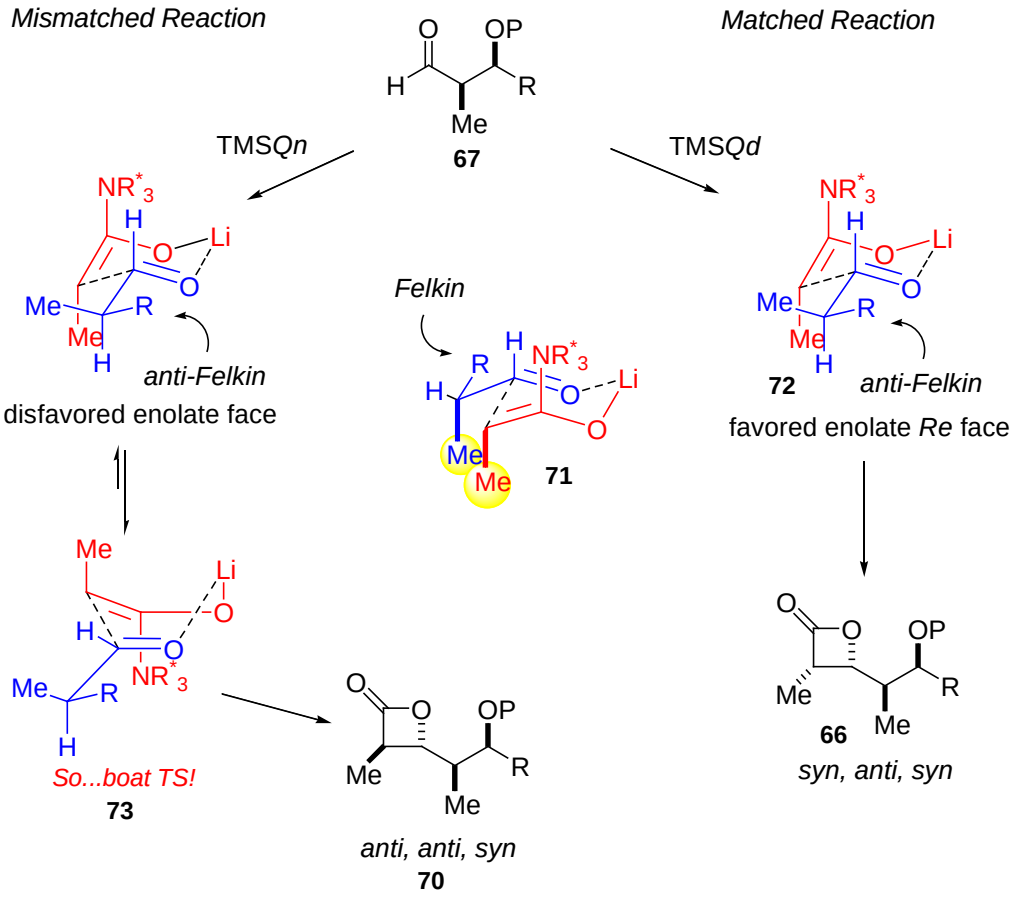


Figure 18. Transition states for the mismatched AAC reaction

The cinchona-alkaloid catalyzed AAC reaction provides an efficient and elegant alternative method for the production of polypropionate units for the following reasons.

i) The reaction can affect a rapid increase in structural and stereochemical complexity using only catalytic sources of chirality utilizing a "direct" aldol approach where the pregeneration of the

enolate is unessential; the activated enolate equivalent (the *N*-acylammonium enolate) is generated in situ.

ii) Use of a catalyst that is prepared easily in one step from the commercially available cinchona alkaloids quinine or quinidine, is an immensely enticing feature of this reaction, as the use of stoichiometric amounts of auxiliaries or expensive transition metal catalysts is avoided.

iii) Flexibility in reaction conditions allow for optimization of the AAC reaction for specific aldehydes.

iv) The stereochemical outcome of the the diastereoselective AAC reactions can be accurately predicted by the same Zimmermann-Traxler type models that are commonly used to predict stereoselectivities in aldol reactions. Predictability is a desired quality that determines the choice of a reaction in complex target oriented synthesis.

v) The β-lactone product of the AAC reaction is amenable to easy functional group transformations leading back to an aldehyde that can act as substrate in a subsequent AAC reaction. Iterative application of AAC followed by functional group transformations to aldehyde will enable rapid and efficient synthesis of valuable polyketide structures.

The potential of this cyclocondensation for the iterative synthesis of polypropionate units will be further demonstrated in this thesis through its application in the synthesis of erythronolide B.

2.0 APPLICATION OF AAC TO THE SYNTHESIS OF ERYTHRONOLIDE B: THE FIRST GENERATION APPROACH

2.1.1 Retrosynthetic Analysis

Ketene-aldehyde cycloadditions represent surrogates for catalytic asymmetric aldol additions exploiting ketenes as enolate equivalents. Extrapolating this reaction design to iterative catalyst-controlled couplings with methyl ketene for propionate chain elongation would provide the basis for our erythronolide B synthesis (Figure 19). Disconnection of the erythronolide B aglycone across the C_1-O and the C_7-C_8 bonds revealed two modified propionate trimer equivalents **74** and **75**. The *syn*, *anti*, *syn* synthon **74** could be accessed through two successive iterations of the alkaloid-catalyzed AAC reaction between propionaldehyde and methylketene using the alkaloid catalysts TMS*Qd* (**68a**) and TMS*Qn (***69a)** respectively. The all-*syn* synthon **75** would be derived from the alkaloid catalyzed cyclocondensation of methacrolein with methylketene; ensuing homologation of the resulting C_4-C_5 via an alkaloid-catalyzed cyclocondensation reaction was unsuccessful at providing the desired C_3-C_4 *syn* arrangement. Therefore while our research group was still working on the identification of new catalysts for the synthesis of *syn, syn, syn* polypropionate segment, we would use Crimmins' chiral auxiliary-based method[32] to gain access

[32] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K.; *J. Org. Chem.* **2001**, *66*, 894-902.

to this fragment in order to explore the feasibility of the route. The tertiary alcohol center at C_6 in **75** could be efficiently incorporated using Sharpless' asymmetric dihydroxylation reaction. Subsequent coupling of the key fragments would be realized through a ring-opening of epoxide **75** with a **74**-derived enolate. Submitting the coupled C_1-C_{13} seco-acid to macrolactonization would provide the aglycone in its cyclized form.

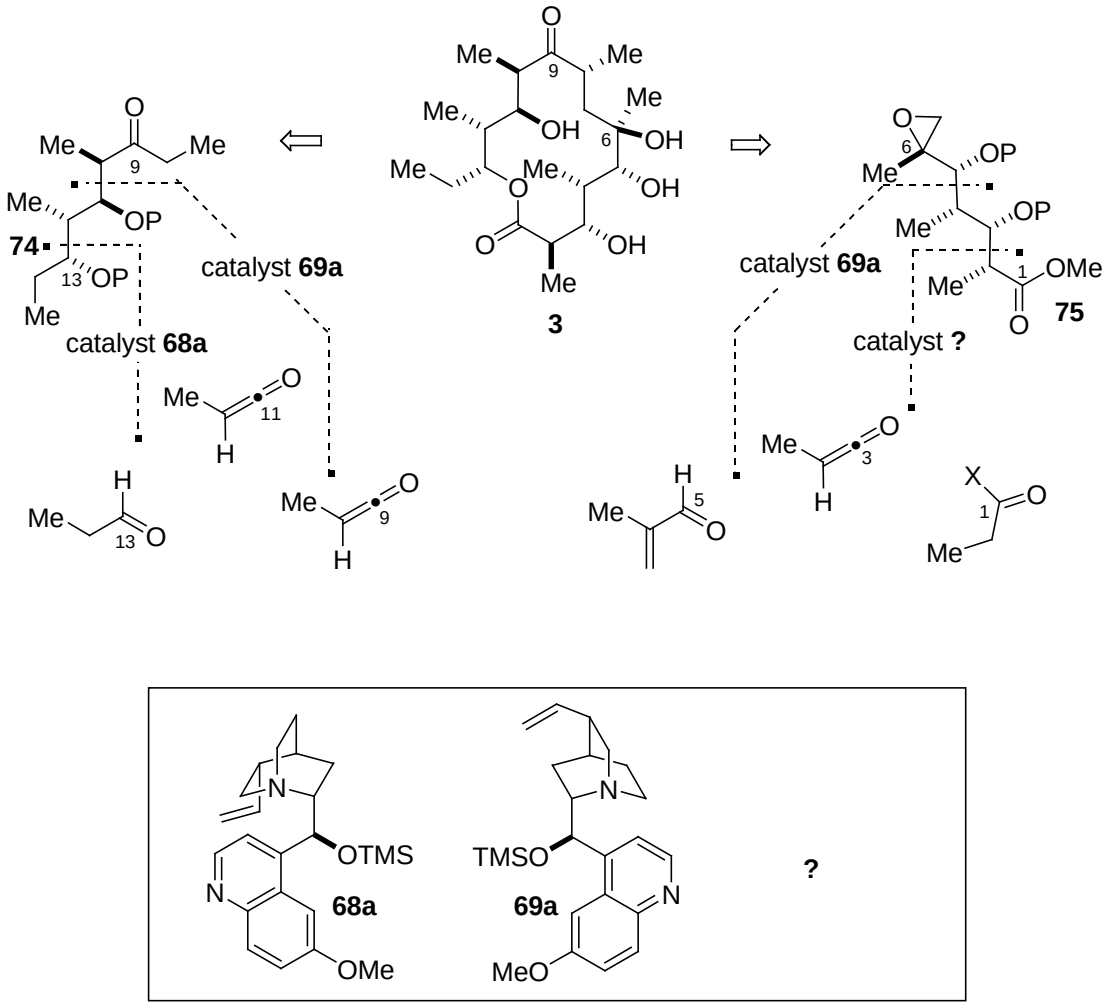


Figure 19. Catalytic asymmetric synthesis of erythronolide B.

With the extensive amount of literature that already exists on macrolactonization studies of 14-membered erythromycin analogues (discussed previously in Figure 4), we anticipated that the macrolactonization of the seco-acid would be relatively free of problems, if the reacting ends of the seco-acid could be constrained through careful choice of cyclic acetal protecting groups on the designated hydroxyls. The key C_7-C_8 fragment coupling reaction of keto-enolate with epoxide however, presented considerable uncertainities due to the lack of related literature precedents involving complex substrates. Examples in the literature where ketone enolates have been used to open sterically hindered epoxides are rare.[33] Due to the limited nucleophilicity of ketone enolates compared with esters and amides, the ring opening of epoxides with the former presented a challenge, that we thought was worthy of exploring. We therefore proceeded for the synthesis of fragment **75**.

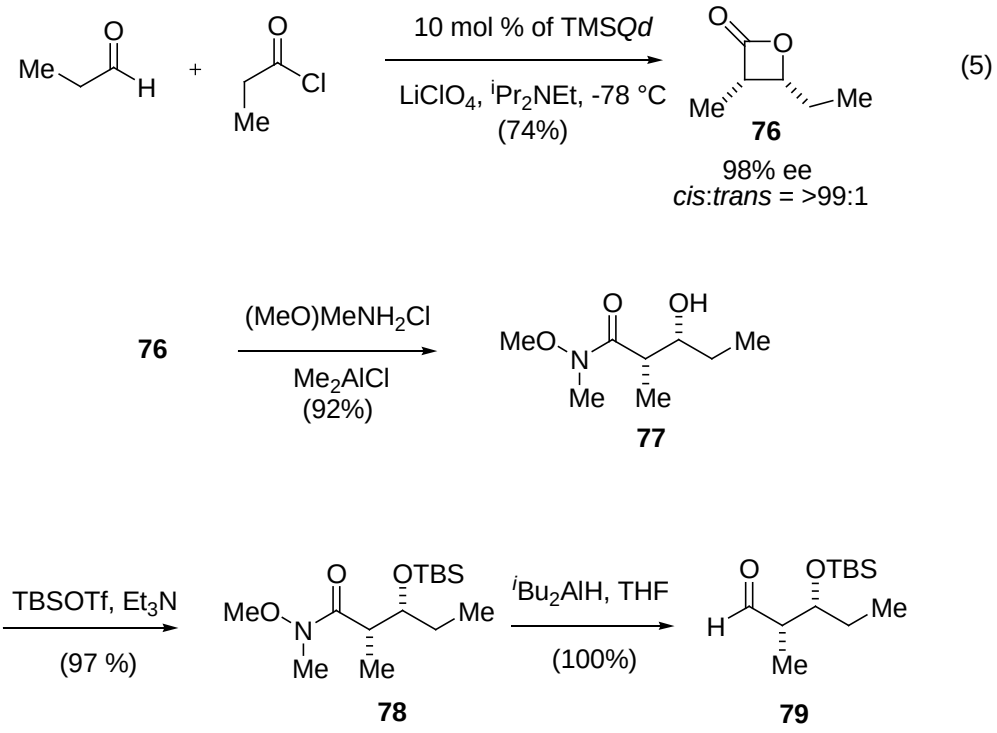
2.1.2 Synthesis of Ketone Fragment 84

According to our reaction design, the first propionate unit would be derived from an alkaloid catalyzed cyclocondensation reaction between methyl ketene and propionaldehyde. The resulting β-lactone would be refunctionalized to the corresponding aldehyde and this aldehyde would be subjected to another round of alkaloid-catalyzed cyclocondensation reaction with methyl ketene to produce the second propionate unit. Thus the synthesis of the C_8-C_{13} ketone fragment **75** commenced with an AAC reaction of propionaldehyde, using TMS*Qd* as catalyst to provide the desired enantiomer of the *syn* β-lactone **76** in 74% yield and 98% ee (*cis*:*trans* = >99:1) (Scheme

[33] For epoxide opening with ketone enolates see: (a) Crotti, P.; Di Bussolo, V.; Favero, L.; Pineschi, M.; Pasero, M. *J. Org. Chem.* **1996**, *61*, 9548–9552. (b) Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M.; Napolitano, E. *Tetrahedron* **1999**, *55*, 5853–5866 and references cited therein.

9, eq 5). The lactone was then ring opened to the Weinreb amide **77** (92%). TBS protection of the secondary alcohol group provided **78** (97%), which upon reduction with DIBAL-H led to aldehyde **79** in quantitative yield (Scheme 9)**.**

Scheme 9: Synthesis of lactone **76** and refunctionalization to aldehyde



Subjecting the aldehyde **79** to a second round of AAC resulted in the formation of β-lactone **80** with the required *syn, anti, syn* arrangement of substituents (eq 6). Because the aldehyde was structurally more hindered, the second round AAC reaction required a stronger Lewis acid compared with the first round. At –78 °C, using the stronger Lewis acid, LiI, and TMS*Qn* as catalyst, lactone **80** was obtained in excellent yield (95%) and as a single diastereomer. The diastereoselectivity could be explained through the chair type transition state

81 where the aldehyde underwent a preferred *anti*-Felkin attack and the TMS*Qn*-derived metalloenolate reacted with its favored *Si* face (Figure 20).

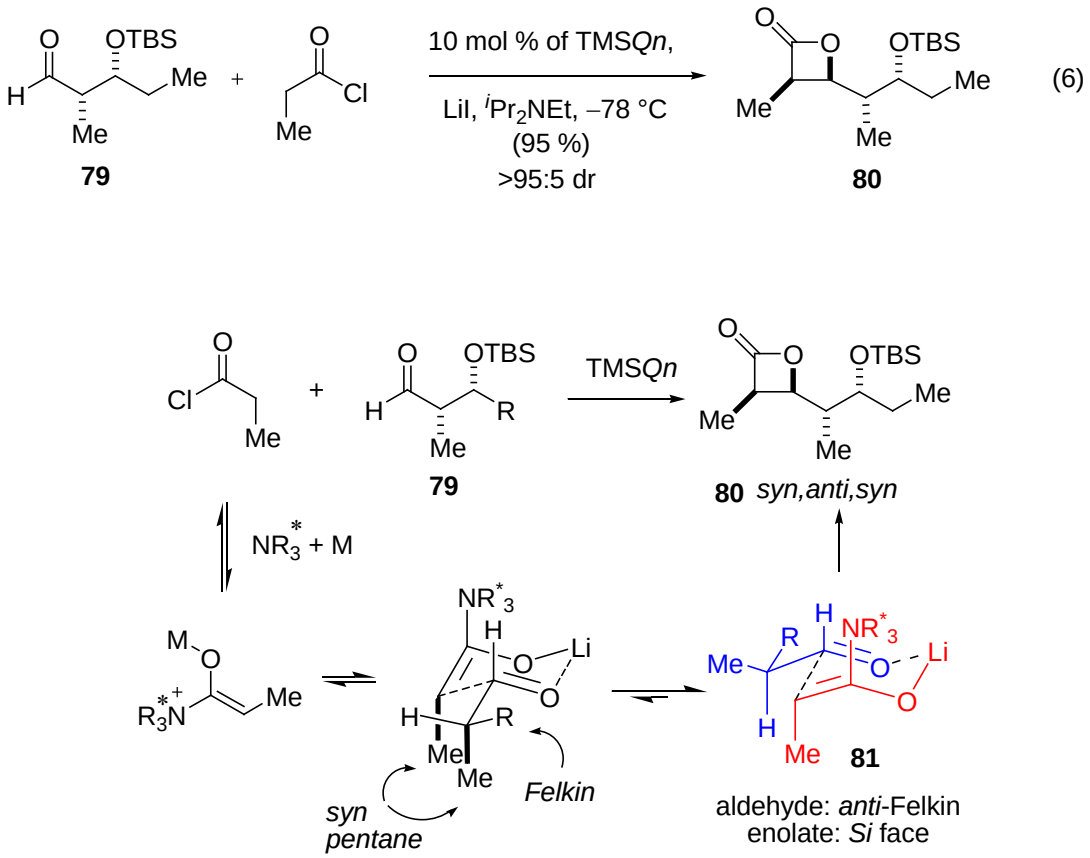
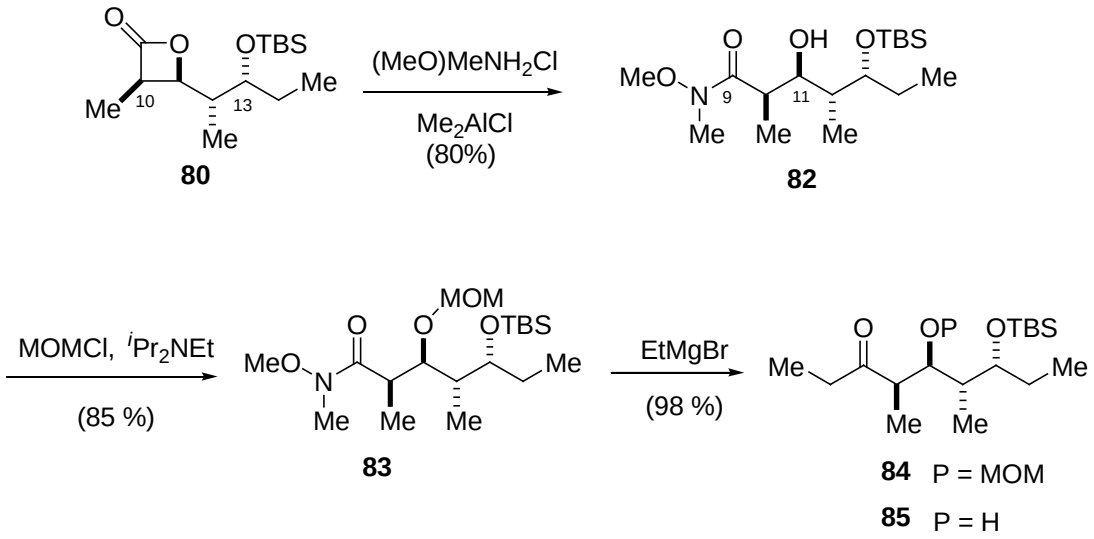


Figure 20. Transition state for formation of **80**

With all the four stereocenters in the C_9-C_{13} fragment installed, the only thing remaining was to convert the β-lactone to the ketone functionality. This was achived by subjecting β-lactone **80** to ring opening with *N*,*O*-dimethylhydroxylamine hydrochloride to provide Weinreb amide **82** (Scheme 10). Subsequent protection of the C_{11}-OH in **82** with a methyloxymethylene (MOM) protecting group followed by addition of ethyl magnesium bromide to **83** completed the synthesis of the ethyl ketone fragment **84**. For successful macrolactonization of the seco-acid at

the end of the synthesis, a *p*-methoxybenzyl (PMB) protecting group at the C_{11}-OH group would have been ideal as it could be tied up with the C_9-OH prior to macrolactonization to provide the required C_9/C_{11} cyclic acetal for efficient macrolactonization.[6b] However, we obtained consistently low yields (<40%) while attempting to protect the C_{11}-OH in **82** or in the corresponding ethyl ketone **85** with the PMB protecting group by reaction with *p*-methoxybenzyl trichloroacetimidate in presence of various Brønsted acid catalysts, as both the starting materials and the products were sensitive to acid and underwent decomposition in the reaction mixture. Therefore, we decided to temporarily use the MOM group in order to quickly gather material for the key coupling reaction.

Scheme 10. Synthesis of ketone **84**

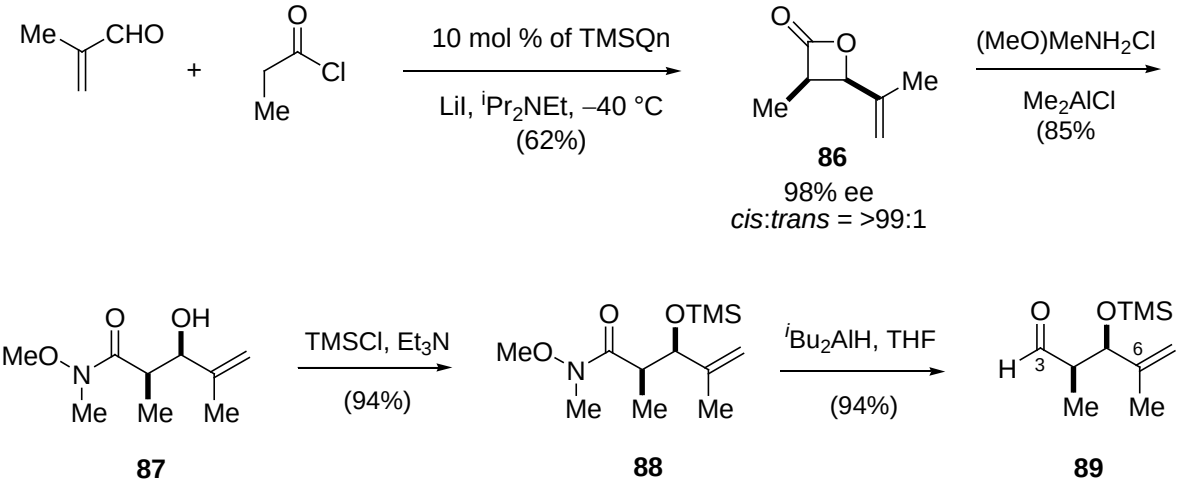


2.1.3 Synthesis of Epoxide 99

The synthesis of the all-*syn* fragment **75** commenced with a TMS*Qn*-catalyzed AAC reaction on the commercially available α,β-unsaturated aldehyde, methacrolein (Scheme 11). α,β-

Unsaturated aldehydes, in general, are not great substrates for the AAC reaction due to the conjugation which makes them less reactive. As expected, under the standard reaction conditions ($LiClO_4$, –78 °C) the reaction of methyl ketene with methacrolein showed negligible conversion. The stronger Lewis acid LiI (5 equiv) and a higher temperature of –40 °C were required for complete conversion to the lactone **86**. The isolated yield of the product was however, lower (62%) because of high volatility of the product. Ring opening of lactone with *N*,*O*-dimethylhydroxylamine to Weinreb amide **87** (85%) followed by protection of the resulting secondary alcohol as the trimethylsilyl (TMS) ether provided **88** (94%), which upon subsequent reduction with $^{i}Bu_2AlH$ provided aldehyde **89** in 94% yield, ready for another iteration of the AAC reaction.

Scheme 11. Synthesis of the C_3-C_7 segment



The 2nd iteration of the AAC reaction on aldehyde **89**, however, failed to provide the desired *syn*, *syn*, *syn* lactone **90** due to the unfavorable *syn* pentane interactions in the Felkin transition state **91** (Figure 21). The undesired *anti*, *anti*, *syn* product **92** was formed under the

TMS*Qn*-catalyzed reaction conditions via boat transition state **93** where *anti*-Felkin attack on the aldehyde through the favored enolate face occurred.

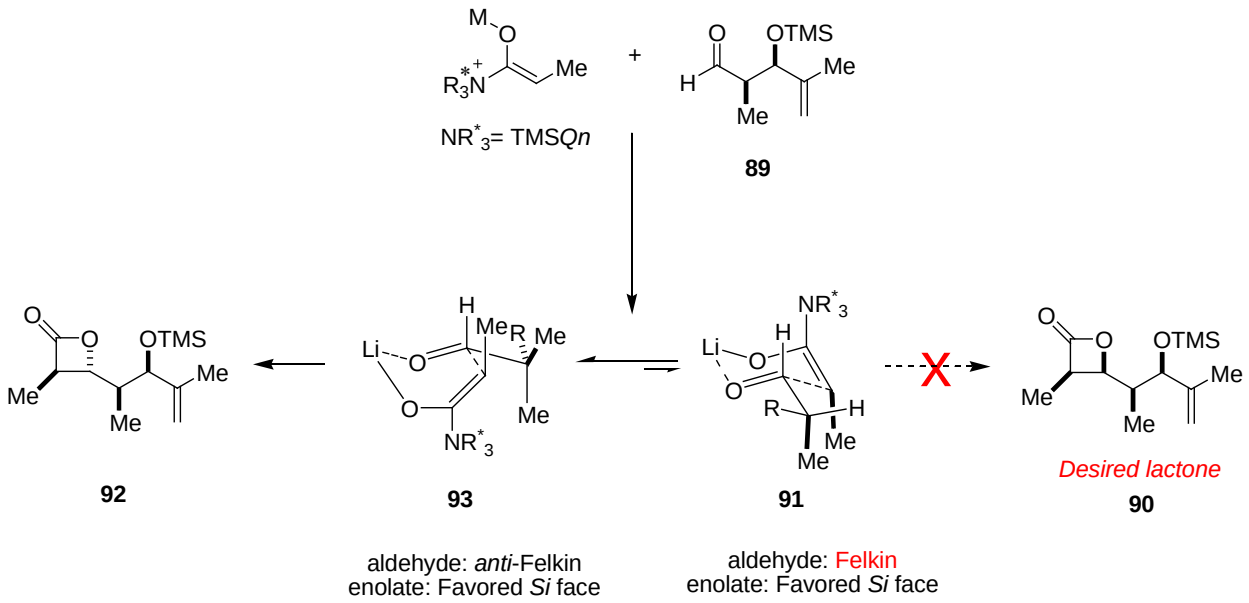
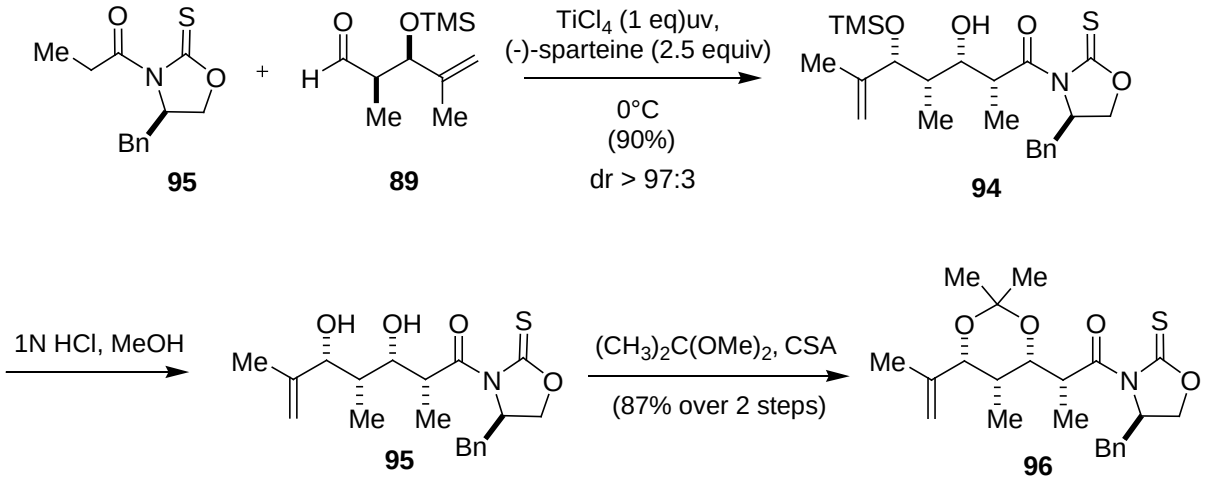


Figure 21. Transition state for TMSQn catalyzed AAC on aldehyde **89**

Due to our inability to access the all-*syn* propionate fragment via the AAC reaction, we resorted to Crimmin's chiral auxiliary based aldol reaction to obtain the stereochemically analogous compound **94**. The development of a successful protocol for the synthesis of this fragment was still required. Enolization of *N*-propionyloxazolidinethione with $TiCl_4$ (1 equiv) and sparteine (2.5 equiv) followed by addition of the aldehyde **89** produced the Evan's *syn* aldol product **94** in 90% yield and as a single diastereomer (dr > 97:3). Acid-mediated deprotection of the TMS group provided the diol **95**. In order to facilitate macrolactonization at a later stage, a cyclic dimethylacetal protecting group was incorporated across the C_3-C_5 hydroxyl groups of the diol **95** to provide compound **96** (Scheme 12). The *syn* stereochemistry across C_3/C_5-OHs in the

acetonide **96** was ascertained from the ^{13}C-shift values of the two methyl groups of the acetal using Rychnovsky's ^{13}C NMR acetonide method of assigning relative configuration.[34] Rychnovsky's group has shown that the ^{13}C NMR signals of the methyl groups in *syn*-1,3-diol acetonides occur at 19 and 30 ppm, whereas the ^{13}C NMR signals of the methyl groups in *anti*-1,3-diol acetonides occur at 25 ppm. The *syn*-l,3-diol acetonides adopt a chair conformation with one methyl axial (19 ppm) and one methyl equatorial (30 ppm). The *anti*-1,3-diol acetonides adopt a twist-boat conformation with "local" C_2 symmetry, and thus both methyl groups have the same chemical shift at about 25 ppm. For **96**, the ^{13}C shifts of the two methyl groups were 19 and 30 ppm, confirming the *syn* relative stereochemistry of the 1,3-diol.

Scheme 12. Auxiliary-mediated synthesis of all-*syn* segment



With the C_2-C_5 all *syn* array in place, the next challenge was to install the tertiary hydroxyl-center at C_6 of erythronolide B. Catalytic asymmetric dihydroxylation (AD), using

[34] Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515.

cinchona alkaloid-derived catalysts developed by Sharpless and co-workers[35] was used to install this tertiary alcohol center at C_6. The mnemonic proposed by Sharpless and co-workers is generally predictive for the sense of facial selectivity in dihydroxylations of a wide range of prochiral alkenes, and can be rationalized in most cases by consideration of the mechanistic model proposed by the Sharpless group.[36] Using enantiopure substrates in the Sharpless asymmetric dihydroxylation (SAD) reaction offers the prospect of matching and mismatching diastereomeric outcomes for AD reactions, depending on the substrate facial selectivity for dihydroxylation and the catalyst-mediated facial selectivity related to the substituents on the double bond. Applying the Sharpless mnemonic on the 1,1-disubstituted alkene **96** would predict that AD-mix α would favor formation of the desired C_6-stereocenter as in **97.** AD-mix β and AD-mix α are reagents for asymmetric dihydroxylation which contain potassium osmate, potassium ferricyanide, potassium carbonate and the chiral ligands dihydroquinidine 1,4-pthalazinediyl diether [$(DHQD)_2PHAL$, in AD-mix β] or dihydroquinine 1,4-pthalazinediyl diether [$(DHQ)_2PHAL$, in AD-mix α]. Accordingly, **96** was subjected to Sharpless asymmetric dihydroxylation with AD-mix α, which produced a single diastereomer of the diol in excellent yield (96%) suggesting a matched double diastereoselective reaction. The resulting primary alcohol function in **97** was then selectively tosylated (TsCl, DMAP) to give **98** (85%), which underwent elimination to epoxide upon treatment with base (K_2CO_3/MeOH) with concominant substitution of the chiral auxiliary to afford the methyl ester **99** in 63% yield (Scheme 13).

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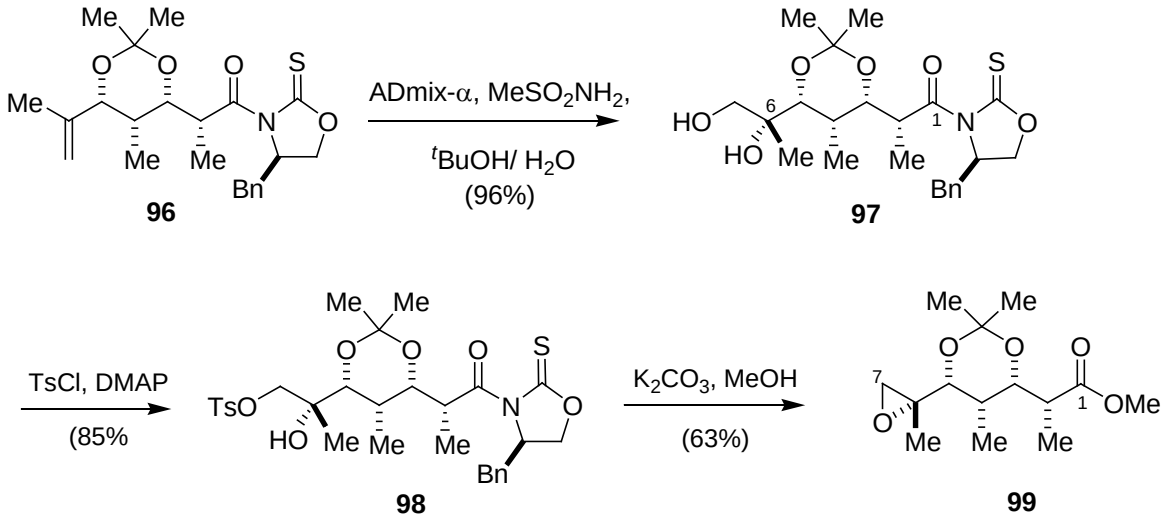
[35] (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768-2771.

[36] (a) Norrby, P.-O.; Kolb, H. C.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 8470-8478. (b) Norrby, P.-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35-42. (c) Nelson, D. W.; Gypser, A.; Ho, P.-T.; Kolb, H. C.; Kondo, T.; Kwong, H.-L.; McGrath, D. V.; Rubin, A. E.; Norrby, P.-O.; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997**, *119*, 1840-1858.

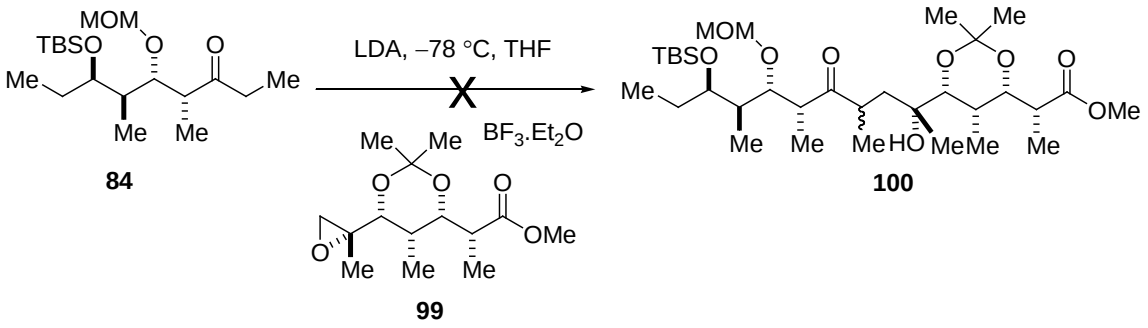
Scheme 13: Synthesis of epoxide fragment **99**



96 97 98 99

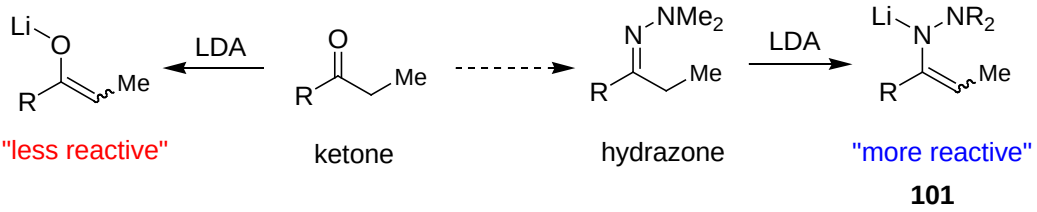
2.1.4 Coupling Studies on Fragments 84 and 99

From a preliminary survey of the literature, we found that epoxides undergo ring opening reactions with various types of organometallic nucleophiles such as alkynyl metals, Grignard reagents, etc. when suitably activated by a Lewis acid and $BF_3{\cdot}Et_2O$ was found to be a very commonly used Lewis acid for this purpose.[33] Therefore, in order to achieve coupling of our two fragments **84** and **99**, we decided to use $BF_3{\cdot}Et_2O$ as the Lewis acid for activating epoxide **99** toward ring-opening with the enolate of ketone **84**. The lithium enolate of **84** was generated using LDA and the epoxide was added to it at –78 °C, followed by addition of the Lewis acid. However, ring opening of the epoxide did not take place even after raising the temperature to –30 °C. After quenching the reaction mixture, the epoxide was found to be intact and none of the coupled material **100** was observed in the crude ^{1}H NMR (eq 7).

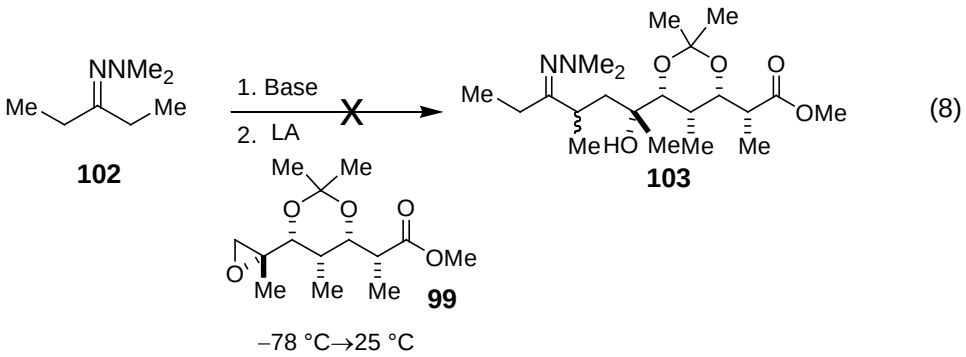


(7)

Lithiated hydrazones **101** are highly nucleophilic species compared to simple enolates due to the lower electronegativity of nitrogen and due to the α-lone pair effect (lone pairs on the adjacent nitrogen strongly destabilize the negative charge through electronic repulsion).[37] To test whether the epoxide could be opened by hydrazones, we first used a simple model *N*, *N*-dimethylhydrazone derivative **102**, prepared from 3-pentanone. Enolization of **102** was carried out followed by addition of the epoxide. A variety of Lewis acids were scanned in the reaction and the results are summarized in eq 8. In most of the cases, the epoxide was present intact even after prolonged reaction times (24-36 hours) at ambient temperature. For LiI and $MgBr_2$, products corresponding to epoxide ring opening with I^- and Br^-, respectively, were obtained along with unreacted epoxide, but the desired coupled product **103** was not observed in any of these reactions.



[37] (a) Smith, A. B.; Doughty, V. A.; Sfouggatakis, C.; Bennett, C. S.; Koyanagi, J.; Takeuchi, M. *Org. Lett.* **2002**, *4*, 783–786. (b) Smith, A. B.; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263–1266.



(8)

To confirm that the lithium hydrazoate was being generated under our reaction conditions, we carried out a control experiment using MeI as the electrophile instead of the epoxide, and in this case, complete conversion to the methylated product took place within an hour. Assuming that the hydrazoate was not sufficiently reactive, we tried several reactions using different chelating agents such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*′-dimethylpropyleneurea (DMPU) and hexamethylphosphoric triamide (HMPA)[38] (no Lewis acids were used in these cases) to the reaction, in order to enhance the reactivity of the anion, but without any success. The lack of reactivity was attributed to the highly sterically hindered nature of the two substrates.

[38] (a) Bernstein, M. P.; Romesberg, F. E.; Fuller, D. J.; Harrison, A. T.; Collum, D. B.; Liu, Q. Y.; Williard, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 5100–5110. (b) Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Jantzi, K. L.; Tzschucke, C. C. *J. Am. Chem. Soc.* **2003**, *125*, 3509–3521. (c) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201–7210.

3.0 THE SECOND GENERATION APPROACH

3.1.1 Revised Aldol Strategy

Due to the problems encountered in the enolate-mediated ring opening of epoxide in the earlier synthetic route, our strategy for fragment coupling had to be revised. To couple the two fragments, the well-known aldol reaction[39] was adopted not only because of its greater reliability in complex substrates but also because the stereochemistry in an aldol reaction can be easily predicted and controlled. Thus, disconnecting the C_7-C_8 bond of erythronolide B provided the ketone and aldehyde fragments **84** and **104**, respectively as shown in Figure 22. Synthesis of the aldehyde **104** required a few simple functinal group manipulations on an advanced intermediate **94** that was already used in the synthesis of the epoxide fragment **99** in the earlier route. Erythronolide B lacks oxygenation at C_7 and, as a result, the C_7 hydroxyl resulting from the aldol reaction between **84** and **104** would be removed by a Barton radical deoxygenation later in the synthesis. However the C_7 alcohol would serve an essential role in the synthesis as the stereochemistry at the C_7 hydroxyl emerging from the aldol coupling would be translated to the desired (*S*)-stereochemistry of the C_9-hydroxyl group via some sort of a directed reduction.

[39] Paterson, I. *Pure & Appl. Chem.* **1992**, *64*, 1821-1830.

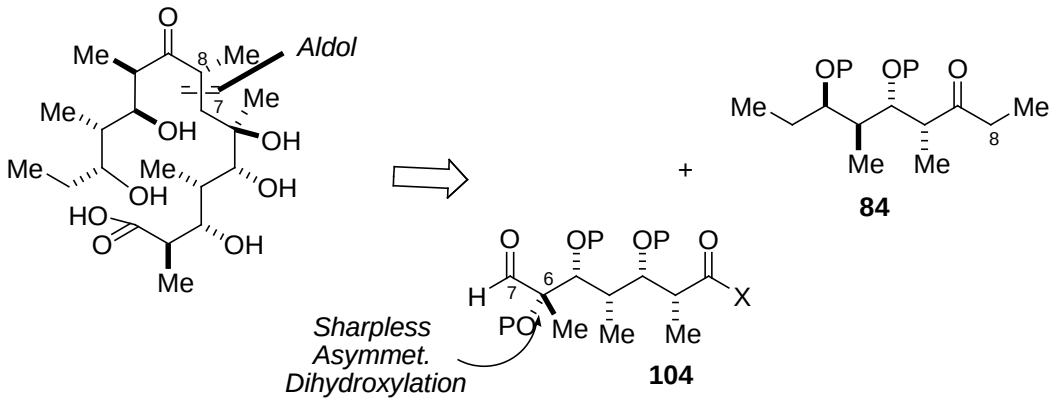


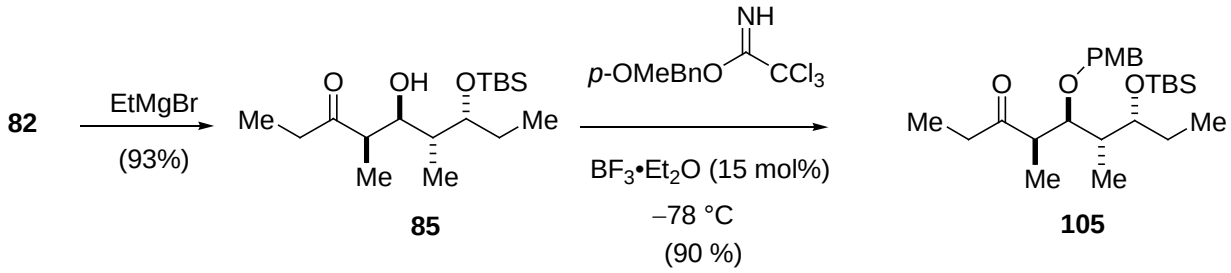
Figure 22. The proposed aldol disconnection

3.1.2 Introduction of the O_{11}-PMB Protecting Group in the Ketone Fragment

For efficient macrocyclization of the eryhronolide B seco-acid, cyclic acetal protecting groups across the C_3/C_5 and C_9/C_{11}-hydroxyl groups would play an extremely important role. In order to protect the C_9/C_{11}-OH groups with a cyclic *p*-methoxyphenyl (PMP)-acetal, we had planned to install a PMB protecting group on the C_{11}-OH. However, as discussed earlier, protecting **82** with *p*-methoxybenzyl trichloroacetimidate had proved to be problematic in presence of various Brønsted acids such as triflic acid, camphor sulfonic acid, and PPTS as catalysts, resulting in exceptionally low yields (<40%) with decomposition of starting material. Repeated addition of reagents or the use of longer reaction times (>12 h) to drive the reaction to completion resulted in more extensive decomposition of the acid sensitive substrate **82**. Fortunately, an effective solution to this problem was reached when a Lewis acid catalyst $BF_3{\cdot}Et_2O$ was used. Reaction of hydroxy-ketone **85** with PMB-trichloroacetimidate in presence of 15 mol% of $BF_3{\cdot}Et_2O$ at −78

˚C provided the PMB-protected product **105** cleanly within 4 h in 90% yield (Scheme 14).[40] Using $BF_3{\cdot}Et_2O$ in combination with the lower reaction temperature of −78 ˚C instead of ambient temperature which was necessary in reaction with the Brønsted acids, prevented decomposition of the acid-sensitive β-hydroxy ketone substrate under the reaction conditions and allowed its efficient conversion to the product.

Scheme 14. Synthesis of ketone **105**



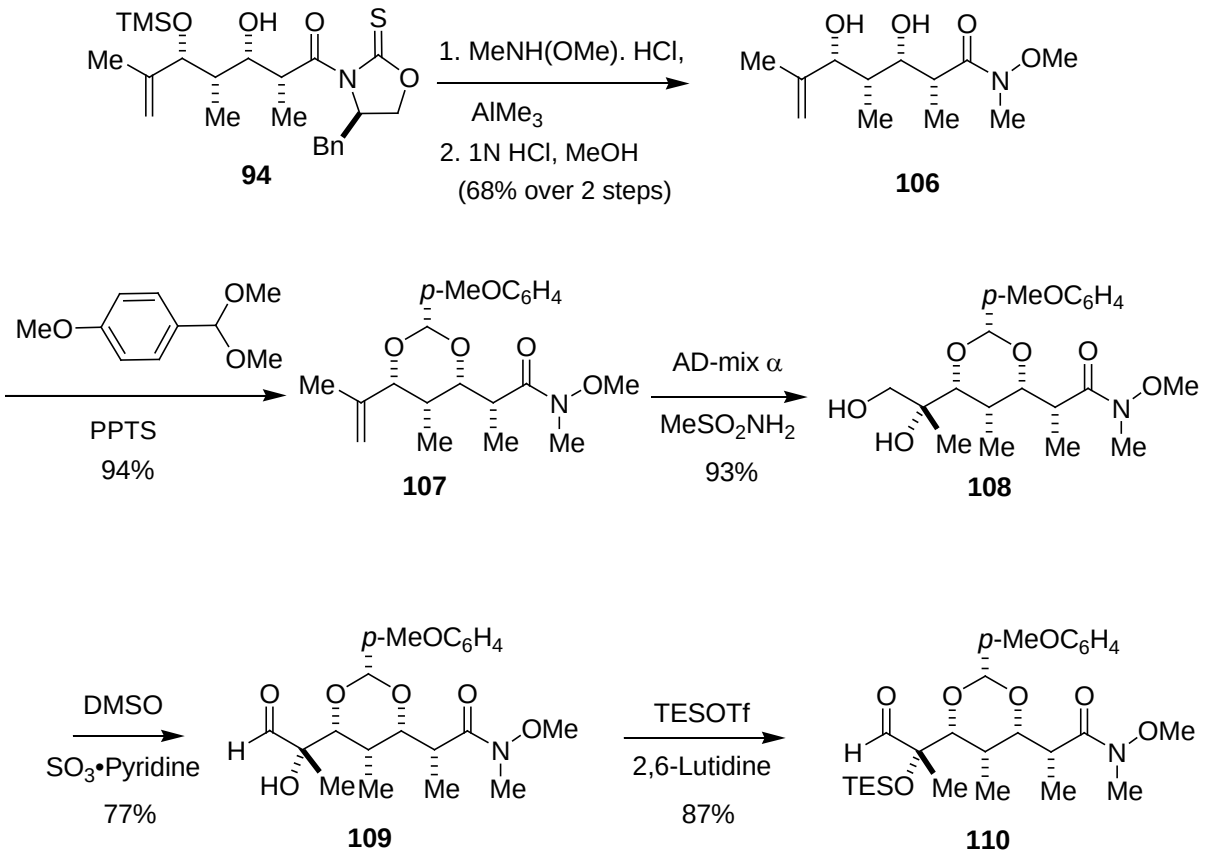
3.1.3 Synthesis of Aldehyde 110

With the synthesis of the ketone fragment **105** in place, the next goal was to synthesize the aldehyde coupling partner **104**. Synthesis of the aldehyde fragment **110** commenced from the common intermediate **94** prepared during the synthesis of epoxide fragment **99**. Conversion of imide **94** to the corresponding Weinreb amide by treatment with *N*, *O*-dimethylhydroxylamine hydrochloride and Me_3Al, followed by removal of the TMS group (1N HCl, 68% over two steps) provided the diol **106**. Protecting the C_3/C_5 hydroxyl groups in **106** with the PMP acetal protecting group using *p*-anisaldehyde dimethylacetal and a catalytic amount of PPTS provided **107** in 94% yield. Upon subjecting **107** to Sharpless asymmetric dihydroxylation with AD-mix

[40] Li, D. R.; Zhang, D-H.; Sun, C-Y.; Zhang, J-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W-S.; Lin, G-Q. *Chem. Eur. J.* **2006**, *12*, 1185-1204.

α, diol **108** was produced in 93% yield and as a single diastereomer. Oxidizing the resulting primary alcohol was initially attempted with Dess-Martin periodinane[41] but a 60:40 mixture of the aldehyde and the methyl ketone resulting from cleavage of the diol, was obtained. However, under SO_3-pyridine-DMSO[42] conditions, the desired aldehyde **109** was obtained as the sole product (93%). The free tertiary alcohol α to the aldehyde carbonyl was then protected with a triethylsilyl (TES) group to yield aldehyde **110** (87%), completing the synthesis of the aldehyde fragment (Scheme 15).

Scheme 15. Synthesis of aldehyde **110**



[41] Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155-4156.
[42] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

3.1.4 The Problem of Diastereoselectivity in the Aldol Coupling

With the requisite streocenters established in the ketone and aldehyde fragments **105** and **110,** respectively, the next goal was to unite the the two fragments in a highly convergent aldol bond construction. Due to the large amount of existing literature on aldol bond construction using *Z*(O)-enolates, our preliminary preference was a *Z*(O)-enolate mediated aldol reaction to couple **105** and **110**. The projected coupling reaction would thus be a *syn* aldol construction. The reaction should be double diastereodifferentiating[43] in nature with both partners being chiral and must result in an *anti* relationship between the C_8 and C_{10} methyl groups as shown in Figure 23.

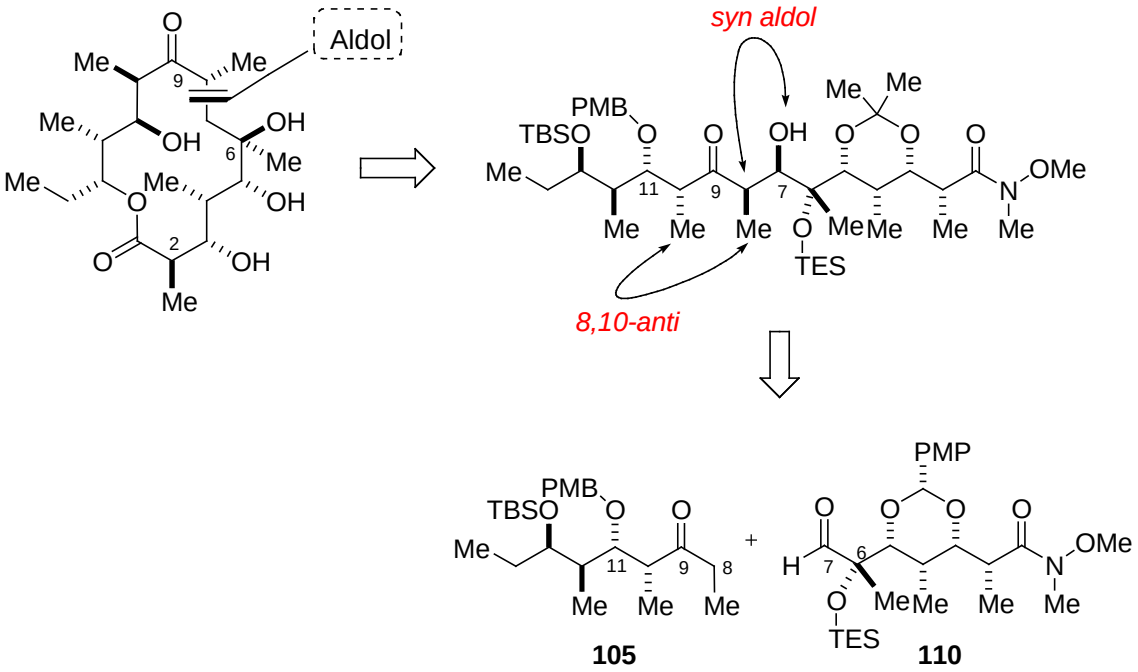


Figure 23. The projected fragment coupling and the requisite stereochemistries

[43] Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151-4157.

A C_7-C_8 aldol bond disconnection has been precedented in Evans' synthesis of 6-deoxyerythronolide B where the C_7-C_8 bond was formed in the key fragment coupling step between aldehyde **111** and enol silane **112** via a BF_3-mediated double-diastereodifferentiating Mukaiyama aldol reaction (Scheme 16). While adopting the C_7-C_8 aldol bond construction for the fragment coupling, we were aware that the major uncertainty associated with the successful execution of this reaction concerned the influence that the chiral partners might have on the stereochemical outcome of this double diastereodifferentiating process. In the aldol reaction between two complex fragments, it has often been found that the high facial selectivity associated with the enolates of chiral ketones provides the controlling influence.[44] Frequently both the selection of the metal in the enolate, and the protecting groups on the adjacent alkoxides has significant effect on the stereochemical course of the aldol reaction. In order to obtain useful levels of stereoselectivities in substrate-controlled aldol couplings involving α-methyl aldehydes, it is usually necessary to impart stereocontrol from the enolate, as the asymmetric induction from the chiral aldehyde alone is insufficient. Although α-methyl aldehydes exhibit high diastereofacial preferences in Mukaiyama aldol reactions with enol silanes,[6b] addition of other metal enolates such as Ti, B, Sn and Li show considerable variability.[45]

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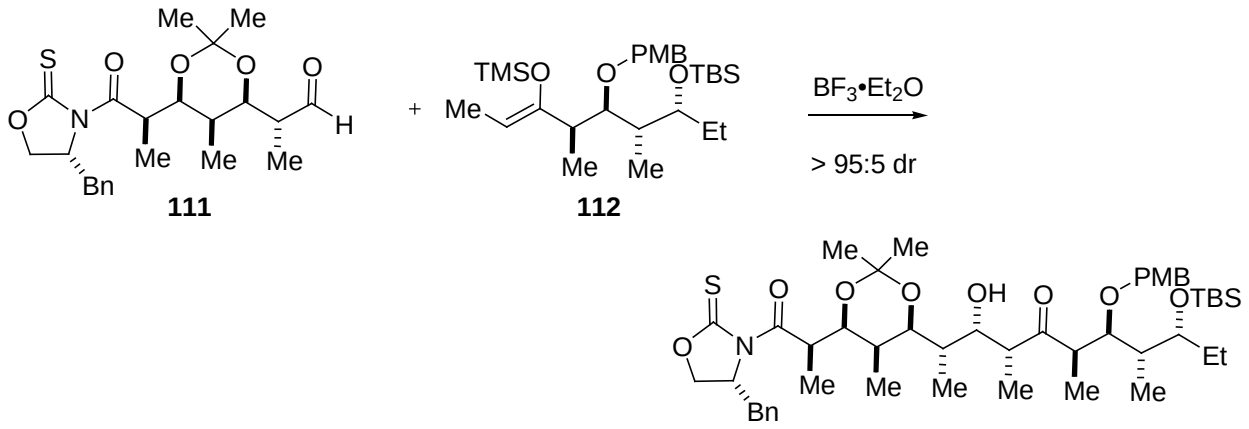
[44] For selected references of aldol additions of chiral ethyl ketones in polypropionates, see: (a) McCarthy, P.; Kageyama, M. *J. Org. Chem.* **1987**, 52, 4681-4686. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049. (c) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447-3450. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073-9074. (e) Martin, S. F.; Lee, W-C. *Tetrahedron Lett.* **1993**, *34*, 2711-2714.

[45] Arikan, F.; Li, J.; Menche, D. *Org. Lett.* **2008**, *10*, 3521-3524.

Scheme 16. Evans' C_7-C_8 Mukaiyama aldol coupling for 6-deoxyerythronolide B



The aldehyde partner in our synthesis is an α-tertiary alkoxy aldehyde and complex aldol reactions of such aldehyde substrates with chiral ethyl ketones are rare in the literature. As a result, in order to gain an idea about the type of reaction conditions to be employed for obtaining the desired stereoselectivities (choosing out of the wide variety of aldol reaction conditions available), we performed a preliminary survey of the literature. Aldol reactions of chiral α-methyl and α-methyl-β-alkoxy aldehyde substrates are the most common.[44a-d] The reaction of α-methyl aldehydes **113** with achiral *E*-enolates usually gives adducts **114** predicted by Felkin-Anh model whereas additions to achiral *Z*-boron, lithium and titanium enolates exhibit *anti*-Felkin facial selectivity, providing **115**, with an increase in selectivity observed for larger R.[43] In the chair transition state model for the *Z*-enolate leading to the unobserved Felkin product **116**, the methyl groups on the enolate and the aldehyde undergo a disfavoring *syn*-pentane interaction which is removed when the aldehyde reacts via the *anti* Felkin face. Thus the *anti*-Felkin *syn* aldol diastereomer **115** is commonly formed as the major product from *Z*(*O*)-enolates when α-methyl aldehydes are used (Figure 24).[43]

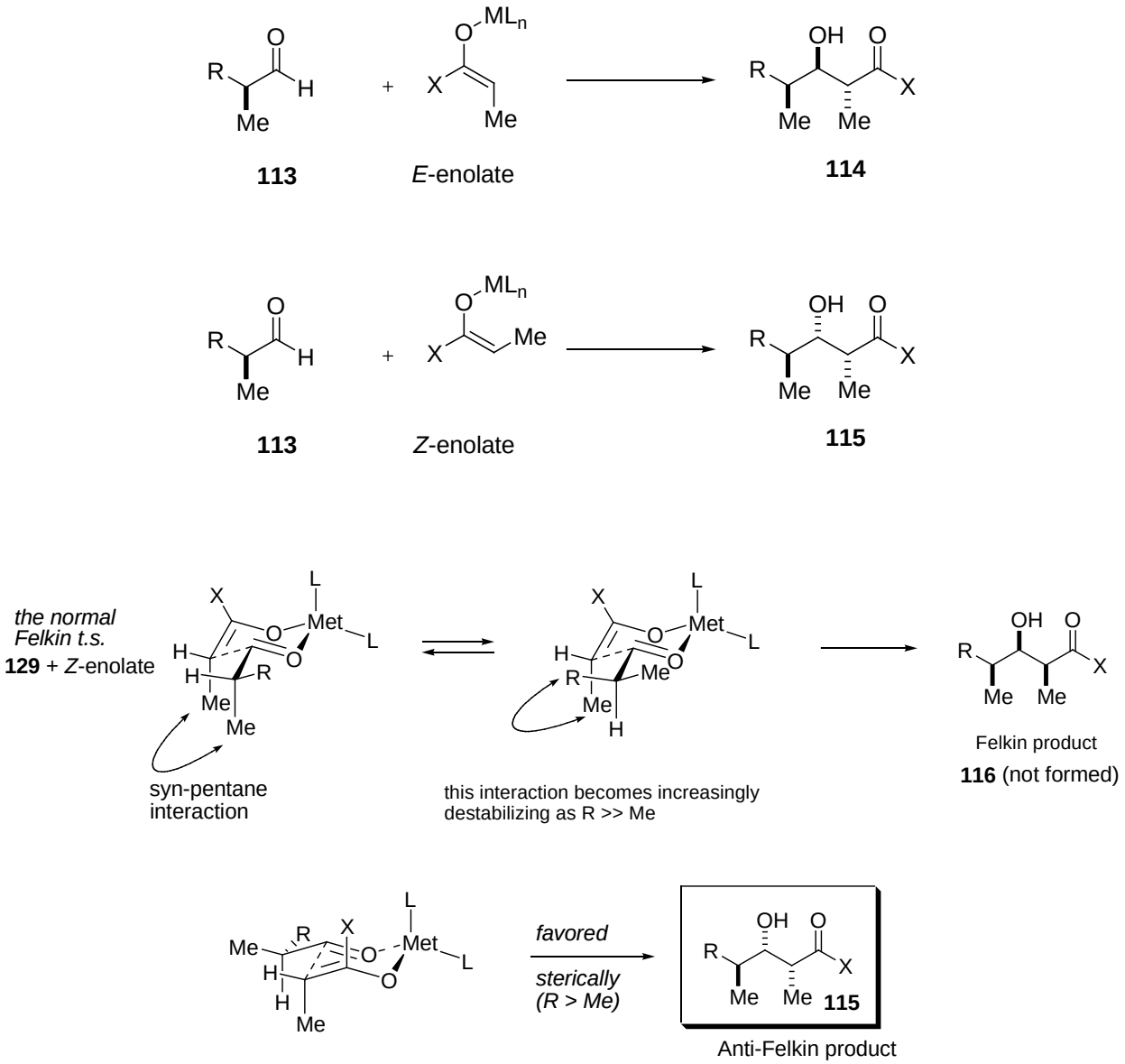
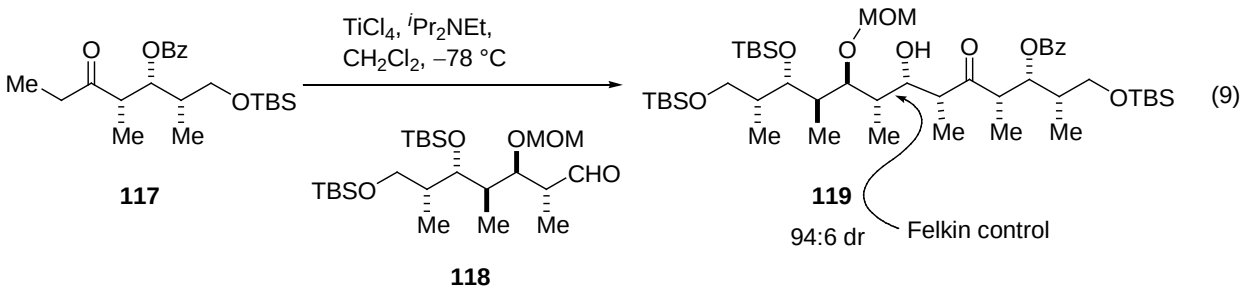


Figure 24. Roush's model for explaining the *anti*-Felkin preference of α-methyl aldehydes with *Z*-enolates

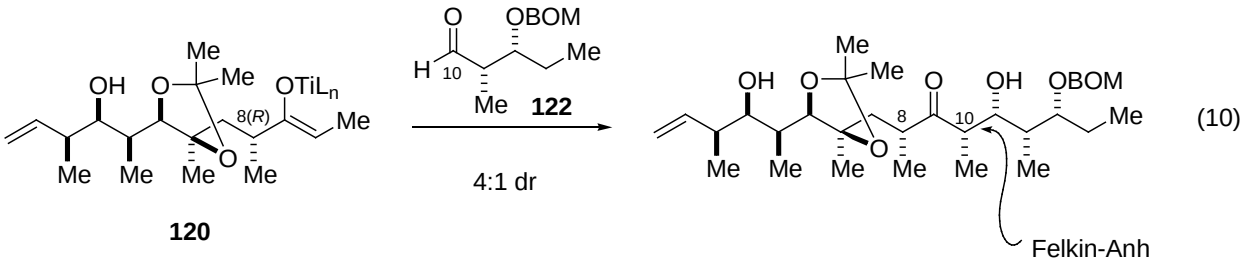
High *anti*-Felkin selectivity is also observed in the reactions of α-methyl-β-alkoxy aldehydes (similar to α-methyl aldehydes) with achiral *Z*-enolates. However, in reactions with "chiral" *Z*-enolates this intrinsic *anti*-Felkin bias of the aldehyde is overridden by the high π-facial selectivity of the enolate. For example the aldol reaction of the *Z*-chlorotitanium enolate derived from the chiral ethyl ketone **117** (structurally related to our ketone **105**) and chiral

aldehyde **118**, provided the Felkin aldol adduct **119** as the major diastereomer. (94:6 Felkin/*anti*-Felkin) (eq 9).[44c]

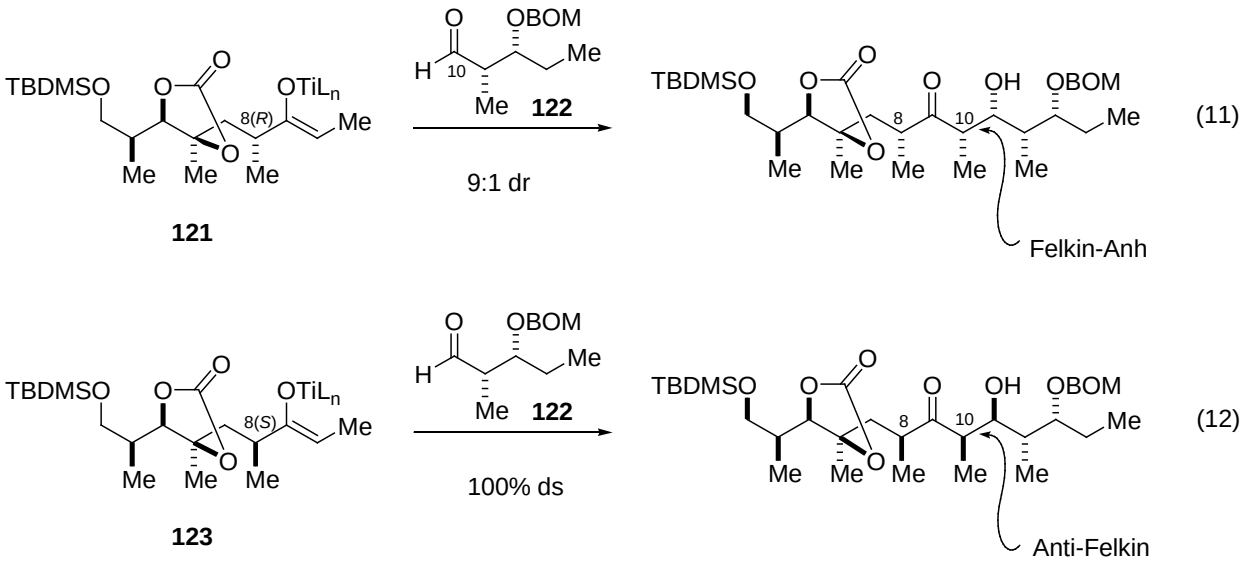


(9)

In three additional related examples from Martin's studies on erythromycin B synthesis,[44e] the titanium enolates **120** and **121** underwent Felkin-selective aldol reactions with aldehyde **122** (eqs 10, 11). In contrast, the ketone **123** with inverted configuration at α-methyl center relative to **120** and **121**, upon reaction with the same aldehyde, produced the *anti*-Felkin aldol adduct as the only diastereomer (eq 12). These results clearly illustrated that in the reactions of the titanium enolates, the stereochemical outcome was controlled by the ketone partner.



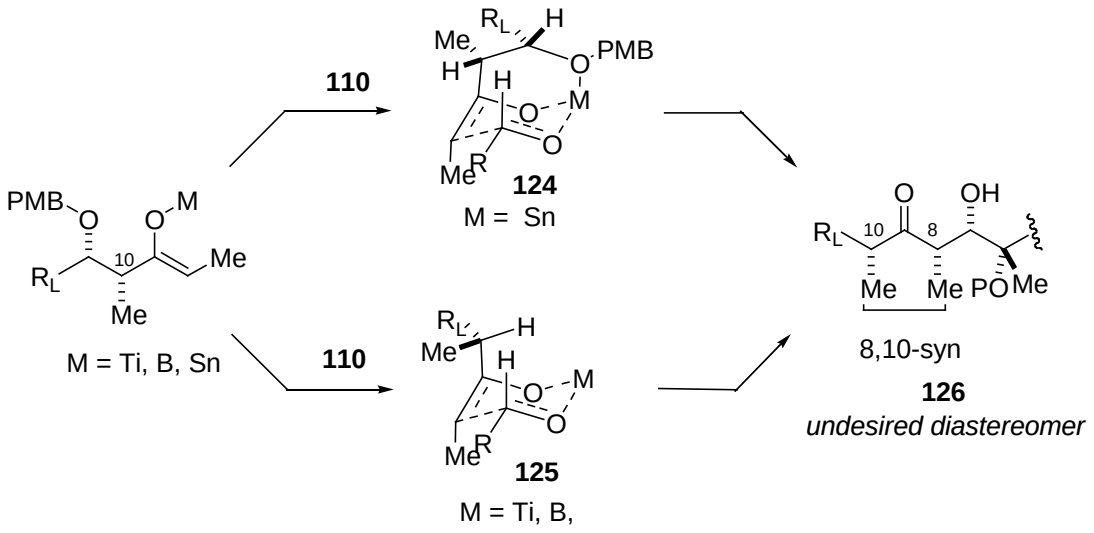
(10)



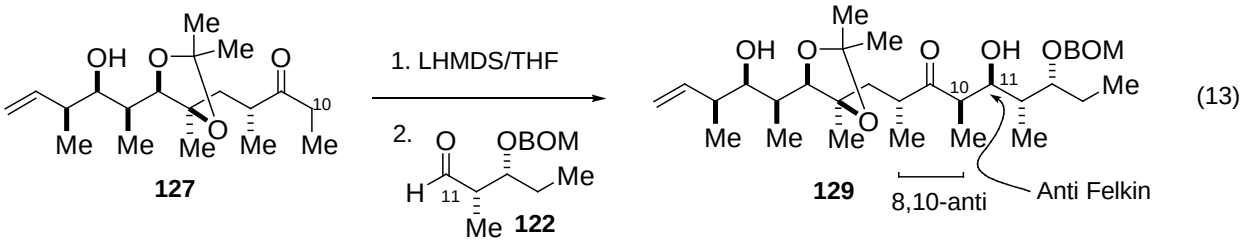
According to the aldol transition state models **124** and **125,** proposed by Paterson (tin enolates)[46] and Evans (for titanium and boron enolates)[47] respectively, it was anticipated that in our system, the ketone would exert the controlling influence and direct attack on the *Si* face of the aldehyde (**110)** leading to the undesired diastereomer **126** where the required 8,10-*anti* relationship was not satisfied (Scheme 17). Thus, the chiral elements in the aldehyde and enolate fragments of our projected aldol coupling reaction were stereochemically "mismatched" in the desired bond construction for Ti, B or Sn enolates because such enolates would exert the controlling influence. In such scenario there were two ways in which the desired diastereoselectivity could be obtained: (1) if the aldehyde exerted very strong Felkin bias; and/or (2) if the enolate facial selectivity was substantially lower than the aldehyde.

[46] Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233-4236.
[47] Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047-1049.

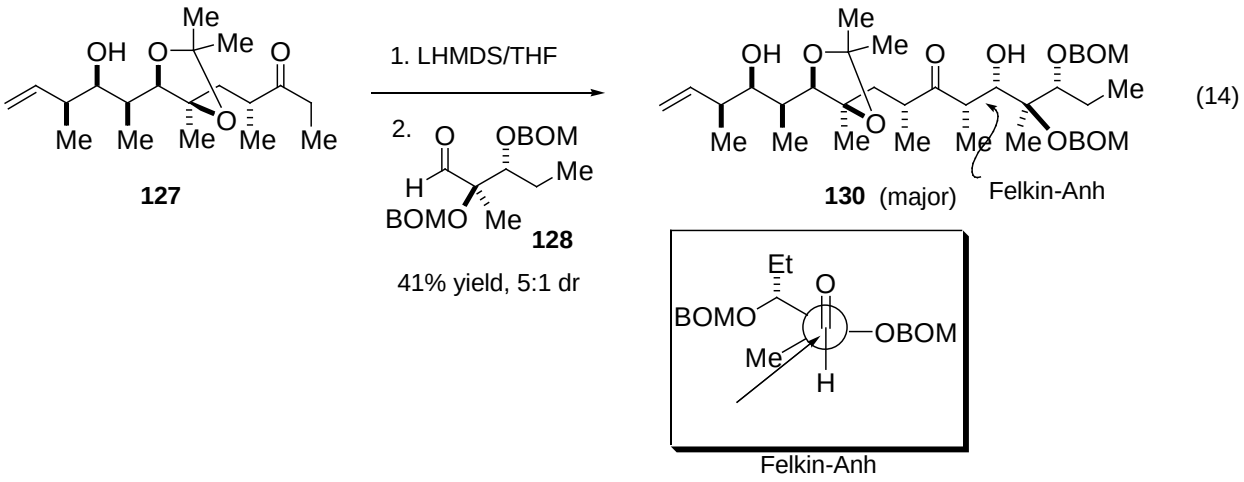
Scheme 17. Expected formation of undesired 8,10-*syn* relationship with Ti, B and Sn enolates



α-Alkoxy aldehydes are expected to possess very strong intrinsic Felkin-bias in their reactions with nucleophiles, much stronger than that of α-methyl aldehydes due to the presence of the heteroatom. Although there are no well known models to predict the selectivities of aldol reactions of α-tertiary alkoxy aldehydes, we were encouraged by the following results obtained by Martin in his erythromycin A synthesis. The reaction of lithium enolate of the chiral ethyl ketone **127** ketone with the α-methyl aldehyde **122** (eq 13) provided the aldol adduct **129** with opposite diastereoselectivity (*anti*-Felkin) compared to the titanium enolate reaction in eq 10. To explain the change in distereoselectivity on going from Ti to Li, the authors suggested that in the lithium enolate aldol, the chirality of the aldehyde became the dominant controlling element and a different transition state was operative. When the α-tertiary alkoxy aldehyde **128** was used in the aldol reaction with the Li-enolate of the same ketone, the stereoisomer **130** predicted by Felkin-Anh model was produced (eq 14).

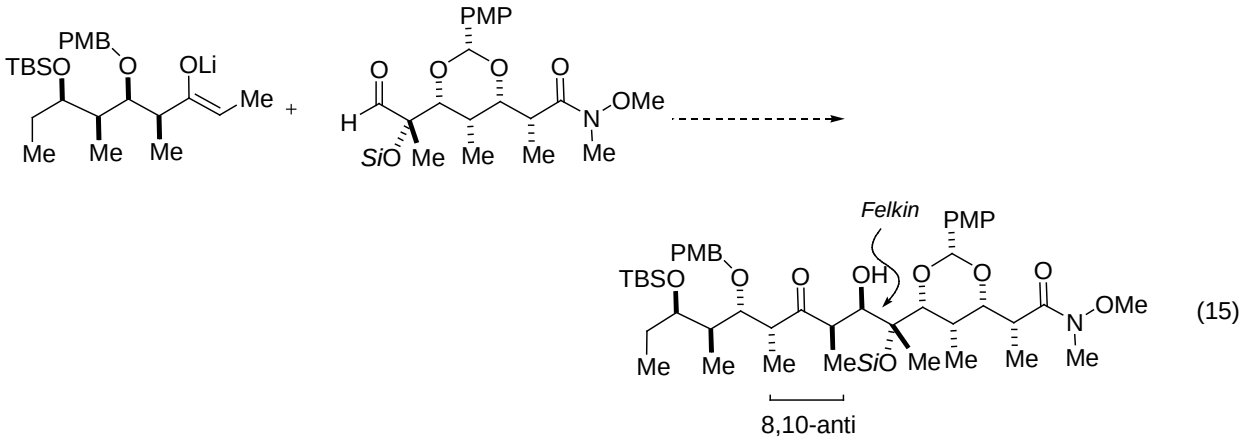


(13)



(14)

The result of the aldol reaction of **127** with the α-tertiary alkoxy aldehyde **128** suggested that the aldehyde possessed a strong intrinsic preference for Felkin selection. In this system the preference of the ketone reinforced the Felkin bias of the aldehyde in leading to the *syn* relationship of the methyl groups across the carbonyl. However, in our system the aldehyde Felkin bias would have to override the ketone's anti-facial selectivity in order to obtain the desired 8,10-*anti* stereochemistry in the coupled product (eq 15).



(15)

A very recent study by Menche and co-workers compared the effect of various metal enolate counterions (Ti, Sn, B and Li) on the diastereoselectivity in the aldol reactions of ethyl ketones **131** and **132** with α-methyl aldehyde **133**. The results clearly demonstrated that out of all the *Z*-enolate forming metals, only Li-enolates allow the aldehyde's preferred *anti*-Felkin addition (products **134** and **135**) whereas Ti and Sn enolates exhibit dominant controlling influences in the aldol additions giving the Felkin addition products **136** and **137**, respectively, as the major products (Figure 25).[45] In view of the above results, it appeared that a possibility of overriding the intrinsic facial bias of the ketone (for producing the undesired 8,10-*syn* relationship) existed if Li was used as the enolate-counterion. In that case, the aldehyde control would dominate and result in the requisite 8,10-*anti* stereochemistry.

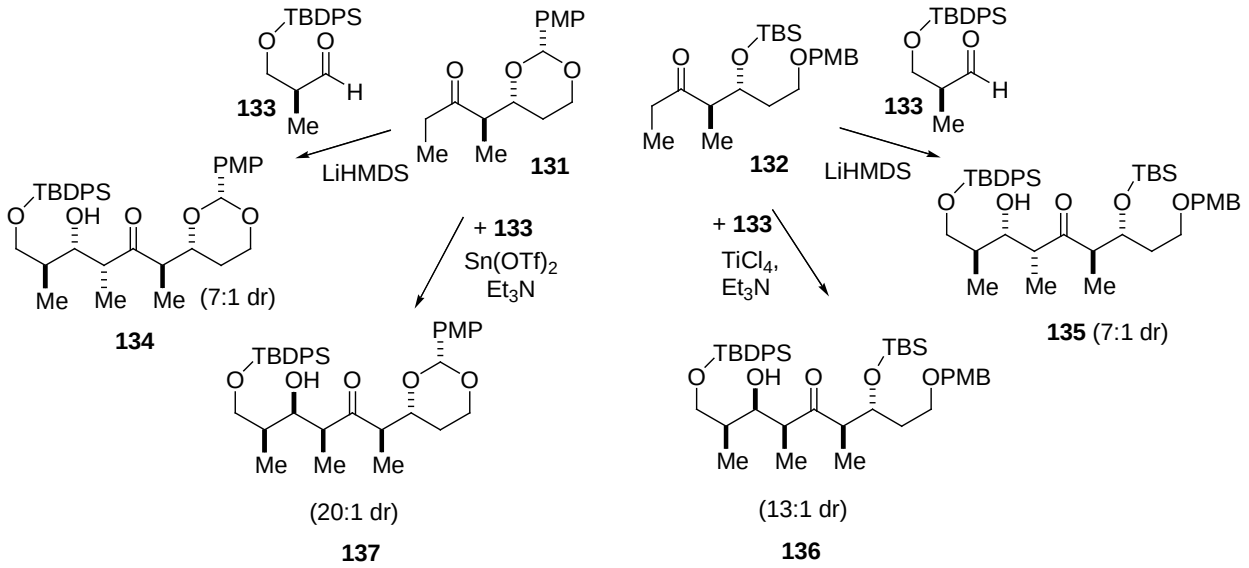


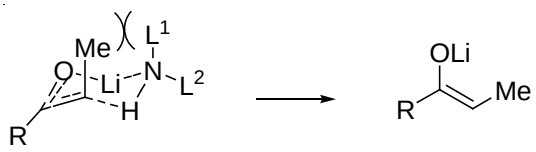
Figure 25. Metal-dependent aldol diastereoselectivities of Z-enolates

3.1.5 Enolization of Ketone 105

For ketone enolization the LiHMDS/THF system usually results in the formation of the kinetic *Z*-enolate.[48] In the Ireland transition state model **138** for the formation of *Z*-enolate, despite the nearly equal A values for TMS (2.5) and the ^{i}Pr (2.2) group, LHMDS (L^1 = TMS) gives better Z-selectivities compared to LDA (L^1 = ^{i}Pr) (Figure 26). An interesting observation was made by Masamune[49] who showed that the use of the highly hindered base lithium bis-(dimethylphenyl)silazide **139**, led to exclusive formation of the *Z*-enolate (*Z*:*E* > 99:1) from ethyl cyclohexyl ketone. To explain why *Z*-enolate is more favored by lithium disilylamides [such as LHMDS and lithium bis-(dimethylphenyl)silazide] than lithium dialkylamides (such as LDA),

[48] (a) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362-3379. (b) Bohlmann, F.; Arndt, C.; Starnick, J. *Tetrahedron Lett.* **1963**, *4*, 1605-1610. (c) House, H. O.; Gall, C. M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324-2336. (d) Munchhof, M. J.; Heathcock, C. J. *Tetrahedron Lett.* **1992**, *33*, 8005-8006. (e) Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Org. Chem.* **1997**, *62*, 7516-7519.
[49] Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526-5528.

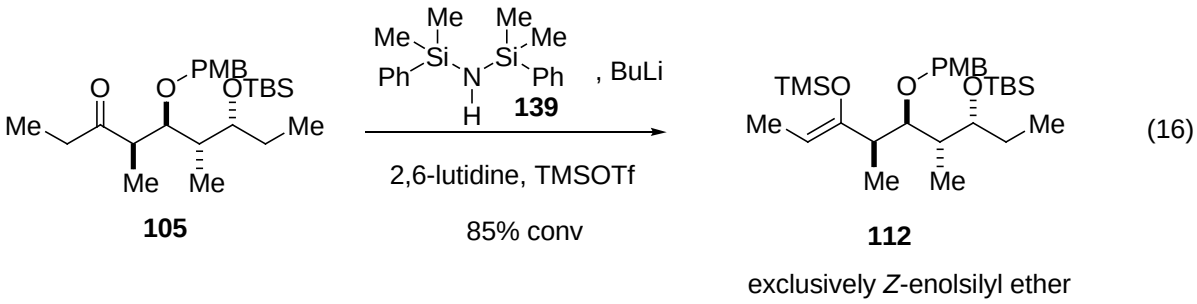
the Xie group undertook a detailed study of the steric vs. electronic effects of the base in controlling ketone enolization geometry and concluded that the electronic nature of the base is also a dominant factor in the enolization.[50] Replacing both isopropyl groups in LDA with electron-withdrawing TMS groups significantly reduces the electron density (and the basicity) on the nitrogen in LHMDS. As a result, the electrostatic interaction between the less basic nitrogen and the lithium ion and the proton in the transition state **138** is much weaker, leading to a later transition state. Consequently, the Me↔L^1 interaction is significantly weakened and the transition state leading to the *Z*-enolate is favored. Similarly introducing a phenyl group on the silicon makes the nitrogen in lithium bis-(dimethylphenyl)silazide even less basic which explains the high selectivities for *Z*-enolate formation with this bulky base. Accordingly, we used the base **139** for enolization of **105**. In order to determine the enolate geometry, the resulting enolate from **105** was trapped with trimethylsilyl trifluoromethanesulfonate (TMSOTf) at 0 °C to give the corresponding *Z*-enol silane **112** exclusively (eq 16).[6b]



138 *Z-enolate*

Figure 26. Ireland transition state leading to Z-enolate

[50] Xie, L.; Isenberger, K. M.; Held, G.; Dahl, L. M. *J. Org. Chem.* **1997**, *62*, 7516-7519.

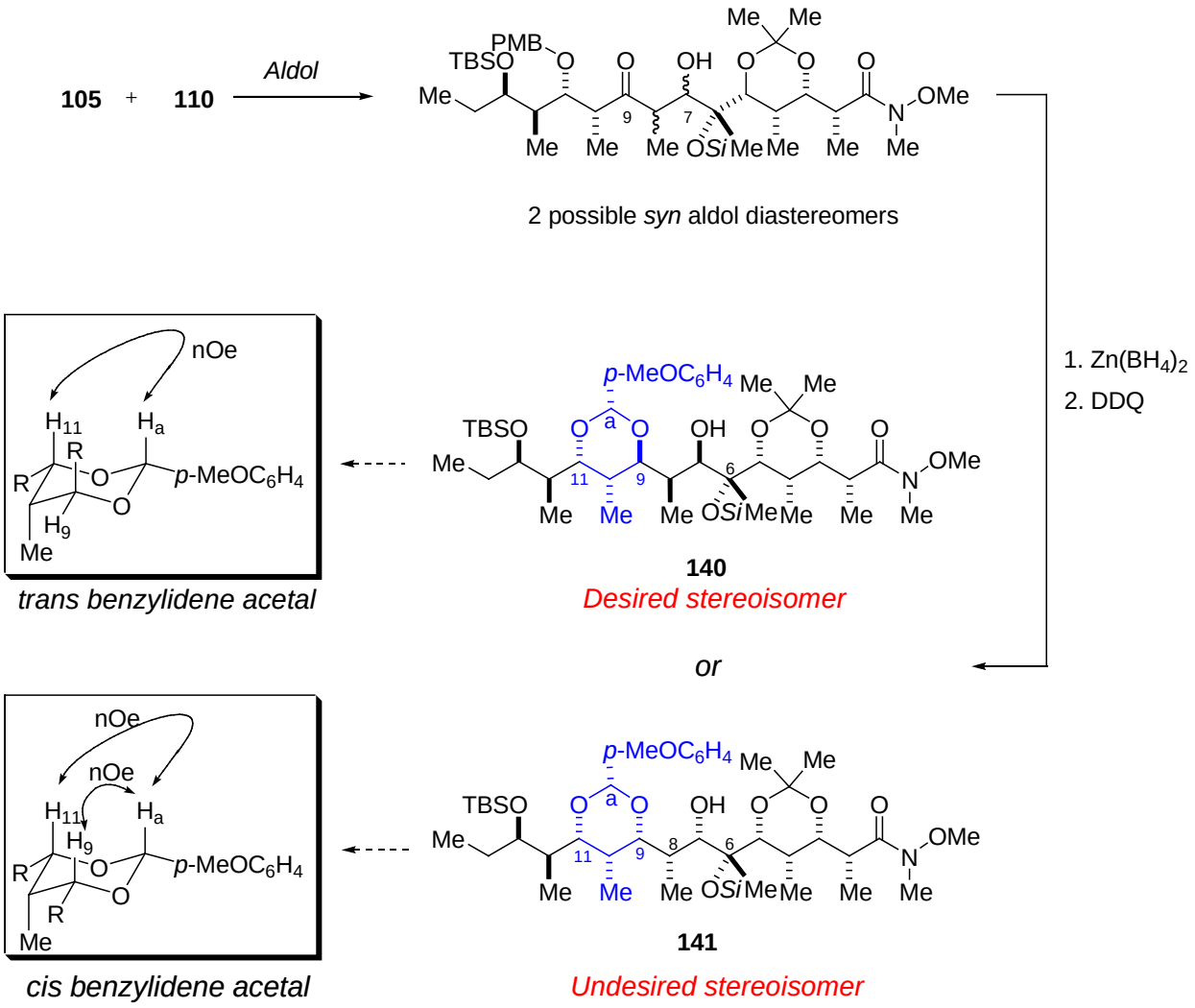


3.1.6 Strategy for Assigning Stereochemistries in the Aldol Products

With a high *Z*:*E* enolate geometry established for ketone **105**, the next goal was to engage the enolate in a *syn*-selective aldol coupling reaction with aldehyde **110**. In order to determine the relative and absolute stereochemistries at the C_7 and C_8 centers that would be newly created in this aldol coupling reaction, the following strategy was designed (Scheme 18). After the aldol coupling between **105** and **110**, a chelating metal hydride reduction of the C_9 ketone in the resulting aldol adduct would be performed using $Zn(BH_4)_2$ to give the corresponding C_9-alcohol having the same stereochemistry as the directing C_7 hydroxyl. Next the C_{11}-PMB protecting group would be converted to the cyclic *p*-methoxybenzylidene (PMP)-acetal protecting group under oxidative DDQ conditions to provide the bezylidine acetal **140** or **141**. The cyclic *p*-methoxybenzilidene acetal moiety on the C_9 and C_{11} hydroxyls would exist in the chair form and the stereochemistry of the substituents on the chair would be easily determined from nOe correlations. Depending on the stereochemistry of the C_9 hydroxyl and hence the C_7 hydroxyl resulting from aldol, either a cis or a trans acetal ring would be formed. In the desired stereoisomer **140**, the *p*-methoxybezylidine acetal ring would be trans, and the acetal proton would show only one nOe correlation with H_{11}. In the undesired stereoisomer **141** resulting from the wrong *syn* aldol adduct, the *p*-methoxybezylidine acetal would be cis and the acetal proton in

this isomer would show correlations with both H_9 and H_{11}. Thus the stereochemistries at the C_7 and C_8 centers resulting from the aldol reaction would be easily determined.

Scheme 18. Strategy for assignment of aldol stereochemistry



3.1.7 Aldol Coupling of Fragments 105 and 110

With fragments **105** and **110** in place, the aldol fragment coupling reaction was attempted. The lithiated base was first generated from (dimethylphenyl)disilazide **139** and ^{n}BuLi at 0 ˚C

followed by addition of ketone at −78 ˚C to generate the lithium enolate. The resulting solution was allowed to warm to 0 ˚C for an hour before it was recooled to −78 ˚C and aldehyde **110** was added. The reaction worked cleanly providing a single diastereomer of a new product. However the mysterious absence of a keto signal in the ^{13}C NMR of this new compound and the presence of two distinct signals instead of one, in the range of 95-105 ppm led us to suspect that the ketone had probably undergone hemiketal formation under the reaction conditions. Based on this assumption, we considered the formation of hemiketal **142** in the reaction (Figure 27).

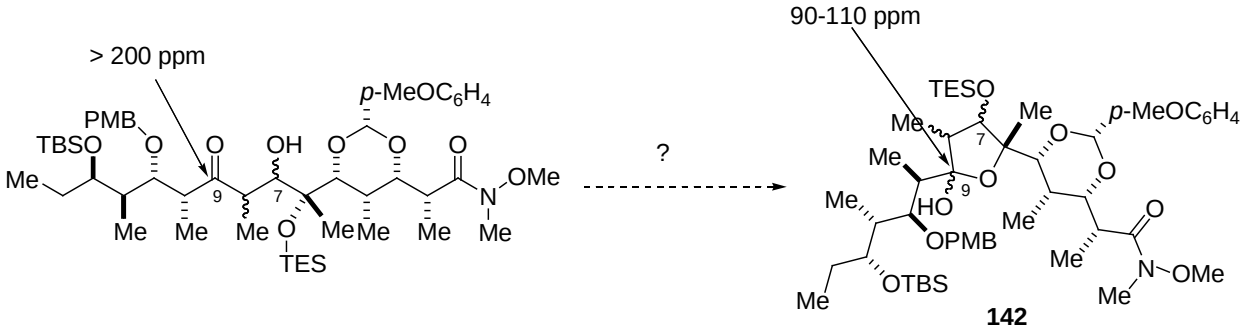
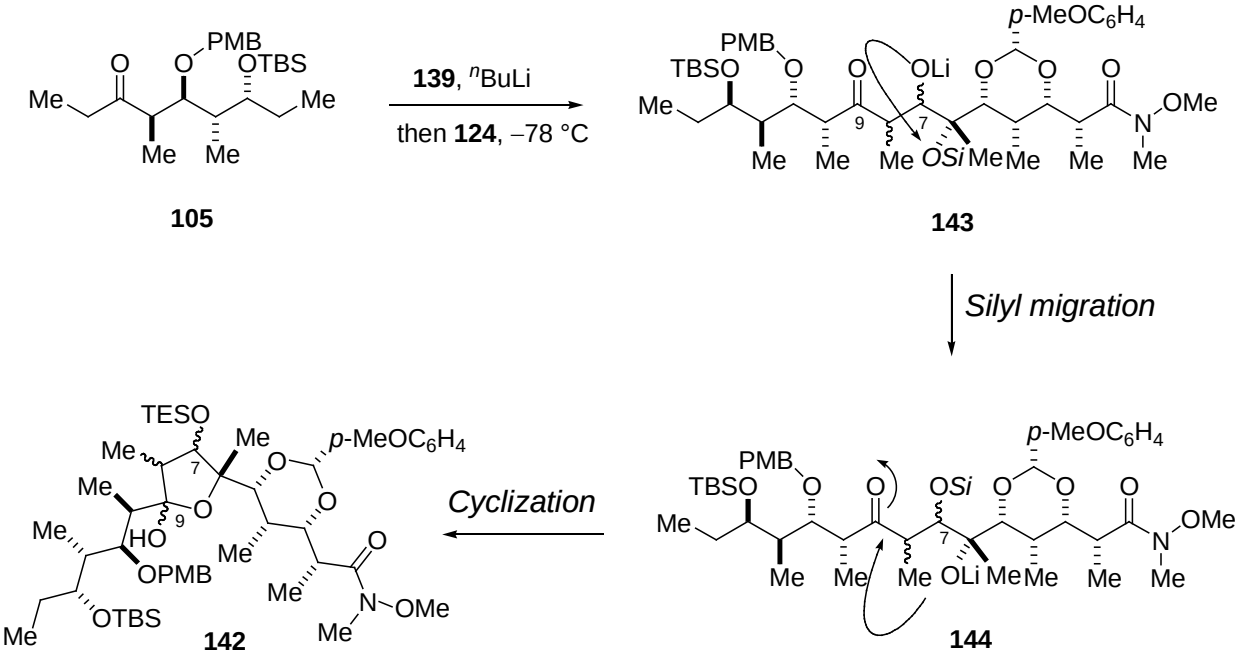


Figure 27. Hemi-ketal formation to explain the absence of the keto signal and presence of an extra acetal signal in ^{13}C NMR of aldol adduct

Formation of hemiketal **142** could occur if the lithium alkoxide **143** generated by the aldol reaction triggered a 1,4-migration of the triethylsilyl group from the C_6-tertiary alcohol to the adjacent secondary C_7 alcohol center of the aldol adduct to produce **144** (Scheme 19). Subsequent cyclization of this resulting C_6 lithium alkoxide intermediate **144,** on to the ketone carbonyl would then result in the formation of the five-membered hemiketal **142**. The migration of trialkylsilyl protecting groups (TBS, TBDPS, TIPS, TMS *etc.*) from oxygen to oxygen is a well-known phenomenon in organic chemistry. Usually, these rearrangements occur in a 1, 4 or

1, 5 fashion, and 1, *n* (n = 6–11 *etc.*) type silyl migration has also been observed.[51] The release of steric strain in going from **143** to **144** as well as the formation of a stable tetrahydrofuran ring provided an enhanced driving force for the reaction.

Scheme 19. Formation of cyclized product **142**



The structure of **142** was determined by detailed ^{1}H-COSY, HMQC and HMBC NMR analysis. Using ROESY correlations (Figure 28), the relative stereochemistries of the C_6-C_9 substituents on the tetrahydrofuran ring were determined. The stereochemistry of the C_6-tertiary alcohol center was used to determine the absolute stereochemistries of the remaining C_7-C_9 centers in the tetrahydrofuran ring of **142** which to our satisfaction, matched completely with the

[51] (a) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620-3622. (b) Yamazaki, T.; Mizutani, K.; Takeda, M.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1992**, 55-57. (c) Yamazaki, T.; Oniki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 11753-11762. (d) Rücker, C. *Chem. Rev.* **1995**, *95*, 1009-1064. (e) Zhao, Z. Q.; Peng, L. Z.; Li, Y. L. *Chin. Chem. Lett.* **2005**, *16*, 290-292.

respective stereochemistris in the desired open chain diastereomer **145** suggesting that the desired Felkin diastereoselection was obtained in the coupling reaction.

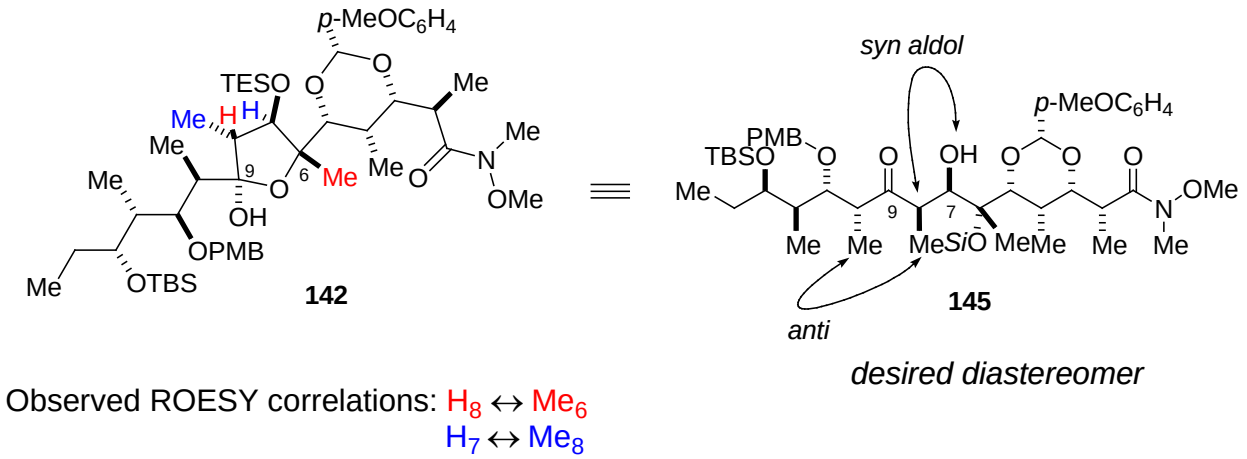
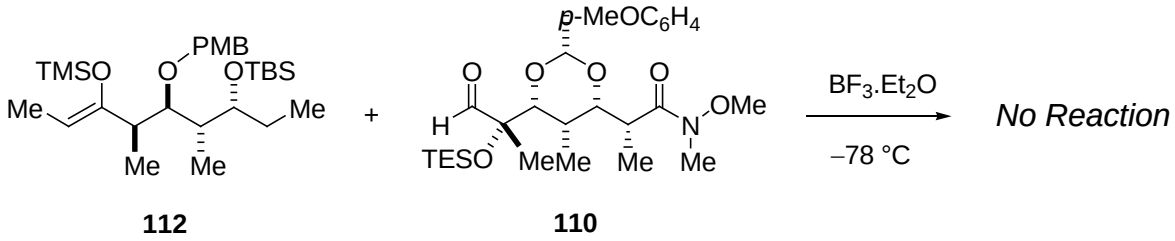


Figure 28. Determination of stereochemistry at C_6-C_9 by ROESY correlations and comparison with desired diastereomer

Despite the excellent Felkin selectivity achieved in the aldol coupling reaction between **105** and **110**, the irreversible cyclization of the lithium aldolate **143** to the tetrahydrofuran **142** posed a serious problem in its further elaboration toward erythronolide B synthesis. We believed that this problem could be solved by eliminating the triethylsilyl group on the C_6-hydroxyl and replacing it with a different protecting group that would not undergo transfer under the basic conditions of the aldol reaction. However, another point of concern in this aldol reaction was its low conversion and unfortunately, all attempts to improve the yield e.g. longer reaction times, increasing the overall concentration of the reaction or increasing the equivalents of the aldehyde were unsuccessful and the conversion remained in the modest 50-55% range. We also attempted a $BF_3{\cdot}Et_2O$ mediated Mukaiyama aldol reaction (see Scheme 16). When preformed enol silane **112** and aldehyde **110** were subjected to the Lewis acid, no reaction occurred at −78 ˚C and the starting materials were recovered intact (Scheme 20). The lack of reactivity was presumably

caused by the hindered quarternary center α to the reacting carbonyl in the aldehyde, as would be expected. We therefore continued with the lithium enolate aldol reaction. Our next goal was to stop the cyclization by using a non-migratory protecting group at C_6-OH.

Scheme 20. Attempted Mukaiyama aldol reaction



112 **110**

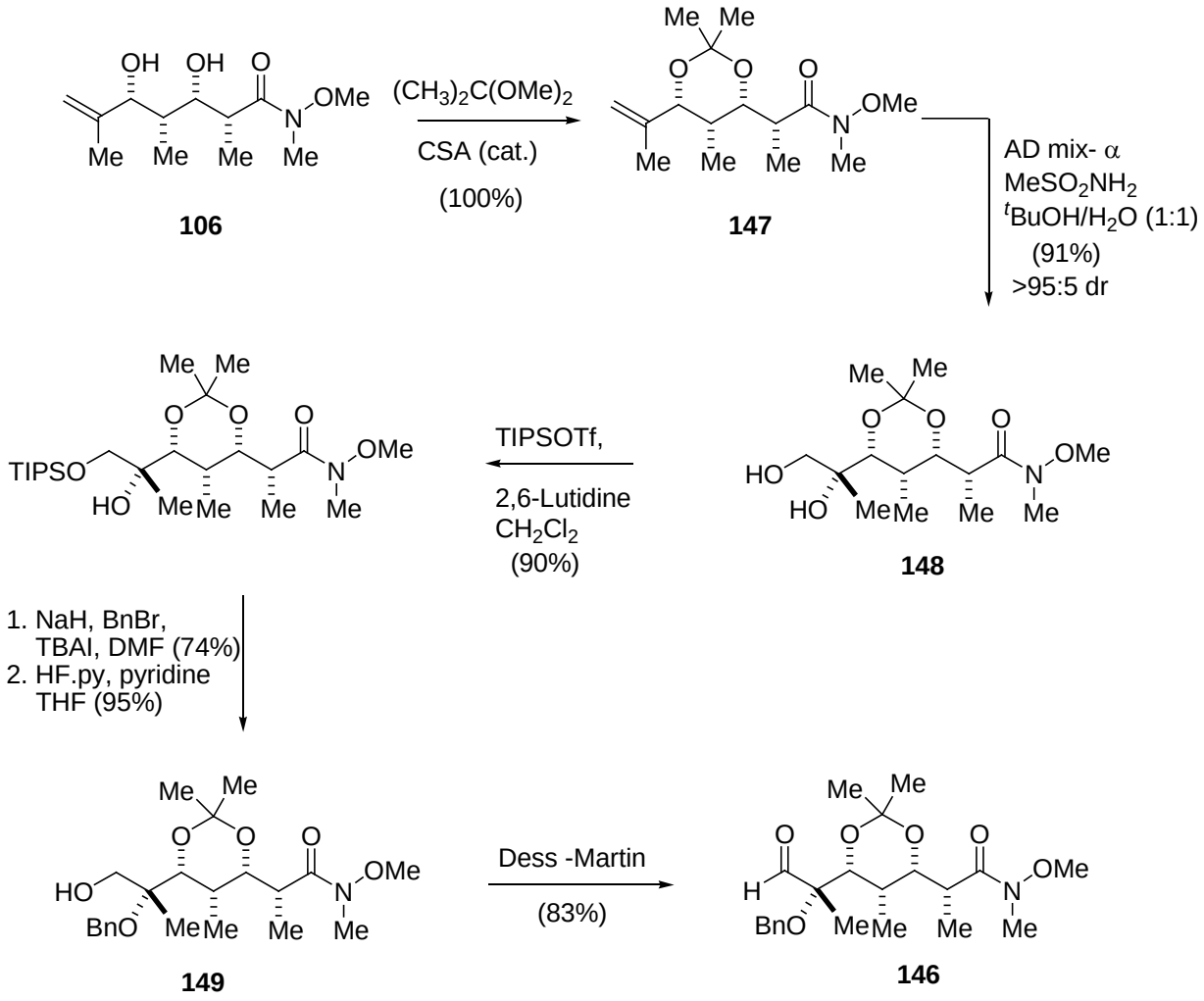
3.1.8 Change in Protecting Group on Aldehyde 110

We substituted the silyl protecting group on the C_6 hydroxyl in **110** with an alkyl protecting group such as benzyl in order to prevent in situ hemi-ketal formation by the lithium aldolate. The nature of protecting group on the α-hydroxyl center of a reacting aldehyde plays an important role in defining the diastereoselection of the aldol reaction. Based on Martin's precedent of erythromycin A synthesis (see eq 14) where they obtained Felkin diatereoselection in a related system, we proceeded to synthesize the benzyloxy group containing aldehyde **146** for the aldol coupling reaction.

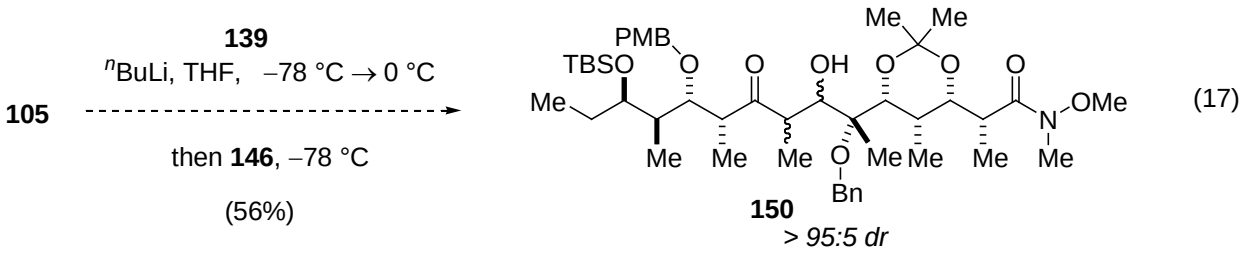
3.1.8.1 Synthesis of α-Benzyloxy Aldehyde 146 and the Aldol Coupling of Fragments 105 and 146

For the synthesis of α-benzyloxy aldehyde **146**, the diol **106** was first protected as the acetonide **147** (100%) and dihydroxylated with AD mix α to provide diol **148** in 91% yield and as a single diastereomer. The primary alcohol group in **148** was then selectively protected with a triisopropylsilyl (TIPS) group. This was followed by benzyl protection of the C_6 tertiary alcohol (74%) with NaH and BnBr in presence of *tert*-butyl ammonium iodide (TBAI). The sterically bulky TIPS protecting group on the C_7 primary hydroxyl group was necessary as the alternative TES and TBS groups were labile under the basic NaH conditions of the subsequent reaction and resulted in multiple product formation (both mono- and di-benzylated products were isolated). Deprotection of the TIPS group using HF.py provided **149** in 95% yield. Subsequent oxidation of the free alcohol with Dess-Martin's reagent provided the requisite aldehyde **146** in 83% yield (Scheme 21).

Scheme 21. Synthesis of α-benzyloxy aldehyde **146**



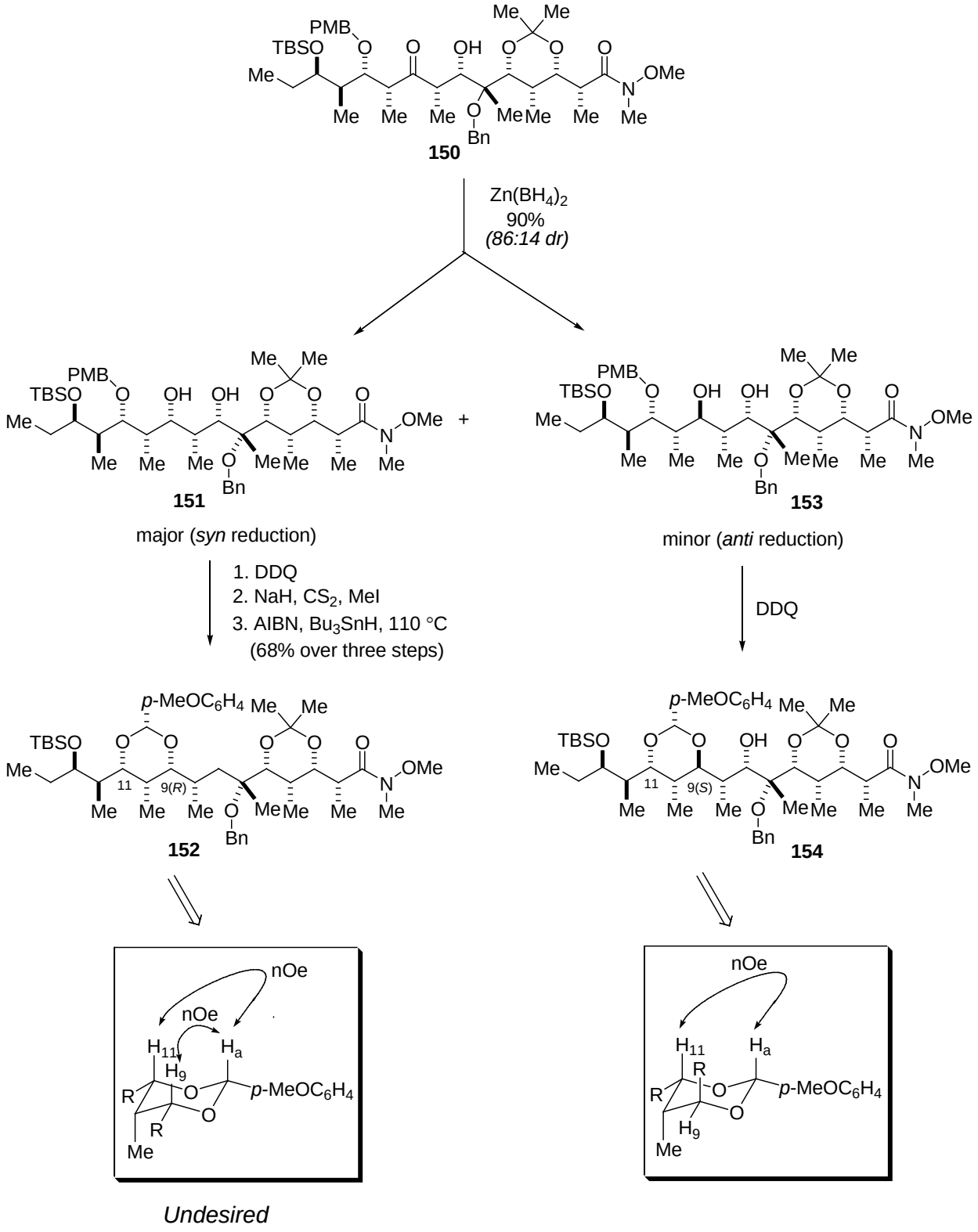
With aldehyde **146** in hand, the coupling reaction was attempted anticipating that the uncyclized aldol adduct would be obtained. Indeed, when **105** and **146** were subjected to the previously used aldol reaction conditions using **139** as the base, the acyclic aldol adduct **150** was obtained in excellent diastereoselectivity in 56% yield (Scheme 6). The absence of the hemiketal carbon signal in the ^{13}C NMR of the product along with the presence of a keto signal confirmed that the acyclic product was isolated. Incomplete conversion was observed once again and the product was isolated in 55% yield along with unreacted starting materials (eq 17).



3.1.8.2 Stereochemistry Determination of the Aldol Product

To determine the stereochemistries at the C_7 and C_8 centers generated in the aldol reaction (eq 17), the aldol adduct **150** was subjected to a *syn*-selective chelate controlled reduction of the C_9-ketone with $Zn(BH_4)_2$. The major product **151** (90% yield, 86:14 dr) was subjected next to oxidation with DDQ to provide the O_9/O_{11} *p*-methoxybenylidine acetal. The ^1H NMR of this compound contained overlapping peaks in the carbinol region, so in order to facilitate unambiguous structure analysis it was futher converted to the deoxygenated product **152** via Barton's deoxygenation protocol. In subsequent ROESY NMR analysis of **152**, the acetal proton H_a was, unexpectedly, found to show correlations with both H_9 and H_{11}, which suggested a *syn* relationship between the two hydroxyls at C_9/C_{11} and hence C_9-OH having the undesired (*R*)-stereochemistry. To be sure, the minor product of the $Zn(BH_4)_2$ reduction **153** was also converted to the corresponding cyclic acetal **154**, whose C_9/C_{11}–*anti* stereochemistry was similarly confirmed from ROESY NMR analysis which showed a single correlation of the acetal proton with C_{11}. A summary of the above results along with the observed ROESY correlations are outlined in Scheme 22 (stereochemistries of all compounds are drawn to represent the information obtained from the ROESY data of the homologous compounds **152** and **154**).

Scheme 22. Stereochemistry determination of aldol adduct **150**



To explain the selective formation of the *anti*-Felkin product **150** in the aldol reaction, Cram chelation of the α-benzyloxy substituent in the aldehyde **146** may be invoked (Figure 29), although this would be in disagreement with Martin's precedent where the Felkin diastereomer was formed as the major product.

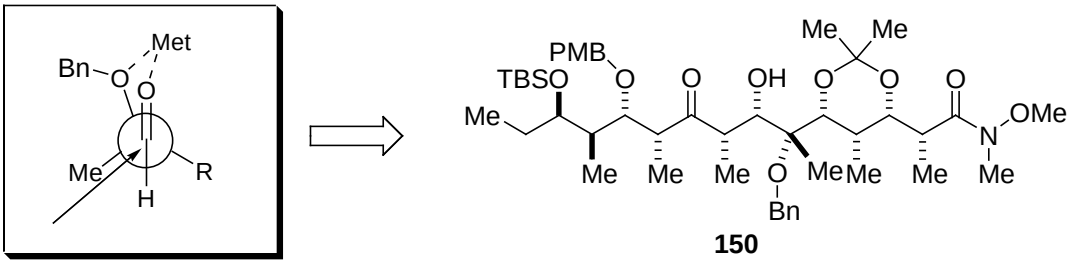


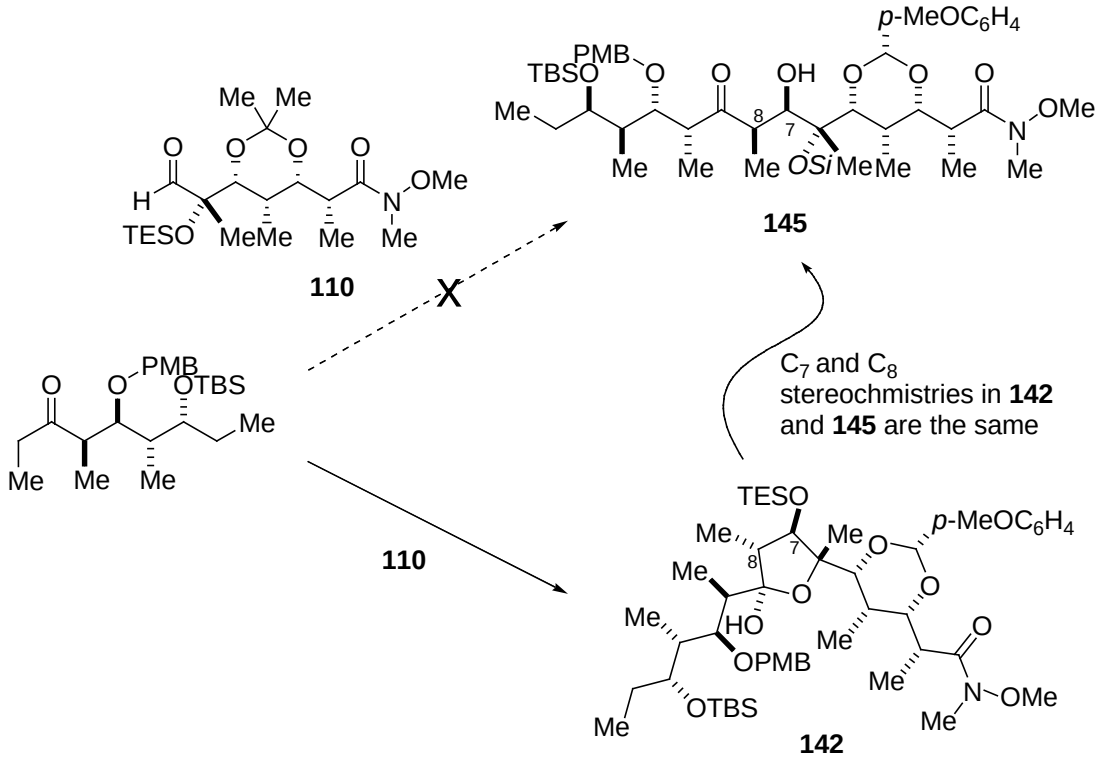
Figure 29. Possibility of Cram-chelation in transition state leading to **150**

3.1.9 The Aldolate-Ketalization Problem Revisited: Use of TBS Group

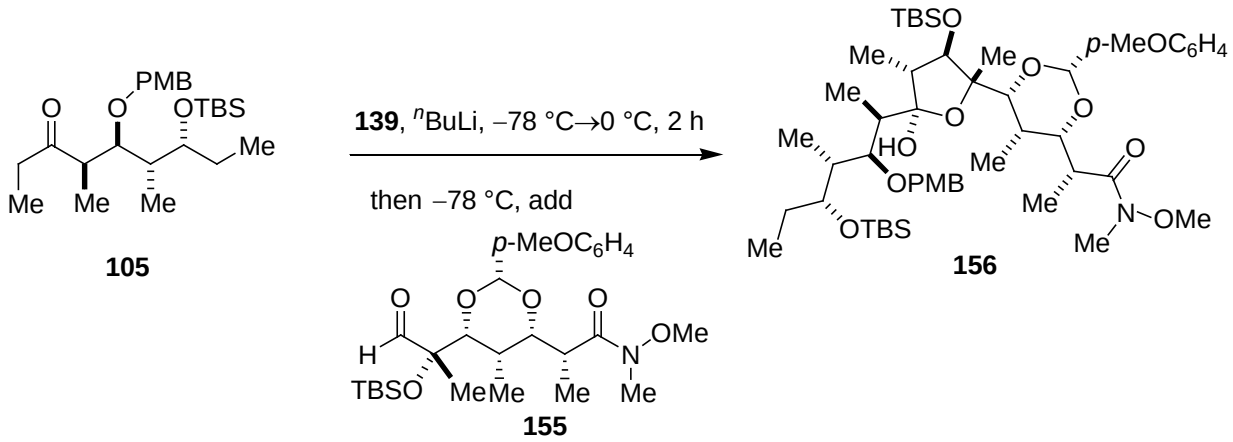
The undesired stereochemical outcome in the aldol reaction of ketone **105** with aldehyde **146** (eq 17) led us to return to the α-triethylsilyloxy aldehyde **110** which provided the desired Felkin selective aldol with competing hemi-ketal formation (Scheme 23). We began to search for a suitable modification that would prevent the unwanted cyclization in this system. We hypothesized that a more bulky silicon-based protecting group such as TBS or TIPS would alleviate attack of the C_7-alkoxide and prevent the silyl transfer process at low temperatures, as formation of the five-coordinated silicon species required in the transition state of such a process would become unfavorable due to steric crowding. To test this hypothesis, the α-*tert*-butylsilyoxy aldehyde **155** was quickly synthesized from aldehyde **109** using TBSOTf and 2,6-lutidine. Aldehyde **155** was then subjected to the usual aldol conditions, which to our

disappointment, led to the exclusive formation of the corresponding cyclized hemi-ketal product **156** (Scheme 24).

Scheme 23. The problem of cyclization in the aldol reaction of **110**



Scheme 24. Formation of ketalized product **156** from aldehyde **155**



Although this result was very disappointing, an interesting observation was made during this aldol reaction which ultimately led us to the solution. During TLC monitoring of the reaction, it was observed that the reaction mixture looked quite different before and after the aqueous NH_4Cl quench. In the post-quench (sat. aqueous NH_4Cl) TLC of the organic layer, the product (**156**) spot was visible as the only major spot other than those of the two unreacted starting materials. However, in the TLC of the reaction mixture immediately before quench, a significantly polar spot was found to be present as the major spot along with a tiny spot corresponding to **156** suggesting that the cyclized product **156** was being formed during or after the aqueous quench and that the compound corresponding to the significantly polar spot was leading to the cyclized product **156** upon quench (Figure 30).

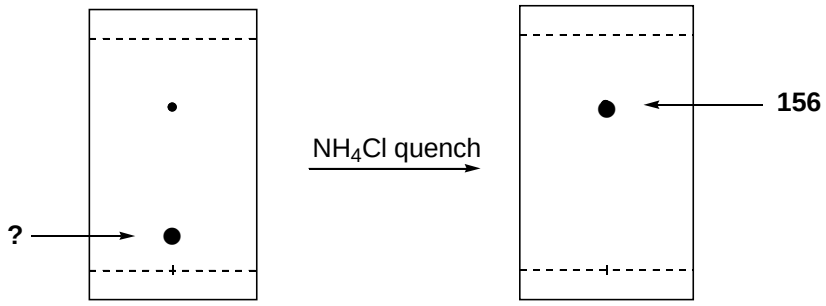
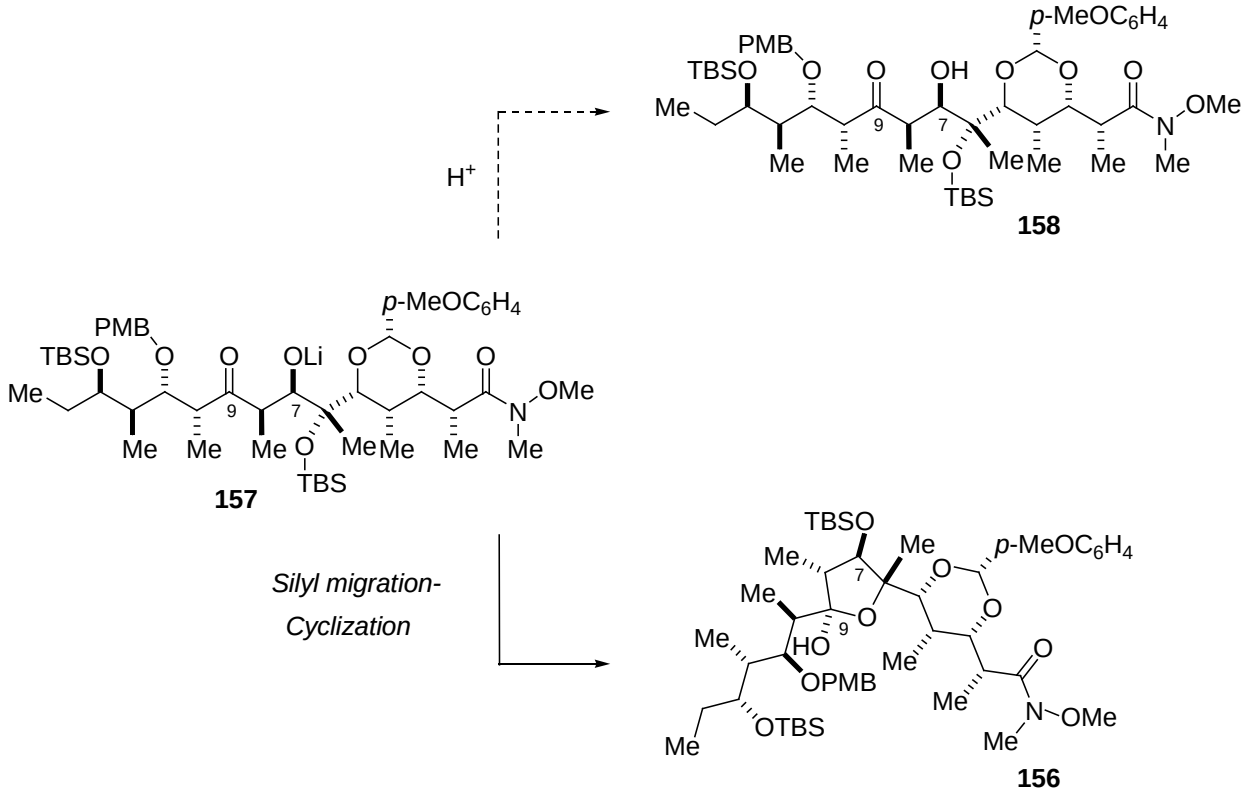


Figure 30. TLCs of the aldol reaction between **105** and **155** (startng material spots have not been shown for clarity)

If the aldol adduct existed as the aldolate **157** until the quench, it would, at first, seem unlikely that the addition of a proton source (NH_4Cl) would result in its cyclization to **156** in preference to the faster process of protonation which would lead to **158** (Scheme 25). However, in the event of addition of aqueous NH_4Cl solution into the reaction mixture at $-78^{\circ}C$, the aqueous phase was caused to freeze leading to a heterogeneous system where the organic and aqueous phases remained separated. As the reaction was then allowed to warm up, the rise of

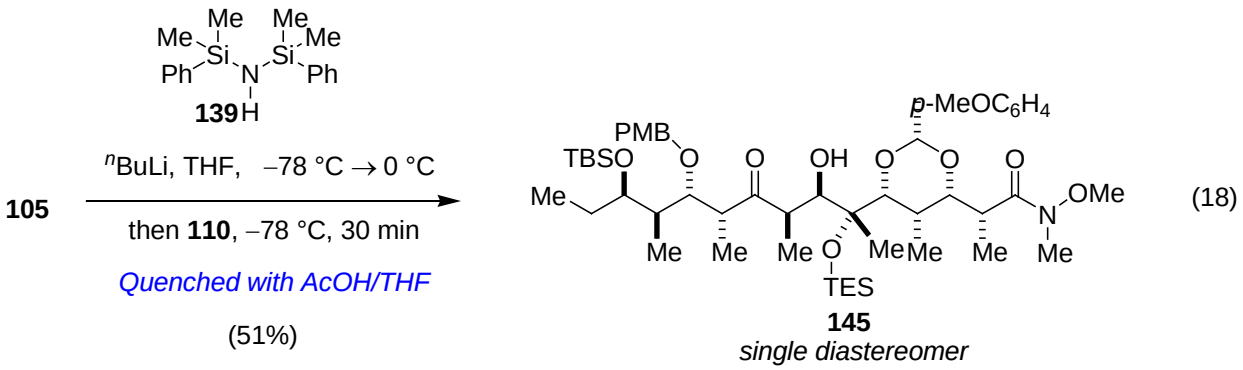
temperature triggered the aldolate **157** in the organic phase to undergo silyl transfer and cyclization to **156**. Thus, completely protonating the aldolate at low temperatures should lead exclusively to the acyclic product **158**. To achieve complete protonation of **157** at low temperature, we proposed to use a homogeneous quench of the aldol reaction in place of an aqueous quench.

Scheme 25. Competing reaction pathways for the lithium aldolate



To test this, the α-triethylsilyloxy aldehyde **110** was subjected to the aldol reaction conditions and after 30 minutes the reaction was quenched with 1 N solution of acetic acid (4 equiv) in THF. The resulting homogeneous solution was allowed to stir for 20 min at the same temperature to allow for complete protonation and then the excess acid was quenched with

aqueous $NaHCO_3$ solution whereupon it was allowed to warm to room temperature. After workup, the acyclic adduct **145** was isolated in 51% yield and as a single diastereomer, along with unreacted starting materials. None of the cyclized adduct **142** was formed (eq 18).

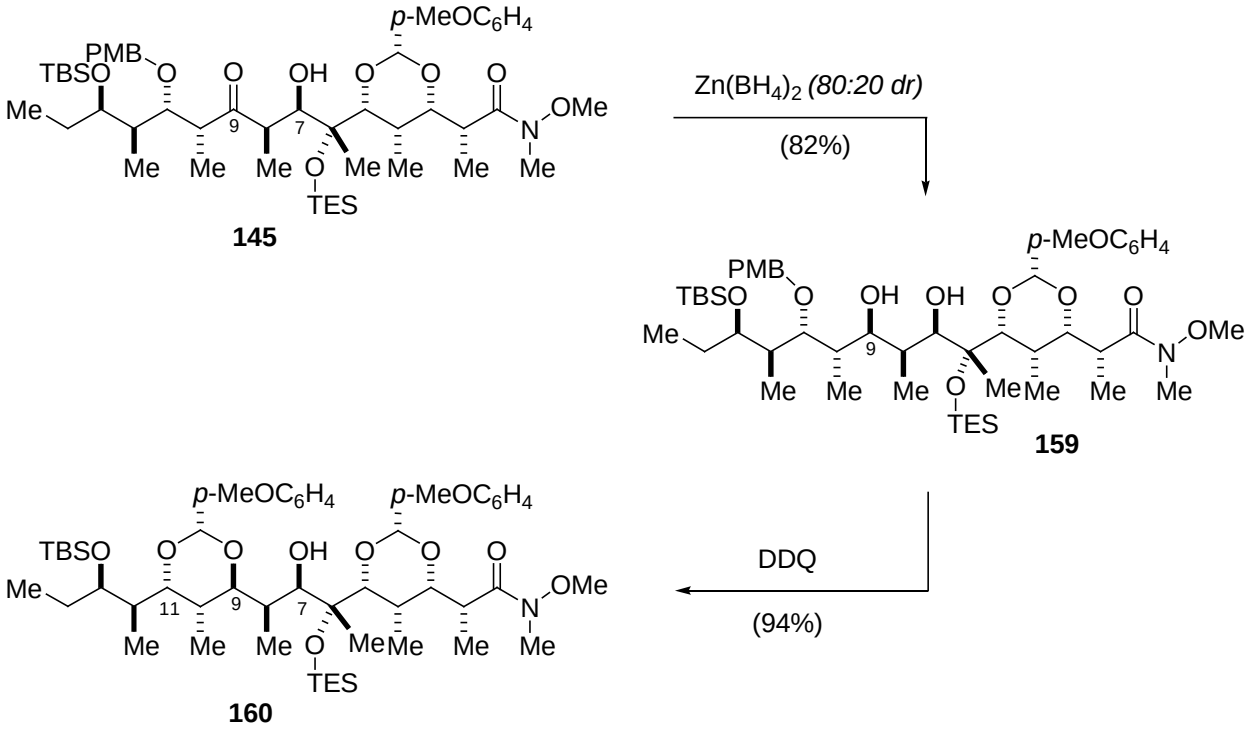


(18)

3.1.10 On the Way to Erythronolide B from Aldol Adduct 145: An Unexpected Problem

After having successfully synthesized the desired aldol adduct **145**, we began its elaboration into erythronolide B. To establish the (9*S*)-hydroxyl configuration in **159** required for macrocyclization, the aldol adduct **145** was subjected to chelate controlled reduction with $Zn(BH_4)_2$ which proceeded in excellent yield and selectivity (94% yield, >85:15 diastereoselection). *p*-Methoxybenzylidene acetal **160** was then formed as a single isomer through an anhydrous DDQ oxidation in 96% yield, differentiating the C_7 and C_9 alcohols and constraining the C_9 and C_{11} hydroxyls in a dioxolane ring required for macrocyclization (Scheme 26).

Scheme 26. Synthesis of the PMP acetal **160** from the aldol adduct **145**



At this point, all the stereocenters in the target had been installed, leaving only final refunctionalizations and macrocyclization to complete the synthesis. Before proceeding with the deoxygenation of the C_7-hydroxyl group in **160** via the Barton McCombie protocol, we wanted to verify the stereochemistry of the C_9/C_{11} acetal and came upon an unexpected problem. As shown below, in the ROESY NMR of compound **160**, the acetal proton H_a showed correlations to both protons H_9 and H_{11} suggesting a cis benzylidine acetal which was very difficult to reconcile with the previous stereochemical assignment of the cyclized aldol adduct **142** which should have produced the trans benzylidene acetal depicted by the structure **160** (Figure 31).

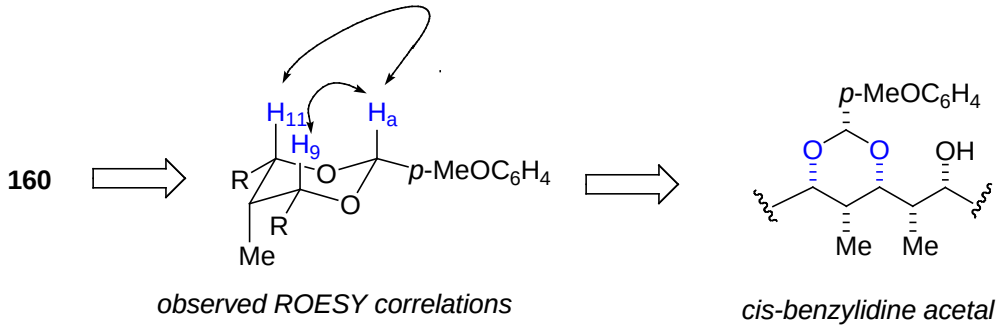
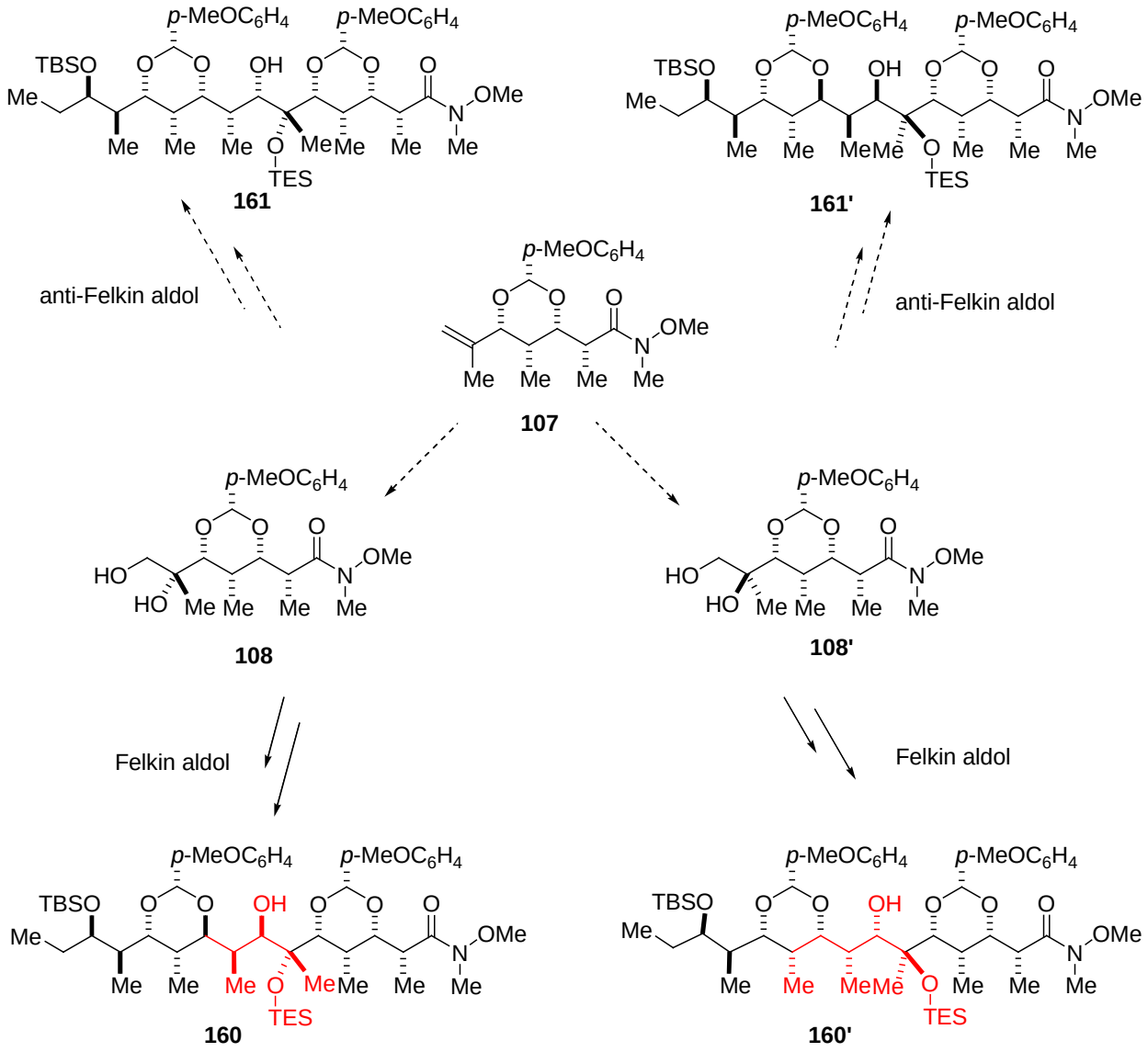


Figure 31. ROESY correlations of **160**

While searching for the source of this discrepancy, we became suspicious of the possibility of an erroneous assignment of the stereochemistry of the C_6-quaternary center. This center was constructed through a highly selective Sharpless asymmetric dihydroxlation reaction of olefin **107** (see Scheme 15). Sharpless's general mnemonic rule for predicting dihydroxylation stereochemistry in prochiral terminal olefins was used in the selection of AD-mix α as the chiral ligand in our system to obtain the desired dihydroxylation stereochemistry. Consequently, the unusually high selectivity achieved in the formation of diol **108**, convinced us that the stereochemical preferences of the chiral substrate and catalyst were *matched* in this case and hence the reaction proceeded with very high selectivity in providing the desired diastereomer **108**. However, since no other confirmatory evidence existed to support this assignment, let us assume that the C_6-epimer **108'** was formed in the Sharpless asymmetric dihydroxylation (SAD) reaction. Depending on Felkin or *anti*-Felkin selectivity in the aldol reaction, **160′** and **161′** should represent the two benzylidene acetal isomers that could be possibly formed from aldehyde precursor **108′**. Similarly, **160** and **161** represent the two possible stereoisomers that could result from the aldehyde precursor **108** (Scheme 27).

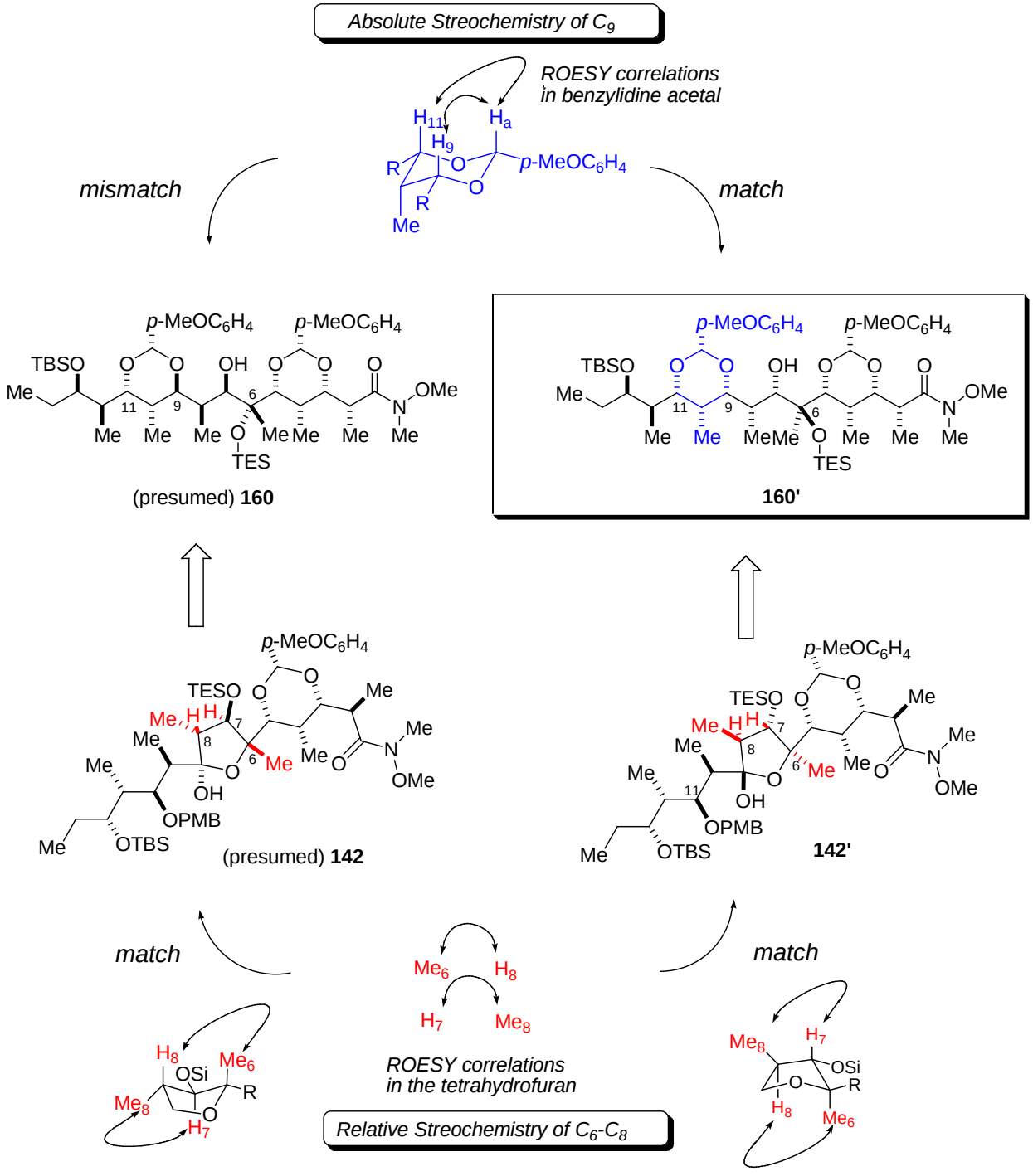
Scheme 27. Possible stereoisomers from **107** depending on the stereochemistry of its dihydroxylation



Only the Felkin diastereomers **160** and **160′** have the *relative* stereochemistry at the C_6-C_8 centers predicted by the ROESY correlations observed in the cyclized aldol product (shown in red, Scheme 28). However out of the two, only the diastereomer **160′** possesses the requisite O_9/O_{11} cis benzylidene acetal stereochemistry established by ROESY correlations in the actual benzylidene acetal (shown in blue, Scheme 28). Thus **142'** (and not **142**) must be the hemiketal

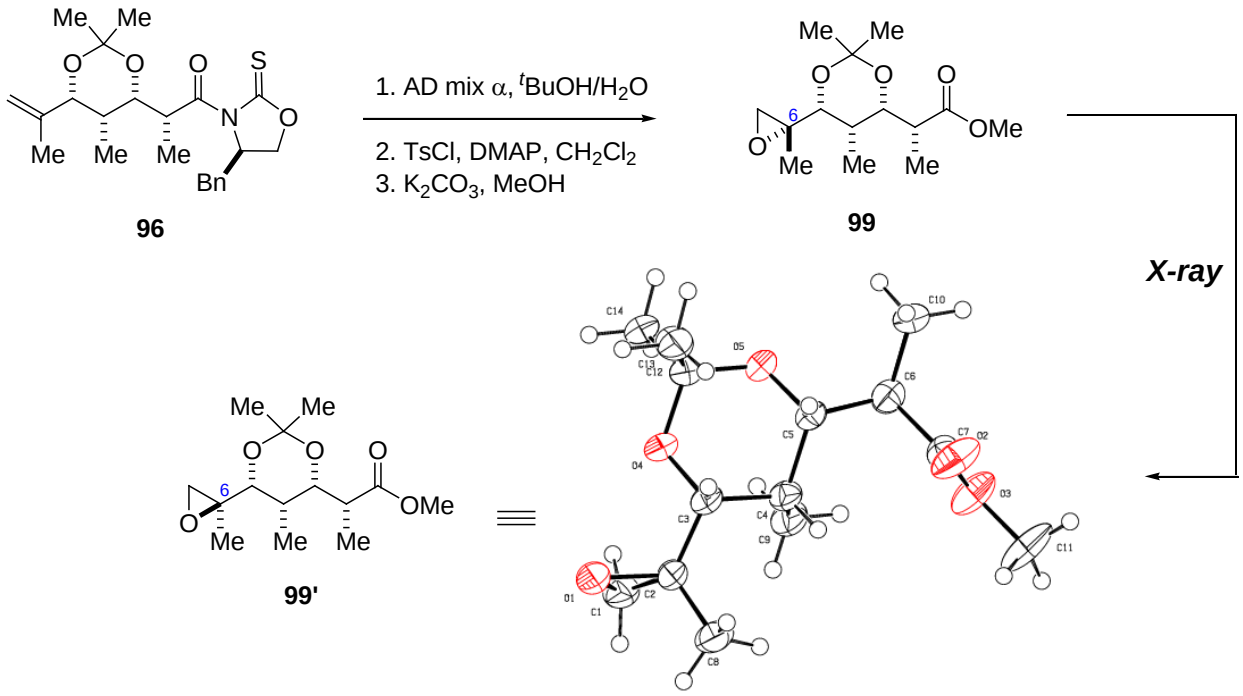
formed in the aldol reaction and **160′** (and not **160**) must be the corresponding benzylidene acetal.

Scheme 28. 160′ (not **160**) is found to match the relative and absolute setereochemistries predicted by ROESY data



The preceding analysis suggested that the C_6-epimeric diol **108′** (and not **108**) was formed in the SAD reaction. In order to unambiguously confirm this, we obtained crystals of the homologous epoxide fragment **99** previously prepared from alkene **96**. The X-ray structure of the epoxide revealed that the absolute configuration at the C_6 center, was indeed the opposite of what had been presumed thus far (Scheme 29).

Scheme 29: Stereochemical proof of SAD product

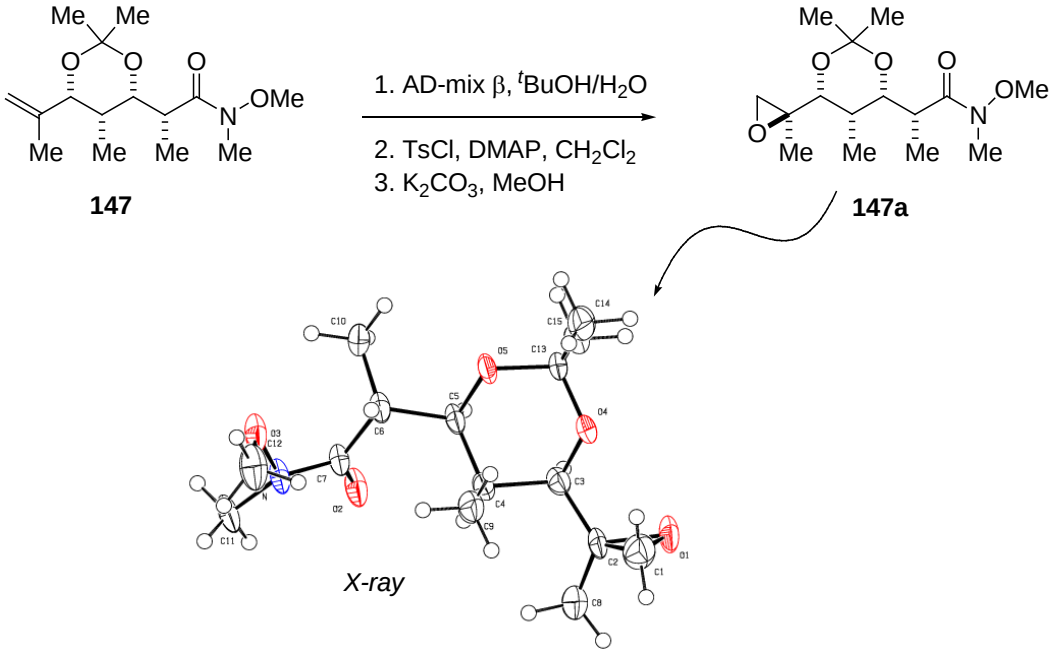


3.1.11 Dihydroxylation of 147 Using AD-mix β

As the Sharpless asymmetric dihydroxylation of **147** using AD-mix α provided the wrong stereochemistry at C_6, we anticipated that switching to the pseudoenantiomeric ligand in AD-mix β would reverse the selectivity. Upon subjecting **147** to catalytic dihydroxylation with AD-mix β, the corresponding diol was produced cleanly and with excellent diastereoselectivity (>95:5). The

diol product isolated in the dihydroxylation reaction, however, was found to possess the incorrect C_6 stereochemistry. Proof of stereochemistry was obtained by derivatization of the diol to epoxide **147a** whose structure was confirmed by X-ray crystallography (Scheme 30).

Scheme 30: Dihydroxylation of **147** with pseudoenantiomeric ligand AD-mix β



Dihydroxylations of **147** with the diastereomeric cinchona alkaloid catalysts AD-mix α and AD-mix β provided the same sense of diastereoselectivity. Therefore it was clear that the allylic alkoxy substituents in the substrate **147**, was providing a strong stereodirecting influence in the dihydroxylation reaction in favor of the undesired diastereomer. These results are in agreement with Kishi's dihydroxylation model[52] as well as the "inside alkoxy effect", which was first proposed by Stork[53] and later supported by Houk[54] to explain the inherent stereoselectivity

[52] Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943-3946.
[53] Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951-3954.
[54] Haller, J.; Strassner, T.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 8031-8034.

of dihydroxylation reactions for allylic alkoxy substrates. This model predicts that the allylic alkoxy substituent prefers to align parallel to the olefin in the reacting conformation due to stereoelectronic effects. This alignment is believed to minimize the destabilizing electron-withdrawing interaction between the C-O σ^* orbital and the C=C π bond orbital within the transition state. Reaction with the electrophilic osmium tetroxide reagent would then be expected to favor approach of the olefin face opposite the more sterically demanding alkyl substituent as shown in Figure 32. This model supports the results of the dihydroxylation selectivity; however, it is surprising that, even under reagent-controlled conditions, the inherent diastereoselectivity could not be overridden.

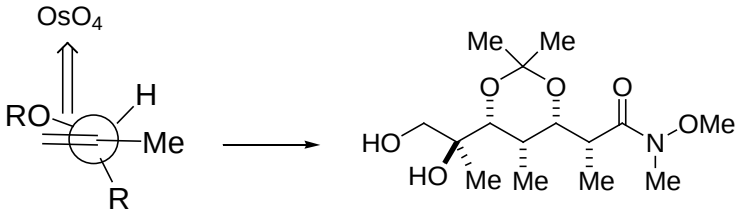


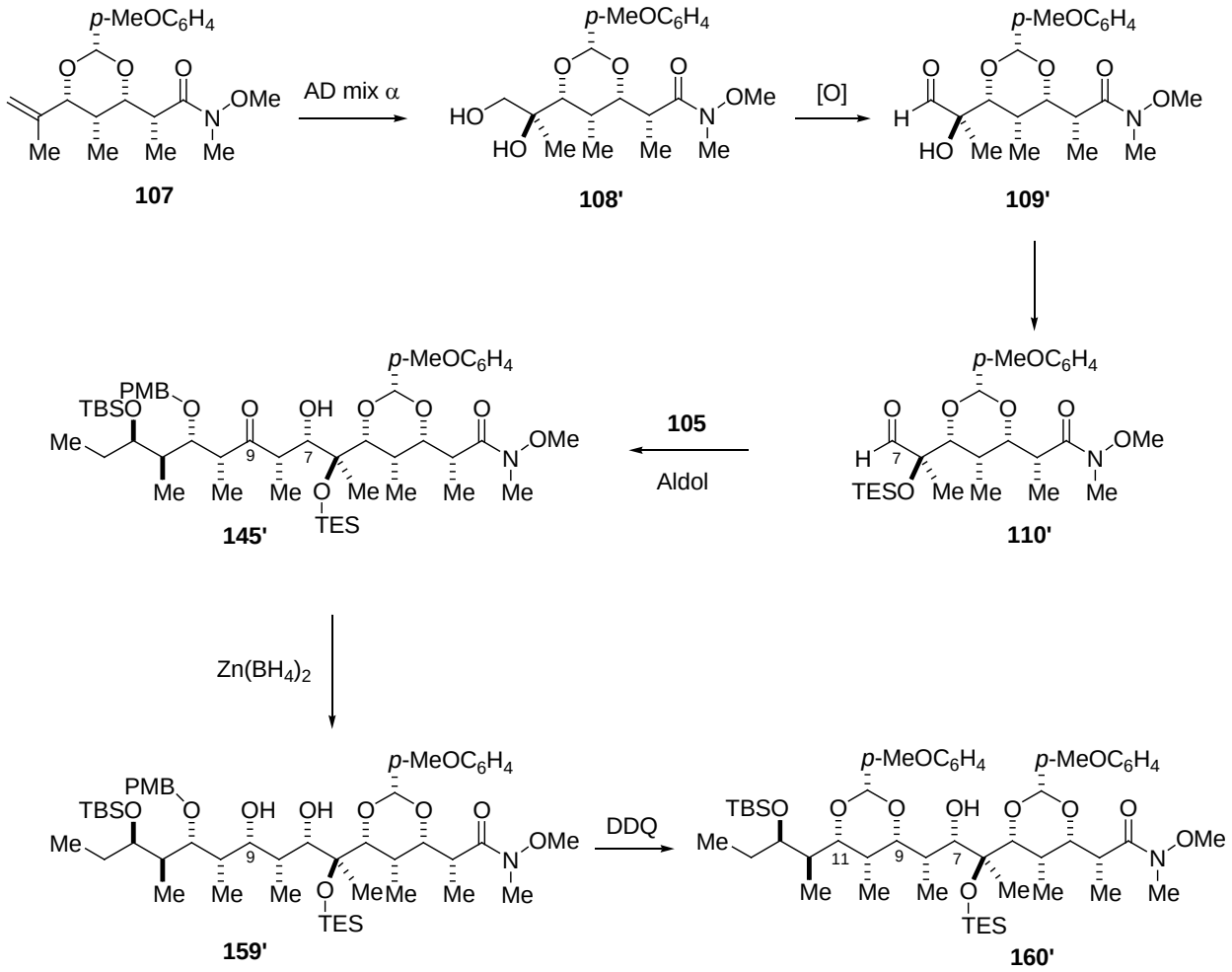
Figure 32. Inside-alkoxy effect in the substrate-controlled dihydroxylation of **147**

3.1.12 Stereochemical Reassignment of C_6-OH Containing Structures

With this stereochemical proof, it now became necessary to look back and reassign the stereochemistries of all compounds where the C_6 center was present i.e all the post-dihydroxylation compounds whose C_7-C_9 stereochemistries had been predicted based on the misassigned C_6-stereochemistry. The corrected sequence of compounds for the TES and Bn protected α-tertiary alkoxide series have been redrawn in Schemes 31 and 32, respectively. For

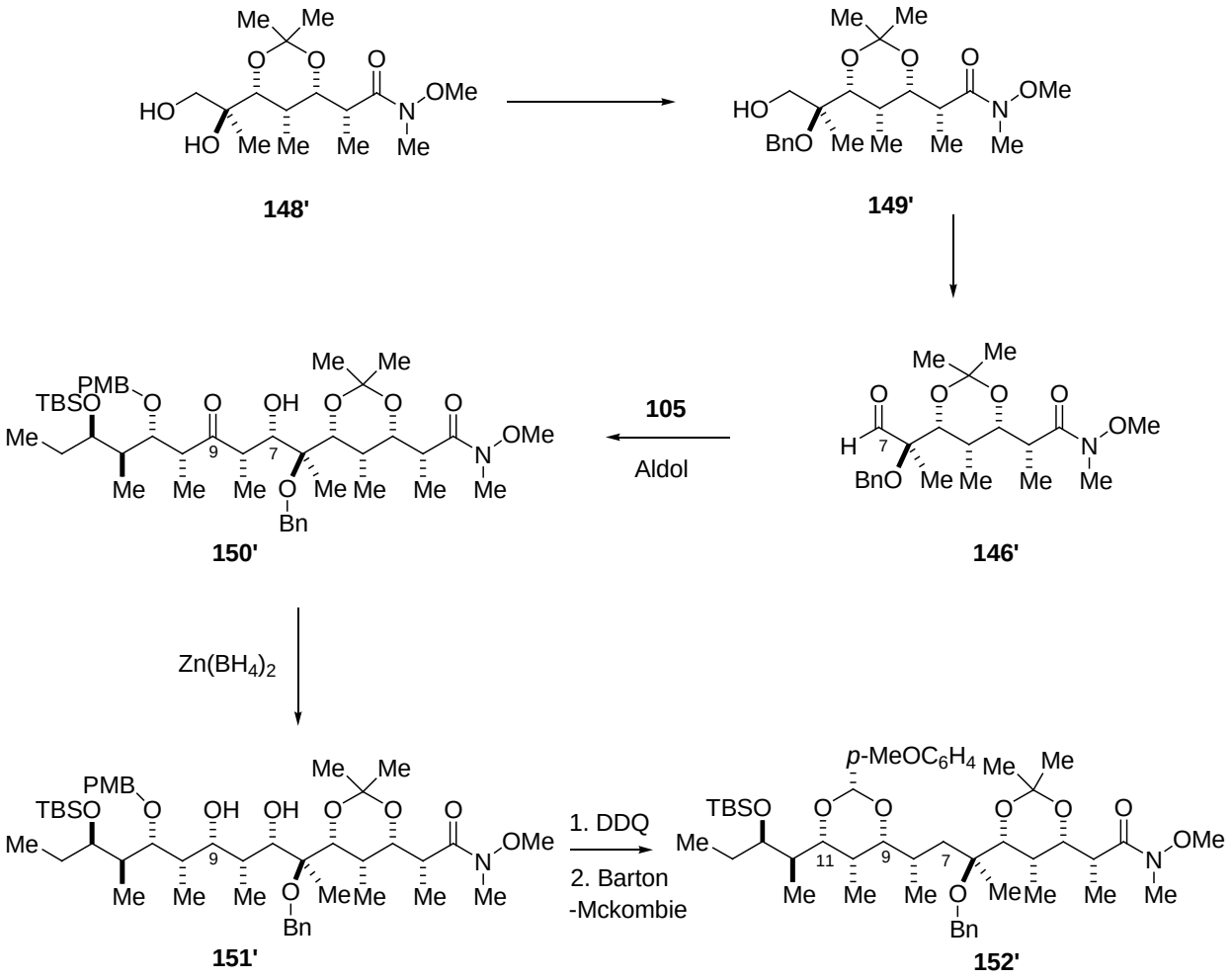
the purpose of clarity, all structures with the corrected stereochemistries are numbered as **N′,** where **N** is the number that represented the compounds with presumed wrong stereochemistries. Thus the aldol reaction of the α-triethylsolyloxy aldehyde **110′** produced the aldol diastereomer **145′**, via Felkin selection which ultimately provided the cis benzylidene acetal **160′** (Scheme 31).

Scheme 31. Corrected stereochemistries and modified numbering sequences for the TES series



Also in the aldol reaction of the α-benzyloxy aldehyde **146′**, instead of presumed aldol adduct **150** (initially proposed to form via a 5-membered chelate-Cram model), the Felkin product **150′** was formed selectively, which led to the cis benzylidene acetal **152′** (Scheme 32).

Scheme 32. Corrected stereochemistries and modified numbering sequences for the Bn series



3.1.13 Conclusion

In conclusion, an unexpected outcome of diastereoselective SAD reaction of the chiral 1,1-disubstituted alkenes **107** and **147** was observed where both *pseudo-enantiomeric* PHAL series AD ligands catalyzed the AD reactions giving the *same sense* of enhanced diastereoselectivity, one thus consistent (β) and one inconsistent (α) with the mnemonic for predicting selectivity preferences. Similar unexpected diastereomeric outcomes in SAD reactions of chiral monosubstituted and *trans*-disubstituted alkene substrates have been reported previously by the groups of Smith[55] and Carreira[56] in their respective syntheses of calyculin and zaragozic acids.

Also in the aldol reactions of α-tertiary-alkoxy aldehydes (e.g. **110′** and **146′**), it was found that the *Felkin* diastereoselection model was favored, irrespective of the type of protecting group on the alkoxide. This observation would be useful in predicting aldol stereoselection in the actual erythronolide B system.

[55] Iwashima, M.; Kinsho, T.; Smith, A. B., III *Tetrahedron Lett.* **1995**, *36*, 2199-2202.
[56] Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1994**, *116*, 10825-10826.

4.0 CORRECTION OF C_6-STEREOCHEMISTRY AND SYNTHESIS OF *SYN, SYN, SYN* POLYPROPIONATE UNIT

So far, the synthesis of the left hand fragment **74,** which contained the *syn*, *anti*, *syn* polypropionate segment has been accomplished by using the cinchona alkaloid catalyzed AAC chemistry. The right hand fragment **75** has been synthesized with a wrong stereochemistry at C_6 center and Crimmins' auxiliary mediated aldol reaction has been utilized for synthesizing the *syn*, *syn*, *syn*-C_2-C_5 segment. The aldol coupling of α-tertiary-alkoxy aldehyde substrate **75** with ketone substrate **74** has also been performed affording the desired Felkin diastereoselection. This result provided useful insight into the type of diastereoselection (Felkin) that should be expected in future aldol reactions of substrate **75** with the correct C_6-stereochemistry. Thus, 1) installation of the correct C_6-stereochemistry and 2) an efficient catalytic synthesis of the *syn*, *syn*, *syn*-C_2-C_5 segment were the two remaining major tasks required to complete our synthesis (Figure 33).

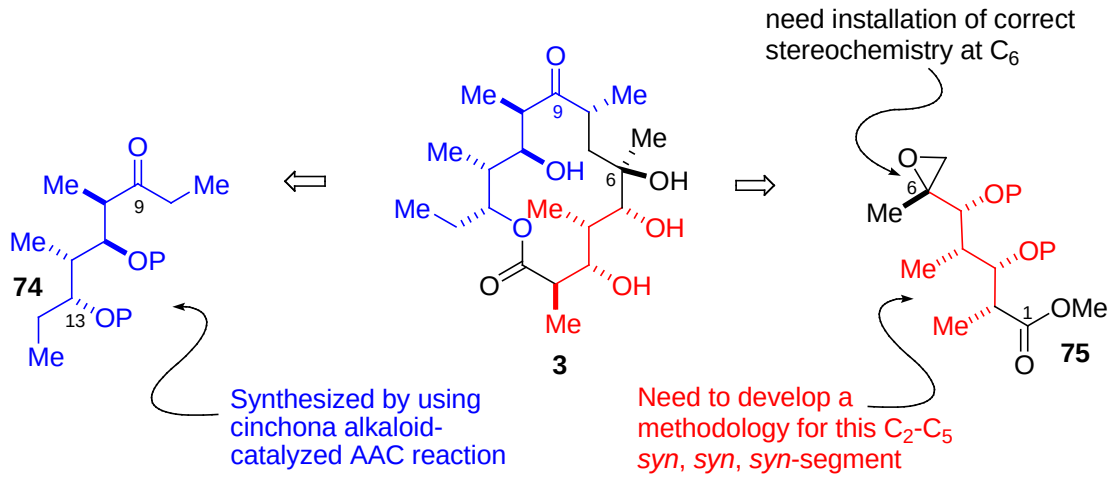


Figure 33. Required tasks for completion of the synthesis

4.1 SYNTHESIS OF THE *SYN, SYN, SYN*-POLYPROPIONATE UNIT

Our next target was to synthesize the C_2-C_5 *syn, syn, syn*-polypropionate unit of erythronolide B. As discussed previously, of the four diastereomers possible for a bispropionate, the *syn, anti, syn*-bispropionate precursor **66** and the *anti, anti, syn*-bispropionate precursor **70** can be prepared by AAC chemistry starting from aldehyde **67**. Bispropionate precursors **162** and **163** possessing C_3-C_4-*syn* stereochemistry cannot be made by AAC chemistry, since the inherent *anti*-Felkin bias of the aldehyde cannot be overridden by catalyst stereocontrol in the closed transition states associated with these reactions (Figure 34).

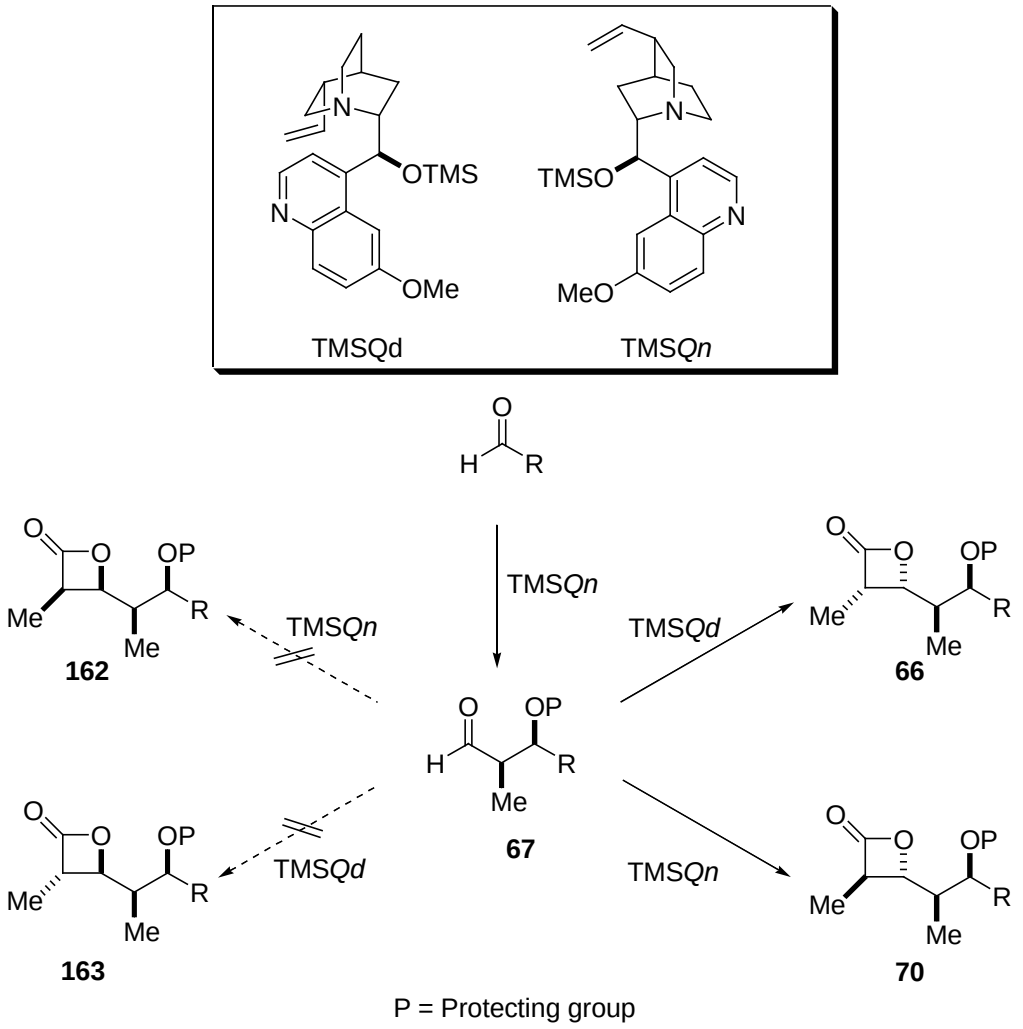


Figure 34. Felkin products unaccessible in diastereoselective AAC reactions

Despite the propensity of α-substituted aldehydes to express *anti*-Felkin diastereoselection in aldol additions with enolates, Evans and Crimmins have each developed auxiliary-controlled enolate additions that are uniquely effective at overriding this stereoelectronic bias. Evans' oxazolidinone[57] and Crimmins' thiazolidinethione-derived[58] metalloenolates mediate stereoselective aldol additions to chiral α-substituted aldehydes wherein

[57] Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866-868.
[58] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894-902.

stereoselection is derived exclusively from the chiral auxiliary. However, these methods for synthesizing the all-*syn* polypropionate unit suffer from the drawback of using a stoichiometric amount of chiral auxiliary. Our group was interested to develop a catalyst-controlled reaction methodology for the synthesis of all-*syn* polypropionate unit which would eliminate the requirement for stoichiometric chiral auxiliary. For successfully designing reactions to access polypropionate architecture complementary to that obtained from the AAC chemistry so far, a catalyst that would override the dominant *anti*-Felkin facial bias expressed by α-chiral aldehydes was necessary. The *anti*-Felkin aldehyde facial bias is generally associated with C−C bond constructions proceeding via *closed*, metal-templated transition states.[59] Therefore, identifying reaction conditions that would enforce the enolate-aldehyde addition through an *open* transition state (e.g., **164**) should result in the α-chiral aldehydes expressing more typical Felkin facial bias due to relief of the *syn* pentane interaction incurred in the closed transition state **165**.[60] Catalyst-based stereocontrol in conjunction with Felkin-selective aldehyde addition would afford highly diastereoselective access to β-lactone propionate dimers **162** possessing C_3-C_4-*syn* relationships. Toward that end, significant efforts were directed on the identification of suitable catalysts and non-coordinatve Lewis acids for the AAC reaction, but when this approach did not lead to the desired results, the Nelson group turned toward the Lewis base catalyzed Mukaiyama aldol reaction, and finally succeeeded at providing a solution (Figure 35).[61]

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[59] Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.
[60] (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151-4157. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingston, A. B. *J. Am. Chem. Soc.* **1995**, *117*, 6619-6620. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073-9074. (d) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761-1765.
[61] The reaction development and optimization studies in this project were all done by Dezhi Fu in the Nelson group.

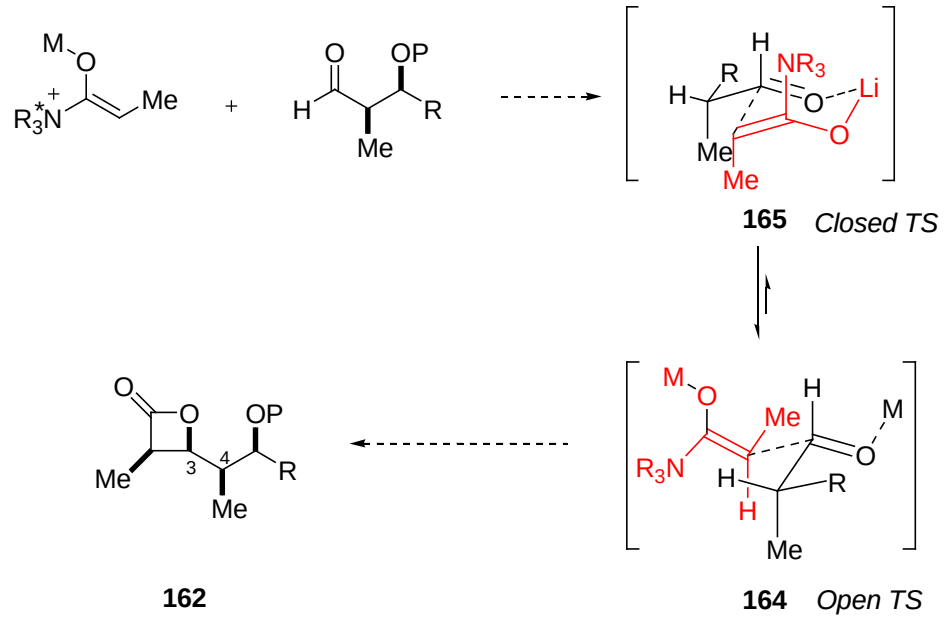


Figure 35. Relief of the *syn*-pentane interaction in open transition state should allow Felkin addition

4.1.1 Lewis Base-Catalyzed Mukaiyama Aldol Reaction: Contributions of the Nelson Group

Activation of simple silyl enolates such as trimethylsilyl enolates **166**, via Lewis base catalysis was first performed by Mukaiyama with Lewis base catalysts such as lithium diphenylamide,[62] lithium 2-pyrrolidone,[63] lithium acetate,[64] lithium phenoxide and ammonium phenoxides[65] to obtain good yields and *syn* selectivities (eq 19). However, these Lewis base-catalyzed Mukaiyama aldol reactions had only been performed on achiral aldehydes providing racemic aldol products. Our group became strongly intrigued by the possibility of application of

[62] Fujisawa, H.; Mukaiyama, T. *Chem. Lett*. **2002**, 182.
[63] Fujisawa, H.; Mukaiyama, T. *Chem. Lett*. **2002**, 858.
[64] Nakagawa, T.; Fujisawa, H.; Nagata, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1555-1567.
[65] Fujisawa, H.; Nagata, Y.; Sato, Y.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 842-843.

the aformentioned chemistry on chiral aldehyde substrates as it came to our realization that the high propensity of *syn* aldol formation in these reactions, combined with Felkin addition on α-chiral aldehydes via open transition states **167** can provide an avenue for the synthesis of *syn*, *syn*, *syn*-bispropionates **168** (Figure 36).

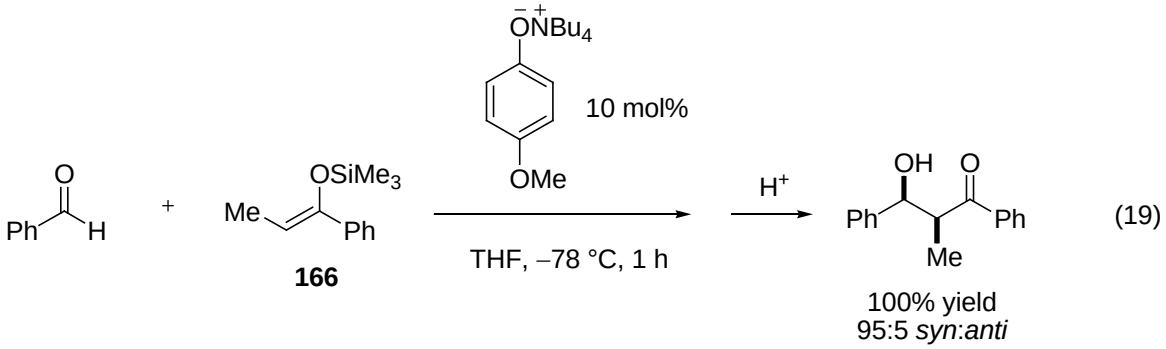
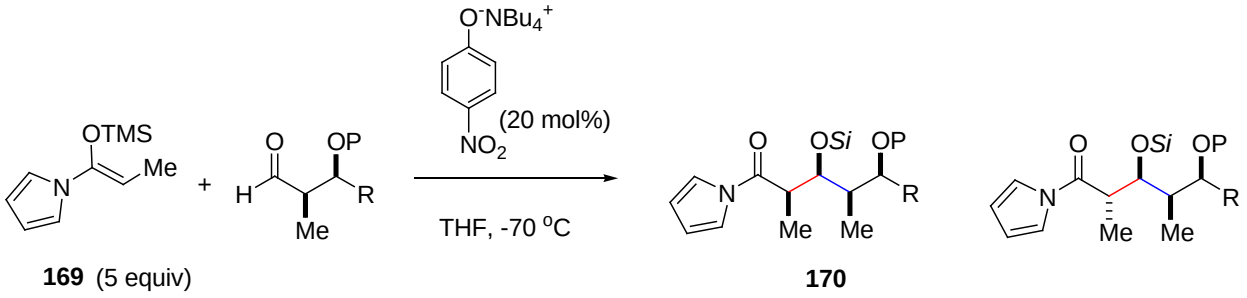


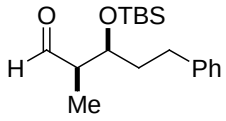
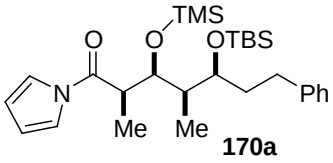
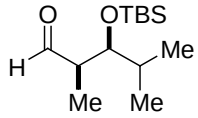
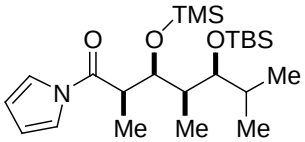
Figure 36. Felkin addition via open transition state will lead to *syn*, *syn*, *syn*-bispropionates

Building on this hypothesis, we soon identified the optimum reaction conditions for the diastereoselective Lewis base catalyzed Mukaiyama aldol reaction. In presence of 20 mol% of the tetrabutylammonium 4-nitrophenoxide catalyst, in THF at 70 ˚C, the propionyl pyrrole derived enol silane **169** reacted with chiral aldehydes to provide the all-*syn* bispropionates **170a** (96%, *syn*:*anti* = >99:1) and **170b** (62%, *syn*:*anti* = 99:1) (Table 1). Control experiments revealed that the *p*-nitrophenoxide catalyst expressed the correct Lewis basicity to promote

efficient enol silane addition without affecting base-promoted epimerization of the α-substituted aldehydes. The pyrrole functionality in the enol silane **169** enhanced nucleophilicity of the donor and also prevented epimerization of the products via deprotonation possible under the basic conditions of the reaction due to developing $A^{1,3}$ strain in the enolate anion (Figure 37).

Table 1. Selected examples of Lewis base-catalyzed Mukaiyama aldol reaction on chiral aldehydes



Aldehyde	Product	yield	syn:anti	Felkin: anti-Felkin
	 **170a**	96%	>99:1	98:2
	 **170b**	62%	99:1	90:10

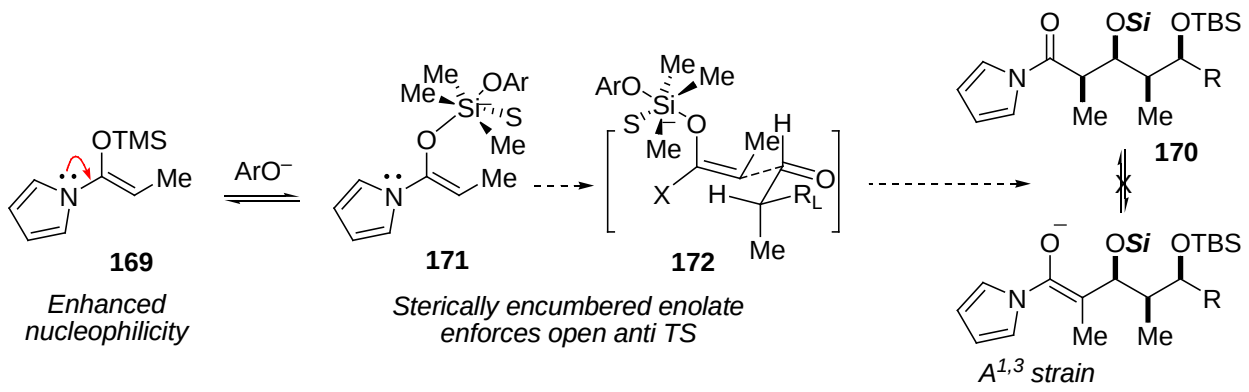


Figure 37. Advantages of the pyrrole functionality

The relative stereoselection emerging from open transition state silyl enolate-aldehyde additions are governed by developing gauche interactions in the competing anti or synclinal transition states.[66] Steric demands of the hypervalent silicate **171** should render the enolate uniquely disposed toward C–C bond construction via the *anti* transition state **172**. Among the competing *anti* transition states **172** and **173** (Figure 38), a significant developing gauche interaction between the enolate methyl and the α-methyl group in the aldehyde would destabilize transition state **173.** Enolate approach through transition state **172** would orient the enolate methyl substituent to minimize developing non-bonded interactions with the aldehyde alkyl chain while providing for Felkin aldehyde selectivity. Ensuing C−C bond construction would afford the all-*syn* propionate dimer **170**.

[66] Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130-5132.

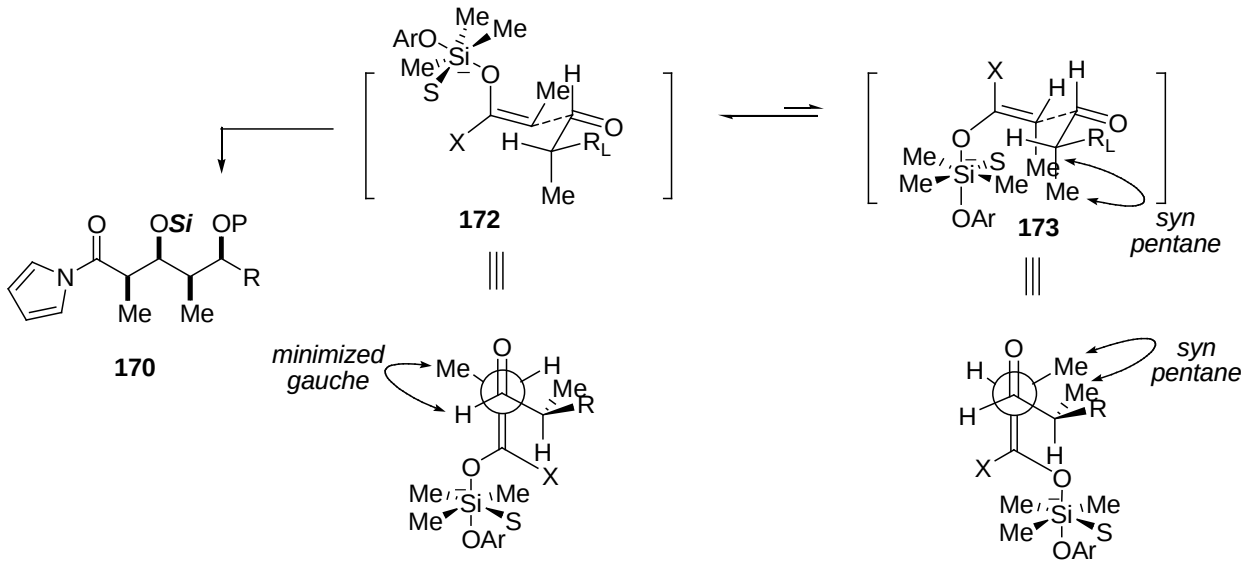


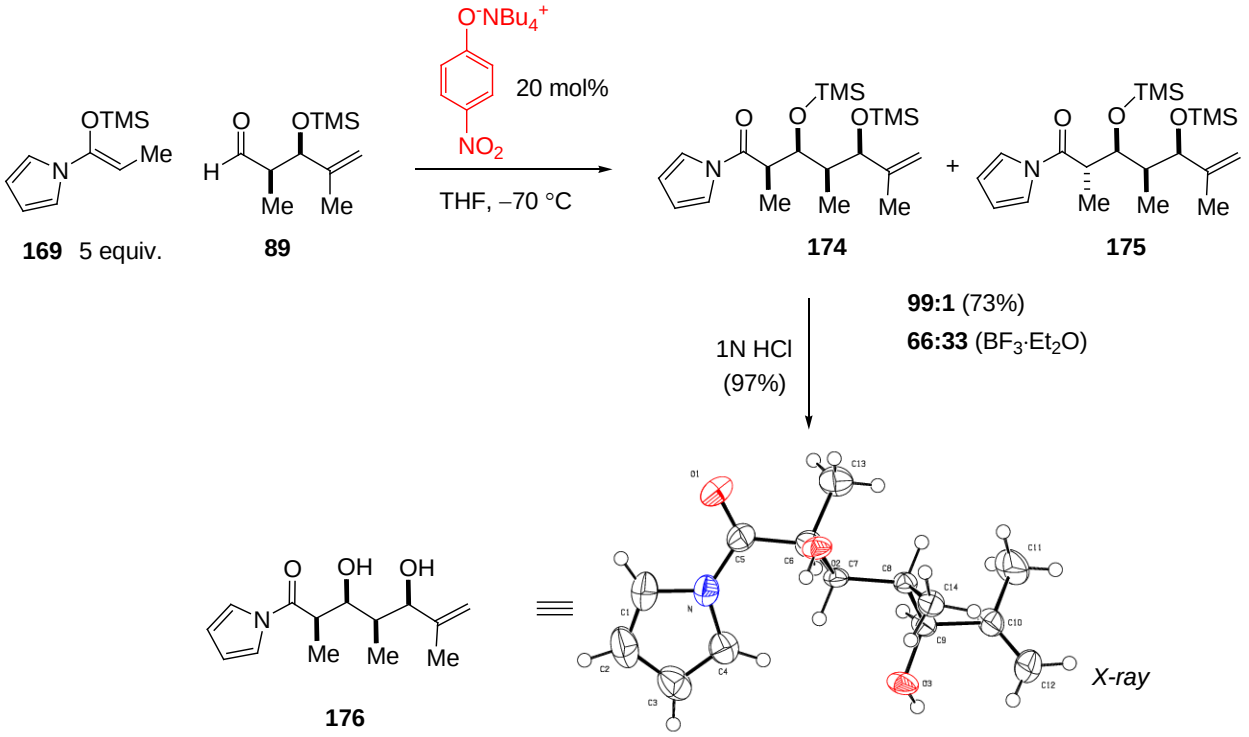
Figure 38. Competing *anti* transition states

4.1.2 Synthesis of the All *Syn* C_2-C_5 Bispropionate of Erythronolide B

Using the *p*-nitrophenoxide catalyzed Mukaiyama aldol protocol, the requisite *syn*, *syn*, *syn*-bispropionate **174** was prepared from aldehyde **89** and enol ether **169** in 73% yield and as a single diastereomer (Scheme 33). The all-*syn* stereochemistry of **174** was confirmed from the X-ray crystal structure of the TMS-deprotected diol **176**. The Lewis base catalyzed Mukaiyama aldol reaction proved to give superior diastereoselectivity when compared to the corresponding $BF_3{\cdot}Et_2O$ catalyzed reaction which provided only a moderate 66:33 dr for the diastereomeric products **174** and **175**. To confirm the stereochemistry of **175**, it was deprotected to the diol which was then reprotected as an acetonide. The *syn* stereochemistry of this acetonide was confirmed via Rychnovsky's protocol providing the stereochemical proof for distereomer **175** (*anti* aldol, Felkin). The more sterically encumbered silicon center of the enolate involved in the Lewis base catalyzed process caused a much greater steric difference between the two competing

Felkin transition states **172** and **173** (see Figure 38). Therefore the *syn* aldol diastereomer **174** was formed more preferentially in this case than in the Lewis acid ($BF_3{\cdot}Et_2O$) catalyzed reaction.

Scheme 33. Synthesis of **174** and its stereochemical proof



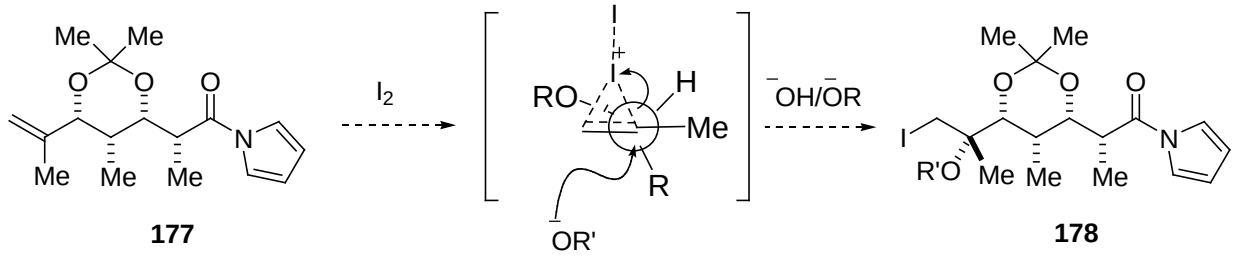
4.2 INSTALLATION OF THE C_6-STEREOCENTER

4.2.1 Correction of C_6 Stereochemistry

Recognizing the strong stereochemical bias of **147** to undergo dihydroxylation via the *inside alkoxy* conformation, we decided to obtain the desired C_6 stereochemistry via an inversion mechanism. The preference for allylic ethers to adopt the *inside alkoxy* conformation holds

generally for any sort of electrophilic additions.[67] Specifically, we envisioned that in the iodination of **177**, the double bond would present the inside alkoxy face for the approach of the electrophilic iodinating agent, as the alkoxy oxygen would provide a stabilizing electrostatic interaction with the partially positive charge on the developing halonium ion in the transition state. If the resulting halonium ion could be trapped with an external oxygen nucleophile such as water or an alkoxide, an inversion would result at C_6 leading to the desired diastereomer **178** (Scheme 34).

Scheme 34: Halonium ion formation followed by inversion with O-nucleophile could lead to desired C_6-stereochemistry



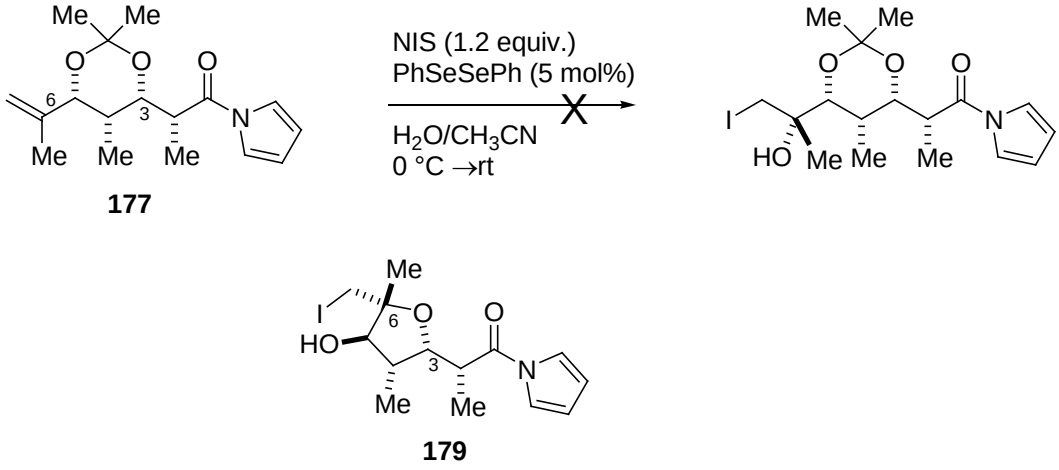
177 **178**

With this in mind, acetonide **177** was first prepared by protection of the diol **176** ($Me_2C(OMe)_2$, cat. CSA, 88%) and then subjected to iodohydrin formation via a diphenyldiselenide-catalyzed protocol[68] using NIS as the iodinating agent in presence of water as the nucleophile (using either molecular I_2 or NIS alone in the absence of the selenium catalyst resulted in substantially slower reaction rates). Although the reaction proceeded cleanly to provide a single product, the ^1H and ^{13}C NMR of the isolated compound indicated absence of the acetonide ring. The compound formed in the reaction was presumably the tetrahydrofuran **179**

[67] Houk, K. N.; Moses, S. R.; Wu, Y. D; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880-3882.
[68] Carrera, I; Brovetto, M. C.; Seoane, G. A. *Tetrahedron Lett.* **2006**, *47*, 7849-7852.

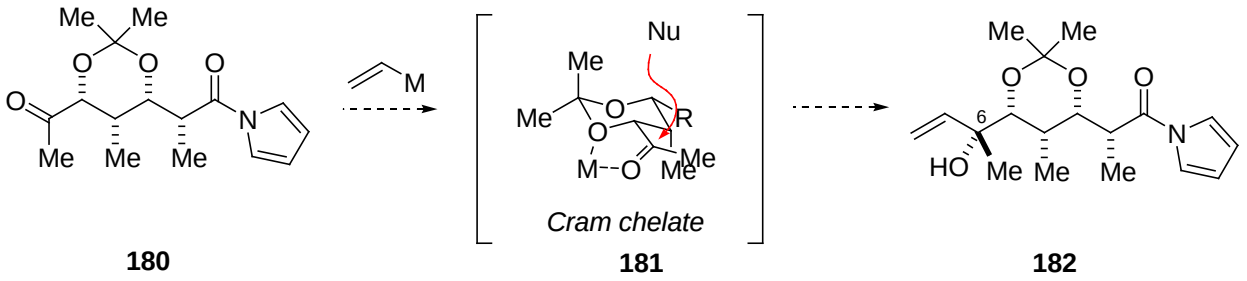
which should result if the iodonium ion is intramolecularly trapped by the C_3-alkoxy oxygen followed by hydrolytic cleavage of the acetonide protecting group (Scheme 35).

Scheme 35: Attempted selenium catalyzed iodohydrin formation reaction of **177**



177 **179**

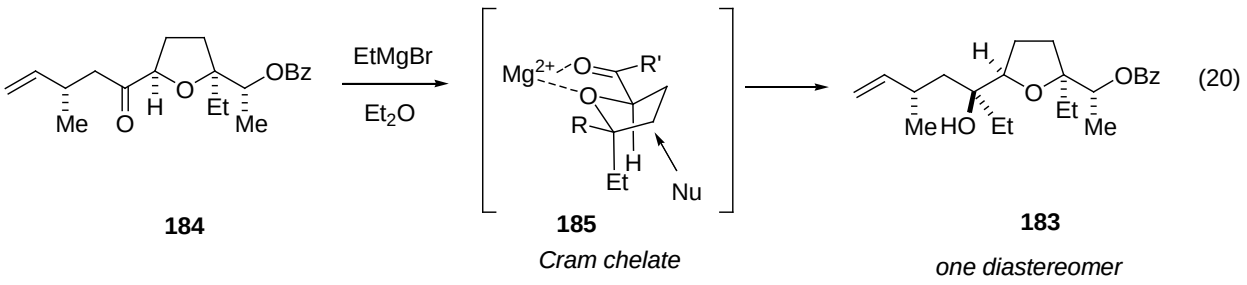
Clearly, the installation of the desired C_6 center by using the alkene as a nucleophile was turning out to be problematic. In order to provide a solution to this problem, we adopted a different strategy as shown in Figure 39. Nucleophilic addition to ketones can provide tertiary alcohols and in case of chiral α-alkoxy ketones, the stereochemistry of addition is determined by the stereochemistry and nature of the alkoxy residue. In order to apply this strategy in our system the terminal alkene in **177** should be first converted to the ketone **180**. Vinyl addition to this ketone via a Cram chelate transition state **181** should lead to the tertiary alcohol product **182** with the desired stereochemistry at C_6.



180 **181** **182**

Figure 39. Nucleophilic addition to ketone to set the C_6-stereocenter

The propensity of the ketone substrate **180** to participate in chelation would depend on the choice of the protecting group on the α-oxy group. In that respect, the acetal protecting group in our substrate would be optimal. The nature of the cation participating in chelate formation is also important. Pioneering studies conducted by Still on the chelate-controlled additions of carbanions to ketones for the synthesis of simple vicinal diols demonstrated that Mg(II) is superior to Li(I) for the formation of chelates and THF is the optimal solvent.[69] Earlier, Kishi had applied this strategy to synthesize **183**, an important intermediate in his synthesis of lasalocid A. The stereoselective addition of ethylmagnesium bromide to ketone **184** proceeded through the chelate **185** to provide a single diastereomer of the tertiary alcohol product (eq 20).[70]



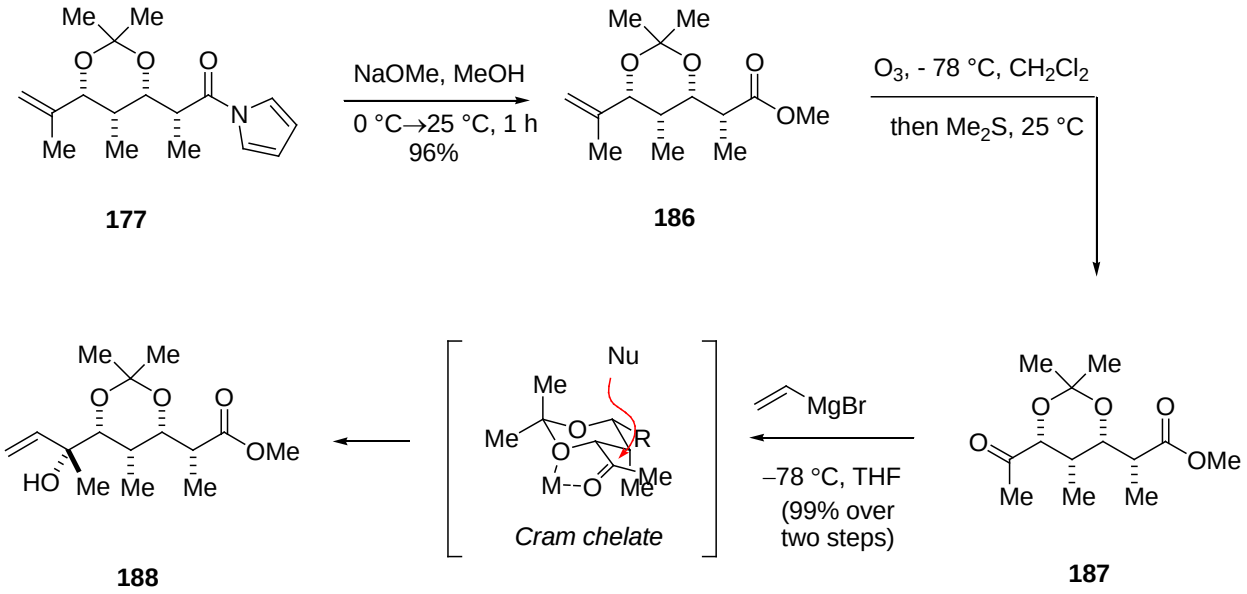
184 **185** **183**

Cram chelate *one diastereomer*

[69] Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031-1034.
[70] Nakata, T.; Schmid, G.; Vranesic, B.; Okigawa, M.; Smith-Palmer, T.; Kishi, Y. *J. Am. Chem. Soc.* **1978**, *100*, 2933-2935.

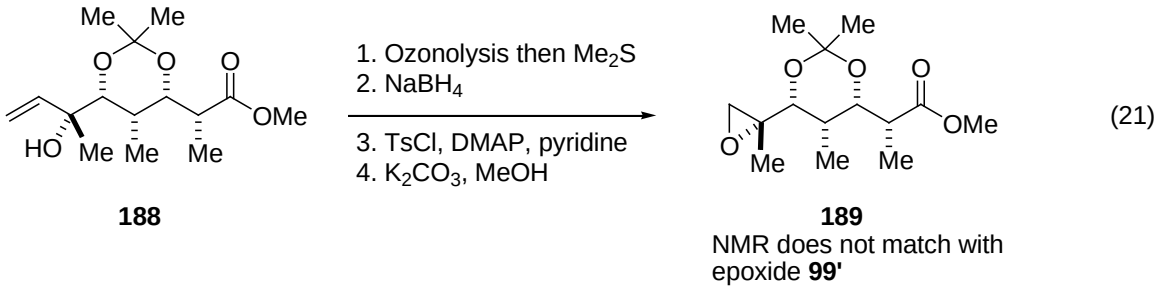
In order to synthesize ketone **180**, the alkene **177** was subjected to standard ozonolysis conditions, which unfortunately led to a complex mixture of products due to the decomposition of the pyrrole moiety under those conditions. Therefore, **177** was converted first to the methyl ester **186** (96%) using sodium methoxide in MeOH and then ozonolyzed to provide the ketone **187** (Scheme 36). Subsequent addition of vinylmagnesium bromide to **187** at −78 ˚C in THF provided **188** cleanly in high yield (99% over two steps) and as a single diastereomer.

Scheme 36. Installation of C_6-tertiary alcohol center



For stereochemical proof, **188** was converted to epoxide **189** (Scheme 37, eq 21) and its NMR spectra was compared to that of epoxide **99′** which possessed the incorrect stereochemistry at C_6. A complete mismatch of the NMR spectra was observed, suggesting that **188** indeed possessed the correct C_6 stereochemistry. With the correct C_6 stereocenter finally in place, **188** was converted to the aldehyde **191** via a two-step sequence involving ozonolysis of the vinylic double bond to provide the α-hydroxy aldehyde **190** (92%) followed by TES-protection of the C_6-oxygen (81%) (Scheme 37).

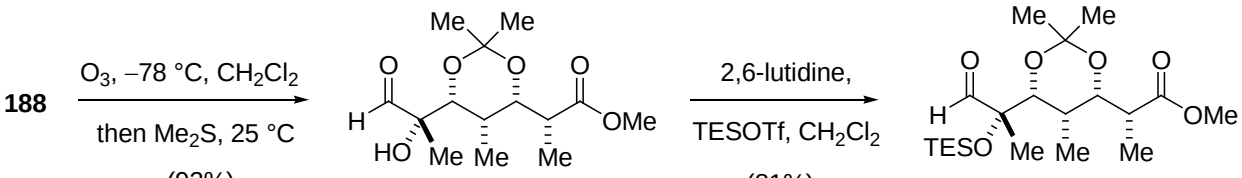
Scheme 37: Stereochemical proof for **188** and synthesis of aldehyde **191**



188 **189**

NMR does not match with epoxide **99'**

(21)

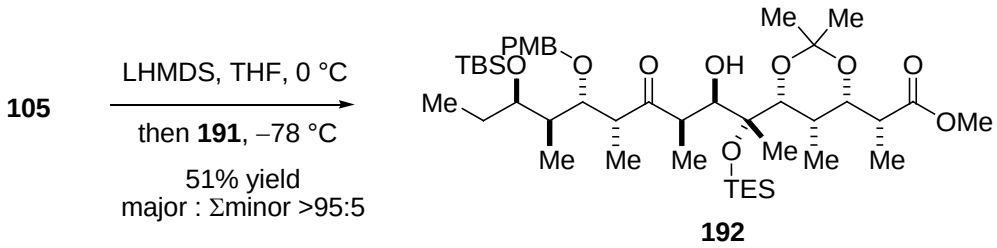


190 **191**

5.0 COMPLETING THE SYNTHESIS OF ERYTHRONOLIDE B

5.1 ALDOL COUPLING OF FRAGMENTS 105 AND 191

With the correct C_6-stereochemistry and the all-*syn* propionate successfully established in the aldehyde fragment **191**, the next goal was to engage it in the aldol coupling reaction with ketone **105**. The enolization of **105** was performed with lithium hexamethyldisilazide (LHMDS) at 0 ˚C for 2 h and the resulting enolate was cooled to −78 ˚C before the aldehyde solution was cannulated. The aldol product **192** was afforded in 51% yield as a single observable diastereomer along with recovery of unreacted starting materials (eq 22). The anticipated Felkin selectivity in the aldol reaction was confirmed later from the ROESY spectra of the ensuing benzylidene acetal intermediate **194**.

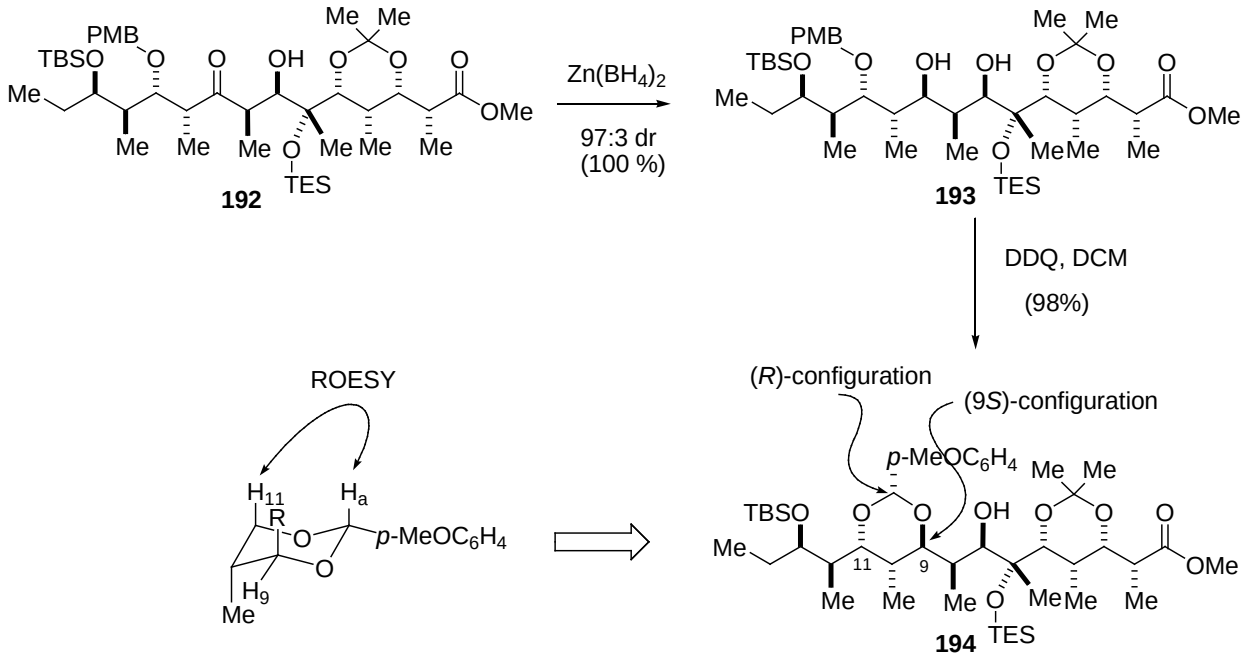


(22)

5.2 SYNTHESIS OF MACROLACTONE 198

Chelate controlled reduction of the aldol adduct **192** with $Zn(BH_4)_2$[71] afforded diol **193** (95% yield, >95:5 diastereoselection), thereby establishing the desired (9*S*)-hydroxyl configuration required for macrocyclization. Benzylidene acetal **194** was then formed as a single isomer through an anhydrous DDQ oxidation (94%), differentiating the C_7 and C_9 alcohols and constraining the C_9 and C_{11} hydroxyls for macrocyclization. Stereochemical characterization of the acetal **194** based on its ROESY spectrum clearly established the (*R*)-configuration of trans acetal (the acetal proton H_a showed correlation with H_{11} but not with H_9) while also confirming the (9*S*)-hydroxyl configuration resulting from a Felkin selective aldol reaction (Scheme 38).

Scheme 38: Stereochemistry verification of benzylidene acetal **194**



[71] Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338-344.

In the DDQ mediated formation of the acetal ring in **194**, a new stereocenter was created. However, out of the two possible isomers, only the *R*-configured acetal isomer was formed selectively (from ROESY). The selective formation of this isomer over the undesired *S*-configured acetal and the importance of this *R*-configured acetal isomer in the macrocyclization deserve some comment here. Conformational analysis of the two isomeric acetals shows that the alternative *S*-configured acetal suffers from a *syn*-pentane interaction between the C_{10} and C_{12} methyl substituents. Therefore, even though the the *R*-configured acetal isomer contains greater number of axial substituents, minimization of *syn*-pentane interactions within its structure leads to the remarkable selectivity found for this acetal isomer. Similarly, in case of the cis benzylidine acetals **152′** and **160′** made previously, the *R*-configured acetal isomers were formed selectively. In Woodward's erythromycin synthesis, the critical function of the C_9/C_{11} cyclic acetal in the preorganization of the seco acid was revealed. In those studies, only the *R*-configured isomer was found to undergo successful lactonization. The spatial orientation of the extending arms R_1 and R_2 determine the ease of lactone formation in each of the acetal isomers. In the *R*-configured isomer of trans benzylidine acetal, the R_1 and R_2 groups (shown in red) are closer together making this isomer predisposed toward macrolactonization. On the other hand the reacting centers in the *S*-configured isomer are farther apart, preventing successful macrolactonization in this isomer (Figure 40).

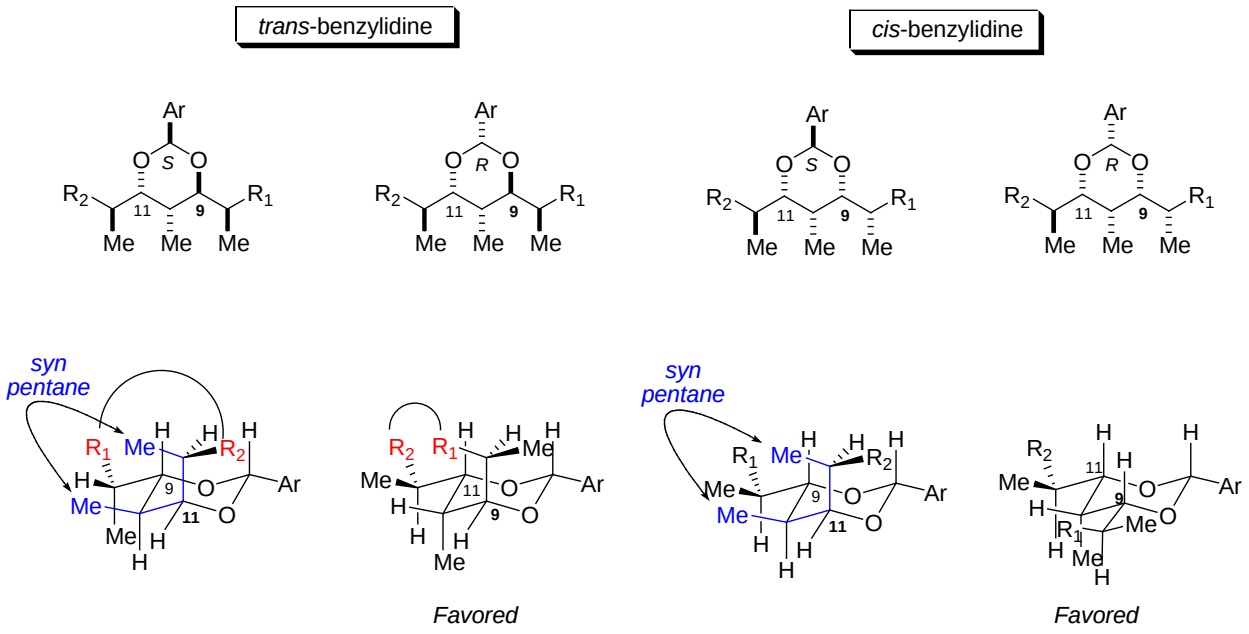


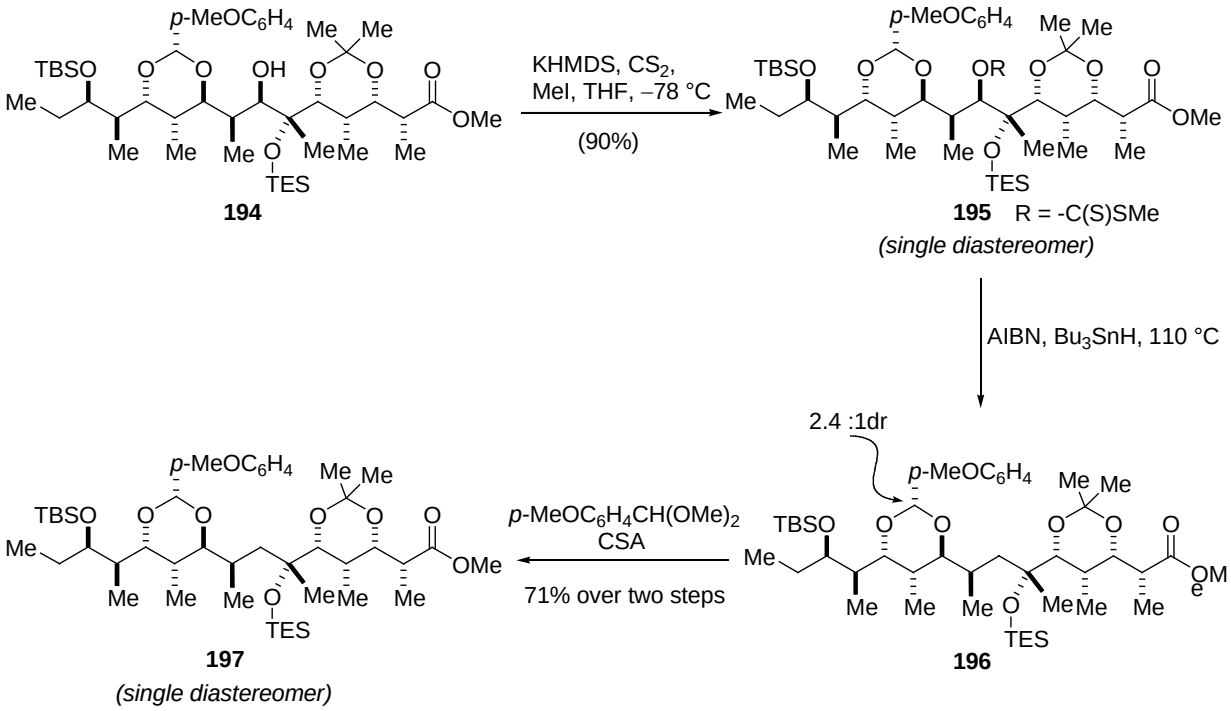
Figure 40. Rationale for selective formation of the *R*-configured acetal

At this point, all the stereocenters in the target had been installed, leaving only the final functional group manipulations and macrolactonization to complete the synthesis. First of all, the C_7-OH in **194** needed to be removed through a radical deoxygenation process. In order to circumvent the problem of silyl-group migration, formation of xanthate was achieved at low temperature (−78 ˚C) using KHMDS as the base and the resulting naked C_7-alkoxide was trapped at the same low temperature with excess CS_2 present in the reaction mixture. This was followed by addition of MeI affording the desired methyl xanthate **195** in 90% yield. The reduction of the xanthate via Barton radical deoxygenation[72] under Evan's modified conditions[6b] using neat Bu_3SnH was accompanied by epimerization of the acetal stereocenter providing a 2.4:1 mixture of deoxygenated *R*- and *S*-benzylidene acetals **196**. A similar problem had been encountered in

[72] (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574-1585. (b) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs. *Tetrahedron* **1992**, *48*, 7435-7446.

Evans' synthesis of 6-deoxyerythronolide B, where the 3.3:1 mixture of deoxygenated benzylidene acetals was converted to the desired *R*-acetal isomer by equilibration with CSA. When **196** was subjected to similar conditions (cat. CSA in CH_2Cl_2), equilibration occurred to provide the desired isomer but extensive decomposition due to PMP-acetal deprotection was also observed in the reaction. To circumvent this problem equilibration was performed in presence of an excess of the acetal forming reagent (4-$MeOC_6H_4CH(OMe)_2$). This allowed reprotection of the deprotected product in the reaction mixture to provide a single isomer of the deoxygenated product **197** (71% over two steps) (Scheme 39).

Scheme 39. Xanthate formation and deoxygenation/equilibration

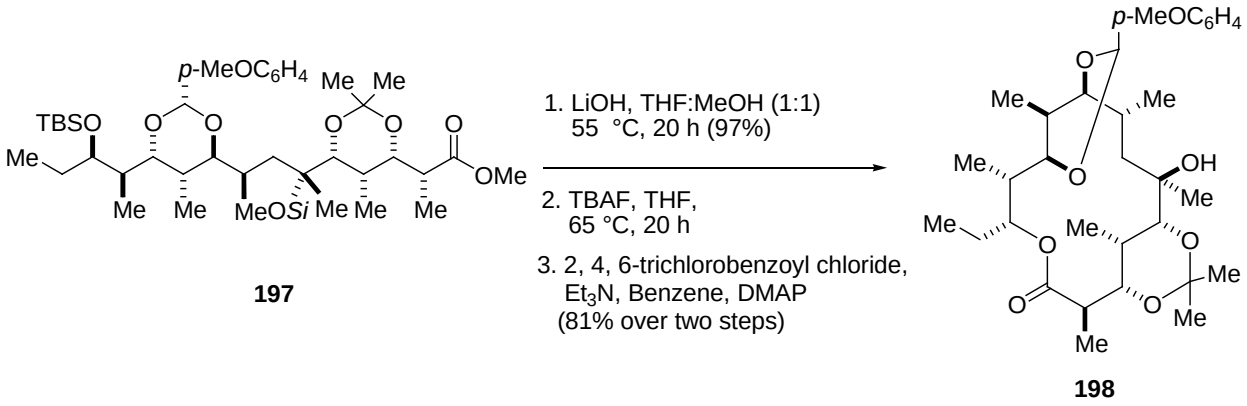


In preparation for macrocyclization, ester hydrolysis from the carboxyl terminus and cleavage of the C_{13}-TBS protecting group was required to afford the seco acid. Hydrolysis of the methyl ester **197** to the free acid was achieved with aq. LiOH in THF/MeOH (1:1 v/v) at a

slightly elevated temperature of 50 ˚C (Scheme 40). The C_{13}-TBS group was then removed with TBAF in refluxing THF to afford the seco acid. Macrolactonization was successfully performed by Yonemitsu's modified Yamaguchi lactonization protocol[73] which does not involve the high dilution conditions which are generally required in the conventional Yamaguchi macrolactonization to prevent intermolecular reactions. This interesting and highly efficient modification of Yamaguchi macrolactonization was reported in 1990 by Yonemitsu in the total synthesis of erythronolide A.[73a] The 14-membered erythronolide A macrocycle was formed by treating a concentrated benzene solution of the mixed anhydride of the seco acid with excess DMAP at ambient temperature to afford the lactone in near quantitative yield. The success of this method had been attributed to the favorable conformation adopted by the seco acid, which greatly enhanced its propensity for cyclization. We incorporated similar lactonization conditions into our own synthetic strategy and obtained the protected erythronolide B macrocycle **198** in good yield (79% from **197**) (Scheme 40). The subsequent conversion of **198** into erythronolide B has been reported previously[5b] and was hence not pursued.

[73] (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367-6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9. (c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

Scheme 40. Macrolactonization of the seco-acid **197**



5.3 CONCLUSION

This synthesis, involving 19 steps in the longest linear sequence upto **198**, constitutes the first catalytic asymmetric formal synthesis of erythronolide B. In pursuit of the synthesis, the integration of two different catalytic asymmetric processes of polypropionate synthesis has been elegantly achieved. The iterative cinchona alkaloid catalyzed AAC method of β-lactone synthesis is nicely showcased in the synthesis of six key stereochemical relationships in the two polypropionate fragments. The need to synthesize the *syn* propionate dimer in a "catalytic asymmetric" fashion inspired the development of the Lewis-base catalyzed Mukaiyama aldol reaction in our group. This methodology was successfully applied for the installation of the C_3-C_4 and C_4-C_5 *syn* stereochemical relationships. This formal erythronolide B synthesis highlights the efficient access to complex polypropionate architecture through asymmetric catalysis.

5.4 EXPERIMENTAL

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100mL, solvent). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) or 600 (^{1}H: 600 MHz; ^{13}C: 150 MHz) spectrometers with chemical shifts reported relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra or residual CH_2Cl_2 (5.32 ppm) for ^{1}H and CD_2Cl_2 (53.8 ppm) for ^{13}C NMR spectra. Unless otherwise stated, all reactions were carried out in flame-dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents (CH_2Cl_2, THF and diethyl ether) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. *N*, *N*-Diisopropylethylamine and triethylamine were distilled under nitrogen from CaH_2. Commercially available propionyl chloride was redistilled under N_2. All the commercial chemicals are purchased from Aldrich Chemical Co. Anhydrous LiI, $LiClO_4$ (ReagentPlus) and *N*,*O*-dimethylhydroxylamine hydrochloride were weighed out in a N_2-filled glovebox. *O*-Trimethylsilylquinidine (TMS*Qd*) and *O*-trimethylsilylquinine (TMS*Qn*) were prepared according to the literature procedure.[74] Flash chromatography was performed on EM silica gel 60 (230-240 mesh) unless noted otherwise.[75] If the reaction was worked up with aqueous extraction, d.r. (diastereomer ratio) was determined from crude NMR.

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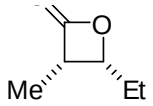
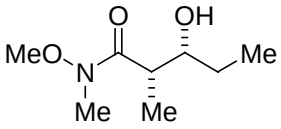
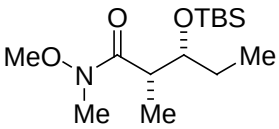
[74] Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007.
[75] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.



(3*S*,4*R*)-4-Ethyl-3-methyloxetan-2-one (76). TMS*Qd* (0.476 g, 1.20 mmol) and $LiClO_4$ (0.638 g, 6.00 mmol) were dissolved in 12 mL diethyl ether and 24 mL CH_2Cl_2 at room temperature and the solution was cooled to −78 °C. *N*, *N*-Diisopropylethylamine (5.22 mL, 30.0 mmol) was added and the reaction was stirred 15 min at −78 °C. Freshly distilled propanal (0.696 g, 0.870 mL, 12.0 mmol) was added whereupon a solution of propionyl chloride (1.08 mL, 24.0 mmol) in 6 mL CH_2Cl_2 was then added over 2 h by syringe pump. Once addition was complete, the reaction was stirred 14 h at −78 °C. The reaction was quenched at the reaction temperature by adding 10 mL Et_2O and sat. aqueous NH_4Cl solution and the resulting mixture was allowed to warm to ambient temperature. The layers were separated and the aqueous portion was extracted with ether (3×25 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude product mixture was purified by flash chromatography (2.5% ether in pentane) affording 1.05 g (74%) of the title compound as a colorless liquid. Separating the enantiomers by chiral GLC [Chirasil-dex CB 25 m x 0.25 mm column, flow rate 0.6 mL/min, method: 60 °C for 5.0 min, ramp @ 5.0 °C/min to 140 °C for 10.0 min, T_r: 18.0 min (3*S*,4*R*), T_r: 18.3 min (3*R*,4*S*)] provided the enantiomer and diastereomer ratios: (*S*,*R*):(*R*,*S*) = 1:99 (98% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ +30.0 (*c* 1.04, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2975, 1820, 1461, 1386, 1119, 1044, 958, 845; ^1H NMR (300 MHz, $CDCl_3$): δ 4.49 (ddd, *J* = 8.7, 6.3, 6.3 Hz, 1H), 3.74 (dq, *J* =7.8, 7.5 Hz, 1H), 1.89-1.65 (m, 2H), 1.28 (d, *J* =7.5 Hz, 3H), 1.05 (t, *J* =7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 76.9, 47.1, 23.3, 9.7, 8.0. HRMS (EI) m/z calcd for $C_6H_{10}O_2$: 114.0681; found: 114.0676.

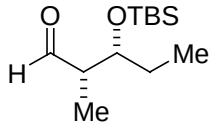


(2*S*,3*R*)-3-Hydroxy-*N*-methoxy-*N*, 2-dimethylpentanamide (77). To a 0 °C stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.11 g, 11.389 mmol) in 20 mL CH_2Cl_2, Me_2AlCl (11.4 mL, 1.0 M in hexane, 11.389 mmol) was added dropwise and the resulting solution was warmed to ambient temperature. After stirring for 2 hours, a solution of lactone **76** (0.65 g, 5.695 mmol) in 5 mL CH_2Cl_2 was added. The resulting mixture was stirred overnight whereupon it was diluted with 15 mL pH=7 phosphate buffer. The resulting biphasic mixture was stirred vigorously for an hour. Then the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resulting crude oil was then purified by flash chromatography (35% ethyl acetate in hexanes) affording 0.92 g (92.0%) of the title compound as a clear colorless oil. $[\alpha]_D$ +16.5 (*c* 1.01, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3432, 2971, 2938, 1638, 1461, 1388, 1180, 1114, 993; ^1H NMR (300 MHz, $CDCl_3$): δ 3.76 (ddd, *J* = 8.1, 5.4, 2.7 Hz, 1H), 3.69 (s, 3H), 3.18 (s, 3H), 3.00-2.80 (m, 1H), 1.65-1.47 (m, 1H), 1.45-1.30 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 73.1, 61.5, 38.1, 31.9, 26.7, 10.3, 10.0. HRMS (EI) m/z calcd for $C_8H_{17}NO_3$: 175.1208.; found: 175.1207.



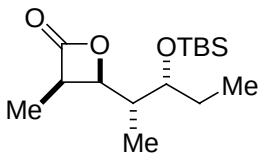
(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylpentanamide (**78**). To a solution of **77** (0.445 g, 2.541 mmol) in 20 mL CH_2Cl_2 at −78 °C, TBSOTf (0.88 mL, 3.811 mmol) was added and the reaction mixture was stirred for ten minutes whereupon Et_3N (0.89 mL, 6.353 mmol) was added. After addition was complete, the reaction mixture was warmed to 0 °C and stirred for 30 minutes, then warmed to ambient temperature. After stirring for additional 3 h, the reaction was quenched by

adding a saturated aqueous solution of $NaHCO_3$ (50 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by flash chromatography (30-35% ethyl acetate in hexanes), affording 0.71 g (97%) of the title compound as clear colorless oil. $[\alpha]_D$ +4.17 (*c* 1.34, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2959, 1665, 1463, 1383, 1254, 1114, 1048, 999, 835, 774; ^1H NMR (300 MHz, $CDCl_3$): δ 3.87 (dt, *J* = 8.7, 4.8 Hz, 1H), 3.68 (s, 3H), 3.16 (s, 3H), 3.10-2.91 (m, 1H), 1.60-1.40 (m, 2H), 1.13 (d, *J* = 7.2 Hz, 3H), 0.88 (s. 9H), 0.86 (t, *J* = 7.5 Hz, 3H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 74.1, 61.4, 39.9, 32.0, 28.1, 25.9, 18.1, 14.6, 8.4, −4.3, −4.5. HRMS (EI) m/z calcd for $C_{14}H_{31}NO_3Si$: 289.2073; found: 289.2067.

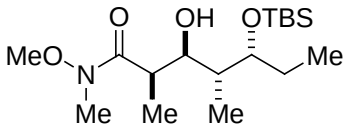


(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpentanal (79). To a solution of **78** (1.88 g, 6.51 mmol) in 50 mL THF at −78 °C, $^iBu_2AlH$ (13.0 mL, 1.0 M in hexane, 13.0 mmol) was added dropwise. The reaction was stirred until complete as monitored by TLC (1.5 h) and quenched by adding a saturated aqueous solution of Rochelle salt solution (30 mL) at −78 °C. The resulting gel-like mixture was warmed to ambient temperature, stirred vigorously until clear and extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (2% ether in pentane), affording 1.50 g (100%) of the title compound as colorless oil. $[\alpha]_D$ +58.5 (*c* 1.10, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2958, 2708, 1726, 1463, 1361, 1254, 1103, 1047, 1029, 837, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (d, *J* = 0.9 Hz, 1H), 4.02 (dt, *J* = 6.6, 3.6 Hz, 1H), 2.45 (tq, *J* = 6.9, 3.6, 0.9 Hz, 1H), 1.58-1.42 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C

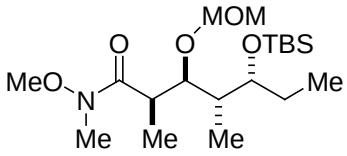
NMR (75 MHz, $CDCl_3$): δ 205.4, 73.4, 50.8, 27.4, 25.8, 18.0, 10.1, 7.6,−4.2, −4.7. HRMS (EI) m/z calcd for $C_{12}H_{26}O_2Si$: 230.1702; found: 230.1691.



(3*R*,4*S*)-4-[(2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)pentan-2-yl]-3-methyloxetan-2-one (80). To a suspension of TMS*Qn* (0.069 g, 0.17 mmol) and LiI (1.16 g, 8.68 mmol) in 0.85 mL ether was added 8 mL CH_2Cl_2 and the reaction mixture was cooled to −78 °C. To this mixture was added *N*, *N*-diisopropylethylamine (0.76 mL, 4.34 mmol) followed by a solution of the aldehyde **79** (0.400 g, 1.74 mmol) in 1 mL CH_2Cl_2. A solution of propionyl chloride (0.300 mL, 3.47 mmol) in 2 mL CH_2Cl_2 was then added over 3 h by syringe pump. After addition was complete, the reaction was stirred an additional 17 h at –78 °C whereupon the reaction was quenched at the reaction temperature by adding ether (20 mL) and a saturated aqueous solution of NH_4Cl (20 mL). The resulting mixture was warmed to ambient temperature and extracted with ether (3×20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product mixture was then purified by flash chromatography (2.5% ethyl acetate in hexanes) giving 0.470 g (95%) of the title compound as clear colorless oil. Analysis of the crude product mixture by $^1H/^{13}C$ NMR indicated a single product diastereomer. $[\alpha]_D$ –30.1 (*c* 1.26, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2958, 2857, 1828, 1463, 1386, 1256, 1149, 1093, 1051, 876, 833, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 4.43 (dd, *J* = 11.1, 6.3 Hz, 1H), 3.81 (ddd, *J* = 8.7, 5.7, 1.5 Hz, 1H), 3.76 (dq, *J* = 7.8, 7.5 Hz, 1H), 1.93-1.80 (m, 1H), 1.60-1.40 (m, 2H), 1.32 (d, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 76.2, 71.2, 46.4, 36.0, 27.7, 25.9, 18.1, 10.1, 8.5, 7.2,−4.2, −4.9; HRMS (EI) m/z calcd for $C_{11}H_{21}SiO_3$ [$(M - {}^tBu)^{\bullet+}$]: 229.1259; found: 229.1255.

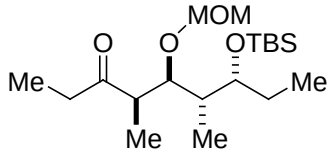


(2*R*,3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylheptanamide (82). To a 0 °C stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.283 g, 2.93 mmol) in 10 mL CH_2Cl_2, Me_2AlCl (2.93 mL, 1.0 M in hexane, 2.93 mmol) was added dropwise and the resulting solution was warmed to ambient temperature. After stirring for 2 h, the reaction mixture was recooled to 0 °C and a solution of **80** (0.420 g, 1.46 mmol) in 2 mL CH_2Cl_2 was added. The reaction was stirred for 12 h at ambient temperature whereupon the reaction mixture was diluted with pH = 7 phosphate buffer (15 mL) at 0 °C. The resulting biphasic mixture was stirred vigorously for 1 h. The layers were separated and the aqueous portion was extracted with CH_2Cl_2 (3×25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by flash chromatography on SiO_2 (7% ethyl acetate in hexanes) to afford 0.500 g (98%) of the title compound as a clear colorless oil. $[\alpha]_D$ –1.4 (*c* 0.30, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3465, 2959, 2856, 1641, 1462, 1387, 1251, 1061, 999, 834, 774; ^1H NMR (300 MHz, $CDCl_3$): δ 4.11 (d, *J* = 1.8 Hz, 1H), 4.03 (dt, *J* = 7.8, 1.5 Hz, 1H), 3.76 (td, *J* = 9, 2.4 Hz, 1H), 3.70 (s, 3H), 3.20 (s, 3H), 3.07-2.95 (m, 1H), 1.70 -1.58 (m, 1H), 1.60-1.42 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.3, 73.3, 72.6, 61.4, 38.1, 36.4, 32.1, 27.5, 26.0, 18.1, 10.6, 9.9, 9.3, −4.2, −4.6; HRMS (EI) m/z calcd for $C_{17}H_{37}NO_4Si$: 347.2492; found: 347.2490.



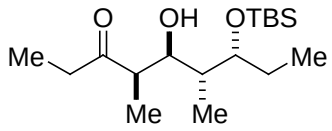
(2*R*,3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-3-(methoxymethoxy)-*N*,2,4-trimethylheptanamide (83). To an ice-cold solution of the alcohol **82** (0.250 g, 0.719 mmol) and *N*,

N-diisopropylethylamine (0.378 mL, 2.16 mmol) in 10 mL CH_2Cl_2, MOMCl (0.109 mL, 1.44 mmol) was added and the reaction mixture was warmed to 70 °C. Additional 3 equivalents of the base and 2 equivalents of MOMCl were added in two separate batches after a gap of 8 hours each and the reaction mixture was stirred until TLC monitoring showed complete consumption of the starting alcohol (if required, excess reagents were added). The reaction was then cooled to ambient temperature, diluted with ether (20 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL) and the layers were separated. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The resulting crude oil was purified by flash chromatography (6% ethyl acetate in hexanes), affording 0.24 g (85% yield) of the title compound as a pale yellow oil. $[\alpha]_D$ −24.51 (c 1.33, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2936, 2885, 1672, 1463, 1379, 1251, 1145, 1095, 1037, 835, 774; ^1H NMR (300 MHz, $CDCl_3$): δ 4.61 (d, *J* = 6.6 Hz, 1H), 4.51 (d, *J* = 6.6 Hz, 1H), 3.94 (dd, *J* = 8.4, 3.3 Hz, 1H), 3.80 (ddd, *J* = 8.1, 4.8, 2.4 Hz, 1H), 3.67 (s, 3H), 3.35 (s, 3H), 3.18 (s, 3H), 3.00 - 2.90 (m, 1H), 1.72-1.62 (m, 1H), 1.58-1.44 (m, 2H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 97.8, 80.5, 72.4, 60.9, 55.9, 39.3, 37.6, 32.5, 28.3, 25.8, 18.2, 10.2, 9.7, 9.4, −3.8, −4.7.



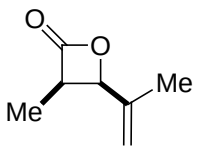
(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-(methoxymethoxy)-4,6-dimethylnonan-3-one (84). To a solution of **83** (0.235 g, 0.600 mmol) in 10 mL Et_2O, ethyl magnesium bromide (0.50 mL, 3.0 M solution in hexanes, 1.5 mmol) was added and the reaction mixture was allowed to stir at ambient temperature until complete as monitored by TLC (3 h). The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (20 mL) and

extracted with ether (2×20 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The crude oil was purified by flash chromatography (5% ethyl acetate in hexane), affording 0.212 g (98% yield) of the title compound as colorless oil. $[\alpha]_D$ −63.6 (c 0.11, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 2936, 1716, 1462, 1382, 1251, 1144, 1039, 834, 773; ^1H NMR (300 MHz, $CDCl_3$): δ 4.58 (d, *J* = 6.6 Hz, 1H), 4.49 (d, *J* = 6.6 Hz, 1H), 4.03 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.84 (ddd, *J* = 8.4, 5.1, 1.8 Hz, 1H), 3.25 (s, 3H), 2.72-2.56 (m, 2H), 2.49-2.35 (m, 1H), 1.73-1.62 (m, 1H), 1.64-1.42 (m, 2H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.9 (s, 9H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.8 (d, *J* = 6.9 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 97.9, 80.8, 72.7, 55.9, 48.4, 39.4, 33.8, 28.4, 26.0, 18.3, 10.1, 9.4, 8.6, 8.0, −3.4, −4.4. MS (ESI): m/z 383.3 (M^++Na); HRMS (EI) m/z calcd for $C_{19}H_{40}SiO_4$: 360.2696. Found: 360.2692.



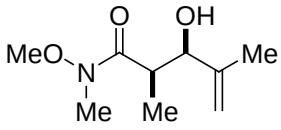
(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4,6-dimethylnonan-3-one (85). To a solution of **82** (0.390 g, 1.12 mmol) in 15 mL Et_2O, ethyl magnesium bromide (1.12 mL, 3.0 M solution in hexanes, 3 equiv, 3.37 mmol) was added and the reaction mixture was allowed to stir at ambient temperature for 1 h during which time, the reaction mixture became cloudy with a white precipitate. Another portion of ethyl magnesium bromide (1.12 mL, 3.0 M solution in hexanes, 3 equiv, 3.37 mmol) was added and stirred until the reaction was complete (as monitored by TLC). The reaction was quenched by adding a saturated aqueous solution of NH_4Cl solution (30 mL) and the resulting mixture was extracted with ether (2×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (4% ethyl acetate in hexanes) to afford 0.330 g (93%) of the title compound as a clear colorless oil. $[\alpha]_D$ +10.3 (*c* 1.18, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3481,

2959, 2937, 2883, 2858, 1704, 1462, 1382, 1253, 1047; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 (dt, *J* = 9.9, 2.1 Hz, 1H), 3.87 (d, *J* = 1.8 Hz, 1H), 3.82 (ddd, *J* = 7.8, 5.5, 2.4 Hz, 1H), 2.60-2.50 (m, 3H), 1.80-1.67 (m, 1H), 1.65-1.48 (m, 2H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.89 (s, 9H), 0.77 (d, *J* = 6.9 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.0, 76.9, 72.9, 48.4, 39.2, 34.0, 25.9, 25.4, 18.0, 11.7, 11.1, 8.2, 7.8, −4.5, −4.6. MS (ESI): m/z 339.2 (M^+ + Na); HRMS (ESI) m/z calcd for $C_{17}H_{36}O_3SiNa$ [$(M+Na)^+$]: 339.2331; found: 339.2360.

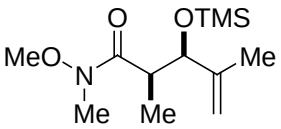


(3*R*,4*R*)-3-Methyl-4-(prop-1-en-2-yl)oxetan-2-one (86). TMS*Qn* (0.565 g, 1.43 mmol) and LiI (3.800 g, 28.53 mmol) were dissolved in 5 mL diethyl ether and 45 mL CH_2Cl_2 at room temperature and then cooled to −40 °C. To this solution was added *N*, *N*-diisopropylethylamine (6.25 mL, 35.7 mmol) and the mixture was stirred 15 min whereupon freshly distilled methacrolein (1.000 g, 1.180 mL, 14.27 mmol) was added. A solution of propionyl chloride (2.730 mL, 31.39 mmol) in 2.3 mL CH_2Cl_2 was then added over 2 h by syringe pump. The reaction was stirred 16 h then at –78 °C by adding 60 mL Et_2O and 60 mL sat. NH_4Cl solution. The resulting mixture was warmed to ambient temperature, the layers were separated and the aqueous portion was extracted with ether (3×25 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude product was purified by flash chromatography (pentane followed by 1-2.5% ether in pentane) giving 0.92 g (62%) of the title compound as a colorless, highly volatile liquid. Crude NMR of the reaction mixture showed the conversion was 80-85%. Separation of the enantiomers by chiral GLC [Chirasil-dex CB 25 m x 0.25 mm column, flow rate 0.5 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to

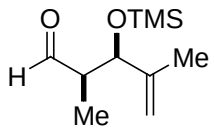
130 °C for 5.0 min, T_r: 23.5 min (3*S*,4*S*), T_r: 24.3 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (*S*,*S*):(*R*,*R*) = 1:99 (98% ee), *cis:trans* = >99:1 (>99% de). $[\alpha]_D$ +10 (*c* 0.92, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2981, 2947, 1829, 1455, 1378, 1262, 1008, 993, 922, 730; ^1H NMR (300 MHz, $CDCl_3$): δ 5.18 (br s, 1H), 5.15 (br s, 1H), 4.92 (d, *J* = 6.6 Hz, 1H), 3.85 (dq, *J* = 7.8, 6.6 Hz, 1H), 1.73 (s, 3H), 1.22 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 138.2, 113.3, 75.9, 48.8, 19.0, 8.5; HRMS (EI) *m/z* calcd for $C_7H_{10}O_2$: 126.0681; found 126.0677.



(2*R*,3*R*)-3-Hydroxy-*N*-methoxy-*N*,2,4-trimethylpent-4-enamide (87). To a 0 °C stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.00 g, 10.3 mmol) in 40 mL CH_2Cl_2, Me_2AlCl (10.31 mL, 1.0 M in hexane, 10.31 mmol) was added dropwise and the resulting mixture was warmed to ambient temperature. After the reaction was stirred for 2 hours, a solution of lactone **86** (0.650 g, 5.15 mmol) in 5 mL CH_2Cl_2 was added. The resulting mixture was stirred overnight, then quenched with 15 mL of pH = 7 phosphate buffer. The resulting biphasic mixture was stirred vigorously for an hour. Then the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (20% ethyl acetate in hexanes) afforded 0.82 g (85%) of the title compound as a white solid. m.p. 73-75 ˚C; $[\alpha]_D$ +15.5 (*c* 1.19, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3434, 3054, 2986, 1632, 1422, 1265, 994; ^1H NMR (300 MHz, $CDCl_3$): δ 5.18 (t, *J* = 2.4 Hz, 1H), 4.99 (app sextet, *J* = 1.8 Hz, 1H), 4.34 (s, 1H), 4.08 (br s, 1H), 3.71 (s, 3H), 3.20 (s, 3H), 3.10-3.00 (m, 1H), 1.70 (s, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 143.1, 111.8, 74.1, 61.5, 36.5, 32.0, 19.5, 9.9; HRMS (EI) m/z calcd for $C_9H_{17}NO_3$: 187.1208; found: 187.1204.

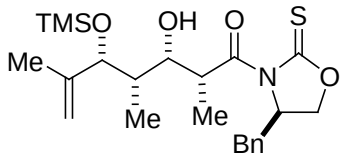


(2*R*,3*R*)-*N*-Methoxy-*N*,2,4-trimethyl-3-(trimethylsilyloxy)pent-4-enamide (**88**). To a solution of **87** (0.758 g, 4.05 mmol) in 20 mL CH_2Cl_2 at room temperature, Et_3N (0.960 mL, 6.88 mmol) was added and the reaction was stirred for 5 min. The reaction mixture was then cooled to 0 °C and TMSCl (0.770 mL, 6.70 mmol) was added dropwise. The reaction was stirred for an additional 4 h, then quenched by adding a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2×30 mL). The combined organics were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (5% ethyl acetate in hexanes) affording 0.94 g (94%) of the title compound as colorless oil. $[\alpha]_D$ −11.2 (*c* 1.70, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3076, 2959, 1665, 1459, 1383, 1251, 1082; ^1H NMR (300 MHz, $CDCl_3$): δ 4.87 (s, 1H), 4.77 (s, 1H), 4.23 (d, *J* = 8.7 Hz, 1H), 3.64 (s, 3H), 3.15-3.05 (m, 1H), 3.11 (s, 3H), 1.70 (s, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 145.6, 112.5, 78.1, 61.2, 40.2, 31.9, 17.0, 14.2, −0.2. HRMS (EI) m/z calcd for $C_{12}H_{25}NO_3Si$: 259.1604; found: 259.1614.



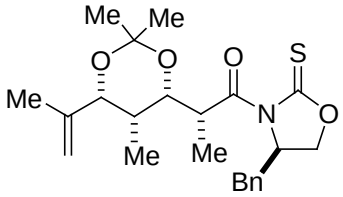
(2*R*,3*R*)-2,4-Dimethyl-3-(trimethylsilyloxy)pent-4-enal (88). To a solution of Weinreb amide **12** (2.12 g, 8.17 mmol) in 50 mL THF at −78 °C, $^iBu_2AlH$ (16.34 mL, 1.0 M in hexane, 16.34 mmol) was added dropwise. After being stirred for another 1 h at the same temperature, the reaction was quenched with 50 mL sat. aqueous Rochelle salt solution at −78 °C. The gel-like mixture was warmed to ambient temperature and stirred vigorously until clear. 50 x 2 mL Et_2O was then added for extraction and the organic layers were combined and washed with brine, dried (Na_2SO_4) and concentrated. The crude oil was purified with flash column (2.5% ethyl acetate in hexanes), affording 1.54 g (94%) of the title compound as a colorless oil. $[\alpha]_D$ +10 (*c* 0.23, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3095, 2959,

2715, 1727, 1452, 1252, 1113, 1036, 872, 843, 752; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.66 (d, *J* = 1.8 Hz, 1H), 4.97 (s, 1H), 4.91 (s, 1H), 4.41 (d, *J* = 5.1 Hz, 1H), 2.54-2.43 (m, 1H), 1.69 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 144.7, 112.7, 75.5, 50.0, 18.4, 8.1, −0.1; HRMS (EI) m/z calcd for $C_{10}H_{20}O_2Si$: 200.1233; found: 200.1233.



(2*R*,3*S*,4*S*,5*R*)-1-[(*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-3-hydroxy-2,4,6-trimethyl-5-(trimethylsilyloxy)hept-6-en-1-one (94). To an ice-cold solution of *N*-propionyloxazolidinone (0.408 g, 1.63 mmol) in 10 mL of CH_2Cl_2, titanium (IV) chloride (0.188 mL, 1.72 mmol) was added dropwise and the solution was stirred for 5 min whereupon a thick yellow slurry was formed. (-)-Sparteine (0.938 mL, 4.08 mmol) was added and the resulting dark red enolate solution was stirred for 20 min at 0 °C. The reaction mixture was then cooled to −78 °C and a solution of aldehyde **89** (0.360 g, 1.80 mmol) in 1 mL CH_2Cl_2 was added dropwise. After addition was complete, the reaction was warmed to 0 °C and stirred for another 1 h. The reaction was quenched with half-saturated ammonium chloride solution (10 mL) and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification by flash chromatography (2.5% ethyl acetate in hexanes) afforded 0.661 g (90%) of the title compound as a single diastereomer as determined by ^{1}H NMR analysis of the crude product mixture. $[\alpha]_D$ −88.9 (c 0.56, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3501, 2962, 1693, 1454, 1366, 1315, 1192, 1154, 1052, 957, 841, 747 ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.20 (m, 5H), 4.95 (s. 1H), 4.92 (s, 1H), 4.85-4.95 (m, 1H), 4.87-4.76 (m, 1H), 4.35-4.23 (m, 2H), 4.10 (d, *J* = 5.7 Hz, 1H), 4.00 (ddd, *J* = 8.4, 3.9, 2.7 Hz, 1H), 3.21 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.75 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.49 (d, *J* = 2.9 Hz, 1H), 1.69 (s, 3H), 1.67-1.62 (m, 1H), 1.39

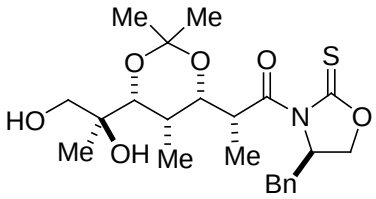
(d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.7, 177.1, 145.8, 135.1, 129.4, 129.1, 127.5, 112.5, 80.1, 74.3, 70.1, 59.9, 41.5, 38.8, 37.5, 18.1, 14.6, 7.9, 0.13; MS (EI, 70 eV): m/z 449, 431, 416, 398, 194, 143, 117, 102, 91, 73; HRMS (EI) m/z calcd for $C_{23}H_{33}NO_3SSi$ [$(M^+–H_2O)^{\bullet+}$]: 431.1950; found: 431.1937.



(*R*)-1-[(*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-2-[(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl]propan-1-one (96). To a stirred solution of the aldol product **94** (0.638 g, 1.42 mmol) in 10 mL MeOH at room temperature, was added a few drops (12-15) of 1 N aqueous HCl solution and the reaction mixture was stirred until complete as monitored by TLC (~15 min). The reaction was diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude diol product **95** was carried to the next step without further purification.

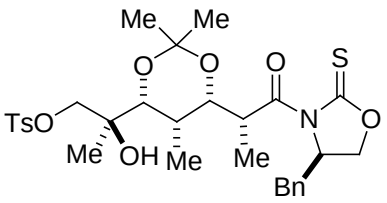
To a solution of the diol (prepared above) in 2,2-dimethoxypropane (10 mL) was added a catalytic amount of camphor sulfonic acid (2.3 mg, 0.010 mmol) and the reaction was stirred for 4.5 h at ambient temperature. Et_3N (2 mL) was added to quench the reaction and the reaction mixture was concentrated. The resulting oil was purified by flash chromatography (5% ethyl acetate in hexanes) to afford the 0.512 g (87% over two steps) of the title compound as a viscous yellow oil. IR $\nu_{max}^{(\text{thin film})}$ cm^{-1}: 3028, 2990, 1694, 1454, 1365, 1194, 1156, 1018, 968; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H), 5.03 (s, 1H), 5.00-4.90 (m, 1H), 4.89 (s, 1H), 4.80-4.66 (m, 1H), 4.44-4.22 (m, 4H), 3.21 (dd, J = 13.5, 3.6 Hz, 1H), 2.76 (dd, J = 13.2, 10.2 Hz, 1H), 1.70-1.65 (m, 1H), 1.64 (s, 3H), 1.48 (s, 3H), 1.45 (s, 3H), 1.37 (d, J = 6.9 Hz, 3H), 0.68 (d, J =

6.9, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 184.8, 175.6, 142.9, 135.4, 129.5, 128.9, 127.4, 109.9, 99.2, 74.8, 74.7, 70.4, 59.8, 40.4, 37.5, 31.1, 29.7, 19.4, 19.1, 15.5, 5.8; MS (EI, 70 eV): m/z 417, 402, 359, 342, 276, 249, 194, 117, 102; HRMS (ESI) m/z calcd for $C_{23}H_{31}NO_4S$ (M^+): 417.1974; found: 417.1989.

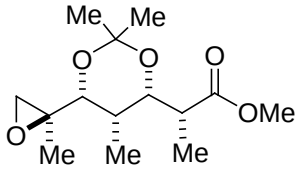


(*R*)-1-[(*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-2-{(4*S*,5*S*,6*R*)-6-[(*S*)-1,2-dihydroxypropan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}propan-1-one (97′). To the acetonide **96** (1.015 g, 2.431 mmol) in ^{t}BuOH/H_2O (1: 1 v/v, 50 mL total), was added methanesulfonamide (0.231 g, 2.43 mmol) followed by AD-mix α (3.646 g). The yellow reaction mixture was allowed to stir at ambient temperature for 20 h whereupon it was diluted with 20 mL EtOAc followed by the addition of Na_2SO_3 (0.919 g, 7.29 mmol). The resulting heterogeneous mixture was stirred for 20 min. The layers were then separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with 1M $NaHSO_4$ solution (1×50 mL), sat. $NaHCO_3$ solution (1×50 mL) and brine, dried over Na_2SO_4 and concentrated. The resulting crude oil was purified by flash chromatography (60% ethyl acetate in hexanes) affording 1.04 g (96%) of the title compound as a colorless viscous oil. IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3435, 2989, 2936, 1735, 1693, 1454, 1376, 1310, 1197, 1155, 1046, 1016, 969, 746, 702; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.19 (m, 5H), 5.00-4.90 (m, 1H), 4.80-4.70 (m, 1H), 4.36-4.26 (m, 2H), 4.15 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.94 (d, *J* = 2.1 Hz, 1H), 3.79 (dd, *J* =11.4, 3.6 Hz, 1H), 3.40 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.19 (dd, *J* = 13.2, 3.3 Hz, 1H), 2.87 (br s, 1H), 2.75 (dd, *J* =13.5, 10.2 Hz, 1H), 2.50-2.35 (br m,1H), 1.76-1.66 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.16 (s, 3H), 0.94 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.4, 175.6, 135.0, 129.3, 129.0,

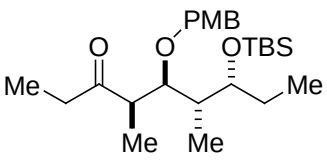
127.5, 127.5, 99.9, 78.9, 76.0, 73.5, 70.1, 67.7, 59.7, 39.7, 37.5, 31.2, 29.8, 21.8, 19.4, 15.6, 7.4; HRMS (EI) m/z calcd for $C_{23}H_{33}NO_6S$: 451.2029; found: 451.2007.



(*S*)-2-{(4*R*,5*S*,6*S*)-6-[(*R*)-1-[(*R*)-4-Benzyl-2-thioxooxazolidin-3-yl]-1-oxopropan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-2-hydroxypropyl 4-methylbenzenesulfonate (98′). To a solution of the diol **97′** (0.840 g, 1.85 mmol) and *N*,*N*-dimethylaminopyridine (0.340 g, 2.79 mmol), in 6 mL CH_2Cl_2 at 0 °C, *p*-toluenesulfonyl chloride (0.425 g, 2.23 mmol) was added. The reaction mixture was allowed to stir at ambient temperature for 24 h, then quenched by adding a saturated aqueous solution of NH_4Cl (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The organic extracts were combined, washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (30% ethyl acetate in hexanes), affording 0.96 g (85% yield) of the title compound as a colorless viscous oil, sometimes as a white foam. IR $\nu_{max}^{(\text{thin film})}$ cm^{-1}: 3501, 2990, 1694, 1455, 1365, 1310, 1190, 1176, 1097, 1018, 975, 837; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.40-7.20 (m, 7H), 5.10-4.95 (m, 1H), 4.80-4.65 (m, 1H), 4.40-4.30 (m, 2H), 4.20-4.10 (m, 1H), 3.99 (d, *J* = 9.6 Hz, 1H), 3.91 (d, *J* = 9.6 Hz, 1H), 3.80 (br s, 1H), 3.25 (dd, *J* = 12.9, 3.3 Hz, 1H), 2.78 (dd, *J* = 13.5, 9.9 Hz, 1H), 2.46 (s, 3H), 2.50-2.30 (m, 1H), 1.78-1.70 (m, 1H), 1.42 (s, 6H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.16 (s, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 184.7, 175.8, 145.1, 135.2, 129.9, 129.8, 129.4, 129.0, 128.0, 127.4, 100.1, 76.2, 75.3, 72.6, 70.4, 60.4, 60.1, 39.7, 37.5, 31.1, 29.7, 23.0, 21.7, 19.5, 15.2, 7.6; HRMS (EI) m/z calcd for $C_{30}H_{39}NO_8S_2$: 605.2117; found: 605.2120.

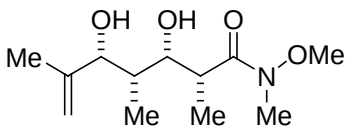


(*R*)-Methyl 2-{(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-[(*S*)-2-methyloxiran-2-yl]-1,3-dioxan-4-yl}propanoate (99′). To a solution of tosylate **98′** (0.600 g, 0.990 mmol) in 10 mL MeOH, solid K_2CO_3 (0.137 g, 0.990 mmol) was added. After stirring for 2 hours at ambient temperature (TLC monitoring indicated complete conversion of starting material), the reaction mixture was concentrated and extracted with ether (3×30 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (10% ethyl acetate in hexanes), affording 0.170 g (63%) of the title compound as colorless oil. $[\alpha]_D$ −20.3 (c 1.33, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2991, 2940, 1738, 1455, 1381, 1259, 1200, 1157, 1108, 1053, 992; ^1H NMR (300 MHz, $CDCl_3$): δ 4.04 (d, *J* = 2.1 Hz, 1H), 3.92 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.71 (s, 3H), 3.05 (d, *J* = 5.7 Hz, 1H), 2.63 (dq, *J* = 9.9, 6.9 Hz, 1H), 2.55 (d, *J* = 5.4 Hz, 1H), 1.55-1.66 (m, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.28 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 99.5,5.9, 74.4, 71.8, 56.7, 51.7, 50.2, 41.9, 31.9, 29.6, 19.3, 18.4, 15.1; MS (EI): m/z 257, 185, 128, 113, 109, 102; HRMS (EI) m/z calcd for $C_{13}H_{21}O_5$ (M^+–CH_3): 257.1389; found: 257.1392.



(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsilyloxy)-5-[(*p*-methoxybenzyl)oxy]-4,6-dimethylnonan-3-one (105). To a solution of **85** (1.12 g, 3.54 mmol) in 30 mL CH_2Cl_2 at −78 °C was added freshly prepared *p*-methoxybenzyl trichloroacetimidate (1.69 g, 6.00 mmol) and BF_3•Et_2O (0.23 mL, 1.0 M solution in CH_2Cl_2, 0.23 mmol) and the reaction mixture was stirred for 2.5 h. At this time, 1.30 g (4.62 mmol) of *p*-methoxybenzyl trichloroacetimidate and 0.22 mL of $BF_3 \cdot Et_2O$ (0.22

mmol) were added. After stirring for an additional 3 h (at which time the reaction was complete as monitored by TLC), the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated to provide a yellow oil that was triturated with 5% EtOAc/hexanes and the resulting white solid was removed by filtration. The filtrate was concentrated and purified by flash chromatography (2.5-5 % ethyl acetate in hexanes) to afford 1.38 g (90%) of the title compound as a clear colorless oil. $[\alpha]_D$ −57.0 (*c* 1.00, CH_2Cl_2); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2957, 2936, 2882, 2857, 1713, 1614, 1514, 1462, 1250, 1095; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.35 (d, *J* = 10.5 Hz, 1H), 4.27 (d, *J* = 10.5 Hz, 1H), 3.97 (dt, *J* = 6, 1.8 Hz, 1H), 3.96 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.80 (s, 3H), 2.69 (dq, *J* = 7.2, 2.4 Hz, 1H), 2.64 (app quint, *J* = 7.2 Hz, 1H), 2.57-2.42 (m, 1H), 1.80-1.66 (m, 1H), 1.65-1.42 (m, 2H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.82 (t, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H),; ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.9, 97.9, 80.8, 72.7, 55.9, 48.4, 39.4, 33.8, 28.4, 26.0, 18.3, 10.1, 9.4, 8.6, 8.0, −3.4, −4.4. HRMS (ESI): m/z calcd for $C_{25}H_{44}O_4SiNa$ [$(M+Na)^+$]: 459.2907; found: 459.2906.

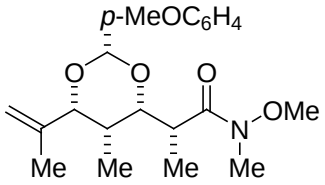


(2*R*,3*S*,4*S*,5*R*)-3,5-Dihydroxy-*N*-methoxy-*N*,2,4,6-tetramethylhept-6-enamide (106). To an ice-cold solution of *N*,*O*-dimethylhydroxylamine hydrochloride (0.438 g, 4.49 mmol) in 9 mL CH_2Cl_2, $AlMe_3$ (2.24 mL, 2 M solution in toluene, 4.49 mmol) was added dropwise. After addition was complete, the reaction mixture was stirred at room temperature for 1 hour. The reaction was then cooled to −20 °C and a solution of the aldol adduct **94** (0.807 g, 1.79 mmol) in 5 mL CH_2Cl_2 was added. The reaction was stirred for additional 2 hours at 0 °C and quenched by adding a saturated

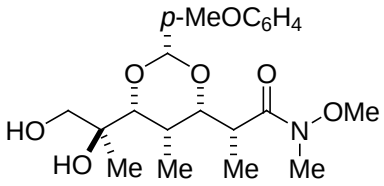
aqueous solution of Rochelle's salt (30 mL). The resulting biphasic mixture was stirred vigorously for 30 minutes at room temperature until two homogeneous layers separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Majority of the product coeluted with the chiral auxiliary upon flash chromatography (20% ethyl acetate in hexanes). A small amount of the pure material was obtained and used for characterization. $[\alpha]_D$ –5.39 (*c* 1.02, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3465, 2962, 1644, 1456, 1385, 1250, 1067, 1044, 996, 901, 841, 751; ^1H NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 1H), 4.87 (s, 1H), 4.10 (d, *J* = 5.1 Hz, 1H), 3.84 (d, *J* = 8.7 Hz, 1H), 3.69 (s, 3H), 3.15 (s, 3H), 3.15-3.00 (m, 1H), 2.86 (s, 1H), 1.80-1.60 (m, 1H), 1.64 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 145.7, 112.1, 80.5, 75.0, 61.6, 38.8, 38.1, 32.0, 18.4, 14.5, 7.5, 0.1; HRMS (EI) m/z calcd. for $C_{15}H_{31}NO_4Si$: 317.2022; found: 307.2010.

To a stirred solution of the crude mixture from above, in 10 mL MeOH at room temperature, was added a few drops (12-15) of 1 N aqueous HCl solution and the reaction mixture was stirred at room temperature until TLC showed no presence of starting material (~20 min). The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (3 ×30 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (40% ethyl acetate in hexanes), affording 0.300 g (68% yield over two steps) of the title compound as colorless oil. $[\alpha]_D$ –29 (*c* 0.25, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3396, 2976, 2938, 1633, 1455, 1388, 1124, 990; ^1H NMR (300 MHz, $CDCl_3$): δ 4.98 (app. d, *J* = <1 Hz, 1H), 4.89 (dq, *J* = 1.5, 3.0 Hz, 1H), 4.20 (s, 1H), 3.97 (dd, *J* = 3.0, 7.5 Hz, 1H), 3.69 (s, 3H), 3.16 (s, 3H), 3.15-3.06 (m, 1H), 2.65 (br s, 1H), 1.75 (tq, *J* = 7.2, 3.0 Hz, 1H), 1.64 (s, 3H), 1.23

(d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.0, 145.9, 110.1, 78.3, 76.3, 61.6, 38.2, 36.8, 32.0, 19.4, 13.7, 5.9; HRMS (Q-Tof) m/z calcd for $C_{12}H_{23}NO_4Na$ [$(M+Na)^+$]: 268.1525; found: 268.1512.

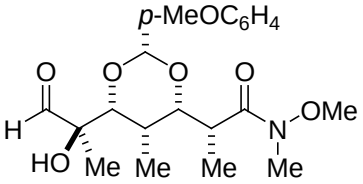


(*R*)-*N*-methoxy-2-[(2*R*,4*S*,5*S*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl]-*N*-methylpropanamide (107). To a solution of **106** (1.05 g, 4.28 mmol) in 20 mL CH_2Cl_2, pyridinium *p*-toluenesulfonate (PPTS) (0.107 g, 0.428 mmol) and *p*-anisaldehyde dimethyl acetal (1.090 mL, 6.415 mmol) were added sequentially. The reaction mixture was allowed to stir at room temperature for 7 hours, concentrated and purified by flash chromatography (8% ethyl acetate in hexanes) to afford 1.457 g (94% yield) of the title compound in the form of a colorless oil. $[\alpha]_D$ –43.7 (*c* 0.16, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2936, 1652, 1519, 1455, 1248, 1070; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 5.60 (s, 1H), 5.11 (s, 1H), 4.93 (s, 1H), 4.29 (d, J = 1.5 Hz, 1H), 4.07 (dd, J = 9.9, 1.5 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 1.90 (tq, J = 1.5, 6.9 Hz, 1H), 1.68 (s, 3H), 1.32 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 159.8, 142.2, 131.6, 127.3, 113.5, 110.5, 101.1, 82.4, 82.2, 61.5, 55.2, 37.7, 32.1, 31.2, 19.2, 15.7, 6.3; HRMS (EI) m/z calcd for $C_{20}H_{29}NO_5$: 363.2046; found: 363.2046.



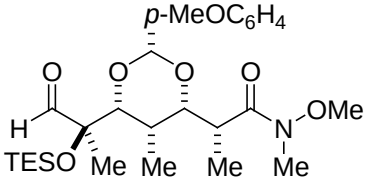
(*R*)-2-{(2*R*,4*S*,5*S*,6*R*)-6-[(*S*)-1,2-dihydroxypropan-2-yl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (108′). To a suspension of **107** (0.325 g, 0.894 mmol) in ^{t}BuOH/H_2O (1: 1 v/v, 18 mL total), was added

methanesulfonamide (0.085 g, 0.89 mmol) followed by AD-mix α (1.341 g). The yellow reaction mixture was allowed to stir at ambient temperature for 36 h whereupon it was diluted with 40 mL EtOAc followed by addition of Na_2SO_3 (0.338 g, 2.68 mmol). The resulting biphasic mixture was stirred for 20 min after which the layers were separated and the aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with 1M $NaHSO_4$ (1 × 30 mL), sat. $NaHCO_3$ solution (1 × 30 mL), and brine, then dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (80% ethyl acetate in hexanes) affording 0.328 g (93% yield) of the title compound as a colorless viscous oil. $[\alpha]_D$ –16.6 (*c* 0.12, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3427, 2972, 2937, 2877, 1639, 1517, 1460, 1391, 1248, 1171, 1107; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.56 (s, 1H), 3.98 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.92 (d, *J* = 2.1 Hz, 1H), 3.82 (dd, *J* = 10.8, 3.0 Hz, 1H),3.81 (s, 3H), 3.73 (s, 3H), 3.44 (dd, *J* = 11.1, 8.7 Hz, 1H), 3.25-3.18 (m, 1H), 3.20 (s, 3H), 2.78 (br s, 1H, OH), 2.30 (dd, *J* = 8.7, 3.3 Hz, 1H, OH), 1.93 (tq, *J* = 1.8, 6.9 Hz, 1H), 1.58 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.24 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 160.0, 131.0, 127.3, 113.6, 102.2, 86.1, 83.7, 73.8, 67.6, 61.6, 55.3, 37.1, 32.1, 31.2, 21.6, 15.7, 8.0; HRMS (EI) m/z calcd for $C_{20}H_{31}NO_7$: 397.2101; found: 397.2096.



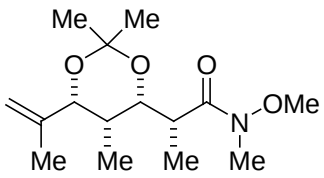
(*R*)-2-{(2*R*,4*S*,5*S*,6*R*)-6-[(*R*)-1-formyl-1-hydroxyethyl]-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (109′). To a solution of the diol **108′** (1.01 g, 2.54 mmol), anhydrous DMSO (1.98 mL, 27.9 mmol) and triethylamine (1.77 mL, 12.7 mmol) in 10 mL dichloromethane at 0 °C, was added pyr.SO_3 complex (1.617 g, 10.16 mmol). The yellow reaction mixture was then stirred at the same temperature for 3 hours whereupon it was

diluted with ether (20 mL). The ether layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography with 40% ethyl acetate in hexanes as eluant affording 0.767 g (77%) of the title compound as a colorless oily liquid. $[\alpha]_D$ −36.2 (*c* 0.37, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3433, 2935, 1733, 1652, 1518, 1462, 1386, 1249, 1171, 1114, 1068, 1030; ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.54 (s, 1H), 3.99 (d, *J* = 1.8 Hz, 1H), 3.98 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.42 (s, 1H), 3.25-3.10 (m, 1H), 3.18 (s, 3H), 1.94 (tq, *J* = 1.8, 6.9 Hz, 1H), 1.35 (s, 3H), 1.28 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.2, 174.9, 160.0, 130.6, 127.3, 113.6, 102.2, 85.2, 83.2, 78.6, 61.5, 55.3, 37.2, 32.1, 31.1, 18.9, 15.6, 8.4; HRMS (Q-Tof) m/z calcd for $C_{20}H_{29}NO_7Na$ $[(M+Na)^+]$: 418.1842; found: 418.1878.

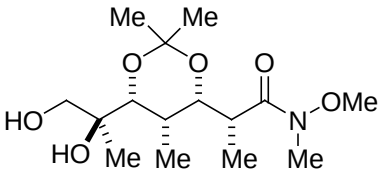


(*R*)-2-{(2*R*,4*S*,5*S*,6*R*)-6-[(*R*)-1-(triethylsilyloxy)-1-formylethyl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (110′). To a solution of the aldehyde **109′** (0.767 g, 1.94 mmol) in 10 mL dichloromethane at −30 °C was added 2,6-lutidine (0.340 mL, 2.91 mmol). After stirring for 5 minutes, TESOTf (0.520 mL, 2.33 mmol) was added and the solution was allowed to stir for 2 h at −30 °C followed by 2 h at 0 °C . The reaction was then quenched with sat. NH_4Cl solution and the two layers were separated. The aqueous layer was extracted with ether (2 × 15 mL) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (10% ethyl acetate in hexanes) affording 0.859 g (87%) of the title compound as a colorless oil. $[\alpha]_D$ −21.2 (*c* 0.67, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2955, 2876, 1735, 1659, 1616, 1518, 1460,

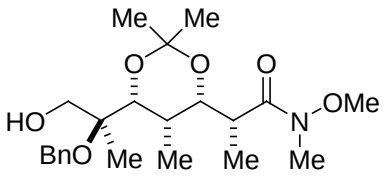
1384, 1248, 1168, 1111, 1013; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.64 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.50 (s, 1H), 3.96 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.96 (d, *J* = 2.1 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.23-3.17 (m, 1H), 3.18 (s, 3H), 1.87 (tq, *J* = 2.1, 6.6 Hz, 1H), 1.33 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.0, 175.2, 159.8, 131.0, 127.3, 113.4, 102.0, 85.4, 83.5, 80.4, 61.6, 55.3, 37.1, 32.1, 31.2, 19.2, 15.6, 7.7, 6.9, 6.5; HRMS (Q-Tof) m/z calcd for $C_{26}H_{43}NO_7SiNa$ [$(M+Na)^+$]: 532.2707; found: 532.2673.



(*R*)-*N*-methoxy-*N*-methyl-2-[(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl]propanamide (147). To a solution of the diol **106** (0.320 g, 1.30 mmol) in 2,2-dimethoxypropane (10 mL) was added camphor sulfonic acid (0.030 g, 0.130 mmol) and the resulting solution was stirred at ambient temperature for 1 h. The reaction was quenched by adding 2 mL of Et_3N and the reaction mixture was concentrated and the resulting crude oil was purified by flash chromatography (30% ethyl acetate in hexanes) to afford the 0.370 g of the acetonide **147** (100%) as a colorless oil. $[\alpha]_D$ –15 (*c* 0.44, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2989, 2938, 1661, 1459, 1384, 1254, 1200, 1160, 1104, 955; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.00 (app. s, 1H), 4.86 (m, 1H), 4.29 (d, *J* = <1 Hz, 1H), 4.07 (dd, *J* = 1.8, 9.6 Hz, 1H), 3.70 (s, 3H), 3.18 (s, 3H), 3.14-3.00 (m, 1H), 1.73 (tq, *J* = 6.9, 1.8 Hz, 1H), 1.62 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 142.8, 110.1, 99.1, 75.1, 74.9, 61.5, 37.8, 32.1, 31.1, 29.9, 19.6, 19.3, 15.6, 5.4; HRMS (EI) m/z calcd for $C_{14}H_{24}NO_4$ [$(M-CH_3)^{\bullet+}$]: 270.1705; found: 270.1694.



(*R*)-2-{(4*S*,5*S*,6*R*)-6-[(*S*)-1,2-dihydroxypropan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (148′). To a suspension of **147** (0.710 g, 2.49 mmol) in ^{t}BuOH/H_2O (1: 1 v/v, 50 mL total), was added methanesulfonamide (0.236 g, 2.49 mmol) followed by AD-mix α (3.73 g). The yellow reaction mixture was allowed to stir at ambient temperature for 36 h whereupon it was diluted with 50 mL EtOAc followed by addition of Na_2SO_3 (0.940 g, 7.47 mmol). The resulting biphasic mixture was stirred for 20 min after which the layers were separated and the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with 1M $NaHSO_4$ (1×50 mL), sat. $NaHCO_3$ solution (1×50 mL), and brine, then dried over Na_2SO_4 and concentrated. The crude oil was purified by flash chromatography (60-70% ethyl acetate in hexanes) affording 0.725 g (91% yield) of the title compound as a colorless viscous oil. mp 102-103 °C; $[\alpha]_D$ +0.74 (*c* 0.45, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3427, 2989, 2938, 1638, 1459, 1389, 1200, 1050; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.92 (d, *J* = 2.1 Hz, 1H), 3.79 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.71 (s, 3H), 3.38 (dd, *J* = 10.8, 8.7 Hz, 1H), 3.17 (s, 3H), 3.15-3.00 (m, 1H), 2.90 (s, 1H), 2.57 (dd, *J* = 8.7, 2.1 Hz, 1H), 1.80-1.68 (m, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.14 (s, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 99.9, 79.6, 76.4, 73.5, 67.8, 61.6, 37.1, 32.1, 31.2, 29.8, 21.6, 19.5, 15.6, 6.9; HRMS (Q-Tof) m/z calcd for $C_{15}H_{29}NO_6Na$ [$(M+Na)^+$]: 342.1893; found: 342.1877.



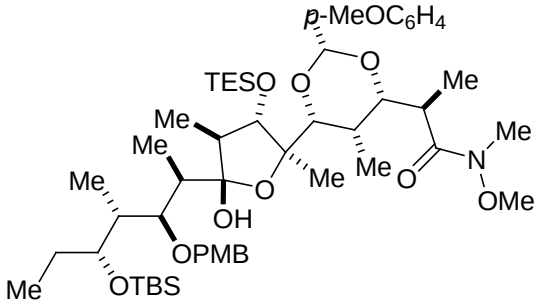
(*R*)-2-{(4*S*,5*S*,6*R*)-6-[(*S*)-2-(benzyloxy)-1-hydroxypropan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (149′). To a CH_2Cl_2 solution (5 mL) of **148′** (0.135

g, 0.421 mmol) at 0 °C, were added 2,6-lutidine (0.293 mL, 2.53 mmol) and TIPSOTf (0.226 mL, 0.842 mmol). After stirring the reaction mixture for 3 h at room temperature, the reaction was quenched by the addition of sat. $NaHCO_3$ solution, and the organic materials were extracted with CH_2Cl_2 (2×10 mL), then the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* after filtration. Purification by flash column chromatography (5% ethyl acetate in hexanes) gave 0.165 g (90%) of TIPS ether.

To a suspension of NaH (60%, 45.6 mg, 1.15 mmol) in DMF (1.5 mL) at 0 °C was added a solution of the above TIPS ether(0.165 g, 0.382 mmol) in DMF (1.5 mL). After stirring the reaction mixture for 30 min, benzyl bromide (0.113 mL, 0.955 mmol) and TBAI (1.5 mg, 0.0040 mmol as a solution in DMF) were added at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous layer was extracted with ether (2×10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification by flash column chromatography (5% ethyl acetate in hexanes) afforded 0.160 g (74%) of the tertiary benzyl ether.

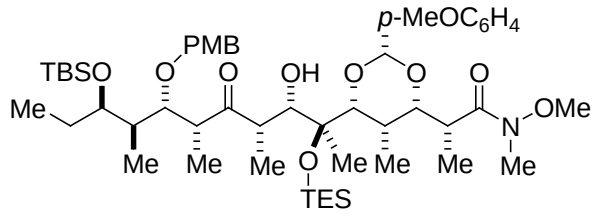
To a solution of the compound (prepared above) in THF (5 mL) was added pyridine (3 mL) followed by HF.pyr complex (2 mL) and the reaction mixture was allowed to stir for 36 h at ambient temperature. The reaction was quenched by adding it dropwise into an ice-cold saturated aqueous $NaHCO_3$ solution (30 mL) which was then extracted with ether (2×30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (30% ethyl acetate in hexanes) afforded 0.116 g (95%) of the title compound as colorless oil. $[\alpha]_D$ +2.31 (*c* 0.52, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3435, 2989, 2937, 2883, 1640, 1458, 1387, 1256, 1199, 1105, 1061; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.08 (d, *J* = 2.1 Hz, 1H), 3.99 (dd, *J* =

9.9, 1.8 Hz, 1H), 3.77-3.68 (m, 1H), 3.71 (s, 3H), 3.51 (dd, *J* = 11.4, 6.9 Hz, 1H), 3.17 (s, 3H), 3.20-3.05 (m, 1H), 2.31 (app t, *J* = 6.3 Hz, 1H), 1.81 (tq, *J* = 2.2, 6.9 Hz, 1H), 1.45 (s, 6H), 1.28 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 139.5, 128.5, 127.3, 127.2, 99.7, 78.8, 77.1, 76.8, 66.4, 64.9, 61.6, 37.2, 32.1, 31.4, 29.9, 19.4, 17.3, 15.6, 7.1; HRMS (Q-Tof) m/z calcd for $C_{22}H_{35}NO_6Na$ [$(M+Na)^+$]: 432.2362; found: 432.2342.



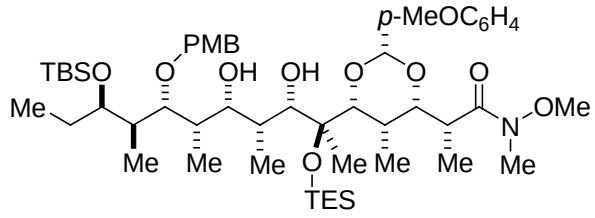
(*R*)-2-[(2*R*,4*S*,5*S*,6*R*)-6-{(2*R*,3*S*,4*S*,5*R*)-5-((2*R*,3*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-4-methylheptan-2-yl}-5-hydroxy-2,4-dimethyl-3-(triethylsilyloxy)tetrahydrofuran-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-*N*-methoxy-*N*-methylpropanamide (142′). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.51 (s, 1H), 4.35 (d, *J* = 10.5 Hz, 1H), 4.32 (d, *J* = 10.5 Hz, 1H), 3.99 (d, *J* = 2.0 Hz, 1H), 3.95 (ddd, *J* = 8.5, 5.0, 2.0 Hz, 1H), 3.92 (dd, *J* = 6.6, <1 Hz, 1H), 3.86 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.82 (d, *J* = 3.5 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.24 (dq, *J* = 7.0, 4.0 Hz, 1H), 3.25-3.15 (m, 1H), 3.11 (s, 3H), 2.76 (br s, 1H), 2.68 (dq, *J* = 7.0, 1.0 Hz, 1H), 1.98-1.93 (app q, *J* = 6.6 Hz, 1H), 1.60-1.50 (m, 2H), 1.50-1.42 (m, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.78 (t, *J* = 7.5 Hz, 3H), 0.63 (q, *J* = 8.0 Hz, 6H), 0.62 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 175.5, 160.4, 159.6, 131.9, 131.4, 129.9, 128.2, 114.0, 113.7, 106.0, 102.8, 87.9, 85.5, 84.5, 79.6, 73.8, 72.4,

61.9, 55.6 (2C), 50.9, 44.7, 38.9, 37.6, 32.0 (2C), 30.1, 28.1, 26.3, 19.0, 18.6, 15.8, 14.6, 10.2, 9.5, 8.8, 7.1, 5.6, –3.1, –3.9.



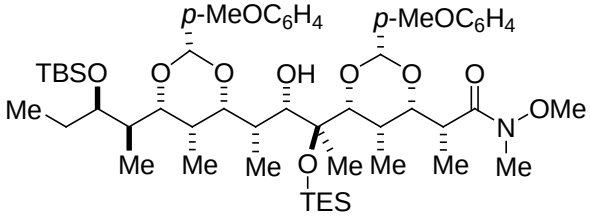
(*R*)-*N*-Methoxy-2-{(2*R*,4*S*,5*S*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-[(5*S*,6*S*,7*S*,9*R*,10*S*,11*R*,12*R*)-3,3,12-triethyl-6-hydroxy-10-(4-methoxybenzyloxy)-5,7,9,11,14,14,15,15-octamethyl-8-oxo-4,13-dioxa-3,14-disilahexadecan-5-yl]-1,3-dioxan-4-yl}-*N*-methylpropanamide (145′). To a solution of 0.143 mL (0.494 mmol) of diphenyltetramethyldisilazine in 2.5 mL of THF at 0 °C was added a 1.55 M solution of *n*-butyllithium in hexanes (0.320 mL, 0.494 mmol). After 20 min, the reaction was cooled to –78 °C and a solution of ketone (0.196 g, 0.449 mmol) in 1.0 mL of THF was added via cannula (with 2 x 0.5 mL rinses). The resultant clear yellow solution was stirred at –78 °C for 20 min, then at 0 °C for 1 h, before the reaction was recooled to –78 °C and a solution of the aldehyde **110′** (0.343 g, 0.673 mmol) in 2.0 mL of THF was added via cannula. The resultant solution was stirred for 24 h at –78 °C, then quenched by dropwise addition of precooled acetic acid (1.8 mL, 1 N in THF, 4 equiv) at the same temperature. After stirring for another 20 min at −78 °C, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added and exttracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford a yellow oil. Analysis of the unpurified mixture by ^{1}H NMR revealed a single diastereomer. Purification by automated flash chromatography (linear gradient 0 to 50% ethyl acetate/hexanes) afforded 0.220 g (51%) of the title compound as colorless oil. $[\alpha]_D$ −0.91 (*c* 0.44, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3412, 2955, 2878, 1699, 1660, 1616, 1515, 1461, 1384, 1249, 1034; ^{1}H NMR (500 MHz,

CD_2Cl_2): δ 7.41 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.51 (s, 1H), 4.35 (d, *J* = 10.5 Hz, 1H), 4.32 (d, *J* = 10.5 Hz, 1H), 3.99 (d, *J* = 2.0 Hz, 1H), 3.95 (ddd, *J* = 8.5, 5.0, 2.0 Hz, 1H), 3.92 (dd, *J* = 6.6, <1 Hz, 1H), 3.86 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.82 (d, *J* = 3.5 Hz, 1H), 3.77 (s, 3H), 3.76 (s, 3H), 3.68 (s, 3H), 3.24 (dq, *J* = 7.0, 4.0 Hz, 1H), 3.25-3.15 (m, 1H), 3.11 (s, 3H), 2.76 (br s, 1H), 2.68 (dq, *J* = 7.0, 1.0 Hz, 1H), 1.98-1.93 (app q, *J* = 6.6 Hz, 1H), 1.60-1.50 (m, 2H), 1.50-1.42 (m, 1H), 1.25 (s, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.88 (s, 9H), 0.78 (t, *J* = 7.5 Hz, 3H), 0.63 (q, *J* = 8.0 Hz, 6H), 0.62 (d, *J* = 7.0 Hz, 3H), 0.05 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 217.7, 175.5, 160.4, 159.4, 132.0, 131.6, 129.3, 128.0, 113.9, 113.7, 102.6, 84.7, 81.9, 80.0, 78.8, 76.3, 73.3, 73.2, 61.9, 55.6 (2C), 47.3, 43.7, 39.6, 37.4, 32.3, 31.7, 28.8, 26.2, 22.3, 18.6, 15.7, 12.7, 10.2, 9.9, 9.8, 8.8, 7.3, 7.2, –3.2, –4.0; HRMS (Q-Tof) *m/z* calcd for $C_{51}H_{87}NO_{11}Si_2Na$ [$(M+Na)^+$]: 968.5715; found: 968.5695.



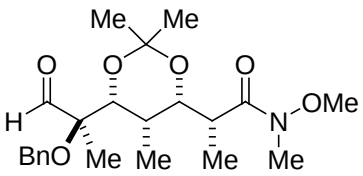
(*R*)-*N*-Methoxy-2-{(2*R*,4*S*,5*S*,6*R*)-2-(4-methoxyphenyl)-5-methyl-6-[(5*S*,6*S*,7*R*,8*R*,9*S*,10*R*,11*R*,12*R*)-3,3,12-triethyl-6,8-dihydroxy-10-(4-methoxybenzyloxy)-5,7,9,11,14,14,15,15-octamethyl-4,13-dioxa-3,14-disilahexadecan-5-yl]-1,3-dioxan-4-yl}-*N*-methyl propanamide (159′). To a solution of aldol adduct **145′** (0.100 g, 0.106 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added 3.03 mL (0.424 mmol, 0.14 M in Et_2O) of $Zn(BH_4)_2$. After 9 h at 0 °C, the reaction was quenched by adding a saturated aqueous solution of NH_4Cl (5 mL) and the resultant mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were

washed with water, dried (Na_2SO_4) and concentrated. The residue was dissolved in 20 mL of MeOH and stirred at 23 °C for 36 h. Following concentration, the residue (80:20 mixture of diastereomers by crude ^{1}H NMR) was purified by flash chromatography (10% EtOAc in hexanes) affording 0.085 g (82%) of the title compound as a white foam. $[\alpha]_D$ −5.4 (*c* 0.93, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3507, 2954, 2879, 1662, 1615, 1515, 1461, 1385, 1249, 1109, 1035; ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.41 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.56 (s, 1H), 4.65 (d, *J* = 10.5 Hz, 2H), 4.57 (d, *J* = 10.5 Hz, 2H), 3.99 (ddd, *J* = 8.5, 5.0, 2.5 Hz, 1H), 3.94 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.83 (d, *J* = 1.5 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.69 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.60 (dd, *J* = 9.0, 1.5 Hz, 1H), 3.30-3.20 (m, 1H), 3.14 (s, 3H), 2.96-2.88 (br s, 1H), 2.30 (ddq, *J* = 7.5, 7.5, 1.5 Hz, 1H),, 1.60-1.45 (m, 3H), 1.43 (s, 6H), 1.41 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 2.23 (br s, 1H), 1.95 (tq, *J* = 7.0, 1.0 Hz, 1H), 1.90 (ddd, *J* = 6.5, 3.5, 2.0 Hz, 1H), 1.86-1.80 (m, 1H), 1.65-1.52 (m, 3H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.03 (t, *J* = 8.5 Hz, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.83 (t, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.71 (q, *J* = 7.5 Hz, 6H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 175.3, 160.3, 159.6, 131.9, 131.1, 129.5, 127.6, 114.1, 113.7, 102.0, 84.2, 83.9, 82.7, 78.4, 77.3, 76.0, 73.7, 73.2, 61.9, 55.6 (2C), 39.0, 37.2, 36.9, 36.3, 32.1, 31.4, 28.6, 26.2, 21.2, 18.6, 15.9, 11.0, 10.0, 9.5, 8.7, 7.4, 7.0, 6.1, -2.9, -4.1 ; HRMS (Q-Tof) *m/z* calcd for $C_{51}H_{89}NO_{11}Si_2Na$ [$(M+Na)^+$]: 970.5872; found: 970.5853.



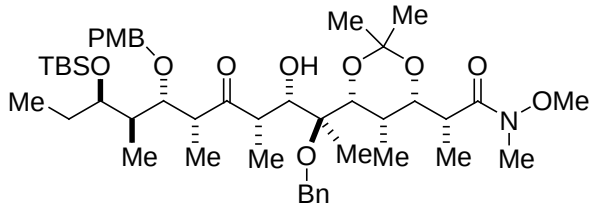
(*R*)-2-[(2*R*,4*S*,5*S*,6*R*)-6-{(2*S*,3*S*,4*S*)-4-((2*R*,4*R*,5*S*,6*R*)-6-((2*R*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)

-5-methyl-1,3-dioxan-4-yl}-3-hydroxy-2-(triethylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]-*N*-methoxy-*N*-methylpropanamide (160′). To a mixture of azeotropically dried **159'** (0.080 g, 0.082 mmol) and 95 mg of activated powdered 4 Å molecular sieves in 2 mL of CH_2Cl_2 was added a solution of DDQ (0.022 g, 0.078 mmol) in 2 mL of CH_2Cl_2 at 0 °C by syringe. After stirring at 0 °C for 1 h, the reaction was filtered through celite and the filtrate washed with saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (10% EtOAc in hexanes) afforded the title compound as a clear colorless oil (0.075 g, 94%). ^{1}H NMR (500 MHz, CD_2Cl_2): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.56 (s, 1H), 5.44 (s, 1H), 4.03 (ddd, *J* = 9.5, 6.0, 1.5 Hz, 2H), 3.95 (dd, *J* = 9.5, 1.5 Hz, 2H), 3.89 (d, *J* = 2.0 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.75 (br s, 1H), 3.72 (s, 3H), 3.70 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.55 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.31-3.23 (m, 1H), 3.14 (s, 3H), 2.32 (dq, *J* = 10.5, 6.5 Hz, 1H), 1.97-1.91 (m, 1H), 1.81-1.75 (m, 1H), 1.73 (ddq, *J* = 10.5, 7.0, 1.5 Hz, 1H), 1.57-1.45 (m, 2H), 1.29 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.03 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H), 0.75-0.63 (m, 6H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 175.3, 160.4, 160.1, 132.4, 131.9, 127.8, 127.6, 113.7, 113.7, 102.2, 101.7, 84.7, 84.2, 82.3, 81.2, 76.6, 73.9, 71.4, 61.9, 55.6 (2C), 37.4, 37.4, 34.7, 32.0, 31.6, 30.9, 28.5, 26.1, 22.2, 18.4, 15.8, 11.2, 10.4, 8.4, 7.4, 6.6, 6.2, 5.5, –3.6, –4.5.



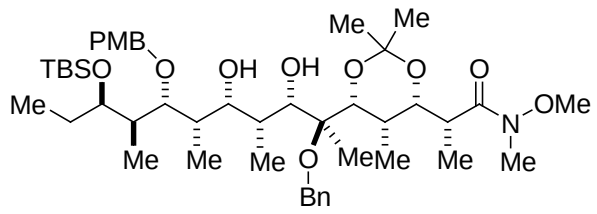
(*R*)-2-{(4*S*,5*S*,6*R*)-6-[(*R*)-1-(benzyloxy)-1-formylethyl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-*N*-methoxy-

***N*-methylpropan amide (146′).** To a stirred solution of **149′** (0.110 g, 0.269 mmol) in CH_2Cl_2 (5 mL) cooled at 0 °C was added Dess-Martin periodinane (0.194 g, 0.456 mmol). After being stirred at room temperature for 1 h, the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (15-20% ethyl acetate in hexanes) afforded 0.092 g (83%) of the title compound as colorless oil. $[\alpha]_D$ +13 (*c* 0.44, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2990, 2938, 2888, 1737, 1659, 1460, 1386, 1200, 1157, 1109; ^1H NMR (300 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.36-7.22 (m, 5H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 2.1 Hz, 1H), 4.00 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.70 (s, 3H), 3.16 (s, 3H), 3.20-3.00 (m, 1H), 1.82-1.72 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.31 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 175.3, 138.7, 128.3, 127.4, 127.0, 99.8, 82.7, 77.2, 76.2, 65.9, 61.5, 37.2, 32.1, 31.3, 29.7, 19.3, 15.5, 14.5, 6.9; HRMS (Q-Tof) m/z calcd for $C_{22}H_{33}NO_6Na$ [$(M+Na)^+$]: 430.2206; found: 430.2226.



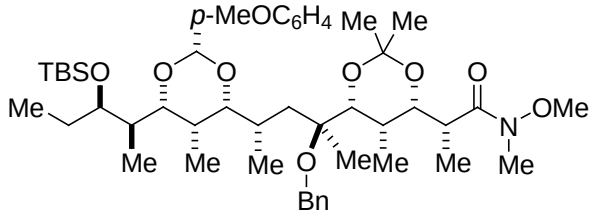
(*R*)-2-{(4*S*,5*S*,6*R*)-6-[(2*S*,3*S*,4*S*,6*R*,7*S*,8*R*,9*R*)-2-(Benzyloxy)-9-(*tert*-butyldimethylsilyloxy)--3-hydroxy-7-(4-methoxybenzyloxy)-4,6,8-trimethyl-5-oxoundecan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (150′). To a solution of 0.102 mL (0.353 mmol) of diphenyltetramethyldisilazine in 2.5 mL of THF at 0 °C was added a 1.6 M solution of *n*-butyllithium in hexanes (0.221 mL, 0.353 mmol). After 20 min, the reaction was cooled to –78 °C and a solution of ketone (0.140 g, 0.321 mmol) in 2.0 mL of THF was added via cannula

(with 2 x 0.5 mL rinses). The resultant clear yellow solution was stirred at –78 °C for 20 min, then at 0 °C for 1 h, before the reaction was recooled to –78 °C and a solution of the aldehyde **146′** (0.170 g, 0.417 mmol) in 2.0 mL of THF was added via cannula. The resultant solution was stirred for 24 h at –78 °C, then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to afford a pale yellow oil. Analysis of the unpurified mixture revealed a >95:5 ratio of diastereomers. Purification by flash chromatography (linear gradient 0 to 50% ethyl acetate/hexanes) afforded 0.153 g (56%) of the title compound as a clear colorless oil. $[\alpha]_D$ −7.6 (*c* 0.85, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3407, 2934, 2856, 1638, 1615, 1513, 1461, 1381, 1250; ^1H NMR (600 MHz, $CDCl_3$): δ 7.23-7.16 (m, 5H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 4.12 (d, *J* = 1.2 Hz, 1H), 4.07 (app t, *J* = 3.6 Hz, 1H), 3.97 (d, *J* = 9.6 Hz, 1H), 3.96 (dd, *J* = 9.6, 1.8 Hz, 1H), 3.91 (ddd, *J* = 8.4, 4.8, 1.2 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.40 (dq, *J* = 7.2, 4.8 Hz, 1H), 3.14 (s, 3H), 3.15-3.10 (m, 1H), 2.73 (d, *J* = 3.0 Hz, 1H), 2.58-2.54 (m, 1H), 1.97-1.90 (m, 1H), 1.62-1.56 (m, 1H), 1.55-1.45 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.76 (t, *J* = 7.2 Hz,, 3H), 0.57 (d, *J* = 7.2 Hz, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 217.7, 175.6, 158.8, 139.7, 131.4, 128.8, 128.1, 127.2, 126.9, 113.6, 99.5, 80.6, 78.8, 76.5, 72.9 (2C), 72.3, 66.0, 61.5, 55.2, 47.1, 42.6, 39.4, 37.2, 32.1, 30.9, 30.1, 29.7, 28.4, 26.1, 19.5, 18.3, 15.5 (2C), 13.0, 10.1, 9.5 (2C), 7.1, –3.4, –4.1; HRMS (Q-Tof) *m/z* calcd for $C_{47}H_{77}NO_{10}SiNa$ $[(M+Na)^+]$: 866.5294; found: 866.5214.



(*R*)-2-{(4*S*,5*S*,6*R*)-6-[(2*S*,3*S*,4*R*,5*R*, 6*S*,7*R*,8*R*,9*R*)-2-(Benzyloxy)-9-(*tert*-butyldim ethylsilyloxy)-3,5-dihydroxy-7-(4-methoxybe nzyloxy)-4,6,8-trimethylundecan-2-yl]-2,2,5-trimethyl-1,3-dioxan-4-yl}-*N*-methoxy-*N*-methylpropanamide (151′). To a solution of aldol adduct **150′** (0.140 g, 0.166 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added 4.74 mL (0.664 mmol, 0.14 M in Et_2O) of $Zn(BH_4)_2$. After 8.5 h at 0 °C, the reaction was quenched with sat. aqueous NH_4Cl and the resultant mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in 20 mL of MeOH and stirred at 23 °C for 24 h. Following concentration, the residue (86:14 mixture of diastereomers by crude NMR) was purified by flash chromatography affording 0.126 g (90%) of the title compound as a white foam. $[\alpha]_D$ −19 (*c* 0.55, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3437, 2935, 2856, 1644, 1513, 1461, 1381, 1249, 1148, 1090, 1040; ^1H NMR (600 MHz, CD_2Cl_2): δ 7.20 (dd, *J* = 1.8, 6.6 Hz, 2H), 7.06-7.00 (m, 5H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.26 (s, 2H), 4.03 (d, *J* = 1.2 Hz, 1H), 3.93 (dd, *J* = 9.6, 1.2 Hz, 1H), 3.90 (ddd, *J* = 8.4, 1.2 Hz, 1H), 3.78 (s, 3H), 3.75 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.74 (d, *J* = 1.2 Hz, 1H), 3.72 (s, 3H), 3.48 (d, *J* = 9.0 Hz, 1H), 3.15 (s, 3H), 3.10-3.03 (m, 1H), 2.45-2.40 (m, 1H), 2.05-1.98 (m, 1H), 1.84-1.77 (m, 1H), 1.73-1.66 (m, 1H), 1.60-1.45 (m, 3H), 1.43 (s, 6H), 1.41 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.90 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.80 (t, *J* = 7.8 Hz, 3H), 0.73 (d, *J* = 7.2 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2): δ 175.9, 159.3, 139.8, 131.6, 129.4, 128.4, 128.3, 127.2, 113.8, 99.8, 81.0, 80.4, 80.2, 78.5, 77.4, 76.9, 73.9, 73.5, 67.3, 61.9, 55.5, 39.7, 38.0, 37.5, 34.6, 32.3, 31.2, 30.3, 28.7, 26.2, 19.4, 18.6, 15.9, 15.8, 10.3, 9.4, 9.2, 8.1, 7.7, −3.1, −4.0; HRMS (Q-

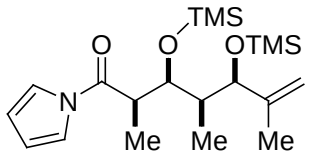
Tof) *m/z* calcd for $C_{47}H_{79}NO_{10}SiNa$ [$(M+Na)^+$]: 868.5371; found: 868.5379.



(*R*)-2-[(4*S*,5*S*,6*R*)-6-{(2*S*,4*S*)-2-(benzyloxy)-4-((2*R*,4*R*,5*S*,6*R*)-6-((2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)pentan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]-*N*-methoxy-*N*-propanamide (152′). To a mixture of azeotropically dried **151'** (0.060 g, 0.071 mmol) and 65 mg of activated powdered 4 Å molecular sieves in 2 mL of CH_2Cl_2 was added a solution of DDQ (0.018 g, 0.078 mmol) in 3 mL of CH_2Cl_2 at 0 °C by syringe. After stirring at the same temperature for 1 h, the reaction was filtered through celite and the filtrate washed with 3 x 5 mL of sat. aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (10% EtOAc in hexanes) afforded the PMP acetal as white foam (0.054 mg, 92%).

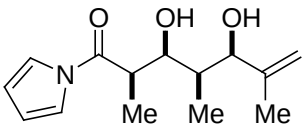
To a solution of the above prepared PMP acetal (0.043 g, 0.051 mmol) in 2 mL of THF at 0 °C was added 60% NaH (16.2 mg, 0.407 mmol), followed by CS_2 (0.031 mL, 0.51 mmol). The resultant suspension was stirred for 1 h at 0 °C and then for 1 h at ambient temperature. The reaction was recooled to 0 °C and methyl iodide (0.127 mL, 2.04 mmol) was added. After stirring for 4 h at 0 °C, the reaction was warmed to ambient temperature and allowed to stir for additional 16 h. The reaction was partitioned between 4 mL of CH_2Cl_2 and 10 mL of H_2O, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (linear gradient 0 to 20% EtOAc/hexanes) yielded 0.043 g (91%) of the xanthate as a yellow oil.

Azeotropically dried (benzene) xanthate (0.042 g, 0.045 mmol) was taken up in 1 mL of tributyltin hydride and heated to 110 °C at which point a catalytic amount of AIBN (1.0 mg) was added. After heating for 30 min, the reaction was cooled to 23 °C and quenched by adding water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated. The resulting colorless oil was passed through a silica column eluting first with hexanes followed by 20% EtOAc in hexanes to afford the deoxygenated product **152′** (0.030 g, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.5 Hz, 2H), 7.30-7.17 (m, 5H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.40 (s, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.03 (ddd, *J* = 8.5, 6.0, 1.5 Hz, 1H), 3.96 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 2.0 Hz, 1H), 3.71 (s, 3H), 3.59 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.32 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.17 (s, 3H), 3.15-3.10 (m, 1H), 2.10-2.00 (m, 1H), 1.91-1.83 (m, 1H), 1.76-1.62 (m, 3H), 1.54-1.46 (m, 2H), 1.47 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.05-1.00 (m, 1H), 0.89 (s, 9H), 0.79 (t, *J* = 7.5 Hz, 3H), 0.73 (d, *J* = 6.5 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.8, 159.5, 140.1, 132.2, 127.9, 127.7, 127.2, 126.7, 113.4, 100.9, 99.4, 86.6, 80.8, 79.0, 78.4, 71.1, 65.8, 61.6, 55.3, 38.5, 37.1, 37.1, 36.6, 32.1, 31.1, 30.3, 30.0, 29.8, 28.2, 26.1, 20.7, 19.4, 19.2, 18.2, 15.7, 10.3, 6.8, 6.5, 5.4, –3.9, –4.4.



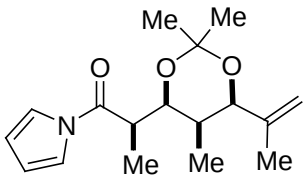
(2*R*,3*S*,4*S*,5*R*)-2,4,6-trimethyl-1-(1H-pyrrol-1-yl)-3,5-bis(trimethylsilyloxy)hept-6-en-1-one (174). To a solution of aldehyde **89** (0.400 g, 1.99 mmol) and enolsilane **169** (1.94 g, 9.99 mmol) in 10 mL THF, was added 0.800 mL of a 0.5 M DMF solution of tetra(*n*-butyl)ammonium *p*-nitrophenoxide (0.399 mmol) at −70 °C. The reaction was stirred for 6 h at

−70 °C then diluted with Et_2O (5 mL) and the resulting mixture was filtered through a silica gel plug. The crude product mixture was purified by column chromatography (3% ethyl acetate in hexanes) to afford 0.571 g (73%) of the title compound as a clear colorless oil. $[\alpha]_D$ –19 (*c* 0.25, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2959, 1713, 1466, 1250, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 2H), 6.31 (t, *J* = 2.4 Hz, 2H), 4.98 (t, *J* = 1.8 Hz, 1H), 4.94 (s, 1H), 3.99 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.93 (d, *J* = 9 Hz, 1H), 3.33-3.28 (m, 1H), 1.64 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.17 (s, 9H), 0,08 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 146.6, 119.0, 114.3, 113.4, 79.0, 74.1, 43.2, 40.6, 16.4, 16.0, 9.9, 1.1, 0.2; HRMS (ESI) *m/z* calcd for $C_{20}H_{37}NO_3Si_2Na$ [$(M+Na)^+$]: 418.2210; found: 418.2190.

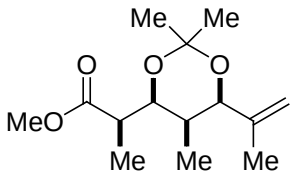


(2*R*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4,6-trimethyl-1-(1H-pyrrol-1-yl)hept-6-en-1-one (176). To a stirred solution of the aldol product **174** (0.638 g, 1.61 mmol) in 10 mL MeOH at room temperature, was added a 12-15 drops of 1 N aqueous HCl solution and the reaction mixture was stirred at room temperature for 15 min. The reaction was then diluted with sat. aqueous $NaHCO_3$ solution (30 mL) and extracted with EtOAc (3×30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (10-15% ethyl acetate in hexanes) to afford 0.393 g (97%) of the title compound as a colorless, crystalline solid. mp 96-98 °C; $[\alpha]_D$ –42 (*c* 0.63, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3400, 2976, 2937, 1707, 1651, 1467, 1372, 1274, 1073; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (t, *J* = 2.1 Hz, 2H), 6.32 (t, *J* = 2.1 Hz, 2H), 4.99 (m, 1H), 4.94 (app sextet, *J* = 1.5 Hz, 1H), 4.30 (br s, 1H), 4.21 (ddd, *J* = 7.8, 2.7, 2.7 Hz, 1H), 3.33 (quint, *J* = 7.8 Hz, 1H), 3.32 (d, *J* = 2.4 Hz, 1H), 2.05-2.02 (m, 1H), 1.90 - 1.80 (m, 1H), 1.66 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* =

6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 145.8, 119.0, 113.6, 110.3, 78.8, 76.4, 41.9, 36.5, 19.4, 15.0, 5.7; HRMS (EI) m/z calcd for $C_{14}H_{21}NO_3$: 251.1521; found: 251.1517.

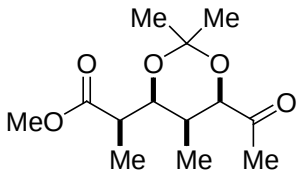


(*R*)-1-(1H-pyrrol-1-yl)-2-[(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl]propan-1-one (177). To a solution of the diol **176** (0.80 g, 3.18 mmol) in 2,2-dimethoxypropane (20 mL) was added camphor sulfonic acid (0.037 g, 0.16 mmol) and the resulting solution was stirred at ambient temperature for 2 h. The reaction was quenched by adding 4 mL of Et_3N and the reaction mixture was concentrated and the resulting crude oil was purified by flash chromatography (3% ethyl acetate in hexanes) to afford the 0.81 g of the acetonide (88%) as a white crystalline solid. mp 73-75 °C; $[\alpha]_D$ –37 (*c* 0.42, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3144, 3100, 2989, 2936, 1702, 1471, 1381, 1273, 1252, 1180; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.35 (s, 2H), 6.32 (t, *J* = 2.4 Hz, 2H), 4.98 (m, 1H), 4.85 (m, 1H), 4.34 (s, 1H), 4.25 (dd, *J* = 9.6, 2.1 Hz, 1H), 3.23 (dq, *J* = 9.6, 6.9 Hz, 1H), 1.80 (tq, *J* = 6.9, 2.4 Hz, 1H), 1.61 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.37 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 172.6, 143.2, 119.3, 113.8, 110.2, 99.6, 75.1, 75.0, 41.4, 31.4, 30.0, 19.8, 19.3, 16.6, 5.8; HRMS (EI) m/z calcd for $C_{17}H_{25}NO_3$: 291.1834; found: 291.1834.

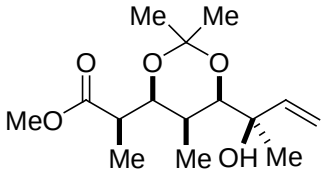


(*R*)-Methyl 2-[(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-(prop-1-en-2-yl)-1,3-dioxan-4-yl]propanoate (186). To a 0 °C solution of **177** (0.810 g, 2.78 mmol) in 30 mL of MeOH was added solid NaOMe (0.451 g, 8.34 mmol) after which the reaction was warmed to ambient temperature and stirred for 1 h. Saturated aqueous NH_4Cl (30 mL) was added and the resulting mixture was extracted with

EtOAc (3×30 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford 0.683 g (96%) of the title compound as a clear colorless oil. $[\alpha]_D$ – 12 (*c* 0.60, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2991, 2940, 2881, 1738, 1457, 1382, 1258, 1198, 1105; ^1H NMR (300 MHz, CD_2Cl_2) δ 7.32 (s, 2H), 6.31 (t, *J* = 2.4 Hz, 2H), 4.98 (t, *J* = 1.8 Hz, 1H), 4.94 (s, 1H), 3.99 (dd, *J* = 8.7, 1.5 Hz, 1H), 3.93 (d, *J* = 9 Hz, 1H), 3.33-3.28 (m, 1H), 1.64 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.17 (s, 9H), 0,08 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 1735.2, 143.2, 110.2, 99.6, 75.4, 75.1, 51.8, 42.9, 32.3, 30.0, 19.7, 19.4, 15.3, 5.4; HRMS (EI) m/z calcd for $C_{13}H_{21}O_4$ [$(M-CH_3)^{\bullet+}$]: 241.1439; found: 241.1431.

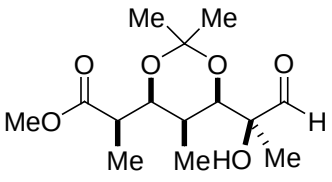


(*R*)-Methyl-2-[(4*S*,5*S*,6*R*)-6-acetyl-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (187). A gaseous stream of ozone in O_2 (generated using a standard ozonizer) was bubbled through a –78 °C solution of **186** (0.245 g, 0.949 mmol) in 10 mL CH_2Cl_2 for ~10 min (until the reaction mixture becomes blue). Dimethyl sulfide (2 mL) was added at –78 °C and the reaction was warmed to ambient temperature and stirred for 2 h. Water (10 mL) was added and the misture was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford 0.260 g of a crude product. (NMR of the crude in $CDCl_3$ showed the product as a mixture of its keto and enol tautomers.) It was carried to the next step without further purification.



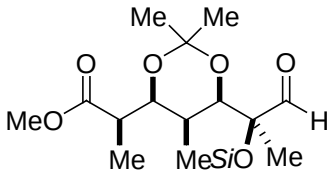
(*R*)-Methyl-2-[(4*S*,5*S*,6*R*)-6-{(*R*)-2-hydroxybut-3-en-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (188). To a solution of crude **187** in 10 mL THF was added vinyl

magnesium bromide (1.52 mL, 1 M in THF, 2.52 mmol) at –78 ^{o}C. The reaction was then stirred for 10 min at –78 ^{o}C followed by 1 h at 0 ^{o}C after which it quenched with sat. aqueous NH_4Cl (20 mL) and extracted with Et_2O (2×20 mL). The crude product was purified by column chromatography (15% ethyl acetate in hexanes) to afford 0.272 g (99% over two steps) of the title compound as a clear colorless oil. $[\alpha]_D$ + 27 (*c* 0.70, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3563, 3055, 2991, 2939, 1734, 1458, 1380, 1265, 1170, 1064; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.22 (dd, *J* = 17.1, 1.2 Hz, 1 H), 5.02 (dd, *J* = 10.5, 1.2 Hz, 1 H), 3.83 (dd, *J* = 9.9, 1.8 Hz, 1 H), 3.68 (s, 3H), 3.67 (d, *J* = 2.1 Hz, 1H), 2.64 (dq, *J* = 9.9, 6.9 Hz, 1 H), 1.66 (tq, *J* = 6.6, 2.1 Hz, 1 H), 1.39 (s, 3H), 1.38 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.21 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3 H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 144.8, 112.1, 99.7, 75.7, 74.0, 51.7, 41.6, 31.7, 29.6, 22.6, 19.5, 15.2, 6.6; HRMS (EI) m/z calcd for $C_{15}H_{26}O_5$: 286.1770; found: 286.1780.



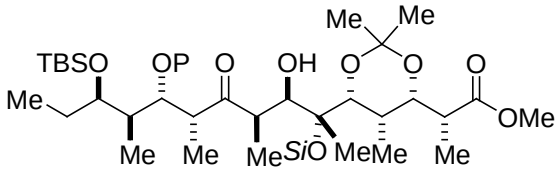
(*R*)-Methyl-2-[(4*S*,5*S*,6*R*)-6-{(S)-2-hydroxy-1-oxopropan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (**190**). A solution of **188** (0.200 g, 0.699 mmol) in 7 mL CH_2Cl_2 at –78 ˚C, was ozonolyzed for 10 min (or until color of the solution turned blue) followed by addition of dimethyl sulfide (1.280 mL, 17.47 mmol) at –78 ˚C. The reaction mixture was then warmed to ambient temperature and stirred for additional 2 h after which it was diluted with water (10 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting crude product was purified by column chromatography (6% ethyl acetate in hexanes) to afford 0.185 g (92%) of the title compound as a clear colorless oil. $[\alpha]_D$ +4.29 (*c* 1.12, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3490, 2991,

2942, 1735, 1459, 1382, 1200, 1099; ^{1}H NMR (300 MHz, CD_2Cl_2): δ 9.61 (s, 1H), 4.12 (d, *J* = 2.4 Hz, 1H), 3.88 (dd, *J* = 9.9, 2.1 Hz, 1H), 3.66 (s, 3H), 3.29 (br s, 1H), 2.60 (dq, *J* = 9.9, 6.9 Hz, 1H), 1.73 (tq, *J* = 6.6, 1.8 Hz, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H) , 1.19 (s, 3H), 0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2): δ 205.4, 174.9, 100.2, 79.1, 76.3, 75.8, 51.9, 42.2, 31.4, 29.6, 19.6, 19.3, 15.2, 6.9. HRMS (EI) m/z calcd for $C_{13}H_{21}O_6$ [$(M–CH_3)^{\bullet+}$]: 273.1338; found: 273.1329.



Si = TES

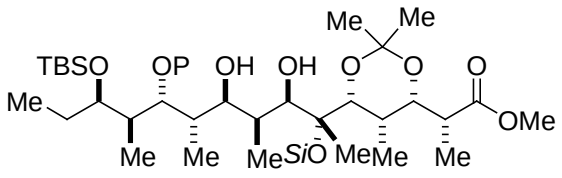
(*R*)-Methyl-2-[(4*S*,5*S*,6*R*)-2,2,5-trimethyl-6-{(*S*)-1-oxo-2-(triethylsilyloxy)propan-2-yl}-1,3-dioxan-4-yl]propanoate (**191**). To a solution of aldehyde **190** (0.120 g, 0.416 mmol) in 5 mL CH_2Cl_2 at 0 °C was added 2,6-lutidine (0.087 mL, 0.75 mmol). After 5 minutes, TESOTf (0.113 mL, 0.499 mmol) was added and the reaction was allowed to stir for 4.5 h at 0 °C. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (2-3% ethyl acetate in hexanes), affording 0.135 g (81%) of the title compound as a clear colorless oil. $[\alpha]_D$ −1.50 (*c* 1.50, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2921, 2852, 1739, 1650, 1457, 1379, 1162, 1061; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (s, 1H), 3.88 (d, *J* = 2.1 Hz, 1H), 3.79 (dd, *J* = 10.2, 2.1 Hz, 1H), 3.65 (s, 3H), 2.62 (dq, *J* = 9.9, 6.6 Hz, 1H), 1.78 (tq, *J* = 4.8, 2.1 Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.30 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.71-0.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.9, 174.8, 99.7, 80.6, 80.4, 75.7, 51.5, 42.0, 31.2, 29.6, 22.5, 19.2, 14.9, 7.0, 6.8, 6.6. HRMS (EI) m/z calcd for $C_{20}H_{39}O_6Si$: 403.2516; found: 403.2523.



P = PMB, *Si* = TES

(R)-Methyl 2-((4S,5S,6R)-6-{(2R,3R,4R,6R,7S,8R,9R)-7-(4-methoxybenzyloxy)-9-(*tert*-butyldimethylsilyloxy)-3-hydroxy-4,6,8-trimethyl-5-oxo-2-(triethylsilyloxy)undecan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (192). To a solution of LHMDS (0.398 mL, 1.0 M in THF, 0.398 mmol) in 0.8 mL THF at −78 °C, was added a solution of the ketone **105** (0.116 g, 0.265 mmol) in 0.5 mL of THF. The resulting solution was stirred for 10 min at −78 °C and at 0 °C for 2.5 h, after which it was recooled to −78 °C and a solution of aldehyde **191** (0.160 g, 0.398 mmol) in 0.5 mL THF was added via cannula. The resulting solution was then allowed to stir for 1 h at −78 °C and quenched by dropwise addition of precooled acetic acid (1.1 mL, 1N in THF, 4 equiv) at the same temperature. After stirring for additional 20 min at −78 °C, the reaction was warmed to 0 °C and quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with ether (3×10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (gradient elution with 0-30% ethyl acetate in hexanes) affording 0.112 g (51%) of the title compound in the form of a clear colorless oil as a single observable diastereomer (by NMR) along with 0.043 g (0.098 mmol, 38%) of the unreacted ketone. $[\alpha]_D$ −32 (*c* 0.38, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3466, 2954, 2936, 2879, 1737, 1613, 1514, 1460, 1380, 1250, 1199, 1098; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.38 (d, *J* = 10.5 Hz, 1H), 4.11 (app t, *J* = 3.0 Hz, 1H), 3.94 (ddd, *J* = 8.0, 5.0, 2.5 Hz, 1H), 3.86-3.81 (m, 2H), 3.80 (dd, *J* = 5.0, 1.5 Hz, 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.52 (d, *J* = 4.0 Hz, 1H), 3.12 (dq, *J* = 7.0, 2.5 Hz, 1H), 2.94 (dq, *J* = 7.0, 2.5 Hz, 1H), 2.66 (dq, *J* = 10.0, 7.0 Hz, 1H), 1.80 – 1.70

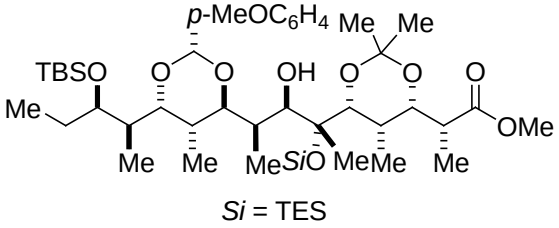
(m, 2H), 1.60-1.48 (m, 2H), 1.44 (s, 3H), 1.42 (s, 3H), 1.27 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.90 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.69-0.60 (m, 6H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.6, 174.8, 159.0, 131.1, 129.1, 113.6, 99.9, 81.2, 79.0, 78.3, 76.5, 74.6, 72.8, 55.2, 51.6, 46.6, 45.9, 41.7, 39.5, 32.0, 29.7, 28.3, 26.0, 23.2, 19.6, 18.3, 15.1, 11.9, 10.4, 9.9, 7.2, 6.9, –3.4, –4.2; HRMS (ESI) *m/z* calcd for $C_{45}H_{82}O_{10}Si_2Na$ [$(M+Na)^+$]: 861.5344; found: 861.5367.



P = PMB, *Si* = TES

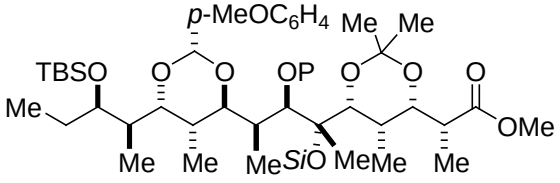
(*R*)-Methyl 2-[(4*S*,5*S*,6*R*)-6-{(2*R*,3*R*,4*S*,5*S*,6*S*,7*R*,8*R*,9*R*)-7-(4-methoxybenzyloxy)-9-(*tert*-butyldimethylsilyloxy)-3,5-dihydroxy-4,6,8-trimethyl-2-(triethylsilyloxy)undecan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (193). To a solution of aldol adduct **192** (0.115 g, 0.137 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added 2.75 mL (0.548 mmol, 0.20 M in Et_2O) of $Zn(BH_4)_2$. After 8.5 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and the resultant mixture was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in 20 mL of MeOH and stirred at 23 °C for 24 h. Following concentration, the residue was purified by flash chromatography (10% EtOAc in hexanes) affording 0.115 g (100%) of the title compound as a white foam as a single diastereomer. $[\alpha]_D$ −4.5 (*c* 0.20, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3402, 2954, 2879, 1736, 1612, 1513, 1458, 1248, 1168, 1066; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.04 (d, *J* = 3.0 Hz, 1H), 4.01 (ddd, *J* = 9, 5.5, 1.5 Hz, 1H),

3.97 (dd, *J* = 9.5, 1.5 Hz, 1H), 3.84 (d, *J* = 2.0 Hz, 1H), 3.80 (s, 3H), 3.80 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.70 (d, *J* = 10.0 Hz, 1H), 3.63 (s, 3H), 3.57 (s, 1H), 2.66 (dq, *J* = 10.0, 6.5 Hz, 1H), 2.10 (q, *J* = 6.5 Hz, 1H), 1.78-1.68 (m, 3H), 1.65-1.48 (m, 2H), 1.43 (s, 6H), 1.33 (s, 3H), 1.21 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.91 (s, 9H), 0.84 (t, *J* = 7.5 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.62 (dq, *J* = 8.0, 3.0 Hz, 6H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 174.8, 159.3, 132.7, 129.2, 113.9, 100.4, 82.8, 81.7, 79.9, 79.0, 78.7, 76.9, 74.6, 74.0, 55.6, 51.9, 42.2, 39.5, 37.9, 33.9, 32.5, 29.9, 29.0, 26.3, 23.9, 19.7, 18.7, 15.2, 10.5, 9.5, 9.4, 7.6, 7.4, 7.3, 6.0, –3.1, –4.0; HRMS (ESI) *m/z* calcd for $C_{45}H_{84}O_{10}Si_2Na$ [$(M+Na)^+$]: 863.5501; found: 863.5435.



(*R*)-Methyl 2-[(4*S*,5*S*,6*R*)-6- -{(2*R*,3*R*, 4*R*)-4-((5*S*,6*R*)-6-((2*R*,3*R*)-3-(*tert*- butyldimeth ylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)-5 -methyl-1,3-dioxan-4-yl)-3-hydroxy-2-triethy- lsilyloxy)pentan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (194). To a mixture of azeotropically dried **193** (28 mg, 0.033 mmol) and 70 mg of activated powdered 4 Å molecular sieves in 0.3 mL of CH_2Cl_2 was added a solution of DDQ (9.1 mg, 0.039 mmol) in 0.2 mL of CH_2Cl_2 at 0 °C by syringe. After stirring at the same temperature for 0.5 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (10% EtOAc in hexanes) afforded the title compound as white foam (27 mg, 98%). $[\alpha]_D$ −8.7 (*c* 0.55, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3364, 2954, 2879, 1738, 1615, 1459, 1383, 1250, 1199, 1102, 1014; ^{1}H NMR (500

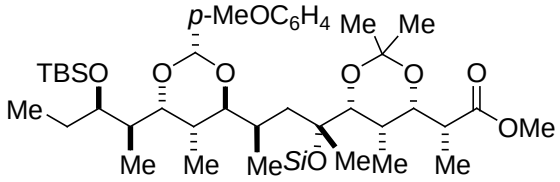
MHz, CD_2Cl_2): δ 7.41 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.53 (s, 1H), 4.03 (ddd, *J* = 9.0, 6.0, <1 Hz, 1H), 3.97 (d, *J* = 2.0 Hz, 1H), 3.86 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.84 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.80 (s, 3H), 3.67 (d, *J* = 5.0 Hz, 1H), 3.66 (s, 3H), 3.65 (d, *J* = 9.5 Hz, 1H), 3.57 (d, *J* = 5.0 Hz, 1H), 2.64 (dq, *J* = 10.0, 7.0 Hz, 1H), 2.51 (dq, *J* = 11.0, 6.5 Hz, 1H), 1.82 (dq, *J* = 6.5, 1.0 Hz, 1H), 1.75 (ddq, *J* = 10.0, 7.0, 1.0 Hz, 1H), 1.69 (tq, *J* = 7.0, 1.5 Hz, 1H), 1.56-1.47 (m, 2H), 1.48 (s, 3H), 1.43 (s, 3H), 1.24 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.5 Hz , 3H), 0.90 (s, 9H), 0.82 (t, *J* = 8.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.72-0.60 (m, 6H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 174.9, 160.2, 132.7, 127.7, 113.7, 100.3, 95.3, 82.7, 80.7, 78.8, 77.7, 76.7, 75.0, 71.2, 55.6, 51.9, 42.1, 37.5, 33.0, 32.5, 29.9, 29.5, 28.5, 26.2, 24.5, 20.4, 18.4, 15.3, 13.6, 10.6, 10.4, 7.9, 7.4, 7.2, 7.0, –4.0, –4.1; HRMS (EI) m/z calcd for $C_{45}H_{82}O_{10}Si_2$: 838.5446; found: 838.5478.



P = C(S)SMe; *Si* = TES

(*R*)-Methyl 2-[(4*S*,5*S*,6*R*)-6-{(2*S*,3*R*,4*S*)-4-((5*S*,6*R*)-6-((2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-(methylthiocarbonothioyloxy)-2-(triethylsilyloxy)pentan-2-yl}-2,2,5-trimethyl-1,3-dioxan-4-yl]propanoate (195). To a solution of **194** (27 mg, 0.032 mmol) and CS_2 (0.078 mL, 1.3 mmol) in 0.5 mL of THF at –78 °C, KHMDS (0.193 mL, 0.5 M in toluene, 0.0970 mmol) was added dropwise. The resultant solution was stirred for 2.5 h at –78 °C and MeI (0.080 mL, 1.3 mmol) was added. After stirring for additional 20 min at –78 °C, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The layers were separated

and the aqueous layer was extracted with ether (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (2.5% EtOAc in hexanes) afforded 27 mg (90%) of the title compound as a foam. $[\alpha]_D$ −35 (*c* 0.20, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2955, 1737, 1613, 1590, 1459, 1380, 1250, 1198, 1170, 1057, 1011; ^1H NMR (500 MHz, CD_2Cl_2): δ 7.39 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.06 (s, 1H), 5.46 (s, 1H), 4.03 (ddd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 3.84 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.80 (s, 3H), 3.69 (d, *J* = 2.0 Hz, 1H), 3.64 (s, 3H), 3.63 (d, *J* = 11.5 Hz, 1H), 2.96 (dq, *J* = 11.0, 7.0 Hz, 1H), 2.60 (dq, *J* = 10.0, 7.0 Hz, 1H), 2.53 (s, 3H), 1.90 (dq, *J* = 7.0, 1.5 Hz, 1H), 1.82 (tq, *J* = 7.0, 2.0 Hz, 1H), 1.77 (ddq, *J* = 10.0, 7.0, 2.0 Hz, 1H), 1.56- 1.49 (m, 2H), 1.44 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.81 (t, *J* = 7.5 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.71 (q, *J* = 7.5 Hz, 6H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (CD_2Cl_3, 125 MHz) δ 215.9, 174.8, 160.2, 132.6, 127.7, 113.7, 100.2, 95.7, 84.5, 80.9, 80.7, 80.0, 76.4, 75.5, 71.3, 55.6, 51.9, 42.3, 37.5, 34.9, 32.4, 30.6, 29.5, 28.7, 26.2, 25.5, 19.6, 19.2, 18.4, 15.3, 13.6, 12.1, 10.4, 8.2, 7.7, 7.4, 7.3, –3.7, –4.4; HRMS (ESI) m/z calcd for $C_{47}H_{84}O_{10}Si_2S_2Na$ $[(M+Na)^+]$: 951.4942; found: 951.4922.

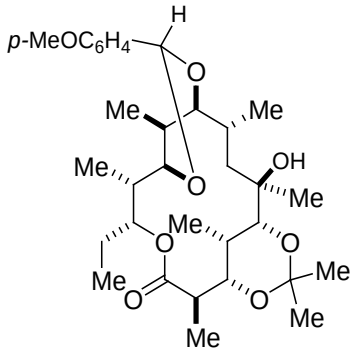


Si = TES

(*R*)-Methyl 2-[(4S,5S,6R)-6- {(2*R*,3*R*, 4*R*)-4-((5*S*,6*R*)-6-((2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)pentan-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-3-hydroxy-2-(triethylsilyloxy)pentan-2-yl}-2,2,5-trimethyl-1,3 -dioxan-4-yl]propanoate (197). Azeotropically dried (benzene) xanthate **195**

(0.160 g, 0.172 mmol) was taken up in 3.20 mL of tributyltin hydride and heated to 110 °C at which point a catalytic amount of AIBN (2.0 mg, 0.014 mmol) was added. After heating for 30 min, the reaction mixture was cooled to 23 °C and quenched by the addition of water (5 mL) and extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The resulting colorless oil was passed through a silica column eluting first with hexanes followed by 20% EtOAc in hexanes to afford the deoxygenated product (111 mg, 78%) as a mixture of (*R*)- and (*S*)- PMP acetals. To a solution of this mixture in 3.0 mL of CD_2Cl_2 were added *p*-anisaldehyde dimethyl acetal (0.110 mL, 0.674 mmol) and CSA (32.0 mg, 0.135 mmol). The reaction was stopped after 25-30 minutes (NMR monitoring showed complete disappearance of minor acetal isomer) by addition of Et_3N (~2 mL). Concentration and further purification by flash chromatography (15% EtOAc/hexanes) afforded the pure diastereomer **197** as a clear colorless oil (0.100 g, 71% over 2 steps). $[\alpha]_D$ −9.4 (*c* 0.18, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 2955, 2878, 1738, 1612, 1515, 1460, 1379, 1251, 1168, 1104, 1057, 1015; ^1H NMR (300 MHz, CD_2Cl_2): δ 7.39 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.50 (s, 1H), 4.01 (ddd, *J* = 8.5, 5.5, 1 Hz , 1H), 3.90 (dd, *J* = 10.0, 2.0 Hz, 1H), 3.81 (dd, *J* = 10.0, 2.0 Hz , 1H), 3.79 (s, 3H), 3.65 (s, 3H), 3.61 (d, *J* = 2.0 Hz, 1H), 3.22 (d, *J* = 10.5 Hz, 1H), 2.62 (dq, *J* = 10.0, 6.5 Hz, 1H), 2.25 – 2.18 (m, 1H), 1.85 (dq, *J* = 7.0, 1.0 Hz, 1H), 1.75 – 1.70 (m, 2H), 1.63 (tq, *J* = 6.5, 1.5 Hz, 1H), 1.55-1.46 (m, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 1.35-1.25 (m, 2H), 1.22 (s, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 175.1, 160.2, 132.6, 127.7, 113.7, 99.9, 95.4, 85.3, 78.2, 77.9, 76.6, 75.0, 71.3, 55.6, 51.8, 44.3, 42.3, 37.6, 32.3, 29.9, 29.4, 28.9, 28.5, 26.5, 26.2, 20.4, 18.6, 18.4, 15.3, 13.6, 10.4, 7.8, 7.5, 7.4,

6.9, –3.9, –4.3; HRMS (ESI) *m/z* calcd for [(M+Na)$^+$] $C_{45}H_{82}O_9Si_2Na$: 845.5395; found: 845.5405.



(2*R*,3*S*,4*R*,5*S*,6S,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-6-hydroxy-9,11-[(*R*)-(*p*-methoxybenzylidine)dioxy]-3,5-[(1-methylethylidene)dioxy]-2,4,6,8,10,12-hexamethyltetradeca-nolide (198). To a solution of **197** (35 mg, 0.043 mmol) in 3 mL of THF/MeOH (1:1 v:v), was added was added 0.210 mL (0.425 mmol) of a 2 M aqueous solution of LiOH. The resultant clear solution was heated at 55 °C with a reflux condenser for 20 h. The reaction mixture was then diluted with water (2.5 mL), acidified to pH 1 with a solution of 1 M $NaHSO_4$ and extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (20-25% EtOAc in hexanes) afforded the carboxylic acid as colorless oil (33 mg, 96%). The acid was immediately carried to the next step as it was unstable.

To a solution of the acid (30 mg, 0.037 mmol) in 2.5 mL of THF at 0 °C was added *n*-Bu_4NF (0.223 mL, 1.0 M in THF, 0.223 mmol). The resultant solution was heated at reflux for 10 h after which another equal amount of *n*-Bu_4NF was added. The reaction was allowed to reflux for additional 10 h, then quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The resultant yellow oil was purified by flash chromatography (50% EtOAc/hexanes followed by 60-100% EtOAc/hexanes with two drops of acetic acid per 100 mL eluant), affording a mixture of the pure seco-acid along with TBAF salts which was carried to

the next step without further purification.

To a stirred solution of the crude azeotropically dried (2×5 mL of benzene) hydroxy acid (24 mg) in 2 mL of benzene at 23 °C was added Et_3N (0.230 mL, 1.65 mmol), followed by 2,4,6-trichlorobenzoyl chloride (0.258 mL, 1.65 mmol). After 24 h, *N*, *N*-(dimethylamino)pyridine (0.400 g, 3.30 mmol) was added as well as 3 mL of benzene and the white cloudy reaction mixture was allowed to stir for additional 15 h at room temperature. The reaction was quenched by the addition of 1 *N* $NaHSO_4$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (20-25% EtOAc/hexanes) afforded **198** as a white solid (18 mg, 81%). m.p. 95-97 ˚C; $[\alpha]_D$ +0.53 (*c* 0.45, $CHCl_3$); IR $\nu_{max}^{(thin\ film)}$ cm^{-1}: 3429, 2971, 2935, 1723, 1615, 1516, 1457, 1384, 1249, 1173, 1098, 1037; 1H NMR ($CDCl_3$, 600 MHz) δ 7.50 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.68 (s, 1H), 5.45 (dd, *J* = 10.2, 4.2 Hz, 1H), 4.05 (s, 1H), 3.89 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 9.6 Hz, 1H), 3.34 (d, *J* = 10.8 Hz, 1H), 2.77 (dq, *J* = 10.8, 6.6 Hz, 1H), 2.50 (m, 1H), 2.23 (br. s, 1H), 1.80-1.67 (m, 4H), 1.52 (s, 3H), 1.47 (s, 3H), 1.50-1.45 (m, 2H), 1.33 (dd, *J* = 15.0, 12.0 Hz, 1H), 1.25 (d, *J* = 6.6 Hz, 3H), 1.24 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); 13C NMR ($CDCl_3$, 75 MHz) δ 175.8, 159.8, 131.7, 127.5, 113.6, 101.1, 95.4, 85.3, 79.9, 77.6, 75.7, 75.2, 74.8, 55.3, 41.8, 39.7, 39.2, 32.1, 29.6, 28.3, 26.8, 26.7, 25.4, 20.1, 17.3, 13.9, 12.6, 10.4, 7.5, 7.0; HRMS (EI) m/z calcd for $C_{32}H_{50}O_8$: 562.3506; found: 562.3498.

6.0 DEVELOPMENT OF A TWO STEP PROTOCOL FOR CONVERSION OF LACTONE TO ALDEHYDE

6.1 REACTION DESIGN AND RESULTS

The iterative AAC methodology has been demonstrated to be a very useful catalytic method for the synthesis of polypropionate frameworks. So far the method relies on a sequence of three steps, ring opening to Weinreb amide, protection and reduction, to convert the lactone to the aldehyde before another iteration can take place, making up to a total of four steps per iterative cycle. In Nature, the iterative process of chain elongation in polyketides requires as few as two steps. Thus, in order to achieve maximum efficiency in iterative AAC-based polypropionate construction, the expedient transformation of the β-lactone propionate surrogates to the corresponding β-alkoxy aldehydes is required. Merging the AAC bond constructions with an efficient (1-2 steps), economical, and operationally simple lactone-to-aldehyde conversion would yield an exceptionally efficient strategy for continued chain extension in the catalytic asymmetric construction of polypropionate units (Figure 41).

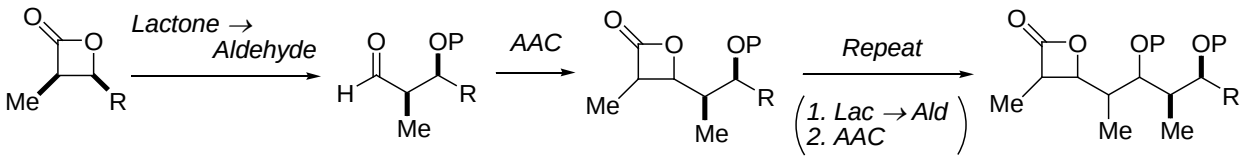


Figure 41. Ideal two step iterative chain elongation via AAC methodology

To that end, we envisioned that the facile nucleophile-mediated β-lactone ring opening by thiolate nucleophiles **199** can be exploited to realize an efficient method for directly converting the enantioenriched β-lactones to the corresponding β-hydroxy aldehydes. A catalytic amount of the reactive thiolate nucleophile **199** will first be generated via reaction of thiol with a suitable base, which will trigger the ring opening of the β-lactone to the thiolate intermediate **200**. Reprotonation of **200** with thiol will regenerate the thiolate catalyst providing the β-hydroxythiol ester **201**. Protection of the free alcohol functionality in **201** in the same pot will enable a one step procedure for conversion of the lactone to the ring opened form (Figure 42).

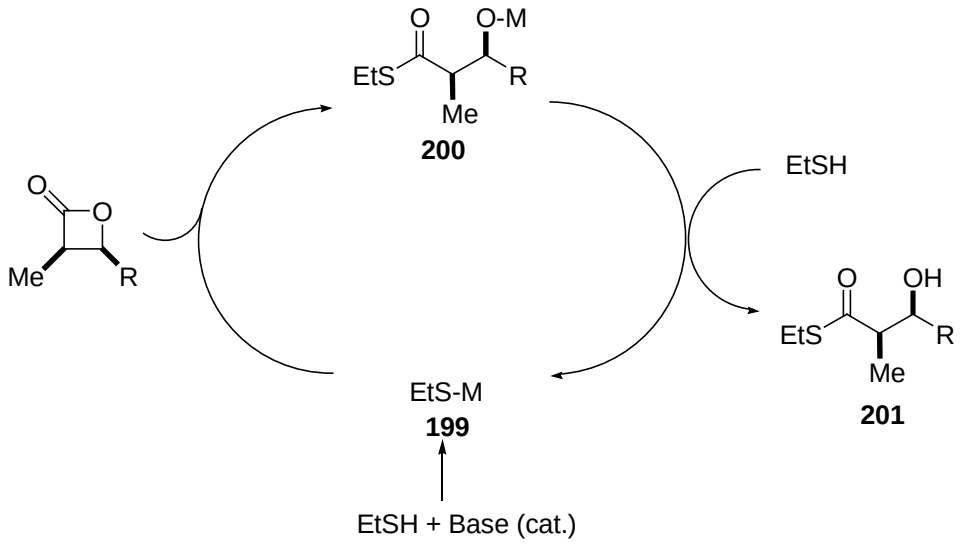
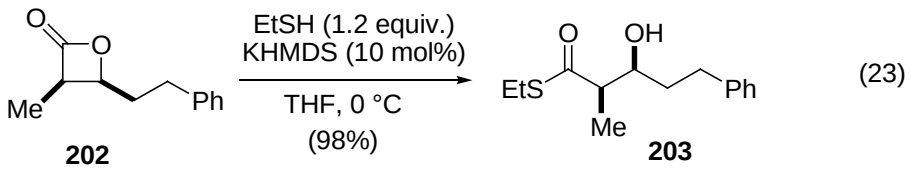


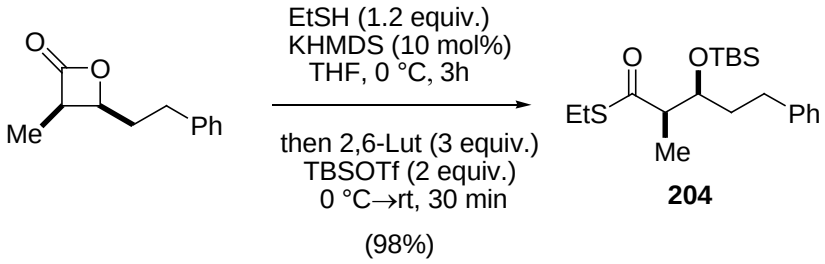
Figure 42. Catalytic cycle for conversion of lactone to thioester

To test this idea, KHMDS was chosen as the base. We were pleased to find that when the ring opening of the β-lactone **202** was carried out with 1.2 equiv of EtSH in presence of 10 mol% of KHMDS at room temperature, the ring opened product **203** was afforded cleanly in 3 h in 98% yield (eq 23). In subsequent experiments, the β-hydroxy thioester product was converted to the protected silyl ether **204** in the same reaction pot (in nearly quantitave yield) by adding 2,6-

lutidine and R_3SiOTf to the reaction mixture after all of the β-lactone starting material had been consumed (by TLC) (eq 24).



(23)

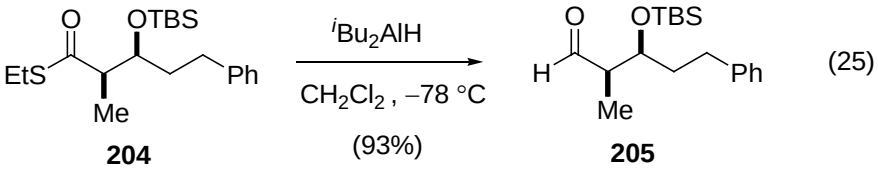


(24)

A commonly used method for the reduction of thioesters to aldehydes is the Fukuyama reaction[76] where H_2 or Et_3SiH is used as the reducing agent in presence of catalytic Pd/C. In addition to using expensive Pd metal, this reaction often suffers from long reaction times as the rate of the reduction highly varies with the activity of the Pd catalyst used. In contrast, reduction with $^{i}Bu_2AlH$ is more convenient and can be achieved in much shorter reaction times. The TBS-protected thioester **204** was thus subjected to reduction with $^{i}Bu_2AlH$ at −78 ˚C in CH_2Cl_2 as solvent to provide the corresponding aldehyde **205** in excellent yield (94%) (eq 25). Over-reduction to alcohol was eliminated by slow addition of MeOH to the reaction mixture at −78 ˚C,

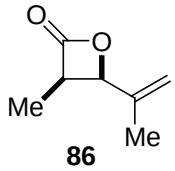
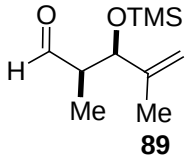
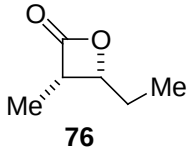
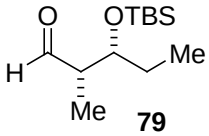
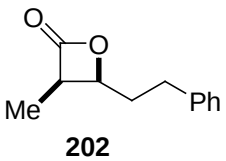
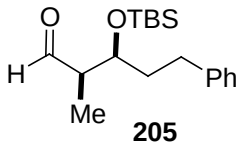
[76] (a) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050-7051. (b) Kanda, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1993**, *115*, 8451-8452. (c) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121-1123.

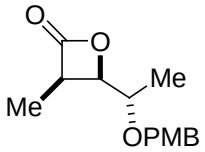
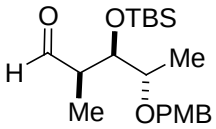
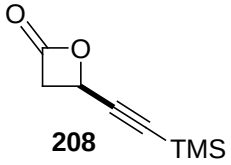
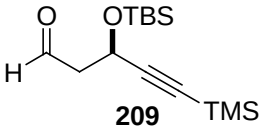
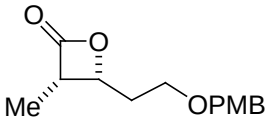
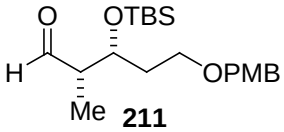
prior to addition of Rochelle's salt solution. In a separate experiment, the reactions in eq 24 and 25 were carried out sequentially without purification of the intermediate **204**. In this case the overall isolated yield of the aldehyde was 80% which is inferior to the combined yield of the two steps when performed with purification of **204** (93%). The substrate scope of the reaction was next examined using other β-lactones which include **76** and **86** involved in erythronolide B synthesis. As shown in Table 2, in all cases the aldehyde products were obtained in good yields.



(25)

Table 2. Conversion of lactones to β-silyloxy aldehydes

Entry	Substrate	Product	Yield
1.	 **86**	 **89**	89%[a]
2	 **76**	 **79**	85%[a]
3	 **202**	 **205**	93%[a] 80%[b]

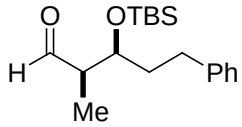
4	 **206**	 **207**	74%[b]
5	 **208**	 **209**	78%[a]
6	 **210**	 **211**	86%[a]

[a]The intermediate siloxy thioester was purified before subjecting to reduction with DIBAL-H. [b]The intermediate siloxy thioester was not purified before subjecting to reduction with DIBAL-H.

6.2 EXPERIMENTAL

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100mL, solvent). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) or 600 (^{1}H: 600 MHz; ^{13}C: 150 MHz) spectrometers with chemical shifts reported relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra or residual CH_2Cl_2 (5.32 ppm) for ^{1}H and CD_2Cl_2 (53.8 ppm) for ^{13}C NMR spectra. Unless otherwise stated, all reactions were carried out in flame-dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and

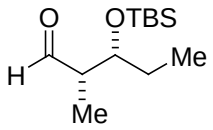
reagents. Anhydrous solvents (CH_2Cl_2, THF) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. All the commercial chemicals are purchased from Aldrich Chemical Co. Flash chromatography was performed on EM silica gel 60 (230-240 mesh) unless noted otherwise.[75]



(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methyl-5-phenylpentanal (205) To a solution of EtSH (0.095 ml, 1.30 mmol) in 5 mL THF at 0 °C, was added KHMDS (0.214 mL, 0.5 M in toluene, 0.107 mmol). After stirring for 5 min, a solution of the lactone **202** (0.204 g, 1.07 mmol) in THF (0.5 mL) was added dropwise and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 4.5 h at 25 °C, then cooled to 0 °C whereupon 2,6-lutidine (0.375 mL, 3.22 mmol) was added followed by TBSOTf (0.490 mL, 2.14 mmol). After stirring for 30 min at 0 °C, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (1-2% ethyl acetate in hexanes) to afford 0.393 g (100%) of the thioester in the form of a colorless oil.

To a solution of the thioester (0.296 g, 0.808 mmol) in 10 mL CH_2Cl_2 at −78 °C, $^{i}Bu_2AlH$ (2.02 mL, 1.0 M in hexane, 2.02 mmol) was added dropwise. After stirring for 30 min, the reaction was quenched by careful dropwise addition of MeOH (10 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (20 mL) was added. The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (5% ethyl acetate in hexanes) afforded 0.230

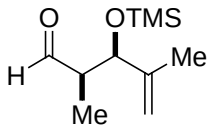
g (93%) of the title compound as colorless oil. $[\alpha]_D$ −22.6 (*c* 0.84, $CHCl_3$); IR $\nu_{max}^{thin\ film}$ cm^{-1} 2953, 2930, 2857, 2709, 1726, 1603, 1459, 1458, 1362, 1254, 1102, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, *J* = 0.9 Hz, 1H), 7.34-7.15 (m, 5H), 4.15 (dt, *J* = 6.3, 3.6 Hz, 1H), 2.76-2.63 (m, 1H), 2.62-2.45 (m, 2H), 1.94-1.72 (m, 2H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 141.6, 128.5, 128.2, 126.0, 71.8, 51.3, 36.4, 32.1, 25.8, 18.0, 7.9, –4.2, –4.6; HRMS (ES) *m/z* calcd for $C_{17}H_{27}O_2Si$: 291.1788; found: 291.1780.



(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpentanal (79) To a solution of EtSH (0.390 ml, 5.26 mmol) in 20 mL THF at 0 °C, was added KHMDS (0.877 mL, 0.5 M in toluene, 0.438 mmol). After stirring for 5 min, a solution of the lactone **76** (0.500 g, 4.38 mmol) in THF (2 mL) was added dropwise. The reaction was stirred for 3.5 h at 0 °C whereupon 2,6-lutidine (1.532 mL, 13.16 mmol) was added followed by TBSOTf (2.02 mL, 8.77 mmol). The reaction was warmed to ambient temperature and stirred for another 1 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The resulting crude oil was purified by flash chromatography (2-3% ethyl acetate in hexanes) and the pure thioester was immediately carried to the next step.

To a solution of the thioester (1.19 g, 4.10 mmol) in 20 mL CH_2Cl_2 at −78 °C, $^iBu_2AlH$ (10.26 mL, 1.0 M in hexane, 10.26 mmol) was added dropwise. After stirring for 45 min, the reaction was quenched by careful dropwise addition of MeOH (10 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (30 mL) was added.

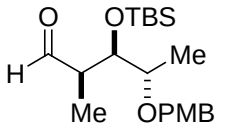
The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated. The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (2% ethyl acetate in hexanes) afforded 0.858 g (86% over two steps) of the title compound as colorless oil. $[\alpha]_D$ +58.5 (*c* 1.10, CH_2Cl_2); IR $\nu_{max}^{\text{thin film}}$ cm^{-1} 2958, 2708, 1726, 1463, 1361, 1254, 1103, 1047, 1029, 837, 775; ^1H NMR (300 MHz, $CDCl_3$): δ 9.76 (d, *J* = 0.9 Hz, 1H), 4.02 (dt, *J* = 6.6, 3.6 Hz, 1H), 2.45 (tq, *J* = 6.9, 3.6, 0.9 Hz, 1H), 1.58-1.42 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 73.4, 50.8, 27.4, 25.8, 18.0, 10.1, 7.6, −4.2, −4.7. HRMS (EI) m/z calcd for $C_{12}H_{26}O_2Si$: 230.1702; found: 230.1691.



(2*R*,3*R*)-2,4-Dimethyl-3-(trimethylsilyloxy)pent-4-enal (89) To a solution of EtSH (0.332 ml, 4.49 mmol) in 15 mL THF at 0 °C, was added KHMDS (0.748 mL, 0.5 M in toluene, 0.374 mmol). After stirring for 5 min, a solution of the lactone **86** (0.471 g, 3.74 mmol) in THF (2 mL) was added dropwise. The reaction was allowed to stir for 3 h at 0 °C whereupon 2,6-lutidine (1.31 mL, 11.2 mmol) was added followed by TMSOTf (1.35 mL, 7.48 mmol). The reaction was warmed to ambient temperature and stirred for additional 3 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (20 mL) and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (1-3% ethyl acetate in hexanes) and the pure thioester was immediately carried to the next step.

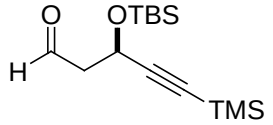
To a solution of the thioester (0.935 g, 3.59 mmol) in 20 mL CH_2Cl_2 at −78 °C, $^iBu_2AlH$ (8.98 mL, 1.0 M in hexane, 8.98 mmol) was added dropwise. After stirring for 15 min, the

reaction was quenched by careful dropwise addition of MeOH (10 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (30 mL) was added. The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated (~1 h). The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (2.5% ethyl acetate in hexanes) afforded 0.667 g (89% over two steps) of the title compound as colorless oil. $[\alpha]_D$ +10 (*c* 0.23, $CHCl_3$); IR $\nu_{max}^{thin\ film}$ cm^{-1} 2959, 2715, 1727, 1452, 1252, 1113, 1036, 872, 843, 752; ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (d, *J* = 1.8 Hz, 1H), 4.97 (s, 1H), 4.91 (s, 1H), 4.41 (d, *J* = 5.1 Hz, 1H), 2.54-2.43 (m, 1H), 1.69 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.5, 144.7, 112.7, 75.5, 50.0, 18.4, -8.01; HRMS (EI) m/z calcd for $C_{10}H_{20}O_2Si$: 200.1233; found: 200.1233.



(2*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxybenzyloxy)-2-methylpentanal (207) To a solution of EtSH (0.053 ml, 0.72 mmol) in 3 mL THF at 0 °C, was added KHMDS (0.12 mL, 0.5 M in toluene, 0.060 mmol). After stirring for 5 min, a solution of the lactone **206** (0.15 g, 0.60 mmol) in THF (2 mL) was added dropwise and the reaction was allowed to warm to ambient temperature. The reaction was stirred for 3 h at 25 °C, then cooled to 0 °C whereupon 2,6-lutidine (0.21 mL, 1.8 mmol) was added followed by TBSOTf (0.276 mL, 1.20 mmol). After stirring for additional 30 min at 0 °C, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ether (2 x 10 mL). The organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (1-3% ethyl acetate in hexanes) and the thioester was immediately carried to the next step.

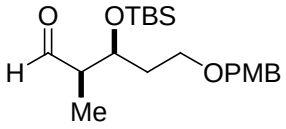
To a solution of the thioester in 3 mL CH_2Cl_2 at −78 °C, $^{i}Bu_2AlH$ (1.50 mL, 1.0 M in hexane, 1.50 mmol) was added dropwise. After stirring for 35 min, the reaction was quenched by careful dropwise addition of MeOH (5 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (10 mL) was added. The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated (~1 h). The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (0%- 2.5% ethyl acetate in hexanes) afforded 0.162 g (74% over two steps) of the title compound as colorless oil. $[\alpha]_D$ +2.39 (*c* 0.67, $CHCl_3$); IR $\nu_{max}^{\text{thin film}}$ cm^{-1} 2955, 2933, 2857, 2708, 1725, 1612, 1513, 1463, 1302, 1250, 1104, 1035; ^1H NMR (300 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.36 (d, *J* = 11.1 Hz, 1H), 4.07 (dd, *J* = 6.3, 3.6 Hz, 1H), 3.80 (s, 3H), 3.44 (dq, *J* = 12.3, 6.0 Hz, 1H), 2.73 (dq, *J* = 6.9, 3.0 Hz, 1H), 1.22 (d, J = 6.3 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 3H), –0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 159.2, 130.4, 129.4, 113.8, 75.9, 74.6, 70.6, 55.2, 49.9, 25.9, 18.2, 16.3, 8.0, –4.0, –4.2; HRMS (Q-Tof) m/z calcd for $C_{20}H_{34}O_4SiNa$ (M^+ + Na): 389.2124; found: 389.2149.



(*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(trimethylsilyl)pent-4-ynal (209) To a solution of EtSH (0.106 ml, 1.43 mmol) in 5 mL THF at 0 °C, was added KHMDS (0.238 mL, 0.5 M in toluene, 0.119 mmol). After stirring for 5 min, a solution of the lactone **208** (0.200 g, 1.19 mmol) in THF (2 mL) was added dropwise. The reaction was allowed to stir for 3 h at 0 °C whereupon 2,6-lutidine (0.346 mL, 2.97 mmol) was added followed by TBSOTf (0.464 mL, 2.023 mmol). The reaction was warmed to ambient temperature and stirred for additional 1 h. The reaction was quenched by

adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with ether (2 x 10 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (1-3% ethyl acetate in hexanes) and the thioester was immediately carried to the next step.

To a solution of the thioester (0.348 g, 1.01 mmol) in 5 mL CH_2Cl_2 at −78 °C, $^{i}Bu_2AlH$ (2.52 mL, 1.0 M in hexane, 2.52 mmol) was added dropwise. After stirring for 15 min, the reaction was quenched by careful dropwise addition of MeOH (8 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (15 mL) was added. The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated (~1 h). The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (2.5% ethyl acetate in hexanes) afforded 0.263 g (78% over two steps) of the title compound as colorless oil. $[\alpha]_D$ +55.56 (*c* 0.54, $CHCl_3$); IR $\nu_{max}^{\text{thin film}}$ cm^{-1} 2958, 2931, 2897, 2858, 2716, 2174, 1730, 1469, 1337, 1252, 1095, 997; ^1H NMR (300 MHz, $CDCl_3$): δ 9.8 (t, *J* = 2.4 Hz, 1H), 4.85 (dd, *J* = 4.8, 7.2 Hz, 1H), 2.76 (ddd, *J* = 2.4, 6.9, 16.2 Hz, 1H), 2.64 (ddd, *J* = 2.1, 4.8, 16.5 Hz, 1H), 0.88 (s, 9H), 0.16 (s, 12H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.4, 105.4, 90.6, 58.7, 51.2, 25.6, 18.1, –0.3, –4.5, –5.1; HRMS (EI) m/z calcd for $C_{14}H_{28}O_2Si_2$: 284.1628; found: 284.1624.



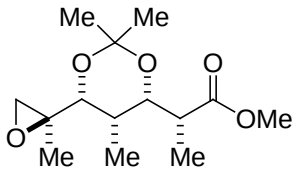
(2*S*,3*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2-methyl-pentanal (211) To a solution of EtSH (0.028 ml, 0.384 mmol) in 1.5 mL THF at 0 °C, was added KHMDS (0.064 mL, 0.5 M in toluene, 0.032 mmol). After stirring for 5 min, a solution of the lactone **210** (0.080 g, 0.32 mmol) in THF (0.5 mL) was added dropwise and the reaction was allowed to warm to

ambient temperature. The reaction was stirred for 4.5 h at 25 °C, then cooled to 0 °C whereupon 2,6-lutidine (0.111 mL, 0.960 mmol) was added followed by TBSOTf (0.146 mL, 0.640 mmol). After stirring for additional 1 h at 0 °C, the reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ether (2 x 5 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and concentrated. The crude oil was purified by flash chromatography (1-2% ethyl acetate in hexanes) and the thioester was immediately carried to the next step.

To a solution of the thioester (0.123 g, 0.289 mmol) in 2 mL CH_2Cl_2 at −78 °C, $^{i}Bu_2AlH$ (0.72 mL, 1.0 M in hexane, 0.72 mmol) was added dropwise. After stirring for 30 min, the reaction was quenched by careful dropwise addition of MeOH (5 mL). After stirring for an additional 20 min at −78 °C, a saturated aqueous solution of Rochelle salt (10 mL) was added. The resulting gel-like mixture was warmed to ambient temperature and stirred vigorously until two homogeneous layers separated (~1 h). The organic layer was separated, dried (Na_2SO_4) and concentrated. Purification by flash chromatography (0-2.5% ethyl acetate in hexanes) afforded 0.100 g (85% over two steps) of the title compound as colorless oil. $[\alpha]_D$ +47.7 (*c* 1.46, $CHCl_3$); IR $\nu_{max}^{\text{thin film}}$ cm^{-1} 1726, 1613, 1514, 1250, 837, 776; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.39 (d, *J* = 11.5 Hz, 1H), 4.31 (ddd, *J* = 7.2, 5.7, 3.7 Hz, 1H), 3.82 (s, 3H), 3.49 (t, *J* = 5.7 Hz, 2H), 2.53-2.44 (m, 1H), 1.82-1.77 (m, 2H), 1. 06 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H), 0.072 (s, 3H), 0.047 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 159.0, 130.1, 129.0, 113.5, 72.4, 69.0, 65.9, 54.8, 51.3, 34.4, 25.5, 17.7, 7.5, –4.7, –4.9; HRMS (ESI) *m/z* calcd for (M^++Na) $C_{20}H_{34}O_4SiNa$: 389.2124; found: 389.2114.

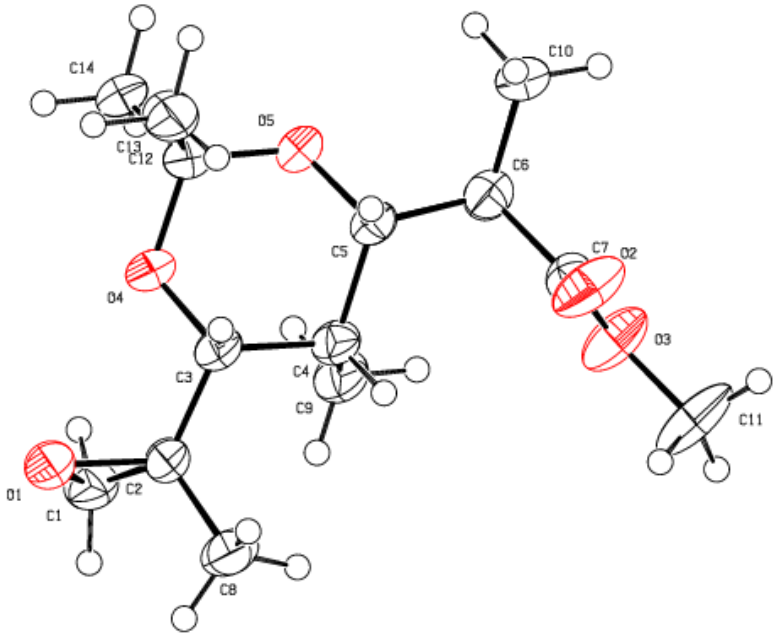
APPENDIX A

X-RAY DATA

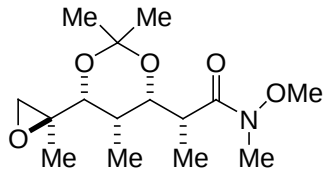


99'

Table 3. Crystal data for **99′**

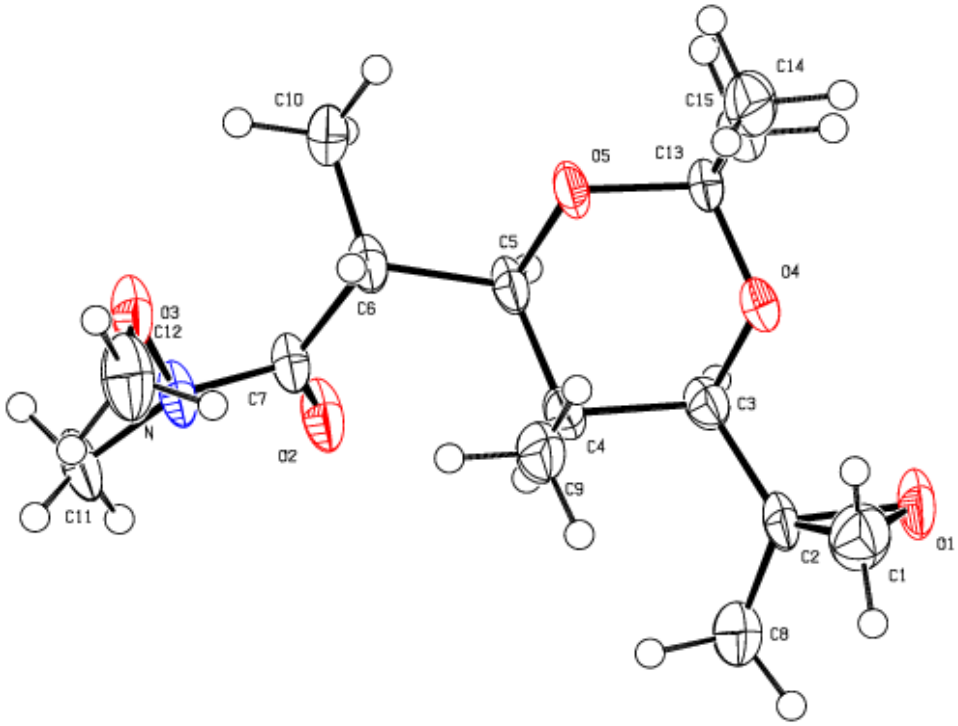


Identification code	bcn411	
Empirical formula	C14 H24 O5	
Formula weight	1089.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 2(1)2(1)2(1)	
Unit cell dimensions	a = 11.545(11) Å	α= 90°.
	b = 8.456(8) Å	β= 90°.
	c = 15.803(15) Å	γ = 90°.
Volume	1543(3) $Å^3$	
Z	4	
Density (calculated)	1.172 Mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	592	
Crystal size	0.18 x 0.22 x 0.26 mm^3	
Theta range for data collection	2.18 to 24.98°.	
Index ranges	-13<=h<=13, -10<=k<=10, -18<=l<=18	
Reflections collected	11811	
Independent reflections	1578 [R(int) = 0.1727]	
Completeness to theta = 24.98°	100.0 %	
Absorption correction	Multi-scan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1578 / 0 / 179	
Goodness-of-fit on F^2	1.010	
Final R indices [I>2sigma(I)]	R1 = 0.0605, wR2 = 0.1378	
R indices (all data)	R1 = 0.1147, wR2 = 0.1551	
Extinction coefficient	0.000(2)	
Largest diff. peak and hole	0.261 and -0.199 $e.Å^{-3}$	



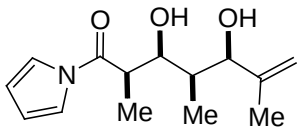
147a

Table 4. Crystal data for **147a**



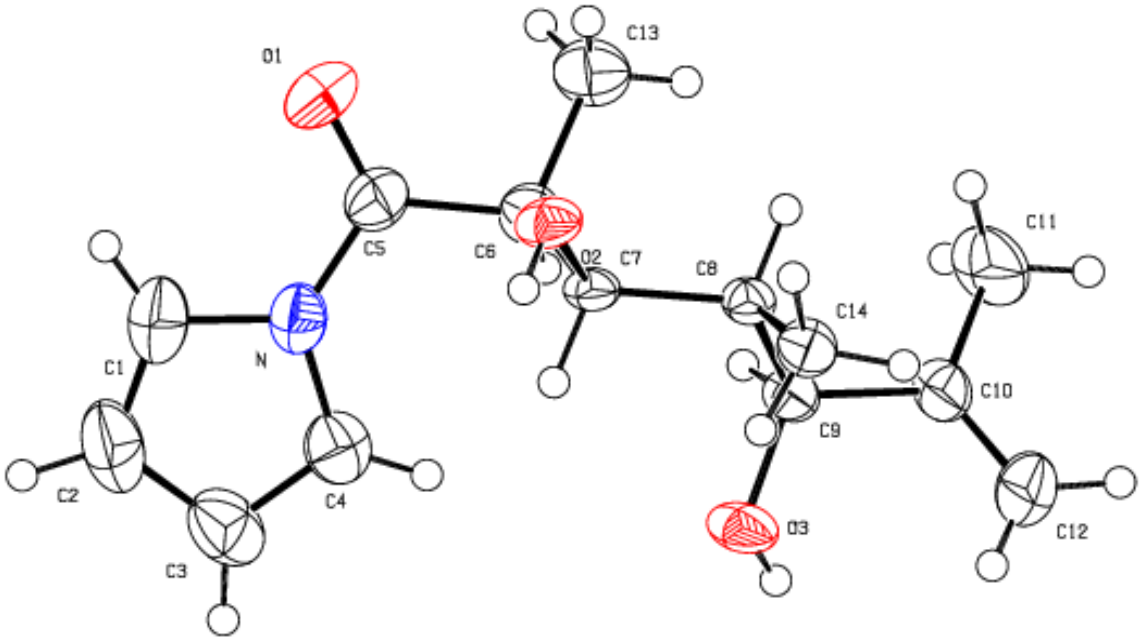
Identification code	binita2s	
Empirical formula	C15 H27 N O5	
Formula weight	301.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.006(3) Å	α= 90°.
	b = 10.545(4) Å	β= 90°.
	c = 20.371(7) Å	γ = 90°.
Volume	1719.8(10) Å^3	

Z	4
Density (calculated)	1.164 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	656
Crystal size	0.25 x 0.25 x 0.03 mm^3
Theta range for data collection	2.00 to 26.00°.
Index ranges	-9<=h<=9, -13<=k<=13, -25<=l<=25
Reflections collected	14583
Independent reflections	1946 [R(int) = 0.1388]
Completeness to theta = 26.00°	100.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9974 and 0.9787
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1946 / 0 / 191
Goodness-of-fit on F^2	1.000
Final R indices [I>2sigma(I)]	R1 = 0.0592, wR2 = 0.1124
R indices (all data)	R1 = 0.1092, wR2 = 0.1250
Extinction coefficient	0.0044(15)
Largest diff. peak and hole	0.210 and -0.265 $e.Å^{-3}$



176

Table 5. Crystal data for **176**



Identification code	df82208s	
Empirical formula	C14 H21 N O3	
Formula weight	251.32	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.009(3) Å	α= 90°.
	b = 6.8235(18) Å	β= 105.554(5)°.
	c = 10.630(3) Å	γ = 90°.
Volume	699.4(3) Å^3	

Z	2
Density (calculated)	1.193 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	272
Crystal size	0.32 x 0.18 x 0.02 mm^3
Theta range for data collection	1.99 to 32.27°.
Index ranges	-14<=h<=14, -10<=k<=9, -15<=l<=15
Reflections collected	8690
Independent reflections	2512 [R(int) = 0.0564]
Completeness to theta = 30.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9983 and 0.9738
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2512 / 1 / 174
Goodness-of-fit on F^2	0.963
Final R indices [I>2sigma(I)]	R1 = 0.0607, wR2 = 0.1267
R indices (all data)	R1 = 0.1144, wR2 = 0.1524
Largest diff. peak and hole	0.255 and -0.173 $e.Å^{-3}$

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