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Kiyoun Lee

Stereoselective Syntheses of Tetrahydropyrans

Applications to the Synthesis of (+)-Leucascandrolide A, (+)-Dactylolide and (±)-Diospongin A

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Doctoral Thesis accepted by
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3. Lee, Kiyoun; Kim, Hyoungsu; Hong, Jiyong*. "A Stereoselective Formal Synthesis of Leucascandrolide A" *Org. Lett.* **2011**, *13*, 2722–2725.
4. Lee, Kiyoun; Kim, Hyoungsu; Hong, Jiyong*. "A Facile and Efficient Synthesis of 4-Hydroxy-2,6-*cis*-tetrahydropyrans via Tandem Cross-Metathesis/Thermal S_N2' Reaction: Protecting-Group-Free Synthesis of Diospongin A" *Org. Lett.* **2009**, *11*, 5202–5205.

To my parents

Supervisor's Foreword

It is my great pleasure to introduce Dr. Kiyoun Lee's work for publication in the *Springer Theses*. A number of areas associated with human health including natural products synthesis, pharmaceutical development, and chemical biology depend on reliable and efficient methods for the synthesis of a chemically diverse range of molecular building blocks and substructures. For this reason, the development of general and selective carbon–carbon and carbon-heteroatom bond-forming reactions, particularly those suited for application in complex molecular systems, has the potential to positively impact these diverse and important areas of research. Tetrahydropyrans are abundantly found as core structures in natural products and pharmaceutically important compounds. Despite continuous interests in the area, currently available methods for the synthesis of tetrahydropyrans possess limitations which include the preferential formation of α,α'-*cis*-tetrahydropyrans.

In his thesis, Kiyoun Lee reports the exploration of tandem and organocatalytic oxa-conjugate addition reactions promoted by the *gem*-disubstituent (Thorpe-Ingold) effect and a tandem cross-metathesis/thermal S_N2' reaction for the stereoselective synthesis of complex tetrahydropyrans. The first part of the thesis details studies of tandem and organocatalytic oxa-conjugate addition reactions in conjunction with a dithiane coupling reaction promoted by the *gem*-disubstituent effect for the stereoselective synthesis of 2,3,6-trisubstituted tetrahydropyrans. The reactions are applicable to a broad range of substrates and proceed with excellent stereoselectivity. The utility of the methodologies has been demonstrated in concise syntheses of (+)-leucascandrolide A and (+)-dactylolide. The second part describes a facile and efficient approach to the synthesis of 2,6-*cis*-4-hydroxy-tetrahydropyrans via a tandem CM/thermal S_N2' reaction. The mildness of the thermal conditions has allowed for the synthesis of 2,6-*cis*-4-hydroxy tetrahydropyrans from base-sensitive substrates without the use of protecting groups. The tandem reaction has enabled a protecting-group-free synthesis of (±)-diospongin A. I strongly believe that the methodologies that Kiyoun Lee has developed will be broadly applicable to the efficient synthesis of a broad range of tetrahydropyran-containing compounds.

December 2013 Prof. Dr. Jiyong Hong

Abstract

Substituted tetrahydropyrans are prevalent in natural products that show interesting biological and pharmacological activities. Therefore, demand for new synthetic approaches for the construction of substituted tetrahydropyrans has recently increased. Specifically, quick and facile access to substrates, excellent stereoselectivity and yield, versatility in substrate scope, and mild reaction conditions compatible with various functional groups are highly desirable characteristics in tetrahydropyran synthesis.

The first part of the dissertation details studies of the tandem and organocatalytic oxa-conjugate addition reactions in conjunction with a dithiane coupling reaction promoted by the *gem*-disubstituent effect for the stereoselective synthesis of 2,3,6-trisubstituted tetrahydropyrans. The reactions were applicable to a broad range of substrates and proceeded with excellent stereoselectivity. It is of note that the present protocol provides an access to thermodynamically less favorable 2,6-*trans*-tetrahydropyrans through a reagent controlled, organocatalytic oxa-conjugate addition. In addition, a temperature-dependent configurational switch allowed the preparation of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate. The synthetic utility of a combination of the tandem and organocatalytic oxa-conjugate addition reaction and the dithiane coupling reaction was demonstrated in the formal synthesis of the cytotoxic macrolide (+)-leucascandrolide A, which possesses both the 2,6-*cis*-disubstituted tetrahydropyran and the 2,3-*trans*-2,6-*trans*-tetrahydropyran. We also demonstrated the potential of the organocatalytic 1,6-oxa-conjugate addition for the formation of the 2,6-*cis*-tetrahydropyran in the total synthesis of (+)-dactylolide.

The second part describes the facile and efficient approach to the synthesis of 2,6-*cis*-4-hydroxy-tetrahydropyrans via a tandem CM/thermal S_N2' reaction. The strategic placement of the hydroxy group at C(4) in the tether resulted in an enhancement of the diastereoselectivity in ring closure. The mildness of the thermal conditions allowed for the synthesis of 2,6-*cis*-4-hydroxy tetrahydropyrans from base-sensitive substrates without the use of protecting groups. The tandem reaction enabled a protecting-group-free synthesis of (±)-diospongin A.

Acknowledgments

First and foremost, I would like to express my sincere gratitude to my research advisor, Prof. Jiyong Hong for giving me the opportunity to join his group and become involved in very interesting projects. It has been an honor to be one of the members of the Hong group. I really appreciate his tremendous scientific guidance and intellectual support during my past 5 years. The skill set I have gained in his laboratory will be an invaluable asset for my future career endeavors, and I am extremely grateful for that. I would also like to thank Prof. Guncheol Kim at Chungnam National University in South Korea, for his guidance in research for my undergraduate and master program in organic chemistry and inspiring me to pursue this graduate career. My current and past committee members, Prof. Steven Baldwin, Prof. Katherine Franz, Prof. Qiu Wang, Prof. Barbara Shaw, and Prof. Don Coltart also deserve special recognition. I am grateful for their insightful comments and suggestions.

I am really grateful to Dr. Hyoungsu Kim, former post-doc, who is now a Professor at Ajou University in South Korea. I was always impressed with his work ethic and wide knowledge base and thank him for all his helpful advice. I would also like to acknowledge the support of the past and present members of the Hong group, Bumki Kim, Tesia Stephenson, Megan Lanier, Do Yeon Kwon, Minhee Lee, Dr. Seongrim Byeon, Dr. Yongcheng Ying, Dr. Amanda Kasper, Dr. Joseph Baker, and Dr. Heekwang Park. I wish them all the best in their future endeavors. I would also like to thank my Korean friends here in the department for supporting me at the difficult times.

Special thanks are extended to Dr. George Dubay for expertise and consistent availability in his help with mass spectrometry-related issues. The financial support from the Department of Chemistry at Duke University is sincerely appreciated.

Finally and most importantly, I would like to thank my wife Mijung for her support and encouragement along the way. She has made a tremendous sacrifice for me during this time even now. I will always be grateful for that.

Contents

Abbreviations

Å	Angstrom
acac	Acetylacetonate
AIBN	Azobisisobutyronitrile
Anti	On the opposing face
aq.	Aqueous
$BF_3{\cdot}Et_2O$	Boron trifluoride diethyl etherate
br s	Broad singlet
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
BRSM	Based upon recovered starting material
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
CM	Cross metathesis
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMAP	4-(*N,N*-dimethylamino)-pyridine
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
EDC/EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
ent	Enantiomer
eq.	Equivalent
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
gem	Geminal

GI_{50}	The concentration required 50 % growth inhibition
HATU	*O*-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium
c-Hex	Cyclohexane
HMPA	Hexamethylphosphoramide
HRMS	High-resolution mass spectrometry
IC_{50}	Inhibitory concentration 50 %
Ipc	Diisopinocampheyl
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminium hydride
LiHMDS	Lithium bis(trimethylsilyl)amide
m	Multiplet
m-CPBA	*meta*-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOH	Methanol
MIC	Minimum inhibitory concentration
min	Minute
MNBA	2-Methyl-6-nitrobenzoic anhydride
MnO_2	Manganese dioxide
MOM	Methoxyl-O-methyl
NBS	*N*-bromosuccinimide
NCI	National Cancer Institute
NOESY	Nuclear Overhauser effect spectroscopy
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NEt_3/TEA	Triethylamine
OTf	Trifluoromethanesulfonate
pH	Negative logarithium of hydrogen ion concentration
PMB	*para*-methoxybenzyl ether
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
i-Pr_2NEt	Diisopropylethylamine
q	Quartet
RCM	Ring-closing metathesis
Rf	Retention factor
rt	Room temperature
s	Singlet
sat.	Saturated
SEM	[2-(trimethylsilyl)ethoxy]methyl
S_N2	Bimoleculare nucleophilic substitution
S_N2'	Bimoleculare nucleophilic substitution with allylic rearrangement
SO_3·Pyr	Sulfur trioxide pyridine complex
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TFA	Trifluoroacetic acid

TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts/Tosyl	*para*-toluenesulfonyl
p-TsOH	*para*-toluenesulfonic acid
Trt	Triphenylmethyl

Chapter 1
Introduction

1.1 Significance

The synthesis of substituted tetrahydropyrans has received a considerable amount of interest due to the prevalence of these substructures in biologically interesting natural products (Fig. 1.1) [1–7]. In addition, their various significant pharmacological activities, including antitumor, antibiotic, antiviral, and antifungal activities, have also attracted the attention of many synthetic organic chemists and biologists [8–10].

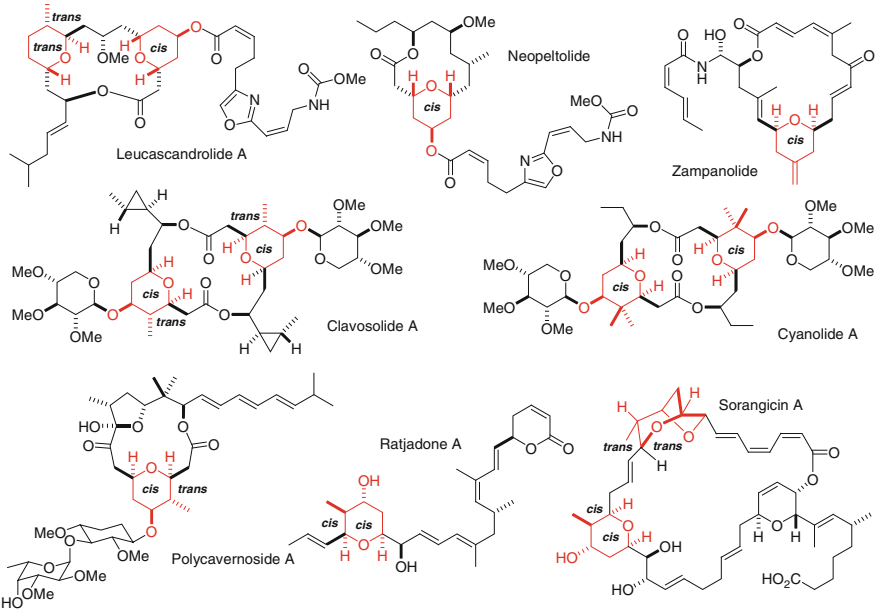

Fig. 1.1 Natural products containing tetrahydropyrans

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Because of these interesting biological activities and the scarcity of materials from their natural sources through isolation, great emphasis has been placed on synthetic approaches toward the efficient construction of tetrahydropyrans. These approaches include the Prins and related cyclization reactions, the hetero-Diels–Alder cyclizations, radical cyclizations, transition metal mediated cyclizations, as well as more traditional methods such as epoxide-mediated cyclizations and oxa-conjugate addition reactions.

Although a wide array of methods for the construction of tetrahydropyrans have been developed, each method has limitations that restrict the scope of its synthetic utility. Major needs for this class of reactions include the facilitated access to substrates, ability to increase molecular complexity of easily obtainable starting materials, excellent stereoselectivity and yield, adaptability of method to a diverse set of substituent patterns of tetrahydropyrans, and lastly, sufficiently mild reaction conditions that are compatible with various functional groups.

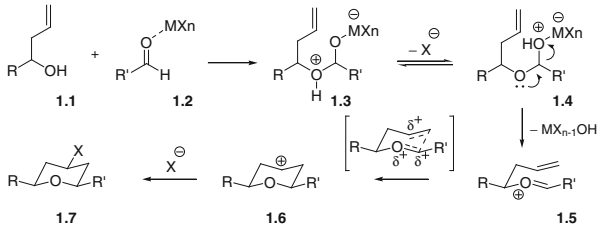
1.2 General Approaches to the Synthesis of Substituted Tetrahydropyrans

In the past decade, given the diversity of tetrahydropyran units in natural products, a large number of methodologies have been developed for both the stereocontrolled and racemic synthesis of substituted tetrahydropyrans. This chapter briefly presents general approaches focused on the enantio- and diastereoselective methods to construct 2,6-disubstituted tetrahydropyrans and describes their related applications for the use in natural product synthesis.

1.2.1 Prins Cyclization Reaction

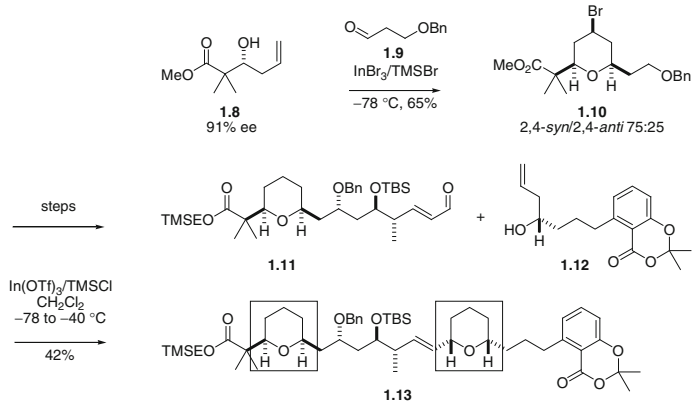
The Prins cyclization has been shown to be a fundamental method for the formation of *O*-heterocyclic derivatives [11, 12]. Thus, to date, there have been numerous examples on the Prins reaction for the formation of tetrahydropyran units. The mechanism involves, in general, the acid-promoted condensation reaction between a homoallyl alcohol and an aldehyde in the presence of a Lewis acid leading to tetrahydropyran units (Scheme 1.1). The key intermediate, an oxocarbenium ion **1.5**, is generated from a hemiacetal and undergoes 6-*endo* cyclization to provide a secondary carbocation **1.6** which can be readily trapped by various nucleophiles.

There are several natural product syntheses which utilize the Prins cyclization reaction as a key step to construct substituted tetrahydropyrans [13–17]. For example, the Loh group has nicely employed the Prins cyclization to furnish the two tetrahydropyranic subunits of (+)-SCH 351448 (Scheme 1.2) [18].



Scheme 1.1 Mechanism of tetrahydropyran synthesis via Prins cyclization

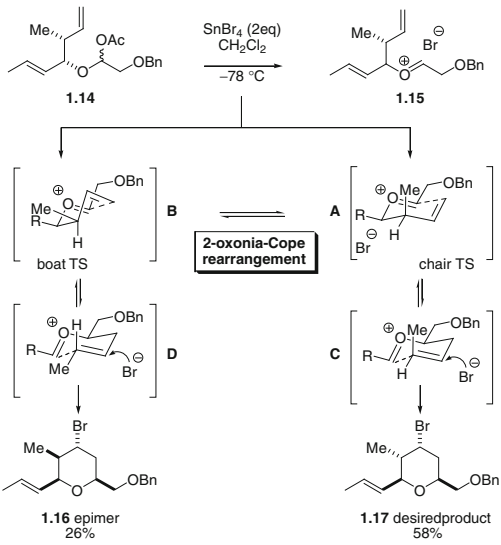
Tetrahydropyran **1.10** was obtained from homoallyl alcohol **1.8** and aldehyde **1.9**. Subunit **1.13** was formed by a second Prins reaction of alcohol **1.12** with aldehyde **1.11** without the deprotection of the acetonide when a combination of $In(OTf)_3$/TMSCl was used.



Scheme 1.2 Prins cyclization in the synthesis of (+)-SCH 351448

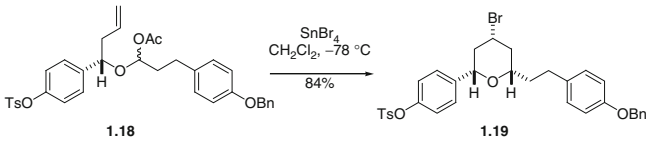
While this reaction has shown great potential for organic synthesis, transformations of this nature have often been encountered by unexpected racemization products, which were presumably caused by the competitive 2-oxonia Cope rearrangement of the oxocarbenium ion intermediate (Scheme 1.3), resulting in a loss in enantiomeric excess. The Speckamp [19] and Rychnovsky [20, 21] groups independently investigated the [3,3]-sigmatropic C–C bond migration of the Prins reaction. The stereochemical outcome of the unexpected epimer **1.16** was attributed to the possible equilibrium of boat transition state **B**, leading to the rearranged oxocarbenium ion bearing *E*-double bond and undergoes Prins cyclization via chair transition state **D**, leading to the epimer **1.16** [20].

To minimize the undesirable reversibility of the 2-oxonia Cope rearrangement and preserve the optical purity of the cyclization products, many modified reaction



Scheme 1.3 Competitive 2-oxonia-Cope rearrangement

conditions, such as solvents, temperature, and structural features were developed. For instance, the Rychnovsky group illustrated the $SnBr_4$-promoted Prins cyclization for the formation of the optically pure 2,6-*cis*-tetrahydropyran in the synthesis of (–)-centrolobine (Scheme 1.4) [22]. The cyclization catalyzed by $BF_3{\cdot}OEt_2$ and AcOH resulted in partial racemization (from 87 to 68 % ee) of the desired product. However, when the $SnBr_4$ was employed, no recemization (from 87 to 85 % ee) of the major product was observed. The outcome of the reaction revealed that the use of $SnBr_4$ suppresses the competing 2-oxonia Cope pathway due to the fact that the Prins cyclizations promoted by $SnBr_4$ are significantly faster than those promoted by $BF_3{\cdot}OEt_2$/AcOH.

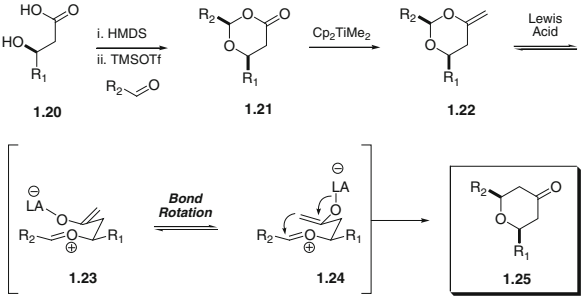


Scheme 1.4 $SnBr_4$-mediated Prins cyclization

1.2.2 Petasis–Ferrier Rearrangement

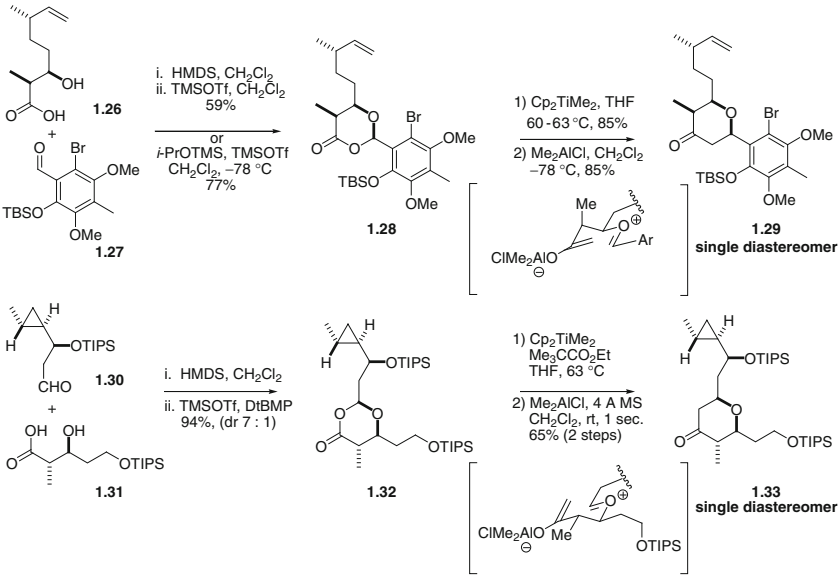
Since the late 1990s, the Smith group developed and utilized the Petasis–Ferrier union/rearrangement for the synthesis of 2,6-*cis*-tetrahydropyran-4-ones. This

three step sequence stems from two independent methods; Ferrier-type reactions in 1962 [23, 24] and Petassis-type reactions in 1996 [25]. As shown in Scheme 1.5, the mechanism of this reaction involves the condensation [26] of chiral, non-racemic β-hydroxy acid **1.20** with an aldehyde to furnish dioxanone **1.21**, which is then succeeded by carbonyl olefination [27, 28] and Lewis-acid promoted rearrangement of the resulting enol acetal **1.22** to give the 2,6-*cis*-disubstituted tetrahydropyran-4-one **1.25** by *endo* attack onto the oxocarbenium intermediate.



Scheme 1.5 Mechanism of the Petasis–Ferrier rearrangement

To demonstrate the versatility of the Petasis–Ferrier rearrangement, Smith has exploited this reaction in the total syntheses of several natural products, such as (+)-phorboxazole A, [29, 30] (+)-zampanolide, [31–33] and (+)-spongistatin [34].



Scheme 1.6 Petassis–Ferrier rearrangement in the synthesis of (–)-kendomycin and (–)-clavosolide A

During the course of the synthesis of (–)-kendomycin, [35, 36] the Smith group utilized the Petasis–Ferrier rearrangement to generate the 2,6-*cis*-tetrahydropyran **1.29** as a key bond forming event (Scheme 1.6). Condensation of aromatic aldehyde **1.27** with β-hydroxy acid **1.26** to generate dioxanone **1.28**, subsequent methylenation using Tebbe reagent, and rearrangement with Me_2AlCl furnished the 2,6-*cis*-tetrahydropyranone **1.29** as a single diastereomer. The high degree of stereoselectivity was explained by a chair like transition state. Given the lability issues of the existing functional groups, careful optimized reaction conditions were exploited. In a later report of (–)-clavosolide A [37] (Scheme 1.6), the necessity of rapid addition of Me_2AlCl to the enol ether as well as the rapid quenching were addressed due to the acid-labile cyclopropylcarbinyl group under such strong Lewis acid conditions. Though quite powerful, due to its incompatible nature with acid labile functional groups, this method has been less utilized in the synthesis of natural products.

1.2.3 Hetero-Diels–Alder Reaction (HDA)

Since the discovery of the Diels–Alder reaction (DA) by Otto Diels and Kurt Alder in 1928, [38] considerable effort has been devoted to developing methods for catalyzing the hetero-Diels–Alder cycloaddition (HDA) between aldehydes and dienes in an asymmetric fashion [39–41]. This transformation is useful since two σ bonds are newly generated in the reaction with the potential for stereochemical control at up to three new chiral centers. In 1982, Danishefsky and coworkers established new types of HDA reactions using unactivated aldehyde heterodienophiles in the presence of Lewis acid catalysts [42]. Since then, a number of groups have been focusing on this area because of the ease with which the dihydropyranone products of the reaction of an aldehyde with Danishefsky's diene can be successfully applied to the generation of pyran rings in natural product synthesis. The mechanism of the initial Lewis acid catalyzed coupling of aldehyde **1.34** with activated dienes **1.35**–**1.36** would lead to the formation of **1.39** through either the Mukaiyama–aldol reaction pathway or the traditional Diels−Alder pathway (Fig. 1.2) [43].

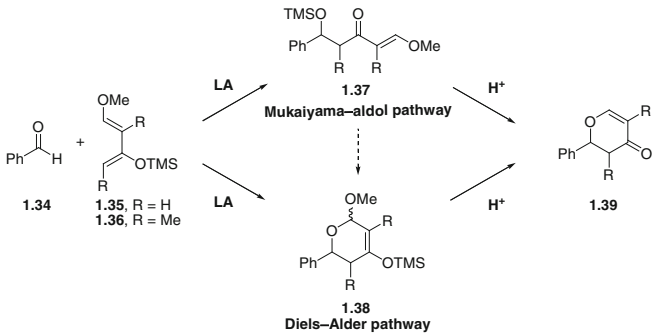
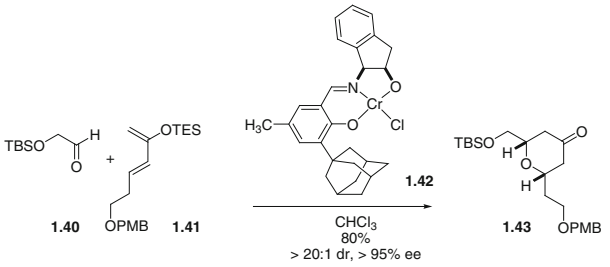


Fig. 1.2 The Mukaiyama–aldol and the Diels–Alder pathway in HDA reactions

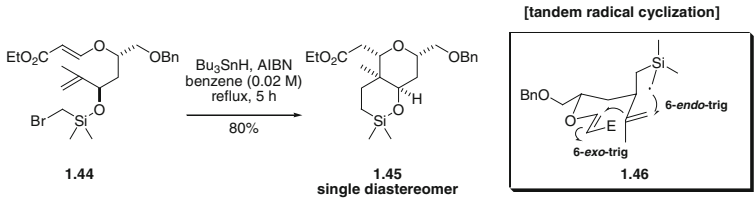
A more significant growth on enantioselective hetero Diels–Alder reactions has been pioneered by the Jacobsen group [44–46]. The HDA reactions of less nucleophilic dienes than Danishefsky's diene were successfully realized by employing Jacobsen's chiral tridentate Schiff base chromium(III) complex **1.42** [46–48]. This powerful method has been utilized on multiple occasions in total synthesis. For example, Patterson and coworkers applied this concept to a synthesis of leucascandrolide A [49]. Aliphatic aldehyde **1.40** coupled with diene **1.41** using Jacobsen's chromium catalyst furnished the 2,6-*cis*-tetrahydropyranone **1.43** with high stereoselectivity (Scheme 1.7).



Scheme 1.7 Synthesis of 2,6-*cis*-tetrahydropyran via HAD

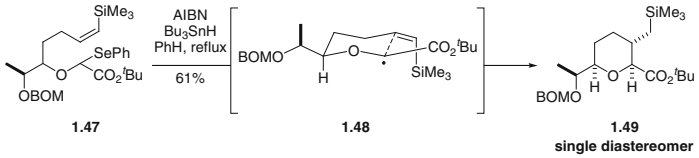
1.2.4 Radical Cyclization

The radical cyclization of *β*-alkoxyacrylates also offers an attractive approach to the formation of 2,6-*cis*-tetrahydropyrans [50, 51]. A noteworthy strategy was demonstrated by the Lee group in the first total synthesis of lasonolide A [52, 53]. Lee and coworkers illustrated the tandem radical cyclization of α,*β*-alkoxyacrylate **1.44** containing a bromomethylsilyloxy substituent to furnish the bicyclic product **1.45** with highly efficient cyclization modes and excellent control of diastereoselectivity (Scheme 1.8). The high degree of stereocontrol can be attributed to the successive 6-*endo* and 6-*exo* modes of radical cyclization in a chair like transition state **1.46**.



Scheme 1.8 Synthesis of tetrahydropyran via tandem radical cyclization

Another systematic study of the radical cyclization was reported by Burke and coworkers [54]. Homolytic cleavage of the carbon-selenium bond in **1.47** provided tetrahydropyran **1.49** as a single diastereomer (Scheme 1.9). The stereochemical outcome of this reaction was explained by the equatorially oriented substituents, which leads to the conformational preference as shown in transition state **1.48**.



Scheme 1.9 Synthesis of tetrahydropyran by substituent effect

1.2.5 Transition Metal-Mediated Cyclization

Transition metal-mediated strategies have also received considerable attention in the context of substituted tetrahydropyran synthesis [55–57]. General mechanism of the transition metal-mediated cyclization involves the intramolecular attack of an oxygen nucleophile onto an activated olefin by metal catalysts. The most common substrates are δ-hydroxy alkenes, which provide the corresponding pyrans with high stereoselectivity. Although a large number of metals are employed, the catalytic olefin activation by Pd(0) and Pd(II) has been thoroughly investigated [58]. As depicted in Fig. 1.3, the initial π-complex evolves through a η^3-complex to a π-allyl cation, a highly reactive intermediate that undergoes π intramolecular attack of the hydroxyl to form the corresponding tetrahydropyran.

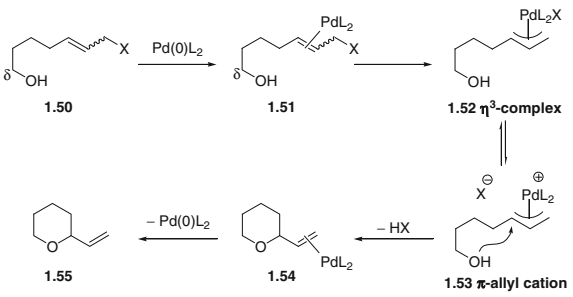
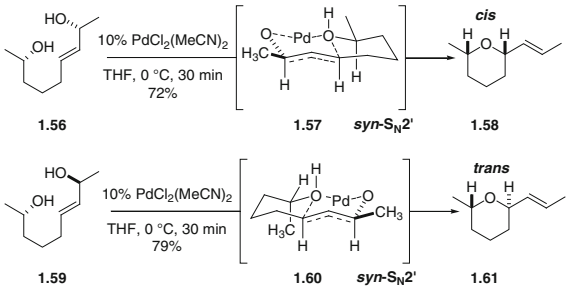


Fig. 1.3 Tetrahydropyran via Pd(0)-mediated cyclization

Uenishi and coworkers reported a particularly attractive intramolecular $PdCl_2(CH_3CN)_2$ catalyzed cyclization reaction of chiral allylic alcohols (Scheme 1.10) [59–61]. A newly generated stereogenic center in tetrahydropyran

is controlled by 1,3-chirality transfer from the chiral allylic alcohol via a *syn*-S_N2' type process. Both 2,6-*cis*-and 2,6-*trans*-tetrahydropyrans (**1.58** and **1.61**) were stereospecifically obtained from *syn*-1,7-diol **1.56** and *anti*-1,7-diol **1.59**, respectively. The excellent facial selectivity of these reactions can be rationalized on the basis of the unfavorable allylic strain and 1,3-diaxial interaction of the Pd π-complex with the allylic alcohols in the transition state. While the ability to produce both the *cis* and *trans* isomers independently is a synthetic advantage, in this case, having to set both stereocenters before the cyclization, in order to form each isomer, is a limitation of this method, which occasionally leads to lengthy syntheses.



Scheme 1.10 Oxypalladation reaction

1.2.6 Epoxide-Mediated Cyclization

Since the seminal discovery by Nicolaou [62, 63] in 1989 that accomplished regio- and stereoselective synthesis of six-membered oxygenated heterocycles, Brønsted- or Lewis acid-catalyzed cyclization of hydroxy epoxides have become very common place in the stereoselective construction of tetrahydropyrans within the context of natural product synthesis [63–65].

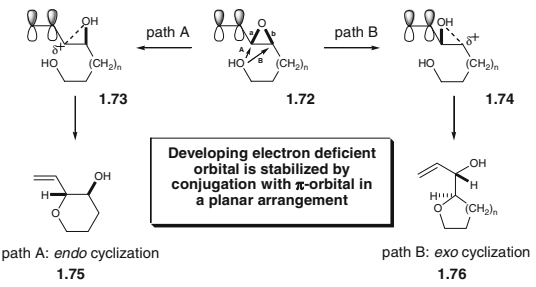
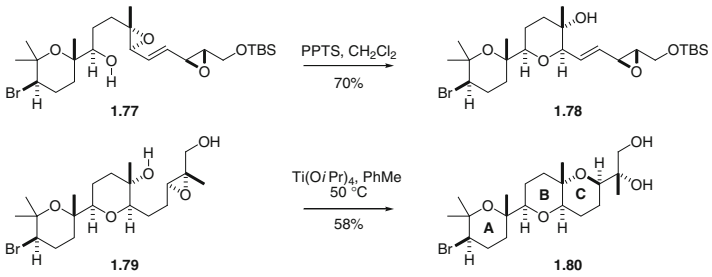


Fig. 1.4 Intramolecular selective 6-*endo* epoxide opening by Nicolaou

As pointed out in Fig. 1.4, *trans*-γ-hydroxy epoxides **1.72** possessing an alkenyl directing group provide the corresponding tetrahydropyrans **1.75**, where the electron-deficient orbital on carbon would be stabilized by the adjacent π-orbital in a parallel arrangement. Thus, the reaction favors 6-*endo* over 5-*exo*-cyclization with high selectivity [62]. In a later report, this chemistry was applied to many biologically significant THP-containing natural products. For example, McDonald and coworkers nicely illustrated this concept during the course of the synthesis of ABC rings in thyrisferol and venustatriol [66]. The B ring of both natural products was rendered by the acid-catalyzed cyclization of *trans*-γ-hydroxy epoxide **1.77** with excellent *endo* selectivity. After two steps of functional group manipulations, it was cyclized upon treatment with Ti(O*i*Pr)$_4$, completing the ABC rings of the natural products (Scheme 1.11).



Scheme 1.11 Construction of the ABC rings of thyrisferol and venustatriol

The main advantage of the epoxide opening reaction is a selective stereochemical outcome. Either 2,6-*cis* or 2,6-*trans*-tetrahydropyran can be selectively obtained since the mechanism involves an S_N2 displacement. However, there are of course drawbacks to this methodology as well. Although a lot of effort has been focused on the ring closure modes of epoxide opening reactions, the elucidation of these modes are far from complete. There is still a large demand for the investigation of different factors that affect the outcome of epoxide opening reactions. In addition, both stereogenicities of the epoxy alcohol should be set prior to the cyclization, which would often lead to lengthy synthetic steps within the complex natural product synthesis.

1.2.7 Summary

In summary, numerous synthetic approaches have emerged as useful and versatile tools for the access of enantio-, diastereoselective construction of substituted tetrahydropyran skeletons, which are commonly encountered in both structurally challenging and biologically active natural products. As described in this chapter,

significant developments including the Prins cyclization, hetero-Diels–Alder cyclization, radical cyclization, transition metal-mediated cyclization and epoxide-mediated cyclization have been made. Although all of these methods have their own distinct advantages, each also has inherent limitations such as regio- and stereochemical outcome issues, highly sensitive reaction conditions, and incompatibility with labile functional groups under reaction conditions. These features lead to the continuous demand for new synthetic approaches for the construction of the tetrahydropyran moiety.

Given that there is much room for advancement, our group has become interested in developing alternative strategies for the efficient construction of stereoselective tetrahydropyrans. Particularly, we have sought flexible methods enough to give access to both *cis* and *trans* 2,6-substitution patterns from a common substrate. The following chapters describe the development of new methods that are designed and utilized within our group. Also the next phase of these efforts, focused on the application of these methods to natural products possessing significant bioregulatory properties, will be discussed.

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Chapter 2
Stereoselective Synthesis of Tetrahydropyrans via Tandem and Organocatalytic Oxa-Conjugate Addition Reactions

2.1 Introduction

Michael reactions have drawn a great amount of interest from the synthetic community due to their ability to form C–C sigma bonds through the conjugate addition of carbon nucleophiles to many different types of Michael acceptors [1]. However, the analogous conjugate additions of other heteroatom nucleophiles such as amines, thiols, phosphines, and alcohols have not progressed at the same rate [2–5]. This is especially true for the application of these conjugate addition methodologies in the context of alcohol nucleophiles and α,β-unsaturated carbonyl compounds (oxa-conjugate addition reaction) in order to stereoselectively form tetrahydropyrans. This comparative lack of interest can be mainly attributed to the major disadvantages of the oxa-conjugate addition reaction, including the poor nucleophilicity of oxygen atoms, reversibility of the addition process (retro-oxa-conjugate addition reaction), and the lack of stereoselectivity [1].

The biggest issue with these types of reaction is the poor nucleophilicity of oxygen nucleophiles. While many different reports have presented the intermolecular oxa-conjugate addition of alcohols to conjugated acceptors [6–16], such as α,β-unsaturated ketones and esters, nitroalkenes, and acrylonitriles, deprotonation of the alcohol through the use of a carefully selected base was critical to all of these cases [6]. Alternatively, the activation of conjugate acceptors by Lewis or Brønsted acids [7], phosphines [8, 9], amines [10–12], and transition metal complexes [15, 16] have also shown to be necessary to overcome the lack of nucleophilicity. Not only are these harsh reaction conditions incompatible with many existing functionalities of the substrate, but even entropically favorable intramolecular conjugate addition to α,β-unsaturated carbonyl compounds necessitates the activation of the oxygen nucleophile. The use of α,β-unsaturated aldehydes as a conjugate acceptor has been particularly difficult due to competitive acetal formation, instability, and enolizability of the aldehyde carbonyls [17].

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To overcome these drawbacks, our group illustrated the stereoselective synthesis of 2,6-*cis*-tetrahydropyrans through a tandem allylic oxidation/oxa-conjugate addition of alcohols to α,β-unsaturated aldehydes [18]. This process was promoted by the *gem*-disubstituent effect, which is the increase in reaction rate of cyclization steps through the replacement of hydrogen atoms of the tethering carbon with more sterically demanding alkyl groups [19]. Preliminary results demonstrated the potential of dithiane coupling for the utilization of the *gem*-disubstituent effect in order to stereoselectively synthesize tetrahydropyrans. The applicability of this tandem method was also shown in the formal synthesis of neopeltolide [18] and the first total synthesis of cyanolide A [20]. This section briefly explains the advantages of this methodology and the extent to which it can be applied to the synthesis of more complex 3-methyl-2,6-disubstituted tetrahydropyrans.

2.2 Preliminary Study

2.2.1 Design of the Tandem Oxidation/Oxa-Conjugate Addition

Given the interest in facilitating access to biologically important natural products with cyclic ethers [21–24], we set out to explore the scope of intramolecular oxa-conjugation additions of alcohols to α,β-unsaturated aldehydes for the stereoselective synthesis of 2,6-disubstituted tetrahydropyrans. In order to overcome the issues of poor nucleophlicity of the oxygen nucleophile and reversibility of the conjugate addition reaction, we envisioned the introduction of a structural element that would promote conformational preorganiztion of a substrate for an intramolecular oxa-conjugate addition. This structural element could also help decrease the potential reversibility of the conjugate addition process to form the oxa-conjugate addition product. A 1,3-dithiane group at the C(4) position of the alcohol nucleophile was hypothesized to fulfill all of these prerequisites by utilizing the *gem*-disubstituent effect [19] (Fig. 2.1).

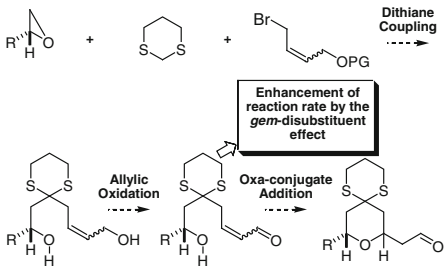


Fig. 2.1 Design of the oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect

While the 1,3-dithiane group is only one of many different structural elements that employ the *gem*-disubstitent effect, arguably, it is definitely one of the most effective and applicable to further extension in the context of natural product synthesis [25]. As an acyl anion equivalent utilizing umpolung-based strategies, it can be further functionalized to a variety of different groups, such as a carbonyl, hydroxy, or olefinic group, or a hydrogen atom (Fig. 2.2) [26–28]. Further advantages of the 1,3-dithane group include facilitated access to a broad scope of substrates by coupling a wide variety of electrophiles, improvement in selectivity by employing a more rigid transition state during cyclization, reduced reversibility, and the ability to serve as a useful precursor to a spectrum of different functional groups.

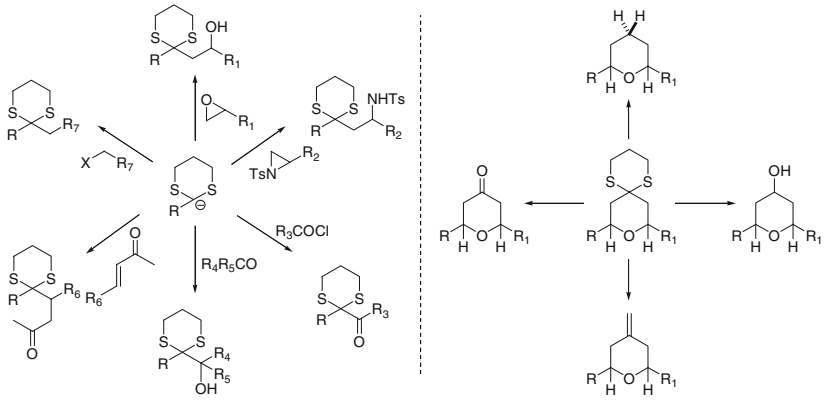
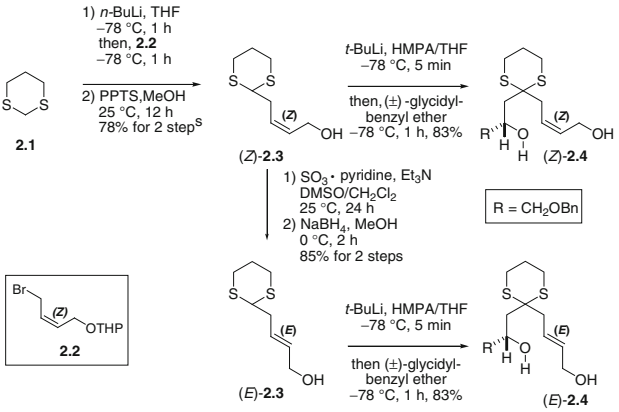
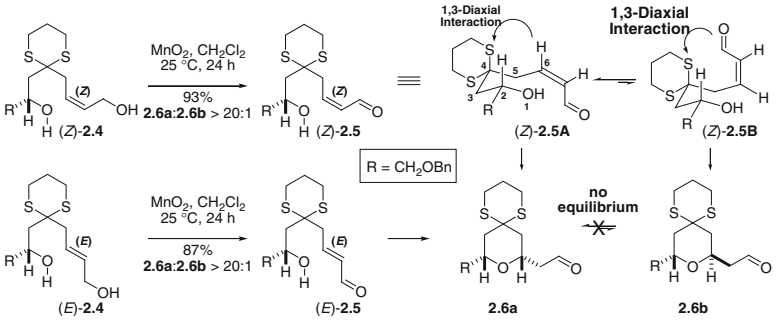


Fig. 2.2 Umpolung based strategies and latent functional groups of 1,3-dithiane

To investigate the effect of the *gem*-disubstituent effect on oxa-conjugate addition reactions, substrate (*Z*)-**2.4** was prepared. The dithiane coupling of **2.1** with allyl bromide **2.2** [29] followed by THP-deprotection provided (*Z*)-**2.3**. The coupling of (*Z*)-**3** with (±)-glycidyl benzyl ether proceeded smoothly to afford allyl alcohol (*Z*)-**2.4**. As expected, the chemoselective oxidation of (*Z*)-**2.4** with MnO_2 and subsequent intramolecular oxa-conjugate addition reaction of the resulting α,β-unsaturated aldehyde (*Z*)-**2.5** provided the desired 2,6-*cis*-tetrahydropyran **2.6a** with excellent stereoselectivity (dr >20:1, 93 %; *tandem allylic oxidation/oxa-conjugate addition reaction*) [30–33]. The relative stereochemistry of the 2,6-disubstituted tetrahydropyran was determined to be *cis* by NMR spectroscopy.



Scheme 2.1 Preparation of allyl alcohols (*E*/*Z*)-**2.4**



Scheme 2.2 Synthesis of 2,6-*cis*-tetrahydropyrans through the tandem allylic oxidation/oxa-conjugate addition reactions

This excellent selectivity is attributed to the large 1,3-diaxial interaction between the C(6) α,β-unsaturated carbonyl group and the C(4) dithiane group in conformation (*Z*)-**2.5B**, compared to the smaller C(6) hydrogen atom and the C(4) dithiane group in conformation (*Z*)-**2.5A** [34, 35].

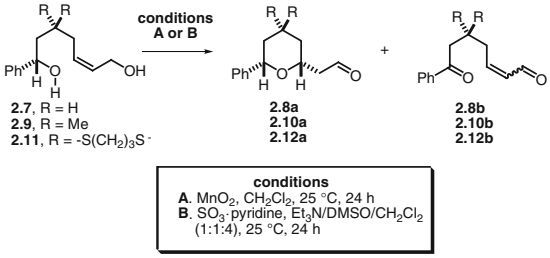
In order to determine if the oxa-conjugate addition is kinetically or thermodynamically controlled, the *trans* isomer **2.6b** was independently synthesized and subjected to tandem reaction conditions. Since it has been very well documented that 2,6-*cis*-tetrahydropyrans are thermodynamically more favorable than 2,6-*trans*- tetrahydropyrans in equilibrium [36–38], thermodynamic control would result in the isomerization of the compound. The complete lack of formation of the *cis* isomer **2.6a** led us to conclude that the formation of the 2,6-*cis*-tetrahydropyrans **2.6a** through tandem oxidation/oxa-conjugate addition is under kinetic control.

To determine the effect of olefin geometry on reaction rate and stereoselectivity, we prepared the (*E*) isomer (*E*)-**2.4** via Parikh–Doering oxidation [39] of (*Z*)-**2.3**, concomitant isomerization to (*E*)-olefin, $NaBH_4$ reduction, and coupling with (±)-glycidyl benzyl ether (Scheme 2.1). The tandem reaction of (*E*)-**2.4** under MnO_2 oxidation conditions also provided **2.6a** (dr >20:1, 87 %), suggesting that the double bond geometry appears to have no effect on the stereoselectivity and conversion of the reaction (Scheme 2.2).

2.2.2 gem-*Disubstituent Effect on Reaction Rate and Stereoselectivity*

The 1,3-dithiane group was expected to overcome the low oxygen nucleophilicity. This would be done through the promotion of an ideal cyclization conformation through the *gem*-disubstituent effect. In order to test this hypothesis, substrates (**2.7** and **2.9**) with no or reduced *gem*-disubstituent effect were prepared and subjected to tandem reaction conditions (Table 2.1).

Table 2.1 *gem*-disubstituent effect on reaction rate and stereoselectivity



Entry	Substrate	Conditions	Product (yield[a], dr[b])
1	**2.7**	**A**	**2.8a:2.8b** = 3:1 (83 %, 7:1)
2	**2.7**	**B**	**2.8b** only (92 %, NA[c])
3	**2.9**	**A**	**2.10a:2.10b** = 4:1 (94 %, 10:1)
4	**2.9**	**B**	**2.10a:2.10b** = 3:1 (94 %, 10:1)
5	**2.11**	**A**	**2.12a** only (96 %, >20:1)
6	**2.11**	**B**	**2.12a** only (94 %, >20:1)

[a] Combined yield of the isolated THP and ketone
[b] The diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) was determined by integration of the ^1H NMR spectrum of the crude product
[c] Not applicable

The MnO_2 mediated oxidation of **2.7** provided the desired 2,6-*cis*-tetrahydropyran **2.8a** (dr = 7:1, entry 1), but the reaction also produced ketone **2.8b** (**2.8a**:**2.8b** = 3:1) as a result of a slower oxa-conjugate addition due to the absence

of the *gem*-disubstituent effect. When oxidation conditions were changed to the Parikh-Doering oxidation, complete failure to produce **2.8a** occurred, leading to the exclusive formation of **2.8b**. When the *gem*-dimethyl group was introduced to **2.7** (entries 3 and 4), the tandem reaction of **2.9** under the MnO_2 or Parikh–Doering oxidation conditions was accelerated to provide **2.10a** with good stereoselectivity (dr = 10:1). However, the competing benzylic oxidation was also observed (**2.10a**:**2.10b** = 3–4:1). These results clearly demonstrated that the *gem*-disubstituent effect accelerated the intramolecular oxa-conjugate addition reaction. As expected, the 1,3-dithiane group showed a vast improvement in stereoselectivity, as well as increased oxa-conjugate addition rate as no benzylic oxidation was observed. These results are most likely due to the increased 1,3-diaxial interaction/more rigid chair-like transition state induced by the cyclic dithiane group compared to the hydrogens or the dimethyl group. This led us to the conclusion that the 1,3-dithiane group promotes reaction rate by the *gem*-disubstituent effect and enhances the stereoselectivity through a more rigid transition state in the cyclization step.

2.3 Result and Discussion

Encouraged by the great potential of a combination of the oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect and the dithiane coupling reaction for the rapid and stereoselective construction of 2,6-*cis*-tetrahydropyrans, we were interested in further investigation of this method to the stereoselective synthesis of a diverse set of structurally more complex 3-methyl-2,6-disubstituted tetrahydropyrans. Among substituted tetrahydropyrans, 3-methyl-2,6-disubstituted tetrahydropyrans are one of the most abundant classes of tetrahydropyrans in natural products, as exemplified in sorangicin A (**2.13**), leucascandrolide A (**2.14**), ratjadone A (**2.17**), polycavernoside A (**2.20**), bistramide A (**2.22**), and these moieties have attracted considerable interest (Fig. 2.3) [40–43]. Although an increasing amount of interest has focused on the generation of these structures, the oxa-conjugate addition reaction of α,β-unsaturated aldehydes has rarely been used for the stereoselective synthesis of 3-methyl-2,6-disubstituted tetrahydropyrans [1, 44–50]. In addition, the stereoselective synthesis of 2,6-*trans*-tetrahydropyrans has been a challenge in organic synthesis because of their poor thermodynamic stability issue. Thus, there are few methods versatile enough for the stereoselective synthesis of 2,6-*trans*-tetrahydropyrans with a wide range of substituent patterns.

In this section, we describe our efforts for exploration of tandem and organocatalytic oxa-conjugate addition reactions of α,β-unsaturated aldehydes for the stereoselective synthesis of structurally complex tetrahydropyrans and their applications to the efficient synthesis of the precursors to the C(21–29) and C(30–37) fragments of *ent*-(+)-sorangicin A. In the following sections, it will also be discussed the extention of the utility and efficiency of the tandem and organocatalytic oxa-conjugate addition reactions in the stereoselective synthesis of (+)-leucascandrolide A and (+)-dactylolide.

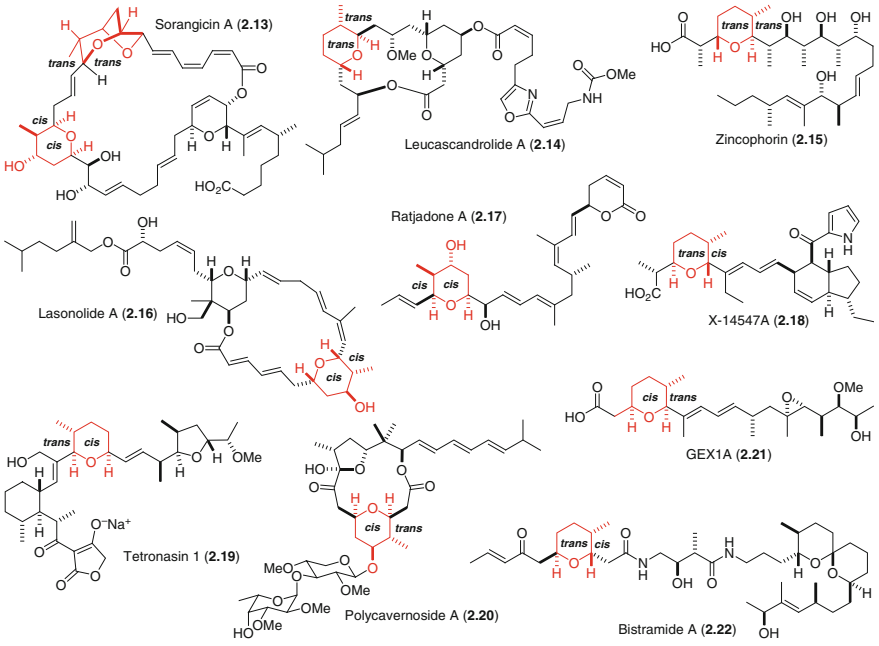


Fig. 2.3 Natural products containing 3-methyl-2,6-disubstituted tetrahydropyrans

2.3.1 Tandem and Organocatalytic Oxa-Conjugate Addition

2.3.1.1 Conformational Analysis of the Oxa-Conjugate Addition Reaction

Given aware that previously designed the tandem oxidation/oxa-conjugate addition reaction necessitated no activation of substrates and proceeded in a substrate-controlled manner under neutral, mild reaction conditions, we envisaged that it would be possible to predict the stereochemical outcome of the oxa-conjugate addition reaction through careful conformational analysis of transition states (Figs. 2.4, 2.5).

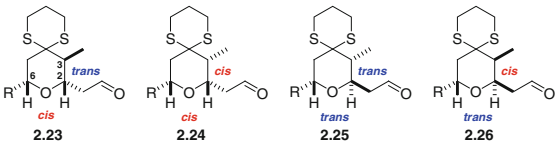


Fig. 2.4 Four diastereomeric 3-methyl-2,6-disubstituted tetrahydropyrans

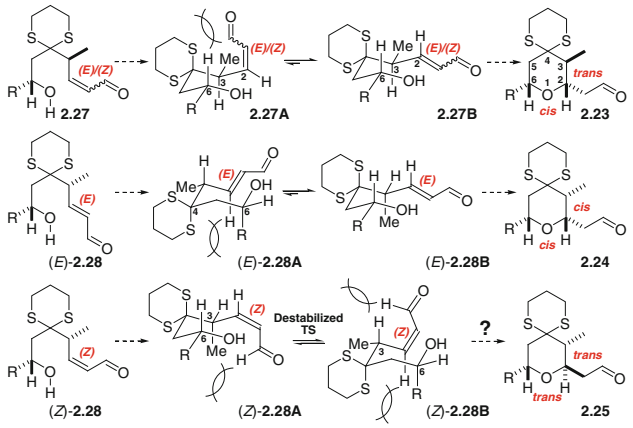


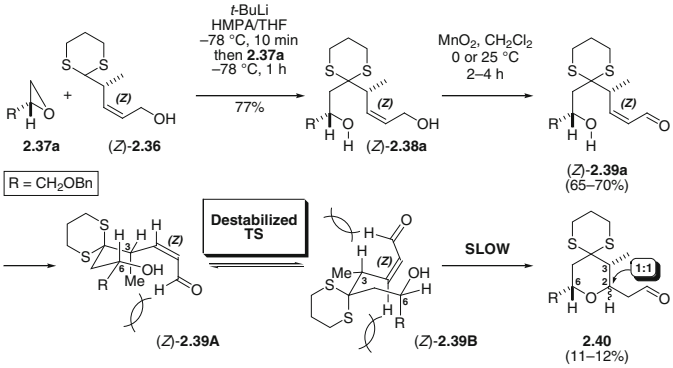
Fig. 2.5 Conformational analysis of the oxa-conjugate addition reaction

From the conformational perspective of the diastereomeric 3-methyl-2,6-disubstitued tetrahydropyrans, we envisioned that **2.23** could be stereoselectively prepared through the most favorable transition state **2.27B** on the basis that the bulky C(2), C(3), and C(6) substituents of 2,3-*trans*-2,6-*cis*-tetrahydropyran **2.23** occupy the equatorial position in the tandem oxidation/oxa-conjugate addition reaction. The formation of 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.24** can be anticipated from the favorable chair-like conformation (*E*)-**2.28B** to stereoselectively afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.24** due to the large 1,3-diaxial interaction between the C(4) dithiane group and the C(6) alkyl group in the competing transition state (*E*)-**2.28A**. However, our conformational anaylsis illustrated that the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.25** through the tandem oxidation/oxa-conjugate addition reaction would be more challenging, due to the stereochemical mismatch between the C(3) methyl group and the C(6) alkyl group in (*Z*)-**2.28A** and (*Z*)-**2.28B** which would significantly hinder the formation of well-defined transition state in the oxa-conjugate addition step to afford **2.25** with high degree of stereoselectivity.

2.3.1.2 Synthesis of 2,3-*trans*-2,6-*trans*-Tetrahydropyrans

With the conformational analysis in mind, our investigation commenced with the stereoselective formation of 2,3-*trans*-2,6-*trans*-tetrahydropyrans. To determine the feasibility of the oxa-conjugate addition reaction for the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyrans, allyl alcohol (*Z*)-**2.38a** was prepared by dithiane coupling of (*Z*)-**2.36** with (*S*)-glycidyl benzyl ether (**2.37a**) and subsequently subjected it to the tandem oxidation/oxa-conjugate addition reaction

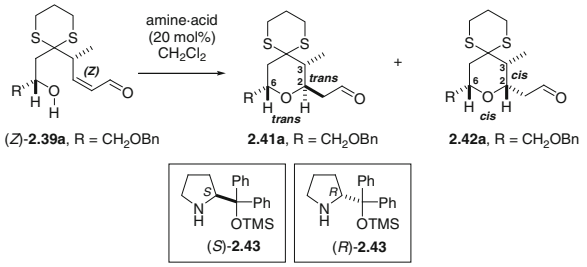
(Scheme 2.3). As predicted, the tandem reaction of (*Z*)-**2.38a** provided aldehyde (*Z*)-**2.39a** as the major product (65–70 %) due to the repulsive interactions in transition states (*vide supra*) and resulted in complete decomposition after the prolonged reaction time (72 h).



Scheme 2.3 Preparation of allyl alcohol (*Z*)-**2.36** and attempts for the synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyrans through the tandem oxa-conjugate addition reaction

To overcome the stereochemical mismatch in transition states, the iminium activation of the resulting aldehyde (*Z*)-**2.39a** was pursued to promote the conjugate addition step by increasing the reactivity of (*Z*)-**2.39a**. The (*Z*)-**2.39a** was converted to the corresponding iminium ion by treatment with amine and acid (Table 2.2). The iminium activation of (*Z*)-**2.39a** by reacting with 20 mol % pyrrolidine·BzOH in dichloromethane at 25 °C greatly promoted the oxa-conjugate addition, but afforded the undesired 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** as a single diastereomer (entry 1). Gratifyingly, attempts of conjugate addition at low temperature (–40 or –78 °C) resulted in the formation of the 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** as the major diastereomer over the formation of 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** (dr = 3.5–4.1:1, entries 2 and 3). An alternative iminium activation by treatment of piperidine further improved the stereoselectivity (dr = 7.4:1, entry 6). These encouraging results prompted us to test the chiral organocatalysts to further improve the stereoselectivity of the oxa-conjugate reaction [12, 13, 51–56]. When (*Z*)-**2.39a** was treated with (*S*)-**2.43** [57, 58] at –40 °C, the organocatalytic oxa-conjugate addition reaction proceeded smoothly to provide **2.41a** with excellent stereoselectivity and yield (dr = 12:1, 96 %, entry 9). When the enantiomeric (*R*)-**2.43** was employed, the organocatalytic oxa-conjugate addition reaction provided **2.41a** with no stereoselectivity (entry 10).

Table 2.2 The organocatalytic oxa-conjugate addition reaction of α,β-unsaturated aldehydes



Entry	Amine	Acid	Temp (°C)	Time (h)	Yield (%)[a]	dr[b]
1	Pyrrolidine	BzOH	25	1	98	**2.42a** only
2	Pyrrolidine	BzOH	–40	4	96	3.5:1
3	Pyrrolidine	BzOH	–78	14	93	4.1:1
4	Pyrrolidine	HOAc	–40	4	95	3:1
5	Pyrrolidine	TFA	–40	5	75	2.5:1
6	Piperidine	BzOH	–40	13	95	7.4:1
7	(*S*)-**2.43**	BzOH	0	3	96	6:1
8	(*S*)-**2.43**	BzOH	–20	5	93	10:1
9	(*S*)-**2.43**	**BzOH**	**–40**	**14**	**96**	**12:1**
10	(*R*)-**2.43**	BzOH	0	3	95	1:1

[a] Combined yield of the isolated **2.41a** and **2.42a**
[b] The diastereomeric ratio (**2.41a**:**2.42a**) was determined by integration of the ^{1}H NMR of the crude product

Our proposed rationales for the stereochemical outcome as a function of reaction temperature observed in the organocatalytic oxa-conjugate addition reactions are illustrated in Fig. 2.6. The formation of both 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** and 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** can be rationalized via two different mechanisms. The **Rationale 1** reveals that at low temperature (–40 or –78 °C), the iminium ion of (*Z*)-**2.39a** would adopt conformation **2.44B** to avoid the severe 1,3-diaxial interaction between the axially-oriented C(3) methyl group and the C(2) iminium diene group to generate 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a**. At 25 °C, (*Z*)-iminium ions (**2.44A** and **2.44B**) readily undergoes isomerization to the more stable (*E*)-iminium ion **2.44C** which subsequently cyclizes to give kinetically and thermodynamically more favorable product 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a**. An alternative mechanism (**Rationale 2**) imply that the iminium ion of (*Z*)-**2.39a** initially forms the kinetically more favorable product **2.41a** at 25 °C, but **2.41a** could be converted to the corresponding (*E*)-enal through the retro-oxa-conjugate addition reaction at 25 °C and eventually lead to **2.42a**. The low reaction temperature could minimize the isomerization of (*Z*)-iminium ions and/or the retro-oxa-conjugate addition/isomerization/oxa-conjugate addition reaction of **2.41a**.

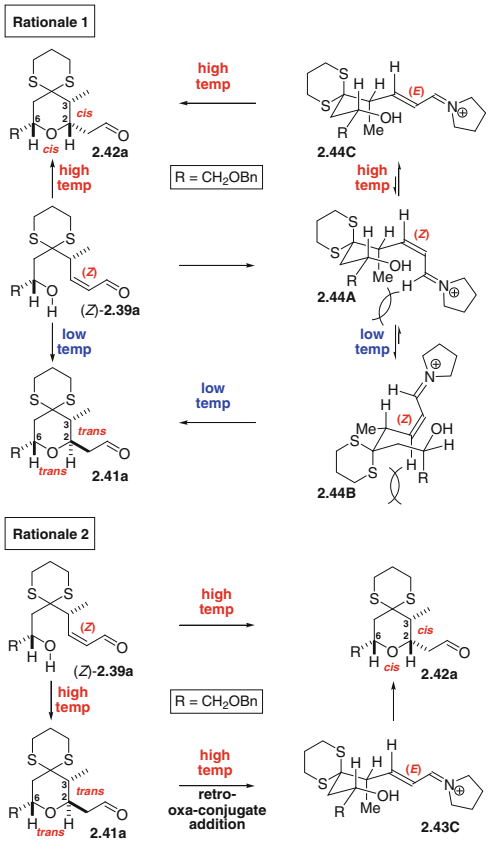
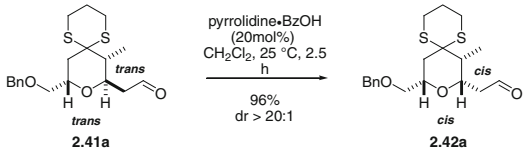


Fig. 2.6 Proposed rationales for the stereochemical outcome of the organocatalytic oxa-conjugate addition reaction

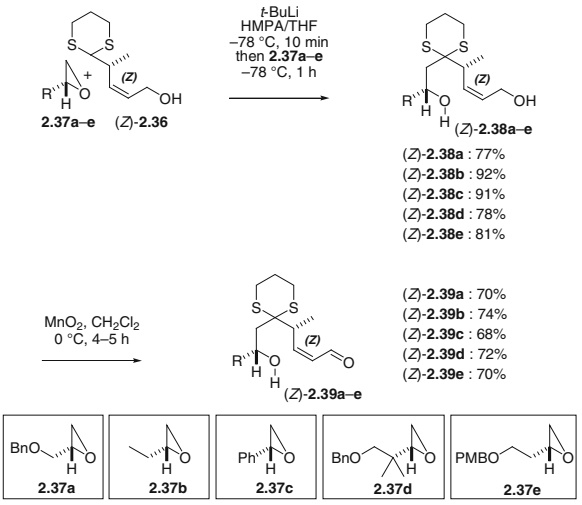


Scheme 2.4 The equilibrium between **2.41a** and **2.42a**

To gain further insight into the mechanism whether the 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** undergoes equilibrium in the oxa-conjugate addition reaction, **2.41a** was resubjected to the oxa-conjugate addition reaction conditions (Scheme 2.4). The reaction of **2.41a** with treatment of pyrrolidine and BzOH resulted in the exclusive formation of **2.42a** (96 %, dr >20:1), revealing that the latter explanation is the more likely one. In the preliminary studies, it was

mentioned that no equilibrium via the retro-oxa-conjugate addition was observed for the tandem oxidation/oxa-conjugate addition reaction [18]. Thus, the equilibrium between **20a** and **21a** observed in the organocatalytic oxa-conjugate addition reaction was attributed to the activation by iminium ion formation and/or the stereochemical mismatch between the C(3) methyl group and the C(6) alkyl chain in **2.41a**. To the best of our knowledge, this is the first report for the synthesis of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate through the oxa-conjugate addition reactions depending on the reaction temperature (*temperature-dependent configurational switch*).

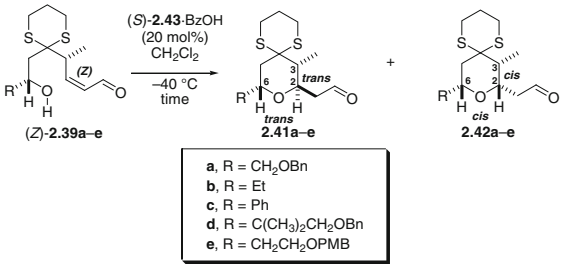
To further broaden the substrate scope and stereochemical outcome of the organocatalytic oxa-conjugate reaction, different α,β-unsaturated aldehydes (*Z*)-**2.39a–e** with a variety of substituents at the C(6) position were prepared by dithiane coupling reaction of (*Z*)-**2.36 a–e** with commercially or readily available chiral epoxides **2.37a–e** (Scheme 2.5).



Scheme 2.5 Preparation of α,β-unsaturated aldehydes (*Z*)-**2.39a-e** for the organocatalytic oxa-conjugate addition reaction

Consistent with our expectation, the organocatalytic oxa-conjugate addition reaction of (*Z*)-**2.39a–e** under the standard reaction conditions ((*S*)-**2.43**, BzOH, CH_2Cl_2, –40 °C) proceeded smoothly to provide the corresponding 2,3-*trans*-2,6-*trans*-tetrahydropyran aldehydes **2.41a–e** with good to excellent stereoselectivities and yields as shown in Table 2.3 (dr = 11–20:1, 95–98 %).

Table 2.3 Substrate scope of the organocatalytic oxa-conjugate addition reaction



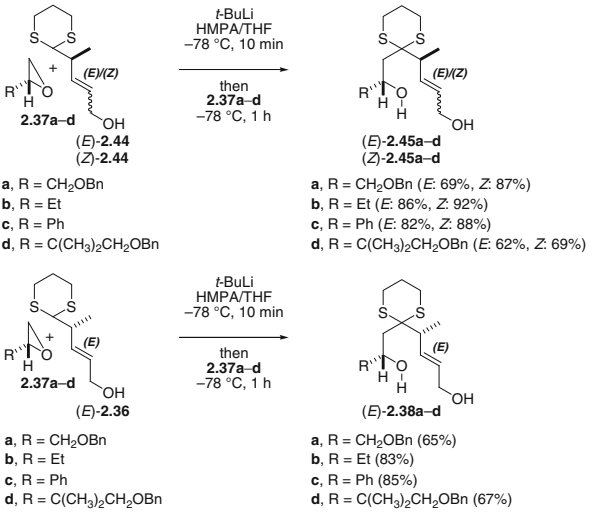
Entry	Substrate	Time (h)	Yield (%)[a]	dr[b]
1	**2.39a**	14	96	12:1
2	**2.39b**	7	97	20:1
3	**2.39c**	8	98	11:1
4	**2.39d**	12	95	13:1
5	**2.39e**	13	98	>20:1

[a] Combined yield of the isolated 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans
[b] The diastereomeric ratio (2,3-*trans*-2,6-*trans*-tetrahydropyran:2,3-*cis*-2,6-*cis*-tetrahydropyran) was determined by integration of the ^{1}H NMR of the crude product

2.3.1.3 Synthesis of 2,3-*trans*-2,6-*cis*- and 2,3-*cis*-2,6-*cis*-Tetrahydropyrans

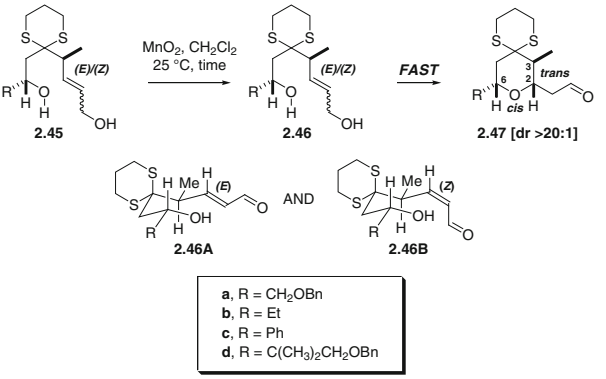
Given the potential outcome of the *temperature-dependent configurational switch* for the construction of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans, the synthesis of the 2,3-*trans*-2,6-*cis*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans were next explored by employing the tandem allylic oxidation/oxa-conjugate addition reaction. As illustrated in Fig. 2.5, we envisaged that the stereoselective synthesis of 2,3-*trans*-2,6-*cis*-tetrahydropyrans and 2,3-*cis*-2,6-*cis*-tetrahydropyrans through the tandem reaction should be straightforward. To explore the utility of the tandem reaction in the stereoselective synthesis of 2,3-*trans*-2,6-*cis*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans, allyl alcohols (*E*)-**2.45a–d**, (*Z*)-**2.45a–d**, and (*E*)-**2.38a–d** were prepared by dithiane coupling reactions of (*E*)-**2.44**, (*Z*)-**2.44**, and (*E*)-**2.36**, respectively, with chiral epoxides **2.37a–d** (Scheme 2.6).

As predicted, the tandem allylic oxidation/oxa-conjugate addition reaction (MnO_2, CH_2Cl_2, 25 °C) of (*E*)- and (*Z*)-**2.45a–d** delivered the desired 2,3-*trans*-2,6-*cis*-tetrahydropyrans **2.47a–d** with excellent stereoselectivities (Table 2.4, entries 1–8). For (*E*)-**2.45**, the competitive oxidation of the benzylic alcohol (8 %) was observed in addition to the tandem oxa-conjugate addition reaction. Reactions of allyl alcohols (*E*)-**2.38a–d**, employing the same reaction conditions, gave rise to 2,3-*cis*-2,6-*cis*-tetrahydropyrans **2.42a–d** as a single diastereomer (Table 2.5, entries 1–4).



Scheme 2.6 Preparation of allyl alcohols

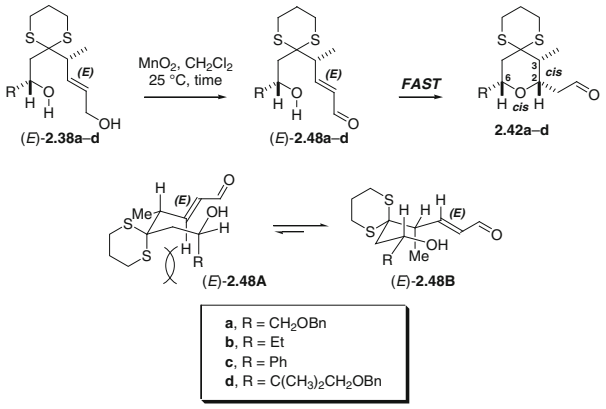
Table 2.4 Synthesis of 2,3-*trans*-2,6-*cis*-tetrahydropyrans **2.47a–d** through the tandem oxa-conjugate addition reaction



Entry	Substrate	Time (h)	Yield (%)[a]	dr[b]
1	(*E*)-**2.45a**	12	83	>20:1
2	(*E*)-**2.45b**	12	90	>20:1
3	(*E*)-**2.45c**	12	83	>20:1
4	(*E*)-**2.45d**	12	82	>20:1
5	(*Z*)-**2.45a**	10	84	>20:1
6	(*Z*)-**2.45b**	10	85	>20:1
7	(*Z*)-**2.45c**	10	81	>20:1
8	(*Z*)-**2.45d**	12	88	>20:1

[a] Combined yield of the isolated 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans
[b] The diastereomeric ratio (2,3-*trans*-2,6-*trans*-tetrahydropyran:2,3-*cis*-2,6-*cis*-tetrahydropyran) was determined by integration of the ^{1}H NMR of the crude product

Table 2.5 Synthesis of 2,3-*cis*-2,6-*cis*-tetrahydropyrans **2.42a–d** through the tandem oxa-conjugate addition reaction



Entry	Substrate	Time (h)	Yield (%)[a]	dr[b]
1	(*E*)-**2.38a**	10	87	>20:1
2	(*E*)-**2.38b**	10	84	>20:1
3	(*E*)-**2.38c**	10	85	>20:1
4	(*E*)-**2.38d**	12	81	>20:1

[a] Combined yield of the isolated 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans
[b] The diastereomeric ratio (2,3-*trans*-2,6-*trans*-tetrahydropyran:2,3-*cis*-2,6-*cis*-tetrahydropyran) was determined by integration of the ^{1}H NMR of the crude product

2.3.1.4 Synthesis of the Tetrahydropyran Cores of *ent*-(+)-Sorangicin A

With the interest in facilitating access to biologically important natural products, we were next interested in applicability of the tandem and organocatalytic oxa-conjugate addition reactions of α,β-unsaturated aldehydes to the stereoselective synthesis of structurally complex tetrahydropyrans and natural products.

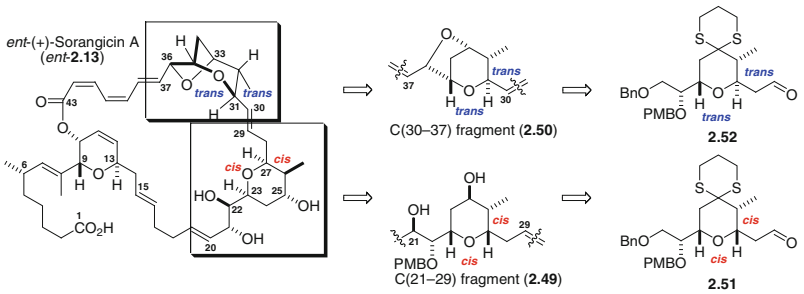
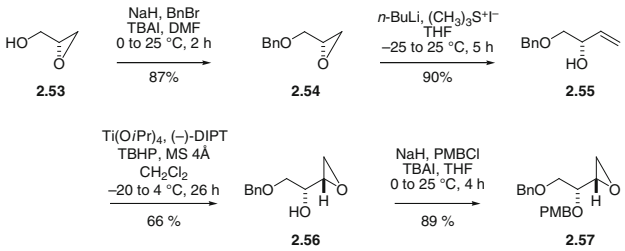


Fig. 2.7 Structure of *ent*-(+)-sorangicin A (*ent*-**2.13**) and synthetic plan for the C(21–29) and C(30–37) fragments

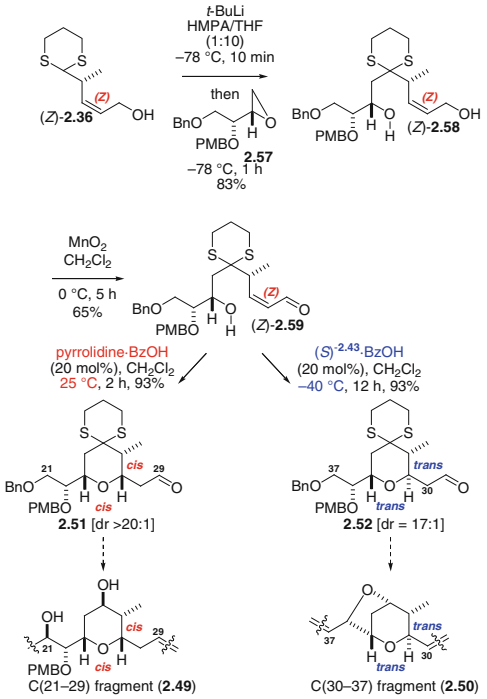
To demonstrate the feasibility of temperature-dependent configurational switch for the stereoselective synthesis of both 2,3-*trans*-2,6-*trans*-tetrahydropyran and 2,3-*cis*-2,6-*cis*-tetrahydropyran from a common substrate, we embarked on the efficient synthesis of the precursors to the C(21–29) and C(30–37) fragments of *ent*-(+)-sorangicin A (Fig. 2.7). The marine macrolide (+)-sorangicin A (**2.13**) was isolated from the myxobacterium *Sorangium cellulosum* by Jansen et al. [59]. (+)-Sorangicin A (**2.13**) is active against both Gram-positive (MIC = 0.01–0.1 μg/mL) and Gram-negative (MIC = 3–30 μg/mL) bacteria [60]. Reichenbach and co-workers determined that **2.13** elicits its antibacterial activity via inhibition of RNA polymerase [60]. Due to its potent antibiotic activity and architectural complexity, the synthesis of **2.13** has attracted considerable interest from a number of groups [61–68], culminating in the first total synthesis by Smith et al. [61]. We envisioned that both 2,3-*trans*-2,6-*trans*-tetrahydropyran and 2,3-*cis*-2,6-*cis*-tetrahydropyran embedded in *ent*-(+)-sorangicin A (*ent*-**2.13**) would arise from a common substrate through the temperature-dependent configurational switch of the organocatalytic oxa-conjugate addition reactions.

The synthesis of the precursors to the C(21–29) and C(30–37) fragments of *ent*-(+)-sorangicin A (*ent*-**2.13**) began with the preparation of chiral epoxide **2.57** (Scheme 2.7). Protection of commercially available (*R*)-(+)-glycidol (**2.53**) as the benzyl ether followed by opening of epoxide **2.54** by treatment with trimethylsulfonium iodide, and subsequent Sharpless asymmetric epoxidation of the resulting allyl alcohol **2.55** provided the known epoxide **2.56** [69]. PMB-protection of **2.56** furnished the requisite chiral epoxide **2.57**.



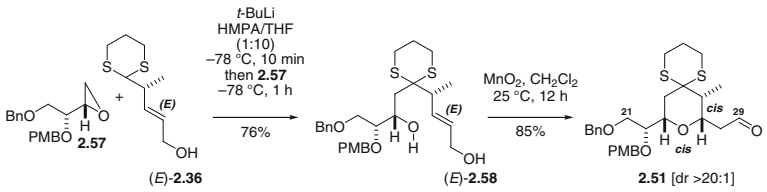
Scheme 2.7 Preparation of chiral epoxide (**2.57**)

Dithiane coupling of (*Z*)-**2.36** with **2.57** followed by MnO_2-oxidation of the corresponding allyl alcohol (*Z*)-**2.59** set the stage for the key organocatalytic oxa-conjugate addition reactions (Scheme 2.8). The organocatalytic oxa-conjugate addition reaction of (*Z*)-**2.59** *at 25 °C* in the presence of pyrrolidine proceeded smoothly to provide 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.51** as a single diastereomer (dr >20:1). When (*S*)-**22** was used for the oxa-conjugate addition reaction of (*Z*)-**2.59** *at −40 °C*, 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.52** was obtained with excellent stereoselectivity (dr = 17:1). The temperature-dependent configurational switch was successfully used to prepare both the diastereomeric tetrahydropyrans (**2.51** and **2.52**) from the common substrate (*Z*)-**2.59**.



Scheme 2.8 Synthesis of the precursors to the C(21–29) and C(30–37) fragments of *ent*-(+)-sorangicin A (*ent*-**2.13**) through the organocatalytic oxa-conjugate addition reaction

In addition, the tandem oxidation/oxa-conjugate addition reaction was effective in the stereoselective synthesis of 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.51** as a single diastereomer (Scheme 2.9). Coupling of (*E*)-**2.36** and **2.57** provided allyl alcohol (*E*)-**2.58** in 76 % yield. The tandem oxidation/oxa-conjugate addition reaction of (*E*)-**32** (MnO_2, CH_2Cl_2, 25 °C, 12 h) smoothly proceeded to provide **2.51** with excellent stereoselectivity and yield (dr >20:1, 85 %). Compounds **2.51** and **2.52** can be further elaborated to the C(21–29) and C(30–37) fragments (**2.49** and **2.50**) of *ent*-(+)-sorangicin A (*ent*-**2.13**).



Scheme 2.9 Synthesis of the precursor to the C(21–29) fragment of *ent*-(+)-sorangicin A (*ent*-**2.13**) through the tandem oxidation/oxa-conjugate addition reaction

2.3.1.5 Conclusion

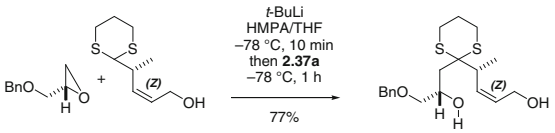
In summary, the utility of the tandem and organocatalytic oxa-conjugate addition reactions was demonstrated for the stereoselective synthesis of structurally complex tetrahydropyrans. In particular, the stereoselective synthesis of thermodynamically unfavorable 2,6-*trans*-tetrahydropyrans was accomplished through the reagent-controlled, organocatalytic oxa-conjugate addition reaction. The temperature-dependent configurational switch allowed the preparation of both 2,3-*trans*-2,6-*trans*- and 2,3-*cis*-2,6-*cis*-tetrahydropyrans from a common substrate, which was nicely applied in the synthesis of the precursors to the C(21–29) and C(30–37) fragments of *ent*-(+)-sorangicin A. We expect that the tandem and organocatalytic oxa-conjugate addition reactions would establish facile routes to the stereoselective synthesis of a diverse set of tetrahydropyrans and be applicable to the efficient synthesis of complex natural products with interesting biological activities.

2.3.1.6 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed on SiO_2 (60 Å) with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel 60 (particle size 4063 μm. 230400 mesh). ^{1}H NMR, ^{13}C NMR, and 2D NMR (COSY, NOESY) spectra were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in $CDCl_3$ by using the signal of residual $CHCl_3$, as an internal standard. All NMR δ values are given in ppm, and all J values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo-Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1 W) polarimeter.

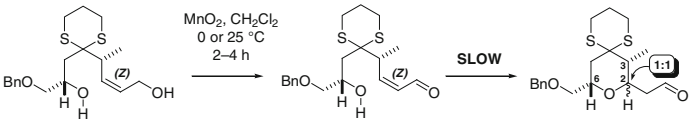
Representative Procedure for Preparation of Diol (*Z*)-2.38a



2.37a (*Z*)-**2.36** (*Z*)-**2.38a**

To a cooled (–78 °C) solution of dithiane (*Z*)-**2.36** (733 mg, 3.59 mmol) in HMPA/THF (1:10, 55 mL) was added dropwise *t*-BuLi (6.33 mL, 1.7 M in pentane, 10.76 mmol), and the resulting mixture was stirred for 10 min before (*S*)-glycidyl benzyl ether (**2.37a**, 883 mg, 5.38 mmol) was added. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to afford diol (*Z*)-**2.38a** (1.018 g, 77 %) as a colorless oil: $[\alpha]^{25}_D$= +14.8 (*c* 1.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.31 (m, 5H), 5.60–5.72 (m, 2H), 4.49 (d, J = 1.5 Hz, 2H), 4.20 (dd, J = 12.5, 8.5 Hz, 1H), 4.14 (br s, 1H), 3.89–3.93 (m, 1H), 3.34–3.41 (m, 3H), 3.16 (dddd, J = 10.0, 7.0, 7.0, 7.0 Hz, 1H), 2.88 (ddd, J = 14.0, 11.0, 3.0 Hz, 1H), 2.74 (ddd, J = 14.0, 11.0, 3.0 Hz, 2H), 2.64 (ddd, J = 14.5, 4.5, 4.5 Hz, 1H), 2.59 (ddd, J = 14.5, 4.5, 4.5 Hz, 1H), 2.12–2.23 (m, 2H), 1.88–1.96 (m, 1H), 1.72–1.81 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8, 132.9, 129.0, 128.3, 127.6, 74.3, 73.2, 68.2, 57.8, 56.7, 39.10, 39.01, 25.89, 25.84, 24.8, 16.7; IR (neat) 3366, 1737, 1452, 1240, 1027, 738 cm^{-1}; HRMS (ESI) *m/z* 367.1392 [(M–H)$^+$, $C_{19}H_{28}O_3S_2$ requires 367.1396].

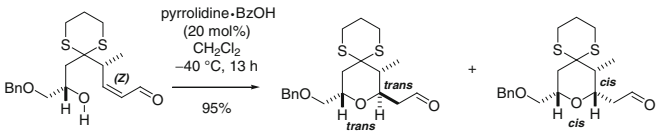
Tandem Oxidation/Oxa-Conjugate Addition Reaction of (*Z*)-2.38a



To a solution of diol (*Z*)-**2.38a** (762 mg, 2.07 mmol) in CH_2Cl_2 (30.0 mL, 0.069 M) was added MnO_2 (899 mg, 10.35 mmol), and the resulting mixture was stirred for 30 min at 25 °C. An addition of MnO_2 (899 mg, 10.35 mmol) was repeated two times every 30 min. After stirring at the same temperature for additional 30 min, the resulting mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford α,β-unsaturated aldehyde (*Z*)-**2.39a** (497 mg, 65 %) along with **2.40** (91 mg, 12 %, dr = 1:1) as colorless oils: [**For (*Z*)-2.39a**]: $[\alpha]^{25}_D$= +19.3 (*c* 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (dd, J = 7.5, 1.0 Hz, 1H), 7.18–7.31 (m, 5H), 6.78 (ddd, J = 11.0, 11.0, 1.0 Hz, 1H), 5.93 (dd, J = 11.5, 7.5 Hz, 1H), 4.50 (s, 2H), 4.17 (br d, J = 5.0 Hz, 1H), 3.90 (dddd, J = 10.5, 6.5, 6.5, 6.5 Hz, 1H), 3.38 (dd, J = 5.5, 1.0 Hz, 2H), 3.05 (br s, 1H), 2.88 (ddd, J = 13.0, 10.0, 2.0 Hz, 1H), 2.78 (ddd, J = 13.0, 10.0, 2.0 Hz, 1H), 2.71 (ddd, J = 14.5, 6.5, 3.5 Hz, 1H), 2.65 (ddd, J = 14.5, 6.5, 3.5 Hz, 1H), 2.08–2.20 (m, 2H), 1.90–1.97 (m, 1H), 1.79–1.85 (m, 1H), 1.20 (d, J = 6.5 Hz,

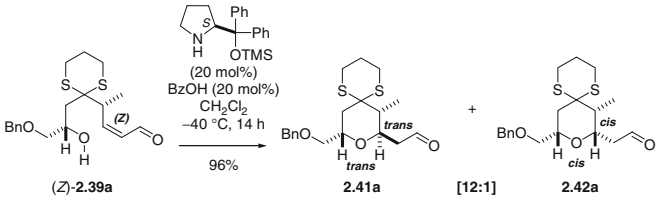
3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 152.0, 137.8, 129.3, 128.4, 127.7, 74.2, 73.3, 67.6, 55.5, 39.16, 39.12, 26.2, 25.6, 24.5, 16.4; IR (neat) 3466, 1720, 1452, 1098, 738, 698 cm^{-1}; HRMS (ESI) *m/z* 367.1399 [(M+H)$^+$, $C_{19}H_{26}O_3S_2$ requires 367.1396].

Representative Procedure for the Secondary Amine-Catalyzed Oxa-Conjugate Addition Reaction



To a cooled (–40 °C) solution of aldehyde (*Z*)-**2.39a** (20.0 mg, 0.054 mmol) in CH_2Cl_2 (2.0 mL, 0.027 M) was added dropwise a mixture of piperidine·BzOH (0.2 mL, 0.055 M in CH_2Cl_2). After stirring at –40 °C for 13 h, the reaction mixture was diluted with hexanes (25.0 mL), and filtered through a short pad of silica gel (hexanes/EtOAc, 3/1) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** (16.7 mg, 84 %) and 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** (2.2 mg, 11 %) as colorless oils: [**For 2,3-*trans*-2,6-*trans*-Tetrahydropyran 2.41a**]: $[\alpha]^{25}_D$= +16.0 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, J = 2.0, 2.0 Hz, 1H), 7.26–7.37 (m, 5H), 4.54 (s, 2H), 4.25 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H), 4.15 (dddd, J = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 3.80 (dd, J = 6.0, 1.5 Hz, 2H), 3.08 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H), 2.96 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H), 2.65–2.75 (m, 5H), 2.26 (dd, J = 14.5, 5.5 Hz, 1H), 2.00–2.07 (m, 1H), 1.94 (dddd, J = 7.0, 7.0, 7.0, 7.0 Hz, 1H), 1.79–1.89 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 138.1, 128.3, 127.6, 73.3, 70.55, 70.37, 69.6, 52.3, 47.5, 43.2, 36.5, 26.1, 25.7, 25.2, 13.9; IR (neat) 1722, 1452, 1277, 1097, 906, 738, 698 cm^{-1}; HRMS (ESI) *m/z* 367.1396 [(M+H)$^+$, $C_{19}H_{26}O_3S_2$ requires 367.1396]. [**For 2,3-*cis*-2,6-*cis*-Tetrahydropyran 2.42a**]: $[\alpha]^{25}_D$= –26.9 (*c* 1.07, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, J = 2.0, 2.0 Hz, 1H), 7.24–7.36 (m, 5H), 4.84 (ddd, J = 9.5, 4.5, 2.0 Hz, 1H), 4.53 (AB, $\Delta\upsilon$ = 16.5 Hz, J_{AB} = 11.5 Hz, 2H), 4.06–4.12 (m, 1H), 3.48 (dd, J = 10.5, 5.5 Hz, 1H), 3.42 (dd, J = 10.5, 4.5 Hz, 1H), 2.66–2.90 (m, 5H), 2.34 (ddd, J = 17.0, 4.5, 2.0 Hz, 1H), 2.03–2.12 (m, 1H), 1.90–2.02 (m, 3H), 1.85 (dd, J = 13.5, 11.5 Hz, 1H), 1.11 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 138.1, 128.3, 127.6, 73.3, 72.59, 72.56, 70.1, 53.3, 47.4, 38.3, 34.6, 26.0, 25.4, 25.2, 8.9; IR (neat) 1722, 1453, 1376, 1108, 1026, 738, 698 cm^{-1}; HRMS (ESI) *m/z* 367.1393 [(M+H)$^+$, $C_{19}H_{26}O_3S_2$ requires 367.1396].

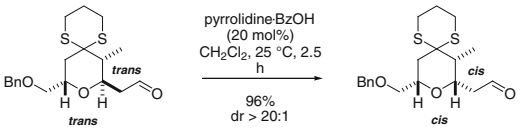
Representative Procedure for the Chiral Organocatalytic Oxa-Conjugate Addition Reaction



(*Z*)-**2.39a** **2.41a** [12:1] **2.42a**

To a cooled (–40 °C) solution of aldehyde (*Z*)-**2.39a** (28.8 mg, 0.079 mmol) in CH_2Cl_2 (2.0 mL, 0.039 M) was added dropwise a mixture of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (5.1 mg, 0.016 mmol) and BzOH (2.0 mg, 0.016 mmol) in CH_2Cl_2 (0.5 mL). After stirring at –40 °C for 14 h, the reaction mixture was diluted with hexanes (25.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** (25.9 mg, 90 %) and 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** (2.1 mg, 7 %) as colorless oils.

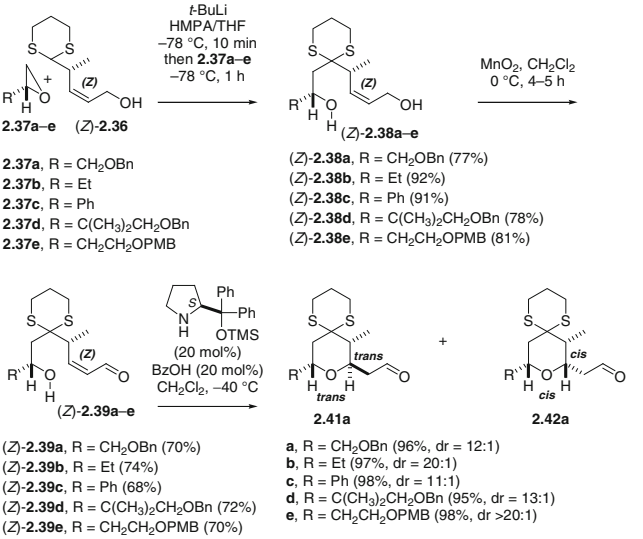
Equilibrium Study in the Organocatalytic Oxa-Conjugate Addition Reaction



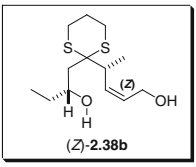
2.41a **2.42a**

To a stirred solution of 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.41a** (32.1 mg, 0.088 mmol) in CH_2Cl_2 (2.0 mL, 0.044 M) was added dropwise a mixture of pyrrolidine (1.3 mg, 0.018 mmol) and benzoic acid (2.2 mg, 0.018 mmol) in CH_2Cl_2 (0.5 mL) at 25 °C. After stirring at the same temperature for 2.5 h, the reaction mixture was diluted with hexanes (30.0 mL), and filtered through a short pad of silica gel (hexanes/EtOAc, 3/1) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** as a colorless oil (30.8 mg, 96 %).

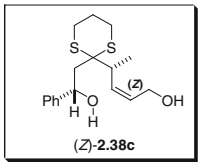
Substrate Scope of the Organocatalytic Oxa-Conjugate Addition Reaction



Compounds (*Z*)-**2.38b**, (*Z*)-**2.38c**, (*Z*)-**2.38d** and (*Z*)-**2.38e** were prepared following the procedures described above.

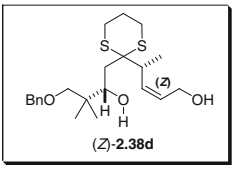


A colorless oil, 92 %: $[\alpha]^{25}_{D}$= +13.9 (*c* 1.63, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65–5.78 (m, 2H), 4.24 (dd, J = 12.5, 7.0 Hz, 1H), 4.05 (dd, J = 13.0, 6.0 Hz, 1H), 3.88–3.93 (m, 1H), 3.62 (br s, 1H), 3.21 (dddd, J = 10.0, 7.0, 7.0, 7.0 Hz, 1H), 2.98 (ddd, J = 14.0, 10.5, 3.0 Hz, 1H), 2.89 (ddd, J = 14.0, 10.5, 2.5 Hz, 1H), 2.69–2.75 (m, 2H), 2.59 (br s, 1H), 2.26 (dd, J = 15.5, 9.5 Hz, 1H), 2.09 (dd, J = 15.0, 1.5, 1H), 1.97–2.04 (m, 1H), 1.79–1.88 (m, 1H), 1.40–1.56 (m, 2H), 1.12 (d, J = 6.5 Hz, 3H), 0.94 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.1, 129.1, 70.0, 58.0, 56.5, 41.7, 38.8, 30.8, 26.1, 25.7, 24.7, 16.3, 9.9; IR (neat) 3359, 2929, 1421, 988 cm^{-1}.



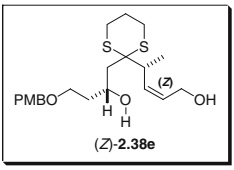
(*Z*)-**2.38c**

A colorless oil, 91 %: $[\alpha]^{25}_{D}$= –26.4 (*c* 1.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.40 (m, 4H), 7.25–7.30 (m, 1H), 5.73–5.84 (m, 2H), 5.12 (d, J = 9.0 Hz, 1H), 4.31 (dd, J = 13.0, 8.0 Hz, 1H), 4.06 (dd, J = 12.0, 5.0 Hz, 1H), 3.80 (br s, 1H), 3.36 (dddd, J = 9.5, 7.0, 7.0, 7.0 Hz, 1H), 3.01 (ddd, J = 14.5, 11.0, 3.0 Hz, 1H), 2.87 (ddd, J = 14.0, 11.0, 3.0 Hz, 1H), 2.71–2.99 (m, 2H), 2.57 (dd, J = 14.5, 9.0 Hz, 1H), 2.31 (dd, J = 16.5, 2.0 Hz, 2H), 2.01–2.08 (m, 1H), 1.84–1.93 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 133.1, 129.0, 128.4, 127.3, 125.6, 71.9, 57.9, 56.9, 44.5, 38.8, 25.98, 25.84, 24.7, 16.6; IR (neat) 3348, 2901, 1025, 700 cm^{-1}.



(*Z*)-**2.38d**

A colorless oil, 78 %: $[\alpha]^{25}_{D}$= +4.2 (*c* 1.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H), 5.79 (dd, J = 11.0, 11.0 Hz, 1H), 5.70 (ddd, J = 11.0, 7.5, 7.5 Hz, 1H), 4.50 (AB, $\Delta\upsilon$ = 16.5 Hz, J_{AB} = 12.5 Hz, 2H), 4.25 (dd, J = 12.5, 8.5 Hz, 1H), 3.98 (d, J = 9.0 Hz, 2H), 3.57 (br s, 1H), 3.29–3.36 (m, 3H), 2.92 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H), 2.83 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H), 2.65-2.75 (m, 2H), 2.46 (br s, 1H), 2.15–2.25 (m, 2H), 1.95–2.00 (m, 1H), 1.81–1.89 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H), 0.97 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 133.5, 128.8, 128.3, 127.53, 127.43, 78.3, 74.6, 73.4, 58.0, 57.4, 39.21, 39.12, 37.0, 26.2, 26.0, 24.9, 22.1, 20.4, 16.9; IR (neat) 3405, 2929, 1076, 736 cm^{-1}.

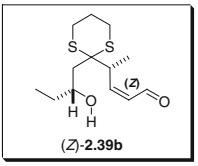


(*Z*)-**2.38e**

A colorless oil, 81 %: $[\alpha]^{25}_{D}$= +17.0 (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2 H), 5.70–5.80 (m, 2H), 4.45 (s, 2H), 4.29 (dd, J = 13.0, 8.5 Hz, 1H), 4.19–4.23 (m, 1H), 4.00–4.03 (m,

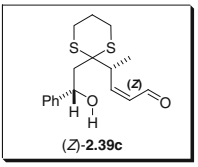
1H), 3.80 (s, 3H), 3.71 (br s, 1H), 3.59–3.68 (m, 2H), 3.25 (dddd, $J = 9.5, 7.0, 7.0, 7.0$ Hz, 1H), 2.97 (ddd, $J = 14.0, 11.0, 3.0$ Hz, 1H), 2.87 (ddd, $J = 14.0, 10.5, 3.0$ Hz, 1H), 2.70–2.76 (m, 2H), 2.43 (br s, 1H), 2.31 (dd, $J = 15.5, 8.5$ Hz, 1H), 2.19 (dd, $J = 15.0, 2.5$ Hz, 1H), 1.98–2.05 (m, 1H), 1.80–1.91 (m, 2H), 1.71–1.79 (m, 1H), 1.18 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 132.9, 129.9, 129.16, 129.02, 113.6, 72.6, 67.6, 67.3, 57.8, 56.6, 55.1, 42.4, 38.8, 37.6, 25.9, 24.7, 16.6; IR (neat) 3398, 1611, 1512, 1440, 1301, 1220, 1088, 1032, 820 cm^{-1}; HRMS (ESI) *m/z* 411.1654 [(M–H)$^+$, $C_{21}H_{32}O_4S_2$ requires 411.1658].

Compounds (*Z*)-**2.39b**, (*Z*)-**2.39c**, (*Z*)-**2.39d** and (*Z*)-**2.39e** were prepared following the procedures described above.



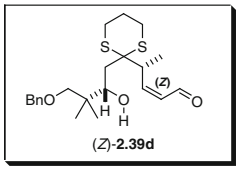
(*Z*)-**2.39b**

A colorless oil, 74 %: $[\alpha]^{25}_D$= +27.7 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (d, $J = 7.5$ Hz, 1H), 6.88 (dd, $J = 11.0, 11.0$ Hz, 1H), 6.04 (dd, $J = 11.5, 8.0$ Hz, 1H), 3.93–4.02 (m, 2H), 3.36 (d, $J = 2.0$ Hz, 1H), 3.01 (ddd, $J = 14.0, 10.0, 3.0$ Hz, 1H), 2.93 (ddd, $J = 14.5, 10.0, 3.0$ Hz, 1H), 2.75–2.82 (m, 2H), 2.32 (dd, $J = 15.5, 9.0$ Hz, 1H), 2.08 (dd, $J = 15.0, 1.5$ Hz, 1H), 2.00–2.06 (m, 1H), 1.85–1.94 (m, 1H), 1.56 (dddd, $J = 13.5, 7.0, 7.0, 7.0$ Hz, 1H), 1.43–1.52 (m, 1H), 1.26 (d, $J = 7.0$ Hz, 3H), 0.98 (dd, $J = 7.5, 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 152.1, 129.3, 69.5, 55.3, 41.7, 38.8, 30.8, 26.4, 25.7, 24.5, 16.2, 9.9; IR (neat) 3444, 2931, 1672, 1139 cm^{-1}.



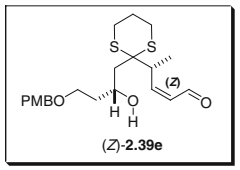
(*Z*)-**2.39c**

A colorless oil, 68 %: $[\alpha]^{25}_D$= –7.0 (*c* 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (d, $J = 8.0$ Hz, 1H), 7.25–7.39 (m, 5H), 6.87 (dd, $J = 11.5, 11.5$ Hz, 1H), 6.01 (dd, $J = 11.5, 7.5$ Hz, 1H), 5.12 (d, $J = 9.0$ Hz, 1H), 4.02 (dddd, $J = 10.5, 6.5, 6.5, 6.5$ Hz, 1H), 3.52 (d, $J = 2.0$ Hz, 1H), 3.00 (ddd, $J = 14.5, 10.5, 3.0$ Hz, 1H), 2.90 (ddd, $J = 14.0, 10.0, 3.0$ Hz, 1H), 2.73–2.83 (m, 2H), 2.55 (dd, $J = 15.5, 9.0$ Hz, 1H), 2.28 (dd, $J = 15.5, 2.5$ Hz, 1H), 1.97–2.08 (m, 1H), 1.83–1.94 (m, 1H), 1.26 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 152.0, 144.3, 129.3, 128.5, 127.5, 125.6, 71.3, 55.5, 44.4, 38.8, 26.2, 25.6, 24.5, 16.3; IR (neat) 3427, 2904, 1673, 1059, 702 cm^{-1}.



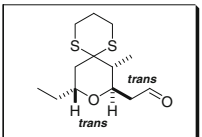
(*Z*)-**2.39d**

A colorless oil, 72 %: $[\alpha]^{25}_{D}$= +13.2 (*c* 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.0 Hz, 1H), 7.26–7.36 (m, 5H), 6.88 (dd, J = 11.0, 11.0 Hz, 1H), 5.97 (dd, J = 11.0, 7.5 Hz, 1H), 4.50 (AB, $\Delta\upsilon$ = 22.0 Hz, J_{AB} = 12.5 Hz, 2H), 4.07 (dddd, J = 11.0, 6.5, 6.5, 6.5 Hz, 1H), 3.91–3.95 (m, 1H), 3.50 (d, J = 3.5 Hz, 1H), 3.35 (d, J = 9.5 Hz, 1H), 3.33 (d, J = 9.0 Hz, 1H), 2.92 (ddd, J = 14.5, 10.0, 3.5 Hz, 1H), 2.76–2.86 (m, 2H), 2.71 (ddd, J = 14.0, 6.5, 3.5 Hz, 1H), 2.10–2.21 (m, 2H), 1.95–2.04 (m, 1H), 1.84–1.93 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.0, 152.5, 138.1, 129.2, 128.3, 127.60, 127.44, 78.3, 74.0, 73.4, 56.0, 39.10, 38.93, 37.4, 26.4, 25.7, 24.6, 22.2, 20.4, 16.7; IR (neat) 3485, 2960, 1675, 1095 cm^{-1}.



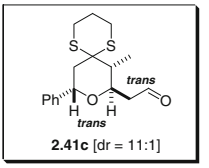
(*Z*)-**2.39e**

A colorless oil, 70 %: $[\alpha]^{25}_{D}$= +24.3 (*c* 2.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.84–6.90 (m, 3H), 6.01 (ddd, J = 11.5, 7.5, 1.0 Hz, 1H), 4.45 (s, 2H), 4.21–4.26 (m, 1H), 4.00 (dddd, J = 11.5, 7.0, 7.0, 7.0 Hz, 1H), 3.80 (s, 3H), 3.60–3.68 (m, 2H), 3.56 (d, J = 2.0 Hz, 1H), 2.96 (ddd, J = 14.0, 10.0, 3.0 Hz, 1H), 2.87 (ddd, J = 14.0, 9.5, 3.0 Hz, 1H), 2.77 (dddd, J = 21.5, 14.0, 6.5, 3.0 Hz, 2H), 2.30 (dd, J = 15.5, 9.0 Hz, 1H), 2.11 (dd, J = 15.5, 1.5 Hz, 1H), 1.97–2.05 (m, 1H), 1.81–1.94 (m, 2H), 1.70–1.77 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 159.0, 152.0, 130.0, 129.1, 113.6, 72.6, 67.3, 66.9, 55.4, 55.0, 42.2, 38.8, 37.5, 26.1, 25.5, 24.4, 16.3; IR (neat) 3433, 1671, 1512, 1245, 1086, 1031, 819 cm^{-1}; HRMS (ESI) *m/z* 411.1653 [$(M+H)^+$, $C_{21}H_{30}O_4S_2$ requires 411.1658].



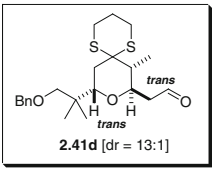
2.41b [dr = 20:1]

A colorless oil, 97 %: $[\alpha]^{25}_{D}$= –3.9 (*c* 0.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, J = 3.5, 2.0 Hz, 1H), 4.28 (ddd, J = 8.5, 6.0, 4.5 Hz, 1H), 3.75–3.81 (m, 1H), 3.01 (ddd, J = 14.0, 10.0, 3.0 Hz, 1H), 2.80–2.95 (m, 2H), 2.71–2.82 (m, 3H), 2.31 (dd, J = 14.5, 7.0 Hz, 1H), 2.21 (dd, J = 14.5, 4.5 Hz, 1H), 1.95–2.06 (m, 2H), 1.83–1.95 (m, 2H), 1.49–1.59 (m, 1H), 1.25 (d, J = 7.0 Hz, 3H), 0.90 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 71.4, 70.5, 52.3, 47.8, 41.9, 39.2, 26.71, 26.35, 25.8, 25.2, 15.2, 10.5; IR (neat) 2929, 1724, 1456, 1137 cm^{-1}; HRMS (ESI) *m/z* 275.1133 [(M+H)$^+$, $C_{13}H_{22}O_2S_2$ requires 275.1134].



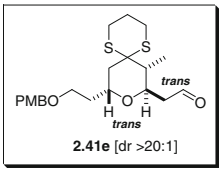
2.41c [dr = 11:1]

A colorless oil, 98 %: $[\alpha]^{25}_{D}$= +4.1 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (ddd, J = 1.0, 1.0, 1.0 Hz, 1H), 7.25–7.38 (m, 5H), 4.99 (dd, J = 8.0, 4.0 Hz, 1H), 4.55 (ddd, J = 8.5, 5.0, 5.0 Hz, 1H), 3.12 (ddd, J = 16.5, 9.0, 3.0 Hz, 1H), 3.04 (ddd, J = 14.5, 10.0, 3.0 Hz, 1H), 2.97 (ddd, J = 17.0, 5.0, 1.5 Hz, 1H), 2.76–2.86 (m, 2H), 2.70 (ddd, J = 14.5, 7.0, 3.5 Hz, 1H), 2.48–2.26 (m, 2H), 2.19 (dddd, J = 7.0, 7.0, 7.0, 5.0 Hz, 1H), 1.99–2.07 (m, 1H), 1.88–1.97 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 141.7, 128.4, 127.5, 125.6, 72.5, 70.5, 52.1, 48.0, 41.8, 40.8, 26.6, 25.8, 25.1, 15.7; IR (neat) 2907, 2727, 1720, 1242, 1089, 700 cm^{-1}; HRMS (ESI) *m/z* 323.1136 [(M+H)$^+$, $C_{17}H_{22}O_2S_2$ requires 323.1134].



2.41d [dr = 13:1]

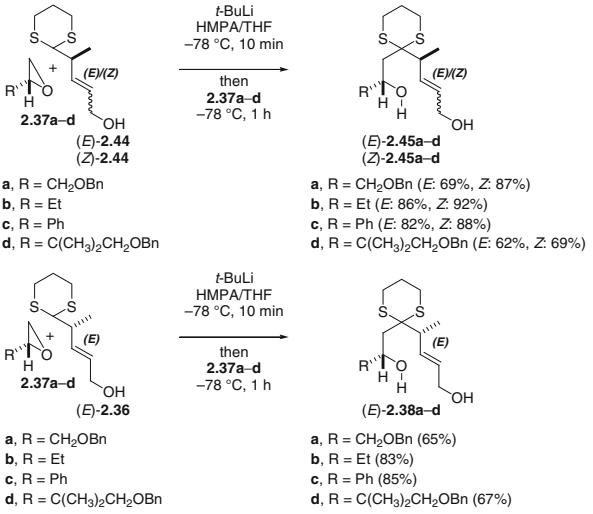
A colorless oil, 95 %: $[\alpha]^{25}_{D}$= –13.7 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (dd, J = 2.0, 2.0 Hz, 1H), 7.24–7.36 (m, 5H), 4.46 (AB, $\Delta\upsilon$ = 26.5 Hz, J_{AB} = 12.0 Hz, 2H), 4.35 (ddd, J = 8.5, 4.0, 4.0 Hz, 1H), 3.84 (dd, J = 12.0, 2.5 Hz, 1H), 3.29 (d, J = 8.5 Hz, 1H), 3.24 (ddd, J = 17.0, 10.0, 2.5 Hz, 1H), 3.16 (d, J = 8.5 Hz, 1H), 2.70–2.89 (m, 5H), 2.19 (dd, J = 14.5, 2.0 Hz, 1H), 2.00–2.13 (m, 2H), 1.90–2.00 (m, 2H), 1.27 (d, J = 7.0 Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 138.8, 128.2, 127.37, 127.30, 76.6, 73.6, 73.2, 70.3, 52.2, 47.8, 39.3, 38.1, 34.0, 26.6, 25.8, 25.1, 21.3, 20.3, 16.9; IR (neat) 2903, 1722, 1099, 1023, 736 cm^{-1}; HRMS (ESI) *m/z* 409.1949 [(M+H)$^+$, $C_{22}H_{32}O_3S_2$ requires 409.1866].



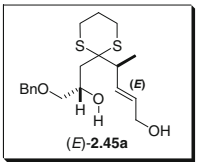
2.41e [dr >20:1]

A colorless oil, 98 %: $[\alpha]^{25}_{D}$= +11.6 (*c* 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (dd, J = 3.0, 1.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.41 (AB, $\Delta\upsilon$ = 15.0 Hz, J_{AB} = 11.5 Hz, 2H), 4.25 (ddd, J = 10.5, 7.0, 4.0 Hz, 1H), 4.11 (dddd, J = 9.5, 4.5, 4.5, 4.5 Hz, 1H), 3.80 (s, 3H), 3.45–3.53 (m, 2H), 3.01 (ddd, J = 14.5, 11.0, 3.0 Hz, 1H), 2.88 (ddd, J = 14.5, 11.0, 3.5 Hz, 1H), 2.81 (ddd, J = 13.0, 9.0, 3.0 Hz, 1H), 2.68–2.76 (m, 3H), 2.41 (dd, J = 14.5, 6.0 Hz, 1H), 2.21–2.29 (m, 2H), 1.92–2.04 (m, 2H), 1.80–1.91 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 159.1, 130.5, 129.4, 113.7, 72.8, 69.7, 67.8, 66.8, 55.3, 52.4, 47.6, 42.6, 39.5, 33.5, 26.2, 25.7, 25.2, 14.6; IR (neat) 1721, 1611, 1511, 1244, 1100, 1031, 818 cm^{-1}; HRMS (FAB) *m/z* 411.1658 [(M+H)$^+$, $C_{21}H_{30}O_4S_2$ requires 411.1658].

Preparation of Allyl Alcohols

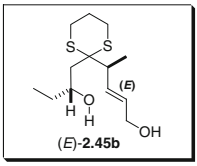


Compounds (*E*)-**2.45a–d**, and (*Z*)-**2.45a–d** were prepared following the procedures described above.



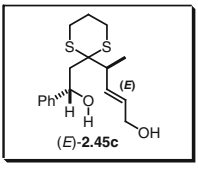
(*E*)-**2.45a**

A colorless oil, 69 %: $[\alpha]^{25}_{D}$= –43.6 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.41 (m, 5H), 5.82 (dd, J = 15.6, 8.8 Hz, 1H), 5.67 (ddd, J = 15.2, 5.6, 5.6 Hz, 1H), 4.56 (s, 2H), 4.18–4.26 (m, 1H), 4.03 (dd, J = 4.4, 4.4 Hz, 2H), 3.43–3.49 (m, 2H), 3.38 (dd, J = 9.6, 5.2 Hz, 1H), 3.03 (ddd, J = 13.6, 10.4, 2.8 Hz, 1H), 2.82–2.93 (m, 2H), 2.72–2.79 (m, 2H), 2.30 (dd, J = 15.6, 8.8 Hz, 1H), 2.14 (d, J = 15.2 Hz, 1H), 1.99–2.06 (m, 1H), 1.83–1.93 (m, 1H), 1.47 (dd, J = 5.6, 5.6 Hz, 1H), 1.30 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 132.4, 131.0, 128.4, 127.85, 127.78, 74.1, 73.3, 67.4, 63.5, 56.2, 43.6, 39.5, 26.2, 25.7, 24.8, 16.5; IR (neat) 3390, 1452, 1369, 1275, 1127, 971, 738, 698 cm^{-1}; HRMS (ESI) *m/z* 369.1552 [$(M+H)^+$, $C_{19}H_{28}O_3S_2$ requires 369.1553].



(*E*)-**2.45b**

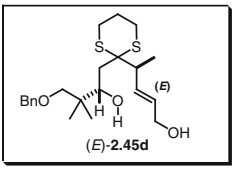
A colorless oil, 86 %: $[\alpha]^{25}_{D}$= –47.5 (*c* 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dd, J = 15.5, 9.0 Hz, 1H), 5.66 (ddd, J = 15.5, 5.5, 5.5 Hz, 1H), 4.08 (d, J = 4.5 Hz, 2H), 3.89–3.94 (m, 1H), 3.66 (s, 1H), 2.99 (ddd, J = 14.0, 10.5, 3.0 Hz, 1H), 2.85–2.92 (m, 2H), 2.72–2.81 (m, 2H), 2.22 (dd, J = 15.5, 9.5 Hz, 1H), 1.94–2.03 (m, 3H), 1.82–1.91 (m, 1H), 1.44–1.53 (m, 1H), 1.34–1.43 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H), 0.91 (dd, J = 7.0, 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.7, 131.0, 69.5, 63.1, 56.2, 43.4, 42.0, 30.6, 26.1, 25.6, 24.7, 16.5, 9.9; IR (neat) 3378, 2929, 971, 732 cm^{-1}.



(*E*)-**2.45c**

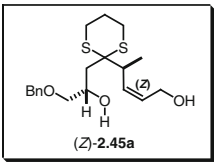
A colorless oil, 82 %: $[\alpha]^{25}_{D}$= –65.6 (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.38 (m, 5H), 5.85 (dd, J = 15.5, 13.5 Hz, 1H), 5.74 (ddd, J = 15.0, 5.5, 5.5 Hz, 1H), 5.12 (d, J = 9.0 Hz, 1H), 4.08 (d, J = 5.0 Hz, 2H),

4.08 (br s, 1H), 3.07 (ddd, $J = 14.0, 10.5, 3.0$ Hz, 1H), 3.00 (dddd, $J = 7.0, 7.0, 7.0, 7.0$ Hz, 1H), 2.88 (ddd, $J = 14.5, 10.5, 3.0$ Hz, 1H), 2.80 (ddd, $J = 14.5, 6.0, 3.0$ Hz, 1H), 2.76 (ddd, $J = 14.5, 6.0, 3.5$ Hz, 1H), 2.53 (dd, $J = 15.5, 9.5$ Hz, 1H), 2.17 (dd, $J = 15.5, 1.5$ Hz, 1H), 1.94–2.07 (m, 2H), 1.84–1.93 (m, 1H), 1.33 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 131.8, 131.1, 128.3, 127.3, 125.5, 70.8, 63.1, 56.3, 44.8, 43.5, 26.1, 25.6, 24.6, 16.6; IR (neat) 3391, 2930, 1055, 701 cm^{-1}.



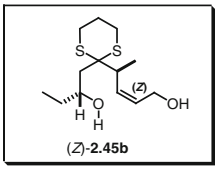
(*E*)-**2.45d**

A colorless oil, 62 %: $[\alpha]^{25}_D = -44.9$ (c 0.47, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5H), 5.92 (dd, $J = 15.0, 8.5$ Hz, 1H), 5.70 (ddd, $J = 15.0, 6.0, 6.0$ Hz, 1H), 4.51 (AB, $\Delta\upsilon = 15.0$ Hz, $J_{AB} = 12.0$ Hz, 2H), 4.09 (d, $J = 5.5$ Hz, 2H), 3.90–3.97 (m, 1H), 3.64 (d, $J = 3.0$ Hz, 1H), 3.39 (d, $J = 9.0$ Hz, 1H), 3.29 (d, $J = 9.0$ Hz, 1H), 3.00 (dddd, $J = 7.0, 7.0, 7.0, 7.0$ Hz, 1H), 2.93 (ddd, $J = 13.5, 10.0, 2.5$ Hz, 1H), 2.71–2.85 (m, 3H), 2.14 (d, $J = 5.5$ Hz, 2H), 1.95–2.01 (m, 1H), 1.84–1.93 (m, 1H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 132.9, 130.5, 128.3, 127.50, 127.43, 78.1, 73.61, 73.43, 63.5, 56.8, 43.1, 39.3, 37.2, 26.13, 25.88, 24.8, 22.6, 20.0, 16.3; IR (neat) 3414, 2929, 1418, 1067, 1007, 735 cm^{-1}.



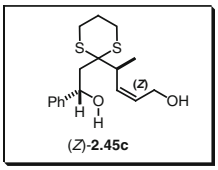
(*Z*)-**2.45a**

A colorless oil, 87 %: $[\alpha]^{25}_D = -35.5$ (c 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21–7.42 (m, 5H), 5.51–5.75 (m, 2H), 4.52 (s, 2H), 4.21 (dd, $J = 7.2$ Hz, 1H), 4.08–4.14 (m, 1H), 3.97–4.02 (m, 1H), 3.52 (d, $J = 2.4$ Hz, 1H), 3.44 (dd, $J = 9.2, 5.6$ Hz, 1H), 3.33 (dd, $J = 8.8, 5.6$ Hz, 1H), 3.16 (dddd, $J = 13.6, 6.8, 6.8, 6.8$ Hz, 1H), 3.01 (ddd, $J = 14.4, 11.2, 2.8$ Hz, 1H), 2.85 (ddd, $J = 14.0, 10.8, 2.8$ Hz, 1H), 2.64–2.73 (m, 2H), 2.50 (br s, 1H), 2.27 (dd, $J = 15.2, 8.0$ Hz, 1H), 2.19 (dd, $J = 15.2, 1.6$ Hz, 1H), 1.95–2.03 (m, 1H), 1.76–1.87 (m, 1H), 1.21 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 132.2, 129.1, 128.3, 127.82, 127.74, 74.0, 73.3, 67.4, 58.0, 56.4, 39.8, 38.9, 26.2, 25.5, 24.7, 16.8; IR (neat) 3391, 1452, 1274, 1074, 1027, 735 cm^{-1}; HRMS (ESI) m/z 386.1827 [$(M+NH_4)^+$, $C_{19}H_{28}O_3S_2$ requires 386.1818].



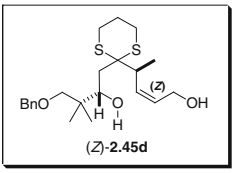
(*Z*)-**2.45b**

A colorless oil, 92 %: $[\alpha]^{25}_{D}$= –22.4 (*c* 1.56, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61–5.68 (m, 2H), 4.22 (dd, J = 12.0, 4.5 Hz, 1H), 4.16 (dd, J = 12.0, 4.5 Hz, 1H), 3.84–3.89 (m, 1H), 3.51 (br s, 1H), 3.15–3.22 (m, 1H), 3.02 (ddd, J = 13.5, 10.0, 3.0 Hz, 1H), 2.89 (ddd, J = 13.0, 9.5, 3.5 Hz, 1H), 2.73–2.80 (m, 2H), 2.24 (dd, J = 15.0, 9.0 Hz, 1H), 1.97–2.05 (m, 2H), 1.83–1.93 (m, 2H), 1.44–1.54 (m, 1H), 1.33–1.44 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H), 0.93 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 129.2, 69.7, 58.4, 56.4, 42.3, 39.5, 30.8, 26.3, 25.7, 24.7, 17.1, 9.9; IR (neat) 3392, 2935 cm^{-1}.



(*Z*)-**2.45c**

A colorless oil, 88 %: $[\alpha]^{25}_{D}$= –25.3 (*c* 1.53, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.38 (m, 5H), 5.66–5.75 (m, 2H), 5.08 (d, J = 9.5 Hz, 1H), 4.26 (dd, J = 13.0, 5.5 Hz, 1H), 4.17 (dd, J = 12.5, 5.5 Hz, 1H), 3.99 (br s, 1H), 3.31 (dddd, J = 8.5, 7.0, 7.0, 7.0 Hz, 1H), 3.05 (ddd, J = 14.5, 11.0, 2.5 Hz, 1H), 2.85 (ddd, J = 13.5, 10.0, 3.0 Hz, 1H), 2.70–2.80 (m, 2H), 2.53 (dd, J = 15.5, 9.5 Hz, 1H), 2.22 (dd, J = 15.5, 1.5 Hz, 1H), 2.20 (br s, 1H), 1.98–2.06 (m, 1H), 1.83–1.92 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 132.4, 129.2, 128.4, 127.2, 125.5, 71.0, 58.3, 56.5, 44.9, 39.3, 26.2, 25.6, 24.6, 16.9; IR (neat) 3401, 2929, 1024, 700 cm^{-1}.

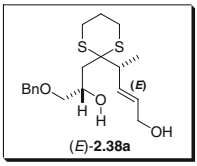


(*Z*)-**2.45d**

A colorless oil, 69 %: $[\alpha]^{25}_{D}$= –38.4 (*c* 2.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.36 (m, 5H), 5.62–5.73 (m, 2H), 4.51 (AB, $\Delta\upsilon$ = 19.5 Hz, J_{AB} = 12.0 Hz, 2H), 4.30 (dd, J = 13.5, 8.0 Hz, 1H), 4.04 (br d, J = 12.5 Hz, 1H), 3.91 (dd, J = 9.0, 1.5 Hz, 1H), 3.79 (d, J = 2.5 Hz, 1H), 3.44

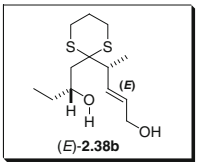
(d, $J = 9.0$ Hz, 1H), 3.27 (dddd, $J = 9.0$, 6.0, 6.0, 6.0 Hz, 1H), 3.17 (d, $J = 9.0$ Hz, 1H), 3.00 (ddd, $J = 14.0$, 11.0, 3.0 Hz, 1H), 2.86 (ddd, $J = 14.0$, 10.5, 3.0 Hz, 1H), 2.74 (ddd, $J = 14.0$, 4.5, 4.5 Hz, 1H), 2.70 (ddd, $J = 14.0$, 4.5, 4.5 Hz, 1H), 2.36 (br s, 1H), 2.24 (dd, $J = 15.0$, 9.0 Hz, 1H), 2.14 (d, $J = 15.0$ Hz, 1H), 1.98–2.04 (m, 1H), 1.81–1.90 (m, 1H), 1.22 (d, $J = 7.0$ Hz, 3H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 132.3, 129.3, 128.3, 127.63, 127.59, 77.8, 73.3, 72.6, 58.3, 56.9, 39.04, 38.97, 37.0, 26.3, 25.6, 24.8, 22.6, 19.6, 17.0; IR (neat) 3437, 2934, 1094, 1028, 667 cm^{-1}.

Compounds (*E*)-**2.38a–d** were prepared following the procedures described above.



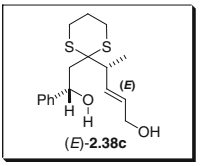
(*E*)-**2.38a**

A colorless oil, 65 %: $[\alpha]^{25}_{D}$= +27.0 (*c* 0.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.40 (m, 5H), 5.99 (dd, $J = 15.0$, 8.0 Hz, 1H), 5.73 (ddd, $J = 15.5$, 6.0, 6.0 Hz, 1H), 4.58 (s, 2H), 4.21–4.24 (m, 1H), 4.14 (d, $J = 5.5$ Hz, 2H), 3.46 (d, $J = 5.5$ Hz, 2H), 3.32 (br s, 1H), 2.96 (ddd, $J = 14.0$, 10.0, 3.0 Hz, 1H), 2.82–2.91 (m, 2H), 2.77 (dddd, $J = 13.5$, 6.5, 3.0, 3.0 Hz, 2H), 2.25 (dd, $J = 16.0$, 8.5 Hz, 1H), 2.13 (dd, $J = 15.5$, 2.0 Hz, 1H), 1.95–2.05 (m, 1H), 1.84–1.93 (m, 1H), 1.20 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 133.0, 130.7, 128.4, 127.7, 74.3, 73.3, 67.6, 63.6, 56.1, 43.1, 39.1, 26.2, 25.7, 24.7, 15.6; IR (neat) 3373, 1733, 1452, 1274, 1088, 971, 733, 697 cm^{-1}; HRMS (ESI) *m/z* 369.1542 [$(M+H)^+$, $C_{19}H_{28}O_3S_2$ requires 369.1553].



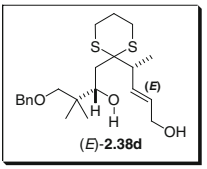
(*E*)-**2.38b**

A colorless oil, 83 %: $[\alpha]^{25}_{D}$= +26.3 (*c* 1.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (dd, $J = 15.0$, 8.5 Hz, 1H), 5.68 (ddd, $J = 14.5$, 6.0, 6.0 Hz, 1H), 4.09 (d, $J = 5.5$ Hz, 2H), 3.86–3.91 (m, 1H), 3.64 (br s, 1H), 2.94 (ddd, $J = 14.0$, 9.5, 3.0 Hz, 1H), 2.83–2.89 (m, 2H), 2.71–2.79 (m, 2H), 2.49 (br s, 1H), 2.21 (dd, $J = 15.5$, 9.5 Hz, 1H), 1.94–2.00 (m, 2H), 1.80–1.89 (m, 1H), 1.36–1.55 (m, 2H), 1.12 (d, $J = 7.0$ Hz, 3H), 0.92 (dd, $J = 8.0$, 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.5, 130.7, 69.4, 63.2, 56.1, 42.7, 41.5, 30.7, 26.2, 25.5, 24.6, 15.4, 9.9; IR (neat) 3363, 2930, 1436, 982 cm^{-1}.



(*E*)-**2.38c**

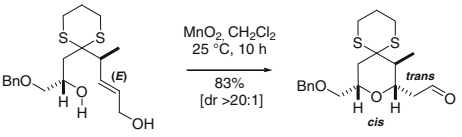
A colorless oil, 85 %: $[\alpha]^{25}_{D}$= –17.2 (*c* 1.83, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.40 (m, 4H), 7.24–7.28 (m, 1H), 6.99 (dd, J = 15.5, 8.5 Hz, 1H), 5.74 (ddd, J = 15.5, 6.0, 6.0 Hz, 1H), 5.11 (d, J = 9.0 Hz, 1H), 4.12 (d, J = 5.0 Hz, 2H), 4.04 (s, 1H), 2.99 (dd, J = 14.0, 7.0 Hz, 2H), 2.73–2.87 (m, 3H), 2.48–2.55 (m, 2H), 2.18 (d, J = 16.0 Hz, 1H), 1.97–2.03 (m, 1H), 1.83–1.91 (m, 1H), 1.21 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5, 132.2, 130.9, 128.3, 127.2, 125.5, 70.9, 63.2, 56.2, 44.4, 42.6, 26.1, 25.5, 24.5, 15.5; IR (neat) 3371, 2930, 667 cm^{-1}.



(*E*)-**2.38d**

A colorless oil, 67 %: $[\alpha]^{25}_{D}$= +10.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.35 (m, 5H), 5.98 (dd, J = 15.5, 8.5 Hz, 1H), 5.71 (ddd, J = 15.5, 6.0, 6.0 Hz, 1H), 4.50 (AB, $\Delta\upsilon$ = 15.0 Hz, J_{AB} = 12.5 Hz, 2H), 4.11 (d, J = 5.5 Hz, 2H), 3.93 (d, J = 9.0 Hz, 1H), 3.65 (d, J = 3.0 Hz, 1H), 3.36 (d, J = 8.5 Hz, 1H), 3.31 (d, J = 9.0 Hz, 1H), 2.98 (dddd, J = 6.5, 6.5, 6.5, 6.5 Hz, 1H), 2.91 (ddd, J = 13.5, 10.0, 3.0 Hz, 1H), 2.71–2.86 (m, 3H), 2.17 (dd, J = 15.5, 9.0 Hz, 1H), 2.10 (d, J = 15.5 Hz, 1H), 1.93–2.00 (m, 1H), 1.82–1.91 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 0.95 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 133.15, 133.02, 130.5, 128.3, 127.4, 77.9, 73.35, 73.24, 63.5, 56.7, 42.5, 39.2, 37.0, 26.3, 25.6, 24.7, 22.2, 20.2, 15.7; IR (neat) 3413, 2961, 1074, 667 cm^{-1}.

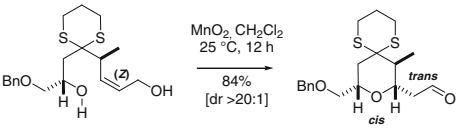
Tandem Oxidation/Oxa-Conjugate Addition Reaction of (*E*)-2.45a



(*E*)-**2.45a** **2.47a**

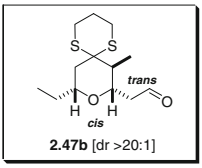
To a stirred solution of diol (*E*)-**2.45a** (15.5 mg, 0.042 mmol) in CH_2Cl_2 (2.0 mL, 0.021 M) was added MnO_2 (18.3 mg, 0.21 mmol), and the resulting mixture was stirred for 1 h at 25 °C. An addition of MnO_2 (18.3 mg, 0.21 mmol) was repeated three times every 1 h. After stirring for additional 6 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*trans*-2,6-*cis*-tetrahydropyran **2.47a** (12.8 mg, 83 %) as a colorless oil: $[\alpha]^{25}{}_D$= +16.4 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (dd, J = 3.5, 1.5 Hz, 1H), 7.26–7.40 (m, 5H), 4.56 (s, 2H), 4.09–4.15 (m, 2H), 3.52 (dd, J = 10.0, 5.0 Hz, 1H), 3.47 (dd, J = 10.5, 5.0 Hz, 1H), 3.14 (ddd, J = 14.5, 12.5, 2.5 Hz, 1H), 2.91 (ddd, J = 14.5, 12.0, 2.5 Hz, 1H), 2.76 (dd, J = 14.0, 1.5 Hz, 1H), 2.62–2.69 (m, 2H), 2.58 (ddd, J = 16.0, 4.0, 2.0 Hz, 1H), 2.44 (ddd, J = 15.5, 9.0, 3.5 Hz, 1H), 2.05–2.12 (m, 1H), 1.77–1.88 (m, 2H), 1.69–1.76 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 138.2, 128.4, 127.7, 73.4, 73.1, 72.8, 72.5, 54.3, 47.4, 45.5, 39.9, 25.68, 25.55, 25.0, 12.2; IR (neat) 1722, 1452, 1380, 1054, 908, 736, 698 cm^{-1}; HRMS (ESI) *m/z* 367.1392 [(M+H)$^+$, $C_{19}H_{26}O_3S_2$ requires 367.1396].

Tandem Oxidation/Oxa-Conjugate Addition Reaction of (*Z*)-2.45a



(*Z*)-**2.45a** **2.47a**

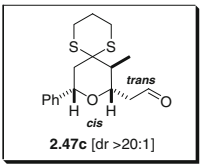
To a stirred solution of diol (*Z*)-**2.45a** at 25 °C (12.0 mg, 0.033 mmol) in CH_2Cl_2 (1.5 mL, 0.022 M) was added MnO_2 (14.3 mg, 0.165 mmol), and the resulting mixture was stirred at the same temperature for 1 h. An addition of MnO_2 (14.3 mg, 0.165 mmol) was repeated three times every 1 h. After stirring for additional 8 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*trans*-2,6-*cis*-tetrahydropyran **2.47a** (10.1 mg, 84 %) as a colorless oil.



2.47b [dr >20:1]

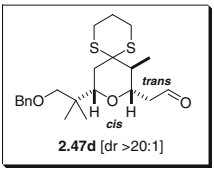
A colorless oil, 90 % from (*E*)-**25b**, 85 % from (*Z*)-**25b**: $[\alpha]^{25}{}_D$= +13.3 (*c* 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (dd, J = 8.5, 1.5 Hz, 1H), 4.04 (ddd, J = 10.0, 10.0, 3.5 Hz, 1H), 3.70–3.76 (m, 1H), 3.14 (ddd, J = 14.5, 12.0, 2.5 Hz,

1H), 2.90 (ddd, $J = 14.5$, 12.0, 3.0 Hz, 1H), 2.63–2.72 (m, 3H), 2.54 (ddd, $J = 15.5$, 3.5, 1.5 Hz, 1H), 2.39 (ddd, $J = 15.5$, 9.0, 3.0 Hz, 1H), 2.04–2.12 (m, 1H), 1.78–1.88 (m, 1H), 1.64–1.71 (m, 2H), 1.39–1.56 (m, 2H), 1.14 (d, $J = 7.0$ Hz, 3H), 0.92 (dd, $J = 7.5$, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 74.8, 72.8, 54.6, 47.4, 45.8, 42.9, 28.2, 25.64, 25.58, 25.0, 12.2, 9.9; IR (neat) 2932, 1722, 1129, 1059 cm^{-1}; HRMS (ESI) *m/z* 275.1127 [(M+H)$^+$, $C_{13}H_{22}O_2S_2$ requires 275.1134].



2.47c [dr >20:1]

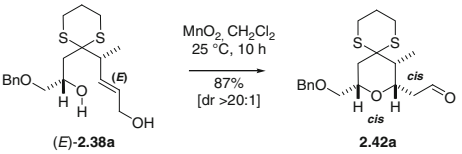
A colorless oil, 83 % from (*E*)-**25c**, 81 % from (*Z*)-**25c**: $[\alpha]^{25}_D$= –11.3 (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (dd, $J = 3.5$, 1.5 Hz, 1H), 7.26–7.37 (m, 5H), 4.96 (dd, $J = 11.0$, 1.5 Hz, 1H), 4.27 (ddd, $J = 9.5$, 9.5, 3.0 Hz, 1H), 3.12 (ddd, $J = 15.0$, 13.0, 3.0 Hz, 1H), 2.99 (ddd, $J = 15.0$, 13.0, 2.5 Hz, 1H), 2.91 (dd, $J = 14.0$, 1.5 Hz, 1H), 2.73 (ddd, $J = 15.0$, 4.0, 4.0 Hz, 1H), 2.63–2.67 (m, 2H), 2.53 (ddd, $J = 15.5$, 8.5, 3.5 Hz, 1H), 2.08–2.14 (m, 1H), 2.02 (dd, $J = 13.5$, 11.0 Hz, 1H), 1.81–1.91 (m, 2H), 1.23 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 141.4, 128.3, 127.6, 125.9, 75.6, 73.2, 54.6, 47.4, 45.3, 25.58, 25.52, 25.0, 12.2; IR (neat) 2908, 1723, 1081, 699 cm^{-1}; HRMS (ESI) *m/z* 323.1129 [(M+H)$^+$, $C_{17}H_{22}O_2S_2$ requires 323.1134].



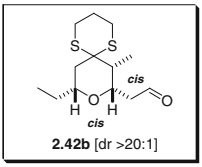
2.47d [dr >20:1]

A colorless oil, 82 % from (*E*)-**25d**, 88 % from (*Z*)-**25d**: $[\alpha]^{25}_D$= –3.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.63 (dd, $J = 4.0$, 1.5 Hz, 1H), 7.24–7.34 (m, 5H), 4.48 (s, 2H), 4.03 (ddd, $J = 9.5$, 9.5, 3.5 Hz, 1H), 3.84 (dd, $J = 10.5$, 1.5 Hz, 1H), 3.28 (d, $J = 9.0$ Hz, 1H), 3.21 (d, $J = 8.5$ Hz, 1H), 3.11 (ddd, $J = 15.0$, 13.0, 2.5 Hz, 1H), 2.80 (ddd, $J = 14.5$, 12.5, 2.5 Hz, 1H), 2.76 (dd, $J = 13.5$, 1.0 Hz, 1H), 2.64 (ddd, $J = 14.5$, 3.5, 3.5 Hz, 1H), 2.56 (ddd, $J = 15.0$, 4.0, 4.0 Hz, 1H), 2.51 (ddd, $J = 15.5$, 3.5, 1.5 Hz, 1H), 2.33 (ddd, $J = 15.0$, 9.5, 4.0 Hz, 1H), 1.98–2.05 (m, 1H), 1.81 (ddd, $J = 12.5$, 3.5, 3.5 Hz, 1H), 1.75 (dd, $J = 13.5$, 11.0 Hz, 1H), 1.63 (dddd, $J = 10.0$, 7.0, 7.0, 7.0 Hz, 1H), 1.14 (d, $J = 7.0$ Hz, 3H), 0.92 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 138.8, 128.2, 127.36, 127.33, 77.3, 76.9, 73.23, 73.03, 55.1, 47.4, 45.7, 38.1, 36.9, 25.61, 25.57, 24.8, 21.05, 20.93, 12.1; IR (neat) 2962, 1725, 1086, 698 cm^{-1}; HRMS (ESI) *m/z* 409.1948 [(M+H)$^+$, $C_{22}H_{32}O_3S_2$ requires 409.1866].

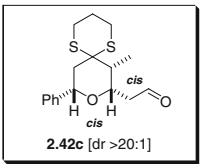
Tandem Oxidation/Oxa-Conjugate Addition Reaction of (*E*)-2.38a



To a stirred solution of diol (*E*)-**2.38a** (26.8 mg, 0.073 mmol) in CH_2Cl_2 (2.0 mL, 0.037 M) was added MnO_2 (31.8 mg, 0.366 mmol), and the resulting mixture was stirred for 1 h at 25 °C. An addition of MnO_2 (55.8 mg, 0.642 mmol) was repeated three times every 1 h. After stirring for additional 6 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.42a** (23.3 mg, 87 %) as a colorless oil.

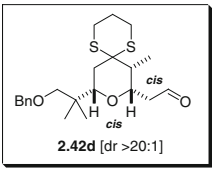


A colorless oil, 84 %: $[\alpha]^{25}_D$= –35.6 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (dd, J = 2.0, 2.0 Hz, 1H), 4.78 (ddd, J = 10.0, 4.0, 2.0 Hz, 1H), 3.68–3.74 (m, 1H), 2.80–2.91 (m, 2H), 2.71 (dddd, J = 14.0, 14.0, 6.5, 3.5 Hz, 2H), 2.64 (ddd, J = 16.5, 9.5, 2.5 Hz, 1H), 2.28 (ddd, J = 16.5, 4.0, 2.0 Hz, 1H), 2.05–2.10 (m, 1H), 1.88–2.04 (m, 3H), 1.66 (dd, J = 14.0, 12.0 Hz, 1H), 1.34–1.52 (m, 2H), 1.09 (d, J = 7.0 Hz, 3H), 0.88 (dd, J = 7.5, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 74.3, 70.1, 53.6, 47.5, 38.20, 37.97, 28.5, 26.0, 25.35, 25.23, 9.7, 9.1; IR (neat) 2906, 1724, 1123, 1072 cm^{-1}; HRMS (ESI) *m/z* 275.1129 [$(M+H)^+$, $C_{13}H_{22}O_2S_2$ requires 275.1134].



A colorless oil, 85 %: $[\alpha]^{25}_D$= –49.3 (*c* 0.93, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (dd, J = 2.0, 2.0 Hz, 1H), 7.25–7.35 (m, 5H), 5.02 (ddd, J = 9.5, 4.5, 2.0 Hz, 1H), 4.93 (dd, J = 12.0, 2.5 Hz, 1H), 2.94 (ddd, J = 14.0, 7.5, 4.0 Hz, 1H), 2.82–2.88 (m, 2H), 2.73–2.81 (m, 2H), 2.42 (ddd, J = 16.5, 4.0, 2.0 Hz, 1H), 2.15–2.23 (m, 2H), 1.95–2.06 (m, 3H), 1.23 (d, J = 7.5 Hz, 3H); ^{13}C

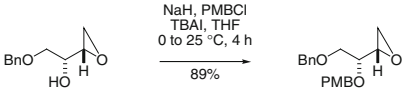
NMR (125 MHz, $CDCl_3$) δ 201.0, 141.5, 128.3, 127.6, 125.8, 75.1, 70.4, 53.6, 47.5, 39.9, 38.4, 26.1, 25.39, 25.20, 9.0; IR (neat) 2903, 1722, 1064, 733 cm^{-1}; HRMS (ESI) *m/z* 323.1135 [$(M+H)^+$, $C_{17}H_{22}O_2S_2$ requires 323.1134].



2.42d [dr >20:1]

A colorless oil, 81 %: $[\alpha]^{25}_D$= –26.9 (*c* 0.30, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (dd, J = 2.0, 2.0 Hz, 1H), 7.26–7.36 (m, 5H), 4.79 (ddd, J = 9.5, 3.0, 3.0 Hz, 1H), 4.47 (s, 2H), 3.83 (dd, J = 11.5, 2.0 Hz, 1H), 3.25 (d, J = 9.0 Hz, 1H), 3.17 (d, J = 8.5 Hz, 1H), 2.81–2.89 (m, 2H), 2.74 (dd, J = 7.0, 3.5 Hz, 1H), 2.72 (dd, J = 6.5, 3.5 Hz, 1H), 2.58 (ddd, J = 16.0, 9.5, 2.5 Hz, 1H), 2.24 (ddd, J = 16.0, 2.5, 2.5 Hz, 1H), 1.92–2.07 (m, 4H), 1.83 (dd, J = 12.0, 12.0 Hz, 1H), 1.08 (d, J = 6.5 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.6, 138.8, 128.2, 127.38, 127.31, 76.60, 76.47, 73.2, 70.2, 54.1, 47.5, 38.40, 38.29, 32.06, 26.0, 25.50, 25.37, 21.0, 20.4, 9.1; IR (neat) 2935, 1726, 1097, 1027 cm^{-1}; HRMS (ESI) *m/z* 409.1951 [$(M+H)^+$, $C_{22}H_{32}O_3S_2$ requires 409.1866].

Preparation of PMB-Ether 2.57

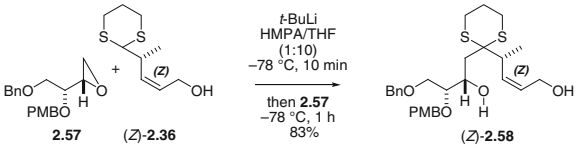


2.56 **2.57**

To a cooled (0 °C) solution of (*R*)-2-(benzyloxy)-1-((*S*)-oxiran-2-yl)ethanol (**2.56**) (1.050 g, 5.41 mmol) in THF (45 mL, 0.12 M) were added NaH (60 % in mineral oil, 432 mg, 10.81 mmol), 4-methoxybenzyl chloride (0.81 mL, 5.95 mmol), and tetrabutylammonuim iodide (199 mg, 0.54 mmol). After stirring at 25 °C for 4 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc) to afford **2.57** (1.514 g, 89 %) as a colorless oil: $[\alpha]^{25}_D$= –7.5 (*c* 1.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.36 (m, 7H), 6.87 (d, J = 8.5 Hz, 2H), 4.60 (AB, $\Delta\upsilon$ = 18.0 Hz, J_{AB} = 11.5 Hz, 2H), 4.58 (s, 2H), 3.80 (s, 3H), 3.66 (dd, J = 5.0, 1.0 Hz, 2H), 3.51 (ddd, J = 5.0, 5.0, 5.0 Hz, 1H), 3.07–3.10 (m, 1H), 2.78 (dd, J = 5.0, 5.0 Hz, 1H), 2.71 (dd, J = 5.0, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 138.0, 130.2, 129.2, 128.2, 127.43, 127.42, 113.6, 76.7, 73.3, 72.0, 70.6, 55.0, 51.2, 45.2; IR (neat) 2862,

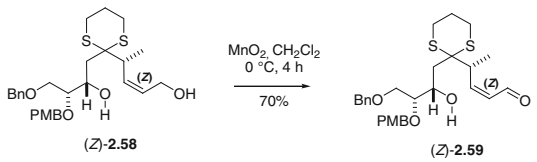
1511, 1244, 1090, 820 cm^{-1}; HRMS (ESI) *m/z* 337.1400 [$(M+Na)^+$, $C_{19}H_{22}O_4$ requires 337.1410].

Preparation of Diol (*Z*)-2.58



To a cooled (–78 °C) solution of (*Z*)-**2.36** (458 mg, 2.24 mmol) in HMPA/THF (1:10, total 16.5 mL) was added dropwise *t*-BuLi (3.95 mL, 1.7 M in pentane, 6.72 mmol), and the resulting mixture was stirred for 10 min before the addition of **2.57** (1056 mg, 3.36 mmol) was added. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to afford (*Z*)-**2.58** (969 mg, 83 %) as a colorless oil: $[\alpha]^{25}_D$= –1.7 (*c* 2.03, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.37 (m, 7H), 6.86 (d, J = 8.0 Hz, 2H), 5.67–5.79 (m, 2H), 4.68 (d, J = 11.5 Hz, 1H), 4.56 (s, 2H), 4.55 (d, J = 11.5 Hz, 1H), 4.26 (dd, J = 8.0, 8.0 Hz, 1H), 4.18 (dd, J = 7.0, 7.0 Hz, 1H), 3.92–4.01 (m, 1H), 3.80 (s, 3H), 3.74 (dd, J = 10.0, 4.5 Hz, 1H), 3.67 (dd, J = 9.5, 5.0 Hz, 1H), 3.49 (ddd, J = 5.0, 5.0, 5.0 Hz, 1H), 3.31 (br s, 1H), 3.18–3.25 (m, 1H), 2.91 (ddd, J = 14.5, 11.5, 3.0 Hz, 1H), 2.82 (ddd, J = 14.0, 11.5, 2.5 Hz, 1H), 2.68 (ddd, J = 14.0, 4.0, 4.0 Hz, 1H), 2.63 (ddd, J = 14.0, 4.0, 4.0 Hz, 1H), 2.41 (d, J = 15.0 Hz, 1H), 2.26 (br s, 1H), 2.18 (dd, J = 16.5, 8.5 Hz, 1H), 1.93–1.97 (m, 1H), 1.78–1.86 (m, 1H) 1.16 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 137.9, 133.0, 130.2, 129.4, 128.9, 128.2, 127.49, 127.46, 113.6, 80.5, 77.2, 73.3, 72.1, 69.7, 57.8, 57.0, 55.1, 39.0, 38.1, 25.83, 25.59, 24.8, 16.6; IR (neat) 3399, 2930, 1512, 1247, 1081, 1031 cm^{-1}.

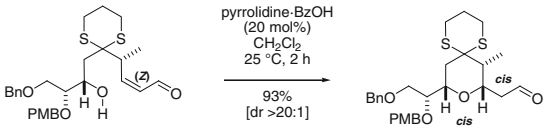
Oxidation of (*Z*)-2.58



To a cooled (0 °C) solution of diol (*Z*)-**2.58** (458.5 mg, 0.88 mmol) in CH_2Cl_2 (13.0 mL, 0.068 M) was added MnO_2 (384 mg, 4.42 mmol), and the resulting mixture was stirred for 30 min at 0 °C. An addition of MnO_2 (384 mg,

4.42 mmol) was repeated two times every 30 min. After stirring at the same temperature for additional 2.5 h, the resulting mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4/1) to afford (*Z*)-**2.59** (321 mg, 70 %) as a colorless oil: $[\alpha]^{25}_{D}$= +3.9 (*c* 2.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.5 (d, J = 8.0 Hz, 1H), 7.25–7.36 (m, 7H), 6.82–6.88 (m, 3H), 5.98 (dd, J = 11.0, 7.5 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.57 (AB, $\Delta\upsilon$ = 13.5 Hz, J_{AB} = 12.5 Hz, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.11–4.19 (m, 1H), 3.94 (dddd, J = 9.5, 7.0, 7.0, 7.0 Hz, 1H), 3.80 (s, 3H), 3.75 (dd, J = 10.0, 4.5 Hz, 1H), 3.68 (dd, J = 10.5, 5.5 Hz, 1H), 3.50 (ddd, J = 5.5, 5.5, 5.5 Hz, 1H), 3.19 (d, J = 3.5 Hz, 1H), 2.92 (ddd, J = 14.0, 10.5, 3.0 Hz, 1H), 2.84 (ddd, J = 14.5, 10.5, 3.0 Hz, 1H), 2.74 (dddd, J = 14.0, 3.5, 3.5, 3.5 Hz, 1H), 2.67 (dddd, J = 14.5, 3.5, 3.5, 3.5 Hz, 1H), 2.37 (d, J = 14.5 Hz, 1H), 2.16 (dd, J = 15.5, 9.0 Hz, 1H), 1.92–2.00 (m, 1H), 1.80–1.90 (m, 1H) 1.24 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.8, 159.2, 152.1, 137.9, 130.2, 129.52, 129.30, 128.3, 127.6, 113.7, 80.2, 73.4, 72.2, 69.7, 69.2, 55.8, 55.1, 39.0, 38.3, 26.1, 25.5, 24.6, 16.4; IR (neat) 3470, 2905, 1672, 1512, 1245, 1075, 734 cm^{-1}.

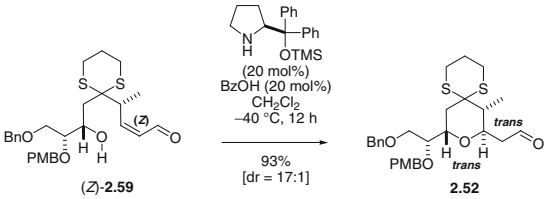
Secondary Amine-Catalyzed Oxa-Conjugate Addition Reaction of (*Z*)-2.59



(*Z*)-**2.59** **2.51**

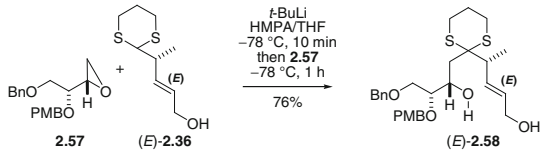
To a solution of aldehyde (*Z*)-**2.59** (33.0 mg, 0.064 mmol) in CH_2Cl_2 (1.5 mL, 0.043 M) was added dropwise a mixture of pyrrolidine·BzOH (0.23 mL, 0.055 M in CH_2Cl_2) at 25 °C. After stirring for 2 h at the same temperature, the resulting mixture was diluted with hexanes (30.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.51** (30.8 mg, 93 %) as a colorless oil: $[\alpha]^{25}_{D}$= –15.2 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (dd, J = 2.0, 2.0 Hz, 1H), 7.24–7.36 (m, 7H), 6.86 (d, J = 8.0 Hz, 2H), 4.80 (ddd, J = 10.0, 4.0, 2.0 Hz, 1H), 4.61 (AB, $\Delta\upsilon$ = 35.5 Hz, J_{AB} = 11.5 Hz, 2H), 4.51 (AB, $\Delta\upsilon$ = 14.0 Hz, J_{AB} = 12.0 Hz, 2H), 4.03 (ddd, J = 11.0, 5.0, 2.5 Hz, 1H), 3.80 (s, 3H), 3.49–3.62 (m, 3H), 2.72–2.88 (m, 4H), 2.59 (ddd, J = 17.0, 10.0, 3.0 Hz, 1H), 2.29 (ddd, J = 16.5, 4.0, 2.0 Hz, 1H), 2.16 (d, J = 12.0 Hz, 1H), 2.04–2.09 (m, 1H), 1.94–1.99 (m, 2H), 1.87 (dd, J = 14.5, 12.0 Hz, 1H), 1.11 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 159.2, 138.3, 130.6, 129.6, 128.4, 127.7, 113.7, 79.5, 73.44, 73.29, 72.8, 70.30, 70.20, 69.9, 55.4, 53.5, 47.5, 38.7, 33.3, 26.1, 25.53, 25.33, 9.1; IR (neat) 2904, 1725, 1513, 1247, 1092 cm^{-1}; HRMS (ESI) *m/z* 539.1891 [(M+Na)$^+$, $C_{28}H_{36}O_5S_2$ requires 539.1896].

Chiral Organocatalytic Oxa-Conjugate Addition Reaction of (*Z*)-2.59



To a cooled (–40 °C) solution of aldehyde (*Z*)-**2.59** (35.1 mg, 0.068 mmol) in CH_2Cl_2 (1.5 mL, 0.045 M) was added dropwise a mixture of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether and BzOH (0.25 mL, 0.055 M in CH_2Cl_2). After stirring at –40 °C for 12 h, the reaction mixture was diluted with hexanes (30.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1 to 3/1) to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.52** (30.9 mg, 88 %) and 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.51** (1.8 mg, 5 %) as colorless oils: [**For 2,3-*trans*-2,6-*trans*-Tetrahydropyran 2.52**]: $[\alpha]^{25}_{D}$= +10.7 (*c* 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, J = 1.0 Hz, 1H), 7.24–7.34 (m, 7H), 6.86 (d, J = 8.0 Hz, 2H), 4.74 (d, J = 11.0 Hz, 1H), 4.52 (s, 2H), 4.47 (d, J = 11.0 Hz, 1H), 4.24–4.28 (m, 1H), 4.20 (ddd, J = 8.5, 8.5, 4.0 Hz, 1H), 3.98 (ddd, J = 10.0, 5.0, 5.0 Hz, 1H), 3.79 (s, 3H), 3.72 (dd, J = 10.5, 3.0 Hz, 1H), 3.54 (dd, J = 10.5, 4.5 Hz, 1H), 3.04 (dd, J = 13.0, 13.0 Hz, 1H), 2.94 (dd, J = 13.0, 13.0 Hz, 1H), 2.83 (dd, J = 14.0, 5.0 Hz, 1H), 2.61–2.73 (m, 4H), 2.28 (dd, J = 14.5, 5.5 Hz, 1H), 1.96–2.04 (m, 1H), 1.91 (dddd, J = 7.5, 7.5, 7.5, 7.5 Hz, 1H), 1.77–1.86 (m, 1H), 1.20 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 159.1, 138.3, 130.8, 129.2, 128.3, 127.68, 127.52, 113.7, 76.9, 73.4, 71.7, 70.1, 69.94, 69.83, 55.3, 52.5, 47.6, 43.2, 35.0, 26.3, 25.8, 25.3, 14.0; IR (neat) 2907, 1723, 1512, 1246, 1095 cm^{-1}; HRMS (ESI) *m/z* 539.1881 [(M+Na)$^+$, $C_{28}H_{36}O_5S_2$ requires 539.1896].

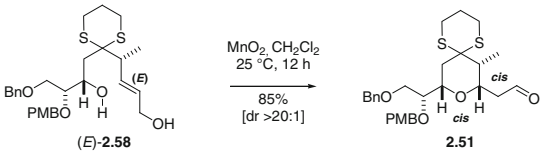
Preparation of Diol (*E*)-2.58



To a cooled (–78 °C) solution of (*E*)-**2.36** (47.0 mg, 0.23 mmol) in HMPA/THF (1:10, total 5.5 mL) was added dropwise *t*-BuLi (0.41 mL, 1.7 M in pentane, 0.69 mmol), and the resulting mixture was stirred for 10 min before the addition of **2.37** (107.5 mg, 0.34 mmol) was added. After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted

with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to afford (*E*)-**2.58** (90.5 mg, 76 %) as a colorless oil: $[\alpha]^{25}{}_D$= +1.1 (*c* 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.35 (m, 7H), 6.86 (d, J = 8.5 Hz, 2H), 5.95 (dd, J = 15.5, 8.5 Hz, 1H), 5.69 (ddd, J = 15.0, 6.0, 6.0 Hz, 1H), 4.69 (d, J = 11.0 Hz, 1H), 4.56 (s, 2H), 4.55 (d, J = 11.0 Hz, 1H), 4.09–4.16 (m, 3H), 3.79 (s, 3H), 3.75 (dd, J = 10.5, 4.0 Hz, 1H), 3.66 (dd, J = 10.0, 5.5 Hz, 1H), 3.50 (ddd, J = 5.5, 5.5, 5.5 Hz, 1H), 3.41 (d, J = 2.5 Hz, 1H), 2.79–2.95 (m, 3H), 2.67–2.75 (m, 2H), 2.28 (d, J = 15.0 Hz, 1H), 2.16 (dd, J = 15.5, 9.0 Hz, 1H), 1.91–1.98 (m, 1H), 1.78–1.88 (m, 2H), 1.16 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 138.2, 132.9, 130.7, 130.5, 129.6, 128.3, 127.62, 127.56, 113.7, 80.6, 73.5, 72.3, 70.0, 69.0, 63.5, 56.5, 55.2, 43.0, 38.2, 26.2, 25.5, 24.8, 15.6; IR (neat) 3440, 2906, 1512, 1246, 1071 cm^{-1}.

Tandem Oxidation/Oxa-Conjugate Addition Reaction of (*E*)-2.58



(*E*)-**2.58** **2.51**

To a stirred solution of diol (*E*)-**2.58** (31.8 mg, 0.061 mmol) in CH_2Cl_2 (2.0 mL, 0.031 M) was added MnO_2 (26.5 mg, 0.305 mmol), and the resulting mixture was stirred for 1 h at 25 °C. An addition of MnO_2 (26.5 mg, 0.305 mmol) was repeated three times every 1 h. After stirring for additional 8 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.51** (23.3 mg, 85 %) as a colorless oil.

2.3.2 Formal Synthesis of (+)-Leucascandrolide A

2.3.2.1 Background

Pietra and co-workers first reported the isolation, structural elucidation, and biologicl activity of a powerfully bioactive marine macrolide, leucascandrolide A, in 1996 [70]. Leucascandrolide A (**2.60**) was isolated from a from a the calcareous sponge of a new genus, *Leucascandra caveolata* collected from the east coast of New Caledonia in 1989 [70]. Leucascandrolide B was also isolated from the same sponge, however, it has shown to have few structural similarities and significantly

reduced biological activity relative to leucascandrolide A (**2.60**) [71]. The structural elucidation and the relative stereochemistry were assigned on the basis of an extensive combination of high-resolution mass spectroscopy, ^{13}C NMR, and DEPT experimentations, as well as two-dimensional NMR studies, while the absolute configuration was secured via correlation of the C(5) stereogenic center by employing the Mosher's ester analysis at the C(5) hydroxyl [72]. Leucascandrolide A (**2.60**) is an extremely potent inhibitor of tumor cell proliferation (IC_{50} values: 71 nM for KB and 357 nM for P388) [70] and also exhibit powerful antifungal activity against *Candida albicans*, a pathogenic yeast that infects HIV patients, presaging the progression to AIDS and other immunocompromised individuals (Fig. 2.8).

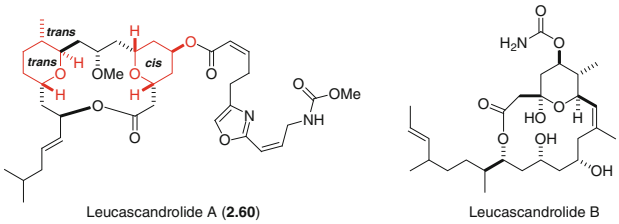


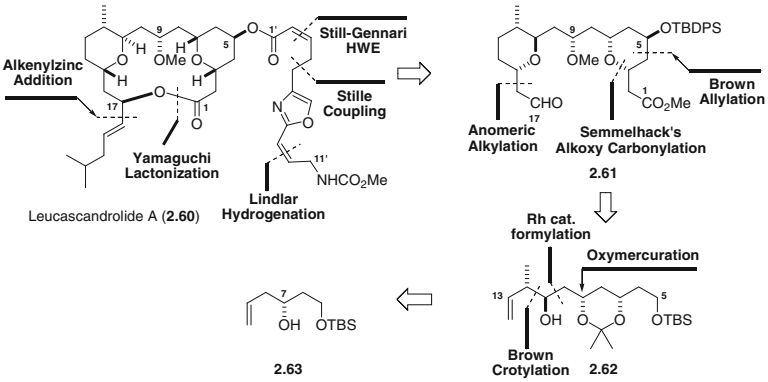
Fig. 2.8 Structures of leucascandrolide A and B

It was recently reported that leucascandrolide A is no longer available from its original natural supply, revealing that leucascandrolide A (**2.60**) is not a metabolite of *Leucascandra caveolata*, but rather that of an opportunistic microbial colonization of extensively dead portions of the sponge isolated earlier [71].

2.3.2.2 Previous Syntheses of Leucascandrolide A

Leucascandrolide A has attracted strong interest due to the interesting structural features, biological activities, and its unavailability from natural sources. These features conspire to make this natural product an important target for chemical synthesis, resulting in fourteen total and formal syntheses of leucascandrolide A [73–90]. This section of the dissertation presents a brief overview of the previous syntheses focusing on major synthetic challenges including the construction of the 2,6-*cis*-, 2,6-*trans*-tetrahydropyrans and the stereoselective installation of the (*E*)-4-methyl-pent-1-enyl appendage at C(17).

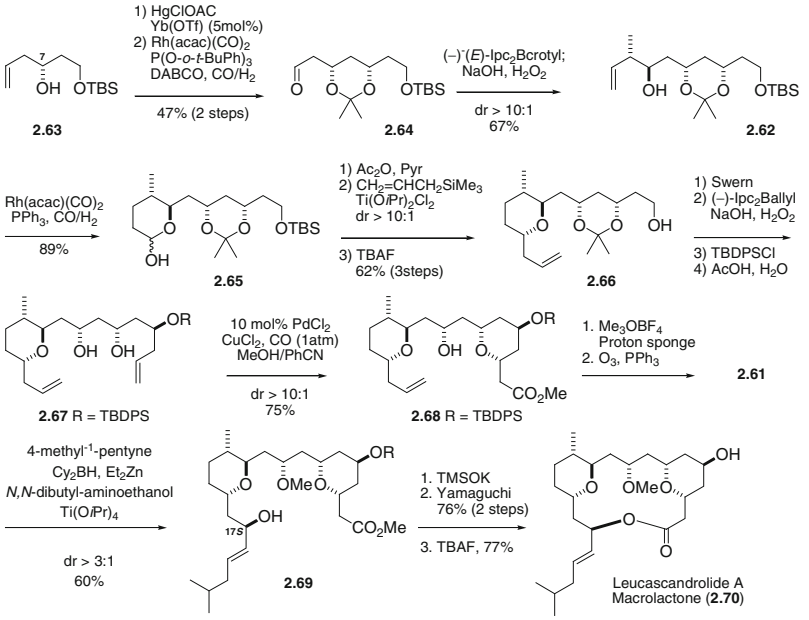
Leighton's Synthesis [74] (Scheme 2.10)



Scheme 2.10 Major disconnections of leucascandrolide A by Leighton

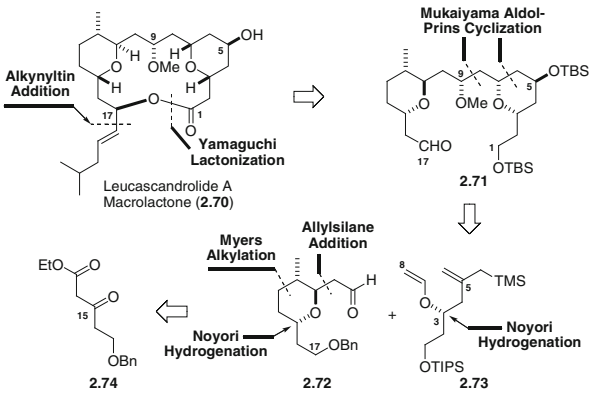
Following the report on the isolation, stuructural elucidation and biological activity of the leucascandrolide A, the Leighton group first disclosed the total synthesis of leucascandrolide A in 2000. Thus, Leighton's synthesis confirmed the relative and absolute stereochemical assignment obtained by Pietra and coworkers based on the extensive 1D- and 2D NMR experimentations and Mosher ester analysis. The key element of Leighton's synthesis involved the application of a metal mediated carbonylation reaction, developed within the Leighton group, for the formation of the both the 2,6-*trans* and 2,6-*cis*-tetrahydropyrans embedded in leucascandrolide A. Late stage macrocyclization was accessed by the Yamaguchi protocol and steregenic center at C(17) was incorporated by alkenylzinc addition to an aldehyde (Scheme 2.11).

The synthesis began with the $Yb(OTf)_3$ catalyzed oxymercuration [91] of homoallyl alcohol **2.63**, followed by Rh(I)-catalyzed formylation [92] to furnish aldehyde **2.64**. Brown asymmetric crotylation [93] of **2.64** (dr >10:1, 67 %), followed by second Rh(I)-catalyzed formylation generated lactol **2.65**. Construction of the 2,6-*trans*-tetrahydropyran **2.66** was achieved by Hosomi–Sakurai allylsilane addition in the presence of $Ti(OiPr)_2Cl_2$ (dr >10:1). Swern oxidation [94] and Brown asymmetric allylation [95] of the resulting aldehyde afforded the homoallyl alcohol, which was followed by protection as the TBDPS ether and subsequent hydrolysis of acetonide to furnish **2.67**. The 2,6-*cis*-tetrahydropyran synthesis was accomplished by utilizing Semmelhack's alkoxycarbonylation protocol [96–98] (cat. $PdCl_2$, $CuCl_2$, 1 atm CO, 1:1 MeOH:PhCN) to provide **2.68** (dr >10:1, 75 %). Having secured both tetrahydropyrans, methylation and oxidative cleavage of the olefin, followed by alkenylzinc addition [99–102] to the aldehyde afforded a 3:1 mixture of diastereomers in 60 % yield. Macrolactonization via the Yonemitsu-modified Yamaguchi protocol [103] followed by deprotection of the silyl group completed the macrolactone **2.70**.



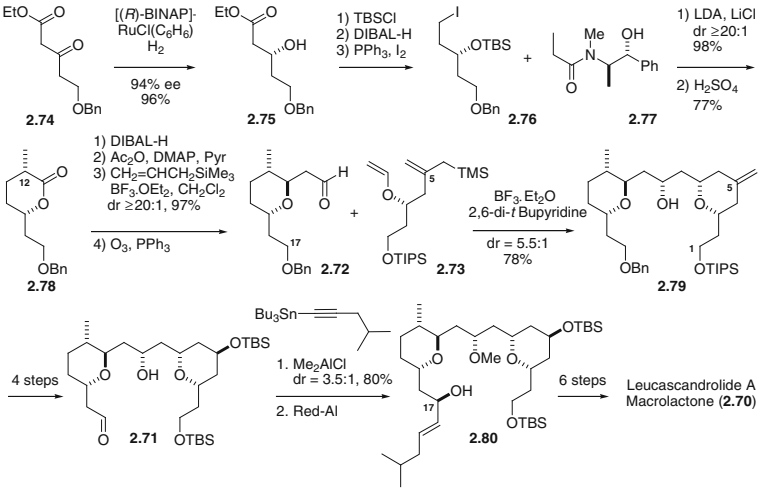
Scheme 2.11 Synthesis of leucascandrolide A by Leighton

Rychnovsky's Synthesis [104]



Scheme 2.12 Major disconnection of leucascandrolide A by Rychnovsky

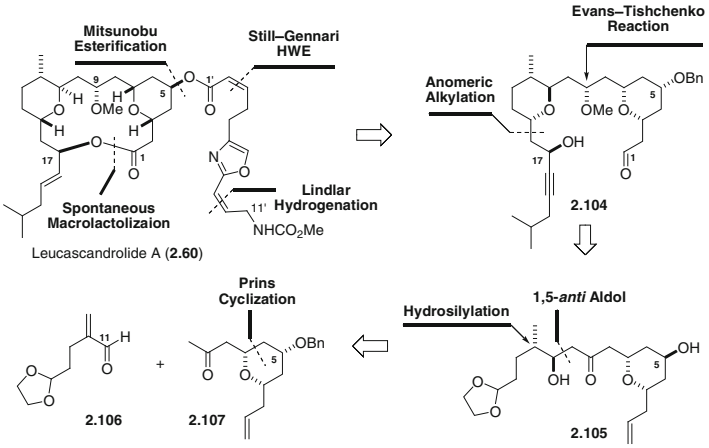
In 2001, Rychnovsky and co-workers completed the synthesis of the leucascandrolide macrolactone. The key features of the Rychnovsky's synthesis are the Mukayama aldol-Prins cascade reaction of alkyl enol ether with the aldehyde forming 2,6-*cis*-tetrahydropyran, and Hosomi–Sakurai allysilane addition to generate 2,6-*trans*-tetrahydropyran (Schemes 2.12, 2.13).



Scheme 2.13 Synthesis of leucascandrolide A by Rychnovsky

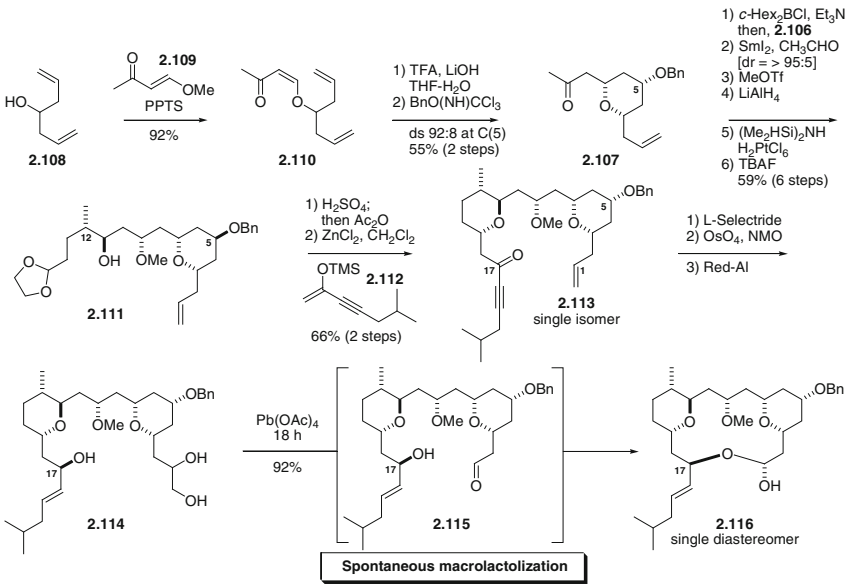
With this strategy in mind, Rychnovsky's synthesis commenced with the preparation of the 2,6-*trans*-tetrahydropyran. Noyori hydrogenation [105] of *β*-keto ester **2.74** furnished *β*-hydroxy ester **2.75** in 96 %, which was converted to iodide **2.76**. Asymmetric alkylation of **2.76**, employing Myers' pseudoephedrine auxiliary [106], generated stereocenter at C(12) and the treatment of acid afforded lactone **2.78** (98 %, ≥ 20:1). Reductive acetylation and Hosomi–Sakurai allylsilane addition gave the axial allylation product (97 %, ≥ 20:1), which was followed by subsequent ozonolysis to furnish the 2,6-*trans*-tetrahydropyran unit **2.72**. The formation of the key 2,6-*cis*-tetrahydropyran was accessed by the Mukaiyama–aldol-Prins reaction between aldehyde **2.72** and enol ether **2.73** in the presence of $BF_3{\cdot}OEt_2$ and 2,6-*di-tert*-butylpyridine at −78 °C to give a 5.5:1 mixture of C(9) epimers in -78 % yield, which was further converted to aldehyde **2.71**. Installation of the C(17) substituent was realized by alkynylstannane addition [107] to the aldehyde **2.71** to afford alcohol at C(17) in a ratio of 3.5:1, which was similar level of selectivity to that of the previous Leighton's synthesis [74]. Red-Al reduction of resulting propargylic alcohol afforded (*E*)-olefin, which was further converted into leucascandrolide macrolactone **2.70**.

Kozmin's Synthesis [76, 84]



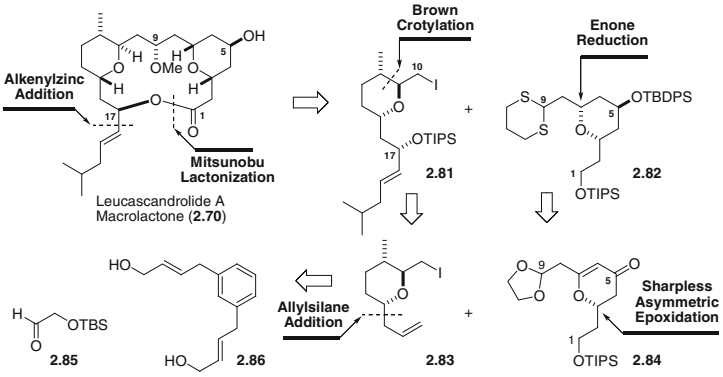
Scheme 2.14 Major disconnections of leucascandrolide A by Kozmin

In 2002, Kozmin and co-workers communicated a fundamentally new method for the late stage macrocyclization by formation of a stable internal lactol. It is worthy to note that this strategy has set a high standard for several future syntheses of leucascandrolide A. Other features are the Prins cyclization for the formation of the 2,6-*cis*-tetrahydropyran unit and anomeric alkylation during construction of the *trans*-tetrahydropyran. The elaboration of the synthesis commenced with the Prins cyclization of the vinylogous ester **2.110**, prepared from heptadienol **2.108**, followed in turn by hydrolysis and subsequent benzylation to deliver the 2,6-*cis*-tetrahydropyran **2.107** with a ratio of 92:8 at C(5). The β-hydroxy ketone was accomplished by the boron-enolate aldol reaction of ketone **2.107** with aldehyde **2.106** by treatment with *c*-Hex_2BCl using Paterson's protocol [108]. Subsequent samarium-catalyzed Evans–Tishchenko reaction [109] of the resulting β-hydroxy ketone incorporated the stereocenter at C(9) (dr >95:5). Following the methylation and a reductive removal of the acetate, stereoselective platinum-catalyzed hydrosilylation [110] led to **2.111** (dr = 87:13). The 2,6-*trans*-tetrahydropyran unit was rendered by utilizing the anomeric alkylation of silyl enol ether **2.112** to the lactol acetate, prepared from acetal **2.111** over two steps, to furnish ynone **2.113** as a single diastereomer. The key transformation, spontaneous macrolactolization of triol **2.114**, was accomplished through the hydroxy aldehyde intermediate **2.115** in a single operation to give lactol **2.116** as a single diatereomer, followed by oxidation and debenzylation sequences to produce macrolide **2.70**, which was further converted into leucascandrolide A **2.60** (Schemes 2.14, 2.15).



Scheme 2.15 Synthesis of leucascandrolide A by Kozmin

Wipf's Synthesis [77]

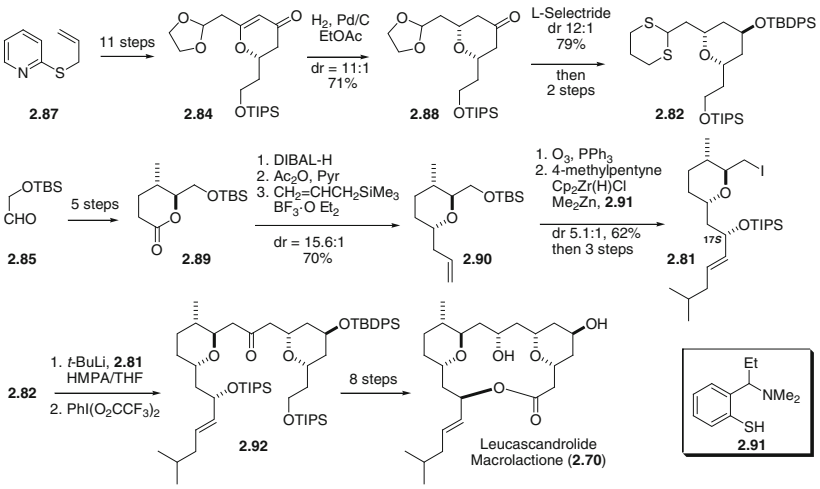


Scheme 2.16 Major disconnections of leucascandrolide A by Wipf

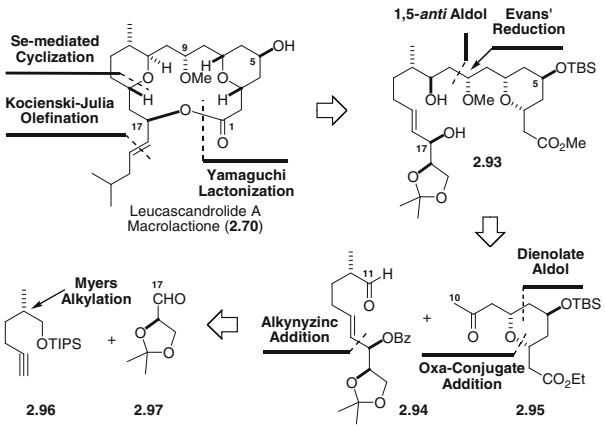
The Wipf's synthesis of the leucascandrolide macrolactone relied on a convergent strategy with the two requisite fragments **2.81** and **2.82**. The late stage macrocyclization utilized the Mitsunobu reaction of the seco-acid. The synthesis began

with synthesis of the 2,6-*cis*-tetrahydropyran moiety. Pyranone **2.84**, prepared from allyl sulfide **2.87** in 11 steps, was hydrogenated to give 2,6-*cis*-tetrahydropyranone **2.88** in a ratio of 11:1 in 71 % yield, followed by L-Selectride reduction of the resulting ketone to furnish the alcohol, which was further functionalized to provide **2.82**. The synthesis of the coupling segment **2.81** commenced with lactone **2.89**, which was prepared from aldehyde **2.85** in 5 steps. Reduction of latone **2.89** and subsequent acetylation gave the lactol acetate, which was followed by allylsilane addition to furnish the 2,6-*trans*-tetrahydropyran **2.90** with 15.6:1 diastereoselectivity in 70 % yield over three steps. Subjection to ozonolytic cleavage of **2.90** to give the corresponding aldehyde, which was exposed to an alkenylzinc reagent, prepared in situ by hydrozirconation of an 4-methylpentyne, afforded C(17*S*)-allyl alcohol as a major diastereomer (62 %, dr = 5.1:1). The two segment coupling reaction of dithiane **2.82** with iodide **2.81**, and subsequent deprotection of dithiane led to the ketone **2.92**. Finally, further functionalizaiton, including stereoselective reduction of the ketone **2.92**, manipulation of protecting groups and Mitsunobu macrocyclization [111] completed the macrolactone **2.70** (Schemes 2.16, 2.17).

Carreira's Synthesis [78, 81]

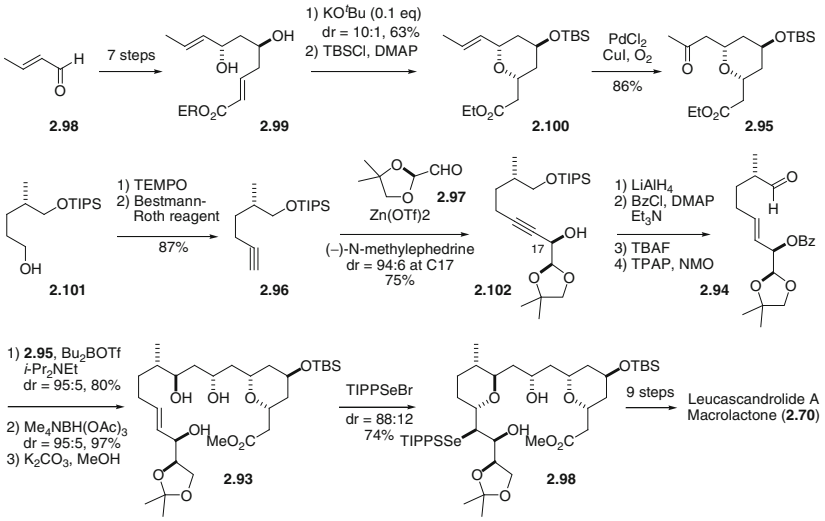


Scheme 2.17 Synthesis of leucascandrolide A macrolactone by Wipf



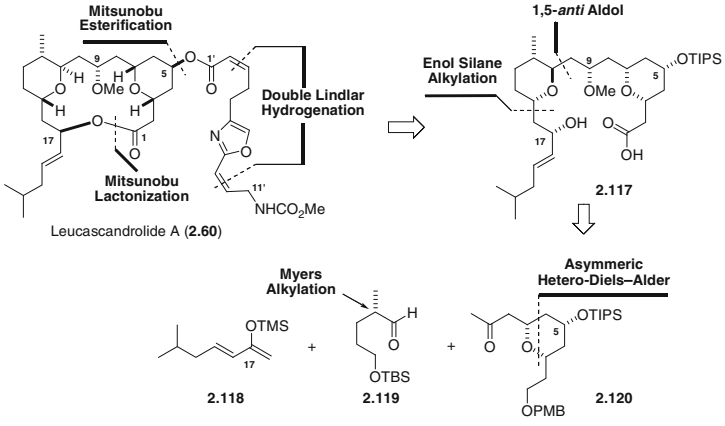
Scheme 2.18 Major disconnections of leucascandrolide A by Carreira

Published in 2002, Carreira's synthesis relied on the catalytic, enantioselective dienolate aldol/oxa-conjugate addition reaction forming the 2,6-*cis*-tetrahydropyran and the use of selenium-mediated cyclization for the construction of the 2,6-*trans*-tetrahydropyran. The synthesis of the diol ester **2.99** involved a seven-step elaboration from enal **2.98**. The conjugation addition precursor **2.99** underwent cyclization upon treatment with catalytic amount of KO^{t}Bu giving the thermodynamically favored 2,6-*cis*-tetrahydropyran adduct **2.100** (63 %, dr = 10:1). Protection as the TBS ether followed by regioselective Wacker oxidation afforded ketone **2.95** in 86 % yield. Aldehyde **2.94**, the key intermediate, was prepared from alcohol **2.101**. TEMPO oxidation of **2.101** and subsequent Bestmann-Roth protocol [112] afforded alkyne **2.96** in 87 % over two steps. The zinc-alkynilide addition to chiral aldehyde **2.97** in the presence of (–)-*N*-methylephedrine provided the propargylic alcohol (75 %, dr = 94:6), which was further converted into aldehyde **2.94** after reduction of the alkyne to the (*E*)-alkene and manipulation of functional groups. Next the boron-enolate aldol reaction [113, 114] of aldehyde **2.94** with the methyl ketone **2.95** yielded the hydroxy ketone in 80 % as a single diastereomer, which was followed by 1,3-*anti* reduction [115] and hydorolysis of benzoate to set the requisite intermediate **2.93** for the construction of the 2,6-*trans*-tetrahydropyran. The critical cyclization event, electrophile-mediated cyclization, was carried out by treatment with the bulky electrophile, 2,4,6-triisopropylphenylselenyl bromide in CH_2Cl_2 at –78 °C, to deliver the desired 2,6-*trans*-tetrahydropyran **2.98** as a major diastereomer (74 %, dr = 88:12). Further, a nine-step elaboration completed the synthesis of leucascandrolide A macrolactone **2.70** (Schemes 2.18, 2.19).



Scheme 2.19 Synthesis of leucascandrolide A macrolactone by Carreira

Paterson's Synthesis [73, 82]

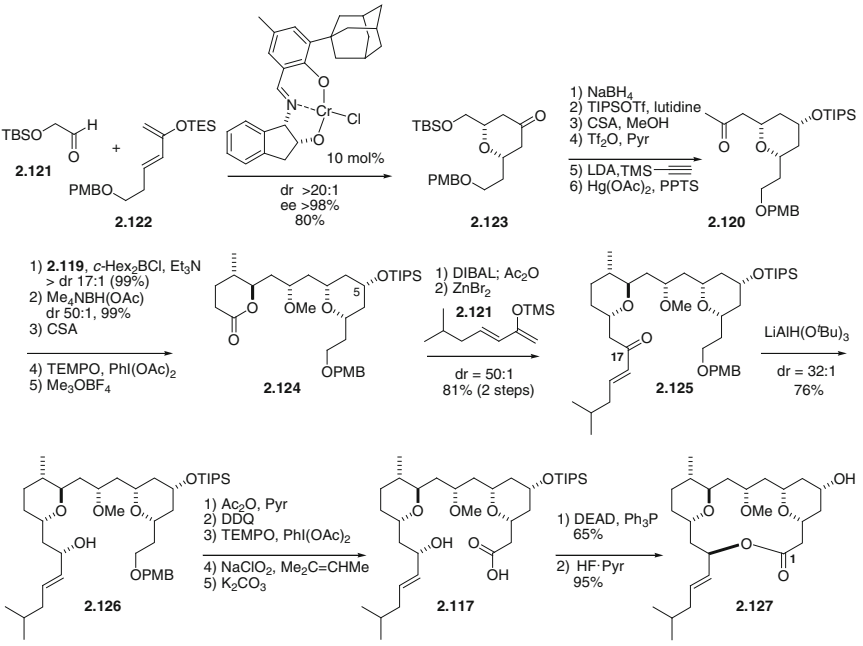


Scheme 2.20 Major disconnections of leucascandrolide A by Paterson

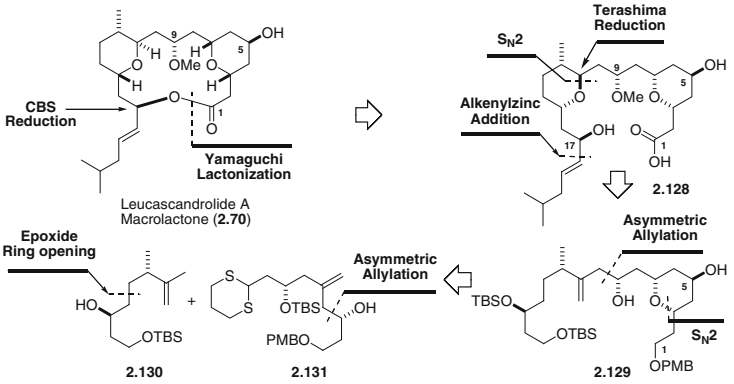
The synthetic plan for leucascandrolide A by Paterson and co-workers in 2003 involved the incorporation of all oxygenated stereocenters in a substrate controlled manner. The synthesis began with the construction of the 2,6-*cis*-tetrahydropyran. An asymmetric hetero-Diels–Alder reaction of silyloxy diene **2.122** with aldehyde **2.121**, catalyzed by the Jacobsen chromium Schiff base complex [116], afforded 2,6-*cis*-tetrahydropyranone **2.123** (80 %, dr >20:1, ee >98 %). Reduction of the

ketone **2.123** to equatorial C(5) alcohol was followed by homologation to methyl ketone **2.120** via alkynylation and subsequent oxymercuration. 1,5-*anti*-aldol reaction [113, 114] of β-alkoxy ketone **2.120** with aldehyde **2.119** and subsequent 1,3-*anti* reduction [115] of the resulting β-hydroxy ketone, followed by a treatment with acid provided the triol. This was followed by chemoselective lactone formation via a TEMPO-mediated procedure to give the corresponding δ-lactone **2.124** after formation of the methyl ether. Reductive acetylation [117] and silyl enol ether addition in the presence of $ZnBr_2$ delivered the 2,6-*trans*-tetrahydropyran unit **2.125** (81 % over two steps, dr = 50:1), which was followed by subsequent reduction of the corresponding β-alkoxy ketone **2.125** by treatment with $LiAlH(O^tBu)_3$ to furnish **2.126** with excellent stereoseletivity (76 %, dr = 32:1). Final stage of the synthesis involved the Mitsunobu macrocyclization of the seco-acid [118], followed by deprotection of silyl group to complete macrolactone **2.127** (Schemes 2.20, 2.21).

Williams' Synthesis [79, 80]

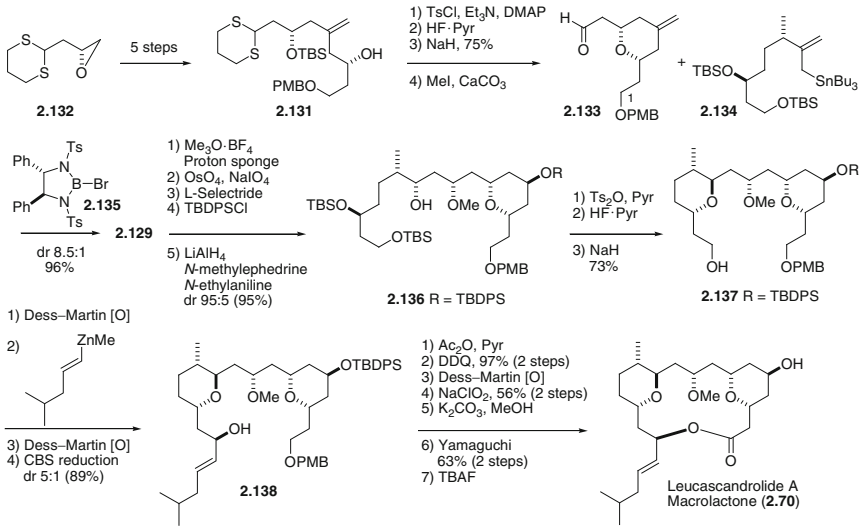


Scheme 2.21 Synthesis of leucascandrolide A macrolactone by Paterson



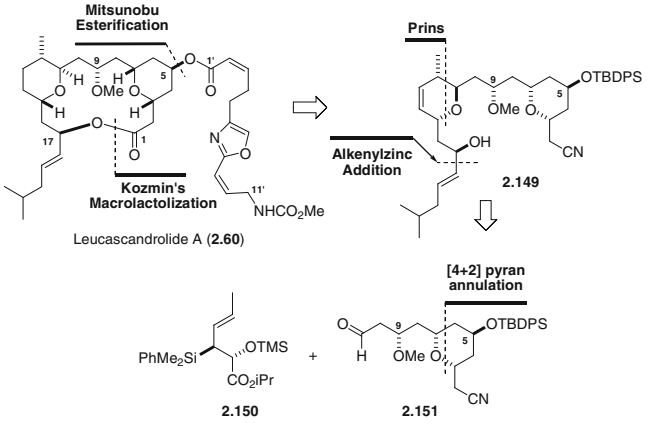
Scheme 2.22 Major disconnections of leucascandrolide A by Williams

Williams' strategy for the synthesis of leucascandrolide A involved an implementation of the intramolecular S_N2 cyclization for the synthesis of both 2,6-*cis*- and 2,6-*trans*-tetrahydropyrans embedded in the macrolide. Other special features are the asymmetric allylation between the chiral allyl stannane and chiral aldehyde, and control of a stereogenic center utilizing the Terashima hydride reduction. The elaboration of the synthesis commenced with preparation of the 2,6-*cis*-tetrahydropyran aldehyde **2.133**. Tosylation of the homoallylic alcohol **2.131**, prepared from chiral epoxide **2.132** in a five-step elaboration, followed by desilylation, and subsequent intramolecular S_N2 cyclization of the corresponding tosylate afforded the requisite aldehyde **2.133** after hydrolysis of the dithiane. The key asymmetric allylation of allyl stannane **2.134** with the aldehyde **2.133** was performed by treatment with (*R*,*R*)-bromoborane **2.135** to yield the homoallylic alcohol **2.129** with good yield and facial selectivity (96 %, dr = 8.5:1). Sequential formation of methyl ether at C(9) was followed by double bond cleavage to give the corresponding ketone, and subsequent selective reduction of ketone and protection at C(5) as the TBDPS ether. Terashima reduction [119] of the ketone at C(11) in the presence of (–)-*N*-methylephedrin as the ligand yielded the corresponding alcohol **2.136** (95 %, dr = 95:5). Introduction of the required configuration at C(11) allowed the following S_N2 displacement for the construction of the 2,6-*trans*-tetrahydropyran **2.137**. Addition of alkenylzinc species to an aldehyde resulted in a 1:1 mixture of diastereomeric allyl alcohols. Oxidation by Dess–Martin periodinane followed by exposure to CBS reagent [120], (*S*)-2-methyloxazaborolidine, resulted in a 5:1 mixuture of diastereomers. Macrocyclization was completed by the Yamaguchi protocol with a seco-acid. Minor manipulation of protecting groups allowed the completion of the synthesis of macrolactone **2.70** (Schemes 2.22, 2.23).



Scheme 2.23 Synthesis of leucascandrolide A macrolactone by Williams

Panek's Synthesis [83, 87]

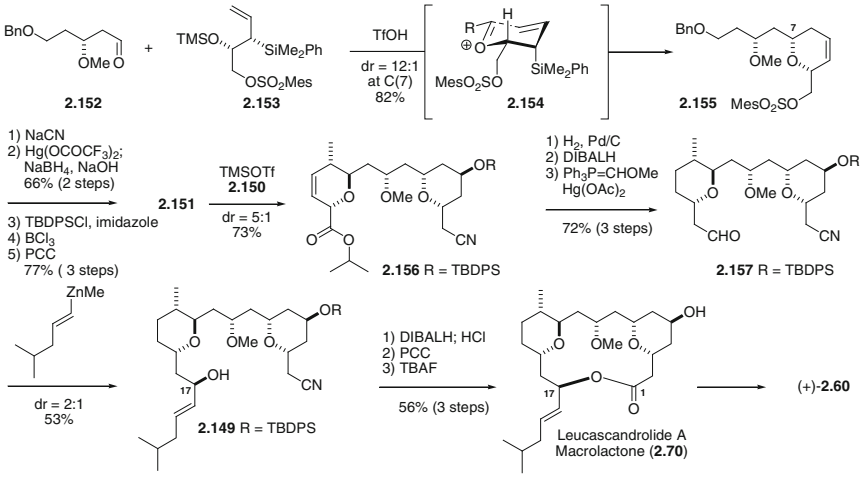


Scheme 2.24 Major disconnections of leucascandrolide A by Panek

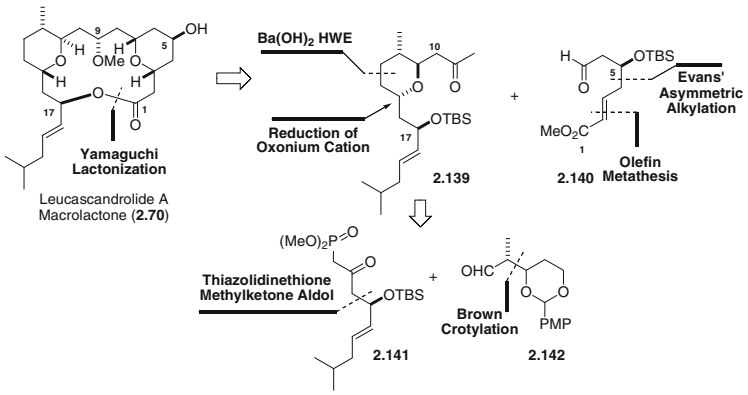
In 2005, Panek and co-workers reported a total synthesis of leucascandrolide A, the highlights of which are based on the two consecutive [4 + 2] annulation reactions between aldehydes and chiral allylsilane and crotylsilane for the construction of bis-tetrahydropyran in leucascandrolide A. The macrocyclization of the synthesis relies upon the spontaneous macrolactolization that Kozimin utilized previously. With the key [4 + 2] annulations reactions in mind, the synthesis

began with the formation of the *cis*-pyran unit. A modified Prins cyclization [121] of chiral *syn*-allylsilane **2.153** with chiral aldehyde **2.152** upon treatment with TfOH furnished 2,6-*cis*-dihydropyran **2.155** (82 %, dr = 12:1). Revealing the resulting *cis*-relationship of the pyran was governed by the bulky electron withdrawing mesylsulfonate which induced the chair-like transition state **2.154** to generate the *cis*-isomer with high stereoselectivity. One carbon homologation by cyanation using the S_N2 dispalcement, was followed by oxymercuration to install the hydroxyl group at C(5) which was protected with TBDPS ether. Subsequent deprotection of benzyl group and oxidation of the resulting alcohol furnished the key aldehyde **2.151**. The second [4 + 2] anuulation of the aldehyde **2.151** with chiral *anti*-allylsilane **2.150** led to the 2,6-*trans*-dihydropyran **2.156** (73 %, dr = 5:1), which was further converted into **2.157** in a three-step elaboration. With the bis-tetrahydropyran in hand, alkenylzinc addition to the aldehyde resulted in allyl alcohol **2.149** with poor diastereomeric ratio of 2:1 in 53 % yield. The macrocycle was realized by a spontaneous macroacetalization sequence reported by Kozmin [76]. Finally, PCC oxidation [122] and deprotecton of silyl group furnished the macrolactone **2.70** (Schemes 2.24, 2.25).

Crimmins' Synthesis [90]

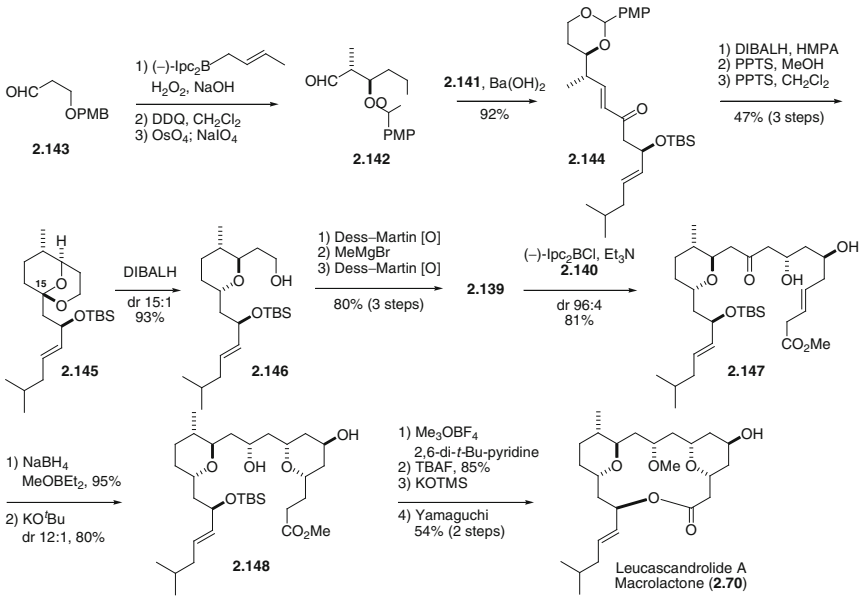


Scheme 2.25 Synthesis of leucascandrolide A macrolactone by Panek



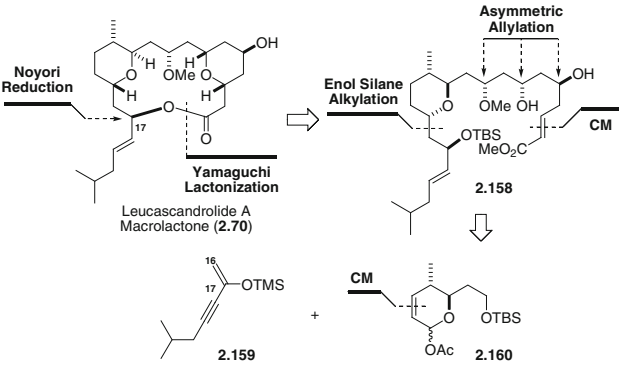
Scheme 2.26 Major disconnections of leucascandrolide A by Crimmins

In 2003, Crimmins and co-workers disclosed the synthesis of the leucascandrolide A macrolactone. The synthesis is highlighted by the diastereoselective reductive opening of a bicyclic acetal, the oxa-conjugate addition reaction forming the two tetrahydropyran units, and the boron-mediated 1,5-*anti*-aldol reaction to incorporate a stereogenic center at C(7), which is a different disconnection site from those of Carreira's, Kozmin's, and Pateson's approaches. The synthesis began with the preparation of the key bicyclic acetal **2.145**. Brown asymmetric crotylation [123] of aldehyde **2.143**, oxidative PMP acetal formation, and oxidative cleavage of the terminal olefin led to aldehyde **2.142**. Subsequent Horner–Wadsworth–Emmons olefination of aldehyde **2.142** with phosphonate **2.141** under Paterson's conditions [124] furnished enone **2.144** in 92 % yield. 1,4-Reduction of the enone to give ketone followed by mixed methyl acetalization and subsequent bridged acetalization resulted in acetal **2.145**. Exposure of **2.145** to *i*-Bu_2AlH under Kotsuki conditions [125] furnished the desired 2,6-*trans*-tetrahydropyran **2.146** (93 %, dr = 15:1). The result can be obtained presumably through the intramolecular hydride delivery by coordination between acetal oxygen and *i*-Bu_2AlH [114]. The next key *β*-hydroxy ketone **2.147** for the all carbon skeleton was realized by the boron enolate 1,5-*anti*-aldol reaction [113] with methyl ketone **2.139** and aldehyde **2.140** by treatment of (−)-Ipc_2BCl forming **2.147** (81 %, dr = 96:4). Formation of 1,3-*syn*-diol followed in turn by exposure to a catalytic amount of KO^tBu furnished the desired 2,6-*cis*-tetrahydropyran **2.148** via intramolecular oxa-conjugate addition reaction (80 %, dr = 12:1). Finally, minor manipulation of functional groups and Yamaguchi macrolactonization completed macrolactone **2.70** (Schemes 2.26, 2.27).



Scheme 2.27 Synthesis of leucascandrolide A macrolactone by Crimmins

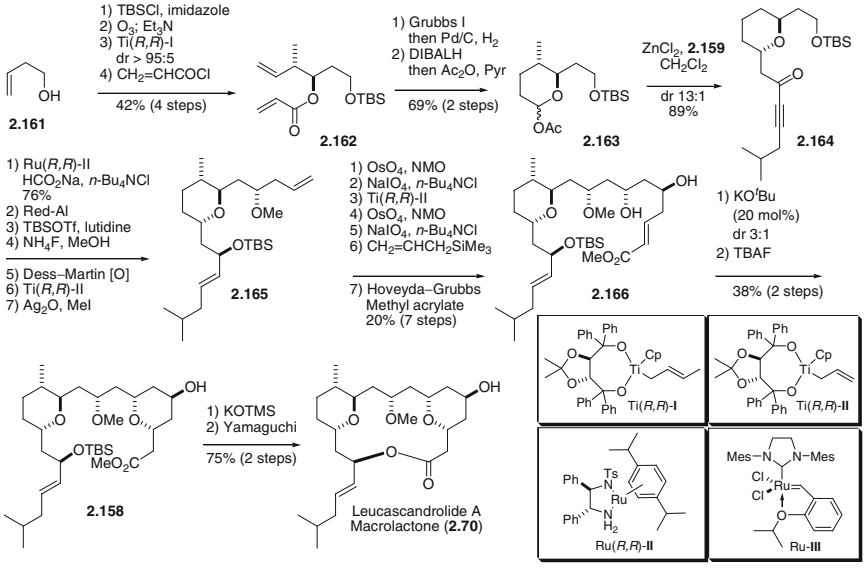
Cossy's Synthesis [85]



Scheme 2.28 Major disconnections of leucascandrolide A by Cossy

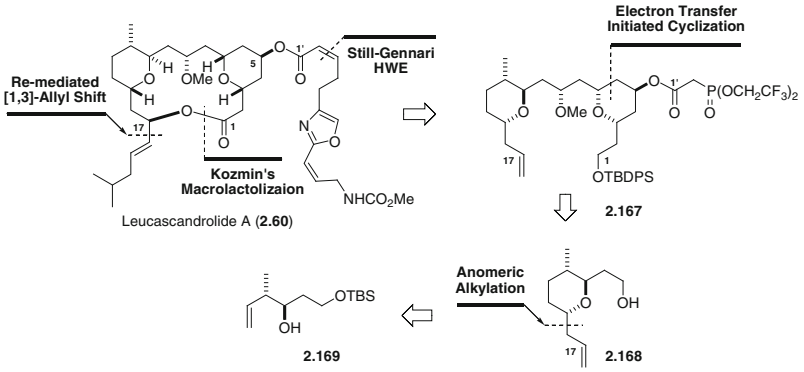
Cossy's approach for the synthesis of leucascandrolide A involved an asymmetric allylmetalation to incorporate the stereogenic centers at C(5), C(7), C(9), C(11) and C(12), and olefin metathesis. Construction of the 2,6-*cis*- and 2,6-*trans*-tetrahydropyrans was achieved by the Mukaiyama enol silane addition and oxa-conjugate addition reaction, respectively. The synthesis commenced with the

preparation of the *trans*-pyran unit. Protection of alchol **2.161** as the TBS ether, oxidative cleavage of the double bond and subsequent asymmetric crotylation by employing the Ti(*R*,*R*)-**I** complex [126] furnished the homoallyl alcohol, which was acrylated to form unsaturated ester **2.162**. Transformation of resultant **2.162** to the lactone via one-pot tandem RCM/hydrogenation [127] and subsequent second one-pot reduction/acetylation [104] afforded lactol acetate **2.163**. The 2,6-*trans*-tetrahydropyran was accessed by the Mukaiyama-type enol silane addition by treatment with $ZnCl_2$ to furnish **2.164** (89 %, dr = 13:1). Noyori asymmetric hydrogenation [128] of ketone afforded the desired allyl alcohol in 75 % yield, which was further transformed into **2.165** in a six-step elaboration. Dihydroxylation of **2.165**, oxidative cleavage by treatment with $NaIO_4$ and subsequent asymmetric allylation to afford homoallyl alcohol which was converted to α,β-unsaturated ester **2.166** after allylation and cross metathesis with methyl acrylate. Construction of the 2,6-*cis*-tetrahydropyran was achieved via intramolecular oxa-conjugate addition reaction by using a catalytic amount of KO^{t}Bu to furnish **2.158** in a modest ratio (dr = 3:1). After deprotection of the silyl group, the macrolide was realized by a modified Yamaguchi protocol [129], thereby completing the synthesis of macrolactone **2.70** (Schemes 2.28, 2.29).



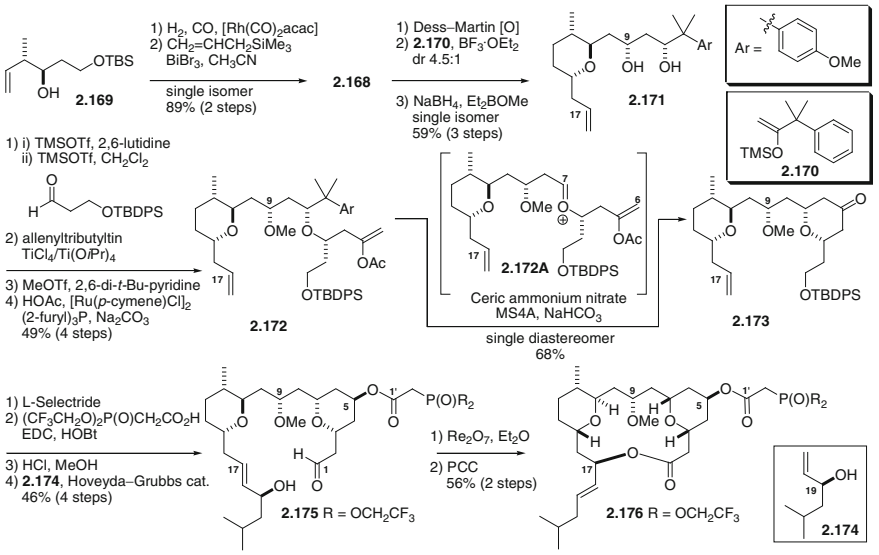
Scheme 2.29 Synthesis of leucascandrolide A macrolactone by Cossy

Floreancig's Synthesis [86]



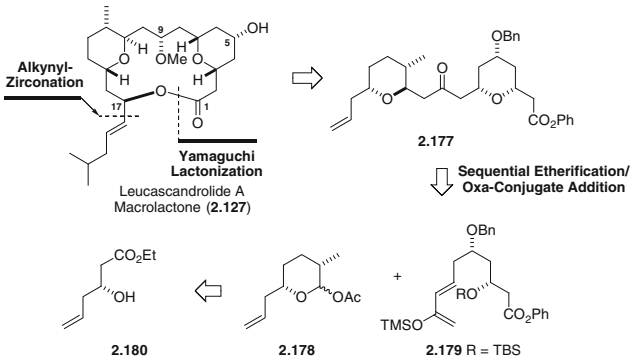
Scheme 2.30 Major disconnections of leucascandrolide A by Floreancig

Published in 2007, the Floreancig synthesis relied on the employment of the electron transfer initiated cyclization (ETIC) method [130–132] forming the *cis*-pyran unit from an advanced intermediate and a $BiBr_3$-mediated allylsilane addition to lead to the *trans*-pyran. In addition, the overall synthesis involved a minimal use of protecting groups and reagent-induced stereogenic centers. The synthesis commenced with the preparation of 2,6-*trans*-tetrahydropyran **2.168**. One step hydroformylation of the **2.169** employing Breit's protocol [133, 134] led to the lactol which was subsequently exposed to allyl trimethylsilane and $BiBr_3$ [135, 136] to provide **2.168** as a single diastereomer in 89 % over two steps. The substrate for the key ETIC reaction was accessed by a sequence of oxidation and Mukaiyama–aldol addition [137] of enol silane **2.170** to the aldehyde by treatment with $BF_3{\cdot}OEt_2$ to furnish β-hydroxy ketone. This was subsequently reduced by employing the Narasaka–Prasad protocol [138] to form the 1,3-*syn*-diol **2.171** as a single diastereomer. Acetalization followed by a Lewis acid-mediated acetal opening set the key substrate **2.172** for the ETIC reaction after formation of methyl ether at C(9) and acetate addition on alkyne. Treatment of **2.172** with ceric ammonium nitrate furnished the 2,6-*cis*-tetrahydropyran in 68 % yield as a single diastereomer. The reaction proceeded through the intermediate **2.172A**, in which the oxidative cleavage of benzylic carbon–carbon bond occurs to generate the oxocarbenium ion, thereby producing high levels of diatereoselectivity. The final stage of the synthesis involved an installation of C(17) appendage and macrolactonization of **2.175**.[1,3]-Allyl shift of **2.175** by employing Re_2O_7 conditions reported by Lee and Hansen [139] formed the lactol, which was then oxidized to lactone, thereby completing the synthesis of macrolactone **2.176** (Schemes 2.30, 2.31).



Scheme 2.31 Synthesis of leucascandrolide A by Floreancig

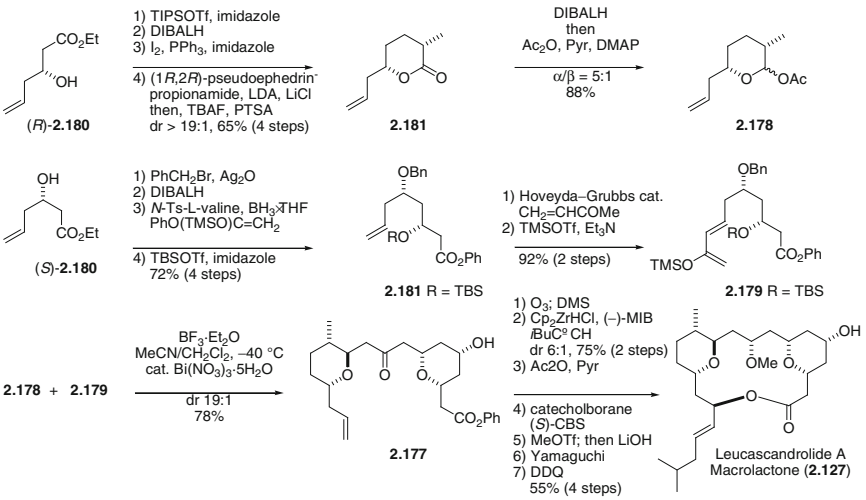
Evans' Synthesis [88]



Scheme 2.32 Major disconnections of leucascandrolide A by Evans

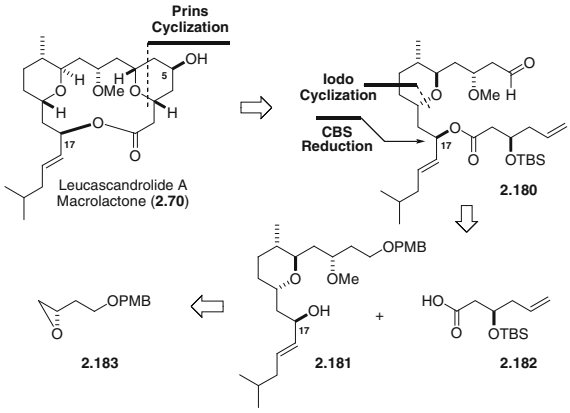
In 2008, Evans and co-workers disclosed the synthesis of the leucascandrolide A macrolactone, based on the highly concise route to leucascandrolide A, that is the sequential two-component etherification/oxa-conjugate addition reaction, developed within the Evans group. With this key reaction in mind, the synthesis commenced with the left-hand fragment from the known homoallyl alcohol (*R*)-**2.180**. Protection as the triisopropylsilyl ether followed by reduction with diisobutylaluminum hydride formed the requisite alcohol, which was converted into

the alkyliodide. The formation of the lactone was accessed by employing the Myers' alkylation of the iodide with the treatment of the pseudoephedrine auxiliary, followed by the in situ removal of the silyl group and concomitant acid-catalyzed lactonization to furnish δ-lactone **2.181** (dr >19:1). Reduction of **2.181** followed by acetylation afforded a mixture of anomeric acetates (88 %, α/β = 5:1) [104]. Synthesis of the requisite coupling partner **2.179** was prepared beginning with protection of β-hydroxy ester (*S*)-**2.180** as a benzyl ether, then selective reduction with diisobutylaluminum hydride furnished the requisite aldehyde. Mukaiyama–aldol reaction [140] of the resultant aldehyde with the trimethylsily enol ether of phenyl acetate in the presence of boron Lewis acid afforded the β-hydroxy ester, which was subsequently protected as the TBS ether **2.181**. The cross-metathesis of the resulting **2.181** with methyl vinyl ketone was further converted into trimethylsilyloxy diene **2.179**. Having secured two critical fragments, the key one-pot sequential two-component etherification/oxa-conjugate addition reaction was performed to yield the bis-tetrahydropyran core **2.177** (78 %, dr >19:1). Double bond cleavage of the terminal alkene in **2.177** to form the aldehyde, and subsequent exposure to alkenylzinc species [141] in the presence of (–)-MIB afforded the allylic alcohol (75 % over 2 steps, dr = 6:1), which was then transformed into the macrolide **2.127** after a five-step elaboration (Schemes 2.32, 2.33).



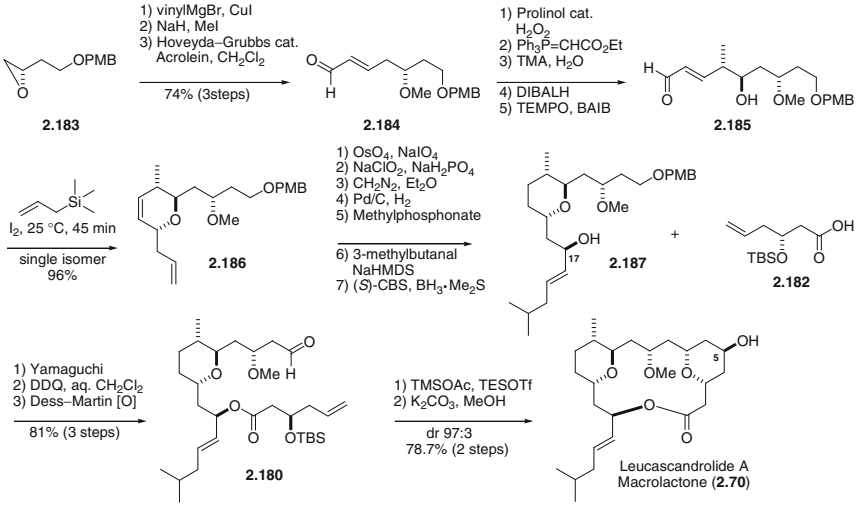
Scheme 2.33 Synthesis of leucascandrolide A macrolactone by Evans

Yadav's Synthesis [89]



Scheme 2.34 Major disconnections of leucascandrolide A macrolactone by Yadav

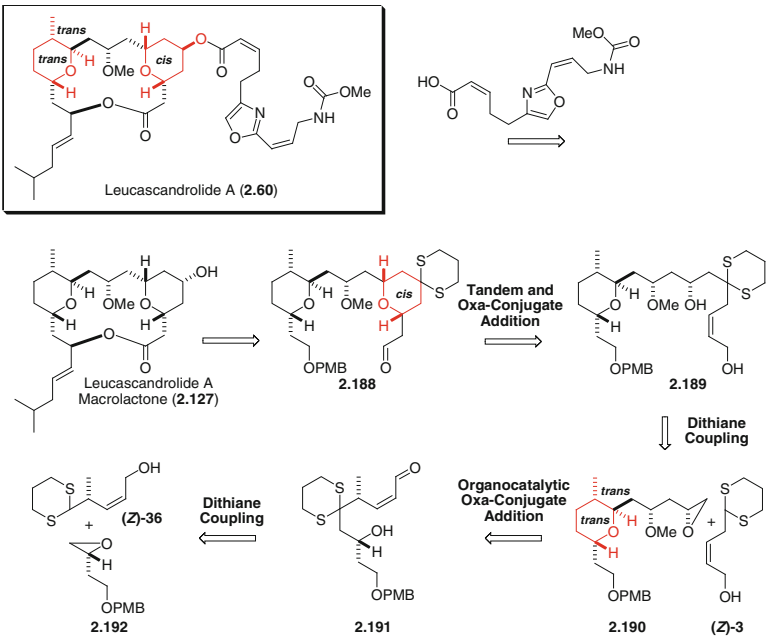
The most recent contributors to the leucascandrolide A are Yadav and co-workers. The key features of Yadav's synthesis are the iodo cyclization [68] for the construction of the *trans*-pyran and a Lewis acid promoted intramolecular Prins-type macrocyclization for an all requisite carbon frame work with an incorporation of three stereogenic centers in the *cis*-pyran unit. With this synthetic approach in mind, the synthesis began with the preparation of the 2,6-*trans*-pyran unit. Copper-mediated epoxide opening followed by cross-metathesis with treatment of Hoveyda–Grubbs [142, 143] catalyst afforded the α,β-unsaturated aldehyde **2.184**, which was then exposed to Jørgensen's epoxidation conditions [144] to furnish an epoxy aldehyde. Subsequent Wittig olefination followed in turn by epoxide opening by trimethyl aluminum and a two-step sequence of reduction and oxidation delivered the δ-hydroxy-α,β-unsaturated aldehyde **2.185**. The iodocyclization of **2.185** with treatment of allyltrimethylsilane and molecular iodine furnished the 2,6-*trans*-pyran **2.186** in 96 % yield as a single diastereomer [68]. Oxidative cleavage of the terminal olefin and Pinnick oxidation [145] led to a carboxylic acid, which in turn was converted into the ester by treatment with diazomethane. Reduction of the internal double bond in the *trans*-pyran moiety followed by Horner–Wardsworth–Emmons olefination and asymmetric reduction by employing Corey–Bakshi–Shibata protocol [120] incorporated a stereogenic center at C(17) in **2.187** with a 12:1 diastereomeric ratio. Coupling reaction of the resulting alcohol **2.187** with acid **2.182** employing Yamaguchi conditions [129] followed by oxidative removal of PMB and oxidation then furnished aldehyde **2.180** in 81 % over three steps. Last stage macrocyclization was realized by the Prins-type cyclization by treatment with TMSOAc and TESOTf in a 0.001 M solution of AcOH which delivered the 2,6-*cis*-tetrahydropyran, followed by hydrolysis, furnished leucascandrolide A macrolactone **2.70** (Schemes 2.34, 2.35).



Scheme 2.35 Synthesis of leucascandrolide A macrolactone by Yadav

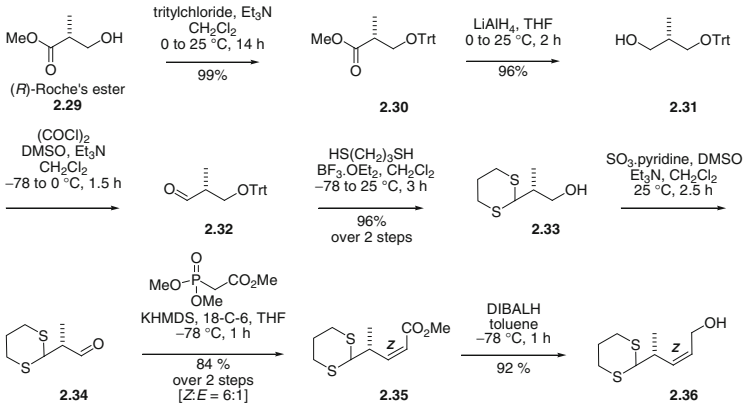
2.3.2.3 Retrosynthetic Analysis of (+)-Leucascandrolide A

A retrosynthetic overview of our (+)-leucascandrolide A (**2.60**) synthesis is depicted in Scheme 2.36. Our synthetic plan for **2.60** relies on the tandem and



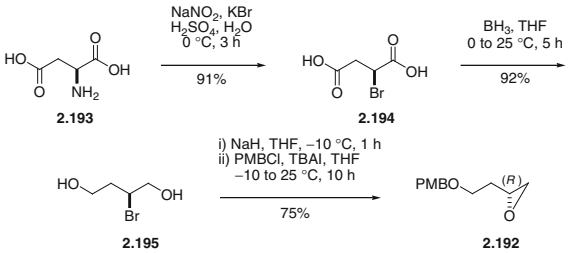
Scheme 2.36 Retrosynthetic analysis of (+)-leucascandrolide A

organocatalytic oxa-conjugate addition reactions in conjunction with the dithiane coupling reactions for the stereoselective synthesis of the 2,6-*cis*-tetrahydropyran and the 3-methyl-2,3-*trans*-2,6-*trans*-tetrahydropyran embedded in **2.60**. Impotantly, the synthesis of both the 2,6-*cis*- and 3-methyl-2,3-*trans*-2,6-*trans*-tetrahydropyrans through the same type of reaction has been achieved only once in the synthesis of **2.60** [83]. We envisioned that bis-tetrahydropyranyl macrolactone **2.127** could be secured from bis-tetrahydropyranyl aldehyde **2.188** through the spontaneous macrocyclization previously reported by Kozmin and co-workers [76]. We anticipated that **2.188** could arise in a stereoselective manner through the tandem allylic oxidation/oxa-conjugate addition reaction [18] of allyl alcohol **2.189**. Further analysis indicated that 3-methyl-2,3-*trans*-2,6-*trans*-tetrahydropyran **2.190** should be accessible by the organocatalytic oxa-conjugate addition reaction of (*Z*)-enal **2.191**.



Scheme 2.37 Synthesis of allyl alcohol **2.36**

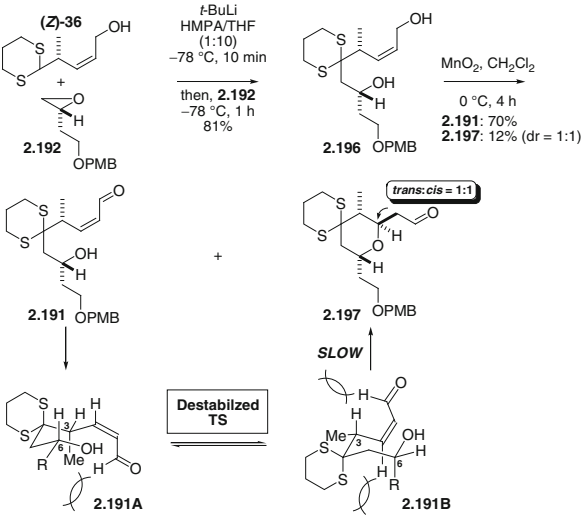
The synthesis of dithiane (*Z*)-allyl alcohol **2.36** began with commercially available (*R*)-3-hydroxy-2-methylpropionate (Roche's ester, **2.29**) (Scheme 2.37). Protection of the primary hydroxyl as the trityl ether and reduction with $LiAlH_4$ afforded alcohol **2.31** in 96 %. Swern oxidation followed by thioacetalization of the corresponding aldehyde without further purification provided dithiane **2.33** in 96 % over two steps. Parikh-Doering oxidation [39] and subsequent Horner–Wadsworth–Emmons olefination of aldehyde **2.34** with a phosphonoacetate furnished a 6:1 mixture of α,β-unsaturated esters, which were separable by column chromatography. The desired major isomer (*Z*)-**2.35** was reduced to afford ally alcohol **2.36**.



Scheme 2.38 Synthesis of epoxide **2.192**

The epoxide **2.192** was prepared from commercially available L-aspartic acid (**2.193**). L-Aspartic acid (**2.193**) was converted into bromosuccinic acid **2.194** by treatment with sodium nitrite and potassium bromide under aqueous sulfuric acid (91 %). Subsequent reduction of the diacid **2.194** furnished the bromodiol **2.195** in 92 % yield. Epoxidation and PMB protection furnished epoxide **2.192** in 75 % yield (Scheme 2.38).

2.3.2.4 Synthesis of 2,3-*trans*-2,6-*trans*-Tetrahydropyran via Organocatalytic Oxa-Conjugate Addition Reaction

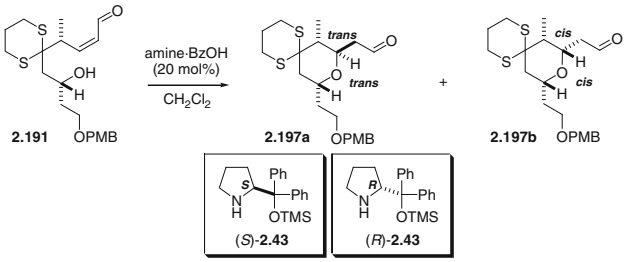


Scheme 2.39 Synthesis of α,β-unsaturated aldehyde **2.191**

Elaboration of the synthesis of leucascandrolide macrolactone (**2.127**) commenced with the preparation of α,β-unsaturated aldehyde **2.191** (Scheme 2.39). The coupling of (*Z*)-**36** and **2.192** proceeded smoothly to afford allyl alcohol **2.196**. As discussed earlier, based on the careful analysis and the initial results associated

with the stereoselective synthesis of the 2,3-*trans*-2,6-*trans*-tetrahydropyran through the tandem allylic oxidation/oxa-conjugate addition reaction, we were well aware that the formation of the 2,3-*trans*-2,6-*trans*-tetrahydropyran through the tandem oxa-conjugate addition reaction would be restricted by the potentially destabilized transition state due to the repulsive interaction of the C(3) methyl group with the C(6) alkyl group in **2.191A** and **2.191B**. Consistent with these results, the tandem allylic oxidation/oxa-conjugate addition reaction [18] (MnO_2, CH_2Cl_2, 0 °C, 4 h) of the (*Z*)-allyl alcohol **2.196** afforded α,β-unsaturated aldehyde **2.191** as the major product (70 %) along with a mixture of 2,3-*cis*-2,6-*cis*- and 2,3-*trans*-2,6-*trans* tetrahydropyrans (12 %, dr = 1:1).

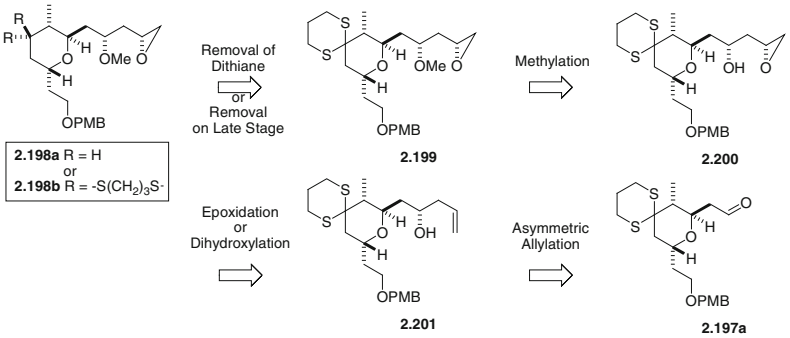
Table 2.6 Organocatalytic oxa-conjugate addition reaction for the stereoselective synthesis of 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.197a**



Entry	Amine	Temp (°C)	Time (h)	Yield[a] (%)	dr[b]
1	pyrrolidine	25	1	98	**2.197b** only
2	pyrrolidine	−40	5	94	7:1
3	piperidine	25	1	98	**2.197b** only
4	piperidine	−40	24	96	10:1
5	(*S*)-**2.43**	0	3	96	6:1
6	(*S*)-**2.43**	−20	6.5	97	10:1
7	(*S*)-**2.43**	**−40**	**13**	**98**	**>20:1**
8	(*R*)-**2.43**	0	3	95	1.5:1

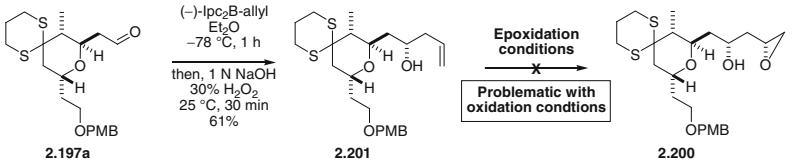
[a] Combined yield of the isolated **2.197a** and **2.197b**
[b] The diastereomeric ratio (**2.197a**:**2.197b**) was determined by integration of the ^{1}H NMR of the crude product

With α,β-unsaturated aldehyde **2.191** in hand, we attempted the organocatalytic oxa-conjugate addition reaction (Table 2.6). The organocatalytic oxa-conjugate addition reaction of **2.191** in the presence of pyrrolidine or piperidine at 25 °C exclusively provided 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.197b** (entries 1 and 3). However, when the reaction was attempted at –40 °C, the desired 2,3-*trans*-2,6-*trans* tetrahydropyran **2.197a** was obtained as the major diastereomer (dr = 7–10:1, entries 2 and 4). After further optimization of the reaction conditions, we successfully prepared **2.197a** in the presence of (*S*)-**2.43** [57, 58] with excellent stereoselectivity and yield (dr >20:1, 98 %, entry 7). These results were practically identical to those from our model studies shown in Table 2.2.



Scheme 2.40 Initial strategy for the synthesis of epoxide **2.198**

Having secured a successful route to the key 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.197a**, we turned our attention to the stereoselective synthesis of epoxide **2.198** for our second dithiane coupling reaction (Scheme 2.40). We initially anticipated that the high reactivity of the 1,3-dithiane group under oxidation conditions would be an obstacle to the direct installation of the epoxide group. We also envisioned that the 1,3-dithiane moiety would be needed to retain until either the successful preparation of epoxide **2.198** or the late stage macrolactonization to shorten synthetic steps and increase efficiency of the synthetic route. Thus, we decided to attempt the direct epoxidation in the presence of 1,3-dithiane. The epoxide would arise from the homoallyl alcohol **2.201** via asymmetric epoxidation or dihydroxylation. Homoallyl alcohol **2.201** could be introduced from the 2,3-*trans*-2,6-*trans*-tetrahydropyran aldehyde **2.197a** through asymmetric allylation.

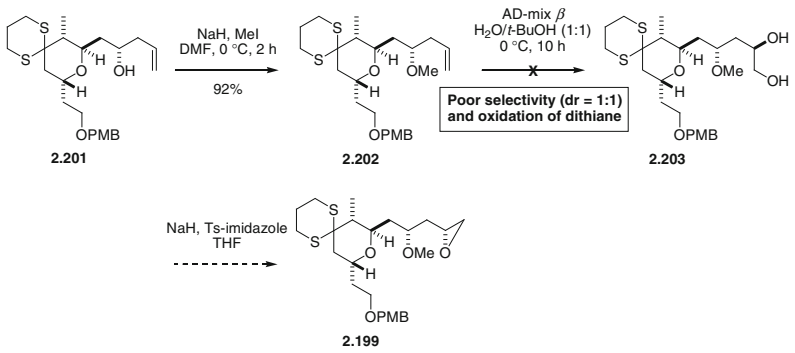


entry	conditions	results
1	$Ti(O^iPr)_4$, (–)-DET, TBHP, 3Å MS, CH_2Cl_2, –20 °C	No epoxide, oxidation of 1,3-dithiane and decomposition
2	$VO(acac)_2$, TBHP, CH_2Cl_2, 0 to 25 °C	No epoxide, oxidation of 1,3-dithiane and decomposition
3	*m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25 °C	No stereoselectivity (dr = 1:1) and loss of PMB group

Scheme 2.41 Attempts for direct epoxidation

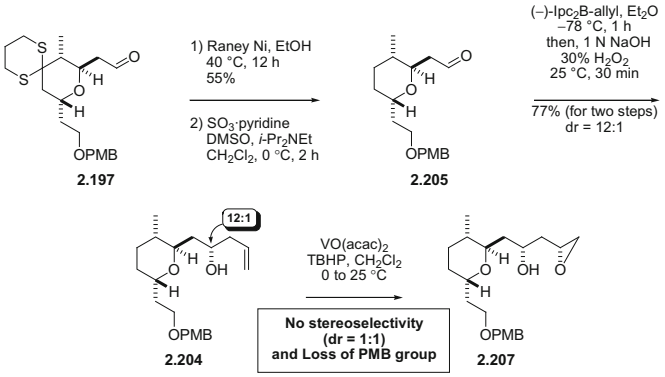
Initial attempts to convert the 2,3-*trans*-2,6-*trans*-tetrahydropyran aldehyde **2.197a** to the epoxide **2.198** through asymmetric allylation and subsequent epoxidation were made (Scheme 2.41). Towards this end, aldehyde **2.198** was transformed to the homoallyl alcohol **2.201** via Brown asymmetric allylation [95], was in turn exposed to a variety of epoxidation conditions, including Sharpless asymmetric epoxidation [146] as well as achiral reagents such as $VO(acac)_2$/*t*-BuOOH [147, 148] and *m*-CPBA. Unfortunately, all attempts were not effective for the installation of the epoxide. Instead, the former two reactions yielded three side products which were the results of the oxidation of the 1,3-dithiane moiety under oxidation reaction conditions. The latter resulted in the epoxide, but the poor diastereoselectivity (dr = 1:1) as well as significant loss of the PMB group were observed.

Next, dihydroxylation of homoallyl alcohol **2.201** was examined for the installation of the stereoselective epoxide (Scheme 2.42). The hydroxyl in **2.201** was protected as the methyl ether **2.202**, which was subsequently subjected to Sharpless asymmetric dihydroxylation reaction [149] conditions to afford **2.203**, however, no diastereoselectivity was observed and the reaction resulted in the oxidation of the dithiane group under such oxidation reaction conditions.



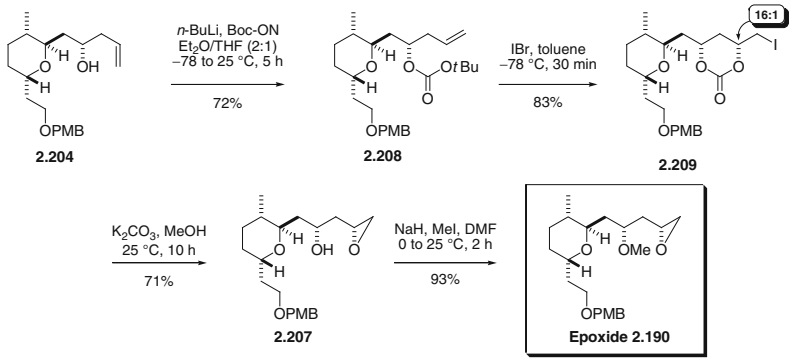
Scheme 2.42 Attempts for asymmetric dihydroxylation

As predicted, all our efforts to stereoselectively prepare epoxide **2.198** in the presence of the dithiane group failed to furnish the desired product under a variety of oxidation conditions. Considering the high reactivity of the 1,3-dithiane group under oxidation conditions, we decided to remove the dithiane group prior to installation of the epoxide group.



Scheme 2.43 Attempt for the synthesis of epoxide **2.207** without 1,3-dithiane

With this strategy in mind, the dithiane **2.197** underwent desulfurization upon treatment with Raney Ni giving the alcohol, followed by Parikh–Doering oxidation [39] and subsequent Brown asymmetric allylation [95] to furnish homoallyl alcohol **2.204** (77 % over two step, dr = 12:1). With the resulting homoallyl alcohol possessing no dithiane functionality, we first examined the direct epoxidation. Direct epoxidation of **2.204** ($VO(acac)_2$, TBHP, CH_2Cl_2, 0–25 °C) provided epoxide **2.207**, but in no stereoselectivity (dr = 1:1), and concomitant deprotection of the PMB group was observed (Scheme 2.43).



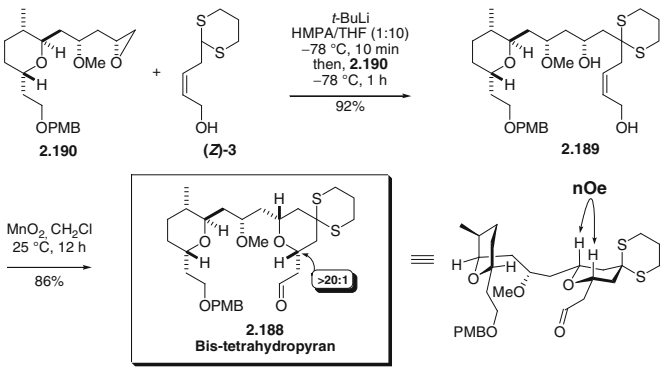
Scheme 2.44 Synthesis of epoxide **2.190** via iodocyclization

After an extensive investigation of epoxidation conditions, we adopted the diastereoselective IBr-induced electophilic cyclization of a homoallylic carbonate to set the 1,3-*syn*-diol system previously developed by Bartlett and Cardillo [150–153] (Scheme 2.44). To this end, Boc protection of homoallyl alcohol **2.204** to yield carbonate **2.208** which was followed by iodocyclization to afford cyclic carbonate **2.209** in 83 % yield with good stereoselectivity, favoring the desired *syn*

relationship (dr = 16:1). Methanolysis of **2.209** afforded the desired 4-hydroxy epoxide **2.207** (71 %) and subsequent protection of the hydroxyl in **2.207** as the methyl ether to furnish **2.190** in 93 % yield.

2.3.2.5 Synthesis of Bis-Tetrahydropyran

Having achieved the critical epoxide **2.190**, we turned our attention to the construction of the 2,6-*cis*-tetrahydropyran. Towards this end, the coupling of **2.190** and (*Z*)-**3** [18] proceeded smoothly to set the stage for the key tandem allylic oxidation/oxa-conjugate addition reaction. The tandem allylic oxidation/oxa-conjugate addition reaction of **2.189** (MnO_2, CH_2Cl_2, 25 °C, 12 h) stereoselectively provided the desired 2,6-*cis*-tetrahydropyran aldehyde **2.188** (86 %, dr >20:1). The relative stereochemistry of **2.188** was determined to be *cis* by extensive 2D NMR studies (Scheme 2.45).

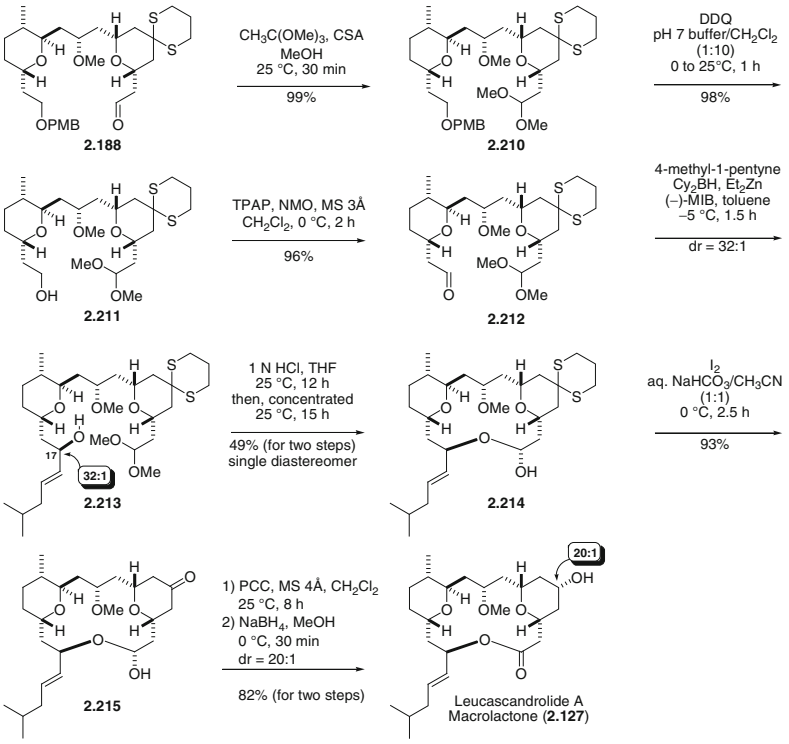


Scheme 2.45 Synthesis of bis-tetrahydropyran **2.188**

2.3.2.6 Completion of Formal Synthesis of (+)-Leucascandrolide A

Having secured a successful route to the preparation of the bis-tetrahydropyran units in leucascandrolide A (**2.60**), we embarked on the final stage of the synthesis of **2.60** (Scheme 2.46). As discussed in the retrosynthetic analysis, the remaining key issues of this synthesis involved the stereoselective installation of the (*E*)-4-methyl-pent-1-enyl appendage at C(17). Although much efforts has been documented to stereoselectively prepare the C(17) appendage by employing the direct addition of the various vinyl groups to aldehydes, stereoselectivities were all low to modest (dr = 1–6:1) [74, 75, 77, 79, 83, 87, 88]. In our search for the high degree of stereoselectivity involving the direct vinylation, (–)-MIB-catalyzed asymmetric vinylation reaction previously illustrated by Walsh and co-workers was chosen because of the great utility of the reaction in this field [154–158].

Toward this end, aldehyde **2.188** was protected as the acetal, which was followed by oxidative removal of PMB group and subsequent TPAP oxidation of resulting alcohol to deliver the aldehyde **2.212**. Gratifyingly, the subjection of **2.212** to the (–)-MIB-catalyzed asymmetric vinylation reaction (4-methyl-1-pentyne, Cy_2BH, Et_2Zn, (–)-MIB, toluene, –5 °C, 1.5 h) afforded the desired (17*R*)-alcohol **2.213** with excellent stereoselectivity (dr = 32:1) as determined by HPLC.



Scheme 2.46 Completion of the formal synthesis of (+)-leucascandrolide A (**2.60**)

Having achieved the successful installation of the C(17) appendage, we next turned to elaboration of the macrocyclization. Removal of the acetal of **2.213** under acidic conditions provided the corresponding hydroxy aldehyde which was then spontaneously transformed into macrolactol as previously observed by Kozmin and co-workers [76] in 49 % over two steps from **2.212**. At this point, we were well aware that oxidation of **2.214** to convert to the lactone in the presence of dithiane group would be problematic due to possible oxidation of the dithiane group. Thus, the removal of dithiane preceded the oxidation. Toward this end, deprotection of the dithiane group in **2.214**, in turn conversion of lactol to lactone by PCC oxidation, and $NaBH_4$ reduction of the ketone accomplished the synthesis of (+)-leucascandrolide A macrolactone (**2.127**), constituting a formal synthesis of (+)-leucascandrolide A (**2.60**).

2.3.2.7 Conclusion

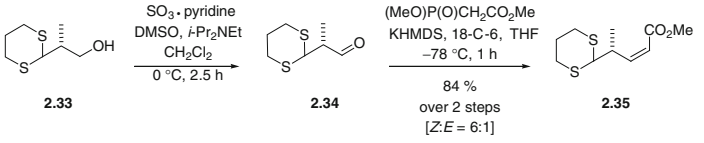
As described above, the formal synthesis of (+)-leucascandrolide A (**2.60**) has been accomplished by exploiting the oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect. We demonstrated that both the 2,6-*cis*- and 3-methyl-2,3-*trans*-2,6-*trans*-tetrahydropyrans embedded in leucascandrolide A can be assembled through the tandem and organocatalytic oxa-conjugate addition reactions with excellent stereoselectivity. Another special feature of the leucascandrolide synthesis is the highly efficient asymmetric vinylation by utilizing (–)-MIB-catalysis for the stereoselective installation of the C(17) stereocenter. We expect that the oxa-conjugate addition reaction promoted by the *gem*-disubstituent effect in conjunction with the dithiane coupling reaction would establish facile routes for the stereoselective synthesis of a diverse set of tetrahydropyrans and be applicable to the efficient and concise synthesis of complex natural products with interesting biological activities.

2.3.2.8 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed on SiO_2 (60 Å) with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel 60 (particle size 4063 μm. 230400 mesh). ^{1}H NMR, ^{13}C NMR, and 2D NMR (COSY, NOESY) spectra were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in $CDCl_3$ by using the signal of residual $CHCl_3$, as an internal standard. All NMR δ values are given in ppm, and all J values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo-Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1 W) polarimeter.

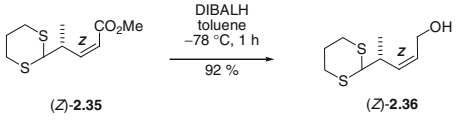
Preparation of Enoates



2.33 **2.34** **2.35**

[**Oxidation**] To a cooled (0 °C) solution of known alcohol **2.33** [241] (1.750 g, 9.83 mmol) in CH_2Cl_2 (110 mL, 0.089 M) were added DMSO (2.79 mL, 39.31 mmol), *i*-Pr_2NEt (3.42 mL, 19.66 mmol), and SO_3·pyridine (3.128 g, 19.66 mmol). After stirring at the same temperature for 2.5 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude aldehyde **2.34** was employed in next step without further purification. [**Horner–Wadsworth–Emmons Olefination**] To a cooled (–78 °C) solution of trimethyl phosphonoacetate (2.83 mL, 19.66 mmol) and 18-Crown-6 (5.197 g, 19.66 mmol) in THF (400 mL, 0.024 M) was added dropwise KHMDS (31.45 mL, 0.5 M in toluene, 15.73 mmol) and the resulting mixture was stirred for 10 min before the above aldehyde **2.34** was added. After stirring at –78 °C for 40 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 20/1) to afford enoates (*Z*)-**2.35** (1.660 g, 73 %) and (*E*)-**2.35** (0.265 g, 12 %) as colorless oils. [**For (*Z*)-2.35**] $[\alpha]^{25}_D$= –35.6 (*c* 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21–6.28 (m, 1H), 5.83 (dd, J = 8.5, 1.0 Hz, 1H), 3.99–4.06 (m, 2H), 3.72 (s, 3H), 2.80–2.92 (m, 4H), 2.04–2.12 (m, 1H), 1.82–1.92 (m, 1H), 1.23 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 150.6, 118.9, 52.4, 50.6, 36.6, 29.4, 25.4, 17.4; IR (neat) 2361, 1715, 1641, 1434, 1197, 871 cm^{-1}; HRMS (ESI) *m/z* 233.0671 $[(M+H)^+$, $C_{10}H_{16}O_2S_2$ requires 233.0670]. [**For (*E*)-2.35**] $[\alpha]^{25}_D$= +36.8 (*c* 0.63, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (ddd, J = 15.6, 8.0, 1.0 Hz, 1H), 5.88 (dd, J = 15.6, 1.2 Hz, 1H), 4.11 (d, J = 6.0 Hz, 1H), 3.73 (s, 3H), 2.78–2.92 (m, 4H), 2.73 (dddd, J = 13.2, 6.4, 6.4, 6.4 Hz, 1H), 2.04–2.16 (m, 1H), 1.78–1.90 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 149.5, 121.4, 52.8, 51.4, 41.3, 30.48, 30.40, 25.6, 16.9; IR (neat) 2360, 1715, 1433, 1270, 1172, 978 cm^{-1}; HRMS (ESI) *m/z* 233.0664 $[(M+H)^+$, $C_{10}H_{16}O_2S_2$ requires 233.0664].

Preparation of Allyl Alcohol (*Z*)-2.36

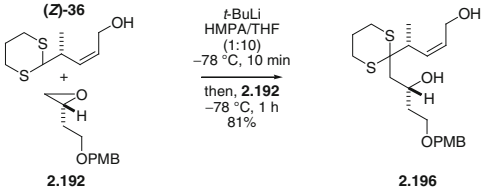


(*Z*)-**2.35** (*Z*)-**2.36**

To a cooled (–78 °C) solution of (*Z*)-**2.35** (420 mg, 1.81 mmol) in toluene (20 mL, 0.09 M) was added DIBAL-H (4.52 mL, 1.0 M in toluene, 4.52 mmol). After stirring at the same temperature for 1 h, the reaction mixture was quenched with MeOH followed by aqueous Rochelle's salt solution and diluted with Et_2O.

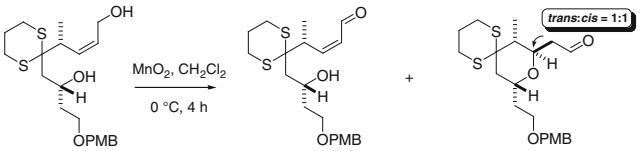
The resulting mixture was stirred for 5 h at 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1 to 1/2) to afford the allyl alcohol (*Z*)-**2.36** (341 mg, 92 %) as a colorless oil: $[\alpha]^{25}{}_D$= –10.4 (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (ddd, J = 11.0, 7.0, 7.0 Hz, 1H), 5.46 (dd, J = 11.0, 11.0 Hz, 1H), 4.22 (dd, J = 12.5, 7.0 Hz, 1H), 4.14 (dd, J = 12.5, 7.0 Hz, 1H), 3.99 (d, J = 6.5 Hz, 1H), 2.77–2.90 (m, 5H), 2.04–2.11 (m, 1H), 1.76–1.87 (m, 1H), 1.73 (br s, 1H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 129.5, 58.0, 53.6, 36.7, 30.29, 30.16, 25.6, 18.5; IR (neat) 3349, 1421, 1275, 985, 907, 736 cm^{-1}; HRMS (ESI) *m/z* 205.0717 [$(M+H)^+$, $C_9H_{16}OS_2$ requires 205.0715].

Preparation of Diol 2.196



To a cooled (–78 °C) solution of dithiane (*Z*)-**36** (1.126 g, 5.510 mmol) in HMPA/THF (1:10, 110 mL) was added dropwise *t*-BuLi (9.73 mL, 1.7 M in pentane, 16.530 mmol). The resulting mixture was stirred for 10 min before the known epoxide **2.192** (1.357 g, 8.265 mmol) was added. After stirring at –78 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to 1/1) to afford diol **2.196** (1.841 g, 81 %) as a colorless oil: $[\alpha]^{25}{}_D$= +17.0 (*c* 0.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2 H), 5.70–5.80 (m, 2H), 4.45 (s, 2H), 4.29 (dd, J = 13.0, 8.5 Hz, 1H), 4.19–4.23 (m, 1H), 4.00–4.03 (m, 1H), 3.80 (s, 3H), 3.71 (br s, 1H), 3.59–3.68 (m, 2H), 3.25 (dddd, J = 9.5, 7.0, 7.0, 7.0 Hz, 1H), 2.97 (ddd, J = 14.0, 11.0, 3.0 Hz, 1H), 2.87 (ddd, J = 14.0, 10.5, 3.0 Hz, 1H), 2.70–2.76 (m, 2H), 2.43 (br s, 1H), 2.31 (dd, J = 15.5, 8.5 Hz, 1H), 2.19 (dd, J = 15.0, 2.5 Hz, 1H), 1.98–2.05 (m, 1H), 1.80–1.91 (m, 2H), 1.71–1.79 (m, 1H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 132.9, 129.9, 129.16, 129.02, 113.6, 72.6, 67.6, 67.3, 57.8, 56.6, 55.1, 42.4, 38.8, 37.6, 25.9, 24.7, 16.6; IR (neat) 3398, 1611, 1512, 1440, 1301, 1220, 1088, 1032, 820 cm^{-1}; HRMS (ESI) *m/z* 411.1654 [$(M–H)^+$, $C_{21}H_{32}O_4S_2$ requires 411.1658].

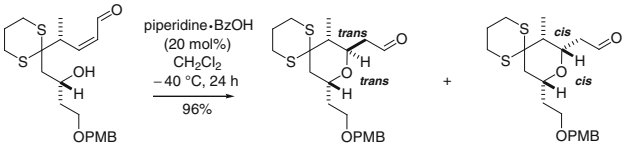
Preparation of α,β-Unsaturated Aldehyde 2.191



2.196 **2.191** (70%) **2.197** (12%)

To a solution of diol **2.196** (1.460 g, 3.54 mmol) in CH_2Cl_2 (50.0 mL, 0.071 M) was added MnO_2 (1.539 g, 17.69 mmol), and the resulting mixture was stirred for 1 h at 0 °C. An addition of MnO_2 (1.539 g, 17.69 mmol) was repeated two times every 30 min. When diol **2.196** was completely consumed, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford α,β-unsaturated aldehyde **2.191** (1.014 g, 70 %) along with a 1:1 mixture (0.169 g, 12 %) of tetrahydropyrans **2.197** as colorless oils: [**For Aldehyde 2.191**] $[\alpha]^{25}_D$= +24.3 (*c* 2.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (d, J = 7.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 6.84–6.90 (m, 3H), 6.01 (ddd, J = 11.5, 7.5, 1.0 Hz, 1H), 4.45 (s, 2H), 4.21–4.26 (m, 1H), 4.00 (dddd, J = 11.5, 7.0, 7.0, 7.0 Hz, 1H), 3.80 (s, 3H), 3.60–3.68 (m, 2H), 3.56 (d, J = 2.0 Hz, 1H), 2.96 (ddd, J = 14.0, 10.0, 3.0 Hz, 1H), 2.87 (ddd, J = 14.0, 9.5, 3.0 Hz, 1H), 2.77 (dddd, J = 21.5, 14.0, 6.5, 3.0 Hz, 2H), 2.30 (dd, J = 15.5, 9.0 Hz, 1H), 2.11 (dd, J = 15.5, 1.5 Hz, 1H), 1.97–2.05 (m, 1H), 1.81–1.94 (m, 2H), 1.70–1.77 (m, 1H), 1.25 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 159.0, 152.0, 130.0, 129.1, 113.6, 72.6, 67.3, 66.9, 55.4, 55.0, 42.2, 38.8, 37.5, 26.1, 25.5, 24.4, 16.3; IR (neat) 3433, 1671, 1512, 1245, 1086, 1031, 819 cm^{-1}; HRMS (ESI) *m/z* 411.1653 [$(M+H)^+$, $C_{21}H_{30}O_4S_2$ requires 411.1658].

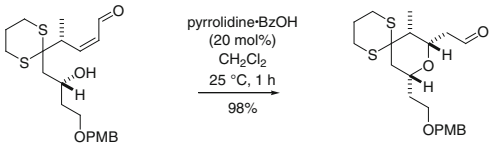
Representative Procedure for the Secondary Amine-Catalyzed Oxa-Conjugate Addition Reaction



2.191 **2.197a** [10:1] **2.197b**

To a cooled (–40 °C) solution of aldehyde **2.191** (29.0 mg, 0.071 mmol) in CH_2Cl_2 (3.0 mL, 0.024 M) was added dropwise a mixture of piperidine·BzOH (0.26 mL, 0.055 M in CH_2Cl_2). After stirring at –40 °C for 24 h, the reaction mixture was diluted with hexanes (30.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford a 10:1 mixture

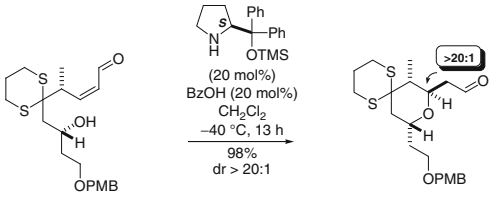
of 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.197a** and 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.197b** in 96 % yield as colorless oils: [**For 2,3-*trans*-2,6-*trans*-Tetrahydropyran 2.197a**]: $[\alpha]^{25}_{D}$= +11.6 (*c* 0.67, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (dd, J = 3.0, 1.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.41 (AB, $\Delta\upsilon$ = 15.0 Hz, J_{AB} = 11.5 Hz, 2H), 4.25 (ddd, J = 10.5, 7.0, 4.0 Hz, 1H), 4.11 (dddd, J = 9.5, 4.5, 4.5, 4.5 Hz, 1H), 3.80 (s, 3H), 3.45–3.53 (m, 2H), 3.01 (ddd, J = 14.5, 11.0, 3.0 Hz, 1H), 2.88 (ddd, J = 14.5, 11.0, 3.5 Hz, 1H), 2.81 (ddd, J = 13.0, 9.0, 3.0 Hz, 1H), 2.68–2.76 (m, 3H), 2.41 (dd, J = 14.5, 6.0 Hz, 1H), 2.21–2.29 (m, 2H), 1.92–2.04 (m, 2H), 1.80–1.91 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 159.1, 130.5, 129.4, 113.7, 72.8, 69.7, 67.8, 66.8, 55.3, 52.4, 47.6, 42.6, 39.5, 33.5, 26.2, 25.7, 25.2, 14.6; IR (neat) 1721, 1611, 1511, 1244, 1100, 1031, 818 cm^{-1}; HRMS (FAB) *m/z* 411.1658 [$(M+H)^+$, $C_{21}H_{30}O_4S_2$ requires 411.1658]. [**For 2,3-*cis*-2,6-*cis*-Tetrahydropyran 2.197b**]: $[\alpha]^{25}_{D}$= – 15.7 (*c* 0.76, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.69 (dd, J = 2.0, 2.0 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 4.78 (ddd, J = 9.5, 3.5, 2.0 Hz, 1H), 4.40 (AB, $\Delta\upsilon$ = 20.0 Hz, J_{AB} = 12.0 Hz, 2H), 3.97–4.04 (m, 1H), 3.80 (s, 3H), 3.48–3.52 (m, 2H), 2.80–2.90 (m, 2H), 2.70–2.79 (m, 2H), 2.60 (ddd, J = 16.5, 9.5, 2.5 Hz, 1H), 2.28 (ddd, J = 16.5, 4.0, 2.0 Hz, 1H), 2.07 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H), 1.91–2.05 (m, 3H), 1.65–1.77 (m, 3H), 1.10 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 159.1, 130.4, 129.3, 113.7, 72.7, 70.3, 70.1, 65.9, 55.2, 53.5, 47.4, 38.43, 38.22, 35.8, 26.0, 25.38, 25.21, 9.0; IR (neat) 1724, 1612, 1512, 1246, 1089, 1032, 819 cm^{-1}; HRMS (ESI) *m/z* 433.1479 [$(M+Na)^+$, $C_{21}H_{30}O_4S_2$ requires 433.1478].



2.191 **2.197b**

To a solution of aldehyde **2.191** (32.3 mg, 0.078 mmol) in CH_2Cl_2 (3.0 mL, 0.026 M) was added dropwise a mixture of pyrrolidine·BzOH (0.28 mL, 0.054 M in CH_2Cl_2) at 25 °C. After stirring at 25 °C for 1 h, the reaction mixture was diluted with hexanes (30.0 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*cis*-2,6-*cis*-tetrahydropyran **2.197b** (31.6 mg, 98 %) as a colorless oil.

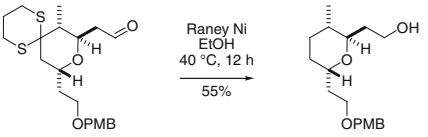
Organocatalytic Oxa-Conjugate Addition Reaction for the Synthesis of 2,3-*trans*-2,6-*trans*-Tetrahydropyran 2.197a



2.191 **2.197a**

To a cooled (–40 °C) solution of aldehyde **2.191** (965 mg, 2.35 mmol) in CH_2Cl_2 (50.0 mL, 0.047 M) was added dropwise a mixture of (*S*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether (*S*)-**2.43**(153 mg, 0.47 mmol) and BzOH (57 mg, 0.47 mmol) in CH_2Cl_2 (2 mL). After stirring at –40 °C for 13 h, the reaction mixture was diluted with hexanes (150.0 mL), and filtered through a short pad of silica gel (hexanes/EtOAc, 3/1) and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford 2,3-*trans*-2,6-*trans*-tetrahydropyran **2.197a** (946 mg, 98 %) as a colorless oil.

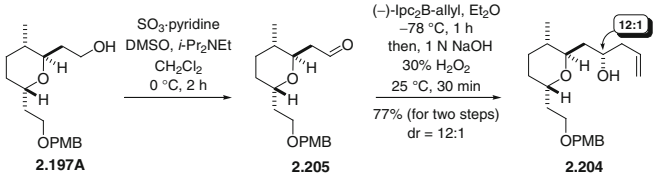
Preparation of Alcohol 2.197A



2.197a **2.197A**

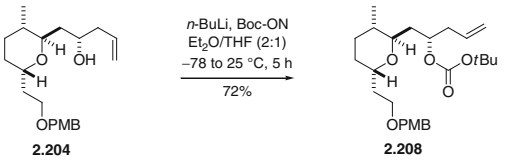
To a stirred solution of aldehyde **2.197a** (851.5 mg, 2.07 mmol) in EtOH (25.0 mL) was added freshly prepared Raney 2400 Ni (~13 g) in EtOH (5.0 mL) at 25 °C. After stirring at 40 °C for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford alcohol **2.197A** (354.3 mg, 55 %) as a colorless oil: $[\alpha]^{25}_{D}$= +47.5 (*c* 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.44 (AB, $\Delta\upsilon$ = 17.5 Hz, J_{AB} = 11.5 Hz, 2H), 4.03–4.08 (m, 1H), 3.80 (s, 3H), 3.67–3.79 (m, 2H), 3.53 (dd, J = 7.0, 5.5 Hz, 2H), 3.44 (ddd, J = 9.0, 9.0, 2.5 Hz, 1H), 3.01 (dd, J = 8.0, 4.0 Hz, 1H), 2.16 (dddd, J = 14.0, 10.0, 5.5, 5.5 Hz, 1H), 1.76–1.84 (m, 2H), 1.66–1.72 (m, 1H), 1.56–1.66 (m, 2H), 1.40–1.50 (m, 2H), 1.29–1.37 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 130.3, 129.3, 113.7, 76.0, 72.7, 69.4, 67.0, 61.3, 55.2, 34.79, 34.64, 30.8, 28.4, 26.9, 18.0; IR (neat) 3439, 1513, 1457, 1247, 1090, 1035, 820 cm^{-1}; HRMS (FAB) *m/z* 309.2059 [(M+H)$^+$, $C_{18}H_{28}O_4$ requires 309.2060].

Preparation of Homoallyl Alcohol 2.204



[**Oxidation**] To a cooled (0 °C) solution of alcohol **2.197A** (480.0 mg, 1.56 mmol) in CH_2Cl_2 (25.0 mL, 0.062 M) were added DMSO (0.44 mL, 6.23 mmol), *i*-Pr_2NEt (0.54 mL, 3.11 mmol), and SO_3·pyridine (495.3 mg, 3.11 mmol). After stirring at 0 °C for 2 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude aldehyde **2.205** was employed in next step without further purification. [**Brown Allylation**] To a cooled (–78 °C) solution of (–)-$Ipc_2B(OMe)$ (984.5 mg, 3.11 mmol) in Et_2O (40.0 mL, 0.08 M) was added dropwise allylmagnesium bromide (3.11 ml, 3.11 mmol, 1.0 M in Et_2O). The reaction mixture was stirred for 15 min at –78 °C and for 1 h at 25 °C. The reaction mixture was recooled to –78 °C, and a solution of **2.205** in Et_2O (2 mL) was added dropwise. After stirring at –78 °C for 1 h, the resulting mixture was quenched with 1 N NaOH/30 % H_2O_2 (1:1, total 20 mL). The resulting mixture was stirred for 30 min at 25 °C, and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1 to 3/1) to afford homoallyl alcohol **2.204** (418.5 mg, 77 %) as a colorless oil: $[\alpha]^{25}{}_D$= +45.5 (*c* 1.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.82 (dddd, J = 16.8, 10.4, 7.2, 7.2 Hz, 1H), 5.05–5.12 (m, 2H), 4.44(AB, $\Delta\upsilon$ = 14.8 Hz, J_{AB} = 11.6 Hz, 2H), 4.00–4.06 (m, 1H), 3.86–3.92 (m, 1H), 3.80 (s, 3H), 3.50–3.56 (m, 3H), 3.07 (d, J = 3.6 Hz, 1H), 2.12–2.29 (m, 3H), 1.74–1.84 (m, 1H), 1.55–1.70 (m, 4H), 1.41–1.51 (m, 2H), 1.28–1.39 (m, 1H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.1, 130.3, 129.2, 117.0, 113.6, 72.71, 72.63, 69.8, 67.23, 67.17, 55.1, 42.0, 38.3, 34.2, 30.7, 28.6, 27.0, 18.0; IR (neat) 3438, 1612, 1512, 1363, 1245, 1033, 819 cm^{-1}; HRMS (FAB) *m/z* 349.2372 [$(M+H)^+$, $C_{21}H_{32}O_4$ requires 349.2373].

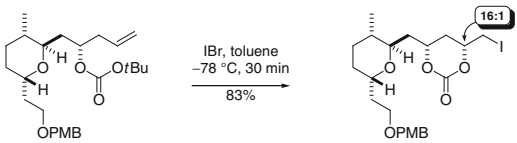
Preparation of *tert*-Butyl Carbonate 2.208



2.204 **2.208**

To a cooled (–78 °C) solution of alcohol **2.204** (103.1 mg, 0.30 mmol) in Et_2O (6.0 mL, 0.05 M) was added dropwise *n*-BuLi (0.14 mL, 0.35 mmol, 2.5 M in hexanes). After stirring for 30 min at the same temperature, the cold reaction mixture was quickly transferred to a solution of Boc-ON (145.3 mg, 0.59 mmol) in THF (3.0 mL) at 0 °C via cannular. After stirring at 25 °C for 5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 8/1) to afford carbonate **2.208** (95.2 mg, 72 %) as a colorless oil: $[\alpha]^{25}{}_D$= +67.9 (*c* 2.45, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, J = 9.0 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.77 (dddd, J = 17.0, 10.0, 7.5, 7.5 Hz, 1H), 5.03–5.11 (m, 2H), 4.91–4.97 (m, 1H), 4.45 (AB, $\Delta\upsilon$ = 31.0 Hz, J_{AB} = 11.0 Hz, 2H), 3.96 (dddd, J = 9.0, 4.5, 4.5, 4.5 Hz, 1H), 3.79 (s, 3H), 3.48–3.57 (m, 2H), 3.36 (ddd, J = 10.0, 7.0, 2.0 Hz, 1H), 2.37 (dd, J = 9.0, 9.0 Hz, 2H), 2.00 (dddd, J = 16.5, 11.5, 6.5, 6.5 Hz, 1H), 1.79 (ddd, J = 18.5, 7.5, 3.0, 1H), 1.58–1.74 (m, 4H), 1.48 (s, 9H), 1.42–1.48 (m, 1H), 1.32–1.37 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 153.1, 133.6, 130.8, 129.3, 117.8, 113.7, 81.5, 73.1, 72.7, 71.8, 68.5, 66.9, 55.2, 39.7, 36.9, 34.3, 32.0, 28.2, 27.8, 26.8, 18.2; IR (neat) 1734, 1514, 1367, 1276, 1169, 1094 cm^{-1}; HRMS (FAB) *m/z* 466.3165 [(M+NH_4)$^+$, $C_{26}H_{40}O_6$ requires 466.3163].

Preparation of Cyclic Carbonate 2.209

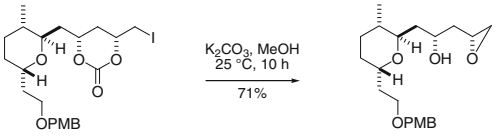


2.208 **2.209**

To a cooled (–78 °C) solution of *tert*-butyl carbonate **2.208** (184.3 mg, 0.41 mmol) in toluene (10.0 mL, 0.041 M) was added dropwise IBr (0.62 mL, 0.62 mmol, 1.0 M in CH_2Cl_2) via syringe. After stirring for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$

and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1/1) to afford cyclic carbonate **2.209** (176.8 mg, 83 %) as a colorless oil: $[\alpha]^{25}_D$= +68.8 (*c* 1.77, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.51–4.58 (m, 1H), 4.46 (AB, $\Delta\upsilon$ = 55.0 Hz, J_{AB} = 11.5 Hz, 2H), 4.19–4.25 (m, 1H), 4.06–4.12 (m, 1H), 3.83 (s, 3H), 3.46–3.58 (m, 3H), 3.34 (dd, J = 10.5, 4.5 Hz, 1H), 3.23 (dd, J = 10.5, 7.0 Hz, 1H), 2.27 (ddd, J = 14.5, 3.0, 3.0 Hz, 1H), 2.15 (dddd, J = 15.0, 10.0, 5.0, 5.0 Hz, 1H), 1.92 (ddd, J = 14.0, 9.5, 2.0 Hz, 1H), 1.77–1.85 (m, 1H), 1.59–1.68 (m, 4H), 1.49–1.54 (m, 1H), 1.29–1.43 (m, 2H), 0.90 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 148.3, 130.7, 129.2, 113.7, 76.9, 75.0, 72.5, 70.1, 68.9, 66.4, 55.3, 39.1, 35.2, 34.0, 30.8, 28.5, 27.0, 17.9, 5.5; IR (neat) 3301, 1742, 1611, 1512, 1243, 1175, 1091, 1031, 818, 762 cm^{-1}; HRMS (FAB) *m/z* 536.1510 [(M+NH_4)$^+$, $C_{22}H_{31}IO_6$ requires 536.1504].

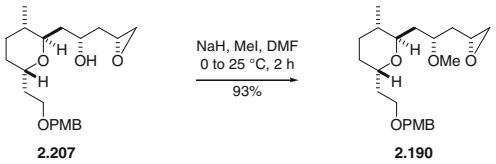
Preparation of Epoxide 2.207



2.209 **2.207**

To a stirred solution of iodo carbonate **2.209** (228.1 mg, 0.44 mmol) in MeOH (10.0 mL, 0.044 M) was added potassium carbonate (182 mg, 1.32 mmol) at 25 °C. After stirring at 25 °C for 10 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford epoxide **2.207** (114.2 mg, 71 %) as a colorless oil: $[\alpha]^{25}_D$= +42.9 (*c* 0.58, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.41 (AB, $\Delta\upsilon$ = 14.0 Hz, J_{AB} = 11.5 Hz, 2H), 4.01–4.10 (m, 2H), 3.79 (s, 3H), 3.50–3.55 (m, 3H), 3.40 (d, J = 3.5 Hz, 1H), 3.04–3.09 (m, 1H), 2.75 (dd, J = 4.5, 4.0 Hz, 1H), 2.48 (dd, J = 5.0, 2.0 Hz, 1H), 2.18 (dddd, J = 18.5, 12.0, 7.5, 7.5 Hz, 1H), 1.76–1.84 (m, 1H), 1.68–1.75 (m, 2H), 1.54–1.67 (m, 4H), 1.43–1.52 (m, 2H), 1.29–1.38 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.3, 129.3, 113.7, 72.71, 72.62, 70.3, 67.4, 66.1, 55.2, 50.1, 46.7, 39.9, 39.1, 34.4, 30.6, 28.8, 27.2, 18.0; IR (neat) 3432, 1612, 1512, 1246, 1089, 1033, 820 cm^{-1}; HRMS (FAB) *m/z* 365.2322 [(M+H)$^+$, $C_{21}H_{32}O_5$ requires 365.2323].

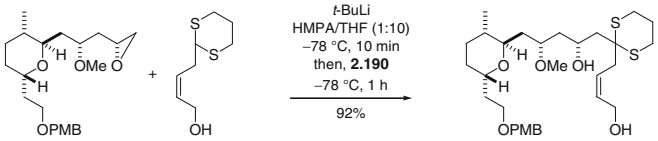
Preparation of Methyl Ether 2.190



2.207 **2.190**

To a stirred solution of alcohol **2.207** (142.5 mg, 0.39 mmol) in DMF (5.0 mL, 0.078 M) were added NaH (28 mg, 1.17 mmol) and MeI (0.05 mL, 0.78 mmol) at 0 °C. After stirring for 2 h at 25 °C, reaction mixture was quenched with saturated aqueous NH_4Cl and H_2O, and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford methyl ether **2.190** (137.4 mg, 93 %) as a colorless oil: $[\alpha]^{25}{}_D$= +63.5 (*c* 1.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.45 (s, 2H), 3.96 (dddd, J = 9.2, 4.8, 4.8, 4.8 Hz, 1H), 3.80 (s, 3H), 3.47–3.62 (m, 4H), 3.31 (s, 3H), 2.95 (m, 1H), 2.76 (dd, J = 5.2, 5.2 Hz, 1H), 2.46 (dd, J = 5.2, 2.8 Hz, 1H), 2.06 (dddd, J = 14.4, 8.4, 6.0, 6.0 Hz, 1H), 1.57–1.80 (m, 7H), 1.45–1.52 (m, 1H), 1.30–1.41 (m, 2H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 130.5, 129.1, 113.7, 74.9, 72.7, 71.9, 68.3, 66.9, 56.7, 55.2, 49.0, 46.7, 38.3, 36.3, 34.3, 32.0, 28.2, 26.7, 18.3; IR (neat) 1612, 1512, 1365, 1245, 1087, 1034, 820 cm^{-1}; HRMS (FAB) *m/z* 379.2477 [(M+H)$^+$, $C_{21}H_{34}O_5$ requires 379.2479].

Preparation of Diol 2.189

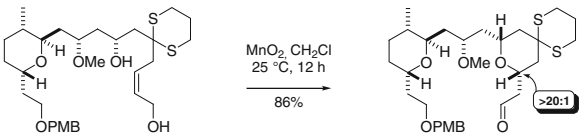


2.190 (*Z*)-**3** **2.189**

To a cooled (–78 °C) solution of dithiane (*Z*)-**3** [82] (113.6 mg, 0.60 mmol) in HMPA/THF (1:10, total 11.0 mL) was added dropwise *t*-BuLi (1.05 mL, 1.7 M in pentane, 1.79 mmol) and the resulting mixture was stirred for 10 min before epoxide **2.190** (147.0 mg, 0.39 mmol) was added. After stirring at –78 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1/1) to afford diol **2.189** (202.9 mg,

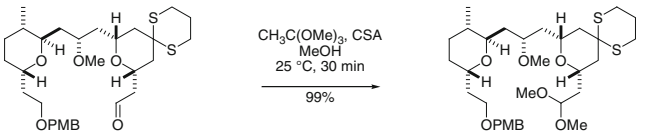
92 %) as a colorless oil: $[\alpha]^{25}_{D}$= +18.8 (*c* 3.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 5.80 (ddd, J = 11.5, 7.0, 7.0 Hz, 1H), 5.70 (ddd, J = 11.0, 7.0, 7.0 Hz, 1H), 4.43 (AB, $\Delta\upsilon$ = 16.0 Hz, J_{AB} = 12.0 Hz, 2H), 4.16–4.21 (m, 1H), 4.08–4.12 (m, 2H), 3.94 (dddd, J = 9.0, 4.5, 4.5, 4.5 Hz, 1H), 3.87 (s, 1H), 3.78 (s, 3H), 3.47–3.57 (m, 3H), 3.41–3.44 (m, 1H), 3.29 (s, 3H), 2.83–2.92 (m, 2H), 2.72–2.83 (m, 5H), 2.17 (dd, J = 15.0, 8.5 Hz, 1H), 1.88–2.04 (m, 4H), 1.78 (ddd, J = 14.0, 9.0, 6.0 Hz, 1H), 1.58–1.73 (m, 5H), 1.44–1.54 (m, 2H), 1.30–1.41 (m, 2H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 131.8, 130.4, 129.2, 126.3, 113.7, 76.6, 72.9, 72.5, 68.5, 66.85, 66.81, 58.1, 56.0, 55.2, 51.8, 45.0, 42.1, 37.7, 36.7, 34.3, 31.9, 28.1, 26.6, 26.2, 26.1, 24.9, 18.3; IR (neat) 3401, 1611, 1512, 1245, 1086, 1031, 818, 733 cm^{-1}; HRMS (FAB) *m/z* 569.2961 [$(M+H)^+$, $C_{30}H_{48}O_6S_2$ requires 569.2965].

Preparation of Bis-Tetrahydropyran 2.188



To a stirred solution of diol **2.189** (73.0 mg, 0.19 mmol) in CH_2Cl_2 (5.5 mL, 0.023 M) was added MnO_2 (55.8 mg, 0.64 mmol), and the resulting mixture was stirred for 1 h at 25 °C. An addition of MnO_2 (55.8 mg, 0.64 mmol) was repeated three times every 1 h. After stirring for additional 8 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford bis-tetrahydropyran **2.188** (62.5 mg, 86 %) as a colorless oil: $[\alpha]^{25}_{D}$= +28.8 (*c* 1.28, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (dd, J = 3.0, 2.0 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.41 (AB, $\Delta\upsilon$ = 16.5 Hz, J_{AB} = 11.5 Hz, 2H), 4.31 (dddd, J = 10.5, 8.5, 4.5, 2.0 Hz, 1H), 3.89–3.97 (m, 2H), 3.79 (s, 3H), 3.48–3.55 (m, 3H), 3.43–3.47 (m, 1H), 3.27 (s, 3H), 2.82–2.95 (m, 2H), 2.71–2.82 (m, 2H), 2.54 (ddd, J = 16.5, 11.0, 3.0 Hz, 1H), 2.41 (ddd, J = 16.0, 4.0, 2.0 Hz, 1H), 2.31 (d, J = 13.5 Hz, 1H), 2.23 (d, J = 13.5 Hz, 1H), 1.93–2.09 (m, 3H), 1.45–1.78 (m, 10H), 1.25–1.39 (m, 2H), 0.91 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.8, 159.0, 130.6, 129.1, 113.6, 74.1, 72.6, 72.0, 69.5, 68.3, 68.2, 67.1, 56.6, 55.1, 48.9, 47.6, 43.3, 42.5, 39.3, 38.4, 34.2, 32.0, 28.1, 26.7, 25.75, 25.67, 25.57, 18.2; IR (neat) 2361, 2337, 1700, 1512, 1436, 1245, 1092, 1033, 819 cm^{-1}; HRMS (FAB) *m/z* 567.2808 [$(M+H)^+$, $C_{30}H_{46}O_6S_2$ requires 567.2809].

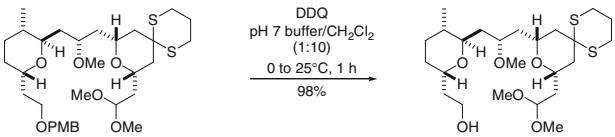
Preparation of Dimethyl Acetal 2.210



2.188 2.210

To a stirred solution of aldehyde **2.188** (72.5 mg, 0.13 mmol) in MeOH (4.0 mL, 0.032 M) were added trimethyl orthoacetate (0.05 mL, 0.38 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (3.0 mg, 0.013 mmol) at 25 °C. After stirring for 30 min at 25 °C, reaction mixture was quenched with saturated aqueous $NaHCO_3$, and diluted with EtOAc and H_2O. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford acetal **2.210** (77.8 mg, 99 %) as a colorless oil: $[\alpha]^{25}{}_D$= +23.6 (*c* 1.66, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.59 (dd, J = 7.5 Hz, 1H), 4.43 (AB, $\Delta\upsilon$ = 13.5 Hz, J_{AB} = 11.5 Hz, 2H), 3.94 (dddd, J = 9.0, 4.5, 4.5, 4.5 Hz, 1H), 3.81–3.87 (m, 2H), 3.79 (s, 3H), 3.50–3.59 (m, 1H), 3.53 (dd, J = 7.0, 6.5 Hz, 2H), 3.43–3.47 (m, 1H), 3.37 (s, 3H), 3.29 (s, 3H), 3.28 (s, 3H), 2.83–2.93 (m, 2H), 2.70–2.80 (m, 2H), 2.24 (d, J = 12.5 Hz, 1H), 2.21 (d, J = 12.5 Hz, 1H), 2.02–2.11 (m, 1H), 1.94–2.01 (m, 2H), 1.80 (ddd, J = 14.5, 8.0, 4.5 Hz, 1H), 1.51–1.77 (m, 11H), 1.44–1.50 (m, 2H), 1.31–1.38 (m, 2H), 0.90 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 102.1, 74.0, 72.7, 71.7, 69.31, 69.29, 68.6, 67.2, 56.6, 55.2, 54.2, 52.8, 47.9, 43.7, 43.2, 39.5, 39.4, 38.5, 34.7, 31.7, 28.4, 27.0, 25.87, 25.78, 25.76, 18.3; IR (neat) 1724, 1512, 1457, 1247, 1093, 1038, 820 cm^{-1}; HRMS (FAB) *m/z* 630.3496 $[(M+NH_4)^+$, $C_{32}H_{52}O_7S_2$ requires 630.3493].

Preparation of Alcohol 2.211

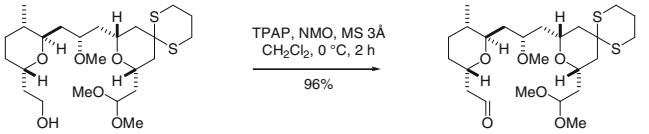


2.210 2.211

To a stirred solution of PMB-ether **2.210** (73.3 mg, 0.12 mmol) in pH 7 buffer/CH_2Cl_2 (1/10, total 5.5 mL) was added DDQ (40.5 mg, 0.18 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h, quenched with saturated aqueous $NaHCO_3$, and diluted with H_2O. The resulting mixture was stirred vigorously for

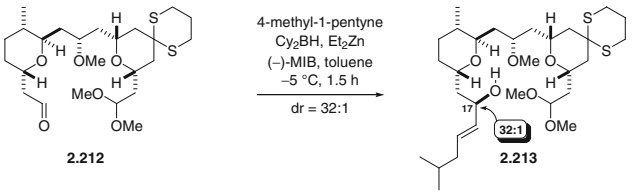
1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1/2) to afford alcohol **2.211** (57.4 mg, 98 %) as a colorless oil: $[\alpha]^{25}_D$= +27.1 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (dd, J = 7.5, 3.5 Hz, 1H), 3.94 (dddd, J = 10.0, 5.0, 5.0, 5.0 Hz, 1H), 3.69–3.86 (m, 4H), 3.54–3.62 (m, 2H), 3.34 (s, 3H), 3.32 (s, 3H), 3.30 (s, 3H), 2.87–2.90 (m, 3H), 2.74–2.77 (m, 3H), 2.23 (d, J = 12.0 Hz, 1H), 2.21 (d, J = 12.0 Hz, 1H), 1.97–2.04 (m, 3H), 1.86 (ddd, J = 13.5, 9.0, 4.5 Hz, 1H), 1.66–1.81 (m, 4H), 1.44–1.64 (m, 7H), 1.34–1.45 (m, 2H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.7, 74.2, 72.6, 69.7, 69.39, 69.30, 60.6, 56.4, 53.4, 52.4, 47.9, 43.6, 43.2, 39.23, 39.10, 37.4, 35.0, 33.7, 28.1, 26.4, 25.88, 25.80, 25.74, 18.4; IR (neat) 2360, 2338, 1733, 1558, 1456, 1243, 1122, 1052, 667 cm^{-1}; HRMS (ESI) *m/z* 510.2918 [(M+NH_4)$^+$, $C_{24}H_{44}O_6S_2$ requires 510.2918].

Preparation of Aldehyde 2.212



To a stirred solution of alcohol **2.211** (85.3 mg, 0.17 mmol) in CH_2Cl_2 (5.0 mL, 0.035 M) were added MS 3Å ($\sim$170 mg), NMO (40.5 mg, 0.35 mmol), and TPAP (3 mg) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was diluted with hexanes (4 mL). The resulting mixture was stirred for 30 min and filtered through a short pad of silica gel to afford aldehyde **2.212** (81.4 mg, 96 %) as a colorless oil: $[\alpha]^{25}_D$= +25.3 (*c* 0.79, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (dd, J = 3.0, 1.5 Hz, 1H), 4.55 (dd, J = 8.0, 3.5 Hz, 1H), 4.39 (dddd, J = 9.0, 4.0, 4.0, 4.0 Hz, 1H), 3.76–3.84 (m, 2H), 3.45–3.51 (m, 2H), 3.34 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 2.84–2.91 (m, 3H), 2.72–2.76 (m, 2H), 2.40 (ddd, J = 16.0, 5.0, 2.0 Hz, 1H), 2.22 (d, J = 13.5 Hz, 1H), 2.18 (d, J = 13.5 Hz, 1H), 1.94–2.02 (m, 2H), 1.79 (ddd, J = 14.0, 8.5, 4.5 Hz, 1H), 1.62–1.76 (m, 4H), 1.53–1.61 (m, 4H), 1.46–1.52 (m, 1H), 1.38–1.45 (m, 1H), 1.28–1.38 (m, 2H), 0.91 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.3, 101.9, 73.8, 72.4, 69.31, 69.21, 66.9, 56.7, 53.9, 52.7, 47.9, 45.9, 43.5, 43.1, 39.6, 39.2, 38.2, 34.1, 28.0, 26.6, 25.8, 25.7, 18.1; IR (neat) 1724, 1457, 1387, 1099, 1052 cm^{-1}; HRMS (ESI) *m/z* 508.2760 [(M+NH_4)$^+$, $C_{24}H_{42}O_6S_2$ requires 508.2761].

Preparation of Allyl Alcohol 2.213

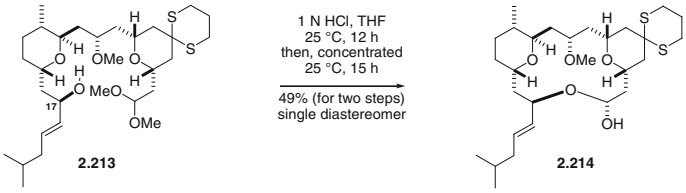


2.212 2.213

To a cooled (–5 °C) solution of (–)-MIB (1.0 mg, 0.004 mmol) and Et_2Zn (0.29 mL, 0.32 mmol, 1.1 M in toluene) in toluene (2.0 mL) was added aldehyde **2.212** (52.0 mg, 0.11 mmol) in toluene (0.5 mL). Vinylborane (0.22 mL, 0.22 mmol, 1.0 M in toluene, freshly prepared according to Oppolzer's report [100]) was slowly added by a syringe pump over 1 h. The reaction mixture was stirred for additional 30 min at –5 °C, quenched with saturated aqueous NH_4Cl, and diluted with Et_2O. The resulting mixture was stirred for 1 h at 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was filtered through a short pad of silica gel (hexanes/EtOAc, 2/1) to afford crude allyl alcohol **2.213** (dr = 32:1) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (dddd, J = 15.0, 7.0, 7.0, 1.0 Hz, 1H), 5.52 (dd, J = 15.5, 6.0 Hz, 1H), 4.69 (dd, J = 7.5, 3.5 Hz, 1H), 4.34 (br d, 3.5 Hz, 1H), 4.08 (dddd, J = 9.5, 5.0, 5.0, 5.0 Hz, 1H), 3.81–3.89 (m, 2H), 3.61–3.67 (m, 1H), 3.56–3.60 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.06 (d, J = 4.5 Hz, 1H), 2.90–2.93 (m, 2H), 2.79 (dd, J = 6.5, 4.5 Hz, 2H), 2.23 (d, J = 13.5 Hz, 1H), 2.26 (d, J = 13.5 Hz, 1H), 1.85–2.04 (m, 6H), 1.68–1.82 (m, 4H), 1.57–1.67 (m, 5H), 1.46–1.55 (m, 2H), 1.35–1.46 (m, 2H) 0.99 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H); IR (neat) 3459, 1717, 1386, 1095, 968, 667 cm^{-1}; HRMS (ESI) *m/z* 592.3693 [(M+NH_4)$^+$, $C_{30}H_{54}O_6S_2$ requires 592.3700].

The diastereomeric ratio was determined by Shimadzu HPLC system through Phenomenex Luna C_{18} (5 micron, 4.60 × 250 mm) column with a flow rate of 1 mL/min and isocratic 80 % MeOH in H_2O using SPD-20A UV/VIS detector (230 nm, 254 nm). The 1:1 mixture of (17*S*)- and (17*R*)-alcohols was prepared by Dess–Martin oxidation of the crude alcohol **2.213** and DIBAL-H reduction of the resulting ketone.

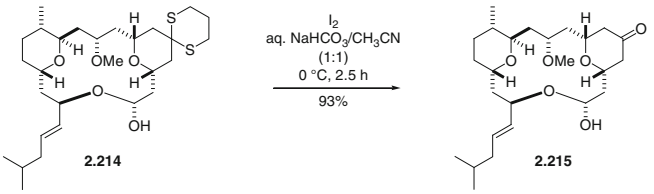
Preparation of Macrolactol 2.214



2.213 2.214

To a stirred solution of the above alcohol **2.213** in THF (2.0 mL) was added 1 N HCl (1.0 mL) at 25 °C. After vigorous stirring for 12 h at the same temperature, the reaction mixture was diluted with H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting crude oil was left for 15 h at 25 °C, and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4/1) to afford macrolactol **2.214** (27.5 mg, 49 % for two steps) as a colorless oil: $[\alpha]^{25}_D$= +59.8 (*c* 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (ddd, J = 14.5, 7.0, 7.0 Hz, 1H), 5.12 (dd, J = 15.0, 9.0 Hz, 1H), 4.71 (ddd, J = 9.5, 9.5, 4.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.34 (ddd, J = 11.0, 11.0, 3.0 Hz, 1H), 3.92 (d, J = 11.5 Hz, 1H), 3.74–3.81 (m, 2H), 3.63 (dd, J = 11.5, 11.5 Hz, 1H), 3.37 (s, 3H), 2.90 (ddd, J = 5.0, 4.5, 4.5 Hz, 2H), 2.78 (dd, J = 7.0, 4.5 Hz, 2H), 2.48 (dd, J = 14.0, 12.5 Hz, 1H), 2.22 (d, J = 14.5 Hz, 1H), 2.18 (d, J = 13.5 Hz, 1H), 1.85–2.04 (m, 5H), 1.69–1.83 (m, 4H), 1.45–1.65 (m, 5H), 1.42 (d, J = 12.0 Hz, 1H), 1.32 (d, J = 14.5 Hz, 1H), 1.26 (dd, J = 13.0, 13.0 Hz, 1H), 1.18 (d, J = 7.5 Hz, 3H), 1.05 (ddd, J = 14.5, 11.0, 2.5 Hz, 1H), 0.88 (dd, J = 6.5 Hz, 3H), 0.86 (dd, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.2, 130.7, 90.9, 74.1, 73.7, 71.8, 71.0, 68.7, 63.2, 57.1, 47.6, 44.2, 43.5, 43.3, 41.7, 39.5, 38.4, 35.8, 31.1, 28.1, 27.2, 26.04, 25.96, 25.7, 24.4, 22.32, 22.27, 18.4; IR (neat) 3481, 1733, 1558, 1456, 1088, 973, 667 cm^{-1}; HRMS (ESI) *m/z* 546.3276 [(M+NH_4)$^+$, $C_{28}H_{48}O_5S_2$ requires 546.3281].

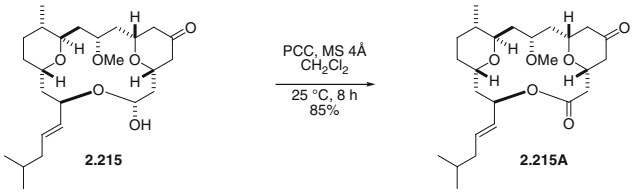
Preparation of Ketone 2.215



To a stirred solution of dithiane **2.214** (12.3 mg, 0.023 mmol) in saturated aqueous $NaHCO_3/CH_3CN$ (1:1, total 1.5 mL) was added I_2 (11.8 mg, 0.046 mmol) at 0 °C. An addition of I_2 (11.8 mg, 0.046 mmol) was repeated two times every 20 min at the same temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4/1) to afford ketone **2.215** (9.4 mg, 93 %) as a colorless oil. $[\alpha]^{25}_D$= +70.8 (*c* 0.17, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (ddd, J = 15.0, 7.0, 7.0 Hz, 1H), 5.11 (dd, J = 15.5, 9.0 Hz, 1H), 4.95 (dd, J = 12.0, 2.5 Hz, 1H), 4.68–4.74 (m, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.27 (dddd, J = 10.5, 10.5, 3.0, 3.0 Hz, 1H), 3.93 (d, J = 11.5 Hz, 1H), 3.68 (dd, J = 11.5, 11.5 Hz, 2H), 3.60 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H), 3.41 (s, 3H), 2.30–2.44 (m, 5H), 2.11

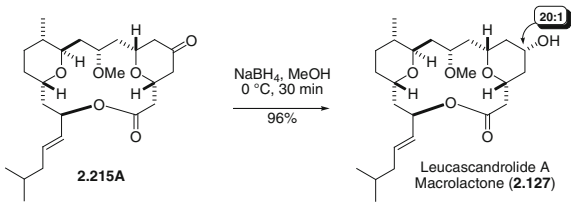
(ddd, $J = 11.5, 11.5, 2.0$ Hz, 1H), 1.84–1.97 (m, 5H), 1.38–1.66 (m, 4H), 1.36 (dd, $J = 12.0, 12.0$ Hz, 1H), 1.25–1.29 (m, 2H), 1.17 (d, $J = 7.5$ Hz, 3H), 1.80 (ddd, $J = 14.5, 10.5, 2.0$ Hz, 1H), 0.88 (d, $J = 6.5$ Hz, 3H), 0.86 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 134.5, 130.4, 90.5, 75.31, 75.09, 73.81, 73.54, 69.0, 63.3, 57.2, 48.0, 47.7, 44.1, 41.7, 40.4, 39.1, 35.8, 30.9, 28.1, 27.1, 24.3, 22.31, 22.26, 18.3; IR (neat) 3499, 1718, 1436, 1365, 1241, 1089, 989 cm^{-1}; HRMS (ESI) *m/z* 456.3317 [$(M+NH_4)^+$, $C_{25}H_{42}O_6$ requires 456.3320].

Preparation of Macrolactone 215A



To a stirred solution of lactol **2.215** (6.5 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL, 0.015 M) were added PCC (16.0 mg, 0.074 mmol) and MS 4Å (13 mg) at 25 °C. After stirring for 8 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through a short pad of silica gel. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford lactone **2.215A** (5.6 mg, 85 %) as a white solid: $[\alpha]^{25}{}_D$= +69.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68–5.77 (m, 1H), 5.30–5.41 (m, 2H), 4.02 (dddd, $J = 11.5, 11.5, 3.0, 3.0$ Hz, 1H), 3.89 (d, $J = 11.5$ Hz, 1H), 3.45–3.56 (m, 3H), 3.38 (s, 3H), 2.64 (dd, $J = 13.0, 3.5$ Hz, 1H), 2.44–2.50 (m, 2H), 2.25–2.38 (m, 3H), 2.11 (ddd, $J = 13.5, 11.5, 2.0$ Hz, 1H), 1.82–1.94 (m, 3H), 1.58–1.75 (m, 3H), 1.41–1.58 (m, 3H), 1.29–1.34 (m, 2H), 1.16 (d, $J = 7.0$ Hz, 3H), 1.05 (ddd, $J = 14.5, 11.0, 2.5$ Hz, 1H), 0.86 (d, $J = 6.5$ Hz, 3H), 0.84 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 168.6, 132.8, 129.8, 74.4, 73.57, 73.55, 73.5, 71.3, 63.1, 57.4, 47.9, 47.4, 43.4, 42.7, 41.6, 39.6, 35.6, 30.9, 28.1, 27.1, 24.1, 22.2, 18.2; IR (neat) 1733, 1372, 1235, 1021, 734 cm^{-1}; HRMS (ESI) *m/z* 454.3164 [$(M+NH_4)^+$, $C_{25}H_{40}O_6$ requires 454.3163].

Preparation of Leucascandrolide A Macrolactone (2.127)

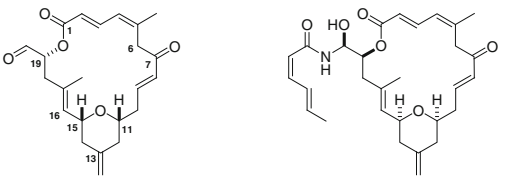


To a stirred solution of ketone **2.215A** (5.4 mg, 0.012 mmol) in MeOH (1 mL) was added $NaBH_4$ (1.8 mg, 0.048 mmol) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature before AcOH (0.02 mL) was added. The resulting mixture was concentrated and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1/1 to 1/2) to afford the known leucascandrolide A macrolactone **2.127** (5.2 mg, 96 % as a 20:1 mixture of diastereomers) as a white solid whose spectral data were identical to those of the known synthetic **2.127** [76, 80, 88]: $[\alpha]^{25}{}_{D}$= +54.1 (*c* 0.07, EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (ddd, J = 14.0, 7.0, 7.0 Hz, 1H), 5.31–5.38 (m, 2H), 3.89 (d, J = 9.0 Hz, 2H), 3.72 (ddddd, J = 7.5, 7.5, 2.0, 2.0, 2.0 Hz, 1H), 3.51 (dd, J = 10.5, 10.5 Hz, 2H), 3.35 (s, 3H), 3.21 (dd, J = 11.5, 11.5 Hz, 1H), 2.56 (dd, J = 13.0, 3.5 Hz, 1H), 2.30–2.42 (m, 2H), 2.00–2.05 (m, 2H), 1.81–1.92 (m, 4H), 1.56–1.74 (m, 3H), 1.47–1.56 (m, 3H), 1.40–1.46 (m, 1H), 1.20–1.33 (m, 4H), 1.16 (d, J = 7.0 Hz, 3H), 1.00 (ddd, J = 14.0, 10.5, 2.0 Hz, 1H), 0.85 (d, J = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 132.4, 130.1, 73.61, 73.54, 73.0, 72.2, 70.8, 68.0, 63.0, 57.3, 43.1, 42.8, 41.6, 41.1, 40.8, 39.1, 35.5, 31.0, 28.1, 27.1, 24.1, 22.2, 18.2; IR (neat) 3438, 1739, 1457, 1261, 1085, 962 cm^{-1}; HRMS (FAB) *m/z* 456.3321 $[(M+NH_4)^+$, $C_{25}H_{42}O_6$ requires 456.3320].

2.3.3 Total synthesis of (+)-Dactylolide

2.3.3.1 Background

In 1996 Higa and Tanaka first disclosed the isolation and partial structure elucidation of the novel macrolide (–)-zampanolide (**2.218**), extracted from the marine sponge *Fasciospongia rimosa*, collected at Cape Zampa on the island of Okinawa, Japan [159]. (–)-Zampanolide was isolated as a minor constituent of the sponge material, while a substantial amount of two known biologically active compounds, (+)-latrunculin A and (–)-laulimalide [160], were isolated as major constituents. The structure of the highly unsaturated 20 membered macrolactone carbon framework and the relative stereochemistry were secured by extensive 1D (^{1}H and ^{13}C), 2D NMR (COSY, TOCSY, HMQC, and HMBC), as well as HR-FABMS studies [159]. Although the determination of the relative configurations between the C(11), C(15), and C(19) stereogenic centers was successful, the configuration of the N-acyl hemiaminal side chain at C(20) was not defined at the time. Five years later, Riccio and co-workers reported the isolation of a structurally related macrolide, (+)-dactylolide(**2.217**), from a different marine sponge belonging to the genus *Dactylospongia* collected off the coast of the Vanuatu islands [161] (Fig. 2.9).



(+)-dactylolide (**2.217**) (–)-zampanolide (**2.218**)

Fig. 2.9 Structures of natural (+)-dactylolide and (–)-zampanolide

Due to the strong structural similarities of **2.217** and **2.218**, it was postulated that dactylolide (**2.217**) is a common biosynthetic precursor to that of zamapanolide or perhaps a degradation product thereof. However, it was revealed that the absolute configuration of the identical macrolide substructures contained in both compounds were enantiomeric to each other [162].

Despit the scarcity of (–)-zampanolide it has been shown to have highly potent cytotoxicity against P388, HT29, A549, and MEL28 cell lines ranging from 1–5 ng/mL (Table 2.7). (+)-dactylolide also exhibited 63 % inhibition of L1210 (lymphatic leukemia of mice) and 40 % inhibition of SK-OV-3 (carcinoma of the ovaries) tumor cell lines at 3.2 μg/mL. However the mode of action has not been fully understood [163].

Table 2.7 Comparison of biological data between (–)-zampanolide, (–)-dactylolide, and (+)-dactylolide [163]

Cell line	(–)-Zampanolide (ng/mL)	(–)-Dactylolide (μg/mL)	(+)-Dactylolide (μg/mL)
A549/ATCC	1–5	1.72	
HT29	1–5	0.101	
SK-Mel-28	1–5	2.0	
SK-OV-3		1.8	3.2[a]
P388	1–5		
L1210			3.2[b]

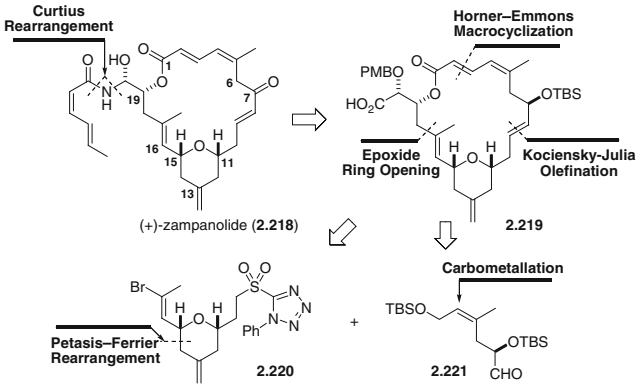
[a] IC_{50} or GI_{50} values
[b] GI_{40} value

2.3.3.2 Previous Syntheses of Dactylolide

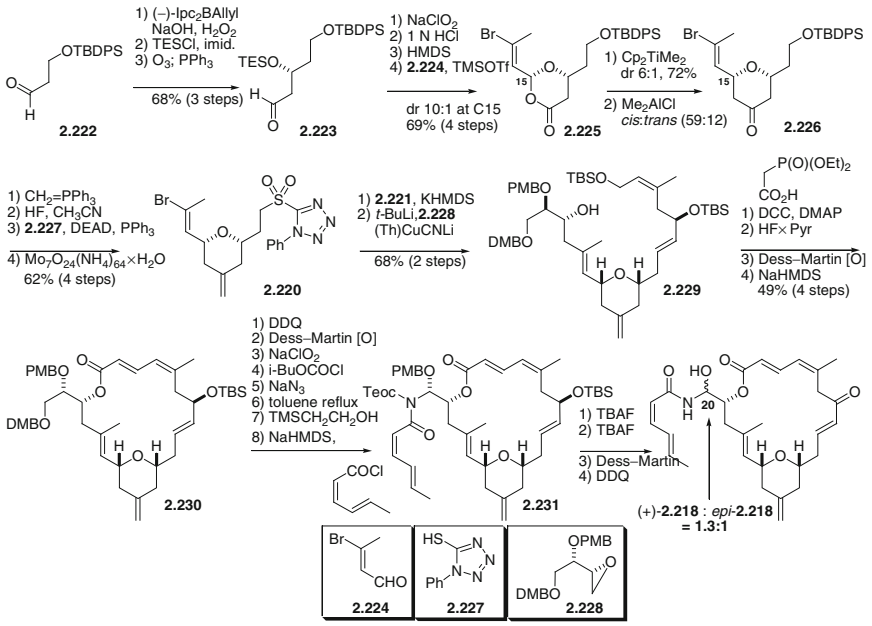
The interesting structural features, biological profile, and enantiorelationship of the macrolactone core in **2.217** with natural (–)-zampanolide (Fig. 2.9) have made (+)-dactylolide (**2.217**) and unnatural (–)-dactylolide attractive targets for total

synthesis from a number of synthetic groups, culminating in the first total synthesis by Smith and co-workers [164, 165]. To date, there have been four zampanolide syntheses [164, 166, 167] and nine dactylolide syntheses [162, 164, 166–174] reported. The syntheses of **2.217** reported to date focus on the diastereoselective construction of the 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran subunit and the efficient formation of the 20-membered macrolactone core, which is one of the most significant challenges associated with the synthesis of **2.217**.

Smith's Synthesis [162, 164, 165]
In 2001 and 2002, the Smith group first disclosed the total synthesis of (+)-zampanolide [164] and (+)-dactylolide [165], respectively. The synthetic strategy of (+)-zampanolide relied on the stereoselective construction of the 2,6-*cis*-tetrahydropyran unit via the Petasis–Ferrier rearrangement and Horner–Wadsworth–Emmons macrocyclization at the C(2)–C(3) junction (Scheme 2.47).

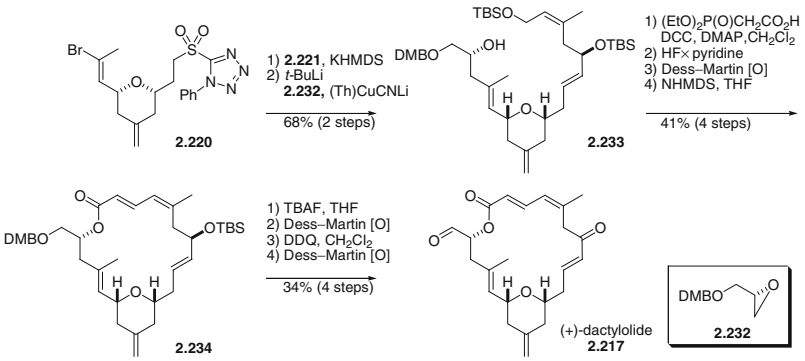


Scheme 2.47 Major disconnections of (+)-dactylolide by Smith



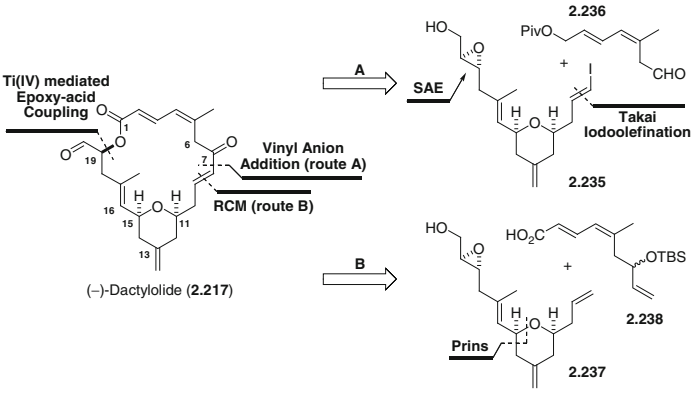
Scheme 2.48 Smith's first total synthesis of (+)-zampanolide

The synthesis began with Brown asymmetric allylation [95, 175] of aldehyde **2.222** followed by TES protection and oxidative cleavage of the terminal olefin afforded aldehyde **2.223**. Subsequent oxidation of **2.223**, removal of the silyl group and bis-silylation then gave the corresponding *β*-hydroxy ester, which was then condensed with aldehyde **2.224** to furnish a 10:1 mixture of dioxane. Methylenation of **2.225** with Petasis–Tebbe reagent [176] (Cp_2TiMe_2) gave a 6:1 mixture of the corresponding vinyl acetals at C(15). The key Petasis–Ferrier rearrangement [177] was carried out by treatment with one equivalent of dimethylaluminum chloride (Me_2AlCl) at –78 °C to provide the desired 2,6-*cis*-pyranone **2.226** in 59 % yield and the minor *trans* isomer (12 %). The Kocienski–Julia olefination of sulfone moiety **2.220** with aldehyde **2.221** furnished the requisite vinyl bromide **2.229** as a single *E*-isomer of the C(8)–C(9) olefin. Macrocyclization to the macrolide **2.230**, one of the key transformations of this synthesis, was achieved via Horner–Wadsworth–Emmons intramolecular macrocyclization [178, 179] of acyl phosphonate in 66 % by treatment with NaHMDS at –78 °C. Installation of the *N*-acyl hemiaminal region via Curtius rearrangement and the final deprotection/oxidation sequences delivered (+)-zampanolide (**2.218**) over 30 linear steps (Schemes 2.48, 2.49).



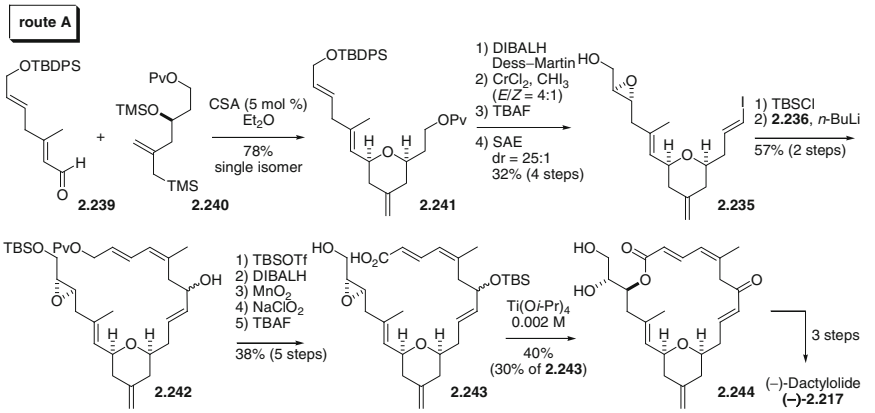
Scheme 2.49 Smith's first total synthesis of (+)-dactylolide

Hoye's Synthesis [166]



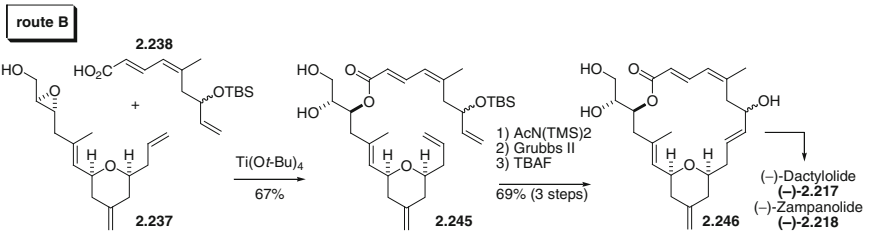
Scheme 2.50 Major disconnections of (+)-dactylolide by Hoye

The synthesis by Hoye and co-workers for **2.217** involved two distinct macrocyclization strategies (Scheme 2.50), including Ti(IV)-promoted macrolactonization of an epoxy-acid **2.243** in route A (Scheme 2.51) and a ring closing metathesis cyclization tactic in route B (Scheme 2.52). The construction of 2,6-*cis*-tetrahydropyran unit **2.241** was achieved by Hosomi–Sakurai–Prins reaction of an enal **2.239** and an allyl silane **2.240** in the presence of camphorsulfonic acid (5 mol %) as a single diastereomer in 78 % yield. Formation of the aldehyde followed by iodoalkenylaiton, desilylation and subsequent Sharpless asymmetric epoxidation [146] furnished **2.235**, which was further functionalized into epoxy-carboxylic acid **2.243** in 7 steps. The key macrocyclization was performed by the treatment of **2.243** with Ti(O*i*-Pr)$_4$ at 75 °C to afford the macrolactone **2.244** in 40 % along with 30 % recovered starting material.



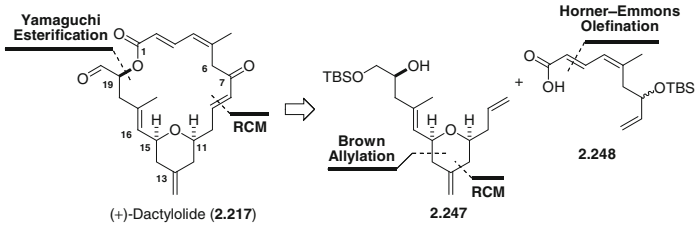
Scheme 2.51 Synthesis of (–)-dactylolide by Hoye (Route A)

The alternative macrocyclization strategy (route B) involved ring closing metathesis. The epoxide opening reaction of **2.237** with trienoic acid **2.238** promoted by $Ti(O\textit{t}\text{-}Bu)_4$ furnished **2.245** in 67 % yield. After silylation of the vicinal diol, macrocyclization was rendered by using Grubbs second generation catalyst to convert to macrolide **2.246** with a single *E*-alkene of C(8)–C(9) geometry.



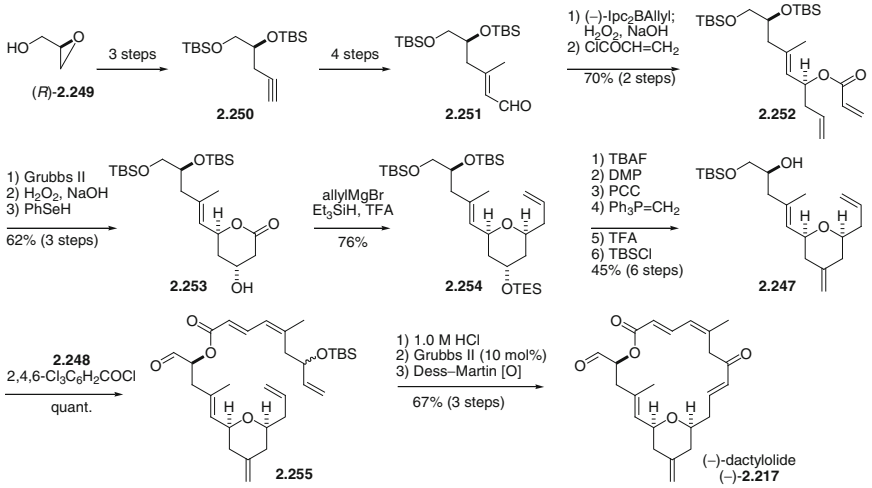
Scheme 2.52 Synthesis of (–)-dactylolide by Hoye (Route B)

Jennings' Synthesis [67, 73]



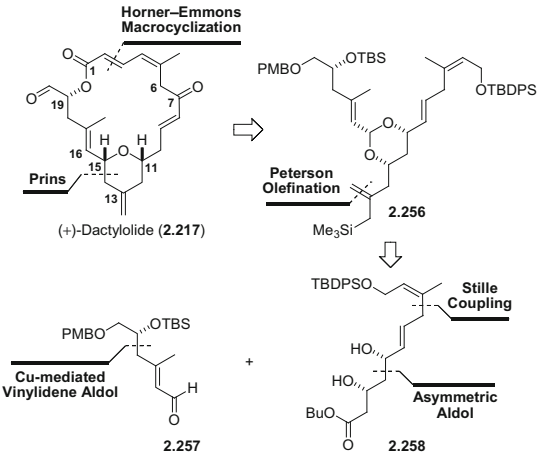
Scheme 2.53 Major disconnections of (–)-dactylolide by Jennings

In 2005, the Jennings group reported a total synthesis of (–)-dactylolide based on the Yamaguchi esterification, ring closing metathesis (RCM) for the late stage macrocyclization, and a stereoselective construction of the key 2,6-*cis*-tetrahydropyran unit via reduction of an oxonium ion (Schemes 2.53, 2.54). The alkyne **2.250**, prepared from glycidol (*R*)-**2.249**, was transformed into enal **2.251** in 4 steps. Brown asymmetric allylation [95] of **2.251** and acrylation of the resulting homoallyl alcohol gave dienic ester **2.252**. Subjection of **2.252** to Grubbs II catalyst, epoxidation, and subsequent regioselective reduction through the use of PhSeH [180] afforded hydroxy lactone **2.253**. The formation of the key 2,6-*cis*-tetrahydropyran **2.254** was accomplished by nucleophilc addition of allylmagnesium bromide to the lactone and a diastereoselective reduction of an oxonium cation by the treatment with Et_3SiH and TFA [181]. Installation of the *exo*-methylene in six steps and Yamaguchi esterification of **2.247** and acid **2.248** set the stage for a ring closing metathesis macrocyclization.



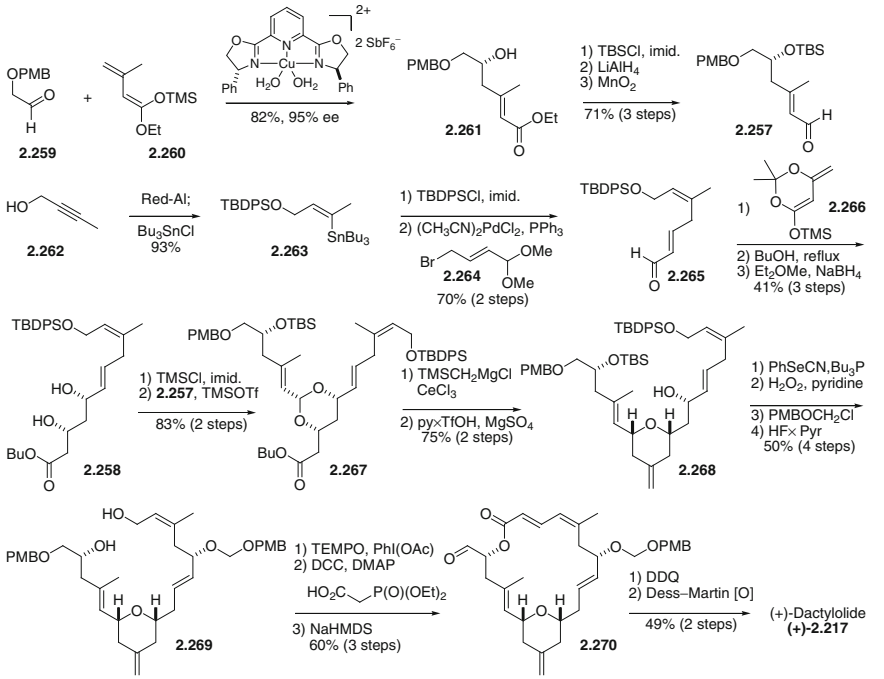
Scheme 2.54 Synthesis of (–)-dactylolide by Jennings

Floreancig's Synthesis [170]



Scheme 2.55 Major disconnections of (+)-dactylolide by Floreancig

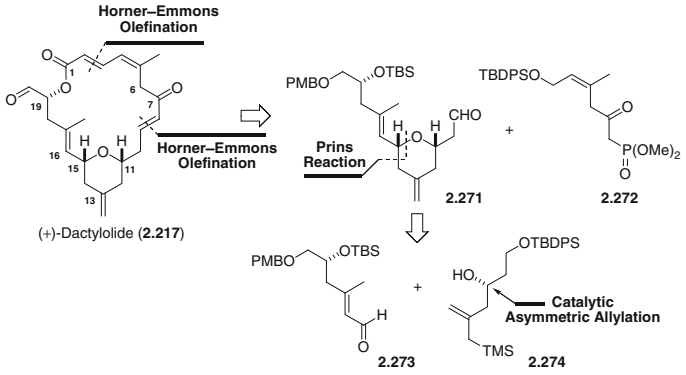
Floreancig and co-workers communicated the synthesis of (+)-dactylolide in 2005. The key step of Floreancig's synthesis involved an asymmetric vinylogous Mukaiyama–aldol reaction and an intramolecular Prins cyclization of the acetal bearing substrate. The macrocyclization of the synthesis was achieved by Honer–Wadsworth–Emmons olefination as demonstrated by the Smith group in the first total synthesis of (+)-zampanolide (Schemes 2.55, 2.56).



Scheme 2.56 Synthesis of (+)-dactylolide by Floreancig

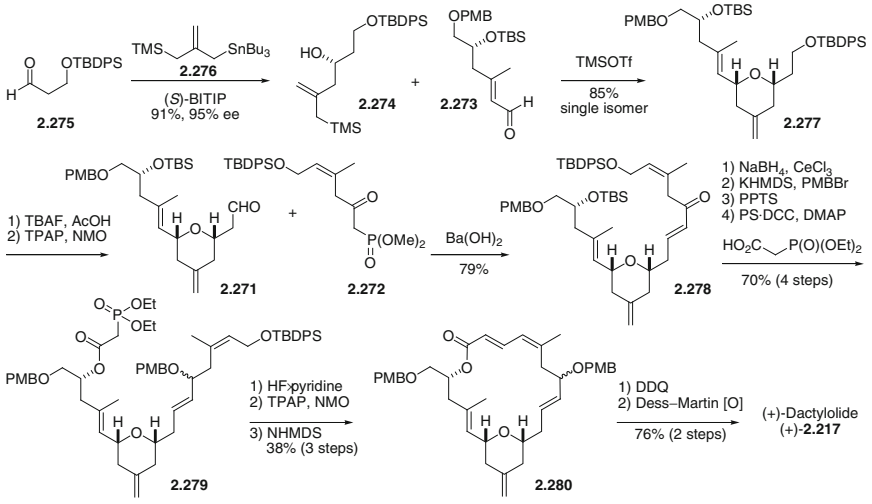
The synthesis commenced with the preparation of aldehyde **2.257**. The vinylogous Mukaiyama–aldol reaction [182] of α-oxy aldehyde **2.259** and ketene acetal **2.260** catalyzed by Cu-pybox complex [183] furnished α,β-unsaturated ester **2.261** with 95 % ee, which was further converted into aldehyde **2.257**. The coupling partner of Prins cyclization was prepared by hydroalumination of 2-butynol followed by stannylation, which was then coupled with bromide **2.264** to generate enal **2.265**. The second vinylogous Mukaiyama–aldol reaction of enal **2.265** and ketene acetal **2.266** upon treatment with Denmark's bisphosphoramide catalyst [184] and $SiCl_4$ provided the alcohol, which was followed by esterification and subsequent *syn*-reduction to afford the diol **2.258**. With both coupling partners, acetal **2.267** was formed using the bis-trimethylsilyl ether and the aldehyde **2.257** promoted by TMSOTf to set the stage for the key 2,6-*cis*-tetrahydropyran unit. Peterson olefination by treatment with $TMSCH_2MgCl$ and $CeCl_3$ to give the allyl silane, followed by Hosomi–Sakurai–Prins cyclization using pyridinium triflate and $MgSO_4$ furnished 2,6-*cis*-tetrahydropyran **2.268** in 75 % yield over two steps. The macrocycle was realized by Honer–Wadsworth–Emmons olefination. Toward this end, esterification with phosphono acetic acid, followed by treatment of NaHMDS furnished macrolactone **2.270**.

Keck's Synthesis [171]



Scheme 2.57 Major disconnections of (+)-dactylolide by Keck

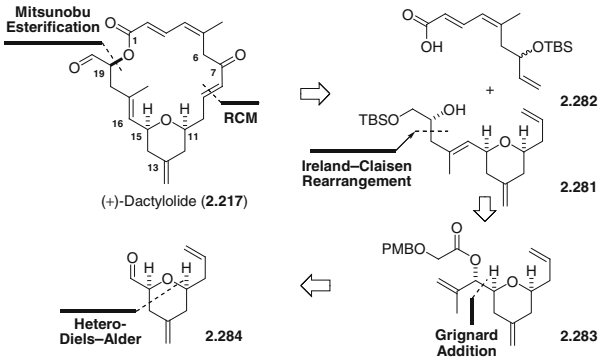
Shortly after the synthesis by Floreancig group, Keck and co-workers completed the synthesis of (+)-dactylolide. Retorosynthetically, Keck's approach to dactylolide is similar to those of previous syntheses, in that the major disconnection at C(2)–C(3) at the late stage macrocyclization is to be achieved through Horner–Wadsworth–Emmons olefination and the Prins cyclization via an allyl silane addition to an aldehyde to build up the 2,6-*cis*-tetrahydropyran unit (Scheme 2.57). However, preparation of the homoallyl alcohol **2.274** fragment via Keck's asymmetric allylation is unique as illustrated in Scheme 2.58.



Scheme 2.58 Keck's total synthesis of (+)-dactylolide

With this strategy in mind, Keck's construction of the 2,6-*cis*-tetrahydropyran unit commenced with the asymmetric allylation [185] of aldehyde **2.275** with allystannane **2.276** promoted by BINOL titanium tetraisopropoxide (BITIP) to furnish the homoallyl alcohol **2.274** (95 %, 95 % ee) [186]. The formation of the key 2,6-*cis*-tetrahydropyran **2.277** was accomplished by the Hosomi–Sakurai–Prins cyclization in the presence of TMSOTf in 85 % yield as a single diastereomer. Silyl deprotection and oxidation, followed by Horner–Wadsworth–Emmons olefination proceeded to provide **2.278**, which was further elongated to the phosphonoacetate **2.279**. Exposure of the resulting phosphonoacetate to NaHMDS after desilylation and subsequent oxidation afforded the macrocycle **2.280** via the Horner–Wadsworth–Emmons olefination protocol.

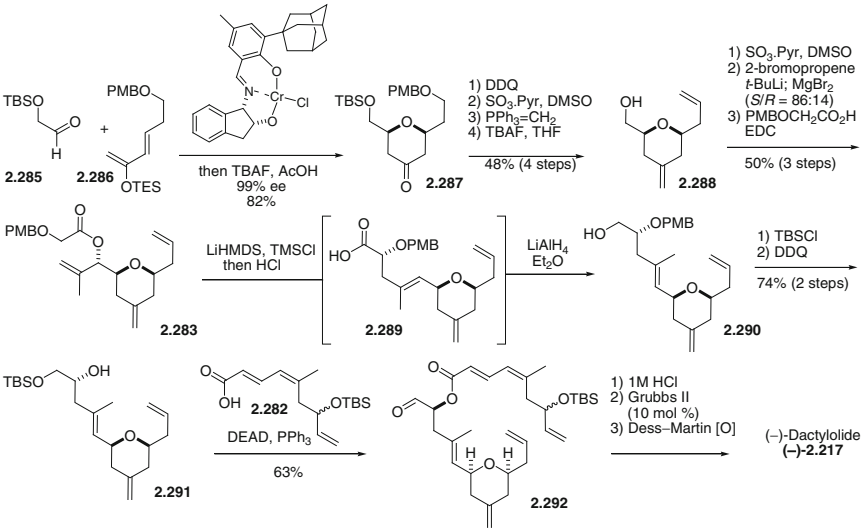
McLeod's Synthesis [172]



Scheme 2.59 Major disconnections of (–)-dactylolide by McLeod

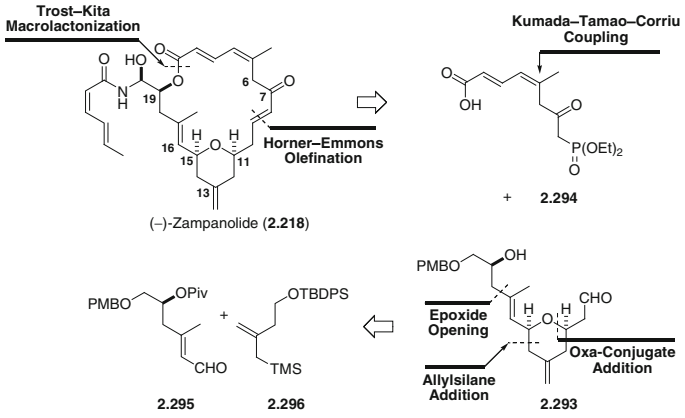
McLeod's strategy for the synthesis of dactylolide involved an asymmetric hetero-Diels–Alder reaction for the construction of the 2,6-*cis*-pyran unit and an implementation of the Ireland–Claisen rearrangement for the formation of C(16)–C(17) *E*-olefin. The macrocyclization of the synthesis relied upon the ring closing metathesis as Hoye [166] and Jennings [163, 169] utilized, affording the C(8)–C(9) double bond (Schemes 2.59, 2.60). The elaboration began with the construction of the 2,6-*cis* pyran moiety. Jacobsen's chiral chromium (III) amino indanol Schiff base [116] catalyzed asymmetric hetero-Diels–Alder reaction between silyl enol ether **2.286** and aldehyde **2.285** furnished 2,6-*cis*-tetrahydropyranone **2.287** (82, 99 % ee). Installation of *exo*-methylene in **2.288** was accessed by a Wittig reaction after protecting group manipulation, and further functionalization led to substrate **2.283** for the Ireland–Claisen rearrangement [187]. Toward this end, the resulting **2.283** was exposed to LiHMDS to form the key 2,6-*cis*-pyran subunit, which generated both the C(16)–C(17) trisubstituted olefin geometry and an incorporation of stereogenicity at (19). Protection of primary alcohol as the TBS ether and

subsequent oxidative removal of PMB, followed in turn by esterification of **2.291** with acid **2.282** generated **2.292**. Deprotection of the silyl group, macrocyclization via ring closing metathesis using 10 mol % of Grubbs second generation catalyst, and oxidation furnished (–)-dactylolide **2.217**.



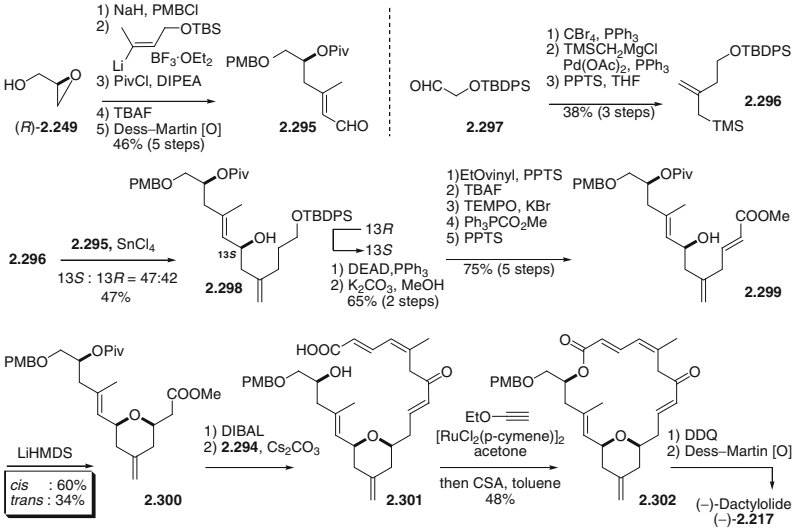
Scheme 2.60 McLeod's total synthesis of (–)-dactylolide

Uenishi's Synthesis [167]



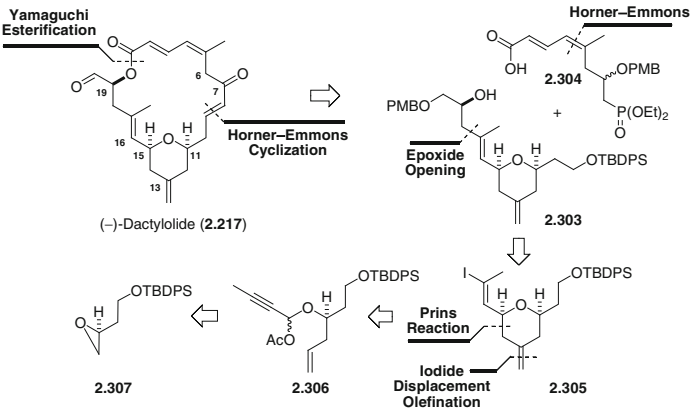
Scheme 2.61 Major disconnections of (–)-dactylolide by Uenishi

In 2009, Uenishi and co-workers disclosed the synthesis of (–)-dactylolide and (–)-zampanolide. The key features of the synthesis are the intramolecular oxa-conjugate addition reaction forming the 2,6-*cis*-tetrahydropyran core, a short access to seco-acid, and completion of the entire carbon framework via the Horner–Wadsworth–Emmons olefination. The macrocycle was rendered by employing the Trost–Kita macrolactonization protocol [188] (Schemes 2.61, 2.62). With this synthetic tactic in mind, the synthesis commenced with the preparation of two the requisite fragments **2.295** and **2.296**. Aldehyde **2.295** was accessed from (*R*)-glycidol **2.249** in 46 % overall yield in a five-step sequence and the coupling partner allylsilane **2.296** was prepared from aldehyde **2.297** in 38 % over three steps. Hosomi–Sakurai reaction between aldehyde **2.295** and allylsilane **2.296** promoted by $SnCl_4$ proceeded to give the corresponding desired alcohol **2.298** (13*S*, 47 %) along with its isomer (13*R*, 42 %), which was converted into 13*S* via the Mitsunobu reaction in 65 % yield. Protection of secondary alcohol as the 1-ethoxyethyl ether followed by desilylation, oxidation and subsequent two carbon homologation via Wittig reaction afforded α,β-unsaturated ester **2.299** after hydrolysis of the ethoxyethyl ether. The formation of the key 2,6-*cis*-tetrahydropyran was accessed by the intramolecular oxa-conjugate addition reaction by the treatment with LiHMDS at 25 °C forming **2.300** as the major product (94 %, dr = 1.8:1). The resulting ester was next reduced to the aldehyde, which in turn was subjected to Horner–Wadsworth–Emmons olefination with phosphonate **2.294** to afford seco-acid **2.301**. The macrocycle **2.302** was achieved by the Trost–Kita macrolactonization [189, 190] protocol in 48 % yield. Their attempts for cyclization by employing the corresponding Yamaguchi [129] and Shiina [191–193] macrolactonization gave the product in only 33 % and 20 % yields, respectively. Finally, oxidative removal of PMB and oxidation of the resulting alcohol furnished **2.217**, thereby completing the synthesis of (–)-dactylolide.



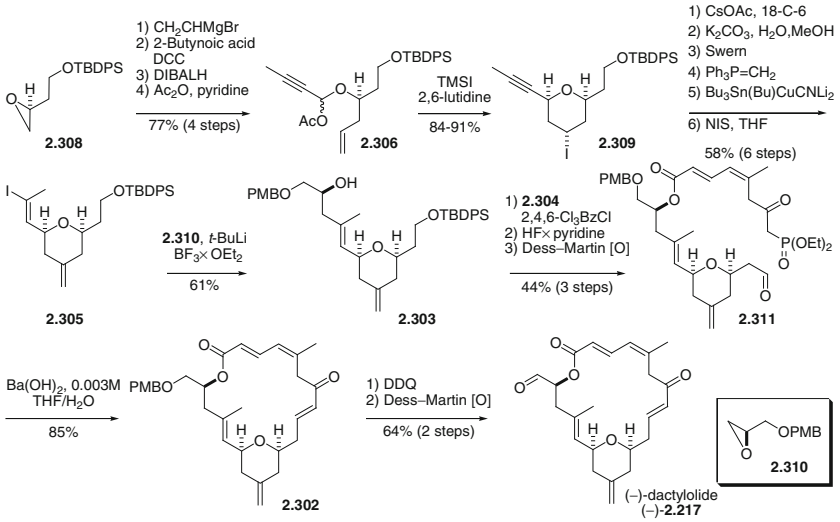
Scheme 2.62 Uenishi's total synthesis of (–)-dactylolide

Altmann's Synthesis [173]



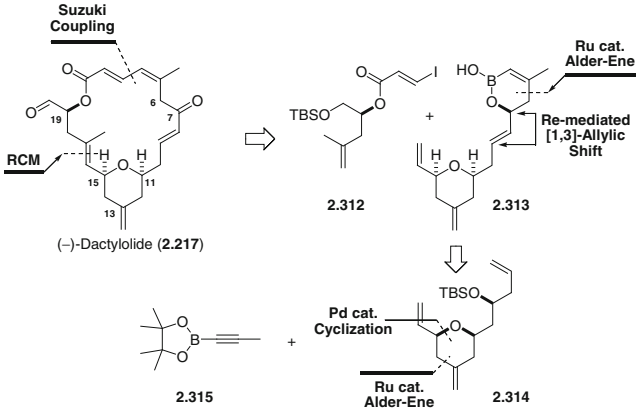
Scheme 2.63 Major disconnections of (–)-dactylolide by Altmann

The synthetic plan for (–)-dactylolide by Altmann and co-workers in 2010 involved an implementation of the intramolecular Horner–Wadsworth–Emmons approach for the closure of the macrolide and utilizing the Prins cyclization for the formation of 2,6-*cis*-tetrahydropyran (Schemes 2.63, 2.64). The synthesis commenced with preparation of the 2,6-*cis*-tetrahydropyran unit. Epoxide opening reaction with vinyl-MgBr provided homoallyl alcohol, followed by esterification, reduction and subsequent acetylation furnished anomeric acetate **2.306**. Sequential formation of 2,6-*cis*-tetrahydropyran by employing Prins reaction and a segment coupling approach as reported by Rychnovsky [104, 194] furnished **2.309** in 91 % yield, which in turn was converted into **2.305** in a six-step elaboration. Coupling reaction between lithiated vinyl iodide **2.305** and PMB protected epoxide **2.310** delivered homoallyl alcohol **2.303** in 61 % as a single diastereomer and subsequent esterification of **2.303** with acid **2.304** provided the substrate **2.311** for the macrocyclization after desilylation and oxidation. Honer–Wadsworth–Emmons cyclization of **2.311** by treatment with activated $Ba(OH)_2$ [195, 196] proceeded to give the cyclization adduct **2.302** in 85 %, which was further elaborated to complete the synthesis of (–)-dactylolide.



Scheme 2.64 Altmann's total synthesis of (–)-dactylolide

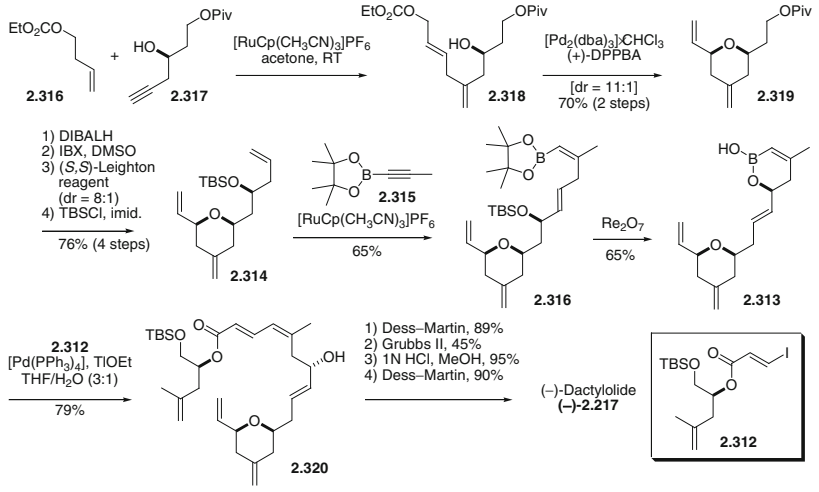
Lee's Synthesis [174]



Scheme 2.65 Major disconnections of (–)-dactylolide by Lee

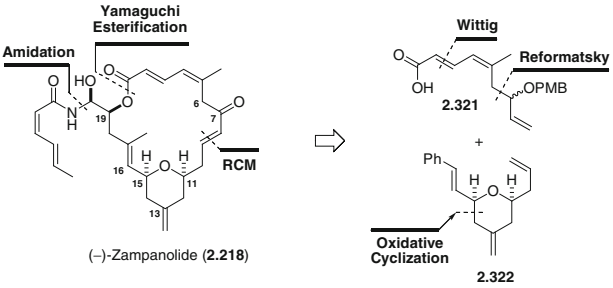
The synthetic plan for (–)-dactylolide by Lee and co-workers in 2010 involved the distinctive transition-metal-catalyzed transformations, including the formation of the 2,6-*cis*-disubstituted tetrahydropyran via the tandem ruthenium-catalyzed Alder-ene reaction [197, 198] and palladium-catalyzed ring closure. The Alder-ene

reaction of alkynyl boronates and subsequent rhenium-catalyzed [1,3]-allylic transposition to set the requisite boronic acid **2.313** (Schemes 2.65, 2.66). The synthesis commenced with the ruthenium-catalyzed Alder-ene reaction between ethyl carbonate **2.316** and homopropargylic alcohol **2.317** to deliver 1,4-diene **2.318**. Subsequent cyclization by treatment of palladium catalyst with Trost's chiral (+)-DPPBA ligand [199] furnished the key 2,6-*cis*-tetrahydropyran **2.319** in a ratio of 11:1 in 70 % over two steps. Deprotection of pivalate of **2.319** and oxidation of the resulting alcohol, followed by the Leighton's allylation [200] and subsequent TBS-protection delivered the corresponding homo allyl silyl ether **2.314**. The second ruthenium-catalyzed Alder-ene reaction of **2.314** with the alkynyl boronate afforded vinyl boronate **2.315**, which was further converted to cyclic boronic acid **2.313** through the 1,3-tranposition of the allyl alcohol in **2.315** by treatment with rhenium oxide [201, 202] in 65 % yield. Suzuki coupling of the resulting **2.313** with iodoacrylate **2.312** to form **2.317**, followed by oxidation of alcohol at C(7) and subsequent RCM using Grubbs second generation catalyst completed the synthesis of (–)-dactylolide **2.217** after minor manipulation of functional groups.



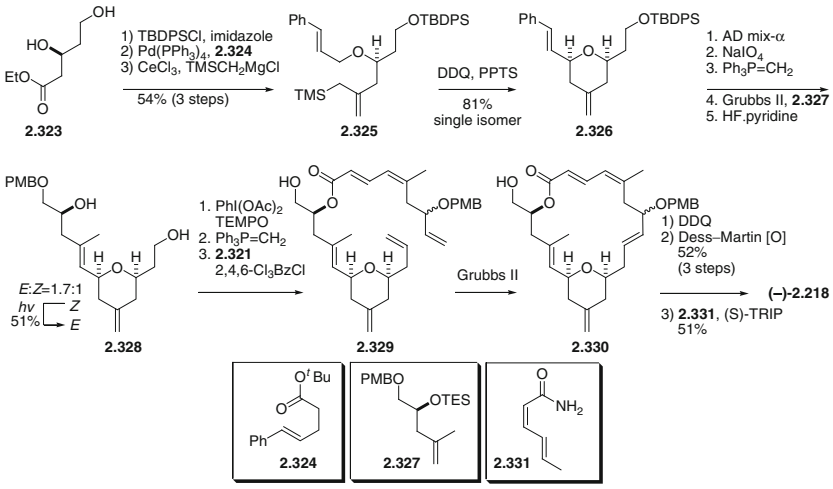
Scheme 2.66 Lee's total synthesis of (–)-dactylolide

Ghosh's Synthesis [168]



Scheme 2.67 Major disconnections of (–)-zampanolide by Ghosh

The most recent synthesis of (–)-dactylolide was accomplished by Ghosh and co-wokers in 2011. The planning behind Ghosh's synthesis is depicted in Scheme 2.67, where the DDQ/Brønsted acid promoted intramolecular oxidative cyclization was employed for the formation of the 2,6-*cis*-tetrahydropyran as a key step. Other key features include a cross metathesis to construct a trisubstituted olefin and a ring closing metathesis to form a macrolide. The formation of the 2,6-*cis*-tetrahydropyran unit was the starting point of the synthesis (Scheme 2.68). Selective protection of primary alcohol in **2.323** as the TBDPS ether and an etherification with *tert*-butyl cinnamyl carbonate **2.324** to afford the cinnamyl ether, was in turn converted to the allylsilane **2.325** by employing the procedure by Narayanan and Bunnelle [203]. The key 2,6-*cis*-tetrahydropyran was accessed by the Sakurai type intramolecular oxidative cyclization [204–206] by treatment with DDQ and pyridinium *p*-toluenesulfonate to furnish pyran **2.326** in 81 % as a single diastereomer. Dihydroxylation, oxidative cleavage of the resulting diol, and subsequent Wittig reaction afforded the methylene chain, which was followed by cross metathesis with **2.327** to furnish an *E*/*Z* mixture (1.7:1) of trisubstituted olefin. Exposure of the undesired *Z*-isomer to photochemical reaction conditions allowed the isomerization to the *E*-isomer **2.328** in 51 % yield. Selective oxidation of the primary alcohol by TEMPO and subsequent Wittig reaction was followed by esterification with acid **2.321** under Yamaguchi conditions to furnish ester **2.329**. Macrocyclization was rendered by ring closing metathesis with **2.329** as shown by the same disconnection as Hoye [166], Jennings [163, 169], and McLeod [172]. Lastly, minor manipulation of protecting groups and the formation of the *N*-acyl aminal group allowed the completion of the synthesis of (–)-zampanolide.

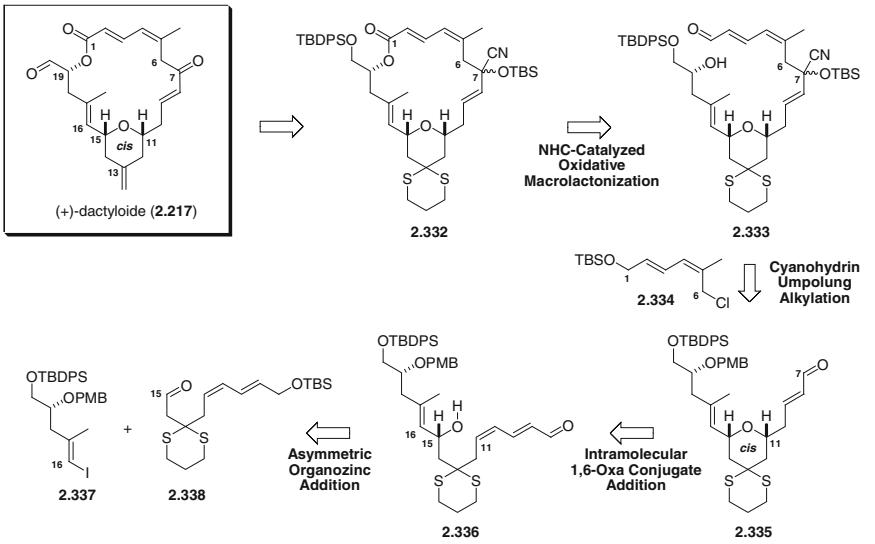


Scheme 2.68 Ghosh's synthesis of (–)-zampanolide

2.3.3.3 Retrosynthetic Analysis of (+)-Dactylolide

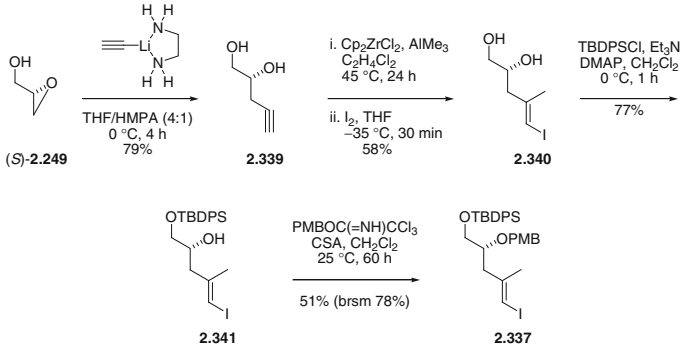
Due to its interesting structural array in conjuction with its biological profile, there have been a number of syntheses reported for **2.217**. Based on the previous syntheses, we were aware of the major synthetic challenges associated with the formation of the 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran and the late stage macrocyclization. It has been documented that dienoic substrates are known to be ineffective for macrolactonization when employing conventional reaction conditions [207]. In particular, the macrolactonization of dienoic substrates for the synthesis of (+)-dactylolide either failed to proceed [171] or gave the desired macrolactones in unsatisfactory yields under Yamaguchi, Shiina, or Trost–Kita conditions [167, 168]. Thus we were particularly interested in the development of a new tactic for the efficient closure of the macrolide.

Our strategy for the synthesis of (+)-dactylolide (**2.217**) is outlined in Scheme 2.69. We envisioned that the 20-membered macrolactone in **2.332** could be constructed by intramolecular *N*-heterocyclic carbene (NHC)-catalyzed oxidative macrolactonization of ω-hydroxy aldehyde **2.333**. Intramolecular NHC-catalyzed oxidative esterification reactions have been recognized as an attractive tool and rapidly growing area in the synthetic community. Indeed, several examples of these reactions have recently been reported [208–216], which clearly provide a new opportunity for the development of *catalytic* acyl transfer agents in macrolactonization reactions of ω-hydroxy aldehydes in the presence of oxidants. The substrate for the macrolactonization reaction would be derived from the cyanohydrin alkylation of 2,6-*cis*-tetrahydropyran enal **2.335** with dienyl chloride **2.334**. 2,6-*cis*-tetrahydropyran enal would in turn be constructed by employing the 1,6-oxa conjugate addition reaction of ω-hydroxy 2,4-dienal **2.336**. Despite the



Scheme 2.69 Retrosynthetic analysis of (+)-dactylolide

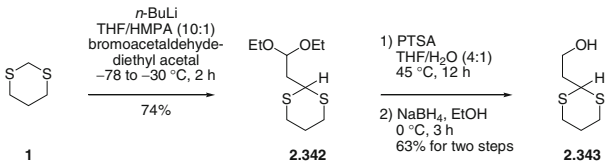
fact that intramolecular oxa-conjugate addition chemistry defines a robust and valuable entry for the synthesis of tetrahydropyrans and related cyclic ethers, the 1,6-oxa conjugate addition has been extremely underutilized in natural product syntheses [217]. Further analysis suggested that **2.336** would be accessible by the asymmetric addition of vinyl iodide **2.337** to aldehyde **2.338** in a reagent-controlled manner.



Scheme 2.70 Preparation of vinyl iodide **2.337**

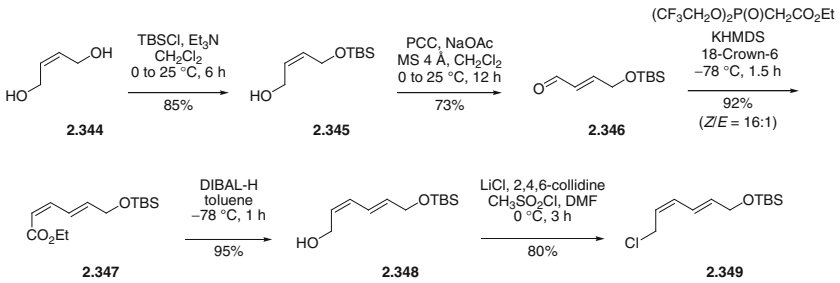
The synthesis of **2.217** initiated with the preparation of chiral vinyl iodide **2.337** and the dithiane **2.343** for the organozinc addition reaction. To this end, epoxide opening reaction of commercially available (*S*)-glycidol (*S*)-**2.249** with treatment

of lithium acetylide·EDA complex afforded the homopropargylic diol **2.339**. Upon treatement of $CpZrCl_2$ and $AlMe_3$ in $ClCH_2CH_2Cl$, zirconium mediated carboalumination [218] of **2.339** proceeded to provide the vinyl aluminum intermediate and subsequent quenching with I_2 furnished vinyl diol **2.340** in 58 % yield. Selective protection of primary hydroxyl of the resulting diol as the TBDPS ether **2.341**, followed by final protection as the PMB ether provided the requisite vinyl iodide **2.337** (Scheme 2.70).



Scheme 2.71 Preparation of 1,3-dithiane-2-ethanol (**2.343**)

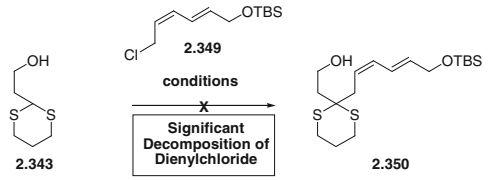
The 1,3-dithiane-2-ethanol (**2.343**) was readily prepared in a three-step elaboration (Scheme 2.71). The coupling of 1,3-dithiane and bromoacetaldehyde diethyl acetal afforded acetal **2.342**. Treatment of the resulting **2.342** with *p*-toluenesulfonic acid generated the dithiane aldehyde and subsequent reduction by $NaBH_4$ furnished alcohol **2.343** in 63 % over two steps.



Scheme 2.72 Preparation of dienylchloride **2.349**

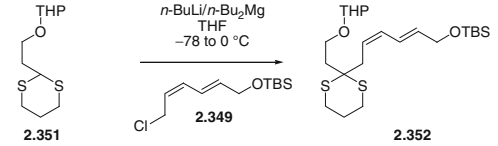
Synthesis of dienyl chloride **2.349**, the dithiane coupling partner for dithiane aldehyde **2.338**, was accomplished in five steps from commercially available *cis*-2-butene-1,4-diol (Scheme 2.72). To this end, monosilylation of **2.344** as the TBS ether and this allyl alcohol was then oxidized with accompanying *Z* to *E* isomerization by PCC [122] to afford the enal **2.346** in 73 % yield. α,β-unsaturated ester **2.347** was accessed by the Still−Gennari modification [219] of the Horner–Wadsworth–Emmons olefination in good yield and selectivity (92 %, $Z/E = 16{:}1$). Reduction of the resulting ester **2.347** to produce allyl alcohol **2.348**, in turn was chlorinated by treatment with LiCl and methanesulfonyl chloride to furnish the requisite dienyl chloride **2.349**.

Table 2.8 Attempts for the dithiane alkylation with (*Z*,*E*)-dienylchloride



Entry	Reagent	Conditions	Yield (%)
1	*t*-BuLi(3 eq), THF/HMPA	−78 °C (3 h)	<5
2	*t*-BuLi(1.9 eq), THF/HMPA	−78 °C (5 h)	28
3	*t*-BuLi(1.9 eq), THF	−78 °C (5 h)	25
4	*n*-BuLi(1.9 eq), THF	−78 °C (15 h)	30
5	*n*-BuLi(1.9 eq), THF/HMPA	−78 to −20 °C (5 h)	22
6	*n*-BuLi(1.9 eq), THF/TMEDA	−78 °C (15 h)	18
7	*n*-BuLi/KO^{t}Bu, THF	−78 °C (15 h)	18
8	*n*-BuLi/Bu_2Mg, THF	−78 °C (5 h)	<5

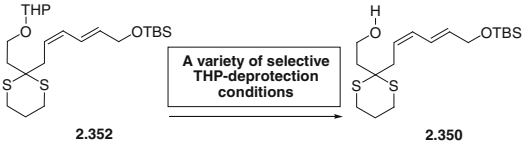
Having secured fragements **2.343** and **2.349**, the coupling reaction was undertaken (Table 2.8). Unfortunately, initial attempts utilizing *t*-BuLi, *n*-BuLi, or a combination of *n*-BuLi and KO^{t}Bu as a base were unsatisfactory. All reaction conditions provided the coupling products but in low yield (5–30 %) even after prolonged reaction time (15 h). Introduction of additives such as HMPA and TMEDA, or changing of the reaction temperature did not improve the coupling yield, but only significant decomposition of dienylchloride was observed. At this point, we assumed that either the lifetime of the resulting dithiane anion was not long enough to complete the reaction, or the lithium alkoxide in **2.343**, generated from the lithiation, might be acting as a base to result in the decomposition of the dienylchloride. Thus, we decided to examine the protected dithiane alcohol. The 1,3-dithiane-2-ethanol was protected as the THP ether **2.351** and the dithiane coupling reaction was revisited. After extensive investigations, we found that the *n*-BuLi/*n*-Bu_2Mg-mixed organometallic base which is long-lived and maintains a good nucleophilicity, was effective [220–222]. Indeed, the lithiation by treatment of dithiane **2.351** with the premixed organometallic base, prepared from 1.2 equiv of *n*-BuLi and 0.3 equiv of *n*-Bu_2Mg, proceeded to provide the coupling adduct **2.352** in 60 % yield (Scheme 2.73). Pleasingly, after extensive experimentation, we found that a premixed reagent prepared by using 1.6 equiv of *n*-BuLi and 0.4 equiv of *n*-Bu_2Mg further improved the coupling yield and consumed the starting materials in less than 2.5 h (72 %).



dithiane	dienyl chloride	*n*-BuLi/*n*-Bu_2Mg (eq)	yield
2 eq	1 eq	1.2 / 0.3	60%
1 eq	**2 eq**	**1.6 / 0.4**	**72%**
1 eq	4 eq	1.6 / 0.4	70%

Scheme 2.73 Dithiane alkylation with *n*-BuLi/*n*-Bu_2 Mg

Having successfully achieved the coupling adduct **2.352**, a selective removal of tetrahydropyranyl (THP) ether in the presence of the *t*-butyldimethylsilyl (TBS) group was explored (Scheme 2.74). Since the TBS group is an acid labile functionality, we needed to consider mild reaction conditions. After many unsuccessful attempts, we found that $ZnCl_2$ chemoselectively cleaved the THP ether in **2.352** without removal of the TBS group to afford alcohol **2.350** in 62 % yield (BRSM 75 %). This alcohol **2.350** was then oxidized to aldehyde **2.338** via Parikh–Doering [39] oxidation (85 %) to set the stage for the asymmetric organozinc addition reaction.



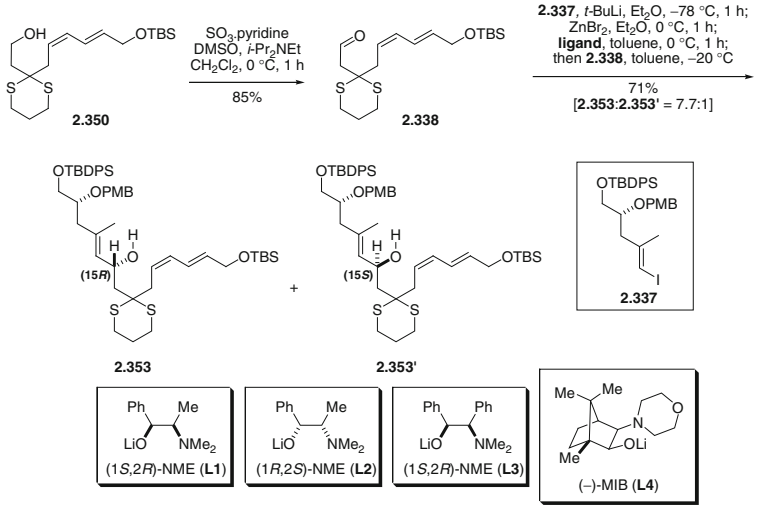
reagents	conditions	yield
PPTS (30 mol%), EtOH/THF (1:3)	25 °C, 4 h	31%
$BF_3{\cdot}Et_2O$, ethanethiol, CH_2Cl_2	–25 °C, 30 min	50%
Me_2AlCl, Et_2O	–25 °C, 1 h	<5%
$ZnBr_2$ (1.0 M in Et_2O), Et_2O	25 °C, 1 h	55%
$ZnCl_2$ (1.0 M in Et_2O), CH_2Cl_2	**25 °C, 3 h**	**62% (BRSM 75%)**

Scheme 2.74 Selective deprotection of THP

With aldehyde **2.338** in hand, we attempted to stereoselectively install the C(15) secondary carbinol by the asymmetric organozinc addition (Scheme 2.75) [223, 224]. We envisioned that the asymmetric addition of a highly functionalized

bromozinc reagent derived from **2.337** to aldehyde **2.338** would be challenging due to the possible chelation of the oxygen atoms to Zn. Indeed, following the procedure described by Shair and co-workers [224], the reaction gave **2.353** with modest stereoselectivity (dr = 3.5:1). At this stage in our experimentation, hoping to enhance the diastereoselectivity, we investigated various chiral ligands, including Li(1*S*,2*R*)-*N*-methylephedrine (**L1**), Li(1*S*,2*R*)-2-*N*,*N*-dimethylamine-1,2-diphenylethoxide (**L3**), and Nugent's reagent (–)-MIB ligand (**L4**) [154, 158]. We also considered changing the order of addition of the reagents, however, all our efforts unsuccessfully resulted in low to moderate diastereoselectivities.

After an extensive search for the optimal reaction conditions, we were delighted to find that the slow addition (4 h) of the dienal **2.338** to a cooled (−20 °C) mixture of the corresponding bromozinc reagent of **2.337** and lithiated (1*S*,2*R*)-

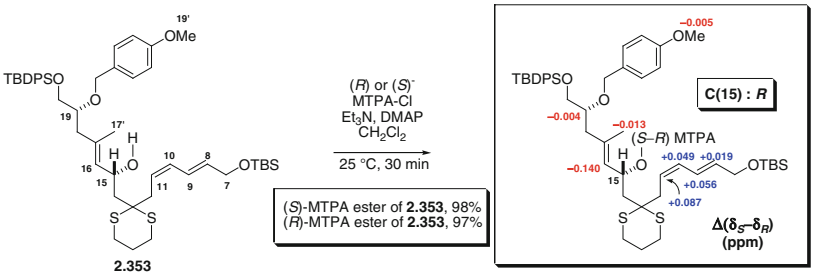


ligand	temp. (°C)	reaction time[a]	yield[b]	dr (15*R*:15*S*)[c]
L1	0	1 h	77%	3.5 : 1 [d]
L1	–20	4 h	79%	5.6 : 1 [d]
L1	**–20**	**4 h**	**71%**	**7.7 : 1** [e]
L1	–40	6 h	<40%	-
L2	–20	4 h	66%	1 : 1.4 [d]
L2	–20	4 h	65%	1 : 1.7 [e]
L3	0	1 h	79%	1 : 1 [d]
L4	–5	1 h	46%	2 : 1 [d]

Scheme 2.75 Asymmetric organozinc addition reaction. [a]reaction time after addition of aldehyde **2.338**. [b]combined yield of **2.353** and **2.353′**. [c]the diastereomeric ratio was determined by integration of the ^{1}H NMR of the mixture. [d]dropwise addition of aldehyde. [e]slow addition of dienal by syringe pump.

NME provided the desired secondary carbinol **2.353** in good stereoselectivity and yield (dr = 7.7:1, 71 %).

Determination of the absolute stereochemistry of the newly generated C(15) stereocenter of **2.353** was achieved by Mosher ester analysis of the major diastereomer following the procedure reported by Kakisawa and co-workers (Scheme 2.76) [225]. The Mosher esters of the organozinc addition reaction product were prepared as shown in Scheme 2.76. Analysis of the (*S*)- and (*R*)-MTPA esters prepared from **2.353** obviously indicated that the C(15) alcohol was of the desired configuration (*R*), which was consistent with the results via reagent controlled asymmetric organozinc addition reaction.

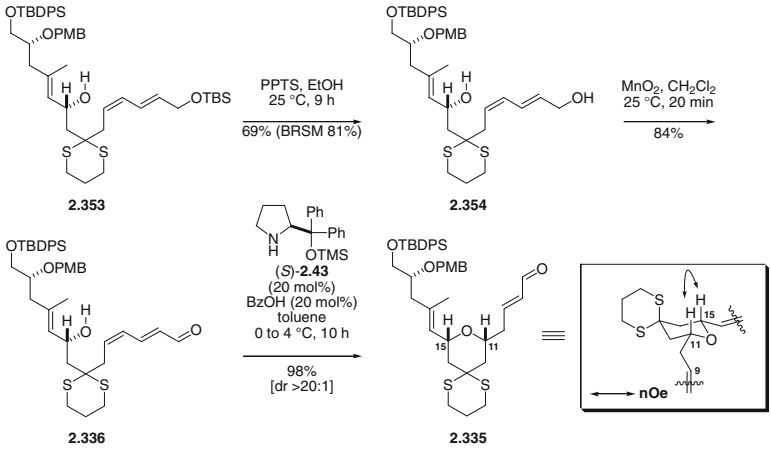


	H-8	H-9	H-10	H-11	H-16	H-17¢	H-19	H-19¢
(*S*)-MTPA ester	5.778	6.470	6.119	5.447	5.143	1.826	3.683	3.782
(*R*)-MTPA ester	5.759	6.414	6.070	5.360	5.283	1.839	3.687	3.787
$\delta_S-\delta_R$ (ppm)	+0.019	+0.056	+0.049	+0.087	–0.140	–0.013	–0.004	–0.005

Scheme 2.76 Determination of absolute stereochemistry of C(15)

2.3.3.4 Synthesis of 2,6-*cis*-Tetrahydropyran via Intramolecular Organocatalytic 1,6-Oxa-Conjugate Addition Reaction

With the requisite alcohol **2.353**, our efforts on the synthesis were directed to the synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran **2.335** (Scheme 2.77). Towards this end, removal of the TBS group in **2.353** by treatment of PPTS in EtOH giving allyl alcohol **2.354**, which was followed by MnO_2-oxidation of the resulting **2.354** furnished ω-hydroxy 2,4-dienal **2.336**, setting the stage for the key intramolecular 1,6-oxa conjugate addition reaction. When **2.336** was treated with (*S*)-**2.43** [58, 226] in toluene at 0 °C, the organocatalytic 1,6-oxa conjugate addition reaction proceeded smoothly to provide the desired 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran **2.335** with excellent stereoselectivity and yield (dr >20:1, 98 %). Treatment of **2.336** with pyrrolidine also afforded desired **2.335** as a single diastereomer but in low yield (56 %). In addition, when **2.336** was



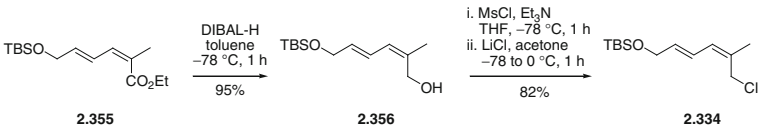
Scheme 2.77 A stereoselective synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran

Table 2.9 1,6-Oxa-conjugate addition reaction

Entry	Catalyst (20 mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	dr (*cis:trans*)[b]
1	pyrrolidine·BzOH	CH_2Cl_2	25	4	56	>20:1
2	piperidine·BzOH	Toluene	0–4	16	89	10:1
3	(*S*)-**2.43**·**BzOH**	**Toluene**	**0–4**	**10**	**98**	**>20:1**
4	(*R*)-**2.43**·BzOH	Toluene	0–4	10	98	2:1

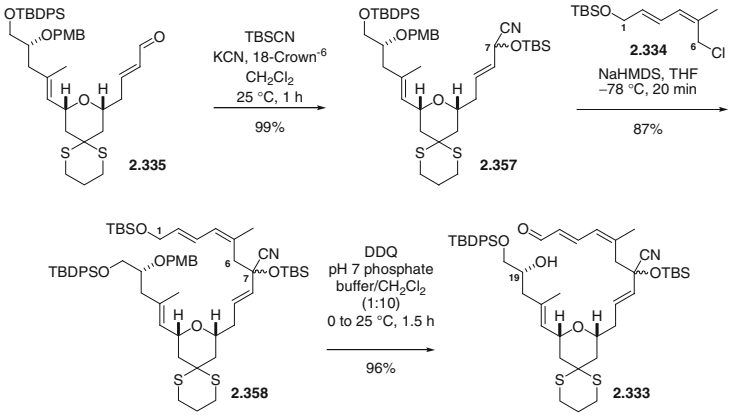
[a] Combined yield of the isolated 2,6-*cis* and 2,6-*trans*-tetrahydropyrans
[b] The diastereomeric ratio was determined by integration of the ^{1}H NMR of the crude product

treated with piperidine or (*R*)-**2.43**, the organocatalytic 1,6-oxa conjugate addition reaction provided **2.335** in 89 % (dr = 10:1) and 98 % (dr = 2:1), respectively (Table 2.9). Notably, to the best of our knowledge, this work is the first successful example of the construction of a tetrahydropyran through an intramolecular 1,6-oxa conjugate addition reaction [227, 228].



Scheme 2.78 Preparation of dienyl chloride **2.334**

The preparation of dienyl chloride **2.334** for the cyanohydrin alkylation was achieved in a two-step sequence from the known ester **2.355**. Reduction of **2.355** and chlorination by treatment with LiCl and methanesulfonyl chloride furnished the dienyl chloride **2.334** (Scheme 2.78).



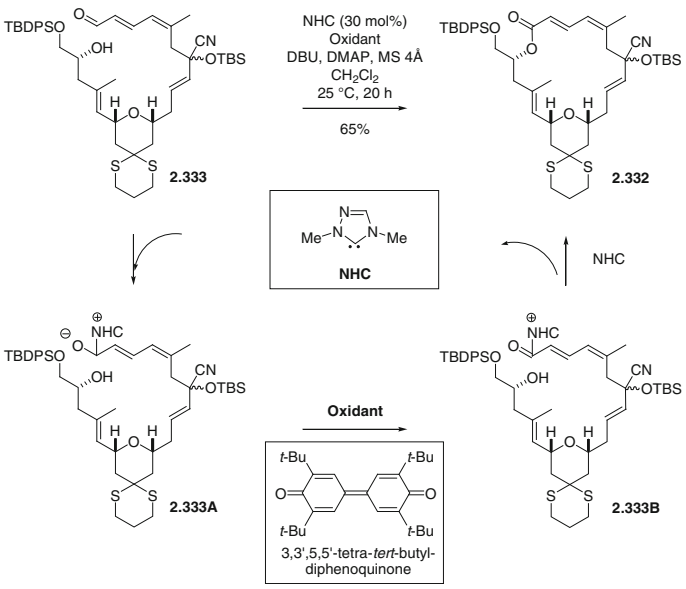
Scheme 2.79 Synthesis of -hydroxy aldehyde

2.3.3.5 Synthesis of ω-Hydroxy Aldehyde

Having successfully secured the desired 2,6-*cis*-tetrahydropyran enal **2.335** employing the intramolecular 1,6-oxa conjugate addition reaction, we continued our investigations leading to the dactylolide macrocycle. To this end, we proceeded to install the C(1)–C(6) fragment of the natural product using an acyl anion equivalent (Scheme 2.79). After extensive experimentation, we utilized a TBS-protected cyanohydrin [229–231] because of the easy preparation and preference for α-alkylation [232, 233] of the corresponding vinyl cyanohydrin anion. Treatment of **2.335** with TBSCN provided cyanohydrin **2.357**, which was followed by coupling reaction of **2.357** and dienyl chloride **2.334** to give **2.358** in 87 % yield. Concomitant oxidative removal of the PMB group and C(1)-oxidation of **2.358** was accomplished by treatment with DDQ to furnish ω-hydroxy aldehyde **2.333**, which set the stage for the pivotal NHC-catalyzed oxidative macrolactonization.

2.3.3.6 NHC-Catalyzed Oxidative Macrolactonization

With the requisite ω-hydroxy aldehyde **2.333** in hand, we directed our attention to NHC-catalyzed oxidative macrolactonization (Scheme 2.80). The results of our efforts are presented in Table 2.10. Initial attempts for the macrolactonization in the presence of dimethyltriazolium iodide, DBU, MnO_2, and MS 4Å in CH_2Cl_2 provided **2.332** in poor yield (<10 %). A series of alternative NHC catalysts, solvent systems, as well as a range of oxidants were next explored. Pleasingly, after significant experimentation, we found that the addition of DMAP, the use of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone as an oxidant [234], and a slow addition of **2.333** (2 h) via a syringe pump proved to be highly effective reaction conditions leading to a higher yield (65 %).

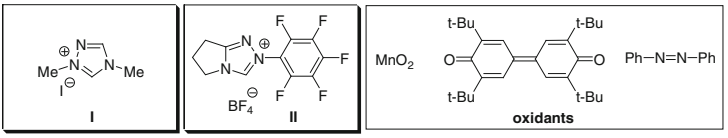


Scheme 2.80 NHC-catalyzed oxidative macrolactonization

Since NHCs have not yet been exploited as acyl transfer agents in macrolactonization reactions, our report, therefore, constitutes the first example of the NHC-catalyzed oxidative macrolactonization of ω-hydroxy aldehydes. Because of significant benefits of the reaction, including the catalytic nature and mild reaction conditions of the reaction, the NHC-catalyzed oxidative macrolactonization reaction would provide a significant advance in the field of macrolactonization.

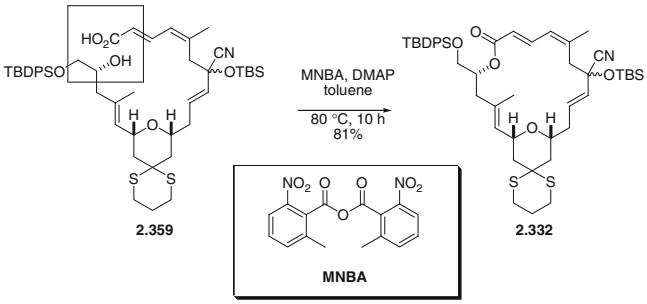
Interested in facilitating access to the macrolactone, we also explored the macrolactonization by employing the Shiina's procedure [191–193] (Scheme 2.81). To this end, the seco-acid **2.359** of the aldehyde **2.333** was independently prepared and subjected to Shiina's MNBA macrolactonization reaction conditions. The reaction smoothly proceeded to provide the macrolactone **2.332** in 81 % yield. At this point, we hypothesized that the result was most likely due to the *gem*-disubstituent effect induced by the TBS-protected cyanohydrin functionality. As mentioned, in the previous syntheses of (+)-dactylolide, several attempts for the macrolactonization of the structurally related substrates without the cyanohydrin group either failed to afford the corresponding macrolactone or resulted in low to modest yields (21–48 %) under various macrolactonization conditions, suggesting that the TBS-protected cyanohydrin in our substrate appears to have a noticeable effect in the NHC-catalyzed oxidative macrolactonization.

Table 2.10 Optimization of macrolactonization



NHC cat.	Amount (mol %)	Oxidant	Solvent	Time (h)	Yield (%)[a]
I	20	MnO_2	CH_2Cl_2	48	17
I	30	MnO_2	CH_2Cl_2	20	49
II	30	MnO_2	CH_2Cl_2	20	36
I	50	MnO_2	CH_2Cl_2	3	50
I	100	MnO_2	CH_2Cl_2	2	65
I	100	MnO_2	THF (65 °C)	2	12
I	30	quinone	CH_2Cl_2	12	57
I	**30**	**quinone**	**CH_2Cl_2**	**20**	**65**[b]
I	30	quinone	THF (65 °C)	14	58[b]
I	30	azobenzene	CH_2Cl_2	20	8[b]
I	8	quinone	CH_2Cl_2	70	24[b]

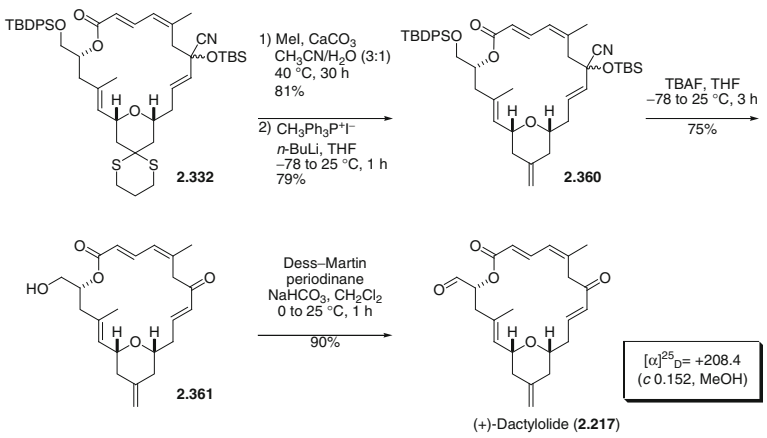
[a] Yield of the isolated **2.332**
[b] Addition of ω-hydroxy aldehyde **2.333** via syringe pump over 2 h period



Scheme 2.81 Shiina's MNBA macrolactonization

2.3.3.7 Completion of Total Synthesis of (+)-Dactylolide

Having successfully assembled macrolactone **2.332**, we embarked on the completion of the synthesis of (+)-dactylolide (**2.217**) by elaborating the C(13) *exo*-methylene group, unveiling the C(7) carbonyl group, and oxidizing the C(20) hydroxyl group to the corresponding aldehyde (Scheme 2.82). Hydrolysis of the 1,3-dithiane group of **2.332** and Wittig olefination of the resulting ketone gave



Scheme 2.82 Completion of total synthesis of (+)-dactylolide (**2.217**)

2.360. Concomitant deprotection of TBS and TBDPS groups followed by Dess–Martin oxidation of alcohol **2.361** afforded (+)-dactylolide (**2.217**) which proved identical in all respects to the natural product.

2.3.3.8 Conclusion

In conclusion, the total synthesis of (+)-dactylolide (**2.217**) has been accomplished in 19 steps for the longest sequence from commercially available 1,3-dithiane with an overall yield of 1.4 % (1.9 % BRSM). Highlights of the synthesis include the organocatalytic 1,6-oxa conjugate addition reaction for the stereoselective synthesis of 2,6-*cis*-2-(4-oxo-2-butenyl)-tetrahydropyran and the NHC-catalyzed oxidative lactonization for the construction of the 20-membered macrolactone. Other notable features in the synthesis are highly efficient carbon–carbon bond formations, including 1,3-dithiane coupling reaction, asymmetric addition of alkenylzinc reagent, and cyanohydrin alkylation, that allow a convergent approach to the carbon skeleton in **2.217**. We strongly believe that the NHC-catalyzed oxidative macrolactonization provides a new approach to a diverse set of macrolactones.

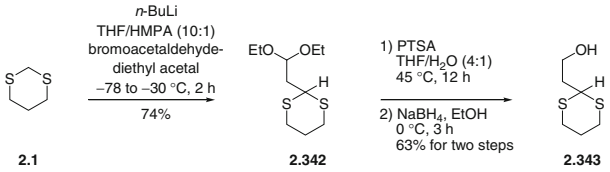
2.3.3.9 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. Anhydrous tetrahydrofuran

(THF) was distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed on SiO_2 (60 Å) with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel 60 (particle size 4063 μm. 230400 mesh). ^{1}H NMR, ^{13}C NMR, and 2D NMR (COSY, NOESY) spectra were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in $CDCl_3$ by using the signal of residual $CHCl_3$, as an internal standard. All NMR δ values are given in ppm, and all J values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo-Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1 W) polarimeter.

Preparation of 1,3-Dithiane-2-Ethanol (2.343) [235]



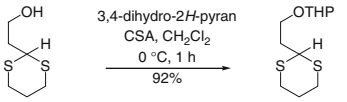
To a cooled (–78 °C) solution of 1,3-dithiane (**2.1**, 1.25 g, 10.396 mmol) in THF/HMPA (10:1, 33 mL) was added *n*-BuLi (2.5 M in hexane, 4.2 mL, 10.396 mmol). After stirring for 1 h at the same temperature, bromoacetaldehyde diethyl acetal (1.8 mL, 12.475 mmol) in THF (2 mL) was added dropwise and the mixture was warmed to –30 °C over a 1-h period. The resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 20/1) to afford the known acetal **2.342** [236] (1.81 g, 74 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (dd, J = 6.0, 6.0 Hz, 1H), 4.08 (dd, J = 7.6, 7.6 Hz, 1H), 3.60–3.69 (m, 2H), 3.47–3.55 (m, 2H), 2.77–2.90 (m, 4H), 2.04–2.13 (m, 1H), 2.02 (dd, J = 7.2, 7.2 Hz, 2H), 1.81–1.93 (m, 1H), 1.19 (dd, J = 7.2, 7.2 Hz, 6H).

To a solution of **2.342** (865 mg, 3.659 mmol) in THF/H_2O (4:1, 25 mL) was added *p*-toluenesulfonic acid (70 mg, 0.366 mmol). After stirring for 12 h at 45 °C, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the aqueous layer

was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a short pad of silica gel, and concentrated *in vacuo* which was employed in the next step without further purification.

To a cooled (0 °C) solution of the resulting aldehyde in EtOH (15 mL) was added $NaBH_4$ (692 mg, 18.295 mmol). After stirring for 3 h at the same temperature, the resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc and H_2O. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 10/1) to afford the known 1,3-dithiane-2-ethanol (**2.343**) (378 mg, 63 % for two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (dd, J = 7.5, 7.5 Hz, 1H), 3.82 (ddd, J = 5.5, 5.5, 5.5 Hz, 2H), 2.81–2.92 (m, 4H), 2.08–2.15 (m, 1H), 2.01 (ddd, J = 6.5, 6.5, 6.5 Hz, 2H), 1.82–1.93 (m, 2H).

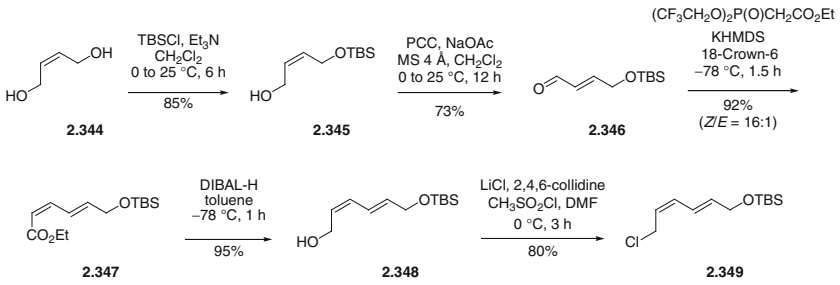
Preparation of THP Ether 2.351



2.343 **2.351**

To a cooled (0 °C) solution of **2.343** (1.541 g, 9.380 mmol) in CH_2Cl_2 (50 mL, 0.188 M) were added 3,4-dihydro-*2H*-pyran (1.03 mL, 11.256 mmol) and (+)-camphorsulfonic acid (218 mg, 0.938 mmol). After stirring at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 8/1) to afford THP ether **2.351** (2.143 g, 92 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, J = 4.0, 4.0 Hz, 1H), 4.20 (dd, J = 7.2, 7.2 Hz, 1H), 3.82–3.92 (m, 2H), 3.46–3.59 (m, 2H), 2.79–2.91 (m, 4H), 2.01–2.15 (m, 1H), 2.04 (ddd, J = 6.4, 6.4, 6.4 Hz, 2H), 1.77–1.93 (m, 2H), 1.65–1.74 (m, 1H), 1.49–1.61 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.3, 63.2, 61.7, 43.6, 35.2, 30.2, 29.6, 25.6, 25.0, 19.1; IR (neat) 2938, 1735, 1422, 1352, 1119, 1032 cm^{-1}; HRMS (ESI) *m/z* 271.0798 [$(M+Na)^+$, $C_{11}H_{20}O_2S_2$ requires 271.0797].

Preparation of the [[(2*E*,4*Z*]-6-Chloro-2,4-hexadienyl)oxy](1,1-dimethylethyl) dimethylsilane (2.349)



To a mixture of *cis*-2-butene-1,4-diol (**2.344**, 1.726 g, 19.589 mmol) and Et_3N (4.1 mL, 29.384 mmol) in CH_2Cl_2 (120 mL), a solution of *t*-butyldimethylsilyl chloride (2.952 g, 19.589 mmol) in CH_2Cl_2 (20 mL) was slowly added over a 1-h period. After stirring for additional 5 h at 25 °C, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2 and H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 6/1) to afford the known alcohol **2.345** [237] (3.369 g, 85 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62–5.76 (m, 2H), 4.23–4.26 (m, 2H), 4.17–4.20 (m, 2H), 2.21 (br s, 1H), 0.90 (s, 9H), 0.08 (s, 6H).

To a cooled (0 °C) solution of **2.345** (2.51 g, 12.403 mmol) in CH_2Cl_2 (100 mL, 0.124 M) were added NaOAc (305 mg, 3.721 mmol), MS 4 Å (2.5 g), and PCC (5.35 g, 24.806 mmol). After stirring for 12 h at 25 °C, the reaction mixture was diluted with Et_2O, filtered through a pad of Celite, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford the known aldehyde **2.346** [238] (1.81 g, 73 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, J = 8.4 Hz, 1H), 6.87 (ddd, J = 15.6, 3.6, 3.6 Hz, 1H), 6.38 (dddd, J = 15.6, 8.4, 2.4, 2.4 Hz, 1H), 4.42–4.44 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H).

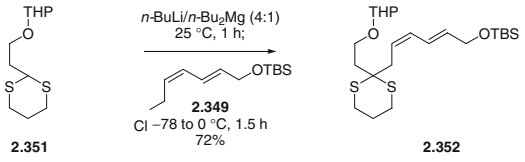
To a cooled (–78 °C) solution of ethyl bis(2,2,2-trifluoroethyl)phosphonoacetate (3.40 g, 10.237 mmol) and 18-Crown-6 (2.71 g, 10.237 mmol) in THF (200 mL, 0.051 M) was added KHMDS (0.5 M in toluene, 19.2 mL, 9.597 mmol). After stirring for 30 min at the same temperature, **2.346** (1.28 g, 6.398 mmol) in THF (3 mL) was added dropwise to the reaction mixture. After stirring for an additional 1 h at –78 °C, the resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/

EtOAc = 10/1) to afford dienoate **2.347** (1.59 g, 92 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.54 (m, 1H), 6.57 (dd, J = 9.2, 9.2 Hz, 1H), 6.09 (ddd, J = 15.5, 5.0, 5.0 Hz, 1H), 5.64 (d, J = 9.6 Hz, 1H), 4.31 (br d, J = 3.6 Hz, 2H), 4.19 (ddd, J = 6.0, 6.0, 6.0 Hz, 2H), 1.29 (dd, J = 5.6, 5.6 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 143.8, 142.5, 125.6, 117.3, 63.2, 59.8, 25.8, 18.3, 14.2, –5.4.

To a cooled (–78 °C) solution of **2.347** (843 mg, 3.117 mmol) in toluene (30 mL, 0.104 M) was added DIBAL-H (9.4 mL, 1.0 M in toluene, 9.351 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with MeOH followed by aqueous Rochelle's salt solution and diluted with Et_2O. The resulting mixture was stirred for 5 h at 25 °C. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford the known alcohol **2.348** [239] (676 mg, 95 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (dd, J = 9.2, 9.2 Hz, 1H), 6.09 (dd, J = 9.2, 9.2 Hz, 1H), 5.81 (ddd, J = 12.0, 3.6, 3.6 Hz, 1H), 5.54–5.60 (m, 1H), 4.30 (br d, J = 3.2 Hz, 2H), 4.23 (d, J = 3.6 Hz, 2H), 1.60 (br s, 1H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 129.47, 129.39, 124.1, 63.2, 58.3, 25.8, 18.2, –5.4.

To a cooled (0 °C) solution of **2.348** (307 mg, 1.344 mmol) in DMF (10 mL, 0.134 M) were added 2,4,6-collidine (0.36 ml, 2.688 mmol), methanesulfonyl chloride (0.21 mL, 2.688 mmol) and lithium chloride (171 mg, 4.032 mmol). After stirring for 3 h at 0 °C, the resulting mixture was quenched with H_2O and diluted with hexanes. The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 10/1) to afford the known [[(2*E*,4*Z*)-6-chloro-2,4-hexadienyl]oxy](1,1-dimethylethyl)dimethylsilane (**2.349**) [239] (265 mg, 80 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45–6.53 (m, 1H), 6.11 (dd, J = 10.8, 10.8 Hz, 1H), 5.83 (ddd, J = 15.2, 4.8, 4.8 Hz, 1H), 5.53 (ddd, J = 8.0, 8.0, 8.0 Hz, 1H), 4.20 (br d, J = 3.6 Hz, 2H), 4.14 (d, J = 8.0 Hz, 2H), 0.86 (s, 9H), 0.02 (s, 6H).

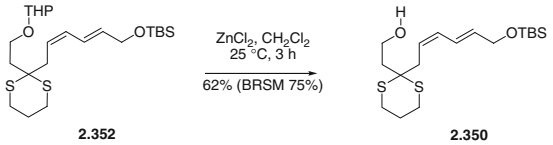
Preparation of Diene 2.352



To a solution of dithiane **2.351** (665.0 mg, 2.677 mmol) in THF (7 mL) was added a mixture of *n*-BuLi/*n*-Bu_2Mg which was prepared from *n*-BuLi (2.5 M in hexane, 1.71 mL, 4.283 mmol) and *n*-Bu_2Mg (1.0 M in heptane, 1.07 mL,

1.071 mmol) at 25 °C. After stirring for 1 h at the same temperature, the reaction mixture was cooled to –78 °C, and dienyl chloride **2.349** (1.321 g, 5.354 mmol) in THF (3 mL) was added dropwise and gradually warmed to 0 °C over a 1.5-h period. The resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc/Et_3N = 10/1/0.1) to afford diene **2.352** (884.3 mg, 72 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49–6.57 (m, 1H), 6.17 (dd, J = 10.8, 10.8 Hz, 1H), 5.79 (ddd, J = 15.2, 5.2, 5.2 Hz, 1H), 5.57 (ddd, J = 10.8, 7.6, 7.6 Hz, 1H), 4.57–4.60 (m, 1H), 4.24 (d, J = 4.8 Hz, 2H), 3.93 (ddd, J = 10.0, 7.2, 7.2 Hz, 1H), 3.83–3.90 (m, 1H), 3.58 (ddd, J = 10.0, 7.2, 7.2 Hz, 1H), 3.47–3.54 (m, 1H), 2.76–2.90 (m, 6H), 2.26 (dd, J = 7.2, 7.2 Hz, 2H), 1.89–2.01 (m, 2H), 1.74–1.84 (m, 1H), 1.66–1.74 (m, 1H), 1.50–1.62 (m, 4H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 130.6, 124.94, 124.69, 98.9, 94.5, 63.9, 63.5, 62.8, 62.2, 51.6, 37.8, 37.2, 30.6, 26.07, 26.06, 25.9, 25.3, 24.9, 19.63, 19.46, 18.3, –5.3; IR (neat) 2928, 2854, 1251, 1121, 1032, 834, 777 cm^{-1}; HRMS (ESI) *m/z* 481.2238 [(M+Na)$^+$, $C_{23}H_{42}O_3S_2Si$ requires 481.2237].

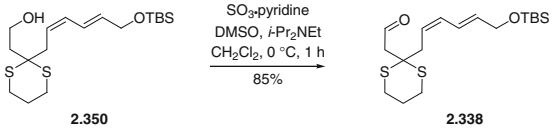
Preparation of Alcohol 2.350



2.352 **2.350**

To a solution of **2.352** (325.3 mg, 0.709 mmol) in CH_2Cl_2 (15 mL, 0.047 M) was added $ZnCl_2$ (1.0 M in Et_2O, 2.13 ml, 2.127 mmol) at 25 °C. After stirring for 3 h, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1) to afford alcohol **2.350** (164.7 mg, 62 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.49–6.56 (m, 1H), 6.18 (dd, J = 11.0, 11.0 Hz, 1H), 5.81 (ddd, J = 15.0, 5.0, 5.0 Hz, 1H), 5.53 (ddd, J = 11.0, 7.5, 7.5 Hz, 1H), 4.24 (d, J = 4.0 Hz, 2H), 3.83 (ddd, J = 6.0, 6.0, 6.0 Hz, 2H), 2.80–2.94 (m, 6H), 2.33 (dd, J = 6.0, 6.0 Hz, 1H), 2.21 (dd, J = 6.0, 6.0 Hz, 2H), 1.90–2.03 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 131.0, 124.51, 124.43, 63.5, 59.4, 51.8, 40.5, 37.4, 26.2, 25.9, 24.8, 18.4, –5.2; IR (neat) 3420, 2952, 2928, 2855, 2360, 2337, 1254, 1046, 835 cm^{-1}; HRMS (ESI) *m/z* 397.1659 [(M+Na)$^+$, $C_{18}H_{34}O_2S_2Si$ requires 397.1662].

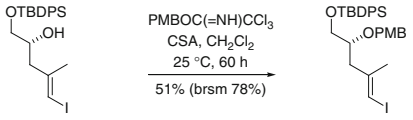
Preparation of Aldehyde 2.338



2.350 **2.338**

To a cooled (0 °C) solution of **2.350** (715 mg, 1.601 mmol) in CH_2Cl_2 (20 mL, 0.095 M) were added DMSO (0.54 mL, 7.633 mmol), *i*-Pr_2NEt (0.67 mL, 3.816 mmol), and SO_3·pyridine (607 mg, 3.816 mmol). After stirring for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5/1) to afford aldehyde **2.338** (604 mg, 85 %) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (dd, J = 2.5, 2.5 Hz, 1H), 6.47–6.54 (m, 1H), 6.23 (dd, J = 10.5, 10.5 Hz, 1H), 5.84 (ddd, J = 15.0, 5.0, 5.0 Hz, 1H), 5.50–5.57 (m, 1H), 4.25 (d, J = 5.0 Hz, 2H), 2.93 (d, J = 7.5 Hz, 2H), 2.88 (dd, J = 5.5, 5.5 Hz, 4H), 2.85 (d, J = 3.0 Hz, 2H), 1.96–2.04 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 135.0, 131.9, 124.0, 123.5, 63.3, 50.2, 49.0, 38.1, 26.19, 25.88, 24.4, 18.3, –5.2; IR (neat) 2927, 2854, 2361, 1717, 1102, 835 cm^{-1}; HRMS (ESI) *m/z* 395.1507 [(M+Na)$^+$, $C_{18}H_{32}O_2S_2Si$ requires 395.1505].

Preparation of PMB Ether 2.337

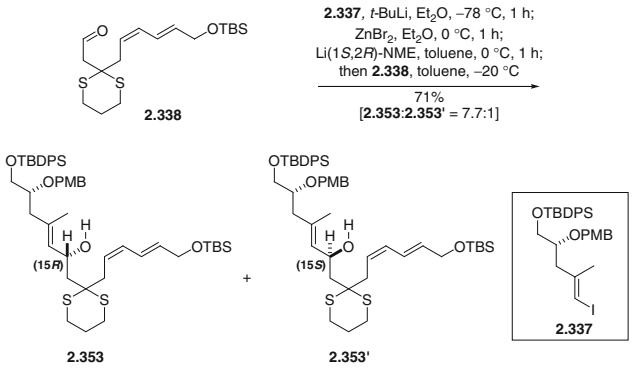


2.341 **2.337**

To a cooled (0 °C) solution of the known 1-(*tert*-butyl-diphenyl-silanyloxy)-(*E*)-5-iodo-4-methyl-pent-4-en-2-ol (**2.341**) [163] (1.120 g, 2.331 mmol) in CH_2Cl_2 (20 mL, 0.117 M) was added 4-methoxybenzyl-2,2,2-trichloroacetimidate (0.97 mL, 4.662 mmol) followed by (+)-camphorsulfonic acid (54 mg, 0.233 mmol). After stirring at 25 °C for 60 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 20/1) to afford PMB ether **2.337** (713 mg, 51 %) as a colorless oil: $[\alpha]^{23}_D$= +18.9 (*c* 2.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.68 (m, 4H), 7.35–7.46 (m, 6H), 7.17 (d, J = 8.5 Hz, 2H), 6.84–6.87 (m, 2H), 5.95 (s, 1H), 4.52

(d, $J = 11.5$ Hz, 1H), 4.35 (d, $J = 11.5$ Hz, 1H), 3.80 (s, 3H), 3.71 (dd, $J = 10.0$, 5.0 Hz, 1H), 3.53–3.61 (m, 2H), 2.49 (dd, $J = 14.0$, 4.5 Hz, 1H), 2.39 (dd, $J = 14.0$, 7.5 Hz, 1H), 1.74 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 144.7, 135.59, 135.56, 133.35, 133.26, 130.5, 129.72, 129.69, 129.43, 127.7, 113.79, 113.73, 77.2, 77.0, 71.7, 65.4, 55.2, 41.8, 26.8, 24.2, 19.2; IR (neat) 2930, 2856, 1737, 1512, 1245, 1119, 702 cm^{-1}; HRMS (ESI) *m/z* 618.1899 [$(M+NH_4)^+$, $C_{30}H_{37}IO_3Si$ requires 618.1895].

Preparation of Alcohol 2.353



To a cooled (–78 °C) solution of vinyl iodide **2.337** (109.2 mg, 0.182 mmol) in Et_2O (1.5 mL) was added dropwise *t*-BuLi (1.7 M in pentane, 0.2 mL, 0.345 mmol). After stirring for 1 h at the same temperature, a solution of $ZnBr_2$ (0.888 M in Et_2O, 0.27 mL, 0.236 mmol) was added dropwise and the resulting mixture was then warmed to 0 °C. After stirring for 1 h at the same temperature, a solution of lithiated (1*S*,2*R*)-*N*-methylephedrine (0.195 M in toluene, 1.12 mL, 0.218 mmol), which was prepared by treatment of (1*S*,2*R*)-*N*-methylephedrine (143 mg) in toluene (4.0 mL) with *n*-BuLi (2.5 M in hexane, 0.32 ml) at 0 °C for 20 min, was added dropwise and the resulting mixture was stirred for an additional 1 h at 0 °C. The combined mixture was cooled to –20 °C, and aldehyde **2.338** (27.0 mg, 0.072 mmol) in toluene (2.5 mL) was slowly added by syringe pump over 30 min. After stirring at –20 °C for additional 3.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford α-alcohol **2.353** (36.1 mg, 59 %), *β*-alcohol **2.353′** (4.6 mg, 8 %), and a mixture of α-alcohol **2.353** and *β*-alcohol **2.353′** (2.7 mg, 4 %) as pale yellow oils.

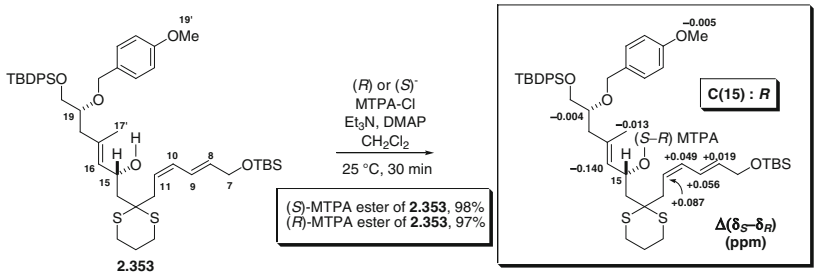
[**For major (15*R*)-alcohol 2.353**] $[\alpha]^{23}_D$= +20.2 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, $J = 7.0$, 1.5 Hz, 4H), 7.35–7.45 (m, 6H), 7.22 (d, $J = 9.0$ Hz, 2H), 6.82–6.86 (m, 2H), 6.52–6.58 (m, 1H), 6.16 (dd, $J = 11.0$,

11.0 Hz, 1H), 5.80 (ddd, J = 15.5, 5.0, 5.0 Hz, 1H), 5.54 (ddd, J = 11.0, 7.0, 7.0 Hz, 1H), 5.29 (d, J = 8.0 Hz, 1H), 4.72–4.77 (m, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.43 (d, J = 11.5 Hz, 1H), 4.24 (d, J = 4.5 Hz, 2H), 3.79 (s, 3H), 3.68–3.76 (m, 1H), 3.57–3.64 (m, 2H), 2.77–2.97 (m, 6H), 2.27–2.33 (m, 2H), 2.16–2.24 (m, 1H), 1.91–2.05 (m, 2H), 1.87 (dd, J = 15.0, 2.5 Hz, 1H), 1.63 (s, 3H), 1.07 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.62, 135.60, 134.6, 134.3, 133.54, 133.50, 130.93, 130.89, 129.7, 129.65, 129.63, 129.3, 127.66, 127.65, 124.63, 124.60, 113.7, 78.0, 71.7, 65.88, 65.85, 63.5, 55.2, 51.9, 45.1, 41.7, 37.6, 26.8, 26.35, 26.13, 25.9, 24.7, 19.2, 18.4, 17.3, –5.2; IR (neat) 3446, 2929, 2855, 1738, 1246, 1111, 1045, 835 cm^{-1}; HRMS (ESI) *m/z* 864.4542 [$(M+NH_4)^+$, $C_{48}H_{70}O_5S_2Si_2$ requires 864.4541].

[**For minor (15*S*)-alcohol 2.353′**] $[\alpha]^{25}_D$= –2.5 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 7.0 Hz, 4H), 7.36–7.45 (m, 6H), 7.20 (d, J = 8.5 Hz, 2H), 6.84–6.87 (m, 2H), 6.53–6.59 (m, 1H), 6.17 (dd, J = 11.5, 11.5 Hz, 1H), 5.80 (ddd, J = 15.0, 4.5, 4.5 Hz, 1H), 5.55 (ddd, J = 10.5, 7.0, 7.0 Hz, 1H), 5.29 (d, J = 8.5 Hz, 1H), 4.74–4.79 (m, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.5 Hz, 1H), 4.25 (d, J = 4.5 Hz, 2H), 3.79 (s, 3H), 3.70–3.78 (m, 1H), 3.60–3.65 (m, 2H), 2.77–2.99 (m, 6H), 2.26–2.38 (m, 2H), 2.17–2.22 (m, 1H), 1.91–2.05 (m, 2H), 1.92 (dd, J = 15.5, 2.0 Hz, 1H), 1.64 (s, 3H), 1.07 (s, 9H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 135.62, 135.59, 134.39, 134.30, 133.48, 133.46, 130.96, 130.90, 129.9, 129.6, 129.1, 127.7, 124.60, 124.47, 113.7, 77.7, 71.7, 66.07, 65.88, 63.5, 55.26, 55.24, 51.9, 44.9, 42.0, 37.6, 26.8, 26.37, 26.09, 25.9, 24.7, 19.2, 18.4, 17.0, –5.2; IR (neat) 3405, 2929, 2855, 1738, 2361, 1246, 1106, 1036, 824 cm^{-1}.

Determination of Absolute Stereochemistry of C(15)

The configuration of the C(15) stereocenter of **2.353** was determined using the procedure reported by Kakisawa and co-workers [225].



To a cooled (0 °C) solution of alcohol **2.353** (10.0 mg, 0.012 mmol) in CH_2Cl_2 (2 mL, 0.006 M) were added Et_3N (16 μL, 0.118 mmol), DMAP (2.9 mg, 0.024 mmol), and (*R*)-(–)-MTPA chloride (15.0 mg, 0.059 mmol). After stirring at 25 °C for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. The layers were separated, and the aqueous

layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5/1) to afford (*S*)-MTPA ester (11.6 mg, 98 %) as a colorless oil. (*R*)-MTPA ester was prepared in the same procedure by using (*S*)-(+)-MTPA chloride (97 %).

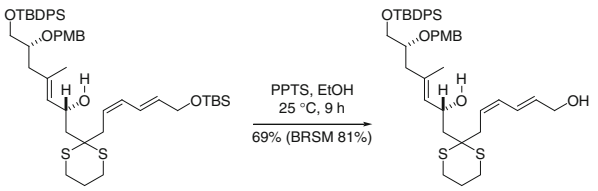
(*S*)-MTPA Ester of 2.353: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.69 (m, 4H), 7.46–7.49 (m, 2H), 7.30–7.45 (m, 9H), 7.16 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.43–6.51 (m, 1H), 6.12 (dd, J = 11.2, 11.2 Hz, 1H), 5.97 (ddd, J = 6.4, 5.2, 5.2 Hz, 1H), 5.78 (ddd, J = 15.2, 5.2, 5.2 Hz, 1H), 5.45 (ddd, J = 11.2, 7.2, 7.2 Hz, 1H), 5.14 (d, J = 9.2 Hz, 1H), 4.45 (d, J = 11.6 Hz, 1H), 4.35 (d, J = 11.6 Hz, 1H), 4.23 (d, J = 4.4 Hz, 2H), 3.78 (s, 3H), 3.65–3.70 (m, 1H), 3.54–3.62 (m, 2H), 3.50 (s, 3H), 2.68–2.79 (m, 6H), 2.40 (dd, J = 15.2, 5.6 Hz, 1H), 2.31 (dd, J = 14.4, 4.4 Hz, 1H), 2.12–2.25 (m, 2H), 1.85–1.94 (m, 2H), 1.82 (s, 3H), 1.06 (s, 9H), 0.92 (s, 9H), 0.07 (s, 6H).

(*R*)-MTPA Ester of 2.353: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.68 (m, 4H), 7.50–7.53 (m, 2H), 7.30–7.45 (m, 9H), 7.16 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H), 6.37–6.45 (m, 1H), 6.07 (dd, J = 11.2, 11.2 Hz, 1H), 5.95–6.01 (m, 1H), 5.76 (ddd, J = 14.8, 5.2, 5.2 Hz, 1H), 5.36 (ddd, J = 10.8, 7.2, 7.2 Hz, 1H), 5.29 (d, J = 10.0 Hz, 1H), 4.46 (d, J = 11.2 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.23 (d, J = 4.8 Hz, 2H), 3.79 (s, 3H), 3.65–3.71 (m, 1H), 3.54–3.61 (m, 2H), 3.49 (s, 3H), 2.63–2.70 (m, 3H), 2.43–2.57 (m, 3H), 2.33–2.39 (m, 2H), 2.19–2.26 (m, 1H), 2.11 (dd, J = 15.6, 4.4 Hz, 1H), 1.84 (s, 3H), 1.78–1.90 (m, 2H), 1.05 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H).

Chemical shift of (*R*) and (*S*)-MTPA Esters of 2.353

	H-8	H-9	H-10	H-11	H-16	H-17′	H-19	H-19′
(*S*)-MTPA ester	5.778	6.470	6.119	5.447	5.143	1.826	3.683	3.782
(*R*)-MTPA ester	5.759	6.414	6.070	5.36	5.283	1.839	3.687	3.787
δ_s–δ_R(ppm)	+0.019	+0.056	+0.049	+0.087	−0.140	−0.013	−0.004	−0.005

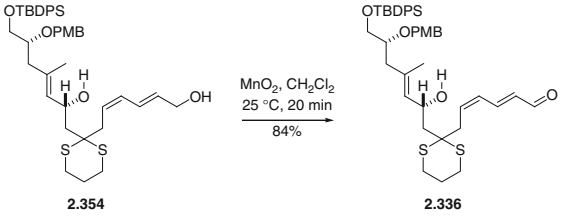
Preparation of Alcohol 2.354



2.353 **2.354**

To a solution of **2.353** (311.0 mg, 0.367 mmol) in EtOH (15 mL, 0.024 M) was added PPTS (18.4 mg, 0.073 mmol) at 25 °C. After stirring for 9 h at the same temperature, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 3/1) to afford alcohol **2.354** (185.6 mg, 69 %) as a colorless oil: $[\alpha]^{25}{}_D$= +22.3 (*c* 2.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 6.4 Hz, 4H), 7.35–7.45 (m, 6H), 7.22 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.52–6.59 (m, 1H), 6.17 (dd, J = 11.2, 11.2 Hz, 1H), 5.86 (ddd, J = 15.2, 5.6, 5.6 Hz, 1H), 5.60 (ddd, J = 11.2, 7.2, 7.2 Hz, 1H), 5.28 (d, J = 8.4 Hz, 1H), 4.73 (dd, J = 8.4, 8.4 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.42 (d, J = 11.2 Hz, 1H), 4.20 (s, 2H), 3.80 (s, 3H), 3.68–3.75 (m, 1H), 3.58–3.64 (m, 2H), 2.75–2.99 (m, 6H), 2.27–2.34 (m, 2H), 2.15–2.21 (m, 1H), 1.88–2.05 (m, 2H), 1.49 (dd, J = 15.2, 2.0 Hz, 1H), 1.63 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 135.53, 135.51, 134.6, 133.7, 133.43, 133.38, 130.8, 130.7, 129.64, 129.58, 129.2, 127.61, 127.59, 125.8, 125.4, 113.6, 77.8, 71.6, 65.87, 65.75, 63.1, 55.2, 51.9, 44.8, 41.6, 37.5, 26.8, 26.26, 26.05, 24.7, 19.1, 17.2; IR (neat) 3387, 2929, 2858, 2361, 2334, 1512, 1248, 1112 cm^{-1}; HRMS (ESI) *m/z* 755.3228 [$(M+Na)^+$, $C_{42}H_{56}O_5S_2Si$ requires 755.3231].

Preparation of ω-Hydroxy 2,4-Dienal 2.336

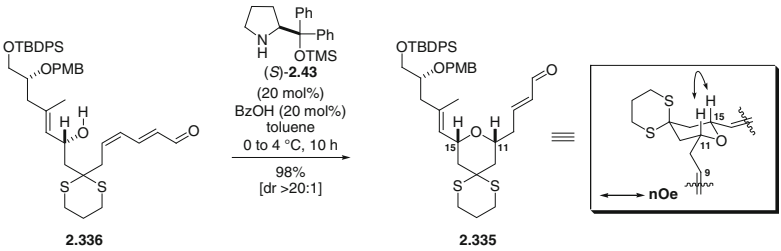


2.354 2.336

To a solution of alcohol **2.354** (217 mg, 0.296 mmol) in CH_2Cl_2 (10 mL, 0.029 M) was added MnO_2 (128 mg, 1.480 mmol), and the resulting mixture was stirred for 5 min at 25 °C. An addition of MnO_2 (128 mg, 1.480 mmol) was repeated two times every 5 min. After stirring at the same temperature for additional 5 min, the resulting mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 4/1) to afford ω-hydroxy 2,4-dienal **2.336** (182 mg, 84 %) as a colorless oil: $[\alpha]^{23}{}_D$= +22.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.2 Hz), 7.35–7.49 (m, 6H), 7.20 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.40 (dd, J = 11.2, 11.2 Hz, 1H), 6.14–6.20 (m, 2H), 5.29 (d, J = 8.8 Hz, 1H), 4.76 (dd, J = 8.8, 8.8 Hz, 1H), 4.56 (d, J = 11.2 Hz, 1H), 4.40 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.68–3.74 (m, 1H), 3.58–3.64 (m, 2H), 2.78–3.10 (m, 6H), 2.15–2.38 (m, 4H), 1.92–2.05 (m, 3H), 1.64

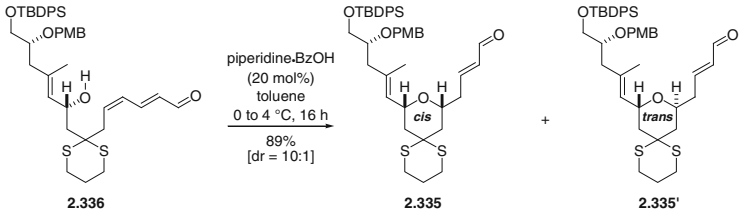
(s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 159.0, 146.2, 137.0, 135.55, 135.53, 134.9, 133.42, 133.37, 132.6, 130.8, 129.68, 129.63, 129.21, 129.17, 127.64, 127.63, 113.6, 77.7, 71.6, 66.0, 65.7, 55.21, 55.19, 51.7, 45.1, 41.6, 38.1, 26.8, 26.27, 26.12, 24.6, 19.1, 17.2; IR (neat) 3370, 2916, 1678, 1513, 1112 cm^{-1}; HRMS (ESI) *m/z* 748.3513 [(M+NH$_4$)$^+$, $C_{42}H_{54}O_5S_2Si$ requires 748.3520].

Preparation of 2,6-*cis*-Tetrahydropyran Enal 2.335 by the Organocatalytic 1,6-Oxa Conjugate Addition



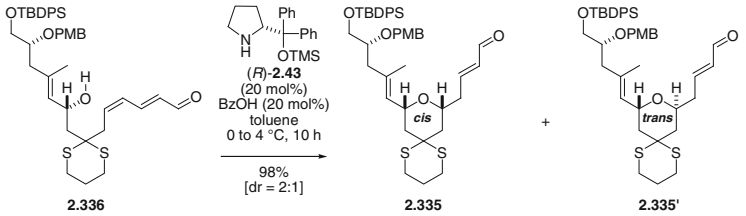
To a cooled (0 °C) solution of **2.336** (30.0 mg, 0.041 mmol) in toluene (3 mL, 0.014 M) was added dropwise a mixture of (*S*)-(–)-α,α-diphenyl-2-pyrrolidine-methanol trimethylsilyl ether ((*S*)-**2.43**) and BzOH (0.15 mL, 0.055 M in toluene). After stirring at 4 °C for 10 h, the reaction mixture was diluted with hexanes (10 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford 2,6-*cis*-tetrahydropyran enal **2.335** (29.4 mg, 98 %, dr >20:1) as a colorless oil: $[\alpha]^{25}{}_D$= +21.7 (*c* 2.88, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 8.0, 1.6 Hz, 4H), 7.35–7.46 (m, 6H), 7.23 (d, J = 8.4 Hz, 2H), 6.82–6.90 (m, 3H), 6.15 (dd, J = 15.6, 7.6 Hz, 1H), 5.21 (d, J = 7.6 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 4.50 (ddd, J = 10.0, 7.6, 2.4 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 3.97–4.03 (m, 1H), 3.79 (s, 3H), 3.67–3.75 (m, 1H), 3.56–3.65 (m, 2H), 2.87 (dd, J = 5.6, 5.6 Hz, 2H), 2.77 (dd, J = 5.6, 5.6 Hz, 2H), 2.46–2.58 (m, 2H), 2.30 (dd, J = 13.6, 7.2 Hz, 1H), 2.17–2.23 (m, 2H), 2.12 (d, J = 13.6 Hz, 1H), 2.00–2.05 (m, 2H), 1.63 (s, 3H), 1.59–1.65 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 159.0, 154.0, 136.6, 135.54, 135.51, 134.6, 133.42, 133.40, 130.8, 129.6, 129.3, 127.62, 127.60, 126.8, 113.5, 77.7, 71.6, 70.8, 70.2, 65.8, 55.2, 47.7, 42.56, 42.51, 41.6, 38.6, 26.8, 25.76, 25.64, 19.1, 17.4; IR (neat) 2930, 2856, 2360, 1734, 1689, 1512, 1242, 1070, 821, 701 cm^{-1}; HRMS (ESI) *m/z* 748.3513 [(M + NH$_4$)$^+$, $C_{42}H_{54}O_5S_2Si$ requires 748.3520].

Organocatalytic 1,6-Oxa Conjugate Addition by Piperidine



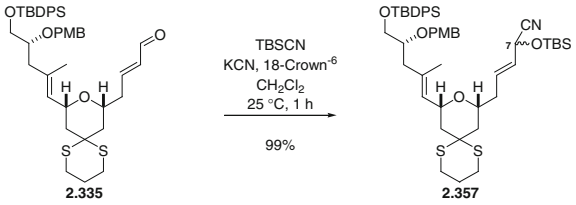
To a cooled (0 °C) solution of **2.336** (67.8 mg, 0.093 mmol) in toluene (8 mL, 0.012 M) was added dropwise a mixture of piperidine·BzOH (0.34 mL, 0.055 M in toluene). After stirring at 4 °C for 16 h, the reaction mixture was diluted with hexanes (20 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford a mixture of 2,6-*cis*-tetrahydropyran enal **2.335** and 2,6-*trans*-tetrahydropyran enal **2.335′**(60.0 mg, 89 %, dr = 10:1) as a colorless oil.

Organocatalytic 1,6-Oxa Conjugate Addition by (*R*)-2.43



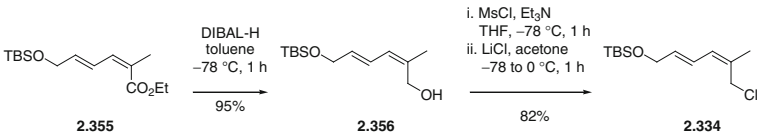
To a cooled (0 °C) solution of aldehyde **2.336** (28.0 mg, 0.038 mmol) in toluene (3 mL, 0.011 M) was added dropwise a mixture of (*R*)-(–)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether ((*R*)-**2.43**) and BzOH (0.14 mL, 0.055 M in toluene). After stirring at 4 °C for 10 h, the reaction mixture was diluted with hexanes (10 mL), filtered through a short pad of silica gel (hexanes/EtOAc, 3/1), and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford a mixture of 2,6-*cis*-tetrahydropyran enal **2.335** and 2,6-*trans*-tetrahydropyran enal **2.335′** (27.4 mg, 98 %, dr = 2:1) as a colorless oil.

Preparation of TBS-Protected Cyanohydrin 2.357



To a solution of **2.335** (110.2 mg, 0.150 mmol) in CH_2Cl_2 (10.0 mL, 0.015 M) were added TBSCN (0.2 M in CH_2Cl_2, 1.50 mL, 0.30 mmol), KCN (2.0 mg, 0.030 mmol), and 18-Crown-6 (8.0 mg, 0.030 mmol). After stirring at 25 °C for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc = 5/1) to afford TBS-protected cyanohydrin **2.357** (130.8 mg, 99 %) as a colorless oil: $[\alpha]^{23}{}_D$= +21.3 (*c* 1.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 4H), 7.35–7.46 (m, 6H), 7.24 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.93–6.01 (m, 1H), 5.59 (dd, J = 15.6, 5.6 Hz, 1H), 5.20 (d, J = 7.6 Hz, 1H), 4.87–4.90 (m, 1H), 4.58 (d, J = 11.2 Hz, 1H), 4.46 (d, J = 11.2 Hz, 1H), 4.44–4.50 (m, 1H), 3.85–3.91 (m, 1H), 3.80 (s, 3H), 3.67–3.72 (m, 1H), 3.57–3.65 (m, 2H), 2.82–2.91 (m, 2H), 2.72–2.80 (m, 2H), 2.14–2.38 (m, 5H), 1.99–2.11 (m, 3H), 1.63 (s, 3H), 1.54–1.63 (m, 2H), 1.07 (s, 9H), 0.90 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 136.70, 136.60, 135.61, 135.58, 133.5, 131.5, 131.3, 130.9, 129.68, 129.66, 129.4, 129.1, 127.68, 127.65, 127.5, 127.3, 126.98, 126.94, 118.7, 113.6, 77.98, 77.95, 71.7, 71.48, 71.45, 70.1, 65.9, 62.52, 62.40, 55.2, 47.9, 42.8, 42.3, 41.71, 41.73. 38.05, 38.01, 26.8, 25.82, 25.76, 25.5, 19.2, 18.1, 17.50, 17.47, –5.03, –5.06; IR (neat) 2929, 2856, 2362, 1512, 1247, 1110, 1066, 837 cm^{-1}; HRMS (ESI) *m/z* 889.4494 $[(M+NH_4)^+$, $C_{49}H_{69}NO_5S_2Si_2$ requires 889.4494].

Preparation of Dienyl Chloride 2.334

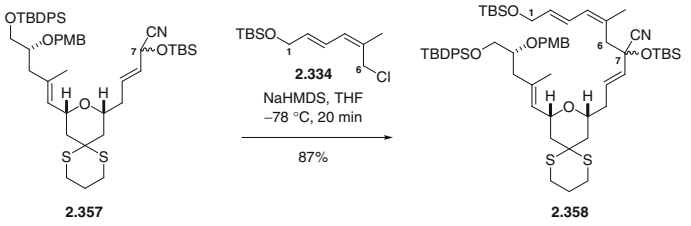


[**Reduction**] To a cooled (–78 °C) solution of the known (2*Z*,4*E*)-ethyl-6-((*tert*-butyldimethylsilyl)oxy)-2-methylhexa-2,4-dienoate (**2.355**) [240] (682 mg, 2.397 mmol) in toluene (20 mL, 0.120 M) was added DIBAL-H (1.0 M in toluene, 7.2 mL, 7.20 mmol). After stirring for 1 h at the same temperature, the reaction

mixture was quenched with MeOH and aqueous Rochelle's salt and diluted with H_2O and Et_2O. The resulting suspension was vigorously stirred at 25 °C until the organic layer turned clean. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 9/1) to afford alcohol **2.356** (552 mg, 95 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47–6.55 (m, 1H), 5.94 (d, J = 11.2 Hz, 1H), 5.71 (ddd, J = 14.8, 4.8, 4.8 Hz, 1H), 4.24 (s, 2H), 4.22 (d, J = 4.8 Hz, 2H), 1.87 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.3, 127.3, 124.7, 63.5, 61.7, 25.9, 21.4, 18.4, –5.2; IR (neat) 3342, 2928, 2856, 1471, 1376, 1250, 1112, 1005, 835 cm^{-1}; HRMS (ESI) *m/z* 265.1596 [(M+Na)$^+$, $C_{13}H_{26}O_2Si$ requires 265.1594].

[**Cholorination**] To a cooled (–78 °C) solution of **2.356** (104 mg, 0.429 mmol) in THF (5 mL, 0.086 M) were added methanesulfonyl chloride (37 μL, 0.472 mmol) and Et_3N (120 μL, 0.857 mmol). After stirring for 1 h at the same temperature, lithium chloride (91 mg, 2.143 mmol) and acetone (5 mL) were added and the reaction mixture was then warmed to 0 °C. After stirring at 0 °C for 1 h, the resulting mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with excessive amount of H_2O and hexanes (30 mL). The layers were separated, and the aqueous layer was extracted with hexanes. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtered through a short pad of silica gel and concentrated *in vacuo*. (silica gel, hexanes/EtOAc/Et_3N = 10/1/0.1) to afford dienyl chloride **2.334** (92 mg, 82 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45–6.52 (m, 1H), 6.00 (d, J = 11.2 Hz, 1H), 5.79 (ddd, J = 15.2, 5.2, 5.2 Hz, 1H), 4.25 (br d, J = 4.4 Hz, 2H), 4.17 (s, 2H), 1.89 (s, 3H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0, 132.5, 129.5, 124.2, 63.4, 43.6, 25.9, 21.8, 18.4, –5.2; IR (neat) 2929, 2856, 2361, 1462, 1380, 1254, 1113, 963, 776 cm^{-1}; HRMS (ESI) *m/z* 259.1284 [(M–H)$^+$, $C_{13}H_{25}ClOSi$ requires 259.1279].

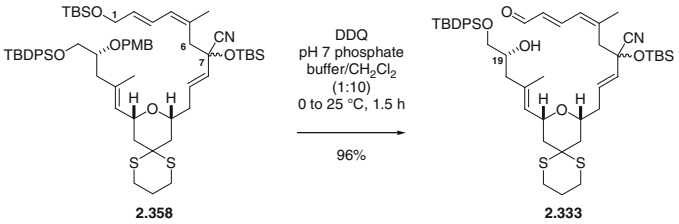
Preparation of Tetraene 2.358



To a cooled (–78 °C) mixture of **2.357** (143 mg, 0.165 mmol) and dienyl chloride **2.334** (86 mg, 0.330 mmol) in THF (8 mL, 0.02 M) was added dropwise NaHMDS (1.0 M in THF, 0.33 mL, 0.330 mmol). After stirring for 20 min at the same temperature, the resulting mixture was quenched with saturated aqueous

NH_4Cl solution and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford tetraene **2.358** (157 mg, 87 %) as a colorless oil (two diastereomers): $[\alpha]^{25}_D$= +17.1 (*c*, 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 7.5 Hz, 4H), 7.35–7.45 (m, 6H), 7.23–7.26 (m, 2H), 6.84 (d, J = 9.0 Hz, 2H), 6.38 (dd, J = 13.0, 13.0 Hz, 1H), 6.00–6.07 (m, 2H), 5.66–5.72 (m, 1H), 5.47 (dd, J = 15.5, 6.0 Hz, 1H), 5.18 (d, J = 7.5 Hz, 1H), 4.55–4.60 (m, 1H), 4.45–4.50 (m, 2H), 4.21 (br s, 2H), 3.82–3.89 (m, 1H), 3.80 (s, 3H), 3.66–3.70 (m, 1H), 3.58–3.65 (m, 2H), 2.80–2.88 (m, 2H), 2.70–2.80 (m, 3H), 2.62 (dd, J = 13.0, 13.0 Hz, 1H), 2.15–2.35 (m, 5H), 1.95–2.09 (m, 3H), 1.91/1.89 (s, 3H), 1.63/1.62 (s, 3H), 1.50–1.63 (m, 2H), 1.07 (s, 9H), 0.91 (s, 9H), 0.88/0.87 (s, 9H), 0.220/0.198 (s, 3H), 0.138/0.114 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 136.3, 135.9, 135.57, 135.54, 133.5, 132.4, 132.3, 132.02, 132.00, 130.9, 130.69, 130.66, 130.18, 130.15, 129.6, 129.30, 129.29, 129.1, 128.9, 128.6, 127.65, 127.62, 127.1, 127.0, 125.71, 125.68, 120.3, 113.6, 78.08, 78.04, 77.2, 73.05, 73.01, 71.61, 71.59, 71.43, 71.42, 70.13, 70.06, 65.83, 65.78, 63.4, 55.2, 47.86, 47.85, 45.69, 45.64, 42.68, 42.62, 42.43, 42.32, 41.63, 41.59, 38.3, 38.1, 26.8, 25.9, 25.8, 25.6, 25.58, 25.56, 25.4, 19.2, 18.3, 18.0, 17.47, 17.44, –2.88, –2.94, –3.82, –3.91, –5.2; IR (neat) 2930, 2856, 2361, 2336, 1734, 1247, 1073, 836 cm^{-1}; HRMS (ESI) *m/z* 1113.6089 [$(M+NH_4)^+$, $C_{62}H_{93}NO_6S_2Si_3$ requires 1113.6090].

Preparation of ω-Hydroxy Aldehyde 2.333

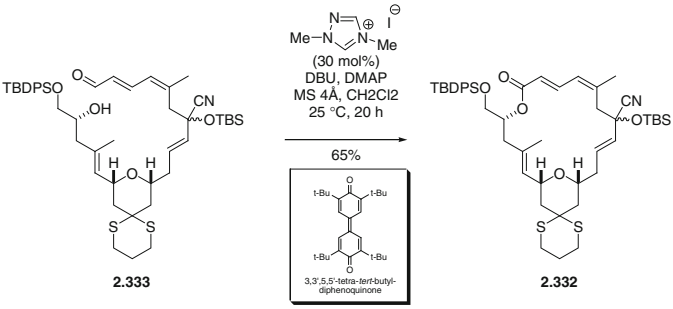


2.358 **2.333**

To a cooled (0 °C) solution of **2.358** (146 mg, 0.133 mmol) in pH 7 phosphate buffer/CH_2Cl_2 (1/10, total 22.0 mL) was added DDQ (60 mg, 0.266 mmol). After stirring at 25 °C for 1.5 h, the mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with excessive amount of H_2O. The resulting mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford ω-hydroxy aldehyde **2.333** (110 mg, 96 %) as a colorless oil (two diastereomers): $[\alpha]^{25}_D$= +11.2 (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56–9.61 (m, 1H), 7.64–7.67 (m, 4H), 7.36–7.47 (m, 6H), 7.24–7.35 (m, 1H), 6.36/6.28 (d,

J = 11.2 Hz, 1H), 6.04–6.17 (m, 2H), 5.50 (ddd, J = 15.2, 6.8, 6.8 Hz, 1H), 5.18 (d, J = 7.2 Hz, 1H), 4.48 (dd, J = 9.2, 9.2 Hz, 1H), 3.83–3.86 (m, 2H), 3.59 (dd, J = 10.4, 3.6 Hz, 1H), 3.47–3.52 (m, 1H), 2.55–2.92 (m, 6H), 1.99–2.33 (m, 11H), 1.673/1.663 (s, 3H), 1.53–1.64 (m, 2H), 1.06 (s, 9H), 0.873/0.864/0.856 (s, 9H), 0.213/0.198/0.184 (s, 3H), 0.138/0.133/0.124/0.121 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.83, 193.79, 147.64, 147.61, 146.98, 146.95, 144.45, 144.40, 144.2, 135.79, 135.73, 135.44, 135.30, 135.28, 133.04, 133.00, 132.00, 131.95, 131.90, 131.87, 131.4, 131.0, 129.8, 129.6, 129.4, 129.3, 129.13, 129.09, 127.73, 127.72, 127.4, 127.27, 127.23, 119.80, 119.78, 119.56, 72.99, 72.96, 72.8, 71.30, 71.26, 71.19, 70.24, 70.21, 70.18, 70.13, 69.87, 69.83, 67.38, 67.33, 53.17, 53.12, 47.7, 46.15, 46.12, 42.9, 42.56, 42.50, 42.45, 38.2, 37.9, 26.80, 26.66, 25.77, 25.65, 25.55, 25.48, 19.46, 19.44, 19.2, 18.0, 17.14, 17.12, 17.11, –2.92, –2.95, –2.98, –3.01, –3.88, –3.97, –4.04; IR (neat) 3426, 2929, 2856, 2361, 2338, 1678, 1628, 1075, 826 cm^{-1}; HRMS (ESI) *m/z* 882.4046 [(M+Na)$^+$, $C_{48}H_{69}NO_5S_2Si_2$ requires 882.4048].

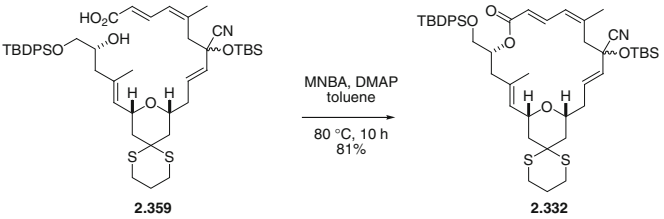
Preparation of Macrolactone 2.332 by NHC-Catalyzed Oxidative Macrolactonization



To a mixture of dimethyltriazolium iodide (4.2 mg, 0.0185 mmol), 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (50.3 mg, 0.1232 mmol), DMAP (7.5 mg, 0.0616 mmol), MS 4Å (250 mg, ca. 500 wt % of ω-hydroxy aldehyde **2.333**) in CH_2Cl_2 (3.0 mL) was added dropwise DBU (0.2 M in CH_2Cl_2, 0.62 mL, 0.1232 mmol). ω-Hydroxy aldehyde **2.333** (53.0 mg, 0.0616 mmol) in CH_2Cl_2 (5.0 mL) was added to the resulting mixture by syringe pump over a 2-h period. After stirring at 25 °C for additional 18 h, the resulting mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 8/1) to afford macrolactone **2.332** (34.2 mg, 65 %) as a colorless oil (two diastereomers): $[\alpha]^{25}{}_D$= +11.8 (c 0.445, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.63–7.72 (m, 4H), 7.46–7.64 (m, 1H), 7.33–7.47 (m, 6H), 5.49–6.30 (m, 3H), 5.14–5.28 (m, 2H), 4.36–4.52 (m, 1H), 3.87–3.97 (m, 1H), 3.73–3.86 (m, 3H), 2.76–2.99 (m, 5H), 2.00–2.64 (m, 7H), 1.90/1.88 (d, J = 1.2 Hz, 3H), 1.85–1.96 (m, 2H), 1.61/1.60 (s,

3H), 1.40-1.58 (m, 2H), 1.023/1.021/1.010/1.018 (s, 9H), 0.904/0.880/0.862/0.857 (s, 9H), 0.237/0.204/0.193/0.189 (s, 3H), 0.161/0.148/0.138/0.115 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.75, 166.68, 166.63, 166.43, 143.3, 142.7, 142.4, 141.9, 141.5, 141.2, 140.1, 136.55, 136.52, 136.50, 136.48, 134.37, 134.34, 134.31, 134.24, 134.23, 134.0, 133.9, 133.4, 132.8, 132.3, 132.0, 131.7, 131.44, 131.35, 131.25, 131.09, 130.9, 130.76, 130.67, 130.0, 129.7, 129.5, 129.4, 128.9, 128.8, 122.3, 122.2, 122.0, 121.6, 121.0, 120.6, 76.5, 74.9, 73.7, 73.2, 73.0, 72.7, 72.56, 72.51, 72.37, 72.28, 71.92, 71.41, 71.20, 71.15, 70.95, 66.80, 66.62, 66.02, 65.78, 52.80, 52.77, 48.80, 48.68, 46.40, 46.24, 44.29, 44.11, 44.05, 43.96, 43.84, 43.77, 42.73, 41.8, 41.5, 39.1, 38.4, 37.3, 30.9, 27.6, 27.4, 26.9, 26.5, 26.4, 26.31, 26.25, 26.21, 26.19, 26.05, 25.5, 21.4, 20.3, 20.06, 20.03, 18.97, 18.90, 18.81, 17.3, 17.0, 16.8, 16.3, –2.12, –2.18, –2.37, –2.50, –3.09, –3.14, –3.16, –3.39; IR (neat) 2929, 2856, 1708, 1427, 1251, 1082, 838 cm^{-1}; HRMS (ESI) *m/z* 880.3889 [(M+Na)$^+$, $C_{48}H_{67}NO_5S_2Si_2$ requires 880.3891].

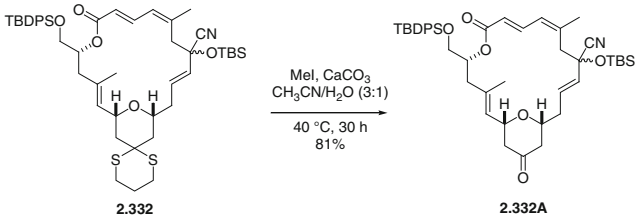
Preparation of Macrolactone 2.332 by Shiina's MNBA protocol [191–193]



2.359 **2.332**

To a solution of 2-methyl-6-nitrobenzoic anhydride (MNBA, 8.1 mg, 0.0234 mmol) and DMAP (7.1 mg, 0.0585 mmol) in toluene (10 mL) was slowly added hydroxy carboxylic acid (17.1 mg, 0.0195 mmol) in toluene (10 mL) at 80 °C by syringe pump over a 4-h period. After stirring for additional 6 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 8/1) to afford macrolactone **2.332** (13.5 mg, 81 %).

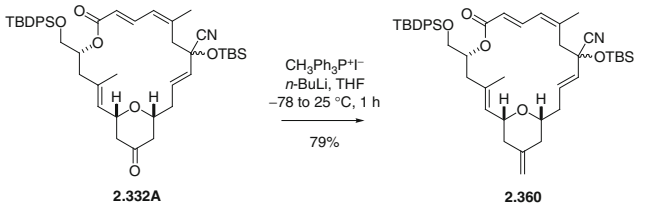
Preparation of Ketone 2.332A



2.332 **2.332A**

To a solution of **2.332** (35.0 mg, 0.041 mmol) in CH_3CN/H_2O (3:1, 13 mL) were added $CaCO_3$ (20.5 mg, 0.204 mmol) and MeI (101 μL, 1.631 mmol). After stirring at 40 °C for 30 h, the resulting mixture was diluted with Et_2O and H_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 6/1) to afford ketone **2.332A** (25.4 mg, 81 %) as a colorless oil (two diastereomers): $[\alpha]^{25}_D$= +10.1 (*c* 0.553, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.70–7.75 (m, 4H), 7.56–7.70 (m, 1H), 7.37–7.75 (m, 6H), 5.58–6.35 (m, 3H), 5.19–5.45 (m, 2H), 4.29–4.49 (m, 1H), 3.76–3.97 (m, 4H), 2.82–3.03 (m, 1H), 2.03–2.69 (m, 9H), 1.98/1.96 (d, J = 1.2 Hz, 3H), 1.64/1.61 (s, 3H), 1.068/1.065/1.055/1.052 (s, 9H), 0.94/0.93/0.91/0.90 (s, 9H), 0.28/0.25/0.24 (s, 3H), 0.20/0.19/0.16 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) 166.62, 166.59, 166.38, 143.3, 142.8, 142.4, 141.9, 141.6, 141.2, 140.22, 140.18, 136.53, 136.49, 136.46, 136.45, 135.0, 134.9, 134.37, 134.34, 134.28, 134.24, 134.20, 133.1, 132.67, 132.60, 132.28, 132.21, 131.6, 131.25, 131.07, 130.86, 130.79, 130.60, 130.44, 130.19, 129.83, 129.65, 129.60, 129.57, 129.36, 128.83, 128.81, 122.16, 122.11, 121.9, 121.5, 121.05, 120.95, 120.66, 120.54, 77.0, 76.7, 76.52, 76.46, 75.86, 75.72, 74.85, 74.77, 73.7, 72.9, 71.9, 71.3, 70.9, 66.77, 66.59, 66.0, 65.6, 53.0, 52.7, 48.6, 48.4, 48.27, 48.19, 48.14, 48.10, 47.5, 46.39, 46.27, 42.69, 42.63, 41.7, 41.2, 39.76, 39.72, 38.4, 38.0, 30.8, 27.36, 27.34, 26.21, 26.16, 26.11, 26.0, 25.6, 21.2, 20.03, 20.01, 19.98, 19.82, 18.89, 18.85, 18.77, 17.2, 17.0, 16.5, 16.0, –2.23, –2.34, –2.49, –2.59, –3.19, –3.27, –3.5; IR (neat) 2929, 2857, 2361, 1713, 1251, 1112, 838 cm^{-1}; HRMS (ESI) *m/z* 790.3923 [(M+Na)$^+$, $C_{45}H_{61}NO_6Si_2$ requires 790.3930].

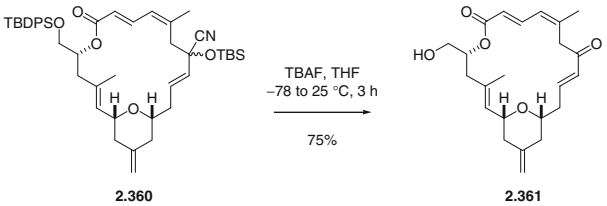
Preparation of Alkene 2.360



To a cooled (–78 °C) solution of methyltriphenylphosphonium iodide (60.0 mg, 0.148 mmol) in THF (2.0 mL) was added dropwise *n*-BuLi (2.5 M in THF, 0.05 mL, 0.124 mmol). The resultant yellow solution was stirred at 0 °C for 20 min before **2.332A** (38.0 mg, 0.049 mmol) in THF (0.5 mL) was added dropwise. After stirring at 0 °C for additional 40 min, the resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/

EtOAc, 10/1) to afford alkene **2.360** (29.9 mg, 79 %) as a colorless oil (two diastereomers): $[\alpha]^{24}_D$= +9.7 (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, acetone-d_6) 7.66–7.71 (m, 4H), 7.48–7.64 (m, 1H), 7.26–7.45 (m, 6H), 5.48–6.29 (m, 3H), 5.15–5.34 (m, 2H), 4.69–4.73 (m, 2H), 3.74–4.01 (m, 4H), 3.30–3.50 (m, 1H), 2.75–2.95 (m, 1H), 1.82–2.63 (m, 9H), 1.91 (s)/1.89 (s, 3H), 1.59 (s)/1.57 (s, 3H), 1.030/1.028/1.016 (s, 9H), 0.90/0.89/0.86/0.85 (s, 9H); ^{13}C NMR (125 MHz, acetone-d_6) 166.71, 166.62, 166.45, 145.69, 145.60, 145.53, 145.48, 143.4, 142.8, 142.4, 141.9, 141.5, 141.2, 140.22, 140.18, 136.56, 136.53, 136.49, 134.42, 134.39, 134.34, 134.29, 134.26, 133.9, 133.4, 132.9, 132.1, 131.8, 131.73, 131.71, 131.5, 131.3, 130.9, 130.8, 130.7, 130.6, 129.7, 129.6, 129.4, 128.8, 122.23, 122.12, 121.99, 121.6, 121.07, 121.04, 120.6, 109.42, 109.23, 109.07, 109.02, 78.59, 78.37, 78.26, 78.04, 77.76, 77.70, 76.59, 76.53, 76.50, 74.9, 73.8, 73.0, 72.0, 71.4, 71.0, 66.84, 66.67, 65.93, 65.65, 52.93, 52.83, 46.47, 46.27, 42.82, 42.80, 41.84, 41.67, 41.62, 41.59, 41.52, 41.50, 41.3, 40.9, 39.6, 38.7, 37.9, 30.8, 27.40, 27.39, 26.26, 26.21, 26.19, 26.16, 26.0, 25.5, 21.3, 20.07, 20.05, 20.02, 18.94, 18.88, 18.81, 17.4, 17.0, 16.6, 16.2, –2.2, –2.3, –2.4, –2.5, –3.15, –3.22, –3.4; IR (neat) 2929, 2856, 2361, 1710, 1251, 1082, 839 cm^{-1}; HRMS (ESI) *m/z* 788.4135 [$(M+Na)^+$, $C_{46}H_{63}NO_5Si_2$ requires 788.4137].

Preparation of Alcohol 2.361

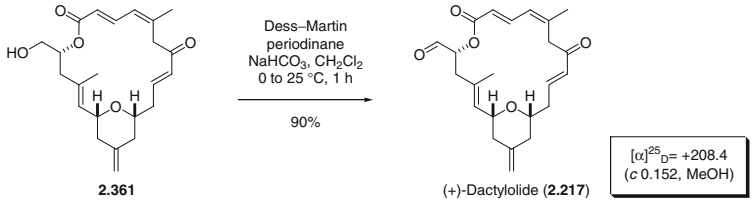


2.360 **2.361**

To a cooled (–78 °C) solution of **2.360** (8.1 mg, 0.0106 mmol) in THF (1.5 mL, 0.007 M) was added TBAF (1.0 M in THF, 21 μL, 0.0211 mmol). The reaction mixture was stirred at –78 °C for 2 h and at 0 °C for 30 min. After stirring for additional 30 min at 25 °C, the resulting mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford alcohol **2.361** (3.1 mg, 75 %) as a colorless oil: $[\alpha]^{25}_D$= +184.1 (*c* 0.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, J = 14.5, 11.5 Hz, 1H), 6.83 (ddd, J = 16.0, 9.5, 4.0 Hz, 1H), 6.11 (d, J = 11.0 Hz, 1H), 5.95 (d, J = 14.5 Hz, 1H), 5.94 (d, J = 16.0 Hz, 1H), 5.26–5.31 (m, 1H), 5.18 (d, J = 8.5 Hz, 1H), 4.73 (s, 2H), 4.15 (d, J = 13.5 Hz, 1H), 3.97 (ddd, J = 11.0, 8.0, 2.0 Hz, 1H), 3.68–3.80 (m, 2H), 3.28 (dd, J = 10.5, 10.5 Hz, 1H), 3.02 (d, J = 13.5 Hz, 1H), 2.38 (dddd, J = 15.0, 10.5, 4.5, 2.0 Hz, 1H), 2.06–2.30 (m, 5H), 1.91–1.98 (m, 2H), 1.80 (s, 3H), 1.73 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 198.0, 166.9, 146.3, 143.6, 143.2, 139.6, 132.3, 131.4, 129.4, 125.4, 120.8, 109.1, 76.5, 75.9, 71.7, 65.2, 45.0, 42.0, 40.93, 40.64, 40.2, 23.5, 16.6; IR (neat) 3437, 2934, 1715, 1668, 1635, 1357, 1286, 1154, 1051, 978 cm^{-1}; HRMS (ESI) *m/z* 409.1981 [$(M+Na)^+$, $C_{23}H_{30}O_5$ requires 409.1985].

Preparation of (+)-Dactylolide (2.217)



2.361 (+)-Dactylolide (**2.217**)

To a cooled (0 °C) solution of **2.361** (5.2 mg, 0.0135 mmol) in CH_2Cl_2 (2.0 mL, 0.007 M) were added $NaHCO_3$ (4.5 mg, 0.0540 mmol) and Dess–Martin periodinane (11.4 mg, 0.0269 mmol). After stirring at 25 °C for 1 h, the resulting mixture was quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1/1) to afford (+)-dactylolide (**2.217**) (4.7 mg, 90 %) as a white solid: $[\alpha]^{25}{}_D$= +208.4 (*c* 0.152, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.63 (dd, J = 15.0, 11.5 Hz, 1H), 6.84 (ddd, J = 16.0, 8.5, 6.0 Hz, 1H), 6.15 (d, J = 11.5 Hz, 1H), 5.94–6.02 (m, 2H), 5.31 (dd, J = 11.0, 2.0 Hz, 1H), 5.24 (d, J = 7.5 Hz, 1H), 4.75 (s, 2H), 3.94 (d, J = 14.5 Hz, 1H), 3.93–3.99 (m, 1H), 3.32 (dddd, J = 11.5, 9.0, 2.5, 2.5 Hz, 1H), 3.24 (d, J = 14.5 Hz, 1H), 2.54 (d, J = 14.0 Hz, 1H), 2.26–2.39 (m, 3H), 2.09–2.19 (m, 2H), 1.93–1.99 (m, 2H), 1.86 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 197.4, 166.3, 146.0, 144.0, 143.5, 140.4, 131.4, 130.9, 130.5, 125.6, 119.8, 109.3, 76.5, 75.7, 75.3, 44.9, 40.8, 40.4, 39.71, 39.66, 24.1, 16.0; IR (neat) 2932, 1703, 1667, 1632, 1432, 1249, 1141, 1049, 975, 887 cm^{-1}; HRMS (ESI) *m/z* 385.2007 [$(M+H)^+$, $C_{23}H_{28}O_5$ requires 385.2010].

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Chapter 3
Synthesis of 4-Hydroxy-2, 6-*cis*-Tetrahydropyrans via Tandem Cross-Metathesis/Thermal S_N2' Reaction

3.1 Introduction

Tandem reactions have long been recognized as a powerful tool used to perform multiple-bond-breaking and multiple-bond-forming reactions in a single chemical operation [1–3]. Hence, the development of tandem reactions is a rapidly growing area in the realm of synthetic organic chemistry [4–6]. Tandem processes offer a powerful approach for conveniently accessing more complex architectures and permit efficient access to unique chemical structures from simple starting materials. Furthermore, they occasionally provide impressive reaction stereoselectivity compared to their stepwise counterparts [4]. The main advantages of tandem reactions are the reduction in overall steps by avoiding isolation of often highly reactive intermediates, minimal use of protecting groups, and the environmental benefits by saving time and reducing waste.

Among a diverse set of tandem processes developed earlier, the diversity of reactions catalyzed by Grubbs' ruthenium alkylidene complexes [7–9] is noteworthy because of their stability and commercial availability. Indeed, there have been several successful synthetic applications employing ruthenium alkylidene mediated tandem processes [10–14] (Fig. 3.1).

Recently developed advances in Grubbs' ruthenium alkylidene complex catalyzed reactions include tandem CM–aza-Michael reactions [10], tandem CM–hydroarylation reactions [11], tandem enyne metathesis–cyclopropanations

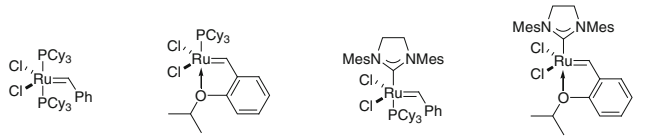

Fig 3.1 Commercially available ruthenium metathesis complexes

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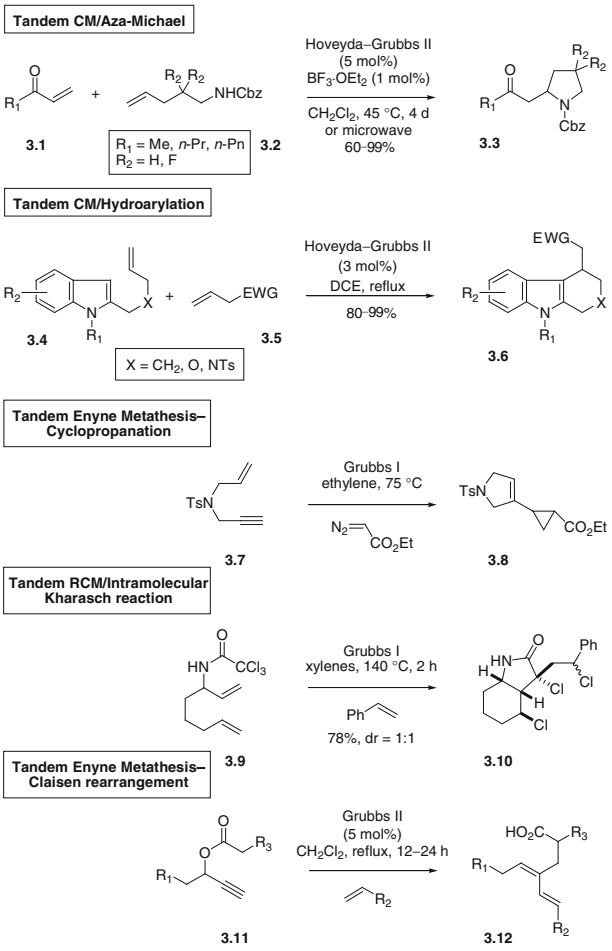
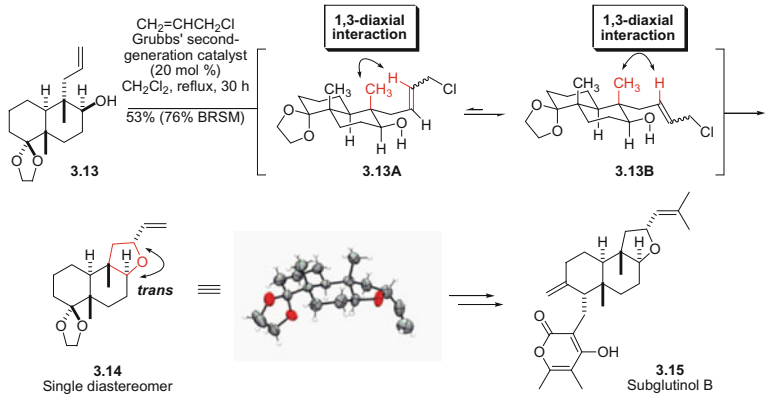


Scheme 3.1 Recent examples of tandem processes involving cross-metathesis

[12] or tandem enyne metathesis–Claisen rearrangement reactions [13], and tandem RCM–Kharasch reactions [14] (Scheme 3.1).

Our main interest described in this chapter is the investigation of the tandem cross metathesis and thermal S_N2' reaction for the efficient formation of 2,6-*cis*-4-hydroxy-tetrahydropyran, ubiquitous structural elements found in complex natural product with interesting biological activities. The detailed utility and scope of this process will be discussed in this chapter.



Scheme 3.2 Tandem CM/S_N2' reaction in the synthesis of subglutinol B

3.2 Preliminary Study

Recently, our group has reported the feasibility of the S_N2' reaction for the stereoselective synthesis of substituted *O*-heterocycles (Scheme 3.2) [15]. We applied the intramolecular S_N2' reaction in conjunction with an olefin cross-metathesis (CM) reaction (tandem CM/S_N2' reaction) to the stereoselective synthesis of the 2,3-*trans*-2,5-*trans*-tetrahydrofuran of subglutinol B (**3.15**).

Treatment of **3.13** with CH_2=$CHCH_2Cl$ in the presence of Grubbs' second-generation catalyst (Grubbs II, $(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh) [16–20] and subsequent intramolecular S_N2' reaction [21] under thermal conditions led to the desired 2,5-*trans*-tetrahydrofuran **3.14** as a single diastereomer in 53 % (BRSM 76 %). The stereochemical outcome of the tandem reaction was rationalized by the fact that the unfavorable 1,3-diaxial interaction of the axially oriented methyl group and the vinyl hydrogen in conformation **3.13A** is larger than that of the axial methyl and vinyl hydrogen in conformation **3.13B**.

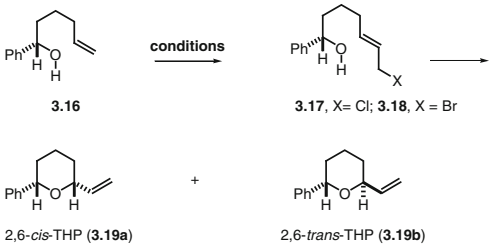
3.3 Results and Discussion

3.3.1 Tandem Cross-Metathesis/Thermal S_N2' Reaction

Considering the potential of the tandem CM/thermal S_N2' reaction for rapid and stereoselective construction of substituted *O*-heterocycles, we were interested in further extending this methodology to the synthesis of tetrahydropyrans (THPs), which are commonly occurring substructures in a broad array of natural products that exhibit a diverse range of biologically significant properties [22–24].

Initial experiments to test the feasibility of the tandem CM/thermal S_N2' process were conducted using hydroxy alkene **3.16** bearing a phenyl group at C(6),

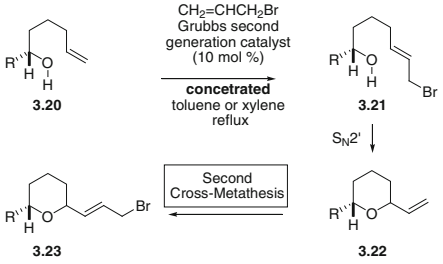
Table 3.1 Initial results of tandem CM/thermal S_N2' reaction



Entry	Conditions	Yield (%)[a]	dr[b]
1	CH_2=$CHCH_2$**Cl**, Grubbs ‖ (10 mol %), CH_2Cl_2, 45 °C, 16 h	66	2:1
2	CH_2=$CHCH_2$**Cl**, Grubbs ‖ (10 mol %), CH_2Cl_2 (0.1 M), 45 °C, 3 h, then, toluene (0.02 M), reflux, 12 h	79	2:1
3	CH_2=$CHCH_2$Br, Grubbs ‖ (10 mol %), CH_2Cl_2 (0.1 M), 45 °C, 2 h, then, toluene (0.02 M), reflux, 10 h	78	2:1

[a] Combined yield of 2,6-*cis*-THP and 2,6-*trans*-THP
[b] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1}H NMR of crude product

Scheme 3.3 Undesired products by second cross metathesis



which was prepared by addition of 4-pentenylmagnesium bromide to PhCHO (84 %). Treatment of **3.16** with CH_2=$CHCH_2Cl$ in the presence of Grubbs II and subsequent intramolecular S_N2' reaction of the corresponding hydroxy allyl chloride **3.17** under thermal conditions (*tandem CM/thermal S_N2' reaction*, Table 3.1) provided the desired 2,6-*cis*-tetrahydropyran **3.19a** in 66 %, but in poor stereoselectivity (**3.19a**:**3.19b** = 2:1, entry 1). Elucidation of the relative stereochemistry of the substituents on the tetrahydropyran was achieved by ^{1}H NMR coupling constants of the products and NOESY correlations. Based on the fact that we isolated the intermediate **3.17** in addition to the desired tetrahydropyran **3.19a**, we anticipated that a higher reaction temperature would promote the S_N2' cyclization step. After the completion of the CM reaction of **3.16** in CH_2Cl_2, addition of toluene to the reaction mixture in refluxing conditions increased the yield of the reaction from 66 to 79 % (entry 2).

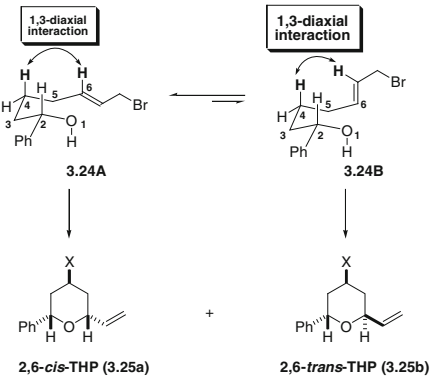


Fig 3.2 Introduction of 1,3-diaxial interaction to tandem CM/thermal S_N2' reaction

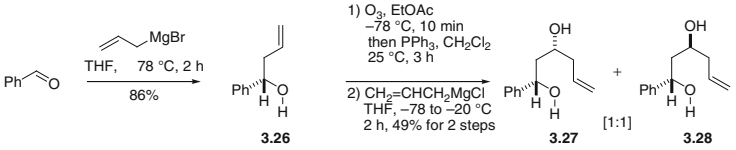
Dilution (0.02 M) of the reaction mixture was required to avoid the undesirable second cross metathesis reaction of tetrahydropyrans with allyl halide to afford allylic halides as described in Scheme 3.3.

We also attempted a different leaving group hoping for the improvement of the stereoselectivity. Use of bromide instead of chloride as a leaving group resulted in no effect on yield, but slightly shortened the reaction time (entry 3). We attributed the low stereoselectivity to a less well-defined transition state of the intramolecular S_N2' reaction [21].

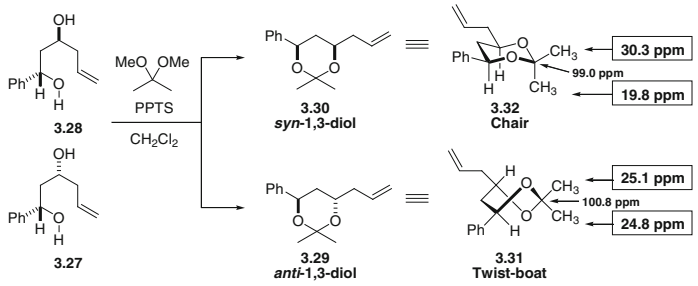
At this point, to improve the stereoselectivity of the tandem reaction, we envisioned the introduction of an axially oriented functional group at the C(4) position, which would increase the 1,3-diaxial interaction with the C(6) allyl substituent (Fig. 3.2). It was anticipated that the unfavorable 1,3-diaxial interaction of the axially oriented C(4) functional and the C(6) allyl substituent in conformation **3.24B** would be larger than that of the hydrogen and the C(4) substituent in conformation **3.24A**, thus preferentially affording 2,6-*cis*-tetrahydropyran **3.25a**. In addition, the C(4) group could be transformed to other useful functional groups. Since 2,6-*cis*-4-hydroxy-tetrahydropyran and 2,6-*cis*-tetrahydropyran-4-one are abundant structural motifs in biologically important natural products, we hypothesized that a hydroxyl group at the C(4) position could satisfy these requirements.

Preparation of hydroxy alkenes **3.27** and **3.28** was accomplished in three steps from commercially available benzaldehyde. To this end, addition of allylmagnesium bromide to benzaldehyde to afford known alcohol **3.26** was followed by ozonolysis and subsequent allylation to furnish a 1:1 mixture of α-hydroxy alkene **3.27** and β-hydroxy alkene **3.28** (Scheme 3.4).

To confirm the configurational assignment of the two hydroxy alkenes, the Rychnovsky's ^{13}C NMR acetonide analysis was employed (Scheme 3.5) [25, 26]. Both 1,3-diols were independently protected as acetonides **3.29** and **3.30** by treatment with 2,2-dimethoxypropane and PPTS. It is known that 1,3-*syn* diol adopts a chair like conformation **3.32**, resulting in diagnostic shift in the spectrum for the geminal methyl carbons of the acetonide, while *anti*-1,3-diols are known to



Scheme 3.4 Preparation of 1,3-diols **3.27** and **3.28**



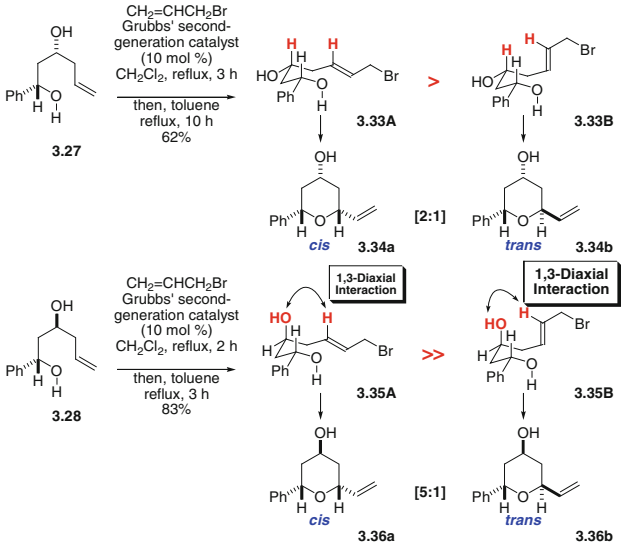
Scheme 3.5 Rychnovsky's ^{13}C NMR acetonide analysis of 1,3-diols

adopt a twist-boat conformation **3.31**. Thus, the ^{13}C chemical shift at 30.3 and 19.8 ppm confirmed the 1,3-*syn*-relationship and at 25.1 and 24.8 ppm confirmed the 1,3-*anti*-relationship, respectively.

With the prepared hydroxy alkenes (**3.27** and **3.28**) in hand, we subjected them to the tandem reaction conditions to test the our hypothesis (Scheme 3.6). Treatment of α-hydroxy alkene **3.27** with CH_2=$CHCH_2Br$ under the tandem reaction conditions provided the desired 2,6-*cis*-4-hydroxy-tetrahydropyran **3.34a**, but in low stereoselectivity (dr = 2:1). However, under the same reaction conditions, the *β*-hydroxy alkene **3.28** provided **3.36a** in a higher stereoselectivity (dr = 5:1). The higher stereoselectivity of the 2,6-*cis*-tetrahydropyran **3.36a** can be rationalized on the basis of the same 1,3-diaxial interaction arguments as discussed above. These results demonstrated that the increased 1,3-diaxial interaction by the axially oriented C(4) hydroxyl group in **3.28** enhanced the stereoselectivity.

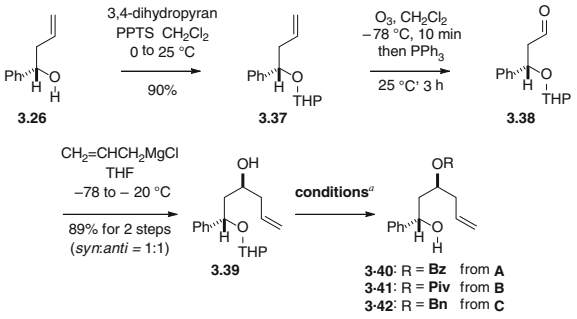
Encouraged by these results, we next hypothesized that the steric bulk of the functionality at C(4) even further might improve the stereoselectivity between the 2,6-*cis*- and 2,6-*trans* tetrahydropyrans. Towards this end, the mono protected (Bz, Piv, and Bn) 1,3-*syn*-diols were prepared by following the procedures described in Scheme 3.7. Subjection of **3.40–42** to the tandem CM/S_N2' rection conditions (CH_2=$CHCH_2Br$, 10 mol % of Grubbs II, CH_2Cl_2, reflux, 3 h, then toluene, reflux, 10 h) gave rise to corresponding tetrahydropyrans with modest levels of diastereoselectivity (dr = 3.1–4.3:1), revealing that bulkiness of the protecting groups gave no effect on diastereoselectivity in our experimentation (Table 3.2).

To gain further insight into the assessement of the effect of thermal conditions on the intramolecular S_N2' reaction, **3.46** and **3.47** were treated with a base such as NaH or KO^{t}Bu. According to our extensive invesitigation, under basic conditions



Scheme 3.6 Synthesis of 2,6-*cis*-4-hydroxy-tetrahydropyrans

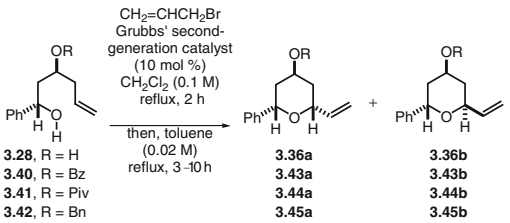
Scheme 3.7 Preparation of mono-protected 1,3-*syn*-diols



A	B	C
1) BzCl, Et_3N, CH_2Cl_2 0 to 25 °C, 12 h 2) PPTS, EtOH 60 °C, 5 h 72% for 2 steps	1) PivCl, pyridine, CH_2Cl_2 0 to 25 °C, 12 h 2) PPTS, EtOH 60 °C, 5 h 79% for 2 steps	1) BnBr, NaH, TBAI, DMF 0 to 25 °C, 8 h 2) PPTS, EtOH 60 °C, 5 h 86% for 2 steps

(NaH or KO^{t}Bu) the S_N2' reaction of **3.46** failed to provide the corresponding THP **3.36a**, but rather only resulted in significant decomposition (Table 3.3). When **3.46** was protected with a benzyl group and subjected to the basic conditions (NaH or KO^{t}Bu), the reaction yielded a significant amount of elimination product **3.48** as well as the desired 2,6-*cis*-THP **3.45a**. It is important to note that, the mildness of the thermal conditions allowed for the synthesis of 2,6-*cis*-4-hydroxy-tetrahydropyran **3.36a** from base-sensitive substrate **3.46** without the use of protecting

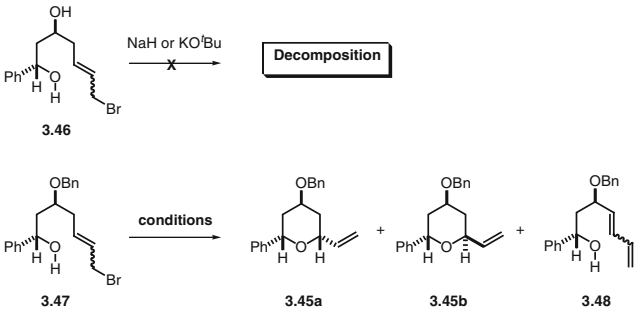
Table 3.2 Tandem CM/thermal S_N2' reaction of mono-protected 1,3-*syn*-diols



Entry	Substrate	Yield[a] (%)	dr[b]
1	**3.28**	83	5:1
2	**3.40**	94	4.3:1
3	**3.41**	87	4:1
4	**3.42**	71	3.1:1

[a] Combined yield of 2,6-*cis*-THP and 2,6-*trans*-THP
[b] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1}H NMR of crude product

Table 3.3 Intramolecular S_N2' reaction under basic conditions



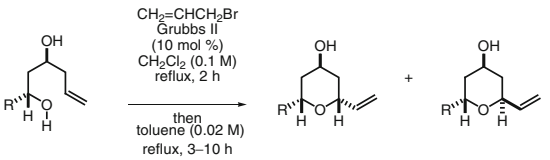
Entry	Conditions	Yield (3.45/3.48, %)	dr[a]
1	NaH, THF, 0 °C to 25 °C, 9 h	30/26	2.6:1
2	NaH, THF/DMF (2/1), 0 °C to 25 °C, 3 h	26/73	1.8:1
3	KO^{t}Bu, THF, −78 °C, 20 min	0/62	NA[b]
4	KO^{t}Bu, THF, 0 °C, 30 min	29/45	1.5:1
5	KO^{t}Bu, THF, 25 °C, 20 min	22/49	1.6:1

[a] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1} H NMR of crude product
[b] Not applicable

groups [27, 28], thereby demonstrating that the thermal conditions of the tandem reaction were critical in determining the success of the intramolecular S_N2' reaction.

At this point we were aware that the axially oriented C(4) hydroxyl group can be an important handle for the stereoselectivity and thermal conditions would play a critical role in the tandem cyclization process; therefore, we decided to extend

Table 3.4 Substrate scope of tandem CM/thermal S_N2' reaction



3.28, R = Ph
3.49, R = $C(CH_3)_2CH_2OBn$
3.50, R = *i*-Pr
3.51, R = CH_2CH_2OBn

3.36a
3.52a
3.53a
3.54a

3.36b
3.52b
3.53b
3.54b

Entry	Substrate	Yield[a] (%)	dr[b]
1	**3.28**	**3.36a, b** (83)	5:1
2	**3.49**	**3.52a, b** (85)	4:1
3	**3.50**	**3.53a, b** (80)	3:1
4	**3.51**	**3.54a, b** (95)	4:1

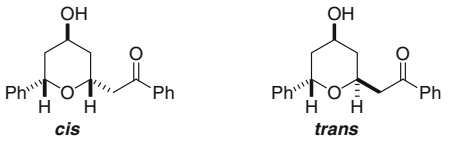
[a] Combined yield of 2,6-*cis*-THP and 2,6-*trans*-THP
[b] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1}H NMR of crude product

the scope of the substrate to various substituents. To investigate the scope and stereochemical outcome of the tandem reaction with respect to substituents at the C(2) position, we prepared 1,3-*syn*-diols (**3.28** and **3.49–51**) and subjected them to tandem reaction conditions (Table 3.4). We were pleased to find that the tandem reaction of **3.28** and **3.49–51** in the presence of CH_2=$CHCH_2Br$ and Grubbs II proceeded smoothly to provide the corresponding 4-hydroxy-2,6-*cis*-tetrahydropyrans (**3.36a** and **3.52–54a**) with decent stereoselectivities (entries 1–4).

To the best of our knowledge, the tandem CM/S_N2' reaction has never been reported for stereoselective synthesis of tetrahydropyrans. Indeed, few approaches for the stereoselective synthesis of tetrahydropyrans involve intramolecular S_N2' reactions [29–31], presumably due to the low nucleophilicity of oxygen and a less well-defined transition state.

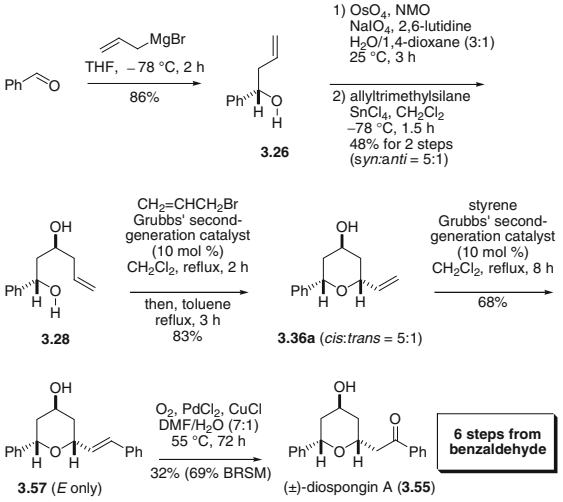
3.3.2 Synthesis of (±)-Diospongin A

To demonstrate the utility of the tandem CM/thermal S_N2' reaction, we embarked on a synthesis of (±)-diospongin A (**3.55**). The diarylheptanoids diospongin A and B (**3.55** and **3.56**, Fig. 3.3) were isolated from the rhizomes of *Dioscorea spongiosa* [32] by Kadota and coworkers in 2004 and have attracted considerable synthetic interest due to antiosteoporotic activity (diospongin B) [33–41]. Their structures, including absolute stereochemistry, were determined by NMR data, Mosher ester analysis and the CD spectrum [42]. We envisioned that the 4-hydroxy-2,6-*cis*-tetrahydropyran embedded in **3.55** could be accessed by using the tandem CM/thermal S_N2' reaction as the key bond-forming event.



(–)-diospongin A (**3.55**) (–)-diospongin B (**3.56**)

Fig 3.3 Structures of (–)-diospongins A and B



Scheme 3.8 Protecting-group-free synthesis (±)-diospongin A

Addition of CH_2=$CHCH_2MgBr$ to PhCHO, oxidative cleavage of alkene **3.26**, treatment of the corresponding aldehyde with allyltrimethylsilane and $SnCl_4$ [43, 44] afforded a mixture of two separable 1,3-diols (*syn*:*anti* = 5:1) (Scheme 3.8). Tandem reaction of 1,3-*syn* diol **3.28** in the presence of CH_2=$CHCH_2Br$ and Grubbs' second-generation catalyst smoothly proceeded to provide the desired 2,6-*cis*-4-hydroxy-tetrahydropyran **3.36a** in 83 % yield (dr = 5:1). A second cross metathesis reaction of **3.36a** with styrene gave rise to **3.57** in 68 %.

At this point, attempts for one-pot CM/S_N2'/CM reaction of **3.28** (CH_2=$CHCH_2Br$, 10 mol % of Grubbs II, CH_2Cl_2, reflux, 2 h, then toluene, reflux, 3 h; styrene, 10 mol % of Grubbs II, reflux, 10 h) provided the corresponding (*E*)-6-styryl-tetrahydropyran **3.57**, but in low yield (16 %). Final stage of the synthesis involved the introduction of the carbonyl group to complete the synthesis of (±)-diospongin A (**3.55**). The regioselective introduction of the ketone was accomplished by a Wacker oxidation as described previously [38]. The final product **3.55** was identical in all respects to the data reported for the natural product. Thus, verifying the efficiency of tandem CM/thermal S_N2' reaction proved for a synthesis of (±)-diospongin A (**3.55**) without the use of protecting groups.

3.4 Conclusion

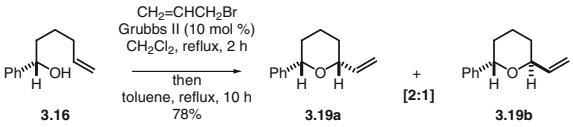
In summary, we investigated the scope and utility of the tandem CM/thermal S_N2' reaction in the context of 2,6-*cis*-4-hydroxy-tetrahydropyran synthesis, due to the prevalence of these structural motifs in complex natural products with interesting biological activities. The key advantage of this methodology is its usefulness in substrates with base-labile functionalities, due to the avoidance of using a base for the S_N2' cyclization step (thermal conditions), while proceeding with modest stereoselectivity (3–5:1 dr). Through the use of the tandem CM/thermal S_N2' reaction, a concise synthesis of (±)-diospongin A (**3.55**) was accomplished with no use of protecting groups.

3.5 Experimental Section

General Methods

All reactions were conducted in oven-dried glassware under nitrogen. All commercial chemical reagents were used as supplied. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Analytical thin layer chromatography (TLC) was performed on SiO_2 (60 Å) with fluorescent indication (Whatman). Visualization was accomplished by UV irradiation at 254 nm and/or by staining with *para*-anisaldehyde solution. Flash column chromatography was performed by using silica gel 60 (particle size 4063 μm. 230400 mesh). ^{1}H NMR, ^{13}C NMR, and 2D NMR (COSY, NOESY) spectra were recorded with a Varian 400 (400 MHz) and a Bruker 500 (500 MHz) spectrometer in $CDCl_3$ by using the signal of residual $CHCl_3$, as an internal standard. All NMR δ values are given in ppm, and all J values are in Hz. Electrospray ionization (ESI) mass spectra (MS) were recorded with an Agilent 1100 series (LC/MSD trap) spectrometer and were performed to obtain the molecular masses of the compounds. Infrared (IR) absorption spectra were determined with a Thermo-Fisher (Nicolet 6700) spectrometer. Optical rotation values were measured with a Rudolph Research Analytical (A21102. API/1 W) polarimeter.

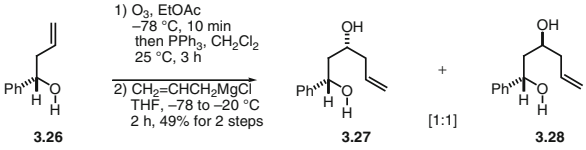
Tandem CM/Thermal S_N2' Reaction



To a solution of the known olefin **3.16** [45] (40.0 mg, 0.227 mmol) in CH_2Cl_2 (2.0 mL, 0.113 M) were added Grubbs' second-generation catalyst ($(IMesH_2)(P\text{-}Cy_3)(Cl)_2Ru{=}CHPh$, Grubbs II) (19.2 mg, 0.023 mmol) and $CH_2{=}CHCH_2Br$ (0.058 mL, 0.681 mmol) under N_2 atmosphere. The resulting mixture was refluxed

under N_2 for 2 h, diluted with toluene (11.0 mL, 0.021 M), and refluxed for additional 10 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 20/1) to afford a 2:1 mixture of 2,6-*cis*-tetrahydropyran **3.19a** and 2,6-*trans*-tetrahydropyran **3.19b** (33.3 mg, 78 %) as a colorless oil whose spectral data were identical to those of the known **3.19a**: **[For 2,6-*cis*-tetrahydropyran 3.19a]** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.41 (m, 2H), 7.34 (dd, J = 7.0, 7.0 Hz, 2H), 7.26 (dddd, J = 5.5, 5.5, 1.5, 1.5 Hz, 1H), 5.96 (ddd, J = 17.0, 10.5, 5.5 Hz, 1H), 5.32 (ddd, J = 17.0, 1.5, 1.5 Hz, 1H), 5.12 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H), 4.45 (dd, J = 11.5, 2.5 Hz, 1H), 4.02–4.07 (m, 1H), 1.96–2.02 (m, 1H), 1.83–1.88 (m, 1H), 1.70–1.80 (m, 2H), 1.49–1.56 (m, 1H), 1.39–1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 139.4, 128.2, 127.1, 125.8, 114.4, 79.7, 78.6, 33.6, 31.2, 23.9; IR (neat) 3028, 2934, 1652, 1299 cm^{-1}. **[For 2,6-*trans*-tetrahydropyran 3.19b]** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.41 (m, 2H), 7.35 (dd, J = 7.5, 7.5 Hz, 2H), 7.26 (dddd, J = 7.0, 7.0, 1.5, 1.5 Hz, 1H), 6.01 (ddd, J = 17.5, 10.5, 4.0 Hz, 1H), 5.28 (ddd, J = 17.0, 1.5, 1.5 Hz 1H), 5.26 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H), 4.81 (dd, J = 8.0, 4.0 Hz, 1H), 4.45–4.47 (m, 1H), 1.69–1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 138.6, 128.3, 127.1, 126.2, 116.1, 72.9, 72.8, 31.6, 28.7, 19.2; IR (neat) 3028, 2936, 1214 cm^{-1}.

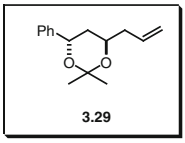
Preparation of 1,3-Diols 3.27 and 3.28



3.26 **3.27** **3.28**

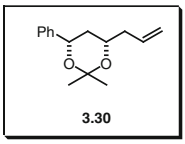
[Ozonolysis] To a cooled (–78 °C) solution of the known alcohol **3.26** (840 mg, 5.668 mmol) in EtOAc (30 mL, 0.189 M) was bubbled by O_3 until blue color was persisted (ca. 10 min). An excess O_3 was removed by N_2 gas and EtOAc was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 mL, 0.283 M) before Ph_3P (2.973 g, 11.336 mmol) was added. The resulting mixture was stirred at 25 °C for 3 h and concentrated *in vacuo*. This residue was directly employed in the next step without further purification. **[Allylation]** To a cooled (–78 °C) solution of crude aldehyde in THF (20 mL) was added CH_2=$CHCH_2MgCl$ (5.67 mL, 2.0 M in THF, 11.336 mmol), and the resulting mixture was allowed warm to –20 °C. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford a 1:1 mixture of 1,3-*anti*-diol **3.27** and 1,3-*syn*-diol **3.28** (541 mg, 49 % for 2 steps) as a colorless oil: **[For 1,3-*anti*-diol 3.27]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.41 (m, 5H),

5.72–5.84 (m, 1H), 5.10–5.16 (m, 2H), 5.05 (dd, $J = 8.0$, 3.6 Hz, 1H), 3.88–3.96 (m, 1H), 2.75 (br s, 2H), 2.21–2.33 (m, 2H), 1.81–1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 134.4, 128.4, 127.3, 125.5, 118.3, 71.5, 68.0, 44.0, 41.9; IR (neat) 3339, 2914, 1641, 1254 cm^{-1}. **[For 1,3-*syn*-diol 3.28]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H), 5.75–5.86 (m, 1H), 5.09–5.15 (m, 2H), 4.92 (dd, $J = 9.6$, 4.0 Hz, 1H), 3.98 (dddd, $J = 9.6$, 6.4, 6.4, 3.6 Hz, 1H), 3.27 (br s, 2H), 2.23–2.28 (m, 2H), 1.77–1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 134.1, 128.5, 127.6, 125.7, 118.4, 75.1, 71.5, 44.8, 42.4; IR (neat) 3345, 3065, 2911, 1722 cm^{-1}; HRMS (EI) found 192.1151 [calcd for $C_{12}H_{16}O_2$ $(M)^+$ 192.1150].



3.29

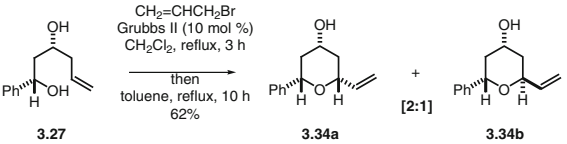
A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.39 (m, 5H), 5.83 (dddd, $J = 17.2$, 10.0, 7.2, 7.2 Hz, 1H), 5.12 (dddd, $J = 17.2$, 1.6, 1.6, 1.6 Hz, 1H), 5.07 (dddd, $J = 10.0$, 1.2, 1.2, 1.2 Hz, 1H), 4.88 (dd, $J = 12.0$, 6.4 Hz, 1H), 4.03 (dddd, $J = 8.8$, 6.4, 6.4, 6.4 Hz, 1H), 2.39 (ddd, $J = 14.0$, 6.8, 6.8 Hz, 1H), 2.28 (ddd, $J = 14.0$, 6.8, 6.8 Hz, 1H), 1.90–2.03 (m, 2H), 1.46 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 134.3, 128.4, 127.4, 126.0, 117.1, 100.8, 68.6, 66.4, 40.2, 39.5, 25.2, 24.8; IR (neat) 3067, 2926, 1642, 1225 cm^{-1}.



3.30

A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.37 (m, 5H), 5.81 (dddd, $J = 17.2$, 10.0, 7.2, 7.2 Hz, 1H), 5.07 (dddd, $J = 17.2$, 1.6, 1.6, 1.6 Hz, 1H), 5.04 (dddd, $J = 9.2$, 1.2, 1.2, 1.2 Hz, 1H), 4.87 (dd, $J = 11.6$, 2.8 Hz, 1H), 4.02 (dddd, $J = 13.6$, 6.4, 6.4, 2.4 Hz, 1H), 2.35 (ddd, $J = 14.0$, 6.0, 6.0 Hz, 1H), 2.17 (ddd, $J = 14.0$, 6.4, 6.4 Hz, 1H), 1.73 (ddd, $J = 13.2$, 2.4, 2.4 Hz, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.43 (ddd, $J = 12.8$, 11.2, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 133.9, 128.4, 127.5, 125.9, 117.3, 99.0, 71.5, 68.8, 40.8, 38.8, 30.3, 19.8; IR (neat) 3067, 2992, 1642 cm^{-1}.

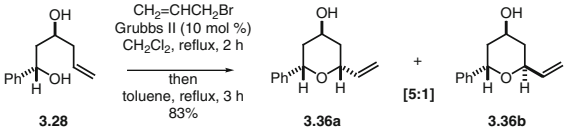
Tandem CM/Thermal S_N2' Reaction of 1,3-*anti*-Diol 3.27



3.27 **3.34a** **3.34b**

To a solution of 1,3-*anti*-diol **3.27** (22.0 mg, 0.114 mmol) in CH_2Cl_2 (1.0 mL, 0.114 M) were added Grubbs II (9.7 mg, 0.011 mmol) and $CH_2 = CHCH_2Br$ (0.029 mL, 0.343 mmol) under N_2 atmosphere. The resulting mixture was refluxed under N_2 for 3 h, diluted with toluene (6 mL, 0.019 M), and refluxed for additional 10 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford a 2:1 mixture of 2,6-*cis*-tetrahydropyran **3.34a** and 2,6-*trans*-tetrahydropyran **3.34b** (14.5 mg, 62 %) as a colorless oil: **[For 4-hydroxy-2,6-*cis*-tetrahydropyran 3.34a]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5H), 5.96 (ddd, $J = 17.6$, 10.4, 5.2 Hz, 1H), 5.34 (ddd, $J = 17.6$, 1.6, 1.6 Hz, 1H), 5.16 (ddd, $J = 10.8$, 1.6, 1.6 Hz, 1H), 4.44 (dd, $J = 11.2$, 1.6 Hz 1H), 3.98–4.07 (m, 2H), 2.21 (dddd, $J = 12.4$, 4.8, 2.4, 2.4 Hz, 1H), 2.12 (dddd, $J = 12.4$, 4.8, 2.4, 2.4 Hz, 1H), 1.59 (s, 1H), 1.51 (ddd, $J = 11.2$, 11.2, 11.2 Hz, 1H), 1.40 (ddd, $J = 11.2$, 11.2, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 138.2, 128.4, 127.5, 125.9, 115.2, 77.5, 76.5, 68.4, 43.0, 40.7; IR (neat) 3349, 3029, 2943, 1647, 1265 cm^{-1}; HRMS (EI) found 204.1147 [calcd for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150]. **[For 4-hydroxy-2,6-*trans*-tetrahydropyran 3.34b]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.39 (m, 5H), 6.00 (ddd, $J = 17.6$, 10.8, 3.6 Hz, 1H), 5.29–5.35 (m, 2H), 4.80 (dd, $J = 2.0$, 2.0 Hz, 1H), 4.67 (dd, $J = 11.2$, 2.0 Hz, 1H), 4.11 (dddd, $J = 11.2$, 11.2, 4.4, 4.4 Hz, 1H), 2.14–2.25 (m, 2H), 1.81 (ddd, $J = 11.2$, 11.2, 6.0 Hz, 1H), 1.59 (ddd, $J = 11.2$, 11.2, 11.2 Hz, 1H), 1.53 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 137.8, 128.4, 127.6, 126.0, 117.0, 73.4, 71.7, 64.8, 43.1, 37.1; IR (neat) 3339, 2925, 1638 cm^{-1}; HRMS (EI) found 204.1153 [calcd for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150].

Tandem CM/Thermal S_N2' Reaction of 1,3-*syn*-Diol 3.28

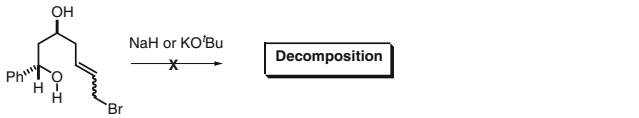


3.28 **3.36a** **3.36b**

To a solution of 1,3-*syn*-diol **3.28** (16.0 mg, 0.083 mmol) in CH_2Cl_2 (1.0 mL, 0.083 M) were added Grubbs II (7.1 mg, 0.008 mmol) and CH_2=$CHCH_2Br$ (0.021 mL, 0.250 mmol) under N_2 atmosphere. The resulting mixture was refluxed under N_2 for 2 h, diluted with toluene (5.0 mL, 0.017 M), and refluxed for additional 3 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford a 5:1 mixture of 2,6-*cis*-4-hydroxy-tetrahydropyran **3.36a** and 2,6-*trans*-4-hydroxy-tetrahydropyran **3.36b** (14.0 mg, 83 %) as a colorless oil: **[For 4-hydroxy-2,6-*cis*-tetrahydropyran 3.36a]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.6$ Hz, 2H), 7.33 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.23–7.28 (m, 1H), 5.93 (ddd, $J = 17.2$, 10.8, 5.6 Hz, 1H), 5.34 (ddd, $J = 17.2$, 1.6, 1.6 Hz, 1H), 5.14 (ddd, $J = 10.8$, 1.6, 1.6 Hz, 1H), 4.92 (dd, $J = 12.0$, 2.0 Hz, 1H), 4.49–4.54 (m, 1H), 4.37 (dd, $J = 1.6$, 1.6 Hz, 1H), 1.91 (dddd, $J = 14.0$, 3.2, 3.2, 3.2 Hz, 1H),

1.75–1.84 (m, 2H), 1.75 (dd, $J = 10.4$, 2.8 Hz, 1H), 1.68 (dd, $J = 14.0$, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 139.0, 128.3, 127.3, 125.9, 114.9, 73.5, 72.6, 64.8, 40.5, 38.2; IR (neat) 3401, 3064, 2919, 1646 cm^{-1}; HRMS (EI) found 204.1145 [calcd for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150]. **[For 4-hydroxy-2,6-*trans*-tetrahydropyran 3.36b]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, $J = 7.2$ Hz, 2H), 7.37 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.24–7.29 (m, 1H), 6.01 (ddd, $J = 17.2$, 10.4, 5.2 Hz, 1H), 5.30 (ddd, $J = 17.2$, 1.2, 1.2 Hz, 1H), 5.25 (dd, $J = 4.8$, 4.8 Hz, 1H), 5.18 (ddd, $J = 10.8$, 1.6, 1.6 Hz, 1H), 4.07–4.14 (m, 1H), 4.03 (dddd, $J = 9.2$, 9.2, 4.4, 4.4 Hz, 1H), 2.50 (ddd, $J = 13.6$, 4.4, 4.4 Hz, 1H), 2.01 (d, $J = 12.8$ Hz, 1H), 1.92 (ddd, $J = 14.4$, 9.6, 4.8 Hz, 1H), 1.51–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.7, 128.6, 127.1, 126.3, 115.3, 71.9, 70.6, 64.6, 39.9, 36.9; IR (neat) 3370, 3085, 2921, 1645, 1263 cm^{-1}; HRMS (EI) found 204.1151 [calcd for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150].

Intramolecular S_N2' Reaction Under Basic Conditions

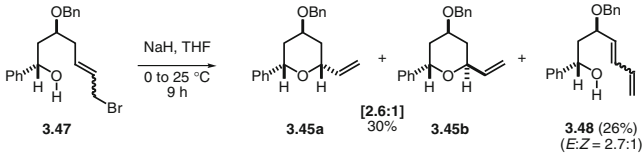


Entry	Conditions	Yield (3.45/3.48, %)	dr[a]
1	NaH, THF, 0 °C to 25 °C, 9 h	30/26	2.6:1
2	NaH, THF/DMF (2/1), 0 °C to 25 °C, 3 h	26/73	1.8:1
3	KO^{t}Bu, THF, −78 °C, 20 min	0/62	NA[b]
4	KO^{t}Bu, THF, 0 °C, 30 min	29/45	1.5:1
5	KO^{t}Bu, THF, 25 °C, 20 min	22/49	1.6:1

[a] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1}H NMR of crude product

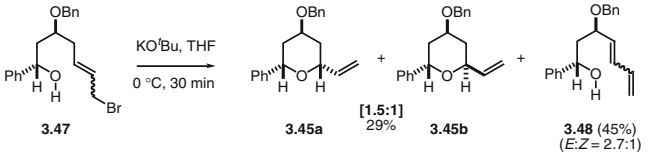
[b] Not applicable

Intramolecular S_N2' Reaction by NaH



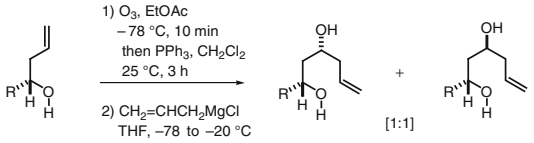
To a cooled (0 °C) solution of alcohol **3.47** (19 mg, 0.069 mmol) in THF (2 mL, 0.035 M) was added NaH (4.2 mg, 60 % dispersion in mineral oil, 0.104 mmol). After the resulting mixture was allowed to warm to 25 °C and stirred for 9 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to provide a 2.6:1 mixture of 2,6-*cis*-tetrahydropyran **3.45a** and 2,6-*trans*-tetrahydropyran **3.45b** (6.2 mg, 30 %) as a colorless oil along with elimination product **3.48** (5.3 mg, 26 %). **[For 2,6-*cis*-tetrahydropyran 3.45a]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.43 (m, 10H), 5.93 (ddd, J = 17.2, 10.4, 5.6 Hz, 1H), 5.32 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H), 5.12 (ddd, J = 10.4, 1.2, 1.2 Hz, 1H), 4.91 (dd, J = 11.6, 2.0 Hz, 1H), 4.63 (s, 2H), 4.48–4.53 (m, 1H), 3.98 (dd, J = 3.2, 3.2 Hz, 1H), 2.10 (dddd, J = 14.0, 2.4, 2.4, 2.4 Hz, 1H), 2.00 (dddd, J = 14.4, 2.4, 2.4, 2.4 Hz, 1H), 1.68 (ddd, J = 14.0, 11.6, 2.8 Hz, 1H), 1.59 (ddd, J = 14.4, 12.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 139.2, 138.9, 128.44, 128.25, 127.58, 127.41, 127.23, 125.9, 114.8, 74.0, 73.1, 71.6, 70.3, 37.6, 35.4; IR (neat) 3064, 2920, 1646 cm^{-1}; HRMS (EI) found 294.1621 [calcd for $C_{20}H_{22}O_2$ $(M)^+$ 294.1620]. **[For (*E*)-isomer of elimination product 3.48]** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.40 (m, 10H), 6.36 (ddd, J = 16.5, 10.0, 10.0 Hz, 1H), 6.25 (dd, J = 15.5, 11.0 Hz, 1H), 5.63 (dd, J = 15.5, 8.5 Hz, 1H), 5.26 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 9.0 Hz, 1H), 4.90 (dd, J = 9.0, 2.0 Hz, 1H), 4.53 (AB, J_{AB} = 11.5 Hz, $\Delta\nu_{AB}$ = 131.5 Hz, 2H), 4.12– 4.18 (m, 1H), 3.81 (s, 1H), 2.08–2.17 (m, 1H), 1.84 (ddd, J = 15.0, 3.5, 3.5 Hz, 1H).

Intramolecular S_N2' Reaction by KO^{t}Bu



To a cooled (0 °C) solution of alcohol **3.47** (14 mg, 0.051 mmol) in THF (1.5 mL, 0.034 M) was added KO^{t}Bu (0.051 mL, 1.0 M in THF, 0.051 mmol). The resulting mixture was stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to provide a 1.5:1 mixture of 2,6-*cis*-tetrahydropyran **3.45a** and 2,6-*trans*-tetrahydropyran **3.45b** (4.3 mg, 29 %) along with elimination product **3.48** (6.8 mg, 45 %) as a colorless oil.

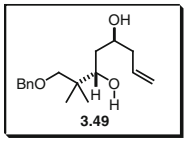
Preparation of 1,3-Diols



3.26, R = Ph — **3.27** — **3.28**
3.26a, R = $C(CH_3)_2CH_2OBn$ — **3.27a** — **3.49**
3.26b, R = ^{i}Pr — **3.27b** — **3.50**
3.26c, R = CH_2CH_2OBn — **3.27c** — **3.51**

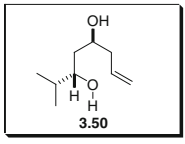
Entry	Substrate	Product[a] Yield[b], [c] (%)
1	**3.26**	49
2	**3.26a**	75
3	**3.26b**	36
4	**3.26c**	58

[a] The relative stereochemistries of 1,3-*anti*-diols and 1,3-*syn*-diols were determined by ^{13}C NMR chemical shifts of the corresponding acetonides. [25, 26]
[b] Yield for 2steps
[c] Combined yield of 1,3-*anti*- and 1,3-*syn*-diols



3.49

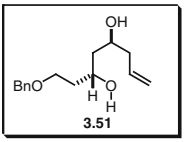
A colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.39 (m, 5H), 5.85 (dddd, J = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.06–5.13 (m, 2H), 4.51 (s, 2H), 4.15 (s, 1H), 3.96 (d, J = 4.0 Hz, 1H), 3.87–3.93 (m, 1H), 3.71–3.75 (m, 1H), 3.35 (AB, J_{AB} = 9.2 Hz, $\Delta\nu_{AB}$ = 39.2 Hz, 2H), 2.20–2.30 (m, 2H), 1.56–1.62 (m, 1H), 1.37–1.47 (m, 1H), 0.91 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.1, 128.5, 127.9, 127.6, 117.2, 80.3, 79.7, 73.7, 72.0, 42.2, 38.2, 36.6, 22.6, 19.7; IR (neat) 3400, 3066, 2922, 1641, 1206 cm^{-1}.



3.50

A colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 5.75–5.87 (m, 1H), 5.08–5.15 (m, 2H), 3.88 (dddd, J = 9.6, 2.4, 2.4, 2.4 Hz, 1H), 3.62 (ddd, J = 10.0, 5.2, 1.6 Hz, 1H), 3.30 (br s, 1H), 3.19 (br s, 1H), 2.21–2.27 (m, 2H), 1.58–1.68 (m, 2H), 1.39–1.49 (m, 1H), 0.91 (d, J = 7.2 Hz, 3H), 0.89 (d, 7.2 Hz, 3H); ^{13}C NMR

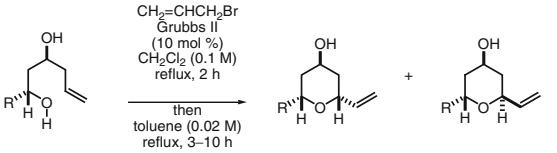
(100 MHz, $CDCl_3$) δ 134.4, 118.1, 77.7, 72.1, 42.6, 38.8, 34.1, 18.2, 17.4; IR (neat) 3334, 2958, 1641, 1144 cm^{-1}.



3.51

A colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H), 5.82 (dddd, $J = 17.6$, 10.4, 6.8, 6.8 Hz, 1H), 5.07–5.14 (m, 2H), 4.52 (s, 2H), 4.04–4.11 (m, 1H), 3.88–3.96 (m, 1H), 3.81 (br s, 1H), 3.62–3.74 (m, 2H), 2.17–2.30 (m, 2H), 1.70–1.86 (m, 2H), 1.50–1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.7, 128.5, 127.79, 127.68, 117.6, 73.3, 72.3, 71.5, 68.7, 42.35, 42.25, 36.9; IR (neat) 3388, 3068, 2931, 1641, 1207 cm^{-1}; HRMS (EI) found 250.1569 [calcd for $C_{15}H_{22}O_3$ $(M)^+$ 250.1569].

Substrate Scope of Tandem CM/Thermal S_N2' Reaction



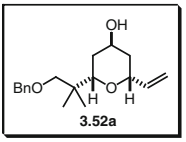
3.28, R = Ph
3.49, R = $C(CH_3)_2CH_2OBn$
3.50, R = *i*-Pr
3.51, R = CH_2CH_2OBn

3.36a
3.52a
3.53a
3.54a

3.36b
3.52b
3.53b
3.54b

Entry	Substrate	Yield[a] (%)	dr[b]
1	**3.28**	**3.36a, b (83)**	**5:1**
2	**3.49**	**3.52a, b (85)**	**4:1**
3	**3.50**	**3.53a, b (80)**	**3:1**
4	**3.51**	**3.54a, b (95)**	**4:1**

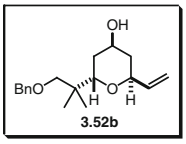
[a] Combined yield of 2,6-*cis*-THP and 2,6-*trans*-THP
[b] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^1H NMR of crude product



3.52a

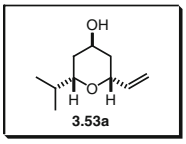
A colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.34 (m, 5H), 5.82 (ddd, $J = 17.2$, 10.4, 4.4 Hz, 1H), 5.24 (ddd, $J = 17.2$, 1.6, 1.6 Hz, 1H), 5.06

(ddd, $J = 10.8$, 2.0, 2.0 Hz, 1H), 4.50 (s, 2H), 4.23–4.31 (m, 2H), 3.77 (dd, $J = 8.4$, 5.2 Hz, 1H), 3.39 (d, $J = 9.2$ Hz, 1H), 3.24 (d, $J = 8.8$ Hz, 1H), 1.71 (d, $J = 14.0$ Hz, 1H), 1.53–1.63 (m, 1H), 1.49 (dd, $J = 11.6$, 2.8 Hz, 1H), 1.45 (dd, $J = 11.6$, 2.8 Hz, 1H), 0.94 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.1, 128.2, 127.28, 127.22, 76.9, 74.7, 73.2, 72.0, 65.0, 38.47, 38.23, 32.2, 21.4, 20.3; IR (neat) 3384, 3030, 2926, 1653, 1194 cm^{-1}; HRMS (EI) found 290.1880 [calcd for $C_{18}H_{26}O_3$ $(M)^+$ 290.1882].



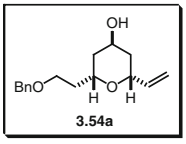
3.52b

A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.35 (m, 5H), 6.20 (ddd, $J = 17.2$, 10.8, 4.0 Hz, 1H), 5.33 (ddd, $J = 17.6$, 1.6, 1.6 Hz, 1H), 5.17 (ddd, $J = 11.2$, 1.6, 1.6 Hz, 1H), 4.51 (AB, $J_{AB} = 12.4$ Hz, $\Delta\nu_{AB} = 26.0$ Hz, 2H), 4.45–4.49 (m, 1H), 4.22 (br s, 1H), 3.95 (dd, $J = 10.8$, 3.2 Hz, 1H), 3.40 (d, $J = 8.8$ Hz, 1H), 3.20 (d, $J = 8.4$ Hz, 1H), 1.98 (ddd, $J = 14.4$, 6.8, 3.6 Hz, 1H), 1.84 (ddddd, $J = 14.8$, 2.0, 2.0, 2.0, 2.0 Hz, 1H), 1.56–1.70 (m, 2H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.0, 128.2, 127.36, 127.26, 115.2, 76.8, 73.2, 71.8, 67.8, 65.4, 38.2, 35.1, 32.3, 21.5, 20.1; IR (neat) 3349, 2925, 1636, 1204 cm^{-1}; HRMS (EI) found 290.1885 [calcd for $C_{18}H_{26}O_3$ $(M)^+$ 290.1882].



3.53a

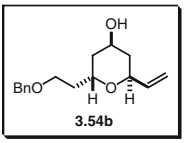
A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, $J = 17.2$, 10.8, 5.2 Hz, 1H), 5.26 (ddd, $J = 17.6$, 2.0, 2.0 Hz, 1H), 5.09 (ddd, $J = 10.8$, 1.6, 1.6 Hz, 1H), 4.24–4.31 (m, 2H), 3.51 (ddd, $J = 12.0$, 6.8, 2.0 Hz, 1H), 1.65–1.74 (m, 2H), 1.43–1.57 (m, 2H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 114.3, 76.2, 72.0, 64.8, 38.5, 35.0, 32.9, 18.7, 18.2; IR (neat) 3380, 2958, 1187, 1065 cm^{-1}; HRMS (EI) found 170.1305 [calcd for $C_{10}H_{18}O_2$ $(M)^+$ 170.1307].



3.54a

A colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H), 5.83 (ddd, $J = 17.5$, 11.0, 5.5 Hz, 1H), 5.24 (ddd, $J = 17.5$, 1.5, 1.5 Hz, 1H), 5.10 (ddd,

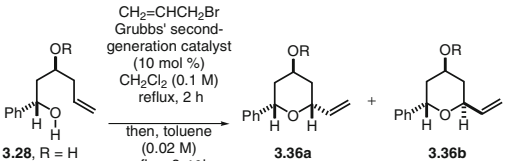
J = 11.0, 1.5, 1.5 Hz, 1H), 4.51 (s, 2H), 4.25–4.31 (m, 2H), 3.97–4.03 (m, 1H), 3.57–3.67 (m, 2H), 1.80–1.87 (m, 1H), 1.69–1.78 (m, 2H), 1.62–1.68 (m, 1H), 1.48–1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.6, 128.3, 127.60, 127.46, 114.7, 72.9, 72.0, 68.6, 66.8, 64.6, 38.6, 38.2, 36.3; IR (neat) 3423, 3030, 2917, 1737, 1646, 1237 cm^{-1}; HRMS (EI) found 262.1564 [calcd for $C_{16}H_{22}O_3$ $(M)^+$ 262.1569].



3.54b

A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H), 5.93 (ddd, J = 17.6, 10.8, 5.6 Hz, 1H), 5.24 (ddd, J = 17.2 1.6 1.6 Hz, 1H), 5.13(ddd, J = 10.2, 1.6, 1.6 Hz, 1H), 4.51 (s, 2H), 4.28 (dddd, J = 9.2, 1.2, 1.2, 1.2 Hz, 1H), 4.13–4.16 (m, 1H), 4.07 (dddd, J = 9.6, 4.8, 4.8, 4.8 Hz, 1H), 3.55–3.60 (m, 2H), 1.99–2.06 (m, 2H), 1.57–1.83 (m, 3H), 1.39–1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.4, 128.4, 127.65, 127.55, 115.2, 73.1, 69.9, 68.3, 67.1, 64.6, 39.8, 38.2, 32.6; IR (neat) 3392, 2941, 1646, 1097 cm^{-1}; HRMS (EI) found 262.1567 [calcd for $C_{16}H_{22}O_3$ $(M)^+$ 262.1569].

Tandem CM/thermal S_N2' reaction of mono-protected 1,3-*syn*-diols



3.28, R = H
3.40, R = Bz
3.41, R = Piv
3.42, R = Bn

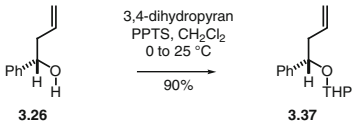
3.36a **3.36b**
3.43a **3.43b**
3.44a **3.44b**
3.45a **3.45b**

Entry	Substrate	Yield[a] (%)	dr[b]
1	**3.28**	83	5:1
2	**3.40**	94	4.3:1
3	**3.41**	87	4:1
4	**3.42**	71	3.1:1

[a] Combined yield of 2,6-*cis*-THP and 2,6-*trans*-THP

[b] Diastereomeric ratio (2,6-*cis*-THP:2,6-*trans*-THP) determined by integration of ^{1}H NMR of crude product

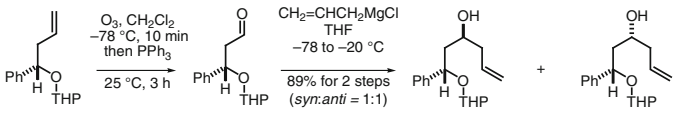
Preparation of THP Ether 3.37



3.26 3.37

To a cooled (0 °C) solution of the known alcohol **3.26** [46] (978 mg, 6.599 mmol) in CH_2Cl_2 (10 mL, 0.660 M) was added 3,4-dihydropyran (0.897 mL, 9.899 mmol). After addition of PPTS (331 mg, 1.320 mmol), the mixture was allowed to warm to room temperature. After stirring at 25 °C for 2 h, the solution was diluted with CH_2Cl_2 and washed with a mixture of brine, saturated aqueous $NaHCO_3$, and water. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to give THP ether **3.37** (1.38 g, 90 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.40 (m, 5H), 5.69–5.90 (m, 1H), 4.99–5.10 (m, 2H), [for one diastereomer 4.88 (dd, J = 3.2, 3.2 Hz) + for the other diastereomer 4.43 (dd, J = 3.6, 3.6 Hz), 1H], [for one diastereomer 4.74 (dd, J = 6.8, 6.8 Hz) + for the other diastereomer 4.66 (dd, J = 6.4, 6.4 Hz), 1H], [for one diastereomer 3.97 (dddd, J = 6.4, 6.4, 6.4, 6.4 Hz) + for the other diastereomer 3.46–3.52 (m), 1H], [for one diastereomer 3.57 (ddd, J = 11.2, 11.2, 2.8 Hz) + for the other diastereomer 3.28–3.34 (m), 1H], 2.41–2.68 (m, 2H), 1.41–1.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 141.8, 135.0, 134.5, 128.2, 128.0, 127.5, 127.0, 126.4, 117.2, 116.9, 97.8, 95.1, 78.1, 76.7, 62.2, 61.8, 42.6, 41.6, 30.66, 30.48, 25.52, 25.39, 19.4, 19.1; IR (neat) 3074, 2940, 1641, 1114 cm^{-1}; HRMS (EI) found 232.1464 [calcd for $C_{15}H_{20}O_2$ $(M)^+$ 232.1463].

Preparation of 1,3-*syn*-Diol Mono-THP Ether 3.39

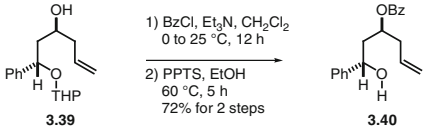


3.37 3.38 3.39 3.39a

[Ozonolysis] To a cooled (–78 °C) solution of the alkene **3.37** (677 mg, 2.91 mmol) in EtOAc (20 mL, 0.146 M) was bubbled by O_3 until blue color was persisted (ca. 10 min). An excess O_3 was removed by N_2 gas and EtOAc was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 mL) before Ph_3P was added. The resulting mixture was stirred at 25 °C for 3 h and concentrated *in vacuo*. This residue was filtered through column chromatography and then directly employed in the next step without further purification. **[Allylation]** To a cooled (–78 °C) solution of crude aldehyde **3.38** in THF (20 mL) was added CH_2=$CHCH_2MgCl$ (1.45 mL, 2.0 M in THF, 2.91 mmol), and the resulting

mixture was stirred for 40 min at –20 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford a 1:1 mixture of **3.39** and **3.39a** diatereomers (714 mg, 89 % for 2 steps) as a colorless oil: **[For one of two THP protected *syn*-diol 3.39]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.35 (m, 5H), 5.83 (dddd, J = 17.2, 10.4, 6.8, 6.8 Hz, 1H), 5.03–5.09 (m, 2H), 4.94 (dd, J = 10.4, 4.0 Hz, 1H), 4.40 (dd, J = 3.2, 3.2 Hz, 1H), 3.88–3.99 (m, 2H), 3.80 (s, 1H), 3.52 (ddd, J = 9.2, 3.6, 3.6 Hz, 1H), 2.25 (dddd, J = 20.8, 13.6, 13.6, 7.2 Hz, 2H), 1.88–1.98 (m, 1H), 1.70–1.81 (m, 2H), 1.45–1.67 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 134.8, 128.5, 127.8, 126.7, 117.3, 95.3, 77.9, 70.9, 62.6, 44.3, 41.9, 30.4, 25.2, 19.5; IR (neat) 3442, 3030, 2940, 1640, 1201 cm^{-1}; HRMS (EI) found 276.1729 [calcd for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725].

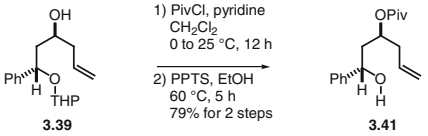
Preparation of 1,3-*syn*-Diol Mono-Benzoate 3.40



[Benzoylation] To a cooled (0 °C) solution of alcohol **3.39** (65.2 mg, 0.236 mmol) in CH_2Cl_2 (4 mL, 0.059 M) were added Et_3N (0.049 mL, 0.354 mmol), BzCl (0.041 mL, 0.354 mmol) and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This crude THP-protected benzoate was employed in the next step without further purification. **[THP-Deprotection]** To the crude THP-protected benzoate in EtOH was added PPTS (17.8 mg, 0.071 mmol) and the resulting mixture was stirred for 5 h at 60 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford alcohol **3.40** (50.5 mg, 72 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–8.04 (m, 2H), 7.57 (dddd, J = 6.4, 6.4, 1.2, 1.2 Hz, 1H), 7.41–7.46 (m, 2H), 7.23–7.35 (m, 5H), 5.81 (dddd, J = 17.2, 9.6, 7.6, 7.6 Hz, 1H), 5.07–5.22 (m, 3H), 4.86 (dd, J = 6.0, 6.0 Hz, 1H), 2.44–2.57 (m, 2H), 2.35 (br s, 1H), 2.31 (ddd, J = 14.4, 7.6, 7.6 Hz, 1H) 2.08 (ddd, J = 14.4, 6.4, 4.8 Hz, 1H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 143.9, 133.09, 132.92, 130.3, 129.5, 128.6, 128.3, 127.8, 125.8, 118.3,

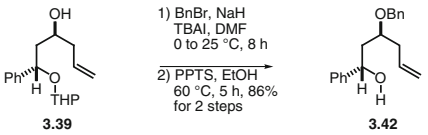
72.00, 71.89, 42.9, 38.8; IR (neat) 3427, 3064, 2922, 1714, 1642, 1271 cm^{-1}; HRMS (EI) found 296.1408 [calcd for $C_{19}H_{20}O_3$ $(M)^+$ 296.1412].

Preparation of 1,3-*syn*-Diol Mono-Pivaloate 3.41



[Pivaloylation] To a cooled (0 °C) solution of alcohol **3.39** (81.0 mg, 0.293 mmol) in CH_2Cl_2 (4 mL, 0.059 M) were added pyridine (0.036 mL, 0.440 mmol), PivCl (0.054 mL, 0.440 mmol) and the resulting mixture was stirred for 12 h at 25 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This crude THP-protected pivaloate was employed in the next step without purification. **[THP-Deprotection]** To the crude THP-protected pivaloate in EtOH was added PPTS (22.1 mg, 0.088 mmol) and the resulting mixture was stirred for 5 h at 60 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford alcohol **3.41** (64.0 mg, 79 %) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.19–7.31 (m, 5H), 5.60–5.72 (m, 1H), 4.98–5.03 (m, 2H), 4.82–4.89 (m, 1H), 4.70 (dd, $J = 6.0$, 6.0 Hz, 1H), 2.22–2.37 (m, 2H), 2.07 (ddd, $J = 15.2$, 8.0, 8.0 Hz, 1H), 1.89 (ddd, $J = 14.4$, 5.6, 4.4 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 144.0, 133.2, 128.6, 127.8, 125.8, 118.1, 72.0, 71.0, 43.0, 38.8, 27.1; IR (neat) 3446, 2978, 1725, 1646, 1237 cm^{-1}; HRMS (EI) found 276.1718 [calcd for $C_{17}H_{24}O_3$ $(M)^+$ 276.1725].

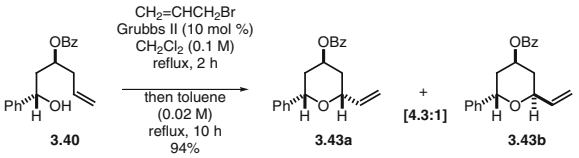
Preparation of 1,3-*syn*-Diol Mono-Benzyl Ether 3.42



[Benzylation] To a cooled (0 °C) solution of alcohol **3.39** (111.0 mg, 0.402 mmol) in DMF (6 mL, 0.067 M) were added NaH (19.3 mg, 0.804 mmol), BnBr (0.071 mL, 0.603 mmol) and the resulting mixture was stirred at 25 °C for

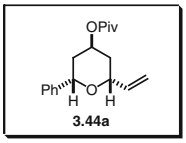
8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with water (50 mL) and CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This crude benzyl ether was employed in the next step without purification. **[THP-Deprotection]** To the crude THP-ether in EtOH was added PPTS (30.3 mg, 0.121 mmol) and the resulting mixture was stirred for 5 h at 60 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford alcohol **3.42** (98.0 mg, 86 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.39 (m, 10H), 5.75–5.87 (m, 1H), 5.08–5.13 (m, 2H), 4.88 (dd, $J = 9.6$, 2.4 Hz, 1H), 4.62 (AB, $J_{AB} = 11.2$ Hz, $\Delta\nu_{AB} = 96.0$ Hz, 2H), 3.83 (s, 1H), 3.78–3.83 (m, 1H), 2.40–2.45 (m, 2H), 1.96–2.06 (m, 1H), 1.84 (ddd, $J = 14.8$, 3.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 137.7, 133.5, 128.6, 128.3, 128.01, 127.94, 127.3, 125.8, 118.0, 79.0, 74.0, 70.9, 43.5, 37.9; IR (neat) 3432, 3029, 2915, 1640, 1063 cm^{-1}; HRMS (EI) found 282.1620 [calcd for $C_{19}H_{22}O_2$ $(M)^+$ 282.1620].

A Representative Procedure for Tandem CM/Thermal S_N2' Reaction



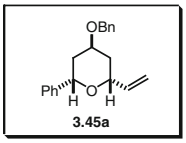
To a solution of benzoate diol **3.40** (29.0 mg, 0.098 mmol) in CH_2Cl_2 (1.0 mL, 0.098 M) was added Grubbs II (8.3 mg, 0.010 mmol) and CH_2=$CHCH_2Br$ (0.025 mL, 0.294 mmol) under N_2 atmosphere. The resulting mixture was refluxed under N_2 for 2 h, diluted with toluene (5 mL, 0.020 M) and refluxed for additional 10 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 15/1) to afford a 4.3:1 mixture of 2,6-*cis*-tetrahydropyran **3.43a** and 2,6-*trans*-tetrahydropyran **3.43b** (28.5 mg, 94 %) as a colorless oil: **[For 2,6-*cis*-tetrahydropyran 3.43a]** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.16 (m, 2H), 7.62 (dddd, $J = 6.8$, 6.8, 1.2, 1.2 Hz, 1H), 7.50 (dd, $J = 8.0$, 8.0 Hz, 2H), 7.25–7.43 (m, 5H), 5.96 (ddd, $J = 17.2$, 10.4, 4.8 Hz, 1H), 5.58 (dddd, $J = 2.8$, 2.8, 2.8, 2.8 Hz, 1H), 5.37 (ddd, $J = 17.2$, 1.6, 1.6 Hz, 1H), 5.18 (ddd, $J = 11.2$, 1.6,

1.6 Hz, 1H), 4.95 (dd, $J = 11.6$, 2.0 Hz, 1H), 4.51–4.56 (m, 1H), 2.20 (dddd, $J = 14.4$, 2.4, 2.4, 2.4 Hz, 1H), 2.09 (dddd, $J = 14.4$, 2.0, 2.0, 2.0 Hz, 1H), 1.91 (ddd, $J = 14.4$, 12.0, 2.8 Hz, 1H), 1.81 (ddd, $J = 14.4$, 12.0, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 142.2, 138.4, 133.2, 130.5, 129.6, 128.51, 128.35, 127.5, 125.9, 115.3, 74.4, 73.5, 68.4, 37.5, 35.3; IR (neat) 3063, 2954, 1716 cm^{-1}. **[For 2,6-*trans*-tetrahydropyran 3.43b]** *Cis* and *trans* two diastereomers were inseparable via column chromatography. The minor *trans*-diastereomer was identified by comparison with **3.36b** after hydrolysis of benzoate group.



3.44a

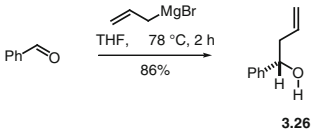
A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.39 (m, 5H), 5.93 (ddd, $J = 17.2$, 10.4, 5.6 Hz, 1H), 5.34 (ddd, $J = 17.6$, 1.6, 1.6 Hz, 1H), 5.27 (dddd, $J = 2.8$, 2.8, 2.8, 2.8 Hz, 1H), 5.16 (ddd, $J = 10.4$, 1.6, 1.6 Hz, 1H), 4.80 (dd, $J = 12.4$, 2.4 Hz, 1H), 4.37–4.42 (m, 1H), 2.01 (dddd, $J = 14.4$, 2.0, 2.0, 2.0 Hz, 1H), 1.91 (dddd, $J = 14.0$, 2.4, 2.4, 2.4 Hz, 1H), 1.80 (ddd, $J = 14.4$, 11.6, 2.4 Hz, 1H), 1.70 (ddd, $J = 14.4$, 12.0, 2.8 Hz, 1H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 142.2, 138.5, 128.3, 127.5, 125.8, 115.2, 74.4, 73.4, 67.3, 39.0, 37.4, 35.2, 27.2; IR (neat) 2957, 1725, 1154 cm^{-1}. **[For 2,6-*trans*-tetrahydropyran 3.44b]** *Cis* and *trans* two diastereomers were inseparable via column chromatography. The minor *trans*-diastereomer was identified by comparison with **3.36b** after hydrolysis of pivaloate group.



3.45a

A colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.43 (m, 10H), 5.93 (ddd, $J = 17.2$, 10.4, 5.6 Hz, 1H), 5.32 (ddd, $J = 17.2$, 1.6, 1.6 Hz, 1H), 5.12 (ddd, $J = 10.4$, 1.2, 1.2 Hz, 1H), 4.91 (dd, $J = 11.6$, 2.0 Hz, 1H), 4.63 (s, 2H), 4.48–4.53 (m, 1H), 3.98 (dd, $J = 3.2$, 3.2 Hz, 1H), 2.10 (dddd, $J = 14.0$, 2.4, 2.4, 2.4 Hz, 1H), 2.00 (dddd, $J = 14.4$, 2.4, 2.4, 2.4 Hz, 1H), 1.68 (ddd, $J = 14.0$, 11.6, 2.8 Hz, 1H), 1.59 (ddd, $J = 14.4$, 12.0, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 139.2, 138.9, 128.44, 128.25, 127.58, 127.41, 127.2, 125.9, 114.8, 74.0, 73.1, 71.6, 70.3, 37.6, 35.4; IR (neat) 3064, 2920, 1646 cm^{-1}; HRMS (EI) found 294.1621 [calcd for $C_{20}H_{22}O_2$ $(M)^+$ 294.1620].

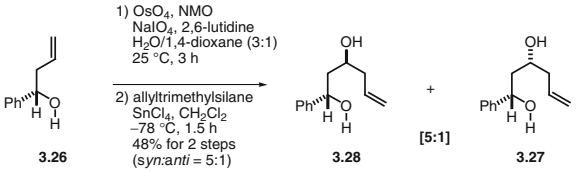
Preparation of the Known Alcohol 3.26 [46]



3.26

To a cooled (–78 °C) solution of PhCHO (168.8 mg, 1.591 mmol) in THF (7 mL, 0.227 mmol) was added CH_2=$CHCH_2MgBr$ (3.18 mL, 1.0 M in THF, 3.182 mmol). After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford the known racemic alcohol **3.26** (203.5 mg, 86 %) as a colorless oil.

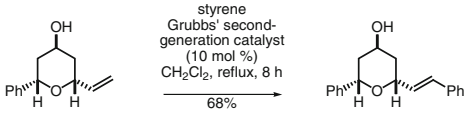
Preparation of 1,3-*syn*-Diol 3.28



3.26 **3.28** **3.27**

[Oxidative Cleavage of the Olefin] To a solution of the known alcohol **3.26** (113 mg, 0.762 mmol) in a dioxane/H_2O (3/1, total 8 mL) at 25 °C were successively added OsO_4 (0.16 mL, 2.5 % in H_2O, 0.015 mmol), 2,6-lutidine (0.177 mL, 1.524 mmol) and $NaIO_4$ (651.9 mg, 3.048 mmol). The solution was stirred at the same temperature for 3 h, quenched by addition of water (10 mL), and diluted with CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. This crude aldehyde directly employed in the next step without further purification. **[Allylation]** A mixture of $SnCl_4$ (0.914 mL, 1 M in CH_2Cl_2), allyltrimethylsilane (0.146 mL, 0.914 mmol), and CH_2Cl_2 (3 mL) was stirred at 25 °C for 12 h and transferred by a canula to a round-bottom flask containing a solution of crude β-hydroxyaldehyde in CH_2Cl_2 at –78 °C. After stirring for 1.5 h at the same temperature, the reaction mixture was quenched with MeOH (2 mL) and saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 5/1) to afford 1,3-*syn*-diol **3.28** (59.6 mg, 41 %) and 1,3-*anti*-diol **3.27** (11.4 mg, 8 %) as colorless oils.

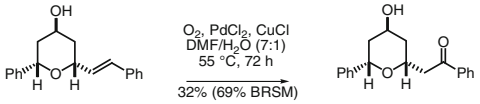
Preparation of 4-Hydroxy-2-Phenyl-6-Styryl-Tetrahydropyran 3.57



3.36a **3.57** (*E* only)

To a solution of olefin **3.36a** (77.0 mg, 0.377 mmol) in CH_2Cl_2 (5.0 mL, 0.075 M) were added Grubbs II (32.0 mg, 0.038 mmol) and styrene (0.086 mL, 0.754 mmol) under N_2 atmosphere. After refluxing for 8 h, the mixture was allowed to warm to room temperature and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford the desired tetrahydropyran **3.57** (72.3 mg, 68 %) as a colorless oil whose spectral data were in accordance with synthetic **3.57** reported previously [38]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.44 (m, 10H), 6.67 (d, $J = 16.0$ Hz, 1H), 6.28 (dd, $J = 16.0$, 6.0 Hz, 1H), 4.97 (dd, $J = 11.6$, 2.0 Hz, 1H), 4.67–4.72 (m, 1H), 4.38 (dddd, $J = 2.8$, 2.8, 2.8, 2.8 Hz, 1H), 1.74–1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 136.9, 130.32, 130.15, 128.44, 128.31, 127.45, 127.36, 126.4, 126.0, 73.7, 72.6, 64.7, 40.4, 38.6; IR (neat) 3413, 3027, 2918, 1653 cm^{-1}; HRMS (EI) found 280.1463 [calcd for $C_{19}H_{20}O_2$ $(M)^+$ 280.1463].

Synthesis of (±)-Diospongin A (3.55)



3.57 (±)-diospongin A (**3.55**)

O_2 was bubbled into a mixture of $PdCl_2$ (20.7 mg, 0.117 mmol), CuCl (23.0 mg, 0.234 mmol), DMF (7 mL), and H_2O (1 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 30 min to give a deep green mixture, and then compound **3.57** (65.5 mg, 0.234 mmol) was added. The temperature of reaction mixture was raised to 55 °C. After stirring for 72 h at the same temperature under O_2 atmosphere, the reaction mixture was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford (±)-diospongin A (**3.55**) (22.3 mg, 32 %) as a colorless oil along with starting material (34.7 mg, 53 %). (±)-diospongin A (**3.55**) was identical in all respects with the spectral data reported previously [34]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.93 (m, 2H), 7.49 (dddd, $J = 6.8$, 6.8, 1.2, 1.2 Hz, 1H), 7.38 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.13–7.24 (m, 5H), 4.86 (dd, $J = 12.4$, 2.0 Hz, 1H), 4.58 (dddd,

J = 11.6, 6.0, 6.0, 1.6 Hz, 1H), 4.30 (dddd, J = 2.8, 2.8, 2.8, 2.8 Hz, 1H), 3.35 (dd, J = 12.0, 6.0 Hz, 1H), 3.00 (dd, J = 12.0, 6.4 Hz, 1H), 1.86–1.91 (m, 2H), 1.72 (br s, 1H), 1.57–1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 142.7, 137.2, 133.1, 128.51, 128.30, 128.22, 127.2, 125.8, 73.8, 69.0, 64.6, 45.1, 40.0, 38.4; IR (neat) 3423, 3061, 2916, 1676, 1210 cm^{-1}; HRMS (EI) found 296.1412 [calcd for $C_{19}H_{20}O_3$ $(M)^+$ 296.1412].

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Biography

Kiyoun Lee was born on July 19, 1978 in Cheongju, South Korea. He received his Bachelor Science degree in Chemistry in June of 2003 and Master of Science degree in organic chemistry from the department of chemistry at Chungnam National University, Daejeon, South Korea in February of 2006. In the fall of 2007, he began his graduate career at Duke University and received his Doctor of Philosophy in organic chemistry in November of 2012.

Honors and Awards

Duke University Graduate School Travel Grant	2011
Kathleen Zielek Fellowship Award, Duke University	2011
C.R. Hauser Memorial Fellowship Award, Duke University	2010

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1. Kaoud, T. S.; Park, H.; Mitra, S.; Yan, C.; Tseng, C.-C. Shi, Y.; Jose, J.; Taliaferro, J. M. Lee, K.; Ren, P.; Hong, J.; Dalby, K. N.* "Manipulating JNK signaling with (–)-zuonin A" *ACS Chem. Biol.***2012**, *7*, 1873–1883.
2. Lee, Kiyoun; Boger, Dale* "Total Syntheses of (–)-Kopsifoline D and (–)-Deoxoapodine: Divergent Total Synthesis via Late Stage Key Strategic Bond Formation" *J. Am. Chem. Soc.* **2014**, DOI: 10.1021/ja500548e
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