Part 1: Total Synthesis of Clavosolide A

Part 2: Total Synthesis of Subglutinols A and B

by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor of Philosophy in the Department of Chemistry in the Graduate School
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ABSTRACT

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Abstract

Nature provides an abundant source of small molecules that can be used to interrogate biological systems. However, these compounds are often available in limited quantities from natural sources and must be synthesized in order to: 1) accumulate useful amounts for further study; 2) provide an efficient means to introduce structural modifications to achieve analogues. Part I demonstrates the asymmetric total synthesis of (–)-clavosolide A, showcasing the tandem allylic oxidation/oxa-Michael reaction in the stereoselective formation of the 2,3-*trans*-2,6-*cis*-tetrahydropyran core. Part II demonstrates the total synthesis of the immunosuppressive compounds, subglutinols A and B through reductive deoxygenation and cross-metathesis/intramolecular S_N2' reactions from a common intermediate to form the substituted 2,3-*trans*-2,5-*trans*-tetrahydrofuran and 2,3-*trans*-2,5-*cis*–tetrahydrofuran cores (subglutinol A and B respectively. Preliminary structure-activity relationships as well as biological studies are presented. In future, the construction of these natural products will aid in the elucidation of their biological mechanisms.

Dedication

For Susan and my parents.

Contents

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List of Abbreviations

Å	angstrom
ALP	alkaline phosphatase
anti	on the opposing face
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl etherate
bis	twice
BMP-2	bone morphogenetic protein 2
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
CSA	camphorsulfonic acid
CM	cross-metathesis
CypA	cyclophilin A
dr	diastereomeric ratio
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMP	Dess–Martin periodinane
DMSO	dimethylsulfoxide
ee	enantiomeric excess
ent	enantiomer

EVE	ethyl vinyl ether
gem	geminal
$K_V1.3$	voltage gated potassium channel 1.3
LAH	lithium aluminum hydride
OTf	trifluoromethanesulfonate
MLR	mixed lymphocyte reaction
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl ether
NBS	*N*-bromosuccinimide
NCI	National Cancer Institute
NHC	*N*-heterocyclic carbine
NIS	*N*-iodosuccinimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance spectroscopy
PCC	pyridinium chlorochromate
PMB	*p*-methoxybenzylether
PPTS	pyridinium *para*-toluenesulfonate
P_{sora}	psoralen
R	Rectus (Latin for right)
S	Sinister (Latin for left)

S_N2	biomolecular nucleophilic substitution
S_N2'	biomolecular nucleophilic substitution with allylic rearrangement
STIM 1	stromal interaction molecule 1
SUPREX	Stability of Unpurified Proteins from Rates of H/D eXchange
syn	on the same face
TBAF	tetra-*n*-butylammonium fluoride
TES	triethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TP	thymocyte proliferation
TPAP	tetrapropylammonium perruthenate
TSAF	tris(dimethylamino)sulfur trimethylsilyl difluoride

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1. The role of natural products in chemical biology

1.1 Classical vs. chemical genetics

Living systems range from simple unicellular organisms (e.g. bacteria) to complex multicellular and multitissue organisms (e.g. humans). Understanding the mechanisms that constitute life is important for the recognition and intervention of aberrant or diseased states. Classical genetic techniques have contributed greatly to the current understanding of biological mechanisms through specific genetic modifications such as overexpression, deletion, or mutation.[1]

Gene modification introduces a perturbation into a system which is then interrogated for differences in phenotype from the normal system. While much insight has been gained from these experiments they can have disadvantages that lead to unwanted global side effects and incompatibility with more complex systems. These drawbacks stem from the irreversible nature of genetic modification. In the case of genetic mutation, the structure of the gene product or protein is altered, leading to a possible inhibition of its function. If the function of the protein is critical for the survival of the organism then death will occur and the function of the protein remains obscure. Gene deletion can also suffer from this drawback.[1-2] A single protein may have multiple functions in the cellular environment. If the gene/protein is deleted then the resultant phenotype could be due to the loss of one specific function, the loss of multiple functions, or a synergistic effect due to the loss of multiple functions.[3]

Chemical genetics seeks to overcome these disadvantages by using small-molecules as the source of perturbation. The advantages of small-molecules over genetic mutation include a reversible, temporal, and dose-dependent response and depending on the specificity of the small-molecule, the perturbation of a single protein function.[3] Other advantages of using small-molecules include access to a wider range of organisms in model systems while providing a functional handle to identify specific targets. The major disadvantage of using small molecules is that they may interact with structurally related biological targets, producing off-target effects. Off-target effects can lead to unclear mechanistic determinations in biological pathways. In the case of drug development, these off-target interactions can lead to unwanted side-effects that can decrease the overall quality of life for the recipient.

1.2 Small molecules in chemical biology

There are two main sources of small-molecules in drug discovery: combinatorial chemistry libraries and naturally derived compounds. Combinatorial libraries have been successful in identifying modulators of significant biological processes, but have only led to the discovery of one FDA approved drug in the previous 20+ years while in contrast, from the 1940's to date, 73% of currently approved drugs are natural products or derivatives.[4-7] The major drawback of combinatorial libraries is the lack of chemical diversity, which stems from the two-dimensional nature of the drug like scaffold

synthesis. Proteins are three-dimensional structures; as such combinatorially derived compounds are unable to take advantage of all three dimensions of chemical space.[8-9]

On the other hand, nature takes full advantage of the natural selection process to produce chemically diverse compounds.[10] The Screening Hypothesis proposes that organisms that could produce and retain chemical diversity at a low energetic cost would be favored by the evolutionary process. The organisms that can screen a large number of compounds will increase their likelihood of generating potent and specific biological molecules.[11] As a consequence, natural products have an immense chemical diversity and are a rich source of biologically active compounds.

Organisms have evolved natural product compounds for their own purposes, but human proteins contain many structural domains that are conserved from the evolutionary process. As such, natural product compounds may have similar molecular targets in humans as their originating organism.[4, 12] This could explain why natural products have been successfully employed as modulators of diseased processes.

In order for a small-molecule to be a useful tool to study biological systems it must be available in sufficient quantities to conduct biological experiments. In addition, it must also possess a certain level of specificity and potency. The availability of a compound is quite often limited from natural sources as shown in the case of the widely used anti-cancer drug Taxol, derived from the bark of the Yew tree. One estimation is

that only a single dose of Taxol could be isolated from one mature tree.[13] Access to the limited supply of natural products necessitates a chemical or biochemical synthesis.

2. The total synthesis of (–)-clavosolide A

2.1 Substituted tetrahydropyrans as a structural motif in nature

Substituted tetrahydropyrans are ubiquitous structural features in a variety of biologically active natural products.[14-15] Samples of such structures are shown in **Figure 1**.

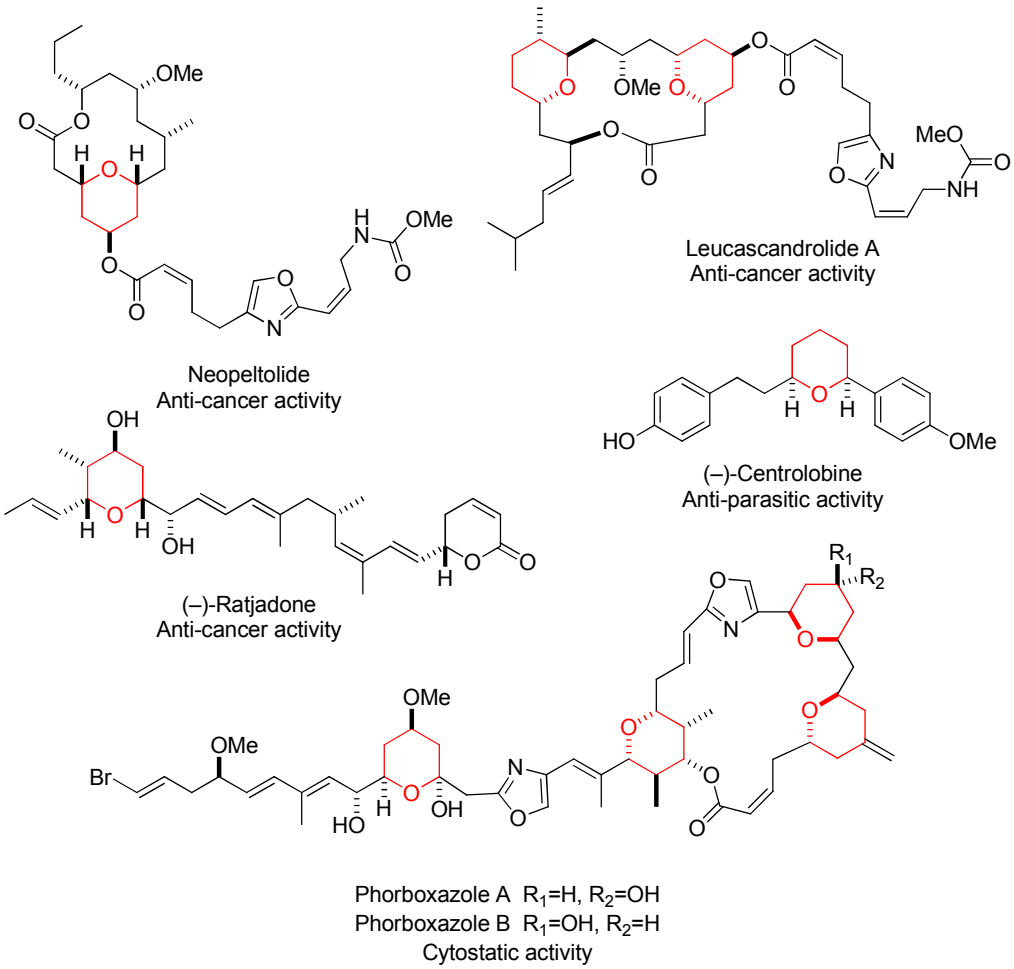


Figure 1: Biologically active natural products containing tetrahydropyrans.

Leucascandrolide A is a potent anti-cancer natural product that was isolated from the marine sponge *Leucascandra caveolata* in 1996.[16] Its biological activity and interesting structural features, consisting of a 2,6-*trans*-tetrahydropyran and a 2,6-*cis*-tetrahydropyran have inspired multiple syntheses.[17-28] Centrolobine, the antiparasitic compound has also been a proving ground for methodologies to achieve 2,6-*cis*-tetrahydropyrans.[29-32] The phorboxazoles contain four distinct tri-, and penta-substituted tetrahydropyrans.[33-34] Likewise, ratjadone and neopeltolide contain 2,6-*cis*-tetrahydropyran cores.[35-36]

2.2 Substituted tetrahydropyrans

2.2.1 Synthetic methods to access tetrahydropyrans

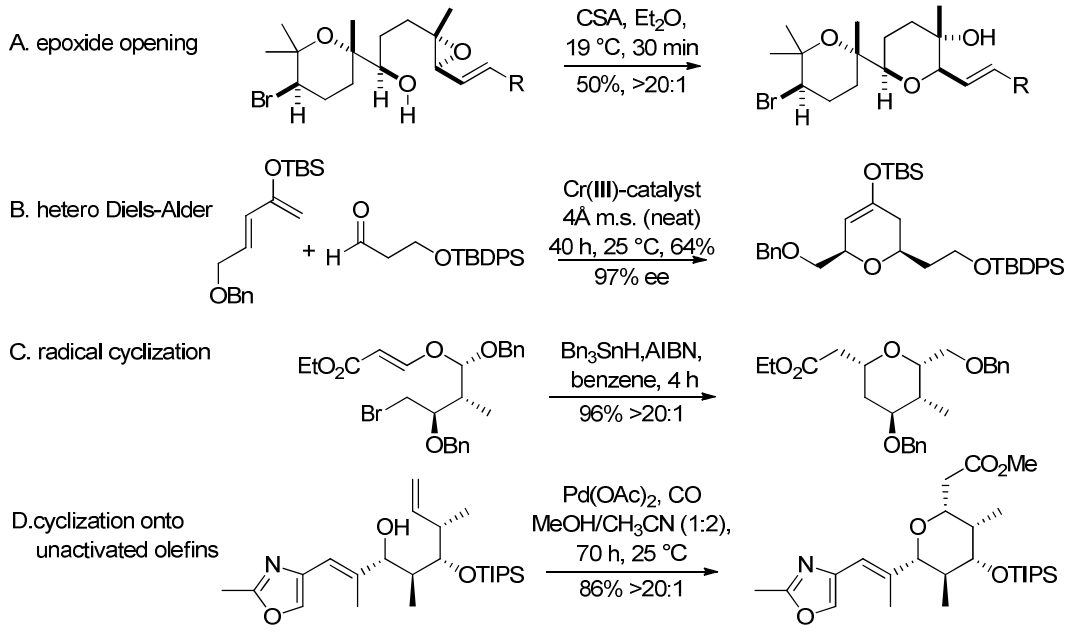


Figure 2: Synthetic methods used to construct substituted tetrahydropyrans.

Efficient and stereoselective access to substituted tetrahydropyrans has been the focus of considerable effort in the synthetic community and addressed by a variety of methodologies.[15] **Figure 2** presents four examples of methods used in natural product synthesis to construct substituted tetrahydropyrans. **Figure 2A** shows an intramolecular acid promoted epoxide opening tactic that was used in the synthesis of the cytotoxic compounds (+)-thyrsiferol and (+)-venustatriol.[37] **Figure 2B** shows a hetero Diels–Alder reaction under reagent control to selectively form an intermediate in the synthesis of the antifungal compound (+)-ambruticin.[38] In **Figure 2C**, the tributyltin radical promotes stereoselective cyclization under substrate control in the synthesis of *ent*-lasonolide.[39] **Figure 2D** demonstrates an intramolecular palladium mediated activation of a terminal olefin and subsequent ring closure by the nucleophilic hydroxyl group en route to the synthesis of phorboxazole A.[33, 40] Although currently available methods of tetrahydropyran formation are useful, there remains a great need for a synthetic strategy to construct this class of molecules that enables rapid and robust access to substrates, proceeds in excellent stereoselectivity and yield, and requires mild reaction conditions compatible with a variety of functional groups. [41]

2.2.2 Tandem allylic oxidation/oxa-Michael reaction

One underexplored method to form substituted tetrahydropyrans is the intramolecular 1,4-addition of oxygen nucleophiles to α,β-unsaturated carbonyl compounds. The lack of interest in this method is due to several factors including low

nucleophilicity of oxygen, retro-Michael addition and poor stereochemical control.[42] These drawbacks necessitate the enhancement of oxygen nucleophilicity through the use of a strong base, or the activation of the Michael acceptor through the use of acid catalysts, amine catalysts or transition-metal complexes. These harsh conditions are often intolerant to other functional groups of the substrate. To meet these goals, a new method was needed that was mild enough to tolerate a variety of functional groups, proceed in good yield, and have high stereoselective control. The Hong lab developed such a method through the introduction of a structural element at the C4 position to promote a favorable conformation, enhance oxygen nucleophilicity and reduce reaction reversibility through the *gem*-disubstituent effect.[41]

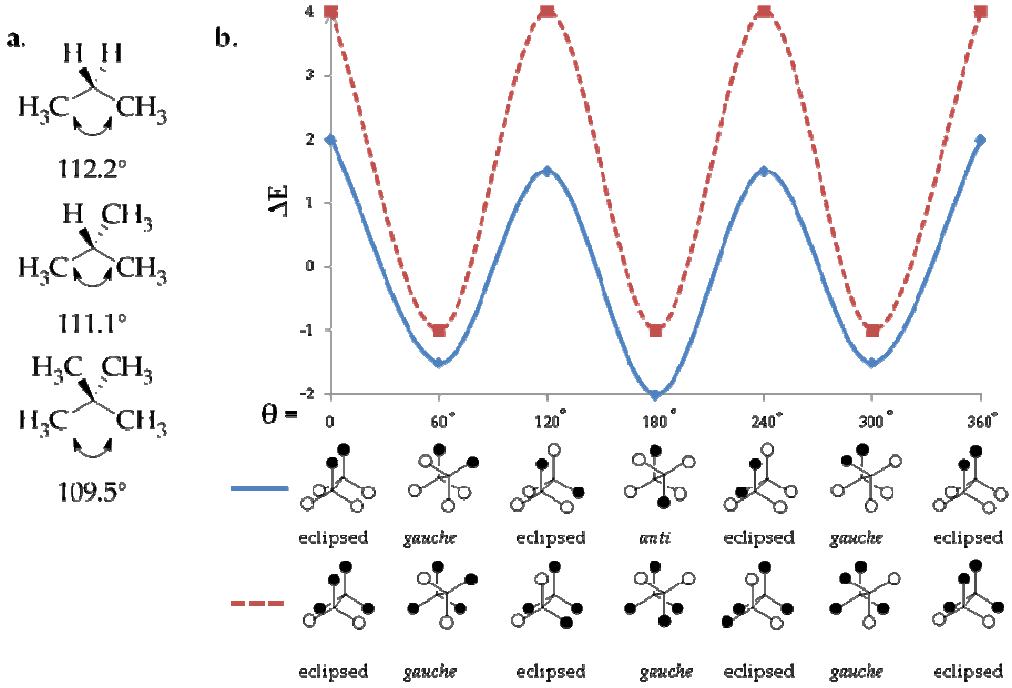


Figure 3: a. Thorpe–Ingold effect on bond angle. b. Relative energies of the rotational conformations of butane and 2,2-dimethylbutane.

The *gem*-disubstituant effect increases the rate of intramolecular cyclization by two distinct processes: 1) it decreases the bond angle between the reactive groups through the Thorpe–Ingold Effect; 2) it decreases the prevalence of the extended chain conformation by eliminating possible *anti* rotational conformations through the Reactive Rotomer effect.[43-45] **Figure 3a** shows the Thorp–Ingold effect on bond angle by increasing methyl substitution at the C2 position of propane. Increasing the substitution decreases the bond angle of the carbon backbone. In the case of intramolecular cyclization reactions, this decreased bond angle serves to decrease the through space distance between the reactive functionalities.

Figure **3b.** demonstrates the relative change in energy of the rotamers of butane (solid line) and 2,2-dimethylbutane (dashed line). Butane is able to adopt 4 possible rotational configurations; eclipsed, *gauche*, or *anti* (or *trans*) with *anti* having the lowest energy. The *anti* configuration in longer chain systems results in an open or extended chain configuration to minimize overall energy. In the case of 2,2-dimethylbutane, there are only two possible configurations: eclipsed and *gauche*. In longer chain systems this results in no difference in energy between the extended form and the coiled or closed conformations. The result in intramolecular cyclization reactions is that molecules that possess this disubstitution effect spend as much time in the closed chain configuration as in the open chain configuration, and consequently the reactive functionalities spend more time in closer proximity to one another resulting in acceleration of the reaction rate. Based on this analysis, it was hypothesized that the *gem*-disubstituant effect could be applied to the allylic oxidation/oxa-Michael reaction to accelerate the reaction rate.

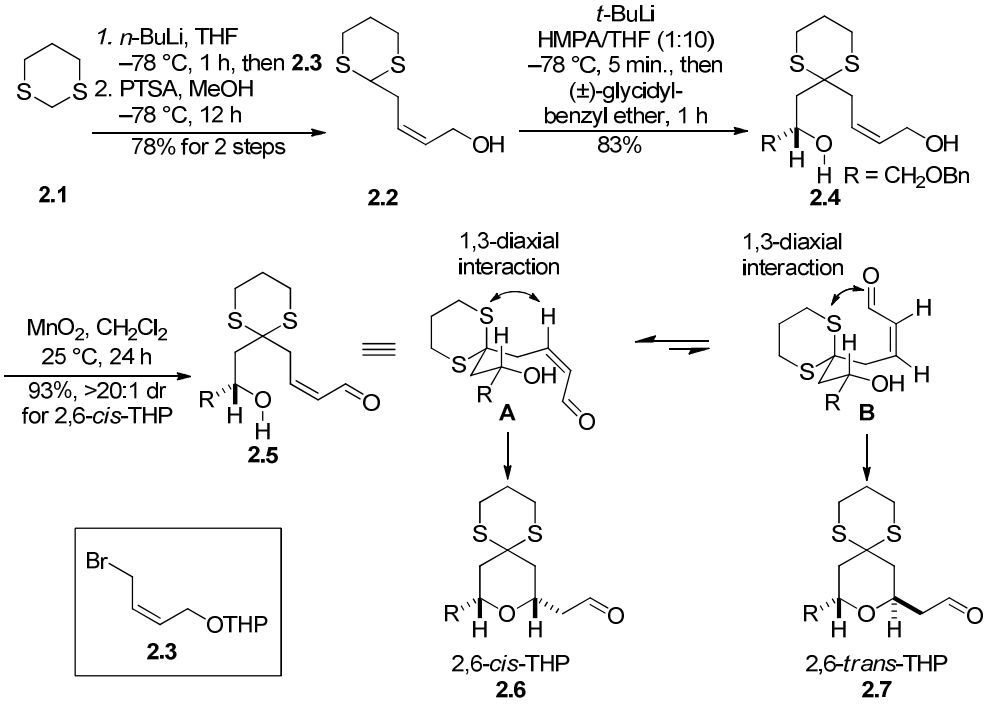


Figure 4: The allylic oxidation/oxa-Michael reaction promoted by the *gem*-disubstituent effect.

The Hong lab devised a model system to test this hypothesis by introduction of 1,3-dithiane at the C4 position (**Figure 4**) to the secondary hydroxyl group. The 1,3-dithiane group was selected because it allows rapid access to substrates and acts as a latent functional group for a carbonyl, olefinic, alcohol, or methylene unit while promoting the *gem*-disubstituant effect.[41]

The substrate for the allylic oxidation/oxa-Michael reaction was prepared in three steps from commercially available 1,3-dithiane **2.1** coupled with allyl bromide **2.3**, followed by hydrolysis of the THP protecting group under acidic conditions to give the allylic alcohol **2.2** in good yield.[46] Dithiane **2.2** was then coupled under basic

conditions with commercially available (±)-glycidyl benzyl ether to afford the allylic alcohol **2.4**.

After testing a variety of oxidative conditions, MnO_2 was determined to provide exclusive chemoselective oxidation of the allylic alcohol without formation of the bis-oxidation product. When **2.4** was subjected to allylic oxidation, α,β-unsaturated aldehyde **2.5** was formed and underwent spontaneous intramolecular conjugate addition to exclusively produce 2,6-*cis*-tetrahydropyran **2.6**. The stereochemical outcome was rationalized on the basis that the unfavorable 1,3-diaxial interaction developed in conformation **B** between the C6 α,β-unsaturated aldehyde and the 1,3-dithiane group is larger than that of the C6 hydrogen and the 1,3-dithiane group in conformation **A**.

To further explore the hypothesis that the *gem*-disubstituant effect could be applied to the allylic oxidation/oxa-Michael reaction, a different model system was devised to determine its role on reaction rate, stereoselectivity and efficiency of the allylic oxidation/oxa-Michael reaction (**Table 1**).

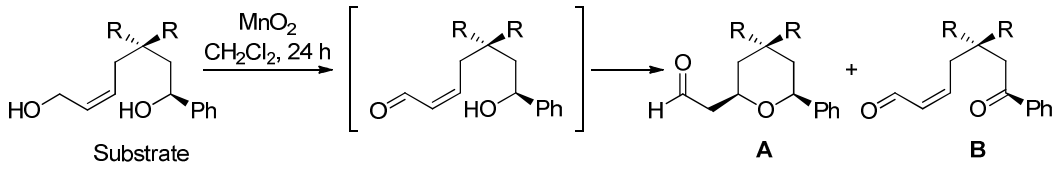


Table 1: Effect of *gem*-disubstituent groups on rate enhancement and stereoselectivity.

Substrate	Ratio of **A** to **B**	2,6-*cis*:2,6-*trans* of **A**[a]	%Yield [b]
2.8, R = H	3:1	7:1	83%
2.9, R = Me	4:1	10:1	94%
2.10, R = -S(CH_2)S-	A only	>20:1	96%

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

Three substrates were prepared with varying degrees of substitution at the C4 position to determine their effect on reaction rate and stereoselectivity in the tandem allylic oxidation/oxa-Michael reaction. When **2.8** was subjected to the allylic oxidation/oxa-Michael reaction it provided a ratio of the tetrahydropyran product **A** to bis-oxidation product **B** in 3:1 with a moderate stereoselectivity of 7:1, favoring the 2,6-*cis*-tetrahydropyran. Increasing the *gem*-disubstituent group to methyl and hydrogen, compound **2.9** slightly decreased the formation of the bis-oxidation product, as well as improved the diastereoselectivity to 10:1. Dithiane **2.10** eliminated the formation of the bis-oxidation product and provided the 2,6-*cis*-tetrahydropyran product as a single diastereomer.

These experiments showed that after the allylic oxidation, the larger *gem*-disubstituent effect accelerated the rate of reaction by promotion of a more favorable conformation, placing the nucleophilic oxygen in closer proximity to the conjugate

acceptor. This increased reaction rate precluded the slower oxidation of the benzylic alcohol in the dithiane case. Increased 1,3-diaxial interactions at the C4 position also improved stereoselectivity and yield. In addition, this methodology has been applied by the Hong lab in the synthesis of neopeltolide, cyanolide A, leucascandrolide A, and SCH 351448.[28, 41, 47-48] We applied this methodology to the synthesis of clavosolide A.

2.3 Isolation of clavosolides A–D

Clavosolides A–D are a family of unique dimeric macrolides, isolated independently by two groups from the extract of the Philippine marine sponge *Myristra clavosa*, in 2002.[49-50] The initial crude extract exhibited differential cytotoxicity and antiproliferative effects when tested in the NCI-60 tumor cell line assay. Upon further purification and testing it was discovered that clavosolides A–D were noncytotoxic. [49-50]

An 18.7 gram crude extract was subjected to extensive chromatography to yield the four clavosolide compounds in only trace amounts: 0.3 mg of clavosolide A, 0.2 mg of clavosolide B, 0.4 mg of clavosolide C, and 0.2 mg of clavosolide D [50]. The recovery of such small quantities of these compounds from natural sources made it imperative to discover synthetic means to accumulate sufficient material for further biological studies.

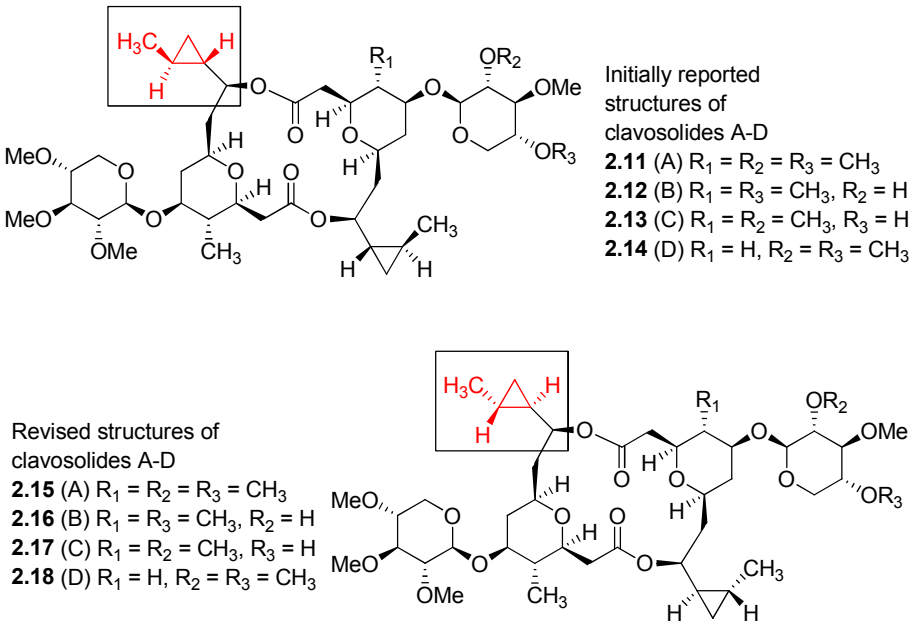


Figure 5: Initial and revised structural assignments of clavosolides A–D.

The structure and stereochemistry of the clavosolides were elucidated by extensive NMR analysis and molecular modeling calculations (**Figure 5**). Clavosolides A–C possess a C_2-symmetric macrolide core, two β-xylose residues with varying degrees of methylation, two symmetrical 2,6-*cis*-tetrahydropyran subunits as well as two *syn*-cyclopropyl appendages. There was some ambiguity in the spectral data concerning the stereochemistry of the cyclopropane moieties that led Faulkner to rely on molecular modeling for their relative assignment.[49-50] Clavosolide D was assigned to be identical to clavosolide A except for the unsymmetrical tetrahydropyran subunits, wherein one tetrahydropyran replaced the methyl group at the C3 position with hydrogen. In 2005, Willis and co-workers completed the first total synthesis of the initially assigned structure of clavosolide A **2.11**.[51] Their spectral data did not match

that of the natural product, which led them to propose a revised structure for the clavosolides, which was confirmed by the Lee group's first total synthesis of clavosolide A(**Figure 5**) [51-52].

2.4 Syntheses of clavosolide A and establishment of the absolute stereochemistry

The unique structure of clavosolide A has attracted considerable interest from the synthetic community. To date, there have been four total and two formal syntheses of clavosolide A [52-58]. The previous syntheses have five different strategies to form the 2,3-*trans*-2,6-*cis*-tetrahydropyran core of the monomeric unit of clavosolide A.

2.4.1 Lee group's total synthesis of (–)-clavosolide A

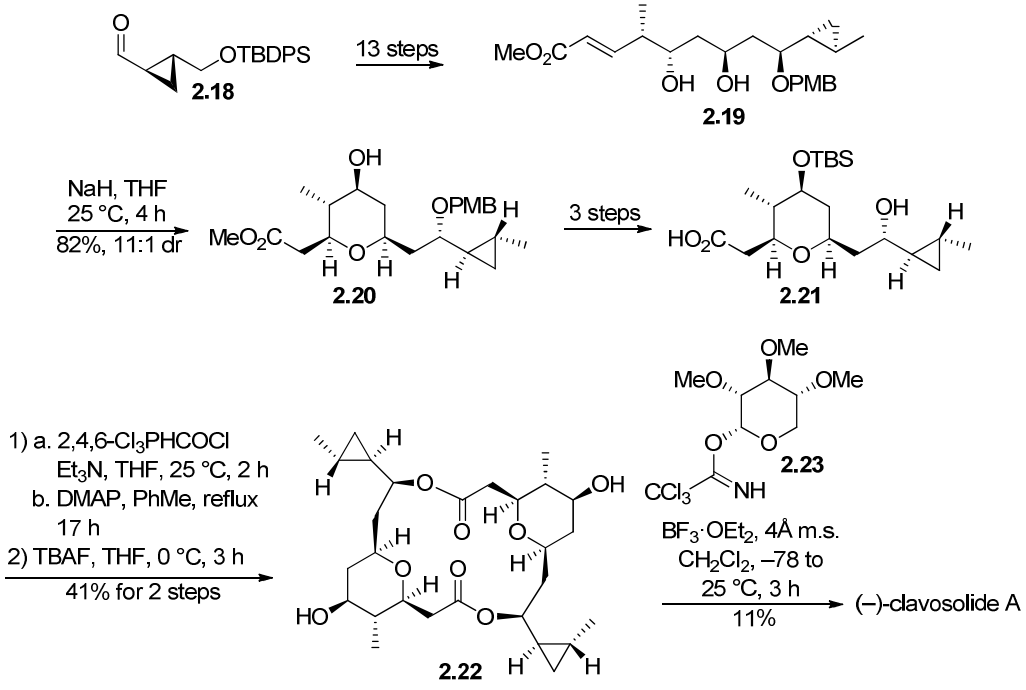


Figure 6: Lee group's synthesis of (–)-clavosolide A.

The first total synthesis of clavosolide A was reported by Lee and co-workers in 2006 (**Figure 6)**.[59] Their method to construct the 2,6-*cis*-tetrahydropyran **2.20** relied upon intramolecular conjugate addition of **2.19** by activation of the oxygen nucleophile under basic conditions (NaH). This reaction proceeded in 82% with 11:1 diastereoselectivity favoring the 2,6-*cis*-tetrahydropyran **2.20**. Protection of the C4 hydroxyl group, hydrolysis of the methyl ester and deprotection of the PMB group furnished the substrate **2.21** for dimerization by modified Yamaguchi macrolactonization protocol. This included a two step/one-pot process whereby the carboxylic acid was activated by forming the mixed anhydride with 2,4,6-trichlorobenzoyl chloride, followed by filtration of $Et_3N{\cdot}HCl$. DMAP was added in toluene to form a second mixed anhydride which underwent macrolactonization upon refluxing to form the clavosolide A aglycon **2.22** in 41% for two steps. **2.22** was then subjected to Schmidt glycosylation with the trichloroacetimidate sugar **2.23** and $BF_3{\cdot}OEt_2$ which proceeded to give the β,β-anomer, clavosolide A in 11% as well as a statistical mixture of α,β- and α,α-anomers.

The Lee group's synthetic clavosolide A matched with all authentic spectra except the sign of optical rotation. This established the relative stereochemistry and was in agreement with the proposed revision of the structure of natural clavosolide made by Willis and co-workers in 2005 and led them to determine that they made (+)-clavosolide

A, the antipode of the natural product.[51] It was later reported that the mistake in optical rotation was a clerical error thus established the absolute stereochemistry.[59]

2.4.2 Smith group's total synthesis of (–)-clavosolide A

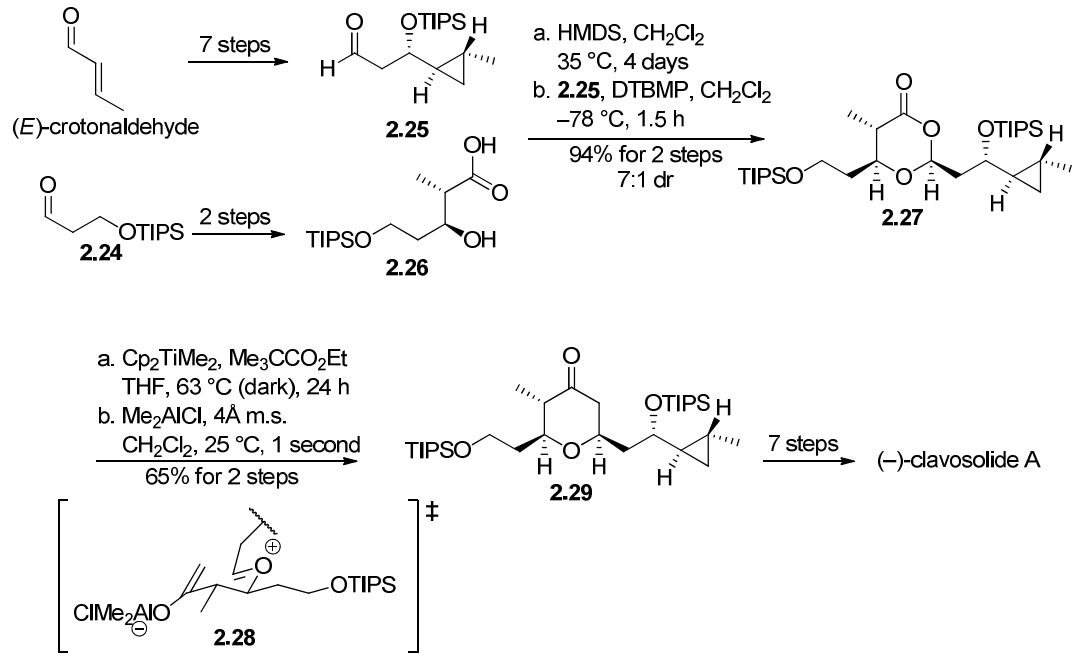


Figure 7: Smith group's synthesis of (–)-clavosolide A.

In 2006, Smith and co-workers published the total synthesis of (–)-clavosolide A (**Figure 7**).[55] Utilizing a stereoselective, Lewis acid promoted condensation reaction, β-hydroxy acid **2.26** was converted to the bis-TMS acid derivative then treated with aldehyde **2.25** to form dioxanone **2.27** as the substrate for their Petasis–Ferrier union/rearrangement tactic. They have applied this methodology in the synthesis of multiple substituted tetrahydropyrans.[34, 60-63]. Upon addition of Petasis–Tebbe reagent (Cp_2TiMe_2) and ethyl trimethylacetate, the C4 olefin is formed and following

filtration, Me_2AlCl is added to act as a Lewis acid. The subsequently formed oxocarbenium opens the acetal ring while simultaneously forming the enol ether (transition state **2.28**). Upon quenching the reaction rearrangement proceeds to give **2.29** in 65% for two steps as a single compound. Ketone reduction, benzylation, silyl deprotection and oxidation provided the substrate for dimerization, deprotection and glycosidation. The same Yamaguchi macrolactonization protocol was used for the dimerization as reported in the Lee synthesis. The final reaction was Schmidt bis-glycosylation where the only difference from the Lee synthesis was that TMSOTf was used as the Lewis acid instead of $BF_3{\cdot}OEt_2$.

2.4.3 Willis group's total synthesis of (–)-clavosolide A

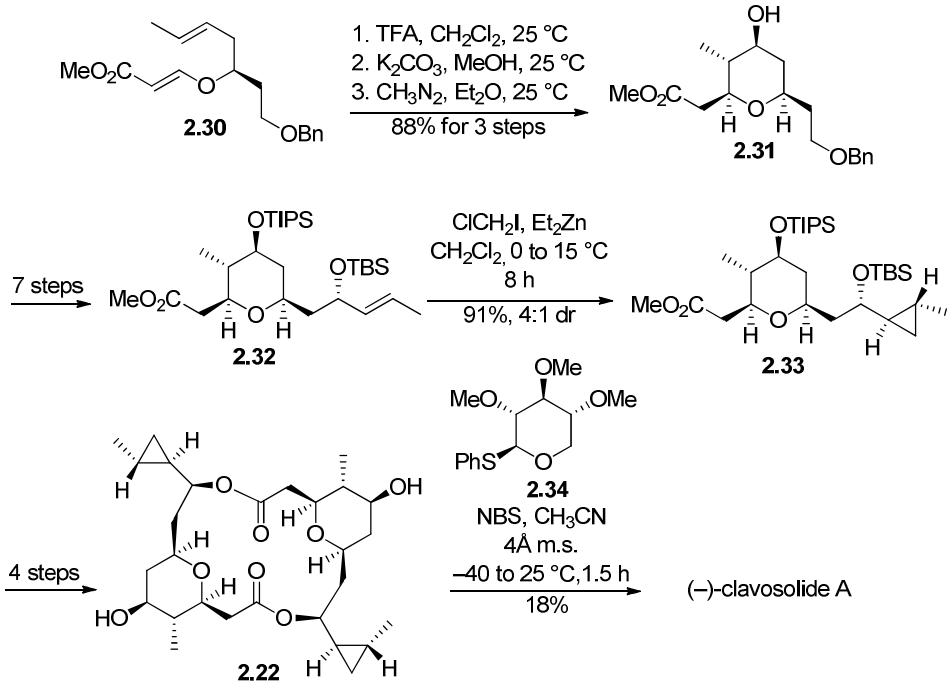


Figure 8: Willis group's synthesis of (–)-clavosolide A.

In 2006, Willis and co-workers reported their synthesis of (–)-clavosolide A (**Figure 8**).[54] They started with the known enol ether **2.30** and subjected it to Prins' reaction in the presence of TFA to achieve three new asymmetric centers with complete stereochemical control.[51] The trifluoroacetyl group was then hydrolyzed with methoxide, followed by addition of diazomethane to convert of the carboxylic acid byproduct from the Prins' reaction into the methyl ester to provide 2,6-*cis*-tetrahydropyran **2.31** in 88% yield for three steps as a single diastereomer.

After successive manipulations, **2.32** was prepared as the substrate for Simmons–Smith cyclopropanation. The TBS protected allylic alcohol **2.32** underwent reaction with diethyl zinc and chloroiodomethane to provide the desired cyclopropane tetrahydropyran **2.33** as a 4:1 mixture of diastereomers. TBS hydrolysis, methyl ester hydrolysis, dimerization using the identical Yamaguchi macrolactonization protocol to Lee (section **2.4.1**) and TIPS hydrolysis provided the clavosolide aglycon **2.22**. The aglycon was subjected to Schmidt glycosylation in which the Lewis acid was NBS and the glycosyl donor was thioglycoside **2.34**. This reaction provided (–)-clavosolide A in 18% yield with the expected α,β- and α,α-anomers.

2.4.4 Chakraborty group's first-generation synthesis of (–)-clavosolide A

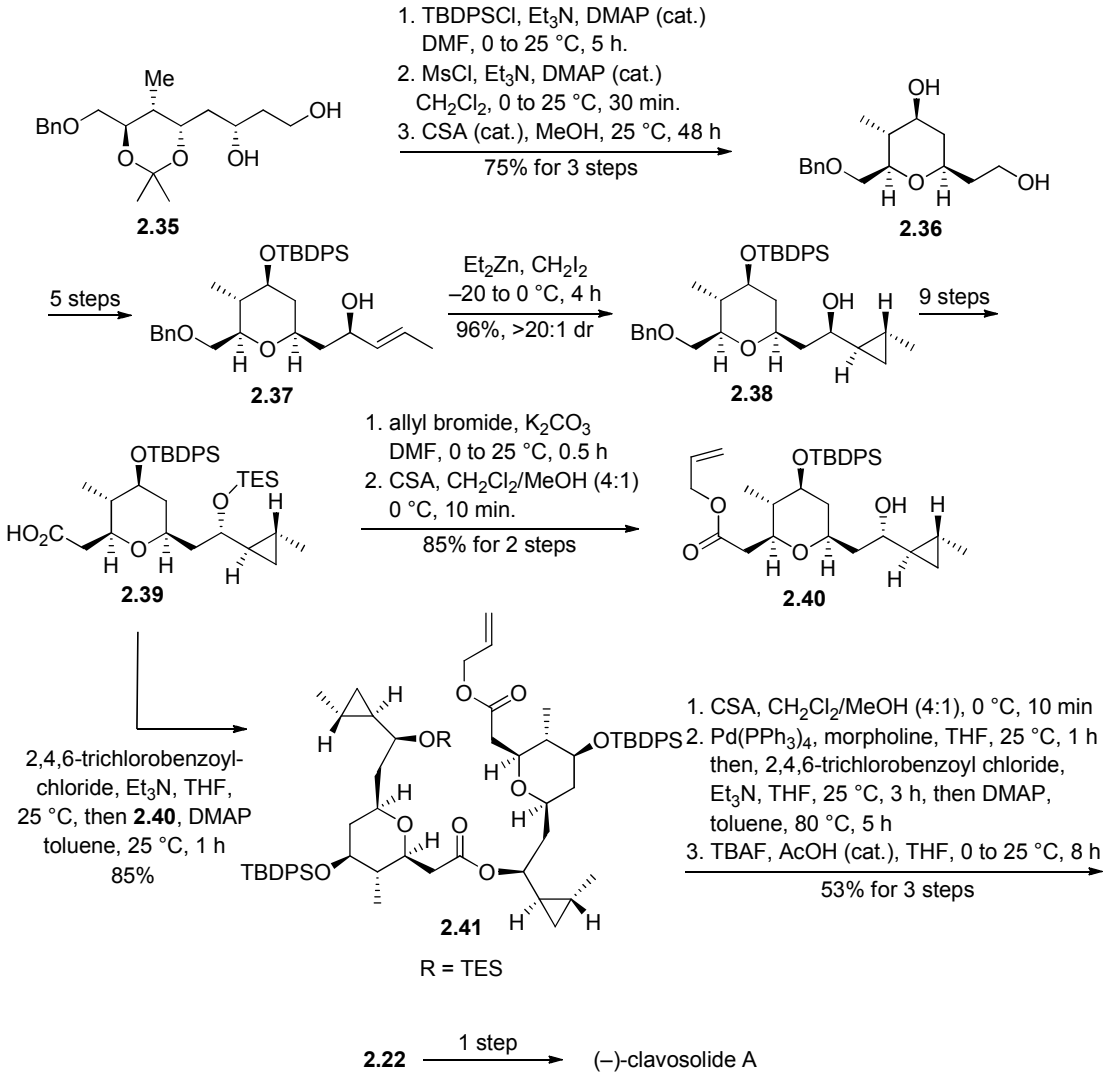


Figure 9: Chakraborty group's first-generation synthesis of (–)-clavosolide A.

As with the Willis group, Chakraborty and co-workers achieved the synthesis of the initially reported structure of clavosolide A, **2.11**, but quickly resolved the structure and subsequently reported their first generation synthesis of (–)-clavosolide A (**Figure 9**).[57, 64] Their synthesis began with their previous synthetic intermediate **2.35**.[65] The

primary alcohol was protected by TBDPS, followed by mesylation of the secondary hydroxyl group. Acetonide hydrolysis under acidic conditions led to spontaneous intramolecular S_N2 cyclization with complete stereochemical control to form the 2,6-*cis*-tetrahydropyran **2.36** in 75% for 3 steps. Through successive protection, oxidation, alkylation and Mitsonobu process, **2.37** was produced as the substrate for stereoselective Simmons–Smith cyclopropanation. The unprotected allylic alcohol was added to diethyl zinc and diiodomethane to give a cyclopropane **2.38** as a single compound in 96% yield.

The secondary hydroxyl group of **2.38** then underwent stereochemical inversion, followed by a series of deprotection, protection, and oxidation reactions to achieve **2.39**. **2.39** was then allylated and the TES group was hydrolyzed to provide **2.40** as the nucleophile for the four step dimerization process. After dimerization, the silyl group was cleaved to provide aglycon dimer **2.22**. Schmidt glycosylation under similar conditions with Lee and Smith (sections **2.4.1** and **2.4.2** respectively) completed (–)-clavosolide A.

2.4.5 Chakraborty group's second-generation synthesis of (–)-clavosolide A

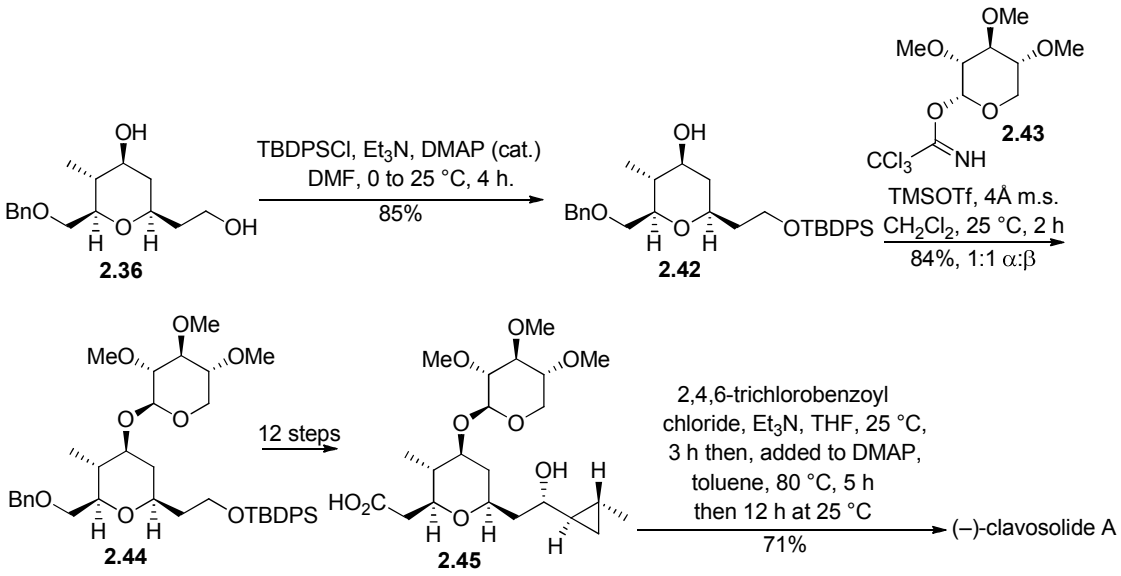


Figure 10: Chakraborty group's second generation synthesis of (–)-clavosolide A.

After a somewhat laborious first generation synthesis, Chakraborty and co-workers developed a more straight forward strategy to obtain (–)-clavosolide A (**Figure 10**). Beginning from their 2,6-*cis*-tetrahydropyran **2.36**, the primary alcohol was protected followed by Schmidt glycosylation to provide **2.44**. The advantage of installing of the glycoside prior to dimerization is the exclusion of forming unwanted α,α- and α,β-anomers as observed in each of the previously discussed syntheses, thus improving the efficiency of synthesis. Tetrahydropyran glycoside **2.44** was then subjected to similar reaction conditions as reported in the first generation synthesis to obtain monomeric **2.45**. Yamaguchi dimerization led to the formation of (–)-clavosolide A in 71% yield.

2.4.6 Jennings group's formal synthesis of (–)-clavosolide A

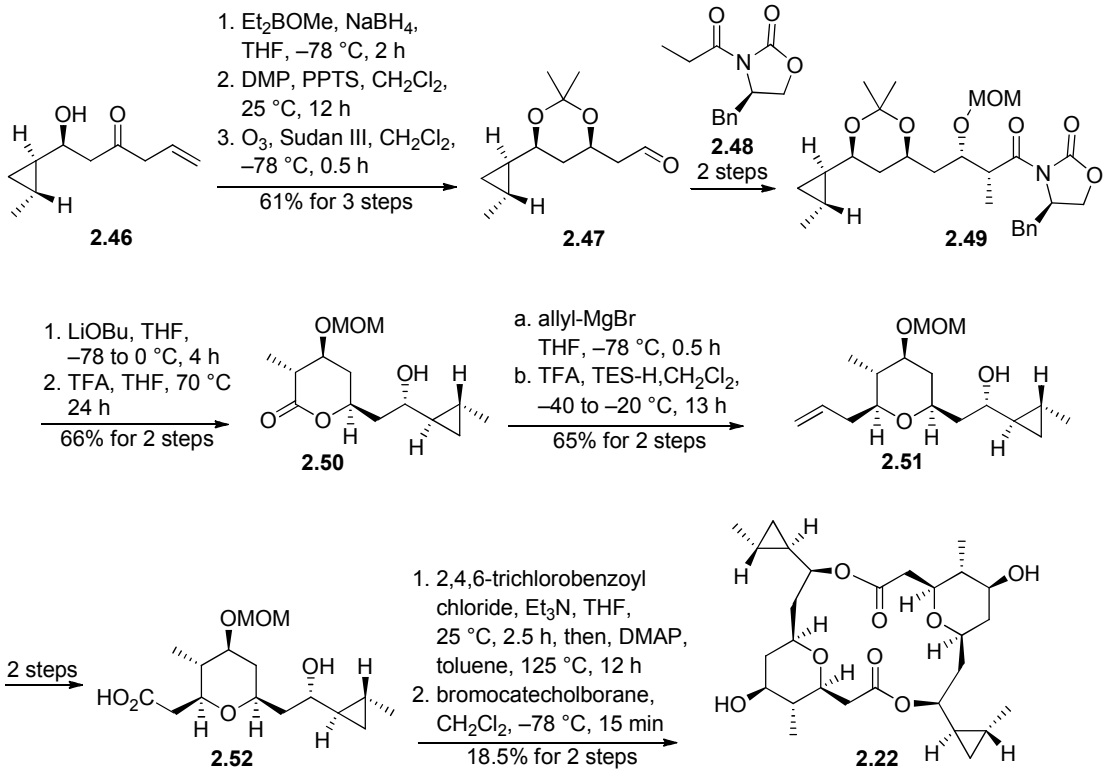


Figure 11: Jennings group's formal synthesis of (–)-clavosolide A.

In an effort paralleling the Smith group's synthesis of **2.26**, Jennings and Carrick exploited Evans aldol chemistry, Simmons–Smith cyclopropanation and Mitsunobu inversion of hydroxyl group stereochemistry to achieve **2.46**.[58] Stereoselective reduction led to the 1,3-*syn*-diol which was immediately protected as the acetonide. The terminal olefin was then oxidized in the presence of buffered ozone to provide **2.47** in 61% yield for three steps (**Figure 11**). Standard Evans' aldol addition of oxazolidinone **2.48** to aldehyde **2.47** were applied followed by MOM protection of the secondary hydroxyl group.

Removal of the chiral auxiliary by conversion of **2.51** to the benzyl ester then acetonide hydrolysis formed the lactone **2.50** as the substrate for alkylation and stereoselective oxocarbenium reduction. **2.50** was treated with allyl bromide to form the alkylated hemi-acetal which was then subjected to the next step without purification. TFA promoted dehydration/oxocarbenium formation occurred which then allowed triethylsilylhydride to add in an axial fashion to the oxocarbenium.[66] This stereoselective reduction provided the 2,6-*cis*-tetrahydropyran **2.51** in 65% for two steps as a single diastereomer. From **2.51**, the clavosolide A aglycon **2.22** was reached by subsequent oxidations and then Yamaguchi macrolactonization and MOM deprotection. This completed Jenning's formal synthesis of (–)-clavosolide A.

2.5 The total synthesis of (–)-clavosolide A

2.5.1 Retrosynthesis

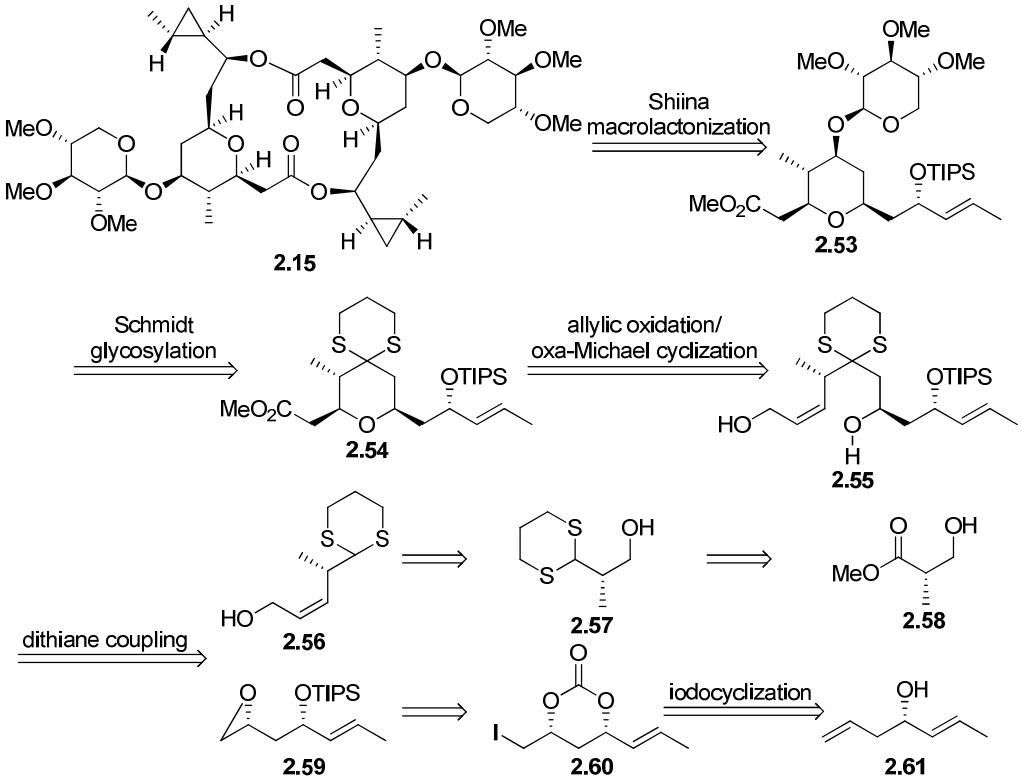


Figure 12: Retrosynthesis of (–)-clavosolide A.

The primary goals of this project were to exploit the tandem allylic oxidation/oxa-Michael methodology developed in our lab to construct the 2,3-*trans*-2,6-*cis*-tetrahydropyran monomeric core of clavosolide A and to accomplish the total synthesis in the most efficient manner to date. To that end the first anticipated disconnect (**Figure 12**) was at the macrolactone, which was thought to be achieved from a one step Shiina dimerization process after Simmons–Smith cyclopropanation, silyl cleavage and methyl ester hydrolysis, from THP glycoside **2.53**. The key transformation

in this synthetic strategy relied upon conversion of the acyclic diol **2.55** to the 2,3-*trans*-2,6-*cis*-tetrahydropyran **2.54** through the tandem allylic oxidation/oxa-Michael reaction in a stereoselective fashion.

The acyclic diol **2.55** could be produced in a convergent coupling of dithiane **2.56** with epoxide **2.59**. Dithiane **2.56** would be produced from the known dithiane compound **2.57** through oxidation and Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate followed by 1,2-reduction of the α,β-unsaturated methyl ester with diisobutylaluminum hydride. **2.57** can be produced following the procedure established by Ley, from the commercially available β-hydroxy methyl ester **2.58**.[67]

Epoxide **2.59** was expected from hydrolysis of the iodocarbonate **2.60** followed by silyl protection. Boc protection and iodocyclization could gain access to **2.60** from the known allylic alcohol **2.61** which was produced from the kinetic resolution of Sharpless asymmetric epoxidation procedure established by Prasad and co-workers.[68]

2.5.2 Synthesis of the dithiane fragment

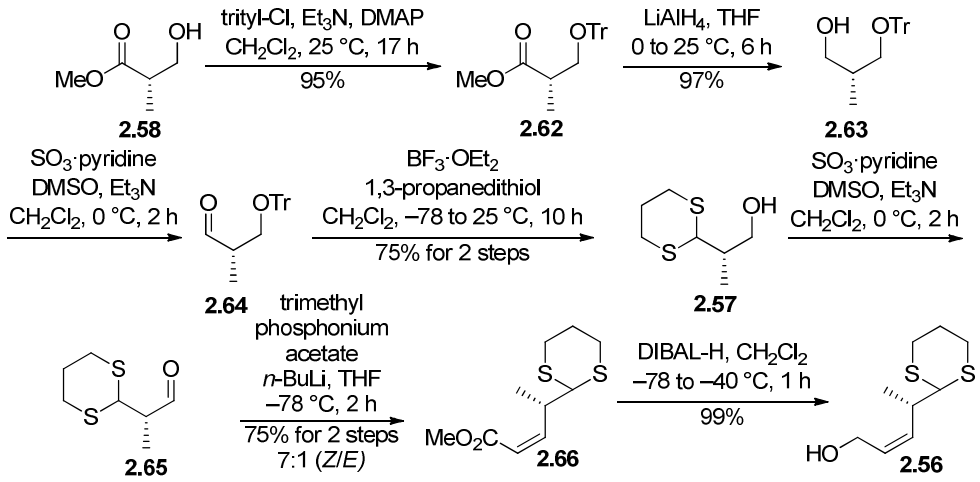


Figure 13: Synthesis of the dithiane coupling fragment 2.56.

Commercially available β-hydroxy methyl ester **2.26** was tritylated under standard conditions followed by LAH reduction of the methyl ester **2.62** to the primary alcohol **2.63** in good yield (**Figure 13**). Parikh–Doering oxidation gave the unstable aldehyde **2.64** which was quickly subjected to Lewis acid mediated dithiane formation and upon warming the trityl group was cleaved to provide dithiane **2.57** in 75% for two steps.[67] A second Parikh–Doering oxidation followed by Horner–Wadsworth–Emmons olefination of **2.65** with trimethyl phosphonoacetate provided **2.66** in 75% for two steps in 7:1 (*Z*/*E*) ratio.[69] 1,2-Hydride addition to the α,β-unsaturated methyl ester gave the dithiane coupling intermediate **2.56**.

2.5.3 Synthesis of the epoxide fragment

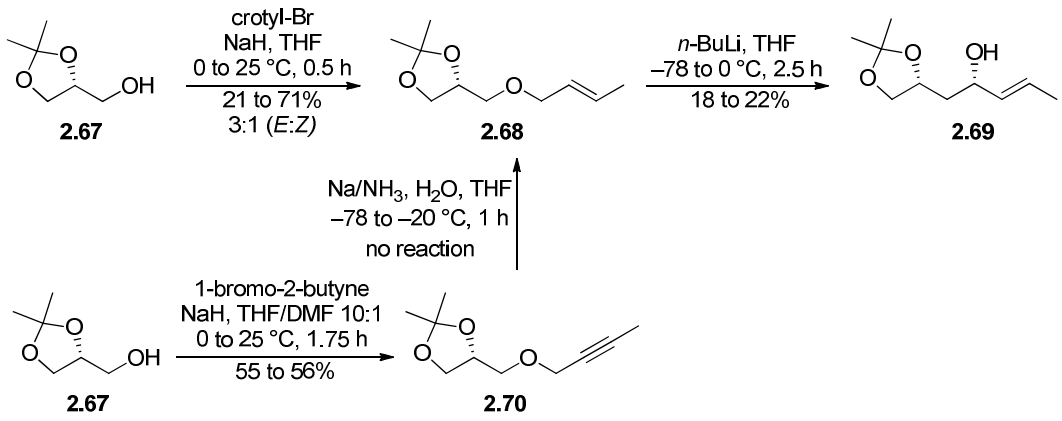


Figure 14: First attempt to synthesize the epoxide fragment.

The first attempted synthesis of the epoxide fragment (**Figure 14**) began with O-alkylation of the commercially available acetonide **2.67** with crotyl bromide to provide allyl ether **2.68** as an inseparable mixture of *E* and *Z* isomers (3/1) that served as substrate for a 1,2-Wittig rearrangement. Unfortunately, **2.68** was volatile under reduced pressure which made handling and purification problematic, leading to inconsistent yields and difficulty interpreting spectra. In an attempt to obtain **2.68** as the pure *E* diastereomer, *O*-alkylation of acetonide **2.67** with 1-bromo-2-butyne was expected to be selectively reduced to the *E* alkene under dissolving metal reduction conditions, but was unsuccessful in all attempts.[70]

Marginal success was achieved when **2.68** was subjected to 1,2-Wittig rearrangement conditions leading to 18 to 22% yields as the single diastereomer **2.69**.[70] The uncertainty in the etherification step, coupled with the low yielding 1,2-Wittig rearrangement was cause for revision in the synthetic plan for the epoxide fragment.

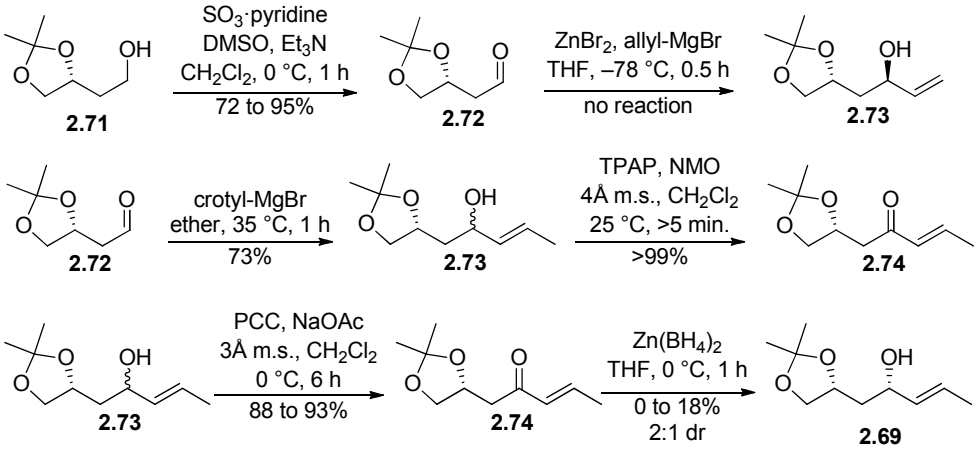


Figure 15: Second attempt to synthesize the epoxide fragment.

The strategy for the second attempt (**Figure 15**) was to employ the stereoselective alkylation of aldehyde **2.72** which was furnished from Parikh–Doering oxidation of the commercially available acetonide **2.71**.[69, 71] It was anticipated that the organozinc nucleophile would preferentially provide the 1,3-*anti* addition product, but all attempts resulted in no reaction.

Aldehyde **2.72** was then subjected to crotylation to provide a mixture of diastereomeric allylic alcohols **2.73** followed by oxidation in the presence of TPAP and NMO or PCC. Stereoselective reduction of **2.74** by zinc borohydride provided the desired diastereomeric alcohol as a single compound **2.69**, but in very low yield.[72] The inefficiency and redundancy of this scheme favored another revision to the synthetic strategy to achieve the epoxide coupling fragment.

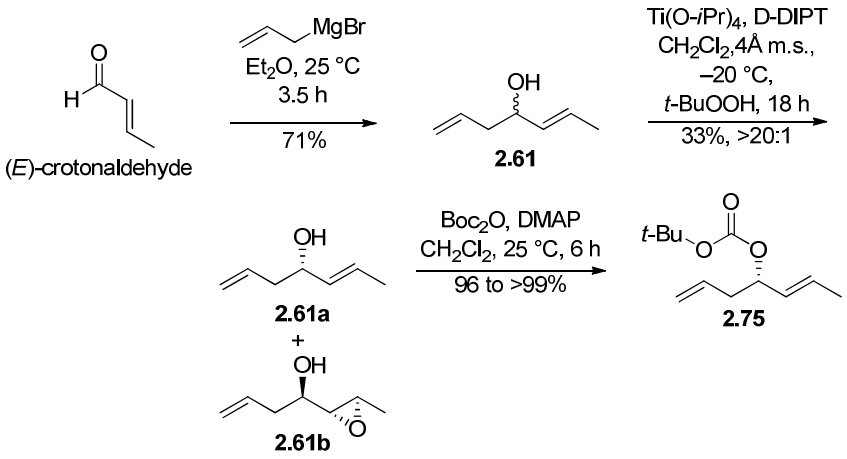


Figure 16: Synthesis of acyclic carbonate 2.75.

The next synthetic approach (**Figure 16**) was to install the epoxide stereocenter rather than begin with it in place. In the known procedure, allyl magnesium bromide was added to (*E*)-crotonaldehyde to prepare the racemate of **2.61**. Kinetic resolution of Sharpless asymmetric epoxidation provided the (*S*)-**2.61** as a single compound as determined by ^{1}H NMR of the Moshers' ester derivative.[53] **2.61** was then converted to the acyclic *tert*-butyl carbonate **2.75** in the presence of di-*tert*-butyl dicarbonate (Boc_2O) and DMAP. The strategy was to employ substrate controlled iodocyclization to transfer chirality from the stereogenic center of **2.75** onto the terminal olefin.[78]

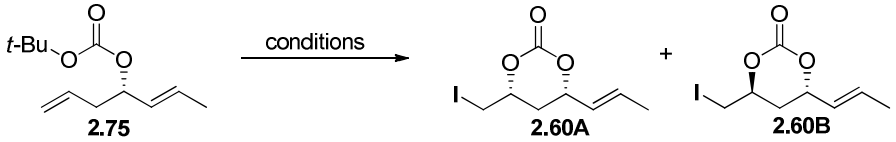


Table 2: Optimization of iodocyclization conditions.

Entry	Electrophile Source	Solvent	Temp. °C	Time	%Yield[a]	Ratio A:B[b]
1	IBr	CH_2Cl_2	–78	<5 min	0%	n.a.
2	IBr	CH_2Cl_2	–20	<5 min	20%	5:1
3	IBr	CH_2Cl_2	0	<5 min	0%	n.a.
4	IBr	toluene	–78	<5 min	38%	6:1
5	IBr	toluene	–40	<5 min	33%	6:1
6	IBr	toluene	–20	<5 min	24 to 51%	2 to 3:1
7	IBr	toluene	0	<5 min	0%	n.a.
8	IBr	CH_3CN	–20	<5 min	0%	n.a.
9	IBr	CH_2Cl_2/CH_3CN (3:1)	–20	<5 min	8 to 25%	5 to 6:1
10	IBr	CH_3CN/toluene (1:1)	–20	<5 min	22 to 73%	6:1
11	I_2	CH_2Cl_2	–78	1 h	0%	n.a.
12	I_2	CH_2Cl_2	–20	1 h	22 to 28%	3:1
13	I_2	CH_3CN	–20	3 h	20 to 33%	5:1
14	I_2	toluene	–20 to 25	6 h	no rxn	n.a.
15	I_2	CH_2Cl_2/CH_3CN (2:1)	–20	4 h	63%	5:1
16	I_2	CH_2Cl_2/CH_3CN (2:1)	–20	12 h	60%	5:1
17	NIS	CH_3CN	–20	5 h	no rxn	n.a.
18	NIS	CH_3CN	0	14 h	90 to 93%	5:1

[a] Isolated yield. [b] Diastereomeric ratio determined by ^1H NMR of crude mixture.

Acyclic carbonate **2.75** was screened under a variety of reaction conditions (**Table 2**) to provide the cyclic iodo carbonate **2.60**. Iodine monobromide was the first I^+ source examined.[73] Using dichloromethane as solvent, the reaction temperature was

varied from –78 °C to 0 °C. In entries 1 and 3 (–78 °C and 0 °C, respectively) the desired product was detected on TLC before quenching, but was not observed prior to aqueous work-up. Entry 2 however, provided the desired product in 20% yield with a diastereoselectivity of 6:1. Toluene was used as the solvent for entries 4–7 while the temperature was varied leading to low, or in the case of entry 6, irreproducible yields. Entry 10 employed a cosolvent system consisting of a 1:1 mixture of acetonitrile and toluene while maintaining a temperature of –20 °C, also giving irreproducible results. The conclusion reached was that the quenching process was too slow to effectively destroy the reactive iodine monobromide, leading to decomposition of the product. It is worth noting that in all cases where more than one equivalent of IBr was used, only trace amounts or no product was obtained.

The electrophile source was exchanged for I_2, a less reactive I^+ donor in the hopes of avoiding the issues that reduced the yields in entries 1–10.[74] Entries 11–14 provided either complete decomposition of starting material, no reaction or low yields. Entries 15 and 16 employed a cosolvent system of dichloromethane and acetonitrile (2:1) that provided the desired compound in 60 to 63% yield, with moderate diastereoselectivity.

The final electrophile source screened was *N*-iodosuccinimide. This reagent (entries 17 and 18) provided milder reaction conditions as well as a dramatic improvement in the overall yield (>90%) while maintaining a 5:1 diastereoselectivity.[75]

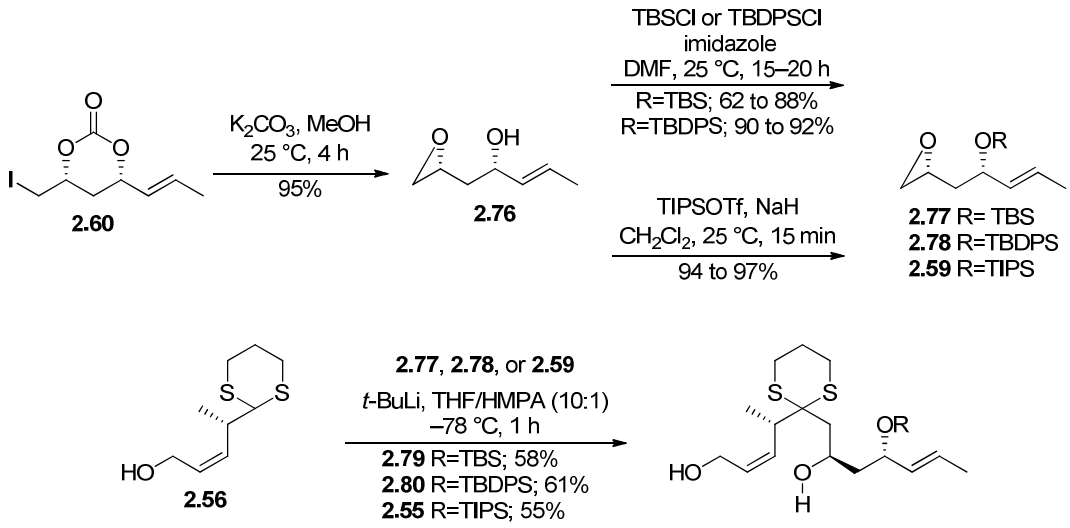


Figure 17: Epoxide fragment synthesis and coupling reactions.

Cyclic iodo carbonate **2.60** was hydrolyzed by methoxide in the presence of potassium carbonate to form the allylic alcohol epoxide **2.76** in good yield (**Figure 17**). **2.76** in turn was protected with TBS, TBDPS, or TIPS according to standard silylation protocol. Deprotonation of the dithiane fragment with *t*-BuLi followed by nucleophilic opening of the epoxide fragment provided the acyclic substrates **2.79**, **2.80** and **2.55** for the tandem allylic oxidation/oxa-Michael reaction in moderate yields.[76]

2.5.4 The tandem allylic oxidation/oxa-Michael reaction

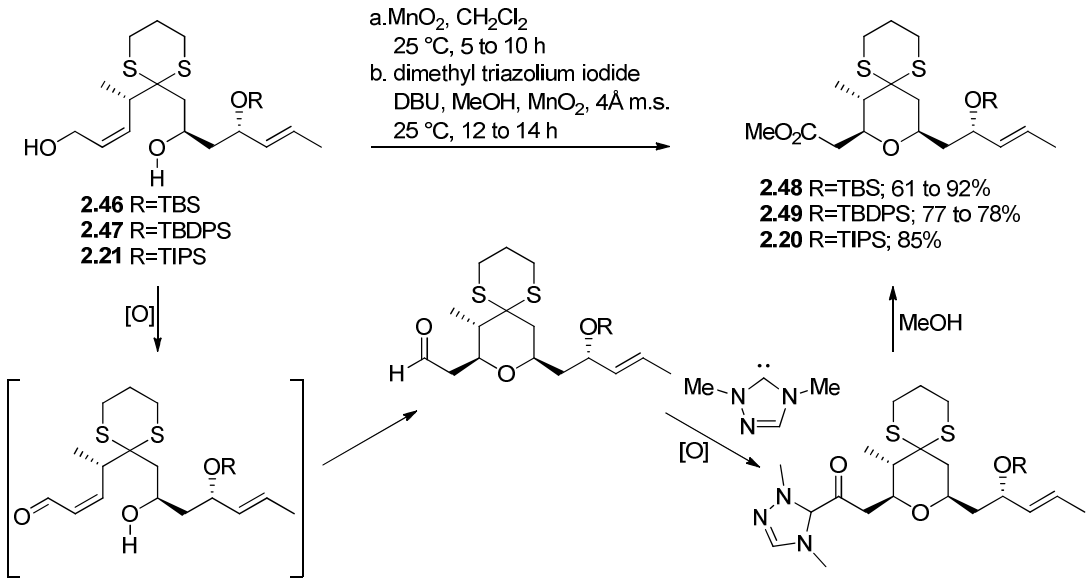


Figure 18: One-pot allylic oxidation/oxa-Michael reaction and oxidation to methyl ester.

The key transformation in the synthesis of clavosolide A was the one-pot, allylic oxidation/oxa-Michael reaction and NHC catalyzed oxidation of the aldehyde to the methyl ester (**Figure 18**).[28, 47] The acyclic allylic alcohol was selectively oxidized to the α,β-unsaturated aldehyde by successive additions of MnO_2, followed by intramolecular conjugate addition by the secondary hydroxyl group, forming the 2,3-*trans*-2,6-*cis*-tetrahydropyran aldehyde. This intermediate was not isolated, but rather subjected to NHC catalyzed oxidation of the aldehyde to the methyl ester in the same pot. This substrate controlled stereoselective process provided **2.48**, **2.49** and **2.20** as single diastereomers (>20:1) in good yield.

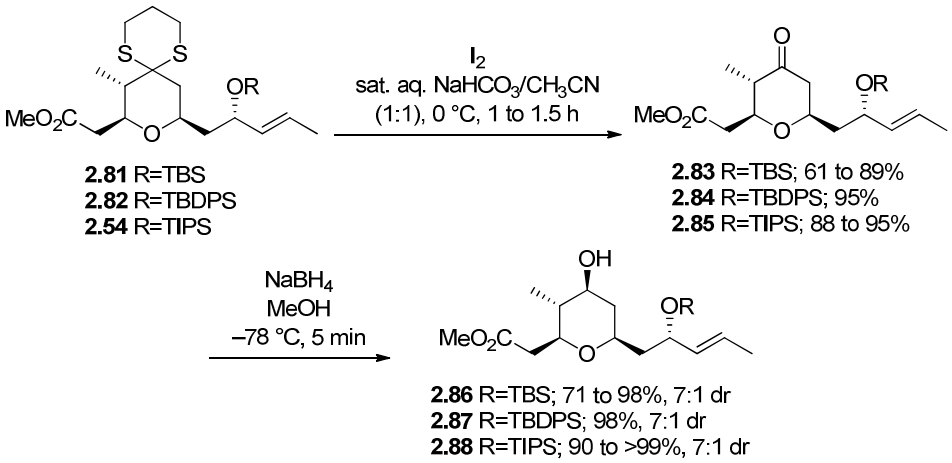


Figure 19: Dithiane cleavage and stereoselective ketone reduction.

Iodine mediated cleavage of the dithiane group proceeded in moderate to good yield for each silyl protected tetrahydropyran as shown in **Figure 19**. Sodium borohydride reduction was conducted at –78 °C in methanol to give excellent yields with 7:1 diastereoselectivity favoring the β-alcohol for each intermediate.[55]

2.5.5 Glycosylation and cyclopropanation

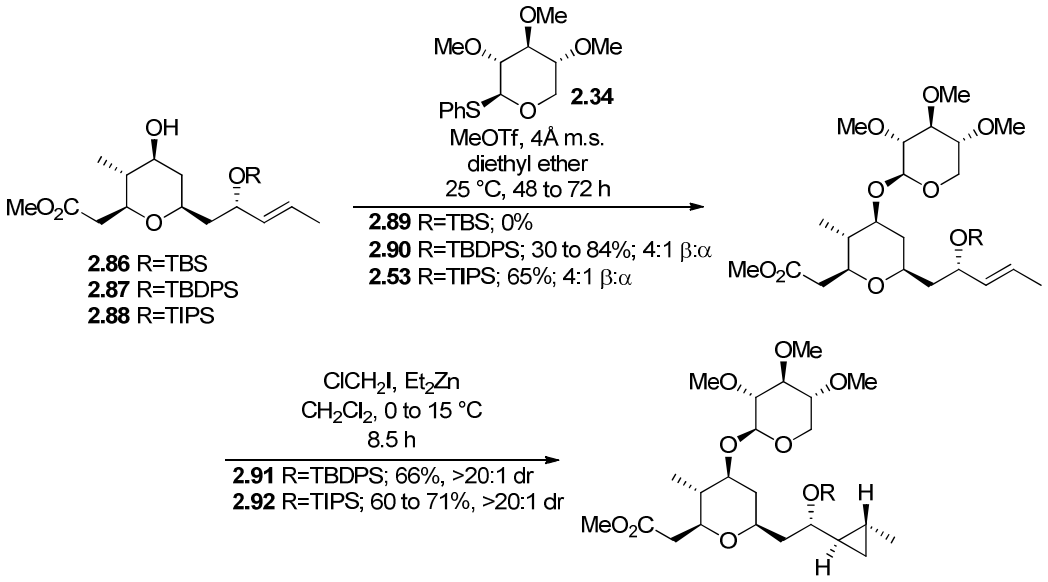


Figure 20: Schmidt glycosylation and Simmons–Smith cyclopropanation.

In **Figure 20**, TBS protected β-alcohol **2.53** was subjected to Schmidt glycosylation with MeOTf and thioglycoside **2.34**. Unfortunately, these conditions were too harsh to maintain the integrity of the TBS group leading to a complex mixture of bis-glycosylated compounds. In order to circumvent this acid promoted hydrolysis issue, the TBDPS protected allylic alcohol **2.87** was synthesized and then subjected to the same glycosylation conditions. The reaction proceeded in 30 to 84% yield with a 4:1 β:α ratio. The TIPS protected allylic alcohol **2.88** was also subjected to glycosylation and proceeded in 65% yield with a diastereoselectivity of 3.8:1 favoring the β-glycoside.[54]

The next step in the synthesis of clavosolide A was the installation of the cyclopropane functionality. This was accomplished by using Simmons–Smith cyclopropanation. Glycoside **2.90** was added to a mixture of diethyl zinc and

chloroiodomethane at 0 °C and slowly warmed to 15 °C over 8.5 hours to provide the cyclopropane **2.91** in 60% as a single diastereomer. Likewise, TIPS protected allylic alcohol **2.53** was subjected to the same reaction conditions and provided **2.92** in 60 to 71% yield as a single diastereomer. Previous syntheses used chelation controlled Simmons–Smith cyclopropanation.[55, 57-58] The drawback to using the stereoselective Simmons–Smith cyclopropanation approach is that after cyclopropanation the secondary hydroxyl group has to be converted to the opposite configuration through the Mitsunobu reaction. Like the Willis group, the stereoselectivity of our approach was due to the steric encumbrance imparted by the silyl group to the olefin, leaving the opposite face as the only option for cyclopropanation to occur.[54]

2.5.6 Completion of the total synthesis of (–)-clavosolide A

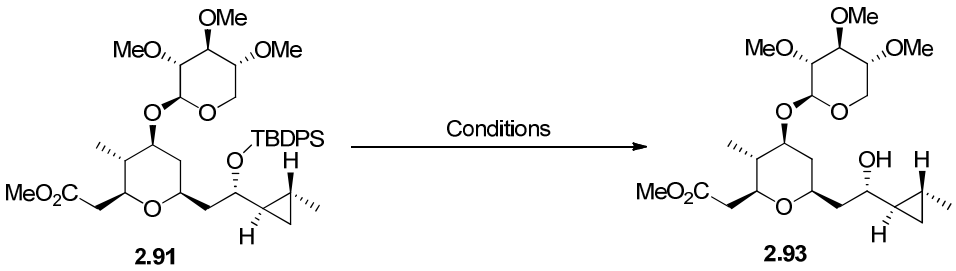


Table 3: TBDPS deprotection attempts

Reaction conditions	Reaction outcome
TBAF, THF, 25–50 °C, 12 h	no reaction
HF·pyridine, THF, 25–40 °C, 12 h	no reaction
TASF, DMF, 75 °C, 24 h	no reaction
CsF, THF or DMF, 25 °C, 1–1.5 h	decomposition

The next step after cyclopropanation was deprotection of the silyl ether. Attempts to cleave the TBDPS group of **2.91** were unsuccessful by a variety of fluoride sources (**Table 3**). Standard desilylation conditions of TBAF and the milder HF·pyridine in THF resulted in no reaction.[78] TSAF was then used as the fluoride source under high temperature for 24 hours, but was also unsuccessful at cleaving the TBDPS group. The final fluoride source tested was CsF, which resulted in complete decomposition of **2.91**. The inability to remove the TBDPS group led to the synthesis of the TIPS containing compound, which is more stable to acid hydrolysis in the glycosylation step, but less hindered. The rational was that a less sterically hindered silyl group would be able to be cleaved under standard conditions.

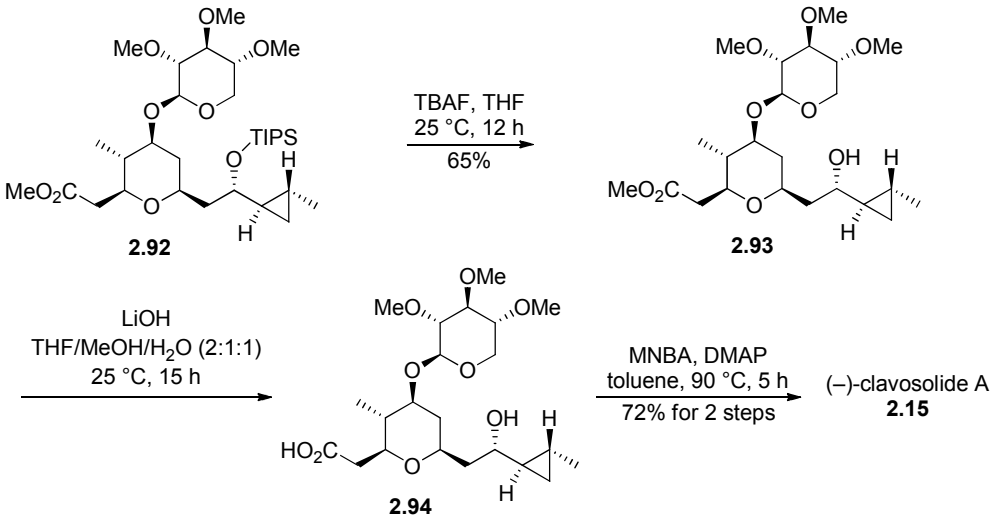


Figure 21: Completion of (–)-clavosolide A.

Figure 21 shows the preparation for the final dimerization step. **2.92** was desilylated in the presence of TBAF over 12 hours to provide **2.93** in 65%. The methyl ester **2.93** was then hydrolyzed under standard condition of LiOH to provide the clavosolide A monomer **2.94**.[77]

The final step in this synthesis of (–)-clavosolide A was dimerization. All previous syntheses of clavosolide A have employed a one-pot, two step or two step Yamaguchi macrolactonization process. Our synthesis of (–)-clavosolide A from **2.94** relied upon Shiina lactonization with MNBA.[77, 79-80] A large excess of DMAP and slight excess of MNBA was added to toluene and heated to 90 °C. Monomer **2.94** was added slowly over 5 hours via syringe pump. MNBA and **2.94** form the first mixed anhydride to which DMAP attacked to form a second anhydride between **2.94** and DMAP. Once the second anhydride formed, lactonization occurred rapidly at high

temperature and in a dilute solution. (–)-Clavosolide A was provided in 72% for 2 steps, completing the synthesis.

The advantages of this synthesis over previous syntheses are as follows. It is the most efficient synthesis to date, being completed in 13 linear steps while the most efficient synthesis completed previously was 17 linear steps (Smith group). The one-pot allylic oxidation/oxa-Michael reaction formed the 2,6-*cis*-tetrahydropyran as a single compound in good yield. Dithiane coupling allowed for rapid access to a late stage intermediate, which also provides rapid access to analogues.

2.6 Future work

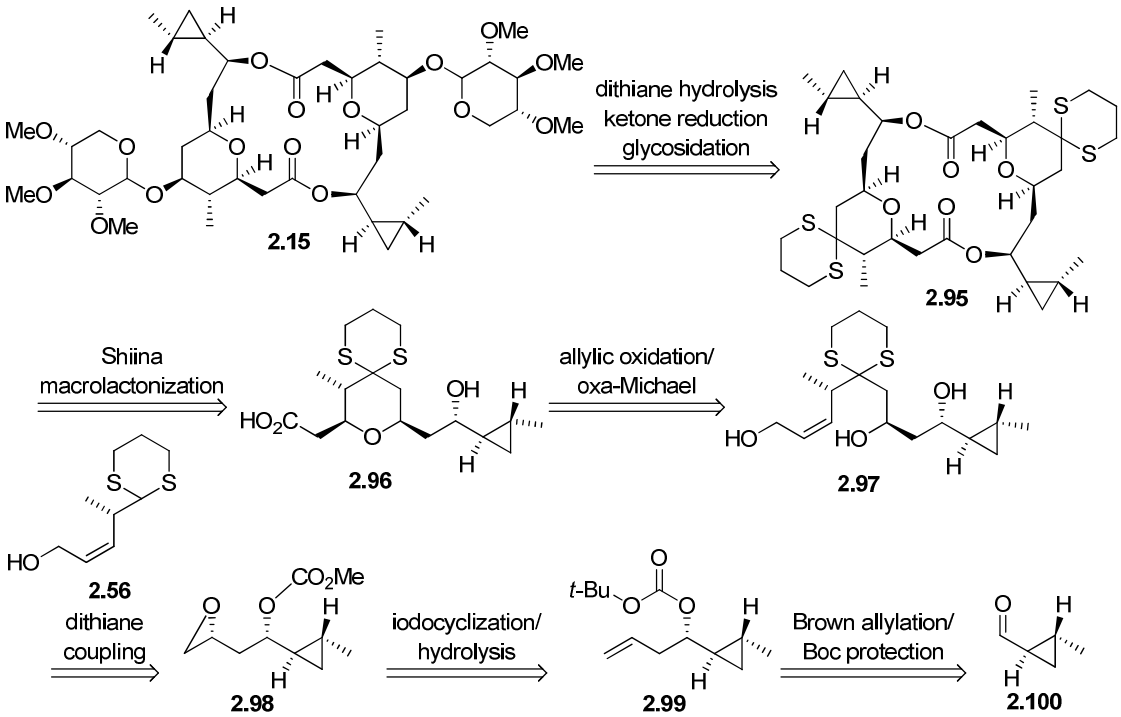


Figure 22: Second generation retrosynthesis for (–)-clavosolide A.

In an effort to improve the synthesis of (–)-clavosolide A, we have devised a plan that could potentially lead to a more efficient pathway for construction. **Figure 22** outlines the plan for our second-generation synthesis. The first disconnect is at the glycosidic linkages, coming from the clavosolide A aglycon. The aglycon could be produced from hydrolysis of the bis-dithiane **2.95** followed by ketone reduction. Carboxylic acid **2.96** would be dimerized by Shiina protocol used in the first-generation synthesis. Tandem allylic oxidation/oxa-Michael reaction is expected to yield similar diastereoselectivity in the 2,6-*cis*-tetrahydropyran **2.96** as in our first-generation synthesis. Coupling of dithiane **2.56** with the cyclopropanated epoxide **2.98** is expected

to furnish the substrate **2.97**. Iodocyclization and carbonate hydrolysis could achieve the epoxide coupling fragment. And finally, asymmetric Brown allylation of the known aldehyde **2.100** and Boc protection could complete the plan.[81]

There are some foreseeable problematic steps in this plan. First, the volatility of the known aldehyde **2.100** has already been established.[81] Our intention is to develop a dry system by which we can distill the aldehyde **2.100** product directly into a flask containing the Brown allylation reagent. The second predictable issue is in the coupling step. Deprotonation of the allylic alcohol occurs before dithiane deprotonation, and it is likely that the allylic alkoxide will attack the acyclic methyl ester portion of the epoxide **2.98**. This may or may not interfere with the dithiane attack of the epoxide. The final problem is to find a method by which to improve the efficiency of the bis-glycosidation of the aglycon dimer. The highest percent yield observed for this reaction to date is 18% by Willis and co-workers.[54]

If these problems could be solved, then this plan would provide an even more efficient route to the construction of clavosolide A. It would also make limited use of protecting groups, depending on what defines a protecting group. Each traditionally defined protecting group described in the plan would serve a purpose besides protection. For example: the dithiane group serves as a carbon nucleophile in the coupling step, while accelerating the rate of reaction and enhancing the stereoselectivity of the oxa-Michael reaction. The Boc protecting group provides the epoxide oxygen and

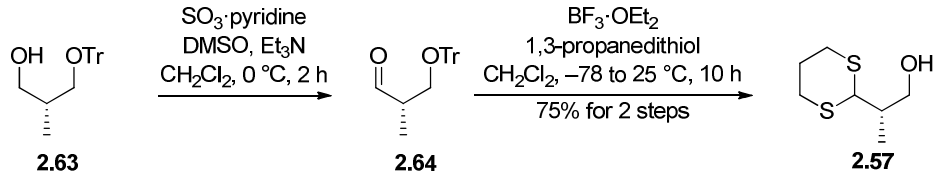
the methyl carbonate eliminates the production of an alkoxide that would decrease the yield in the coupling step through charge repulsion. Given these factors, a protecting group free synthesis of clavosolide would indeed be elegant.

Clavosolide A has been shown to be biologically inactive against the NCI's 60 cancer cell line. It is curious that a molecule that is highly functionalized like clavosolide A would be inactive in all biological systems. In future, it may prove to have some useful biological activity.

2.7 Conclusion

The total synthesis of the marine natural product (–)-clavosolide A has attracted considerable interest from the synthetic community due to its unique structural features: 2,3-*trans*-2,6-*cis*-tetrahydropypran, cyclopropane and xylose moieties. The completion of our synthesis included iodocyclization chirality transfer, dithiane opening of the epoxide, stereoselective tandem allylic oxidation/oxa-Michael reaction to form the tetrahydropyran, and a one step Shiina mediated macrolactonization reaction. This synthesis is the shortest to date in 13 linear steps from the known enantiopure allylic alcohol **2.61**.

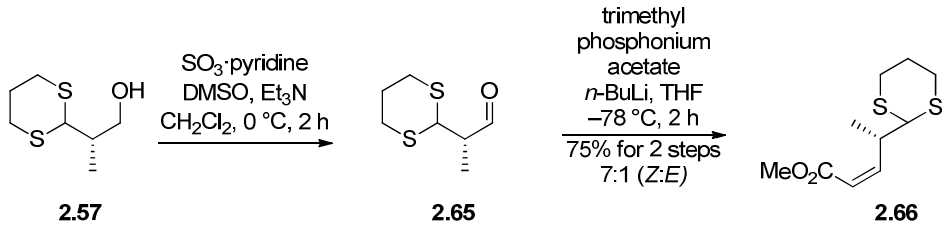
2.8 Experimental



2.63 **2.64** **2.57**

[Oxidation] To a cooled solution (0 °C) of tritylated primary alcohol **2.63** (2.75 g, 8.30 mmol) in CH_2Cl_2 (60 ml, 0.14 M) was added DMSO (3.54 ml, 49.8 mmol), Et_3N (3.47 ml, 24.9 mmol), and SO_3·pyridine (3.96 g, 24.9 mmol) and stirred at same temperature for 2 hours. To the mixture was then added saturated aqueous $NaHCO_3$ (60 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (60 ml, x2). The combined layers were dried over Na_2SO_4 and then concentrated *in vacuo*. The crude aldehyde was then triturated with diethyl ether and the residual solvents removed *in vacuo*. TLC: R_f = 0.69, hexanes/EtOAc, 5/1. The crude aldehyde was then subjected to the next step without further purification. **[Dithiane protection/trityl deprotection]** The crude aldehyde was dissolved in anhydrous CH_2Cl_2 (23 ml, 0.36 M) and cooled to –78 °C. To this solution was added 1,3-propanedithiol (0.916 ml, 9.13 mmol) dropwise and then stirred for 10 minutes. BF_3·OEt_2 (2.08 ml, 16.6 mmol) was then added dropwise and the solution was stirred for 30 minutes then allowed to slowly warm to 25 °C for 12 hours. The mixture was then cooled to 0 °C and quenched with saturated aqueous $NaHCO_3$. The layers were then separated and the aqueous layer was then extracted with CH_2Cl_2 (30 ml, x2). The combined layers were then dried over Na_2SO_4 and concentrated

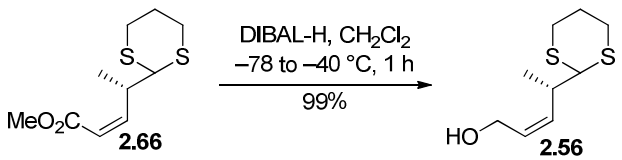
in vacuo. The crude dithiane was purified by column chromatography (silica gel, Hexanes/EtOAc, 3/1) to afford the above dithiane (1.12 g, 6.23 mmol) in 75% for two steps as a pale yellow oil. $[\alpha]^{25}_{D}$ = +23.4; TLC: R_f = 0.31, Hexanes/EtOAc 3/1. ^{1}H NMR (400 MHz; $CDCl_3$) δ 4.27(d, J = 5.2 Hz, 1H), 3.65 (dddd, J = 18, 11.2, 6.8, 6.8 Hz, 2H), 2.94-2.80 (m, 4H), 2.13-2.01(m, 3H), 1.88-1.77 (m, 1H), 1.07 (d, J = 7.2, 3H).



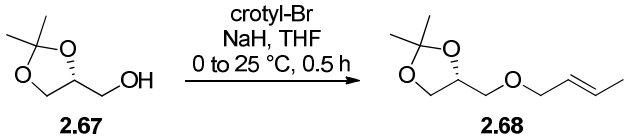
[Oxidation] To a cooled (0 °C) solution of primary alcohol **2.57** (1.55 g, 8.71 mmol) in CH_2Cl_2 (118 ml, 0.074 M) was added DMSO (3.71 ml, 52.26 mmol), Et_3N (3.64 ml, 26.1mmol), and SO_3·pyridine (4.20 g, 26.1 mmol) and stirred at the same temperature for 1.5 hours. Saturated aqueous $NaHCO_3$ was added to the mixture then the layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (x2) and the combined layers were dried over $Na_2S_2O_4$ then concentrated *in vacuo*. The crude aldehyde was then triturated with diethyl ether and concentrated *in vacuo*. The crude aldehyde was then used in the next step without further purification. TLC: R_f = 0.28, hexanes/EtOAc, 3/1.

[Horner–Emmons Reaction] To a cooled (–78 °C) solution of THF (350 ml) and trimethylphosphonoacetate (3.75 ml, 26.13 mmol) was added *n*-BuLi (10.45 ml, 2N in

hexanes, 26.13 mmol) dropwise and then stirred at the same temperature for 20 minutes. The crude aldehyde **2.65** in THF (10 ml) was then added dropwise and stirred for 45 minutes further. Saturated aqueous NH_4Cl was then carefully added then diluted with EtOAc. The layers were then separated and the aqueous layer was then extracted with EtOAc (x2). The combined organic layers were then washed with brine, dried over Na_2SO_4, then concentrated *in vacuo*. The crude mixture was purified by column chromatography (silica gel, Hexanes/EtOAc, 6/1) to afford the α,β-unsaturated methyl ester **2.66** (1.52 g, 6.53 mmol) in 75% as a 5/1 mixture of *Z*/*E* diastereomers. For *Z*-isomer $[a]^{25}_D$ = +36.95 (c 1.00, $CHCl_3$) TLC: R_f = 0.55, hexanes to EtOAc, 6/1. ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.22 (dd, J = 9.6, 9.6 Hz, 1H), 5.80 (d, J = 11.6, 1H), 4.01 (b, 1H), 3.70 (s, 3H), 2.9–2.77 (m, 4H), 2.11–1.78 (m, 2H), 1.21 (d, J = 6.4Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.3, 151.0, 119.5, 52.90, 51.10, 37.05, 29.91, 29.85, 25.82, 17.83. IR (neat) 2953, 1717, 1643, 1437, 1211, 1177 cm^{-1}. For *E*-isomer $[a]^{25}_D$ = –26.19 (c 1.00, $CHCl_3$) TLC: R_f = 0.39, hexanes/EtOAc, 6/1. ^{1}H NMR (400 MHz; $CDCl_3$) δ 6.94 (dd, J = 16.8, 8.4, 1H), 5.86 (d, J = 16 Hz, 1H), 4.09 (d, J = 6 Hz, 1H), 3.71 (s, 3H), 2.92–2.78 (m, 5H), 2.20–2.06 (m, 1H), 1.88–1.76 (m, 1H), 1.24 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.5, 149.6, 121.6, 52.88, 51.51, 41.46, 30.59, 30.50, 25.72, 17.01. IR (neat) 3021, 1718, 1657, 1435, 1275, 1215 cm^{-1}.

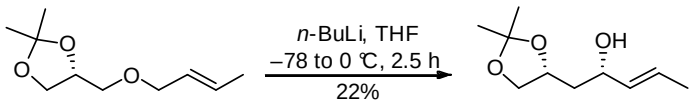


[1,2 reduction] To a cooled (–78 °C) solution of *Z*-α,β-unsaturated methyl ester **2.66** (788 mg, 3.39 mmol) in CH_2Cl_2 (57 ml, 0.06 M) was added diisobutylaluminum hydride (6.78 ml, 1 M in toluene, 6.78 mmol) dropwise and the solution was allowed to warm to -40 °C over 30 minutes and then stirred at –40 °C for an additional 30 minutes. The mixture was then cooled to –78 °C and carefully quenched with saturated aqueous NH_4Cl then diluted with saturated aqueous Rochelle's salt and stirred at ambient temperature for 6 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x3).The combined layers were then dried over Na_2SO_4 then concentrated *in vacuo*. The crude mixture was then purified by column chromatography (silica gel, hexanes/EtOAc, 2/1 to afford the allylic alcohol **2.56** (457 mg, 2.23 mmol) in 99%. $[a]^{25}_D$ = –22.4 (c 0.97, $CHCl_3$); TLC: R_f = 0.22, hexanes/EtOAc, 2:1. ^{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}.



2.67 **2.68**

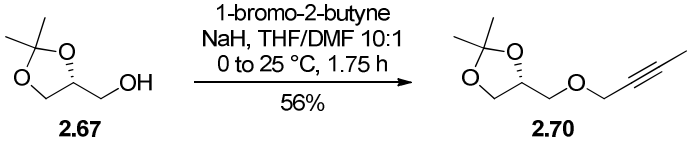
[*O*-alkylation] To a cooled (0 °C) solution of dioxolane **2.67** (500 mg, 3.78 mmol) in THF (100 ml, 0.038 M) was added NaH (757 mg, 19 mmol), then warmed to 25 °C and stirred for 30 minutes. Then crotylbromide (1.16 ml, 11.34 mmol) was added dropwise then stirred at that temperature for 1 hour. The reaction mixture was then cooled to 0 °C and quenched with the addition of saturated aqueous NH_4Cl then diluted with diethyl ether. The layers were separated and then the aqueous layer was extracted with diethyl ether (x3). The combined layers were then washed with brine, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 20/1) to afford a 2.5/1 *E*/*Z* mixture of the dioxolane ether **2.68** in 71% as a clear oil. TLC: R_f = 0.23, hexanes/EtOAc, 40:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 21.6, 12.8, 6.4 Hz, 1 H), 5.61–5.50 (m, 1 H), 4.27 (dd, *J* = 11.6, 5.6 Hz, 1 H), 4.10 (d, *J* = 7.6 Hz, 1 H), 4.06 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.95 (dddd, *J* = 8.8, 2.4, 2.4, 1.2 Hz, 1 H), 3.72 (dd, *J* = 8.0, 6.4 Hz, 1 H), 3.50 (dd, *J* = 9.6, 5.6 Hz, 1 H), 3.41 (dd, *J* = 10.0, 5.6 Hz, 1 H), 1.71 (dd, *J* = 6.4, 1.2 Hz, 3 H), 1.42 (s, 3 H), 1.36 (s, 3 H).



2.68 **2.69**

[1,2-Wittig rearrangement] To a cooled (–78 °C) solution of the dioxolane ether **2.68** (144 mg, 0.77 mmol) in THF (20 ml, 0.039 M) under nitrogen atmosphere was added *n*-BuLi (0.50 ml, 1.24 mmol, 2.5 M in hexanes) dropwise over 30 minutes. The solution was then

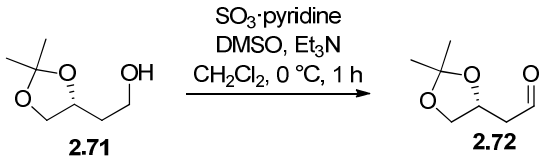
allowed to slowly warm to 0 °C over 2 hours. The mixture was then cooled to –78 °C and quenched with saturated aqueous NH_4Cl then diluted with EtOAc. The layers were separated and the aqueous layer was then extracted with EtOAc (x2). The combined layers were washed with brine and then dried over Na_2SO_4. The solvents were removed under reduced pressure. The crude residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to give the allylic alcohol **2.69** as a single diastereomer in 22% as a clear oil. TLC: R_f = 0.25, hexanes/ EtOAc, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddd, *J* = 13.2, 13.2, 6.4 Hz, 1 H), 5.51 (ddd, *J* = 14.8, 14.8, 6.8 Hz, 1 H), 4.34–4.20 (m, 2 H), 4.08 (dd, *J* = 8.0, 6.0 Hz, 1 H), 3.58 (dd, *J* = 7.6, 7.6 Hz, 1 H), 2.75 (s, 1 H), 1.81–1.72 (m, 1 H), 1.70 (d, 6.4 Hz, 3 H), 1.61 (s, 1 H), 1.42 (s, 3 H), 1.36 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 133.2, 126.9, 109.3, 75.11, 71.70, 69.69, 53.40, 40.81, 40.21, 26.88, 25.77, 17.63.



2.67 **2.70**

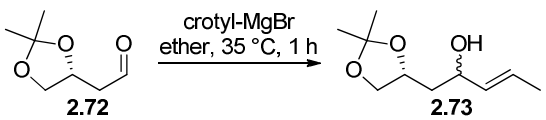
[O-alkylation] To a cooled (0 °C) solution of the dioxolane **2.67** (500 mg, 3.78 mmol) in THF/DMF (10:1, 11 ml total, 0.34 M) was added NaH (750 mg, 18.9 mmol) and the solution was warmed to 25 °C for 45 minutes. Then added 1-bromo-2-butyne (606 mg, 4.54 mmol) dropwise then stirred for an additional 1 hour. The mixture was then cooled to –10 °C and carefully quenched with the addition of saturated aqueous NH_4Cl then

diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (x2). The organic layers were washed with brine, then dried over Na_2SO_4. The solvents were removed *in vacuo* to provide a crude oil. The crude product was separated by column chromatography (silica gel, hexanes/EtOAc, 40/1) to give the propargyl ether **2.70** (388 mg, 2.12 mmol) in 56% as a clear oil**.** TLC: R_f = 0.35, hexanes/ EtOAc, 45:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (ddd, *J* = 18.0, 12.0, 6.0 Hz, 1 H), 4.15 (dd, *J* = 2.8, 2.8 Hz, 2 H), 4.07 (dd, *J* = 8.4, 8.4 Hz, 1 H), 3.74 (dd, *J* = 8.4, 6.4 Hz, 1 H), 3.58 (ddd, 18.8, 16.0, 6.0 Hz, 2 H), 1.84 (dd, *J* = 2.0, 2.0 Hz, 3 H), 1.41 (s, 3 H), 1.34 (s, 3 H).



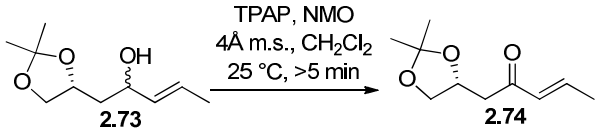
2.71 **2.72**

[Oxidation] To a cooled (0 °C) solution of primary alcohol **2.71** (125 mg, 0.85 mmol) was added DMSO (362 ml, 5.10 mmol), Et_3N (355 ml, 2.55 mmol), and SO_3·pyridine (406 mg, 2.55 mmol) in that order and stirred for 1 hour at the same temperature. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was then extracted with CH_2Cl_2 (x2). The combined layers were then dried over Na_2SO_4.



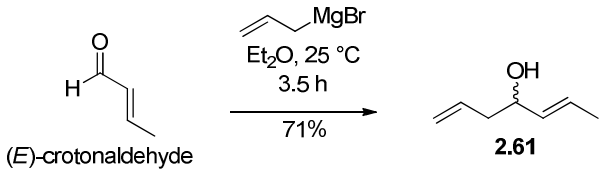
2.72 **2.73**

[Grignard Rxn] To a dry solution of diethylether (4 ml, 0.08M) was added Mg^0 (81 mg, 3.33 mmol) then was heated to reflux (35 °C) for 2h. The solution was cooled to 25 °C and then was added dropwise via syringe to a stirring solution of the crude aldehyde (0.33 mmol) in diethylether (0.5 ml, 0.66 M). The mixture was stirred for an additional 1 hour and then cooled to 0 °C and carefully quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous layer was extracted once with EtOAc. The combined layers were then washed with brine, dried over Na_2SO_4, then concentrated *in vacuo*. The residue was then purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to give a 1:1 mixture of diastereomers in 73% yield.

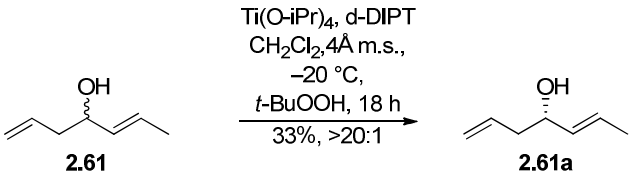


[Allylic oxidation] To a stirred solution of allylic alcohols **2.73** (7 mg, 0.037 mmol) in CH_2Cl_2 (1 ml 0.037 M) was added powdered 4Å molecular sieves (15 mg, ~150%wt), NMO (17 mg, 0.148), and TPAP (1.3 mg, 10mol%) then stirred for approximately 5 minutes then filtered through a small plug of silica gel. The crude mixture was then concentrated *in vacuo* and then purified by column chromatography (silica gel, hexanes/EtOAc, 1/1) to give the *E*-α,β-unsaturated ketone **2.74** in 6.80 mg, 0.037 mmol) in 99% as a clear oil. TLC: R_f = 0.61, hexanes/ EtOAc, 3:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (ddd, *J* = 22.8, 13.6, 6.8 Hz, 1 H), 6.14 (dd, *J* = 30.0, 1.6 Hz, 1 H), 4.54 (ddd, *J* = 12.4,

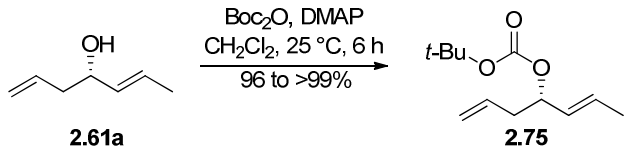
6.0, 6.0 Hz, 1 H), 4.23 (dd, *J* = 8.4, 6.0 Hz, 1 H), 3.58 (dd, *J* = 8.0, 6.4 Hz, 1 H), 3.11 (dd, *J* = 16.8, 5.6 Hz, 1 H), 2.72 (dd, *J* = 16.4, 7.6 Hz, 1 H), 1.93 (d, *J* = 7.2 Hz, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H).



[Grignard addition] To a stirred solution of Mg^0 (3.6 g, 13.9 mmol) in diethyl ether (300 ml, 0.03 M) was slowly added allyl bromide (10.0 ml, 9.92 mmol) then stirred at ambient temperature for 2 hours. (*E*)-crotonaldehyde (8.27 ml, 100 mmol) was added dropwise over 30 minutes then the mixture stirred for 1 hour further. The reaction was cooled to 0 °C then quenched with addition of H_2O (50 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (50 ml, x2) then the pooled organic layers were washed with saturated brine solution then dried over Na_2SO_4. The crude mixture was then concentrated *in vacuo* and then purified by column chromatography (silica gel, pentane/diethyl ether, 5/1) to give allylic alcohol **2.61** (7.95 g, 70.9 mmol) in 71% as a clear oil. TLC: R_f = 0.35, hexanes/ EtOAc, 3:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 17.5, 10.0, 7.5, 7.5 Hz, 1 H), 5.68 (dd, *J* = 16.5, 7.5 Hz, 1 H), 5.49 (ddd, J = 15.5, 7.0, 1.5 Hz, 1 H), 5.15–5.08 (m, 2 H), 4.10 (d, *J* = 6.5 Hz, 1 H), 2.40–2.21 (m, 2 H), 1.76 (d, *J* = 3.0 Hz, 1 H), 1.69 (d, *J* = 6.5 Hz, 3 H).

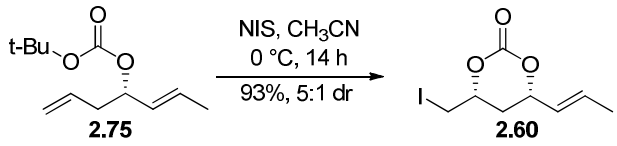


[Sharpless asymmetric epoxidation] To a cooled (–20 °C) solution of allylic alcohol **2.61** (516 mg, 4.60 mmol) and 4Å molecular sieves (516 mg, 100%wt) in CH_2Cl_2 (38.3 ml, 0.12 M) was added d-diisopropyl tartrate (135 μl, 0.644 mmol) and titanium (IV) isopropoxide (135 μl, 0.46 mmol) and stirred for 20 minutes. Then *tert*-butylhydroperoxide (498 μl, 2.99 mmol, 5.5 M in decane) was added dropwise then the mixture was stirred at the same temperature for 6 hours. The reaction mixture was then placed into a –20 °C freezer for an additional 12 hours. Saturated aqueous Na_2SO_4 (50 ml) and stirred at ambient temperature for 5 hours then filtered through a small pad of Celite®. The solvents were removed *in vacuo* and then purified by column chromatography (silica gel, pentane/diethyl ether, 5/1) to give allylic alcohol **2.61a** (170 mg, 1.52 mmol) in 33% as a clear oil.



[Boc-protection] To a stirred solution of allylic alcohol **2.61a** (1 g, 8.92 mmol) in CH_2Cl_2 (100 ml, 0.09 M) at 25 °C was added di-*tert*-butyl dicarbonate (1.95 g, 8.92 mmol) in CH_2Cl_2 (5 ml), then DMAP (500 mg, 50mol%) and was stirred for 12 hours at the same

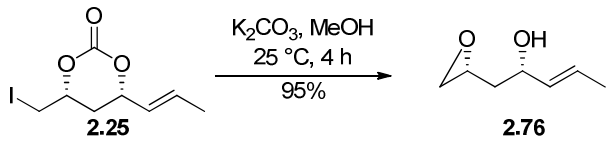
temperature. When all of the starting material was consumed the reaction was quenched with saturated aqueous $NaHCO_3$ and stirred vigorously for 30 minutes. The layers were separated then the aqueous layer was extracted with CH_2Cl_2 (x3). The pooled organic layers were then washed with brine and dried over Na_2SO_4. The crude material was then purified by column chromatography (silica gel, hexanes/EtOAc, 40:1) to provide acyclic carbonate **2.75** (1.887 g, 8.89 mmol) in 99% yield as a clear oil. TLC: R_f = 0.75, hexanes/ EtOAc, 9:1. $[a]^{25}_D$ = –76.3 (c 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.66 (m, 2 H), 5.45 (dd, *J* = 15.5, 6.0 Hz, 1 H), 5.09 (dd, *J* = 16.5, 16.5 Hz, 2 H), 5.00, (dd, *J* = 10.0, 5.0 Hz, 1 H), 2.44 (ddd, *J* = 16.5, 11.0, 2.0 Hz, 1 H), 2.36 (ddd, *J* = 15.5, 10.0, 4.0 Hz, 1 H), 1.68 (d, *J* = 5.6 Hz, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 133.3, 129.8, 128.8, 117.8, 81.8, 77.1, 39.1, 27.8, 17.7; IR (neat) 3727, 3628, 2983, 2360, 2340, 1739, 1276, 1162, 967, 770, 669 cm $^{-1}$.



2.75 **2.60**

[Iodocyclization] To a cool (0 °C) solution of **2.75** (167 mg, 0.787 mmol) in acetonitrile (4.4 ml, 0.18 M) was added *N*-iodosuccinimide (885 mg, 3.94 mmol) and stirred for a further 14 hours. The reaction was diluted with saturated aqueous sodium thiosulfate then stirred vigorously for 2 hours then diluted with CH_2Cl_2 (5 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml, x2). The pooled

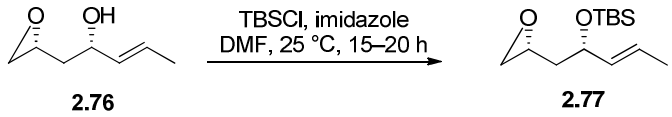
organic layers were then washed with brine, dried over Na_2SO_4. The crude material was then purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to provide *syn*-carbonate **2.60** (206 mg, 0.732 mmol) as a colorless oil. TLC: R_f = 0.30, hexanes/ EtOAc, 3:1. $[\alpha]^{25}_D$ = +13.9 (c 0.95, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 14.1, 8.5 Hz, 1 H), 5.60 (dd, *J* = 14.8, 7.7 Hz, 1 H), 4.63 (dd, *J* = 15.5, 8.5 Hz, 1 H), 4.62 (dd, *J* = 11.9, 5.9 Hz, 1 H), 3.27 (ddd, *J* = 16.6, 11.1, 5.5 Hz, 2 H), 2.54–2.43 (m, 2 H), 1.76 (d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.2, 131.9, 126.9, 78.8, 76.8, 33.6, 17.6, 5.46. For *anti*-carbonate **2.60**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.53 (ddd, *J* = 19.0, 13.5, 8.0 Hz, 1 H), 5.01 (dd, *J* = 9.5, 5.0 Hz, 1 H), 4.54 (ddd, *J* = 16.5, 8.5, 4.5 Hz, 1 H), 4.43 (dd, *J* = 11.0, 5.0 Hz, 1 H), 3.28 (dd, *J* = 10.5, 8.0 Hz, 1 H), 2.27–2.14 (m, 2 H), 1.78 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 131.2, 126.7, 76.3, 74.8, 31.4, 17.7, 4.7.



2.25 **2.76**

[Carbonate hydrolysis] To a stirred solution of cyclic iodo carbonate **2.25** (471 mg, 1.67 mmol) in MeOH (4.2 ml, 0.04 M) at 25 °C was added K_2CO_3 (692 mg, 5.01 mmol) and stirred for 4 hours. Saturated aqueous $NaHCO_3$ (5 ml) was added then diluted with diethyl ether (10 ml) and the layers were separated. The aqueous layer was extracted with diethyl ether (10 ml, x4). The combined layers were dried over Na_2SO_4 and the solvents were removed *in vacuo*. The crude mixture was purified by column

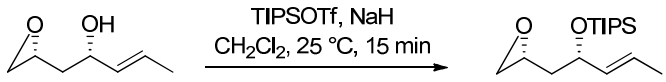
chromatography (silica gel, hexanes/EtOAc, 3:1) to provide epoxide **2.76** (203 mg, 1.59 mmol) as a clear oil in 95%. TLC: R_f = 0.2, hexanes/ EtOAc, 5:1. $[\alpha]^{25}_D$ = +6.01 (c 0.83, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 18.5, 8.5 Hz, 1 H), 5.50 (dd, *J* = 19.0, 9.5 1 Hz, 1 H), 5.22 (dd, *J* = 17.0, 8.5 1 Hz, 1 H) 2.98 (m, 1 H), 2.76 (dd, *J* = 6.5, 6.5 Hz, 1 H), 2.48 (dd, *J* = 6.5, 3.5 Hz, 1 H) 1.88 (dd, *J* = 16.0, 8.0 Hz, 2 H), 1.72 (d, *J* = 8.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.2, 127.4, 71.2, 50.0, 46.7, 39.9, 17.5; IR (neat) 3423, 2998, 2924, 1429, 1256, 971, 838, 757 cm^{-1}.



2.76 **2.77**

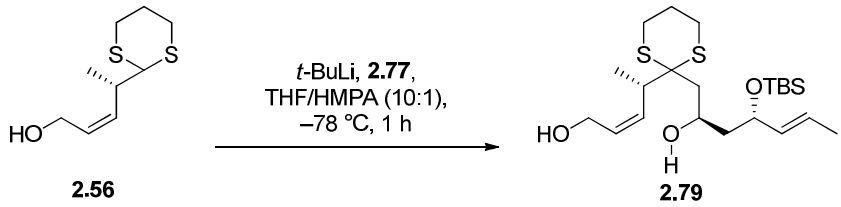
[Silylation] To a 25 °C solution of **2.76** (84 mg, 0.66 mmol) in DMF (8 ml, 0.08 M) was added imidazole (67 mg, 0.99 mmol) and *tert*-butyl dimethylsilyl chloride (497 mg, 3.30 mmol) and stirred for 20 hours before quenching with saturated aqueous $NaHCO_3$ and diluted with EtOAc (20 ml) and H_2O (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (20 ml, x3). The combined organic layers were washed with saturated brine solution then dried over Na_2SO_4 and the solvents were removed *in vacuo*. The crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 8:1) to provide epoxide **2.77** (99 mg, 0.41 mmol) in 62% as a yellow oil. TLC: R_f = 0.65, hexanes/ EtOAc, 8:1. ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, *J* = 20.0, 14.0, 7.2 Hz, 1 H), 5.48 (dd, *J* = 17.6, 10.0 Hz, 1 H), 4.26 (dd, *J* = 12.4, 4.0 Hz, 1 H), 2.89 (m, 1 H),

2.74 (dd, *J* = 4.2, 4.2 Hz, 1 H), 2.47 (dd, *J* = 4.1, 4.1 Hz, 1 H), 1.80–1.72 (m, 2 H), 1.68 (d, *J* = 8.2 Hz, 3 H), 0.82 (s, 9 H), 0.01 (s, 6 H).



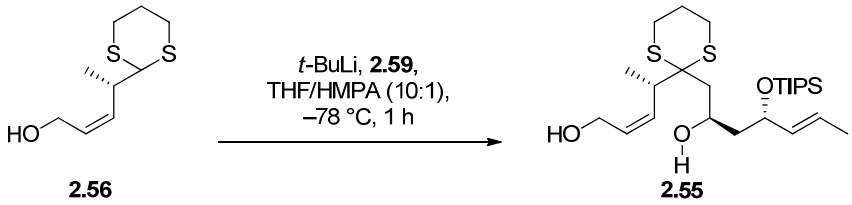
2.76 **2.59**

[TIPS protection] To a cooled (0 °C) solution of **2.76** (273 mg, 2.13 mmol) in THF (41 ml, 0.05 M) was added NaH (426 mg, 10.7 mmol) then stirred for 30 minutes. Then TIPSOTf (575 μl, 2.13 mmol) was added and stirred for 15 minutes. The reaction was quenched with saturated aqueous $NaHCO_3$ (30 ml) then diluted with EtOAc (50 ml). The layers were separated and the aqueous layer was extracted with EtOAc (50 ml, x2). The organic layers were combined and washed with saturated brine solution then dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to provide epoxide **2.59** (570 mg, 2.0 mmol) as a clear oil in 94%. TLC: R_f = 0.2, hexanes/ EtOAc, 5:1. $[\alpha]^{25}_D$ = +25.2 (c 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (dddd, *J* = 21.5, 18.0, 9.5, 9.5 Hz, 1 H), 5.07–4.98 (m, 2 H), 3.48 (dd, *J* = 17.5, 9.0 Hz, 1 H), 3.27 (dd, *J* = 8.5, 8.5 Hz, 1 H), 3.12 (dd, *J* = 16.0, 7.5 Hz, 1 H), 2.31–2.21 (m, 2 H), 1.01 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 18 H), 0.03 (d, *J* = 10.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 126.0, 71.9, 49.3, 47.1, 41.8, 18.1, 18.0, 17.9, 12.3.



2.56 2.79

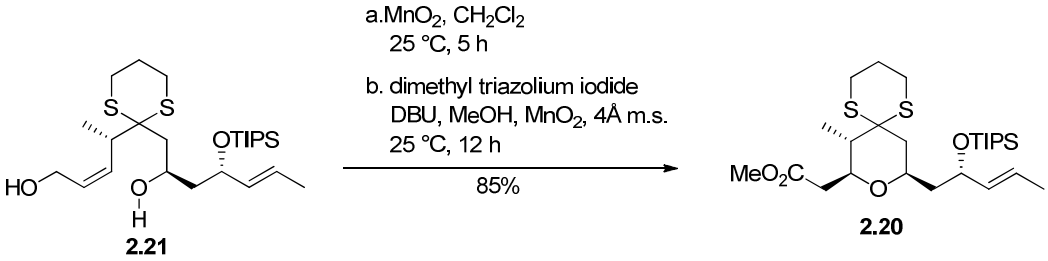
[Dithiane coupling] To a cooled (–78 °C) solution of dithiane **2.56** (28 mg, 0.136 mmol) in THF/HMPA (1.85 ml, 10/1) was added *t*-BuLi (168 μl, 0.286 mmol, 1.7 M in hexanes) and stirred for 5 minutes. The solution turned a bright orange color. Then epoxide **2.77** (30 mg, 0.124 mmol) in THF (0.5 ml) was added dropwise and the solution was stirred at the same temperature for 1 hour. Saturated aqueous NH_4Cl (1 ml) was added then diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (50 ml, x2). The organic layers were combined and washed with saturated brine solution then dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to provide dithiane **2.79** (32 mg, 0.072 mmol) in 58% as a clear oil. TLC: R_f = 0.30, hexanes/ EtOAc, 5:1. ^1H NMR (500 MHz, $CDCl_3$) δ 5.76–5.65 (m, 2 H), 5.61 (dd, *J* = 19.0, 8.0 Hz, 1 H), 5.42 (dd, *J* = 19.5, 9.0 Hz, 1 H), 4.24 (dd, *J* = 17.0, 8.0 Hz, 1 H), 4.13 (dd, *J* = 16.5, 6.0 Hz, 4.07 (dd, *J* = 10.5, 10.5 Hz, 1 H), 3.69 (s, 1 H), 3.25 (ddd, *J*= 20.0, 17.5, 9.0 Hz, 1 H), 2.99 (ddd, *J* = 17.5, 13.0, 4.5 Hz, 1 H), 2.89–2.70 (m, 4 H), 2.24 (dd, *J* = 19.5, 10.5 Hz, 1 H), 2.05 (d, *J* = 19.0 Hz, 1 H), 2.02–1.73 (m, 4 H), 1.69 (d, *J* = 8.0 Hz, 3 H), 1.50 (dd, *J* = 17.5, 8.0 Hz, 1 H), 1.21 (d, *J*= 8.5 Hz, 3 H), 0.88 (s, 9H), 0.07 (d, *J* = 19.5 Hz, 6 H).



2.56 **2.55**

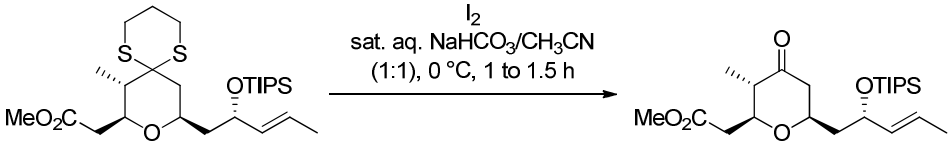
[Dithiane coupling] To a cooled (–78 °C) solution of **2.56** (43 mg, 0.21 mmol) in THF/HMPA (5 ml, 10:1, 0.04 M) was added *t*-BuLi (0.50 ml, 0.84 mmol, 1.7M in pentane) and the dark orange solution was stirred for 5 minutes. Epoxide **2.59** (50 mg, 0.176 mmol) in THF (0.5 ml) was added dropwise and then stirred for 1 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (5 ml) and stirred until solution turned clear and then diluted with EtOAc (10 ml). The layers were separated then the aqueous layer was extracted with EtOAc (10 ml, x2). The organic layers were combined and washed with a saturated brine solution then dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 6:1) to provide **2.55** (47 mg, 0.96 mmol) in 55% as a clear oil. TLC: R_f = 0.30, hexanes/ EtOAc, 5:1. $[\alpha]^{25}_D$ = +17.5 (c 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, *J* = 5.5 Hz, 2 H), 5.62 (dd, *J*= 15.5, 6.5 Hz, 1 H), 5.46 (ddd, *J* = 15.5, 7.5, 1.5 Hz, 1 H), 4.43 (dd, *J* = 13.5, 7.5 Hz, 1 H), 4.24 (ddd, *J* = 12.5, 5.0, 5.0 Hz, 1 H), 4.17–4.10 (m, 1 H), 4.04 (dd, *J* = 10.0, 10.0 Hz, 1 H), 3.57 (s, 1 H), 3.22 (ddd, *J* = 16.5, 13.5, 6.5 Hz, 1 H), 3.01 (ddd, *J* = 14.0, 10.5, 3.0 Hz, 1 H), 2.87 (ddd, *J* = 14.0, 10.0, 3.5 Hz, 1 H), 2.78–2.72 (m, 2 H), 2.27 (dd, *J* = 15.0, 8.5 Hz, 1 H), 2.07–1.79 (m, 5 H), 1.70 (dd, *J* = 6.5, 1.5 Hz, 3 H), 1.51–1.45 (m, 2

H), 1.22 (d, *J* = 6.5 Hz, 3 H), 1.06 (br s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 133.2, 130.1, 126.8, 113.6, 72.3, 66.3, 66.1, 63.5, 61.0, 54.4, 46.6, 45.2, 37.4, 26.9, 24.6, 23.6, 20.1.



[One-pot THP formation] To a stirred solution of **2.21** (117 mg, 0.205 mmol) in CH_2Cl_2 (4 ml, 0.05 M) at 25 °C was added MnO_2 (89 mg, 1.03 mmol) and stirred for 1 hour followed by addition of MnO_2 (89 mg, 1.03 mmol) every 1 hour for 4 hours then added MeOH (400 μl, 10.25 mmol), MnO_2 (89 mg, 1.03 mmol), 4Å molecular sieves (585 mg, 500%wt) then dimethyl triazolium iodide (5 mg, 0.021 mmol, 5mol%) in DBU (410 μl, 1 M in CH_2Cl_2) and stirred for 12 hours. The crude mixture was then filtered through a small plug of Celite®. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to provide **2.20** (104 mg, 0.17 mmol) in 85% as a clear oil. TLC: R_f = 0.75, hexanes/ EtOAc, 3:1. $[a]^{25}_D$ = +12.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 15.0, 13.0, 6.0 Hz, 1 H), 5.39 (ddd, *J* = 15.0, 7.0, 1.5 Hz, 1 H), 4.31 (ddd, *J* = 9.0, 9.0, 4.0 Hz, 1 H), 3.89 (ddd, *J* = 9.5, 9.5, 3.0 Hz, 1 H), 3.81 (dd, *J* = 9.5, 9.5 Hz, 1 H), 3.67 (s, 3 H), 3.12 (ddd, *J* = 15.0, 12.5, 3.0 Hz, 1 H), 2.89 (ddd, *J*= 15.0, 12.5, 3.0 Hz, 1 H), 2.66 (dd, *J* = 13.5, 1.5, 1 H), 2.62 (dd, *J* = 9.5, 4.5 Hz, 1 H),

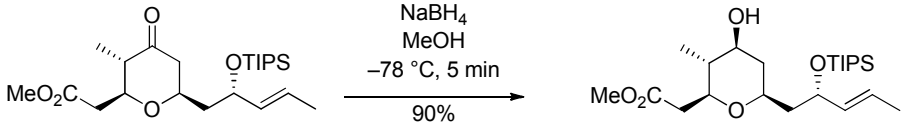
2.53 (dd, *J* = 15.0, 3.5 Hz, 1 H), 2.30 (dd, *J* = 14.5, 9.5 Hz, 1 H), 2.07 (ddd, *J* = 14.0, 3.0, 3.0 Hz, 1 H), 1.86–1.79 (m, 2 H), 1.7 (dd, *J*= 6.5, 1.5 Hz, 3 H), 1.64 (dd, *J* = 10.5, 7.0 Hz, 1 H), 1.50 (ddd, *J* = 13.0, 9.0, 3.5 Hz, 1 H), 1.14 (d, *J* = 6.5 Hz, 3 H), 1.04 (s, 21 H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 134.0, 125.8, 73.7, 70.8, 70.4, 54.8, 51.5, 45.5, 44.1, 43.7, 39.5, 25.7, 25.6, 25.1, 18.1, 18.0, 17.7, 12.3; IR (neat) 2944, 2909, 2362, 2357, 2118, 1554, 1168, 921, 811, 725 cm^{-1}.



2.20 **2.52**

[Dithiane deprotection] To a cooled (0 °C) solution of saturated aqueous $NaHCO_3$ and CH_3CN (1:1, 1 ml, 0.14 M) and **2.20** (83.8 mg, 0.140 mmol) was added I_2 (36 mg, 0.14 mmol) and stirred for 15 minutes followed by I_2 (36 mg, 0.14 mmol) every 15 minutes for 1.25 hours then the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (3 ml) and saturated aqueous $NaHCO_3$ (3 ml) and stirred vigorously until all brown/yellow color disappears. The solution was then diluted with diethyl ether (10 ml) and the layers were separated. The aqueous layer was extracted with diethyl ether (10 ml, x2) then the organic layers were pooled and washed with saturated brine solution then dried over Na_2SO_4. The solvents The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to provide **2.52** (62.3

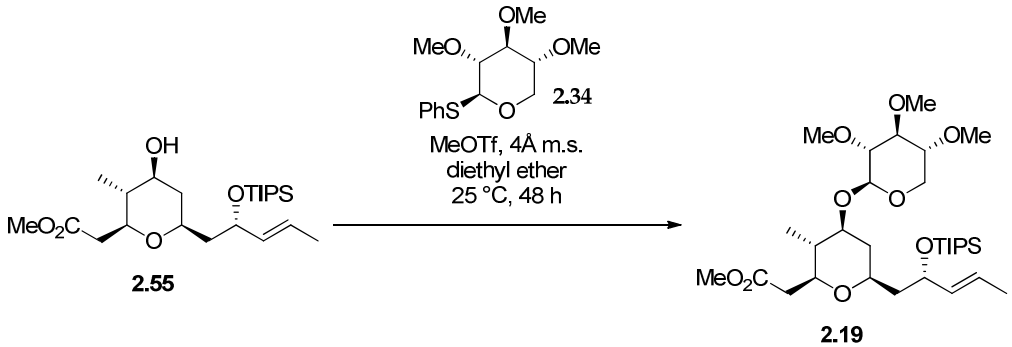
mg, 0.12 mmol) in 88% as a clear oil. TLC: R_f = 0.64, hexanes/ EtOAc, 3:1. $[a]^{25}_D$ = +3.1 (c 0.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (dd, *J* = 13.3, 7.1 Hz, 1 H), 5.34 (dd, *J* = 15.5, 8.0 Hz, 1 H), 4.31 (ddd, 11.0, 9.5, 4.0 Hz, 1 H), 3.65 (ddd, *J* = 13.5, 13.5, 3.0 Hz, 1 H), 3.60–3.54 (m, 1 H), 2.71 (dd, *J* = 15.0, 3.0 Hz, 1 H), 2.55 (dd, *J* = 15.5, 9.5 Hz, 1 H) 2.36 (d, 6.5 Hz, 2 H), 2.32 (dd, 10.5, 6.5 Hz, 1 H), 1.93 (ddd, *J* = 13.0, 13.0, 10.0 Hz, 1 H), 1.68 (d, *J* = 6.5 Hz, 3 H), 1.53 (ddd, *J* = 13.5, 13.5, 10.0 Hz, 1 H) 1.03 (s, 18 H), 1.00 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 134.0, 126.6, 79.0, 74.2, 70.8, 51.7, 49.5, 48.0, 44.9, 39.6, 18.1, 18.0, 17.6, 12.3, 9.23; IR (neat) 3801, 2970, 2913, 2424, 2350, 2342, 1744, 1088, 936, 811, 770 cm^{-1}.



2.52 **2.55**

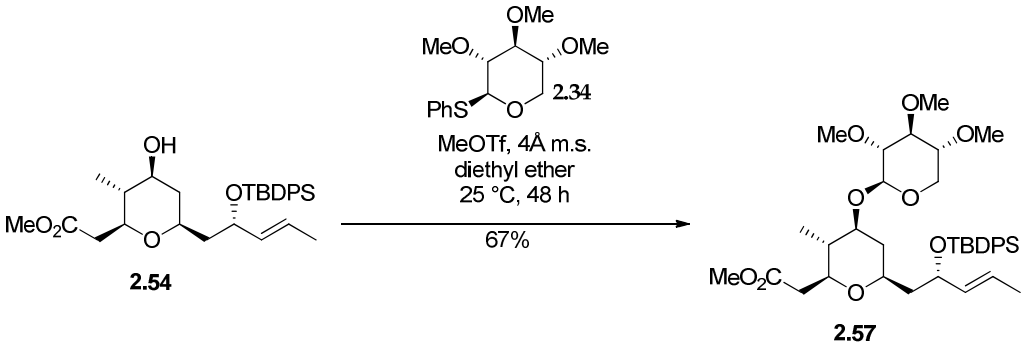
[Reduction] To a cooled (–78 °C) solution of **2.52** (49 mg, 0.115 mmol) in MeOH (2 ml, 0.06M) was added $NaBH_4$ (9 mg, 0.238 mmol) and stirred for 5 minutes. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (1 ml) and then warmed to ambient temperature. The mixture was diluted with diethyl ether (10 ml) and the layers were separated. The aqueous layer was extracted with diethyl ether (10 ml, x3) then the combined layers were washed with saturated brine and dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc 3:1) to provide the β-alcohol **2.55** (39 mg, 0.09 mmol) in 90%

yield as a clear oil. TLC: R_f = 0.40, hexanes/ EtOAc, 2:1. $[a]^{25}_D$ = +16.2 (c 0.17, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (dd, *J* = 15.0, 6.0 Hz, 1 H), 5.34 (dd, *J* = 16.0, 8.0 Hz, 1 H), 4.27 (ddd, *J* = 9.0, 9.0, 4.0 Hz, 1 H), 3.68 (s, 3 H), 2.61 (dd, *J* = 15.0, 2.5 Hz, 1 H), 2.04 (s, 1 H), 1.88 (ddd, *J* = 13.0, 5.0, 2.0 Hz, 1 H), 1.82 (ddd, *J* = 13.5, 9.5, 4.0 Hz, 1.69 (d, *J* = 6.5 Hz, 3 H), 1.46 (ddd, *J* = 12.5, 10.0, 3.0 Hz, 2 H), 1.31 (dd, *J* = 23.5, 11.0 Hz, 2 H), 1.03 (s, 18 H), 0.97 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 134.3, 126.0, 77.6, 73.3, 72.2, 70.9, 44.7, 43.7, 41.4, 38.8, 18.1, 18.0, 17.6, 12.8, 12.3; IR (neat) 3727, 3599, 2943, 2866, 2361, 2340, 1744, 1085 cm^{-1}. For α-alcohol TLC: R_f = 0.40, hexanes/ EtOAc, 2:1. ^1H NMR (500 MHz, $CDCl_3$) δ 5.54 (ddd, *J* = 15.5, 13.0, 6.0 Hz, 1 H), 5.35 (ddd, *J* = 15.5, 7.5, 3.5 Hz, 1 H), 4.30 (ddd, *J* = 14.0, 11.0, 4.0 Hz, 1 H), 3.92 (s, 3 H), 3.85 (ddd, *J* = 10.0, 10.0, 3.0 Hz, 1 H), 3.73–3.62 (m, 5 H), 3.43–3.28 (m, 2 H), 1.69 (d, *J* = 8.0 Hz, 3 H), 1.03 (br s, 21 H), 0.91 (d, *J* = 6.5 Hz, 3 H); ^1H NMR (500 MHz, $CDCl_3$) δ 234.5, 231.6, 193.5, 134.3, 126.0, 113.2, 107.6, 82.3, 70.9, 69.3, 44.8, 40.0, 18.1, 18.0, 17.4, 12.3.



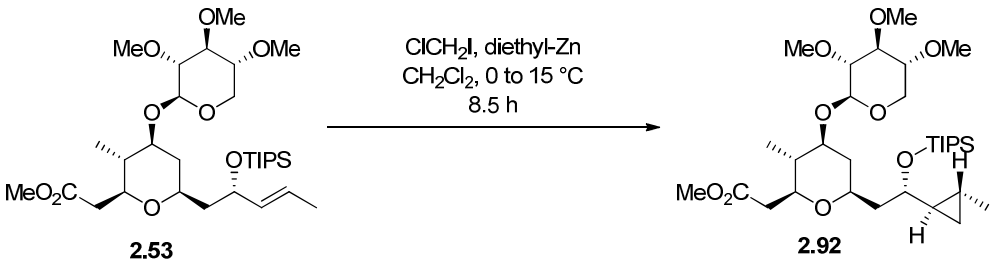
[Glycosidation] To a 25 °C solution of **2.55** (25 mg, 0.058 mmol), **2.34** (29 mg, 0.117 mmol) and 4Å molecular sieves (50 mg, 200%wt) in diethyl ether (1 ml, 0.07 M) was added MeOTf (16.5 μl, 0.146 mmol) and the solution was stirred for 48 hours. $NaHCO_3$ powder (50 mg, 200%wt) was added and the solution was stirred for 6 hours before addition of saturated aqueous $NaHCO_3$ then diluted with diethyl ether (5 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (10 ml, x3). The organic layers were combined and then dried over Na_2SO_4. . The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc 8:1) to provide the β-anomer **2.19** (28 mg, 0.046 mmol) in X% as a clear oil. TLC: R_f = 0.35, hexanes/ EtOAc, 2:1. $[a]^{25}_D$ = +15.3 (c 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (ddd, *J* = 15.5, 13.0, 13.0, 6.5 Hz, 1 H), 5.36 (dd, *J* = 15.5, 8.0 Hz, 1 H), 4.28 (d, *J* = 7.5 Hz, 1 H), 3.97 (dd, *J* = 11.0, 4.5 Hz, 1 H), 3.70 (s, 3 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.49 (d, 3 H), 3.33–3.23 (m, 2 H), 3.10 (dd, *J* = 18.0, 9.0 Hz, 1 H), 2.99 (dd, *J* = 8.0, 8.0 Hz, 1 H), 2.63 (dd, *J* = 15.0, 2.5 Hz, 1 H), 2.40 (dd, *J*= 14.5, 10.0 Hz, 1 H), 2.03 (dd, *J*= 12.5, 4.0 Hz, 1 H), 1.83 (ddd, *J* = 14.5, 10.0, 4.5 Hz, 1 H), 1.71 (d, *J* = 5.5 Hz, 3 H), 1.46 (dd, *J* = 12.5, 12.5 Hz, 1 H), 1.05 (br s, 21 H), 1.02 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 192.7, 190.8, 187.8, 172.1, 170.7, 142.9, 125.9, 105.5, 95.3, 77.7, 70.9, 69.3, 58.8, 44.6, 40.3, 18.1, 18.0, 12.7, 12.3, 7.4; IR (neat) 3629, 2943, 2867, 2249, 1737, 1166, 1092, 909 cm^{-1}. For **2.19** α-anomer: TLC: R_f = 0.31, hexanes/ EtOAc, 2:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.52 (ddd, *J* = 15.0, 12.5, 6.5 Hz, 1 H), 5.33 (dd, *J* = 15.5, 8.0, 1 H), 5.05 (d, *J* = 4.0 Hz, 1 H), 4.272

(ddd, *J* = 11.5, 9.5, 4.0 Hz, 1 H), 3.67 (s, 3 H), 3.62 (s, 3 H), 3.49 (s, 3 H), 3.47 (s, 3 H), 3.41 (dd, *J* = 18.5, 9.5 Hz, 2 H), 3.28–3.21 (m, 1 H), 3.16 (dd, *J* = 9.5, 3.5 Hz, 1 H), 2.6 (dd, *J* = 15.0, 3.0 Hz, 1 H), 2.37 (dd, *J* = 14.5, 9.5 Hz, 1 H), 1.98 (dd, *J* = 11.0, 4.5 Hz, 1 H), 1.84 (ddd, *J* = 13.5, 10.0, 4.0 Hz, 1 H), 1.69 (d, *J* = 6.0 Hz, 3 H), 1.45 (ddd, *J* = 13.0, 10.0, 3.0 Hz, 1 H), 1.33–1.20 (m, 2 H), 1.02 (br s, 21 H), 0.98 (d, *J* = 6.5 Hz, 3 H).



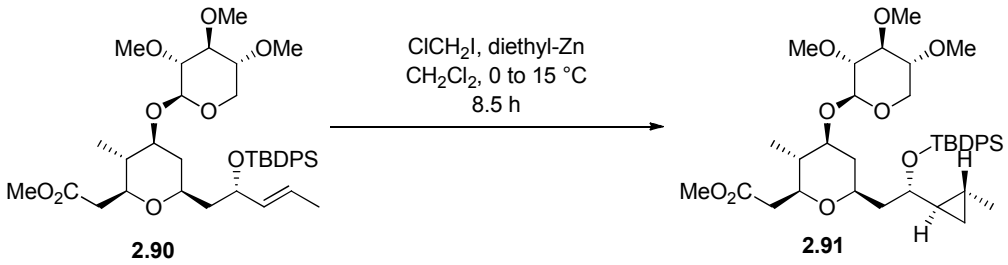
[Schmidt glycosylation] To a stirred solution of thioglycoside **2.54** (17 mg, 0.059 mmol), alcohol **2.54** (15 mg, 0.029 mmol) and 4Å molecular sieves (30 mg, 200%wt) in diethyl ether (1 ml, 0.03 M) was added MeOTf (8.5 μl, 0.074 mmol) and then stirred at the same temperature for 48 hours. The reaction was quenched by addition of solid $NaHCO_3$ (30 mg) followed by vigorous stirring for 6 hours. The solution was diluted with diethyl ether (5 ml) and saturated aqueous $NaHCO_3$ (5 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (5 ml, x3). The combined organic layers were washed with a saturated aqueous brine solution and then dried over anhydrous Na_2SO_4. The solvents were removed in vacuo and the crude residue was purified by

column chromatography (silica gel, hexanes/EtOAc, 6:1) to afford β-anomer **2.57** (10.2 mg, 0.015 mmol) in 54% as a colorless oil: TLC: R_f = 0.24, hexanes/EtOAc, 5:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (ddd, *J* = 8.0, 4.3, 4.3 Hz, 4 H), 7.40– 7.29 (m, 6 H), 5.30 (ddd, *J* = 19.1, 9.5, 2.2 Hz, 1 H), 5.16 (dd, *J* = 18.0, 7.5, 1 H), 4.29–4.19 (m, 2 H), 3.92 (dd, *J* = 14.4, 6.5, 1 H), 3.61 (s, 3H), 3.57 (s, 3H), 3.46 (s, 3H), 3.42 (s, 3H), 3.42 (s, 3H), 3.37–3.15 (m, 6 H), 3.08 (dd, *J* = 10.9, 10.9, 2 H), 3.03 (dd, *J* = 14.4, 14.4, 1 H), 2.95 (dd, *J* = 11.6, 9.5, 1 H), 2.55 (dd, *J* = 18.7, 4.0, 1 H), 2.30 (dd, 18.3, 13.3, 1 H), 1.97 (dd, 14.5, 6.5, 1 H), 1.81 (ddd, *J* = 17.0, 11.5, 6.1 Hz, 1 H), 1.51 (d, 7.9 Hz, 3 H), 1.49–1.41 (m, 2 H), 1.25 (s, 3 H), 1.03 (br s, 9H), 0.96 (dd, 8.2, 3.1 Hz, 3 H). α-anomer: TLC: R_f = 0.21, hexanes/EtOAc, 5:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 19.5, 6.5 Hz, 4 H), 7.42–7.29 (m, 6 H), 5.32 (dd, *J* = 15.0, 7.5 Hz, 1 H), 5.23 (ddd, *J* = 12.5, 12.5, 6.5 Hz, 1 H), 4.26 (ddd, *J* = 8.5, 8.5, 4.5 Hz, 1 H), 3.67 (dd, *J* = 11.0, 6.0 Hz, 1 H), 3.62 (s, 3 H), 3.48 (s, 3 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 3.34 (ddd, *J* = 10.0, 10.0, 3.5 Hz, 2 H), 3.28–3.21 (m, 2 H), 3.14 (dd, *J* = 9.5, 3.5 Hz, 1 H), 2.56 (dd, *J* = 14.5, 3.0 Hz, 1 H), 2.30 (dd, *J* = 14.0, 9.5 Hz, 1 H), 1.91 (dd, *J* = 12.5, 4.5 Hz, 1 H), 1.80 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 1 H), 1.54 (d, *J* = 6.5 Hz, 3 H), 1.52–1.42 (m, 2 H), 1.23 (dd, *J* = 7.0, 7.0 Hz, 1 H), 1.11 (dd, *J* = 23.0, 11.5 Hz, 1 H), 1.03 (s, 9 H), 0.94 (d, *J* = 6.5 Hz, 3 H).



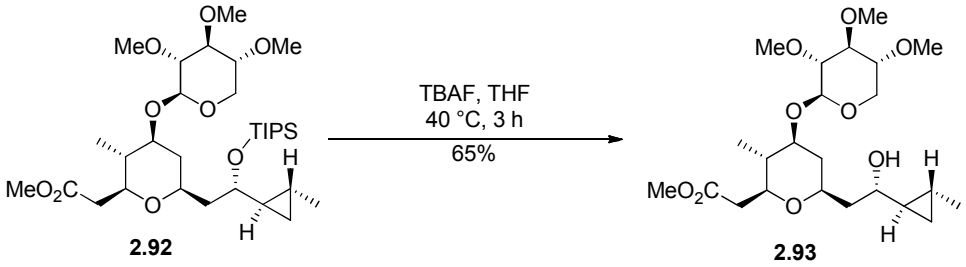
[Cyclopropanation] To a cooled (0 °C) solution of diethyl zinc (165 μl, 1 M in hexanes, 0.165 mmol) was added $ClCH_2I$ (24 μl, 0.33 mmol) and stirred for 25 minutes until a white precipitate formed. Olefin **2.53** (10 mg, 0.0165 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise with two washings with CH_2Cl_2 (0.25 ml) then slowly warmed to 15 °C over 7 hours then stirred at 15 °C for 1.5 hours. The reaction was quenched with saturated aqueous NH_4Cl (1 ml) and diluted with CH_2Cl_2 (10 ml). The layers were separated and the aqueous layer was then extracted with CH_2Cl_2 (10 ml, x3). The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to provide cyclopropane **2.92** (7.2 mg, 0.0117 mmol) as a clear oil in 71%. TLC: Rf = 0.45, hexanes/ EtOAc, 2:1. $[a]^{25}_D$ = X (c 0.X, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.28 (d, *J* = 7.5 Hz, 1 H), 3.96 (s, 3 H), 3.64 (s, 3 H), 3.61 (s, 3 H), 3.58 (s, 3 H), 3.47 (s, 3 H), 3.33–3.20 (m, 3 H), 3.09 (dd, *J* = 8.5, 4.0 Hz, 1 H), 2.96 (dd, *J* = 8.5, 8.5 Hz, 1 H), 2.61 (dd, *J* = 14.5, 3.0 Hz, 1 H), 2.35 (dd, *J* = 15.0, 10.0 Hz, 1 H, 2.05 (dd, *J* = 13.0, 3.5 Hz, 1 H), 1.83 (ddd, *J* = 14.0, 9.5, 4.0 Hz, 1 H), 1.67 (d, *J*= 6.5 Hz, 3 H), 1.03 (br s, 12 H), 0.63–0.48 (m, 2 H), 0.43 (ddd, 13.0, 8.5, 6.0 Hz, 1 H), 0.17 (ddd, 13.0, 9.0, 4.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 105.5, 85.6, 83.1, 83.2, 79.4, 77.7, 73.1, 72.3, 63.2, 60.8,

58.8, 51.5, 45.4, 42.1, 40.8, 39.0, 29.7, 25.9, 18.7, 18.2, 12.8, 12.7, 10.7; IR (neat) 2937, 2866, 1740, 1463, 1161, 1094, 911, 733, 648 cm^{-1}.



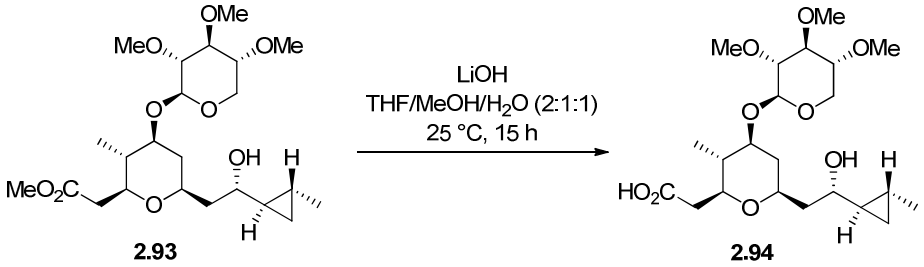
[Cyclopropanation] To a cooled (0 °C) solution of diethyl zinc (234 μl, 0.24 mmol, 1 M in hexanes) was added $ClCH_2I$ (x μl, x mmol) and stirred for 25 minutes until a white precipitate formed. Silyl ether **2.90** (16.0 mg, 0.023 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise followed by two washings with CH_2Cl_2 (0.25 ml) then slowly warmed to 15 °C over 8.5 hours. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 ml) and diluted with CH_2Cl_2 (10 ml) and H_2O (5 ml). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml, x2). The pooled organic layers were then dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 4:1) to provide cyclopropane **2.91** (10.8 mg, 0.015 mmol) as a clear oil in 66%. TLC: R_f = 0.24, hexanes/EtOAc, 5:1. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79–7.19 (m, 10 H), 4.27 (d, *J* = 9.5 Hz, 1 H), 3.99 (dd, *J* = 14.5, 6.0 Hz, 1 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 3.61 (s, 3 H), 3.59 (s, 3 h), 3,56 (d, *J* = 4.5 Hz, 3 H), 3.37 (dd, *J* = 14.5, 4.0 Hz, 1 H), 3.32–3.12 (m, 5 H), 3.10 (dd, *J* =

11.5, 11.5 Hz, 2 H), 2.97 (dd, *J* = 11.0, 11.0 Hz, 1 H), 2.73 (dd, *J* = 17.5, 8.5 Hz, 1 H), 2.61 (dd, *J* = 18.5, 4.0 Hz, 1 H), 2.43 (dd, *J* = 17.0, 10.0 Hz, 1 H), 2.14 (dd, *J* = 16.0, 7.0 Hz, 1 H), 1.57 (br s, 1 H), 1.15 (d, *J* = 9.0 Hz, 3 H), 1.05–1.00 (m, 4 H), 0.96 (dd, *J* = 16.0, 8.5 Hz, 1 H), 0.73–0.54 (m, 2 H), 0.49 (dd, *J* = 11.0, 5.5 Hz, 1 H), 0.38 (ddd, *J*= 12.0, 4.0, 4.0 Hz, 1 H), 0.26 (dd, *J*= 12.0, 7.0 Hz, 1 H).

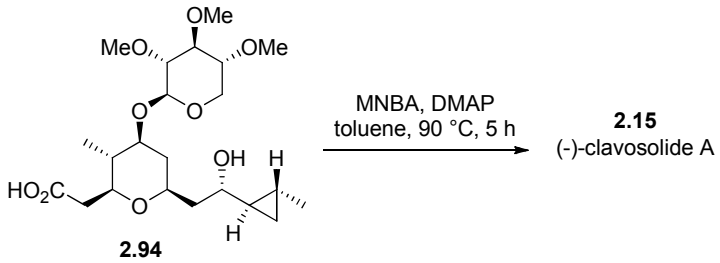


[TIPS hydrolysis] To a 25 °C solution of **2.92** (7.2 mg, 0.012 mmol) was added TBAF (120 μl, 0.12 mmol, 1 M in THF) then the solution was heated to 40 °C for 2 hours. TBAF (120 μl, 0.12 mmol, 1 M in THF) was added and the mixture was stirred for an additional hour then cooled to 25 °C and quenched with saturated aqueous NH_4Cl (2 ml) and stirred for an additional hour. The mixture was diluted with Et_2O (10 ml) and H_2O (3 ml) and the layers were separated. The aqueous layer was extracted with Et_2O (10 ml, x3) then the pooled organic layers were dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to provide alcohol **2.93** (3.5 mg, 0.008 mmol) in 65% as a clear oil. TLC: R_f = 0.25, hexanes/ EtOAc, 1:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.19 (d, *J* = 9.5 Hz, 1 H),

3.87 (dd, *J* = 14.5, 6.5 Hz, 1 H), 3.62 (s, 3 H), 3.55 (s, 3 H), 3.52 (s, 3 H), 3.40 (s, 3 H), 3.23–3.10 (m, 1 H), 3.03 (dd, *J* = 11.0, 4.0 Hz, 1 H), 3.00 (dd, *J* = 8.5, 3.0 Hz, 1 H), 2.90 (dd, *J* = 9.5, 9.5 Hz, 1 H), 2.60 (dd, *J* = 19.5, 3.5 Hz, 1 H), 2.34 (dd, *J* = 19.0, 12.0, 1 H), 2.00 (dd, *J* = 13.5, 4.0 Hz, 1 H), 1.73–1.55 (m, 3 H), 1.39 (dd, *J* = 11.5, 11.5 Hz, 1 H), 1.18 (s, 1 H), 0.97 (d, *J* = 7.5 Hz, 3 H), 0.94 (d, *J* = 8.0 Hz, 3 H), 0.68 (ddd, *J* = 13.5, 11.0, 8.0 Hz, 1 H), 0.50 (ddd, *J* = 16.0, 10.5, 4.5 Hz, 1 H), 0.21 (ddd, *J* = 11.0, 10.5, 5.5 Hz, 1 H), 0.09 (ddd, *J* = 11.0, 10.5, 5.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 186.0, 179.0, 155.3, 141.7, 138.1, 127.0, 118.4, 105.6, 95.6, 85.5, 83.8, 79.3, 60.8, 47.4, 41.9, 37.1, 27.9, 26.1, 15.3, 12.7, 4.4.



[Methyl ester hydrolysis] To a 25 °C solution of methyl ester **2.93** (3.5 mg, 0.008 mmol) in THF/MeOH/H_2O (2:1:1, 1 ml, 0.008 M) was added LiOH (0.023 ml, 0.024 mmol, 1 M in H_2O) and stirred for 15 hours. The reaction mixture was then cooled to 0 °C and acidified with 1 M HCl, and diluted with diethyl ether (5 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (5ml, x 3). The combined organic layers were dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude mixture subjected to the next step without further purification.



[Shiina macrolactonization] To a stirred solution of MNBA (7.8 mg, 0.023 mmol) and DMAP (18.6 mg, 0.152 mmol) in toluene (2 ml) was added the crude acid **2.94** in toluene (2.5 ml) by syringe pump at 90 °C for 5 hours. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to afford clavosolide A **2.15** (2.3 mg, 0.0027 mmol) in 72% for 2 steps as a white solid. TLC: R_f = 0.6, hexanes/ EtOAc, 1:1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (dd, *J* = 9.0, 9.0 Hz, 2 H), 4.26 (d, *J* = 8.0 Hz, 2 H), 3.95 (dd, *J* = 11.5, 5.0 Hz, 2 H), 3.61 (s, 6 H), 3.58 (s, 6 H), 3.46 (s, 6 H), 3.48–3.23 (m, 4 H), 3.24 (dd, *J* = 11.5, 11.5 Hz, 2 H), 3.24 (ddd, *J* = 8.5, 8.5, 5 Hz, 2 H), 3.09 (dd, *J* = 8.5, 8.5 Hz, 2 H), 3.08 (dd, *J* = 11.5, 8.5 Hz, 2 H), 2.95 (dd, *J* = 8.5, 8.5 Hz, 2 H), 2.54 (dd, *J* = 17.0, 3.0 Hz, 2 H), 2.41 (dd, *J* = 17, 6.5 Hz, 2 H), 2.04 (dd, *J* = 11.5, 4.5 Hz, 2 H), 1.88 (ddd, *J* = 15.0, 15.0, 9.0 Hz, 2 H), 1.68 (br d, *J* = 15.0 Hz, 2 H), 1.38 (m, 2 H), 1.37 (dd, *J* = 11.5, 11.5 Hz, 2 H), 0.96 (d, *J* = 6.5 Hz, 6 H), 0.81 (m, 2 H), 0.71 (ddd, *J* = 9.0, 9.0, 5.0 Hz, 2 H), 0.34 (ddd, *J* = 8.5, 8.5, 5.0 Hz, 2 H), 0.22 (ddd, *J* = 8.5, 5.0 Hz, 2 H).

3. Total synthesis of Subglutinols A and B

3.1 Organ transplant rejection and autoimmunity

Organ transplant rejection can occur when the recipient's immune system recognizes the implanted organ as a foreign entity and mounts an attack. Transplant rejections are classified into three categories: hyperacute, acute, and chronic rejection.[82] Acute rejection occurs to some extent in almost all organ transplant recipients. Hyperacute rejection occurs in patients that have preexisting antibodies to the donor organ, leading to immediate systemic inflammation. The only recourse is immediate removal of the rejected organ. The mechanisms that contribute to chronic rejection are poorly understood. An inhaled form of cyclosporin A has met with limited success, but the most common treatment is re-transplantation or bone marrow transplantation from the donor of the organ.[83]

Rejection occurs when the recipient immune system recognizes mismatched histone compatibility complex antigens of the donor organ as a foreign object. The current paradigm in organ transplant rejection is that alloreactive T-cells primed with alloantigens and recipient antigen presenting cells (APC's) function as the primary mediators of the rejection response.[84] This response is due to induced cytotoxicity and cytokine promoted inflammation. The most common method of treating this process is through immunosuppressive chemotherapy. Patients who receive donated organs can

expect to continue an immunosppressive chemotherapy regimen for the remainder of their lifespan.

3.1.1 T-cell activation

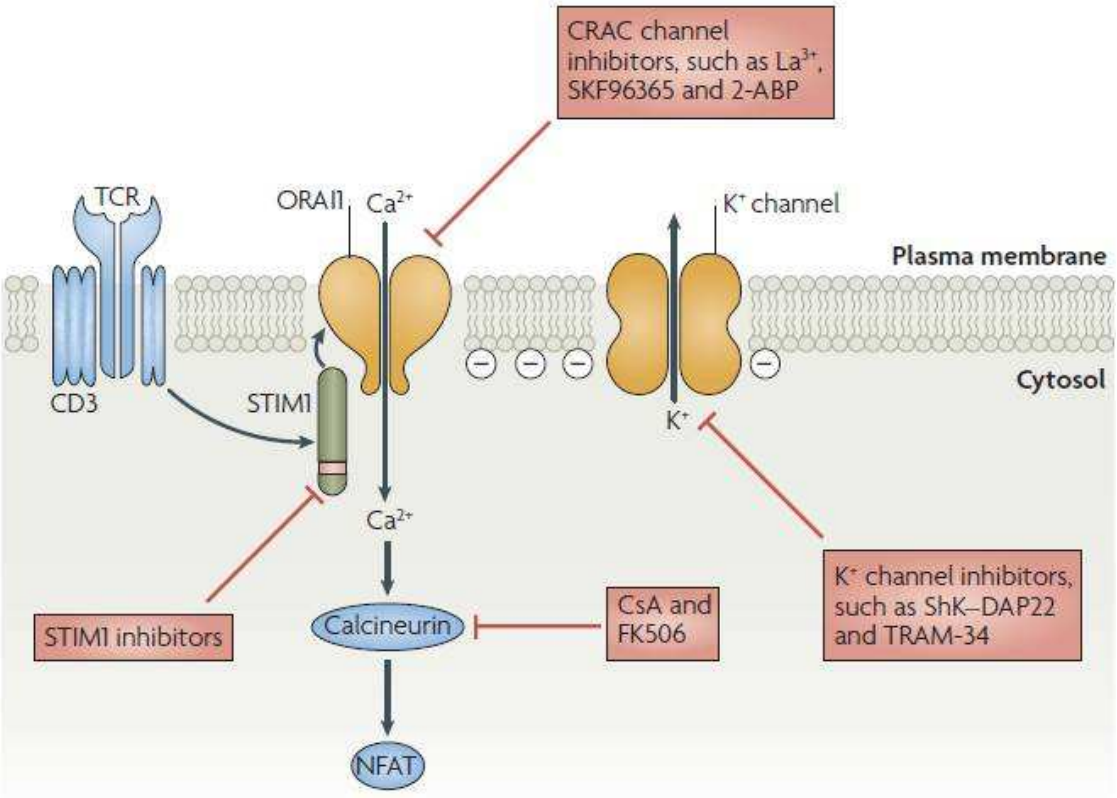


Figure 23: T-cell activation and Ca^{2+} signaling pathway. (Figure reproduced with permission of Nature Publishing Group[85].)

Current immunosuppressive chemotherapies focus on suppression of the T-cell mediated immune response. The adaptive immune response is initiated when a foreign antigen particle is presented by the major histone compatibility complex in a binding event to the T-cell receptor (**Figure 23**). This binding event promotes a cascade of secondary messengers leading to release of Ca^{2+} from the endoplasmic reticulum into the

cytosol. An increase of intracellular Ca^{2+} ions promotes activation of calcineurin, leading to upregulation of genes associated with proliferation and differentiation of naive T-cells into either helper T-cells or cytotoxic T-cells. [85–88]

After depletion of the stored intracellular Ca^{2+}, STIM 1 (stromal interaction molecule 1) translocates to the cell membrane and binds to calcium-release calcium current channel (CRAC) which opens a pore for extracellular Ca^{2+} to enter the cell. Ca^{2+} ions enter the cell due to a voltage gradient caused by the efflux of K^+ through a voltage gated potassium channel. The replenishment of Ca^{2+} ions propagates the proliferation and differentiation signals of T-cells and therefore continues the immune response. [85]

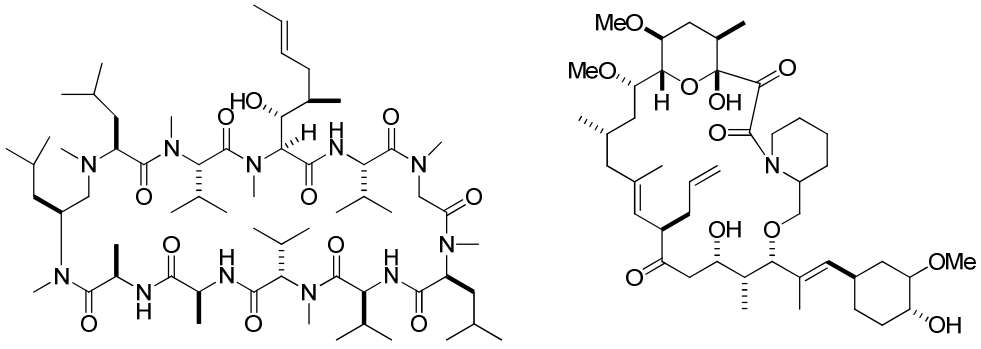


Figure 24: Examples of FDA approved immunosuppressive drugs.

The two major clinically approved compounds used to treat organ transplant rejection are cyclosporin A and FK-506 (**Figure 24**). These compounds are also used to treat other immune disorders including multiple sclerosis, ulcerative colitis, eczema, rheumatoid arthritis and insulin dependent diabetes. [88]

Cyclosporin A is a cyclic peptide that inhibits the immune response by binding to cyclophilin A, forming a complex that inhibits the function of calcineurin. FK-506 or Tacrolimus® is a macrolactone natural product that binds to calmodulin, thereby preventing its activation of calcineurin. While these compounds are effective at suppressing the immune response they also have detrimental off-target effects manifesting as gastrointestinal irritation, neuropathy, nephrocytoxicity, and an overall poor quality of life.[89–90] These off target effects necessitate a better understanding of the biology governing the immune response so that chemotherapies lacking these side effects can be developed. [86, 88]

3.2 Isolation and characterization of subglutinols A and B

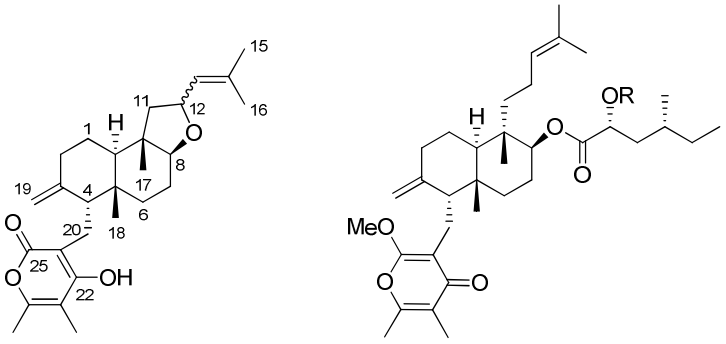


Figure 25: Subglutinols A and B with assigned configuration based on viridoxins A and B.

Subglutinols A and B (**Figure 25**) are diterpene pyrones that were first isolated by Clardy and co-workers in 1995, from the endophytic fungus *Fusarium subglutinans*

harvested from the intercellular spaces of the twining vine *Tripterygium wilfordii* [91]. The structure and relative stereochemistries for subglutinols A and B were determined through NMR and X-ray crystallographic analysis. The absolute stereochemistry was tentatively assigned to be in agreement with the structurally related natural products viridoxins A and B (**Figure 25**). Subglutinols A and B possess a *trans*-fused decalone core, trisubstituted tetrahydrofuran ring and α-pyrone appendage at the C4 position. The subglutinols A and B differ only at the stereogenic C12 position.

Clardy and co-workers examined subglutinols A and B in the mixed lymphocyte reaction assay (MLR assay) and in the thymocyte proliferation assay (TP assay) where they were equipotent, suggesting that the stereogenic center that differentiates the two compounds may have limited interaction with the biological target. Cyclosporin A was also tested in the same assay systems and showed to be roughly as potent as the subglutinols in the MLR assay but 10^4 times more potent in the TP assay. The most noticeable difference was the lack of cytotoxicity of the subglutinols. The lack of cytotoxicity of the subglutinols merits further study of their mode of action, possibly elucidating a novel target for immunosuppression. The lack of access to the subglutinols from natural sources necessitated a synthetic means to obtain the compounds for further biological study.

3.3 Synthetic methods to access substituted tetrahydrofurans

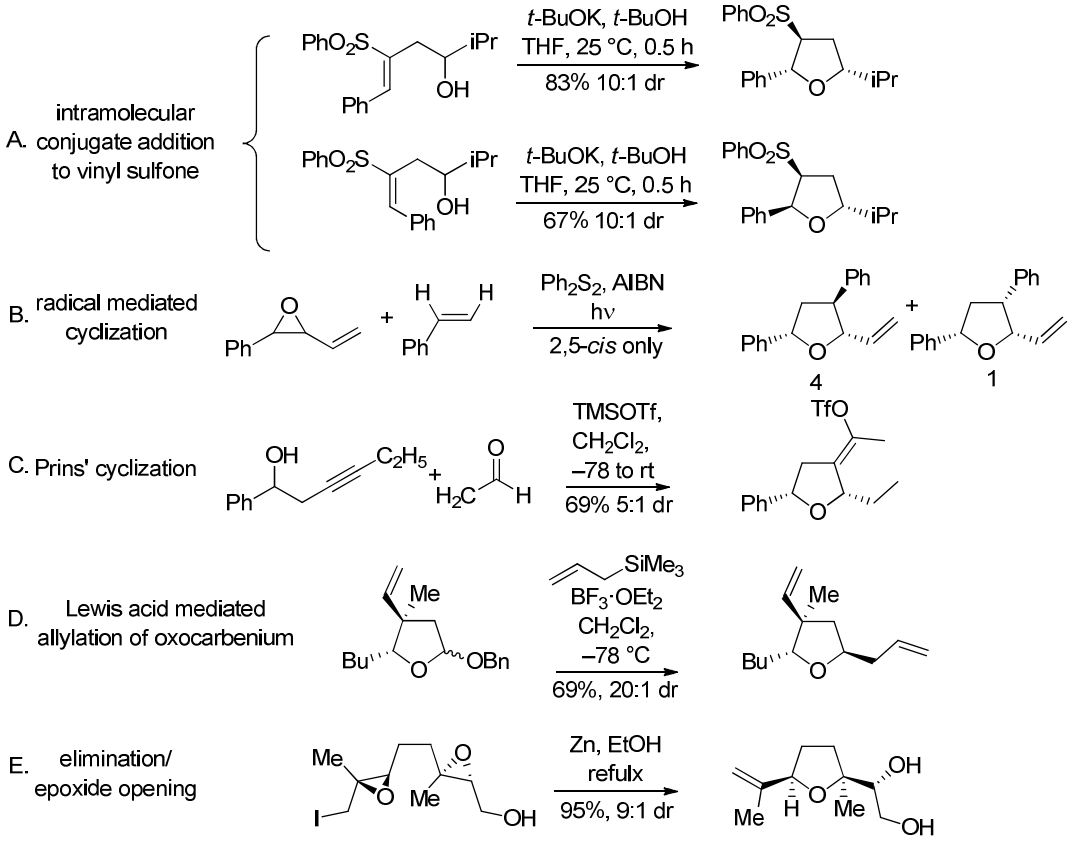


Figure 26: Synthetic methods to access substituted tetrahydrofurans.

There have been many reported strategies for the stereoselective construction of substituted tetrahydrofurans (**Figure 26**). Base promoted intramolecular 1,4-conjugate addition of vinyl sulfones (**Figure 26A**) shows that formation of 2,5-*cis*-tetrahydrofurans and 2.5-*trans*-tetrahydrofurans can be achieved in good diastereoselectivity, with olefin geometry determining the relative configuration of the product.[92] The radical mediated cyclization of an epoxide to an olefin in **Figure 26B** was able to achieve the 2,6-

cis-tetrahydrofuran as a single configuration, but with a 4:1 ratio of 2,4-*trans*- to 2,4-*cis*-tetrahydrofurans.[93] The Lewis acid promoted Prins cyclization in **Figure 26C** proceeded in 69% yield with a 5:1 diastereomeric ratio to provide the triflate enol ether. Oxocarbenium formation of the Oshima–Utimoto intermediate (**Figure 26D**) followed by stereoselective alkylation provided the trisubstituted 2,5-*trans*-tetrahydrofuran intermediate in greater than 20:1 diastereoselectivity.[94-95] The final entry E shows a zinc mediated cascade reaction wherein elimination of iodine opens the first epoxide which serves a nucleophile that internally opens the second epoxide to provide a 9:1 diastereoselectivity for the 2,5-*cis*-tetrahydrofuran.[96] This is not an exhaustive list, but serves to illustrate the need for complex substrate manipulation necessary to gain access to tetrahydrofurans formation (entries A and E) and the potentially incompatible conditions used to construct tetrahydrofurans with highly functionalized compounds (entries B, C, and D).

3.4 Structurally similar natural products and their biological activities

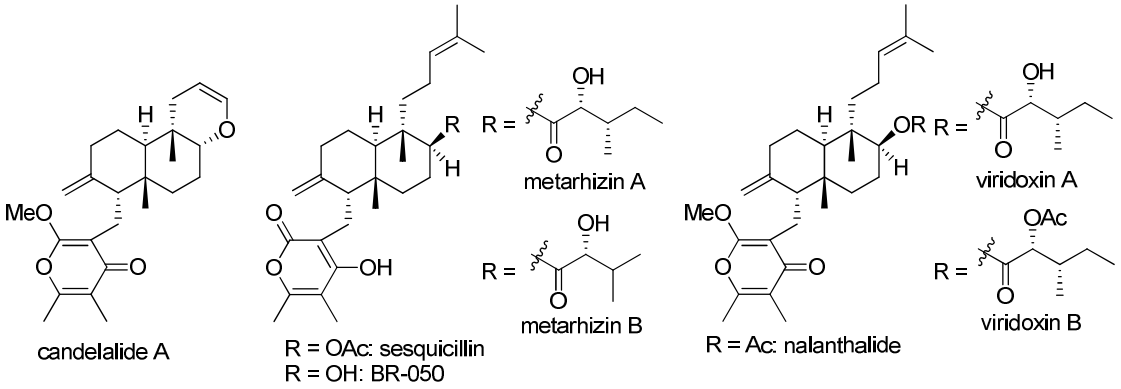


Figure 27: Structurally similar natural products to subglutinols A and B.

There have been reported several structurally related compounds to the subglutinols that possess interesting biologically activity. Metarhizins A and B have shown potent antiproliferative effects against human cancer cell lines K562 (leukemia), A549 (lung cancer), and HCT116 (colon cancer) [97]. Viridoxins A and B have been shown to be a potent insect toxins [98]. Interestingly, the toxicity of both metarhizins and viridoxins is dependent upon the functionality of the R group attached to the *trans*-decaline core shown in **Figure 27**. BR-050 has been patented as a bone resorption inhibitor.[99]

Sesquicillin was isolated from the fermentation broth of *Acremonium* sp., strain 132-94 in an effort to discover new glucocorticoid receptor antagonists [100]. Glucocorticoid receptors have been implicated in the proliferation of naive T-cells and

thus have an effect in the immune response, as such, sesquicillin has shown to be a potential target in immunosuppression.[101-103]

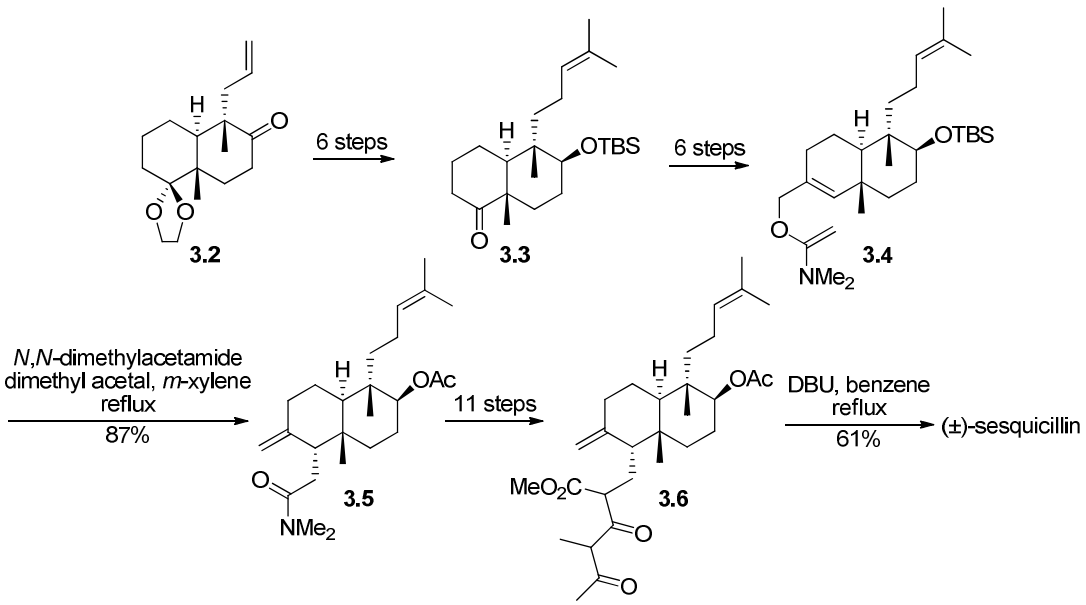


Figure 28: Danishefsky's synthesis of (±)-sesquicillin.

The first synthesis of (±)-sesquicillin was reported by Danishefsky and co-workers (**Figure 28**), and employed Uda's intermediate ketone **3.2** as the starting point. [104-105] Through stepwise manipulation the homoprenyl subunit was installed followed by selective deprotection of the ketal group at C4 to provide **3.3**. Formylation, ee protection, reduction, mesylation, elimination, reduction and *O*-alkylation provided ether **3.4** as the substrate for the Eschenmoser–Claisen rearrangement. Rearrangement led to the installation of the C3 *exo*-methylene functionality as well as the desired stereochemistry at the C4 position shown in structure **3.5**. They finished the synthesis

through a linear approach to install the α-pyrone precursor **3.6** and finally conducted DBU mediated enol lactonization to furnish (±)-sesquicillin.

Candelalide A and nalanthalide are voltage gated potassium channel blockers ($K_V1.3$). Blockage of these channels disallows efflux of K^+, which prohibits formation of the necessary voltage gradient to allow replenishment of intracellular Ca^{2+} levels needed to sustain the T-cell activation signal. This indirectly inhibits the immune response.

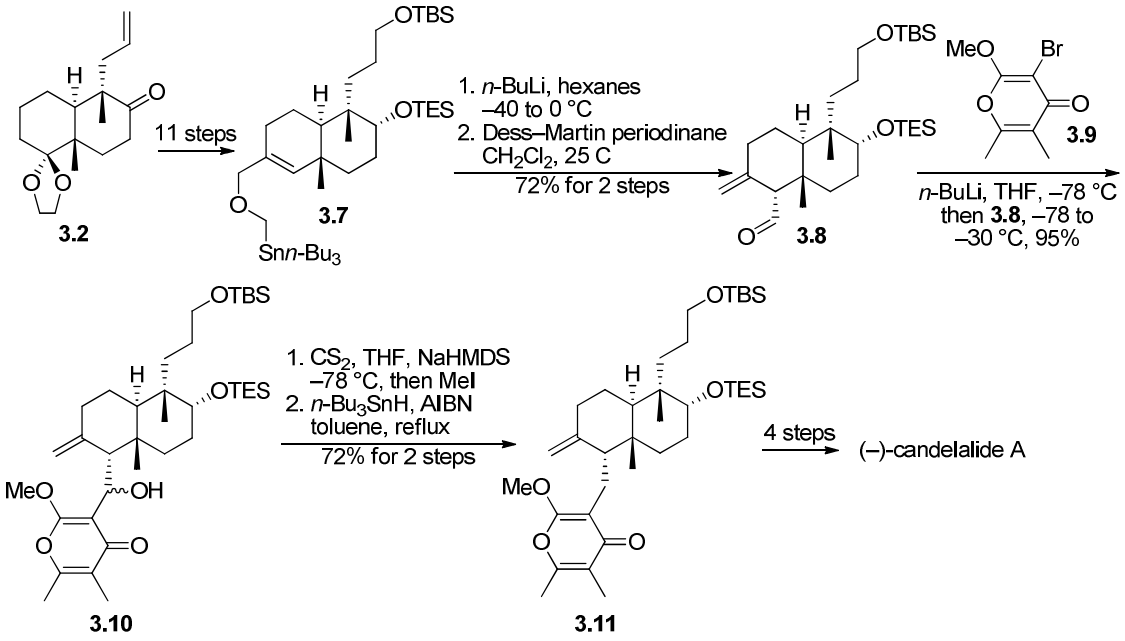


Figure 29: Katoh's synthesis of (–)-candelalide A.

Candelalide A was isolated by a research group at Merck in 2001 from the culture broth of *Sesquicillium candelabrum,* in an effort to discover new $K_V1.3$ inhibitors [106]. In 2005 Katoh's group reported the first total synthesis of candelalide A (**Figure 29**). [107] This method was similar to the Danishefsky synthesis of sesquicillin, in that both used the same Uda intermediate as a starting point **3.2** as well as installing the

allylic alcohol precursor to the *exo*-methylene functionality. Katoh's method employed the stannyl ether **3.7** as precursor to [2,3]-Wittig rearrangement to install the *exo*-methylene group as well as the correct stereocenter at the C4 position, and was then converted to the aldehyde **3.8** through DMP oxidation. Direct addition of the lithio-γ-pyrone **3.9** led to a mixture of secondary alcohols **3.10** which were cleaved through Barton–McCombie protocol to give **3.11**. Desilylation, oxidation, mesylation, and elimination led to (–)-candelalide A.

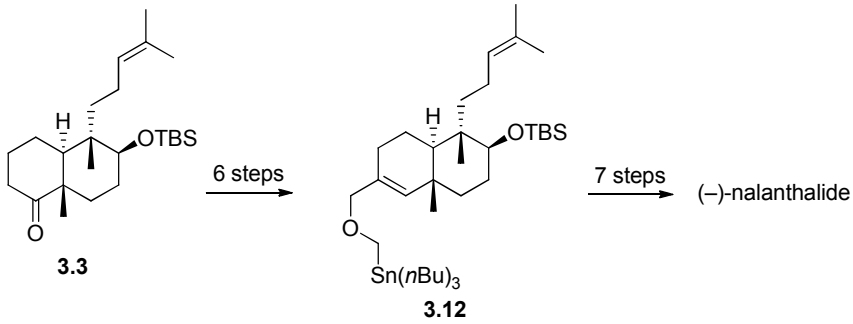


Figure 30: Katoh's synthesis of (–)-nalanthalide.

Katoh's group also reported the first total synthesis of (–)-nalanthalide in 2006 [108]. Nalanthalide, like candelalide is a Kv1.3 inhibitor. The total synthesis of nalanthalide followed Danishefsky's procedure with very slight modifications to achieve the known structure **3.3** (**Figures 28** and **30**). At this stage, the stannyl ether **3.12** was constructed for the [2,3]-Wittig rearrangement followed by installation of the γ-pyrone appendage using the identical protocol as shown in **Figure 29** for the synthesis of (–)-candelalide in 7 steps.[108]

3.5 The total synthesis of subglutinols A and B

3.5.1 Retrosynthesis

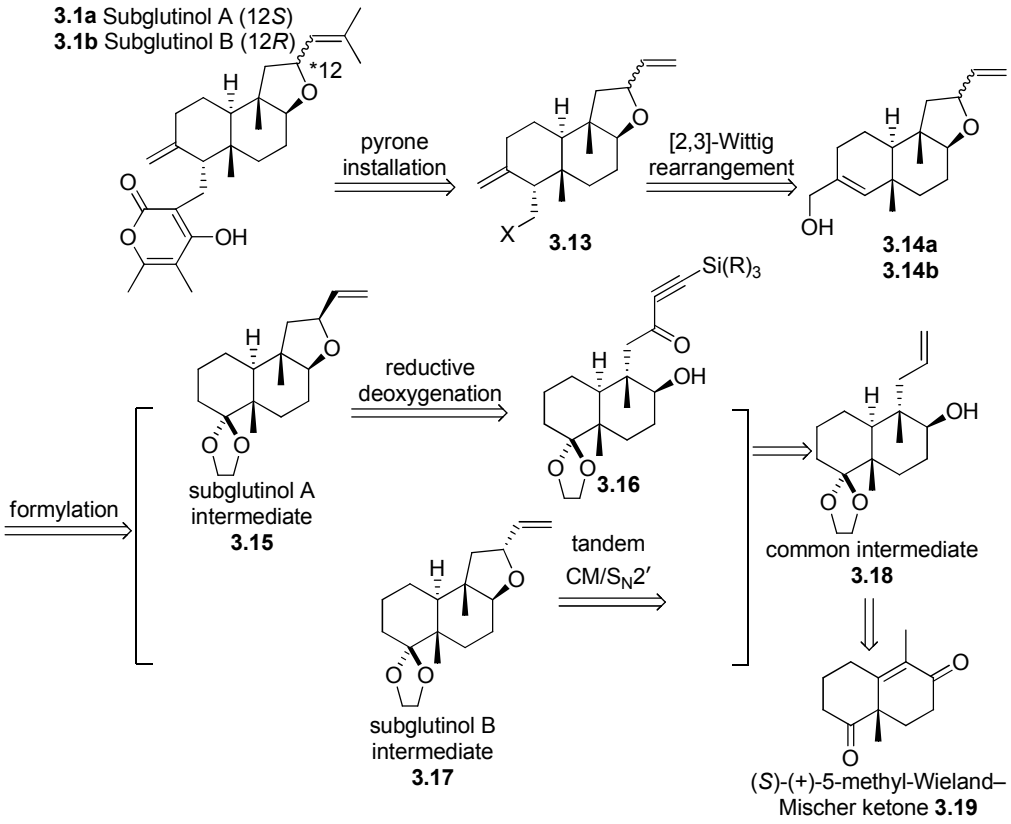


Figure 31: Retrosynthesis for subglutinols A and B.

The retrosynthetic strategy for the subglutinols **3.1** (**Figure 31**) was designed to install the C12 stereocenters from a common intermediate **3.18** which could be prepared from the known **3.19** (*S*)-(+)-5-methyl-Wieland–Mischer ketone.[109] The subglutinol A intermediate **3.15** was envisioned from the stereoselective, Lewis acid promoted reductive deoxygenation of the hemiketal **3.16**. The C12 stereocenter for the subglutinol B intermediate **3.17** could be prepared through tandem cross-metathesis/S_N2' process.

The subglutinol intermediates **3.15** and **3.17** would then be subjected to the same sequence of reactions to install the allylic alcohols at the C3 position **3.14** and the α-pyrone appendages, including 2,3-Wittig rearrangement, and direct coupling of the pyrone.

It should be noted that my contribution to the subglutinol project mainly focused on construction of intermediate **3.15** while the method for construction of **3.17** and pyrone installation was conducted by the Hong lab's former post-doc Hyoungsu Kim.

3.5.2 Synthesis of the (12*S*)-2,3-*trans*-2,5-*cis*-tetrahydrofuran 3.22

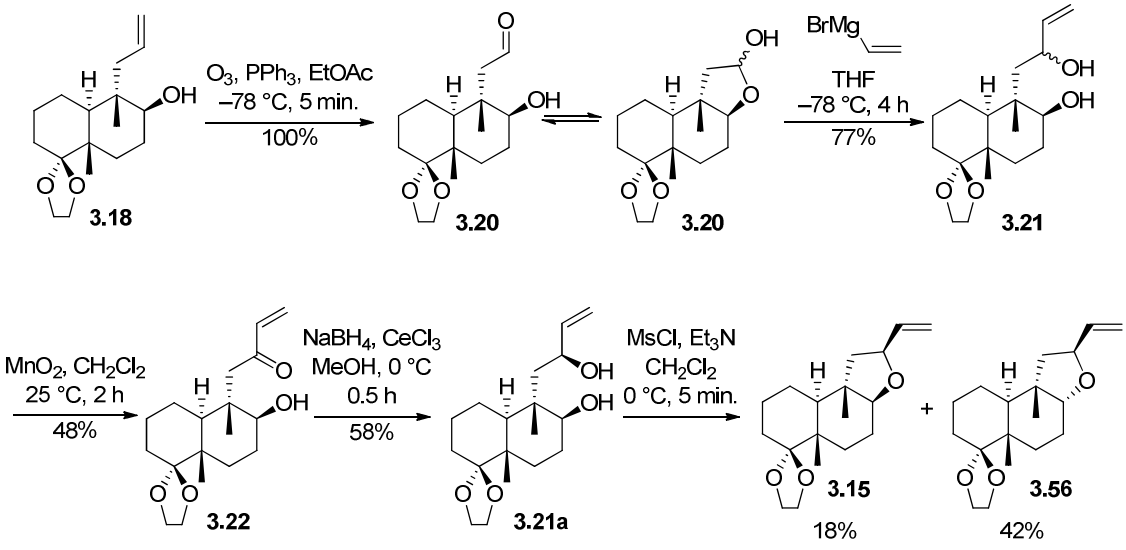


Figure 32: Leuche reduction pathway

The first attempt at installation of the C12 stereocenter of subglutinol A (**Figure 32**) began with the ozonolysis of the terminal alkene of **3.18** to provide the lactol **3.20** in quantitative yield. Addition of vinylmagnesiumbromide to aldehyde **3.20** provided

allylic alcohols **3.21** in 77%, followed by allylic oxidation with MnO_2 to provid hemiketal **3.22** in 48%. Stereoselective reduction of the α,β-unsaturated ketone under Leuche conditions provided the allylic alcohol **3.21a** in a 3:1 diastereoselectivity in 58% for the desired diastereomer.[110] Selective mesylation of the allylic alcohol proved challenging as was observed in the subsequent intramolecular S_N2 reaction that provided the desired subglutinol A intermediate **3.15** in 18% with the major side product **3.22** in 42%. The low yield, redundant oxidation/reduction process, and lack of chemoselective mesylation led to the abandonment of this pathway and a revision of the synthetic strategy.

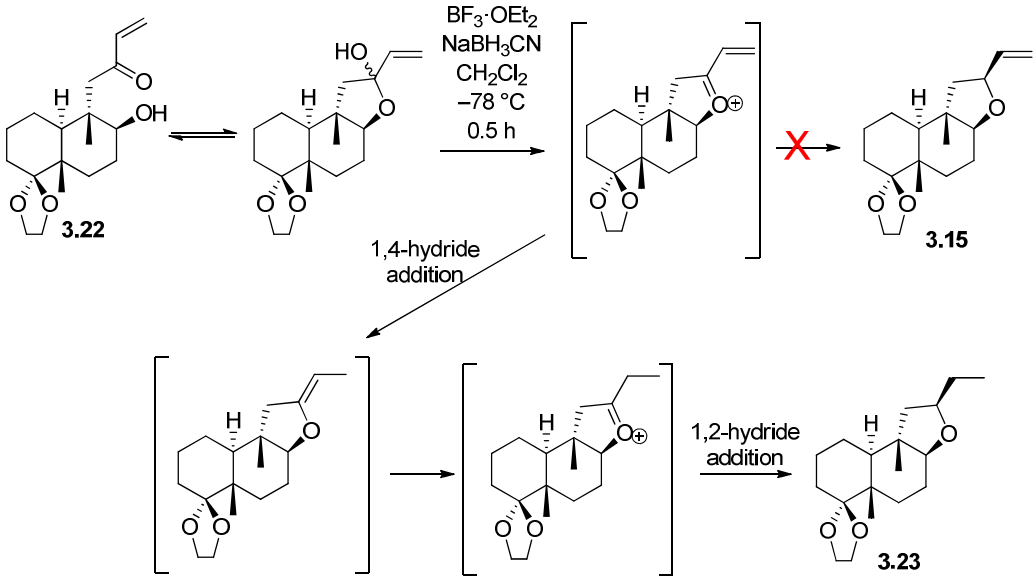


Figure 33: Reductive deoxygenation, 1,4-hydride addition.

The next attempt toward the subglutinol A intermediate **3.15** relied upon chemoselective and stereoselective hydride addition to a Lewis acid promoted oxocarbenium intermediate (**Figure 33**).[112] Upon addition of $BF_3{\cdot}OEt_2$ and $NaBH_3CN$,

the oxocarbenium intermediate was formed, but unexpectedly the fully reduced adduct **3.23** was observed as a single compound. The rationale behind the observed product is that the hydride first undergoes 1,4 conjugate addition followed by a second oxocarbenium formation and subsequent 1,2-hydride addition. Although this sequence failed to provide the desired product, the stereochemical outcome at the C12 position was determined to be in the desired *S* configuration through careful NMR analysis.

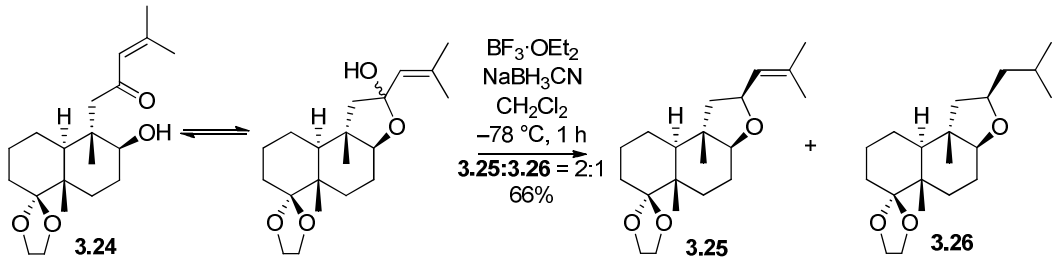


Figure 34: β-dimethyl substitution effect on 1,4- vs. 1,2-hydride addition.

Encouraged by the stereochemical outcome of the previous reaction, it was expected that increasing the steric influence at the β position could hinder 1,4 hydride addition and lead to the desired product. To that end, **3.22** was reacted with Grubbs' second generation catalyst and isopropylidine to form **3.24** in 25%. It was then subjected to reductive deoxygenation conditions to provide the desired product **3.25** and the fully reduced adduct **3.26** in a 2:1 ratio (**Figure 34**).

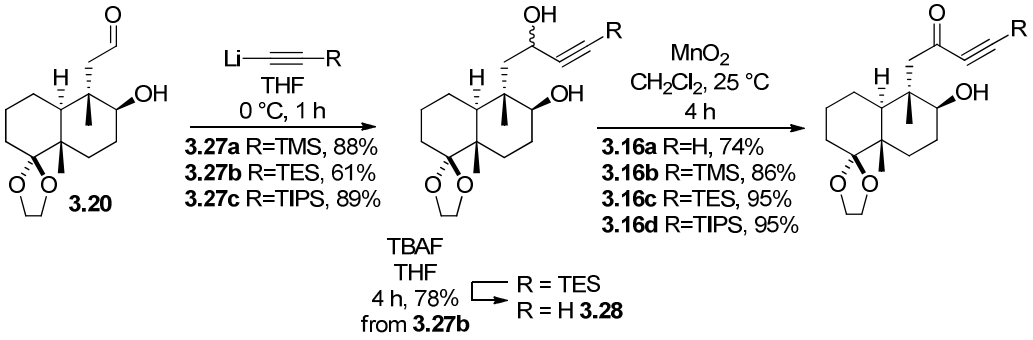


Figure 35: Synthesis of α,β-unsaturated propargyl ketones.

In an effort to improve chemoselectivity of the reductive deoxygenation process it was necessary to further minimize the 1,4-hydride contribution, presumably through steric hindrance. To achieve this goal, four propargylic compounds were constructed (**Figure 35**) with terminal groups of varying steric bulkiness. Silylated lithio-yne reagents were added to aldehyde **3.20** to form mixtures of the propargyl alcohols which were then selectively oxidized to the α,β-unsaturated compounds **3.16a–d**.[112] TES alkyne was desilylated with TBAF to provide **3.28** in 78% yield.

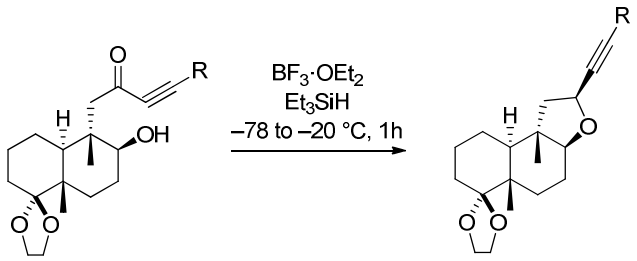


Table 4: Steric influence on chemoselectivity and stereoselectivity of hydride addition.

Substrate	R	Yield	1,2- vs. 1,4-Hydride[a] Addition	Diastereoselectivity[a]
3.16a	H	29%	1:1	12*S* only
3.16b	TMS	67%	1,2-addition with trace 1,4-addition	12*S* only
3.16c	TES	86%	Only 1,2-addition	12*S* only
3.16d	TIPS	91%	Only 1,2-addition	12*S* only

[a] Chemoselectivity and diastereoselectivity were determined from crude ^{1}H NMR.

The propargylic system with the terminal hydrogen **3.16a** underwent reductive deoxygenation to provide a 1.1:1 ratio of 1,2 to 1,4 hydride addition with low yield (**Table 4**).[111] The added steric bulk of the terminal trimethylsilyl (TMS) group **3.16b** provided the desired 1,2 adduct with trace amounts of the 1,4 adduct as a single diastereomer in modest yield. As the steric influence increased (triethylsilyl, **3.16c** and triisopropyl **3.16d**) only the 1,2 adducts were observed as single diastereomers in good yields.

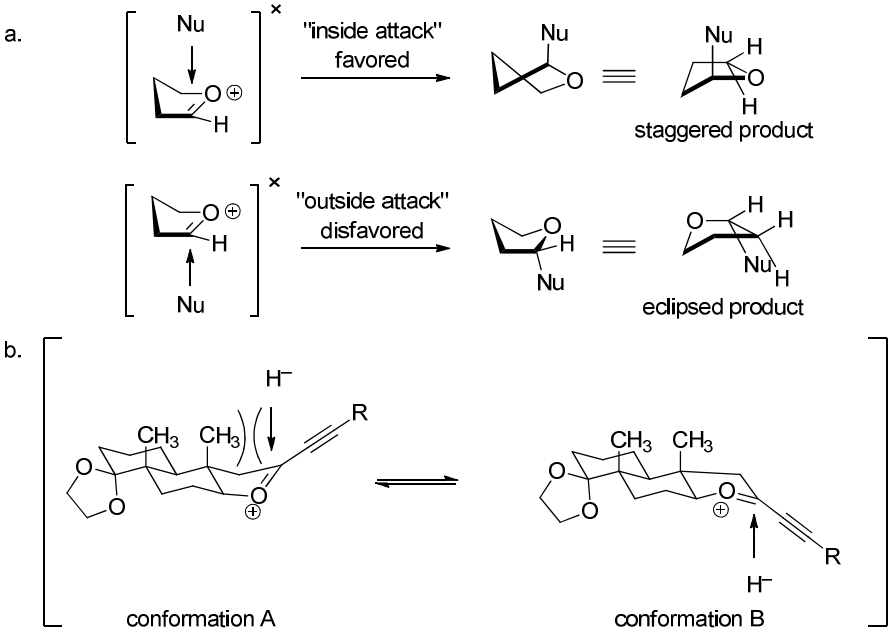


Figure 36: a. Inside envelope attack of hydride to oxocarbenium; b. hydride addition to the face opposite C17 methyl group.

In order to explain the stereochemical outcome of the hydride addition in the properglyic systems (**Table 4**), we turned to Woerpel's model.[111] In **Figure 36a** the five membered oxocarbenium intermediate is susceptible to nucleophilic attack from either the top face or the bottom face. Nucleophilic addition from the inside attack model produces a more favorable staggered product while addition from the outside attack model leads to the less favorable eclipsed product. The thermodynamically favorable staggered product leads to nucleophilic attack primarily from the inside envelope conformation.

Nucleophilic attack from the inside envelope conformation leads to two possible conformations for hydride attack in the propargylic systems as shown in **Figure 36b**.

Conformation A is less favorable for hydride attack due to the steric interaction with the C17 methyl group and would lead to the (12*R*) product. Conformation B, lacking in this steric interaction is more favorable for hydride attack, leading exclusively to the observed (12*S*) product.

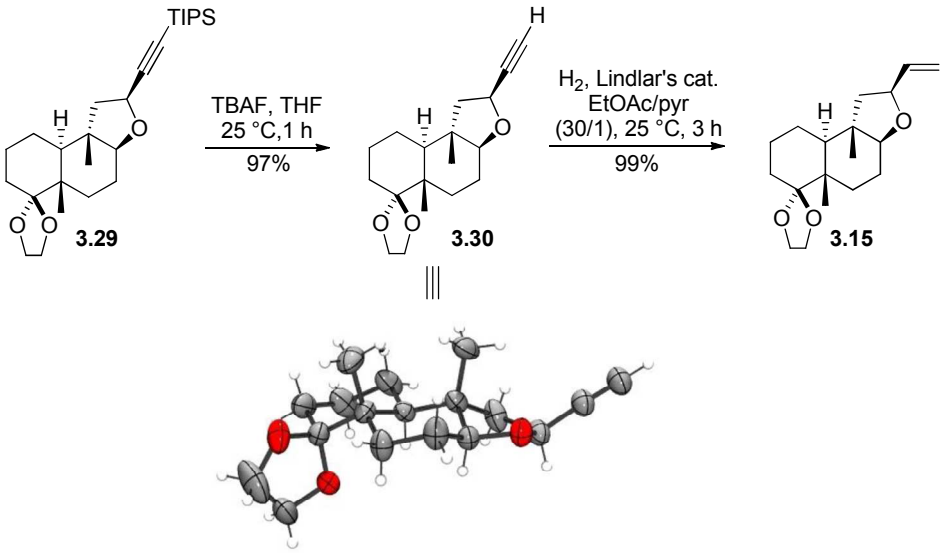


Figure 37: X-ray crystal structure of 3.30 and completion of intermediate 3.15.

After optimization of the reductive deoxygenation reaction the triisopropylsilyl group of **3.16d** was cleaved with tetrabutylammoniumflouride (TBAF) to provide **3.30** in 91% yield. An X-ray crystallographic analysis of alkyne **3.30** was used to determine the relative stereochemistry at the C12 position (**Figure 37**). The alkyne was then reduced with hydrogen in the presence of Lindlar's catalyst in 99% yield to provide the desired subglutinol A intermediate **3.15**.

3.5.3 Synthesis of the (12*R*) 2,3-*trans*-2,5-*trans*-tetrahydrofuran 3.17

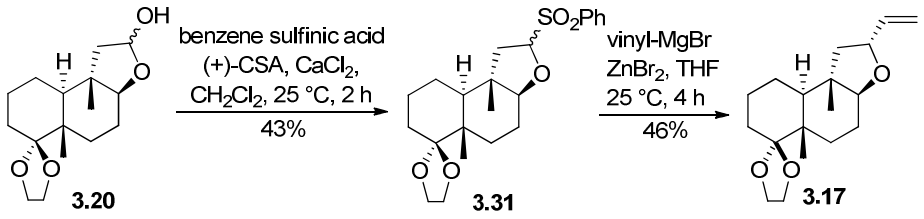


Figure 38: Reductive alkylation of sulfone to form subglutinol B intermediate.

The first attempt to construct the subglutinol B intermediate began from the lactol **3.20** which was substituted by benzene sulfinic acid to form the sulfone **3.31** as a mixture of diastereomers in 43% yield (**Figure 38**).[112] Nucleophilic addition by the organozinc reagent proceeded via the inside envelope attack model from the bottom face to selectively provide **3.17** as a single diastereomer.

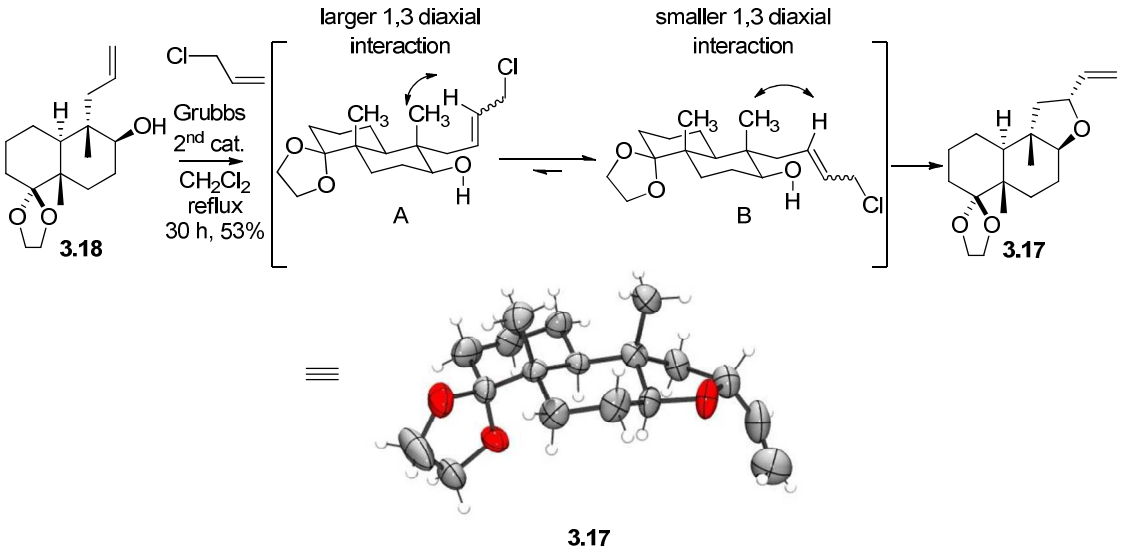


Figure 39: Tandem cross-metathesis/S_N2' reaction to form subglutinol B intermediate.

In an effort to improve the efficiency and significance of the subglutinol story, a new method was developed for the stereoselective formation of the 2,3-*trans*-2,5-*trans*-tetrahydropyran ring for the subglutinol B intermediate **3.17**. This method relied upon tandem cross-metathesis of the common intermediate **3.18** with allyl chloride followed by spontaneous S_N2' intramolecular cyclization to provide compound **3.17** as a single diastereomer.[113-116] The origin of stereoselectivity in this process can be rationalized from the conformational analysis shown in **Figure 39**. In conformation A, there is a larger 1,3-diaxial interaction between the vinyl hydrogen and the C17 up axial methyl group. In conformation B, the 1,3-diaxial interaction is lessened, leading to a more favorable conformation leading exclusively to the observed product **3.17**.

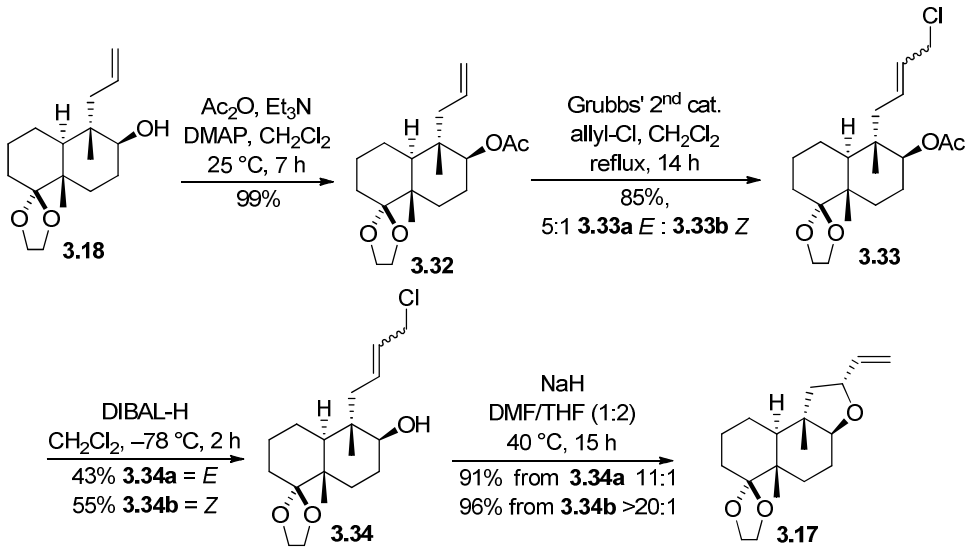


Figure 40: Effect of olefin geometry on diastereoselectivity.

In order to explore this reaction further, it was important to understand the role of the alkene geometry (**Figure 40**). The common intermediate **3.18** was acylated to

prevent spontaneous S_N2' cyclization during the cross-metathesis process. Both *E* and *Z* products were obtained from the cross-metathesis reaction with allyl chloride in the presence of Grubbs' second generation catalyst. These compounds were separated and then subjected independently to deacetylation with diisobutylaluminum hydride followed by addition of sodium hydride to promote the S_N2' cyclization process. The *E*-isomer **3.34** provided the desired tetrahydrofuran **3.17** in 91% with a diastereomeric ratio of 11:1 favoring the 2,5-*trans* configuration. The *Z*-isomer provided **3.17** in 96% yield in >20:1 diastereomeric ratio favoring the 2,5-*trans* configuration. This indicated that the largest unfavorable 1,3-diaxial interaction (**Figure 39,** conformation A) introduced by the *Z* olefin precludes the formation of the 2,5-*cis*-tetrahydrofuran, while the *E* olefin does so to a lesser extent with both olefins favoring **3.17** as the major product.

3.5.4 First-generation installation of α-pyrone group

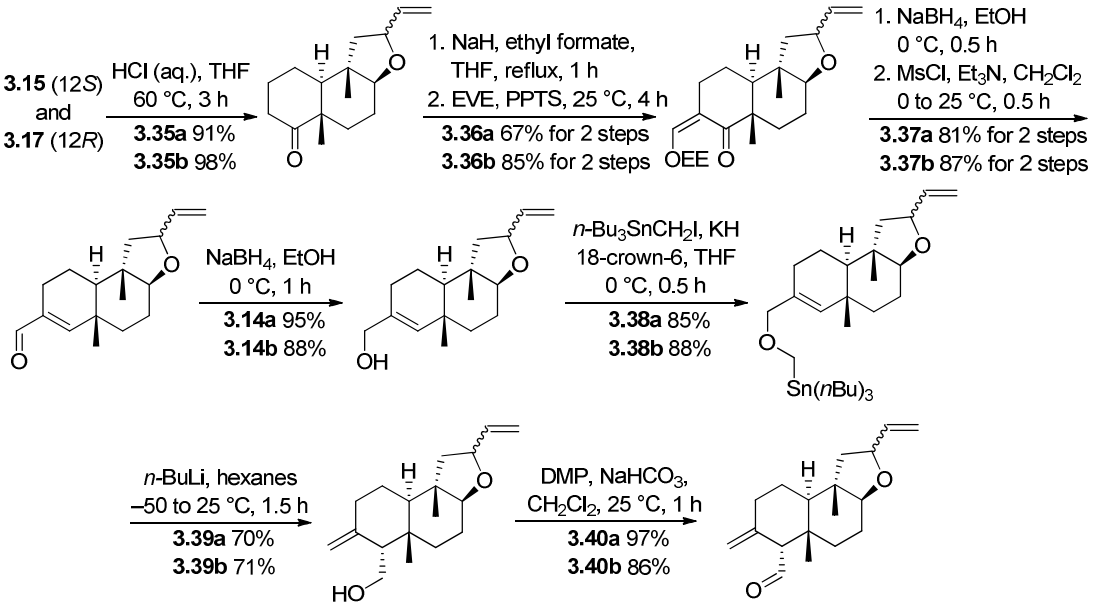


Figure 41: First generation *exo*-methylene installation.

After achieving the desired tetrahydropyran intermediates for subglutinols A and B (**3.15** and **3.17**, respectively) the next step was the installation of the *exo*-methylene group at the C3 position as well as the C4 homoallylic alcohol. Following Danishefsky and Katoh's lead, the ketal was hydrolyzed under acidic conditions followed by formylation and ethoxyethylether protection to provide **3.36a and 3.36b**.[105, 107] The α,β-unsaturated ketone was then reduced to the alcohol followed by mesylation, which resulted in spontaneous elimination to provide **3.37a** and **3.37b.** Sodium borohydride reduction followed by etherification led to the stannyl methyl ethers **3.38a** and **3.38b**. [2,3]-Wittig rearrangement proceeded in the expected fashion to provide homoallylic

alcohols **3.39a** and **3.39b**.[117] Dess–Martin oxidation provided the aldehydes **3.40a** and **3.40b**.

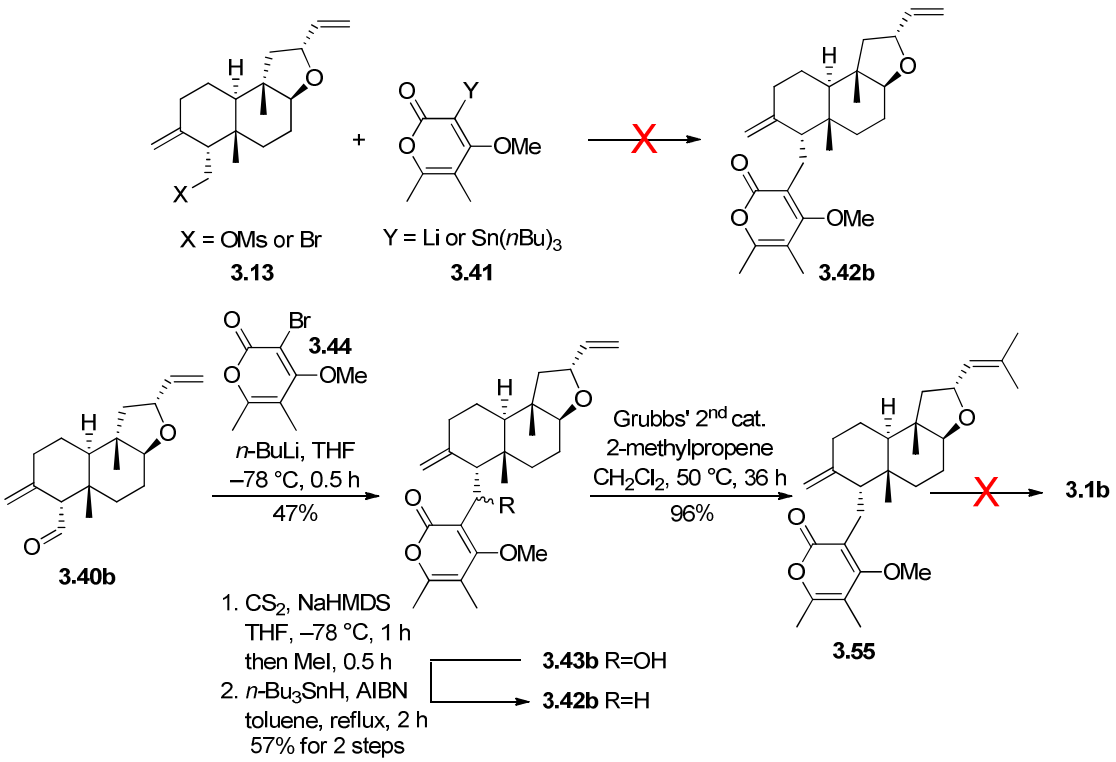


Figure 42: Failed attempts at coupling α-pyrone.

It was anticipated that subglutinols A and B could be achieved by conversion of the aldehydes **3.40a** and **3.40b** into an appropriate leaving group followed by direct coupling with the metallated α-pyrone **3.41** (**Figure 42**). These attempts at direct coupling resulted in no reaction. This is presumably due to the steric congestion provided by the decalin core surrounding the leaving group as noted by both Katoh and Danishefsky.[105, 107] Direct coupling of the lithiated α-pyrone **3.44** to **3.40b** proceeded in 47% yield to provide the diastereomeric alcohols **3.43b**. The alcohols were subjected to

xanthate formation followed by Barton–McCombie deoxygenation to form **3.42b**.[118] Cross-metathesis with 2-methylpropene gave the methyl protected subglutinol B, **3.55**. Unfortunately, all attempts to hydrolyze the pyrone methoxy group failed, leading us to apply Katoh's method of γ-pyrone installation.

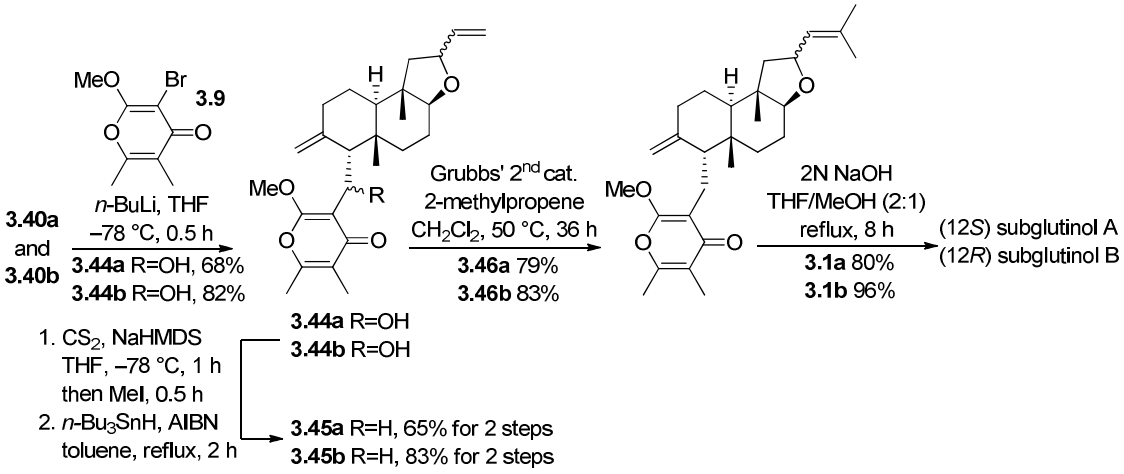


Figure 43: Installation of γ-pyrone from Katoh's method.

To circumvent the problems associated with hydrolyzing the protected α-pyrone functionality, the lithio-γ-pyrone **3.9** was added to aldehydes **3.40a** and **3.40b** to provide diastereomeric alcohols **3.44a** and **3.44b**, followed by Barton–McCombie protocol to achieve **3.45a** and **3.56b** in 65% and 83% yield for 2 steps, respectively (**Figure 43**). The isopropenyl functionality was installed through cross-metathesis and finally the methyl protecting group of the vinylogous ester was hydrolyzed and spontaneously underwent tautomerization to subglutinols A and B (**3.1a** and **3.1b**). The synthetic subglutinols A

and B were identical in all ways to the isolated natural products, establishing the absolute stereochemistries as 12*S* and 12*R* for subglutinols A and B respectively.

3.5.5 Second-generation installation of *α*-pyrone group

The next task was to improve the efficiency of the pyrone installation to provide better access to analogues for biological study. Katoh and Danishefsky both utilized sigmatropic rearrangements to install the C3 *exo*-methylene and the appropriate functionality at the sterically congested C4 position in preparation for the α- or γ-pyrone appendage. Our next approach was through a Cu^{I}-mediated intramolecular S_N2' pathway (**Table 5**).[119-121]

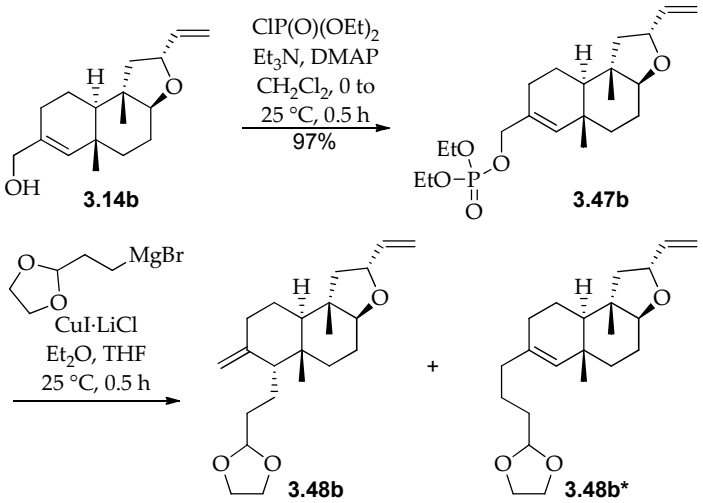


Table 5: CuI-mediated intermolecular SN2′ alkylation of phosphate 28b with [2-(1,3-dioxolan-2-yl)ethyl]magnesium bromide.

Entry	Solvent	Temperature °C	%Yield[a]	Ratio of **3.48b/3.48b*** [b]
1	THF	–30	89	1:3
2	THF	0	100	1:1
3	THF	25	82	2:1
4	Et_2O/ THF 1:1	25	91	3:1
5	Et_2O/ THF 3:1	25	95	5:1
6	Et_2O/ THF 3:1	50	ND[c]	1:1

[a] Combined yield of isolated **3.48b** and **3.48b***. [b] Determined by integration of *exo*-methylene and vinyl protons in ^{1}H NMR spectrum of the crude product. [c] Not determined.

Allylic alcohol **3.14b** was converted to the phosphate **3.47b** by *O*-alkylation with $ClP(O)(OEt)_2$ under standard conditions in good yield. **3.47b** was then subjected to varying conditions of Cu^I-mediated alkylation to optimize S_N2' yield. At low temperature (–30 °C) in THF, the major product was the S_N2 adduct **3.48b***. Increasing the temperature under these conditions improved the chemoselectivity up to 3:1 favoring the S_N2' product at 25 °C. A co-solvent system of Et_2O and THF was then tested to determine the solvent effect on chemoselectivity. A 3:1 mixture of Et_2O/THF at 25 °C

provided the best ratio of S_N2'/S_N2 (5:1) in 95% yield. The ketal functionality also provided a functional handle to follow Danishefski's linear method for the pyrone installation.[105, 119-121]

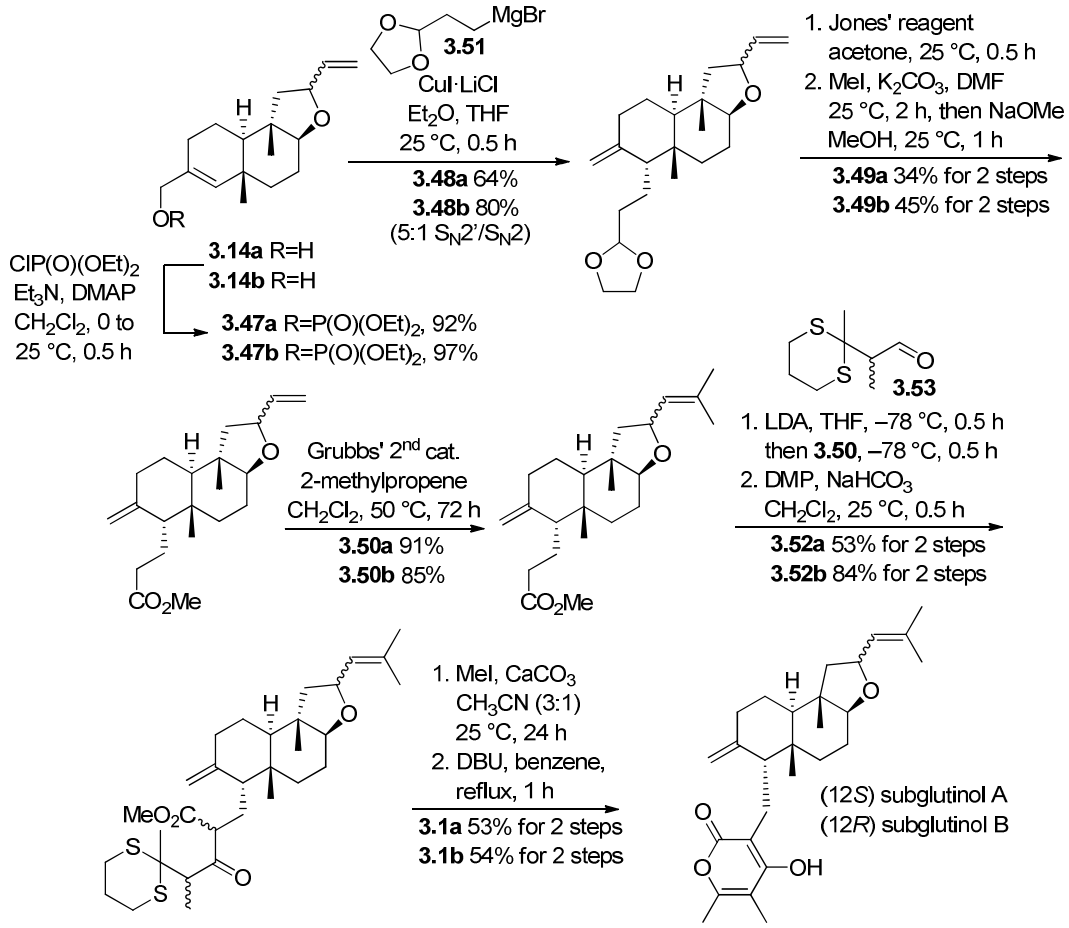


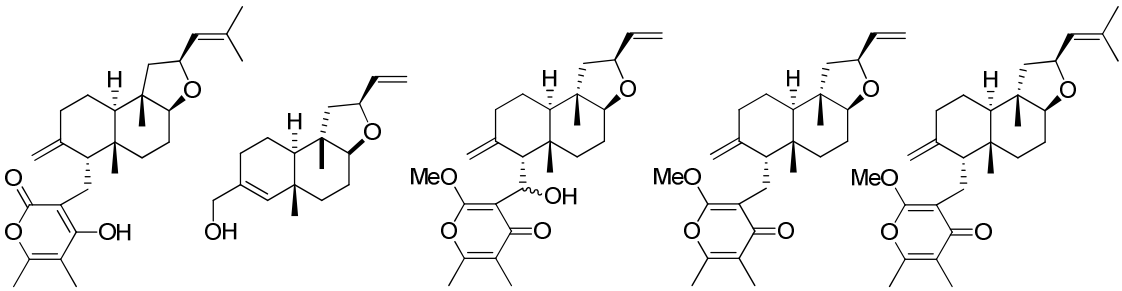
Figure 44: Second-generation synthesis of the α-pyrone group.

Allylic alcohols **3.14a** and **3.14b** were converted into the phosphates **3.47a** and **3.47b** (**Figure 44**). Cu^I-mediated intramolecular S_N2' addition of the Grignard reagent **3.51** converted the allylic phosphates to the ketals **3.48a** and **3.48b** both as a 5:1 mixture of S_N2'/S_N2 products. Deketalization followed by oxidation led to the methyl esters **3.49a**

and **3.49b**. Cross-metathesis with 2-methylpropene installed the isopropenyl group followed by enolate addition to aldehyde dithiane **3.53** then oxidation to provide **3.52a** and **3.52b**. Dithiane hydrolysis followed by DBU mediated cyclization provided subglutinols A and B.[105]

3.6 Biological activity of subglutinols A and B

3.6.1 Structure-activity relationships of subglutinols A and B in the mixed lymphocyte reaction assay



3.1a **3.14a** **3.44a** **3.45a** **3.46a**

Table 6: Structure-activity relationship in the mixed lymphocyte reaction.

Compound	IC_{50} [nM]
Subglutinol A **3.1a**	25
3.14a	Inactive
3.44a	Inactive
3.45a	838
3.46a	109
Cyclosporin A	89

Experimental conditions: Single cell suspension of lymph node cells (2×10^5 cells) from C57BL/6 mouse were plated with irradiated (3,500 rads) allogeneic splenocytes (5×10^5 cells) from BALB/c in 100 µl RPMI-1640 supplemented with 10% fetal calf serum (Hyclone, Logan, UT), 10–5 M β-mercaptoethanol (Sigma-Aldrich), 2 mM L-glutamine (Gibco-BRL), 10 mM HEPES (Gibco-BRL) and 1x antibiotic-antimycotic (Gibco-BRL) in 96 well tissue culture plates. Testing agents were added at the final concentrations of 0, 0.0016, 0.008, 0.04, 0.2, 1, 5 µM in triplicate wells. Cells were cultured at 37 °C for 4 days in a humidified 5% CO_2 incubator, and the number of viable cells in culture based on quantity of ATP, was measured by the CellTiter-Glo® Luminescent Cell Viability Assay kit (Promega, Madison, WI).

In collaboration with professor Dong-Sup Lee at the Immunology Cancer Research Institute College of Medicine, Seoul National University Seoul 110-799 (Korea), subglutinol A, as well as four other late stage intermediates were subjected to the mixed lymphocyte reaction assay to determine which functionalities were important to the observed biological effect (**Table 6**).[122] Subglutinol A proved to be more potent than cyclosporin A, while **3.46a** and **3.45a** provided lower, but significant levels of immunosuppressive activity. Compounds **3.14a** and **3.44a** were inactive. The conclusion from this experiment is that the pyrone functionality is crucial to the subglutinols immunosuppressive activity of the subglutinols. We hypothesized that the pyrone could possibly serve as an electrophile to amino acids located within the active site of the biological target to form covalent linkages.

3.6.2 SUPREX assay

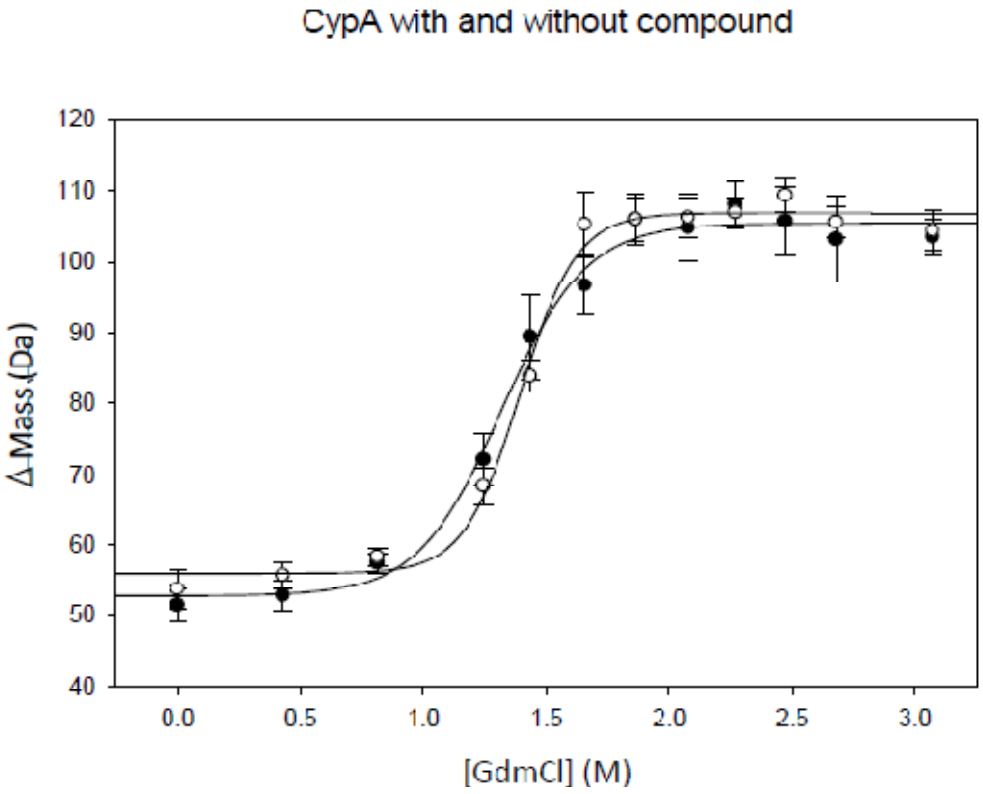


Figure 45: A SUPREX binding assay for cyclophilin. Human CypA was obtained through recombinant DNA method and incubated in deuterated SUPREX buffer. MALDI-TOF mass spectrometry was used to determine the change in mass of CypA and by analogy, its binding affinity to subglutinol A and DMSO.

In collaboration with the Fitzgerald group at Duke University, we set out to determine if subglutinol A **3.1a** shares the same molecular target as cyclosporin A. The SUPREX (Stability of Unpurified Proteins from Rates of H/D eXchange) technique has been previously used to determine the binding affinity of cyclosporin A to cyclophilin A (CypA) [111]. Subglutinol A was subjected to the SUPREX assay as well as 10% DMSO for the control. **Figure 45** indicates there was no significant binding of subglutinol A to

cyclophilin A. The absence of a significant shift (> 0.3 M from the control) at the $C^{1/2}_{SUPREX}$ midpoint indicates the dissociation constant is approximately 20 μM. Conversely, cyclosporin A has a dissociation constant with CypA of 1.5 to 3 M under similar assay conditions. These results indicate that subglutinol A is likely to have a different molecular target than Cyp A.

3.6.3 Patch-clamp assay

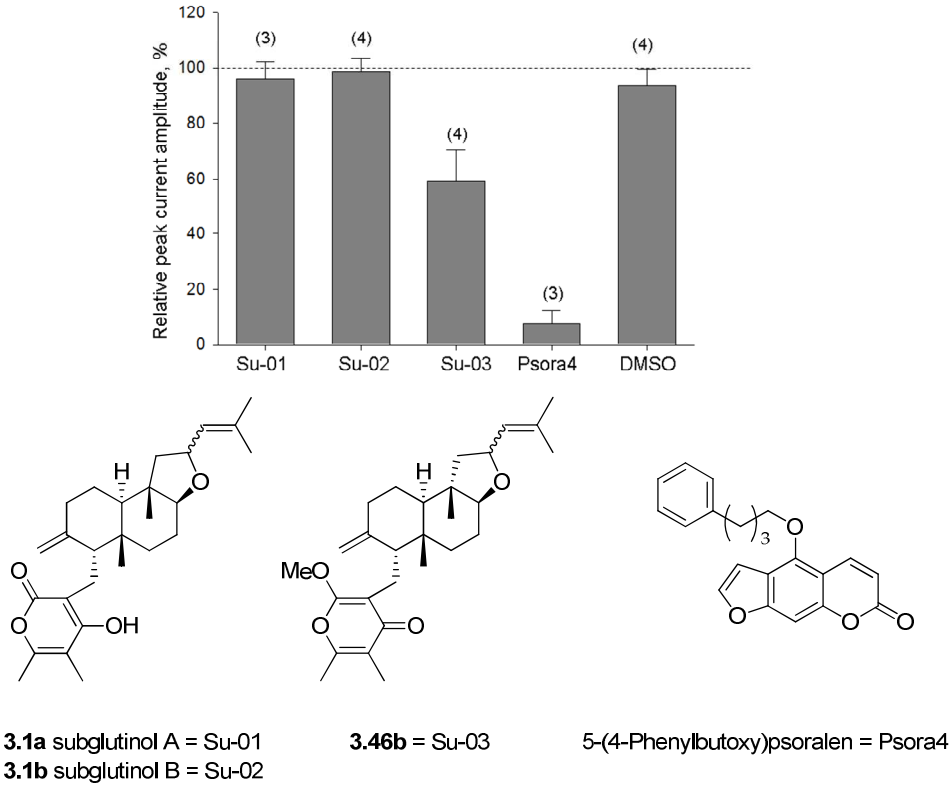


Figure 46: Patch-clamp assay for voltage-gated potassium channel. CHO cells, transfected with Kv1.3 cDNA were used in these experiments and all compounds were tested at 10 μM concentration in DMSO.

After excluding Cyp A as a possible target for the subglutinols, the next step was to determine if Kv1.3 (the molecular target of nalanthalide and candelalide) was the molecular target. In collaboration with professor Seok-Yong Lee in the Duke University biochemistry department, subglutinols A and B, as well as subglutinol B late stage intermediate **3.46b**, and 5-(4-phenylbutoxy) psoralen (Psora, a potent inhibitor of the Kv1.3 potassium channel) were screened in a patch clamp assay wherein depolarization of the cell membrane is measured as a function of current flow.[124]

Figure 46 shows subglutinols A and B had no effect on membrane depolarization, while subglutinol B-γ-pyrone **3.46b** had a marginal effect. Psora was used as a positive control and showed a significant inhibition of peak current amplitude, while DMSO, the negative control, had no effect, thus validating the experimental conditions. These data indicates that the molecular target is unlikely to be the Kv1.3 potassium channel.

3.6.4 Osteogenic activity of subglutinols A

The currently approved immunosuppressant drugs cyclosporin A and FK-506 possess many undesired off-target effects including a dose-dependent biphasic effect on osteoblast differentiation and bone density [125-127]. At low concentrations cyclosporin A and FK-506 elicit an anabolic effect on bone tissue, but at therapeutic concentrations they have a negative or catabolic effect on bone mass leading to osteopenia, osteoporosis, and increased incidences of bone fractures [128-129].

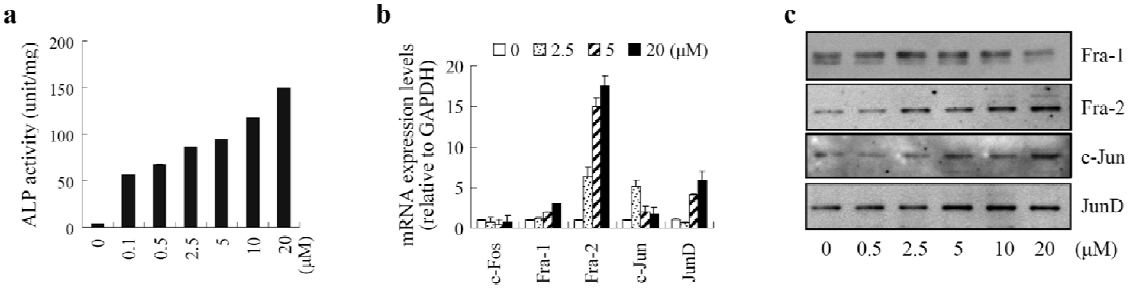


Figure 47: Effect of subglutinol A on a. ALP protein expression level/activity in murine C2C12 cells, b. mRNA expression level of AP-1 family transcription factors, and c. protein expression levels in the nucleus of AP-1 family transcription factors.

BMP-2 is a crucial regulator of differentiation and proliferation of pluripotent osteoblast precursors in a variety of human bone tissues [130]. To determine the effect subglutinol A **3.1a** has on BMP-2 induced differentiation, pluripotent murine mesenchymal C2C12 cells were treated with **3.1a** and examined for alkaline phosphatase (ALP), an early phase marker of osteoblast differentiation. **Figure 47a** shows a dose-dependent upregulation of ALP, indicating that subglutinol A promotes bone cell growth.

Fra-1, an AP-1 family transcription factor has been implicated in the osteoblast differentiation activity of cyclosporin A at low concentrations [131-132]. Because of this activity, we tested the effect of subglutinol A on mRNA expression of Fra-1 and other AP-1 family transcription factors: c-Fos, Fra-2, c-Jun and JunD (**Figure 47b**). With the notable exception of c-Fos, subglutinol A increased expression of these AP-1 family transcription factors on the transcriptional level. Furthermore, the western blot analysis

in **Figure 47c** shows an increase of Fra-1, Fra-2, c-Jun and JunD protein expression levels in the nucleus, implicating the AP-1 family of transcription factors as key regulators of the anabolic activity of subglutinol A.

3.7 Future work

One piece of information in the subglutinol story that remains elusive is the identification of their molecular target/mode of action. One possibility to identify the molecular target would be to develop an affinity probe by modifying the subglutinols by attaching a handle that could "fish out" the target from cell lysate. This could be achieved by attaching a linker to the olefin through cross-metathesis and then connecting it to a "tag". The subglutinol-construct could then be added to cell lysate followed by electrophoretic separation and visualization via the tag.

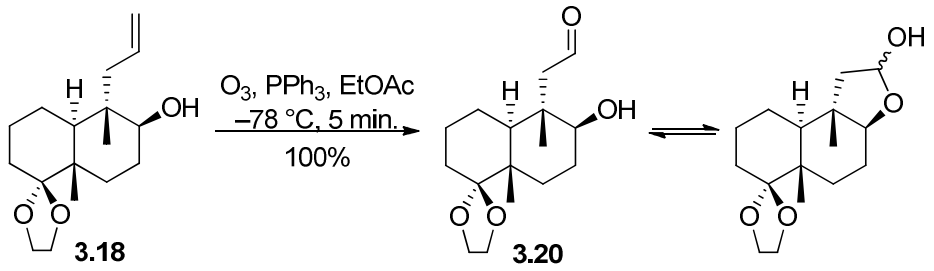
3.8 Conclusion

The stereoselective synthesis of subglutinols A and B was completed from the common intermediate **3.18**, as well as the establishment of the absolute stereochemistries based on comparison of $[\alpha]^{25}_{D}$ values of the synthetic subglutinols to the natural subglutinols. Subglutinol A was achieved through reductive deoxygenation of **3.16**, while subglutinol B was achieved through a tandem cross-metathesis/S_N2' intramolecular stereoselective cyclization process. It was also shown that the *exo*-methylene functionality as well as the stereocenter at the C4 position can be produced

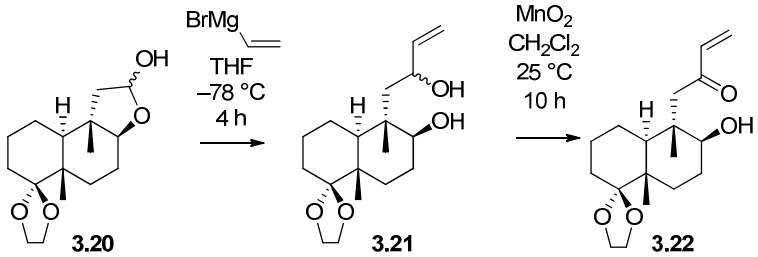
by an intermolecular Cu^{I}-mediated S_N2' alkylation reaction, leading to an efficient method for the installation of the α-pyrone subunit.

Preliminary structure-activity relationships were developed that implicate the pyrone functionality as the pharmacophore. The dose dependant positive anabolic osteogenic activity of subglutinol A and the notable lack of cytotoxicity showcase the great potential of this compound in therapeutic applications.

3.9 Experimental

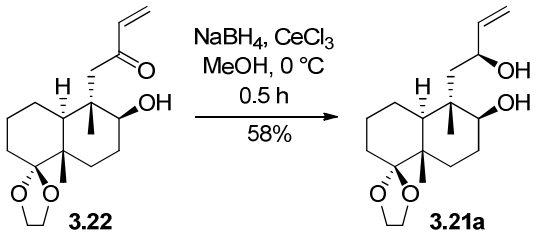


[Ozonolysis] alcohol **3.18** (143 mg, 0.512 mmol) in EtOAc (25 mL, 0.02 M) was cooled to –78 °C and treated with O_3 for 5 minutes without stirring (until the blue color persisted). Triphenylphosphene (402 mg, 1.54 mmol) was then added in one portion and the resulting mixture was stirred at 25 °C for 6 h. The solvents were removed *in vacuo* and the residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford lactol **3.20** as a colorless oil (145 mg, 100%): R_f 0.25 (hexanes/EtOAc, 3/1).

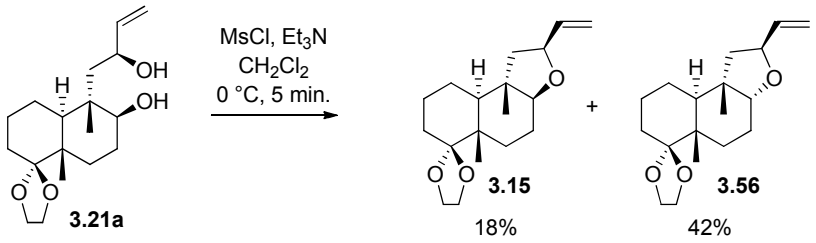


[Alkylation] To a cooled (–78 °C) solution of lactol **3.20** (264.0 mg, 0.93 mmol) in THF (10 mL, 0.09 M) was added vinylmagnesium bromide (9.3 mL, 1.0 M, 9.3 mmol) in a dropwise manner over 15 min. The solution was allowed to warm to 0 °C and stirred for 6.5 h. The reaction mixture was then cooled to –78 °C, quenched with saturated aqueous NH_4Cl solution, and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). 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, 2/1) to give a mixture of diastereomeric alcohols as colorless oils (173.0 mg, 59%); Rf 0.25 (hexanes/EtOAc, 6/1). **[MnO_2-Oxidation]** To a stirred solution of allylic alcohols **3.21** (102.0 mg, 0.327 mmol) in CH_2Cl_2 (20 mL, 0.02 M) was added MnO_2 (268 mg, 3.27 mmol) and allowed to stir for 10 h at 25 °C. The mixture was then filtered through a small pad of celite, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 3/1) to afford enone **3.22** as a colorless oil (49.0 mg, 48%): R_f 0.25 (hexanes/EtOAc, 7/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.41 (dd, *J* = 17.6, 10.4 Hz, 1 H), 6.23 (d, *J* = 17.2 Hz, 1 H), 5.76 (d, *J* = 10.8 Hz, 1 H), 3.77–3.94 (m, 4 H), 3.55–3.62 (m, 1 H), 2.84

(d, *J* = 14.0 Hz, 1 H), 2.61 (s, 1 H), 2.46 (d, *J* = 14.0 Hz, 1 H), 1.35–1.72 (m, 11 H), 1.07 (s, 3 H), 0.9 (s, 3 H).

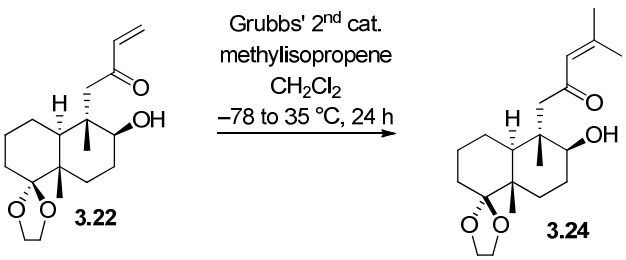


Allylic alcohol 3.21a [Leuche reduction] α, β-unsaturated ketone **3.22** (10.7 mg, 0.0345 mmol) was dissolved in 2 mL of MeOH (2 ml, 0.017M) then cooled to 0 °C. Dry $CeCl_3$ (10.2 mg, 1.2 mmol) was added followed by $NaBH_4$ (1.6 mg, 1.2 mmol) then stirred for 3 hours. The reaction was quenched with NH_4Cl then diluted with EtOAc. The layers were separated and the aqueous layer was extracted twice with EtOAc and washed once with brine then dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude oil was purified by column chromatography (silica gel, hexanes/EtOAc, 3:1) to afford the major diastereomer in 58% and the minor diastereomer in 19%. For the major diastereomer **3.21a**: ^1H NMR ($CDCl_3$, 400MHz): δ 5.88 (ddd, 6.8, 5.6, 4.4 Hz, 1H), 5.14 (dd, 54.4, 17.4 Hz, 2H), 4.26 (dd, 6.8, 3.6 Hz, 1H), 3.87 (m, 4H), 3.43 (m, 1H), 1.85 (d, 15.6 Hz, 1H), 1.45 (m, 27H), 1.10 (s, 3H), 0.89 (s, 3H).



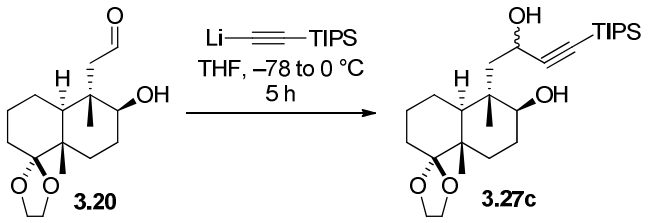
[Intramolecular alkoxylation] To a cooled (0 °C) solution of allylic alcohol **3.21a** (11 mg, 0.034 mmol) in CH_2Cl_2 (3 ml, 0.01M) was added Et_3N (143 μL, 0.102 mmol) followed by mesyl-Cl (3.2 μL, 0.041 mmol) and stirred for 5 minutes. Saturated aqueous $NaHCO_3$ was added and diluted with CH_2Cl_2 (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (x 2). The layers were pooled and dried over Na_2SO_4, then the solvents were removed *in vacuo* and the crude mixture was purified by silica gel chromatography (silica gel, hexanes/EtOAc, 5:1) to afford the desired 2,3-*trans*-2,5-*cis*-tetrahydrofuran **3.15** as a white solid in 18% yield. R_f 0.46 (hexanes/EtOAc, 7/1); $[\alpha]^{25.0}_D$ = –37.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1 H), 5.21 (d, *J* = 17.2 Hz, 1 H), 5.06 (d, *J* = 10.8 Hz, 1 H), 4.37–4.43 (m, 1 H), 3.88–3.96 (m, 3 H), 3.80–3.86 (m, 1 H), 3.15 (dd, *J* = 11.6, 3.2 Hz, 1 H), 1.47–1.91 (m, 13 H), 1.09 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 114.8, 113.2, 87.0, 78.3, 65.2, 64.6, 48.7, 46.4, 44.2, 43.8, 30.4, 29.8, 23.0, 22.8, 21.7, 18.3, 16.5; IR (neat) 2940, 2877, 1172, 1102, 1027, 952, 902 cm^{-1}; HRMS (FAB) found 291.1956 [calcd for C18H27O3 $(M–H)^+$ 291.1960].

[Reductive deoxygenation] To a cooled (–78 °C) solution of γ-hydroxy enone **3.22** (4.0 mg, 0.013 mmol) in CH_2Cl_2 (1 mL) was added dropwise $NaBH_3CN$ (0.39 mL, 0.1 M in CH_3CN, 0.039 mmol). After the resulting mixture was stirred at the same temperature for 10 min, $BF_3{\cdot}Et_2O$ (0.39 mL, 0.1 M in CH_2Cl_2, 0.039 mmol) was added. The reaction mixture was stirred for 30 min at the same temperature, quenched with saturated aqueous $NaHCO_3$ solution, and diluted with EtOAc (5 mL). 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, 15/1 to 8:1) to afford 2,3-*trans*-2,5-*cis*-tetrahydrofuran **3.23** (2.9 mg, 76%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77–3.97 (m, 5 H), 3.09 (dd, *J* = 11.6, 2.8 Hz, 1 H), 1.45–1.85 (m, 13 H), 1.31 (dd, *J* = 11.6, 4.0 Hz, 2 H), 1.09 (s, 3 H), 0.94 (dd, *J* = 7.6, 7.6 Hz, 3 H), 0.84 (s, 3 H).



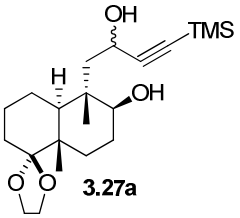
[Cross-metathesis] α,β-unsaturated ketone **3.22** (16 mg, 0.052 mmol) was dissolved in CH_2Cl_2 (2 mL, 0.026M) in a Schlenk flask. The flask was cooled to −78 °C then 2-methylisopropene was condensed into the flask until the volume increased by half. 5mol% of Grubbs' second generation catalyst was added. The flask was sealed and then warmed to 35 °C. After 2 hours 5mol% of Grubbs' second generation catalyst was added. After 12 hours 5mol% of Grubbs' second generation catalyst was added. After 10 hours the reaction was filtered through a plug of silica gel. The crude product mixture was then purified via flash chromatography where the mobile phase was 5:1 hexanes to EtOAc to provide **3.24** as a yellow oil in 23% yield (28% based on recovered starting material). ^{1}H NMR ($CDCl_3$, 400MHz): δ 6.09 (s, 1H), 3.86 (m, 4H), 3.59 (dd, 5.8, 4.6 Hz, 1H), 2.73 (d, 14 Hz, 1H), 2.34 (d, 14.4 Hz, 1H), 2.13 (s, 3H), 2.05 (s, 2H), 1.89 (s, 3H), 1.55 (m, 23H), 1.07 (s, 3H), 0.88 (s, 3H).

Representative example for propargylation:



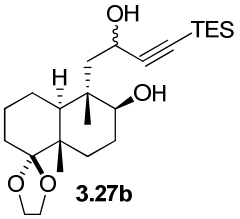
[Propargylation] To a cooled (–78 °C) solution of triisopropylsilyl acetylene (846.4 mg, 4.64 mmol) in THF (15 mL, 0.077 M) was added dropwise *n*-BuLi (2.90 mL, 1.6 M in hexanes, 4.64 mmol), and the resulting mixture was stirred at the same temperature for

10 min. To this solution was lactol **3.20** (327.4 mg, 1.16 mmol) added and the reaction mixture was allowed to slowly warm to 0 °C for 5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). 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, 2/1) to afford two diastereomeric TIPS-propargylic alcohols **3.27c** as a colorless oil (478.4 mg, 89%): **[For Less Polar Alcohol]** R_f 0.38 (hexanes/EtOAc, 2/1); $[\alpha]^{25.6}_D$ = +16.4 (*c* 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 8.8, 3.2 Hz, 1 H), 3.89–3.95 (m, 3 H), 3.80–3.86 (m, 1 H), 3.51–3.56 (m, 1 H), 3.28 (br s, 1 H), 2.08 (dd, *J* = 14.8, 3.2 Hz, 1 H), 1.31–1.72 (m, 11 H), 1.09 (s, 3 H), 1.05–1.07 (m, 21 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ113.2, 109.8, 84.1, 77.0, 65.1, 64.7, 59.0, 50.2, 46.7, 43.2, 41.5, 30.3, 28.3, 26.1, 22.9, 20.7, 18.5, 17.0, 12.5, 11.0. **[For More Polar Alcohol]** R_f 0.31 (hexanes/EtOAc, 2/1); $[\alpha]^{25.3}_D$ = +34.1 (*c* 0.23, CHCl3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, *J* = 8.8, 2.8 Hz, 1 H), 3.89–3.95 (m, 3 H), 3.80–3.84 (m, 1 H), 3.67 (dd, *J* = 10.0, 5.6 Hz, 1 H), 2.45 (br s, 1 H), 1.93 (dd, *J* = 15.6, 8.4 Hz, 1 H), 1.82 (dd, *J* = 15.6, 2.8 Hz, 1 H), 1.30–1.70 (m, 11 H), 1.08 (s, 3 H), 1.05–1.07 (m, 21 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 109.9, 84.3, 74.4, 65.2, 64.7, 59.2, 46.7, 44.3, 43.1, 41.6, 30.3, 28.7, 25.9, 22.8, 20.4, 18.5, 17.2, 16.3, 11.0; HRMS (FAB) found 463.3242 [calcd for $C_{27}H_{47}O_4Si$ $(M–H)^+$ 463.3244].



3.27a

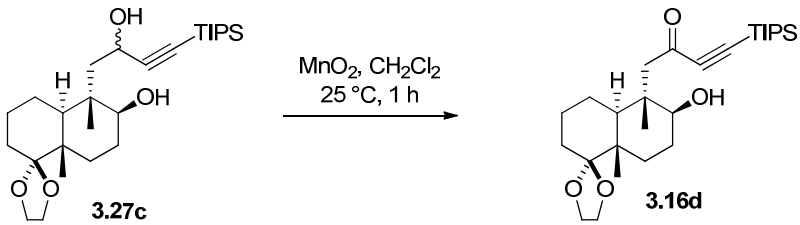
Two diastereomeric alcohols **3.27a** (203 mg, 88%): **[For Less Polar Alcohol]** R_f 0.25 hexanes/EtOAc, 15/1); $[\alpha]^{25.6}_D$ = +10.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 9.6, 2.4 Hz, 1 H), 3.78–3.93 (m, 4 H), 3.47 (dd, *J* = 10.8, 4.8 Hz, 1 H), 2.04 (dd, *J* = 12.0, 2.4 Hz, 1 H), 1.20–1.73 (m, 12 H), 1.08 (s, 3 H), 0.85 (s, 3 H), 0.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.5, 108.0, 88.4, 77.3, 65.4, 65.0, 59.4, 50.3, 47.0, 43.5, 41.8, 30.5, 28.7, 26.7, 23.2, 21.0, 17.3, 12.9, 0.1; IR (neat) 3330, 2951, 2875, 2158, 2019, 1451 cm^{-1}. **[For More Polar Alcohol]** R_f 0.25 (hexanes/EtOAc, 13/1); $[\alpha]^{25.3}_D$ = +18.7 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 8.8, 2.4 Hz, 1 H), 3.79–3.94 (m, 4H), 3.60–3.70 (m, 1 H), 1.91 (dd, *J* = 15.6, 8.8 Hz, 1 H), 1.78 (dd, *J* = 15.4, 2.6 Hz, 1 H), 1.25–1.70 (m, 11 H), 1.07 (s, 3 H), 0.88 (s, 3 H), 0.85 (s, 1 H), 0.16 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 88.6, 74.6, 65.2, 64.8, 59.7, 46.5, 44.4, 43.2, 41.6, 30.4, 30.3, 28.7, 26.4, 22.9, 20.5, 17.3, 16.4, 0.1; IR (neat) 3330, 2951,2875, 2158, 2019, 1451 cm^{-1}; HRMS (EI) found 381.2392 [calcd for $C_{21}H_{36}O_4Si$ $(M)^+$ 381.2383].



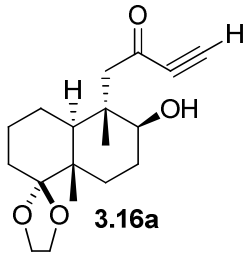
3.27b

Two diastereomeric alcohols **3.27b** (63.0 mg, 61%): **[For Less Polar Alcohol]** R_f 0.25 (hexanes/EtOAc, 10/1); $[\alpha]^{25.6}_D$ = +22.6 (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (dd, *J* = 9.2, 3.2 Hz, 1 H), 3.77–3.95 (m, 4 H), 3.49 (dd, *J* = 10.4, 4.4 Hz, 1 H), 2.05 (dd, *J* = 15.2, 2.8 Hz, 1 H), 1.22–1.73 (m, 12 H), 1.08 (s, 3 H), 0.97 (dd, *J* = 7.6, 7.6 Hz, 9 H), 0.85 (s, 3 H), 0.59 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 109.0, 85.7,76.9, 65.2, 64.8, 59.3, 50.1, 46.6, 43.3, 41.6, 30.3, 28.5, 26.4, 23.0, 20.8, 17.1, 12.9, 7.39, 4.23; IR (neat) 3322, 2934, 2873, 2168, 1456 cm^{-1}; **[For More Polar Alcohol]** R_f 0.25 (hexanes/EtOAc, 10/1); $[\alpha]^{25.3}_D$ = +5.11 (*c* 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, *J* = 8.4, 2.8 Hz, 1 H), 3.78–3.94 (m, 4 H), 3.67 (dd, *J* = 10.0, 5.2 Hz, 1 H), 1.91 (dd, *J* = 15.6, 8.4 Hz, 1 H), 1.79 (dd, *J* = 15.2, 2.4 Hz, 1 H), 1.28–1.72 (m, 11 H), 1.07 (s, 3 H), 0.97 (dd, *J* = 8.0, 8.0 Hz, 9 H), 0.87 (s, 3 H), 0.58 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 109.0, 85.8, 74.5, 65.2, 64.8, 59.5, 46.6, 44.3, 43.2, 41.7, 30.3, 28.7, 26.2, 22.9, 20.5, 17.3, 16.3, 7.40, 4.25; IR (neat) 3269, 2952, 2874, 2247, 1460 cm^{-1}; HRMS (EI) found 422.2851 [calcd for $C_{24}H_{42}O_4Si$ $(M)^+$ 422.2852].

Representative example of propargylic oxidation:



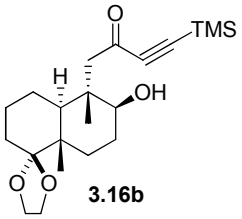
γ-hydroxy TIPSynone 3.16d [MnO_2 oxidation] To a solution of TIPSpropargylic alcohols **3.27c** (478.4 mg, 1.033 mmol) in CH_2Cl_2 (30 mL, 0.034 M) was added MnO_2 (179.9 mg, 2.066 mmol) at 25 °C, and the resulting mixture was stirred at the same temperature for 20 min. An addition of MnO_2 (89.8 mg, 1.033 mmol) was repeated twice every 20 min. 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, 4/1) to afford γ-hydroxy TIPSynone **3.16d** as a colorless oil (454.9 mg, 95%): R_f 0.39 (hexanes/EtOAc, 4/1); $[\alpha]^{25.6}_D$ = +18.0 (*c* 0.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.86–3.93 (m, 3 H), 3.75–3.83 (m, 2 H), 2.78 (d, *J* = 13.2 Hz, 1 H), 2.58 (d, *J* = 13.6 Hz, 1 H), 2.08 (d, *J* = 5.2 Hz, 1 H), 1.35–1.68 (m, 11 H), 1.07–1.12 (m, 21 H), 1.06 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 112.7, 106.1, 94.4, 74.0, 64.9, 64.5, 53.1, 45.1, 44.8, 43.0, 30.0, 28.1, 26.4, 22.5, 21.0, 18.2, 16.7, 15.3, 10.8; IR (neat) 3480, 2941, 2865, 1652 cm^{-1}; HRMS (FAB) found 461.3085 [calcd for $C_{27}H_{45}O_4Si$ $(M–H)^+$ 461.3087].



3.16a

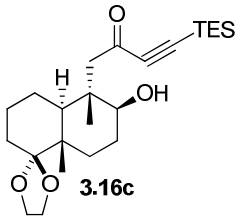
[Desilylation] To a solution of TES-propargylic alcohol **3.27b** (57.0 mg, 0.134 mmol) in THF (10.0 mL, 0.013 M) was added TBAF (0.27 mL, 1.0 M THF, 0.269 mmol), and the resulting mixture was stirred at 25 °C for 30 minutes. The reaction mixture was diluted

with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 5 mL). 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 two diastereomeric propargylic alcohols **3.16a** (32.0 mg, 78%): **[For Less Polar Alcohol]** R_f 0.25 (hexanes/EtOAc, 10/1); $[\alpha]^{25.6}_D$ = +5.3 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (dd, *J* = 9.6, 1.2 Hz, 1 H), 3.78–3.95 (m, 4 H), 3.48 (dd, *J* = 9.6, 3.8 Hz, 1 H), 2.46 (s, 1 H), 2.09 (d, *J* = 15.2 Hz, 1 H), 1.22–1.72 (m, 12 H), 1.08 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 86.0, 71.9, 65.2, 64.8, 58.7, 50.4, 47.0, 43.2, 41.5, 30.3, 28.4, 26.8, 23.0, 20.8, 17.0, 12.6; IR (neat) 3296, 2949, 2876, 2219, 1450 cm^{-1}; **[For More Polar Alcohol]** R_f 0.25 (hexanes/EtOAc, 10/1); $[\alpha]^{25.3}_D$ = +17.3 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 (d, *J* = 8.4 Hz, 1 H), 3.78–3.95 (m, 4 H), 3.69 (dd, *J* = 9.2, 6 Hz, 1 H), 2.46 (s, 1 H), 1.94 (dd, *J* = 15.6, 8.8 Hz, 1 H), 1.80 (d, *J* = 15.2 Hz, 1 H), 1.20–1.71 (m, 11 H), 1.07 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3, 85.8, 74.6, 72.2, 65.3, 64.8, 58.9, 46.4, 44.4, 43.2, 41.6, 30.3, 28.7, 26.4, 22.8, 20.5, 17.3, 16.4; IR (neat) 3296, 2949, 2876, 2219, 1450 cm^{-1}; HRMS (EI) found 308.1986 [calcd for $C_{18}H_{28}O_4$ (M)+ 308.1988].



3.16b

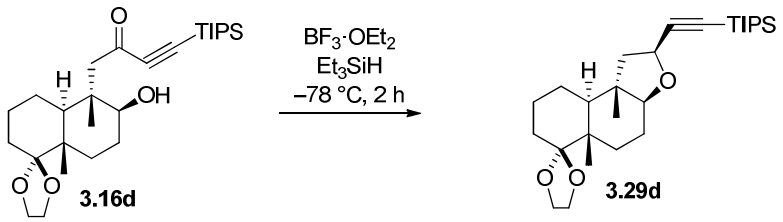
3.16b As a colorless oil (55.0 mg, 86%): R_f 0.25 (hexanes/EtOAc, 5/1); $[\alpha]^{25.6}_D$ = –2.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.85 (m, 4 H), 3.62–3.68 (m, 1 H), 2.65 (d, *J* = 13.2 Hz, 1 H), 2.60 (d, *J* = 13.2 Hz, 1 H), 2.08 (s, 1 H), 1.34–1.74 (m, 11 H), 1.06 (s, 3H), 0.92 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.0, 103.8, 97.6, 74.4, 65.2, 64.8, 53.1, 45.4, 44.8, 43.3, 30.3, 28.4, 26.5, 22.7, 21.2, 17.0, 15.5, –0.8; IR (neat) 2950, 2874, 1651, 1450 cm^{-1}; HRMS (EI) found 378.2228 [calcd for $C_{21}H_{34}O_4Si$ $(M)^+$ 378.2226].



3.16c

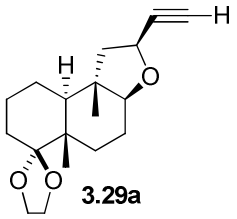
3.16c As a colorless oil (39.0 mg, 95%): R_f 0.25 (hexanes/EtOAc, 5/1); $[\alpha]^{25.6}_D$ = +4.3 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.77–3.92 (m, 4 H), 3.72 (dd, *J* = 10.4, 5.2 Hz, 1 H), 2.72 (d, *J* = 13.2 Hz, 1 H), 2.62 (d, *J* = 13.2 Hz, 1 H), 2.08 (s, 1 H), 1.35–1.73 (m, 11 H), 1.06 (s, 3 H), 1.01 (dd, *J* = 8.0, 8.0 Hz, 9 H), 0.92 (s, 3 H), 0.67 (dd, *J* = 15.6, 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.2, 112.9, 105.2, 95.8, 74.5, 65.2, 64.8, 53.4, 45.4, 45.0, 43.3, 30.2, 28.4, 26.5, 22.7, 21.2, 17.0, 15.5, 7.3, 3.8; IR (neat) 2954, 2875, 1651, 1452, 1215 cm^{-1}; HRMS (EI) found 420.2695 [calcd for $C_{24}H_{40}O_4Si$ $(M)^+$ 420.2696].

Representative procedure for formation of 2,3-*trans*-2,5-*cis*-tetrahydrofuran.



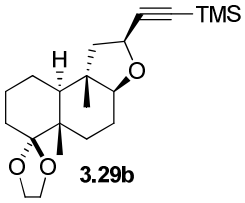
[reductive deoxygenation] To a stirred solution of γ-hydroxy TIPS-ynone **3.16d** (454.9 mg, 0.983 mL) in CH_2Cl_2 (40 mL, 0.025 M) was added Et_3SiH (0.47 mL, 2.95 mmol) at –78 °C. The resulting mixture was stirred at the same temperature for 20 min, and $BF_3{\cdot}Et_2O$ (0.37 mL, 2.95 mmol) was added. The reaction mixture was allowed to warm slowly to –20 °C for 2 h, and quenched with saturated aqueous $NaHCO_3$ solution, and the resulting mixture was stirred vigorously at 25 °C for 20 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). 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 2,3-*trans*-2,5-*cis*-tetrahydrofuran **3.29d** (398.4 mg, 91%) as a colorless oil. R_f 0.38 (hexanes/EtOAc, 10/1); $[\alpha]^{25.4}_D$ = –16.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (dd, *J* = 10.0, 3.2 Hz, 1 H), 3.89–3.96 (m, 3 H), 3.80–3.86 (m, 1 H), 3.06 (dd, *J* = 12.0, 3.6 Hz, 1 H), 1.70–1.90 (m, 3 H), 1.46–1.73 (m, 10 H), 1.09 (s, 3 H), 1.07–1.12 (m, 21 H), 1.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.1, 108.6, 87.4, 85.6, 66.2, 65.2, 64.6, 49.0, 48.5, 44.4,

43.7, 30.4, 29.7, 22.97, 22.90, 21.9, 18.5, 18.2, 15.6, 11.1; IR (neat) 2940, 2863 1462 cm^{-1} ; HRMS (FAB) found 445.3136 [calcd for $C_{27}H_{45}O_3Si$ $(M–H)^+$ 445.3138].



3.29a

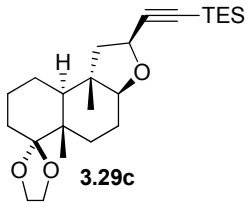
3.29a A colorless oil (15.0 mg, 29%) R_f 0.25 (hexanes/EtOAc, 10/1); $[\alpha]^{25.6}_D$ = –29.6 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.60 (dddd, *J* = 9.2, 4.4, 2.4, 1.2 Hz, 1 H), 3.80–3.97 (m, 5 H), 3.08 (dd, *J* = 12, 3.2 Hz, 1 H), 2.51 (dd, *J* = 2.4, 1.2 Hz, 1 H), 1.20–1.88 (m, 11 H), 1.09 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 87.7, 84.6, 73.3, 65.6, 65.3, 64.7, 48.6, 48.0, 44.5, 43.8, 30.4, 29.8, 23.0, 22.9, 21.9, 18.3, 15.7; IR (neat) 3305, 2941, 2876, 1451, 1101, 753 cm^{-1}; HRMS (EI) found 290.1874 [calcd for $C_{18}H_{26}O_4$ $(M)^+$ 290.1882].



3.29b

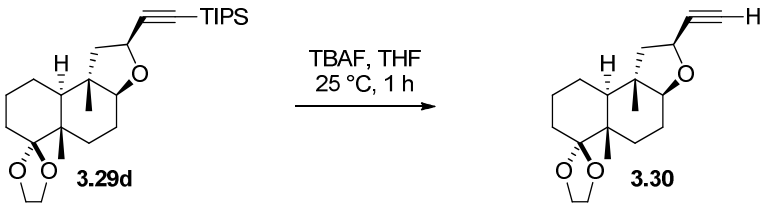
3.29b A colorless oil. R_f 0.20 (hexanes/EtOAc, 10/1); $[\alpha]^{25.4}_D$ = –25.1 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400MHz): δ 4.60 (dd, *J* = 4.4, 4.4 Hz, 1 H), 3.80–3.94 (m, 4 H), 3.06 (dd, 12.2, 2.8 Hz, 1 H), 1.23–1.88 (m, 11 H), 1.09 (s, 3 H), 0.98 (s, 3 H), 0.14 (s, 9 H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 113.2, 106.3, 89.7, 87.6, 66.2, 65.3, 64.7, 48.6, 48.4, 44.5, 43.8, 30.4, 29.8, 23.1, 23.0, 21.9, 18.3, 15.8, –0.2; IR (neat) 3010, 2950, 2878, 1452 cm^{-1}; HRMS (EI) found 362.2275 [calcd for $C_{21}H_{34}O_3Si$ $(M)^+$ 362.2277].



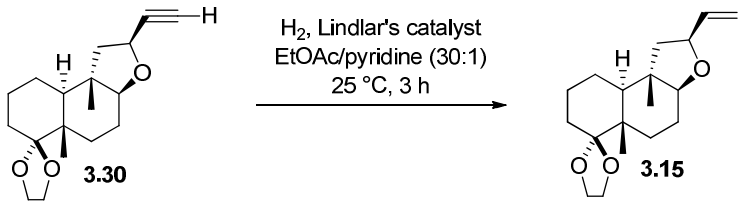
3.29c

3.29c A white solid (24.0 mg, 86%): R_f 0.25 (hexanes/EtOAc, 12/1); $[\alpha]^{25.6}_D$ = –28.6 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.61 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.78–3.95 (m, 4 H), 3.06 (dd, *J* = 12.0, 3.6 Hz, 1 H), 1.23–1.90 (m, 13 H), 1.09 (s, 3 H), 1.0 (s, 3 H), 0.97 (dd, *J* = 8.0, 8.0 Hz, 9 H), 0.58 (ddd, *J* = 8.0, 8.0, 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 107.7, 87.6, 87.0, 66.2, 65.3, 64.7, 48.8, 48.6, 44.5, 43.8, 30.4,29.8, 23.0, 22.9, 18.3, 15.7, 7.39, 4.27; IR (neat) 3342, 2952, 2875, 1458, 1114, 1017, 740 cm^{-1}.



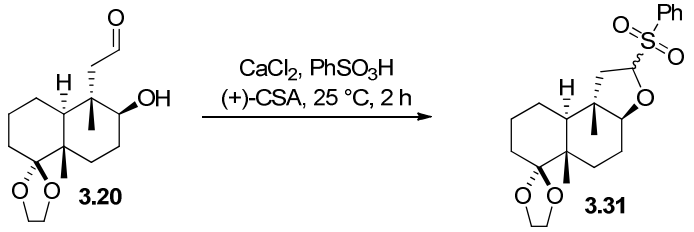
[Desilylation] To a stirred solution of alkyne **3.29d** (324.8 mg, 0.727 mmol) in THF (10 mL) was added TBAF (1.45 mL, 1.0 M in THF, 1.45 mmol). The resulting mixture was stirred for 1 h at 25 °C, quenched with saturated aqueous NH_4Cl solution, and diluted

with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 5 mL). 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, 7/1 to 4/1) to afford alkyne **3.30** as a white solid (204.2 mg, 97%): R_f 0.37 (hexanes/EtOAc, 7/1); R_f 0.25 (hexanes/EtOAc, 10/1) $[\alpha]^{25.0}_D$ = –34.8 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (ddd, *J* = 9.2, 4.4, 2.4 Hz, 1 H), 3.89–3.95 (m, 3 H), 3.79–3.86 (m, 1 H), 3.08 (dd, *J* = 12.0, 3.6 Hz, 1 H), 2.51 (d, *J* = 2.0 Hz, 1 H), 1.79–1.89 (m, 3 H), 1.45–1.74 (m, 10 H), 1.09 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.1, 87.6, 84.5, 73.3, 65.4, 65.2, 64.6, 48.4, 47.9, 44.4, 43.7, 30.3, 29.7, 22.92, 22.81, 21.8, 18.2, 15.7; IR (neat) 3305, 2941, 2876, 1451, 1101, 753 cm^{-1}; HRMS (EI) found 290.1874 [calcd for $C_{18}H_{26}O_3$ $(M)^+$ 290.1882].



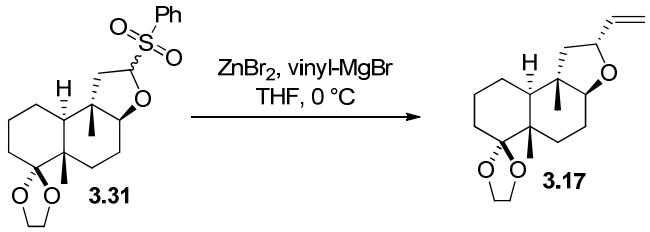
[Alkyne reduction] To a solution of alkyne **3.30** (204.2 mg, 0.703 mmol) in ethyl acetate/pyridine (30:1, total 31 mL, 0.023 M) was added Lindlar's catalyst (20.4 mg, 10 wt%) under H_2 atmosphere at 25 °C. The reaction mixture was stirred at the same temperature for 3 h. The reaction mixture was filtered through a pad of Celite, concentrated *in vacuo*, and purified by column chromatography (silica gel,

hexanes/EtOAc, 7/1) to give alkene **3.15** (204.2 mg, 99%) as a white solid: R_f 0.46 (hexanes/EtOAc, 7/1); $[\alpha]^{25.0}_D$ = –37.2 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.2, 10.4, 7.2 Hz, 1 H), 5.21 (d, *J* = 17.2 Hz, 1 H), 5.06 (d, *J* = 10.8 Hz, 1 H), 4.37–4.43 (m, 1 H), 3.88–3.96 (m, 3 H), 3.80–3.86 (m, 1 H), 3.15 (dd, *J* = 11.6, 3.2 Hz, 1 H), 1.47–1.91 (m, 13 H), 1.09 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 114.8, 113.2, 87.0, 78.3, 65.2, 64.6, 48.7, 46.4, 44.2, 43.8, 30.4, 29.8, 23.0, 22.8, 21.7, 18.3, 16.5; IR (neat) 2940, 2877, 1172, 1102, 1027, 952, 902 cm^{-1}; HRMS (FAB) found 291.1956 [calcd for $C_{18}H_{27}O_3$ $(M–H)^+$ 291.1960].

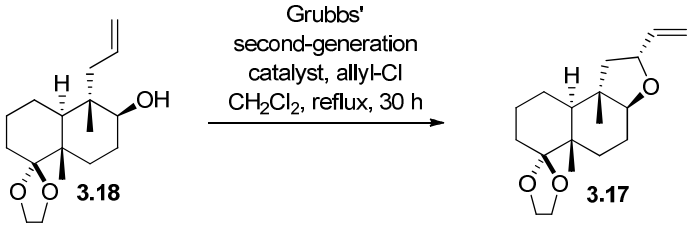


[Sulfonation] Compound **3.20** (58.5 mg, 0.206 mmol) was dissolved in 4 mL of CH_2Cl_2 followed by $CaCl_2$ (60 mg) as a drying agent then $PhSO_3H$ (59 mg, 0.413 mmol). A few crystals of camphor sulfonic acid was added. The solution was stirred for 2 hours then quenched with saturated sodium bicarbonate then extracted twice with EtOAc followed by a rinse with brine. The crude mixture was purified via flash chromatography where the mobile phase was 6:1 hexanes to EtOAc to give **3.31** in 43% a clear oil. ^1H NMR ($CDCl_3$, 400MHz): δ 5.97 (ddd, 6.4, 4Hz, 1H), 5.21 (dt, 17.2, 1.4Hz, 1H), 5.07 (dt, 10, 2Hz,

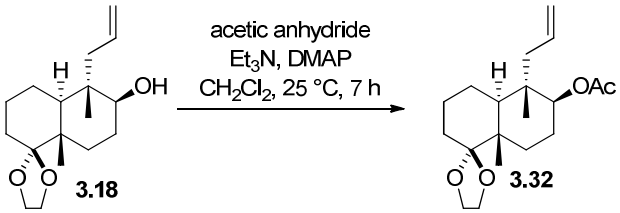
1H), 4.41 (m, 1H), 3.85 (m, 4H), 3.15 (dd, 8.4, 3.6Hz, 1H), 1.7 (m, 7H), 1.5 (m, 24), 1.25 (s, 3H), 1.09 (s, 3H), 0.83 (s, 3H).



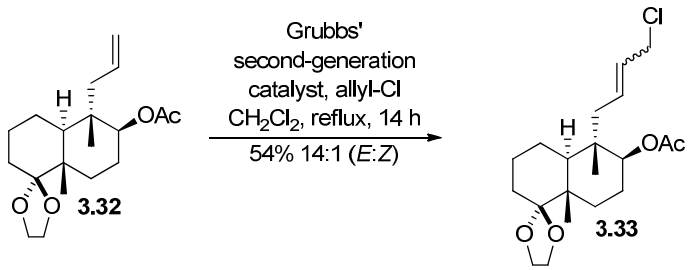
[oxocarbenium alkylation] Compound **3.31** (36mg, 0.088 mmol) was dissolved in THF followed by $ZnBr_2$ (24 mg, 0.11 mmol) then cooled to 0 °C. Vinyl MgBr (0.193 mL, 0.193 mmol) was added and warmed to room temperature then stirred for 2 hours. Added $ZnBr_2$ (24 mg, 0.11 mmol) then cooled to 0 °C. Vinyl MgBr (0.193 mL, 0.193 mmol) was added and warmed to room temperature and stirred for 2 hours. Cooled reaction to 0 °C then added 10 equivalents of $ZnBr_2$ followed by 20 equivalents of vinyl-MgBr. Quenched the reaction with NH_4Cl and extracted twice with EtOAc followed by one rinse with brine. The crude product was separated via flash chromatography where the mobile phase was 9:1 hexanes to EtOAc. The solvents were removed under reduced pressure to give **3.17** as a clear oil in 46% yield as a single compound.



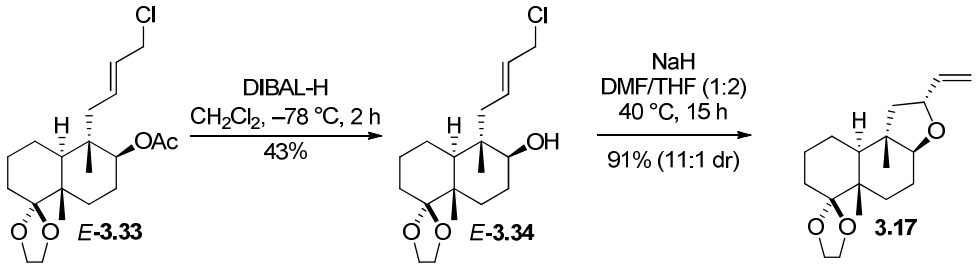
[Tandem cross-metathesis/S_N2' reaction] To a solution of olefin **3.18** (1.412 g, 5.04 mmol) in CH_2Cl_2 (50 mL, 0.10 M) were added allyl chloride (1.23 mL, 15.1 mmol) and Grubbs' second-generation catalyst (213.7 mg, 0.252 mmol) at 25 °C. The resulting mixture was refluxed for 1.5 h. An addition of allyl chloride (0.412 mL, 5.04 mmol) and Grubbs' second-generation catalyst (213.7 mg, 0.252 mmol) was repeated three times every 1.5 h. The reaction mixture was refluxed for further 24 h, cooled to 25 °C, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 10/1 to 6/1) to afford 2,3-*trans*-2,5-*trans*-tetrahydrofuran **3.17** as a white solid (781.3 mg, 53%, 76% based on recovered starting material): R_f 0.42 (hexanes/EtOAc, 7/1); $[\alpha]^{25.9}{}_D$ = –25.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1 H), 5.18 (dd, *J* = 16.8, 1.2 Hz, 1 H), 5.08 (dd, *J* = 10.0, 1.2 Hz, 1 H), 4.49 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 1 H), 3.89–3.96 (m, 3 H), 3.80–3.86 (m, 1 H), 3.21–3.26 (m, 1 H), 1.88 (dd, *J* = 11.6, 3.2 Hz, 1 H), 1.80–1.85 (m, 1 H), 1.44–1.69 (m, 9 H), 1.24–1.33 (m, 2 H), 1.08 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 113.9, 113.3, 85.9, 78.2, 65.4, 64.8, 48.5, 47.5, 45.2, 43.9, 30.5, 29.9, 23.2, 22.9, 22.1, 18.4, 15.5; IR (neat) 2934, 2872, 1455, 1380, 1174, 1102, 1027, 952, 902 cm^{-1}; HRMS (FAB) found 293.2111 [calcd for $C_{18}H_{29}O_3$ $(M+H)^+$ 293.2117].



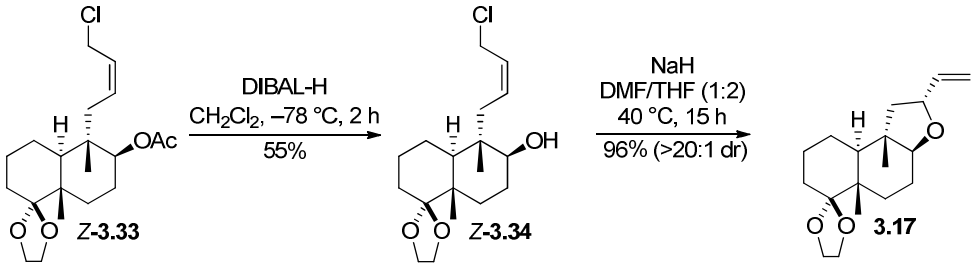
[Acetylation] Compound **3.18** (0.143 mmol), and a few small crystals of 4-dimethylaminopyridine were placed in a 50 mL round bottom flask then placed under vacuum for 15 minutes then refilled with N_2 (x3). Dry CH_2Cl_2 was then added via syringe along with 4 equivalents of triethylamine (0.573 mmol) followed by 2 equivalents of acetic anhydride (0.286 mmol). The reaction stirred at 23 °C for 5 hours then added 2 equivalents of triethylamine (0.286 mmol) followed by 1 equivalent of acetic anhydride (0.143 mmol). The reaction mixture stirred for one hour then an additional 2 equivalents of triethylamine followed by 1 equivalent of acetic anhydride was added. After stirring for 1 hour the reaction was quenched with ammonium chloride. The reaction mixture was washed with ammonium chloride twice followed by a wash of aqueous saturated sodium chloride and then dried over magnesium sulfate and filtered. The solvents were removed under reduced pressure. The crude product was then separated on a silica gel column where the mobile phase used was 20:1 hexanes to ethyl acetate. The solvents were removed under reduced pressure to yield **3.32** as a white crystalline solid in quantitative yield. ^{1}H NMR ($CDCl_3$, 400MHz): δ 5.78 (ddd, 9.6, 7.6, 1H), 5.06 (d, 10.4Hz, 1H), 4.93 (d, 16Hz, 1H), 4.68 (m, 1H), 3.85 (m, 4H), 2.04 (s, 3H), 1.98 (t, 7.6Hz, 2H), 1.50 (m, 15H), 1.08 (s, 3H), 0.90 (s, 3H).



[Cross-methasis] Compound **3.32** (66 mg, 0.205 mmol) was dissolved in 30 mL of CH_2Cl_2 with allyl chloride (78.6 mg, 1.03 mmol) and 5mol% of Grubbs' second generation catalyst. The solution was heated to reflux for one hour. 5mol% of Grubbs' second generation catalyst was added and stirred for one hour. 5mol% of Grubbs' second generation catalyst was added and stirred for 12 hours. The crude mixture was filtered through a small plug of silica gel. The crude product was purified via flash chromatography where the mobile phase was 20:1 hexanes to EtOAc to give **3.33** as a brown oil in 85% yield. ^{1}H NMR ($CDCl_3$, 400MHz): δ 5.74 (dt, 8, 7.2Hz, 1H), 5.53 (dt, 7.6, 7.2 Hz, 1H), 4.64 (m, 1H), 4.05 (d, 7Hz, 2H), 3.86 (m, 4H), 2.04 (s, 3H), 1.98 (t, 8Hz, 2H), 1.50 (m, 14H), 1.07 (s, 3H), 0.90 (s, 3H).

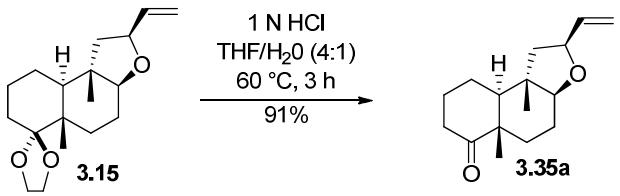


[Acetyl hydrolysis] To a cooled (–78 °C) solution of (*E*)-olefin **3.33** (66mg, 0.171 mmol) in CH_2Cl_2 (5 ml, 0.03 M) was added DIBAL-H (0.513 ml, 0.513 mmol, 1 M in CH_2Cl_2) and stirred at the same temperature for 2 hours. The reaction was quenched by addition of saturated aqueous NH_4Cl (1 ml) and warmed to ambient temperature. The mixture was diluted with saturated aqueous potassium sodium tartrate (4 ml) then stirred vigorously for 5 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml, x 3).The combined layers were dried over Na_2SO_4 then the solvents were removed *in vacuo*. The crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 20:1) to give **3.34** (24 mg, 0.074 mmol) in 43% as a clear oil. **[Intramolecular S_N2' cyclization]** To (*E*)-olefin **3.34** (24 mg, 0.074 mmol) in DMF/THF (1:2, 0.024 M) at 0 °C was added NaH (14.8 mg, 0.37 mmol) then the mixture was heated to 40 °C for 15 hours. The mixture was cooled to 0 °C then quenched with addition of saturated aqueous $NaHCO_3$ (1 ml). The solution was diluted with EtOAc (10 ml) and H_2O (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (10 ml, x2). The combined organic layers were then washed with saturated aqueous brine solution and dried over Na_2SO_4. The solvents were removed *in vacuo* and the crude oil was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to provide **3.17** (mg, 0.067 mmol) in 91% (11:1 dr) as a clear oil.

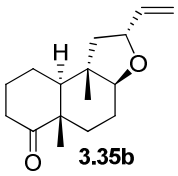


[Acetyl hydrolysis] To a cooled (–78 °C) solution of (*Z*)-olefin **3.33** (10.2 mg, 0.027 mmol) in CH_2Cl_2 (1 ml, 0.027 M) was added DIBAL-H (0.027 ml, 0.027 mmol, 1 M in CH_2Cl_2) and stirred at the same temperature for 2 hours. The reaction was quenched by addition of saturated aqueous NH_4Cl (0.25 ml) and warmed to ambient temperature. The mixture was diluted with saturated aqueous potassium sodium tartrate (1 ml) then stirred vigorously for 5 hours. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (1ml, x 3).The combined layers were dried over Na_2SO_4 then the solvents were removed *in vacuo*. The crude mixture was purified by column chromatography (silica gel, hexanes/EtOAc, 20:1) to give (*Z*)-**3.34** (5.1 mg, 0.015 mmol) in 55% as a clear oil. **[Intramolecular S_N2' cyclization]** To (*Z*)-olefin **3.34** (5.1 mg, 0.015 mmol) in DMF/THF (1:2, 0.024 M) at 0 °C was added NaH (3.0 mg, 0.075 mmol) then the mixture was heated to 40 °C for 15 hours. The mixture was cooled to 0 °C then quenched with addition of saturated aqueous $NaHCO_3$ (1 ml). The solution was diluted with EtOAc (3 ml) and H_2O (3 ml). The layers were separated and the aqueous layer was extracted with EtOAc (3 ml, x2). The combined organic layers were then washed with saturated aqueous brine solution and dried over Na_2SO_4. The solvents were removed *in vacuo* and

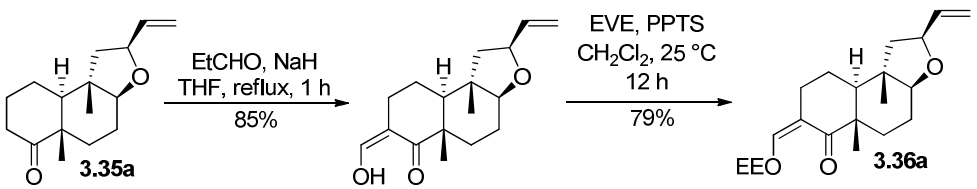
the crude oil was purified by column chromatography (silica gel, hexanes/EtOAc, 5:1) to provide **3.17** (4.8 mg, 0.014 mmol) in 96% (>20:1 dr) as a clear oil.



[Ketal hydrolysis] To a solution of **3.15** (191.3 mg, 0.654 mmol) in THF/H_2O (4:1, total 10 mL, 0.065M) was added 1 N HCl (0.5 mL) at 25 °C. The resulting mixture was stirred at 60 °C for 3 h, cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution, and diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 20 mL). 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, 7/1) to afford ketone **3.35a** as a colorless oil (147.3 mg, 91%): R_f 0.31 (hexanes/EtOAc, 7/1); $[\alpha]^{24.7}_D$ = –52.2 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.23 (ddd, *J* = 16.8, 1.2, 1.2 Hz, 1 H), 5.09 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 4.40–4.46 (m, 1 H), 3.08 (dd, *J* = 11.6, 3.2 Hz, 1 H), 2.57 (ddd, *J* = 13.6, 13.6, 6.8 Hz, 1 H), 2.21 (dd, *J* = 13.6, 4.4 Hz, 1 H), 2.04–2.10 (m, 1 H), 1.86–1.98 (m, 2 H), 1.52–1.78 (m, 7 H), 1.30 (dd, *J* = 12.8, 2.8 Hz, 1 H), 1.19 (s, 3 H), 0.93 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.1, 139.6, 115.1, 86.5, 78.1, 52.9, 49.1, 46.0, 44.9, 37.3, 31.8, 26.3, 22.9, 21.5, 20.3, 16.8; IR (neat) 2940, 2870, 1700 cm^{-1}; HRMS (EI) found 248.1779 [calcd for $C_{16}H_{24}O_2$ $(M)^+$ 248.1776].



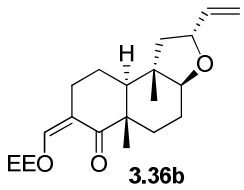
[For 3.35b] A colorless oil (583.1 mg, 98%): R_f 0.29 (hexanes/EtOAc, 7/1); $[\alpha]^{29}_D$ = –48.2 (*c* 1.01, $CHCl_3$); $[\alpha]^{25.9}_D$ = –25.9 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1 H), 5.20 (ddd, *J* = 16.8, 1.2. 1.2 Hz, 1 H), 5.06 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 4.52 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 1 H), 3.17 (dd, *J* = 12.4, 3.6 Hz, 1 H), 2.58 (ddd, *J* = 14.0, 14.0, 7.2 Hz, 1 H), 2.21 (dddd, *J* = 14.0, 8.8, 2.0, 2.0 Hz, 1 H), 2.08 (ddddd, *J* = 11.2, 6.4, 4.0, 2.0, 2.0 Hz, 1 H), 1.88 (dd, *J* = 11.6, 7.2 Hz, 1 H), 1.81–1.87 (m, 2 H), 1.66 (dddd, *J* = 14.0, 14.0, 14.0, 4.0 Hz, 1 H), 1.46–1.61 (m, 4 H), 1.23 (dd, *J* = 13.6, 2.8 Hz, 1 H), 1.20 (ddd, *J* = 11.2, 8.8, 0.8 Hz, 1 H), 1.13 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.0, 139.2, 114.1, 85.2, 77.9, 52.4, 48.9, 46.9, 45.6, 37.3, 31.7, 26.2, 22.8, 21.6, 20.2, 15.5; IR (neat) 2939, 2870, 1706, 1454, 1247, 1106, 924 cm^{-1}; HRMS (EI) found 248.1776 [calcd for $C_{16}H_{24}O_2$ $(M)^+$ 248.1776].



[Formylation] To a solution of ketone **3.35a** (427.3 mg, 1.72 mmol) in THF (30 mL, 057 M) were added ethylformate (1.39 mL, 17.2 mmol) and NaH (258.2 mg, 60% dispersion

in mineral oil, 5.16 mmol) at 0 °C. After stirred for 1 h under refluxing condition, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution, and diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). 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 enol as a colorless oil (404.2 mg, 85%). **[EE protection]** To a solution of enol ketone (404.2 mg, 1.46 mmol) in CH_2Cl_2 (20 mL, 0.073 M) were added ethyl vinyl ether (1.4 mL, 14.6 mmol) and PPTS (73.5 mg, 0.0.292 mmol) at 25 °C. After stirred at the same temperature for 12 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). 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, 4/1) to afford EE-protected enol **3.36a** as a colorless oil (401.9 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) **[For Two Diastereomers]** δ [7.41 (br dd, *J* = 2.0, 2.0 Hz for one diastereomer) and 7.40 (br dd, *J* = 2.0, 2.0 Hz for the other diastereomer), 1 H], 5.96 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.22 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.03–5.11 (m, 2 H), 4.40–4.46 (m, 1 H), [3.70 (dddd, *J* = 7.2, 7.2, 7.2, 0.8 Hz for one diastereomer) and 3.68 (dddd, *J* = 7.2, 7.2, 7.2, 0.8 Hz for the other diastereomer), 1 H], [3.49 (ddd, *J* = 7.2, 7.2, 7.2 Hz for one diastereomer) and 3.46 (ddd, *J* = 7.2, 7.2, 7.2 Hz for the other diastereomer), 1

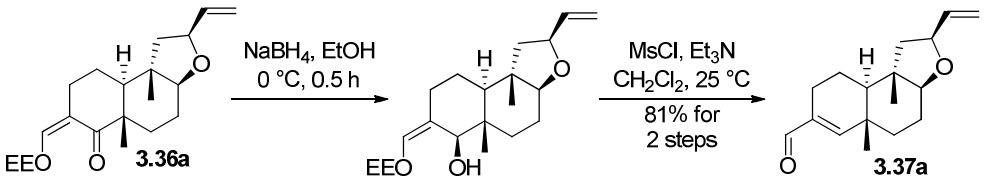
H], 3.11 (dd, *J* = 12.0, 3.6 Hz, 1 H), [2.70 (dddd, *J* = 16.8, 1.6, 1.6, 1.6 Hz for one diastereomer) and 2.69 (dddd, *J* = 17.2, 2.0, 2.0, 2.0 Hz for the other diastereomer), 1 H], 2.26–2.37 (m, 1 H), 1.99 (ddd, *J* = 13.6, 2.8, 2.8 Hz, 1 H), 1.81–1.92 (m, 2 H), 1.78 (dd, *J* = 10.4, 10.4 Hz, 1 H), 1.70 (dddd, *J* = 12.4, 12.4, 12.4, 2.8 Hz, 1 H), 1.54–1.62 (m, 3 H), 1.49 (ddd, *J* = 13.2, 3.2, 1.6 Hz, 1 H), [1.42 (d, *J* = 5.2 Hz for one diastereomer) and 1.41 (d, *J* = 5.2 Hz for the other diastereomer), 3 H], [1.20 (dd, *J* = 7.2, 7.2 Hz for one diastereomer) and 1.19 (dd, *J* = 7.2, 7.2 Hz for the other diastereomer), 3 H], 1.14 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) **[For Two Diastereomers]** δ 205.1, 151.37, 151.26, 139.6, 114.8, 113.58, 113.46, 103.4, 103.2, 86.5, 78.2, 63.39, 63.32, 48.1, 46.4, 46.0, 44.7, 32.9, 21.72, 21.58, 20.8, 20.3, 19.9, 16.7, 14.7.



3.36b

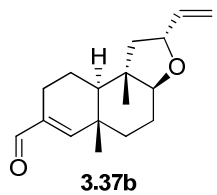
A colorless oil (679.2 mg, 94%): R_f 0.23 (hexanes/EtOAc, 7/1); $[\alpha]^{27.1}_D$ = –27.1 (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) **[For Two Diastereomers]** δ 7.40 (br s, 1 H), 5.88 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1 H), 5.19 (d, *J* = 16.8 Hz, 1 H), 5.02–5.09 (m, 2 H), 4.53 (ddd, *J* = 8.0, 6.9, 6.8 Hz, 1 H), 3.68 (dddd, *J* = 8.0, 7.2, 7.2, 7.2 Hz, 1 H), 3.47 (dddd, *J* = 8.8, 7.2, 7.2, 7.2 Hz, 1 H), 3.20 (dd, *J* = 11.2, 3.2 Hz, 1 H), 2.70 (dddd, *J* = 16.8, 1.6, 1.6, 1.6 Hz, 1 H), 2.69 (dd, *J* = 16.8, 7.6 Hz, 1 H), 2.25–2.36 (m, 1 H), 1.94–2.00 (m, 2 H), 1.80–1.91 (m, 2 H), 1.47–

1.64 (m, 3 H), 1.49 (d, J = 12.8 Hz, 1 H), [1.41 (d, J = 5.2 Hz for one diastereomer) and 1.40 (d, J = 5.2 Hz for the other diastereomer), 3 H], 1.29 (dd, J = 11.2, 9.2 Hz, 1 H), [1.194 (dd, J = 7.2, 7.2 Hz for one diastereomer) and 1.191 (dd, J = 7.2, 7.2 Hz for the other diastereomer), 3 H], 1.13 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) **[For Two Diastereomers]** δ 205.2, 151.46, 151.32, 139.3, 113.9, 113.61, 113.48, 103.49, 103.27, 85.3, 78.0, 63.46, 63.39, 47.8, 47.0, 46.4, 45.5, 32.9, 21.8, 20.9, 20.4, 19.9, 15.5, 14.8; HRMS (FAB) found 347.2221 [calcd for $C_{21}H_{31}O_4$ $(M–H)^+$ 347.2222].



[$NaBH_4$-Reduction] To a cooled (0 °C) solution of EE-protected enol ketone **3.36a** (401.9 mg, 1.15 mmol) in EtOH (10 mL, 0.12 M) was added $NaBH_4$ (87.3 mg, 2.31 mmol). After stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, diluted with EtOAc (100 mL), and the resulting mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give crude alcohol (352.4 mg). The residue was employed in the next step without further purification. **[Mesylation & Elimination]** To a cooled (0 °C) solution of the crude alcohol (352.4 mg)

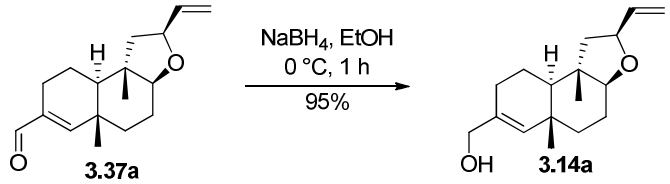
in CH_2Cl_2 (20 mL) were added Et_3N (0.42 mL, 3.02 mmol) and methanesulfonyl chloride (0.16 mL, 2.01 mmol). After stirred at 25 °C for 30 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). 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 enal **3.37a** as a colorless oil (242.7 mg, 81% for two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 6.49 (s, 1 H), 6.00 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.25 (dd, *J* = 16.8, 0.8 Hz, 1 H), 5.10 (d, *J* = 10.4 Hz, 1 H), 4.43–4.49 (m, 1 H), 3.16 (dd, *J* = 12.4, 3.6 Hz, 1 H), 2.41 (dd, *J* = 18.4, 6.8 Hz, 1 H), 2.16 (dddd, *J* = 18.8, 8.4, 8.4, 2.0 Hz, 1 H), 1.90–1.97 (m, 1 H), 1.58–1.89 (m, 6 H), 1.47 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1 H), 1.33 (dd, *J* = 12.8, 2.8 Hz, 1 H), 1.08 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 161.1, 139.9, 137.7, 115.2, 87.5, 78.6, 49.9, 46.1, 44.4, 37.0, 22.41, 22.23, 19.7, 16.5; IR (neat) 2925, 2851, 1682, 1266, 1116, 987, 919 cm^{-1}; HRMS (EI) found 260.1772 [calcd for $C_{17}H_{24}O_2$ $(M)^+$ 260.1776].



3.37b

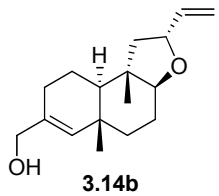
For 3.37b: A colorless oil (443.8 mg, 87% for two steps): R_f 0.27 (hexanes/EtOAc, 7/1); $[\alpha]^{27.0}_D$ = –18.2 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 6.45 (s, 1 H),

5.86 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1 H), 5.17 (ddd, *J* = 16.8, 1.2, 1.2 Hz, 1 H), 5.02 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 4.52 (ddd, *J* = 8.0, 6.8, 6.8 Hz, 1 H), 3.20 (dd, *J* = 12.8, 3.6 Hz, 1 H), 2.36 (ddd, *J* = 19.2, 6.4, 1.2 Hz, 1 H), 2.11 (ddd, *J* = 18.8, 10.0, 10.0 Hz, 1 H), 1.94 (dd, *J* = 11.6, 7.2 Hz, 1 H), 1.85–1.90 (m, 1 H), 1.59–1.76 (m, 4 H), 1.42 (ddd, *J* = 12.8, 12.8, 3.2 Hz, 1 H), 1.29 (dd, *J* = 12.4, 2.4 Hz, 1 H), 1.24 (dd, *J* = 11.2, 10.0 Hz, 1 H), 1.04 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 160.8, 139.3, 137.5, 114.1, 86.0, 78.1, 49.2, 46.8, 45.0, 36.7, 22.16, 22.12, 19.4, 15.1; IR (neat) 2935, 2871, 1682, 1457, 1376, 1115, 989 cm^{-1}; HRMS (EI) found 260.1778 [calcd for $C_{17}H_{24}O_2$ $(M)^+$ 260.1776].



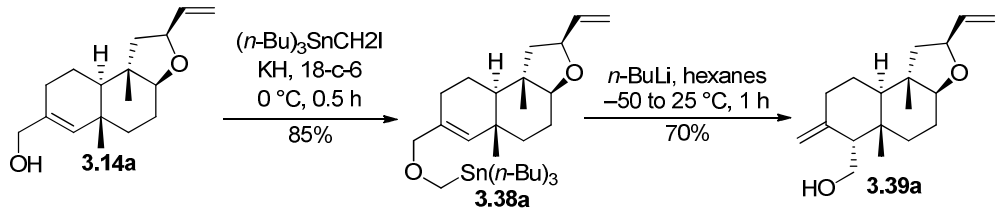
To a cooled (0 °C) solution of α,β-unsaturated aldehyde **3.37a** (242.7 mg, 0.932 mmol) in EtOH (10 mL, 0.093 M) was added $NaBH_4$ (70.4 mg, 1.86 mmol). After stirred at the same temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and diluted with EtOAc (40 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). 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 allylic alcohol **3.14a** as a colorless oil (231.4 mg, 95%): R_f 0.42 (hexanes/EtOAc, 2/1);

$[\alpha]^{24.3}_D$ = –18.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.37 (s, 1 H), 5.17 (d, *J* = 17.2 Hz, 1 H), 5.02 (d, *J* = 10.4 Hz, 1 H), 4.35–4.41 (m, 1 H), 3.85 (s, 2 H), 3.07 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.39 (br s, 1 H), 1.96–2.10 (m, 2 H), 1.79 (dddd, *J* = 12.0, 3.6, 3.2, 3.2 Hz, 1 H), 1.61–1.74 (m, 3 H), 1.56 (ddd, *J* = 13.2, 3.2, 3.2 Hz, 1 H), 1.47–1.53 (m, 2 H), 1.19–1.29 (m, 2 H), 0.91 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 135.0, 133.5, 114.9, 87.7, 78.4, 66.7, 50.1, 45.9, 44.0, 38.0, 35.1, 26.4, 23.2, 22.2, 20.3, 16.1; IR (neat) 3392, 2925, 2865, 1456, 1103, 1034, 988 cm^{-1}; HRMS (EI) found 262.1931 [calcd for $C_{17}H_{26}O_2$ $(M)^+$ 262.1933].



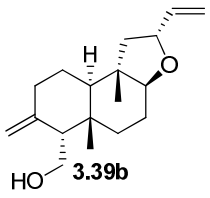
3.14b

For 3.**14b:** A colorless oil (379.9 mg, 88%): R_f 0.45 (hexanes/EtOAc, 2/1); $[\alpha]^{27.0}_D$ = –15.2 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 16.8, 10.0, 6.8, 1.2 Hz, 1 H), 5.37 (s, 1 H), 5.15 (dd, *J* = 17.2, 1.2 Hz, 1 H), 4.99 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.49 (ddd, *J* = 7.6, 7.6, 6.8 Hz, 1 H), 3.85 (s, 2 H), 3.17 (dd, *J* = 12.4, 2.8 Hz, 1 H), 2.30 (br s, 1 H), 1.98–2.10 (m, 2 H), 1.90 (dd, *J* = 11.2, 7.2 Hz, 1 H), 1.49–1.80 (m, 5 H), 1.17–1.29 (m, 2 H), 0.92 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.0, 133.6, 114.0, 86.4, 78.1, 66.7, 49.7, 46.9, 44.8, 37.9, 35.0, 26.4, 23.1, 22.3, 20.3, 15.0; IR (neat) 3400, 2926, 2868, 1451, 1378, 1100, 993 cm^{-1}; HRMS (EI) found 262.1935 [calcd for $C_{17}H_{26}O_2$ $(M)^+$ 262.1933].



[***O*-Alkylation]** To a cooled (0 °C) solution of allylic alcohol **3.14a** (231.4 mg, 0.882 mmol) in THF (10 mL, 0.088 M) were added KH (106.1 mg, 2.65 mmol) in THF (1.0 mL), 18-crown-6 (466.3 mg, 1.76 mmol), and $(n\text{-Bu})_3SnCH_2I$. After stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 20 mL). 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, 50/1) to afford **3.38a** as a colorless oil (423.1 mg, 85%). **[2,3]-Wittig Rearrangement]** To a cooled (–50 °C) solution of **3.38a** (108.4 mg, 0.192 mmol) in hexanes (5 mL, 0.022 M) was added *n*-BuLi (1.2 mL, 1.6 M in hexanes, 1.92 mmol). After stirred at the same temperature for 10 min, the reaction mixture was slowly allowed to warm to 25 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 × 10 mL). 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

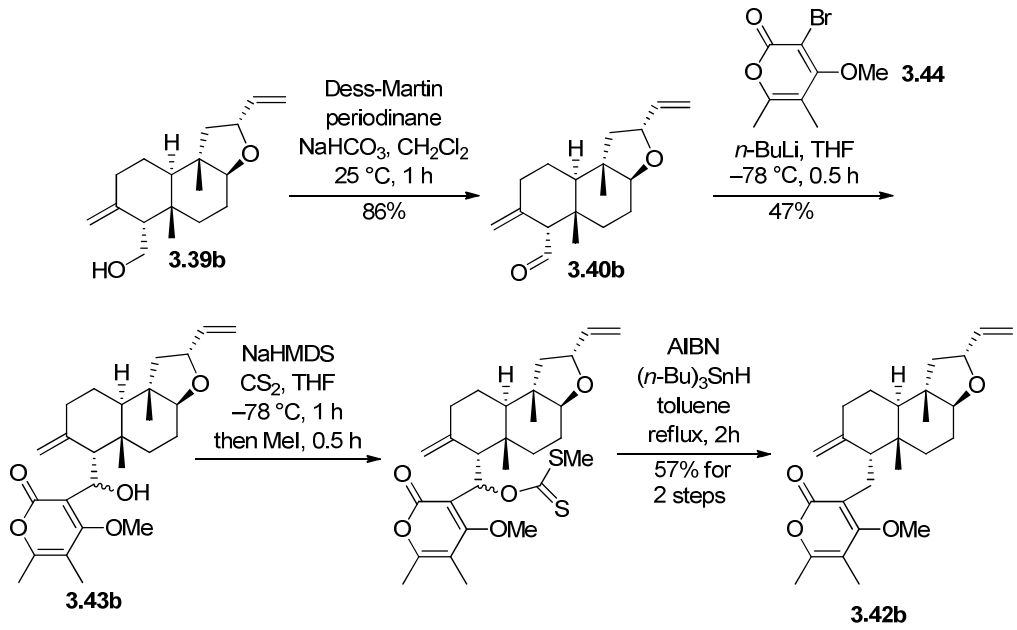
(silica gel, hexanes/EtOAc, 3/1) to afford homoallylic alcohol **3.39a** as a colorless oil (37.4 mg, 70%): R_f 0.44 (hexanes/EtOAc, 2/1); $[\alpha]^{26.7}_D$ = –43.7 (*c* 0.57, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.22 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.06 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 4.92 (s, 1 H), 4.76 (s, 1 H), 4.38–4.44 (m, 1 H), 3.77 (br s, 1 H), 3.60 (dd, *J* = 10.4, 10.4 Hz, 1 H), 3.06 (dd, *J* = 12.0, 2.8 Hz, 1 H), 2.28 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.14 (ddd, *J* = 13.2, 13.2, 2.8 Hz, 1 H), 1.95 (dd, *J* = 10.4, 4.8 Hz, 1 H), 1.83 (dddd, *J* = 12.0, 7.6, 3.2, 3.2 Hz 1 H), 1.66–1.77 (m, 3 H), 1.24–1.47 (m, 4 H), 0.98 (s, 3 H), 0.81 (s, 3 H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 139.8, 115.1, 113.5, 87.4, 78.3, 60.5, 59.1, 46.78, 46.66, 44.3, 38.0, 35.0, 30.8, 24.8, 24.5, 22.2, 17.0; IR (neat) 3416, 2926, 2868, 1445, 1037, 1022, 986, 923, 887 cm^{-1}; HRMS (EI) found 277.2090 [calcd for $C_{18}H_{28}O_2$ $(M)^+$ 276.2089].



3.39b

For 3.39b: A colorless oil (42.7 mg, 71%): R_f 0.44 (hexanes/EtOAc, 2/1); $[\alpha]^{27.1}_D$ = –34.2 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 16.8, 10.4, 6.8 Hz, 1 H), 5.20 (dd, *J* = 16.6, 1.6 Hz, 1 H), 5.06 (dd, *J* = 10.4, 1.6 Hz, 1 H), 4.94 (s, 1 H), 4.78 (s, 1 H), 4.51 (ddd, *J* = 7.6, 6.8, 6.8 Hz, 1 H), 3.77 (ddd, *J* = 9.6, 9.6, 4.8 Hz, 1 H), 3.60 (dd, *J* = 10.4, 10.4 Hz, 1 H), 3.15 (dd, *J* = 11.6, 3.2 Hz, 1 H), 2.28 (dd, *J* = 14.0, 4.0 Hz, 1 H), 2.14 (ddd, *J* = 13.2, 13.2, 2.8

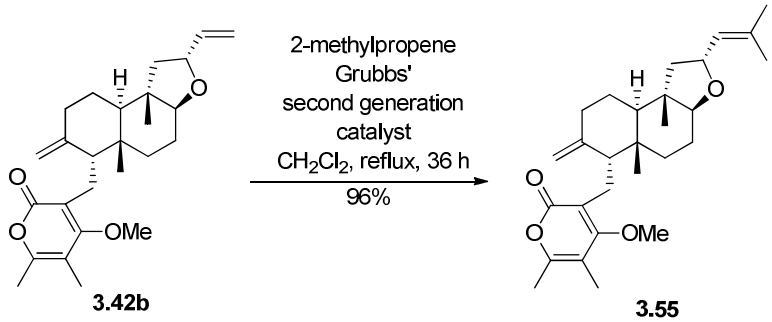
Hz, 1 H), 1.90–2.01 (m, 2 H), 1.83 (dddd, J = 12.0, 7.6, 3.2, 3.2 Hz, 1 H), 1.45–1.74 (m, 5 H), 1.20–1.28 (m, 2 H), 0.99 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 139.6, 114.1, 113.6, 86.1, 78.1, 60.5, 59.1, 47.8, 46.3, 45.0, 38.0, 35.0, 30.7, 24.7, 24.4, 22.3, 15.8; IR (neat) 3424, 2929, 2871, 1452, 1384, 1115, 1023, 954, 919, 889 cm^{-1}; HRMS (EI) found 276.2086 [calcd for $C_{18}H_{29}O_2$ $(M)^+$ 276.2089].



[Dess–Martin Oxidation] To a solution of homoallylic alcohol **3.39b** (31.3 mg, 0.113 mmol) in CH_2Cl_2 (5 mL, 0.023 M) were added $NaHCO_3$ (38.0 mg, 0.452 mmol) and Dess–Martin periodinane (96.1 mg, 0.223 mmol) at 25 °C. After stirred for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution, and the resulting mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 10 mL). 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 aldehyde **3.40b** as a colorless oil (29.1 mg, 86%). **[α-Pyrone Addition]** To a cooled (–78 °C) solution of bromo-α-pyrone **3.44** (197.8 mg, 0.849 mmol) in THF (8 mL, 0.11 M) was added dropwise *n*-BuLi (0.53 mL, 1.6 M in hexanes, 0.848 mmol), and the resulting mixture was stirred for 5 min at the same temperature. To this solution was added aldehyde **3.40b** (28.4 mg, 0.103 M) in THF. The reaction mixture was stirred at the same temperature for 30 min, quenched with saturated aqueous NH_4Cl solution, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). 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, 2/1) to afford two diastereomeric alcohols **3.43b** as colorless oils (20.7 mg, 47%). **[Methyl Xanthate Formation]** To a cooled (–78 °C) solution of alcohols **3.43b** (20.7 mg, 0.048 mmol) was added CS_2 (0.029 mL, 0.48 mmol) in THF (5 mL, 0.01 M), and the resulting mixture was stirred at the same temperature for 10 min. To this solution was added dropwise NaHMDS (0.48 mL, 0.2 M in THF, 0.08 mmol) at –78 °C. The resulting mixture was stirred for 1 h at the same temperature, and excess MeI was added in one portion. After stirred for 30 min at –78 °C, the reaction 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 (2 × 10 mL). The combined

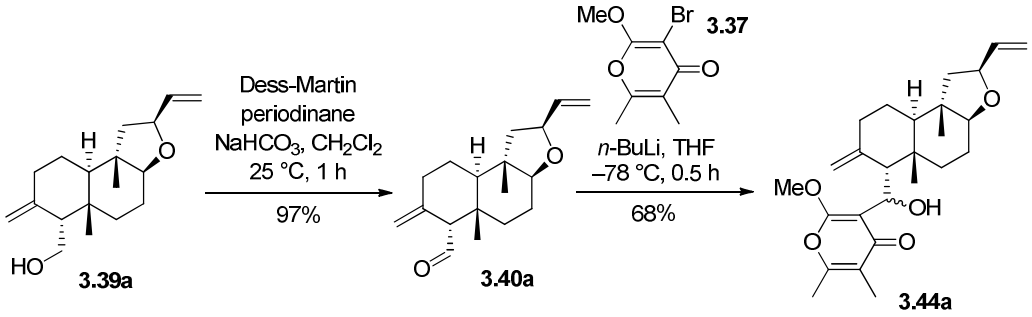
organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtrated by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford two diastereomeric xanthates as colorless oils (17.6 mg, 70%). **[Barton–McCombie Radical Deoxygenation]** To a solution of two diastereomeric xanthates in toluene (1 mL) were added AIBN (2.4 mg, 0.014 mmol) and (*n*-Bu)$_3$SnH (0.036 mL, 0.17 mmol). The resulting mixture was cooled to 0 °C, degassed by repeating to vacuum, and refilled with argon three times. The reaction mixture was refluxed for 2 h, cooled to 25 °C, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford **3.42b** as a colorless oil (11.4 mg, 81%): R_f 0.32 (hexanes/EtOAc, 2/1); $[\alpha]^{27.2}_D$ = –73.8 (*c* 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.6, 10.0, 6.4 Hz, 1 H), 5.22 (d, *J* = 17.2 Hz, 1 H), 5.07 (d, *J* = 10.4 Hz, 1 H), 4.54 (s, 1 H), 4.52 (ddd, *J* = 7.2, 7.2, 7.2 Hz, 1 H), 4.28 (s, 1 H), 3.72 (s, 3 H), 3.23 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.70 (dd, *J* = 12.8, 11.6 Hz, 1 H), 2.61 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.43 (dd, *J* = 13.2, 13.2 Hz, 1 H), 2.19 (s, 3 H), 2.12 (d, *J* = 16.4 Hz, 1 H), 2.08 (dd, *J* = 11.6, 4.0 Hz, 1 H), 1.95 (dd, *J* = 11.6, 6.8 Hz, 1 H), 1.80–1.91 (m, 2 H), 1.91 (s, 3 H), 1.57–1.72 (m, 2 H), 1.39–1.48 (m, 2 H), 1.32 (dd, *J* = 10.4, 9.6 Hz, 1 H), 0.96 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.5, 156.2, 147.8, 139.8, 114.04, 113.87, 110.7, 108.8, 86.3, 78.2, 60.3, 55.9, 47.8, 45.08, 44.96, 38.4, 34.8, 30.5, 24.9, 24.3, 22.50, 22.37, 17.4, 15.7, 10.6; IR (neat) 2924, 2854, 1708, 1645, 1559, 1456, 1100, 988 cm^{-1}; HRMS (FAB) found 413.2690 [calcd for $C_{26}H_{37}O_4$ $(M+H)^+$ 413.2692].



3.42b **3.55**

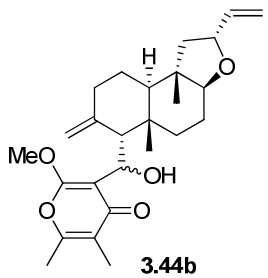
To a cooled (–78 °C) solution of alkene **3.42b** (11.4 mg, 0.028 mmol) in 2-methylpropene/CH_2Cl_2 (2:1, total 3 mL, 0.009 M) was added Grubbs' second-generation catalyst (2.3 mg, 0.0028 mmol). The resulting mixture was refluxed for 12 h. An addition of Grubbs' second-generation catalyst (2.3 mg, 0.0028 mmol) was repeated two times every 12 h. The reaction mixture was cooled to –78 °C and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford alkene **3.55** as a white foam (11.7 mg, 96%): R_f 0.32 (hexanes/EtOAc, 2/1); $[\alpha]^{27.6}_D$ = –67.6 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, *J* = 9.2 Hz, 1 H), 4.81 (ddd, *J* = 8.8, 8.8, 7.2 Hz, 1 H), 4.54 (s, 1 H), 4.27 (s, 1 H), 3.73 (s, 3 H), 3.24 (dd, *J* = 12.0, 2.8 Hz, 1 H), 2.70 (dd, *J* = 12.4, 11.6 Hz, 1 H), 2.61 (dd, *J* = 12.8, 4.0 Hz, 1 H), 2.43 (br dd, *J* = 13.6, 13.6 Hz, 1 H), 2.19 (s, 3 H), 2.12 (d, *J* = 15.6 Hz, 1 H), 2.08 (dd, *J* = 11.2, 3.6 Hz, 1 H), 1.84–1.95 (m, 3 H), 1.91 (s, 3 H), 1.73 (s, 3 H), 1.69 (s, 3 H), 1.54–1.77 (m, 3 H), 1.38–1.47 (m, 2 H), 1.25 (dd, *J* = 10.0, 10.0 Hz, 1 H), 0.96 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.5, 156.2, 147.8, 134.7, 126.9, 113.9, 110.6, 108.8, 86.0, 73.7, 60.3, 56.0, 48.5, 45.0, 38.4, 34.9, 30.6, 25.9, 25.0, 24.4, 22.6, 22.4, 18.0, 17.4, 15.7, 10.6; IR (neat) 2927, 2866, 1709,

1645, 1561, 1448, 1367, 1233, 1103 cm^{-1}; HRMS (FAB) found 441.3013 [calcd for $C_{28}H_{41}O_4$ $(M+H)^+$ 441.3005].



[Dess–Martin Oxidation] To a solution of homoallylic alcohol **3.39a** (31.3 mg, 0.113 mmol) in CH_2Cl_2 (5 mL, 0.023 M) were added $NaHCO_3$ (38.0 mg, 0.452 mmol) and Dess–Martin periodinane (96.1 mg, 0.223 mmol) at 25 °C. After stirred for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution, and the resulting mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 10 mL). 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 aldehyde **3.40a** as a colorless oil (29.1 mg, 97%). **[γ-Pyrone Addition]** To a cooled (–78 °C) solution of bromo-γ-pyrone **3.37** (134.2 mg, 0.580 mmol) in THF (5 mL) was added dropwise *n*-BuLi (0.36 mL, 1.6 M in hexanes, 0.576 mmol), and the resulting mixture was stirred for 5 min at the same temperature. To this solution was added aldehyde **3.40a** (29.1 mg, 0.106 mmol) in THF (2 mL, 0.053 M). The reaction mixture was

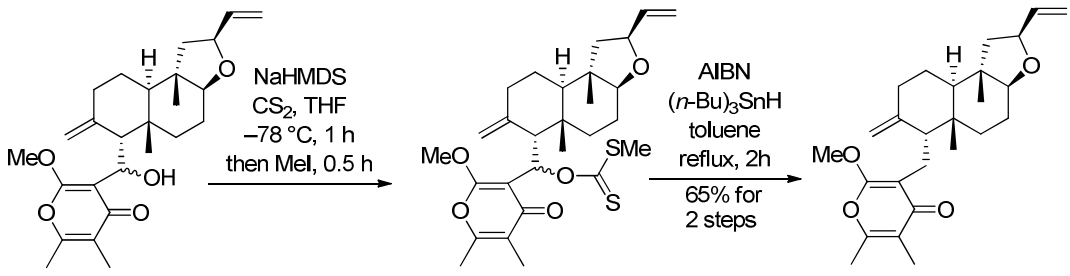
stirred at the same temperature for 30 min, quenched with saturated aqueous NH_4Cl solution, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford alcohols **3.44a** as colorless oils (32.7 mg, 68%): IR (neat) 3271, 2954, 2873, 1665, 1573, 1466, 1425, 1378, 1321, 1185, 1152, 1100, 1034, 990 cm^{-1}; HRMS (FAB) found 429.2640 [calcd for $C_{26}H_{37}O_5$ $(M+H)^+$ 429.2141].



3.44b

Two diastereomeric alcohols **3.44b** as a colorless oil (52.3 mg, 82%): **[For Less Polar Alcohol]** R_f 0.38 (hexanes/EtOAc, 1/2); $[\alpha]^{27.1}_D$ = –18.3 (*c* 0.64, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 16.8, 10.0, 6.8 Hz, 1 H), 5.19 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.00–5.09 (m, 3 H), 4.76 (s, 1 H), 4.49 (ddd, *J* = 7.6, 7.2, 7.2 Hz, 1 H), 4.46 (s, 1 H), 3.95 (s, 3 H), 3.30 (dd, *J* = 11.6, 2.8 Hz, 1 H), 2.50 (ddd, *J* = 13.2, 13.2, 6.0 Hz, 1 H), 2.31 (dd, *J* = 13.2, 3.6 Hz, 1 H), 2.26 (s, 3 H), 2.11 (dd, *J* = 12.8, 3.2 Hz, 1 H), 2.05 (d, *J* = 5.2 Hz, 1 H), 1.93 (dd, *J* = 11.2, 6.8 Hz, 1 H), 1.87 (s, 3 H), 1.53–1.81 (m, 4 H), 1.49 (br s, 1 H), 1.35 (dd, *J* = 10.4, 10.0 Hz, 1 H), 1.17–1.26 (m, 1 H), 0.91 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6,

160.5, 155.6, 147.3, 139.8, 119.5, 114.1, 112.6, 105.5, 86.0, 78.3, 66.9, 61.8, 55.6, 47.8, 45.3, 45.2, 38.7, 34.5, 33.7, 24.9, 24.5, 22.5, 16.9, 15.7, 9.6; HRMS (FAB) found 429.2646 [calcd for $C_{26}H_{37}O_5$ $(M+H)^+$ 429.2641]. **[For More Polar Alcohol]** R_f 0.31 (hexanes/EtOAc, 1/2); $[\alpha]^{27.7}_D$ = –47.7 (*c* 0.82, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (ddd, *J* = 16.8, 10.4, 6.8 Hz, 1 H), 5.21 (d, *J* = 16.8 Hz, 1 H), 5.05 (d, *J* = 10.0 Hz, 1 H), 4.97 (d, *J* = 8.4 Hz, 1 H), 4.51 (ddd, *J* = 8.0, 6.8, 6.8 Hz, 1 H), 4.45 (s, 2 H), 3.93 (s, 3 H), 3.33 (dd, *J* = 12.0, 2.8 Hz, 1 H), 2.54 (d, *J* = 8.4 Hz, 1 H), 2.24–2.30 (m, 1 H), 2.24 (s, 3 H), 1.92–2.06 (m, 3 H), 1.85 (s, 3 H), 1.80–1.88 (m, 2 H), 1.19–1.69 (m, 6 H), 0.96 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.6, 160.8, 155.8, 147.7, 139.9, 119.4, 113.9, 111.0, 105.4, 86.2, 78.0, 67.0, 63.9, 55.5, 48.2, 46.1, 45.1, 39.0, 35.9, 32.2, 25.2, 24.8, 22.5, 16.9, 15.7, 9.5; HRMS (FAB) found 429.2630 [calcd for $C_{26}H_{37}O_5$ $(M+H)^+$ 429.2641].

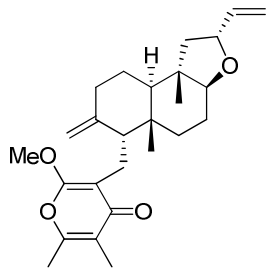


3.44a **3.45a**

[Methyl Xanthate Formation] To a cooled (–78 °C) solution of alcohols **3.44a** (32.7 mg, 0.0763 mmol) was added CS_2 (0.046 mL, 0.763 mmol) in THF (5 mL, 0.0153 M), and the resulting mixture was stirred at the same temperature for 10 min. To this solution was added NaHMDS (0.38 mL, 0.2 M in THF, 0.76 mmol) dropwise at –78 °C. The resulting

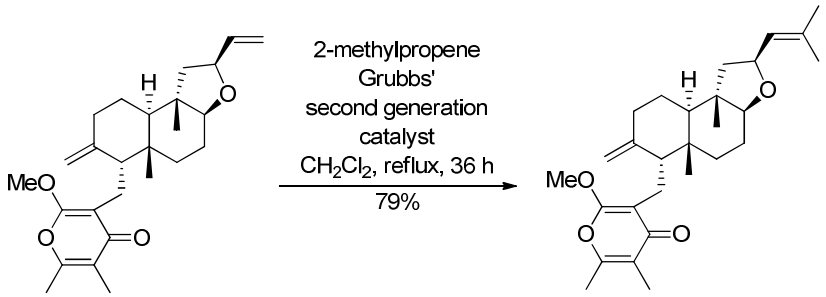
mixture was stirred for 1 h at the same temperature, and excess MeI was added in one portion. After stirred for 30 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was filtrated by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford the crude xanthates as colorless oils. **[Barton–McCombie Radical Deoxygenation]** To a solution of xanthates in toluene (1 mL) were added AIBN and (*n*-Bu)$_3$SnH. The resulting mixture was cooled to 0 °C, degassed, and refilled with argon three times. The reaction mixture was refluxed for 2 h, cooled to 25 °C, and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, hexanes/EtOAc, 2/1) to afford **3.45a** as a colorless oil (20.6 mg, 65% for two steps): R_f 0.32 (hexanes/EtOAc, 1/1); $[\alpha]^{25.2}_D$ = –60.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.22 (d, *J* = 17.2 Hz, 1 H), 5.07 (d, *J* = 10.4 Hz, 1 H), 4.51 (s, 1 H), 4.40–4. 45 (m, 1 H), 4.21 (s, 1 H), 3.85 (s, 3 H), 3.15 (dd, *J* = 12.4, 2.8 Hz, 1 H), 2.65 (dd, *J* = 12.8, 3.2 Hz, 1 H), 2.49 (dd, *J* = 12.4, 12.4 Hz, 1 H), 2.43 (br dd, *J* = 12.4, 12.4 Hz, 1 H), 2.24 (s, 3 H), 2.09 (br d, *J* = 13.2 Hz, 1 H), 1.85–1.97 (m, 3 H), 1.90 (s, 3 H), 1.79 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 2 H), 1.57–1.62 (m, 2 H), 1.38–1.47 (m, 2 H), 0.94 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 162.8, 154.9, 148.5, 140.1, 118.6, 115.0, 109.6,

103.1, 87.6, 78.4, 55.9, 55.3, 46.9, 45.2, 44.3, 38.5, 34.7, 30.5, 25.1, 24.4, 22.3, 20.0, 16.94, 16.89, 10.0; IR (neat) 2940, 2870, 1700, 1457, 1429, 1266, 1246, 1115, 974, 929 cm^{-1}.



3.45b

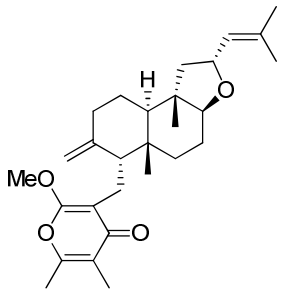
For 3.45b: A colorless oil (17.2 mg, 83% for two steps): R_f 0.39 (hexanes/EtOAc, 1/1); $[\alpha]^{24.0}_D$ = –54.6 (*c* 0.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 16.8, 10.0, 6.8 Hz, 1 H), 5.21 (d, *J* = 16.8 Hz, 1 H), 5.05 (d, *J* = 10.0 Hz, 1 H), 4.48–4.54 (m, 1 H), 4.52 (s, 1 H), 4.21 (s, 1 H), 3.85 (s, 3 H), 3.24 (dd, *J* = 12.4, 3.6 Hz, 1 H), 2.65 (dd, *J* = 12.4, 3.6 Hz, 1 H), 2.49 (dd, *J* = 12.0, 12.0 Hz, 1 H), 2.39–2.43 (m, 1 H), 2.24 (s, 3 H), 2.10 (d, *J* = 12.0 Hz, 1 H), 1.85–1.99 (m, 4 H), 1.90 (s, 3 H), 1.57–1.73 (m, 3 H), 1.25–1.45 (m, 3 H), 0.94 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 162.8, 154.9, 148.5, 139.9, 118.6, 114.0, 109.7, 103.1, 86.4, 78.2, 55.8, 55.3, 47.8, 45.1, 44.8, 38.3, 34.7, 30.5, 25.0, 24.3, 22.5, 20.0, 16.9, 15.6, 10.0; IR (neat) 2924, 2858, 1670, 1599, 1459, 1417, 1375, 1318, 1149, 1111, 988 cm^{-1}; HRMS (FAB) found 413.2691 [calcd for $C_{26}H_{37}O_4$ $(M+H)^+$ 413.2692].



3.45a **3.46a**

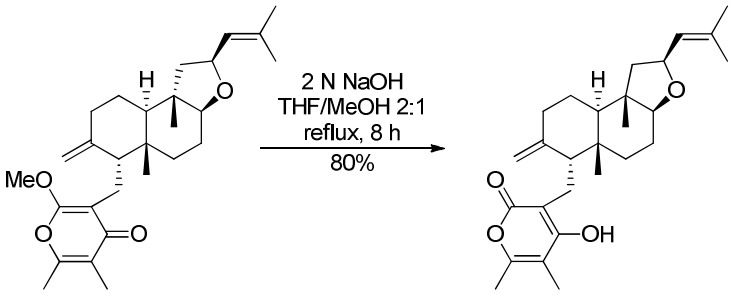
To a cooled (–78 °C) solution of alkene **3.45a** (20.6 mg, 0.0499 mmol) in 2-methylpropene/CH_2Cl_2 (2:1, total 3 mL, 0.017M) was added Grubbs' second-generation catalyst (2.1 mg, 0.0025 mmol). The resulting mixture was refluxed for 12 h. An addition of Grubbs' second-generation catalyst (2.1 mg, 0.0025 mmol) was repeated twice every 12 h. The reaction mixture was cooled to –78 °C and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford alkene **3.46a** as a colorless oil (22.0 mg, 79%): R_f 0.32 (hexanes/EtOAc, 1/1); $[\alpha]^{26.8}_D$ = –55.6 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (d, *J* = 8.8 Hz, 1 H), 4.67 (ddd, *J* = 10.0, 10.0, 3.2 Hz, 1 H), 4.51 (s, 1 H), 4.20 (s, 1 H), 3.85 (s, 3 H), 3.09 (dd, *J* = 12.0, 3.2 Hz, 1 H), 2.65 (dd, *J* = 12.8, 3.6 Hz, 1 H), 2.49 (dd, *J* = 12.4, 11.6 Hz, 1 H), 2.41 (br d, *J* = 12.4 Hz, 1 H), 2.24 (s, 3 H), 2.09 (d, *J* = 14.0 Hz, 1 H), 1.94 (dd, *J* = 11.6, 3.2 Hz, 1 H), 1.89 (s, 3 H), 1.75–1.88 (m, 3 H), 1.71 (s, 3 H), 1.69 (s, 3 H), 1.55–1.74 (m, 3 H), 1.43 (d, *J* = 11.2 Hz, 1 H), 1.42 (d, *J* = 12.4 Hz, 1 H), 0.94 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 162.9, 154.9, 148.6, 135.4, 127.4, 118.6, 109.6, 103.2, 87.3, 74.1, 56.0, 55.3, 47.9, 45.3, 44.5, 38.5, 34.7, 30.6, 25.7, 25.1, 24.5, 22.4, 20.0, 18.1, 17.02, 16.94, 10.0; IR (neat) 2925, 2866, 1668, 1596,

1457, 1437, 1417, 1374, 1318, 1252, 1115, 988 cm^{-1}; HRMS (FAB) found 441.2996 [calcd for $C_{28}H_{41}O_4$ $(M+H)^+$ 441.3005].



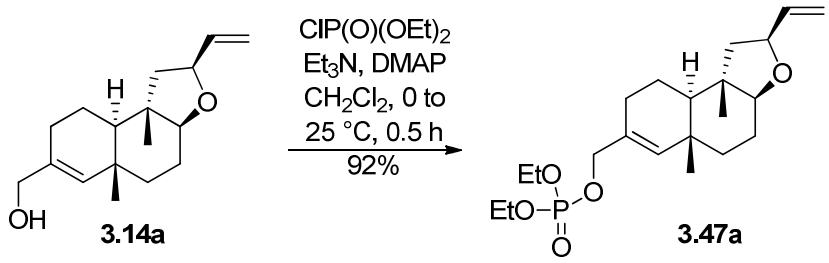
3.46b

For 3.46b: A colorless oil (29.2 mg, 83%): R_f 0.39 (hexanes/EtOAc, 1/1); $[\alpha]^{26.8}_D$ = –55.6 (*c* 0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.33 (d, *J* = 8.0 Hz, 1 H), 4.80 (ddd, *J* = 8.8, 8.8, 8.0 Hz, 1 H), 4.51 (s, 1 H), 4.21 (s, 1 H), 3.85 (s, 3 H), 3.25 (dd, *J* = 12.4, 3.6 Hz, 1 H), 2.65 (dd, *J* = 12.8, 3.2 Hz, 1 H), 2.49 (dd, *J* = 12.0, 12.0 Hz, 1 H), 2.41 (br d, *J* = 12.8 Hz, 1 H), 2.24 (s, 3 H), 2.10 (d, *J* = 12.8 Hz, 1 H), 1.84–1.99 (m, 4 H), 1.90 (s, 3 H), 1.73 (s, 3 H), 1.69 (s, 3 H), 1.56–1.71 (m, 3 H), 1.44 (d, *J* = 2.8 Hz, 1 H), 1.41 (ddd, *J* = 3.2, 3.2, 3.2 Hz, 1 H), 1.25 (dd, *J* = 10.8, 10.8 Hz, 1 H), 0.94 (s, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 162.9, 154.9, 148.6, 134.6, 127.0, 118.6, 109.6, 103.2, 86.0, 73.7, 55.8, 55.3, 48.5, 45.0, 44.8, 38.4, 34.7, 30.5, 25.9, 25.0, 24.3, 22.6, 20.0, 17.9, 16.9, 15.7, 10.0; IR (neat) 2924, 2865, 1670, 1600, 1456, 1416, 1376, 1318, 1252, 1149, 1109, 987, 882 cm^{-1}; HRMS (FAB) found 441.3001 [calcd for $C_{28}H_{41}O_4$ $(M+H)^+$ 441.3005].

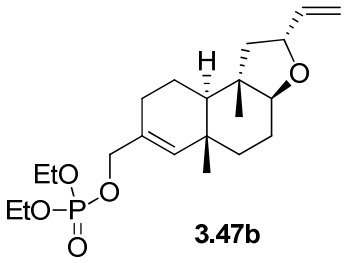


3.46a **3.1a** (12*S*) subglutinol A

To a stirred solution of **3.46a** (8.1 mg, 0.0184 mmol) in THF/MeOH (2/1, total 1.5 mL, 0.012 M) was added 2 N NaOH (0.5 mL, 1 mmol) at 25 °C. The resulting mixture was refluxed for 8 h, cooled to 25 °C, neutralized with saturated aqueous NH_4Cl, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/MeOH, 10/1) to afford **(–)-subglutinol A** (**3.1a**) as a white solid (6.2 mg, 80%) whose spectral data is identical to those of natural material: $[\alpha]^{25.0}_D$ = –59.5 (*c* 0.12, MeOH), nat. $[\alpha]^{25.0}_D$ = –58.7 (*c* 0.027, MeOH); HRMS (FAB) found 427.2836 [calcd for $C_{27}H_{39}O_4$ $(M+H)^+$ 427.2848]. For **(–)-subglutinol B (3.1b)** as a white solid (9.8 mg, 96%) whose spectra data is identical to those of natural material: $[\alpha]^{26.8}_D$ = –73.3 (*c* 0.11, MeOH), nat. $[\alpha]^{25.0}_D$ = –75.0 (*c* 0.288, MeOH).

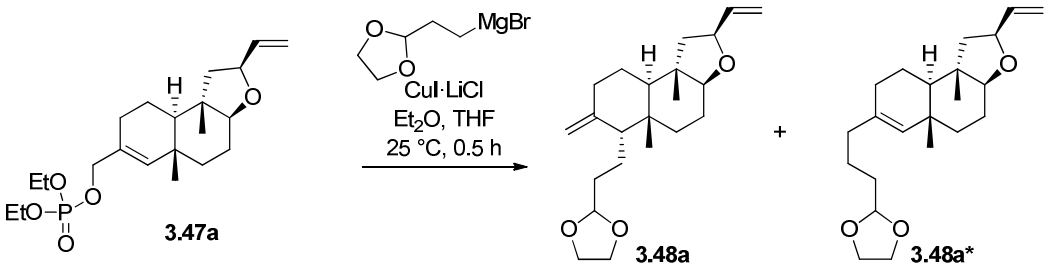


[Phosphate addition] To a cooled (0 °C) solution of alcohol **3.14a** (297.3 mg, 1.133 mmol) in CH_2Cl_2 (3 mL, 0.38 M) were added Et3N (0.316 mL, 2.266 mmol), DMAP (13.8 mg, 0.1133 mmol), and diethylchlorophosphate (0.164 mL, 1.133 mmol). The resulting mixture was allowed to warm to 25 °C with stirring for 30 min before quenched with saturated aqueous $NaHCO_3$ (0.05 mL) and diluted hexanes. The resulting crude mixture was purified directly by column chromatography (silica gel, hexanes/EtOAc, 1/2) to afford phosphate **3.47a** (413.2 mg, 92%) as a colorless oil: R_f 0.45 (hexanes/EtOAc, 1/2); $[\alpha]^{26.3}_D$ = –0.66 (*c* 1.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.50 (s, 1 H), 5.20 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.05 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.38–4.44 (m, 1 H), 4.23–4.34 (m, 2 H), 4.04–4.12 (m, 4 H), 3.10 (dd, *J* = 11.6, 3.6 Hz, 1 H), 2.01–2.17 (m, 2 H), 1.83 (dddd, *J* = 12.0, 3.6, 3.6, 3.6 Hz, 1 H), 1.65–1.78 (m, 3 H), 1.51–1.62 (m, 3 H), 1.31 (dd, *J* = 7.2, 7.2 Hz, 6 H), 1.24–1.29 (m, 2 H), 0.95 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 138.8, 129.41, 129.34, 115.0, 87.7, 78.5, 71.56, 71.51, 63.60, 63.55, 49.9, 46.0, 44.1, 37.8, 35.4, 26.4, 23.0, 22.2, 20.3, 16.21, 16.13, 16.06; IR (neat) 2989, 2935, 1458, 1370, 1264, 1034, 988, 752 cm^{-1}; HRMS (EI) found 398.2220 [calcd for $C_{21}H_{35}O_5P$ $(M)^+$ 398.2222].



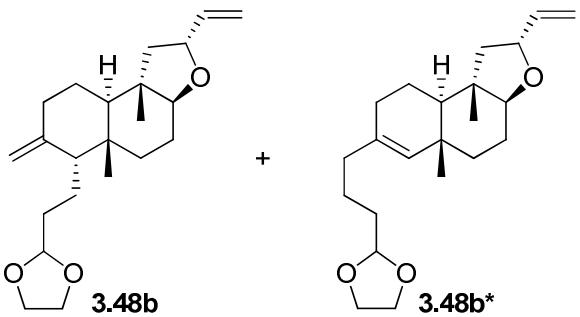
3.47b

For 3.47b: A colorless oil (191.8 mg, 97%): R_f 0.45 (hexanes/EtOAc, 1/2); $[\alpha]^{28.0}_D$ = –10.9 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.48 (s, 1 H), 5.15 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 4.99 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 4.49 (ddd, *J* = 8.4, 8.4, 6.8 Hz, 1 H), 4.23–4.32 (m, 2 H), 4.01–4.09 (m, 4 H), 3.16 (dd, *J* = 12.8, 3.2 Hz, 1 H), 1.97–2.15 (m, 2 H), 1.90 (dd, *J* = 11.2, 6.8 Hz, 1 H), 1.79 (dddd, *J* = 12.4, 3.6, 3.6, 2.8 Hz, 1 H), 1.50–1.75 (m, 6 H), 1.28 (dd, *J* = 6.8, 6.8 Hz, 6 H), 1.24–1.29 (m, 1 H), 0.92 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 138.6, 129.39, 129.32, 113.9, 86.3, 78.1, 71.46, 71.41, 63.52, 63.46, 49.4, 46.9, 44.9, 37.7, 35.3, 26.3, 22.9, 22.3, 20.2, 16.06, 15.99, 15.0; IR (neat) 2932, 1457, 1372, 1263, 1025, 979 cm^{-1}; HRMS (EI) found 398.2216 [calcd for $C_{21}H_{35}O_5P$ $(M)^+$ 398.2222].



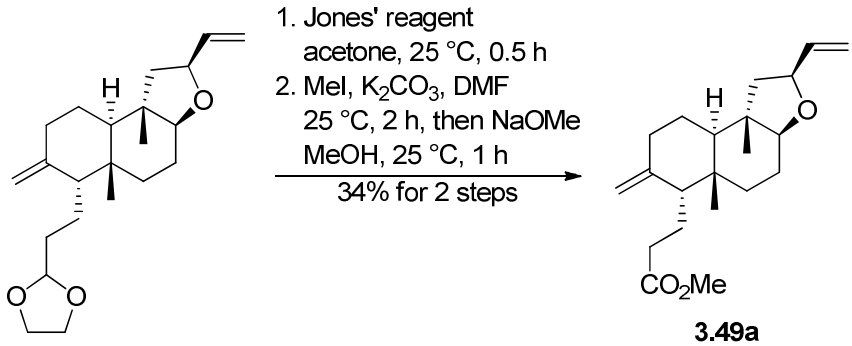
[Cu(I)-Mediated S_N2' Reaction] To a yellowish green solution of CuI·2LiCl (2.44 mL, 0.5 M in THF, 1.22 mmol) was added Et_2O (10 mL). The resulting mixture was stirred at 25 °C for 10 min before Grignard reagent (2.44 mL, 0.5 M in THF, 1.22 mmol) was added dropwise. The resulting dark green solution was stirred until turned to dark black, then phosphate **3.47a** (121.4 mg, 0.305 mmol) in Et_2O (5 mL) was added dropwise. The reaction mixture was stirred at the same temperature for 30 min before quenched with saturated aqueous NH_4Cl and NH_4OH and diluted with Et_2O. The resulting cloudy solution was stirred vigorously until the aqueous layer turned to clean light blue. 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* to afford a ~5:1 mixture of S_N2'-adduct **3.48a** and S_N2-adduct **3.48a*** which was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford S_N2'-adduct **3.48a** (67.8 mg, 64%) and S_N2-adduct **3.48a*** (12.8 mg, 12%) as colorless oils: **[For S_N2'-Adduct 3.48a]** R_f 0.32 (hexanes/EtOAc, 6/1); $[\alpha]^{24.9}_D$ = –44.5 (*c* 0.17, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.21 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.05 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 4.82 (dd, *J* = 4.4, 4.4 Hz, 1 H), 4.69 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.54 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.36–4.42 (m, 1 H), 3.81–3.97 (m, 4 H), 3.08 (dd, *J* = 11.6, 3.6 Hz, 1 H), 2.15 (ddd, *J* = 13.6, 5.2, 1.6 Hz, 1 H), 2.08 (ddd, *J* = 13.6, 13.6, 5.6 Hz, 1 H), 1.36–1.85 (m, 13 H), 1.21 (dd, *J* = 10.0, 2.8 Hz, 1 H), 0.93 (s, 3 H), 0.79 (d, *J* = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 140.0, 115.0, 110.6, 104.7, 87.5, 78.3, 64.8, 58.1,

46.8, 45.3, 44.2, 38.4, 34.8, 32.5, 30.5, 25.0, 24.6, 22.3, 20.6, 16.8; HRMS (EI) found 346.2511 [calcd for $C_{22}H_{34}O_3$ $(M)^+$ 346.2508]. **[For S_N2-Adduct 3.48a*]** R_f 0.42 (hexanes/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.21 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.16 (s, 1 H), 5.06 (ddd, *J* = 10.4, 1.6, 1.6 Hz, 1 H), 4.83 (dd, *J* = 4.8, 4.8 Hz, 1 H), 4.39–4.44 (m, 1 H), 3.81–3.97 (m, 4 H), 3.12 (dd, *J* = 12.0, 3.6 Hz, 1 H), 1.98 (dd, *J* = 8.8, 5.2 Hz, 2 H), 1. 89 (dd, *J* = 7.2, 7.2 Hz, 2 H), 1.81 (dddd, *J* = 11.2, 3.6, 3.6, 3.6 Hz, 1 H), 1.65–1.77 (m, 3 H), 1.44–1.63 (m, 7 H), 1.26 (ddd, *J* = 12.8, 12.8, 4.0 Hz, 1 H), 1.24 (dd, *J* = 13.2, 2.4 Hz, 1 H), 0.92 (s, 3 H), 0.82 (d, *J* = 1.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 134.6, 133.1, 114.9, 104.5, 87.9, 78.5, 64.8, 50.3, 46.1, 44.2, 38.5, 36.9, 35.4, 33.4, 29.1, 23.5, 22.4, 22.2, 20.9, 16.2.



For 3.48b: A 5:1 mixture of S_N2′-adduct **3.48b** and S_N2-adduct **3.48b*** was purified by column chromatography (silica gel, hexanes/EtOAc, 10/1) to afford S_N2′-adduct **3.48b** (34.5 mg, 80%) and S_N2- adduct **3.48b*** (6.7 mg, 15%) as colorless oils: **[For S_N2′-Adduct 3.48b]** R_f 0.39 (hexanes/EtOAc, 6/1); $[\alpha]^{28.0}_D$ = –39.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 16.2, 10.4, 6.8 Hz, 1 H), 5.19 (ddd, *J* = 17.2, 2.0, 2.0 Hz, 1 H), 5.04

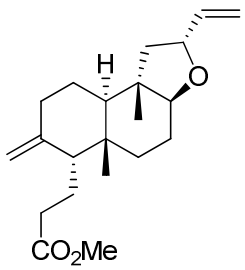
(ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 4.81 (dd, *J* = 4.4, 4.4 Hz, 1 H), 4.69 (dd, *J* = 2.4, 2.4 Hz, 1 H), 4.54 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.48 (ddd, *J* = 8.4, 6.8, 6.8 Hz, 1 H), 3.80–3.97 (m, 4 H), 3.16 (dd, *J* = 11.6, 3.6 Hz, 1 H), 2.15 (ddd, *J* = 13.6, 4.8, 2.0 Hz, 1 H), 2.02–2.11 (m, 1 H), 1.90 (dd, *J* = 11.2, 6.8 Hz, 1 H), 1.78–1.83 (m, 1 H), 1.50–1.75 (m, 6 H), 1.37–1.48 (m, 4 H), 1.18–1.27 (m, 2 H), 0.93 (s, 3 H), 0.83 (d, *J* = 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 139.8, 113.9, 110.6, 104.7, 86.1, 78.1, 64.8, 58.0, 47.7, 44.96, 44.85, 38.3, 34.7, 32.5, 30.5, 25.0, 24.5, 22.4, 20.6, 15.5; IR (neat) 2933, 1730 cm^{-1}; HRMS (EI) found 346.2513 [calcd for $C_{22}H_{34}O_3$ $(M)^+$ 346.2508]. **[For S_N2-Adduct 3.48b*]** R_f 0.45 (hexanes/EtOAc, 1/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.20 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1 H), 5.15 (s, 1 H), 5.02 (ddd, *J* = 10.4, 1.2, 1.2 Hz, 1 H), 4.82 (dd, *J* = 4.8, 4.8 Hz, 1 H), 4.52 (ddd, *J* = 8.4, 6.8, 6.8 Hz, 1 H), 3.80–4.00 (m, 4 H), 3.20 (dd, *J* = 12.0, 3.2 Hz, 1 H), 1.86–1.99 (m, 5 H), 1.19–1.29 (m, 3 H), 0.92 (s, 3 H), 0.85 (d, *J* = 1.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 134.6, 133.1, 113.9, 104.5, 86.6, 78.2, 64.8, 49.9, 47.1, 45.0, 38.4, 36.9, 35.3, 33.3, 29.0, 23.5, 22.5, 22.2, 20.8, 15.1.



3.48a **3.49a**

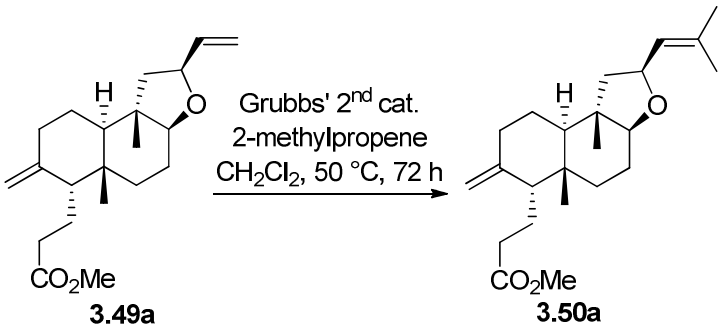
[One-Pot Deketalization/Oxidation] To a solution of dioxolane **3.48a** (52.4 mg, 0.151 mmol) in acetone (0.076 M, 2 mL) was added dropwise Jones' reagent (0.28 mL, 2.67 M in H_2O, 0.73 mmol) at 25 °C. The resulting red solution was stirred for 30 min, quenched with *i*-PrOH (0.1 mL), and diluted with H_2O (5 mL) and EtOAc (20 mL). 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* to afford the crude acid which was employed in the next step without purification. **[Esterification]** To the crude acid in DMF (1 mL) was added K_2CO_3 (208.7 mg, 1.51 mmol) at 25 °C. The resulting mixture was stirred for 10 min at the same temperature before MeI (0.094 mL, 1.51 mmol) was added dropwise. The reaction mixture was stirred for 2 h at 25 °C and diluted with MeOH (4 mL). NaOMe (78.3 mg, 1.45 mmol) was added, and the resulting mixture was stirred vigorously for 1 h before 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, and 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 methyl ester **3.49a** (17.3 mg, 34% for two steps, 44% BRSM) as a colorless oil: R_f 0.42 (hexanes/EtOAc, 6/1); $[\alpha]^{24.3}_D$ = –29.8 (*c* 0.58, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.21 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H), 5.06 (ddd, *J* = 10.4 , 1.6, 1.6 Hz, 1 H), 4.72 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.54 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.38–4.44 (m,

1 H), 3.64 (s, 3 H), 3.09 (dd, *J* = 11.2, 3.2 Hz, 1H), 2.04–2.27 (m, 4 H), 1.38–1.94 (m, 11 H), 1.23 (dd, *J* = 9.6, 2.8 Hz, 1 H), 0.94 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 147.3, 139.9, 115.0, 111.1, 87.4, 78.3, 57.6, 51.4, 46.8, 45.3, 44.2, 38.4, 34.7, 32.6, 30.5, 25.0, 24.5, 22.3, 21.6, 16.8; HRMS (EI) found 332.2346 [calcd for $C_{21}H_{32}O_3$ $(M)^+$ 332.2351].

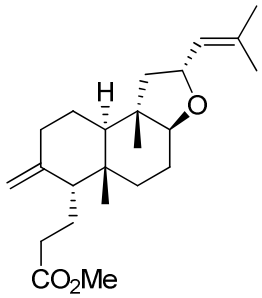


3.49b

For 3.49b: A colorless oil (21.4 mg, 45% for two steps, 57% BRSM): R_f 0.45 (hexanes/EtOAc, 6/1); $[\alpha]^{28.0}_D$ = –12.5 (*c* 0.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 16.8, 10.0, 6.4 Hz, 1 H), 5.20 (d, *J* = 16.8 Hz, 1 H), 5.06 (d, *J* = 10.0 Hz, 1 H), 4.73 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.54 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.50 (ddd, *J* = 8.4, 6.8, 6.8 Hz, 1 H), 3.65 (s, 3 H), 3.18 (dd, *J* = 11.6, 3.6 Hz, 1 H), 2.04–2.27 (m, 4 H), 1.81–1.94 (m, 3 H), 1.54–1.74 (m, 5 H), 1.39–1.48 (m, H), 1.21–1.28 (m, 2 H), 0.94 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 147.3, 139.7, 114.0, 111.1, 86.1, 78.1, 57.5, 51.5, 47.7, 44.9, 38.3, 34.7, 32.6, 30.4, 24.9, 24.4, 22.4, 21.6, 15.6; IR (neat) 2930, 1736 cm^{-1}; HRMS (EI) found 332.2360 [calcd for $C_{21}H_{32}O_3$ $(M)^+$ 332.2351].

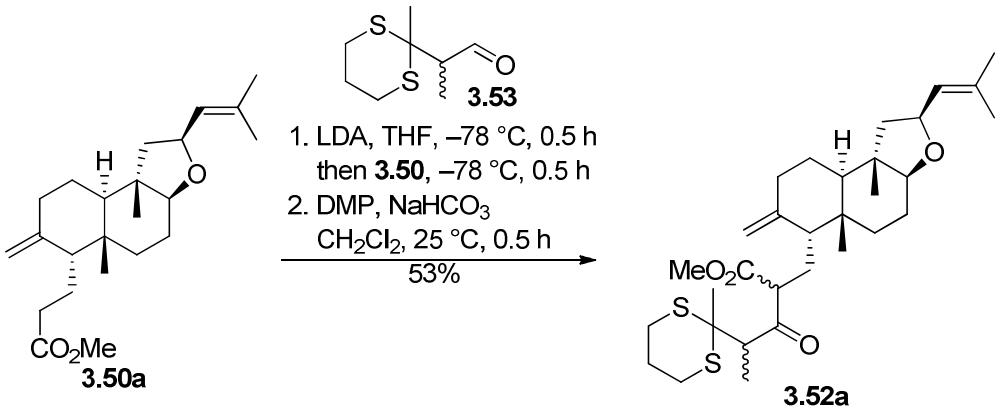


[Cross-metathesis] To a cooled (–78 °C) solution of alkene **3.49a** (34.8 mg, 0.105 mmol) in 2-methylpropene/CH_2Cl_2 (1:1, total 4 mL, 0.026 M) was added Grubbs' second-generation catalyst (4.5 mg, 0.005 mmol). The resulting mixture was refluxed for 24 hours. An addition of Grubbs' second-generation catalyst (4.5 mg, 0.005 mmol) was repeated two times every 24 hours. The reaction mixture was cooled to –78 °C and concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel; hexanes/EtOAc, 4/1 to 2/1) to afford alkene **3.50a** as a colorless oil (34.3 mg, 91%): R_f 0.42 (hexanes/EtOAc, 6/1); $[\alpha]^{25.0}_D$ = –31.9 (*c* 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (ddd, *J* = 8.8, 1.2, 1.2 Hz, 1 H), 4.71 (dd, *J* = 2.0, 2.0, Hz, 1 H), 4.64 (ddd, *J* = 9.6, 9.6, 3.6 Hz, 1 H), 4.53 (dd, *J* = 1.6, 1.6 Hz, 1 H), 3.64 (s, 3 H), 3.03 (dd, *J* = 11.2, 3.2 Hz, 1 H), 2.02–2.26 (m, 4 H), 1.52–1.93 (m, 9 H), 1.69 (s, 3 H), 1.68 (d, *J* = 1.2 Hz, 3 H), 1.53–1.71 (m, 5 H), 1.39–1.49 (m, 2 H), 1.67–1.25 (m, 2 H), 0.94 (s, 3 H), 0.85 (d, *J* = 0.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 147.3, 135.4, 127.2, 111.0, 87.1, 74.1, 57.6, 51.4, 47.8, 45.4, 44.4, 38.4, 34.7, 32.6, 30.5, 25.7, 25.0, 24.5, 22.3, 21.6, 18.1, 16.9; HRMS (EI) found 360.2653 [calcd for $C_{23}H_{36}O_3$ $(M)^+$ 360.2664].



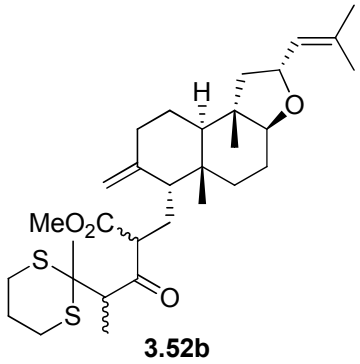
3.50b

For 3.50b: A colorless oil (36.4 mg, 85%): R_f 0.45 (hexanes/EtOAc, 6/1); $[\alpha]^{29.2}_D$ = –24.3 (*c* 0.61, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (ddd, *J* = 9.2, 1.2, 1.2 Hz, 1 H), 4.79 (ddd, *J* = 8.8, 6.8, 6.8 Hz, 1 H), 4.73 (dd, *J* = 2.0, 2.0 Hz, 1 H), 4.54 (dd, *J* = 2.0, 2.0 Hz, 1 H), 3.65 (s, 3 H), 3.19 (dd, *J* = 11.6, 3.6 Hz, 1 H), 2.05–2.27 (m, 4 H), 1.77–1.94 (m, 3 H), 1.73 (d, *J* = 1.2 Hz, 3 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 1.53–1.71 (m, 5 H), 1.39–1.49 (m, 2 H), 1.67–1.25 (m, 2 H), 0.94 (s, 3 H), 0.85 (d, *J* = 0.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 147.3, 134.7, 126.9, 111.0, 85.8, 73.7, 57.5, 51.4, 48.4, 44.99, 44.91, 38.3, 34.7, 32.6, 30.4, 25.9, 24.9, 24.4, 22.5, 21.6, 17.9, 15.6; IR (neat) 2929, 1736 cm^{-1}; HRMS (EI) found 360.2666 [calcd for $C_{23}H_{36}O_3$ $(M)^+$ 360.2664].



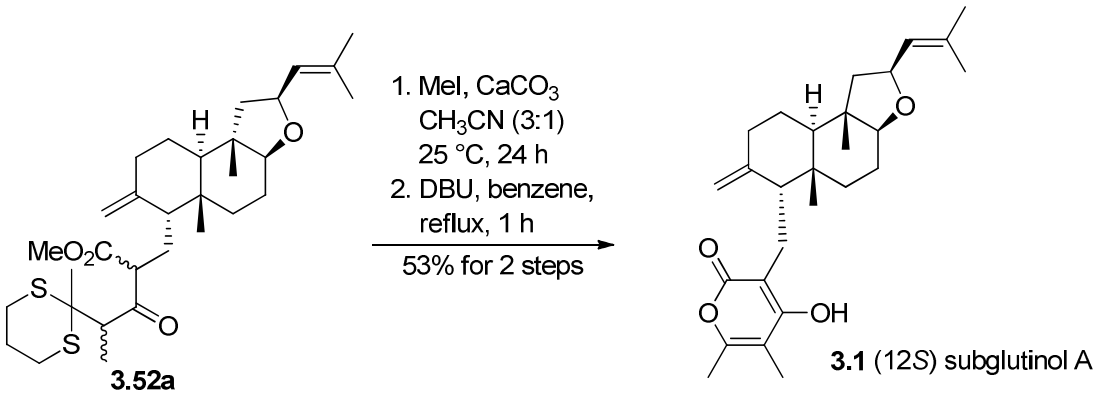
[Aldol Reaction] To a cooled (–78 °C) solution of LDA (2 mL, 0.24 M in THF, 0.475 mmol) was added methyl ester **3.50a** (34.3 mg, 0.095 mmol) in THF (1 mL, 0.010 M). The resulting mixture was stirred for 30 min before aldehyde **3.53** (90.4 mg, 0.475 mmol) in THF (0.5 mL, 0.95 M) was added. The reaction mixture was stirred at the same temperature for 30 min, 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, 2/1) to afford a diastereomeric mixture of β-hydroxy esters (37.6 mg, 74%): HRMS (FAB) found 550.3149 [calcd for $C_{31}H_{50}O_4S_2$ $(M)^+$550.3151]. **[Dess–Martin Oxidation]** To a stirred solution of β-hydroxy ester (30.3 mg, 0.055 mmol) in CH_2Cl_2 (4 mL, 0.014 M) were added $NaHCO_3$ (18.5 mg, 0.22 mmol) and Dess–Martin periodinane (35.0 mg, 0.83 mmol) at 25 °C. The reaction mixture was stirred for 1 h at the same temperature and 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 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 a mixture of β-keto esters **3.52a** (21.7 mg, 72%): HRMS (FAB) found 548.3013 [calcd for $C_{31}H_{48}O_4S_2$ $(M)^+$ 548.2994].



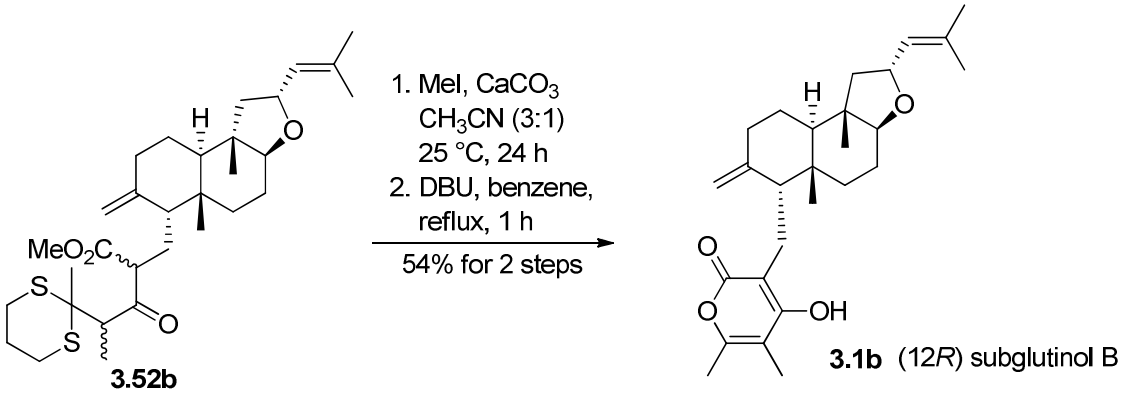
3.52b

For 3.52b: A colorless oil (19.48 mg, 92%): HRMS (FAB) found 548.2992 [calcd for $C_{31}H_{48}O_4S_2$ $(M)^+$ 548.2994].



[Deketalization] To a stirred solution of dithiane **3.52a** (18.4 mg, 0.0335 mmol) in CH_3CN/H_2O (3:1, 2 mL, 0.017 M) were added $CaCO_3$ (67.1 mg, 0.67 mmol) and MeI (0.042 mL, 0.67 mmol) at 25 °C, and the reaction mixture was stirred vigorously for 24 h at the same temperature. The reaction mixture was 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* to afford the crude mixture of 2,4-diketo esters. Without further purification, this crude mixtue of 2,4-diketo esters was used in the next step. **[Pyrone-Annulation]** To a stirred solution of the crude 2,4-diketo esters in benzene (3 mL) was added DBU (0.05 mL, 0.335 mmol), and the resulting mixture was refluxed for 1 h before cooled to 25 °C. The reaction mixture was neutralized carefully with 2 N HCl 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, 1/1) to afford subglutinol A (**3.1a**) (7.6 mg, 53% for 2 steps) as a white solid.



[Deketalization] To a stirred solution of alcohol dithian**e 3.52b** (19.4 mg, 0.0353 mmol) in CH_3CN/H_2O (3:1, 2 mL, 0.018 M) were added $CaCO_3$ (70.7 mg, 0.706 mmol) and MeI (0.044 mL, 0.706 mmol) at 25 °C, and the reaction mixture was stirred vigorously for 24 h at the same temperature. The reaction mixture was 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* to afford the crude mixture of 2,4-diketo esters. Without further purification, this crude mixture of 2,4-diketo esters was used in the next step. **[Pyrone-Annulation]** To a stirred solution of the crude 2,4-diketo esters in benzene (3 mL) was added DBU (0.053 mL, 0.353 mmol), and the resulting mixture was refluxed for 1 h before cooled to 25 °C. The reaction mixture was neutralized carefully with 2 N HCl 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, 1/1) to afford subglutinol B (**3.1b**) (8.1 mg, 54% for 2 steps) as a white solid.

References

1. Kasper, A. C.; Baker, J. B.; Kim, H.; Hong, J., *The end game of chemical genetics: target identification.* Future Medicinal Chemistry, 2009. **1**: p. 727–736.

2. Kawasumi, M. and P. Nghiem, *Chemical Genetics: Elucidating Biological Systems with Small-Molecule Compounds.* Journal of Investigative Dermatology, 2007. **127**(7): p. 1577–1584.

3. Burdine, L. and T. Kodadek, *Target Identification in Chemical Genetics: The (Often) Missing Link.* Chemistry & Biology, 2004. **11**(5): p. 593–597.

4. Hong, J., *Role of natural product diversity in chemical biology.* Current Opinion in Chemical Biology, 2011. **15**(3): p. 350–354.

5. Wurdak, H., et al., *A small molecule accelerates neuronal differentiation in the adult rat.* Proceedings of the National Academy of Sciences, 2010.

6. Bradner, J.E., et al., *Chemical genetic strategy identifies histone deacetylase 1 (HDAC1) and HDAC2 as therapeutic targets in sickle cell disease.* Proceedings of the National Academy of Sciences, 2010.

7. Newman, D.J. and G.M. Cragg, *Natural Products as Sources of New Drugs over the Last 25 Years⊥.* Journal of Natural Products, 2007. **70**(3): p. 461–477.

8. Schreiber, S.L., *Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery.* Science, 2000. **287**(5460): p. 1964–1969.

9. Tan, D.S., *Diversity-oriented synthesis: exploring the intersections between chemistry and biology.* Nature Chemical Biology, 2005. **1**(2): p. 74–84.

10. Firn, R.D. and Jones, C.G., *Natural products - a simple model to explain chemical diversity.* Natural Product Reports, 2003. **20**(4): p. 382–391.

11. Jones, C.G., Firn, R.D. and Malcolm, S.B., *On the Evolution of Plant Secondary Chemical Diversity [and Discussion].* Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 1991. **333**(1267): p. 273–280.

12. Bon, R.S. and H. Waldmann, *Bioactivity-Guided Navigation of Chemical Space.* Accounts of Chemical Research, 2010. **43**(8): p. 1103–1114.

13. Goodman, J. and Walsh, V., *The Story of Taxol: Nature and Politics in the Pursuit of an Anti-Cancer Drug*. 1 ed. 2001: Cambridge University Press.

14. Boivin, T.L.B., *Synthetic routes to tetrahydrofuran, tetrahydropyran, and spiroketal units of polyether antibiotics and a survey of spiroketals of other natural products.* Tetrahedron, 1987. **43**(15): p. 3309–3362.

15. Larrosa, I., P. Romea, and F. Urpí, *Synthesis of six-membered oxygenated heterocycles through carbon-oxygen bond-forming reactions.* Tetrahedron, 2008. **64**(12): p. 2683–2723.

16. D'Ambrosio, M., et al., *Leucascandrolide A, a New Type of Macrolide: The first powerfully bioactive metabolite of calcareous sponges (Leucascandra caveolata, a new genus from the coral sea).* Helvetica Chimica Acta, 1996. **79**(1): p. 51–60.

17. Hornberger, K.R., Hamblett, C.L., Leighton, J.L., *Total Synthesis of Leucascandrolide A.* Journal of the American Chemical Society, 2000. **122**(51): p. 12894–12895.

18. Kopecky, D.J. Rychnovsky, S.D., *Mukaiyama Aldol–Prins Cyclization Cascade Reaction: A Formal Total Synthesis of Leucascandrolide A.* Journal of the American Chemical Society, 2001. **123**(34): p. 8420–8421.

19. Wipf, P., Reeves, J.T., *A formal total synthesis of leucascandrolide A.* Chemical Communications, 2002(18): p. 2066–2067.

20. Fettes, A. and E.M. Carreira, *Leucascandrolide A: Synthesis and Related Studies.* The The Journal of Organic Chemistry, 2003. **68**(24): p. 9274–9283.

21. Paterson, I., Tudge, M., *Stereocontrolled Total Synthesis of (+)-Leucascandrolide A.* Angewandte Chemie International Edition, 2003. **42**(3): p. 343–347.

22. Williams, D.R., Patnaik, S., Plummer, S.V., *Leucascandrolide A: A Second Generation Formal Synthesis.* Organic Letters, 2003. **5**(26): p. 5035–5038.

23. Su, Q., Dakin, L.A., Panek, J.S., *[4 + 2]-Annulations of Chiral Organosilanes: Application to the Total Synthesis of Leucascandrolide A.* The Journal of Organic Chemistry, 2006. **72**(1): p. 2–24.

24. Ferrié, L., et al., *Formal Chemoselective Synthesis of Leucascandrolide A.* Organic Letters, 2007. **9**(13): p. 2461–2464.

25. Jung, H.H., Seiders, J.R., Floreancig, P.E., *Oxidative Cleavage in the Construction of Complex Molecules: Synthesis of the Leucascandrolide A Macrolactone.* Angewandte Chemie International Edition, 2007. **46**(44): p. 8464–8467.

26. Evans, P.A., Andrews, W.J., *A Sequential Two-Component Etherification/Oxa-Conjugate Addition Reaction: Asymmetric Synthesis of (+)-Leucascandrolide A Macrolactone.* Angewandte Chemie International Edition, 2008. **47**(29): p. 5426–5429.

27. Yadav, J.S., et al., *Iodocyclization and Prins-Type Macrocyclization: An Efficient Formal Synthesis of Leucascandrolide A.* Organic Letters, 2011. **13**(7): p. 1710–1713.

28. Lee, K., Kim, H., Hong, J., *A Stereoselective Formal Synthesis of Leucascandrolide A.* Organic Letters, 2011: p. 2722–2725.

29. Bohrsch, V., Blechert, S., *A concise synthesis of (–)-centrolobine via a diastereoselective ring rearrangement metathesis-isomerisation sequence.* Chemical Communications, 2006(18): p. 1968–1970.

30. Schmidt, B., Hölter, F., *A Stereodivergent Synthesis of All Stereoisomers of Centrolobine: Control of Selectivity by a Protecting-Group Manipulation.* Chemistry – A European Journal, 2009. **15**(44): p. 11948–11953.

31. Colobert, F., et al., *First Enantioselective Total Synthesis of (−)-Centrolobine.* Organic Letters, 2002. **4**(10): p. 1723–1725.

32. Marumoto, S., et al., *Synthesis of (−)-Centrolobine by Prins Cyclizations that Avoid Racemization.* Organic Letters, 2002. **4**(22): p. 3919–3922.

33. White, J.D., Kuntiyong, P., Lee, T.H., *Total Synthesis of Phorboxazole A. 1. Preparation of Four Subunits.* Organic Letters, 2006. **8**(26): p. 6039–6042.

34. Smith, A.B., et al., *Total Synthesis of (+)-Phorboxazole A Exploiting the Petasis–Ferrier Rearrangement.* Journal of the American Chemical Society, 2001. **123**(44): p. 10942–10953.

35. Cossey, K.N., Funk, R.L., *Diastereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyran-4-ones via Prins Cyclizations of Enecarbamates: A Formal Synthesis of (+)-Ratjadone A.* Journal of the American Chemical Society, 2004. **126**(39): p. 12216–12217.

36. Custar, D.W., et al., *Total Synthesis and Structure−Activity Investigation of the Marine Natural Product Neopeltolide.* Journal of the American Chemical Society, 2009. **131**(34): p. 12406–12414.

37. Hashimoto, M., et al., *Total syntheses of (+)-thyrsiferol, (+)-thyrsiferyl 23-acetate, and (+)-venustatriol.* The Journal of Organic Chemistry, 1990. **55**(17): p. 5088–5107.

38. Liu, P., Jacobsen, E.N., *Total Synthesis of (+)-Ambruticin.* Journal of the American Chemical Society, 2001. **123**(43): p. 10772–10773.

39. Lee, E., et al., *Lasonolide A: Structural Revision and Synthesis of the Unnatural (−)-Enantiomer.* Journal of the American Chemical Society, 2001. **124**(3): p. 384–385.

40. White, J.D., Kranemann, C.L., Kuntiyong, P., *Intramolecular Palladium(II)-Mediated Alkoxy Carbonylation as a Route to Functionalized Tetrahydropyrans. Synthesis of the C9−C32 Segment of Phorboxazole A.* Organic Letters, 2001. **3**(25): p. 4003–4006.

41. Kim, H., Park, Y., Hong, J., *ChemInform Abstract: Stereoselective Synthesis of 2,6-cis-Tetrahydropyrans Through a Tandem Allylic Oxidation/Oxa-Michael Reaction Promoted by the gem-Disubstituent Effect: Synthesis of (+)-Neopeltolide Macrolactone.* ChemInform, 2010. **41**(5): p. 7577–7581.

42. Nising, C.F., Brase, S., *The oxa-Michael reaction: from recent developments to applications in natural product synthesis.* Chemical Society Reviews, 2008. **37**(6): p. 1218–1228.

43. Jung, M.E. and Piizzi, G., *gem-Disubstituent Effect: Theoretical Basis and Synthetic Applications.* Chemical Reviews, 2005. **105**(5): p. 1735–1766.

44. Dale, J., *Conformational Aspects of Many-Membered Rings.* Angewandte Chemie International Edition in English, 1966. **5**(12): p. 1000–1021.

45. Jung, M.E., *Substituent and Solvent Effects in Intramolecular Diets-Alder Reactions.* Synlett, 1990. **1990**(04): p. 186,190.

46. Roduit, J.-P. and Wyler, H., *Synthesis of 1,2-Dihydropyridines, 2,3-Dihydro-4(1H)-pyridinone, and 1,2,3,4-Tetrahydropyridines via N-Acyl N,O-Hemiacetal Formation.* Helvetica Chimica Acta, 1985. **68**(2): p. 403–414.

47. Park, H., Kim, H., Hong, J., *A Formal Synthesis of SCH 351448.* Organic Letters, 2011: p. 3742-3745.

48. Kim, H., Hong, J., *Total Synthesis of Cyanolide A and Confirmation of Its Absolute Configuration.* Organic Letters, 2010. **12**(12): p. 2880-2883.

49. Rao, M.R., Faulkner, D.J., *Clavosolides A and B, Dimeric Macrolides from the Philippines Sponge Myriastra clavosa.* Journal of Natural Products, 2002. **65**(3): p. 386–388.

50. Erickson, K.L., et al., *New Dimeric Macrolide Glycosides from the Marine Sponge Myriastra clavosa.* Journal of Natural Products, 2002. **65**(9): p. 1303–1306.

51. Barry, C.S., et al., *Total synthesis of a diastereomer of the marine natural product clavosolide A.* Chemical Communications, 2005(40): p. 5097–5099.

52. Son, J.B., et al., *Total Synthesis, Structural Revision, and Absolute Configuration of (+)-Clavosolide A.* Organic Letters, 2006. **8**(4): p. 661–664.

53. Yakambram, P., Puranik, V.G., Gurjar, M.K., *Towards the total synthesis of clavosolide A.* Tetrahedron Letters, 2006. **47**(22): p. 3781–3783.

54. Barry, C.S., et al., *Total Synthesis of the Marine Natural Product (−)-Clavosolide A.* Organic Letters, 2006. **8**(15): p. 3319–3322.

55. Smith, A.B. Simov, V., *Total Synthesis of the Marine Natural Product (−)-Clavosolide A. A Showcase for the Petasis−Ferrier Union/Rearrangement Tactic.* Organic Letters, 2006. **8**(15): p. 3315–3318.

56. Chakraborty, T.K., Reddy, V.R., Gajula, P.K., *Total synthesis of clavosolide A.* Tetrahedron, 2008. **64**(22): p. 5162–5167.

57. Chakraborty, T.K., Reddy, V.R., Chattopadhyay, A.K., *Total synthesis of (–)-clavosolide A.* Tetrahedron Letters, 2006. **47**(42): p. 7435–7438.

58. Carrick, J.D., Jennings, M.P., *An Efficient Formal Synthesis of (−)-Clavosolide A Featuring a "Mismatched" Stereoselective Oxocarbenium Reduction.* Organic Letters, 2009. **11**(3): p. 769–772.

59. Son, J.B., et al., *Total Synthesis, Structural Revision, and Absolute Configuration of (+)-Clavosolide A.* Organic Letters, 2006. **8**(15): p. 3411–3411.

60. Smith, A.B., et al., *(+)-Phorboxazole A Synthetic Studies. A Highly Convergent, Second Generation Total Synthesis of (+)-Phorboxazole A.* Organic Letters, 2005. **7**(20): p. 4399–4402.

61. Smith, A.B., et al., *Spongistatin Synthetic Studies. Evolution of a Scalable Synthesis for the EF Fragment of (+)-Spongistatin 1 Exploiting a Petasis−Ferrier Union/Rearrangement Tactic.* Organic Letters, 2004. **6**(20): p. 3637–3640.

62. Smith, A.B., Safonov, I.G., Corbett, R.M., *Total Syntheses of (+)-Zampanolide and (+)-Dactylolide Exploiting a Unified Strategy.* Journal of the American Chemical Society, 2002. **124**(37): p. 11102–11113.

63. Smith, A.B., Mesaros, E.F., Meyer, E.A., *Total Synthesis of (−)-Kendomycin Exploiting a Petasis−Ferrier Rearrangement/Ring-Closing Olefin Metathesis Synthetic Strategy.* Journal of the American Chemical Society, 2005. **127**(19): p. 6948–6949.

64. Chakraborty, T.K., Reddy, V.R., *Studies directed towards the total synthesis of clavosolides: synthesis of an isomer of clavosolide A.* Tetrahedron Letters, 2006. **47**(13): p. 2099–2102.

65. Chakraborty, T.K., Das, S., *Diastereoselective opening of trisubstituted epoxy alcohols: Application in the studies directed toward the synthesis of octenoic acid moiety of cryptophycins.* Journal of the Indian Chemical Society, 1999. **76**: p. 611–616.

66. Romero, J.A.C., Tabacco, S.A., Woerpel, K.A., *Stereochemical Reversal of Nucleophilic Substitution Reactions Depending upon Substituent: Reactions of Heteroatom-Substituted Six-Membered-Ring Oxocarbenium Ions through Pseudoaxial Conformers.* Journal of the American Chemical Society, 1999. **122**(1): p. 168–169.

67. Gaunt, M.J., et al., *Synthesis of the C-1−C-28 ABCD Unit of Spongistatin 1.* Organic Letters, 2003. **5**(25): p. 4819–4822.

68. Yadav, J.S., et al., *Stereoselective synthesis of (+)-cryptocarya diacetate by an iterative Prins cyclisation and reductive cleavage sequence.* Tetrahedron Letters, 2007. **48**(8): p. 1469–1471.

69. Sato, K.; Sasaki, M., Convergent synthesis of the BCDEFGHIJ-ring polyether core of gambienic acids, potent antifungal polycyclic ethers. Tetrahedron, 2007. **63**(26): p. 5977–6003.

70. Schreiber, S. L.; Goulet, M. T., Stereochemistry of the 1,2-Wittig rearrangement: A synthesis of syn-1,3-diol monoethers. Tetrahedron Letters, 1987. **28**(10): p. 1043–1046.

71. Pihko, A., et al, Enantioselective synthesis of a hindered furyl substituted allyl alcohol intermediate: a case study in assymetric synthesis. Tetrahedron: Assymetry, 2004. **15**: p. 1637–1643.

72. Richardson, D. P., et al, Stereoselective synthesis of either (±)-exo- or (±)-endo-brevicomin via hydride reduction of a 2-acylpyranyl intermediate. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-organic Chemistry (1972–1999), 1990. **10**: p. 2857–2859.

73. Felpin, F. –X.; Lebreton, J., A Highly Stereoselective Asymmetric Synthesis of (–)-Lobeline and (–)-Sedamine. Journal of Organic Chemistry, 2002. **67**(26): p. 9192–9199.

74. Bates, R. W.; Song, P., Synthesis of diaspongin A. Tetrahedron, 2007. **63**(21): 4497–4499.

75. Mohapatra, D. K., et al, Iodo-cyclization: Novel Strategy for the Total Synthesis of Polyrhacitide A and epi-Cryptocaryolone. Organic Letters, 2011. **13**(4): p. 744–747.

76. Yus, M., et al, The role of 1,3-Dithiane in Natural Product Synthesis. Tetrahedron, 2003. **59**(33): p. 6147–6212.

77. Kim, H.; Hong, J., Total Synthesis of Cyanolide A and Confirmation of Its Absolute Configuration. Organic Letters, 2010. **12**(12): p. 2880–2883.

78. Wuts, P. G. M., Greene, T.W.., *Green's Protective Groups in Organic Synthesis*. Fourth Edition ed. 2007, Hoboken, New Jersey: John Wiley & Sons, Inc. 1082.

79. Shiina, I., et al., *An Effective Use of Benzoic Anhydride and Its Derivatives for the Synthesis of Carboxylic Esters and Lactones: A Powerful and Convenient Mixed Anhydride Method Promoted by Basic Catalysts.* The Journal of Organic Chemistry, 2004. **69**(6): p. 1822–1830.

80. Shiina, I., Fukui, H., Sasaki, A., *Synthesis of lactones using substituted benzoic anhydride as a coupling reagent.* Nat. Protocols, 2007. **2**(10): p. 2312–2317.

81. Son, J.B., et al., *ChemInform Abstract: Enantioselective Total Synthesis of (–)-Clavosolide A and B.* ChemInform, 2010. **41**(31).

82. Azimzadeh, A.M., et al., *Immunobiology of Transplantation: Impact on Targets for Large and Small Molecules.* Clinical Pharmacololgy & Therapeutics, 2011.

83. Niven, R.W., *Toward managing chronic rejection after lung transplant: The fate and effects of inhaled cyclosporine in a complex environment.* Advanced Drug Delivery Reviews. **63**(1–2): p. 88–109.

84. Bromberg, J.S., Heeger, P.S., Li, X.C., *Evolving Paradigms That Determine the Fate of an Allograft.* American Journal of Transplantation, 2010. **10**(5): p. 1143–1148.

85. Feske, S., *Calcium signalling in lymphocyte activation and disease.* Nature Reviews Immunology, 2007. **7**(9): p. 690–702.

86. Trama, J., et al., *The NFAT-Related Protein NFATL1 (TonEBP/NFAT5) Is Induced Upon T Cell Activation in a Calcineurin-Dependent Manner.* The Journal of Immunology, 2000. **165**(9): p. 4884–4894.

87. Kim, H.-P., et al., *Calcium-dependent Activation of Interleukin-21 Gene Expression in T Cells.* Journal of Biological Chemistry, 2005. **280**(26): p. 25291–25297.

88. Clardy, J., *The chemistry of signal transduction.* Proceedings of the National Academy of Sciences, 1995. **92**(1): p. 56–61.

89. Fung, J.J., Alessiani, M., Abu-Elmagd, K., Todo, S., Shapiro, R., Tzakis, A., Van Thiel, D., Armitage, J., Jain, A., McCauley, J., Selby, R., and Starzl, T.E., *Adverse Effects Associated With the Use of FK 506.* Transplant Proceedings., 1991. **23**(6): p. 3105–3108.

90. O'Neill, L.A.J., *Targeting signal transduction as a strategy to treat inflammatory diseases.* Nature Reviews Drug Discovery, 2006. **5**(7): p. 549–563.

91. J. C. Lee, E.L., N. B. Pliam, G. Strobel, J. Clardy, The Journal of Organic Chemistry, 1995. **60**: p. 7076–7077.

92. Craig, D., et al., *Stereoselective synthesis of 2,5-dialkyl-3-(phenylsulfonyl) tetrahydrofurans via cyclisation of Z-Sulfonyl-substituted homoallylic alcohols.* Tetrahedron Letters, 1995. **36**(41): p. 7531–7534.

93. Feldman, K.S., Fisher, T.E., *Tetrahydrofuran synthesis via free radical mediated addition of functionalized alkenes to aryl vinyl oxiranes.* Tetrahedron, 1989. **45**(10): p. 2969–2977.

94. Dueñes, R.A., Morken, J.P., *Catalytic, Diastereoselective Allylation of Oshima-Utimoto Products.* Synlett, 2007. **2007**(04): p. 0587,0590.

95. Cuellar, R.A.D., *The Total Synthesis of Alternaric Acid and Progress Toward the Synthesis of Subglutinol*, in *Chemistry*. 2008, University of North Carolina: Chapel Hill. p. 153.

96. Marshall, J.A., Chobanian, H.R., *Synthesis of 2,5-Disubstituted Tetrahydrofurans by Stereospecific Elimination−Cyclization of 1-Iodomethyl-1,5-bis-epoxides.* Organic Letters, 2003. **5**(11): p. 1931–1933.

97. Kikuchi, H., et al., *New diterpene pyrone-type compounds, metarhizins A and B, isolated from entomopathogenic fungus, Metarhizium flavoviride and their inhibitory effects on cellular proliferation.* Tetrahedron, 2009. **65**(2): p. 469–477.

98. Gupta, S., et al., *Viridoxins A and B: novel toxins from the fungus Metarhizium flavoviride.* The Journal of Organic Chemistry, 1993. **58**(5): p. 1062–1067.

99. Kagamizono, T.M.,; Kawashima, A.; Akiyama, T.;Ando, T.; Isogai, K.; Morimoto, S., *BONE RESORPTION INHIBITING SUBSTANCES BR-050 AND BR-051*, in *WO/1995/006646*, W.I.P. Organization, Editor. 1995: Japan.

100. Engel, B., Erkel, G., Anke, T., Sterner, O., *Sesquicillin, an Inhibitor of Glucocorticoid Mediated Signal Transduction.* Journal of Antibiotics, 1988. **51**: p. 518–521.

101. Webster, J.I., Tonelli, L., Sternberg, E.M., *NEUROENDOCRINE REGULATION OF IMMUNITY*.* Annual Review of Immunology, 2002. **20**(1): p. 125–163.

102. Winoto, A., Littman, D.R., *Nuclear Hormone Receptors in T Lymphocytes.* Cell, 2002. **109**(2, Supplement 1): p. S57–S66.

103. Laue, L., et al., *Receptor-mediated effects of glucocorticoids on inflammation: Enhancement of the inflammatory response with a glucocorticoid antagonist.* Journal of Steroid Biochemistry, 1988. **29**(6): p. 591–598.

104. Hagiwara, H., Uda, H., *Total synthesis of (+)-dysideapalaunic acid.* Journal of the Chemical Society, Chemical Communications, 1988(12): p. 815–817.

105. Zhang, F., Danishefsky, S.J., *An Efficient Stereoselective Total Synthesis of dl-Sesquicillin, a Glucocorticoid Antagonist.* Angewandte Chemie International Edition, 2002. **41**(8): p. 1434–1437.

106. Singh, S.B., et al., *Candelalides A−C: Novel Diterpenoid Pyrones from Fermentations of Sesquicillium candelabrum as Blockers of the Voltage-Gated Potassium Channel Kv1.3.* Organic Letters, 2000. **3**(2): p. 247–250.

107. Watanabe, K., et al., *Enantioselective Total Synthesis of (−)-Candelalide A, a Novel Blocker of the Voltage-Gated Potassium Channel Kv1.3 for an Immunosuppressive Agent.* Organic Letters, 2005. **7**(17): p. 3745–3748.

108. Abe, T., et al., *Convergent and enantioselective total synthesis of (–)-nalanthalide, a potential Kv1.3 blocking immunosuppressant.* Tetrahedron Letters, 2006. **47**(19): p. 3251–3255.

109. Hagiwara, H., Uda, H., *Optically pure (4aS)-(+)- or (4aR)-(–)-1,4a-dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione and its use in the synthesis of an inhibitor of steroid biosynthesis.* The Journal of Organic Chemistry, 1988. **53**(10): p. 2308–2311.

110. Kuo, Y.-L., Dhanasekaran, M., Sha, C.-K., *Total Syntheses of (±)-Axamide-1 and (±)-Axisonitrile-1 via 6-Exo-dig Radical Cyclization.* The Journal of Organic Chemistry, 2009. **74**(5): p. 2033–2038.

111. Larsen, C.H., et al., *A Stereoelectronic Model To Explain the Highly Stereoselective Reactions of Nucleophiles with Five-Membered-Ring Oxocarbenium Ions.* Journal of the American Chemical Society, 1999. **121**(51): p. 12208–12209.

112. Kim, H., et al., *Nucleophilic Addition of Organozinc Reagents to 2-Sulfonyl Cyclic Ethers: Stereoselective Synthesis of Manassantins A and B.* Organic Letters, 2008. **11**(1): p. 89–92.

113. Lee, J., Hong, J., *First Synthesis and Structural Elucidation of (−)-Presphaerene1.* The Journal of Organic Chemistry, 2004. **69**(19): p. 6433–6440.

114. Kim, D., et al., *An asymmetric synthesis of (+)-isonitramine by [`]triple allylic strain-controlled' intramolecular SN2' alkylation.* Tetrahedron Letters, 1996. **37**(9): p. 1433–1434.

115. Paquette, L.A., Stirling, C.J.M., *The intramolecular SN' reaction.* Tetrahedron, 1992. **48**(36): p. 7383–7423.

116. Scholl, M., et al., *Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands§.* Organic Letters, 1999. **1**(6): p. 953–956.

117. Still, W.C., Mitra, A., *A highly stereoselective synthesis of Z-trisubstituted olefins via [2,3]-sigmatropic rearrangement. Preference for a pseudoaxially substituted transition state.* Journal of the American Chemical Society, 1978. **100**(6): p. 1927–1928.

118. Pettus, T.R.R., et al., *A Fully Synthetic Route to the Neurotrophic Illicinones: Syntheses of Tricycloillicinone and Bicycloillicinone Aldehyde.* Journal of the American Chemical Society, 2000. **122**(26): p. 6160–6168.

119. Nakamura, E., et al, Carbon-carbon bond-forming reactions of zinc homoenolate of esters. A novel three-carbon nucleophile with general synthetic utility. Journal of the American Chemical Society, 1987. **109**(26): p. 8056–8066.

120. Baeckvall, J.E.; Sellen, M., A dual regiocontrol in the copper-catalysed Grignard reaction with primary allylic acetates. Journal of the Chemical Society, Chemical Communications, 1987. p. 827–829.

121. Baeckvall, J.E., et al, Regiocontrol in copper-catalysed Grignard reactions with allylic substrates. Journal of the American Chemical Society, 1990. **112**(18): p. 6615–6621.

122. Kim, H., et al, Total Synthesis, Assignment of the Absolute Stereochemistry, and Structure-Activity Relationship Studies of Subglutinols A and B. Chemistry: An Asian Journal, 2010. **5**: p. 1902–1910.

123. Wang, M.Z., et al., *Thermodynamic Analysis of Cyclosporin A Binding to Cyclophilin A in a Lung Tumor Tissue Lysate.* Analytical Chemistry, 2004. **76**(15): p. 4343–4348.

124. Neher E., S.B., *The patch clamp technique*, in *Scientific American*. 1992, Nature Publishing Group: United States. p. 44–51.

125. Orcel, P., et al., *Cyclosporin a induces in vivo inhibition of resorption and stimulation of formation in rat bone.* Journal of Bone and Mineral Research, 1989. **4**(3): p. 387–391.

126. Lin Tang, S.E., Satoshi Kawasaki, Shinji Wakabayashi, Toshio Nikaido, and Kunio Takaoka, *FK506 Enhanced Osteoblastic Differentiation in mesenchymal Cells.* Cell Biology International, 2002. **26**: p. 75–84.

127. Aroldi, A., et al., *EFFECTS OF THREE IMMUNOSUPPRESSIVE REGIMENS ON VERTEBRAL BONE DENSITY IN RENAL TRANSPLANT RECIPIENTS: A Prospective Study.* Transplantation, 1997. **63**(3): p. 380–386.

128. Epstein, S., Shane, E., Bilezikian, J.P., *Organ transplantation and osteoporosis.* Current Opinion in Rheumatology, 1995. **7**(3): p. 255.

129. MOVSOWITZ, C., et al., *Cyclosporin-A in Vivo Produces Severe Osteopenia in the Rat: Effect of Dose and Duration of Administration.* Endocrinology, 1988. **123**(5): p. 2571–2577.

130. Marie, P.J., Debiais, F., Hay, E., *Regulation of human cranial osteoblast phenotype by FGF-2, FGFR-2 and BMP-2 signaling.* Histology and Histopathology, 2002. **17**: p. 877–885.

131. Yeo, H., et al., *Cyclosporin A elicits dose-dependent biphasic effects on osteoblast differentiation and bone formation.* Bone, 2007. **40**(6): p. 1502–1516.

132. McCabe, L.R., et al., *Developmental expression and activities of specific fos and jun proteins are functionally related to osteoblast maturation: role of Fra-2 and Jun D during differentiation.* Endocrinology, 1996. **137**(10): p. 4398–408.

Biography

Joseph grew up in Old Fort, North Carolina. After high school he enlisted into the U.S. Navy where he served as an electrician for six years. In 2006 Joseph received a bachelor's degree in chemistry from Western Carolina University. He enjoys spending time with family, friends and animals.

Education

- 2006 B.S. Chemistry, summa cum laude, Western Carolina University
- 2011 Ph.D. Chemistry, Duke University
- 2011 Graduate certificate, Pharmacoloy and Cancer Biology

Fellowships and awards

- 2008–2010 Pharmacological Sciences Training Program (PSTP) graduate fellowship, Duke University Department of Pharmacology and Cancer Biology
- 2006 Most outstanding senior, Western Carolina University Chemistry Department
- 2005 Most outstanding junior, Western Carolina University Chemistry Department
- 1994 Eagle Scout, Boy Scout troop 811, Old Fort, NC 28762

Research and experience

- Inorganic: Investigated the relaxation rates of fluoride ion from Iron(III) and Mn(II) complexes to develop a predictive model of reactivity to other metal complexes toward superoxide.
- Organic: Natural product synthesis of the biologically interesting compounds Subglutinols A and B and (–)-clavosolide A.
- Teaching assistant for general and organic chemistry
- Lab manager
- Safety officer
- Laboratory waste coordinator

Publications and presentations

- Measured rates of fluoride/metal association correlate with rates of superoxide/metal reactions for Fe(III)EDTA(H2O)- and related complexes. Summers JS*, Baker JB, Meyerstein D, Mizrahi A, Zilbermann I, Cohen H, Wilson CM, Jones JR. *J. Am. Chem. Soc.* **2008**, *130*, 1727–1734.

- Stereoselective Synthesis and Osteogenic Activity of Subglutinols A and B. Kim H, Baker JB, Lee SU, Park Y, Bolduc KL, Park HB, Dickens MG, Lee DS, Kim Y, Kim SH, Hong J*. *J. Am. Chem. Soc.* **2009**, *131*, 3192–3194.

- The end game of chemical genetics: target identification. Kasper AC, Baker JB, Kim H, Hong J. *Fut. Med. Chem.* **2009**, *1*, 727–736.

- Duke University Cancer Biology Conference Poster: "Biological Activity of Subglutinols A and B." September 2009.

- Total synthesis of Subglutinols A and B and initial Structure-Activity Relationship. Kim H, Baker JB, Park Y, Park H-B, Dearmond PD, Fitzgerald MC, Lee D-S, Hong J. *Chem. Asia. J.* **2010**, *5*, 1902–1910.

- WCU Seminar Series Presentation: "Substituted Tetrahydropyrans in Natural Product Chemistry: Efforts Toward the Total Synthesis of Clavosolide A" November 2010.