An Improved Synthesis of the AB Spiroketal of Spongistatin and Synthetic Studies Toward Yokonolide A

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Abstract

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An Improved Synthesis of the AB Spiroketal of Spongistatin
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(Under the direction of Professor Michael T. Crimmins)

An improved synthesis of the AB spiroketal of spongistatin is reported by making use of an asymmetric Mukaiyama-type aldol to install the C5 hydroxyl group selectively. A hetero-Diels-Alder cycloaddition-elimination sequence provides the pyrone core, upon which spiroketalization and further elaboration occurs to provide the completed AB spiroketal

The synthesis of the protected aglycon of yokonolide A is also presented. This synthesis makes use of several asymmetric aldol and alkylation reaction to produce the main fragments. The endgame strategy adopts the use of an esterification-ring closing metathesis sequence to complete the protected core.

Efforts toward the total synthesis of yokonolide A are also reported. Studies indicate that the success of the glycosylation reaction is dependent upon the structure of the glycosyl acceptor. Successful glycosyl donors have also been synthesized for use with these acceptors. Several routes have been explored which have led to protecting group challenges along the way. Efforts have also been made toward completion of the unprotected aglycon. This was undertaken to investigate a deprotection strategy for the natural product when a successful route is developed.

For Mom and Dad

Acknowledgements

I need to thank all of the people that I worked with during my time at Carolina and for my family and friends for their support, encouragement, and patience in helping me to become the chemist and person that I am today. My advisor, Michael Crimmins, has been a great teacher of chemistry and problem-solving and I am thankful for the opportunity to study in his group.

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I need to thank my family for all of their support and encouragement. There were many times that a phone call home or a visit would give me the energy to face all of the obstacles over the years. Thank you for always being there to listen and provide that word of advice that I needed. Thank you for the sacrifices that you've made to get me where I am today and for the unconditional love that has kept me motivated throughout my education.

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List of Abbreviations

2,6-lut.	2,6-lutidine
4 A MS	4 Angstom Molecular Sieves
Bn	benzyl
BOM	benzyloxymethyl
Bu	butyl
Cbz	benzyloxycarbonyl
DAST	diethylaminosulfur trifloride
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DTBMP	2,6-di-t-butyl-4-methylpyridine
EE	ethyl vinyl ether
Fmoc	9-fluorenylmethylcarbonyl
HMDS	hexamethyldisilylizane
HMPA	hexamethylphosphoramide
Icr	isocarenyl
Ipc	isopinocampheyl

LAH	lithium aluminum hyrdide
LDA	lithium diisopropylamide
NIS	N-iodosuccinimide
NMO	N-methylmorpholine-N-oxide
NMP	N-Methylpyrrolidine
PMB	p-methoxybenzyl
PMP	p-methoxyphenyl
PPTS	pyridinium p-toluenesulfonate
p-TsOH	p-toluenesulfonic acid
pyr.	pyridine
TBAF	tetrabutylammonium fluoride
TBDPS	t-butyldiphenylsilyl
TBS	t-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyl-N-oxide
TES	triethylsilyl
Tf	tifluoromethanesulfonyl
TFA	trifluroacetic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethyloxycarbonyl

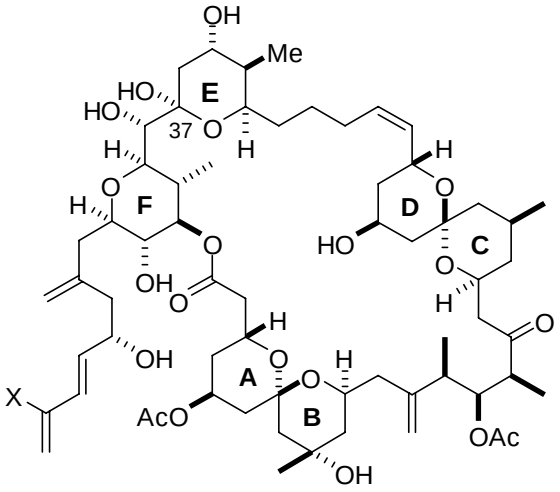
Chapter 1

Spongistatin AB Background

1.1 Introduction

The spongistatins (Figure 1, **1.1, 1.2**), initially isolated in 1993 from marine sponges of the genus *Spongia* by Kitagawa/Kobayashi, and Fusetani, are a family of bisspiroketal-containing natural products that exhibity potent antitumor activity.[1-4] The potential clinical importance of the spongistatins has created substantial interest in their synthesis, and several total syntheses have been accomplished.

Figure 1. The Spongistatins



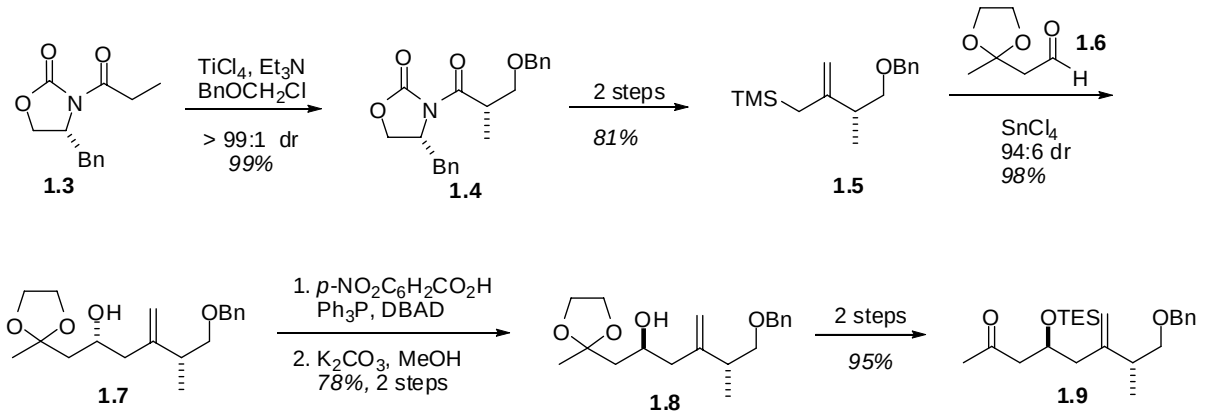
spongistatin 1 X = Cl, (**1.1**)
spongistatin 2 X = H, (**1.2**)

1.2 Previous Syntheses of the AB Spiroketal

1.2.1 Evans Condensation of Diketone Approach

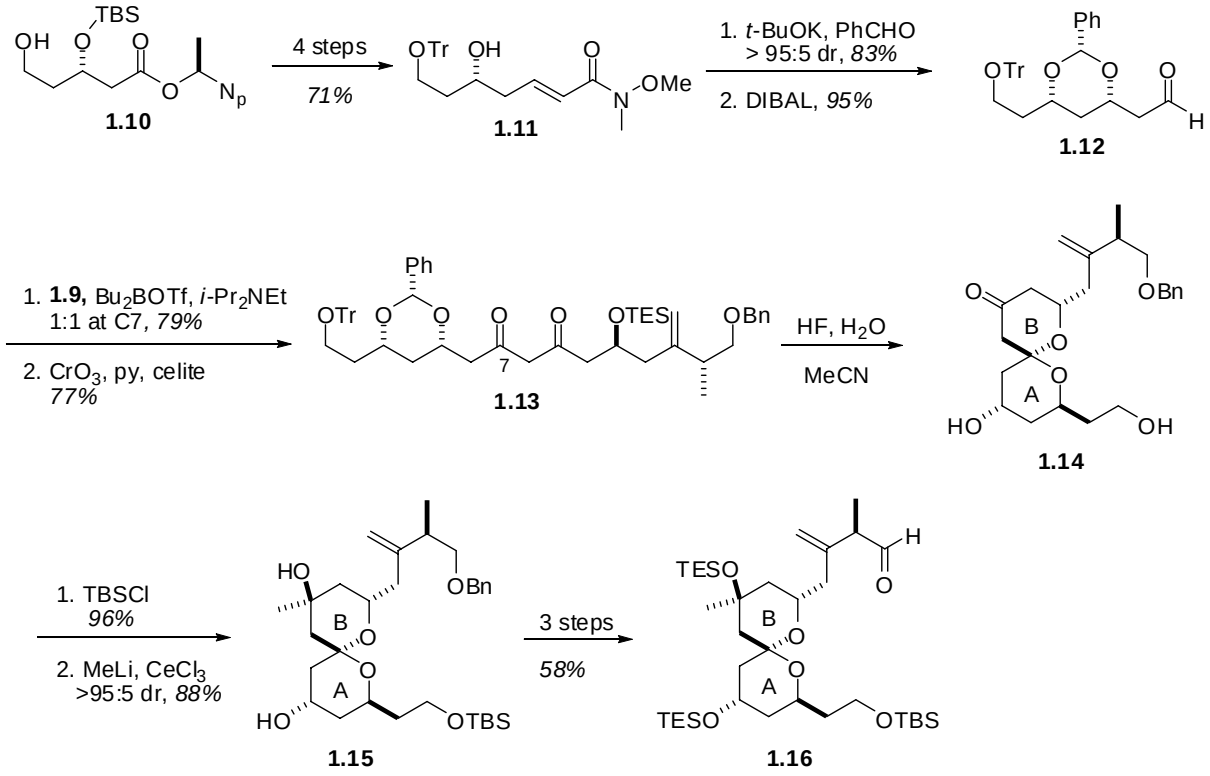
Evans and coworkers reported the total synthesis of spongistatin in 1997.[5-8] Their approach deconstructs the molecule into 4 main fragments including a C1-C15 AB spiroketal fragment.

Scheme 1 Evans Approach to the AB Spiroketal



Evans began the synthesis of the AB spiroketal fragment with the alkylation of *N*-propionyloxazolidinone **1.3** with chloromethylbenzyl ether to form **1.4** (Scheme 1)**.** Further functionalization led to the allylsilane **1.5**. Upon reaction with aldehyde **1.6** in the presence of tin(IV) chloride, alcohol **1.7** is formed. Treatment under Mitsunobu conditions and hydrolysis of the resultant ester led to inversion of the hydroxyl group at C11 and formation of alcohol **1.8**. Further functionalization to **1.9** completed the methyl ketone coupling partner necessary for the formation of the AB spiroketal.

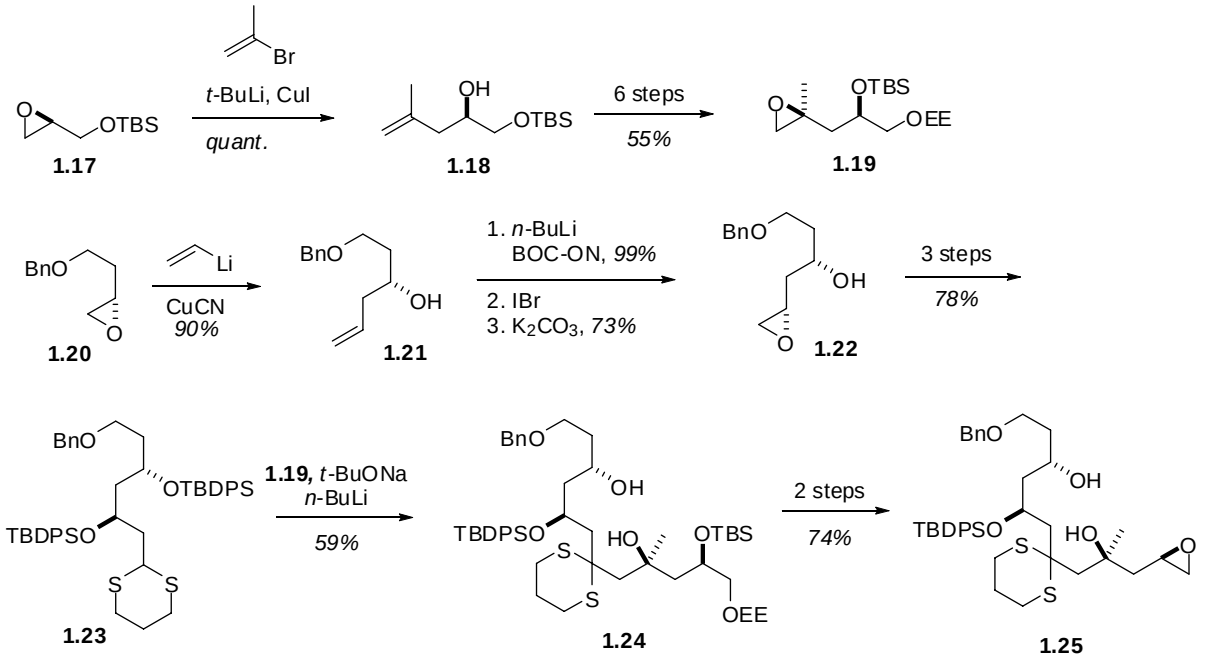
Scheme 2. Diketone Spiroketalization



Starting from the (*S*)-naphthylethyl ester derivative **1.10** (Scheme 2)**,** Evans and co-workers were able to form the optically pure amide **1.11** in 4 steps**.** Treatment with benzaldehyde under basic conditions led to the formation of the benzylidene moiety upon 1,4-addition. Partial reduction to the aldehyde was then effected upon exposure to DIBAL. An aldol addition between aldehyde **1.12** and methyl ketone **1.9** followed by an oxidation of the newly formed alcohol provided diketone **1.13**. Under the acidic conditions of hydrogen fluoride, deprotection of the protecting groups and spiroketalization occurred to give the AB spiroketal core. TBS protection and methylation of the ketone provided diol **1.15.** Further elaboration provided the finished AB spiroketal fragment.

1.2.2 Kishi's Approach to the AB spiroketal

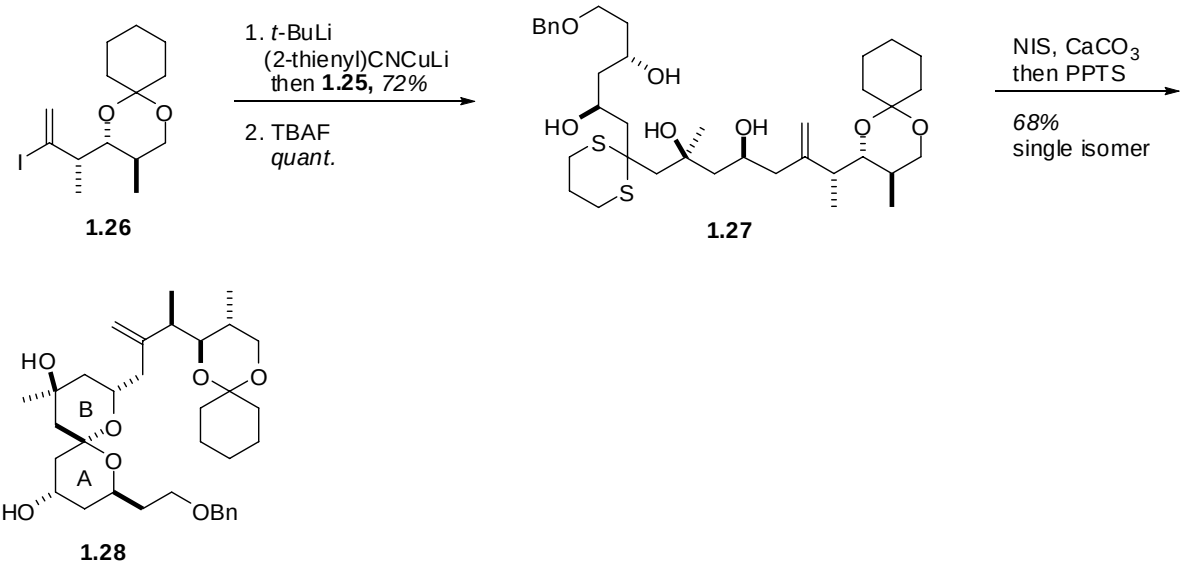
Scheme 3. Kishi's Iterative Epoxide Approach



Kishi[9,10] adopted a different strategy than Evans in the approach to the AB spiroketal of spongistatin 1. He first elaborated the acyclic core to include the sidechain prior to the spiroketalization event. This chemistry relies heavily upon an iterative epoxide opening approach. To this end, starting from epoxide **1.17** (Scheme 3), treatment with 2-bromopropene and *t*-butyl lithium provided homoallylic alcohol **1.18**. Further functionalization converted this to epoxide **1.19.**

The coupling partner of this epoxide is synthesized from epoxide **1.20.** Copper-mediated epoxide opening with vinyl litium led to the homoallylic alcohol **1.21.** Iodocarboxylation-decarbonylation then provided epoxide **1.22.** Further functionalization introduced the dithiane moiety to provide **1.23.** Lithiation, followed by epoxide opening of **1.19** provided the tertiary alcohol **1.24.** The terminal epoxide **1.25** was then formed in two steps.

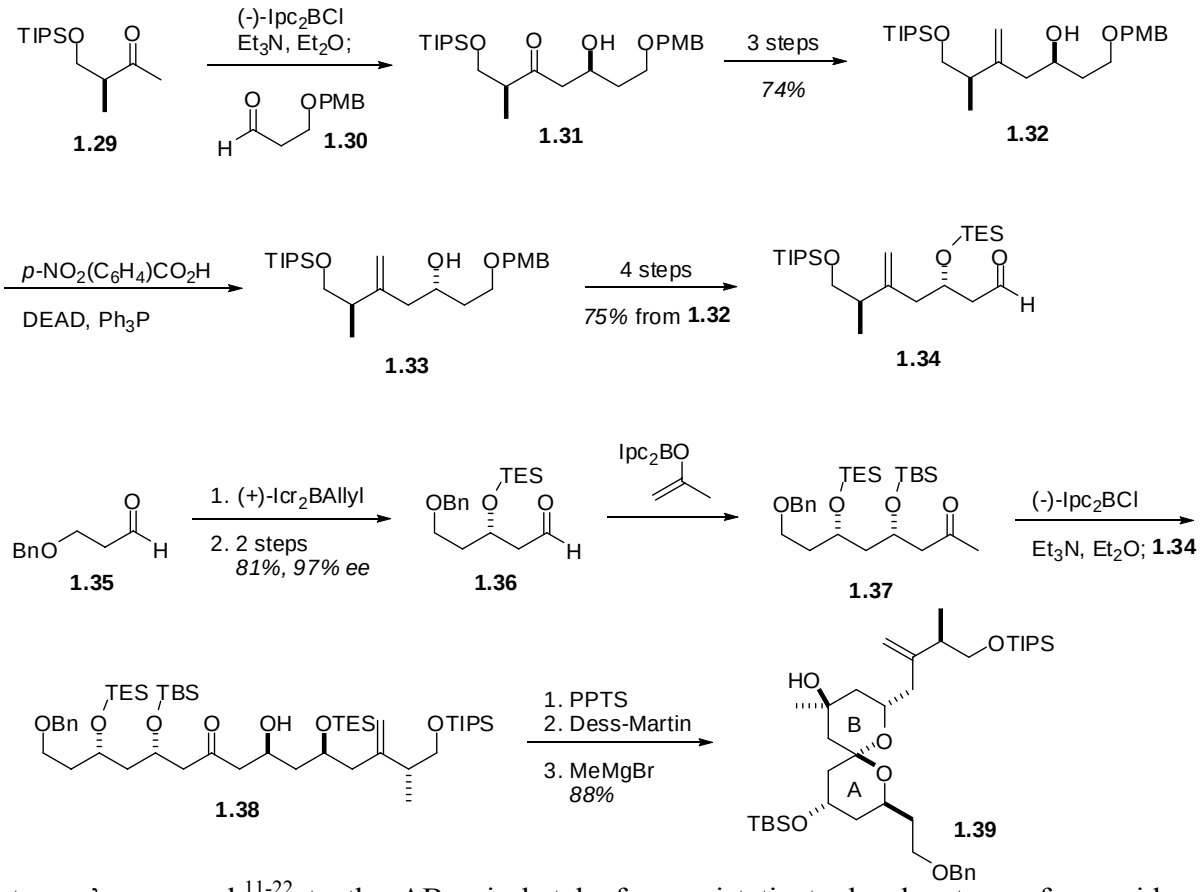
Scheme 4. Formation of AB spiroketal



To complete the AB spiroketal fragment (Scheme 4), vinyl iodide **1.26** was lithiated, converted into the organocuprate, and treated with epoxide **1.25** to provide diol **1.27** upon deprotection. The dithiane moiety is removed under NIS conditions, with the resultant ketone used in the acid-catalyzed condensation to form the AB spiroketal core **1.28**.

1.2.3 Paterson's Approach to the AB Spiroketal

Scheme 5. Paterson's Synthesis of the AB Spiroketal



Paterson's approach[11-22] to the AB spiroketal of spongistatin took advantage of an acid-catalyzed cyclization event and several boron-mediated ketone aldol additions. His synthesis began from methyl ketone **1.29** as shown in Scheme 5. Conversion to the boron-enolate took place upon exposure to the chiral boron chloride and subsequent exposure to aldehyde **1.30** provided aldol adduct **1.31**. Further elaboration installed the methylene unit at C13 over 3 steps. Mitsunobu inversion of the hydroxyl group at C11 provided the correct configuration

| 瞅 | 瞟 | 瞇 | 瞉 | **砳** | **簣** | **籠** | **簇** | 维 | **蓑** | **蔦** | 蘑 | **蔬** | **蕢** | 襪 | ú | □ | å |

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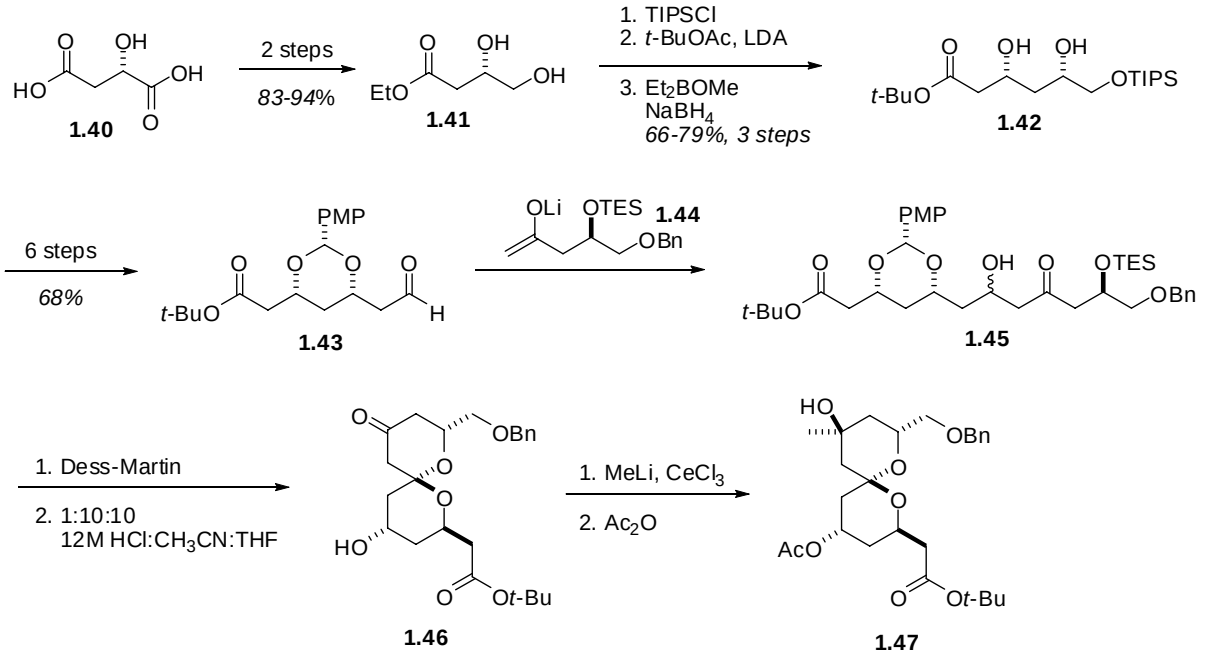
37 was synthesized from aldehyde **1.35** through a Brown allylboration, conversion to the aldehyde, and addition of acetone through another boron aldol addition. With both coupling partners in hand, Paterson achieved a boron aldol addition through formation of the boron

aldol addition through formation of the boron enolate and exposure to aldehyde **1.34** to provide the cyclization precursor **1.38**. Treatment with catalytic acid induced the spiroketalization event to provide the spiroketal. Further elaboration introduced the methyl group at C9 to provide the completed AB spiroketal **1.39.**

1.2.4 Heathcock's Approach to the AB Spiroketal

Scheme 6. Heathcock's synthesis of the AB Spiroketal



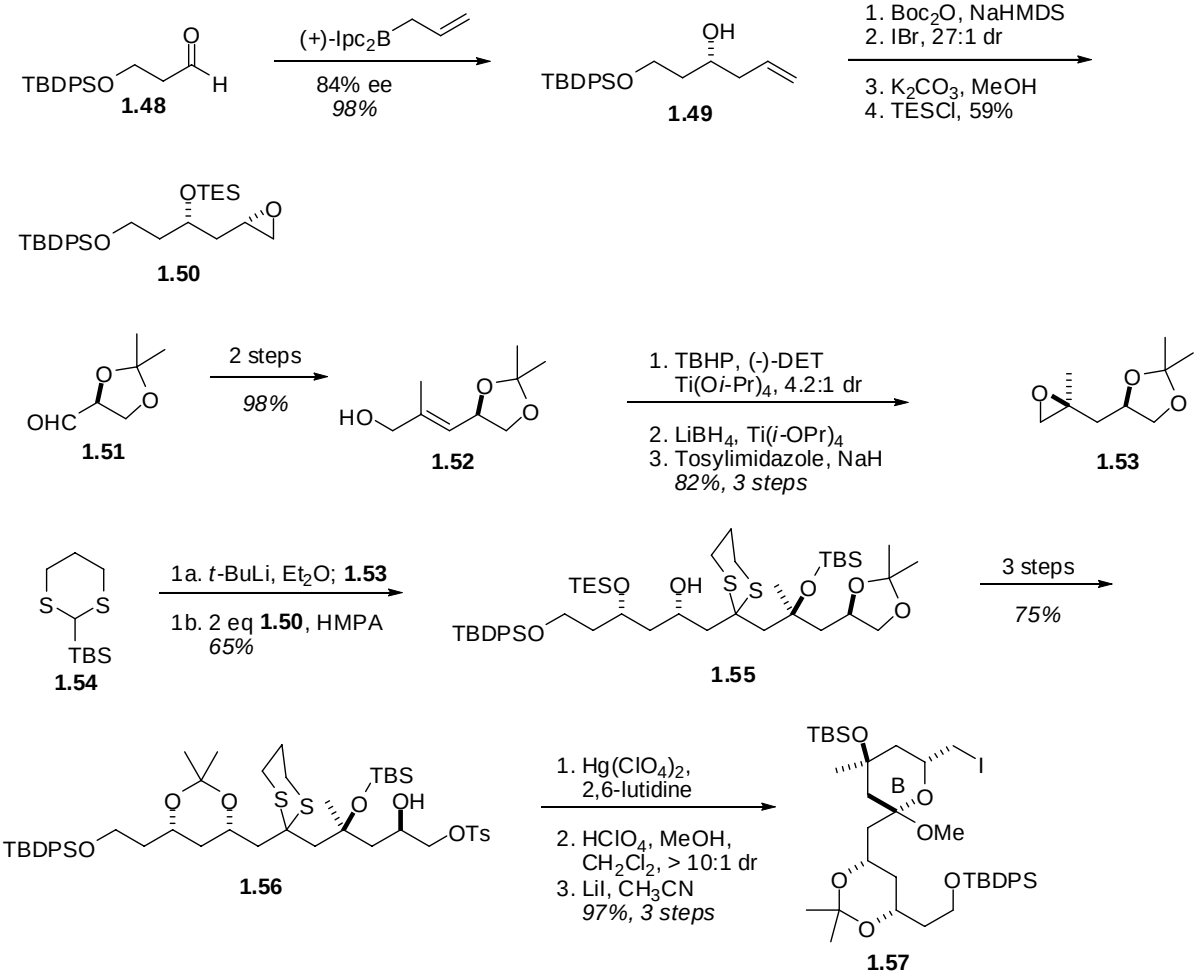
Heathcock's approach took advantage of an acid-catalyzed condensation onto a ketone for the spiroketalization step. This precursor was synthesized starting from (*S*)-malic acid **1.40** (Scheme 6). Elaboration provided diol **1.41** in two steps. Selective silyl protection of the primary alcohol followed by a Claisen condensation with the enolate of *tert*-butyl acetate provided the β-ketoester. The ketone was reduced under conditions selective for the *syn* isomer to provide diol **1.42.** Further functionalization provided aldehyde **1.43**. An unselective addition of the lithium enolate **1.44** provided a mixture of diastereomers at C7 in aldol adduct

1.45. Oxidation under Dess-Martin conditions provided the diketone. Treatment with hydrochloric acid facilitated protodesilylation and cyclization to the AB spiroketal. The resultant ketone **1.46** was treated with methyllithium to form the tertiary alcohol at C9. Formation of the acetate provided the functionalized AB spiroketal **1.47**.

1.2.5 Smith's Approach to the AB Spiroketal

Smith[23-30] took a different approach to the other total syntheses of the spongistatins in his formation of the AB spiroketal. While he did make use of an acid catalyzed spiroketalization, he first elaborated the B ring to include the CD spiroketal moiety before forming the AB spiroketal.

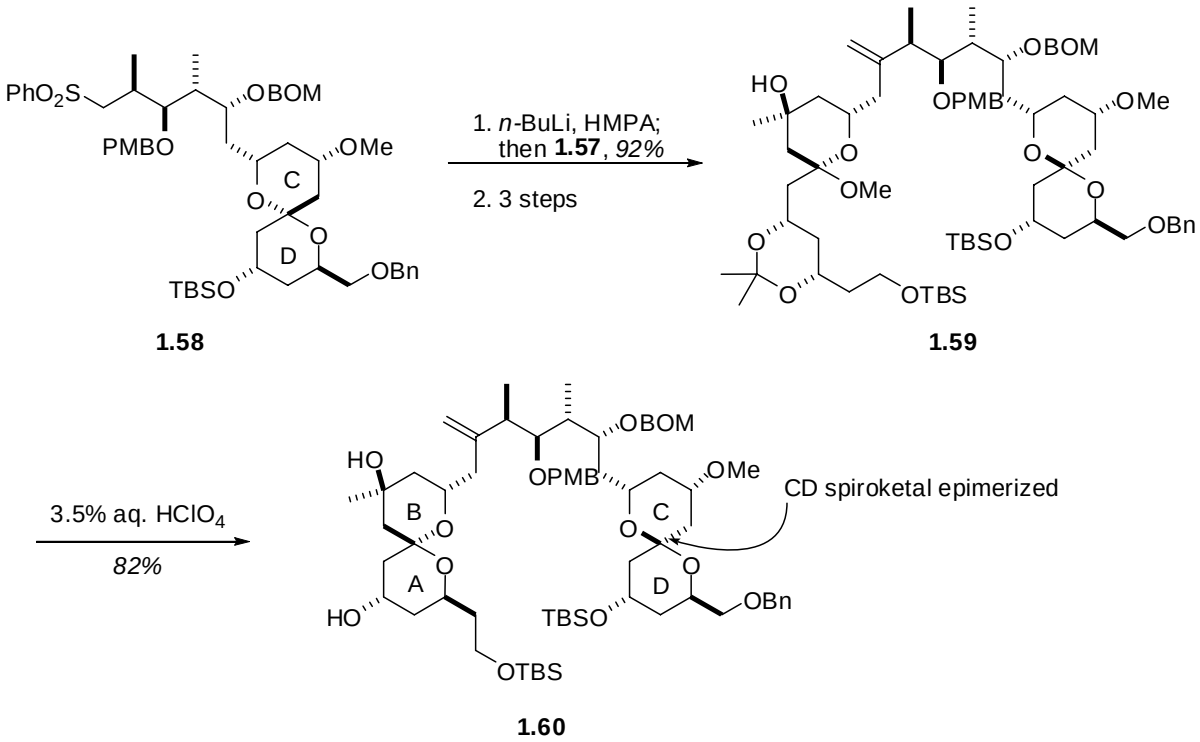
Scheme 7. Smith's Synthesis of the B Ring



Smith began his synthesis of the B-ring fragment from the protected hydroxypropanal **1.48** (Scheme 7). Treatment with the Brown allylboration[31-34] reagent provided the homoallylic alcohol **1.49**. Iodocarboxylation-decarbonylation then provided the terminal epoxide. The free alcohol was then protected as a triethylsilyl ether to provide the epoxide coupling partner **1.50** for a dithiane addition. The synthesis of the other dithiane coupling partner began from protected aldehyde **1.51** which was functionalized to the allylic alcohol **1.52** in two steps. Sharpless' epoxidation installed the internal epoxide, which was then reductively opened with lithium borohydride and titanium (IV) isopropoxide. Selective tosylation of the terminal hydroxyl group, followed by treatment with base installed the terminal epoxide **1.53**.

Lithiation of dithiane **1.54** followed by addition of epoxide **1.53**, an HMPA-induced Brook rearrangement, and addition of epoxide **1.50** provided coupled product **1.55** in one pot. Further elaboration provided the precursor **1.56** to the first cyclization event. Formation of the B-ring was then facilitated through hydrolysis of the dithiane to form a mixture of methyl acetals, which was treated with acid to equilibrate to the desired B-ring fragment **1.57**.

Scheme 8. Smith's Completion of AB Spiroketal

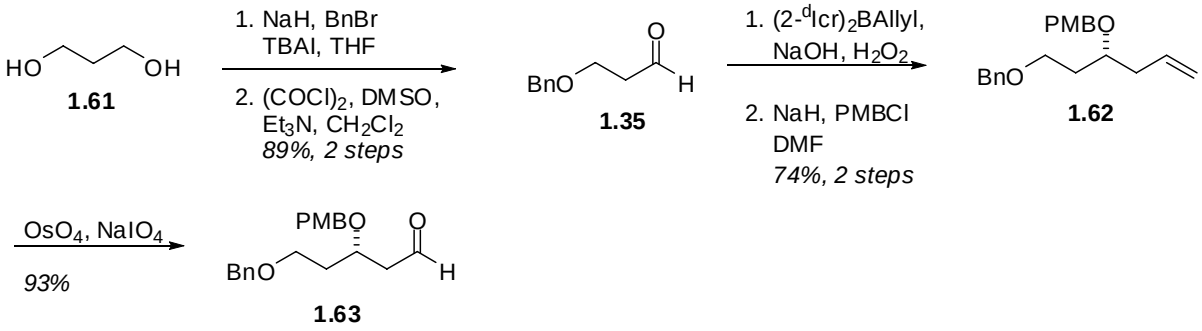


The B-ring fragment **1.57** was coupled to the CD-spiroketal fragment through the addition of the lithiated sulfone of **1.58** (Scheme 8). Installation of the methylene unit at C13 and further elaboration provided the BCD fragment **1.59**. Treatment with catalytic perchloric acid induced cyclization and formation of the AB-spiroketal **1.60**. During this process, however, epimerization of the CD-spiroketal occurred. This was readily corrected through an equilibration event at the end of the synthesis.

1.2.6 Crimmins First Generation Approach to the AB Spiroketal

The total synthesis of spongistatins 1 and 2 (**1.1**, **1.2**) from our laboratory was also based on the assembly of three fragments including the C1-13 AB spiroketal (Figure 1).

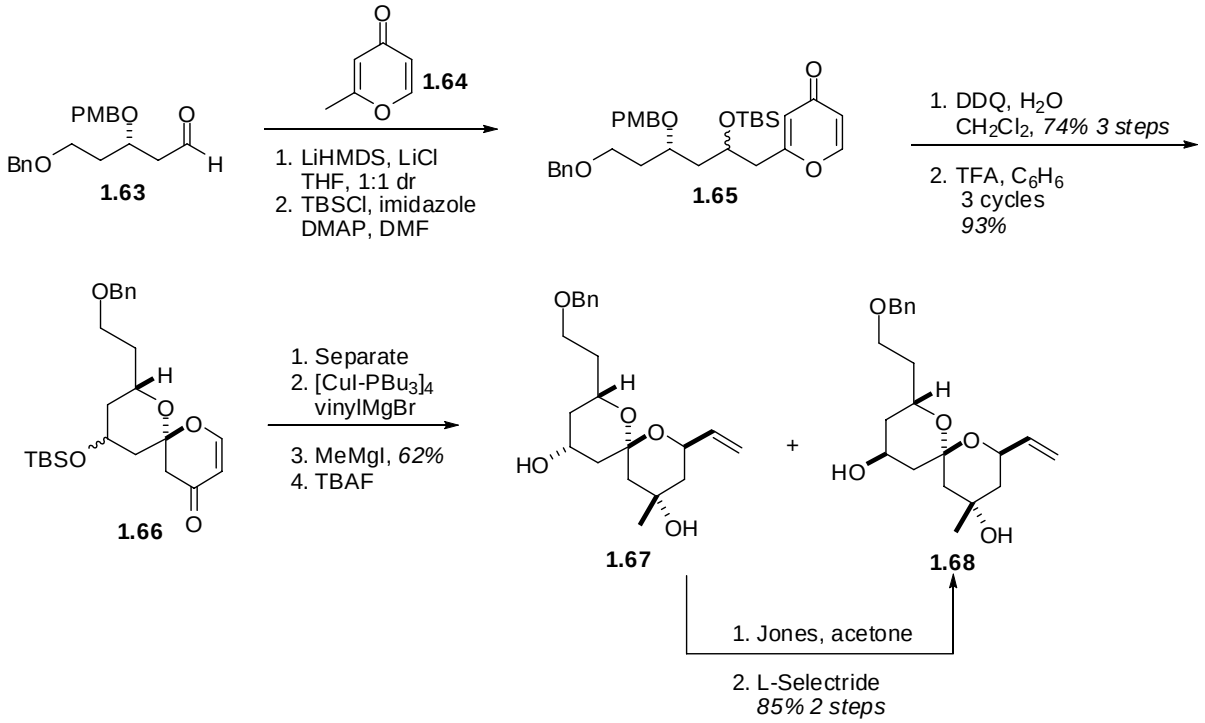
Scheme 9. Synthesis of Aldehyde X



The Crimmins group took a different approach[35-38] to the synthesis of the AB spiroketal. The synthesis of the AB spiroketal centered on the preparation of pyrone **1.64** (Scheme 9) through addition of a metalated pyrone to an aldehyde. Instead of the more traditional approach consisting of condensation of a diol onto a ketone or ketone equivalent, an acid-catalyzed 1,4-addition forms the spiroketal core.

Our group's synthesis began from 1,3-propanediol **1.61**. Monoprotection and oxidation under Swern conditions provided the aldehyde **1.35**. Brown allylboration with oxidative work-up and protection of the resultant alcohol provided the terminal olefin **1.62**. Oxidation under Johnson-Lemieux conditions provided the aldehyde **1.63**.

Scheme 10. Crimmins Completion of AB Spiroketal



Reaction of the aldehyde **1.63** with lithiated pyrone **1.64** (Scheme 10), provided a 1:1 inseparable mixture of alcohol diastereomers. All attempts to improve the diastereoselection of the addition by changing the counterion, solvents, and additives were unsatisfactory. Additionally, attempts to prepare the silyl enol ether of pyrone **1.64** to investigate Mukaiyama-type additions to aldehyde **1.63** were thwarted since all silylating conditions led to C-silylation of the pyrone.[39] Silyl protection and deprotection of the *p*-methoxybenzyl ether provided the β-hydroxypyrone. Treatment with catalytic trifluoroacetic acid provided spiroenone **1.66** in high yield after 3 cycles. At this point, the diastereomers were separated by flash column chromatography. Each diastereomer was then independently treated to a copper-mediated vinyl addition, methylation, and deprotection with TBAF to provide spiroketals **1.67** and **1.68**. The undesired diastereomer **1.67** was then oxidized and selectively reduced with L-Selectride to provide the desired diastereomer **1.68**.

1.3 Summary

Several syntheses have been reported to form the AB spiroketal of spongistatin (**1.1,1.2**). These attempts included syntheses of functionalized acyclic skeletons, followed by condensations onto ketone or ketone equivalents using acid catalysis. The synthesis from the Crimmins lab included an internal 1,4-addition into a pyrone to form the spiroketal core with diastereoselective functionalization responsible for further elaboration on the ring system. A problem in the synthesis occurred with respect to the initial formation of the stereocenter at C5, however.

Chapter 2

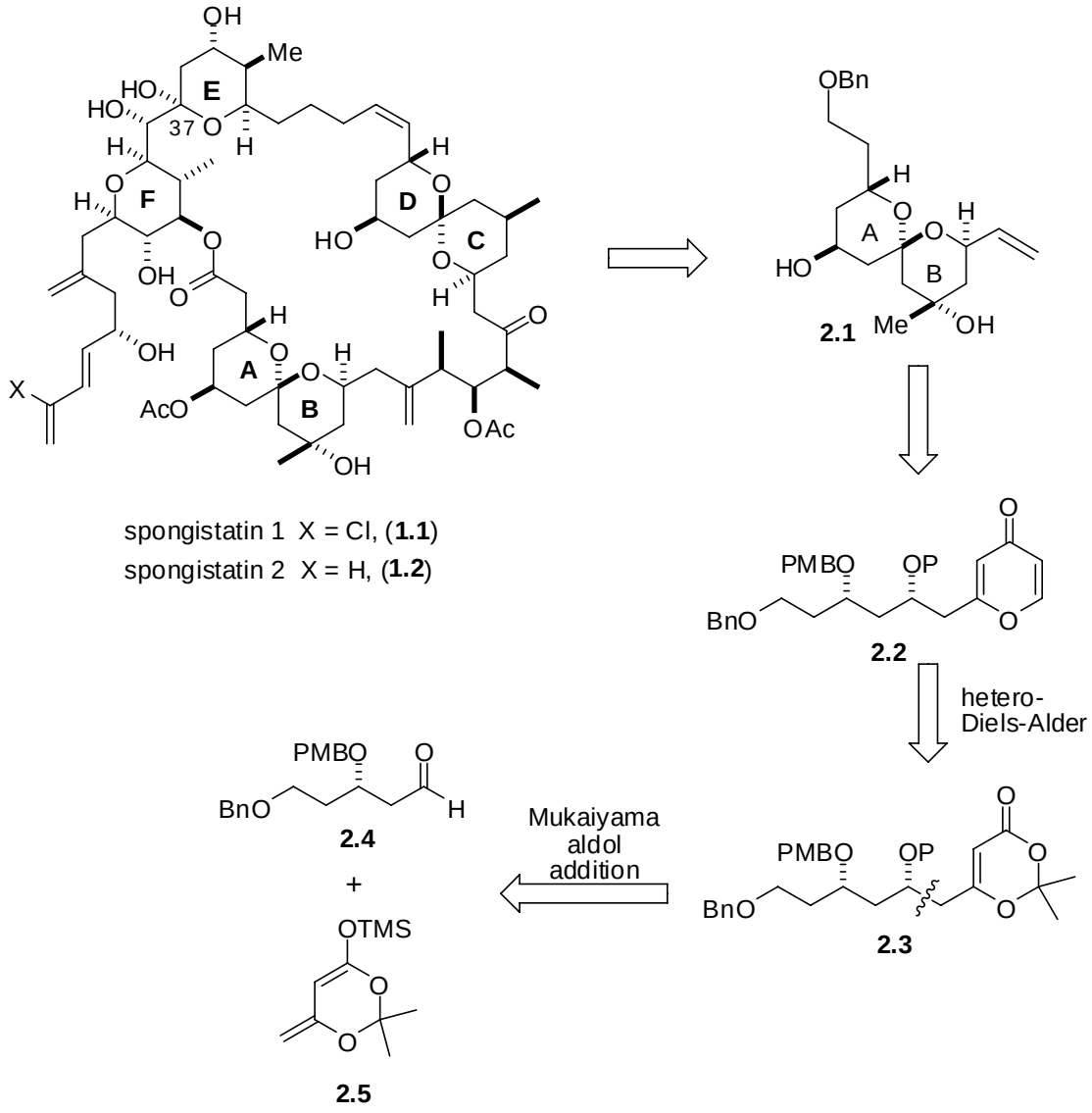
An Improved Synthesis of the C1-C13 AB Spiroketal of Spongistatin

2.1 Introduction

As shown in Chapter 1 (Scheme 10), deprotonation of pyrone **1.64** with LiHMDS followed by addition of aldehyde **1.63** led to the generation of a 1:1 mixture of diastereomers at C5. This lack of stereocontrol at C5 required a four-step sequence to correct and could not be accomplished until after the spiroketalization event, thus requiring that both diastereomers be carried forward several steps prior to convergence. To overcome this stereochemical shortcoming, an improvement in the preparation of the pyrone was then investigated.[40]

2.2 Retrosynthetic Analysis

Scheme 11. Retrosynthetic Analysis of the AB Spiroketal

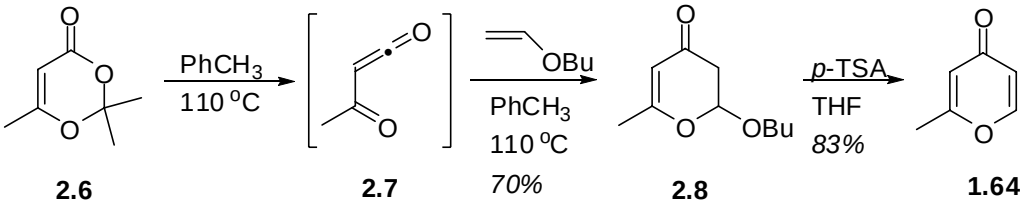


Under the proposed, improved route to spongistatin, C1-C13 AB spiroketal subunit **2.1** was envisioned to come from an acid-catalyzed cyclization[41] of pyrone **2.2** (Scheme 11). This would be formed through a hetero-Diels-Alder cycloaddition-elimination sequence from dioxinone **2.3**. The dioxinone would in turn derive from a selective Mukaiyama aldol addition of silyl dienolate **2.5** to aldehyde **2.4**.

2.3 Development of the Hetero-Diels-Alder Reaction

2.3.1 Background

Scheme 12. Conversion of Dioxinone 2.6 to Pyrone 1.64

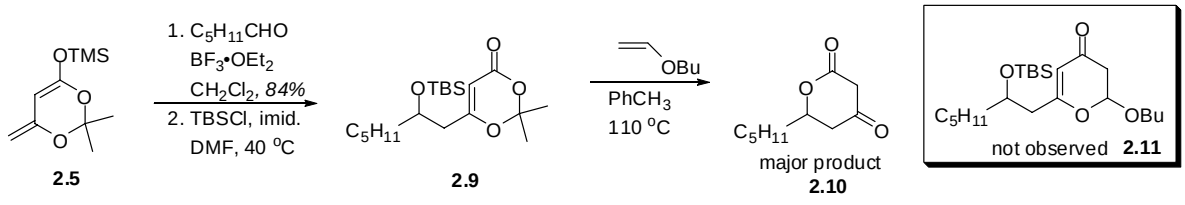


Coleman and Grant[42,14] reported the conversion of dioxinone **2.6** to butyl acetal **2.8** in 1990 (Scheme 12). In this reaction they observed that when dioxinone **2.6** is heated in toluene, acyl ketene **2.7** is formed. This intermediate could then be trapped through a cycloaddition with butyl vinyl ether to provide the butyl acetal **2.8.** This product was then converted to pyrone **1.64** through heating with *p*-toluenesulfonic acid to facilitate the elimination of butyl alcohol.[43]

2.3.2 Model System

Prior to extending this methodology to the synthesis of the AB spiroketal, an extension to a simpler model system was undertaken (Scheme 3).

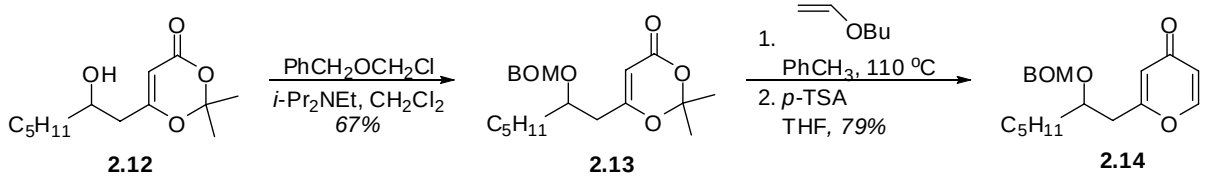
Scheme 13. Hetero-Diels-Alder Model System



The silyl dienolate **2.5** was reacted with hexanal in the presence of boron trifluoride-diethyl etherate in a Mukaiyama-type aldol addition (Scheme 13). The resultant alcohol was protected as a *tert*-butyldimethylsilyl ether to mimic the protecting group present in the first

generation approach to the AB spiroketal. Applying the conditions of Coleman and Grant to the system at hand by heating dioxinone **2.9** with butyl vinyl ether did not provide the desired butyl acetal **2.11**. Instead, the β-ketolactone **2.10** was formed. This likely occurred through the interception of the acyl ketene intermediate with the C5 ether oxygen[44,45] with protodesilylation of the TBS group. This was also observed in previous work performed in our lab when the TES protecting group was employed.[46]

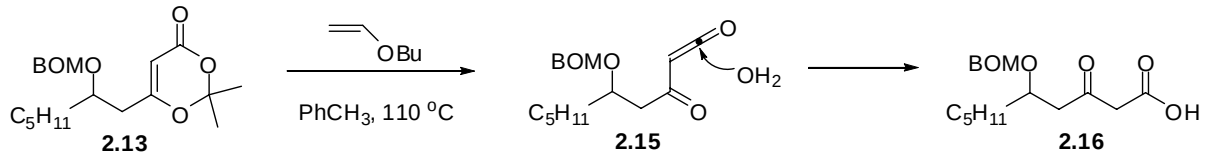
Scheme 14. Protecting Group Change in the Diels-Alder Reaction



2.12 **2.13** **2.14**

To preclude the formation of the β-ketolactone, a more robust protecting group needed to be employed. Protection of alcohol **2.12** with benzylchloromethyl ether proceeded to give the benzyloxymethyl ether **2.13** (Scheme 14). Exposure to heat and butyl vinyl ether provided the desired butyl acetal, which upon treatment with *p*-toluenesulfonic acid provided the desired pyrone **2.14**.

Scheme 15. Effect of Adventitious Water on the Diels-Alder

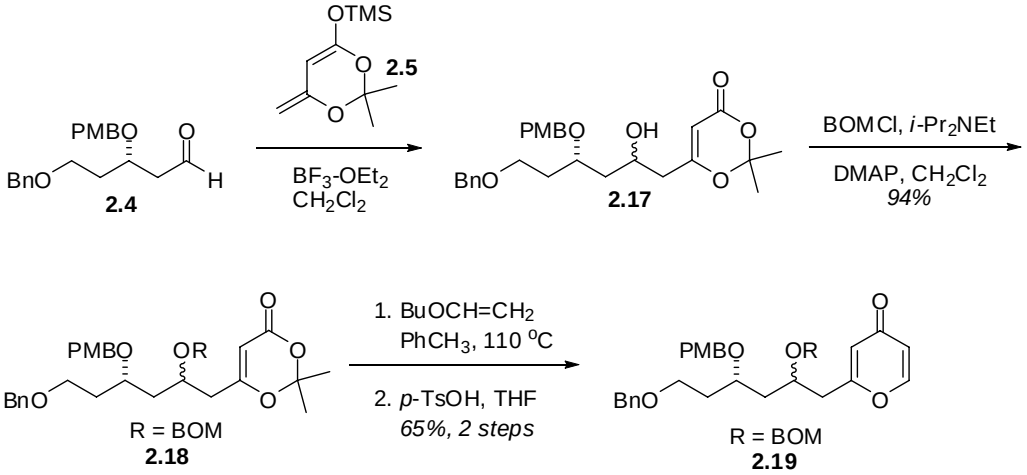


2.13 **2.15** **2.16**

It is worthwhile to note that efficient conversion of the dioxinone **2.13** to the butyl acetal required that all materials be rigorously dried to avoid trapping of the acyl ketene intermediate **2.15** by adventitious water (Scheme 15). Failure to scrupulously dry the dioxinone, the solvent, or butyl vinyl ether led to formation of β-keto acid **2.16** as a major product.

2.3.3 Application to Desired System

Scheme 16. Application to Desired System



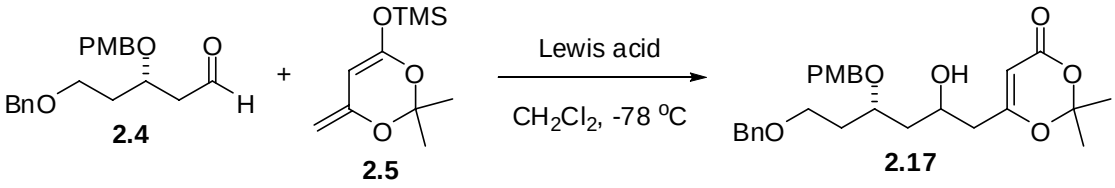
Before investigating a method for introducing selectivity into the Mukaiyama-type aldol addition, the hetero-Diels-Alder cycloaddition-elimination was applied to a mixture of diastereomers of alcohol **2.17** with the substitution pattern of the spongistatin AB spiroketal (Scheme 16). This was synthesized from the reaction of silyl dienolate **2.5** with aldehyde **2.4** in the presence of boron trifluoride-diethyl etherate. Alcohols **2.17** were protected as benzyloxymethyl ethers **2.18**. Subjection to the hetero-Diels-Alder conditions provided the desired butyl acetal. Acid catalyzed elimination then provided the desired pyrones **2.19.**

2.4 Introduction of Selectivity into the Mukaiyama Aldol Addition

With the optimal conditions for the hetero-Diels-Alder cycloaddition worked out, a general method to selectively access the Mukaiyama aldol adduct of silyl dienolate **2.5** with aldehyde **2.4** was next needed for the improved route to the spongistatin AB spiroketal.

2.4.1 Attempts at Substrate-Controlled Selectivity

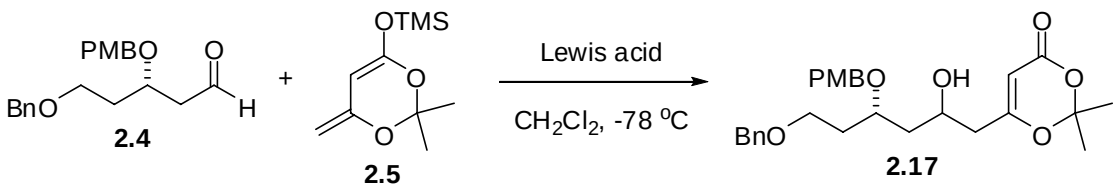
Table 1. Use of Lewis Acids in Addition to Aldehyde



	Lewis Acid	Yield (%)	Selectivity (anti:syn)
1	$BF_3{\cdot}OEt_2$	90	1:1
2	Me_2AlCl	45	1.3:1
3	$TiCl_4$	61	1.5:1
4	$Ti(O\textit{i}\text{-}Pr)_4$	0	-
5	$Ti(O\textit{i}\text{-}Pr)Cl_3$	82	2.0:1
6	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	89	3.3:1
7	$Ti(O\textit{i}\text{-}Pr)_3Cl$	21	2.4:1

Initial attempts to achieve this goal focused on the use of different Lewis acids to take advantage of the potential directing ability of the β-alkoxyaldehyde. The use of a common Lewis acid, boron trifluoride-diethyl etherate (Table 1, entry 1), proved nonselective, albeit high yielding. Stronger chelating Lewis acids, such as Me_2AlCl (entry 2), have been used in similar cases to achieve rigid chelating transition states with β-alkoxyaldehydes and the addition of silyl enol ethers leading to high *anti* selectivity.[47] Unfortunately, only a slight preference (1.3:1) in favor of the *anti* diastereomer was observed. The use of titanium Lewis acids (entries 3-7) slightly improved the *anti* selectivity, but the best case with titanium(IV) dichlorodiisopropoxide (entry 6) provided only a 3.3:1 preference for the *anti* diastereomer.

Table 2. Use of Chiral Ligands in Addition of Silyl Dienolate 2.5 and Aldehyde 2.4

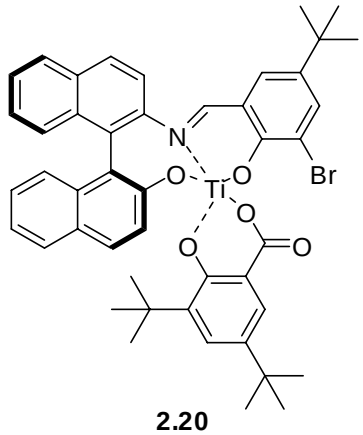


	Lewis Acid	Ligand	Yield (%)	Selectivity (anti:syn)
1	Ti(O*i*-Pr)$_4$	*S*-BINOL	28	1:1
2	Ti(O*i*-Pr)$_2$Cl$_2$	(*S*,*S*)-(+)-TADDOL	64	5:1
3	Ti(O*i*-Pr)$_2$Cl$_2$	(*R*,*R*)-(-)-TADDOL	60	1:2.1
4	Ti(O*i*-Pr)$_4$	(-)-**2.20**	81	8.6:1
5	Ti(O*i*-Pr)$_4$	(+)-**2.20**	95	1:10

2.4.2 Attempts at Reagent and Catalyst Controlled Selectivity

Chiral ligands were next explored in an attempt to use reagent control to influence the diastereoselectivity of the reaction. BINOL in conjunction with Ti(O*i*-Pr)$_4$ has been reported to result in good selectivity in Mukaiyama aldol additions,[48,49] but when applied to the case at hand (Table 2, entry 1), low yield and poor selectivity were observed. TADDOL has also been shown to provide high levels of reagent control in Lewis acid-catalyzed aldol additions.[50,51] Exposure of dienolate **2.5** and aldehyde **2.4** to titanium(IV) dichlorodiisopropoxide and *S*,*S*-TADDOL (entry 2) delivered a 5:1 mixture favoring the *anti* diastereomer. Unfortunately, *R*,*R*-TADDOL gave only a 2:1 preference for the *syn* diastereomer (entry 3).

Figure 2. Carreira's Catalyst



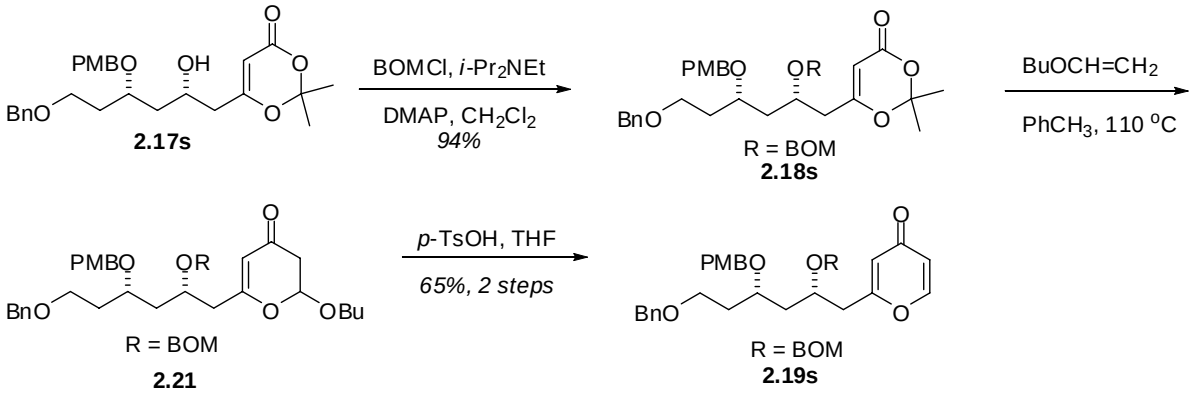
2.20

Satisfactory diastereoselection was ultimately obtained by taking advantage of Carreira's catalyst (Figure 2),[52] which has been reported to effect enantioselective Mukiayama aldol additions of silyl dienolate **2.5** with a variety of achiral aldehydes. Use of the Carreira protocol with dienolate **2.5** and aldehyde **2.4** allowed access to either the *syn* diastereomer **2.17s** or anti diastereomer **2.17a** in high yield and selectivity with low catalyst loadings. Using the (+)-enantiomer of **2.20** (entry 5) led to formation of a 10:1 mixture of aldol adducts favoring the desired *syn* diastereomer **2.17s** (95% yield), while (-)-**2.20** produced the *anti* diastereomer **2.17a** (entry 4) as the major product (8.6:1 dr, 81% yield).

2.5 Synthesis of the AB Spiroketal

2.5.1 Application of Hetero-Diels-Alder Cycloaddition-Elimination

Scheme 17. Hetero-Diels-Alder Cycloaddition

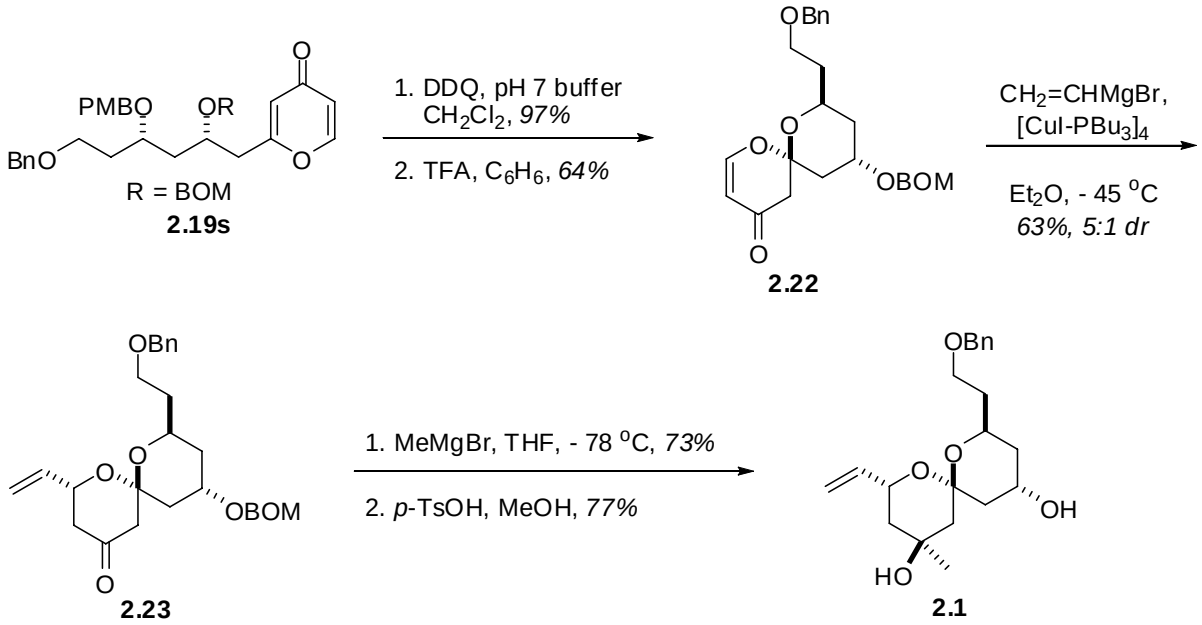


Having accomplished an efficient synthesis of the desired dioxinone **2.17s**, its conversion to the required pyrone was then undertaken. To this end, the C5 hydroxyl was readily protected as a benzyloxymethyl ether to provide hetero-Diels-Alder precursor **2.18s** (Scheme 17). Heating this in toluene in the presence of butyl vinyl ether led to formation of butyl acetal **2.21** through a hetero-Diels-Alder reaction. Immediate exposure of the butyl acetal to

p-toluenesulfonic acid in THF led to rapid elimination of butyl alcohol to produce pyrone **2.19s** (65% over two steps).[43]

2.5.2 Completion of the Synthesis and Interception of the AB Spiroketal

Scheme 18. Completion of AB Spiroketal

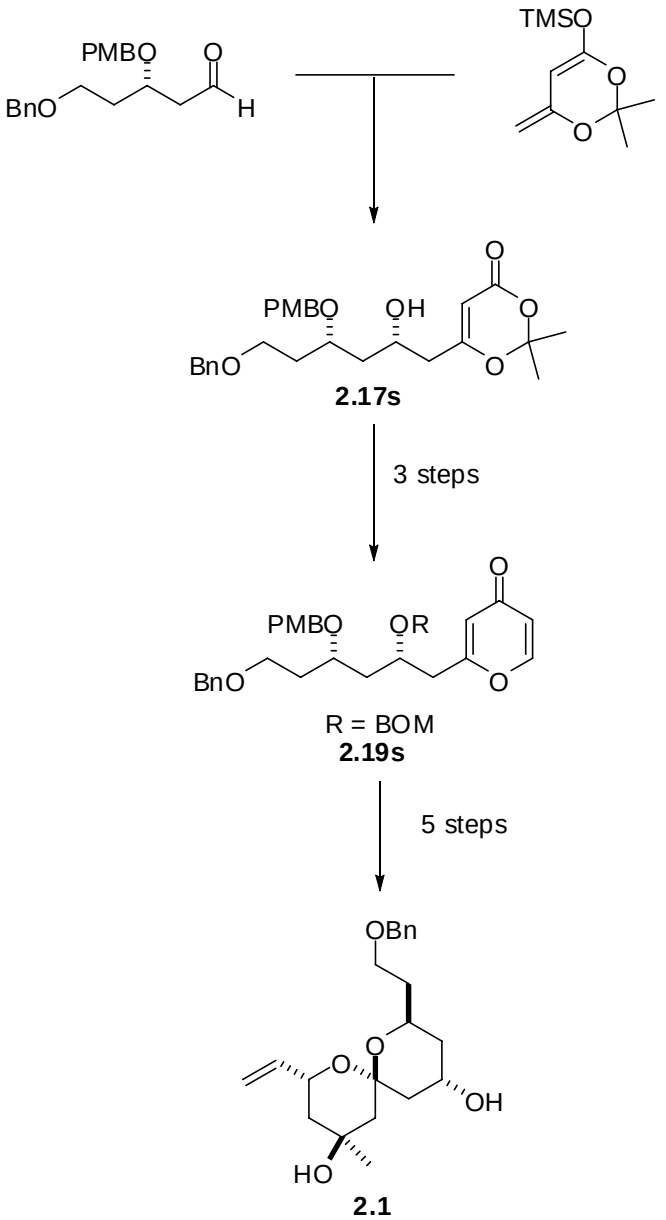


Taking advantage of the chemistry previously employed in the total synthesis of spongistatin, the *p*-methoxybenzyl group was removed by the action of DDQ to provide the free alcohol at C3 (Scheme 18). Exposure of the hydroxypyrone to catalytic trifluoroacetic acid in benzene provided spiroenone **2.22** in 64% yield after recycle. The minor diastereomer (<10%, which had been introduced in the Mukaiyama aldol addition) could be readily removed after the spiroketalization. Treatment of the spiroenone **2.22** with the vinyl cuprate reagent formed from vinylmagnesium bromide and tetrakis[copper(I) iodide-tributylphosphine] led to the formation of alkene **2.23** as the major diastereomer (5:1 dr). The C9 tertiary carbinol was then introduced by addition of methylmagnesium iodide to the C9 ketone. Cleavage of the benzyloxymethyl ether occurred upon treatment with acid to provide

the desired diol **2.1**. Comparison of spectral data confirmed the interception of the previously synthesized fragment utilized in the reported total synthesis of spongistatin.[35-38]

2.6 Conclusions

Scheme 19. Summary of the Improved Synthesis of the AB Spiroketal of Spongistatin



In summary, an improved synthesis of the AB spiroketal subunit of spongistatin has been developed (Scheme 19). This synthesis takes advantage of a diastereoselective Mukaiyama

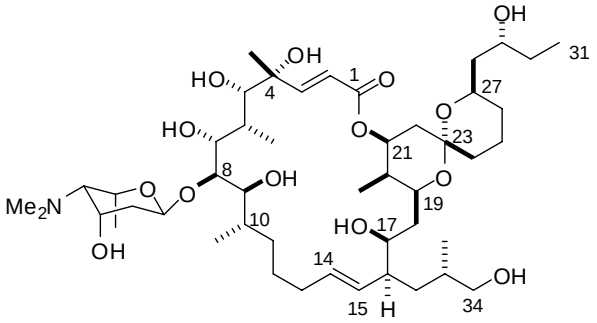
aldol reaction to provide **2.17s**. Subsequent hetero-Diels-Alder cycloaddition and elimination constructed the pyrone **2.19s**. Functionalization of this core led to the fully elaborated AB spiroketal of spongistatin.

Chapter 3

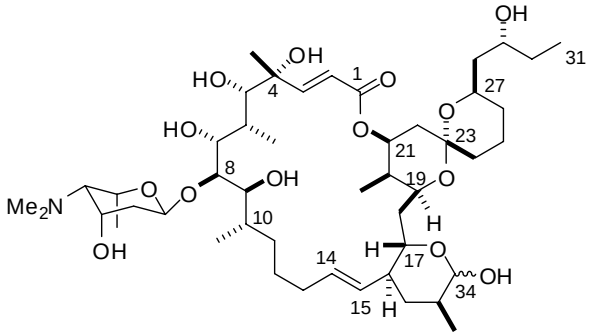
Background

3.1 Introduction

Figure 3. The Yokonolides



yokonolide A
3.1



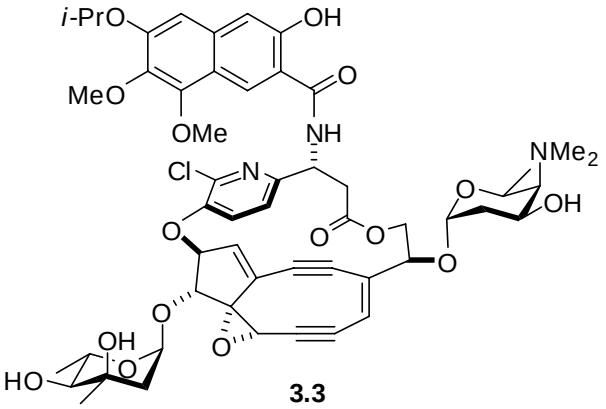
yokonolide B
(A82548A)
3.2

3.1.1 Isolation and Structure Determination

Yokonolide A[53] and B (previously referred to as A82548A)[54] are biologically active compounds isolated from *Streptomyces diastatochromogenes* B59 (Figure 3). Yokonolide B was isolated in 1995, while yokonolide A was isolated and characterized later in 2001. These are 22-membered macrolides containing spiroketal subunits and an aminosugar moiety. Yokonolide A contains 20 stereogenic centers, while yokolide B additionally contains a hemiacetal feature that exists as a 6:4 α:β ratio at C34. The structure was determined using various NMR techniques including, ^{1}H, ^{13}C, DEPT, COSY, TOCSY, HMBC, and HMQC. X-ray crystallography[54] determined the relative configuration of yokonolide B and chemical

degradation yielded the L-kedarosamine sugar to indicate the absolute configuration. Furthermore, reduction of yokonolide B with sodium borohydride led to formation of yokonolide A to confirm the structure and stereochemistry.

Figure 4. Conformational Difference of Kedarosamine in the Natural Product Kedarcidin



3.3

One of the interesting structural features of the molecule relates to the presence of the L-kedarosamine amino sugar. This naturally-occurring sugar has also been observed in the natural product, kedarcidin.[55-57] The conformations of the amino sugar moiety differ in each of these natural products, however. In kedarcidin (**3.3**, Figure 4), the sugar adopts the conformation that places the aglycon and the dimethylamino substituent in an axial orientation. In the yokonolides, however, the aglycon and the dimethylamino substituents are both oriented equatorially.

3.1.2 Biological Activity

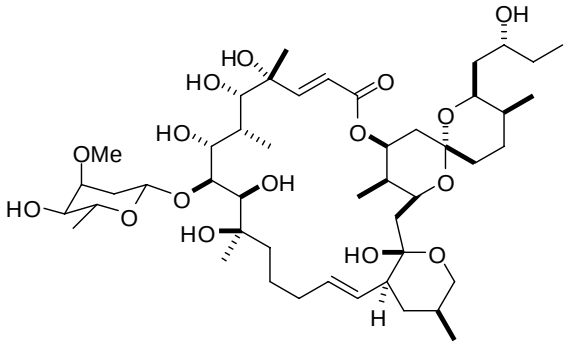
Both yokonolide A and B are inhibitors of auxin-inducible gene expression, while yokonolide B exhibits antifungal properties as well. Experiments found that both yokonolide A and B completely inhibited the auxin-induced transcription of the reporter gene GUS (β-glucuronidase) at 5 and 1 μM, respectively when screened with an Arabidopsis transgenic line harboring the auxin-inducible promoter derived from *PS-IAA4/5*. They were selective in

this action as they did not inhibit the gibberellin-induced α-amylase expression at 100 μM in barley aleurone cells. The plant hormone auxin regulates various aspects of plant growth and development by controlling cell division, cell elongation, and cell differentiation.[58] It also causes significant changes in the expression pattern of a several genes.[59]

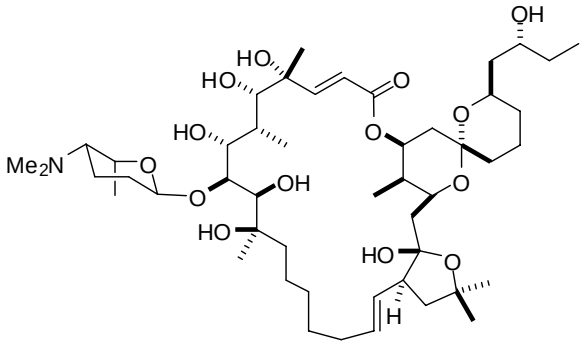
3.2 Similar Natural Products

The yokonolides are part of a larger family of molecules with similar structures (Figure 5) which include cytovaricin,[60-63] oligomycins,[63] rutamycins,[63] ossamycin,[64,65] and phthoramycin.[66,67]

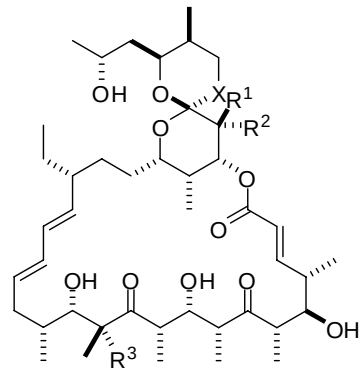
Figure 5. Selected Natural Products Similar to the Yokonolides

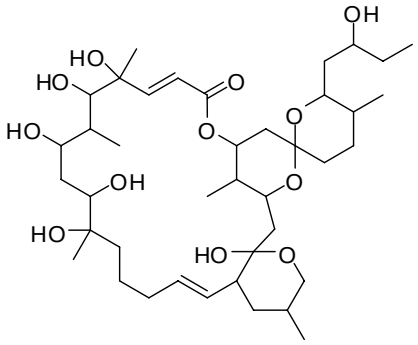


cytovaricin
Evans, D. A. 1990



ossamycin





kaimonolide A

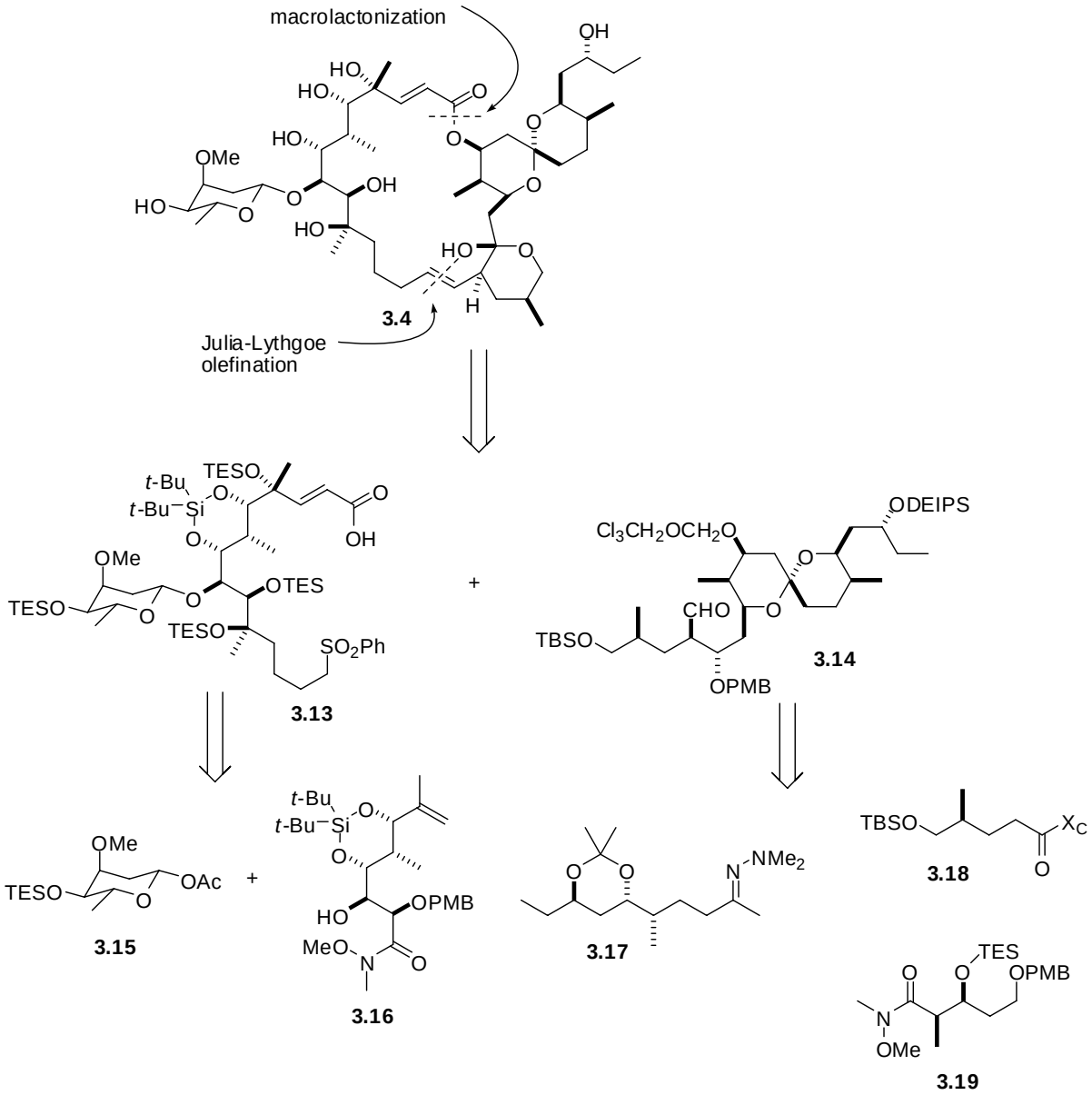
Derivative	R^1	R^2	R^3	X	Syntheses
oligomycin A	Me	H	CH	CH_2	
oligomycin B	Me	H	CH	CO	
oligomycin C	Me	H	H	CH_2	Panek, J. S., 1998
oligomycin E	Me	CH	CH	CO	
rutamycin A	H	H	CH	CH_2	
rutamycin B	H	H	H	CH_2	Panek, J. S., 2001 White, J. D., 2001 Evans, D. A., 1993

3.3 Synthetic Efforts Toward Related Spiroketal Macrolides

3.3.1 Evans Synthesis of Cytovaricin

3.3.1.1 RetrosyntheticAnalysis

Scheme 20. Evans Retrosynthetic Analysis of Cytovaricin

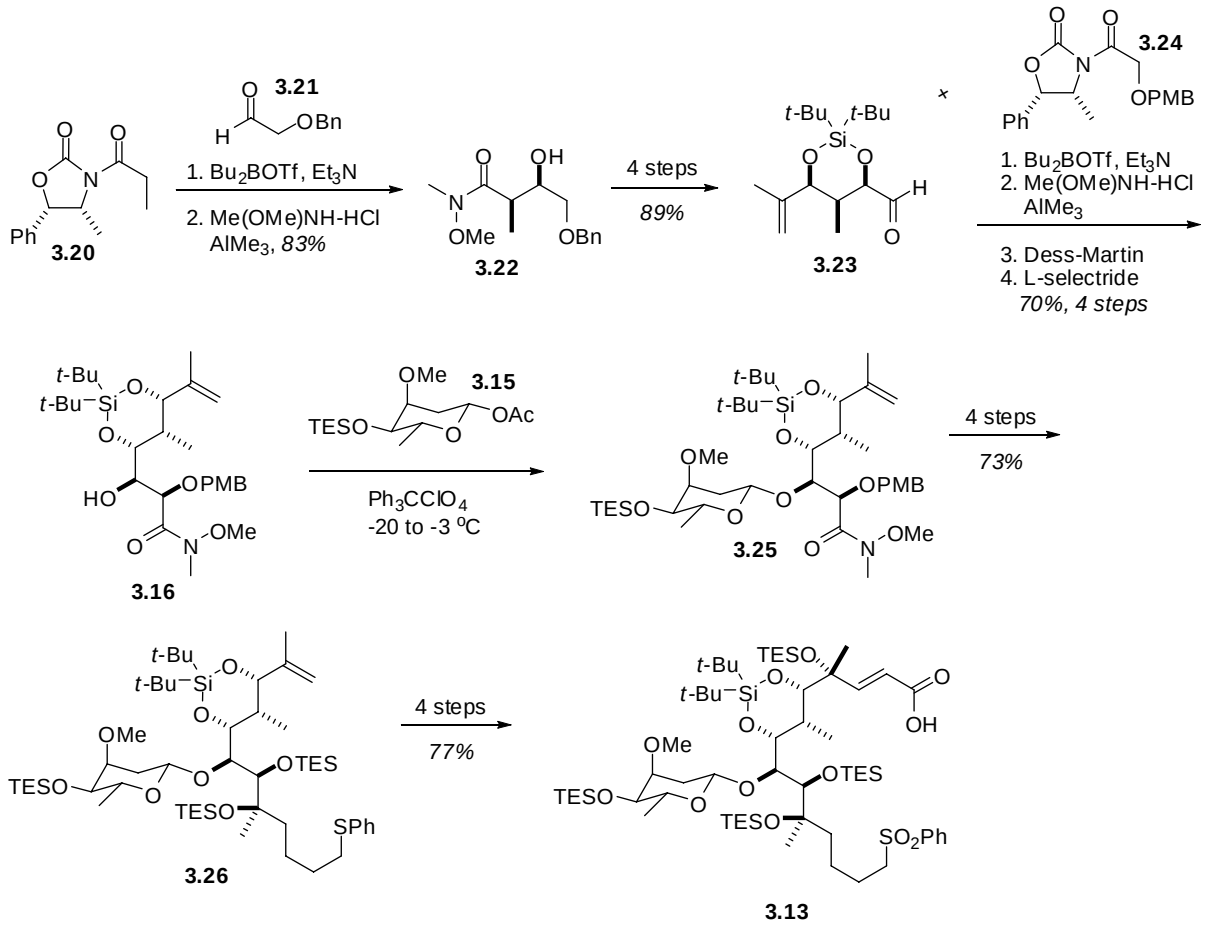


Evans synthesized the similar spiroketal-macrolide natural product, cytovaricin, in 1990.[68] He adopted a convergent approach, making disconnections at the macrolactone ester and

C14-C15 olefin via a Julia-Lythgoe olefination (Scheme 20). The C1-C14 fragment **3.13** was derived from a glycosylation with the cymarose-derived sugar **3.15** and glycosyl acceptor **3.16.** The acceptor fragment **3.16** was synthesized through the use of asymmetric aldol additions. The spiroketal C15-C34 fragment **3.14** was formed through an acid-catalyzed spiroketalization after convergence of the three main fragments: hydrazone **3.17**, side chain acylated auxiliary **3.18**, and Weinreb's amide **3.19.**

3.3.1.2 Evans Synthesis of the C1-C14 Fragment of Cytovaricin

Scheme 21. Evans Synthesis of the C1-C14 fragment of cytovaricin

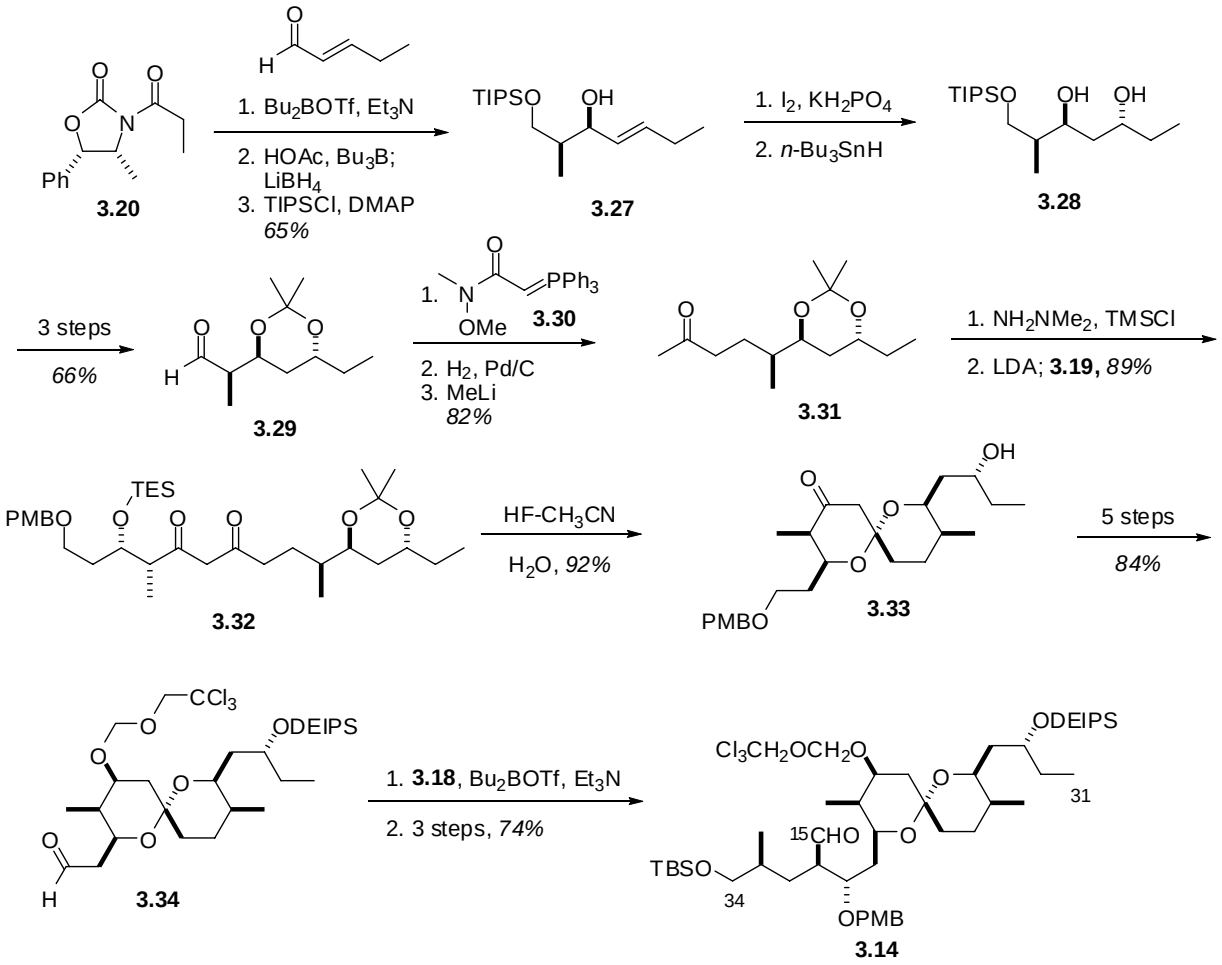


Evans synthesis of the C1-C14 fragment **3.13** (Scheme 21) begins with an asymmetric propionate aldol addition[69] to aldehyde **3.21**, followed by transamidation[70] to the *N,O*-dimethylhydroxylamide **3.22**. Further elaboration introduces the propene and di-*t*-butylsilylidene moieties to form aldehyde **3.23**. An unexpected, highly selective *anti*-aldol addition takes place under the standard aldol conditions to provide the undesired configuration at C8. Oxidation,[71] followed by selective reduction[72] provided the desired *syn* relationship in alcohol **3.16**. β-selective glycosylation[73] with the glycosyl donor **3.15** provided the desired coupled product **3.25**. Protecting group manipulation and introduction

of the C10-C14 chain provided **3.26**. Conversion to the sulfone and further elaboraton led to the formation of the completed C1-C14 fragment **3.13.**

3.3.1.3 Evans Synthesis of the C15-C34 Spiroketal Fragment of Cytovaricin

Scheme 22. Evans Synthesis of the C15-C34 Spiroketal Fragment of Cytovaricin

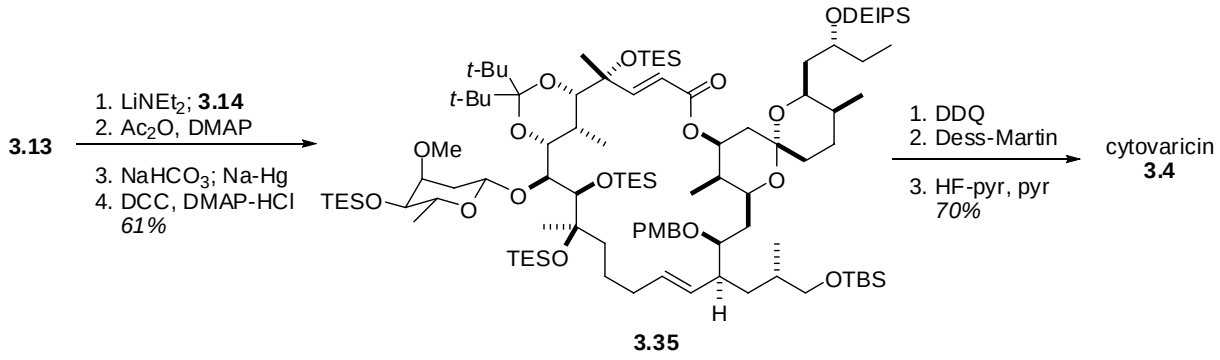


The synthesis of the C15-C34 fragment **3.14** (Scheme 22) began with *N*-propionyloxazolidinone **3.20**. A boron-mediated aldol addition[69] to 2-pentenal provided the aldol adduct, the auxiliary was removed, and the subsequent primary alcohol was protected as the TIPS ether **3.27**. Iodohydroxylation[74] was used to install the hydroxyl group at C29 while the iodide was homolytically cleaved through the action of tributyltin hydride to provide diol **3.28**. Further elaboration provided aldehyde **3.29**. Wittig olefination with ylide

3.30, hydrogenation, and methylation provided ketone **3.31**. The ketone was converted to the hydrazone and the lithium enamide was produced with LDA. This was then reacted with amide **3.19** to produce diketone **3.32** upon workup. Treatment with hydrofluoric acid-acetonitrile both removed the TES group and promoted cyclization to form spiroketal **3.33**. Further functionalization over 5 steps provided aldehyde **3.34**. Treatment of acylated oxazolidinone **3.18** with dibutyl boron triflate and introduction of aldehyde **3.34** was used to form the *syn* aldol adduct. Removal of the auxiliary and protection provided the completed C15-C34 fragment **3.14**.

3.3.1.4 Evans Coupling and Completion of the Synthesis of Cytovaricin

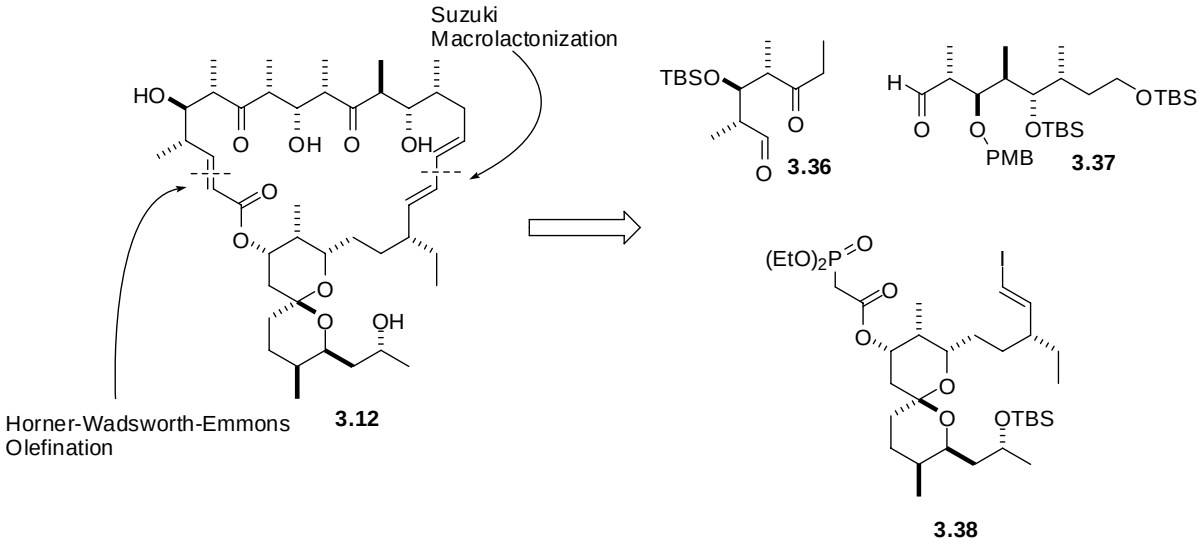
Scheme 23. Evans Completion of Cytovaricin



To couple the major fragments for the synthesis of cytovaricin, Evans employed the Julia-Lythgoe[75] conditions with sulfone **3.13** and aldehyde **3.14** to form the olefin between C14 and C15 (Scheme 23). Macrolactonization[76,77] then ensued through the use of dicyclohexylcarbodiimide and DMAP to provide the protected natural product. A three step removal of the protecting groups provided cytovaricin.

3.3.2 White's Strategy for Rutamycin

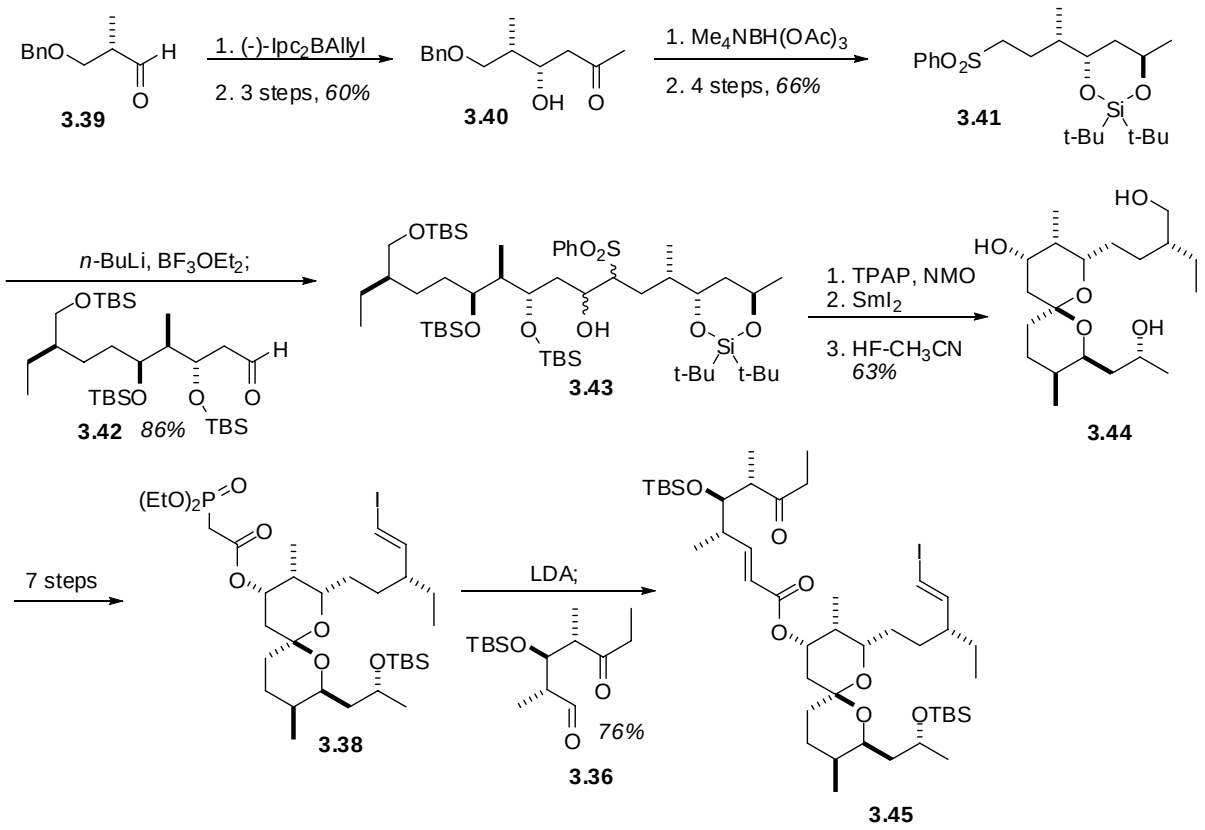
Scheme 24. White's Main Disconnections for Rutamycin B



White's[78] strategy for the synthesis of the antioboitic rutamycin B (**3.12**) takes advantage of a Suzuki macrolactonization event preceeded by coupling of the main fragments, aldehyde **3.36** and phosphonate **3.38,** via a Horner-Wadsworth-Emmons olefination (Scheme 24).[79] An aldol addition incorporates aldehyde **3.37**.

3.3.2.1 White's Approach to the Spiroketal Fragment

Scheme 25. White's Synthesis of the Spiroketal Fragment

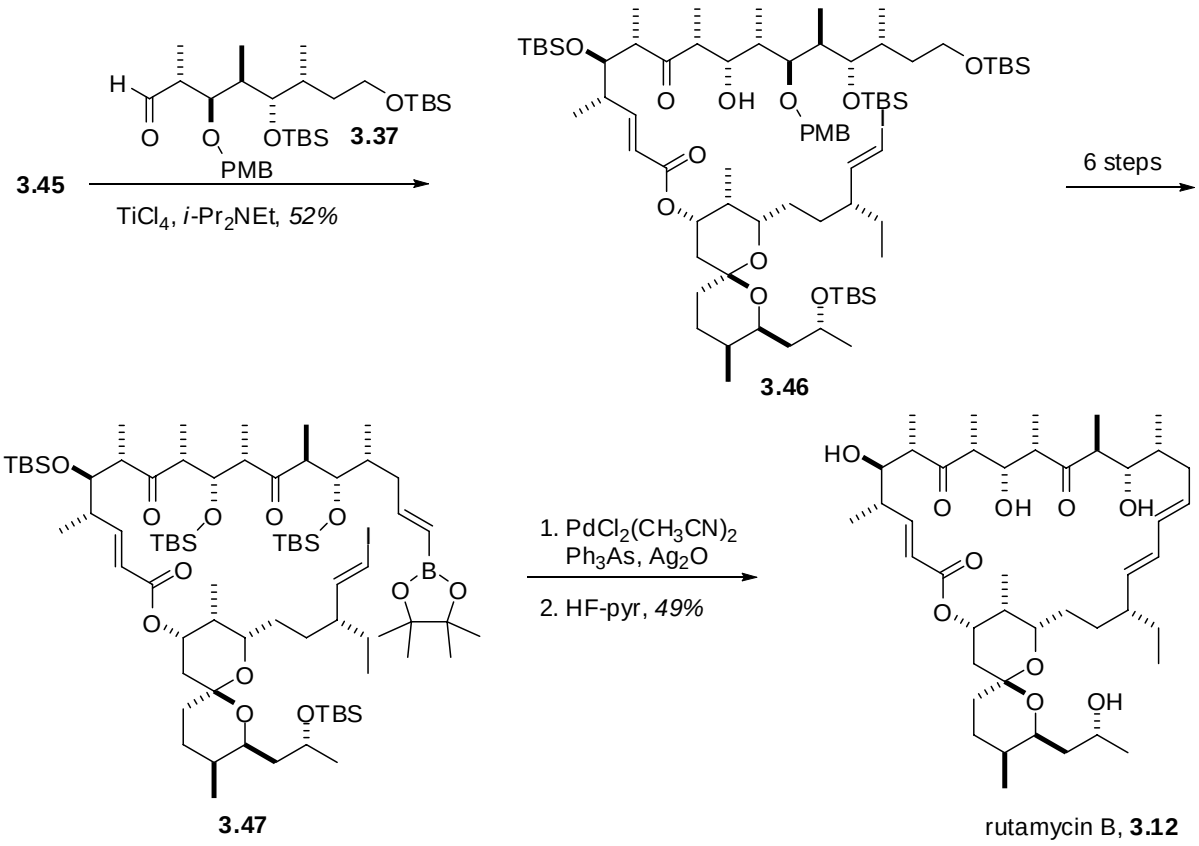


White's synthesis of the spiroketal fragment began with an asymmetric allylboration[80] of aldehyde **3.39** (Scheme 25). Further elaboration provided the methyl ketone **3.40**. Selective reduction with tetramethylammonium triacetoxyborohydride[81] provided the *anti*-1,3-diol, which upon further functionalization led to sulfone **3.41**. Lithiation of the sulfone followed by introduction of aldehyde **3.42** provided the sulfone **3.43**.[82] The alcohol was oxidized[83] to the ketone and reductive desulfurization[84] with samarium(II) iodide occurred. The silyl protecting groups were then removed by the action of hydrogen fluoride-acetonitrile and the spiroketal formed concurrently to provide spiroketal **3.44**. Further elaboration installed the vinyl iodide and phosphonate moieties in **3.38**. Deprotonation with LDA and introduction of

aldehyde **3.36** led to olefination under Horner-Wadsworth-Emmons[79] conditions to provide the completed fragment **3.45**.

3.3.2.2 White's Completion of the Rutamycin Synthesis

Scheme 26. White's Completion of Rutamycin B

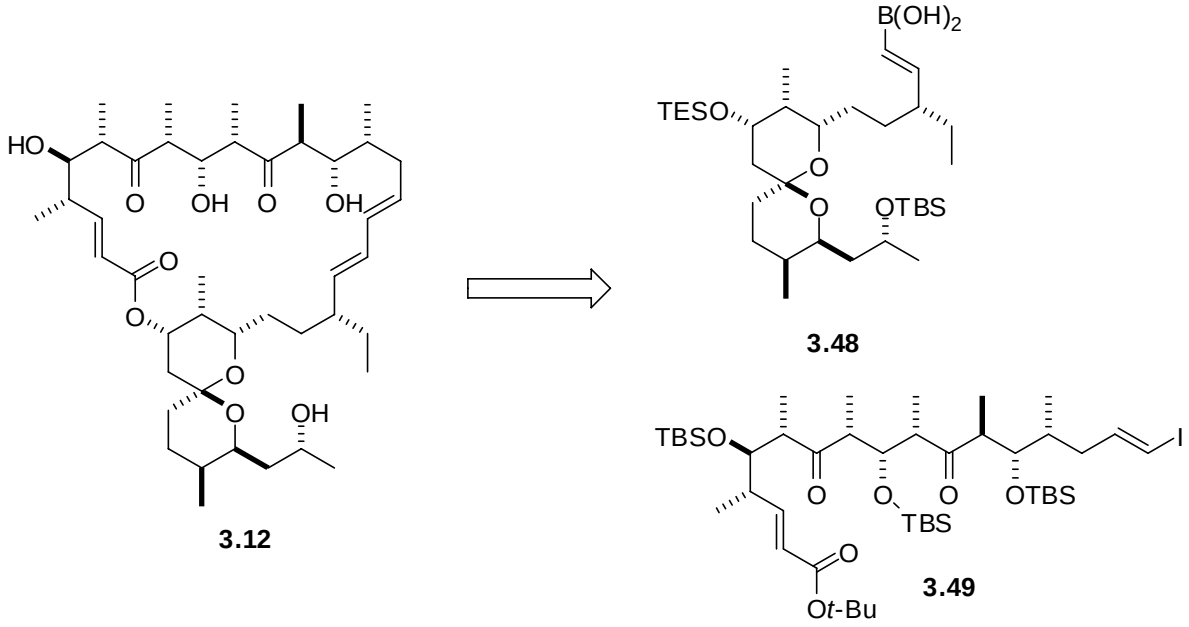


Spiroketal propionate **3.45** was treated with titanium (IV) chloride and Hünig's base to enolize (Scheme 26),[85] followed by introduction of aldehyde **3.37** to complete the aldol addition and form alcohol **3.46**. This was then brought forward to vinyl boronic ester **3.47**. Upon treatment with palladium catalysis, a Suzuki[86] marcolactonization proceeded to give the protected natural product. Global deprotection with hydrogen fluoride-pyridine provided rutamycin B (**3.12**) to complete the synthesis.

3.3.3 Evans Approach to Rutamycin B

3.3.3.1 Retrosynthetic Analysis

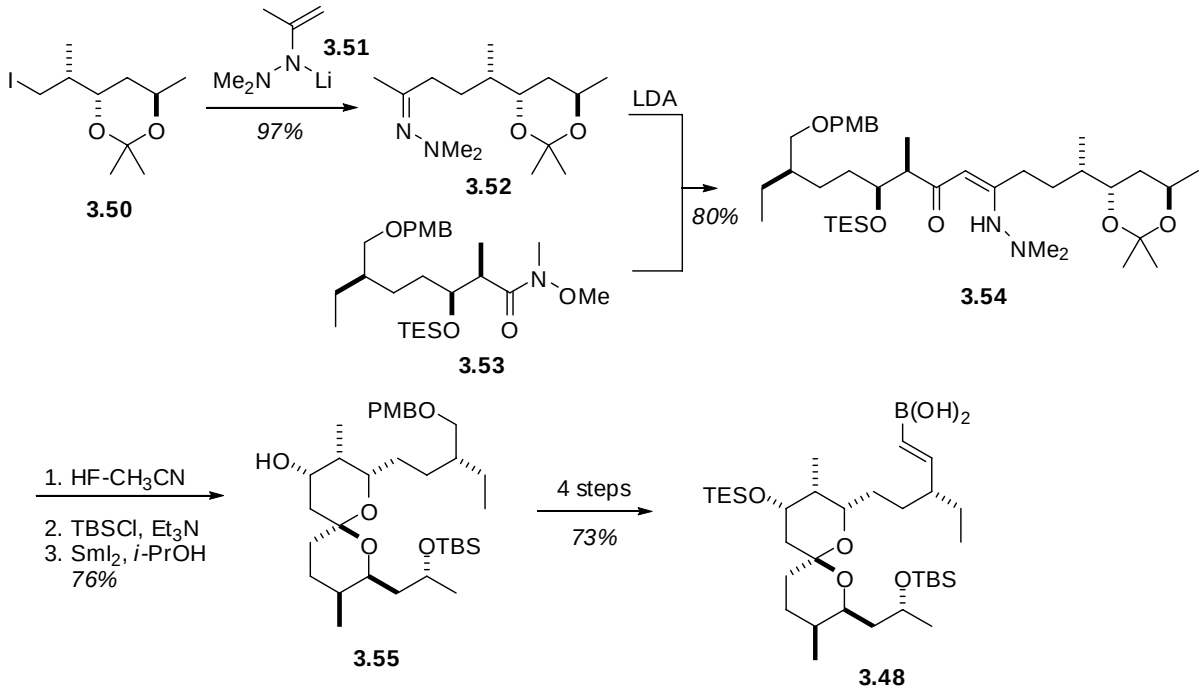
Scheme 27. Evans Retrosynthetic Analysis of Rutamycin B



In addition to synthesizing cytovaricin, Evans and co-workers also synthesized rutamycin B (**4.12**) in 1993. Their approach made use of a Suzuki coupling between boronic ester **3.48** and vinyl iodide **3.49** followed by a Yamaguchi-type macrolactonization to form the core (Scheme 27).

3.3.3.2 Synthesis of the Spiroketal Fragment

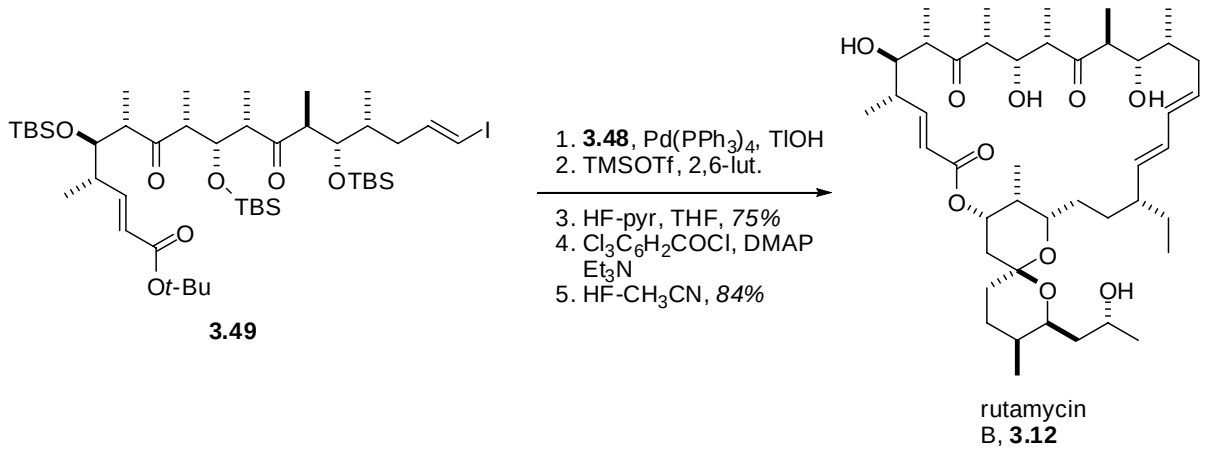
Scheme 28. Evans Synthesis of the Spiroketal Fragment of Rutamycin



Evans' synthesis of the spiroketal began from primary iodide **3.50** (Scheme 28). Treatment with the lithiated dimethylhydrazone of acetone (**3.51**) with this iodide led to the formation of hydrazone **3.52**. Exposure to the *N*,*O*-dimethylhydroxylamide **3.53** providde enamine **3.54** Deprotection of the alcohols and spiroketalization was effected with hydrogen fluoride-acetonitrile. The resultant alcohol was reprotected as the TBS ether. Reduction under Meerwein-Ponndorf-Verley conditions provided the desired alcohol **3.55** selectively. Further functionalization introduced the boronic acid into **3.48**.

3.3.3.3 Evans Coupling and Completion of Rutamycin B

Scheme 29. Evans Coupling and Completion of Rutamycin B

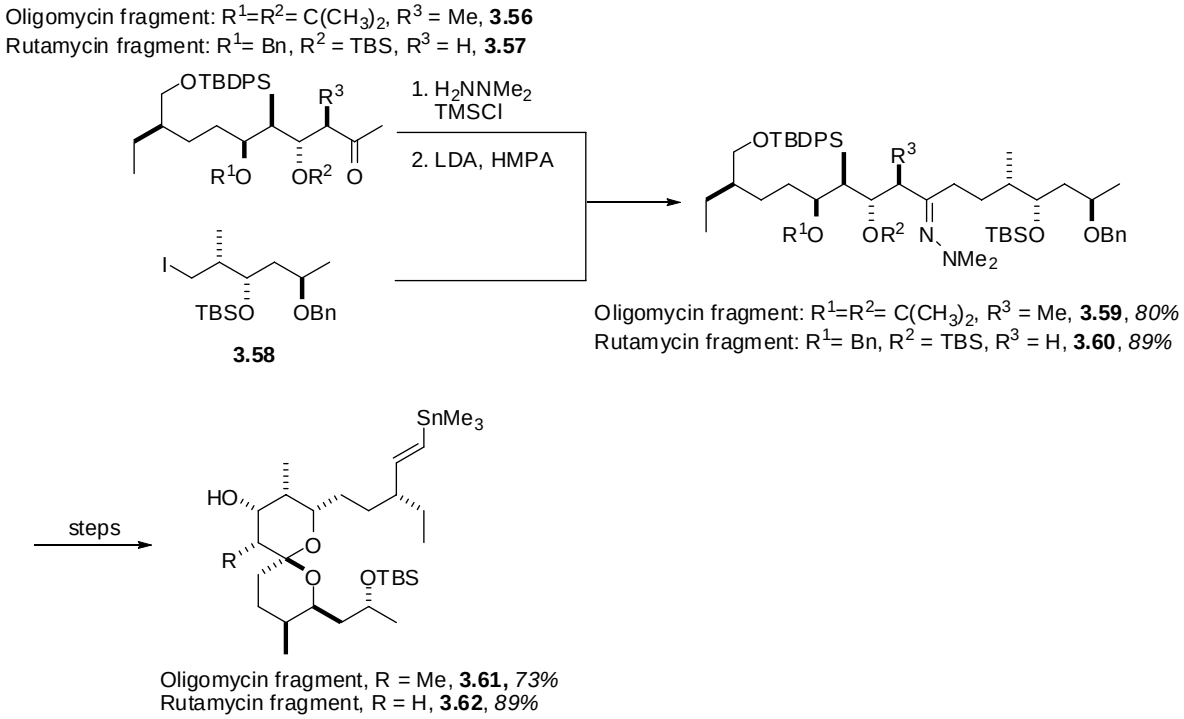


To complete the synthesis of rutamycin, Evans and co-workers coupled the vinyl iodide **3.49** with the boronic acid **3.48** under Suzuki conditions (Scheme 29). Conversion of the resultant ester to the carboxylic acid was effected with acidic conditions. Yamaguchi[87] macrolactonization provided the macrocycle. Global deprotection then led to formation of rutamycin B (**3.12**).

3.3.4 Panek's Approach to Rutamycin B and Oligomycin C

3.3.4.1 Synthesis of the Spiroketal Fragment

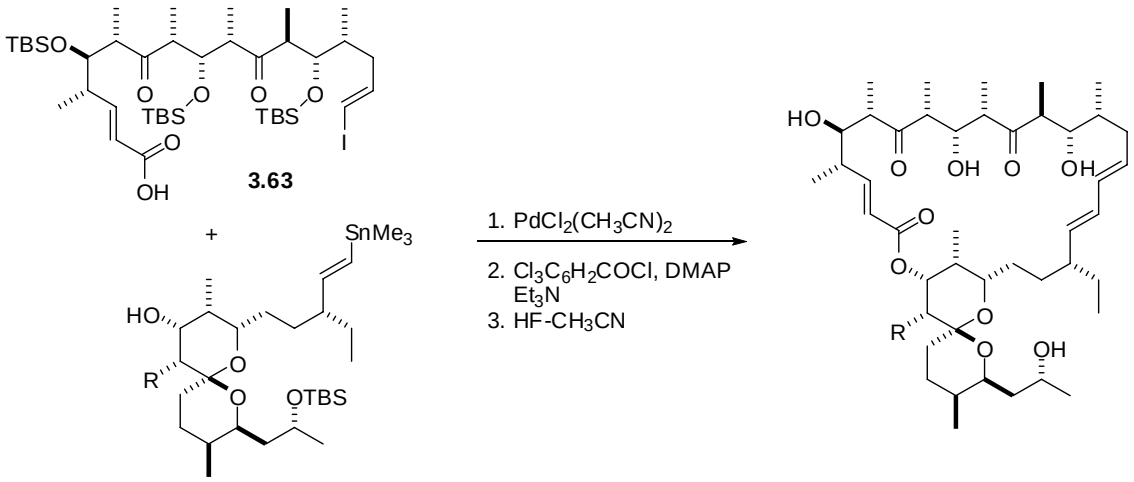
Scheme 30. Panek's Approach to the Spiroketalization of Rutamycin B and Oligomycin C



Panek's group[88] synthesized rutamycin B and oligomycin C, using similar chemistry for both molecules. Beginning with methyl ketones **3.56** and **3.57** (Scheme 30), conversion to the hydrazone occurred, followed by lithiation with LDA. Exposure to primary iodide **3.58** then provided the coupled products **3.59** and **3.60**. Further elaboration leads to spiroketalization under acidic conditions and formation of vinyl stannanes **3.61** and **3.62**.

3.3.4.2 Panek's Coupling Strategy to Rutamycin B and Oligomycin C

Scheme 31. Panek's Coupling and Completion Strategy for Oligomycin and Rutamycin



R = Me, Oligomycin C fragment, **3.61**
R = H, Rutamycin B fragment, **3.62**

R = Me, Oligomycin C, **3.9** ,*27%*
R = H, Rutamycin B, **3.12**, *26%*

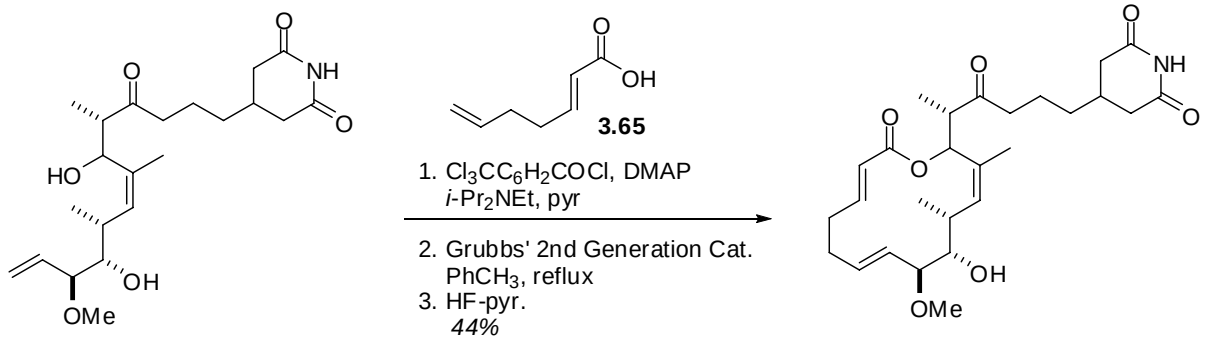
Vinyl iodide **3.63** was coupled with vinyl stannanes **3.61** and **3.62** under Stille conditions (Scheme 31).[89] Yamaguchi[87] macrolaconization then provided the macrocycle, which upon global deprotection led to oligomycin C (**3.9**) and rutamycin B (**3.12**).

3.4 Ring-Closing Metathesis to Form Macrolides in Natural Product Synthesis

The use of ring-closing metathesis reactions for the formation of medium ring lactones, ethers, and other ring systems has been studied extensively. The use of Grubbs' metathesis catalyst in larger ring systems[90-93] is much less documented in natural product synthesis, however, with few elegant uses.

3.4.1 Danishefsky's Synthesis of Migrastatin

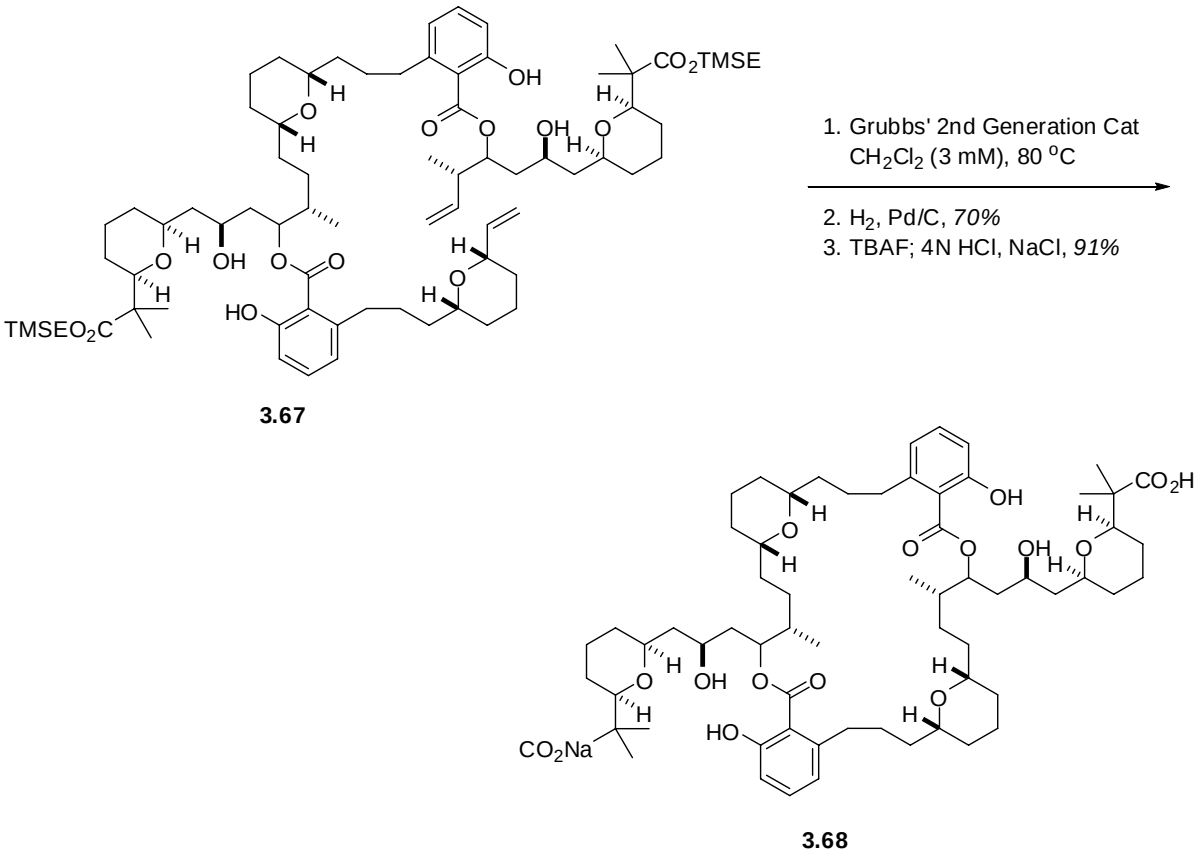
Scheme 32. Esterification/Ring-Closing-Metathesis Strategy for Migrastatin



An excellent example of this large-ring closing metathesis was recently reported by Danishefsky and co-workers (Scheme 31). They reported the total synthesis of the biologically-active (+)-migrastatin (**3.66**)[94] in 2003. Their approach to this macrolide involved an esterification under modified Yamaguchi conditions[87] to couple the two major fragments, alcohol **3.64** and carboxylic acid **3.65**. Ring-closing metathesis was then employed using Grubbs' 2nd generation catalyst to provide the *E* olefin selectively. Global deprotection then provided the natural product.

3.4.2 Lee's Synthesis of (+)-SCH 351448

Scheme 33. Lee's RCM completion of (+)-SCH 351448



3.67

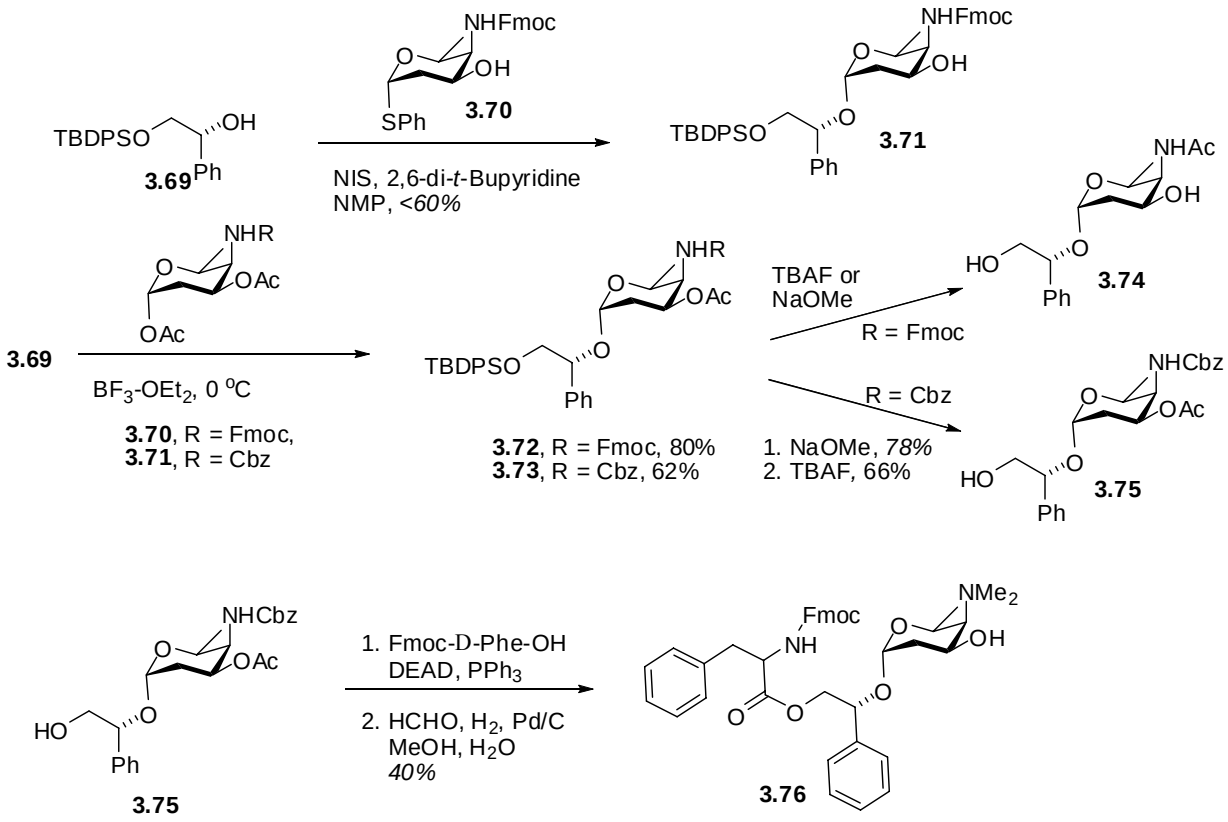
3.68

Lee and co-workers have also recently applied a large-ring RCM to the total synthesis of the biologically active natural product (+)-SCH 351448 (Scheme 32, **3.68**).[95] In their approach they use diene **3.67** in the ring-closing metathesis event to form a 28-membered macrodiolide. Hydrogentation and global deprotection then provided the natural product.

3.5 Synthesis and Literature Precedent for Glycosylation of the Kedarosamine Sugar

3.5.1 Synthetic Efforts Toward Kedarcidin Chromophore

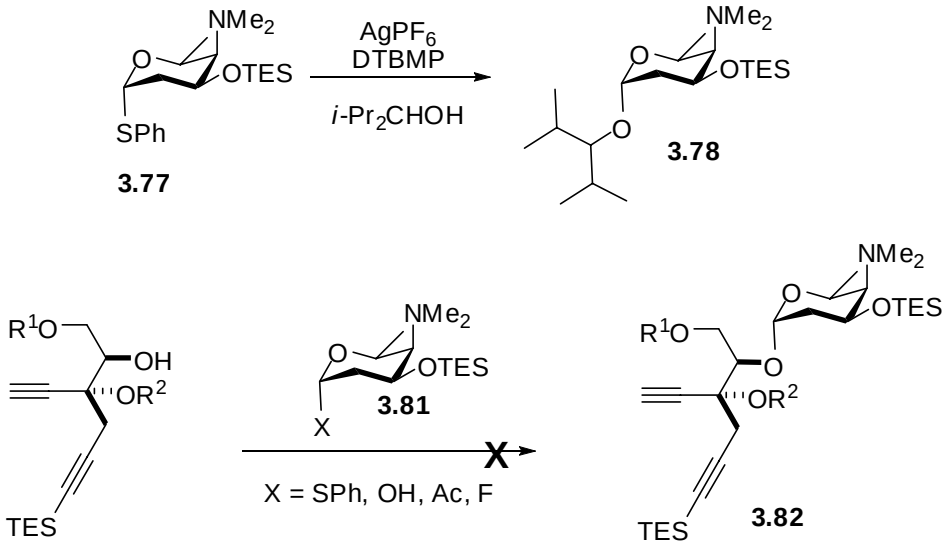
Scheme 34. Kedarcidin Chromophore Model System Glycosylation



The only reported natural product to include the kedarosamine sugar in the structure is kedarcidin chromophore (Scheme 34, **3.3**). Somfai and co-workers[96] have been working toward the total synthesis of the antitumor antibiotic for several years. In their efforts, they constructed a model system to test various glycosylation conditions in the construction of analogue **3.71**. Beginning from glycosyl acceptor **3.69,** treatment with thioglycoside **3.70** with *N*-iodosuccinimide to promote glycosylation provided the desired product **3.71**. Their route to the synthesis of the thioglycoside was unsatisfactory, however, and alternate methods were attempted. By utilizing bis-acetate glycosyl donors **3.70** and **3.71**, they were able to effect glycosylation in acceptable yields when R = Cbz (**3.73**) or Fmoc (**3.72**). The

subsequent selective cleavage of either the acetate or the TBDPS protecting group proved problematic however when R = Fmoc. Treatment with either TBAF or NaOMe led to loss of the Fmoc followed by O → N acetyl transfer to lead to the undesired amide **3.74.** When R = Cbz (**3.75**), however, the silyl protecting group and acetate were selectively removed. Conversion to their completed model system then proceeded to give their desired product **3.76.**

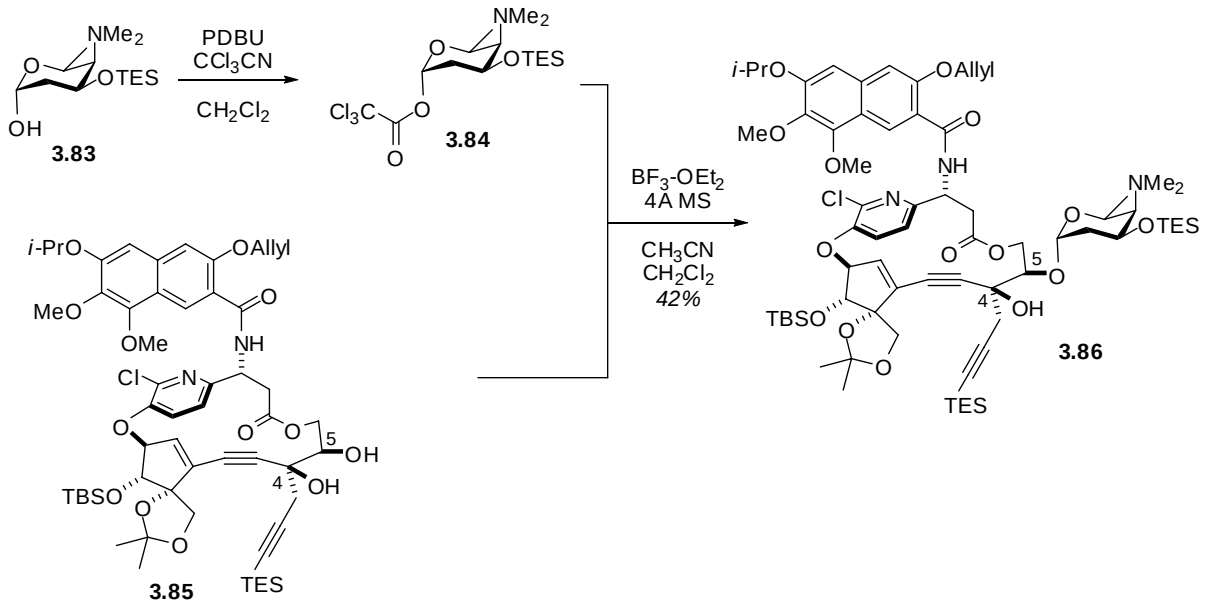
Scheme 35. Glycosylation Attempts with Kedarosamine Sugar Derivatives



R^1 = Piv, R^2 = H, TES, MOM, **3.79**
R^1 = R^2 = $CHMe_2$, **3.80**

Lear, Hirama, and co-workers[97,98] in their studies into the total synthesis of kedarcidin chromophore (Scheme 35, **3.3**) have reported problems with the glycosylation step to include kedarosamine into model systems. The incorporation of the secondary alcohol, 2,5-dimethylpentan-3-ol, was met with success utilizing thioglycoside **3.77** and silver(I) hexafluorophosphate as the promoter. When these conditions (and others noted above) were applied to a more complex glycosyl acceptor, however, decomposition or unreactivity was observed trying to produce the model system **3.82**.

Scheme 36. Glycosylation of Kedarcidin Fragment



After many studies, the ideal conditions for this system required conversion of hemiacetal **3.83** to trichloroacetimidate **3.84** using polymer-supported DBU and trichloroacetonitrile (Scheme 36). Reaction with diol **3.85** as the acceptor and BF_3-OEt_2 as the promoter provided the desired glycosylation product **3.86** at C5 in 42% yield. Notably, glycosylation at C4 occurred in 40% yield, indicating a very low regioselective preference for the secondary hydroxyl. Success of this reaction relied upon the hydroxyl group at C4 remaining unprotected.

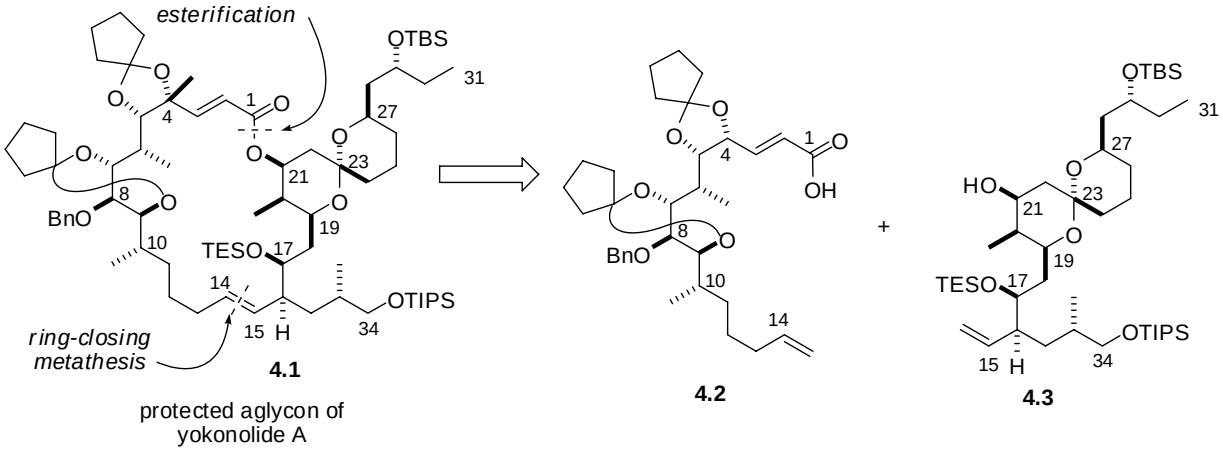
Chapter 4

Synthesis of the Protected Aglycon of Yokonolide A

4.1 RetrosyntheticAnalysis

4.1.1 Retrosynthetic Analysis of the Macrolide

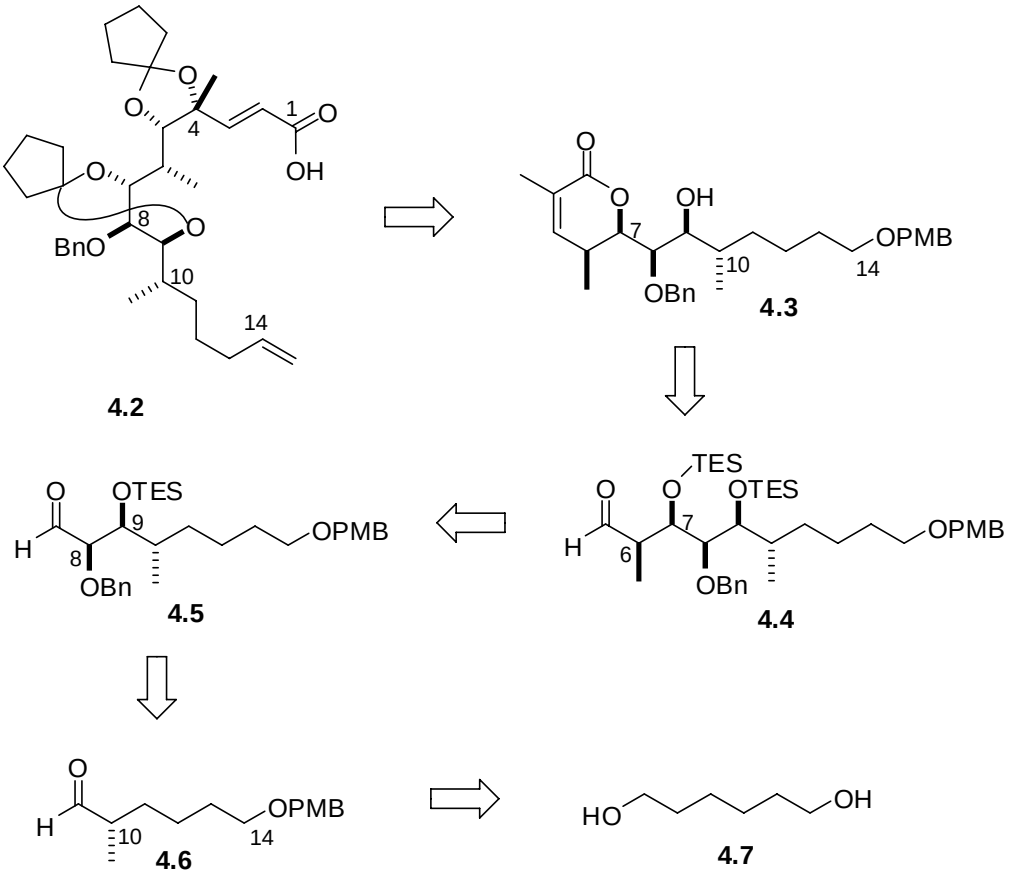
Scheme 37. Retrosynthetic Analysis of Yokonolide A Aglycon



Before investigating the total sythesis of yokolonide A, the synthesis of the aglycon was undertaken to investigate the necessary chemistry. The retrosynthetic analysis (Scheme 37) of the protected aglycon of yokonolide A (**4.1**) was envisioned to derive from an esterification coupling of carboxylic acid **4.2** with alcohol **4.3**. Ring closing metathesis between the two terminal olefins would form the C14-C15 bond and provide the fully elaborated aglycon **4.1.**

4.1.2 Retrosynthetic Analysis of of C1-C14 Carboxylic Acid Fragment

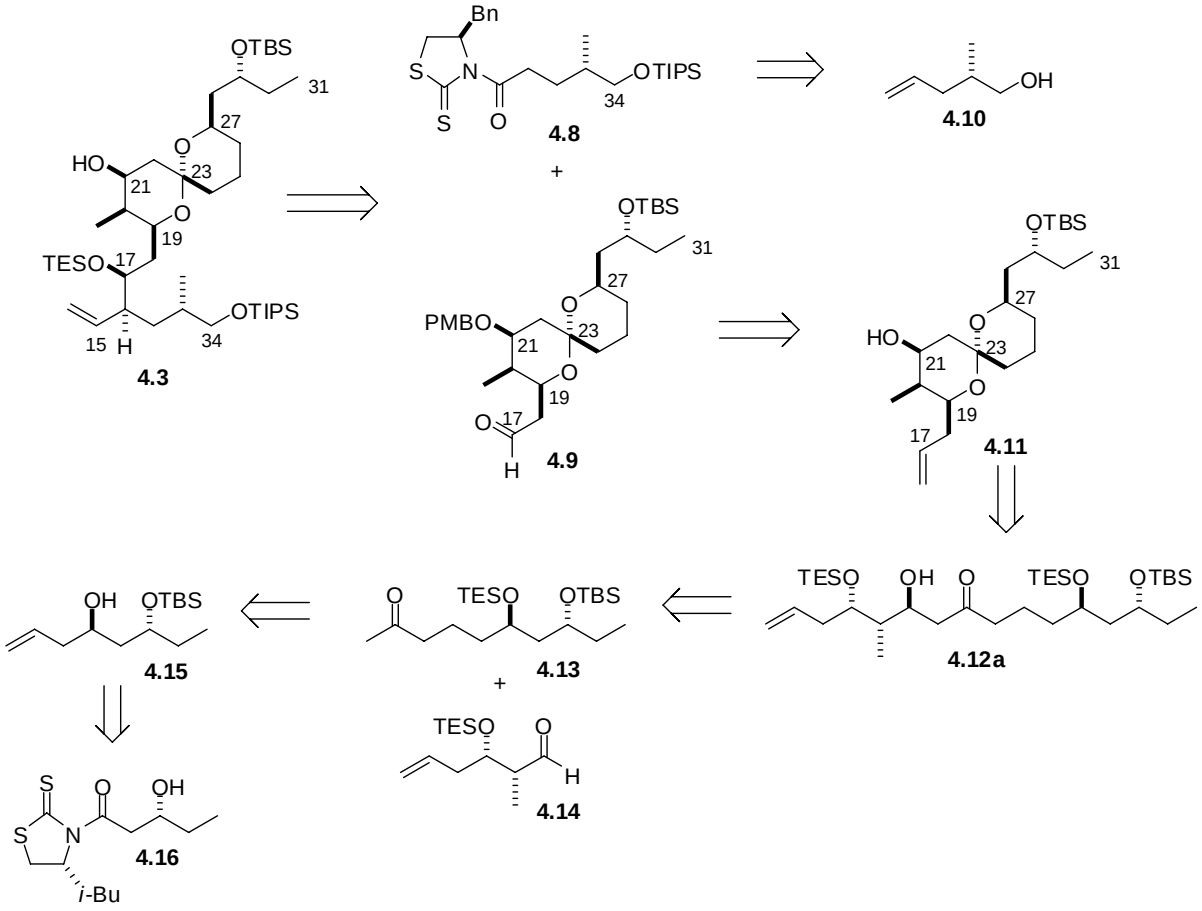
Scheme 38. Retrosynthetic Analysis of C1-C14 Acid Fragment



The C1-C14 fragment **4.2** (Scheme 38) would derive from lactone **4.3**, which would be formed through the Still-Gennari modification of a Horner-Wadsworth-Emmons olefination of aldehyde **4.4**. This aldehyde would derive from an asymmetric propionate aldol addition with aldehyde **4.5** to form the C6-C7 bond. This aldehyde would in turn derive from an asymmetric glycolate aldol addition of aldehyde **4.6** to install the C8-C9 bond. Aldehyde **4.6** would be formed from commercially-available 1,6-hexanediol through a Myers alkylation to introduce the methyl group.

4.1.3 Retrosynthetic Analysis of the C15-C34 Spiroketal-Alcohol Fragment

Scheme 39. Retrosynthetic Analysis of C15-C34 Spiroketal Fragment

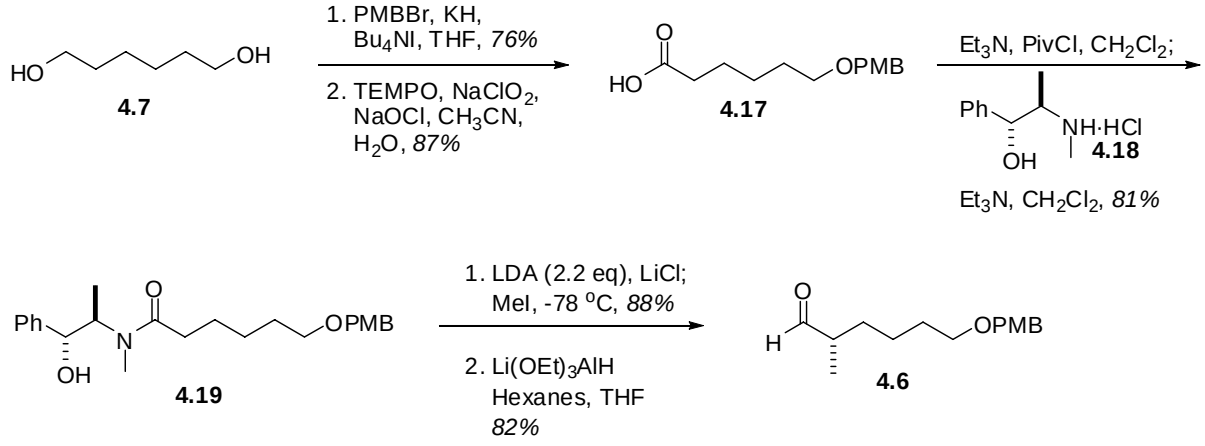


The C15-C34 fragment (Scheme 39) would derive from an asymmetric aldol addition between **4.8** and **4.9** to form the C16-C17 bond and install the side chain. The acylated thiazolidinethione would be formed from known alcohol **4.10**. The spiroketal C17-C31 fragment would derive from acyclic ketone **4.12** using acidic conditions to promote cyclization. The ketone **4.12** in turn would be formed from an aldol addition of methyl ketone **4.13** and aldehyde **4.14**. Aldehyde **4.14** would be formed through an asymmetric aldol addition. Methyl ketone **4.13** would be formed through a cross-metathesis reaction of methyl vinyl ketone with alkene **4.15**, which in turn would be formed through an acetate aldol addition/Brown allylation sequence.

4.2 Synthesis of C1-C14 fragment

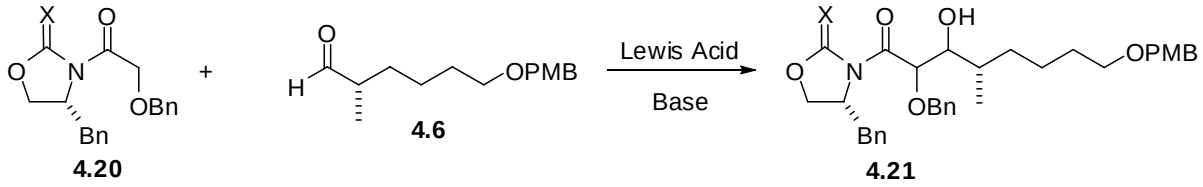
4.2.1 Myers' Alkylation and Glycolate Aldol Addition

Scheme 40. Synthesis of Aldehyde 4.6



The synthetic approach to yokonolide A began by performing a monoprotection of 1,6-hexanediol with *p*-methoxybenzyl bromide (PMBBr), which occurred in 76% yield (Scheme 40). Oxidation under Jones' conditions was then attempted. Due to the acidic nature of this oxidant, yields were low due to deprotection of PMB ether. Making use of the conditions developed at Merck,[99] involving the use of catalytic TEMPO, sodium chlorite, and sodium hypochlorite in buffered aqueous acetonitrile, an 87% yield was obtained for acid **4.17**. To setup the necessary alkylation, acylation of (*1S,2S*)-(+)- pseudoephedrine (**4.18**) took place by first forming the mixed anhydride from carboxylic acid **4.17,** followed by addition of the auxiliary to form amide **4.19** in 81% yield. Treatment under Myers' conditions[100] by adding lithium diisopropylamide (LDA) in the presence of lithium chloride, followed by the addition of methyl iodide led to the methylated product. Reduction with lithium triethoxyaluminum hydride then led to formation of aldehyde **4.6**.

Table 3. Glycolate Aldol Addition Attempts

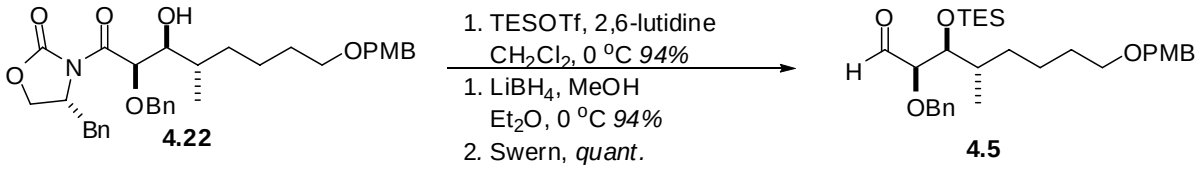


Entry	X	R	Lewis Acid	Base	Result
1	S	*i*-Pr	$TiCl_4$	2.5 eq *i*-Pr_2NEt	1.5:1 anti:anti
2	S	*i*-Pr	$TiCl_4$	1.0 eq (-)-sparteine 1.0 eq NMP	2.7:2:1 anti:anti:syn
3	O	Bn	$TiCl_4$	2.5 eq *i*-Pr_2NEt	1:1 anti:anti
4	O	Bn	Bu_2BOTf	1.4 eq Et_3N	74%, 10:1, syn:anti

At this stage, installation of the glycolate moiety became necessary to form the C8-C9 bond and set the configuration at those positions. To effect this transformation, a glycolate aldol addition was then attempted between glycolate **4.20** and aldehyde **4.6**. Several conditions were attempted leading to varying results as shown in Table 3. When oxazolidinethione was employed as the auxiliary, a mixture of *anti* aldol products[101] were observed when used in conjuction with either Hünig's base or (-)-sparteine and *N*-methylpyrrolidinone. When oxazolidinone was used with titanium tetrachloride and Hünig's base, a mixture of the undesired *anti* diastereomers was again observed. After these attempts were met with failure, the use of an Evans *syn* glycolate aldol addition[102] with dibutylboron triflate was investigated (entry 4). These well-behaved conditions provided the expected major diastereomer (10:1, Evans *syn:*non-Evans *syn*) in 74% yield. The diastereomers were separated and the major product brought forward.

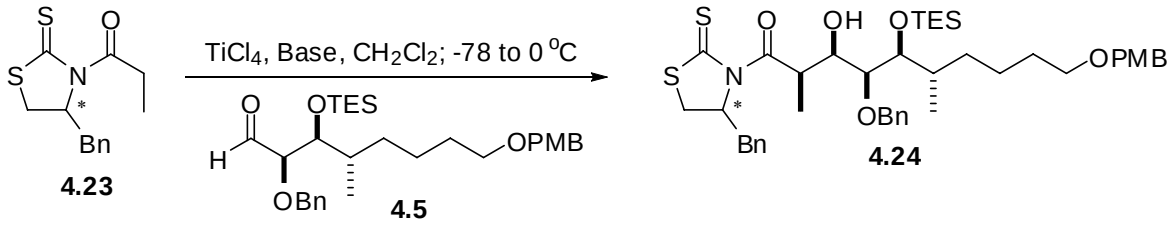
4.2.2 Installation of the C3 to C6 Subunit

Scheme 41. Synthesis of Aldehyde 4.5



The aldol adduct **4.22** was then protected as the triethylsilyl ether (Scheme 41). The auxiliary was removed under reductive conditions to provide the primary alcohol. Swern[103] oxidation provided the desired aldehyde **4.5** to be used in an asymmetric aldol addition.

Table 4. Propionate Aldol Addition

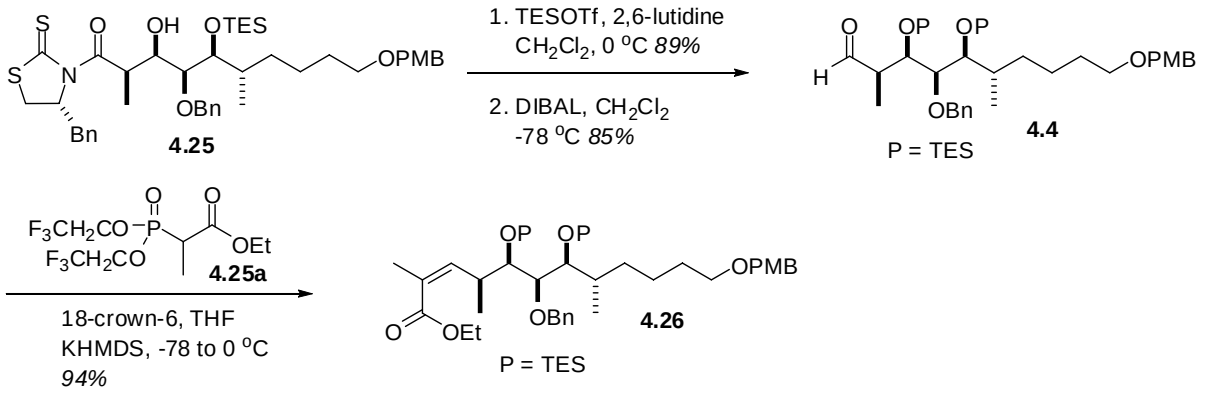


Entry	Auxiliary (*R* or *S*)	Base	Yield (%, major)	Result
1	*S*	2.5 eq *i*-Pr_2NEt	53	significant by-product formed
2	*R*	2.2 eq (-)-sparteine	67	syn (non-chelate)
3	*R*	1.3 eq (-)-sparteine 1.3 eq NMP	80	syn (non-chelate)

This aldehyde was then subjected to an aldol addition with *N*-priopionylthiazolidinethione **4.23.**[104,105] This was first attempted under conditions to provide the non-Evans *syn* product by employing 2.5 equivalents of Hünig's base to favor the chelated transition state (Table 4, entry 1). The desired product was formed as the major component, but an unidentified by-product was also formed, which led to the need for further optimization of reaction conditions. When the opposite enantiomer of auxiliary was employed in the reaction with 2.2 equivalents of (-)-sparteine (entry 2), the Evans product was obtained as the major

diastereomer in 67% yield by going through the non-chelate transition state. When 1.3 equivalents of (-)-sparteine was used with 1.3 equivalents of *N*-methylpyrrolidinone as a ligand, an 80% yield was obtained for the major diastereomer.

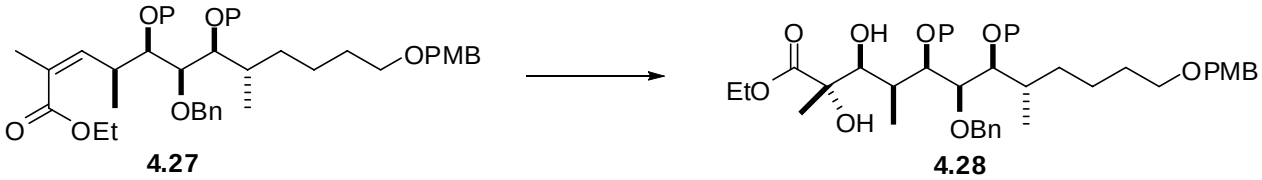
Scheme 42. Synthesis of *Z*-Enoate 4.26



With the desired aldol adduct in hand, further manipulation was necessary to complete the fragment (Scheme 42). The aldol adduct **4.24** was protected as the triethylsilyl ether and the auxiliary was then selectively reduced to the aldehyde using diisobutylaluminum hydride. The aldehyde **4.4** was converted to the *Z*-enoate **4.26** using the Still-Gennari modification of the Horner-Wadsworth-Emmons olefination.[106]

4.2.3 Installation of the Hydroxyl Groups at C4 and C5

Table 5. Dihydroxylation Conditions

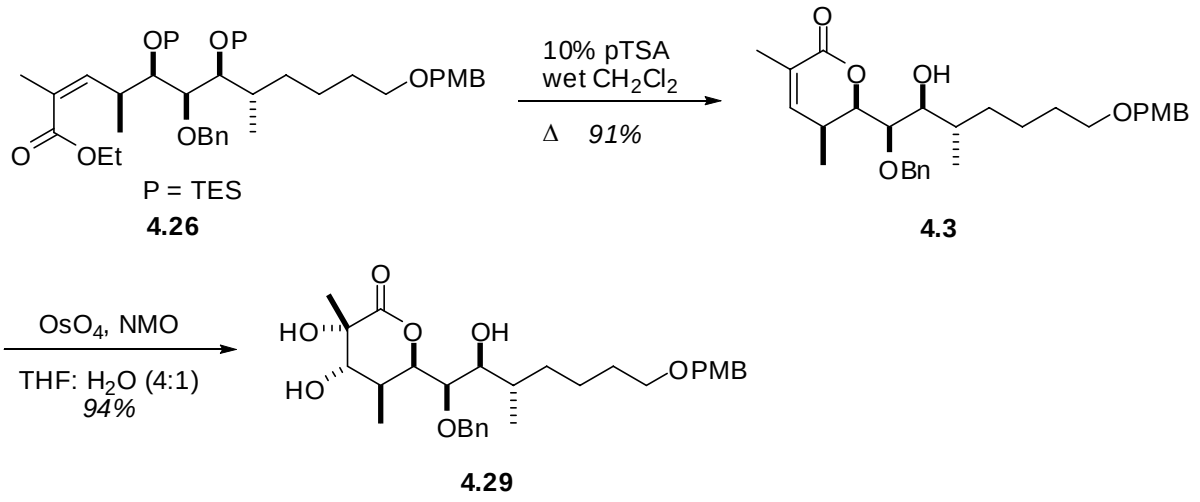


Entry	P	Oxidant	Solvent	Result
1	TES	OsO_4 / NMO	THF:H_2O (4:1)	No Reaction
2	TES	OsO_4 / NMO	acetone:H_2O (2:1)	No Reaction
3	TES	OsO_4 / NMO	acetone:H_2O (5:1)	No Reaction
4	TES	AD-mix α	*t*BuOH:H_2O (1:1)	No Reaction
5	TES	AD-mix α	*t*BuOH:H_2O (2:1)	No Reaction

6	TES	AD-mix α	acetone:H_2O (5:1)	No Reaction
7	$C(CH_3)_2$	OsO_4 / NMO	acetone:H_2O (3:1)	2:1 (10% yield)
8	$C(CH_3)_2$	AD-mix α	THF:H_2O (4:1)	No Reaction
9	$C(CH_3)_2$	AD-mix α	*t*BuOH:H_2O (1:1)	No Reaction
10	H	OsO_4 / NMO	THF:H_2O (1:1)	2:1 high yield
11	H	AD-mix α	*t*BuOH:H_2O (1:1)	No Reaction
12	H	AD-mix β	*t*BuOH:H_2O (1:1)	No Reaction

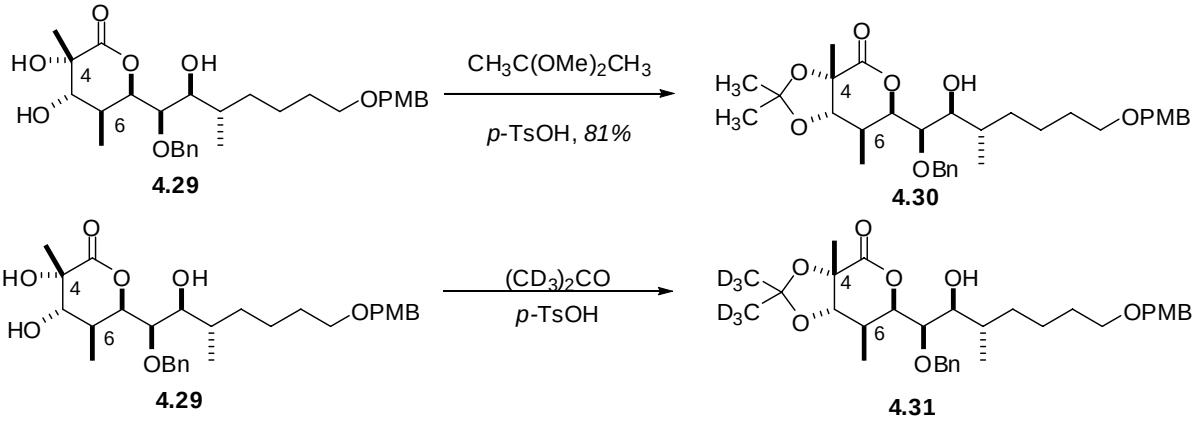
With this olefin in place, dihydroxylation then became necessary to install the two hydroxyl groups at C4 and C5 in **4.28**. This was first attempted diastereoselectively by using osmium tetroxide and *N*-methylmorpholine-*N*-oxide with trisubstituted alkene **4.27** (Table 5, entry 1). Unfortunately, this led to no reaction, most likely do to the insolubility of the nonpolar fully protected starting material. The solvent conditions were changed to no avail, (entries 2,3). Utilizing the Sharpless asymmetric dihydroxylation[107] conditions also proved unfruitful, regardless of the solvent system employed (entries 4-6). The nonpolar bistriethylsilyl groups were then replaced with an acetonide moiety (entries 7-9) and exposed to similar conditions as before. The only positive result was the slow appearance of a 2:1 mixture of dihydroxylation products when osmium tetroxide and NMO were employed (entry 7). When the asymmetric conditions were employed, no visible product was formed. As a last attempt to study the reaction on this core skeleton, the protecting groups at C7 and C9 were removed and the diol was exposed to the previous conditions. On small scale, a high yield of a 2:1 mixture was obtained (entry 10). Any attempts to increase this selectivity failed, however, as the trisubstituted electron-poor *Z*-olefins are reported to react sluggishly, if at all, when Sharpless' conditions are used. This substrate was then abandoned in its current form since the low selectivity and low yields observed precluded its use in the synthesis.

Scheme 43. Selective Dihydroxylation of Lactone 4.3



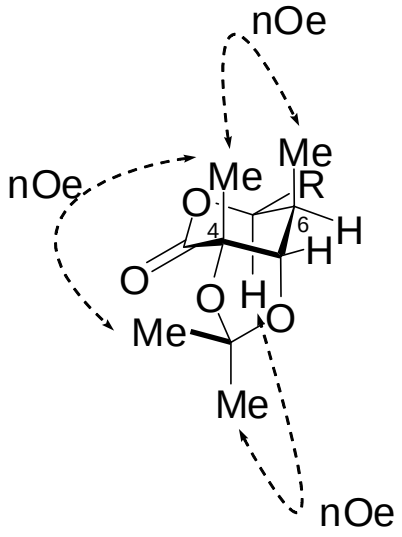
Since the Sharpless' asymmetric conditions were not a good candidate for this type of olefin, modification of the structure was investigated to increase the stereoselectivity This was done by converting the ester **4.26** into the lactone **4.3** through exposure to acidic conditions, which, also removed the two silyl protecting groups (Scheme 43). This substrate was then exposed to osmium tetroxide and NMO and only one diastereomer of diol **4.29** was observed in high yield. In order to determine the configuration of this diastereomer via 2D NMR experiements, formation of the acetonide was first necessary to elucidate the chemical shifts of the relevant protons.

Scheme 44. Confirmation of Stereochemistry of Dihydroxylation



The acetonide **4.30** was readily formed through exposure to dimethoxypropane and catalytic acid (Scheme 44). The chemical shifts of the methyl protons initially could not be assigned due to the similarity of the newly formed acetonide methyl groups and the tertiary methyl group at C4. This was alleviated through the formation of the deuterated acetonide from **4.29** with acetone-*d*6 under acidic conditions, which removed the acetonide methyl peaks from the spectrum. The chemical shift of the tertiary methyl group could then be assigned.

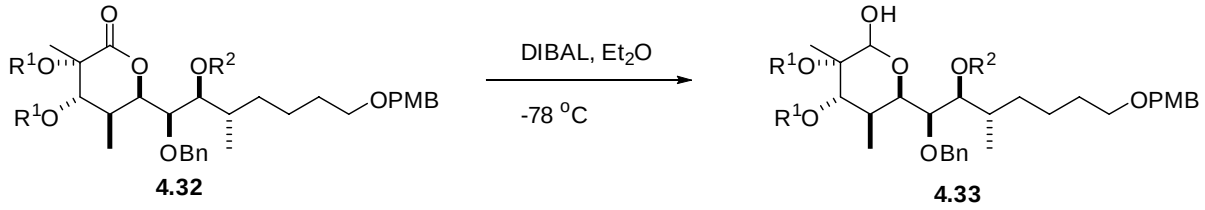
Figure 6. Observed Nuclear Overhauser Effects on Lactone 4.30



With the acetonide in hand and the proton assignments correctly determined, nuclear Overhauser effects (nOe) were observed (Figure 6). The observed nOe interactions could then be assigned between the tertiary methyl group at C4 and the methyl group at C6 on the 6-membered ring. An nOe was also observed between one of the acetonide methyl groups and the methine proton at C5.

4.2.4 Installation of C1-C2

Table 6. Selective Reduction of Lactone to Lactol



4.32 **4.33**

Entry	R^1	R^2	Result
1[1]	TES	TES	No Reaction
2	H	H	No Reaction
3	$C(CH_3)_2$	H	81%
4[2]	$C(CH_2)_4$	H	95%

[1] formed by reaction of **4.29** with TESCl, imid., DMAP, DMF

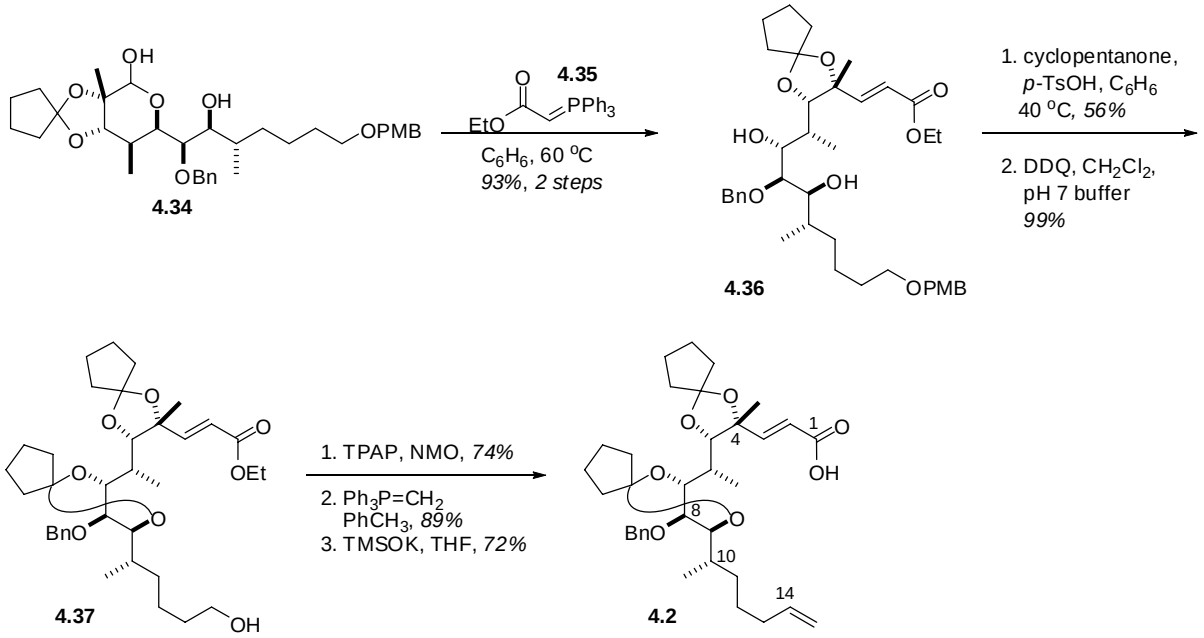
[2] formed by reaction of **4.29** with cyclopentanone and *p*-TsOH

With a stereoselective method for introducing the hydroxyl groups at C4 and C5 in place, a strategy to form the completed carboxylic acid fragment from this lactone was investigated. There have been many reports to partially reduce lactone rings to lactols through the use of DIBAL.[108] This was then attempted on the current system, by first protecting the newly formed hydroxyl groups as bis-TES ethers. Exposure of this substrate to DIBAL at – 78 °C, however, was problematic (Table 6, entry 1). Decomposition and low mass recovery were the major obstacles. This was speculated to arise from the sterically hindered environment surrounding the carbonyl, as a bulky TES group was positioned on the tertiary alcohol located α to the desired reaction center. Removal of the TES groups did not solve the problem in this reaction, as decomposition and low mass recovery were again major problems when DIBAL was reacted with the diol (entry 2). By employing the acetonide protecting group that was used to determine the stereochemistry of the dihydroxylation, however, these problems were overcome and the lactol was observed as the major product

(entry 3). Before proceeding, however, the viability of the acetonide as a protecting group was questioned as harsh acidic conditions are often required to remove this type of functionality. Since this was proposed to occur near or at the end of the synthesis, a more labile cyclopentylidene was then employed (entry 4), which reacted similarly to the partial reductive conditions.

4.2.5 Completion of the Carboxylic Acid C1-C4 Fragment

Scheme 45. Completion of C1-C14 Fragment



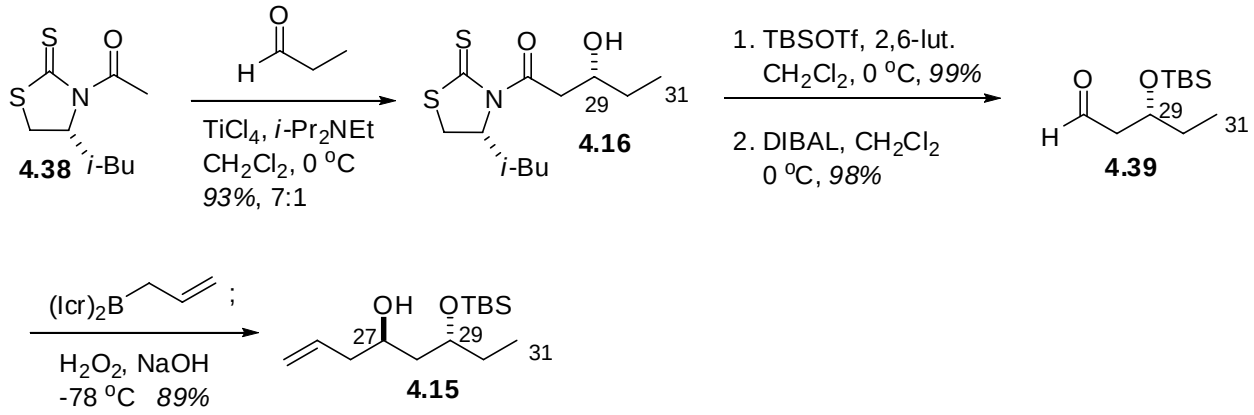
Lactol **4.34** was treated to the stabilized ylide **4.35** and the Wittig reaction proceeded to trap the aldehyde and provide the α,β-unsaturated ester **4.36** (Scheme 45). The newly formed 1,3-diol was also protected as the cyclopentylidene. At this point, the primary alcohol was unmasked through PMB removal via DDQ oxidation to reveal the 1° alcohol **4.37**. Oxidation under catalytic TPAP conditions[83] led to the aldehyde, which was then reacted under methylene Wittig conditions to provide the terminal olefin. Conversion of the ester to the desired carboxylic acid **4.2** was performed under the basic conditions of potassium

trimethylsilanolate with an acidic workup. With this fragment completed, attention was turned to the proposed coupling partner, spiroketal-alcohol **4.3**.

4.3 Synthesis of Spiroketal Alcohol C15-C34 fragment

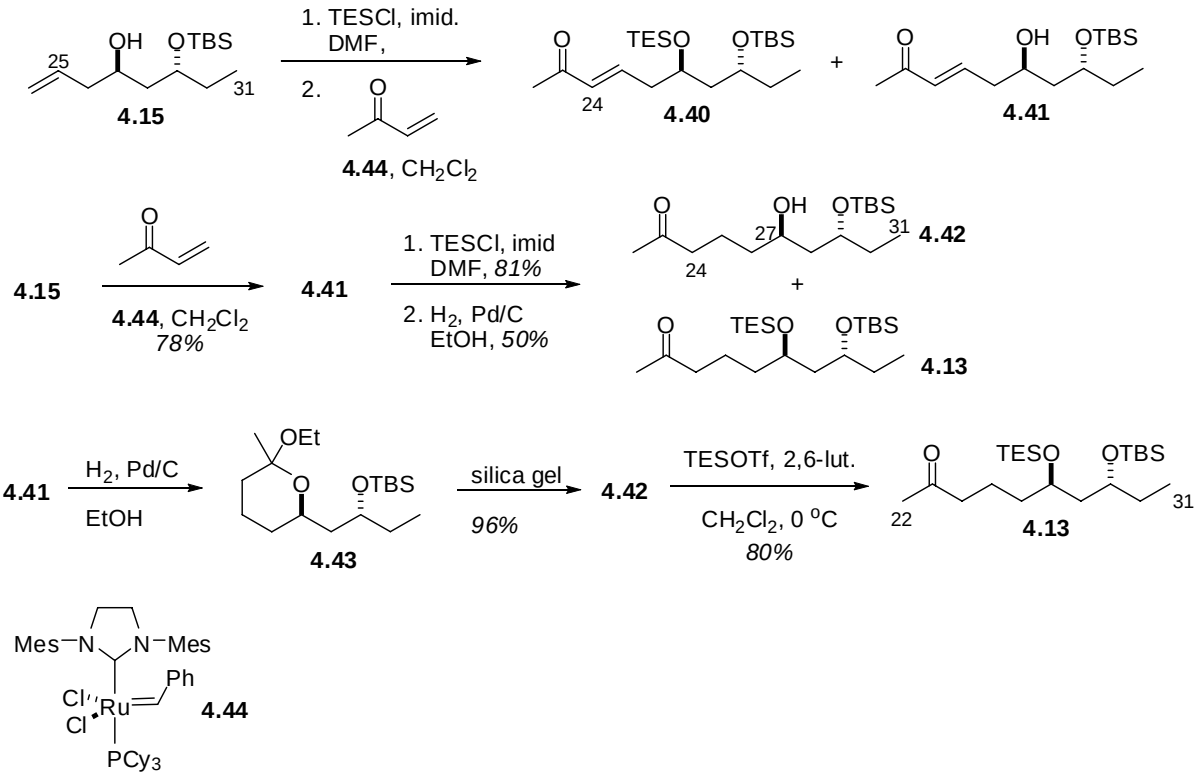
4.3.1 Synthesis of the C25-C31 Methyl Ketone Fragment

Scheme 46. Acetate Aldol Addition and Synthesis of Cross-Metathesis Precursor



Synthesis of the spiroketal fragment commenced with an acetate aldol reaction between *N*-acetylthiazolidinethione and propionaldehyde (Scheme 46). This was performed under chelation conditions taken from unpublished results by Dr. Kleem Chaudhary. The reaction performed well providing a 93% combined yield and 7:1 selectivity in favor of the *syn* diastereomer. The resultant aldol adduct **4.16** was then protected as the TBS ether and the auxiliary reductively cleaved to provide aldehyde **4.39**. Treatment with Brown allylboration[33] conditions with an oxidative workup led to formation of homoallylic alcohol **4.15**.

Scheme 47. Optimization of the Cross-Metathesis/Hydrogenation Sequence

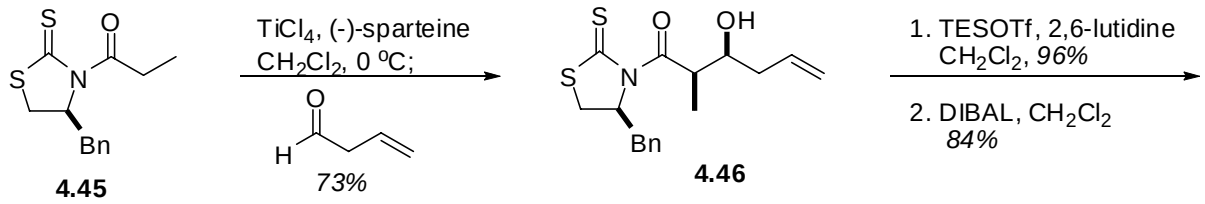


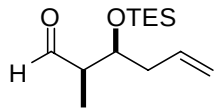
The alcohol **4.15** was then protected as a TES ether to provide the cross-metathesis precursor (Scheme 47). Upon treatment with methyl vinyl ketone and Grubbs 2nd generation catalyst (**4.44**),[109] however, low yields were obtained . The products of this reaction were difficult to separate, but the major isolated product was alcohol **4.41** formed from the desired cross-metathesis reaction with methyl vinyl ketone followed by loss of the TES protecting group. A small amount of the desired product **4.40** was formed, however. Further attempts at optimization of the conditions with this substrate did not improve the results. By reordering these steps and performing the cross-metathesis reaction on the free homoallylic alcohol **4.15** instead, the desired cross-metathesis reaction provided 78% yield in a much cleaner conversion. The alcohol **4.41** was then protected as the TES ether and subjected to hydrogenation conditions. This reaction was initially problematic. Partial deprotection of the TES ether provided multiple products. This was solved by again reordering the steps in this

sequence. Hydrogenation of the olefin on the free alcohol provided the mixed acetal **4.43**. Upon purification on silica gel, however, the acetal was hydrolyzed to provide the free alcohol **4.42**. Finally, protection as the TES ether provided the completed methyl ketone **4.13** and the precursor to an aldol addition.

4.3.2 Synthesis of the C17-C21 Aldehyde Fragment

Scheme 48. Synthesis of Aldehyde 4.14



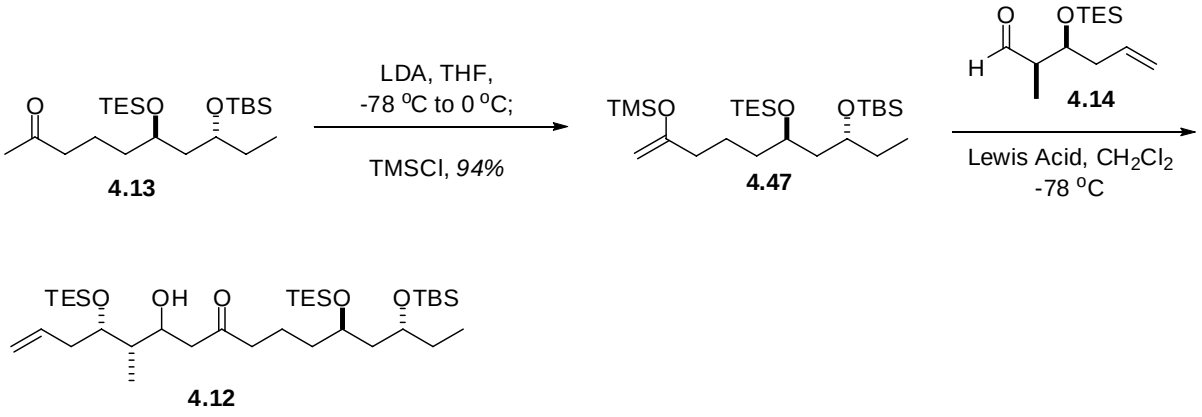


4.14

The synthesis of the aldehyde fragment **4.14** began with the formation of 3-butenal.[110] Application of the asymmetric aldol addition conditions previously developed in our lab[111] led to formation of the non-Evans *syn* aldol adduct **4.46**. (Scheme 48). Protection as the TES ether and reduction to the aldehyde then provided the aldol precursor **4.14**.[111]

4.3.3 Synthesis of the C17-C31 Methyl Ketone Fragment

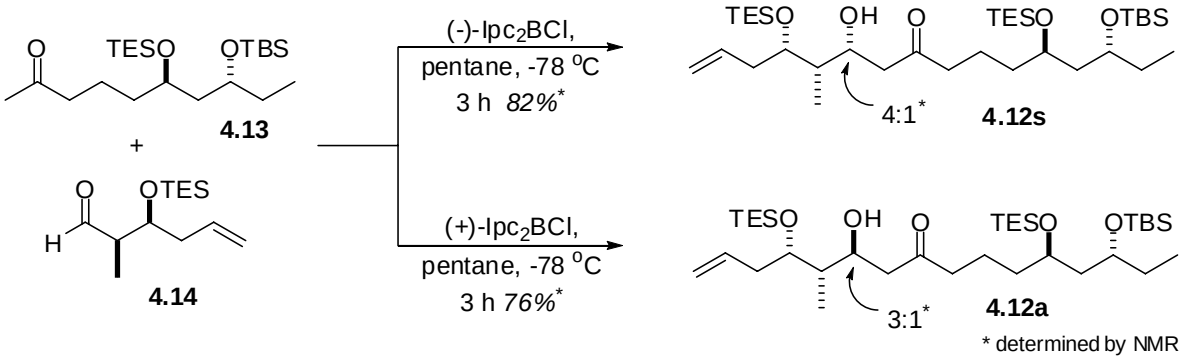
Table 7. Mukaiyama-type Aldol Addition Attempts



Entry	Lewis Acid		Yield*	Selectivity*
	(eq)		(%)	(anti:syn)
1	1.0	$TiCl_4$	42	syn
2	1.0	$Ti(Oi\text{-}Pr)_2Cl_2$	NR	-
3	1.0	$BF_3{\cdot}OEt_2$	30	syn
4	2.5	Me_2AlCl	45	1:1.5
5	2.5	$MeAlCl_2$	42	1:5
*estimated by ^1H NMR analysis				

Investigation into a selective aldol addition between the ketone **4.13** and aldehyde **4.14** then began. To effect this transformation stereoselectively, a Mukaiyama-type aldol was investigated (Table 7). Conversion of the methyl ketone **4.13** to the silyl enol ether **4.47.** proceeded smoothly through treatment with LDA and trapping of the enolate with TMSCl. Reactions of this substrate with aldehyde **4.14** were attempted with a variety of Lewis acid promoters. Unfortunately, all of the reactions provided low yields, a preference for the undesired *syn* diastereomer, and the presence of unidentified decomposition products.

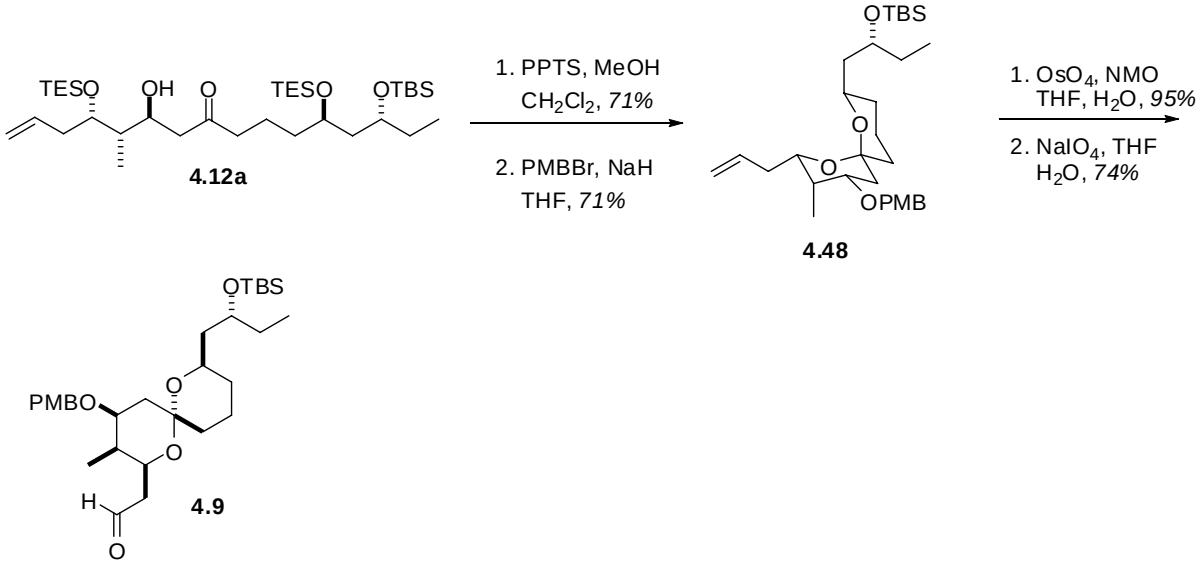
Scheme 49. Boron-Mediated Selective Aldol Addition



By using Patterson's boron aldol conditions[112] (Scheme 49), the desired *anti* diastereomer **4.12a** was synthesized in a 3:1 mixture in 76% yield. Utilizing the opposite enantiomer of the boron reagent led to formation of a 4:1 mixture in favor of undesired *syn* diastereomer **4.12s** in 82% yield. Moving forward with the most favorable result obtained through the boron enolate, spiroketalization was next required.

4.3.4 Spiroketalization

Scheme 50. Spiroketalization and Formation of Aldehyde 4.9

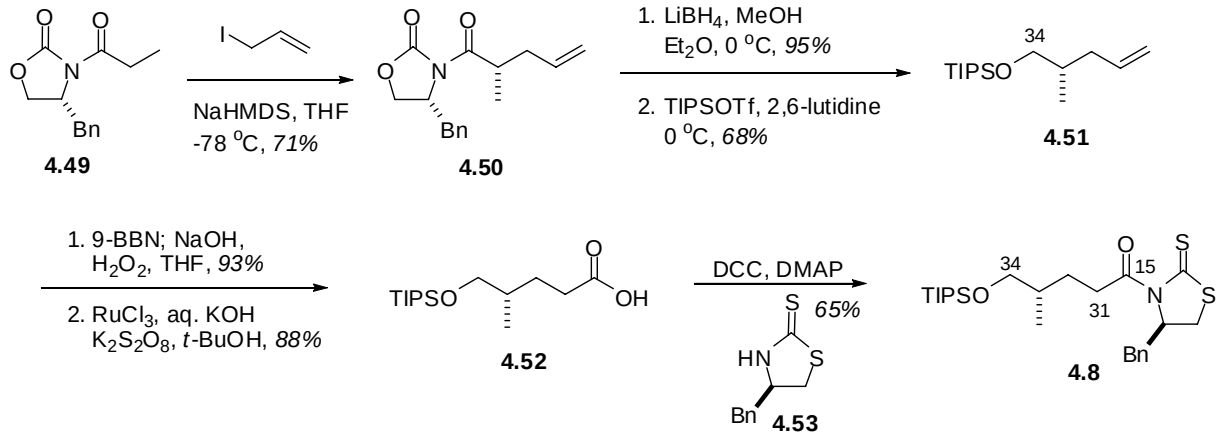


The aldol adduct **4.12a** was treated with PPTS in methanol, which effected deprotection of the TES groups and catalyzed cyclization to the spiroketal (Scheme 50). NMR analysis of the

spiroketal indicated that the correct diastereomer had been formed as the major thermodynamic product. This spiroketal is further stabilized through the double anomeric effect. Protection of the free alcohol as the PMB ether then provided **4.48**. Dihydroxylation, followed by oxidative cleavage of the terminal olefin provided aldehyde **4.9**, the precursor to the aldol addition necessary to install the side chain present at C16.

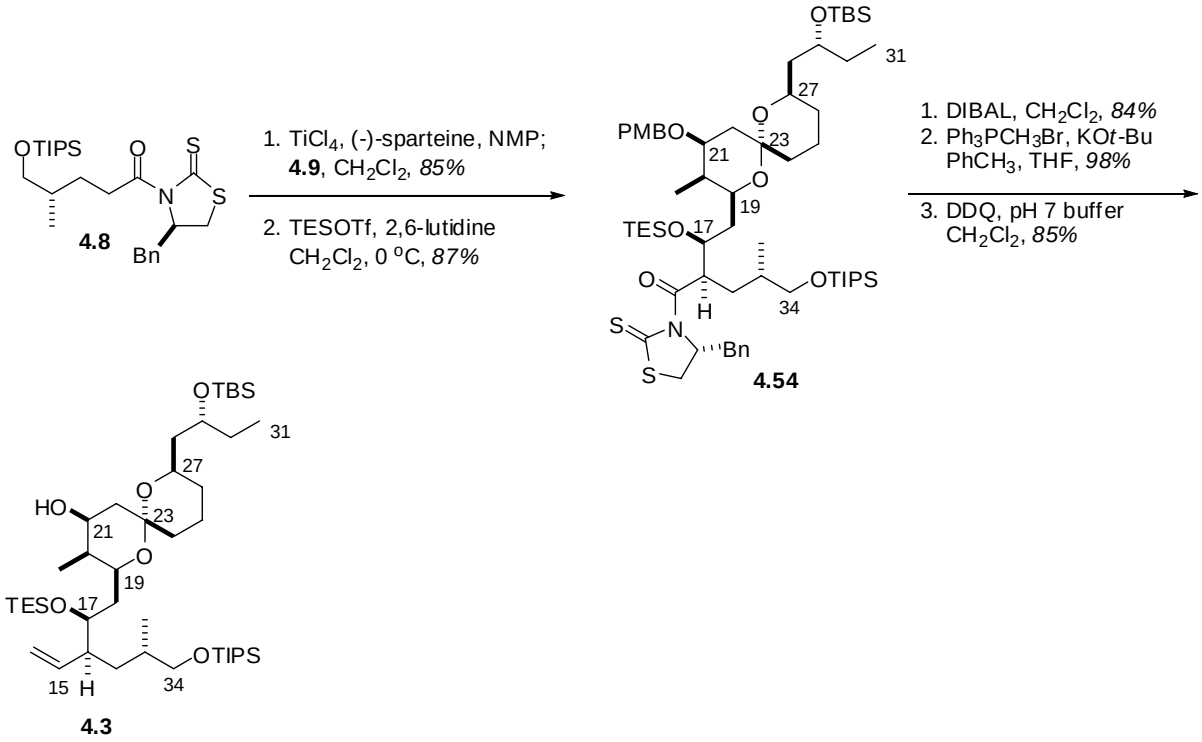
4.3.5 Synthesis of Acylated Thiazolidinethione 4.8 and Installation of the Side Chain

Scheme 51. Synthesis of the Side Chain



The acylated thiazolidinethione **4.8** was synthesized by following a sequence reported by Evans with an alternate protecting group.[68] Starting from the asymmetric alkylation product **4.50**,[113] the auxiliary was reduced to the primary alcohol with lithium borohydride (Scheme 51). This was then protected as the TIPS ether to provide alkene **4.51.** Hydroboration and oxidation to the carboxylic acid with ruthenium tetroxide provided carboxylic acid **4.52**. Coupling with thiazolidinethione **4.53** proceeded with DCC and DMAP to provide **4.8**.

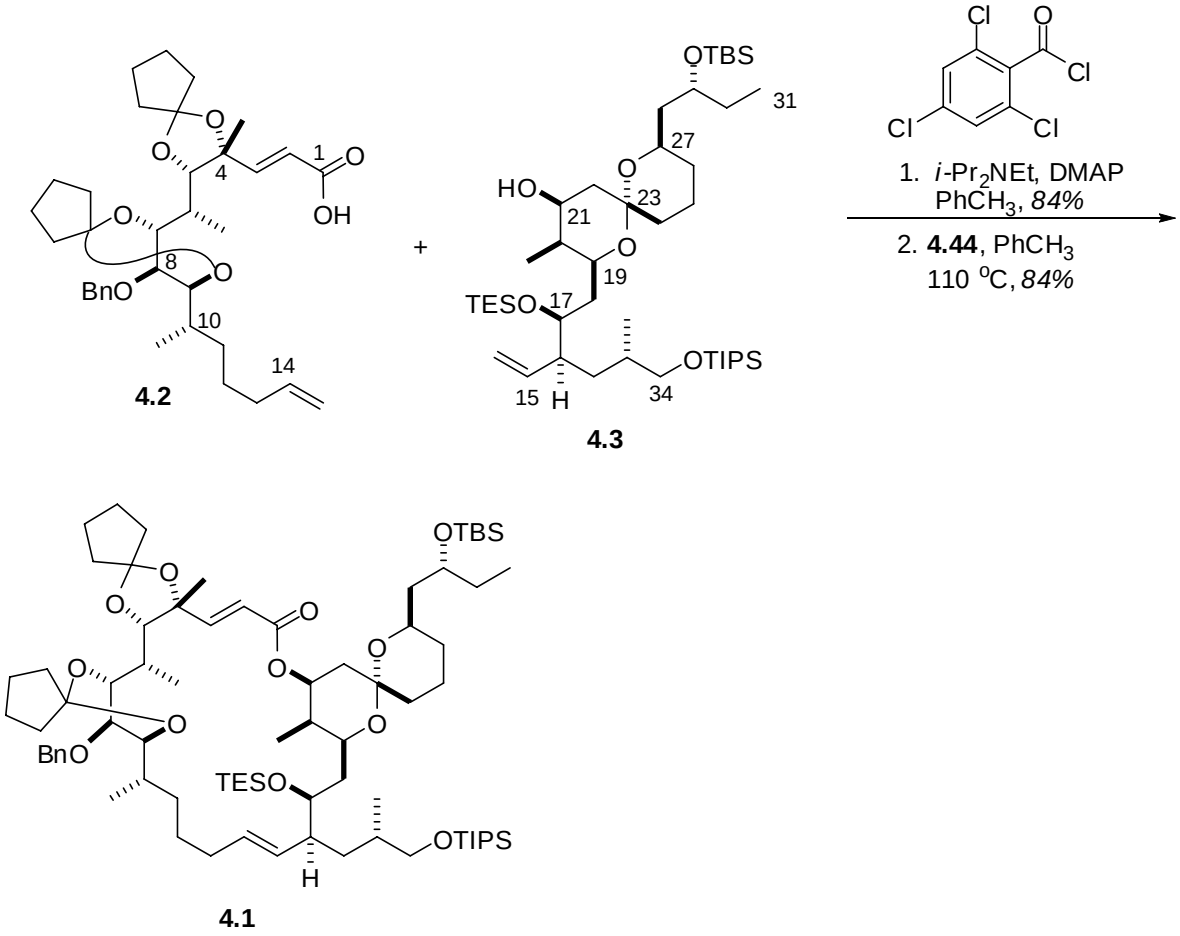
Scheme 52. Completion of Spiroketal Fragment



Installation of the side chain began with acylated thiazolidinethione **4.8** (Scheme 52). Enolization with titanium tetrachloride, (-)-sparteine, and NMP,[104,105] followed by the addition of aldehyde **4.9** led to the aldol adduct as the only observable diastereomer. Protection of the alcohol as the TES ether proceeded to form **4.54**. Reduction of the auxiliary led to aldehyde. Treatment with the methylene Wittig reagent provided the terminal olefin. Deprotection of the PMB ether then led to formation of the alcohol at C21 to finish the C15-C34 spiroketal fragment **4.3** and set up the coupling of the two major fragments.

4.4 Coupling of Major Fragments and Synthesis of the Protected Aglycon

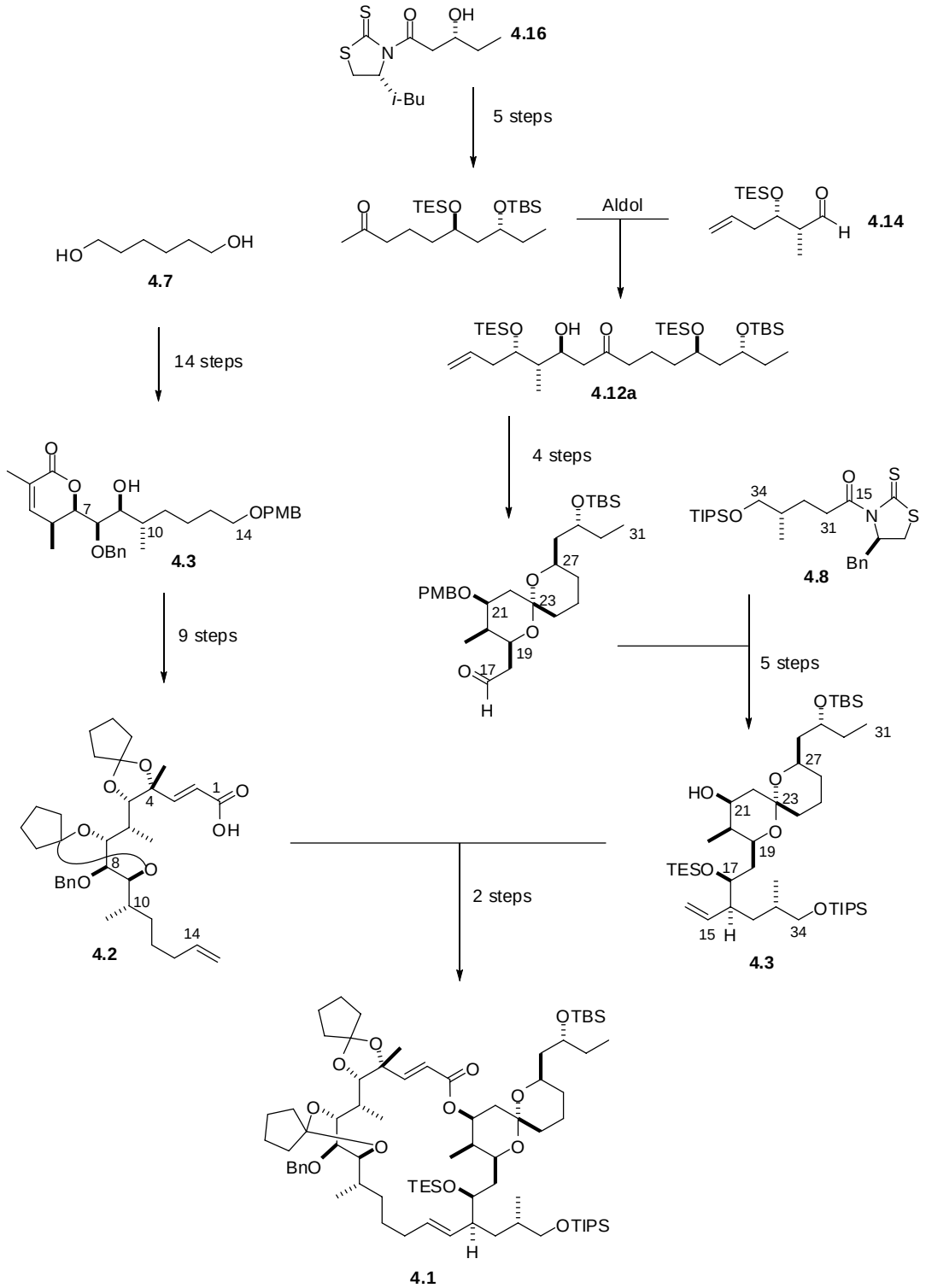
Scheme 53 Esterification/Ring-Closing-Methathesis



Treatment of the carboxylic acid **4.2** with Yamaguchi esterification[87] conditions consisting of 2,4,6-trichlorobenzoyl chloride, Hünig's base, DMAP, and alcohol **4.3** provided the desired coupled product in high yield (Scheme 53). Treatment with Grubb's 2nd generation catalyst (**4.44**) led to formation of the *E*-olefin of the macrolide[94] **4.1** and marked the completion of the fully protected yokonolide A aglycon.

4.5 Summary

Scheme 54. Summary of the Synthesis of the Protected Aglycon of Yokonolide A



The successful synthesis of the protected aglycon of yokonolide A (**4.1**) has been reported. The strategy began at hexanediol and made use of several asymmetric aldol additions and alkylations to set the configurations at many of the stereocenters in the formation of lactone **4.3** (Scheme 54). A diastereoselective dihydroxylation incorporated the hydroxyl groups at C4 and C5 and further elaboration provided carboxylic acid **4.2**.

Aldol adduct **4.16** was formed through a selective acetate aldol addition and elaborated to the methyl ketone. An asymmetric aldol addition coupled this fragment to aldehyde **4.14**. The resultant ketone was cyclized to the spiroketal. An aldol addition connected the side chain **4.8** to provide fully elaborated spiroketal **4.3**.

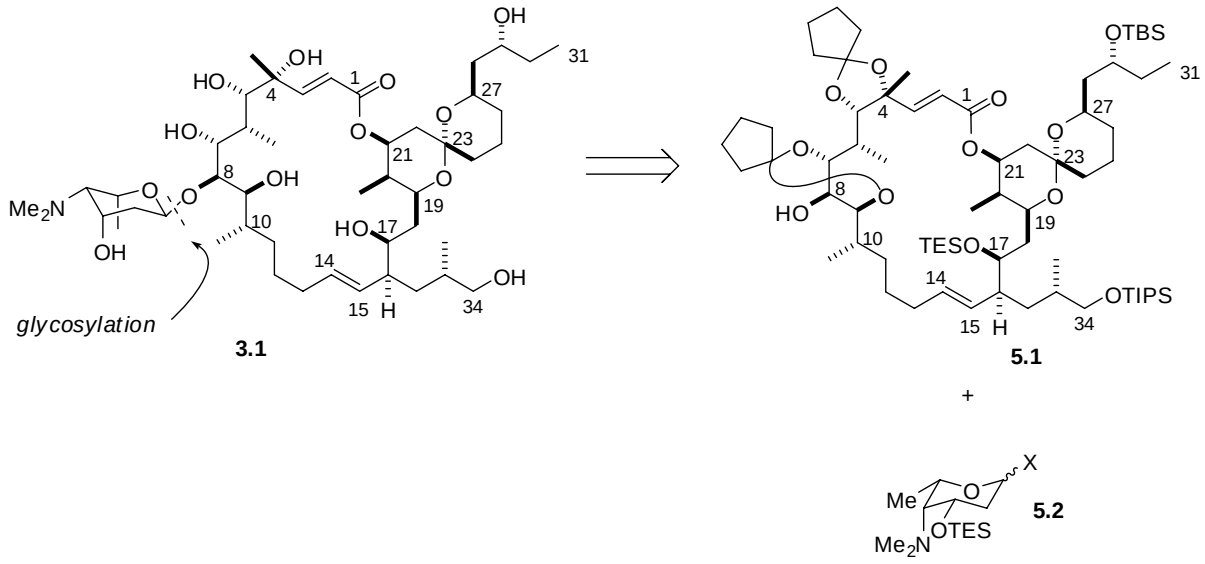
An esterification-macrocyclization sequence via Yamaguchi conditions and ring-closing metathesis was used to couple the main fragments in a convergent synthesis.

Chapter 5

Efforts Toward the Total Synthesis of Yokonolide A

5.1 RetrosyntheticAnalysis

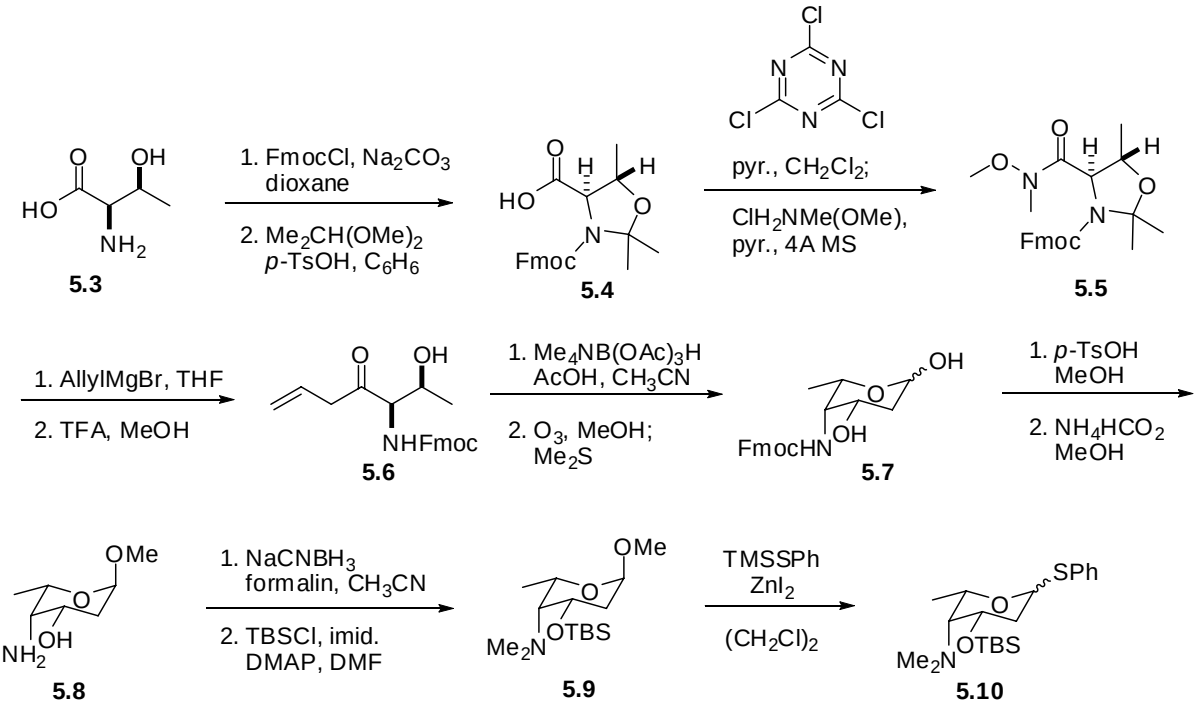
Scheme 55 Retrosynthetic Analysis of Yokonolide A



The total synthesis of yokonolide A (Scheme 55, **3.1**) was proposed to arise from a glycosylation with kedarosamine-derived sugar **5.2** after selective deprotection of the benzyl ether at C8 of the protected aglycon. Global deprotection would then provide the completed natural product.

5.2 Synthesis of Kedarosamine and Derivatives

Scheme 56. Synthesis of Kedarosamine-Derived Sugar



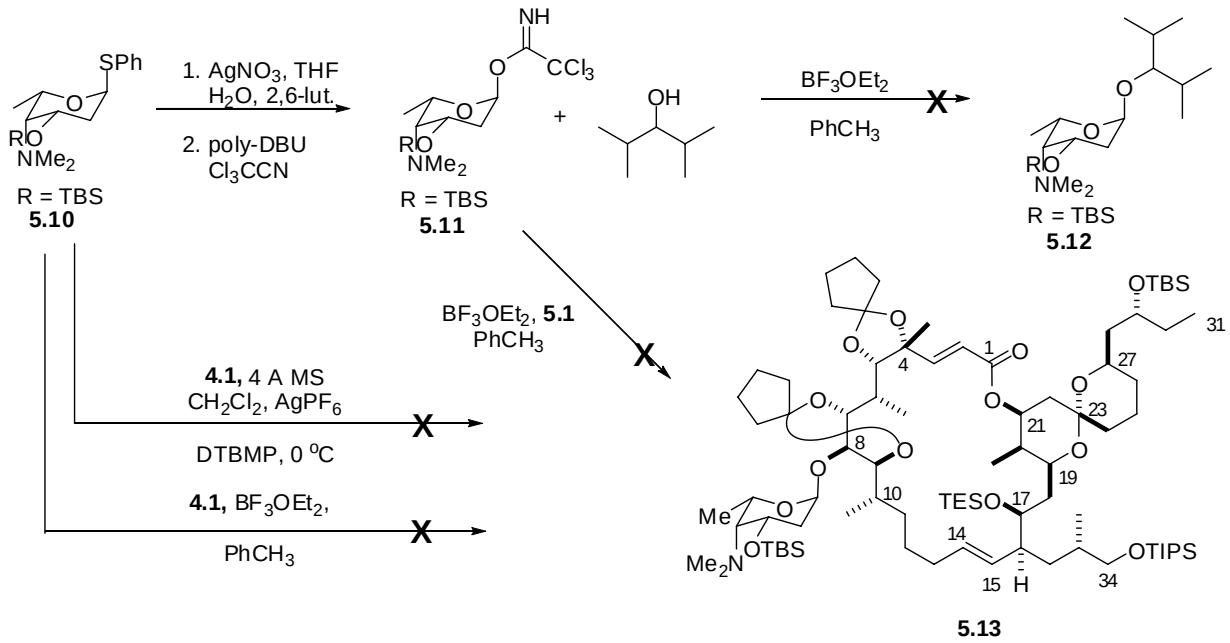
Before attempting a glycosylation, the synthesis of the core structure of kedarosamine was carried out by following the preparations of Vuljanic and coworkers.[96] Starting from D-threonine (Scheme 56, **5.3**), protection of the free amine as the Fmoc (9-fluorenylmethoxycarbonyl) group took place with FmocCl. Formation of the *N*,*O*-acetal **5.4** proceeded through exposure to 2,2-dimethoxypropane and acidic conditions. Conversion to the Weinreb amide **5.5** occurred by first forming the acid chloride with cyanuric chloride, followed by exposure to *N*,*O*-dimethylhydroxylamine hydrochloride. Allylation, followed by deprotection of the cyclic protecting group provided the β-hydroxyketone **5.6**. 1,3-*Anti* reduction took place using tetramethylammonium triacetoxyborohydride.[81] Ozonolysis cleaved the terminal olefin and in situ cyclization to the hemiacetal provided the core kedarosamine skeleton. Conversion to the methyl acetal occurred through exposure to acidic

methanol. The amine protecting group was removed via transfer hydrogenolysis to provide the free amine **5.8.** Reductive amination with formalin and sodium cyanoborohydride provided the desired dimethyl amine **5.9** upon silyl protection of the hydroxyl group. It is worthwhile to note that the published reductive amination relied upon palladium catalyzed hydrogenation of the imine formed in situ. This reaction proved very problematic, however, due to low mass recovery and incomplete conversion. The reductive amination adapted from the procedure of Kakinuma and co-workers[114] on a similar substrate was utilized to provide the desired product in good yields. Conversion to the thioglycoside **5.10** was then effected with thiophenyltrimethylsilane.[97]

5.3 Initial Efforts at Glycosylation

5.3.1 Late-Stage Glycosylation Attempts

Scheme 57. Attempted Glycosylation with Glycosyl Donors 5.10 and 5.11

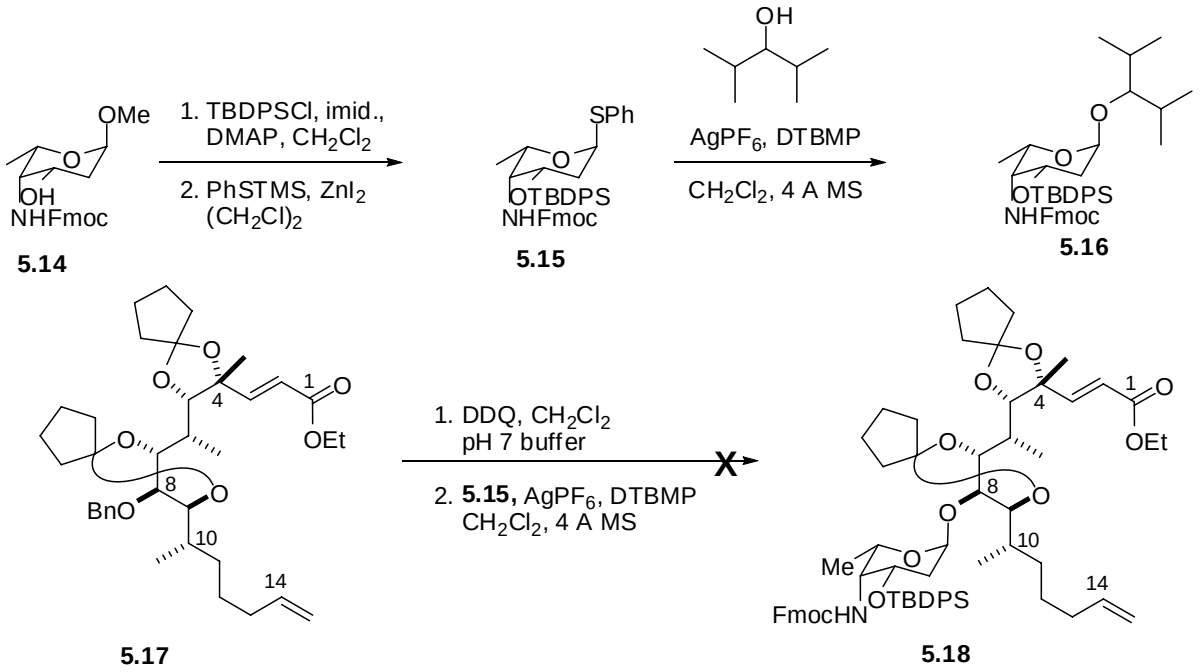


With the desired sugar in hand, conversion into an appropriate glycosyl donor was required. Based on studies of Martin and Lear,[97] conversion of the sugar to the acetimidate and activation with Lewis acids provided the most promising results with their complex glycosyl acceptor. To this end, hydrolysis of thioglycoside **5.10** with silver(I) nitrate and water provided the hemiacetal, which was converted into the trichloroacetimidate **5.11** with trichloroacetonitrile and polymer-supported DBU (Scheme 57). This reaction did not provide the conversion reported in the reported procedure. However, the crude mixture was exposed to several Lewis acids in the presence of diisopropylcarbinol as a model substrate. None of the conditions attempted provided the desired result, however. When attempted on the complex system at hand, similar results were expectedly observed. Thioglycoside **5.10** was also directly used as a glyocosyl donor with both silver(I) hexafluorophosphate and boron trifluoride-diethyl etherate. Neither of these conditions provided the desired reaction with the aglycon **5.1** and only decomposition of the sugar was observed.

5.3.2 Modification of Glycosyl Donor to Include Deactivated Nitrogen

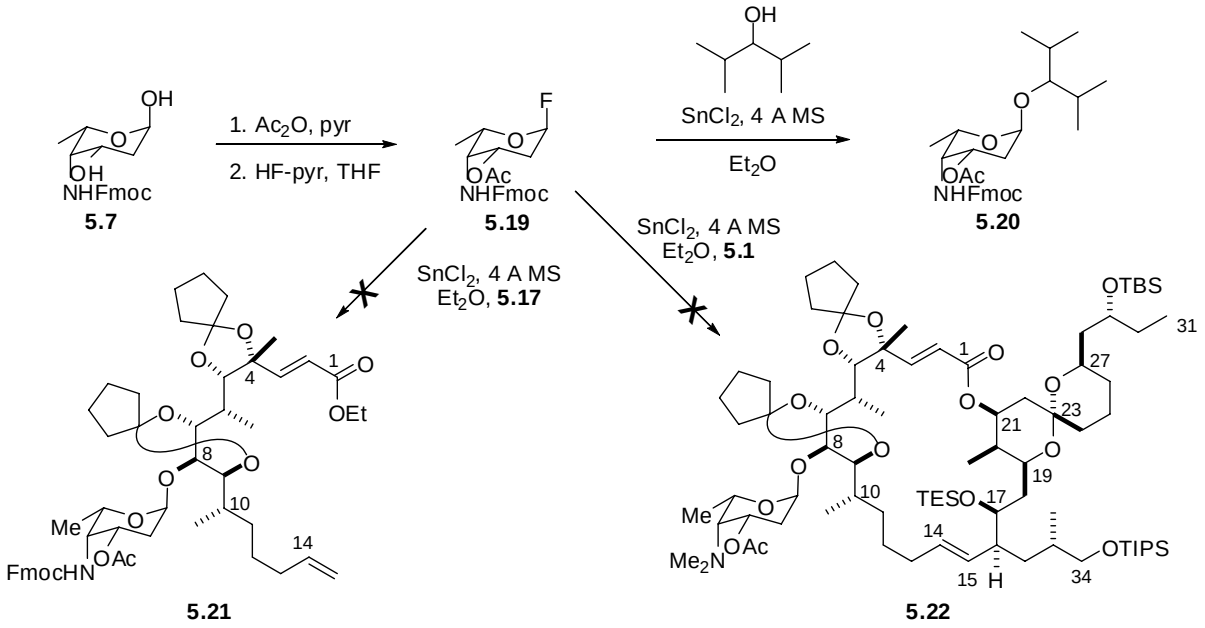
After the problems observed with these glycosylations, regardless of the acceptor used, a modification of the glycosyl donor was then undertaken. Due to the problems associated with unprotected amines' reactivity, the proposed new glycosyl donor would include a deactivated amine which could be manipulated to the dimethyl amine following the glyocosylation.

Scheme 58. Glycosylation Attempt with Protected Nitrogen



To this end, alcohol **5.14** was protected as a TBDPS ether and the methyl ketal converted to the thioglycoside **5.15** with thiophenyl trimethylsilane and zinc(II) iodide (Scheme 58). Treatment with the model alcohol, 2,4-dimethylpentanol, and silver (I) hexafluorophosphate provided the desired product in high conversion. However, when these conditions were applied to the C8-hydroxyl-containing ester (formed from DDQ removal of the benzyl group of **5.17**), the desired reaction was not observed to occur. With the steric environment of the donor in question with the large TBDPS ether present, a different glyocsyl donor was synthesized.

Scheme 59. Late Stage Glycosylation Attempts with Glycosyl Fluroide 5.19

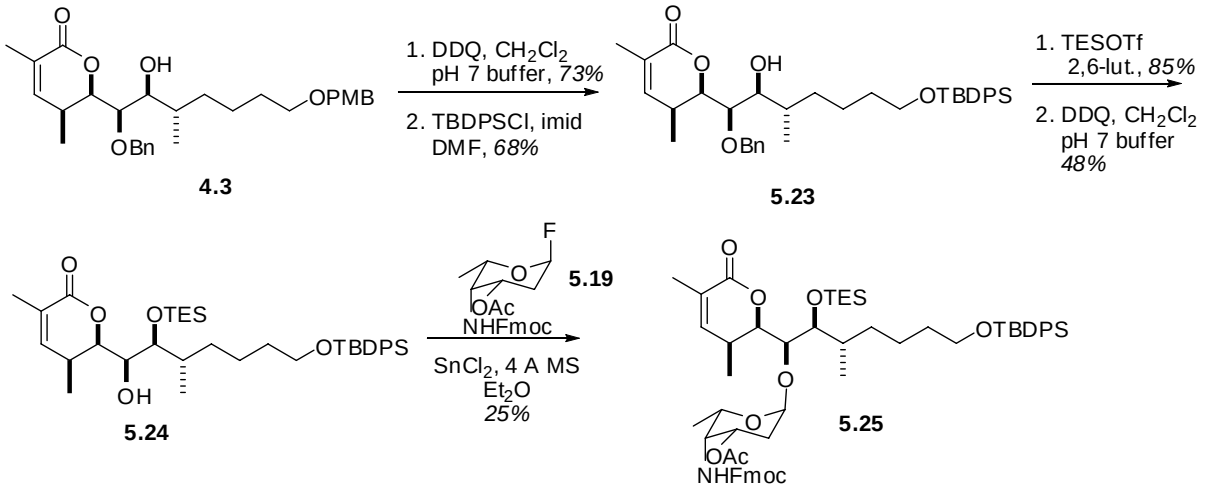


At this stage, another glycosyl donor was synthesized for testing with the model glycosyl acceptor (Scheme 59). Conversion of hemiacetal **5.7** to the di-*O*-acetyl sugar proceeded smoothly. Conversion of the anomeric acetate to the glyocsyl fluoride **5.19** readily occurred with hydrogen fluoride-pyridine. Treatment with tin (II) chloride, 4 Angstrom molecular sieves, and the model alcohol proceeded smoothly to provide **5.20**. When applied to the desired glycosyl acceptors **5.17** or **5.1,** however, no desired product was formed. At this stage, it became apparent that the steric environment around the C8 hydroxyl group was inhibiting the reactivity with any of the desired substrates. Modeling shows that this hydroxyl group is likely in the less reactive axial orientation in the six-membered ring that comprises the cyclopentylidene protecting group. Therefore, modifications of the glycosyl acceptor were made to incorporate the sugar at an earlier stage or with a different protecting group strategy in place to avoid the formation of the axial hydroxyl group.

5.3.3 Glycosylation of a Simpler Fragment

5.3.3.1 Glycosylation with α,β-Unsaturated Lactone 5.24

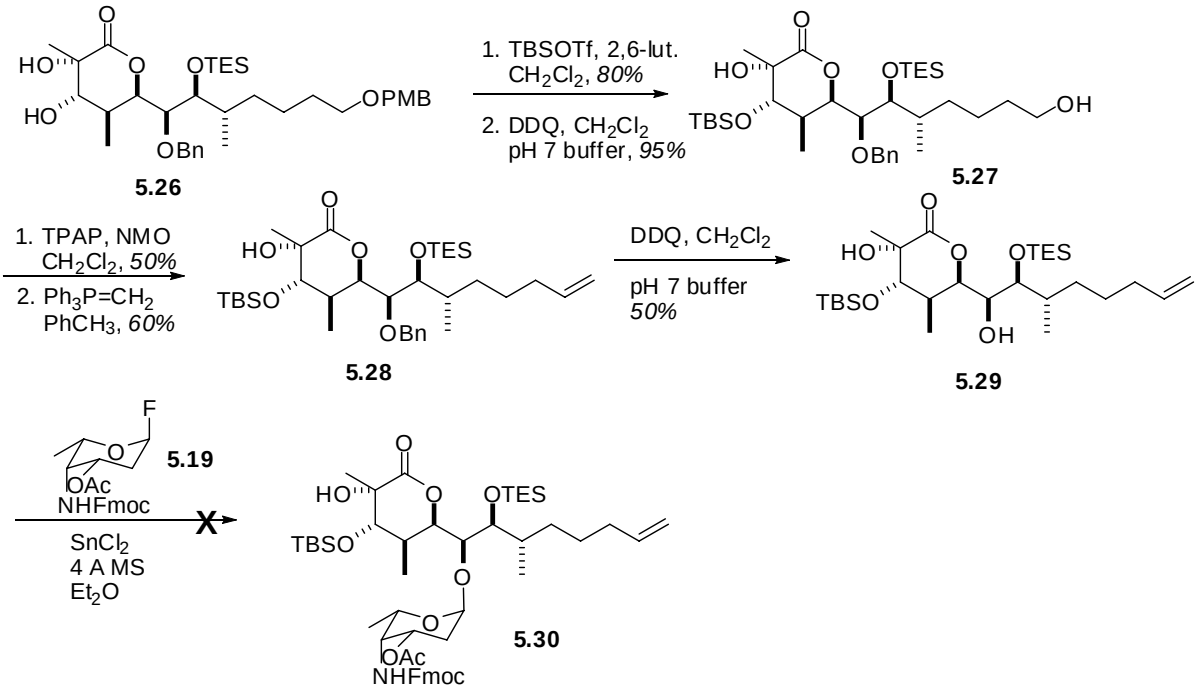
Scheme 60. Glycosylation with an Earlier Fragment



Reverting to alcohol **4.3** (Scheme 60), removal of the PMB group through the action of DDQ and reprotection as the TBDPS ether provided alcohol **5.23**. The TBDPS ether was selected due to its stability under acidic conditions. Protection of the 2° alcohol as the TES ether proceeded smoothly. Finally, oxidative removal of the benzyl group occurred in satisfactory yield (the major byproduct was the diol formed from loss of the TES ether) to provide the new glycosyl acceptor **5.24**. This time, treatment with glycosyl fluoride **5.19** with tin(II) chloride provided the desired product **5.25**, marking the first time that the kedarosamine-derived sugar had been incorporated with any desired acceptor. Parital deprotection of the TES ether was partly responsible for the low yield. Also, due to the predicted problems which could occur later in the synthesis in removing the TBDPS group in the presence of the base sensitive Fmoc group, however, a slightly more advanced substrate was brought forward for testing in the glycosylation.

5.3.3.2 Glycosylation Attempts on a More Advanced Substrate

Scheme 61. Glycosylation Attempt on an Advanced Fragment



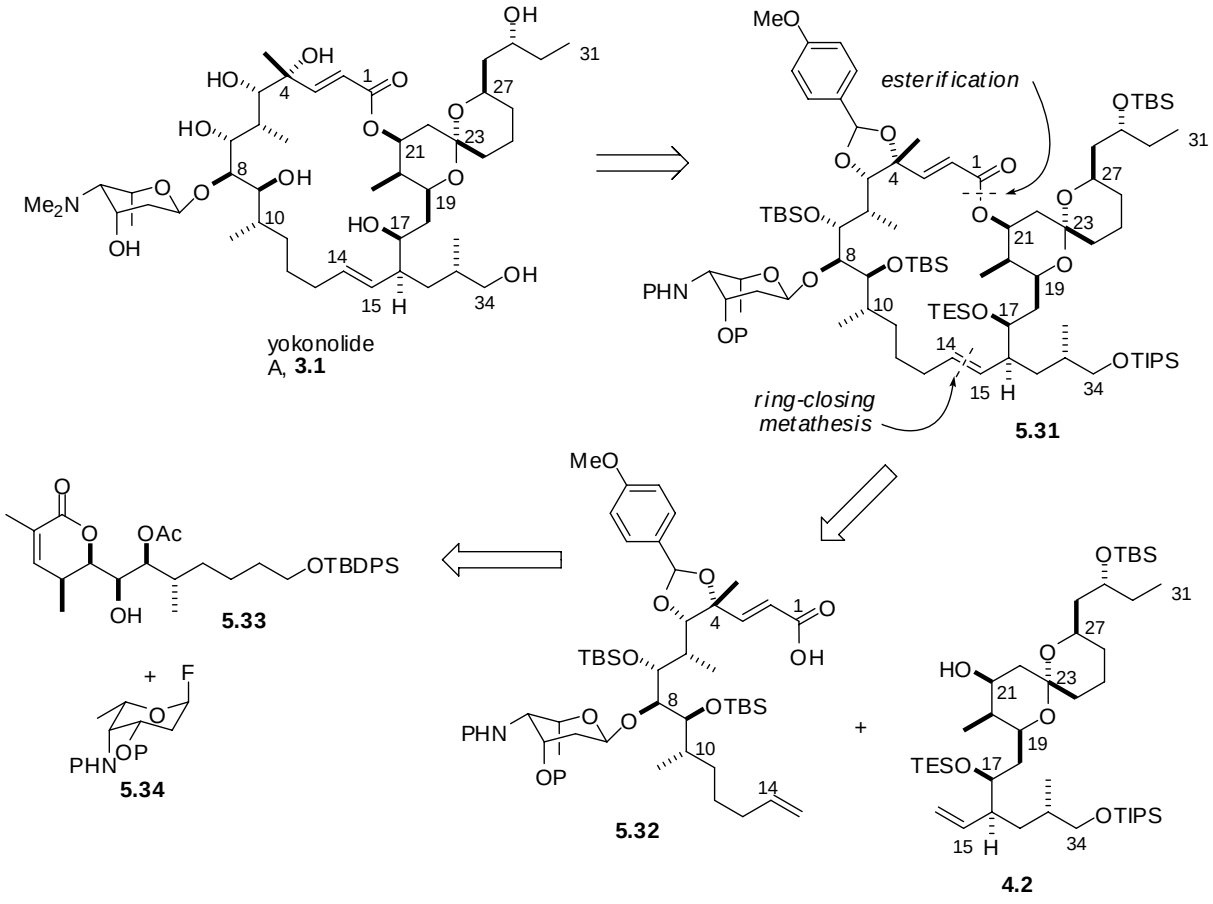
To this end, diol **5.26** was selectively protected as the TBS ether and the PMB group removed to form diol **5.27** (Scheme 61). Oxidation with TPAP and NMO[83] provided the aldehyde in low yield. This was not a concern prior to studying the glycosylation, however, as other oxidation methods were available for optimization. The aldehyde was treated to methylene Wittig conditions to provide the terminal olefin **5.28**. Oxidative removal of the benzyl ether then provided the proposed glycosyl acceptor **5.29**. When the optimized glycosylation conditions were applied to the system at hand, however, the desired product was not formed. Instead, only the starting acceptor was observed, along with decomposed sugar derivatives. By comparing this acceptor with the successful acceptor **5.29**, the steric environment can be seen as problematic. With the α,β-unsaturated lactone **5.24,** which is relatively planar in models, the hydroxyl group appears more accessible. After dihydroxylation and protection, however, the lactone is no longer planar and the C8 hydroxyl

group is less accessible. Therefore, the successful acceptor was then modified from lactone **5.24** to include a protecting group strategy that would allow for completion of the total synthesis and utilize a protecting group more robust than TES, which was partially removed during the debenzylation reaction.

5.4 More Glycosylation Studies and Efforts Toward the Total Synthesis

5.4.1 Revised Retrosynthetic Analysis for the Total Synthesis of Yokonolide

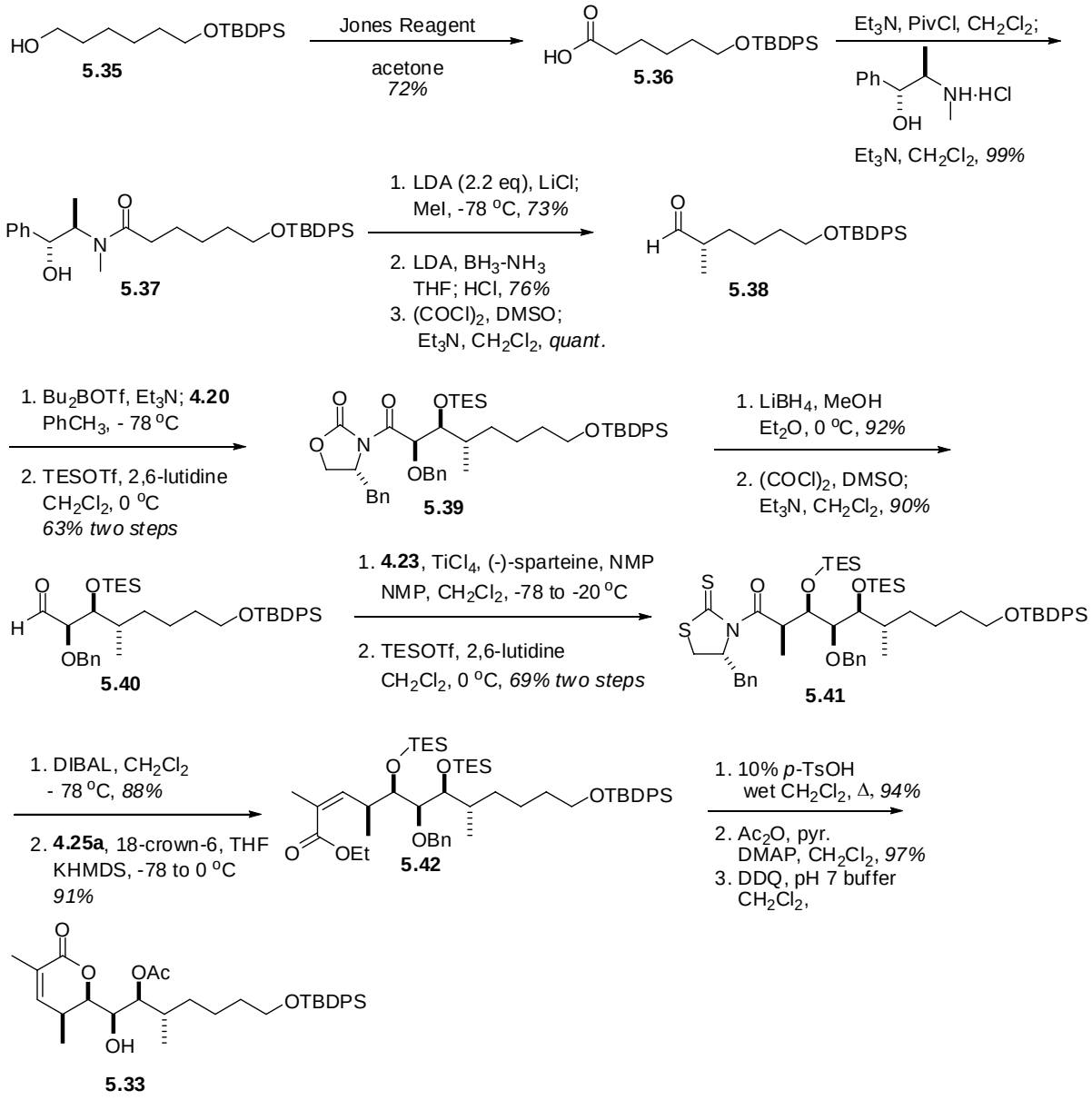
Scheme 62. Revised Retrosynthetic Analysis



With the problems encountered attempting late stage glycosylations and the success with glycosylation of an earlier fragment, a revised route was devised (Scheme 62). An esterification/ring-closing metathesis sequence would still be used to complete the macrocycle between carboxylic acid **5.32** and alcohol **4.2**. Glycosylation would be used to incorporate glycosyl fluoride **5.34** into alcohol **5.33**.

5.4.2 Synthesis of a New Glycosyl Acceptor 5.33

Scheme 63. Synthesis of New Glyocosyl Acceptor, Lactone 5.33

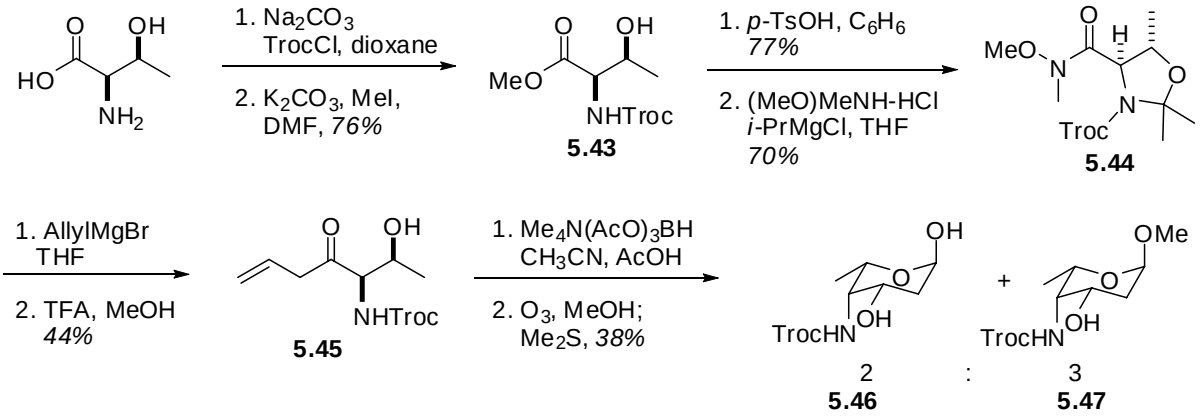


The synthesis of the glycosyl acceptor **5.33** with a different protecting group strategy took place in a similar manner to the previously synthesized protected aglycon. Beginning from 1,6-hexanediol (Scheme 63), selective monoprotection as the TBDPS ether followed by oxidation to the carboxylic acid **5.36** proceeded under Jones conditions.[115] Amidation with pseudoephedrine provided amide **5.37**. Methylation was effected under Myers alkylation

conditions.[100] Reductive removal of the acylated auxiliary[100] followed by oxidation under Swern conditions[103] provided aldehyde **5.38**. Treatment with *syn* glycolate conditions and protection of the resultant aldol adduct provided the TES ether **5.39**. Reductive cleavage of oxazolidinone and oxidation provided aldehyde **5.40**. Exposure to *syn* propionate aldol conditions then provided the desired aldol adduct. Protection as the TES ether and partial reduction of the auxiliary with DIBAL provided the aldehyde. Olefination under Still-Gennari conditions provided the Z-enoate **5.42**. Treatment with catalytic acid promoted protodesilylation and lactonization. Acetylation, followed by debenzylation provided lactone **5.33**.

5.4.3 Synthesis and Incorporation of Troc-Protected Sugar

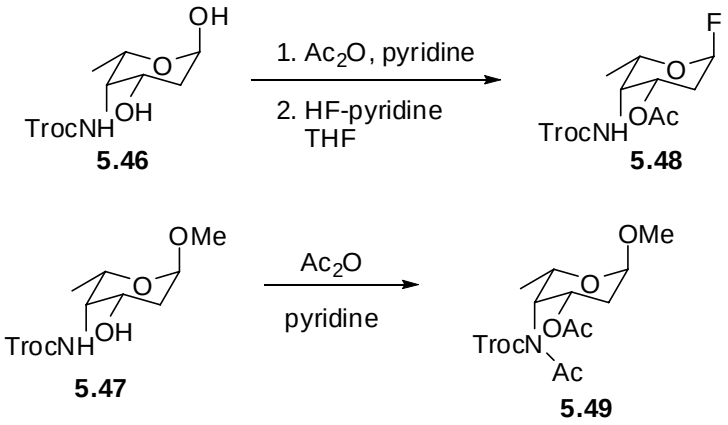
Scheme 64. Synthesis of Troc-Protected Kedarosamine-Derived Sugar 5.46



To synthesize the Troc protected sugar, a similar protocol was used as for the Fmoc protected sugar. To that end, D-threonine was protected to provide the Troc-D-threonine (Scheme 64). Conversion to the methyl ester took place with methyl iodide and potassium carbonate in DMF to provide ester **5.43**. Formation of the *N*,*O*-acetal took place with 2,2-methoxypropane under acid catalysis, followed by conversion to the *N*,*O*-methylhydroxylamide **5.44**.[116] Allylation to the ketone, followed by treatment with

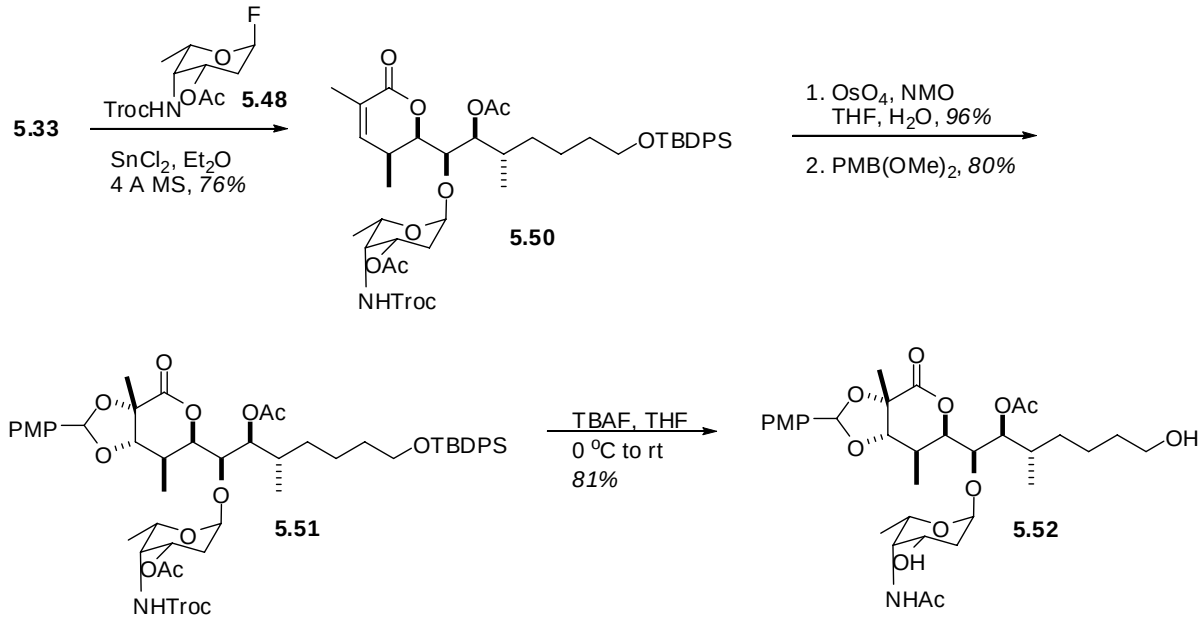
trifluroacetic acid with methanol provided ketone **5.45** in disappointing yields, likely due to parital deprotection of the Troc group under these conditions. 1,3-*anti* reduction[81] provided the desired diol. Upon treatment with ozonolysis conditions, however, a 2:3 mixture of the desired hemiacetal **5.46** to the undesired methyl acetal **5.47** was observed in low yields. When other protecting groups were employed in this reaction, only clean conversion to the desired hemiacetal was observed. Based upon the low yields observed in this sequence, further use of the Troc-protected sugar would require optimization to bring through significant amounts of material.

Scheme 65. Synthesis of Glycosyl Fluoride 5.48



Before investigating these optimization conditions, however, adequate quantities of hemiacetal **5.46** were in hand for further investigations into the glycosylation. Acetylation of the hemiacetal **5.46**, provided the desired di-*O*-acetate (Scheme 65). Treatment with hydrogen fluoride-pyridine was then used to form the glycosyl fluoride **5.48**. In an effort to recover the by-product from the ozonolysis, methyl acetal **5.47** was treated with acetic anhydride and pyridine. Unexpectedly, instead of the desired mono-*O*-acetate being formed, the *N*,*O*-diacetate **5.49** was the major product observed. This was not previously observed when the Fmoc protecting group was employed.

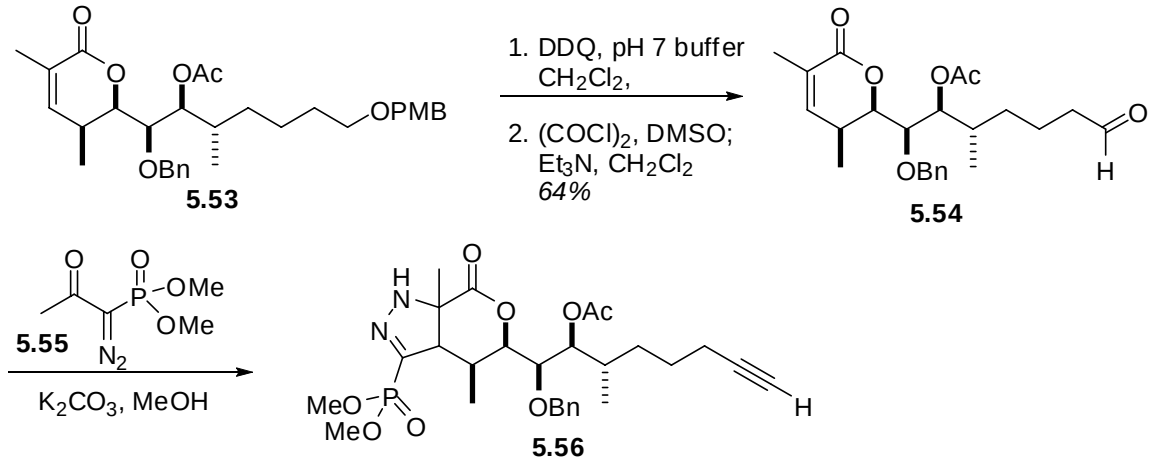
Scheme 66. Glycosylation with Troc-Protecting Glycosyl Donor



With the synthesis of the glyocsyl donor **5.48** complete, incorporation into acceptor **5.33** was promoted with tin(II) chloride to provide the desired product **5.50** in a 7:1, α:β ratio (Scheme 66). Dihydroxylation[117,118] and protection of the resultant diol provided **5.51**. At this stage, it became necessary to remove the silyl protecting group. Upon treatment with TBAF, however, an unexpected and undesired reaction occurred in addition to removal of the TBDPS. The Troc group was cleaved and an O → N acetyl transfer occurred, leading to the unusable amide **5.52**. In an effort to overcome the problem with TBAF, installation of a terminal alkyne was proposed as a way to later access the terminal olefin without the need for a protecting group on the primary alcohol.

5.4.4 Modification of Glycosyl Acceptor to Preclude Silyl Deprotection

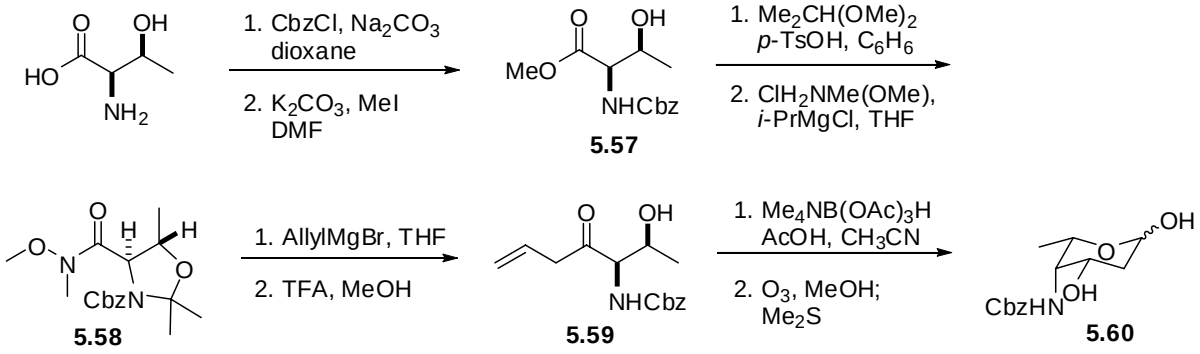
Scheme 67. Attempt at Synthesizing the Terminal Alkyne



To that end, the PMB group was removed with DDQ and the resultant alcohol treated to a Swern oxidation[103] to provide aldehyde **5.54** (Scheme 67). Exposure to the Ohira-Bestmann[119,120] reagent (**5.55**) to install the terminal alkyne provided disappointing results, however. While formation of the terminal alkyne was observed, the α,β-unsaturated lactone moiety reacted in a [3+2] cycloaddition to form the dihydropyrazole **5.56**.[121] Further efforts to preclude the use of a protecting group at C14 were unsuccessful.

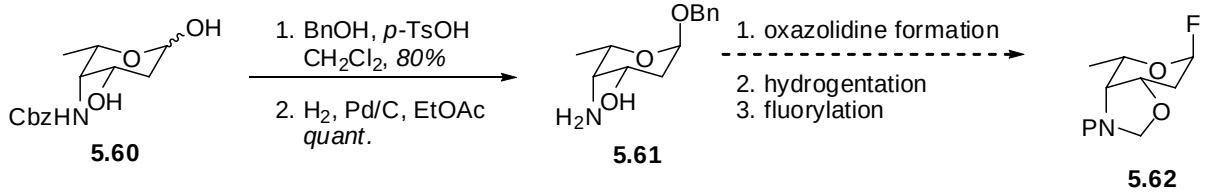
5.4.5 Design and Incorporation of a Cyclic Protecting Group on the Glycosyl Donor

Scheme 68. Synthesis of Kedarosamine



Modification of the glycosyl donor was then undertaken to prevent the acetyl transfer from occurring by changing the acetate to a less problematic protecting group. The kedarosamine-derived sugar was synthesized with incorporation of the Cbz, which could be readily switched upon the completion of the functionalized sugar (Scheme 68). The synthesis of the core structure of kedarosamine was therefore carried about by following the preparations of Evans and Vuljanic.[96,122] Starting from D-threonine, protection of the free amine was carried out through exposure to benzylchloroformate, followed by conversion to the methyl ester with potassium carbonate and methyl iodide to provide **5.57.** Formation of the *N*,*O*-acetal took place upon treatment with dimethoxypropane under acidic conditions. Conversion of the methyl ester to the Weinreb amide **5.58** occurred utilizing the Merck method.[116] Allylation, followed by deprotection of the cyclic protecting group provided the β-hydroxyketone **5.59**. 1,3-*anti* reduction took place using tetramethylammonium triacetoxyborohydride.[81] Ozonolysis cleaved the terminal olefin and in situ cyclization to the hemiacetal provided the core kedarosamine skeleton **5.60**.

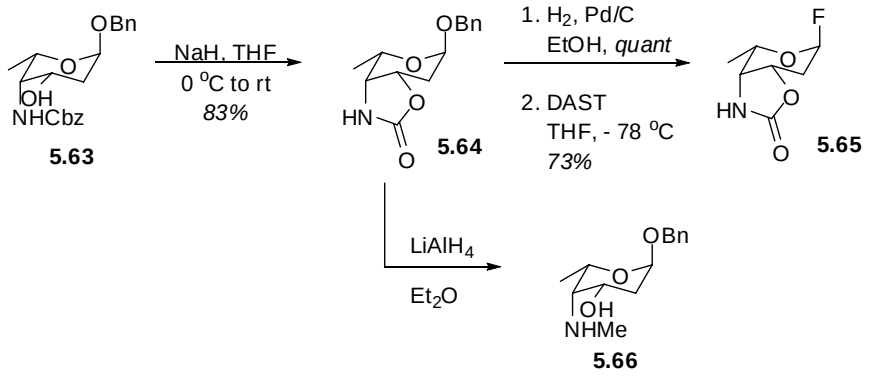
Scheme 69. Attempts at Formation of the Oxazolidine



The synthesis of a cyclic *N*,*O*-protecting group was briefly explored to achieve oxazolidine **5.62** (Scheme 69). This was conducted through formation of the benzyl acetal to facilitate easier formation of the glyocosyl fluoride, followed by selective hydrogentation of the Cbz group to provide aminoalcohol **5.61**. All attempts to form a usable oxazolidine, including

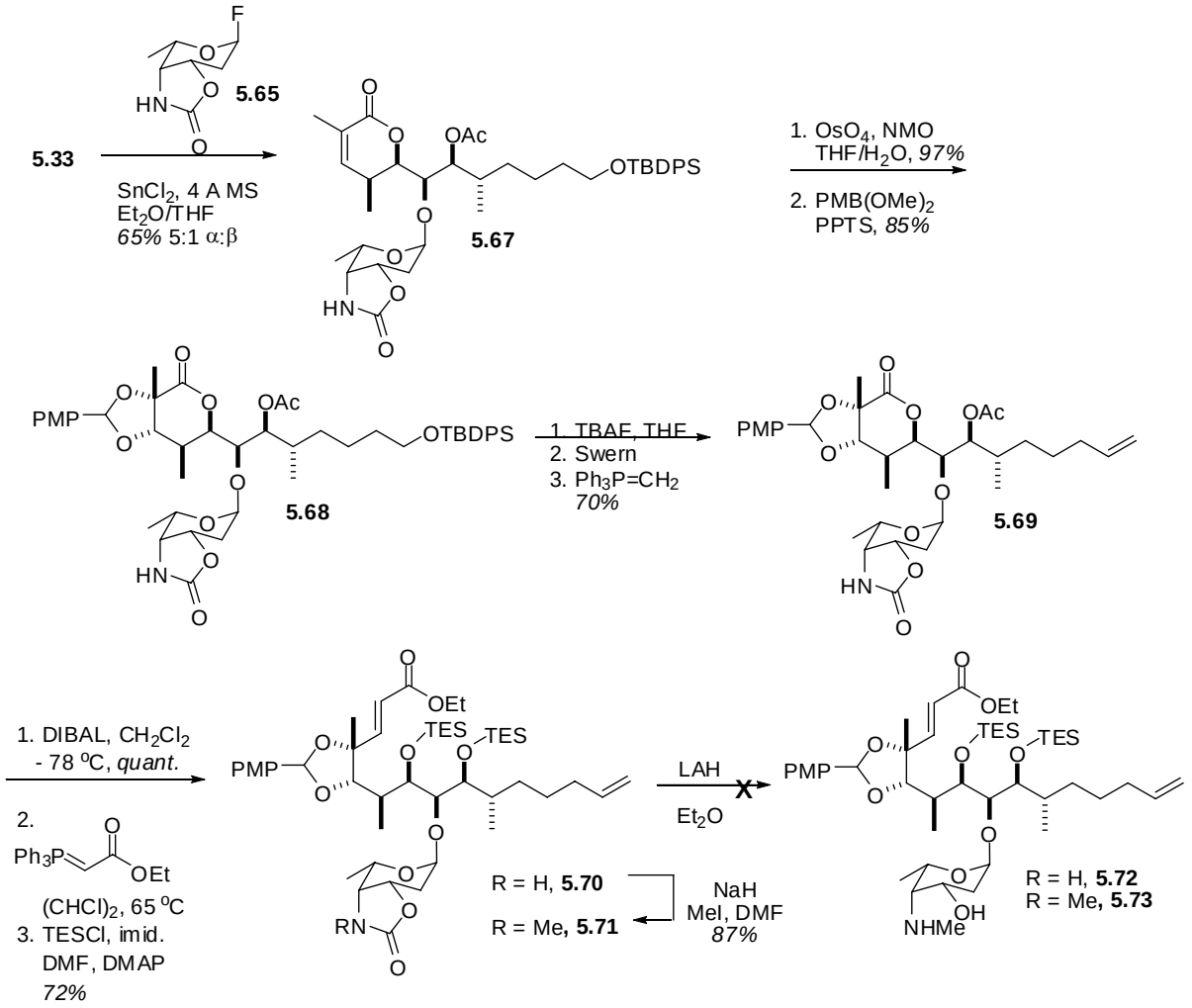
formaldehyde and paraformaldehyde, were low yielding and unreliable and further efforts were halted for a more reliable protecting group.

Scheme 70. Synthesis of Glycosyl Fluoride with Oxazolidinone Protecting Group



While the oxazolidine substrate was inaccessible, the oxazolidinone substrate could be a useful substrate and significantly easier to synthesize (Scheme 70). Numerous reports have shown that both carbamate and oxazolidinone functionalities can be reductively removed to form monomethylamines. To test the utility of the oxazolidinone, the synthesis of oxazolidinone **5.64** was undertaken. Exposure of Cbz-protected sugar **5.63** to basic conditions then led to displacement of benzyl alcohol and formation of the oxazolidinone **5.64**. At this stage, it was necessary to study the removal of the oxazolidinone moiety through reduction to the methyl amine. Treatment with lithium aluminum hydride at room temperature cleanly provided the desired methyl amine **5.66**. With this simple model indicating that removal of the oxazolidinone should not pose a major problem, incorporation into a glycosyl acceptor was necessary. Therefore, conversion of the benzyl acetal **5.64** to the glycosyl fluoride **5.65** proceeded through hydrogenolysis and incorporation of fluoride by exposure to diethylaminosulfur trifluoride (DAST).[123]

Scheme 71. Glycosylation and Elaboration with Oxazolidinone Protecting Group

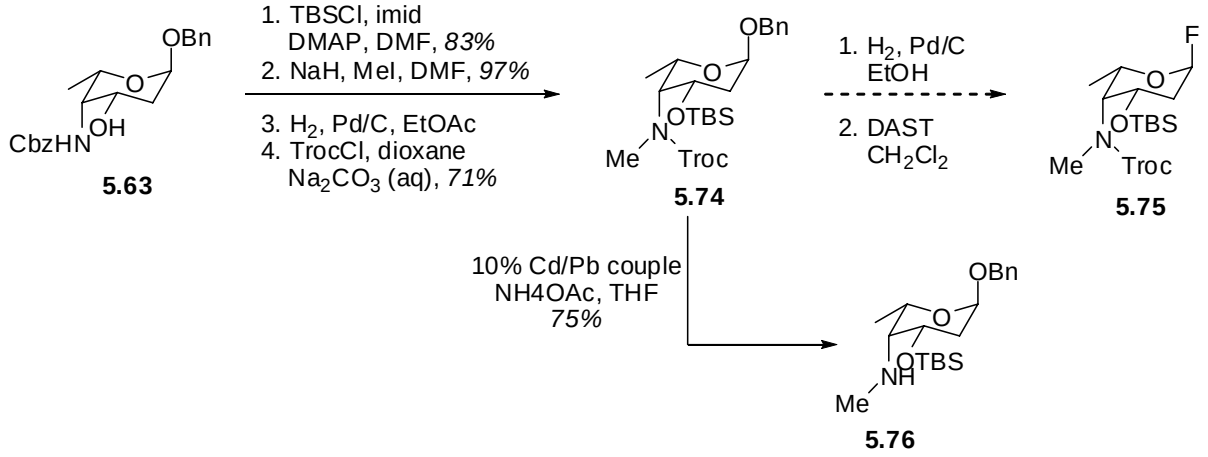


Glycosylation with glycosyl fluoride **5.65** and acceptor **5.33** provided the desired glycosylation product **5.67** as a 5:1 anomeric mixture favoring the α-anomer (Scheme 71). Dihydroxylation provided one diastereomer exclusively. Protection as the *para*-methoxybenzylidene proceeded to provide **5.68**. Removal of the silicon protecting group with TBAF provided the primary alcohol. Swern oxidation[103] followed by a methylene Wittig provided the terminal olefin **5.69.** Partial reduction of the lactone led to formation of the lactol. The aldehyde was trapped under stabilized Wittig conditions and the resultant diol protected as the bis-triethylsilyl ether **5.70**. Application of the reductive conditions which

proved successful on the model system (Scheme 70) unfortunately did not lead to formation of the desired product **5.72**. Several decomposition products were formed stemming from reduction of the ester, loss of the silyl protecting groups, as well as possible internal 1,4 addition. Literature precedent indicates that *N*-methyloxazolidinones are more reactive that the corresponding unalkylated oxazolidinones. Therefore oxazolidinone **5.70** was methylated and again exposed to the reductive conditions. Similar problems were again observed and the utility of carrying the dimethylamine moiety through the rest of the synthesis was questioned. With these problems brought to light, an alternate route needed to be investigated.

5.4.6 Progress Toward Incorporation of the Troc-Protected Sugar For Total Synthesis

Scheme 72. Synthesis of Methylated Carbamate Sugar

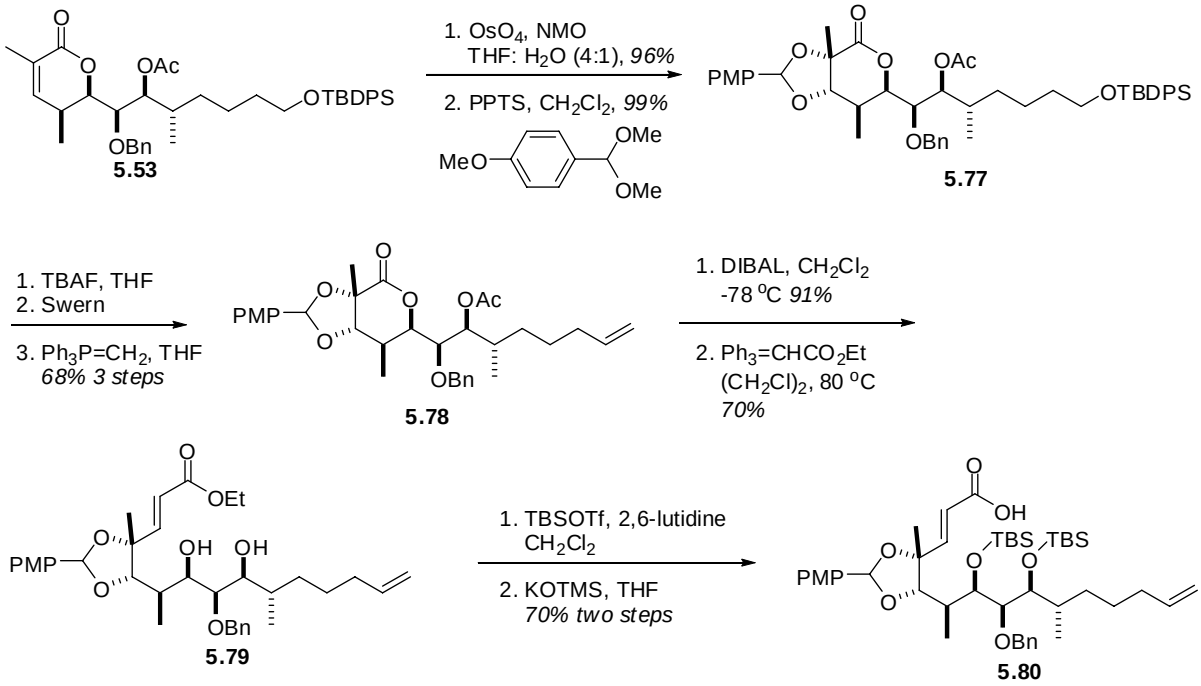


In an effort to revisit the utility of the Troc protecting group and solve these problems of unwanted Troc removal and transfer of oxygen protecting group, the synthesis of glycosyl fluoride **5.75** was investigated (Scheme 72), where a methyl group has been incorporated to further reduce the reactivity toward TBAF and basic conditions. Beginning from alcohol **5.63,** TBS protection and methylation proceeded smoothly to provide the methylcarbamate. A protecting group exchange was then effected through selective hydrogenation of the Cbz

group and incorporation of the Troc moiety to provide benzyl acetal **5.74.** Removal of the benzyl group proved problematic, however, as an unidentifiable mixture of decomposition products was observed. This problem is proposed to be eliminated through conversion of the benzyl acetal **5.74** to the thioglycoside prior to conversion to the glycosyl fluoride. Prior to investigating these events, Troc amine **5.74** was exposed to 10% Pb/Cd couple in the presence of ammonium acetate to effect efficient deprotection and lead to **5.76**. These conditions should be mild enough to be successful on more advanced substrates near the endgame. This will be investigated in the future.

5.5 Progress Toward the Completion of the Fully Deprotected Aglycon

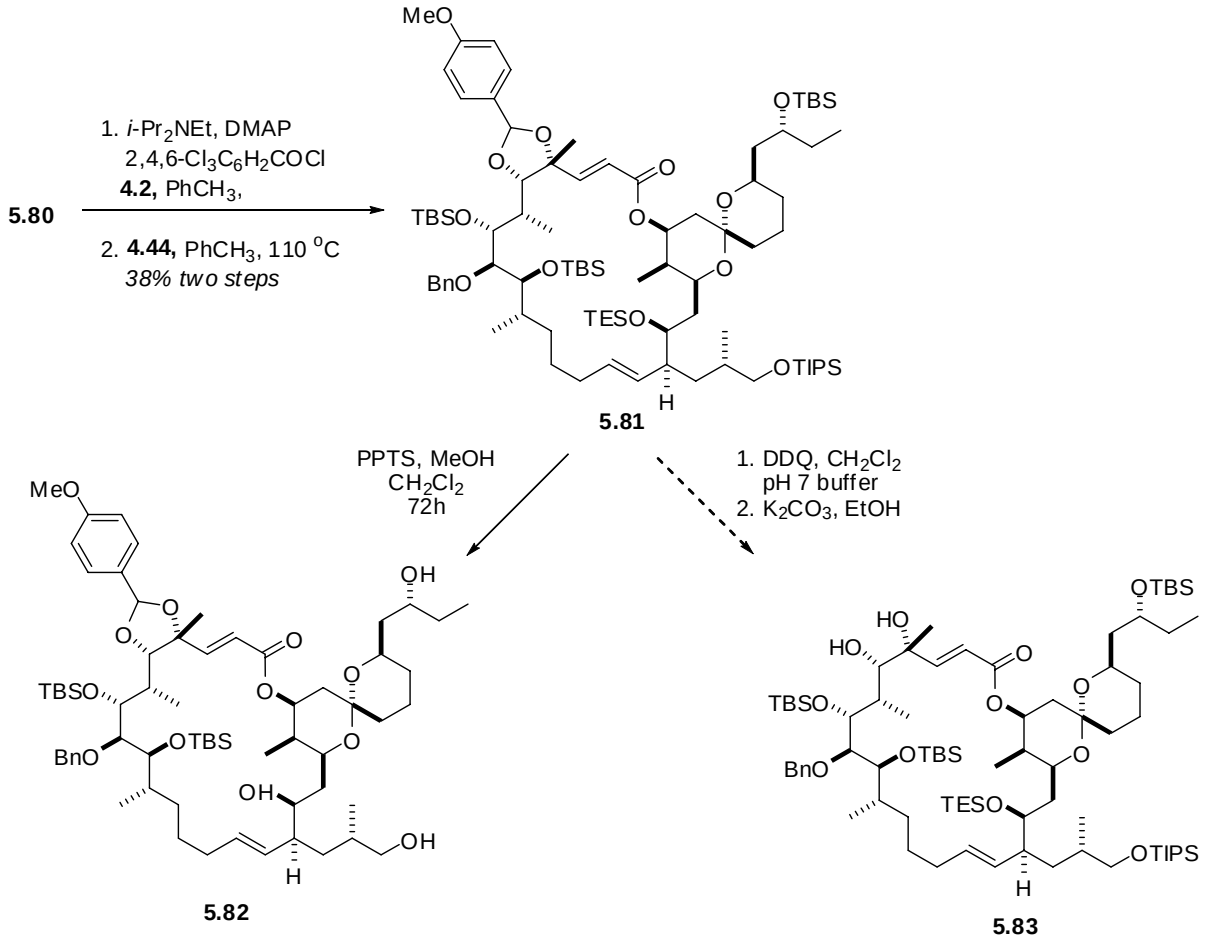
Scheme 73. Completion of Carboxylic Acid Fragment



In an effort to study the removal of the protecting groups, the synthesis of the unprotected aglycon was undertaken (Scheme 73). Beginning with lactone **5.53**, dihydroxylation and protection as the *p*-methoxybenzylidene provided **5.77**. Removal of the TBDPS group, oxidation of the resultant hydroxyl group, and exposure to methylene Wittig conditions

provided lactone **5.78**. Partial reduction to the lactol and interception of the aldehyde with the stabilized ylide provide the α,β-unsaturated ester **5.79**. Protection as the bis-TBS ether and hydrolysis provided carboxylic acid **5.80**.

Scheme 74. Attempted Deprotections of Macrolactone 5.81

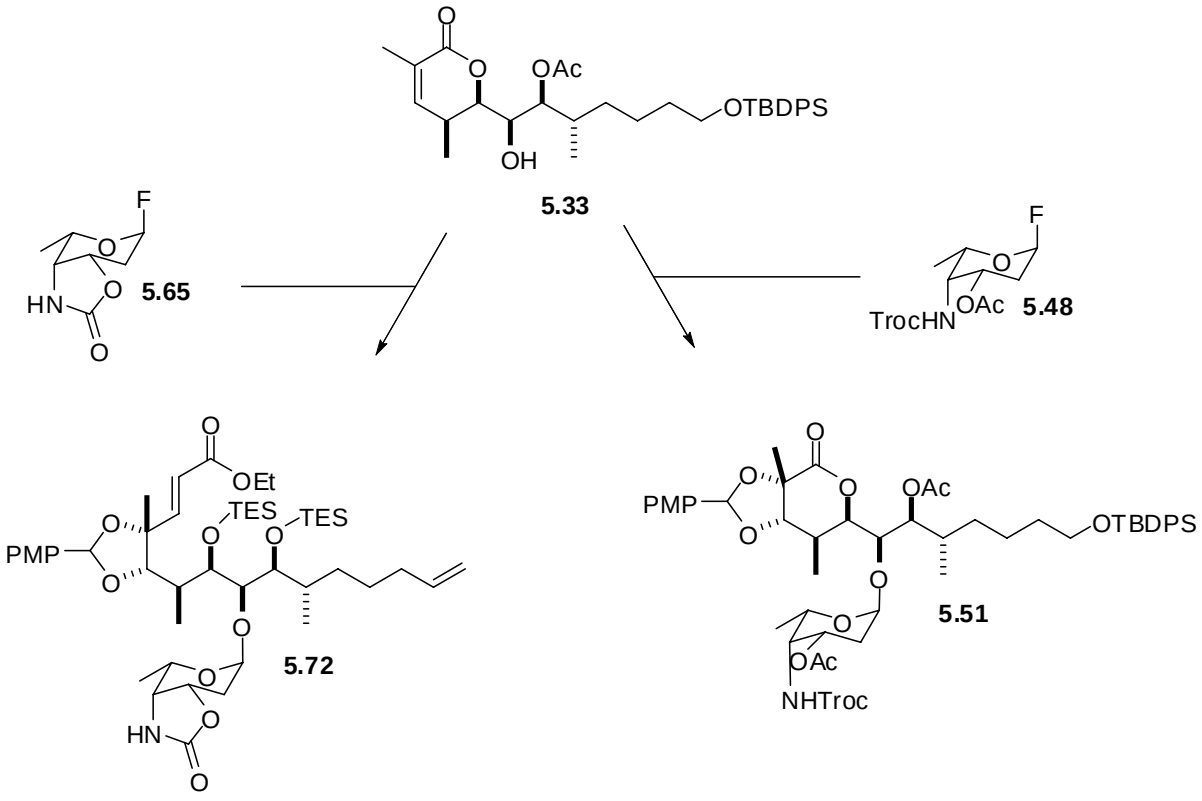


Coupling of the two major fragments (Scheme 74), carboxylic acid **5.80** and alcohol **4.2** provided the ester under Yamaguchi conditions.[87] Ring-closing metathesis[94] then provided a differentially-protected aglycon **5.81**. Exposure to mild acid conditions removed a TES and TBS group. Further exposure removed the 1° TIPS, while leaving the acetal intact to provide **5.82**. DDQ-mediated removal of the benzyl group on **5.81** also effected conversion of the *p*-methoxybenzylidene to a mixture of *p*-methoxybenzoate. Treatment under basic conditions

of potassium carbonate and ethanol led to significant decomposition including likely deprotection or silyl transfer and internal 1,4 addition into the enoate. Efforts are underway to complete the unprotected aglycon from **5.81**.

5.6 Summary

Scheme 75. Efforts Toward the Total Synthesis of Yokonolide



In efforts toward the total synthesis of yokonolide A, several glycosyl acceptor and donor pairs were investigated (Scheme 75). The studies have concluded that the glycosyl acceptor requires the presence of the α,β-unsaturated lactone moiety in **5.33** for successful incorporation of the kedarosamine-derived sugar. Attempts to bring the glycosylated material (**5.51** and **5.72**) forward to complete the total synthesis have been met with problematic protecting group strategies, each presenting a unique challenge. Attempts to move beyond these shortcomings are underway in efforts to achieve the total synthesis.

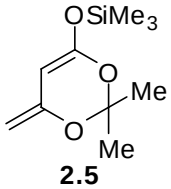
Progress has also been made toward removing the protecting groups from the aglycon to prepare for a similar deprotection sequence following a successful route to the protected macrocycle coupled with the sugar moiety.

Chapter 6

Experimental Procedures and Data

Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm^{-1}. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using silica gel (32 to 63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, chlorotrimethylsilane, benzene, and toluene were distilled from calcium hydride immediately prior to use. Butyl vinyl ether was distilled over sodium immediately prior to use. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one was distilled under vacuum (2 mm) immediately prior to use. Methylmagnesium iodide was synthesized using standard Grignard techniques from iodomethane. LDA was generated *in situ* from diisopropylamine (1.1 eq) and *n*-butyllithium (1.0 eq) in THF (1M) at –78 ^{o}C. Titanium (IV) Lewis acids were generated in solution using the desired equivalents of titanium (IV) isopropoxide and titanium (IV) chloride in solvent immediately prior to use. Optically pure NOBIN used for Carreira's catalyst was synthesized

using Hoveyda's reported procedure.[1] All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were performed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.



2.5

Preparation of Silyl Dienolate 2.5[2]:

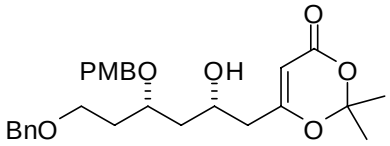
To a stirred solution of freshly prepared LDA (1.1 eq) in THF (0.4 M) at -78 ºC was added 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (1.0 eq) dropwise. Stirring was continued for 1 h. Chlorotrimethylsilane was then added and allowed to react for 10 min. Reaction was warmed to room temperature briefly to ensure completion, then cooled down to 0 ºC. Anhydrous pentane was then added to precipitate the lithium salts. The reaction was then filtered through a pad of celite and the flasked rinsed with pentane and filtered. Solvents were removed and pentane addition-filtration was repeated until most of the precipitates were removed. Solvents were removed and the oil was distilled under reduced pressure (75 ^{o}C, 2 mm Hg) to provide silyl dienolate **2.5**.

General procedure for Lewis acid promoted aldol addition of silyl dienolate 2.5 with aldehyde 2.4:

[1] Supporting Information in Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H.; *J. Am. Chem. Soc*. **2002,** *124*, 4954.; Ito, Y.; Miyake, T.; Hatano, S.; Shima, R.; Ohara, T.; Suginome, M. *J. Am. Chem. Soc.* **1998,** *120,* 11880.

[2] Adapted from the procedure of Grunwell, J. R.; Karipides, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91-95.

Aldehyde **2.4** was dissolved in methylene chloride and cooled to -78 ºC. Lewis acid was then added dropwise and allowed to stir 10 minutes. Silyl dienolate **2.5** was then added dropwise. Reaction proceeded for 1.5 hours upon which time the reaction was quenched with water and warmed to room temperature. The layers were separated and the aqueous layer was extracted with methylene chloride. Combined organic layers were then washed with brine and dried over sodium sulfate. Solvents were removed in vacuo and the aldol adduct was obtained after flash column chromatography.



2.17s

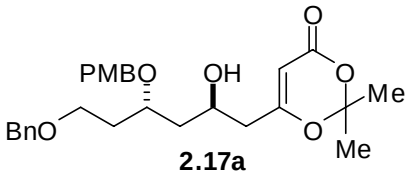
Aldol addition using Carreira's catalyst:

Carreira's catalyst was prepared in situ following the reported procedure[3] to provide a 5.5 mM solution of 5% catalyst in ethyl ether. The solution was cooled to 0 ºC and 2,6-lutidine (0.48 mmol), aldehyde **2.4** (1.2 mmol), and silyl dienolate **2.5** (1.8 mmol) were sequentially added and the reaction was allowed to react for 15 h at 0 ºC. The reaction was quenched by pouring into water and then extracted with ethyl ether, dried over sodium sulfate, filtered, and concentrated in vacuo. 10% trifluoroacetic acid in THF was then added to the residue and the reaction was stirred for 5 minutes and diluted in ether. Layers were separated and the organic layer was washed with 5% bicarbonate solution (x2) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography provided alcohol **2.17s** (540 mg, 95% yield, 10:1, **2.17s:2.17a**).

[3]Supporting Information in: Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995,** *117,* 12360.

Alcohol 2.17s:

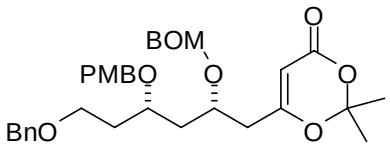
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.28 (s, 1H), 4.47 (s, 2H), 4.45 (AB_q, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 89.0 Hz, 2H), 3.97 (m, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 3.67 (OH, bs, 1H), 3.53 (m, 2H), 2.31 (dd, *J* = 7.9, 14.5 Hz, 1H), 2.23 (dd, *J* = 4.8, 14.5 Hz, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.70-1.60 (m, 2), 1.65 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 161.0, 159.5, 138.2, 129.7, 129.6, 129.6, 128.4, 127.7, 127.7, 114.0, 106.4, 95.1, 95.1, 76.6, 73.1, 70.7, 68.2, 66.4, 55.2, 41.7, 41.1, 34.0, 25.3, 24.7; IR(film): 3453.9, 3033.48, 2998.7, 2938.0, 2865.7, 1726.0, 1633.4, 1610.3, 1585.2, 1513.9, 1390.4, 1273.8, 1248.7 cm^{-1}; ESI-MS $C_{27}H_{34}O_7$ [M+Na] calc 493.2, found 493.3; $[\alpha]_D^{21}$= +6.3º (c=1.0, THF).



2.17a

Alcohol 2.17a*:*

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.25 (s, 1H), 4.46 (AB_q, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 8.3 Hz, 2H), 4.44 (AB_q, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 13.8 Hz, 2H), 4.11 (m, 1H), 3.87 (m, 1H), 3.77 (m, 3H), 3.53 (m, 2H), 3.02 (brs, OH), 2.29 (dd, *J* = 8.1, 14.5 Hz, 1H), 2.22 (dd, *J* = 4.7, 14.5 Hz, 1H), 1.98 (m, 1H), 1.78 (m, 2H), 1.65 (s, 3H), 1.64 (s, 3H), 1.64-1.56 (m,1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 161.0, 159.3, 138.1, 129.8, 129.7, 128.3, 127.7, 127.6, 113.8, 106.4, 95.0, 94.9, 73.6, 73.0, 71.0, 66.5, 65.7, 55.2, 41.6, 39.6, 33.7, 25.3, 24.6; IR(film): 3455.8, 2928.4, 2857.0, 1726.9, 1632.5, 1513.9, 1390.4, 1249.7 cm^{-1};ESI-MS for $C_{27}H_{34}O_7$ [M+Na] calc 493.3 found 493.3; $[\alpha]_D^{22}$= -1º (c=0.25, CH_2Cl_2).

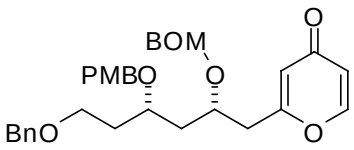


2.18s

Benzyloxymethyl ether 2.18s:

Alcohol **2.17s** (1.15 mmol) was brought up in methylene chloride (12 mL) and the flask was charged with Hünig's base (1.0 mL, 5.75 mmol), benzyloxymethylchloride (0.48 mL, 3.45 mmol), and catalytic DMAP (28 mg, 0.23 mmol). The reaction was heated to reflux and allowed to react 16 hours. Reaction was quenched with the addition of sodium bicarbonate. The aqueous layer was extracted with methylene chloride and the combined organics washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography provided ether **2.18s** (1.09 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.25 (m, 10H), 7.19 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 5.31 (s, 1H), 4.72 (AB_q, J_{AB} = 7.4 Hz, $\Delta\nu_{AB}$ = 3.5 Hz, 2H), 4.56 (AB_q, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 11.0 Hz, 2H), 4.42 (AB_q, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 6.0 Hz, 2H), 4.40 (s, 2H), 4.02 (dq, J = 6.2, 6.2, 6.2 Hz, 1H), 3.76 (s, 3H), 3.70 (dq, J = 6.0, 6.0, 6.0 Hz, 1H), 3.53 (m, 2H), 2.44 (d, J = 6.2 Hz, 2H), 1.97 (dt, J = 6.5, 14.3 Hz, 1H), 1.84 (q, J = 6.4 Hz, 2H), 1.68 (dt, J = 6.0 , 14.3 Hz, 1H), 1.63 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (125 MHz): δ 168.7, 160.6, 159.2, 138.4, 137.6, 130.6, 129.2, 128.3, 128.2, 127.5, 127.4, 113.8, 106.3, 95.1, 93.7, 72.9, 72.6, 72.1, 70.4, 69.7, 66.6, 55.1, 39.3, 39.2, 34.3, 25.0; IR(film): 2924.5, 2858.0, 1728.9, 1633.4, 1610.3, 1512.9, 1454.1, 1390.4, 1375.0, 1248.7 cm^{-1}; ESI-MS for $C_{35}H_{42}O_8$ [M+Na] calc 613.3, found 613.3; $[\alpha]_D^{24}$= -11.0º (c=0.65, THF).



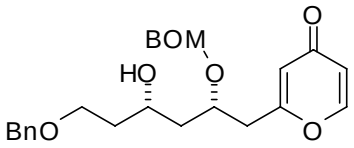
2.19s

Pyrone 2.19s:

Dioxinone **2.18s** (2.0 g, 3.4 mmol) was dissolved in benzene and concentrated under reduced pressure at room temperature to azeotropically dry the material. A round bottomed flash was charged with toluene (120 mL) and butyl vinyl ether (2.59 mL, 20 mmol). The reaction was heated to reflux and dioxinone was dissolved in toluene (5 mL) and added via syringe pump over 2 hours. Reaction was allowed to proceed for 1.5 hours after the final addition. Reaction was then cooled to room temperature and solvents removed under reduced pressure. The crude butyl acetal was then charged with THF (40 mL) and catalytic *p*-TsOH (65 mg, 0.34 mmol) was added. The reaction was heated to reflux and allowed to stir 2 hours. Upon cooling to room temperature, the reaction was quenched through the addition of saturated sodium bicarbonate solution. Ethyl acetate was then added and the layers separated. The aqueous layer was extracted with ethyl acetate (x2) and the combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo.* The residue was purified via flash column chromatography to provide pyrone **2.19s** (1.24g, 2.22 mmol, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, 5.7 Hz, 1H), 7.34-7.22 (m, 10H), 7.19 (d, J = 6.6 Hz, 2H), 6.81 (d, J = 6.6 Hz, 2H), 6.18 (m, 2H), 4.67 (AB_q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 34.6 Hz, 2H), 4.47-4.35 (m, 6H), 4.15-4.08 (m, 1H), 3.76 (s, 3H), 3.69 (m, 1H), 3.58-3.48 (m, 2H), 2.67 (dd, J = 4.4, 14.6 Hz, 1H), 2.57 (dd, J = 7.6, 14.6 Hz, 1H), 1.98-1.62 (m, 4H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 178.6, 166.4, 159.1, 154.7, 138.3, 137.5, 130.4, 129.4, 128.3, 128.2, 127.6, 127.5, 127.4, 127.4, 116.7, 113.7, 93.2, 73.0, 72.4, 72.0, 70.4, 69.5, 66.5, 55.1, 39.3, 39.0, 34.2; IR(film): 2924.5, 2849.31, 1720.2, 1659.5, 1612.2, 1512.9, 1455.0, 1247.7 cm^{-1}; ESI-MS $C_{34}H_{38}O_7$ [M+H] calc 559.3, found 559.3, [M+Na] calc 581.3, found 581.3; $[\alpha]_D^{21}$= +3.7º (c=0.53, THF).

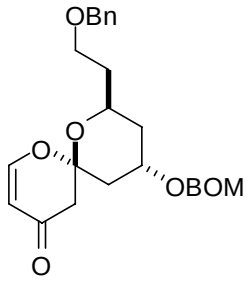


Hydroxypyrone:

Pyrone **2.19s** (1.22 g, 2.18 mmol) was placed in a round-bottomed flask and charged with methylene chloride (44 mL) and pH 7 buffer (2.2 mL). DDQ (544 mg, 2.4 mmol) was then added and the reaction was stirred for 1 hour until starting material had disappeared. The reaction was quenched through the addition of saturated sodium bicarbonate and the layers separated. The organic layer was washed with sodium bicarbonate and the aqueous layers extracted with methylene chloride (x2). The organic layers were combined and dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography provided hydroxypyrone (906 mg, 2.08 mmol, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 6.2 Hz, 1H), 7.34-7.25 (m, 10H), 6.22 (s, 1H), 6.21(m, 1H), 4.72 (AB_q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 27.5 Hz, 2H), 4.51 (AB_q, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 14.2 Hz, 2H), 4.48 (s, 2H), 4.22 (m, 1H), 3.98 (m, 1H), 3.66 (m, 1H), 3.60 (m, 1H), 3.29 (bs, OH), 2.81 (dd, J = 5.1, 14.6 Hz, 1H), 2.73 (dd, J = 7.3, 14.6 Hz, 1H), 1.87 - 1.70 (m, 3H), 1.64 (ddd, J = 3.5, 6.3, 14.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9, 166.5, 155.0, 137.8,137.4, 129.5, 128.4, 128.3, 127.7, 127.6, 127.6, 127.5, 116.8, 116.7, 93.3, 73.3, 73.2, 69.7, 68.6, 68.4, 41.5, 39.1, 36.8; IR(film): 3410.5, 2924.5, 1715.37, 1655.6, 1604.5,

1454.1, 1416.5, 1379.8, 1273.8 cm^{-1}; MS (ESI) for $C_{26}H_{30}O_6$ [M + H] calc 439.2, found 439.2, [M + Na] calc 461.2, found 461.2; $[\alpha]_D^{24}$= -2.6 º (c= 0.88, THF).



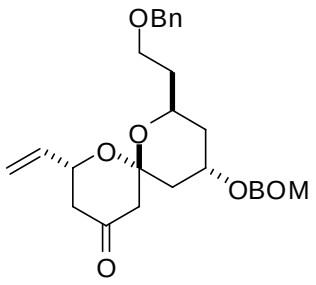
2.22

Spiroenone 2.22:

Hydroxypyrone (174 mg, 0.40 mmol) was dissolved in benzene and catalytic trifluroacetic acid (5 μL) was added. The reaction was allowed to stir 3 days. Reaction was quenched through the addition of triethylamine (10 μL) and concentrated *in vacuo*. Residue was purified via flash column chromatography to provide desired spiroenone **2.22** as well as recovered starting material. Starting material was resubjected for a total of 5 cycles to provide pure spiroenone **2.22** (112 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.28 (m, 10H), 7.18 (d, 6.2 Hz, 1H), 5.45 (d, *J* = 6.2 Hz, 1H), 4.89 (AB_q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 10.1 Hz, 2H), 4.67 (AB_q, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 10.4 Hz, 2H), 4.47 (AB_q, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 10.2 Hz, 2H), 4.35-4.29 (m, 1H), 4.19-4.15 (m, 1H), 3.56-3.52 (m, 2H), 2.76 (d, *J* = 16.4 Hz, 1H), 2.54 (d, *J* = 16.4 Hz, 1H), 3.50 Hz (dt, *J* = 1.9, 15.1 Hz, 1H), 1.95-1.89 (m, 1H), 1.81-1.67 (m, 3H), 1.55 (ddd, *J* = 3.1, 11.9, 14.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.5, 159.0, 138.4, 137.7, 128.4, 128.3, 127.7, 127.7, 127.7, 127.5, 127.4, 106.9, 103.1, 93.1, 73.0, 69.6, 68.2, 66.1, 63.6, 48.0, 36.7, 35.4, 34.5; IR(film): 3063.4, 3028.7, 2924.5, 2856.0, 1680.7, 1603.5, 1494.6, 1455.0, 1402.0, 1363.4,

1273.8, 1230.4 cm^{-1}; MS (ESI) for $C_{26}H_{30}O_6$ [M + H] calc 439.2, found 439.2, [M + Na] calc 461.2, found 461.3; $[\alpha]_D^{24}$= -192.0 º (c=0.28, THF).

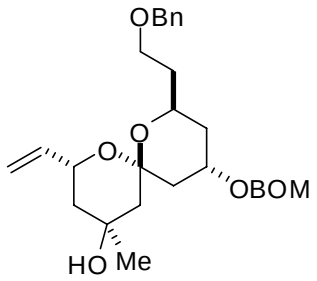


2.23

Alkene 2.23:

Tetrakis(copper iodide-tributylphosphine) complex (156 mg, 0.10 mmol) was dissolved in ethyl ether (11 mL), and cooled to – 55 ºC. Vinyl magnesium bromide (1M, 2.3 mmol, 2.3 mL) was transferred to the reaction via cannula. The reaction changed from reddish brown to milky yellow during the addition. Reaction stirred for 1 hour and then cooled further to – 78 ºC. Spiroenone **2.22** (146 mg, 0.33 mmol) was then dissolved in ethyl ether and added dropwise to the reaction mixture. Reaction was stirred until starting material had disappeared (60-90 minutes) at which time the reaction was quenched with a 1:1 mixture of saturated ammonium chloride:10% ammonium hydroxide. Reaction was allowed to warm to room temperature and ethyl ether was added. Layers were separated and the organic layer was washed with a 1:1 mixture of saturated ammonium chloride:10% ammonium hydroxide (x 3) until the blue color disappeared. Aqueous layers were combined and back-extracted with ethyl ether (x2). Organic layers were combined and dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (20% to 35% ethyl acetate/hexanes) provided a 5:1 mixture of diastereomers of alkene **2.23** (96 mg, 0.21 mmol, 63%) which could be separated following the next step.

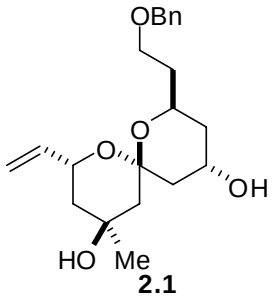
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.20 (m, 10H), 5.84, (ddd, *J* = 5.2, 10.7, 17.2 Hz, 1H), 5.25 (dt, *J* = 1.2, 17.3 Hz, 1H), 5.09 (dt, *J* = 1.2, 10.6 Hz, 1H), 4.83 (AB_q, J_{AB} = 7.2 Hz, $\Delta\nu_{AB}$ = 35.8 Hz, 2H), 4.63 (s, 2H), 4.43 (s, 2H), 4.41 (m, 1H), 4.18 (m, 1H), 4.05 (m, 1H), 3.57 (ddd, *J* = 5.2, 9.1, 9.1 Hz, 1H), 3.47 (m, 1H), 2.44-2.23 (m, 5H), 1.86-1.81 (m, 1H), 1.79-1.71 (m, 1H), 1.67 (ddd, *J* = 5.2, 10.1, 14.3 Hz, 1H), 1.57 (dd, *J* = 4.0, 14.6 Hz, 1H), 1.46 (ddd, *J* = 3.2, 11.7, 14.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 138.7, 138.4, 137.6, 128.8, 128.7, 128.3, 128.1, 127.9, 116.1, 99.5, 93.6, 73.4, 69.8, 69.7, 69.5, 66.6, 62.3, 52.5, 46.7, 37.8, 36.0, 35.8, 30.1; IR(film): 2958.3, 2924.5, 2855.1, 1724.1, 1261.2 cm^{-1}; MS(ESI) for $C_{28}H_{34}O_6$ [M + H] calc 467.2, found 467.3 [M + Na] calc 489.2 found 489.3; $[\alpha]_D^{21}$= -42.5 º (c=0.15, THF)



Tertiary Alcohol:

Alkene **2.23** (35 mg, 0.075 mmol) was dissolved in THF (1 mL) and cooled to – 78 ºC. MgMgI (0.75 mmol, 1.0 M 0.75 mL) was added dropwise. Reaction was stirred for 4 hours at – 78 ºC. Reaction was quenched through the addition of saturated ammonium chloride and ethyl ether. The layers were separated and the aqueous layer was extracted with ethyl ether (x2). Organic extracts were combined and dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (25% ethyl acetate/hexanes) separated the minor diastereomer from the previous step and provided tertiary alcohol (26.5 mg, 73% yield, 22 mg major).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.24 (m, 10H), 5.82 (ddd, J = 4.7, 10.5, 17.0 Hz, 1H), 5.24 (dt, J = 1.6, 17.3 Hz, 1H), 5.04 (dt, J = 1.6, 10.6 Hz, 1H), 4.81 (AB_q, J_{AB} = 7.2 Hz $\Delta\nu_{AB}$ = 20.9 Hz, 2H), 4.63 (bs, OH), 4.61 (s, 3H), 4.47 (AB_q, J_{AB} = 12.0 Hz, $\Delta\nu_{AB}$ = 12.3 Hz, 2H), 4.38 (m, 1H), 4.23 (m, 1H), 4.02 (m, 1H), 3.52 (t, J = 5.6 Hz, 2H), 2.03 (m, 1H), 1.82 (m, 1H), 1.72 (m, 5H), 1.57-1.44 (m, 2H), 1.34 (t, J = 12.7, 1H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 138.5, 128.3, 128.2, 127.8, 127.7, 127.5, 127.4, 114.3, 98.2, 92.9, 73.1, 69.2, 68.8, 68.1, 67.1, 66.3, 63.1, 45.9, 43.1, 45.9, 43.1, 37.5, 35.8, 35.6, 29.9; IR (film): 3477.0, 2925.5, 2854.1, 1673.0, 1455.0, 1405.9, 1359.6, 1260.3, 1201.4 cm^{-1}; MS(ESI) for $C_{29}H_{38}O_6$ [M+H]: calc 483.3 found 483.3, [M+Na]: calc 505.3 found 505.3; $[\alpha]_D^{24}$= -22.8º (c=0.05, THF)

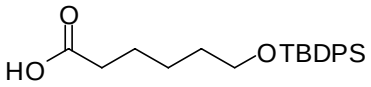


2.1

AB Spiroketal 2.1:

Alcohol (22 mg, 0.045 mmol) was dissolved in methanol and *p*-toluenesulfonic acid (1 mg, 0.005 mmol) was added and stirred at room temperature for 3 days. The reaction was quenched through the addition of sodium bicarbonate and ethyl ether. The layers were separated and the aqueous layer was extracted with ethyl ether (x2). Organic extracts were combined and dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash column chromatography (30% ethyl acetate/hexanes) provided the functionalized AB spiroketal **2.1** (12 mg, 0.034 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5H), 5.75 (ddd, *J* = 6.0, 10.8, 16.8 Hz, 1H), 5.08 (m, 2H), 4.48 (AB_q, J_{AB} = 11.8 Hz $\Delta\nu_{AB}$ = 16.8 Hz, 2H), 4.40 (ddq, *J* = 0.8, 4.0, 9.2 Hz, 1H), 4.18 (m, 1H), 4.00 (m, 2H), 3.55 (m, 2H), 1.87 (dt, *J* = 2.0, 14.0 Hz, 1H), 1.78 (m, 3H), 1.72 (dt, *J* = 2.4, 5.6 Hz, 1H), 1.70 (t, *J* = 2.4 Hz, 1H), 1.60 (s, 1H), 1.50 (d, *J* = 14.0 Hz, 2H), 1.38 (dd, *J* = 8.0, 13.6 Hz, 1H), 1.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 137.6, 128.3, 127.9, 127.5, 115.5, 100.1, 73.2, 67.6, 67.5, 66.9, 64.4, 62.8, 45.1, 43.2, 39.7, 38.0, 35.4, 29.8; IR(film): 3517.5, 2924.5, 2855.1, 2358.5, 1721.2, 1663.3 1407.8 cm^{-1}; MS (ESI) for $C_{21}H_{30}O_5$ [M + Na] calc 385.2, found 385.3; $[\alpha]_D^{21}$= -46.2º (c=0.25, CH_2Cl_2).

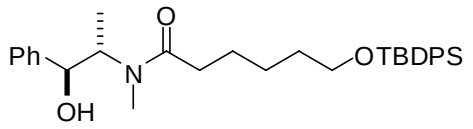


5.36

Acid 5.36:

A 1L round-bottomed flask was charged with 6-(*tert*-butyldiphenylsilyloxy)hexan-1-ol (21.3 g, 60.0 mmol) and acetone (100 mL) and cooled to 0 °C. Jones reagent (2M, 75 mL, 150 mmol) was added dropwise via addition funnel. The reaction was then warmed to room temperature for 5 minutes. The reaction was quenched via the addition of isopropanol to oxidize the excess Jones reagent. Stirring was continued for 5 minutes. The reaction mixture was then filtered through a celite pad and 50% ether/hexanes was added along with water. The layers were separated and the aqueous was extracted with ether (x3). The combined organic layers were then washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (10% to 25% ethyl acetate/hexanes) then provided the pure carboxylic acid **5.36** (16.0 g, 43 mmol) in 72% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, 4H, *J* = 7.3 Hz), 7.46 (bands, 6H), 3.74 (t, 2H, *J* = 6.3 Hz), 2.39 (t, 2H, *J* = 7.4 Hz), 1.71-1.63 (bands, 4H), 1.50 (bands, 2H), 1.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.4, 135.5, 134.0, 129.5, 127.6, 63.5, 34.1, 32.1, 26.8, 25.3, 24.4, 19.2. IR(film):2931, 2858, 1709, 1473, 1459, 1428, 1389, 1283, 1242. MS (ESI): calc (M+H): 371.21 obs: 371.3, calc (M+Na): 393.19 obs: 393.3.



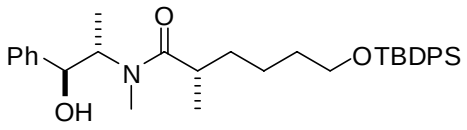
5.37

Amide 5.37:

A 1L round bottomed flask was charged with acid **5.36** (58.5 mmol)**,** triethylamine (70.2 mmol, 9.8 mL), and tetrahydrofuran (200 mL). The reaction mixture was cooled to -78 °C and trimethylacetyl chloride (70.2 mmol, 8.65 mL) was added dropwise. The reaction was then warmed to 0 °C and stirred for 1 hour, then warmed to room temperature for 15 minutes. The reaction was then cooled back to 0 °C and a solution of (1S, 2S)-(+)-pseudoephedrine (70.2 mmol, 11.6 g) and triethylamine (70.2 mmol, 9.8 mL) in tetrahydrofuran (200 mL) was added via cannula. The reaction was then stirred for 1 hour and warmed to room temperature for 15 minutes. The reaction was quenched via addition of water. Ethyl acetate was then added and the layers were separated. The aqueous layer was then extracted with ethyl acetate (x3), washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (30% to 50% ethyl acetate/hexanes) provided amide **5.37** (57.6 mmol, 30.2 g) as a pale yellow oil in 99% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major rotamer): 7.68-7.65 (bands, 4H), 7.43-7.21 (bands, 11H), 4.58 (d, *J* = 7.8 Hz, 1H), 4.42 (bs, 1H), 3.68 (t, *J* = 6.3 Hz, 2H), 2.78 (s, 3H), 2.25

(dddd, J = 7.8, 7.8, 7.8, 15.5 Hz, 2H), 1.67-1.52 (bands, 3H), 1.42-1.35 (bands, 3H), 1.10 (d, J = 6.9 Hz, 3H), 1.05 (s, 9H). (minor rotamer): 7.67-7.61 (bands, 4H), 7.43-7.19 (bands, 11H), 4.53 (d, J = 7.6 Hz, 1H), 3.95 (m, 1H), 3.64 (m, 2H), 2.90 (s, 3H), 2.45-2.30 (bands, 2H), 1.67-1.48 (bands, 3H), 1.35-1.25 (bands, 3H), 1.02 (s, 9H), 0.97 (d, J = 6.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (both rotamers): 175.4, 174.2, 142.4, 141.2, 135.5, 134.0, 134.0, 129.4, 129.4, 128.6, 128.2, 127.5, 126.8, 126.3, 76.4, 75.4, 63.8, 58.3, 34.3, 33.6, 32.4, 32.3, 26.8, 25.7, 25.5, 25.1, 24.7, 19.1, 15.3, 14.4. IR(film): 3373, 3061, 2931, 2857, 1619, 1472, 1427, 1404, 1363, 1306, 1260, 1197. $[\alpha]_D^{26}$ (c = 1.8, CH_2Cl_2): +53. MS(ESI) for $C_{32}H_{43}NO_3Si$ (M+H) calc: 518.31, found: 518.4, (M+Na): calc: 540.29, found: 540.4

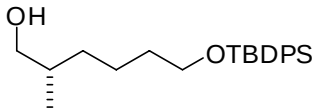


Methylated Amide

A 500 mL round-bottomed flask was charged with lithium chloride (342.6 mmol, 15.4 g) and a large magnetic stir bar. The flask and lithium chloride were then flame dried together with stirring to dry the hygroscopic reagent. After cooling to room temperature under argon, tetrahydrofuran (70 mL) was added along with diisopropylamine (18.4 mL, 131.3 mmol). The mixture was then cooled to – 78 °C. Butyl lithium (2.5M in hexanes, 50.2 mL, 125.62 mmol) was then added dropwise over 15 minutes and the reaction was stirred for 15 minutes. The solution was then warmed to 0 °C for 5 minutes and cooled back down to -78 °C. The amide (57.1 mmol) from the previous reaction was added via cannula in a solution of THF (150 mL). The reaction was stirred for 1 h, warmed to 0 °C for 15 minutes, warmed to room

temperature for 5 minutes, and cooled back down to -78 °C. Iodomethane (10.7 mL, 171.3 mmol) was then added dropwise and the reaction was placed in a cryobath at -70 °C for 17 h. The reaction was quenched through the addition of saturated ammonium chloride and ethyl acetate and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted (x 3). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the desired methylated amide (21.4 g, 41.4 mmol) in 73% yield as one diastereomer and observed in solution as a 3.3:1 mixture of rotamers.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major rotamer): 7.67-7.61 (bands, 4H), 7.43-7.19 (bands, 11H), 4.62 (t, *J* = 7.1 Hz, 1H), 4.22 (bs, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.73 (s, 3H), 2.52 (dddd, *J* = 7.1, 7.1, 7.1, 13.7 Hz, 1H), 1.67-1.48 (bands, 3H), 1.35-1.25 (bands, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.05 (s, 9H), 0.99 (d, *J* = 6.8Hz, 3H). (minor rotamer): 7.67-7.61 (bands, 4H), 7.43-7.19 (bands, 11H), 4.55 (d, *J* = 7.3 Hz, 1H), 4.08 (m, 1H), 3.64 (m, 2H), 2.90 (s, 3H), 2.63 (d, *J* = 2.0 Hz, 1H), 1.67-1.48 (bands, 3H), 1.35-1.25 (bands, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H), 0.98 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (both anomers): 178.9, 177.8, 142.6, 135.5, 134.0, 129.5, 128.6, 128.3, 128.2, 127.5, 127.3, 126.8, 126.1, 76.3, 63.7, 36.5, 34.4, 33.6, 32.5, 26.8, 23.6, 19.1, 17.3, 14.4. IR(film): 3352, 3070, 2931, 2858, 1617, 1472, 1428, 1302, 1254. $[\alpha]_D^{26}$ (c = 0.15, CH_2Cl_2): +60. MS(ESI) for $C_{48}H_{65}NO_6Si_2$ (M+Na) calc:, found:

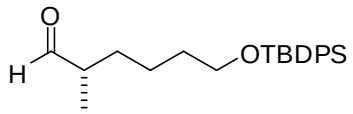


Alcohol From Reduction of Amide:

A solution of LDA (161.5 mmol) was made following the above procedure in a 1L round-bottomed flask. This was warmed to 0 °C and borane-ammonia (85% tech grade, 5.11 g, 165.6 mmol) was added in one portion. This was then stirred for 30 minutes and warmed to room temperature and stirred for 15 minutes. A solution of the amide (21.4 g, 41.4 mmol) from the previous reaction in tetrahydrofuran (50 mL) was then added via cannula. The reaction was then allowed to stir for 2 hours. The reaction was then quenched via the dropwise addition of 3M HCl (400 mL) and stirred for 30 minutes at 0 °C. Ethyl ether was then added and the layers were separated. The aqueous layer was extracted with ethyl ether (x3) and the organic fractions combined. The organic was then sequentially washed with 3M HCl (100 mL), 2M NaOH (100 mL), and brine. The organic layer was then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20% ethyl acetate/hexanes with 5% acetic acid to remove any tertiary amine byproduct) then provided the desired alcohol (11.6g, 31.4 mmol) in 76% yield as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.7 Hz, 4H), 7.45-7.36 (bands, 6H), 3.68 (t, *J* = 6.0 Hz, 2H), 3.50 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.40 (dd, *J* = 6.5, 10.2 Hz, 1H), 1.63-1.51 (bands, 4H), 1.50-1.33 (bands, 3H), 1.10 (m, 1H), 1.07 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 134.1, 129.5, 127.5, 68.2, 63.8, 35.7, 32.8, 32.7, 26.8, 23.1, 19.2, 16.5. IR(film): 3343, 2931, 2858, 1472, 1462, 1428, 1389, 1362, 1111. $[\alpha]_D^{27}$ (c = 2.8, CH_2Cl_2): -4 MS(ESI) for $C_{23}H_{34}O_2Si_2$ (M+Na) calc: 393.22 , found: 393.3.



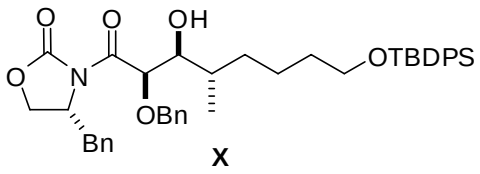
5.38

Aldehyde 5.38:

A 500 mL round-bottomed flask was charged with methylene chloride (160 mL) and oxalyl chloride (2M in methylene chloride, 34.4 mL, 68.8 mmol). The mixture was cooled to – 78 °C and methylsulfoxide (7.33 mL, 103.0 mmol) was added dropwise as a solution in methylene chloride (20 mL). The solution was stirred for 20 minutes. The alcohol (165 mg, 11.4g, 31.3 mmol) from the previous reaction was then added dropwise as a solution in methylene chloride (30 mL). The solution was stirred for 30 minutes and triethylamine (34.9 mL, 250.4 mmol) was added dropwise. The mixture was allowed to warm to 0 °C, at which time the reaction was quenched through the addition of water. The layers were separated and the aqueous was extracted once with methylene chloride. The combined organic layers were washed sequentially with saturated sodium hydrogensulfate, saturated sodium bicarbonate, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentratred in vacuo. Flash column chromatography then yielded aldehyde **5.38** (11.4 g, 31.3 mmol) as an oil in quanitative yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.58 (d, *J* = 1.9 Hz, 1H), 7.68-7.61 (bands, 4H), 7.42-7.32 (bands, 6H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.30 (ddddd, *J* = 2.0, 6.9, 6.9, 6.9, 13.8 Hz, 1H), 1.67 (m, 1H), 1.60-1.53 (bands, 2H), 1.46-1.28 (bands, 3H), 1.06 (t, $\underline{J}$ = 7.0 Hz, 3H), 1.03 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 135.6, 134.0, 129.5, 127.6, 63.5, 46.2, 32.4, 30.2, 26.9, 23.2, 19.2, 13.2. IR(film): 2932, 2858, 1706, 1471, 1428, 1389, 1360. $[\alpha]_D^{24}$ (c = 1.1, CH_2Cl_2): +3. MS(ESI) for $C_{23}H_{32}O_2Si$ (M+Na) calc:, found:.

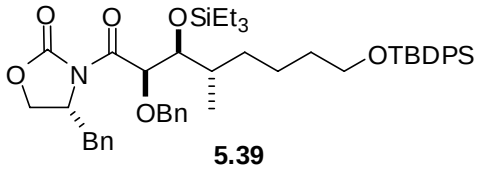


X

Aldol Adduct From Reaction With Glycolate 4.20:

A round-bottomed flask was charged with glycolate **4.20** (13.2 g, 40.4 mmol), toluene (300 mL), and cooled to – 78 °C. Freshly distilled dibutylboron triflate (9.7 mL, 38.8 mmol) was added dropwise and the reaction allowed to stir for 5 minutes. Triethylamine (6.3 mL, 45.8 mmol) was then added dropwise and the reaction allowed to stir for 45 minutes. The reaction was warmed to 0 °C and stirred for 45 minutes. The reaction was then cooled to – 78 °C and aldehyde **5.38** (11.4g, 31.3 mmol) was added slowly as a solution of toluene (50 mL) via cannula. The reaction was allowed to proceed for 3 h and then warmed to – 45 °C for 5 minutes. The reaction was quenched through the addition of a mixture of 6.9 mL methanol and 57 mL pH 7 buffer at such a rate as to keep the internal temperature below – 40 °C. The reaction was then warmed to – 25 °C. Tetrahydrofuran (400 mL, precooled to 0 °C) was then added rapidly, maintaining the temperature below – 10 °C. A mixture of 57 mL hydrogen peroxide (30% solution) and 120 mL tetrahydrofuran was then added very slowly, keeping the temperature below 0 °C. The mixture was vigorously stirred for 45 minutes. Saturated sodium bicarbonate was then added and the layers separated. The aqueous layer was extracted with ethyl acetate (x3). The combined aqueous layers were then washed with sodium bicarbonate, sodium thiosulfate to quench the unreacted peroxides, and brine. The

organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography was not able to separate glycolate **X** from the major diastereomer **X** and the mixture was taken on to the next reaction for separation.



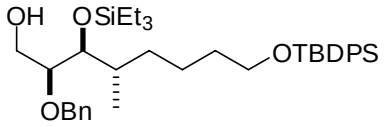
5.39

TES ether 5.39:

A 500 mL round bottomed flask was charged with the mixture from the previous reaction, methylene chloride (150 mL), and 2,6-lutidine (7.3 mL, 62.6 mmol) and cooled to 0 °C. Triethylsilyl triflate (7.0 mL, 31.3 mmol) was then added dropwise. The reaction was stirred for 1 hour. The reaction was then quenched with saturated sodium bicarbonate and the layers separated. The aqueous layer was then extracted with methylene chloride (x2) and the organic layers combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided TES ether **5.39** (15.9 g, 19.7 mmol) as a colorless oil in 63% yield over two steps.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67-7.63 (bands, 4H), 7.41-7.17 (bands, 16H), 5.29 (d, J = 4.7 Hz, 1H), 4.64 (AB_q, 2H, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ =22.2 Hz), 4.49 (m, 1H), 4.09-4.02 (bands, 2H), 3.94 (t, J = 4.7 Hz, 1H), 3.64 (t, J = 6.3 Hz, 2H), 3.14 (dd, J = 3.0, 13.4 Hz, 1H), 2.55 (dd, J = 9.9, 13.4 Hz, 1H), 1.59-1.50 (bands, 2H), 1.48-1.44 (bands, 3H), 1.20-1.00 (bands, 2H), 1.02 (s, 9H), 0.97-0.90 (bands, 12H), 0.6 (q, J = 4.6 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 152.8, 137.6, 135.5, 135.4, 135.2, 134.1, 134.0, 129.4, 129.4, 129.3, 128.9,

128.5, 128.2, 127.8, 127.5, 127.5, 127.3, 77.7, 77.2, 73.2, 66.4, 64.0, 55.9, 37.4, 36.6, 32.8, 31.2, 26.8, 23.7, 19.1, 16.2, 7.0, 5.3. IR(film):2954, 2933, 2874, 1784, 1704, 1588, 1497, 1456, 1428, 1383, 1348, 1288, 1233. $[\alpha]_D^{25}$ (c = 2.4, CH_2Cl_2): -38° MS (ESI) for $C_{48}H_{65}NO_6Si_2$ (M+Na) calc: 830.43, found: 830.4.

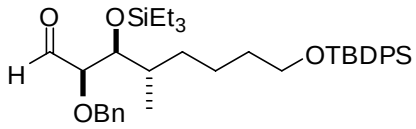


Alcohol from Reduction of TES ether 5.39:

A round bottomed flask was charged with TES ether **5.39** (15.9 g, 19.7 mmol), ethyl ether (200 mL), and methanol (1.12 mL, 27.6 mmol) and cooled to 0° C. Lithium borohydride (2.0 M in tetrahydrofuran, 13.8 mL, 27.6 mmol) was then added dropwise. The reaction was then stirred at 0 °C for 1 hour. The reaction was quenched with the addition of sodium/potassium tartrate solution and stirred for 1 hour. The layers were separated, and the aqueous layer was then extracted with ethyl acetate (x3), washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (4 to 10% ethyl acetate/hexanes) provided alcohol (11.43 g, 17.9 mmol) as colorless oil in 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.63 (bands, 4H), 7.41-7.25 (bands, 11H), 4.61 (AB_q, 2H, J_{AB} = 11.8 Hz, $\Delta\nu_{AB}$ = 48.9 Hz), 3.80-3.73 (m, 1H), 3.68-3.58 (bands, 4H), 3.51 (q, 1H, *J* = 5.0 Hz), 2.04 (t, 1H, *J* = 6.0 Hz), 1.64-1.38 (bands, 5H), 1.25-1.04 (bands, 2H), 1.03 (s, 9H), 0.97 (m, 3H), 0.94 (t, 9H, *J* = 8.0 Hz), 0.59 (q, 6H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 135.4, 134.0, 129.3, 128.3, 127.6, 127.5, 127.4, 82.1, 76.3, 72.4, 63.8, 61.6, 35.6, 32.8, 31.5, 26.7, 23.4, 19.0, 16.6, 6.8, 5.0. IR(film): 2932, 2874, 1457, 1427, 1388,

1237, 1110. $[\alpha]_D^{24}$ (c = 0.75, CH_2Cl_2): -14° MS(ESI) for $C_{38}H_{58}O_4Si_2$ [M+H] calc: 635.40 found: 635.4 [M+Na] calc: 657.38 found: 657.3.



5.40

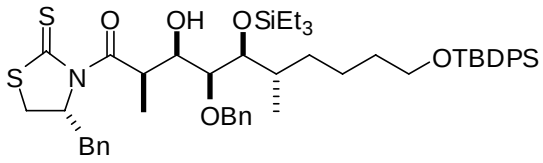
Aldehyde 5.40:

A 500 mL round-bottomed flask was charged with methylene chloride (80 mL) and oxalyl chloride (2M, 45.6 mL, 22.8 mmol). The mixture was cooled to – 78 °C and methylsulfoxide (4.85 mL, 68.4 mmol) was added dropwise as a solution in methylene chloride (20 mL). The solution was stirred for 20 minutes. The alcohol from the previous reaction (12.9 g, 20.3 mmol) was then added dropwise as a solution in methylene chloride (20 mL). The solution was stirred for 30 minutes and triethylamine (23.1 mL, 166 mmol) was added dropwise. The mixture was allowed to warm to 0 °C, at which time the reaction was quenched through the addition of water. The layers were separated and the aqueous was extracted once with methylene chloride. The combined organic layers were washed sequentially with saturated sodium hydrogensulfate, saturated sodium bicarbonate, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentratred in vacuo. Flash column chromatography then yielded aldehyde **5.40** (11.6 g, 18.3 mmol) in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (d, 1H, J = 1.2 Hz), 7.67-7.64 (m, 4H), 7.42-7.22 (m, 11H), 4.60 (AB_q, 2H, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 76.3 Hz), 3.81-3.74 (m, 2H), 3.63 (t, 2H, J = 6.2 Hz), 1.70-1.62 (m, 1H), 1.55-1.35 (m, 5H), 1.27-1.15 (m, 1H), 1.03 (s, 9H), 0.89 (t, 9H, J = 8.0 Hz), 0.85 (d, 3H, J = 6.8 Hz), 0.54 (q, 6H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 137.2, 135.5, 134.1, 129.5, 128.5, 128.4, 128.1, 127.6, 85.3, 77.3, 72.9, 63.9, 36.7,

32.8, 31.7, 26.8, 23.5, 19.2, 15.8, 6.9, 5.0. IR(film): 2955, 2871, 1732, 1461, 1427, 1385, 1237. $[\alpha]_D^{25}$ (c = 0.85, CH_2Cl_2): + 7° MS (ESI): decomposed, MS not observed.

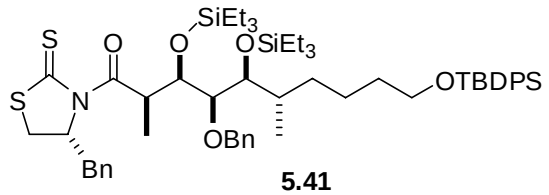
Aldol Adduct X:



A round bottomed flask was charged with *N*-propionylthiazolidinethione **4.20** (5.93g, 22.33 mmol) and methylene chloride (200 mL) and cooled to 0 °C. Titanium (IV) chloride (2.34 mL, 21.3 mmol) was then added dropwise and the reaction stirred for 5 minutes. (-)-Sparteine (6.1 mL, 26.4 mmol) was then added dropwise and the reaction was stirred for 30 minutes. *N*-methylpyrrolidinone (2.53 mL, 26.4 mmol) was then added dropwise and the reaction stirred an additional 15 minutes. The reaction was then cooled to – 78 °C and aldehyde **5.40** (11.6 g, 18.3 mmol) in methylene chloride was then added via cannula. The reaction was stirred for 15 minutes at – 78 °C and transferred to a – 20 °C freezer and allowed to stand for 12 h. The reaction was then quenched via the addition of saturated ammonium chloride. The layers were separated, and the aqueous layer was then extracted with methylene chloride (x3), washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography yielded an intractable mixture of the major diastereomer of the aldol adduct and the recovered propionate **4.23** as a bright yellow oil. This was taken onto the next reaction for separation.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.61 (m, 4H), 7.40-7.18 (m, 16H), 5.12 (ddd, 1H, *J* = 4.0, 7.1, 10.5 Hz), 4.64 (AB_q, 2H, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 164 Hz), 4.53 (dddd, 1H, *J* = 7.0, 7.0, 7.0, 7.0 Hz), 3.88 (t, 1H, *J* = 8.8 Hz), 3.80 (dd, 1H, *J* = 3.0, 6.8 Hz), 3.66 (t, 2H, *J* = 6.1 Hz), 3.22 (d, 1H, *J* = 7.0 Hz), 3.18-3.10 (m, 2H), 2.97 (dd, 1H, *J* = 11.0, 13.0 Hz), 2.76 (d,

1H, *J* = 11.6 Hz), 2.48 (d, 1H, *J* = 9.9 Hz), 1.70-1.39 (m, 6H), 1.36 (d, 3H, *J* = 6.7 Hz), 1.34-1.08 (m, 2H), 1.04 (s, 9H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.93 (t, 9H, *J* = 7.9 Hz), 0.59 (q, 6H, *J* = 7.8 Hz). IR(film): 2932, 2874, 1686, 1588, 1496, 1455, 1427, 1361, 1340, 1292, 1259. $[\alpha]_D^{24}$ (c = 1.45, CH_2Cl_2): -100° MS (ESI) for $C_{51}H_{71}NO_5SSi_2$ [M+H] calc: 898.44, found: 898.4 [M+Na] calc: 920.42, found: 920.4.



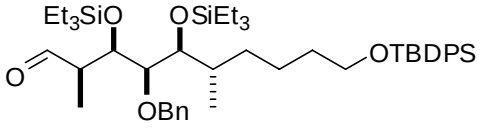
5.41

TES Ether 5.41:

A round-bottomed flask was charged with the mixture from the previous reaction, methylene chloride (140 mL), and 2,6-lutidine (3.4 mL, 29.3 mmol). The reaction was cooled to 0 °C and triethylsilyl triflate (3.97 mL, 17.6 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched via the addition of saturated sodium bicarbonate. The layers were separated and the aqueous layer extracted with methylene chloride (x2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided pure TES ether **5.41** (12.85 g, 12.64 mmol) as a bright yellow oil in 69% yield for two steps.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.41-7.20 (m, 13H), 7.15-7.08 (m, 3H), 4.59-4.42 (m, 5H), 3.69-3.61 (m, 3H), 3.38 (dd, 1H, *J* = 2.9, 8.0 Hz), 3.07 (dd, 1H, *J* = 2.9, 13.1 Hz), 2.91-2.83 (m, 2H), 2.52 (d, 1H, *J* = 11.4 Hz), 1.80 (m, 1H), 1.67-1.30 (m, 5H), 1.24 (d, 3H, *J* = 6.6 Hz), 1.18-1.10 (m, 1H), 1.05 (s, 9H), 1.01 (t, 9H, *J* = 8.0 Hz), 0.95 (m, 3H), 0.94 (t, 9H, *J* = 8.0 Hz), 0.72-0.59 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 176.9,

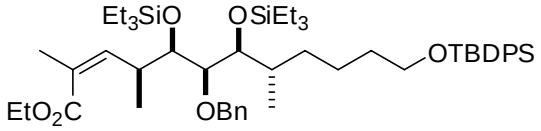
138.3, 136.6, 135.5, 134.2, 129.4, 128.6, 128.3, 128.0, 127.6, 127.5, 127.0, 84.6, 73.2, 72.5, 69.0, 64.3, 39.3, 36.0, 34.3, 33.6, 31.4, 30.1, 26.8, 23.8, 19.2, 18.0, 15.7, 14.1, 7.2, 7.1, 5.6, 5.0. IR(film): 2955, 2875, 1692, 1588, 1456, 1427, 1386, 1363, 1342, 1261. $[\alpha]_D^{24}$ (c = 2.35, CH_2Cl_2): -63° MS (ESI) for $C_{57}H_{85}NO_5SSi_3$ [M+H] calc: 1012.53, found: 1012.5 [M+Na] calc: 1034.51, found: 1034.5.



Aldehyde from DIBAL Reduction of TES ether 5.41:

A round bottomed flask was charged with TES ether **5.41** and methylene chloride and cooled to – 78 °C. DIBAL (1.0 M in heptane, 18 mL) was added dropwise until the yellow color disappeared (indicating deacylation of thiazolidinethione). The solution was then immediately quenched through the addition of saturated potassium/sodium tartrate. The mixture was warmed to room temperature and stirred for 1 hour until the layers could be separated. The layers were then separated. The aqueous layer was then extracted with methylene chloride (x2), the organic layers combined and dried over sodium sulfate. This was then filtered and concentrated in vacuo. Flash column chromatography (4% ethyl acetate/hexanes) provided the aldehyde (9.13g, 11.18 mmol) as a colorless oil in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.72-7.66 (m, 4H), 7.45-7.20 (m, 11H), 4.58 (AB_q, 2H, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 63.8 Hz), 4.28 (t, 1H, J = 4.8 Hz), 3.81 (t, 1H, J = 5.2 Hz), 3.68 (t, 2H, J = 6.4 Hz), 3.37 (t, 1H, J = 5.2 Hz), 2.74 (m, 1H), 1.69-1.45 (m, 5H), 1.29-1.20 (m, 1H), 1.15-1.10 (m, 1H), 1.08, (d, 3H, J = 6.0 Hz), 1.07 (s, 9H), 1.01 (d, 3H, J = 6.8 Hz), 0.93 (q, 18H, J = 8.0 Hz), 0.63-0.53 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.4, 138.5,

135.5, 129.5, 128.1, 127.6, 127.2, 127.1, 81.4, 76.3, 73.3, 72.7, 64.0, 49.7, 36.1, 33.1, 31.9, 26.9, 23.7, 19.2, 17.0, 9.7, 7.1, 6.9, 5.6, 5.5. IR(film): 2955, 2934, 2876, 1723, 1589, 1461, 1428, 1388, 1361, 1238, 1109. $[\alpha]_D^{24}$ (c = 1.55, CH_2Cl_2): -11° MS (ESI) for $C_{47}H_{76}O_5Si_3$ [M+Na] calc: 827.49, found: 827.5.



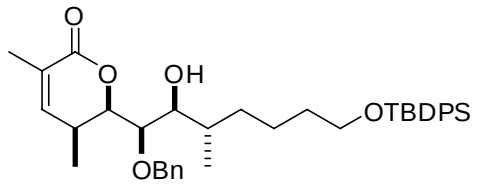
5.42

Enoate 5.42:

A flask was charged with the Still-Gennari reagent **4.25a** (ethyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)propanoate, 415 mg, 1.2 mmol), tetrahydrofuran (20 mL), and 18-crown-6 (1.45 g, 5.5 mmol) and cooled to – 78 °C. Potassium hexamethyldisilazide (0.5 M in toluene, 1.0 mmol, 1.97 mL) was then added dropwise. The reaction was allowed stir for 30 minutes at which point the aldehyde from the previous reaction (810 mg, 1.0 mmol) was added as solution in tetrahydrofuran (5 mL). The reaction proceeded for 30 minutes and was then warmed to room temperature for 30 minutes and monitored for disappearance of starting material. The reaction was then quenched through the addition of saturated ammonium chloride. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the Z-enoate **5.42** (810 mg, 0.91 mmol) as a colorless oil in 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.43-7.21 (m, 11H), 5.99 (dd, 1H, J = 1.0, 2.0 Hz), 4.62 (AB_q, 2H, J_{AB} = 12.1 Hz, $\Delta\nu_{AB}$ = 12.8 Hz), 4.14 (m, 2H), 3.70-3.63 (m, 3H),

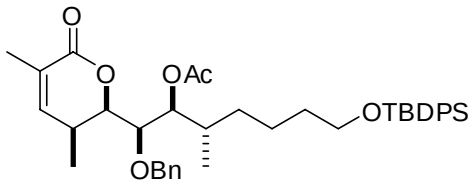
3.61 (dd, 1H, *J* = 2.3, 7.7 Hz), 3.51 (m, 1H), 3.33 (dd, 1H, *J* = 3.6, 7.7 Hz), 1.88 (s, 3H), 1.90-1.80 (m, 1H), 1.68-1.38 (m, 5H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.20-1.10 (m, 2H), 1.05 (s, 9H), 1.01 (d, 3H, *J* = 6.6 Hz), 0.94 (t, 9H, *J* = 8.0 Hz), 0.94 (m, 3H), 0.87 (t, 9H, *J* = 8.0 Hz), 0.59 (q, 6H, *J* = 8.0Hz), 0.51 (q, 6H, *J* = 8.0Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 146.5, 139.2, 135.4, 134.0, 129.3, 127.9, 127.4, 126.7, 136.5, 124.3, 83.8, 77.3, 75.6, 72.8, 64.1, 59.8, 36.2, 34.4, 33.3, 30.3, 26.7, 23.7, 20.7, 19.0, 17.3, 17.2, 14.0, 7.0, 7.0, 5.2, 5.1. IR(film): 2955, 2875, 1713, 1461, 1428, 1382, 1218, 1157. $[\alpha]_D^{24}$ (c = 1.45, CH_2Cl_2): +29.7° MS (ESI) for $C_{52}H_{84}O_6Si_3$ [M+Na] calc: 911.55, found: 911.6.



Lactone from Cyclization of Enoate 5.42:

A 250 mL round-bottomed flask was charged with the *Z*-enoate (810 mg, 0.91 mmol) methylene chloride (40 mL), water (1 mL), and *p*-toluenesulfonic acid (38 mg, 0.2 mmol) and heated to reflux. The reaction was heated for 72 h at which time saturated sodium bicarbonate solution was added to quench. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the lactone (523 mg, 0.85 mmol) in 94% yield as a colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.69 (d, 4H, J = 6.6 Hz), 7.45-7.28 (m, 11H), 6.64 (dd, 1H, J = 1.2, 6.5 Hz), 4.97 (AB_q, 2H, J_{AB} = 10.7 Hz, $\Delta\nu_{AB}$ = 191.0 Hz), 4.75 (dd, 1H, J = 3.0, 8.8 Hz), 3.80 (d, 1H, 8.8 Hz), 3.68 (t, 2H, 6.3 Hz), 3.09 (dd, 1H,11.1, 9.8 Hz), 2.49 (m, 1H), 1.92 (s, 3H), 1.75-1.65 (m, 2H), 1.62-1.40 (m, 3H), 1.32-1.20 (m, 1H), 1.15-1.00 (m, 1), 1.05 (s, 9H), 1.02 (d, 3H, J = 7.0 Hz), 0.80 (d, 3H, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 145.1, 138.0, 135.4, 133.9, 129.4, 128.4, 128.2, 127.8, 127.4, 127.0, 82.8, 77.1, 75.5, 74.8, 63.7, 35.7, 32.67, 32.0, 29.9, 26.7, 22.6, 20.9, 19.1, 16.8, 15.5, 11.4. IR(film): 3429.8, 2931.3, 2860.9, 2356.6, 1721.2, 1471.4, 1455.0, 1428.0, 1385.6, 1364.4. $[\alpha]_D^{25}$ (c = 0.35, CH_2Cl_2): +48º ESI-MS: $C_{38}H_{50}O_5Si$: calc (M+Na): 637.33 obs: 637.3



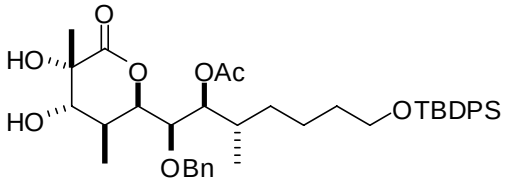
5.53

Acetate 5.53:

To a 100 mL round-bottomed flask was added alcohol **5.42** (523 mg, 0.85 mmol), methylene chloride (10 mL), pyridine (2 mL), acetic anhydride (2 mL), and DMAP (5 mg). The reaction was allowed to stir for 1 hour upon which time solvents were removed in vacuo. Toluene was added to facilitate more complete removal of acetic anhydride and pyridine. Flash column chromatography (20% ethyl acetate/hexanes) yielded acetate **5.53** (542 mg, 0.82 mmol) as a white foam in 97% yield.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.50-7.20 (m, 11 H), 6.61 (d, 1H, J = 6.6 Hz), 4.96 (AB_q, 2H, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 153.1 Hz), 4.67 (d, 1H, J = 9.8 Hz), 4.45 (dd, 1H, J =

3.0, 9.2 Hz), 3.89 (d, 1H, J = 9.2 Hz), 3.65 (t, 2H, J = 6.3 Hz), 2.55 (m, 1H), 2.06 (s, 3H), 1.90 (s, 3H), 1.60-1.20 (m, 5H), 1.07 (s, 9H), 1.05-1.00 (m, 1H), 1.02 (d, 3H, J = 7.0 Hz), 0.73 (d, 3H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 165.3, 145.2, 137.9, 135.4, 133.9, 129.4, 128.6, 128.2, 127.7, 127.5, 126.9, 81.7, 77.2, 75.8, 75.7, 75.6, 63.6, 33.2, 32.5, 31.4, 29.5, 26.7, 22.7, 20.9, 19.1, 16.7, 15.2, 11.5. IR(film): 2931.3, 2857.0, 2360.4, 2342.1, 1726.9, 1468.5, 1453.1, 1428.0, 1372.1, 1238.1. $[\alpha]_D^{25}$ (c = 0.70, CH_2Cl_2): +21º ESI-MS: $C_{40}H_{52}O_6Si$: calc (M+Na): 679.34 obs: 679.3.

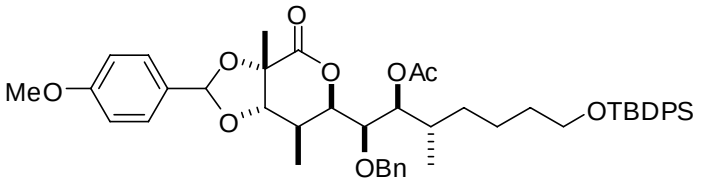


Diol from Dihyrdoxylation of Lactone 5.53:

A round bottomed flask was charged with alkene **5.53** (657 mg, 1.0 mmol), tetrahydrofuran (10 mL), and water (2 mL). Osmium tetroxide (20 mg/mL solution, 0.64 mL, 0.05 mmol) was then added along with *N*-methylmorpholine-*N*-oxide (234 mg, 2.0 mmol). The reaction was allowed to stir overnight (12 h). Upon disappearance of starting material, the reaction was quenched through the addition of saturated sodium sulfite and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (40 to 50% ethyl acetate/hexanes) provided the diol (662 mg, 0.96 mmol) as a single diastereomer in 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, 7.3 Hz, 4H), 7.42-7.25 (bands, 11H), 4.96 (dd, *J* = 3.8, 8.0 Hz, 1H), 4.75 (ABq, *J* = 11.2 Hz, $\Delta\nu_{AB}$ = 16.9 Hz, 2H), 4.65 (t, *J* = 3.8 Hz, 1H), 3.79 (t, *J* = 3.7 Hz, 1H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.54 (t, *J* = 7.7 Hz, 1H), 3.50 (s, OH), 2.98

(d, J = 7.4 Hz, OH), 2.31 (m, 1H), 2.00 (s, 3H), 1.98 (m, 1H), 1.60-1.30 (bands, 4H), 1.28 (s, 3H), 1.29-1.17 (m, 1H), 1.13-1.01 (bands, 13H), 0.91 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 170.7, 137.1, 135.5, 134.0, 129.5, 128.4, 127.9, 127.5, 79.3, 77.2, 76.0, 75.4, 73.9, 73.7, 71.8, 63.7, 35.1, 33.5, 32.7, 31.6, 26.8, 23.8, 22.8, 20.9, 19.2, 15.8, 12.7. IR(film): 3405, 2933, 2857, 1738, 1455, 1428, 1373, 1234, 1111. $[\alpha]_D^{24}$ (c =1.15, CH_2Cl_2): -39° MS (ESI) for $C_{40}H_{54}O_8Si$ [M+H] calc: 691.37, found: 691.4 [M+Na] calc: 713.35, found: 713.4.

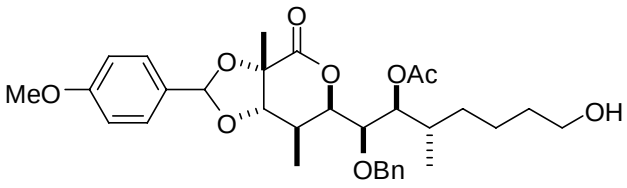


5.77

Acetal 5.77:

A round-bottomed flask was charged with the diol from the previous reaction (662 mg, 0.96 mmol) and methylene chloride (10 mL) Anisaldehyde dimethylketal (0.20 mL, 1.15 mmol) was then added, followed by pyridium *para*-toluenesulfonate (24 mg, 0.096 mmol). The reaction was then stirred for 18h. The reaction was quenched through the addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous was extracted with methylene chloride (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (20 to 30% ethyl acetate/hexanes) provided the acetal **5.77** (770 mg, 0.95 mmol) in 99% yield. Isolated as a >6:1 mixture of acetal diastereomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 6.8 Hz, 4H), 7.42-7.27 (bands, 13H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.86 (s, 1H), 5.11 (d, *J* = 11.6 Hz, 1H), 5.04 (d, *J* = 8.7 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 9.7 Hz, 1H), 3.98 (s, 1H), 3.85 (d, *J* = 8.6 Hz, 1H), 3.79 (s, 3H), 3.62 (t, *J* = 3.8 Hz, 2H), 2.31 (q, *J* = 7.0 Hz, 1H), 2.07-1.97 (m, 1H), 1.68 (s, 3H), 1.65 (s, 3H), 1.51-1.38 (bands, 3H), 1.29-1.11 (bands, 2H), 1.16 (s, 9H), 1.01-0.95 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.4, 160.7, 138.0, 135.5, 134.0, 129.5, 128.6, 128.3, 128.0, 127.8, 127.5, 127.2, 113.8, 113.8, 102.4, 84.5, 79.8, 77.7, 76.8, 75.8, 75.3, 63.7, 55.2, 33.4, 33.1, 32.6, 31.4, 26.8, 22.9, 22.6, 20.4, 19.2, 15.2, 9.4. IR(film): 2933, 2878, 1746, 1615, 1588, 1519, 1461, 1428, 1389, 1311, 1235, 1172, 1111. $[\alpha]_D^{25}$ (c =1.15, CH_2Cl_2): -21° MS (ESI) for $C_{48}H_{60}O_9Si$ [M+Na] calc: 831.39, found: 831.5.

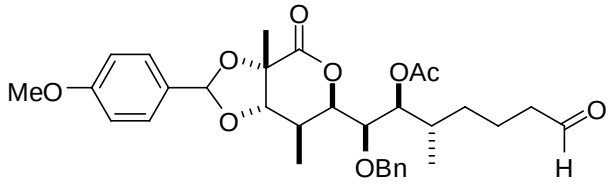


Alcohol from TBAF of TBDPS ether 5.77:

A flask was charged with TBDPS ether **5.77** (770 mg, 0.95 mmol) and tetrahydrofuran (10 mL). The reaction was cooled to 0 °C and tetrabutylammonium fluoride (1.0M in THF, 1.2 mL, 1.2 mmol) was added dropwise. The reaction was then allowed to warm to room temperature and reacted for 2.5 h. The reaction was then quenched through the addition of water and ethyl acetate. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organic layers were then dried over sodium sulfate, filtered, and

concentrated in vacuo. Flash column chromatography provided the alcohol (503 mg, 0.88 mmol) in 93% yield as a colorless oil. Isolated as a >6:1 mixture of acetal diastereomers.

Characterization data for major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.26 (bands, 7H), 6.86 (d, J = 8.5 Hz, 2H), 5.82 (s, 1H), 5.00 (d, J = 8.5 Hz, 1H), 4.89(AB_q, J_{AB} = 11.4 Hz, $\Delta\nu_{AB}$ = 148.2 Hz, 2H), 4.67 (d, J = 11.3 Hz, 1H), 3.94 (s, 1H), 3.78 (d, J = 8.6 Hz, 1H), 3.76 (s, 3H), 3.54 (t, J = 5.9 Hz, 2H), 2.28 (q, J = 7.0 Hz, 1H), 2.02-1.91 (m, 1H), 1.80-1.71 (bands, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.49-1.32 (bands, 3H), 1.30-1.12 (bands, 2H), 0.92 (d, J = 7.3 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.4, 160.6, 137.9, 128.5, 128.3, 128.0, 127.8, 127.1, 113.7, 102.4, 84.4, 79.6, 77.7, 76.8, 75.7, 75.3, 62.4, 55.2, 33.3, 33.0, 32.6, 31.3, 22.5, 20.3, 15.2, 9.3. IR(film): 3461, 2938, 1742, 1615, 1588, 1519, 1497, 1455, 1391, 1374, 1311, 1237, 1173, 1115. $[\alpha]_D^{25}$ (c =0.85, CH_2Cl_2): -33° MS (ESI) for $C_{32}H_{42}O_9$ [M+Na] calc: 593.27, found 593.3.

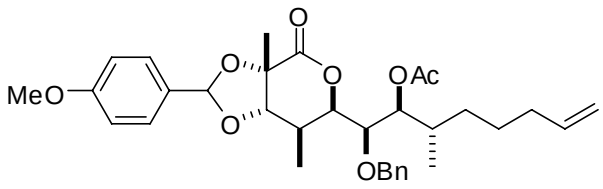


Aldehyde from Oxidation of Previous Alcohol:

A 50 mL round-bottomed flask was charged with methylene chloride (8 mL) and oxalyl chloride (2.0 M in hexanes, 1.45 mL, 2.90 mmol). The mixture was cooled to – 78 °C and methylsulfoxide (0.27 mL, 3.87 mmol) was added dropwise as a solution in methylene chloride (2 mL). The solution was stirred for 20 minutes. The alcohol from the previous reaction (503 mg, 0.88 mmol) was then added dropwise as a solution in methylene chloride

(5 mL). The solution was stirred for 20 minutes and triethylamine was added dropwise (0.98 mL, 7.0 mmol). The mixture was allowed to warm to 0 °C, at which time the reaction was quenched through the addition of water. The layers were separated and the aqueous was extracted once with methylene chloride. The combined organic layers were washed sequentially with saturated sodium hydrogensulfate, saturated sodium bicarbonate, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentratred in vacuo. Flash column chromatography then yielded the aldehyde (501 mg, 0.88 mmol) in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.41-7.25 (bands, 7H), 6.87 (d, J = 8.0 Hz, 2H), 5.83 (s, 1H), 5.01 (d, J = 8.6 Hz, 1H), 4.91 (AB_q, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 150.6 Hz, 2H), 4.67 (d, J = 9.6 Hz, 1H), 3.95 (s, 1H), 3.82 (d, J = 8.8 Hz, 1H), 3.77 (s, 3H), 2.35-2.23 (bands, 3H), 2.02-1.94 (m,1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.49-1.32 (m, 1H), 1.29-1.19 (m, 1H), 1.02-0.97 (m, 1H), 0.93 (d, J = 7.2 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 170.9, 168.4, 160.7, 137.9, 128.6, 128.4, 128.0, 127.9, 127.2, 113.8, 102.5, 84.4, 79.6, 77.7, 76.8, 75.5, 75.4, 55.3, 43.8, 33.4, 33.0, 31.1, 22.6, 20.4, 19.1, 15.2, 9.4. IR(film): 2937, 2726, 1744, 1614, 1588, 1519, 1455, 1391, 1373, 1311, 1236, 1173, 1146, 1125. $[\alpha]_D^{25}$ (c = 1.0, CH_2Cl_2): -29° MS (ESI) for $C_{32}H_{40}O_9$ [M+H] calc: 569.28, found: 569.4 [M+Na] calc: 591.26, found: 591.3.

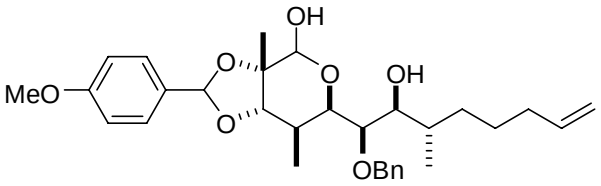


5.78

Alkene 5.78:

A 50mL round-bottomed flask was charged with methyltriphenylphosphonium bromide (1.26 g, 3.52 mmol) and tetrahydrofuran (10 mL). Potassium *tert*-butoxide (1M in THF, 2.64 mL, 2.64 mmol) was then added dropwise. The solution turned yellow and was allowed to stir at room temperature for 30 minutes. The aldehyde from the previous reaction (501 mg, 0.88 mmol) was then added as a solution of tetrahydrofuran (5 mL). The reaction was quenched through the addition of ammonium chloride solution and the layers separated. The aqueous was extracted with ethyl acetate (x3) and the organic layers combined. They were then dried over sodium sulfate, filtered and concentrated in vacuo. Flash column chromatography provided terminal alkene **5.78** (370 mg, 0.65 mmol) in 74 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.25 (bands, 7H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.84 (s, 1H), 5.73 (dddd, *J* = 6.8, 6.8, 10.3, 17.0 Hz, 1H), 5.01 (d, *J* = 8.7 Hz, 1H), 4.97-4.87 (bands, 2H), 4.90 (AB_q, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 146.8 Hz, 2H), 4.67 (d, *J* = 9.7 Hz, 1H), 3.96 (d, *J* = 2.2 Hz, 1H), 3.83 (dd, *J* = 1.4, 8.6 Hz, 1H), 3.77 (s, 3H), 2.31 (q, *J* = 7.1 Hz, 1H), 2.02-1.87 (bands, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.44 (m, 1H), 1.30-1.15 (bands, 2H), 1.08-0.93 (m, 1H), 0.94 (d, *J* = 7.4 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 168.5, 160.7, 138.7, 138.6, 138.6, 138.0, 128.6, 128.3, 128.0, 127.8, 127.2, 114.45, 113.8, 102.5, 84.5, 79.7, 77.7, 76.9, 75.8, 75.3, 55.3, 33.7, 33.4, 33.0, 31.1, 26.0, 22.6, 20.4, 15.3, 9.4. IR(film): 2970, 2937, 1746, 1639, 1615, 1588, 1519, 1497, 1456, 1441, 1390, 1373, 1311, 1235, 1172, 1113. $[\alpha]_D^{24}$ (c = 2.1, CH_2Cl_2): -35° MS (ESI) for $C_{33}H_{42}O_8$ [M+Na] calc: 589.28, found: 589.3.

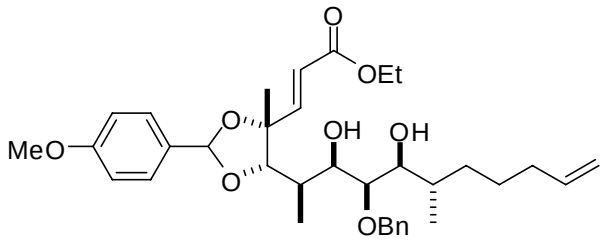


Lactol from Reduction of 5.78:

A round bottomed flask was charged with lactone **5.78** (370 mg, 0.65 mmol), methylene chloride (20 mL), and cooled to – 78 °C. DIBAL (1.0 M in hexanes, 6.5 mL, 6.5 mmol) was then added dropwise. The reaction was allowed to stir for 2 h. The reaction was quenched through the addition of potassium/sodium tartrate solution and allowed to stir for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with methylene chloride (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentratred in vacuo. Flash column chromatography then yielded the lactol (311 mg, 0.55 mmol) in 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.35-7.25 (bands, 5H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.92 (s, 1H), 5.80 (dddd, *J* = 6.6, 6.6, 10.1, 16.9 Hz, 1H), 4.98 (d, *J* = 17.3, 1H), 4.92 (d, *J* = 11.7 Hz, 2H), 4.75 (d, *J* = 4.8 Hz, 1H), 4.71 (d, *J* = 11.8 Hz, 1H), 4.22 (dd, *J* = 2.3, 8.9 Hz, 1H), 3.82-3.77 (m, 1H), 3.89 (s, 3H), 3.67 (d, *J* = 8.8 Hz, 1H), 3.11 (t, *J* = 9.5 Hz), 2.62 (t, *J* = 5.1 Hz, 1H), 2.41 (q, *J* = 7.4 Hz, 1H), 2.08 (dddd, *J* = 6.8, 6.8, 6.8, 6.8 Hz, 2H), 1.93 (d, *J* = 11.1 Hz, 1H), 1.78-1.65 (m, 2H), 1.56-1.41 (m, 1H), 1.50 (s, 3H), 1.37-1.25 (m, 1H), 1.18-1.10 (m, 1H), 1.06 (d, *J* = 7.5 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.2, 139.3, 139.0, 129.9, 128.3, 128.2, 127.7, 127.5, 127.4, 114.3, 113.7, 102.6, 99.6, 88.0, 78.7, 78.0, 75.2, 74.6, 55.3, 36.1, 34.1, 32.4, 32.1, 26.0, 16.3, 15.8, 11.4. IR(film):3445, 2929, 1614, 1517, 1455, 1389, 1303, 1250, 1172. $[\alpha]_D^{27}$ (c = 0.6, CH_2Cl_2):

+20 MS (ESI) for $C_{31}H_{42}O_7$ [M+H] calc: 527.30, found: 527.4 [M+Na] calc: 549.28, found: 549.4.



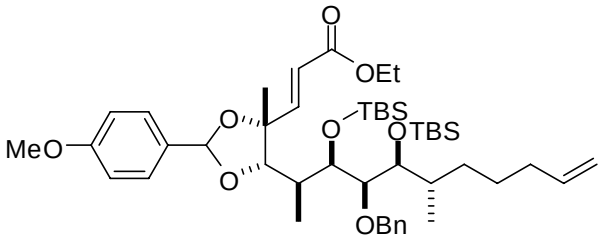
5.79

α,β-Unsaturated Ester 5.79:

A round bottomed flask was charged with the lactol from the previous reaction (297 mg, 0.56 mmol), stabilized ylide (934 mg, 2.8 mmol), and dichloroethane (5 mL). The reaction was heated to 70 °C and allowed to stir for 48 h. The reaction was then concentrated and loaded onto silica gel. Flash column chromatography then provided α,β-unsaturated ester **5.79** (233 mg, 0.39 mmol) in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.7 Hz, 2H), 7.39-7.27 (bands, 5H), 7.11 (d, *J* = 15.6 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.09 (d, *J* = 15.6 Hz, 1H), 5.82 (dddd, *J* = 6.7, 6.7, 10.2, 17.0 Hz, 2H), 5.80 (s, 1H), 5.00 (dddd, *J* = 1.5, 1.5, 1.5, 7.1 Hz, 1H), 4.93 (ddd, *J* = 0.9, 1.9, 10.3 Hz, 1H), 4.73 (AB_q, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 17.8 Hz, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.05 (d, *J* = 9.0 Hz, 1H), 3.98 (d, 8.6 Hz, 1H), 3.80 (s, 3H), 3.61 (d, 8.4 Hz, 1H), 3.09 (t, *J* = 8.4 Hz, 1H), 2.84 (d, *J* = 8.4 Hz, 1H), 2.37 (s, 1H), 2.06 (m, 2H), 1.89 (dddd, *J* = 7.6, 7.6, 7.6, 7.6 Hz, 1H), 1.79-1.67 (bands, 2H), 1.52 (s, 3H), 1.52-1.45 (m, 1H), 1.36-1.28 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20-1.08 (m, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 160.3, 148.9, 138.9, 138.8, 138.8, 137.7, 128.8, 28.5, 128.1, 128.0, 127.9, 121.4, 114.2, 113.6, 101.3, 88.1, 81.0, 79.8, 75.3, 74.3, 70.4, 60.5, 55.1, 35.8, 35.0, 34.0, 31.9, 25.7, 25.0, 15.8, 14.0, 9.7. IR(film): 3505, 3066, 2975, 2934, 1716,

1656, 1615, 1588, 1518, 1497, 1455, 1397, 1368, 1306, 1251, 1171. $[\alpha]_D^{28}$ (c = 2.4, CH_2Cl_2): -10. MS (ESI) for $C_{35}H_{48}O_8$ [M+H] calc: 597.34, found: 597.4 [M+Na] calc: 619.32, found: 619.4.

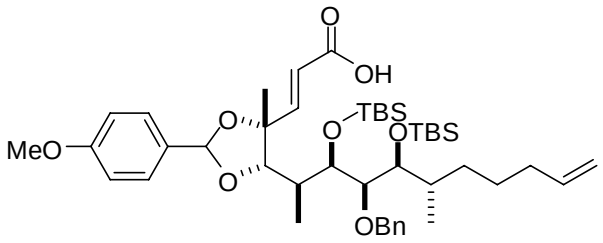


bis-TBS ether from Diol 5.79:

A round bottomed flask was charged with diol (50 mg, 0.086 mmol), methylene chloride (3 mL), and 2,6-lutidine (0.1 mL, 0.86 mmol), and cooled to 0 °C. *tert*-Butyldimethysilyl trifluoromethylsulfonate (0.06 mL, 0.26 mmol) was then added dropwise. The reaction was allowed to stir for 2 hours at which time the reaction was quenched through the addition of saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with methylene chloride (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (50 mg, 0.064 mmol) then yielded the bis-TBS ether in 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (bands, 5H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 15.5 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.97 (d, *J* = 15.5 Hz, 1H), 5.78 (dddd, *J* = 6.7, 6.7, 10.4, 17.0 Hz, 1H), 5.29 (s, 1H), 4.97 (dd, *J* = 1.5, 17.1 Hz, 1H), 4.91 (dd, *J* = 1.2, 10.2 Hz, 1H), 4.69 (AB_q, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 87.1 Hz, 2H), 4.17 (dddd, *J* = 3.0, 7.1, 7.1, 7.1 Hz, 2H), 3.80 (s, 3H), 3.72 (t, *J* = 3.5 Hz, 1H), 3.66 (dd, *J* = 3.4, 7.0 Hz, 1H), 3.42 (dd, *J* = 3.6, 7.0 Hz, 1H), 2.10-1.93 (bands, 3H), 1.59-1.42 (bands, 3H), 1.37 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26-1.05 (bands, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.92 (s, 9H),

0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), -0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 160.1, 149.5, 139.9, 138.8, 129.2, 128.2, 127.8, 126.4, 126.1, 120.5, 114.1, 113.3, 101.3, 85.8, 81.2, 79.8, 76.5, 74.8, 73.3, 60.2, 55.1, 36.7, 35.5, 34.1, 30.3, 26.7, 26.0, 25.9, 24.1, 18.1, 18.0, 17.6, 14.1, 10.7, -3.5, -4.1, -4.1, -4.1, -4.5. IR(film): 2954, 2929, 2857, 1720, 1657, 1615, 1519, 1497, 1463, 1389, 1365, 1304, 1251, 1208, 1171. $[\alpha]_D^{25}$ (c = 1.15, CH_2Cl_2): -43° MS (ESI) for $C_{47}H_{76}O_8Si_2$ [M+Na] calc: 847.50, found: 847.5.

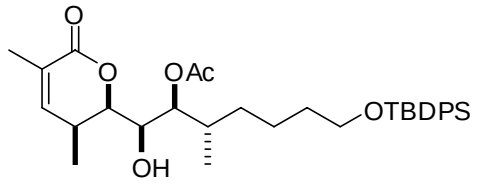


Carboxylic Acid 5.80:

A round bottomed flask was charged with the ester from the previous reaction (23 mg, 0.028 mmol) and THF (1 mL). Potassium trimethylsilanolate (36mg, 0.28 mmol) was then added and the reaction was allowed to stir for 18 h. Citric acid was then added and allowed to stir for 15 minutes. Ethyl acetate was then added and the layers separated. The aqueous layer was extracted with ethyl acetate (x2) and the layers combined. The organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided carboxylic acid **X** (21 mg, 0.026 mmol) in 94 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.19 (bands, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 15.5 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.97 (d, *i* = 15.4 Hz, 1H), 5.76 (dddd, *J* = 6.7, 6.7, 10.3, 17.0 Hz, 1H), 5.30 (s, 1H), 4.96 (d, *J* = 7.1 Hz, 1H), 4.90 (d, *J* = 10.2 Hz, 1H), 4.66 (AB_q, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 87.4 Hz, 2H), 4.29 (s, 1H), 3.78 (s, 3H), 3.71 (t, *J* = 3.4 Hz, 1H), 3.64 (dd, *J* = 3.8, 6.5 Hz, 1H), 3.39 (dd, *J* = 3.8, 6.6 Hz, 1H), 2.11-1.93 (bands, 3H),

1.59-1.40 (bands, 2H), 1.36 (s, 3), 1.28-1.04 (bands, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.83 (s, 9H), 0.03 (s, 3H), -0.01 (s, 6H), -0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 160.1, 152.3, 139.8, 138.7, 129.0, 128.1, 127.8, 126.5, 126.1, 114.2, 113.4, 101.4, 81.2, 80.0, 73.3, 55.0, 35.5, 34.1, 30.4, 26.7, 26.0, 25.9, 24.0, 18.1, 18.0, 17.5, 10.6, -3.6, -4.0, -4.1, -4.5. IR(film):3414, 2954, 2929, 2857, 1698, 1654, 1616, 1519, 1497, 1462, 1439, 1402, 1362, 1304, 1251, 1207, 1170. $[\alpha]_D^{24}$ (c = 0.95, CH_2Cl_2): -42° MS (ESI) for $C_{45}H_{72}O_8Si_2$ [M+H] calc: 796.48, found: 797.5. [M+H] calc: 819.47, found: 819.5.



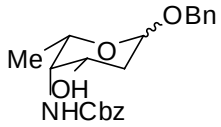
5.33

Alcohol 5.33:

To a 50 mL round-bottomed flask was added the benzyl ether (482 mg, 0.73 mmol), methylene chloride (15 mL), pH 7 buffer (1.5 mL), and DDQ (833 mg, 3.67 mmol). Reaction was stirred at room temperature for 24 hours. Reaction was quenched with the addition of sodium bicarbonate and filtered through celite. The layers were separated and the aqueous was extracted with methylene chloride (x2). The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided alcohol **5.33** (289 mg, 0.51 mmol) in 70% yield

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.63 (m, 4H), 7.40-7.30 (bands, 6H), 6.59, (bd, 1H, J = 6.5 Hz), 4.70 (d, 1H, J = 9.5 Hz), 4.22 (dd. 1H, J = 3.2, 7.9 Hz), 4.03 (dd, 1H, J = 3.6, 7.5 Hz),

3.62 (t, 2H, J = 6.1 Hz), 2.78 (d, 1H, 4.0 Hz), 2.60 – 2.52 (m, 1H), 2.12-2.06 (m, 1H), 2.08 (s, 3H), 1.87 (s, 3H), 1.60-1.40 (m, 3H), 1.39-1.21 (m, 2H), 1.08-1.00 (m, 1H), 1.03 (s, 9H), 1.00 (d, 3H, J = 7.0 Hz), 0.97 (d, 3H, 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 165.1, 145.6, 135.4, 133.9, 129.4, 127.5, 126.7, 80.5, 75.7, 69.1, 63.6, 33.4, 32.6, 31.8, 30.0, 26.7, 22.7, 20.8, 19.1, 16.7, 15.3, 11.9. IR(film): 3449.1, 2932.2, 2858.0, 2360.4, 1725.0, 1457.9, 1428.0, 1372.1, 1239.0, 1110.8. $[\alpha]_D^{25}$ (c = 1.0, CH_2Cl_2): +35. MS (ESI):



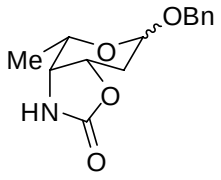
5.63

Benzyl Acetal 5.63:

A 100 mL round-bottomed flask under argon was charged with hemiacetal **X** (820 mg, 2.9 mmol) and 30 mL methylene chloride. Benzyl alcohol (1.5 mL, 14.6 mmol) was then added, followed by *p*-toluenesulfonic acid monohydrate (1.11 g, 5.82 mmol) and allowed to stir for hours. The reaction was then quenched by the addition of saturated sodium bicarbonate solution and allowed to stir 5 minutes. The organic layers were separated, and the aqueous layer was extracted twice with methylene chloride. The combined organic extracts were then dried with sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (gradient from 20% to 50% ethyl acetate/hexanes) then provided a mixture of benzyl acetal anomers as a pale yellow oil (53%, 1.53 mmol, 569 mg).

α: MS (ESI) for $C_{21}H_{25}NO_5$: calc 394.16 obs: 394.2

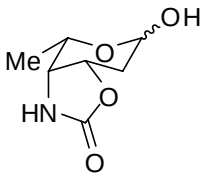
α_D^{26} (CH_2Cl_2, c = 1.05) = -78



5.64

Oxazolidinone 5.64:

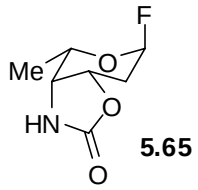
A 100 mL round-bottomed flask was charged with benzyl acetal **5.63** (40 mg, 0.11 mmol) and tetrahydrofuran (3 mL). The mixture was cooled to 0 °C and sodium hydride (60%, 7 mg, 0.17 mmol) was then added. The reaction was stirred for 10 minutes then warmed to room temperature and reacted 3 hours. Reaction was quenched with the addition of saturated ammonium chloride solution. Ethyl acetate was then added and the layers were separated. The aqueous layer was extracted with ethyl acetate (x2), the organics combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (gradient from 75% to 100% ethyl acetate/hexanes) yielded oxazolidinone **5.64** (25 mg, 0.095 mmol) as a crystalline solid (4.3:1 ratio of anomers) in 86% yield.



Hemiacetal from Reduction of 5.64:

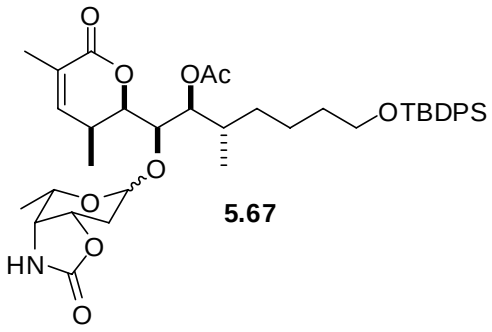
To a round-bottomed flask was added benzyl acetal **5.64** (95 mg, 0.36 mmol), ethanol (5 mL), and palladium on carbon (10%, 35 mg, 0.036 mmol). A balloon of hydrogen was then connected to the flask with a 3-way adapter. The air was evacuated under vacuum and displaced with hydrogen gas several times. Reaction was stirred for 24 hours at room temperature. Reaction was filtered through celite and washed several times with methanol.

The reaction was concentrated in vacuo to provide the hemiacetal (61 mg, 0.35 mmol) as a mixure of anomers in 98% yield.



5.65

Glycosyl Fluoride 5.65:

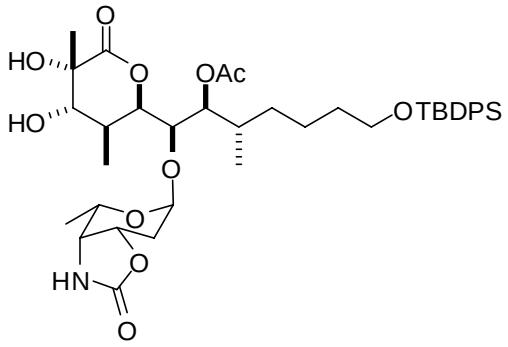


5.67

Glycosylation Product 5.67:

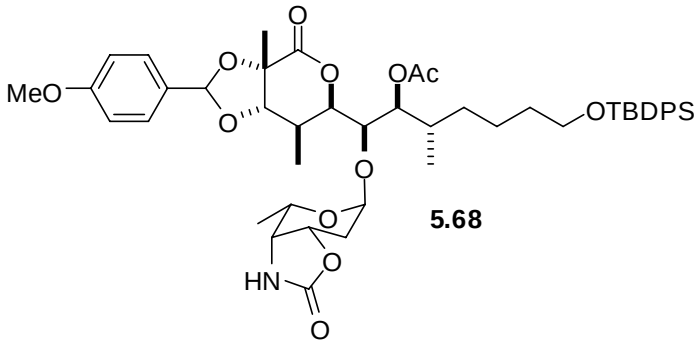
A 25 mL round bottomed flask was charged with alcohol **5.33** (375 mg, 0.66 mmol), glycosyl fluoride **5.65** (122 mg, 0.69 mmol), 4 Angstrom molecular sieves (350 mg), ether (7 mL), and tetrahydrofuran (9 mL). Tin(II) chloride (150 mg, 0.79 mmol) was then added in one portion. The reaction was then stirred at room temperature for 2 hours and quenched via the addition of sodium bicarbonate solution. The mixture was then filtered through celite and washed with ethyl acetate. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (50% to 75% ethyl acetate/hexanes)

then provided the glycosylation product **5.67** (361 mg, 0.50 mmol) as a 5:1 (α:β) inseparable mixture of anomersin 76% yield.



Diol from Dihydroxylation of Alkene 5.67:

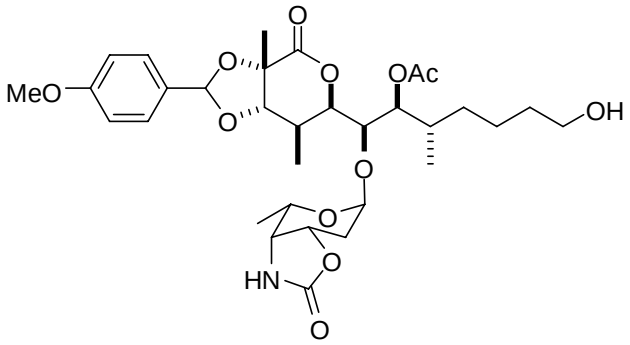
A round bottomed flask was charged with alkene **5.67** (361 mg, 0.50 mmol), tetrahydrofuran (6 mL), and water (0.9 mL). Osmium tetroxide (20 mg/mL solution, 0.64 mL, 0.05 mmol) was then added along with *N*-methylmorpholine-*N*-oxide (88 mg, 0.75 mmol). The reaction was allowed to stir overnight (12 h). Upon disappearance of starting material, the reaction was quenched through the addition of saturated sodium sulfite and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the diol (326 mg, 0.43 mmol, both anomers). At this stage, 273 mg of the pure α anomer was separated as a white solid residue.



5.68

***p*-Methoxybenzylidene 5.68:**

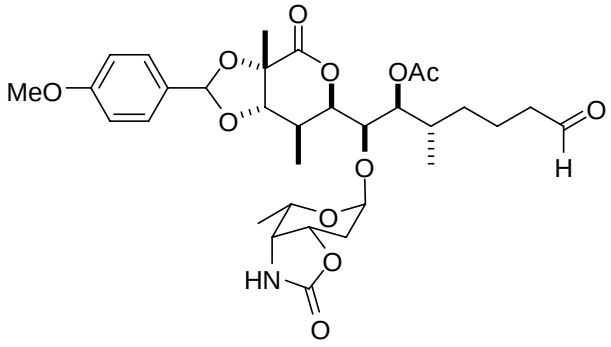
A round-bottomed flask was charged with the diol from the previous reaction (263 mg, 0.35 mmol) and methylene chloride (10 mL). Anisaldehyde dimethyl ketal (0.15 mL, 0.86 mmol) was then added, followed by pyridinium *para*-toluenesulfonate (6 mg, 0.02 mmol). The reaction was then stirred for 7 h. The reaction was quenched through the addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous was extracted with methylene chloride (x2). The combined organic layers were then dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the acetal **5.68** (267 mg, 0.31 mmol) in 87% yield isolated as a white foam.



Alcohol from TBAF of TBDPS ether 5.68:

A 50 mL round-bottomed flask was charged with **5.68** (265 mg, 0.31 mmol) and tetrahydrofuran (6 mL). The solution was cooled to 0 °C and tetrabutylammonium fluoride

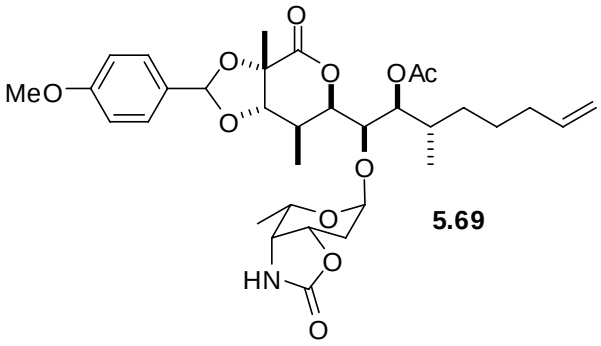
(1M, 0.37 mL, 0.37 mmol) was added dropwise and reacted for 4 hours. Another 0.1 mL TBAF was added and the reaction was warmed to room temperature and stirred for 1 hour. The reaction was quenched through the addition of saturated ammonium chloride and ethyl acetate and the layers were separated. The aqueous was extracted with ethyl acetate (x3) and the organic layers combined. They were then dried over sodium sulfate, filtered and concentrated in vacuo. Flash column chromatography (100% ethyl acetate) provided the alcohol (169 mg, 0.27 mmol) as a colorless oil in 87% yield.



Aldehyde from Oxidation of Previous Alcohol:

A 50 mL round-bottomed flask was charged with methylene chloride (7 mL) and oxalyl chloride (2M, 0.58 mL, 1.16 mmol). The mixture was cooled to – 78 oC and methylsulfoxide (0.10 mL, 1.46 mmol) was added dropwise as a solution in methylene chloride (3 mL). The solution was stirred for 20 minutes. The alcohol from the previous reaction (165 mg, 0.26 mmol) was then added dropwise as a solution in methylene chloride (5 mL). The solution was stirred for 20 minutes and triethylamine was added dropwise (0.30 mL, 2.12 mmol). The mixture was allowed to warm to 0 °C, at which time the reaction was quenched through the addition of water. The layers were separated and the aqueous was extracted once with methylene chloride. The combined organic layers were washed sequentially with saturated

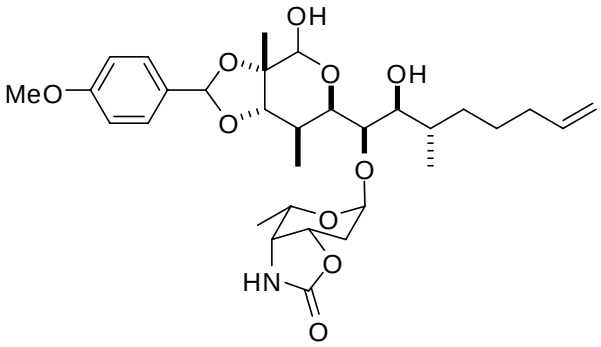
sodium hydrogensulfate, saturated sodium bicarbonate, and saturated brine. The organic layer was then dried over sodium sulfate, filtered, and concentratred in vacuo. Flash column chromatography (75% to 100% ethyl acetate) then yielded the aldehyde (95 mg, 0.15 mmol) in 58 % yield.



5.69

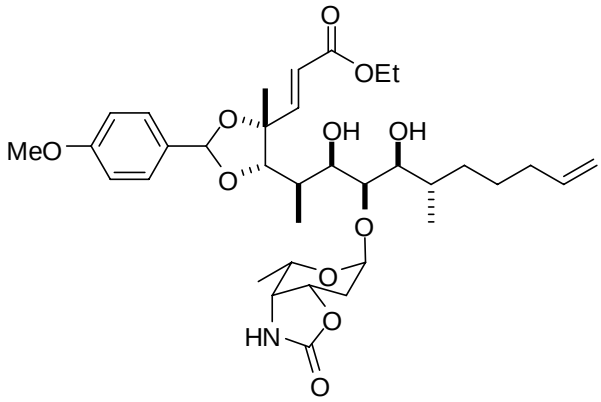
Alkene 5.69:

A 50mL round-bottomed flask was charged with methyltriphenylphosphonium bromide (214 mg, 0.6 mmol) and tetrahydrofuran (6 mL). Potassium *tert*-butoxide (1M in THF, 0.45 mL, 0.45 mmol) was then added dropwise. The solution turned yellow and was allowed to stir at room temperature for 30 minutes. The aldehyde (95 mg, 0.15 mmol) from the previous reaction was then added as a solution of tetrahydrofuran (4 mL). The reaction was quenched through the addition of ammonium chloride and the layers separated. The aqueous was extracted with ethyl acetate (x3) and the organic layers combined. They were then dried over sodium sulfate, filtered and concentrated in vacuo. Flash column chromatography provided (75% ethyl acetate/hexanes) alkene **5.69** (60 mg, 0.095 mmol) in 63% yield.



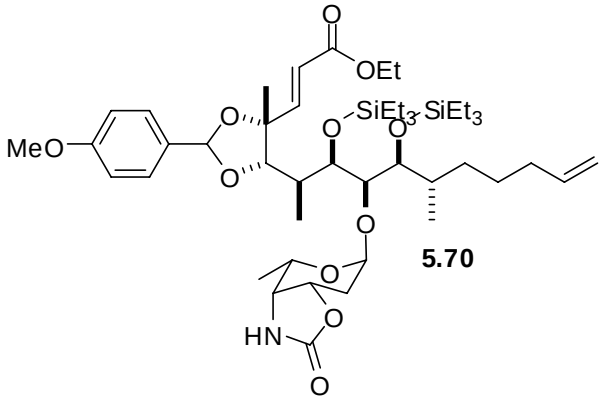
Lactol from DIBAL reduction of Lactone 5.69:

A 50 mL round-bottomed flask was charged with lactone **5.69** (58 mg, 0.092 mmol) and methylene chloride (10 mL) and cooled to –78 °C. Diisobutylaluminum hydride (1M in heptane, 0.9 mL, 0.9 mmol) was then added dropwise. The reaction was allowed to stir for 2 hours at which time a saturated solution of potassium/sodium tartrate was added and allowed to stir for 1 hour. The layers were separated and the aqueous was extracted with ethyl acetate (x3). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography (ethyl acetate) then provided the lactol (46 mg, 0.073 mmol) in 79 % yield.



α,β-Unsaturated Ester from Wittig with Lactol:

A round bottomed flask was charged with lactol (46 mg, 0.073 mmol) from the previous reaction, stabilized ylide (126 mg, 0.36 mmol), and dichloroethane (3 mL). The reaction was heated to 65 °C and allowed to stir for 14 h. The reaction was then concentrated and loaded onto silica gel. Flash column chromatography then provided the α,β-unsaturated ester contaminated with triphenylphospine oxide. The mixture was brought forward to the next reaction



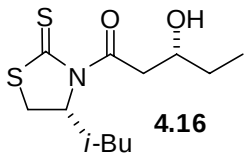
5.70

bis-TES ether 5.70:

A round-bottomed flask was charged with the diol from the previous reaction (0.073 mmol), imidazole (40 mg, 0.584 mmol), DMAP (4 mg), and DMF (1 mL). Chlorotriethylsilane (0.5 mL, 0.365 mmol) was then added and the reaction was allowed to stir for14 h. The reaction was quenched through the addition of water and diethyl ether. The layers were separated and the aqueous layer was extracted with diethyl ether (x5). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided bis-TES ether **5.70** (47 mg, 0.053 mmol) as a white foam in 72 % yield.

^{1}H NMR(400 MHz, $CDCl_3$): δ 7.39 (d, 2H, *J* = 8.7 Hz), 6.92 (d, 1H, *J* = 15.5 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 6.12 (s, 1H), 6.10 (d, 1H, *J* = 15.5 Hz), 5.80 (dddd, 1H, *J* = 17.0, 10.2, 6.7,

6.7 Hz), 5.76 (s, 1H), 5.03-4.90 (m, 4H), 4.21 (s, 1H), 4.17 (m, 2H), 3.98 (dd, 1H, *J* = 3.6, 6.0 Hz), 3.91 (m, 1H), 3.79 (s, 3H), 3.71 (dd, 1H, *J* = 2.0, 7.6 Hz), 3.63 (dd, 1H, *J* = 3.7, 7.5 Hz), 3.57 (dd, 1H, *J* = 1.5, 9.1 Hz), 2.47 (ddd, 1H, *J* = 3.7, 5.6, 15.8 Hz), 2.15 (m, 1H), 2.03 (m, 2H), 1.80 (m, 2H), 1.71 (s, 1H), 1.45-1.38 (m, 2H), 1.43 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.24-1.10 (m, 2H), 1.06 (d, 3H, *J* = 6.5 Hz), 0.97-0.88 (m, 24H), 0.63-0.56 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 160.4, 159.5, 149.3, 139.0, 139.0, 129.2, 128.1, 120.6, 114.2, 113.7, 101.4, 81.6, 75.5, 73.1, 63.1, 60.4, 55.3, 54.3, 35.3, 35.3, 34.5, 30.4, 29.6, 27.2, 25.1, 17.7, 15.7, 14.2, 11.4, 7.1, 7.1, 5.5, 5.1. IR(film): 3267, 2955, 2917, 2877, 1758, 1719, 1656, 1615, 1518, 1460, 1439, 1385, 1338, 1305, 1250. $[\alpha]_D^{26}$ (c = 2.1, CH_2Cl_2) = -37º. ESI-MS: calc (M+Na): obs:



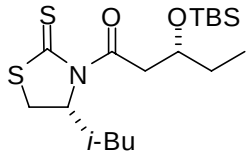
4.16

Aldol Adduct 4.16:

A round-bottomed flask was charged with acetate **4.38** (10.6 g, 48.8 mmol) and methylene chloride (500 mL) and cooled to -78 °C. Titanium (IV) chloride (5.1 mL, 46.5 mmol) was then added dropwise and the reaction allowed to stir 5 minutes. Hünig's base (8.14 mL, 46.5 mmol) was then added dropwise and the reaction was allowed to stir for 30 minutes. Freshly distilled propionaldehyde (3.35 mL, 46.5 mmol) was then added dropwise and the reaction was allowed to stir 2 hours at -78 °C. The reaction was then quenched via the addition of saturated sodium bicarbonate. The layers were separated and the aqueous was extracted (x2) with methylene chloride. The organic layers were combined, dried over sodium sulfate,

filtered, and concentrated in vacuo. Flash column chromatography provided aldol adduct **4.16** (11.8 g, 42.9 mmol) as a bright yellow oil in 93% yield for both isomers (7:1 ratio). Pure aldol adduct was isolated (10.4 g, 37.8 mmol) in 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.25 (ddd, *J* = 3.5, 7.2, 10.4 Hz, 1H), 4.02 (m, 1H), 3.58-3.49 (bands, 2H), 3.06 (dd, *J* = 9.4, 17.7 Hz, 1H), 2.88 (d, *J* = 11.3 Hz), 2.79 (s, OH), 1.87 (ddd, *J* = 4.2, 10.3, 13.8 Hz), 1.67-1.43 (bands, 4H), 0.98-0.90 (bands, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 173.0, 69.1, 65.8, 45.3, 39.6, 33.1, 29.2, 25.3, 23.5, 21.2, 9.8. IR(film): 3449, 2959, 2933, 2874, 1694, 1465, 1338, 1257, 1217, 1160. $[\alpha]_D^{24}$ (c = 1.2, CH_2Cl_2): -303° MS(ESI) for $C_{12}H_{21}NO_2S_2$ [M+H] calc: 276.11 found: 276.1. [M+Na] calc: 298.11 found: 298.1.

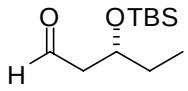


TBS Ether from Aldol Adduct 4.16:

A round bottomed flask was charged with aldol adduct **4.16** (9.8 g, 35.6 mmol), methylene chloride (180 mL), and 2,6-lutidine (8.3 mL, 71.2 mmol) and cooled to 0 °C. *t*-Butyldimethylsilyl triflate (9.0 mL, 39.1 mmol) was then added dropwise. The reaction was stirred for 1 hour. The reaction was quenched with saturated sodium bicarbonate and the layers separated. The aqueous layer was then extracted with methylene chloride (x2) and the organic layers combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided the TBS ether (13.7 g, 35.2 mmol) in 99 % yield as a bright yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.14 (m, 1H), 4.24 (m, 1H), 3.51-3.43 (bands, 2H), 3.07 (dd, *J* = 3.7, 16.8 Hz, 1H), 2.89 (d, *J* = 11.2 Hz, 1H), 1.91 (m , 1H), 1.70-1.48 (bands, 4H), 0.98

(d, J = 4.6 Hz, 3H), 0.96 (d, J = 4.6 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H), 0.83 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 172.1, 70.1, 66.1, 45.0, 39.2, 33.2, 30.2, 25.6, 25.3, 23.4, 21.1, 17.8, 9.1. IR(film): 2957, 2930, 2856, 1702, 1464, 1438, 1368, 1339, 1319, 1291, 1271, 1254, 1216. $[\alpha]_D^{24}$ (c =1.35, CH_2Cl_2): -239° MS(ESI) for $C_{18}H_{35}NO_2S_2Si$ [M+H] calc: 390.20 found: 390.3 [M+Na] calc: 412.20 found: 412.3.

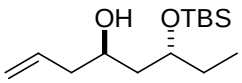


Aldehyde 4.39:

A round bottomed flask was charged with the TBS ether (15.1 g, 38.6 mmol) from the previous reaction and methylene chloride (300 mL) and cooled to -78 °C. Diisobutylaluminum hydride (1.0M in hexanes, 45 mL, 45 mmol) was then added slowly until the yellow color disappears. The reaction was quenched via the addition of saturated potassium/sodium tartrate solution and warmed to room temperature. The reaction was stirred for 1 hour and the layers separated. The aqueous layer was then extracted with methylene chloride (x2), the organic layers combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided aldehyde **4.39** (8.4 g, 38.0 mmol) in 99% yield as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (t, J = 2.4 Hz, 1H), 4.09 (dddd, J = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 2.52-2.40 (bands, 2H), 1.52 (dddd, J = 6.9, 6.9, 6.9, 6.9 Hz, 2H), 0.87-0.83 (bands, 12H), 0.03 (s, 3H), 0.02 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 69.3, 50.3, 30.5, 25.7, 18.0, 9.4, -4.5, -4.8. IR(film): 2957, 2925, 2855, 1699, 1464, 1369, 1256, 1163.

$[\alpha]_D^{28}$ (c = 1.3, CH_2Cl_2): -2. MS(ESI): decomposed, MS not observed.



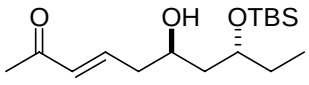
4.15

Homoallylic Alcohol 4.15:

A three-neck round-bottomed flask was charged with a stir bar and three stoppers and tared. To this flask was added THF (50 mL) and borane-dimethyl sulfide (2.0 M in ether, 39 mL, 77.7 mmol). (-)-α-pinene (25.4 g, 186 mmol) was then added slowly with stirring. Stirring was discontinued and the reaction was allowed to sit for 24 h. Excess solvent was removed via cannula. The solids were washed three times with pentane and solvents again removed via cannula. The flask was then placed under vacuum for several hours. 15.26 g (53.3 mmol) of isopinocampheylborane was formed. The flask was then fitted with a jacketed addition funnel and an internal thermometer. Ether (50 mL) was added and the flask was cooled to 0 °C. Ether (10 mL) was also placed in the addition funnel with methanol (2.16 mL, 53.3 mmol). The methanol solution was then added over 1 hour to ensure the temperature stayed at 0 °C during this exothermic reaction. After the solution turned clear (1 – 2 h), Allylmagnesium (1.0M, 50 mL, 50 mmol) was then added slowly at 0 °C. The reaction was stirred for 30 minutes and warmed to room temperature briefly and cooled to – 78 °C. Aldehyde **4.39** (8.4 g, 38 mmol) was then added slowly as a solution in ether. The reaction was then stirred at – 78 °C for 3 hours at which time the reaction was quenched through the addition of 3M NaOH (20 mL, 60 mmol) and hydrogen peroxide (30%, 40 mL). The reaction was allowed to warm to room temperature and stir for 12 h. After complete oxidation has occurred, the layers were separated. The aqueous layer was extracted with ethyl acetate (x3) and the combined organic layers washed with sodium sulfite solution until

potassium iodide strips indicate the absence of peroxides in the organic layer. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided homoallylic alcohol **4.15** (9.49 g, 37.1 mmol) in 96% yield as a 5:1 mixture of inseparable diastereomers which was carried on to the next step.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99 (m, 1H), 5.16-5.08 (bands, 2H), 4.01 (m, 1H), 3.95 (m, 1H), 3.37 (bs, OH), 2.27 (m, 1H), 2.21 (m, 1H), 1.65-1.56 (bands,), 0.92 (s, 9H), 0.88 (t, *J* = 7.7 Hz, 3H), 0.12 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.1, 117.3, 72.3, 67.6, 42.4, 40.4, 29.0, 25.8, 18.0, 10.1, -4.6, -4.8. IR(film): 3447, 2959, 2923, 2852, 1731, 1464, 1375, 1261. $[\alpha]_D^{26}$ (c =0.05, CH_2Cl_2): -12. MS (ESI):

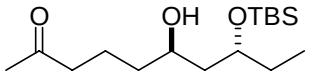


4.41

α,β-Unsaturated Ketone 4.41:

A round-bottomed flask was charged with homoallylic alcohol **4.15** (9.49 g, 37.1 mmol) and methylene chloride (75 mL). The reaction was degassed by bubbling argon through for 30 minutes. Methyl vinyl ketone (freshly distilled after being dried over calcium chloride, 6.18 mL, 74.2 mmol) was then added. Grubbs' second generation metathesis catalyst **4.44** (473 mg, 0.56 mmol) was then added in one portion and the reaction heated to reflux for 2 h. The reaction was then cooled to room temperature and air was bubbled through the solution for 1 hour to quench the catalyst. The solution was concentrated in vacuo and loaded onto silica gel. Flash column chromatography then provided the desired cross-methathesis product **4.41** (8.7 g, 29 mmol) in 78% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (dt, *J* = 7.2, 16.0 Hz, 1H), 6.14 (dt, *J* = 1.2, 16.1 Hz, 1H), 4.17-4.12 (bands, 2H), 3.93 (m, 1H), 2.44-2.32 (bands, 2H), 2.26 (s, 3H), 1.71-1.55 (bands, 4H), 0.91 (s, 9H), 0.88 (t, *J* = 7.5 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 144.7, 133.3, 73.1, 67.2, 40.8, 40.3, 28.6, 26.7, 25.8, 17.9, 10.2, -4.7, -4.8. IR(film): 3474, 2930, 2857, 1674, 1627, 1464, 1362, 1255, 1041. $[\alpha]_D^{26}$ (c = 0.6, CH_2Cl_2): -1 MS(ESI) for $C_{16}H_{32}O_3Si$ [M+H] calc: 301.22 found: 301.3 [M+Na] calc: 323.20 found: 323.3.



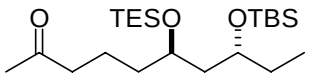
4.42

Ketone 4.42:

A round-bottomed flask was charged with α,β-Unsaturated ketone **4.41** (8.7 g, 29 mmol) and ethanol (300 mL). Palladium on carbon (617 mg, 0.58 mmol) was then added and the flask fitted with a 3-way adapter. A balloon of hydrogen was placed on one end of the adapter and reduced pressure on the third end. The flask was evacuated and filled with hydrogen three times to remove air from the vessel. The reaction was stirred for 1 hour at which time the hydrogen was evacuated and replaced with air. The solution was filtered through celite and rinsed with ethanol, making sure that that the palladium stays moist. The solution was then concentrated in vacuo. Flash column chromatography then provided ketone **4.42** (8.36 g, 27.6 mmol) in 95% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89-3.86 (bands, 2H), 3.53 (s, O*H*), 2.43 (dt, *J* = 1.4, 7.6 Hz, 2H), 2.09 (s, 3H), 1.76-1.51 (bands, 7H), 1.48-1.31 (bands, 3H), 0.86 (s, 9H), 0.83 (t, *J* = 7.5 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.2, 73.0, 67.8, 43.6,

40.7, 37.3, 29.8, 28.9, 25.8, 19.7, 17.9, 10.1, -4.6, -4.8. IR(film): 3491, 2930, 2857, 1713, 1463, 1412, 1362, 1254. $[\alpha]_D^{26}$ (c =0.55, CH_2Cl_2): -7 MS(ESI) for $C_{16}H_{34}O_3Si$ [M+H] calc: 303.22 found: 303.3 [M+Na] calc: 325.20 found: 325.3.

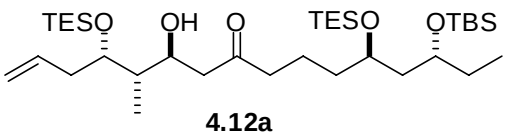


4.13

Ketone 4.13:

A round-bottomed flask was charged with ketone **4.42** (8.36 g, 27.6 mmol), dimethylformamide (60 mL), imidazole (5.64 g, 82.8 mmol), DMAP (168 mg, 1.38 mmol), and chlorotriethylsilane (5.56 mL, 33.12 mmol). The reaction was stirred for 1.5 h and quenched via the addition of saturated water and ether. The layers were separated and the aqueous layer extracted with ether (x4). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided TES ether **4.13** (10.05 g, 24 mmol) as a colorless oil.

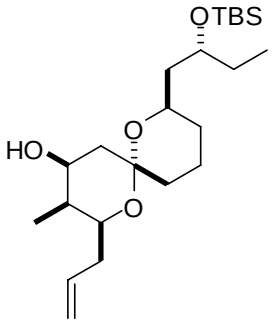
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.72 (dddd, *J* = 5.8, 5.8, 5.8, 5.8 Hz, 1H), 3.64 (dddd, *J* = 5.8, 5.8 5.8, 5.8 Hz), 2.4 (t, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 1.65-1.52 (bands, 4H), 1.49-1.35 (bands, 4H), 0.92 (t, *J* = 8.0 Hz, 9H), 0.86 (s, 9H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 71.2, 69.9, 44.8, 43.8, 37.3, 30.3, 29.8, 25.9, 19.6, 18.1, 9.2, 7.0, 5.3, -4.1, -4.3. IR(film): 295, 2878, 1720, 1462, 1414, 1361, 1253, 1160, 1101. $[\alpha]_D^{26}$ (c = 0.35, CH_2Cl_2): -3 MS (ESI):



4.12a

Alcohol 4.12a:

A 25 mL round bottomed flask was charged with (+)-DIPCl (71 mg, 0.22 mmol) in an inert atmosphere glove box. Pentane (2 mL) was then added and the flask cooled to 0 °C. Triethylamine (34 μL, 0.24 mmol) was then added dropwise to provide a cloudy solution. Reaction was allowed to stir for 10 minutes. Methyl ketone **4.13** (83 mg, 0.2 mmol) was then added in pentane (2 mL) dropwise to provide a milky solution. Reaction was stirred for 90 minutes. The reaction was cooled to – 78 °C and aldehyde **4.14**[4] (49 mg, 0.2 mmol) was added as a solution in pentane (2 mL) dropwise. The reaction proceeds for 3 h. The reaction was quenched through the addition of a 1:1 MeOH:pH 7 buffer (2 mL) and warmed to 0 °C. 1:1, 30% H_2O_2:pH 7 buffer (2 mL) was then added and the reaction was stirred for 1 h. The reaction was diluted with ether and the layers separated. The organic layer was washed with water then brine. The organic layer were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the desired **4.12a** as a 3:1 mixture of diastereomers. The mixture was taken on to the spiroketalization for separation and characterization.

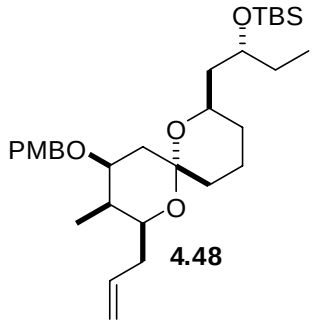


Spiroketal from Cyclization of Ketone 4.12a:

A round-bottomed flask was charged with the reaction mixture of ketone **4.12a**, methylene chloride, and methanol. Pyridinium *p*-tolunesulfonate was then added and the reaction

[4] Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128-9.

allowed to stir 1 hour. The reaction was quenched via the addition of saturated sodium bicarbonate. The layers were separated and the aqueous was extracted with methylene chloride (x2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography then provided the desired spiroketal. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (dddd, *J* = 6.3, 8.0, 10.1, 16.6 Hz, 1H), 5.09 (dq, *J* = 1.6, 17.1 Hz, 1H), 5.02 (dt, *J* = 10.2, 1.9 Hz, 1H), 4.16 (dt, *J* = 4.8, 11.8 Hz, 1H), 3.64-3.58 (bands, 2H), 3.55 (dddd, *J* = 2.1, 6.3, 6.3, 11.4 Hz, 1H), 2.34 (m, 1H), 2.10 (m, 1H), 1.90-1.77 (bands, 2H), 1.69 (ddd, *J* = 0.7, 4.8, 12.7, 1H), 1.65-1.33 (bands, 11H), 1.14 (m, 1H), 0.87 – 0.81 (bands, 15H), 0.02 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.3, 116.7, 97.3, 71.7, 70.3, 67.5, 67.2, 43.9, 39.0, 37.6, 37.0, 34.9, 31.3, 30.1, 25.8, 18.7, 18.0, 9.4, 3.8, -4.4, -4.5. IR(film): 3376, 2935, 2857, 1463, 1440, 1374, 1254, 1224, 1180, 1119. $[\alpha]_D^{27}$ (c =0.75, CH_2Cl_2): - 56 MS(ESI) for $C_{23}H_{44}O_4Si$ [M+H] calc: 413.31 found: 413.4 [M+Na] calc: 435.29 found: 435.4.



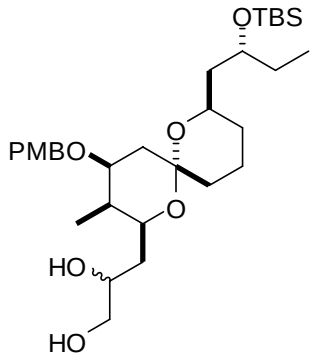
4.48

PMB Ether 4.48:

A round-bottomed flask was charged with the alcohol from the previous reaction and tetrahydrofuran and cooled to 0 °C. Potassium hydride was then added and the reaction

allowed to stir for 1 hour. *p*-Methoxybenzyl bromide was then added and the reaction was warmed to room temperature and allowed to stir for hours. The reaction was then quenched via the slow addition of saturated ammonium chloride. The mixture was then extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the PMB ether **4.48** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.6 Hz, 2H), 5.85 (m, 1H), 5.11 (d, *J* = 7.1 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.41 (AB_q, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 61.3 Hz, 2H), 3.88 (dt, *J* = 4.7, 11.8 Hz, 1H), 3.78 (s, 3H), 3.60 (m, 2H), 3.55 (m, 1H), 2.37 (ddd, *J* = 7.4, 7.4, 13.8 Hz, 1H), 2.12 (ddd, *J* = 7.0, 7.0, 13.8 Hz, 1H), 2.04 (m, 1H), 1.83 (dt, *J* = 3.5, 13.3 Hz, 1H), 1.77 (dd, *J* = 4.7, 13.0 Hz, 1H), 1.67-1.47 (bands, 7H), 1.37 (dddd, *J* = 1.40 (dd, *J* = 4.6, 12.7 Hz, 1H), 1.35 (dd, *J* = 6.4, 13.7 Hz, 1H), 1.14 (dddd, *J* = 3.8, 13.3, 13.3, 13.3 Hz, 1H), 0.90- 0.85 (bands, 15H), 0.03 (s, 3H), 0.03 (s, 3H). C NMR (125Hz, $CDCl_3$): δ 159.0, 135.5, 130.9, 129.1, 116.7, 113.7, 97.5, 74.0, 71.9, 70.3, 69.1, 67.6, 55.2, 44.0, 37.2, 36.8, 35.0, 34.5, 31.4, 30.2, 25.9, 18.9, 18.1, 9.5, 4.4, -4.3, -4.4. IR(film): 2936, 2857, 1613, 1514, 1463, 1440, 1372, 1361, 1302, 1249, 1224. $[\alpha]_D^{26}$ (c = 1.15, CH_2Cl_2): - 69

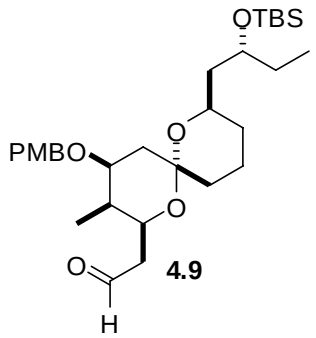
MS(ESI):



Diol from Alkene 4.48:

A round bottomed flask was charged with alkene **4.48** (1.37 g, 2.6 mmol), tetrahydrofuran (26 mL), and water (6.5 mL). Osmium tetroxide (20 mg/mL solution, 1.65 mL, 0.13 mmol) was then added along with *N*-methylmorpholine-*N*-oxide (610 mg, 5.2 mmol). The reaction was allowed to stir overnight (16 h). Upon disappearance of starting material, the reaction was quenched through the addition of saturated sodium sulfite and ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the diol (1.4 g, 2.47 mmol) as a mixture of hydroxyl diastereomers in 95% yield that was taken on to the next step for characterization.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 158.8, 130.6, 130.5, 128.9, 113.6, 98.1, 97.5, 73.5, 73.1, 72.5, 72.3, 72.0, 71.4, 69.0, 68.8, 68.7, 67.6, 67.0, 66.5, 66.3, 55.1, 55.0, 43.7, 43.2, 36.6, 36.5, 35.5, 35.4, 35.4, 35.1, 34.7, 34.2, 31.6, 30.8, 29.8, 25.8, 25.7, 18.8, 18.1, 17.9, 9.8, 9.3, 4.6, 4.5, -4.3, -4.5, -4.6. IR(film): 3452, 2937, 2857, 1613, 1586, 1514, 1463, 1441, 1387, 1362, 1302, 1249, 1180, 1114. $[\alpha]_D^{27}$ (c = 2.45, CH_2Cl_2): -67. ESI-MS: $C_{31}H_{54}O_7Si$: calc (M+Na): 589.35 obs: 589.4



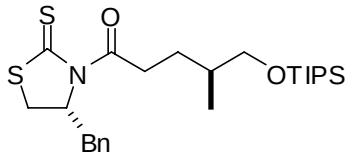
4.9

Aldehyde 4.9:

A round bottomed flask was charged with the alkene (1.29 g, 2.28 mmol) from the previous reaction, tetrahydrofuran (22 mL), and water (5.5 mL). Sodium periodate (537 mg, 2.51 mmol) was then added. The reaction was allowed to stir for 2 h. Upon disappearance of starting material, the reaction was filtered through a pad of celite and rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided aldehyde **4.9** (896 mg, 1.68 mmol) in 74% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (dd, *J* = 1.7, 2.5 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.41 (AB_q, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 49.2 Hz, 2H), 4.21 (ddd, *J* = 2.3, 3.5, 9.8 Hz, 1H), 3.95 (dt, *J* = 4.7, 11.8 Hz, 1H), 3.77 (s, 3H), 3.67 (dddd, *J* = 4.6, 4.6, 6.7, 7.4 Hz, 1H), 3.55 (dddd, *J* = 2.0, 6.2, 6.2, 11.4 Hz, 1H), 2.72 (ddd, *J* = 2.6, 9.9, 16.2 Hz, 1H), 2.35, (ddd, *J* = 1.6, 3.7, 16.2 Hz, 1H), 2.03 (m, 1H), 1.79 (dd, *J* = 4.7, 13.0 Hz, 1H), 1.73 (dt, *J* = 3.8, 13.2 Hz, 1H), 1.70-1.32 (bands, 10H), 1.14 (dq, *J* = 3.8, 13.3 Hz, 1H), 0.88-0.83 (bands, 17H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8, 159.1, 130.7, 129.1, 113.8, 97.8, 73.4, 71.7, 69.2, 67.8, 65.8, 55.2, 46.6, 43.9, 36.5, 34.9, 34.9, 31.4, 30.2, 25.9, 25.9, 25.9, 18.7, 18.1, 9.5, 4.8, -4.4, -4.4. IR(film):2936, 2856, 2721, 1729, 1613, 1586, 1514, 1463, 1440, 1387, 1357, 1302, 1249, 1180, 1115. $[\alpha]_D^{25}$ (c = 1.65, CH_2Cl_2): -73

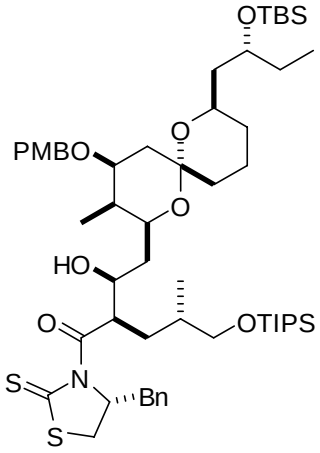
MS(ESI) for $C_{30}H_{50}O_6Si$ [M+H] calc: 535.35 found: 535.5 [M+Na] calc: 557.33 found: 557.4.



Acylated Thiazolidine Thione 4.8:

A 100 mL round bottomed flask was charged with carboxylic acid **4.52** (1.5 g, 5.2 mmol)**,** methylene chloride (20 mL), DCC (1.3 g, 6.3 mmol), and DMAP (63 mg, 0.52 mmol). Thiazolidinethione (1.3 g, 6.3 mmol) was then added in one portion. The reaction was allowed to stir for 2 h, cooled to -78 °C and filtered through celite. The mixture was concentrated in vacuo and brought up in hexanes, cooled, and filtered again to remove the byproducts from the reaction. Flash column chromatography then provided the desired acylated auxiliary (1.62 g, 3.38 mmol) in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (bands, 5H), 5.33 (ddd, *J* = 3.9, 6.9, 10.6 Hz, 1H), 3.55-3.46 (bands, 2H), 3.42 (ddd, *J* = 5.3, 10.1, 17.3 Hz, 1H), 3.33 (ddd, *J* = 0.9, 7.2, 11.5 Hz, 1H), 3.21-3.09 (bands, 2H), 3.00 (dd, *J* = 10.6, 13.1 Hz, 1H), 2.83 (d, *J* =11.6 Hz, 1H), 1.78 (dddd, *J* = 5.3, 5.3, 10.6, 13.2 Hz, 1H), 1.66 (dddd, *J* = 5.9, 5.9, 5.9, 12.5 Hz, 1H), 1.55 (dddd, *J* = 5.2, 7.7, 10.0, 13.1 Hz, 1H), 1.10-1.00 (bands, 21H), 0.91 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 174.2, 136.5, 129.4, 128.8, 127.1, 68.6, 68.2, 36.7, 36.3, 35.5, 31.8, 28.1, 17.9, 16.6, 11.9. IR(film): 2942, 2865, 1698, 1496, 1456, 1363, 1341, 1293, 1264, 1190, 1164, 1137, 1103. $[\alpha]_D^{27}$ (c = 0.95, CH_2Cl_2): -119. ESI-MS: $C_{25}H_{41}NO_2S_2Si$: calc (M+Na): 502.22 obs: 502.4.

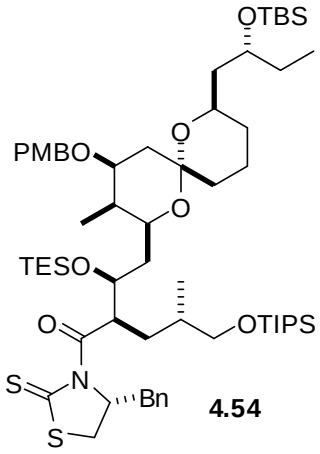


Aldol Adduct from 4.8 and 4.9:

A round bottomed flask was charged with thiazolidine thione **4.8** (888 mg, 1.85 mmol) and methylene chloride (17 mL) and cooled to 0 °C. Titanium (IV) chloride (0.18 mL, 1.68 mmol) was then added dropwise and the reaction stirred for 5 minutes. (-)-Sparteine (0.50 mL, 2.18 mmol) was then added dropwise and the reaction was stirred for 30 minutes. *N*-methylpyrrolidinone (0.21 mL, 2.18 mmol) was then added dropwise and the reaction stirred an additional 15 minutes. The reaction was then cooled to – 78 °C and aldehyde **4.9** (764 mg, 1.43 mmol) in methylene chloride (5 mL) was then added via cannula. The reaction was stirred for 15 minutes at – 78 °C and warmed to 0 °C for 1h. The reaction was then quenched via the addition of saturated ammonium chloride. The layers were separated, and the aqueous layer was then extracted with methylene chloride (x3), washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography yielded the desired aldol adduct (1.24 g, 1.22 mmol) as a bright yellow oil in 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.19 (bands, 7H), 6.81 (d, J = 8.5 Hz, 2H), 5.31 (ddd, J = 3.8, 6.9, 10.7 Hz, 1H), 5.24 (m, 1H), 4.36 (AB_q, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 50.5 Hz, 2H), 4.15 (dt, J = 5.1, 10.0 Hz, 1H), 3.85 (bands, 2H), 3.76 (s, 3H), 3.67-3.62 (bands, 1H), 3.57-3.49 (bands, 2H), 3.52 (d, J = 3.4 Hz, 1H), 3.28 (dd, J = 7.3, 11.4 Hz, 1H), 3.23 (dd, J = 3.2, 13.2 Hz, 1H), 3.02 (dd, J = 10.8, 13.0 Hz, 1H), 2.81 (d, J = 11.5 Hz, 1H), 2.67 (d, J = 3.6 Hz, 1H), 1.92 (m, 1H), 1.82-1.30 (bands, 17H), 1.15 (m, 1H), 1.11-0.95 (bands, 21H), 0.93 (d, J = 5.6 Hz, 3H), 0.85-0.82 (bands, 12H), 0.80 (t, J = 7.5 Hz, 3H), 0.00 (s, 3H), - 0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.4, 176.3, 158.9, 136.5, 130.8, 129.3, 129.0, 128.8, 127.1, 113.7, 97.3, 77.1, 73.8, 72.7, 70.2, 69.4, 68.9, 67.8, 67.4, 66.1, 55.2, 46.7, 43.5, 36.7, 36.6, 36.6, 35.5, 34.9, 34.1, 31.7, 30.6, 29.9, 25.9, 19.0, 18.1, 18.0, 17.4, 11.9, 9.9, 4.6, -4.1, -4.2. IR(film):3476, 2939, 2864, 1695, 1613, 1595, 1513, 1462, 1363, 1341, 1293, 1250,

1163, 1134. $[\alpha]_D^{27}$ (c = 0.85, CH_2Cl_2): -73. ESI-MS: $C_{55}H_{91}NO_8S_2Si_2$: calc (M+Na): 1036.56 obs: 1036.7.



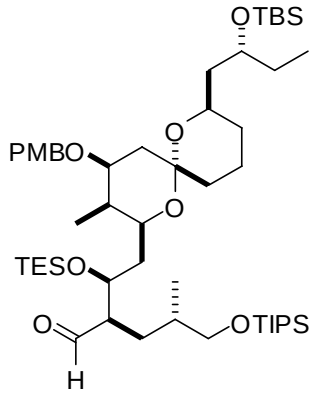
4.54

TES Ether 4.54:

A round-bottomed flask was charged with aldol adduct from the previous reaction (1.21 g, 1.19 mmol), methylene chloride (15 mL), and 2,6-lutidine (0.28 mL, 2.38 mmol). The reaction was cooled to 0 °C and triethylsilyl triflate (0.27 mL, 1.19 mmol) was added dropwise. The reaction was stirred for 1 hour and quenched via the addition of saturated sodium bicarbonate. The layers were separated and the aqueous layer extracted with methylene chloride (x2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided TES ether **4.54** (1.2 g, 1.04 mmol) as a bright yellow oil in 87% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.22 (bands, 7H), 6.83 (d, *J* = 6.8 Hz, 2H), 5.22 (ddd, *J* = 3.6, 6.7, 10.6 Hz, 1H), 4.92 (m, 1H), 4.41 (AB_q, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 62.4 Hz, 2H), 3.96 (ddd, *J* = 3.6, 3.6, 7.2 Hz, 1H), 3.89 (dt, *J* = 4.6, 11.9 Hz, 1H), 3.77 (s, 3H), 3.69-3.62 (bands, 2H), 3.57 (dd, *J* = 5.4, 9.4 Hz, 1H), 3.56 (m, 1H), 3.45 (dd, *J* = 6.4, 9.4 Hz, 1H), 3.25 (m, 1H), 3.08 (AB_q, J_{AB} = 11.4 Hz, $\Delta\nu_{AB}$ = 214.4 Hz, 2H), 3.02 (dd, *J* = 8.9, 13.0 Hz, 1H), 2.02

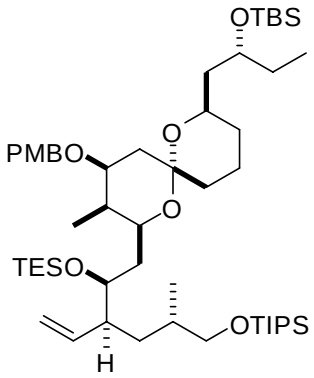
(m, 1H), 1.91 (ddd, J = 3.2, 6.5, 14.8 Hz, 1H), 1.87-1.42 (bands, 14H), 1.40-1.30 (bands, 2H), 1.30-1.21 (bands, 2H), 1.15 (dq, J = 3.0, 13.1 Hz, 1H), 1.11-1.01 (bands, 22H), 0.95-0.90 (bands, 13H), 0.89-0.83 (bands, 17H), 0.58 (q, J = 7.8 Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 175.7, 158.9, 136.6, 130.9, 129.4, 129.0, 128.8, 127.0, 113.6, 97.3, 77.1, 74.0, 73.3, 70.8, 69.6, 69.3, 69.1, 68.6, 68.1, 55.2, 47.7, 44.1, 38.4, 36.9, 36.4, 35.5, 34.0, 31.7, 31.3, 30.8, 30.5, 25.8, 18.6, 18.0, 17.9, 17.0, 11.9, 9.6, 6.9, 5.2, 4.5, -4.4, -4.5. IR(film): 2953, 2866, 1698, 1614, 1513, 1462, 1438, 1362, 1340, 1293, 1250, 1165, 1112. $[\alpha]_D^{24}$ (c = 0.95, CH_2Cl_2): -71. ESI-MS:



Aldehyde from DIBAL reduction:

A round bottomed flask was charged with TES ether **4.54** (1.32 g, 1.17 mmol) and methylene chloride (12 mL) and cooled to – 78 °C. DIBAL (1.0 M in heptane) was added dropwise until the yellow color disappeared (indicating deacylation of thiazolidinethione). The solution was then immediately quenched through the addition of saturated potassium/sodium tartrate. The mixture was warmed to room temperature and stirred for 1 hour until the layers could be separated. The layers were then separated. The aqueous layer was then extracted with methylene chloride (x2), the organic layers combined and dried over sodium sulfate. This was then filtered and concentrated in vacuo. Flash column chromatography provided the aldehyde (770 mg, 0.84 mmol) as a colorless oil in 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (d, J = 1.9 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.40 (AB_q, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 59.0 Hz, 2H), 4.18 (ddd, J = 2.6, 4.1, 6.9 Hz, 1H), 3.89 (dt, J = 4.7, 11.8 Hz, 1H), 3.78 (s, 3H), 3.69 (m, 1H), 3.64 (m, 1H), 3.55-3.43 (bands, 3H), 2.68 (m, 1H), 2.50-1.95 (bands, 2H), 1.78-1.65 (bands, 5H), 1.64-1.32 (bands, 12H), 1.19-0.98 (bands, 23H), 0.94-0.86 (bands, 25H), 0.83 (d, J = 6.8 Hz, 3H), 0.55 (q, J = 8.0 Hz, 6H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.9, 159.0, 130.8, 129.0, 113.7, 97.5, 73.8, 72.5, 71.2, 69.9, 69.1, 67.7, 55.7, 55.2, 44.1, 38.3, 35.7, 35.0, 30.9, 30.0, 26.6, 25.8, 18.0, 17.9, 17.0, 11.9, 9.5, 6.7, 4.9, 4.9, 4.7, -4.5, -4.7. IR(film): 2953, 2867, 1722, 1614, 1514, 1463, 1384, 1249, 1180. $[\alpha]_D^{27}$ (c = 0.15, CH_2Cl_2): -8 MS (ESI):

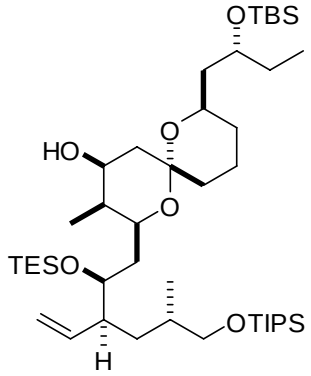


Alkene from Wittig Reaction with Aldehyde:

A round bottomed flask was charged with toluene (20mL) and methyltriphenylphosphium bromide (1.43 g, 4.0 mmol). Potassium *tert*-butoxide (1M in THF, 3.0 mL, 3.0 mmol) was then added dropwise and the solution turned bright yellow. The solution was stirred for 30 minutes at which point the aldehyde from the previous reaction (770 mg, 0.84 mmol) was added as a solution in toluene (4 mL). The reaction was stirred for 15 minutes and quenched through the addition of saturated ammonium chloride. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organics were dried over

sodium sulfate, filtered and concentrated in vacuo. Flash column chromatography provided the alkene (760 mg, 0.83 mmol) in 98 % yield.

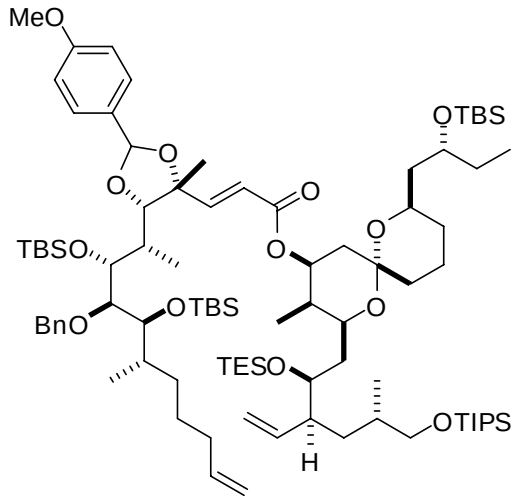
^{1}H NMR (500 MHz, $CDCl_3$): δ (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 5.79 (ddd, *J* = 8.8, 10.2, 17.4 Hz, 1H), 5.03 (dd, *J* = 1.8, 10.4 Hz, 1H), 4.96 (dd, *J* = 1.4, 17.2 Hz, 1H), 4.39 (AB_q, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 65.3 Hz, 2H), 3.88 (dt, *J* = 5.7, 11.8 Hz, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.67-3.57 (bands, 3H), 3.50 (m, 1H), 3.33 (dd, *J* = 7.5, 9.4 Hz, 1H), 2.32 (m, 1H), 2.02 (m, 1H), 1.87-1.77 (bands, 2H), 1.76 (dd, *J* = 4.7, 13.0 Hz, 1H), 1.70-1.32 (bands, 14H), 1.25-1.11 (bands, 3H), 1.10-1.00 (bands, 22H), 0.96-0.91 (bands, 12H), 0.88-0.82 (bands, 16H), 0.58 (q, *J* = 8.0 Hz, 6H), 0.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 140.1, 131.0, 129.1, 115.2, 113.7, 97.5, 77.2, 76.1, 74.1, 71.5, 70.4, 69.1, 67.9, 67.7, 55.2, 47.8, 44.3, 37.6, 36.8, 35.8, 35.2, 33.7, 32.4, 31.1, 30.3, 25.9, 18.8, 18.4, 18.1, 12.0, 9.6, 7.0, 5.3, 4.7, -4.3, -4.5. IR(film):2952, 2866, 1614, 1514, 1463, 1417, 1383, 1302, 1249, 1181. $[\alpha]_D^{24}$ (c = 0.60, CH_2Cl_2): -18. MS (ESI) for $C_{52}H_{98}O_7Si_3$ [M+Na]: calc. 941.65 found 941.8.



4.3

Alcohol 4.3:

A 50 mL round-bottomed flask was charged with the PMB ether from the previous reaction (735 mg, 0.80 mmol), methylene chloride (10 mL), pH 7 buffer (1 mL), and cooled to 0 °C. DDQ (200 mg, 0.88 mmol) was then added and the reaction was stirred vigorously for 1 hour. The reaction was quenched through the addition of sodium bicarbonate. The layers were separated and the aqueous was extracted with methylene chloride (x2), the layers combined, dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided alcohol **4.3** (533 mg, 0.67 mmol, 85% yield) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77 (ddd, *J* = 9.7, 9.7, 18.3 Hz, 1H), 4.98 (d, *J* = 10.3 Hz, 1H), 4.94 (d, *J* = 17.2 Hz, 1H), 4.14 (dt, *J* = 5.5, 11.7 Hz, 1H), 3.72 (m, 1H), 3.67 (m, 1H), 3.63-3.57 (bands, 2H), 3.50 (m, 1H), 3.32 (dd, *J* = 7.9, 8.9 Hz, 1H), 2.32 (t, *J* = 8.9 Hz, 1H), 1.87-1.32 (bands, 16H), 1.21-1.13 (m, 2H), 1.05-1.01 (bands, 21H), 0.95-0.91 (bands, 12H), 0.87 (d, 3H), 0.86 (s, 9H), 0.80 (d, 3H), 0.56 (q, *J* = 8.0 Hz, 6H), 0.03 (s,3H), 0.02 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.9, 115.0, 97.3, 76.0, 71.3, 70.4, 67.8, 67.7, 67.0, 47.7, 44.2, 39.0, 38.9, 37.7, 35.1, 33.6, 32.1, 31.0, 30.2, 31.0, 25.7, 18.7, 18.3, 17.9, 11.9, 9.5, 6.9, 5.1, 4.1, -4.5, -4.6. IR(film):3357, 2955, 2867, 1463, 1416, 1383, 1253, 1225, 1098. $[\alpha]_D^{24}$ (c = 0.95, CH_2Cl_2): -16° MS (ESI) for $C_{44}H_{90}O_6Si_3$ [M+Na]: calc. 821.59 found 821.7.

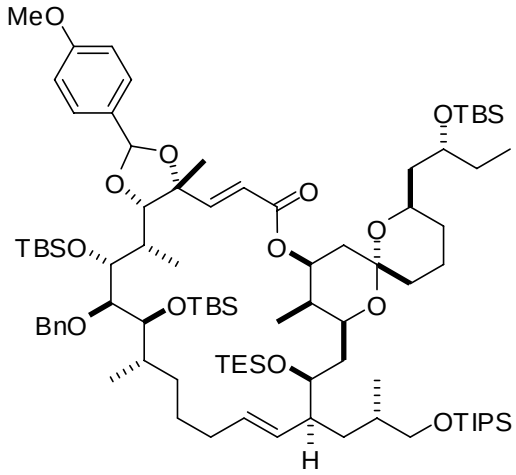


Diene from Esterification:

A round bottomed flask was charged with carboxylic acid **5.80** (21 mg, 0.026 mmol), toluene (1 mL), and Hünig's base (15 μL, 0.074 mmol). 2,4,6-trichlorobenzoyl chloride (7 μL, 0.0435 mmol) was then added dropwise. 4-Dimethylaminopyridine (5 mg, 0.0435 mmol) was then added. Alcohol **4.2** (23 mg, 0.028 mmol) was then added as a solution in toluene (1 mL). The reaction was then allowed to stir for 2 hours. The reaction was then quenched via the addition of saturated sodium bicarbonate solution. The layers were separated and the aqueous was extracted with ethyl acetate (x2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. Flash column chromatography provided the ester (40 mg, 0.025 mmol) in 97% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (bands, 4H), 7.22 (m, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 15.5 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.93 (d, *J* =15.5 Hz, 1H), 5.82-5.73 (bands, 2H), 5.28 (dt, *J* = 4.9, 12.1 Hz, 1H), 5.24 (s, 1H), 5.05-4.88 (bands, 4H), 4.68 (AB_q, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 117.1 Hz, 2H), 4.36 (s, 1H), 3.79 (s, 3H), 3.77 (m, 1H), 3.73-3.69 (bands, 2H), 3.67-3.56 (bands, 3H), 3.50 (m, 1H), 3.41 (dd, *J* = 3.0, 7.2 Hz, 1H), 3.32 (dd, *J* = 7.6, 9.1 Hz, 1H), 2.34 (m, 1H), 2.08-1.95 (bands, 4H), 1.87-1.79 (bands, 2H), 1.75-1.32 (bands, 22H), 1.22-0.99 (bands, 22H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.95-0.84 (bands, 45H), 0.79 (d, *J* = 6.9 Hz, 3H), 0.56 (q, *J* = 7.8 Hz, 6H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.00 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2, 160.2, 149.4, 141.0, 140.0, 138.8, 129.3, 128.3, 127.8, 126.4, 126.1, 120.8, 114.9, 114.2, 113.9, 101.3, 97.2, 81.3, 79.7, 77.1, 76.0, 75.9, 74.8, 73.4, 71.3, 71.3, 71.3, 70.3, 70.0, 69.9, 69.9, 67.7, 55.2, 55.1, 47.7, 44.1, 37.5, 37.0, 35.9, 35.9, 35.6, 35.5, 35.0, 34.2, 33.6, 32.0, 30.9, 30.2, 26.8, 26.1, 26.0, 26.0, 25.8, 25.8, 24.2, 24.1, 18.3, 18.3, 18.2, 18.0, 18.0, 17.8, 11.9, 10.8, 9.5, 9.5, 6.9, 5.1, -3.4, -3.5, -

4.4, -4.4, -4.6, -4.6. IR(film): 3074, 2953, 2932, 2862, 1720, 1640, 1616, 1519, 1462, 1387, 1306, 1252, 1170. $[\alpha]_D^{26}$ (c = 0.8, CH_2Cl_2): -36. ESI-MS: $C_{89}H_{160}O_{13}Si_5$: calc (M+Na): 1600.07 obs: 1600.0.



5.81

Macrolactone 5.81:

A round-bottomed flask was charged with toluene (100 mL) and brought to reflux while bubbling argon through to degas. After 15 minutes, the diene from the esterification reaction (16 mg, 0.010 mmol) was added as a solution in toluene. Grubbs' 2nd generation catalyst **4.44** (2.5 mg, 0.0027 mmol) was then added and the reaction was allowed to proceed at 110° C for 10 minutes. At this time, the solution was removed from heat and immersed in an ice bath while air was bubbled through the reaction. The ice bath was removed and the air was bubbled through for 20 minutes to kill the catalyst. The solution was concentrated in vacuo. Flash column chromatography then provided the desired macrolactone **5.81** (6 mg, 0.0038 mmol) in 40% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.20 (bands, 7H), 6.91 (d, *J* = 15.4 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.02 (d, *J* = 15.6 Hz, 1H), 5.59 (s, 1H), 5.42-5.24 (bands, 3H), 4.72 (AB_q, J_{AB} =

12.4 Hz, $\Delta\nu_{AB}$ = 63.4 Hz, 2H), 3.99 (m, 1H), 3.94 (d, *J* = 6.9 Hz, 1H), 3.81 (m, 1H), 3.79 (s, 3H), 3.69 (m, 1H), 3.64 (m, 1H), 3.61 (dd, *J* = 4.8, 9.7 Hz, 1H), 3.57-3.50 (bands, 2H), 3.44 (dd, *J* = 2.0, 6.7 Hz, 1H), 3.31 (dd, *J* = 8.2, 8.9 Hz, 1H), 2.24-2.03 (bands, 3H), 1.97-1.91 (bands, 2H), 1.87-1.75 (bands, 4H), 1.70 (ddd, *J* = 4.4, 7.9, 13.2 Hz, 1H), 1.68-1.49 (bands, 16H), 1.47-1.31 (bands, 9H), 1.30-1.15 (bands, 5H), 1.15-0.75 (bands, 88H), 0.59 (q, *J* = 7.9 Hz, 6H), 0.12 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), -0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8, 160.4, 148.1, 139.5, 132.2, 130.9, 129.1, 128.4, 128.3, 127.9, 126.6, 126.5, 126.3, 126.2, 121.4, 113.6, 101.3, 97.4, 87.5, 81.1, 77.2, 77.1, 74.0, 71.5, 70.2, 67.9, 67.8, 67.7, 55.3, 46.1, 43.9, 36.9, 36.8, 36.2, 35.7, 35.1, 35.0, 34.4, 34.3, 33.7, 33.0, 32.0, 31.2, 30.3, 30.2, 29.7, 27.0, 26.3, 26.2, 26.1, 25.9, 24.4, 18.7, 18.6, 18.4, 18.3, 18.1, 18.0, 18.0, 12.0, 9.5, 7.2, 7.0, 5.7, 5.1, 5.0, -3.1, -3.2, -3.3, -3.7, -4.2, -4.4. IR(film): 2930, 2859, 1722, 1615, 1518, 1463, 1442, 1387, 1361, 1304, 1252, 1101. $[\alpha]_D^{26}$ (c = 0.30, CH_2Cl_2): -27. ESI-MS: $C_{87}H_{156}O_{13}Si_5$: calc (M+Na): 1572.04 obs: 1572.0.

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