



Studies towards the synthesis of the C(8)-C(15) fragment of tedanolide
by David James Cole

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in
Chemistry

Montana State University

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Abstract:

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Progress towards the synthesis of tedanolide is described with specific attention given to the synthesis of the C(8)-C(15) portion of the molecule. The approach involves the use of rigid bicyclic ring systems to control the stereocenters found in the natural product. The approach contained herein has not yet led to the total synthesis of tedanolide but has led to a precursor of the 18-membered ring.

STUDIES TOWARDS THE SYNTHESIS OF THE
C(8)-C(15) FRAGMENT OF TEDANOLIDE

by

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A thesis submitted in partial fulfillment
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in

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APPROVAL

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David James Cole

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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LIST OF ABBREVIATIONS

Ac	acetyl
Bn	benzyl
br	broad
Bu	butyl or normal-butyl
n-Bu	normal-butyl
tBu	tert-butyl
c	concentration
cat	catalytic
COSY	correlated spectroscopy
cm ⁻¹	wavenumber
CSA	camphorsulfonic acid
°C	degrees Celsius
CI	chemical ionization
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEIPS	diethylisopropylsilyl
DIBAH	diisobutylaluminium hydride
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide

LIST OF ABBREVIATIONS - CONTINUED

DMP	dimethoxyphenol
DMPM	3,4-dimethoxybenzyl or dimethoxyphenylmethyl
dt	doublet of triplets
ee	enantiomeric excess
EI	electron impact
equiv	equivalents
Et	ethyl
g	gram
h	hour
HRMS	high resolution mass spectrometry
Hz	hertz
Ipc	isopinocamphenyl
IR	infrared
J	coupling constant in hertz
kg	kilogram
KHMDS	potassium hexamethyl disilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m	multiplet
M	molarity

LIST OF ABBREVIATIONS - CONTINUED

M ⁺	parent ion peak
mCPBA	meta-chloroperbenzoic acid
Me	methyl
M/e	mass to charge ratio
mg	milligram
MHz	megahertz
min	minutes
mL	milliliter
μg	microgram
μL	microliter
μm	micrometer
mmol	millimole
MOM	methoxymethyl
MP	methoxyphenol
Ms	methanesulfonyl
MS	mass spectrum or molecular sieves
NMR	nuclear magnetic resonance
OAc	acetoxy
PCC	pyridinium chlorochromate
Ph	phenyl

LIST OF ABBREVIATIONS - CONTINUED

Piv	pivaloyl
PMB	4-methoxybenzyl
i-Pr	iso-propyl
ppm	parts per million
PPTS	pyridinium para-toluenesulfonate
py	pyridine
Rf	retention or retardation factor
rt	room temperature
s	singlet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	tert-butyldimethylsilyl
TBDPS	tert-butyldiphenylsilyl
TES	triethylsilyl
Tf	Triflate
THF	tetrahydrofuran
TIPS	tert-butyldiisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
p-Ts	para-toluenesulfonyl

ABSTRACT

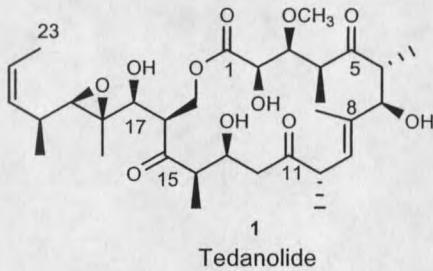
Tedanolide is a 18-membered macrolide of marine origin which displays antitumor activity and presents a synthetic challenge. To date, the total synthesis of tedanolide has not been reported however the synthesis of 13-deoxytedanolide, another closely related macrolide isolated from a different sea sponge, was recently accomplished.

Progress towards the synthesis of tedanolide is described with specific attention given to the synthesis of the C(8)-C(15) portion of the molecule. The approach involves the use of rigid bicyclic ring systems to control the stereocenters found in the natural product. The approach contained herein has not yet led to the total synthesis of tedanolide but has led to a precursor of the 18-membered ring.

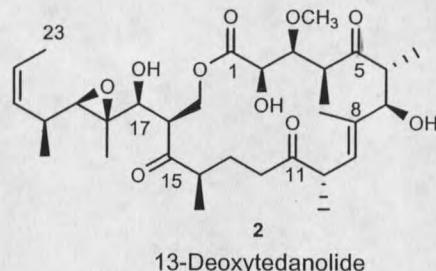
INTRODUCTION

Background

Tedanolide **1** was first isolated in 1984 by Schmitz and co-workers¹ from the sea sponge *Tedania ignis* also known as the fire sponge because of the burning sensation caused upon exposure to skin. The extracts from this sponge are of interest because they exhibited cytotoxicity as well as in vivo tumor inhibition. Tedanolide, which was believed to be a metabolite due to its presence in small amounts, was found in sponge specimens collected off the coast of Florida. Tedanolide was isolated using a series of methanol and chloroform extractions. Schmitz and co-workers found that tedanolide increased the lifespan of mice implanted with lymphocytic leukemia cells 23% at 1.56 µg/kg.² In 1991, Fusetani and co-workers isolated 13-deoxytedanolide **2** from the sea sponge *Mycale adhaires* collected off the coast of Hiburi, a small island southwest of Tokyo.³ 13-Deoxytedanolide was also a remarkably cytotoxic metabolite.³



Tedanolide



13-Deoxytedanolide

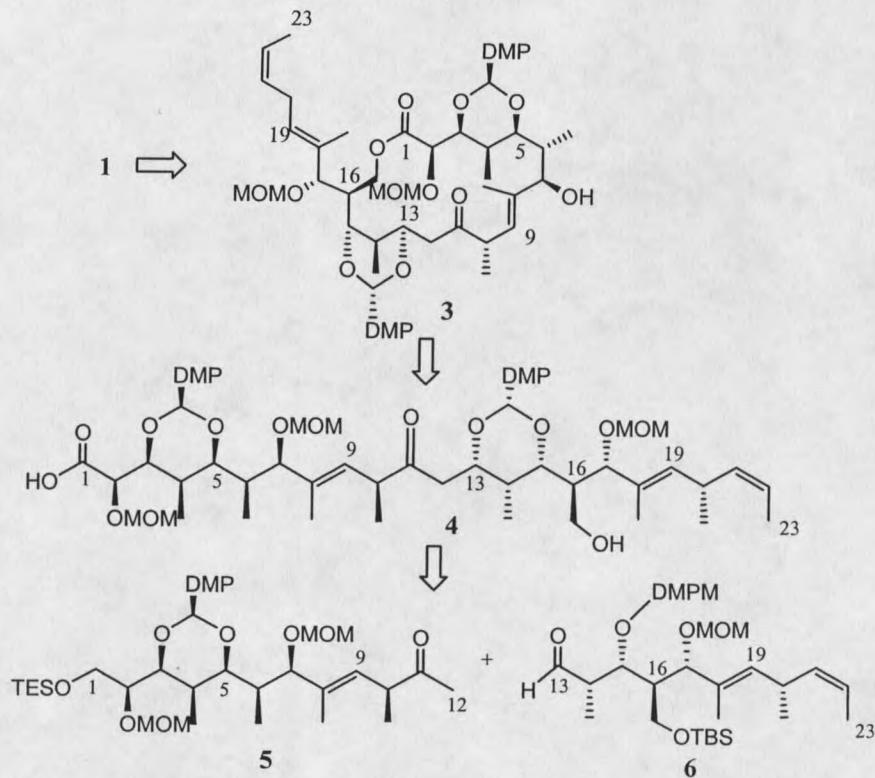
The structures of tedanolide and 13-deoxytedanolide differ from other macrolides in that the 18-membered lactone is constructed using a primary (instead of the usual

secondary) hydroxyl group.⁴ Structural features which make this molecule synthetically challenging are the six readily epimerizable centers and the high degree of functionality on the carbon backbone.⁵

Due to the interesting and highly functionalized structure of the tedanolides, many research groups have taken up the synthetic challenge these molecules present.^{2,4-8} To date, there has been no reported total synthesis of tedanolide and only one successful synthesis of 13-deoxytedanolide.⁵ Most groups, including those of Roush, Yonemitsu, and Taylor, have envisioned the C(12)-C(13) bond being formed from an aldol reaction.^{2,4,6-8} All the groups working on the tedanolides have planned to use a Yamaguchi macrolactonization⁹ in order to form the 18-membered lactone.^{2,4-8}

Using computer modeling, the Yonemitsu strategy first involved finding a suitable seco-acid to undergo lactonization. Trying to keep the conformation as close as possible to the desired lactone, Yonemitsu found that the seco-acid 4 should undergo macrolactonization and give rise to intermediate 3 (Scheme 1). The seco-acid was seen to come from a Felkin controlled aldol reaction between the C(1)-C(12) and the C(13)-C(23) fragments, **5** and **6** respectively. Unfortunately the aldol reaction gave rise to a mixture of the desired Felkin aldol product **4** and the C(13) epimer. The resulting ratios varied from 1:1.2-1:1.9 with the undesired C(13) epimer as the major product.^{4a}

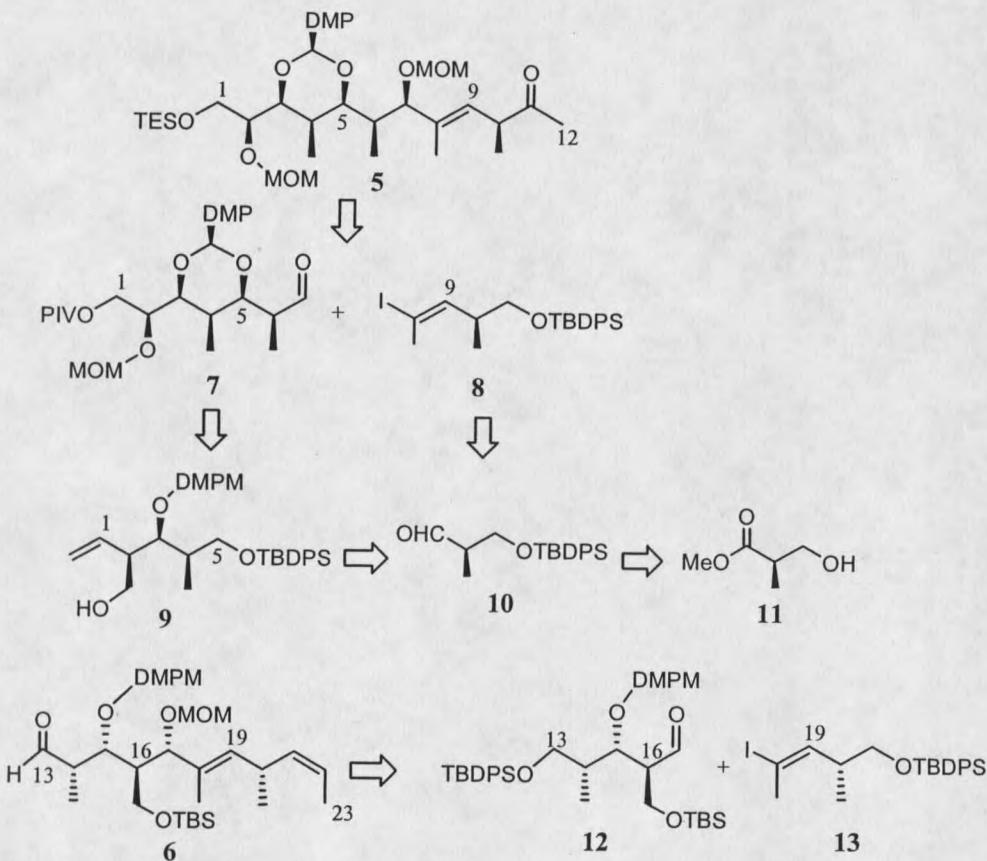
Scheme 1. Later Steps in Yonemitsu's Synthetic Strategy



Yonemitsu prepared the C(1)-C(12) fragment **5** by tert-butyl lithium mediated reaction of vinyl iodide **8** with aldehyde **7**. The desired C(13) stereocenter is expected on the basis of Felkin-Ahn control (Scheme 2). Indeed the desired alcohol was the major product.^{4a} Both the C(1)-C(7) **7** and the C(8)-C(11) **8** fragments used in this coupling were generated from chiral aldehyde **10** which was derived from (R)-3-hydroxy-2-methylpropionate **11**.^{4a} The C(13)-C(23) fragment **6** was formed via tert-butyl lithium mediated addition of vinyl iodide **13** to aldehyde **12** giving rise to the undesired cramp product. The resulting alcohol was oxidized and reduced thus giving rise to the desired alcohol.^{4c} Yonemitsu prepared the vinyl iodides **8** and **13** by reaction of the

corresponding alkyne, generated using the Corey-Fuchs procedure,^{11c} with Schwartz reagent.^{10,4}

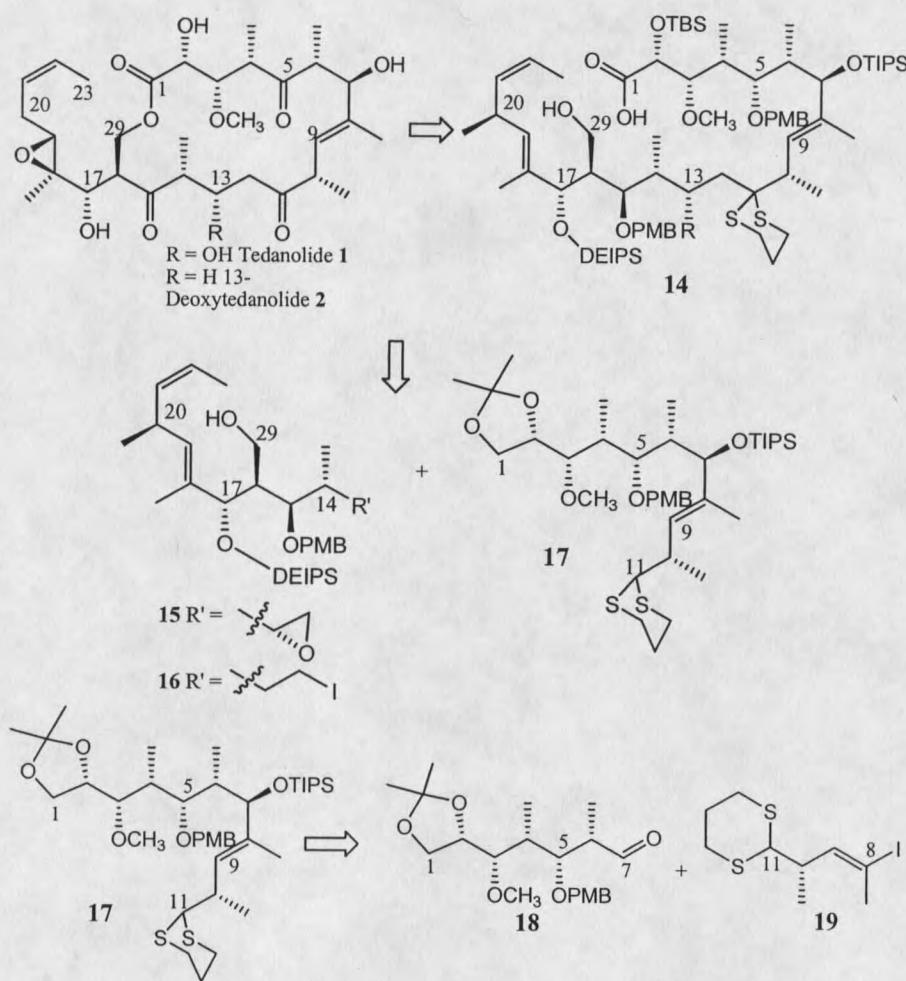
Scheme 2. Early Steps in Yonemitsu's Synthetic Strategy



In the successful synthesis of 13-deoxytedanolide **2**, the Smith group employed dithiane **17** and iodide **16** (Scheme 3). For the synthesis of tedanolide it was envisioned that the C(13) hydroxyl of tedanolide would be formed from nucleophilic ring opening of an epoxide at C(12) and C(13) (see compound **15**).⁵ The C(1)-C(11) fragment was generated from tert-butyl lithium mediated addition of the C(8)-C(11) portion **19** to

aldehyde **18**. The correct stereochemistry at C(7) was expected on the basis of Felkin-Ahn control. Both the C(1)-C(7) fragment **18** and the C(13)-C(23) fragment **15** were obtained from iterative Evans aldol condensations.⁵

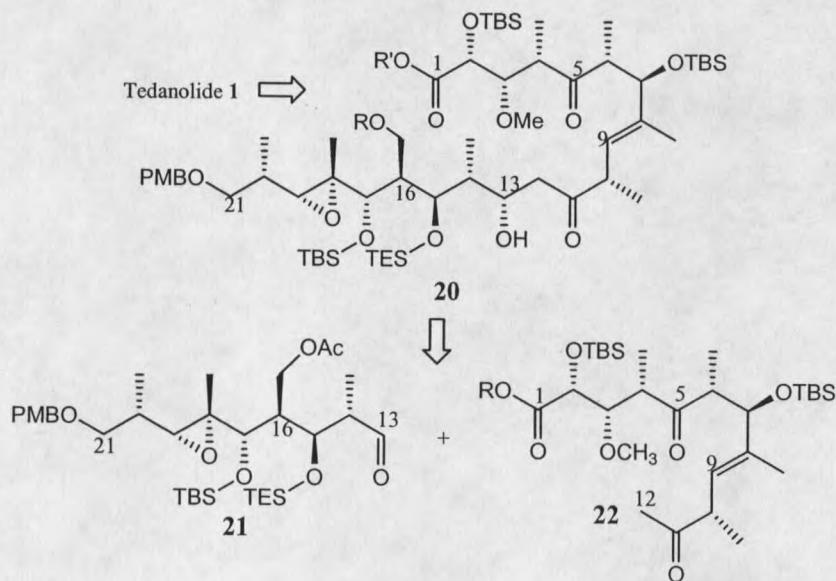
Scheme 3. The Smith Synthetic Strategy

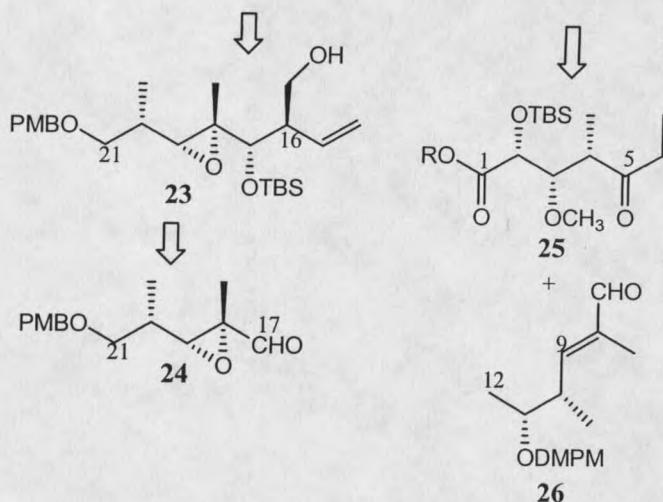


Roush envisioned forming tedanolide from seco-acid **20** which was to be prepared from the corresponding C(5)-C(21) fragment (Scheme 4). The seco-acid was prepared by a Felkin-Ahn controlled aldol reaction to form the C(13) hydroxyl group

with the desired stereochemistry. This strategy was based on earlier studies in the Roush group which indicated that aldehyde **21** should give rise to the syn stereochemistry. The C(13)-C(21) fragment **21** was formed from alkene **23**. This transformation involved acylation of the alcohol, oxidative cleavage of the olefin using osmium tetroxide in the presence of periodate, asymmetric crotylboration of the resulting aldehyde, followed by protection of the resulting alcohol as the TBS ether and finally another oxidative cleavage of the alkene. Alkene **23** was synthesized from aldehyde **24** using a chiral crotonate imide. The C(1)-C(12) fragment **22** was obtained from a titanium catalyzed coupling of the C(1)-C(6) ester-ketone **25** with enal **26**. The formation of ester-ketone **25** from methyl-3-oxopentanoate involved allyl stannane addition, oxidative cleavage of the olefin, followed by oxidation and esterification at the C(1) carbon.⁶

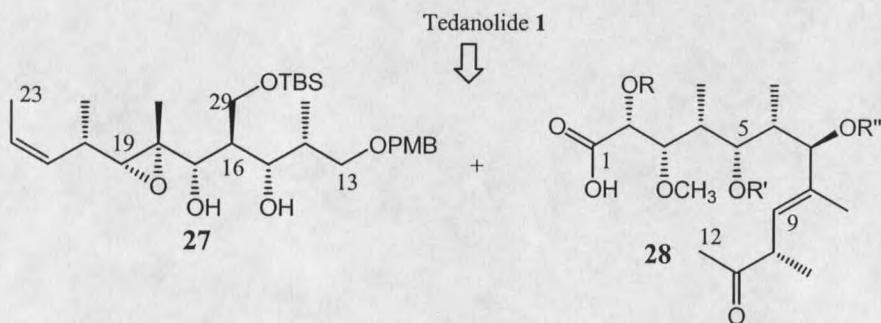
Scheme 4. The Roush Synthetic Strategy

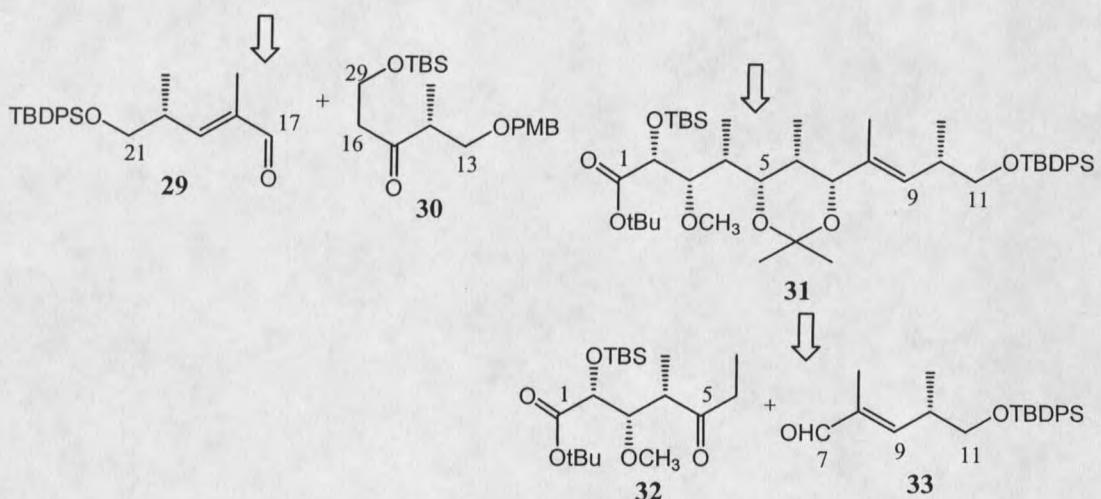




Loh's strategy involved a Yamaguchi macrolactonization to construct the macrolide ring and an aldol reaction between ketone **28** and the C(13) aldehyde derived from **27** to form the C(12)-C(13) bond (Scheme 5). Ester **31** was prepared using a syn-syn selective boron-mediated aldol reaction between **32** and **33** to form the C(6)-C(7) bond. The C(16)-C(17) bond on the C(13)-C(21) fragment **27** was also constructed using a boron-mediated aldol.²

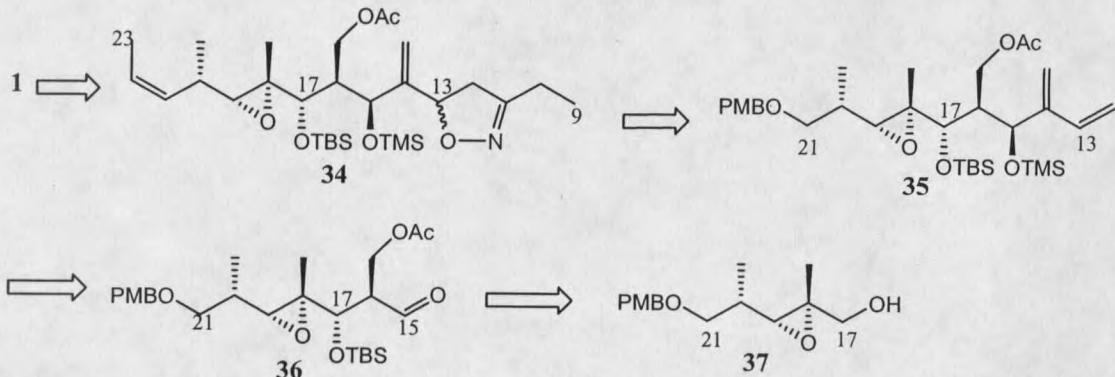
Scheme 5. The Loh Synthetic Strategy





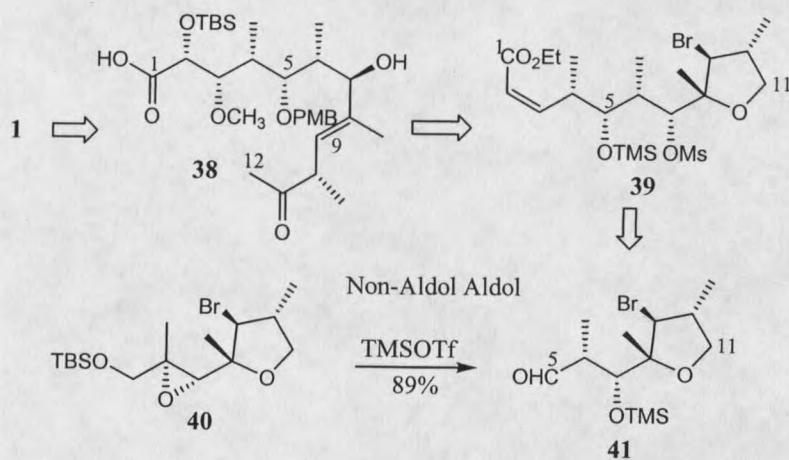
The Taylor group has done work towards the synthesis of the C(9)-C(21) portion of tedanolide (Scheme 6). Their approach was to form the corresponding β -hydroxyketone from isoazoline **34**. This isoazoline **34** was formed by reacting diene **35** with a nitrile oxide resulting in a 3:1 mixture of the C(13) diastereomers. This isoazoline was transformed into **34** by paramethoxybenzyl group cleavage, oxidation to the aldehyde, followed by the Wittig reaction to install the Z-olefin. Diene **35** was formed in moderate yield, as a single diastereomer, by reaction of aldehyde **36** with a homoallenylboron. Aldehyde **36** was synthesized from **37** by oxidation to the aldehyde followed by treatment with Evans oxazolidinone followed by periodate cleavage of the resulting olefin. The synthesis of **37** from methyl (S)-3-hydroxy-2-methylpropionate involved vinyl lithium attack of the C(19) aldehyde followed by an allylic rearrangement and asymmetric epoxidation.⁷

Scheme 6. The Taylor Synthetic Strategy



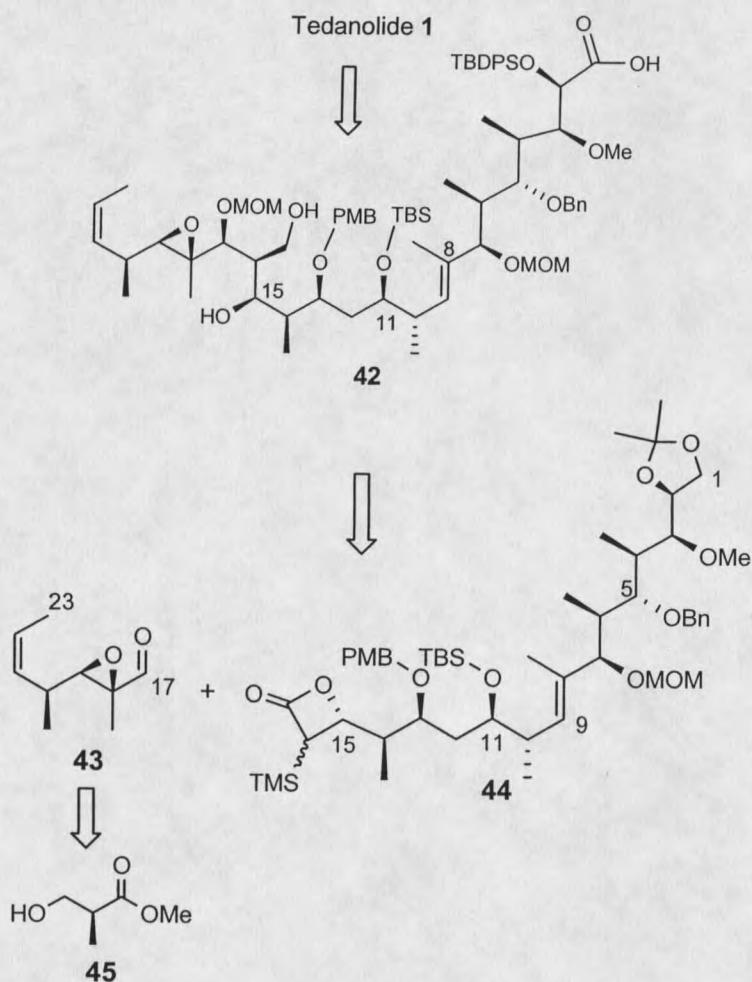
Finally, the Jung group has also published some work on the synthesis tedanolide in order to showcase their non-aldol aldol reaction. This work focused on the synthesis of the C(1)-C(11) fragment (Scheme 7) and went as far as the vinylogous ester **39**. The non-aldol aldol involves lewis acid catalyzed opening of epoxide **40** forming the more stable carbocation. The protected alcohol undergoes rearrangement to the aldehyde via a 1,2-hydride shift.⁸

Scheme 7. The Jung Synthetic Strategy

Synthetic Strategy

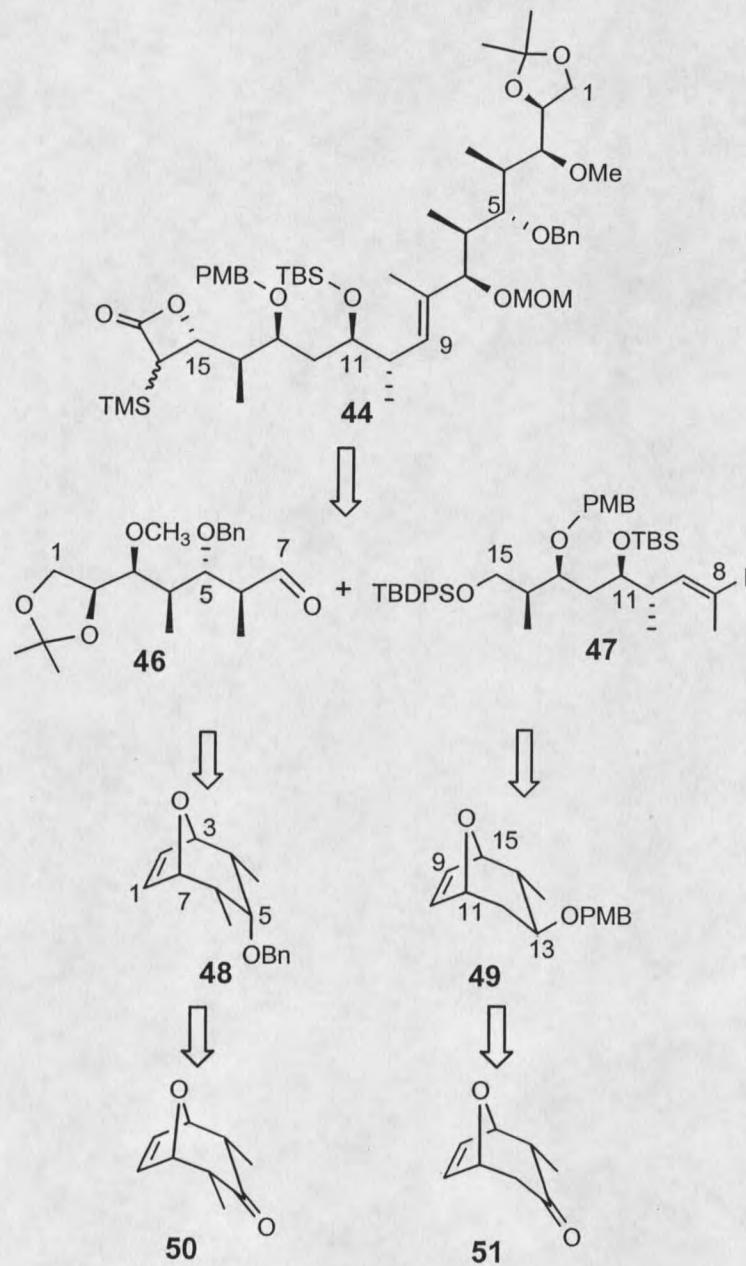
The proposed route to tedanolide described herein will rely on a Yamaguchi macrolactonization⁹ to couple the C(1) acid and the C(29) hydroxyl of seco acid **42** (Scheme 8). Formation of the C(16)-C(17) bond in fragment **42** was to come from condensation of the enolate, generated from silyl β -lactone **44**, with aldehyde **43** (Scheme 8). The C(17)-C(23) aldehyde **43** was to be obtained from the chiral, commercially available starting material methyl (S)-3-hydroxy-2-methylpropionate **45**.

Scheme 8. Synthetic Approach to Tedanolide



Silyl β -lactone **44** was to be derived from a [2+2] cycloaddition between silylketene and the C(15) aldehyde corresponding to **44** (Scheme 9).¹² The C(15) aldehyde was seen to come from formation of the C(7)-C(8) bond using lithium mediated coupling of aldehyde **46** and vinyl iodide **47** with the stereochemical outcome of the C(7) alcohol determined by Felkin-Ahn control.^{10,11,13}

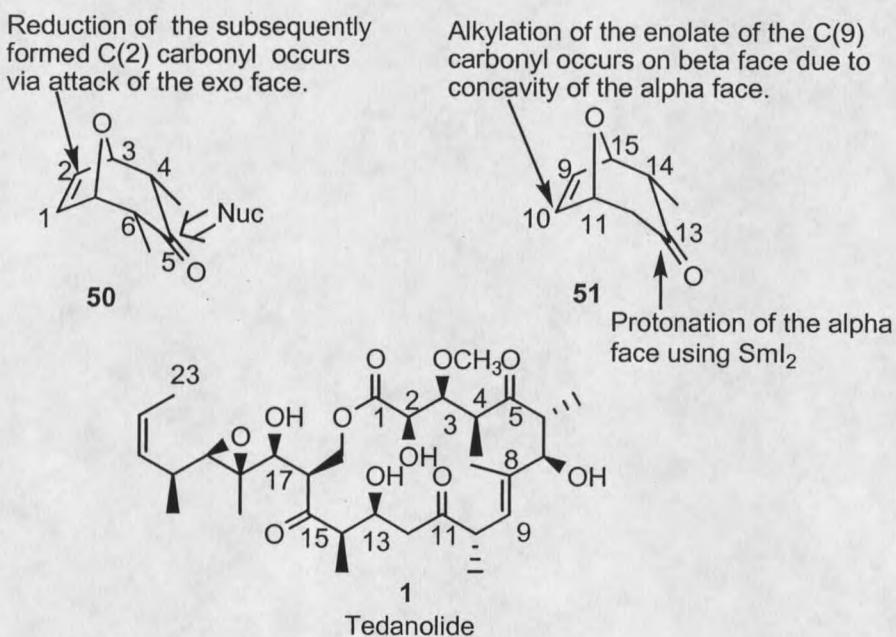
Scheme 9. Early Steps in the Synthetic Approach to Tedanolide



Oxabicyclo[3.2.1]octenones, such as **50** and **51**, are useful templates to set and direct stereochemistry for the synthesis of acyclic carbon chains. In this approach to the

synthesis of tedanolide, oxabicyclo[3.2.1]octenones ring systems **50** and **51** were used to form both the C(1)-C(7) fragment as well as the C(9)-C(15) fragment. These oxabicyclo[3.2.1]octenones allow direct stereocontrol of the methyl groups at the C(4), C(6), and C(14) as well as the C(3) hydroxyl group (Figure 1).¹⁴⁻¹⁶ The stereochemistry of the hydroxyl groups at C(2), C(5) and C(13) can be achieved by taking advantage of the properties of these ring systems. In addition, the steric hindrance present in the ring system also allows attack from the enolate anion, generated from a carbonyl at C(9), to occur exclusively from the exo face. This can be used to direct stereochemistry of the C(10) methyl, and allows control over most of the stereochemistry required for the C(1)-C(15) portion of tedanolide.

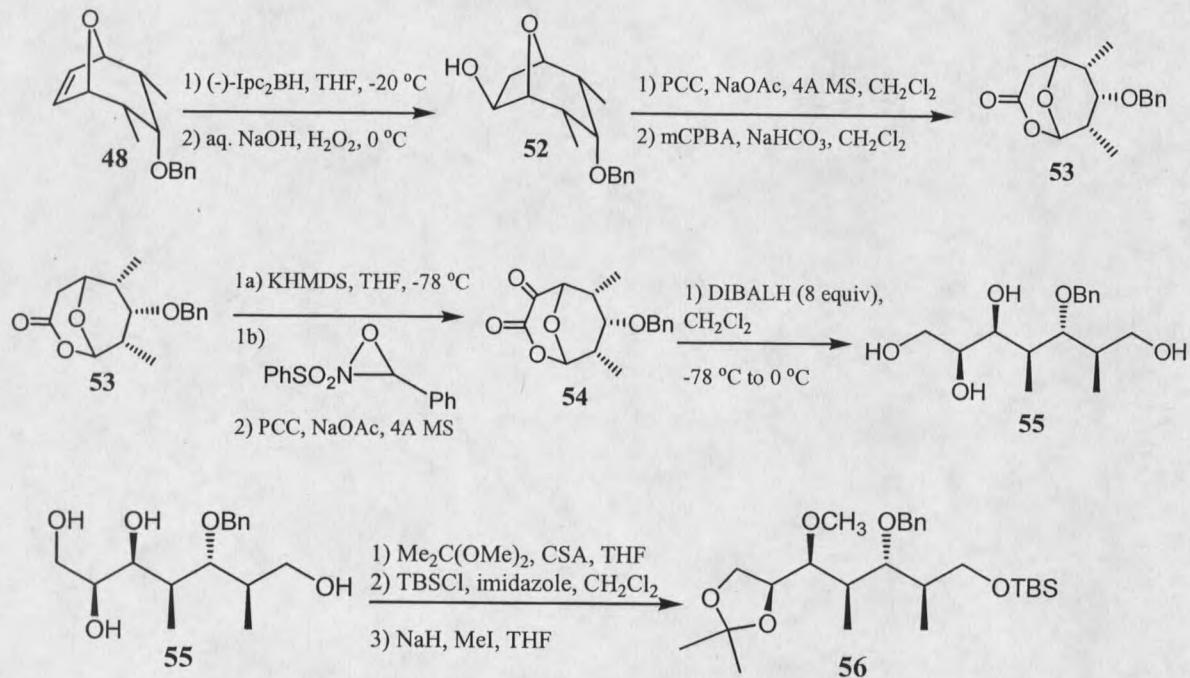
Figure 1. Stereodirection Utilizing Oxabicyclo[3.2.1]octenones



Synthesis of the C(1)-C(7) Fragment

Yong Wang is responsible for the basic approach of this synthesis and has made molecules **46** and **47**. Efforts were initially directed towards the synthesis of aldehyde **46** which could be obtained utilizing bicyclic benzyl ether **48**. Compound **48** was synthesized from oxabicyclo[3.2.1]octenone **50** via known chemistry (Scheme 9).^{15b} In order to obtain aldehyde **46**, oxabicyclic benzyl ether **48** was first asymmetrically hydroborated using (-)-diisopinocampheylborane followed by oxidation of the borane to form alcohol **52** (Scheme 10).^{15b-e} The subsequent alcohol was oxidized to the ketone using pyridinium chlorochromate and was converted into oxabicyclic lactone **53** using a Baeyer-Villiger oxidation with mCPBA.¹⁵ Lactone **53** was treated with potassium hexamethyldisilylazide to form the enolate followed by hydroxylation using Davies reagent¹⁷ to form a α -hydroxy lactone which was subsequently oxidized with pyridinium chlorochromate to form ketolactone **54**. This ketolactone was subjected to reduction using diisobutylaluminum hydride in dichloromethane which opened up the oxabicyclic ring system and resulted in tetraol **55**. Compared to related structures, the reduction of ketolactone **54** resulted in the highest yield of the desired tetraol.¹⁸ Treatment of **55** with 2,2-dimethoxypropane in the presence of camphorsulfonic acid resulted in acetonide protection of the C(9) and C(11) hydroxyl groups. The C(7) primary hydroxyl was protected using tertbutyldimethylsilyl chloride and the only remaining C(3) hydroxyl was methylated resulting in **56**. The silyl protected primary hydroxyl **56** was deprotected with tetrabutylammonium fluoride and oxidized to aldehyde **46** using Dess-Martin periodinane reagent.¹⁹

Scheme 10. Wang's Synthesis of the C(1)-C(7) Fragment

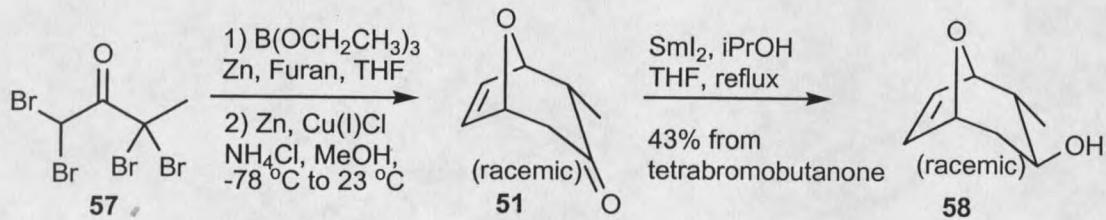


EXPERIMENTAL RESULTS

Results and Discussion

The C(8)-C(15) portion of tedanolide was constructed from the known 2-methyl-8-oxabicyclo[3.2.1]oct-6-en-3-one **51**¹⁴ (Scheme 11). Treatment of 1,1,3,3-tetrabromobutanone with a mixture of triethylborate, zinc, and furan gave rise to a mixture of oxabicyclo[3.2.1]octenones which upon further reduction with zinc, catalytic copper(I) chloride, and ammonium chloride gave rise to oxabicyclo[3.2.1]octenone **51**. The [4+3] cycloaddition is reported to be produced through an enol-borate which upon loss of bromide ion generates the corresponding allyl cation species which undergoes subsequent cycloaddition with furan.¹⁶

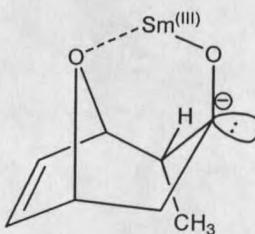
Scheme 11. Early Synthetic Work on the C(8)-C(15) Fragment



The resulting oxabicyclo[3.2.1]octenone **51** was reduced selectively using freshly prepared samarium iodide in tetrahydrofuran to provide oxabicyclo[3.2.1]octenol **58** wherein the hydroxyl group is equatorial (Scheme 11). A review of the literature revealed samarium iodide/tetrahydrofuran is superior to the more common use of lithium

metal in liquid ammonia. The samarium iodide reduction of **51** was reported to yield 57% of the desired equatorial β -alcohol with no trace of the α -face alcohol observed. Use of lithium metal in liquid ammonia was reported to give a better 89% yield of the alcohol mixture (both equatorial and axial) but resulted in a 1:2 ratio of β and α alcohol epimers respectively in favor of the undesired isomer. In addition, the reduction of oxabicyclo[3.2.1]octenone **51** using sodium metal in ethanol yielded a 4:1 mixture in favor of the desired β -face alcohol but resulted in a lower 41% yield.¹⁴ Based upon these results, samarium iodide reduction seemed to be the best choice giving 100% selectivity and a fairly high yield on this substrate. The good selectivity obtained in the samarium iodide reduction of oxabicyclic ketones could be attributed to an intermediate where the samarium(III) metal is bridging the alkoxide and the oxabicyclic bridge oxygen to block the top face of the molecule from protonation by isopropanol (Figure 2).¹⁴

Figure 2. Samarium Bridged Intermediate



During the process of forming an equatorial alcohol from the 1,1,3,3-tetrabromobutanone **55**, the yields obtained were higher than those previously reported.¹⁴ Wang's approach was to run this sequence of reactions without purification. After the [4+3] cycloaddition the partially brominated product was not isolated due to its light and

air sensitivity. The alcohol reduction occurred with 2-2.5 equivalents and was refluxed overnight. When the reduction to the alcohol had been accomplished, the result was a black solution containing the desired product that was difficult to purify by column chromatography. Extra hexane extractions were used to separate out some of the many impurities but this also led to product loss due to some of the product going into the hexanes layer (visible by TLC of the undesired extract). This method of obtaining oxabicyclo[3.2.1]octenol **58** seemed beneficial because a yield of 30% over the three steps was obtained from the tetrabromobutanone which was 4% higher than the previously reported procedure.

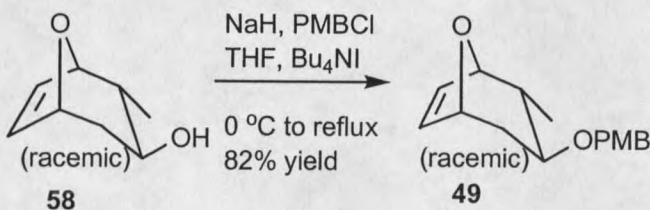
In Hoffmann's protocol the metal salts were filtered after the [4+3] cycloaddition. The [4+3] adduct was not isolated due to the products light and air sensitivity. The adduct was immediately subjected to further reduction. The resulting oxabicyclo[3.2.1]octenone **51** was purified by chromatography or distillation. A disadvantage with this approach is that ketone **51** was volatile and very hard to completely purify by flash chromatography so following this protocol also led to loss of product via evaporation. The reduction of the ketone occurred with 2-2.5 equivalents of samarium iodide over a time period of two hours. The yields reported for this method when combined over the three steps was 26%.

The approach found to work best in this work combined parts of the other methods by removing the metal salts before the bromine reduction and roughly purifying the ketone with a quick column to remove many of the contaminants. This approach did not involve distillation of the furan from potassium hydroxide before the [4+3] cycloaddition, because the distillation did not seem to add any benefit when performed.

The oxabicyclo[3.2.1]octenone **51** product was exposed to samarium iodide selectively reducing the keto functionality to the exo alcohol. One of the advantages of this approach is that oxabicyclo[3.2.1]octenone **51** was volatile as well as difficult to completely separate so it seemed to save time, effort, and avoided some of the loss due to evaporation compared to Hoffmann's method. The reduction to the alcohol occurred with 4.5 equivalents of samarium iodide under reflux overnight. Unlike Wang's procedure it involved no extra extractions and avoided emulsions. The procedure gave a relatively high yield of 43%, higher than the other two methods of 26% and 30% previously reported.

With oxabicyclo[3.2.1]octenol **58** in hand, the alcohol group was protected using sodium hydride, paramethoxybenzyl chloride, in the presence of tetrabutylammonium iodide and tetrahydrofuran to form the paramethoxybenzyl ether **49** (Scheme 12).

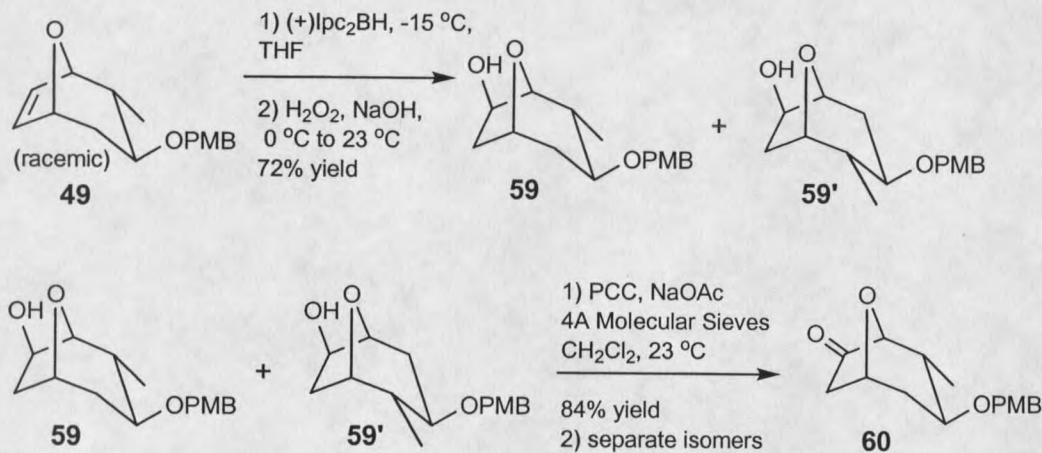
Scheme 12. Protection of the Alcohol



The paramethoxybenzyl ether **49** was purified and subjected to asymmetric hydroboration employing (+)-diisopinocampheylborane followed by oxidation of the resulting borane. This oxidation to the alcohol was obtained using hydrogen peroxide and sodium hydroxide giving rise to a 1:1 mixture of the C(9) exo alcohols **59** and **59'**

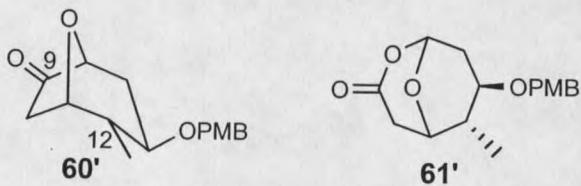
(Scheme 13). The selectivity of the diisopinocamphenylborane reaction has been shown to have a similar selectivity on other oxabicyclo[3.2.1]octene substrates.¹⁵ The two isomeric alcohols **59** and **59'** formed in this reaction were not separable so the isomers were separated as the corresponding ketones. Transformation to the ketones was achieved using a pyridinium chlorochromate oxidation. The ketones were separated using column chromatography in order to give a single product **60**.

Scheme 13. Selective Hydroboration and Oxidation



During the oxidation of the C(9) alcohol, the ketone with the methyl group on the C(12) position **60'** was formed from **59'**. Lactone **61'** was obtained by performing the Baeyer-Villiger reaction before separating the two isomeric compounds (Figure 3).

Figure 3. Isomers of the Desired Products Synthesized.



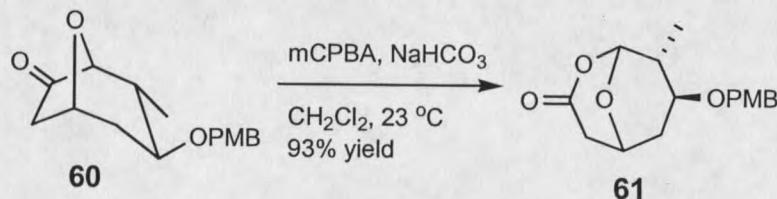
The hydroboration diastereomeric excess of 95% was determined by Yong Wang by reduction of ketone **60** with sodium borohydride and transforming it into the Mosher ester, which was analyzed by fluorine NMR.²⁰

Ketone **60** was treated with meta-chloroperbenzoic acid and sodium bicarbonate in dichloromethane to undergo Baeyer-Villiger oxidation resulting in a 93% yield of lactone **61** (Scheme 14).¹⁵ The lactones **61** and **61'**, derived from **60** and **60'** were formed during the course of this research and checked, in order to determine if they were the correct isomers, by 2D ¹H-¹H COSY NMR and a difference NOE experiment.

In a NOE experiment carried out on lactone **61**, irradiation of the methyl group protons (1.15 ppm) resulted in an enhancement of the oxobicyclic bridgehead proton closest to the electron withdrawing lactone (5.58 ppm). In addition, enhancements were also seen for the proton nearest to the paramethoxybenzyl group (3.45 ppm) and the proton α to the methyl (2.00-1.90) when the methyl group (1.15 ppm) was irradiated. When the farthest downfield bridgehead proton (5.58 ppm) was irradiated, enhancements for the methyl group and the proton attached to the paramethoxybenzyl ether group occurred (1.15 and 3.45 ppm respectively). This indicated that the lower R_f lactone was **61**, the desired isomer.

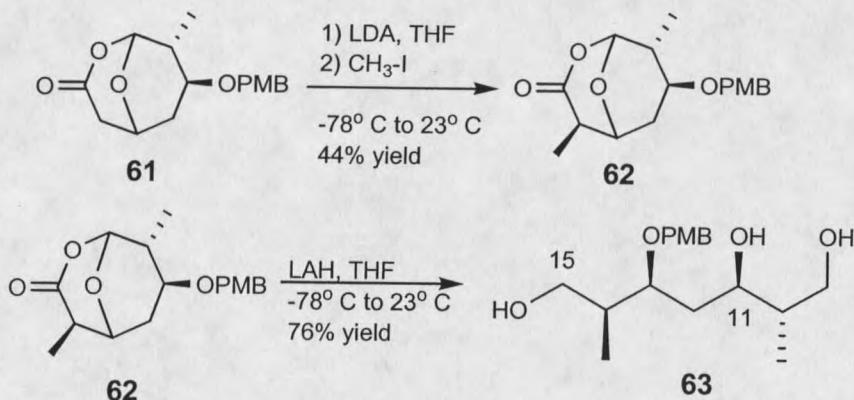
The ^1H - ^1H COSY NMR of lactone **61'** (Figure 3) showed a correlation between the bridgehead proton closest to the lactone (5.82 ppm) and the methylene proton α to the most downfield bridgehead proton (1.66 ppm). In addition, the peak at 1.66 ppm had no interaction with the methyl group (0.94). In the same spectra, the most shielded bridgehead proton (4.18 ppm) was coupled to the proton at 2.14-2.06, which is the only proton coupled to the methyl group (0.94 ppm). This indicated that the higher R_f lactone was the undesired isomer **61'**.

Scheme 14. Baeyer-Villiger Oxidation



Lactone **61** was deprotonated to form the enolate using lithium diisopropylamide and alkylated with methyl iodide to give alkylated lactone **62** (Scheme 15).^{15b} The oxabicyclic ring system favored methylation on the β -face of the molecule because of the steric congestion on the concave α -face. The resulting β -methyl lactone **62** was reduced with lithium aluminum hydride in tetrahydrofuran to open up the ring to the triol chain **63** with the C(10), C(13), and C(14) stereocenters in place.^{15b}

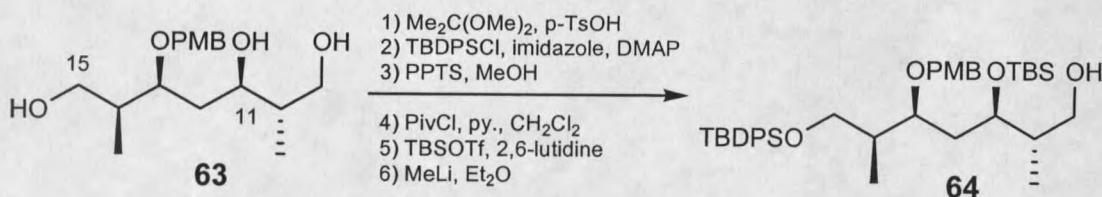
Scheme 15. Synthetic Work to Obtain the Triol

Synthesis of the C(8)-C(15) Fragment from the Triol

In addition to forming triol **63**, Wang did the following work on the C(8)-C(15) fragment beyond the triol. The C(9) and C(11) hydroxyl groups of triol **63** were protected as the acetonide using 2,2-dimethoxypropane in the presence of a catalytic amount of p-toluenesulfonic acid (Scheme 16). This reaction protected one of the primary hydroxyl groups in the presence of another. Then the C(15) primary alcohol was protected using tertbutyldiphenylsilyl chloride, imidazole, and dimethylaminopyridine. Next, the acetonide was treated with pyridinium para-tolunesulfonate in methanol to obtain the C(9) and C(11) diol. The C(9) primary hydroxyl group was reprotected using pivaloyl chloride in the presence of pyridine. This allowed the C(11) secondary alcohol to be protected using tertbutyldimethylsilyl triflate in the presence of 2,6-lutidine. The C(9) primary alcohol **64** was obtained after pivaloate cleavage using methylolithium in diethyl ether. At this point the compound in hand had a primary alcohol and three other

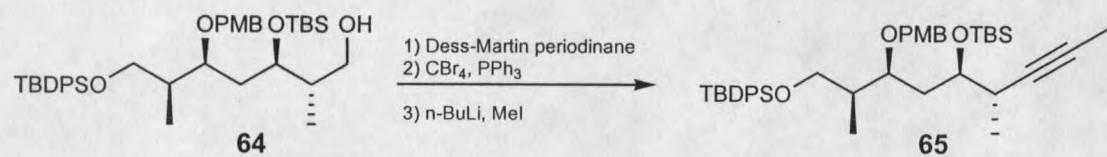
differentially protected alcohol functionalities with all the stereocenters required for the C(8)-C(15) fragment of tedanolide in place.

Scheme 16. Differential Protection of the Alcohols



The primary alcohol **64** was then transformed into the corresponding aldehyde using Dess-Martin Periodinane (Scheme 17).¹⁹ This sensitive aldehyde was then subjected to Corey-Fuchs conditions to form a divinylbromide compound which was then treated with normal butyllithium and methyliodide to form the internal alkyne **65**.

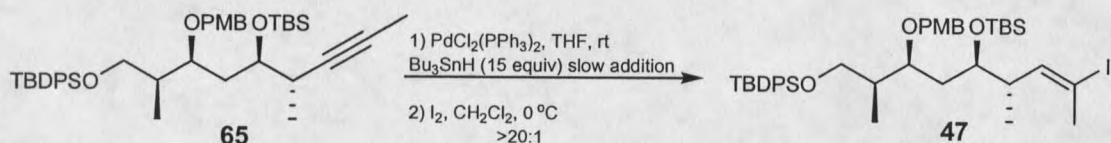
Scheme 17. Formation of the Alkyne



Alkyne **65** was then transformed into the vinyl halide in order to allow lithium mediated coupling between the C(1)-C(7) and the C(8)-C(15) fragments. Early attempts to form the desired vinyl halide using Schwartz reagent were unsatisfactory resulting in a

2:1 ratio in favor of the desired isomer with a 50% yield or no reaction.^{10,13} Using palladium catalyzed hydrostannylation of the alkyne **65** followed by treatment with iodine resulted in a 82% yield of the vinyliodide with high regioselectivity (>20:1) in favor of the desired isomer **47** (Scheme 18). With the C(8)-C(15) and the C(1)-C(7) fragments in hand the next step would be lithium halogen exchange with vinylhalide **47** and coupling to aldehyde **46**.¹¹ This concludes the currently completed work on this approach to tedanolide.

Scheme 18. Formation of the Vinyl Iodide

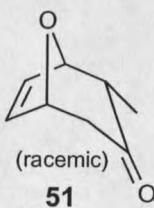


ExperimentalGeneral Procedure

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 250 MHz on a Bruker DRX 250 spectrometer, at 300 MHz using a Bruker DRX 300 spectrometer, or at 500 MHz on a Bruker DRX 500 spectrometer as indicated and are reported in parts per million (δ). ^1H NMR spectra were obtained in deuterated solvents and were referenced against the residual protic solvent signal as follows: chloroform-d (δ 7.26). Carbon 13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 62.5 MHz using a Bruker DRX 250 spectrometer, 75 MHz on a Bruker DRX 300 spectrometer, or at 125 MHz on a Bruker DRX 500 spectrometer as indicated and are reported in parts per million (δ). ^{13}C spectra were obtained in deuteriochloroform solution and were referenced against the deuteriochloroform carbon signal (δ 77.16). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrophotometer as neat samples. Reactions were monitored by thin layer chromatography (TLC) using E. Merck precoated silica gel 60 F-254 (0.25 mm) plates. The plates were visualized by immersion in a para-anisaldehyde solution and warming on a hot plate. Flash chromatography was performed using Sorbent Technologies silica gel 60 Å (32-63 μm) mesh or 60 Å (63-200 μm) mesh according to the method reported by Still.²¹

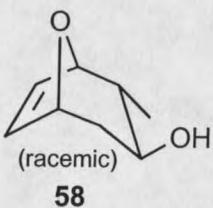
Unless otherwise stated, all experiments were run in oven-dried or flame-dried glassware under an argon atmosphere using anhydrous solvents. The solvents were dried and distilled as indicated below. Tetrahydrofuran and diethyl ether were purified by distillation from sodium. Diisopropylamine and dichloromethane were purified by

distillation from calcium hydride. Methyl iodide was distilled from calcium chloride. Other reagents and solvents were reagent grade and were used as received unless otherwise noted.



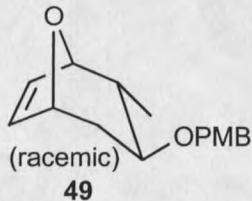
2-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-one (51): Zinc (12.2 g, 187 mmol) was flame dried under argon in a one-neck round-bottomed flask equipped with a water condenser. The flask was allowed to cool to room temperature then tetrahydrofuran (35 mL) and furan (25 mL, 0.43 mol) were added. In a separate flask 1,1,3,3-tetrabromobutanone (69.792 g, 180.0 mmol) was dissolved in a mixture of tetrahydrofuran (35 mL) and triethyl borate (46.5 mL, 273 mmol). While periodically heating the zinc-furan solution to initiate the reaction, the tetrabromobutanone-triethyl borate solution was added dropwise via cannula over 3 h. The reaction was allowed to stir with a magnetic stirbar at room temperature for 22 h then was quenched with water. The metal salts were filtered through Celite on a fritted filter. The organic layer was washed with brine and the aqueous layer was extracted with ether. The organics were then dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude product was immediately subjected to debromination due to the light and air sensitivity of this compound.

To 3-necked flask equipped with a reflux condenser, a mechanical stirrer, and an addition funnel, zinc (58.3 g, 891 mmol), anhydrous ammonium chloride (48.4 g, 905 mmol), and copper(I) chloride (9.0 g, 91 mmol) were added respectively. While stirring, the solid mixture was flame dried under argon to remove all water and activate the zinc. When the flask had cooled to room temperature, anhydrous methanol (153 mL) was added and the solution was cooled to -78 °C. The ketone from the [4+3] cycloaddition was dissolved in anhydrous methanol (44 mL) and added dropwise to the solid mixture over 3.5 h via the addition funnel. The reaction mixture was then stirred for 13.5 h at room temperature before being quenched with water. The metal salts were filtered off. Dichloromethane was added to the filtrate and the layers were separated. The organic layer was washed with brine then the combined aqueous layers were washed with dichloromethane. The combined organic phases were dried over magnesium sulfate, filtered, and evaporated in vacuo. The compound was purified by flash chromatography on silica gel (hexanes-ether, 7:3) to give a yellow oil (8.54 g). R_f 0.38 (hexanes: ethyl acetate, 4:1); IR (film) 3083, 2961, 2904, 2874, 1705, 1591, 1462, 1449, 1377, 1347, 1244, 1185, 1149, 1084, 1040, 981, 955, 915, 885, 826, 720, 620, 571 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.31 (dd, $J = 6.0, 1.9$ Hz, 1H), 6.28 (dd, $J = 6.0, 1.5$ Hz, 1H), 5.02 (dt, $J = 4.9, 1.5$, 1H), 4.85 (dd, $J = 4.9, 1.9$ Hz, 1H), 2.80-2.73 (m, 2H), 2.30 (d, $J = 16.0$ Hz, 1H), 0.97 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 207.4, 135.0, 132.0, 81.9, 78.3, 51.7, 46.1, 10.2.



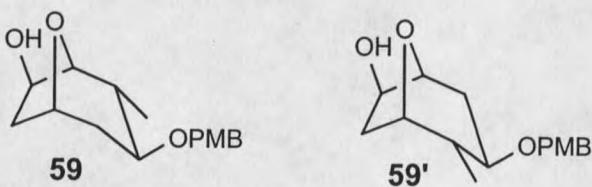
2-methyl-8-oxa-bicyclo[3.2.1]oct-6-en-3-ol (2α eq) (58): Samarium metal (44.6 g, 297 mmol) was placed in a one-neck round bottom flask and flame dried under a stream of argon. After the flask had cooled to room temperature, tetrahydrofuran (445 mL) was added. The reaction flask was cooled to 0 °C and diiodomethane (22.0 mL, 297 mmol) was added over 1 h 20 min. After an additional 15 min at 0 °C the ice bath was removed and replaced with an oil bath. The solution was heated at reflux for 5 h, during this time the solution changed from a dark green to a deep blue-purple color. Oxabicyclo[3.2.1]octenone **51** was then dissolved in isopropanol (21.5 mL, 281 mmol) and added dropwise to the reaction flask. The reaction was allowed to reflux overnight (15 h). Heating was discontinued and the reaction was cooled to 0 °C, and the basic solution was quenched with cold water. 10% hydrochloric acid (200 mL) was added. Sodium chloride was added to the two-phase mixture. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organics were dried over magnesium sulfate, filtered, and evaporated in vacuo. Purification by flash chromatography on silica gel (hexanes-ethyl acetate, 1:1 then 1:2) gave 10.9 g (43% from the tetrabromoketone) of the alcohol. R_f 0.23 (hexanes-ethyl acetate, 1:1); ^1H NMR (250 MHz, CDCl_3) δ 6.15 (s, 2H), 4.78 (s, 1H), 4.54 (d, J = 3.5 Hz, 1H), 3.41-3.33 (m, 1H), 1.91 (dd, J = 12.6, 6.8 Hz,

1H), 1.78-1.45 (m, 3H), 0.94 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 132.5, 129.5, 82.3, 78.7, 70.9, 41.1, 35.3, 14.2.



3-(4-methoxy-benzyloxy)-2-methyl-8-oxa-bicyclo[3.2.1]oct-6-ene (49): Sodium hydride (3.7 g, 92.5 mmol, 60% dispersion in mineral oil) was first washed with three portions of HPLC grade pentane to remove the mineral oil. The reaction flask was flushed with argon then tetrahydrofuran (10 mL) was added. Oxabicyclo[3.2.1]octenol **58** (4.35 g, 31.0 mmol) was dried by azeotropic distillation (benzene), dissolved in tetrahydrofuran (31 mL) and added slowly via cannula to the reaction flask at 0 °C. The reaction was then slowly warmed to reflux and refluxed for 2.5 h. Tetrabutylammonium iodide was added to the reaction flask. 15 min later, paramethoxybenzyl chloride was added dropwise to the flask over 2 h. The solution was allowed to reflux overnight (17 h). The solution was allowed to cool to room temperature and was quenched with a saturated ammonium chloride solution (75 mL). The layers were separated and the organic layer was washed with brine. The combined aqueous layers were then extracted with ethyl acetate. The organics were dried over magnesium sulfate, filtered, and evaporated in vacuo. The product was purified using flash chromatography on silica gel (hexanes-ethyl acetate, 4:1) to produce a yellow oil (6.65 g, 82%). R_f 0.70 (hexanes-ethyl

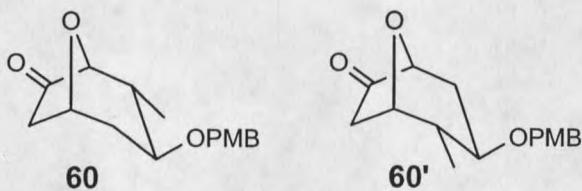
acetate, 1:1); ^1H NMR (300 MHz, CDCl_3) δ 7.23-7.20 (m, 2H), 6.86-6.83 (m, 2H), 6.13 (m, 2H), 4.79 (m), 4.52 (d, $J = 3.6$ Hz, 1H), 4.48 (AB, $J_{\text{AB}} = 11.2$ Hz, 1H), 4.27 (AB, $J_{\text{AB}} = 11.2$ Hz, 1H), 3.78 (s, 3H), 3.16 (td, $J = 9.2, 6.2$ Hz, 1H), 1.95 (ddd, $J = 12.9, 6.2, 1.8$ Hz, 1H), 1.89-1.79 (m, 1H), 1.63 (ddd, $J = 12.9, 9.2, 3.6$ Hz, 1H), 0.88 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 132.4, 131.5, 129.8, 129.4, 113.9, 82.9, 78.6, 77.7, 70.6, 55.4, 38.7, 31.8, 14.7.



(1S, 3S, 4R, 5S, 6R)-3-(4-methoxy-benzyloxy)-4-methyl-8-oxa-bicyclo[3.2.1]octan-6-ol (59) and (1S, 2R, 3R, 5S, 6R)-3-(4-methoxy-benzyloxy)-2-methyl-8-oxa-bicyclo[3.2.1]octan-6-ol (59'): To a cold (0°C) solution of 1s-(-)- α -pinene (22.0 mL, 128 mmol) in tetrahydrofuran (21 mL), borane-dimethylsulfide (6.2 g, 54.8 mmol) complex was added dropwise without stirring over 32 min. The reaction was allowed to sit and warm up to room temperature over 7.25 h. The flask was then placed in the fridge ($0-4^\circ\text{C}$) overnight (15 h) to ensure complete crystal formation. The flask was removed from the fridge and the excess (-)- α -pinene, tetrahydrofuran, and dimethylsulfide were removed via syringe. The (+)-diisopinocamphenylborane crystals were washed three times with anhydrous ether and dried under vacuum. The white crystals were broken up with a spatula under a stream of argon. To increase the enantioselectivity of the crystal,

additional (-)- α -pinene (3.40 mL, 21.3 mmol) was added. The crystals were again placed in the fridge and periodically shaken over 99 h. The crystals were cooled to -78 °C and tetrahydrofuran (6.5 mL) was added.

The alkenes **49** (9.17 g, 35.2 mmol), dissolved in tetrahydrofuran (11 mL), were added dropwise over 30 min to the (+)-diisopinocamphenylborane solution at -78 °C. The reaction was stirred with a magnetic stirbar at -78 °C for 2 2/3 h. The reaction was moved to the cold room (-15 °C to -20 °C) and stirred for 28 days. 3 M aqueous sodium hydroxide (25 mL) and 30% aqueous hydrogen peroxide (22.5 mL) were slowly added at 0 °C. The reaction mixture was stirred using a magnetic stirbar at 0°C for 2 h, warmed to room temperature and stirred for an additional 19.5 h. The layers were separated and the organic layer was washed with brine. The combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and evaporated in vacuo. The product was purified by flash chromatography on silica gel (hexane-ethyl acetate, 3:1, 2:1, 1:1, followed by 1:3) to produce a mixture of alcohol isomers (7.09 g, 72% yield of two alcohol constitutional isomers) as a white powder. mp 105.6-121 °C.



(1R, 3S, 4R, 5S)-3-(4-methoxy-benzyloxy)-4-methyl-8-oxa-bicyclo[3.2.1]octan-6-one

(60) and **(1S, 2S, 3R, 5S)-3-(4-methoxy-benzyloxy)-2-methyl-8-oxa-bicyclo[3.2.1]octan-6-one (60')**: To a solution of the alcohol mixture (4.0189 g, 14.545 mmol), 4 Å molecular sieves (7.1375 g, 247 mg per mmol of pyridinium chlorochromate), and sodium acetate (7.3780 g; 87.043 mmol) in dichloromethane (84.0 mL) pyridinium chlorochromate (6.44 g, 29.9 mmol) was added. The reaction was stirred using a magnetic stirbar at room temperature for 65 min. Next the mixture was filtered through sand and silica gel and the filter rinsed with dichloromethane. The organics were concentrated under vacuum and purified by flash column chromatography on silica gel (hexanes: ethyl acetate, 9:1) to give 1.764 g (44%) of **60'** and 1.579 g (40%) of ketone **60**, both as white solids. The enantiomer excess of hydroboration (95%) was determined by Yong Wang using ¹⁹F NMR of the Mosher's ester of the corresponding alcohol derived from sodium borohydride reduction of ketone.

Analytical data for **60**: mp 50-51 °C; R_f 0.63 (hexanes-ethyl acetate, 1:1); [α]_D²⁵ +32.9° (c 0.065, CHCl₃); IR (film) 3483, 2919, 2845, 1754, 1670, 1602, 1508, 1461, 1355, 1302, 1243, 1173, 1079, 1026, 820 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23 (m, 2H), 6.87 (m, 2H), 4.82 (br d, J = 6.0 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.35 (d, J = 11.0 Hz, 1H), 3.84 (d, J = 4.0 Hz, 1H), 3.81 (s, 3H), 3.27 (td, J = 10.5, 5.5 Hz, 1H), 2.63 (dd, J = 18.0, 8.0 Hz, 1H), 2.14 (d, J = 18.0 Hz, 1H), 2.11 (ddd, J = 13.3, 5.5, 1.7 Hz, 1H), 2.04 (m, 1H), 1.90 (ddd, J = 13.3, 10.5, 4.0 Hz, 1H), 1.05 (d, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 214.1, 159.7, 130.6, 129.7, 114.3, 80.8, 75.0, 74.3, 71.1, 55.7, 42.4, 42.0, 36.1, 12.7; high-resolution MS (EI) calculated for C₁₆H₂₀O₄ (M⁺) m/e 276.1362 found 276.1369.

