STUDIES TOWARD A STEREOSELECTIVE SYNTHESIS

OF THE LOWER HALF OF TETRONOLIDE

by

Susan E. Drozda

SUBMITTED TO THE DEPARTMENT OF CHEMISTRY

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ABSTRACT

A stereoselective approach to the lower half of the antitumor antibiotic tetronolide (16) is described. The key step is the intramolecular Diels-Alder cyclization of tetraene 17. Several routes to the precursor of 17, differentiated dialdehyde 38, have been explored. The most promising route involves the condensation of (D)-glyceraldehyde acetonide 54 with (R,R)-(E)-crotylboronate 55, protection, and ozonolysis, to give 58. Aldehyde 58 is then condensed with (R,R)-(Z)-crotylboronate 100 to give 28 with a hydroxyl at the (C7) position. Deoxygenation will be delayed until after the cyclization of 16. Preliminary investigations into the incorporation of the diene and dienophilic portions of 17 have also been made.

Thesis Supervisor: Dr. William R. Roush
Title: Associate Professor of Chemsitry

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I would first like to thank Professor Roush for his continuous encouragement, and seldom wavering optimism toward this project. His energy, enthusiasm, and high standards for research have given me a new perspective on organic synthesis that I hope to keep with me as I continue my career in chemistry.

I would also like to extend my sincere thanks to my proofreaders, Michael Dane, Alan Palkowitz, and Julie Straub, for catching all the typos and making numerous useful suggestions.

ABBREVIATIONS

Bzl	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DIBAL	diisobutylaluminium hydride
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMS	dimethylsilicone
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide
MOM	methoxymethyl
PCC	pyridinium chlorochromate
PPh_3	triphenylphosphine
PPTS	pyridinium p-toluenesulfonate
Pv	pivalate
TBDMS	t-butyldimethylsilyl
TBDPS	t-butyldiphenylsilyl
TBHP	t-butyl hydroperoxide
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran

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Introduction

Tetrocarcin is an antitumor antibiotic which was first isolated from Micromonospora chalcea KY1109 obtained from a soil sample in Sendai-shi, Miyagi, Japan by Tomita and co-workers in 1980.[1] The structure was determined later that same year by Hirayama and co-workers.[2] Tetrocarcin is isolated as a mixture which contains three separate compounds, tetrocarcins A, B, and C. This complex is active against gram positive, but not gram negative, bacteria.[1,3]

Tetrocarcin A shows strong bacteriocidal activity against Bacillus subtilis, and moderate activity against Staphylococcus aureas. It also shows marked activity against experimental tumors such as mouse sarcoma 180 and mouse leukemia P388. Tetrocarcin A has been found to operate by inhibiting RNA synthesis. It has a minor effect on protein synthesis and no effect on DNA synthesis.[1,3]

All three tetrocarcins contain the aglycone tetronolide 1 and five sugar residues.[1,4] Tetronolide is very similar in structure to kijanolide 2 the aglycone of the antibiotic kijanamycin which is isolated from Actinomadura kijaniata.[5] Another structurally related compound is chlorothricolide (3), the aglycone of chlorothricin, which was isolated from Streptomyces antibioticus in 1969.[6] The
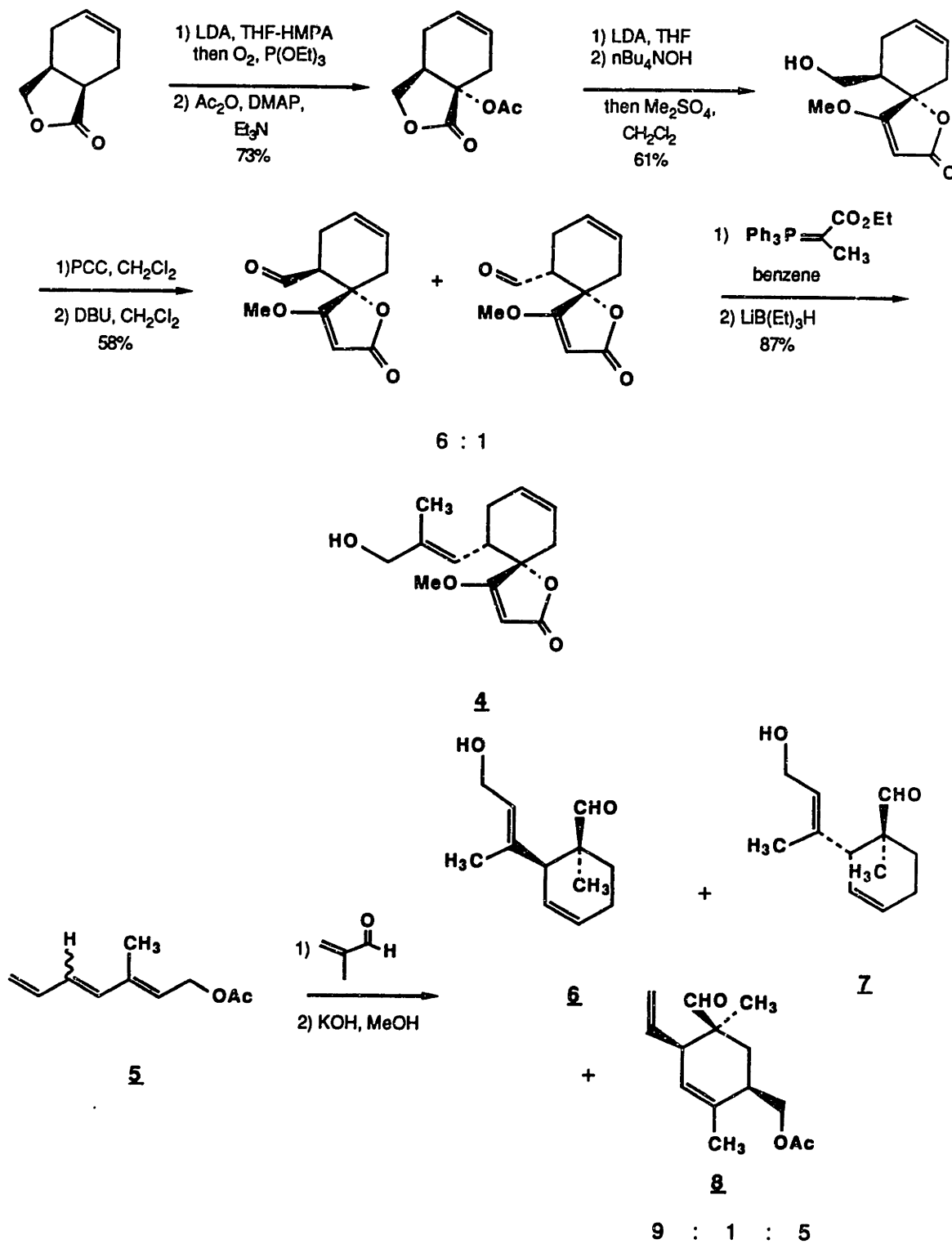

1   2   3
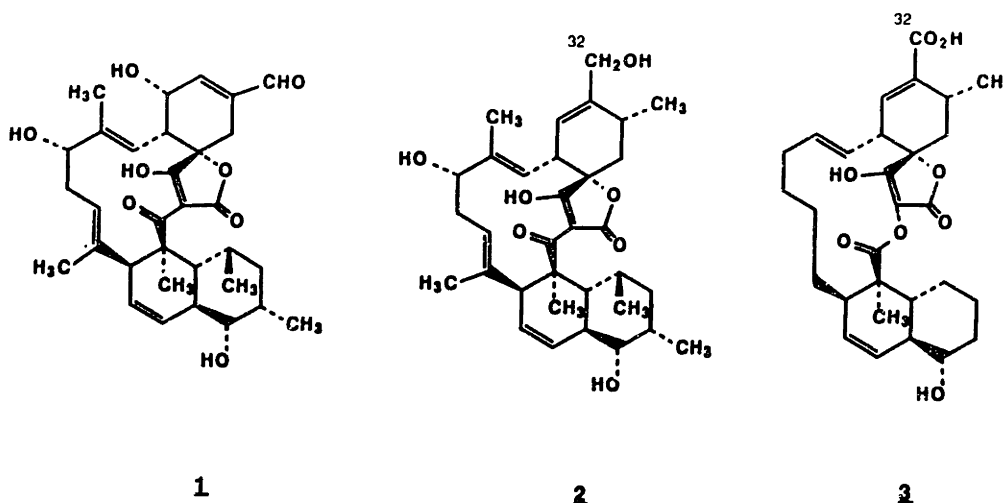
structure was determined three years later by Keller-Schierlein and co-workers.[7] Although it lacks three of the methyl substituents in the lower half, the upper half of chlorothricolide is virtually identical to that of kijanolide. The major difference between the two upper halves is the oxidation state of C(32). In addition, chlorothricolide is a macrolide whereas the macrocycles of 1 and 2 possess unbroken carbon chains.

These interesting and biologically important compounds provide a plethora of synthetic challenges for the organic chemist. Most of the synthetic work to date has been directed towards chlorothricolide and kijanolide.[8,9] A brief discussion of some of the results pertaining to the synthesis of the bottom halves of these molecules via intramolecular Diels-Alder reactions will be presented shortly.
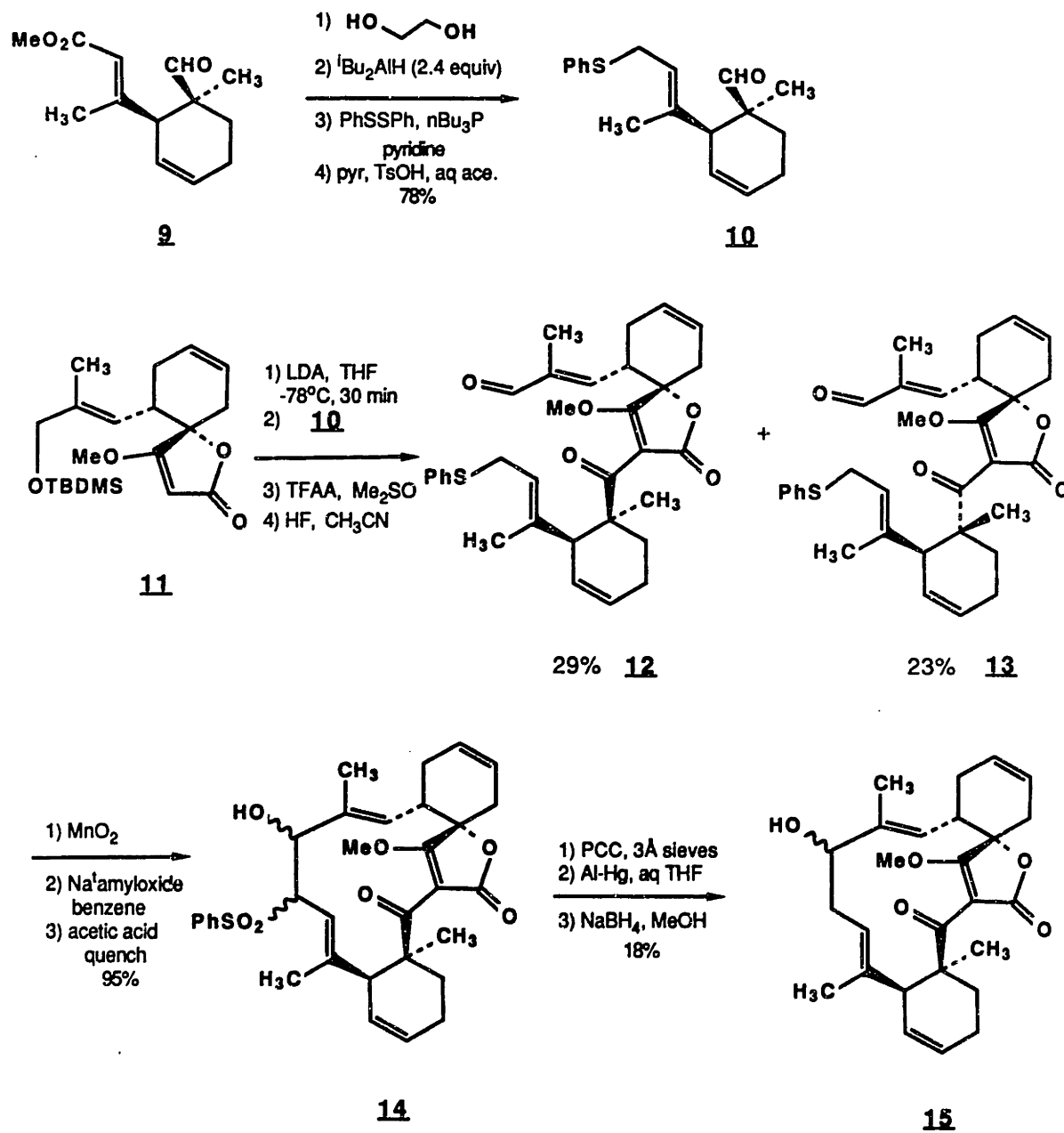
Yoshii and co-workers,[10] however, have reported preliminary studies on a racemic synthesis of tetronolide. As a model for the top half, they chose compound 4 the synthesis of which is shown in Scheme I.[11] A model for the bottom half was prepared via the Diels-Alder reaction of methacrolein and 5. This cyclization gave a mixture of 6, 7, and 8 (9:1:5) in an 86% combined yield based on (E,E)-5. The coupling of the two halves proceeded as shown in Scheme II, to give tetronolide model 15 in 5% overall yield from 11.
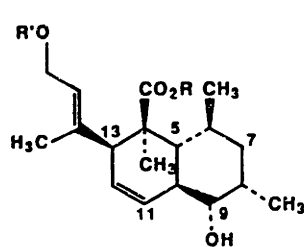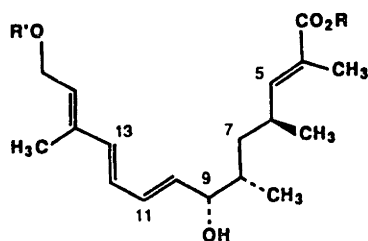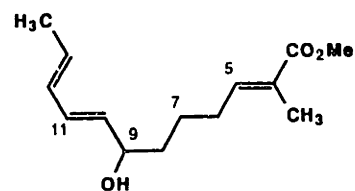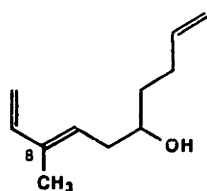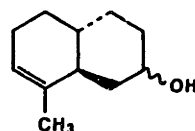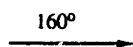
The lower half of tetronolide 16, in addition to the synthetic challenge of controlling multiple stereocenters, offers an opportunity to study the stereochemistry of the intramolecular Diels-Alder reaction. The Diels-Alder precursor to 16 would be tetraene 17. In preliminary studies directed towards the lower half of chlorothricolide, Roush and Hall showed that with unadorned triene esters such as 18 the cis ring fused cycloadducts are favored.[8b] In other studies Wilson and co-workers found that a substituent at C(8) of the diene greatly enhanced the selectivity of cyclizations leading to trans ring fused cycloadducts.[15]

Scheme I

6 : 1

4

5

1) ![acrolein]

2) KOH, MeOH

6

7

8

9 : 1 : 5

Scheme II

9

1) HO⌒OH

2) ^{i}Bu$_2$AlH (2.4 equiv)

3) PhSSPh, nBu$_3$P
pyridine

4) pyr, TsOH, aq ace.
78%

10

11

1) LDA, THF
-78°C, 30 min

2) 10

3) TFAA, Me$_2$SO

4) HF, CH$_3$CN

29% 12   +   23% 13

1) MnO$_2$

2) Na^{i}amyloxide
benzene

3) acetic acid
quench
95%

14

1) PCC, 3Å sieves

2) Al-Hg, aq THF

3) NaBH$_4$, MeOH
18%

15

16   17   18

19   160°   >95% trans
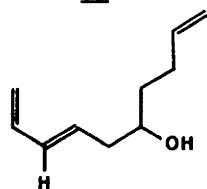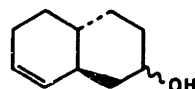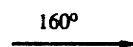
20   160°   55 : 45 trans : cis

This may be a result, in part, of increased steric interactions in the transition states leading to cis-fused products. This observation has been used to improve the selectivity of the Diels-Alder reaction of 18. When X is a hydrogen atom, the four cycloadducts derived from transition states 21-24 (Scheme III) were obtained in a ratio of 15%, 13%, 23%, and 49% respectively.[8b] If, however, X is a bromine atom[8j] or a trimethylsilyl group,[8h] transition state 22 experiences a more severe allylic strain, and transition states 23 and 24 experience unfavorable pseudo 1,3 diaxial interactions. Only transition state 21, the one leding to the desired
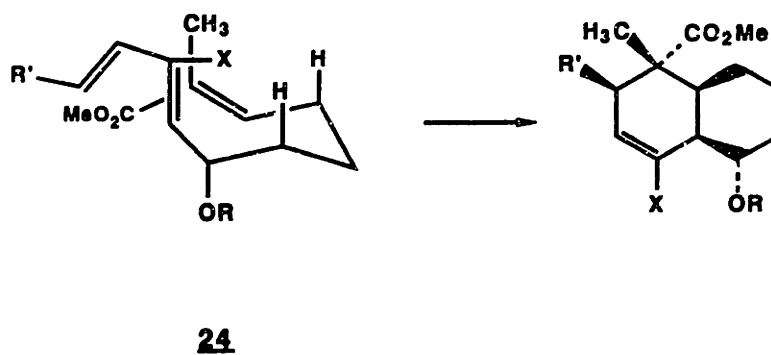
Scheme III

21

22

23

24
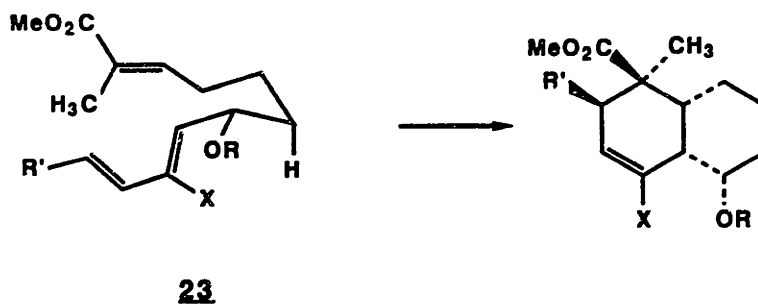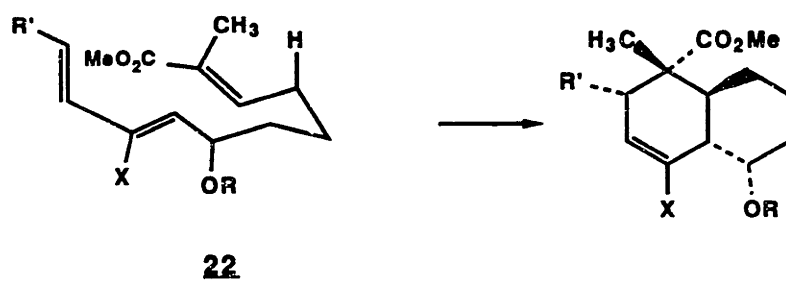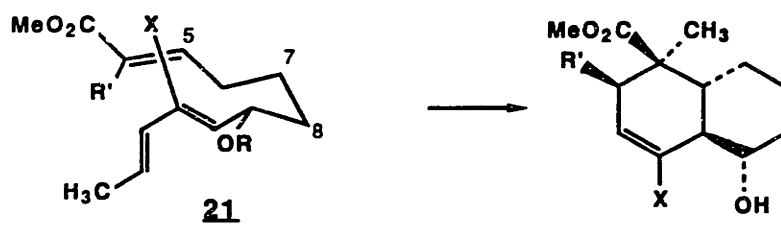
trans-fused product, is free from such steric interactions. In fact, when X=SiMe₃, the cycloadduct of 21 is the sole reaction product.[8h] When X=Br, the cycloadducts of 21 and 24 are obtained in a ratio of up to 3.5:1, depending on the nature of R'.[8j]

It remains to be seen, of course, what the stereoselectivity of the cyclization of tetronolide precursor 17 will be. One would expect, however, that the added methyl groups of 17 relative to 18 would tip the balance further in favor of the desired transition state 25 (Scheme IV).

In transition states 26 and 28 there will be a significant amount of the 1,3 allylic strain between the C(6) and the C(8) methyl groups. Thus, these transition states should be substantially destabilized relative to 25 and 27. Assuming that the bridging chain adopts a chair-like orientation in the transition state, the pseudo 1,3-diaxial interactions in transition state 27 between the C(18) hydrogen (X=H) and the C(4) methyl will be too large to ignore. If, however, cyclization were to occur via one of these undesired transition states, it could be supressed by the use of the steric directing group strategy (X=Br,TMS) mentioned earlier.

In addition to steric effects, Lewis acid catalysis has also been shown to enhance the endo/exo selectivity in some intramolecular Diels-Alder reactions.[16] As can be seen from some representative examples in Table I, Lewis acids dramatically increase endo selectivity. In their synthesis of the hexahydronapthalene portion of compactin, Funk and Zeller found that Lewis acids greatly enhanced selectivity of certain triene esters (Table I, entry 6) for the trans ring fusion. Roush and Hall, on the other hand, found that the triene ester 29 decomposed when exposed to even mild Lewis acids.[8b]

Scheme IV

25

26

27

28
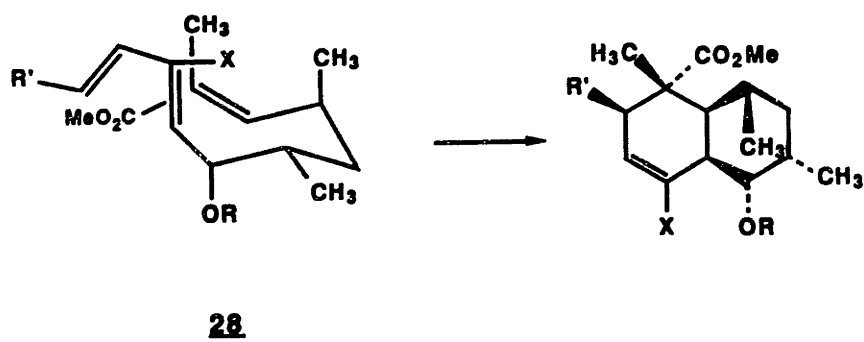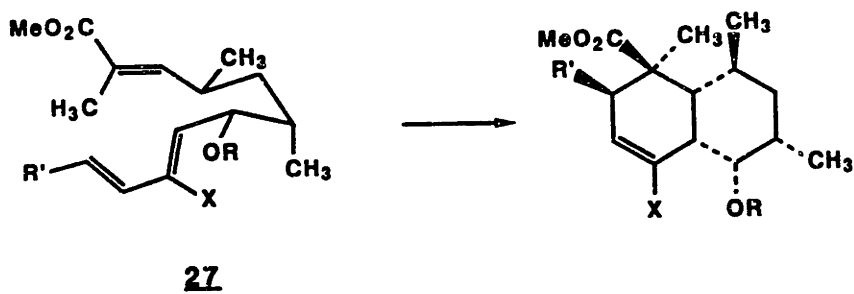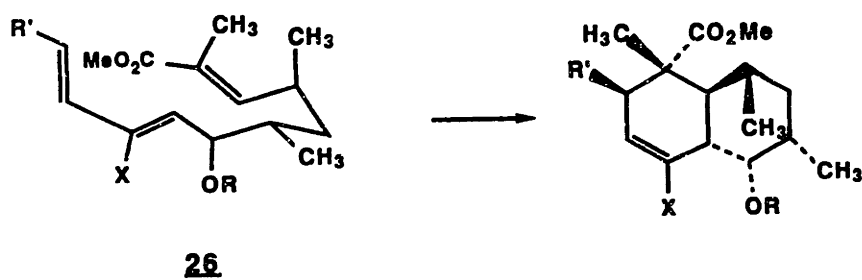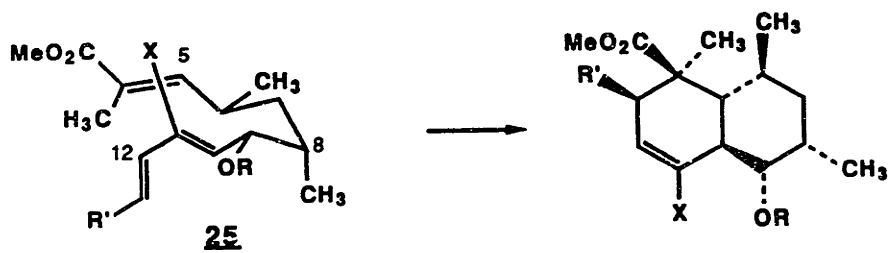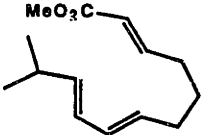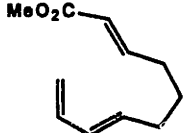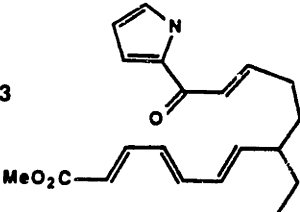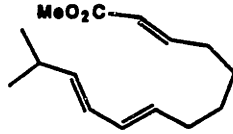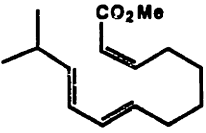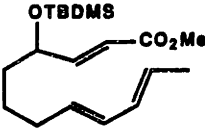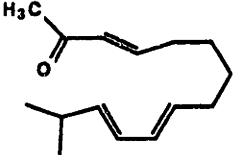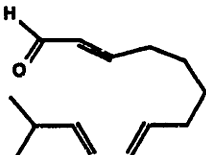
Table I

Entry	Triene	Conditions	Ratio Trans:Cis	Ref.
1	MeO₃C—	150°, 40h	72 : 28	16a
		AlCl₃ (0.1eq) 23°, 18h	>99 : 1	
2	MeO₂C—	150°, 24h	51 : 49	16a
		AlEtCl₂ (0.9 eq) 23°, 36h	>99 : 1	
3	(pyrrole) O / MeO₂C—	110°, 24h	82 : 18	16b
		EtAlCl₂ (0.95 eq) CH₂Cl₂, 0°->RT	>95 : <5	
4	MeO₂C—	160°, 48h	50 : 50	16d
		EtAlCl₂ CH₂Cl₂, 3h	88 : 12	
5	CO₂Me	180°, 3h	55 : 45	16d
		EtAlCl₂ CH₂Cl₂, 1h	<8 : >92	
6	OTBDMS —CO₂Me	140°, 120h	78 : 22	16c
		EtAlCl₂ 25°, 72h	100 : 0	
7	H₃C / O	150°	66 : 34	34
		EtAlCl₂ -78°	>100 : 1	
8	H / O	150°	75 : 25	34
		EtAlCl₂ 25°	70 : 1	
		EtAlCl₂ -78°	>100 : 1	

OR

R''— MeO₂C. R'

Lewis acid ──────────────→ Decomposition
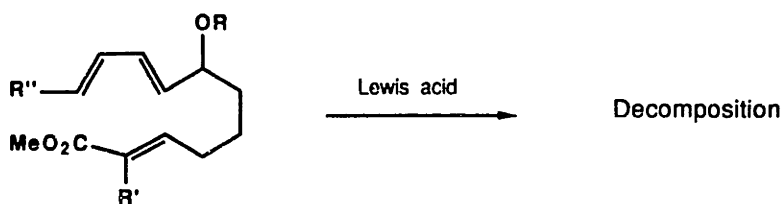
29

Marshall and co-workers, in their studies on the synthesis of kijanolide and chlorothricolide, devised a solution to the Lewis acid catalysis decomposition problem.[8f] Instead of using an ester to activate the dienophile, their strategy employs an aldehyde at that position. The aldehydic moiety should be a more effective dienophile activator, especially with a Lewis acid catalyst.[17] Because of this increase in dienophile activity, the rate of the cyclization should be increased. This is indeed what was found. The aldehyde analogue (**30**) of Funk and Zeller's ester (Table I, entry 6) cyclized rapidly at -50° C when exposed to 0.2 equiv. of EtAlCl₂ (equation 1). A more rigorous test of this methodology was the preparation of

Equation 1

OHC OTBDMS

EtAlCl₂ ──────────→ -50°

CHO OTBDMS
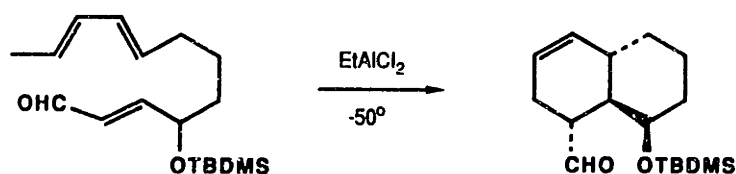
30

the aldehyde analogue **31** of triene ester **29** (equation 2). The stronger Lewis acids such as EtAlCl₂ caused decomposition, but use of the milder Lewis acid, Et₂AlCl, effected smooth cyclization to **32** and **33**. No cis-fused products were

observed. It should be noted, however, that this cyclization places the alkoxy

substituent in an axial position, whereas equatorial stereochemistry occurs in the

natural product.

Equation 2

8 : 1
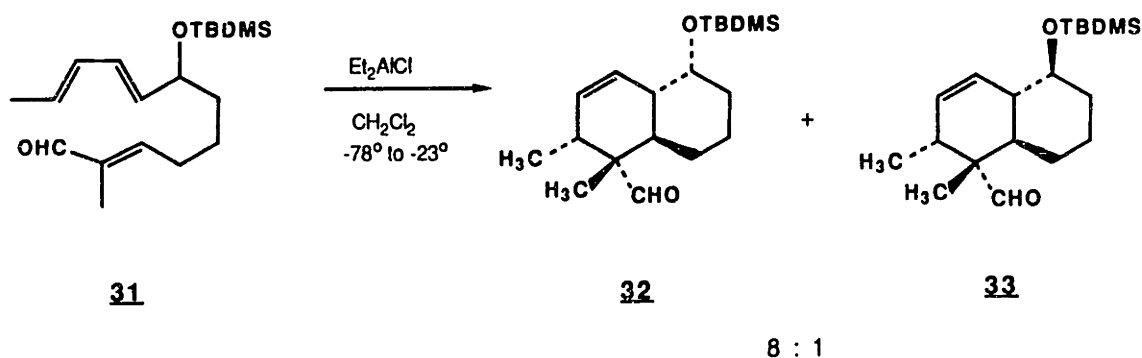
Marshall's route to the lower half of kijanolide,[9c] published after the work

described in this thesis was initiated, is outlined in Scheme V. The major drawback

to this synthesis is the 1:1 mixture of C(9) hydroxy epimers introduced in the

seventh step. Separation of the diastereomers was postponed until after the Diels-

Alder cyclization. It is interesting to note that Marshall did not report the Diels-

Alder cyclization of the ester precursor to **35** (**34**). From the information that

Marshall provides, it is not apparent that **34** would decompose upon attempted

cyclization with Lewis acids. Since the ester is a precursor, it would have been a

simple experiment to perform. With the increased branching and functionality it is

possible that the decomposition observed with triene ester **29** would not be an issue

with tetraene **34**.

It should also be noted that, even though **35** is a mixture of benzyloxy epimers, it

appears that the Diels-Alder cyclization proceeded with a high degree of selectivity.

The individual epimers cyclized to give exclusively trans-fused products (**36** and

37). No cis-fused products were observed.

Scheme V

34

35

36   1 : 1   **37**
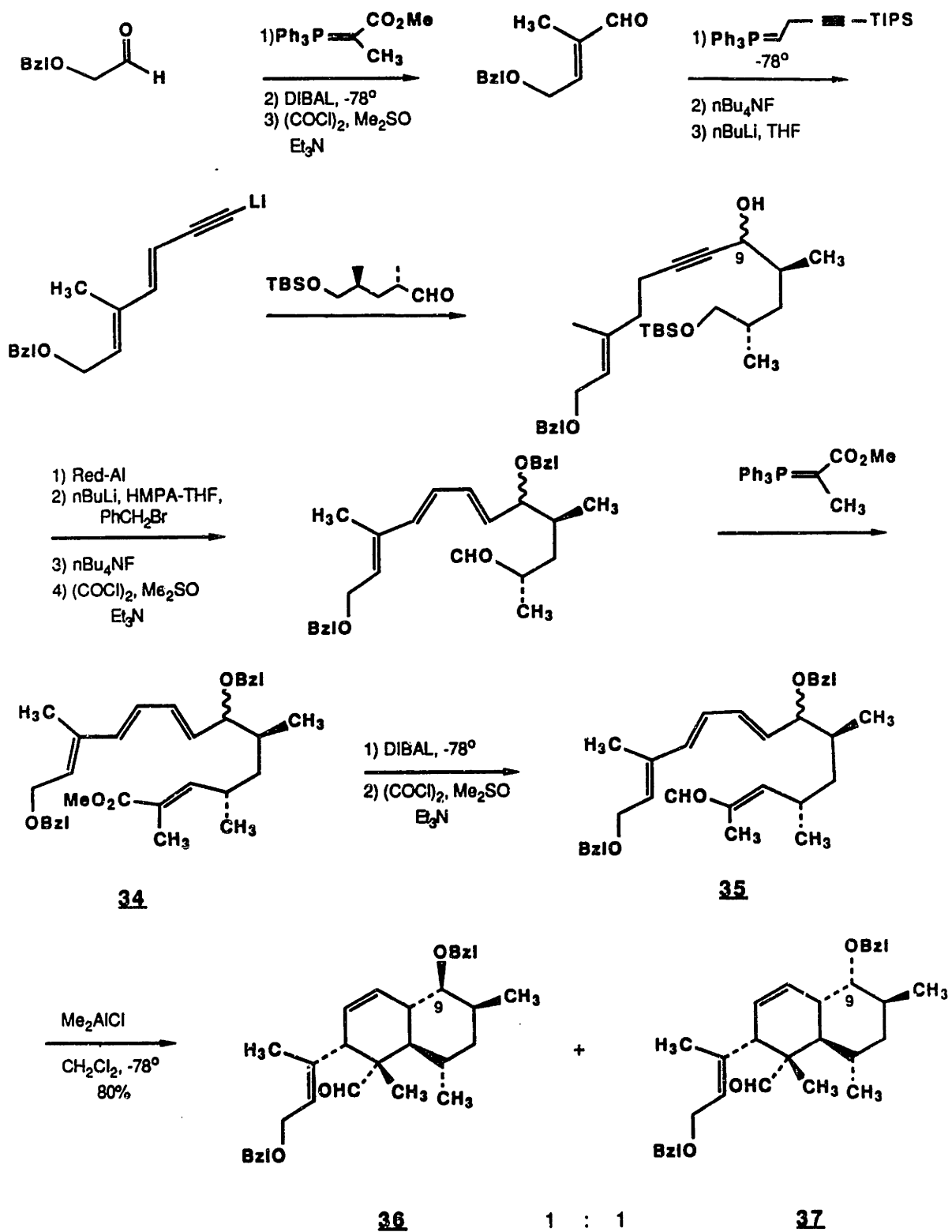
Initial Strategy

Our approach to the synthesis of the lower half of tetronolide 16 is shown in

Scheme VI. The strategy involves an intramolecular Diels-Alder reaction of tetraene

17 to establish the ring junction stereochemistry, as well as the stereochemistry at

C(4) and C(13). The stereochemistry at C(6), C(8), and C(9) of 16 will be es-

tablished in differentiated dialdehyde 38 through the use of the chiral crotylboronic

ester methodology being developed in these laboratories.[18-20] The cyclization of 17

is expected to proceed to the desired product, as was discussed earlier.

Scheme VI
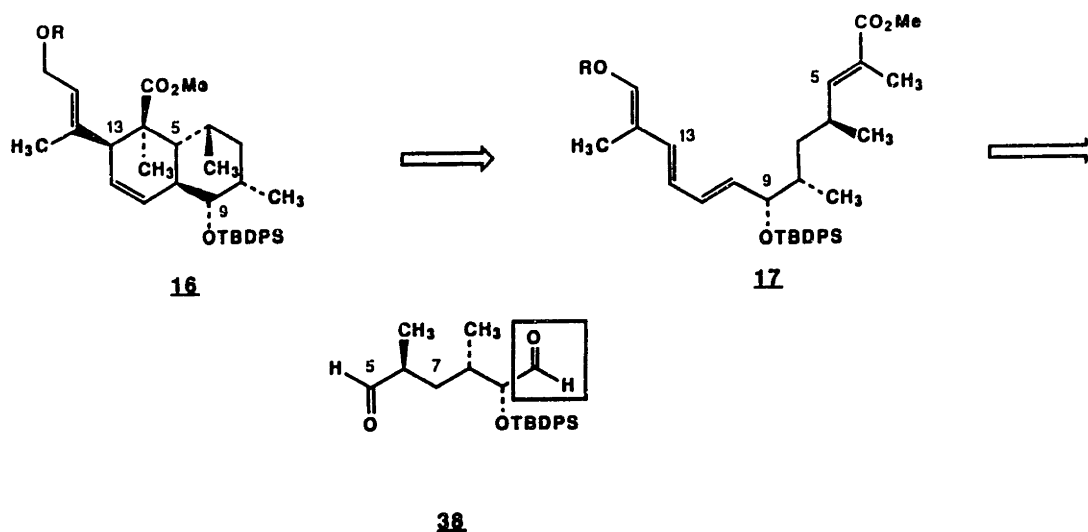
Our initial approach to 38 is outlined in Scheme VII, and involves the reaction of

(D)-glyceraldehyde cyclohexyl ketal 39 with substituted crotylboronate 40. This

step, unfortunately, gave a 60:40 mixture of the 2,3-anti-3,4-anti (41) and 2,3-

syn-3,4-anti (42) products.[20] Separation of the mixture by column

chromatography afforded pure 41 in ca. 30% yield. The stereochemistry was

assigned by comparison with the NMR spectrum of the corresponding acetonide which

Scheme VII

39 + **40** → CH_2Cl_2, 23° / 56%

41 + **42** → TBDPS-Cl / imidazole, DMF / 74%

43 → 1) SeO_2, TBHP CH_2Cl_2, 0° / 2) $NaBH_4$, EtOH / 75% → **44** → H_2 (20 psi) / EtOH, Rh/Al$_2$O$_3$ / 60%

45 + **46** + **47**
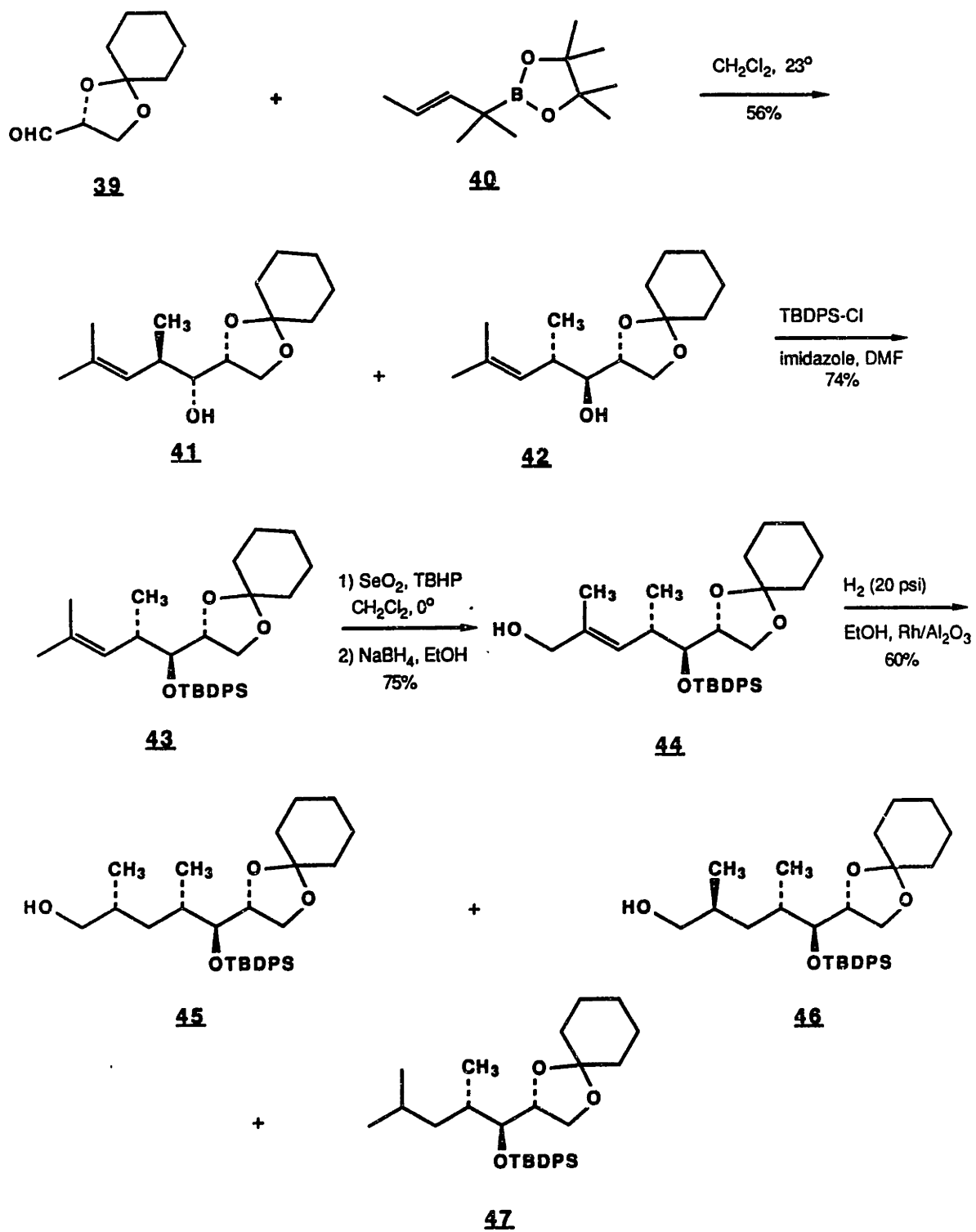
had been previously prepared and characterized in these laboratories by M. Adam.[20]

Subsequent protection and allylic oxidation[21] gave allylic alcohol 44. The SeO_2

oxidation step was mildly tedious in that it was necessary to stop the reaction at

approximately 50% completion to avoid over-oxidation (equation 3). Even with

halting the reaction before completion, a small amount of aldehyde 48 was usually

Equation 3
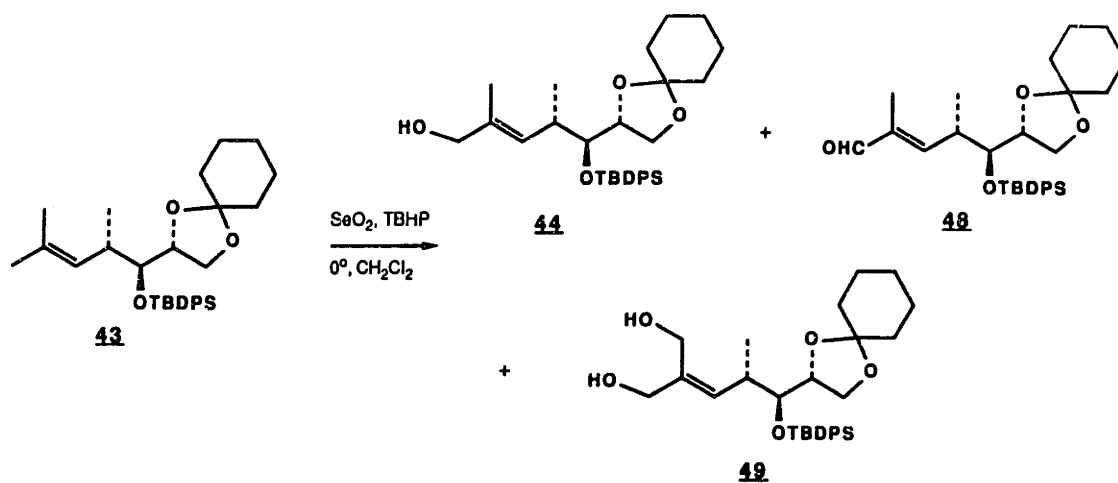
formed. Quenching the reaction with $NaBH_4$ in MeOH reduced 48 to the desired

alcohol 44. Formation of the diol 49 was a problem only if the reaction was run at

room temperature. The unreacted starting material could always be recovered and

resubjected to the reaction conditions. In this fashion a large amount of allylic

alcohol 44 was prepared. Starting with 1.00 g of 43 and recycling four times,

0.78 g of 44 (75% based on reacted 43) and 48 mg (5%) of recovered 43 were

obtained. It should be noted, in a procedure such as this, that as the scale of the

reaction becomes smaller, the returns become increasingly less valuable in terms of

time and effort.

Hydrogenation of 44 was expected to occur from the less hindered face of the most

stable conformation of the compound (see Figure 1) to give the desired relative

stereochemistry at C(6) (Scheme VII). The use of a palladium on carbon, or a

rhodium on carbon catalyst gave substantial amounts of the hydrogenolysis product

47 (with minimal stereoselection in the pathway leading to 45 and 46), and the

hydroxyl directing catalysts developed by Stork and Evans[22] failed to react with 44

Figure 1
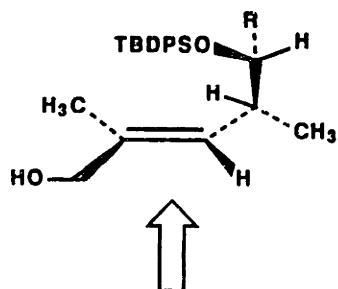
to any significant degree. The best results were obtained with a 5% rhodium on

alumina catalyst at 20 psi. Under these conditions a 1:1 mixture of diastereomers

45 and 46, and a minimal amount of hydrogenolysis product (47), were obtained.

The two diasteremers can be separated by careful chromatography.

With both pure diastereomers in hand, the relative stereochemistry of each was

determined by 400 MHz ^{1}H NMR spectroscopy after performing the manipulations

shown in Scheme VIII. 2-D NMR (COSY) was used to help assign chemical shifts in

the cyclization products 52 and 53. The compound with syn methyl groups (45)

was converted to ether 52 having both methyl groups equatorial, whereas compound

46 cyclized to give 53 having one methyl group axial and one equatorial. Coupling

constants for protons a and b of 52 and 53 are markedly different depending on

whether proton c is axial (52) or equatorial (53) (see Figure 2). Examination of

the coupling constants for proton d establishes that the other methyl group is,

indeed, equatorial. Long-range w-coupling with proton g was also observed for

proton a in both 52 and 53.

Scheme VIII

45

pTsCl
85% pryidine
0°

46

pTsCl
89% pyridine
0°

50

67% nBu₄NF

51

70% nBu₄NF

52

53
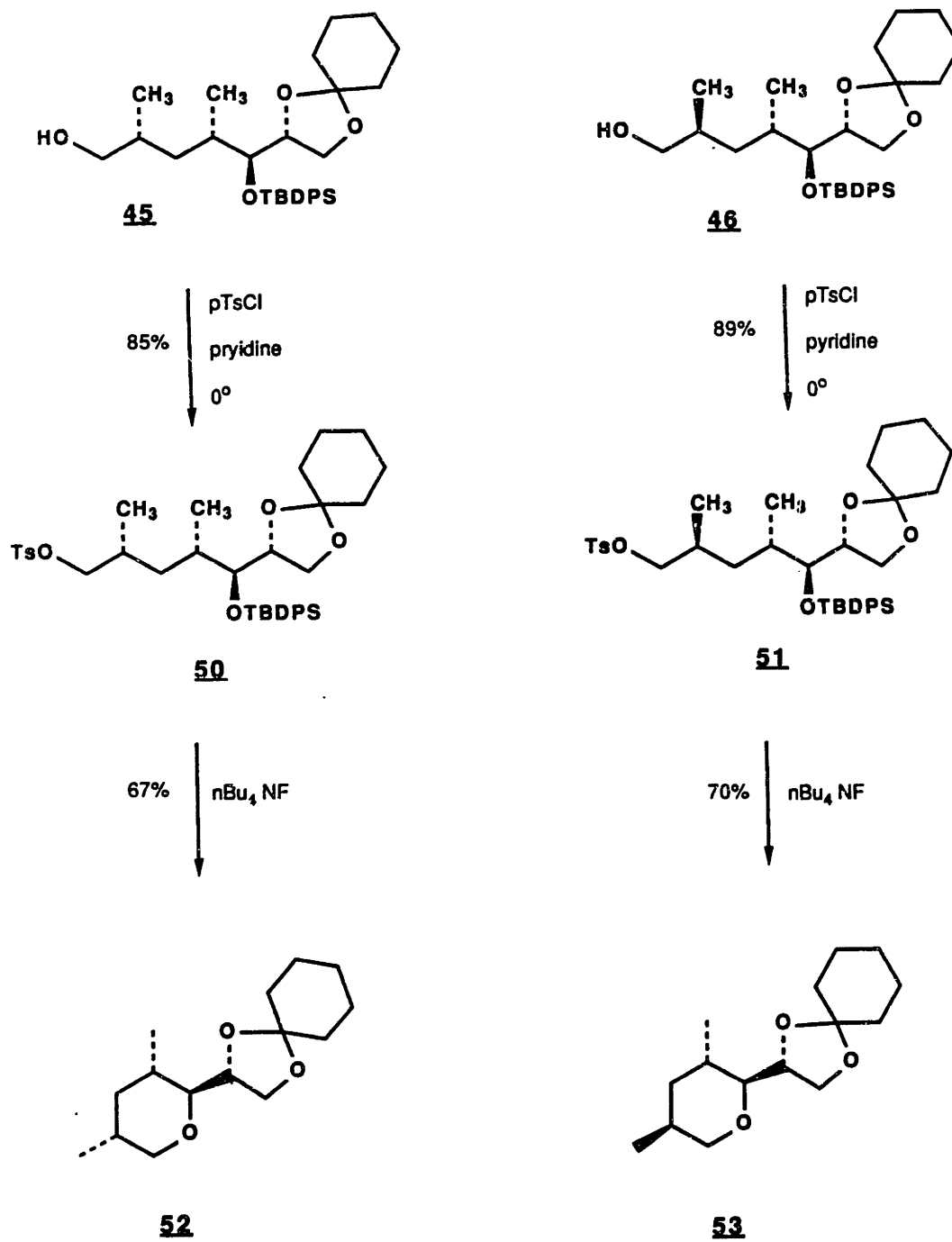
Although the strategy outlined in Scheme VII is direct and brief on paper, there were some obvious drawbacks. Two of the four steps gave approximately 1:1 mixtures of diastereomers, and another (the SeO_2 allylic oxidation) had to be stopped at around 50% completion to avoid over-oxidation. In the first (the allylic boronate addition), the 1:1 selectivity was expected.[20] The reason for this lack of selectivity probably lies in the fact that the aldehyde is providing the only source of chirality.

Figure 2

$$J_{a,b} = 11 \text{ Hz}$$
$$J_{a,c} = 4.0 \text{Hz}$$
$$J_{b,c} = 7.0 \text{Hz}$$
$$J_{d,e} = 8.5 \text{Hz}$$
$$J_{d,f} = 6.5 \text{Hz}$$
$$J_{a,g} = 2.1 \text{Hz}$$

52

$$J_{a,b} = 11 \text{ Hz}$$
$$J_{a,c} = 2.5 \text{Hz}$$
$$J_{b,c} = 2.7 \text{Hz}$$
$$J_{d,e} = 8.6 \text{Hz}$$
$$J_{d,f} = 5.9 \text{Hz}$$
$$J_{a,g} = 2.6 \text{Hz}$$

53
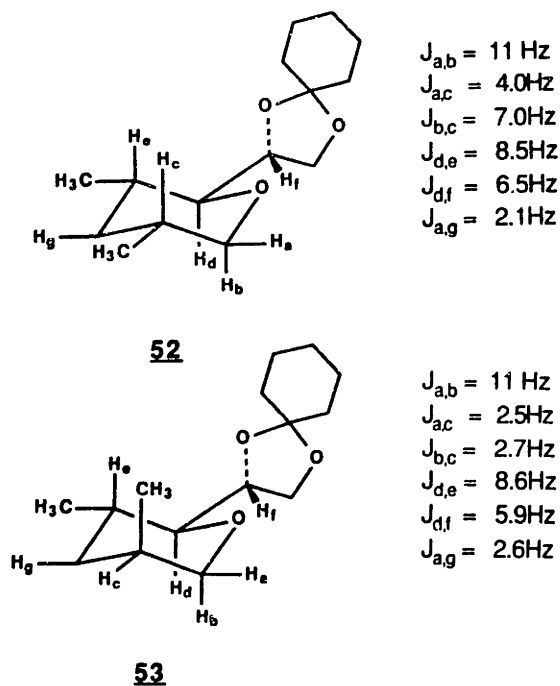
Examination of molecular models shows that despite this asymmetry there is very little difference between the two faces of the aldehyde. Use of a crotylboronate incorporating a chiral auxiliary such as DIPT would be expected to help overcome this problem of poor selectivity.[18,19]

The hydrogenation step, however, was a big disappointment. What we had expected (shown in Figure 1) was for the hydrogenation catalyst to recognize the -CH(OTBDPS)R substituent as being larger than the -CH$_3$ group, and for

hydrogenation to occur selectively from the side of the methyl. The experimental results, however, indicate that the expected differentiation is non-existent.

Figure 1
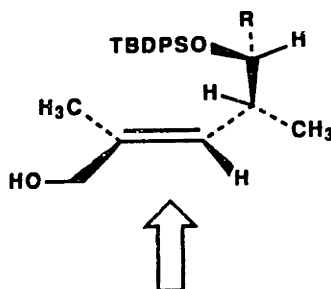
Perhaps (for reasons unknown at this time) the preferred conformation of the molecule is one different than the one shown in Figure 1. Unmasking (or not protecting in the first place) the C(9)-OTBDPS group of **44** and using one of the hydroxyl directing hydrogenation catalysts[22] would probably result in the wrong stereochemistry at the newly formed chiral center. This approach, therefore, was not pursued further and a new strategy for the synthesis of tetronolide precursors was initiated.

Revised Approach

Because of the problems that plagued the initial approach described in the

preceding chapter, it was shelved in favor of the one shown in Scheme IX.

Condensation of (D)-glyceraldehyde acetonide **54** with (R,R)-(E)-crotylboronate

<u>Scheme IX</u>
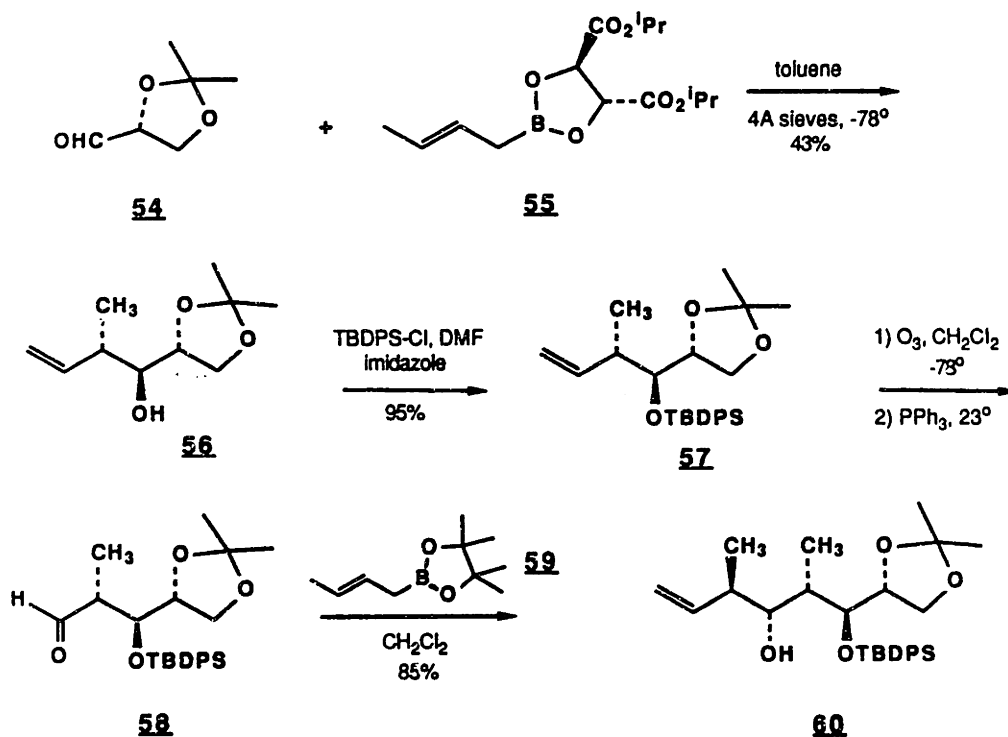
55 afforded alcohol **56** with 89% diastereoselectivity.[19] The diastereomer ratio was

determined by gas chromatography using a capillary SE-54 column. The major

diastereomeric impurity (11%) was the 2,3-syn-3,4-anti product (**61**) arising

from boronate addition to the "front" face of the aldehyde (see Figure 3). There was

also 4% of the 2,3-anti-3,4-syn product arising from minor amounts of the (Z)

Figure 3
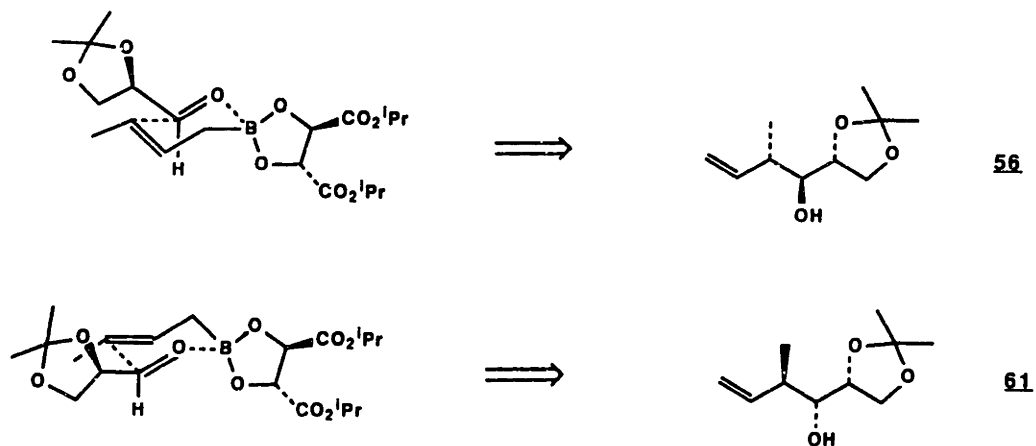
isomer of **55**. Despite the high selectivity, there are some problems with this reaction that have yet to be ironed out.

The low yields which sometimes accompany the reaction can be avoided by making sure that the glyceraldehyde acetonide is freshly distilled (to assure minimal oligimerization), and water-free (to avoid boronic ester decomposition).

The major problems associated with this reaction can be traced to the preparation and handling of the boronic ester **55**, and to the amount of it used in the additon reaction. Ester **55** is prepared from the corresponding boronic acid **62** (equation 4). It was initially thought that the boronic acid was relatively stable as long as it was in solution. Concentration resulted in decomposition and/or polymerization of the acid. Recent extensive work by a co-worker, Lee Hoong, with the allylboronic acid **63** suggests that it is very air sensitive. Boronic acids **62** and **63** are now immediately treated with tartrate ester (even before concentration of the crude extracts), to minimize decomposition prior to the esterification.

Equation 4
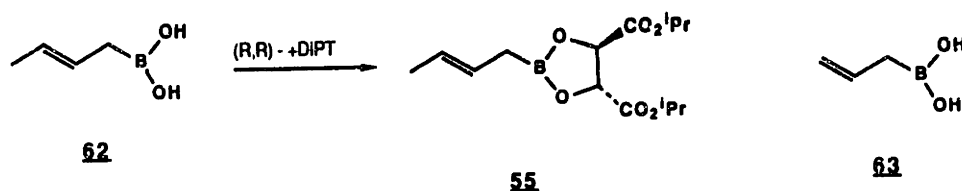
A second major problem is the formation of an impurity of uncertain structure that co-elutes with the desired product. Separation of the two can only be achieved after protection of the hydroxyl of 56 . A GC/MS of the isolated impurity shows that it is actually two compounds each having a molecular weight of 110 amu.

Control experiments established that these impurities are derived from the boronic acid. Subjection of the boronic acid 62, as well as the boronic ester 55 to the various workup conditions for this reaction ($NaBH_4$ in EtOH quench followed by a 1 M NaOH wash or an H_2O wash, and only a 1 M NaOH wash) produced this material.

In addition, when 55 was used as the limiting reagent there was little or impurity formed, but with an excess of 55, large quantities were produced.

After obtaining pure 56, it was protected as the TBDPS ether (57). An ozonolysis set the stage for the condensation of aldehyde 58 with achiral pinacol (E)-crotyl-boronate 59 to give diastereomer 60 with 90% selectivity. The selectivity of the reaction was determined by product isolation, with the stereochemistry of the major product being assigned based on similar work by Hoffmann[23]. He showed that anti aldehyde 64 condensed with pinacol (E)-crotylboronate 59, to give an 89:11 preference for the 3,4-anti-4,5-syn product (equation 5). The minor product of the condensation of 58 and 59 has a different ^{1}H NMR spectrum than that of the 3,4-

syn-4,5-anti product (76), which suggests that it has a structure similar to 66.

Equation 5

64   59   65   66

89 : 11
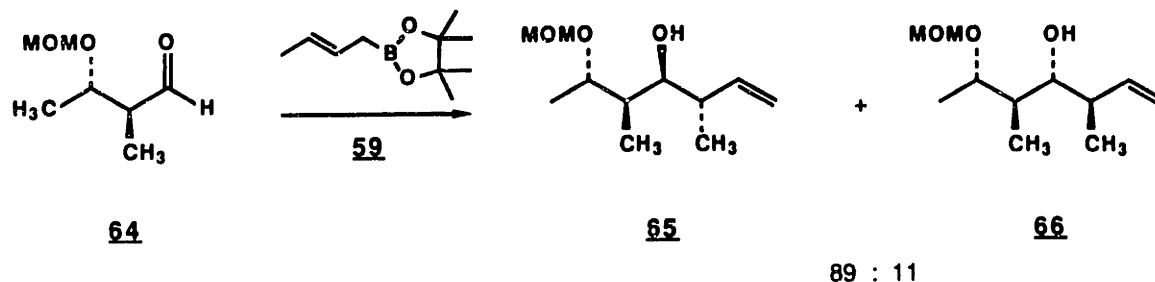
Thus, in just a few steps, all the stereocenters present in differentiated

dialdehyde 38 were established with the correct absolute and relative

stereochemistry. All that remained to be accomplished at this stage was to

deoxygenate at C(7).[24] This one step, however, proved to be immensely

troublesome. Numerous deoxygenation conditions were tried, very few of which gave

positive results.

Attempts to form the phenyl thionocarbonate derivative[25] 67 (Scheme X) under a

variety of conditions (catalytic DMAP, pryridine; stoichiometric DMAP, CH_3CN;

stoichiometric DMAP, CH_3CN, Et_3N; nBuLi, THF, 0°C) gave no reaction (this proved

to be a foreshadowing of the extremely hindered nature of that position), and

formation of the xanthate ester (68) under a modification of the standard

procedure[26] gave multiple decomposition products. Attempted formation of the

phosphonate derivative[27] (69) gave inconclusive results. The products obtained

were difficult to separate, and the toxicity of the phosphorous reagent made large

scale reactions undesirable.

The two methods which were successful were the formation of thioimidazole ester

70 and mesylate 71. Subsequent reduction of the mesylate with $LiAlH_4$, however,

Scheme X

60

PhOC(S)Cl
DMAP, CH₃CN

67

1) KOᵗBu, 18-C-6
CS₂, CH₂Cl₂
2) CH₃I

68

nBuLi, THF
ClP(O)(OEt)₂

69

(imid)₂C=S
toluene, Δ

82%

70

MsCl, Et₃N, 0°

47%

71
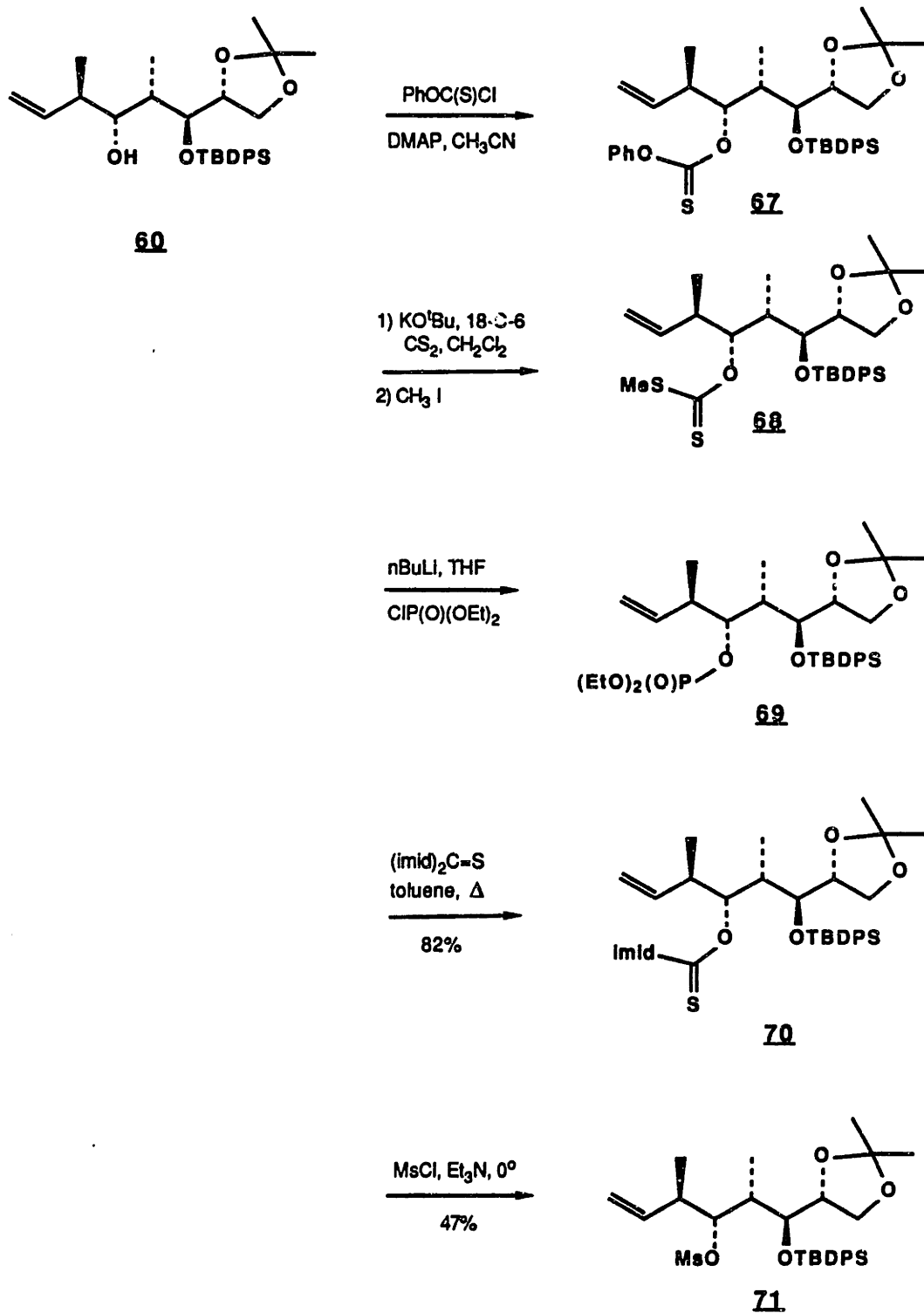
appeared to give a cyclic ether 74. What evidently happens is summarized in Scheme XI. Support for this mechanism comes from our obsevation that 71 is unstable and rearranges to alcohol 75 upon standing at room temperature; presumably through a mechanism similar to the one shown in Scheme XI, but with trace amounts of water acting as the nucleophile (on 73) instead of hydride.

Mesylation of the hydroxy epimer of 60 (76) also produced a rearrangement product (78) on standing. When mesylate 77 was treated with LiAlH$_4$ within a few hours of preparation, however, an inseparable 3:1 mixture of reduction (79) and elimination (80) products was obtained (equation 6). This experiment provides a

<u>Scheme XI</u>
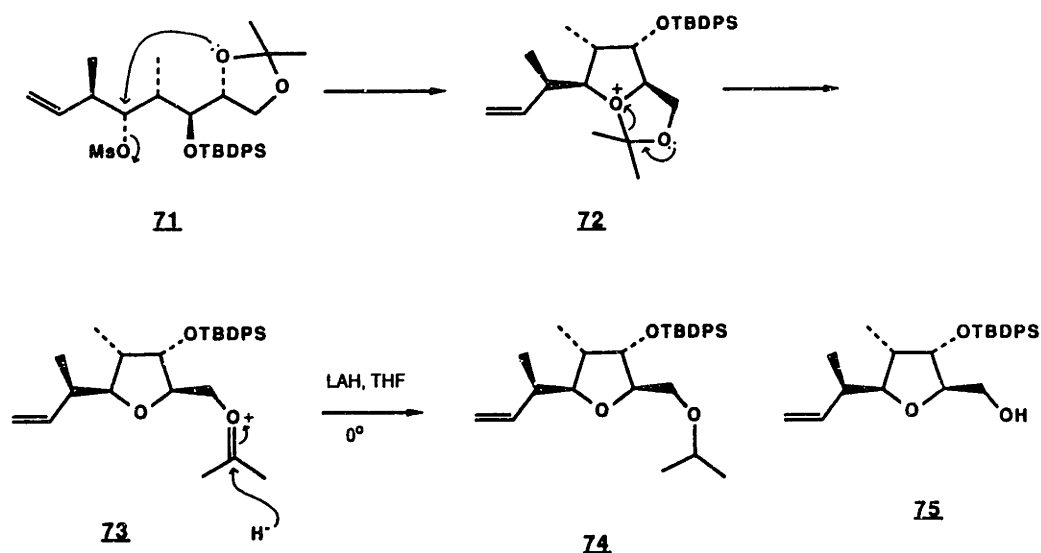
glimmer of hope to the deoxygenation impasse discussed below. We have not attempted to improve this result, although one method might be the use of a smaller protecting group for the C(9) hydroxyl. Such studies await future experimentation.

Equation 6
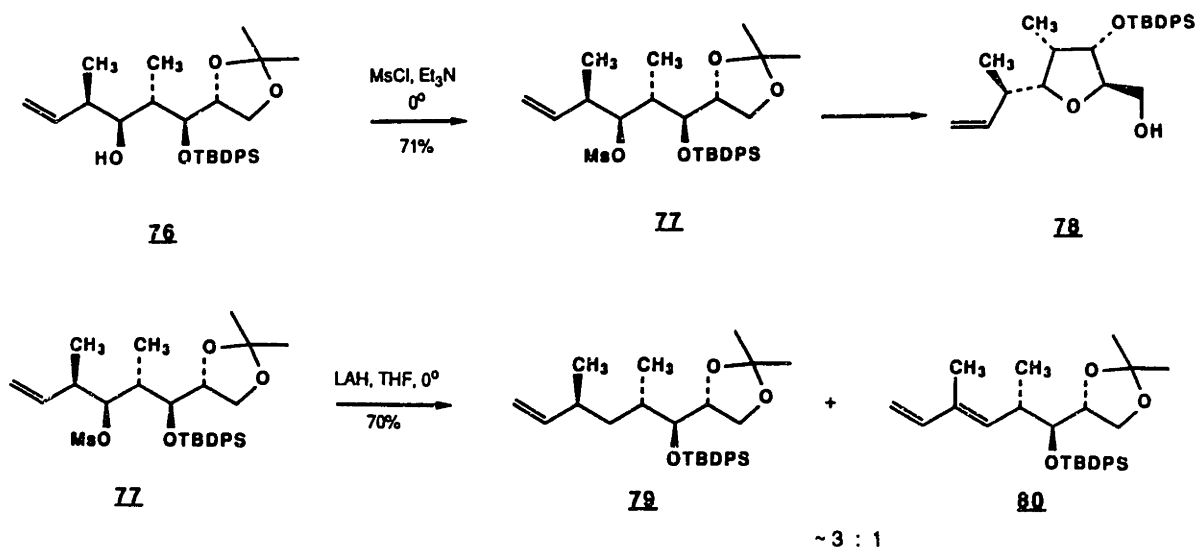
Treatment of 60 with 1,1'-thiocarbonyl diimidazole in toluene at 80° gave 70 (Scheme X) in 82% yield.[28] Reduction of the derivative with nBu_3SnH,[29] however, gave a product with no olefinic protons. We suspect that the intermediate homo-allylic radical attacked the double bond to give either a cyclopropane (81) or a cyclobutane (82) derivative (equation 7). If the reduction product were a cyclopropane derivative, one would expect to see three, or perhaps four, methyl doublets in the ^1H NMR spectrum because of the possibility of diastereomeric products. Two are definitely visible, and a third is partially hidden by the signal from the t-butyl group. Chemical shifts for cyclopropyl methine protons are expected to occur at about 1 ppm which, unfortunately, is a region where several other signals for this compound occur. Chemical shifts for cyclobutyl methylene protons should appear around 1.9 ppm, but that region of the spectrum shows no signals. Since formation of the cyclobutane adduct appears improbable based on stereoelectronic considerations, it is likely that a cyclopropane (81) is the product of this reaction.

Equation 7
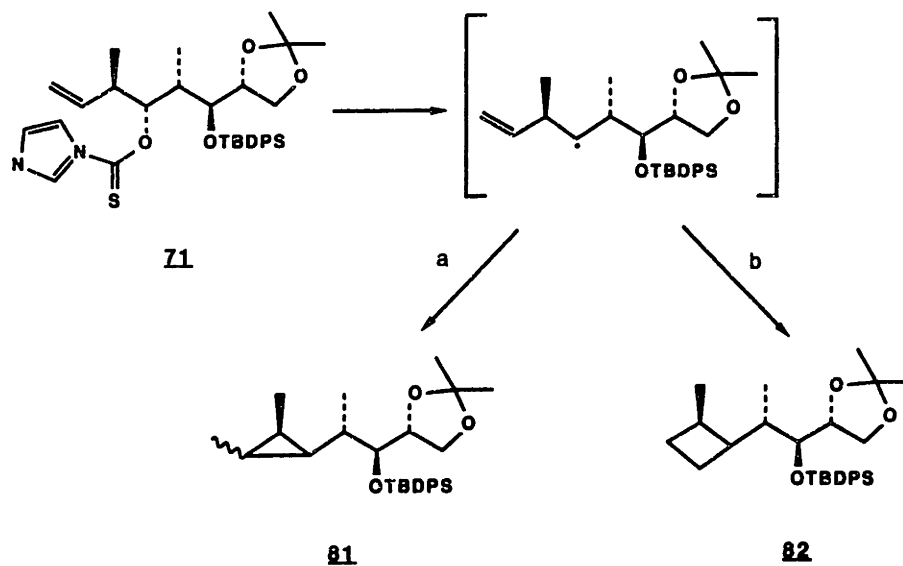
Forming the thioimidazole derivative **83** from **76**, the hydroxy epimer of **60**, and then reducing with nBu₃SnH also gave a compound with no olefinic protons. The ^{1}H
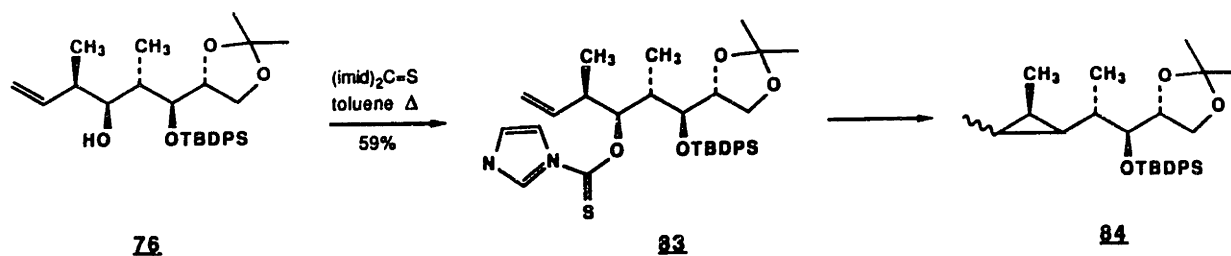
NMR spectrum of the reduction product (**84**) clearly shows three methyl doublets, suggesting again that a cyclopropane derivative was formed. Suffice to say that the desired product was not obtained from either diastereomer by this method.

In an attempt to circumvent the problem of cyclopropane formation in the radical deoxygenation of **60**, the olefin was masked as the epoxide **85** (see Scheme

XII). This time, however, treatment with 1,1'-thiocarbonyl diimidazole gave rise to multiple products. Apparently the epoxide underwent undesired reactions with the

Scheme XII
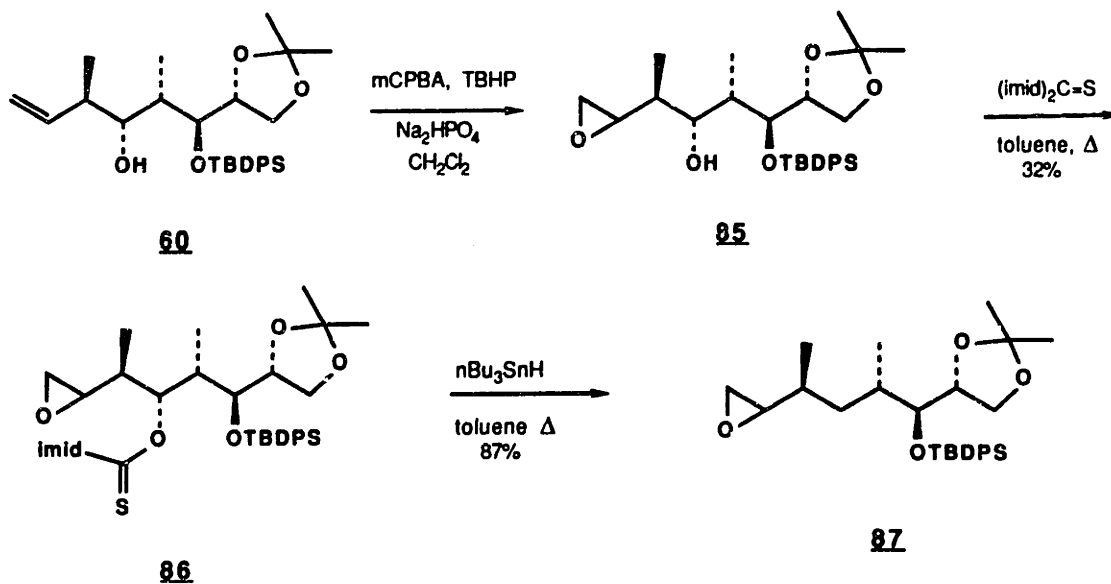
reagent, or possibly intramolecular reactions after functionalization of the hydroxyl. The small amount of desired product (86) that was obtained could be cleanly deoxygenated in 87% yield by treatment with nBu$_3$SnH in refluxing toluene[29] (Scheme XII). Formation of the benzyl thionocarbonate and phosphonate derivatives were no more successful with epoxide 85 than they were with olefin 60.

The next deoxygenation strategy involved ozonolysis of 60 followed by in situ reduction to give the 1,3-diol (88). Selective protection at the primary position gave the β-hydroxy pivalate ester 89 (equation 8). Our hope was that deoxygenation of 89 would proceed smoothly, and that the terminal -CH$_2$OPv group could be unmasked and then oxidized to give the requisite aldehyde at a subsequent stage of the synthesis. This route, however, also proved fruitless. The bulky pivalate group coupled with the already highly hindered position of the alcohol rendered this compound virtually inert to derivative formation.

Equation 8
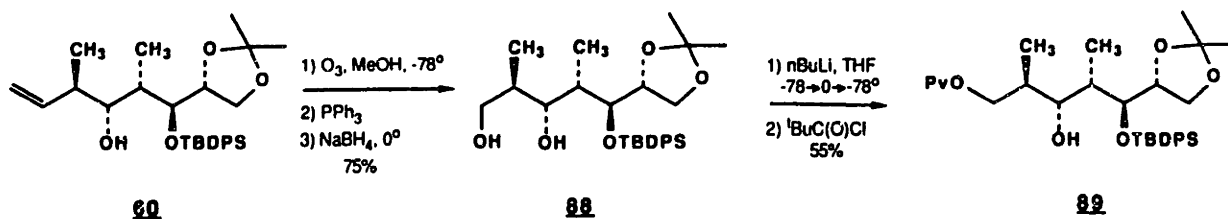
Reaction of **89** with either 1,1'-thiocarbonyl diimidazole or phenyl chloro-thionocarbonate (with catalytic DMAP) gave no reaction. Use of stoichiometric DMAP with phenyl chlorothionocarbonate resulted in rearrangement to a product similar to **74** and **75**, with the probable structure of **90**, and use of diethyl chlorophosphate again gave inconclusive results due to the difficulty of product separation. The only successful reaction with **89** was the formation of the acetate

90
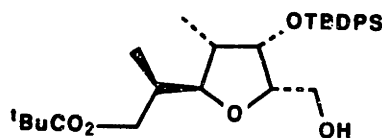
derivative. This normally facile transformation proved very sluggish with this compound, an indication of just how hindered this position is.

Scheme XIII
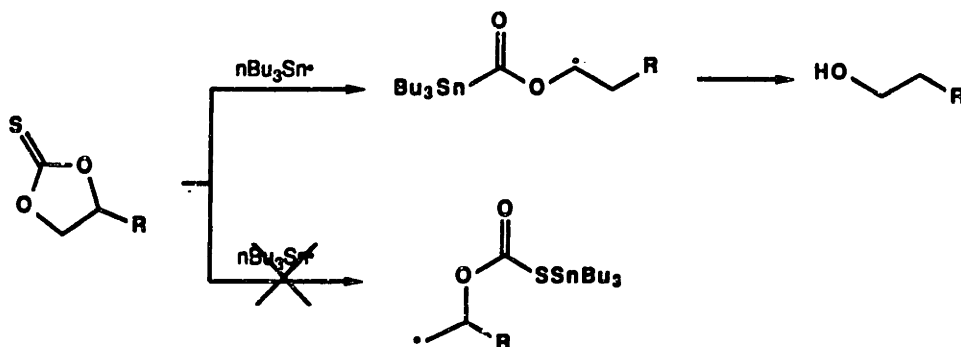
A procedure investigated by Barton and others[30,31] involves the formation of the thiocarbonate of 1,2 or 1,3 diols, followed by reduction with nBu_3SnH. Due to the radical mechanism of the reduction, fragmentation of the thiocarbonate proceeds exclusively through the $2°$ radical[30] to give the $1°$ alcohol (Scheme XIII). Attempts to use this procedure on diol 88 resulted primarily in decomposition products.

A rather different approach to the deoxygenation problem made use of an idea borrowed from Danishefsky.[32] In work involving Lewis acid catalyzed cyclocondensations of functionalized dienes with aldehydes, he showed that hydrogenation of certain α,β-unsaturated lactones gave a single diastereomer as shown in equation 9. Our adaptation of this strategy is shown in Scheme XIV. DCC coupling of alcohol 57 with phosphono ester 93 gave phosphonate 94 in 67-87% yield. The intramolecular Wittig reaction (to give 95) was accomplished, following ozonolysis, by treatment with LiCl and $^iPr_2NEt$ in CH_3CN[33]. One drawback to this strategy was the varying amounts (16-35%) of unsaturated aldehyde (96) that were formed. The critical hydrogenation step once again gave a 1:1 mixture of

Equation 9

91   **92**
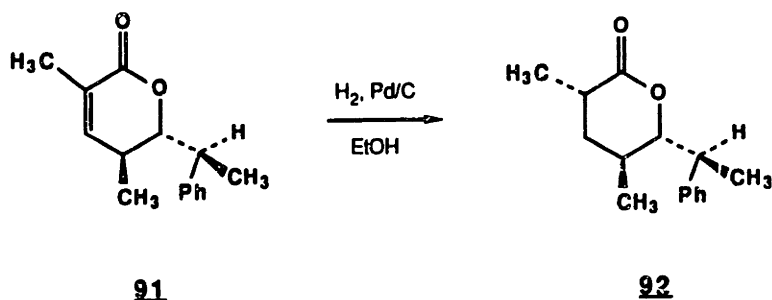
diastereomers (**97**). Several different catalysts and reaction conditions were tried with no improvement in selectivity.

Since deoxygenation at this point was looking pretty bleak, it was decided to protect the hydroxyl as the acetate and renew deoxygenation attempts after the Diels-Alder cyclization. This requires the hydroxyl to have the opposite stereochemistry so that the desired transition state is not destabilized by an axial acetoxy substituent (see Scheme XV).

This new strategy required a slight modification of Scheme IX. Instead of condensing aldehyde **58** with crotylboronate **59**, **58** was condensed with (R,R)-(Z)-crotylboronic ester **100** to give **76** (equation 10). The selectivity for this reaction is 94:6 (based on product isolation) in favor of the diastereomer shown.[19,20] The minor diastereomer is **60**, which arises, presumably, from (E)-crotylboronate contaminants in **100**. The isomeric purity of **100** is 92-93%.

Scheme XIV

57

(ETO)$_2$P(O)CH(CH$_3$)CO$_2$H **93**

DCC, DMAP
CH$_2$Cl$_2$, 23°
87%

94

1) O$_3$, MeOH, -78°
2) Me$_2$S

3) LiCl, ^{i}Pr$_2$NEt
CH$_3$CN

95

+

96

57 - 75%

16 - 35%

H$_2$, Pd/C

EtOH
90%

97

Scheme XV

98

99

Equation 10

58

toluene, -78°
4A sieves
81%

76

+

60

94 : 6
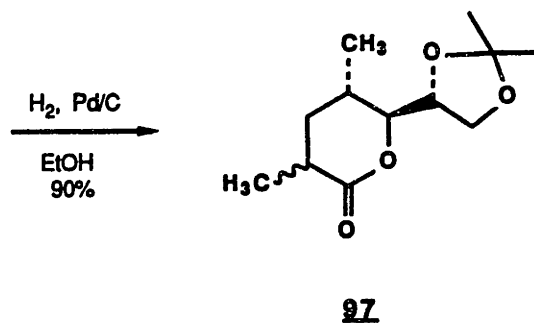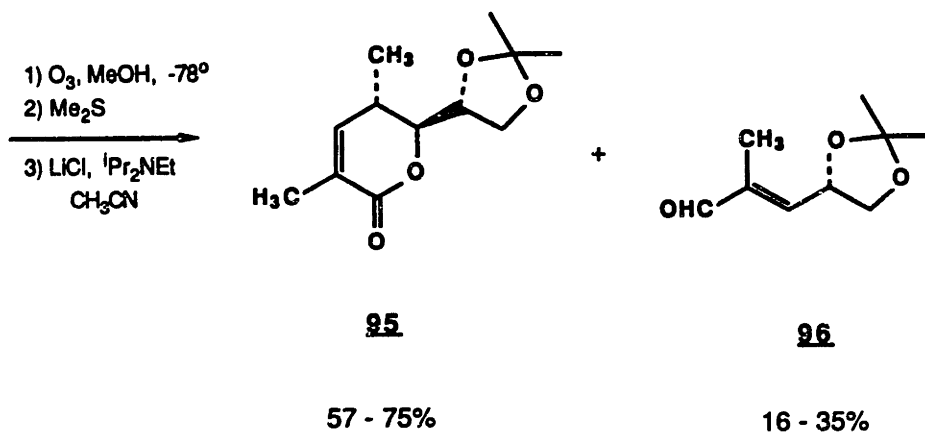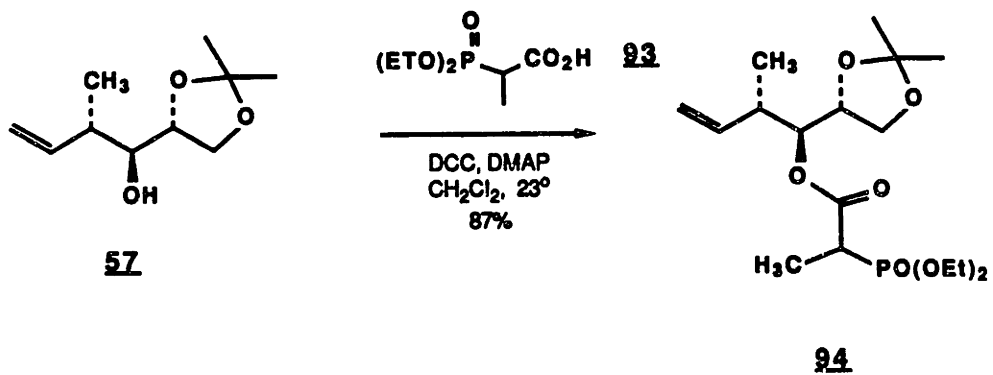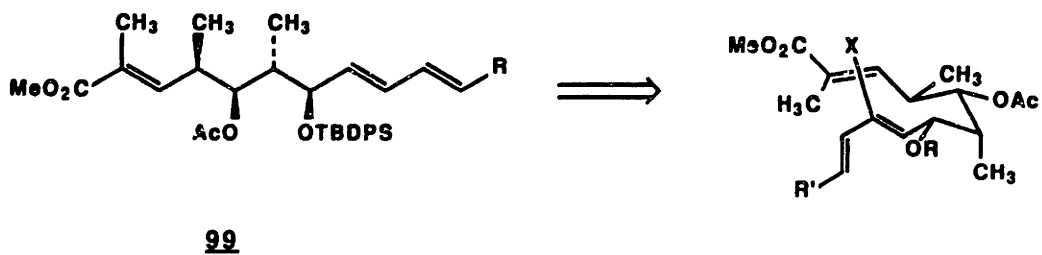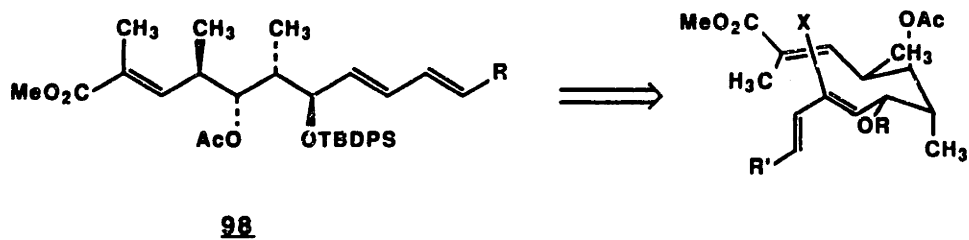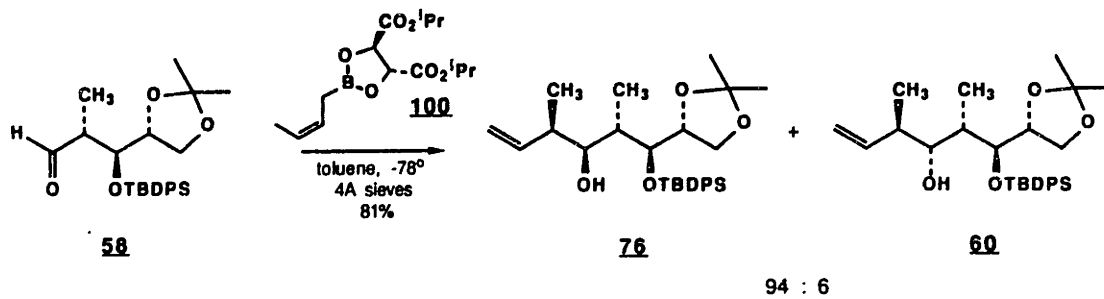
With differentiated dialdehyde equivalent, 76, in hand, we briefly studied methods

for the introduction of the diene and dieneophile. Incorporation of the dienophilic

Equation 11
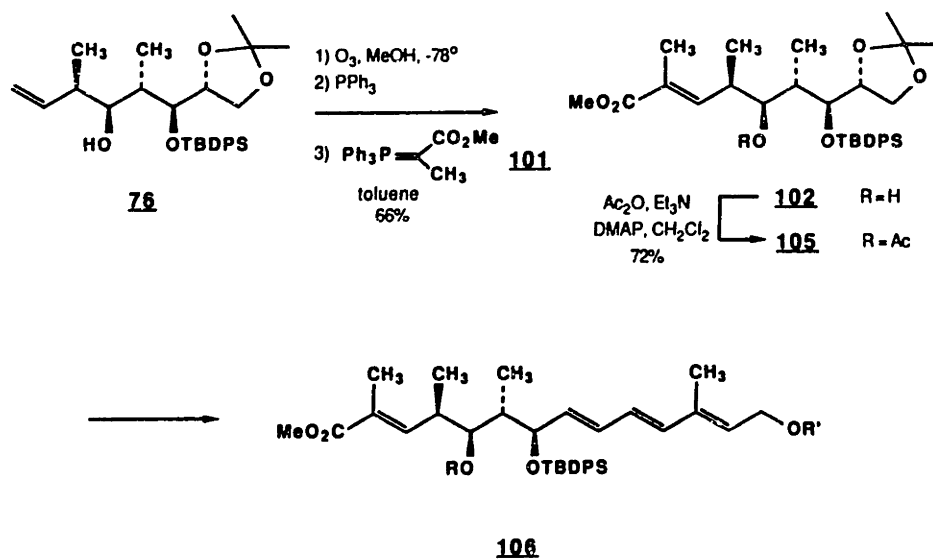
moiety was readily accomplished by ozonolysis of 76 followed by *in situ* treatment

with methyl 2-(triphenylphosphanylidene)-propionate (101, Equation 11) in

toluene at 50°. If the acetonide were cleaved to the aldehyde at this stage, it is

probable that the molecule would prefer to exist as the hemiacetal 104 rather than

the aldehyde 103 (Equation 12). As that might interfere with the incorporation of

the diene, 102 was protected as the acetate 105 (Equation 11). Attempts to cleave

the acetonide with mild acid (TsOH, MeOH; PPTS, MeOH; 50% HOAc, MeOH),

however, appeared to also hydrolyze the acetate.

Equation 12

103   104
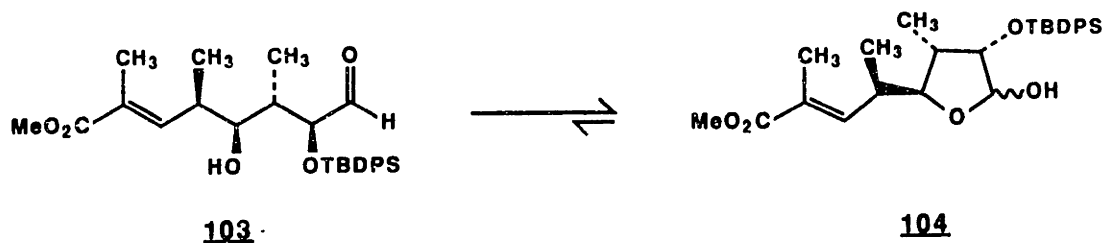
Further work on the selective cleavage of the acetonide was put aside in order to explore the possibilities for formation of the diene. One promising idea comes from Suzuki and co-workers[36] and involves the coupling of a vinyl halide and a vinyl boronic ester with a palladium(0) catalyst (Equation 13). As a model system we

Equation 13

$X = (Sia)_2$ $L = PPh_3$
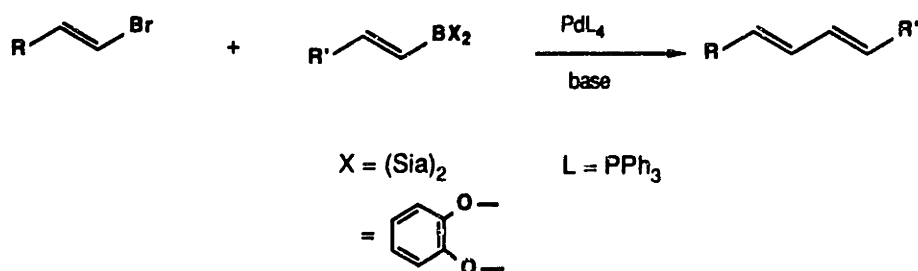
looked at the coupling of dibromo olefin 107 and boronic ester 108 (Equation 14). Following the procedure of Corey and Fuchs,[37] 107 was prepared from (D)-glyceraldehyde acetonide by treatment with triphenylphosphine and carbon tetrabromide in dicholoromethane. Boronic ester 108 was prepared from catechol borane and 1-hexyne as described by Brown (Equation 14).[38] This pathway is

advantageous in that it incorporates a steric directing group (see p. 11) without adding additional steps to the synthesis. Preliminary investigations into the coupling of 107 with 108 show promise. When the reaction was heated to 80° for 1 hour with 1.1 equiv. of 108, a 2:1 mixture of unreacted 107 and desired diene 109 were obtained.

It would appear, then, that with minor adjustments to the reaction conditions, the palladium coupling should provide a direct route to tetraene 17. Having reached this point, the intramolecular Diels-Alder cyclization of 17 should proceed smoothly and stereoselectively to the desired compound: the lower half of tetronolide (16).

Equation 14
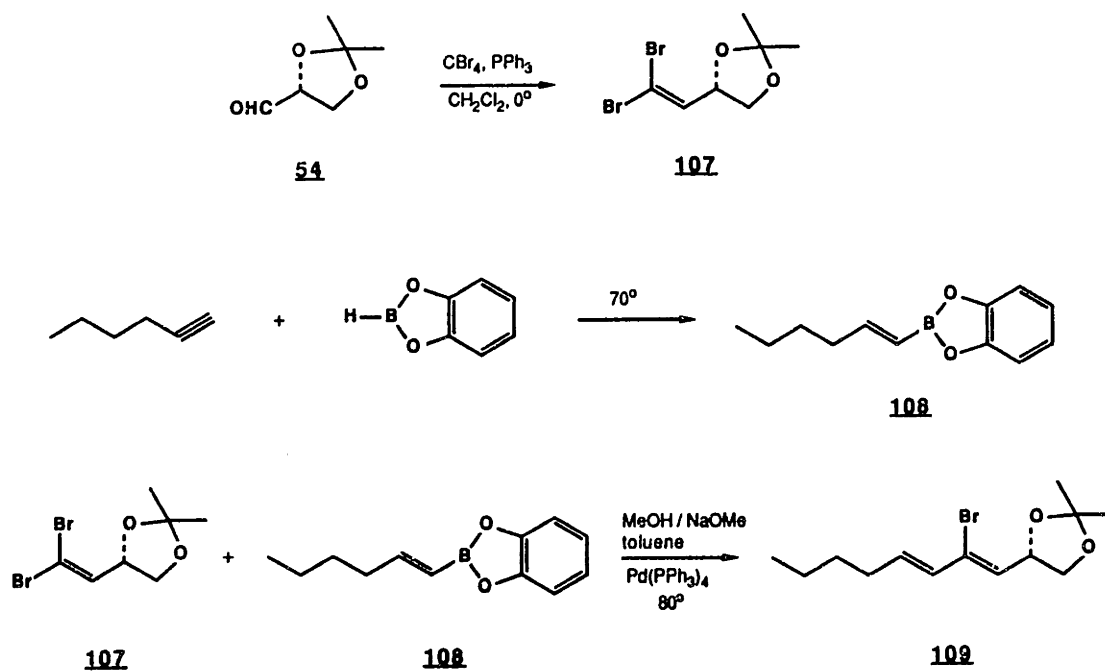
Experimental Section

<u>General</u>:

Proton (^{1}H) NMR spectra were measured at 250 MHz on a Bruker WM250, and at 300 and 400 MHz on a Varian XL300 or XL400 instrument. Chemical shifts are reported in δ units using the 7.24 ppm resonance of residual $CHCl_3$ as an internal reference. The tetronolide numbering system is used for all ^{1}H NMR assignments. Infrared spectra were measured on a Perkin-Elmer model 1420 or a Perkin-Elmer model 280 infrared spectrophotometer, and were calibrated using the 1601 cm^{-1} absorption of polystyrene. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1cm^3 quartz cell (10 cm path length). Low resolution mass spectra were measured at 70eV on a Finnegan MAT 8200 or on a Hewlet-Packard model 5990A gas chromatograph/mass spectrometer.

Capillary gas chromatograph analyses were performed on a Shimadzu GC-9A gas chromatograph using a 10% crosslinked DMS column (12M x 0.2mm) or an Alltech SE-54 column (50M x 0.2mm), using helium as the carrier gas.

All reactions were conducted in oven (140º) or flame dried glassware under atmospheres of dry argon or nitrogen. All solvents were distilled prior to use. Ether, THF, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride, dimethyl sulfide, and pyridine were distilled from calcium hydride. Methanol was distilled from magnesium methoxide and stored over 3Å sieves.

Analytical thin layer chromatography (TLC) was performed by using 2.5cm x 10cm plates coated with a 0.25mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin layer chromatography (PTLC) was performed by using 20cm x 20cm plates coated with a 0.25, 0.5, 1.0, or 1.5mm thickness of silica gel containing PF 254 indicator (Analtech). Compounds were

visualized by short-wave UV, by charring with 10% $(NH_2)SO_4$, or by charring with ethanolic PMA. Compounds were eluted from the adsorbants with ether or ethyl acetate. Flash column chromatogaphy was performed using Kieselgel 60 (230-400 mesh) or Kiesegel 60 (70-230 mesh) as described by Still.[35] All chromatography solvents were distilled prior to use.
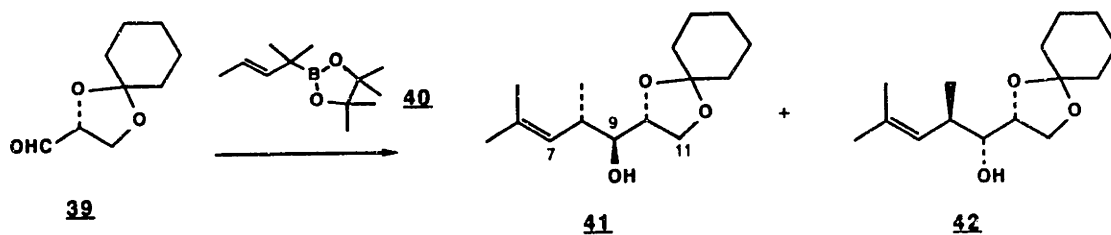
Substituted crotylboronate **40**[20] (1.06 g, 5.06 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to -78°C. Aldehyde **39** (0.78 g, 4.6 mmol) was added dropwise over 10 min. The reaction mixture was then warmed to room temperature and stirred overnight. It was then partitioned between CH_2Cl_2 and water. The aqueous phase was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was then purified by flash chromatography (6 cm column, 6" of silica gel) using a 3:1 hexane:ether eluant to give 0.367 g (31%) of **41** and 0.219 g (19%) of **42**.

Data for **41**: R_f 0.21 (3:1 hexane-ether); $[\alpha]_D^{23}$ = -4.6° (C=0.26, CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 5.03 (dd, J=2.1, 9.1 Hz, 1H, H_7), 3.85-4.05 (m, 3H, H_{10} and H_{11}), 3.57 (m, 1H, H_9), 2.55 (m, 1H, H_8), 1.85 (d, J=4.2 Hz, 1H, OH), 1.73 (d, J=2.1 Hz, 3H, CH_3), 1.65 (d, J=2.1 Hz, 3H, CH_3), 1.6 (br m, 10 H, cyclohexyl), 1.0 (d, J=6.2 Hz, 3H, CH_3); IR (neat) 3470, 2930-2860, 1450, 1362, 1280, 1162, 1100, 1042, 930, 850 cm^{-1}; mass spectrum m/e 252 (M$^+$ - H_2).

Data for **42**: R_f 0.39 (3:1 hexane-ether); $[\alpha]_D^{23}$ = -10.4° (C=0.45,

CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 5.16 (dd, J=2.1, 10.4 Hz, 1H, H_7), 4.04 (br

ddd, J=6.2, 9.6 Hz, 1H, H_{10}), 3.97 (dd, J=7.3, 6.2 Hz, 1H, H_{11}), 3.73 (dd, J=7.3,

6.2 Hz, 1H, H_{11}), 3.35 (m, 1H, H_9), 2.45 (m, 1H, H_8), 2.26 (d, J=4.22 Hz, 1H,

OH), 1.71 (d, J=2,1 Hz, 3H, CH_3), 1.59 (d, J=2.1 Hz, 3H, CH_3), 1.59 (br m, 10

H, cyclohexyl), 1.03 (d, J=7.9 Hz, 3H CH_3); IR (neat) 3480, 2960-2860,

1450, 1368, 1280, 1160, 1100, 1040, 990 930, 910 845 cm^{-1}; mass

spectrum m/e 252 (M^+ - H_2).
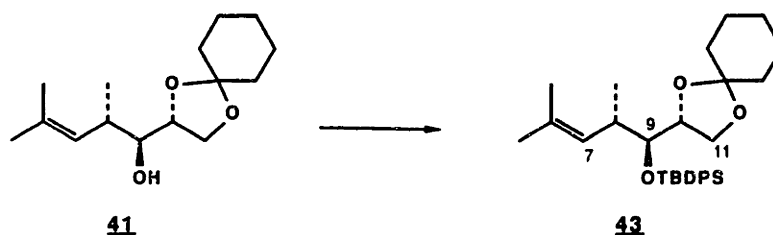
Alcohol **41** (0.724 g, 2.86 mmol) was dissolved in 2.8 mL of dry DMF. Imidazole

(0.48 g, 7.15 mmol) was then added and the reaction mixture stirred for 5 minutes.

TBDPS-Cl (1 ml, 5.7 mmol) was then added dropwise. The reaction was heated to

45°C and stirred overnight. The crude reaction mixture was partitioned between

ether and water. The aqueous phase was washed three times with ether. The

combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The

crude product was purified by flash chromatography (6 cm column, 6.5" of silica

gel) using a 25:1 hexane:ether eluant to give 1.04 g (74%) of **43** as a pale yellow

liquid: R_f 0.45 (25:1 hexane-ether); $[\alpha]_D^{23}$ = -0.44° (C=0.95, CH_2Cl_2); NMR

(250 MHz, $CDCl_3$) δ 7.3-7.8 (m, 10H, phenyl), 5.03 (br dd, J=8.4 Hz, 1H, H_7),

5.0-5.4 (m, 1H, H_{10}), 4.73-4.86 (m, 3H, H_9 and H_{11}), 2.47 (m, 1H, H_8), 1.6

(s, 3H, CH_3), 1.53 (br m, 10H, cyclohexyl), 1.23 (s, 3H, CH_3), 1.06 (s, 9H,

^tBu), 0.85 (d, J=8.3 Hz, 3H, CH_3); IR (neat) 3060, 3040, 2975-2850, 1475,

1460, 1415, 1410, 1377, 1175, 1115, 951, 840, 755, 723 cm^{-1}; mass

spectrum m/e 237 (M$^+$ - OTBDPS).
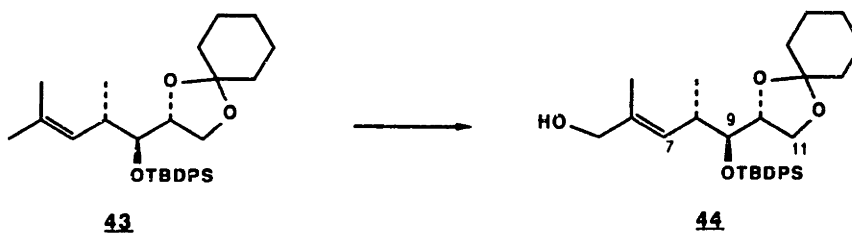
SeO$_2$ (62 mg, 0.57 mmol) was dissolved in 0.33 mL (1.13 mmol) of TBHP

(3.43 M solution in CH$_2$Cl$_2$) and 0.4 mL of CH$_2$Cl$_2$. This solution was stirred for 15

min at room temperature, then cooled to 0°C. Olefin **43** (480 mg, 1.14 mmol) was

added as a solution in 0.8 mL of CH$_2$Cl$_2$ and the reaction mixture was stirred

overnight at 0°C. Any aldehyde produced by overoxidation of **43** was reduced by

addition of a solution of 48 mg of NaBH$_4$ in 3 mL of MeOH at 0°C, and stirring for 20

min at room temperature. The reaction mixture was then partitioned between

CH$_2$Cl$_2$ and 15% aqueous NaOH. The aqueous phase was washed with CH$_2$Cl$_2$. The

combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated to give

a clear yellow liquid. The crude product was purified by flash chromatography (3

cm column, 6" of silica gel) using a 1:1 hexane:ether eluant to give 285 mg (47%)

of recovered **43** and 330 mg (53%) of desired **44**: R$_f$ 0.32 (1:1 hexane-ether);

$[\alpha]_D^{21}$ = -9.8° (C=0.80, CHCl$_3$); NMR (250 MHz, CDCl$_3$) δ 7.3-6.75 (m, 10H,

phenyl), 5.36 (br dd, J=10.4 Hz, 1H, H$_7$), 3.57-4.15 (m, 6H, H$_5$, H$_9$, H$_{10}$, and

H$_{11}$), 1.75 (br s, 1H, OH), 1.5 (br m, 10H, cyclohexyl), 1.3 (s, 3H, CH$_3$), 1.7

(s, 9H, ^{t}Bu), 0.89 (d, J=7.5 Hz, 3H, CH$_3$); IR (neat) 3380, 3060, 3040, 2980-

2840, 1480, 1445, 1410, 1377, 1290, 1100, 960, 977, 845, 765, 725 cm^{-1}.
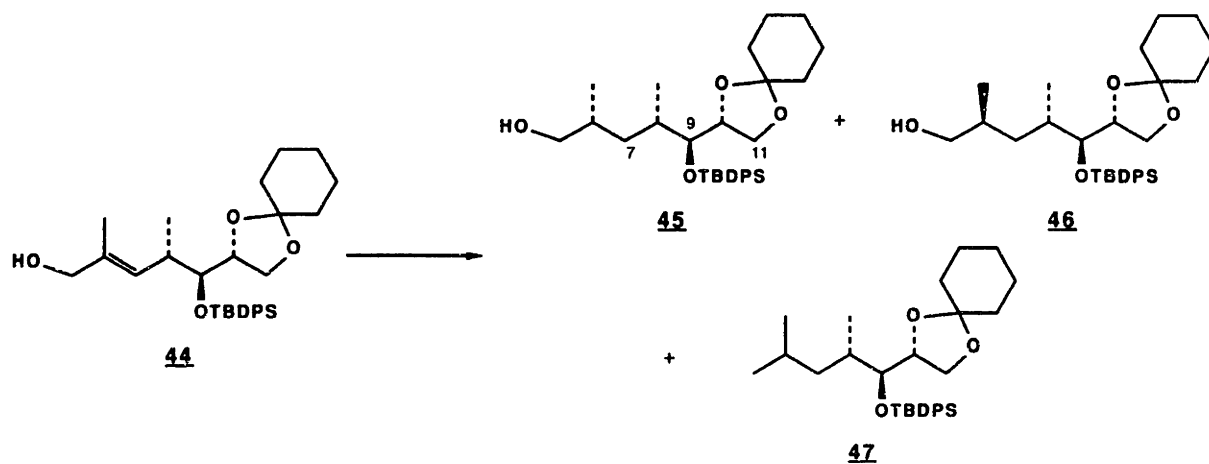
Olefin **44** (259 mg, 0.510 mmol) in 5 mL of MeOH was added to the hydrogenation catalyst (5% Rh/Al_2O_3, 136 mg, 0.102 mmol) in a test tube, and the reaction mixture put under 20 psi H_2 with agitation for 24 hours. The hydrogenation catalyst was then filtered off through a small column of silica gel. The solution of crude product was concentrated and then purified by preparative tlc (1.5 mm silica gel plate, 3:1 hexane:ether, 4 elutions) to give 69 mg (35%) of **45**, 88 mg (44%) of **46** and 30 mg (12%) of **47**.

Data for **45**: R_f 0.19 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{21}$ = -2.0° (C=0.92, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 7.35-7.76 (m, 10H, phenyl), 4.17 (m, 1H, H_{10}), 3.87 (dd, 1H, J=8.3, 6.2 Hz, 1H, H_{11}), 3.76 (dd, J=2.1, 6.7 Hz, 1H, H_9), 3.65 (dd, J=8.4, 6.6 Hz, 1H, H_{11}), 3.27 (br m, 2H, H_5), 1.53 (br m, 10H, cyclohexyl), 1.06 (s, 9H, ^tBu), 0.9 (d, J=6.6 Hz, 3H, CH_3), 0.80 (d, J=6.2 Hz, 3H, CH_3); IR (neat) 3480, 3025-2875, 1470, 1460, 1445, 1425, 1380, 1360, 1120 cm^{-1}.

Data for <u>46</u>: R_f 0.17 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{21}$ = -0.5° (C=1, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 7.3-7.75 (m, 10H, phenyl), 4.1 (m, 1H, H_{10}), 3.9 (dd, J=6.2, 7.3 Hz, 1H, H_{11}), 3.78 (m, 2H, H_9 and H_{11}), 3.23 (br s, 2H, H_5), 1.53 (br m, 10H, cyclohexyl), 1.05 (s, 9H, ^tBu), 0.82 (d, J=7.9 Hz, 3H, CH_3), 0.55 (d, J=7.5 Hz, 3H, CH_3); IR (neat) 3480, 3010-2855, 1467, 1455, 1435, 1400, 1375, 1275, 1115 cm^{-1}.

Data for <u>47</u>: R_f 0.69 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{21}$ = +5.1° (C=0.45, $CHCl_3$); NMR (250 MHz, $CDCl_3$) δ 7.36-7.7 (m, 10H, phenyl), 3.77-3.95 (m, 3H, H_9 abd H_{11}), 4.05-4.15 (m, 1H, H_{10}), 1.55 (br s, 10H, cyclohexyl), 1.7 (s, 9H, ^tBu), 0.81 (d, J=6.2 Hz, 3H, CH_3), 0.68 (d, J=6.2 Hz, 3H, CH_3), 0.52 (d, J=7.5 Hz, 3H, CH_3); IR (neat) 3025-2875, 1475, 1460, 1445, 1410, 1325, 1120 cm^{-1}.
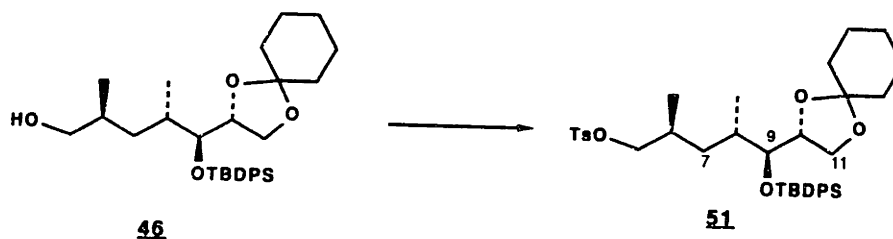
Alcohol **46** (67.6 mg, 0.132 mmol) was dissolved in 1.3 mL of pyridine and cooled to 0°C. p-Toluenesulfonyl chloride (50.5 mg, 0.264 mmol) was added and the reaction stirred overnight. The reaction mixture was then partitioned between ether and water. The aqueous phase was washed twice with ether. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was then purified by preparative tlc (0.5 mm silica gel plate, 5:1 hexane:ether, 2 elutions) to give 78.1 mg (89%) of **51**.

Data for **51**: R_f 0.42 (3:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 7.32-7.8 (m, 14H, phenyl), 4.3 (m, 1H, H_{10}), 3.88 (dd, J=7.5, 7.9 Hz, 1H, H_{11}), 3.65 (m, 3H, H_5 and H_9), 3.45 (dd, J=7.9, 8.3 Hz, 1H, H_{11}), 2.33 (s, 3H, CH_3 - C_6H_4), 1.5 (br m, 10H, cyclohexyl), 1.4 (s, 9H, ^tBu), 0.83 (d, J=7.9 Hz, 3H, CH_3), 0.62 (d, J=6.2 Hz, 3H, CH_3).

Data for **50**: R_f 0.46 (3:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 7.25-7.75 (m, 14H, phenyl), 4.3 (m, 1H, H_{10}), 3.85 (dd, J=7.9, 7.9 Hz, 1H, H_{11}), 3.68 (m, 2H, H_5 and H_9), 3.48 (m, 1H, H_{11}), 2.44 (s, 3H, CH_3 - C_6H_4), 1.5 (br m, 10H, cyclohexyl), 1.03 (s, 9H, ^tBu), 0.83 (d, J=7.5 Hz, 3H, CH_3), 0.63 (d, J=7.5 Hz, 3H, CH_3).

Tosylate **51** (78.1 mg, 0.118 mmol) was dissolved in 1 mL of THF and then 0.24 mL of nBu_4NF (1 M in THF) was added. The yellow solution was then stirred for 48 hours at room temperature. The reaction mixture was then partitioned between ether and water. The aqueous phase was washed twice with ether. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by preparative tlc (0.25 mm silica gel plate, 5:1 hexane:ether) to give 29.0 mg (70%) of **53**.

Data for **53**: R_f 0.57 (3:1 hexane-ether); $[\alpha]_D^{21}$ = +2.8° (C=1.03, $CHCl_3$); NMR (400 MHz, $CDCl_3$) δ 4.14 (br ddd, J=6.3, 13.4 Hz, 1H, H_{10}), 4.04 (dd, J=6.1, 8.0 Hz, 1H, H_{11}), 3.93 (br dd, J=7.7 Hz, 1H, H_{11}), 3.60 (br ddd, J=2.1, 11.1, Hz, 1H, H_{5eq}), 3.52 (dd, J=2.8, 11.2 Hz, 1H, H_{5ax}), 3.03 (dd, J=5.9, 8.6 Hz, 1H, H_9), 1.6 (br m, 10H, cyclohexyl), 1.04 (d, J=6.9 Hz, 3H, CH_3), 0.95 (d, J=6.6 Hz, 3H, CH_3); IR (neat) 3010-2860, 1485, 1470, 1410, 1385, 1360, 1310, 1180, 1165, 1110, 1060, 990, 975, 945, 860 cm^{-1}; mass spectrum m/e 252 (M^+ - H_2).

Data for $\underline{52}$: R_f 0.58 (3:1 hexane-ether); $[\alpha]_D^{21}$ = +31.1° (C=0.68, $CHCl_3$);

NMR (400 MHz, $CDCl_3$) δ 4.13 (br ddd, J=6.5, 7.2 Hz, 1H, H_{10}), 4.02 (dd,

J=6.2, 8.4 Hz, 1H, H_{11}), 3.92 (br dd, J=8.0 Hz, 1H, H_{11}), 3.85 (ddd, J=2.6, 4.4,

11.4 Hz, 1H, H_{5eq}), 2.97 (dd, J=9.7, 5.2 Hz, 1H, H_9), 2.91 (br dd, J=11.4 Hz,

1H, H_{5ax}), 1.80 (m, 1H, H_6 or H_8), 1.75 (m, 1H, H_6 or H_8), 1.6 (br m, 10H,

cyclohexyl), 0.97 (d, J=7.0 Hz, 3H, CH_3), 0.77 (d, J=7.0 Hz, 3H, CH_3);   IR (neat)

3020-2875, 1465, 1455, 1385, 1375, 1285, 1175, 1110, 1050, 945, 865

cm^{-1};   mass spectrum m/e 252 (M^+ - H_2).
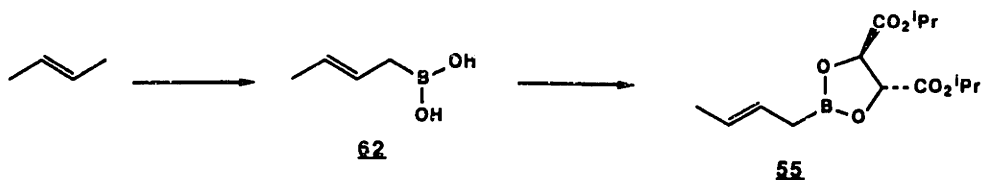
KO^{t}Bu (13.35 g, 180 mmol) was dissolved in 150 mL of THF and cooled to

-78°C. Trans-2-butene (30 mL, 343 mmol) was condensed at -78°C and

transferred to the reaction flask via cannula. n-BuLi (59.5 mL, 3.1 M in hexanes)

was added dropwise keeping the internal reaction temperature at or below -70°C.

The slightly cloudy yellow solution was transferred to a -45°C bath for 15 min and

then recooled to -78°C. Freshly prepared and distilled FB(OMe)$_2$ (32.4 mL, 180

mmol) was added dropwise keeping the internal temperature below -70°C. The

virtually colorless solution was then partitioned between 50% 1M HCl/NaCl solution

and ether before warming. The organic phase was further acidified by washing again

with 50% 1M HCl/NaCl (the aqueous phase should be acidic by pH paper). The

aqueous phase was then washed twice with ether. The combined organic extracts

were dried over Na$_2$SO$_4$, filtered, and concentrated under argon to a total volume of

~75 mL. To the crude boronic acid 62 is added DIPT (26.4 mL, 126 mmol) and a

scoop of MgSO$_4$. The reaction is stirred overnight at room temperature. Filtration

and concentration under argon gives >100% of 55 as a viscous yellow oil. The

product is used without purification in the next step.
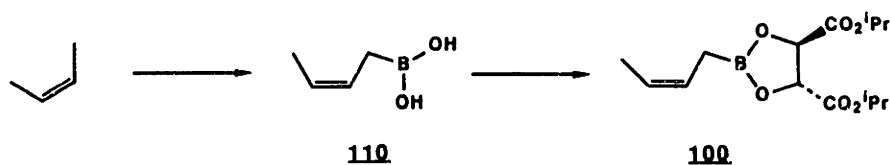
KO^{t}Bu (4.45 g, 60 mmol) was dissolved in 60 mL of THF and cooled to -78°C.

(Z)-2-butene (10 mL, 114 mmol) was then added. nBuLi (19.5 mL of a 3.1 M

solution in hexanes) was added dropwise keeping the internal temperature below

-70°C. The bright yellow cloudy mixture was then warmed to room tenperature and

stirred for an hour. The deep orange-red reaction mixture was then re-cooled to

-78°C (the color returned to bright yellow). Freshly distilled FB(OMe)$_2$ (10.8

mL, 60 mmol) was added dropwise keeping the internal temperature below -70°C

until the reaction mixture was virtually colorless. It was then partitioned cold

between a 1:1 mixture of 1 M HCl and saturated NaCl solution and ether. The organic

phase was re-extracted with 1:1 1 M HCl/NaCl to ensure the acidity of the organic

phase. The combined aqueous phases were back-extracted with ether. The combined

ether extracts were concentrated to a total volume of ~30 mL. DIPT (8.8 mL, 42

mmol) was added to the crude boronic acid 110, followed by a scoop of MgSO$_4$, and

the reaction stirred overnight. The MgSO$_4$ was removed by filtering through a

Schlenck funnnel under N$_2$. Concentrating gave 13.1 g >100% of 100. The product

is used without purification in the next step.
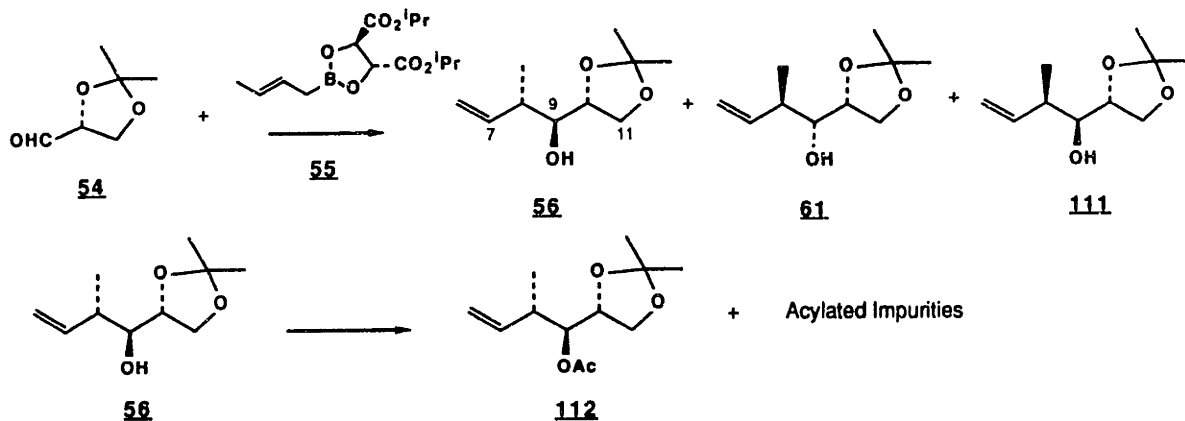
(R,R)-(E)-crotylboronate **55** (26.3 g, 88.15 mmol) was dissolved in 30 mL of toluene over 4Å powdered molecular sieves (2.5 g) and cooled to -78°C. Aldehyde **54** [prepared by $NaIO_4$ cleavage of commercially available manitol diacetonide] (2.5 g, 19.39 mmol) was then added dropwise in 35 mL of toluene. After stirring for 2 hours at -78°C, the reaction mixture was partitioned between 1M NaOH and ether and stirred vigorously for an hour to remove excess tartrate. The aqueous phase was then washed twice with ether. The combined organic extracts were dried over Na_2SO_4 and concentrated by removing the solvent by distillation. The crude product was purified by column chromatography (3:1 hexane:ether as eluant) to separate the diastereomers. Product ratios as determined by GC anaylsis were: 85% of **56**, 11% of **61**, and 4% of **111**. The major fraction was then acylated by standard procedures (Ac_2O, Et_3N, DMAP, CH_2Cl_2) and purified by column chromatography (5:1 hexane:ether) to give **112** free of the impurities. Deacylation (catalytic K_2CO_3, MeOH) gave 986 mg of pure **56**.

Data for **56**:[20] R_f 0.17 (3:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 5.75-5.9 (m, 1H, H_7), 5.08-5.12 (m, 2H, H_6), 3.85-4.7 (m, 3H, H_9, H_{10}, H_{11}), 3.47 (dd, J=7.3, 14.6 Hz, 1H, H_{11}), 2.3-2.45 (m, 1H, H_8), 1.95 (br s, 1H, OH), 1.38 (s, 3H, CH_3 acetonide), 1.31 (s, 3H, CH_3 acetonide), 1.05 (d, J=7.9 Hz, 3H, CH_3); IR (neat) 3420, 2960-2850, 1460, 1265, 1125, 1100, 1070, 910 cm^{-1}.

Data for <u>112</u>: R_f 0.29 (5:1 hexane-ether); $[\alpha]_D^{23}$ = +26.6° (C=1.24, CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 5.68 (ddd, J=9.2, 11.7, 17.5 Hz, 1H, H_7), 4.92-5.08 (m, 3H, H_9 and H_6), 4.08 (br ddd, J=5.4, 12.5 Hz, 1H, H_{10}), 3.9 (dd, J=6.2, 8.7 Hz, 1H, H_{11}), 3.7 (dd, J=6.2, 7.5 Hz, 1H, H_{11}), 2.4-2.54 (m, 1H, H_8), 2.0 (s, 3H, CH_3 acetate), 1.32 (s, 3H, CH_3 acetonide), 1.26 (s, 3H, CH_3 acetonide), 0.96 (d, J=7.9 Hz, 3H, CH_3); IR (neat) 3070, 2980-2870, 1745, 1640, 1455, 1420, 1371, 1230, 1158, 1070, 1020, 918, 845 cm^{-1}; mass spectrum m/e 213 (M^+ - CH_3).

Data for acylated impurities: R_f 0.56 (5:1 hexane-ether); NMR (250 MHz, $CDCl_3$) δ 5.64 (ddd, J=6.3, 9.2, 16.7 Hz), 5.33-5.41 (m), 4.83-5.96 (m), 4.01 (t, J=7.1 Hz), 2.0 (s), 1.21-1.7 (m), 0.95 (d, J=8.8 Hz).

Silyl ether **57** was prepared in 95 % yield from **56** using the procedure described for the preparation of **43**.

Data for **57**: R_f 0.56 (5:1 hexane-ether); $[\alpha]_D^{21}$ = +18.6° (C=0.42, CHCl$_3$); NMR (250 MHz, CDCl$_3$) δ 7.4-7.65 (m, 10H, phenyl), 5.75 (ddd, J=7.3, 10.4, 17.3 Hz, 1H, H$_7$), 4.92 (dd, J=1.3, 10.4 Hz, 1H, H$_{6cis}$), 4.82 (dd, J=1.4, 17.3 Hz, 1H, H$_{6trans}$), 4.05 (br ddd, J=6.6, 13.1 Hz, 1H, H$_{10}$), 2.29 (m, 3H, H$_{10}$ and H$_{11}$), 1.28 (s, 3H, CH$_3$ acetonide), 1.26 (s, 3H, CH$_3$ acetonide), 1.06 (s, 9H, ^{t}Bu), 0.93 (d, J=6.9 Hz, 3H, CH$_3$); IR (neat) 3070, 3042, 2980-2860, 1640, 1490, 1472, 1461, 1430, 1390, 1380, 1370, 1255, 1215, 1155, 1110, 1060, 1000, 915, 865, 820, 740, 705 cm^{-1}; mass spectrum m/e 185 (M$^+$ - TBDPS).

57   58
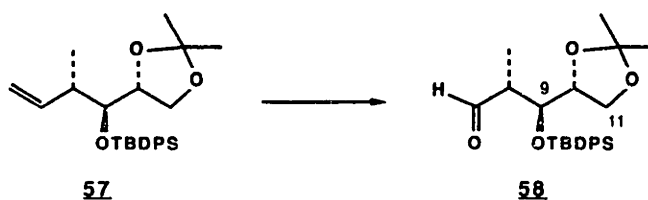
Method A:

Olefin **57** (1.07 g, 2.5 mmol) was dissolved in 25 mL of dry CH_2Cl_2 and cooled to -78°C. A stream of ozone in oxygen was bubbled through until the solution was pale blue. Excess ozone was removed by purging with N_2, and then PPh_3 (0.99 g, 3.8 mmol) was added. The solution was then warmed to room temperature, stirred for several hours, and concentrated, giving aldehyde **58**, which was used without further purification.

Method B:

Olefin **57** (297 mg, 0.70 mmol) was dissolved in 7 mL of dry CH_2Cl_2 and cooled to -78°C. A stream of ozone in oxygen was bubbled through until the solution was pale blue. After removal of excess ozone by purging with N_2, 5 mL (68 mol) of Me_2S were added. The solution was warmed to room temperature, stirred for several days, and concentrated giving aldehyde **58**, which was used without further purification.

Data for **58**: R_f 0.27 (5:1 hexane-ether); $[\alpha]_D^{23}$ = -14.3° (C=1.19, CH_2Cl_2); NMR (crude, 250 MHz, $CDCl_3$) δ 9.49 (s, 1H, C$\underline{H}$O), 7.35-7.73 (m, 10H, phenyl), 4.13 (m, 1H, H_{10}), 4.03 (dd, J=2.5, 7.9 Hz, 1H, H_9), 3.92 (dd, J=6.3, 8.3 Hz, 1H, H_{11}), 3.53 (dd, J=6.3, 9.6 Hz, 1H, H_{11}), 2.45 (dq, J=7.5, 2.5 Hz, 1H, H_8), 1.22 (s, 3H, CH_3 acetonide), 1.15 (s, 3H, CH_3 acetonide), 1.15 (d, J=7.5 Hz, 3H, CH_3), 1.05 (s, 9H, ^tBu); IR (pure, neat): 3070, 3045, 2880, 2850, 2710, 1725, 1590, 1472, 1460, 1370, 1260, 1212, 1156, 1085, 1000, 940, 860, 820, 740, 700 cm^{-1}; mass spectrum m/e 187 (M^+ - TBDPS).
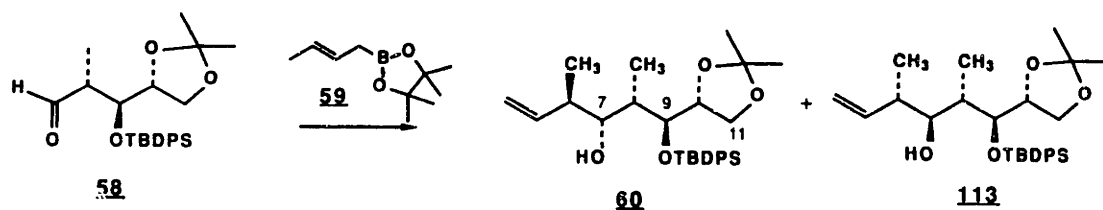
Crude aldehyde **58** (theoretically 1.1 g, 2.6 mmol) prepared via method A was dissolved in 2.7 mL of CH_2Cl_2 at room temperature. (E)-crotylboronate **59** (1.2 g, 6.5 mmol) was dissolved in an additional 2.7 mL of CH_2Cl_2 and added to the aldehyde solution. After being stirred for 36 hours at room temperature the reaction was partitioned between CH_2Cl_2 and aqueous $NaHCO_3$. The aqueous phase was washed twice with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (6 cm column, ~6" of silica gel, 5:1 hexane:ether as eluant) to give 1.09 g (87%) of **60** and 70 mg (6%) of **113**.

Data for **60**: R_f 0.22 (5:1 hexane-ether); $[\alpha]_D^{23}$ = +9.0° (C=1.0, CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 7.33-7.68 (m, 10H, phenyl), 5.7 (ddd, J=7.9, 10.0, 17.9 Hz, 1H, H_5), 4.97 (br dd, J=16.7 Hz, 1H, H_{4trans}), 4.95 (br dd, J=10.4 Hz, 1H, H_{4cis}), 4.15-4.26 (m, 1H, H_{10}), 4.05 (dd, J=5.8, 8.7 Hz, 1H, H_7), 3.55-3.68 (m, 3H, H_9 and H_{11}), 3.16 (d, J=8.3 Hz, 1H, OH), 2.05-2.15 (m, 1H), 1.9-2.0 (m, 1H), 1.30 (s, 3H, CH_3 acetonide), 1.25 (s, 3H, CH_3 acetonide), 1.08 (s, 9H, ^tBu), 1.00 (d, J=8.3 Hz, 3H, CH_3), 0.61 (d, J=7.5 Hz, 3H, CH_3); IR (neat) 3480, 3070, 3042, 2980-2860, 1640, 1590, 1475, 1460, 1430, 1382, 1370, 1260, 1215, 1160, 1110, 1065, 1000, 910, 865, 820, 740, 700 cm^{-1}; mass spectrum m/e 187 (M^+ - TBDPS and crotyl).

Data for <u>113</u>: R_f 0.15 (5:1hexane-ether); NMR (250 MHz, $CDCl_3$) δ 7.3-7.78

(m, 10H, phenyl), 5.71 (ddd, J=9.1, 10.9, 16.9 Hz, 1H, H_5), 5.02 (dd, J=3.0,

10.9 Hz, 1H, H_{4cis}), 4.95 (dd, J=3.0, 16.9 Hz, 1H, H_{4trans}), 4.26 (br ddd, J=5.4,

12.1 Hz, 1H, H_{10}), 3.83-3.89 (m, 2 H, H_7 and H_{11}), 3.67 (dd, J=6.1, 9.1 Hz, 1H,

H_9), 3.55-3.62 (m, 1H, H_{11}), 2.06 (d, J=3.6 Hz, 1H, O<u>H</u>), 1.95-2.05 (m, 1H,

H_8), 1.78-1.88 (m, 1H, H_6), 1.29 (s, 3H, CH_3 acetonide), 1.23 (s, 3H, CH_3

acetonide), 1.05 (s, 9H, ^tBu), 0.87 (d, J=7.3 Hz, 3H, CH_3), 0.72 (d, J=6.1 Hz,

3H, CH_3).
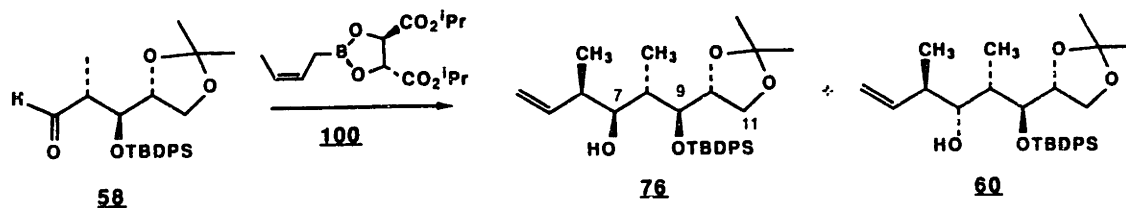
To a dry flask under argon were added 1.3 g of 4Å molecular sieves. After the addition of 12 mL of toluene and 3.6 mL of **100** (7.19 mmol based on ~60% purity of reagent), the reaction mixture was cooled to -78°C. Crude aldehyde **58** (theoretically 1.02 g, 2.39 mmol) prepared _via_ method A was added dropwise in 12 mL of toluene. After being stirred for three hours at -78°C the cold reaction mixture was partitioned between 1M NaOH and ether and stirred vigorously for an hour to remove excess tartrate. The layers were then separated and the organic one washed twice with water. The combined aqueous phases were back-extracted with ether. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification by flash chromatography (5:1 hexane:ether as eluant) gave 821 mg (71%) of **76** and 75 mg (6.5%) of **60**.

Data for **76**: R_f 0.27 (5:1 hexane-ether); $[\alpha]_D^{23}$ = +11.1° (C=2.24, CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 7.3-7.7 (m, 10H, phenyl), 5.68 (ddd, J=6.2, 10.0, 16.7 Hz, 1H, H_5), 4.89 (br dd, J=16.7 Hz, 1H, H_{4trans}), 4.86 (br dd, J=10.4 Hz, 1H, H_{4cis}), 4.13-4.21 (m, 2H, H_{10} and H_7), 3.94-4.0 (m, 1H, H_{11}), 3.6-3.69 (m, 1H, H_9), 3.3-3.4 (m, 1H, H_{11}), 2.32 (d, J=7.5 Hz, 1H, OH), 2.1-2.21 (m, 1H, H_6), 1.81-1.92 (m, 1H, H_8),1.29 (s, 3H, CH_3 acetonide), 1.23 (s, 3H, CH_3 acetonide), 1.05 (s, 9H, ^tBu), 0.93 (d, J=7.9 Hz, 3H, CH_3), 0.72 (d, J=7.9 Hz, 3H, CH_3); IR (neat) 3475, 3070, 3045, 2980-2860, 1640, 1590, 1465, 1460, 1430, 1376, 1260, 1215, 1155, 1110, 1065, 995, 915, 865, 820, 7400, 700 cm^{-1}; mass spectrum m/e 187 (M$^+$ - TBDPS and crotyl).
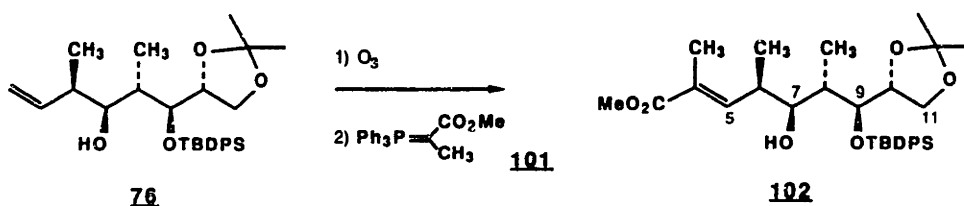
Olefin **76** (335 mg, 0.695 mmol) was dissolved in 7 mL of MeOH and cooled to

-78°C under an argon atmosphere. A stream of ozone in oxygen was bubbled through

until the reaction mixture was saturated (blue in color). The excess ozone was then

removed by purging with N_2. The ozonide was quenched by treatment with PPh_3

(273 mg, 1.04 mmol) at room temperature for 30 min. The solvent was then

removed and the residue taken up in 2.5 mL of toluene. The ylide (**101**) (484 mg,

1.39 mmol) was added and the reaction warmed to ~50°C. After being stirred for 24

hours the reaction was complete. The solvent was then removed *in vacuo* and the

crude product was purified by column chromatography (5 cm column, ~7" of silica

gel, 5:1 hexane:ethyl acetate) to give 0.254 g (66%) of **102**: R_f 0.4 (2:1 hexane-

ether) 0.23 (3:1 hexane-ether); $[\alpha]_D^{23}$ = +12.2° (C=1.05, CH_2Cl_2); NMR

(250 MHz, $CDCl_3$) δ 7.3-7.66 (m, 10H, phenyl), 6.67 (dd, J=0.8, 9.6 Hz, 1H,

H_5), 4.14 (br ddd, J=8.3, 14.6 Hz, 1H, H_{10}), 3.94-4.04 (m, 2H, H_9), 3.66 (s,

3H, OCH_3), 3.53 (dd, J=7.9, 7.9 Hz, 1H, H_{11}), 3.35 (br ddd, J=8.3, 12.5 Hz, 1H,

H_7), 2.62 (d, J=8.3 Hz, 1H, OH), 2.42-2.56 (m, 1H, H_8), 1.85-1.98 (m, 1H,

H_6), 1.72 (s, 3H, CH_3), 1.30 (s, 3H, CH_3 acetonide), 1.22 (s, 3H, CH_3 acetonide),

1.03 (s, 9H, ^tBu), 0.97 (d, J=7.5 Hz, 3H, CH_3), 0.78 (d, J=7.5 Hz, 3H, CH_3); IR

(neat) 3470, 3070, 3045, 2980-2860, 1715, 1645, 1580, 1460, 1430,

1375, 1295, 1262, 1221, 1190, 1158, 1110, 1070, 995, 865, 820, 740, 700

cm^{-1}; mass spectrum m/e 539 (M^+ - CH_3).

102   105
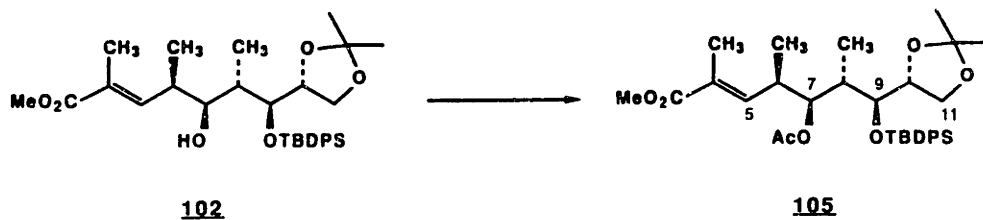
Alcohol 102 (369 mg, 0.665 mmol) was dissolved in 6.6 mL of CH_2Cl_2.

Triethylamine (0.46 mL, 3.33 mmol) and a few crystals of DMAP were added followed by the acetic anhydride (0.13 mL, 1.33 mmol). The reaction mixture was stirred at room temperature overnight. It was then partitioned between ethyl acetate and aqueous $NaHCO_3$. The aqueous phase was washed twice with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated.

Purification by column chromatography (3 cm column, 6" of silica gel, 6:1 hexane:ethyl acetate) then provided 286 mg (72%) of 105: R_f 0.24 (3:1 hexane-ether); $[\alpha]_D^{23}$ = +0.33° (C=1.88, CH_2Cl_2); NMR (250 MHz, $CDCl_3$) δ 7.33-7.76 (m, 10H, phenyl), 6.41 (dd, J=2.1, 10.4 Hz, 1H, H_5), 4.85 (dd, J=4.2, 9.6 Hz, 1H, H_7), 4.11-4.21 (m, 1H, H_{10}), 3.91-4.02 (m, 2H, H_{11} and H_9), 3.77 (dd, J=8.3, 8.3 Hz, 1H, H_{11}), 3.7 (s, 3H, OCH_3), 2.56-2.7 (m, 1H, H_8), 1.83-1.98 (m, 1H, H_6), 1.80 (s, 3H, CH_3 acetate), 1.74 (d, J=2.1 Hz, 3H, CH_3), 1.29 (s, 3H, CH_3 acetonide), 1.27 (s, 3H, CH_3 acetonide), 1.08 (s, 9H, ^tBu), 0.92 (d, J=7.9 Hz, 3H, CH_3), 0.73 (d, J=8.3 Hz, 3H, CH_3); IR (neat) 3070, 3050, 2990-2860, 1745, 1720, 1650, 1590, 1460, 1430, 1375, 1300, 1240, 1160, 1110, 1060, 1020, 915, 875, 825, 740, 705 cm^{-1}.

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