PART I. STUDIES TOWARD THE SYNTHESIS OF SESBANIMIDE A

PART II. TOTAL SYNTHESIS OF THE NATURAL ENANTIOMER OF OLIVIN

By

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ABSTRACT

PART I.

Studies toward the total synthesis of sesbanimide A led to the first highly diastereoselective synthesis of the AB ring system. The synthesis is unique in that the three asymmetric centers of the B ring were introduced with excellent control using stereoselective organic reactions. The first stereochemically critical step was the reaction of γ-alkoxyboronate reagent **41** with glyceraldehyde cyclohexyl ketal **42**. The second step involved the epoxidation of homoallylic alcohol **43** which proceeded with unusually high selectivity to provide **69** as the sole product.

The cornerstone of our strategy towards the synthesis of the C ring was the preparation of chiral allylboronate **117**. Unfortunately, attempts to prepare isomerically pure precursors to **117** were unsuccessful. In connection with these studies toward the synthesis of the C ring, the preparation of allylboronate **108** and its reaction with chiral aldehyde **51** were investigated. Additionally, allylboronate **124** was synthesized and applied to a synthesis of a C ring model compound.

PART II.

The first total synthesis of the natural enantiomer of olivin is described. The synthesis is highly stereoselective, featuring the reaction of a γ-methoxy-allylboronate with chiral aldehyde **17** and the vinyl cuprate addition to unsaturated aldehyde **49** as the critical diastereoselective transformations. The anthracenone nucleus of **1** was elaborated via the coupling of unsaturated ester **51** with phthalide **61** and a subsequent Dieckman ester condensation (**67** to **68**). Introduction of the C(2)-hydroxyl functionality was accomplished by the epoxidation of a TBDMS enol ether intermediate, and all five acid labile protecting groups were removed in a single operation to complete the synthesis of the title compound.

Thesis Supervisor: Dr. William R. Roush

Title: Associate Professor in Organic Chemistry

To Barbara

and

my parents

Με ολη μου την αγαπη

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I would like to thank Professor Roush for his support and guidance throughout my stay in his group. His enthusiasm for organic chemistry, his high professional standards, and his dedication to the academic and professional development of his students were a source of inspiration.

I would also like to thank Professor F. Johnson and Professor P. Magriotis who sparked my interest in organic chemistry.

I will fondly remember the members of the Roush group who made my time at M.I.T. and Indiana University an enjoyable one. Special thanks to Dr.'s W. K. M. Chong, T. Cagiano, A. E. Walts, and M. Adam, for help early in my graduate studies. I will particularly cherish the time spent with Jim Kowalczyk, and the group members who moved to Indiana (Heritage Apartments), Joe Warmus, Lee Hoong, Alan Palkowitz, Jotham Coe and Kaori Ando. Thanks to Brad Brown for initiating us to life in Bloomington and to Tom Bannister for his insight to Hoosier basketball. Thanks also to Al, Joe and Jotham for countless rides to Indianapolis airport.

I am indebted to all the people who contributed to the preparation of this thesis. Jotham Coe and Lee Hoong provided dilligent and thorough proofreading; Lee also helped me out of many difficult situations with the group Macintosh. Finally, I thank my wife Barbara for typing the entire thesis spending many long nights in the process.

Additionally I would like to aknowledge the following people for their contributions to the total synthesis of olivin: Dr. Lesur who developed the synthesis of **7** from D-galactose and also investigated the stereochemistry of vinyl cuprate additions to enoates **20** and **24** and enones **23** and **25**; Dr. Harris who developed the first diastereoselective synthesis of **7** based on the reaction of allylboronate **18** and aldehyde **17** ; Dr. Chong who carried out exploratory studies on the

construction of the anthracenone nucleus, culminating in preparation of phthalide **61** and optimization of the condensation with methyl crotonate; Dr. Tai whose numerous contributions included a solution to the problem of establishing the C(3) stereochemistry in an efficient manner, the synthesis of the napthalene nucleus, the oxidation of aldehyde **66** to ester **67** and the preparation of the first small samples of protected olivin **73**.

SPECIAL AKNOWLEDGEMENTS

I would like to thank my wife Barbara for her tremendous support, love and encouragement throughout my graduate career. Her support was most appreciated during and especially after the move of our research group from Boston to Bloomington. I hope one day I can repay her many kindnesses.

The steadfast love and encouragement of my parents has been a source of inspiration throughout my studies. They have given me much more than can be aknowledged in a few short words.

Appreciation is also extended to my Mother-in law, Sister and Brother-in-law for their assistance over the years.

ABBREVIATIONS

Anal.	-	combustion analysis
9-BBN	-	9-borabicyclononane
BOMCl	-	benzyloxymethyl chloride
Bn, Bzl	-	benzyl
mCPBA	-	m-chloroperbenzoic acid
DIBAL	-	diisobutylaluminum hydride
DET	-	diethyl tartate
DMF	-	dimethylformamide
DMSO	-	methyl sulfoxide
LDA	-	lithium diisopropylamide
MOMCl	-	chloromethyl methyl ether
MsCl	-	methanesulfonylchloride
NBS	-	N-bromosuccinimide
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
TBDMS	-	t-butyldimethylsilyl
TBDPS	-	t-butyldiphenylsilyl
TBHP	-	tert-butylhydroperoxide
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran
TLC	-	thin layer chromatography
TMS	-	trimethylsilyl
TsCl	-	p-toluenesulfonyl chloride
TsOH	-	p-toluenesulfonic acid

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PART I

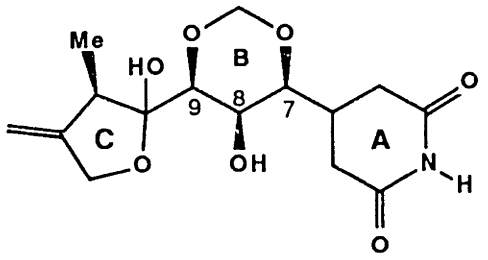
CHAPTER 1

INTRODUCTION

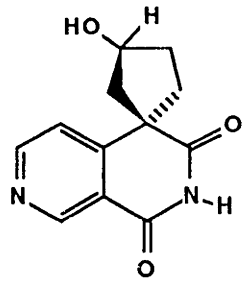
I. Background

Sesbanimide A (**1**) is a structurally novel alkaloid isolated from the seeds of *Sesbania drummondii*[1] and the related *Sesbania* species *S. punicea*,[2] desiduous shrubs found throughout the southern United States and South America. Both have exhibited a long history of toxicity to livestock and fowl.

Powell and co-workers had reported as early as 1976, that extracts of these plants showed pronounced antitumor activity in experimental systems.[3] Extensive purification procedures guided by *in vivo* (P388 leukemia) and *in vitro* (KB cell culture) bioassays ultimately resulted in the isolation of sesbanine (**2**), which was proposed to be the active component.[4] However testing of sesbanine, synthesized in several laboratories,[5] showed it to be totally inactive.



1



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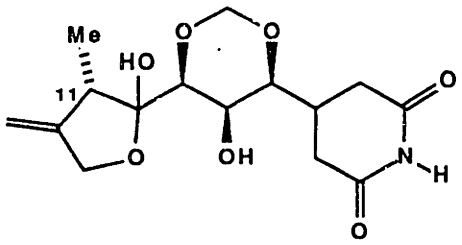
Sesbanimide A, present in very small amounts (5 x 10^{-4} mg / g of dry seeds), was separated from sesbanine by a complex scheme that involved successive application of open-column chromatography on silica, preparative HPLC, preparative TLC and semipreparative HPLC. Several isomers and structural analogues of **1** were also isolated; most notable among them sesbanimide B (epimeric at C-11) (**3**) and sesbanimide C (**4**).[6]

Sesbanimide A is a potent anitumor substance exhibiting ED_{50} values of 7.7 x 10^{-3} µg/mL against KB cells *in vitro* and T/C values (T/C = days test animals live/ days control animals live x 100) of 140-181 in the 0.008-0.032 mg/kg range.

Sesbanimides B and C show similar activity in limited testing but at approximately ten times these dose levels.



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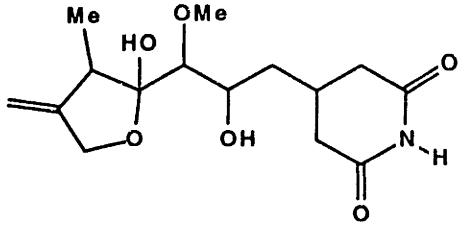


4

Although sesbanimides A and B bear an obvious structural relationship to the glutarimide antibiotics (e.g., cycloheximide, streptovitacin A or streptimidone),[7] their tricyclic structure is unique in nature. The structure of **1** was assigned on the basis of both a single crystal X-ray analysis[1] and detailed NMR studies[2] while those of **3** and **4** were established using high field ^{1}H NMR, ^{13}C NMR and mass spectral correlations.

Three total syntheses of **1** have been reported to date.[8,9,10] Virtually all of them employ the same synthetic strategy, starting with the synthesis of ring B and the introduction of the remaining rings in the sequence B to AB to ABC. In addition to these syntheses, three reports have appeared describing the synthesis of the A-B ring system.[11,12,13]

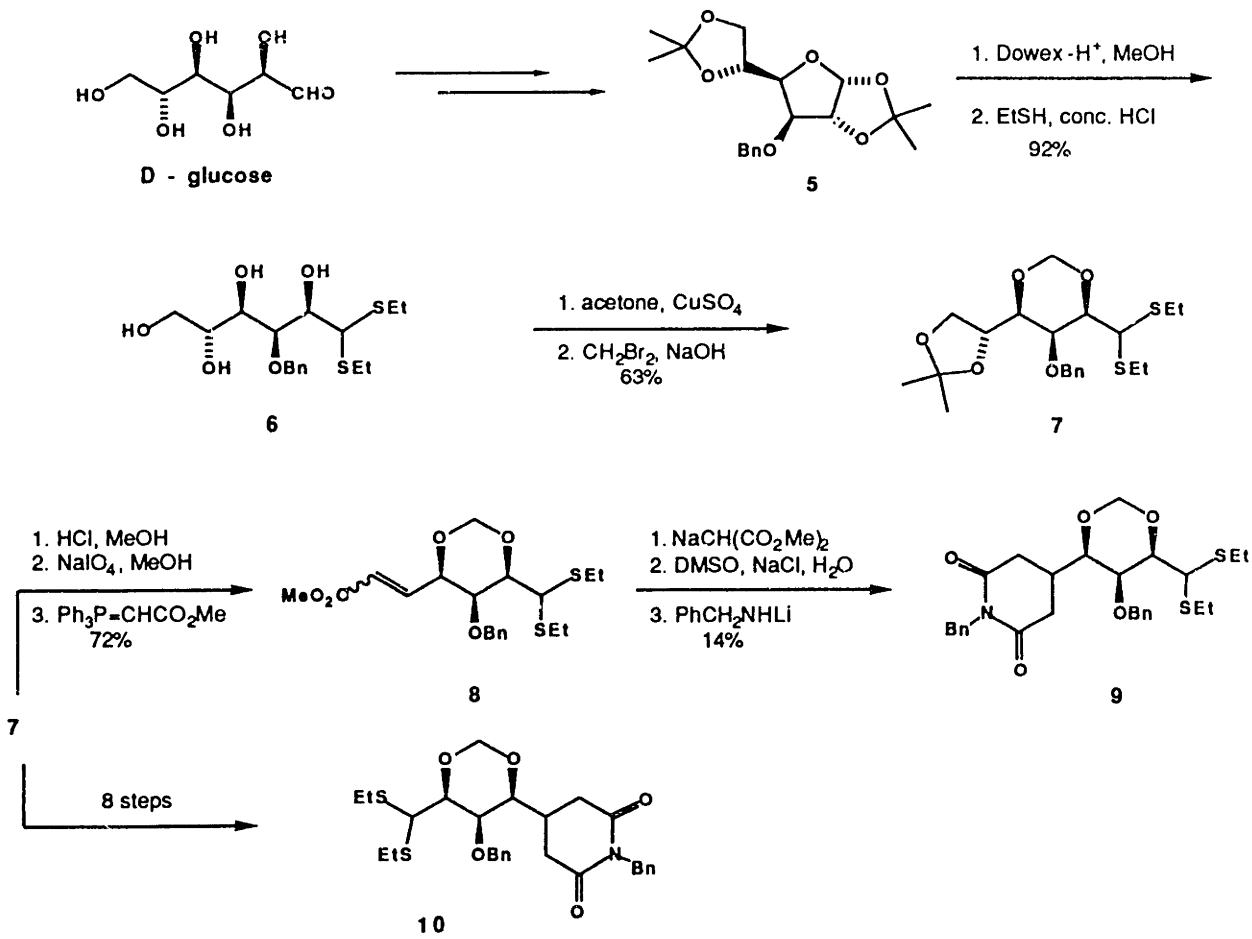
II. Synthesis of the AB Ring System.

The carbohydrate-like ring B seems to be an ideal target for employing a "chiron" approach.[14] Such would appear to be the case, as indeed all of the reported syntheses have used carbohydrate starting material as the source of the three asymmetric centers in ring B. The three stereocenters at C-7, C-8 and C-9 are all arranged in a syn relationship. An examination of possible carbohydrate

precursors that can easily accomodate these stereochemical relationships, as well as provide potential functional groups for further elaboration into rings A and C, leads to the identification of three closely related carbohydrates D-xylose, D-glucose and D-sorbitol as starting material.

The first synthesis of the AB ring system was reported by Fleet in 1984.[11] D-glucose was converted to glucofuranoside **5** (Scheme 1.1) according to a known procedure. Hydrolysis of **5** and subsequent treatment with ethanethiol afforded protected glucose **6** in which the 3-OH is differentiated as a benzyl ether. Kinetic acetonation, followed by standard methylenation gave B ring intermediate **7**.

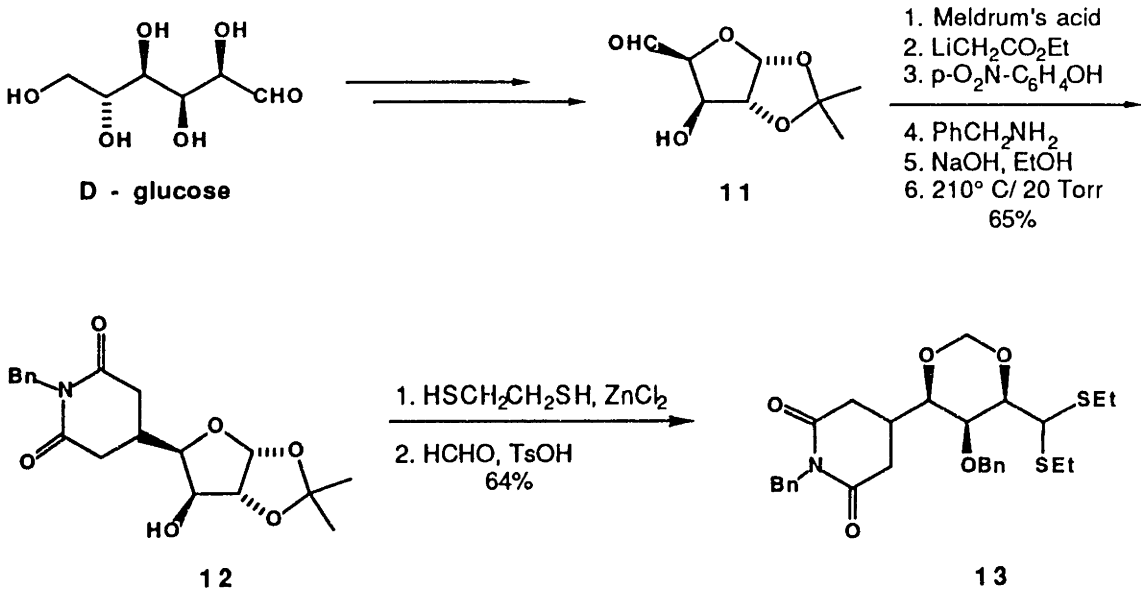
Scheme 1.1



Synthesis of ring A presents no significant new problems, as an array of methods exists for building glutarimides.[15] In this particular synthesis, the protocol used required initial generation of an aldehyde at C-5 of **7**. Thus, the diol was deprotected and oxidatively cleaved to give an aldehyde that after standard olefination gave unsaturated ester **8**. Michael addition of dimethyl malonate followed by decarboxylation and treatment of the diester obtained with lithiobenzylamine, provided glutarimide **9** in rather low yield. Alternatively, the heterochirally-related imide **10** was built by an analogous sequence originating from C-1 of **7**.

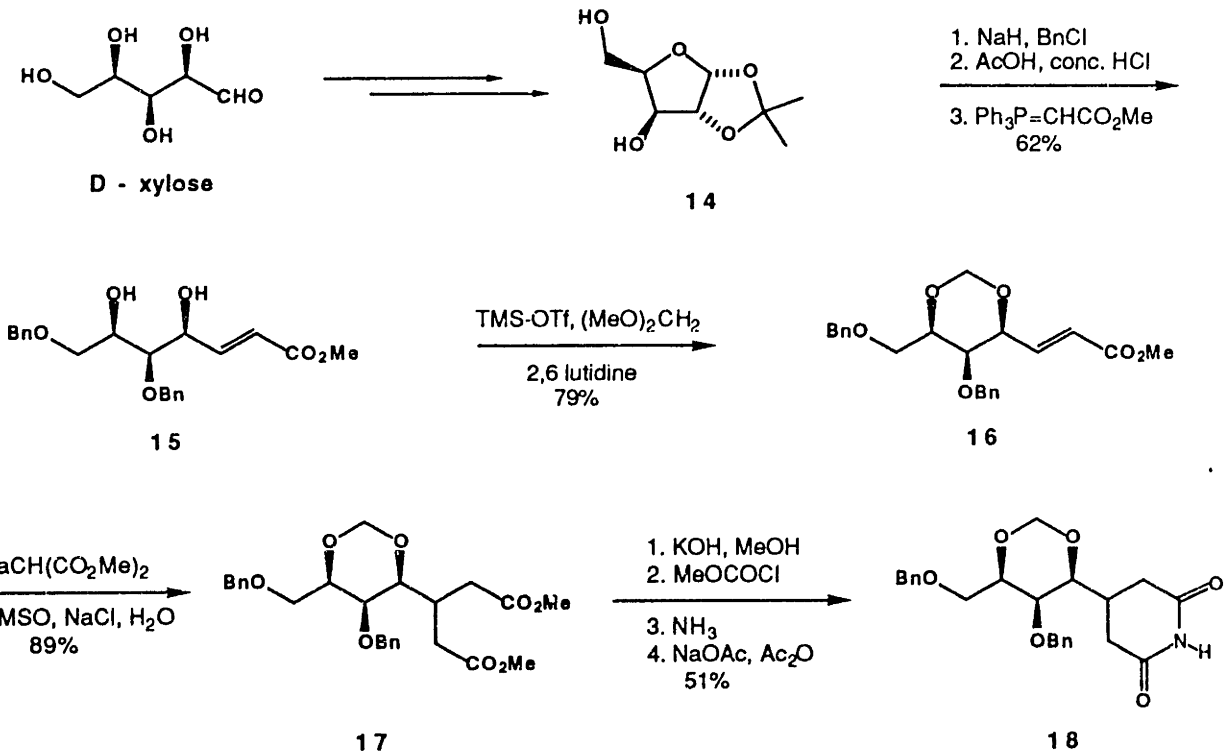
Shibuya's synthesis of the AB ring moiety, similarly uses D-glucose as starting material and is highlighted in Scheme 1.2.[12] The aldehyde **11**, prepared according to the established procedure,[16] was elaborated to the glutarimide **12** in excellent overall yield. Dithioacetalization of the furanoside followed by methylenation afforded **13**.

Scheme 1.2



In Terashima's work[10] D-xylose was converted into D-1,2-O-isopropylidene-*xylo*-furanoside **14** (see Scheme 1.3) in two steps.[17] Protection of the free alcohols as benzyl ethers followed by removal of the acetonide group under acidic conditions and olefination of the lactol so obtained produced **15** in good overall yield. Treatment of **15** with TMS-OTf and dimethoxymethane effected the construction of the dioxane ring, thus completing the transformation of the C-2, C-3 and C-4 stereocenters of D-xylose into a functionalized precursor of the sesbanimide B ring. The imide ring was then built by using methodology similar to the one used by Fleet. Thus decarboxylation of the Michael adduct of dimethyl

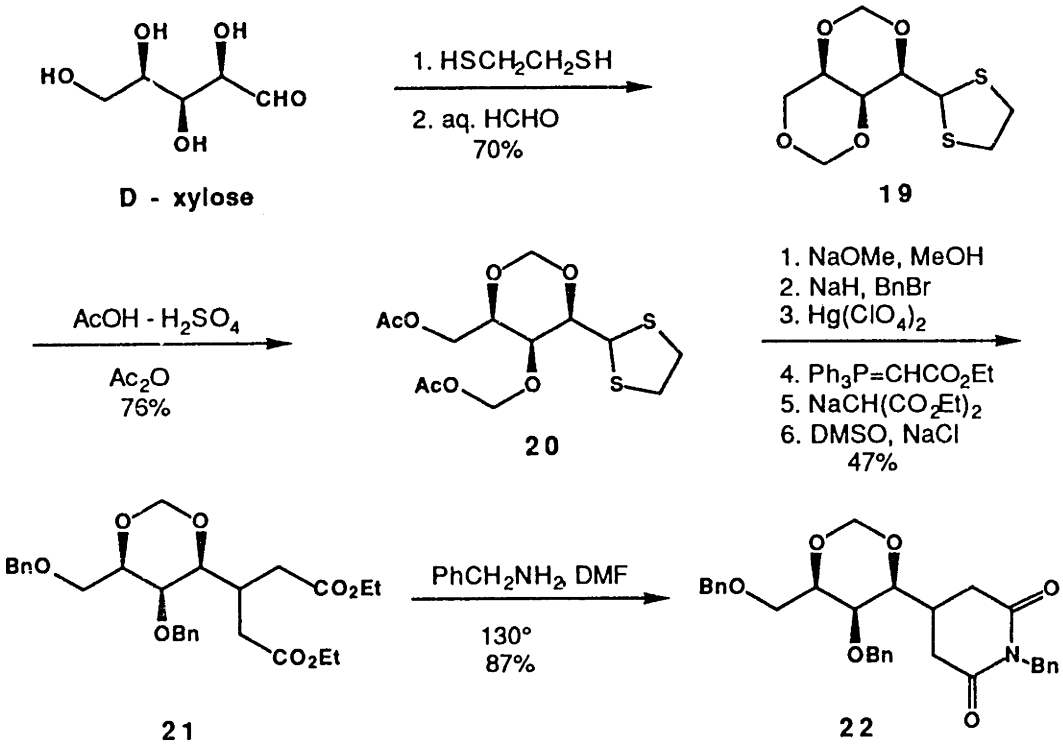
Scheme 1.3



malonate to the α,β-unsaturated ester **16** gave the diester **17**. Base hydrolysis afforded the diacid which, after activation as an anhydride, underwent

ammonolysis to the amide acid. Finally, treatment with acetic anhydride effected cyclization to imide **18**.

Scheme 1.4

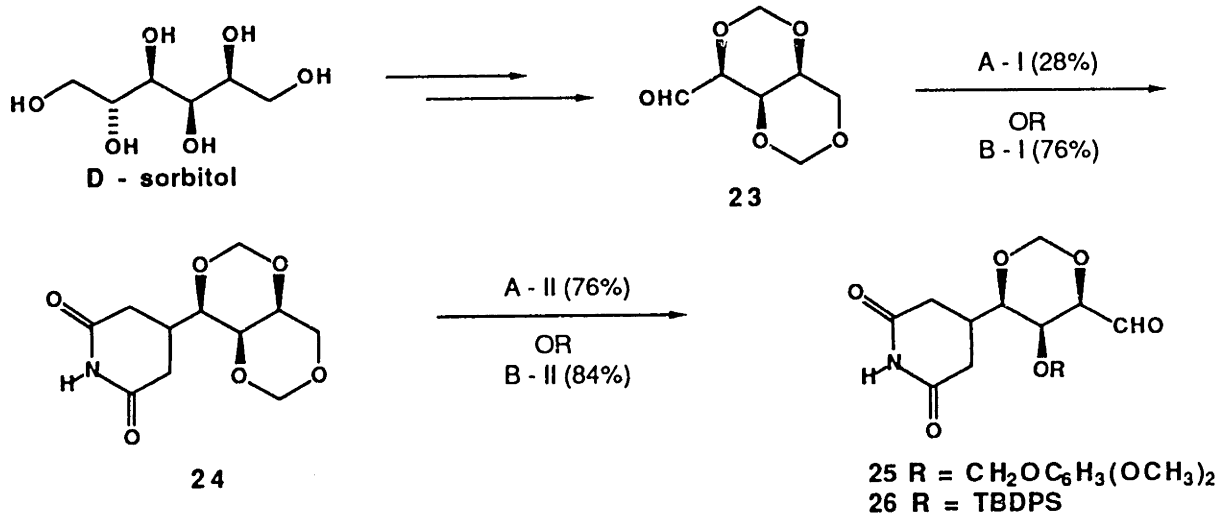


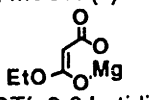
Rao and co-workers also used D-xylose as the starting material (Scheme 1.4) for their synthesis of the A-B ring system.[13] Protection of the aldehyde as the dithioacetal followed by treatment with aqueous formaldehyde afforded the 2,4:3,5 di-O-methylene acetal **19**. Elaboration of this intermediate requires the selective removal of the 3,5-O-methylene acetal. This was accomplished by using a mixture of Ac_2O, AcOH and H_2SO_4 which afforded the diacetate **20**. A series of standard reactions let to diester **21** (similar to intermediate **17** in Terashima's synthesis) which was directly converted into imide **22** upon treatment with benzylamine in DMF at 170 °C in a sealed tube. The use of benzylamine rather than

lithiobenzylamine, as in Fleet's synthesis, significantly improved the yield of cyclization.

The synthetic routes followed by Pandit[8] and Schlessinger[9] in their total syntheses of sesbanimide A begin with aldehyde **23**, derived from D-sorbitol, and proceed along very similar lines (Scheme 1.5). Imide **24** was built in the

Scheme 1.5



Pandit:
A - I. (a) $Ph_3P{=}CHCO_2Me$ (b) $H_2NCOCH_2CO_2t$-Bu (c) TFA/ DMF, Δ
A - II. (a) AcOH, Ac_2O (b) NaOMe, MeOH (c) ArCHO (d) Et_2AlCl, Et_3SiH (e)CrO_3, pyridine
Schlessinger:
B - I. (a) $(iPrO)_2POCH_2CO_2Et$ (b)  (c) NH_4OH / 155 - 210°
B - II (a) TFAA, AcOH (b) TBDPSOTf, 2,6 Lutidine (c) DIBAL (d) Swern

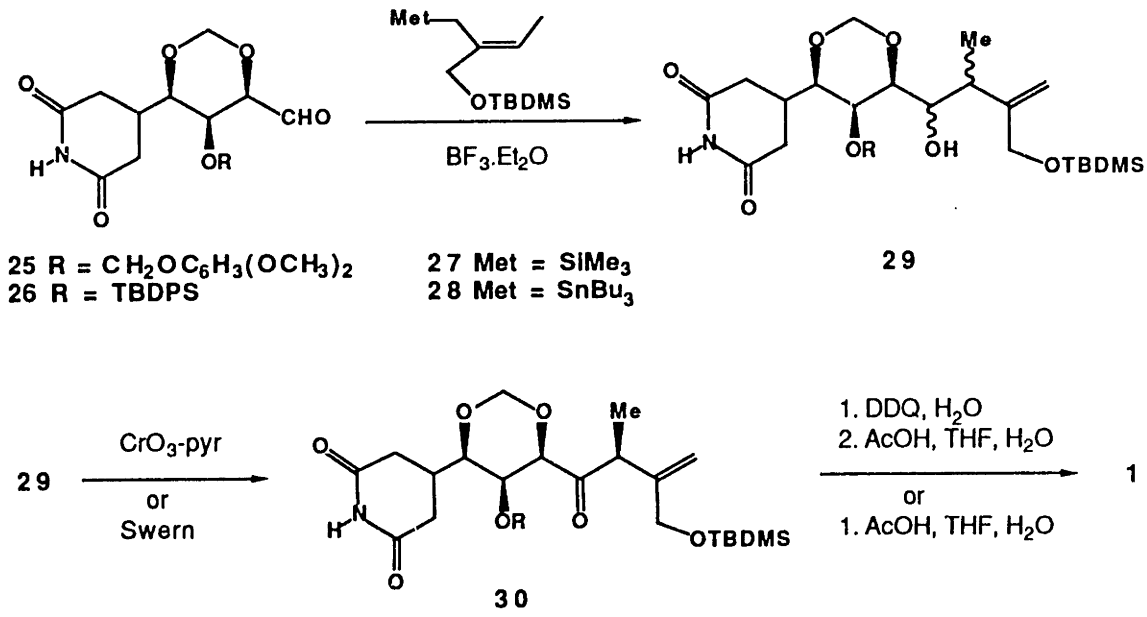
laboratories of Pandit in three practical steps: (1) olefination to an α,β-unsaturated ester; (2) treatment with $CH_2(CONH_2)CO_2{}^tBu$ in the presence of base resulting in Michael addition and cyclization; and (3) removal of the t-butoxycarbonyl function by first hydrolyzing and then heating the acid obtained. Similarly Schlessinger prepared **24** very efficiently in 3 steps (76% overall yield). Both groups then set the stage for completion of the sesbanimide syntheses by effecting a selective removal

of the C-8, C-10 methylene using Ac_2O, AcOH and then performing the necessary functional manipulations to obtain aldehydes **25** and **26**.

III. Synthesis of Ring C.

Construction of ring C and thus completion of the total synthesis of sesbanimide A, requires the introduction of a C_5 unit into the C-10 carbon with control of the stereochemistry at the C-11 methyl group. The solution to this problem in each of the successful syntheses involved the addition of appropriate allyl metal species onto a suitably functionalized C-10 aldehyde intermediate.

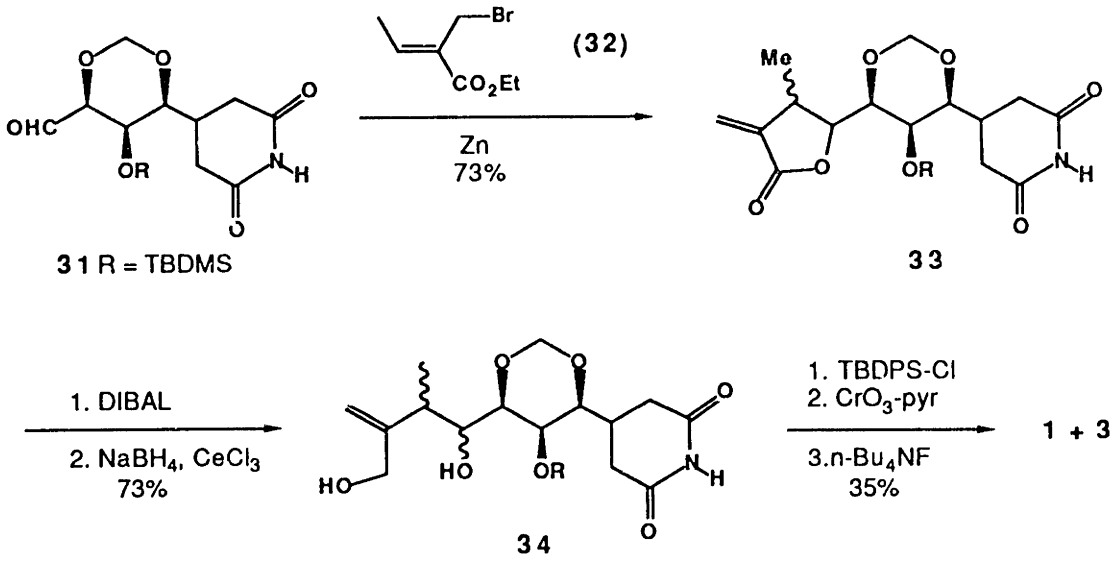
Scheme 1.6



In the Pandit and Schlessinger syntheses the C ring was built via a sequence initiated by the $BF_3{\cdot}Et_2O$ catalyzed reaction of allylsilane **27** or allylstannane **28** and aldehydes **25** and **26**, respectively (Scheme 1.6). These

sequences provided **29** as a mixture of diastereomers; the ratio of isomers at the crucial C(11) methyl group was only 1.6 or 1.7 to 1, slightly favoring the sesbanimide A configuration. The low level of selectivity is somewhat surprising, as the Lewis acid catalyzed reactions of allylsilanes and allylstannanes with α-alkoxyaldehydes are often highly diastereoselective.[18] The major product was then converted to **1** via oxidation to ketone **30** and subsequent removal of the protecting groups.

Scheme 1.7



The Terashima synthesis involved the non-diastereoselective Reformatsky reaction of aldehyde **31** and allylbromide **32** (Scheme 1.7) and led ultimately to a 1:1 mixture of sesbanimides A and B. The diastereomeric mixture of exo-methylene-γ -lactones **33** was reduced stepwise to diol **34**. The intermediate diol (mixture of four diastereomers) was converted into a 1:1 mixture of **1** and **3** by the sequence: (1) selective protection of the primary alcohol (2) Collins oxidation and (3) removal of both silyl groups.

CHAPTER 2

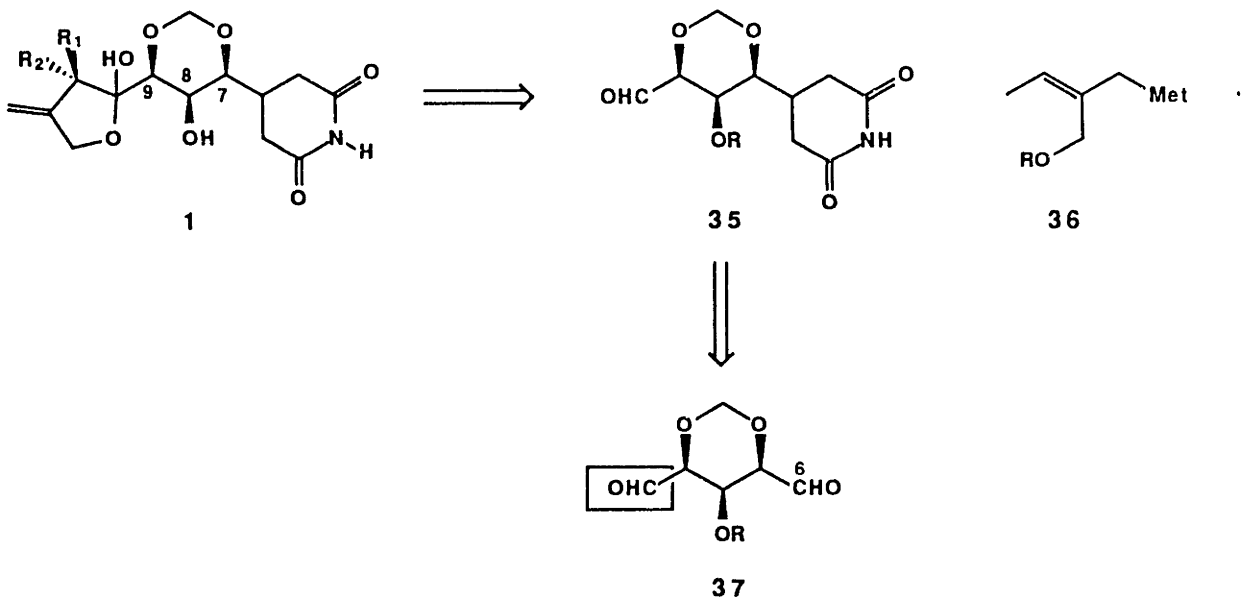
SYNTHETIC STUDIES TOWARD SESBANIMIDE A

I. Synthetic Considerations

The major chemical problem associated with a synthesis of sesbanimide A is the construction of the carbohydrate-like C-7 to C-13 segment which contains all the asymmetric centers in the molecule. In addressing this problem we sought to develop novel methodology that could find broad application in the arena of asymmetric and diastereoselective synthesis.

The synthetic strategy we hoped to follow is outlined in Scheme 2.1. We were concerned that the C-10 ketone would activate the elimination of the axial C-8 alcohol. Indeed sesbanimide has been reported to undergo rapid elimination of AcOH to give the C(8)-C(9) unsaturated ketone upon treatment with Ac_2O and pyridine suggesting that the hemiketal unit should not be introduced until a late stage of the synthesis.[2] We independently envisaged that we could build ring C by fine-tuning the stereochemical output of the reaction of an appropriate crotyl metal species **36** and aldehyde **35**.

Scheme 2.1



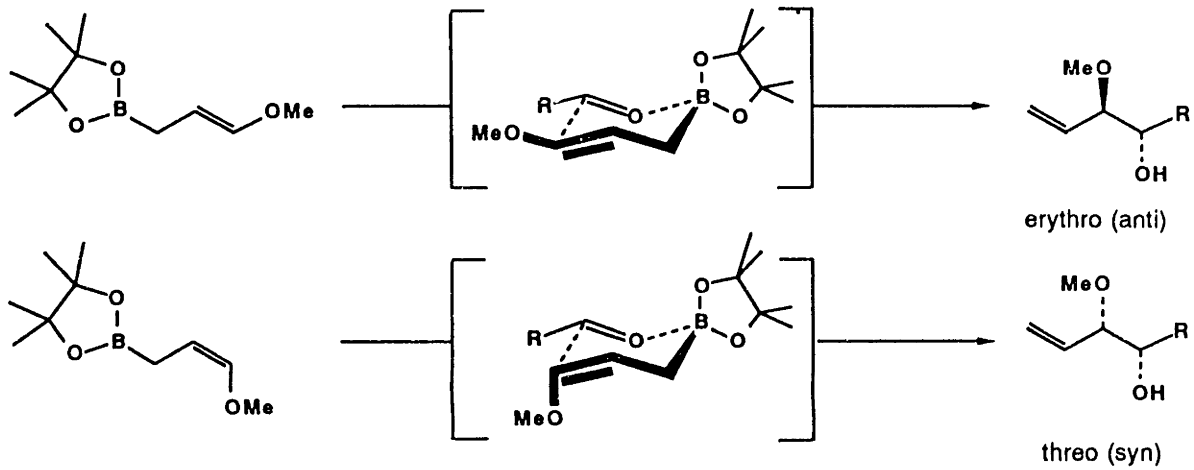
It was our plan to synthesize **35** via **37** by constructing the glutarimide onto the C-6 aldehyde. Our primary goal then was to develop methodology that would allow us to accomplish a synthesis of the B ring intermediate **37**. Such an intermediate is particularly useful as it allows easy access to either enantiomer of **1** depending on which end of the molecule is elaborated first.

II. Synthesis of the AB Ring System

We began our synthetic efforts focussing on a strategy involving the introduction of the three chiral centers of ring B through the use of highly diastereoselective reactions.

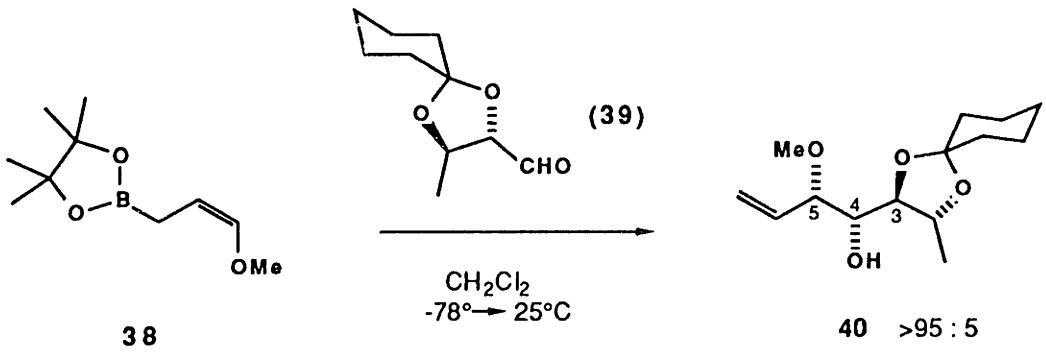
Previous studies by Roush explored the synthetic utility of the reactions of allylic boronates with chiral aldehydes in the context of acyclic stereoselective synthesis.[19] Particularly useful for the synthesis of carbohydrate-like molecules is the reaction between γ-alkoxyboronates and α-alkoxyaldehydes. The first studies of the reactions of γ-alkoxyboronates were carried out by Hoffman[20] and Wuts[21]

Scheme 2.2



(Scheme 2.2). These groups demonstrated that the stereochemical relationship between the two new chiral centers generated can be established with very high levels of control depending on the stereochemistry of the reagent. Roush, Harris, Adam and Walts then investigated the reactions of these reagents with chiral aldehydes in order to elucidate the critical parameters associated with controlling the stereochemical relationship between the two new chiral centers and the α-alkoxy chiral center present in the aldehyde.[19a] The greatest level of diastereofacial selectivity was exhibited by (Z)-γ-substituted allylboronate reagents. In one of the most impressive examples, reaction of **38** with threonine-derived aldehyde **39** gave alcohol **40** with greater than 95% diastereoselectivity. (Scheme 2.3).[22]

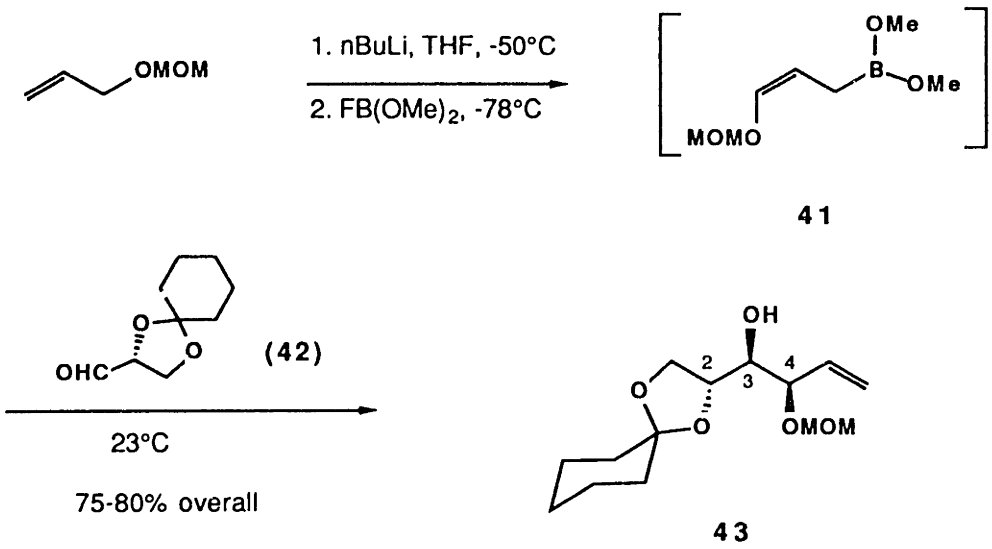
Scheme 2.3



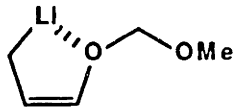
Based on these results we anticipated that homoallylic alcohol **43** could be prepared by the addition of boronate **41** to glyceraldehyde cyclohexyl ketal **42**.[23] (Scheme 2.4). The alkoxyallylboronate reagent was generated from 1.0 equiv of allyl MOM ether, 0.95 equiv n-BuLi in THF-hexane (-35 °C, 2h) and 0.95 equiv $FB(OMe)_2$ (-78 ° to 0 °C, 2h). In contrast to other allyl ethers, metallation proceeded efficiently in the absence of additives such as TMEDA.[24] The proclivity of allyl ether

anions to react predominantly with various electrophiles at the γ-position with exclusive formation of (Z)-vinyl ether was first reported by Evans and Still,[25] who

Scheme 2.4



postulated that the species generated by metallation might be better represented as an internally coordinated metallocycle (cf., **44**).



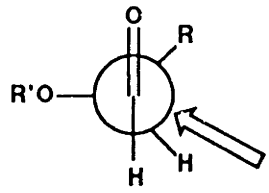
44

Treatment of **42** (0.5 equiv) with reagent **41** prepared *in situ* as described above provided **43**, isolated in 75-80% yield by direct crystallization and chromatography of the mother liquors. The ease of preparation of reagent allows for convenient scale-up of the reaction; up to 170 mmol of **43** has been prepared in high yield. Since none of the stereoisomers of **43** were observed, the diastereoselectivity of this reaction must be >20:1.

We expected that the stereochemical outcome of this reaction would follow that of the closely related reaction of aldehyde **39** and reagent **38**. A comparison of ^{1}H NMR coupling constants between **40** and **43** further supports this hypothesis, as in **43**, the couplings observed are $J_{2,3}$ = 3.1 Hz and $J_{3,4}$ = 7.4 Hz in accordance to the anti coupling between H-3 and H-4 (2.9 Hz) and the syn coupling between H-4 and H-5 (7.7 Hz) in **40**. A more rigorous proof of the stereochemistry, based on a chemical correlation, will be discussed later in this chapter.

The MOM protecting group attached to what will eventually be the C-8 alcohol of the sesbanimide target is one of the most difficult alcohol protecting groups to remove. Therefore, we investigated the preparation of reagents accomodating more labile protecting groups. Unfortunately, the overall yield of addition product from allyl alcohol protected as a THP, MEM or 1-methyl-1-methoxylethyl ether was exceedingly low. Use of methyl thiomethyl ether failed altogether, perhaps due to Wittig rearrangement [26] of the anion prior to reaction with $FB(OMe)_2$. Wuts has reported that trialkyl silyl and benzyl ethers fail due to Brook[27] and Wittig rearrangements of their respective anions. A recent report by Keck, however, describes the successful preparation of γ-alkoxy allylstannanes via lithiation of allyl silyl ethers and subsequent reaction with tri-n-butyltin chloride.[28]

The addition of nucleophiles to chiral aldehydes creates a new center of chirality and is therefore a diastereogenic process. Several theoretical models have been proposed to explain the stereoselectivity observed in such reactions. The most widely used model for explaining anti selectivity in the reactions with α-alkoxyaldehydes is the one proposed by Felkin[29] and later refined by Ahn.[30] Ahn's MO calculations show that **45** is the most reactive conformation because $\pi^*_{C=O}$ - σ^*_{C-O} interactions provide a low lying C=O LUMO. This translates into a stabilization of the developing C-C bond through favorable stereolectronic interactions with the α-alkoxy-bond.

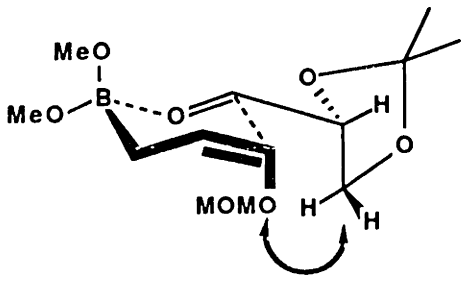


45

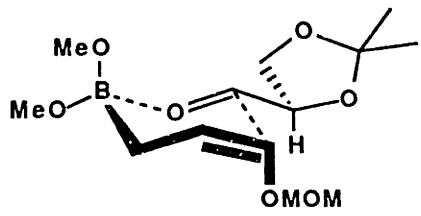
Although the outcome of the reaction of **41** with glyceraldehyde (**42**) is superficially consistent with a Felkin-Ahn transition state, a closer examination

Figure 2.1

2, 3 - anti

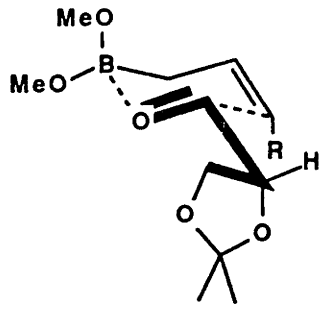


46

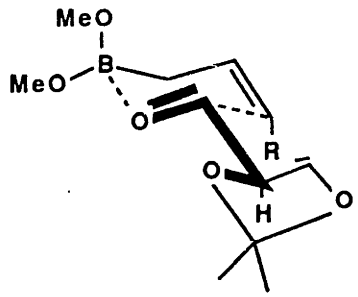


47

2, 3 - syn



48



49

rules out this interpretation. Space-filling molecular models of the Felkin transition

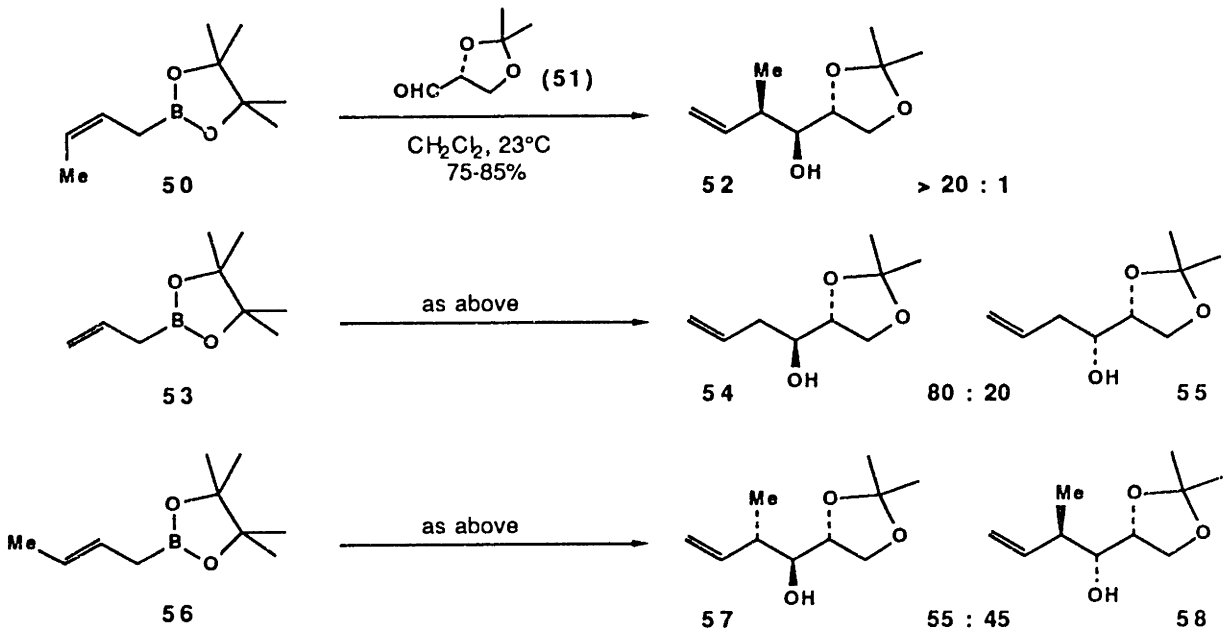
state **46** (Figure 2.1) reveal a severe non-bonded interaction between the axial OMOM group and C-1 making it difficult for the olefin to come within bonding distance to the carbonyl. An analysis of other possible transition states, based on minimization of non-bonded interactions and an antiperiplanar relationship between the developing C-C and the C-(1)-C-(2) bond,[31] points to the Cornforth-like[32] transition state **47** as the most probable one. Note that in **47** the OMOM group is eclipsed with the smallest (e.g., H) of the aldehydic α-substituents. The level of selectivity is very high in part because the syn selective transition states suffer from long range non-bonded interactions; for example the OMOM group in **48** is eclipsed with the C-2 oxygen while transition state **49** suffers from a gauche type interaction between the OMOM group and C-1. In addition, however, the Cornforth-like transition state **47** may be stabilized by favorable electronic interactions. Ahn's calculations in fact show this aldehyde rotational isomer to be the second most favorable, following behind only **45**.[30]

A more thorough investigation of the various factors affecting the stereochemical outcome of the reaction between allylboronate reagents and α-alkoxyaldehydes was carried out by Roush and Adam.[33] These studies (Scheme 2.5) revealed that the reaction between glyceraldehyde acetonide **(51)** and either allylboronate **(53)** or (E)-crotylboronate **(56)** is much less selective than the corresponding reaction with the (Z)-crotylboronate **(50)**. These results provide conclusive evidence that a Felkin transition state is not important in these reactions, because were a Felkin transition state involved, one would expect the reactions of **53** and **56** to be more anti selective than the reaction of **50** as the destabilizing non-bonded interaction between the axial (Z)-substituent and C-1 is alleviated (e.g., **46**).

Conventional models such as the Felkin-Ahn model may not even apply to these reactions, as they require approach of the nucleophile along the Burgi-

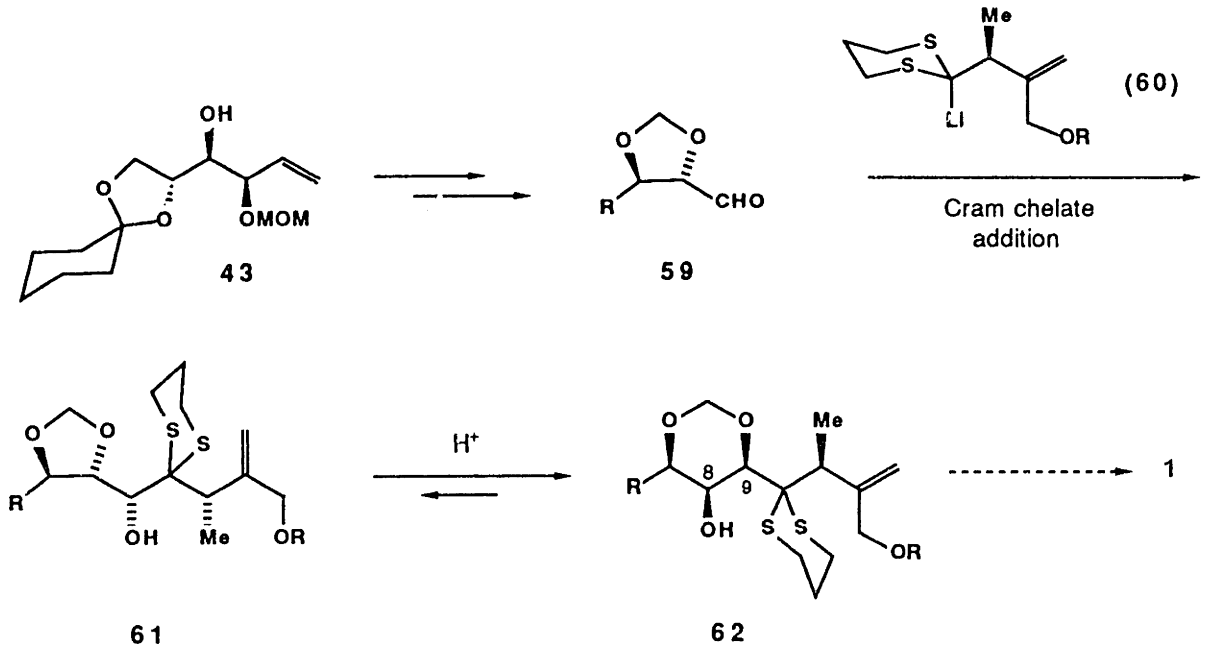
Dunitz[34] trajectory (~109°). These reactions might better be viewed as bis-heteroatom Claisen rearrangements.

Scheme 2.5



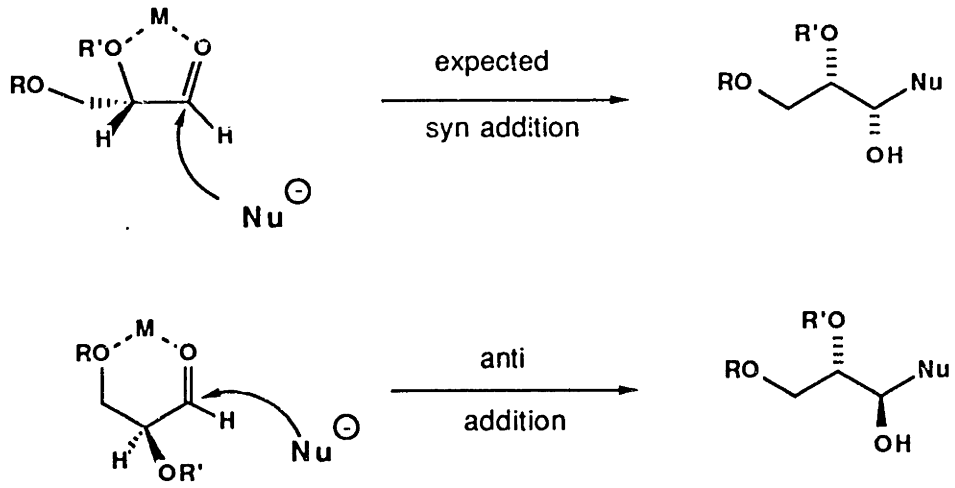
The next critical step in the synthesis involved the introduction of the third chiral center of the B ring. At one point we hoped to control this center by employing a syn selective addition of a substituted dithiane nucleophile to an aldehyde such as **59** (Scheme 2.6). This approach had the potential to be highly convergent, as in the coupling of **59** and **60**. Based on reports from the carbohydrate literature[35] we believed it would then be possible to effect an acid catalyzed isomerization of **61** to the B-ring intermediate **62**. Note also that the sensitive C-10 carbonyl unit would remain protected as a dithiane until late in the synthesis.

Scheme 2.6

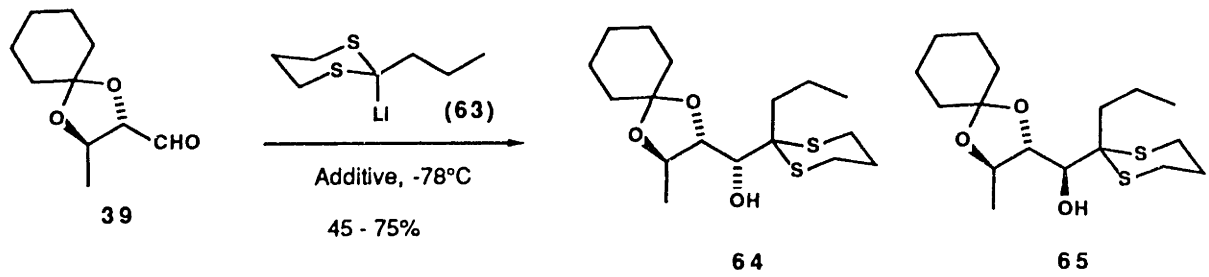


The problem of achieving syn selectivity in the reaction of nucleophiles with chiral α-alkoxy aldehydes has received considerable attention.[36] The strategy most often employed involves use of Lewis-acidic reagents which form intermediate chelates (chelation control). The conformationally biased, cyclic chelate is then attacked stereoselectively from the less hindered side affording syn products.

With polyfunctional carbonyl compounds such as **59**, however, several chelate structures are feasible and each, in principle, may contribute to the stereochemical outcome of addition. The critical role of the counter ion in determining the stereoselectivity of nucleophilic addition was established by Still,[37] and later defined by Reetz,[38] Macdonald[39] and others. These studies indicate that the metal of choice for achieving syn products is Mg^{+2} which shows a marked preference for α-chelation (5-membered chelate).



Based on these studies we felt confident that a high syn selectivity could be achieved. The only example, however, involving a dithiane anion nucleophile known at the time of our studies was the addition of 2-lithio-1,3-dithiane to glyceraldehyde acetonide. As expected the reaction afforded the anti product preferentially (undefined stereoselectivity).[40] Accordingly we carried out model studies involving the addition of 2-propyl-1,3-dithiane **63** to aldehyde **39** as



summarized in Table 2.1. The best selectivity for the syn product **64** was obtained using an *in situ* prepared Grignard reagent. Choice of solvent is critical; when the reaction is carried out in THF the selectivity is reversed in favor of the anti product, presumably because of strong solvation of Mg^{+2}. Reetz has reported high syn selectivity associated with addition of Lewis acidic titanium reagents (eg. $RTiCl_3$) to α-alkoxyaldehydes. Unfortunately we were unable to successfully exploit this

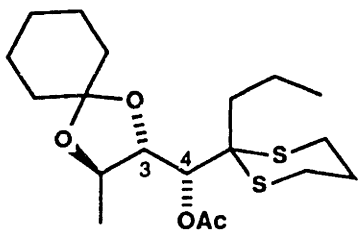
methodology, probably due to steric hindrance of **63** and reactivity of ketal groups with Lewis acids.

Table 2.1

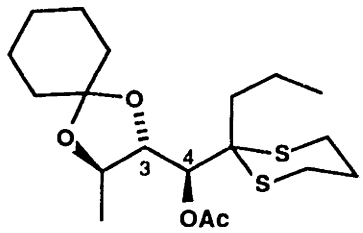
Solvent	Additive	64[a]	65[a]
THF	–	15	85
Et_2O	-	35	65
Et_2O	$MgBr_2$	65	35
THF	$MgBr_2$	15	85
THF	Cl-Ti(OiPr)$_3$	45	55
CH_2Cl_2	Cl-Ti(OiPr)$_3$	Decomposition	
THF	$ZnCl_2$	Decomposition	
THF	$TiCl_4$	Decomposition	

a) Relative ratios of the two diastereomers

The stereochemistry of **64** and **65** was assigned on the basis of ^1H NMR coupling constants of their acetate derivatives **66** and **67** respectively. The critical coupling between H-3 and H-4 was measured to be close to 0 Hz in **66** and close to 8 Hz in **67** corresponding to a syn and anti relationship respectively.[41]



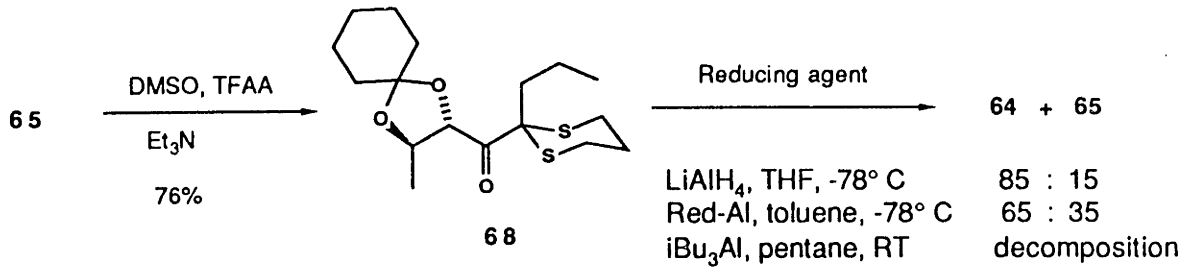
66



67

The 2:1 level of selectivity cannot be considered synthetically useful. One possibility for improving the reaction is to convert the minor product, **65**, to **64**. Attempts to invert the alcohol by using the Mitsunobu reaction were unsuccessful because of the greatly hindered steric environment. An indirect solution to this problem was achieved via oxidation to ketone **68** and diastereoselective reduction. Preferential reduction of **68** to **64** requires attack of hydride through a Felkin mode of addition. Thus use of a reagent incapable of chelation in a strongly coordinating solvent is advantageous.[42] In accordance with this strategy, use of the $LiAlH_4$ in THF at -78 °C afforded **64** with greater than 5:1 selectivity (Table 2.2).[43]

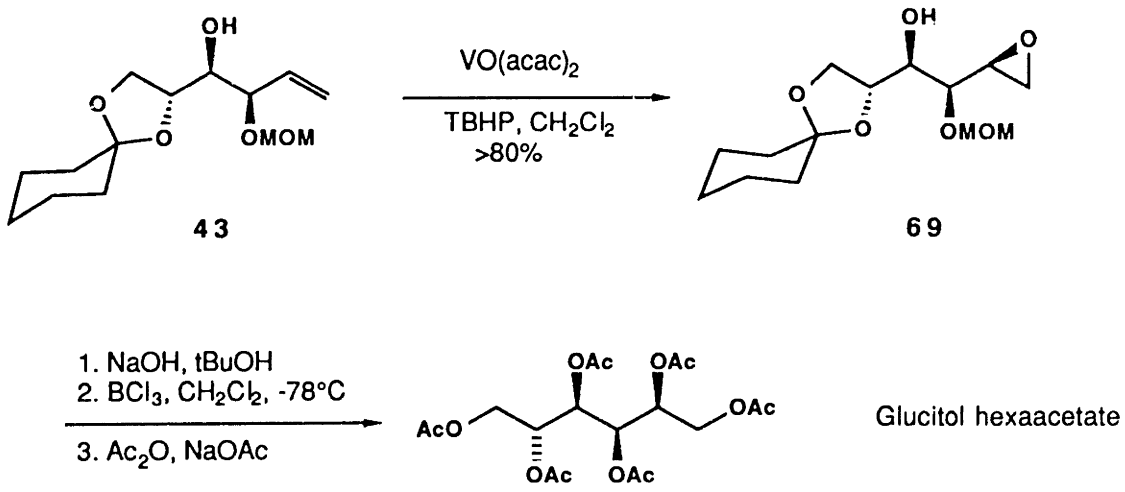
Table 2.2



Although these results were encouraging we decided to redesign our synthetic strategy in favor of a more direct approach. Thus we began exploring the possibility of introducing the chiral center at C-9 via selective epoxidation of **43**.

Whereas a mixture of diastereomers (~1:1) was obtained when mCPBA was used, application of the TBHP-$VO(acac)_2$[44] system (room temperature, 24-48 h) provided **69** as the sole product in excellent yield (Scheme 2.7). The stereochemistry of **69** was assigned by an unambiguous chemical correlation. Epoxide **69** was first treated with aqueous NaOH in t-BuOH. The protecting groups were then removed by using BCl_3 in CH_2Cl_2 at -78 °C to provide a hexaol. Peracetylation gave a hexaacetate that was identical to an authentic sample

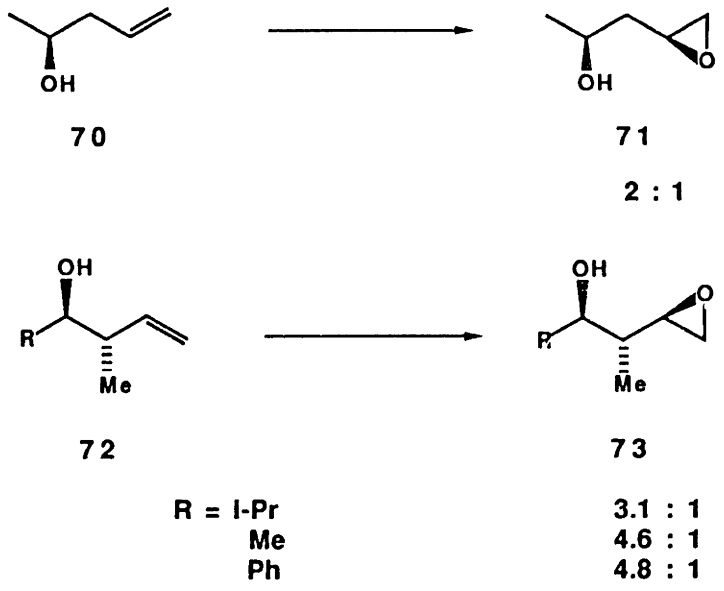
Scheme 2.7



of glucitol hexaacetate. Assuming that hydroxide attacked the more accessible C-1 position of **69**, as would be expected based on literature precedent[45] and the reaction of **69** with PhSNa discussed subsequently, the stereochemistry of **69** must be as shown.

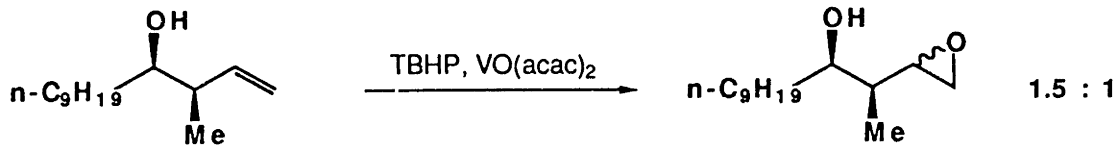
The epoxidation of **43** is one of the most highly selective epoxidations

Scheme 2.8



reported for a homoallylic alcohol lacking a cis-olefin substituent. Typical levels of selectivity previously reported vary from 2:1 to 4.8:1 (Scheme 2.8).[44]

We were unaware, however, of any examples in the literature involving syn homoallylic alcohols lacking a cis olefin substituent. Therefore we carried out the epoxidation of **74**. This epoxidation also exhibits low selectivity, giving a mixture of two epoxides in a 3 to 2 ratio.



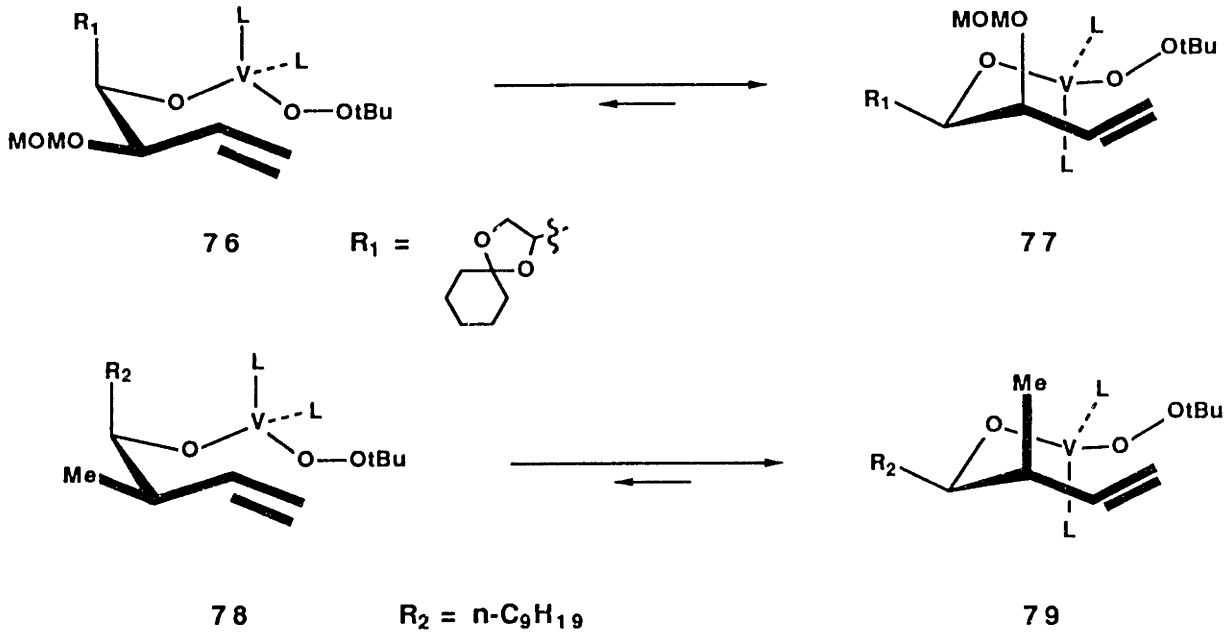
74 **75**

Mihelich proposed that these reactions proceed via a vanadate ester transition state in which the metal is tetrahedrally coordinated.[44a] Minimization of steric interactions among the various substitutents according to commonly accepted principles of conformational analysis determines the direction of asymmetric induction. The product observed in the reaction of **43** is consistent with epoxidation having occured via conformation **77** in which the bulky R_1 group occupies the equatorial position (Figure 2.2).

The very high level of selectivity is surprising in view of the low selectivities observed in the epoxidations of **70**, **71** and, in particular, **74** which has the same strereochemisty as **43**. An analysis in terms of non-bonded interactions reveals that the epoxidation of **43** should indeed be more selective than that of **74** because the R_1 group of **43** is slightly bulkier than R_2 of **74** (both groups are placed equatorially in **77** and **79** respectively). Additionally, the OMOM group occupying the unfavorable axial position in **77** is smaller than the methyl group of **74** placed axially in **79**. These steric interactions alone are insufficient to explain

the great difference in selectivity observed. A more important factor in making the epoxidation of **43** so selective is the presence of the allylic alkoxy group which enhances the relative reactivity of conformation **77** versus that of **76**, by inductively deactivating conformation **76** (e.g., inside alkoxy effect).[46]

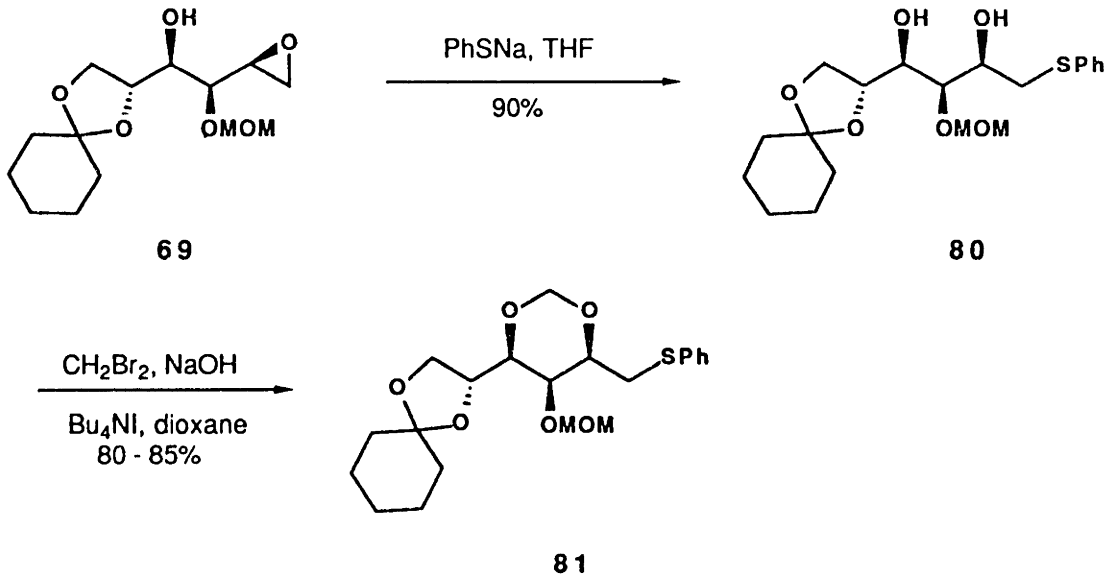
Figure 2.2



With the three stereocenters of the B ring now in place, epoxide **69** was treated with PhSNa in THF (Scheme 2.9). The thiophenyl appendage will serve as an aldehyde equivalent, in analogy to the work of Sharpless and Masamune in their synthesis of the L-hexoses.[47] The crystalline 1,3-diol **80** so obtained was subjected to standard methylenation conditions[48] providing **81** in 80-85% yield. This critical intermediate was synthesized in four steps from D-glyceraldehyde cyclohexyl ketal in very good overall yield (50-58%).

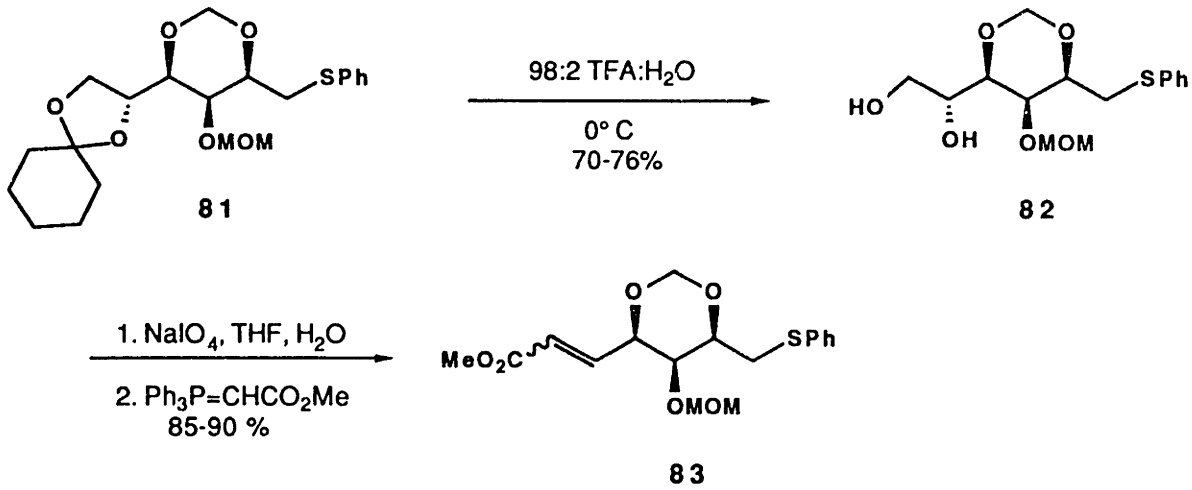
The absolute stereochemistry of sesbanimide was not known at the time of our studies, so we arbitrarily chose to elaborate the imide ring onto C-2 of **81**.

Scheme 2.9



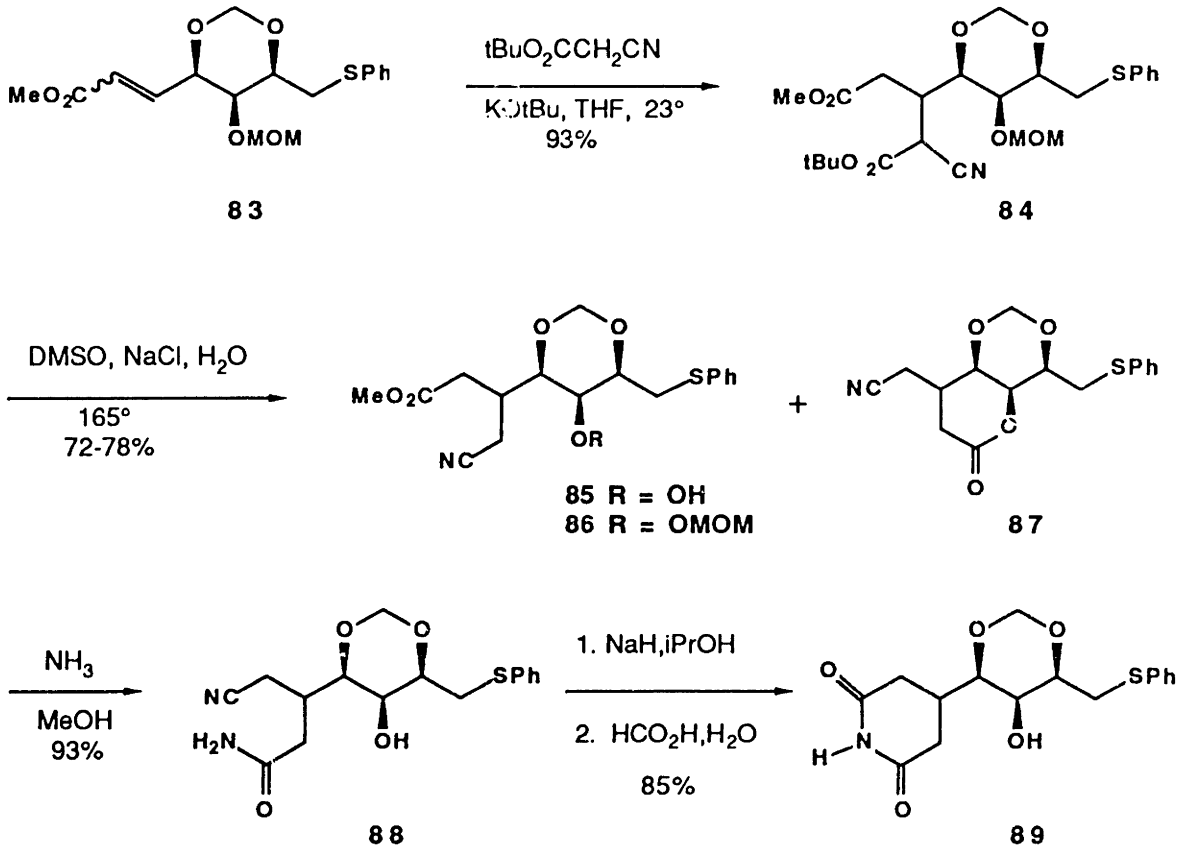
Selective hydrolysis of the cyclohexyl ketal was achieved using 98:2 TFA:H_2O (0 °C, 5 min) giving **82** in 70-76% yield (Scheme 2.10). Periodate cleavage of the 1,2 diol followed by Wittig olefination gave unsaturated ester **83** (85-90% yield for two steps) as a 3.5:1 (Z):(E) mixture of olefin isomers.

Scheme 2.10



An efficient method for elaboration of the glutarimide is summarized in Scheme 2.11. The Michael reaction of **83** (routinely used as a mixture of isomers) with t-butyl cyanoacetate proceeded smoothly to give **84** as a mixture of diastereomers. Subjection of **84** to the Krapcho decarboxylation procedure (NaCl, H_2O, DMSO, 160°C, 4.5 h)[49] effected the expected cleavage of the $-CO_2C(Me)_3$ unit as well as deprotection of the MOM ether to give a mixture (~1:1) of cyanoester **85** and cyanolactone **87**. If shorter reaction periods were employed (2 h) the MOM ether **86** could be isolated in low yield. The resulting mixture of **85** and **87** underwent smooth ammonolysis in MeOH providing amide **88** in excellent yield. Finally the imide synthesis was completed by treatment of **88** with NaOiPr in iPrOH

Scheme 2.11

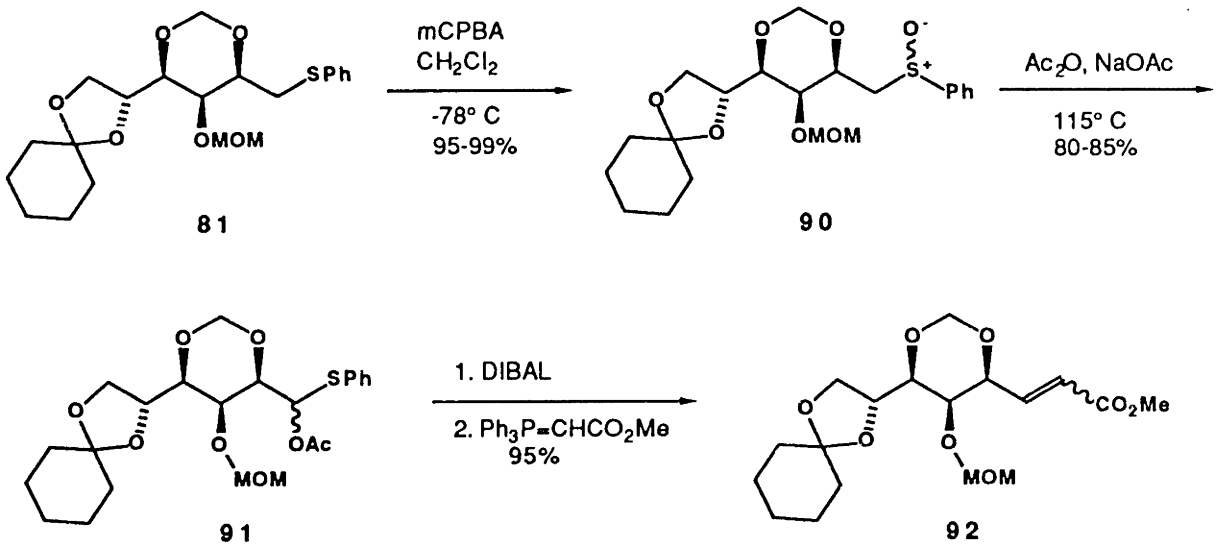


followed by mild formic acid hydrolysis. The yield of glutarimide **89** was 53% from **83** and 17-21% overall from **42**.

At the time our synthesis of **89** was nearly completed, Pandit reported the first total synthesis of **1**. This work established for the first time the absolute stereochemistry of sesbanimide, which unfortunately corresponded to the enantiomer of the AB ring intermediate **89**.

The heterochirally related AB intermediate was then synthesized by unmasking and elaborating the opposite end (C-6) of intermediate **81**, by using the Pummerer-Wittig sequence described by Masamune and Sharpless (Scheme 2.12).

Scheme 2.12

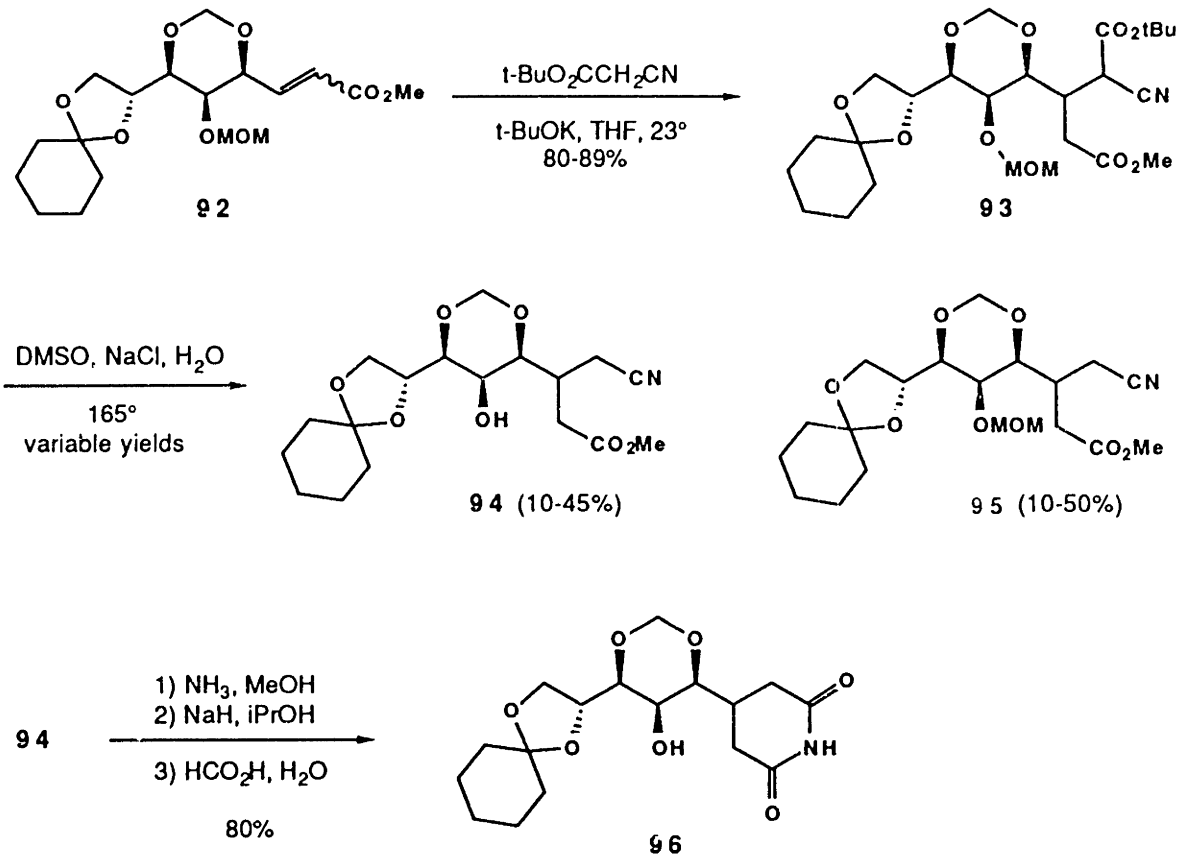


Thus the thioether **81** underwent facile oxidation to a mixture of diastereomeric sulfoxides **90** (mCPBA, -78 °C, CH_2Cl_2; quantitative yield). Pummerer rearrangement[50] (Ac_2O, NaOAc, 115 °C, 18-26 h) proceeded to provide in 80-85% yield thioacetate **91**. Treatment of the mixture of diastereomers, so obtained, with DIBAL at -78 °C followed by standard Wittig olefination gave

unsaturated ester **92** (95% for two steps) as a 1.4:1.0 (Z):(E) mixture of olefin isomers.

The glutarimide was originally elaborated using the same methodology described for **89.** (Scheme 2.13). Subjection of the Michael adduct **93** to the Krapcho decarboxylation procedure provided **94** in only 10-45% yield along with variable amounts of **95** (10-50% yield). This reaction is clearly unsatisfactory

Scheme 2.13

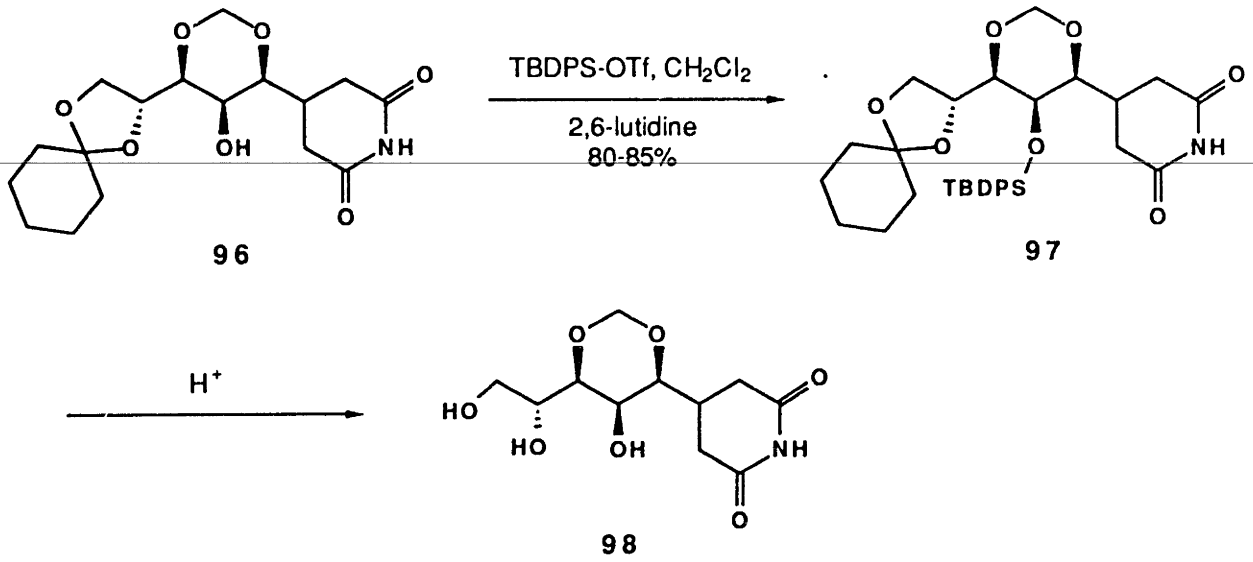


because of the highly erratic yields. In addition very poor results were obtained on attempted scale up. The cyanoester **94** was then elaborated in good yield to imide **96**.

The highly variable yields associated with the decarboxylation of **93** prompted us to undertake a more careful investigation of the lability of MOM ethers under the Krapcho decarboxylation conditions. We used cholesterol MOM ether as a model and found that it could be deprotected in quantitative yield upon refluxing in DMSO in the presence of either water and NaCl or water alone. However, when the reaction was repeated in the presence of $NaHCO_3$ no cholesterol was obtained. These results indicate an acid catalyzed mechanism of deprotection of MOM ethers in the decarboxylation of **84** and **93**.

The next problem we faced was the protection of the free alcohol at C-8 of **96**. Attempted protection as a 3,4-dimethoxybenzyl ether resulted in exclusive isolation of recovered starting material,[51] presumably due to steric hinderance. Alcohol **96**, however, was successfully converted to the TBDPS ether (**97**) using the conditions described by Schlessinger[9] (TBDPS-OTf, 2,6-lutidine, CH_2Cl_2) in 80-85% yield. Elaboration of the C-ring requires the generation of an aldehyde at C-10 of **97**, thus necessitating the selective hydrolysis of the cyclohexyl

Scheme 2.14

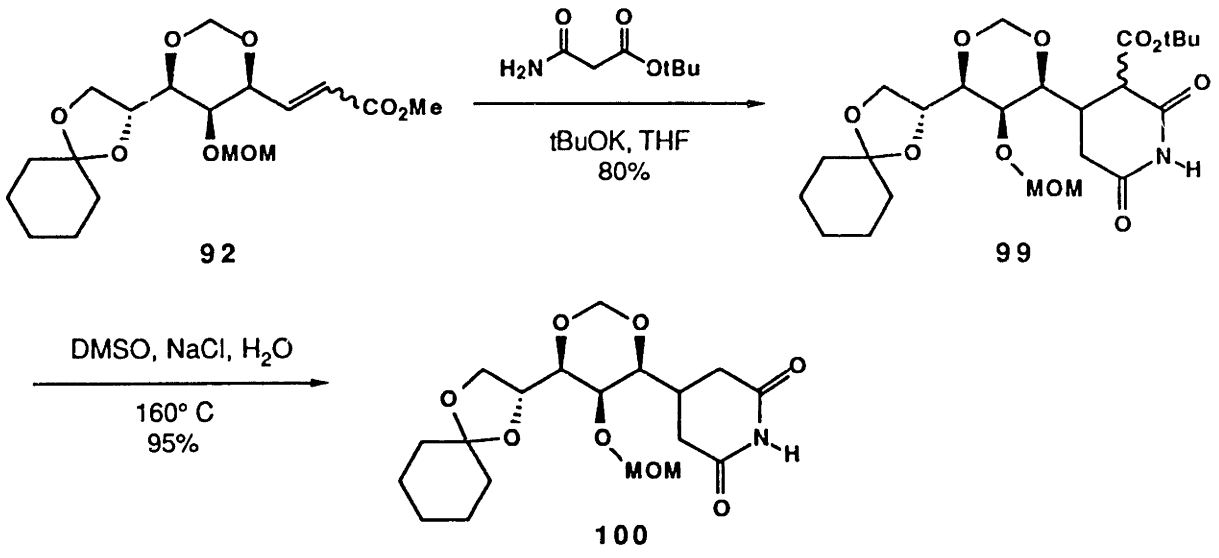


96 **97** **98**

ketal. Unfortunately use of various reagents, such as 60% AcOH, TFA-H_2O, TsOH-MeOH, aqueous AcOH (pH=3), resulted in loss of both protecting groups providing triol **98** (Scheme 2.14).

In view of the low yield of **94** from **93** and our inability to selectively remove the cyclohexyl ketal, we decided to prepare the MOM protected alcohol **100**. Using the methodology developed by Pandit for synthesis of glutarimides,[12] **100** was prepared efficiently in two steps from ester **92**. (Scheme 2.15). The Michael reaction of **92** with t-butyl carbamoylacetate gave **99** as a mixture of diastereomers, in 80% yield. As expected the decarboxylation of the more active β-keto ester **99** was much more facile than that of the β-cyano ester **93**. The reaction (DMSO, 2 equiv NaCl, 3 equiv H_2O, 160°) was complete within one hour, affording the imide **100** in excellent yield (90-98%).

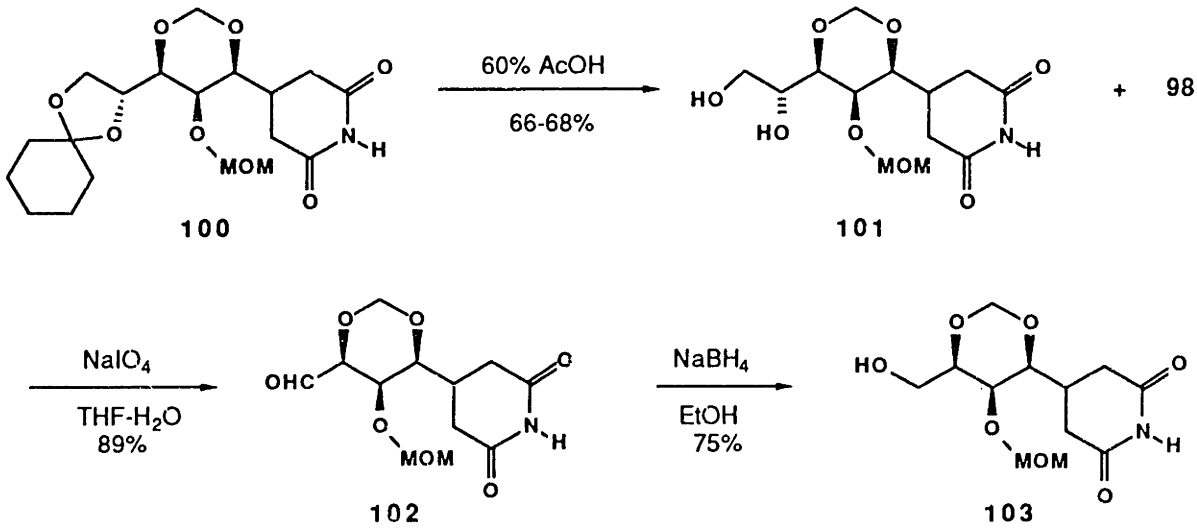
Scheme 2.15



We had anticipated that the cyclohexyl ketal in **100** could be cleaved without any competing loss of the MOM group, as seen in the TFA:H_2O mediated hydrolysis of **81** to **82**. However, use of 98:2 TFA:H_2O or catalytic amounts of HCl

or TsOH in MeOH resulted in isolation of both **101** and triol **98**. A satisfactory rate difference in the hydrolysis of the cyclohexyl ketal and the MOM ether was finally achieved by using aqueous 60% AcOH (Scheme 2.16). This reaction afforded **101** in 66-68% yield along with triol **98** (10-15% yield). Periodate cleavage of **101** afforded aldehyde **102** (89% yield after chromatography). This aldehyde was prone towards hydration making characterization very difficult, thus a sample was reduced to the alcohol **103** for characterization purposes.

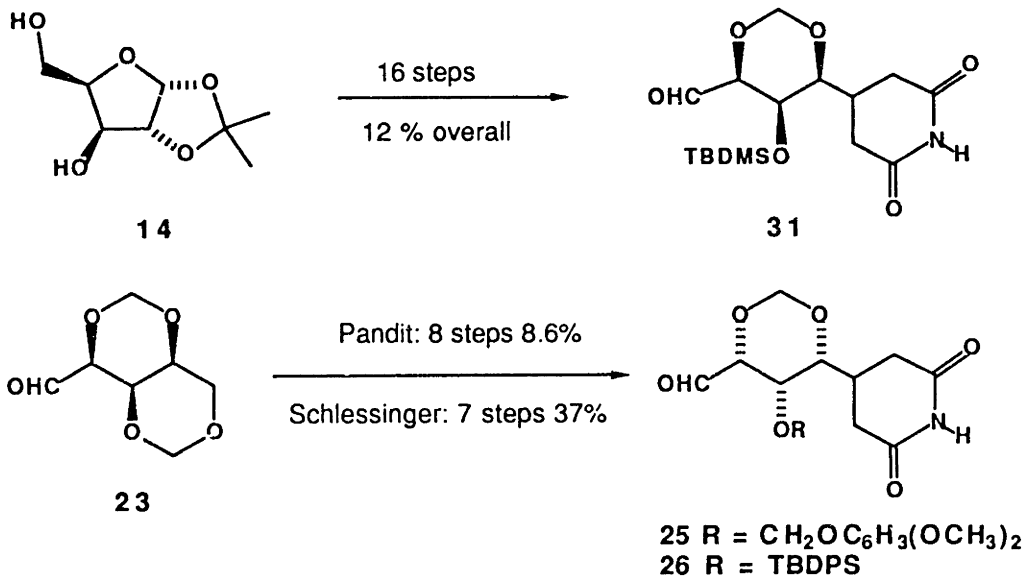
Scheme 2.16



In summary, aldehyde **102** has been prepared in twelve steps from glyceraldehyde cyclohexyl ketal (**42**) in good overall yield (16-20%). It is noteworthy that the three asymmetric centers of **102** have been introduced with excellent control by using stereoselective organic reactions. The brevity and efficiency of our synthesis rivals the other approaches, discussed in chapter 1, in which the B ring originates entirely from a readily available carbohydrate. For example, Terashima prepared the closely related aldehyde **31** from **14** in sixteen steps with a 12% overall yield; while Pandit's synthesis of **25** required eight steps

from **23** and proceeded in only 8.6% overall yield (Scheme 2.17). Schlessinger's synthesis of **26** is clearly the most efficient requiring only seven steps with an excellent overall yield (37%).

Scheme 2.17



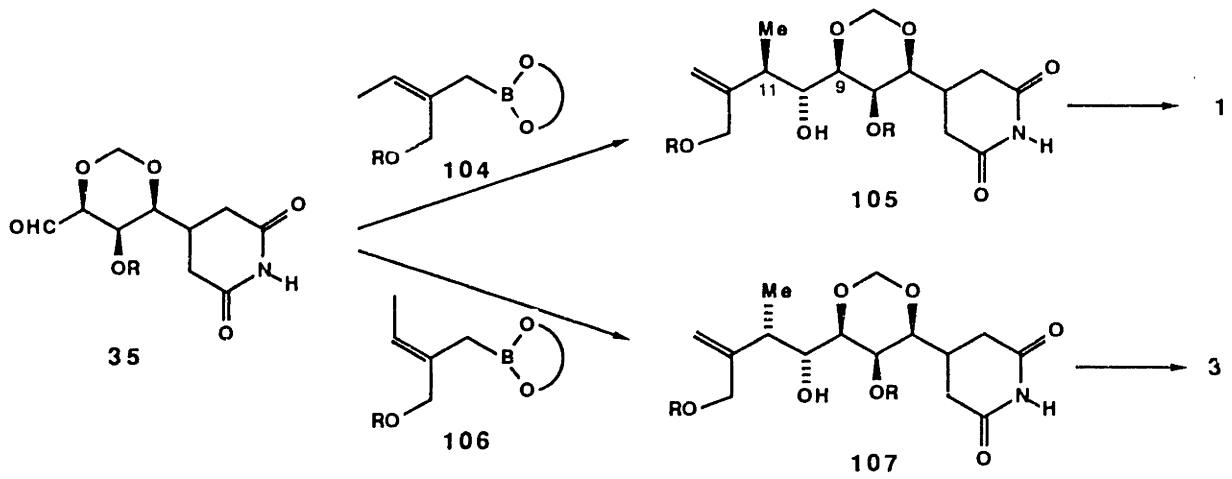
Our synthesis nicely illustrates the power of emerging methodology for solving complex stereochemical problems. It is conceivable that the allyboration-epoxidation sequence will find use in the synthesis of other carbohydrate-like molecules.

III. Studies Toward the Synthesis of Ring C

Our strategy called for the C ring to be constructed via the reaction of aldehyde **35** with a suitably functionalized allylboronate (Scheme 2.18). The boronate adduct **105** or **107** could easily be converted to sesbanimide A and B respectively via oxidation and removal of the protecting groups.

The choice of boronate reagent is crucial in determining the C-11 methyl stereochemistry. Based on the studies of the reactions of crotylboronates and α,β-dialkoxyaldehydes previously discussed, we believed that use of a (Z)-allylboronate such as **106** would provide **107** and thus sesbanimide B with very high levels of stereocontrol. That is, in the reactions of (Z)-crotylboronates and α,β-dialkoxyaldehydes the 3,4-syn-4,5-anti diastereomer (as in **107**) is obtained with extremely high selectivity. Therefore synthesis of sesbanimide A with a 1,3-syn relationship between C-11 and C-9 requires the use of an (E)-allylboronate reagent such as **104**.

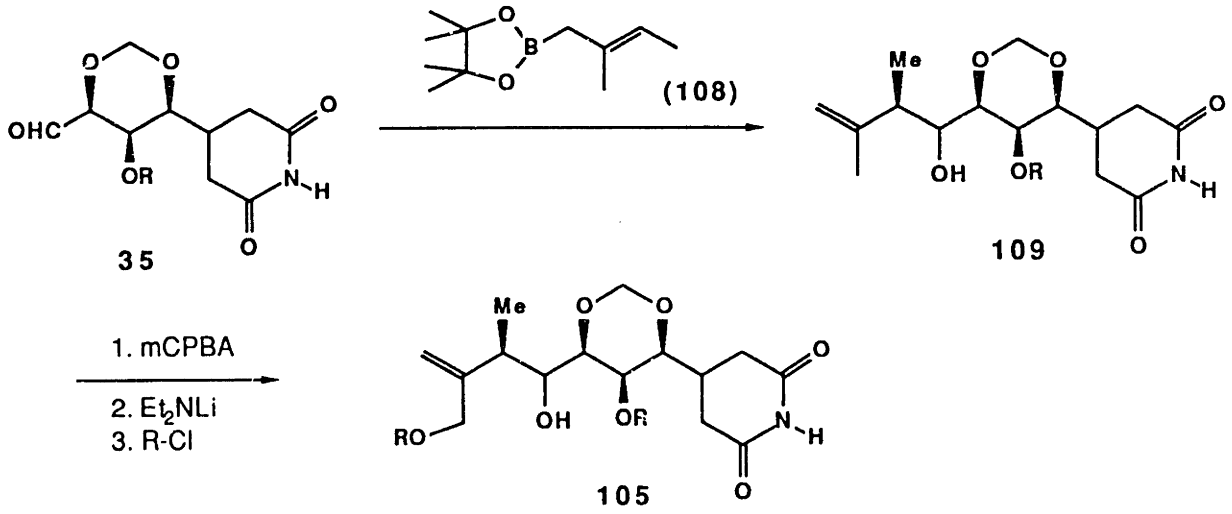
Scheme 2.18



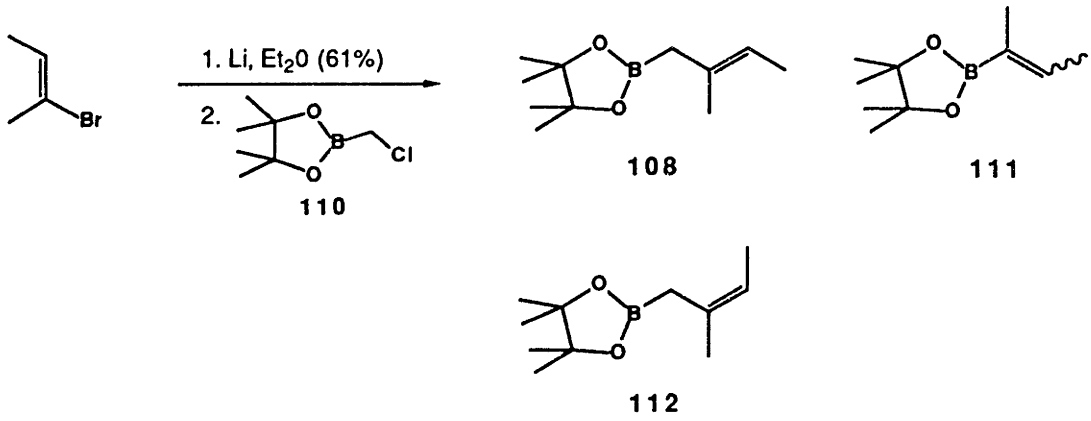
At one point we hoped that the reactions of achiral (E)-allylboronates with chiral aldehydes would be as selective as the reactions of the corresponding (Z)-allylboronates. Boronate reagent **108** seemed particularly attractive as a model of the reactions of substituted crotylboronates with α,β-dialkoxyaldehydes because of its relative ease of preparation. In addition we envisaged that the homoallylic alcohol **109** derived from addition of **108** to **35** could be converted in only three steps to the sesbanimide A precursor **105** by a sequence involving (i) epoxidation,

(ii) base isomerization of the epoxide to the allylic alcohol [52] and (iii) selective protection of the primary alcohol (Scheme 2.19).

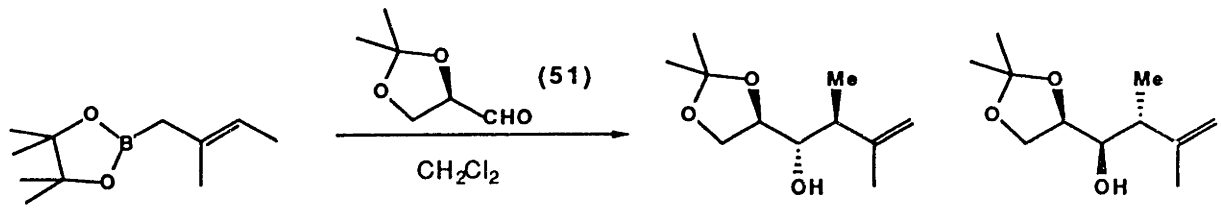
Scheme 2.19



Allylboronate **108** was prepared by addition of (Z)-2-lithio-2-butene[53] to chloromethylboronate **110**.[54] This method, however, was inefficient as the highest yield of **110** obtained was only 25%, due to formation of vinylboronate **111** in greater than 50% yield. Formation of **111** could be eliminated if the corresponding Grignard was used in place of the lithium reagent, but unfortunately formation of the Grignard reagent prepared from (Z)-2-bromo-2-butene occurs with poor stereospecificity resulting in a 2 to 1 mixture of **111** and **112**.[55]



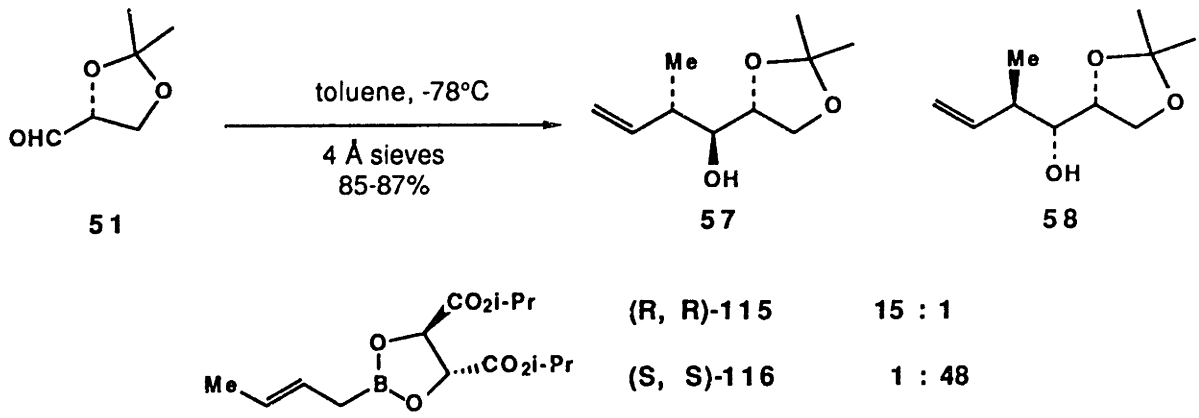
The addition of allylboronate **108** to glyceraldehyde acetonide **51** proved to be totally non-selective, giving a mixture of two products in a 1 to 1 ratio.



108 **113** **1 : 1** **114**

Extensive studies in these laboratories[22,33] have demonstrated that reactions of (E)-allylboronates with chiral α,β-dialkoxyaldehydes are generally non-selective. The problem of poor diastereoselectivity can be overcome by applying the strategy of double asymmetric synthesis[56], that is, by employing a chiral reagent powerful enough to determine the stereochemical output of the reaction independent of any diastereofacial preference on the part of the aldehyde. The tartrate ester modified allylboronates developed in these laboratories are particularly useful in this context.[57] For example, the reaction of D-glyceraldehyde acetonide **51** and the (R-R)-reagent **115** provides the 2,3-anti-3,4-syn product **57** with 15 to 1 selectivity (Scheme 2.20). On the other hand, reaction with the

Scheme 2.20



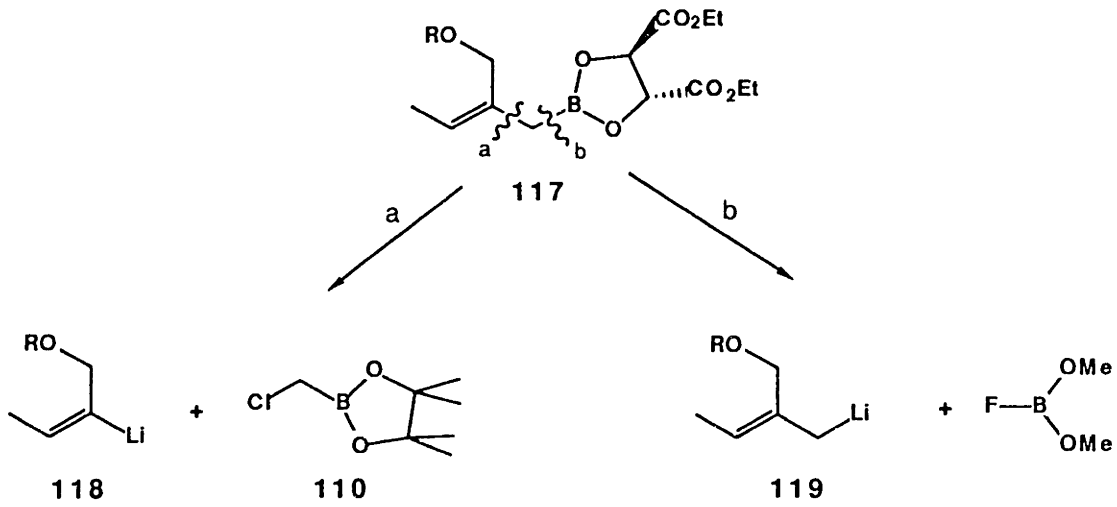
51 **57** **58**

(R, R)-115 **15 : 1**

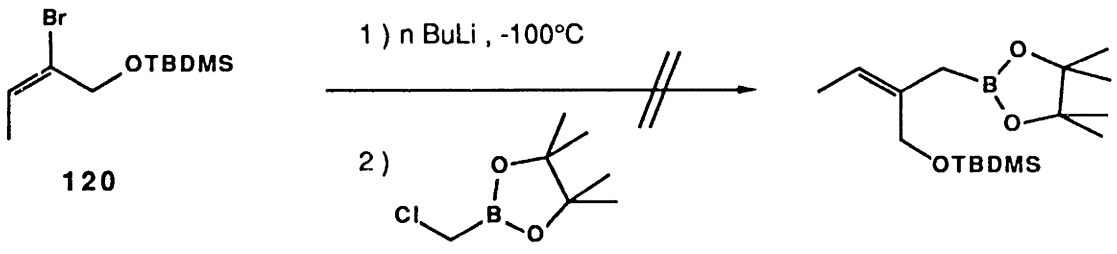
(S, S)-116 **1 : 48**

enantiomerically related (S,S) reagent **116** allows access to the 2,3-syn-3,4-anti product **58** with exceptional control (48 to 1 selectivity).

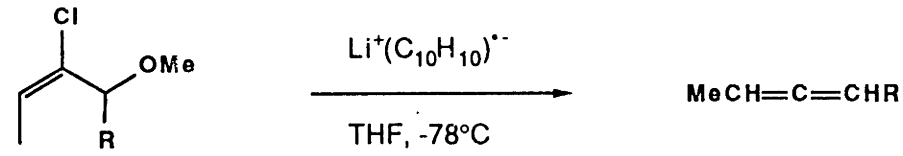
Thus, our objective became the synthesis of the chiral allylboronate **117.** We considered two distinct carbon-carbon bond forming reactions. Route **a** utilizes the homologation reaction between vinyllithium species **118** and chloromethyl-boronate **110**. Route **b** involves the addition of substituted crotyllithium **119** to fluorodimethoxyborane.



To employ route **a**, we attempted to prepare the requisite vinyllithium species from bromide **120**. Although the generation and use of α-lithioallyl ethers is well precedented,[58] this reaction failed since the intermediate vinyllithium



species decomposed very rapidly to the corresponding allene. Barluenca and coworkers have reported that O-methylated chlorohydrin **121** upon treatment with lithium naphthanelide at -78 °C undergoes elimination to afford an allene **122**.[59]



121

R = n-C_4H_9, i-C_4H_9

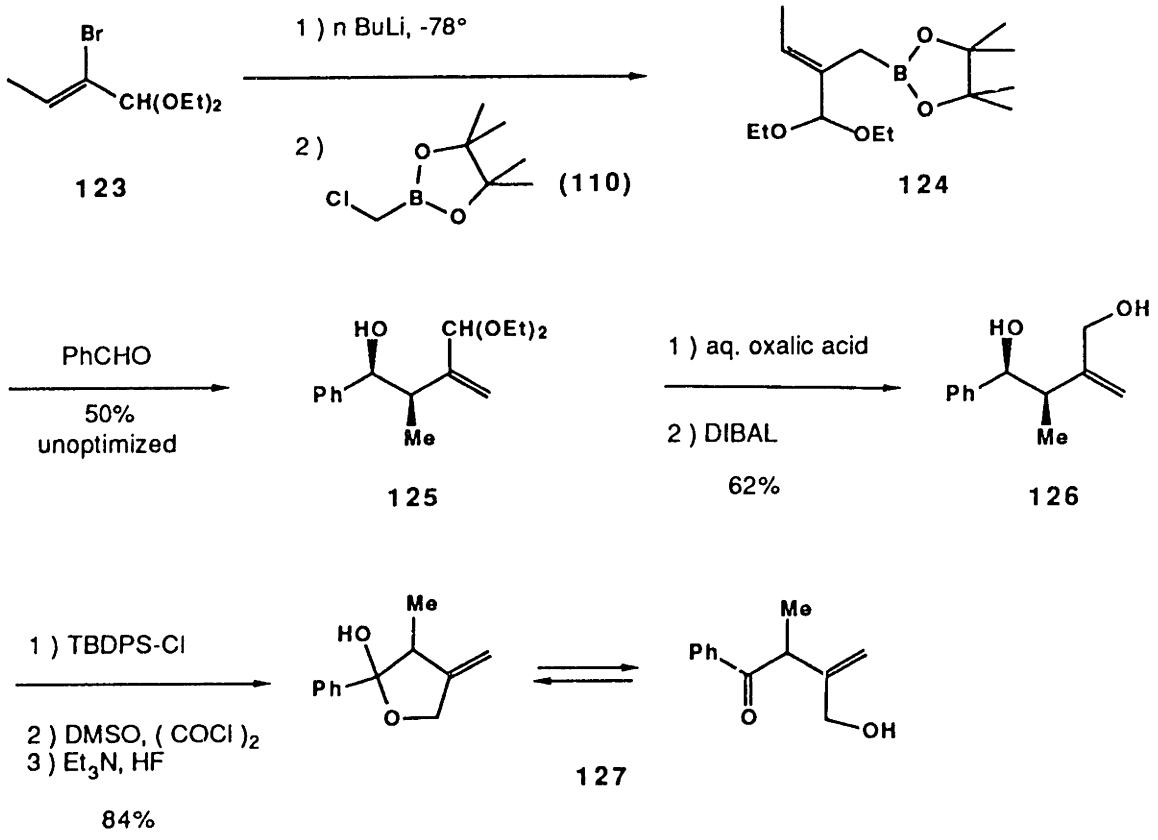
122

A solution to this problem of elimination involved use of the more stable α-lithio acetal as demonstrated by the synthesis of substituted (Z)-crotylboronate **124**. Thus, lithiation of **123**[60] followed by treatment with **110**, proceeded smoothly to provide allylboronate **124**. This reagent was successfully applied to a synthesis of C ring model compound **127** (Scheme 2.21). The crude reagent, **124** was treated with benzaldehyde to provide homoallylic alcohol **125** as the sole product. Deprotection of the diethyl acetal yielded the corresponding α,β–unsaturated aldehyde in quantitative yield. The aldehyde was then reduced with DIBAL (82%) to the allylic alcohol **126**. Selective conversion of the primary alcohol to a TBDPS ether followed by Swern oxidation and subsequent removal of the silyl ether gave a compound we believe to be **127**. It should be noted that a compound analogous to **126** with the AB ring system replacing the phenyl substituent (**34**) has functioned as an intermediate in Terashima's synthesis.[10]

We decided not to apply this sequence to a synthesis of sesbanimide since we would prefer to generate a reagent in which the sesbanimide C(13)-CH_2OH unit is introduced in the correct oxidation state. In addition, because **124** is a (Z)-

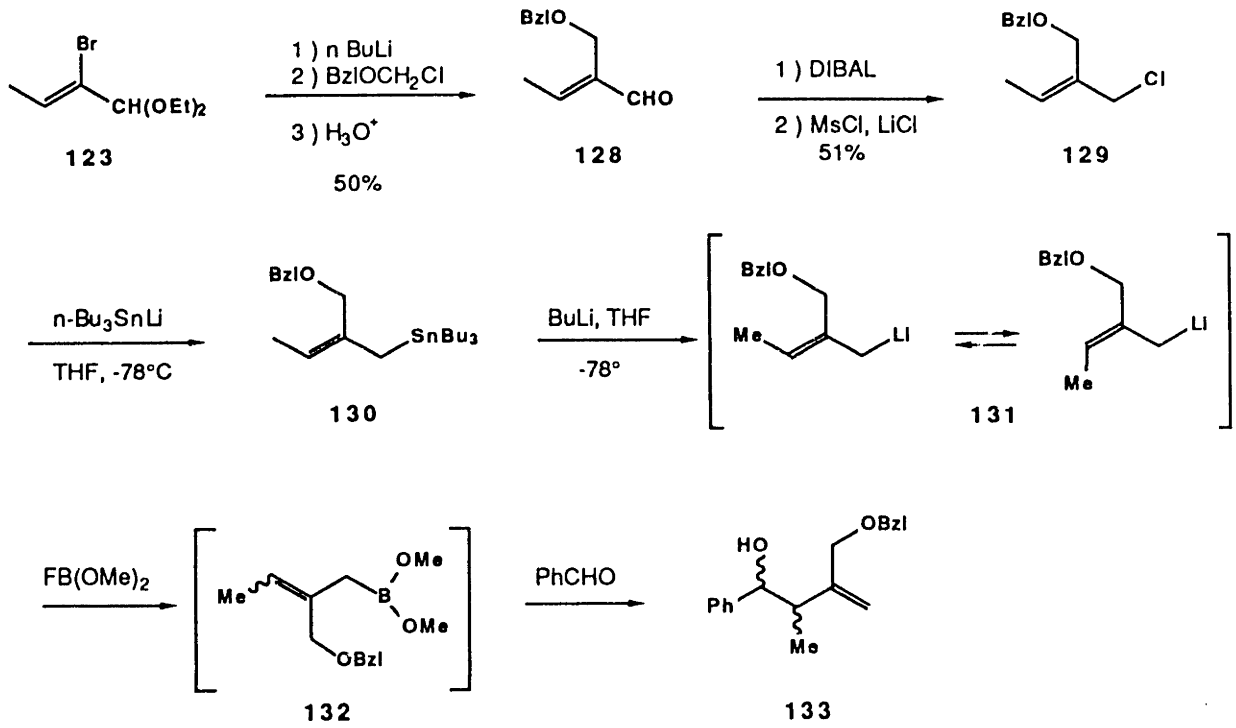
crotylboronate, use of this reagent would lead to the sesbanimide B stereochemistry and not to the more biologically active sesbanimide A.

Scheme 2.21



The second approach that we considered for preparation of precursors to **117** (path **b**) is summarized in Scheme 2.22. DIBAL reduction of aldehyde **128** (prepared in three steps from **123** according to a known procedure)[61] gave the corresponding alcohol, which was converted in good yield (83%) to the allylic chloride **129**, using the conditions described by Meyers.[62] The chloride **129** underwent substitution with n-Bu_3SnLi with retention of the double bond configuration, (30% yield; 72% based on consumed chloride) to give crotylstannane **130**.[63]

Scheme 2.22

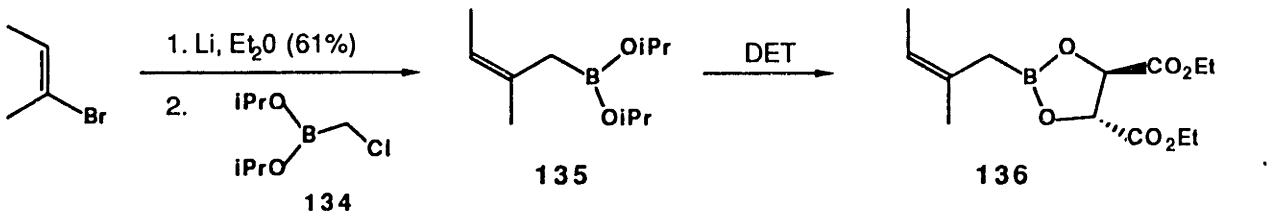


Treatment of **130** with n-BuLi at -78 °C followed by $FB(OMe)_2$ gave the *in situ* generated allylic boronate **132** that, without isolation, was treated with benzaldehyde. The product **133**, however is a ca. 1:1 mixture of diastereomers, probably due to stereochemical erosion occuring at the stage of allyllithium **131**. The configurational instability of allyllithium species is well documented.[64] Attempted lithiation at lower temperatures (-100 °C) as well as lithiation in the presence of $(iPrO)_3B$ so as to immediately trap the anion proved unsuccessful, as no substantial amount of homoallylic alcohol **133** was obtained. Since allylpotassium compounds are known to have much greater configurational stability,[65] we attempted to prepare the potassium analog of **131**. Unfortunately, treatment of **130** with n-BuLi in the presence of KOtBu, subsequent quench with $F\text{-}B(OMe)_2$ and addition to benzaldehyde led to a multitude of products. It is

possible that C-H abstraction is competitive with C-Sn cleavage under these conditions.[66]

By this time three total syntheses of sesbanimide A had already been published (see Chapter 1). In all of them ring C was constructed via the addition of a substituted crotyl metal species onto a C-10 aldehyde intermediate. Therefore, we felt that an additional synthesis on our part would be merited only if it represented a significant improvement in terms of brevity and overall efficiency.

In view of these requirements, we were clearly dissapointed at our inability to prepare isomerically pure precursors to **117**. We considered using other chiral allylboronate reagents, such as the tartrate derived analog of the previously prepared pinacol (E)-allylboronate **108**, that would also allow access to the C ring. We anticipated that **136** could be prepared via treatment of the vinyl lithium species derived from (Z)-2-bromo-2-butene with diisopropyl chloromethylboronate **135**.[67] The diisopropyl allylboronate **135**, so obtained, could then be converted to either enantiomer of **136**. Any such synthesis, though, must compete in terms of



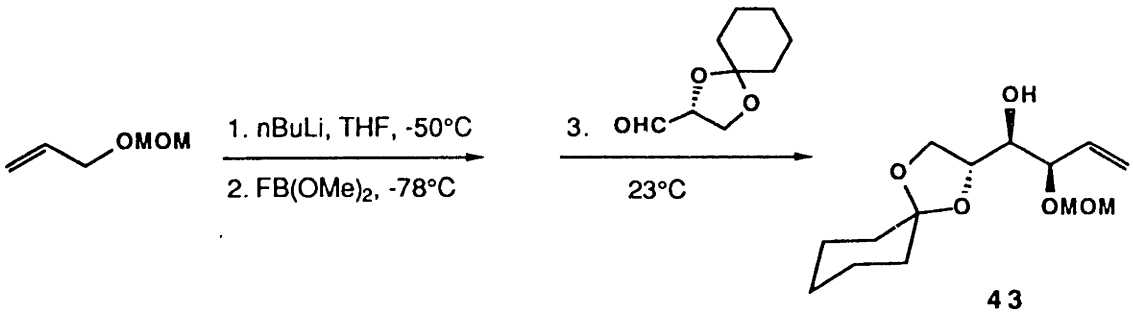
brevity to the aforementioned total syntheses. Approaches using allylboronate reagents other than **117**, such as **136** or **115**, would be more stereoselective but much lengthier. Therefore we felt it was no longer justifiable to continue our work in this area, and opted instead to re-direct our efforts towards the completion of the total synthesis of olivin. This work is presented in part two of this thesis.

EXPERIMENTAL SECTION

Proton (^1H) NMR spectra were measured at 250 MHz on a Bruker WM 250 instrument and at 300 and 400 MHz on a Varian XL-300 and XL-400. Chemical shifts are reported in δ units using the 7.26 ppm resonance of residual chloroform as internal reference. Infrared spectra were measured on Perkin-Elmer Model 283B or 237B infrared spectrophotometers calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 or a Finnegan MAT 8200 instrument. High-resolution mass spectra were measured at 70 eV on the Finnegan MAT 8200. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Autopol III or a Perkin-Elmer Model 241 polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Elemental analyses were performed by either Robertson Laboratory, Inc., of Florham Park, New Jersey or Midwest Microlab, Inc., of Indianapolis, Indiana.

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, benzene, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2.

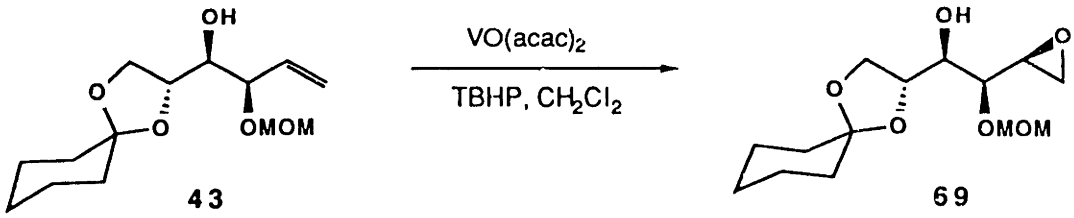
Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.25 or 0.5 mm thickness of silica gel containing PF 254 indicator (Analtech). Flash chromatography was performed as described by Still,[68] using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid, or p-anisaldehyde/H_2SO_4, or by staining with iodine vapor.



43

Preparation of homoallylic alcohol 43.

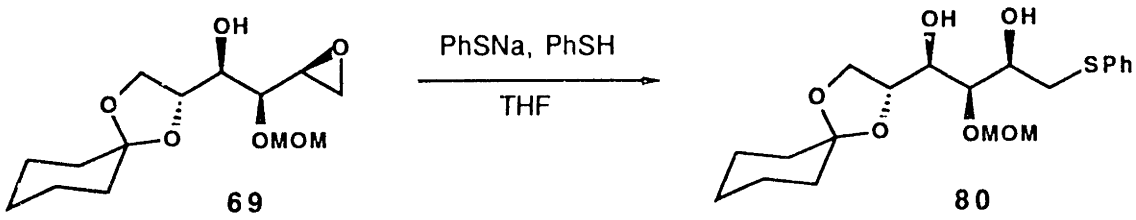
To a -35 °C solution of allyl methoxymethyl ether (37.0 g, 360 mmol) in dry THF (350 mL) was added dropwise n-BuLi (140 mL, 2.5 M in hexane, 350 mmol) over a period of 0.5 h. The resulting solution was stirred for 1.5 h at -35° to -30 °C and then cooled to -78 °C. The dark orange solution was treated with fluorodimethoxyborane (36.3 g, 316 mmol) and the colorless mixture was stirred for 0.25 h at -78 °C, 0.5 h at 0 °C and then recooled to -78 °C. A solution of glyceraldehyde cyclohexyl ketal (29.7 g, 174 mmol) in THF (50 mL) was then added and the resulting mixture was allowed to warm slowly to room temperature. After being stirred for 2 d the reaction mixture was treated with triethanolamine (46.5 mL, 350 mmol), stirred for 2 h, poured into water and extracted twice with ether (2 x 450 mL). The combined ethereal extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Crystallization of the crude product from pentane afforded 28.8 g (61%) of **43**. The mother liquor was purified by flash chromatography (silica gel, 1:1 ether-hexane) to yield an additional 8.2 g (17%) of product: R_f 0.31 (2:1 ether-hexane); m.p. 64-65 °C; $[\alpha]_D^{25}$ -59.5° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.36-5.30 (m, 2H), 4.73 (d, J = 6.6 Hz, 1H), 4.60 (d, J = 6.6 Hz, 1H), 4.25 (dd, J = 3.1, 7.3 Hz, 1H), 4.14-3.99 (m, 2H), 3.95 (dd, J = 5.4, 7.7 Hz, 1H), 3.54 (ddd, J = 3.1, 7.1, 7.1 Hz, 1H), 3.39 (s, 3H), 2.35 (d, J = 7.1 Hz, 1H), 1.57 (m, 10H); IR (CH_2Cl_2) 3565, 2930, 2890, 1450, 1365, 1330, 1280 cm^{-1}; mass spectrum m/e 272 (parent ion). Anal. Calcd. for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.52; H, 8.71.



43 69

Preparation of epoxide 69.

A 0 °C solution of olefin **43** (9.3 g, 34.2 mmol) in dry CH_2Cl_2 (250 mL) under N_2 was treated successively with vanadyl acetylacetonate (450 mg, 1.69 mmol) and t-butyl hydroperoxide (37.5 mL, 3.64 M in toluene, 136 mmol). After being stirred at room temperature for 3 d the reaction was quenched with saturated aq. Na_2SO_4 and concentrated *in vacuo* to afford crude product **69** (14.6 g) which was used without any further purification in the following experiment: R_f 0.12 (2:1 ether-hexane); $[\alpha]_D^{25}$ -33.2° (c 1.46, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 4.95 (d, J = 6.8 Hz, 1H), 4.77 (d, J = 6.0 Hz, 1H), 4.14-3.98 (m, 3H), 3.60 (dd, J = 2.9, 8.4 Hz, 1H), 3.53 (dd, J = 2.5, 7.3 Hz, 1H), 3.44 (s, 3H), 3.24 (ddd, J = 2.7, 4.3, 7.0 Hz, 1H), 2.83 (dd, J = 4.4, 4.4 Hz, 1H), 2.60 (dd, J = 2.4, 5.0 Hz, 1H), 2.49 (d, J = 7.5 Hz, 1H), 1.56 (m, 10H); IR (neat) 3445, 2930, 2860, 1695, 1445, 1365, 1280, 1155, 1025, 925 cm^{-1}; mass spectrum m/e 288 (parent ion); high resolution mass spectrum for $C_{14}H_{24}O_6$, calcd. 288.1573, found 288.1589.

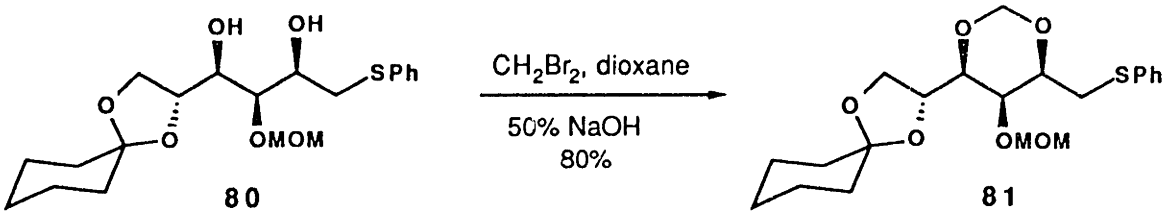


69 80

Preparation of diol 80.

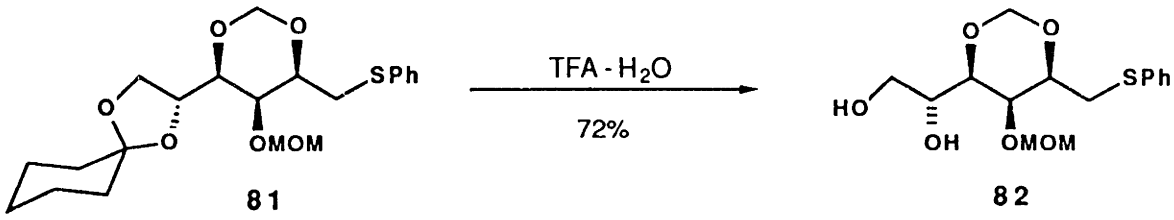
Thiophenol (12.3 mL, 119.7 mmol) was added dropwise to a 0 °C suspension of NaH (4.37 g, 60% dispersion in oil, 109 mmol, pre-washed with ether to remove oil) in THF (60 mL). The resulting milky suspension was then treated with a solution of crude epoxide **69** (maximum amount 34.2 mmol) in THF (15 mL). After being stirred for 1 d, the reaction mixture was poured into cold saturated aq. NH_4Cl (100 mL) and extracted with ether (3 x 100 mL). The combined ethereal extracts were washed with 10% NaOH (150 mL), H_2O (150 mL) and brine (150 mL), dried over Na_2SO_4 and concentrated. Crystallization of the product from pentane-ether and column chromatography (silica gel, 1:1 hexane-ether) of the mother liquor afforded a total of 9.56 g (70% for 2 steps) of diol **80** along with 1.93 g (24%) of olefin **43**.

Data for **80**: R_f 0.48 (5% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ +15.5° (c 1.0, CH_2Cl_2); m.p. 55-56 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.18 (m, 5H), 4.82 (d, J = 6.6 Hz, 1H), 4.72 (d, J = 6.6 Hz, 1H), 4.11 (m, 1H), 3.99-3.93 (m, 3H), 3.82 (t, J = 3.4 Hz, 1H), 3.66 (m, 1H), 3.43 (s, 3H), 3.31 (d, J = 3.9 Hz, 1H), 3.24-3.03 (m, 3H), 1.54 (m, 10H); IR ($CHCl_3$) 3450, 2940, 1585, 1480, 1450, 1365, 1280 cm^{-1}; mass spectrum m/e 398 (parent ion). Anal. Calcd for $C_{20}H_{30}O_6S$: C, 60.28; H, 7.59; S, 8.04. Found: C, 60.13; H, 7.77; S, 8.06.



Preparation of B ring intermediate 81.

A solution of diol **80** (11.8g, 29.6 mmol) in dioxane (200 mL) was treated successively with dibromomethane (21.2 mL, 296 mmol), n-Bu_4NI (1.53 g, 4.1 mmol) and 50% aqueous NaOH (415 g). After being stirred at 70 °C for 2.1 h, the mixture was cooled to room temperature and then partitioned between ether (300 mL) and water (200 mL). The aqueous layer was further extracted with ether (200 mL) and the combined extracts were washed with water, brine and saturated aqueous NH_4Cl. Removal of solvent and purification of the product by column chromatography (silica gel, 3:1 hexane-ether) afforded 9.69 g (80%) of **81**: R_f 0.42 (2:1 ether-hexane); $[\alpha]_D^{25}$ +79.4° (c 3.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 5H), 5.13 (d, J = 6.3 Hz, 1H), 5.01 (d, J = 6.4 Hz, 1H), 4.78 (d, J = 6.5 Hz, 1H), 4.72 (d, J = 6.3 Hz, 1H), 4.19-4.07 (m, 2H), 3.90 (dd, J = 4.3, 8.2 Hz, 1H), 3.83 (s, 1H), 3.69 (dt, J = 1.5, 6.1 Hz, 1H), 3.49 (s, 3H), 3.40 (dd, J = 1.3, 9.1 Hz, 1H), 3.24 (d, J = 6.6 Hz, 1H), 3.24 (d, J = 6.1 Hz, 1H), 1.58 (m, 10H); IR ($CHCl_3$) 3450, 2940, 2880, 1580, 1475, 1445 cm^{-1}; mass spectrum m/e 410 (parent ion). Anal. Calcd. for $C_{21}H_{30}O_6S$: C, 61.44; H, 7.57; S, 7.81. Found: C, 61.33; H, 7.50; S, 8.01.

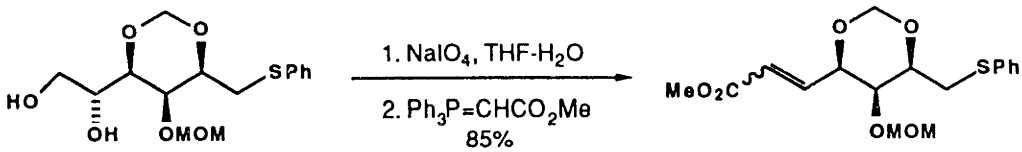


81 82

Preparation of diol 82.

Sulfide **81** (596 mg, 1.44 mmol) was treated with 5.45 mL of a 98:2 TFA-H_2O mixture and the resulting solution was stirred at 0 °C for 8 min, poured into cold (0 °C) aqueous saturated $NaHCO_3$ and extracted with EtOAc (4 x 50 mL). Drying of the combined organic extracts over Na_2SO_4 followed by filtration, removal of solvent and column chromatography (silica gel, 3% MeOH-CH_2Cl_2) afforded 325 mg (72%) of diol **82** along with 34.3 mg (6%) of recovered starting material.

Data for **82**: R_f 0.33 (5% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ +34.2° (c 0.36, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 5.10 (d, J = 6.1 Hz, 1H), 4.90 (d, J = 6.8 Hz, 1H), 4.85 (d, J = 6.8 Hz, 1H), 4.70 (d, J = 6.2 Hz, 1H), 4.25 (d, J = 5.0 Hz, 1H), 3.97 (s, 1H), 3.91-3.81 (m, 2H), 3.70-3.63 (m, 2H), 3.54 (s, 3H), 3.25 (dd, J = 5.4, 13.7 Hz, 1H), 3.07 (dd, J = 8.7, 13.7 Hz, 1H), 2.13 (t, J = 7.5 Hz, 1H); IR ($CHCl_3$) 3440, 3030, 3010, 2930, 2850, 1475, 1435, 1365, 1095, 1030 cm^{-1}; mass spectrum m/e 330 (parent ion). Anal. Calcd for $C_{15}H_{22}O_6S$: C, 54.53; H, 6.71. Found: C, 54.32; H, 6.84.



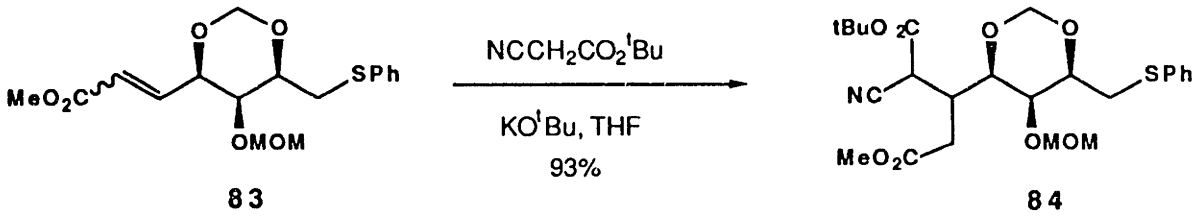
82 83

Preparation of α,β-unsaturated ester 83.

A solution of diol **82** (552.0 mg, 1.66 mmol) in THF (10 mL) was successively treated with H_2O (2 mL), $NaIO_4$ (356 mg, 1.66 mmol) and then stirred at room temperature for 1.5 h. Addition of Na_2SO_4, CH_2Cl_2 (75 mL) followed by filtration through adsorbent cotton and removal of solvent *in vacuo* afforded the crude aldehyde which was immediately re-dissolved in CH_2Cl_2 (7 mL) and treated with methyl (triphenylphosphoranylidine)acetate (1.10 g, 3.32 mmol). After being stirred overnight at room temperature, the mixture was filtered through a pad of silica gel, concentrated and purified by column chromatography to yield 498 mg (85% for 2 steps) of **83** as a 3.5 : 1 (Z) : (E) mixture of olefin isomers. This mixture was used without separation in the following experiment. A small amount, however, was separated for characterization purposes.

Data for 83(Z): R_f 0.34 (1:1 hexane-ether); $[\alpha]_D^{25}$ -3.4° (c 2.27, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.38 (m, 2H), 7.33-7.19 (m, 3H), 6.36 (dd, J = 6.5, 11.7 Hz, 1H), 5.94 (dd, J = 1.6, 11.7 Hz, 1H), 5.19 (dd, J = 2.0, 6.5 Hz, 1H), 5.18 (d, J = 6.2 Hz, 1H), 4.81 (d, J = 6.2 Hz, 1H), 4.66 (s, 2H), 4.04 (s, 1H), 3.83 (m, 1H), 3.73 (s, 3H), 3.41 (s, 3H), 3.22 (dd, J = 7.1, 14.3 Hz, 1H), 3.13 (dd, J = 6.1, 14.5 Hz, 1H); IR (neat) 3055, 2993, 2951, 1720, 1660, 1583, 1260 cm^{-1}; mass spectrum m/e 354 (parent ion). Anal. Calcd for $C_{17}H_{22}O_6S$: C, 57.61; H, 6.26. Found: C, 57.58; H, 6.34.

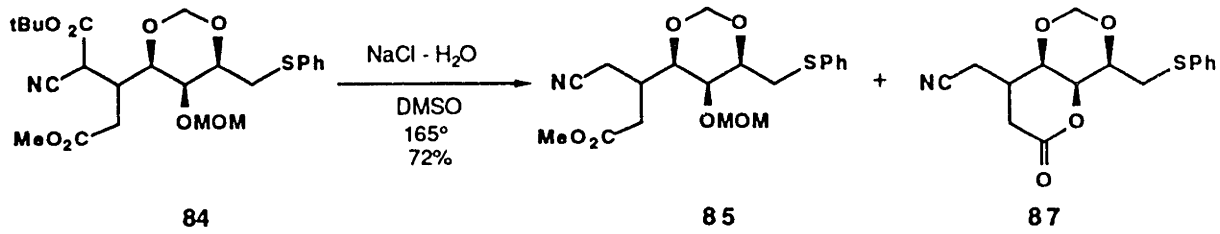
Partial data for 83(E): R_f 0.30 (1:1 hexane-ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.15 (m, 5H), 6.89 (dd, J = 3.3, 15.5 Hz, 1H), 6.33 (dd, J = 1.9, 15.5 Hz, 1H), 5.18 (m, 2H), 4.76 (d, J = 6.2 Hz, 1H), 4.68 (d, J = 6.9 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.27 (m, 1H), 3.80 (s, 1H), 3.71 (s, 3H), 3.34 (s, 3H), 3.21-3.12 (m, 2H).



83 84

Preparation of cyanoester 84.

t-Butyl cyanoacetate (121.5 mg, 0.81 mmol) was added to a cold (0 °C) solution of potassium t-butoxide (91.2 mg, 0.81 mmol) in dry THF (1 mL) and the resulting mixture was stirred for 0.5 h at room temperature. A solution of ester **83** (120.7 mg, 0.34 mmol) in THF (0.5 mL) was added and the mixture was stirred overnight at room temperature, then poured into saturated aqueous NH_4Cl and extracted twice with ether. The combined ethereal extracts were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 1:1 hexane-ether) to afford 154 mg (93%) of **84** as a mixture of diastereomers: R_f 0.37 (1:1 hexane-ether); $[\alpha]_D^{25}$ +22.7° (c 3.1, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$, data reported for major diastereomer) δ 7.37-7.21 (m, 5H), 5.03 (d, J = 7.2 Hz, 1H), 4.81 (d, J = 5.9 Hz, 1H), 4.76 (d, J = 7.5 Hz, 1H), 4.68 (d, J = 6.2 Hz, 1H), 3.97 (d, J = 1.8 Hz, 1H), 3.75 (s, 1H), 3.70 (s, 3H), 3.63-3.53 (m, 2H), 3.44 (s, 3H), 3.34-3.03 (m, 3H), 2.64 (m, 1H), 2.33 (dd, J = 11.3, 16.9 Hz, 1H), 1.45 (s, 9H); IR (neat) 3059, 2981, 2952, 2249, 1749, 1583, 1481, 1440, 1370, 1040, 842, 740 cm^{-1}; mass spectrum m/e 495 (parent ion); high resolution mass spectrum for $C_{24}H_{33}NO_8S$, calcd. 495.1927, found 495.1926.

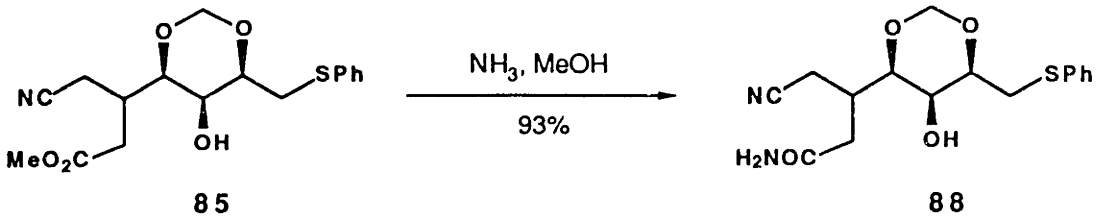


Decarboxylation of cyanoester 84.

To a solution of **84** (59.6 mg, 0.12 mmol) in dry DMSO (2 mL) were added water (7 mg, 0.36 mmol), NaCl (21 mg, 0.36 mmol), and the resulting mixture was stirred at 165 °C for 4.5 h. After being cooled to room temperature the reaction mixture was poured into water (5 mL) and extracted three times with ether (3 x 15 mL). The combined ethereal extracts were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (2:1 ether-hexane) to afford 16.0 mg (38%) of cyanoester **85** and 13.1 mg (34%) of cyanolactone **87**.

Data for **85**: R_f 0.30 (2:1 ether-hexane); $[\alpha]_D^{25}$ +51.1° (c 0.54, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.21 (m, 5H), 5.10 (d, J = 6.2 Hz, 1H), 4.70 (d, J = 6.1 Hz, 1H), 3.72 (s, 3H), 3.67 (d, J = 12.2 Hz, 1H), 3.65 (t, J = 6.8 Hz, 1H), 3.53 (d, J = 9.1 Hz, 1H), 3.17 (d, J = 7.0 Hz, 2H), 2.74 (d, J = 4.2 Hz, 2H), 2.65-2.44 (m, 3H), 2.35 (d, J = 11.7 Hz, 1H); IR (neat) 3461, 3058, 2953, 2862, 1737, 1583, 1439, 1170 cm^{-1}; mass spectrum for $C_{17}H_{21}NO_5S$, calcd 351.1141, found 351.1151.

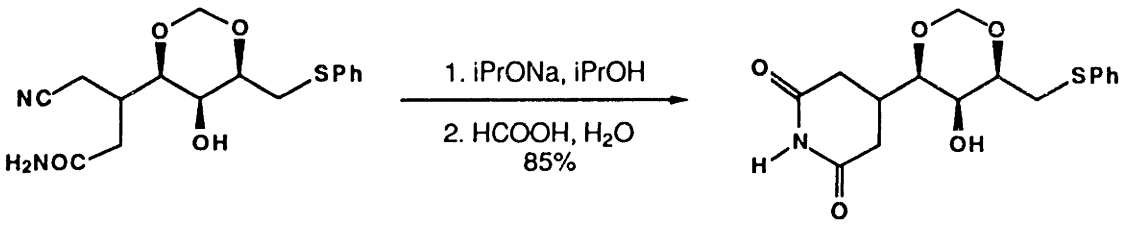
Data for **87**: R_f 0.07 (2:1 ether-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5H), 5.10 (d, J = 6.7 Hz, 1H), 4.67 (d, J = 6.7 Hz, 1H), 4.30 (d, J = 3.0 Hz, 1H), 3.91 (t, J = 2.1 Hz, 1H), 3.80 (dt, J = 2.0, 7.7 Hz, 1H), 3.31 (d, J = 7.5 Hz, 1H), 3.28 (d, J = 6.4 Hz, 1H), 2.83 (dd, J = 5.0, 15.6 Hz, 1H), 2.66 (dd, J = 7.5, 18.6 Hz, 1H), 2.53-2.36 (m, 3H); IR ($CHCl_3$) 2930, 2850, 1755, 1580, 1440 cm^{-1}.



85 88

Preparation of cyanoamide 88.

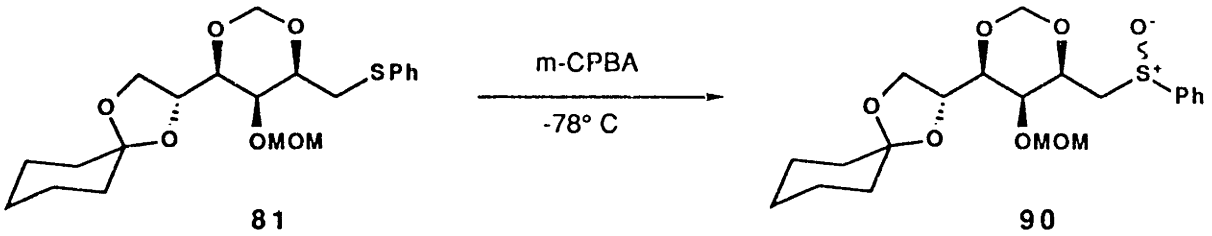
A solution of **85** (20.1 mg, 0.057 mmol) in dry MeOH (2 mL) was saturated with gaseous NH_3 and stirred at room temperature for 2 d. The methanol and ammonia were removed *in vacuo* and the residue was triturated with EtOAc. The triturate was then filtered through Celite and concentrated to yield 17.9 mg (93%) of **88** which was pure enough to be used in the following step without any further purification: R_f 0.12 (5% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ +48.6° (c 0.45, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 5.64 (s, 1H), 5.50 (s, 1H), 5.10 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 6.2 Hz, 1H), 3.73-3.65 (m, 2H), 3.57 (d, J = 9.4 Hz, 1H), 3.19 (d, J = 6.5 Hz, 2H), 2.74 (d, J = 4.0 Hz, 2H), 2.68-2.55 (m, 1H), 2.51 (d, J = 4.5 Hz, 1H), 2.39 (dd, J = 7.0, 16.6 Hz, 1H); IR ($CHCl_3$) 3410, 3005, 2925, 2855, 1680, 1590, 1220, 1030 cm^{-1}; mass spectrum m/e 336 (parent ion); high resolution mass spectrum for $C_{16}H_{20}N_2O_4S$, calcd 336.1144, found 336.1130.



88 89

Preparation of imide 89.

Amide **88** (15.5 mg, 0.046 mmol) was dissolved in dry isopropanol (2.5 mL) and NaH (18.5 mg, 60% dispersion in oil, 0.46 mmol) was added. The mixture was stirred for 5 h at room temperature, neutralized with formic acid (0.020 mL, 0.53 mmol), concentated *in vacuo* and the residue was purified by preparative TLC (5% MeOH-CH_2Cl_2) to afford 13.2 mg (85%) of glutarimide **89**: R_f 0.27 (5% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ +55.0° (c 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_2$) δ 8.04 (s, 1H), 7.38-7.18 (m, 5H), 5.07 (d, J = 6.3 Hz, 1H), 4.66 (d, J = 6.3 Hz, 1H), 3.66-3.62 (m, 2H), 3.32 (d, J = 8.4 Hz, 1H), 3.16 (d, J = 6.6 Hz, 2H), 2.91 (ddd, J = 2.2, 4.8, 17.9 Hz, 1H), 2.74 (ddd, J = 2.2, 4.7, 18.2 Hz, 1H), 2.60 (m, 1H), 2.45 (dd, J = 9.6, 17.1 Hz, 1H), 2.34 (dd, J = 10.5, 17.4 Hz, 1H), 2.30 (d, J = 12.0 Hz, 1H); IR ($CHCl_3$) 3650, 3370, 3050, 2850, 1710, 1390, 1255 cm^{-1}; mass spectrum m/e 337 (parent ion). Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68. Found: C, 56.67; H, 5.56.

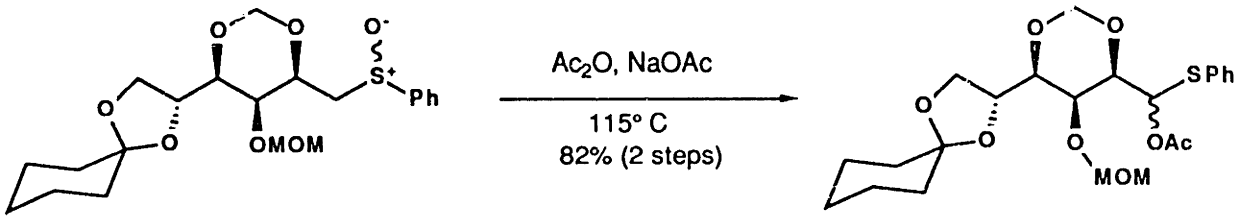


81 90

Preparation of sulfoxide 90.

To a -78 °C solution of sulfide **81** (2.71 g, 6.60 mmol) in CH_2Cl_2 (5 mL) was added dropwise a solution of mCPBA (1.26 g, 95%, 6.94 mmol) in CH_2Cl_2 (25 mL). After being stirred for 0.5 h at -78 °C, the reaction mixture was poured into a cold 1:1 mixture of saturated aqueous $NaHSO_3$ and $NaHCO_3$, and then extracted twice with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were washed with aqueous saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 2.80 g (99%) of **90** as a mixture of diastereomers. The product was pure enough to be used in the next step without any further purification. A small amount was separated for characterization purposes.

Data for **90** (less polar diastereomer): R_f 0.25 (2:1 ether-hexane); $[\alpha]_D^{25}$ -116.5° (c 3.56, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67-7.63 (m, 2H), 7.56-7.49 (m, 3H), 5.19 (d, J = 6.2 Hz, 1H), 4.91 (d, J = 7.1 Hz, 1H), 4.90 (d, J = 6.2 Hz, 1H), 4.64 (d, J = 6.4 Hz, 1H), 4.34 (dd, J = 1.9, 8.1 Hz, 1H), 4.17-4.06 (m, 2H), 3.98 (dd, J = 3.7, 8.3 Hz, 1H), 3.60 (s, 1H), 3.51 (d, J = 7.5 Hz, 1H), 3.17 (s, 3H), 3.13 (dd, J = 3.1, 13.8 Hz, 1H), 2.94 (dd, J = 2.0, 13.8 Hz, 1H), 1.60 (m, 10H); IR ($CDCl_3$) 2940, 2850, 2240, 1440, 1035 cm^{-1}; mass spectrum m/e 426 (parent ion); high resolution mass spectrum for $C_{21}H_{30}O_7S$; calcd 426.1712, found 426.1709.



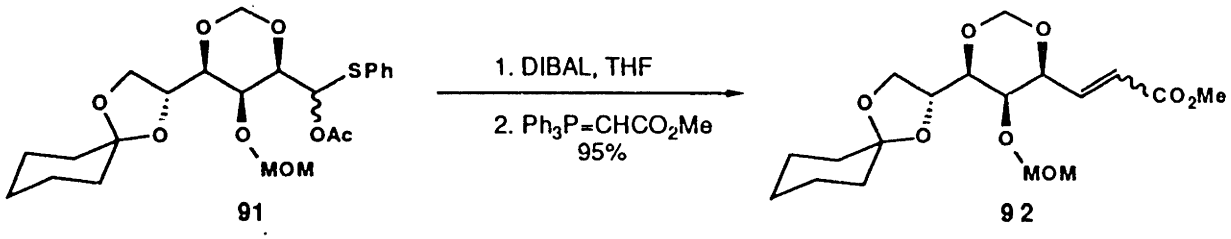
90 91

Pummerer rearrangement of sulfoxide 90.

A stirred mixture of sulfoxide **90** (2.80 g, 6.60 mmol) and sodium acetate (5.62 g, 13.2 mmol) in acetic anhydride (25 mL) was heated to 115-120 °C for 22 h. After excess acetic anhydride and acetic acid were removed under reduced pressure, the residue was eluted through a pad of silica gel, using 2:1 ether-hexane. Evaporation of solvent and purification of the residue by column chromatography (silica gel, 2:1 hexane-ether) afforded 2.54 g (82% for two steps) of **91** as a mixture of diastereomers. A small amount was separated for characterization purposes.

Data for **91** (more polar diastereomer): R_f 0.34 (2:1 ether-hexane); $[\alpha]_D^{25}$ -34.3° (c 4.86, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.36-7.30 (m, 3H), 6.34 (d, J = 9.7 Hz, 1H), 5.08 (d, J = 5.7 Hz, 1H), 5.01 (d, J = 6.7 Hz, 1H), 4.90 (d, J = 6.7 Hz, 1H), 4.57 (d, J = 5.7 Hz, 1H), 4.17 (m, 1H), 4.11 (s, 1H), 4.06 (m, 1H), 3.93 (dd, J = 4.1, 9.2 Hz, 1H), 3.50 (s, 3H), 3.49 (d, J = 5.8 Hz, 1H), 3.24 (d, J = 9.0 Hz, 1H), 2.14 (s, 3H), 1.57 (m, 10H); IR (neat) 2935, 2860, 1825, 1745, 1710, 1475, 1450, 1440, 1375 cm^{-1}; mass spectrum m/e 468 (parent ion); high resolution mass spectrum for $C_{23}H_{32}O_8S$, calcd 468.1818, found 468.1818.

Partial data for **91** (less polar diastereomer): R_f 0.46 (2:1 ether-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.37-7.22 (m, 3H), 5.89 (d, J = 10.0 Hz, 1H), 5.19 (d, J = 6.4 Hz, 1H), 4.87 (d, J = 7.0 Hz, 1H), 4.70 (d, J = 7.0 Hz, 1H), 4.53 (d, J = 5.8 Hz, 1H), 4.11-4.07 (m, 2H) 3.86 (m, 1H), 3.70(s, 1H), 3.36(d, J = 9.1 Hz, 1H), 3.34 (s, 3H) 3.27 (d, J = 8.1 Hz, 1H), 2.14 (s, 3H), 1.56 (m, 10H)



91 92

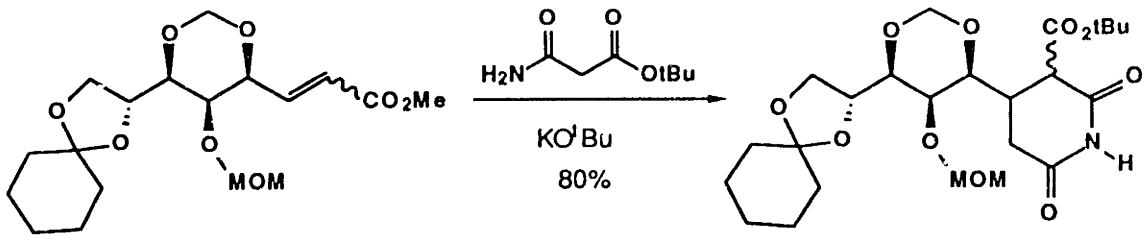
Preparation of α,β-unsaturated ester 92.

To a -78 °C solution of **91** (2.84 g, 6.06 mmol) in dry ether (30 mL) was added dropwise DIBAL (13 mL, 1 M in hexane, 13 mmol). The mixture was stirred for 0.5 h, then MeOH (10 mL) was added dropwise and the resulting mixture was partitioned between ether and aqueous Rochelle's salt. The aqueous phase was extracted four times with ether (4 x 100 mL) and the combined ethereal extracts were dried over Na_2SO_4. Removal of solvent followed by azeotropic removal of water using CH_2Cl_2 afforded the crude aldehyde that was immediately redissolved in toluene (45 mL) and treated with methyl (triphenylphosphoranylidene)acetate (4.0 g, 11.9 mmol). After being stirred overnight the mixture was filtered through a pad of silica gel, concentrated and purified by column chromatography (silica gel, 2:1 ether-hexane) to yield 2.13 g (95% for 2 steps) of **92** as an unseparated 1.4:1.0 (Z):(E) mixture of olefin isomers.

Data for **92** (E): R_f 0.27 (1:1 hexane-ether); $[\alpha]_D^{25}$ +9.4° (c 1.1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J = 3.6, 16.3 Hz, 1H), 6.21 (dd, J = 1.8, 15.5 Hz, 1H), 5.21 (d, J = 6.3 Hz, 1H), 4.97 (d, J = 7.7 Hz, 1H), 4.38 (dd, J = 1.5, 3.7 Hz, 1H), 4.20-4.08 (m, 2H), 3.96 (dd, J = 3.8, 8.8 Hz, 1H), 3.87 (s, 1H), 3.75 (s, 3H), 3.51 (d, J = 8.6 Hz, 1H), 3.35 (s, 3H), 1.56 (m, 10H); IR (neat) 2940, 2855, 2250, 1725, 1665, 1435, 1365, 1310 cm^{-1}; mass sectrum m/e 372 (parent ion); high resolution mass spectrum for $C_{18}H_{28}O_8$, calcd 372.1784, found 372.1779.

Data for **92** (Z): R_f 0.32 (1:1 hexane-ether); ^1H NMR (300 MHz, $CDCl_3$) δ 6.34 (dd, J = 7.2, 12.5 Hz, 1H), 5.88 (dd, J = 1.6, 12.5 Hz, 1H), 5.22 (d, J = 6.3 Hz,

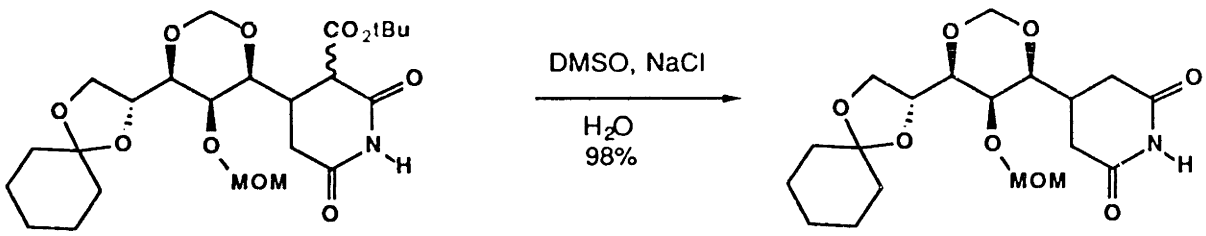
1H), 5.08 (d, J = 6.2 Hz, 1H), 4.83 (d, J = 7.2 Hz, 1H), 4.79 (d, J = 6.3 Hz, 1H), 4.62 (d, J = 6.6 Hz, 1H), 4.12-4.01 (m, 2H), 3.99 (s, 1H), 3.88 (dd, J = 4.8, 8.8 Hz,1H), 3.67 (s, 3H), 3.55 (dd, J = 1.9,8.5 Hz, 1H), 3.32 (s, 3H), 1.56 (m, 10H).



92 99

Preparation of glutarimide 99.

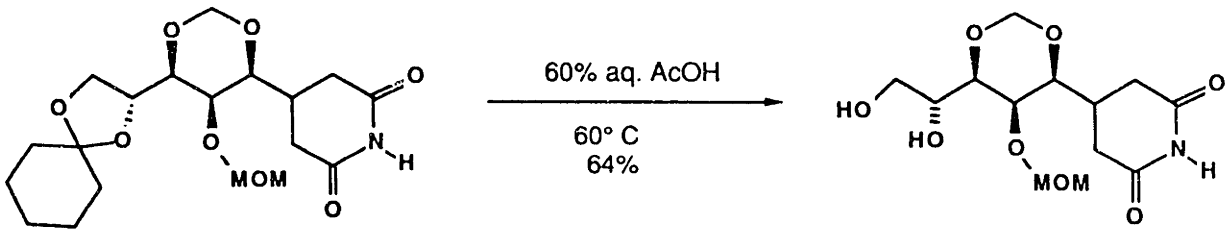
Potassium-t-butoxide (342 mg, 3.05 mmol) was added to a 0 °C solution of t-butyl carbamoyl-acetate (606 mg, 3.81 mmol) in THF (12 mL) and the mixture was stirred until the t-butoxide had dissolved. A precooled solution of **92** (1.134 g, 3.05 mmol) in THF (4 mL) was then added via cannula. After being stirred at 0 °C for 5 h, the reaction was quenched with acetic acid (0.17 mL, 3.05 mmol) and partitioned between H_2O and EtOAc. The aqueous phase was further extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography afforded 1.21 g (80%) of **99** as a mixture of diastereomers: R_f 0.41 (1:1 hexane-ethyl acetate); $[\alpha]_D^{25}$ +53.5° (c 2.34, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 5.10 (d, J = 6.2 Hz, 1H), 5.06 (d, J = 7.1 Hz, 1H), 4.76 (d, J = 7.1 Hz, 1H), 4.67 (d, J = 6.2 Hz, 1H), 4.15-4.08 (m, 2H), 3.10 (m, 1H), 2.87 (dd, J = 5.5, 17.8 Hz, 1H), 2.72 (dd, J = 3.9, 16.1 Hz, 1H), 1.58 (m, 10H), 1.49 (s, 9H); IR ($CHCl_3$) 3370, 2935, 2855, 1730, 1710 cm^{-1}; mass spectrum m/e 499 (parent ion); high resolution mass spectrum for $C_{24}H_{37}NO_{10}$, calcd 499.2417, found 499.2416.



99 100

Preparation of glutarimide 100.

To a solution of **99** (406 mg, 0.81 mmol) in dry DMSO (20ml) were added H_2O (45 mg, 2.5 mmol), NaCl (94 mg, 1.6 mmol) and the resulting mixture was stirred at 160 °C for 1.25h. After being cooled to room temperature the reaction mixture was poured into water (20ml) and extracted three times with ethyl acetate (3x100ml). The combined organic extracts were dried over Na_2SO_4 and concentrated to yield 318 mg (98%) of **100** which was pure enough to be used in the following step without any purification: R_f 0.39 (5% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ +51.5° (c 1.81, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 8.02 (s,1H), 5.13 (d, J = 6.3 Hz, 1H), 5.06 (d, J = 6.5 Hz, 1H), 4.74 (d, J = 6.5 Hz, 1H), 4.72 (d, J = 6.3 Hz, 1H), 4.14-4.07 (m, 2H), 3.92 (m,1H), 3.72 (s,1H), 3.41 (s, 3H), 3.41 (d, J = 9.4 Hz, 1H), 3.36 (d, J = 9.3 Hz, 1H), 3.05-2.95 (m, 2H), 2.69 (m, 1H), 2.44 (dd, J = 10.1, 17.0 Hz, 1H), 2.33 (dd, J = 10.5, 17.4 Hz, 1H), 1.62 (m, 10H); 1R ($CHCl_3$) 3360, 2930, 2850, 1705, 1145, 1035, cm^{-1}; mass spectrum m/e 399(parent ion); high resolution mass spectrum for $C_{19}H_{29}NO_8$, calcd 399.1893, found 399.1887.

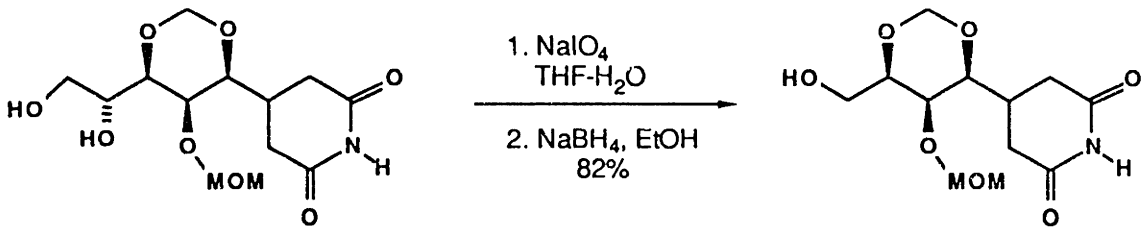


100 101

Preparation of diol 101.

Imide **100** (190 mg, 0.47 mmol) was treated with 60% aqueous AcOH (2 mL) and the resulting solution was stirred at 60 °C for 2.75 h. After being cooled to room temperature the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 10% MeOH-CH_2Cl_2) to provide 95 mg (64%) of diol **101** and 20.0 mg (15%) of triol **98**. In addition 8.0 mg (5%) of starting material **100** was recovered.

Data for **101**: R_f 0.25 (10% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ + 62.3° (c 4.12, CH_3CN); ^1H NMR (300 MHz, CD_3CN) δ 8.66 (s,1H), 4.96 (d, J = 6.4 Hz, 1H), 4.91 (d, J = 6.4 Hz, 1H), 4.66 (t, J = 6.4 Hz, 2H), 3.71 (s,1H), 3.62 (dd, J = 1.9, 10.6 Hz,1H), 3.58-3.39 (m, 4H), 3.32 (s,3H), 2.80-2.68 (m, 2H), 2.57-2.49 (m, 2H), 2.35 (dd, J = 10.6, 17.4 Hz,1H), 2.27 (dd, J = 10.6, 16.5 Hz, 1H); IR (CH_3CN) 3510, 3270, 1705, 1255 cm^{-1}; mass spectrum m/e 268 (M^+ - CH_3O); high resolution mass spectrum for $C_{12}H_{18}NO_7$, calcd 288.1083, found 288.1085.



101 103

Preparation of alcohol 103.

A solution of diol **101** (35 mg, 0.11 mmol) in 3:1 THF-H_2O (2 mL) was treated with $NaIO_4$ (24 mg, 0.11 mmol), and then stirred at room temperature for 0.5 h. After removal of solvent *in vacuo* the residue was triturated with CH_3CN (5 mL) and $CHCl_3$ (5 mL). The triturate was concentrated and purified by column chromatography (silica gel, 10% MeOH-CH_2Cl_2) to yield 28.0 mg (89%) of aldehyde **102**. The aldehyde was prone to hydration, making acquisition of data very difficult. Thus, a sample of **102** (16 mg) was dissolved in absolute EtOH (1 mL) and treated with $NaBH_4$ (3 mg) at 0 °C. After being stirred for 2 minutes, the mixture was treated with excess acetone, concentrated and purified by column chromatography (silica gel, 4% MeOH-CH_2Cl_2) to provide 12.9 mg (82%) of alcohol **103**.

Data for **103**: R_f 0.38 (10% MeOH-CH_2Cl_2); $[\alpha]_D^{25}$ + 23.1° (c 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s,1H), 5.18 (d, J = 6.3 Hz, 1H), 4.97 (d, J = 6.3 Hz, 1H), 4.77 (d, J = 5.5 Hz, 1H), 4.72 (d, J = 7.1 Hz, 1H), 3.82-3.68 (m, 3H), 3.66 (s, 1H), 3.45 (s, 3H), 3.40 (dd, J = 1.8, 8.5 Hz, 1H), 2.96 (ddd, J = 2.0, 3.8, 17.1 Hz, 1H), 2.82 (ddd, J = 1.7, 4.3, 16.9 Hz, 1H), 2.66-2.52 (m, 2H), 2.50 (dd, J = 9.4, 17.0 Hz, 1H), 2.37 (dd, J = 10.2, 16.3 Hz, 1H); IR ($CDCl_3$) 3370, 2950, 2850, 1710, 1300, 1145 cm^{-1}; mass spectrum m/e 258 (M^+- CH_3O); high resolution mass spectrum for $C_{11}H_{16}NO_6$, calcd 258.0977, found 258.0965.

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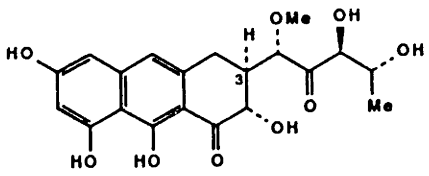
PART II

CHAPTER 1

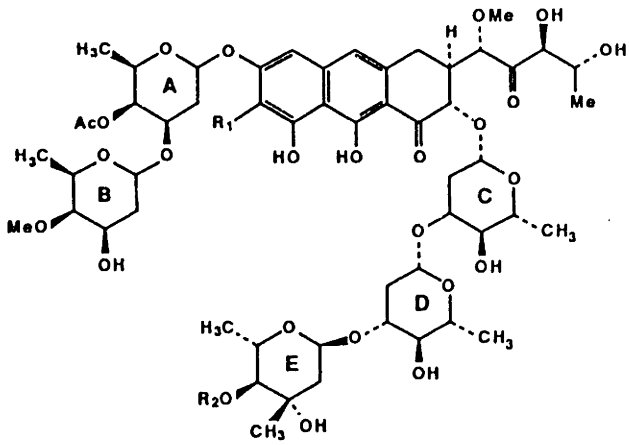
A HIGHLY STEREOSELECTIVE SYNTHESIS OF THE NATURAL ENANTIOMER OF OLIVIN

I. Background

Olivin (**1**) is the aglycone of olivomycin A (**2**), a member of the aureolic acid family of antitumor antibiotics. Included in this group are the olivomycins, the chromomycins and the mithramycins. The olivomycins differ from one another in the nature of the carbohydrate residues and from the mithramycins and chromomycins by the absence of a methyl group at C-7 of the aglycone. The discovery, isolation, mode of action and structure activity correlation of these compounds have been extensively reviewed.[1]

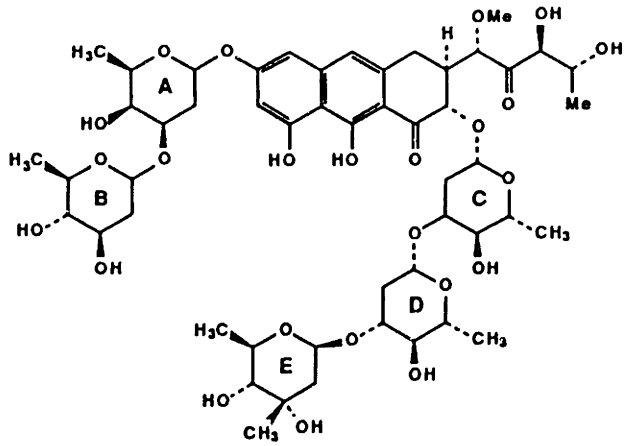


OLIVIN (1)



Olivomycin A (2) R_1 = H, R_2 = $(CH_3)_2CHCO$-

Chromomycin A_3 (3) R_1 = CH_3, R_2 = CH_3CO-



Aureolic Acid (4)

A number of the aureolic acid antibiotics have undergone successful clinical trials as anti-cancer drugs.[2] Olivomycin A has been reported to be used in the Soviet Union for the treatment of testicular and tonsilar tumors. Chromomycin A_3

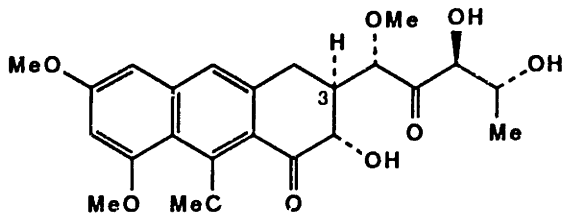
(**3**) and aureolic acid (**4**) have also been approved for clinical use in Japan and the United States respectively.

These compounds are known to function as inhibitors of DNA-dependent RNA polymerase,[3] but the exact site of binding to DNA is still unclear.[4] The binding to DNA affects both normal and cancerous cells, resulting in acute toxicity, as well as side effects such as anorexia, internal bleeding and anemia among others.[5] Therefore the development of synthetic routes to analogues with improved therapeutic efficacy is highly desirable.

The total synthesis of olivomycin A has been the focus of attention of several research groups. There are three distinct areas of interest associated with a synthesis of olivomycin: (i) synthesis of the aglycone, olivin; (ii) synthesis of the A-B disaccharide and the C-D-E trisaccharide; and (iii) coupling of the carbohydrate moieties to the aglycone.

Thiem has performed significant pioneering studies on the synthesis of the di- and trisaccharide units which confirmed the structures of these oligosaccharides.[6] Roush and Straub have recently reported a total synthesis of the A-B disaccharide from non-carbohydrate precursors.[7] With the exception of a model study,[8] efforts to attach the oligosaccharides to the aglycone have not yet been reported.

The bulk of the work thus far has been devoted to the synthesis of olivin. Two syntheses of tri-O-methylolivin (**5**) have been reported to date. In the first synthesis, reported by Weinreb in 1984,[9] **5** was prepared in racemic form. Two



5

years later Franck reported an efficient total synthesis of the natural enantiomer of **5**.[10] In addition, there have been several reports describing studies related to the synthesis of either the tricyclic nucleus or the carbohydrate-like side chain.[11] These reports have been thoroughly discussed in a recent review by Franck and Weinreb.[12]

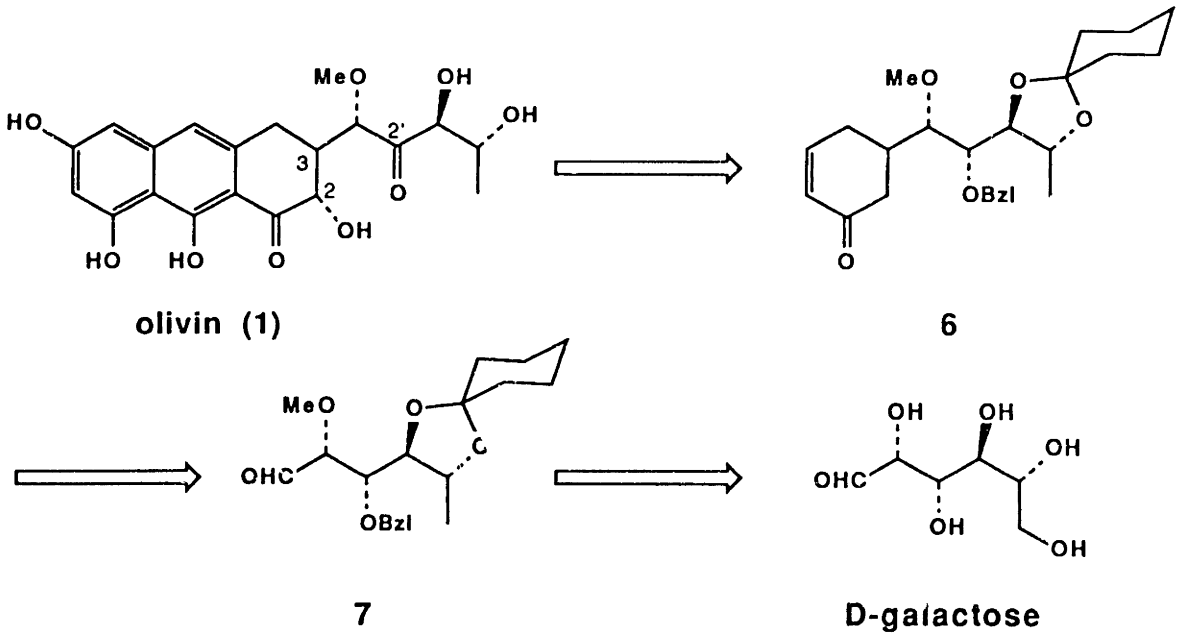
The first synthesis of olivin in the naturally occuring enantiomeric form has been completed in these laboratories,[13] and is the subject of this chapter. This successful total synthesis has been accomplished through the efforts of several investigators in our group. Early work on the carbohydrate-like side chain was carried out by Dr. Lesur who developed the synthesis of **7** from D-galactose (Scheme I) and Dr. Harris who developed the first diastereoselective synthesis of **7** based on the reaction of allylboronate **18** and aldehyde **17** (Scheme III). Dr. Lesur also investigated the stereochemistry of vinyl cuprate additions to enoates **20** and **24** and enones **23** and **25**. Dr. Chong's primary contibution involved exploratory studies on the construction of the anthracenone nucleus, culminating in preparation of phthalide **61** and optimization of the condensation with methyl crotonate. Among Dr. Tai's numerous contributions the most important are a solution to the problem of establishing the C(3) stereochemistry in an efficient manner, by using enal **49** as the Michael acceptor, the synthesis of the napthalene nucleus and the oxidation of aldehyde **66** to ester **67**. In addition Dr. Tai prepared the first small samples of protected olivin **73**, however Tai's route proved unworkable on attempted scale-up by this author. My contribution to this work involved completion and optimization of the olivin synthesis, which by necessity required the development of new procedures for the conversion of **67** to **68**, the introduction of the C(2) hydroxyl group and the final removal of protecting groups. This chapter constitutes a complete appraisal of this work in its entirety.

II. Total Synthesis of the Natural Enantiomer of Olivin

A. Synthetic Considerations

Our strategy from the outset called for the carbohydrate-like side chain to be assembled in the form of a differentially protected D-fucose derivative (**7**, Figure 1), the resident chirality of which would be used to induce the correct stereochemistry at C(3) of **1** in a subsequent C-C bond forming reaction. Because the side-chain fragment would be carried through a major portion of the synthesis, we decided that the potentially sensitive C(2') carbonyl unit of **1** would be masked in **7** as an alcohol derivative. We also envisaged that cyclohexenone **6** would serve as the

Figure 1. Original Synthetic Strategy

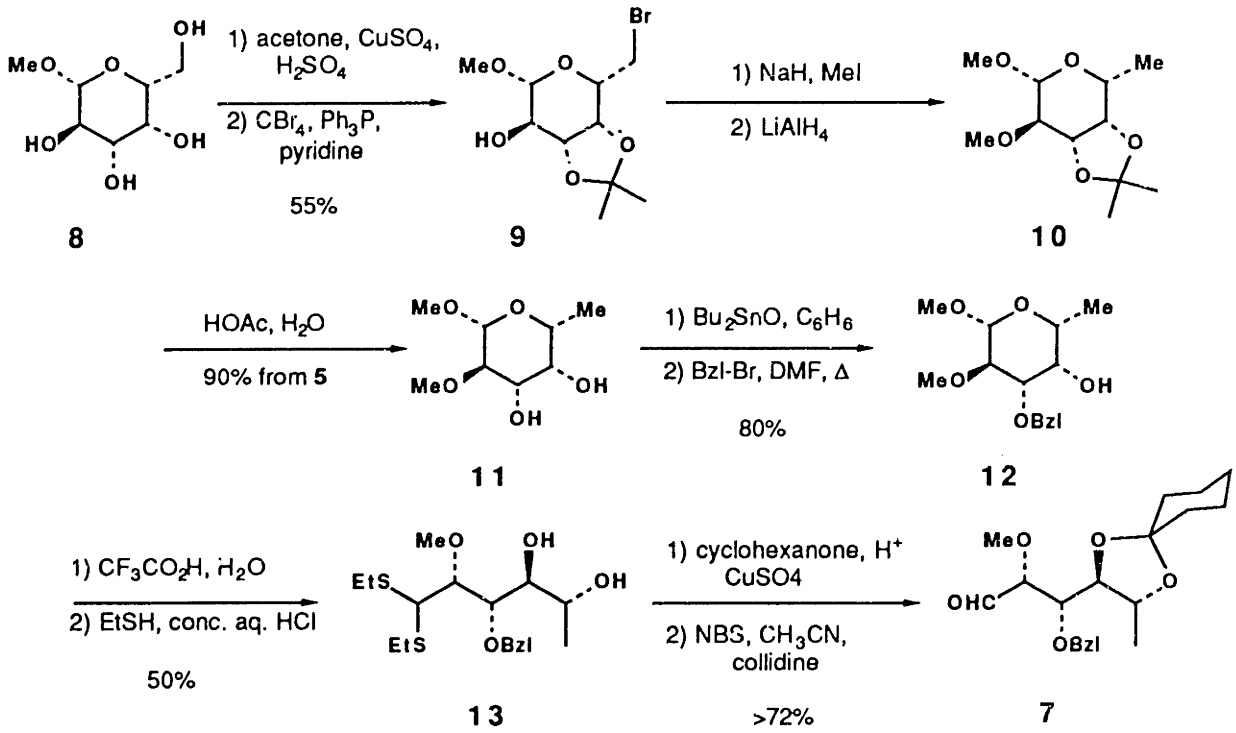


key intermediate in an annelation sequence leading to the establishment of the anthracenone nucleus of **1**. Finally, the stereochemistry of the hydroxyl group at C(2) of **1** was regarded to be strategically insignificant since it is trans to the side chain at C(3) and presumably could be controlled either by kinetic or thermodynamic experimental conditions.

B. Synthesis of the Carbohydrate-like Side Chain

The first problem to be solved was how to synthesize D-fucose derivative **7** in an efficient manner. Intermediate **7** was first synthesized in our laboratory via a classical "chiron" approach using D-galactose as the ultimate starting material.[14] At the time this chemistry was initiated, it was not at all obvious to us that *any* diastereoselective synthesis could be more efficient than one originating from this

Scheme I

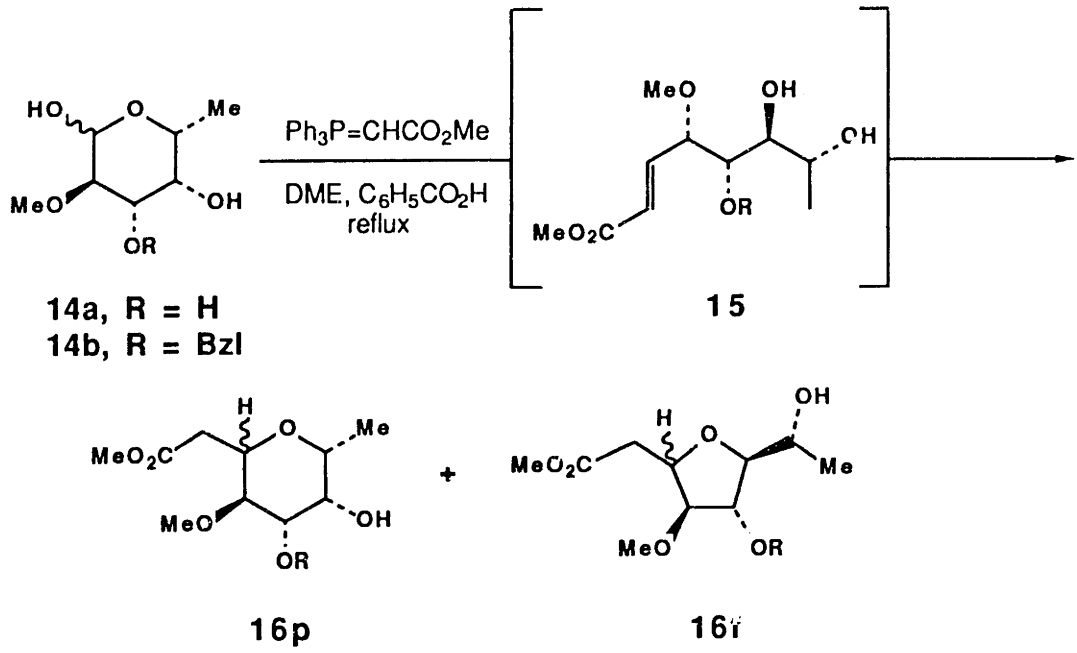


readily available hexose. In fact, D-galactose was regarded to be an ideal starting material since each of the six carbon atoms and four chiral centers mapped directly into **7**; only the hydroxyl group at C(6) would need to be removed. That is, this seemed to be a situation where a 'chiron' approach was clearly called for.

Commercially available methyl β-D-galactopyranoside was converted into the known compound **9** by using modifications of Vasella's published procedures

(Scheme I).[15] The free hydroxyl group at C(2) was then methylated and the C(6) bromomethyl group reduced with $LiAlH_4$ to give **10**. After hydrolysis of the acetonide unit, the axial C(3)-hydroxyl group of **11** was selectively benzylated via the intermediacy of a 3,4-dibutylstannylene derivative.[16] At this stage, we had hoped to perform Wittig reactions on the free sugars prepared from either **11** or **12** (e.g., **14**) as a means of generating unsaturated esters (e.g., **15**) or enones desired for subsequent C-C bond forming reactions. Unfortunately, attempts to condense **14a** with $Ph_3P{=}CHCO_2Me$ under a variety of conditions led to a mixture of pyran and furan derivatives, **16p** and **16f**, respectively,[17] while **14b** failed to react to any significant extent even when benzoic acid was added to catalyze the reaction (Scheme II).[17a]

Scheme II



These problems were avoided by protecting the C(5),C(6) diol prior to the unmasking of the aldehyde unit (Scheme I). Thus, treatment of **14b** (a mixture of pyranose and furanose anomers prepared by hydrolysis of **12** with aqueous

trifluoroacetic acid) with excess EtSH and concentrated HCl (as solvent) at 0°C[18] provided dithioacetal **13** in 50% yield, along with 25% of a mixture thiopyranosides and thiofuranosides that could be recycled to **14b** in high yield by treatment with $HgCl_2$ and $CaCO_3$ in aqueous CH_3CN. Finally, the diol unit was protected as a cyclohexylidene ketal, and then the thioacetal was hydrolyzed under oxidative conditions[19] to arrive at the key intermediate **7**.

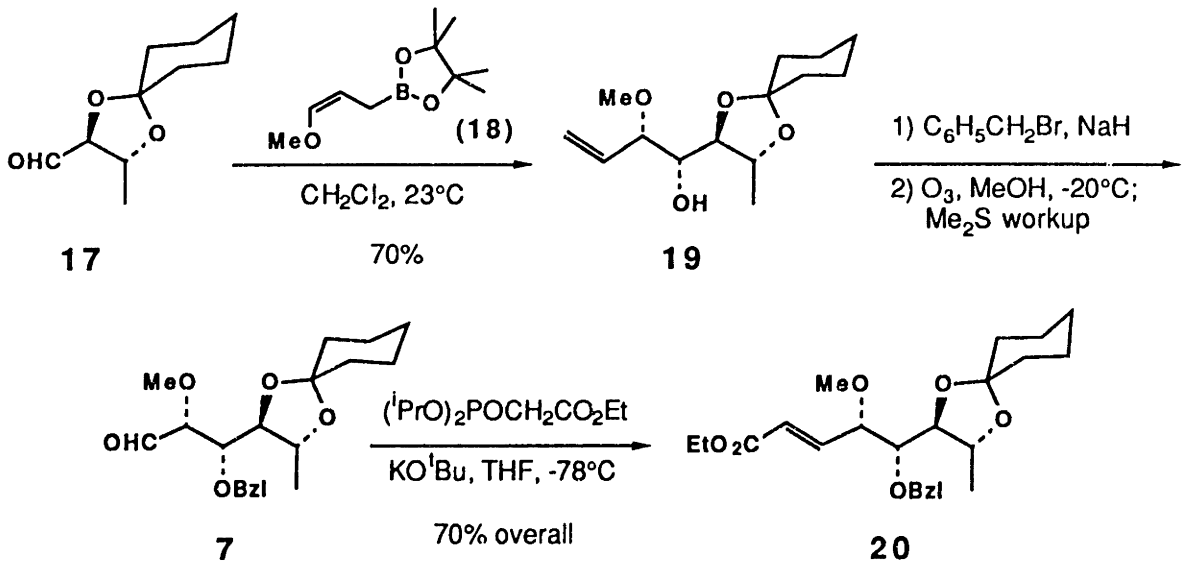
Although the desired subgoal had been reached, and while sufficient quantities of this and related intermediates were available to begin exploring methods for inducing the critical C(3) stereocenter in more advanced olivin precursors, we were not satisfied with what had been accomplished. First of all, this synthesis required 11 steps from D-galactose and was not nearly so efficient as we would have liked (14% yield overall from **8**). Second, no new chemistry had been developed. And, finally, the brutally harsh conditions[18] required for the conversion of **12** to **13** suggested that more desirable protecting groups for C(3)-OH (e.g., silyl ethers) would not be compatible with this route. As will be shown subsequently, intermediates containing a TBDMS ether at this position ultimately were used in completing the olivin synthesis.

The shortcomings of the 'chiron' approach to the synthesis of the D-fucose derivative **7** pointed out the need for development of highly diastereoselective reactions that would allow for alternative syntheses of carbohydrate-like molecules from acyclic precursors. Particularly attractive was the idea that carbohydrates could be constructed via the reaction of an allyl ether anion equivalent and an α-alkoxyaldehyde (Figure 2).[20,21] For this approach to be successful, it would be necessary to control (i) the regioselectivity of the reaction of the allyl ether anion,[20] (ii) to control the syn (threo) or anti (erythro) relationship generated in concert with the new C-C bond, and (iii) to be able to control this new syn or anti relationship with respect to the chiral center already present in the aldehydic component.

Figure 2

As already discussed in Chapter 2 of Part I, solutions to problems (i) and (ii) were at hand by virtue of studies by Hoffmann and Wuts on the reactions of γ-alkoxyallylboronates with *achiral* aldehydes.[21-23] At the time that it was decided to examine the applicability of this methodology towards the olivin synthesis, however, relatively little information was available regarding the stereochemistry of such reactions with chiral aldehydes. Hoffmann had published several examples of reactions of (E)- and (Z)-crotylboronates with chiral aldehydes such as 2-methylbutanal, but the best diastereofacial selectivity that had been reported was only 83:17.[24] Thus, it was by no means certain that the chemistry summarized in Scheme III would be successful.[13b]

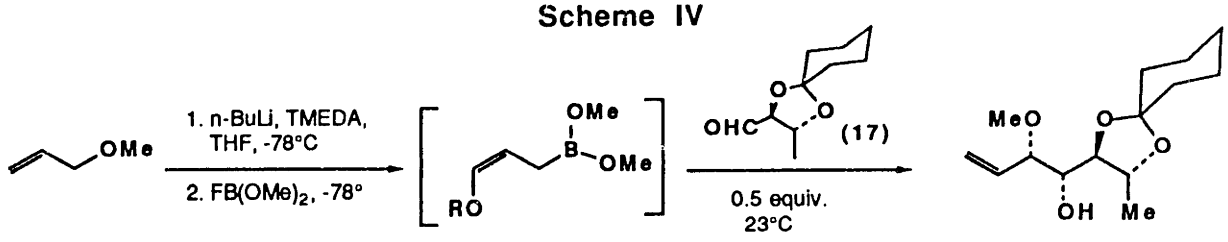
Scheme III



Aldehyde **17**, readily prepared by a four step synthesis from L-threonine (ca. 50% yield overall),[13b,25] was treated with the known (Z)-γ-methoxyallylboronate **18**[22a,c] in hexane or CH_2Cl_2. This reaction, as with other reactions of pinacol allylboronates, was relatively slow and required 24-48h at room temperature to reach completion. To our surprise, however, it was extremely selective and provided homoallyl alcohol **19** in 70% yield with greater than 95% diastereoselectivity. The stereochemistry of this compound was quickly verified by conversion to **7** as shown in Scheme III.[13b]

Thus, an interesting synthesis of **7** had emerged that was relatively brief (seven steps from L-threonine) and considerably more efficient (25% overall) in comparison to the D-galactose based synthesis described at the outset. One problem with this new sequence, however, was the synthesis of reagent **18** which, in our hands, was low yielding, tedious, and not readily amenable to scale up.[22a,c] Previous work related to the synthesis of the B ring of sesbanimide (see Chapter 2 of Part I) demonstrated that the dimethyl (Z)-γ-methoxymethoxyallylboronate (**22**) could be prepared *in situ* very efficiently, thus allowing for convenient scale-up. In accordance th these results, use of *in situ* generated dimethyl (Z)-γ-methoxy-allylboronate (**21**)[26] was extremely convenient and actually provided **19**

Scheme IV



21 R = Me
22 R = MOM

75-83%

19

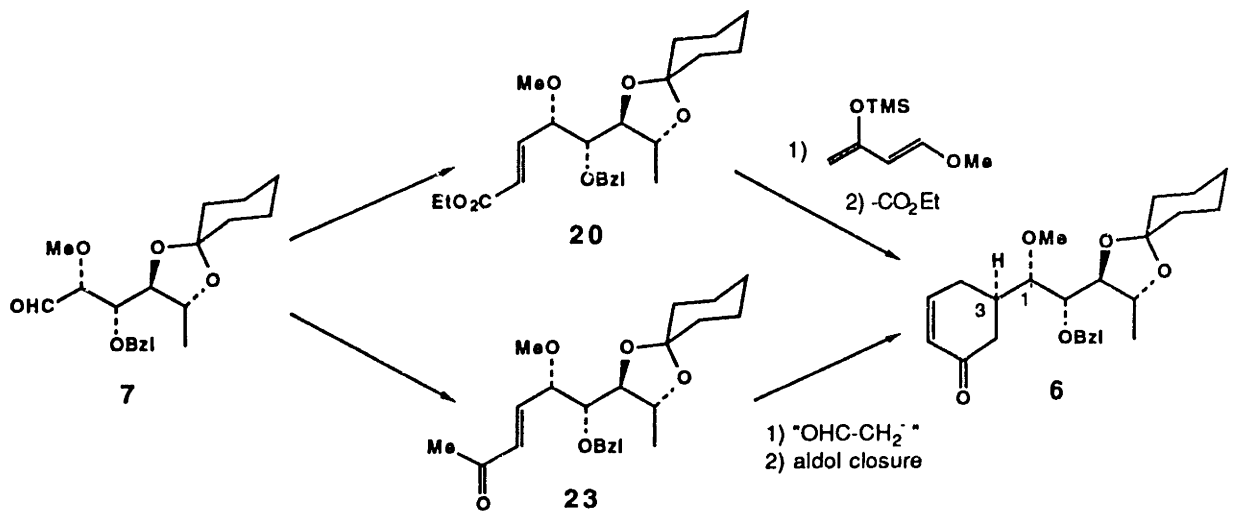
in higher yield (75-83%) than the original method involving **18** (Scheme IV). It is this modified procedure that is now used for all large scale work.

It is interesting to note, that the C(3) side chain of olivin and the B ring of sesbanimide, both of which are carbohydrate-like in nature, were synthesized very efficiently from acyclic precursors using the highly diastereoselective reactions of allylboronate reagents with chiral α-alkoxyaldehydes. Thus, this approach promises to be an important addition to the arsenal of synthetic techniques available for the synthesis of carbohydrate-like molecules.

C. Establishment of the C(3) Stereocenter of Olivin

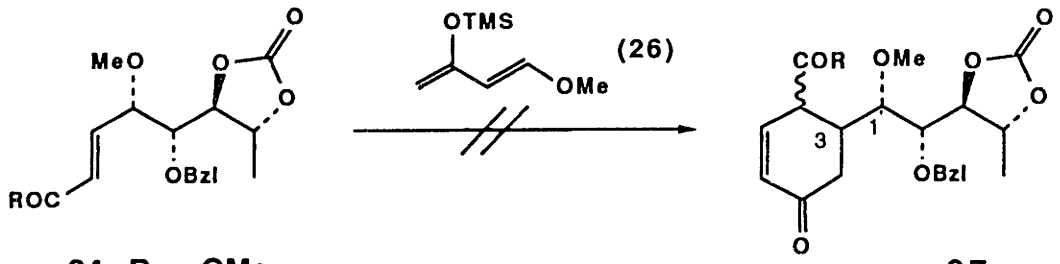
The next critical hurdle in this approach to olivin involved devising a diastereoselective method for introducing the C(3) stereocenter in intermediates suitably functionalized for elaboration to the natural product. As mentioned previously, our original intention was to proceed by way of a cyclohexenone intermediate such as **6**. This, in turn, suggested that the conversion of D-fucose derivative **7** to **6** might involve a Wittig olefination followed by a Diels-Alder reaction with Danishefsky's diene or, alternatively, a diastereoselective 1,4-addition of an acetaldehyde equivalent and a subsequent aldol ring closure (Figure 3).

Figure 3



Exploratory studies were initiated with enoate **24** and enone **25**, which were prepared from diol **13** (see experimental section) and were available before the syntheses of **7** in Scheme I and III had been completed. Surprisingly, however, these compounds failed to react smoothly with the well-known diene **26**[27] under a

Scheme V



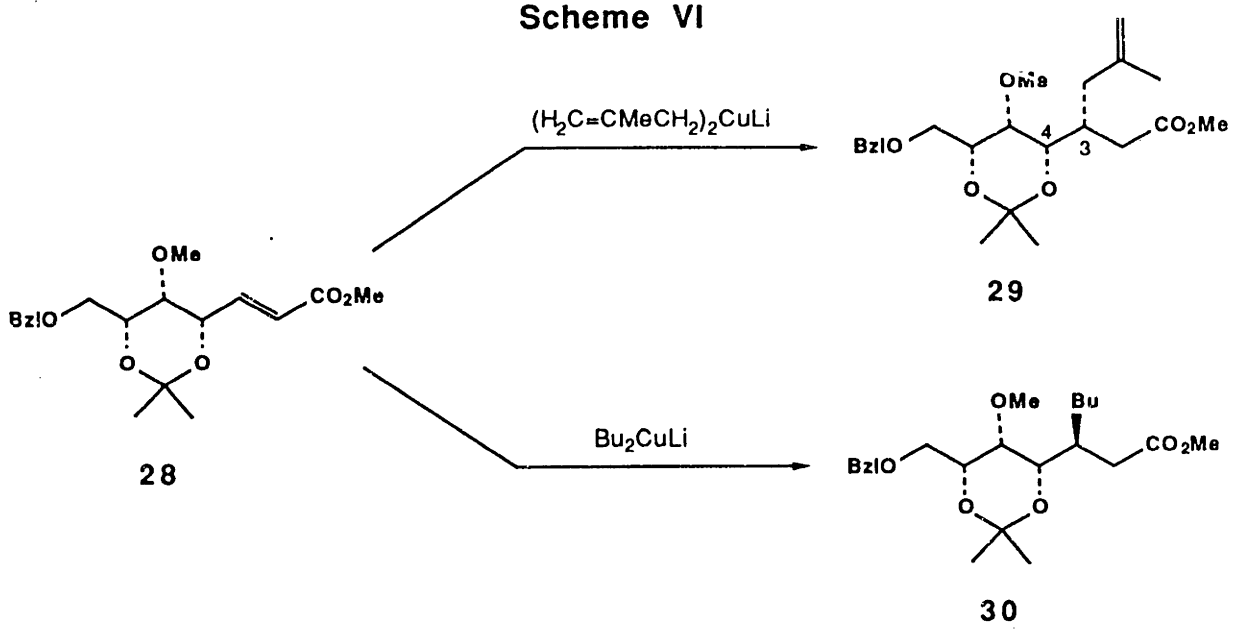
24, R = OMe
25, R = Me

27

variety of conditions, even when **26** was used as solvent in a sealed tube at 170 °C. Enoate **20** similarly failed to yield detectable quantities of the desired cycloadduct from thermal or Lewis acid mediated experiments. This unexpected lack of reactivity, together with Franck's publication of a very similar approach to olivin, persuaded us to discontinue this line of investigation. Interestingly, Franck subsequently reported a synthesis of a cyclohexenone related to **6** via the Diels-Alder reaction of **26** and an unsaturated lactone as dienophile,[28] but has not yet completed an olivin synthesis from this intermediate.[10]

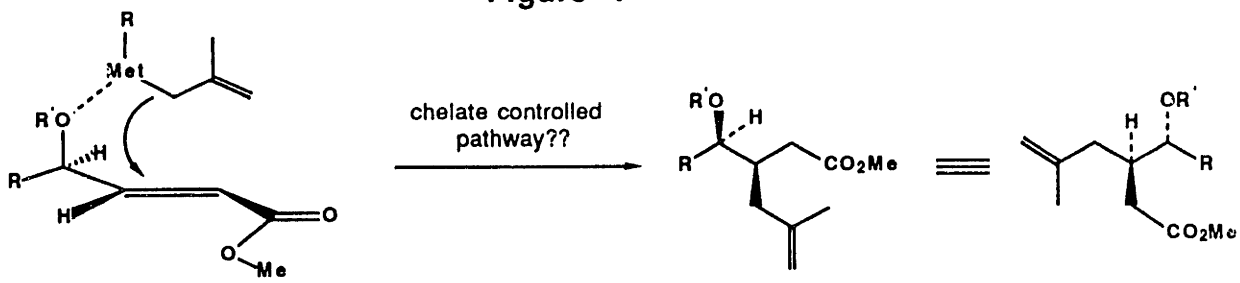
We turned instead to an examination of methodology for construction of cyclohexenone **6** via the 1,4-addition of an acetaldehyde equivalent to **25**. When this research was initiated, relatively little was known about the diastereoselectivity of the 1,4-additions of organometallic reagents to γ-alkoxy-α,β-unsaturated carbonyl systems. Isobe had reported several examples of highly diastereoselective additions of alkyllithium reagents to γ-alkoxy-α-trimethylsilyl-α,β-

Scheme VI



unsaturated sulfones that apparently proceed by way of chelated intermediates,[29] and Nicolaou had shown that dimethallylcuprate reacted with carbohydrate derivative **28** to give **29** with very high selectivity.[30] This result also could be rationalized by invoking chelated reaction intermediates (Figure 4), and was very interesting for our purposes since the stereochemical relationship between C(3) and C(4) of **29** was exactly that needed for C(3) and C(1') of cyclohexenone **6**. On

Figure 4

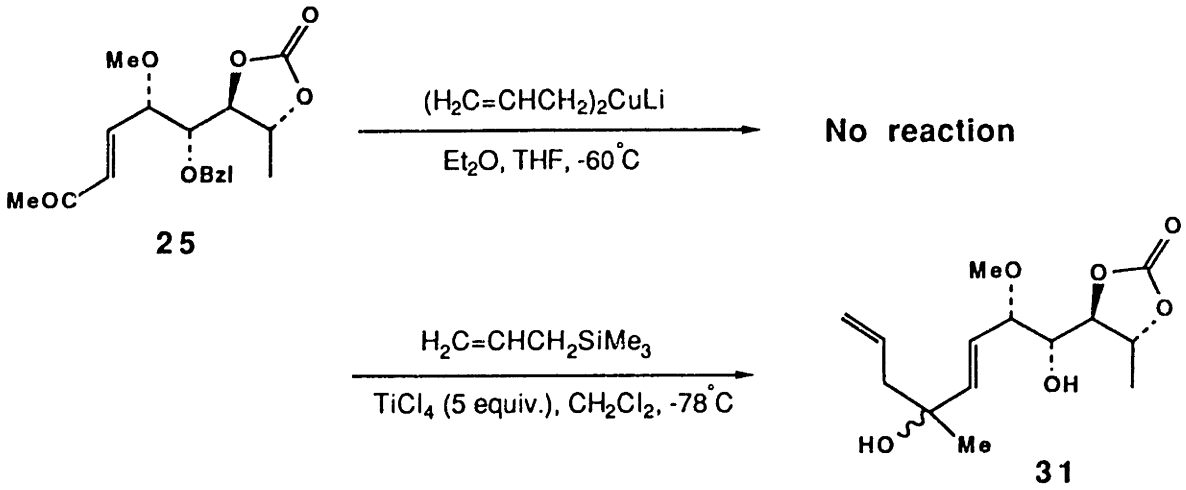


the other hand, it was unclear as to the generality of this process, since Ziegler had reported that the stereochemistry of this reaction was completely reversed when

Bu_2CuLi was used (**28**→**30**, Scheme VI).[31] We proceeded cautiously, therefore, into investigations of diastereoselective 1,4-addition reactions with enone **25**.

Preliminary experiments involving the reaction of **25** and diallylcuprate were unsuccessful (Scheme VII). Evidently, our technique for generating and handling this sensitive reagent[32] was flawed, since attempts to perform the 1,4-allylation of cyclohexenone likewise failed. When CH_2=$CHCH_2MgBr$ and CuBr-Me_2S were employed with **25**, only products of 1,2-addition were detected.

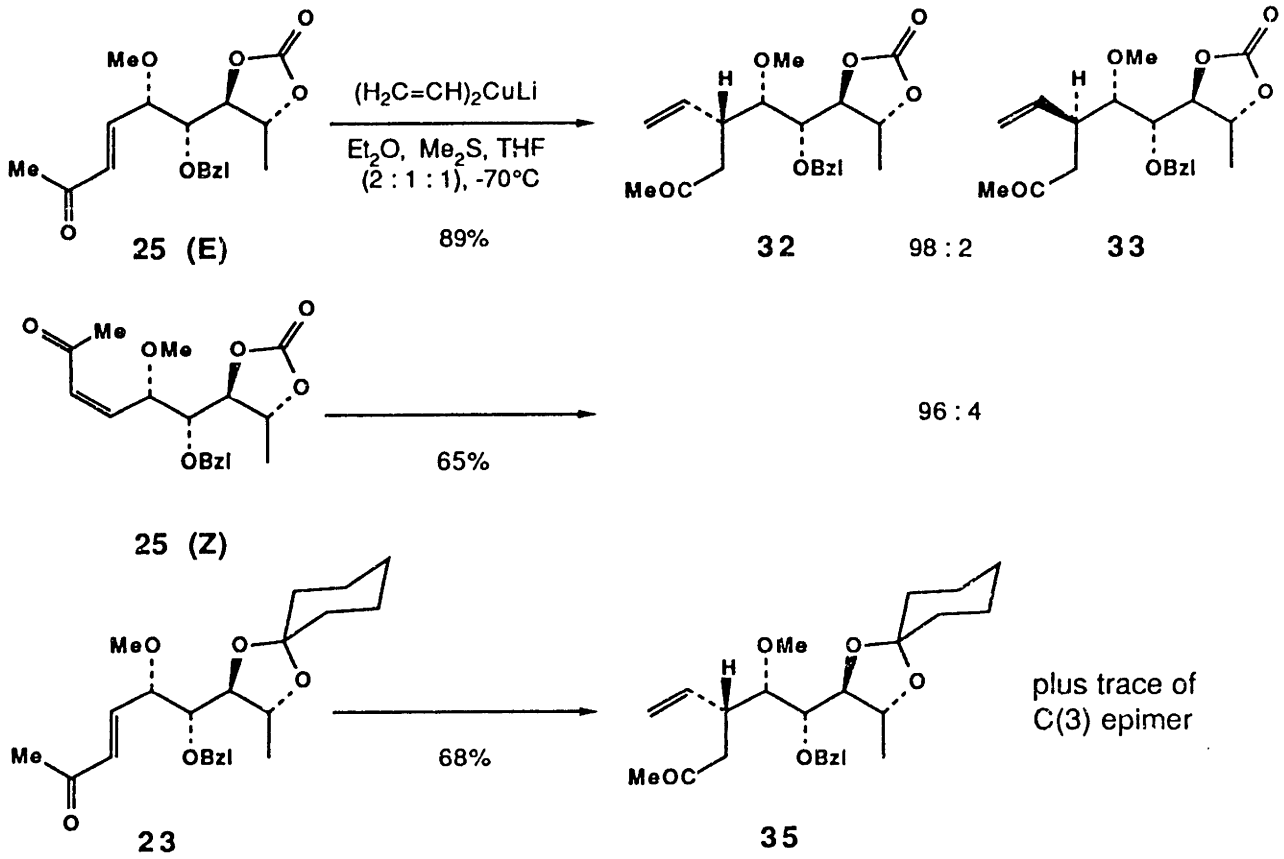
Scheme VII



In light of these negative results we briefly examined the applicability of the Sakurai reaction to this problem (Scheme VII).[33] Surprisingly, no reaction occurred when 1-2 equiv. of $TiCl_4$ and allyltrimethylsilane were employed. Evidently, the Lewis acid was binding preferentially to the ethereal or carbonate carbonyl oxygen atoms, thereby precluding reaction at the enone. When a much greater excess of the reagents was employed, a mixture of products was obtained including **31** resulting from carbonyl 1,2-addition and benzyl ether cleavage.

Success was finally realized in the reactions of **25** and divinylcuprate (Scheme VIII).[34] Only one diastereomer (**32**) could be detected by NMR analysis

Scheme VIII

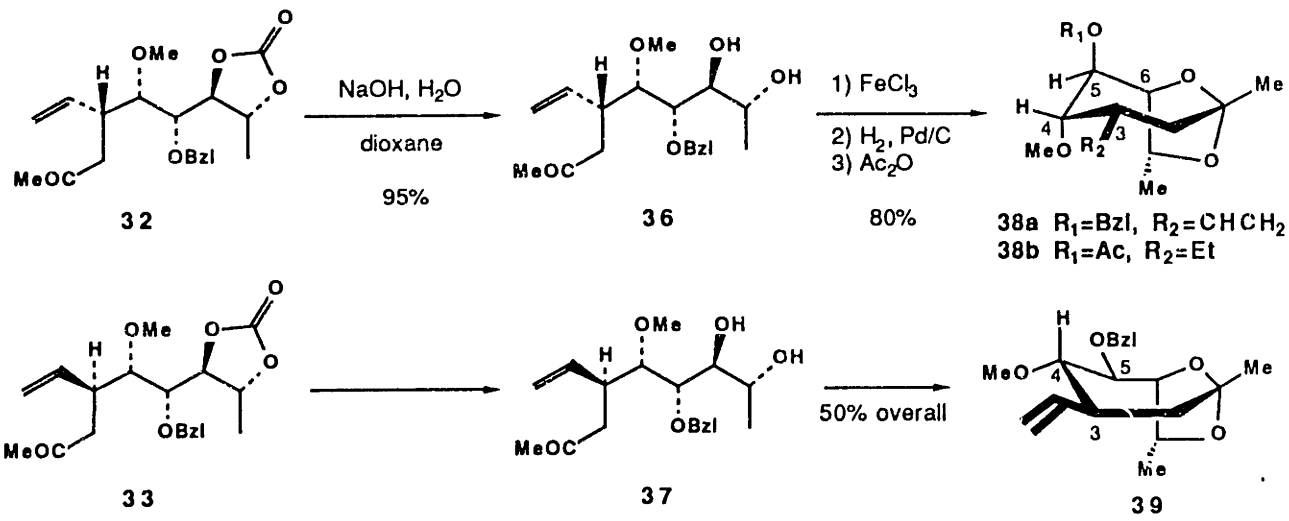


of the crude reaction product, but small quantities of the second diastereomer (**33**) were isolated by chromatography. Similar results were subsequently achieved with enone **23**. Interestingly, the stereochemistry of this reaction proved insensitive to the geometry of the enone, an important observation since mixtures of enone and enoate isomers frequently are obtained in the olefination reactions of carbohydrate derivatives.

The stereochemistry of the C(3) center in adducts **32**, **33**, and **35** was assigned according to the studies summarized in Scheme IX. Hydrolysis of the carbonate units afforded diols **36** and **37**, respectively, which cyclized upon treatment with $FeCl_3$ in CH_2Cl_2[35] to give bicyclic acetals **38a** and **39**. Acetal **38a**, which was also obtained directly from **35** by exposure to 98:2 TFA-H_2O (77%

yield), was converted to **38b** by hydrogenolysis and acylation in order to ensure first-order behavior of the H(4)-H(5) and H(5)-H(6) spin systems. The observation of a W-couple ($J_{4,6}$ = 1.7 Hz) in **38b** and its absence in **39**, together with the presence of two large coupling constants for H(4) in **39** ($J_{3,4}$ = 10.2 Hz; $J_{4,5}$ = 7.5 Hz; in addition, $J_{5,6}$ = O Hz) versus very small values in **38b** ($J_{3,4}$ = O Hz, $J_{4,5}$ = 3.5 Hz, and $J_{5,6}$ = 1.7 Hz) enables the conformations and stereochemistry of **38** and **39** to be assigned as indicated in Scheme IX. It was evident, therefore, that adducts **32** and **35** possess the wrong stereochemistry at C(3) for use in this approach to olivin.

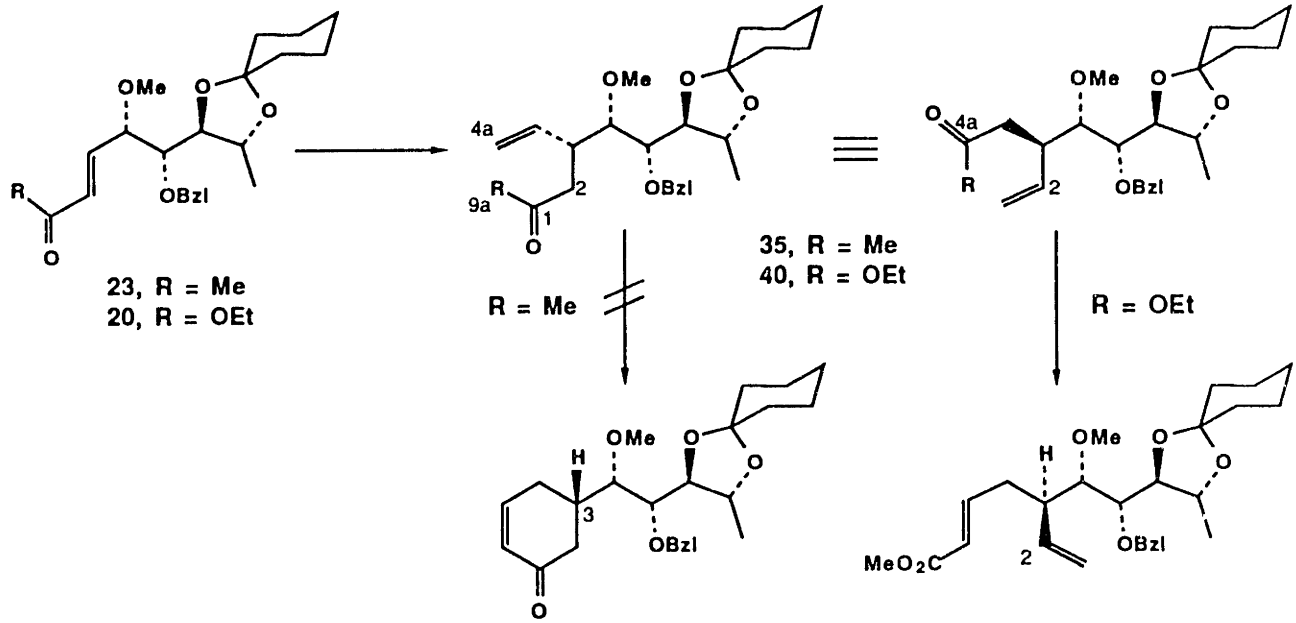
Scheme IX



In view of these results, a reevaluation of our synthetic plan was called for. Although cyclohexenone **41**, the C(3) epimer of **6**, would be produced if a bond were constructed between C(4a) and C(9a) of **35** (olivin numbering system), it was readily apparent that 1,4-adducts **40** prepared from enoate **20** could be used if the plan to proceed via **6** was abandoned (Figure 5). That is, we envisiaged that the roles of the vinyl and acetic ester appendages in subsequent C-C bond forming reactions could be reversed. For example, reduction of the ester unit in **40** to the

corresponding aldehyde followed by a Wittig olefination would give **42**. The unsaturated ester unit would provide a handle for constructing the naphthalene core of the aglycone, while the vinyl appendage ultimately would contribute C(2) to the natural product structure.

Figure 5. Revised Synthetic Plan

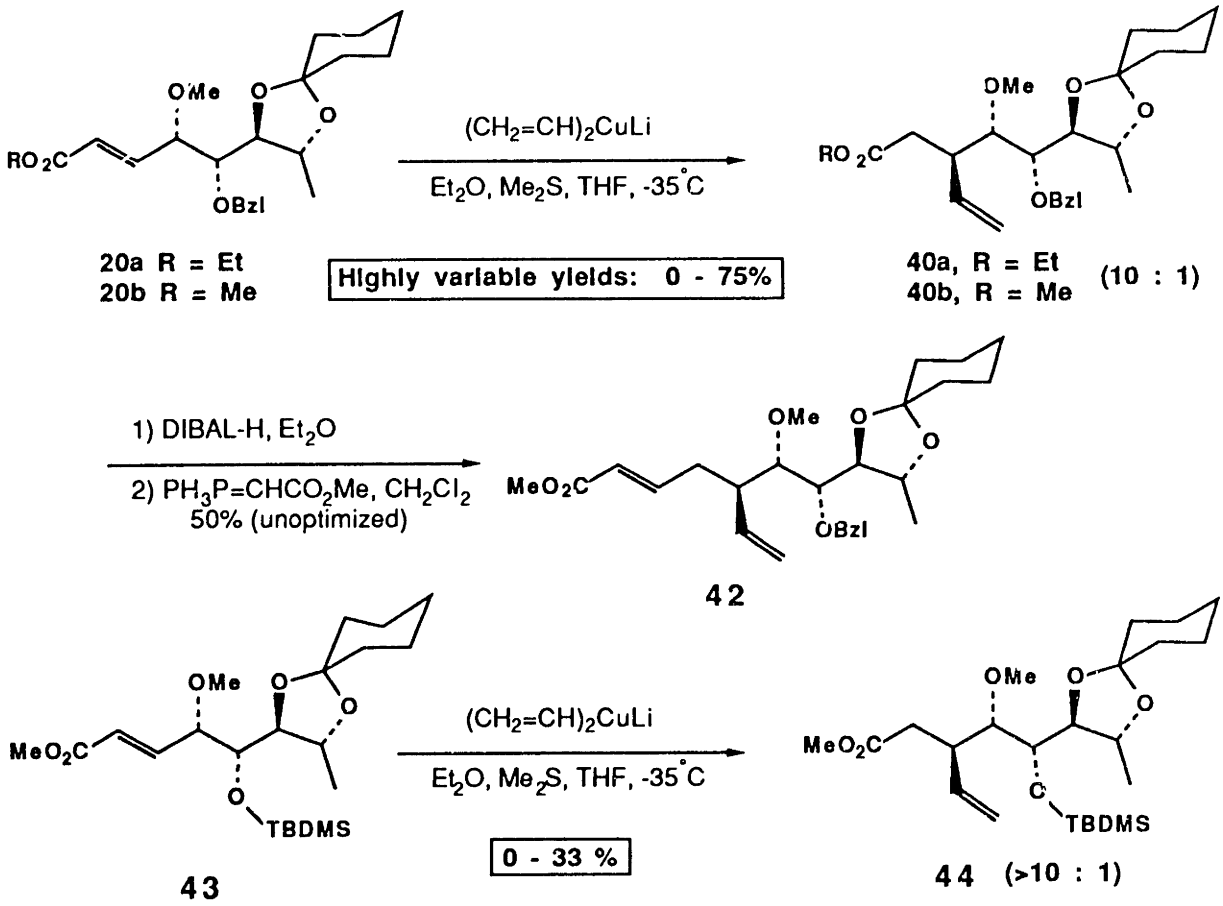


Fortunately, for our purposes, the stereochemical outcome of the reactions of vinyl cuprates with enoates such as **20** proved to be the same as with enones **23** and **25**.[34a] As shown in Scheme X, the reaction of either **20a** or **20b** and $(CH_2=CH)_2CuLi$ at -35 °C yielded **40a** and **40b** respectively as a 10:1 mixture of C(3) epimers. The major product was then smoothly elaborated to **42**.

While this sequence appeared to solve the problem concerning the establishment of the C(3) stereocenter in olivin precursors, it proved unsatisfactory on two counts. First of all, the yield of **40** proved to be highly variable (0-75%) and very poor results were obtained on attempted scale up. Second, the benzyl ether

unit, an artifact of the original synthesis of aldehyde **7** from D-galactose (Scheme I), was regarded as an unsatisfactory protecting group for later stages of the synthesis. In a parallel series of experiments, therefore, TBDMS ether **43** was prepared from **19** which, in turn, was synthesized via the allylboronate chemistry summarized in Scheme III. While compound **43** also displayed excellent diastereoselectivity (>10:1) in the reaction with $(CH_2{=}CH)_2CuLi$, this compound proved to be even less reactive than **20** and the best yield of **44** ever obtained was 33%.

Scheme X

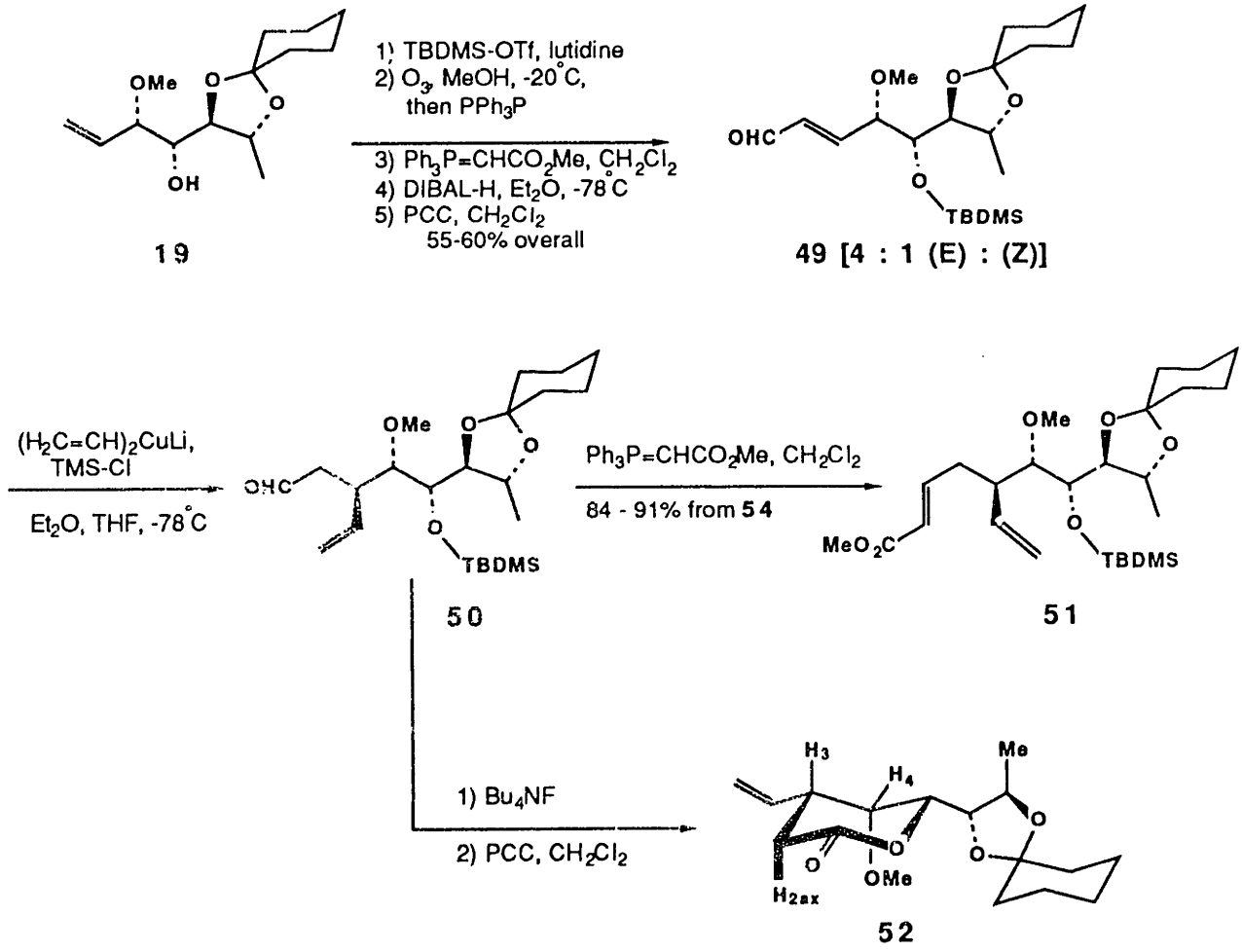


The poor reactivity of **20** and **43** as cuprate acceptors[32] together with the sensitivity of the vinyl cuprate towards O_2 and Cu^{+2} impurities presumably

contributed to these poor results. The reagent rapidly decomposed (visual evidence) when the reactions were attempted at temperatures above -35 °C, and enoates **20/43** were too unreactive for the experiments to be performed at temperatures below -40 °C. Attempts to improve the situation by using $(CH_2=CH)_2CuLi/BF_3$,[36] $CH_2=CHCu/BF_3$,[37] or $(CH_2=CH)_2Cu(CN)Li_2$[38] gave equally unsatisfactory results.

Fortunately, these problems were solved by using unsaturated aldehyde **49** as the electrophilic component in this reaction (Scheme XI).[39] The greater

Scheme XI



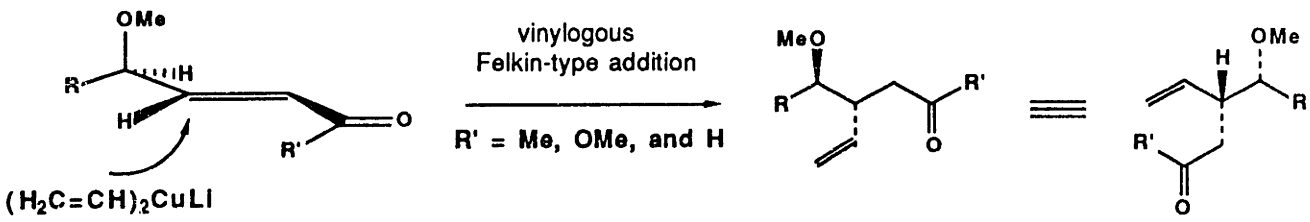
reactivity of the enal as opposed to an enoate permitted this transformation to be performed at -78 °C, conditions under which the stability of $(CH_2=CH)_2CuLi$ was

not an issue. This reaction is highly stereoselective (a single diastereomer was observed), high yielding (>84-91%), highly reproducible, and multigram quantities of **50** have been prepared in this way. It should be noted that this cuprate reaction is performed in the presence of TMS-Cl; when omitted, the reaction is still successful and provides **50** in 75% yield.[40] In addition, it is also worthy of mention that the stereoselectivity of this step was not influenced by the isomeric purity of **49** (used in most cases as a mixture of olefin isomers). Aldehyde **49** was synthesized from **19** in excellent overall yield via a sequence involving: (i) protection of the free alcohol as the TBDMS-ether **45** (82%); (ii) ozonolysis to provide aldehyde **46**, followed by Wittig olefination to give α,β-unsaturated ester **43** (70%); and (iii) reduction of **43** to the allylic alcohol and subsequent PCC oxidation (90%). Direct preparation of **49** from **46** using Ph_3P=CHCHO was inefficient (33%).

The stereochemistry of **50** was assigned following conversion to lactone **52**. In particular, the multiplicity of H(4) (broad t, J = 2 Hz) and the diaxial coupling constant (J =10 Hz) between H(3) and $H(2_{ax})$ require that the stereochemistry of C(3) must be as indicated.

In summary, it is interesting to note that the stereochemical outcome of the vinyl cuprate additions to enones **23** and **25**, enoates **20** and **43**, and enal **49** are the same. The stereochemistry in these cases is consistent with the addition of the organometallic reagent anti to the allylic C-O bond from a rotamer in which the smallest allylic substituent, H, lies in the plane of the C-C double bond (Figure 6).

Figure 6



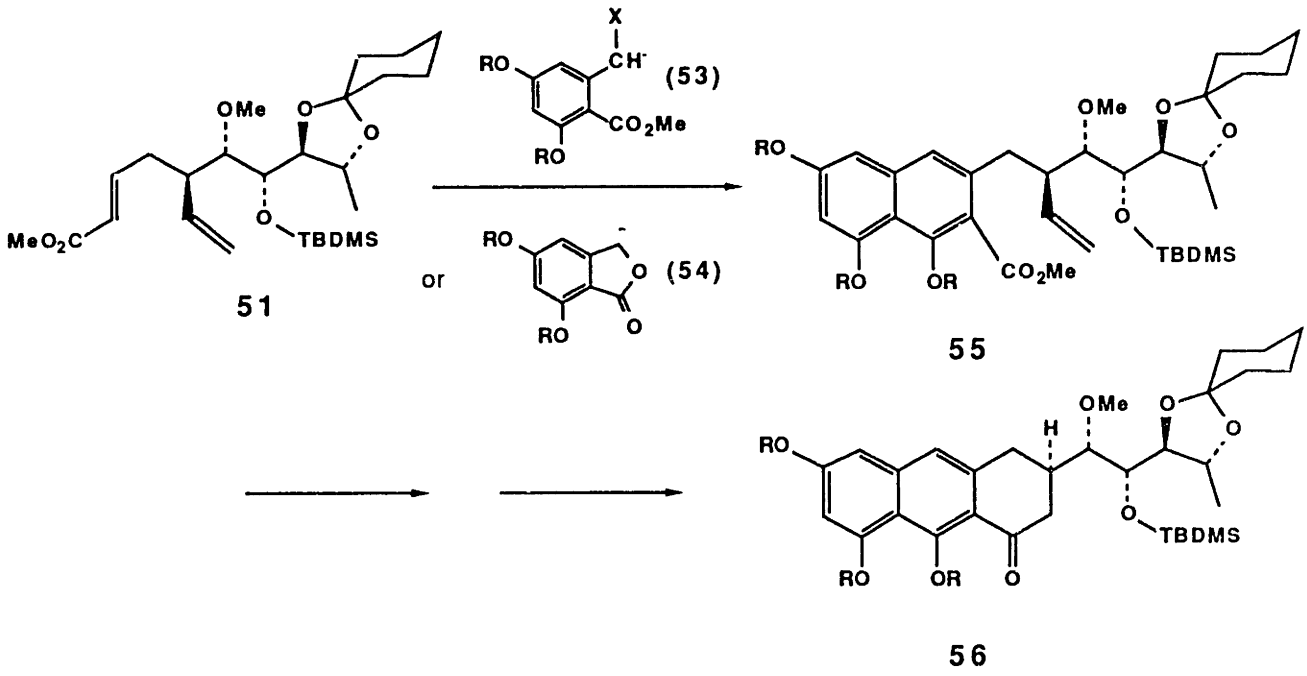
This is termed here a "vinylogous Felkin-type addition" to reflect the absence of chelation in the reaction transition state and to emphasize the role that stereoelectronics undoubtedly play.[41] The alternative allylic rotamer in which R eclipses the C=C is presumably disfavored for steric reasons, and is especially bad when the double bond is (Z). While we recognize that the allylic rotamer indicated in Figure 6, reflecting the energetically favored ground state conformation, may not actually be the reactive species in the transition state,[42] this picture is consistent with our observation that both olefin isomers of enone **25**, enoate **23**, and enal **49** give rise to the same (anti) diastereomer in the 1,4-addition reactions. Additional examples have been published that are consistent with this model.[43] The only organometallic 1,4-addition reactions that deviate markedly from the results reported here involve allylic cuprates,[30,31] allyllithium reagents,[30c,31,43a] and the additions of $RCu\text{-}BF_3$ to (Z)-enoates.[42] In each of these cases, the observed diastereoselectivity is consistent with a chelated transition state as depicted in Figure 4. Further experimentation is clearly called for to resolve the striking differences that exist, for example, in the behavior of allylic vs. vinylic cuprates.

D. Completion of the Olivin Synthesis

With a highly selective and efficient solution to the major stereochemical problems well in hand (Schemes III and XI), we turned our attention to the construction of the anthracenone nucleus of olivin. Two related methods for elaborating **51** to naphthoate **55** were envisaged (Figure 7). First, the reaction of **51** with an orsellinate derivative **53** (X = SPh, SO_2Ph, SePh, etc.) was regarded as a reasonable approach to this problem since several laboratories had previously reported syntheses of simpler naphthoates via the reactions of sulfur-or selenium-substituted toluate anions with unsaturated esters.[44] Alternatively, we imagined that phthalide anion **54** could also be used as the nucleophilic component of an

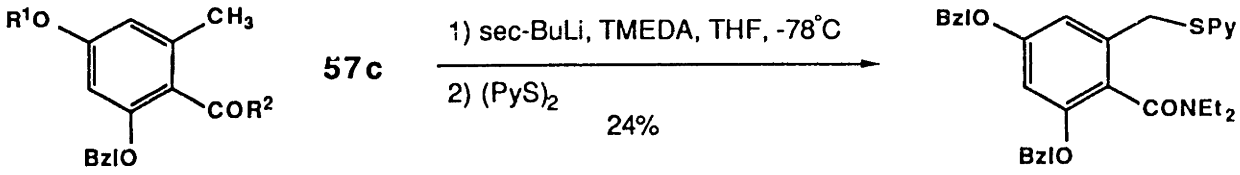
aromatic annulation sequence.[45] Because the toluate anion method leads directly to the desired aromatic system--an extra dehydration step is required in the phthalide approach[45]--and because the reported yields were generally higher, we concentrated first on the orsellinate anion chemistry.

Figure 7



Unfortunately, however, we were unable to develop an efficient synthesis of a suitably protected reagent. In spite of considerable literature precedent,[46] all attempts to functionalize orsellinates **57a-c** with $(PhS)_2$, $(PyS)_2$, PhSCl, NBS, I_2, and related oxidants after treatment with bases such as LDA, LiTMP, LHMDS, or sec-BuLi (in the cases where R^2=OH or NEt_2) in THF at -78 °C led to low yields of the desired product, some recovered starting material, dimeric products,[46a] and occasionally products in which one of the benzyl ether protecting groups had been removed. The greatest success was realized by using amide **57c** as the substrate, but the yields were very low as illustrated here by the reaction with dipyridyl

disulfide. Attempts to brominate **57a** (R^2=OMe) by direct reaction with NBS (2.2 equiv.)[47] was non-selective and gave a mixture of four products in comparable amounts.

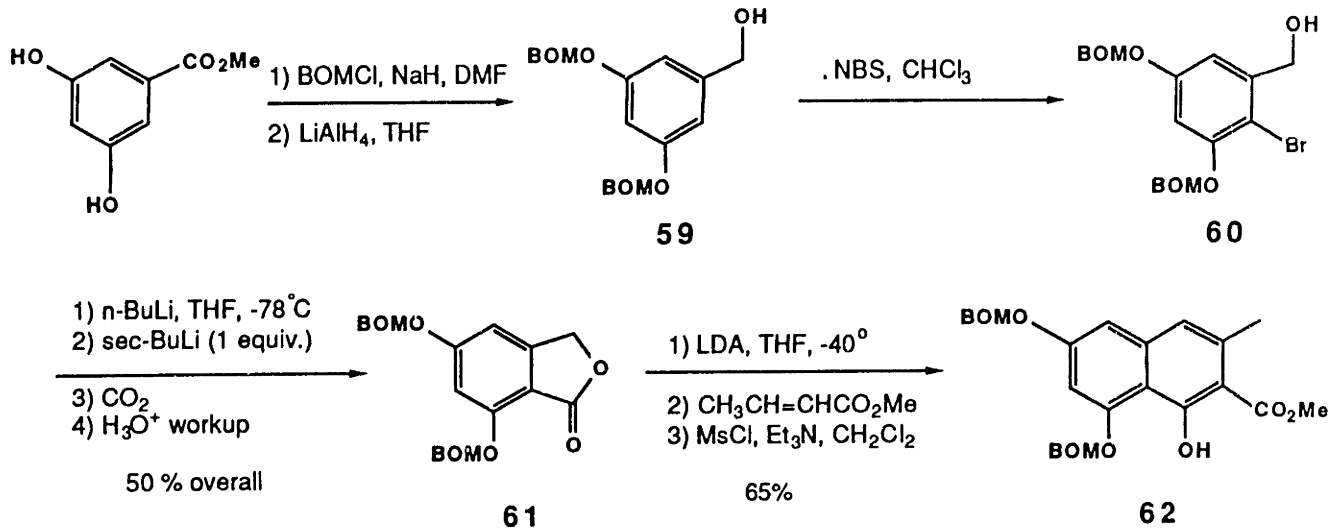


58

57a, R^1 = Bzl, R^2 = OMe or H
57b, R^1 = MEM, R^2 = OMe or H
57c, R^1 = Bzl, R^2 = NEt_2

We turned, therefore, to an examination of the phthalide route for preparing naphthoate **55**. Phthalide **61** was prepared by a four step sequence in 50% overall yield starting from methyl 3,5-dihydroxybenzoate (Scheme XII).[48] The lithium anion, generated by using 3 equiv. of LDA in THF at -40 °C, readily condensed with methylcrotonate (used in excess) to give an intermediate

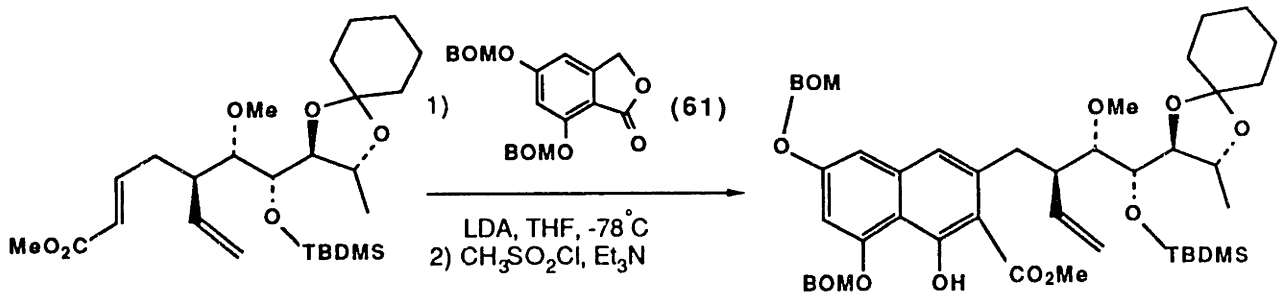
Scheme XII



hydroxytetralone that smoothly aromatized upon exposure to methanesulfonyl chloride (1.1 equiv. based on **61**) and Et_3N. In this way, naphthoate **62** was obtained in 65% yield. We elected not to use the aromatization conditions described by Sammes (CF_3CO_2H or BF_3-Et_2O), since we were concerned that the acid-labile protecting groups present in **61** and enoate **51** might not survive these conditions.

A similar protocol was used for the coupling of phthalide **61** and enoate **51** with the exception that **51** and **61** were used in equimolar amounts (Scheme XIII). This reaction provided naphthoate **63** in 30-35% yield together with 5-10% of the corresponding phenolic mesylate. While the efficiency of this step is lower than we would like sufficient quantities of **63** were prepared to permit completion of the synthesis.

Scheme XIII

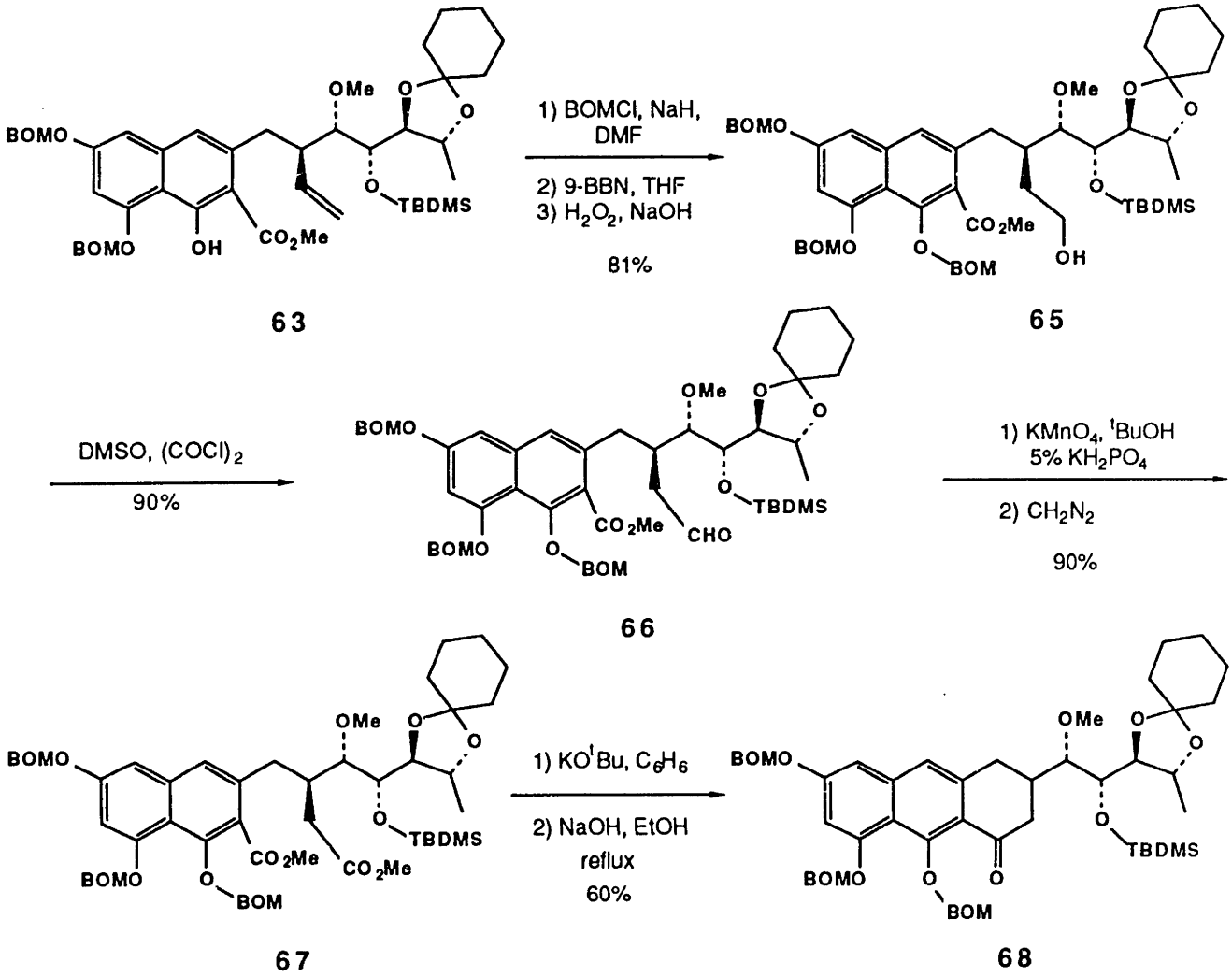


51 **63**

Protection of the free phenol of **63** as a BOM ether proceeded smoothly to provide naphthoate **64** in 91% yield (Scheme XIV). The vinyl appendage was then oxidized to aldehyde **66** via alcohol **65**. Further oxidation of the aldehyde **66** to diester **67** proved to be non-trivial, as of a variety of standard procedures for the oxidation of aldehydes to carboxylic acids, such as PDC, Jones and mCPBA were

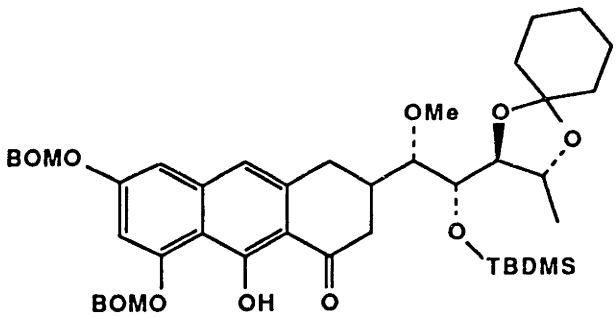
completely inefficient. Fortunately, use of Masamune's recently introduced method ($KMnO_4$, KH_2PO_4)[49] afforded **67** in excellent yield of product (90%).

Scheme XIV

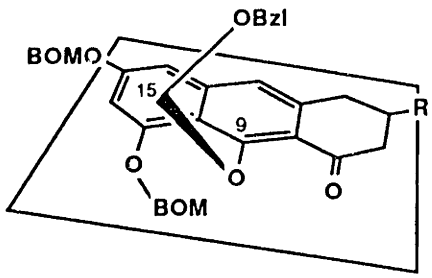


The final C-C bond was then established via Dieckman cyclization of the diester **67**. Thus, treatment of **67** with excess of KO^tBu in benzene at room temperature afforded the corresponding β-keto ester. Subsequent exposure of the crude product to 0.4 M NaOH in aqueous EtOH at reflux effected decarbomethoxylation, thereby providing anthracenone **68** in 60% overall yield. It is interesting to note that if longer reaction periods were employed the free phenol

69 along with other side products resulting from air oxidation of **69** could be isolated in variable amounts. Products arising from loss of the C(9)-BOM group were also the major products if the Dieckman cyclization was carried out at reflux. The ease of loss of the C(9)-BOM group can be attributed to the parallel arrangement of the C(15)-O bond and the aromatic π-system (see **70**). This arrangement allows for an interaction between $\sigma^*_{C(15)-O}$ and the π orbital, thus activating cleavage of the C(15)-O bond. This conformation is believed to be favorable as it alleviates steric interaction between the C(9)-OBOM unit and the C(8)-BOM group and the C(1) ketone.



69

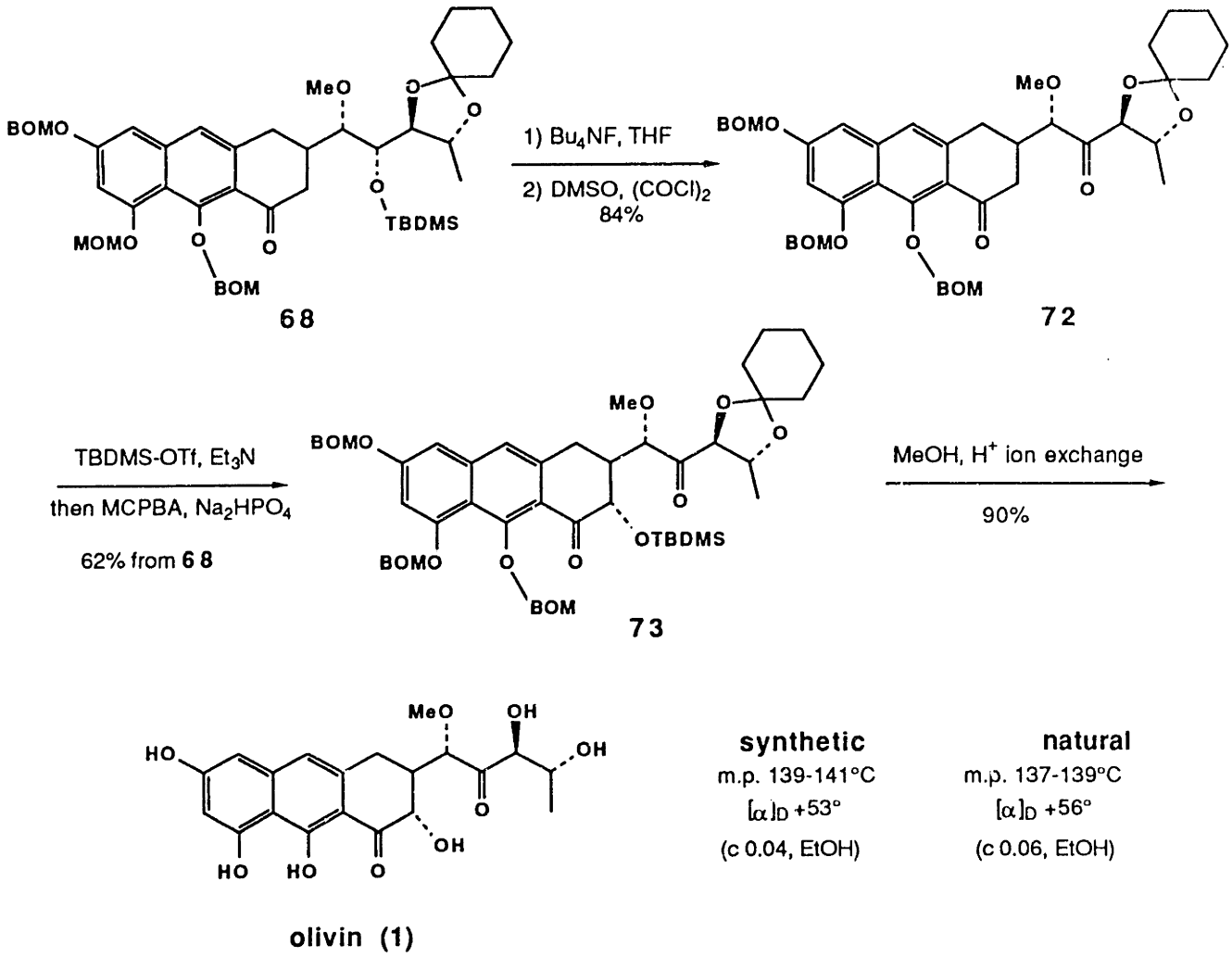


70

The side chain TBDMS ether in **68** was then cleaved by treatment with Bu_4NF in THF (93%) and the resulting hydroxyl group in **71** oxidized to the C(2') ketone **72** via a standard Swern procedure (90%) (Scheme XV).[50] Selective conversion of the C(1) carbonyl to the corresponding TBDMS enol ether was smoothly accomplished according to Mander's method,[51] and as previously reported by Franck, thus setting the stage for the oxidative introduction of the C(2) hydroxyl group. Initial attempts using both catalytic and stoichiometric amounts of OsO_4[52] generated a multitude of products. The same result was obtained when we attempted a Rubottom oxidation[53] (mCPBA). However, when this reaction was

repeated in the presence of Na_2HPO_4 buffer, protected olivin **73** was obtained in 76% overall yield. The success of this last step was also dependent on the purity of the TBDMS enol ether, and it proved necessary to filter this intermediate through silica gel before exposure to mCPBA.

Scheme XV



The final step was the removal of the protecting groups. All protecting groups were chosen to be acid labile in order to avoid use of basic conditions to which olivin is known to be unstable.[1b] Olivin is, however stable to relatively

vigorous acidic conditions (e.g. 0.1 N MeOH, H_2SO_4, reflux, 3 h or 2 M HCl, MeOH, 23 °C).[54] Initial attempts to remove all protecting goups in a single step by using TsOH in MeOH were disappointing as even after 4 d only a small amount of olivin could be obtained. The major compound produced is what we believe to be a C(8)-C(9) methylene acetal which is one of the most acid-stable protecting groups. Formation of this intermediate was troublesome because deprotection of bisphenolic methylene acetals often requires use of drastic conditions such as $AlBr_3$, EtSH.[55] Attempted deprotecton of **73** with BCl_3 at -78 °C resulted in decomposition. The reaction of chromomycinone, the C(7)-methylated analogue of olivin, with BCl_3 has previously been reported to result in cleavage of the methyl ether.[56] An additional complication was the difficulty of isolating olivin. The olivin, present in very small amounts (~1 mg), could not be separated from TsOH·Et_3N salt (Et_3N was used to quench the reaction; we were reluctant to subject such small samples to an exctractive workup owing to the potential water solubility of olivin) even after repeated chromatographic purification. Fortunately use of a acidic ion-exchange resin proved to be a solution to the above problems. Thus all five protecting groups of **73** were removed very efficiently (90%) by treatment with Dowex 50W-X8 H^+ resin in MeOH at room temperature for 5-6 days. Removal of the acidic resin was accomplished simply by filtration through a Kimwipe plug. Direct crystallization of the crude product from ether-hexane provided synthetic olivin m.p. 139-141° C; $[\alpha]_D^{25}$ + 53° (c 0.04, EtOH). Synthetic olivin so obtained was identical by all the usual criteria with an authentic sample (m.p. 137-139° C; $[\alpha]_D^{25}$ + 56° (c 0.05, EtOH)) prepared by acidic methanolysis of olivomycin A and chromatographic purification.[54b] It is noteworthy that olivin decomposes rapidly even upon storage at -20 °C, presumably due to air oxidation. The measurement of the optical rotation proved to be indicative of the rapid rate of decomposition: older samples exhibited reduced rotation. For example a sample that was stored

for 2 weeks had a rotation of $[\alpha]_D^{25}$ -20° (c 0.04, EtOH), with a rotation reversed relative to olivin. Examination of this material by TLC revealed a mixture of materials had formed.

In summary, a highly stereoselective synthesis of the natural enantiomer of olivin has been accomplished. This also happens to be the first synthesis of olivin in unprotected form.

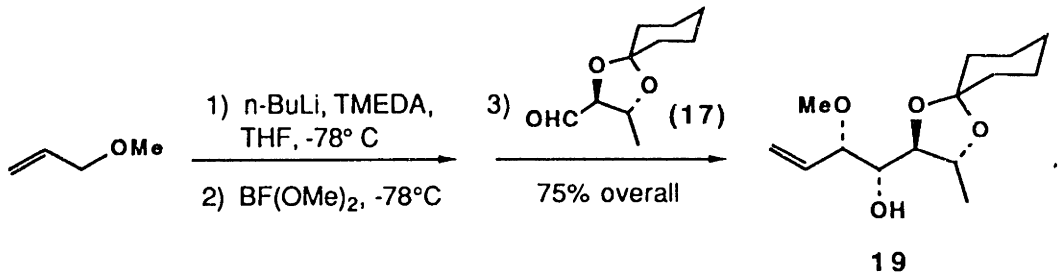
The completion of a total synthesis of olivomycin A is a project of great interest in these laboratories. In order to complete such a synthesis, sufficient amounts of olivin must be available to develop technology for constructing the five glycosidic bonds with acceptable levels of yield and stereoselectivity. Olivin and olivomycin A itself, however, are not readily available to members of the academic community. Commercial sources of olivomycin A are prohibitively expensive ($13.45 per mg, Sigma). Thus, we hope that this synthetic route will prove useful for preparing the olivin needed for the glycosidation studies.

EXPERIMENTAL SECTION

Proton (^1H) NMR spectra were measured at 250 MHz on a Bruker WM 250 instrument and at 300 and 400 MHz on a Varian XL-300 and XL-400. Chemical shifts are reported in δ units using the 7.26 ppm resonance of residual chloroform or the 1.93 ppm resonance of residual acetonitrile as internal reference. Infrared spectra were measured on Perkin-Elmer Model 283B or 237B infrared spectrophotometers calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 or a Finnegan MAT 8200 instrument. High-resolution mass spectra were measured at 70 eV on the Finnegan MAT 8200. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Autopol III or a Perkin-Elmer Model 241 polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Elemental analyses were performed by either Robertson Laboratory, Inc., of Florham Park, New Jersey or Midwest Microlab, Inc., of Indianapolis, Indiana.

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, benzene, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2.

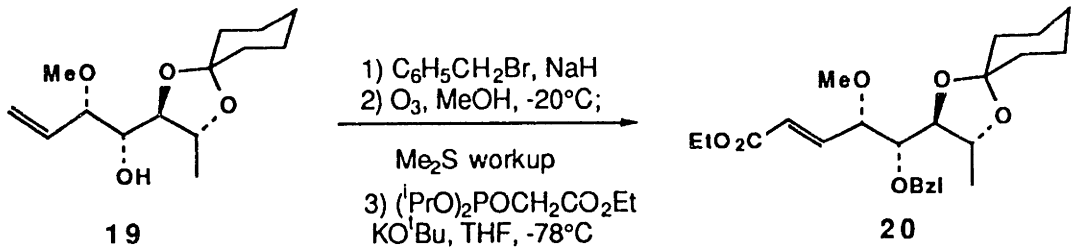
Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with a 0.25 mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography (PTLC) was performed by using 20 cm x 20 cm plates coated with 0.25 or 0.5 mm thickness of silica gel containing PF 254 indicator (Analtech). Flash chromatography was performed as described by Still,[57] using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh). Compounds were visualized by charring with ethanolic vanillin/H_2SO_4, phosphomolybdic acid, or p-anisaldehyde/H_2SO_4, or by staining with iodine vapor.



19

Preparation of Homoallylic Alcohol 19.

A -78 °C solution of 19.6 g (160 mmol) of TMEDA in 100 mL of dry THF was treated successively with 80 mL of n-BuLi (2.0 M solution in hexane, 160 mmol) and 11.52 g (160 mmol) of methyl allyl ether. The resulting yellow solution was stirred at -78 °C for 1 h and then treated with 27.52 g (160 mmol) of freshly distilled fluorodimethoxyborane. The reaction mixture was allowed to warm over a period of 1 h to 0 °C, stirred at this temperature for another hour and then recooled to -78 °C. A solution of 13.0 g (70 mmol) of aldehyde **17** in 5 mL of dry THF was then added and the resulting mixture was slowly warmed up to room temperature. After being stirred overnight, the reaction mixture was poured into saturated aq. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and purified by flash chromatography (silica gel, 20% ether-hexane) to afford 27.0 g (75%) of **19** as white needles: R_f 0.15 (20% ether-hexane); m.p. 6l-62°C; $[\alpha]_D^{\beta}$ +32.0° (c 0.30, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 5.81 (ddd, J = 2.3, 6.1, 12.2 Hz, 1H), 5.34 (d, J = 2.3 Hz, 1H), 5.30 (d, J = 12.2 Hz, 1H), 4.11 (m, 1H), 3.78 (dd, J = 2.9, 7.2 Hz, 1H), 3.58 (t, J = 7.7 Hz, 1H), 3.45 (dt, J = 2.9, 7.7 Hz, 1H), 3.33 (s, 3H), 2.30 (d, J = 7.7 Hz, 1H), 1.68-1.43 (m, 10H), 1.34 (d, J = 7.4 Hz, 3H); IR (CH_2Cl_2) 3560, 2920, 1450, 1370, 1110, 1095, 940 cm^{-1}; mass spectrum m/e 256 (parent ion). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.35.



19 **20**

70% overall

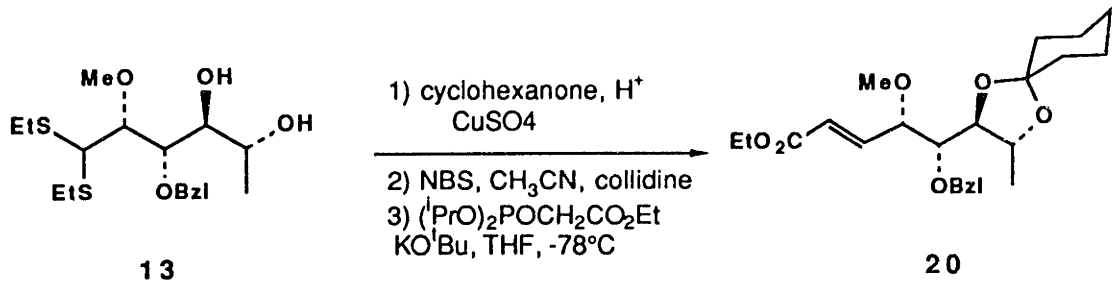
Preparation of α,β-Unsaturated Ester 20.

Method A: To a stirred suspension of NaH (hexane washed; 339 mg of a 50% by weight dispersion in oil, 7.04 mmol) in DME (10 mL) was added dropwise a solution of alcohol **19** (0.90 g, 3.5 mmol) in DME (25 mL). The resultant orange suspension was heated to reflux for 30 min, treated with benzyl bromide (0.84 mL, 7.0 mmol, 2 equiv), refluxed for another 30 min, and then allowed to cool to room temperature. The mixture was carefully partitioned between Et_2O (50 mL) and saturated aqueous NH_4Cl (50 mL). The aqueous layer was separated and extracted with Et_2O (25 mL). The combined ethereal layers were washed with brine (35mL), diluted with CH_2Cl_2 (100 mL), dried over Na_2SO_4 and evaporated to give a yellow-orange oil which was purified upon Kugelrohr distillation. The desired benzyl ether was isolated as a pale yellow oil, 1.16 g (95% yield): b.p. 140-146° (1.7 Torr); $[\alpha]_D^{25}$ + 2.2 (c 0.78, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.93-7.65 (m, 5H), 5.32 (d,J = 15.6 Hz, 1H), 5.27 (d, J = 9.2 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 4.58 (d, J = 11.1 Hz, 1H), 4.04 (m, 1H), 3.78 (m, 2H), 3.52 (dd, J = 3.6, 6.4 Hz, 1H), 3.32 (s, 3H), 1.93-1.48 (m, 10H), 1.28 (d, J = 6.0 Hz, 3H); IR (neat) 2950, 2890, 1445, 1360, 1275, 1160, 1090 cm^{-1}; mass spectrum m/e 346 (parent ion).

A -20 °C solution of the benzyl ether (300 mg, 0.79 mmol) and a drop of 0.1% Sudan III in dry CH_2Cl (10 mL) was treated with a stream of ozone (0.9 mmol/min) until no color remained. The reaction was allowed to warm to room temperature, and the ozonide was carefully quenched by dropwise addition of dry

dimethylsulfide (10 mL). After 6.5 h at room temperature, the aldehyde was concentrated *in vacuo* to a red oil, which was subsequently azeotropically dried from benzene: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.45-7.22 (m, 5H), 4.58 (d, J = 11.5 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.05 (m, 1H), 3.95-3.75 (m, 3H), 3.58 (s, 3H), 1.72-1.53 (m, 10H), 1.32 (d, J = 5.5Hz, 1H).

To a suspension of KH (0.14 g of a 35% by weight dispersion, 1.2 mmol) in THF (5mL) at 0 °C was added a solution of diisopropyl ethoxycarbonylmethyl-phosphonate (496 mg, 1.96 mmol) in THF (5 mL). After one hour at 0 °C, the red solution was cooled to -78 °C and added via cannula to a solution of the above aldehyde in THF (15 mL) at -78 °C. The mixture was allowed to slowly warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted into Et_2O (3x15 mL). The combined ethereal layers were washed with 1M NaOH (2x15 mL) and brine (3x10 mL) and dried over Na_2SO_4. After removal of solvent *in vacuo* the residue was purified by flash chromatography (silica gel, 20% ether-hexane) to yield 270 mg (68%) of (E)-α, β-unsaturated ester **20** as a single olefin isomer: R_f 0.26 (20 % ether-hexane); $[\alpha]_D^{25}$ + 21.5° (c 0.77, CH_2Cl_2); ^{1}H NMR (270 MHZ, $CDCl_3$) δ 7.40-7.25 (m, 5H), 6.99 (dd, J = 5.6, 15.7 Hz, 1H), 6.12 (dd, J = 1.6, 15.7 Hz, 1H), 4.67 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 4.25 (q, J = 7.3 Hz, 2H), 4.09-3.98 (m, 2H), 3.76 (t, J = 7.7 Hz, 1H), 3.52 (dd, J = 3.2, 7.7 Hz, 1H), 3.40 (s, 3H), 1.70-1.20 (m,10H), 1.32 (t, J = 7.3 Hz, 3H), 1.30 (d, J = 7.7 Hz, 3H); IR (neat) 2935, 2850, 1720, 1450, 1365, 1275, 1165, 1100 cm^{-1}; mass spectrum m/e 418 (parent ion). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.18. Found C, 68.88; H, 8.48.



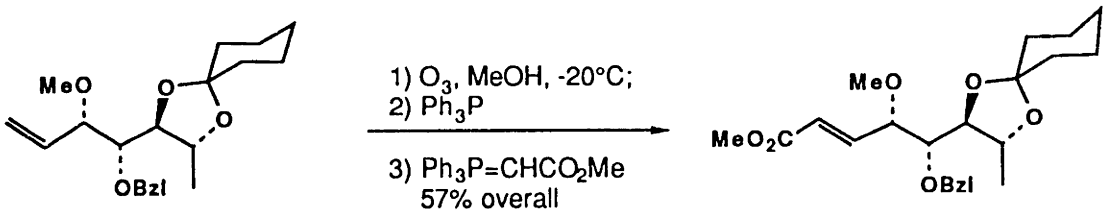
13 **20**

51% overall

Method B: A solution of diol **13** (35 mg, 0.09 mmol) in dioxane (2ml) was treated successively with cyclohexanone (0.03 mL, 2.8 mmol), $CuSO_4$ (0.1 g) and a catalytic amount (~ 0.002 mL) of H_2SO_4. After being stirred at room temperature for 3 h the reaction mixture was diluted with $CHCl_3$, and filtered through glass fritted funnel. The filtrate was washed with saturated aq. $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC (5% EtOAc-hexane) to give 32 mg (75%) of the cyclohexyl ketal : R_f 0.34 (5% EtOAc-hexane); $[\alpha]_D^{25}$ -23.3° (c 0.67, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 4.85 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.13 (d, J = 7.3 Hz, 1H), 4.11-4.02 (m, 2H), 3.75 (d, J = 8.5 Hz, 1H), 3.62 (dd, J = 4.0, 7.3 Hz, 1H), 2.76-2.67 (m, 4H), 1.59 (m,10H), 1.40-1.24 (m, 6H); IR (CH_2Cl_2) 3020, 2915, 2860, 1600, 1490, 1445, cm^{-1}; mass spectrum m/e 454 (parent ion).

A solution of the cyclohexyl ketal (370 mg, 0.81 mmol) in CH_3CN (5mL) was added dropwise to a 0 °C solution of NBS (0.6 g, 3.2 mmol) and collidine (1.3 mL, 9.8 mmol) in CH_3CN (10mL). After being stirred for 5 minutes at 0 °C the reaction mixture was partitioned between saturated aq. Na_2SO_3 and CH_2Cl_2. The organic layer was repeatedly washed with saturated aq. $Cu(NO_3)_2$ (6x5mL). The aqueous phase was back extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford crude aldehyde **7** (278 mg) which was immediately redissolved in dry THF (5 mL). The aldehyde

solution was then added dropwise via cannula to a -78 °C solution of freshly prepared $(iPrO)_2POCHKCO_2Et$ (2.2 mmol) in THF (5 mL). The reaction was then worked up as previously described for preparation of **20** from **19**. The residue was purified by flash chromatography (silica gel, 10% EtOAc-hexane) to yield 240 mg (72% for 2 steps) of α,β-unsaturated ester **20** as a single olefin isomer. The ester, so obtained, was found to be identical by all standard means of comparison to the ester prepared via method A.

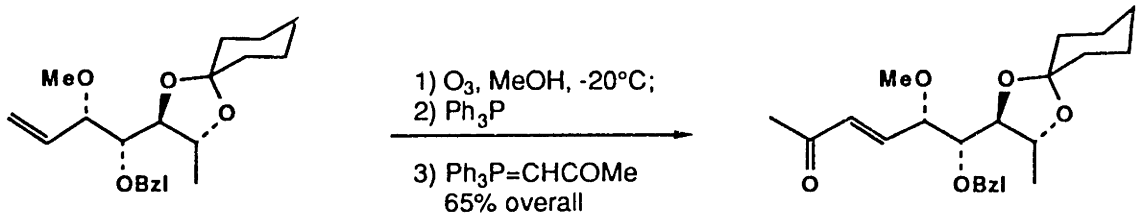


20b

Preparation of α,β-Unsaturated Ester 20b.

A -20 °C solution of the benzyl ether (0.97 g, 2.8 mmol) and a catalytic amount of Sudan III in CH_2Cl_2 (15 mL) was treated with a stream of ozone until no color remained. To the resultant solution was added triphenylphosphine (1.0 g, 3.8 mmol) and the reaction mixture was allowed to warm to room temperature over 20 min, it was then treated with methyl (triphenylphoshoranylidene) acetate (2.0 g, 6.0 mmol) and benzoic acid (30 mg). After being stirred for 24 h, the reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography (silica gel, 10% ether-hexane) to give 0.64 (57%) of the (E)-ester **20b** and 0.13 g (12%) of the (Z)-α,β-unsaturated ester.

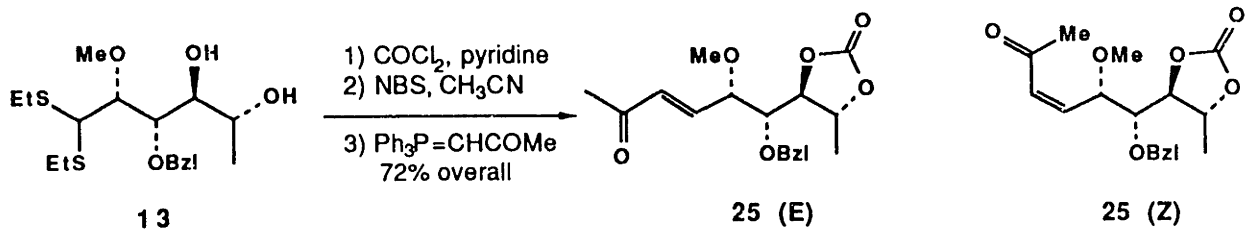
Data for **20b(E)**: R_f 0.36 (20% EtOAc-hexane); $[\alpha]_D^{25}$ + 25.4° (c 3.91, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.32-7.29 (m, 5H), 6.96 (dd, J = 5.7, 15.8 Hz, 1H), 6.13 (dd, J = 1.1, 15.8 Hz. 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.06-4.00 (m, 2H), 3.77 (s, 3H), 3.73 (m, 1H), 3.53 (dd, J = 3.4, 7.6Hz, 1H), 3.40 (s, 3H), 1.70-1.47 (m, 10H), 1.30 (d, J = 6.0 Hz, 3H); IR (neat) 2925, 2850, 1725, 1445, 1170, 1090 cm^{-1}; mass spectrum m/e 404 (parent ion).



23

Preparation of Enone 23.

A sample of the benzyl ether (2.0 g, 5.77 mmol) was subjected to the ozonolysis procedure described for preparation of **20b**. The aldehyde so obtained was treated with 1-triphenylphosphoranylidene-2-propanone (3.7 g, 11.54 mmol), also under conditions as described for preparation of **20b** to afford after workup and purification via flash chromatography (silica gel, 15% EtOAc-hexane) 1.45 g (65%) of enone **23**, which was geometrically pure: R_f 0.18 (15% EtOAc-hexane); $[\alpha]_D^{25}$ + 25.9° (c 1.20, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 6.79 (dd, J = 6.4, 17.0 Hz, 1H), 6.33 (dd, J = 1.0, 17.0 Hz, 1H), 4.67 (d, J = 10.5 Hz, 1H), 4.58 (d, J = 10.5 Hz, 1H), 4.12-3.99 (m, 2H), 3.78 (t, J = 7.8 Hz, 1H), 3.56 (dd, J = 3.5, 7.8 Hz, 1H), 3.41 (s, 3H), 2.26 (s, 3H), 1.78-1.50 (m, 10H), 1.33 (d,J = 7.8 Hz, 3H); IR (neat) 2945, 2865, 1680, 1625, 1445, 1355, 1265, 975, 940 cm^{-1}; mass spectrum m/e 388 (parent ion).



13 25 (E) 25 (Z)

Preparation of 25 (E) and 25 (Z) from 13.

Phosgene was bubbled through a 0 °C solution of diol **13** (1.48 g, 3.9 mmol) in pyridine (15 mL). After being stirred for 50 minutes at 0 °C, the mixture was carefully poured onto a cold mixture of water and CH_2Cl_2. The aqueous layer was further extracted with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4 and concentrated to give 1.58 g (100%) of carbonate that was pure enough to be used in the next step without further purification: R_f 0.65 (30% EtOAc-hexane); $[\alpha]_D^{25}$ -8.9° (c 0.54, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.37-7.31(m, 5H), 4.87 (d, J = 11.2 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.62 (m, 1H), 4.62 (m, 1H), 4.35 (dd, J = 5.4, 5.4 Hz, 1H), 4.29 (dd, J = 3.4, 5.8 Hz, 1H), 4.05 (d, J = 7.3 Hz, 1H), 3.61 (s, 3H), 3.49 (dd, J = 3.4, 7.3 Hz, 1H), 2.85-2.65 (m, 4H), 1.44 (d, J = 5.8 Hz, 3H), 1.28 (t, J = 3 Hz, 6H); IR (CH_2Cl_2) 2960, 2925, 1800, 1490, 1450 cm^{-1}; mass spectrum m/e 400 (parent ion). Anal. Calcd for $C_{19}H_{28}O_5S_2$: C, 56.97; H, 7.04. Found: C, 56.81; H, 7.26.

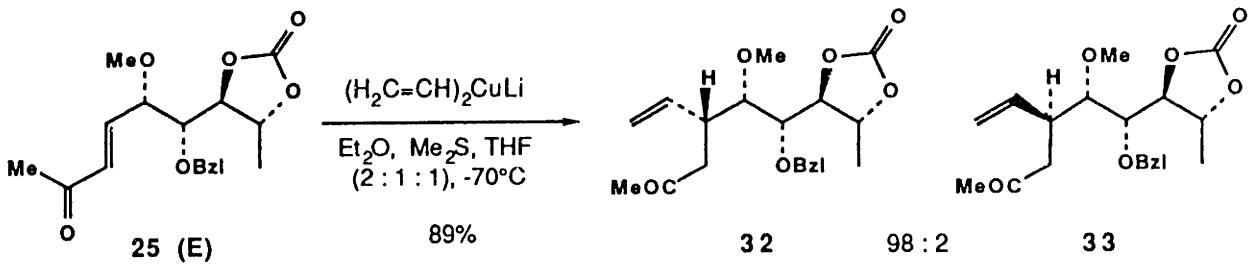
A 0 °C solution of the above carbonate (0.46 g, 0.12 mmol) in CH_3CN (9mL) was successively treated with $NaHCO_3$ (0.49 g) and NBS (0.83 g, 0.48 mmol). The colorless mixture was stirred for 5 min and then poured into a cold mixture of saturated aq Na_2SO_3, CH_2Cl_2 and hexane. After separating the two phases, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were combined and extracted several times with $CHCl_3$ until TLC analysis revealed no aldehyde was left in the aqueous layer. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 0.36 g

(100%) of crude aldehyde which was used without any further purification in the next experiment: ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.39-7.24 (m, 5H), 4.74 (dq, J = 6.0, 6.0 Hz, 1H), 4.55 (s, 2H), 4.39 (dd, J = 5.4, 5.4 Hz, 1H), 4.16 (dd, J = 3.0, 5.4 Hz, 1H), 3.79 (d, J = 3.0 Hz, 1H), 1.45 (d, J = 6.3Hz, 3H); IR (CH_2Cl_2) 3400, 3050, 2980, 1800, 1750, 1700, cm^{-1}.

A solution of the crude aldehyde (0.36 g) in dry CH_2Cl_2 (4 mL) was treated with 1-triphenylphosphoranylidene-2-propanone (0.37 g, 0.12 mmol) and stirred at room temperature for 4.5 h. After removal of solvent the residue was directly purified by column chromatography (silica gel, 40% EtOAc-hexane) to afford 240 mg (62%) of ester **25(E)** and 42 mg (11%) of **25(Z)**.

Data for **25(E)**: R_f 0.42 (40% EtOAc-hexane); m.p 71-73 °C; $[\alpha]_D^{25}$ + 29.5° (c 0.8, CH_2Cl_2); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5H), 6.70 (dd, J = 5.8, 16.1 Hz, 1H), 6.30 (dd, J = 1.5, 16.1 Hz, 1H), 4.74 (d q, J = 5.0, 6.4 Hz, 1H), 4.65 (s, 2H), 4.38 (dd, J = 4.0, 5.4 Hz, 1H), 3.95 (ddd, J = 1.5, 4.0, 5.8 Hz, 1H), 3.83 (dd, J = 4.0, 4.0 Hz, 1H), 3.33 (s, 3H), 2.25 (s,3H), 1.43 (d, J = 6.3 Hz, 3H); IR (CH_2Cl_2) 3025, 2935, 1800, 1695, 1675, 1630, 1450, 1360, CM^{-1}; mass spectrum m/e 334 (parent ion). Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found C, 64.64; H, 6.91.

Data for **25(Z)**: R_f 0.60 (40% EtOAc-hexane); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H), 6.27 (d, J = 11.7 Hz, 1H), 6.08 (dd, J = 7.8, 11.7 Hz,1H), 4.97 (dq, J = 6.0, 6.0 Hz, 1H), 4.80 (m. 1H), 4.66 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.41 (dd, J = 2.9, 5.6 Hz, 1H), 4.06 (t, J = 3.0 Hz, 1H), 3.23 (s, 3H), 2.24 (s, 3H), 1.35 (d, J = 6.3 Hz, 3H); IR (CH_2Cl_2) 3050, 2930, 1800, 1690, 1620, 1450, 1400, 1375, 1350 cm^{-1}.

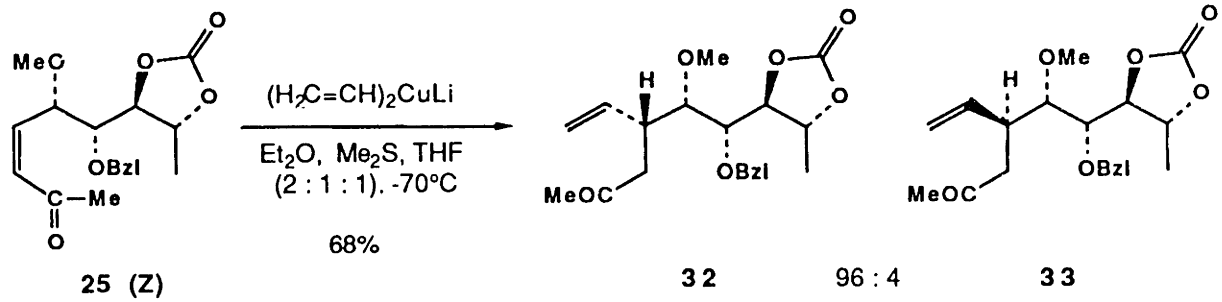


Reaction of 25 with $(H_2C=CH)_2CuLi$.

To a - 65 °C solution of CuBr-Me_2S (0.20 g, 0.99 mmol) in ether (5 mL) and Me_2S (5 mL) was added vinyllithium (5 mL, 0.36 M in THF, 1.8 mmol). The mixture was stirred at -65 °C to -70 °C for 0.75 h and then treated with a solution of enone **25**(E) (0.15 g, 0.45 mmol) in ether (5 mL). After being stirred at - 65 °C for 1 h and an additional 0.5 h at - 45 °C the reaction mixture was poured onto a cold mixture of ether and saturated aq NH_4Cl. Aq NH_4OH was then added and the resulting mixture was stirred until a homogeneous organic phase and a dark blue aqueous layer were obtained. The two layers were separated, the aqueous layer was further extracted with ether and the combined organic extracts were washed with brine, dried over $MgSO_4$, concentrated and purified by column chromatography (silica gel, 40% EtOAc-hexane) to provide 140 mg (86%) of **32** and 3 mg (2%) of **33**.

Data for **32**: $[\alpha]_D^{25}$ - 15.6° (c 1.01, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.45-7.30 (m, 5H), 5.76 (ddd, J = 8.6, 10.6, 17.0 Hz, 1H), 5.3-5.08 (m, 2H), 4.74 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 11.0 Hz, 1H), 4.65 (m, 1H), 4.35 (dd, J = 5.4, 5.4 Hz, 1H), 3.80 (dd, J = 3.5, 5.9 Hz, 1H), 3.23 (dd, J = 3.4, 7.8 Hz, 1H), 3.09 (m, 1H), 2.74 (dd, J = 4.9, 16.6 Hz, 1 H), 2.53 (dd, J = 8.3, 16.6 Hz, 1H), 2.13 (s, 3H), 1.46(d, J = 6.0 Hz, 3H); IR (CH_2Cl_2) 3060, 2920, 1800, 1710, 1635, 1495, 1450, 1370, 1360 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6$: C, 66.27; H, 7.23. Found: C, 66.04; H, 7.32.

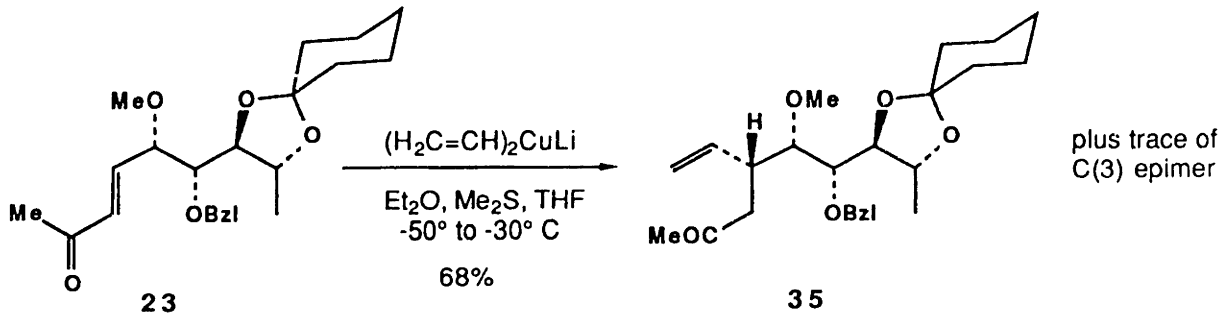
Data for **33**: $[\alpha]_D^{25}$ + 23.2 (c 0.41, CH_2Cl_2); ^1H NMR (270 MHz, $CDCl_3$) δ 7.42 - 7.30 (m, 5H), 5.80 (ddd, J = 8.7, 10.1, 17.5 Hz, 1H), 5.15 (m, 2H), 4.93 (dq, J = 6.4, 6.4 Hz, 1H), 4.70 (s, 2H), 4.36 (dd, J = 2.4, 5.3 Hz, 1H), 3.84 (dd, J = 2.4. 7.4 Hz, 1H), 3.44 (s, 3H), 3.21 (dd, J = 3.0, 7.4 Hz, 1H), 2.90 (dd, J = 7.7, 17.1 Hz, 1H), 2.75 (m, 1H), 2.51 (dd, J = 4.4, 17.1 Hz, 1H), 2.12 (s, 3H), 1.55 (d, J = 6.4 Hz,3H).



25 (Z) **32** **33**

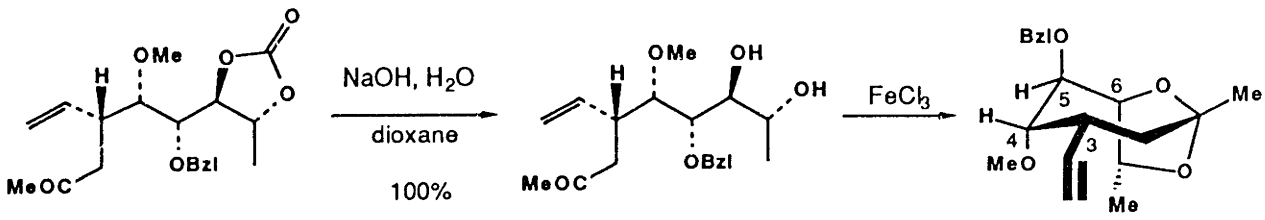
Addition of Vinylcuprate to 25 (Z).

A sample of **25**(Z) (39 mg, 0.12 mmol) was treated with divinylcuprate as described for **25**(E). The reaction afforded 26 mg (65%) of **32** and 1.5 mg (3%) of **33**.



Preparation of 35 from 23.

To a -55 °C suspension of CuBr-Me_2S (1.53 g, 7.5 mmol) in Et_2O (10 mL) and Me_2S (10mL), was added vinyllithium (8.3 mL, 1.80 M in THF, 14.9 mmol) over a period of 0.5 h. This mixture was then treated with a solution of enone **23** (1.44 g, 3.7 mmol) in Et_2O (40 mL). The reaction mixture was stirred at -50 °C to -30 °C for 1 h, then poured into saturated aq. NH_4Cl (35 mL). The mixture, so obtained, was treated with 58% aq. NH_4OH (5 mL) and diluted with H_2O until a blue aq. layer was obtained. The two phases were separated and the aq. layer was extracted with Et_2O (3 x 50 mL). The combined ethereal layers were washed with saturated aq. NH_4Cl, brine, dried over K_2CO_3 and concentrated. The residue was purified by column chromatography (silica gel, 8% to 15% EtOAc-hexane) to yield 1.04 g of **35** (68% yield) plus a very small amount of the C(3) epimer: R_f 0.54 (40% EtOAc-hexane); $[\alpha]_D^{25}$ - 24.5° (c, 1.11, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.56-7.25 (m, 5H), 5.73 (ddd, J = 8.6, 10.3, 18.8 Hz, 1H), 5.11 (d, J = 10.3 Hz, 1H), 5.06 (d, J = 18.8 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.07 (m, 1H), 3.76 (t, J = 6.1 Hz, 1H), 3.57 (dd, J = 2.7, 6.1 Hz, 1H), 3.49 (s, 3H), 3.12 (dq, J = 2.7, 6.1 Hz, 1H), 2.76 (dd, J = 5.0, 15.9 Hz, 1H), 2.51 (dd, J = 8.6 , 15.9 Hz, 1H), 2.12 (s, 3H), 1.82-1.47 (m, 10H), 1.34 (d, J = 6.1 Hz, 3H); IR (neat) 2885, 2810, 1715, 1440, 1355, 1270, 1090, cm^{-1}; mass spectrum m/e 416 (parent ion).



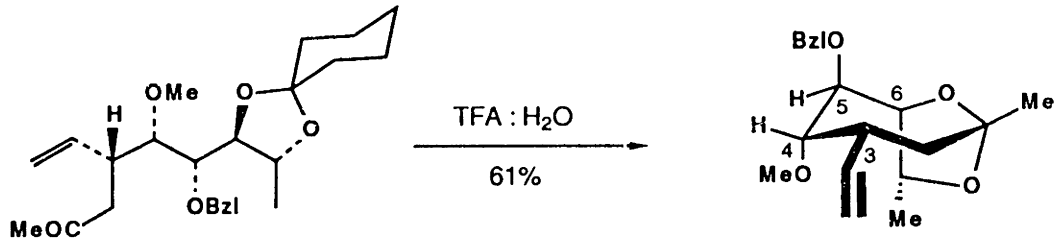
32 36 38a

Preparation of Bicyclic Acetal 38a from 32.

A 0 °C solution of the Michael adduct **32** (80 mg, 0.22 mmol) in water (0.3 mL) and dioxane (0.3 mL) was treated with 0.5 M aq. NaOH (1 mL) and the resulting mixture was stirred for 1 h, then neutralized with 5N HCl. The mixture was partitioned between $CHCl_3$ and H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 73 mg (quantative yield) of diol **36**, which was used in the following step without any further purification: ^1H NMR (250 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 5.77 (m, 1H), 5.04 (m, 2H), 4.66 (s, 2H), 3.97 (m, 1H), 3.70-3.60 (m, 2H), 3.42 (s, 3H), 3.45 (m, 1H), 3.11 (m, 1H), 3.00 (m, 1H), 2.75 (dd, J = 5.5, 16.2 Hz, 1H), 2.50 (dd, J = 8.1, 15.8 Hz, 1H), 2.23 (m, 1H), 2.11 (s, 3H), 1.24 (d, J = 6.8 Hz, 3H).

To a solution of diol **36** (61 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added $FeCl_3$ (~ 20 mg) and the resulting mixture was stirred at room temperature for 20 minutes. Addition of saturated aq. $NaHCO_3$ followed by extraction with CH_2Cl_2, drying over $MgSO_4$, removal of solvent and purification via preparative TLC (15% EtOAc-hexane) provided 48 mg (84%) of acetal **38a**: R_f 0.65 (20% EtOAc-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-7.25 (m, 5H), 5.97 (ddd, J = 8.0, 9.9, 17.0 Hz, 1H), 5.12 (d, J = 17.0 Hz, 1H), 5.03 (d,J = 9.9 Hz, 1H), 4.67 (s, 2H), 4.30 (d q, J = 2.3, 6.3 Hz, 1H), 4.17 (dd, J = 1.6, 3.5 Hz, 1H), 3.53 (dd, J = 1.6, 3.5 Hz, 1H), 3.46 (m, 1H), 3.34 (s, 3H), 2.97 (m, 1H), 2.10 (dd, J = 11.0, 14.6 Hz, 1H), 1.85 (dd, J =

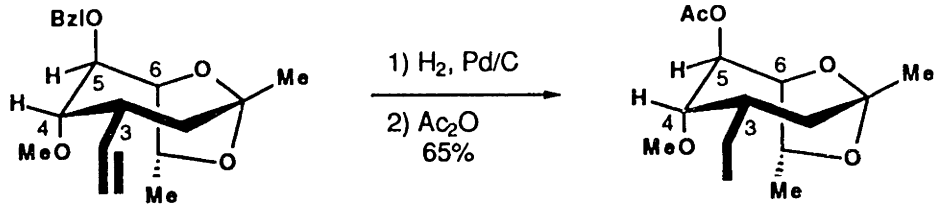
5.3, 14.6 Hz, 1H) 1.48 (s, 3H), 1.18 (d, J = 6.3 Hz, 1H); IR (CH_2Cl_2) 3070, 3030, 1450, 1375, 1230, 1200, 1030 cm^{-1}; mass spectrum m/e 318 (parent ion).



35 **38a**

Preparation of acetal 38a from 35.

Cyclohexylidene ketal **35** (139 mg, 0.337 mmol) was dissolved in 98:2 TFA-H_2O (10 mL) at 0 °C. After 45 minutes the resultant yellow solution was carefully poured into saturated aq. $NaHCO_3$ (200 mL) and extracted into Et_2O (3 x 30 mL). The combined ethereal layers were diluted with CH_2Cl_2 (50 mL), dried over Na_2SO_4 and evaporated to give a green oil. Pure ketal **38a** was obtained after two successive flash column chromatographic separations, with 5% EtOAc-benzene and CH_2Cl_2, respectively. In this manner 65 mg (61.0% yield) of **38a** was isolated as a pale yellow oil.



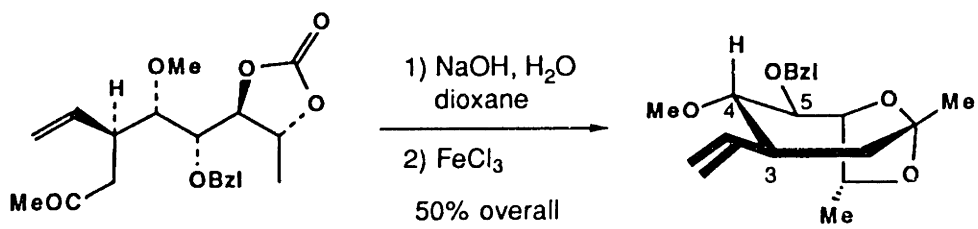
38a **38b**

Preparation of 38b.

To a solution of **38a** (37 mg, 0.12 mmol) in absolute EtOH (2 mL) was added 20% $Pd(OH)_2$/Carbon (8 mg) and the resulting mixture was placed under a

hydrogen atmosphere (40 psi) and shaken for 3.5 h. After removing the catalyst via filtration through Celite, the filtrate was concentrated to give 28 mg (98%) of the corresponding alcohol: R_f 0.30 (20% EtOAc-hexane); m.p. 95.5-96.5 °C; $[\alpha]_D^{25}$ + 65.9° (c 0.47, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 4.35 (dq, J = 3.9, 6.0 Hz, 1H), 4.12 (m, 1H), 3.82 (m, 1H), 3.42 (s, 3H), 3.41 (m, 1H), 2.38 (m, 1H), 1.99-1.68 (m, 3H), 1.48 (s, 3H), 1.42-1.36 (m, 2H), 1.24 (d, J = 6.1 Hz, 3H), 0.92 (t, J = 7.3 HZ, 3H); IR 3570, 2930, 1750, 1600, 1460, 1375; mass spectrum m/e 230 (parent ion).

A mixture of the alcohol (9 mg, 0.04 mmol), Ac_2O (0.1 mL) and pyridine (0.1 mL) were stirred at room temperature for 5.5 h. After removal of volatiles, the residue was purified by preparative TLC (15% EtOAc-hexane) to give 7 mg (65%) of acetate **38b**: R_f 0.57 (20% EtOAc-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 5.06 (d q, J = 1.7, 3/5 Hz, 1H), 4.40 (d q, J = 2.3, 6.3 Hz, 1H), 4.08 (dd, J = 1.8, 3.7 Hz, 1H), 3.42 (s, 3H), 3.33 (dd, J = 1.7, 3.5 Hz, 1H), 2.13 (s, 3H), 2.10-1.75 (m, 3H), 1.50 (s, 3H), 1.39 (d, J = 6.3 Hz, 3 H), 1.48-1.15 (m, 2H), 0.9 (t, J = 7.4 Hz, 3H).

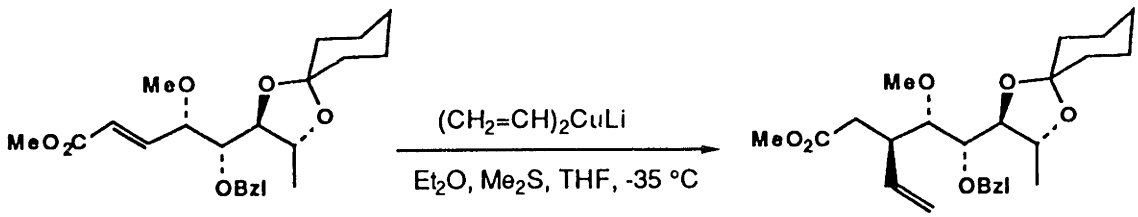


33 **39**

Preparation of bicyclic acetal 39.

A sample of **33** (6.8 mg, 0.02 mmol) was hydrolyzed to diol **37**, as described for the preparation of **38a**. The diol underwent intramolecular ketalization upon treatment with $FeCl_3$ in CH_2Cl_2 to give 3.0 mg (50%) of acetal **39**: R_f 0.56 (20% EtOAc-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.75 (ddd, J = 8.5, 10.2, 17.1 Hz, 1H), 5.07-5.00 (m, 2H), 4.72 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 11.7 Hz,

1H), 4.15 (dq, J = 3.0, 6.1 Hz, 1H)< 4.02 (d, J = 2.9 Hz, 1H), 3.50 (s, 3H), 3.46 (d, J = 7.5 Hz, 1H), 3.37 (dd, 7.5, 10.2 Hz, 1H), 2.56 (m, 1H)< 1.82 (dd, J = 3.4, 14.2 Hz, 1H), 1.68 (m, 1H), 1.45 (s, 3H), 1.16 (d, J = 6.1 Hz, 3H); mass spectrum m/e 318 (parent ion).



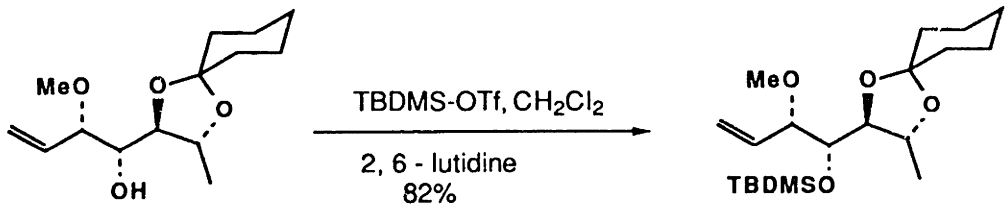
20b **40b**

Addition of Vinylcuprate to Enoate 20b.

To a flask charged with Argon and CuBr.Me_2S (1.23 g, 5.94 mmol) was added freshly distilled Me_2S (5 mL) and Et_2O (5 mL). The resultant yellow solution was cooled to -55 °C, whereupon the resultant white suspension was treated with a solution of vinyllithium in THF (6.8 mL of 1.76 M), which was added dropwise over 40 minutes with the aid of a syringe pump. To the resultant blue-black suspension was added a solution of α,β-unsaturated ester **20b** (400 mg, 1.0 mmol) in Et_2O at -40 °C over 3 minutes via cannula. After 60 minutes at -40 °C the greenish-black suspension was stirred with 9:1 saturated aq. NH_4Cl : 58% NH_4OH (25 mL) and H_20 (300 mL) for 60 minutes, until two discrete layers were obtained. The aq. layer was separated, saturated with NaCl and extracted with Et_2O (2 x 25 mL). The organic layers were washed with saturated aq. NH_4Cl (2 x 25 mL), dried over K_2CO_3 and evaporated to give after purification via flash column chromatography (silica gel, ether-hexane) 166.0 mg (39%) of **40** and 11.0 mg (3% yield) of its (C)3 epimer.

Data for **40**: $[\alpha]_D^{25}$ - 15.9° (c 2.16, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-7.23 (m, 5H), 5.78 (ddd, J = 8.3, 9.1, 16.2 Hz, 1H), 5.16 (d, J = 9.1 Hz, 1H), 5.13 (d, J = 16.2 Hz, 1 H), 4.74 (d, J = 11.5 Hz, 1H), 4.58 (d,J = 11.5 Hz, 1H), 4.06 (m, 1H), 3.76 (t, J = 6.7 Hz, 1H), 3.75 (s, 3H), 3.57 (dd, J = 1.2, 6.7 Hz, 1H), 3.52 (s, 3H), 3.42 (dd, J = 1.2, 6.7 Hz , 1H), 3.11 (dq, J = 6.7, 9.1 Hz, 1H), 2.76 (dd, J = 6.7, 15.0 Hz, 1H), 2.43 (dd, J = 9.1, 15.0 Hz, 1H), 1.75-1.39 (m, 10H), 1.23 (d,J = 6.7 Hz,3H); IR (neat) 2935, 2855, 1740, 1450, 1360, 1275, 1165, 1080 cm^{-1}; mass spectrum m/e 432 (parent ion).

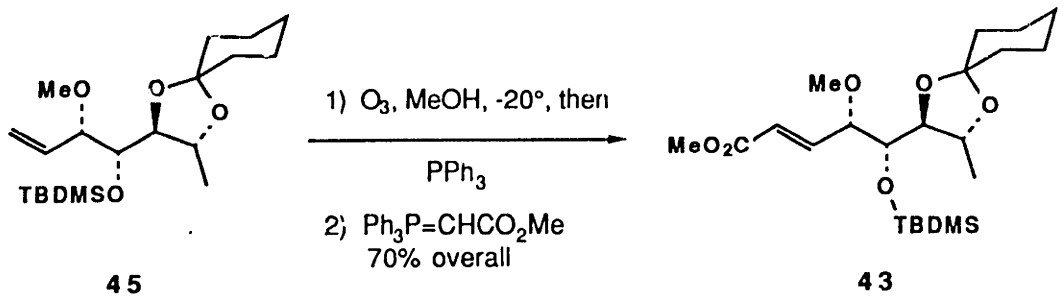
Data for **C(3) epimer** of **40**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.43 (m, 5H), 5.88 (ddd, J = 7.9, 8.7, 17.8 Hz, 1H), 5.19 (d, J = 8.7 Hz, 1H), 5.15 (d, J = 17.8 Hz, 1 H), 4.76 (d, J = 13.9 Hz, 1H), 4.69 (d,J = 13.9 Hz, 1H), 4.17 (m, 1H), 3.77-3.66 (m, 1H), 3.67 (s, 3H), 3.53 (s, 3H), 3.32 (dd, J = 4.4, 6.3 Hz, 1H), 3.06-2.93 (m, 2H), 2.65 (dd, J = 6.7, 15.0 Hz, 1H), 2.48 (dd, J = 7.1, 15.0 Hz, 1H), 1.83-1.50 (m, 10H), 1.35 (d, J = 7.1 Hz,3H); IR (neat) 2925, 2860, 1735, 1445, 1365, 1165, 1100, 940 cm^{-1}.



19 **45**

Preparation of Silyl Ether 45.

To a solution of 25.6 g (100 mmol) of alcohol **19** and 26.8 mL (250 mmol) of 2,6-lutidine in 150 mL of dry CH_2Cl_2 was added 31.7 mL (120 mmol) of TBDMS-OTf. After being stirred at room temperature overnight, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, 10% ether-hexane) to afford 30.2 g (82%) of **45**: R_f 0.38 (10% ether-hexane); $[\alpha]_D^{22}$ +1.8° (c 1.7, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.23 (m, 2H), 4.14 (dq, J = 7.2, 7.2 Hz, 1H), 3.82 (dd, J = 5.6, 7.2 Hz, 1H), 3.67 (dd, J = 5.6, 7.6 Hz, 1H), 3.47 (t, J = 7.6 Hz, 1H), 3.24 (s, 3H), 1.56 (s, 10H), 1.27 (d, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); IR ($CHCl_3$) 3000, 2915, 2850, 1470, 1460, 1445, 1360, 1250 cm^{-1}; high resolution mass spectrum for $C_{20}H_{38}O_4Si$, calcd 370.2539, found 370.2538.



45 43

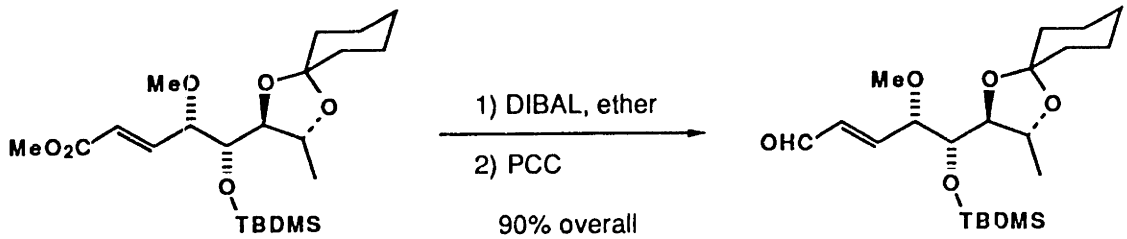
Preparation of α,β-Unsaturated Ester 43.

Ozone was bubbled into a -20 °C solution of the olefin **45** (11 g, 30 mmol) in MeOH (200 mL) and the reaction was monitored by TLC. Upon consumption of all the starting material, triphenylphosphine (6 g, 22.8 mmol) was added. The resulting mixture was stirred for 1 h at -20 °C and then allowed to warm to room temperature over a period of 2 h. MeOH was then removed by fractional distillation and the crude product was filtered through a short silica gel column using CH_2Cl_2 as eluant. The filtrate was concentrated *in vacuo* and the crude aldehyde **46** redissolved in CH_2Cl_2 (100 mL) and treated with methyl (triphenylphosphoranylidine)acetate (15 g, 44.9 mmol). The mixture was stirred overnight at room temperature, then concentrated. The residue was purified by column chromatography (silica gel, 20% ether-hexane) to yield 8.9 g (70% for two steps) of **43** as a 1.2 : 1.0 (Z) : (E) mixture of olefin isomers.

Data for **46**: R_f 0.17 (10% ether-hexane); $[\alpha]_D^{22}$ +4.6° (c 0.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.65 (d, J = 1.9 Hz, 1H), 4.08 (m, 1H), 3.94 (dd, J = 5.0, 7.0 Hz, 1H), 3.64 (t, J = 7.0 Hz, 1H), 3.57 (dd, J = 2.0, 5.0 Hz, 1H), 3.42 (s, 3H), 1.6-1.4 (br, 10H), 1.30 (d, J = 2.0 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); IR ($CDCl_3$) 2940, 2860, 2250, 1730, 1445, 1365 cm^{-1}; mass spectrum m/e 372 (parent ion); high resolution mass spectrum for $C_{19}H_{36}O_5Si$, calcd 372.2332, found 372.2335.

Data for **43** (E): Rf 0.48 (20% ether-hexane); $[\alpha]_D^{25}$ +7.4° (c 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 6.86 (dd, J = 5.8, 15.8 Hz, 1H), 6.00 (d, J = 15.8 Hz, 1H),

4.07 (m, 1H), 3.75 (m, 5H), 3.61 (dd, J = 5.6, 7.2 Hz, 1H), 3.30 (s, 3H), 1.61-1.40 (br, 10H), 1.28 (d, J = 6.0 Hz, 3H), 0.87 (s, 9H), 0.55 (s, 6H); IR ($CHCl_3$) 3005, 2930, 2850, 1720, 1470, 1460, 1450, 1435, 1280, 1250 cm^{-1}; mass spectrum m/e 428 (parent ion), 385 (13), 299 (25), 281 (25), 273 (20), 255 (62), 241 (44), 201 (20), 155 (100); high resolution mass spectrum for $C_{22}H_{40}O_6Si$, calcd 428.2595, found 428.2597.



43 49

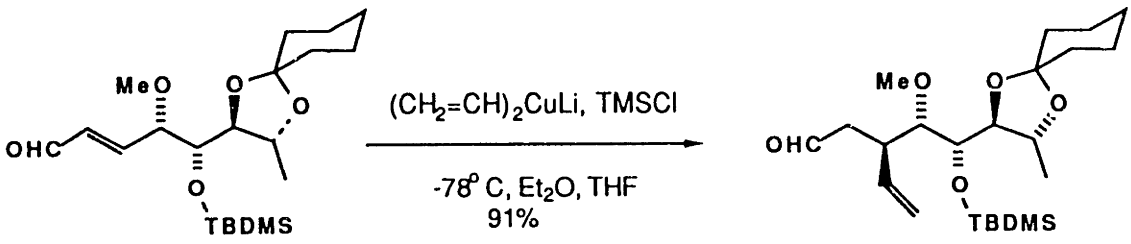
Preparation of Enal 49.

To a -78 °C solution of a mixture of cis and trans unsaturated esters **43** (9.5 g, 22.0 mmol) in dry ether (80 mL), was added DIBAL (60 mL, 1M in THF, 60.0 mmol). The mixture was stirred for 1 h, then MeOH (50 mL) was added dropwise and the resulting solution was slowly poured into cold (0 °C) 1N HCl. The aq. phase was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. Filtration and removal of solvent afforded 8.4 g (95%) of crude alcohol **48** that was used without any further purification in the following reaction.

Data for **48**: R_f 0.20 (20% ether-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.65 (m, 1H), 4.20-4.05 (m, 3H), 3.78 (t, J = 5.9 Hz, 1H), 3.64 (dd, J = 5.0, 7.4 Hz, 1H), 3.54 (t, J = 6.8 Hz, 1H), 3.27 (s, 3H), 1.57 (m, 10H), 1.29 (d, J = 6.3 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); IR (neat) 3420, 2930, 2850, 1470, 1460, 1450, 1360, 1250 cm^{-1}; mass spectrum m/e 400 (parent ion).

PCC (15 g, 69.0 mmol) was added to a solution of crude alcohol **48** (8.4 g, 21.0 mmol) in CH_2Cl_2 (150 mL) and the reaction mixture was stirred at room temperature for 15 h. The mixture was then filtered, the solids washed with ether, concentrated and directly purified by flash chromatography (silica gel, 20% ethyl acetate-hexane) to give 7.5 g (90%) of aldehyde **49** as a mixture of olefin isomers (7 : 3 trans : cis).

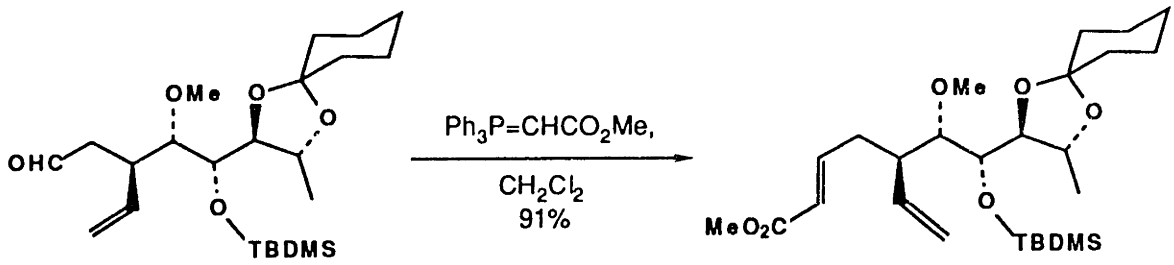
Data for **49** (E): R_f 0.45 (20% ether-hexane); $[\alpha]_D^{25}$ -4.2° (c 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.61 (d, J = 7.9 Hz, 1H), 6.80 (dd, J = 6.0, 15.8 Hz, 1H), 6.27 (dd, J = 7.0, 15.8 Hz, 1H), 4.07 (m, 1H), 3.87 (dt, J = 5.6, 6.6 Hz, 1H), 3.79 (t, J = 5.8 Hz, 1H), 3.58 (t, J = 6.6 Hz, 1H), 3.32 (s, 3H), 1.56 (s, 10H), 1.29 (d, J = 6.1 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 6H); IR ($CDCl_3$) 2940, 2860, 1680 cm^{-1}; high resolution mass spectrum for $C_{21}H_{38}O_5Si$, calcd 398.2489, found 398.2490.



49 50

Preparation of Aldehyde 50.

To a -78 °C solution of CuI (1.52 g, 8.0 mmol) in ether (60 mL) under argon was added vinyllithium (10 mL, 2.2 M in THF, 22.0 mmol) and an additional 10 mL of THF. The mixture was allowed to slowly warm to -35 °C to -40 °C, held at that temperature for 15 min and then recooled to -78 °C. This mixture was then treated with TMS-Cl (0.3 mL, 2.3 mmol) followed by a solution of aldehyde **49** (1.0 g, 2.5 mmol) in ether (10 mL). The reaction mixture was stirred at -78 °C for 10 min, then poured into saturated aq. NH_4Cl solution. The resulting mixture was stirred for 2 h and then extracted with CH_2Cl_2. The organic extracts were eluted (1:1 ether-hexane) through a silica gel column and concentrated to afford 1.0 g (91%) of aldehyde **50** which was pure enough to be used in the next step without any further purification: R_f 0.65 (1:1 ether-hexane); $[\alpha]_D^{25}$ -16.1° (c 1.20, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.58 (t, J = 2.0 Hz, 1H), 5.75 (m, 1H), 5.07 (d, J = 7.4 Hz, 1H), 5.01 (s, 1H), 4.04 (m, 1H), 3.72 (dd, J = 3.7, 7.4 Hz, 1H), 3.60 (t, J = 7.0 Hz, 1H), 3.32 (s, 3H), 3.13 (dd, J = 3.7, 6.3 Hz, 1H), 3.04 (m, 1H), 2.46 (m, 2H), 1.49 (br, 10H), 1.27 (d, J = 6.1 Hz, 3H), 0.84 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); IR ($CDCl_3$) 2950, 2840, 1730, 1640 cm^{-1}; mass spectrum m/e (rel. intensity) 426 (parent ion, 1), 398 (5), 299 (25), 271 (30), 255 (35), 239 (44), 155 (91), 73 (100).

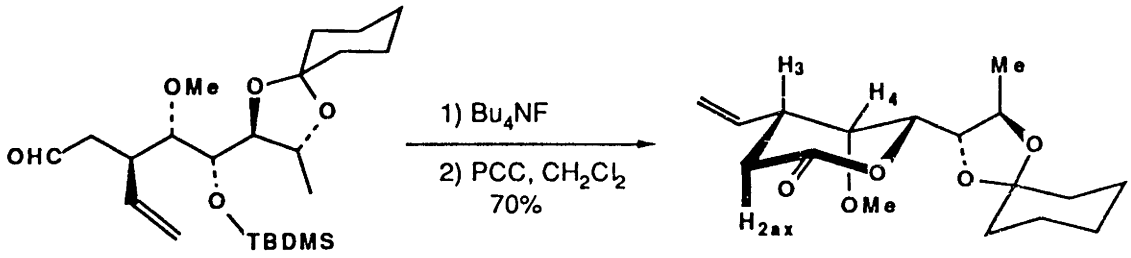


50 51

Preparation of α,β-Unsaturated Ester 51.

A solution of aldehyde **50** (1.0 g, 2.3 mmol) in CH_2Cl_2 (10 mL) and methyl (triphenylphosphoranylidine)acetate (1.0 g, 3.0 mmol) was stirred overnight at room temperarure. Workup consisted simply of filtering the mixture through a silica gel column (100 g of silica gel, 1:1 ether-hexane) and removal of solvent *in vacuo*, giving 1.1 g (91%) of a >9 : 1 mixture of olefin isomers **51** (E) and **51** (Z).

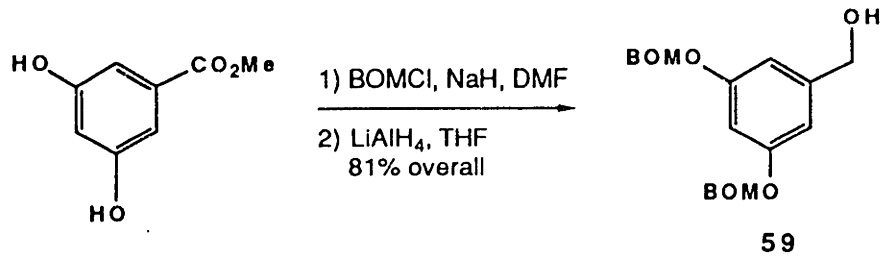
Data for **51** (E): R_f 0.70 (1:1 ether-hexane); $[\alpha]_D^{22}$ +8.9° (c 3.7, CH_2Cl_2); ^1H NMR (250 MHz, $CDCl_3$) δ 6.88 (m, 1H), 5.80 (d, J = 15.4 Hz, 1H), 5.63 (m, 1H), 5.03 (m, 2H), 4.09 (m, 1H), 3.80 (dd, J = 5.3, 6.3 Hz, 1H), 3.70 (s, 3H), 3.60 (t, J = 6.7 Hz, 1H), 3.43 (s, 3H), 3.13 (t, J = 5.3 Hz, 1H), 2.56 (m, 2H), 2.25 (m, 1H), 1.56 (m, 10H), 1.31 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); IR (neat) 2930, 2850, 1725, 1655, 1470, 1460, 1445, 1435, cm^{-1}; mass spectrum m/e 482 (parent ion); high resolution mass spectrum for $C_{26}H_{46}O_6Si$, calcd 482.3064, found 482.3068. Anal. Calcd for $C_{26}H_{46}O_6Si$: C, 64.69; H, 9.60. Found: C, 64.83; H, 9.48.



50 52

Preparation of Lactone 52.

To a solution of aldehyde **50** (10 mg, 0.023 mmol) in THF (1 mL) was added n-Bu_4NF (8 drops, 1 M in THF). After being stirred at room temperature for 1 h, the mixture was partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude alcohol so obtained was dissolved in CH_2Cl_2 (2 mL), treated with PCC (120 mg, 0.56 mmol). The mixture was stirred at room temperature overnight, and then filtered. The solvent was removed *in vacuo* and the residue was directly purified by preparative TLC (1:1 ether-hexane) to afford 5 mg (70%) of lactone **50**: Rf 0.15 (1:1 ether-hexane); $[\alpha]_D^{22}$ -60° (c 0.09, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.17 (d, J = 10 Hz, 1H), 5.15 (d, J = 16.2 Hz, 1H), 4.12 (m, 2H), 3.76 (dd, J = 7.5, 9.1 Hz, 1H), 3.67 (br t, J = 2 Hz), 3.53 (s, 3H), 2.8-2.5 (m, 3H), 1.65 (m, 10H), 1.45 (d, J = 7.0 Hz, 3H); IR ($CHCl_3$) 2930, 2850, 1745, 1450, 1365 cm^{-1}; mass spectrum m/e 312 (parent ion).



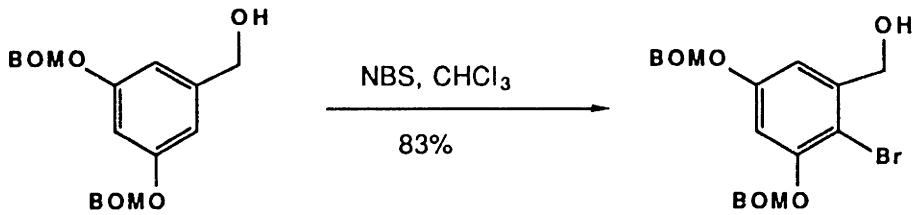
59

Preparation of Benzyl Alcohol 59.

To a 0 °C suspension of NaH (5.5 g, 60% dispersion in oil, 137.5 mmol) in dry DMF (100 mL) was added dropwise a solution of Methyl 3,5-dihydroxybenzoate (10 g, 59.6 mmol) in DMF (30 mL). After being stirred at room temperature for 60 min, the mixture was treated with benzyloxymethyl chloride (18.5 mL, 126 mmol) and then stirred for 30 min. The suspension was then poured into water, acidified with 1 N HCl and extracted three times with benzene. The combined extracts were washed with brine, dried (K_2CO_3) and concentrated *in vacuo* to give 21.92 g (90%) of protected benzoate which was used in the next step without any further purification: R_f 0.54 (1:1 ether-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45 (d, J = 2.9 Hz, 2H), 7.36 (m, 10 H), 7.03 (t, J = 2.9 Hz, 1H), 5.33 (s, 4H), 4.76 (s, 4H), 3.93 (s, 3H); IR (neat) 3050,2940, 2875, 1780, 1600, 1455, 1300, 1160, 1020 cm^{-1}; mass spectrum m/e 408 (parent ion).

To a suspension of $LiAlH_4$ (4.0 g, 105 mmol) in THF (100mL) was added dropwise a solution of the above benzoate (21.92 g, 53.7 mmol) in THF (50 mL). After being stirred at room temperature for 2 h, the mixture was treated successively with 4 mL of water, 4 mL of 15% NaOH and 10 mL of water. The resulting suspension was filtered and the filtrate so obtained was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 40% ethyl acetate-hexane) to afford 18.49 g (90%) of **59**: R_f 0.40 (2:1 ether-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 10 H), 6.77 (s, 3H), 5.29 (s, 4H), 4.73 (s, 4H), 4.64 (s, 2H),

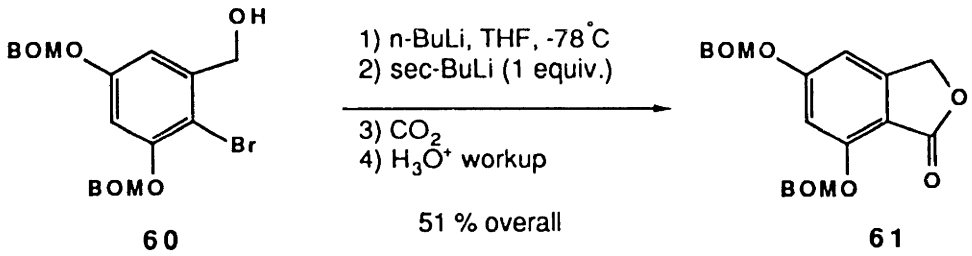
1.75 (s, 1H); IR (neat) 3600-3150 (br), 3025, 2790, 1600, 1455, 1170, 1080, 1035 cm^{-1}; mass spectrum m/e 381 (M+1).



59 60

Preparation of Aryl Bromide 60.

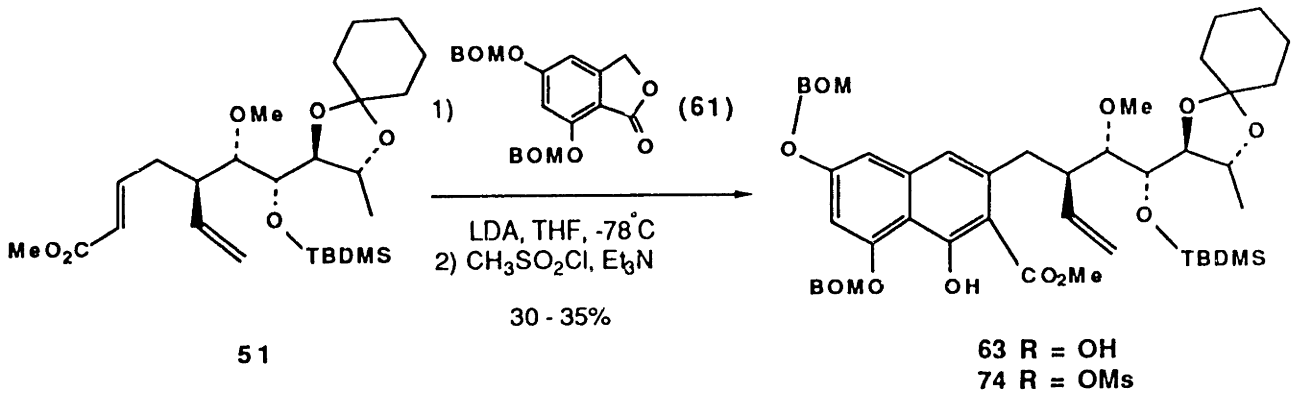
To a solution of 3,5-di(benzyloxy)methoxybenzyl alcohol **59** (16.67 g, 43.8 mmol) in dry $CHCl_3$ (150 mL) was added recrystallized NBS (7.80 g, 43.8 mmol). The solution was heated at reflux for 90 min, then allowed to cool to room temperature, treated with freshly prepared saturated aq. $Na_2S_2O_3$ (200 mL), washed with water (2 x 200 mL), dried over K_2CO_3 and concentrated. The residue was purified by column chromatography (silica gel, 30% ethyl acetate-hexane) to yield 16.68 g (83%) of the aryl bromide **60** as a low melting, yellow crystalline solid: R_f 0.29 (1:1 ether-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 7.50-7.10 (m, 10H), 6.97 (m, 2H), 5.38 (s, 2H), 5.30 (s, 2H), 4.87 (s, 2H), 4.73 (s, 2H), 4.67 (d, J = 4.9 Hz, 1H), 2.65 (s, 1H); IR ($CHCl_3$) 3400, 2890, 1585, 1450, 1400, 1310, 1165, 1095, 1040, 1015 cm^{-1}.



60 51 % overall **61**

Preparation of Phthalide 61.

To a -78 °C solution of aryl bromide **60** (14.58 g, 32.0 mmol; azeotropically dried from toluene) in THF (150 mL) under nitrogen was added sequentially n-BuLi (16.0 mL, 2.0 M in hexane, 32.0 mmol) and sec-BuLi (32.0 mL, 1.0 M in cyclohexane, 32.0 mmol) and the resulting solution was stirred at -78 °C for 70 min. Dry CO_2 gas was then bubbled through the orange anion solution for about 2.5 h. At the same time the solution was allowed to warm to -20 °C and then to room temperature overnight. The mixture was carefully diluted with water (20 mL), whereupon vigorous gas evolution was observed, then acidified with 10% aq. HCl (20 mL), saturated with NaCl and extracted with ether (2 x 150 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, 1:1 ether-hexane) to give 6.62 g (51%) of phthalide **61:** R_f 0.20 (1:1 ether-hexane); m.p. 82-83°; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50-7.24 (m, 10H), 6.95 (d, J = 1.5 Hz, 1H), 6.79 (d, J = 1.5 Hz, 1H), 5.49 (s, 2H), 5.34 (s, 2H), 5.18 (s, 2H), 4.80 (s, 2H), 4.72 (s, 2H); IR (KBr) 1765, 1610, 1485, 1450, 1385, 1340, 1315, 1285, 1235, 1210, 1175, 1155, 1090, 1045 cm^{-1}; mass spectrum m/e 406 (parent ion). Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H, 5.46. Found: C, 70.88; H, 5.31.



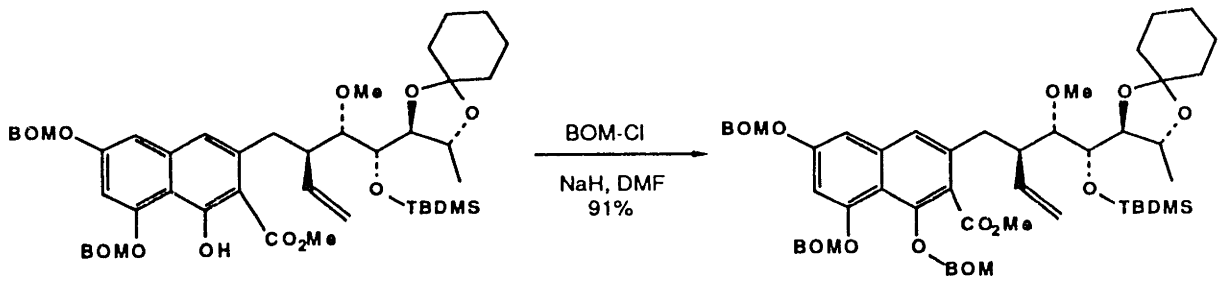
Preparation of Naphthol 63.

A solution of LDA was prepared by the addition of n-BuLi (2.0 mL, 2.5 M in hexane, 5.0 mmol) to diisopropylamine (0.5 mL, 3.5 mmol) in THF (5 mL) at -78 °C, followed by stirring at 0 °C for 15 min. The solution was cooled to -40 °C and treated with a solution of phthalide **61** (406 mg, 1.0 mmol) in THF (4 mL) resulting in an orange-yellow color. Ten minutes later, a solution of ester **51** (482 mg, 1.0 mmol) in THF (2 mL) was added dropwise over a period of 20 min. The red solution so obtained was stirred at -40 °C for another 20 min and then was diluted with saturated aq. NH_4Cl. This mixture was extracted with CH_2Cl_2 , dried over $MgSO_4$ and concentrated *in vacuo* to give the crude hydroxytetralone. This material was dissolved in CH_2Cl_2 (40 mL) along with triethylamine (5 mL, 35.8 mmol). Methanesulfonyl chloride was then added dropwise until all the starting material (R_f 0.19 (1:1 ether-hexane)) was consumed, as evidenced by TLC analysis. The mixture was then treated with 1 N HCl, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. Purification of the residue by column chromatography (silica gel, 15 to 25% ether-hexane) afforded 62 mg of an unknown mixture, 342 mg (35%) of phenol **63** and 105 mg (10%) of mesylate **74**.

Data for **63**: R_f 0.35 (1:1 ether-hexane); $[\alpha]_D^{22}$ -15.0° (c 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.4-7.25 (m, 10H), 6.95 (s, 2H), 6.88 (d, J = 2.1

Hz, 1H), 5.68 (m, 1H), 5.45 (s, 2H), 5.33 (s, 2H), 4.90-4.68 (m, 6H), 4.12 (m, 1H), 3.97 (s, 3H), 3.92 (t, J = 5.6 Hz, 1H), 3.70 (dd, J = 4.7, 6.8 Hz, 1H), 3.48 (s, 3H), 3.25 (d, J = 9.6 Hz, 1H), 3.12 (t, J = 4.8 Hz, 1H), 2.64 (m, 2H), 1.56 (m, 10H), 1.31 (d, J = 5.6 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); IR ($CDCl_3$) 2940, 2860, 1715, 1660, 1625, 1610, 1590 cm^{-1}; mass spectrum m/e 870 (parent ion) (2), 621 (1), 531 (2), 479 (3), 155 (17), 91 (100).

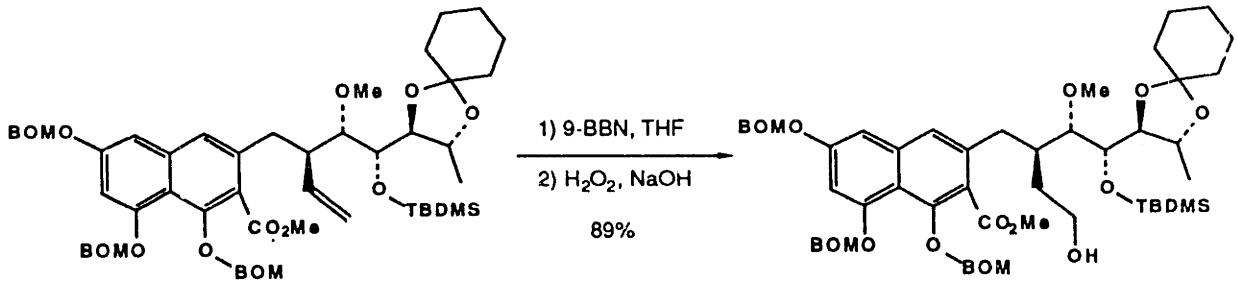
Data for **74**: R_f 0.30 (1:1 ether-hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.24 (m, 10H), 7.06 (d, J = 2.6 Hz, 1H), 7.03 (d, J = 1.7 Hz, 1H), 5.63 (m, 1H), 5.45 (s, 2H), 5.38 (s, 2H), 4.87-4.65 (m, 6H), 4.12 (m, 1H), 3.96 (s, 3H), 3.88 (t, J = 6.0 Hz, 1H), 3.68 (dd, J = 5.9, 7.8 Hz, 1H), 3.48 (s, 3H), 3.28 (dd, J = 3.0, 13.9 Hz, 1H), 3.13 (s, 3H), 2.68 (m, 2H), 1.56 (m, 10H), 1.31 (d, J = 5.7 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H).



63 64

Preparation of Naphthoate 64.

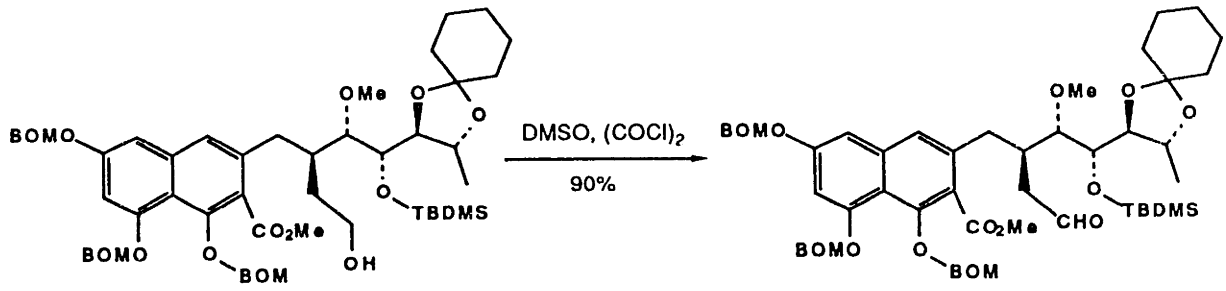
To 10 mL of dry THF containing 300 mg of NaH was added a solution of phenol (800 mg, 0.92 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 20 min, treated with benzyloxymethyl chloride (1.5 mL, 10.7 mmol) and stirred for an additional 1h. The reaction was quenched with water and extracted with methylene chloride. The extracts were dried over $MgSO_4$, filtered, the solvent was removed *in vacuo* to afford 820 mg (91%) of **64**: R_f 0.35 (2:1 hexane-ether); $[\alpha]_D^{22}$ +6.8° (c 3.4, $CH_2C'_2$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-7.25 (m, 16H), 7.03 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 5.70 (m, 1H), 5.36 (s, 2H), 5.35 (s, 2H), 5.22 (s, 2H), 4.9-4.7 (m, 8H), 4.14 (m, 1H), 3.98-3.87 (m, 4H), 3.72 (t, J = 5.6 Hz, 1H), 3.49 (s, 3H), 3.23-3.10 (m, 2H), 2.74-2.60 (m, 2H), 1.7-1.5 (m, 10H), 1.33 (d, J = 6.0 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); IR ($CDCl_3$) 2950, 2935, 2860, 1725, 1625, 1610, 1575 cm^{-1}; mass spectrum m/e 990 (parent ion). Anal. Calcd for $C_{58}H_{74}O_{12}Si$: C, 70.35; H, 7.43. Found: C, 70.44; H, 7.41.



64 65

Preparation of Alcohol 65.

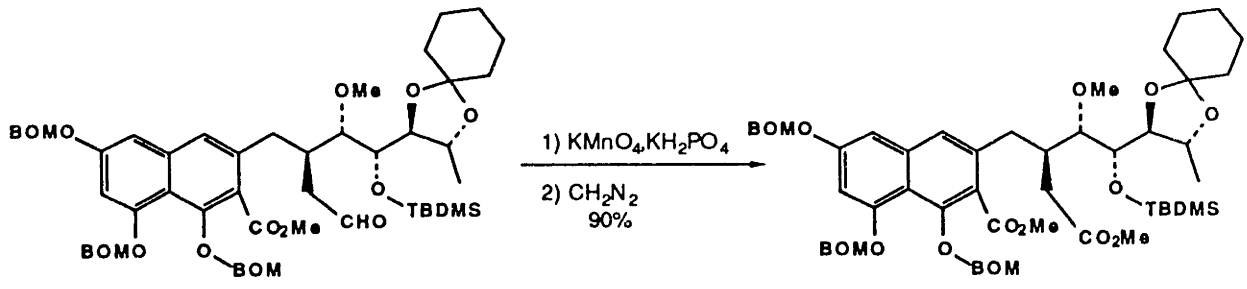
Naphthoate **64** (418 mg, 0.42 mmol) was dissolved in THF (3 mL) under N_2, cooled to 0 °C and treated with 9-BBN (8.0 mL, 0.5 M in THF, 4.0 mmol). The mixture was allowed to slowly warm up to room temperature (0.5 h), stirred for 2 h, re-cooled to 0 °C and quenched with MeOH (3 mL). When gas evolution had subsided, 3 mL each of 3 M aq. NaOH and 30% aq. H_2O_2 were added simultaneously dropwise. The solution (containing a white precipitate) was warmed to room temperature and stirred for 2 h. Workup consisted of partitioning the mixture between water (50 mL) and CH_2Cl_2 (100 mL). The aq. layer was further extracted with CH_2Cl_2 (100 mL) and the combined organic extacts were washed with aq. $Na_2S_2O_3$ and dried over Na_2SO_4. After removal of solvent *in vacuo* the residue was purified by flash chromatography (silica gel, 35% ethyl acetate-hexane) to give 423 mg (89%) of **65**: R_f 0.46 (40% ethyl acetate-hexane); $[\alpha]_D^{22}$ +2.0° (c 0.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.25 (m, 16H), 7.03 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 5.37 (s, 2H), 5.35 (s, 2H), 5.22 (s, 2H), 4.76 (s, 2H), 4.75 (s, 2H), 4.73 (s, 2H), 4.16 (m, 1H), 3.99-3.90 (m, 4H), 3.60 (dd, J = 4.0, 7.9 Hz, 1H), 3.57-3.48 (m, 4H), 3.13 (dd, J = 2.0, 7.7 Hz, 1H), 3.02 (dd, J = 4.0, 14.4 Hz, 1H), 2.64 (dd, J = 10.0, 14.4 Hz, 1H), 2.18 (m, 1H), 1.81-1.43 (m, 10H), 1.33 (d, J = 5.8 Hz, 3H), 0.96 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); IR ($CDCl_3$) 3605, 3430, 2940, 2880, 1730, 1625, 1610, 1575 cm^{-1}; mass spectrum m/e 1008 (parent ion).



65 66

Preparation of Aldehyde 66.

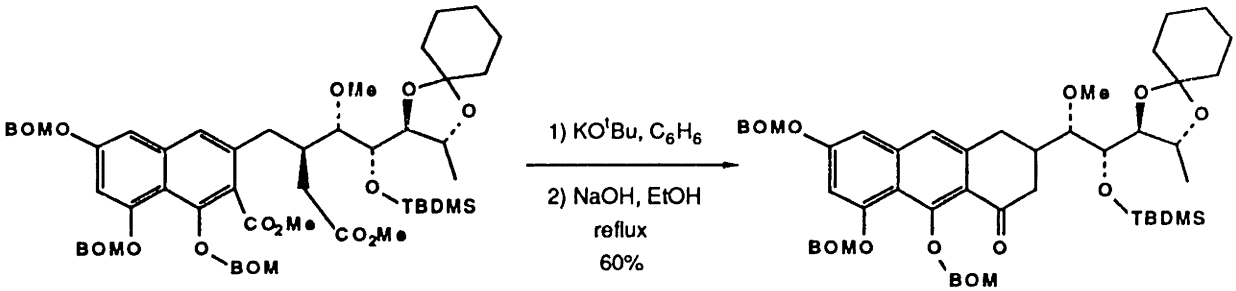
DMSO (0.75 mL, 10.5 mmol) was added dropwise to a -78 °C solution of oxalyl chloride (0.5 mL, 5.7 mmol) in methylene chloride (10 mL) under Ar. This mixture was stirred for 10 min, then a solution of alcohol **65** (400 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added. The cloudy mixture was stirred at -78 °C for 10 min, treated with triethylamine (4 mL, 28.6 mmol) and then allowed to warm slowly to room temperature. The resulting mixture was partitioned between water and CH_2Cl_2. The organic layer was separated and dried over Na_2SO_4, then concentrated. The residue was dissolved in ether and filtered through a Kimwipe plug. Removal of solvent *in vacuo* afforded 360 mg (90%) of aldehyde **66**, which was used without any further purification in the subsequent reaction: R_f 0.82 (40% ethyl acetate-hexane); ^1H NMR (250 MHz, $CDCl_3$) δ 9.57 (s, 1H) 7.4-7.24 (m, 16H), 7.04 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H), 5.37 (s, 2H), 5.36 (s, 2H), 5.21 (m, 2H), 4.77 (s, 2H), 4.75 (s, 2H), 4.73 (s, 2H), 4.17 (m, 1H), 4.00 (dd, J = 4.4, 8.0 Hz, 1H), 3.91 (s, 3H), 3.68 (dd, J = 4.0, 7.5 Hz, 1H), 3.49-3.43 (m, 4H), 3.10 (t, J = 7.5 Hz, 1H), 2.70-2.30 (m, 4H), 1.7-1.50 (m, 10H), 1.36 (d, J = 6.2 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); IR ($CDCl_3$) 2930, 1720, 1625, 1607, 1580 cm^{-1}.



66 67

Preparation of Diester 67.

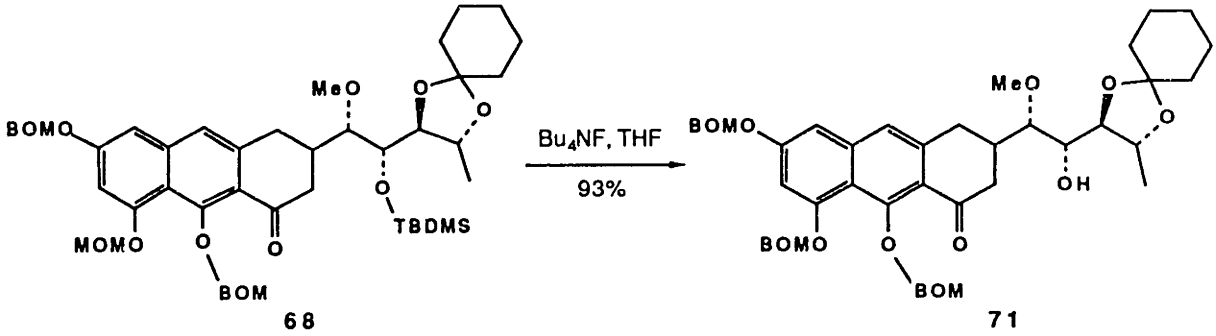
To a solution of aldehyde **66** (360 mg, 0.36 mmol) in DMF (2 mL) were sequentially added t-butanol (8 mL), $KMnO_4$ (5 mL, 1 M aq. solution) and KH_2PO_4 (3 mL, 1.25 N aq. solution). The mixture was stirred for 30 min, treated with 3 mL of saturated aq. $NaHSO_3$ and acidified to pH 2 with 0.1N HCl. The clear solution was extracted with CH_2Cl_2, concentrated to about 20 mL and then treated with excess ethereal diazomethane. About 5 min later the solvent was removed *in vacuo* to give 325 mg (90%) of diester **67**, which was used in the following experiments without any further purification: R_f 0.38 (20% ethyl acetate-hexane); $[\alpha]_D^{22}$ +12.5° (c 1.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.4-7.24 (m, 16H), 7.03 (d, J = 2.6 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 5.36 (s, 2H), 5.34 (s, 2H), 5.21 (m, 2H), 4.76 (s, 2H), 4.75 (s, 2H), 4.73 (s, 2H), 4.20 (m, 1H), 4.01 (dd, J = 2.8, 8.8 Hz, 1H), 3.91 (s, 3H), 3.66 (dd, J = 3.0, 7.5 Hz, 1H), 3.53 (s, 3H), 3.44 (s, 3H), 3.11-3.03 (m, 2H), 2.60-2.23 (m, 4H), 1.70-1.45 (m, 10H), 1.33 (d, J = 6.4 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); IR ($CDCl_3$) 2950, 2935, 1730, 1625, 1605, 1580 cm^{-1}; mass spectrum m/e 1036 (parent ion). Anal. Calcd. for $C_{59}H_{76}O_{14}Si$: C, 68.31; H, 7.38. Found: C, 68.06; H, 7.52.



67 68

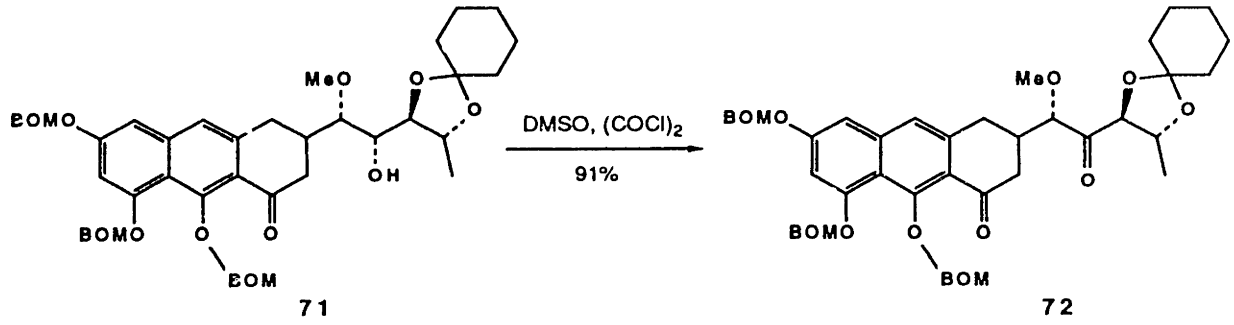
Preparation of Anthracenone 68.

A solution of diester **67** (152 mg, 0.15 mmol) in dry benzene (9 mL) under N_2, was treated with potassium t-butoxide (180 mg, 1.5 mmol). The resulting mixture was stirred at room temperarure for 1.5 h. It was then treated with saturated aq. NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a β-ketoester as a mixture of diastereomers. The crude product was dissolved in 30 mL of absolute ethanol and 20 mL of 0.1 N NaOH solution. The mixture was heated at reflux for 2 h, then was cooled to room temperature, poured into aq. NH_4Cl and extracted twice with CH_2Cl_2 (2 x 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford crude **68**. This material was purified by column chromatography (silica gel, 10% ethyl acetate-hexane) to give 83 mg (60 %) of **68**: R_f 0.44 (20% ethyl acetate-hexane); $[\alpha]_D^{22}$ +13.5° (c 0.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 16H), 7.01 (d, J = 2.0 Mz, 1H), 6.93 (d, J = 2.0 Mz, 1H), 5.38 (s, 2H), 5.36 (s, 2H), 5.25 (s, 2H), 4.87 (s, 2H), 4.86 (s, 2H), 4.75 (m, 2H), 4.13 (m, 1H), 3.90 (t, J = 5.5 Hz, 1H), 3.59 (t, J = 6.6 Hz, 1H), 3.47 (s, 3H), 3.15-2.94 (m, 3H), 2.63-2.45 (m, 2H), 1.55 (s, 10H), 1.30 (d, J = 5.6 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); IR ($CDCl_3$) 2940, 1675, 1620, 1565 cm^{-1}; mass spectrum m/e 946 (parent ion).



Preparation of Alcohol 71.

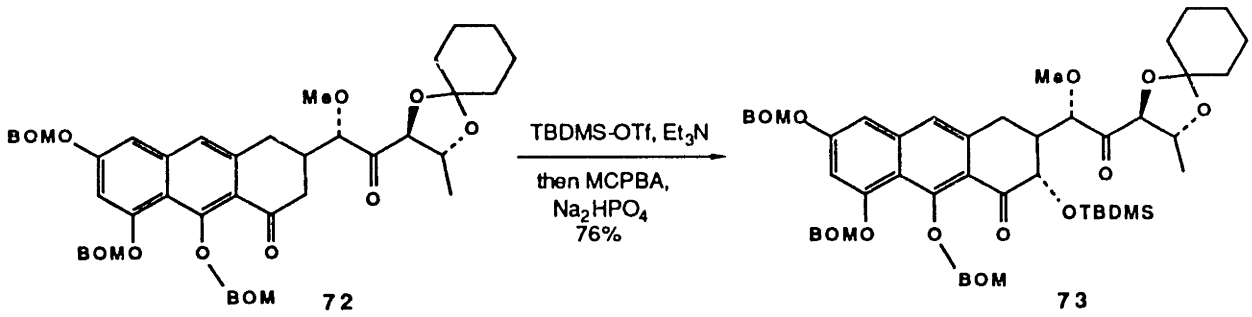
To a solution of **68** (68 mg, 0.071 mmol) in dry THF (3 mL) under Ar, was added n-Bu_4NF (0.25mL, 1 M in THF, 0.25 mmol). After being stirred at room temperature for 1 h the mixture was partitioned between water and CH_2Cl_2. The aq. layer was further extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. Removal of solvent *in vacuo*, followed by column chromatography (silica gel, 40% ethyl acetate-hexane) of the crude product provided 53.9 mg (93%) of **71**: R_f 0.07 (20% ethyl acetate-hexane); $[\alpha]_D^{22}$ +41° (c 0.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 16H), 7.01 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 5.38 (s, 2H), 5.36 (s, 2H), 5.25 (m, 2H), 4.86-4.71 (m, 6H), 4.10 (m, 1H), 3.58 (s, 3H), 3.54-3.40 (m, 2H), 3.22 (d, J = 10.0 Hz, 1H), 2.94 (m, 1H), 2.63 (d, J = 10.0 Hz, 1H), 2.50 (m, 2H), 2.21 (d, J = 7.0 Hz, 1H), 1.55 (m, 10H), 1.38 (d, J = 5.6 Hz, 3H); IR ($CDCl_3$) 3650-3150 (br), 2940, 1675, 1620, 1565 cm^{-1}; mass spectrum m/e 832 (parent ion).



71 72

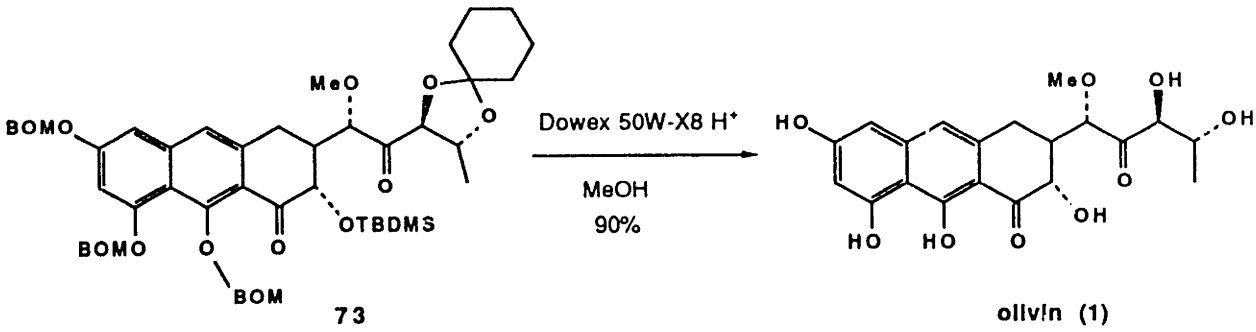
Preparation of Diketone 72.

DMSO (0.07mL, 1.0 mmol) was added dropwise to a -78 °C solution of oxalyl chloride (0.06 mL, 0.74 mmol) in methylene chloride (3 mL) under Ar. This solution was stirred for 10 min, then a pre-cooled (-78 °C) solution of alcohol **71** (52 mg, 0.062 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise via cannula. The cloudy mixture was stirred at -78 °C for 1.25 h , treated with triethylamine (0.21 mL, 1.48 mmol) and then gradually warmed up to -5 °C over 2 h. The resulting mixture was poured into water and extracted three times with CH_2Cl_2 (3 x 30 mL). The combined extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The residue was triturated 3 times with ether (3 x 15 mL), the combined triturate was filtered through a Kimwipe plug and then concentrated. The residue was purified by column chromatography (silica gel, 1:1 ether-hexane) to give 47 mg (91%) of diketone **72**: R_f 0.19 (1:1 ether-hexane); $[\alpha]_D^{22}$ -33° (c 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 16H), 6.99 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 5.38 (s, 2H), 5.36 (s, 2H), 5.23 (m, 2H), 4.86-4.71 (m, 6H), 4.10 (m, 3H), 3.42 (s, 3H), 3.04-2.60 (m, 5H), 1.55 (m, 10H), 1.38 (d, J = 8.8 Hz, 3H); IR ($CDCl_3$) 2940, 1720, 1675, 1618, 1566 cm^{-1}.



Preparation of Protected Olivin 73.

To a solution of diketone **72** (15.5 mg, 0.018 mmol) in dry CH_2Cl_2 (1.5 mL) under N_2, was added sequentially Et_3N (0.07 mL, 0.50 mmol) and TBDMS-OTf (0.04 mL, 0.17 mmol). After being stirred for 10 min the reaction was diluted with CH_2Cl_2 and washed with saturated aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, concetrated and the residue was purified by column chromatography (silica gel, 50:50:1 ether-hexane-triethylamine). The silyl enol ether (R_f 0.57 (1:1 ether-hexane)) so obtained was immediately dissolved in CH_2Cl_2 (1 mL), cooled to -20 °C and treated successively with NaH_2PO_4 (46 mg, 0.32 mmol) and 97% mCPBA (46 mg, 0.32 mmol). The reaction mixture was stirred at -20 °C for 25 min and then quenched with a cold 1:1 mixture of saturated aq. $NaHSO_3$ and $NaHCO_3$ solutions. The aq. layer was further extracted with CH_2Cl_2 and the combined extracts were washed with saturated aq. $NaHCO_3$ and dried over Na_2SO_4. Purification of the crude product by column chromatography (silica gel, 150:50:1 hexane-ether-triethylamine) afforded 11.6 mg (76%) of protected olivin **73**: R_f 0.55 (1:1 ether-hexane); $[\alpha]_D^{22}$ -35° (c 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.26 (m, 15H), 7.22 (s, 1H), 6.99 (d, J = 2.4 Mz, 1H), 6.95 (d, J = 2.4 Hz, 2H), 5.41-5.39 (m, 4H), 5.31 (s, 2H), 4.95-4.50 (m, 8H), 4.10 (d, J = 8.9 Hz, 1H), 3.98 (m, 1H), 3.41 (s, 3H), 3.32 (m, 1H), 2.47-2.67 (m, 2H), 1.61 (m, 10H), 1.40 (d, J = 5.8 Hz, 3H), 1.03 (s, 9H), 0.32 (s, 3H), 0.12 (s, 3H); IR ($CDCl_3$) 2940, 1715, 1700, 1620, 1565 cm^{-1}; mass spectrum m/e 960 (parent ion).

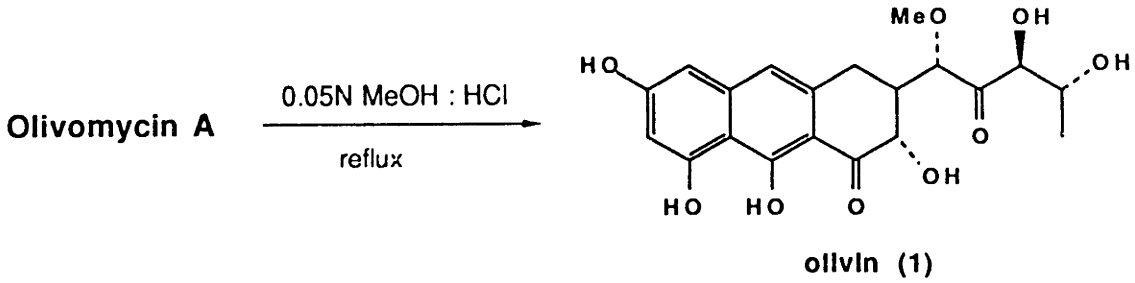


73 olivin (1)

Preparation of Olivin (1).

Protected olivin **73** (9.1 mg, 0.008 mmol) was dissolved in dry MeOH (2 mL) and treated with 20 mg of activated Dowex 50W-X8 resin. The resulting mixture was stirred at room temperature for 6 d. Workup consisted of filtering the suspension through a Kimwipe plug and removal of MeOH *in vacuo*. The residue was crystallized from hexane-ether to afford 3.1 mg (95%) of olivin as a yellow solid.

Data for **synthetic olivin:** R_f 0.15 (94:5:1 CH_2Cl_2-MeOH-HCOOH); m.p. 139-141°C; $[\alpha]_D^{22}$ +53° (c 0.04, EtOH); ^1H NMR (300 MHz, CD_3CN) δ 6.77 (s, 1H), 6.50 (d, J = 1.1 Hz, 1H), 6.34 (d, J = 1.1 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.17-4.13 (m, 2H), 3.36 (s, 3H), 2.98-2.93 (m, 1H) 2.69-2.53 (m, 2H), 1.20 (d, J = 7.0 Hz, 3H); IR ($CHCl_3$) 3500-3200 (br), 2920, 2850, 1730, 1635 cm^{-1}; mass spectrum m/e 406 (parent ion).



olivin (1)

Preparation of Olivin from Olivomycin A.

A solution of olivomycin A (32.9 mg, 0.028 mmol) in 3 mL of 0.05 N methanolic HCl was refluxed under nitrogen for 4 h. After being cooled to room temperature the reaction mixture was neutralized with Ag_2CO_3. The resulting silver salts were filtered off and the filtrate was concentrated *in vacuo*. The residue was then dissolved in 10 mL of water and extracted four times with EtOAc (4 x 5 mL). The combined extracts were concentrated to give a yellow oil which was crystallized from chloroform-ethanol-hexane. The yellow solid so obtained was further purified by column chromatography (silica gel, 94:5:1 CH_2Cl_2-MeOH-HCOOH) to afford 0.7 mg of olivin. The yield of olivin could be increased if the mother liquor is further crystallized.

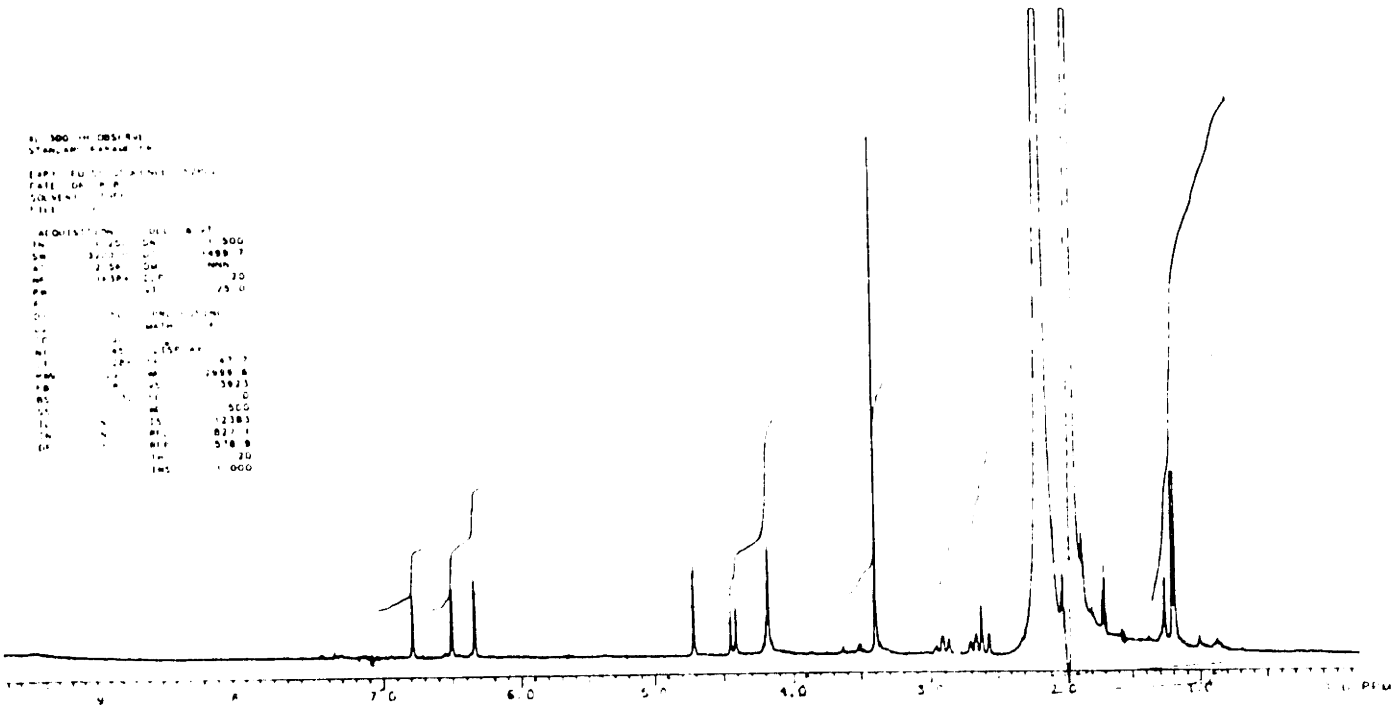
Data for **natural olivin:** R_f 0.15 (94:5:1 CH_2Cl_2-MeOH-HCOOH); m.p. 136-139°C; $[\alpha]_D^{22}$ +56° (c 0.07, EtOH); ^1H NMR (300 MHz, CD_3CN) δ 6.77 (s, 1H), 6.50 (d, J = 1.1 Hz, 1H), 6.34 (d, J = 1.1 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 4.17-4.13 (m, 2H), 3.36 (s, 3H), 2.98-2.93 (m, 1H) 2.69-2.53 (m, 2H), 1.20 (d, J = 7.0 Hz, 3H); IR ($CHCl_3$) 3500-3200 (br), 2920, 2850, 1730, 1635 cm^{-1}; mass spectrum m/e 406 (parent ion).

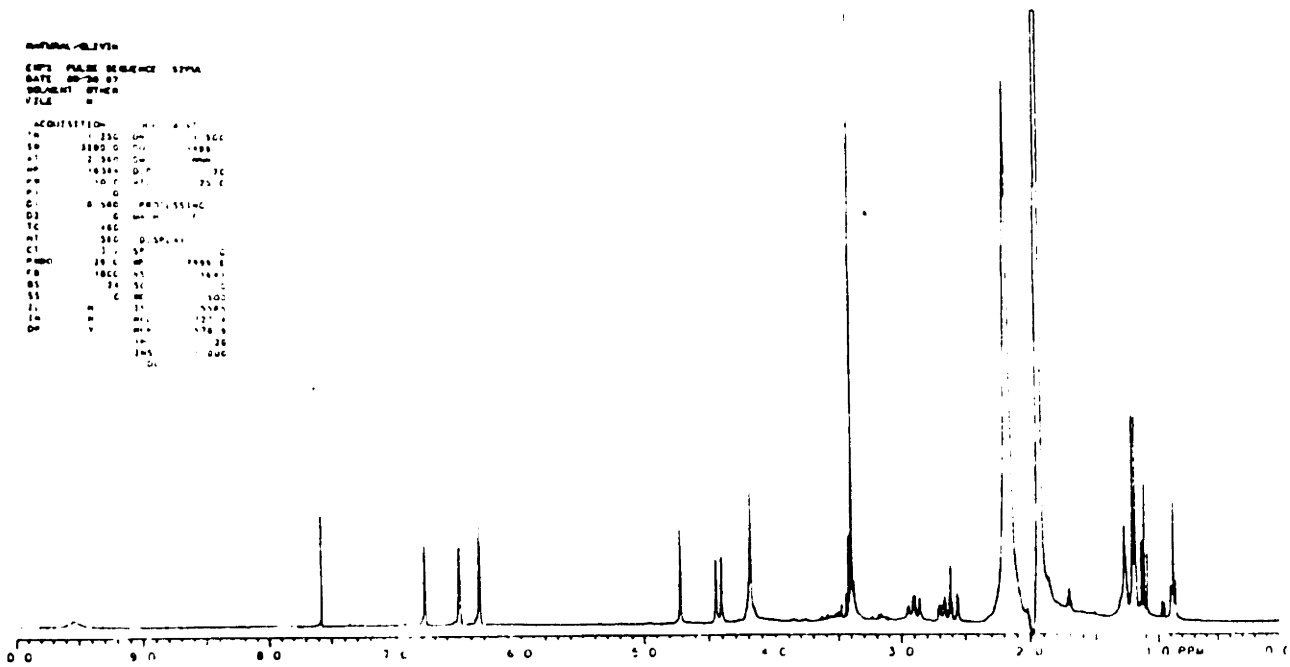
^{1}H NMR SPECTRA OF SYNTHETIC AND NATURAL OLIVIN

^1H NMR spectra (300 MHz, CD_3CN)

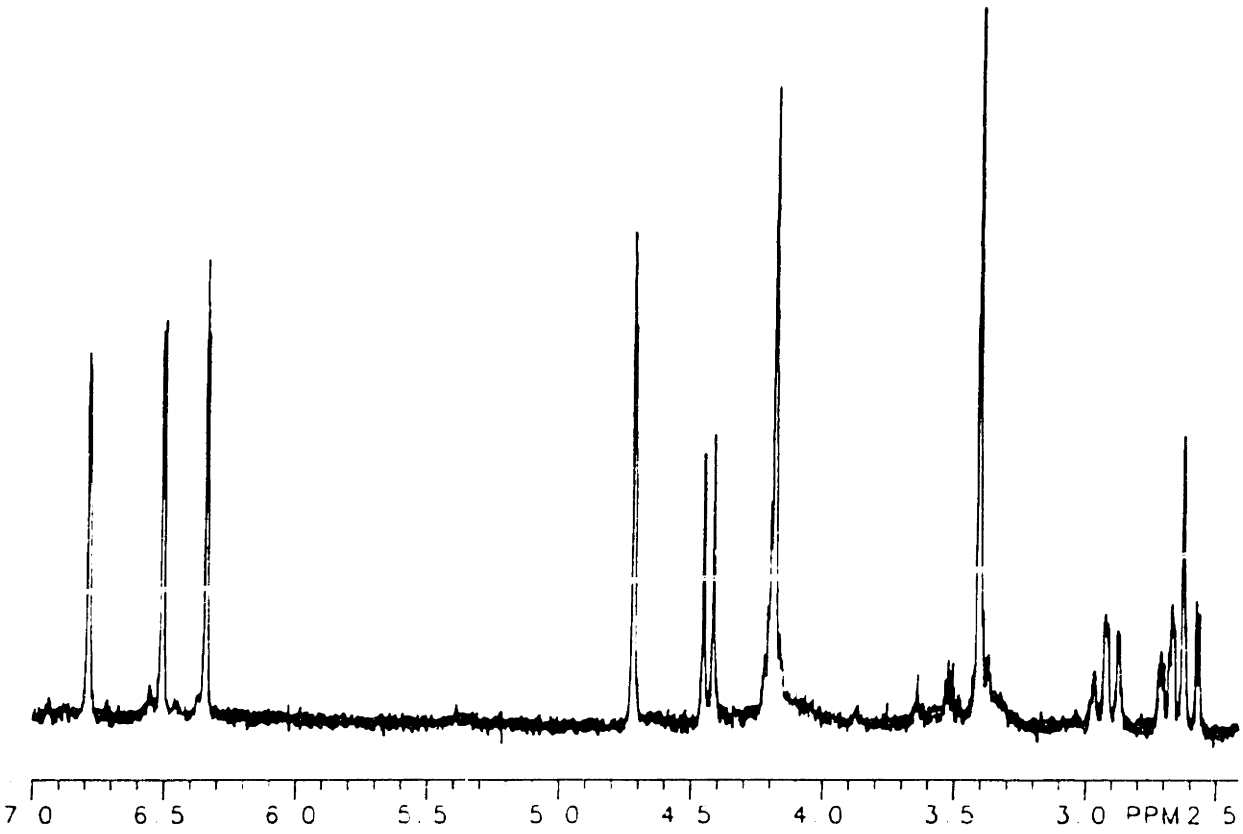
Top spectrum : Synthetic olivin

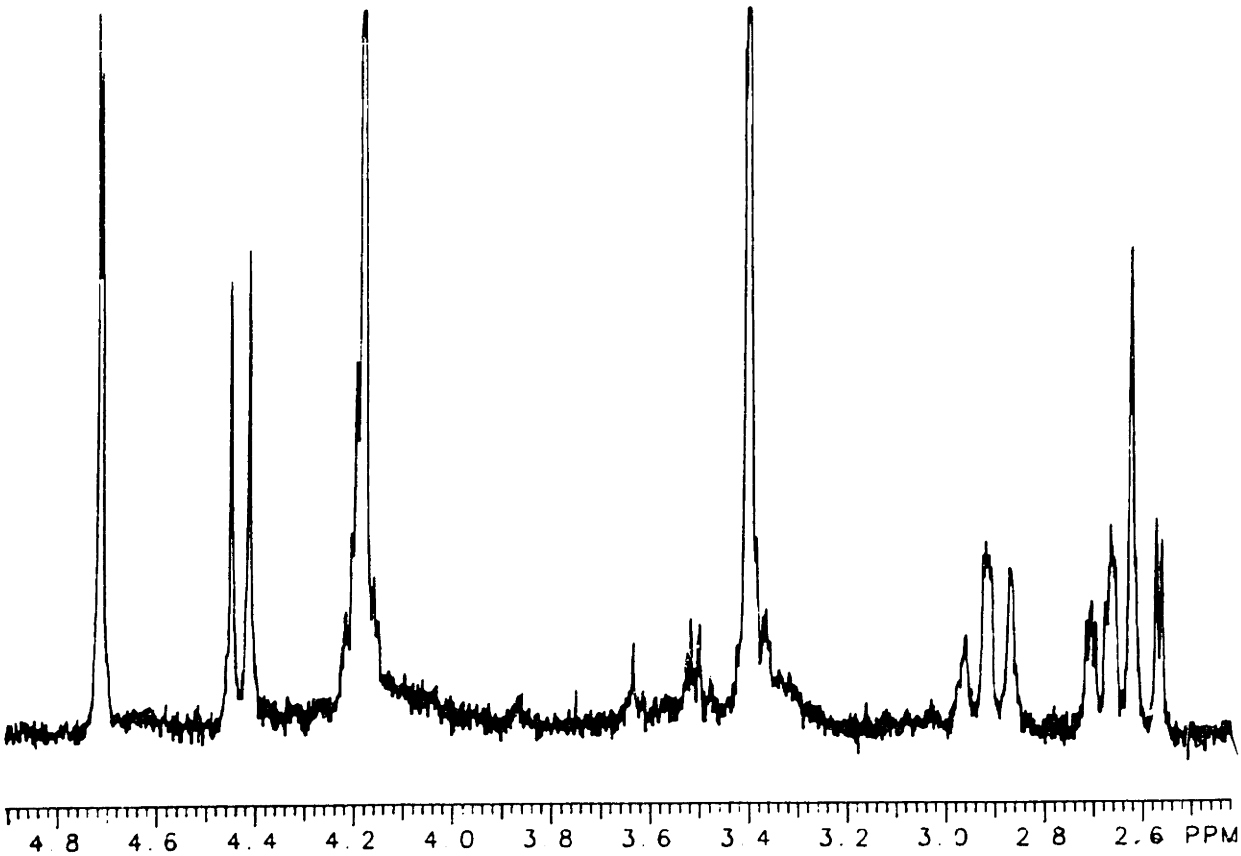
Bottom spectrum : Natural olivin





Synthetic olivin : ^1H NMR spectra (300 MHz, CD_3CN)





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