STEREOCHEMISTRY OF CROTYLBORONATE ADDITIONS TO α, β-DIALKOXYALDEHYDES

by

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Submitted to the Department of Chemistry
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ABSTRACT

A survey of crotylmetal reactions with aldehydes is presented. Particular attention is focused on the diastereoselectivity of C-C bond formation in these reactions, especially in cases where chiral aldehydes are employed.

The stereochemical outcome of the reactions of pinacol crotylboronates 4-7 with α, β-dialkoxyaldehydes 2 and 8 have been investigated. This study revealed that (Z)-crotylboronates 4 and 5 are very selective in their reactions with 2 and 8 affording almost exclusively the 3,4-syn,4,5-anti adducts (27, 31, 35, and 39). The facial selectivity in these reactions was 20-30:1 with aldehyde 8 and >90:1 with 2. However, reactions of (E)-crotylboronates 6 and 7 with 2 and 8 showed a lack of facial selectivity leading to 1:1 mixtures of 3,4-anti,4,5-anti (28, 32, 36, and 40) and 3,4-anti,4,5-syn (29, 33, 37, and 41) products. These results have been rationalized in terms of a transition state model which relies heavily on non-bonded interactions between the vinylic crotylboronate substituent and the aldehyde C(2) substituents.

The structural assignment of adducts 27-42 was attempted by ^{1}H and ^{13}C NMR analysis, but examination of this data and the ^{1}H NMR data of the corresponding acetates (43-56) did not allow for the unambiguous assignment of stereochemistry to these products. Therefore, the primary boronate adducts (27-29, 31-33, 35-37, and 39-41) were degraded to the corresponding 1,3-diacetates (59-66). The stereochemistry of these 1,3-diacetates (and therefore the primary boronate adducts) was confirmed by independent synthesis.

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Title: Associate Professor of Chemistry
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Foundation 1982-1986

Szeretettel Mariannak és Péternek

FORWARD

The research described in this thesis was performed between October, 1983 and April, 1985 on the stereochemical outcome of reactions of crotylboronates with α, β-dialkoxy-aldehydes. Portions of this work have been published recently (see reference 1 of Chapter II). Research performed between January, 1981 and March, 1982 involved the total synthesis of (±)-methyl shikimate and pentaacetyl-DL-(1,3,5/2,4)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol. A description of this work does not appear here. Work performed between April, 1982 and October, 1983 involved the regioselective opening of 2,3-epoxyalcohols. A portion of this work describing the regioselective openings of 2,3-epoxyalcohols with trialkylaluminum reagents has been published (see reference 37 of Chapter II); the remainder of this work involved the directed openings of 2,3-epoxyalcohols via reaction of isocyanates and an application of this methodology to a short stereoselective synthesis of (+)-erythro-dihydrosphingosine. This latter work has been recently submitted for publication and a manuscript is attached in the Appendix.

ACKNOWLEDGEMENTS

I would like to thank Professor William R. Roush for his guidance and support during my stay at M.I.T. His dedication to science and the academic development of his students provided a stimulating environment in which to learn and grow.

I would like to express my thanks and appreciation to the past and present members of the Roush research group for their help in my many projects and also for their friendship which made the time at M.I.T. an enjoyable one. Special thanks to Drs. B. Lesur, W.K.M. Chong, S.M. Peseckis, T. Caggiano and A. Spada for valuable discussions. Also, special thanks to A. Essenfeld, M. Palmer, M. Michaelides, L. Hoong, J. Coe, and Drs. R. Halterman and D. Tai for help in proofreading parts of this manuscript.

I am thankful to Dr. S. Peseckis for collaboration on a project involving regioselective opening of 2,3-epoxyalcohols, which is not described here. Also, thanks to Dr. D. Harris for collaborating on the structural assignment aspect of the work described in this thesis.

I would like to thank Drs. D. Bolin and P. McNamara for their suggestions and support during my early days at M.I.T.. Thanks to Professors Danheiser, Masamune and Sharpless, and their research groups for the use of their GC facilities.

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Special thanks to Marianna Adam for drawing the bulk of the structures in this manuscript. Also, thanks for her support and love during our time at M.I.T., especially during the past two months.

ABBREVIATIONS

9-BBN	-9-borabicyclononane
Bzl	-benzyl
Cp	-cyclopentadienyl
DET	-diethyl tartrate
Dibal-H	-diisobutyl aluminum hydride
DIPT	-diisopropyl tartrate
ee	-enantiomeric excess
equiv	-equivalents
Et_2O	-ethyl ether
EtOAc	-ethyl acetate
MeOH	-methanol
MsCl	-methanesulfonyl chloride
Ph	-phenyl
TBHP	-tert-butylhydroperoxide
THF	-tetrahydrofuran
p-TsOH	-para-toluenesulfonic acid

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CHAPTER I

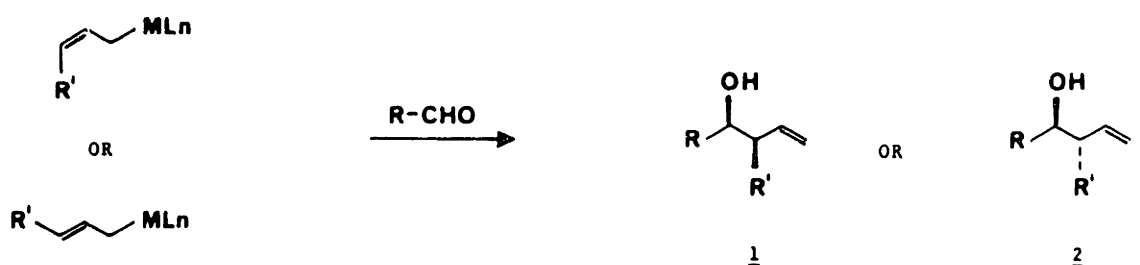
SURVEY OF CROTYLMETAL REACTIONS WITH ALDEHYDES

A. INTRODUCTION

Modern synthetic organic chemistry has progressed to the point that it is now faced with synthesizing targets that are adorned with numerous asymmetric centers. Macro- and acyclic molecules such as the macrolide and ionophore antibiotics, carbohydrates, and others, contain contiguous chiral centers arranged in such a fashion that classical methods for the control of stereochemistry using rigid, cyclic intermediates are not generally effective.[1] Consequently, during the past decade there has been rapid progress in the development of methods for control of stereochemistry in flexible acyclic systems.[1-4]

Methods which involve C-C bond formation with the establishment of two new chiral centers are of particular interest.[1-4] For such methods to be generally applicable in synthesis, however, it is necessary that the stereochemistry generated relative to preexisting chiral centers be predictable and easily controlled.[5] The aldol reaction has been extensively studied in this context, and the results realized by Heathcock, Masamune, Evans and others on the design of efficient chiral reagents are of particular note.[3,4]

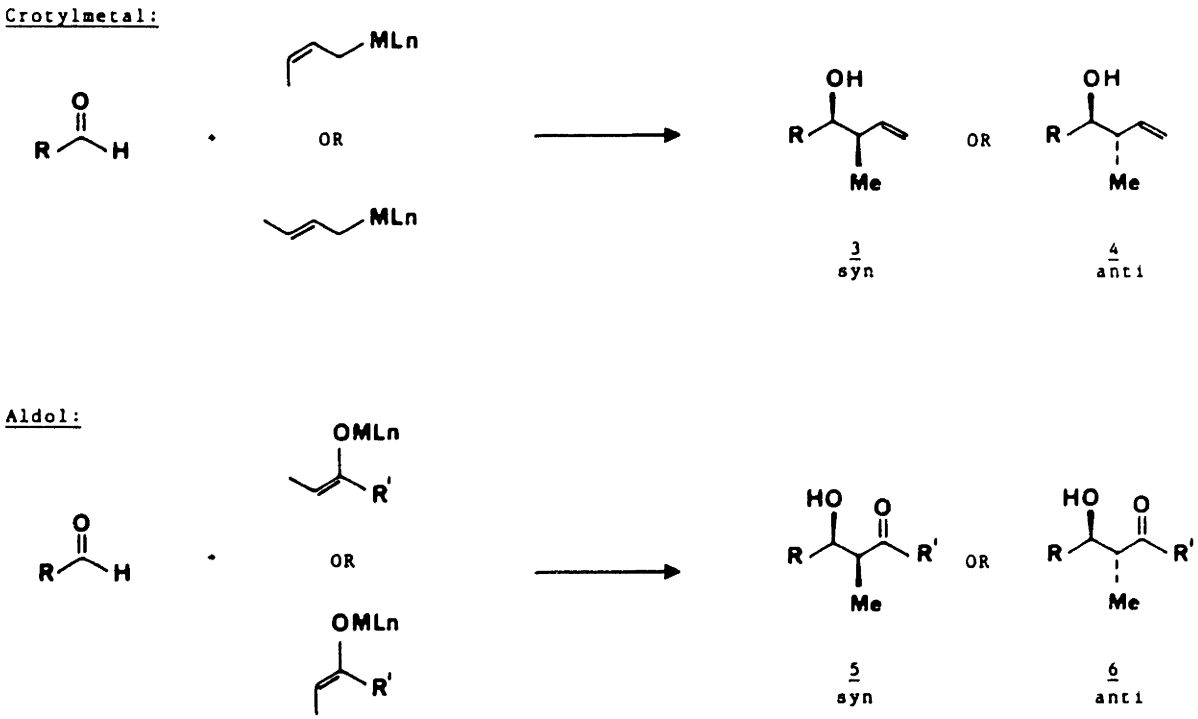
Another class of reactions which show great promise in synthesis are the condensations of crotylmetal compounds with



1 2

aldehydes.[2] The stereochemistry of this reaction is determined by the metal, its ligands, the olefin configuration of the reagent, and the specific reaction conditions. These variables influence the mechanism of the addition reaction and thus the overall stereochemical outcome.[6] Although this chemistry is less well developed than the aldol reaction, it is widely recognized that homoallylic alcohols such as 1 or 2 are useful synthetic intermediates. They can be readily functionalized or manipulated to give a variety of useful products. They can also be viewed as aldol equivalents, since oxidative cleavage of the olefin generates carbonyl derivatives.

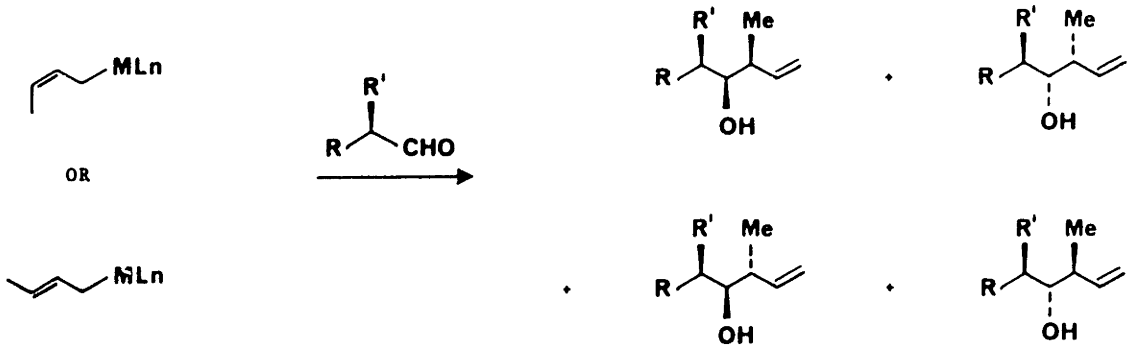
Consider, for example, the reaction of an aldehyde with a crotylmetal derivative (Scheme 1). The product homoallylic



Scheme 1

alcohols 3 and 4 are propionate aldol equivalents (e.g. 5 and 6). Although the propionate aldol has been successfully applied in synthesis, extensive research has so far produced efficient access only to the syn aldol product 5 deriving from [Z(O)]-enolates.[4] This limitation is especially apparent with chiral enolates, where a suitable chiral [E(O)]-enolate equivalent necessary for the synthesis of the anti adduct 6 is not yet available.[3,4,7] Since a number of (E)-crotylmetal compounds suitable for the synthesis of anti[8] adduct 4 are available, there is hope that these reagents may provide a solution to these longstanding aldol problems.

The ultimate goal of work in this area is the design of reagents that when treated with a chiral aldehyde will lead selectively to any one of the four possible diastereomeric products (Scheme 2). Since the stereochemical outcome of the C_3-C_4 bond formation in reactions of crotylmetals with aldehydes is dependent on the metal atom and other specific reaction variables, it is appropriate to survey the literature before selecting specific reagents for further study.

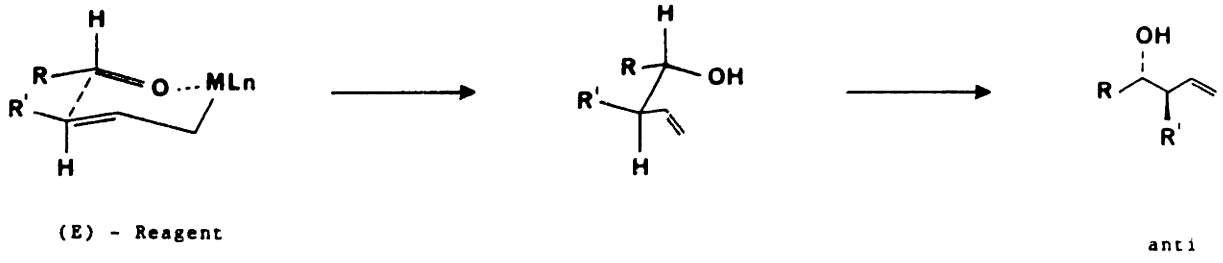


Scheme 2

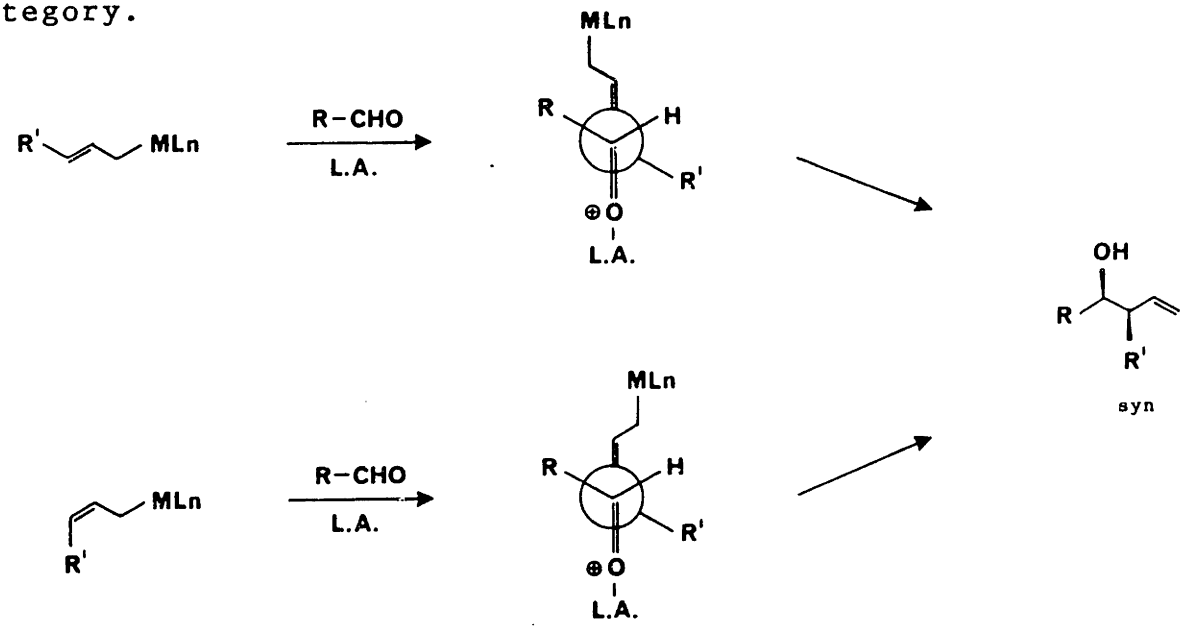
B. BACKGROUND

The condensation reactions of aldehydes with a variety of crotylmetal reagents have been studied (e.g. Li, Mg, Cd, Al, B, Sn, Si, Ti, Zr, Cr).[2] These reagents have been classified according to the overall stereochemical outcome of their reactions with aldehydes as summarized below.[6a]

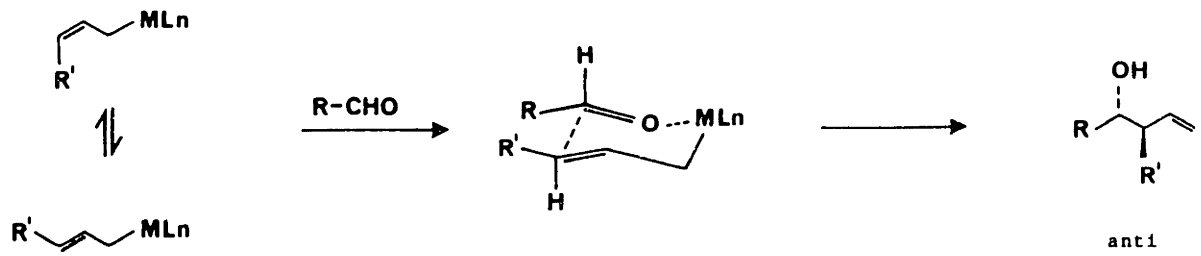
Type I reagents are ones in which the reagents' olefin geometry is transmitted directly to a stereochemical relationship in the product. That is, the geometric purity of the reagent is reflected in the ratio of anti and syn carbonyl addition products. These reactions are thought to proceed via rigid, six-membered, cyclic transition states in which the metal is coordinated to the carbonyl oxygen and R of RCHO orients preferentially in an equatorial position. A necessary consequence of this arrangement is a synclinal orientation between the olefin and carbonyl group.[9] In this way, reagents with (Z)-olefin geometry lead to syn products whereas (E)-reagents lead to anti products. Reagents incorporating boron, aluminum, and tin (thermal reaction) belong in this category.



Type II reagents undergo Lewis acid catalyzed carbonyl additions in which the product stereochemistry is not a function of the reagent olefin configuration. That is, both geometric isomers of the reagent converge to the same product diastereomer. These reactions proceed presumably through open, acyclic transition states in which the carbonyl oxygen is coordinated with a Lewis acid and the reagent double bond approaches the carbonyl oxygen in an antiperiplanar fashion.[10] However, recent work on these reactions suggests that the synclinal orientation of the olefin and carbonyl group may be preferred.[6] Reagents based on tin, silicon and titanium belong in this category.

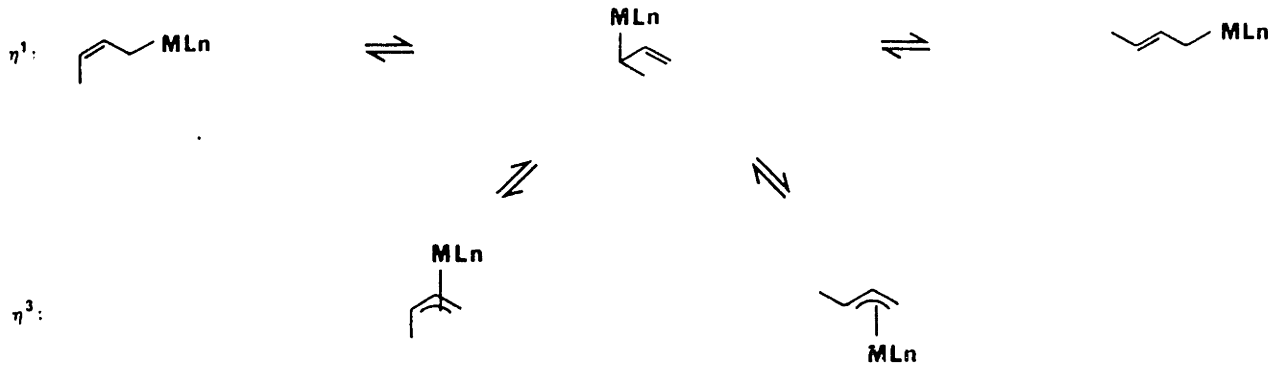


Finally, the Type III reagents are those which react with aldehydes to give mainly the anti addition product regardless of the olefin geometry of the reagent (or precursors). These reagents (Cr, Ti, Zr) presumably equilibrate to the more stable (E)- olefin isomer which then reacts via a cyclic transition state to give the anti adduct.[6a]



Before describing examples of aldehyde addition reactions to Type I-III crotylmetal reagents, note should be made of the configurational stability of these reagents. The stereoselectivity of reactions involving Type I reagents depends critically on the geometrical stability of the reagent. This is not as important with the Type II reagents since both geometric isomers converge to the same product. However, the lack of stability may be important in reactions of Type III reagents, if in fact, stereoselectivity depends on the extent and rate of reagent equilibration to the (E)-isomer.

Allylmetal compounds can exist in either the monohapto (η^1)- or trihapto (η^3)-forms. Reagents which exist in the monohapto, or sigma bound, form are generally sensitive to metallotropic rearrangements (sequential 1,3-shifts) which affect (E) to (Z) isomerization (Scheme 3). The trihapto, or π-bond, reagents can exist in either of two forms; the extended or (E)-geometry and the U-shaped or (Z)-geometry. These reagents can also isomerize presumably if the η^1-methallyl intermediate is energetically accessible to them.



Scheme 3

Some of the crotylmetal reagents which have been studied are not useful for diastereoselective C-C bond formation because the energy barrier for the interconversion of the η^1- and/or η^3-forms is too low.[2a] For example, allyl- or crotyl-lithium, magnesium, and cadmium isomerize readily even at low temperatures.[11,12] In contrast, crotylpotassium,[12] a stable η^3-compound, can be generated with high isomeric purity but fails to undergo preparatively useful carbonyl addition reactions.[13]

Other crotylmetals such as silicon and tin have been of more use synthetically. Crotylsilane is reported to be isomerically stable but since it is a Type II metal, the isomeric purity is not as important.[14] The stannane reagents on the other hand can isomerize even at temperatures below 100°C and in the presence of Lewis acids.[15]

Of the family of boron compounds, the dialkylcrotylboranes isomerize most readily and require handling at temperatures below -78°C for isomerization to be suppressed.[16] However, replacing the alkyl ligands on boron with electron donating ligands, such as alkoxy or amino groups, stabilizes the reagent

by resonance and suppresses boratropic rearrangement. Replacement of one alkyl ligand of allyldialkylborane with an alkoxy group stabilizes the reagent at temperatures up to -20°C, but using an amino ligand instead suppressed the boratropic rearrangement at temperatures up to 150°C.[17] Replacement of both alkyl ligands with oxygen substituents gives boronic acid esters which can be handled at room temperature without isomerization. All of these stabilized boron compounds, however, readily isomerize in the presence of Lewis acids.[18]

Trihapto-titanium compounds such as dicyclopentadienyl reagents are configurationally stable [19] but monohapto-titanium compounds isomerize more easily.[20] Monohapto-zirconium[21] and chromium[22] compounds are also configurationally labile but tend to favor the formation of the (E)-isomer upon equilibration.

In the following section a survey of the reactions of crotylmetal reagents with aldehydes is presented. Examples of reactions involving chiral aldehydes and chiral reagents have also been included. This discussion is organized according to the Type I, II, and III reagent categories described previously.

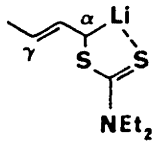
C. REAGENTS

1) Type I Crotylmetal Reagents

1.1) Lithium

Crotyllithium undergoes rapid (E) to (Z) isomerization[11a,12] and shows a lack of both regio- and stereoselectivity in aldehyde addition reactions.[23] The regioselectivity of these reactions can be controlled by using reagents such as 7-11,[24]

which gave >90% of γ-addition products in reactions with aliphatic aldehydes. However, stereoselectivity is only moderate (65:35) with reagents such as 10[25] and 11[26]. Reagents 7-9[20,27,28] exist as α-chelated structures which help to preserve their isomeric constitution. These reagents show greater levels of diastereoselectivity in reactions with aldehydes (Scheme 4).[27] These results can be rationalized by invoking



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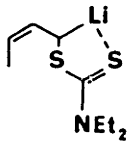

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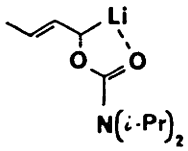

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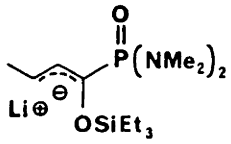

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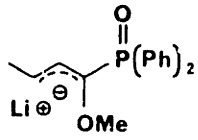

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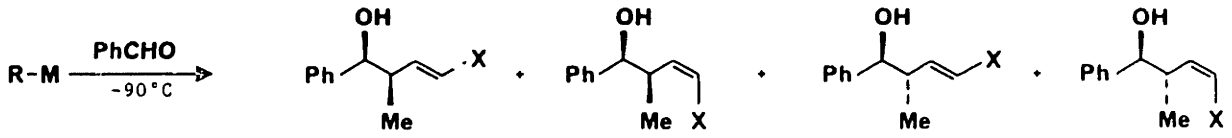
cyclic transition states in which the $SCSNEt_2$ group adopts an equatorial position (Scheme 5).



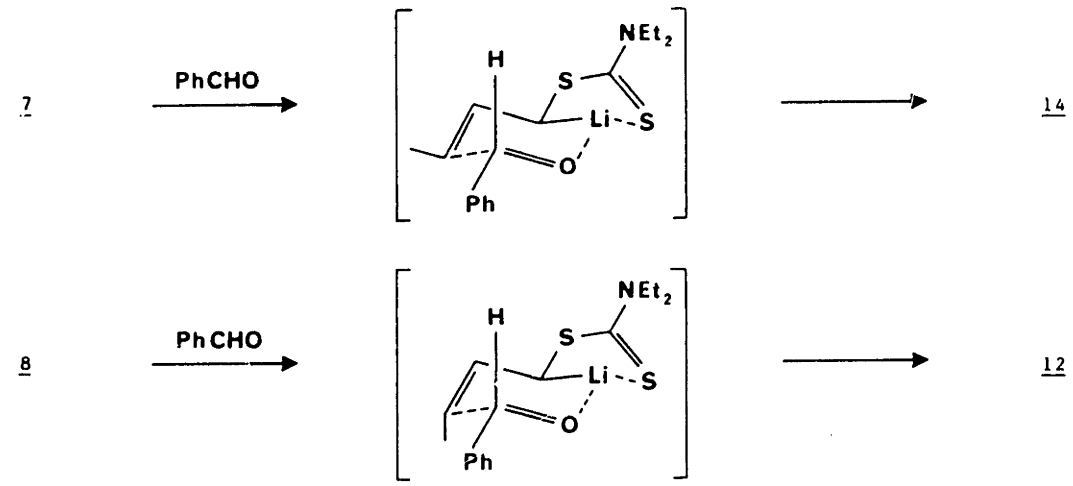
12 13 14 15

X = $SCSNEt_2$

R-M	Yield	Product Ratios 12:13:14:15	Syn:Anti[a]
7	85%	10: 8:75: 7	18:82
8	84%	92: 0: 8: 0	92: 8

(a) Syn = (12 + 13) and Anti = (14 + 15)

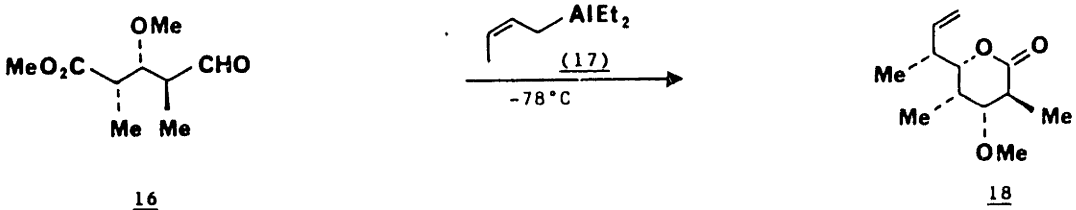
Scheme 4



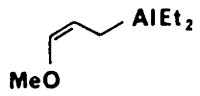
Scheme 5

1.2) Aluminum

Unsubstituted crotylaluminum reagents have not been thoroughly investigated. The (Z)-crotylaluminum reagent 17 has been generated at low temperature (≤-78°C) from the reaction of an alkali crotylmetal with diethylaluminum chloride.[29] The reaction of 16 with 17 displayed good 3,4-syn selectivity as expected for a Type I (Z)-crotylmetal reagent, but only 3:1 diastereoselectivity with respect to the preexisting chiral center of 16.[5,29,30] Alkoxy substituted reagents, 19 and



20, have been prepared via analogous procedures.[31] These species showed excellent diastereoselectivities in reactions with chiral aldehydes.



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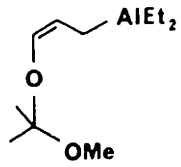

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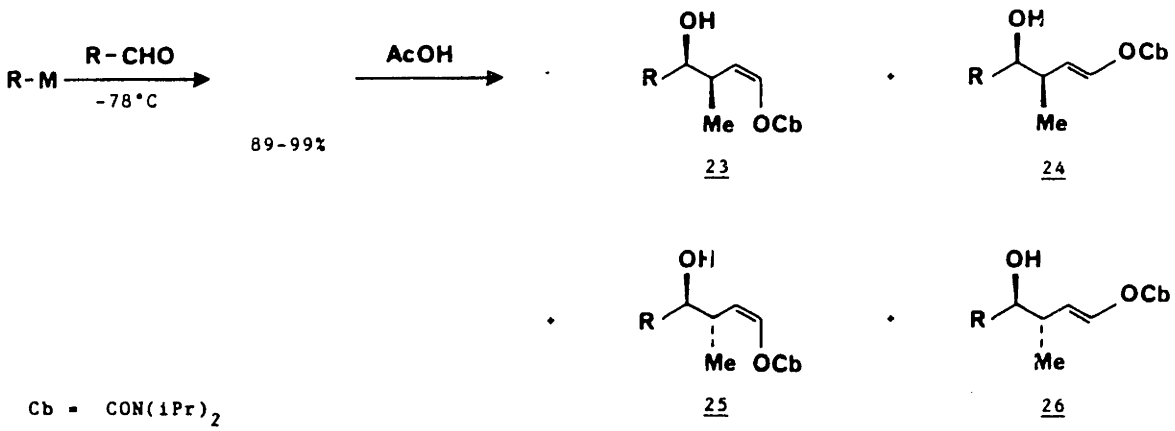
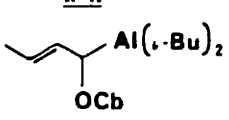
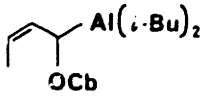
(E)- and (Z)- crotylaluminum reagents 21 and 22 have been generated at low temperature by treating the corresponding lithium reagents (e.g. 9) with either $(iBu)_2AlCl$ or the corresponding methanesulfonate.[32] These reagents gave reasonable levels of stereoselectivity in reactions with aliphatic aldehydes (Scheme 6). Here again, these reactions occur presumably via cyclic transition states with preferential equatorial placement of the allylic $OCON(iPr)_2$ substituent (Scheme 5).

Scheme 6



Cb = $CON(iPr)_2$

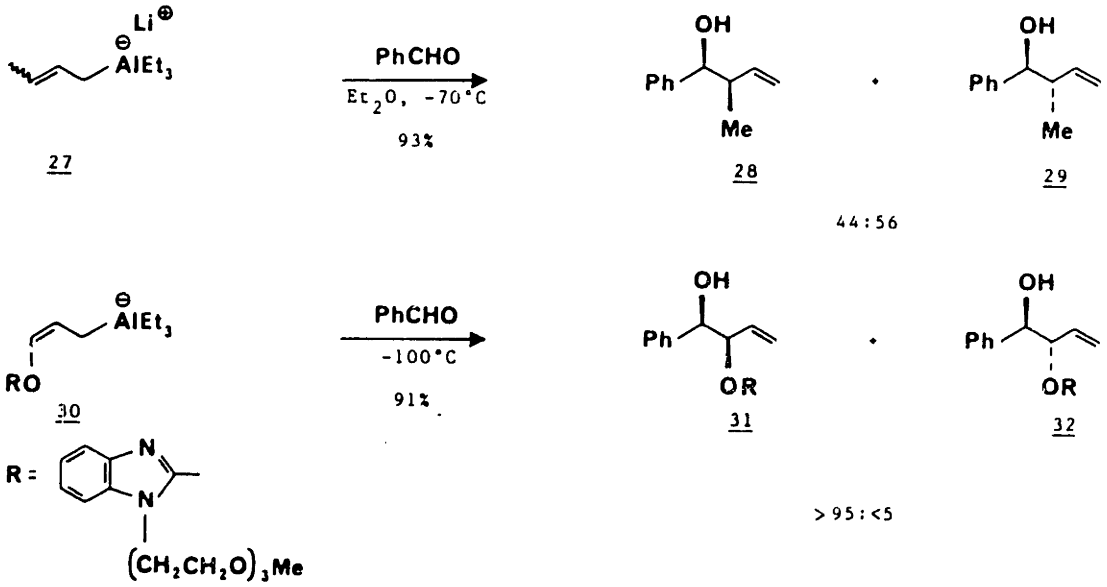
R-M	R-CHO	23:24:25:26	Syn:Anti[a]
	Ph	<1:16: 6:77	17:83
	Me	<1: 8:13:78	9:91
	iPr	<1: 5: 4:90	6:94
	Ph	3:87: 2: 8	90:10
	Me	6:79: 7: 8	85:15
	iPr	6:80: 7: 7	86:14

21

22

(a) Syn = (23 + 24) and Anti = (25 +26)

In contrast to these results, the aluminate complex 27 generated from crotyllithium and triethylaluminum displayed no diastereoselectivity in reactions with benzaldehyde.[33] This lack of selectivity is presumably due to the configurational instability of 27. However, heterosubstituted aluminate complexes such as 30 give good diastereoselectivity in aldehyde addition reactions.[34]



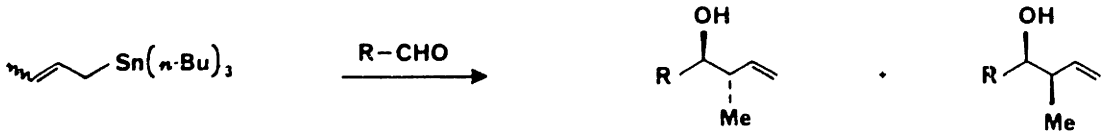
1.3) Tin

Type I crotylstannane reactions with aldehydes have been reported to occur both thermally (20-200°C) and under high pressure (10 kbar). The first investigation of the thermal reaction was performed with isomerically impure crotyltributylstannane (33).[35] By comparing the isomeric purity of the stannane with the ratio of syn and anti products, it appeared that the (E)-reagent led preferentially to the anti adduct and the (Z)-reagent to the syn adduct (Scheme 7). This conclusion was later confirmed by using essentially isomerically pure

reagents (entries 3 and 5).[36]

Yamamoto has noted that crotylstannanes are thermally unstable at elevated temperatures but an in depth study of

Scheme 7



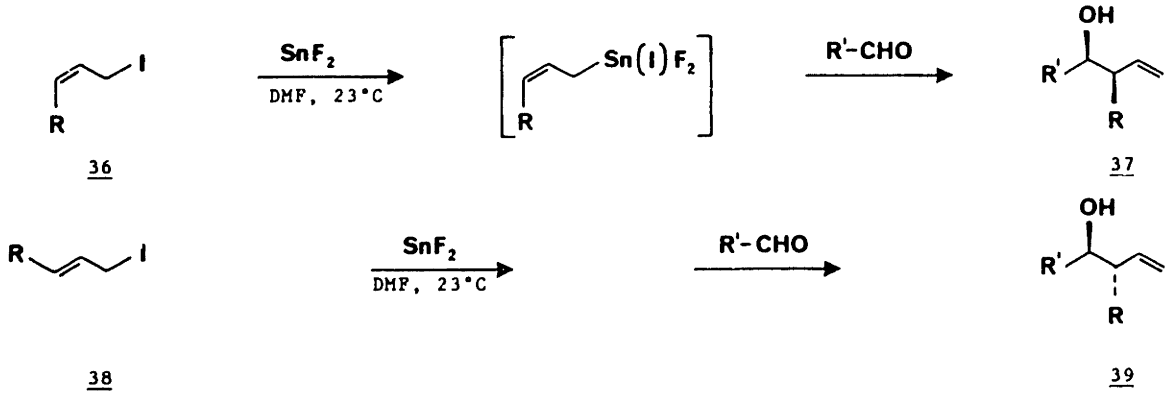
33 34 35

Entry	R-CHO	33 ((E):(Z))	Temp.(°C)/Time(h)	34:35
(1)	CCl_3CHO	90:10	20°/10	90:10
(2)	CCl_3CHO	65:35	20°/10	67:33
(3)	CCl_3CHO	0:100	25°	1:99
(4)	PhCHO	60:40	200°/16	62:38
(5)	PhCHO	92:8	200°/16	87:13

this isomerization has not been reported.[36] Instead, milder conditions using high pressures (10 kbar, 23°C) for reactions of aldehydes with crotyltrialkylstannanes have been investigated.[37] However, the reaction of (E)-33 with benzaldehyde under these conditions was only 65-80% selective for the anti adduct 34 (17-41% yield).

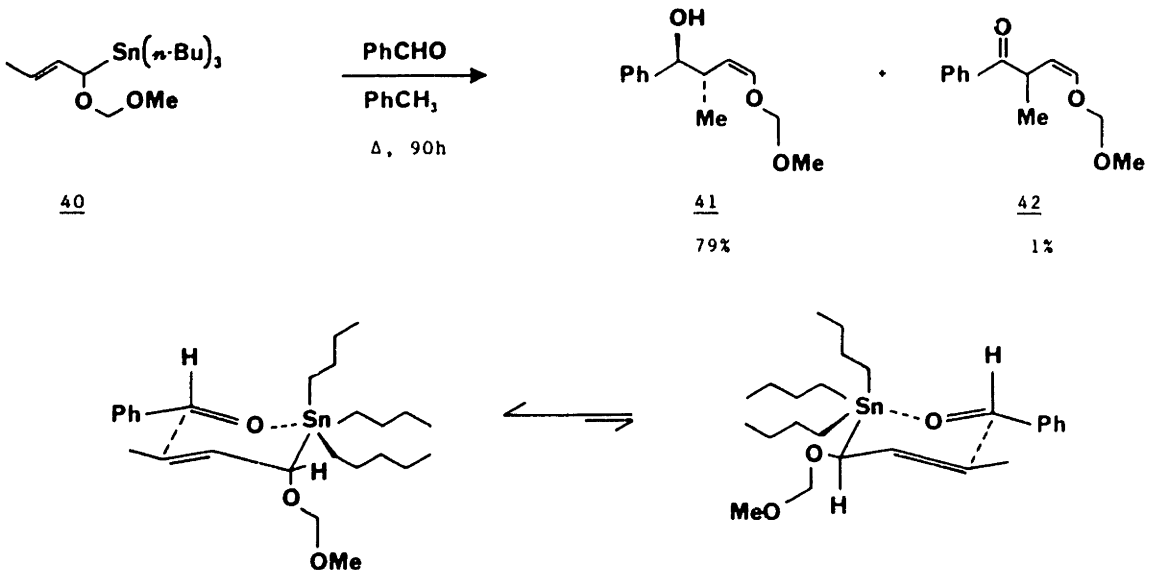
The reactivity of allylic stannane reagents is strongly influenced by the substituents on tin.[38] Crotylstannane derivatives have the following relative reactivities: $-SnX_3 > -Sn(nBu)X_2 > -Sn(nBu)_2X > -Sn(nBu)_3$.[38] The trihalocrotylstannanes are prepared in situ by reaction of allyliodide and SnF_2 (Scheme 8).[39] The reactions of isomeric mixtures of (crotyl)-$Sn(nBu)X_2$ and (crotyl)$SnX(nBu)_2$ have also been investigated

at different temperatures.[40] These reactions are thought to occur via cyclic transition states, but the stereochemical outcome does not always reflect the isomeric purity of the starting reagent.



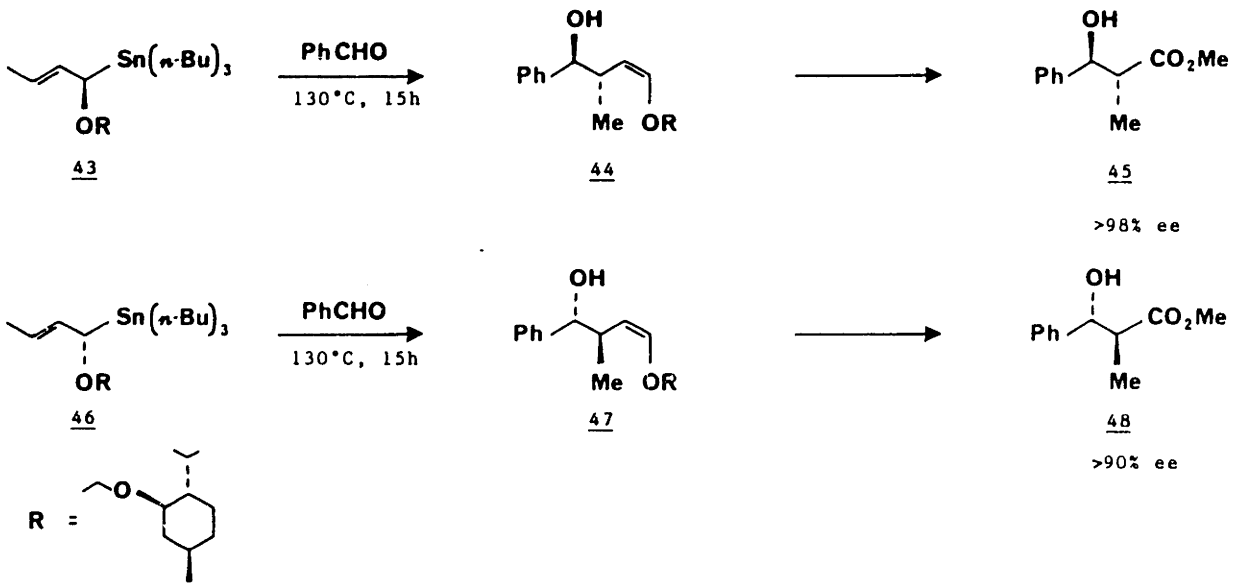
Scheme 8

Alkoxysubstituted reagents such as 40 react with a variety of aliphatic aldehydes with excellent diastereoselectivity.[41a] The stereochemistry of 40 requires that the α-alkoxy substituent be oriented in an axial position in the cyclic transition state, presumably to avoid steric interactions with the butyl groups on tin (Scheme 9).[41,42]



Scheme 9

Inspection of the transition states in Scheme 9 reveals that only one face of the reagent is accessible to the aldehyde. This observation has been successfully used in the enantioselective synthesis of 45 and 48 (Scheme 10).[41b] Chiral stannanes 43 and 46 were prepared by a sequence involving resolution with (-)-menthol. The thermal reaction of each gave a single adduct, 44 and 47. Conversion of these compounds to 45 and 48 showed that excellent enantioselectivity was realized in the aldehyde addition reaction.



Scheme 10

1.4) Boron

In the family of allylic boron compounds, dialkylallylicboranes are the most reactive but also the least configurationally stable.[16] Crotyldialkylboranes have been used for diastereoselective C-C bond formation only at -100°C. At

this temperature reagents such as 49 and 50 react with aldehydes to give the expected products with excellent selectivities (compound 51 was >10:1 (Z)-olefin in each case).[16c] However, the need to generate and use these reagents at -100°C (working at -78°C led to isomerization) severely limits their potential synthetic application.

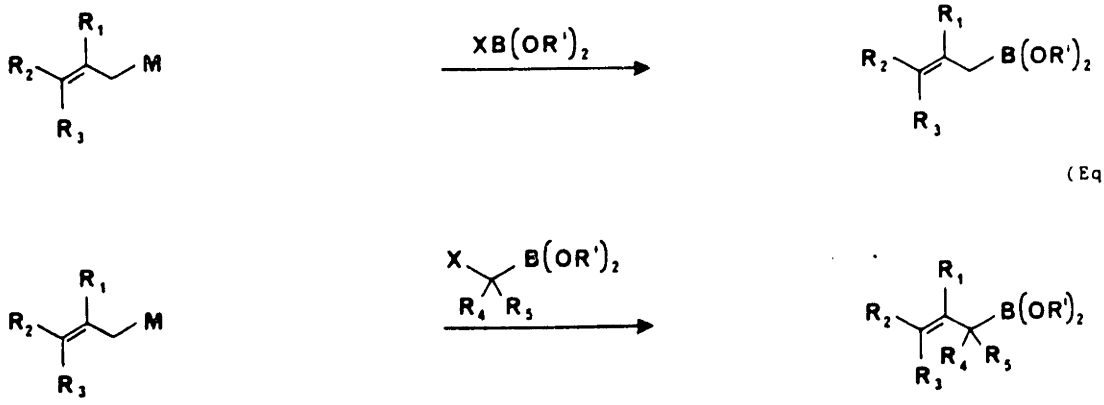
49, R= nBu
50, R= Et

51 52

>95:<5

These problems can be overcome by using crotylboronic esters. These reagents can be generated by the addition of an appropriate crotylmetal species to halodialkoxyborane or trialkylborate (Eqn. 1).[16b,43,44] Perhaps the most general preparative route involves the addition of vinyllithium or Grignard reagents to α-haloalkylboronates such as 53 and 54

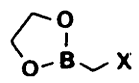
Scheme 11



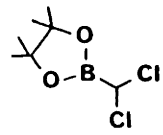
(Eqn. 1)

(Eqn. 2)

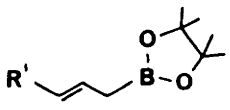
M= Li, MgX, K
X= F, Cl, Br



53, X= I, Cl

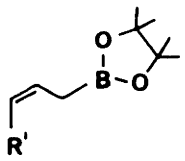


54



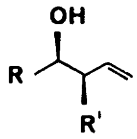
55

OR

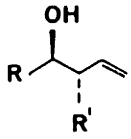


56

R-CHO →



57



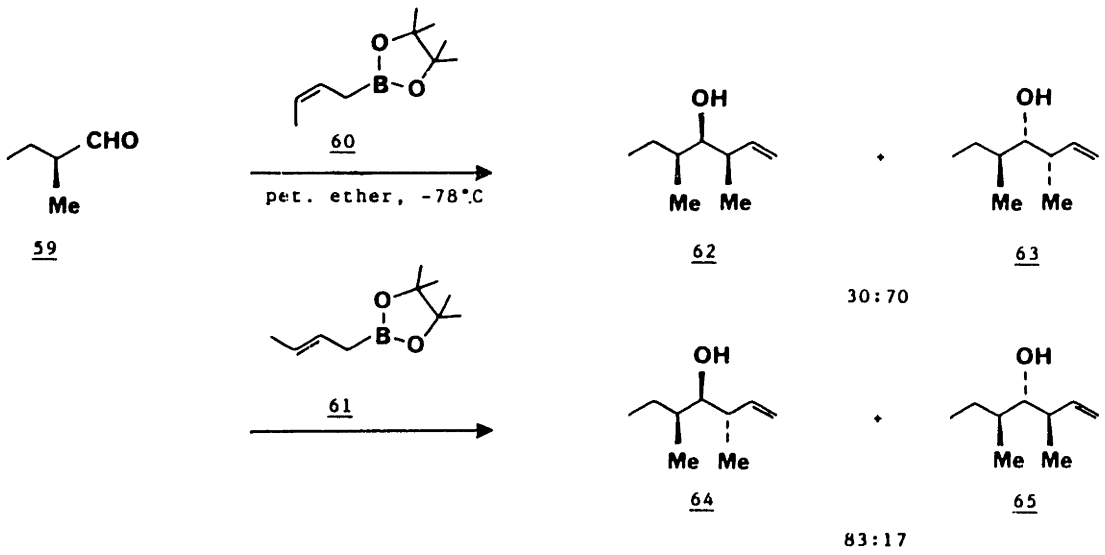
58

Boronate	R-CHO	57:58
55, R' = Me	PhCHO	6:94
	EtCHO	7:93
	iPrCHO	4:96
56, R' = Me	PhCHO	96: 4
	EtCHO	97: 3
	iPrCHO	96: 4
55, R' = OMe	PhCHO	5:95
	iPrCHO	2:98
56, R' = OMe	PhCHO	95:5
	iPrCHO	89:11
55, R' = $SiMe_3$	PhCHO	2:98
	$nC_7H_{15}CHO$	2:98
56, R' = $SiMe_3$	PhCHO	98: 2
	iPrCHO	95: 5

Scheme 12

(Eqn. 2).[45] These reagents are configurationally stable (except in the presence of Lewis acids) and can be handled at room temperature. The use of cyclic esters such as pinacol or ethylene glycol adds stability (reduces the sensitivity towards hydrolysis) and allows for easy handling.

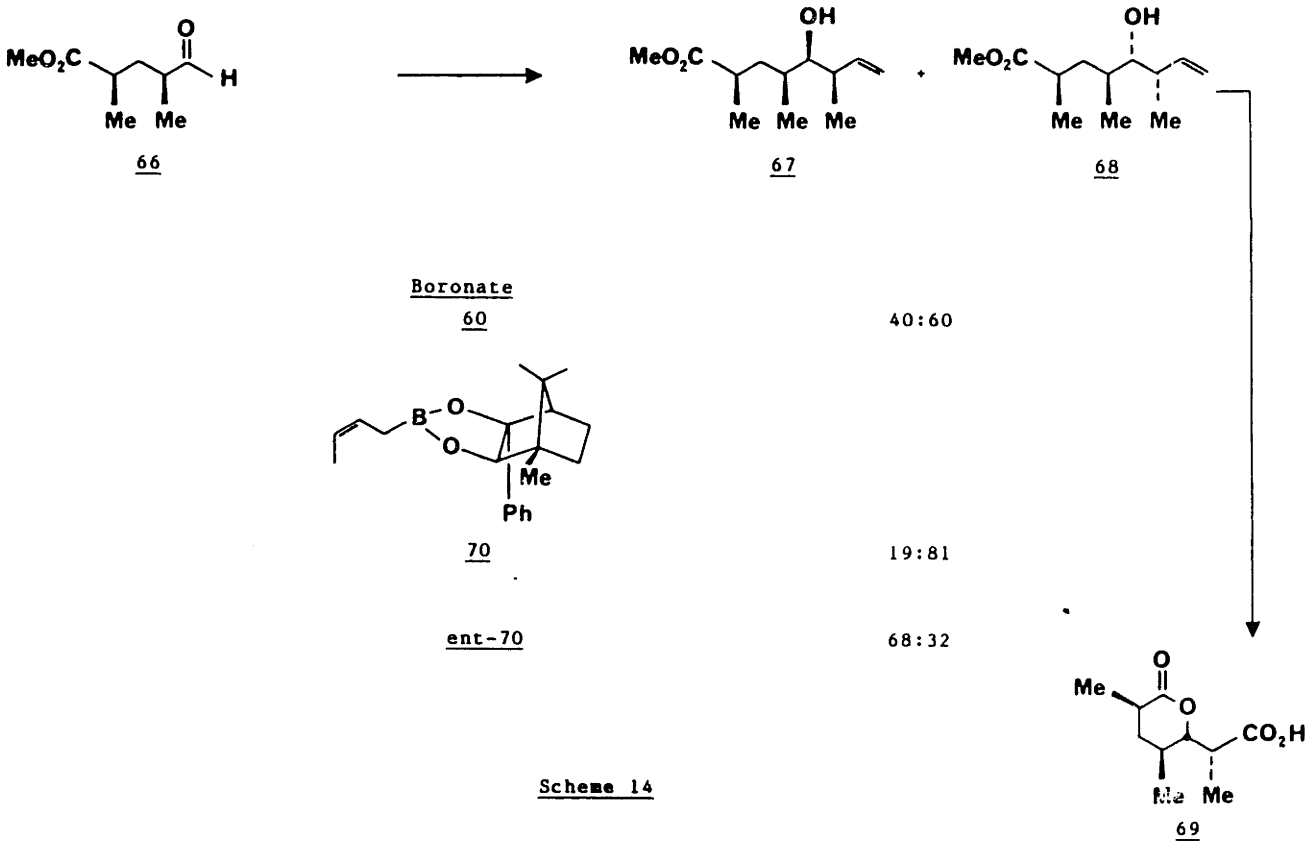
The diastereoselectivity of the aldehyde addition reactions of crotyl- and heteroatom-substituted allylic boronic esters has been investigated by a number of groups. Representative examples are summarized in Scheme 12,[43,46-48] which shows that excellent diastereoselectivity is realized in reactions with a variety of reagents and aldehydes.



Scheme 13

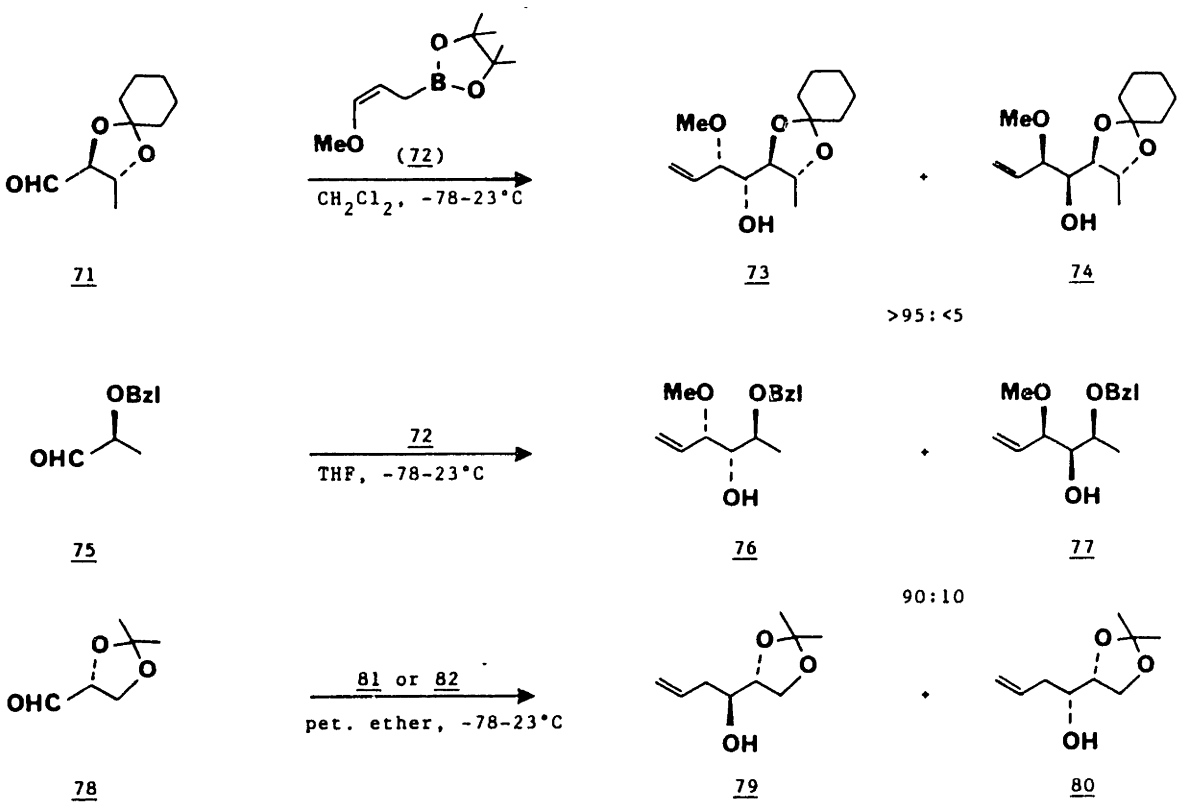
Several studies of the reactions of crotylboronates with chiral aldehydes have been reported. Reaction of α-methylbutanal 59 with the (Z)- and (E)-crotylboronates, 60 and 61, resulted in modest levels of 1,2-asymmetric induction (Scheme 13).[46d,e,h,i] The reaction of 60 with aldehyde 66 was used in a synthesis of Prelog-Djerassi lactone 69 (Scheme 14).[46d] The level of asymmetric induction when using 60 was low (60:40

favoring 68) but was raised to a moderate level (81:19) by using chiral ester 70. Interestingly, the selectivity obtained by using the enantiomer of 70 was 68:32 favoring 67. This is one of the first examples of double asymmetric induction in allylic organometallic chemistry.[4a]



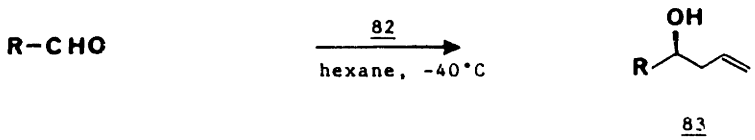
Scheme 14

The first highly stereoselective example of an allylic boronate reaction with a chiral aldehyde was reported by Roush, Harris and Lesur[49] who found that treatment of 71 with 72 afforded 73 with >95% stereoselectivity (Scheme 15). Shortly thereafter additional examples of reactions of allylic boronates with alkoxysubstituted aldehydes were reported by Wuts (75 & 72)[50] and Hoffmann (78 & 81)[46c] (Scheme 15). Although the latter reaction occurred with only moderate 1,2-asymmetric induction use of the chiral ester 82 improved the selectivity to >20:1.[46c]


OHC
MeO
(72)
CH_2Cl_2, -78-23°C
MeO
OH
MeO
OH
71
73
74
>95:<5
OBzl
OHC
72
THF, -78-23°C
MeO
OBzl
OH
MeO
OBzl
OH
75
76
77
90:10
OHC
81 or 82
pet. ether, -78-23°C
OH
OH
78
79
80
81
80:20
Ph
82
96: 4

Scheme 15

Applications of chiral allylic boronates such as 82 to enantioselective synthesis of homoallylic alcohols have been studied. The reactions of chiral boronate 82 with aldehydes afforded homoallylic alcohols with only moderate enantiomeric excesses (36-86% ee) (Scheme 16).[51,52] Unfortunately, selectivity decreases with increasing steric bulk of the aldehyde R group. Also as seen in Scheme 14 this chiral auxiliary is not highly effective in controlling facial selectivity in reactions with chiral aldehydes.



83

	R-CHO	Yield(%)	%ee	Configuration(83)
(1)	MeCHO	86	86	R
(2)	EtCHO	91	77	R
(3)	iPrCHO	88	70	S
(4)	tBuCHO	85	45	S
(5)	PhCHO	90	36	S

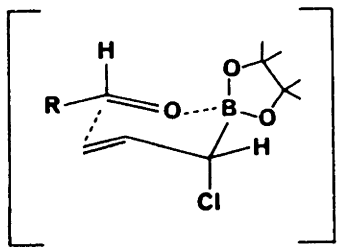
Scheme 16

Reactions of allylboronates with a chiral center adjacent to the boron atom have been found to be much more successful in this regard. The reaction of ca. 90% optically pure 84 with aldehydes gave excellent levels of 1,2-asymmetric induction.[53] These transformations proceed via the transition state shown in Scheme 17 with an axial placement of Cl.[54] These reactions are the most enantioselective transformations of a chiral allylic boronate reported to date. However, attempts

to extend this result to other allylic boronates have not been successful.[55]

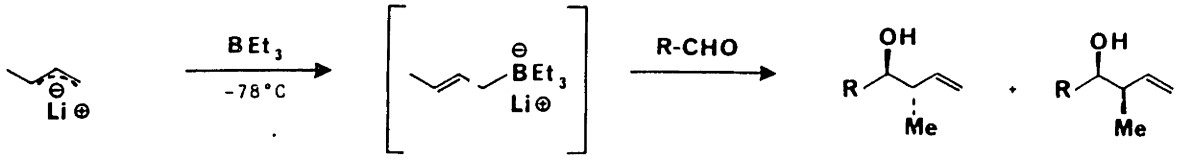
84 85 86

	R-CHO	85:86	%ee(85)	Configuration(85)
(1)	MeCHO	93: 7	90-93	S
(2)	EtCHO	94: 6	90-93	S
(3)	iPrCHO	96: 4	90-93	R
(4)	PhCHO	95: 5	90-93	R



Scheme 17

Diastereoselective reactions of crotylboron ate complexes with aldehydes have been investigated. Ate complex 87 was prepared by the addition of crotyllithium to BEt_3 (BBu_3 and Bu-9-BBN were also used) and was found to be mainly the (E)-crotyl isomer.[56] Reactions of 87 with aldehydes display modest selectivity for the anti diastereomer 88 (Scheme 18). Ate complex 90 was prepared by the addition of nBuLi (pyridine was also used) to crotylborane 91.[57] Reactions of 90 with aliphatic aldehydes show excellent diastereoselectivity for anti adduct 92 (Scheme 19).

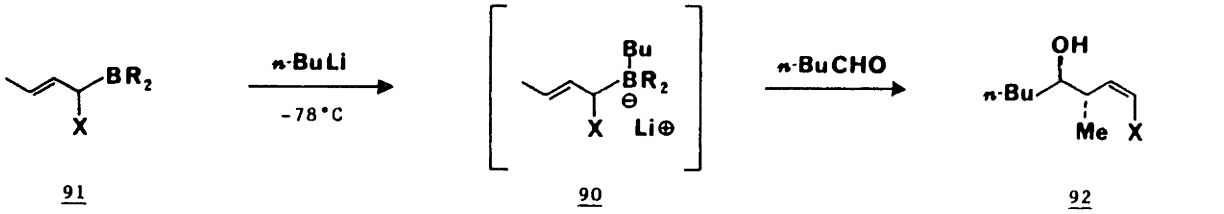


87 88 89

	R-CHO	88:89
(1)	PhCHO	83:17
(2)	MeCHO	85:15
(3)	iPrCHO	68:32

Scheme 18

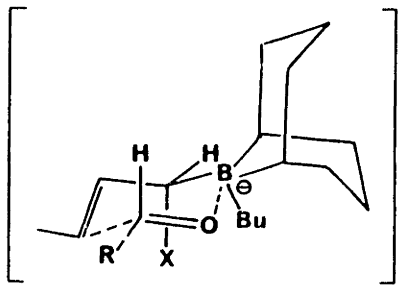
Yamamoto has rationalized these results by invoking cyclic transition states in which boron is coordinated with the carbonyl oxygen. In the case of 90 the X substituent is oriented in the axial position to minimize steric interactions (cf. 93). However, a transition state such as 93 seems unlikely, since the boron atom in these ate complexes has a full octet and therefore should not be able to coordinate with the carbonyl oxygen. If so, the diastereoselection observed in the reactions of 87 and 90 is not clearly explained at the present time.



91
R_2 = 9-BBN
X = $SiMe_3$, $Sn(nBu)_3$

90

92
>98% selectivity



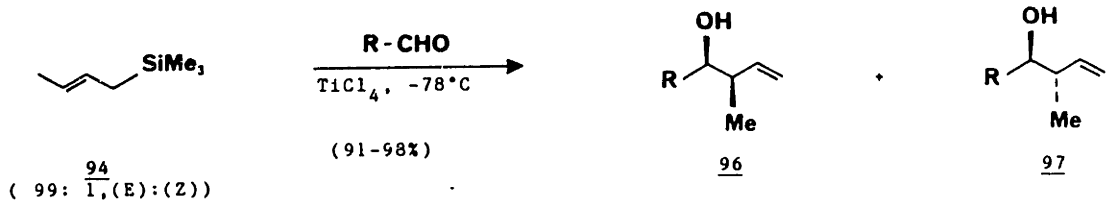
93

Scheme 19

2. Type II Crotylmetal Reagents

2.1) Silicon

The reaction of substituted allylsilanes with aldehydes occurs at low temperature (-78°C) in the presence of Lewis acids.[58,59] As expected for such Type II reagents, the reactions of 94 and 95 with aldehydes favored the formation of the syn adduct 96 (Scheme 20).[59] Surprisingly, however, the (E)-crotylreagent 94 was significantly more selective than the (Z)-isomer 95. The origin of this difference in selectivity is not apparent upon examination of the acyclic, extended

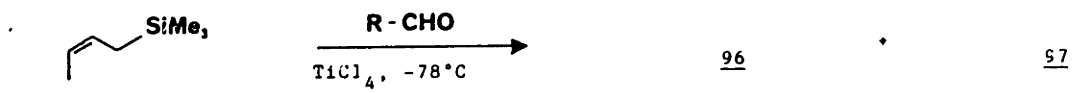


94 (99: 1, (E):(Z))

(91-98%)

96 97

	R-CHO	96:97
(1)	tBuCHO	>99:<1
(2)	iPrCHO	97: 3
(3)	EtCHO	95: 5



95 (97: 3, (Z):(E))

(87-98%)

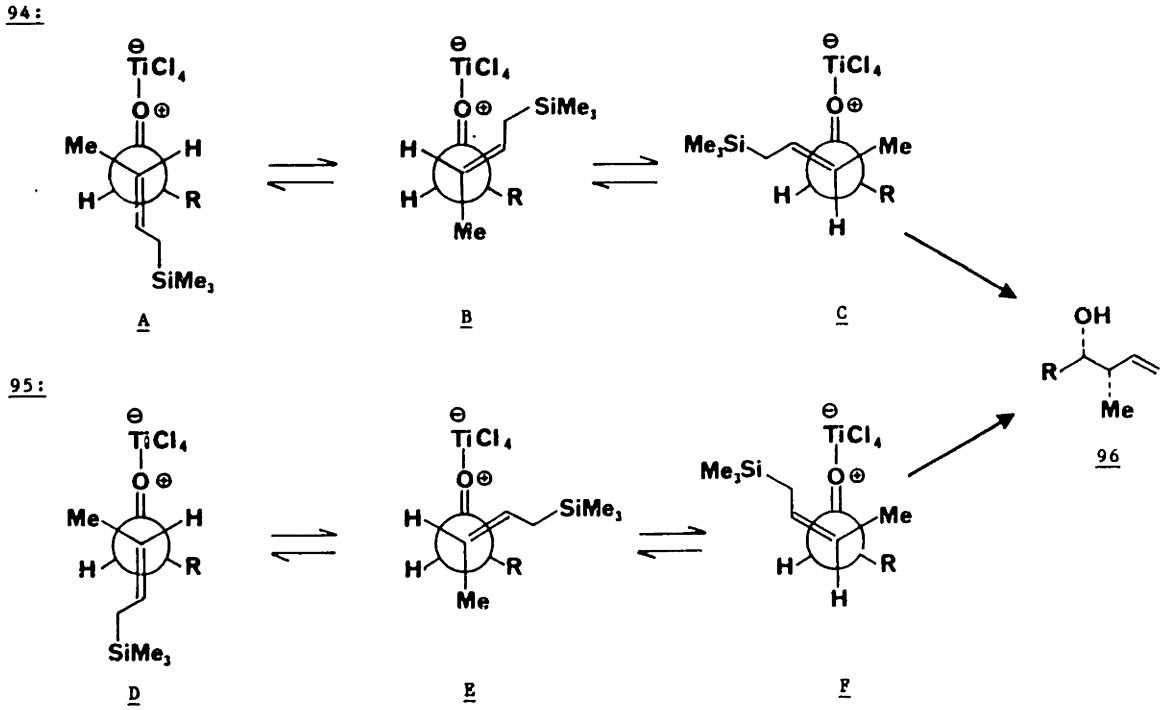
96 97

	R-CHO	96:97
(1)	tBuCHO	65:35
(2)	iPrCHO	64:36
(3)	EtCHO	69:31

Scheme 20

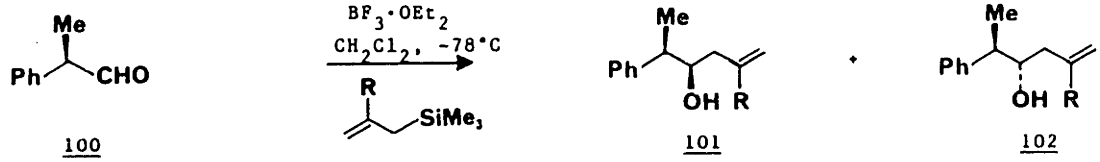
transition states proposed for such Type II reactions (compare transition states A (for 94) and D (for 95) (Scheme 21)).

The lower syn selectivity in the reactions of 95 may reflect a preference for synclinal orientation of the olefin and carbonyl group in the transition state. Recent studies by Denmark on the intramolecular addition of allylsilane to an aldehyde have shown a modest preference for synclinal orientation.[6a] Of the two syn-selective synclinal transition states available to 95, one (E) is severely hindered, enabling anti-selective transition states (not shown) to compete more effectively (Scheme 21).

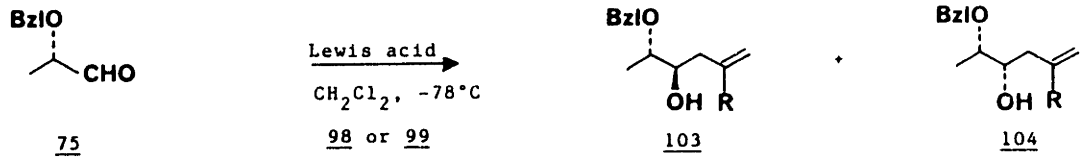


Scheme 21: Syn-Selective Transition States For 94 and 95.

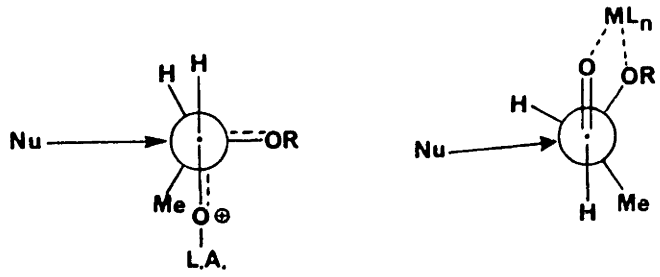
The reaction of allylsilanes 98 and 99 with a number of chiral aldehydes show moderate to excellent levels of 1,2-asymmetric induction depending on the structure of the aldehyde and the Lewis acid employed.[60,61] Examples of these reactions are shown in Scheme 22. Although the extent of facial diastereoselectivity in the reactions of 100 depends on the Lewis acid (best results were obtained with $BF_3 \cdot OEt_2$), reversal of selectivity to give 102 as the major product could not be achieved. In contrast, α-alkoxyaldehyde 75 showed excellent diastereoselectivity in reactions catalyzed by $SnCl_4$, and facial selectivity could be reversed by $BF_3 \cdot OEt_2$ as catalyst (Scheme 22). The results of the BF_3 catalyzed reactions can be interpreted in terms of the Felkin model for 1,2-asymmetric induction; whereas in the reactions of 75 catalyzed by $SnCl_4$, the stereochemical outcome is presumably determined by the Cram chelated model (Scheme 22).[30]



98, R = H	67:33
99, R = Me	88:12



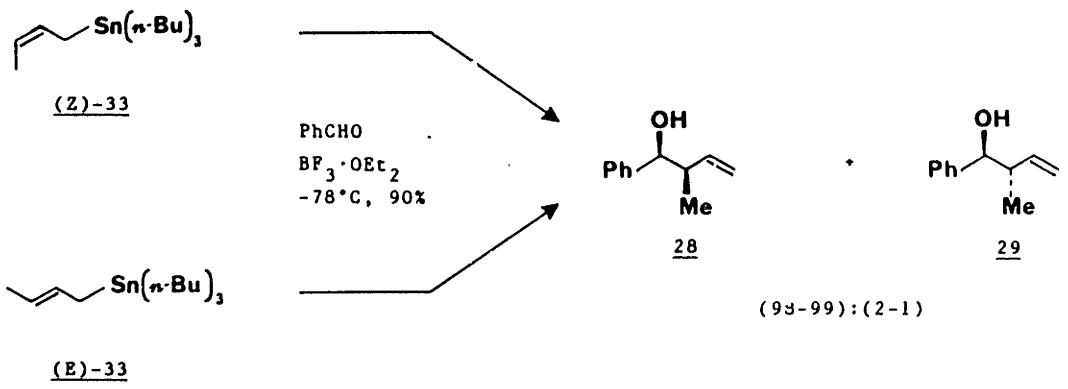
Reagent	Lewis Acid	103:104
98	$SnCl_4$	3:97
99	$SnCl_4$	2:98
98	$BF_3 \cdot OEt_2$	75:25
99	$BF_3 \cdot OEt_2$	86:14



Scheme 22

2.2) Tin

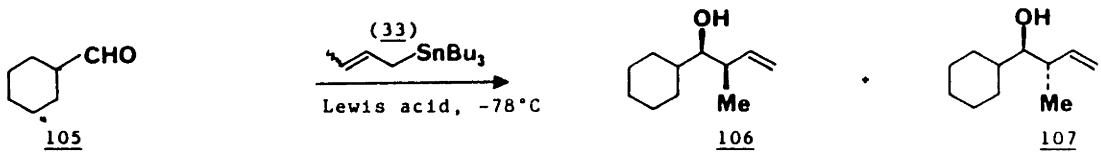
Crotylstannanes react with aldehydes in the presence of Lewis acids to give mainly the syn diastereomer.[58a] This stereochemical convergence of the reactions of (E)- and (Z)-crotylstannanes is shown in Scheme 23. The isomeric purity of 33 does not influence the diastereoselectivity of this reaction; each olefin isomer shows 98-99% selectivity for syn adduct 28.[62] In this respect the crotylstannanes differ from the crotylsilanes. However, when the "spectator" ligands on tin are changed from methyl or n-butyl to phenyl, the syn selectivity falls from 98:2 to 83:17.[63]



Scheme 23

A detailed study of the effect of the Lewis acid on the reactions of crotylstannane with aldehydes has revealed that both the ratio of the stannane to Lewis acid and the order of mixing of the reagents can influence the stereochemical outcome.[64] This is illustrated in Scheme 24 for the reaction of cyclohexane carboxaldehyde 105 and crotyltributylstannane.[64b]

The change in selectivity is especially drastic when $TiCl_4$ is used (entries 8 and 9). When the ratio of aldehyde to stannane to $TiCl_4$ is 1:1:1 and the reaction is performed by first premixing 105 with $TiCl_4$ and then adding 33, the syn isomer 106 predominates by a ratio of 13:1 (entry 8). However, when the $TiCl_4$ and stannane (2 equivalents each) are premixed before the addition of one equivalent of 105 (i.e. inverse addition), reverse selectivity favoring anti adduct 107 is seen by a factor of 21:1 (entry 9). The reversal of selectivity realized in the latter case most probably reflects the formation of a transmetallated product, e.g. $CH_3CH{=}CHCH_2{-}TiCl_3$, which



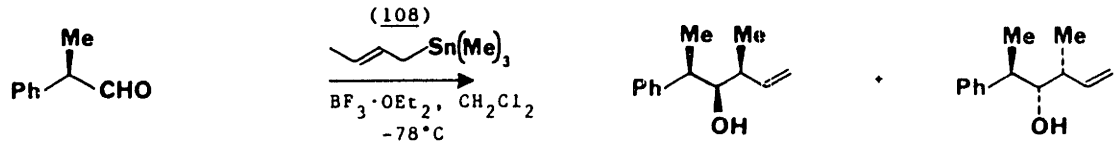
	Lewis Acid(equiv)	33(equiv)	106:107
(1)	$BF_3{\cdot}OEt_2$(1.05)	1.0	9:1
(2)	$BF_3{\cdot}OEt_2$(1.05)	2.1	25:1
(3)	$BF_3{\cdot}OEt_2$(1.05)[a]	2.1	25:1
(4)	$MgBr_2$(1.0)	1.0	1.4:1
(5)	ZnI_2(1.0)	1.0	1.1:1
(6)	$SnCl_4$(1.3)	0.8	1:1.1
(7)	$SnCl_4$(1.3)[a]	0.8	1:3.4
(8)	$TiCl_4$(1.05)	1.05	13:1
(9)	$TiCl_4$(2.1)[a]	2.0	1:21

(a) Inverse addition

Scheme 24

reacts with the aldehyde via a Type III mechanism (see Section 3.3). The normal Type II reaction pathway best accounts for the formation of 106 under the standard set of experimental conditions.

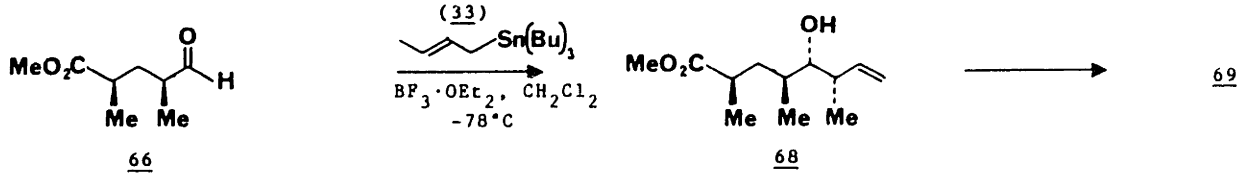
Several reactions of crotylstannanes with chiral aldehydes have been investigated. The $BF_3 \cdot OEt_2$ catalyzed reaction of 100 and 108 gave modest facial selectivity favoring the Cram-Felkin product 109. The 3,4-syn selectivity of this reaction was >99:1.[62]



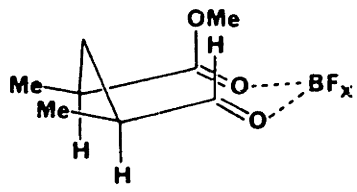
100 109 110

88:12

The $BF_3 \cdot OEt_2$ catalyzed addition of crotyltributylstannane (33) to 66 was applied to the synthesis of Prelog-Djerassi lactone 69.[62,65] The surprisingly high anti-Cram selectivity of this reaction has been attributed to the reactive intermediate 111 in which both carbonyl groups are coordinated to boron and only one face of the aldehyde is available for reaction with 33.



66 68 >94% selectivity

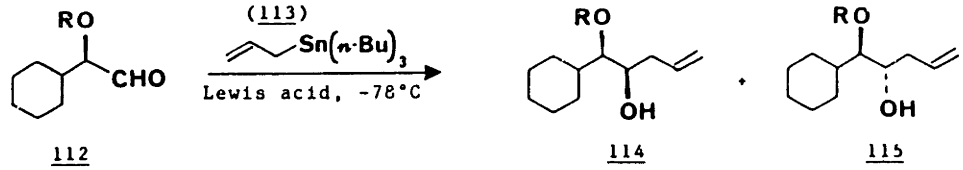


111

The effect of α- and β-alkoxysubstituents on the diastereoselectivity of allyl and crotylstannane reactions with chiral aldehydes has also been studied.[64] As in the reactions of allylsilanes with such aldehydes, the choice of Lewis acid strongly influences the stereochemical outcome. Moreover, the hydroxyl protecting group is also an important variable in these reactions. This is illustrated in Scheme 25 for reactions of α-alkoxyaldehyde 112 and allyltributylstannane (113). Selectivity for syn adduct 114 is greatest when $MgBr_2$ and a benzyl protecting group is used. Reversal of selectivity is best accomplished with $BF_3 \cdot OEt_2$ in combination with a t-butyldimethysilyl protecting group. The latter pair favors reaction via the Felkin transition state, whereas with $MgBr_2$ the reaction occurs primarily via a chelated intermediate (cf. Scheme 22). The use of the large silyl protecting group apparently inhibits chelate formation and also decreases electron density on oxygen thus stabilizing the Felkin transition state leading to anti adduct 115 (Scheme 25).[64a]

Attempts to extend these results to reactions with crotylstannanes have not been as successful. The reactions summarized in Scheme 26 for 116 are illustrative.[64b] Use of $MgBr_2$ in reactions of 33 with 116a or 116b gave excellent selectivity for the 3,4-syn,4,5-syn product where the facial selectivity is again chelation controlled. The use of $BF_3 \cdot OEt_2$ in these reactions, however, was only moderately effective in reversing the facial selectivity.

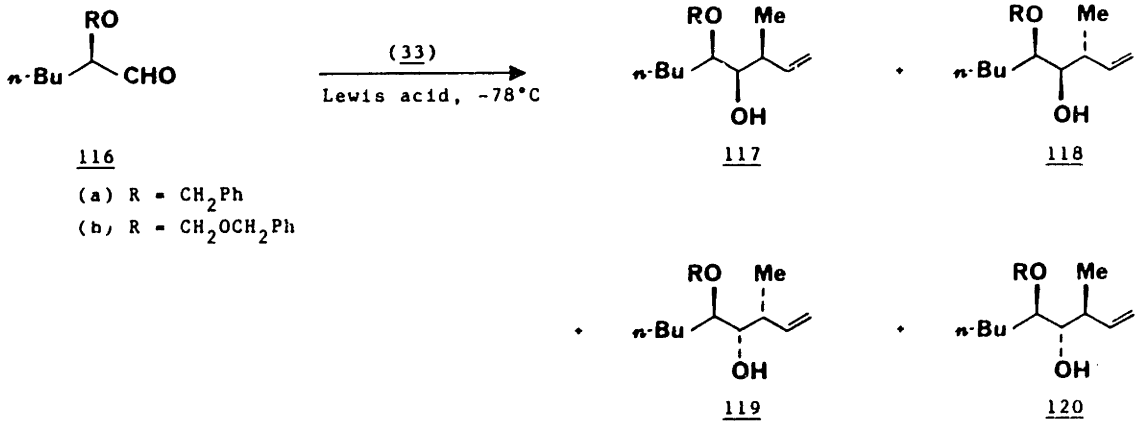
Reasonable levels of selectivity have been achieved in



112 114 115

112	Lewis Acid	114:115
(a) R = CH_2Ph	$MgBr_2$	>99: 1
	$BF_3 \cdot OEt_2$	39:61
(b) R = $Si(tBu)Me_2$	$MgBr_2$	21:79
	$BF_3 \cdot OEt_2$	5:95

Scheme 25



116

(a) R = CH_2Ph

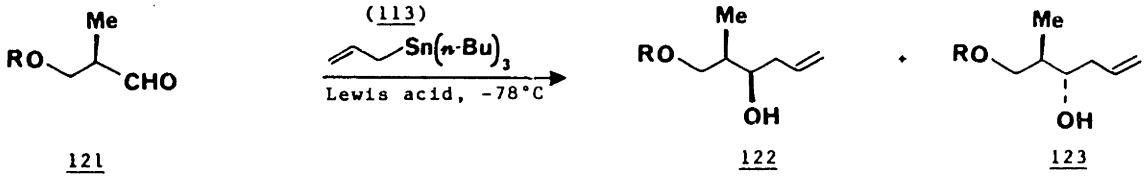
(b) R = CH_2OCH_2Ph

117 118 119 120

	Aldehyde	Lewis acid	117:118:119:120
(1)	116a	$MgBr_2$	93: 7 - -
(2)	116a	$BF_3 \cdot OEt_2$	39: 4 : 45: 12
(3)	116b	$MgBr_2$	91: 9 - -
(4)	116b	$BF_3 \cdot OEt_2$	23: 3 : 66: 8

Scheme 26

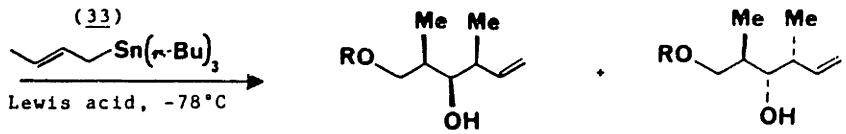
Lewis acid catalyzed reactions of allyl- and crotylstannane with β-alkoxyaldehydes (Scheme 27).[64c] Here again, it was not possible to reverse the aldehyde facial selectivity by varying the experimental conditions.



121
(a) R = CH_2Ph
(b) R = $Si(tBu)Ph_2$

122 123

	Aldehyde	Lewis Acid	122:123
(1)	121a	$BF_3 \cdot OEt_2$	52:48
(2)	121a	$MgBr_2$	72:28
(3)	121a	$TiCl_4$	82:18
(4)	121a	$SnCl_4$	90:10



124 125

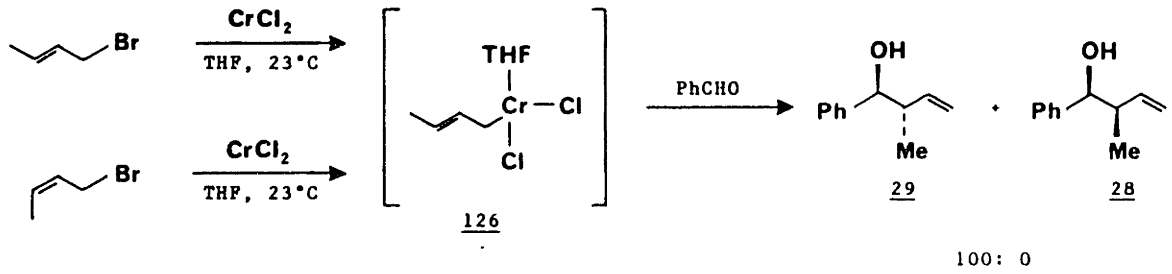
			124:125
(5)	121a	$TiCl_4$	41:59
(6)	121a	$SnCl_4$	42:58
(7)	121b	$BF_3 \cdot OEt_2$	90:10
(8)	121b	Et_2AlCl	83:17

Scheme 27

3. Type III Crotylmetal Reagents

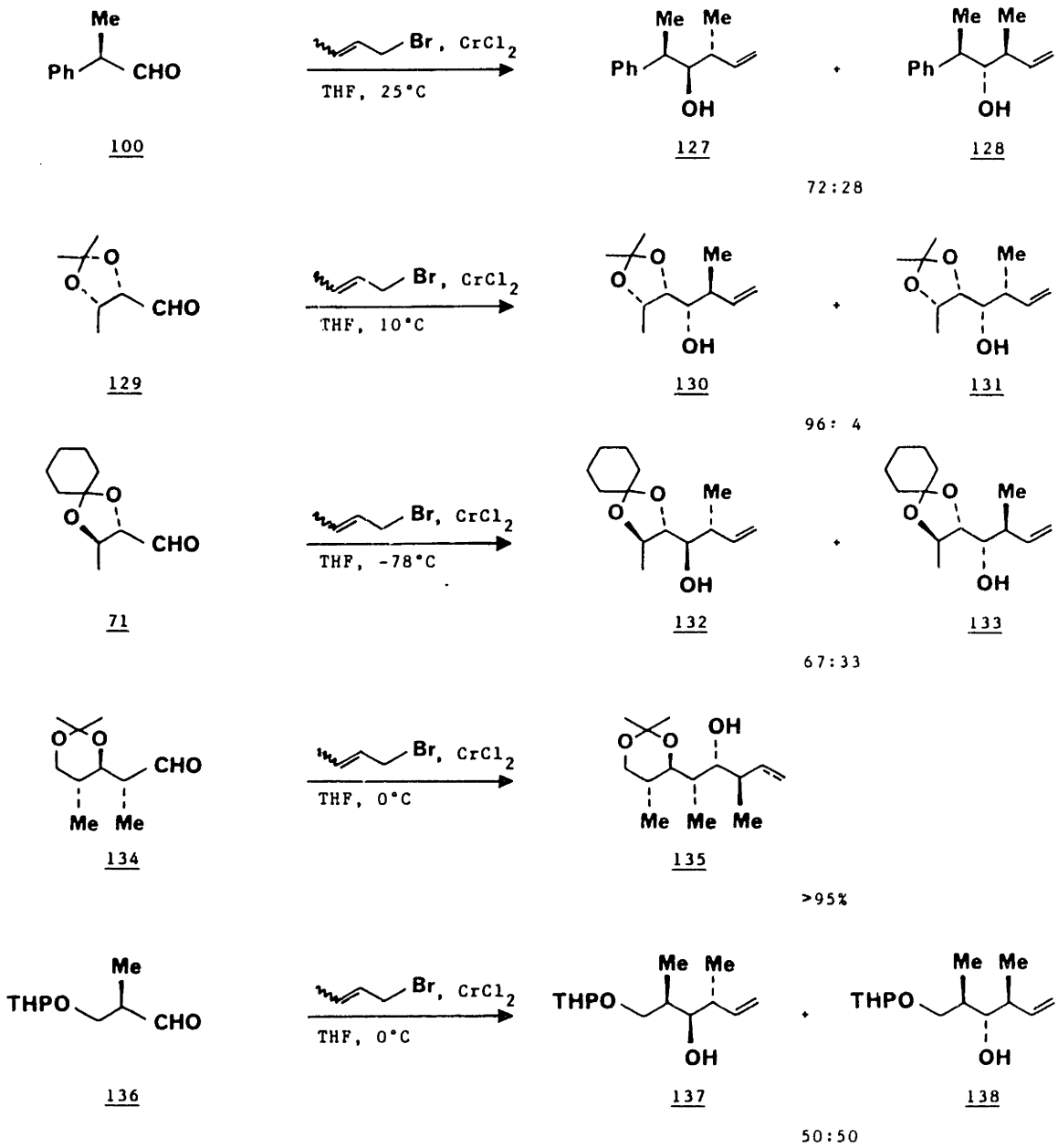
3.1) Chromium

Crotylchromium reagents prepared from an (E)- or (Z)-crotyl halide (Br or I) and chromous chloride react with aldehydes to give preferentially the anti diastereomer.[22,66,67] This stereochemical convergence can be explained by the formation of an intermediate crotylchromium-solvent complex 126 which exists as the more stable (E)-isomer, and which then reacts via a cyclic Type I transition state.[67]



Several examples of reactions of crotylchromium complexes with chiral aldehydes have been reported. As shown in Scheme 28, the facial selectivity varies from low to excellent depending on the structure of the aldehyde. The reaction of 100 with crotylchromium gave only moderate facial preference for the Cram predicted 3,4-anti,4,5-syn product 127.[67] The reaction of α, β-dialkoxyaldehydes 129[68] and 71[69] with crotylchromium showed surprisingly different facial selectivities. Similarly the reaction of aldehydes 134[39b,70] and 136[70] with crotylchromium showed large differences in stereoselectivity. The preference in these reactions for the 4,5-syn products

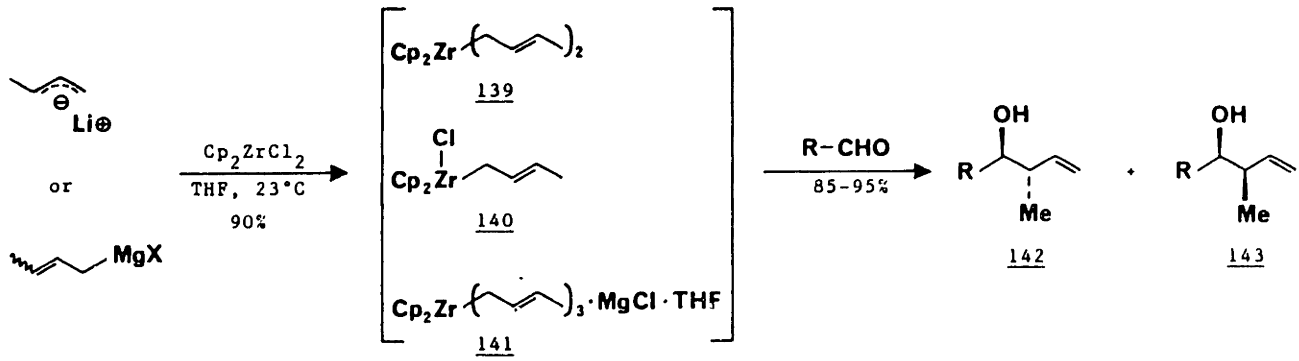
is rationalized in terms of a chelated transition state model. However it is apparent that the selectivities in these reactions are highly structure dependent.



Scheme 28

3.2) Zirconium

Crotylzirconium reagents such as 139-141[71] are prepared by addition of the appropriate stoichiometry of crotyllithium or crotyl Grignard reagent to bis(cyclopentadienyl)zirconium chloride. Reactions of reagents 139-141 with aliphatic aldehydes favor the formation of the anti-adduct 142 (Scheme 29).[72,73] Variable temperature NMR experiments have shown that 139 is a 60:40 mixture of (E):(Z)-isomers at 30°C and an 87:13 mixture at -70°C. Therefore a decrease in reaction temperature increases



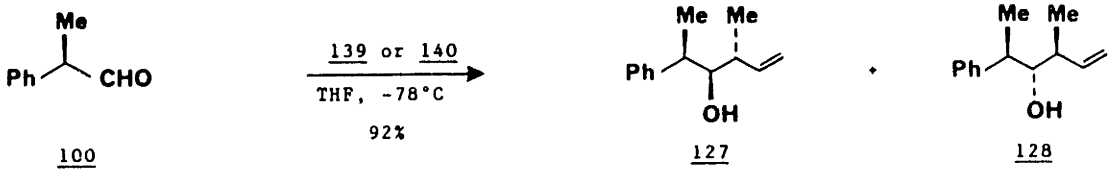
	Reagent	R-CHO(temp °C)	142:143
(1)	139	MeCHO(30°)	78:22
(2)	139	MeCHO(0°)	80:20
(3)	139	MeCHO(-78°)	88:12
(4)	139	MeCHO(-110)	91: 9
(5)	140	MeCHO(-78°)	77:23
(6)	140	EtCHO(-78°)	78:22
(7)	140	iPrCHO(-78°)	74:26
(8)	140	$MeO_2C(CH_2)_2CHO$(-78°)	94: 6
(9)	141	MeCHO(-78°)	58:42
(10)	141	iPrCHO(-78°)	55:45
(11)	$Cp_2Zr(OC_5H_{11})$(Crotyl)(144)	MeCHO(-78°)	90:10
(12)	144	iPrCHO(-78°)	89:11

Scheme 29

the concentration of (E)-139 which is reflected in the increased stereoselectivity of the reaction. Similar behavior is exhibited by 140 and 141 which exist as 85:15 and 55:45 mixtures of (E)- and (Z)-isomers respectively at -70°C.

As indicated by entries (11) and (12) in Scheme 29 crotylzirconium complexes with alkoxyl ligands are about as diastereoselective as 139 or 140. Optically active reagents, $Cp_2Zr(OR^*)$-(Crotyl) were prepared using (+)-menthol and (+)-amylalcohol in an attempt to achieve asymmetric synthesis. These reagents, however, showed no asymmetric induction suggesting that the alkoxyl asymmetric center is too far removed from the reacting termini to be effective.[72]

The reactions of reagents 139 and 140 with chiral aldehyde 100 have been investigated.[73] These reactions showed moderate selectivity for the 3,4-anti,4,5-syn adduct 127. The 4,5-syn preference in these reactions is as predicted by the Cram or Felkin transition state models.[30] The selectivity in these cases is very similar to that obtained using the crotylchromium reagent (See Scheme 28).

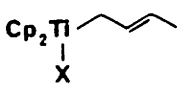


100 127 128

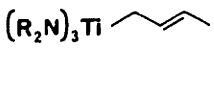
Reagent	
139	75:25
140	73:27

3.3) Titanium

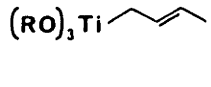
Crotyltitanium compounds of both the monohapto- and trihapto-form have been used in condensation reactions with aldehydes. Monohapto-reagents such as 145,[74] 146,[21] 147,[21] and 148[20,24] when treated with aldehydes favor formation of the anti diastereomer (Scheme 30).



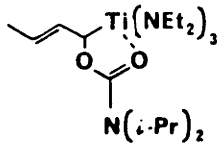
145
(a) X = Cl
(b) X = Br



146
(a) R = Me
(b) R = Et



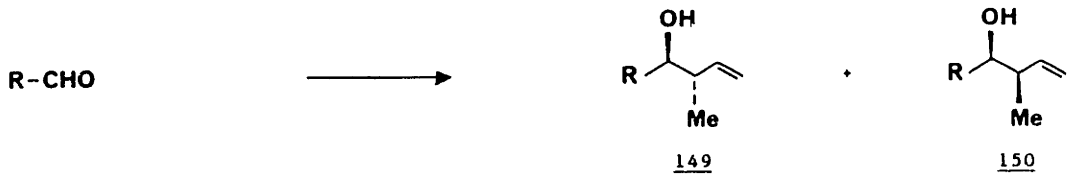
147
(a) R = Ph
(b) R = iPr



148

Reagents 145-147 are prepared by reaction of $CH_3CH{=}CHCH_2MgX$[75] with the appropriate titanium halide, for example Cp_2TiX_2, $(R_2N)_3TiCl$ or $(RO)_3TiCl$. These reagents presumably equilibrate to the more stable (E)-isomer prior to reaction with the aldehyde which occurs through cyclic Type I transition states.

The diastereoselectivity of the reactions of 145 with aldehydes can be reversed by performing the reactions in the presence of Lewis acids. Reetz has shown that the addition of $BF_3 \cdot OEt_2$ to the reaction of 145b with an aliphatic aldehyde results in formation of the syn diastereomer with good to excellent selectivities.[76] These reactions presumably proceed via an acyclic Type II transition state (Scheme 30). Interestingly, addition of $BF_3 \cdot OEt_2$ to reactions involving 147b did not



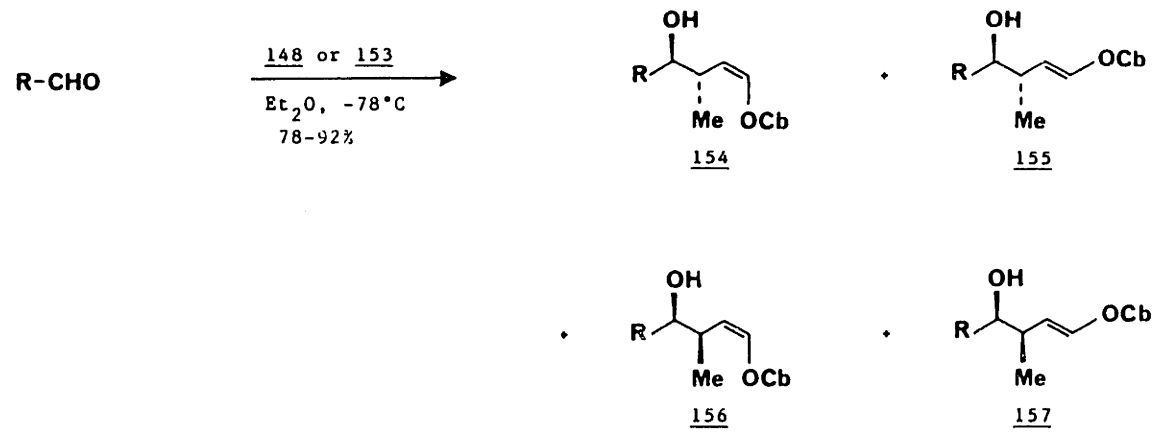
149 150

	R-CHO (temp °C)	Reagent	149:150
(1)	EtCHO(-35°)	145a	66:34
(2)	PhCHO(-35°)	145a	60:40
(3)	EtCHO(-35°)	145b	96: 4
(4)	PhCHO(-35°)	145b	99: 1
(5)	PhCHO(-78°)	146a	48:52
(6)	PhCHO(-78°)	146b	70:30
(7)	PhCHO(-78)	147a	85:15
(8)	PhCHO(-78°)	147b	80:20

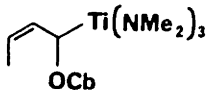
151 152

	R-CHO	151:152
(1)	PhCHO	14:86
(2)	iPrCHO	9:91

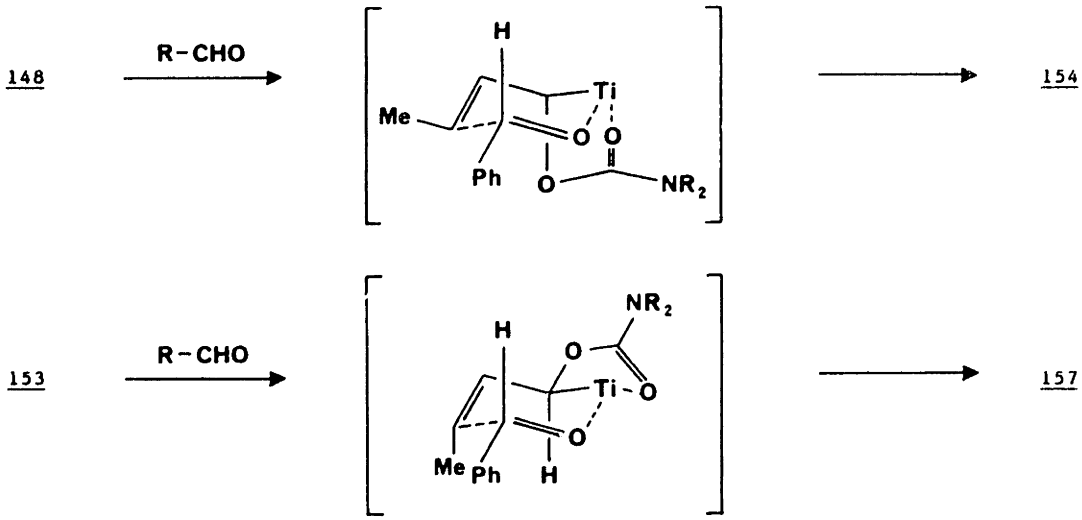
Scheme 30



Cb = $CON(iPr)_2$

	R-CHO	Crotylreagent	154:155:156:157
(1)	MeCHO	148	97 - 3 -
(2)	tBuCHO	148	85 - 15 -
(3)	tBuCHO		11: 18: 12: 59

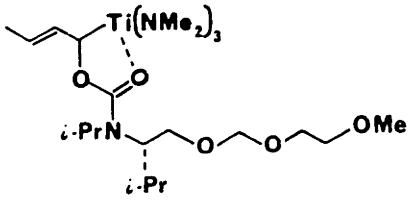
153



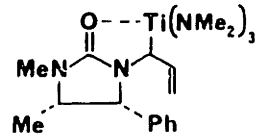
Scheme 31

affect a change in diastereoselectivity.

Reagent 148 is available with high isomeric purity via the transmetallation of the lithiocarbamate 9.[20] The (Z)-crotyltitanium reagent 153 was prepared in an analogous fashion. Reagent 148 reacts with aldehydes via a cyclic transition state where the OCb group is oriented in the axial position leading selectively to the 3,4-anti diastereomer (Scheme 31). The selectivity realized with 153, however, was substantially lower.[20,24] Attempts at using a chiral reagent such as 158 to induce asymmetry in the reaction with acetaldehyde gave only a 60:40 diastereomeric ratio.[24] However, recent work with the rigid system 159 shows more promise.[77] This species exhibited diastereofacial selectivities between 94-98% in reactions with aliphatic aldehydes.

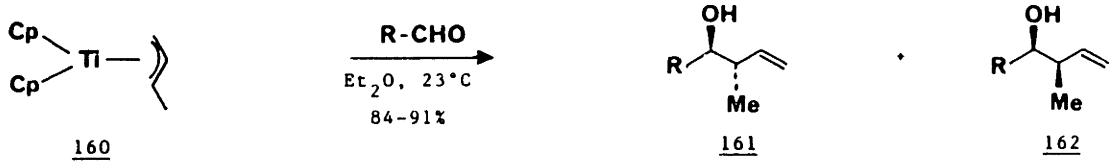


158



159

The reactions of trihapto-crotyltitanium reagents with aldehydes have not been extensively studied. However, Sato has shown that the reaction of π-crotyldicyclopentadienyltitanium(II), (160), with benzaldehyde and propionaldehyde are selective for the anti adduct 161 (Scheme 32).[74] Reactions of 163(a-c) with propionaldehyde also favor the 3,4-anti product.[74]

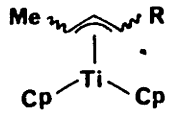


160 161 162

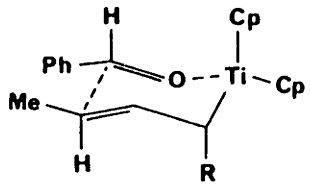
R-CHO	
PhCHO	95: 5
EtCHO	93: 7

Scheme 32

Sato suggests that the stereochemical preference in these reactions is consistent with a cyclic transition state where reaction occurs via the η^1-form (164).



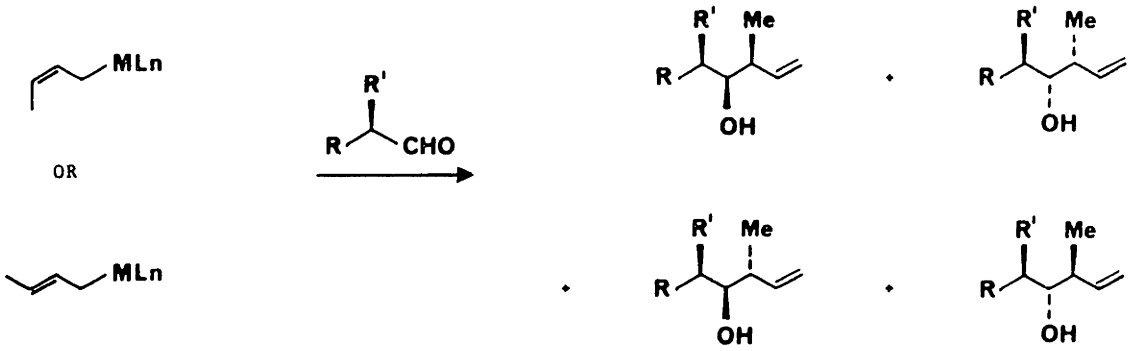
163
(a) R = $SiMe_3$
(b) R = OPh
(c) R = SPh



164

D. SUMMARY

As stated at the outset of this survey, the ultimate goal of work in this area is the design of reagents which enable the selective synthesis of any one of the diastereomers in Scheme 33. It is clear from the preceding literature review



Scheme 33

that a number of methods exist for controlling diastereoselectivity in reactions of crotylmetal compounds with achiral aldehydes. However, control of diastereofacial selectivity in reactions with chiral aldehydes and/or chiral reagents has not yet been fully realized.

Of the many crotylmetal reagents which have been studied, crotylboronates seem particularly attractive for many appli-

cations:

(i) stereochemically defined (Z)- or (E)- reagents are accessible by several flexible synthetic routes;

(ii) these reagents react stereoselectively with aldehydes via Type I cyclic transition states enabling the predictable control of one of the two stereochemical variables in Scheme 33 (i.e. the C_3-C_4 stereochemistry);

(iii) these reagents are easily handled, are compatible with a wide range of functionality, and reactions with aldehydes occur under mild conditions; and

(iv) the potential exists for the development of chiral reagents.

Since very little information was available regarding the stereochemical features of the reactions of crotylboronates with chiral aldehydes, we decided to address this question by performing a detailed study of the stereochemical outcome of the reactions of pinacol crotylboronates with α,β-dialkoxy-aldehydes. This study is described in the following chapter.

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75. The equilibrium mixture of C_4H_7MgCl in ether is 60:40, (E):(Z); see reference 11(c).

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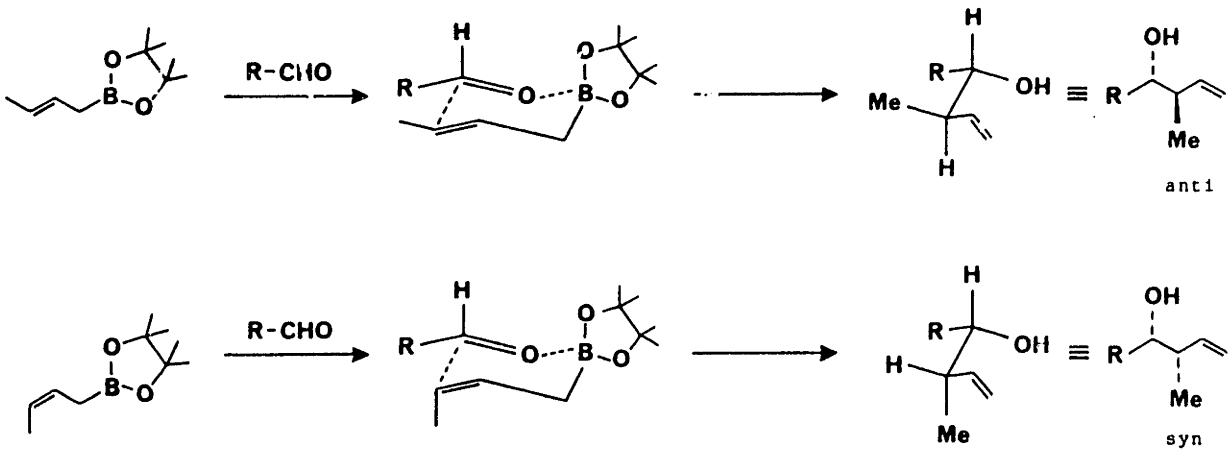
CHAPTER II

STEREOCHEMISTRY OF THE REACTIONS OF PINACOL CROTYLBORONATES WITH α, β-DIALKOXYALDEHYDES

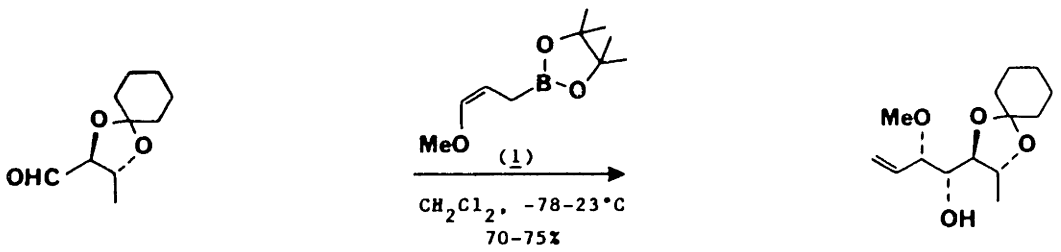
A. INTRODUCTION

A transformation with broad significance for the control of acyclic stereochemistry is the reaction of chiral carbonyl compounds with organometallic reagents.[1,2] Crotylmetal compounds[3] (and related propionate aldol equivalents[4]) which generate two new stereochemical relationships in the C-C bond forming step are of considerable interest in this context. Of the numerous crotylmetal reagents which have been studied,[3] crotylboronates seem particularly attractive since stereochemically defined (Z)- or (E)-reagents are readily accessible,[3h-j,5] and because the olefinic geometry is transmitted predictably to a syn or anti relationship in the product via cyclic transition states (Scheme 1).[3i] Remarkably, prior to the initiation of our studies, relatively little information was available regarding the stereochemistry of crotylboronate reactions with chiral aldehydes.[6]



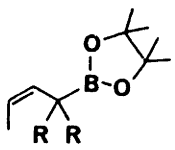
Scheme 1

The observation recorded by Roush and Harris [6b] that the reaction of γ-methoxyallylboronate 1 and L-deoxythreose-cyclohexylketal 2 proceeds with exceptional stereoselectivity, prompted us to examine the reactions of crotylboronates 4-7 with 2 and D-glyceraldehyde acetonide 8. Aldehydes such



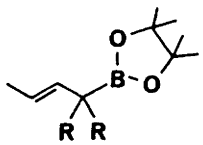
2 → 3 (>19:1)

as 2 and 8 have been used extensively to probe the diastereofacial selectivity of reactions with a range of nucleophiles, and therefore are regarded as useful model systems.[2b,c,7]



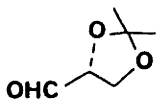
4, R=H

5, R=Me



6, R=H

7, R=Me



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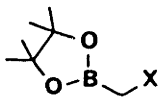
B. SYNTHESIS OF REAGENTS

1.) Preparation of Crotylboronates 4-7

A number of routes are available for the synthesis of functionalized allylic boronates.[3h-j,5,8] A method that is particularly attractive due to its generality involves the addition of a stereochemically defined vinyllithium species[9] to an α-haloalkylboronate.[3h,5,10-12] Since reagents 4-6

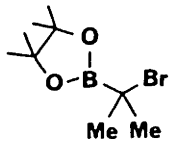
had already been prepared by using this methodology,[3h,i] we selected this chemistry as the starting point for our investigations.

α-Halomethylboronates 9 and 10 were synthesized by the procedures described by Wuts[12] whereas 2-bromo-2-propylboronate (11) was prepared by using the method reported by Brown.[5] (Z)-Propenylbromide (12) of >99% isomeric purity was obtained by spinning band distillation of the commercial mixture (70:30, (E):(Z)).[9e] (E)-Propenylbromide (13) however, could not be purified in this manner because of the ease with which it isomerizes. Therefore, bromide 13 was prepared by treating the commercial 70:30 mixture of 12 and 13 with 0.75 equivalents of NaOH in n-butanol at reflux, which selectively eliminates HBr from 12.[3f] Flash distillation (0°C, 1mm) of 13 directly from the reaction mixture gave material of >99% isomeric purity. Both 12 and 13 were distilled directly

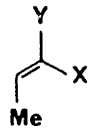


9, X=Cl

10, X=I



11



12, X=Br, Y=H

13, X=H, Y=Br

14, X=Li, Y=H

15, X=H, Y=Li

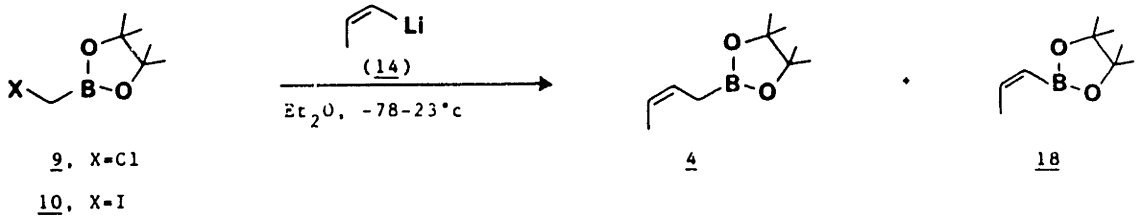
16, X=MgBr, Y=H

17, X=H, Y=MgBr

onto K_2CO_3 and were either used immediately or stored under argon at -78°C to prevent isomerization. Finally, bromides 12 and 13 were lithiated by treatment with 1% Na-Li dispersion in ether at 10°C using the procedure described by Whitesides.[9e,13] Under these carefully controlled conditions, lithiation of 12 and 13 is accompanied by less than 1% and 3.5% isomerization, respectively.[9e,13]

Wuts has reported that the reaction of 9 with 2 equivalents of 14 affords 4 in 47% yield.[3h] In our hands this method afforded 4 (89-95% isomeric purity) in variable and nonreproducible yields. The product obtained by this procedure contained at least 20-30%, and sometimes even 80% of propenylboronate 18 (Table 1). Attempts to suppress the formation of 18 by varying the stoichiometry, temperature and reaction time were of no avail. We presume that 18 is produced either from 19 or 20 (see Scheme 2). Addition of 14 to 9 gives ate complex 19 which decomposes to 4. This material can react with a second equivalent of 14 to give a new ate complex 20 which can decompose on workup to give 18. It is also possible that ate complex 19 undergoes α-elimination to afford

Table 1



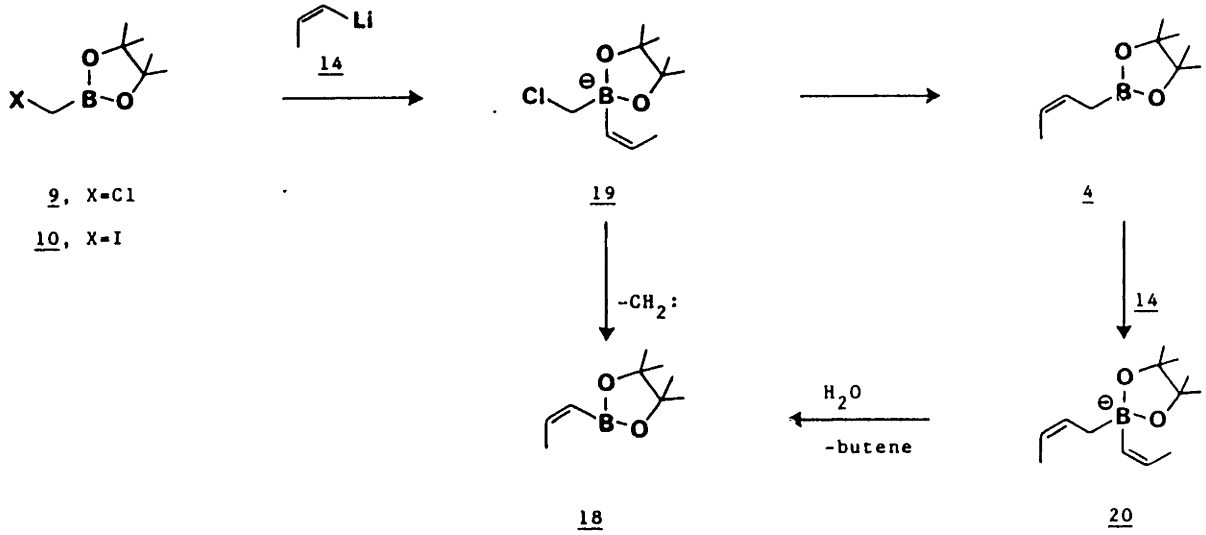
9, X=Cl
10, X=I

4 18

Substrate	14(equiv)	Yield	4:18
9	2.0	50%	20:80
9	1.2	--	-- --[a]
9	0.9	48%	73:27
10	1.2	48%	72:28

(a) Reaction failed altogether.

18 directly with loss of methylene. (Scheme 2).



9, X=Cl
10, X=I

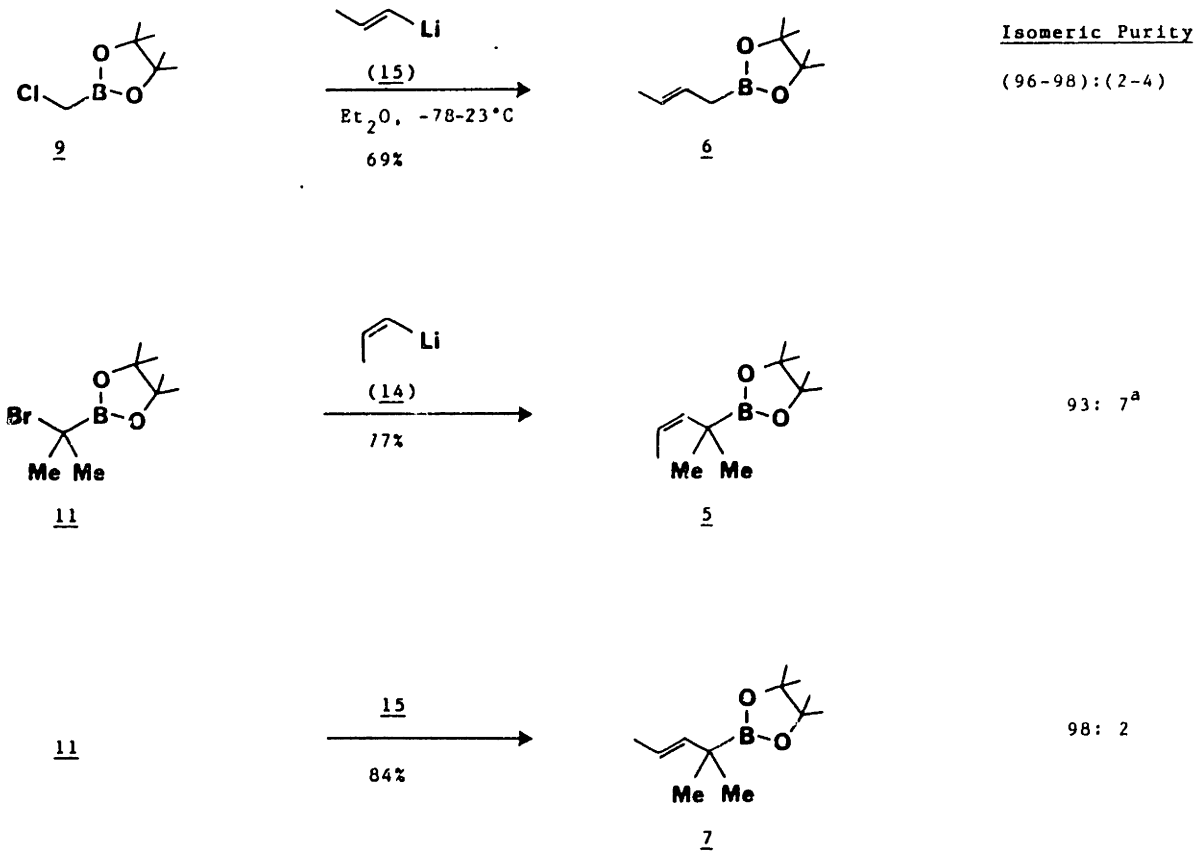
19 4 18 20

Scheme 2

Fortunately, these problems were not encountered in the synthesis of boronates 5-7 (Table 2). These reagents were prepared by dropwise addition of a solution of 14 or 15 (1.1 equivalents) to the appropriate α-haloboronate (9-11) in

Et_2O at -78°C. The reaction mixtures were allowed to warm to room temperature and stirred for 6-10h. The products were purified by distillation and the isomeric purity assessed by capillary GC analysis. Reagents 5-7 prepared in this manner contained <5% propenylboronate 18. Also, it is important to note that under the conditions of GC analysis or distillation no evidence for reagent isomerization was detected. Thus, boronates 5, 6, and 7 are stable at temperatures of up to 100°C at least for short periods of time (see Experimental). These reagents can be handled at room temperature, exposed to the atmosphere and even chromatographed on silica gel without extensive decomposition. They can also be stored

Table 2



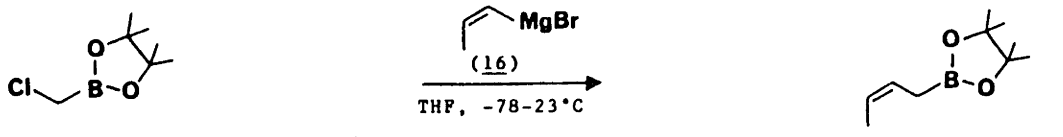
(a) This experiment was performed with 14 prepared from bromide 12 of only 94% isomeric purity. It should be possible to prepare 5 of higher isomeric purity by using 14 of higher purity.

at -20°C under an inert atmosphere for extended periods of time.

The synthesis of (Z)-crotylboronate 4 remained an unsolved problem. Matteson has used $ZnCl_2$ to catalyze the substitution of α-haloboronic esters with a range of organolithium reagents.[14] The $ZnCl_2$ apparently functions by catalyzing the decomposition of intermediate ate complexes such as 19. Attempts to employ this methodology in the preparation of 4 were unsuccessful (starting material (9 or 10) was recovered).[15]

Similarly, attempts to synthesize 4 by the reaction of 9 with the Grignard reagent 16 prepared *in situ* from $MgBr_2$ and propenyllithium 14 were unsuccessful. Presumably these experiments failed due to the insolubility of 16 in Et_2O[16] (a solution of $MgBr_2$ in Et_2O-C_6H_6[17] added to 14 in Et_2O). In addition, attempts to perform this reaction in THF were analogously unsuccessful owing presumably to the low solubility of $MgBr_2$ in this solvent.

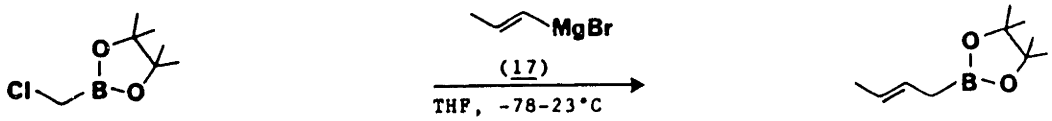
A good yield of 4 was finally obtained by the reaction of chloride 9 and (Z)-propenyl Grignard 16 (1.1 equivalents), prepared from 12 and Mg in THF using the procedures described by Seyferth.[18]



9 4 (95:5, (Z):(E))

Crotylboronate 4 prepared in this manner was 95% isomerically pure and contained <1% propenylboronate 18. The propenyl Grignard route was also successfully applied to the synthesis of 6, but in this case the isomeric purity was ≤90% (Table 3).

Table 3

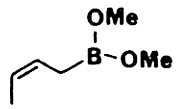


9 6

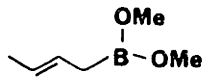
	17(equiv)	Isomeric Purity((E):(Z))	Isolated Yield
(1)	1.0	87.0:13.0	78%
(2)	1.3	89.6:10.4	74%
(3)	1.45	89.9:10.1	79%
(4)	1.7	90.1: 9.9	--
(5)	2.0	91.0: 9.0	70%

The high isomeric purity of 4 and 6 obtained by the Grignard route was surprising since work from other laboratories has shown that the isomeric purity of (Z)-propenyl Grignard 16 (prepared from >99% pure bromide 12) is only 90-95%, and that the isomeric purity of (E)-propenyl Grignard 17 is only ca. 80%.[19] The data in Table 3 suggest that 17 may be slightly more reactive than 16, since the isomeric purity of 6 increases as the number of equivalents of 17 was increased. This does not satisfactorily explain the 87% isomeric purity of 6 obtained when 9 was treated with 1.0 equivalents of 17 (Table 3, entry 1). We did not, however, determine the isomeric purity of 17 by independent methods.

Although 95% isomerically pure (Z)-crotylboronate 4 was now available, we were still interested in preparing this reagent with a higher degree of stereoselectivity. We therefore turned to modification of methodology reported originally by Schlosser who prepared boronates 21 and 22 with 97% and 98% selectivity, respectively.[3j,20] Thus, metallation of

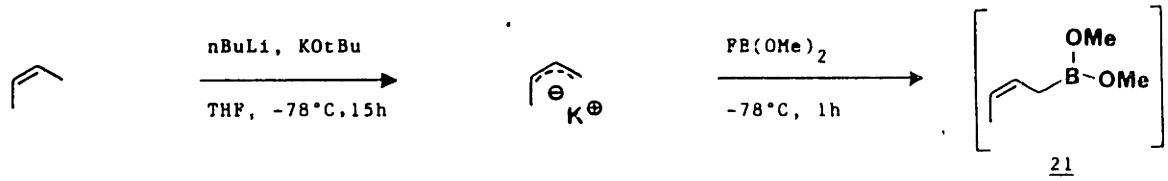


21

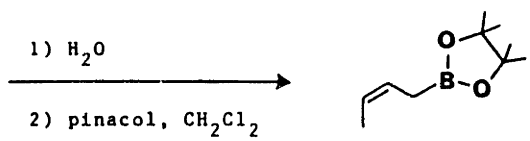


22

(Z)-2-butene with 1.0 equivalents of the complex base generated from nBuLi and KOtBu in THF at -78°C for 15h followed by treatment with 1.1 equivalents of fluorodimethoxyborane at -78°C for 1h generated 21. The reaction mixture was hydrolyzed by diluting with water and the crude crotylboronic acid was esterified with pinacol to afford 4 in 68-75% yield with an isomeric purity of 97-98%. It should be noted that this procedure is much more direct and convenient than that reported by Hoffmann for the preparation of 4.[3i]



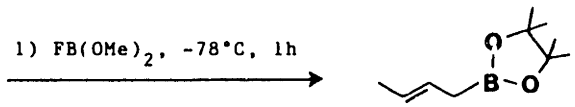
21



4

97-98% isomeric purity

Application of this method to the preparation of (E)-crotylboronate 6 was not successful in our hands. The lower isomeric purity realized in this case is due to the ease of iscmerization of (E)-crotylpotassium to the more stable (Z)-isomer.[21] Our best effort afforded 6 in 50% yield and 90% isomeric purity. Recently this procedure has succeusfully been used to prepare 6 with an isomeric purity of 96%.[22]



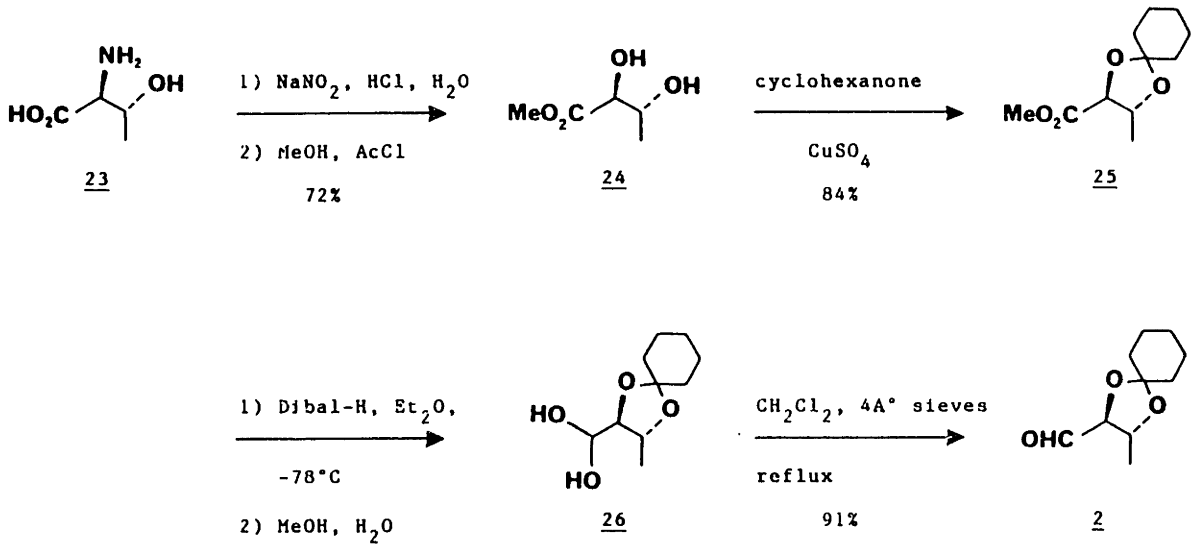
6

(90:10, (E):(Z))

In summary, the synthesis of 4 which gave the highest isomeric purity was the (Z)-crotylpotassium route. Reagents 5-7, on the other hand, were best prepared via the propenyllithium/ α-haloalkylboronate route summarized in Table 2.

2.) Synthesis of 4-Deoxythreose Cyclohexylketal (2)

Aldehyde 2 was prepared form L-threonine (23) by the sequence summarized in Scheme 3.[6b] The synthesis of methyl ester 25 is well established.[23] The Dibal-H reduction of 25 affords hydrate 26 after quenching with MeOH and extraction with water.[23b] This intermediate was smoothly dehydrated by



Scheme 3

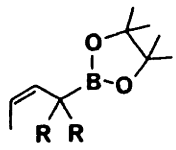
heating a CH_2Cl_2 solution of 26 to reflux in a Soxhlet apparatus containing 4Å molecular sieves. Pure 2 was then obtained by distillation under reduced pressure. Aldehyde 2 prepared in this manner contained 1-5% of C(2) epimer from one batch to the next.

D-Glyceraldehyde acetonide 8 was prepared from D-mannitol via known literature procedures.[24]

C. RESULTS

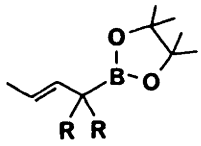
With the synthesis of boronates 4-7 well in hand we turned to an examination of the reactions of these reagents with aldehydes 2 and 8. Special care was taken to distill each reagent and determine its isomeric purity prior to each experiment. The reactions were performed by adding the neat aldehyde (also freshly distilled) to a 0.1-1M solution of crotylboronate in CH_2Cl_2 at -78°C under an inert atmosphere. The reaction mixtures were allowed to warm to room temperature with the cooling bath in place and then stirred until complete (usually 12-48h.). The reaction mixture was then diluted with ether and extracted with water to hydrolyze the intermediate borate esters. Product mixtures were then analyzed by capillary gas chromatography (see Table 4). Pure samples of all products except 30, 34, 38, and 42 were obtained by chromatography of the reaction mixtures on silica gel. The combined yield of products after chromatography was 75-90%. The presence of 30 and 34 in entries 1-4 of Table 4 were confirmed by coinjection of authentic samples synthesized as described in a later section. Structures 38 and 42 (entries 5-7) were assigned by analogy to 30 and 34 to minor products detected in the GC analyses.

From the results in Table 4 it is immediately striking that the (Z)-boronates 4 and 5 are highly stereoselective in their reactions with 2 and 8 (entries 1-7). The selectivity for the major 3,4-syn,4,5-anti diastereomers (27, 31, 35, and 39) approaches the limit defined by the isomeric purity



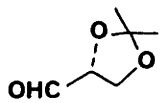
4, R=H

5, R=Me

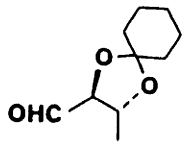


6, R=H

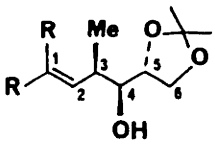
7, R=Me



8

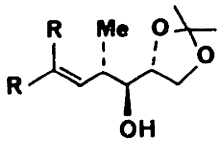


2



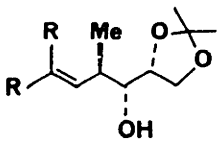
27, R=H

35, R=Me



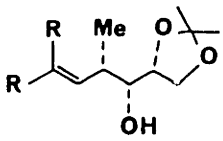
28, R=H

36, R=Me



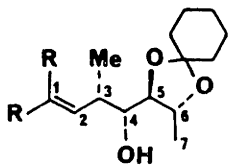
29, R=H

37, R=Me



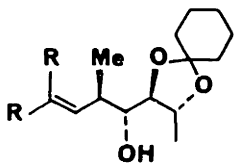
30, R=H

38, R=Me



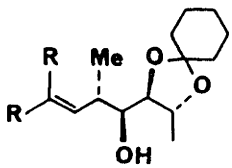
31, R=H

39, R=Me



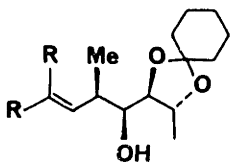
32, R=H

40, R=Me



33, R=H

41, R=Me



34, R=H

42, R=Me

Table 4[a]

Entry	Aldehyde	Boronate	Isomeric[b] Purity, %	Product Ratios[c-d] 27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
1	8	4	98	91	5	1	3												
2	8	4	89	80	11	6	3												
3	2	4	97					96	2	1	1								
4	2	4	89					84	10	6	--								
5	8	5	95									90	4	2	4				
6	8	5	87									83	6	7	4				
7	2	5	93													93	3	3	1
8	8	6	98	6	52	42	--												
9	8	6	87	14	46	40	--												
10	2	6	98					2	51	47	--								
11	2	6	89					11	50	39	--								
12	8	7	>98									--	44	56	--				
13	8	7	93									6	43	51	--				
14	2	7	97													1	40	59	--
15	2	7	93													4	40	56	--

(a) All reactions were performed by the addition of a slight excess of the aldehyde to the boronate in CH_2Cl_2 at -78°C. The reactions were allowed to warm to room temperature and stirred until complete (24- 48 h). (b) Isomeric purity of 4-7 was determined by capillary GC (see experimental section). (c) Product ratios were determined by GC analysis before chromatographic separation (see experimental section). (d) The isolated product yields ranged from 75-85%.

of the starting crotylboronates 4 and 5. Although four products were detected in each experiment, the minor 3,4-anti,4,5-anti (28, 32, 36, and 40) and the 3,4-anti,4,5-syn (29, 33, 37, and 41) diastereomers can be attributed primarily to the contaminating (E)-boronate isomer 6 or 7 present in 4 and 5. Of course, these minor anti-anti and anti-syn diastereomers are also possible products from minor reaction pathways wherein the aldehyde carbon chain is oriented in an axial position of the chair-like transition state (cf. Scheme 1). The data recorded in entries 1, 3, 5, and 7 of Table 4 for reaction of reagents with higher purity, however, suggest that less than 4% of such stereochemical crossover occurs.[3i] The last set of products, namely the 3,4-syn,4,5-syn (30, 34, 38, and 42) diastereomers, serve to define the level of aldehyde facial selectivity in the reactions with 2 and 8. In the reactions of 4 or 5 with 8, the facial selectivity is at least 20-30:1, whereas in reactions with 2 the facial preference is >90:1!

In sharp contrast are the results obtained for the reactions of (E)-crotylboronates 6 and 7 with 2 and 8 (entries 8-15). Here the major products are the 3,4-anti,4,5-anti (28, 32, 36, and 40) and the 3,4-anti,4,5-syn (29, 33, 37, 41) diastereomers which derive from different facial approaches of the boronate to the aldehyde. These data clearly show that no significant facial preference exists in these reactions. The product distributions obtained for these reactions, however, do reflect the isomeric purity of the starting boronates

and, the facial selectivity issue notwithstanding, are consistent with cyclic transition state models in which the aldehyde carbon chain orients preferentially in an equatorial position (Scheme 1).

A brief look was taken at how variations of the reaction conditions affect the product distribution. As shown in Table 5, the ratio of 27, 28, and 29 obtained from the reaction of 6 and 8 was not significantly affected whether the reaction was performed at 23°C, -20°C or at -78°C. However, the reactions performed at the lower temperatures were considerably slower than at 23°C.

Table 5[a]

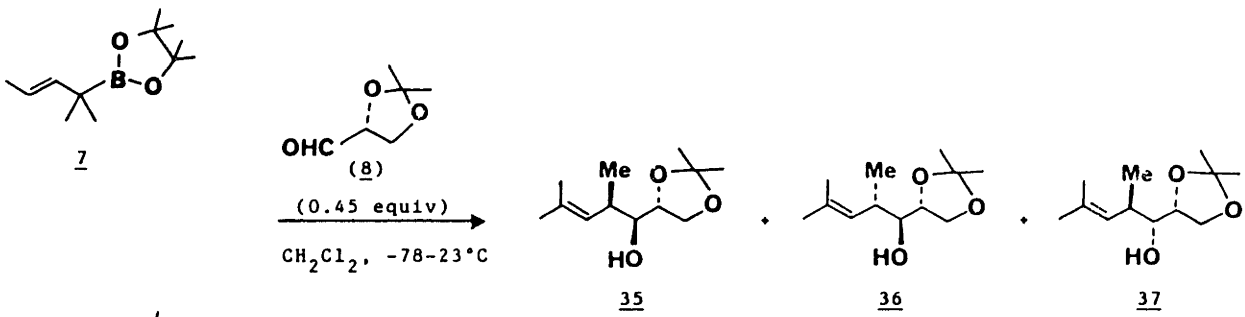
	Isomeric Purity of 6	Equivalents of 8 (temp. °C)	27:28:29
(1)	98%	1.3 (-78-23)	6:52:42
(2)	93%	0.9 (-78-23)	5:52:43
(3)	98%	1.2 (-78)	- 53:47[b]
(4)	98%	1.2 (-20)	3:51:46[c]
(5)	98%	1.2 (23)	5:51:44

(a) All reactions were performed in CH_2Cl_2 (ca. 0.1 M) at the temperature indicated and were stirred until complete. The reactions in entries 1, 2, and 5 were complete within 24 h. (b) Reaction was not complete after 2 weeks. The isomeric purity of the boronate remaining was >>99.5% (E) (no (Z)-boronate was detected). The amount of 27 was not determined. (c) Reaction was not complete after 1 week.

The reactions of boronates 4-7 with 2 or 8 in CH_2Cl_2[25] were performed at boronate concentrations of 0.03 to 1 molar. Product ratios were not noticeably affected by this variation; however, changes in concentration did effect the rate of reaction, with faster reactions occurring as expected with increasing reactant concentrations.

One variable which can influence the product distribution

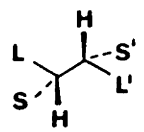
is reaction stoichiometry, since it has been noted that (E)-crotylboronates react at a faster rate with aldehydes than the (Z)-isomers.[3i,26] To examine this point, a 52:48 mixture of 7 and 5 (0.1M) was treated with 0.45 equivalents of glyceraldehyde acetonide (8). After all of 8 had been consumed, the unreacted boronate was analyzed by GC which revealed



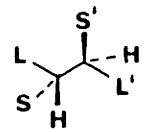
that this material was highly enriched in 5 (92% isomeric purity). The ratio of 35:36:37 was 12:40:48, confirming that (E)-boronate 7 had reacted at a faster rate than 5. In principle this difference in reactivity can be used to enrich the isomeric purity of (Z)-crotylboronates by selective consumption of contaminating (E)-isomers.[3i,26]

D. STEREOCHEMICAL ASSIGNMENTS

At the outset of this work we had hoped that the stereochemistry of adducts 27-42 could be assigned by using ^{1}H-NMR coupling constant data. In general, the coupling constants observed between vicinal hydrogens in acyclic systems are the weighted averages of the coupling constants of the various conformations available to the system.[27] As long as L and L^1 are much different in size than S and S^1, the staggered conformations shown below will be favored for a given set



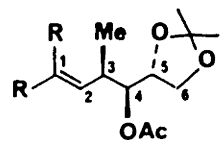
syn



anti

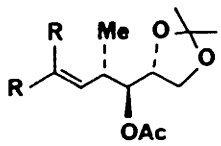
of syn and anti diastereomers. As a consequence, J_{anti} will typically be 6-10Hz and J_{syn} 2-6Hz. Of course, as the equilibrium constant or difference in energy between the staggered conformations decreases, the values of J_{syn} and J_{anti} begin to converge to an average value between 6-7Hz which is very difficult to interpret. Moreover, numerous examples have been reported in which J_{syn} and J_{anti} fall outside of the usual ranges due to unusual conformational effects.[28] In spite of these problems, coupling constant data have been used extensively for the assignment of stereochemistry in acyclic systems.[29]

A noted complication with NMR analysis of compounds such as 27-42 is internal hydrogen bonding which can bias the conformation of the system.[29a,e] Accordingly, alcohols 27-42 were converted to the corresponding acetates 43-56 (acetyl-



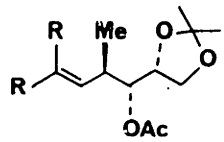
43, R=H

51, R=Me



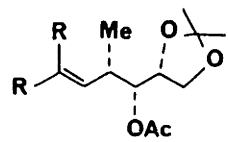
44, R=H

52, R=Me

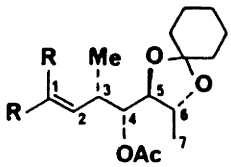


45, R=H

53, R=Me

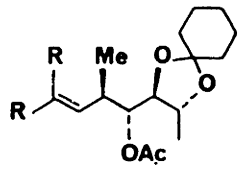


46, R=H



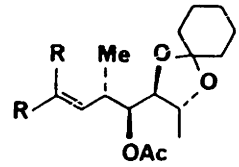
47, R=H

54, R=Me



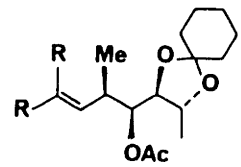
48, R=H

55, R=Me



49, R=H

56, R=Me



50, R=H

Table 6 : Selected ^{1}H-NMR Data For 43 - 56[a]

Primary Crotylboronate Adduct	Acetate Derivative	^{1}H-Chemical Shifts									Coupling Constants[c]	
		$H_{1(E)}$	$H_{1(Z)}$	H_2	H_3	H_4	H_5	$H_{6a,b}$	H_7	3'(Me)	$J_{3,4}$	$J_{4,5}$
27	43	5.08	5.01	5.72	2.39	5.06	4.18	3.96, 3.81	--	1.03	6.6	6.6
28	44	5.09	5,01	5.68	2.51	5.03	4.12	3.94, 3.75	--	1.01	4.5	6.4
29	45	5.04	4.98	5.70	2.41	4.85	4.20	3.98, 3.64	--	1.03	6.1	6.1
30	46	5.09	5.04	5.69	2.54	4.79	4.24	3.94, 3.61	--	1.00	8.0	4.2
31	47	5.07	5.01	5.76	2.58	5.02	3.65	4.05	1.25	1.05	6.4	7.4
32	48	5.09	5.01	5.72	2.61	4.94	3.58	3.96	1.22	1.01	4.3	7.9
33	49	5.05	4.99	5.68	2.58	4.78	3.67	3.78	1.25	1.06	7.6	3.1
34	50	5.12	5.07	5.71	2.65	4.74	3.68	3.68	1.22	0.99	9.0	1.6
35	51	--	--	4.89	2.49	4.94	4.16	3.87	--	0.92	8.0	4.2
36	52	--	--	4.97	2.72	5.01	4.06	3.88, 3.75	--	0.92	4.2	6.1
37	53	--	--	4.98	2.61	4.80	4.16	3.93, 3.64	--	0.94	5.9	5.9
39	54	--	--	4.97	2.66	4.97	3.64	4.05	1.22	0.96	6.3	6.3
40	55	--	--	4.99	2.82	4.91	3.50	3.95	1.21	0.92	3.9	8.2
41	56	--	--	4.97	2.78	4.72	3.67	3.80	1.23	0.97	7.5	3.5

(a) Spectra recorded on a Bruker WM 250 instrument (250 MHz) in $CDCl_3$ at 296°K. (b) Chemical shifts are reported in ppm relative to $CHCl_3$ (7.24). (c) Coupling constants are reported in Hz.

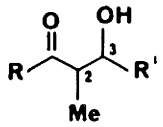
chloride, pyridine) for NMR analysis; selected ^{1}H-NMR data are summarized in Table 6. Unfortunately, many of the relevant $J_{3,4}$ and $J_{4,5}$ values fall in the nebulous 6-7Hz range. Moreover, three of these compounds (49, 51, and 56) have coupling constants which fall well outside of the J_{syn} and J_{anti} ranges "expected" for these compounds. This greatly complicated our efforts to assign the stereochemistry of these adducts; in fact, we initially misassigned the stereochemistry of a number of these compounds.

Consider the $J_{4,5}$ data which defines the stereochemistry at C(4) and therefore the facial selectivity of the reaction. Seven of the adducts (46, 47, 48, 49, 50, 55, and 56) have $J_{4,5}$ values which can be used to correctly assign the stereochemistry at C(4). Six others (43, 44, 45, 52, 53, and 54) have $J_{4,5}$ values in the range of 5.9-6.6Hz, making the stereochemical assignment unreliable. Also note that it is not possible to distinguish the diastereomers 43, 44 and 45 or 52 and 53 on this basis. Finally, the $J_{4,5}$ value for 51 (4.2Hz) is such that the C(4) stereochemistry would have been (and was) misassigned using the ^{1}H-NMR data alone.

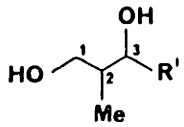
Assuming that the C(3) methyl group is larger than the vinyl substituent[30] and therefore defines the main chain of the acyclic backbone, the $J_{3,4}$ data for seven compounds (44, 46, 48, 50, 51, 52 and 55) can be used to correctly assign the stereochemistry at C(3). Five compounds (43, 45, 47, 53, and 54), however, have $J_{3,4}$=5.9-6.6Hz and two others (49 and 56) have $J_{3,4}$=7.5-7.6Hz which predicts the

wrong stereochemistry in these cases.

Heathcock[31] has reported that the 2,3-syn or anti stereochemistry of aldols and related structures, such as 57 and 58, can be assigned by using ^{13}C-NMR spectroscopy. This



57



58

analysis relies on the chemical shift of the C(2)-methyl group which appears at 8-13ppm for the syn adduct and 13-18ppm for the anti diastereomer. The data summarized in Table 7, however, shows that this analysis is not reliable for making stereochemical assignments of 27-42.[32] It is interesting to note that the C(7)-Me resonance for the 3,4-anti,4,5-syn diastereomers 33 and 41 (derived from reactions with 2) appears at higher field than the analogous resonance in the syn-anti and anti-anti adducts (31, 32, 39, and 40). Whether this will prove to be a general observation, and therefore useful in making stereochemical assignments, remains to be determined.

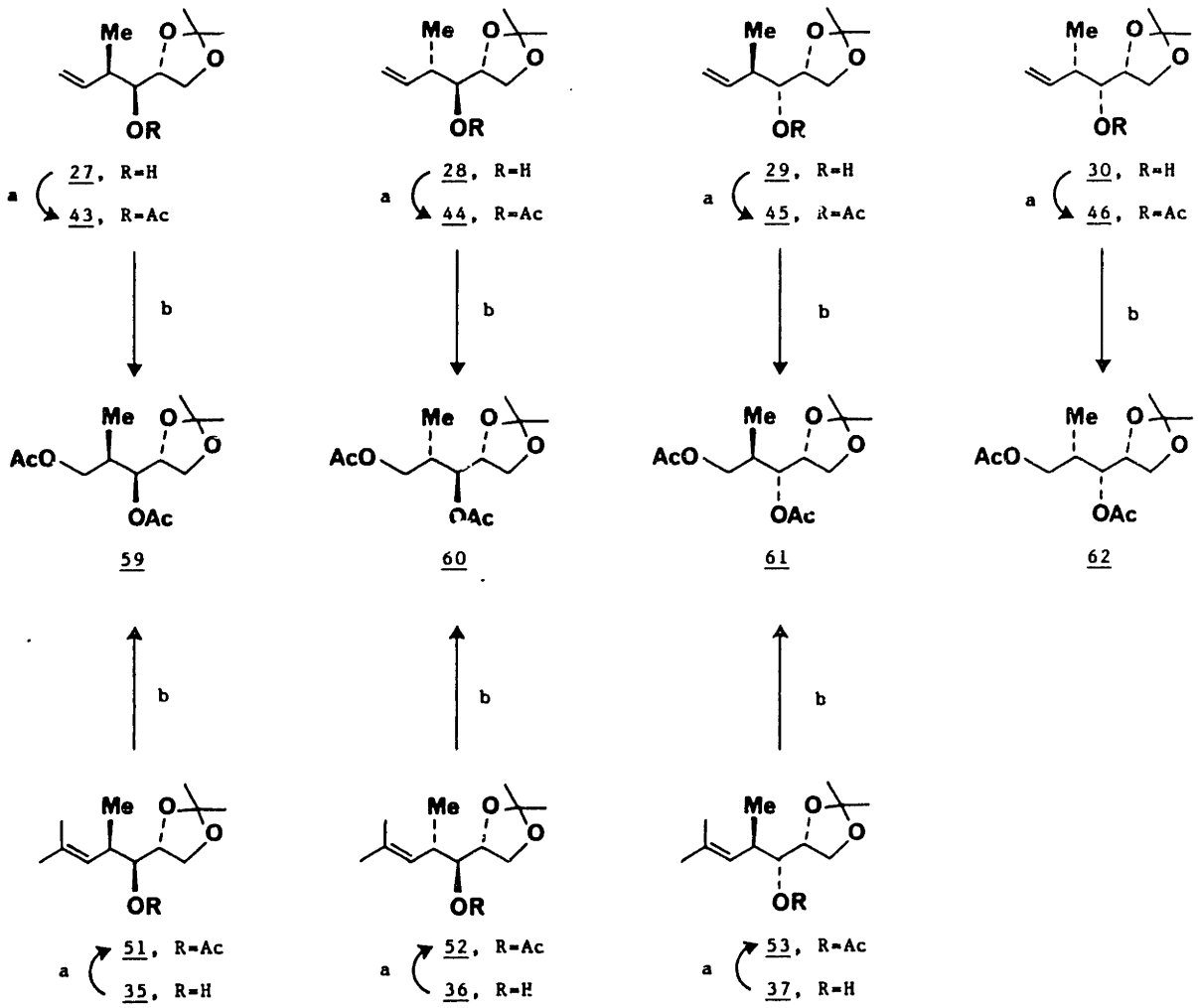
In an attempt to simplify the structures for NMR analysis and as the first step in a series of chemical correlations each of the adducts 27-37 and 39-41 was degraded to the corresponding 1,3-diacetate derivative 59-66 by using the ozonolysis, reduction and acylation sequence summarized in Schemes 4 and 5. The diols corresponding to 59-62 have previously

Table 7 : Selected ^{13}C-NMR Data For 27 - 41[a]

Crotylboronate Adduct	^{13}C-Chemical Shifts							
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(3)-Me
27	115.5	140.1	40.5	73.6	77.2	64.5	--	15.3
28	116.0	139.1	40.0	74.6	77.3	65.4	--	16.4
29	115.4	139.5	41.3	75.2	77.0	66.1	--	16.7
31	115.7	140.5	39.7	74.2	81.8	74.7	19.8	14.2
32	116.5	139.1	40.2	74.8	82.3	75.8	19.7	16.2
33	115.4	140.0	42.0	72.6	81.9	73.1	17.8	16.2
35	131.9	126.1	35.3	74.1	77.1	64.1	--	17.3
36	133.5	125.4	35.4	75.4	77.4	65.2	--	17.8
37	132.4	125.3	35.2	75.8	77.0	66.1	--	17.4
39	132.1	126.3	34.8	72.9	82.3	75.6	19.6	16.6
40	134.1	125.3	35.8	74.8	82.7	76.9	19.8	17.8
41	132.8	126.3	37.1	73.1	81.9	73.4	17.9	17.2

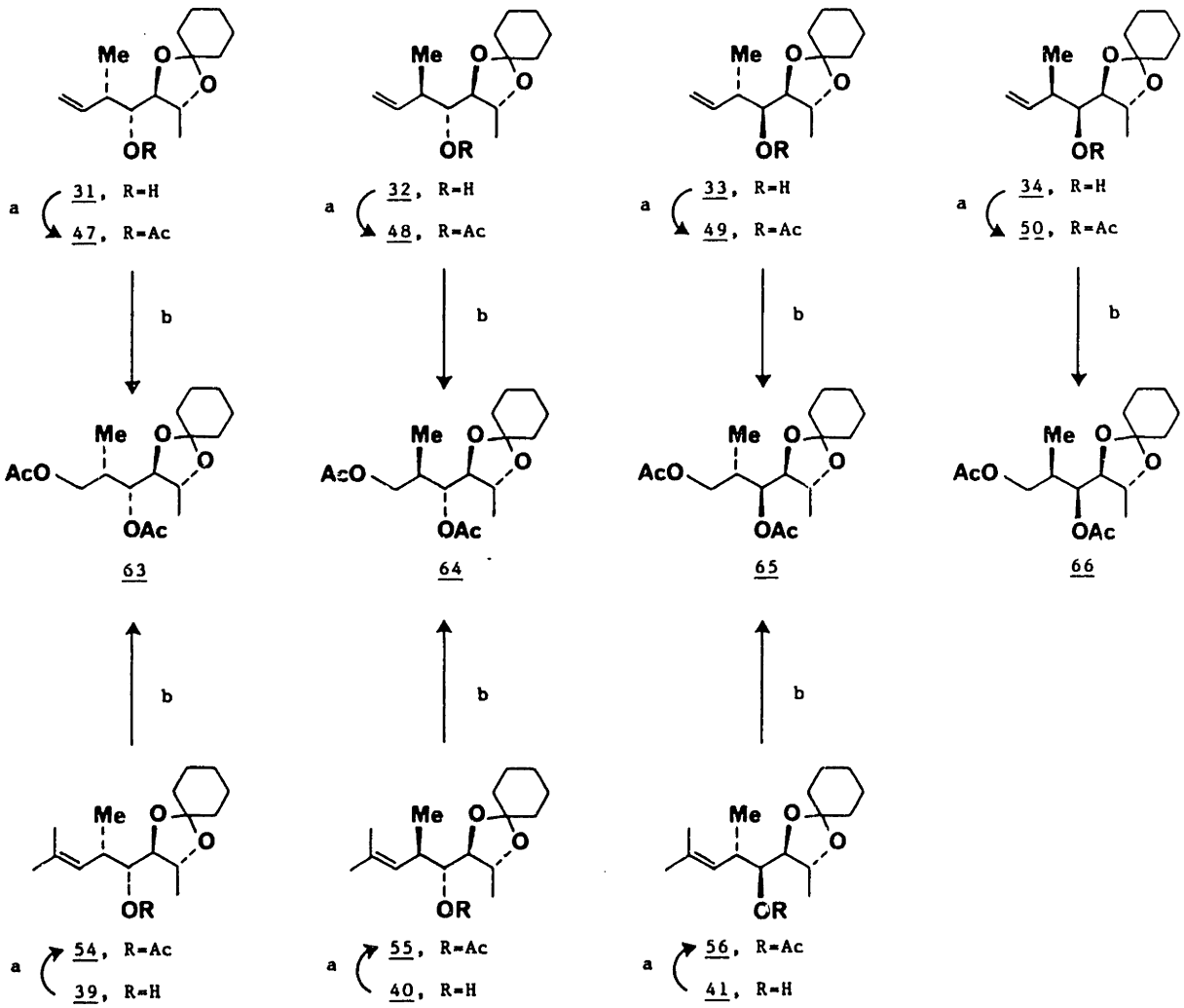
(a) Spectra recorded on a Bruker WM 270 (67.9 MHz) instrument in $CDCl_3$ (77.0 ppm) at 296°K.

Scheme 4: Correlations of Crotylboronate Adducts in the Glyceraldehyde Series.



(a) AcCl, pyridine, CH_2Cl_2, 23°C; (b) O_3, CH_2Cl_2, -78°C; $(CH_3)_2S$, -78-23°C; $LiAlH_4$, THF, 0°C; AcCl, pyridine, CH_2Cl_2, 23°C.

Scheme 5: Correlations of Crotylboronate Adducts in the Deoxythreose Series.



(a) AcCl, pyridine, CH_2Cl_2, 23°C; (b) O_3,CH_2Cl_2, -78°C; $(CH_3)_2S$, -78-23°C; $LiAlH_4$, THF, 0°C; AcCl, pyridine, CH_2Cl_2, 23°C.

Table 8 : Selected ^{1}H-NMR Data For 59 - 66[a]

Diacetate	^{1}H-Chemical Shifts[b]							Coupling Constants[c]	
	H_1	H_2	H_3	H_4	$H_{5a,b}$	H_6	3'(Me)	$J_{2,3}$	$J_{3,4}$
59	4.02	2.25	5.08	4.14	3.91, 3.77	--	0.96	3.2	7.4
60	4.05	2.16	5.02	4.21	3.98, 3.74	--	0.98	5.0	6.6
61	4.01	2.19	4.90	4.29	3.99, 3.65	--	1.03	7.6	4.0
62	3.97	2.13	4.99	4.25	3.97, 3.65	--	0.97	5.1	5.1
63	3.95	2.33	5.07	3.59	3.95	1.22	0.98	3.0	8.4
64	4.06	2.24	5.01	3.66	3.95	1.23	0.99	4.4	7.9
65	4.03	2.29	4.86	3.67	3.67	1.26	1.05	8.3	1.9
66	4.04	2.19	4.95	3.65	3.78	1.26	0.99	5.7	3.1

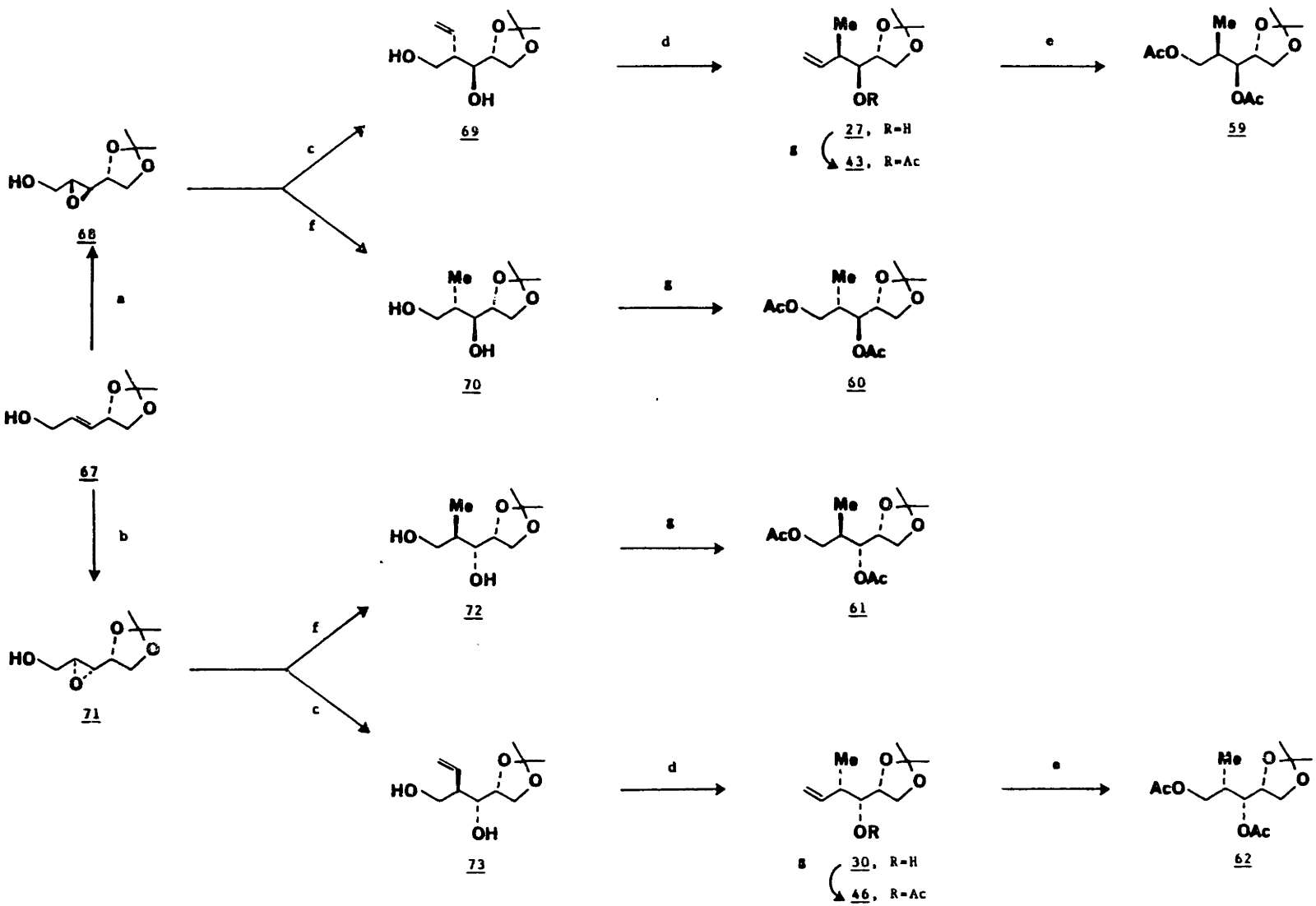
(a) Spectra recorded on a Bruker WM 250 instrument (250 MHz) in $CDCl_3$ at 296°K. (b) Chemical shifts are reported in ppm relative to $CHCl_3$ (7.24). (c) Coupling constants are reported in Hz.

been described by Heathcock.[31a] Selected NMR data for these eight diacetates are shown in Table 8. The assignment of stereochemistry at C(3) (e.g. $J_{3,4}$) is now reasonably straightforward for all compounds, especially the deoxythreose adducts 63-66. Similarly, the $J_{2,3}$ data for 59, 61, 62, 63, and 65 are consistent with the values expected for these compounds, assuming that the acetoxymethyl substituent defines the larger group at C(2). The $J_{2,3}$ values for 60, 64, and 66, however, are problematic and complicate the stereochemical assignments (cf. 60/62 and 63/64).

The stereochemistry of diacetates 59-66, and therefore also 27-56, was confirmed by synthesizing all eight compounds by stereochemically unambiguous routes (see Schemes 6 and 7). This work was done primarily by Dr. David J. Harris.[33]

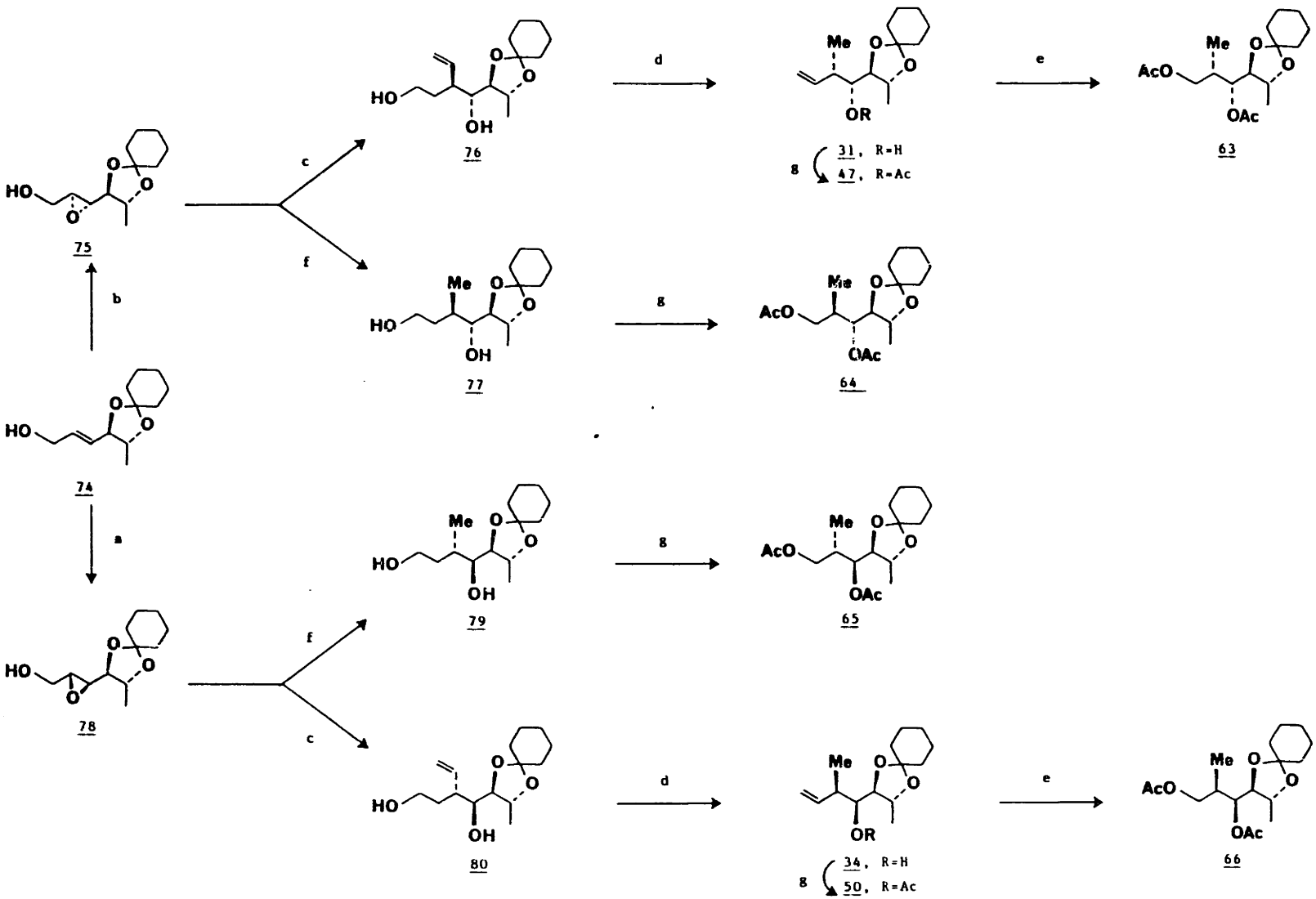
Syntheses of 59 and 60 are described here as illustrative cases. Epoxide 68 was synthesized starting from D-glyceraldehyde acetonide 8 using the methodology described by Sharpless, Masamune, and Kishi.[34] Treatment of 68 with CH_2=CHMgBr and $CuBr \cdot S(CH_3)_2$ according to the procedure of Tius[35a] afforded an 11:1 mixture of 69 and unreated 68. After chromatographic separation, pure 69 was monomesylated (MsCl,pyridine,0°C)[35b,36] and reduced (LAH,THF,0°C)[35b] to afford an authentic sample of 27. This compound was then degraded to 59 using the procedure described previously (Scheme 4). Alternatively, exposure of 68 to Me_2CuLi in Et_2O at -40°C [35b,c,37] followed by treatment with $NaIO_4$ in aqueous THF[38] afforded diol 70 which upon acylation (AcCl,pyridine) gave isomerically pure 60. Similar

Scheme 6 : Synthesis of Diacetates 59 - 62 (Glyceraldehyde Series).



(a) $Ti(OiPr)_4$, (-)-DET, TBHP, CH_2Cl_2, -23°C; (b) $Ti(OiPr)_4$, (+)-DIPT, TBHP, CH_2Cl_2, -23°C;
(c) CH_2=CHMgBr, CuBr·$S(CH_3)_2$, Et_2O, -23°C; (d) MsCl, pyridine, 0°C; $LiAlH_4$, THF, 0°C; (e) O_3, CH_2Cl_2, -78°C; $(CH_3)_2S$, -78-23°C; $LiAlH_4$, THF, 0°C; AcCl, pyridine, CH_2Cl_2, 23°C;
(f) $(CH_3)_2CuLi$, Et_2O, -40°C; $NaIO_4$, THF, H_2O, 23°C; (g) AcCl, pyridine, CH_2Cl_2, 23°C.

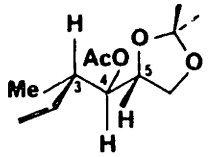
Scheme 7 : Synthesis of Diacetates 63 - 66 (Deoxythreose Series).



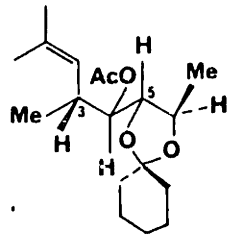
(a) $Ti(OiPr)_4$, (-)-DET, TBHP, CH_2Cl_2, -23°C; (b) $Ti(OiPr)_4$, (+)-DIPT, TBHP, CH_2Cl_2, -23°C; (c) CH_2=CHHgBr, $CuBr \cdot S(CH_3)_2$, Et_2O, -23°C; $NaIO_4$, THF, H_2O, 23°C; (d) MsCl, pyridine, 0°C; $LiAlH_4$, THF, 0°C; (e) O_3, CH_2Cl_2, -78°C; $(CH_3)_2S$, -78-23°C; $LiAlH_4$, THF, 0°C; AcCl, pyridine, CH_2Cl_2, 23°C; (f) $(CH_3)_2CuLi$, Et_2O, -40°C; $NaIO_4$, THF, H_2O, 23°C; (g) AcCL, pyridine, CH_2Cl_2.

treatments of epoxides 71, 75, and 78 afforded authentic samples of 1,3-diacetates 61-66.

With the structures of 27-42 secured, it is possible in retrospect to rationalize the ^{1}H-NMR data summarized in Table 6. Consider first compounds 44, 46, 48, 50, 52, and 55 for which the $J_{3,4}$ and $J_{4,5}$ values are in reasonable agreement with the stereochemical assignments. Each of these compounds is either a 3,4-syn,4,5-syn or a 3,4-anti,4,5-anti diastereomer and consequently has a 3,5-syn relationship when drawn in the usual acyclic manner (with the vinyl group defining the main chain backbone at C(3)). Presumably, each can adopt a staggered conformation as shown below for 46 and 55. Note also that the best staggered conformation for the C(3,4) and C(4,5) relationships is maintained in each case, if methyl is assumed to be larger than vinyl. Therefore,



46



55

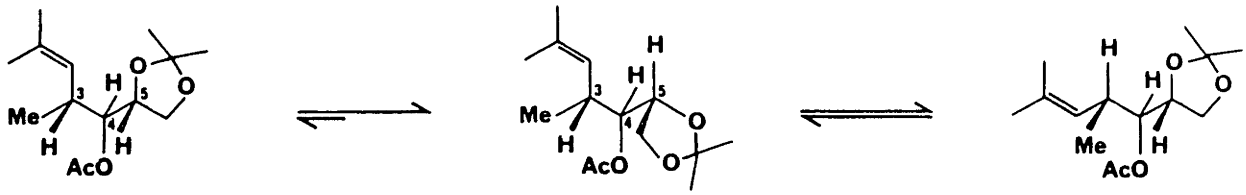
the coupling constants recorded for these compounds fall within the expected values of J_{syn} and J_{anti} measured for simpler acyclic systems.[27]

Essentially, all of the problematic coupling constant data in Table 6 are for compounds with 3,5-anti relationships (when drawn in the convention adopted throughout this chapter).

These compounds, for example 51 (a representative 3,4-syn,4,5-anti diastereomer) and 49 (a 3,4-anti,4,5-syn adduct) are unable to adopt a single conformation which simultaneously maintains the best staggered arrangement about the C(3,4) and C(4,5) bonds, due to serious 1,3-interactions between substituents at C(3) and C(5) (e.g. conformations A and D in Scheme 8).

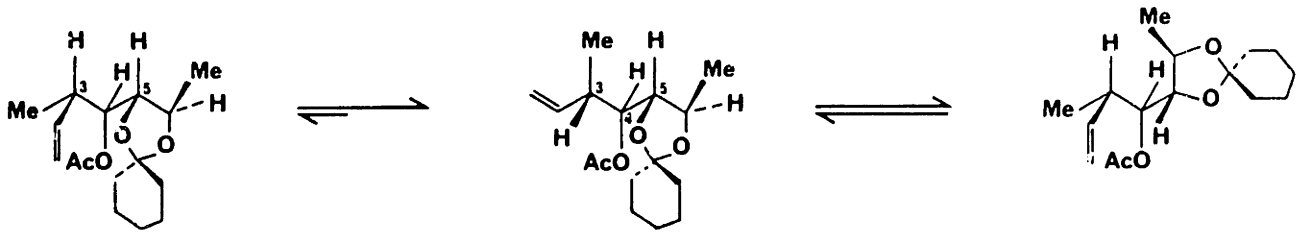
Scheme 8

Conformations of 51:



A B C

Conformations of 49:



D E F

These 1,3-interactions are relieved by rotating about the C_3-C_4 and C_4-C_5 bonds. Of the possible conformations for 51, B is probably the most important contributor since $J_{3,4}$=8.0Hz (anti) and $J_{4,5}$=4.2Hz(syn relationship). For 3,4-syn,4,5-anti diastereomers 43, 47, and 54, however, conformations

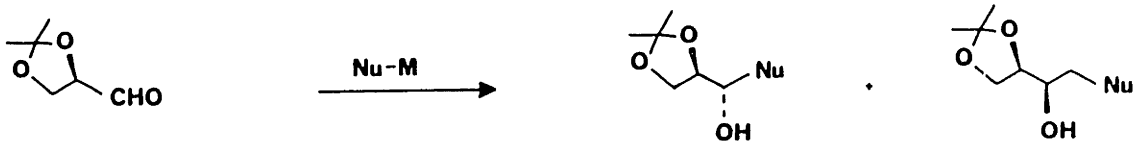
B and C appear to be significant since $J_{3,4}$=6.3-6.6Hz and $J_{4,5}$=6.3-7.4Hz in these cases. Regarding the compounds with a 3,4-anti,4,5-syn relationship, conformation E is probably the largest contributor for 49 and 56 since $J_{3,4}$=7.5-7.6Hz and $J_{4,5}$=3.1-3.5Hz. For 45 and 53, however, conformations E and F must both be significant contributors since $J_{3,4}$ and $J_{4,5}$=5.9-6.1Hz.

In summary, coupling constants for compounds with 3,5-anti relationships, as described for 49 and 51, are strongly influenced by nonbonded interactions involving the C(3) and C(5) substituents which have a profound effect on the conformational preferences of the system. Of course, the specific details of the analysis presented above will certainly vary as the size of the substituents at C(3) or C(5) are varied (causing reversal of the group priorities which define the backbone of the acyclic chain, cf. Table 6). Consequently, in the absence of detailed information regarding the conformational preferences of a given acyclic system, extreme care must be exercised when using coupling constants for acyclic stereochemical assignments.

E. DISCUSSION

Based on the excellent selectivity seen in the reaction of 1 with 2,[6b] we had anticipated at the outset that both sets of crotylboronates (4/5 and 6/7) would display excellent anti (Felkin-Ahn)[39] selectivity in these carbonyl addition reactions. First, reagents such as 4-7 are capable of coordinating with only one ligand (the aldehydic carbonyl group) so α- or β-chelate controlled pathways (cf. Scheme 9) would not be possible. Second, aldehydes such as 2 and 8 are highly electrophilic and have a marked tendency to undergo anti nucleophilic addition even with reagents capable of chelation.[2b,7] Although the data for the reactions of (Z)-crotylboronates 4 and 5 summarized in Table 4 are superficially consistent with Felkin-Ahn transition states (e.g. A_Z, Scheme 10), the data for 6 and 7 suggest that the excellent results in these cases may be fortuitous. Compare for example Felkin-Ahn transition states A_Z and A_E shown in Schemes 10 and 11. Whereas A_Z is severely destabilized by non-bonded interactions involving the axial R_1 and the C(3)-aldehyde substituents (space filling molecular model analysis), A_E appears to be less seriously congested. On this basis and assuming that Felkin selectivity should dominate these reactions, we would predict that the (E)-crotylboronates would be more 4,5-anti selective than the (Z)-isomers. Clearly our data is inconsistent with this analysis, suggesting instead that factors other than conventional acyclic stereochemical considerations (Scheme 9)[39-43] must play an important role in determining

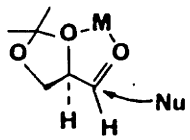
Scheme 9 : Models for Acyclic 1,2-Asymmetric Induction in Reactions of Nucleophiles With α,β-Dialkoxyaldehydes.



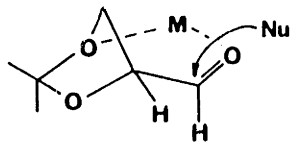
8 anti syn

Outcome Predicted By: B,E,F A,C,D

Chelated Models[2b,7b,40]

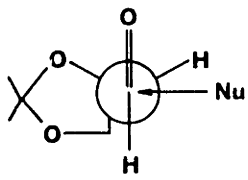


A, α-chelate

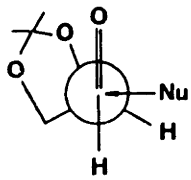


B, β-chelate

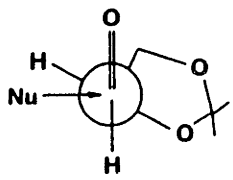
Non-chelated Models



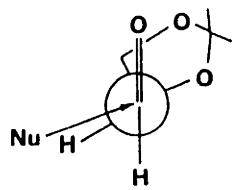
C (Cram)[41]



D (Karabatsos)[42]



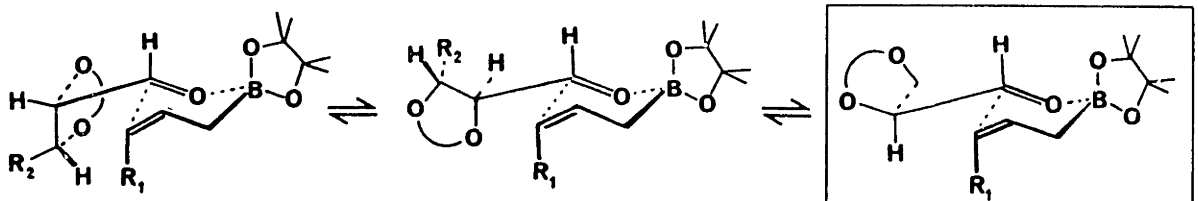
E (Cornforth)[43]



F (Felkin)[39]

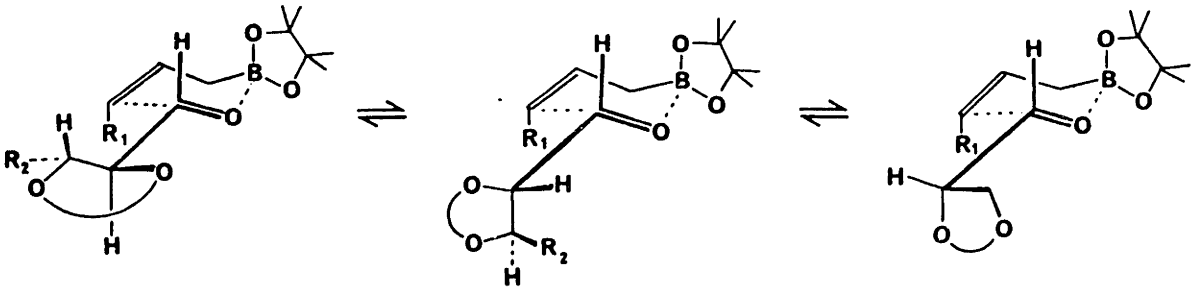
Scheme 10 : Transition States for the Reactions of (Z)-Crotylboronates with α,β-Dialkoxyaldehydes.[44]

4,5-Anti Selective:



A_Z B_Z C_Z

4,5-Syn Selective:



D_Z E_Z F_Z

the stereochemical course of these transformations.

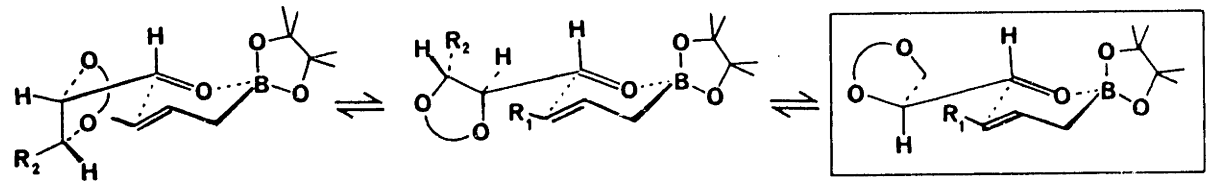
Consider first the reactions of (Z)-crotylboronates 4 and 5 with aldehydes 2 and 8 which are highly selective for the 4,5-anti diastereomers. Inspection of space-filling molecular models of 4,5-anti selective transition states[44] A_Z, B_Z, and C_Z reveals that A_Z (as noted previously) and B_Z are severely destabilized by non-bonded interactions involving R_1 and the aldehyde C(2)-C(3) substituents. The Cornforth-like[43] transition state C_Z, however, experiences the least non-bonded interactions. Consequently, it is probably C_Z and not the theoretically favored Felkin transition state A_Z which accounts for formation of the major 3,4-syn,4,5-anti diastereomers. Facial selectivity is very high in these reactions since the 4,5-syn selective transition states (D_Z, E_Z, and F_Z) suffer from non-bonded interactions comparable in magnitude to those present in A_Z and B_Z.

The lower degree of aldehyde facial selectivity in the reactions of 6 and 7 with 2 and 8 can be rationalized by similar transition state arguments (Scheme 11). Examination of the 4,5-anti transition states A_E, B_E and C_E reveals that the Cornforth-like transition state C_E is probably the most accessible of these three arrangements (but less so than C_Z in the (Z)-crotylboronate series, Scheme 10). Similarly of the three syn selective transition states the best arrangement appears to be F_E. Note that F_E is more accessible than F_Z, since the 1,3-interaction involving R_1 and C(2)-OR in F_Z is relieved by movement of R_1 to an equatorial position

in F_E (cf. Scheme 10 and 11). As a consequence, no great preference exists for reactions via C_E or F_E.

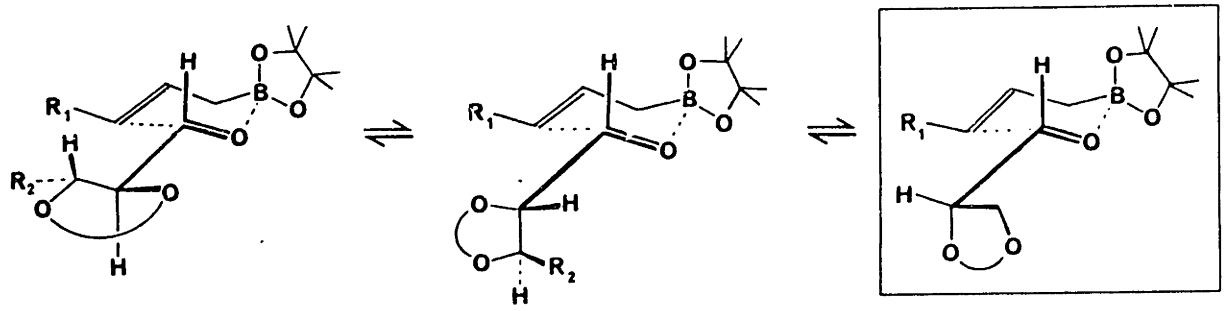
Scheme 11 : Transition States for the Reactions of (E)-Crotylboronates with α,β-Dialkoxyaldehydes.[44]

4,5-Anti Selective:



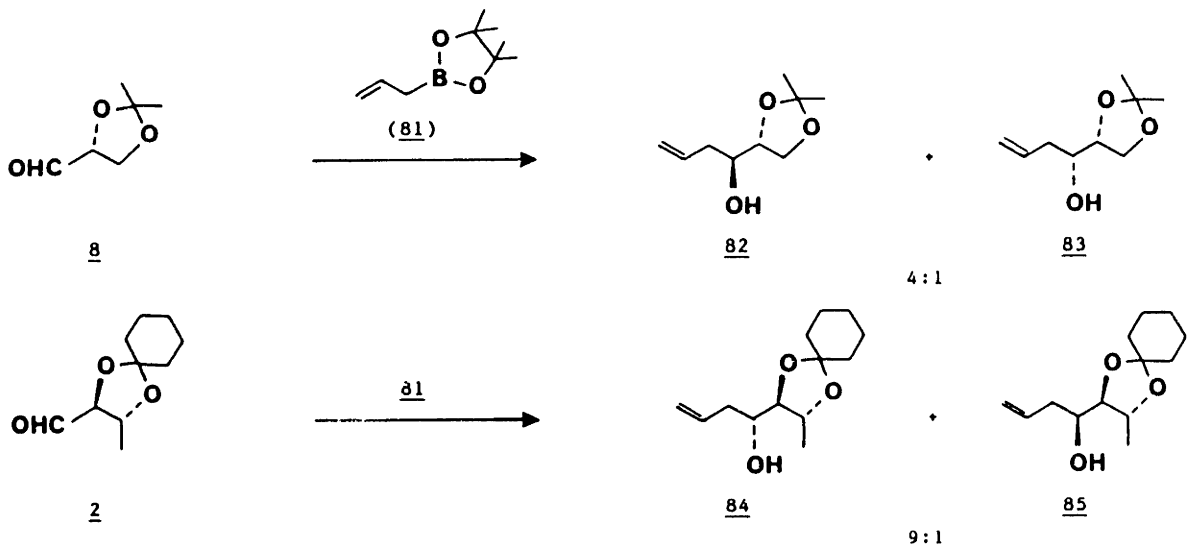
A_E B_E C_E

4,5-Syn Selective:



D_E E_E F_E

However, from a purely steric viewpoint it is surprising that the reactions of (E)-crotylboronates 6 and 7 show as much selectivity as they do, since F_E appears to be less hindered than C_E. A similar problem exists in the interpretation of the 4-9:1 anti selectivity seen in reactions of pinacol allylboronate (81) with aldehydes 2 or 8.[25,45] Note that for reactions of 81, non-bonded interactions in transition states C and F (R_1=H) appear essentially equivalent (cf. Scheme 10 or 11). The extent of erythro selectivity



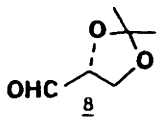
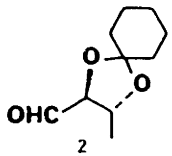
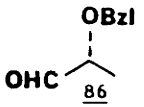
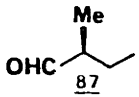
8 82 83

2 84 85

in these cases (reactions of 6, 7 and 81), therefore, may require that Felkin transition states (A) play a role in spite of the steric interactions noted previously, or that the Cornforth-like transition state C is electronically activated [39a,b] relative to the Karabatsos-like transition state F_E and contributes more heavily to the product distribution than expected otherwise.

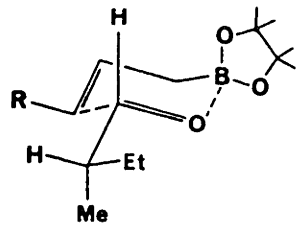
The latter interpretation is consistent with data recently reported by Hoffmann for reactions of allylic boronates 4, 6, and 81 with α-methyl branched aldehydes such as 87 (see Table 9 entry 4).[46] The difference between Hoffmann's data and ours is that α-alkoxy substituted aldehydes such as 2 and 8 are more anti facial selective than 87 in reactions with 4, 6, and 81. It is interesting to note, first, that Hoffmann has performed a transition state analysis identical to the one we have described here. That is, Hoffmann suggests that transition states G (analogous to F_E, Scheme 11) and

Table 9 : Diastereoselectivity of Addition Reactions of Pinacol Allylic Boronates With α-Chiral Aldehydes; Ratio of 4,5-Syn to 4,5-Anti Products.

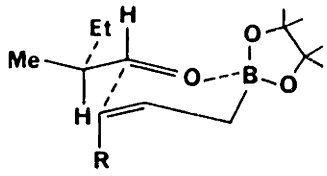
		(Z)-Crotyl (4)	(Z)-γ-Methoxy (1)	Allyl (81)	(E)-Crotyl (6)
(1)	 8	3:97	5: 95[a]	20:80[e,f]	45:55
(2)	 2	1:99	5: 95[b]	10:90[e]	48:52
(3)	 86	---	10:90[c]	50:50[g]	---
(4)	 87	30:70[d]	---	62:38[d]	83:17[d]

(a) Roush, W.R. ; Michaelides, M.R. unpublished results; (b) see reference 6b; (c) see reference 6c; (d) see reference 46; (e) see reference 25, 45; (f) see reference 6d; (g) Roush, W.R. ; Palmer, M.A.J. unpublished results.

H (analogous to C_Z, Scheme 10) are responsible for formation of the major products in reactions of 6/81 and 4, respectively.



G



H

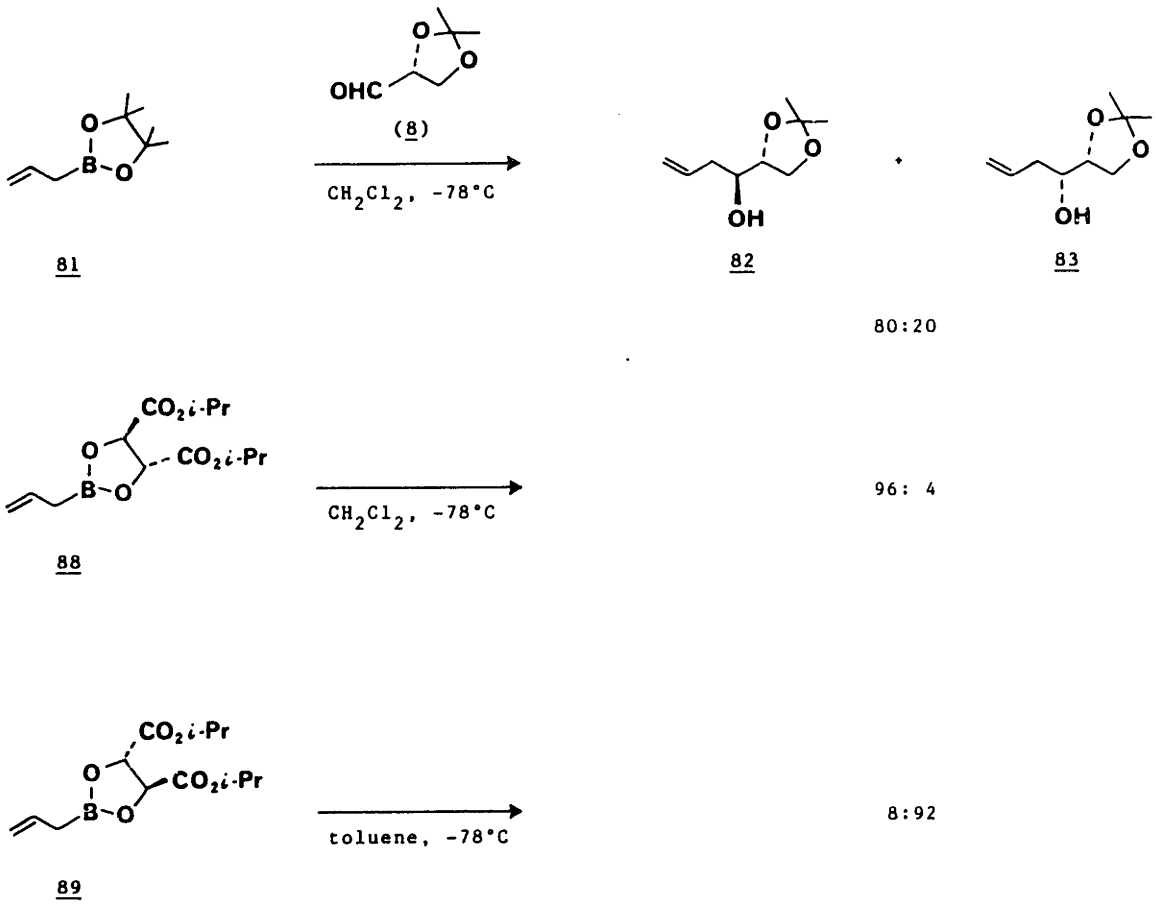
Second, the increase in anti selectivity of reactions of 6, 81, and 4, in that order, with α-alkoxysubstituted aldehydes such as 2 roughly parallels the increase in anti selectivity of these reactions with 87. This strongly supports our thesis that favorable electronic activation of transition states C_Z, C_E, and C_A (allylboronate) increases the anti selectivity of reactions of 4, 6 and 81 with α,β-dialkoxyaldehydes 2 and 8.[47]

In summary we suggest that these allylic boronate aldehyde addition reactions be viewed as [3,3]-sigmatropic rearrangements of intermediate allylic boronate-aldehyde complexes (a metallo-Claisen rearrangement) in which the stereochemical outcome is strongly influenced by steric effects. Diastereofacial selectivity in reactions with chiral aldehydes is determined both by the substitution pattern of the reagent as well as the electronic structure of the aldehyde (cf. Table 9). Conventional models for acyclic 1,2-asymmetric induction,[39-43] which do not take into account long-range non-bonded interactions such as those described here, are not generally useful in predicting the stereochemical outcome of these reactions. In retrospect, perhaps we should not have assumed the applic-

ability of the Felkin-Ahn model since allylic boronates are weak (soft) nucleophiles and the trajectory of reagent approach to the carbonyl is constrained by virtue of the cyclic transition states to a value considerably smaller than in bimolecular carbonyl addition reactions.[48]

It has become increasingly apparent that synthetically useful levels (>9:1) of aldehyde diastereoselectivity in reactions of allylic boronates with chiral aldehydes is the exception rather than the rule (Table 9). A practical solution to this problem may involve the development of chiral reagents capable of controlling facial selectivity independent of any stereochemical preference on the part of the chiral aldehyde ("double asymmetric synthesis").[49]

Recent developments in these laboratories have shown that tartrate esters are quite efficient chiral auxiliaries in reactions of allylboronates with chiral aldehydes (Scheme 12).[45,50] Whereas the reaction of pinacol allylboronate 81 with 8 gave a 4:1 ratio of anti(82) and syn(83) products, the selectivity could be enhanced to 96:4 by employing the (+)-diisopropyl tartrate derived reagent 88. With the enantiomeric reagent 89 prepared from (-)-diisopropyl tartrate, syn diastereomer 83 was obtained with 92% selectivity. Reagents 88 and 89 are the most highly enantioselective allylic boronate reagents developed thus far. We are optimistic that this strategy can be extended to the crotylboronate family and work towards this goal has recently been initiated.[22]



81 82 83

88

89

Scheme 12

In conclusion, we have investigated the reactions of chiral aldehydes 2 and 8 with the pinacol ester of crotylboronic acids 4-7. The reactions of (Z)-boronates 4 and 5 show excellent selectivity for the 3,4-syn,4,5-anti products whereas the (E)-boronates 6 and 7 show no facial preference leading to essentially 1:1 mixtures of the 3,4-anti,4,5-syn and 3,4-syn,4,5-anti products. The stereochemical outcome of these reactions has been rationalized in terms of a transition state model which relies heavily on non-bonded inter-

actions involving the vinylic substituents of the allylic boronate reagents. Although our original goal of high diastereofacial selectivity was not uniformly met, our work provides a solid foundation for future studies on the design of efficient chiral reagents.

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CHAPTER III

EXPERIMENTAL PROCEDURES

General

Proton (^1H) NMR spectra were measured in $CDCl_3$ at 250 MHz on a Bruker WM 250 instrument. Chemical shifts are reported in δ units using the 7.24 ppm resonance of residual chloroform as internal reference. Carbon (^{13}C) NMR spectra were measured at 67.9 MHz on a Bruker WM 270 instrument. Carbon chemical shifts are reported on δ_C units using the 77.0 ppm resonance of $CDCl_3$ 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. IR spectra are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 144 Polarimeter or a Rudolph Autopol® III Automatic Polarimeter using a 1 cm^3 quartz cell (10 cm path length). 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. Elemental analyses were performed by Robertson Laboratory, Inc. of Florham Park, New Jersey.

Capillary GC analyses were performed on a Hewlett-Packard Model 5890 Gas Chromatograph equipped with a Hewlett-Packard Model 3392A Integrator. These analyses were performed on Alltech SE-54 (0.2 mm x 50 m) and Hewlett-Packard dimethylsilicone (0.25 mm x 12m) fused silica columns using helium as carrier gas (1 mL/min flow rate and 100:1 split ratio). Packed column GC analyses were performed on a Perkin-Elmer Sigma 3 Model Gas Chromatograph using a

4.1% Carbowax on Chrom G (80/100) column (0.25 in x 9 ft) and using nitrogen as carrier gas.

All reactions were conducted in oven dried (125 °C) or flame dried glassware under atmospheres of dry argon. All solvents were purified before use. Ether, THF, benzene, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride, dimethyl sulfide and pyridine were distilled from CaH_2. Hexane was distilled from NaH. Acetyl chloride was distilled from PCl_5. Diisopropyl tartrate, diethyl tartrate and titanium tetraisopropoxide were distilled before use.

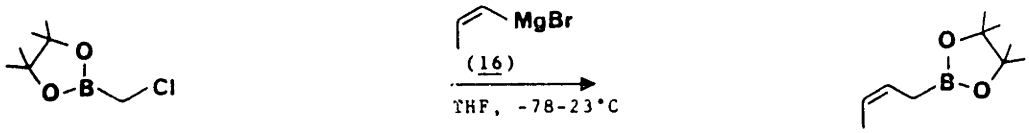
Butyllithium, methyllithium, propenyllithium and propenyl Grignard solutions were titrated before use with isopropanol or sec-butanol in benzene or toluene using 1,10-phenanthroline as indicator.[51]

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 thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by either charring with $(NH_4)_2SO_4$ or by staining with iodine vapor. Compounds were eluted from the adsorbents with either ether or ethyl acetate. Column chromatography was performed using Woelm 70-230 mesh silica gel (Merck) as described by Still.[52] Radial chromatography was performed on a Harrison Research

Chromatotron Model 7924T using 24 cm diameter plates coated with 1 mm thickness of silica gel containing PF 254 indicator (Merck). All chromatography solvents were distilled prior to use.

Preparation of Pinacol (Z)-2-butenylboronate(4)

Method A - Propenyl Grignard Route



9 4

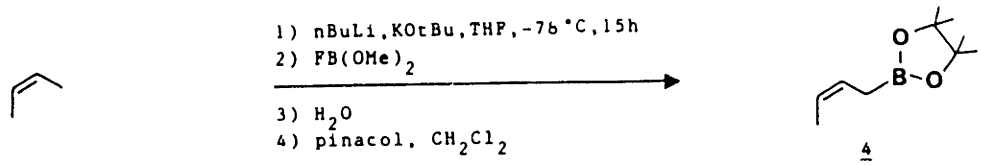
Propenyl Grignard 16[19] (5.3 mL of a 0.77 M THF solution, 4.08 mmol) was added dropwise under an argon purge to a solution of 9[12] (0.66 g, 3.80 mmol) in 22 mL of THF at -78 °C. The resulting solution was stirred at -78 °C for 30 min then allowed to warm to room temperature overnight. Removal of the solvent in vacuo gave an oil which was triturated with 50% Et_2O-pentane and filtered through a pad of silica gel to afford 0.58 g of a clear liquid. Capillary GC analysis of this material showed it was 95% isomerically pure 4. Kugelrohr distillation (54 °C, 3mm) then afforded 0.56 g (82%) of 4 (95% isomeric purity) containing < 2% of 18.

Data for 4: R_f 0.66 (4:1 hexane-Et_2O); ^1H NMR δ 5.45 (m, 2H, H.2, H.3), 1.58 (br d, J = 6.6 Hz, 3H, vinyl-CH_3), 1.48 (br d, J = 4.2 Hz, 2H, H.1), 1.22 (s, 12H, pinacol -CH_3's).

Capillary GC analysis of mixtures of 4 and 6 were performed by using a 0.25 mm x 12 m dimethylsilicone on fused silica column. The temperature program used was as follows: 70 °C held for 4 min then increase temperature at a rate of 10°/min to 130 °C, from where the temperature was increased at 30°/min to a final temperature of 200° which was held for 1 min. Under these conditions the retention times of 18, 6

and 4 were: 18, 4.58 min; 6, 6.47 min; 4, 6.58 min.

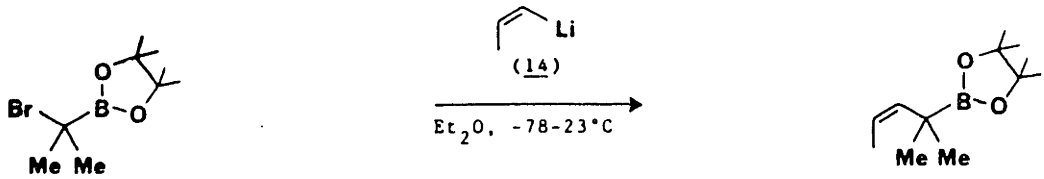
Method B - Crotylpotassium Route



4

A solution of (Z)-2-butene (8.0 mL, 4.97 g, 88.6 mmol) in 85 mL THF was treated with KOtBu (9.56 g, 85.2 mmol) and nBuLi (55.6 mL of a 1.53 M solution in hexane, 85.1 mmol) at -78 °C for 15 h.[3j,20] The reaction mixture was then treated with $FB(OMe)_2$ (8.22 g, 89.4 mmol) at -78 °C for 1 h. The cold solution was then poured into 50% saturated NaCl and extracted with Et_2O (6 x 150 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated to afford 10.2 g (97%) of crotylboronic acid which was immediately dissolved in CH_2Cl_2 (50 mL) and treated with pinacol (12.1 g, 0.102 mol). The resulting solution was stirred at room temperature overnight. Concentration gave an oil which was distilled through a glass helices packed vigreaux column (72-78 °C, > 5 mm) to afford 12.1 g (78% from (Z)-2-butene) of a clear, colorless liquid which was 97% isomerically pure 4 by capillary GC analysis.

Preparation of Pinacol 2-[1,1-Dimethyl-2-(Z)-butenyl]boronate (5).



11 5

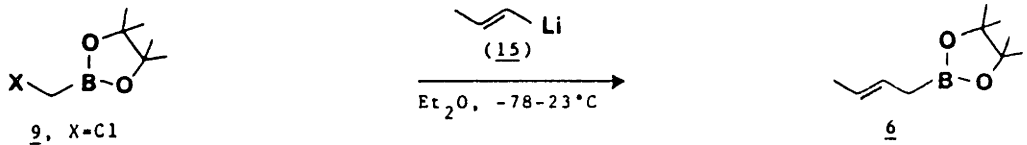
Propenyllithium (14)[9e,13] (6.8 mL of a 0.85 M solution in Et_2O) was added dropwise to a solution of 11 [3i,5] (1.18 g, 4.76 mmol) in 48 mL of Et_2O at -78°C under an argon purge. The resulting solution was stirred at -78 °C for 6 h and then allowed to warm to room temperature overnight. The solvent was then removed and the resulting residue was triturated with 50% Et_2O-pentane, filtered through a pad of silica gel and concentrated to afford 0.91 g (92%) of crude product. This material was Kugelrohr distilled (55-60 °C, 5 mm) to afford 0.77 g (77%) of 5 which was 93% isomerically pure ((Z)-propenyl-lithium (14) used on this experiment was prepared from 94% isomerically pure (Z)-propenylbromide (12). It should be possible to prepare 5 of higher isomeric purity by using 14 of higher purity.) No propenylboronate was detected in this experiment.

Data for 5: R_f 0.73 (4:1 hexane - Et_2O); ^1H NMR δ 5.38 (m, 2H, H.2, H.3), 1.59 (d, J = 5.9 Hz, 3H, vinyl-CH_3), 1.22 (s, 12H, pinacol-CH_3's), 1.09 (s, 6H, gem-CH_3); IR (CH_2Cl_2) 2970, 2940, 2870, 1480, 1450, 1370, 1120 cm^{-1}; mass spectrum, m/e 210 (parent ion), 195 (M^+-CH_3).

Capillary GC analyses of 5 and 7 were performed using a 0.25 mm x 12 m dimethylsilicone on fused silica column. The

temperature program used was as follows: 70 °C held for 4 min, then ramped at 10°/min to 130 °C from where the temperature was increased at 30°/min to a final temperature of 200° which was held for 5 min. Under these conditions the retention times of 18, 5 and 7 were: 18, 4.56 min; 5, 7.66 min; 7, 8.15 min.

Preparation of Pinacol (E)-2-Butenylboronate (6).



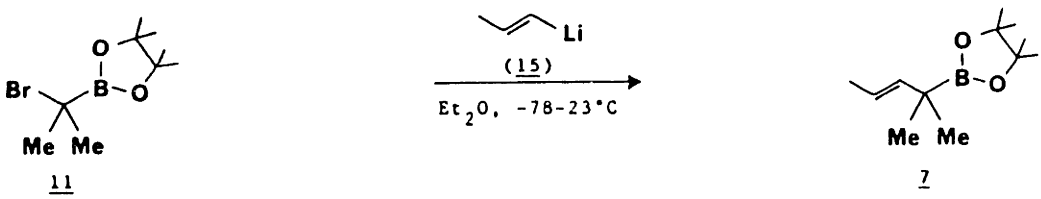
9, X=Cl
10, X=I

6

Propenyllithium (15)[9e,13] (16.5 mL of a 0.82 M solution in Et_2O, 13.5 mmol) was added dropwise over 1 h to a solution of 9 (2.06 g, 11.7 mmol) in 97 mL of Et_2O at -78 °C. The resulting solution was allowed to warm to room temperature overnight. Removal of the solvent afforded a yellow residue which was triturated with 2:1 pentane-CH_2Cl_2 and the resulting solution filtered through a pad of silica gel and concentrated to afford 1.95 g (91%) of crude product. Kugelrohr distillation (68 °C, 1 mm) afforded 1.46 g (69%) of 6 which was 96% isomerically pure and contained < 4% of 18.

Data for 6: R_f 0.65 (4:1 hexane-Et_2O); ^1H NMR δ 5.42 (m, 2H, H.2, H.3), 1.62 (d, J = 6.3 Hz, 3H, vinyl-CH_3), 1.55 (br s, 2H, H.1), 1.24 (s, 12 H, pinacol-CH_3's).

Preparation of Pinacol 2-[1,1-Dimethyl-2-(E)-butenyl]boronate (7).



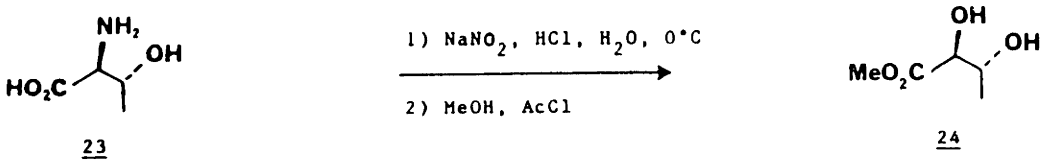
11 7

Propenyllithium (15) (8.4 mL of a 0.82 M Et_2O soltion, 6.87 mmol) was added dropwise over a 45 min period under an argon purge to a solution of 11 (1.542 g, 6.21 mmol) on 60 mL of Et_2O at -78 °C. The resulting yellow solution was allowed to warm to room temperature over 6-8 h and then the solvent was removed in vacuo. The residue (containing solids) was triturated with 2:1 pentane-CH_2Cl_2, filtered through a pad of silica gel, and concentrated to afford 1.42 g of crude product. Kugelrohr distillation (68-70 °C, 0.5 mm) of this material afforded 1.09 g (84%) of 7 which was 98% isomerically pure and contained < 4% of propenylboronate 18.

Data for 7: R_f 0.76 (4:1 hexane-Et_2O); ^1H NMR δ 5.50 (br d, J = 15.4 Hz, 1 H, H.2), 5.33 (dq, J = 6.3, 6.1 Hz, 1H, H.3), 1.63 (dd, J = 6.1, 1.2 Hz, 3 H, vinyl-CH_3), 1.19 (s, 12 H, pinacol-CH_3's), 1.00 (s, 6H, gem-CH_3); IR (neat) 2940, 2850, 1630, 1460, 1380, 1300, 1140 cm^{-1}; mass spectrum, m/e 210 (parent ion), 209 (boron isotope). High resolution mass spectrum. Calcd. for $C_{12}H_{23}{}^{11}BO_2$: 210.1791. Found: 210.2338.

Preparation of L-4-Deoxythreose Cyclohexylketal (2)

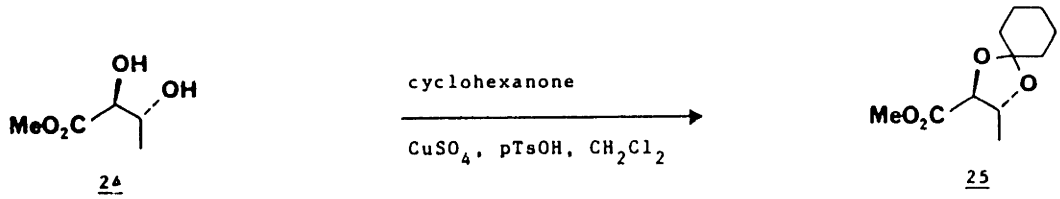
(a) Methyl-L-Threo-2,3-Dihydroxybutyrate (24)



23 24

A solution of L-threonine (23) (40.9 g, 0.34 mol) in 1.7 L H_2O was treated with concentrated HCl (51 mL, 0.62 mol) and $NaNO_2$ (28.5 g, 0.41 mol) at 0 °C for 9 h and then allowed to stir at room temperature overnight. Water was removed in vacuo and the resulting oil was dried by azeotropic distillation of toluene. The resulting crude dihydroxyacid was dissolved in MeOH (0.55 L) and treated with AcCl (4.9 mL, 0.07 mol) at 0 °C. The reaction mixture was stirred overnight at room temperature, then cooled to 0 °C and neutralized by the addition to solid Na_2CO_3 (7.3 g, 0.07 mol). The resulting slurry was filtered through Celite and concentrated. The crude product was distilled (95-101 °C, 3.7 mm) to afford 33 g (72%) of pure 24[23a]: R_f 0.49 (9:1 EtOAc-hexane); ^1H NMR δ 3.98 - 4.08 (m, 2 H, H.1, H.2), 3.76 (s, 3 H, CO_2CH_3), 2.95 (br s, 1 H, O-H), 2.72 (br s, 1 H, O-H), 1.26 (d, J = 6.0 Hz, 3 H, CH_3); IR (neat) 3490, 2980, 2940, 1750, 1450, 1380, 1250, 1100, 1040, 910, 850, 800, 760 cm^{-1}.

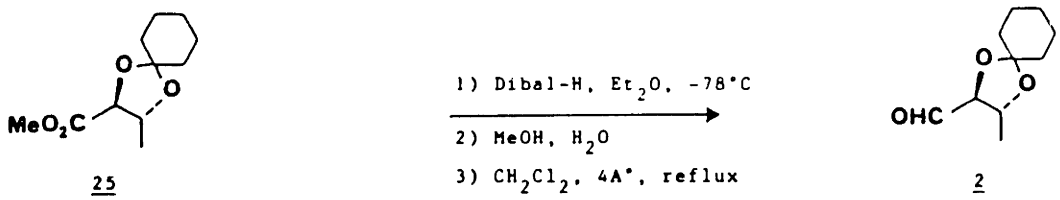
(b) Methyl-L-Threo-2,3-Dihydroxybutyrate Cyclohexylketal (25).



24 25

A solution of 24 (10.0 g, 0.75 mol) on CH_2CL_2 (70 mL) was treated with $CuSO_4$ (11.1 g, 0.07 mol), $pTsOH \cdot H_2O$ (0.36 g, 1.88 mmol) and cyclohexanone (9.6 mL, 0.92 mol).[23] The resulting slurry was stirred at room temperature overnight then filtered through Celite and concentrated to afford 16.9 g of crude product. Distillation of this material (68 °C, 0.7 mm) gave 13.5 g (84%) of a 4:1 mixture of 25 + C(2) epimer. (The amount of C(2) epimer varies from one batch of this material to the next but both are successfully converted to 2 in the next step: R_f 0.45 (4:1 hexane-EtOAC); $[\alpha]_D^{22}$ - 10.8° (c = 6.5, CH_2Cl_2); ^1H NMR δ 4.12 -4.28 (m, 1 H, H.1), 4.09 (d, J = 8.2 Hz, H.2), 3.80 (s, 3 H, CO_2CH_3, minor), 3.75 (s, 3 H, CO_2CH_3, major), 1.52 -1.75 (m, 10 H, cyclohexyl), 1.42 (d, J = 6.0 Hz, 3 H, $-CH_3$, major), 1.3 (d, J = 6.0 Hz, 3 H, $-CH_3$, minor); IR (neat) 2920, 2840, 1770, 1740, 1460, 1380, 1290, 1220, 1170, 1130, 1020, 945, 920 cm^{-1}.

(c) Aldehyde (2).

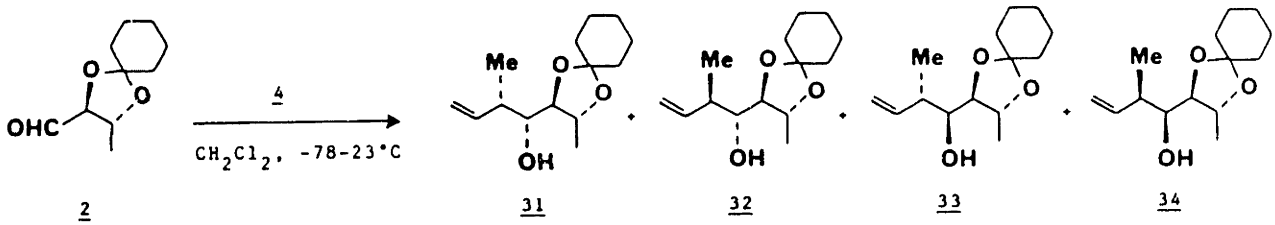


25 2

Dibal-H (21.3 mL of a 20% wt solution in hexane, 37.0 mmol) was added dropwise over a 25 min period to a solution of 25 (2.1 g, 9.88 mmol) in Et_2O (60 mL) at -78 °C. After 1 h at -78 °C the reaction was complete by TLC and was then quenched with dry MeOH (22 mL, 55 mmol). The resulting slurry was allowed to warm to room temperature over 2 h. The reaction mixture was washed with saturated aqueous Rochelle's salt solution and saturated aqueous NaCl solution. The organic layers were dried over Na_2SO_4, filtered and concentrated. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and heated to reflux in a Soxhlet apparatus packed with 4 Å molecular sieves for 20 h. After cooling and concentration, the resulting material was Kugelrohr distilled (70-85 °C, 0.95 mm) to give 1.65 g (91%) of 2[6b,23] which contained ca. 1-5% by ^1H NMR of the C(2) epimer from one batch to the next.

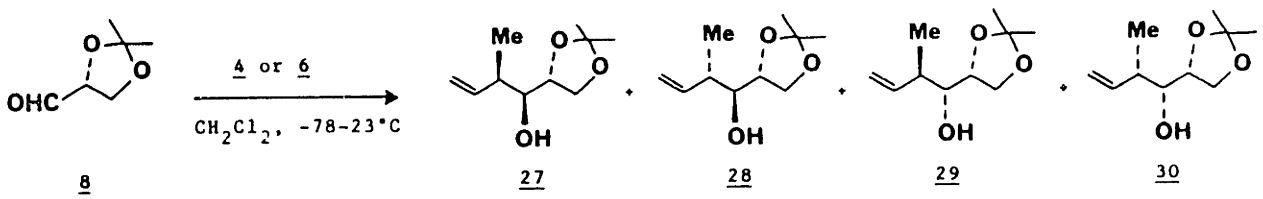
Data for 2: R_f 0.39 (4:1 hexane-EtOAc); $[\alpha]_D^{22}$ -25.2° (C = 1.5, CH_2Cl_2); ^1H NMR δ 9.71 (d, J = 3.4 Hz, 1 H, -CHO), 4.12 (br quint, J = 6.3 H, 1 H, H.2), 3.85 (dd, J = 7.8, 3.4 Hz, 1 H, H.1), 1.74-1.28 (m, 10 H, cyclohexyl), 0.92 (d, J = 6.3 Hz, 3H, $-CH_3$).

General Procedure for Reactions of Crotylboronates (4-7) with Aldehydes 2 and 8



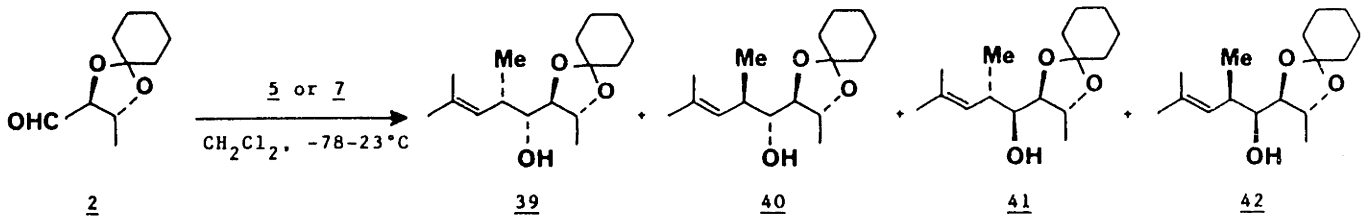
2 31 32 33 34

The reaction of 2 and 4 is described as an illustrative case: A solution of boronate 4 (98% isomeric purity, 0.92 g, 5.07 mmol) in CH_2Cl_2 (50 mL) was treated with aldehyde 2 (1.08 g, 5.85 mmol) at -78 °C. The resulting solution was allowed to warm gradually to room temperature overnight. The progress of the reaction was monitored by TLC until all of 4 was consumed (usually 12-24 h). The reaction mixture was then poured into H_2O (50 mL), extracted with Et_2O (4 x 50 mL), dried over Na_2SO_4, filtered and concentrated. The crude product (2.23 g) was a 96:2:1:1 mixture of 31, 32, 33 and 34 respectively, as determined by capillary GC analysis (0.2 mm x 50 m SE-54 on fused silica column, temperature program: 70 °C held for 4 min, then 5°/min to a final temperature of 200° held for 3 min; retention times: 34, 32.85 min; 33 33.54 min; 32, 33.95 min; and 31, 34.17 min). Chromatography of the mixture on silica gel (50 x 160 mm) using 3:1 hexane-Et_2O as eluant gave 0.76 g (63%) pure 31 and 0.40 g (33%) of a mixture of 31-34. Pure samples of 32-34 were obtained by radial chromatography of ca. 100 mg mixtures on silica gel (1 mm plate) using 10:1 hexane-Et_2O as eluant.



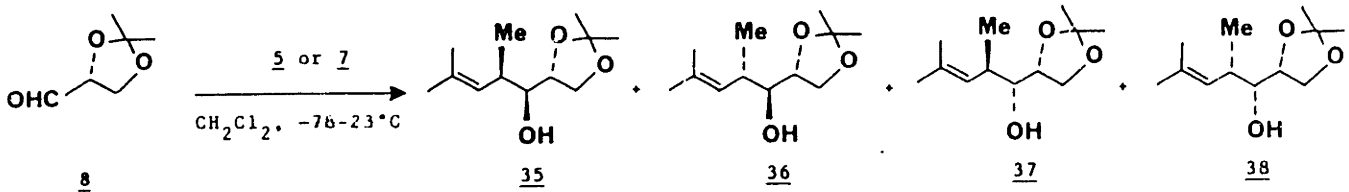
8 27 28 29 30

Mixtures of 27-30 obtained from the reaction of 8 with 4 or 6 were analyzed by capillary GC (0.2 mm x 50 m SE-54 on fused silica column, temperature program: 70 °C held for 45 min, then 30°/min to a final temperature of 200° held for 1 min). The rentention times observed were: 30, 35.06 min; 29, 37.50 min; 27, 38.71 min; and 28, 40.83 min. These adducts were separated by radial chromatography (1 mm silica gel plate) using 10:1 hexane-Et_2O as eluant or by PTLC (3:1 hexane-Et_2O, 2 elutions).



2 39 40 41 42

Mixtures of 39, 40, and 41 obtained from the reactions of 2 with 5 or 7 were analyzed by GC (0.2 mm x 50 m SE-54 on fused silica column, temperature program starting at 70 °C for 4 min, then 10°/min to 200° held for 5 min). The retention times of 39-41 were: 41, 20.40 min; 40, 20.60 min; 39, 21.05 min. A peak with a retention time of 19.88 min was assigned to 42. Pure samples of 39-41 were obtained either by PTLC (3:1 hexane-Et_2O, 2 elutions) or by radial chromatography (1 mm silica gel plate) using 10:1 hexane-Et_2O as eluant.

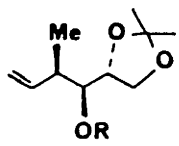


8 35 36 37 38

Finally, mixtures of 35-37 obtained from the reactions of 8 with 5 or 7 were analyzed as follows: Mixtures of 36 and 37 were analyzed by GC (0.25 in x 9 ft 4.1% Carbowax on Chrom G (80/100) column, temperature program starting at 80 °C for 2 min then increased at 10°/min to a final temperature of 190° held for 10 min). The retention times observed for 36 and 37 were: 37, 18.3 min; 36, 20.8 min. Isomer 35 coelutes with 36 under these conditions. Capillary GC analysis (0.2 mm x 50 m SE-54 on fused silica column, temperature program: 100 °C held for 2 min then increased at a rate of 3°/min to 130° where the rate was increased to 50°/min until a final temperature of 200° held for 3 min) resolves 35 from 36 and 37 (which coelute under these conditions); retention times: 38, 14.67 min; 36 and 37, 15.70 min; 35, 16.03 min. The peak at 14.67 min was assigned to 38 by analogy to 42. Pure samples of 35-37 were obtained by chromatography using the conditions described for the other product mixtures.

Each of the primary boronate adducts 27-37 and 39-41 were converted to the corresponding acetate derivatives (43-56, respectively) for characterization purposes. A general procedure is as follows (conversion of 27 to 43): Alcohol 27 (22.2 mg, 0.12 mmol) was treated with pyridine (0.09 mL, 1.19 mmol) and AcCl (0.04 mL, 0.059 mmol) in 2 mL of CH_2Cl_2 at room temperature until 27 was completely consumed (TLC analysis). The reaction mixture was then treated with MeOH (0.5 mL) and concentrated. The resulting oil was chromatographed (0.5 mm silica gel plate, 2:1 hexane-Et_2O) to afford 14.3 mg (69%) of pure 43. Yields of acetates 44-56 obtained using this procedure were typically 70-90%.

Spectroscopic data and physical constants for 27-56 are tabulated below. Selected ^{13}C NMR data for 27-41 are listed in Table 7 (see Chapter II) and are not repeated here.

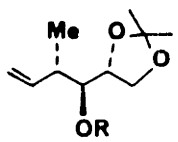


27, R=H
43, R=Ac

Data for 27: R_f 0.39 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ + 47.6° (c = 2.1, CH_2Cl_2), ^1H NMR δ 5.72 (br m, 1 H, H.2), 5.07 (br d, J = 16.6 Hz, 1 H, H.1a), 5.01 (br d, J = 11.4 Hz, 1 H, H.1b), 4.09 (br q, $J_{5,6}$ = 6.8 Hz, 1 H, H.5), 3.98-3.84 (m, 2 H, H.6a, H.6b), 3.64 (dd, $J_{3,4}$ = 6.8 Hz,

$J_{4,5}$ = 4.7 Hz, 1 H, H.4), 2.26 (m, 1 H, H.3), 2.02 (br s, 1 H, O-H), 1.39 (s, 3 H, acetonide-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 1.07 (d, J = 6.7 Hz, 3 H, CH_3); IR (neat) 3500, 3110, 3020, 2950, 1450, 1370, 1200, 1050, 910, 850 cm^{-1}, mass spectrum, m/e 171 (M^+ -CH_3).

Data for 43: R_f 0.55 (2:1 hexane-Et_2O); $[\alpha]_D^{20}$ + 35.1° (c = 1.1, $CHCl_3$); ^1H NMR δ 5.72 (br m, 1 H, H.2), 5.08 (br d, J = 18.3 Hz, 1 H, H.1a), 5.06 (t, $J_{3,4}$ = $J_{4,5}$ = 6.6 Hz, 1 H, H.4 superimposed on H.1a and H.1b), 5.01 (br d, J = 10.3 Hz, 1 H, H.1b), 4.18 (q, J = 6.6 Hz, 1 H, H.5), 3.96 (t, J = 6.3 Hz, 1 H, H.6a), 3.81 (t, J = 7.6 Hz, 1 H, H.6b), 2.39 (br m, 1 H, H.3), 2.06 (s, 3H, acetyl-CH_3), 1.35 (s, 3 H, acetonide-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 1.03 (d, J = 6.7 Hz, 3 H, -CH_3); IR (neat) 3050, 2950, 2900, 2860, 1750, 1650, 1470, 1425, 1375, 1250, 1200, 1050, 950, 840 cm^{-1}; mass spectrum, m/e 213 (M^+ -CH_3). Anal Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.03; H, 8.90.

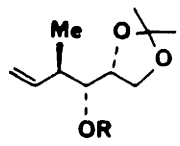


28, R=H
44, R=Ac

Data for 28: R_f 0.30 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{22}$ + 6.3° (c = 1.25, CH_2Cl_2); ^1H NMR δ 5.84 (br m, 1 H, H.2), 5.14 (dd, J = 12.9, 1.6 Hz, 1 H, H.1a), 5.08 (dd, J = 16.2, 1.6 Hz, 1 H, H.1b), 4.04 (br q, J = 5.9 Hz, 1 H, H.5), 3.93 (m, 2 H, H.6a, H.6b), 3.59 (t, $J_{3,4}$ = $J_{4,5}$ = 5.9 Hz, 1

H, H.4), 2.37 (m, 1 H, H.3), 1.40 (s, 3 H, acetonide-CH_3), 1.34 (s, 3 H, acetonide-CH_3), 1.07 (d, J = 7.2 Hz, 3 H, CH_3); IR (neat) 3480, 2980, 2940, 2900, 1460, 1370, 1250, 1210, 1070, 910, 850 cm^{-1}; mass spectrum, m/e 171 (M^+ -CH_3).

Data for 44: R_f 0.65 (1:1 hexane-ether); $[\alpha]_D^{22}$ + 23.9° (c = 0.8, CH_2Cl_2); ^1H NMR δ 5.68 (br m, 1 H, H.2), 5.09 (br d, J = 19.5 Hz, 1 H, H.1a), 5.03 (dd, $J_{3,4}$ = 4.5 Hz, $J_{4,5}$ = 6.4 Hz, 1 H, H.4 superimposed on H.1b), 5.01 (br d, J = 10.7 Hz, 1 H, H.1b), 4.12 (q, J = 6.4 Hz, 1 H, H.5), 3.94 (dd, J = 8.2, 6.3 Hz, 1 H, H.6a), 3.75 (dd, J = 8.0, 6.3 Hz, 1 H, H.6b), 2.51 (m, 1 H, H.3), 2.05 (s, 3 H, acetyl-CH_3), 1.35 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3), 1.01 (d, J = 6.8 Hz, -CH_3); IR (neat) 3080, 2980, 2940, 2880, 1750, 1640, 1455, 1420, 1360, 1230, 1150, 1060, 1020, 910, 840 cm^{-1}; mass spectrum, m/e 213 (M^+ -CH_3). Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.36; H, 9.08.

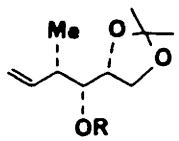


29, R=H
45, R=Ac

Data for 29: R_f 0.50 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ + 14.5° (c = 0.95, CH_2Cl_2); ^1H NMR δ 5.86 (br m, 1 H, H.2), 5.07 (dd, J = 17.0, 1.5 Hz, 1 H, H.1a), 5.04 (dd, J = 8.8, 1.5 Hz, 1 H, H.1b), 4.08 (q, J = 6.6 Hz, 1 H, H.5), 3.98 (dd, $J_{6a,6b}$ = 8.2 Hz, $J_{5,6a}$ = 6.6 Hz, 1 H, H.6a), 3.71 (dd,

$J_{6a,6b}$ = 8.2 Hz, $J_{5,6b}$ = 6.6 Hz, 1 H, H.6b), 3.37 (m, 1 H, H.4), 2.25 (br m, 1 H, H.3), 1.40 (s, 3 H, acetonide-CH_3), 1.34 (s, 3 H, acetonide-CH_3), 1.08 (d, J = 6.9 Hz, 3 H, CH_3); IR (CH_2Cl_2) 3580, 2980, 2930, 2880, 1450, 1380, 1370, 1210, 1070, 910, 850 cm^{-1}; mass spectrum, m/e 171 (M^+ -CH_3).

Data for 45: R_f 0.59 (1:1 hexane-ether); $[\alpha]_D^{22}$ + 8.2° (c = 0.9, CH_2Cl_2); ^1H NMR δ 5.70 (br m, 1 H, H.2), 5.04 (dd, J = 16.6, 1.2 Hz, 1 H, H.1a), 4.98 (br d, J = 11.5 Hz, 1 H, H.1b), 4.85 (t, $J_{3,4}$ = $J_{4,5}$ = 6.1 Hz, 1 H, H.4), 4.20 (q, J = 6.1 Hz, 1 H, H.5), 3.98 (dd, J = 8.4, 1.6 Hz, 1 H, H.6a), 3.64 (dd, J = 8.4, 6.1 Hz, 1 H, H.6b), 2.41 (br m, 1 H, H.3), 2.08 (s, 3H, acetyl-CH_3), 1.39 (s, 3 H, acetonide-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 1.03 (d, J = 6.9 Hz, 3 H, -CH_3); IR (CH_2Cl_2) 2960, 2920, 1735, 1370, 1230, 1060, 1015, 920, 840, 800 cm^{-1}; mass spectrum, m/e 229 (M^+ + 1), 228 (parent ion). Anal Calcd. for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.39; H, 9.07.

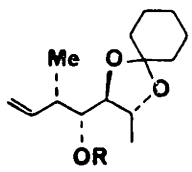


30, R=H
46, R=Ac

Data for 30: R_f 0.37 (2:1 hexane-ether); $[\alpha]_D^{22}$ - 11.4° (c = 0.9, $CHCl_3$); ^1H NMR δ 5.71 (m, 1 H, H.2), 5.08 (br d, J = 16 Hz, 1 H, H.1a), 5.03 (br d, J = 10.2 Hz, 1 H, H.1b), 4.13 (dq, J = 6.8, 4.6 Hz, 1 H, H.5), 3.96 (dd, J = 6.4, 8.1 Hz, 1 H, H.6a), 3.72 (br t, J = 7.6 Hz, 1 H, H.6b), 3.29 (dt, J =

5.0, 6.8 Hz, 1 H, H.4), 2.26 (br m, 1 H, H.3), 2.18 (d, J = 6.8 Hz, -OH), 1.41 (s, 3 H, acetonide-CH_3), 1.34 (s, 3 H, acetonide-CH_3), 1.08 (d, J = 6.8 Hz, 3 H, -CH_3); IR (CH_2Cl_2) 3580, 3080, 2980, 2950, 2890, 1450, 1380, 1360, 1200, 1160, 1050, 990, 860 cm^{-1}.

Data for 46: R_f 0.47 (2:1 hexane-ether); $[\alpha]_D^{20}$ + 21.4° (c = 0.8, $CHCl_3$); ^1H NMR δ 5.69 (br m, 1 H, H.2), 5.09 (br d, J = 17.3 Hz, 1 H, H.1a), 5.04 (br d, J = 10.4 Hz, 1 H, H.1b), 4.79 (dd, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 4.2 Hz, 1 H, H.4), 4.24 (dt, $J_{4,5}$ = 4.2 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 6.4 Hz, 1 H, H.5), 3.94 (dd, J = 8.5, 6.4 Hz, 1 H, H.6a), 3.61 (dd, J = 8.4, 6.4 Hz, 1 H, H.6b), 2.54 (br m, 1 H, H.3), 2.09 (s, 3 H, acetyl-CH_3), 1.39 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3), 1.00 (d, J = 6.7 Hz, 3 H, -CH_3); IR ($CHCl_3$) 3090, 2990, 2890, 1740, 1455, 1370, 1230, 1050, 1020, 920 cm^{-1}; mass spectrum, m/e 228 (M^+-CH_3).

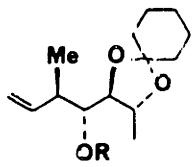


31, R=H
47, R=Ac

Data for 31: R_f 0.42 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ - 12.1° (c = 1.95, $CHCl_3$); ^1H NMR δ 5.80 (br m, 1 H, H.2), 5.12 (br d, J = 17.7 Hz, 1 H, H.1a), 5.06 (br d, J = 9.9 Hz, 1 H, H.1b), 4.11 (br quint, J = 6.3 Hz, 1 H, H.6), 3.61 (m, 2 H, H.4, H.5), 2.45 (br m, 1 H, H.3), 1.82 (d, J = 2.1 Hz, 1 H, O-H), 1.43-1.59 (m, 10 H, cyclohexyl), 1.33 (d,

J = 6.1 Hz, 3 H, H.7), 1.08 (d, J = 6.8 Hz, 3 H, CH_3); IR (CH_2Cl_2) 3600, 3040, 2960, 2880, 1360, 1100 cm^{-1}; mass spectrum, m/e 240 (parent ion).

Data for 47: R_f 0.42 (6:1 hexane-ether); $[\alpha]_D^{23}$ - 13.0° (c = 1.1, $CHCl_3$); ^1H NMR δ 5.76 (br m, 1 H, H.2), 5.07 (br d, J = 17.5 Hz, 1 H, H.1a), 5.02 (dd, $J_{3,4}$ = 6.4 Hz, $J_{4,5}$ = 7.4 Hz, 1 H, H.4), 5.01 (br d, J = 10.8 Hz, 1 H, H.1b), 4.05 (br quint, J = 6.2 Hz, 1 H, H.6), 3.65 (t, J = 7.4 Hz, 1 H, H.5), 2.58 (br m, 1 H, H.3), 2.03 (s, 3 H, acetyl-CH_3), 1.41-1.57 (m, 10 H, cyclohexyl), 1.25 (d, J = 6.1 Hz, 3 H, H.7), 1.05 (d, J = 6.7 Hz, 3 H, -CH_3); IR (neat) 3140, 3030, 2970, 2900, 1750, 1650, 1450, 1370, 1325, 1275, 1225, 1160, 1100, 1040, 950, 920, 850 cm^{-1}; mass spectrum, m/e 282 (parent ion), 239 (M^+-CH_3CO). Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.12; H, 9.29.

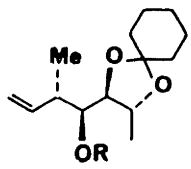


32, R=H
48, R=Ac

Data for 32: R_f 0.30 (1:1 hexane-ethyl ether); $[\alpha]_D^{24}$ = +22.5 (c = 0.7, CH_2Cl_2); ^1H NMR δ 5.86 (br m, 1 H, H.2), 5.17 (br d, J = 17.3 Hz, 1 H, H.1a), 5.10 (br d, J = 10.1 Hz, 1 H, H.1b), 4.09 (br quint, J = 6.3 Hz, 1 H, H.6), 3.48 (br m, 2 H, H.4, H.5), 2.49 (m, 1 H, H.3), 1.52-1.72 (br m, 10 H, cyclohexyl), 1.33 (d, J = 6.0 Hz, 3 H, H.7), 1.08 (d, J = 7.0

Hz, 3 H, CH_3); IR (CH_2Cl_2) 3600, 3040, 2960, 2860, 1445, 1360, 1160, 1100, 1050, 990, 940, 910, 680 cm^{-1}; mass spectrum, m/e 241 ($M^+ + 1$), 240 (parent ion).

Data for 48: R_f 0.65 (2:1 hexane-ether); $[\alpha]_D^{23}$ - 3.7° (c = 0.9, CH_2Cl_2); ^1H NMR δ 5.72 (br m, 1 H, H.2), 5.09 (br d, J = 17.3 Hz, 1 H, H.1a), 5.01 (br d, J = 9.1 Hz, 1 H, H.1b), 4.94 (dd, $J_{3,4}$ = 4.3 Hz, $J_{4,5}$ = 7.9 Hz, 1 H, H.4), 3.96 (br quint, J = 6 Hz, 1 H, H.6), 3.58 (t, J = 7.9 Hz, 1 H, H.5), 2.61 (m, 1 H, H.3), 2.04 (s, 3 H, acetyl-CH_3), 1.27-1.58 (m, 10 H, cyclohexyl), 1.22 (d, J = 6.0 Hz, 3 H, H.7), 1.01 (d, J = 7.1 Hz, 3 H, -CH_3); IR (neat) 3080, 2950, 2880, 1740, 1450, 1370, 1280, 1230, 1170, 1100, 1020, 950, 920, 850, 740 cm^{-1}; mass spectrum, m/e 283 ($M^+ + 1$), 282 (parent ion), 239 (M^+-CH_3CO). Anal Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.03; H, 9.11.

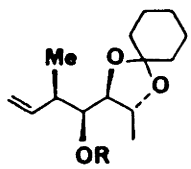


33, R=H
49, R=Ac

Data for 33: R_f 0.53 (1:1 hexane-ether); $[\alpha]_D^{24}$ - 2.3° (c = 1.2, CH_2Cl_2); ^1H NMR δ 5.91 (br m, 1 H, H.2), 5.10 (br d, J = 17.4 Hz, 1 H, H.1a), 5.04 (br d, J = 10.7 Hz, 1 H, H.1b), 4.05 (br quint, J = 6.1 Hz, 1 H, H.6), 3.55 (dd, $J_{4,5}$ = 2.7 Hz, $J_{5,6}$ = 8.2 Hz, 1 H, H.5), 3.29 (m, 1 H, H.4),

2.37 (br q, J = 6.6 Hz, 1 H, H.3), 2.20 (d, J = 8.0 Hz, 1 H, O-H), 1.32-1.69 (br m, 10 H, cyclohexyl), 1.25 (d, J = 6.1 Hz, 3 H, H.7), 1.07 (d, J = 6.8 Hz, 3 H, CH_3); IR (neat) 3520, 2930, 2850, 1440, 1360, 1270, 1220, 1160, 1100, 930, 900 cm^{-1}; mass spectrum, m/e 240 (parent ion).

Data for 49: R_f 0.56 (2:1 hexane-ether); $[\alpha]_D^{23}$ - 16.3° (c = 0.7, CH_2Cl_2); ^1H NMR δ 5.68 (br m, 1 H, H.2), 5.05 (dd, J = 16.9, 1.3 Hz, H.1a), 4.99 (dd, J = 9.7, 1.4 Hz, 1 H, H.1b), 4.78 (dd, $J_{3,4}$ = 7.6 Hz, $J_{4,5}$ = 3.1 Hz, 1 H, H.4), 3.78 (br quint, J = 6.1 Hz, 1 H, H.6), 3.67 (dd, $J_{4,5}$ = 3.1 Hz, $J_{5,6}$ = 7.9 Hz, 1 H, H.5), 2.58 (br m, H.3), 2.04 (s, 3 H, acetyl-CH_3), 1.29-1.65 (m, 10 H, cyclohexyl), 1.25 (d, J = 6.0 Hz, 3 H, H.7), 1.06 (d, J = 6.9 Hz, 3 H, -CH_3); IR (neat) 3070, 2980, 2930, 2860, 1740, 1370, 1230, 1020, 940 cm^{-1}; mass spectrum, m/e 282 (parent ion), 239 (M-CH_3CO). Anal Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.94; H, 9.20.

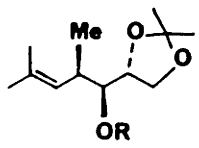


34, R=H
50, R=Ac

Data for 34: R_f 0.41 (4:1 hexane-ether); $[\alpha]_D^{22}$ + 30.1° (c = 2.8, $CHCl_3$); ^1H NMR δ 5.73 (m, 1 H, H.2), 5.05 (br d, J = 16 Hz, 1 H, H.1a), 5.03 (br d, J = 10 Hz, H.1b), 4.03 (m, 1 H, H.6), 3.59 (dd, J = 8.4, 1.5 Hz, 1 H, H.4), 3.22 (dt,

J = 7.1, 1.5 Hz, 1 H, H.5), 2.33 (m, 1 H, H.3), 2.13 (d, J = 9.9 Hz, 1 H, -OH), 1.33-1.57 (br m, 10 H, cyclohexyl), 1.22 (d, J = 6.1 Hz, 3 H, H.7), 1.08 (d, J = 6.8 Hz, 3 H, $-CH_3$); IR (CH_2Cl_2) 3530, 2935, 2840, 1445, 1370, 1360, 1325, 1275, 1200, 1160, 1100, 940, 900, 710 cm^{-1}; mass spectrum, m/e 240 (parent ion).

Data for 50: R_f 0.33 (6:1 hexane-ether); $[\alpha]_D^{22}$ - 19.2° (c = 1.5, $CHCl_3$); ^1H NMR δ 5.71 (br m, 1 H, H.2), 5.12 (br d, J = 23.9 Hz, 1 H, H.1a), 5.07 (dd, J = 17.2, 1.3 Hz, 1 H, H.1b), 4.74 (dd, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 1.6 Hz, 1 H, H.4), 3.68 (m, 2 H, H.5, H.6), 2.65 (m, 1 H, H.3), 2.08 (s, 3 H, acetyl-CH_3), 1.26-1.58 (m, 10 H, cyclohexyl), 1.22 (d, J = 5.4 Hz, 3 H, H.7), 0.99 (d, J = 6.8 Hz, 3 H, $-CH_3$); IR ($CHCl_3$) 2930, 1725, 1500, 1440, 1400, 1350, 1175, 1075, 1000, 910 cm^{-1}; mass spectrum, m/e 282 (parent ion), 239 (M^+-CH_3CO).

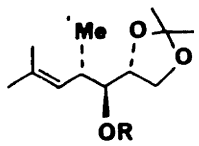


35, R-H
51, R-Ac

Data for 35: R_f 0.48 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ + 47.4° (c = 3.7, CH_2Cl_2); ^1H NMR δ 4.91 (br d, J = 9.9 Hz, 1 H, H.2), 4.09 (dt, $J_{4,5}$ = 3.5 Hz, $J_{5,6}$ = 7.0 Hz, 1 H, H.5), 3.87 (m, 2 H, H.6a, H.6b), 3.57 (br d, $J_{3,4}$ = 7.0 Hz, 1 H, H.4), 2.26 (br m, 1 H, H.3), 2.09 (br s, 1 H, O-H), 1.67

(d, J = 0.8 Hz, 3 H, vinyl-CH_3), 1.58 (d, J = 1.0 Hz, 3 H, vinyl-CH_3), 1.41 (s, 3 H, acetonide-CH_3), 1.35 (s, 3 H, acetonide-CH_3, 1.02 (d, J = 6.5 Hz, CH_3); IR (neat) 3500, 3050, 3000, 2940, 1450, 1375, 1325, 1200, 1150, 1050, 980, 940, 850 cm^{-1}; mass spectrum, m/e 214 (parent ion), 199 (M^+-CH_3).

Data for 51: 0.79 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 22.6° (c = 2.5, CH_2Cl_2); ^1H NMR δ 4.94 (dd, $J_{3,4}$ = 8.0 Hz, $J_{4,5}$ = 4.2 Hz, 1 H, H.4), 4.89 (br d J = 9.8 Hz, 1 H, H.2), 4.16 (dt, $J_{5,6a} = J_{5,6b}$ = 6.7 Hz, $J_{4,5}$ = 4.2 Hz, 1 H, H.5), 3.87 (m, 2 H, H.6a, H.6b), 2.49 (br m, 1 H, H.3), 2.06 (s, 3 H, acetyl-CH_3), 1.66 (d, J = 0.9 Hz, 3 H, vinyl-CH_3), 1.58 (d, J = 1.3 Hz, 3 H, vinyl-CH_3), 1.33 (s, 3 H, acetonide-CH_3), 1.30 (s, 3 H, acetonide-CH_3), 0.92 (d, J = 6.7 Hz, 3 H, -CH_3); IR (neat) 2950, 2900, 2840, 1750, 1480, 1400, 1270, 1230, 1170, 1080, 1000, 940, 925, 875 cm^{-1}; mass spectrum, m/e 241 (M^+-CH_3). Anal Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.85; H, 9.57.

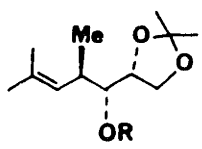


36, R-H
52, R-Ac

Data for 36: R_f 0.35 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ - 0.5° (c = 2.2, CH_2Cl_2); ^1H NMR δ 5.02 (br d, J = 9.7 Hz, 1 H, H.2), 4.01 (m, 1 H, H.5), 3.91 (m, 2 H, H.6a, H.6b),

3.56 (br t, J = 4.7 Hz, 1 H, H.4), 2.54 (br m, 1 H, H.3), 1.87 (br s, 1 H, O-H), 1.70 (d, J = 0.9 Hz, 3 H, vinyl-CH_3), 1.62 (d, J = 1.0 Hz, 3 H, vinyl-CH_3), 1.39 (s, 3 H, acetonide-CH_3), 1.33 (s, 3 H, acetonide-CH_3), 0.98 (d, J = 6.8 Hz, 3 H, CH_3); IR (neat) 3500, 2980, 2920, 1450, 1370, 1250, 1210, 1150, 1060, 840 cm^{-1}; mass spectrum, m/e 215 (M+1), 214 (parent ion), 199 (M^+-CH_3).

Data for 52: R_f 0.44 (3:1 hexane-ether); $[\alpha]_D^{23}$ + 27.6° (c = 0.5, CH_2Cl_2); ^1H NMR δ 5.01 (dd, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 6.1 Hz, 1 H, H.4), 4.97 (br d, J = 9.8 Hz, 1 H, H.2), 4.06 (q, $J_{4,5} = J_{5,6}$ = 6.1 Hz, 1 H, H.5), 3.88 (dd, J = 7.9, 6.2 Hz, 1 H, H.6a), 3.75 (t, J = 7.9 Hz, 1 H, H.6b), 2.72 (br m, 1 H, H.3), 2.05 (s, 3H, acetyl-CH_3), 1.68 (d, J = 1.0 Hz, 3 H, vinyl-CH_3), 1.61 (d, J = 1.1 Hz, 3 H, vinyl-CH_3), 1.34 (s, 3 H, acetonide-CH_3), 1.30 (s, 3 H, acetonide-CH_3), 0.92 (d, J = 6.8 Hz, 3 H, -CH_3); IR (neat) 2980, 2930, 2890, 1750, 1450, 1370, 1230, 1150, 1050, 1025, 840 cm^{-1}; mass spectrum, m/e 256 (parent ion), 241 (M^+-CH_3), 196 (M^+-CH_3CO_2H). Anal Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.82; H, 9.4[illegible]

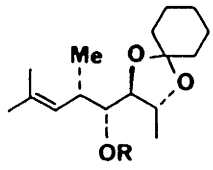


37, R=H
53, R=Ac

Data for 37: R_f 0.55 (3:1 hexane-ether, 2 elutions); $[\alpha]_D^{23}$ + 22.5° (c = 0.8, CH_2Cl_2); ^1H NMR δ 5.10 (br d, J =

9.6 Hz, 1 H, H.2), 4.03 (q, $J_{4,5} = J_{5,6}$ = 6.3 Hz, 1 H, H.5), 3.94 (dd, J = 7.6, 6.3 Hz, 1 H, H.6a), 3.71 (dd, J = 7.6, 6.3 Hz, 1 H, H.6b), 3.32 (m, 1 H, H.4), 2.41 (br m, 1 H, H.3), 2.21 (d, J = 3.4 Hz, 1 H, O-H), 1.68 (d, J = 1.0 Hz, 3 H, vinyl-CH_3), 1.58 (d, J = 1.1 Hz, 3 H, vinyl-CH_3), 1.39 (s, 3 H, acetonide-CH_3), 1.33 (s, 3 H, acetonide-CH_3), 0.99 (d, J = 6.8 Hz, 3 H, CH_3); IR (neat) 3500, 2980, 2920, 2860, 1450, 1370, 1250, 1210, 1150, 1050, 840 cm^{-1}; mass spectrum, m/e 214 (parent ion), 199 (M^+-CH_3).

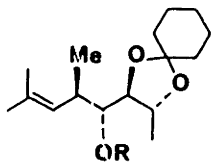
Data for 53: R_f 0.44 (3:1 hexane-ether); $[\alpha]_D^{24}$ + 3.5° (c = 0.7, CH_2Cl_2); ^1H NMR δ 4.98 (br d, J = 9.8 Hz, 1 H, H.2), 4.80 (t, $J_{3,4} = J_{4,5}$ = 5.9 Hz, 1 H, H.4), 4.16 (q, $J_{4,5} = J_{5,6}$ = 5.9 Hz, 1 H, H.5), 3.93 (dd, J = 8.4, 6.4 Hz, 1 H, H.6a), 3.64 (dd, J = 8.4, 6.4 Hz, 1 H, H.6b), 2.61 (br m, 1 H, H.3), 2.05 (s, 3 H, acetyl-CH_3), 1.66 (s, 3 H, vinyl-CH_3), 1.58 (s, 3 H, vinyl-CH_3) 1.38 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3), 0.94 (d, J = 6.8 Hz, 3 H, -CH_3); IR (neat) 2980, 2940, 2870, 1740, 1450, 1370, 1235, 1150, 1060, 1025, 840 cm^{-1}; mass spectrum, m/e 256 (parent ion), 241 (M^+-CH_3), 196 (M^+-CH_3CO_2H). Anal Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.47; H, 9.67.



39, R=H
54, R=Ac

Data for 39: R_f 0.58 (1:1 hexane-ether); $[\alpha]_D^{23}$ - 10.5° (c = 1.2, CH_2Cl_2); ^1H NMR δ 5.01 (br d, J = 9.4 Hz, 1 H, H.2), 4.07 (br quint, J = 6.2 Hz, 1 H, H.6), 3.58 (m, 2 H, H.4, H.5), 2.48 (br m, 1 H, H.3), 1.99 (d, J = 3.1 Hz, O-H), 1.43-1.79 (m, 16 H, cyclohexyl and both vinyl-CH_3), 1.24 (d, J = 6.1 Hz, 3 H, H.7), 1.01 (d, J = 6.7 Hz, 3 H, CH_3); IR (neat) 3500, 2930, 2860, 1440, 1360, 1320, 1270, 1220, 1160, 1100, 1040, 980, 940, 830 cm^{-1}; mass spectrum, m/e 268 (parent ion).

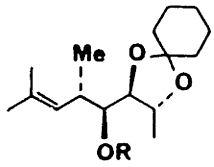
Data for 54: R_f 0.82 (1:1 hexane-ether); $[\alpha]_D^{22}$ + 4.4° (c = 1.5, CH_2Cl_2); ^1H NMR δ 4.97 (t, $J_{3,4} = J_{4,5}$ = 6.3 Hz, 1 H, H.4, superimposed on br d, 1 H, H.2), 4.05 (br quint, J = 6.2 Hz, 1 H, H.6), 3.64 (dd, $J_{4,5}$ = 6.3 Hz, $J_{5,6}$ = 7.9 Hz, 1 H, H.5), 2.66 (br m, 1 H, H.3), 2.05 (s, 3 H, acetyl-CH_3), 1.34-1.74 (m, 16 H, cyclohexyl, vinyl-CH_3), 1.22 (d, J = 6.0 Hz, H.7), 0.96 (d, J = 7.0 Hz, -CH_3); IR (neat) 2960, 2920, 2860, 1745, 1445, 1360, 1270, 1230, 1160, 1100, 1040, 1010, 970, 940 cm^{-1}; mass spectrum, m/e 311 (M^+ + 1), 310 (parent ion). Anal Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.65; H, 9.78.



40, R=H
55, R=Ac

Data for 40: R_f 0.51 (1:1 hexane-ether); $[\alpha]_D^{24}$ + 35.6° (c = 1.0, CH_2Cl_2); ^1H NMR δ 4.97 (br d, J = 9.7 Hz, 1 H, H.2), 4.09 (br quint, J = 6.2 Hz, 1 H, H.6), 3.43 (m, 2 H, H.4, H.5), 2.62 (m, 1 H, H.3), 1.56-1.72 (m, 16 H, cyclohexyl and both vinyl-CH_3), 1.32 (d, J = 6.0 Hz, 3 H, H.7), 1.00 (d, J = 7.0 Hz, 3 H, CH_3); IR (neat) 3480, 2920, 2860, 1450, 1360, 1330, 1270, 1250, 1225, 1160, 1100, 1050, 980, 940, 900, 840 cm^{-1}; mass spectrum, m/e 269 (M^+ + 1), 268 (parent ion).

Data for 55: R_f 0.72 (1:1 hexane-ether); $[\alpha]_D^{23}$ - 3.2° (c = 1.0, CH_2Cl_2); ^1H NMR δ 4.99 (br d, J = 9.8 Hz, 1 H, H.2), 4.91 (dd, $J_{3,4}$ = 3.9 Hz, $J_{4,5}$ = 8.2 Hz, 1 H, H.4), 3.95 (br quint, J = 6 Hz, 1 H, H.6), 3.50 (t, J = 8.2 Hz, 1 H, H.5), 2.82 (m, 1 H, H.3), 2.04 (s, 3 H, acetyl-CH_3), 1.69 (s, 3 H, vinyl-CH_3), 1.63 (s, 3 H, vinyl-CH_3), 1.28-1.58 (m, 10 H, cyclohexyl), 1.21 (d, J = 6.1 Hz, 3 H, H.7), 0.92 (d, J = 6.9 Hz, 3 H, -CH_3); IR (neat) 2940, 2860, 1740, 1450, 1370, 1275, 1235, 1100, 1030, 970, 940, 840 cm^{-1}; mass spectrum, m/e 311 (M^+ + 1), 310 (parent ion). High resolution mass spectrum. Calcd. for $C_{18}H_{30}O_4$: 310.2144. Found: 310.2150.

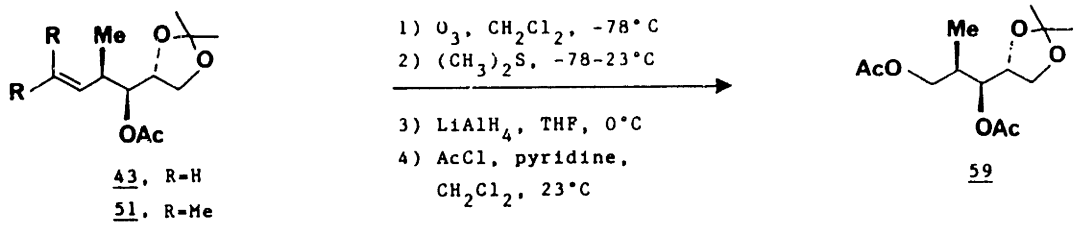


41, R=H
56, R=Ac

Data for 41: R_f 0.65 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 1.8° (c = 1.9, CH_2Cl_2); ^1H NMR δ 5.07 (br d, J = 9.4 Hz, 1 H, H.2), 4.04 (br quint, J = 6.1 Hz, 1 H, H.6), 3.53 (dd, $J_{4,5}$ = 3.0 Hz, $J_{5,6}$ = 7.9 Hz, 1 H, H.5), 3.23 (dt, $J_{3,4}$ = 6.4 Hz, $J_{4,5}$ = 3.0 Hz, 1 H, H.4), 2.55 (m, 1 H, H.3), 2.19 (d, J = 6.8 Hz, 1 H, O-H), 1.36-1.69 (m, 16 H cyclohexyl and both vinyl-CH_3), 1.22 (d, J = 6.1 Hz, 3 H, H.7), 0.98 (d, J = 6.8 Hz, 3 H, CH_3); IR (neat) 3540, 2940, 2860, 1450, 1370, 1280, 1230, 1170, 1100, 990, 940, 725 cm^{-1}; mass spectrum, m/e 269 (M^+ + 1), 268 (parent ion).

Data for 56: R_f 0.71 (1:1 hexane-ether); $[\alpha]_D^{25}$ - 9.8° (c = 1.6, CH_2Cl_2); ^1H NMR δ 4.97 (br d, J = 9.5 Hz, 1 H, H.2), 4.72 (dd, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 3.5 Hz, 1 H, H.4), 3.80 (br quint, J = 6.0 Hz, 1 H, H.6), 3.67 (dd, $J_{4,5}$ = 3.5 Hz, $J_{5,6}$ = 8.0 Hz, H.5), 2.78 (m, 1 H, H.3), 2.01 (s, 3 H, acetyl-CH_3), 1.28-1.75 (m, 16 H, cyclohexyl, vinyl-CH_3), 1.23 (d, J = 6.0 Hz, 3 H, H.7), 0.97 (J = 6.9 Hz, 3 H, -CH_3); IR (neat) 2920, 2880, 2800, 1740, 1460, 1360, 1250, 1080, 1010, 930 cm^{-1}; mass spectrum, m/e 310 (parent ion), 267 (M^+-CH_3CO). High resolution mass spectrum. Calcd. for $C_{18}H_{30}O_4$: 310.2144. Found: 310.2158.

General Procedure for Degradation of 27-37 and 39-41 to 1,3-Diacetates 59-66 (See Schemes 4 and 5).

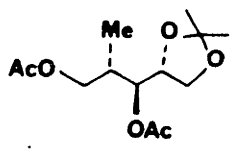


43, R-H
51, R-Me

59

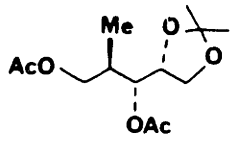
A solution of 43 (45 mg, 0.19 mmol) in CH_2Cl_2 (10 mL) was treated with a stream of ozone in O_2 for 1.5 min (0.9 mmol/min, 1.4 mmol) at -78 °C. The resulting blue solution was then purged with oxygen for 20 min with the temperature maintained at -78 °C. The reaction was quenched by addition of $(CH_3)_2S$ (1 mL) and allowed to warm to room temperature. Solvent was removed in vacuo and the residue dissolved in THF (10 mL) and treated with excess lithium aluminum hydride (110 mg, 2.9 mmol) at 0 °C. Fifteen minutes later, the reaction was quenched by the addition of 0.25 mL of H_2O and 0.75 mL of I N NaOH and allowed to warm to room temperature. The resulting slurry was filtered through Celite, dried over Na_2SO_4, filtered and concentrated to afford 36 mg (96%) crude diol. This material was dissolved in CH_2Cl_2 (5 mL) and treated with pyridine (0.2 mL, 1.9 mmol) and AcCl (0.07 mL, 0.99 mmol) overnight. The reaction mixture was concentrated in vacuo and the residue chromatographed (1 mm silica gel preparative plate, 2:1 hexane-ether, 2 elutions) to afford 43 mg (80%) of pure 59: R_f 0.49 (2:1 ether-hexane); $[\alpha]_D^{23}$ + 6.2°

(c = 1.1, CH_2Cl_2); ^1H NMR δ 5.08 (dd, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 7.4 Hz, 1 H, H.3), 4.14 (br q, J = 6 Hz, 1 H, H.4), 4.02 (dd, J = 8.5, 6.2 Hz, 2 H, H.1), 3.91 (dd, J = 8.5, 5.7 Hz, 1 H, H.5b), 3.77 (dd, J = 8.5, 6.0 Hz, 1 H, H.5a), 2.25 (m, 1 H, H.2), 2.05 (s, 3 H, acetyl-CH_3), 2.03 (s, 3 H, acetyl-CH_3), 1.38 (s, 3 H, acetonide-CH_3), 1.33 (s, 3 H, acetonide-CH_3), 0.96 (d, J = 7.0 Hz, 3 H, -CH_3); IR (neat) 2970, 2930, 2860, 1760, 1460, 1375, 1225, 1100, 830 cm^{-1}; mass spectrum, m/e 259 (M^+-CH_3). High resolution mass spectrum. Calcd. for $C_{12}H_9O_6$ (M^+-CH_3) 259.1181. Found: 259.1179.



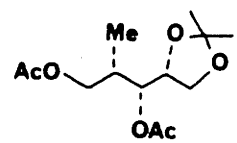
60

Data for 60 (prepared from 44 and 52): R_f 0.35 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 6.0° (c = 0.8, CH_2Cl_2); ^1H NMR δ 5.02 (dd, $J_{2,3}$ = 5.0 Hz, $J_{3,4}$ = 6.6 Hz, 1 H, H.3), 4.21 (q, J = 6.6 Hz, 1 H, H.4), 4.05 (br d, J = 6.4 Hz, 2 H, H.1), 3.98 (dd, J = 8.3, 6.6 Hz, 1 H, H.5a), 3.74 (dd, J = 8.3, 6.6 Hz, 1 H, H.5b), 2.16 (br m, 1 H, H.2), 2.04 (s, 3 H, acetyl-CH_3), 2.03 (s, 3 H, acetyl-CH_3), 1.35 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3), 0.98 (d, J = 7.1 Hz, 3 H, -CH_3); IR (neat) 2980, 2890, 1740, 1370, 1220, 1040, 840 cm^{-1}; mass spectrum, m/e 259 (M^+-CH_3). Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 57.01; H, 8.09.



61

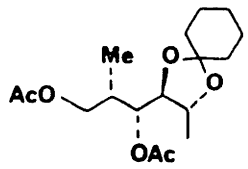
Data for 61 (prepared from 45 and 53): R_f 0.32 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 25.4° (c = 0.7, CH_2Cl_2); ^1H NMR δ 4.90 (dd, $J_{2,3}$ = 7.6 Hz, $J_{3,4}$ = 4.0 Hz, 1 H, H.3), 4.29 (dt, $J_{3,4}$ = 4.0 Hz, $J_{4,5}$ = 6.3 Hz, 1 H, H.4), 4.01 (d, J = 5.2 Hz, 2 H, H.1), 3.99 (dd, J = 8.5, 6.7 Hz, 1 H, H.5a), 3.65 (dd, J = 8.5, 6.1 Hz, 1 H, H.5b), 2.19 (br m, 1 H, H.2), 2.08 (s, 3 H, acetyl-CH_3), 2.02 (s, 3 H, acetyl-CH_3), 1.40 (s, 3 H, acetonide-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 1.03 (d, J = 7.1 Hz, 3 H, -CH_3); IR (neat) 2980, 2930, 2880, 1740, 1450, 1370, 1240, 1060, 970, 840 cm^{-1}; mass spectrum, m/e 259 (M^+-CH_3). Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08. Found: C, 57.25; H, 8.23.



62

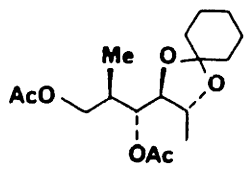
Data for 62 (prepared from 46): R_f 0.56 (2:1 ether-hexane); $[\alpha]_D^{22}$ + 18.0° (c = 0.25, CH_2Cl_2); ^1H NMR δ 4.99 (t, $J_{2,3}$ = $J_{3,4}$ = 5.1 Hz, 1 H, H.3), 4.25 (br q, J = 5.9 Hz, 1 H, H.4), 3.97 (br m, 3 H, H.1, H.5a), 3.65 (dd, J = 8.5,

6.1 Hz, 1 H, H.5b), 2.13 (br m, 1 H, H.2 superimposed on acetyl-CH_3), 2.10 (s, 3 H, acetyl-CH_3), 2.05 (s, 3 H, acetyl-CH_3), 1.39 (s, 3 H, acetonide-CH_3), 1.32 (s, 3 H, acetonide-CH_3), 0.97 (d, J = 7.2 Hz, 3 H, -CH_3); IR (neat) 2940, 1740, 1450, 1370, 1220, 1030 cm^{-1}; mass spectrum, m/e 274 (parent ion), 259 (M^+-CH_3).



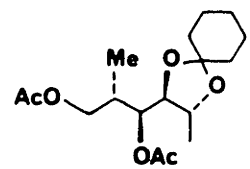
63

Data for 63 (prepared from 47 and 54): 0.53 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 5.1° (c = 0.9, CH_2Cl_2); ^1H NMR δ 5.07 (dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 8.4 Hz, 1 H, H.3), 3.95 (br m, 3 H, H.1, H.5), 3.59 (t, J = 8.4 Hz, 1 H, H.4), 2.33 (br m, 1 H, H.2), 2.05 (s, 3 H, acetyl-CH_3), 2.03 (s, 3 H, acetyl-CH_3), 1.35-1.58 (br m, 10 H, cyclohexyl), 1.22 (d, J = 6.0 Hz, 3 H, H.6), 0.98 (d, J = 7.1 Hz, 3 H, -CH_3); IR (neat) 2920, 2880, 2800, 1760, 1500, 1450, 1375, 1225, 1100, 1040, 940 cm^{-1}; mass spectrum, m/e 328 (parent ion), 285 (M^+-CH_3CO). Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 61.94; H, 8.87.



64

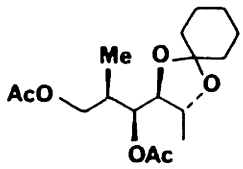
Data for 64 (prepared from 48 and 55): 0.56 (1:1 hexane-ether); $[\alpha]_D^{23}$ + 9.4° (c = 2.0, CH_2Cl_2); ^1H NMR δ 5.01 (dd, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 7.9 Hz, 1 H, H.3), 4.06 (br m, 2 H, H.1 partially superimposed on H.5), 3.95 (br m, 1 H, H.5), 3.66 (t, $J_{3.4} = J_{4,5}$ = 7.9 Hz, 1 H, H.4), 2.24 (br m, 1 H, H.2), 2.04 (s, 3 H, acetyl-CH_3), 2,03 (s, 3 H, acetyl-CH_3), 1.32-1.66 (br m, 10 H, cyclohexyl) 1.23 (d, J = 5.9 Hz, 3 H, H.6), 0.99 (d, J = 7.1 Hz, 3 H, -CH_3); IR (CH_2Cl_2) 2930, 2850, 1770, 1360, 1140, 1090, 1020 cm^{-1}; ,mass spectrum, m/e 328 (parent ion), 285 (M^+-CH_3CO). Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 61.93; H, 8.67.



65

Data for 65 (prepared from 49 and 56): R_f 0.57 (1:1 hexane-ether); $[\alpha]_D^{23}$ - 30.3° (c = 1.1, CH_2Cl_2); ^1H NMR δ 4.86 (dd, $J_{2,3}$ = 8.3 Hz, $J_{3,4}$ = 1.9 Hz, 1 H, H.3), 4.03 (d, J = 4.8 Hz, 2 H, H.1), 3.67 (br m, 2 H, H.4, H.5), 2.29 (br m, 1 H, H.2), 2.07 (s, 3 H, acetyl-CH_3), 2.02 (s, 3 H, acetyl-CH_3), 1.34-1.59 (br m, 10 H, cyclohexyl), 1.26 (d, J =

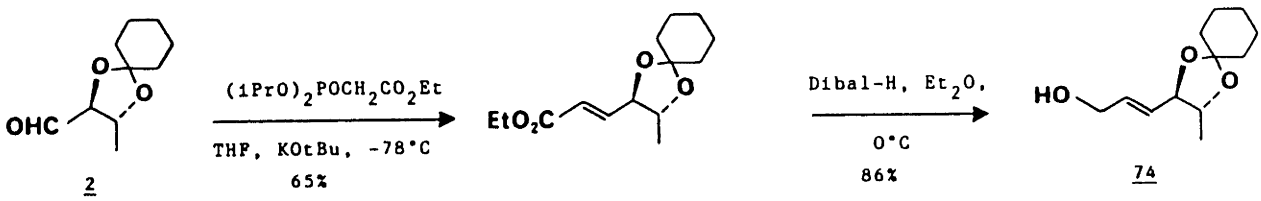
5.6 Hz, 3 H, H.6), 1.05 (d, J = 6.9 Hz, 3 H, $-CH_3$); IR (CH_2Cl_2) 2930, 2840, 1760, 1420, 1360, 1240, 1090, 1020, 940 cm^{-1}; mass spectrum, m/e 328 (parent ion), 285 (M^+-CH_3CO). Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.18; H, 8.59. Found: C, 62.08; H, 8.69.



66

Data for 66 (prepared from 50): R_f 0.48 (1:1 hexane-ether); $[\alpha]_D^{22}$ + 12.0 (c = 0.5, CH_2Cl_2); ^1H NMR δ 4.95 (dd, $J_{2,3}$ = 5.7 Hz, $J_{3,4}$ = 3.1 Hz, 1 H, H.3), 4.04 (br m, 2 H, H.1), 3.78 (m, 1 H, H.5), 3.65 (dd, $J_{3,4}$ = 3.1 Hz, $J_{4,5}$ = 8.3 Hz, 1 H, H.4), 2.19 (br m, 1 H, H.2), 2.09 (s, 3 H, acetyl-CH_3), 2.05 (s, 3 H, acetyl-CH_3), 1.33-1.57 (br m, 10 H, cyclohexyl), 1.26 (d, J = 6.0 Hz, 3 H, H.6), 0.99 (d, J = 6.9 Hz, 3 H, $-CH_3$); IR (neat) 2950, 2870, 1740, 1370, 1230, 1100, 1030 cm^{-1}; mass spectrum, m/e 329 (M^+ + 1), 328 (parent ion), 285 (M^+-CH_3CO).

Preparation of Allylic Alcohol 74



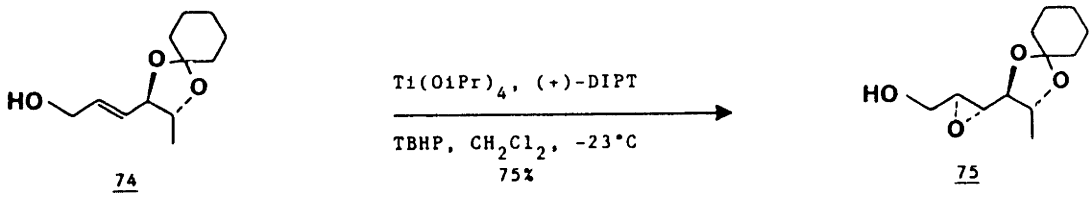
2 74

Ethyl diisopropylphosphonoacetate (8.8 g, 34.9 mmol) in 100 mL THF was treated with KOtBu (3.52 g, 31.4 mmol) at 0 °C for 1 h.[35c] The resulting solution was cooled to -78 °C and 2 (2.14 g, 11.6 mmol) was added. After 2.5 h, the reaction mixture was poured into aqueous NH_4Cl, diluted with Et_2O and extracted with CH_2Cl_2. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was chromatographed over silica gel (60 x 160 mm column) eluting with 10% ether-hexane to give 1.93 g (65%) of pure α,β-unsaturated ester: R_f 0.61 (4:1 hexane-ether); ^1H NMR δ 6.88 (dd, J = 16.0, 5.0 Hz, 1 H, H.2), 6.12 (dd, J = 14.7, 2.1 Hz, 1 H, H.1), 4.20 (q, J = 7.6 Hz, 3 H), 4.05 (br t, J = 6.3 Hz, 1 H, H.3), 3.82 (br quint, J = 5.5 Hz, 1 H, H.5), 1.35-1.68 (m, 10 H, cyclohexyl), 1.32 (t, J = 7.6 Hz, 3 H), 1.28 (d, J = 6.3 Hz, 3 H, H.6).

Dibal-H (25 mL of a 1.33 M solution in hexane, 33.2 mmol), was added dropwise to a solution of the above ethyl ester (1.68 g, 6.60 mmol) on 215 mL of Et_2O at 0 °C. After 4 h, saturated Na_2SO_4 (7 mL) was added. The mixture was stirred at room temperature for 2.5 h, and then the resulting slurry was filtered through Celite. The filtrate was washed

with aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was Kugelrohr distilled (100-120 °C, 2.8 mm) to afford 1.20 g (86%) of 74: R_f 0.10 (1:1 hexane-ether); ^1H NMR δ 5.95 (dt, J = 15.2, 4.9 Hz, 1 H, H.2), 5.68 (br dd, J = 15.7, 7.5 Hz, 1 H, H.3), 4.17 (br t, J = 5.3 Hz, 2 H, H.1), 3.92 (t, J = 7.9 Hz, 1 H, H.4), 3.78 (br quint, J = 6 Hz, 1 H, H.5), 1.29-1.71 (m, 11 H, cyclohexyl, O-H), 1.23 (d, J = 6.0 Hz, 3 H, H.6).

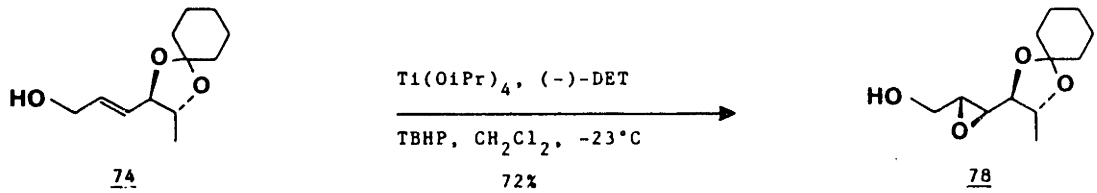
Synthesis of Epoxyalcohols 75 and 78[54]



74 75

A solution of $Ti(OiPr)_4$ (0.85 mL, 2.86 mmol) on 17 mL of CH_2Cl_2 was treated with (+)-diisopropyl tartrate (0.9 g, 3.82 mmol) at -23 °C for 15 min allylic alcohol 74 (0.5 g, 2.39 mmol) was then added, followed 15 min later, by TBHP (1.97 mL of a 3.64 M solution in toluene, 7.17 mmol). This mixture was stored in a -20 °C freezer overnight and then was treated with $(CH_3)_2S$ (1.0 mL, 14.3 mmol). This solution was stirred at room temperature for 24 h and then saturated aqueous Na_2SO_4 (3 mL) was added. The resulting slurry was filtered through Celite, concentrated and the residue partitioned between Et_2O (50 ml) and brine (50 mL). The resulting biphasic mixture was treated with NaOH (4 mL of a 3.75 M solution, 15 mmol). When no more tartrate was detected by TLC analysis, the mixture was extracted with EtOAc, dried over Na_2SO_4 and concentrated. The crude residue was chromatographed over silica gel (50 x 160 mm column) eluting with 2:1 hexane-ether to afford 0.41 g (75%) of pure 75: Rf 0.36 (2:1 ether-hexane); $[\alpha]_D^{22}$ - 22.5° (c = 1.3, $CHCl_3$); ^1H NMR δ 4.08 (br quint, J = 5.9 Hz, 1 H, H.5), 4.00 (m, 1 H, H.1a), 3.93 (m, 1 H, H.1b), 3.35 (dd, J = 8.0, 5.6 Hz, 1 H,

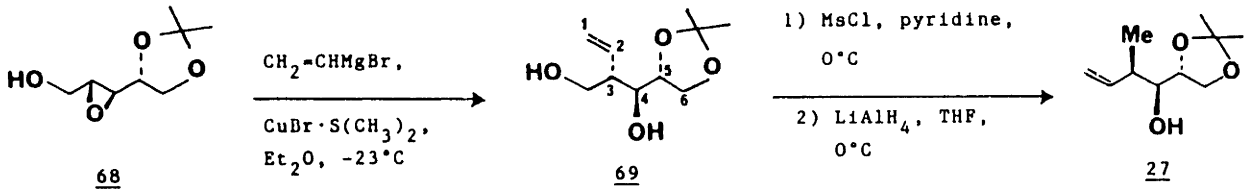
H.4), 3.13 (m, 1 H, H.2), 3.04 (dd, J = 5.9, 2.1 Hz, 1 H, H.3), 1.54-1.69 (m, 11 H, cyclohexyl, O-H), 1.30 (d, J = 6.1 Hz, 3 H, H.6); IR ($CHCl_3$) 3600, 2950, 2870, 1450, 1370, 1270, 1100, 940, 910 cm^{-1}.



74 78

Epoxide 78 was prepared by the same procedure employing (-)-diethyl tartrate as the chiral auxiliary: R_f 0.38 (2:1 ether-hexane); $[\alpha]_D^{22}$ + 19.8° (c = 1.7, $CHCl_3$); ^1H NMR δ 4.04 (br quint, J = 6 Hz, 1 H, H.5), 3.97 (m, 1 H, H.1a), 3.66 (m, 1 H, H.1b), 3.48 (dd, J = 8.3, 4.4 Hz, 1 H, H.4), 3.17 (m, 1 H, H.2), 3.06 (dd, J = 4.5, 2.2 Hz, 1 H, H.3), 1.87 (s, 1 H, O-H), 1.39-1.61 (m, 10 H, cyclohexyl), 1.30 (d, J = 6.0 Hz, 3 H, H.6); IR (CH_2Cl_2) 3680, 2940, 2840, 1440, 1360, 1330, 1090, 930 cm^{-1}.

General Procedure for Reaction of Epoxides 68, 71, 75, and 78 with Vinyl Grignard and $CuBr \cdot S(CH_3)_2$ (see Schemes 6 and 7).



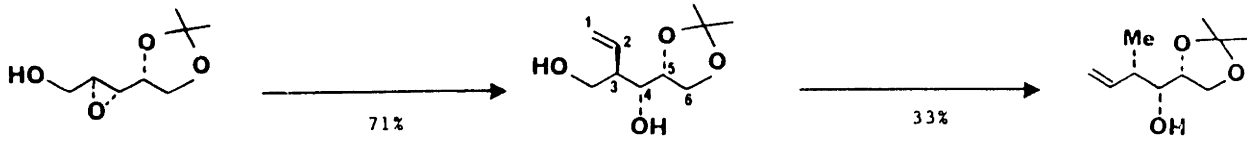
A solution of CH_2 = CHMgBr in THF (2.9 mL of a 1.38 M solution, 4.04 mmol) was added to a mixture of $CuBr \cdot S(CH_3)_2$ (0.33 g, 1.62 mmol) and 2 mL of $(CH_3)_2S$ in 8 mL of Et_2O at -23 °C.[35a] After 10 min, a solution of epoxide 68[34a] (75 mg, 0.43 mmol) in 1 mL of Et_2O was added. The reaction mixture was maintained at -23 °C for 9 h and then was poured into pH 8.5 NH_4Cl/NH_4OH solution; extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated. The crude product (85 mg, 97%) was a 6:1 mixture of 69 and 68 by ^1H NMR analysis. Pure 69 (51 mg, 59%) was obtained by PTLC (0.5 mm plate, 10:1 CH_2Cl_2-ether, 2 elutions): R_f 0.51 (10:1 CH_2Cl_2-ether, 2 elutions); ^1H NMR δ 5.68 (m, 1 H, H.2), 5.18 (br d, J = 10.2 Hz, 1 H, H.1a), 5.13 (dd, J = 16.5, 1.4 Hz, 1 H, H.1b), 4.12 (m, 1 H, H.5), 3.94 (br m, 3 H, H.4, H.6a, H.6b), 3.88 (m, 1 H, $-CH_2OH$), 3.66 (m, 1 H, $-CH_2OH$), 2.77 (br t, J = 5.4 Hz, 1 H, O-H), 2.71 (d, J = 2.8 Hz, 1 H, O-H), 2.24 (m, 1 H, H.3), 1.40 (s, 3 H, acetonide-CH_3), 1.33 (s, 3 H, acetonide-CH_3).

Diol 69 (51 mg, 0.25 mmol) was dissolved in 2 mL of pyridine and treated with methanesulfonyl chloride (0.03 mL, 0.35 mmol) at 0 °C for 5 h and then at -10 °C overnight.[35b,36]

The reaction mixture was then poured into saturated aqueous $NaHCO_3$, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product (81 mg) was taken on to the next step without purification.

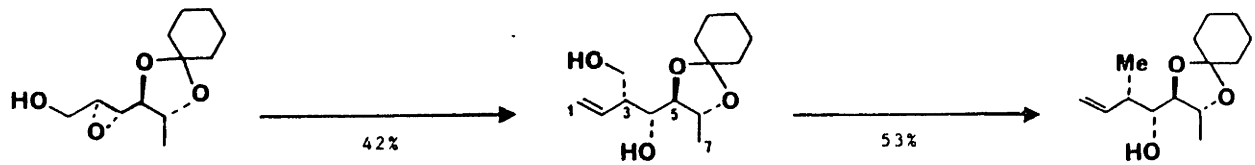
Data for monomesylate: R_f 0.44 (2:1 benzene-EtOAc); ^1H NMR δ 5.72 (br m, 1 H, H.2), 5.23 (br d, J = 8.7 Hz, 1 H, H.1a), 5.21 (br d, J = 24.5 Hz, 1 H, H.1b), 4.41 (dd, J = 9.6, 6.1 Hz, 1 H, $-CH_2-OMs$), 4.33 (dd, J = 9.6, 3.6 Hz, 1 H, $-CH_2-OMs$), 4.10 (dt, J = 6.5, 3.9 Hz, 1 H, H.5), 3.89 (m, 3 H, H.4, H.6a, H.6b), 2.98 (s, 3 H, CH_3SO_2-), 2.37 (br s, 1 H, O-H), 2.33 (m, 1 H, H.3), 1.39 (s, 3 H, acetonide-CH_3), 1.31 (s, 3 H, acetonide-CH_3).

A solution of crude monomesylate (81 mg, 0.33 mmol) in 3 mL of THF was treated with lithium aluminum hydride (34 mg, 0.88 mmol) at 0 °C for 3 H.[35b,c] The reaction was quenched with 4 mL of H_2O and 1 mL of 15 % aqueous NaOH. The resulting biphasic mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated to afford 36 mg (66% from 69) of crude product. Pure 27 (21 mg, 38%) was obtained by PTLC (0.5 mm silica gel plate, 4:1 benzene-EtOAc, R_f 0.39). Compound 27 prepared in this manner was identical with the sample obtained from the reaction of 8 and 4.



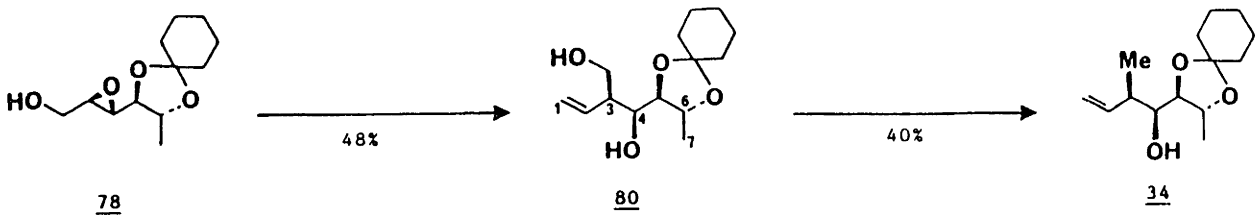
71 → 73 (11:1, 73:71) → 30

Data for 73: R_f 0.12 (10:1 CH_2Cl_2-ether, 3 developments); ^1H NMR δ 5.60 (br m, 1 H, H.2), 5.19 (br d, J = 9.0 Hz, 1 H, H.1a), 5.16 (br d, J = 17.6 Hz, 1 H, H.1b), 4.16 (dt, J = 6.7, 4.2 Hz, 1 H, H.5), 3.96 (br t, J = 6.7 Hz, 1 H, H.6a), 3.60-3.82 (br m, 3 H, H.6b, H.4, $-CH_2-OH$), 3.55 (m, 1 H, $-CH_2-OH$), 2.61 (br m, 2 H, O-H), 2.45 (m, 1 H, H.3), 1.41 (s, 3 H, acetonide-CH_3), 1.33 (s, 3 H, acetonide-CH_3).



75 → 76 → 31

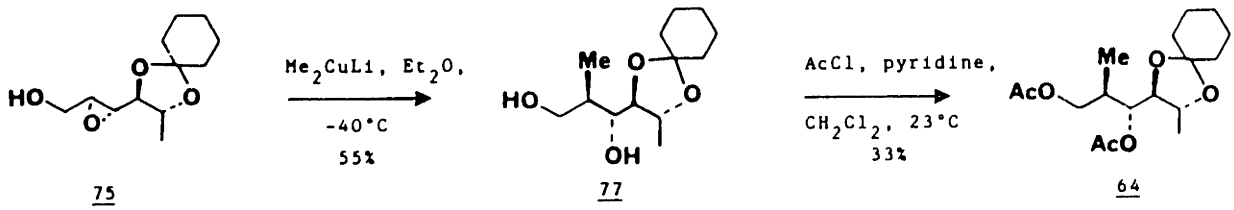
Data for 76: R_f 0.28 (2:1 hexane-EtOAc); ^1H NMR δ 5.74 (m, 1 H, H.2), 5.20 (dd, J = 9.4, 1.9 Hz, 1 H, H.1a), 5.16 (dd, J = 19.7, 1.2 Hz, 1 H, H.1b, 4.13 (br quint, J = 6 Hz, 1 H, H.6), 3.73-3.90 (br m, 3 H, H.4, and $-CH_2-OH$), 3.63 (dd, J = 7.7, 5.1 Hz, 1 H, H.5), 3.05 (br s, 1 H, O-H), 2.86 (br s, 1 H, O-H), 2.42 (m, 1 H, H.3), 1.21-1.73 (m, 10 H, cyclohexyl), 0.92 (d, J = 6.8 Hz, 3 H, H.7).



78 80 34

Data for 80: R_f 0.31 (1:1 hexane-EtOAc); $[\alpha]_D^{19}$ + 30.4° (c = 1.7, $CHCl_3$); ^1H NMR δ 5.66 (br m, 1 H, H.2), 5.20 (br d, J = 14.1 Hz, 1 H, H.1a), 5.19 (br d, J = 10.1 Hz, 1 H, H.1b), 4.07 (br quint, J = 6 Hz, 1 H, H.6), 3.82 (m, 1 H, $-CH_2-OH$), 3.76 (m, 1 H, $-CH_2-OH$), 3.62 (br d, J = 9.1 Hz, 1 H, H.5), 3.51 (br t, J = 9.3 Hz, 1 H, H.4), 2.62 (br t, J = 6.1 Hz, 1 H, O-H), 2.46 (br m, 2 H, H.3, O-H), 1.30-1.59 (br m, 10 H, cyclohexyl), 1.24 (d, J = 6.0 Hz, 3 H, H.7); IR (CH_2Cl_2) 3540, 2930, 2850, 1440, 1360, 1350, 1250, 1100, 1020, 940, 670 cm^{-1}.

General Procedure for Reaction of Epoxides 68, 71, 75 and 78 with Me_2CuLi (see Schemes 6 and 7).



75 77 64

MeLi (1.5 mL of a 1.15 M solution in Et_2O, 1.68 mmol) was added dropwise to a slurry of CuI (0.16 g, 0.84 mmol) in 6 mL of Et_2O at 0 °C. After 30 min, the resulting colorless solution was cooled to -40 °C and 75 (0.08 g, 0.35 mmol) was added.[35b,c,37] This mixture, now containing a yellow precipitate, was maintained at -40 °C for 4.5 h and then was poured into aqueous NH_4Cl, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Concentration of the filtrate afforded 76 mg (89%) of crude diol. This material was dissolved in 14 mL of THF-H_2O (1:1) and treated with $NaIO_4$ (0.11 g, 0.49 mmol) for 2.5 h.[38] The reaction mixture was then diluted with brine, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. The resulting crude residue (70 mg) was purified by PTLC (0.5 mm thickness silica gel plate) eluting with 2:1 Et_2O-hexane (R_f 0.30) to afford 48 mg (55%) of pure 77.

Diol 77 (48 mg, 0.200 mmol) was dissolved in 3 mL of CH_2Cl_2 and treated with pyridine (0.32 mL, 3.9 mmol) and acetyl chloride (0.14 mL, 1.95 mmol) for 5 h. The reaction mixture was then poured into aqueous $NaHCO_3$ solution and

extracted with CH_2Cl_2. The combined extracts were washed with 1 N HCl and then brine, dried over Na_2SO_4, filtered and concentrated. The resulting oil was purified by PTLC (0.5 mm silica gel plate) using 2:1 ether-hexane (R_f 0.69) to afford 21 mg (33%) of pure 64. Compound 64 prepared in this manner was identical with the sample obtained from degradation of 48 and 55.

APPENDIX

DIRECTED OPENINGS OF 2,3-EPOXYALCOHOLS VIA REACTION OF ISOCYANATES : SYNTHESIS OF (+)-ERYTHRO-DIHYDROSPHINGOSINE

Directed Openings of 2,3-Epoxyalcohols Via Reactions With Isocyanates: Synthesis of (+)-Erythro Dihydrosphingosine

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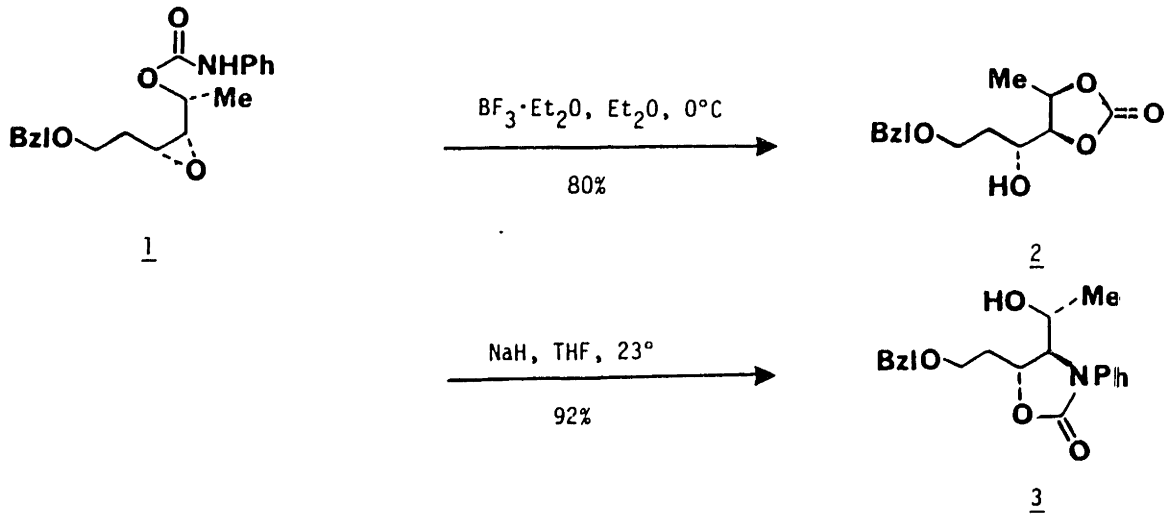
Abstract

Two methods for the synthesis of 2-N-alkylamino-1,3-diols from 2,3-epoxyalcohols are described. In one procedure (Method A) an epoxy urethane (5, 8, 11, 14, 16) prepared from the corresponding epoxyalcohol by standard procedures is cyclized to a 2-oxazolidinone derivative (6, 9, 12, 15, 17) in 81-90% yield by treatment with NaH in THF or NaOMe in MeOH. The second procedure (Method B) involves treatment of the epoxyalcohol (4, 7, 10, 13, 24) with benzyl isocyanate, a NH_3 synthetic equivalent, and NaH in THF at reflux. Hydrolysis of the crude isoxazolidinones by exposure to LiOH in EtOH at reflux smoothly affords 2-N-benzylamino-1,3-diols (22, 23, 30, 31) in 68-72% overall yield. These procedures are highly regioselective; products resulting from intramolecular addition of the urethane nitrogen atom to the epoxide β-position were not detected. This methodology was applied to a short, highly stereoselective synthesis of (+)-erythro-dihydrosphingosine (26) from palmitic aldehyde (47-54% overall yield).

Renewed interest in the use of 2,3-epoxyalcohols as intermediates in organic synthesis has been greatly stimulated by the discovery of the Sharpless asymmetric epoxidation reaction.[2-4] Indeed, highly selective methods for converting the epoxyalcohol unit into a variety of useful functional groups via hydride reduction[5] or by nucleophilic substitution reactions (e.g., carbon,[6] oxygen,[7] and sulfur[7e,8] nucleophiles) have been developed in the past several years. During this period one of our interests has been the use of 2,3-epoxyalcohols in the synthesis of carbohydrates and related compounds.[9] We have observed, for example, that treatment of epoxyurethanes such as 1 with Lewis acids under aprotic conditions effected a highly regioselective α-epoxide opening leading to differentiated triol derivatives (2) in excellent yield.[7a,b] Under basic conditions, however, complementary chemoselectivity occurred with internal delivery of a nitrogen nucleophile to the epoxide α-position (1 → 3).[10]

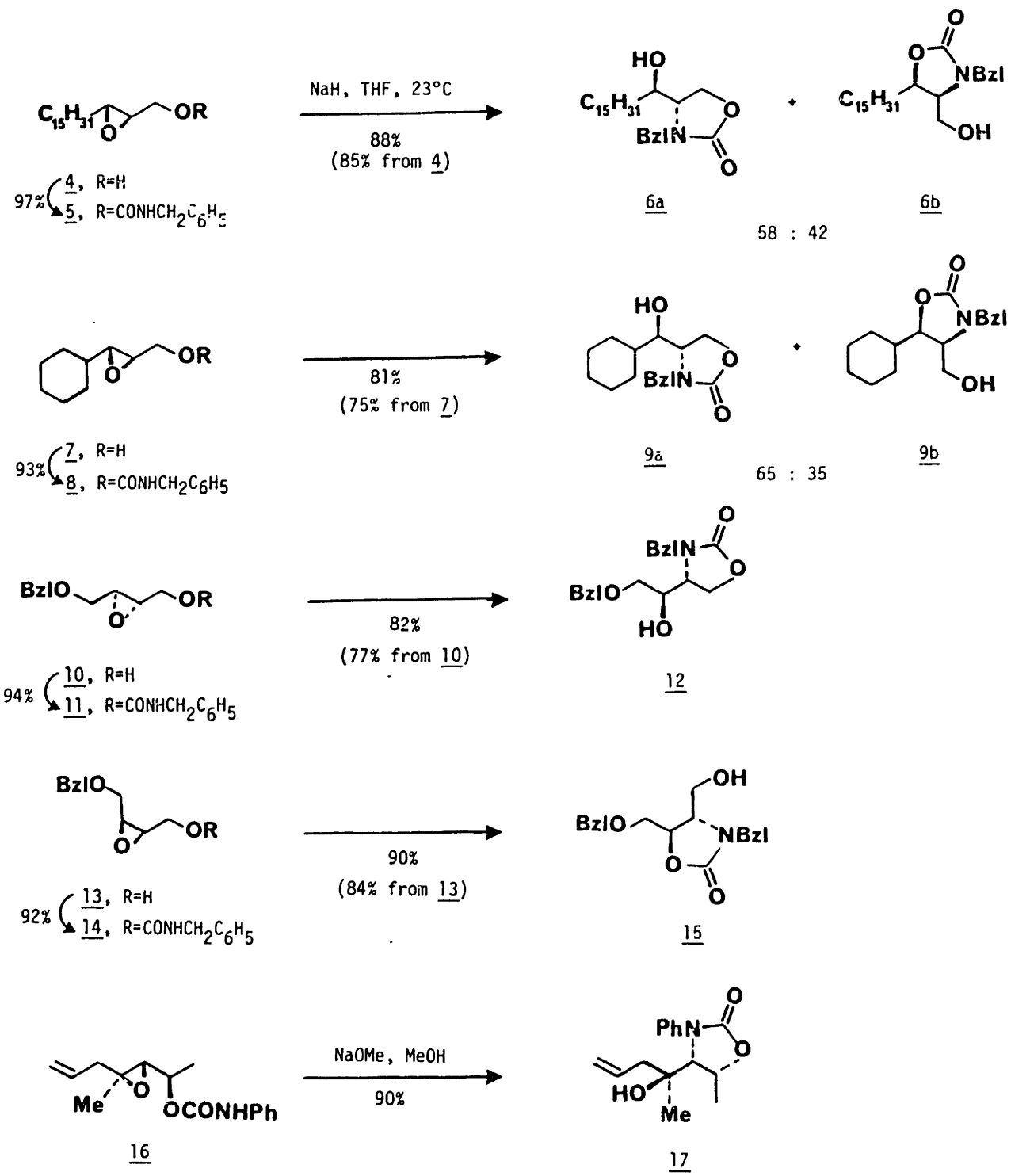


1 2 3

We recognized that the intramolecular opening of epoxides by urethane anions, if general, would nicely complement existing methodology.[11,12] Although it has been known for some time that amines add preferentially to C(3) of 2,3-epoxyalcohols,[7e,13] a satisfactory method for selective addition of nitrogen nucleophiles to C(2) of such systems was unavailable.[14] We now describe extensions of our initial study including the finding that the reaction of 2,3-epoxyalcohols with an isocyanate and NaH constitutes a convenient one-pot procedure for regioselective delivery of nitrogen nucleophiles to C(2) of epoxyalcohol systems.

Table I summarizes the results of cyclization experiments with epoxyurethanes 5, 8, 11, 14 and 16. With one exception, best results were

Table I


NaH, THF, 23°C
88%
(85% from 4)
97%
4, R=H
5, R=CONHCH2C6H5
6a
6b
58 : 42
81%
(75% from 7)
93%
7, R=H
8, R=CONHCH2C6H5
9a
9b
65 : 35
82%
(77% from 10)
94%
10, R=H
11, R=CONHCH2C6H5
12
90%
(84% from 13)
92%
13, R=H
14, R=CONHCH2C6H5
15
NaOMe, MeOH
90%
16
17

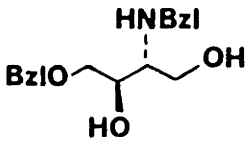
realized by exposure of these compounds to NaH in THF at 23°C (Method A); NaOMe in MeOH was preferred in the case of 16.[15] In contrast to the results reported by Kishi,[7c] acyl transfer was a serious problem in the cyclizations of 5, 8, and especially 14 for which complete isomerization to 15 was observed. Attempts to suppress acyl transfer in the cyclization of 5 to 6 by modifying the counter ion (K^+, Na^+, Li^+), solvent, and reaction temperature were unsuccessful.

A second and more direct procedure for accomplishing these epoxide substitution reactions was developed as follows. We reasoned that the urethane anion 20, the key intermediate in the cyclization of generalized epoxyurethane 18 to carbamate 21, could also be generated by treatment of the parent epoxyalcohol 19 with a strong base (e.g., NaH) and an isocyanate in an aprotic medium[16] (Method B). This indeed proved to be the case (see Table II).

Table II

Substrate	Method[a]	Products	Yield
4	B	6a + 6b (1:1)	76%
7	B	9a + 9b (1:1)	81%
10	B,C	22	68%
13	B,C	23	72%
24	B	25	55%

(a) Method B: NaH, $C_6H_5CH_2NCO$, THF, reflux; Method C: LiOH, aqueous EtOH, reflux



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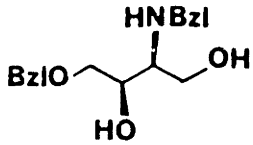
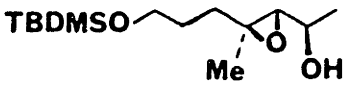


23



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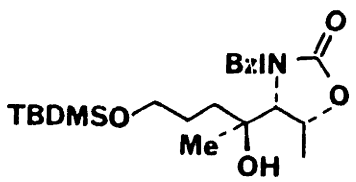

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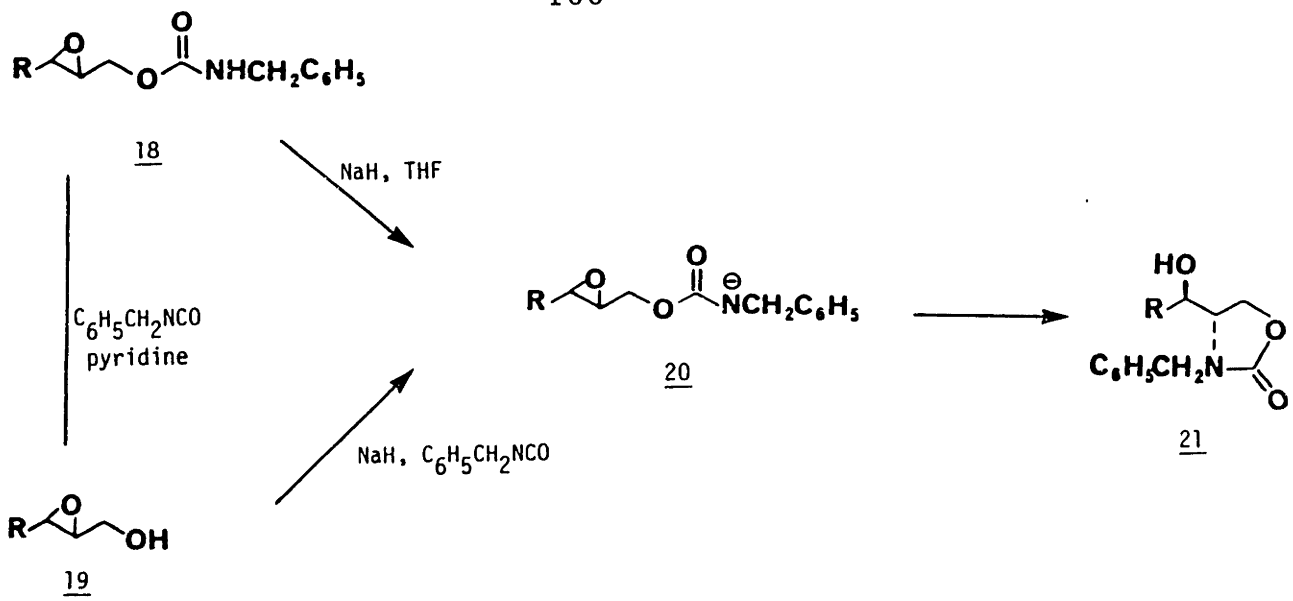


18 20 21 19

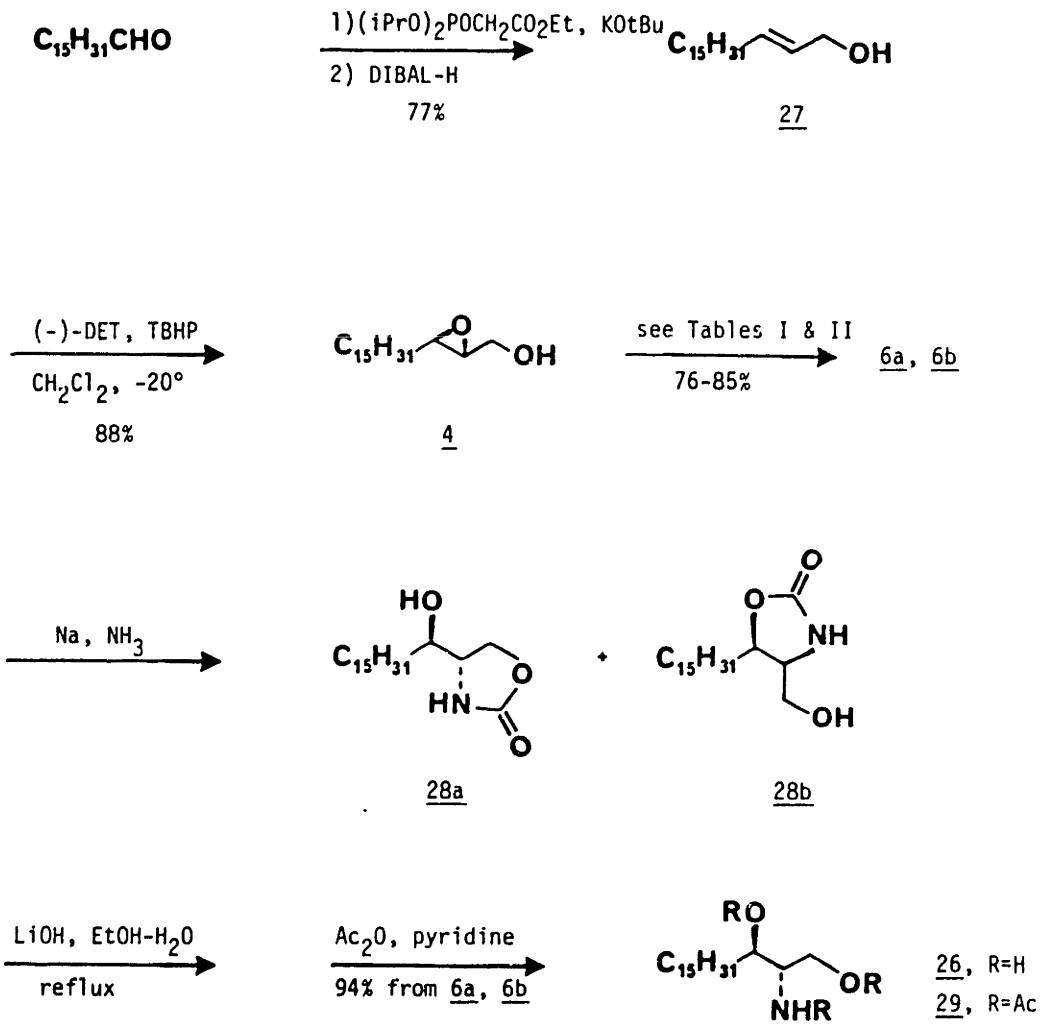
Best results were obtained when all reactants (epoxyalcohol, THF, and benzyl isocyanate) were purified immediately before use, and care taken to exclude moisture and oxygen from the reaction mixtures. These conversions were complete usually within a 1-2 h period in THF at reflux. Longer reaction times (18-24 h) were required for experiments performed at ambient temperature. Mixtures of acyl transfer products were obtained in the transformations of 4 and 7 and, here again, attempts to suppress this problem by use of modified reaction conditions were unsuccessful.

Comparison of the data in Table II with Table I indicates that the efficiency of the one pot conversion (Method B) is comparable to the two-step procedure (Method A) for simple epoxides 4, 7, 10, and 13. Note that for 10 and 13 (Table II) a hydrolysis step was performed prior to chromatographic purification of benzylamino diols 22 and 23. Only for hindered epoxides such as 16 and 24 does there appear to be a distinct advantage to the two-step procedure.

Each of the transformations summarized in Tables I and II is highly regioselective. Isomeric products resulting from intramolecular addition of the urethane nitrogen atom to the epoxide β-position were not detected. Structural assignments in all cases are based on the spectroscopic data summarized in the Experimental Section and the chemical conversions described below. In this connection it is interesting to note that the complete acyl transfer isomerization which occurs in the conversion of 14 to 15 (compare 11 → 12) is fully consistent with the expected threo stereochemistry of 15.

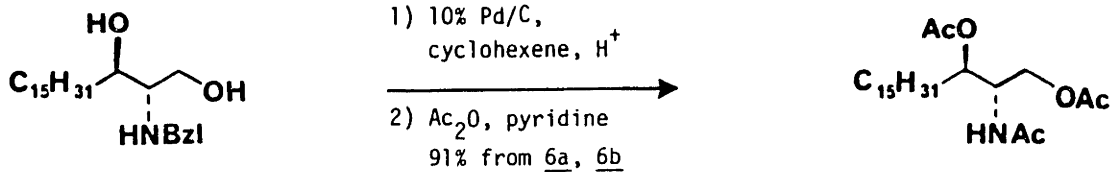
As an illustration of this methodology we describe a synthesis of (+)-erythro-dihydrosphingosine (26; see Scheme I).[17] Although several

Scheme I



syntheses of this compound have already been recorded,[13c,f,18] each suffers either from a low yielding step or low stereo- or regioselectivity. This is especially apparent in approacnes based on the ammonolysis of epoxyalcohol intermediates.[13c,f,g] In the present work the known allylic alcohol 27[13b,c] was prepared from palmitic aldehyde by a modified Horner-Emmons reaction[19] followed by DIBAL-H reduction of the intermediate α,β-unsaturated ester. Asymmetric epoxidation of 27 then afforded epoxyalcohol 4 in 88% yield and >95% optical purity as determined by Mosher ester analysis.[20] Conversion of 4 to a mixture of urethanes 6a and 6b was accomplished in 76-85% yield as outlined previously. Treatment of this mixture with sodium in liquid ammonia effected smooth debenzylation to give the corresponding mixture of carbamates

28a and 28b which could be separated if desired. On a routine basis, however, this mixture was directly hydrolyzed (LiOH in aqueous EtOH) to afford dihydrosphingosine 26 which was fully characterized as the triacetyl derivative 29 (94% yield from 6a/6b). An alternative deprotection sequence[21] involved hydrolysis of 6a/6b to give N-benzylamine 30 which was smoothly debenzylated by transfer hydrogenolysis (10% Pd/C, cyclohexene).[22] This procedure provided 29 in 91% overall yield following acylation of crude 26. The physical constants for (+)-D-dihydrosphingosine triacetate obtained by either sequence were in excellent agreement with literature values.



30 29

This synthesis of 29 is much simpler and more efficient than the routes previously reported.[13c,f,18] It also nicely illustrates a useful strategy for the synthesis of 2-amino-1,3-diol units which occur in a variety of natural products including aminosugars.[23,24] Although the present study has concentrated on the use of benzyl isocyanate as a synthetic equivalent of NH_3, this methodology should also be applicable to other isocyanates when the objective is the synthesis of 2(-N-alkylamino)-1,3-diols.[12d]

Experimental Section

^{1}H NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in δ units relative to internal $CHCl_3$ (7.24 ppm). Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. Mass spectra were measured at 70 eV on a Varian MAT 44 instrument. High resolution mass spectra were provided by the facility supported by NIH Grant RR00317 (Principal Investigator, Professor K. Biemann) from the Biotechnology Resources Branch, Division of Research Resources, and were obtained on a CEC 21-110B high resolution mass spectrometer equipped with a PDP-1145 based computer system to process data recorded on photographic plates. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 144 polarimeter or a Rudolph Autopal III polarimeter using a 1 cm^3 capacity quartz cell (10 cm path length). Elemental analyses were performed by Robertson Laboratories, Inc., Florham Park, N.J.

All reactions were conducted in oven-dried (120°C) glassware under atmospheres of dry argon or nitrogen. All solvents were freshly distilled before use: THF was distilled first from Na-benzophenone ketyl and then from lithium aluminum hydride; CH_2Cl_2 was distilled from P_2O_5; benzene was distilled from Na-benzophenone ketyl.

Analytical thin-layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with a 0.25 mm-layer of silica gel containing PF254 indicator (Analtech). Preparative thin layer chromatography was performed on 20 x 20 cm plates coated with 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with ethyl acetate. Flash chromatography was performed as described by Still.[25] All chromatography solvents were distilled prior to use.

(E)-Octadec-2-en-1-ol (27)

To a 0°C solution of ethyl α-(diisopropylphosphono)acetate (5.81 g, 23.1 mmol) in 40mL of THF was added KO-t-Bu (2.53 g, 22.5 mmol). This mixture was stirred at room temperature for 1 h and then was cooled to -78° C. Palmitic aldehyde (3.56 g, 14.8 mmol) as a solution in 10 mL of THF was added and the resulting solution was stirred for 1.5 h at this temperature. The reaction mixture was then poured into 120 mL of saturated aqueous NH_4Cl and extracted

with CH_2Cl_2 (4x70 mL). The combined organic layers were washed with 100 mL of saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography (50x160 mm column, 1% ether-hexane as eluant) giving 4.30 g (94%) of pure (E)-octadecenoic acid ethyl ester:[26] R_f 0.37 (2% ether-hexane); ^1H NMR (270 MHz) δ 6.92 (dt, J=16, 7 Hz, 1 H, H_3), 5.78 (d, J=16 Hz, 1 H, H_2), 4.15 (q, J=6 Hz, 2 H, CH_2), 2.18 (br q, J=7 Hz, 2 H, H_4), 1.15-1.50 (m, 29 H), 0.85 (t, J=6 Hz, 3 H, CH_3).

To a 0° solution of 3.62 g (11.7 mmol) of the above unsaturated ester in 100 mL of Et_2O was added dropwise 35 mL (35.0 mmol) of DIBAL-H (1M in hexane). The resulting mixture was allowed to warm to room temperature over 0.5 h, then recooled to 0°C and treated with 75 mL in 1N HCl. The resulting gel was dissolved by dropwise addition of 6N HCl. The ethereal phase was separated and the aqueous was extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were washed with 75 mL of saturated aqueous $NaHCO_3$, then dried over $MgSO_4$, filtered and concentrated in vacuo. The crude allylic alcohol was cnromatographed on a 40x160 mm flash silica gel column using 5:1 hexane-Et_2O as eluant to give 2.84 g (91%) of pure 27: R_f 0.49 (1:1 hexane-Et_2O); mp: 46-48°C [lit. 47-48°C[13b,c]]; ^1H NMR (250 MHz) δ 5.64 (m, 2 H, $H_{2,3}$), 4.07 (t, J=5.3 Hz, 2 H, H_1), 2.03 (br q, J=6 Hz, 2 H, H_4), 1.17-1.36 (m, 27 H), 0.86 (t, J=6.5 Hz, 3 H, CH_3); IR (melt) 3350, 3000, 2950, 2860, 1480, 1200, 1050, 950 cm^{-1}; mass spectrum m/e 268 (parent ion).

(E)-2,3-Epoxyoctadecan-1-ol (4)

Freshly distilled $Ti(OiPr)_4$ (3.8 mL, 12.7 mmol) was added to CH_2Cl_2 (115 mL) and the resulting solution was cooled to a temperature between -30 and -20° (dry ice/CCl_4). Freshly distilled (-)-diethyl tartrate (2.89 mL, 16.9 mmol) was then added. The resulting mixture was stirred for 15 min and then a solution of the allylic alcohol 27 (2.83 g, 10.6 mmol) in CH_2Cl_2 (20 mL) was added. Ten minutes later tert-butyl hydroperoxide solution (8.7 mL of 3.64 M solution in toluene; 31.7 mmol)[27] was added and the reaction mixture was then stored in a -20°C freezer for 24 h. The reaction was then quenched by adddition of dimethyl sulfide (3 mL, 41 mmol). The resulting mixture was stirred at -20°C for 30 min and then saturated aqueous Na_2SO_4 (13 mL) was added. This suspension was allowed to warm to room temperature, then was filtered through a pad of Celite and washed with Et_2O. Concentration of the

filtrate provided an oil which was chromatographed on a 50 x 160 mm flash silica gel column with solvent increasing in polarity from hexane to 5:1 hexane-Et_2O. The appropriate fractions were combined and concentrated in vacuo to give 2.65 g (88%) of crystalline 4 (R_f 0.30, 1:1 Et_2O-hexane) which proved to be >95% optically pure by Mosher ester analysis: mp 77-78°C (pet. ether) [lit. m.p.[13f] 78-79°C]; $[\alpha]_D^{23}$ + 22.5° (c=0.79, $CHCl_3$) [lit.[13f] $[\alpha]_D^{22}$ + 21.6° (c=0.49, $CHCl_3$)]; ^1H NMR (250 MHz) δ 3.90 (ddd, J=12.6, 5.5, 2.5 Hz, 1 H, H_{1a}), 3.61 (ddd, J=12.6, 4.2, 3.1 Hz, 1 H, H_{1b}), 2.91 (m, 2 H, $H_{2,3}$), 1.65 (dd, J=7.3, 5.6 Hz, 2 H), 1.23-1.57 (m, 27 H), 0.86 (t, J=6.6 Hz, 3 H, CH_3); IR (CH_2Cl_2): 3780, 3210, 2915, 2860, 1420, 1250, 1110 cm^{-1}; mass spectrum, m/e 284 (parent ion).

1-[(N-Benzylcarbamoyl)oxy]-trans-2,3-epoxyoctadecane (5)

To a solution of 4 (547 mg, 1.93 mmol) in CH_2Cl_2 (20 mL) were added sequentially triethylamine (0.35 mL, 3.8 mmol) and freshly distilled benzyl isocyanate (0.31 mL, 2.5 mmol). After being stirred overnight at room temperature the reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x10 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting crude product was chromatographed on a 40x160 mm silica gel column with 5:1 hexane-EtOAc as eluent affording 781 mg (97%) of pure crystalline urethane 5: mp 80-81°C; R_f 0.64 (2:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.31 (m, 5 H, aromatic), 5.16 (broad s, 1 H, NH), 4.45 (dd, J=12.1, 3.1 Hz, 1 H, H_{1a}), 4.39 (d, J=6.3 Hz, 2 H, benzylic, partially superimposed on H_{1a}), 3.93 (dd, J=12.1, 6.3 Hz, 1 H, H_{1b}), 2.98 (m, 1 H, H_2), 2.85 (broad s, 1 H, H_3), 1.55 (t, J=6.2 Hz, 2 H), 1.26-1.46 (m, 27 H), 0.86 (t, J=6.6 Hz, 3 H, CH_3); IR (melt) 3285, 2910, 2850, 1687, 1270, 678 cm^{-1}; mass spectrum, m/e 417 (parent ion). Anal. Calcd. for $C_{26}H_{43}NO_3$: C, 74.78; H, 10.38. Found: C, 74.52; H, 10.21.

1-[(N-Benzylcarbamoyl)oxy]-3-cyclohexyl-trans-2,3-epoxypropane (8) was prepared from racemic epoxyalcohol 7[5a] in 93% yield using the procedure described for 5: mp 94-94.5°C (hexane-EtOAc); R_f 0.82 (1:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.24-7.35 (m, 5 H, aromatic), 5.05 (broad s, 1 H, NH), 4.38 (dd, J=12.0, 3.1 Hz, 1 H, H_{1a}), 4.36 (d, J=5.4 Hz, 2 H, benzylic, partially superimposed on H_{1a}), 3.92 (dd, J=12.0, 6.2 Hz, 1 H, H_{1b}), 3.00 (m, 1 H, H_2), 2.63 (d, J=5.0 Hz, 1 H, H_3), 1.03-1.84 (m, 11 H); IR (neat) 3380, 2920, 2850,

1710, 1533, 1490, 1455, 1260, 1235, 1140, 1040 cm^{-1}; mass spectrum m/e 289 (parent ion). Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.71; H, 8.30.

[N-Benzylcarbamoyl)oxy]-4-benzyloxy-trans-2,3-epoxybutane (11) was prepared from racemic 10[8] in 94% yield: mp 45-46°C (hexane-EtOAc); R_f 0.61 (1:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.23-7.39 (m, 10 H, aromatic), 5.15 (broad s, 1 H, NH), 4.58, 4.54 (AB, J=12 Hz, 2 H, O-benzyl), 4.42 (dd, J=12.1, 3.3 Hz, 1 H, H_{1a}), 4.35 (d, J=7.5 Hz, 2 H, N-benzyl), 3.95 (dd, J=12.1, 5.6 Hz, 1 H, H_{1b}), 3.75 (dd, J=11.2, 2.7 Hz, 1 H, H_{4a}), 3.48 (dd, J=11.2, 2.7 Hz, 1 H, H_{4b}), 3.12 (m, 2 H, H_2 and H_3); IR (melt) 3330, 3060, 3030, 2940, 2860, 1720, 1520, 1450, 1360, 1240, 1110, 1040, 980, 860 cm^{-1}; mass spectrum m/e 327 (parent ion). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47. Found: C, 69.77; H, 6.63.

1-[(N-Benzylcarbamoyl)oxy]-4-benzyloxy-cis-2,3-epoxybutane (14) was prepared from racemic 13[8] in 92% yield: R_f 0.38 (2:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.24-7.32 (m, 10 H, aromatic), 5.09 (broad s, 1 H, NH), 4.60, 4.51 (AB, J=11.9 Hz, 2 H, O-benzyl), 4.35 (d, J=5.9 Hz, 2 H, N-benzyl, superimposed on m, 1 H, H_{1a}), 4.03 (dd, J=12.1, 6.8 Hz, 1 H, H_{1b}), 3.72 (dd, J=11.1, 3.5 Hz, 1 H, H_{4a}), 3.56 (dd, J=11.1, 6.0 Hz, 1 H, H_{4b}), 3.27 (m, 2 H, H_2 and H_3); IR (neat) 3325, 3025, 2920, 1740, 1520, 1450, 1250, 1095, 730, 690 cm^{-1}; mass spectrum m/e 327 (parent ion). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.21; H, 6.46; N, 4.28. Found: C, 69.50; H, 6.53; N, 4.30.

General Procedure for Epoxyurethane Cyclization (Table I).

A solution of urethane 5 (780 mg, 1.87 mmol) in THF (25 mL) at room temperature was treated with NaH (180 mg, 7.50 mmol). After 5 h the reaction was quenched by careful addition of saturated aqueous NH_4Cl (20 mL) and then was extracted with CH_2Cl_2 (4x20 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crystalline crude product which was chromatographed on a 40x160 mm column with 5:1 hexane-EtOAc as eluent. This afforded 685 mg (88%) of a crystalline mixture (58:42) of 6a and 6b (NMR analysis). Separation of 6a and 6b could be accomplished by careful chromatography of small samples (0.5 mm silica gel preparative plate, six developments with 4:1 hexane-EtOAc).

Data for 3-Benzyl-4-(1'-hydroxyhexadecyl)-2-oxazolidinone (6a): R_f 0.36

(2:1 hexane-EtOAc); mp 51-52°C; $[\alpha]_D^{23}$ - 2.8° (c=1.2, CH_2Cl_2); ^1H NMR (250 MHz) δ 7.27-7.41 (m, 5 H, aromatic), 4.61 (d, A of AB, J=15.4 Hz, 1 H, benzylic), 4.32 (d, B of AB, J=15.4 Hz, 1 H, superimposed on m, 2 H, H_5), 3.72 (broad m, 1 H, H_4), 3.54 (m, 1 H, $H_{1'}$), 1.14-1.58 (m, 28 H), 0.86 (t, J=6.4 Hz, 3 H, CH_3); IR (melt): 3440, 3070, 3050, 3030, 2920, 2850, 1760, 1460, 1425, 1225, 1075, 710 cm^{-1}; mass spectrum, m/e 417 (parent ion).

Data for 3-Benzyl-cis-4-hydroxymethyl-5-pentadecyl-2-oxazolidinone (6b): R_f 0.32 (2:1 hexane-EtOAc); mp 100-101°C; $[\alpha]_D^{23}$ + 15.6° (c=0.64, CH_2Cl_2); ^1H NMR (250 MHz) δ 7.27-7.41 (m, 5 H, aromatic), 4.75 (d, A of AB, J=15.3 Hz, 1 H, benzylic), 4.46 (m, 1 H, H_5), 4.29 (d, B of AB, J=15.3 Hz, 1 H), 3.73 (m, 2 H), 3.59 (m, 1 H, H_4), 1.13-1.56 (m, 29 H), 0.85 (t, J=6.4 Hz, 3 H, CH_3); IR (melt) 3400, 3100, 3010, 2960, 2890, 1700, 1440, 1425, 1410, 1250, 1075, 810 cm^{-1}; mass spectrum, m/e

3-Benzyl-4(1-cyclohexylhydroxymethyl)-2-oxazolidinone (9a) and 3-Benzyl-4--hydroxymethyl-5-cyclohexyl-2-oxazolidinone (9b).

Urethane 8 was cyclized according to the general procedure described above to give a 65:35 mixture of 9a and 9b in 81% yield. Analytical samples of each isomer were obtained by preparative TLC (2:1 hexane-EtOAc, 2 developments).

Data for 9a: mp 128-129°C (hexane-EtOAc); R_f 0.50 (1:1 hexane-EtOAc); ^1H NMR (270 MHz) δ 7.24-7.37 (m, 5 H, aromatic), 4.70 (d, A of AB, J=15.3 Hz, 1 H, benzylic), 4.36 (t, J=7.0 Hz, 1 H, H_{5a}), 4.17 (m, 2 H, B of AB, J=15.3 Hz, superimposed on H_{5b}), 3.72 (broad t, J=7.0 Hz, 1 H, H_4), 3.54 (m, 1 H, $H_{1'}$), 2.42 (m, 1 H, OH), 1.89 (br d, J=13.1 Hz, 1 H), 0.77-1.41 (m, 9 H); IR (CH_2Cl_2) 3562, 2925, 2850, 1745, 1448, 1062 cm^{-1}; mass spectrum, m/e 289 (parent ion), 290 (M^++1). Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.75; H, 8.00; N, 4.90.

Data for 9b: mp 172-173°C; R_f 0.46 (1:1 hexane-EtOAc); ^1H NMR (270 MHz) δ 7.32-7.37 (m, 5 H, aromatic), 4.85 (d, A of AB, J=15.3 Hz, 1 H, benzylic), 4.21 (d, B of AB, J=15.3 Hz, 1 H), 4.06 (dd, J=10.1, 7.0 Hz, 1 H, H_5), 3.78 (broad m, 2 H, CH_2OH), 3.47 (m, 1 H, H_4), 2.09 (m, 2 H), 0.86-1.85 (m, 10 H); IR (CH_2Cl_2) 2925, 2850, 1740, 1048 cm^{-1}; mass spectrum, m/e 289 (parent ion). Anal. calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.64; H, 7.75; N, 4.89.

3-Benzyl-4-(2'-benzyloxy-1'-hydroxyethyl)-2-oxazolidinone (12) was prepared in 82% yield by cyclization of 11: R_f 0.36 (1:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.21-7.36 (m, 10 H, aromatic), 4.71 (d, A of AB, J=15.4 Hz, 1 H, N-benzyl), 4.46 (s, 2 H, O-benzyl), 4.35 (dd, J=8.8, 6.6 Hz, 1 H, H_{5a}), 4.18 (d, B of AB, J=15.4 Hz, superimposed on m, 1 H, H_{5b}), 3.99 (broad s, 1 H, H_4), 3.73 (dt, J=6.5, 2.1 Hz, 1 H, $H_{1'}$), 3.41 (m, 2 H, $H_{2'}$), 2.61 (s, 1 H, OH); IR (neat) 3395, 3060, 3030, 2890, 1730, 1435, 1360, 1250, 1070 cm^{-1}; mass spectrum, m/e 327 (parent ion), 328 (M^++1). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.46; N, 4.28. Found: C, 69.49; H, 6.44; N, 4.34.

3-Benzyl-trans-4-hydroxymethyl-5-benzyloxymethyl-2-oxazolidinone (15): Treatment of urethane 13 with NaH according to the general procedure afforded 15 in 91% yield: mp 95-95.5°C (hexane-EtOAc); R_f 0.21 (1:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.24-7.37 (m, 10 H, aromatic), 4.72 (d, A of AB, J=15.4 Hz, 1 H, N-benzyl), 4.55 (d, J=7.2 Hz, 2 H, O-benzyl, superimposed on m, 1 H, H_5), 4.28 (d, B of AB, J=15.4 Hz, 1 H), 3.62 (broad m, 5 H, H_4, CH_2OH and CH_2OBzl), 2.39 (broad s, 1 H, OH); IR (melt) 3400, 3080, 2920, 1745, 1430, 1260, 1070 cm^{-1}; mass spectrum, m/e 327 (parent ion), 328 (M^++1). Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47. Found: C, 70.11; H, 6.30.

Ribo-2,4-dihydroxy-3-(N-phenylamino)-4-methylhept-6-ene-3,4-Carbamate (17): A solution of 16[9b] (61 mg, 0.23 mmol) in 3 mL of NaOMe/MeOH (3 mL) was stirred at 45°C for 4 h. The reaction mixture was then filtered through Dowex 50W-X8(H^+) resin using MeOH as eluant. Concentration of the filtrate gave an oil which was purified by preparative TLC (1:1 hexane-Et_2O, two developments) to afford 55 mg (90%) of pure carbamate 17: mp 144.5-145.5°C; R_f 0.56 (Et_2O); ^1H NMR ($CDCl_3$-D_2O, 250 MHz) δ 7.21-7.47 (m, 5 H, aromatic), 5.65 (m, 1 H, H_6), 5.17 (br d, J=10.1 Hz, 1 H, H_{7a}), 4.98 (br d, J=16.4 Hz, 1 H, H_{7b}, partially superimposed on H_2), 4.94 (m, 1 H, H_2), 4.22 (d, J=6.9 Hz, 1 H, H_3), 1.94 (d, J=7.5 Hz, 2 H, H_5), 1.72 (d, J=7.0 Hz, 3 H, H_1), 1.33 (s, 3 H, CH_3); IR (CH_2Cl_2) 3540, 3020, 2920, 1775, 1595, 1500, 1390, 1210, 1130, 1090, 970 cm^{-1}; mass spectrum, m/e 261 (parent ion), 262 (M^++1); high resolution mass spectrum, calcd. for C_{15}, H_{19}, NO_3, m/e 261.1365, found m/e 261.1369.

General Procedure for the Reaction of Epoxyalcohols with Isocyanates and NaH (Table II): Synthesis of 6a and 6b

A solution of epoxy alcohol 4 (560 mg, 1.97 mmol) in THF (25 mL) was treated with NaH (100 mg, 4.2 mmol) and stirred for 10 min at room temperature. Freshly distilled benzyl isocyanate (0.316 mL, 2.56 mmol) was added and the reaction mixture heated to reflux for 1.5 h. The mixture was then cooled to 0°C, quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x10 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated to yield the crude product. This material was purified by flash chromatography on a 40x160 mm column with 5:1 hexane-EtOAc as eluent to afford 624 mg (76%) of a crystalline 1:1 mixture of 6a and 6b (NMR analysis).

Epoxy alcohol 7 was converted to a 1:1 mixture 9a and 9b in 81% yield by using this procedure.

Threo-4-Benzyloxy-2-N-benzyl-1,3-butanediol (23).

To a solution of 13 (105 mg, 0.54 mmol) in THF (8 mL) was added NaH (26 mg, 1.1 mmol). Five minutes later freshly distilled benzyl isocyanate (80 µl, 0.65 mmol) was added. The reaction mixture was heated to reflux for 2.5 h, then was quenched by careful addition of saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (4x10 mL). The combined extracts were filtered through a cotton plug and concentrated to afford 235 mg of crude product which consisted of a 5:1 mixture of 15 and 23 (NMR analysis). This mixture was dissolved in 30% aqueous EtOH (10 mL) and treated with LiOH (390 mg, 16.2 mmol) at reflux for 9 h. The resulting solution was cooled to room temperature, diluted with 50% saturated NaCl solution (10 mL) and extracted with CH_2Cl_2 (4x10 mL). The organic extracts were filtered through a cotton plug and concentrated to give crude 23 which was purified by chromatography on a 1.5 mm preparative TLC plate (9:1 CH_2Cl_2-MeOH). Subsequent extraction of the adsorbent with 6:4 CH_2Cl_2-MeOH afforded 121 mg (72%)of pure 23: R_f 0.54 (9:1 CH_2Cl_2-MeOH); ^1H NMR (250 MHz) δ 7.22-7.34 (m, 10 H, aromatic), 4.52 (s, 2 H, O-benzyl), 3.89 (d, A of AB, J=13.0 Hz, 1 H, N-benzyl), 3.82 (m, 1 H, H_3), 3.75 (d, B of AB, J=13.0 Hz, 1 H, N-benzyl, partially superimposed on H_3), 3.57 (m, 4 H, H_1 and H_4), 2.72 (m, 1 H, H_2), 2.28 (broad s, 3 H, NH, and 2 x OH); IR (neat) 3380, 3040, 2900, 1600, 1490, 1450, 1360, 1260, 1205, 1090, 760, 690 cm^{-1}; mass spectrum, m/e 270 (M^+-31). Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.41; H, 7.51.

Erythro-4-Benzyloxy-2-N-benzyl-1,3-butanediol (22) was prepared from 10 in 68% yield using the procedure described for synthesis of 23: mp 85-85.5°C, (EtOAc-hexane); R_f 0.55 (9:1 CH_2Cl_2-MeOH); ^1H NMR (250 MHz) δ 7.24-7.36 (m, 10 H, aromatic), 4.51 (s, 2 H, O-benzyl), 3.93 (br q, J=5 Hz, 1 H, H_3), 3.80 (d, J=4.1 Hz, 2 H, N-benzyl), 3.66 (br d, J=4 Hz, 2 H, H_4), 3.47-3.58 (m, 2 H, H_1), 2.75 (m, 4 H, H_2, NH, and 2 x OH); IR (CH_2Cl_2) 3550, 3040, 2860, 1500, 1250, 1090, 680 cm^{-1}; mass spectrum, m/e 270 (M^+-31). Anal. Calcd. for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69. Found: C, 71.51; H, 7.88.

Ribo-2,4-dihydroxy-3-(N-phenylamino)-7-(O-tert-butyldimethylsilyl)-4-methyl-heptane-3,4-Carbamate (25) was prepared from epoxy alcohol 24 in 63% yield by using the procedure (Method B) described for preparation of 6a and 6b: mp 100-101°C (hexane); R_f 0.29 (12:1 CH_2Cl_2-Et_2O); ^1H NMR (250 MHz) δ 7.25-7.32 (m, 5 H, aromatic), 4.91 (d, J=14.6 Hz, 1 H, A of AB), 4.29 (d, J=14.6 Hz, B of AB), 4.09 (m, 1 H, H_2), 3.53-3.62 (m, 2 H, H_7), 3.20 (d, J=2.3 Hz, 1 H, H_3), 2.15 (br s, 1 H, O-H), 1.57-1.81 (br m, 4 H, $H_{5,6}$), 1.26 (d, J=6.3 Hz, 3 H, H_1), 1.14 (s, 3 H, CH_3), 0.86 (s, 9 H, $(CH_3)_3C$), 0.01 (s, 6 H, $(CH_3)_2Si$); IR (CH_2Cl_2) 3490, 3020, 2920, 2850, 1745, 1490, 1470, 1460, 1380, 1230, 1090,1000, 940, 830 cm^{-1}; mass spectrum, m/e 391 (M^+-15). Anal. Calcd. for $C_{22}H_{37}NO_4Si$: C, 64.82; H, 9.15; N, 3.44. Found: C, 65.04; H, 8.89; N, 3.70.

Synthesis of Dihydrosphingosine Triacetate from 6a/6b

Method A: Anhydrous NH_3 (40 mL) was condensed into a three-necked reaction flask containing a solution of 6a and 6b (610 mg, 1.46 mmol) in THF (15 mL) maintained at -78°C. Sodium metal was then added until a dark blue color persisted. The reaction was stirred for 1 h and then was quenched by addition of solid NH_4Cl. After the NH_3 was removed by slow evaporation the residue was dissolved in saturated aqueous NH_4Cl (15 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated to yield 482 mg of a mixture of 28a and 28b. On a routine basis this mixture was used directly in the next reaction. Analytical samples, however, were obtained by chromatographic separation of the mixture (silica gel, 1:1 hexane-EtOAc).

Data for 28a: mp 75-76°C (hexane); R_f 0.44 (3:1 EtOAc-hexane); $[\alpha]_D^{18}$ + 12.5° (c=1.4, CH_2Cl_2); ^1H NMR (270 MHz) δ 6.54 (s, 1 H, NH), 4.39 (m, 2 H, H_1), 3.82 (m, 1 H, H_2), 3.66 (broad s, 1 H, H_3), 3.29 (broad s, 1 H, OH),

1.10-1.48 (m, 28 H), 0.85 (t, J=6.7 Hz, CH_3); IR (melt) 3440, 2910, 2840, 1780, 1460, 1240, 1080, 1030, 720 cm^{-1}; mass spectrum, m/e 327 (parent ion). Anal. Calcd. for $C_{19}H_{37}NO_3$: 69.68; H, 11.39; N, 4.28. Found: C, 69.57; H, 11.50; N, 4.47.

Data for 28b: mp 103-104°C (hexane-benzene); R_f 0.35 (3:1 EtOAc-hexane); $[\alpha]_D^{18}$ + 0.9° (c=0.44, EtOH); ^1H NMR (270 MHz) δ 5.60 (s, 1 H, NH), 4.62 (m, 1 H, H_3), 3.82 (m, 1 H, H_2), 3.67 (m, 2 H, H_1), 2.18 (m, 1 H, OH), 1.08-1.74 (m, 26 H), 0.86 (t, J=6.4 Hz, 3 H, CH_3); IR (melt) 3400, 2915, 2845, 1695, 1468, 1073 cm^{-1}; mass spectrum, m/e 327 (parent ion), 328 (M^++1); high resolution mass spectrum, calcd. for $C_{19}H_{37}NO_3$, m/e 327.5090, found m/e 327.2773.

The mixture of crude oxazolidinones 28a and 28b (478 mg, 1.46 mmol) was dissolved in 30% aqueous EtOH (20 mL) and treated with LiOH (1.05 g, 43.8 mmol) at reflux overnight. The cooled solution was diluted with brine (20 mL) and extracted with EtOAc (4x20 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated to afford crude dihydrosphingosine 26 (R_f 0.11, 3:1 EtOAc-hexane).

To a solution of this material in CH_2Cl_2 (20 mL) was added pyridine (1.5 mL, 15.4 mmol), dimethylaminopyridine (one crystal), and acetyl chloride (1.1 mL, 15 mmol). After being stirred for 1.5 h the reaction was quenched with MeOH (3 mL), poured into saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (4x20 mL). The combined extracts were washed with 1N HCl (80 mL) and saturated aqueous $NaHCO_3$ (80 mL), filtered through a cotton plug and concentrated. The crude triacetate was purified by column chromatography (40 x 160 mm silica gel packed column, 1:1 hexane-EtOAc as eluent, R_f 0.56, 3:1 EtOAc-hexane) to afford 564 mg (94%) of pure D-(+)-dihydroxyphingosine triacetate (29): mp 93-94°C (hexane); [lit.[13f] mp 94-96° and mp[18a] 97-98°]; $[\alpha]_D^{23}$ + 17.5° (c=1.0, $CHCl_3$) [lit. $[\alpha]_D^{22}$ + 17.0° (c=1.1, $CHCl_3$)[13f] and $[\alpha]_D^{19}$ + 17.4° (c=1.4, $CHCl_3$)[18a]]; ^1H NMR (250 MHz) δ 5.83 (d, J=9.0 Hz, 1 H, NH); 4.88 (q, J=5.5 Hz, 1 H, H_3), 4.37 (m, 1 H, H_2), 4.23 (dd, J=11.4, 6.0 Hz, 1 H, H_{1a}), 4.03 (dd, J=11.4, 3.9 Hz, 1 H, H_{1b}), 2.05 (s, 6 H, two Ac), 1.98 (s, 3 H, Ac), 1.02-1.37 (m, 28 H), 0.85 (t, J=6.6 Hz, 3 H, CH_3); IR (melt) 3280, 2910, 2845, 1718, 1640, 1540, 1368, 1235, 1040 cm^{-1}; mass spectrum, m/e 427 (parent ion), 428 (M^++1). Anal. Calcd. for $C_{24}H_{45}NO_5$: C, 67.41; H, 10.61; N, 3.28. Found: C, 67.64; H, 10.34; N, 3.23.

Method B: A mixture of 6a and 6b (429 mg, 1.03 mmol) was dissolved in 30% aqueous EtOH (20 mL). LiOH (800 mg, 33.3 mmol) was added and the mixture

heated at reflux overnight. The cooled mixture was then diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (4x25 mL). The combined organic extracts were filtered through a cotton plug and concentrated to afford 413 mg of crude N-benzylamine 30 (R_f 0.19, 2:1 hexane:EtOAc). This material was used immediately in the next reaction without purification.

A solution of crude 30 in MeOH (15 mL) was treated with 10% Pd-C (410 mg), 1 N HCl (1.03 mL, 1.03 mmol), and cyclohexene (0.31 mL, 3.08 mmol).[26] The resulting slurry was heated at reflux for 2 h, then cooled to room temperature, filtered through a pad of Celite and concentrated to give 315 mg of crude 26.

A solution of this material in CH_2Cl_2 (10 mL) was treated with pyridine (1.5 mL, 15.4 mmol), acetyl chloride (0.8 mL, 11.1 mmol) and a crystal of 4-DMAP. The resulting solution was stirred for 2 h at room temperature , then quenched with MeOH (5 ML) and diluted with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (10 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (5x25 mL). The combined organic extracts were washed with 1 N HCl (100 ml), saturated aqueous $NaHCO_3$ (100 ml), filtered through a cotton plug and concentrated to afford crude 29. This material was purified by chromatography on a 40x160 mm silica gel column using 1:1 hexane-EtOAc as eluent to yield 399 mg (91%) of pure dihydrosphingosine triacetate.

Erythro-2-(N-benzamido)-3-cyclohexyl-1,3-dibenzoyloxypropane (31) was prepared in 78% yield from the mixture of oxazolidinones 9a/9b by using a slightly modified version of the deprotection sequences described for the synthesis of 29 (substitution of benzoyl chloride for acetyl chloride in the final step of Method A and B): mp 63-64°C; R_f 0.50 (3:1 hexane-EtOAc); ^1H NMR (250 MHz) δ 7.31-8.16 (m, 15 H, aromatic), 7.06 (d, J=8.6 Hz, 1 H, NH), 5.22 (dd, J=6.8, 4.1 Hz, 1 H, H_3), 5.04 (ddd, J=10.3, 6.1, 4.2 Hz, 1 H, H_2), 4 58 (m, 2 H, H_1), 1.64-1.94 (m, 6 H), 1.06-1.30 (m, 5 H); IR (melt) 3330, 3060, 2930, 2880, 1790, 1720, 1640, 1600, 1580, 1530, 1490, 1450, 1270, 1070, 1025, 710 cm^{-1}; mass spectrum, m/e 485 (parent ion). Anal. Calcd. for $C_{30}H_{31}NO_5$: C, 74.20; H, 6.43; N, 2.88. Found: C, 73.93; H, 6.57; N, 2.75.

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