PART I. TOTAL SYNTHESIS OF (-)-PTILCAULIN

PART II. STEREOSELECTIVE REACTIONS OF ALLYLBORONIC ESTERS WITH SUBSTITUTED ALDEHYDES

by

ALAN EDMUND WALTS

B.S., St. John Fisher College (1981)

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

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ORGANIC CHEMISTRY

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

September 1985

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Signature of Author: ..

Department of Chemistry
June 7, 1985

Certified by: .

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Accepted by: .........................................................

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Professor William R. Roush Thesis Supervisor

Professor Glenn A. Berchtold
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ABSTRACT

PART I.

A stereoselective total synthesis of (-)-ptilocaulin (7), the
enantiomer of the naturally occurring antitumor antibiotic, is
described. The synthesis proceeds in 14 steps, with an overall yield of
7.4% and establishes the absolute stereochemistry of the natural
product to be that shown for 3. A key step in this sequence is the use
of an intramolecular 1,3-dipolar nitrene cycloaddition to establish the
cis-fused perhydroindane ring system, as well as two of the four chiral
centers present in 7. In the course of this work it was determined that
the natural product is the thermodynamically preferred isomer of a
number of possible ring fusion and double bond isomers. In the final
guanidine step a mixture of such isomers is obtained via a low
temperature (120°C, 15-45 min) reaction of amino ketone 26 with GDMP;
equilibration with a catalytic amount of guanidine provides the natural
product. Alternatively, the reaction of 26 and GDMP can be carried out
at higher temperature (150°C, 4 h) which provides ptilocaulin directly.

PART II.

A brief review of aldehyde addition chemistry of allylic
organometallic reagents is presented in Chapter II. Special emphasis
is placed on diastereofacial selectivity during reactions with chiral
aldehydes, as well as the utility of allylic boronate reagents in this
context. The strengths and limitations of several groups of reagents
for the control of acyclic stereochemistry are highlighted.

Our contributions to this area involving new, highly selective
allylic boronate reagents are described in Chapter III. A brief study
of the reaction of pinacol allylboronate with two α,β-dialkoxyaldehydes
provided clues to the source of facial selectivity in reactions of
allyl and crotylboronates, and established the role of solvent and
temperature in achieving selectivity. This information was then
utilized in the development of a new class of highly selective tartrate
erster modified allylic boronates. These reagents provided
synthetically useful levels of selectivity in both matched and
mismatched reactions with aldehyde 3, allowing the obtention of either
facial isomer. Extension of these reagents to reactions with achiral
aldehydes provided products in 58-87% e.e., with highest selectivity
observed with substituted aldehydes (e.g. pivaldehyde and
cyclohexanecarboxaldehyde). These reagents are the most enantioselective allylic boronates reported to date and the first chiral allylmetal compounds to display useful levels of mismatched diastereoselectivity in reactions with chiral aldehydes. Dramatic effects of solvent and temperature on the selectivity of these reagents were noted, indicating that selectivity in these reactions is affected by a number of experimental variables. The selectivity in these reactions is proposed to arise from electrostatic, as opposed to strictly steric, interactions in the transition state, indicating that the design of highly effective chiral reagents needs not depend exclusively on steric considerations.

Finally, a synthetic application of the functionalized, (Z)-substituted allylic boronate 27 in a synthesis of the antibiotic X-14547A precursor 6 is described in Chapter IV. In the key boronate addition step, reaction of 27 with D-glyceraldehyde acetonide 26 afforded the functionalized alcohol 28 with 10:15:1 facial selectivity. This adduct was converted in three steps to aldehyde 5, an important intermediate in a synthesis of antibiotic X-14547A developed by Dr. S.M. Peseckis in this laboratory. This sequence was developed only after three alternative routes to 6 investigated by Peseckis proved to be unsatisfactory in terms of yield and/or enantioselectivity. The sequence from aldehyde 26 to 6 proceeds in 49% overall yield (4 steps), thereby establishing this sequence as a useful synthetic method.

Thesis Supervisor: Dr. William R. Roush

Title: Associate Professor of Chemistry
Fellow of the Alfred P. Sloan Foundation 1982-1986
To Lisa and
my family
Biographical Note

The author was born May 21, 1959 in Rochester, New York where he lived for 21 years. He attended St. John Fisher College in Rochester, where he received a Bachelor of Science (cum laude) in May, 1981. He then moved to Boston to pursue graduate studies in chemistry at M.I.T., where he spent three and one-half years working with Professor William R. Roush. Upon receipt of his doctorate he will pursue post-doctoral studies in the biochemistry laboratories of Professor Christopher T. Walsh.
Acknowledgements

First and foremost I would like to express my deepest appreciation to Professor Roush for his inspiration and guidance throughout my stay in his group. His professional standards of the highest level set a standard against which any future accomplishments must be measured. Most importantly, his enthusiasm for science, sense of perspective, and the numerous opportunities of which I have been the beneficiary will be remembered always.

I also extend my appreciation to the people who sparked my interest in chemistry. Professors Teegarden and Turner were especially helpful in first making chemistry fun; Professor Piccolo expanded on this and provided the foundation for future studies in synthetic chemistry. His enthusiasm, guidance and indefatigable willingness to teach and listen were pivotal in my decision to pursue graduate studies.

I would like to thank the members of the Roush group, past and present, for making the past four years so much fun. Amy Essenfeld as social coordinator has done a tremendous job of promoting group comaraderie, which I will dearly miss in the future. Being associated with everyone has broadened my outlook and horizons considerably.

A special thanks goes to all the people at MIT who have been so helpful along the way. M.G. Finn and Joel Hawkins generously provided invaluable advice, assistance and helpful discussions in various stages of the boronate project; Dr. David Harris performed many of the early experiments which helped get the project off the ground. Bob
Foglesong, Mark DuPriest and Brigitte Lesur each provided timely suggestions and advice at several stages of the ptilocaulin project.

I must of course thank the several people who contributed to the preparation of this thesis. Sandra Russo-Rodriguez, Amy Essenfeld, Jotham Coe and Mike Michaelides each provided diligent proofreading and helpful comments for various chapters. I also thank Professor Roush for his comments, and rapid and efficient turnover of the many drafts of each chapter. The use of Professor Walsh's word processor and typewriter is greatly appreciated, as is the technical assistance of several members of his research group. Finally I thank Lisa Hiley, and especially my wife Lisa, for typing portions of this thesis, without which it would never have been completed on time.

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Special Acknowledgements

I especially express my thanks and appreciation to my wife Lisa for her love, support and understanding during both my graduate work and while completing this thesis. Her support has been a source of strength and motivation, and has provided an important sense of balance in my life.

I also thank my parents and family for their support and help in innumerable ways during my college and graduate career. Their support has helped me through several difficult times, and helped keep me on a steady course.

In consideration of the support received from the National Cancer Institute of the National Institutes of Health, the author hereby grants to the United States Government an irrevocable, non-exclusive, royalty-free license to reproduce, translate, publish, use and dispose of copies of this work for Government purposes.
### ABBREVIATIONS

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>9-BBN</td>
<td>9-borabicyclononane</td>
</tr>
<tr>
<td>Bz</td>
<td>benzyl</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>DAT</td>
<td>diadamantyl tartrate</td>
</tr>
<tr>
<td>DET</td>
<td>diethyl tartrate</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>GDMP</td>
<td>guanyl-1,3-dimethylpyrazole</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>NGDMP</td>
<td>N-nitroguanyl-1,3-dimethylpyrazole</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td>t-butyldiphenyilsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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PART I
CHAPTER I

TOTAL SYNTHESIS OF (-)-PTILOCAULIN
Background\textsuperscript{1,2}

The isolation of ptilocaulin and isoptylcauln from the orange Caribbean sponge Ptilocaulis aff. P. spiculifer (Lamarck, 1814) was reported by Rinehart and coworkers in 1981.\textsuperscript{3,4} These two novel guanidine containing natural products, isolated as nitrate salts, display anti-microbial activity against gram-positive and gram-negative bacteria, yeasts and filamentous fungi, and significant cytotoxicity towards L1210 leukemia cells. Other notable members of the relatively small class of

\begin{align*}
\text{Structure 1} & \quad \text{Structure 2} \\
\text{Structure 3} & \quad \text{Structure 4} \\
\text{Structure 5}
\end{align*}


guanidine containing natural products include saxitoxin (4)\textsuperscript{5} and tetrodotoxin (5),\textsuperscript{6} both of which are also highly bioactive. The very interesting chemistry of this group of compounds has been recently reviewed by Chevolot.\textsuperscript{7}

Ptilocaulin and isoptylcauln contain a unique tricyclic ring system in which a guanidine is fused to a substituted perhydroindene nucleus. Structures 1 (ptilocaulin) and 2 (isoptylcauln) were assigned on the basis of detailed spectroscopic analyses, with 10 Hz coupling constants.
between H.8b and H.5a in both compounds suggesting trans ring fusions. The assignment for ptilocaulin, however, was amended to that shown in 3 after an x-ray analysis revealed that the ring fusion was in fact cis. Rinehart has suggested that ptilocaulin may be derived from addition of guanidine to a polyketonide chain and may actually be produced by a symbiont rather than the sponge itself.³

The unique structure and impressive biological activity of ptilocaulin prompted us to undertake a total synthesis. We initially considered a synthetic approach based on Rinehart's biosynthetic proposal (Scheme I). After examination of molecular models, however, we assumed (incorrectly!)

\[
\text{Scheme I}
\]

that a synthesis involving condensation of 6 with guanidine would be unsatisfactory. This analysis revealed that Michael addition should occur preferentially to the more exposed convex face of 6 resulting in the incorrect stereochemistry at C.3a. Thus, a synthesis of 3 from 6 as indicated in Scheme I would require thermodynamically controlled conditions, and we feared that a number of side reactions could interfere.⁹

We sought instead to develop an approach which would fix each of the stereocenters of 3 in a rational manner. Our retrosynthesis thus took the form shown in Scheme II, in which an intramolecular 1,3-dipolar cycloaddition¹⁰ of the nitrone derived from aldehyde 18 constitutes the key
step. Completion of the synthesis from isoxazolidine 19 would involve

Scheme II

\[
\begin{align*}
\text{1} & \Rightarrow \text{18} & \Rightarrow \text{19} \\
& \Rightarrow \text{12} & \Rightarrow \text{8}
\end{align*}
\]

adjustment of oxidation state at C.8a followed by introduction of a guanidine residue. We were confident that the key C.5a stereocenter in 18 could be introduced via conjugate addition of an appropriate propionaldehyde equivalent to enone 12, which in turn would be prepared from the readily available homochiral 3-methylcyclohexanone 8.\textsuperscript{11-13} Since the absolute configuration of ptilocaulin had not been established, this synthesis would resolve this final stereochemical issue.

The synthesis of (-)-7 described herein proceeds in 14 steps (7.4% overall yield) from 8 and establishes the absolute stereochemistry of ptilocaulin to be that shown for 3.\textsuperscript{8}

Synthesis of Isoxazolidine 19

Our immediate target was cyclohexenone 12 (Scheme III) which we hoped to prepare from enone 10. Thus, R-(+)-3-methylcyclohexanone (8)\textsuperscript{14} was treated with LDA in THF at -78°C followed by diphenyldisulfide to give the corresponding \(\alpha\)-ketosulfide, which was oxidized with MCPBA to give a mixture of diastereomeric sulfoxides 9 (65% from 8). Heating a \(\text{CCl}_4\) solution of 9 in the presence of \(\text{CaCO}_3\) then afforded the known cyclohexenone 10 (65%).\textsuperscript{15} All attempts to alkylate the kinetic enolate of 10 with 1-iodobutane, unfortunately, resulted in the formation of mixtures
of unidentified products. It was possible, however, to prepare 12

Scheme III

by alkylation of the dianion. Thus, treatment of 9 with LDA (2.2 equiv of 1M solution in THF, 6 equiv HMPA, -35°C, 3 h) followed by quenching with 1-iodobutane (1.2 equiv, -35°C, 2 h) afforded a mixture of diastereomeric butylated sulfoxides 11. Under these carefully controlled conditions 11 was obtained reproducibly in yields of 75-82% in up to ten gram quantities. Heating a CCl₄ solution of 11 with 0.95 equiv of CaCO₃ afforded the desired cyclohexenone 12a,b in 65% yield. Compound 12a,b was a ca. 6:1 mixture of inseparable diastereomers, with the major isomer (12b) assigned the β-configuration at C.8.19,20

With 12a,b in hand we turned to establishment of the crucial C.5a center. Ample precedent exists for the axial 1,4-addition²¹ of cuprates to cyclohexenone 10 and we felt that 1,4-additions to 12a,b (especially 12b) would proceed in an analogous manner. Although 12a can in principle react via either of two reasonable conformations, axial 1,4-addition to conformation B (leading to the unnatural configuration at C.5a) should be
1,4-addition reaction with chlorodiethyl phosphate afforded 14a, b in only 16% yield. Conjugate addition of 2-(1,3-dioxolan-2-yl)ethyl magnesium bromide\(^{23}\) to 12a, b also proved unsatisfactory.

These disappointing results prompted us to examine the Sakurai reaction\(^{24}\) for synthesis of 13a, b (Scheme IV). We were delighted, therefore, to discover that treatment of 12a, b with TiCl\(_4\) in CH\(_2\)Cl\(_2\) at -78°C followed by allyltrimethylsilane afforded a 6:1 mixture of allylcyclohexanones 13b:13a in >95% yield with complete control of stereochemistry at C.5a.\(^{25,26,27}\) These isomers could be separated
chromatographically, and each has been brought independently through the synthesis to (−)-7. On a routine basis, however, such mixtures were used without separation.

The conversion of 13a,b to isoxazolidine 19a,b is summarized in Scheme IV. Deprotonation of 13a,b with LDA in THF-HMPA followed by

Scheme IV

\[
\begin{align*}
12a,b & \xrightarrow{\text{SiMe}_3, \text{TiCl}_4, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}, >95\%} 13a,b \\
14a,b & \xrightarrow{1) \text{BBN,THF}, 2) \text{H}_2\text{O}_2, \text{NaOH}, 90\%} 16a,b \\
17a,b & \xrightarrow{\text{PCC, NaOAc}, \text{CH}_2\text{Cl}_2, 90\%} 18a,b \\
19a,b & \xrightarrow{\text{Ph}+\text{NHOH}}
\end{align*}
\]

quenching with chlorodiethyl phosphate afforded 14a,b in 77% yield. 28

15a,b

Attempts to reduce 14a,b to diene 15a,b by treatment with Li in EtNH₂ afforded inseparable mixtures of 15a,b and material which had suffered competing reactions of the terminal vinyl group. Alternatively, 14a,b
could be converted to alcohol 16a,b in 90% yield by a hydroboration sequence using 9-BBN, with no interference from the enolphosphate functionality. Reduction of 16a,b with Li\(^{+}\) in EtNH\(_2\) containing \(t\)\(BuOH\) proceeded smoothly to give alcohol 17a,b (99%), which was oxidized to aldehyde 18a,b by treatment with PCC in the presence of NaOAc (90%). Aldehyde 18a,b, without purification, was immediately dissolved in dry benzene (0.05 M solution) and treated with 1.0 equiv of benzylhydroxylamine.\(^{29}\) The mixture was heated to reflux (80°C) for 6 h while allowing the benzene vapors to condense in a column containing 3Å molecular sieves. After removal of solvent and chromatography of the crude product the desired isoxazolidine 19a,b was obtained in 80% yield.\(^{30}\) When pure 18a or 18b (from isomerically pure 13a or 13b, respectively) was used in this reaction a single isomer 19a or 19b was obtained. Isoxazolidines 19a,b were readily separable by column chromatography and separation of the C8-butyl isomers was often postponed until this stage of the synthesis.

The structures assigned to 19a and 19b are fully consistent with the coupling constant data summarized in the adjacent figure.\(^{31}\) It is noteworthy that the cis-\(H\)\(_{8b,5a}\) coupling constants in 19a (9.0 Hz) and 19b (7.9 Hz) are similar in magnitude to the large 10 Hz coupling observed in the natural product. Examination of molecular models of 19a,b reveals that H.8b and H.5a, as in ptilocaulin, possess a dihedral angle close to 0° due to the rigid tricyclic ring system. The stereochemical outcome of this
reaction is consistent with either a (Z)-nitrone (the thermodynamically preferred\textsuperscript{32a,b} and usually invoked\textsuperscript{32c} geometric isomer) undergoing cyclization via exo transition state A or an (E)-nitrone proceeding via endo transition state B. The alternative (Z)-endo (C) and (E)-exo (D) transition states, leading to the unobserved C.3a epimers of 19a,b, suffer serious torsional strain and non-bonded interactions.\textsuperscript{33}

![Images of molecular structures A, B, C, and D]

**Synthesis of (-)-Ptilocaulin**

At this juncture the complete carbon skeleton of the natural product was in place, and we were ready to turn to the seemingly straightforward task of converting 19a,b to ptilocaulin. We began by investigating the
Scheme V

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Reaction Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Hg,THF-H₂O</td>
<td>2-3 days</td>
<td>91%</td>
</tr>
<tr>
<td>Na-Hg,EtOH</td>
<td>very slow</td>
<td>-</td>
</tr>
<tr>
<td>LiAlH₄,THF, Δ</td>
<td>22h</td>
<td>70%</td>
</tr>
<tr>
<td>Zn,10 M AcOH, 55°C</td>
<td>3.5h</td>
<td>95%</td>
</tr>
</tbody>
</table>

cleavage of the isoxazolidine nitrogen-oxygen bond (Scheme V). Treatment of **19a,b** with a large excess of freshly prepared Al-Hg₃⁵,3⁶ in aqueous THF afforded the desired benzylamino alcohol **20a,b** in 91% yield after extended reaction (2-3 days). The use of Na-Hg₃⁶ in EtOH was even slower, affording only a trace of product (as judged by TLC) after two days, while treatment with LiAlH₄ in refluxing THF (22 h) provided **20a,b** in 70% yield. However, heating **19a,b** in 10M aqueous AcOH containing a large excess of Zn₃³⁵ dust cleanly afforded the desired product **20a,b** in 95% yield. We found that the best yields were obtained when the Zn dust was added to a pre-heated solution of **19a,b** in 10M aqueous AcOH; addition of Zn dust at room temperature followed by warming to 55°C gave lower yields of impure product. The reaction was conveniently monitored by TLC and additional Zn was added periodically until the starting material had been consumed. Because of the rapid reaction and reproducible high yields we adopted this procedure for routine preparation of **20a,b**.

We next attempted the oxidation of **20a,b** to ketone **21a,b**. Jones' reagent is generally quite useful for the oxidation of amino alcohols to
amino ketones since the nitrogen atom can be protonated, and thereby protected by performing the oxidation in the presence of dilute aqueous HCl. Thus, 20a,b was dissolved in acetone and treated sequentially with 10% HCl and a large (>100 fold) excess of Jones' reagent. Reaction was very slow, requiring approximately 24 h to go to completion, and was accompanied by production of a substantial amount of 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol). More significantly, aminoketone 21a,b was found to consist of several epimers (typically 15-30% epimerized), the ratio of which varied from reaction to reaction. These results were obtained whether pure 20a, pure 20b or mixtures of 20a,b were used. We recognized that this epimerization had grave consequences for our planned stereoselective synthesis, and briefly investigated the use of other oxidants to effect this conversion. While less epimerization was seen (ca. 10%) using PCC, the yields were lower (50%).

Assuming that the epimerization problem could be resolved in the future, we briefly investigated further functionalization of 21a. Nitroguanyl-1,3-dimethylpyrazole (NGDMP, 22) is a useful reagent for 

\[ \text{NGDMP} \, (22) \]
\[ \text{GDMP} \, (23) \]
guanidination of amines, affording non-polar N-nitro guanidino derivatives. Treatment of partially isomerized 21a with 22 in CHCl₃, however, resulted in complete recovery of starting material. The reagent Si(NCS)₄ is very reactive, resulting in the formation of a thioamide upon reaction with an amine. However, aminoketone 21a gave no identifiable products upon treatment with this reagent in benzene. As an alternative we attempted to introduce the guanidine before oxidation of 20a,b. We hoped that oxidation would be accompanied by immediate cyclization of the guanidine onto the newly formed ketone, thus avoiding epimerization. However, treatment of 20b with NGDMP (22) in methanol or tetrahydrofuran provided only recovered starting material and decomposed reagent.

Reasoning that compounds 20a,b and 21a,b containing secondary amines were too hindered to allow functionalization, we decided to remove the benzyl group from 20a,b. This transformation was most easily accomplished by transfer hydrogenation using 10% formic acid in methanol and freshly prepared Pd-black as catalyst (3 h, 23°C), giving 24a,b in 96% yield after
workup. However, this material also proved resistant to further functionalization with either NGDMP (22) or 1-guanyl-3,5-dimethylpyrazole nitrate (GDMP, 23).\(^\text{42}\) The latter reagent has been reported to react with primary and secondary amines, typically by melting the reagent with the amine in the absence of solvent. When amino alcohol \(24b\) was melted with 1 equiv of GDMP no reaction was observed. Interestingly, when the melt procedure was applied to NGDMP (22) and \(24b\) a new product (not \(25b\), \(X=N-\text{NO}_2\) or \(\text{NH}_2\text{NO}_3\)) was obtained. The structure of this material, however, was not determined.

Since amino alcohol \(24a,b\) was easily obtained in pure form as a single isomer we investigated methods for its oxidation to ketone \(26a,b\). Treatment of an acetone solution of \(24a,b\) containing aqueous HCl with a
large excess of Jones' reagent afforded 26a,b which was again substantially epimerized (30%) and contaminated with diacetone alcohol. Attempts to oxidize 24b by use of Swern's oxalyl chloride-DMSO procedure led to no reaction. When 24b was treated with 1.5 equiv of this reagent in refluxing CHCl₃ for 24 h, oxidation products were still not observed. Under these more vigorous conditions, however, a less polar material was produced which appeared to be the product of phenyl transfer from Ph₃BiCO₃ to the amino functionality of 24b. Although the identity of this compound was not rigorously determined, such transfers have been previously observed with triphenylbismuth diacetate and triphenylbismuth carbonate.

Plagued by the inability to cleanly oxidize either 20a,b or 24a,b and the failure to introduce a guanidine moiety to any of these intermediates, we attempted yet another approach. The essence of this strategy is shown in Scheme VI.

Scheme VI

27a,b

in Scheme VI. We reasoned that if the guanidino group could be introduced at the stage of 27a,b, subsequent reductive cleavage of the nitrogen-oxygen bond followed by oxidation should be accompanied by cyclization to give ptilocaulin (7).

We found that the benzyl group in 19b could be cleanly removed by
applying the same transfer hydrogenation procedure described earlier

(95% yield). Functionalization of 27b either by treatment with benzylisocyanate, GDMP (melt) or NGDMP (melt) smoothly afforded 28b, 29b and 30b, respectively (72-95% yields). These encouraging results were soon tempered by the reluctance of 28b and 29b to undergo nitrogen-oxygen bond cleavage under conditions used successfully in the conversion of 19a,b to 20a,b (Zn/HOAc, Δ; Al-Hg; Na-Hg; starting material was recovered in each case). More vigorous conditions such as Zn dust in refluxing aqueous HCl caused extensive decomposition of 29b.

At this stage it appeared that the conversion of 19a,b to ptilocaulin would be considerably more challenging than originally anticipated. In a reanalysis of our strategy we decided to modify the route so that C-8a would be maintained in the correct oxidation state throughout the synthesis, thus eliminating the need to oxidize amino alcohol intermediates. The key step of this new approach would be an intramolecular 1,3-dipolar cyclization of the nitrone derived from aldehyde
Scheme VII

31 (Scheme VII). In such an approach the need for reductive removal of the C.8a oxygen atom (cf. 16 → 17) would be eliminated, as would subsequent reoxidation of this position. Since we had already determined that the guanidino group could be cleanly introduced at the stage of isoxazolidine 27b (cf. 27b → 29b) we felt that this approach merited investigation.

Toward this end, enolphosphate 16a, b was cleanly oxidized with PCC to give aldehyde 34a, b in 82% yield. However, several attempts to effect an intramolecular cycloaddition by treatment of 34a, b with benzylhydroxylamine in benzene met with failure. Only very complex mixtures of products resulted, from which no desired cycloadduct was isolated.

Studies involving enol carbonate 36b were only slightly more successful (Scheme VIII). When 36b was treated with benzylhydroxylamine a
complex mixture of products was again obtained, from which only trace amounts (<10%) of cycloadduct 37b were isolated. This material was identified by comparison of its $^1$H-NMR spectrum with that of isoxazolidine 19b.

Literature precedent suggested that intramolecular nitrene cycloadditions with enol ether derivatives should be a feasible process. We speculated that intermediates 34a,b and 36b might undergo competitive nucleophilic attack by benzylhydroxylamine at the labile enolphosphate or carbonate centers. In an effort to ameliorate this problem enol pivaloate 38b was investigated. This intermediate was efficiently prepared in 80% overall yield from 13b by simple modification of the chemistry outlined in Schemes IV and VIII. When 38b was treated with benzylhydroxylamine in
refluxing benzene a clean reaction ensued, generating nitrone 39b (structure assigned by $^1$H NMR analysis). Unfortunately, heating 39b in benzene at 80°C (6 h) left this material unchanged, while heating at 110°C in toluene (6.5–17 h) caused extensive decomposition, leading to a mixture of unidentified products. This approach was therefore regrettably discontinued and we returned to the sequences discussed previously.47

Hoping that ptilocaulain could be obtained from a pure sample of amino ketone 26a,b (c.f. Scheme II) we sought a method for avoiding the epimerization problems associated with the oxidation of 20a,b and 24a,b. A key advancement was made when we observed that oxidation of 20a,b with CrO$_3$-$\text{H}_2\text{SO}_4$ proceeded much more rapidly in glacial acetic acid than in aqueous acetone.48 Indeed, by conducting this oxidation in glacial acetic acid containing 2M aqueous HCl, complete conversion of 20a,b to 21a,b was achieved (95% yield) after only 2.5 h at 0°C (Scheme IX). Under these conditions the epimerization problem was largely avoided, although in some runs as much as 5–10% of epimers were detected. Significantly, the formation of acetone derived by-products was now eliminated, thereby
simplifying the isolation of 21a,b. Although this intermediate could be purified by careful chromatography, we routinely used crude 21a,b immediately in the next step. In initial experiments, however, 21a,b was chromatographed and epimers 40a (from experiments with 20a) and 40b (from pure 20b) were separated. The spectroscopic data for these compounds were consistent with the trans-fused structures indicated in the accompanying diagram.

\[
\begin{align*}
\text{RNH} & \quad \text{O} \\
\text{40a, R=Br} & \quad \text{44a, R=H}
\end{align*}
\]

\[
\begin{align*}
\text{RNH} & \quad \text{O} \\
\text{40b, R=Br} & \quad \text{44b, R=H}
\end{align*}
\]

Benzylamino ketones 21a,b were smoothly deprotected by transfer hydrogenation (Scheme IX), affording amino ketone 26a,b in 95% yield. Unfortunately, additional epimerization (15-30%) occurred even under these relatively mild reaction conditions. A clue to the source of this problem was found when we determined that the formate salt of 26b, obtained by simple filtration of the hydrogenation mixture to remove the catalyst and concentration in vacuo, consisted primarily of a single epimer. After neutralization (by washing a CHCl₃ solution of 26b with saturated aqueous NaHCO₃), however, $^1$H NMR analysis revealed the presence of epimeric material (30%). Thus, epimerization apparently occurs spontaneously at the stage of 26a,b after reaction workup. Although epimerization of 26a,b was apparently unavoidable, isolation of the formate salt of 26a,b and subsequent neutralization immediately before use in the final step of the synthesis was adopted as standard procedure.

Amino ketone 26a,b could also be prepared by Jones' oxidation of 24a,b
in glacial acetic acid (94% yield). While the reaction proceeded more rapidly than in aqueous acetone, substantial epimerization was again observed (30%). Because isolation of 26a,b from the transfer hydrogenation deprotection of 21a,b was much more convenient than from the Jones' oxidation of 24a,b, the former procedure was the preferred method for preparation of this intermediate (see Scheme IX).

With amino ketone 26a,b in hand (albeit epimeric!) we were optimistic about obtaining at least some ptilocaulin (7) from the reaction of 26a,b with GDMP (23). When 26b was subjected to the melt conditions used previously (1 equiv 23, 120°C, 15 min), a mixture of three guanidine containing compounds was obtained in an approximate 2:1:1 ratio (48-51% yield). The major product possessed 1H-NMR characteristics consistent with ptilocaulin (7), while the other two compounds were tentatively assigned structures 41 and 42. Compound 41 is derived presumably from trans-fused 44b while 42 represents an olefinic regioisomer of the natural product. Unfortunately, these compounds were inseparable by chromatography. When the same guanidination procedure was applied to 26a we were dismayed to find that virtually no ptilocaulin was obtained. Instead, two major guanidine containing compounds were produced (ca. 1:1), one of which corresponded to 41 and the other which was assigned structure 43. Interestingly, 26a underwent guanidination with GDMP (23) in benzene (80°C, 18 h, ca. 40% yield) to give a mixture of 43 and 41 in a ca.
3:1 ratio. Again, only a trace of 7 was detected.

These results can be rationalized by inspection of the presumed intermediates 45-48 (Scheme X) in the guanidination reaction. Thus, in 46 (from 26b) the axial C.8 hydrogen is perpendicular to the adjacent C=Nm-system and therefore is suitably oriented for tautomerization to ptilocaulin 7. In 45 (from 26a), however, the C.8 hydrogen is equatorial and thus not favorably oriented for isomerization to 7. In both 45 and 46 the axial C.8b hydrogen possesses favorable geometry for isomerization, to 43 and 42, respectively. Presumably, the trans-fused intermediates derived from
Scheme X

44a and 44b would exist in the conformations shown for 47 and 48. In both cases the C.8 hydrogen is axial, thereby allowing the formation of 41 from both intermediates. In addition, elimination of H.8b can occur in either intermediate leading to 43 and 42, respectively.

While these studies were in progress, Snider reported that the reaction of enone 6 and guanidine afforded ptilocaulin as the sole product (35% yield)\textsuperscript{13a}. This strongly implied that ptilocaulin should be the most
stable isomer, and we were immediately able to test this hypothesis. Indeed, the mixture of 7, 41, and 42 obtained from 26b was dissolved in benzene and treated with a catalytic amount of guanidine. After 24 h at reflux the reaction was neutralized with 1% HNO₃ and worked up by extraction with CHCl₃ and saturated aqueous NaNO₃. Examination of the ¹H-NMR spectrum of the material so obtained revealed that it consisted of virtually homogeneous ptilocaulin. The recovery of 7 after chromatography was 89%, indicating that equilibration and not selective destruction of the minor isomers had occurred. In a similar manner, the mixture of 41 and 43 (with trace 7) from 26a also yielded only 7 after guanidine equilibration. It was now obvious that the epimerization(s) encountered in the preceding steps were no longer a concern. Moreover, we also quickly discovered that 7 could be obtained directly from 26a,b in 58-65% yield by simply conducting the melt reaction with 1.1 equiv of 23 at higher temperatures (145-155°C) for 5-6 h (equilibrating conditions).

1) GMDF (23), 110-120°C
15-45 min

2) guanidine, C₆H₆, 80°, 12-24h
43% overall

-or-

The synthetic ptilocaulin so obtained (m.p. 183-184°C; lit.³ 183-185°C) possessed an optical rotation of ([α]D³₂ 73.9° (c=0.31, 99.9% CH₃OH)) equal, but opposite in sign, to that of the natural material⁵₀.
Natural (+)-ptilocaulin thus possesses the absolute stereochemistry depicted in 3.

In final analysis it is evident that ptilocaulin is the thermodynamically most stable of the possible double bond and ring fusion isomers. Moreover, it is somewhat ironic (and disappointing) that the element of thermodynamic control which we rejected in initial synthetic planning (Scheme I) proved to be the saviour of this synthesis. Nonetheless, the strategy to control the stereochemistry of C(3a) in the intramolecular nitrone cycloaddition did pay positive dividends, since the efficiency of the final step of this synthesis (26 $\rightarrow$ 7, 58-65%) is substantially better than in approaches defined by 6 $\rightarrow$ 7 (35-40%).
EXPERIMENTAL SECTION
$^1$H NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270 instruments. Chemical shifts are reported in $\delta$ units relative to internal CHCl$_3$ ($\delta$ 7.24). $^{13}$C NMR spectra were measured at 68 MHz on the Bruker 270, or at 22.5 MHz on a Jeol FX90Q instrument; carbon resonances are reported in $\delta_c$ units calibrated against the 77.0 ppm line of CDCl$_3$. Infrared spectra were measured on a Perkin-Elmer Model 283B Infrared Spectrophotometer and were calibrated with the 1601 cm$^{-1}$ absorption of polystyrene. Mass spectra were measured at 70 ev on a Varian MAT 44 instrument. Melting points were recorded on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 cm$^3$ capacity quartz cell (10 cm path length). Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ.

The standard ptilocaulin numbering system is used for all proton assignments. All intermediates in the "a" series possess $\alpha$-butyl groups, whereas in the "b" series the butyl group is on the $\beta$-face of the intermediates as drawn in text. All compounds containing the guanidine group were isolated and characterized as nitrate salts.

All reactions were conducted in oven (170°C) and/or flame dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from calcium hydride and tert-butanol was distilled from sodium metal. Diisopropylamine was distilled from KOH and stored over activated 4Å molecular sieves. Hexamethyolphosphoric triamide was dried by storage over activated 4Å molecular
sieves. Formic acid and acetic acid were distilled before use. All other reagents were used as obtained.

Analytical thin layer chromatography (TLC) was performed by using 2.5 cm x 10 cm plates coated with 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- and 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with either ethyl acetate or ether. Flash chromatography was performed as described by Still,\textsuperscript{52} using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh). Compounds were visualized with short-wave UV light, or by staining with either iodine vapor or charring with ethanolic H\textsubscript{2}SO\textsubscript{4}. All chromatography solvents were distilled prior to use.
Butylated sulfoxides 11. A solution of LDA was prepared by addition of 39.8 mL of n-butyllithium (2.54 M in hexane, 101 mmol, 2.2 equiv) to a solution of dry diisopropylamine (10.7 g, 106 mmol, 2.3 equiv.) in 100 mL of THF at -78°C. This solution was stirred for 1.5 h and then added dropwise via cannula over 1 h to a solution of carefully dried sulfoxide 10 (10.9 g, 46.2 mmol, 1.0 equiv) in THF (75 mL) containing 52 g (290 mmol, 6.4 equiv) of dry HMPA at -40°C. After ca. 1.0 equiv of LDA had been added the sulfoxide solution changed from yellow to orange and finally dark red after the addition was complete. This red solution was stirred at -35 - -40°C for 2 h and treated with freshly distilled i-iodobutane (10.1 g, 55.0 mmol, 1.2 equiv; distilled from MgSO₄) in one portion. The red color was almost immediately dispersed, resulting in a pale yellow solution. After being stirred for an additional 2 h at -35 - -40°C the mixture was treated with 150 mL of 10% aqueous HCl and allowed to warm to room temperature. Workup consisted of transferring the solution to a separatory funnel containing Et₂O and 10% HCl (400 mL each), washing with additional portions of 10% HCl (2x400 mL), extraction of the combined aqueous layers with Et₂O (5x350 mL), washing the combined organic extracts with saturated aqueous NaHCO₃ (800 mL) and saturated aqueous NaCl (800 mL). After drying over MgSO₄, filtration and removal of the solvent in vacuo the oily residue was purified by flash chromatography (silica gel, 95 mm column, 1:1
EtOAc-hexane) to afford 10.2 g (76%) of 11 as a mixture of diastereomers.
(TLC: series of partially resolved spots, R_f 0.28-0.64, 1:1 EtOAc-hexane).

^1_H NMR (CDCl_3, 270 MHz) δ 7.8-7.3 (m, 5 H), 3.8-3.3 (3 m's, 1 H), 2.7-1.2 (series of m, 12 H), 1.2-0.75 (series of d's and t's, 6 H); ^13_C NMR (CDCl_3, 22.5 MHz) δ 206.8, 186.9, 177.5, 142.1, 131.3, 129, 125.9, 124.5, 74.3, 73.8, 60.1, 58, 39, 37.2, 33.3, 29, 28.2, 27.5, 25.2, 23.1, 22.8, 22.5, 20.8, 19.9, 14, 13.7; IR (neat) 3050, 2945, 2920, 2860, 1705, 1580, 1460, 1445, 1378, 1084, 1042, 995, 915, 745, 730, 684, 640 cm^{-1}; mass spectrum, m/e 292 (parent ion).
Butylcyclohexenone 12a,b. A solution of 11 (3.62 g, 12.4 mmol) in CCl₄ (100 mL) was treated with CaCO₃ (1.19 g, 11.9 mmol, 0.96 equiv) under N₂. The mixture was warmed to 65°C while being stirred rapidly and maintained at this temperature for 24 h. After being cooled to room temperature the mixture was filtered through a pad of Celite and the solvent was removed in vacuo. Chromatography of the residue (silica gel, 60 mm column, 4:1 hexane-ether) afforded 1.37 g (66%) of 12 as a ca. 6:1 mixture of β- and α-C₈ isomers: TLC, Rf 0.41 (4:1 hexane-ether); [α]²²D - 69.8° (c=0.92, CHCl₃); ¹H NMR data for 12a (CDCl₃, 270 MHz) δ 6.81 (m, 1 H, H.8), 5.95 (m, 1 H, H.8b), 2.6-2.3 (m, 2 H), 2.25-2.0 (m, 2 H), 1.8-1.5 (m, 2 H), 1.4-1.15 (m, 4 H), 0.95 (d, J=6.7 Hz, 3 H, -CH₃), 0.89 (t, J=7.1 Hz, 3 H, -CH₃); ¹H NMR data for 12b (CDCl₃, 270 MHz) δ 6.81 (m, 1 H, H.8), 5.95 (m, 1 H, H.8b), 2.6-2.3 (m, 2 H), 2.25-2.0 (m, 2 H), 1.8-1.5 (m, 2 H), 1.4-1.15 (m, 4 H), 1.06 (d, J=6.5 Hz, 3 H, -CH₃), 0.89 (t, J=7.1 Hz, 3 H, -CH₃); ¹³C NMR data for 12b (CDCl₃, 22.5 MHz) δ 201.8, 147.4, 128.9, 53.5, 32.5, 32.3, 28.5, 27.4, 22.9, 19.6, 13.9. IR (neat) 3032, 2955, 2930, 2870, 2830, 1673, 1460, 1425, 1390, 1246, 1203, 1103, 915, 893, 835, 805, 775, 731, 700 cm⁻¹; mass spectrum m/e 166 (parent ion). (Found: C, 79.40; H, 10.94. Calc. for C₁₁H₁₈O: C, 79.46; H, 10.91%).
Allylcyclohexenone 13a,b. A solution of cyclohexenone 12a,b (1.96 g, 11.8 mmol) in CH₂Cl₂ (43 mL) was cooled to -78°C. TiCl₄ (2.69 g, 14.2 mmol, 1.2 equiv) was added dropwise during 5 min under a stream of Ar, resulting in the formation of an orange-red solution containing a small amount of orange precipitate. This mixture was stirred for 5 min at -78°C and then allyltrimethylsilane (2.02 g, 17.7 mmol, 1.5 equiv) in CH₂Cl₂ (33 mL) was added dropwise over a 2 h period. The resultant deep red solution was stirred for 1.5 h at -78°C and then treated with H₂O (20 mL), added dropwise. The mixture was stirred at -78°C until the red color had faded to give a colorless solution. After being warmed to room temperature the reaction mixture was partitioned between Et₂O and saturated aqueous NaCl (125 mL each). The aqueous layer was further extracted with ether (5x75 mL) and the combined organic extracts were washed with saturated aqueous NaCl (300 mL). The extracts were dried (MgSO₄), filtered and concentrated in vacuo to give 2.51 g of crude 13a,b. ¹H NMR analysis of this material revealed that it was an approximate 5:1 mixture of 13b:13a of >95% purity. Flash chromatography of a 1.00 g portion of this material (silica gel, 60 mm column, 10:1 hexane-ether) afforded 13b (0.751g, 15:1 mixture of 13b:13a), 13a (0.152 g, ~8:1 13a:13b) and a single mixed fraction containing 13a,b (0.099 g, ~4:1 13b:13a). The total recovery was thus 1.00 g (100%). Chromatography of the remaining material (and the mixed fraction) afforded a total of 2.35 g (96%) of 13a,b.
Data for 13a: TLC, Rf 0.63 (4:1 hexane-ether); $[\alpha]_D^{22} = -24.9^\circ$ (c=2.08, CHCl₃); $^1$H NMR (CDCl₃, 270 MHz) $\delta$ 5.77 (m, 1 H, H.4), 5.03 (d, J=12.3 Hz, 1 H, Z-H.3a), 5.03 (d, J=15 Hz, 1 H, E-H.3a), 2.46-2.36 (m, 3 H), 2.14-1.93 (m, 4 H), 1.80-1.59 (m, 3 H), 1.38-1.15 (m, 5 H), 0.89 (t, J=6.8 Hz, 3 H, -CH₃), 0.77 (d, J=7.0 Hz, 3 H, -CH₃); $^{13}$C NMR (CDCl₃, 68 MHz) $\delta$ 212.5, 135.7, 116.5, 57.1, 54.0, 48.1, 41.1, 38.9, 34.7, 34.2, 29.5, 25.9, 22.8, 14.0; IR (neat) 3070, 2950, 2920, 2865, 2858, 1708, 1640, 1450, 1380, 1230, 1224, 1202, 1158, 1092, 990, 910 cm⁻¹; mass spectrum, m/e 208 (parent ion). (Found: C, 80.84; H, 11.37. Calc. for C₁₄H₂₄O: C, 80.71; H, 11.61%)

Data for 13b: TLC, Rf 0.58 (4:1 hexane-ether); $[\alpha]_D^{22} = +41.8^\circ$ (c=1.43, CHCl₃); $^1$H NMR (CDCl₃, 270 MHz) $\delta$ 5.72 (m, 1 H, H.4), 5.03 (d, J=11.7 Hz, 1 H, Z-H.3a), 5.02 (d, J=15.6 Hz, 1 H, E-H.3a), 2.33-2.04 (m, 7 H), 1.77-1.45 (m, 4 H), 1.35-1.18 (m, 4 H), 0.99 (d, J=6.7 Hz, 3 H, -CH₃), 0.88 (t, J=6.7 Hz, 3 H, -CH₃); $^{13}$C NMR (CDCl₃, 68 MHz) $\delta$ 213.7, 135.7, 116.4, 56.9, 44.7, 39.8, 34.4, 34.1, 29.5, 22.5, 20.1, 13.7; IR (neat) 3078, 2948, 2923, 2861, 1705, 1640, 1458, 1443, 1423, 1380, 1346, 1234, 990, 910 cm⁻¹; mass spectrum, m/e 208 (parent ion). (Found: C, 80.55; H, 11.70. Calc. for C₁₄H₂₄O: C, 80.71; H, 11.61%).
Equilibration of 13a and 13b. Isomerically pure cyclohexanone 13a (23 mg, 0.11 mmol) was dissolved in CH$_3$OH (2.0 mL) and treated with 76 mg (0.55 mmol, 5 equiv) of powdered anhydrous K$_2$CO$_3$. After being stirred for 2h the CH$_3$OH was removed in vacuo. The residue was dissolved in Et$_2$O (30 mL) and washed with H$_2$O (3x30 mL). The extracts were dried (MgSO$_4$), filtered and concentrated in vacuo to afford 21 mg of a 1.9:1 mixture of 13a:13b ($^1$H NMR analysis). An identical 1.9:1 mixture of 13a:13b was obtained when pure 13b was subjected to these conditions.
Enolphosphate 14a,b. A solution of LDA was prepared by the addition of 1.19 mL of 2.61 M n-butyllithium in hexane (3.11 mmol, 1.6 equiv) to diisopropylamine (418 mg, 4.14 mmol, 2.1 equiv) in THF (6.2 mL) at -78°C. To this solution at -78°C was added carefully dried ketone 13b (404 mg, 1.94 mmol) in 3.1 mL of cold (-78°C) THF. After being stirred for 1.5 h the solution was warmed to 0°C, treated with HMPA (696 mg, 3.88 mmol, 2.0 equiv) and stirred for an additional 30 min. Freshly distilled chlorodiethylphosphate (938 mg, 5.44 mmol, 2.8 equiv; distilled from K₂CO₃) was then added dropwise, and the resulting mixture was warmed to room temperature and stirred for 3 h. Workup involved addition of saturated aqueous NaHCO₃ (50 mL) and repeated extraction with Et₂O (5x50 mL). The combined extracts were washed successively with H₂O (50 mL), saturated aqueous NaCl (50 mL) and dried over MgSO₄. After filtration and removal of the solvent in vacuo, chromatography of the residue (silica gel, 40 mm column, 2:1 hexane-EtOAc) afforded 506 mg (77%) of 14b.

Data for 14a: R₉ 0.36 (2:1 hexane-EtOAc); [α]D²⁰ + 41.7° (c=0.96, CHCl₃; sample contained ca. 10% 14b); ¹H NMR (CDCl₃, 250 MHz) δ 5.78 (m, 1 H, H.4), 5.40 (br s, 1 H, H.8b), 5.02 (br d, J=15.6 Hz, 1 H, E-H.3a), 5.01 (br d, J=10.4 Hz, 1 H, Z-H.3a), 4.15 (quint, J=6.9 Hz, 4 H), 2.29 (br s, 2 H), 2.07 (m, 3 H), 1.7–1.5 (m, 2 H), 1.4–1.2 (m, 6 H), 1.34 (two overlapping t, J=7.2 Hz, 6 H), 0.90–0.88 (overlapping d and t, 6 H, two -CH₃'s); ¹³C NMR (CDCl₃, 68 MHz) δ 150.3, 136.8, 116.1, 113.3 (d), 64.0 (d), 41.4, 40.4,
33.6, 31.8, 29.9, 28.8, 27.2, 23.0, 16.1 (d), 15.1, 14.0; IR (neat) 3065, 2950, 2922, 2865, 1665, 1638, 1452, 1442, 1378, 1272, 1040, 1030, 980, 910, 810 cm$^{-1}$; mass spectrum, m/e 344 (parent ion). (Found: C, 62.26; H, 9.71.
Calc. for C$_{18}$H$_{33}$P$_{4}$O$_{4}$: C, 62.77; H, 9.66%).

Data for 14b: $[\alpha]_{D}^{20}$ = 18.0° (c=1.01, CHCl$_{3}$); $^1$H NMR (CDCl$_{3}$, 270 MHz) $\delta$
5.83-5.70 (m, 1 H, H.4), 5.43 (br s, 1 H, H.8b), 5.03 (br d, J=16.1 Hz, 1 H, E-H.3a), 5.02 (br d, J=11.2 Hz, 1 H, Z-H.3a), 4.15 (quint, J=7.1 Hz, 4 H), 2.30 (br s, 1 H), 2.08 (br t, J=6.9 Hz, 2 H), 2.0-1.8 (m, 2 H),
1.75-1.55 (m, 1 H), 1.5-1.2 (m, 7 H), 1.35 (two overlapping t, J=7.0 Hz, 6 H), 0.98 (d, J=6.9 Hz, 3 H, -CH$_{3}$), 0.90 (t, J=6.3 Hz, 3 H, -CH$_{3}$); $^{13}$C NMR (CDCl$_{3}$, 68 MHz) $\delta$
150.2, 136.6, 116.2, 113.2 (d), 64.0 (d), 44.2, 40.2; 31.6, 31.0, 29.5, 29.4, 22.8, 19.3, 16.0, 14.0; IR (neat) 3075, 2955, 2930, 2870, 1672, 1642, 1458, 1445, 1378, 1275, 1132, 1094, 1040, 970, 910, 870, 815, 750 cm$^{-1}$; mass spectrum, m/e 344 (parent ion). (Found: C, 62.84; H, 9.57.
Calc. for C$_{18}$H$_{33}$P$_{4}$O$_{4}$: C, 62.77; H, 9.66%).
Hydroxyenolphosphate 16a,b. Enolphosphate 14b (506 mg, 1.47 mmol) was dissolved in 4 mL of THF under Ar. This solution was cooled to 0°C, treated with 5.20 mL of a freshly prepared solution of 9-BBN (0.5 M in THF, 3.02 mmol, 2.05 equiv) and stirred for 3 h. The mixture was allowed to warm to room temperature (0.5 h) and then was recooled to 0°C and treated with CH₃OH (2 mL). When gas evolution had subsided 1.0 mL each of 3 M aqueous NaOH and 30% aqueous H₂O₂ were simultaneously added dropwise. The solution (which contained a white precipitate) was warmed to room temperature and stirred for 2 h. Workup consisted of dilution with ether (50 mL) and extraction with saturated aqueous NaCl (50 mL). The aqueous layer was further extracted with ether (4x50 mL) and the combined organic extracts were washed with saturated aqueous Na₂S₂O₃, saturated acqueous NaHCO₃, saturated aqueous NaCl and dried over MgSO₄. After filtration and removal of the solvent in vacuo the residue was purified by flash chromatography (silica gel, 40 mm column, 20:1 CH₂Cl₂-CH₃OH) to give 480 mg of 16b (90%). The yield of 16a from 14a using this procedure was 94%.

Data for 16a: TLC, Rf 0.46 (20:1 CHCl₃-CH₃OH); [α]D¹⁹ + 20.8° (c=1.00, CHCl₃; sample contained ca. 10% 16b): ¹H NMR (CDCl₃, 250 MHz) δ 5.42 (br s, 1 H, H.8b), 4.14 (quint, J=7.3 Hz, 4 H), 3.62 (t, J=6.5 Hz, 2 H, -CH₂-OH), 2.26 (br s, 2 H), 2.2-2.0 (m, 1 H), 1.82 (br s, 3 H), 1.7-1.5 (m, 4 H), 1.5-1.2 (m, 9 H), 1.35 (two overlapping t, J=7.1 Hz, 6 H), 0.90-0.88 (overlapping d and t, 6 H, two -CH₃'s); IR (neat) 3440, 2925, 2860, 1668,
1445, 1378, 1263, 1148, 1035, 975, 815, 728 cm\(^{-1}\); mass spectrum m/e 362 (parent ion). (Found: C, 59.47; H, 9.89. Calc. for C\(_{18}H_{35}PO_5\): C, 59.65; H, 9.73%).

Data for 16b: \([\alpha]_D^{19} = 16.7^\circ\) (c=0.46, CHCl\(_3\)); \(^1H\) NMR (CDCl\(_3\), 250 MHz) \(\delta\) 5.43 (br s, 1 H, H.8b), 4.14 (quint, J=7.2 Hz, 4 H), 3.64 (t, J=6.4 Hz, 2 H, -CH\(_2\)OH), 2.24 (br s, 1 H), 2.0-1.5 (m, 9 H), 1.5-1.2 (m, 12 H), 1.36 (two overlapping t, J=7.1 Hz, 6 H), 0.97 (d, J=6.9 Hz, 3 H, -CH\(_3\)), 0.89 (t, J=6.2 Hz, 3 H, -CH\(_3\)); \(^13C\) NMR (CDCl\(_3\), 68 MHz) \(\delta\) 150.1, 113.8 (d), 63.9 (d), 62.9, 44.4 (d), 32.1, 31.7, 31.4, 31.1, 30.1, 29.8, 29.4, 22.8, 19.4, 16.0 (d), 13.9; IR (neat) 3430, 2950, 2930, 2865, 1675, 1455, 1380, 1268, 1130, 1040, 970, 815 cm\(^{-1}\); mass spectrum, m/e 362 (parent ion). (Found: C, 59.75; H, 9.62. Calc. for C\(_{18}H_{35}PO_5\): C, 59.65; H, 9.73%).
Alcohol 17a,b. A solution of Li° in ethylamine was prepared by adding lithium wire (85 mg, 12.3 mmol, 10 equiv) to anhydrous ethylamine (25 mL) at 0°C. When the lithium wire had been consumed, the resulting deep blue solution was treated with 0.23 mL of dry t-butylalcohol (182 mg, 2.46 mmol, 2.0 equiv). To this stirred solution was rapidly added enolphosphate 16a,b (446 mg, 1.23 mmol) as a solution in 4 ml of THF containing 0.43 ml of t-butylalcohol (342 mg, 4.61 mmol, 3.75 equiv). After being stirred for 1.5 h at 0°C the solution was treated with excess solid ammonium chloride (ca. 5 g, in several portions). The ethylamine was evaporated by gentle warming and the residue was treated with H_2O (25 mL). The aqueous layer was extracted with ether (4x50 mL) and the combined organic extracts were washed with saturated aqueous Na_2S_2O_3, saturated aqueous NaCl and dried over MgSO_4. After filtration and removal of the solvent in vacuo the residue was purified by column chromatography (silica gel, 40 mm, 1:1 EtOAc-hexane) affording 256 mg of 17a,b (99%).

Data for 17a: (data obtained on mixture containing ~15% of 17b): TLC, R_f 0.58 (1:1 EtOAc-hexane); ¹H NMR (CDCl_3, 270 MHz) δ 5.48 (A of AB, J_AB = 10.2 Hz, 1 H), 5.41 (B of AB, J_AB = 10.2 Hz, 1 H), 3.61 (t, J=6.5 Hz, 2 H, -CH_2OH), 2.15-1.8 (m, 3 H), 1.7-1.5 (m, 4 H), 1.45-1.1 (m, 9 H), 0.87 (br t, 3 H), 0.78 (d, J=6.9 Hz, 3 H, -CH_3); ¹³C NMR (CDCl_3, 68 MHz) δ 130.5, 130.2, 63.2, 39.0, 36.1, 32.3, 31.9, 30.1, 29.5, 29.2, 22.9, 14.1, 13.5; IR (neat) 3330, 3010, 2960, 2920, 2850, 1450, 1375, 1050 cm⁻¹; mass spectrum,
m/e 210 (parent ion).

Data for 17b: $[^{19}\alpha]_D$ - 11.0° (c=0.2, CHCl$_3$); $^1$H NMR (CDCl$_3$, 250 MHz) δ 5.63 (br s, 2 H, H.8b and H.8a), 3.64 (t, J=6.6 Hz, 2 H, -CH$_2$OH), 2.05 (m, 1 H), 1.7-1.1 (m, 15 H), 0.94 (d, J=6.4 Hz, 3 H, -CH$_3$), 0.89 (br t, 3 H, -CH$_3$); $^{13}$C NMR (CDCl$_3$, 68 MHz) δ 130.7, 130.3, 63.2, 42.3, 34.3, 34.0, 32.7, 32.1, 30.6, 29.5, 29.1, 23.0, 20.1, 14.0; IR (neat) 3340, 3010, 2920, 2860, 1648, 1455, 1375, 1052, 720 cm$^{-1}$; mass spectrum, m/e 210 (parent ion). (Found: 79.69; H, 12.47. Calc. for C$_{14}$H$_{26}$O: C, 79.93; H, 12.46%).
Aldehyde 18a,b. To 5 mL of dry CH₂Cl₂ containing ca. 30 mg of NaOAc was added 395 mg of pyridinium chlorochromate (1.83 mmol, 1.5 equiv). This suspension was treated with a solution of alcohol 17a,b (17b:17a = ~1.5:1) in 2 mL of CH₂Cl₂ and vigorously stirred. TLC analysis after 1.5 h revealed the complete consumption of starting material. Addition of ether (40 mL) to the rapidly stirred reaction mixture resulted in the formation of a black granular precipitate. This solution was filtered through Florisil and the precipitate was thoroughly washed with ether (ca. 150 mL total). After removal of the solvent in vacuo 229 mg (90%) of crude 18a,b (95% pure by ¹H NMR analysis) was obtained. A portion of 18b (from an oxidation of isomerically pure 17b) was purified by preparative thin layer chromatography (silica gel, 2:1 hexane-EtOAc) for characterization. In preparative runs, however, crude 18a,b was used immediately in the subsequent step.

Data for 18b: TLC, Rf 0.71 (1:1 EtOAc-hexane); [α]_D^29 - 11.5° (c=0.34, CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 9.79 (t, J=1.8 Hz, 1 H, H.3a), 5.7-5.5 (m, 2 H), 2.48 (d of t, J₃a,₄ = 1.8 Hz, δ₄,₅ = 7.7 Hz, 2 H, H.4), 2.07 (m, 1 H), 1.8-1.5 (m, 4 H), 1.5-1.2 (m, 8 H), 0.96-0.80 (overlapping d and t, two CH₃'s, 6 H); IR (neat) 3010, 2950, 2920, 2860, 2720, 1727, 1650, 1458, 1410, 1375, 1200, 742, 730 cm⁻¹; mass spectrum, m/e 208 (parent ion).
Benzylisoxazolidine 19a,b. Freshly prepared aldehyde 18a,b (18b:18a = ~1.9:1) (229 mg, 1.10 mmol) was dissolved in dry benzene (20 mL) and the solution was degassed by flushing with Ar. The solution was treated with benzylhydroxylamine 29,30 (137 mg, 1.11 mmol, 1.01 equiv) and gently heated to reflux. Removal of water was accomplished by allowing the benzene to condense in a column containing 3Å molecular sieves. After 8 h TLC analysis revealed that reaction was complete, so the solvent was removed in vacuo. Purification of the residue by flash chromatography (silica gel, 40 mm column, 9:1 hexane-ether) afforded isomerically pure 19b (185 mg), and 105 mg of a 7:1 mixture of 19a:19b). The combined yield of 19a,b was thus 290 mg (84%).

Data for 19a: TLC, Rf 0.50 (4:1 hexane-ether); [α]D19 + 5.2° (c=0.81, CHCl₃; sample contained ca. 10% of 19b); ¹H NMR (CDCl₃, 250 MHz) δ 7.45-7.2 (m, 5 H, aromatic), 4.35 (d of d, J₈₈=1.9 Hz, J₈₈=5.5 Hz, 1 H, H.8a), 4.19 (A of AB, Jₐb=12.6 Hz, 1 H, benzylic H), 3.90 (B of AB, Jₐₐ=12.6 Hz, 1 H), 3.60 (t, J₃₄₄=J₃₄₄=5.5 Hz, 1 H, H.3a), 2.77 (t of d, J₈₈₈₈=9.1 Hz, J₈₈₈₈=J₈₈₈₈=5.5 Hz, 1 H, H.8b), 2.12 (m, 1 H, H.7), 2.0-1.8 (m, 2 H), 1.8-1.55 (m, 2 H), 1.55-1.0 (m, 10 H), 0.94 (t, J=6.5 Hz, 3 H, -CH₃), 0.87 (d, J=7.0 Hz, 3 H, -CH₃); ¹³C NMR (CDCl₃, 68 MHz) δ 137.7, 129.2, 128.3, 127.1, 178.3, 72.1, 61.8, 45.1, 39.4, 37.0, 34.5, 31.5, 31.2, 30.0, 25.5, 23.1(2), 18.6, 14.1; IR (neat) 3085, 3060, 3030, 2910, 1950, 1840, 1810, 1605, 1495, 1452, 1375, 1325, 1300, 1265, 1218, 1180, 1142, 1070, 1030,
1012, 990, 940, 901, 825, 750, 730, 694, 630 cm⁻¹; mass spectrum, m/e 313 (parent ion). (Found: C, 80.43; H, 9.81. Calc. for C₂¹H₃₁NO: C, 80.46; H, 9.97%).

**Data for 19b**: TLC, Rf 0.57 (4:1 hexane-ether); [α]D¹⁹ - 50.6° (c=0.52, CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 7.45 - 7.2 (m, 5 H, aromatic), 4.39 (d of d, J₈ₐ,₈₈ = 2.7 Hz, J₈₈₈₈ = 6.0 Hz, 1 H, H₈ₐ), 4.12 (A of AB, J_AB = 12.6 Hz, 1 H, benzyl H), 3.85 (B of AB, J_AB = 12.6 Hz, 1 H), 3.61 (d of d, J₃ₐ,₄₉₉ = 6.1 Hz, J₃₈₈,₈₈ = 6.0 Hz, 1 H, H₈₈), 2.77 (t of d, J₈₈,₅₅ = 7.9 Hz, J₈₈₈₈,₃₈ = 6.0 Hz, 1 H, H₈b), 2.0-1.8 (m, 2 H), 1.8-1.2 (m, 13 H), 0.89 (overlapping d and t, 6 H, two CH₃'s); ¹³C NMR (CDCl₃, 68 MHz) δ 137.7, 129.2, 128.6, 127.1, 75.1, 71.8, 61.4, 48.6, 43.8, 37.4, 36.8, 35.1, 30.5, 29.3, 28.9, 24.9, 23.1, 20.3, 14.1; IR (neat) 3082, 3060, 3025, 2950, 2870, 1605, 1495, 1452, 1378, 1335, 1172, 1155, 1028, 925, 725, 692, 630; mass spectrum, m/e 313 (parent ion). (Found: C, 80.60; H, 9.70. Calc. for C₂¹H₃₁NO: C, 80.46; H, 9.97%).
Benzylamino alcohol 20a,b. Benzylisoxazolidine 19b (105 mg, 0.335 mmol) was dissolved in 8 mL of 10M aqueous acetic acid. The solution was heated to 55°C and then excess zinc dust (220 mg, 3.36 mmol, ~10 equiv) was added with vigorous stirring. An additional portion of Zn (~100 mg) was added after 40 min. After 3h TLC analysis revealed the complete consumption of 19b. Thus, the reaction mixture was cooled, diluted with 25 mL of H₂O and basified (pH 14) by addition of 6 M KOH. The solution was extracted with CHCl₃ (4x50 mL) and the extracts filtered through adsorbent cotton. Removal of solvent in vacuo afforded 100 mg (95%) of analytically pure 20b, which was used in subsequent steps as obtained. The yield of 20a was 95% following this procedure.

Data for 20a: TLC, Rₚ 0.45 (20:1 CHCl₃-CH₃OH); [α]D²² + 4.0° (c=3.43, CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 7.39-7.26 (m, 5 H, aromatic), 4.02 (t, J=3.8 Hz, 1 H, H.8a), 3.84 (A of AB, JAB = 13 Hz, 1 H, benzylic H), 3.77 (B of AB, JAB = 13 Hz, 1 H), 3.48 (m, 1 H, H.3a), 2.75 (broad s, 2 H, -OH, -NH), 2.26 (m, 1 H), 2.2-1.85 (m, 4 H), 1.65-1.03 (m, 11 H), 0.89 (d, J=6.9 Hz, 3 H, -CH₃), 0.88 (t, J=6.2 Hz, 3 H, -CH₃); ¹³C NMR (68 MHz), δ 140.0, 128.4, 128.1, 127.1, 69.8, 61.5, 53.6, 45.1, 40.5, 37.7, 31.0, 30.7, 29.5, 24.2, 23.3, 23.1, 18.5, 14.1; IR (neat) 3400, 3300, 3038, 2960, 2940, 2878, 1500, 1458, 1030, 745, 698 cm⁻¹. (Found: C, 79.81; H, 10.84. Calc. for C₂₁H₃₃NO: C, 79.95; H, 10.54%).

Data for 20b: TLC, Rₚ 0.36 (20:1 CHCl₃-CH₃OH); mp 48-50°C; [α]D²⁰ -
26.0° (c=0.4, CHCl₃); 'H NMR (CDCl₃, 270 MHz), δ 7.36-7.26 (m, 5 H, aromatic), 4.06 (m, 1 H, H.8a), 3.82 (s, 2 H, benzylic H), 3.46 (m, 1 H, H.3a), 2.50-1.10 (m, 18 H), 0.91 (t, J=7.3 Hz, 3 H, -CH₃), 0.89 (d, J=7.3 Hz, 3 H, -CH₃); IR (neat): 3410, 3310, 3060, 3025, 2955, 2930, 2865, 1605, 1495, 1454, 1375, 1112, 1065, 1028, 960, 908, 732, 694 cm⁻¹; mass spectrum, m/e 315 (parent ion). (Found: C, 79.76; H, 10.72. Calc. for C₂₁H₃₃NO: C, 79.95; H, 10.54%).
Benzylamino ketone 21a,b. Benzylamino alcohol 20a (76 mg, 0.241 mmol) was dissolved in 5 mL of glacial acetic acid and treated with 75 drops (ca. 2.5 mL) of 2 M aq. HCl at 23°C. After being stirred for 15 min the solution was cooled to 0-5°C and slowly treated with 120 drops (ca. 4 mL) of Jones' reagent. A cloudy orange-brown solution resulted, which after 2.5 h became clear orange with a small amount of dark precipitate. The cold solution was transferred slowly via pipette to a separatory funnel containing saturated aqueous NaHCO₃ and CHCl₃. The aqueous phase was extracted thoroughly with CHCl₃ (6x30 mL) and the combined organic extracts were filtered through adsorbent cotton. After removal of the solvent in vacuo 77 mg (quantitative yield) of 21a was obtained as a pale yellow oil.

Analysis of the product by ¹H NMR indicated that the oxidation product (containing ~5-20% of 40a) was 95% pure. The yield of 21b using this procedure was 87-95%. Because 21a,b was prone to epimerize this intermediate was typically used immediately in the next step. However, ketones 21a or 21b (from 20b) could be purified by careful chromatography on silica gel (0.5 mm silica gel preparative plate, 20:1 CH₂Cl₂-CH₃OH) with mass recoveries of roughly 75%. Small quantities of trans-fused isomers 40a and 40b were separated in such purifications.

Data for 21a: TLC, Rf 0.41 (20:1 CHCl₃-CH₃OH); [α]ᵢ²₀ - 69° (c=0.3, CHCl₃; sample contained ca. 20% of 40a; ¹H NMR (CDCl₃, 250 MHz) δ 7.34-7.20 (m, 5 H, aromatic), 3.76 (A of AB, J=13 Hz, 1 H, benzylic H), 3.68 (B of
AB, J=13 Hz, 1 H), 3.30 (q, J=7.1 Hz, 1 H, H.3a), 2.82 (t, J=7.1 Hz, 1 H, H.8b), 2.52-2.35 (series of m, 3 H), 2.30-2.20 (m, 1 H), 2.05-1.90 (m, 1 H), 1.86-1.45 (series of m, 6 H), 1.42-1.15 (m, 5 H), 0.92-0.87 (overlapping d and t, 6 H, two -CH₃'s); IR (neat) 3335, 3060, 3030, 2960, 2930, 2870, 1695, 1620, 1608, 1494, 1455, 1380, 732, 698 cm⁻¹.

Data for 21b: TLC, Rf 0.33 (20:1 CHCl₃-CH₃OH); [α]D<sup>20</sup> - 19.5° (c=0.56, CHCl₃; sample contained ~10% 40b); <sup>1</sup>H NMR (CDCl₃, 250 MHz) δ 7.38-7.19 (m, 5 H, aromatic), 3.83 (A of AB, J=12.8 Hz, 1 H, benzylic H), 3.70 (B of AB, J=12.8 Hz, 1 H), 3.08 (t of d, J=8.7, 5.1 Hz, 1 H, H.3a), 2.73 (d of d, J=5.1, 8.0 Hz, 1 H, H.8b), 2.6-2.4 (m, 1 H, H.5a), 2.10-1.9 (m, 2 H), 1.9-1.5 (m, 9 H), 1.4-1.2 (m, 4 H), 1.02 (d, J=5.9 Hz, 3 H, -CH₃), 0.90 (t, J=6.8 Hz, 3 H, -CH₃); IR (neat) 3335, 3085, 3065, 3030, 2955, 2930, 2870, 1700, 1608, 1495, 1465, 1455, 1382, 1185, 1153, 1030, 734, 698 cm⁻¹; mass spectrum, m/e 313 (parent ion); high resolution mass spectrum, obsd.
313.241 (±.001), C₂₁H₃₃NO requires 313.2406.

Data for trans-ring fusion isomer 40a: TLC, Rf 0.5 (20:1 CHCl₃-CH₃OH); <sup>1</sup>H NMR (CDCl₃, 250 MHz) δ 7.34-7.22 (m, 5 H, aromatic), 3.80 (A of AB, J=13.1 Hz, 1 H, benzylic H), 3.68 (B of AB, J=13.1 Hz, 1 H), 3.39 (t of d, J=9.1, 5.8 Hz, 1 H, H.3a), 2.44 (m, 2 H), 2.22 (d of d, J=9.1, 12.5 Hz, 1 H, H.8b), 2.1-1.9 (m, 2 H), 1.84-1.60 (m, 4 H), 1.6-1.45 (m, 2 H), 1.4-1.1 (m, 6 H), 0.89 (t, J=6.9 Hz, 3 H, -CH₃), 0.76 (d, J=7.0 Hz, 3 H, -CH₃).

Data for trans-ring fusion isomer 40b: TLC, Rf 0.5 (20:1 CHCl₃-CH₃OH); <sup>1</sup>H NMR (CDCl₃, 250 MHz) δ 7.35-7.15 (m, 5 H, aromatic), 3.83 (A of AB, J=13 Hz, 1 H, benzylic H), 3.69 (B of AB, J=13 Hz, 1 H), 3.38 (t of d, J=9, 6 Hz, 1 H, H.3a), 2.39 (d of d, J=9, 12.5 Hz, 1 H, H.8b), 2.25-1.4 (series of m, 12 H), 1.35-1.15 (m, 4 H), 0.97 (d, J=7 Hz, 3 H, -CH₃), 0.88 (t, J=7 Hz, 3 H, -CH₃).
Amino alcohol 24a,b. Benzylamino alcohol 20b (33.4 mg, 0.106 mmol) was dissolved in 3 mL of anhydrous CH₃OH and treated with 0.30 mL of anhydrous formic acid. Freshly prepared Pd black⁴¹ (40 mg) was added to the rapidly stirring solution. After 19 h the reaction mixture was filtered through Celite, washed with CH₃OH (30 mL) and concentrated. Redissolution in CHCl₃, treatment with anhydrous K₂CO₃, filtration through adsorbent cotton and removal of solvent in vacuo afforded 24b (22.9 mg, 96%) as white leafs (mp 84-86°C).

Data for 24a: Rf 0.11 (3:1 CHCl₃-CH₃OH); H NMR (CDCl₃, 250 MHz), δ 3.98 (t, 1 H), 3.73 (m, 1 H), 2.5-1.8 (series of m, 7 H), 1.6-1.1 (series of m, 12 H), 1.0-0.8 (overlapping d and t, 6 H).

Data for 24b: Rf 0.11 (3:1 CHCl₃-CH₃OH); H NMR (CDCl₃, 270 MHz), δ 4.04 (t, J=1.9 Hz, 1 H), 3.71 (m, 1 H), 2.1-1.0 (series of m, 18 H), 0.95-0.80 (overlapping d and t, 6 H); mass spectrum, m/e 225 (parent ion); high resolution mass spectrum, obsd. 225.209 (±0.001), C₁₄H₂₇NO requires 225.209.
Amino ketone 26a,b.

**Method A.** Benzylation of ketone 21a,b (18 mg, 0.058 mmol) was dissolved in 2 mL of anhydrous CH$_3$OH and treated with 0.20 mL of anhydrous HCO$_2$H. Freshly prepared Pd black$^{41}$ (40 mg) was added to the rapidly stirring solution. After 1.5-2.0 h the mixture was filtered through Celite, washed with CH$_3$OH (20 mL) and concentrated in vacuo. Immediately before use in the subsequent guanidination reaction the residue was dissolved in CH$_2$Cl$_2$, washed with saturated aqueous NaHCO$_3$ and concentrated in vacuo to give 13 mg of epimeric 26a,b (quantitative yield).

**Method B.** Amino alcohol 24a (7 mg, 0.031 mmol) was dissolved in 1 mL glacial acetic acid and treated with 10 drops of 2 M aqueous HCl. After being cooled to 0°C the mixture was treated with 20 drops of Jones' reagent. After 2.5 h the mixture was diluted with saturated aqueous NaHCO$_3$ and extracted with CHCl$_3$ (4x6 mL). Filtration through adsorbent cotton and removal of solvent in vacuo afforded epimeric 26a (6.5 mg, 94%): TLC of mixture: $R_f$ 0.22 (3:1 CHCl$_3$-CH$_3$OH).

**Data for 26a** (sample contained ca. 30% of C.8b and C.8 isomers): $^1$H NMR (CDCl$_3$, 270 MHz) δ 3.54 (m, 1 H, H.3a), 2.75-1.10 (series of m, 18 H), 1.00-0.80 (overlapping d and t, 6 H, two -CH$_3$'s); IR (neat) 2960, 2935, 2865, 1708, 1585, 1460, 1380 cm$^{-1}$.

**Data for 26b** (sample contained ca. 30% of C.8b and C.8 isomers): $^1$H NMR (CDCl$_3$, 270 MHz) δ 3.35 (m, 1 H), 2.75-2.4 (series of m, 3 H),
2.35-1.10 (series of m, 15 H), 1.05 (d, J=7.0 Hz, 3 H, -CH₃), 0.92 (t, J=7.0 Hz, 3 H, -CH₃); IR (neat) 2960, 2935, 2865, 1705, 1575, 1460, 1380 cm⁻¹; mass spectrum, m/e 223 (parent ion).
Isoxazolidine 27b. Benzylisoxazolidine 19b (10 mg, 0.03 mmol) was dissolved in 1.0 mL of anhydrous CH$_3$OH and treated with 0.1 mL of anhydrous HCO$_2$H. Freshly prepared Pd black$^{41}$ (30 mg) was added to the rapidly stirring solution. After 2 h TLC analysis revealed that reaction was complete. The mixture was filtered through Celite, washed with CH$_3$OH (10 mL) and concentrated in vacuo. Redissolution in CHCl$_3$, stirring with anhydrous K$_2$CO$_3$, filtration through adsorbent cotton and removal of solvent in vacuo afforded 7 mg of 27b. Purification by chromatography (silica gel, 250 µ preparative plate, 3:1 Et$_2$O-hexane) afforded 6.7 mg (95%) of 27b: TLC, $R_f$ 0.60 (20:1 CHCl$_3$-CH$_3$OH); mp 109-110°C; $^1$H NMR (CDCl$_3$, 250 MHz), $\delta$ 3.94 (t, J=6.6 Hz, 1 H, H.8a), 3.66 (d of d, J=2.7, 3.0 Hz, 1 H, H.3a), 2.65 (q, J=6.9 Hz, 1 H, H.8b), 2.0-1.8 (m, 2 H), 1.8-1.1 (series of m, 14 H), 1.0-0.8 (overlapping d and t, 6 H, -CH$_3$'s); IR (CH$_2$Cl$_2$) 2948, 2855, 1458, 1378, 1345, 1178, 1082, 1025, 998, 920, 870, 852, 832; mass spectrum, m/e (relative intensity) 223 (M$^+$, 3), 206 (100).
(-)-Ptilocaulin (7).

Method A: Amino ketone 26b (7.8 mg, 0.035 mmol) was transferred to a 1 mL pear tipped reaction tube and mixed with 7.0 mg (0.035 mmol, 1 equiv) of GDMP (23). After degassing and flushing with Ar the mixture was heated to 120°C for 15-45 min. The mixture was cooled to 23°C and the brown residue purified by chromatography (silica gel, 10 mm column, 83:17 CHCl₃-CH₃OH) to afford 5.6 mg (51%) of a mixture of 3 compounds tentatively assigned structures 7, 41 and 42 (≈2:1:1). When 26b (24 mg, 0.108 mmol) was heated with 23 (22.7 mg, 0.113 mmol, 1.05 equiv) for 1.25 h at 125°C a similar 2:1:1 mixture was obtained (16.2 mg, 48%) after chromatographic purification. Performing the reaction at 100°C (30 min) afforded a ca. 1:1:1 mixture of 7, 41 and 42. When 26a was heated with 23 at 120°C (15 min.) a ca. 1:1 mixture of products, tentatively assigned structures 41 and 43, was obtained along with a trace of 7.

Data for mixture of 7, 41 and 42: TLC of mixture: Rf 0.65 (3:1 CHCl₃-CH₃OH); ¹H NMR (CDCl₃, 270 MHz), δ 9.29, 9.23, 9.15 (3s, ca. 2:1:1, 1 H, NH), 8.20, 8.15, 7.92 (series of s and m, 1 H, NH), 7.6-7.3 (series of bs, 2 H, NH₂), 4.25 (m, 0.25 H, H.3a of 41), 3.92 (m, 0.25 H, H.3a of 42), 3.78 (m, 0.50 H, H.3a of 7), 2.7-1.15 (series of m, 15 H), 1.15-0.70 (series of d and t, 6 H).

Data for mixture of 41, 43 and 47: TLC of mixture: Rf 0.65 (3:1 CHCl₃-CH₃OH); ¹H NMR (CDCl₃, 250 MHz, data reported for crude sample), δ
9.15, 8.86, 8.75, 8.32, 8.25, 8.18 (series of s), 8.75-7.2 (series of s and m), 4.25 (m, ca. 0.45 H, H.3a of 41), 3.85 (m, ca. 0.45 H, H.3a of 43), 3.78 (m, ~0.1H, C.3a of 7), 2.7-1.2 (series of m), 1.15-0.70 (series of d and t). A sample containing 7, 41 and 42 (4.5 mg, 2:1:1) was dissolved in 1.5 mL of dry benzene and treated with a crystal of guanidine. The mixture was heated at 80°C for 24 h, cooled to 23°C, treated with 2 drops of 1% aqueous HNO₃ and extracted with CHCl₃ and 10 mL saturated aqueous NaNO₃. Removal of solvent in vacuo and chromatography of the residue (silica gel, 10 mm column, 85:15 CHCl₃-CH₃OH) afforded 4.0 mg (89%) of (-)-ptilocaulin (7) containing only a trace (<5%) of 41. The ¹H NMR data of 7 was identical to that summarized below. Application of this procedure to a mixture of 43 and 41 (ca. 3:1) likewise afforded homogeneous 7 (74% after chromatography).

Method B: Amino ketone 26b (27 mg, 0.121 mmol) was transferred to a 1 mL pear tipped reaction tube and mixed with GDMP (26 mg, 0.129 mmol, 1.1 equiv). After thorough degassing and flushing with Ar, the mixture was gradually warmed to 150°C over 1 h and maintained at this temperature for 4 h. After being cooled to 23°C the dark reaction mixture was purified by chromatography (silica gel, 30 mm, CHCl₃ (75 mL) then 2-17% gradient of CH₃OH-CHCl₃) to afford 21.5 mg of 7 (58%, >90% isomeric purity). Application of the high temperature melt procedure (155°C, 6h) to 26a (24 mg, 0.107 mmol) afforded 7 (22.5 mg, 66%, >80% isomeric purity (~8:1:1-7:41:43)). After washing a CHCl₃ solution of 7 with saturated aqueous NaNO₃ (10 mL, containing 3 drops of 1% HNO₃) removal of solvent and repeated washing of the residue with anhydrous ether, pure crystalline 7 was obtained (>99% isomeric purity): mp 183-184°C (lit. 3 183-185°C); TLC Rₖ
0.27 (5:1 CHCl₃-CH₃OH), 0.33 (4:1 CHCl₃-CH₃OH), 0.41 (5:1 CH₂Cl₂-CH₃OH); $[\alpha]_D^{22} = -73.9^\circ$ (c=0.31, 99.9% CH₃OH); lit.$^{50}$ $[\alpha]_D^{23} = +74.4^\circ$ (99.5% CH₃OH); $^1$H NMR (CDCl₃, 270 MHz), $\delta$ 8.86 [9.20]$^{51}$ (s, 1 H, -NH), 8.33 [8.62]$^{51}$ (br d, 1 H, -NH), 7.45 [7.55]$^{51}$ (s, 2 H, -NH₂), 3.75 (m, 1 H, H.3a), 2.50-2.35 (m, 4 H), 2.1-1.90 (m, 2 H), 1.75-1.6 (m, 2 H), 1.55-1.20 (two m's, 7 H), 1.02 (d, J=6.7 Hz, 3 H, CH₃), 0.87 (t, J=7.3 Hz, 3 H, -CH₃); $^{13}$C NMR (CDCl₃, 68 MHz), $\delta$ 151.7, 127.1, 121.0, 53.2, 36.5, 34.0, 33.1, 32.2, 29.6, 27.8, 26.8, 24.6, 22.4, 19.5, 13.9; IR (CHCl₃) 3260, 3018, 2960, 2930, 2870, 1680, 1608, 1540, 1465, 1458, 1402, 1378, 1344, 1265, 1200, 710, 660 cm$^{-1}$; UV (EtOH)$\lambda_{225}$ (ε=8500); mass spectrum (EI), m/e (relative intensity %)$^{247}$A$(M^+, 31), 232 (77), 204 (100), 190 (63), 176 (19); high resolution mass spectrum, obsd. 247.206 (±.001), C₁₅H₂₅N₃ requires 247.2050.
\(^1\)H NMR spectra (CDCl\(_3\), 270 MHz)

Top spectrum (A): Synthetic (-)-Ptilocaulin
Bottom spectrum (B): Natural (+)-Ptilocaulin
$^1$H NMR spectra (CDCl$_3$, 270 MHz. Spectra recorded after samples had been previously dissolved in CH$_3$OH; see ref. 51)

Top spectrum (A): Synthetic (-)-Ptilocaulin
Bottom spectrum (B): Natural (+)-Ptilocaulin
Infrared spectra (10mg/mL in CHCl₃)
Top spectrum (A): Synthetic (-)-Ptilocaulin
Bottom spectrum (B): Natural (+)-Ptilocaulin
Mass spectra

Top spectrum (A): Natural (+)-Ptilocaulin
Bottom spectrum (B): Synthetic (-)-Ptilocaulin
REFERENCES

2. A complete account of the work described herein has been submitted for publication: Walts, A.E.; Roush, W.R. Tetrahedron (Symposia in Print), in press.


8. While our work was in progress Snider reported a synthesis of racemic 3 which proceeds along the lines of Scheme I, and subsequently a synthesis of (-)7 which confirmed our assignment of absolute stereochemistry: (a) Snider, B.B.; Faith, W.C. Tetrahedron Lett. 1983, 24, 861. (b) Snider, B.B.; Faith, W.C. J. Am. Chem. Soc. 1984, 106, 1443.


12. The absolute configuration of (+)—pulegone has been determined unambiguously to be (R): Eisenbraun, E.J.; McElvain, S.M. J. Am. Chem. Soc. 1955, 77, 3383.

13. 3-Methylcyclohexanone is commercially available from Aldrich Chemical Co.


18. In an effort to improve the overall efficiency of the sequence 8 $\rightarrow$ 12 the pyridyl sulfoxide 1 was prepared (88% yield from 8). Unfortunately, attempted alkylation of 1 under conditions similar to those used with 9 were unsuccessful. $\alpha$—Keto—pyridyl sulfoxides are known to undergo very efficient thermolyses: Dubs, P.; Stüssi, R. Helv. Chim. Acta 1978, 61, 998; Roush, W.R.; Spada, A.P. Tetrahedron Lett. 1983, 24, 3693.

19. The C.8 $\alpha$—butyl isomer is designated as the "a" series and the C.8 $\beta$—butyl isomer as "b" throughout this paper. Yields for all transformations were comparable whether pure a, pure b or a:b mixtures were used.

20. This assignment is based in part on the observation that the C.7 methyl group in the major isomer (12b) appears at $\delta$ 1.06 while that of the minor isomer (12a) appears at $\delta$ 0.95 ppm. This suggests that the
methyl group in 12a is in an axial position.


25. We originally noted (ref. 1) that the ratio of 13a to 13b varied as a function of reaction scale, with a 2:1 mixture of 13a:13b being produced on scales larger than ca. 6 mmol. Further experimentation revealed that this epimerization occurs on workup. Essentially no epimerization occurred, even in large-scale experiments, when the dark-red reaction mixture was quenched with H₂O and maintained at -78°C until the solution turned colorless.


27. (a) Treatment of pure 13a or pure 13b with K₂CO₃ in methanol established identical 2:1 (13a:13b) equilibrium mixtures. (b) HPLC and NMR analysis failed to detect any other isomers of 13a,b.

28. Attempts to prepare 14a,b directly from 12a,b by quenching the Sakurai reaction with ClPO(OEt)₂ afforded only 13a,b.


30. Benzylhydroxylamine decomposes gradually during storage. Use of freshly prepared benzylhydroxylamine in this reaction gave 19a,b in up to 90% yield.

31. The stereochemical outcome of this reaction is in agreement with an example from a recent biotin synthesis: Confalone, P.N.; Pizzolato, G.; Confalone, D.L.; Uskokovic, M.R. J. Am. Chem. Soc. 1980, 102, 1954. In this case the nitronone i cyclized selectively to isoxazolidine ii, the stereochemistry of which was confirmed by an x-ray analysis of the oxime iii derived from ii.

33. This is the first example of the use of a 1,3-dipolar cycloaddition to establish the cis-perhydroindane system in a complex natural product. The cyclization of nitrone i has been described, but the stereochemistry of the cycloadduct(s) was not reported: LeBel, N.A. N.Y. Acad. Sci. Trans. 1965, 27, 858.


37. For an example, see: Roush, W.R. J. Am. Chem. Soc. 1980, 102, 1390.


41. Felix, A.M.; Jimenez, M.H.; Meienhofer, J. Organic Syntheses, 1979, 59, 152. It is crucial that this catalyst be freshly prepared immediately before use.


45. Similar reactions with 30b were not investigated. The N-nitro group of nitroguanidines is removed with a variety of reducing agents: Bodanszky, M.; Klausner, Y.S.; Ondetti, M.A. Peptide Synthesis 1976, 2nd Ed. Wiley, N.Y. pp. 67-68.


47. Since isoxazolidines 19a,b and 29b are formally in the same oxidation state as ptilocaulin (7), a fragmentation of such intermediates was briefly considered (c.f. 29b T 7). However, such fragmentations are not generally successful (see for example ref. 15). Moreover, the ca. 90° N-O-C-H dihedral angle in 29b is stereoelectronically unfavorable in this case.

![Chemical Structure](image)

48. This solvent effect has been observed previously: Mueller, R.H.; DiPardo, R.M. J. Org. Chem. 1977, 42, 3210.

49. No signals attributable to isoptilocaulin (ref. 3) were observed in any of the 1H-NMR spectra of the crude guanidination products from 26a or 26b.

50. Natural ptilocaulin nitrate has $\lbrack \alpha \rbrack_2^{23} + 74.4^\circ (99.5\% \text{CH}_2\text{OH})$ (Prof. K.L. Rinehart). We thank Prof. Rinehart for providing the optical rotation data, as well as a sample of natural ptilocaulin nitrate (3). We are also grateful to Prof. B.B. Snider for providing spectral data and a sample of racemic 3.
51. The chemical shifts of the guanidinium protons of ptilocaulin depend on the previous handling of the sample. The values in brackets are those obtained for both synthetic and natural ptilocaulin after dissolution in CH₃OH. Chemical shifts identical to those reported by Rinehart are restored after a CHCl₃ solution of ptilocaulin is washed with saturated aqueous NaN₃ solution.


53. Guanidina was prepared by treatment of commercially available (Fluka A.G.) guanidine hydrochloride (99%) with an equimolar quantity of NaOMe in CH₃OH, followed by filtration and removal of solvent in vacuo.
PART II
CHAPTER II

CHEMISTRY OF ALLYLIC

ORGANOMETALLIC REAGENTS
Section I: General

1. Introduction

The efficient stereo- and enantioselective construction of complex arrays of acyclic stereocenters constitutes one of the most intriguing challenges in modern synthetic organic chemistry. The multitude of these acyclic stereocenters in macrolides, polyether antibiotics and numerous other natural products behooves the organic chemist to devise methodology which is practical, efficient and applicable to a broad spectrum of problems. Indeed, considerable effort has been devoted in recent years to the problem of acyclic stereocontrol.\textsuperscript{1, 2}

One strategic solution to this problem relies on cyclic stereocontrol, wherein stereochemical relationships are established on a five- or six-membered ring which is subsequently converted to an acyclic system. The foundation of this approach is the wealth of knowledge available in conformational analysis of cyclic systems. Thus, although syntheses following this strategy are sometimes lengthy and inefficient, a high level of predictability and often ingenuity are present.\textsuperscript{3} However, the problem of acyclic stereocontrol ultimately demands solution via methodology which generates acyclic arrays directly, without recourse to cyclic systems.

A major step towards the development of a more direct, practical solution to acyclic stereocontrol occurred with the development of the chiral directed aldol reaction by the Masamune,\textsuperscript{1a} Heathcock,\textsuperscript{1g} and Evans\textsuperscript{1f} groups. The efficacy of this approach was demonstrated in Masamune's elegant synthesis of 6-deoxyerythronolide B\textsuperscript{4}.
The chemistry of allyl metal compounds potentially offers a complementary approach to acyclic stereocontrol. Besides serving conceptually as "enolate equivalents" (equation 1), in many instances further manipulation of the product olefin moiety may be desired. Additional versatility is available in the ease of preparation of substituted allylic organometallics, and in the ability to store many of these reagents (e.g. B, Si, Sn based reagents) for use when needed. While a tremendous amount of work has been done in studying the chemistry and selectivity of these reagents, their full potential is far from realized. Due to their diversity in number, chemo- and stereoselectivity and reactivity, these reagents offer one of the most fertile areas for new contributions to the problem of acyclic stereocontrol.

2. **Background**

Allylic organometallic reagents derived from a variety of metals including lithium, boron, magnesium, aluminum, silicon, potassium, titanium, chromium, copper, zinc, zirconium, cadmium, and tin are known and have been investigated to some extent. Two factors are of primary importance in considering the efficacy of these reagents in acyclic stereochemical synthesis. First, the ability to predict and control the syn/anti ratio of the newly formed chiral centers at C.3 and C.4 (i.e. $\frac{2}{4}$ vs $\frac{3}{5}$) when using substituted reagents ($R^2$ or $R^3 \neq H$) is fundamental (equation 2) for predicting diastereomeric ratios. Indirectly, of course, 

$$
\text{RCHO} + M \rightarrow \text{RCH(OH)CH(OH)CH}_2\text{R} \nonumber
$$

*equation 1*
selectivity during reactions with chiral aldehydes (i.e. 2/3 vs 4/5, equation 2) is perhaps even more important, especially when considering synthetic sequences involving complex aldehydes. This second problem has only recently been addressed. Reagents which are configurationally unstable due to the metallotropic shift\textsuperscript{2a} generally lead to syn/anti mixtures of C.3/C.4 isomers (i.e. 2/4 vs 3/5, equation 2) and thus are not useful in this context. Reagents limited in this respect include those derived from lithium, potassium, magnesium, zinc and cadmium. Acyclic stereochemical research involving crotyl metal reagents has therefore centered on compounds of boron, aluminum, silicon, titanium, chromium, zirconium and tin.

These reagents all offer some degree of stereochemical predictability during reactions with aldehydic electrophiles, depending on the metal and specific reaction conditions used. Denmark's classification of these reagents into three groups is based on the stereochemical outcome of their reactions with achiral aldehydes\textsuperscript{5a}:
Type 1: The syn/anti ratio reflects the Z/E ratio in the allyl moiety. Includes B, Al, and Sn reagents.

Type 2: Syn selective reactions independent of allyl geometry. Includes reagents of Sn, Si and Ti; reactions involve Lewis acid catalysis.

Type 3: Anti selective reactions independent of allyl geometry. Includes reagents of Ti, Cr, and Zr.

It is instructive to compare these reagents, first briefly with regard to syn/anti selectivity in reactions with achiral aldehydes, and then in more detail with regard to their diastereoselectivity in reactions with chiral aldehydes.

3. Reactions with Achiral Aldehydes

1) Type 1 Reagents

Reactions of carbonyl compounds with allylic boron, aluminum and tin reagents have been rationalized by invoking a rigid, chair-like cyclic transition state\(^2\) which explains the transmission of reagent olefin geometry to a syn or anti relationship in the product. The aldehyde

\[ \text{R}^3 \text{ substituent is assumed to occupy an equatorial position, with a synclinal orientation of double bonds. Cases in which the product syn/anti ratio is lower than the (Z)/(E) reagent ratio can be explained by invoking} \]
competing transition states in which the aldehyde $R^3$ substituent occupies an axial position, or by prior isomerization of the olefinic moiety. The latter problem is particularly evident with allylic boranes (6) which undergo rapid isomerization, even at $-78^\circ C$. Substituted boronates (7), however, are configurationally stable at temperatures up to $\sim 100^\circ C$ for short periods of time and can be manipulated at normal temperatures without problems.

Type 1 reagents offer perhaps the greatest potential for synthetic applications, particularly where methodology is available for preparation of substituted, configurationally defined (Z)- or (E)-reagents. In terms of these considerations the allylic boronates are unmatched. A large number of (Z)- and (E)-reagents (8) have been described and have been shown to react in a highly stereoselective manner with aldehydes. Listed in Table I are several examples which illustrate the structural diversity available with these reagents. It is noteworthy that the reagent (Z)/(E) ratio is efficiently expressed in the product syn/anti ratio, affording a high
degree of control over the stereochemistry about the newly formed carbon-carbon bond. Of particular importance for the synthesis of macrolides and carbohydrates are those reagents (8) where R\textsuperscript{1} or R\textsuperscript{2} is methyl, alkyl or alkoxy.

Table I

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<tr>
<th>Entry</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>R\textsuperscript{4}</th>
<th>R\textsuperscript{5}</th>
<th>(Z):(E)</th>
<th>Aldehyde</th>
<th>syn/anti ratio</th>
<th>Ref.</th>
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<td>H</td>
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<td>&quot;</td>
<td>6:94</td>
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<td>H</td>
<td>H</td>
<td>H</td>
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<td>95:5</td>
<td>&quot;</td>
<td>95:5</td>
<td>10h</td>
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<td>H</td>
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<td>11:89</td>
<td>&quot;(0.9 equiv)&quot;</td>
<td>5:95</td>
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<td>H</td>
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<tr>
<td>j</td>
<td>H</td>
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<td>-</td>
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<td>H</td>
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<td>H</td>
<td>Cl</td>
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<td>CH\textsubscript{3}</td>
<td>95:5</td>
<td>&quot;</td>
<td>97:3</td>
<td>10b</td>
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Substituted allylic aluminum compounds are generally not as readily available as allylic boron compounds. Some reagents (e.g. 10-13) are
known, however, and these undergo addition to aldehydes with varying levels of selectivity\textsuperscript{11}. Unfortunately, the crotylaluminum reagent \textsuperscript{11} undergoes a metallotrope shift and must therefore be prepared and used at -78°C,\textsuperscript{11b} a problem which limits its general utility.

\[
\text{CH}_2\text{O} \quad \text{AlEt}_2 \quad \text{AlEt}_2 \quad \text{N}^\left(\text{i-Pr}\right)_{2} \\
\text{10} \quad \text{11} \quad \text{12} \quad \text{13}
\]

Configurationally pure crotylstannanes undergo stereoselective thermal type 1 additions to aldehydes.\textsuperscript{12} This reaction, however, has found little synthetic application due to the forcing reaction conditions required (often 200°C).\textsuperscript{12a} In addition, a propensity for isomerization of the (Z)-crotylstannanes has been noted.\textsuperscript{12b} A potentially useful high pressure - low temperature variant of this procedure has been described, although syn/anti selectivities are only 3-4:1.\textsuperscript{13} One very interesting sequence which utilizes the activated stannane \textsuperscript{14} has been reported\textsuperscript{14b,c}. In this case, thermal reaction of \textsuperscript{14} with benzaldehyde at 130°C (15 h) afforded adduct \textsuperscript{15} in 70-80% yield. Further conversion of \textsuperscript{15} to its Mosher ester, followed by ozonolysis, oxidation and esterification afforded the ester \textsuperscript{16} which was greater than 98% enantiomerically pure (equation 3).

\[
\text{\textsuperscript{14} SnBu}_3\text{OR} \quad \xrightarrow{\text{PhCHO}} \quad \text{PhCHO} \quad \text{OMTPA} \quad \text{CO}_2\text{CH}_3 \\
\text{OR} \quad \text{130°C, 15 h} \quad \text{15} \quad \text{16} \\
\text{R=} \quad \text{70-80%} \quad \text{98% e.e.}
\]

\textit{equation 3}
2) Type 2 Reagents

This group of allylic stannane and silane compounds gives syn products independent of the reagent olefin geometry, although the overall stereoselectivity can vary. Reactions occur only in the presence of a Lewis acid and are believed to proceed via acyclic transition states.

The syn selective reactions of (E)- and (Z)-crotylsilanes are illustrative of this general phenomenon.\textsuperscript{15,16} For example, the (E)-reagent \textsuperscript{17} is quite selective, affording syn adduct \textsuperscript{18} with 97:3 selectivity, while the corresponding (Z)-reagent provides only a 64:36 ratio of \textsuperscript{18}:\textsuperscript{19}.

\textbf{Scheme III}

\[
\begin{align*}
\begin{array}{c}
\text{SiMe}_3 \quad \text{CHO} \quad \text{TlCl}_4 \\
\text{CH}_2\text{Cl}_2, -78^\circ\text{C}
\end{array}
\end{align*}
\]

In contrast to the crotylsilanes, both (E)- and (Z)-crotylstannanes undergo highly syn selective reactions with aldehydes (Scheme IV).\textsuperscript{14,15,17,18} For example, both (E)- and (Z)-crotyl reagents \textsuperscript{21} and \textsuperscript{24} afford syn product \textsuperscript{22} from benzaldehyde with >98% selectivity. These
results are noteworthy since geometrically pure reagents are not required to achieve useful levels of selectivity. Keck has made the interesting observation that anti selectivity can be obtained with crotylstannanes simply by altering the mode of Lewis acid addition (Scheme V). These anti selective reactions, however, may well proceed via Type III crotyl titanium species formed in situ which react via a cyclic chair transition state.

As noted above, these reactions are believed to proceed via acyclic transition states (Scheme VI). While Yamamoto has proposed that transition
states A and B with anti carbonyl orientations are important, recent work by Denmark calls this interpretation into question. Careful examination of the intramolecular reactions of aldehydes 29a,b revealed that both compounds cyclized primarily to syn-30, suggesting the involvement of synclinal transition state 32 (Scheme VII). It is possible then that transition states C and D shown in Scheme VI play a greater role in these reactions than previously thought.

Scheme VII

29
\[ \text{CHO} \]
\[ \text{MR}_3 \]
\[ \text{Lewis acid} \quad (\text{e.g. } \text{SnCl}_4, \text{FeCl}_3, \text{AlCl}_3, \text{BF}_3\cdot\text{OEt}_2, \text{Et}_2\text{AlCl}) \]
\[ \text{30 (syn)} \]
\[ \text{31 (anti)} \]
\[ \text{Ratio 30:31} \quad 50-80:50-20 \]
\[ 82-99:18-1 \]
3) **Type 3 Reagents**

Type 3 reagents (Cr, Ti, Zr)\(^{19}\) react with aldehydes to give primarily anti adducts from either the (Z)- or (E)-isomer. These reagents presumably undergo rapid equilibration, with preferential reaction of the (E)-isomer occurring via a cyclic chair (type 1) transition state.

Representative reactions of these reagents are illustrated in Scheme VIII. The selectivity is generally good, although a dependence on substrate structure has been noted. The dicyclopentadienyl titanium reagents \(^{39}\) have also been reported to provide anti adducts \(^{40}\) with outstanding selectivity. Interestingly, pre-addition of BF\(_3\) to the aldehydic substrate results in a reversal of selectivity, affording syn adducts \(^{41}\) preferentially (Scheme IX).\(^{24}\) These latter reactions may well proceed via type 2 acyclic transition states (c.f. Scheme VI).
4. Reactions with Chiral Aldehydes

1) **Type 1 Reagents**

Diastereofacial selectivity during reactions of allylboron reagents with chiral aldehydes is discussed in Section 2 of this chapter. In contrast to the many results obtained with boron compounds, relatively little work has been done with other members (Al, Sn compounds) of this class. One noteworthy example is shown in equation 4 where reaction of (Z)-crotyl aluminate 10 with aldehyde 42 provided the monensin intermediate 43 with 3:1 selectivity. 11b

2) **Type 2 Reagents**

Good diastereofacial selectivity has been realized in reactions of allylic silanes with alkoxy substituted aldehydes. Chelation controlled
products have been observed by Heathcock\textsuperscript{25} and Reetz\textsuperscript{26} in the SnCl\textsubscript{4} mediated reactions of 44 with chiral aldehydes 45, 48 and 51 (Scheme X). Attempts to reverse the facial selectivity by using BF\textsubscript{3} (which cannot form a chelate), however, were not very successful (entries 1-3). When the non-alkoxy substituted aldehyde 54 was used, only marginal 2:1 selectivity for Felkin adduct (55) was observed. Reactions of allylsilanes with chiral acetals have also been described\textsuperscript{27}, as have the preparation and reactions of homochiral silanes such as 57\textsuperscript{28} (equation 5). This latter example illustrates a potentially useful strategy for reagent-based control of aldehyde diastereofacial selectivity.
The reactions of allylic stannanes with chiral alkoxy substituted aldehydes have been studied in depth by Keck. An important conclusion of this study is that aldehyde facial selectivity is strongly influenced by choice of Lewis acid, solvent and alcohol protecting group (see Scheme XI for two examples). While either threo or erythro adducts 61 and 62 could be obtained from 59, only the chelation product 64 was available with high selectivity from aldehyde 63. Other studies have focused on the addition of crotyl stannanes to α-alkoxy and α-methyl, β-alkoxy aldehydes such as 66 and 69 (Scheme XII). Impressive selectivity of >200:1 for chelation
controlled product 67 was observed with aldehyde 66, although the syn/anti selectivity around the newly formed C.3,4 bond was only 91:9. A maximum of 74:26 selectivity for Felkin adduct 68 was obtained using BF₃-Et₂O as Lewis acid, and again only 89:11 syn/anti selectivity at C.3,4 was observed. Use of BF₃-Et₂O as catalyst with aldehyde 69 afforded Felkin adduct 70 with 95:5 selectivity, with only the C.3,4 syn adducts observed. Use of MgBr₂ as catalyst afforded the chelate product 71 (91:9), although again the C.3,4 syn selectivity was only 89:11. Thus, while impressive results have been obtained with these reagents, further effort is needed in controlling the C.3,4 syn selectivity as well as in selectively obtaining Felkin adducts such as 68 from α-alkoxy aldehydes.

The reactions of non-alkoxy substituted aldehydes 54 and 74 have also been investigated (Scheme XIII). Good selectivity (86:14) for Felkin adduct 72 was observed with 54, where the C.3,4 syn selectivity was 99:1.
Scheme XIII

\[ \text{Reaction of 74 with 21 interestingly afforded the anti-Felkin adduct 75 with an overall selectivity of 94:6.} \]

Yamamoto has proposed the involvement of the cyclic chelate species 76 to explain the high selectivity in this reaction.

3) Type 3 Reagents

Diastereofacial selectivity in the use of crotyl chromium reagents has been reported with several systems. Kishi has investigated several complex aldehydes\(^{30}\) (Scheme XIV) and observed a general trend for syn facial selectivity. Some substrates (e.g. 77) displayed good selectivity, while others (e.g. 79) did not. Based on results obtained with several aldehydes...
Kishi has proposed that the syn C.2,4 methyl groups are important for obtaining high selectivity in these reactions. Substrate dependent selectivity has also been observed with other aldehyde substitution patterns. For example, good selectivity was observed with aldehyde 81\textsuperscript{31a}, while aldehyde 84 showed poor selectivity\textsuperscript{31b} (Scheme XV).

Finally, Heathcock has investigated the reaction of 33 with the non-alkoxy substituted aldehyde 54 and observed 72:28 selectivity for Felkin adduct 87 (equation 6).

While reactions of allylic titanium reagents with chiral
aldehydes have not been investigated, an interesting sequence using chiral reagent 89 has been described (Scheme XVI). Reactions of 89 with a variety of aldehydes proceed with high selectivity and since the product diastereomers can be purified, homochiral alcohols of high enantiomeric purity are available after removal of the chiral auxiliary. Finally, allylic zirconium reagent 91 has been reported to undergo marginally selective additions to chiral aldehyde 54 (Scheme XVI).

Scheme XVI
Section 2: Chemistry of Allylic Boronates

1. Introduction

As type 1 reagents, allylic boronates presumably react via cyclic chair transition states in what is perhaps best described as a [3,3]-sigmatropic rearrangement of a bis-hetero-1,5-diene system. The ease of preparation of a range of substituted allylic boronates, as well as the predictive power associated with the transition state model, renders these reagents valuable tools in organic synthesis. Boronates are commonly prepared via one of two general sequences: i) nucleophilic substitution at boron or ii) boron assisted nucleophilic substitution at an α-carbon (Scheme XVII). Several variants on these general themes have been

Scheme XVII
developed. After introduction of the desired allyl moiety via sequence (i) or (ii), treatment with an appropriate alcohol or diol provides the final boronate reagent. The range of boronates which can be prepared is thus limited only by the availability of appropriate allyl or vinyl anions. A key feature of these syntheses is the ability to easily introduce various ester moieties, particularly those which are homochiral, in the ligand exchange step. The oxidation state of boron is particularly important since it is the electron donating oxygen atoms which slow the borotropic shift sufficiently to prevent olefin isomerization in substituted reagents \( R_1 \) or \( R_2 \neq H \). Crotol boranes, however, do undergo the borotropic shift at temperatures above \(-78^\circ C\), and thus configurationally pure reagents are available only at very low temperatures. As a consequence, the general utility of these reagents is severely limited.

2. Aldehyde Addition Reactions

While reactions of achiral substituted boronates with achiral aldehydes have been thoroughly investigated (see also Section 1 of this chapter), reactions with chiral aldehydes have only recently received attention. Recent examples are summarized in Scheme XVIII. In one of the first cases (entry 1) Hoffmann observed marginal selectivity for anti facial isomer with chiral \( \alpha \)-methyl aldehyde. Excellent selectivity for Felkin adduct from threonine derived aldehyde was observed by Roush, who reported the first boronate addition to a chiral \( \alpha \)-alkoxy
Scheme XVIII

1. \( \text{CHO} \xrightarrow{(99)} \text{CH}_3 \xrightarrow{(98)} \text{CH}_2 \text{CH}_3 \) 100 + 101 2:3:1

2. \( \text{CHO} \xrightarrow{(103)} \text{OMe} \xrightarrow{(102)} \text{OMe} \) 104 + 105 19:1

3. \( \text{CHO} \xrightarrow{(107)} \text{OR} \xrightarrow{(106)} \text{OR} \) 108 \text{III} R = \text{TBOM}

4. \( \text{CHO} \xrightarrow{(111)} \xrightarrow{(110)} \text{OR} \xrightarrow{(106)} \text{OR} \) 112 + 113 4:1

5. \( \text{N-OH} \xrightarrow{(111)} \xrightarrow{(110)} \text{Fe}^{2+} \text{dihydropicolinic acid} \) 115 + 116 2.3:1

6. \( \text{CHO} \xrightarrow{(118)} \xrightarrow{(117)} \text{OMe} \xrightarrow{(116)} \text{OMe} \) 119 + 120 + 121 8.7:1:1.2 selectivity

\( \text{CHO} \xrightarrow{(116)} \text{OMe} \) 119
aldehyde.\textsuperscript{38} In a second example (entry 3) the addition of boronate 107 to aldehyde 106 also proceeded with good selectivity (10-15:1), providing Felkin-type adduct 108 which was further elaborated in a synthesis of antibiotic X-14547A (see also Chapter IV of this thesis).\textsuperscript{39} Examples of the use of allylboronate 111 have been described by Hoffmann (entries 4\textsuperscript{40}, 5\textsuperscript{41}), although only modest selectivity for Felkin adducts was observed. Finally, Wuts has utilized the reaction of (Z)-methoxyboronate 118 with aldehyde 117 in a synthesis of oleandrose (122).\textsuperscript{42} In the key boronate addition the three adducts 119, 120 and 121 were obtained in an 8.7:1:1.2 ratio.

The first systematic study of the reactions of crotyl boronates with chiral aldehydes has been performed by Roush, who investigated additions of (Z)- and (E)-crotylboronates such as 99 and 123 to aldehydes 106 and 102 (Scheme XIX).\textsuperscript{43} A general conclusion of this work was that the (Z)-reagent

\textbf{Scheme XIX}
99 displays excellent selectivity, while the (E)-reagent 123 shows poor selectivity. These results have been rationalized by proposing that transition states 133-136 are important in determining facial selectivity of these reactions. While 134 is clearly favored in reactions of (Z)-crotylboronate 99, both 134 and 135 are accessible for the (E)-reagent 123 and thus the facial selectivity is low. Further discussion of this model can be found in Chapter III of this thesis.

A complementary study of the reactions of boronates 99 and 123 with chiral α-methyl aldehydes has recently been described by Hoffmann (Scheme XX). 44 While he observed results qualitatively similar to those of Roush, his data are shifted more towards the syn-selective end of the selectivity spectrum, and observed greatest selectivity with (E)-boronates. For
example, (E)-reagent 123 provides the syn adduct 140 with 98:2 selectivity, while the (Z)-reagent 99 affords a 60:40 mixture of 139/138. Similar results were observed with aldehyde 98. Interestingly, Hoffmann has proposed a transition state model to account for his results which is essentially identical to that proposed by Roush (see 133-136).

It is apparent from the examples in Schemes XVIII-XX that synthetically useful diastereofacial selectivity is the exception, rather than the rule in reactions of allyl and crotylboronate reagents. One approach to increasing the selectivity in these reactions involves double asymmetric synthesis\(^{45}\); i.e. the use of chiral boronate reagents. Ideally
a chiral reagent should display high enough innate selectivity to override any facial bias of the substrate, thus allowing the ready obtention of either stereofacial isomer.

Progress in this direction has been reported by Hoffmann.\textsuperscript{2a} Reagents prepared from camphor derived diol 144 indeed show enhanced selectivity relative to achiral boronate esters, although the improvement is not outstanding (Scheme XXI). For example, (Z)-reagent 145 provides only a 55:45 mixture of 101/100 upon reaction with 98, as opposed to the 70:30 mixture of 100/101 obtained with achiral reagent 99, and the (E)-reagent 146 affords a 92:8 ratio of 147/148 in contrast to the 83:17 ratio obtained with 123\textsuperscript{37,44} (Scheme XXI; compare Scheme XX). The sequence leading from aldehyde 149 to Prelog-Djerassi lactone precursor 150 is also illustrative of the marginal selectivity of these reagents. Thus, while achiral reagent 99 affords a 60:40 mixture of 150/151, this ratio is enhanced to only 81:19 using (+)-145, and to 32:68 using (-)-145.
Further applications of this methodology to reactions of aldehyde 106\textsuperscript{40} and oxime 114\textsuperscript{41} with chiral allyl reagent 153 are shown in Scheme XXII, where fair enhancements relative to the achiral reagent 111 are seen.

Scheme XXII

\[
\begin{align*}
\text{CHO} & \quad \text{Ph} \quad (153) \\
106 & \quad \rightarrow \\
\text{OH} & \quad + \quad \text{OH} \\
112 & \quad 96 : 4 \\
113 & \\
\text{(with chiral 111: 80 : 20)} & \\
\end{align*}
\]

\[
\begin{align*}
\text{N} \quad \text{OH} & \quad 1) \quad 153 \quad 2) \quad \text{Fe}^{2+}, \text{dihydrolipoic acid} \\
114 & \quad \rightarrow \\
\text{NH}_2 & \quad + \quad \text{NH}_2 \\
115 & \quad 90 : 10 \\
116 & \\
\text{(with achiral 111: 70 : 30)} & \\
\end{align*}
\]

Finally, the selectivity obtained during reaction of 106 with achiral reagents 99 and 123 is improved only marginally by using chiral reagents 145 and 146\textsuperscript{40} (Scheme XXIII; compare Scheme XIX).

Scheme XXIII

\[
\begin{align*}
\text{CHO} & \quad \text{Ph} \quad (145) \\
106 & \quad \rightarrow \\
\text{OH} & \quad + \quad \text{OH} \\
124 & \quad 97 : 3 \\
125 & \\
\text{with (+)-145: 98 : 2} & \quad \text{(with achiral 99: 97 : 3)} \\
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{Ph} \quad (146) \\
106 & \quad \rightarrow \\
\text{OH} & \quad + \quad \text{OH} \\
126 & \quad 67 : 33 \\
127 & \\
\text{with (+)-146: 72 : 28} & \quad \text{(with achiral 123: 55 : 45)} \\
\end{align*}
\]
The relatively poor results obtained with 153 in reactions with chiral (and thus necessarily hindered) aldehydes is consistent with results with achiral aldehydes, where highest e.e.'s are observed with unbranched substrates.\(^46\) The enantioselectivity in reactions of 153 ranges from a maximum of 86\% e.e. with non-hindered acetaldehyde to 30\% e.e. with benzaldehyde and 45\% e.e. with highly hindered trimethylacetaldehyde (Scheme XXIV).

![Scheme XXIV](image)

<table>
<thead>
<tr>
<th>R-CHO</th>
<th>%e.e. (154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCHO</td>
<td>30%</td>
</tr>
<tr>
<td>t-BuCHO</td>
<td>45%</td>
</tr>
<tr>
<td>(CH(_3))(_2)CHCHO</td>
<td>70%</td>
</tr>
<tr>
<td>CH(_3)CH(_2)CHCHO</td>
<td>72%</td>
</tr>
<tr>
<td>CH(_3)CHO</td>
<td>86% (reaction in propane at -90\degree C)</td>
</tr>
</tbody>
</table>

A series of chiral allylic boranes have been described by Brown (Scheme XXV)\(^47\). These reagents display impressive enantioselectivity (83-99\% e.e.) in reactions with achiral aldehydes, and again best results are obtained with unbranched substrates. No results have been reported for reactions with chiral substrates. A drawback to the use of these reagents is that, due to the borotropic shift\(^9\) which occurs readily with crotylboranes, this methodology may not be extendable to more highly functionalized, synthetically interesting members of the allylic boron family.
Note should also be made of the chiral allenylboronic esters developed by Yamamoto. Impressive enantioselectivity during reactions with achiral aldehydes has been observed (Scheme XXVI), although here again only data for reactions with achiral aldehydes is available.

Finally, a conceptually different approach to controlling facial
selectivity with allyl boronates has been described by Hoffmann. Homochiral \( \alpha \)-chloro allylboronate 158 undergoes highly selective reactions with aldehydes (Scheme XXVII). This selectivity is a consequence of the preference of the \( \alpha \)-chlorine atom to occupy an axial position in the preferred transition state A. While this sequence is potentially quite useful, independent work in our laboratory has revealed that extension of this methodology to crotylboronates poses serious problems in manipulation and preparation of the requisite reagents.
3. Summary

From the brief review presented here it is apparent that an "ideal" allylic organometallic reagent has not yet been discovered. While recent work has begun to address the problem of diastereofacial selectivity, the limitations of existing methods and strategies (both substrate and reagent based) have also become apparent. Clearly then, more general and more selective reagents must be developed if the goal of obtaining synthetically useful levels of selectivity with any chiral or achiral aldehyde is to be achieved. Our contributions in this area are described in Chapter III.
REFERENCES


31. (a) Fronza, G.; Fuganti, C.; Graselli, P.; Pedrocchi-Fantoni, G.; Zirotti, C. Chemistry Lett. 1984, 335. (b) Harris, D.J.; Roush, W.R. unpublished results.


36. Aldehyde addition reactions of crotolylboranes have nevertheless been investigated. One interesting example is shown below, where addition of the silyl substituted borane 162 to benzaldehyde proceeded with excellent anti selectivity. The selectivity is predicated on the pre-formation of a boron ate complex with either n-BuLi, sec-BuLi or pyridine, which presumably freezes the allyl moiety in an (E)-configuration. See: Yamamoto, Y.; Yatagai, H.; Maruyama, K. J. Am. Chem. Soc. 1981, 103, 3229. See also ref. 2b for further examples of aldehyde addition chemistry of borane compounds.


44. Hoffmann, R.W.; Weidmann, U. Chem. Ber., submitted. We thank Professor Hoffmann for providing a copy of this manuscript prior to publication.


51. Attempts to prepare boronate 166 were thwarted by the obtention instead of alkenylboronate 165, thus precluding the use of such a sequence in preparing homochiral 166.

\[
\text{Cl} \quad \text{CH}_2\text{Li} \quad \text{O} \quad \text{Cl} \\
\text{O} \quad \text{Cl} \\
\text{164} \\
\]

\[
\quad \text{X} \\
\text{CH}_3 \\
\text{B} \quad \text{O} \\
\text{165} \\
\]

\[
\quad \text{Cl} \quad \text{CH}_3 \\
\text{O} \quad \text{B} \\
\text{Cl} \quad \text{O} \\
\text{166} \\
\]

52. Hoffmann, R.W. Chem. Scripta, in press. We thank Professor Hoffmann for providing a copy of this manuscript prior to publication.
CHAPTER III

CHEMISTRY OF CHIRALLY MODIFIED ALLYLIC BORONATES
1. Introduction

The chemistry of allyl and crotylmetal compounds has broad potential for the control of acyclic stereochemistry. After comparing and contrasting the numerous organometallic reagents which have been studied (see Chapter II), advantages of allylic boron compounds for such purposes becomes evident. Indeed, due to their versatility, ease of preparation and stereoselectivity in reactions with aldehydes the family of organoboron reagents has assumed a prominent position in the research efforts of several groups worldwide.

Certain aspects of allyl- and crotylboronate chemistry, however, require further development. While early workers have shown that the isomeric purity of the reagent is predictably expressed in the syn/anti product ratio (a consequence of a cyclic chair transition state), the problem of diastereofacial selectivity in reactions with chiral aldehydes remains unsolved. This problem has received continuing attention in our group, where M. Adam has investigated diastereofacial selectivity in reactions of (Z)- and (E)-crotylboronates with aldehydes (Scheme I). One unexpected conclusion of this study is that only the
(Z)-crotyl reagent 1 displays useful levels of diastereofacial selectivity [32-99:1 for anti (erythro) isomers]; the (E)-crotyl reagent 2 is, in fact, virtually non-selective resulting in ca. 1:1 mixtures of facial isomers. Qualitatively similar results have recently been obtained by Hoffmann in studies of reactions of 1 and 2 with α-methyl branched chiral aldehydes.
(Scheme II).\textsuperscript{4f,g} Hoffmann's data however, are shifted more to the syn-selective end of the selectivity spectrum, and in his reactions the greatest selectivity occurs with (E)-boronates. Nonetheless, the two groups have suggested essentially identical transition state models to account for the observed results\textsuperscript{3,4g} (see also Scheme IV).

It is becoming increasingly apparent that high diastereofacial selectivity in reactions of allylic boronates with chiral aldehydes is the exception rather than the rule. One potential solution to this problem involves double asymmetric synthesis;\textsuperscript{6} i.e. the use of chirally modified reagents to control diastereofacial selectivity. Prior to the initiation of our work, two classes of chirally modified allylic boron reagents had been reported - the bornanediol derived boronates \textsuperscript{23} and pinene derived borane \textsuperscript{24a}.\textsuperscript{8a}
Reagents 23 described by Hoffmann appeared unsuitable for our purposes, due to their marginal selectivity in reactions with chiral aldehydes\(^7\) (see e.g. Scheme III and Chapter II of this thesis). Their modest enantioselectivity (30-70% ee) with substituted achiral aldehydes (see e.g. Scheme XXIV, Chapter II of this thesis) also discouraged further studies.\(^{7b,c}\)

While borane 24\textsubscript{a} and the recently reported reagents 24\textsubscript{b-d} displayed quite impressive levels of enantioselectivity in reactions with achiral aldehydes\(^8\) (see Scheme XXV, Chapter II of this thesis), we felt that due to the well known borotropic shift of allylic boranes\(^9\) (which
results in (E)-(Z) isomerization of acyclic reagents$^{10}$ extension of this methodology to crotyl reagents would be problematical.

In light of these considerations, and in spite of the fact that Hoffmann had already devoted considerable effort towards the development of effective chiral boronates, we decided to initiate studies on the design of more selective reagents. Since the lack of symmetry in chiral reagents such as$^{23}$ complicates predictions and analyses of stereoselectivity our strategy from the outset was predicated on two factors: the chiral auxiliary should be symmetrical (preferably of$^{C_2}$ symmetry, thereby reducing the degrees of freedom available to the reagent), and should be readily available. In this chapter, therefore, we describe studies leading to the development of tartrate ester modified allylboronates - the most highly enantioselective allylic boronates reported to date and the first chiral allylmetal compounds to display useful levels of mismatched diastereoselection in reactions with chiral aldehydes.
2. Reactions of Pinacol Allylboronate (25) with 
\( \alpha,\beta \)-Dialkoxyaldehydes 3 and 4\(^{11}\)

To aid in the design of efficient chiral reagents we felt that a thorough study of the factors influencing aldehyde diastereofacial selectivity was warranted. In particular, an understanding of the influence of solvent, temperature, and boronate structure on stereoselectivity was deemed important. Accordingly, a detailed study of the reactions of pinacol allylboronate (25)\(^{12}\) with aldehydes 3 and 4 was undertaken\(^{13}\) to complement the work of Adam mentioned earlier (Scheme I) and to define a model system suitable for effective screening of chiral auxiliaries.\(^ {14}\)

Results of this study are summarized in Table I. It is readily apparent that the reactions of 25 with 3 and 4 are more selective than those involving (E)-crotylboronate 2 but less so than with the (Z)-crotyl reagent 1 (compare Scheme I). It is also apparent that these reactions are mildly sensitive to solvent and temperature. Maximal selectivity for 26 was obtained in CH\(_2\)Cl\(_2\) at -78\(^{0}\)C (80:20; entry 1);\(^{13}\) the same reaction at 23\(^{0}\)C gave a slightly lower ratio (77:23, entry 2). Interestingly, the reactions in toluene and hexane (entries 3-6) were slightly more selective at 23\(^{0}\)C than at -78\(^{0}\)C, but maximal selectivity in either case was less than that obtained in CH\(_2\)Cl\(_2\). While the reaction in ether (entry 7) was also mildly discriminating (77:23), the use of more polar solvents such as THF or DMF (entries 8-9) resulted in decreased selectivity. This may well be the consequence of coordination of the boron atom by solvent, resulting in
Table I

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Ratio 26:27&lt;sup&gt;b,c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>-78°</td>
<td>80:20&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>23°</td>
<td>77:23</td>
</tr>
<tr>
<td>3</td>
<td>toluene</td>
<td>-78°</td>
<td>71:29</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>23°</td>
<td>73:27</td>
</tr>
<tr>
<td>5</td>
<td>hexane</td>
<td>-78°</td>
<td>75:25</td>
</tr>
<tr>
<td>6</td>
<td>hexane</td>
<td>23°</td>
<td>79:21</td>
</tr>
<tr>
<td>7</td>
<td>ether</td>
<td>23°</td>
<td>77:23</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>23°</td>
<td>71:29</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>0-23°</td>
<td>58:42</td>
</tr>
<tr>
<td>10</td>
<td>toluene, (+)-DIPT (1 equiv)</td>
<td>-78°</td>
<td>80:20</td>
</tr>
<tr>
<td>11</td>
<td>CH₂Cl₂, (+)-DIPT (1 equiv)</td>
<td>-78°</td>
<td>79:21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
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<th>Ratio 28:29&lt;sup&gt;b,c&lt;/sup&gt;</th>
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<td>CH₂Cl₂</td>
<td>-78°</td>
<td>90:10&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>CH₂Cl₂</td>
<td>23°</td>
<td>87:13</td>
</tr>
<tr>
<td>14</td>
<td>toluene</td>
<td>-78°</td>
<td>90:10</td>
</tr>
<tr>
<td>15</td>
<td>toluene</td>
<td>23°</td>
<td>87:13</td>
</tr>
<tr>
<td>16</td>
<td>THF-nBuLi (1 equiv)&lt;sup&gt;g&lt;/sup&gt;</td>
<td>-78°-23°</td>
<td>79:21</td>
</tr>
</tbody>
</table>
Key to Table I

(a) All analytical scale reactions were performed by addition of 1.5 equiv of aldehyde to a solution of 25 (0.2 M) at the indicated temperature. See experimental section for details.

(b) Ratios of 25:27 and 28:29 were determined by gas chromatographic analysis (0.25 m x 10 4.1% Carbowax on Chrom. G column) before chromatographic purification.

(c) Alcohols 26 and 27 are known compounds (ref. 7a, 14a).

(d) The isolated yield of 26 and 27 was 75-79% in preparative scale experiments (1.0 equiv of 3, 1.2 equiv of 25; product purified by chromatography and distillation).

(e) Alcohols 28 and 29 were separated by careful preparative TLC. Spectroscopic and analytical data for both isomers is reported in the experimental section. Stereochemical assignments were confirmed by methanalysis (1:1 MeOH:HOAc, reflux) to the corresponding triols which were compared with authentic samples (ref. 15).

(f) The yield of a 90:10 mixture of 28 and 29 was 85% in preparative scale experiments (see experimental section).

(g) One equiv of n-Buli in hexane was added to 25 in THF at -78°C followed by addition of 4.
a change of reaction mechanism.\textsuperscript{16} Finally, performing the reaction in the presence of 1 equiv of (+)-DIPT gave interesting results: the selectivity in toluene was increased to 80:20 (compare entries 10 and 3) while in CH\textsubscript{2}Cl\textsubscript{2} the selectivity was essentially unchanged (entries 11 and 1). These last two results most likely reflect changes in solvent polarity rather than intimate involvement of (+)-DIPT in the transition state.

The reaction of 25 with threonine derived aldehyde 4, in contrast to that with 3, was considerably more selective (Table I). Identical product ratios (90:10) were obtained using either CH\textsubscript{2}Cl\textsubscript{2} or toluene solutions at -78\textdegree C; reactions at 23\textdegree C were only slightly less selective (entries 12-15). The selectivity was significantly affected only when an ate complex derived from n-BuLi was used (79:21 ratio, entry 16).\textsuperscript{16}

The source of the greater anti facial preference of 4 relative to 3 (also apparent in their reactions with (Z)-crotylboronates)\textsuperscript{3} was probed by using cyclohexylidene ketal derivative 30\textsuperscript{17} as a substrate. The reaction of 30 and 25 resulted in virtually the same ratio of anti/syn products 34-anti and 34-syn as obtained with 3 (entry 2, Table I). The greater selectivity observed with 4 thus appears to be a function of the C.4 methyl moiety and not the diol protecting group.

Consideration of the results obtained for aldehyde addition reactions of crotylboronates has led Roush, Adam and Harris to suggest that the stereochemical course of such reactions is strongly influenced by
non-bonded interactions in the competing transition states\textsuperscript{3,5}. Specifically, the relative contributions of transition states A-D (Scheme IV)\textsuperscript{18} are decisive in determining facial selectivity in additions to

Scheme IV

aldehydes 3 and 4. The observation that the reactions of allylboronate 25 display intermediate selectivity relative to the extrema observed with (Z)- and (E)-crotyl reagents is consistent with this analysis. Consideration of the transition states leading to anti adduct 31 reveals that both A and B should be more accessible in reactions involving allylboronate 25 ($R_1=R_2=H$) than (E)-crotylboronate 2 ($R_1=H; R_2=CH_3$) since steric interactions involving $R_2$ are less serious when $R_2=H$.\textsuperscript{19a} Transition state C, however, is less significantly affected by changing $R_2$ from CH$_3$ to H\textsuperscript{19b} and as a result the reactions of 25 are somewhat more anti selective than those of 2. Similar comparison of transition states B, C and D for 25 ($R_1=R_2=H$) and (Z)-crotylboronate 1 ($R_1=CH_3; R_2=H$) reveals that syn selective transition states C and D are much more accessible for 25 than for 1, consistent with our finding that 25 is less anti selective than 1.

On the basis of the steric effects outlined above it is perhaps
surprising that the reactions of 25 display a substantial (4-9:1) net anti selectivity, since the steric interactions in the two most important transition states (B and C) appear comparable. We initially attributed this effect to the involvement of Felkin transition state A in this series.\textsuperscript{11,19a} However, it may be that the electronic activation expected of a Cornforth-like transition state (i.e., B)\textsuperscript{20b,c} actually accounts for the enhanced anti selectivity of these reactions (B>C). This must be considered a likely possibility since the results obtained in this laboratory for reactions of 3 and 4 are much more anti selective (with (Z)-crotyl, allyl and (E)-crotylboronates) than the corresponding reactions with α-methyl branched aldehydes reported by Hoffmann.\textsuperscript{2g} Since the latter electrophiles are much less subject to polar effects, our data can be reconciled with Hoffmann's only by invoking an anti selective stereoelectronic effect which is superimposed on the steric interactions highlighted here.\textsuperscript{3,11}

In summary, these reactions are perhaps best viewed as [3,3]-sigmatropic rearrangements of intermediate allylic boronate-aldehyde complexes (a bis-hetero-1,5-diene system) in which the stereochemical outcome is strongly influenced by steric effects.\textsuperscript{21} It is clear, however, that the structure of the aldehyde also plays an important role in determining stereoselectivity and that conventional acyclic stereochemical theories do not adequately account for the observed results.\textsuperscript{20}

Considering the objectives of this study, the experiments with allylboronate 25 served a dual purpose. In one respect they added an important piece to the puzzle of analyzing, predicting and explaining the source of diastereofacial selectivity in reactions of allylic boronates with chiral aldehydes. In another respect the mediocre selectivities observed with 25 reinforced our belief that recourse to chirally modified reagents
is necessary to achieve synthetically useful levels of stereoselectivity. Finally, the temperature and solvent effects summarized in Table I hint that both variables may possibly play a role in defining levels of stereoselectivity in allylic boronate-aldehyde addition reactions.

3. Chemistry of Chiral Allylic Boronic Esters

A. Methods of Preparation

We initially envisioned that chiral allylic boronic esters could be prepared by esterification of allylboronic acid with the appropriate diol (Scheme V, Method A). Although this approach indeed proved feasible, it was inconvenient since the instability of necessitated its preparation immediately before use in each preparation of 37. This greatly burdened exploratory experiments where a range of diols were examined as chiral auxiliaries. The instability of (especially when neat) also precluded an exact determination of its yield, thus requiring estimation of the amount of diol required for esterification. Nevertheless, reagents containing a slight excess of diol (generally 0.3-1.0 equiv) were
readily obtained via this procedure and in fact our early work utilized reagents prepared in this manner. In many cases it is possible to remove excess diol via distillation of the reagents if so desired.

An alternative approach involved transesterification of diisopropyl allylboronate 38 with an appropriate diol (Scheme VI, Method B). Boronate

\[
\begin{align*}
\text{Ph}_3\text{H}/
\end{align*}
\]

38 is easily stored under Ar at 0°C and provides a convenient source of a protected equivalent of 35. Transesterification proceeds smoothly and allows the simple preparation of 37 as needed. This procedure was used in most of the exploratory work described in this chapter, including the preparation of many of the tartrate-based reagents for which data are presented. This route, however, was not completely satisfactory since the diisopropyl boronate 38 prepared from 35 invariably contained ca. 25% of triisopropyl borate 39 which could not be separated efficiently by

\[
\text{B(O}_2\text{-Pr)}_3
\]

(39)

distillation. The use of a slight excess of diol in the transesterification step, however, assured the complete esterification of all boron species and provided material which typically contained 50-65% of \( r_{37} \), 25-35% of diol 36 and 10-15% of impurity derived from 3923
(data for preparation of tartrate diol based reagents). Nonetheless, reactions with reagents prepared in this way were reproducible and gave essentially identical results as with reagents prepared via Method A.

A more aesthetically pleasing procedure (Method C) for preparing 37 is shown in Scheme VII. This involves the reaction of triallylborane 40 with an appropriate diol 36. While this route requires the preparation of triallylborane (40), this precursor to 37 is easily stored under Ar (0°C) and can be used as required. More significantly, the reactions leading to 37 are clean, simple and high-yielding, allowing the preparation of very pure reagents (>95% yield).

In conclusion, reagents prepared via each of these three procedures (Schemes V-VII; Methods A-C) give essentially identical results in aldehyde addition reactions. Although procedure C is considered the method of choice for preparing very pure reagents, Method A may be preferable when large quantities of 37 are required for use in a single operation.

B. Aldehyde Addition Reactions

Considering the objective of using readily available chiral adjuvants
of $C_2$ symmetry we initially focussed our attention on diols 41 and 42.

\[
\begin{align*}
&\text{Me} & \text{OH} \\
&\text{Me} & \text{OH} \\
&\text{Me} & \text{OH} \\
&\text{Me} & \text{OH} \\
\end{align*}
\]

Diol 41 proved quite effective in the homologation sequence described by Matteson, where chiral boronates 44 were obtained with excellent 

\[
\begin{array}{c}
\text{Me} \quad \text{O} \quad \text{B-} \quad \text{R} \\
\text{Me} \quad \text{Cl} \\
\end{array}
\]

\[\text{L.CHCl}_2\]

\[\text{THF, -78°C} \]

\[
\begin{align*}
&\text{Me} \quad \text{O} \quad \text{B-} \quad \text{R} \\
&\text{Me} \quad \text{O} \\
&\text{Me} \quad \text{O} \\
&\text{Me} \quad \text{O} \\
\end{align*}
\]

R=CH$_3$, Ph, Bu, CH$_2$Ph 

91-96% diastereoselectivity

Both diols have also been used as chiral auxiliaries in allylsilane additions to acetals, and we hoped that they might prove effective here. Thus, boronates 45 and 46 were prepared as shown in Scheme VIII. Reagent 46, prepared via reaction of 42 with triallylborane (40), was obtained as a pure compound upon removal of solvent, while reagent 45 was obtained via Method A as a mixture with 25% Et$_2$O after distillation.

**Scheme VIII**

\[
\begin{align*}
&\text{HO}_2\text{B-} \quad \text{Me} \quad \text{OH} \\
&\text{Et}_2\text{O} \\
&\text{Me} \quad \text{OH} \\
&\text{Me} \quad \text{OH} \\
\end{align*}
\]

The reactions of 45 and 46 with various aldehydes are summarized in Table II. It is readily apparent that both diols are ineffective in enhancing or significantly altering aldehyde facial selectivity relative to results obtained with the achiral pinacol allylboronate (25). For example,
### Table II

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Diol</th>
<th>Conditions</th>
<th>Product Ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(45)</td>
<td>(+)-2, 3-butanediol (41)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°-23°C</td>
<td>81 : 19</td>
</tr>
<tr>
<td>2</td>
<td>(45)</td>
<td></td>
<td>toluene, -78°c&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76 : 24</td>
</tr>
<tr>
<td>3</td>
<td>(46)</td>
<td>(+)-2, 4-pentanediol (42)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°C</td>
<td>68 : 32</td>
</tr>
<tr>
<td>4</td>
<td>(25)</td>
<td>pinacol (47)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°C</td>
<td>80 : 20</td>
</tr>
<tr>
<td>5</td>
<td>(45)</td>
<td>(+)-2, 3-butanediol (41)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°-23°C</td>
<td>86 : 14</td>
</tr>
<tr>
<td>6</td>
<td>(25)</td>
<td>pinacol (47)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°C</td>
<td>90 : 10</td>
</tr>
<tr>
<td>7</td>
<td>(45)</td>
<td>(+)-2, 3-butanediol (41)</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;, -78°-23°C</td>
<td>17% e.e. c,d</td>
</tr>
<tr>
<td>8</td>
<td>(46)</td>
<td>(+)-2, 4-pentanediol (42)</td>
<td>toluene, -78°C</td>
<td>3% e.e. c,d</td>
</tr>
</tbody>
</table>

**Key to Table II**

(a) Ratio of products determined by gas chromatographic analysis (0.25"x10' 4.1% Carbowax/Chrom. G column).

(b) 1 equiv of 41 was added to reagent 45 before addition of 3.

(c) Enantiomeric excesses were determined by analysis of product Mosher ester derivatives.<sup>27</sup>

(d) The absolute configuration (S) in both cases was assigned by comparison of the optical rotations with the literature value (ref. 8a).
reaction of 3 with chiral reagent 45 affords an 81:19 ratio of 26:27 (entry 1) while the achiral reagent 25 affords an 80:20 mixture of the same products (entry 4). The selectivity obtained with (-)-2,4-pentanediol derived reagent 46 was 68:32 (entry 3) indicating marginal selectivity in a mismatched sense. The reaction of 45 with aldehyde 4 (also mismatched) afforded only an 86:14 ratio of 28:29 (entry 5), in contrast to that of achiral reagent 25 which afforded 90:10 selectivity (entry 6). Finally, while reagent 45 was marginally enantioselective during reaction with benzaldehyde (17% e.e.; entry 7) the (−)-2,4-pentanediol derived reagent 46 afforded virtually racemic product (3% e.e.; entry 8).

These sobering results indicated that significant improvements in selectivity would require further experimentation with other diols. However, our efforts in this area were thwarted by the failure of several diols to form boronate esters via reaction with 38 (Method B). Thus, R-(+)-BINAL (51) failed to provide any allylboronate species, while mannitol diacetonide (52) gave only a trace of product (<10%). The major products in the latter case appeared to be 52 and its decomposition

![Chemical Structures](image)

products. Likewise, diol 53 failed to produce an identifiable product, while diol 54 failed to react completely. Evidently the formation of a
7-membered ring in the case of diols 51 and 53 and an 8-membered ring with 54 is unfavorable, resulting in lack of product formation. We therefore turned our attention to other chiral auxiliaries.

Tartrate esters comprise an attractive family of chiral diols since they are commercially available in both antipodal forms. These diols have found extensive use, both as chiral starting materials as well as chiral auxiliaries in the Sharpless asymmetric epoxidation. We therefore attempted the preparation of tartrate modified boronate 56 using readily available (+)-diisopropyl tartrate ((+)-55; Scheme IX). Treatment of allyl boronic acid (38) with (+)-55 indeed provided the desired boronate 56, as a ca. 1:1 mixture with 55. Initial results obtained from reaction of 56 with glyceraldehyde acetonide (3) and benzaldehyde (48) (Scheme X)

![Scheme IX](image)

![Scheme X](image)
indicated that boronate 56 was superior to the chiral reagents investigated initially. The reaction of 56 and 3 in toluene afforded a 93:7 mixture of 26:27, in contrast to the 71:29 ratio obtained with pinacol allylboronate (25; Table I). Obtention of alcohol 49 of 61% e.e. from the reaction with benzaldehyde also was encouraging as a first step. We therefore decided to further investigate the utility of tartrate diols as chiral auxiliaries.

The results of reactions of a variety of tartrate modified reagents with chiral aldehydes 3 and 4 are shown in Table III. Data are included for reagents prepared by methods A, B and C. It is noteworthy that the chiral tartrate ester auxiliary effectively enhances or overrides the intrinsic facial selectivity of aldehydes 3 and 4, as measured in reactions with achiral pinacol allylboronate (25). Thus, while aldehyde 3 displays only modest facial selectivity in reactions with achiral 25 (entries 3,4), selectivity for anti adduct 26 is enhanced to 96:4 by using reagent (-)-56 prepared from (+)-DIPT. More importantly, switching from (-)-56 to (+)-56 effectively reverses the facial selectivity, affording syn isomer 27 with 90:10 selectivity (entry 6). This sequence thus makes possible the most selective preparation of either 26 or 27 yet reported. In a similar manner the reagent (+)-56 prepared from (-)-DIPT enhances the selectivity for anti adduct 28 to 98:2 (entry 7), in contrast to the 90:10 ratio obtained using achiral reagent 25 (entries 8,9). The highest selectivity for syn adduct 29 is achieved using the antipodal reagent (-)-58 prepared
Table III

Reactions of Chiral Allylic Boronic Esters with Chiral Aldehydes 3 and 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Diol b</th>
<th>Method c</th>
<th>Conditions</th>
<th>Product Ratio d (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(-)-56</td>
<td>(+)-DIPT [(+)-55]</td>
<td>A, B, C</td>
<td>CH₂Cl₂, -78°C</td>
<td>96:4 (91%) e</td>
</tr>
<tr>
<td>2</td>
<td>(-)-56</td>
<td>(+)-DIPT [(+)-55]</td>
<td>B</td>
<td>toluene, -78°C</td>
<td>93:7 (86%) e</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>pinacol (47)</td>
<td>A</td>
<td>CH₂Cl₂, -78°C</td>
<td>80:20 (75%) f</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>pinacol (47)</td>
<td>A</td>
<td>toluene, -78°C</td>
<td>71:29 f</td>
</tr>
<tr>
<td>5</td>
<td>(+)-56</td>
<td>(-)-DIPT [(-)-55]</td>
<td>B</td>
<td>CH₂Cl₂, -78°C</td>
<td>39:61</td>
</tr>
<tr>
<td>6</td>
<td>(+)-56</td>
<td>(-)-DIPT [(-)-55]</td>
<td>B, C</td>
<td>toluene, -78°C</td>
<td>10:90 (79%) g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Diol b</th>
<th>Method c</th>
<th>Conditions</th>
<th>Product Ratio d (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>(-)-56</td>
<td>(-)-DIPT [(-)-55]</td>
<td>B</td>
<td>CH₂Cl₂, -78°C</td>
<td>98:2 (98%) e</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>pinacol (47)</td>
<td>A</td>
<td>CH₂Cl₂, -78°C</td>
<td>90:10 (85%) f</td>
</tr>
<tr>
<td>9</td>
<td>25</td>
<td>pinacol (47)</td>
<td>A</td>
<td>toluene, -78°C</td>
<td>90:10 f</td>
</tr>
<tr>
<td>10</td>
<td>(-)-56</td>
<td>(+)-DIPT [(+)-55]</td>
<td>A</td>
<td>CH₂Cl₂, -78°C</td>
<td>71:29</td>
</tr>
<tr>
<td>11</td>
<td>(-)-56</td>
<td>(+)-DIPT [(+)-55]</td>
<td>B</td>
<td>toluene, -78°C</td>
<td>36:64</td>
</tr>
<tr>
<td>12</td>
<td>(-)-58</td>
<td>(+)-DET [(+)-57]</td>
<td>B</td>
<td>toluene, -78°C</td>
<td>32:68 (63%) g</td>
</tr>
<tr>
<td>13</td>
<td>(-)-60</td>
<td>(+)-DAT [(+)-59]</td>
<td>A</td>
<td>toluene, -78°C</td>
<td>40:60</td>
</tr>
</tbody>
</table>
Key to Table III

(a) Analytical scale reactions were performed by addition of 1.5 equiv of aldehyde to an anhydrous 0.25 M solution of allylboronic ester at -78°C. Reaction times were typically 24-48 h. Workup consisted of dilution with water and extraction with ether.

(b) Diol used in preparation of boronate ester. Tartrate allylboronates 56, 58 and 60 contained 0.2-0.7 equiv of excess tartrate ester.

(c) Method used for reagent preparation (see text and experimental).

(d) Ratios of 26:27 and 28:29 were determined by gas chromatography (0.25" x 10' 4.1% Carbowax/Chrom. G column).

(e) Yields are for preparative scale experiments and are based on aldehyde as limiting reagent (see experimental section).

(f) See experimental section.

(g) Yield based on boronate as limiting reagent.
from (+)-diethyl tartrate ((+)-57) which affords 29 with 68:32 selectivity (entry 12).

Several features of these reactions deserve further comment. It is especially significant that the mild solvent selectivity observed with reagent 25 (entries 3, 4, 8, 9; see also Table I) is dramatically manifested with the chiral tartrate reagents. Apparently methylene chloride enhances anti selectivity in the matched cases (cf. entries 1, 2) while toluene enhances syn selectivity in the mismatched sense (entries 5, 6, 10, 11). This effect is particularly significant in the mismatched reactions of 3 where selectivity for syn adduct 27 increases from 61:39 in CH₂Cl₂ (entry 4) to 90:10 in toluene (entry 5). With aldehyde 4 the major product from the mismatched reaction with (-)-56 is in fact still the anti adduct 28 (71:29) when CH₂Cl₂ is used as solvent (entry 10); only with toluene is it possible to achieve syn selectivity for 29 (entries 11-13). It is also interesting that diethyl tartrate appears to be more efficient in mismatched reactions with 4 than either diisopropyl or diadamantyl tartrate 33 (entries 11-13).

The effect of excess (free) tartrate on selectivity was investigated in some detail for the mismatched reaction of (+)-56 with 3 (Table IV).
**Table IV**

**Effect of Excess (-)-DIPT on the Reaction of (+)-56 and 3**

<table>
<thead>
<tr>
<th>(-)-DIPT (equiv)</th>
<th>Ratio 26:27</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8:92</td>
</tr>
<tr>
<td>0.13</td>
<td>7:93</td>
</tr>
<tr>
<td>0.20</td>
<td>8:92</td>
</tr>
<tr>
<td>0.30</td>
<td>9:91</td>
</tr>
<tr>
<td>0.40</td>
<td>10:90</td>
</tr>
<tr>
<td>1.20</td>
<td>12:88</td>
</tr>
<tr>
<td>2.50</td>
<td>15:85</td>
</tr>
</tbody>
</table>

**Key to Table IV**
(a) Reactions were performed in toluene at -78°C as described in Table I (1.5 equiv of 3, 1.0 equiv of 56).
(b) Equivalents of excess DIPT (relative to 56) present in each experiment.

Pure (+)-56 was readily prepared via reaction of triallylborane (40) with a slight deficiency (0.85 equiv) of (-)-DIPT (>95% yield). Additional (-)-DIPT was then added to give the final quantities indicated. The results of these experiments show that maximal selectivity for 27 occurs when the concentration of excess tartrate is minimized (0-0.2 equiv), and that larger excesses of DIPT have only a modest negative effect on stereoselectivity. The use of a slight excess (ca. 0.2 equiv) of tartrate is recommended, however, to prevent adventitious hydrolysis of the moisture sensitive reagents.

As expected, these reagents also undergo enantioselective reactions with achiral aldehydes (Table V). Highest selectivity was obtained with
Reactions of Chiral Allylic Boronic Esters with Achiral Aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Reagent</th>
<th>Diol</th>
<th>Method</th>
<th>Conditions</th>
<th>Yield</th>
<th>% e.e.</th>
<th>(config)</th>
</tr>
</thead>
</table>
| 1     | 2,2-dimethylpropionaldehyde
(61) | (-)-56  | (+)-DIPT | B  | toluene, -78°C | -     | 80     | (S)      |
| 2     | cyclohexanecarboxaldehyde
(62) | (-)-56  | (+)-DIPT | A  | toluene, -78°C | 77    | 78     | (S)      |
| 3     | "                    | (+)-56  | (-)-DIPT | B  | toluene, -78°C | 70    | 82     | (R) (87) |
| 4     | benzaldehyde
(48) | (-)-56  | (+)-DIPT | A  | toluene, -78°C | 66    | 61     | (S)      |
| 5     | "                    | (-)-56  | (+)-DIPT | A  | CH₂Cl₂, -78°C  | 55    | 54     | (S)      |
| 6     | "                    | (-)-56  | (+)-DIPT | A  | CH₂Cl₂, 23°C   | 61    | 30     | (S)      |
| 7     | "                    | (-)-60  | (+)-DAT  | B  | CH₂Cl₂, -78°C  | -     | 60     | (S)      |
| 8     | "                    | (+)-58  | (-)-DET  | B  | CH₂Cl₂, -78°C  | -     | 20     | (R)      |
| 9     | decanal
(63) | (-)-56  | (+)-DIPT | B  | toluene, -78°C | 96    | 58     | (R)      |
| 10    | "                    | (-)-56  | (+)-DIPT | B  | CH₂Cl₂, -78°C  | 98    | 26     | (R)      |
Key to Table V

(a) See Table III.
(b) See Table III.
(c) Yield of chromatographically purified product. The yield in entry 1 was not determined owing to the volatility of the product.
(d) Optical purities were determined by $^1$H NMR analysis of the Mosher ester derivatives.27
(e) Absolute configurations for all products except entries 9 and 10 were assigned by comparison of the optical rotations with those reported in the literature (see ref. 8a and 26b).
(f) Absolute configuration assigned by analogy to the other examples.
(g) In a recent experiment using pure (+)-56 prepared via Method C reaction with cyclohexanecarboxaldehyde (62) afforded product of 87% e.e. This result indicates that the other examples in this table must be considered unoptimized, since reagents used in each case contained excess (ca. 0.5-1 equiv) DIPT. See text for further discussion.
hindered, branched aldehydes 61 and 62 (78-82% e.e.; entries 1-3) and modest selectivity (ca. 60% e.e.) with aromatic (48; entry 4) and unbranched aliphatic (63; entry 9) aldehydes. It must be pointed out that these data were obtained with reagents prepared via methods A and B (containing up to 1 equiv of free tartrate) and are thus unoptimized (cf. Table IV). Indeed, preliminary results using pure (+)-56 prepared via procedure C indicate that higher levels of enantioselectivity are achieved when no free DIPT is present. Specifically, reaction of cyclohexanecarboxaldehyde with (+)-56 in toluene at -78°C afforded product of 87% e.e., a marked improvement over previous results, and of much significance for future work with achiral substrates. Entries 4-6 and 9, 10 indicate that toluene is superior to CH₂Cl₂ as solvent and that low temperature is necessary to achieve maximal selectivity (entries 5, 6).

Finally, although reagent 58 derived from (-)-DET is clearly inferior to 56 in these reactions (entries 4, 5 vs 8), diadamantyl tartrate³³ derivative 60 may be slightly better (cf. entries 5 and 7).

The results outlined above are in contradistinction to those of Brown⁸a,d and Hoffmann⁷b,c whose reagents generally display highest selectivity with unbranched aldehydes. It is noteworthy that the tartrate modified reagents are more highly enantioselective than Hoffmann's 3-phenyl-exo-2,3-bornadiol derivatives ²³⁷b,c except in reactions with simple unsubstituted systems (e.g. entry 9). Although the chiral allylic borane reagents ²⁴ give superior results, especially in reactions with unbranched aldehydes, the selectivity obtained here with pivaldehyde (entry 1) and recently with cyclohexanecarboxaldehyde approaches that obtained by Brown for the same or related substrates.
The source of selectivity in these reactions constitutes an intriguing aspect of this chemistry. Any hypothesis regarding the basis of selectivity must account both for the relatively small effect of ester bulk (cf. entries 11-13, Table III) as well as the impressive effect of solvent on selectivity. Moreover, both reagents 45 and (-)-56 (with chiral adjuvants of opposite chirality) induce the same absolute configuration during carbonyl addition reactions (compare Tables II and III). The results obtained with the tartrate-based reagents are consistent with the transition state models A and B, where A is favored based on electrostatic repulsive interactions involving the aldehydic oxygen atom and the β-face ester group which destabilizes B relative to A. These interactions are possible since a favored conformation of α-heteroatom substituted carbonyl systems is one in which the heteroatom and carbonyl are syncoplanar. Thus, while the ester carbonyl can come reasonably close to the aldehydic oxygen in either A or B, the non-bonded electron pair of the aldehydic carbonyl interacts more strongly with the cis ester group in B than in A. The role of the tartrate ester in these reactions is thus substantially different than in the reactions of chiral allenylboronates.
described by Yamamoto, who advances a steric argument to explain the effect of the chiral diol on stereoselectivity. Presumably selectivity in these reactions is a result of nonbonded interactions between the aldehydic R substituent and the tartrate ester moieties, in which case the transition state shown below would be favored.

![Diagram]

To the best of our knowledge, the electrostatic model proposed here is only the second example where selectivity in reactions of a chiral reagent is not primarily steric in origin. This model is supported by the data in Tables III-V where greatest selectivity in reactions of 56, 58 and 60 with achiral aldehydes and in mismatched reactions with 3 and 4 occurs in media of lowest dielectric constant (toluene vs toluene-tartrate ester mixtures vs CH$_2$Cl$_2$). It is not clear, however, why CH$_2$Cl$_2$ is more effective than toluene in promoting anti selectivity, both with the achiral pinacol reagent 25 and the tartrate reagent (-)-56 (cf. entries 1-4; Table III). It appears likely that there is some influence of solvent on the distribution of rotamers A-D in the transition state (Scheme IV), although the nature of this effect remains obscure. In final analysis it appears that the selectivity in these reactions is the result of a complex balance between steric and electronic effects of the substrate, reagent and solvent.

Finally, the use of tartramide 64 and (-)-tartaric acid 65 as chiral
auxiliaries was briefly investigated. Both diols might be expected to be more selective than the tartrate esters in light of the electrostatic repulsion argument set forth earlier, since the carbonyl oxygens in 64 and 65 should be more electron-rich. Unfortunately, neither 64 nor 65 gave readily identifiable products upon attempted boronate formation. Thus, the reaction of 64 with allylboronic acid yielded a product of unknown structure, which upon treatment with glyceraldehyde acetonide (3) afforded a 71:29 ratio of 26:27. This sequence was not pursued further. Similarly, the reaction of allylboronic acid and tartaric acid gave a new compound of undetermined structure which was not pursued.

C. Summary

The tartrate modified boronate compounds described here constitute an interesting class of reagents which should prove useful in synthesis. From a mechanistic standpoint they are very interesting in light of the proposed electrostatic origin of selectivity and illustrate that the design of highly effective asymmetric reagents needs not depend exclusively on steric considerations. Most significantly, the results obtained here with
allylboronates suggest that the tartrate diols hold much promise for increasing the selectivity of the (E)-crotylboronates and therefore that much interesting chemistry remains to be discovered.
EXPERIMENTAL SECTION
\(^1\)H NMR spectra were measured at 250 or 270 MHz on a Bruker WM-250 or WM-270 instrument. Chemical shifts are reported in \(\delta\) units relative to internal \(\text{CHCl}_3\) (7.24 ppm). \(^{13}\)C NMR spectra were measured at 69 MHz on a Bruker 270 using the 77.0 ppm resonance of \(\text{CDCl}_3\) as internal standard. \(^{11}\)B NMR spectra were measured at 28.7 MHz on a Jeol FX-90Q instrument and are reported in \(\delta\) units relative to external \(\text{BF}_3\)-\(\text{OEt}_2\). Infrared spectra were measured on a Perkin-Elmer Model 237B Infrared Spectrophotometer and were calibrated with the 1601 cm\(^{-1}\) absorption of polystyrene. Low and high resolution mass spectra were measured at 70 eV on a Finnegan MAT 8200 instrument. Optical rotations were measured on a Rudolph Autopol 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 (120°C) and/or flame dried glassware under atmospheres of dry argon or nitrogen. All solvents were freshly distilled before use: THF, \(\text{Et}_2\text{O}\) and toluene were distilled from Na-benzophenone ketyl; \(\text{CH}_2\text{Cl}_2\) was distilled from CaH\(_2\).

Gas chromatographic analyses were carried out using a Perkin-Elmer Sigma 3 instrument equipped with a 0.25" x 10' 4.1% Carbowax/Chromosorb G column. 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 PF 254 indicator (Analtech). Preparative thin layer chromatography was performed on 20 x 20 cm plates coated with 0.25 or 0.5-mm thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with diethyl ether. Flash chromatography was performed
as described by Still,\textsuperscript{42} using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh). All chromatography solvents were distilled prior to use.
Method A

Allylmagnesium bromide (10.0 mL of freshly prepared 0.94 M solution in ether, 9.4 mmol, 0.9 equiv) and a solution of freshly distilled trimethyl borate (1.07 g, 10.3 mmol) in 10 mL of ether were added simultaneously, but separately over a 30 min period to 10 mL of ether maintained at -78°C. The mixture was stirred at -78°C for 3 h (mechanical stirring is required due to the heavy precipitate) and then was warmed to 0°C at which point 10 mL of cold (0°C) 2 M aqueous HCl was added. The two phase mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with 10 mL portions (4X) of 5:1 Et₂O-CH₂Cl₂. The combined extracts were dried (Na₂SO₄), filtered and concentrated in vacuo without removal of all of the solvent (anhydrous, concentrated allylboronic acid is unstable). TLC analysis (2:1 EtOAc-hexane, I₂ visualization) showed a single spot at Rf 0.57.

One half of the crude allylboronic acid prepared above (theoretically 4.7 mmol) was dissolved in 10 mL of anhydrous ether under Ar. L-(+)-diisopropyl tartrate (1.07 g, 4.6 mmol) was added and the solution was stirred at 23°C for 14 h. Anhydrous MgSO₄ (ca. 1 g) was added and 20 min later the solution was filtered under Ar. The filtrate was concentrated, diluted with THF and again concentrated in vacuo, and finally heated at 90°C at 1-2 mm Hg for 30 min to remove final traces of
volatile materials. This gave 1.35 g of a colorless oil which proved to be a 61:39 mixture of \((-\))-56 and \((+\))-DIPT (NMR analysis). This mixture therefore contained 0.89 g (3.0 mmol) of 56 (65% yield based on allylmagnesium bromide).

A second portion (approximately 25%) of the crude allylboronic acid 35 was esterified with 498 mg (2.13 mmol) of D-\((-\))-DIPT using the procedure described above to give 604 mg of a 68:32 mixture of 56 and DIPT (440 mg, 1.4 mmol of 56, 65% yield).

Since completion of this work, recent experiments by a coworker have revealed that the tartrate ester derived reagents (e.g. 56) can be obtained free of DIPT via distillation (Kugelrohr, 75°C, 0.01 torr), a fact which further enhances the utility of this method for their preparation.

Analytical and physical data for 56 is included following the experimental procedure for method C.
Method B

Allylboronic acid was prepared from 162 mmol of allylmagnesium bromide and 135 mmol of trimethyl borate using the procedure described in Method A. A solution of the crude acid in 300 mL of reagent grade benzene was treated with 200 mmol of isopropanol (2 equiv assuming a 75% yield of allylboronic acid) and heated to reflux until evolution of H₂O was complete (Dean-Stark trap). The solution was then fractionally distilled to give 7.5 g (bp 62-64°C, 40 mm) of a 3:1 mixture of diisopropyl allylboronate (38) and triisopropylborate (NMR analysis). Such mixtures could not be separated efficiently, and we have been so far unsuccessful in attempts to suppress formation of triisopropyl borate. Consequently, material prepared in this manner was used directly in the next step. Data for mixture of 38 and triisopropyl borate: ¹H NMR (CDCl₃, 250 MHz) δ 5.98-5.80 (m, 1 H), 4.92 (br d, J=17.0 Hz, 1 H), 4.88 (br d, J=12.1 Hz, 1 H), 4.45-4.28 (m of 18 lines, -OCH(CH₃)₂ of 38 and triisopropyl borate, 3 H total), 1.69 (d, J=8.3 Hz, 2 H), 1.3-1.08 (series of d, CH(CH₃)₂ of 38 and triisopropyl borate, 22 H total).

To a solution of diisopropyl allylboronate (38) [2.83 g of a 3:1 mixture containing triisopropyl borate, thus 2.1 g (12.1 mmol) of 38] in 15 mL of dry THF was added 4.18 g (17.9 mmol, 1.1 equiv per boron present) of (-)-DIPT. The solution was stirred at 23°C for 24 h and then all volatiles
were removed in vacuo [rotary evaporation followed by exposure to vacuum (1-2 mm Hg) at 100° C, 30 min]. NMR analysis of the colorless oil thus obtained (5.6 g) indicated a 53:33:14 mixture of (+)-56, (-)-DIPT, and a minor tartrate containing impurity, presumably deriving from triisopropyl borate. This mixture, therefore, contained roughly 3.1 g of (+)-56 (90% yield based on available allylboronate). Tartrate modified boronates prepared in this manner were typically 50-65% pure, containing 25-35% of free tartrate ester and 10-15% of the triisopropyl borate-derived impurity.

Analytical and physical data for 56 is included following the experimental procedure for Method C.
Method C

To a solution of 238 mg (1.78 mmol) of triallylborane (40) in 2.4 mL of dry THF under Ar was added 354 mg (1.51 mmol, 0.85 equiv) of D-(-)-diisopropyl tartrate. This mixture was stirred at room temperature for 2 h and then was heated at reflux for 1 h. The solution was cooled and all volatile components (including excess triallylborane) were removed in vacuo (1 mm Hg, 23°C) to give pure (+)-56 in quantitative yield: 

\[ [\alpha]^2 \text{D} + 47.9^\circ \] (c=1.96, CH\textsubscript{2}Cl\textsubscript{2}); \( ^1\text{H} \text{NMR (CDCl}_3, 270 \text{ MHz}) \delta 5.91-5.78 \) (m, 1 H), 5.15-4.93 (overlapping m's, 4 H), 4.74 (s, 2 H), 1.98 (d, J=7.3 Hz, 2 H), 1.26 (d, J=6.2 Hz, 12 H); \( ^1\text{H} \text{NMR (toluene-d}_8, 250 \text{ MHz}) \delta 6.03-5.86 \) (m, 1 H), 5.06 (d, d, J=1.5, 17 Hz, 1 H), 4.96 (br d, J=11.4 Hz, 1 H), 4.85 (quint, J=6.2 Hz, overlapping s at 4.81, 4 H total), 1.86 (d, J=7.2 Hz, 2 H), 0.93 (d, J=6.6 Hz, 12 H); \( ^{13}\text{C} \text{NMR (CDCl}_3, 69 \text{ MHz}) \delta 168.8, 132.6, 115.8, 77.7, 70.0, 21.5; ^{11}\text{B} \text{NMR (CDCl}_3, 28.7 \text{ MHz}) \delta 35 \) (broad; sample contained 17% (+)-DIPT); IR (CH\textsubscript{2}Cl\textsubscript{2}) 3065, 2980, 2940, 2880, 1750, 1640, 1535, 1490, 1470, 1375 (br), 1280 (br), 1220 (br), 1145, 1100, 985, 960, 910, 820 cm\textsuperscript{-1}.

Reagents prepared in this manner can be stored at 0°C under Ar for several weeks without apparent decomposition. Hydrolysis readily occurs, however, upon exposure to moist air, wet solvents, or upon TLC analysis.
General Procedures for Tartrate Modified Allylboronate-Aldehyde Additions

Reagent (-)-56 was prepared from 913 mg (6.81 mmol) of triallylborane and 1.92 g (8.18 mmol, 1.2 equiv) of (+)-DIPT in 9 mL of THF using the procedure described in Method C. This gave 2.24 g (97%) of a 4.8:1 mixture of (-)-56 and (+)-DIPT (NMR analysis).

To a solution of 1.64 g of this reagent [containing 1.40 g (4.9 mmol) of (-)-56] in 10 mL of dry CH₂Cl₂ at -78°C was added dropwise a solution of 0.53 g (4.1 mmol) of freshly distilled D-glyceraldehyde acetonide (3) in 6.4 mL of dry CH₂Cl₂. The resulting mixture was kept at -78°C until reaction was judged complete by TLC analysis and then was worked up by pouring into water and extracting with ether (80 mL). The aqueous phase was washed with additional portions of ether (3x20 mL). The combined organic extracts were dried (Na₂SO₄), filtered, and then solvent was removed in vacuo. In experimental runs the composition of the crude product was determined by GC analysis before continuing on to the next step.

The residue was dissolved in ether (50 mL), treated with aqueous 1 M KOH (50 mL), and stirred vigorously at 23°C for 25 h. The aqueous phase was separated and extracted with ether (4x20 mL). The combined organic
extracts were washed with saturated aqueous NaHCO₃ (40 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was then distilled (Kugelrohr, 90°C, 1 mm Hg) to give 596 mg (85%) of a 95.3:4.7 mixture of 26:27 (GC analysis, 0.25" x 10' 4.1% Carbowax on Chrom G column). Stereochemical assignments for these known compounds⁴d,¹⁴a were confirmed by repeating the correlation studies described by Mulzer.¹⁴a

A preparative scale experiment (480 mg of 3) using (-)-56 prepared via Method B (ratio of 56 to free (+)-DIPT to impurity = 2.8:1:1) afforded 578 mg (91%) of a 96:4 mixture of 26:27. The same result was obtained in analytical scale experiments using reagent prepared via Method A.

Data for 26 (96% isomeric purity): [α]D²⁰ + 16° (c=1.80, CHCl₃); Rf 0.40 (1:1 ether-hexane); ¹H NMR (CDCl₃, 250 MHz) δ 5.92-5.75 (m, 1 H), 5.15 (d, J=16 Hz, 1 H), 5.13 (d, J=10.5 Hz, 1 H), 4.05-3.87 (m, 3 H), 3.77 (d, q, J=8.8, 4.4 Hz, 1 H), 2.43-2.10 (m, 2 H), 2.0 (d, J=3.4 Hz, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H); IR (neat) 3470 (br), 3070, 2980, 2915, 2890, 1660, 1360, 1240, 1205, 1150, 1060, 980, 910, 855 cm⁻¹; mass spectrum m/e 157 (M-15).
To a solution of 1.32 g of reagent (+)-56 prepared from (−)-DIPT as described in procedure B [a 6.4:2.6:1 mixture of 56, (−)-DIPT, and impurity; containing, therefore, 0.87 g (3.1 mmol) of (+)-56] in 13.4 mL of dry toluene at −78°C was added dropwise a solution of freshly distilled D-glyceraldehyde acetonide (3, 0.598 g, 4.60 mmol, 1.5 equiv) in 4.5 mL of toluene. The solution was kept at −78°C until reaction was judged complete by TLC analysis, and then was worked up using the procedure described for preparation of 26. Distillation of the crude product (Kugelrohr, 80–90°C, 1 mm Hg) afforded 420 mg (79%) of a 90:10 mixture of 27:26 (GC analysis). This mixture is not easily separated by chromatography (Rf 0.40, 1:1 ether-hexane). Separation of the diastereomers, however, is easily accomplished after benzoylation according to Mulzer's procedure.\textsuperscript{14a}

Data for 27 (90% isomeric purity): [α]_D\textsuperscript{20} = 10.2° (c=1.82, CHCl₃); \textsuperscript{1}H NMR (CDCl₃, 250 MHz) δ 5.93-5.76 (m, 1 H), 5.12 (d, J=17 Hz, 1 H), 5.11 (d, J=10.5 Hz, 1 H), 4.07-3.95 (m, 2 H), 3.78-3.67 (m, 1 H), 3.58 (quint, J=6.3 Hz, 1 H), 2.27-2.19 (m, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H); IR (neat) 3480 (br), 3080, 2980, 2930, 2890, 1645, 1375, 1260, 1215, 1160, 1060, 915, 860 cm\textsuperscript{-1}.  

To a solution of 1.97 g of (+)-56 prepared from (-)-DIPT according to Method B [a 3.8:2.3:1 mixture of 56, DIPT and impurity; containing, therefore, 1.1 g (3.8 mmol) of 56] in 7.7 mL of dry CH₂Cl₂ at -78°C was added dropwise a solution of freshly distilled 4 (584 mg, 3.18 mmol) in CH₂Cl₂ (5 mL). The mixture was maintained at -78°C until reaction was judged complete by TLC analysis, and then was worked up using the general procedure described for preparation of 26. The crude product was distilled (Kugelrohr, 120°C, 2 mm Hg) to give 680 mg (94%) of a 98:2 mixture of 28 and 29 (GC analysis).

Data for 28 (98% isomeric purity): [α]_D^{19} + 9.7° (c=2.03, CHCl₃); R_f 0.35 (2:1 hexane-ether); ^1H NMR (CDCl₃, 250 MHz) δ 5.92-5.76 (m, 1 H), 5.15 (br d, J=16.3 Hz, 1 H), 5.14 (br d, J=11.5 Hz, 1 H), 4.09 (d, q, J=7.7, 6.1 Hz, 1 H), 3.79-3.71 (br m, 1 H), 3.49 (d, d, J=5.5, 7.8 Hz, 1 H), 2.43-2.32 (m, 1 H), 2.26-2.14 (m, 1 H), 1.97 (d, J=3.0 Hz, 1 H), 1.70-1.50 (m, 9 H), 1.48-1.3 (m and overlapping d, J=6.0 Hz, 5 H); IR (neat) 3450 (br), 3080, 2940, 2870, 1642; mass spectrum, m/e 226 (M⁺).


Diastereomer 29 could be purified by careful preparative TLC (4:1 hexane-ether, multiple elutions) of 28/29 mixtures: [α]_D^{19} + 7.9° (c=0.19, CHCl₃); R_f 0.38 (2:1 hexane-ether); ^1H NMR (CDCl₃, 250 MHz) δ 5.91-5.78 (m, 1 H), 5.12 (br d, J=17.7 Hz, 1 H), 5.10 (br d, J=9.9 Hz, 1 H), 4.04 (d, q,
J=7.9, 6.1 Hz, 1 H), 3.60-3.45 (series of m, 2 H), 2.30 (br t, J=7.1 Hz, 2 H), 2.12 (d, J=7.7 Hz, 1 H), 1.7-1.5 (m, 8 H), 1.48-1.3 (m, 2 H), 1.27 (d, J=6.0 Hz, 3 H); high resolution mass spectrum, obsd. 226.1568 (+0.002), C_{13}H_{22}O_{3} requires 226.1569.

In some experiments a small amount (0-5%) of a third diastereomer 66 was produced. This compound derives from erythro aldehyde 67, small amounts of which (<5%) are present in the various batches of 4 used in this study. Data for 66: ^1^H NMR (CDCl$_3$, 250 MHz) $\delta$ 5.93-5.76 (m, 1 H), 5.19 (br d, J=11.7 Hz, 1 H), 5.18 (br d, J=15 Hz, 1 H), 4.34 (d, q, J=5.7, 6.5 Hz, 1 H), 3.79 (d, d, J=5.6, 8.8 Hz, 1 H), 3.75-3.65 (m, 1 H), 2.68-2.55 (m, 1 H), 2.26-2.14 (5 lines, 1 H), 1.68-1.50 (br m, 8 H), 1.45-1.30 (br m, 2 H), 1.28 (d, J=6.4 Hz, 3 H).

Stereochemical assignments for 28, 29 and 66 were confirmed by methanolysis to the corresponding triols which were compared with authentic samples (see general experimental procedure).
General methanolysis procedure: A solution of alcohol 29 (1 mg) in CH$_3$OH/HOAc (1 mL each) was heated at reflux for 25 h. The solvent was then removed in vacuo, azeotroping several times with CH$_2$Cl$_2$ and the residue was pumped at <0.1 torr (23°C). Comparison of the $^1$H NMR spectrum of the triol so obtained with that of an authentic sample$^{15}$ revealed the stereochemistry to be as shown. Analogous experiments with 28 and 66 confirmed the relative stereochemistry assigned to each.
General Procedure for Achiral Aldehyde Additions (Described for decanal)

To a solution of 140 mg of (-)-56 prepared from (+)-DIPT according to method B [a 3.3:1:1.5 mixture of 56, DIPT and impurity; containing, therefore, 80 mg (0.28 mmol) of (-)-56] in 1.5 mL dry toluene at -78°C was added neat decanal (66 mg, 0.42 mmol, 1.5 equiv). The mixture was maintained at -78°C for 3 days, and then was worked up by adding the cold reaction mixture to water (5 mL) and extracting with ether (4x5 mL). The combined extracts were dried (Na$_2$SO$_4$), filtered and then solvent was removed in vacuo. Purification of the residue by preparative thin layer chromatography (2-0.5 mm plates, 3:1 hexane-ether) afforded 54 mg (96%) of addition product. Analytical and physical data for each product are listed below.

Enantiomeric excesses were determined in each case by conversion of the product alcohol to its $\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetate (MTPA derivative$^{27}$ and integration of its $^1$H NMR spectrum.
Data for 68: 58% e.e.; (R)-configuration assigned by analogy to configurations observed for 69-71 and to results obtained with 3 and 4.  
$[\alpha]_D^{20} +5.0^\circ$ (c=2.20, CHCl$_3$); R$_f$ 0.44 (3:1 hexane-ether); $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 5.89-5.73 (m, 1 H), 5.11 (d, t, J=1.1, 13.9 Hz, 2 H), 3.61 (br m, 1 H), 2.35-2.23 (m, 1 H), 2.17-2.08 (m, 1 H), 1.54 (d, J=3.9 Hz, 1 H), 1.50-1.35 (br m, 3 H), 1.35-1.20 (br m, 13 H), 0.86 (t, J=6.1 Hz, 3 H); IR (neat) 3360 (br), 3080, 2935, 2860, 1645, 1465, 900 cm$^{-1}$; mass spectrum m/e 157 (M-41).

Data for 49: 66% yield, 61% e.e.; (S)-configuration assigned by comparison of optical rotation with literature value (ref. 8a).  
$[\alpha]_D^{23} -30.8^\circ$ (c=1.91; benzene); R$_f$ 0.51 (2:1 hexane-ether); $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.35-7.2 (m, 5 H), 5.80 (m, 1 H), 5.15 (br d, J=17.5 Hz, 1 H), 5.13 (br d, J=9.2 Hz, 1 H), 4.72 (t, J=6.6 Hz, 1 H), 2.60-2.40 (m, 2 H).
Data for 70: 77% yield, 78% e.e.; (S)-configuration assigned by comparison of optical rotation with literature value (ref. 26b).

\[ \alpha \]_D^{22} -8.3^\circ \quad \text{(c=0.12; abs. EtOH); R_f 0.62 (1:1 hexane-ether);} \quad ^1H \text{ NMR (CDCl}_3, 250 \text{ MHz)} \delta 5.90-5.73 \text{ (m, 1 H)}, 5.12 \text{ (d, J=15.4 Hz, 1 H)}, 5.11 \text{ (d, J=11.9 Hz, 1 H)}, 3.37 \text{ (m, 1 H)}, 2.4-2.25 \text{ (m, 1 H)}, 2.2-2.15 \text{ (m, 1 H)}, 1.9-1.5 \text{ (series of m, 7 H)}, 1.45-0.9 \text{ (series of m, 7 H).}

Data for 71: Yield not determined owing to volatility (~83% recovery after chromatography), 80% e.e.; (S)-configuration assigned by comparison of optical rotation with literature value (ref. 8a).

\[ \alpha \]_D^{20} -3.8^\circ \quad \text{(c=1.51, benzene); R_f 0.52 (3:1 hexane-ether);} \quad ^1H \text{ NMR (CDCl}_3, 250 \text{ MHz)} \delta 5.74 \text{ (m, 1 H)}, 5.02 \text{ (br d, J=15.3 Hz, 1 H)}, 5.01 \text{ (br d, J=11.4 Hz, 1 H)}, 3.14 \text{ (br d, J=10.6 Hz, 2 H)}, 2.32-2.20 \text{ (m, 1 H)}, 1.92-1.79 \text{ (m, 1 H)}, 1.47 \text{ (br s, 1 H, OH), 0.80 (s, 9 H).}
Preparation of Pinacol Allylboronate (25)

\[
\begin{align*}
\text{(MeO)}_3B & \xrightarrow{1) \text{MgBr}} \text{O-B} \\
& \xrightarrow{2) \text{H}_3\text{O}^+} \text{O} \\
& \xrightarrow{3) \text{OH}} \text{O} \\
\end{align*}
\]

The general procedure of Matteson was followed (ref. 12). Thus, allylmagnesium bromide (182 mL of 1.2 M solution in ether, 0.22 mol) and a solution of freshly distilled trimethyl borate (25 g, 0.24 mol, 1.1 equiv in 157 mL ether) were added simultaneously, but separately, over a 2.5 h period to 200 mL of ether maintained at -78°C. The mixture was stirred at -78°C for 2.5 h (mechanical stirring is required due to the heavy precipitate) and then was warmed to 0°C at which point 233 mL of cold (0°C) 2 M aqueous HCl was added. The two phase mixture was stirred at room temperature for 1 h and then the aqueous layer was extracted with 150 mL portions (4x) of 5:1 ether-CH₂Cl₂. The combined extracts were dried (Na₂SO₄), filtered and concentrated in vacuo without removal of all of the solvent (anhydrous, concentrated allylboronic acid is unstable).

The solution of allylboronic acid was diluted to 500 mL with anhydrous ether under argon, treated with anhydrous pinacol (19.4 g, 164 mmol, 0.75 equiv) and stirred at room temperature (14 h). Anhydrous Na₂SO₄ was added and the solution was filtered through adsorbent cotton. Distillation (b.p. 55-60°C; 30 torr, lit.12 50-53°C, 5 torr) afforded 19.4 g (53% from allylmagnesium bromide) of 25. Rₖ 0.6 (23:2 hexane-ether); ¹H NMR (CDCl₃, 250 MHz) 5.85 (m, 1 H), 4.97 (br d, J=16 Hz, 1 H), 4.93 (br m, J=9 Hz, 1 H), 1.72 (d, J=7.5 Hz, 2 H), 1.24 (s, 12 H); IR (neat) 3085, 2985, 2940, 1640, 1350 (br), 1272, 1214, 1145 (br), 1114, 992, 970, 900, 878, 847 cm⁻¹; mass spectrum m/e 168 (M+).
General Procedure for Pinacol Allylboronate-Aldehyde Additions

To 437 mg (2.60 mmol, 1.2 equiv) of pinacol allylboronate (25) in 7 mL of dry CH$_2$Cl$_2$ at -78°C was added dropwise 400 mg (2.17 mmol) of freshly distilled in 7 mL dry CH$_2$Cl$_2$. After 2 h at -78°C the mixture was allowed to warm to room temperature with the cooling bath in place. The mixture was stirred at 23°C (3 days) and then added to water (40 mL) and washed with ether (6x40 mL). The combined organic extracts were dried (Na$_2$SO$_4$), filtered and solvent was removed in vacuo. Purification of the residue by flash chromatography (silica gel, 40 mm column, 2:1 hexane-ether) afforded 415 mg (85%) of a mixture of 28 and 29. Analysis by gas chromatography (both before and after purification) indicated that the ratio of 28/29 was 90:10.

Repetition of this procedure using D-glyceraldehyde acetonide (3) as substrate (1.0 g, 7.7 mmol) afforded 1.0 g (75%) of a 3.5:1 mixture of 26/27 (analysis by gas chromatography).

Analytical and physical data for 26, 27, 28 and 29 are summarized in the experimental section describing their preparation via chirally modified boronate reagents (vide supra).
REFERENCES


10. In a recent publication Brown has demonstrated the apparent lack of borotropic isomerization in reagent i which undergoes highly enantioselective aldehyde addition reactions. It is not clear, however, that such isomerization is in fact averted. The isomers resulting from a borotropic shift in this case are diastereomers, thus raising the possibility that the reported enantioselective reactions reflect the equilibrium mixture of reagents or that one diastereomer reacts much faster with electrophiles than the other. No configurationally stable, well-defined acyclic crotvlboranes have been described in the literature to date.


13. The reaction of 3 with 25 has been reported previously, but the effect of solvent and temperature has not been examined (see ref. 7a).

14. We prefer to use chiral aldehydes such as 3 and 4 for studying reagent facial selectivity, since product analysis of diastereomers by gas chromatography is straightforward. Studying enantioselectivity (an approach taken by many other practitioners in this field) is by comparison much more tedious, requiring purification and further derivatization and/or careful NMR studies with chiral shift reagents for optical purity analysis. For references to the use of aldehydes 3 and 4 as stereochemical probes see refs. 1c, 3 and: (a) Mulzer, J.; Angermann, A. Tetrahedron Lett. 1983, 24, 2843. (b) Mead, K.; Macdonald, T.L. J. Org. Chem. 1985, 50, 422.


18. Transistion states A-B and C-D are derived from successive 120° rotations about the aldehyde C.1-C.2 bond. Discussion of these distinct rotameric structures is meaningful since each should have a relatively high rotational barrier in the transition state (see: Caramella, P.; Rondan, N.G.; Paddo-Row, M.N.; Houk, K.N. J. Am. Chem. Soc. 1981, 103, 2438). On the basis of careful analysis of space-filling molecular models rotamers ii and iii were considered to have serious steric interactions and thus have been excluded from this discussion.
19. (a) We believe that transition state A does not contribute significantly to the reactions of (E)− or (Z)-crotylboronates (see ref. 3). (b) Transition state D is probably insignificant in reactions of (E)-crotylboronates.


21. Several unsuccessful attempts were made to detect intermediate boron-aldehyde ate complexes iv in the reaction of benzaldehyde (48) and boronate 25 by low temperature 1H NMR experiments. Unfortunately, no signals other than those arising from 48, 25 and 49' were observed. Similar results were obtained by following the reaction of 48 and 25 by 11B NMR at 23°C. These data suggest that the equilibrium concentration of iv is very small or that formation of iv is slow and that decomposition to 49' is very fast. In either case, the steady state concentration of iv is apparently too low to allow detection by NMR techniques.

\[
\begin{array}{c}
\text{CHO} \\
\text{(25)}
\end{array} \quad \xrightarrow{\text{Ph}} \quad \left[ \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \right] \quad \xrightarrow{\text{C}} \quad \left[ \begin{array}{c}
\text{O} \\
\text{B}
\end{array} \right]
\]


23. The composition of these reagents was established by integration of their 1H NMR spectra before use.


25. Diols 41 and 42 are commercially available from Aldrich Chemical Co.


28. Diol 53 was obtained via reaction of v with PhMgCl.

\[
\begin{array}{c}
\text{O} \\
\text{COOEt}
\end{array} \quad \text{v} \quad \begin{array}{c}
\text{O} \\
\text{COOEt}
\end{array}
\]

29. Diol 54 was kindly provided in racemic form by J. Hawkins of Professor Sharpless's laboratory.
30. L-(+)-diethyl tartrate, L-(+)- and D-(−)-diisopropyl tartrate were obtained from Aldrich Chemical Co.


33. L-(+)-diadamantyl tartrate was synthesized from tartaric acid using methods developed by Professor K.B. Sharpless.

34. Excess triallylborane was removed in vacuo at the end of the reaction.

35. The selectivity predicted on steric grounds is opposite to that observed with the tartrate based reagents, but consistent with results obtained with boronate 45 (R=CH₃; Table II). Nonbonded interactions of the R substituent and axial allylic hydrogen in the cyclic transition state presumably would favor vi over vii.

36. Stereochemical studies of crotylboronate-aldehyde addition reactions strongly suggest that R of RCHO occupies an equatorial position of a cyclic transition state (ref. 2a).


40. NMR studies of carbonyl compounds suggest that solvent-carbonyl association occurs in aromatic solvents. It is possible that a such association of toluene with the tartrate ester carbonyl moieties plays a role in augmenting the selectivity of these reagents. This may also explain the slightly better selectivity observed with diethyl tartrate vis-a-vis diadamantyl tartrate in mismatched reactions with 4, where solvent association would be disfavored by the bulky adamantyl group. For general discussion of this phenomenon see: (a) Karabatsos, G.J.; Fenoglio, D.J.; Lande, S.S. J. Am. Chem. Soc. 1969, 91, 3572. (b) Karabatsos, G.J.; Taller, R.A. Tetrahedron 1968, 24, 3923.

41. Tartramide 64 was prepared from L- (+)-diethyl tartrate via the general procedure of Sharpless. See: Lu, L.D.-L.; Johnson, R.A.; Finn, M.G.; Sharpless, K.B. J. Org. Chem. 1984, 49, 728. We thank M.G. Finn for providing details of this procedure.


43. Interactions of lone pair electrons on oxygen require explicit consideration during molecular mechanics calculations on oxygenated compounds, suggesting that such interactions are significant. For a general discussion of this phenomenon see: Benkert, U.; Allinger, N.L. "Molecular Mechanics", American Chemical Society, USA, 1982.

44. The first such example was noted in the asymmetric reduction of ketones with BINAL modified reducing agents. See: (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. J. Am. Chem. Soc. 1984, 106, 6709. (b) Noyori, R. Pure Appl. Chem. 1981, 53, 2315.
CHAPTER IV

SYNTHETIC APPLICATION OF A FUNCTIONALIZED ALLYLBORONATE:
PREPARATION OF AN ANTIBIOTIC X-14547A SYNTHETIC INTERMEDIATE
1. Introduction

Antibiotic X-14547A (1) has attracted considerable attention since initial reports in 1978 of its structure and activity. As a structurally unique member of the ionophore class, X-14547A displays potent gram-positive antibacterial activity, antitumor activity, and ruminant growth promotant properties. Remarkably, X-14547A is able to transport mono-, di- and trivalent cations across solvent barriers, even though it has only a single tetrahydropyranyl residue. While X-14547A crystallizes as a 2:1 complex with (p-bromophenethyl) ammonium ion, kinetic data suggest that it functions as a 1:1 complex with Pr$^{3+}$ during cation transport.

Several unique structural features distinguish X-14547A from other members of its class, including the 1,3-butadiene moiety, pyrrole ring and trans-fused hexahydroindene system. The hypothesis by Roush, Myers and Peseckis that the biosynthesis of 1 may involve an intramolecular Diels-Alder reaction led to the retrosynthetic analysis shown in Scheme I. Following this analysis, a successful synthesis of 1 was developed by Peseckis. 

Scheme I

\[
\begin{align*}
1 & \rightarrow 2 \\
3 & \rightarrow 4 + 5
\end{align*}
\]
However, a key problem in this synthesis was the lack of a suitable route to intermediate 6, a precursor of fragment 4. Three initial routes to 6

(or its synthetic equivalent 9) are summarized in Scheme II. Each presented various difficulties, necessitating the further search for an effective route to this compound. 7

The first approach (a) utilized an Evans type alkylation of 7 with allyl iodide. Conversion to aldehyde 9 proceeded smoothly, although the optical purity of 9 could not be rigorously established. 8 Further multistep conversions of 9 afforded pentaene 11 which was selectively oxidized to 12 using a 9-BBN hydroboration-oxidation sequence. However, 12 could not be separated from the hydroboration byproduct cis-1,5-cyclooctanediol. In addition, the 1H NMR spectrum of 12 revealed the presence of multiple diastereomers, the spectra of which were inconsistent with simple olefinic isomers. Since optically pure 3 (derived from natural X-14547A) was used in the conversion of 10 to 11, the obtention of diastereomers was tentatively attributed to either a lack of optical purity in 10 (and by extension 9) or racemization at one of the epimerizable centers in 3 during the coupling reaction. Although this route was abandoned, 12 served as a convenient relay point for assessing the optical purity of intermediates in approaches b and c.

A second strategy involved the stereoselective nucleophilic opening of
epoxides 15 (route b) or 20 and 23 (route c). In the approach outlined in route b epoxide 15 was obtained via a Sharpless asymmetric epoxidation of 14. Unfortunately, several attempts to open epoxide 15 with ethyl organometallic reagents resulted in formation of mixtures of 16, 17 and 18. The best results were obtained using either Et₄AlNa, Et₂Mg or EtMgBr-CuI (but not Et₃Al which gave substantially racemized 19) resulting in essentially optically pure 19 as verified by conversion to 12. However, the low yields (18-31%) of 6 necessitated discontinuing this approach.

An alternative route (c) involved hydride opening of tri-substituted epoxides 20 and 23. Again mixtures of regioisomers were obtained, but more significantly, the optical rotations observed for 19 were consistently lower than for 19 prepared via sequence b. This indicated that either racemization was occurring during the reduction step or, more probably, that the epoxides 20 and 23 derived from Sharpless epoxidations were of inferior optical purity. The low optical purity of 19 from route c was verified by conversion to diastereomeric 12.

In spite of these problems, sufficient quantities of material were available via sequence b (Et₄AlNa or Et₂Mg routes) for Peseckis to complete the synthesis. Clearly, however, a need remained for an efficient route to aldehyde 6.
Scheme II

**Pathway a**

1) LDA, THF  
2) R'CH = CH  

1) LiAlH₄  
2) DMSO/SO₃⁻ pyr

(R'O)₂P  
R' = CH₃, i-Pr

**Pathway b**

1) 9-BBN  
2) H₂O₂, NaOH

1) TBHP, Ti(Oi-Pr)₄  
2) (+)-DIPT

**Pathway c**

1) NaIO₄  
2) Wittig

R = TBDPS
2. Synthesis of Aldehyde 6 via Allylboronate Chemistry

We recognized the possibility of preparing this intermediate by exploiting boronate chemistry similar to that used previously in our laboratory. In particular, we imagined that aldehyde 6 could be prepared from boronate adduct 28, which in turn would be formed (hopefully with high selectivity) during reaction of reagent 27 with D-glyceraldehyde acetonide.

![Scheme III](image)

(26, Scheme III). The key task thus became preparation of the highly functionalized (Z)-substituted boronate reagent 27.

Envisioning an approach along the lines of equation 1, we felt that 27 could be prepared via reaction of (Z)-alkenyllithium reagent 29 with pinacol halomethylboronate 28 (equation 1). Our initial attempt at

![Equation 1](image)

preparing 29 involved preparation of (Z)-bromide 31 from the readily available acetylene 30. Treatment of 30 with catechol borane (1.1 equiv)
followed by heating at 68-72°C, treatment with bromine (2.2 equiv) at -20°C (CH₂Cl₂, 1 h) and 2.2 equiv of aqueous NaOH (0°C, 1 h) provided the desired bromide 31 in 53% yield after chromatography (equation 2). Unfortunately, attempts to metallate 31 (t-BuLi, -120°C; Li⁺-Et₂O, -78°C) were unsuccessful and resulted only in the isolation of acetylene 30 or olefin 32.

We next turned to iodide 34, which was expected to undergo efficient metallation. Iodination of 30 proceeded smoothly (n-BuLi-THF, 1.3 equiv; I₂, 1.6 equiv) to acetylenic iodide 33, which was reduced to (Z)-iodide 34 via a hydroboration-protonolysis sequence (equation 3).

Lithiation of 34¹² indeed proved to be straightforward, with no complications arising from acetylide formation. Treatment of an ethereal solution of 34 at -78°C with 2.2 equiv of t-BuLi (1 h) provided the desired vinyllithium species 29. The -78°C solution of 29 was then transferred
via cannula to a \(-78^\circ\text{C}\) ethereal solution of 28\textsuperscript{14} (1.0 equiv) and the resulting mixture was stirred at \(-78^\circ\text{C}\) for at least seven hours before being warmed to room temperature. Removal of lithium salts via precipitation with CH\(_2\)Cl\(_2\)-pentane provided the desired boronate 27 (70%,

Scheme IV)

![Scheme IV](image)

Scheme IV). However, examination of the \(^1\text{H}\) NMR spectrum of crude 27 revealed the presence of several additional olefinic species. These compounds were separable by chromatography, and such purification afforded pure 27 as well as olefin 32 and alkenylboronate 35.\textsuperscript{15} The ratio of 27:32:35 was determined to be 70:24:5 by integration of the \(^1\text{H}\) NMR spectrum of the crude reaction product. While olefin 32 presumably arises from protonation of alkenyllithium 29, the source of 35 is more perplexing. The amount of alkenylboronate 35 formed is ca. 5% if the reaction mixture is maintained at \(-78^\circ\text{C}\) for \(>7\) h; if the temperature rises above \(-78^\circ\text{C}\) either during or after addition to 28, the amount of 35 increases. As much as 23% of 35 was obtained if the reaction mixture was allowed to warm immediately to room temperature after addition of 29.
Several attempts to suppress the formation of olefin 32 were unsuccessful. Varying the amounts of t-BuLi, iodide $34$ or chloride $28$ did not decrease the amount of $32$ which formed. Attempts to carefully dry and purify iodide $34$ (and chloride $28$) were likewise unsuccessful in altering the amount of $32$ produced. Since the presence of $32$ and $35$ is not detrimental in reactions of boronate $27$ the crude mixtures of $27/32/35$ were routinely used directly in the next step.

With boronate $27$ in hand, we were pleased to find that reaction with aldehyde $26$ indeed proceeded smoothly. Simply adding a $\text{CH}_2\text{Cl}_2$ solution of $27$ to aldehyde $26$ in $\text{CH}_2\text{Cl}_2$ at $-78^\circ\text{C}$ (3 h) followed by warming to room temperature (24 h) afforded adduct $28$ after triethanolamine workup (equation 4). Product $28$ (65-75% based on $26$; 50-52% from iodide $34$) was easily purified by chromatography, effecting complete separation from olefin $32$ and alkenylboronate $35$. In addition to $28$ a minor diastereomer (36) was obtained (4%). Although the stereochemistry of $36$ was not rigorously determined, it is probably as shown by analogy to the results reported by Roush, Adam and Harris. The selectivity for $28$, as determined by product separation and isolation, was typically 10-15:1.

Alcohol $28$ possesses the desired configuration at C.4 for use in a
synthesis of aldehyde 6. In this context the glyceraldehyde acetonide 65 serves as a chiral auxiliary for the preparation of an α-chiral aldehyde.

The remaining conversion of 28 to aldehyde 6 is shown in Scheme V. Hydrogenation of 28 was initially effected with H₂/Pd-C in methanol. However, this procedure was not highly reproducible, and resulted in occasional cleavage of the silyl moiety. Diimide reduction of 28,

Scheme V

however, provided 37 in good yield. This reaction is easily monitored by TLC and excess NH₂-NH₂/NaI₀₄ can be added as required to force the reduction to completion. Heating an acetic acid-methanol-water solution (4:1:1) of 37 for 45 minutes effected smooth acetonide hydrolysis. Again the conversion of 37 to 38 is readily monitored by TLC and reaction can be easily terminated when 37 is consumed, thus avoiding loss of the TBDPS protecting group. Finally, periodate cleavage of triol 38 afforded the desired aldehyde 6 in 93% yield after chromatography. Aldehyde 6 possessed spectral and physical constants, including optical rotation, essentially identical to those reported by Peseckis. This confirms the mode of facial selectivity in the addition of 27 to 26, and also illustrates the utility of the strategy for α-chiral aldehyde synthesis embodied in this sequence. Aldehyde 6 was further transformed to diene ester 19 as described by
Peseckis (equation 5). Careful chromatography afforded 19 as well as a small amount (ca. 5%) of an olefinic isomer 39 (tentative assignment). The rotation observed for 19 \([\alpha]_D^{20} + 8.4^\circ \) (C=1.12; CHCl₃) was slightly higher than that reported by Peseckis \([\alpha]_D^{22} + 7.2-7.8^\circ \) (CHCl₃) for optically pure material. Since the minor isomer 39 possessed a rotation of ca. \([\alpha]_D^{20} -11^\circ \) (C=0.1; CHCl₃) the presence of a small amount of 39 in 19 could account for the lower value reported previously by Peseckis.

The sequence from aldehyde 26 to 6 proceeds in four steps, with an overall yield of 49%. While three steps are required to prepare the boronate 27, the ease of carrying out the reactions as well as the selectivity obtained in the key boronate addition reaction makes this an attractive route for preparing homochiral 6, thereby establishing this sequence as a useful synthetic method.
EXPERIMENTAL SECTION
$^1$H NMR spectra were measured at 250 and 270 MHz on Bruker 250 and 270
ingstruments. Chemical shifts are reported in $\delta$ units relative to internal
CHCl$_3$ ($\delta$7.24). $^{13}$C NMR spectra were measured at 68 MHz on the Bruker 270,
or at 22.5 MHz on a Jeol FX-90Q instrument; Carbon resonances are reported
in $\delta$$_C$ units calibrated against the 77.0 ppm line of CDCl$_3$. $^{11}$B NMR spectra
were measured at 28.7 MHz on the Jeol FX-90Q instrument; boron resonances
are reported in $\delta$$_B$ units relative to external BF$_3$-OEt$_2$ ($\delta$0.00). Infrared
spectra were measured on a Perkin-Elmer Model 283B or 237B Infrared
Spectrophotometer and were calibrated with the 1601 cm$^{-1}$ absorption of
polystyrene. Mass spectra were measured at 70 ev on a Varian MAT 8200
instrument. Melting points were recorded on a Fisher-Johns hot stage
melting point apparatus and are uncorrected. Optical rotations were
measured on a Rudolph Autopol III polarimeter using a 1 cm$^3$ capacity quartz
cell (10 cm path length). Elemental analyses were performed by Robertson
Laboratories, Florham Park, NJ.

All reactions were conducted in oven (120$^\circ$C) and/or flame dried
glassware under atmospheres of dry argon or nitrogen. All solvents were
purified before use. Ether and THF were distilled from sodium benzophenone
ketyl. Methylene chloride and pentane were distilled from calcium hydride. All
other reagents were used as obtained.

Analytical thin layer chromatography (TLC) was performed by using 2.5
cm x 10 cm plates coated with 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- and 0.5-mm
thicknesses of silica gel containing PF 254 indicator (Analtech). Compounds were eluted from the adsorbents with either ethyl acetate or
ether. Flash chromatography was performed as described by Still,\textsuperscript{19} using Kieselgel 60 (230-400 mesh) or Kieselgel 60 (70-230 mesh). Compounds were visualized with short-wave UV light, or by staining with either iodine vapor or charring with ethanolic H\textsubscript{2}SO\textsubscript{4}. All chromatography solvents were distilled prior to use.
To 18.7 g (68.1 mmol) of tert-butylchlorodiphenylsilane in 50 mL of dry DMF at 23°C was added 10.2 g (150 mmol, 2.2 equiv) of imidazole and 6.35 mL (71.5 mmol, 1.05 equiv) of 4-pentyn-1-ol. This mixture was stirred for 41 h and then the pale yellow mixture was diluted with 100 mL of half saturated aqueous NaCl and extracted with 1:1 hexane-ether (5x100 mL). The combined organic extracts were dried, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 40 mm column, 2 liters of hexane and then 1 liter of 3:1 hexane-ether as eluant) to give 21.9 g (100%) of 30: Rf 0.73 (3:1 hexane-ether); $^{1}$H NMR (CDCl$_3$, 270 MHz) $\delta$ 7.71 (m, 4 H), 7.44 (m, 6 H), 3.78 (t, J=5.9 Hz, 2 H), 2.39 (dt, J=2.6, 7.2 Hz, 2 H), 1.95 (t, J=2.6 Hz, 1 H), 1.86-1.76 (m, 2 H), 1.09 (s, 9 H); IR (neat) 3310, 3070, 3050, 2960, 2930, 2860, 2120 (w), 1960 (w), 1890 (w), 1820 (w), 1590 cm$^{-1}$; mass spectrum m/e 265 (M-57), Anal. Calcd. for C$_{21}$H$_{26}$OSi: C, 78.20; H, 8.12. Found: C, 78.53; H, 8.02.
To 18.2 g (56.4 mmol) of acetylene 30 in 550 mL of dry THF at -78°C was added 39.2 mL (73.3 mmol, 1.3 equiv) of 1.87 M n-BuLi in hexane over 20 min. The solution was stirred at -78°C for 1.5 h and then 22.9 g (90.2 mmol, 1.6 equiv) of I₂ was added in three portions. The solution was stirred at -78°C for an additional 30 min and then warmed to -30°C over 1.5 h. The cold solution was poured into 400 mL of H₂O/Et₂O (1:1). Excess I₂ was destroyed by adding solid Na₂S₂O₃ until the brown color dissipated. The aqueous layer was extracted with ether (4×150 mL) and the combined organic extracts were washed successively with saturated aqueous NaHCO₃ (300 mL), saturated aqueous Na₂S₂O₃ (300 mL), and saturated aqueous NaCl (300 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 60 mm column, 48:1 hexane-Et₂O) to afford 24.3 g (95%) of 33: Rf 0.47 (48:1 hexane-ether); ¹H NMR (CDCl₃, 250 MHz) δ 7.68-7.64 (m, 4 H), 7.42-7.34 (m, 6 H), 3.72 (t, J=5.8 Hz, 2 H), 2.53 (t, J=7.0 Hz, 2 H), 1.75 (quintet, J=6.5 Hz, 2 H), 1.04 (s, 9 H); ¹³C NMR (CDCl₃, 68 MHz) δ 135.4, 133.7, 129.5, 127.6, 62.1, 31.3, 26.8, (3-CH₃'s), 19.2, 17.3, -7.1; IR (neat) 3075, 3055, 2960, 2938, 2900, 2862, 1590, 1470, 1428, 1392, 1362, 1187, 1108, 995, 958, 823, 739, 700, 688, 610 cm⁻¹; mass spectrum m/e 391 (M-57); Anal. Calcd. for C₂₁H₂₅SIO: C, 56.25; H, 5.62; I, 28.30. Found: C, 56.43; H, 5.88; I, 27.97.
To 4.71 g (10.5 mmol) of thoroughly dried 33\(^{18}\) was added 18.0 mL (12.6 mmol, 1.2 equiv) of freshly prepared 0.70 M 9-BBN in THF. After being stirred for 30 min at 23\(^{0}\)C the solution was heated to 70\(^{0}\)C. TLC analysis (48:1 hexane-Et\(_2\)O) after 3.5 h indicated complete consumption of 33; thus the mixture was cooled to 23\(^{0}\)C and then 14.4 mL (250 mmol, 24 equiv) of glacial acetic acid was added. TLC analysis (48:1 hexane-Et\(_2\)O) after 15 min showed complete conversion to 34. The reaction mixture was added carefully to 200 mL of cold saturated aqueous Na\(_2\)CO\(_3\) and Et\(_2\)O (1:1). The aqueous layer was extracted with ether (4x100 mL). The combined organic extracts were washed with saturated aqueous NaHCO\(_3\) (200 mL) and dried over MgSO\(_4\). After filtration and removal of solvent in vacuo the residue was purified by flash chromatography (silica gel, 65 mm column, 75:1 hexane-Et\(_2\)O) to afford 3.37 g (71\%) of 34: R\(_f\) 0.46 (48:1 hexane-ether); \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.68-7.64 (m, 4 H), 7.41-7.33 (m, 6 H), 6.19-6.13 (m, 2 H), 3.67 (t, J=6.3 Hz, 2 H), 2.22 (dq, J=5.3, 2.4 Hz, 2 H), 1.66 (quin, J=6.4 Hz, 2 H), 1.04 (s, 9 H); \(^{13}\)C NMR (CDCl\(_3\), 68 MHz) \(\delta\) 140.8, 135.5, 133.8, 129.5, 127.6, 82.6, 63.1, 31.4, 30.9, 26.9, 19.2; IR (neat) 3075, 3055, 2960, 2938, 2862, 1608, 1590, 1472, 1430, 1390, 1362, 1312, 1280, 1242, 1188, 1165, 1108, 1062, 1008, 1000, 938, 824, 808, 738, 702, 690, 612 cm\(^{-1}\); mass spectrum, m/e 393 (M-57); Anal. Calcd. for C\(_{21}\)H\(_{27}\)SiO\(_1\): C, 55.99; H, 6.04; I, 28.17. Found: C, 56.31; H, 6.26; I, 27.98.
To 469 mg (1.04 mmol) of dry 34 in 3 mL of dry Et₂O at -78°C was added dropwise 1.22 mL (2.29 mmol, 2.2 equiv) of 1.87 M t-BuLi in pentane. After being stirred for 1 h at -78°C, the reaction mixture was transferred via cannula to a solution of 184 mg (1.04 mmol, 1.0 equiv) of freshly distilled pinacol chloromethaneboronate¹⁴ in 2 mL of dry Et₂O at -78°C. The reaction mixture was stirred for 7 h and then allowed to warm slowly (with a CO₂/acetone bath in place) to 23°C over 2 h. The mixture was stirred for 12 h at 23°C and then solvent was removed in vacuo. CH₂Cl₂/pentane (1:1) was added to the residue in order to precipitate the lithium halide and the heterogenous mixture was transferred to a centrifuge tube and spun for 10 min. The solid plug was washed twice with CH₂Cl₂/pentane (centrifuge each time) and the organic extracts were combined. After removal of the solvent in vacuo the entire procedure was repeated until addition of CH₂Cl₂/pentane to the oily reaction product caused no further precipitation of LiX. Final removal of volatile compounds in vacuo gave 440 mg of crude product. Analysis by ¹H NMR showed that this material consisted of 71% of 27 (338 mg, 70% yield), 24% of 32 and 5% of 35. Purification of a 100 mg portion by flash chromatography (silica gel, 20 mm column prewashed with Et₂O, 10:1
hexane-Et₂O) provided a sample of 27 (32 mg) contaminated with 7% 35. The yield is low because 27 partially decomposes during chromatography. On a routine basis, crude 27 was used in the next step without purification.

Data for 27: Rf 0.40 (23:2 hexane-ether) H NMR (CDCl₃, 250 MHz) δ 7.68-7.64 (m, 4 H), 7.44-7.32 (m, 6 H), 5.53-5.28 (m, 2 H), 3.65 (t, J=6.5 Hz, 2 H), 2.09 (q, J=7.2 Hz, 2 H), 1.67-1.55 (m, 4 H), 1.21 (s, 12 H), 1.03 (s, 9 H); ¹¹B NMR (CDCl₃, 28.7 MHz), δ 33 (br s); ¹³C NMR (CDCl₃, 69 MHz) δ 135.6, 134.2, 129.5, 129.3, 127.6, 124.5, 63.7, 32.6, 26.9, 24.8, 24.76, 23.4, 19.2; IR (neat) 3075, 3055, 3020, 3000, 2982, 2964, 2940, 2900, 2862, 1592, 1472, 1430, 1382, 1323, 1345, 1330, 1275, 1265, 1218, 1145, 1108, 1030, 1010, 1000, 968, 940, 880, 848, 825, 740, 705, 688, 612 cm⁻¹; mass spectrum m/e 407 (M-57).
To 60.1 mg (0.462 mmol) of freshly distilled glyceraldehyde acetonide (26) in 0.2 mL of dry CH₂Cl₂ at -78°C was added 258 mg (0.55 mmol, 1.2 equiv; amount determined by ¹H NMR integration to be present in 335 mg of crude product from the previous step) of boronate 27 in 0.5 mL of dry CH₂Cl₂. After being stirred for 3 h at -78°C the reaction mixture was warmed to 23°C and stirred for 24 h. Triethanolamine (83 mg, 0.55 mmol, 1.2 equiv) in 2 mL of CH₂Cl₂ was added and stirring was continued for 2 h. The solvent was removed in vacuo and the crude oil so obtained was treated with 3 mL of Et₂O. This mixture (including a precipitate) was transferred to a separatory funnel, extracted with ether (5×5 mL) and the combined organic extracts were dried over MgSO₄. After filtration and removal of the solvent in vacuo the residue obtained was purified by flash chromatography (silica gel, 30 mm column, 2:1 hexane-Et₂O) to afford 139 mg (65%) of 28 and 9 mg (4%) of an isomer of 28 (36) (69% total; 15:1 diastereoselectivity). In repeated preparations of 28 the diastereoselectivity observed was typically 10-15:1; with overall yields of 50-52% from iodide 34: Rf 0.30 (2:1 hexane:ether), 0.43 (1:1 hexane:ether); [α]D²⁰ +15.7° (c=0.67, CHCl₃); ¹H NMR (CDCl₃; 250 MHz) δ 7.66-7.62 (m, 4 H), 7.43-7.32 (m, 6 H), 5.50 (dt, J=17.0, 9.6 Hz, 1 H), 5.07 (dd, J=1.8, 10.3 Hz, 1 H), 4.98 (dd, J=1.7 Hz, 17.1 Hz, 1 H), 4.1 (ddd, J=3.6, 6.4, 7.6 Hz, 1 H), 3.88 (quin, J=7.7 Hz, 2 H), 3.70 (dt, J=2.9, 8.1 Hz, 1 H), 3.63
(t, J=6.4 Hz, 2 H), 2.12 (d, J=2.4 Hz, 1 H), 1.95-1.82 (m, 2 H), 1.65-1.55 (m, 1 H), 1.5-1.2 (m, 2 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.02 (s, 9 H); $^{13}\text{C} \text{ NMR} (\text{CDCl}_3, 69 \text{ MHz}) \delta 138.2, 135.5, 134.1, 129.4, 127.5, 117.2, 108.6, 77.0, 72.6, 63.9, 63.8, 47.2, 29.8, 26.8, 26.7, 26.4, 25.3, 19.2; \text{IR (neat)} 3480, 3080, 3060, 2990, 2965, 2940, 2900, 2865, 1642, 1590, 1462, 1430, 1382, 1374, 1258, 1218, 1194, 1160, 1110, 1062, 1030, 1000, 970, 940, 920, 860, 823, 800, 743, 705, 690, 610 \text{ cm}^{-1}; \text{mass spectrum, m/e 453 (M-15)}; \text{Anal. Calcd. for C}_{28}\text{H}_{40}\text{SiO}_4: C, 71.75; H, 8.60. \text{Found: C, 71.38; H, 8.74.}
To 138 mg (0.294 mmol) of 28 in 6 mL of THF-CH₃OH (1:1) was added 0.69 mL (11.8 mmol, 40 equiv) of an 85% aqueous solution of hydrazine. Two drops of glacial acetic acid were added followed by two drops of saturated aqueous CuSO₄ solution. The mixture was stirred rapidly in an open flask while 315 mg (1.47 mmol, 5 equiv) of NaI₀₄ in 3 mL of H₂O was added over a 60 min period. The reaction mixture was stirred at 23°C for 3 h at which point TLC analysis (1:1 hexane-Et₂O) revealed the presence of 37 with a small amount of 28 still present. After an additional 12 h no change in product composition was observed by TLC analysis. Therefore, an additional 0.69 mL of 85% aqueous hydrazine was added, followed by 5 drops of saturated aqueous CuSO₄ solution. An additional 315 mg of NaI₀₄ in 3 mL of H₂O was added. TLC analysis after 10 h showed the reaction to be complete. The mixture was diluted with 20 mL of H₂O/CH₂Cl₂ (1:1), the layers were separated and the aqueous phase was extracted with CH₂Cl₂ (5x15 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed in vacuo. The residue obtained was purified by preparative thin layer chromatography (silica gel, 1.5 mm plate, 3:2 hexane-Et₂O) to afford 128 mg (93%) of 37: Rᵢ 0.39 (1:1 hexane:ether); [α]ᴰ + 5.70° (c=1.14, CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 7.67-7.64 (m, 4 H), 7.44-7.33 (m, 6 H), 4.13 (m, (X of ABX), 1 H), 3.99-3.86 (A & B of ABX, 2 H), 3.72-3.69 (m, 1 H), 3.64 (t, J=6.1 Hz, 2 H), 1.83 (d, J=3.2 Hz, 1 H,
OH), 1.70-1.45 (m, 3 H), 1.45-1.2 (m, 4 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.03 (s, 9 H), 0.87 (t, J=7.0 Hz, 3 H); $^{13}$C NMR (CDCl$_3$; 68 MHz) $\delta$ 135.6, 134.2, 129.5, 127.6, 76.9, 72.5, 65.2, 64.3, 41.2, 29.9, 28.3, 26.9, 26.6, 25.4, 24.5, 22.4, 19.2, 11.1; IR (neat) 3470, 3080, 3060, 2995, 2970, 2945, 2865, 1590, 1472, 1462, 1430, 1394, 1384, 1373, 1270, 1255, 1217, 1160, 1112, 1088, 1070, 1008, 999, 965, 938, 910, 855, 825, 795, 740, 705, 688, 615 cm$^{-1}$; mass spectrum, m/e 455 (M-15).

The acetate derivative gave a satisfactory combustion analysis. Anal. Calcd. for C$_{30}$H$_{44}$SiO$_5$: C, 70.27; H, 8.65. Found: C, 69.98; H, 8.69.
To 78 mg (0.166 mmol) of 37 in 1 mL of CH$_3$OH was added 1 mL of H$_2$O. Glacial acetic acid (4 mL) was added, and the mixture was then heated to 63°C. After 30 min TLC analysis (1% CH$_3$OH/EtOAc) showed a substantial amount of 38 with a trace of 37. After an additional 15 min TLC analysis showed that 37 had been completely consumed. The reaction mixture was cooled to 23°C and the solvent was removed in vacuo, azeotroping several times with CH$_2$Cl$_2$. Purification of the residue by chromatography (silica gel, 20 mm column, 1% CH$_3$OH-EtOAc) afforded 63 mg (88%) of 38: R$_f$ 0.57 (1% CH$_3$OH in EtOAc); $[\alpha]_D^{21} - 3.6^\circ$ (c=1.05; CHCl$_3$); $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.66-7.63 (m, 4 H), 7.44-7.34 (m, 6 H), 3.90-3.60 (two broad m, 6 H), 2.70 (br s, 1 H; OH), 2.23 (br s, 2 H, OH), 1.7–1.2 (series of m, 7 H), 1.03 (s, 9 H), 0.87 (t, J=7.3 Hz, 3 H); $^{13}$C NMR (CDCl$_3$, 69 MHz) $\delta$ 135.6, 134.0, 129.6, 127.6, 75.2, 71.4, 64.2, 63.8, 40.5, 29.5, 26.9, 24.1, 22.5, 19.2, 10.9; IR (neat) 3390 (br), 3075, 3055, 3000, 2960, 2938, 2862, 1592, 1465, 1430, 1390, 1365, 1112 (br), 914, 825, 802, 739, 702, 612 cm$^{-1}$; mass spectrum, only ions of multiple fragmentations observed (e.g., m/e 369 (M-61)).

The triacetate derivative gave a satisfactory combustion analysis.

To 63 mg (0.147 mmol) of 38 in 1 mL of THF was added 1 mL of H₂O. Solid NaIO₄ (78 mg, 0.37 mmol, 2.5 equiv) was added and stirring was continued at 23°C. After 3.5 h the reaction was judged to be complete by TLC analysis (3:1 hexane- Et₂O) and was diluted with 10 mL of saturated aqueous NaCl/CH₂Cl₂ (1:1). Extraction with CH₂Cl₂ (5x5 mL), filtration of the combined extracts through adsorbent cotton and removal of the solvent in vacuo afforded crude 6, which was purified by flash chromatography (silica gel, 20 mm column, 5:1 hexane- Et₂O) to afford 50 mg (93%) of pure 6: Rf 0.62 (3:1 hexane:ether), 0.54 (5:1 hexane:ether); [α]D²¹ + 1.2° (c=1.26, CHCl₃); Lit: [α]D + 1.6° (c=1.44; CHCl₃); ¹H NMR (CDCl₃, 250 MHz) δ 9.57 (d, J=2.6 Hz, 1 H), 7.67 (m, 4 H), 7.40 (m, 6 H), 3.67 (t, J=5.9 Hz, 2 H), 2.20 (m, 1 H), 1.73-1.49 (m, 6 H), 1.06 (s, 9 H), 0.92 (t, J=7.6 Hz); IR (CH₂Cl₂) 3005, 2930, 2860, 2715, 1960, (w), 1890 (w), 1840 (w), 1720 (s), 1590 cm⁻¹; mass spectrum m/e 311 (M-57).
Diene ester 19 was prepared according to the procedure of Peseckis\textsuperscript{6}. Purification by careful preparative thin layer chromatography afforded 19 (75\%) as well as a small amount (<5\%) of an olefin isomer, tentatively assigned structure 39. The product 19 possessed $[\alpha]_D^{20} + 8.4^\circ$ (C=1.12, CHCl\textsubscript{3}) versus Peseckis' best rotation of $+7.8^\circ$ (CHCl\textsubscript{3}). The presence of a small amount of 39 $[\alpha]_D^{20} - 11^\circ$ (C=0.1, CHCl\textsubscript{3}) in 19 may account for the slightly lower rotation of Peseckis' sample.
REFERENCES


8. Several methods, including Mosher ester preparation and $^1$H NMR analysis in the presence of chiral shift reagents, proved unsuccessful.


15. The presence of alkenylboronate species such as 35 has also been observed after treatment of 28 with (Z)-propenylolithium. Roush, W.R.; Adam, M.A. unpublished results.


18. Acetylene 33 was dried by successive azeotroping with benzene and pumping at <.01 torr for 12 h.